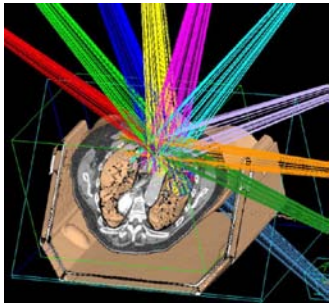
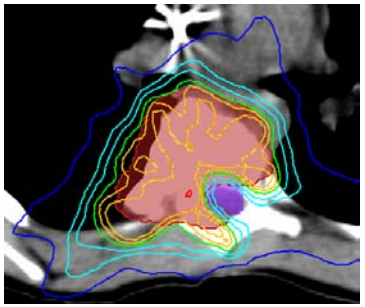
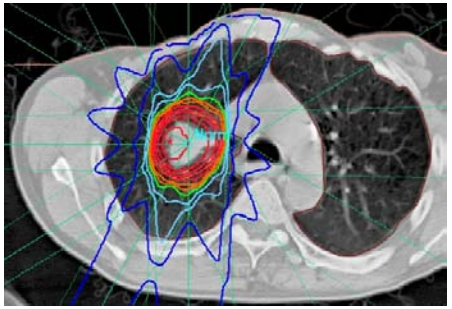
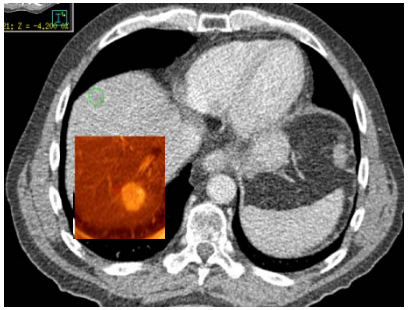
ESTRO

Implementation & Practice of Image-Guided Stereotactic Body Radiotherapy

5.6. – 9.6. 2016 in Athens, Greece

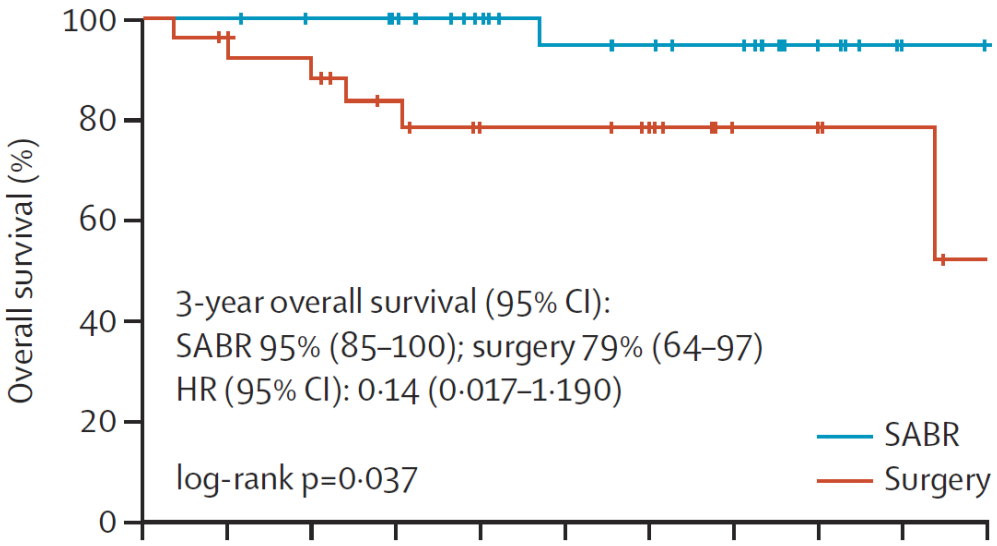





Matthias Guckenberger, Dirk Verellen

UniversityHospital Zurich

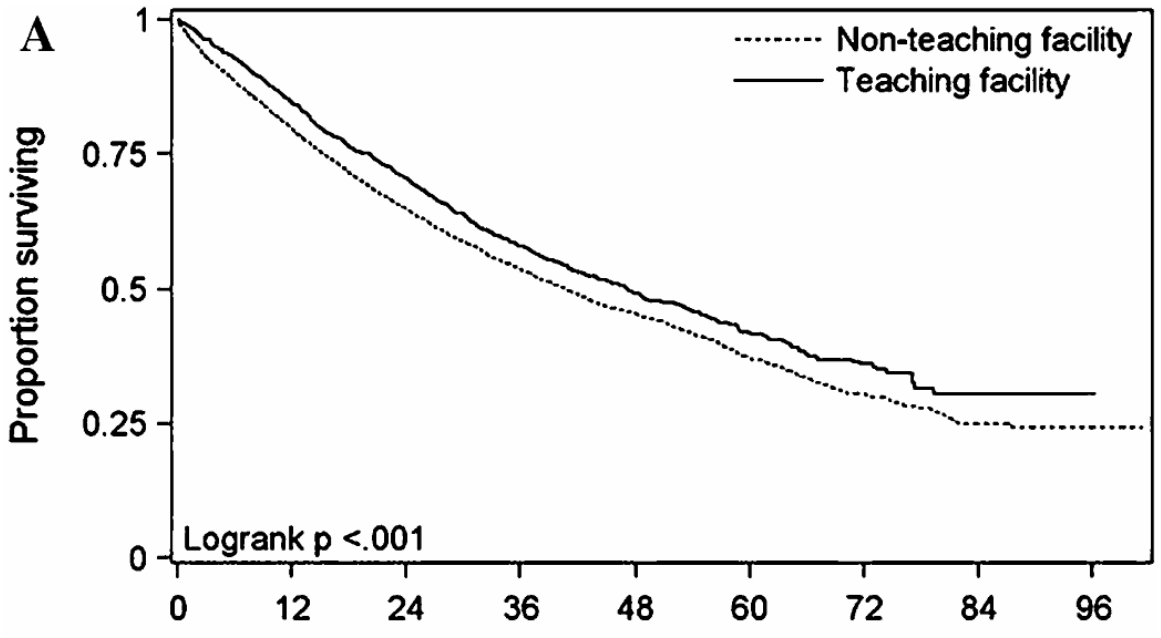
Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

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



Lessons to be learned from surgery

13469 lung resections in Florida



	Teaching facility	Non-teaching facility
90 day death rate	3.8%	6.8%
Median OS	47.1 months	50.5 months

SBRT of lung cancer

Stereotactic body radiotherapy and treatment at a high volume facility is associated with improved survival in patients with inoperable stage I non-small cell lung cancer

Matthew Koshy [a,b,*], Renuka Malik [b], Usama Mahmood [c], Zain Husain [d], David J. Sher [e]

[a] Department of Radiation Oncology, University of Illinois at Chicago; [b] Department of Radiation and Cellular Oncology, The University of Chicago; [c] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston; [d] Department of Radiation Oncology, Yale University; and [e] Department of Radiation Oncology, Rush University Medical Center, Chicago, USA

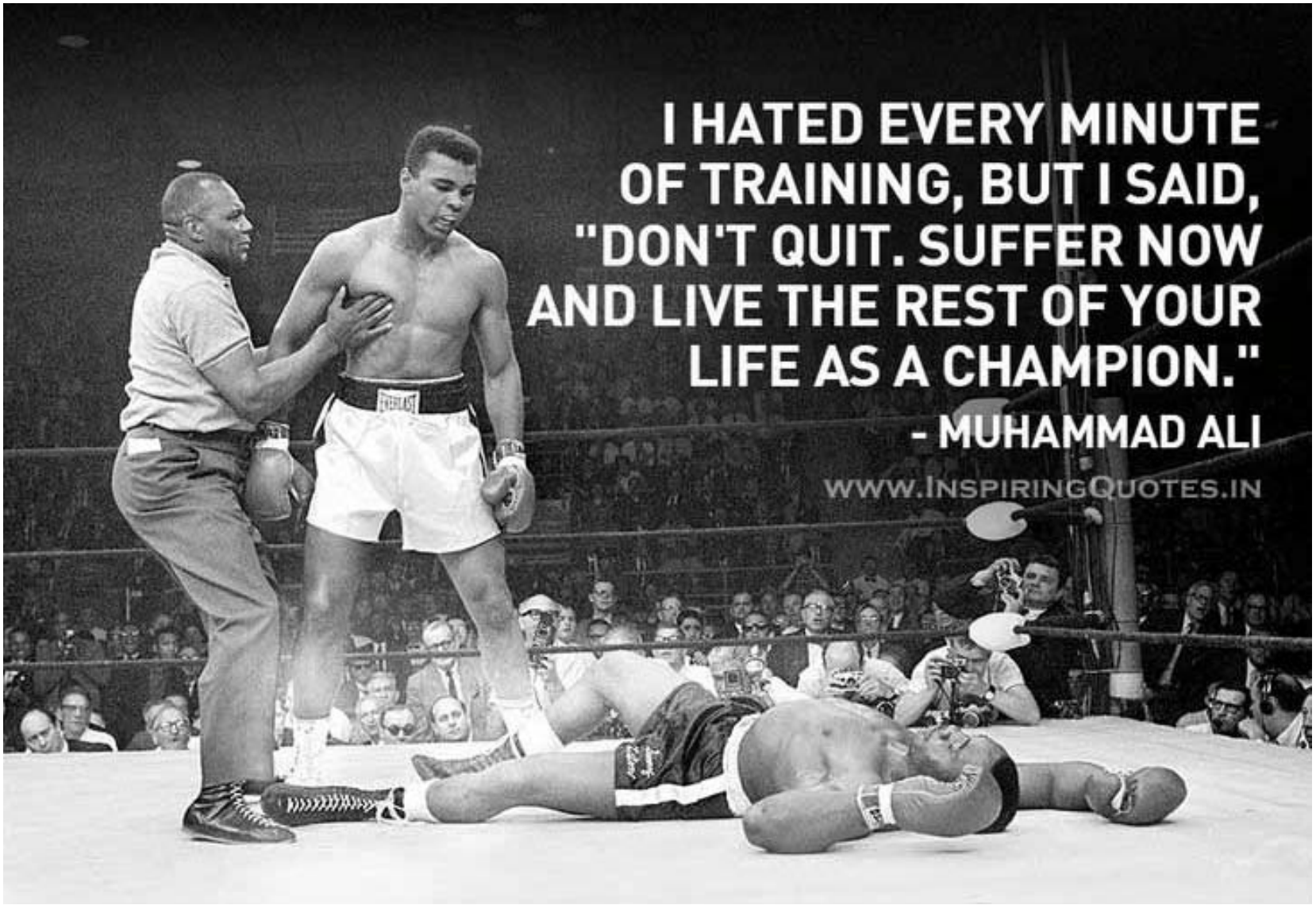
GreenJ 2015

„Patients who were treated at high volume centers were also noted to have a superior survival“

„This finding was also independent of the fact that SBRT was mainly performed at high volume centers.„

I believe …

… that we need this course (and others) more than ever!


I HATED EVERY MINUTE
OF TRAINING, BUT I SAID,
"DON'T QUIT. SUFFER NOW
AND LIVE THE REST OF YOUR
LIFE AS A CHAMPION."
- MUHAMMAD ALI
WWW.INSPIRINGQUOTES.IN


GER, FAST

Our Faculty

Physicists

Dirk Verellen

Stephanie Lang

Mischa S. Hoogeman

Coen Hurkmans

Clinicians

Matthias Guckenberger

Karin Diekmann

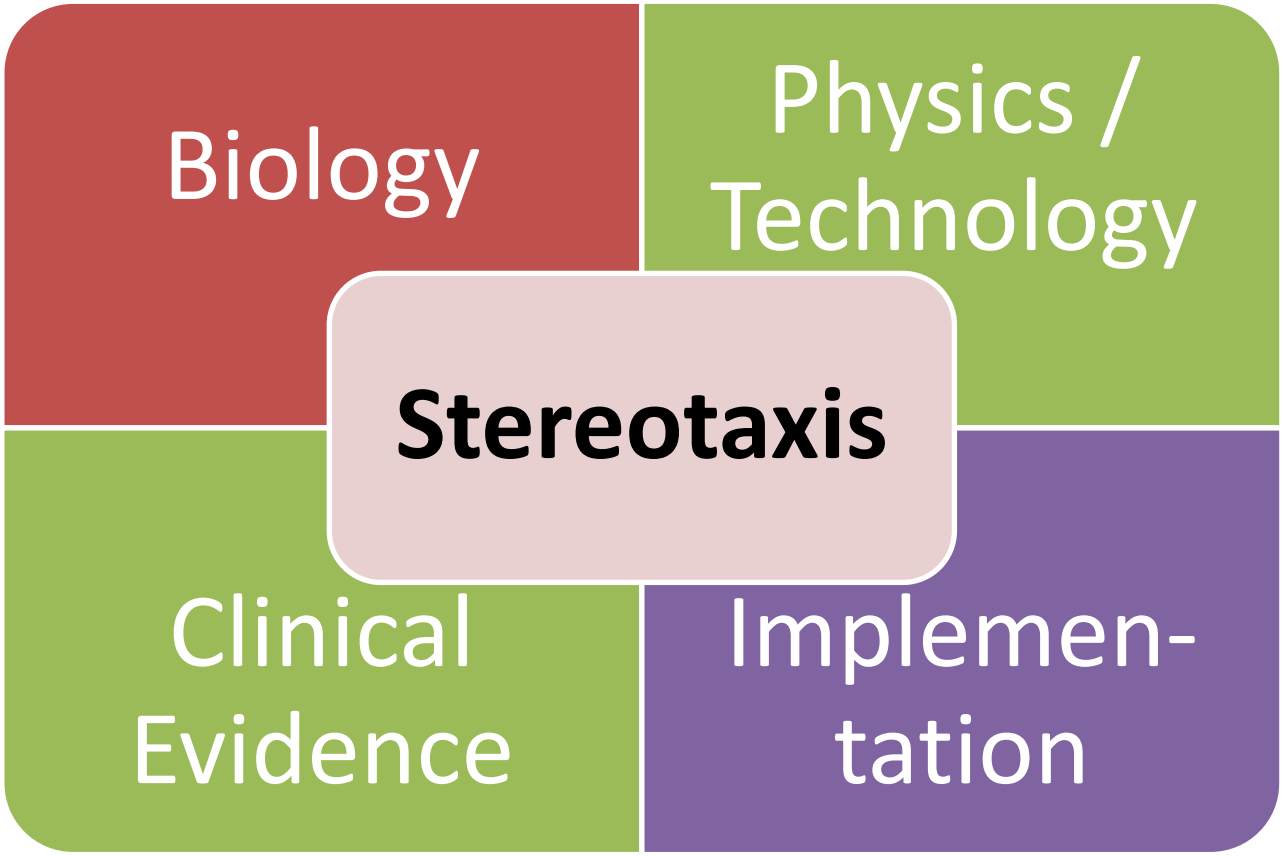
Morten Hoyer

Alejandra Méndez Romero

RTT

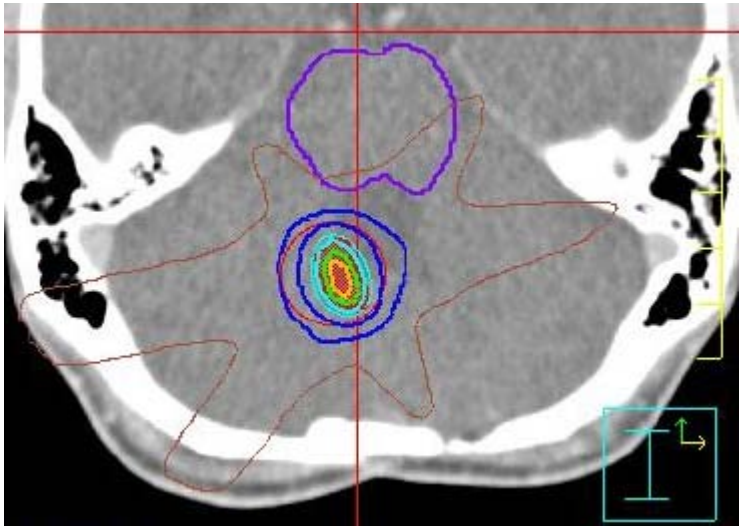
Lineke van der Weide

Our program

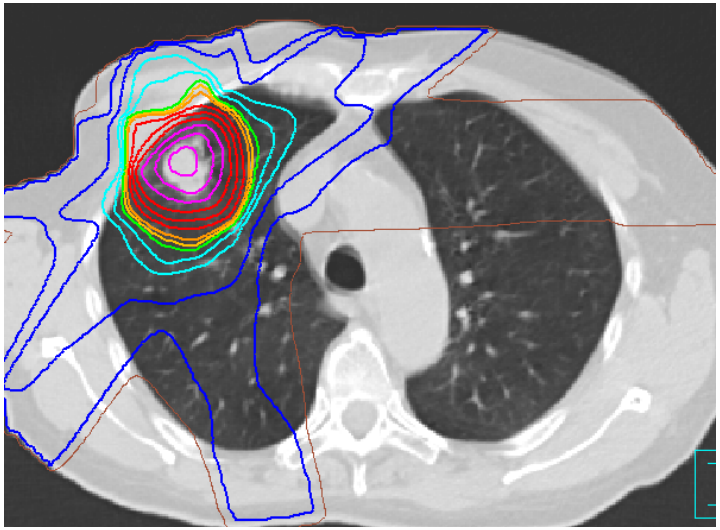

Biology
Physics / Technology
Stereotaxis
Clinical Evidence
Implemen-tation

Topics of our course

Cranial stereotactic radiotherapy
SRS



Stereotactic body radiotherapy
SBRT



Course program

Sunday: Introduction day

- Historical background
- Radiobiology / Modeling
- SBRT in the context of Oncology
- Errors

Monday: Technology and Physics day

- Margins
- Management of targets w/o respiration induced motion
- Management of targets with respiration induced motion
- SBRT treatment planning and plan evaluation
- QA and safety

Course program

Tuesday & Wednesday: Lectures

- Stage I NSCLC
- Best practice recommendations
- Oligometastatic disease
- Vertebral metastases
- Primary liver cancer
- Prostate and pancreatic cancer

Tuesday and Wednesday: Split-up sessions

Course program

Tuesday Morning: Split-up sessions clinicians & physicists

11:15	12:45	Practical split-session for SBRT lung - Linac
		Practical split-session for SBRT lung - Linac
		Practical split-session for SBRT lung - Linac
		Practical split-session for SBRT liver - Cyberknife

Interactive case demonstration and discussion

Course program

Tuesday Afternoon – F R E E

Course program

Wednesday afternoon:

Split-up sessions

1. Spine SBRT
2. Brain SRS
3. Physics in implementation of SBRT
4. Practice of SBRT from a RTT perspective

YOU CAN ATTEND 2 / 4 of these split up sessions

Course program

Thursday: Practical implementation

- Starting a SBRT program: a clinicians view
- Starting a SBRT program: a physicists view
- Starting a SBRT program: a RTT view
- Panel discussion

✓ Broad overview of current technologies and their specific pos / cons

✓ Evidence-based presentation of SBRT & it`s limitations

✓ Room for close interaction in spilt-up sessions

➢ **To build up a successful SBRT program**

Acknowledgements

ESTRO:

- Carolina Goradesky
- Melissa Vanderijst
- Christine Verfaillie

Teachers:

- Stephanie Lang
- Karin Diekmann
- Mischa S. Hoogeman
- Morten Hoyer
- Coen Hurkmans
- Alejandra Méndez Romero
- Lineke van der Weide

ESTRO School

WWW.ESTRO.ORG/SCHOOL

From Frame-based to Frameless: a historical overview part II

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

Karin Dieckmann & Dirk Verellen

DV is involved in an on-going scientific collaboration with BrainLAB AG, RaySearch, MIM

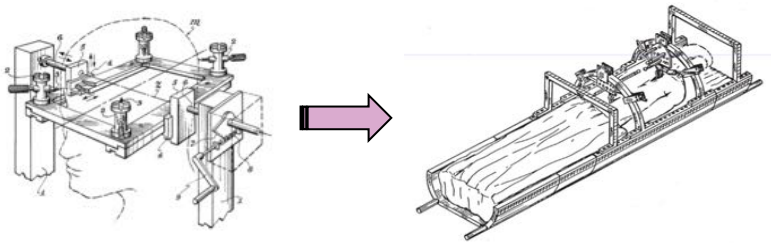
ESTRO School

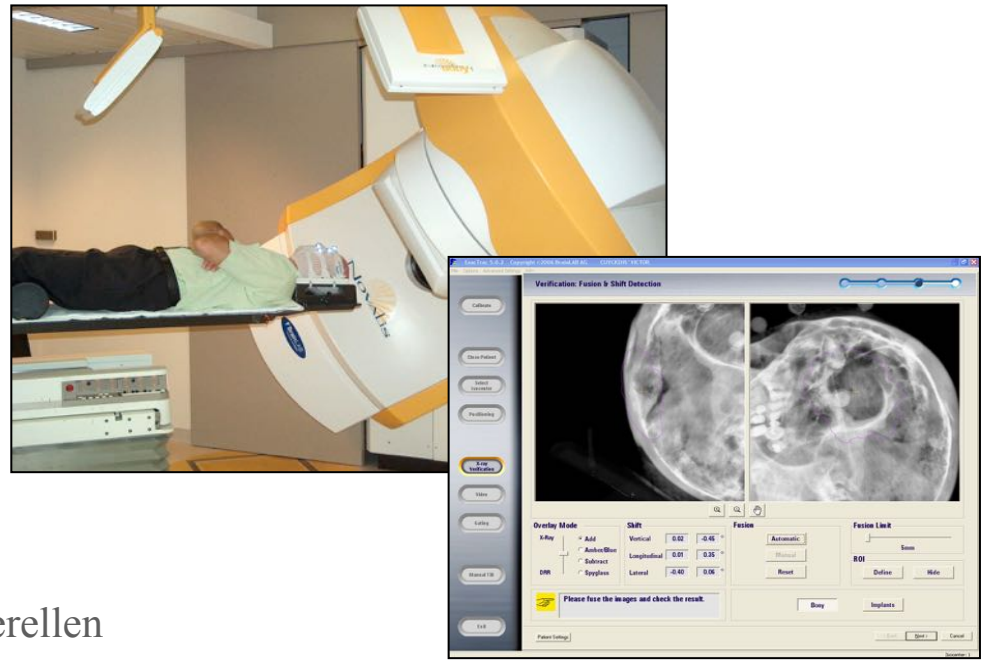
Learning objectives

- 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.
- Much more information in the handouts, this presentation is only a selection to illustrate the essentials.

To frame or not to frame …

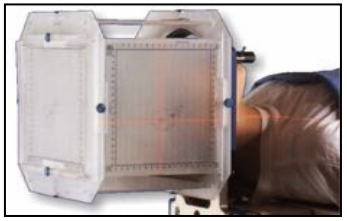
- Why evolving towards frameless intracranial SRS?
- Historical evolution:
  - SRS with frame to SBRT with frame
  - SBRT from frame (SBF) to IGRT
  - SRS following the evolution in SBRT
  - Accuracy of frameless SRS



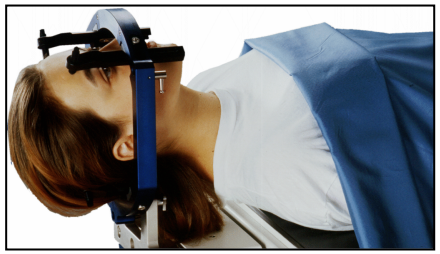
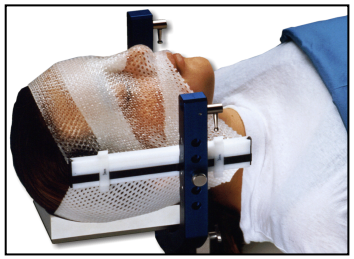


Some definitions

- 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

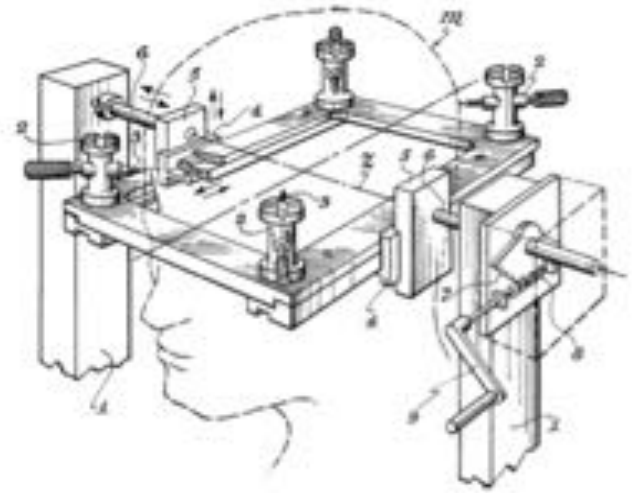



- Invasive versus non-invasive
  - Whether the patient is rigidly fixed to the stereotactic system using invasive techniques or a ‘patient friendly’ immobilization system is used allowing multiple fractions

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 / radiotherapy

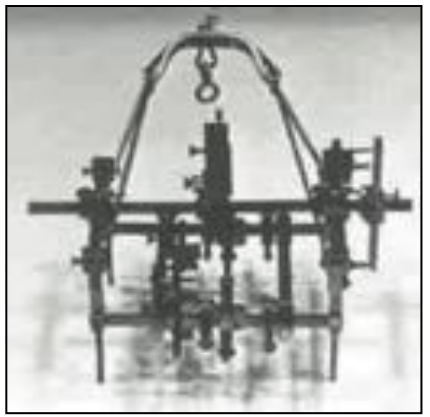
A short history of intracranial SRS

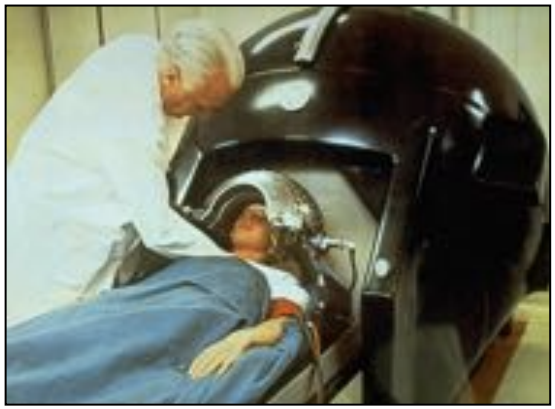
- **1908:**
  - **Robert Henry Clarke and Victory Horsley:** Stereotactic technique based on the reproducibility of the relationships between landmarks on the skull (external auditory canals, midline) and anatomical structures within the brain
- **1950s:**
  - **Lars Leksell:**

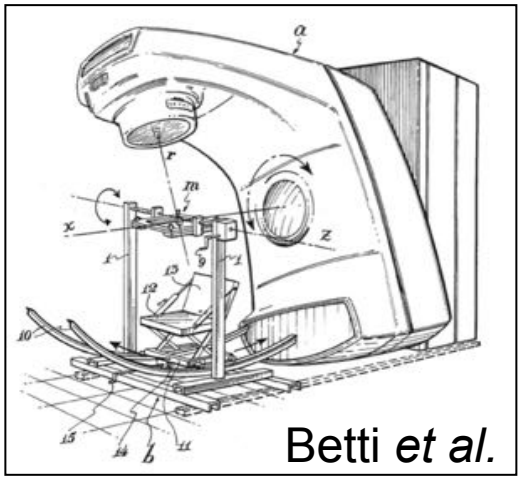
    Experiments with 250 kV rotating X-ray source (1951) and stereotactic proton therapy (1955)
- **1967:**
  - **Lars Leksell:**

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

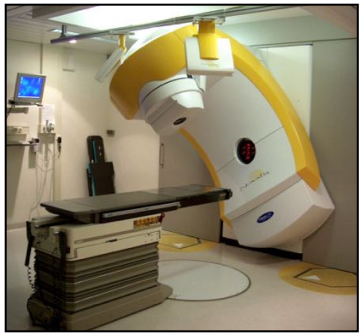
    CT-localization and linac-based SRS







Mechanical accuracy, in phantom!

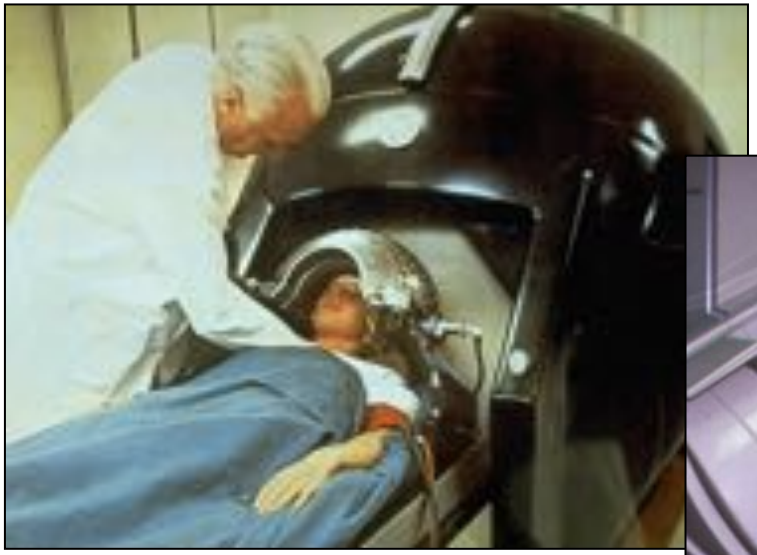


	Mechanical accuracy	Overall treatment accuracy
Gamma Knife Perfexion♮	**0.30 mm**	**0.93 mm**
Dedicated Linac: Novalis	**0.31 mm**	**0.50 – 1.5 mm**
Cyberknife*	**0.50 mm**	**0.85 mm**

* Hoogeman 2008 & Murphy 2009
♮ Wu & Maitz & Massagier 2007

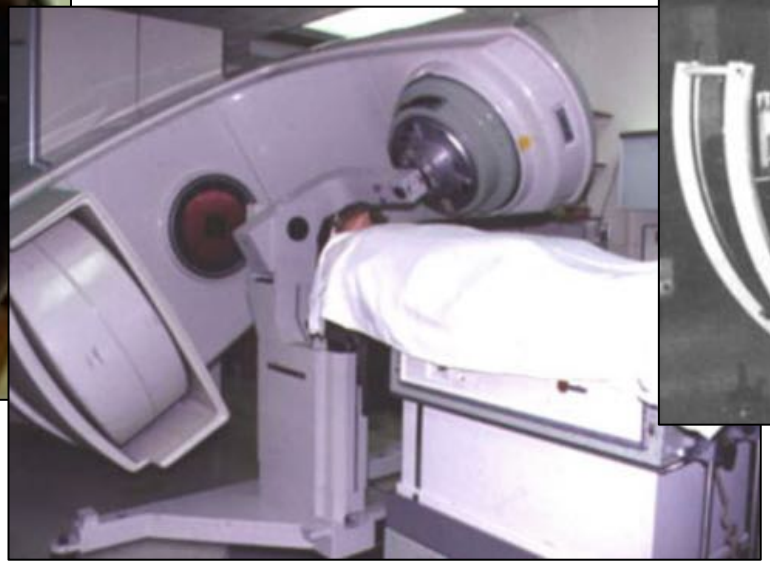
Frame-based SRS

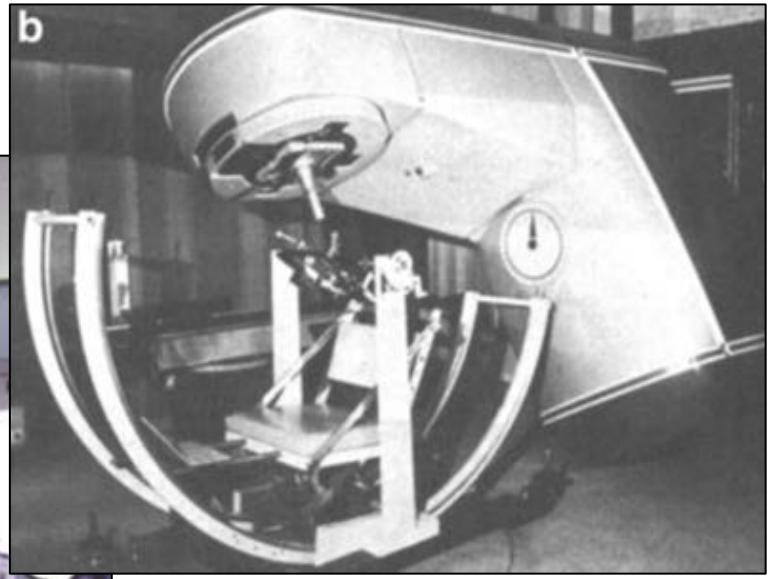
- Frame makes sense in setup with physical-rigid connection between patient and radiation source



Leksell *et al.*

Bova-Friedman *et al.*





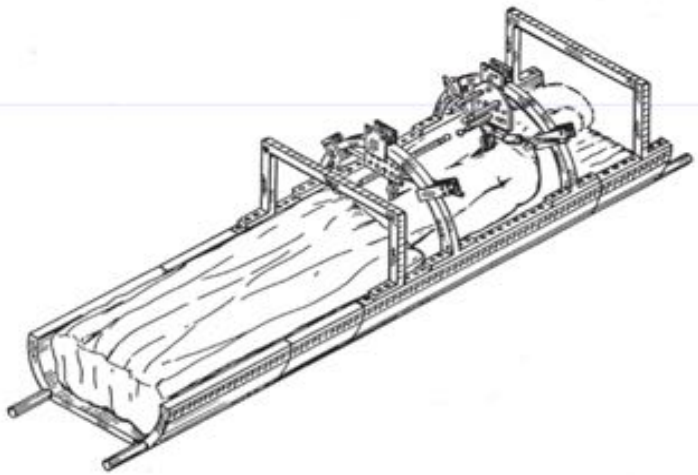
Betti *et al.*

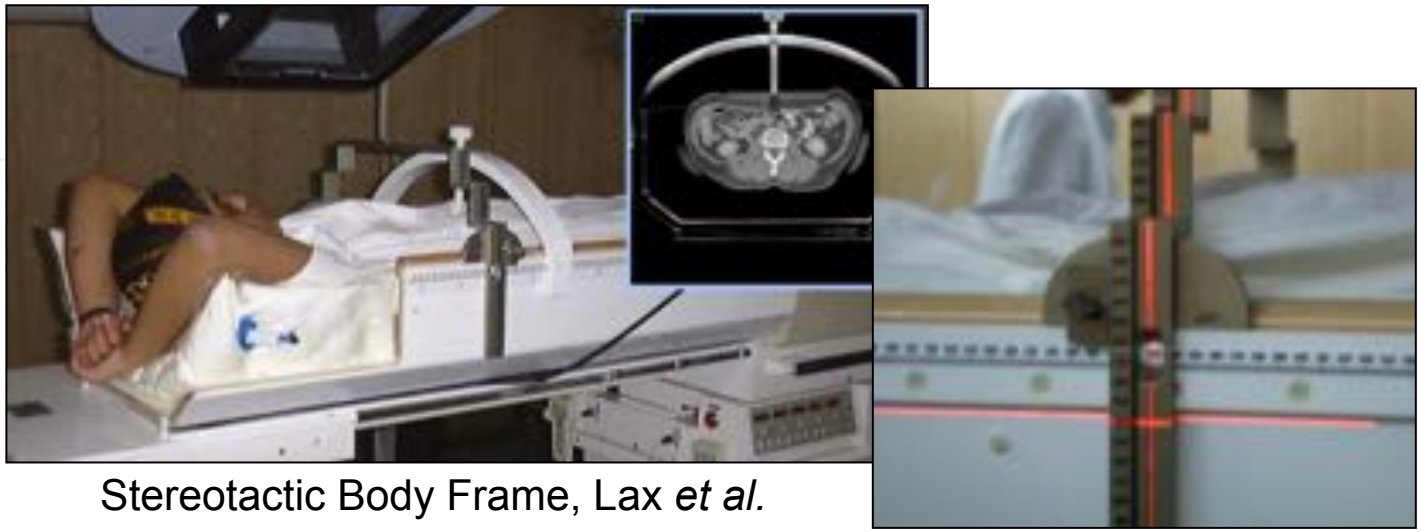
Frame-based SRS

- Frame makes sense in setup with 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





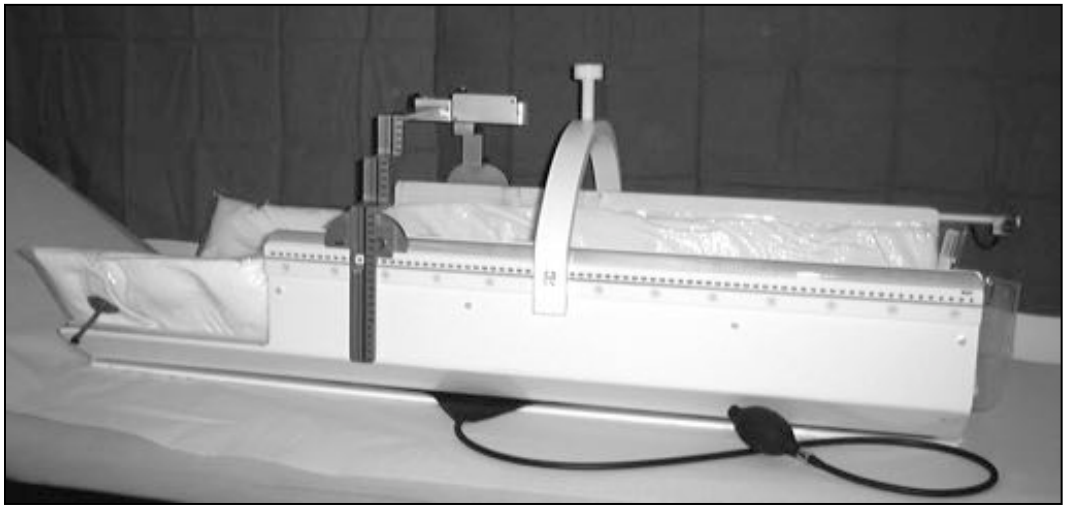
Stereotactic Body Frame, Lax *et al.*

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

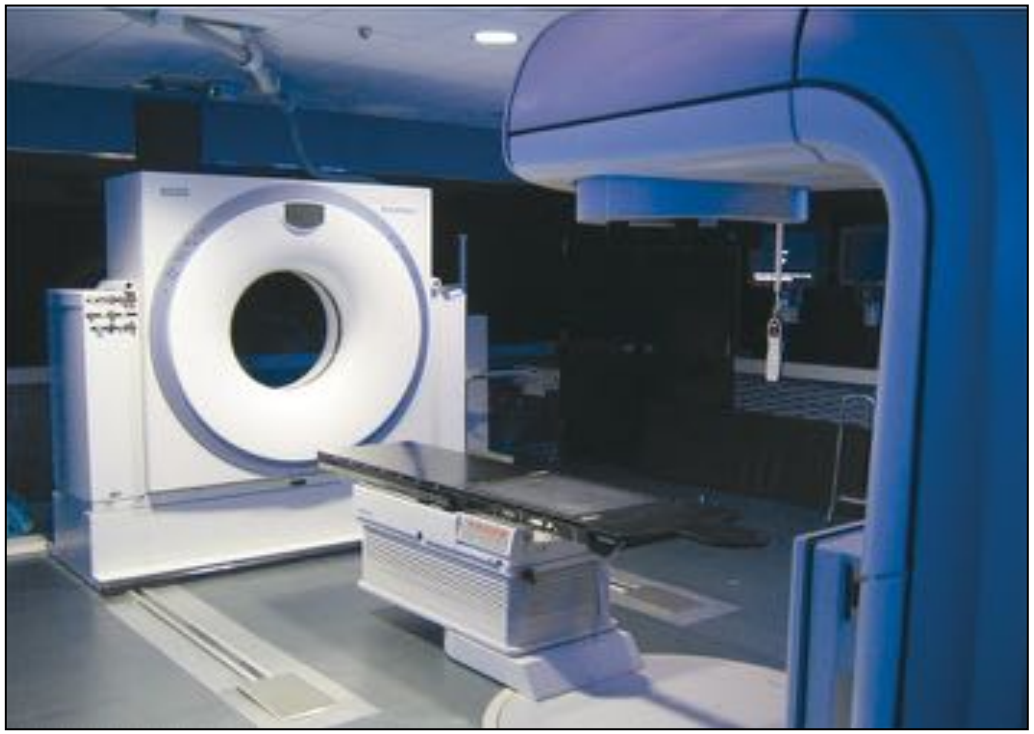
!Pioneers in SBRT!

Towards extracranial SRS: body frames

… still requires IGRT



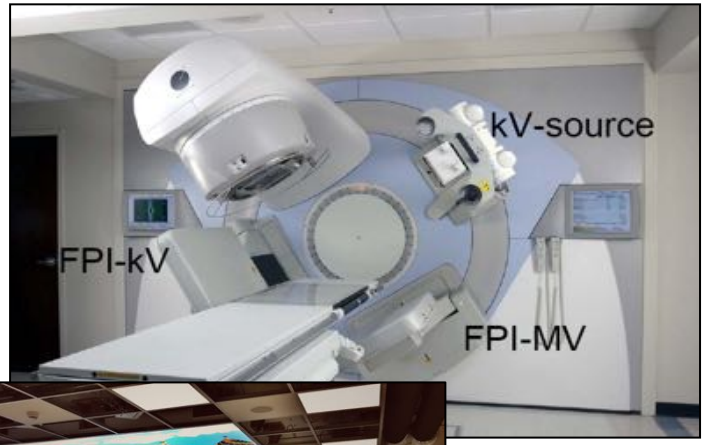
Stereotactic Body Frame, Lax *et al.*



- 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"

Evolution of IG-SBRT

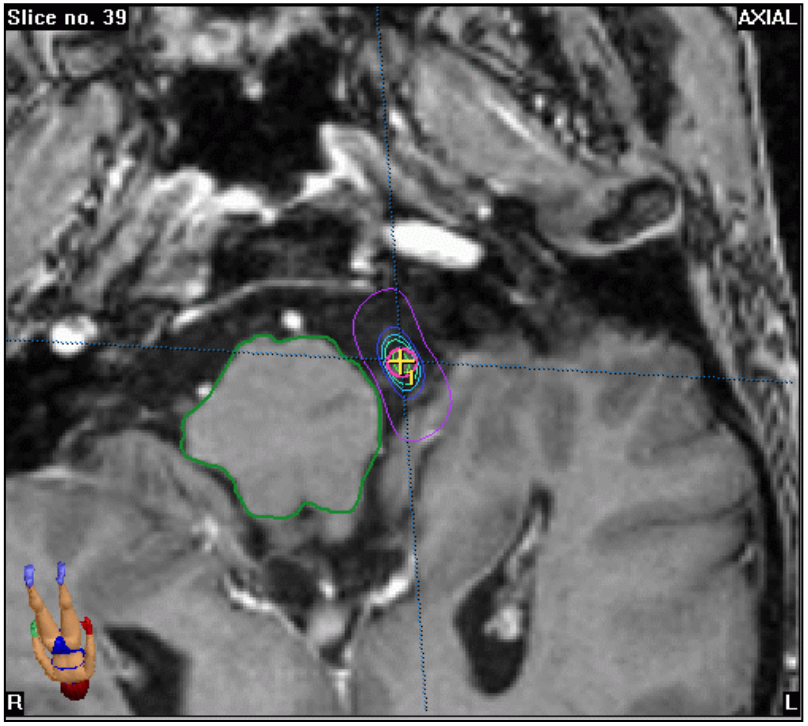
- SBRT and motion management



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

Frameless SRS

- High precision “frameless” stereotactic radiosurgery:

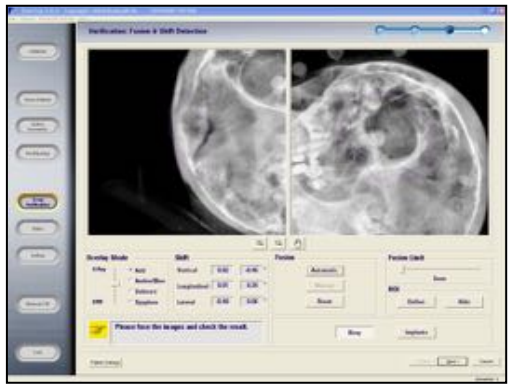


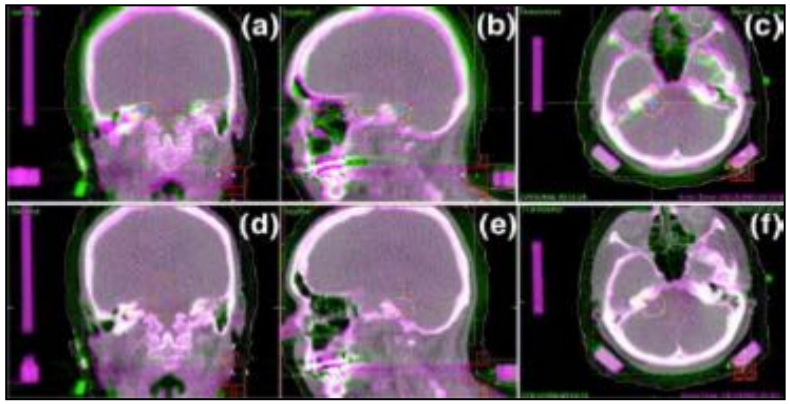
- … **also** requires implementation of image guided systems for target localization and positioning on the linac!

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**

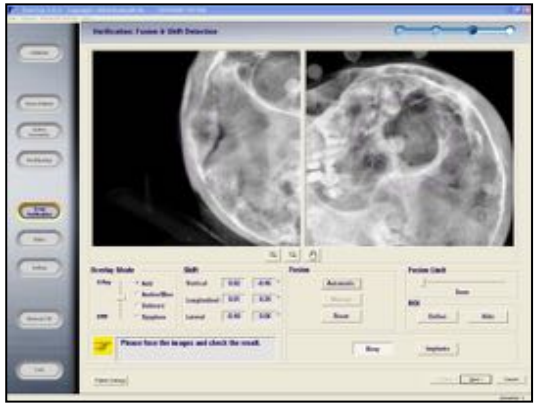


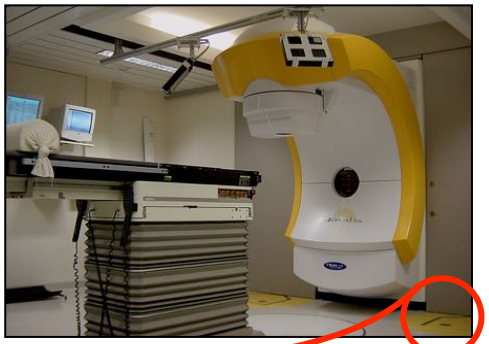


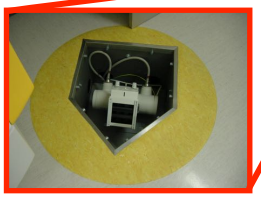
  - Making use of **internal anatomy rather than external landmarks** to localize target, position patient, and avoid geographic miss during treatment.

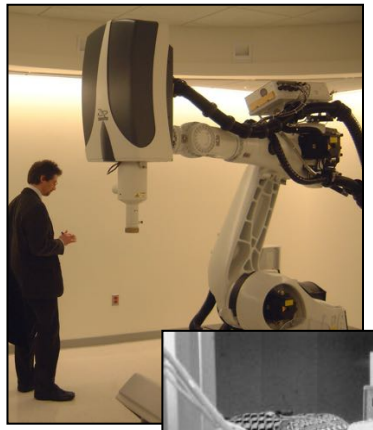
Image-guided frameless SRS

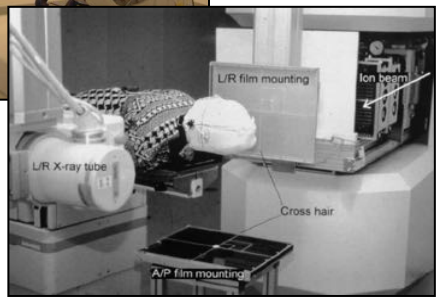
- 2D/3D, planar imaging



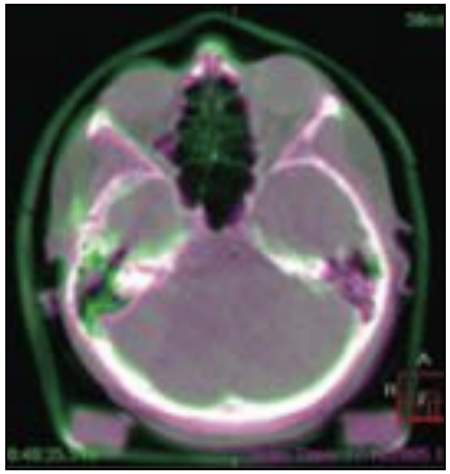


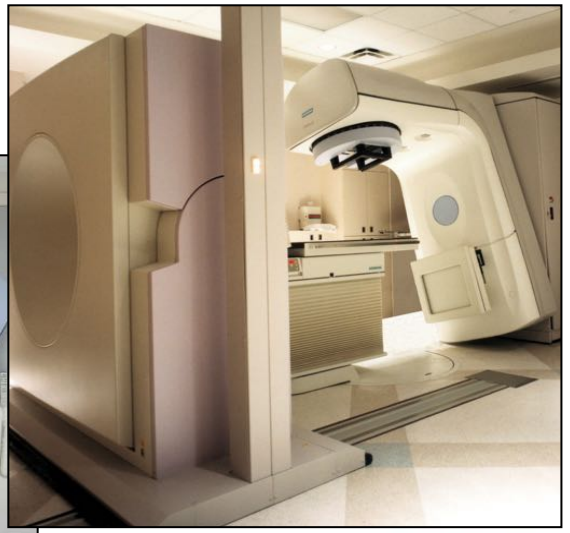






- 3D, volumetric imaging





Outline

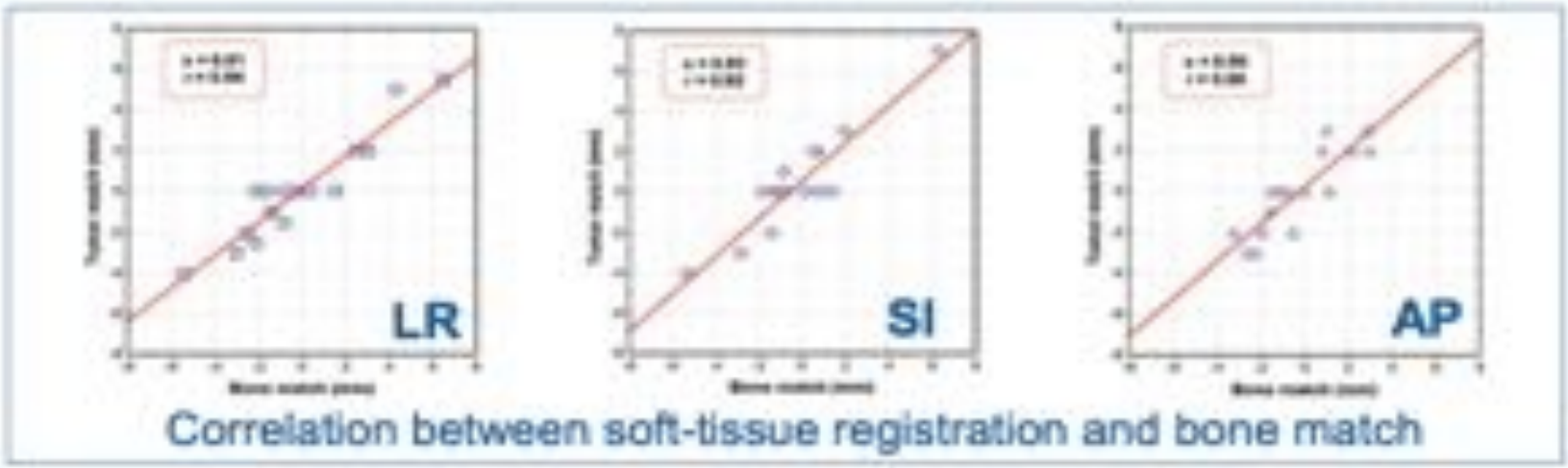
- Can we use bony structures for target localization?
- What accuracy can be achieved?
  - In phantom
  - Clinical validation
- Frame versus frameless
- Some words of caution
- Conclusions and food for thought

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

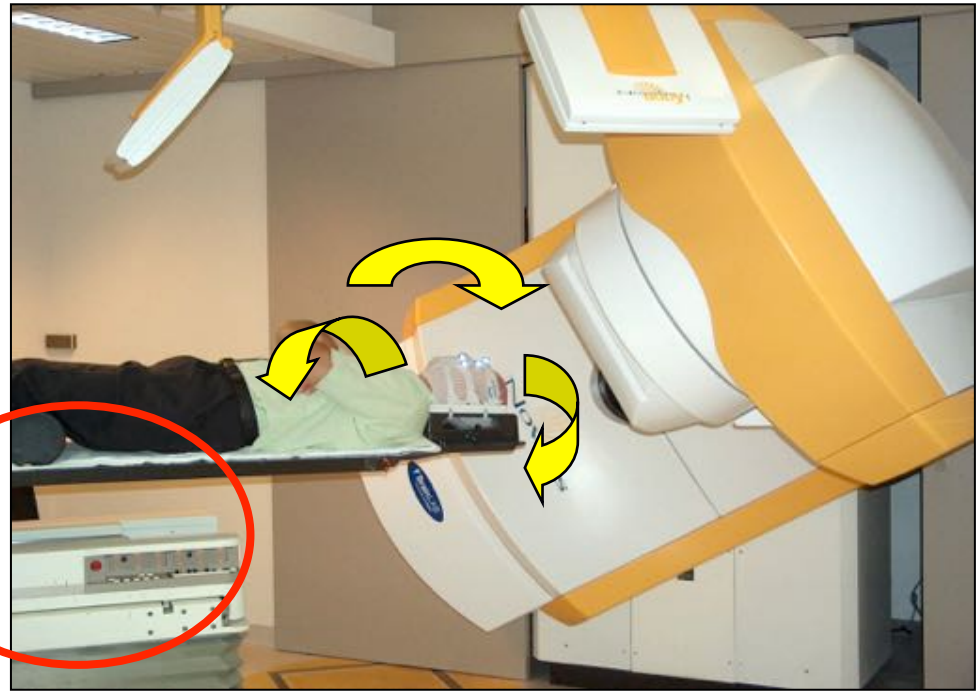
	Differences between bone and tumor match (mm)			
	LR	SI	AP	3D
Mean ± SD	-0.6 ± 1.0	0.0 ± 1.1	-0.2 ± 1.0	1.7 ± 0.7
Maximum	1.8	2.3	2	2.8

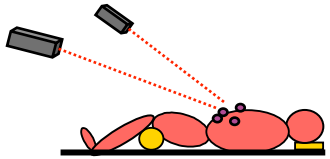
Stable tumor position relative to the skull for one week interval between planning and treatment

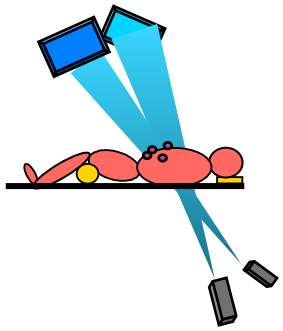
No influence of pre-treatment steroids

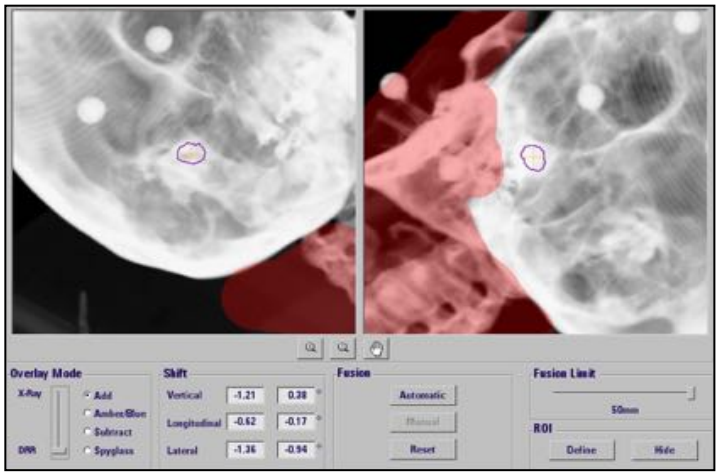
M. Guckenberger *et al.* IJROBP 2007

Is the skull a suitable reference?



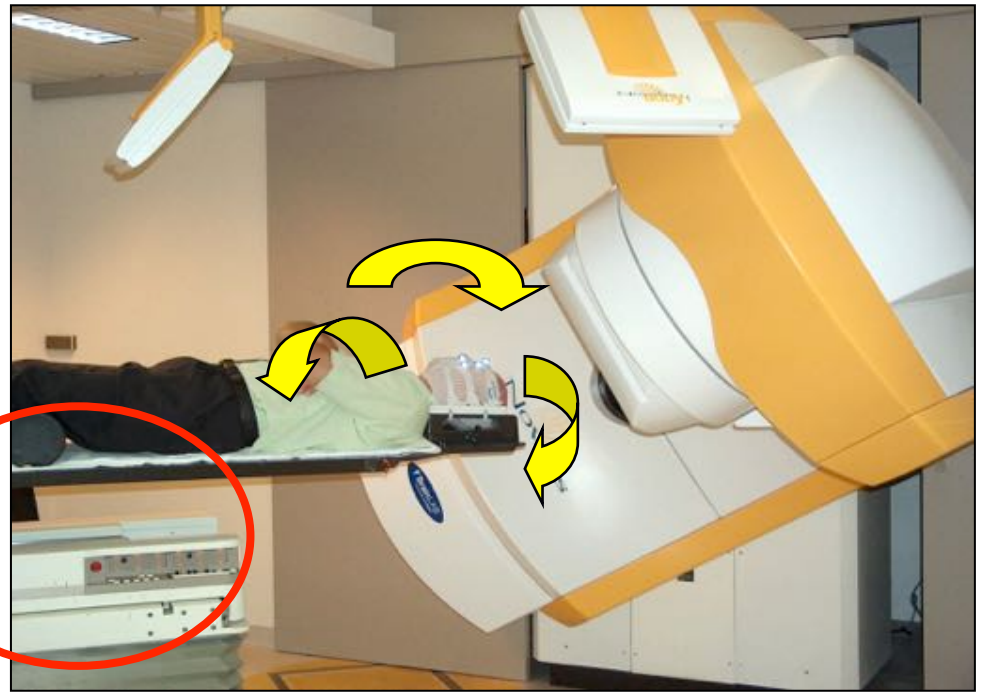


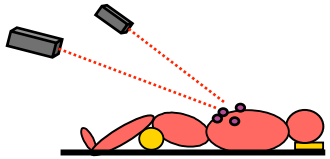


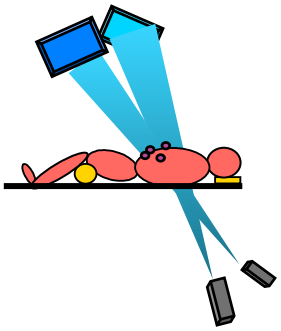


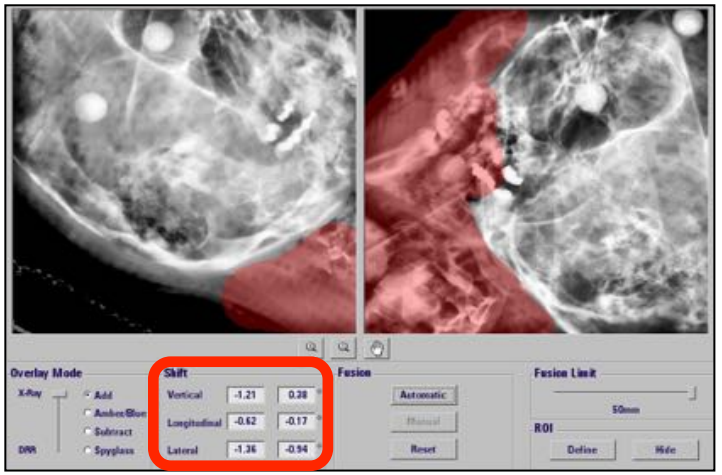
Full 6 DOF automated patient set-up

Is the skull a suitable reference?





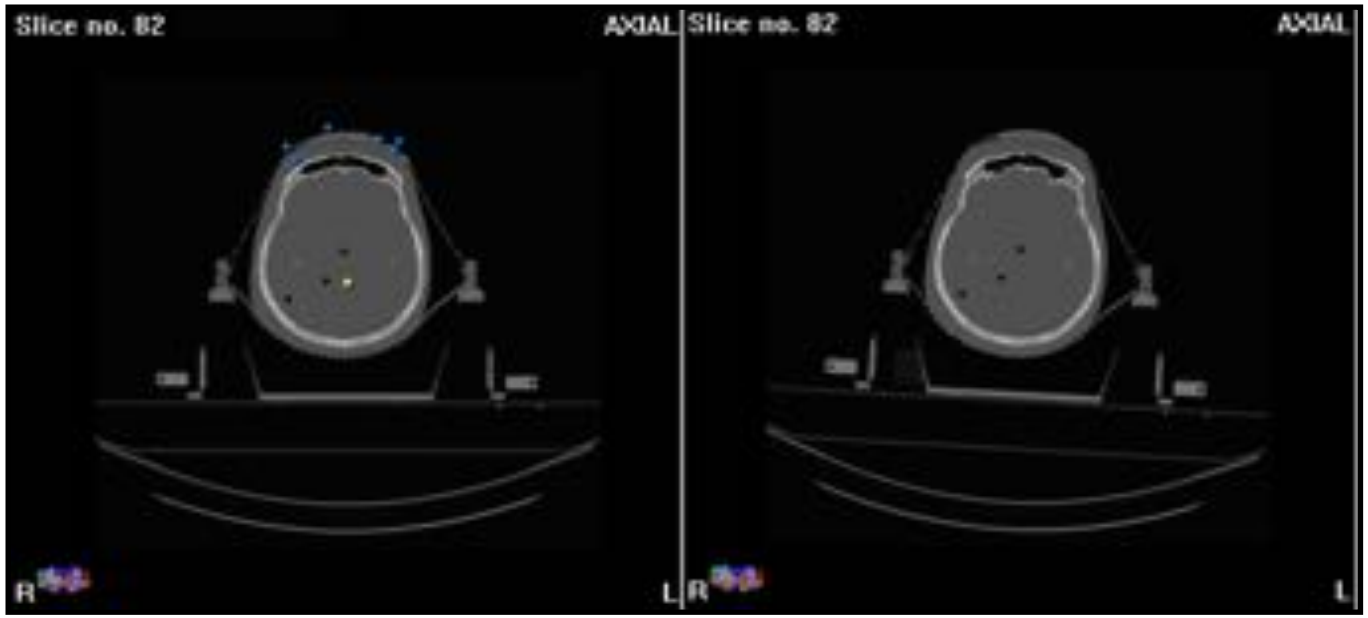


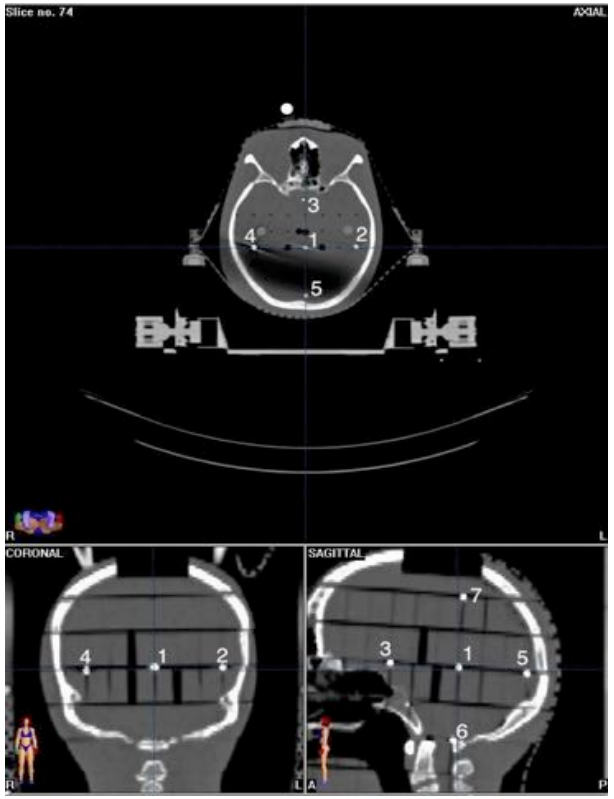


Full 6 DOF automated patient set-up

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

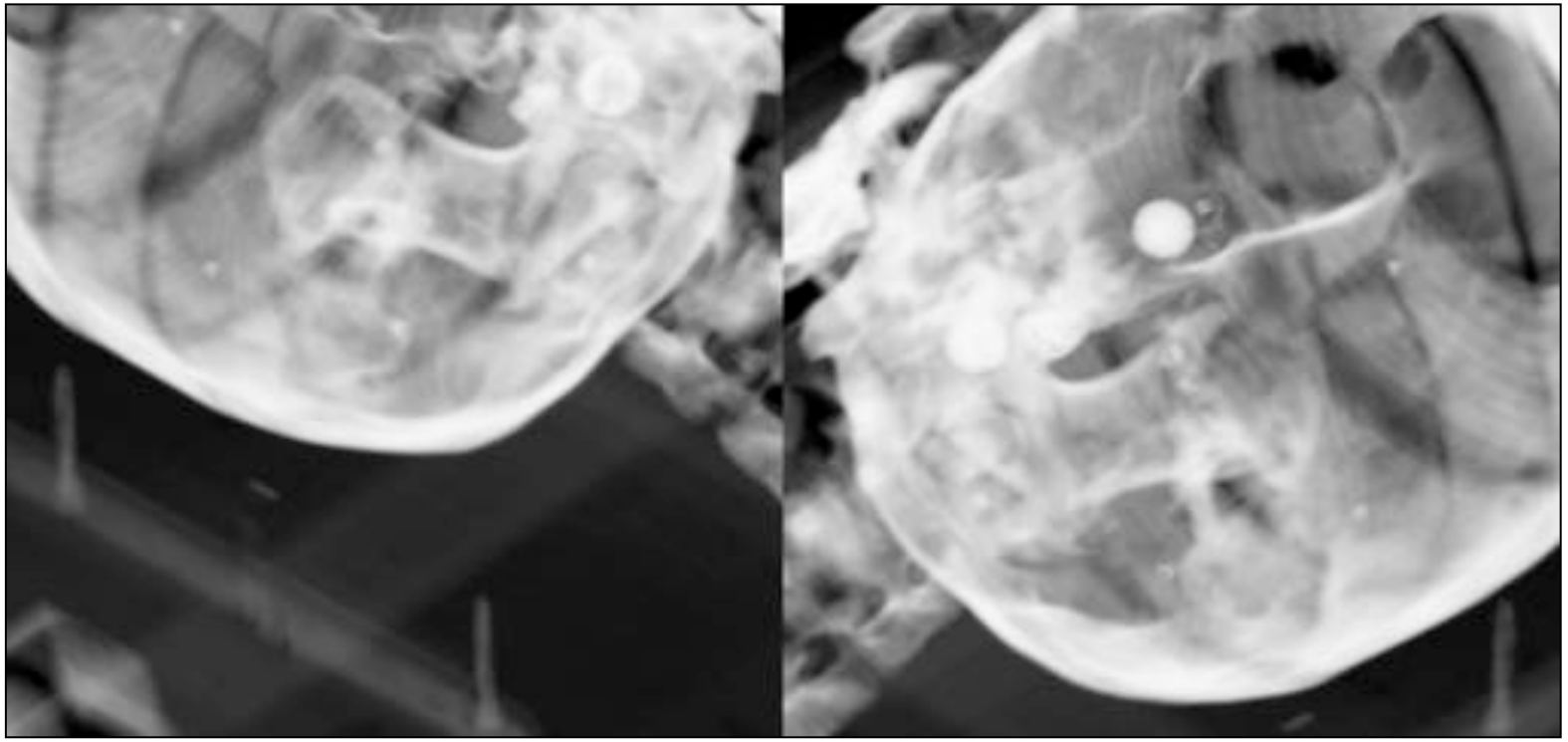




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

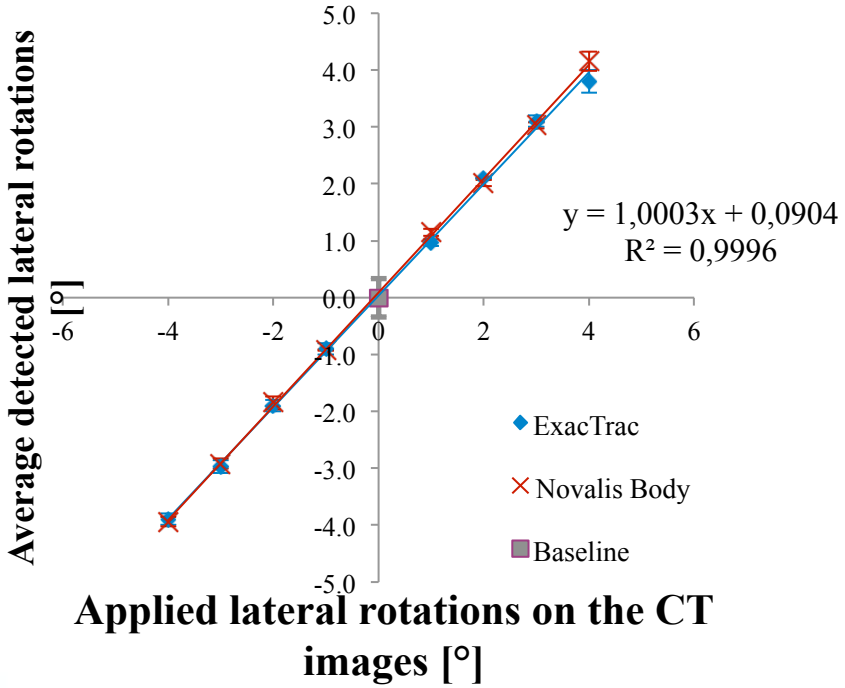
Is the skull a suitable reference?

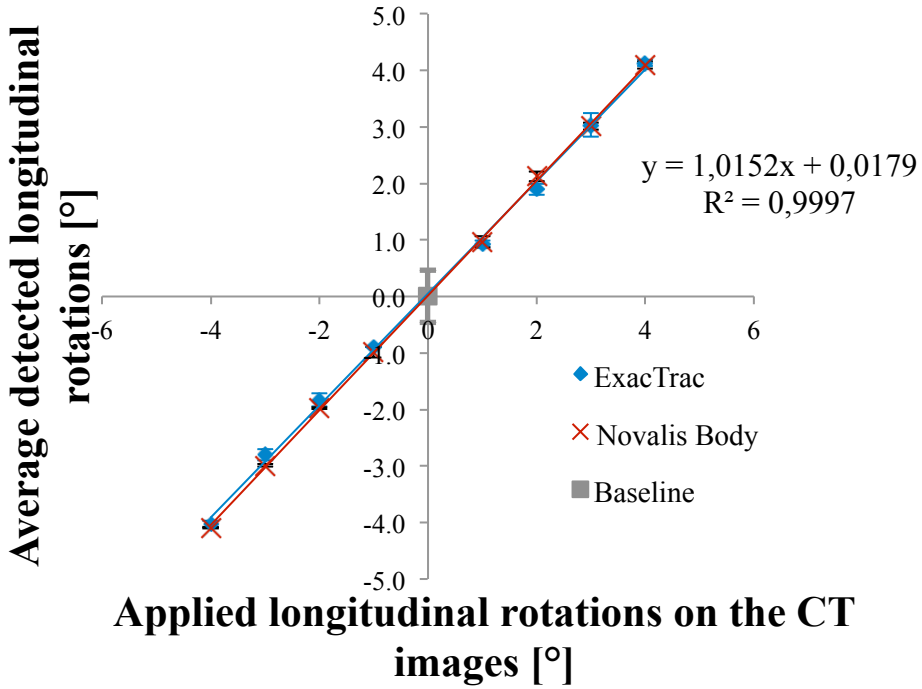
Different locations were chosen to investigate the sensitivity of the registration algorithm on presence/absence of bony fiducials



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

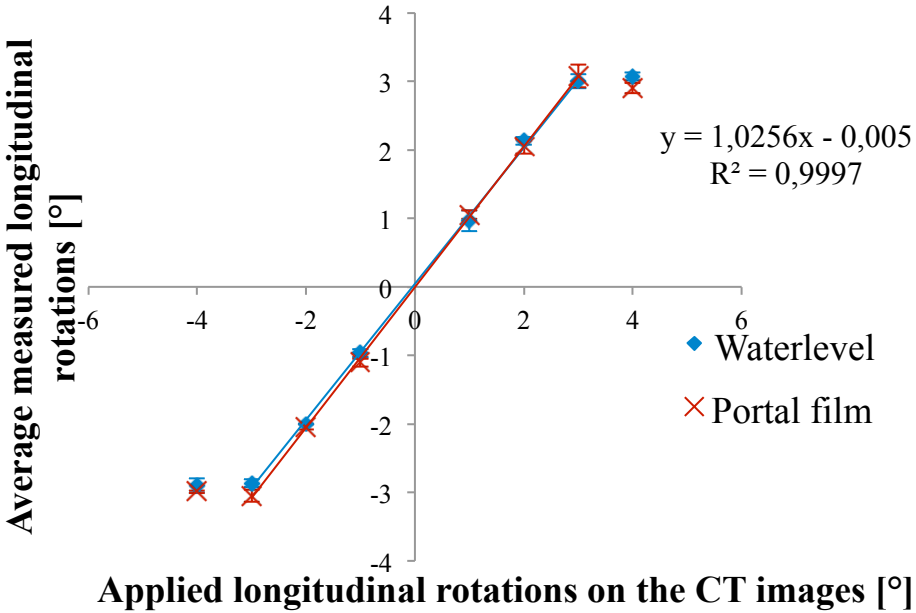
Detection accuracy

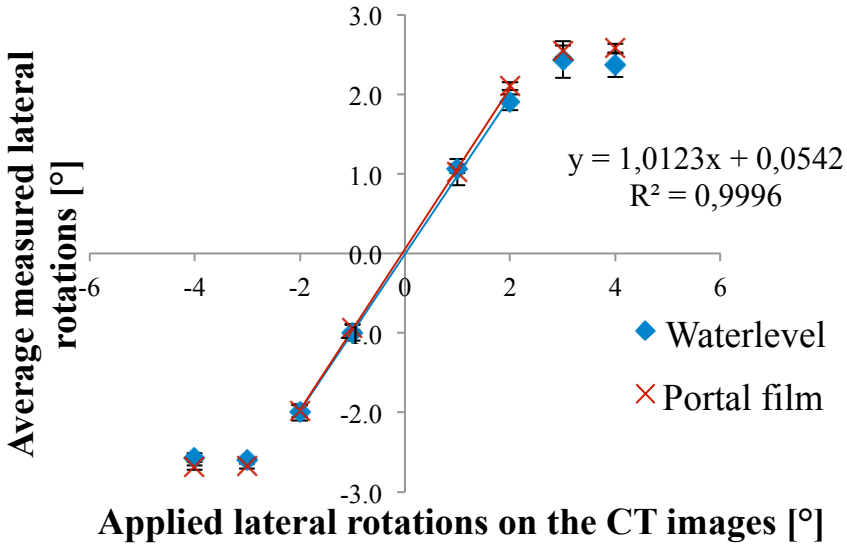




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Positioning accuracy (Robotics)

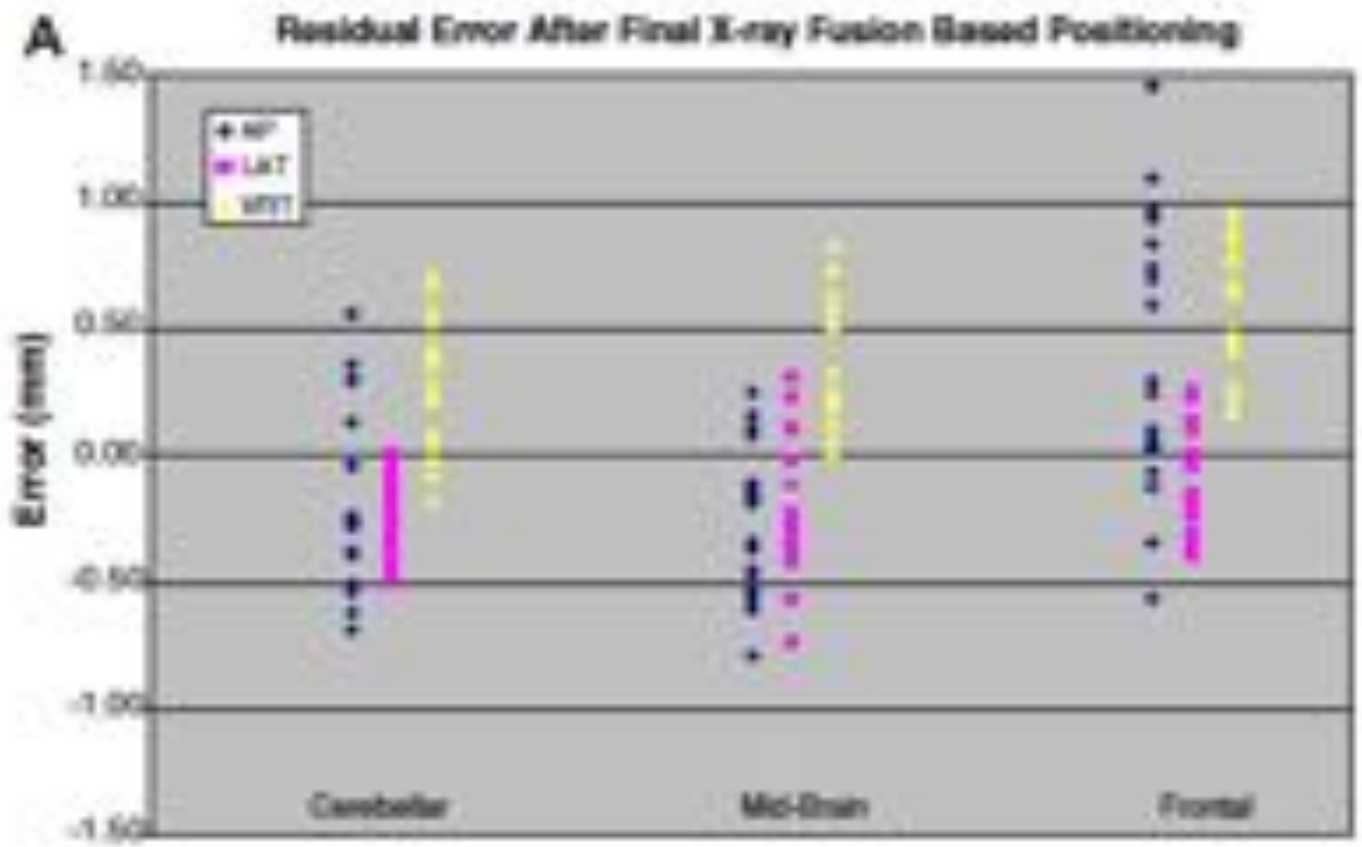




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Accuracy of IGRT/frameless SRS: HTT

- 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 achieved sub-millimeter accuracy **in phantom studies**

Meyer *et al.* IJROBP 2008

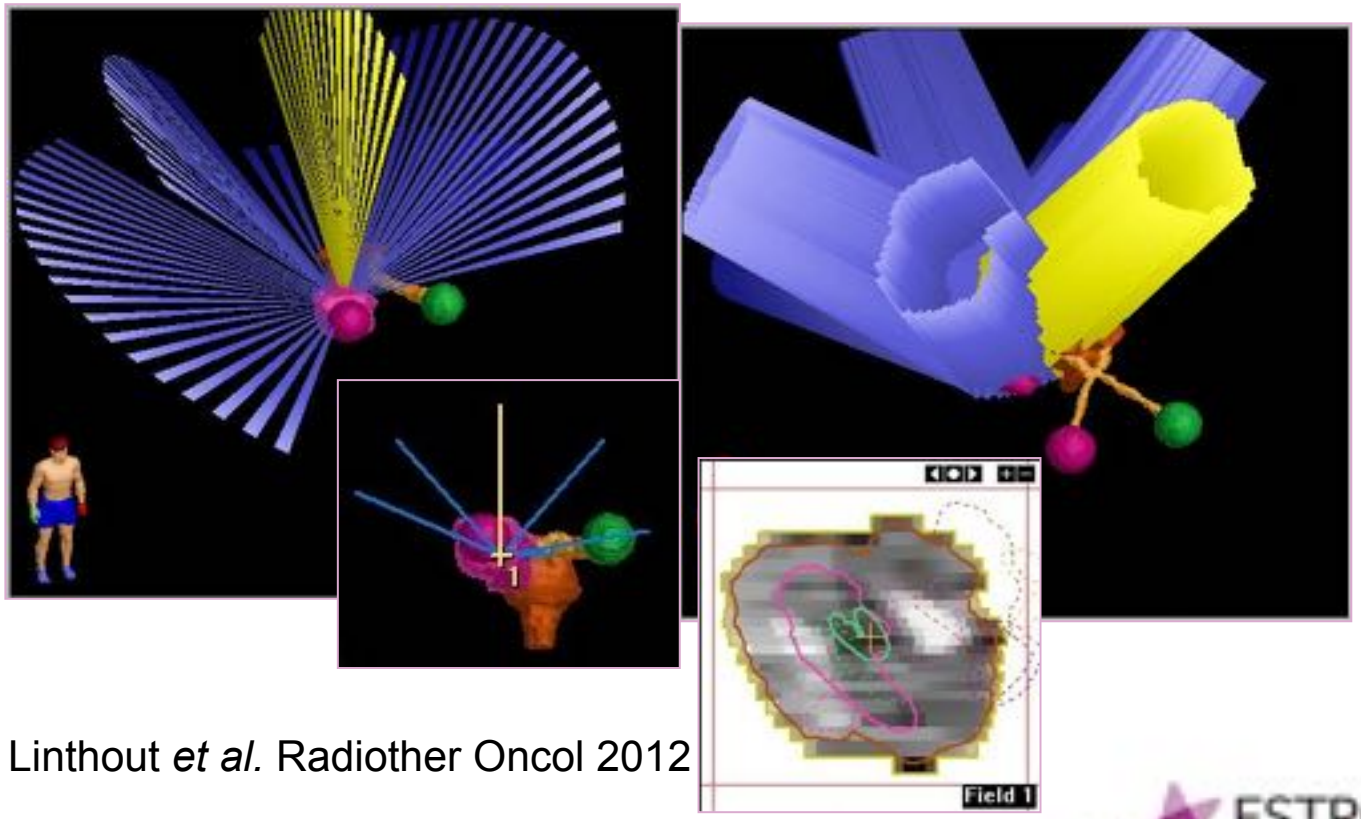
IGRT/frameless: Clinical validation

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

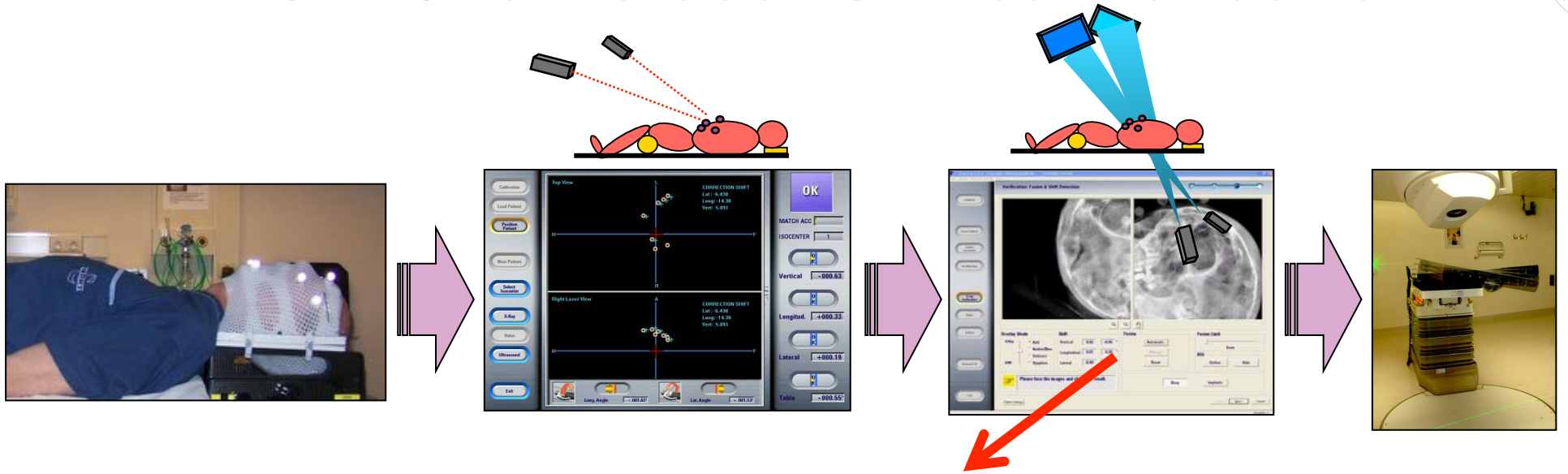
IGRT/frameless: Clinical validation

- 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

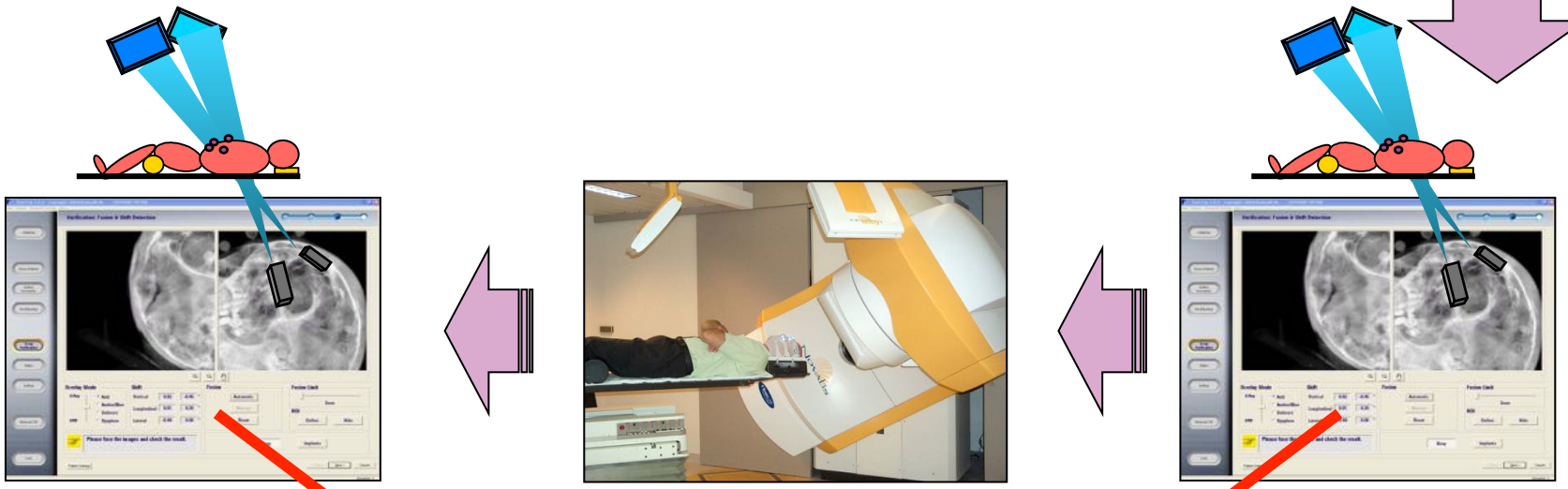


Linthout *et al.* Radiother Oncol 2012

IGRT/frameless: Clinical validation

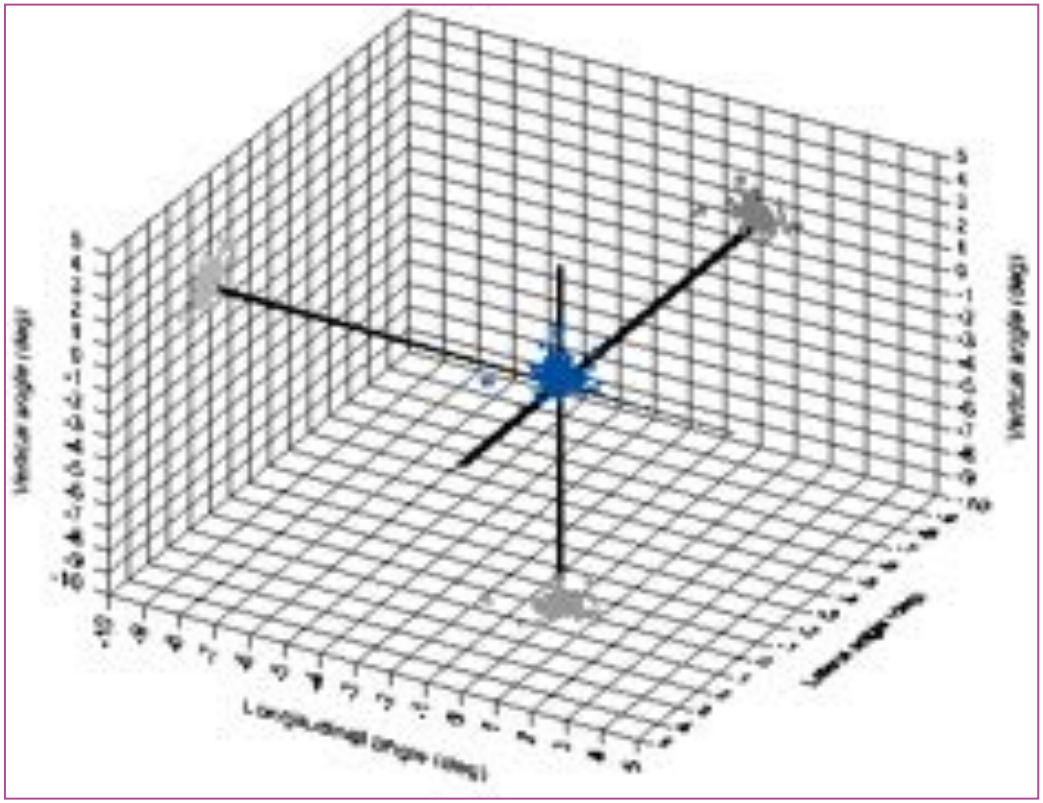


IR Setup



intrafractional **X-ray residual**

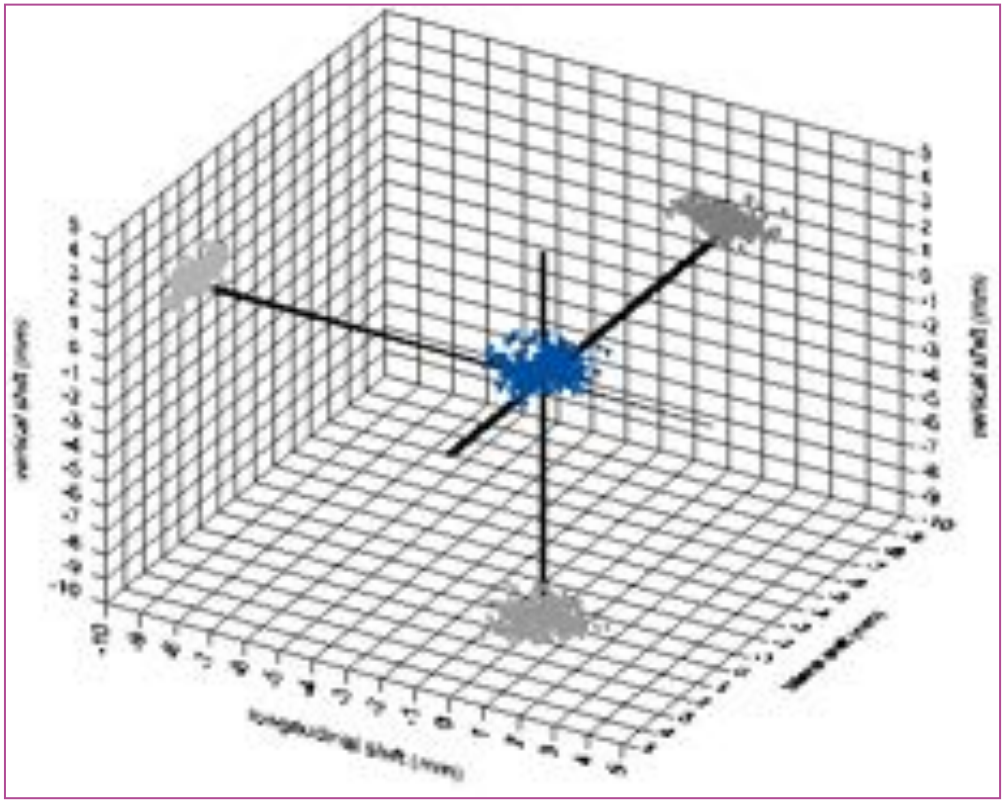
Results: X-ray residual rotations



- 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



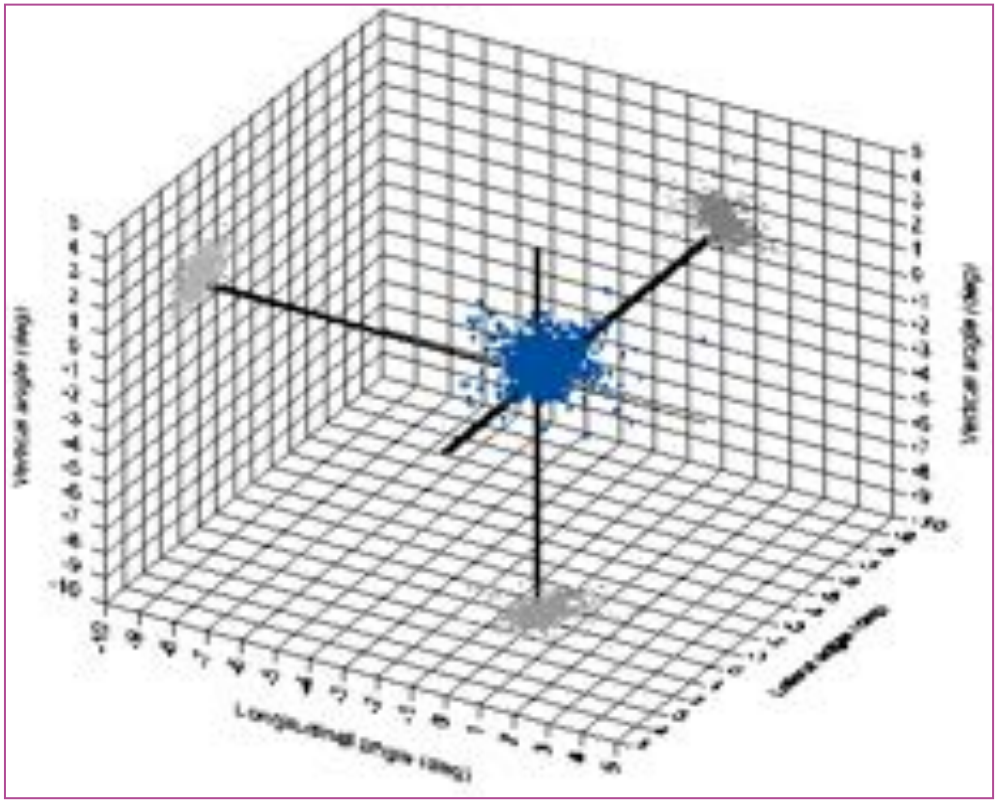
- Lateral
  - Mean: 0.02mm, SD: 0.66mm
  - **-1.59mm – 1.66mm**
- Longitudinal
  - Mean: 0.04mm, SD: 0.53mm
  - **-1.67mm – 1.67mm**
- Vertical
  - Mean: 0.04mm, SD: 0.32mm
  - **-1.11mm – 1.22mm**

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

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

Linthout *et al.* Radiother Oncol 2012

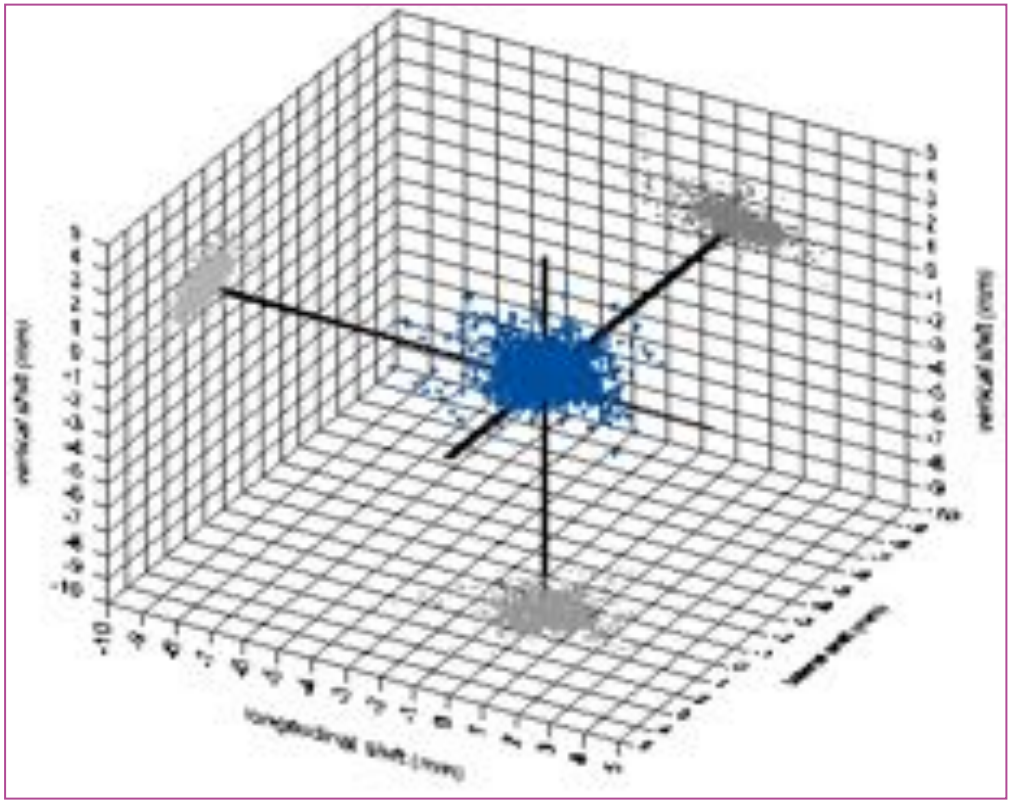
Results: Intrafraction rotations



- 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**

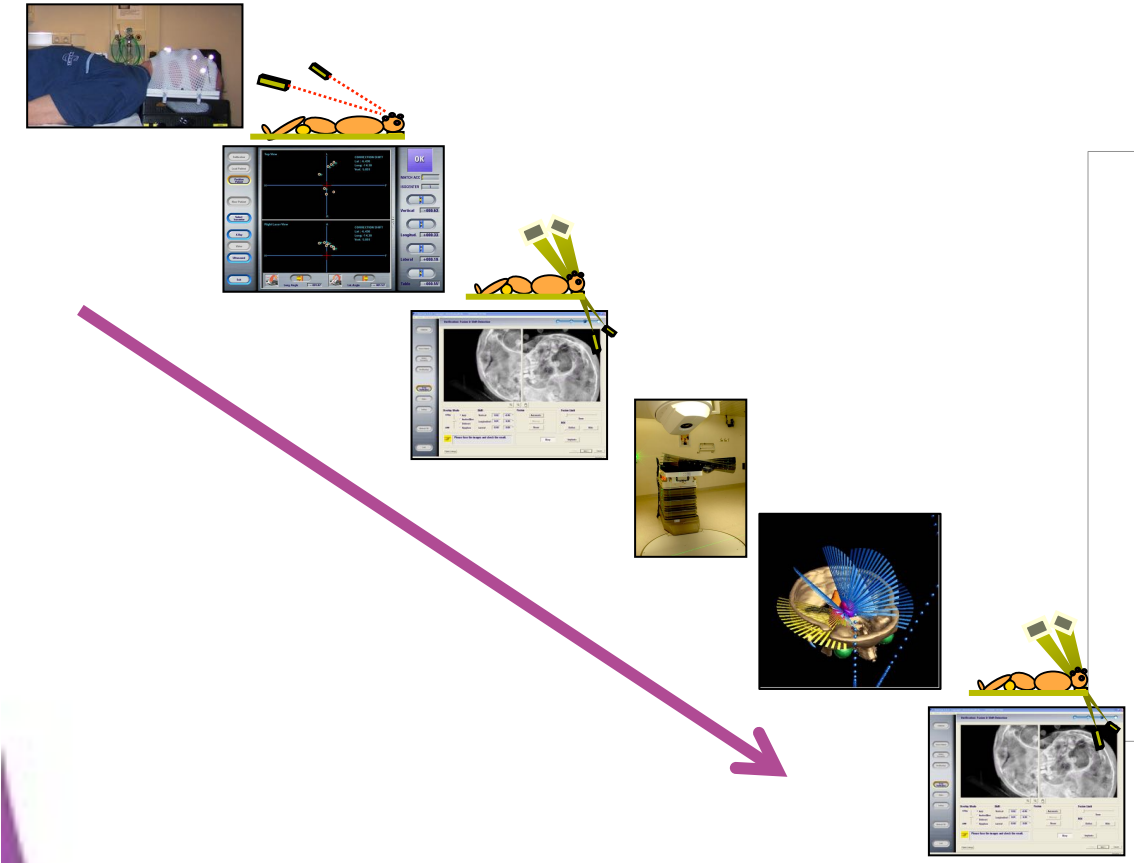
Van Herk formula ($2.5\sum+0.7\sigma$)

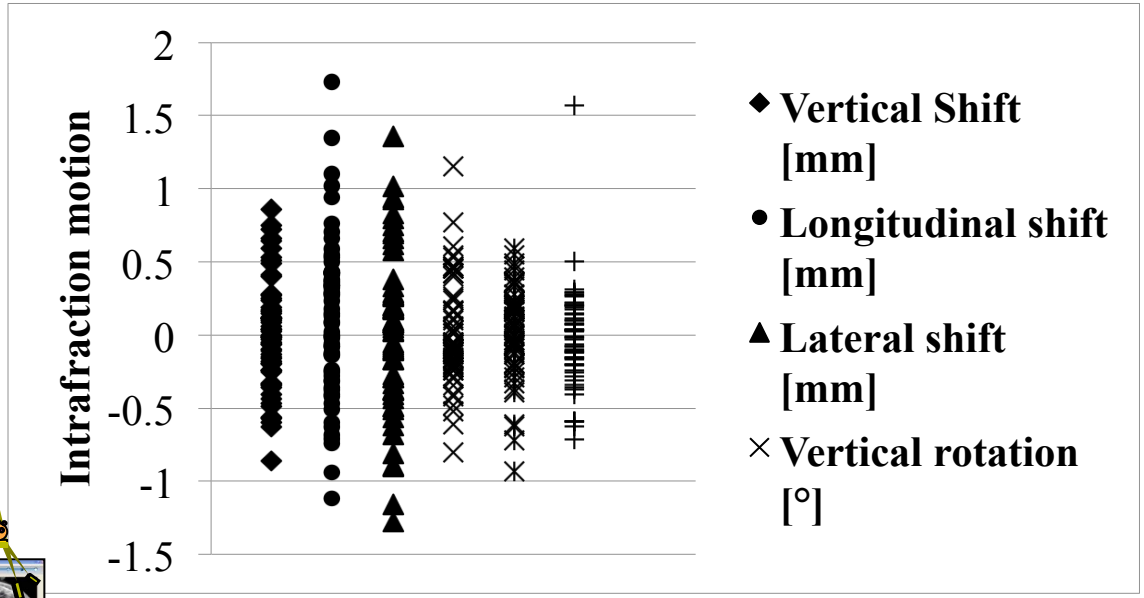
- Lateral **1.37mm**; longitudinal **1.85mm**; vertical **1.00mm**

Linthout *et al.* Radiother Oncol 2012

IGRT/frameless: Intrafraction motion

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





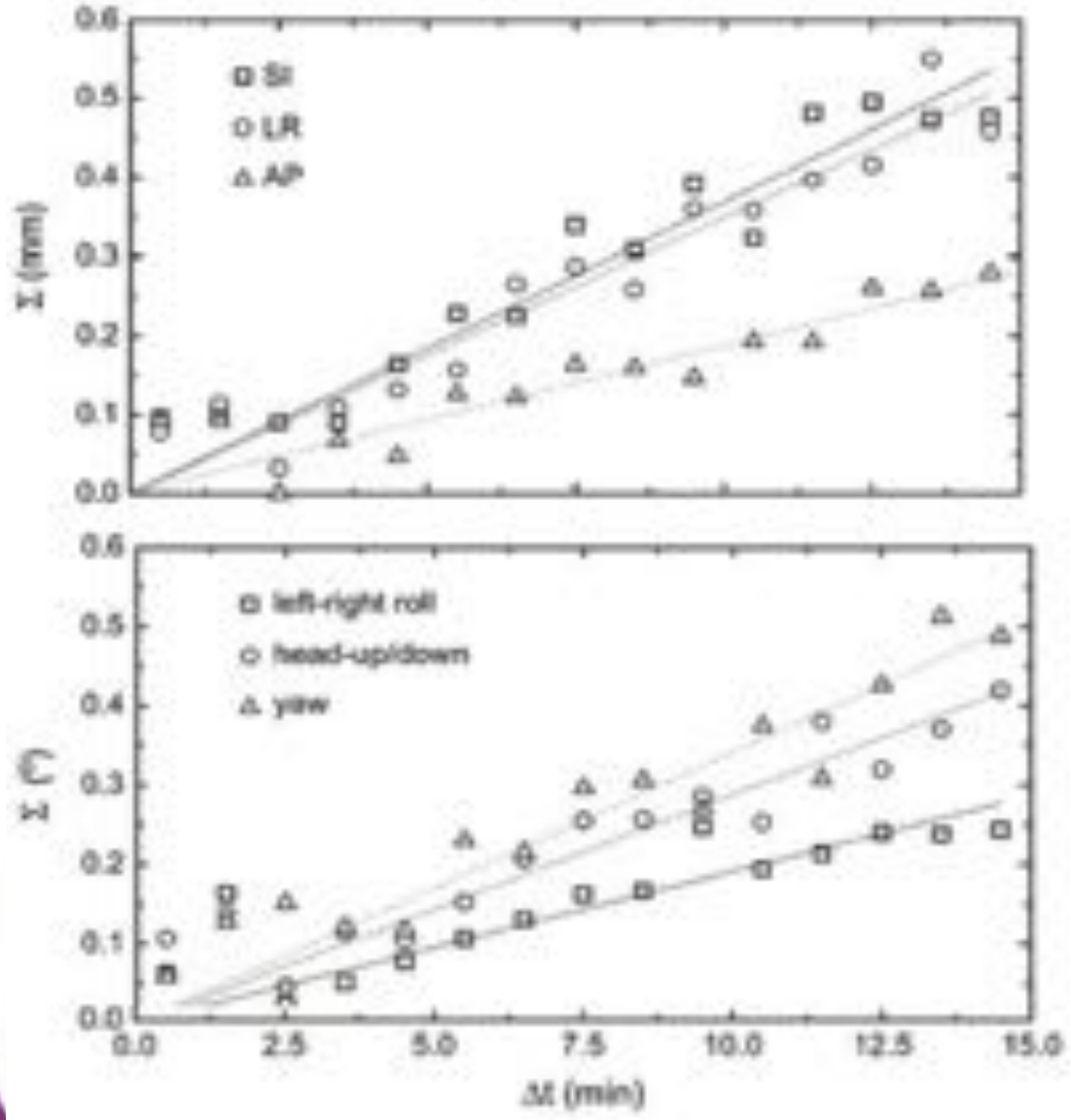
- Intrafraction motion: **mean 3D of 0.58 mm (SD: 0.42 mm)**

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



- 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

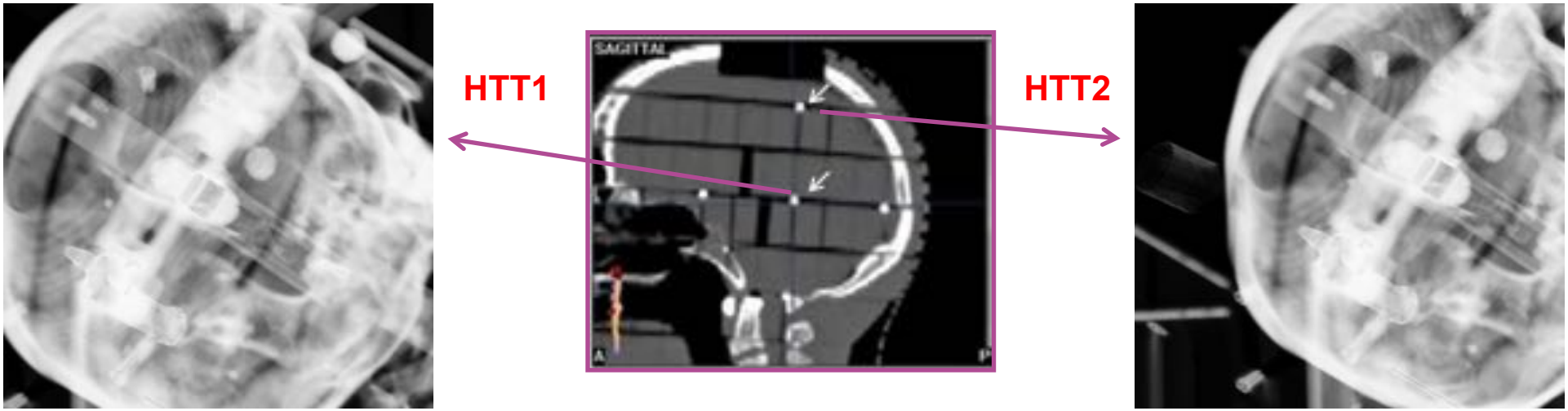
Accuracy: Frame-based versus IGRT-frameless

- 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

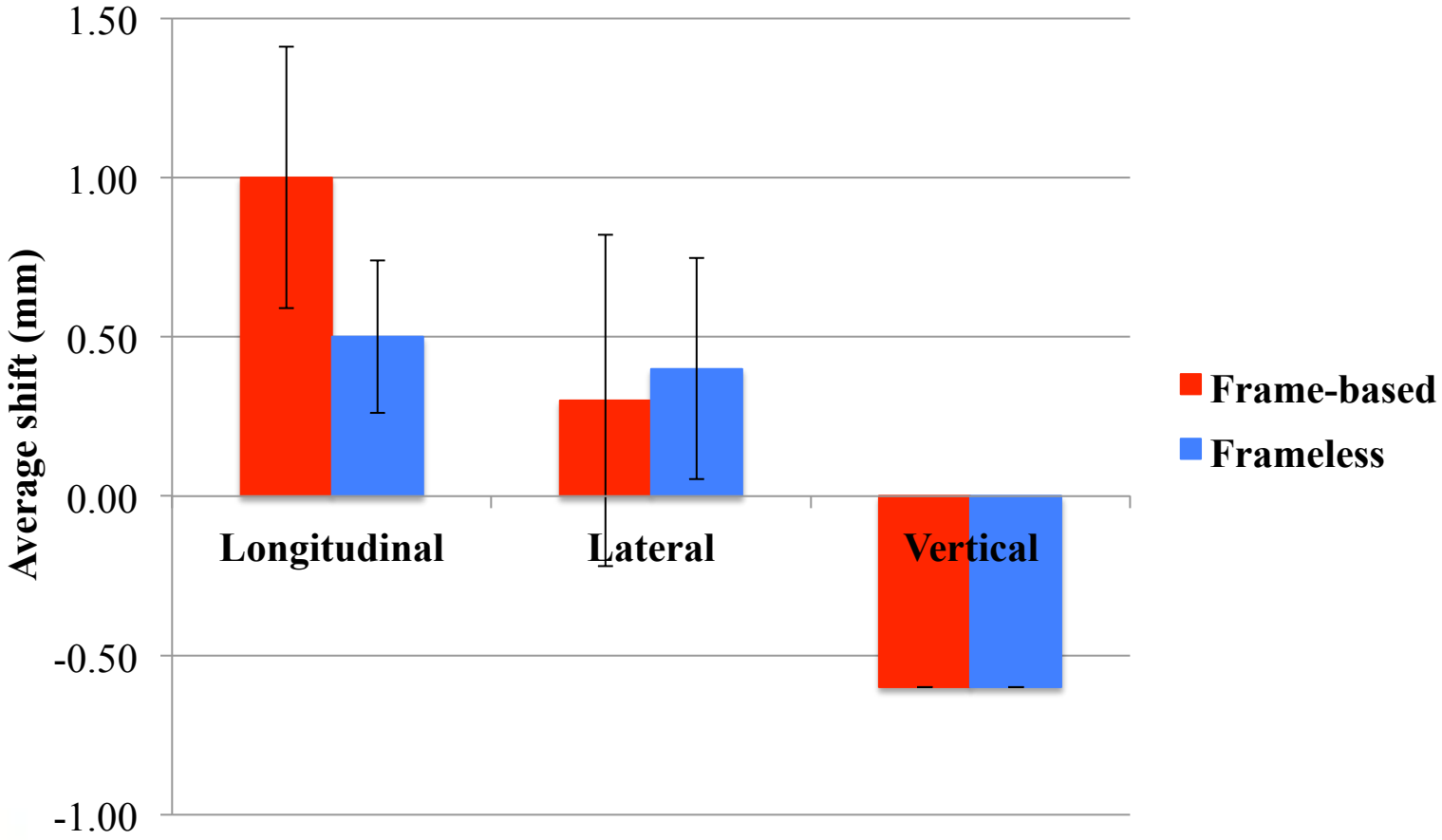
CT Slice Thickness (mm)	Measurement	Leksell (mm)
1	Mean ± 3 SE_M	1.7 ± 0.10
	99% CI for the mean	1.60 to 1.80
1 canted	Mean ± 3 SE_M	N/A
	99% CI for the mean	N/A
4	Mean ± 3 SE_M	2.6 ± 0.14
	99% CI for the mean	2.46 to 2.75
8	Mean ± 3 SE_M	5.4 ± 0.24
	99% CI for the mean	5.16 to 5.64

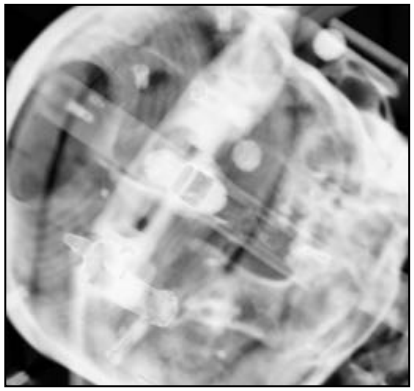
Accuracy: Frame-based versus IGRT-frameless



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

Accuracy: Frame-based versus IGRT-frameless

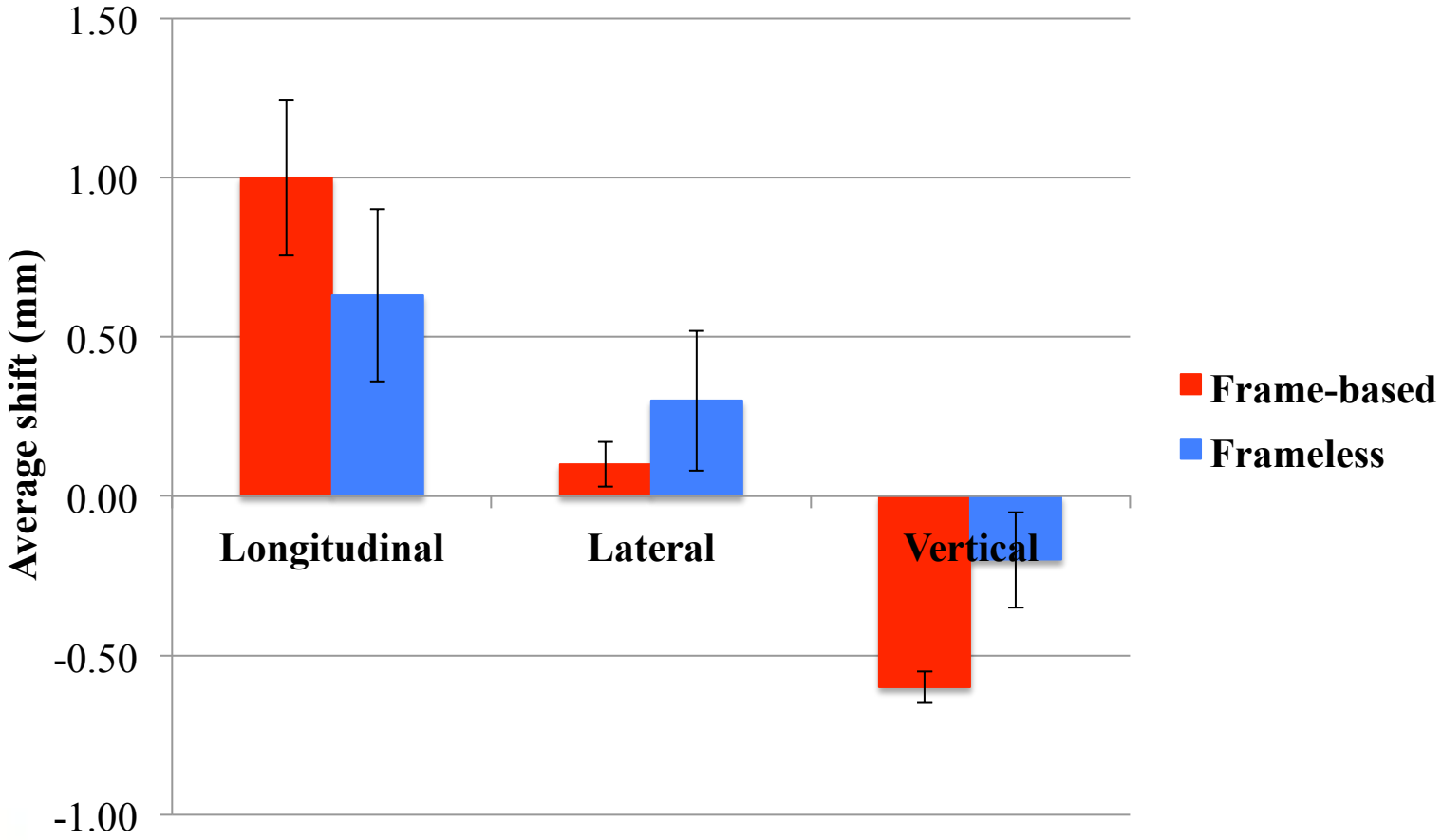


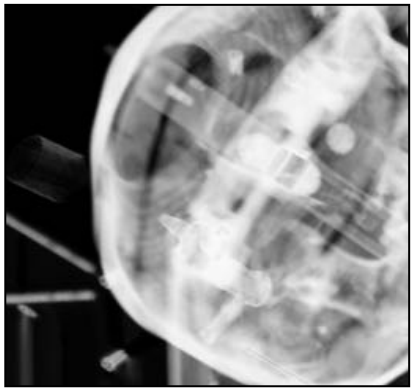


Overall 3D accuracy: 1.20 mm SD 0.66 mm (frame-based)
0.88 mm SD 0.42 mm (frameless)

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

Accuracy: Frame-based versus IGRT-frameless



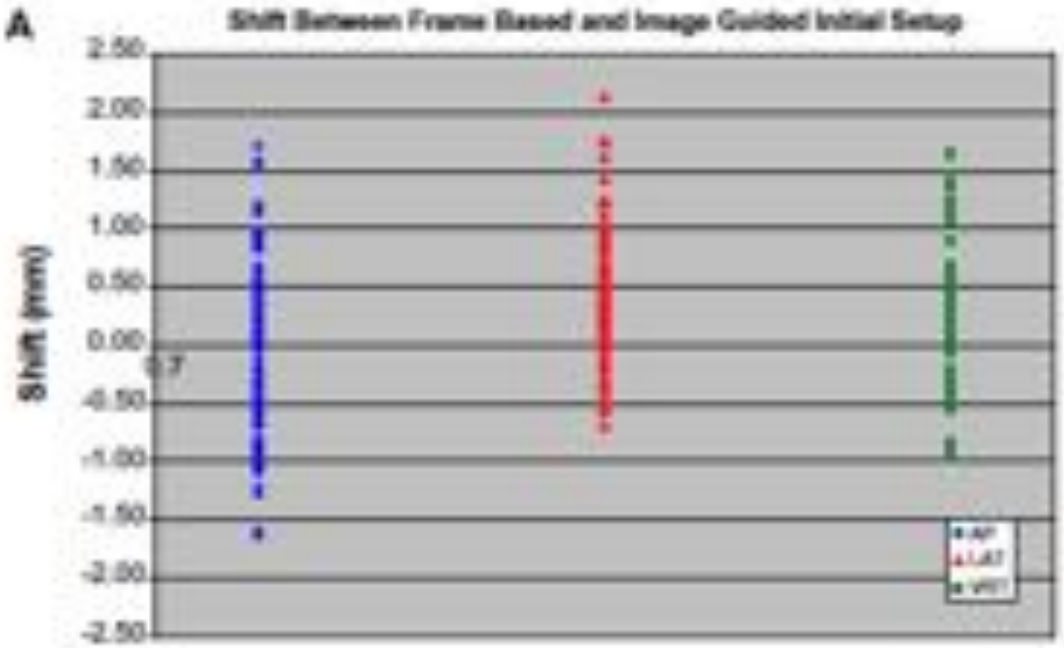


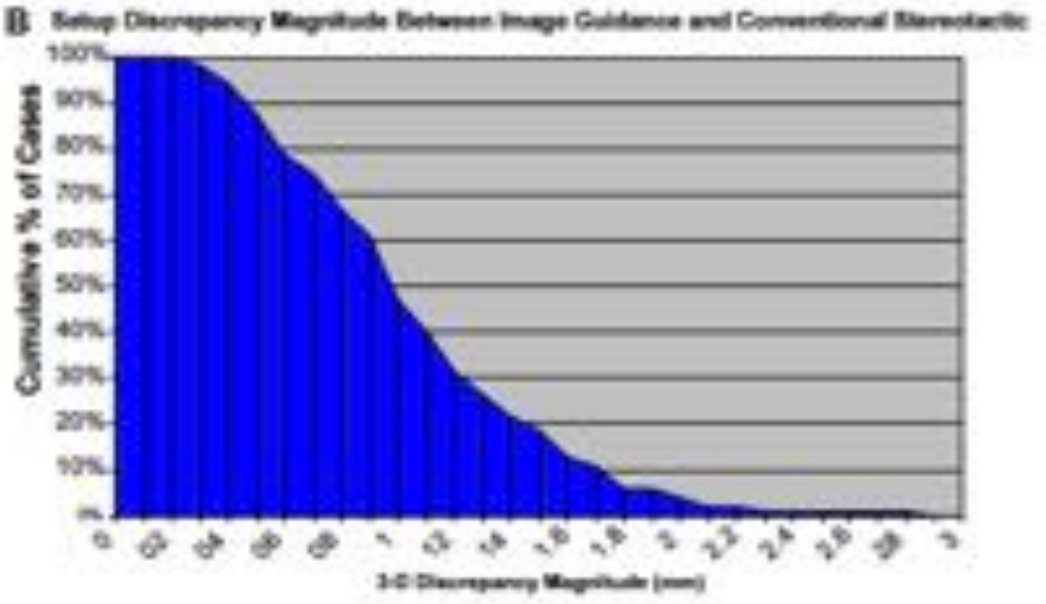
Overall 3D accuracy: 1.17 mm SD 0.24 mm (frame-based)
0.85 mm SD 0.52 mm (frameless)

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

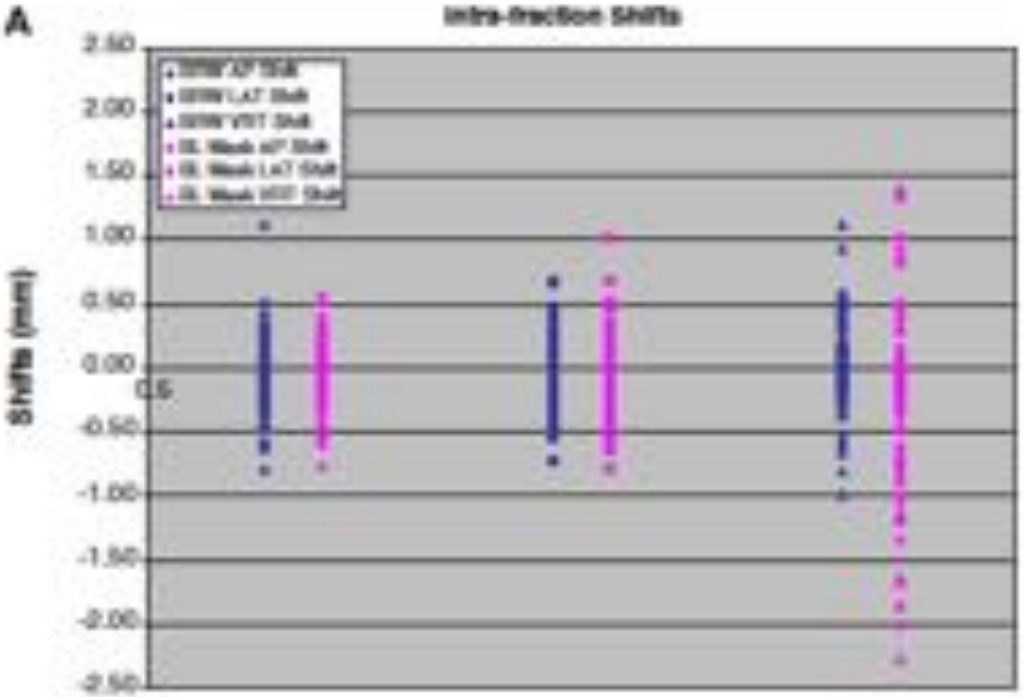


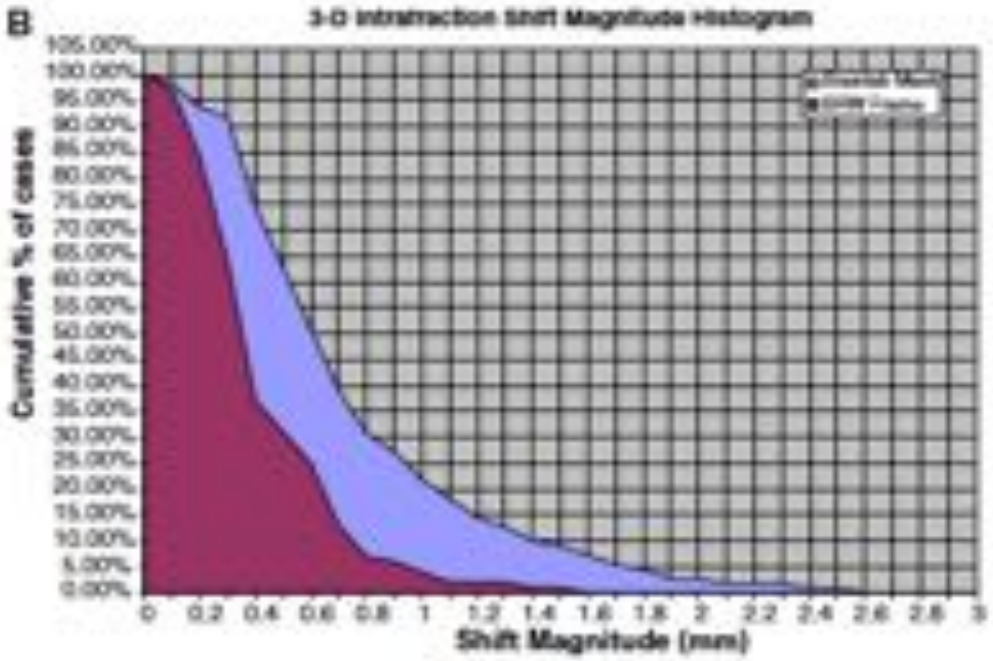


Ramakrishna *et al.* Radiother Oncol 2010

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)





Ramakrishna *et al.* Radiother Oncol 2010

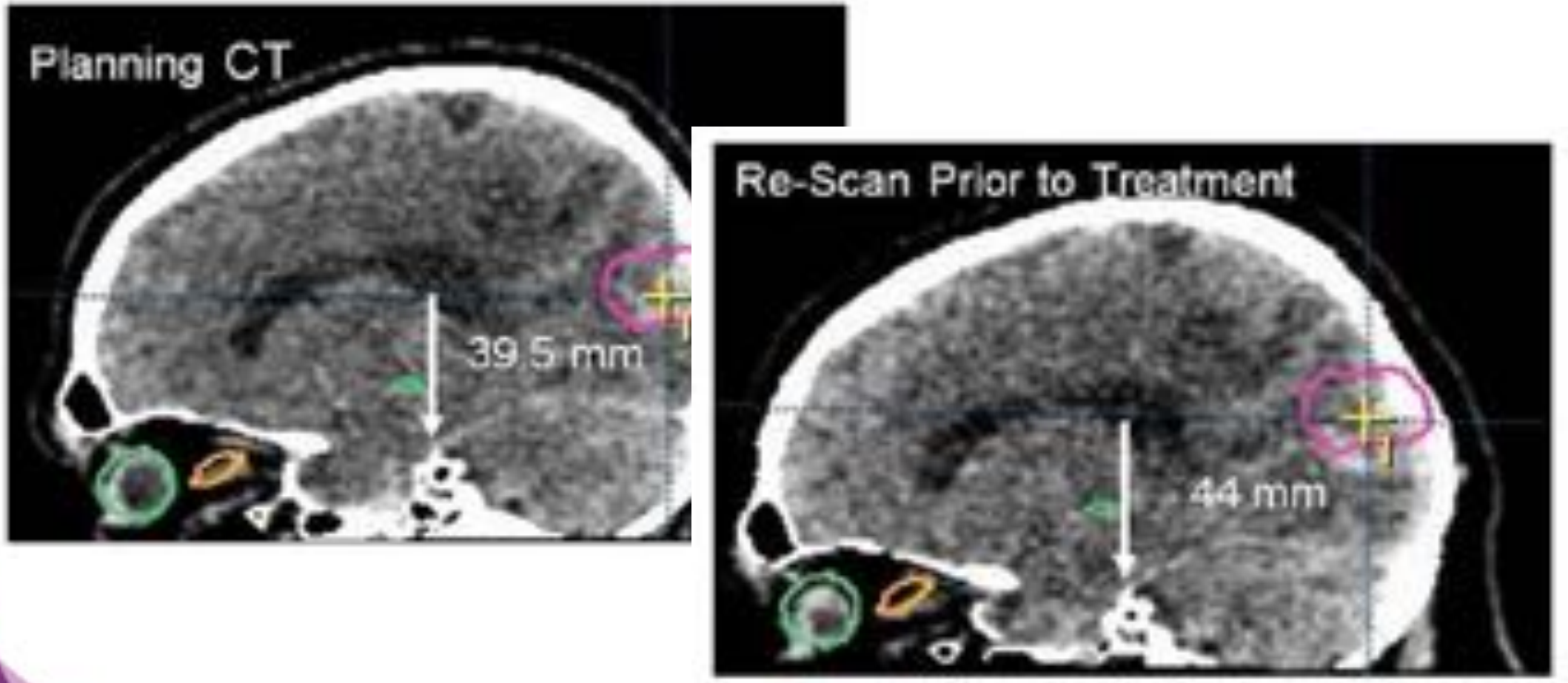
Margins: Frame-based versus IGRT-frameless

- 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

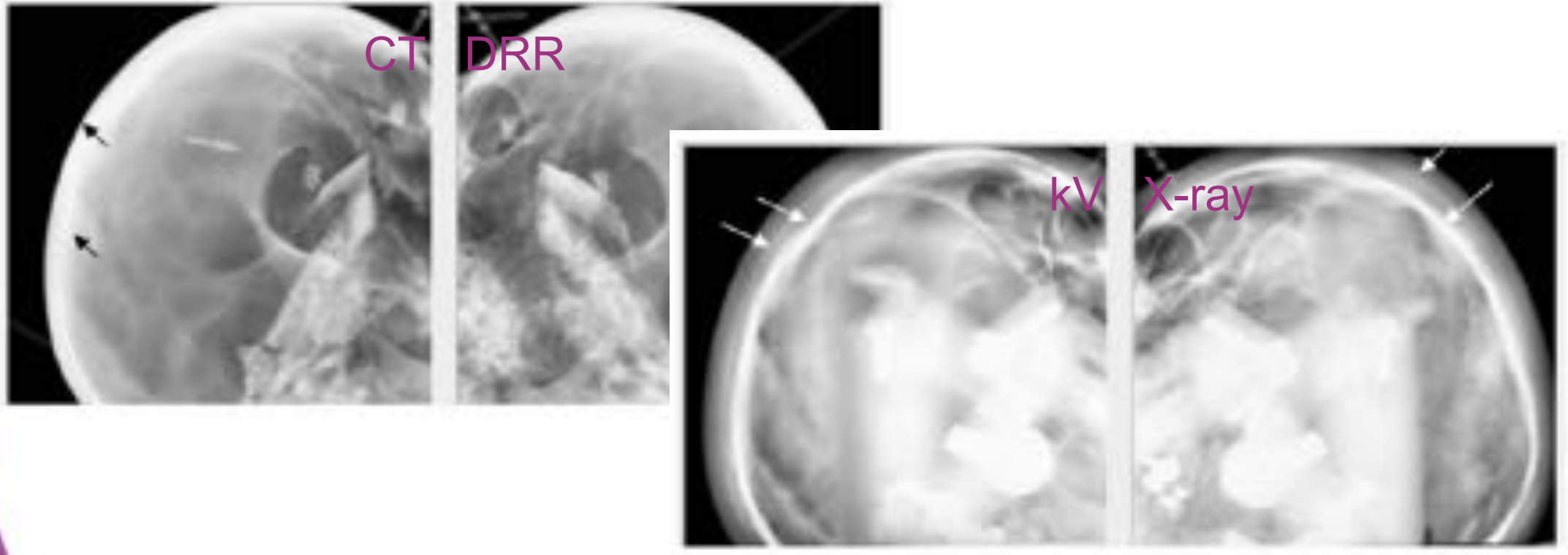
- Frame slippage (4.23 mm) observed with image-guided monitoring of frame-based SRS, confirmed with CT-scan.



Ramakrishna *et al.* Radiother Oncol 2010

IGRT/Frameless: Automated co-registration

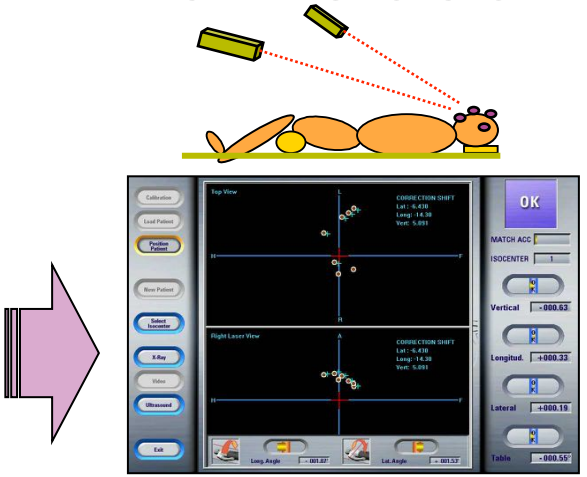
- kV X-ray images might display difference in skull density contours relative to CT-DRR, resulting in erroneous image co-registration.



Ramakrishna *et al.* Radiother Oncol 2010

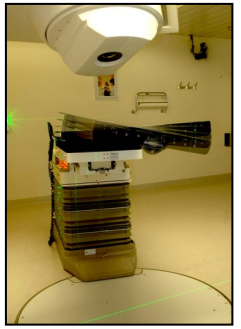
How about table rotations?

Phantom 0°

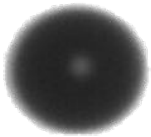


IR pre-positioning

6DOF registration

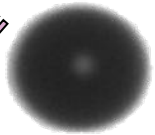


6DOF positioning



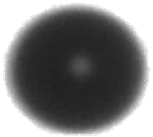
HTT

Phantom 90°



HTT

Phantom 270°



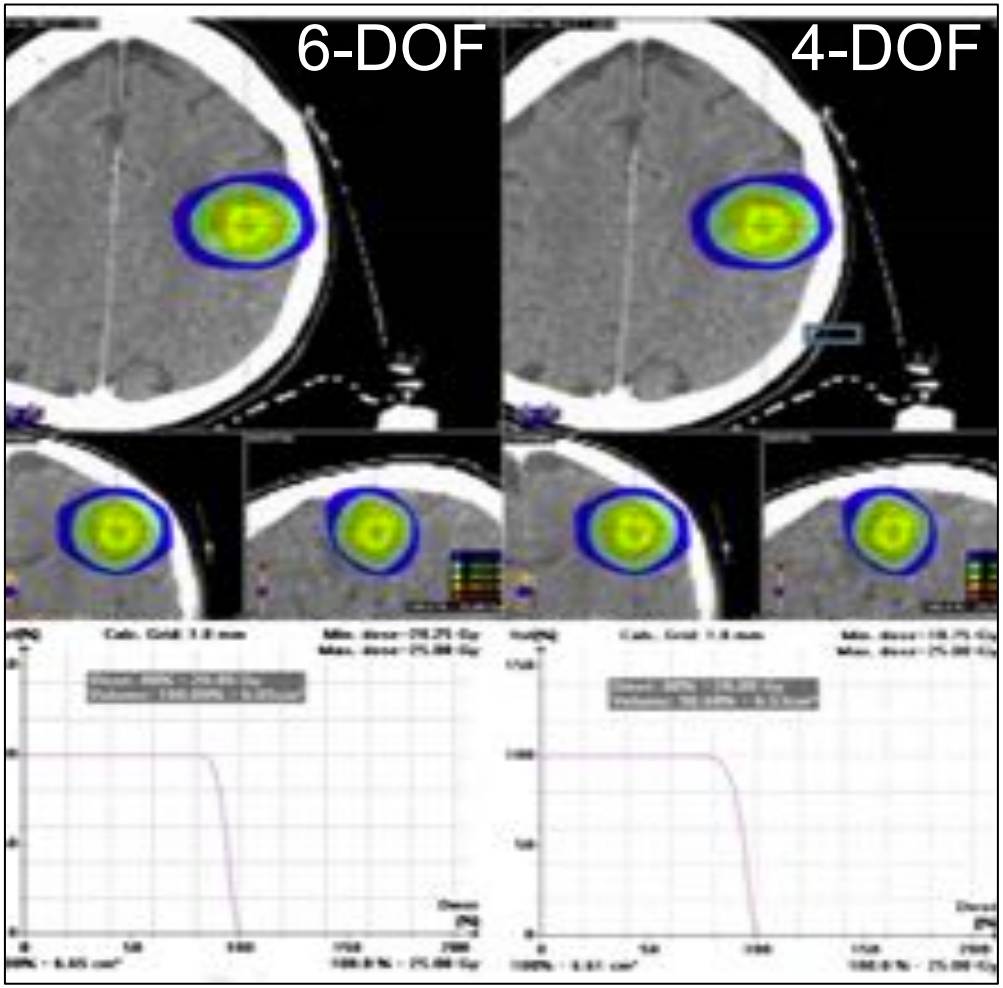
HTT

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)

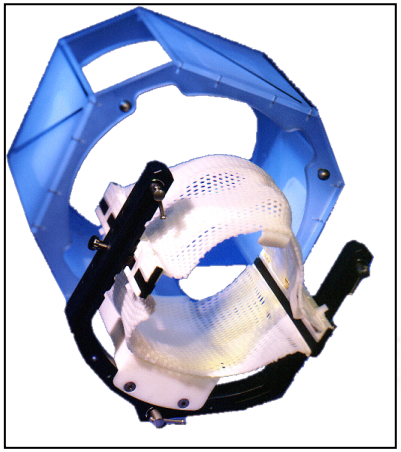
    Mean 3D of 0.89 mm (SD 0.35 mm)
  - Mean rotations:
    - Vertical: -0.08°(SD 0.25°)
    - Longitudinal: 0.09°(SD 0.29°)
    - Lateral: -0.05°(SD 0.20°)

Gevaert *et al.* Radiother Oncol 2012

Non-invasive, frame-based???

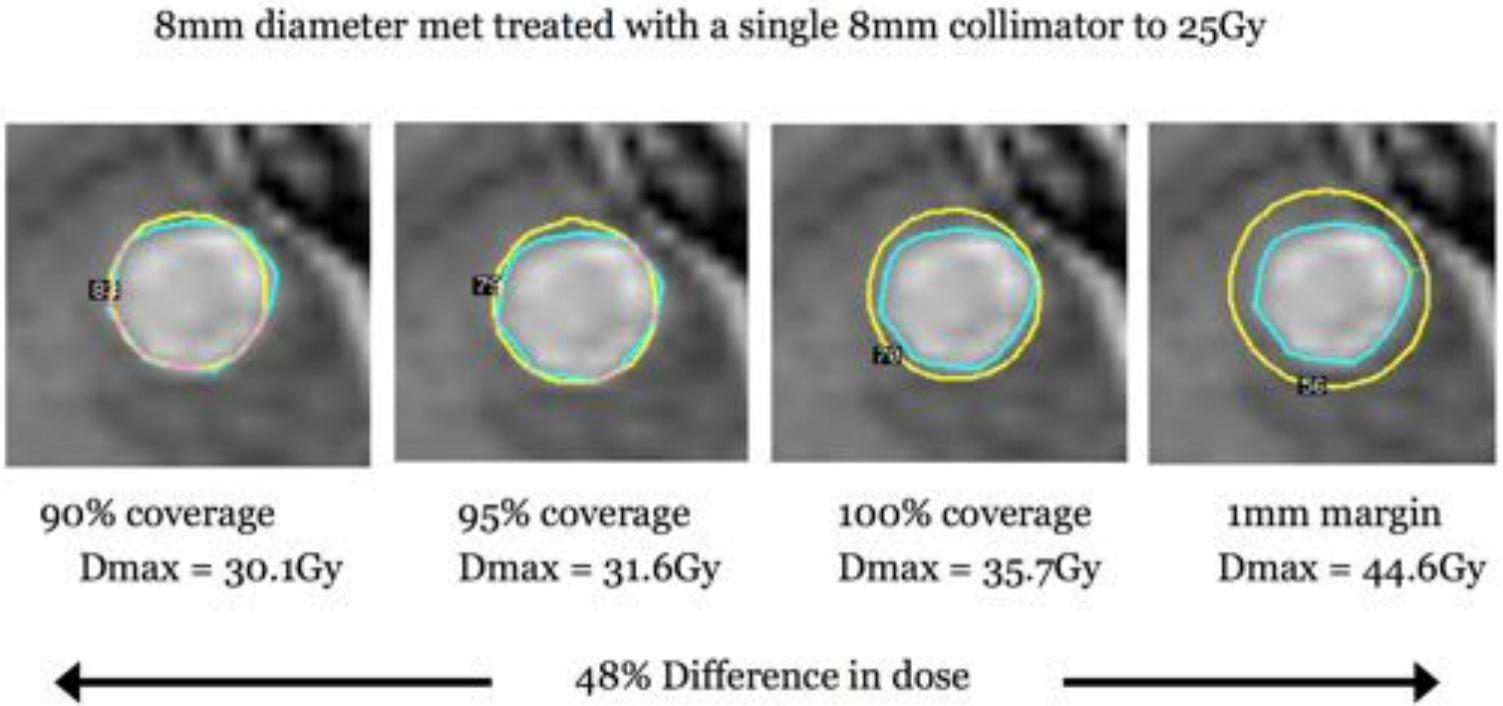
Study	SRT positioning system	Imaging modality	Positioning error
2D-2D image registration for verification of set-up			
Rosenthal 1995	Dental fixation	Orthogonal radiographs	2.3mm ± 1.6mm
Sweeney 2001	Vogele Bale Hohner head holder	Portal imaging	1.9mm ± 1.2mm
Kumar 2005	Gill-Thomas-Cosman	Portal imaging	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
- Increased errors compared to invasive techniques
- **"Worst" of both worlds**



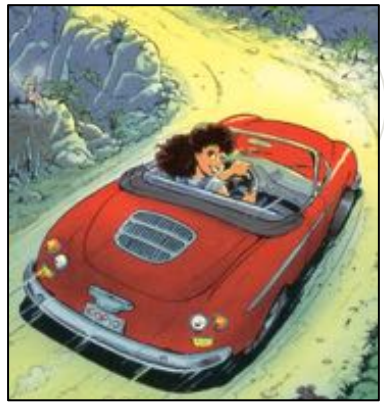
Dose prescription and margins

- 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



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

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

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!!!

MEDICAL UNIVERSITY OF VIENNA

COMPREHENSIVE CANCER CENTER VIENNA

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

From frame-based Stereotaxy to frameless image-guidance a historical perspective

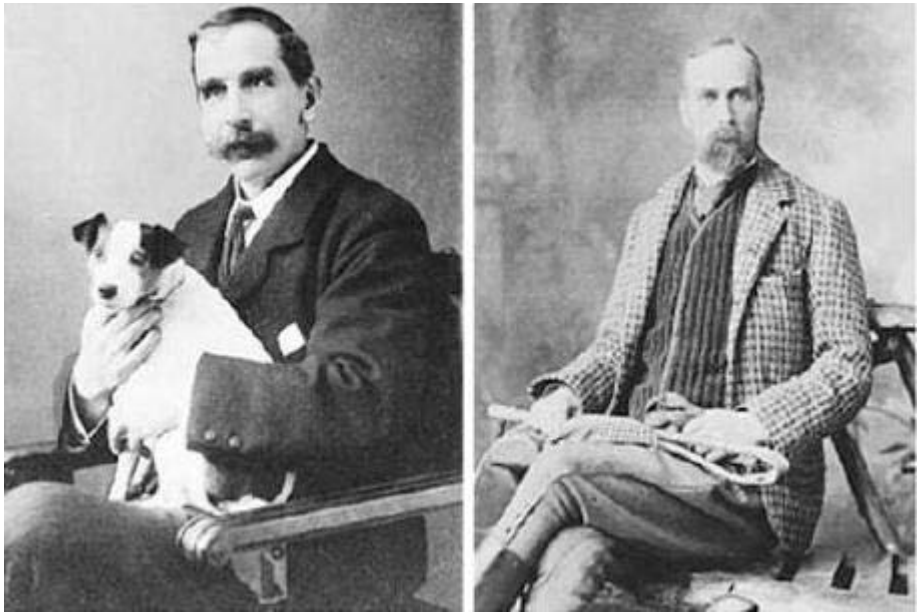
Karin Dieckmann

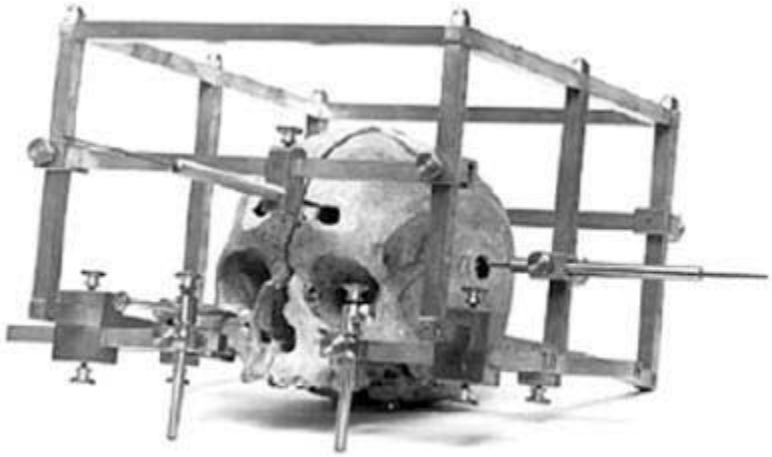
Department of Radiation Oncology,

General Hospital Vienna

Medical University of Vienna, Austria

History of Stereotactic Radiotherapy I

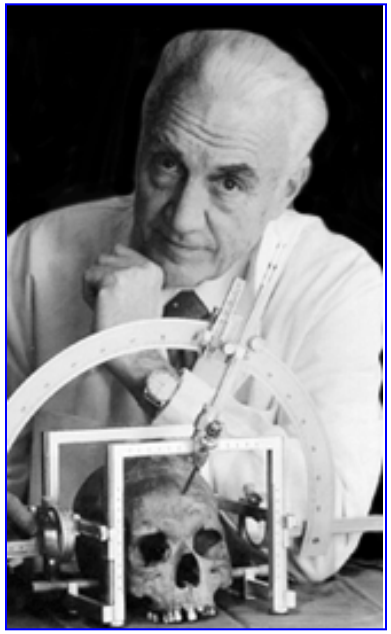




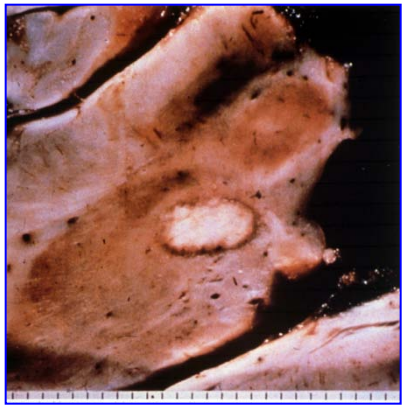
1908: Sir Victory Horsley and Robert H. Clarke

- Stereotactic technique based on the reproducibility of the relationships between **landmarks on the skull** (external auditory canals, midline) and **anatomical structures within the brain**

History of stereotactic Radiotherapy II



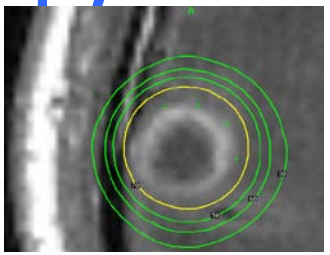
1951, using the **Uppsala University** **cyclotron**, **Lars Leksell** and the physicist and radiobiologist **Borje Larsson**, developed the concept of **radiosurgery**.

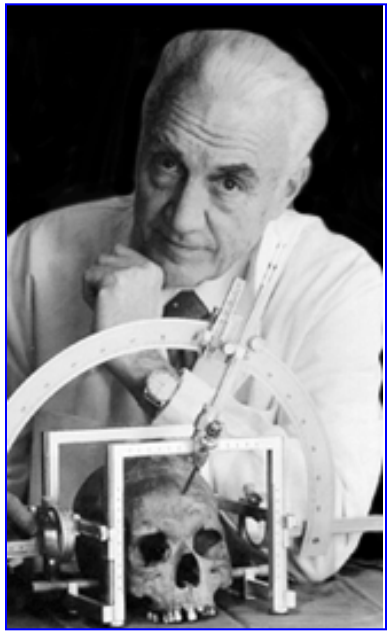


Leksell and Larsson first employed **proton beams** coming from several directions into a small area into the brain, in experiments in animals and in the first treatments of human patients.

He called this technique **"strålkniven"** (ray knives).

History of stereotactic Radiotherapy III





Leksell achieved a **new method** of destroying discrete anatomical Regions within the brain while minimizing the effect on the surrounding tissues.

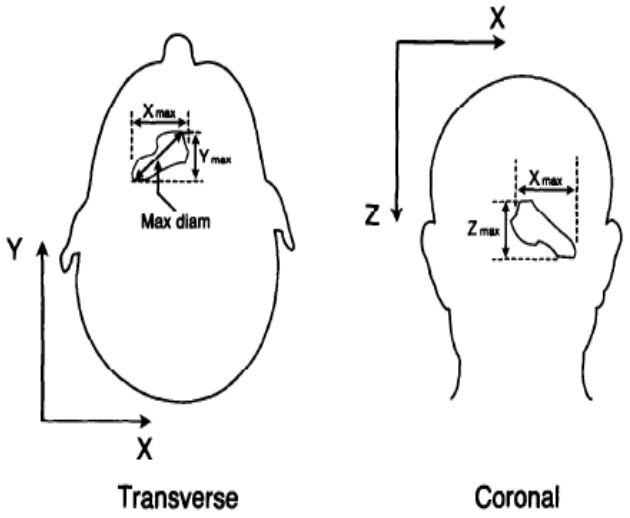
That **GammaKnife** unit was primarily intended for use in **functional brain surgery** for the section of deep fiber tracts, as in the treatment **of intractable pain and movement disor**

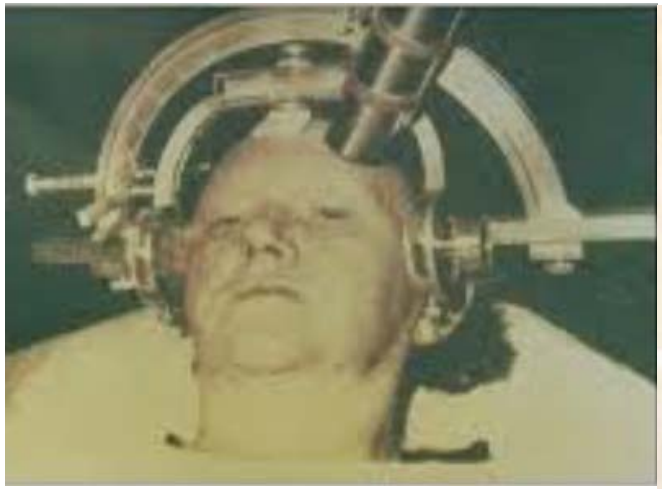
„Stereo“

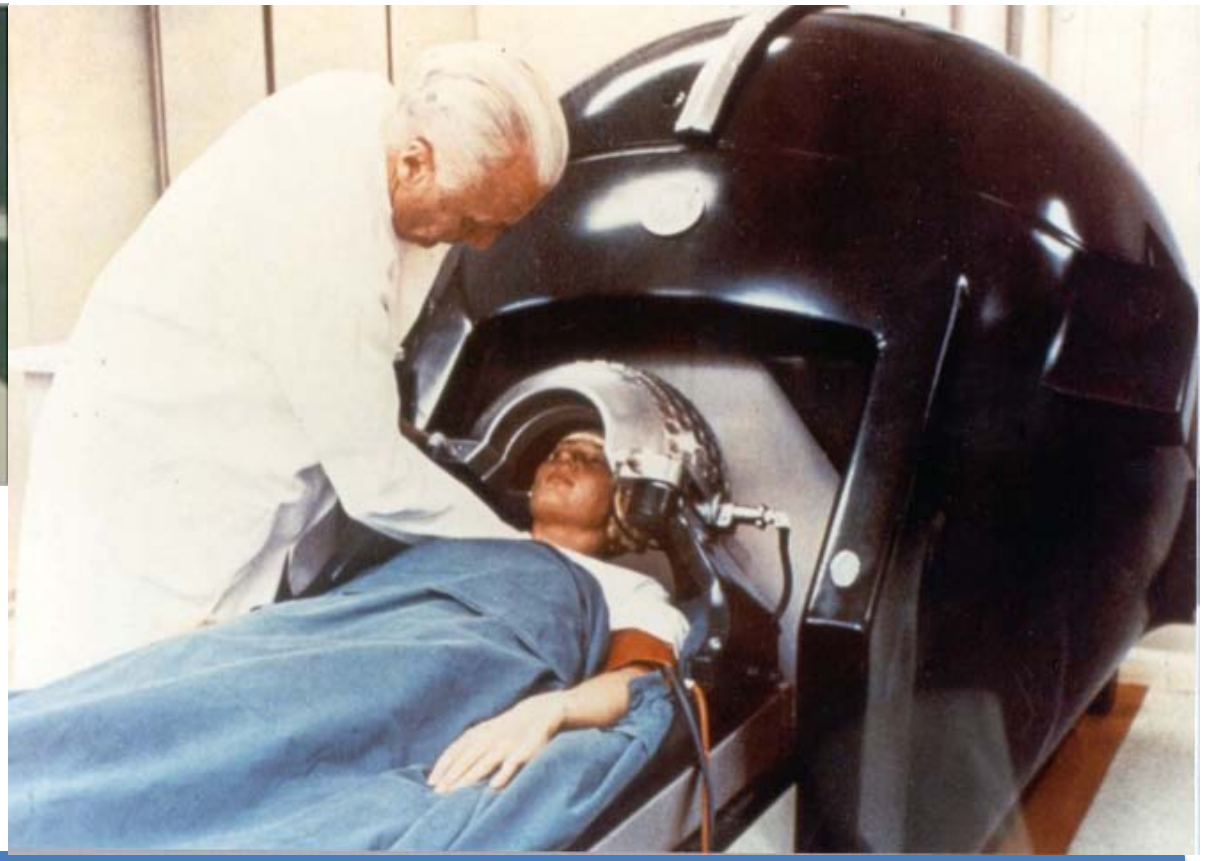
(Greek: „ solid“ or „ 3 dimensional“)

„tact“

(Latin: „To touch“)



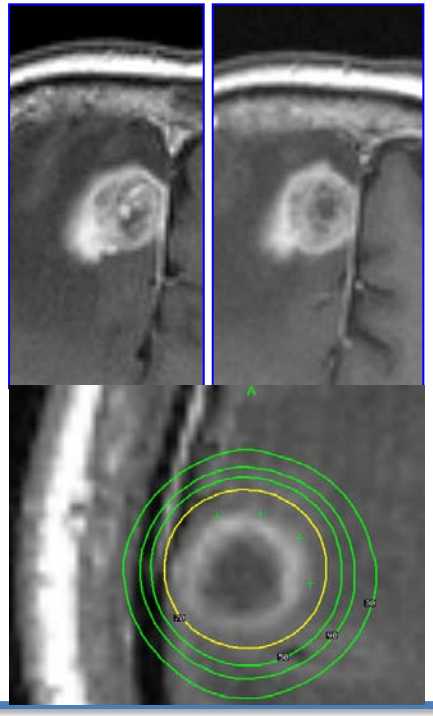




- **First surgery performed at Karolinska** on an
- Acoustic schwannoma in (1969)
- Pituitary tumors (1969),
- AVM (1970),
- Craniopharyngiomas, Meningiomas (in 1976),
- Metastases and skull base tumors (in 1986)

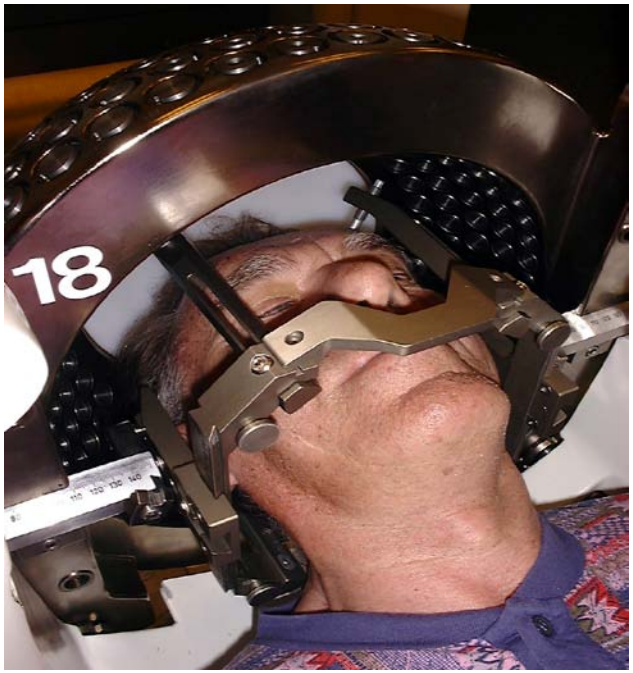
Frame-based stereotactic Radiotherapy

- A stereotactic system of **external coordinates** used for localisation and positioning
- The patient is rigidly fixed to a stereotactic system using **invasive techniques**, **ideal for single fraction**



x-Position

z - Position



High doses of > 80 Gy could be applied in a single fraction local control of **metastases** could be achieved in 80-90 %

Frame-based stereotactic Radiotherapy at a LINAC

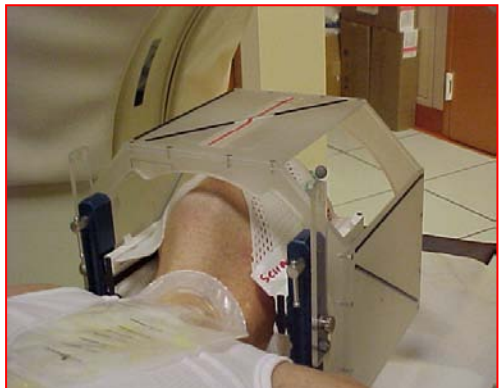
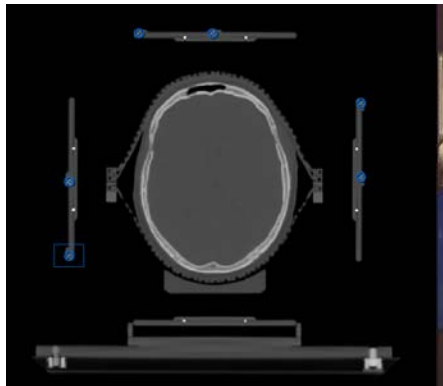
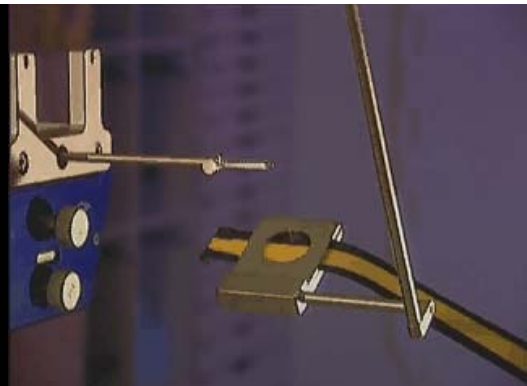
1980-1990 ies Heidelberg/Harvard:

LINAC based stereotactic RT of the brain

- LINAC most widely available

  Majority are modified multi-use LINACS

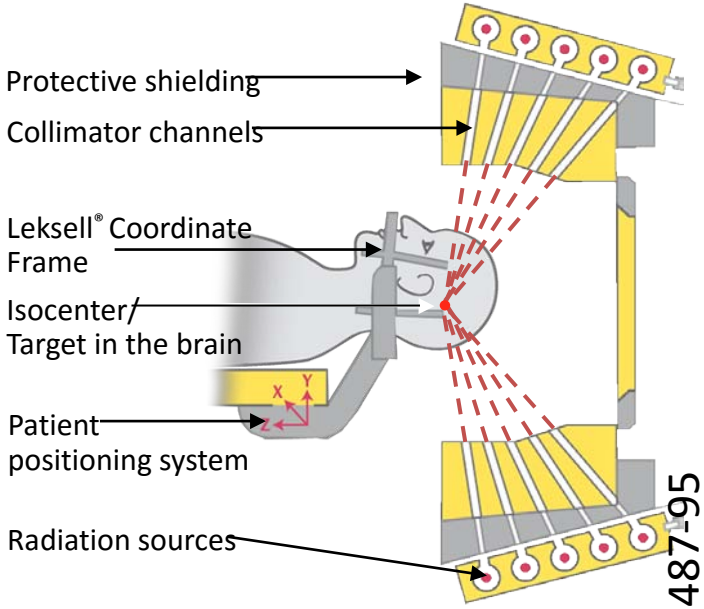
  Some are specially designed for SRS

Frame-based Stereotactic Radiosurgery Positioning Accuracy

Accuracy and stability of positioning in radiosurgery: long –term results of the Gamma Knife system.

Heck B et al



Med Phys 2007 Apr; 34(4): 1487-95

Graf Chromic films densitometric measurements

X: - 0.014+/- 0.09mm

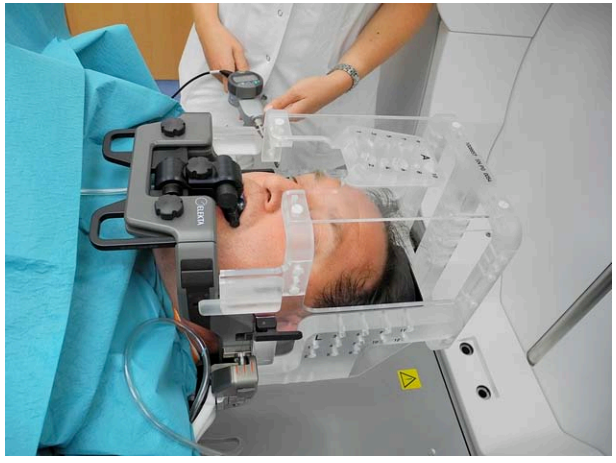
Y: 0.013+/- 0.09mm

Z: - 0.002+/- 0.06mm

MRI-based target definition

X: 0.06+/-0.09mm

Y: 0.04+/-0.09mm



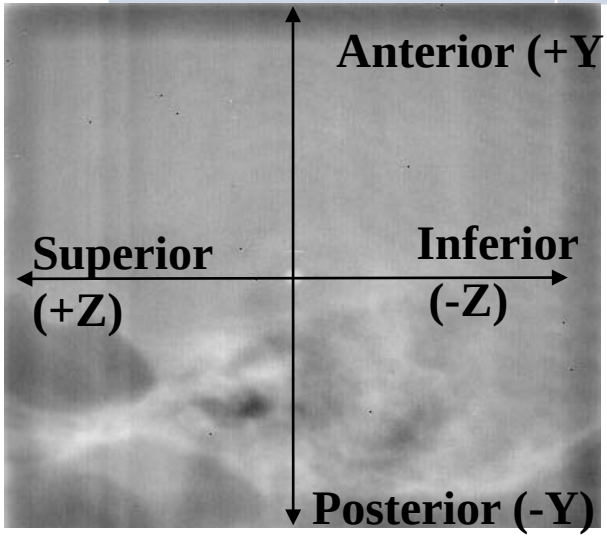
All measured data were within a sphere of 0.2mm radius

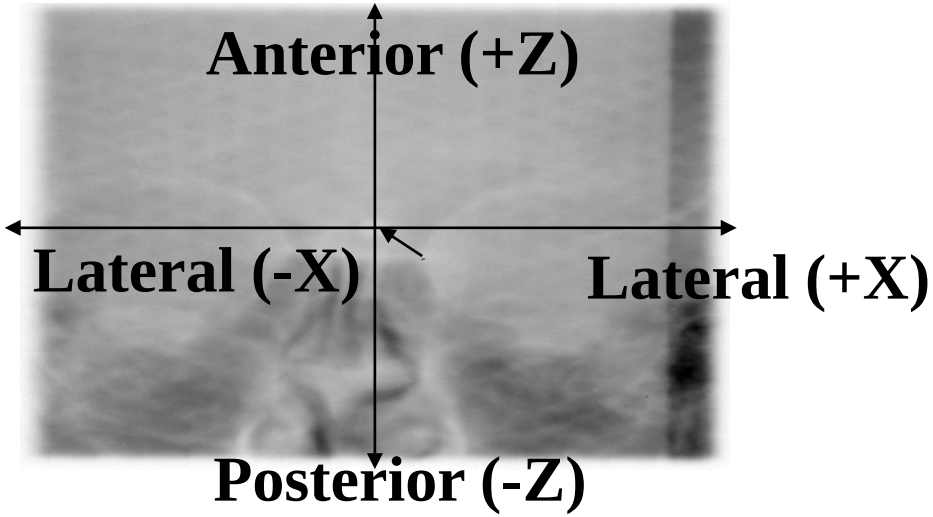
Target delineation: GTV=PTV

Accuracy of non invasive Mask systems

2D-2D image registration for verification set-up

Author	Positioning error	
Alheit 2001	< 2mm	Simulix xy Oldelft
Kumar 2005	1.8mm±0.8	PI
Georg 2006	1.3mm±0.9	PI



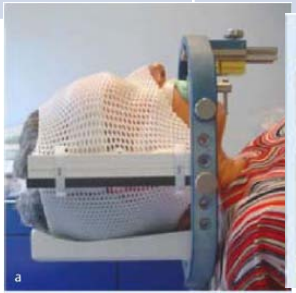


Accuracy of non invasive fixation systems
3D-3D image registration for verification set-up

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

CBCT /CT controls of demonstrated positioning errors of > 3mm

Target delineation: GTV plus 2mm= PTV



Radiosurgery of Brain Metastases

Margin Dose and Local Tumor control

Table 1. SUMMARY OF BRAIN METASTASIS PATIENTS TREATED WITH RADIOSURGERY

First Author	RS Type	Year	Number of Patients	Number of Lesions	Dose (Gy)	Response Rate (%)	Local Control* (%)	Median Survival (months)
Sturm	L	1991	39	54	MPD 18.0	86	93	6.5
Mehta	L	1992	40	58	MPD 18.0	71	82	6.5
Engenhart	L	1993	69	102	MCD 21.5	55	95	6.0
Kihlstrom	G	1993	160	235	MPD 29.0	NA	94	NA
Voges	L	1994	46	66	MPD 20.0	53	85	6.0
Flickinger	G	1994	116	116	MPD 17.5	NA	85	11.0
Jokura	G	1994	25	77	MPD 26.1	NA	99	8.5
Alexander	L	1995	248	421	MPD 15.0	NA	85	9.4
Valentino	L	1995	139	139	MCD 50.0	86	NA	13.5
Kida	G	1995	20	55	MPD 18.9	53	97	6.4
Whang	G	1995	28	60	MPD 30.0	88	NA	15.0
Bindal	L	1996	31	>31	MPD 18.7	NA	60	8.0
Fukuoka	G	1996	130	>215	PD 14.0–30.0	NA	93	8.0
Gerosa	G	1996	225	343	MPD 21.1	NA	88	9.3
Joseph	L	1996	120	189	MPD 26.6	NA	96	8.0
Chamberlain	L	1996	50	>50	Med 20.0	NA	NA	6.5
Alleyne	L	1997	40	41	MPD 14.9	33	71	9.0
Breneman	L	1997	84	145	MPD 16.0	NA	25	11.0
Shirato	L	1997	39	39	MCD 25.0	92	84	8.7
Shiau	G	1997	100	219	MPD 18.5	47	77	12.0
Weltman	L	1998	34	69	Med 18.0	NA	NA	6.4

GammaKnife: Local control 85%-99% ; Dose 14Gy-30 Gy ;

Single fraction

Radiosurgery of Brain Metastases

Margin Dose and Local Tumor control

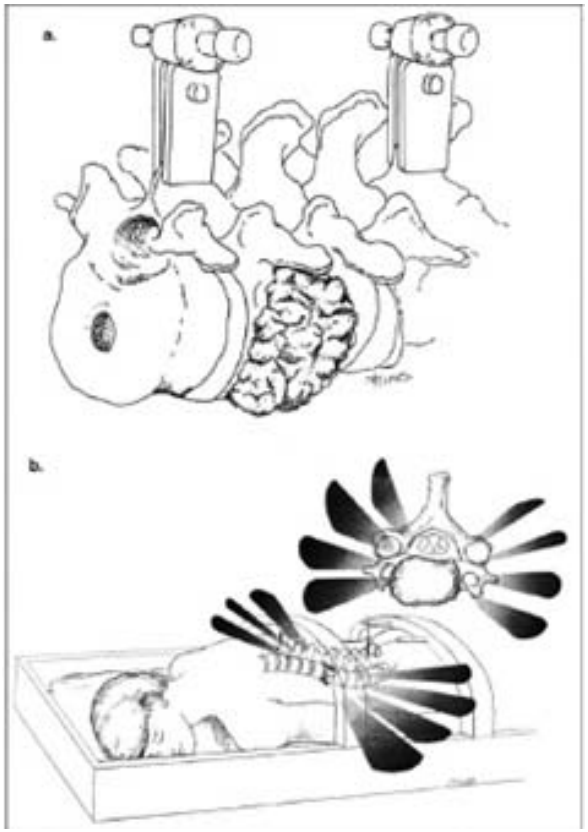
Table 1. SUMMARY OF BRAIN METASTASIS PATIENTS TREATED WITH RADIOSURGERY

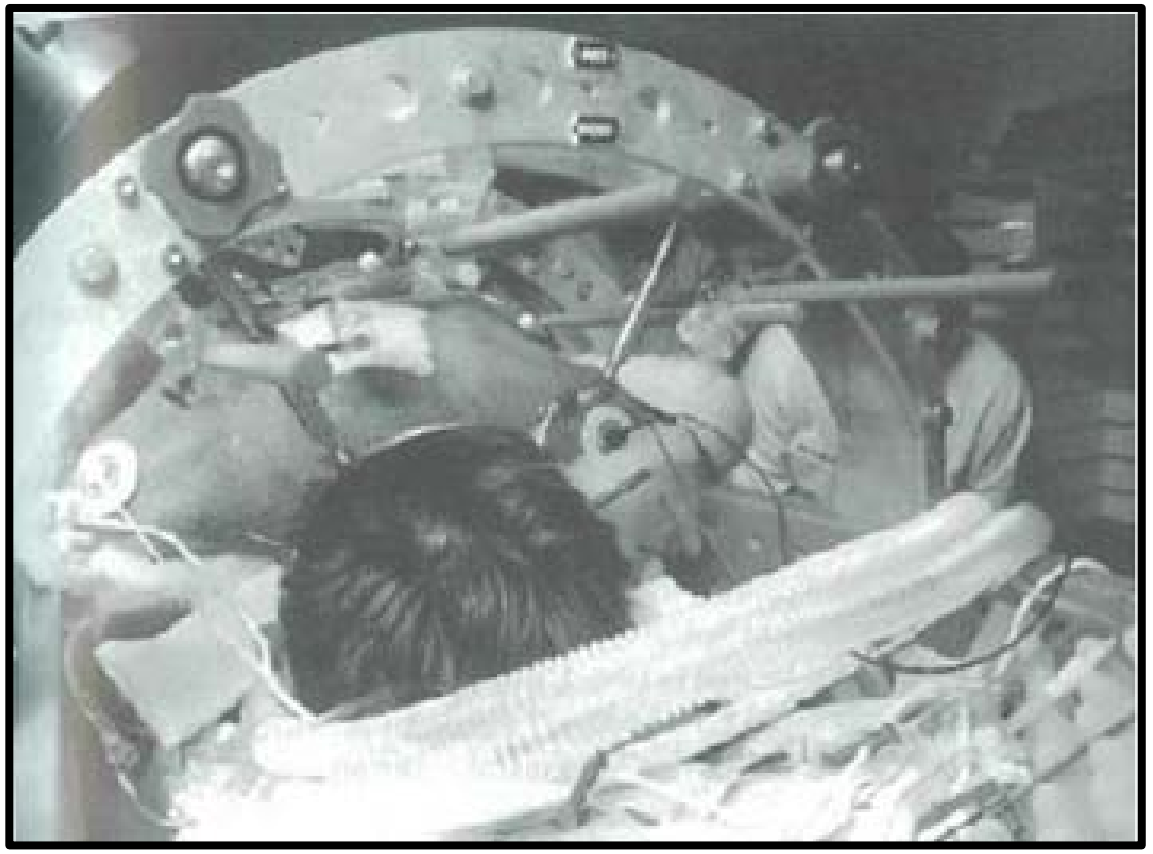
First Author	RS Type	Year	Number of Patients	Number of Lesions	Dose (Gy)	Response Rate (%)	Local Control* (%)	Median Survival (months)
Sturm	L	1991	39	54	MPD 18.0	86	93	6.5
Mehta	L	1992	40	58	MPD 18.0	71	82	6.5
Engenhart	L	1993	69	102	MCD 21.5	55	95	6.0
Kihlstrom	G	1993	160	235	MPD 29.0	NA	94	NA
Voges	L	1994	46	66	MPD 20.0	53	85	6.0
Flickinger	G	1994	116	116	MPD 17.5	NA	85	11.0
Jokura	G	1994	25	77	MPD 26.1	NA	99	8.5
Alexander	L	1995	248	421	MPD 15.0	NA	85	9.4
Valentino	L	1995	139	139	MCD 50.0	86	NA	13.5
Kida	G	1995	20	55	MPD 18.9	53	97	6.4
Whang	G	1995	28	60	MPD 30.0	88	NA	15.0
Bindal	L	1996	31	>31	MPD 18.7	NA	60	8.0
Fukuoka	G	1996	130	>215	PD 14.0–30.0	NA	93	8.0
Gerosa	G	1996	225	343	MPD 21.1	NA	88	9.3
Joseph	L	1996	120	189	MPD 26.6	NA	96	8.0
Chamberlain	L	1996	50	>50	Med 20.0	NA	NA	6.5
Alleyne	L	1997	40	41	MPD 14.9	33	71	9.0
Breneman	L	1997	84	145	MPD 16.0	NA	25	11.0
Shirato	L	1997	39	39	MCD 25.0	92	84	8.7
Shiau	G	1997	100	219	MPD 18.5	47	77	12.0

Linac: Local Control 25-95%; MPD 16-26.6 Gy.

BED of > 80Gy are necessary for local control

Frames for fractionated extracranial /SBRT with a spine frame



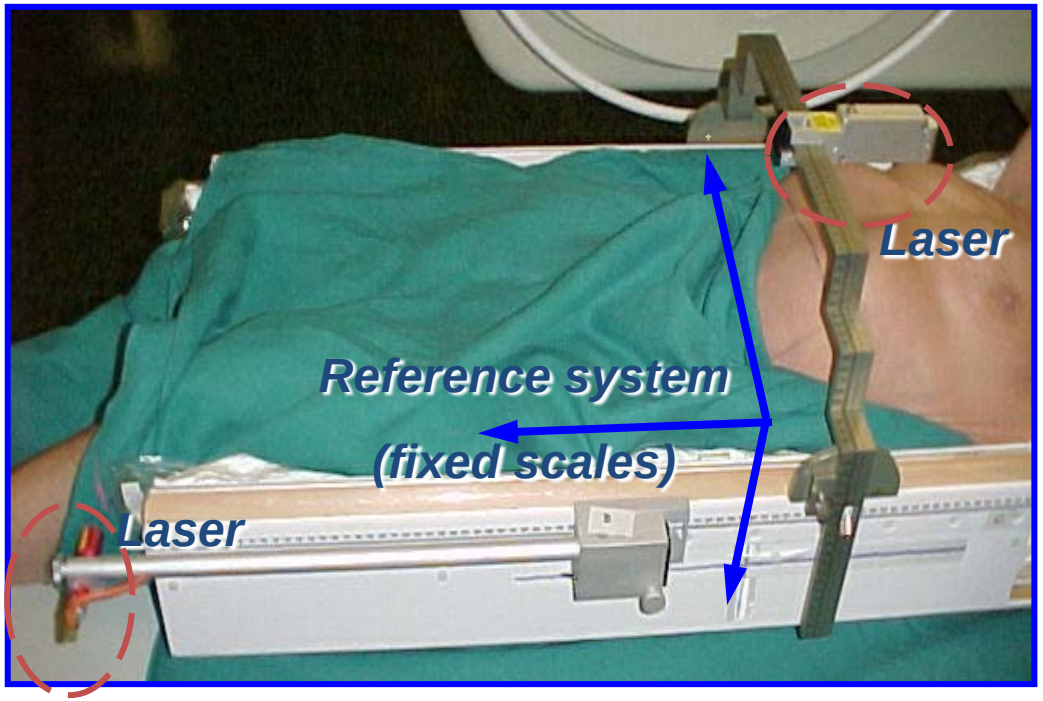


Fractionated stereotactic RT of the Vertebras was possible

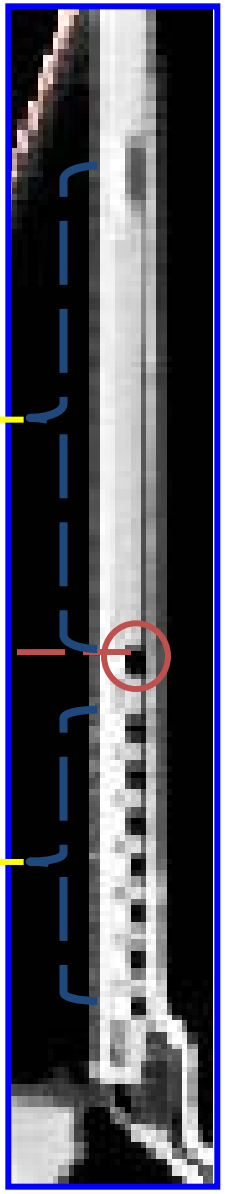
Hamilton et al. Neurosurgery 36 (2): 311-19, 1995
Hamilton et al. Stereotactic Funct NS, 1995

Extracranial Stereotactic Radiotherapy by Lax and Blomgreen in the early 90ies

- Localization of the target with respect to a coordinate system in space
  - 'Head localizer box' in conventional SRT
  - Bodyframe for extra-cranial SRT - CT and MR indicators
  - Belly press for reduction of organ motion
  - Dual vacuum technology



'INDICATORS'



measure y in mm

FIX 95 mm

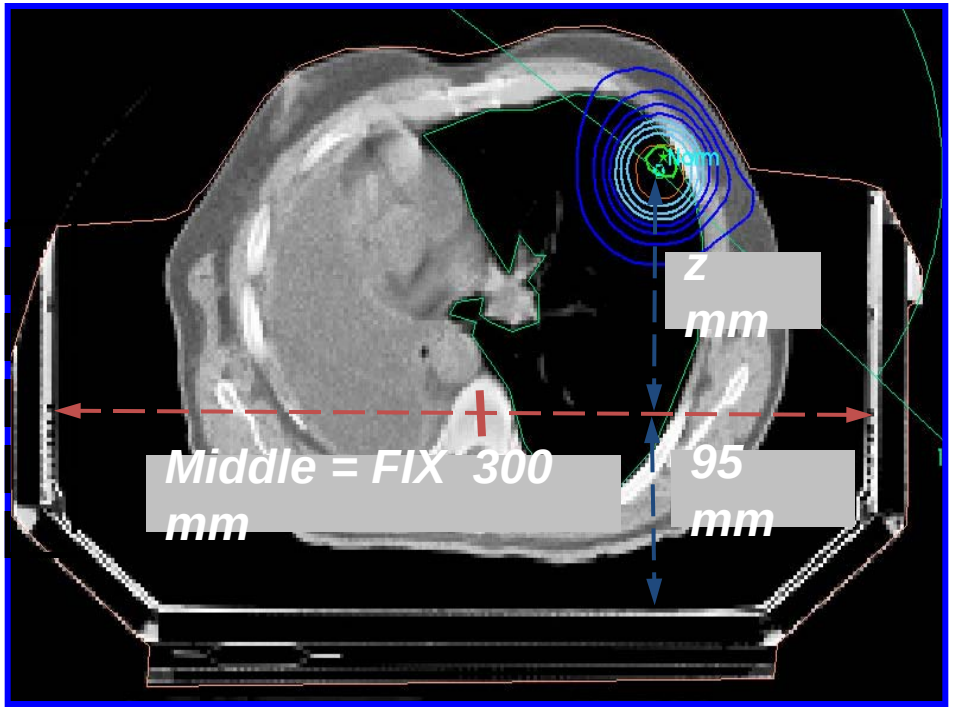
Y + 7 x 100 mm in cranial direction

ISOCENTER POSITION

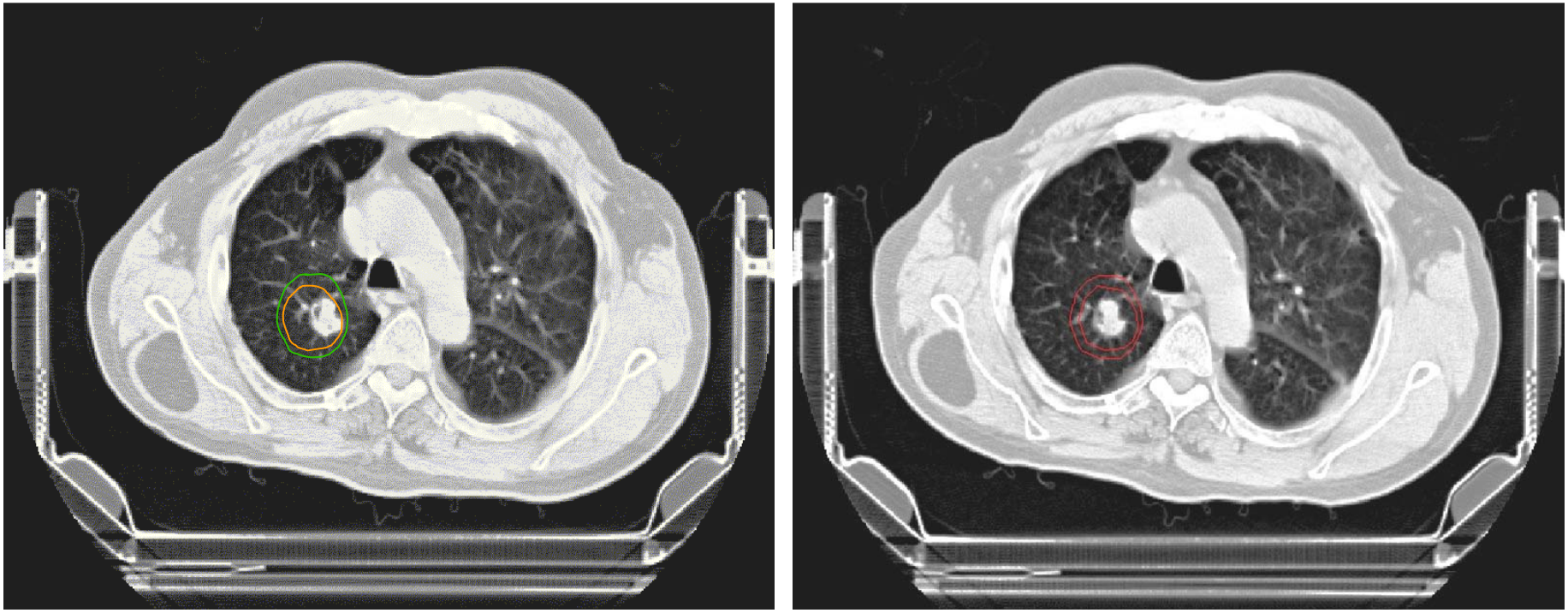
X = 300 ± x [mm]

Y = y + (counts) x 100 [mm]

Z = ± z + 95 [mm]



Preliminaries for SBRT



- highly reproducible **non invasive** patient positioning system
- highly reproducible target position
- reduction of organ motion
- Fixation system compatible with CT, MRI, PET/CT

EXTRACRANIAL STEREOTACTIC RADIATION THERAPY: SET-UP ACCURACY OF PATIENTS TREATED FOR LIVER METASTASES

K. K. HERFARTH *et al.*

Body set-up

Table 1A. Body set-up deviations between treatment planning and treatment in 26 consecutive stereotactic single dose radiation treatments of liver metastases

	Median [mm]	Minimum [mm]	Maximum [mm]	Mean [mm]	STD-DEV [mm]
Latero-lateral	1.8	0.3	5.0	2.0	1.2
Anterior-posterior	2.0	0.8	3.8	1.9	0.6
Vectorial (transversal plane)	3.1	1.0	5.4	3.1	1.2

Target set-up

Table 1B. Target set-up deviations between treatment planning and treatment in 26 consecutive stereotactic single dose radiation treatments of liver metastases

	Median [mm]	Minimum [mm]	Maximum [mm]	Mean [mm]	STD-Dev [mm]
Latero-lateral	1.6	0.2	7.0	2.2	1.7
Anterior-posterior	2.3	0.0	6.3	2.2	1.8
Cranio-caudal	4.4	0.0	10.0	4.0	2.5
Vectorial (3D)	5.7	2.5	10.4	5.7	2.1

Body set-up deviations and target set-up deviations for liver metastases can be variable, especially in the c-c direction.

PTV= CTV +individual organ motion

Int. J. Radiation Oncology Biol. Phys., Vol. 46, No. 2, pp. 329–335, 2000

Local liver metastases Control after SBRT

Author/ Year of publication	Study design	Number of Patients	Fractionation	Median Follow-up (m)	Local control (%) 1, 2 years	Survival (%) 1, 2 years
Hoyer 2006	Phase I/II	44	3x 15Gy (isocenter)	51.6	?, 78*	67**, 38**
Mendez Romero 2006	Phase I/II	17	3 x 10-12.5Gy	12.9	100, 86	85, 62
Rusthoven 2009	Phase I/II	47	3 x 12-20Gy	16	95, 92	77, 30
Lee 2009	Phase I	68	6 x 4.6-10Gy	10.8	71, ?	60, 39
Goodman 2010	Phase I	19	1 x 18-30Gy	17.3	77, 75 (primary/ metastases)	62, 49
Rule 2010	Phase I	27	3 x 10Gy 5 x 10Gy 5 x 12Gy	20	56, 56 100, 89 100, 100	90, 50 78, 67 75, 56
Scorsetti 2013	Phase II	61	3 x 25Gy	12	94, 91	83, 38

Local control after hypofractionated SBRT **75% to 100%** after 2 years according to dose

Local lung metastases Control after SBRT

Author/ Year of publication	Study design	Number of Patients	Fractionation	Median Follow-up (m)	Local control (%) 1, 2 years	Survival (%) 1, 2 years
Wulf 2004	Dose escalation	41	3 x 10-12.5Gy 1 x 26Gy	9	80, 80	85, 33
Hof 2007	Phase I/II	61	1 x 12-30Gy (isocenter)	14	≥26Gy and ≤10cc: 100, 83 Rest: 86, 71	78, 65
Rusthoven 2009	Phase I/II	38	3 x 16-20Gy	15.4	100, 96	65, 39
Ricardi 2012	Retrospective	61	1 x 26Gy 3 x 15Gy 4 x 9Gy	20.4	95, 89	79, 67
Singh 2013	Retrospective	34	5 x 10Gy	16.7	93, 88	62, 44
Niibe 2015	Retrospective	34	4x12-12.5Gy 7-10x 5-8Gy		90 , 79	85 , 66*
Nuyttens 2015	Phase II	30	3x20Gy 1x30Gy 7x8Gy/5x12Gy	36	79, NRP	NRP, 63

Local control after hypofractionated SBRT 79% to 89% after 2 years according to dose

New developments of the new machines opened the doors for high precision frame-less RT:

Implementation of IGRT systems for localization at the LINACs

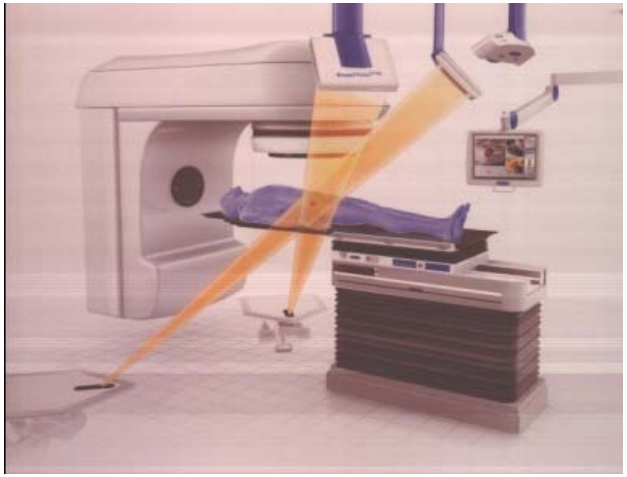
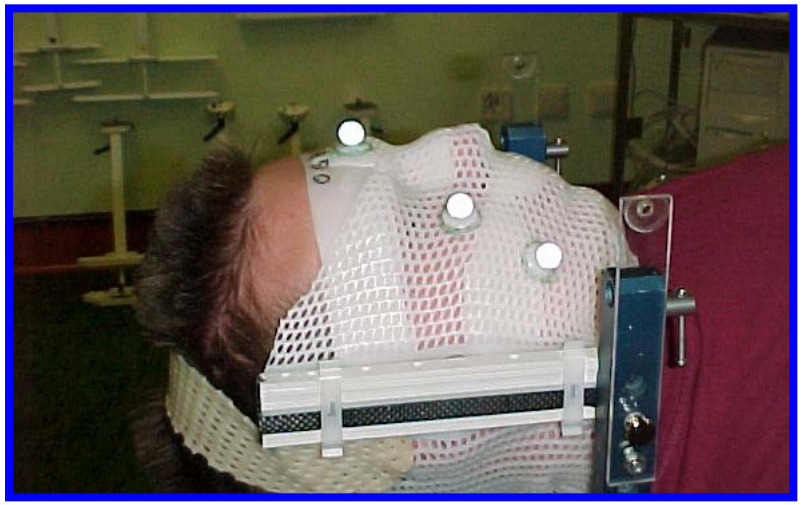
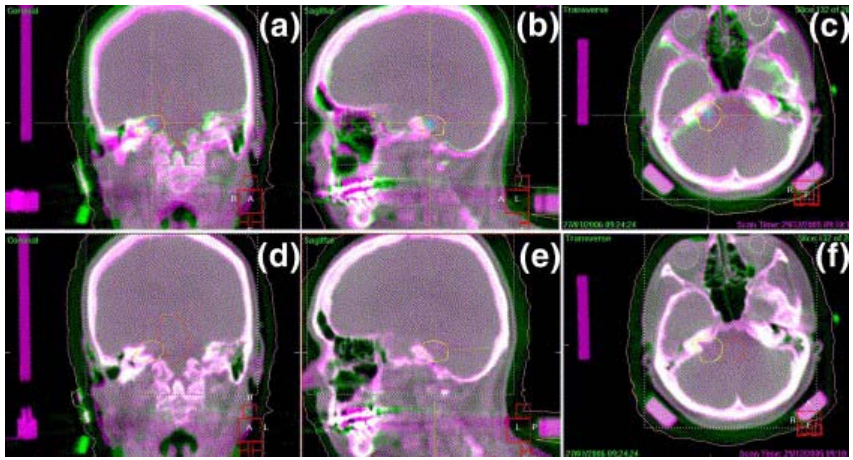


Image guided frame-less Stereotactic Radiotherapy

Replacement of the stereotactic systems with external coordinates for patient positioning by **direct imaging** before the treatment and **online correction**

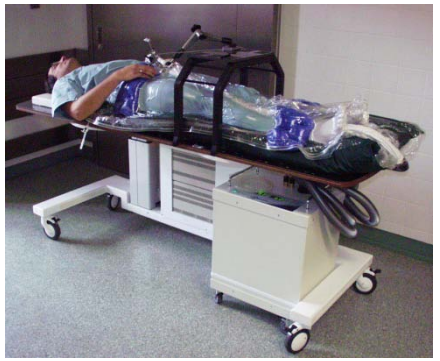




Boda-Heggemann 2006

Use of **internal anatomy rather than external landmarks** **to avoid geographic miss**

Image Guidance for SBRT

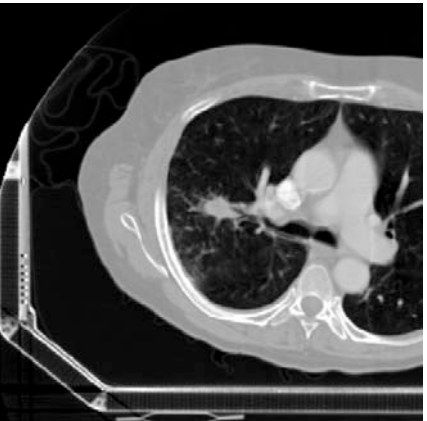


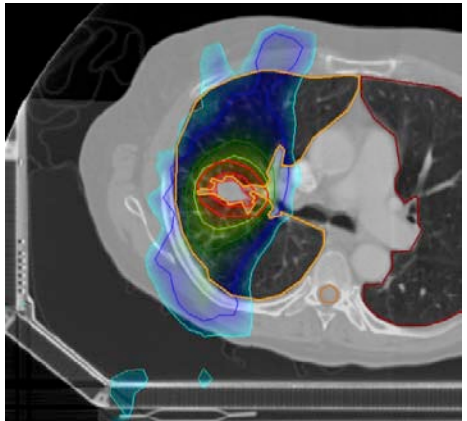
- Challenges for Liver and Lung
  - Small margins vs. respiration

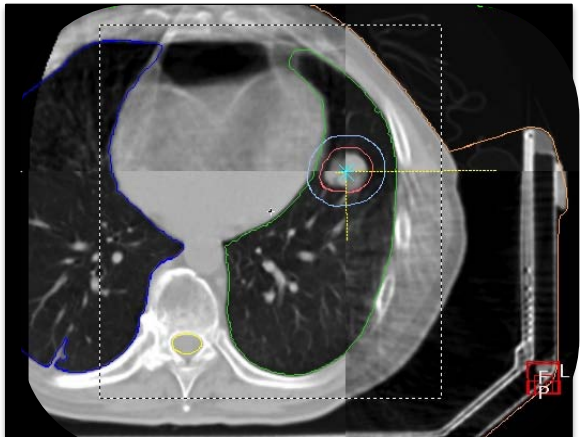
  → **Intra-fractional changes of the tumor position**
- Target verification prior each fraction
  - ➢ Pre-CBCT aera: Logistic issues on CT and Linac
  - ➢ Transport prolongs "overall time for treatment"

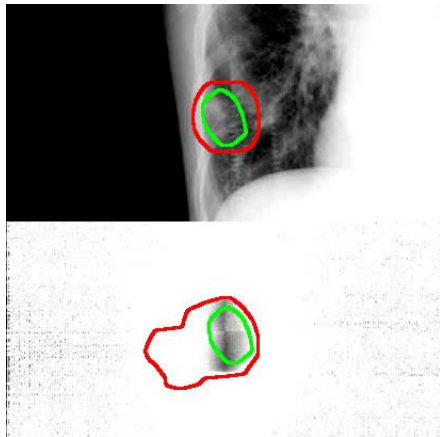
„get the patient from the CT to the linac"

IGRT technology contributed to simplify logistics for SBRT



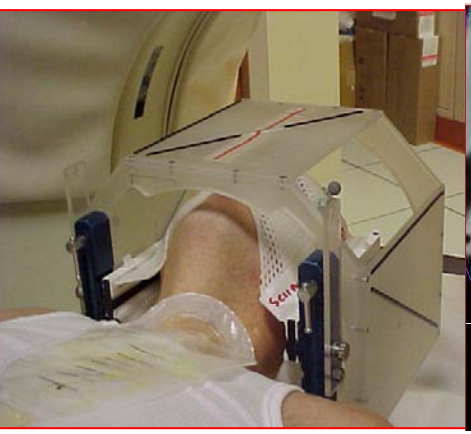
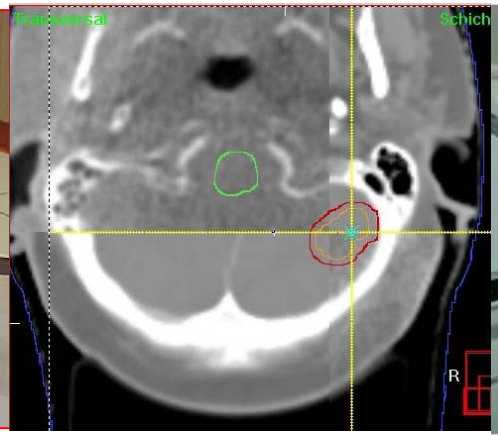
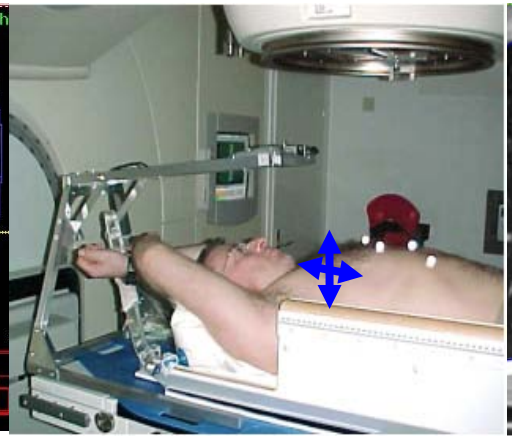
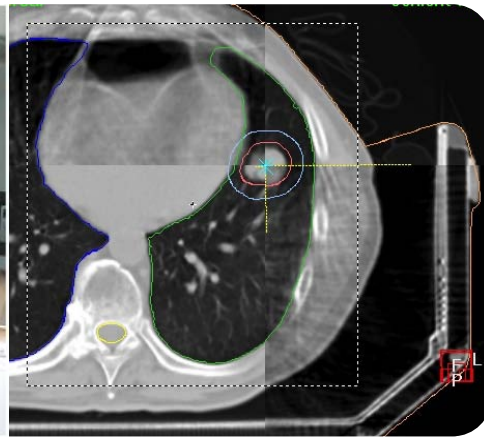






Non invasive frame-based Stereotactic RT

Work-Flow: Interval between planning in performance

1. **Non Invasive mask/body frame**
2. Localisation system
3. Imaging (CT/MRI image fusion)
4. Target delineation
5. Isocenter (s) positioning
6. Control CT
7. **RT-Treatment a few days after the planning CT/MRI**

Indications increased for SBRT

- Lung tumors/ Lung metastases
- Liver tumors/ Liver metastases
- Spinal cord
- Bone metastases (oligometastases)
- Paravertebral lesions
- Pancreatic tumors/ metastases
- Adrenal glands
- Lymph nodes
- *Re-irradiations*

A Survey of Stereotactic Body Radiotherapy Use in the United States

Hubert Pan

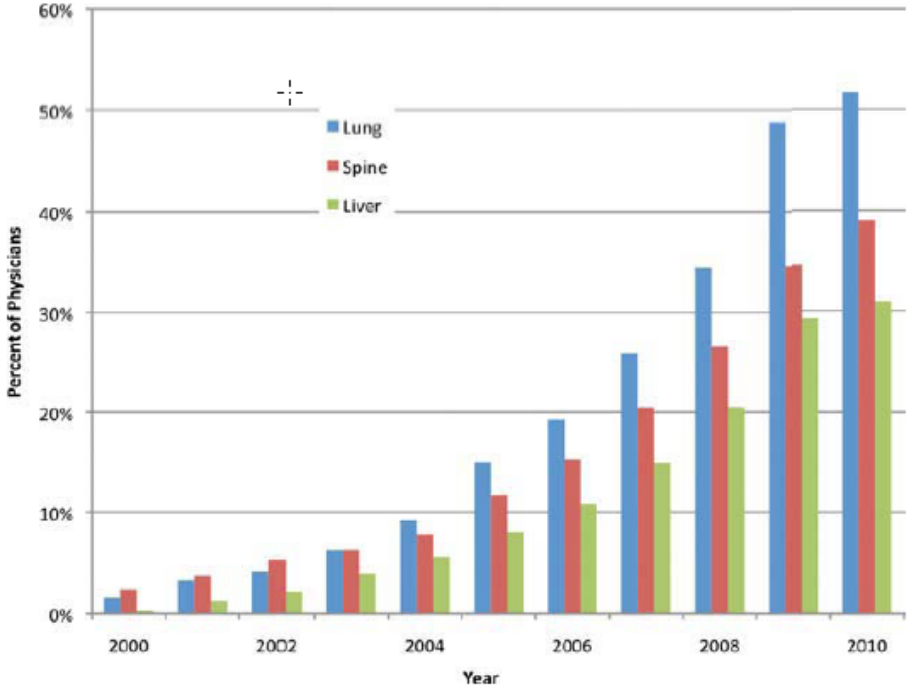


Figure 4. Cumulative adoption of stereotactic body radiotherapy is shown for the 3 most common disease sites treated: lung, spine, and liver.

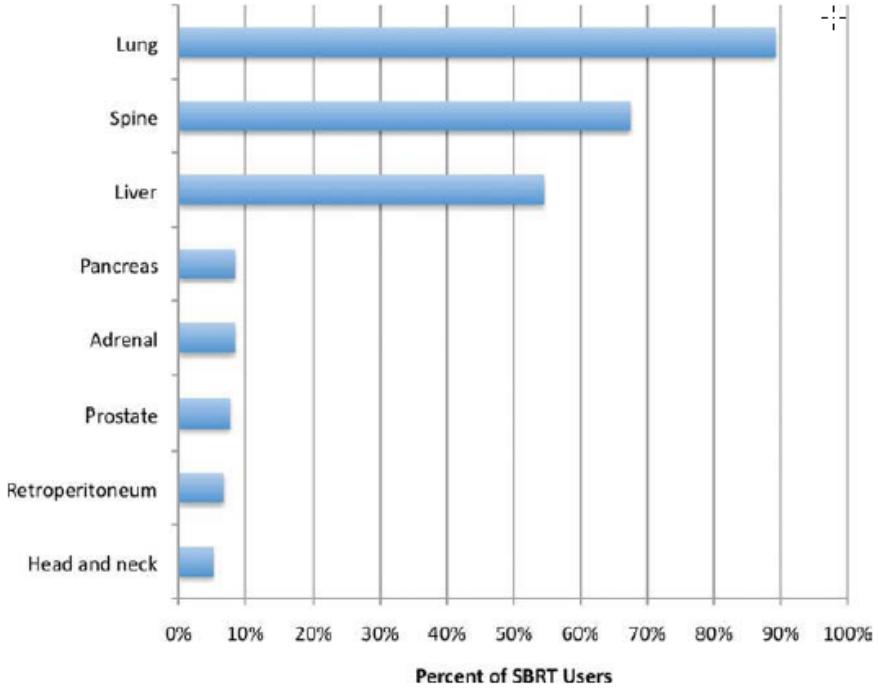


Figure 5. Disease sites treated by stereotactic body radiotherapy (SBRT) users who responded to the survey are shown.

Reasons for adopting SBRT are:

- The delivery of higher than conventional radiation dose
- The retreatment

Cancer October 1, 2011

Conclusion
Why is the step to frame-less Image Guided Stereotactic RT successful?

- SRS/SBRT

High patient comfort; no pain

Image fusion based on the tumor not on external marker ⟹ **High accuracy**

- **f SBRT**

Comfortable for the patients

Image fusion based on the tumor not on external marker

High accuracy in relocability

Bigger tumor volumes can be treated

Proper immobilization during treatment in combination with X-ray based positioning, can replace the use of traditional frame

Conclusion

- SRS/SBRT

Image fusion based on the tumor not on external marker

⟹ **High accuracy**

High patient comfort; no pain

- **f SBRT**

Bigger tumor volumes can be treated

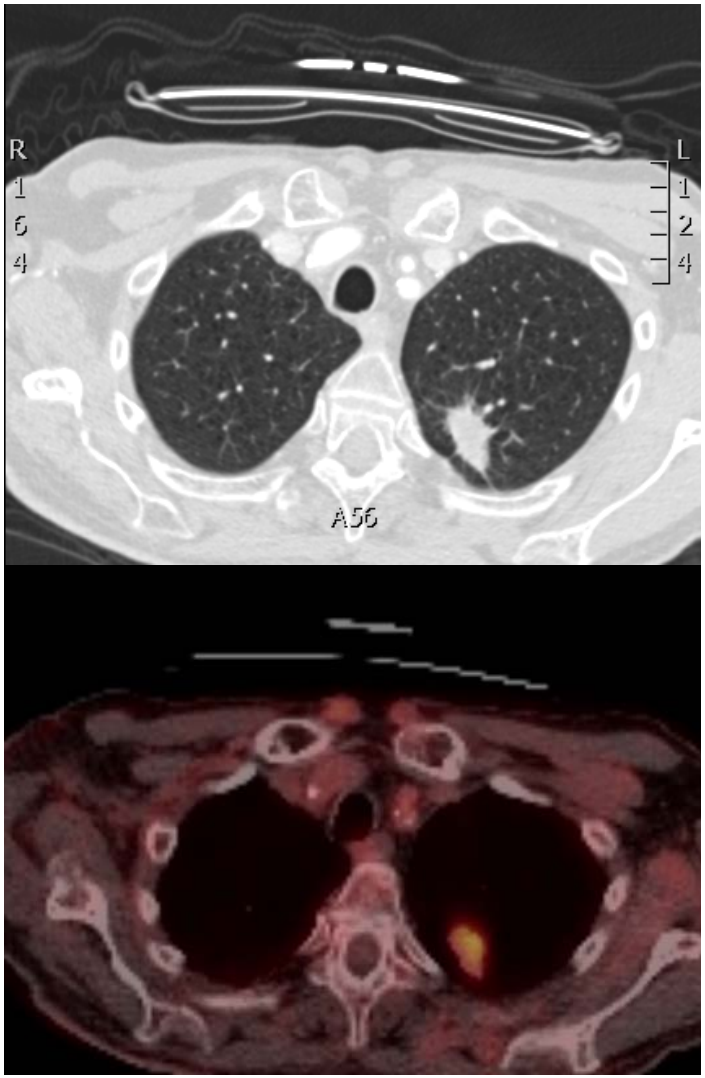
High accuracy in relocability

Proper immobilization during treatment in combination with X-ray based positioning, can replace the use of traditional frame

Example I:
SBRT for NSCLC stage I

Morten Høyer Professor, PhD
Danish Canter for Particle therapy
Aatrhus University Hospital
Denmark
hoyer@aarhus.rm.dk

Case I: NSCLC stage I



66 years old male

T1N0M0

Adenocarcinoma, ALK-neg

Comorbidities:

- Cerebral apoplexy
- Moderate hemiparesis
- Alcoholism

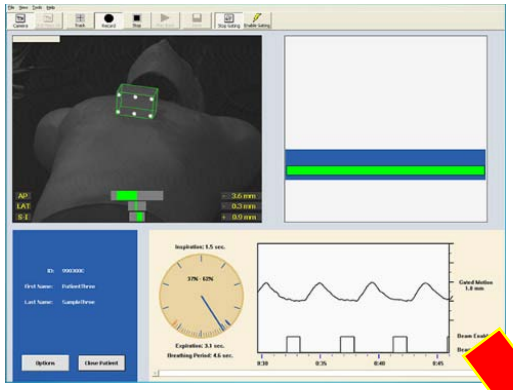
PS (WHO): 2-3

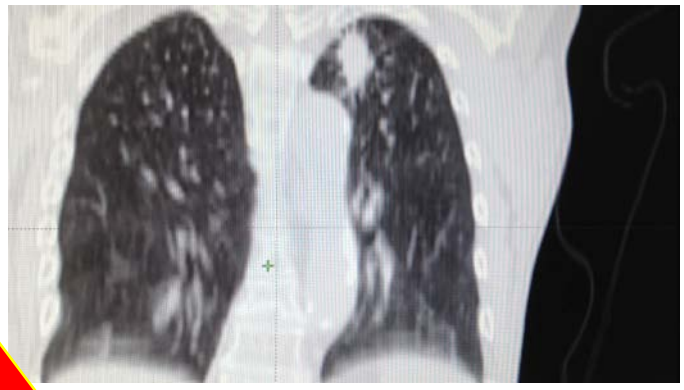
FEV1: 1.58 (51%)

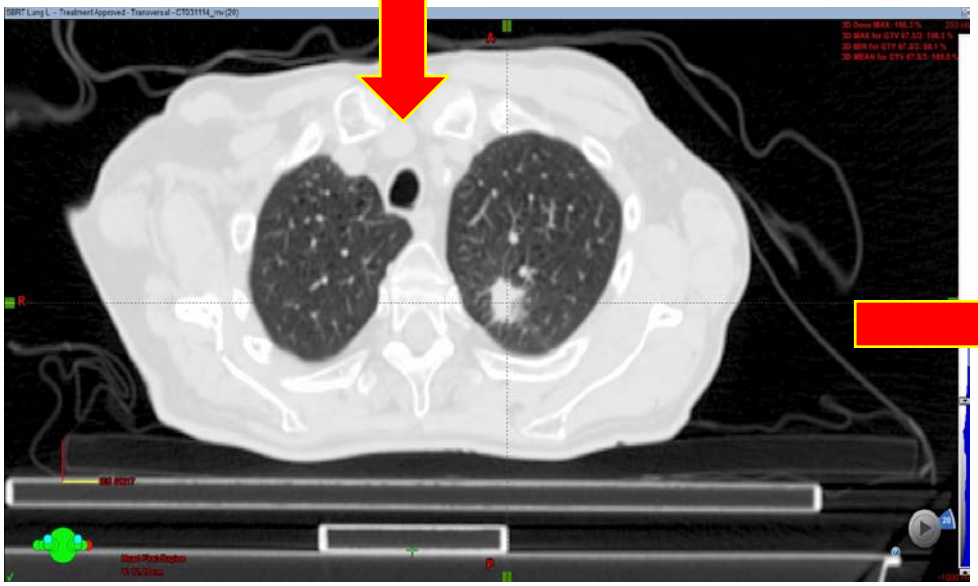
FVC: 1.61 (42%)

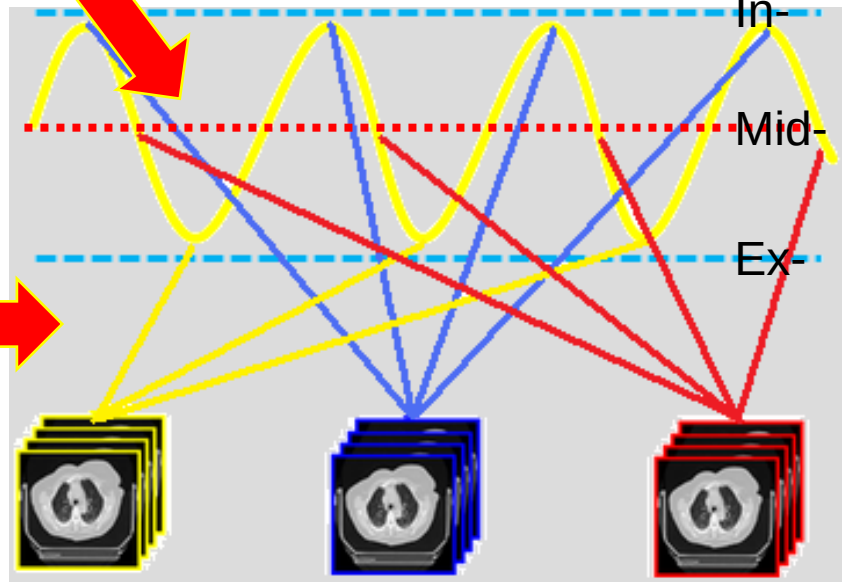
Immobilization

4D-CT skanning

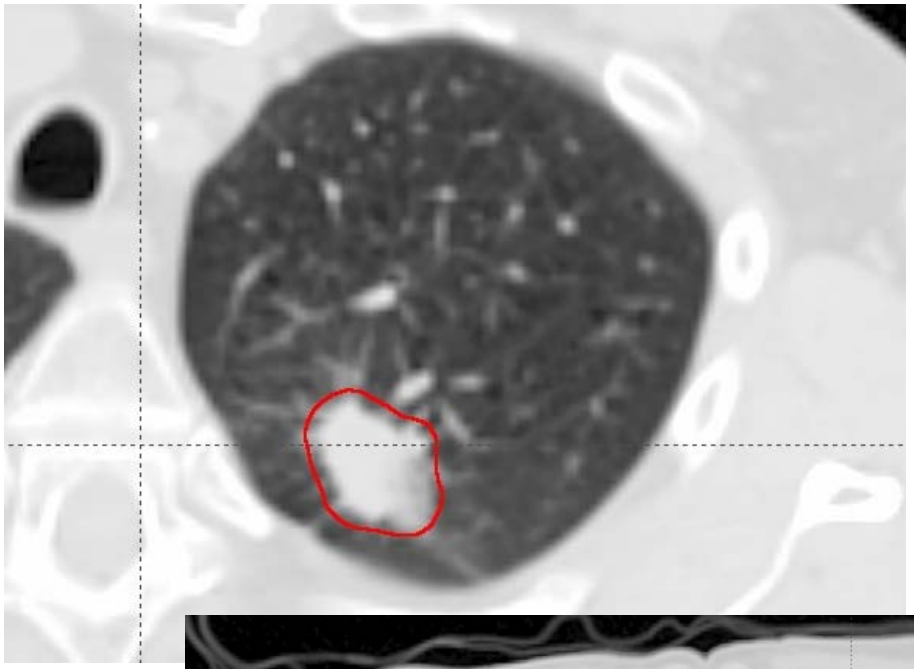


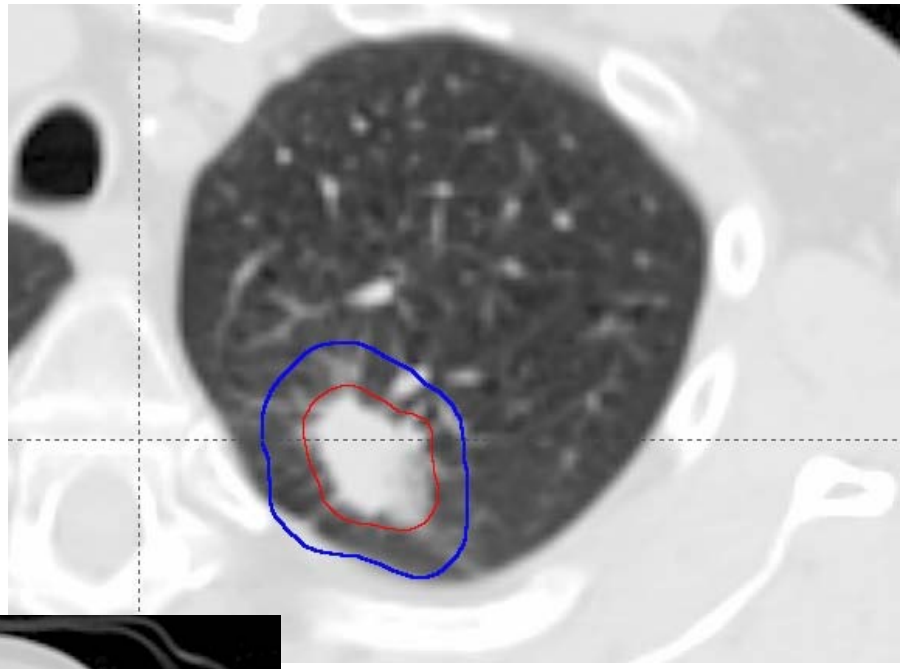


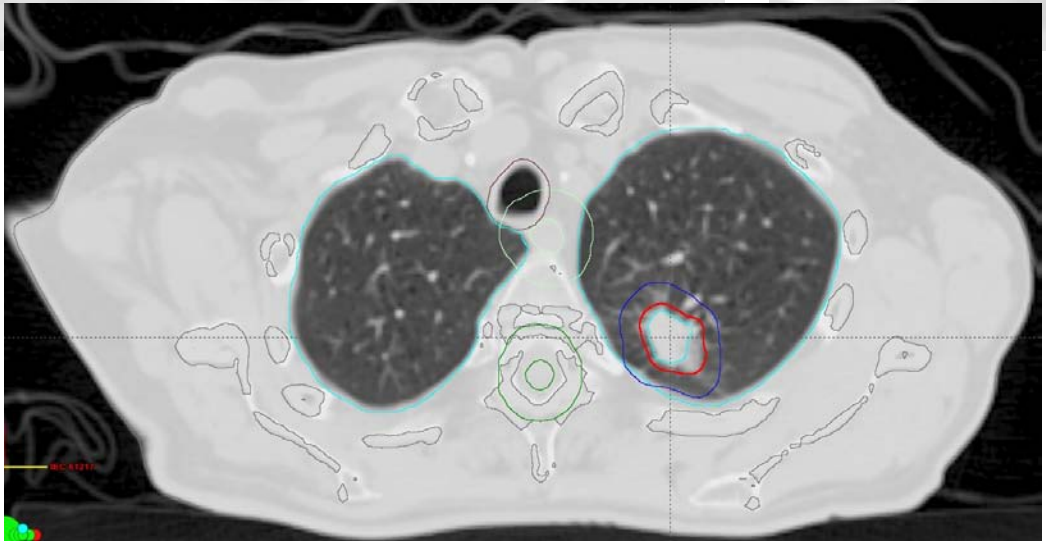




CTV, PTV and OARs



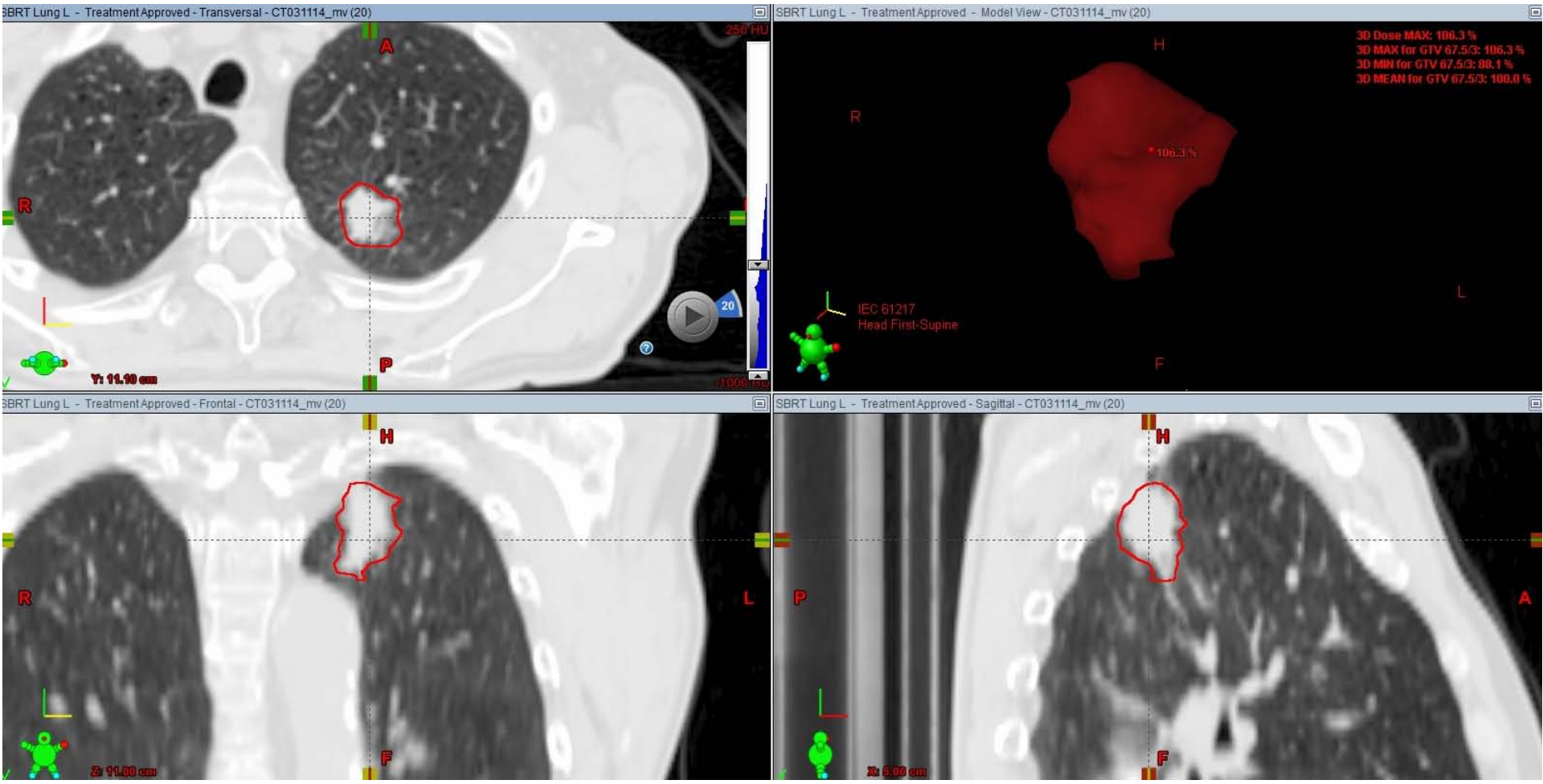




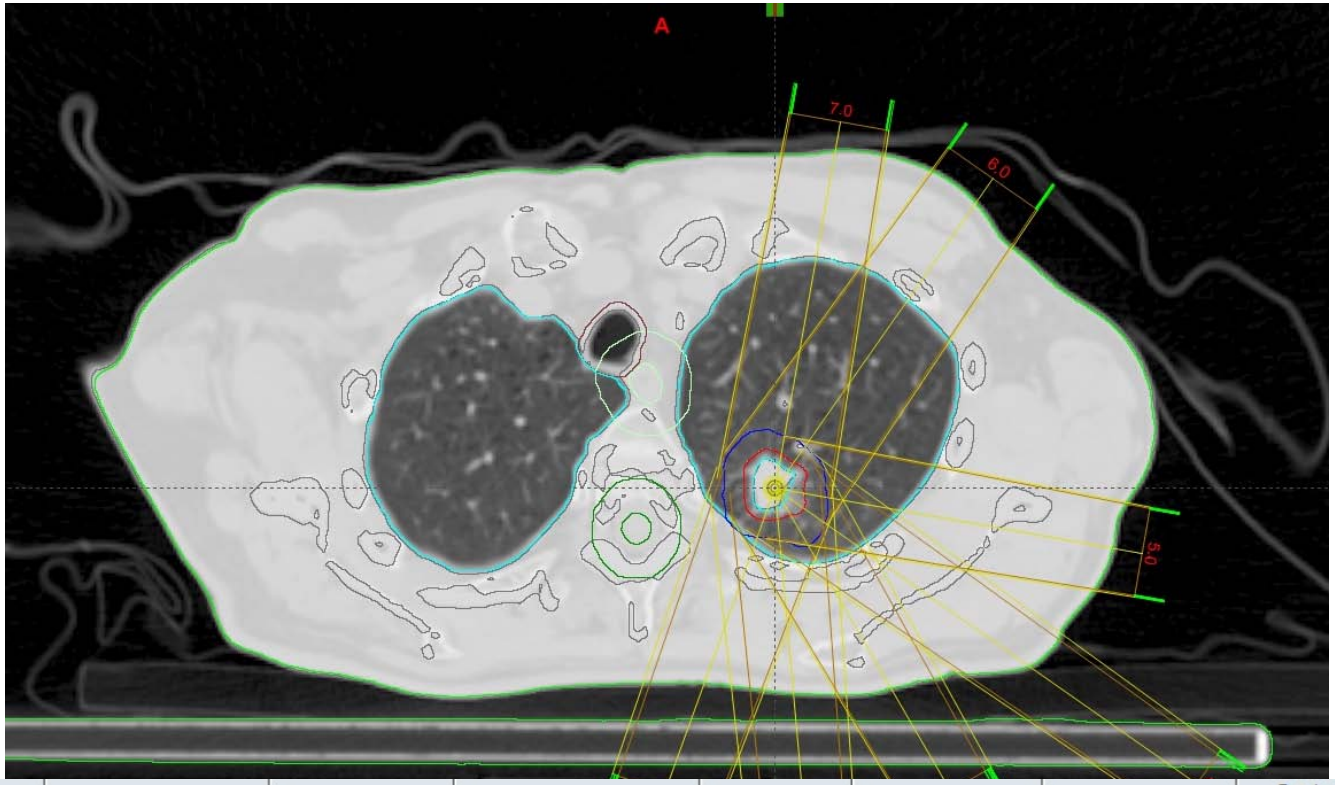
OARs:

- Lungs
- Trachea & bronchi (L+R)
- Esophagus
- Spinal cord
- Heart
- Ribs & subcutaneous tissue

CTV in 3-D


SBRT Lung L - Treatment Approved - Transversal - CT031114_mv (20)
A
R
P
Y: 11.10 cm
SBRT Lung L - Treatment Approved - Model View - CT031114_mv (20)
3D Dose MAX: 106.3 %
3D MAX for GTV 67.5/3: 106.3 %
3D MIN for GTV 67.5/3: 88.1 %
3D MEAN for GTV 67.5/3: 100.0 %
H
R
106.3 %
L
IEC 61217
Head First-Supine
F
SBRT Lung L - Treatment Approved - Frontal - CT031114_mv (20)
H
R
L
F
SBRT Lung L - Treatment Approved - Sagittal - CT031114_mv (20)
H
P
A
F

Seven static fields

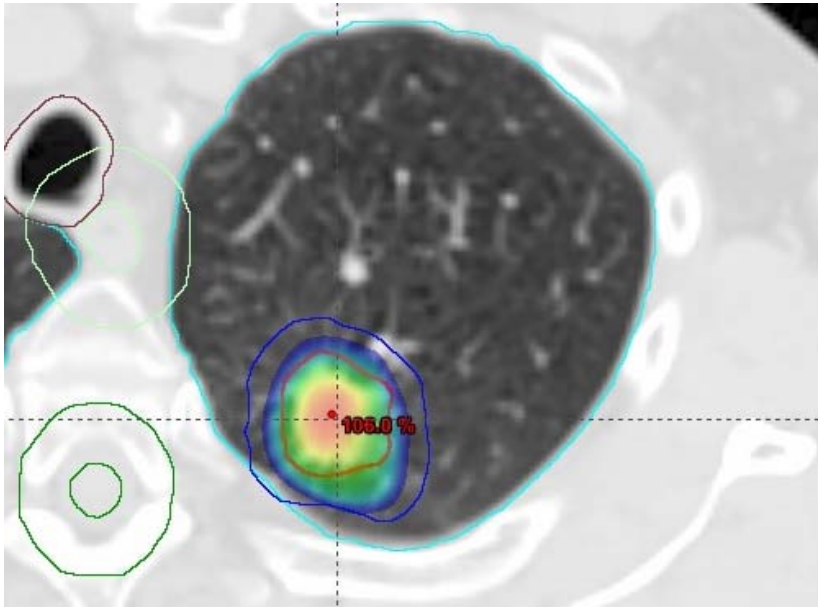


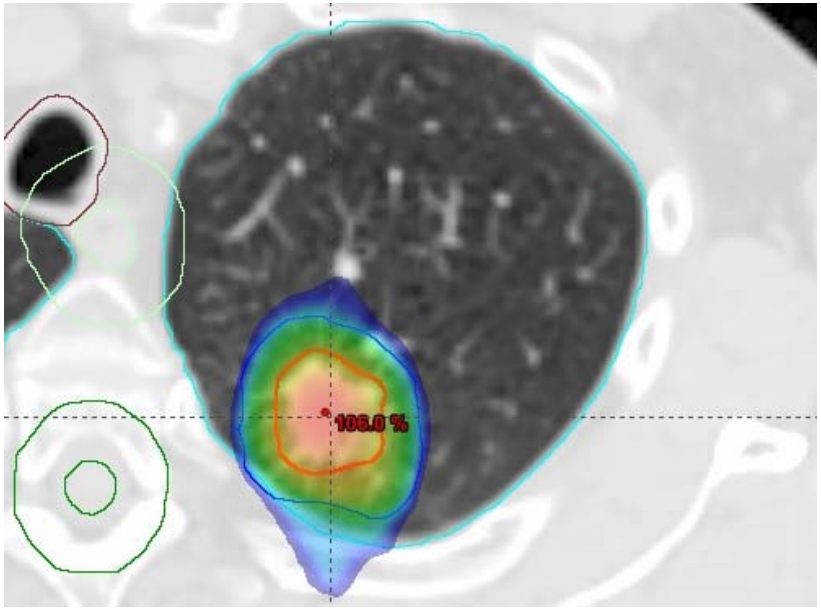
Group	Field ID	Technique	Machine/Energy	MLC	Field Weight	Scale	Gantry Rtn [deg]
☑	Setup CBCT	STATIC-I	A02_AUH - 6X		0.000	IEC61217	0.0
☑	2.0	STATIC-I	A02_AUH - 6X	Static	0.800	IEC61217	175.0
☑	3.0	STATIC-I	A02_AUH - 6X	Static	0.800	IEC61217	150.0
☑	4.0	STATIC-I	A02_AUH - 6X	Static	1.000	IEC61217	125.0
☑	5.0	STATIC-I	A02_AUH - 6X	Static	1.000	IEC61217	100.0
☑	6.0	STATIC-I	A02_AUH - 6X	Static	1.200	IEC61217	35.0
☑	7.0	STATIC-I	A02_AUH - 6X	Static	1.300	IEC61217	10.0
☑	1.0	STATIC-I	A02_AUH - 6X	Static	0.700	IEC61217	200.0

Dose; 90%- and 67% isodose

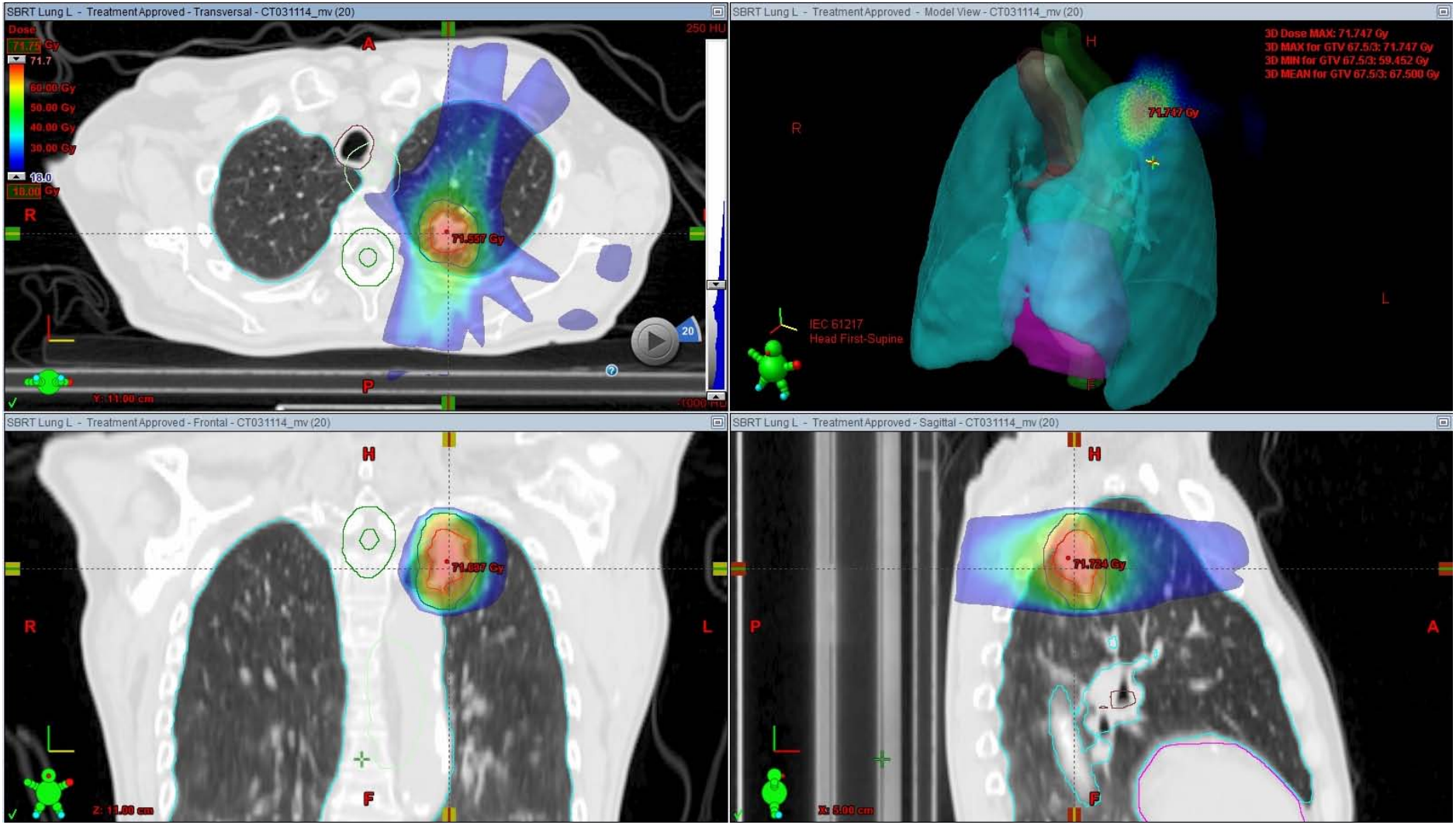
Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

Fractionation Id	Dose / Fraction [Gy]	Number of Fractions	Total Dose [Gy]	Target Volume	Primary Reference Point [Volume]	Total Dose at Primary [Gy]
2	22.500	3	67.500	GTV 67.5/3	GTV 67.5/3 [GTV 67.5/3]	67.500

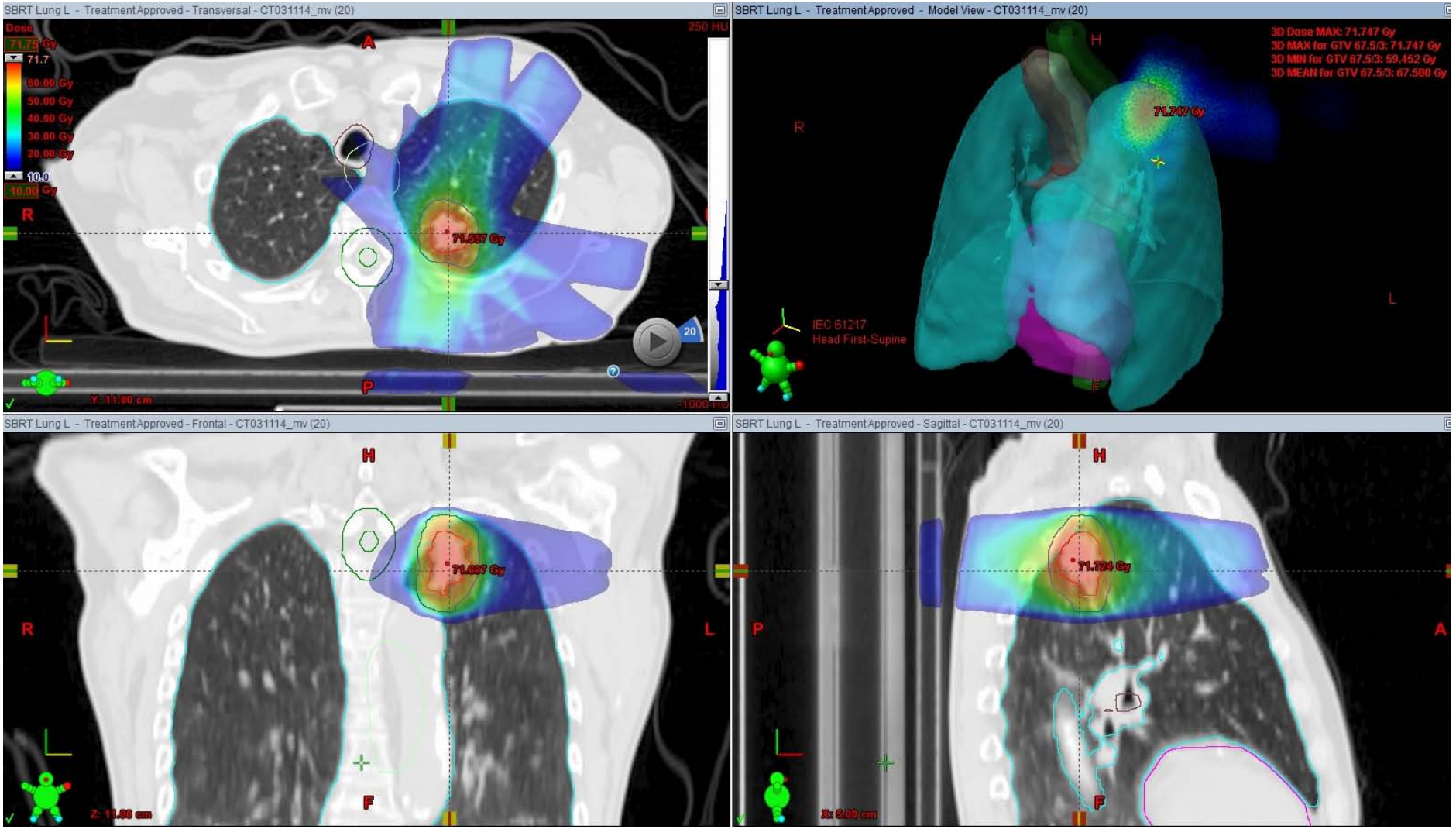




18 Gy isodose wash



10 Gy isodose wash



DP-vejledning: SBRT lunge

<< Vejledninger i dosisplanlægning | **<< SBRT**

SBRT-lunge

Den kliniske protokol `Lung SBRT` indeholder en 7-felts konventionel plan (`SBRT Lung LR`) til SBRT-behandling af lunge-tumorer. 7 felter er minimum, efter ønske fra Morten Høyer, grundet kraftige hudreaktioner hos nogle patienter. **Forsøg:** at anvede den nye kliniske protokol `DP_SBRT_Lung` der anvender de ny o Fit srukturer beskrevet herunder.

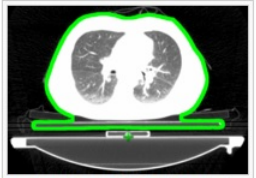
- Note: Det har i en periode været udgangspunktet at lave en RI-plan, men det nu ændret tilbage til konventionel plan. Tidsbesparelsen ved RI har sig vist begrænset i forhold til de udfordringer det har givet med den dosimetriske kvalitetssikring.

Generelt

- Der er foretaget 4D-CT-scanning med kontrast og maximum-inspiration breath-hold scanning, som er registreret til mid-vent fasen af 4D-CT'en.
- Indtegning er foretaget på **mid-vent-fasen** - altså *ikke på MIP* som for almindelig lunge.
- Fraktionering normalt 67.5Gy/3fx, men 45/3 og andet kan forekomme.
- Plan Target er GTV, som normaliseres til Target Mean=100%.
- Vær opmærksom på at centralt beliggende tumorer kan være omfattet af **HILUS-protokollen**. I så fald er der ordineret 56 Gy på 8 fraktioner.

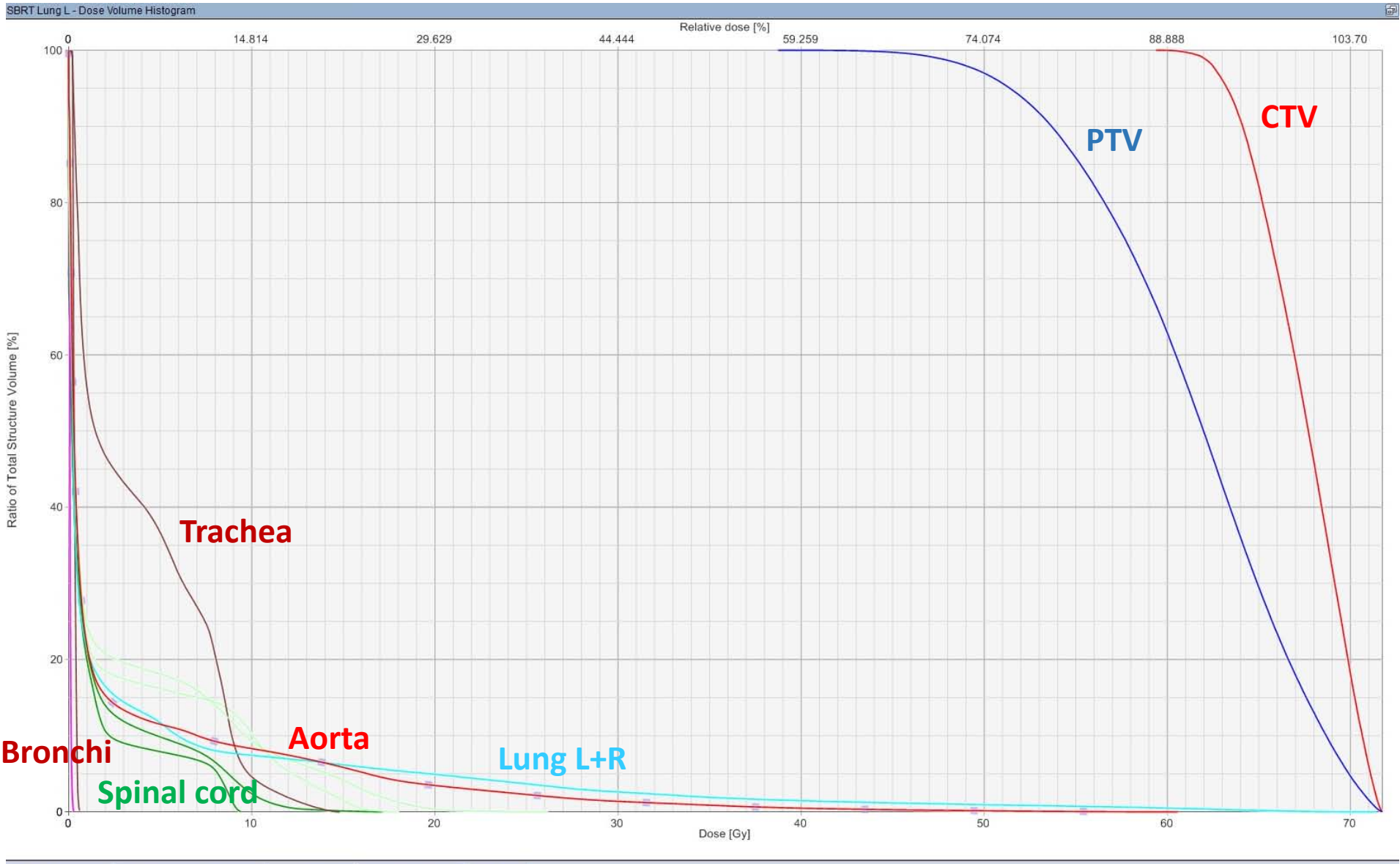
Generering af hjælpestrukturer

- Tjek at Body outline følger standard for fixationen, typisk SBRT Fixture. Der findes et AutoIT-script til generering af afledte strukturer **undtagen Skin 10mm** idet denne kræver bruger-interaktion til ROI-definering.

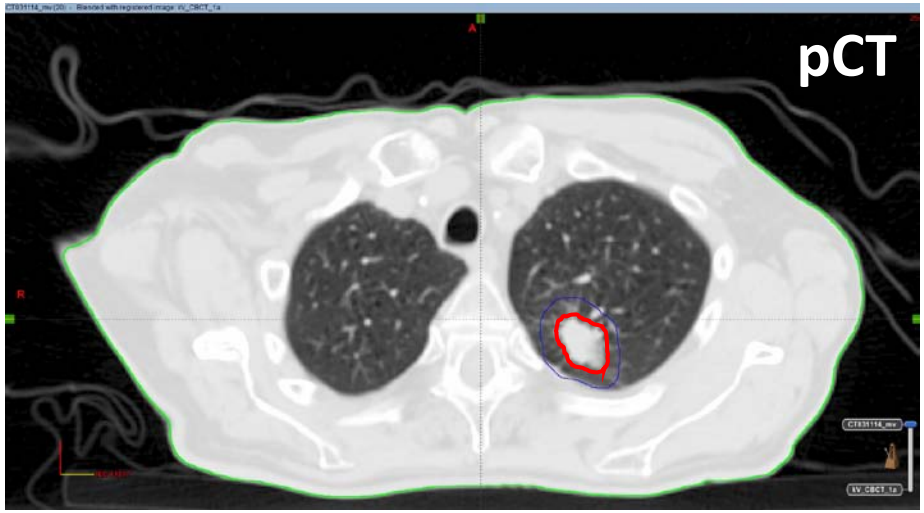

Body outline ved SBRT på Thorax-board

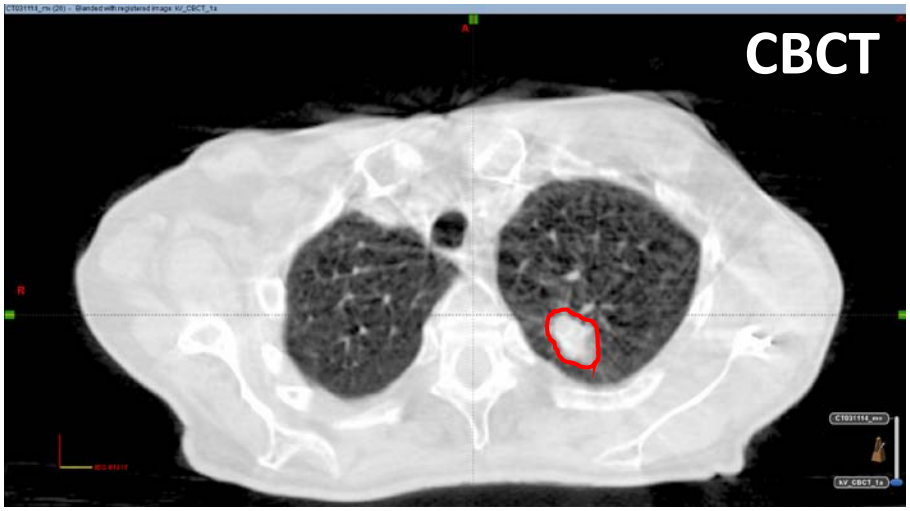
Struktur	Generering
PTV	*Check* ***respirationsamplituden*** *(peak-to-peak-bevægelse (p-t-p) af center of mass af GTV) i tasknoten eller på 4D-faserne.* Hvis 1/3*p-t-p ≤ 5mm AP/LR og 10mm CC benyttes **5mm AP+LR og 10mm CC** som margen til GTV Hvis 1/3*p-t-p > 5mm AP/LR og 10mm CC benyttes 1/3*p-t-p i den pågældende retning}} *Ex1: AP-amplitude = 18mm → 1/3*18mm = 6mm , altså 6mm PTV i AP retning.* *Ex2: CC-amplitude = 15mm → 1/3*15mm = 5mm → under standard 10mm CC, dvs. behold standard 10mm margen.*
PRV Spinalcord10	Spinal Cord + 10 mm isotropt *PRV kan indskrænkes til min. 5 mm hvis targetdækning kompromitteres.* **Match-constraint 10 eller 5 mm noteres** på checkark og behandlingskort, samt i Plan Comment.
PRV Esophagus10	Esophagus + 10 mm isotropt *Hvis PRV Spinalcord indskrænkes til 5 mm, indskrænkes PRV Esophagus tilsvarende. Ellers ikke.*
Bronchi	Bronchus R + Bronchus L, hvis de er opdelt
Lung total	Lung R + Lung L
o lung sub GTV	Lung total sub GTV 67.5/3, ingen margen
Skin 10mm	*For tumorer nær thorax-væggen eller med behov for overlappende eller nær-opponerende feltretninger, hvor 30Gy isodosen nærmer sig thoraxvæggen og huden:* Sæt en ROI omkring tumoren og udvid den til at indeholde det område af huden der *risikerer at få over 30Gy*. Indskrænk cranio-caudalt. Lav symmetrisk "Inner margin" 1.0cm ud fra RC surface. Dernæst Skin 10mm = Boolean: "RC surface" sub "Skin 10mm" hvilket giver en 10mm bræmme indenfor Body, som benyttes som "Hud". "Skin 10mm" skal ikke være huden på hele Body, af hensyn til evt. IMRT-optimering.
Skin 15mm endnu ikke i template	Som Skin 10mm, blot med 15mm margen.
o Lung or GTV	Lung total or GTV 67.5/3, Post processing: Fill all cavities
o FitSmall	GTV 67.5/3 + 2mm isotrop
o FitLarge	GTV 67.5/3 + 6mm,6mm,12mm
o Fit	("o FitLarge" AND "o Lung or GTV") OR "o FitSmall"
RC-strukturer	Se RadCalc/Oprettelse af RC strukturer i Eclipse.

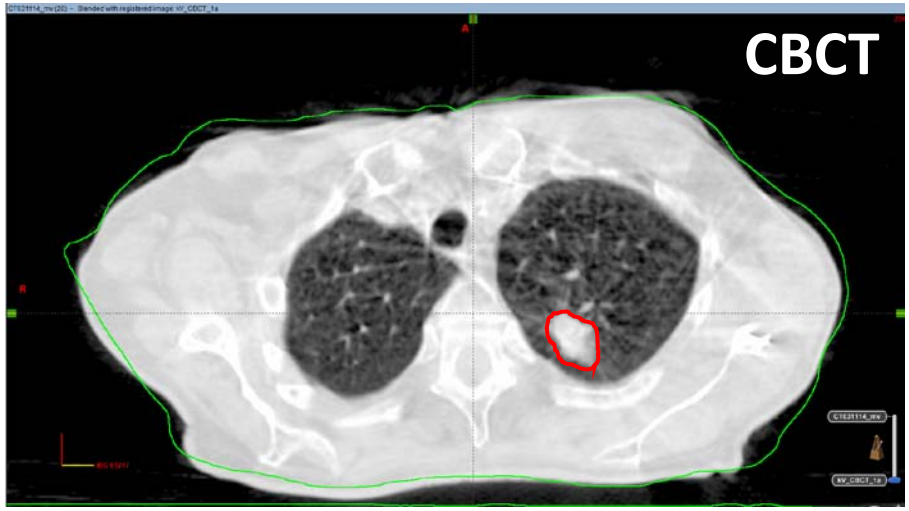
Conclusions – SBRT of oligometastases



Tumor CT/CBCT match







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

SBRT in synchronous metastatic NSCLC

Matthias Guckenberger

UniversityHospital Zurich

ESTRO

Patient presentation

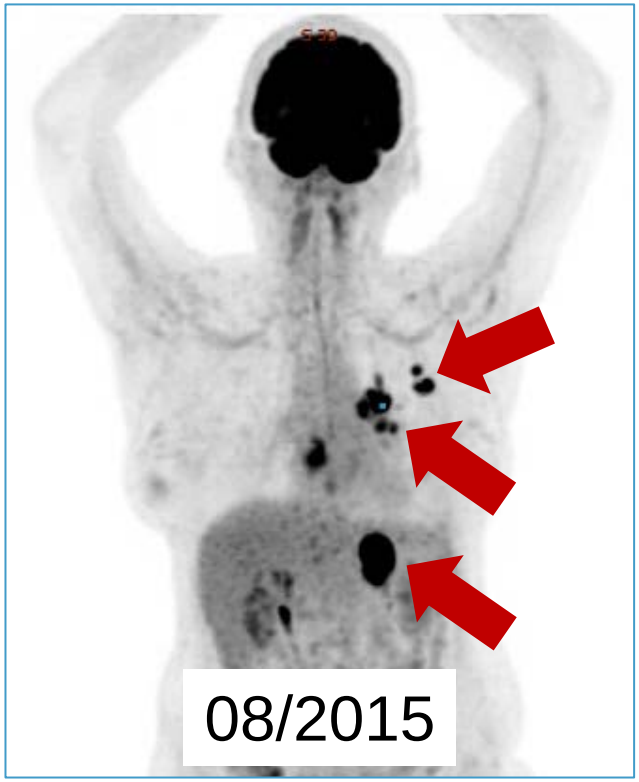
- 65 year old female
- Performance status 90%

- Comorbidities:
  - No relevant until diagnosis of cancer

- Paraneoplastic syndroms:
  - Anemia

- Depression after diagnosis of cancer

Initial staging & histopathology



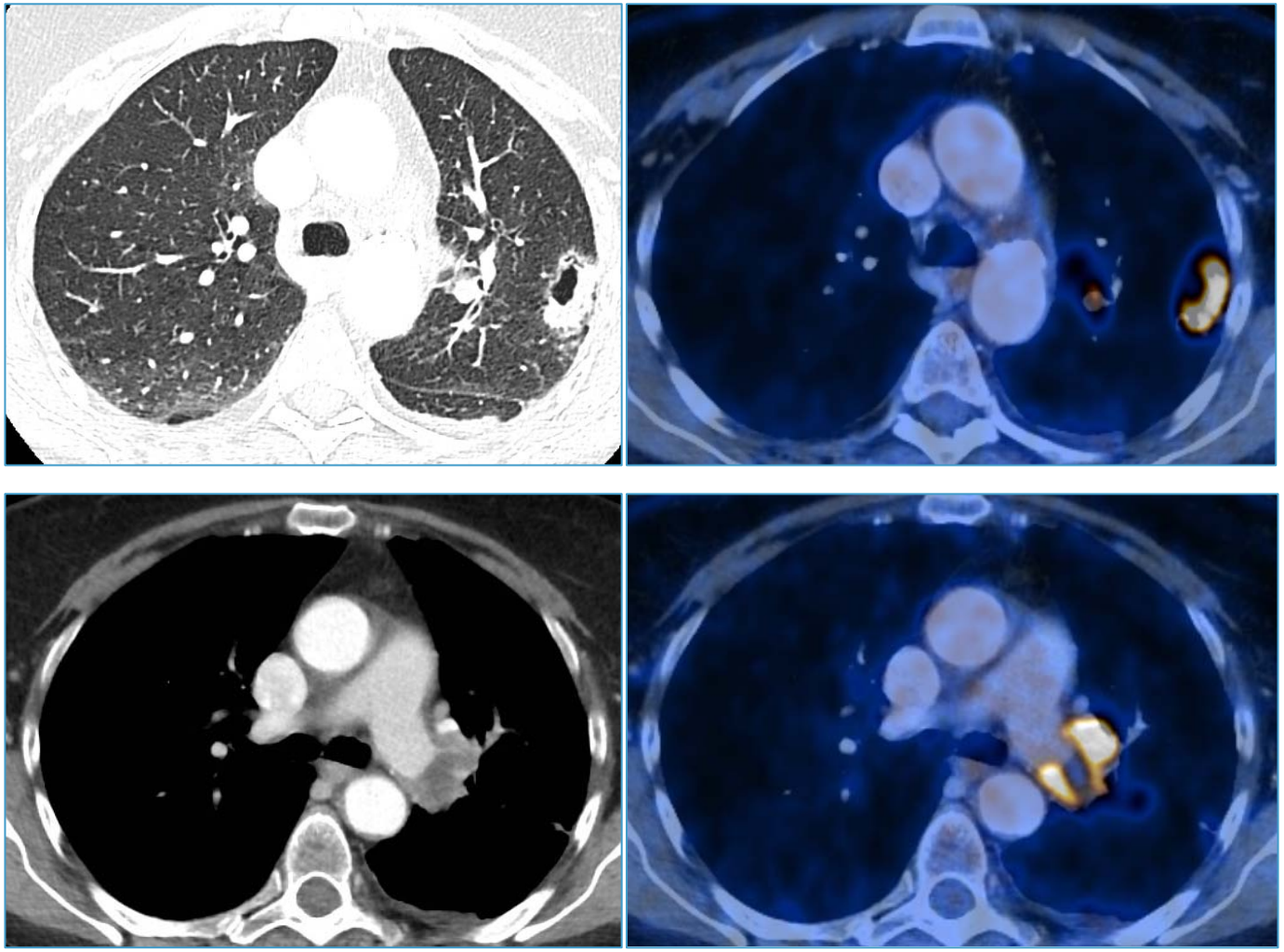
Primary

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

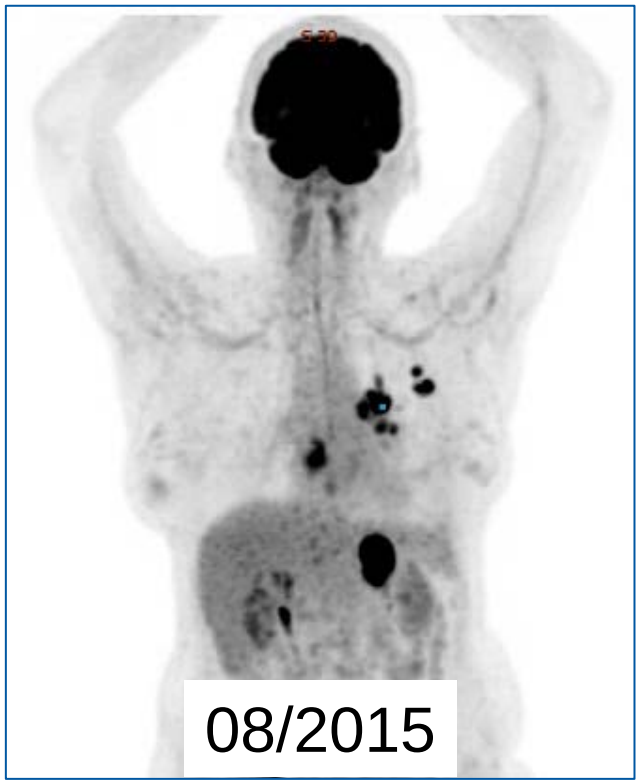
Initial staging & histopathology

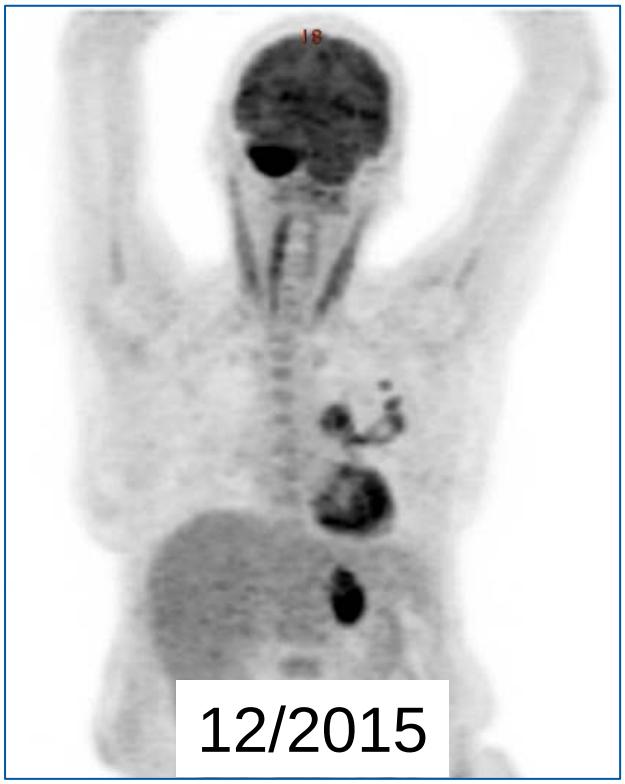
Paraneoplastic and / or chemotherapy complications:

- 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

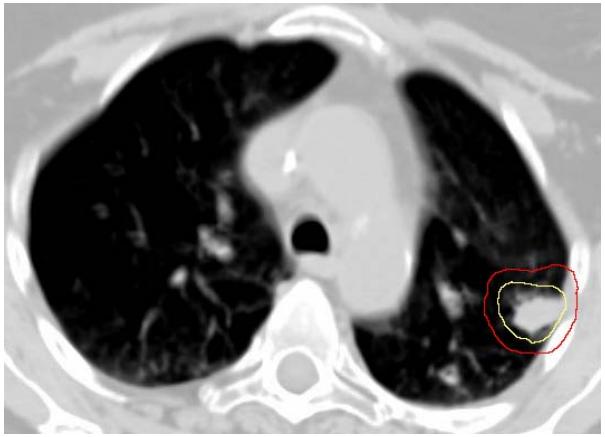
Restaging prior to radiotherapy

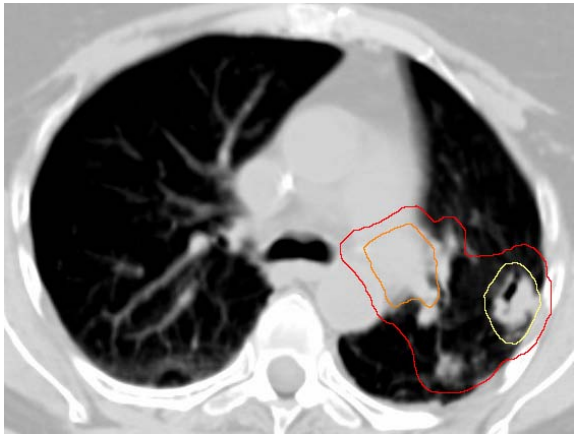


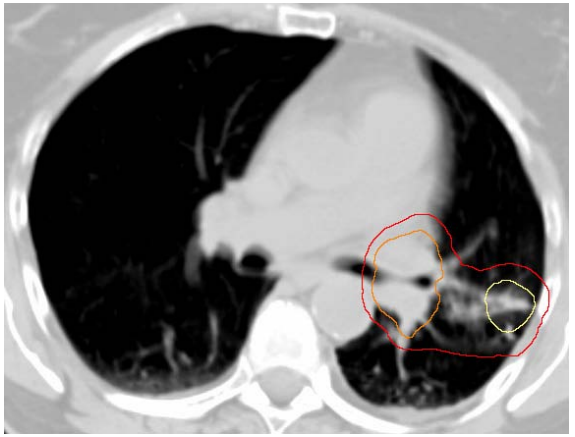


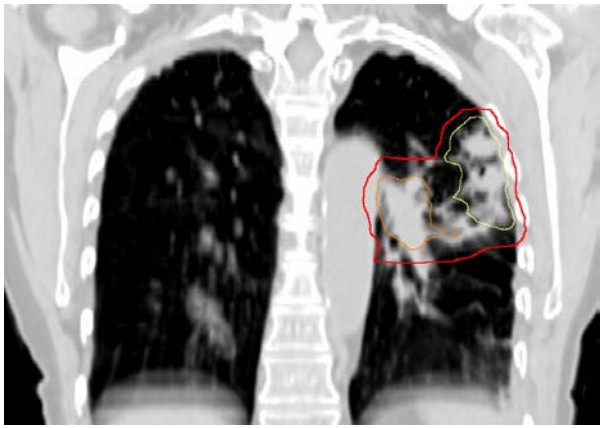
- Partial response

Radiotherapy planning - primary



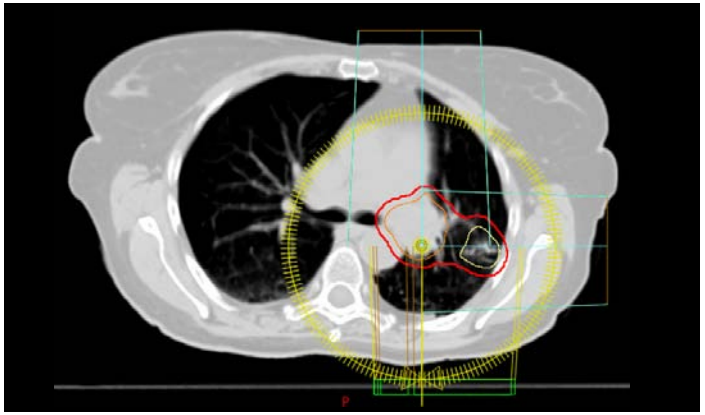


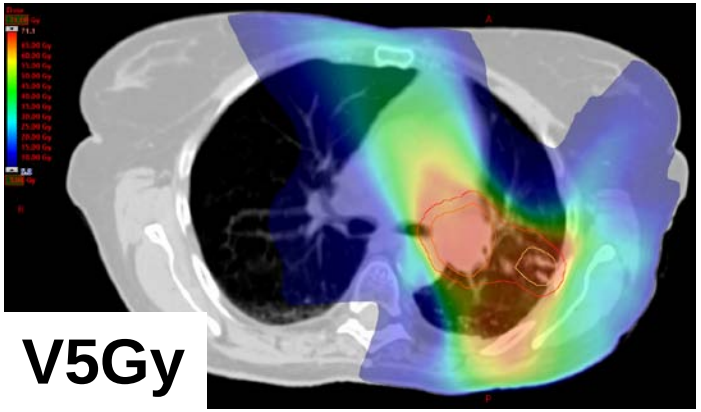




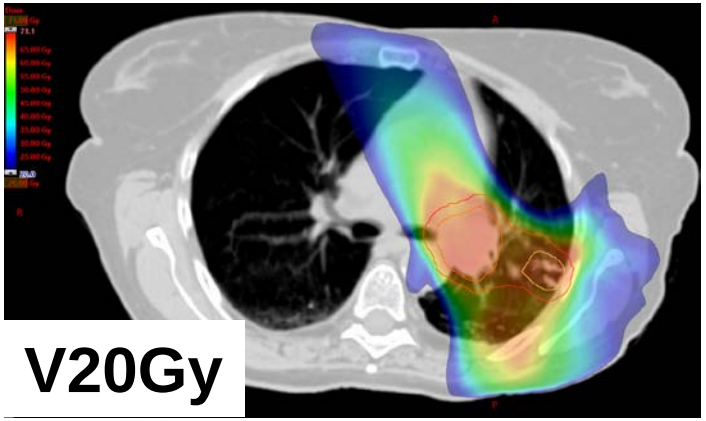
- Involved-field target volume concept
- 4D CT
- ITV motion compensation
- 10mm ITV to PTV margins

Radiotherapy planning - primary

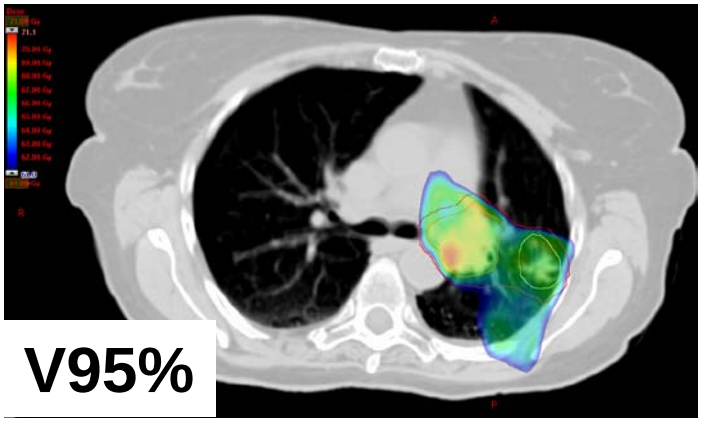




V5Gy



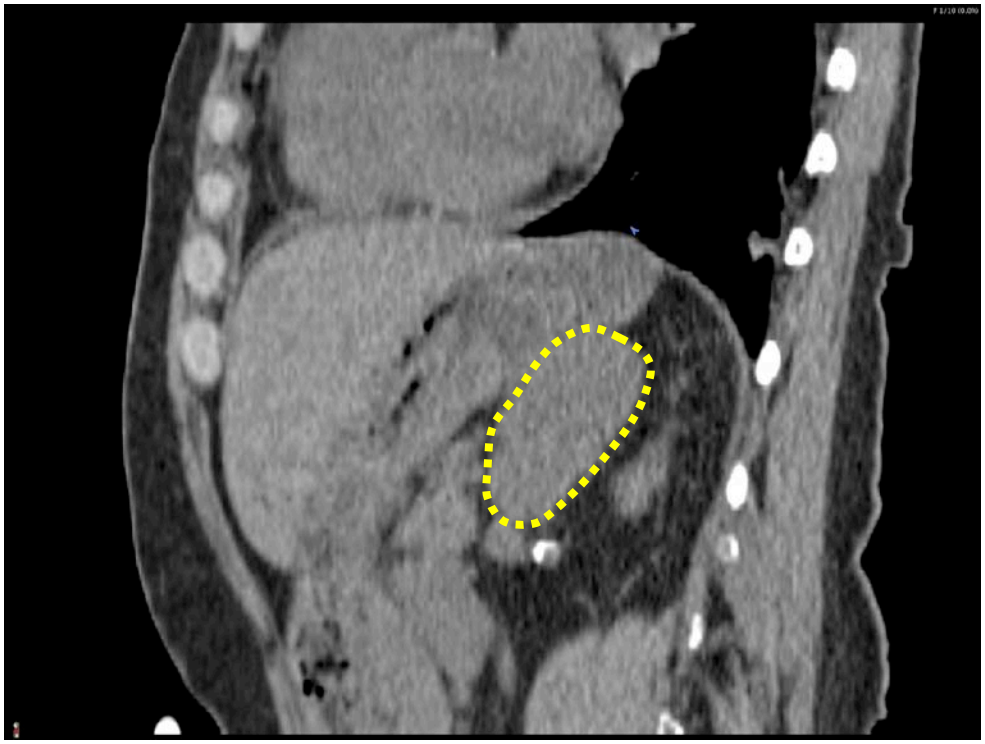
V20Gy



V95%

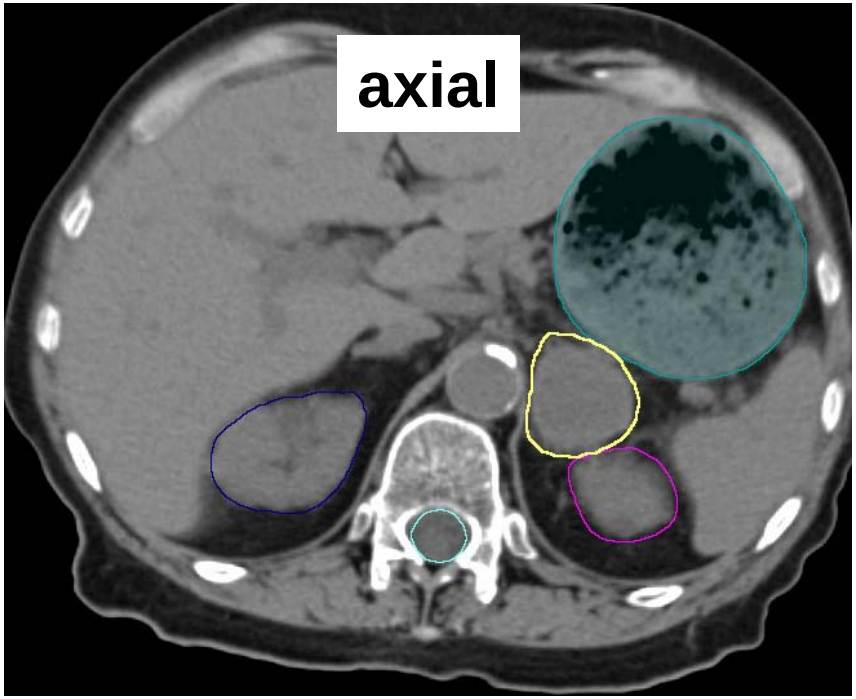
- RapidArc planning
- Fractionation: 24 x 2.75Gy

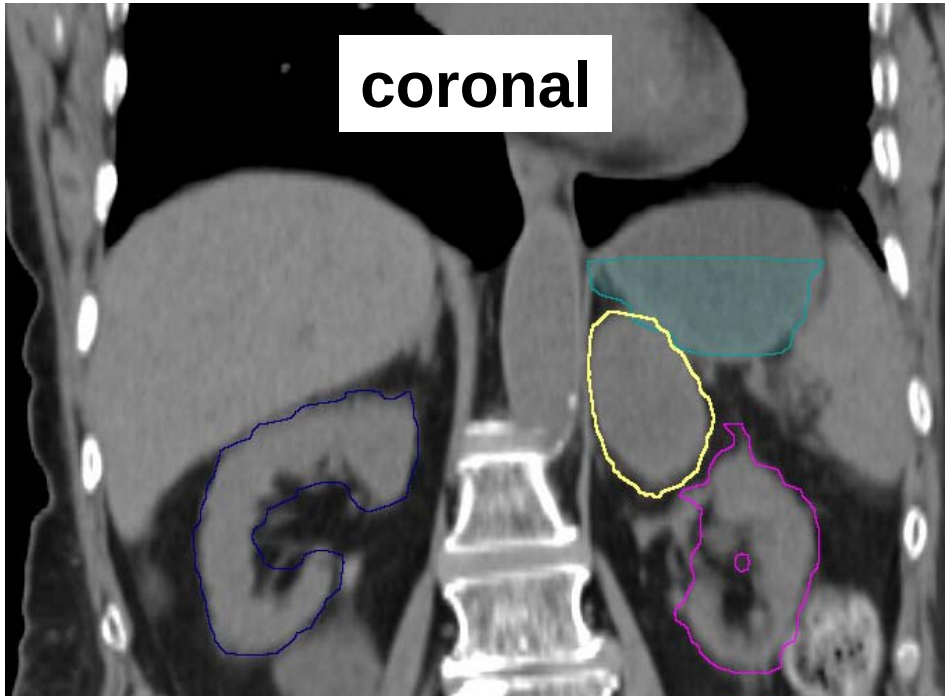
Radiotherapy planning - adrenal



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

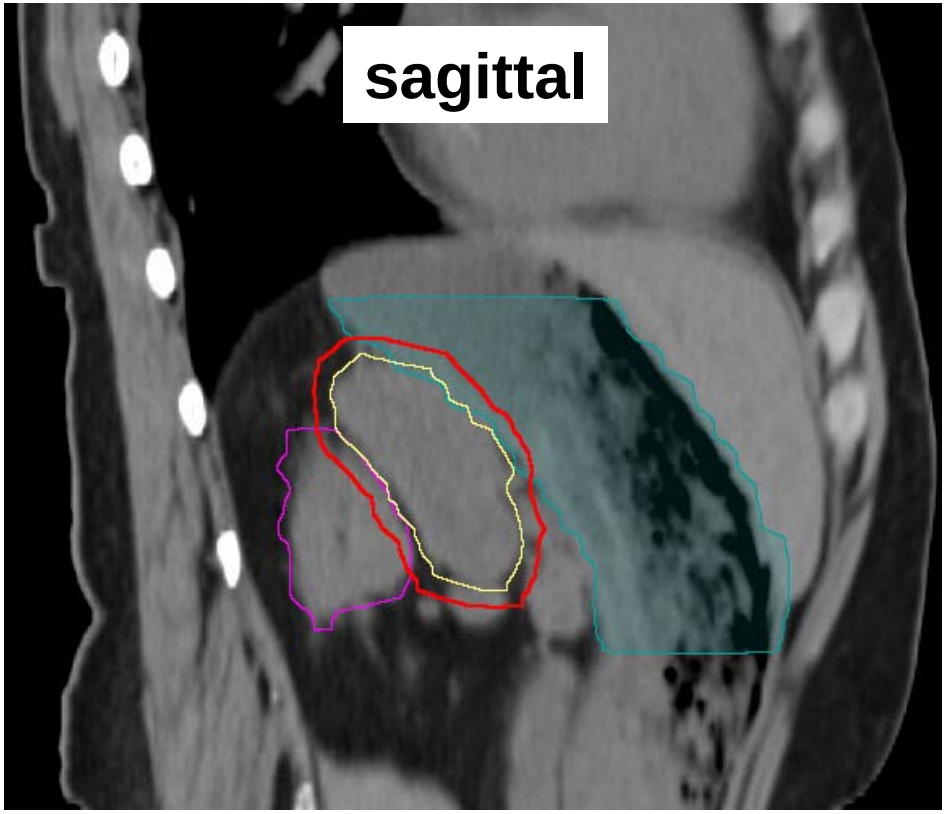
Radiotherapy planning - adrenal





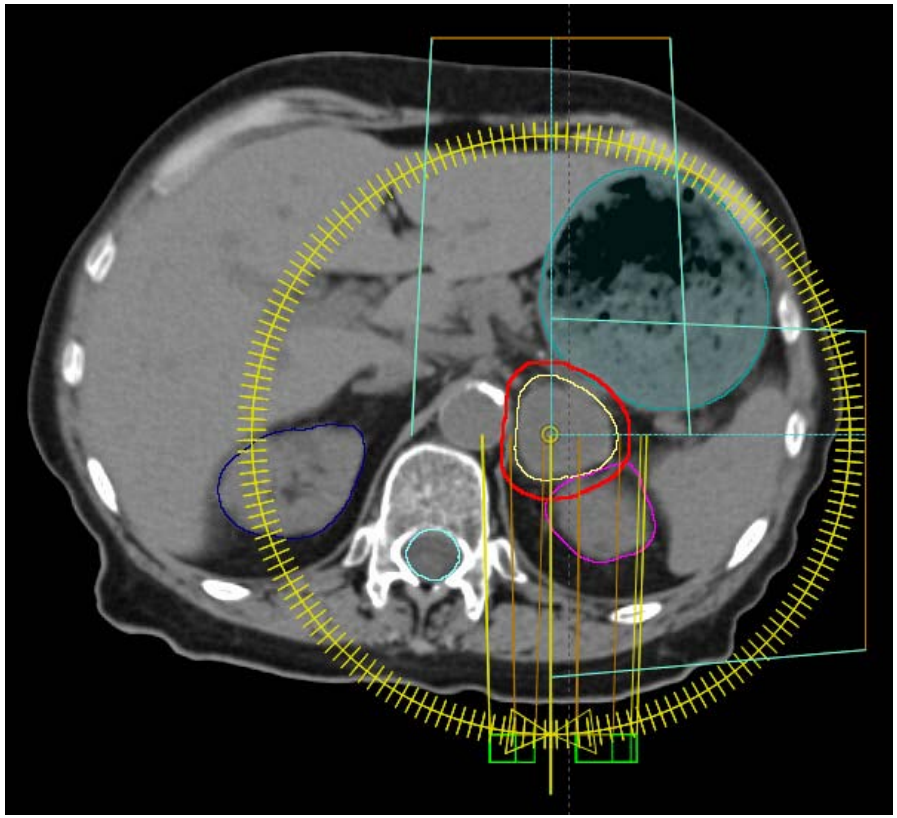
- Tumor broadly abutting stomach and left kidney
- ITV concept with 5mm ITV-to-PTV margin

Radiotherapy planning - adrenal



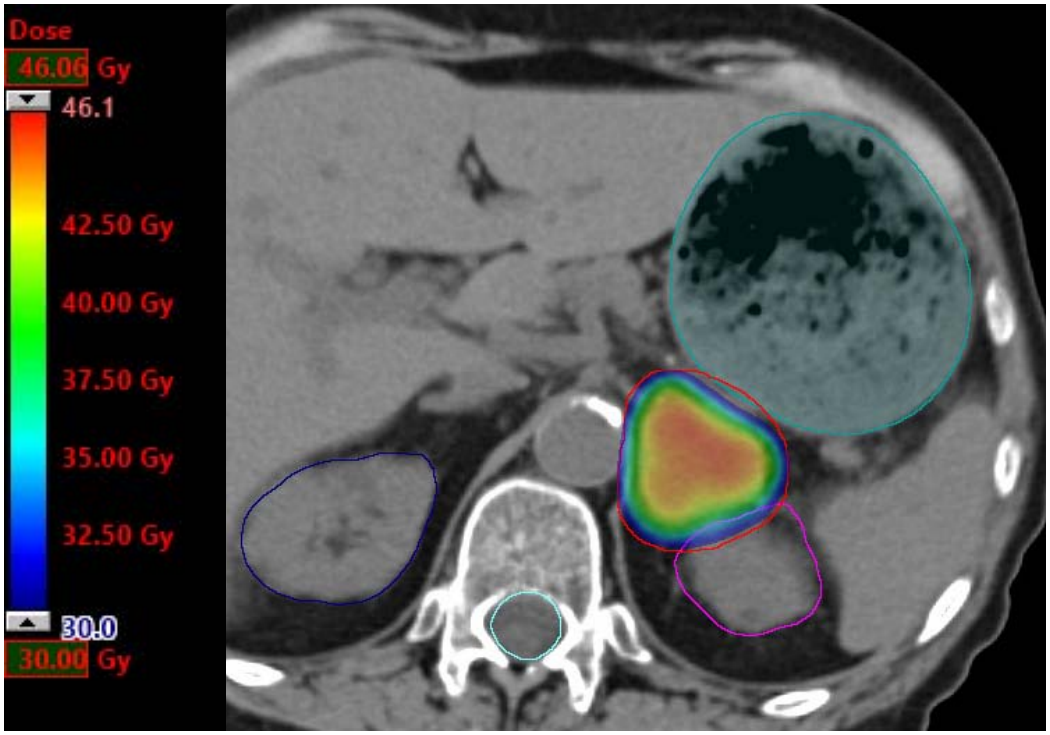
- Broad overlap between PTV, stomach and kidney

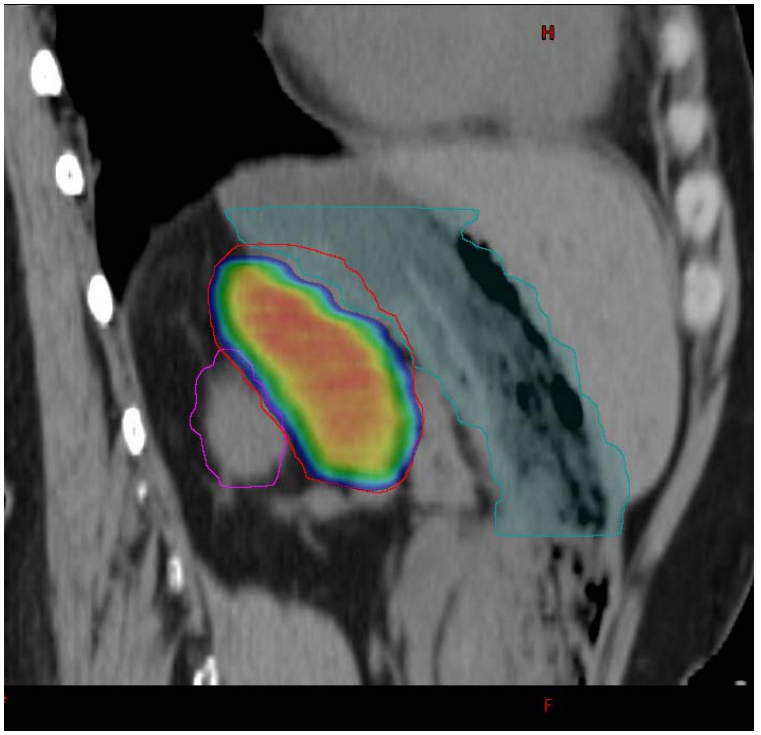
Radiotherapy planning - adrenal



- VMAT (RaidArc) planning
- 3 arcs

Radiotherapy planning - adrenal



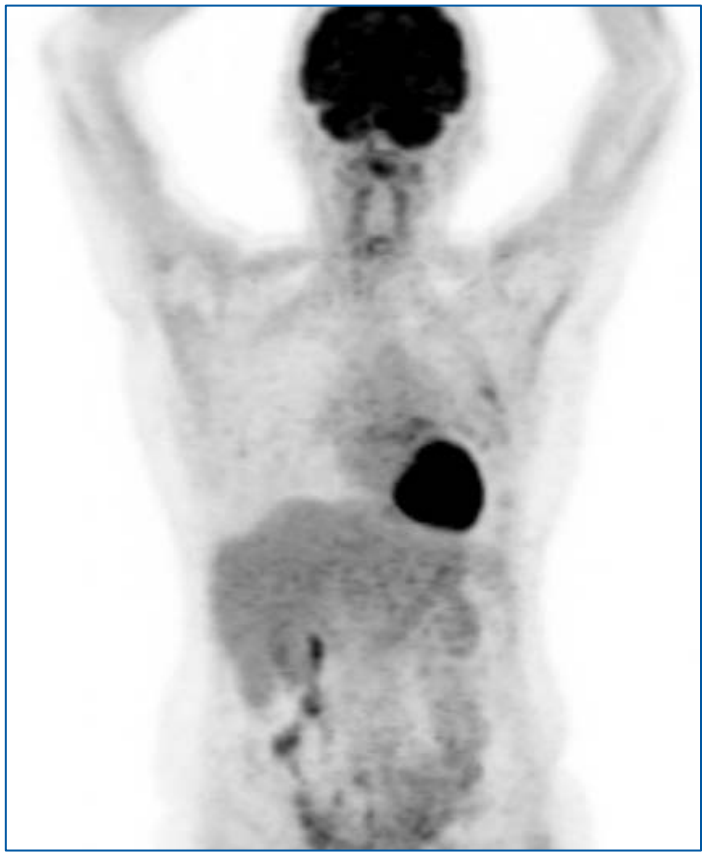


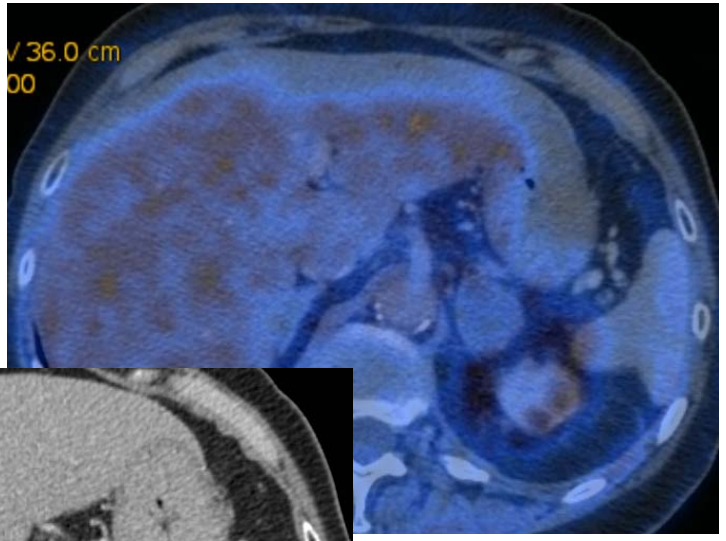
- 5 fractions of 7 Gy prescribed to 65%

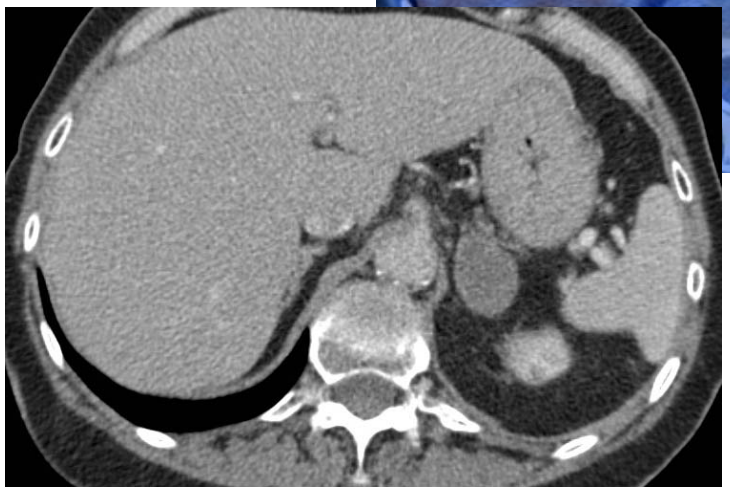
Radiotherapy planning - adrenal

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

Follow-up 3 months after Tx







- Metabolic complete response
- No systemic progression

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

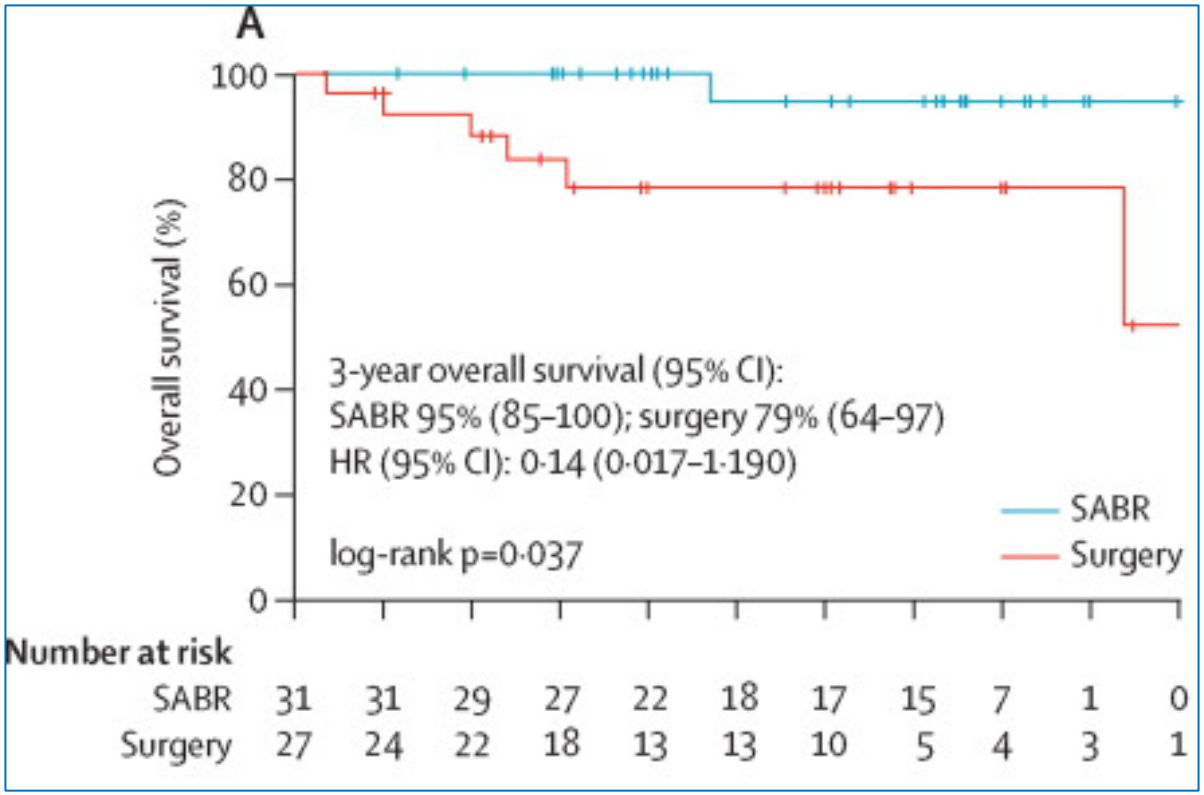
SBRT in the context of current developments in oncology

Matthias Guckenberger

UniversityHospital
Zurich

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
- Competition from minimal invasive Tx

➢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
- Competition from minimal invasive Tx

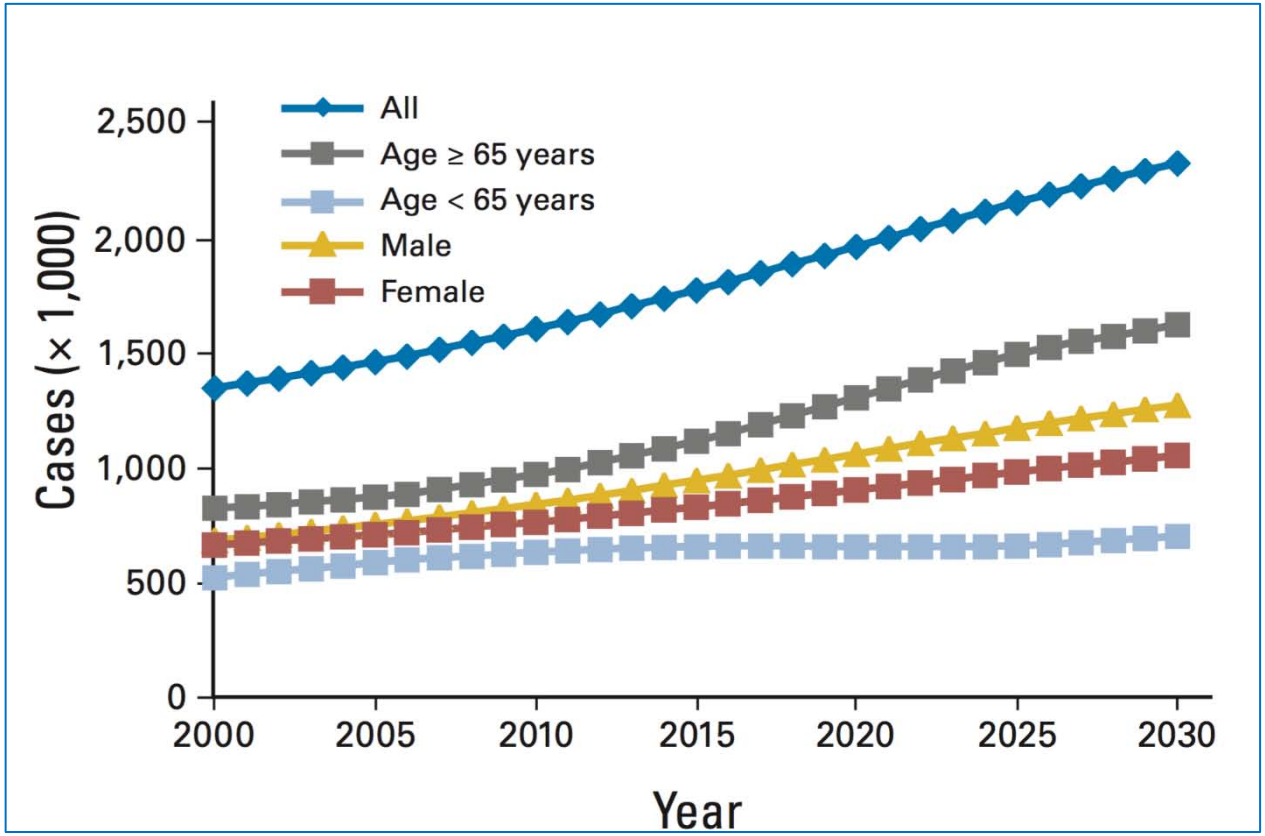
Life expectancy

	At birth
Men	+ 81
Woman	+ 85

Switzerland - Bundesamt für Statistik

- Definition of elderly > 65 years not true anymore

Development of cancer incidence rates



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

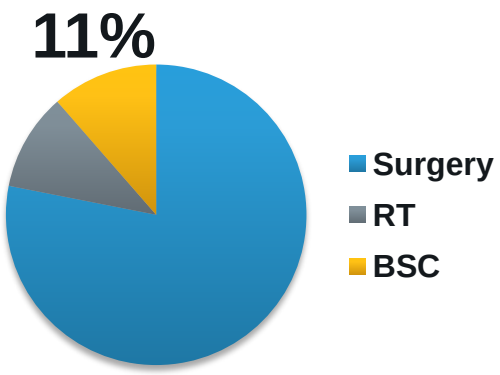
Recent randomized studies in Radation Oncology

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

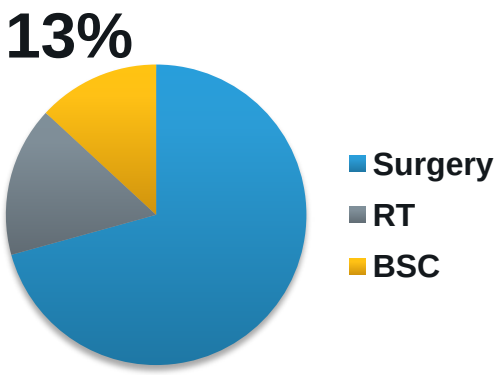
Treatment given to patients with curable stage I NSCLC

Overall population



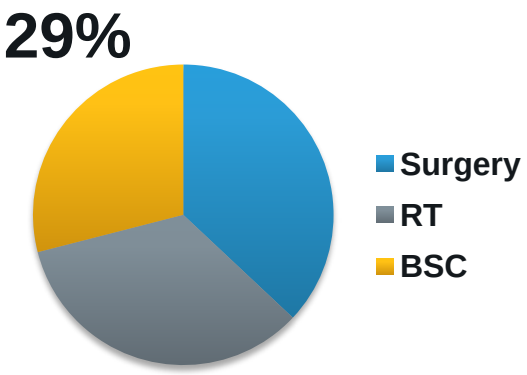
Raz Chest 2007

SEER > 65 years



Shirvani IJROBP 2012

Netherlands >75a



Haasbeek Ann Oncol 2012

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

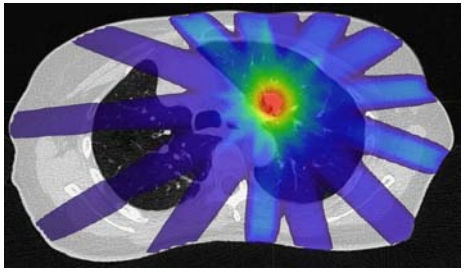
Safety & efficacy in elderly patients

	Patients	Median Age
Takeda 2013	109	83
Sandhu 2013	24	85
Haasebeek 2010	193	79

- Low mortality and morbidity despite very old age

➢ Excellent safety profile

SBRT in the context of an aging and comorbid patient population

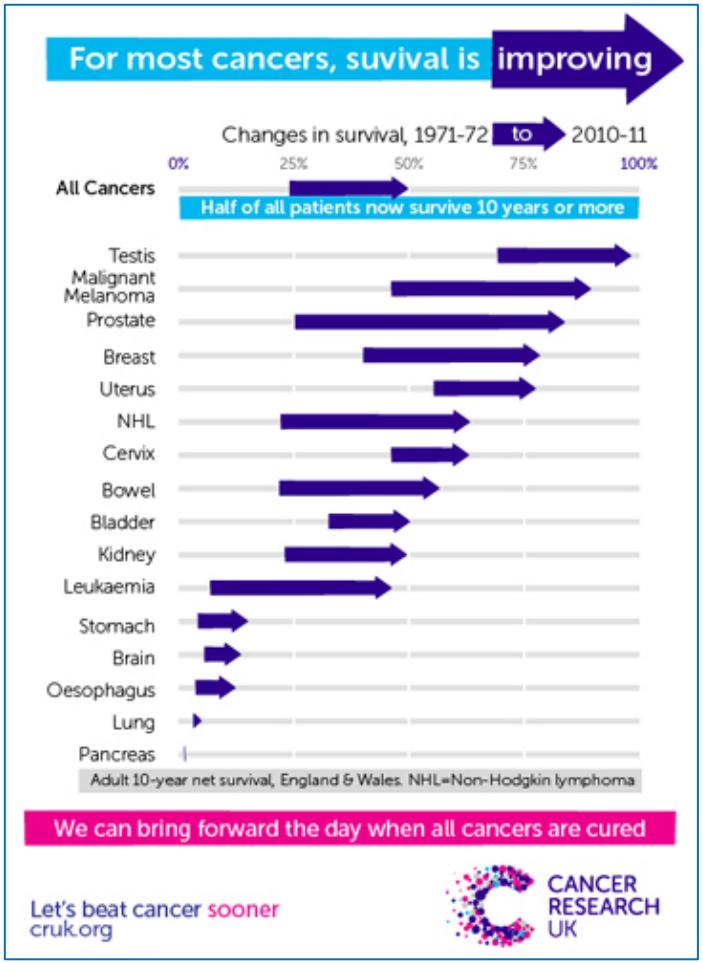


- Few fractions
- Outpatient procedure
- Non-invasive not requiring anaesthesia
- Low toxicity in small tumor distant to serial critical OARs

„Mega“ trends & challenges in Oncology

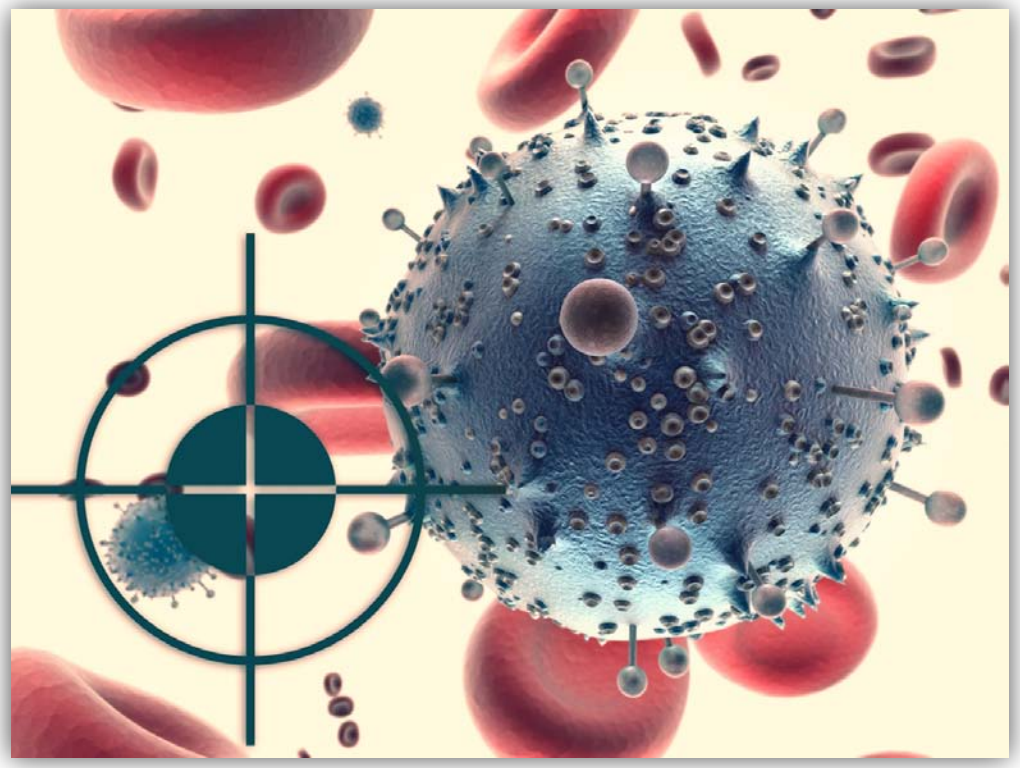
- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources
- Competition from minimal invasive Tx

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

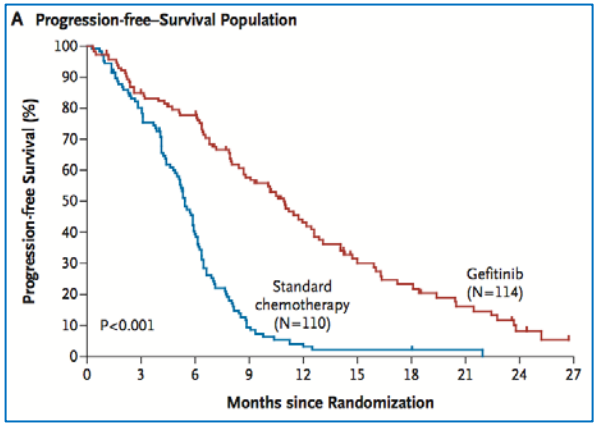
Cetuximab	Colorectal
Panatimumab	Breast
Erlotinib	Pancreas
Trastuzumab	NSCLC
Lapatinib	Glioblastoma
Bevacizumab	Kidney
Axatinib	GIST
Sorafenib	Thyroid
Sunitinib	Head & Neck
Pazopanib	
Ipilimumab	
Vandetanib	

Radio-Oncology

Cetuximab	Head & Neck

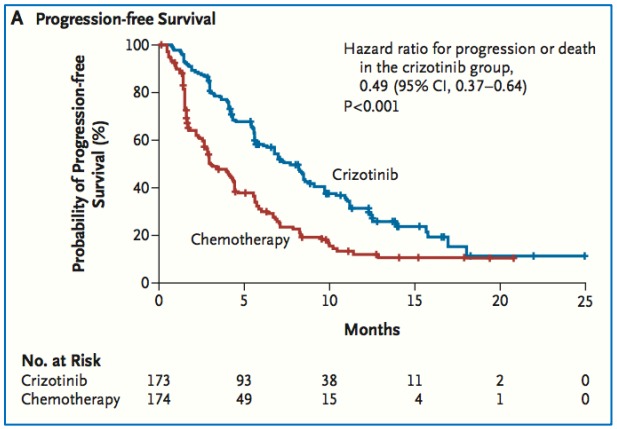
Progression under targeted systemic

Gefitinib
in mutant EGFR



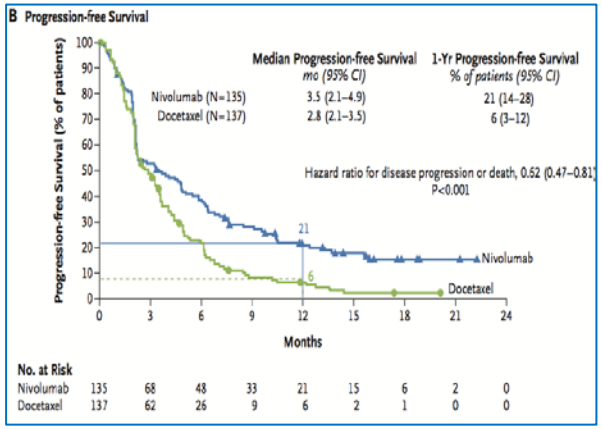
Maemondo NEJM 2010

Crizotinib
in ALK positive



Shaw NEJM 2013

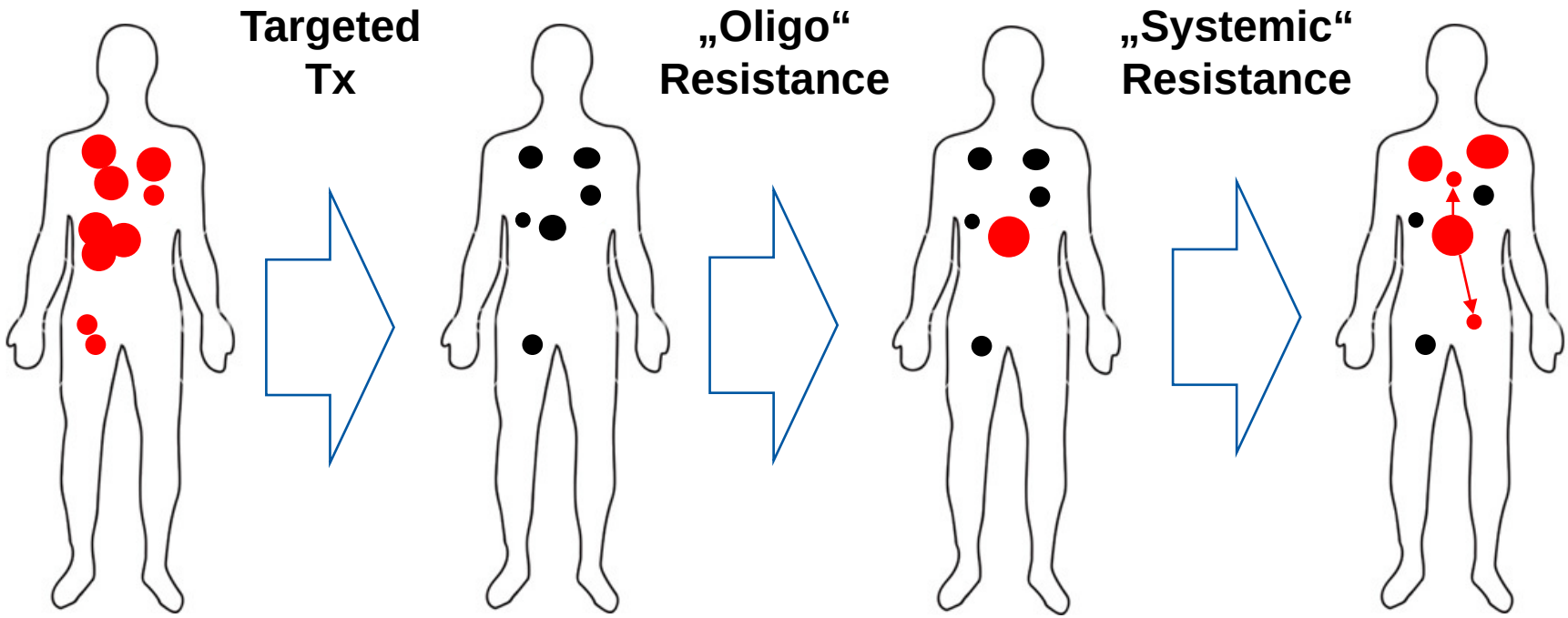
Nivolumab
in unselected patients



Brahmer NEJM 2015

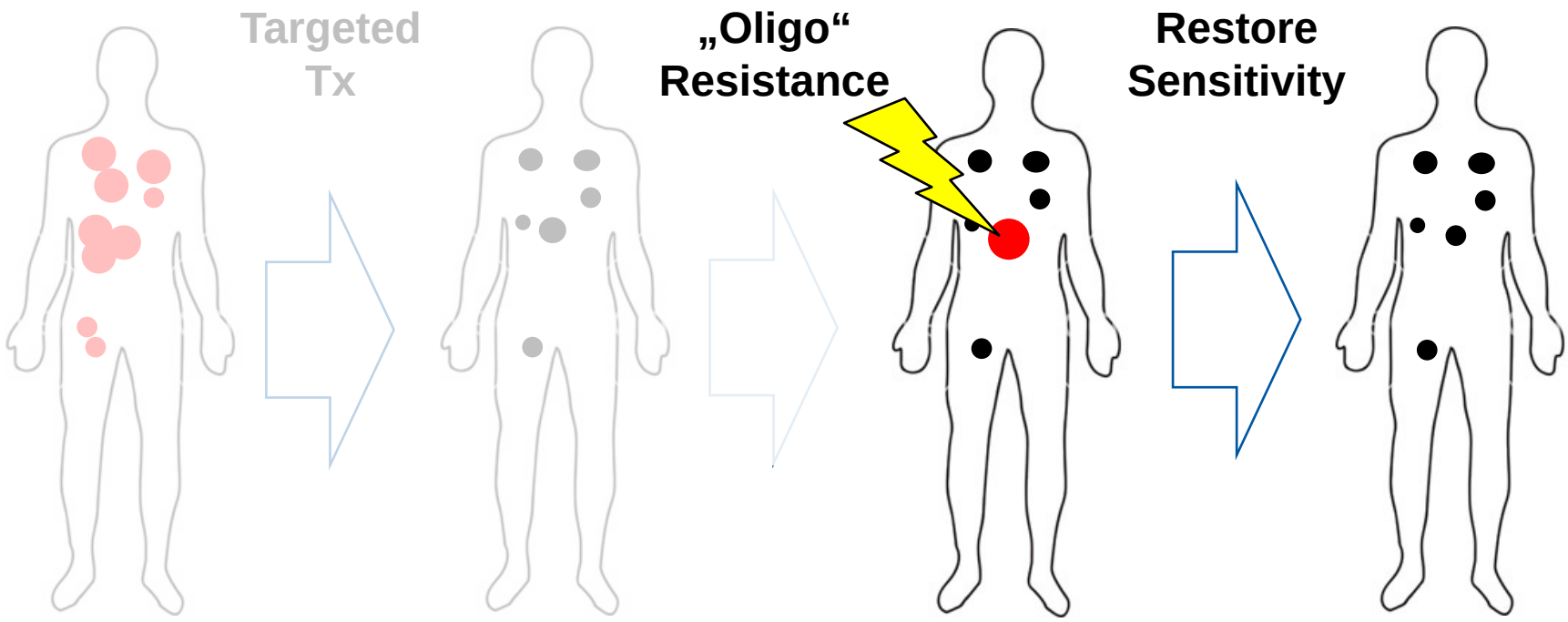
- Substantial and clinically relevant improvement
- Still: 60 – 80% develop progressive disease after 12 months

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

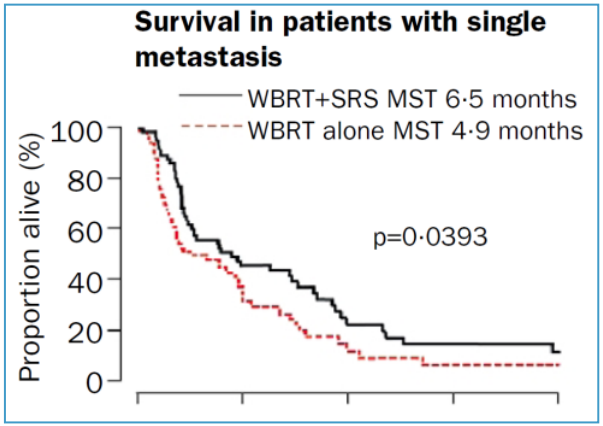
Evidence of combining SBRT & targeted drugs

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

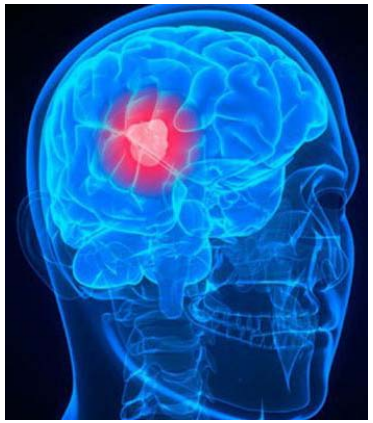
Brain metastases

Low tech
Whole brain irradiation



Andrews Lancet 2004

High tech
Radiosurgery



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

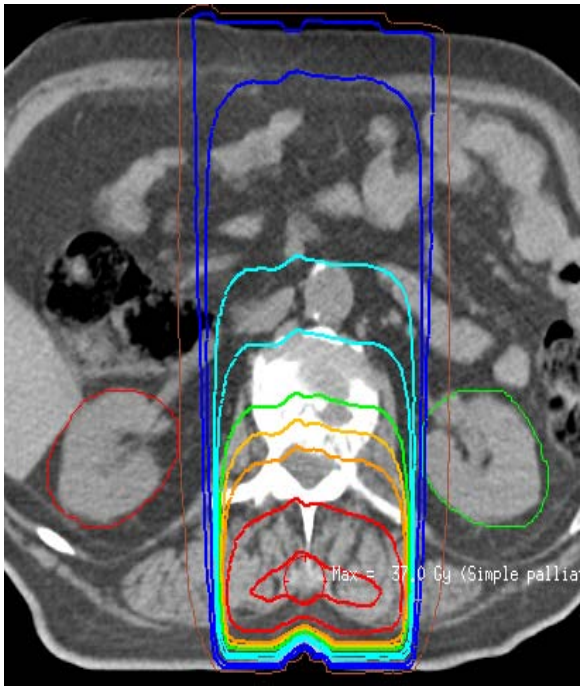
Brain metastases

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

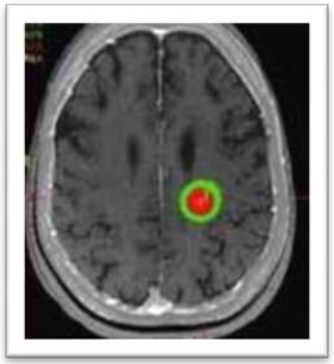
Painful bone / vertebral metastases

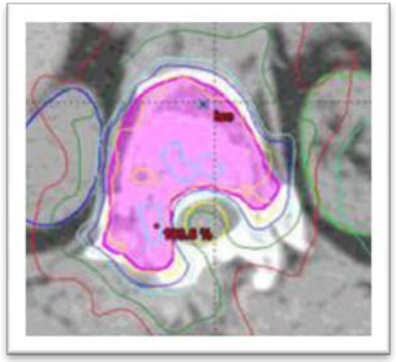


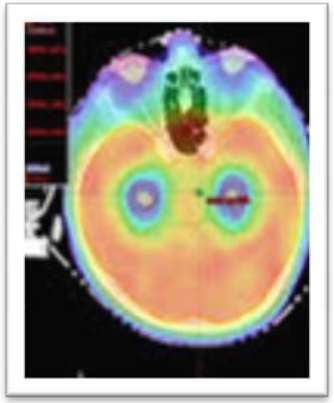
	Palliative RT	Pain response	Duration
Prince 1986	1 x 8Gy 10 x 3Gy	73% 64%	**59% @ 3 mo** **50% @ 3 mo**
Gaze 1997	1 x 10Gy 5 x 4.5Gy	84% 89%	**Median 3.5 mo** **Median 3.5 mo**
Steenland 1999	1 x 8Gy 6 x 4Gy	72% 69%	**Median 5 mo** **Median 6 mo**
Roos 2005	1 x 8Gy 5 x 4Gy	61% 53%	**Median 3.5mo** **Median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

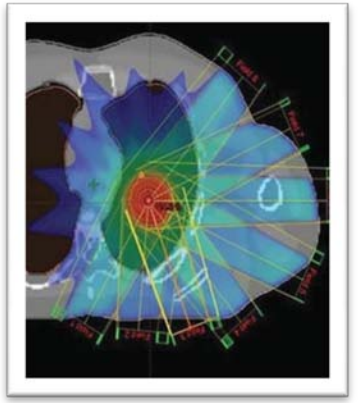
- Conventional radiotherapy = Short term palliation
  - ➢ Patients with better OS will develop pain recurrence

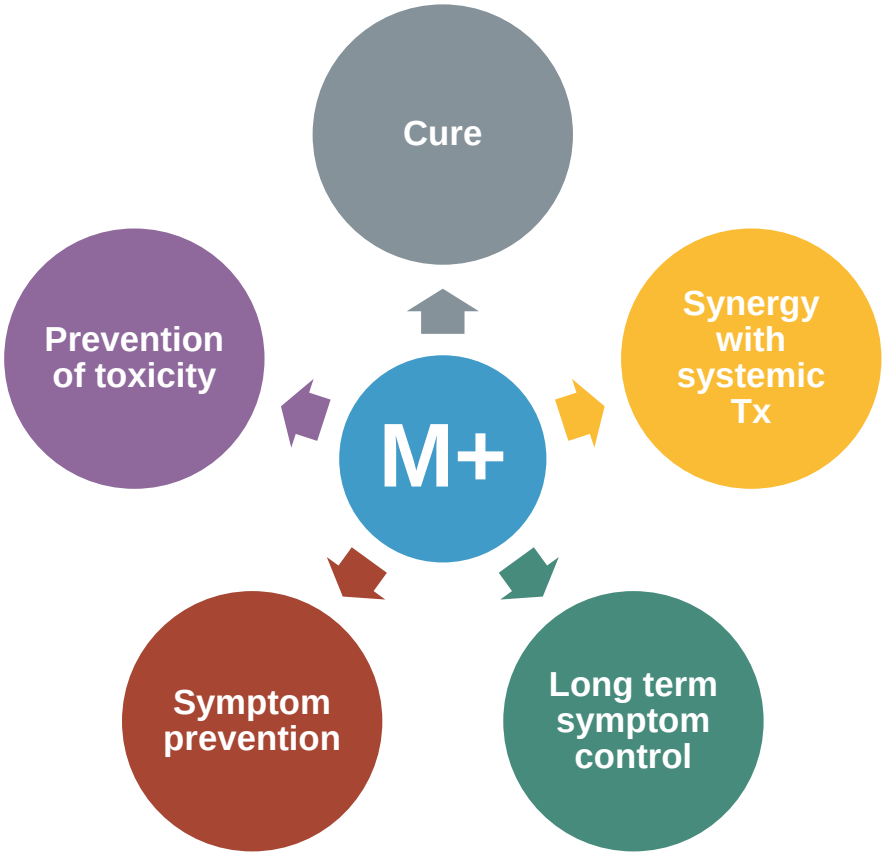
Goals of high-tech RT in the metastatic setting









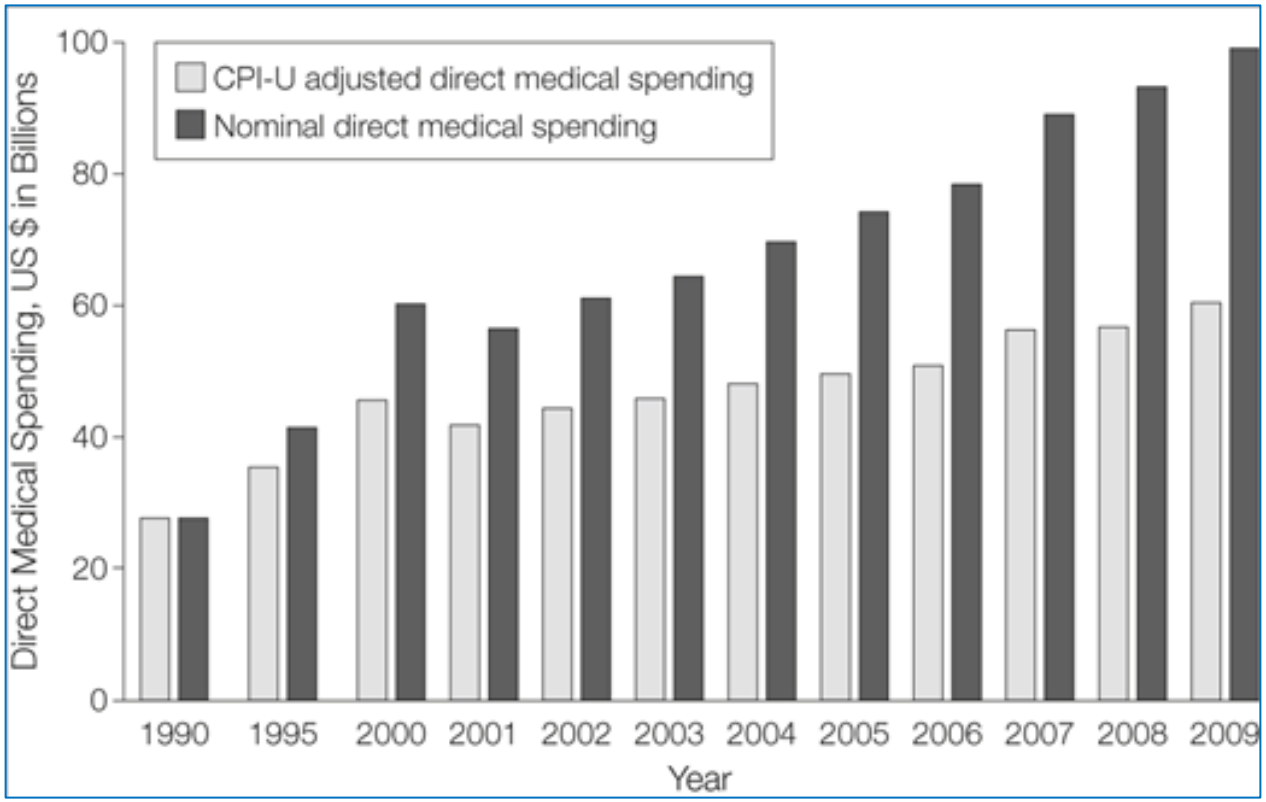


„Mega“ trends & challenges in Oncology

- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources
- Competition from minimal invasive Tx

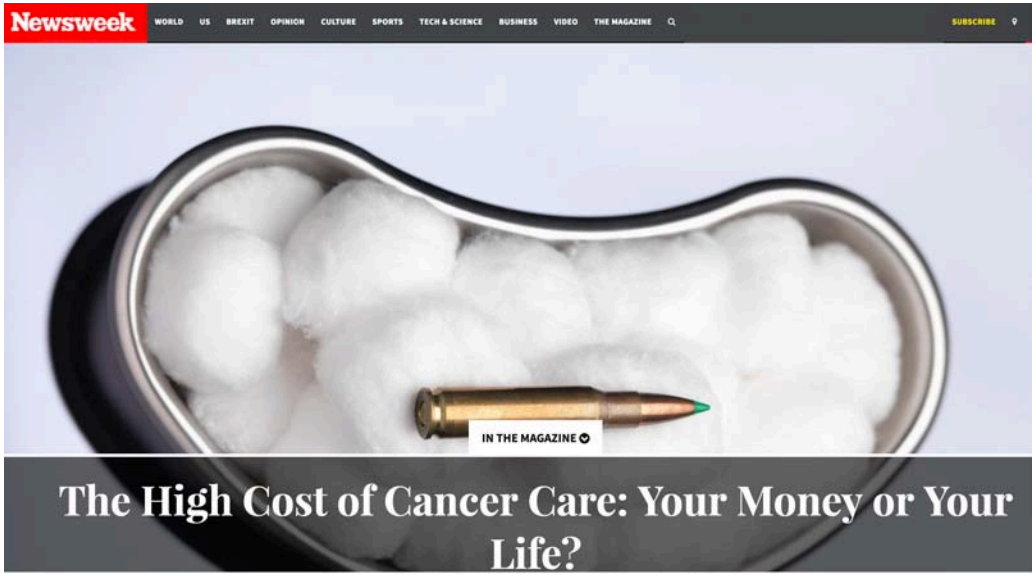
Health care spending on cancer care

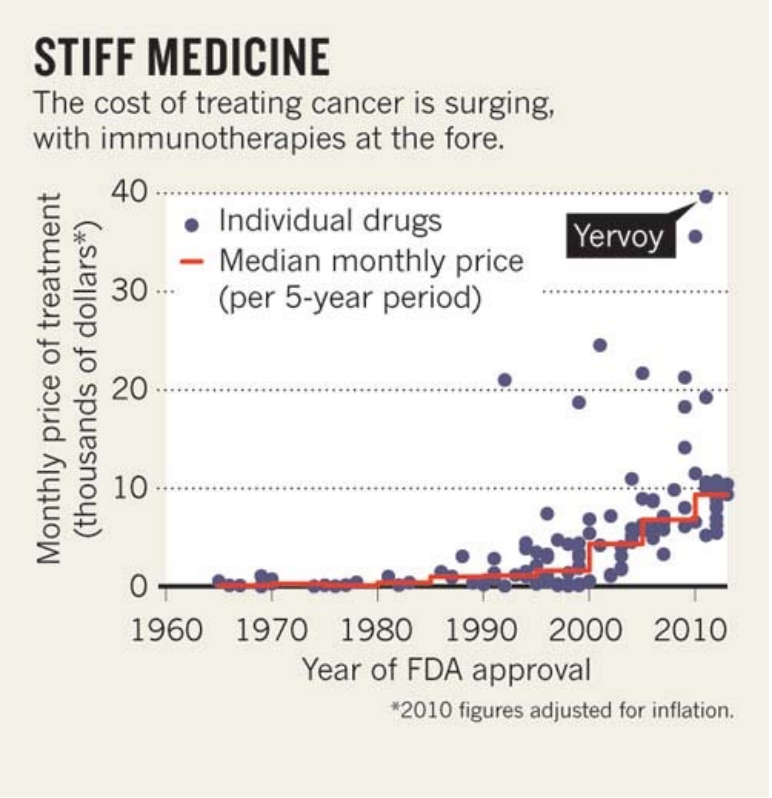
Elkin JAMA 2010



- Continuous and above-inflation increase of cancer care costs

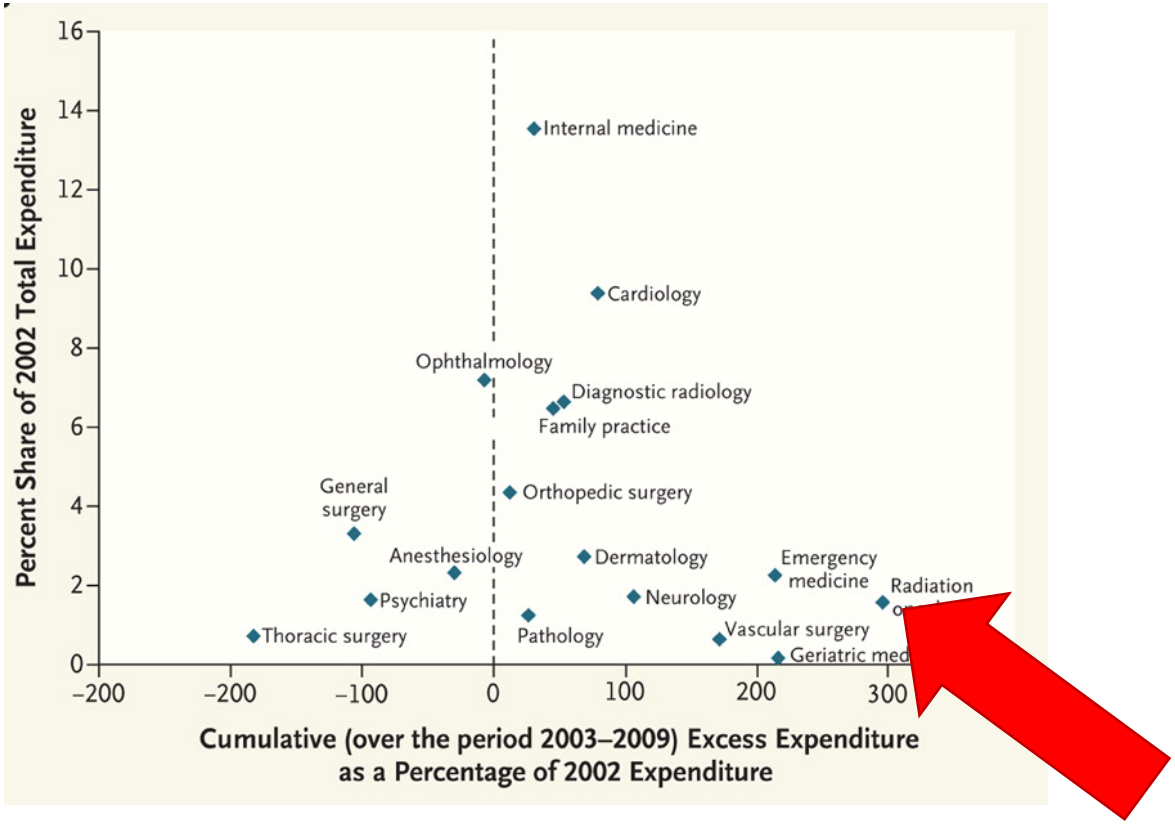
Health care spending on cancer care





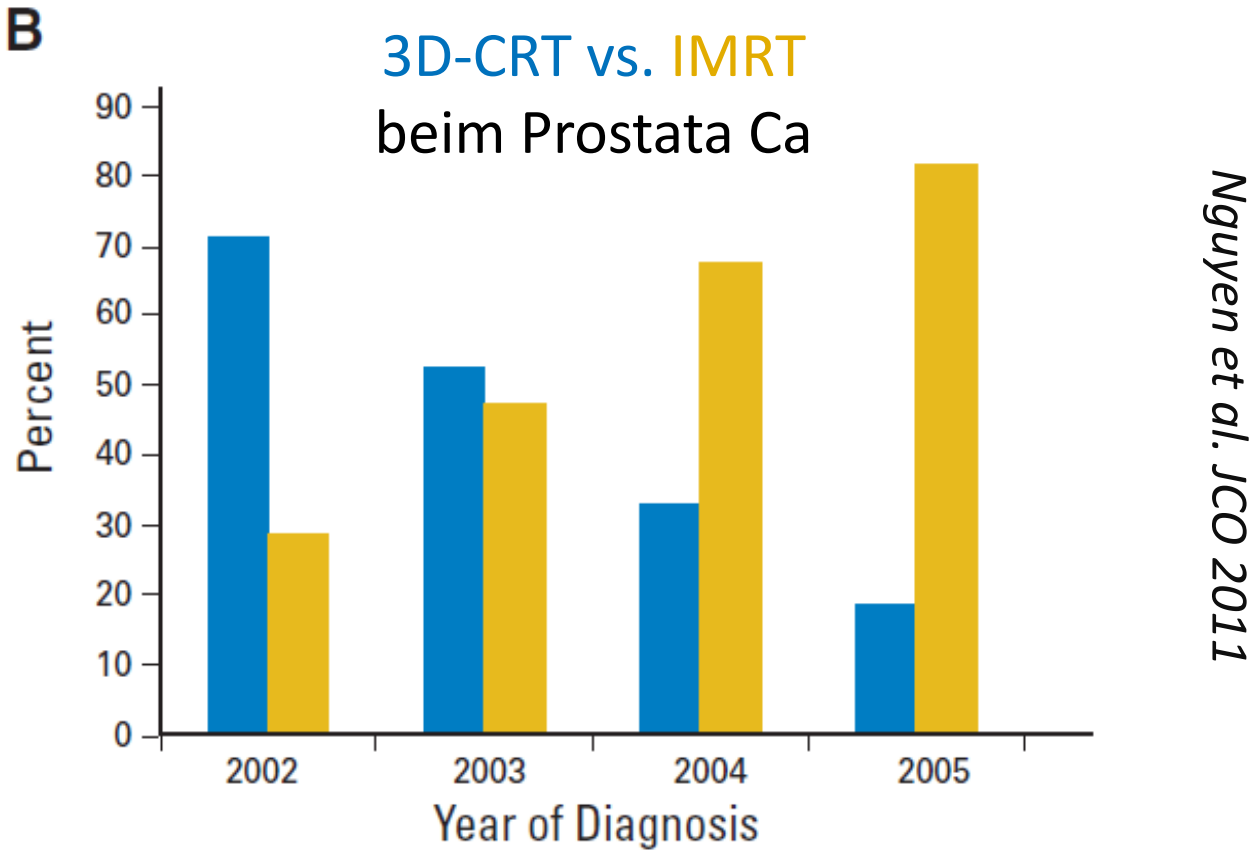
- Excessive prices for modern cancer drugs

Increase in costs caused by discipline



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

The IMRT and prostate story ...



Nguyen et al. JCO 2011

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

Protons

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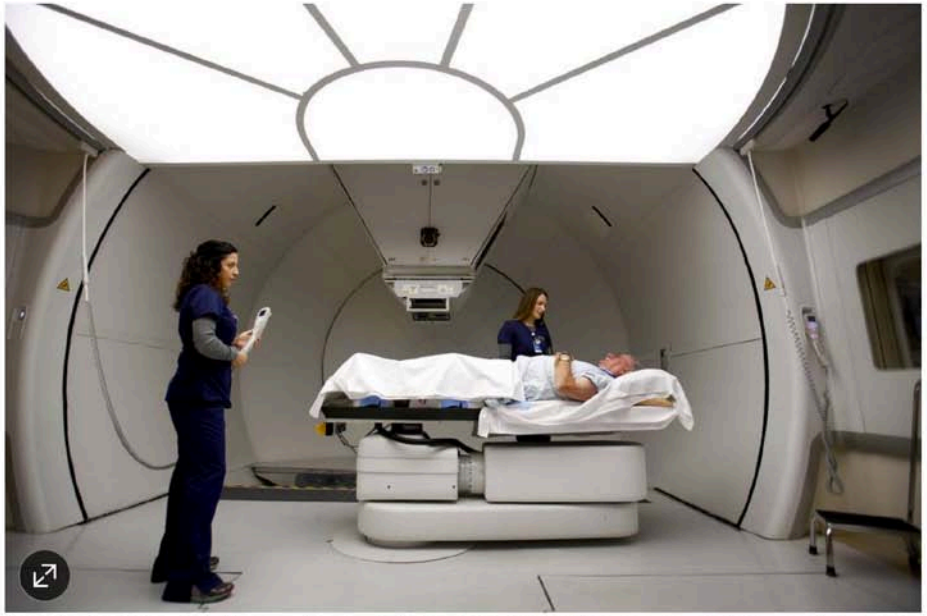
BUSINESS

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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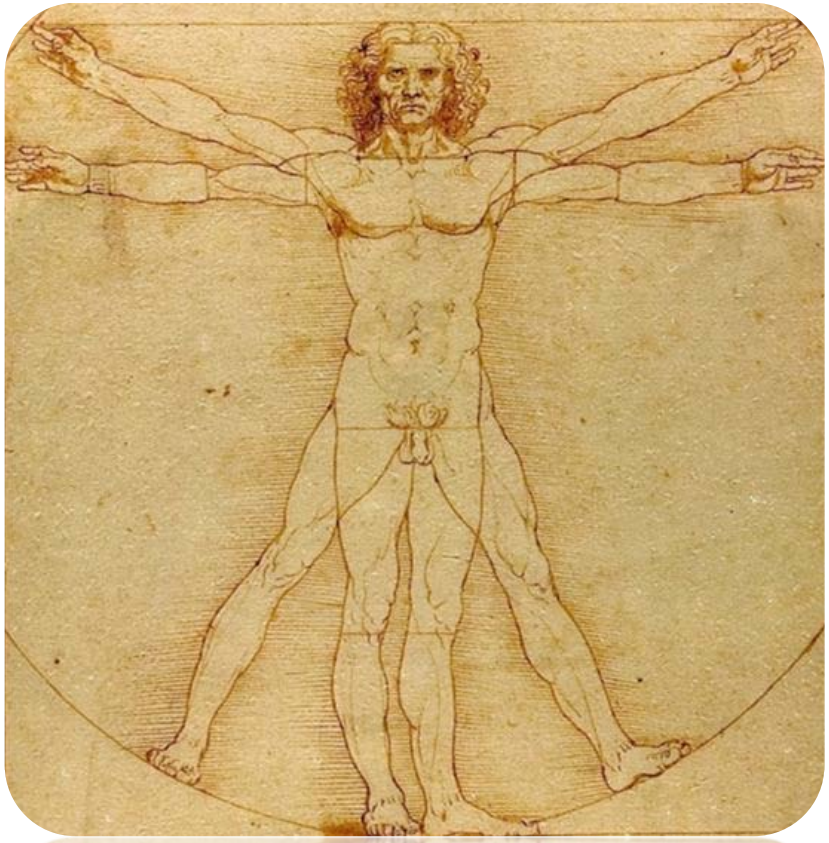
Potential application of SBRT

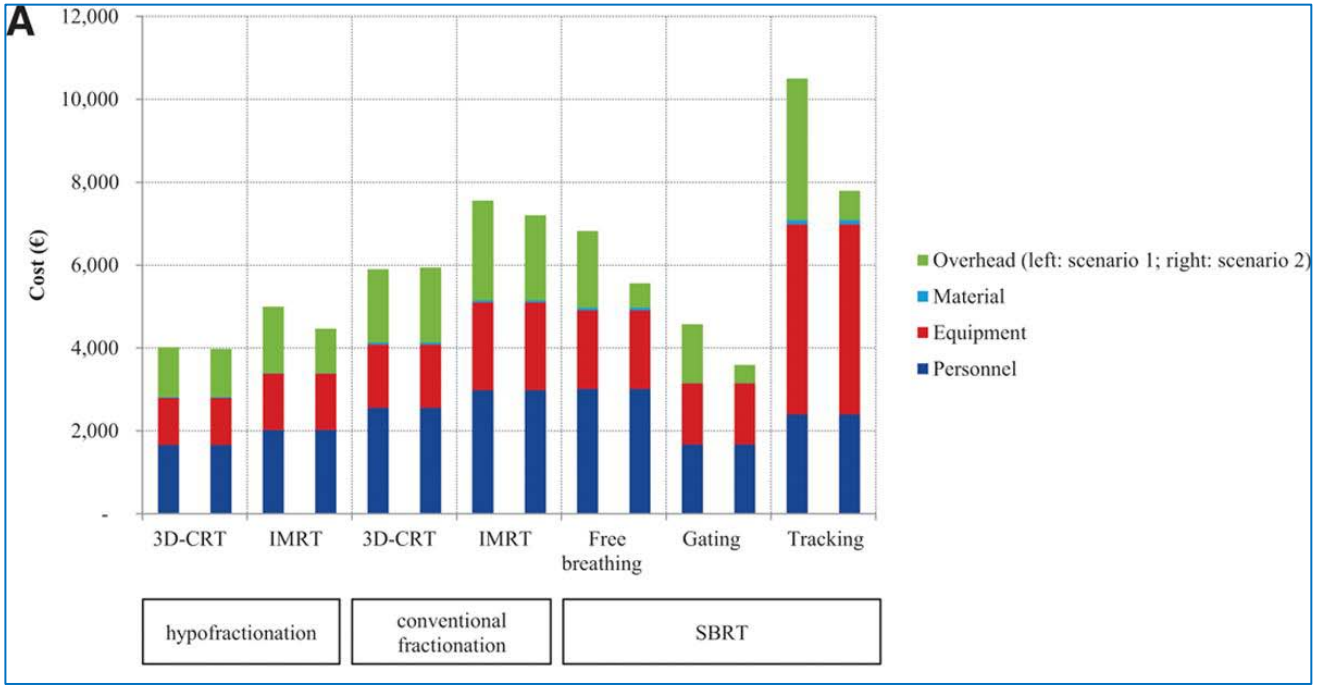


Brain metastases
Primary brain tumors
Recurrent head & neck
Breast Cancer
Primary lung cancer
SBRT for locally advanced NSCLC
Lung metastases
Spine SBRT
Primary liver cancer
Liver metastases
Pancreatic cancer
Lymph node metastases
Prostate cancer
Cervical cancer
...

Costs (not reimbursement) of SBRT

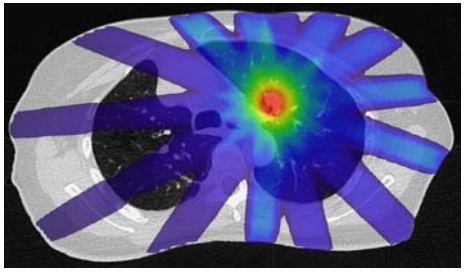
- Time-driven activity-based costing model
- 10 Belgian radiotherapy centers

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



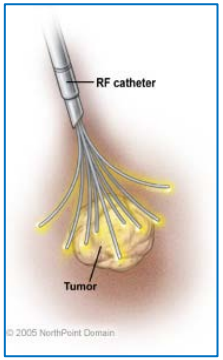
- Costs for radiotherapy / new technologies have increased substantially
- Costs of SBRT are highly dependent on
  - Technology
  - Staffing

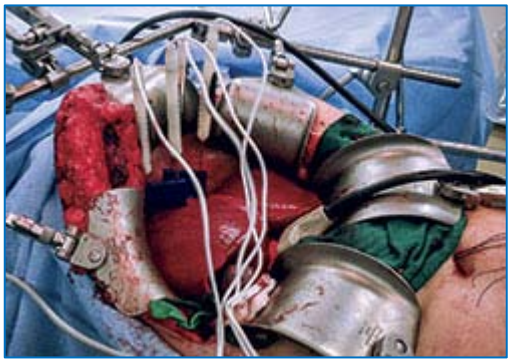
➢ Potential to achieve LOWER costs than conventional radiotherapy

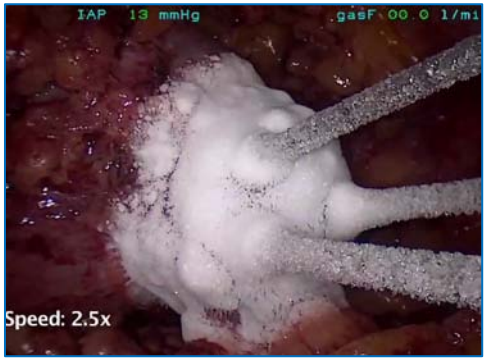
„Mega“ trends & challenges in Oncology

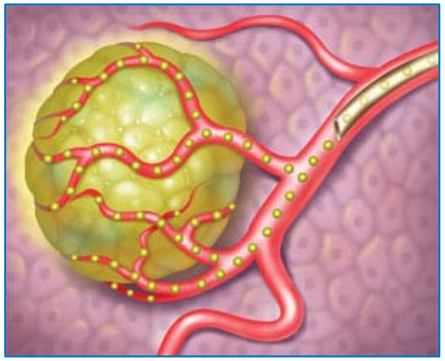
- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources
- Competition from minimal invasive Tx

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”

CONCLUSIONS

- 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

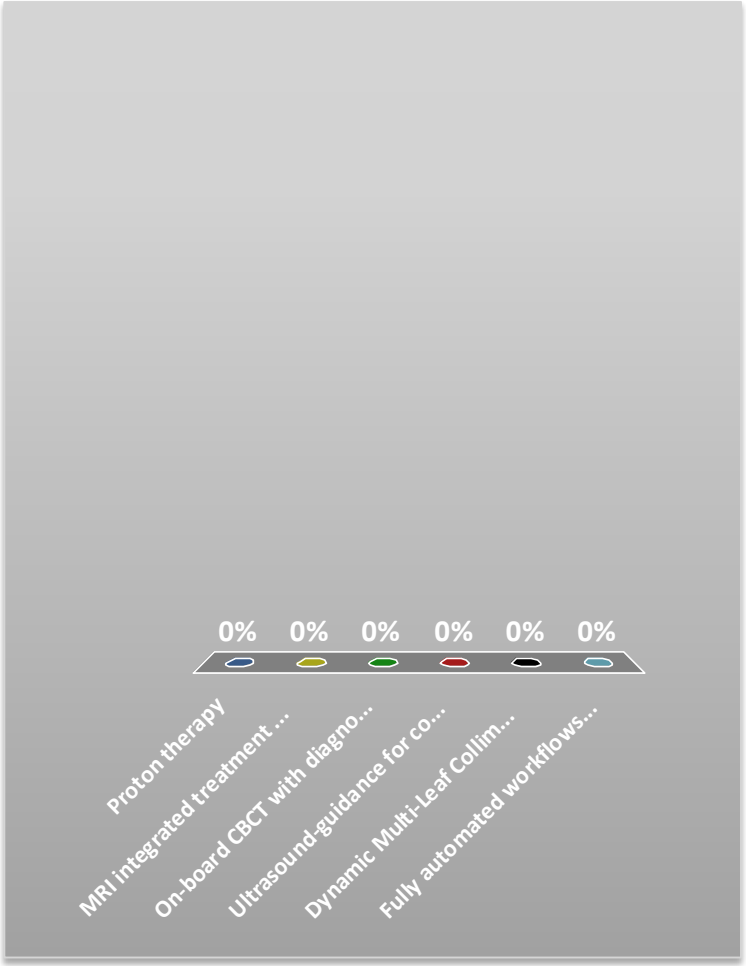
Mischa Hoogeman

Outline

- Describe upcoming technologies and discuss the impact on SBRT
  - Proton therapy
  - Technology for improved image-guidance and correction
  - Automated SBRT workflows

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

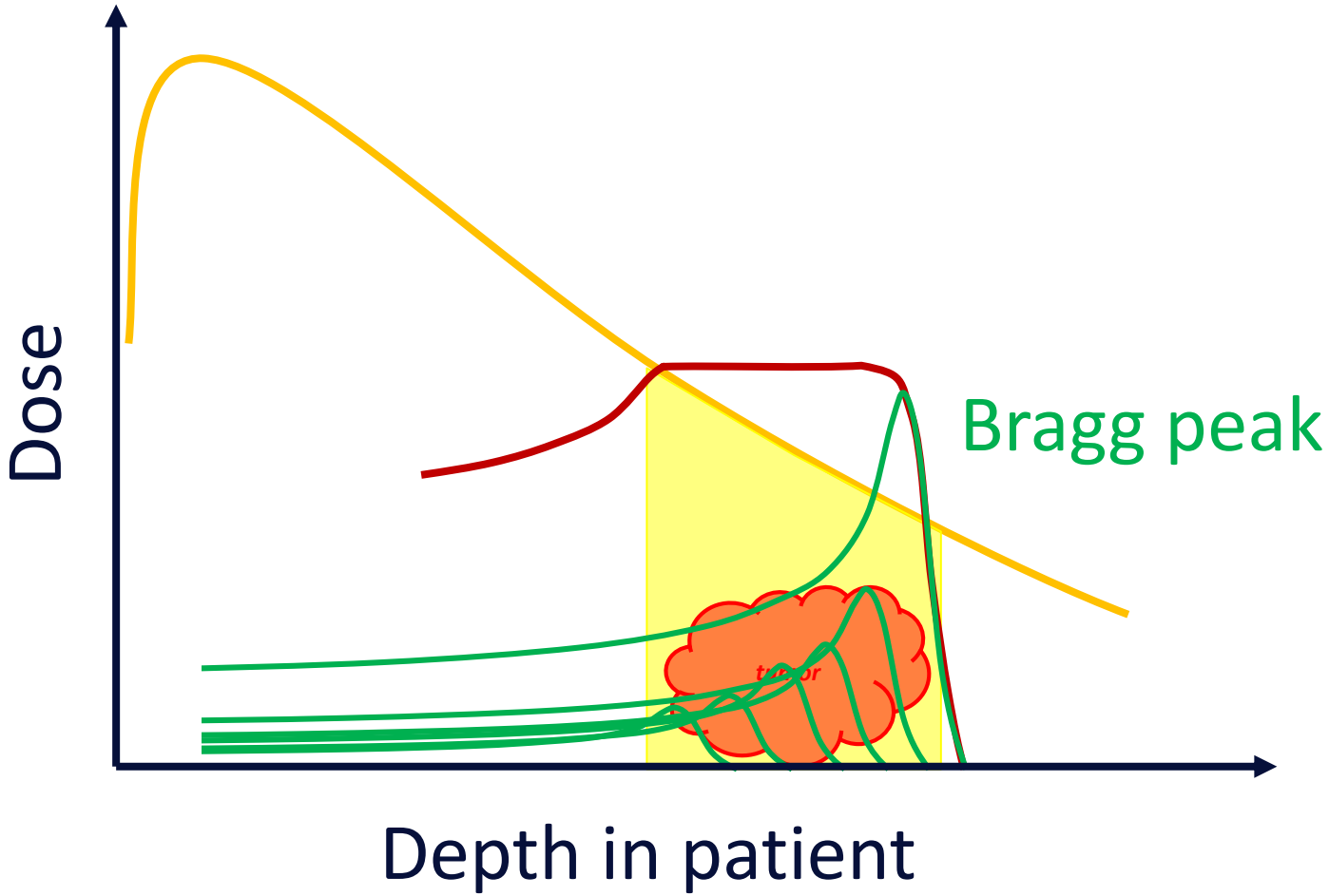
A. Proton therapy
B. MRI integrated treatment units
C. On-board CBCT with diagnostic image-quality
D. Ultrasound-guidance for cost-effective radiation therapy
E. Dynamic Multi-Leaf Collimator
F. Fully automated workflows (single push button treatments, one stop shops)



PROTON THERAPY

Erasmus MC Cancer Institute

How to Improve Precision?



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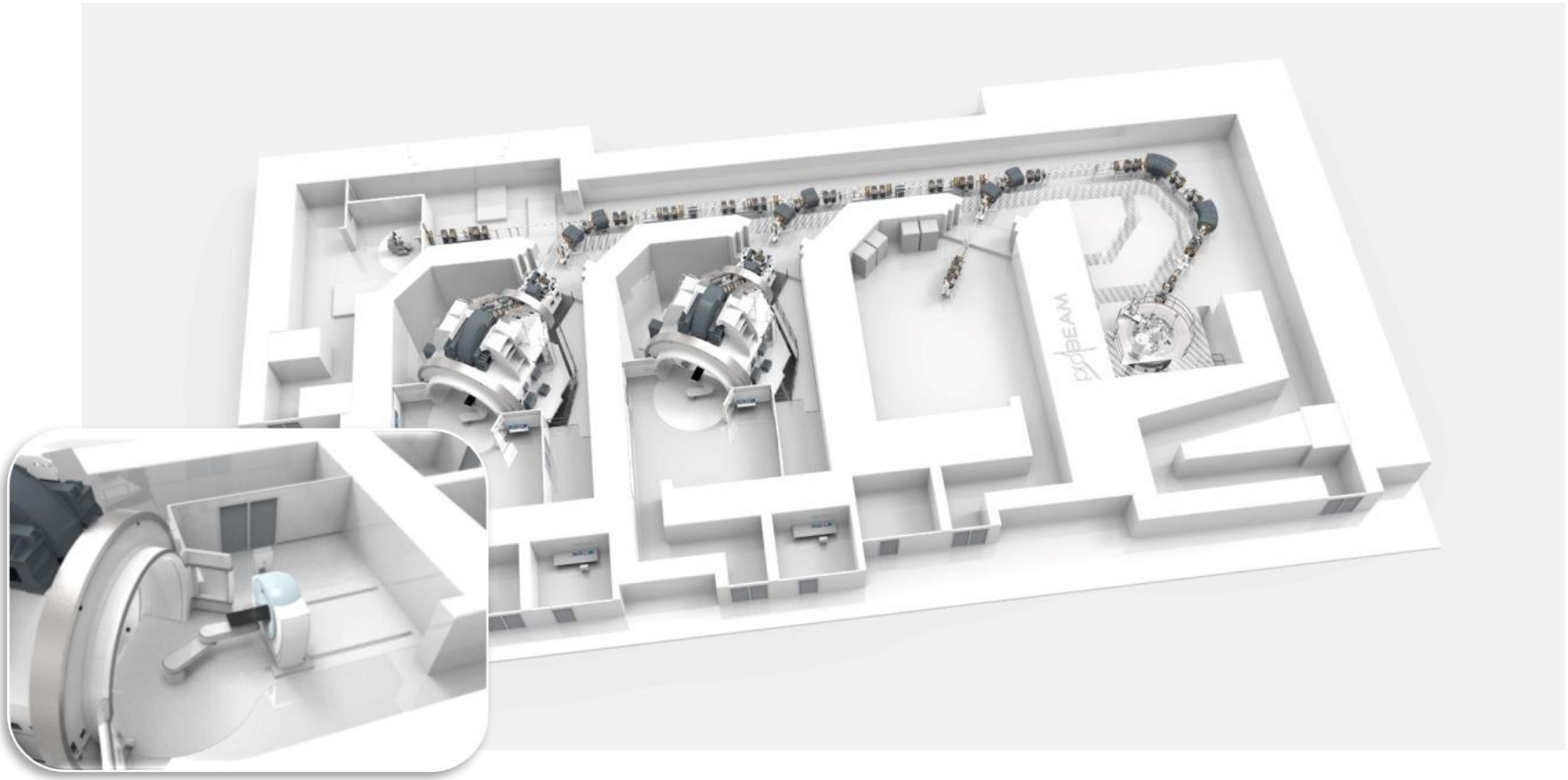
Proton Therapy



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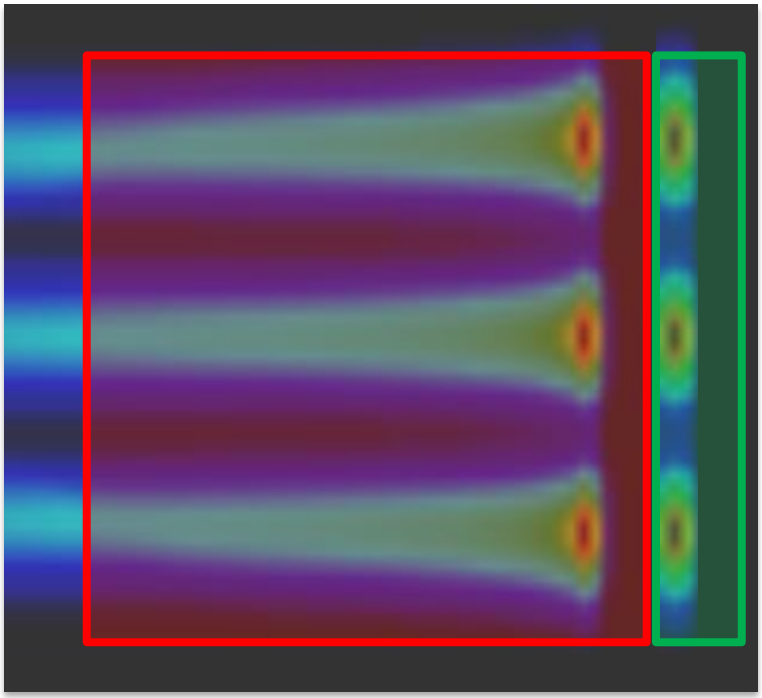
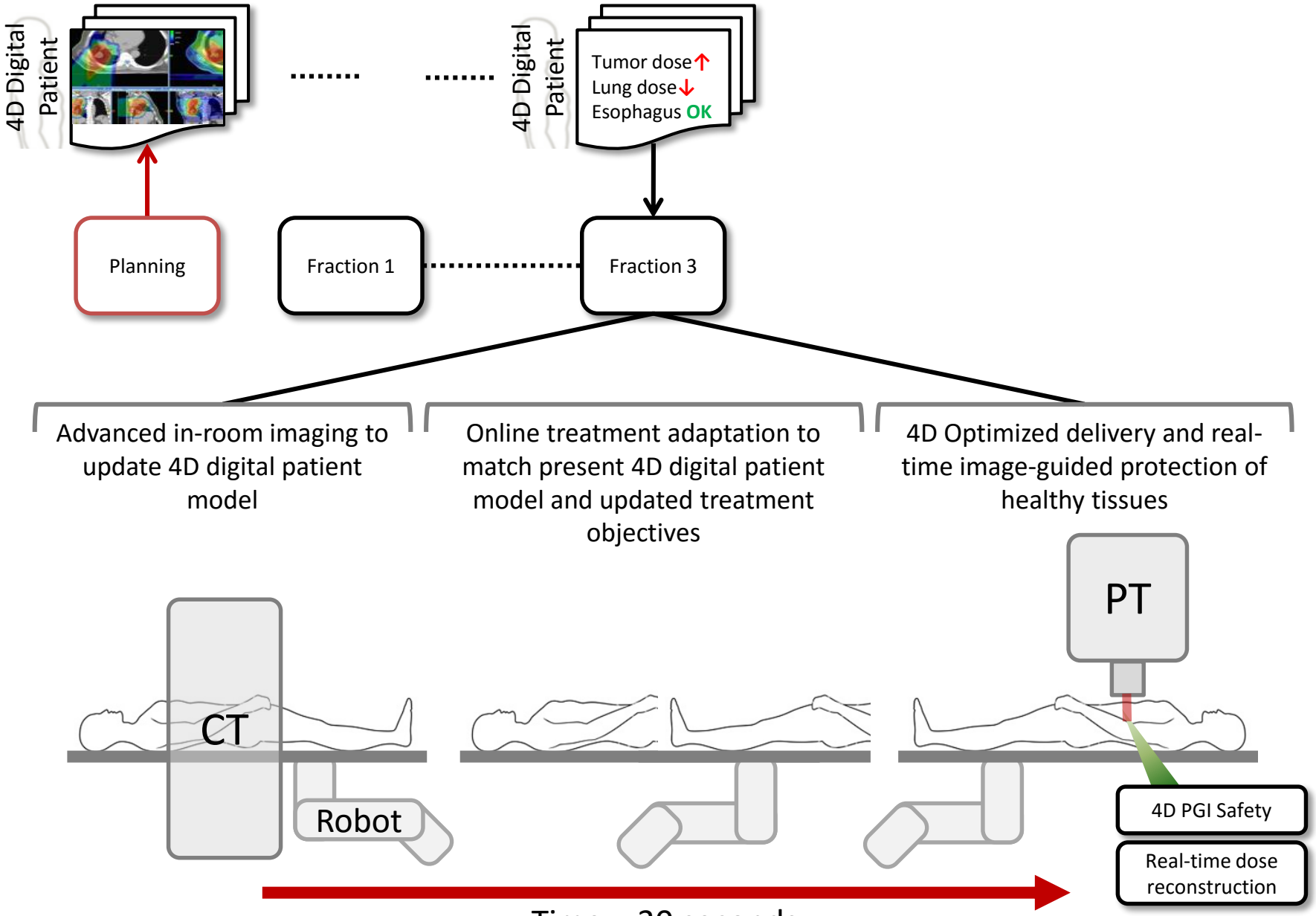
Protons Stop, But Where?

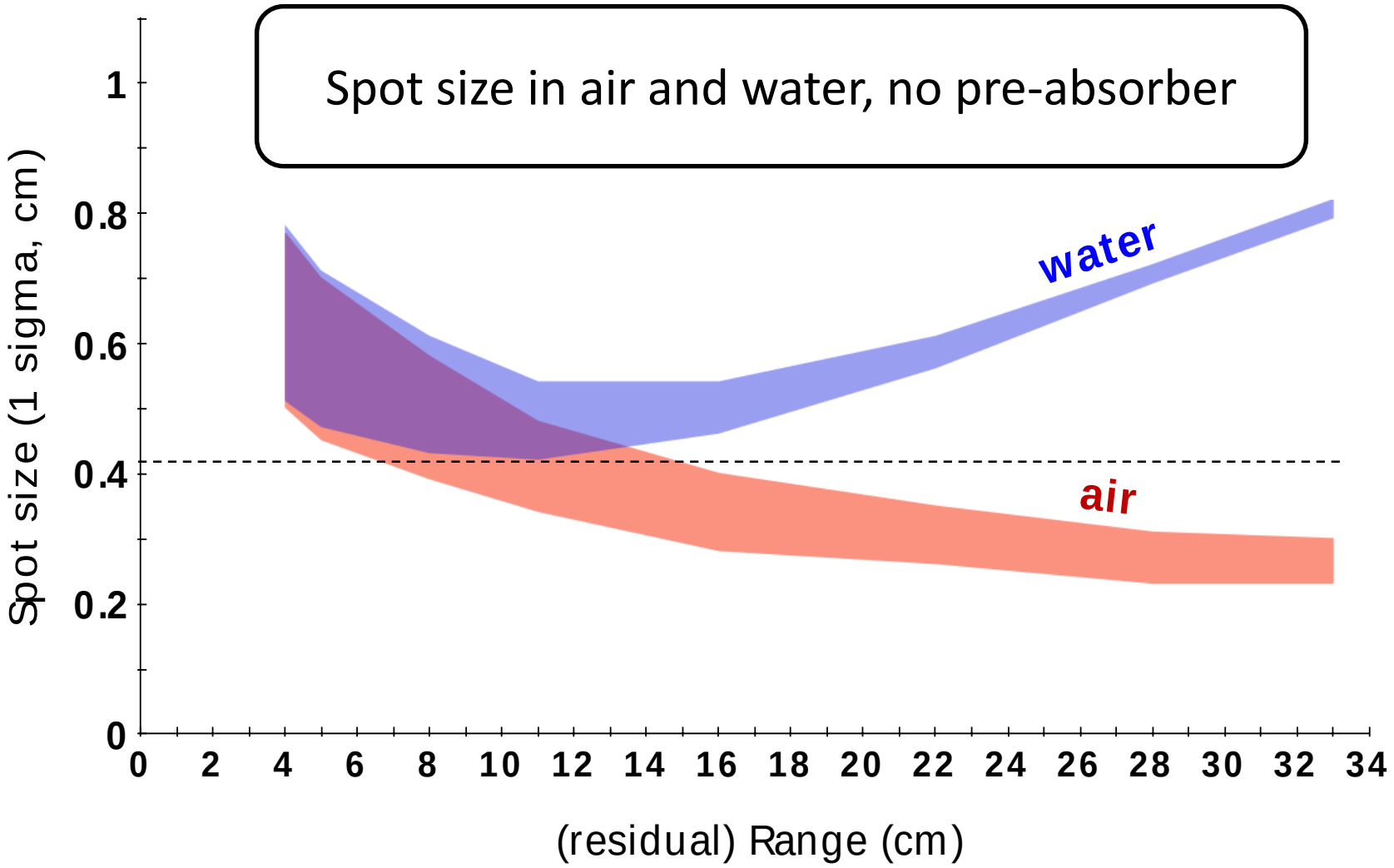


- Dose calculation uncertainties (stopping power)
- Patient setup variation that induce range errors
- Internal organ motion (interplay effects)
- Anatomical changes


4D Digital Patient
4D Digital Patient
Tumor dose ↑
Lung dose ↓
Esophagus OK
Planning
Fraction 1
Fraction 3
Advanced in-room imaging to update 4D digital patient model
Online treatment adaptation to match present 4D digital patient model and updated treatment objectives
4D Optimized delivery and real-time image-guided protection of healthy tissues
CT
Robot
PT
4D PGI Safety
Real-time dose reconstruction
Time = 30 seconds

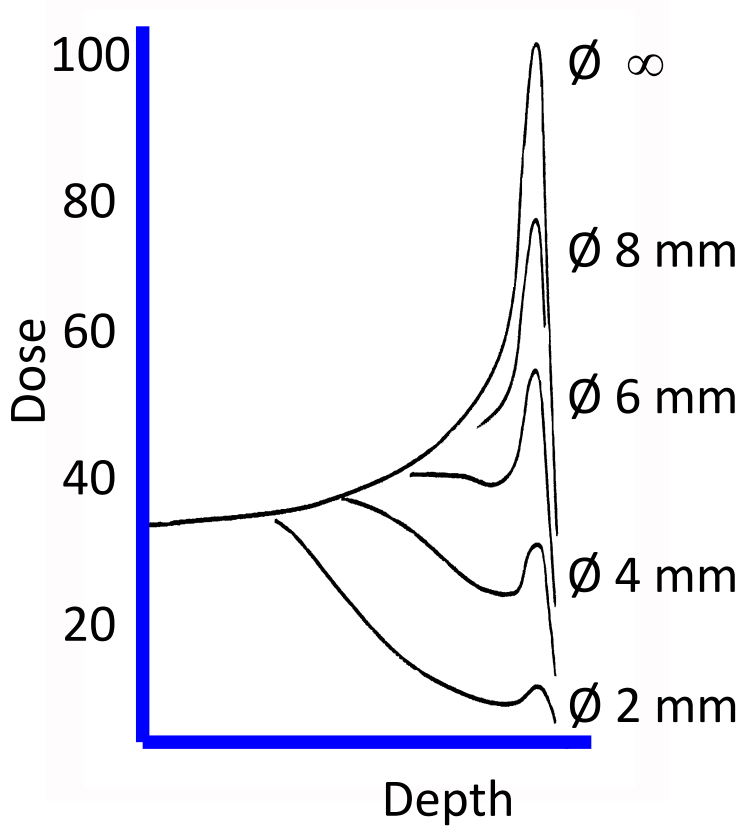
M. Hoogeman

Typical Spot Sizes



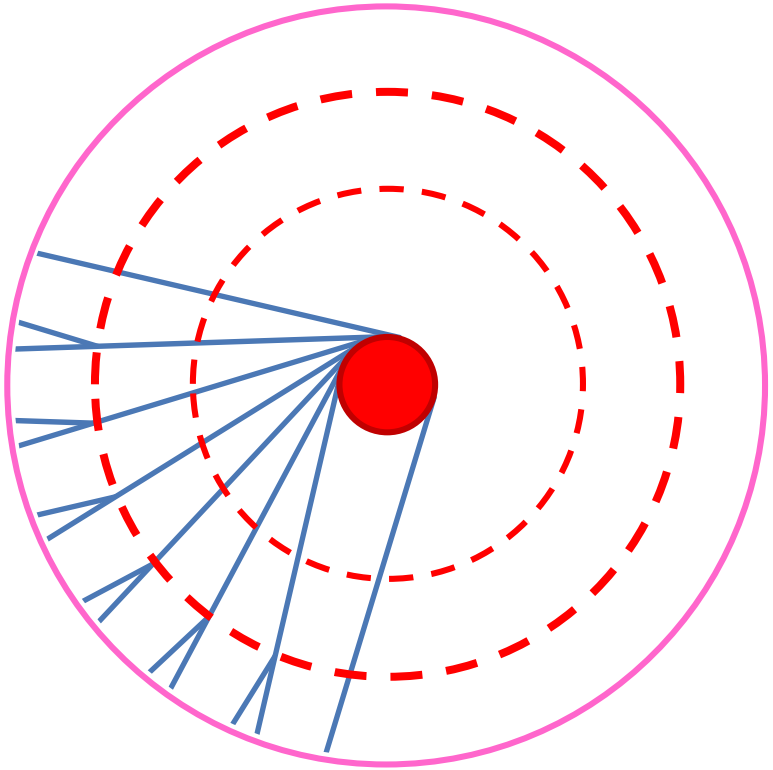
Courtesy by M. Engelsman

Multiple Coulomb Scattering: Effect on Depth Dose

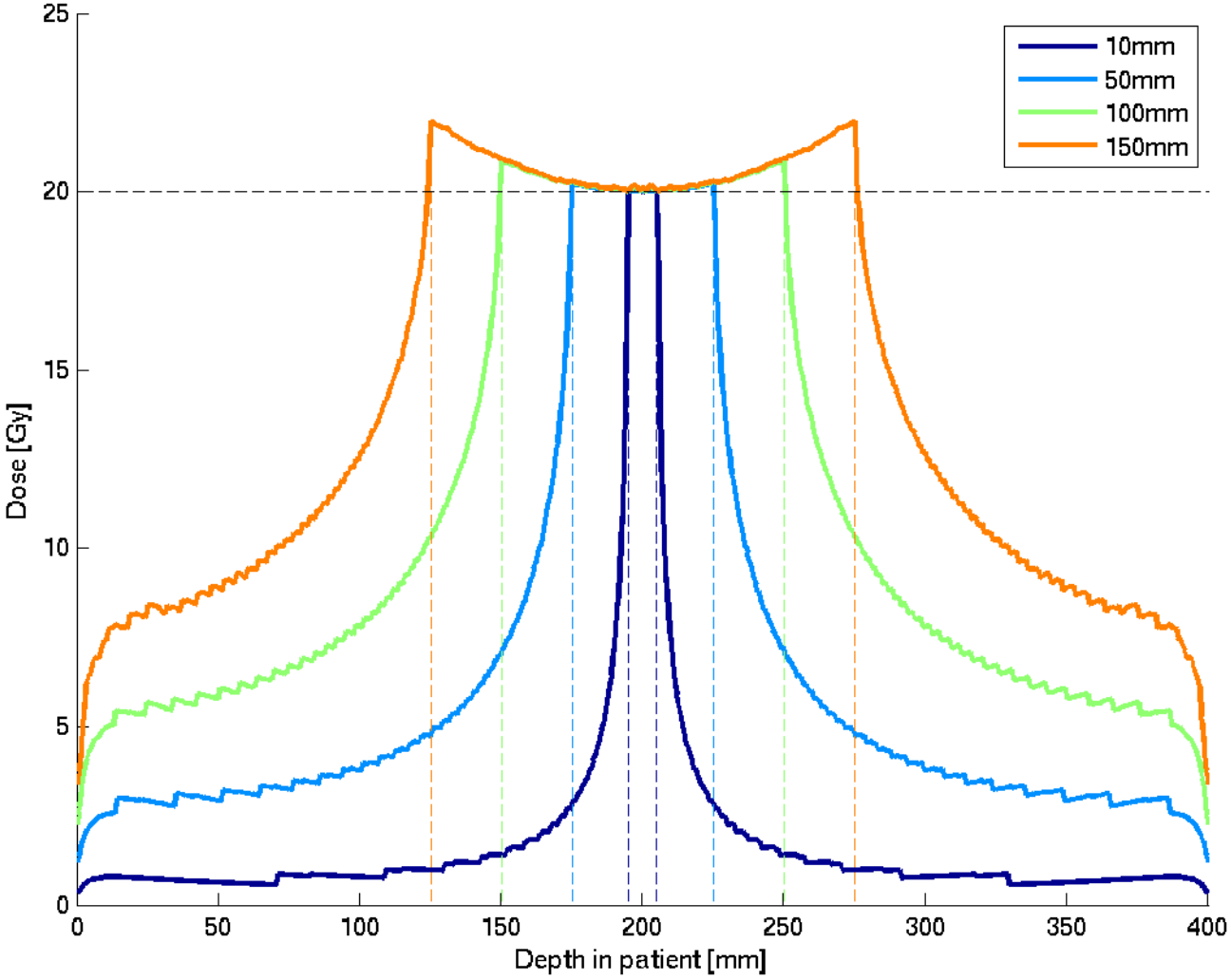


Courtesy by M. Engelsman

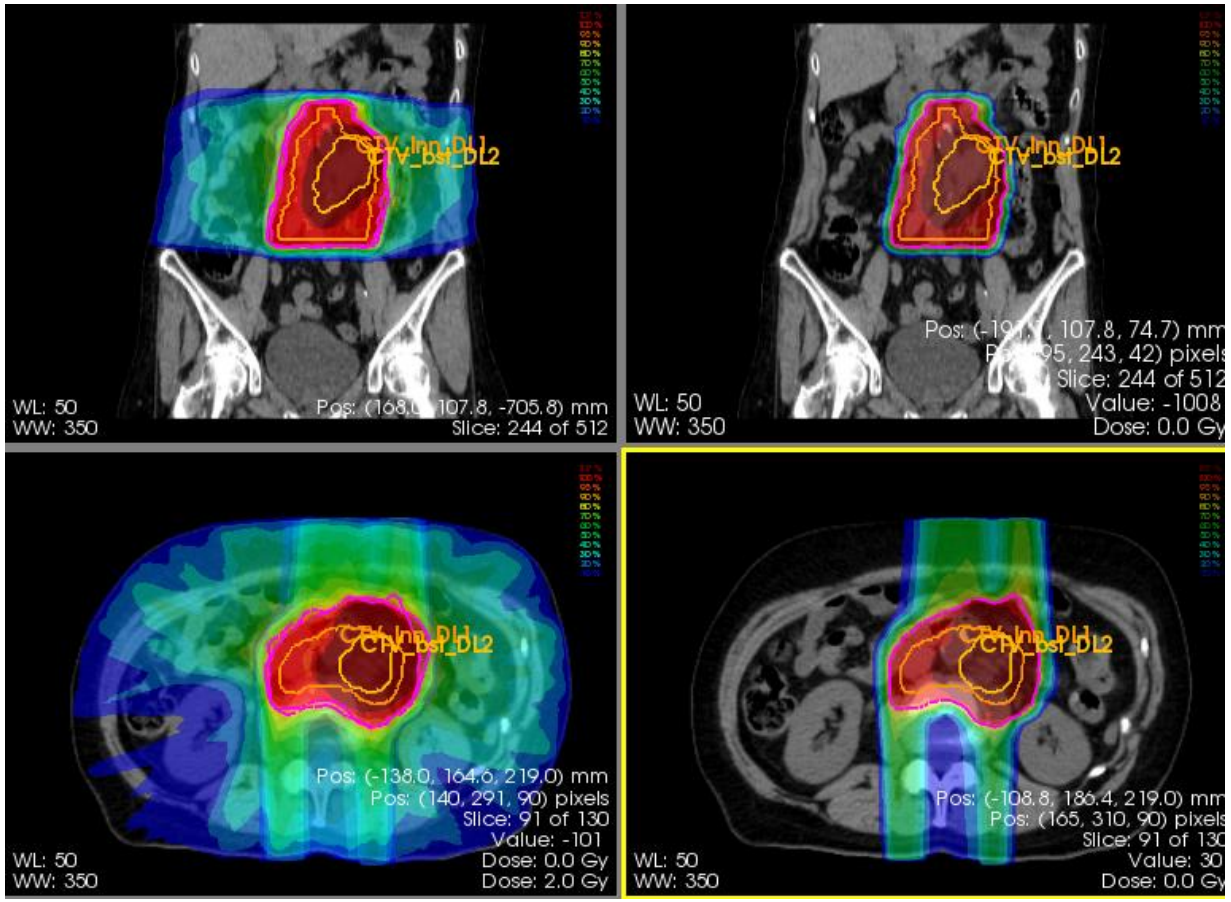
Photons: Target-Size Effect on Dose in Healthy Tissues



Target-Size Effect



Photon vs. Proton Radiation Tx



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

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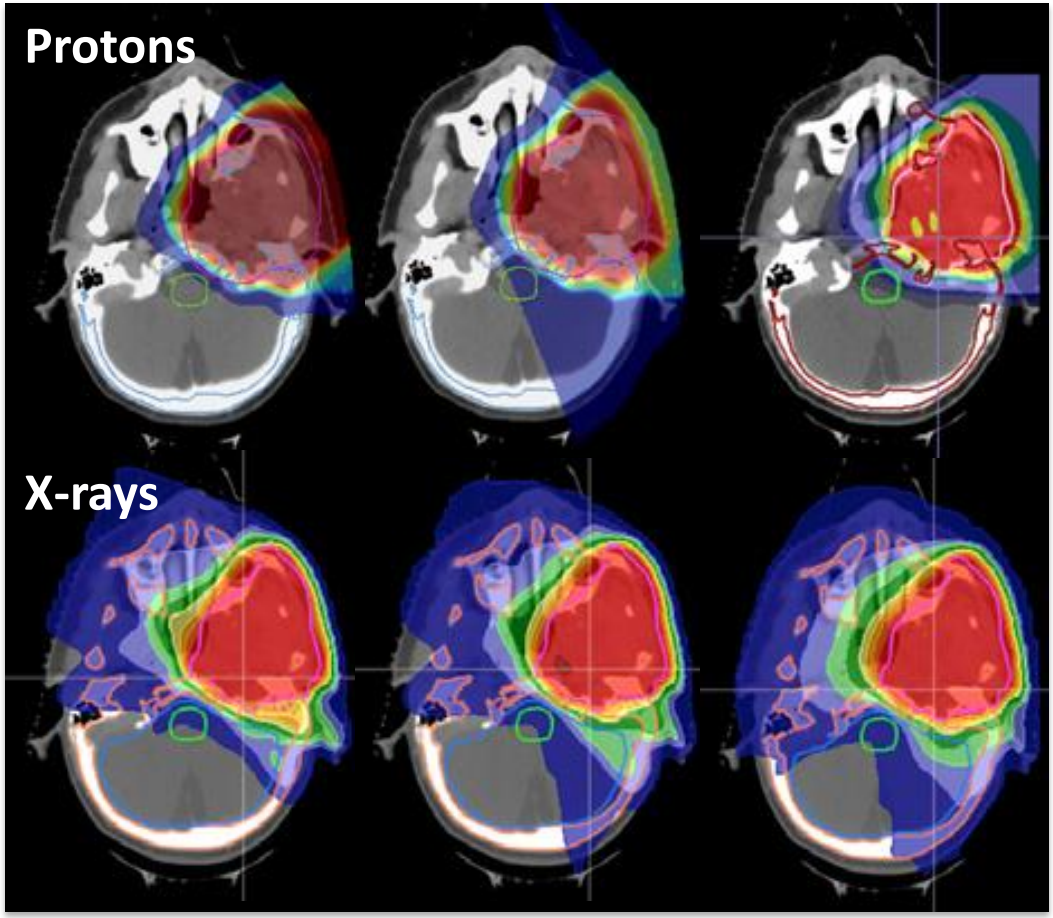
Protons vs. X-rays



Moteabbed M, Yock TI, Paganetti H. The risk of radiation-induced second cancers in the high to medium dose region: a comparison between passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors. Phys Med Biol. 2014 Jun 21;59(12):2883-99.

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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

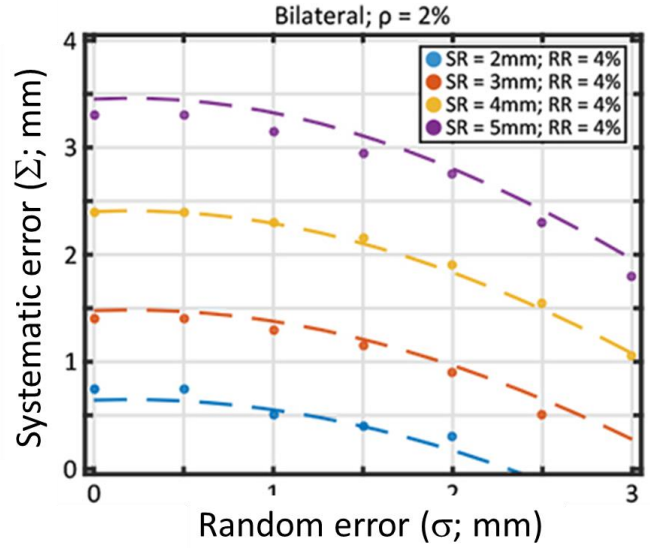
EVIDENCE AND JUSTIFICATION

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)

Equipoise

- What about the principle of equipoise?
- Clinical equipoise means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial. This applies also for off-label treatments performed before or during their required clinical trials.



Robustness recipe vs. margin recipe

van der Voort S, van de Water S, Perkó Z, Heijmen B, Lathouwers D, Hoogeman M. Robustness Recipes for Minimax Robust Optimization in Intensity Modulated Proton Therapy for Oropharyngeal Cancer Patients. IJROBP 2016 May 1;95(1):163-70.

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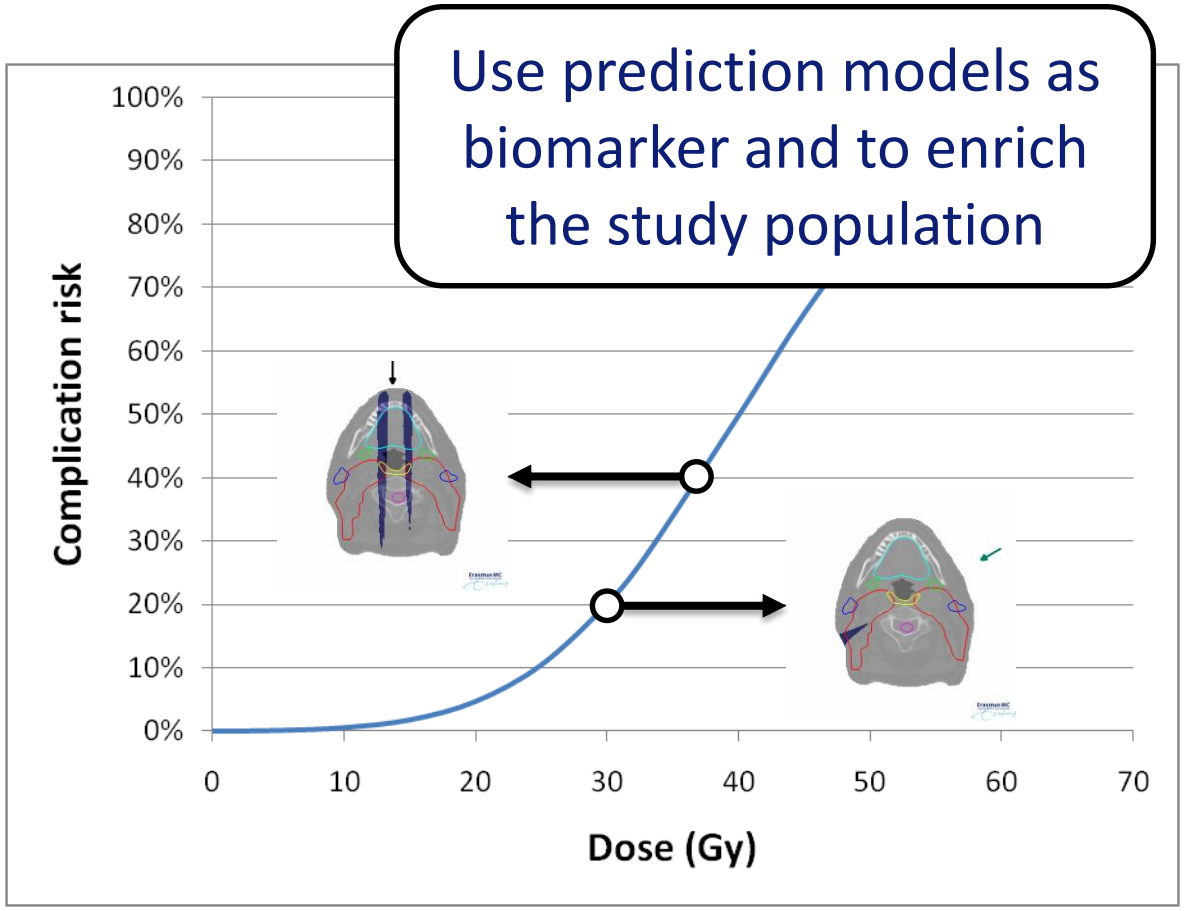
Equipoise Is Not Missing If …

1. There is a risk of reduced outcome in terms of tumor or regional control
2. If the costs of the new technology outweigh the costs of the standard technology such that it has a societal impact
3. In case the tumor dose is escalated

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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IMPROVED IMAGE-GUIDANCE AND CORRECTION FOR PHOTON RT

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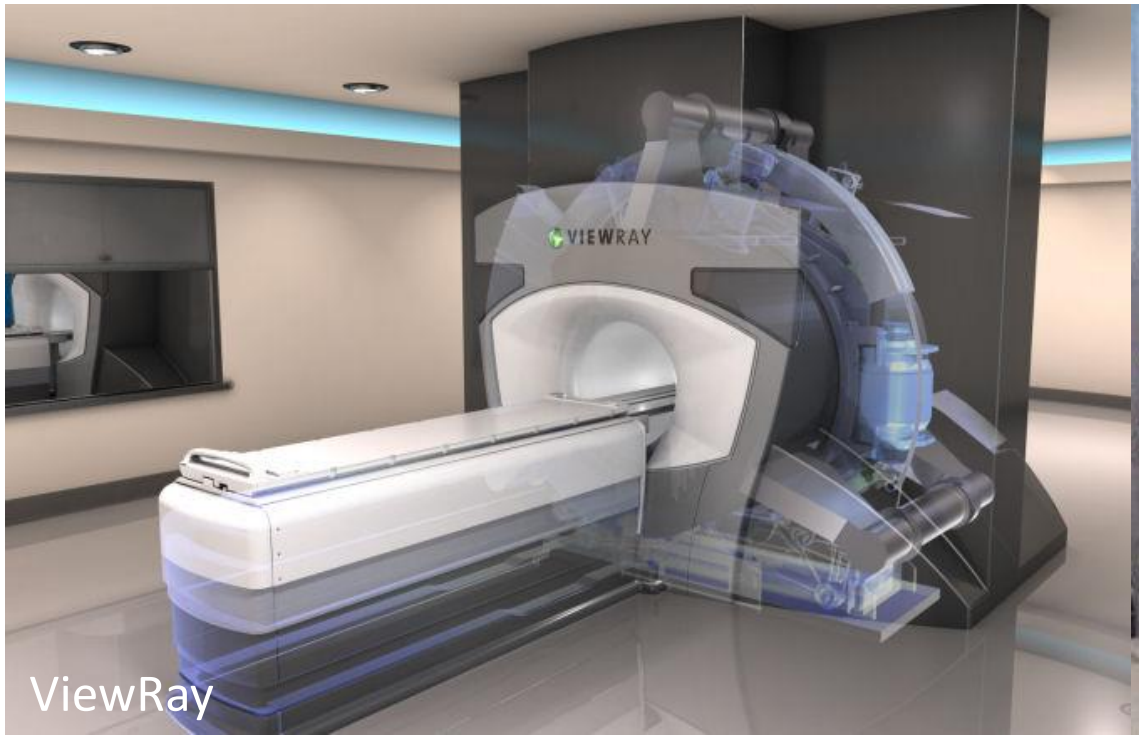
MRI-Integrated Radiotherapy Systems



ViewRay


Elekta-Philips Utrecht

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

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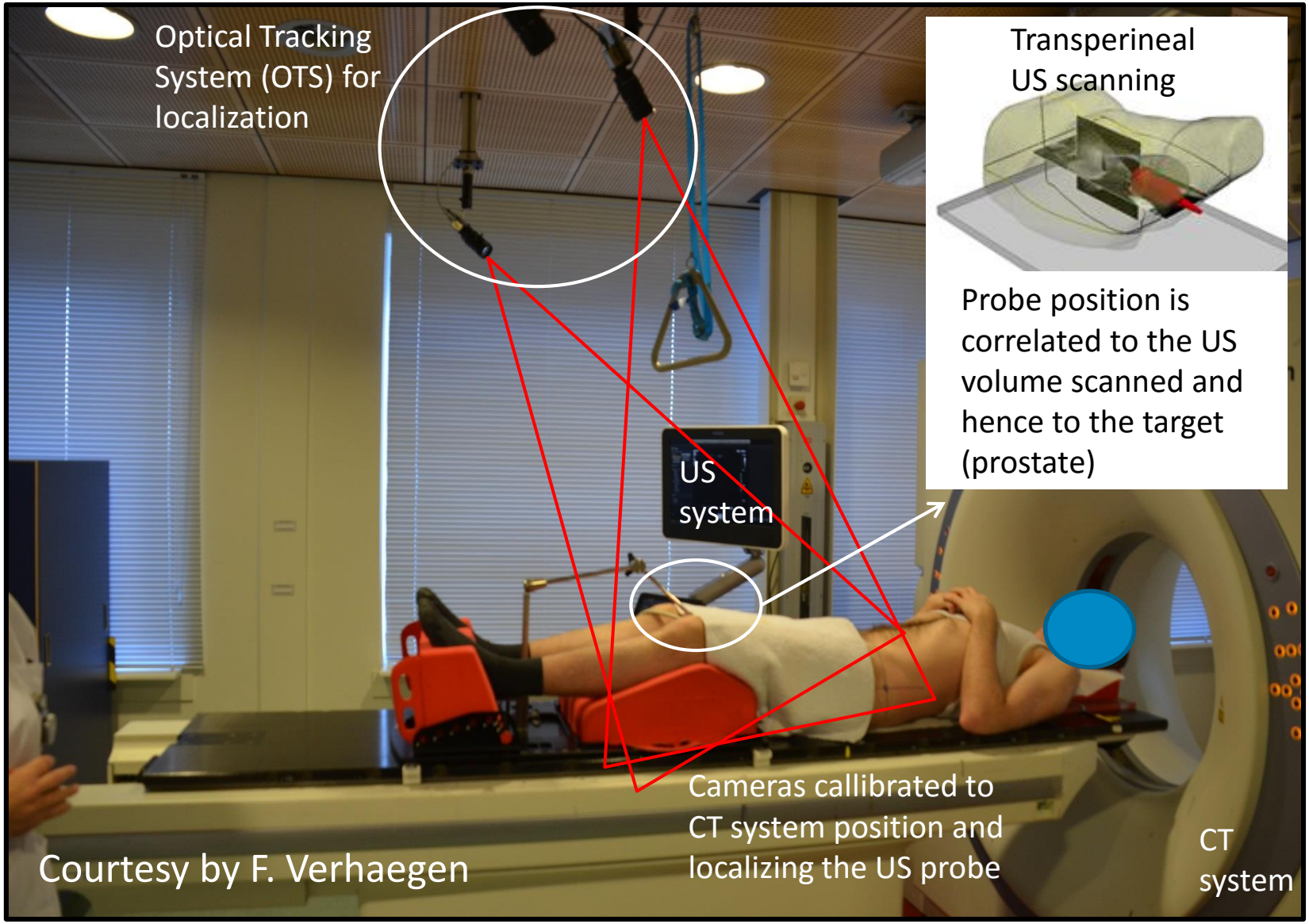
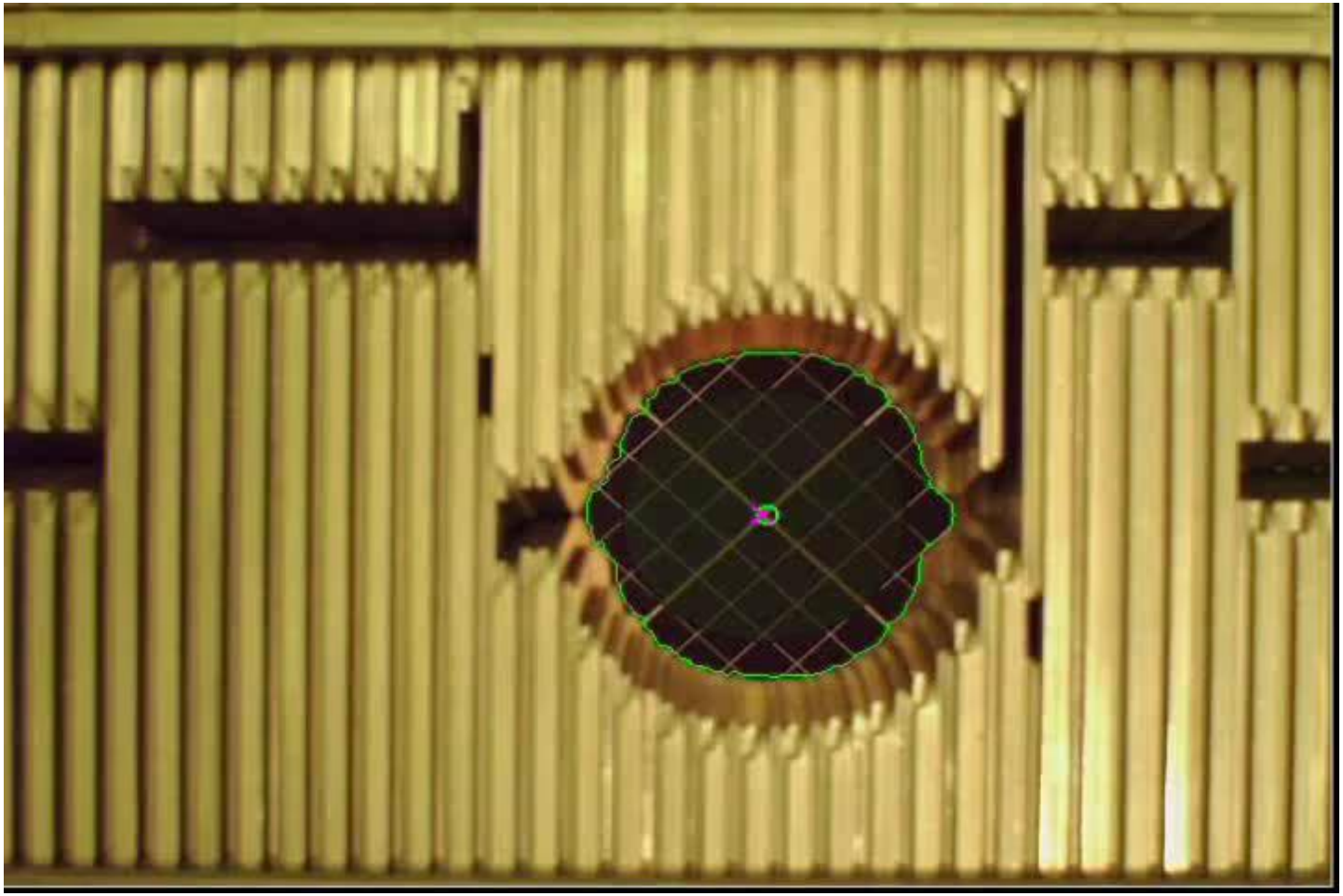
Soft-Tissue Contrast: CT on Rails



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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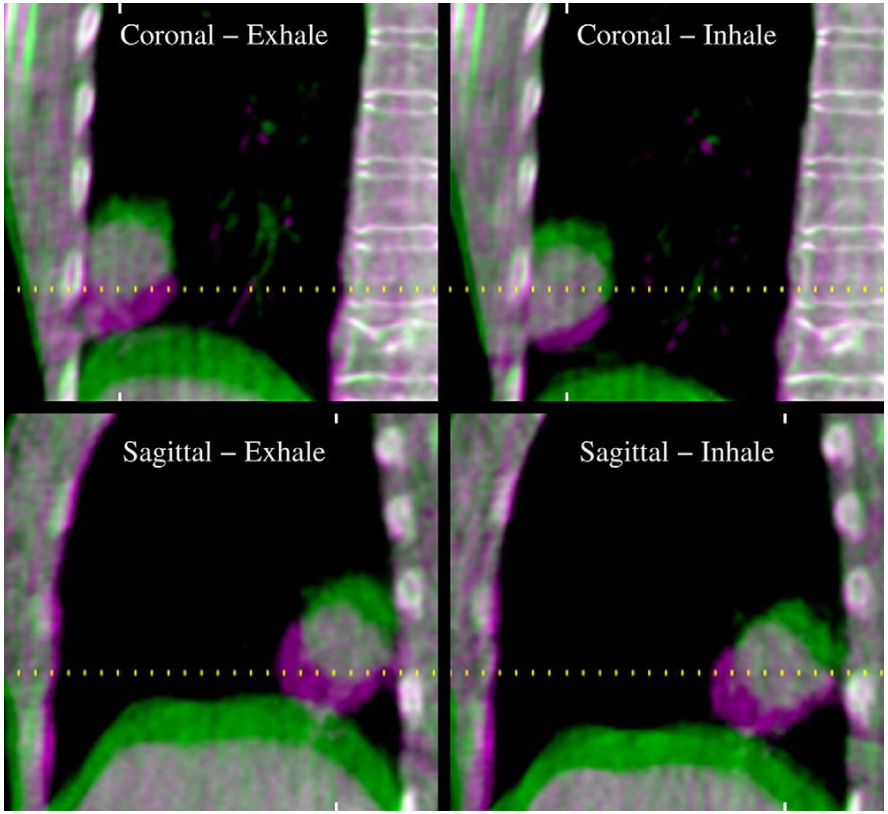
Ease of Use: Frameless Lung SBRT and SRS

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



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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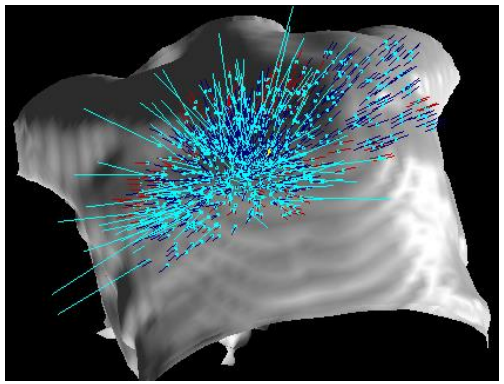
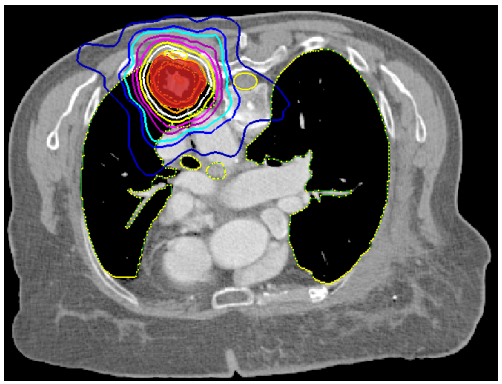
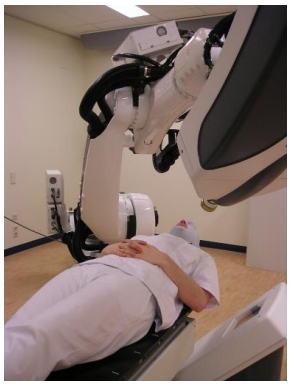
AUTOMATION

Radiotherapy Workflow







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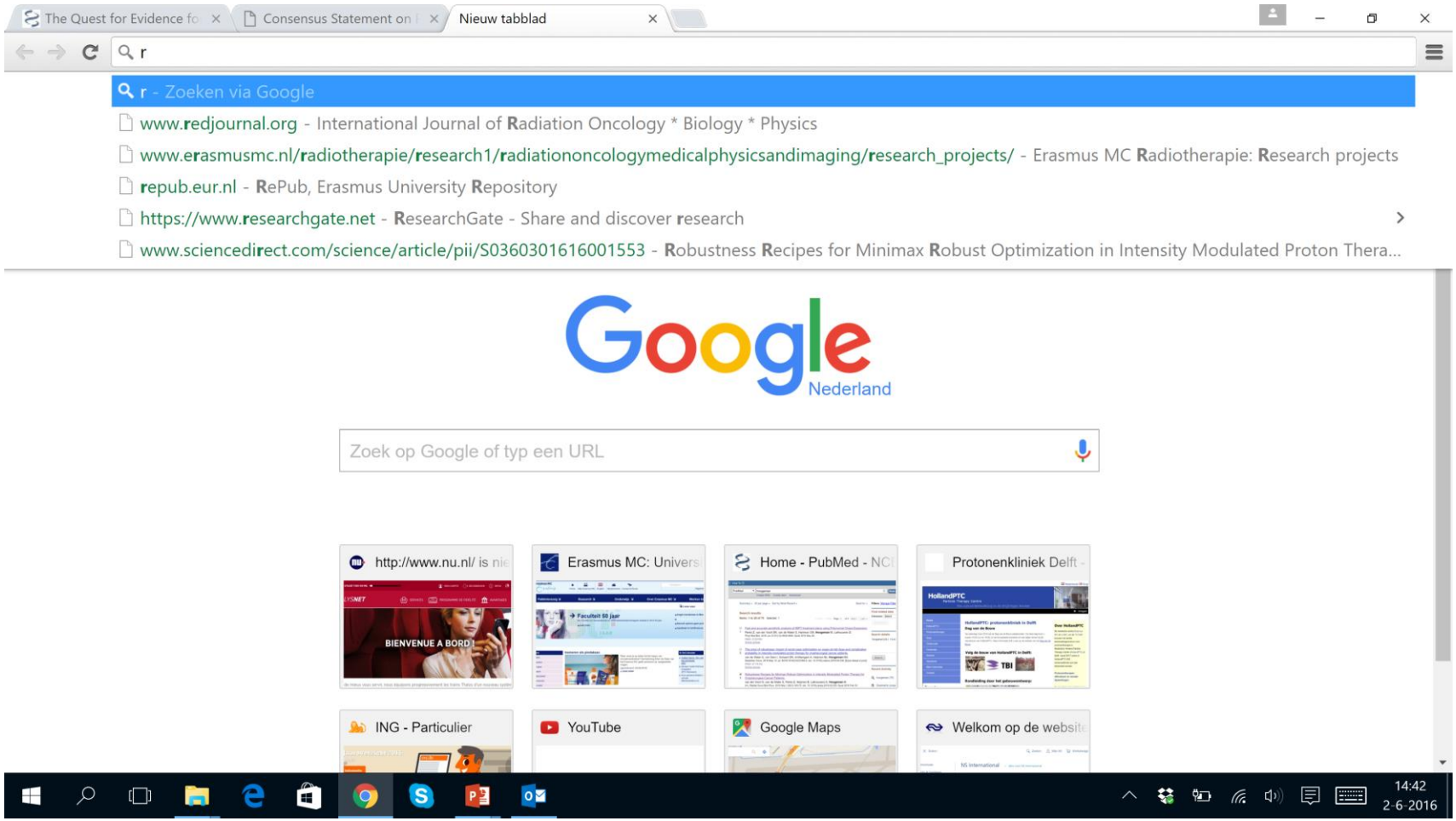
Automation, Why Not?

Knowledge-based Automation, Big-data Analytics



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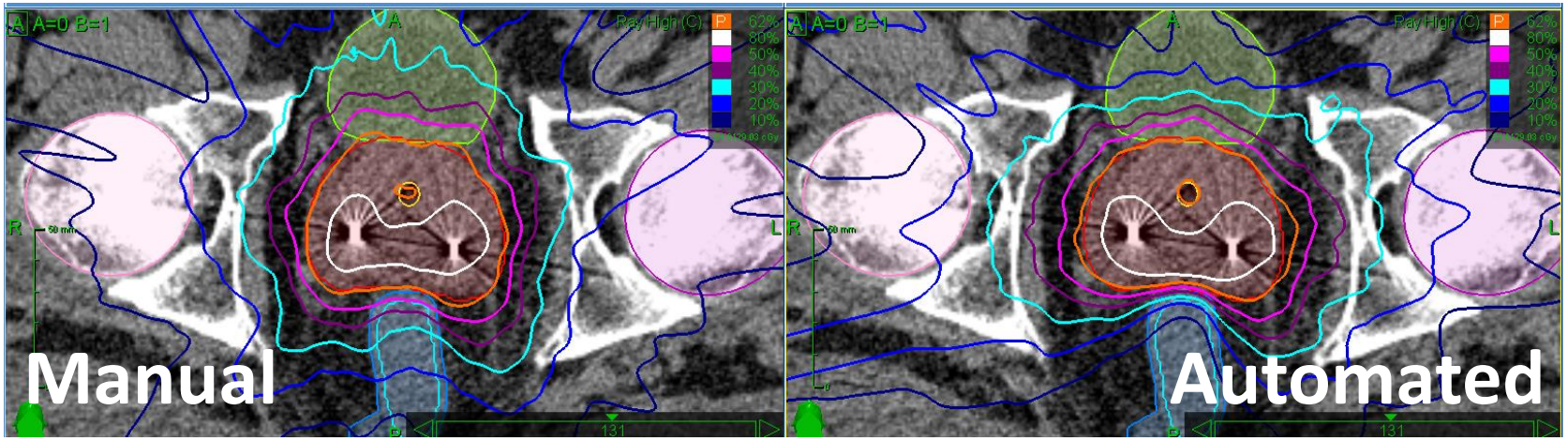
Automated Knowledge Based Treatments

- Knowledge based dose prescription
- Automated knowledge based auto-segmentation
- Automated Knowledge based treatment plan generation
- …

Widen therapeutic window

Lower costs

Does both



Courtesy by Linda Rossi

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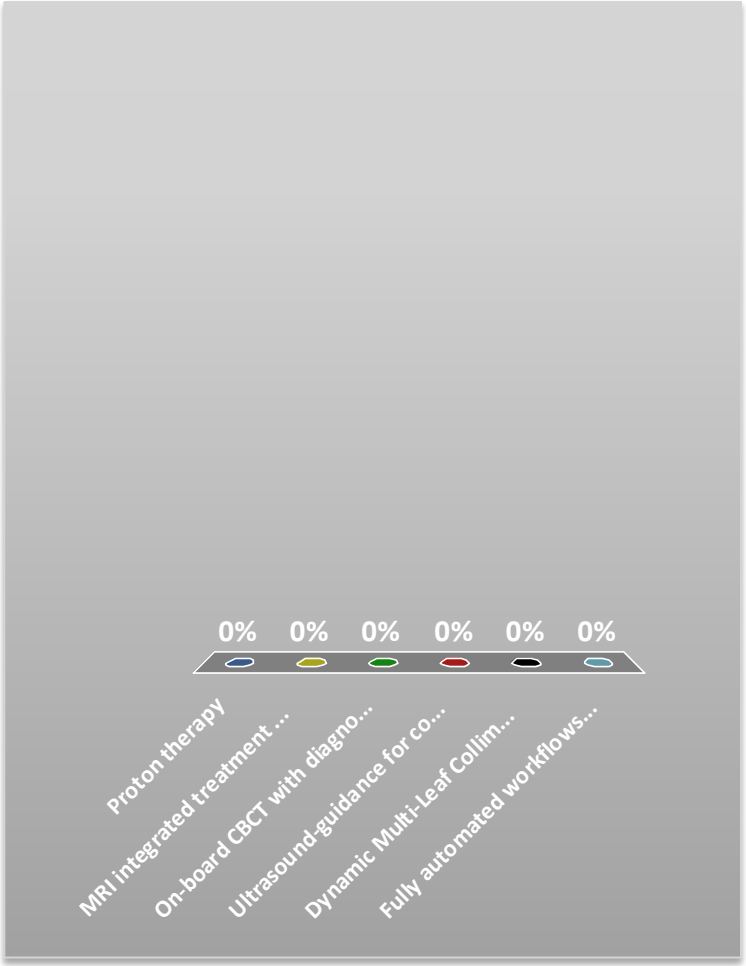
Which technology do you consider to have the greatest impact on SBRT in clinical practice in the coming 5-10 years?

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)



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

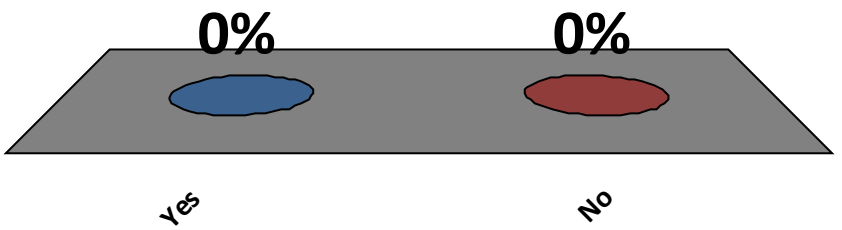
Radiobiology of SBRT

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

hoyer@aarhus.rm.dk

Do you believe that the linear-quadratic model should be used to convert SBRT doses to EQD_{2Gy} doses?

A. Yes
B. No

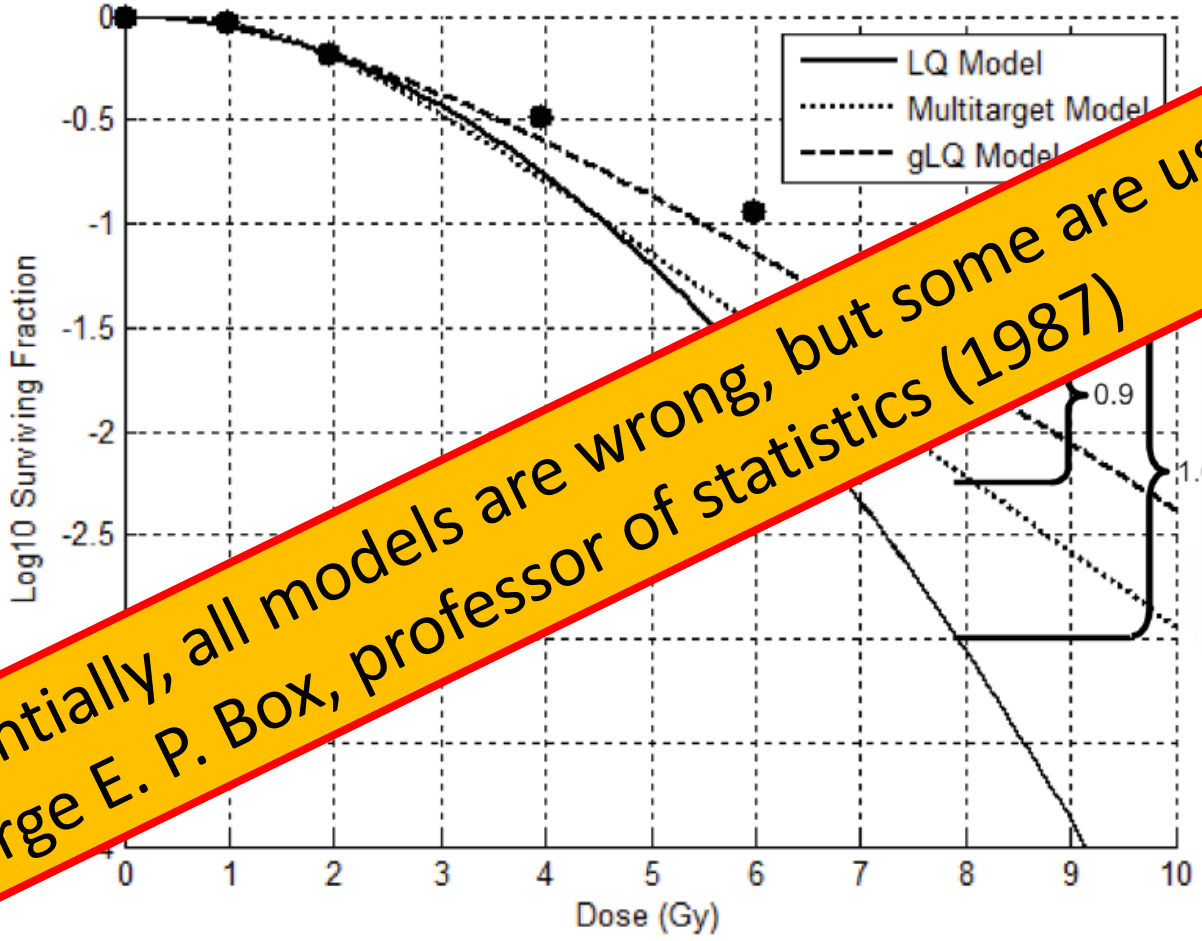


How does a RO prescribe *'a treatment' (forget about the volumes…..)*

- The RO prescribes a dose in Gray
- The RO believes that the dose is a surrogate of cell kill
- The RO does not prescribe XX% cancer cell kill
- The RO expects a close relationship between dose and cancer cell kill (due to DNA-strand break)
- The RO uses a model: the Linear-Quadratic Model etc.

Modeling survival after radiation therapy

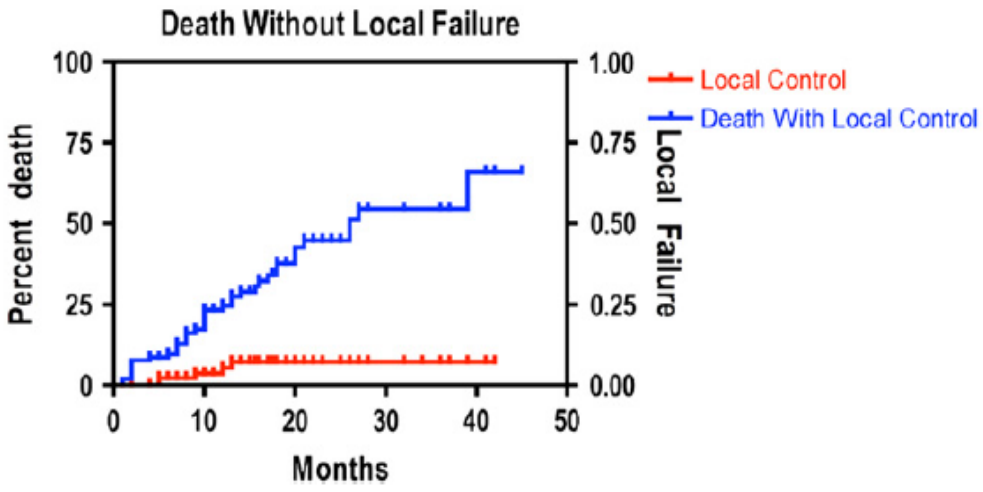
Linear-quadratic-, multitarget- and generalized linear-quadratic models

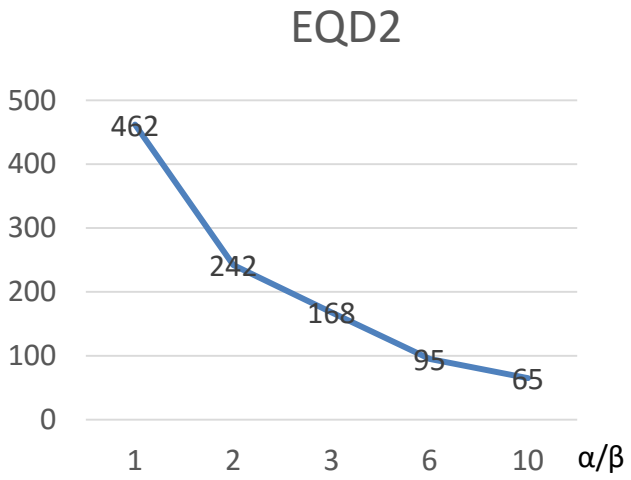


"Essentially, all models are wrong, but some are useful."
George E. P. Box, professor of statistics (1987)

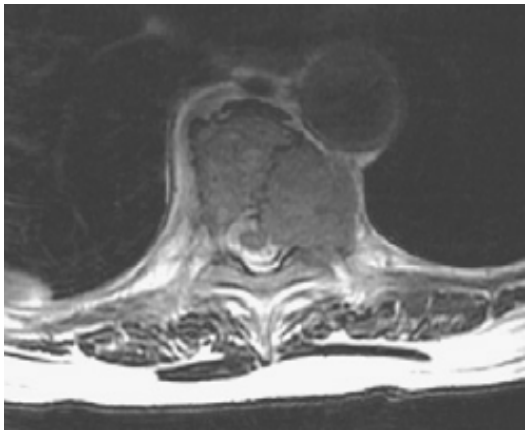
Ohri et al: IJROBP 2012; 83 (1): 385

The success of SBRT

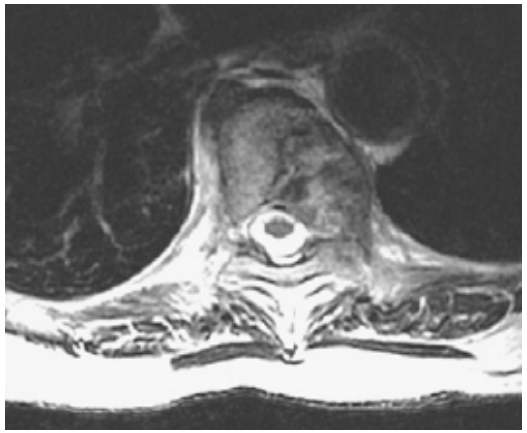




Pre-SBRT



3 months post-SBRT (1 x 21 Gy)



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

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

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	?	?

Vascular effects

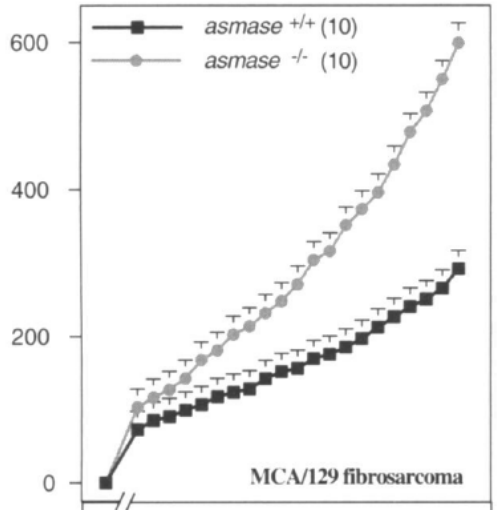
Endothelial response to high RT doses

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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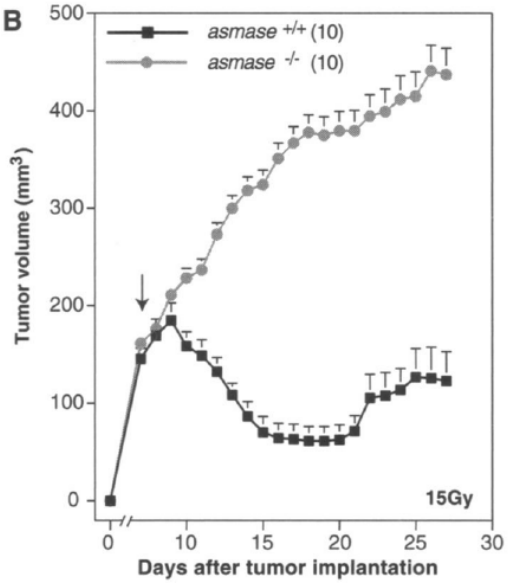
Tumors with apoptosis-resistent vascular endothelium were resistant to radiation



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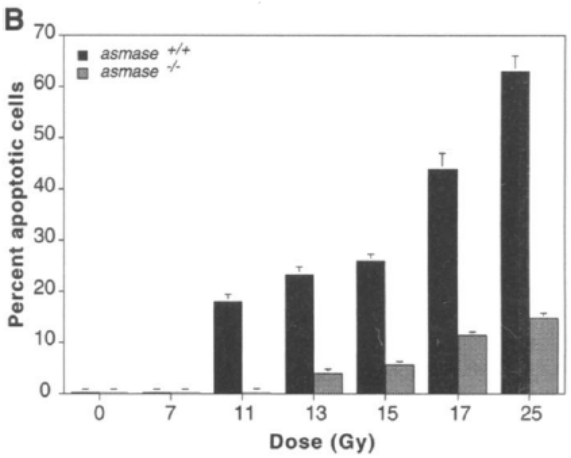
Tumors with apoptosis-resistent vascular endothelium Were resistant to radiation

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



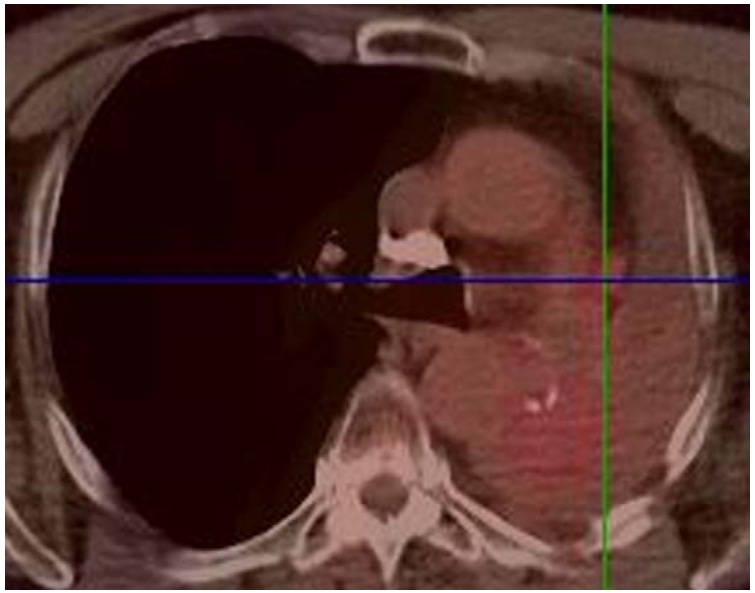
Science 300: 1155; 2003

Immune effects


Before SBRT
6 months post SBRT

FDG-PET response following SBRT

23 months post-SBRT



SUV = 5.87

39 months post-SBRT

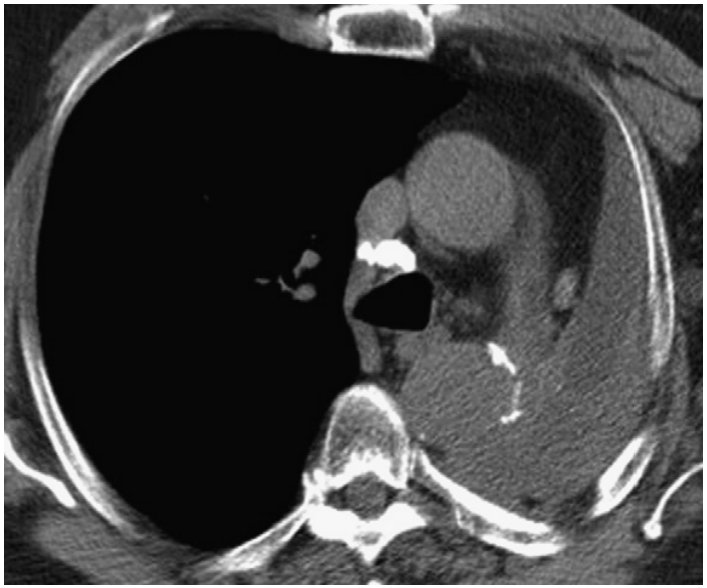
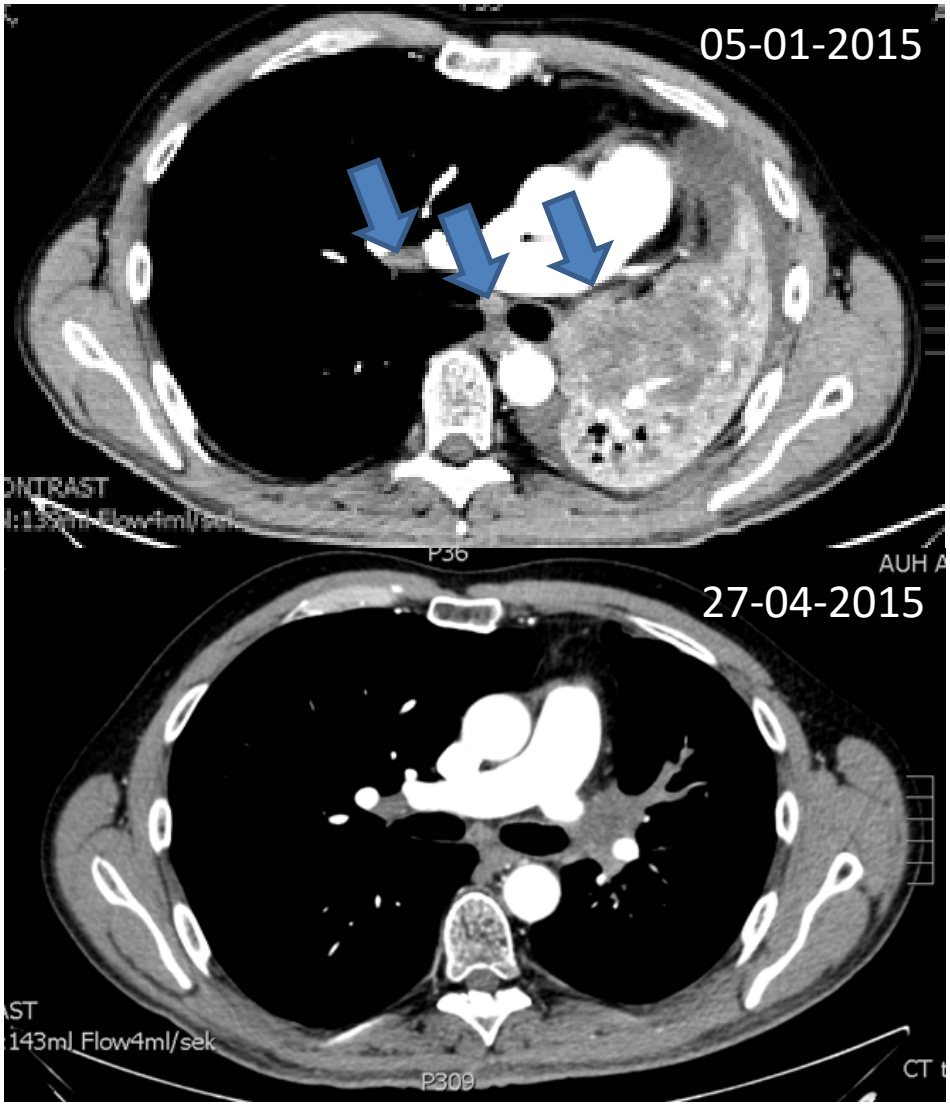


Table 4 Patients with concerning SUVs without evidence of failure

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

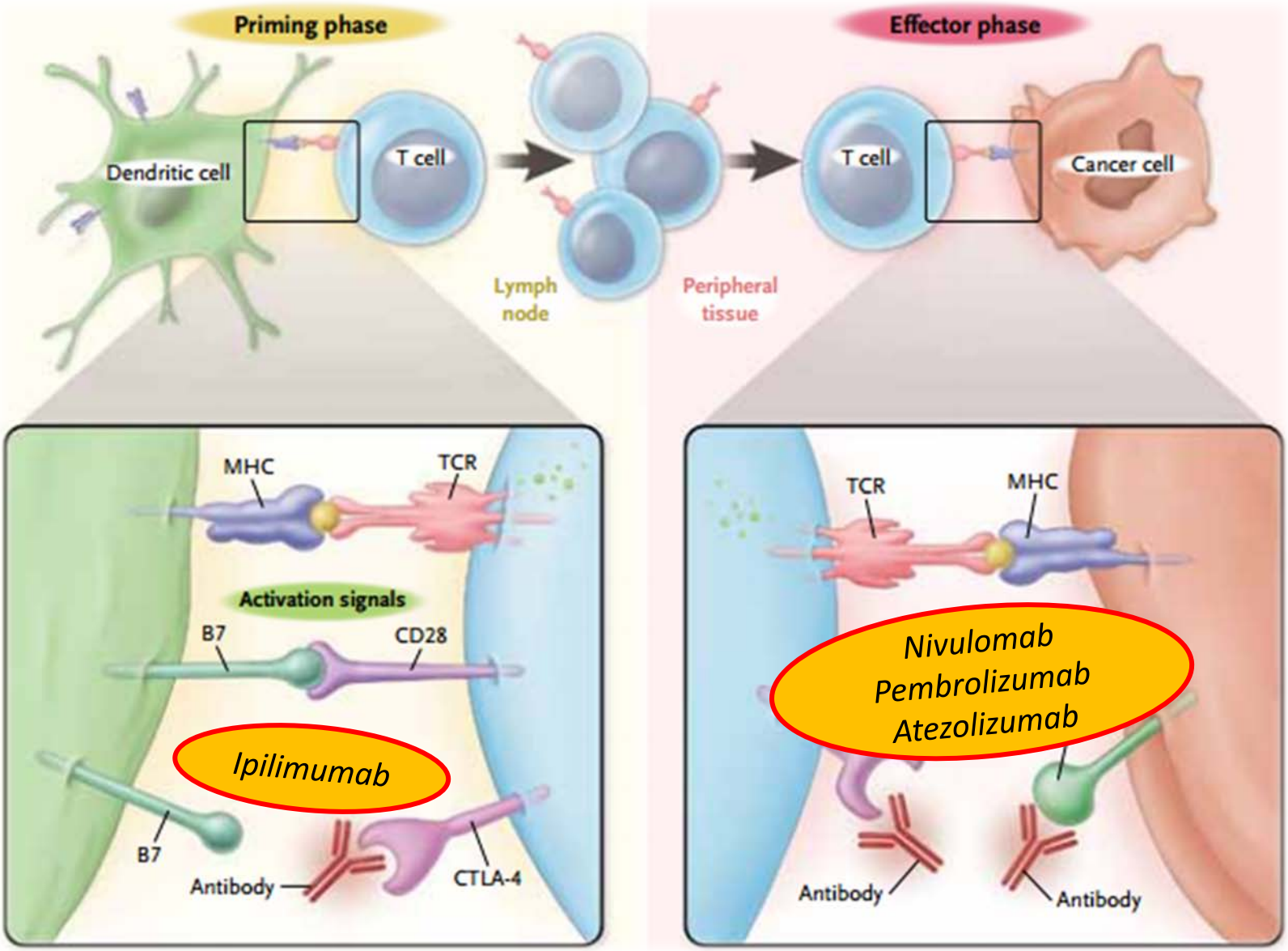
A recent case from AUH



56-year old male with metastatic melanoma

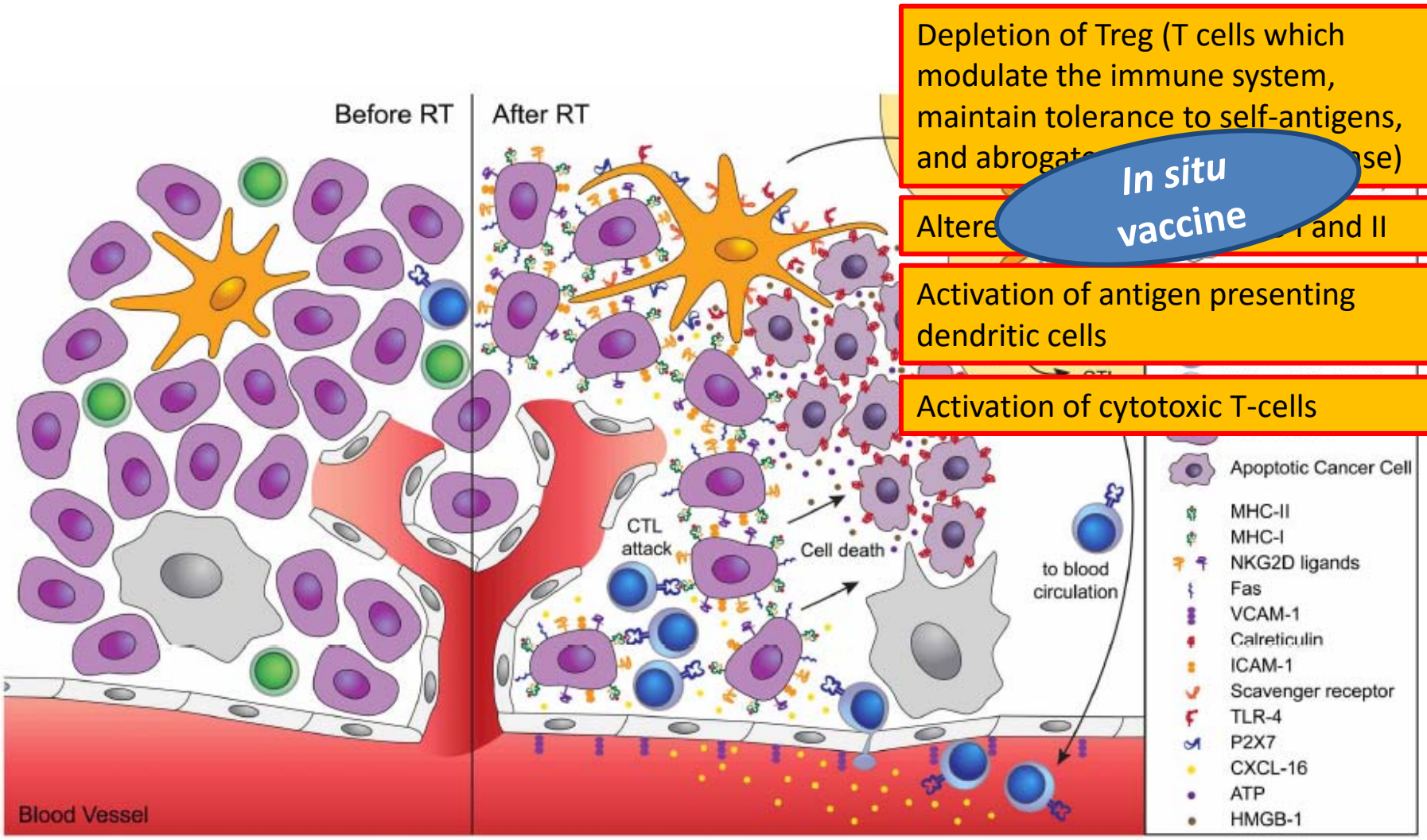
- IL-2
- Ipilumimab
- Re-induction Ipilimumab
- Temodal
- Activated T-cells
- January 2-6, 2015: Palliative RT 20 Gy/4 frx
- January 20, 2015 Pembrolizumab
- Still without progression

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)

In situ vaccine

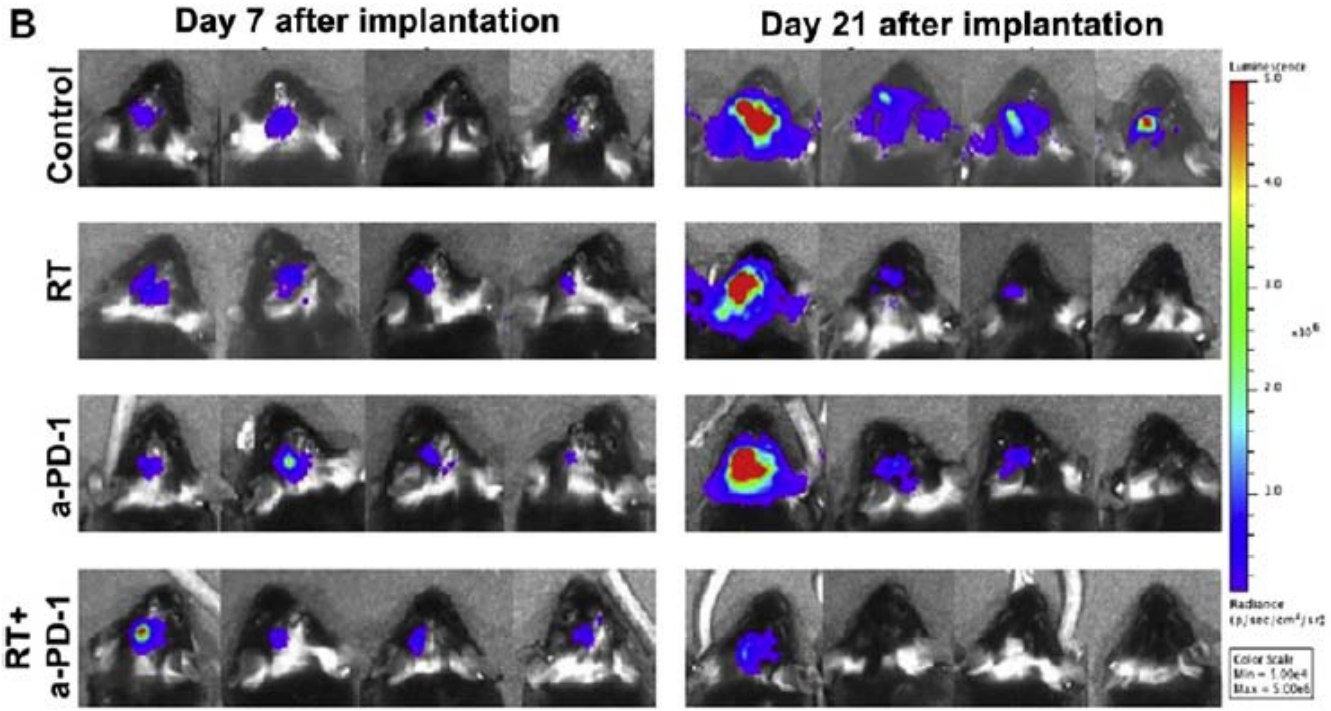
Altere… …I and II

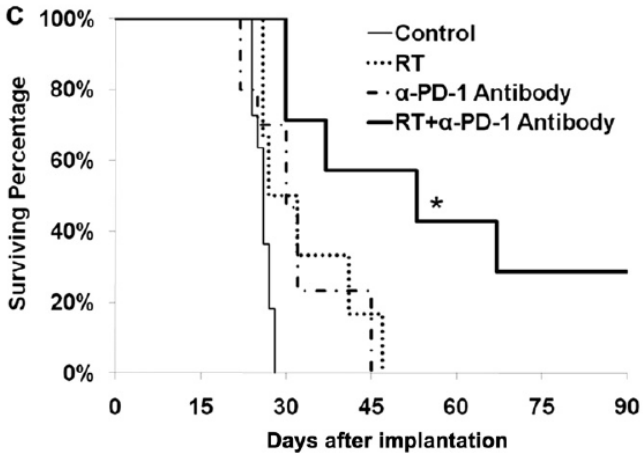
Activation of antigen presenting dendritic cells

Activation of cytotoxic T-cells

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

PD-1 antibody and radiation

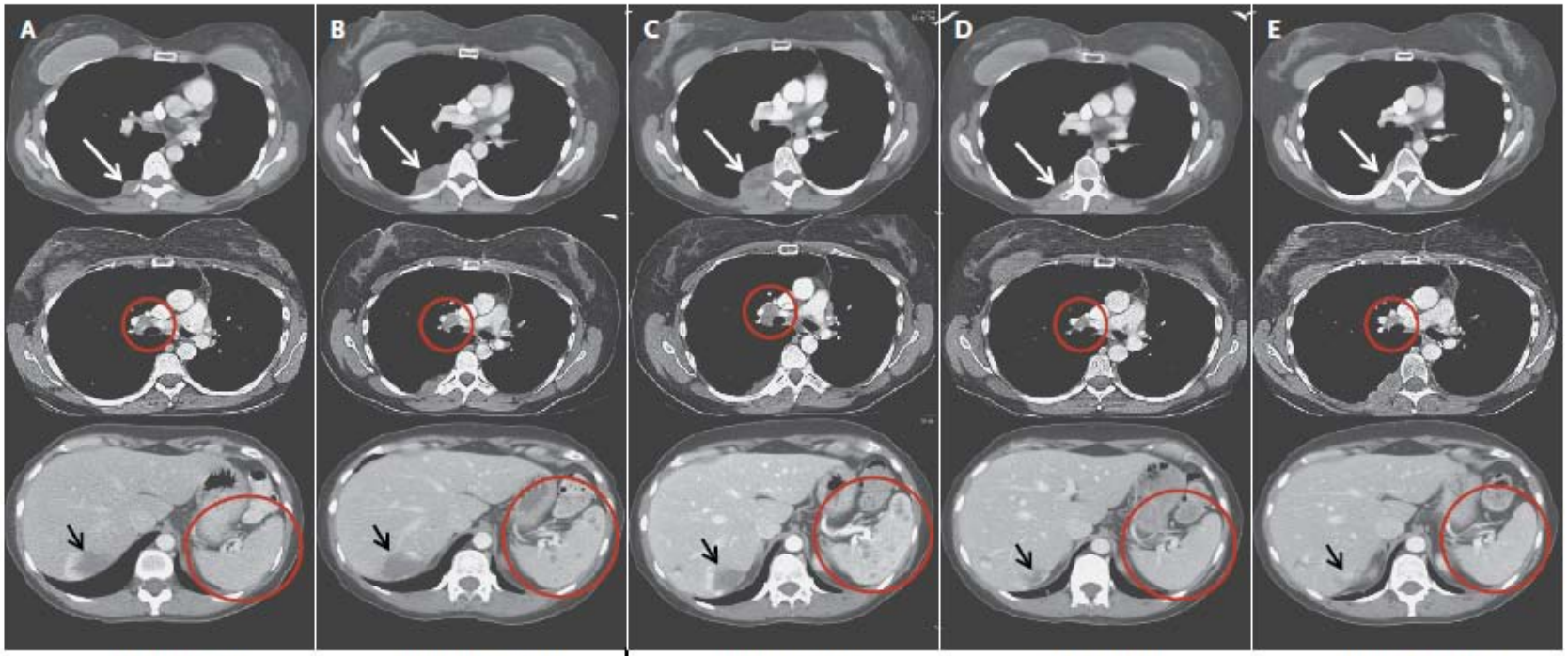




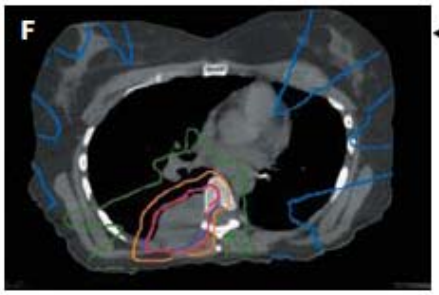
PD-1 mediates inhibition of activated T-lymfocytes
Nivolumab: PD-1 antibody

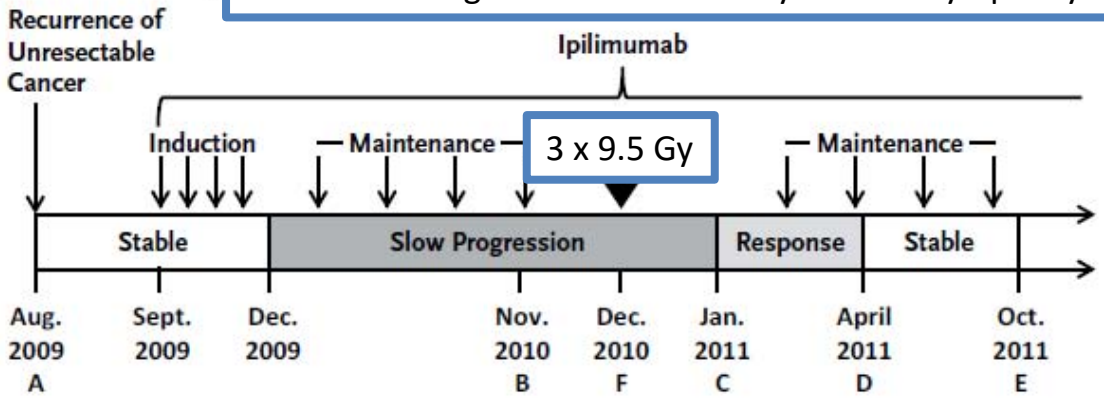
Zeng et al. IJROBP 2012; 86(2): 343

Abscopal immune effects



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





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.

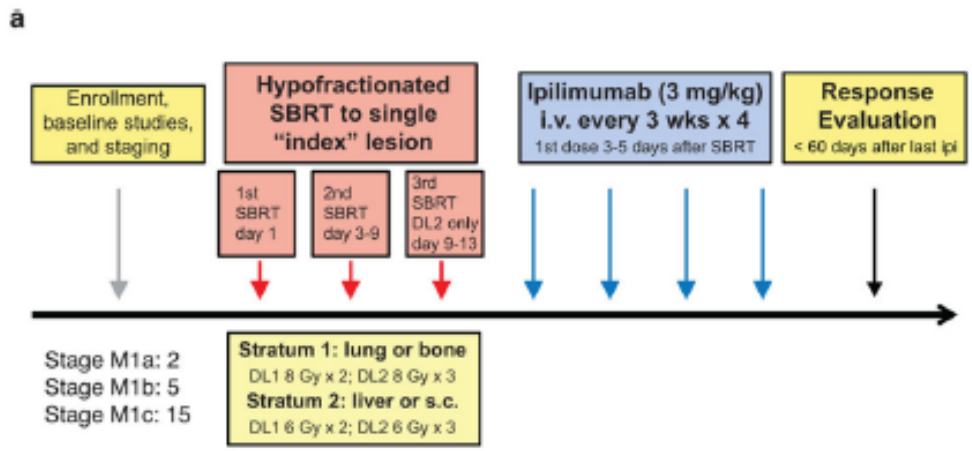
Author	Year	Sex	Age	Site of RT	RT dose/ fractionation	Biological equivalent Dose (BED)	Immunological agent	Areas of abscopal regression	Time interval	Duration of response	Patient out come	Overall survival
Postow [122]	2012	F	33	Paraspinal mass	28.5 Gy/3/3	55.6 Gy	Ipilumimab	R hilar lymph nodes, spleen	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

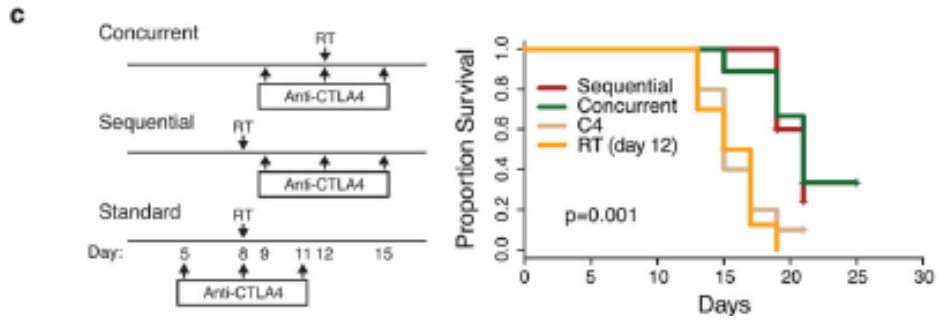
* Personal communication.

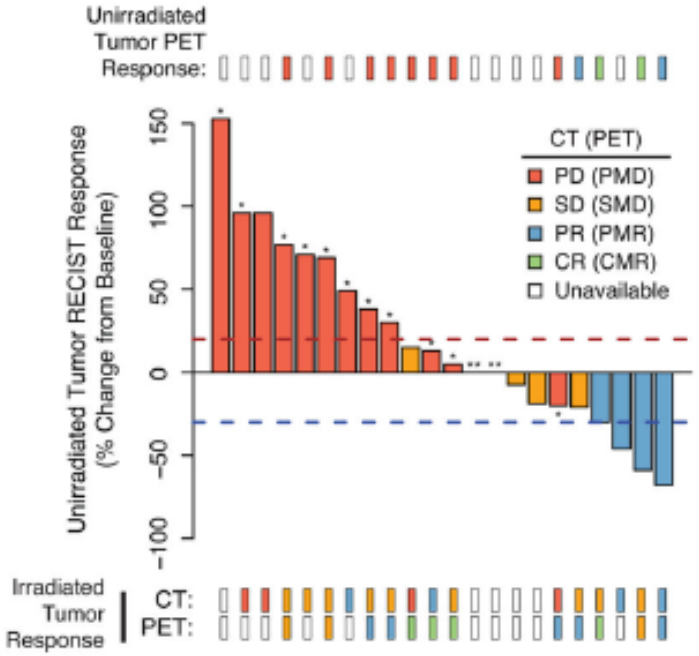
Siva et al. Cancer letters 2015; 356: 82

Abscopal effects in metatatic melanoma

Clinical results: Phase I study





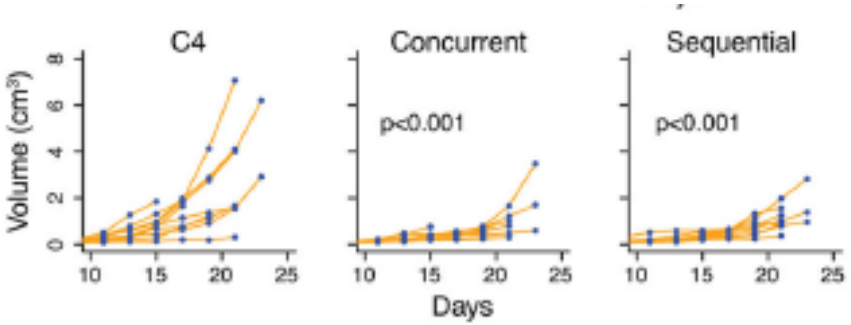


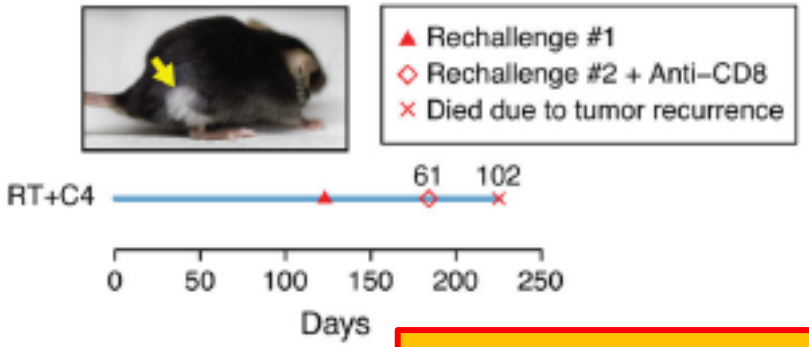
RECIST-response:
PR: 18%; SD: 18%; PD: 64%

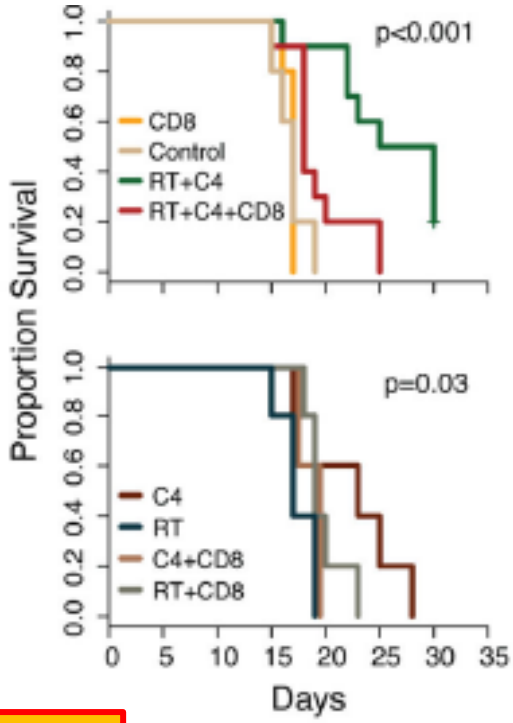
Twyman-Saint Victor et al. Nature 2015; 520(7547): 373

Abscopal effects in metastatic melanoma

Experimental data







Resistance depends on:

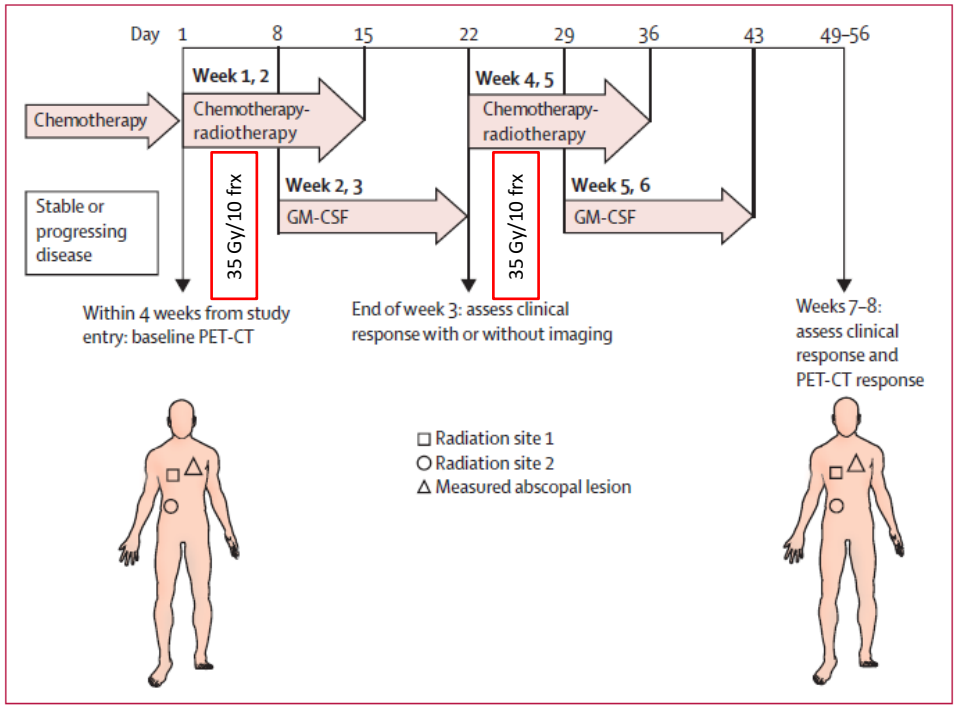
- PD-L1 upregulation on melanoma cells
- T-cell exhaustion (low tumor CD8 count)

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



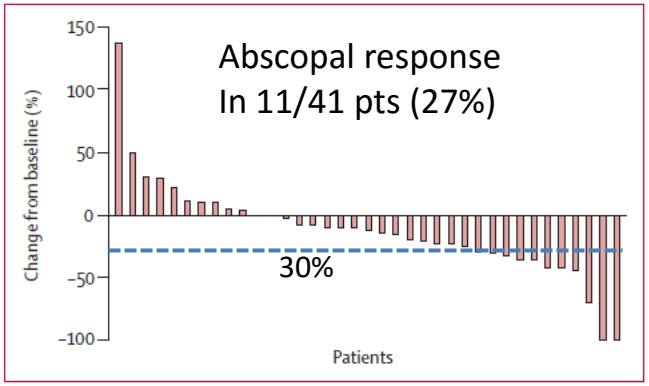


Figure 2: Waterfall plot of best abscopal responses

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

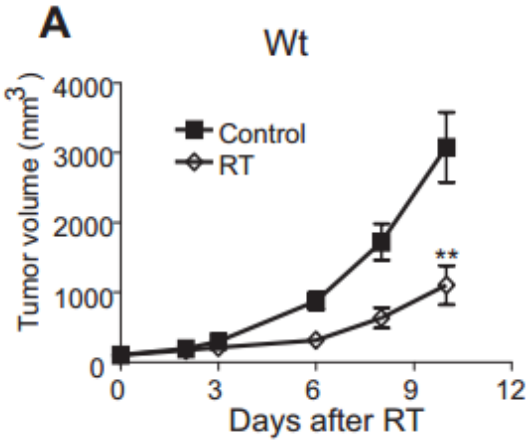
Patients with stable or progressing metastatic solid tumours, on single-agent chemotherapy or hormonal therapy, with at least three distinct measurable sites of disease

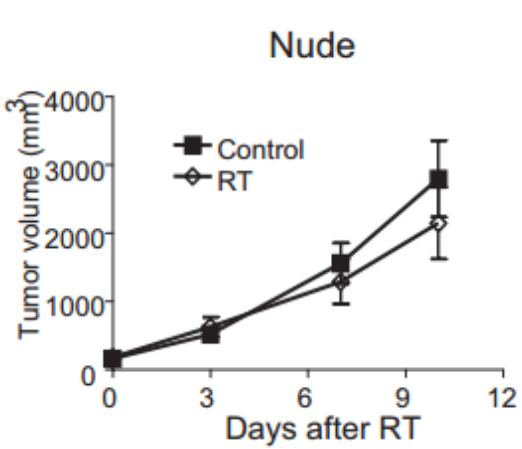
Golden et al. Lancet Oncol 2015; 16: 795

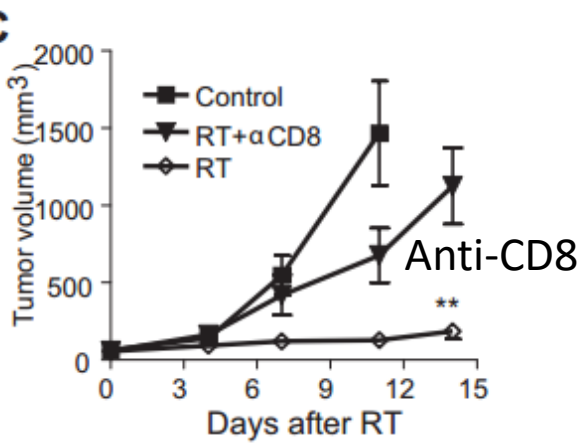
CD8 T-lymphocytes and response to RT

B16 experimental melanoma in nude and wild-type mice

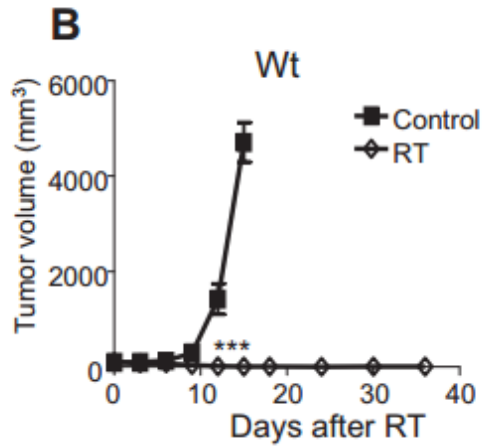
20 Gy

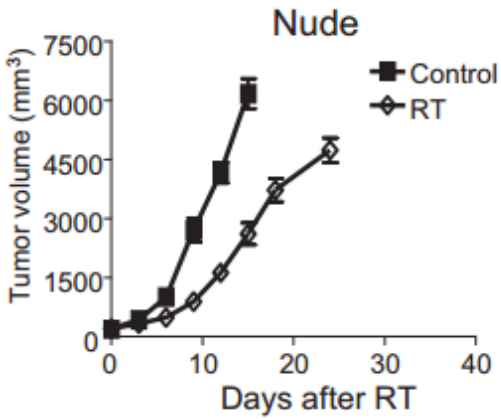


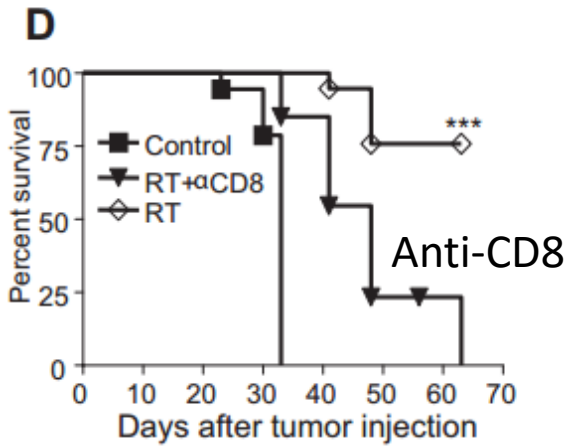




25 Gy

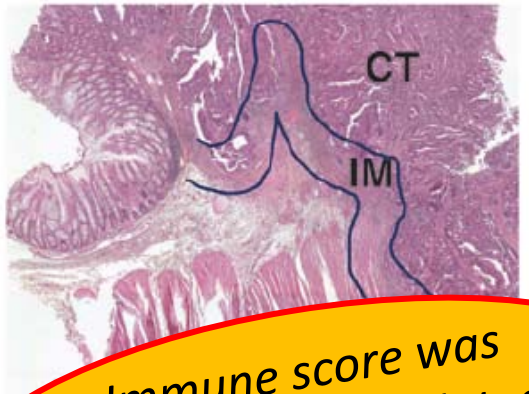




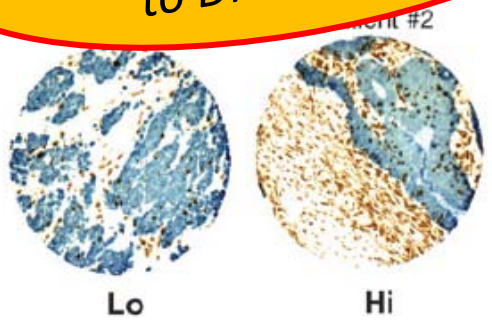


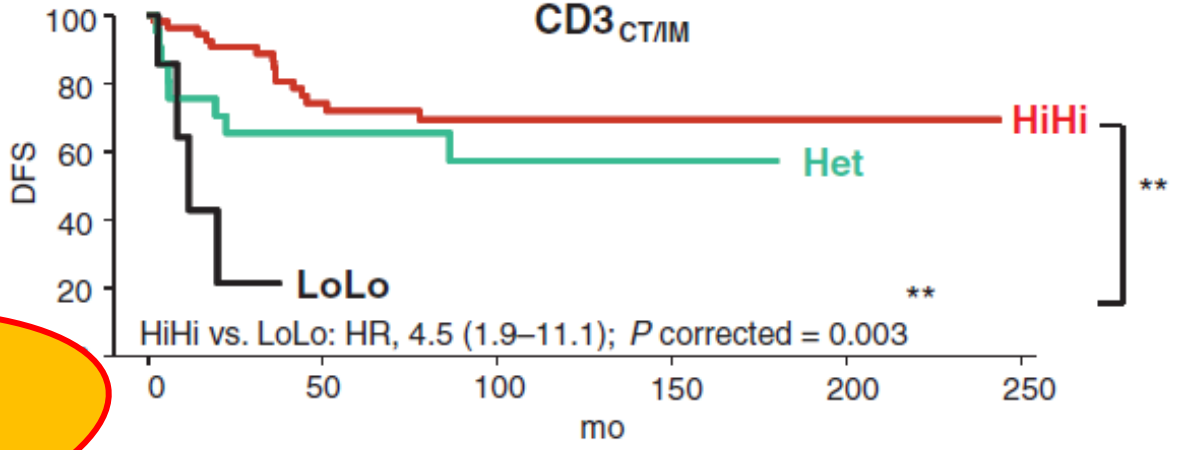
Lee et al. Blood 2009; 114: 589

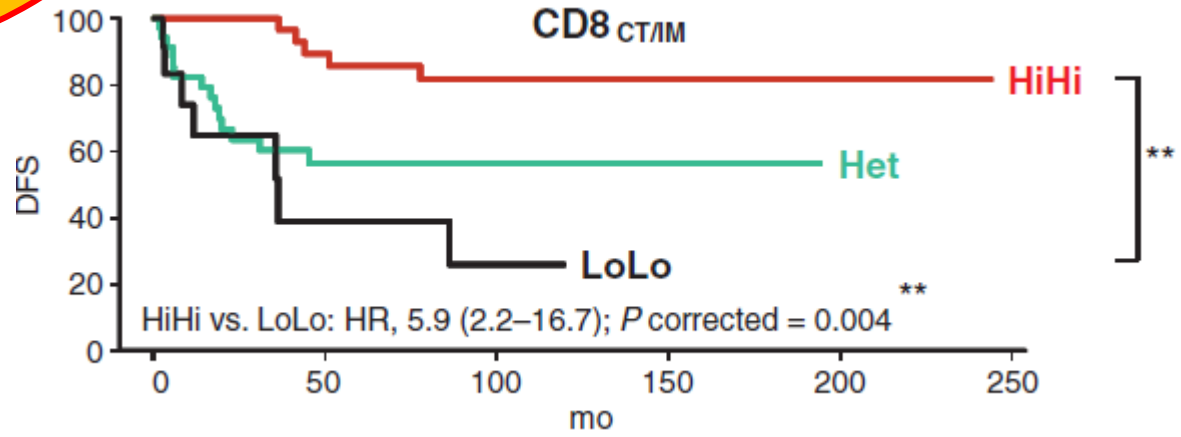
Effect on tumor infiltrating T-cells on PFS after preop chemo-RT for rectal cancer



Immune score was independently related to DFS and OS

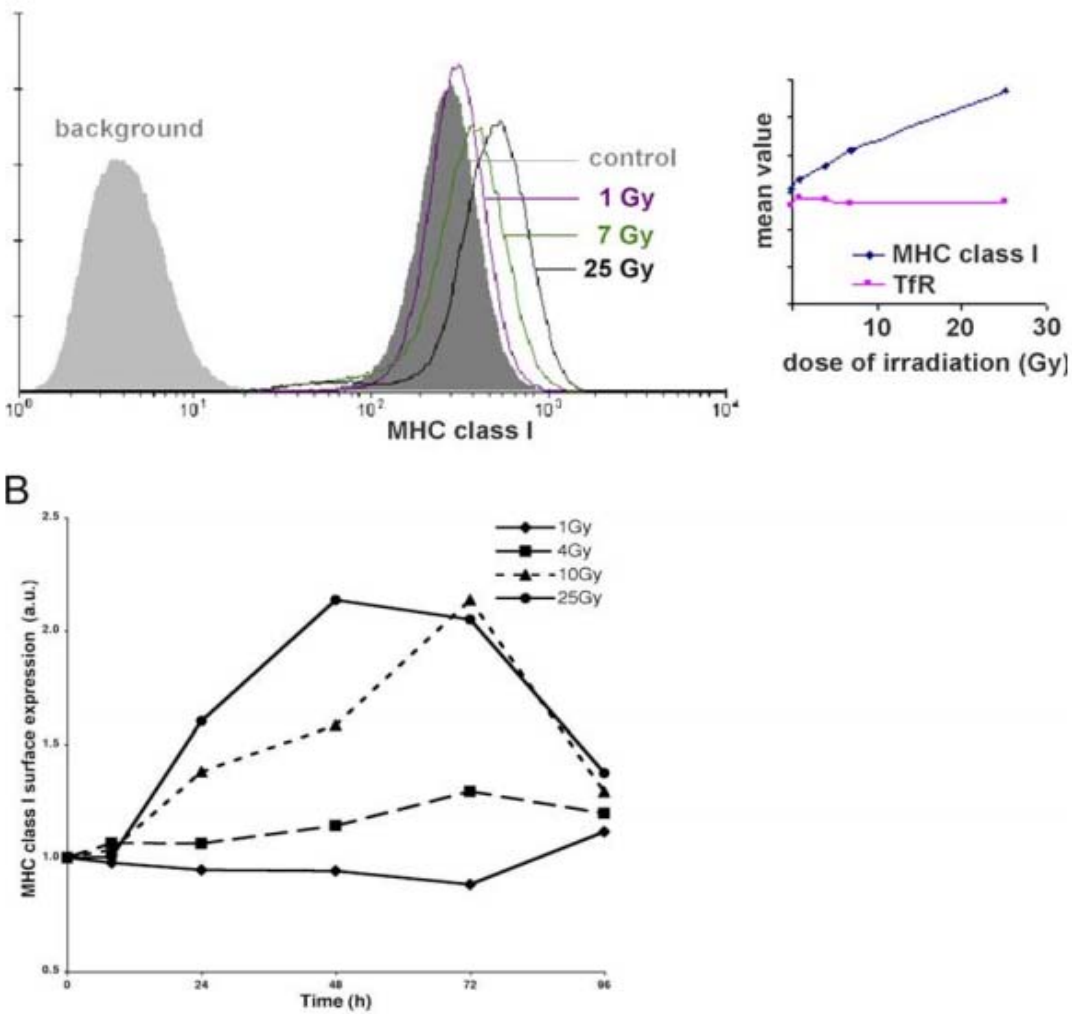






Anitei et al Clin Cancer Res 2014; 20(7): 1892

Effect on tumor cell expression of MHC class I



Reits et al J. Exp Med. 2006; 203: 1259

Somatic mutations affects the immunogenic response

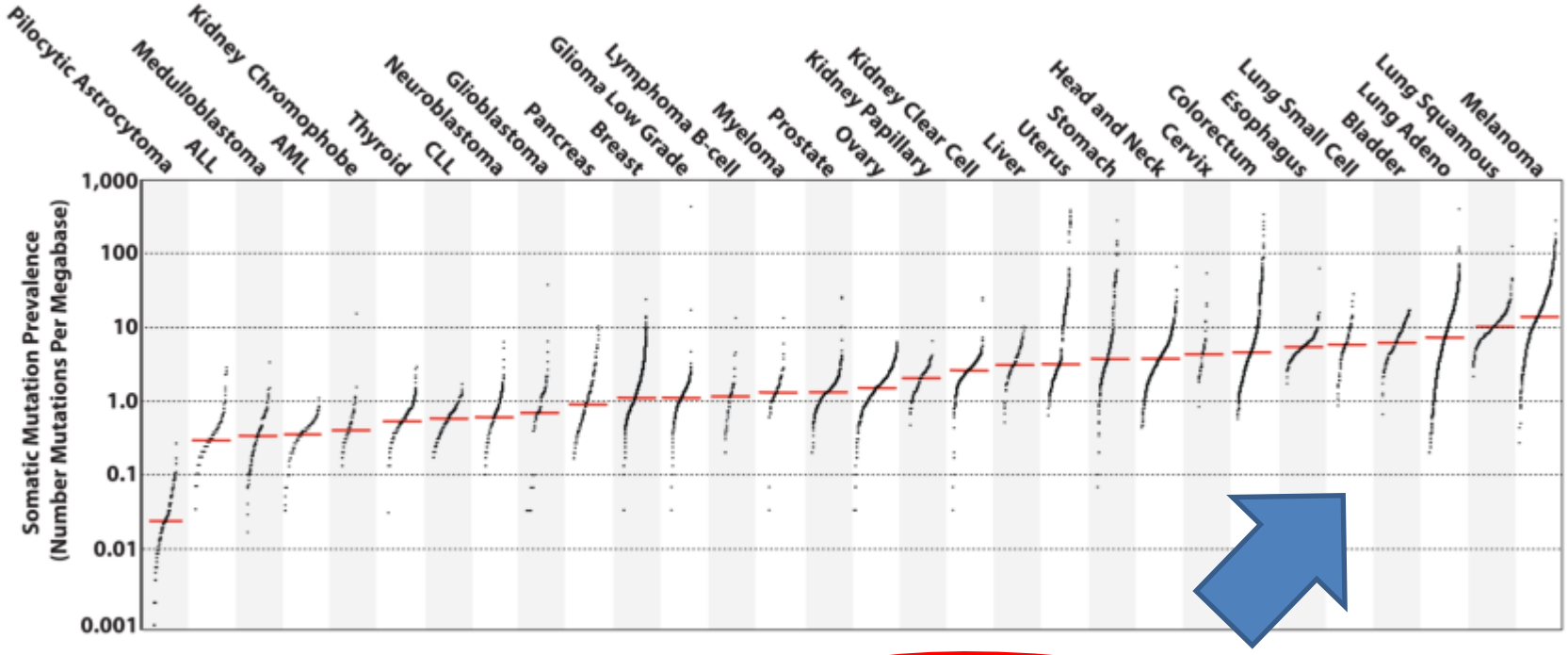
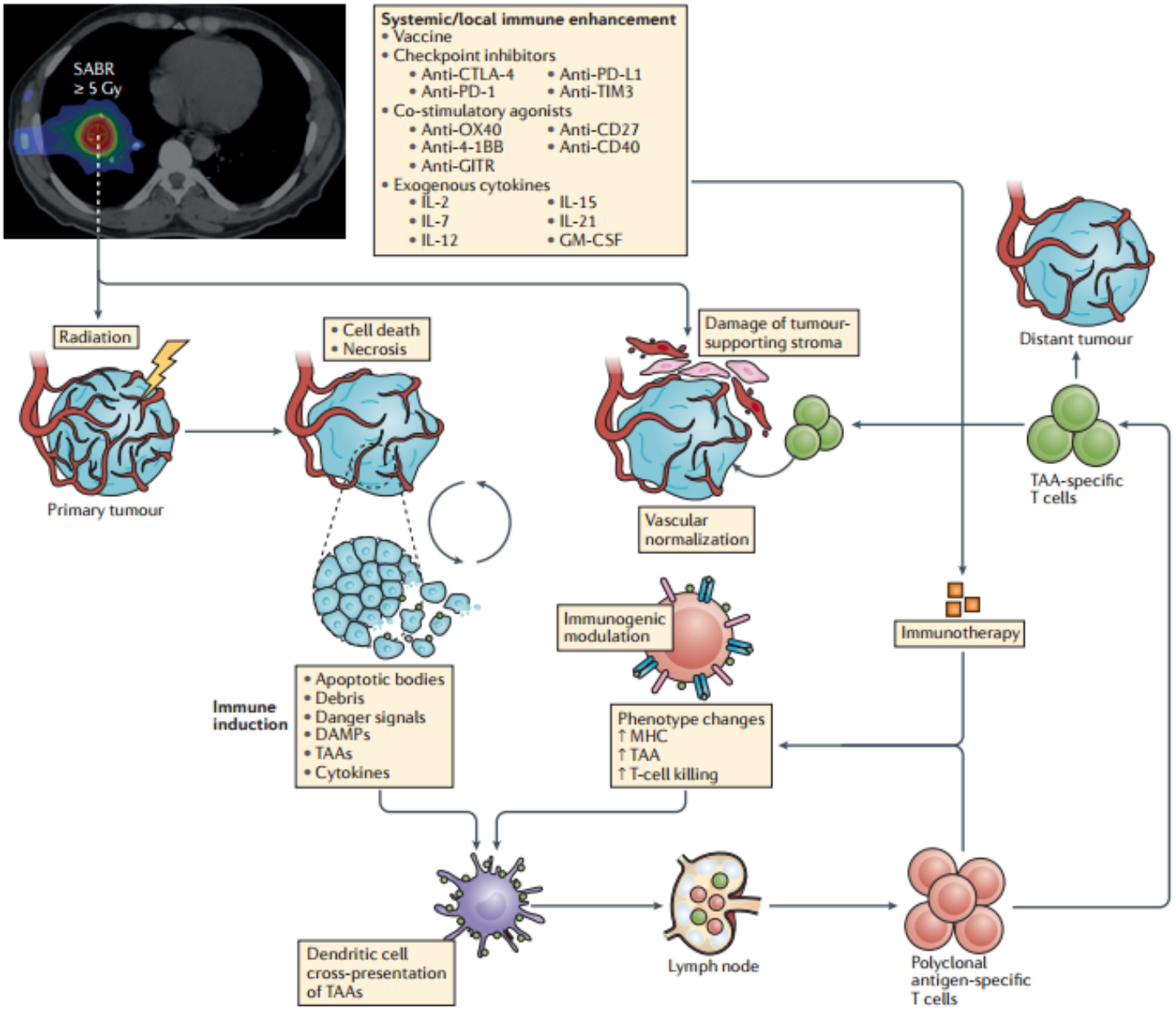


Figure 1. The prevalence of somatic mutation

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

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

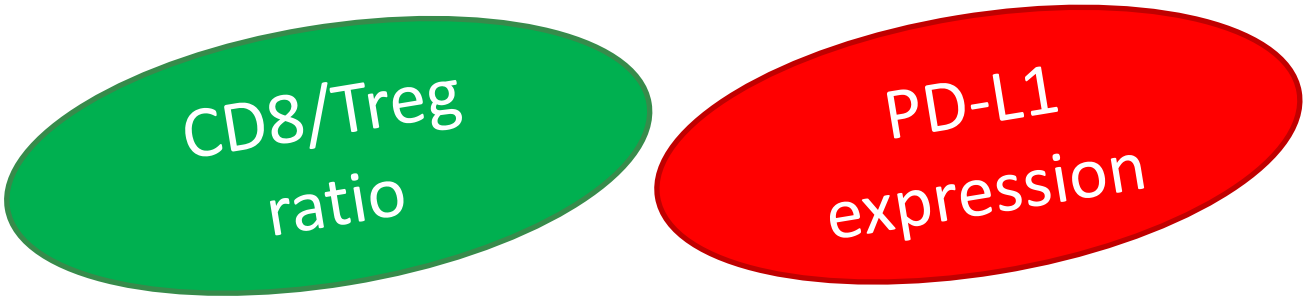
Abscopal immune response



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

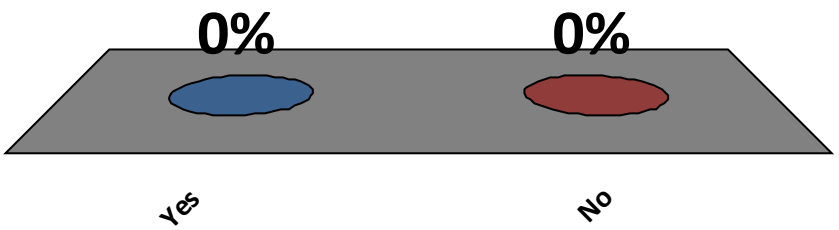
Biomarkers related to abscopal response

- 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



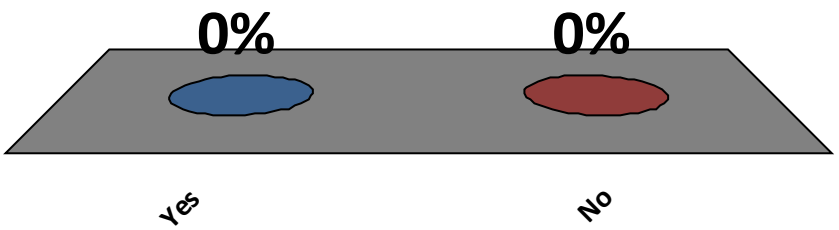
Have you <u>personally</u> experienced an abscopal effect?

A. Yes
B. No



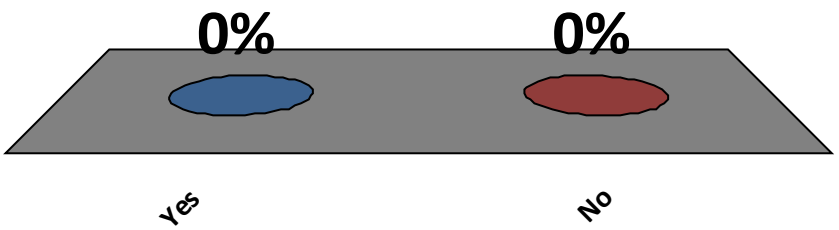
Abscopal effects: They only occur with immune stimulating agents?

A. Yes
B. No



Abscopal effects: They only occur with doses higher than 6 Gy?

A. Yes
B. No



Ongoing studies on iSBRT in the US

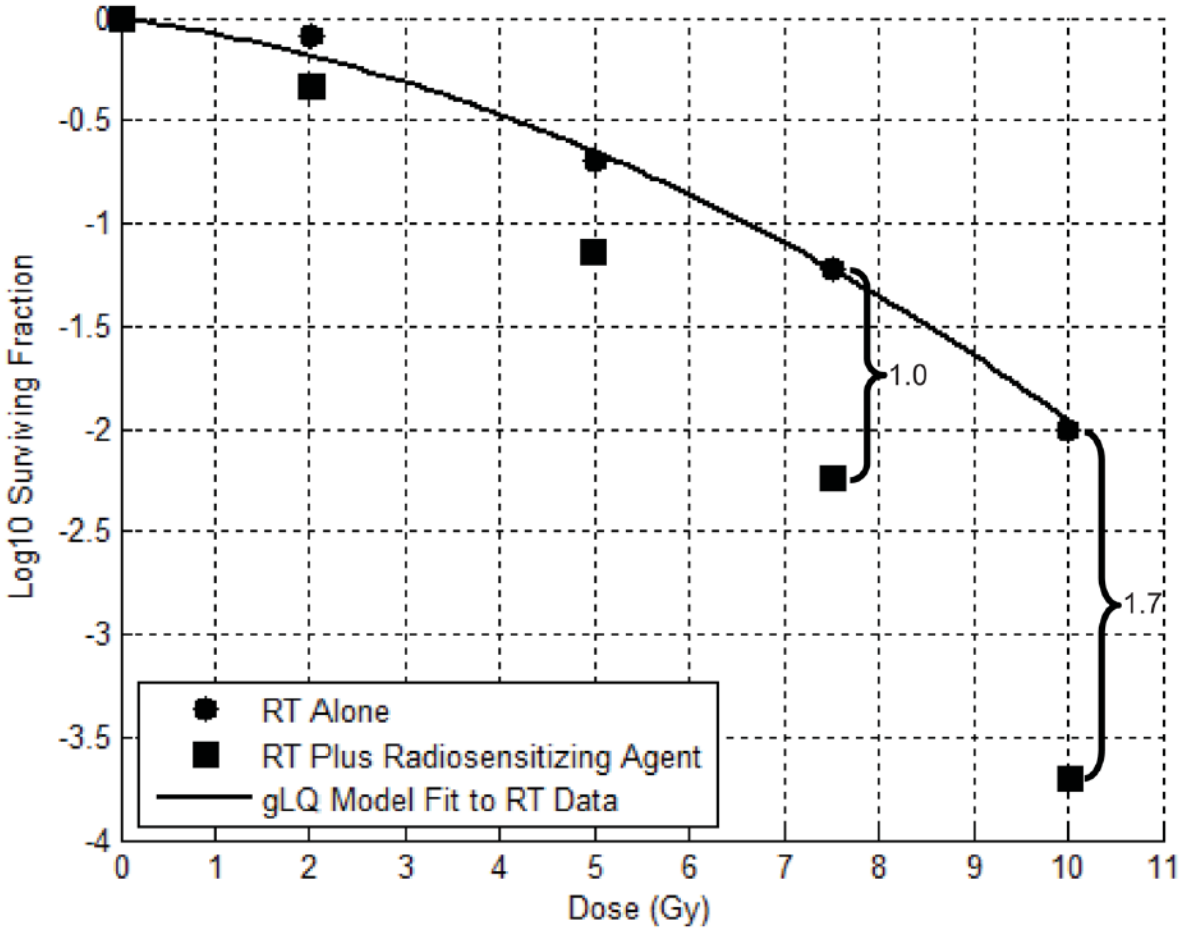
Table 2 | **Selected ongoing clinical trials investigating the efficacy of ISABR**

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.

Concommittant chemotherapy

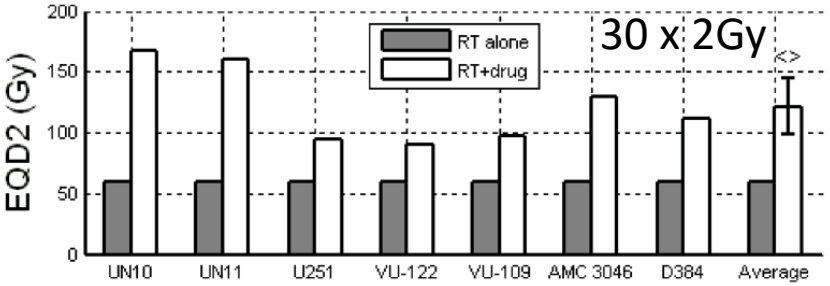
Radiosensitizing chemotherapy

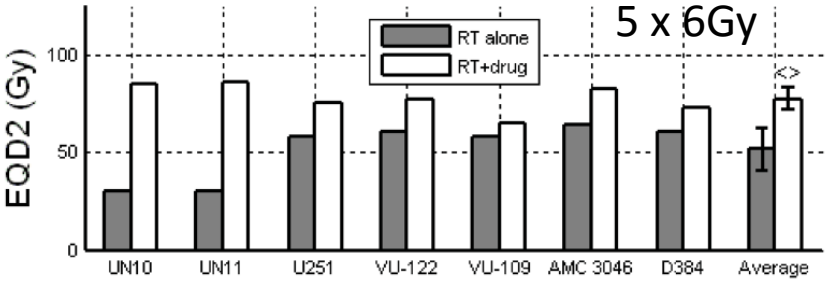


Ohri et al: IJROBP 2012; 83 (1): 385

Radiosensitizing chemotherapy

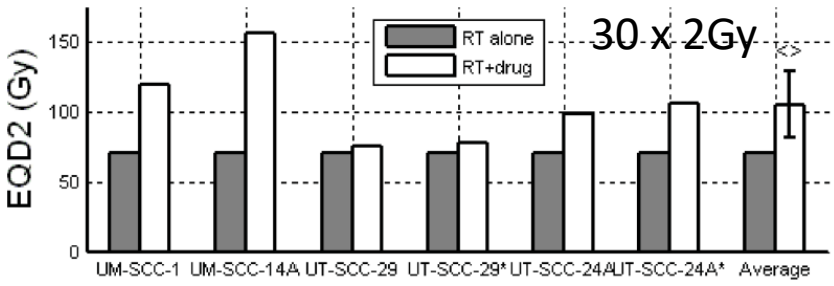
GBM

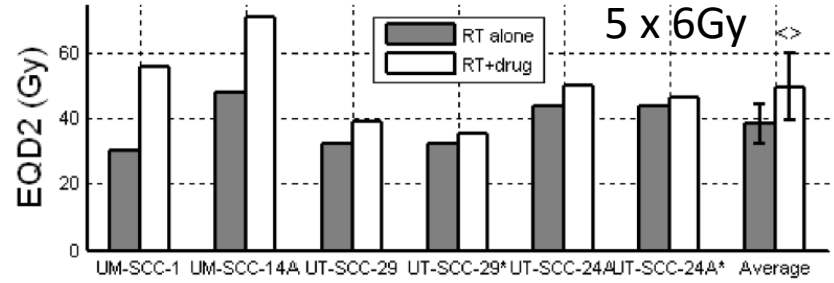




RT +/- concurrent temozolomide

HNC

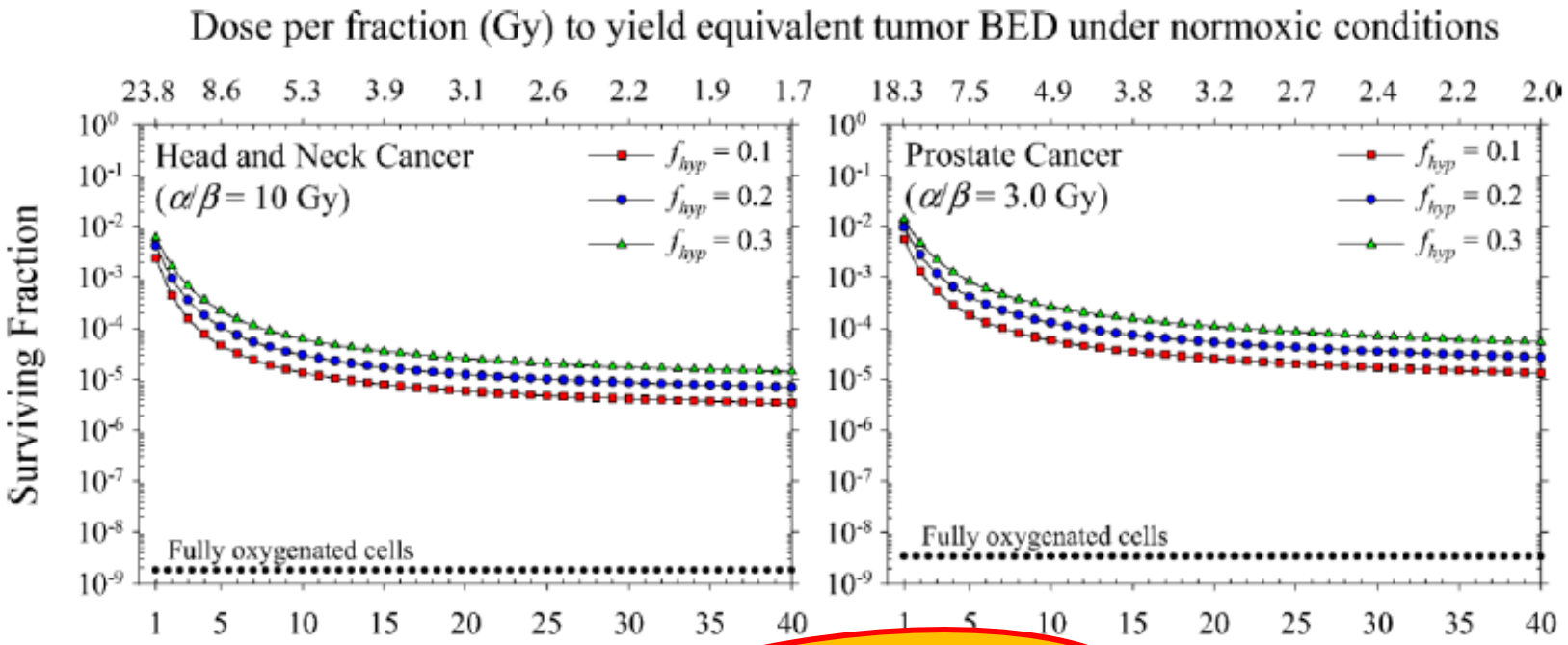




RT +/- concurrent cisplatin

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

The effect of hypoxia is dependent of the number of fractions



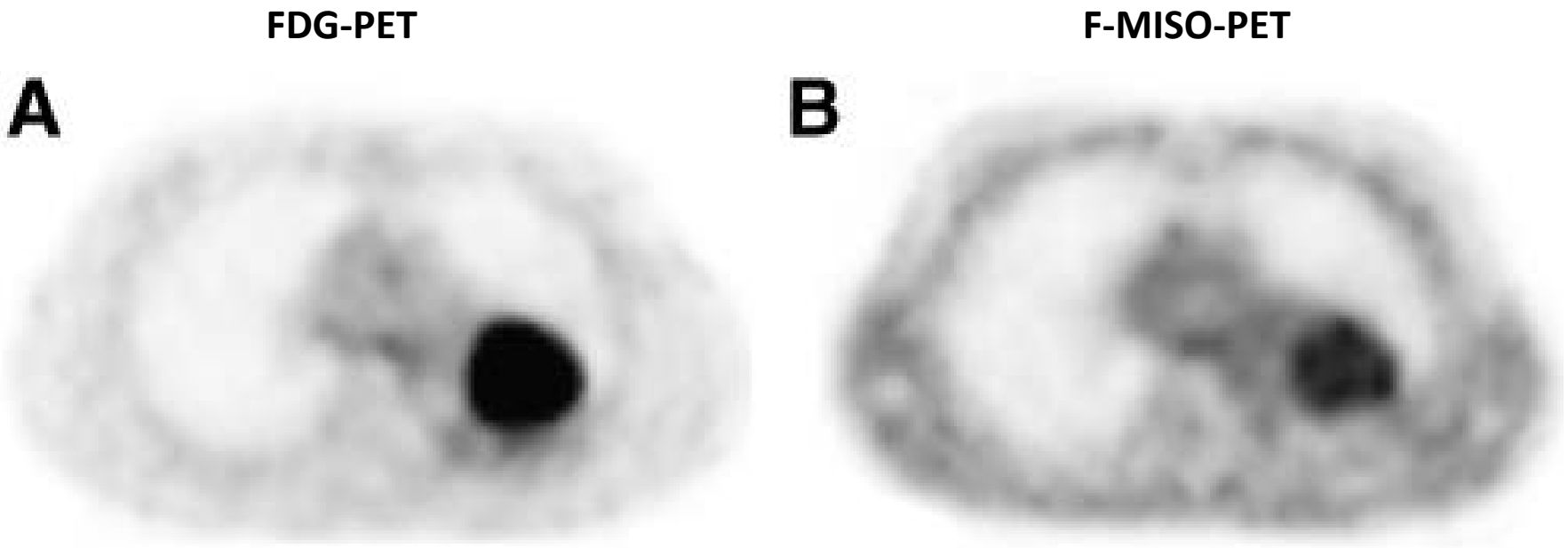
….so, why don't we add nimorazole to SBRT?

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

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

SBRT – What we know about dose & fractionation

Matthias Guckenberger

UniversityHospital Zurich

Question

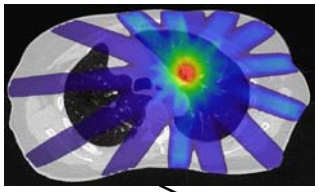
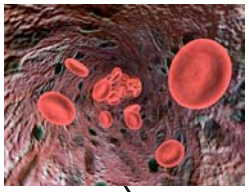
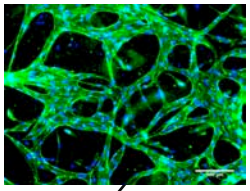
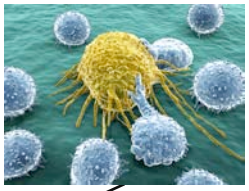
Which of the following questions is TRUE

1) The linear quadratic model should not be used in SBRT
2) Single fraction radiosurgery is always preferable to fractionated SBRT
3) The maximum tolerated dose in SBRT depending on mostly on tumor size and location

Technology meets Biology

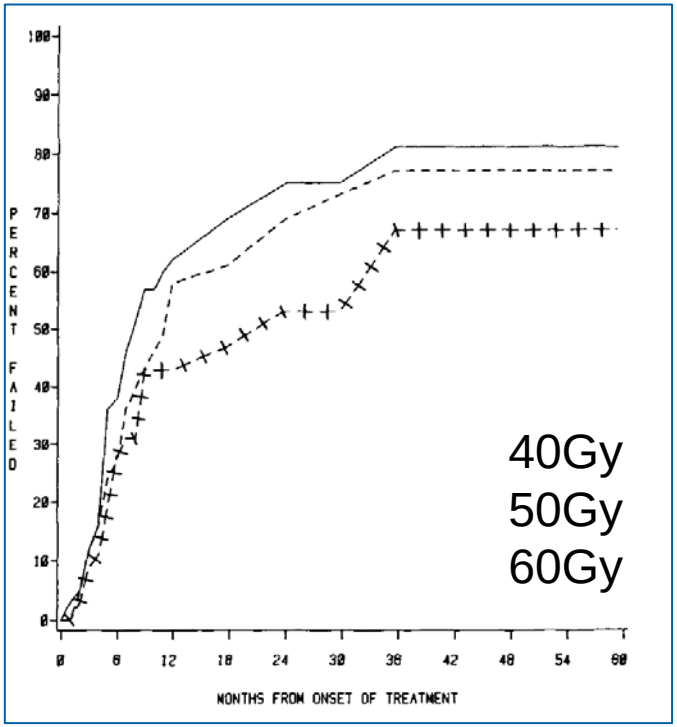
Biology of Stereotactic Body radiotherapy

Ablative RT dose	Endothelial damage	Anti-vascular effect	Immune effect

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

Dose effect relationship in NSCLC



Perez Cancer 1987

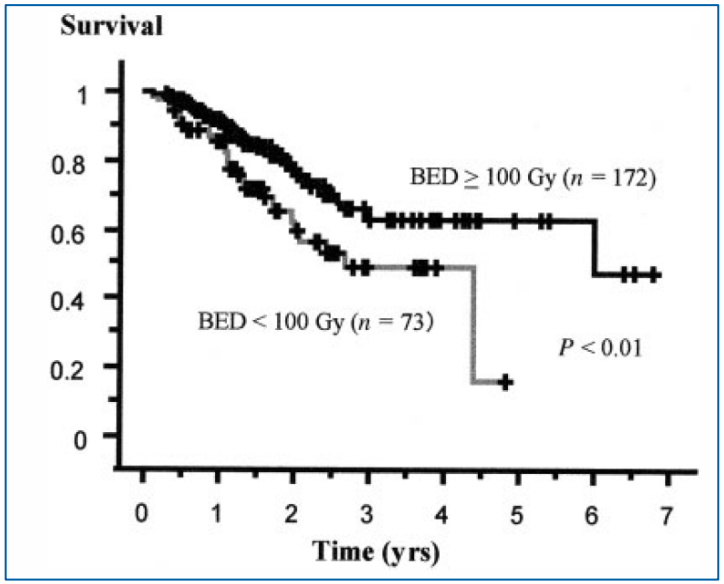
Isocenter dose	Estimated LPFS (%) at:		
	12 months	24 months	30 months
>70 Gy group, mean = 75 Gy (%)	81	61	38
<70 Gy group, mean = 65 Gy (%)	53	26	26
Dose at 50% LPFS (Gy)	64	72	84.5

Martel Lung Cancer 1999

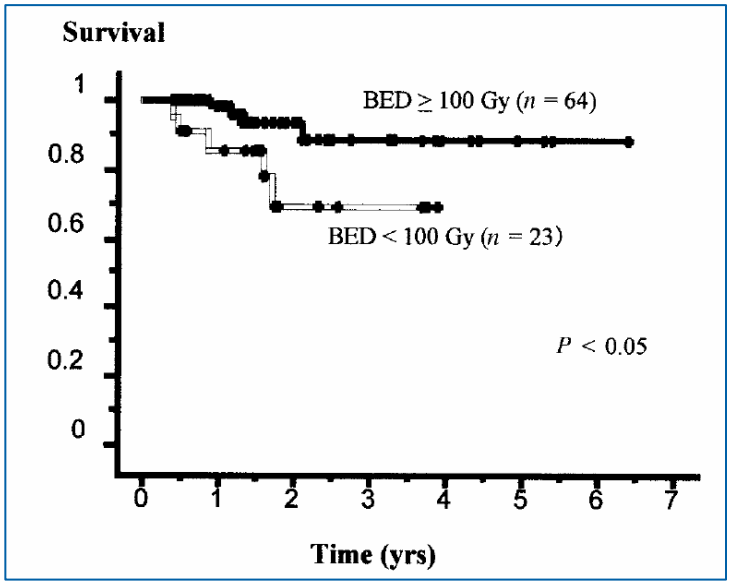
- High irradiation doses required for local tumor control
- Effect on OS limited due to competing risk of systemic progression

Dose effect relationship in SBRT for NSCLC

Onishi Cancer 2004



All patients

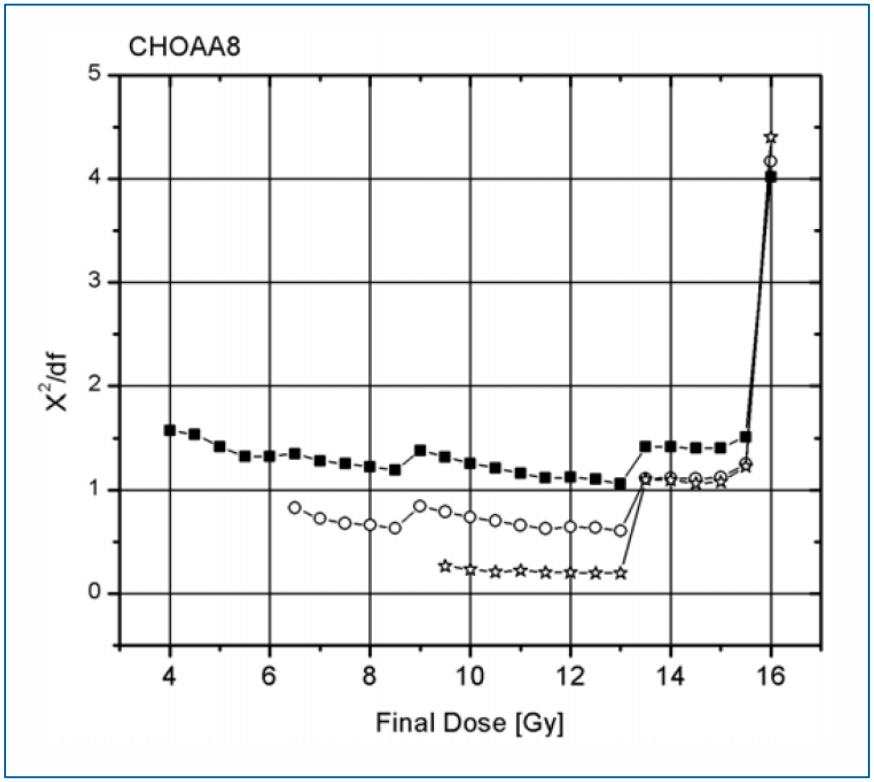


Medically operable patients

- 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

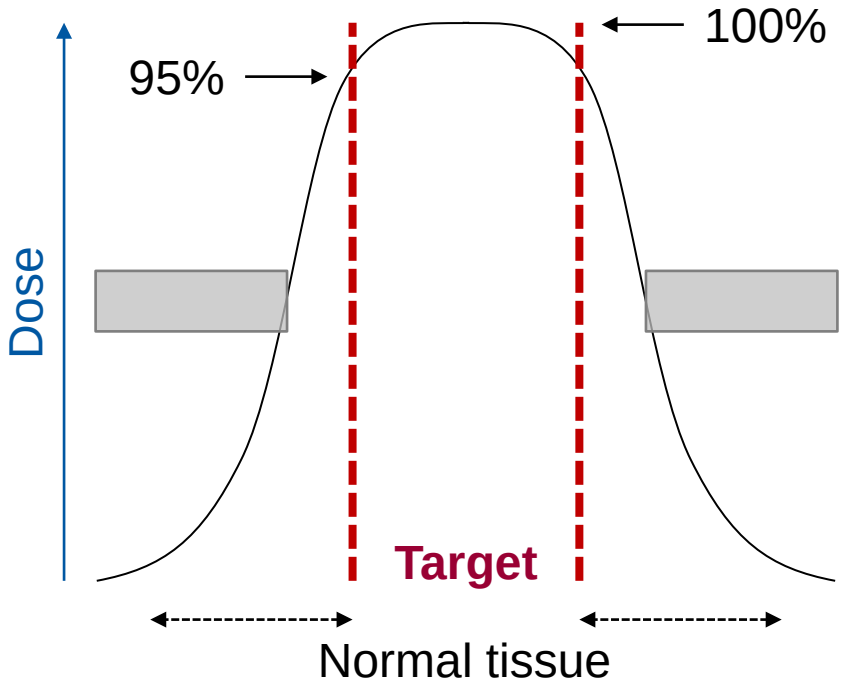


In cell lines (*fibroblasts, glioblastoma, prostate cancer*)

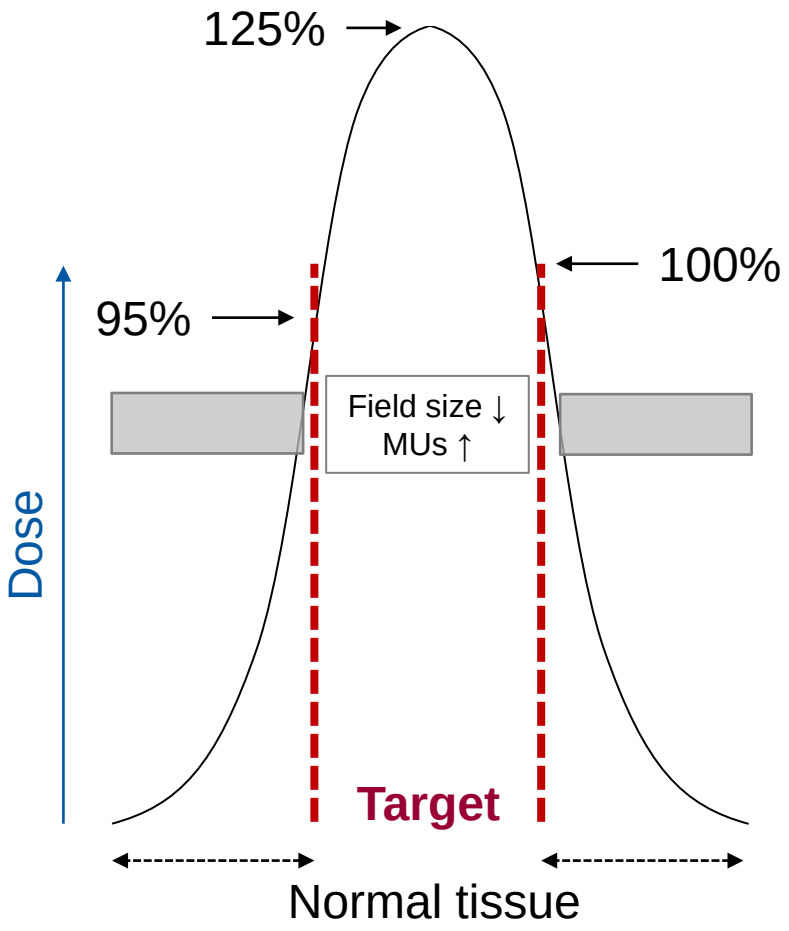
- LQ accurate up to single fraction doses of ~15Gy

Dose in SBRT – dose prescription

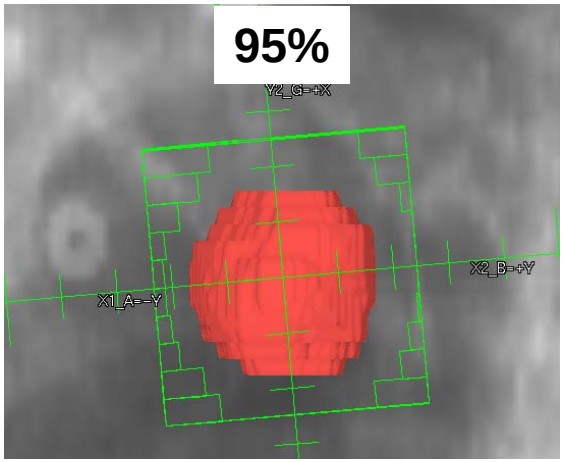
Conventional radiotherapy

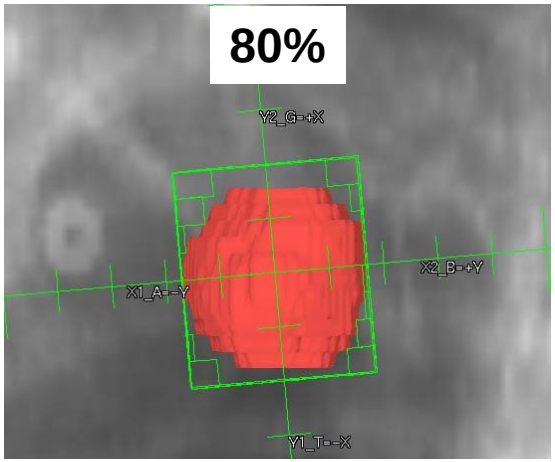


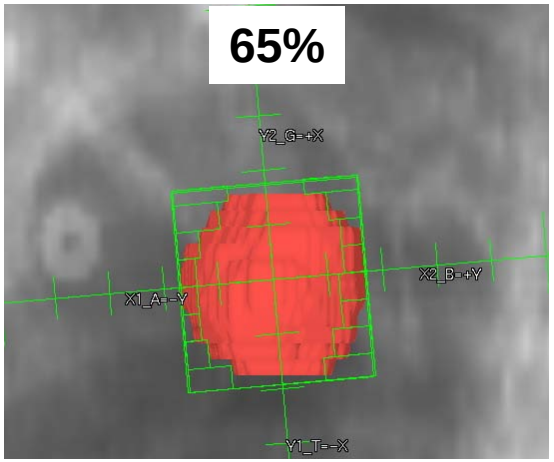
Stereotactic radiotherapy

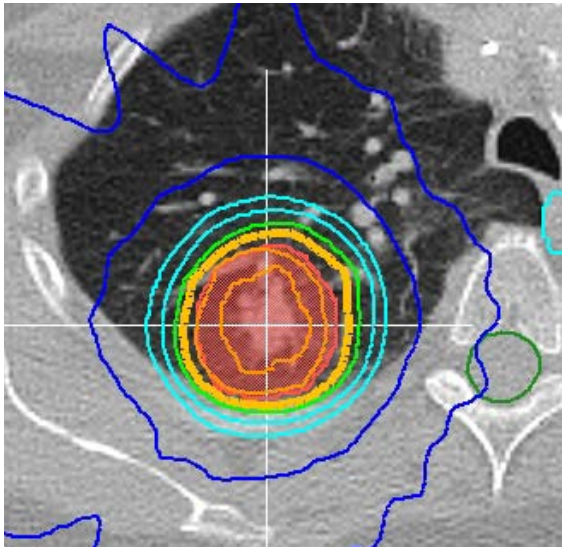


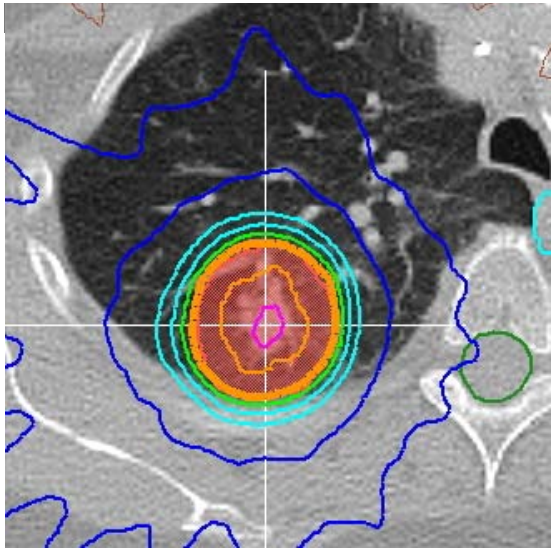
Dose in SBRT – dose prescription

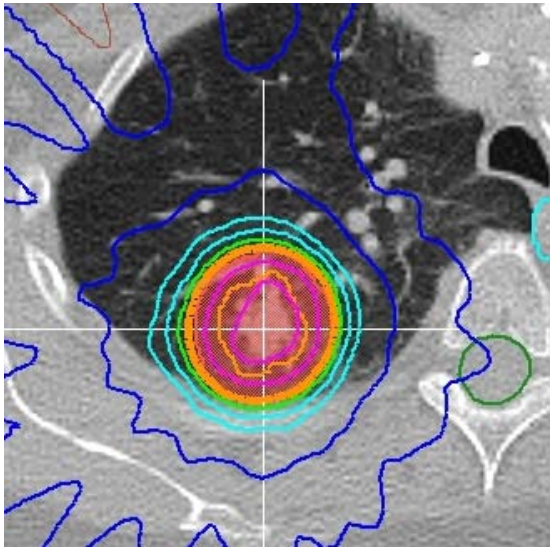




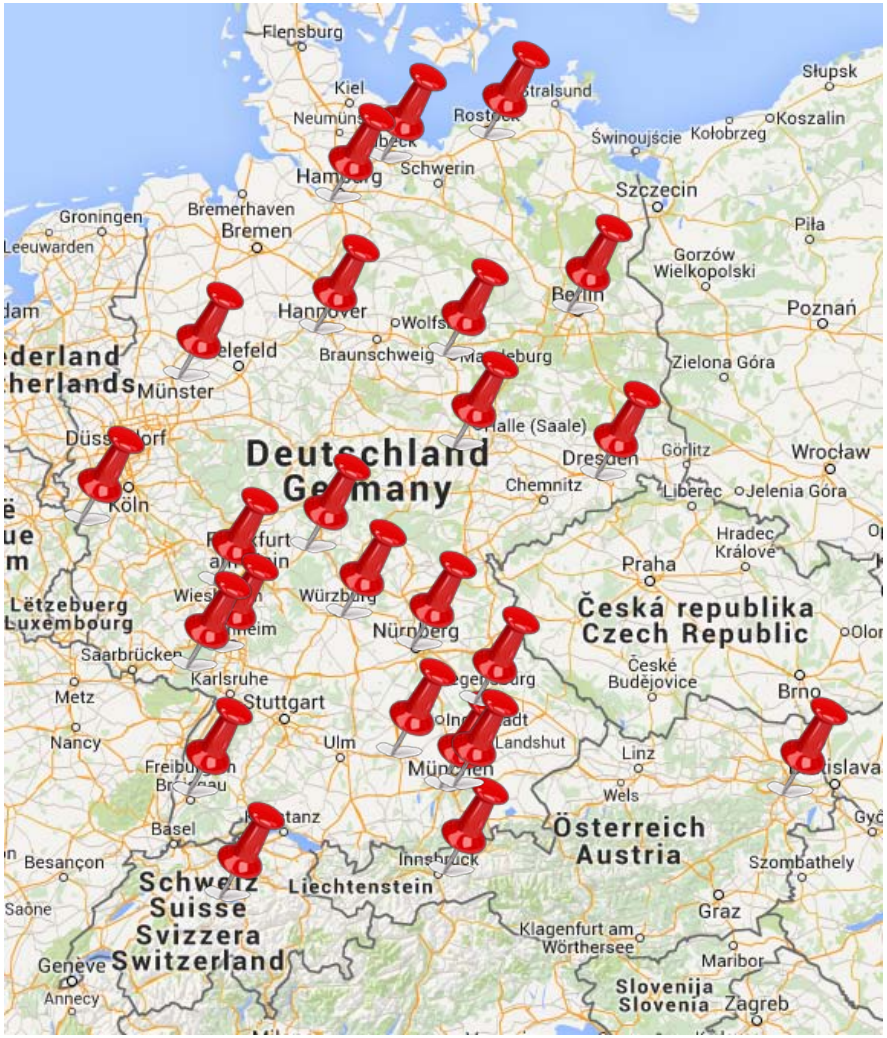








Applicability of LQ model in SBRT



Study Design

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

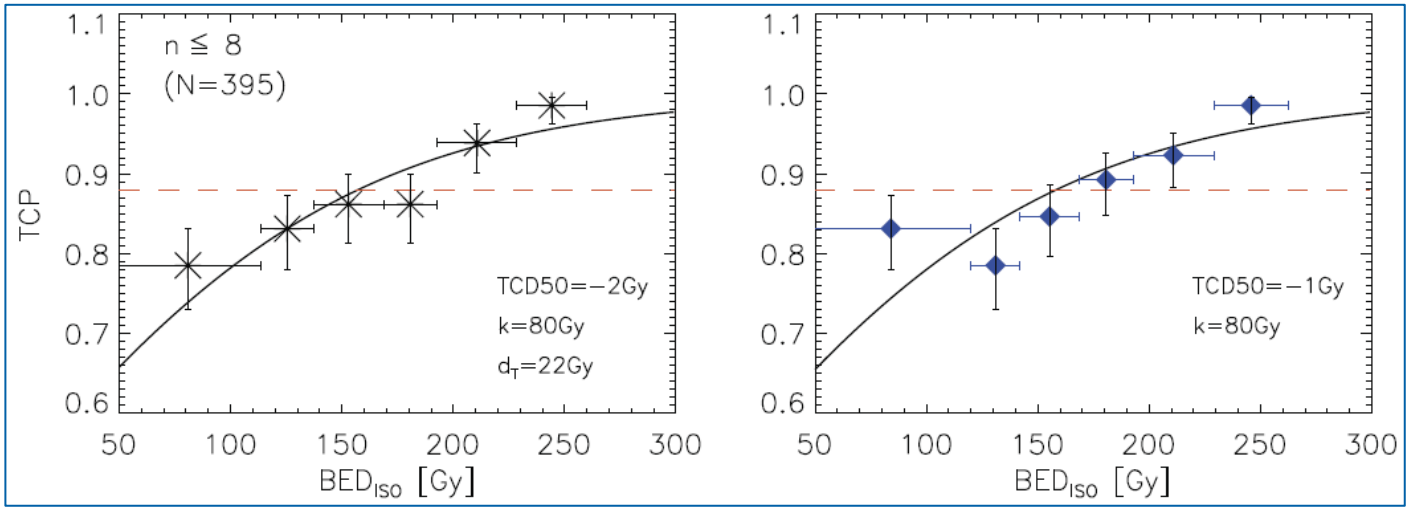
DEGRO AG Stereotactic Radiotherapy

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

LQ model versus “extended” biological models

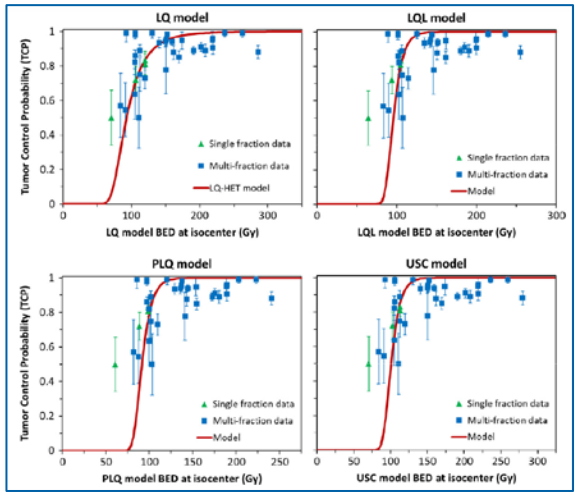
Linear quadratic model

Linear quadratic linear model

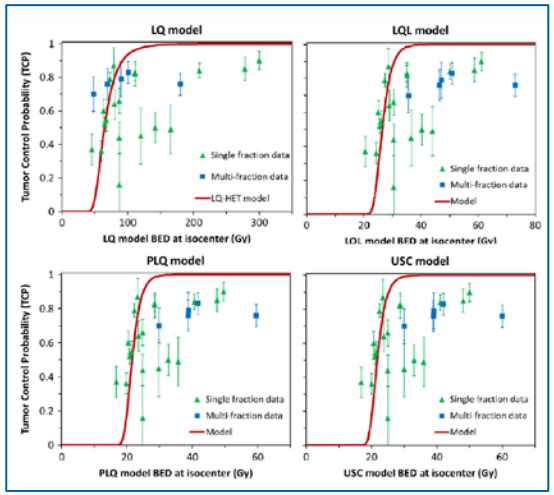
Universal Survival Curve

Pade Linear Quadratic

SBRT - stage I NSCLC



SRS & SRT - brain mets

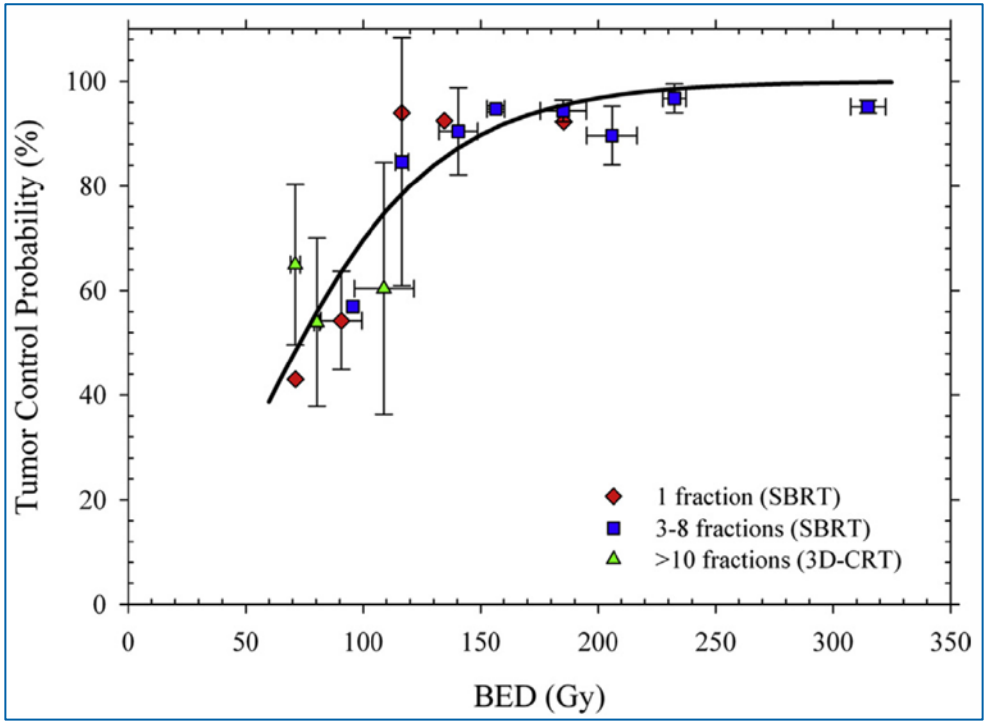


Shuryak Radiother Oncol 2015

➢ LQ model sufficient for description of clinical data

TCP modeling considering different fractionations

Brown IJROBP 2013

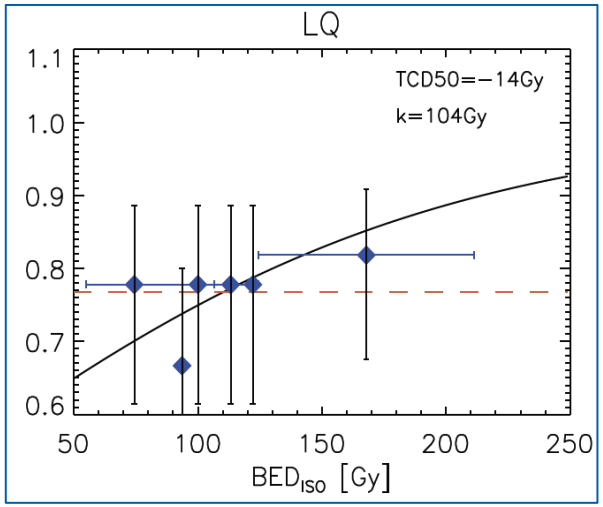


- One TCP model describing outcome of various fractionations

Single fraction SRS versus fractionated stereotactic radiotherapy

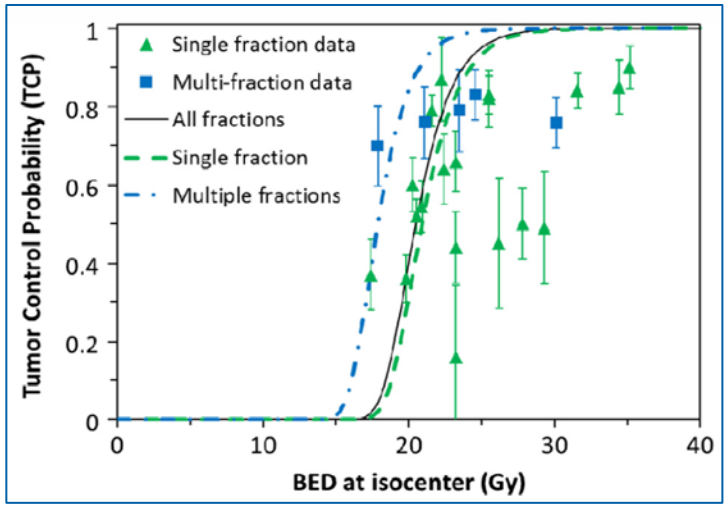
SBRT for stage I NSCLC

Guckenberger Radiother Oncol 2013



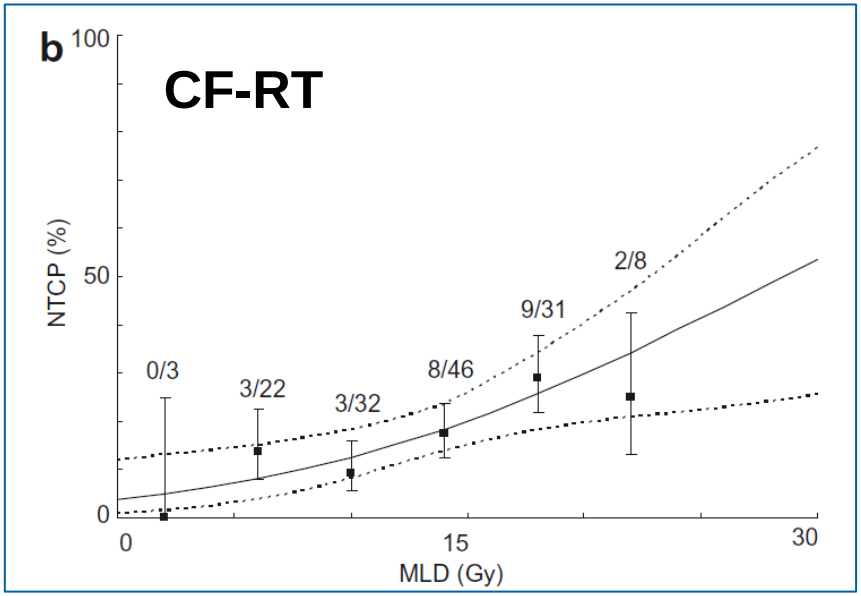
SRS for brain metastases

Shuryak Radiother Oncol 2015

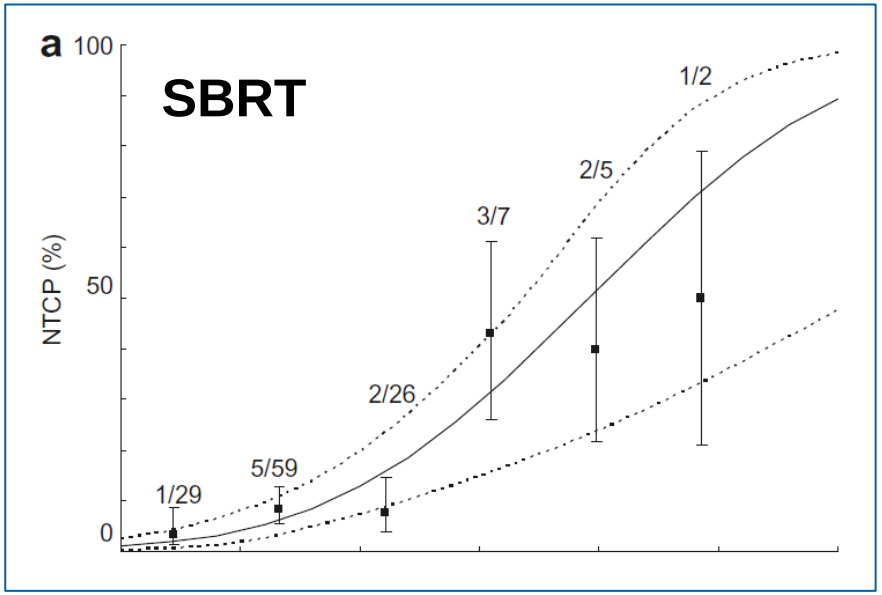


- ***Stage I NSCLC***: No dose effect relationship for 15-33Gy
- ***Brain metastases***: Higher efficacy of SRT vs SRS

Applicability of LQ model in SBRT: NTCP of pneumonitis



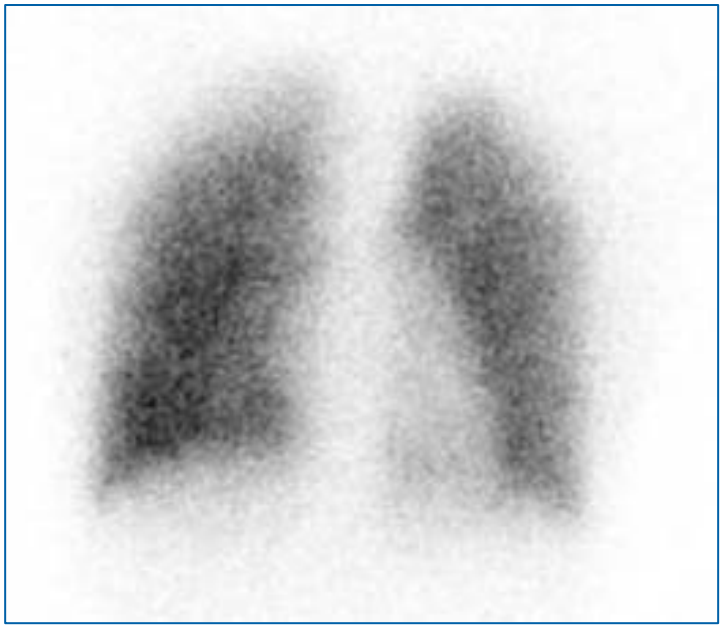
Borst Radiother Oncol 2009

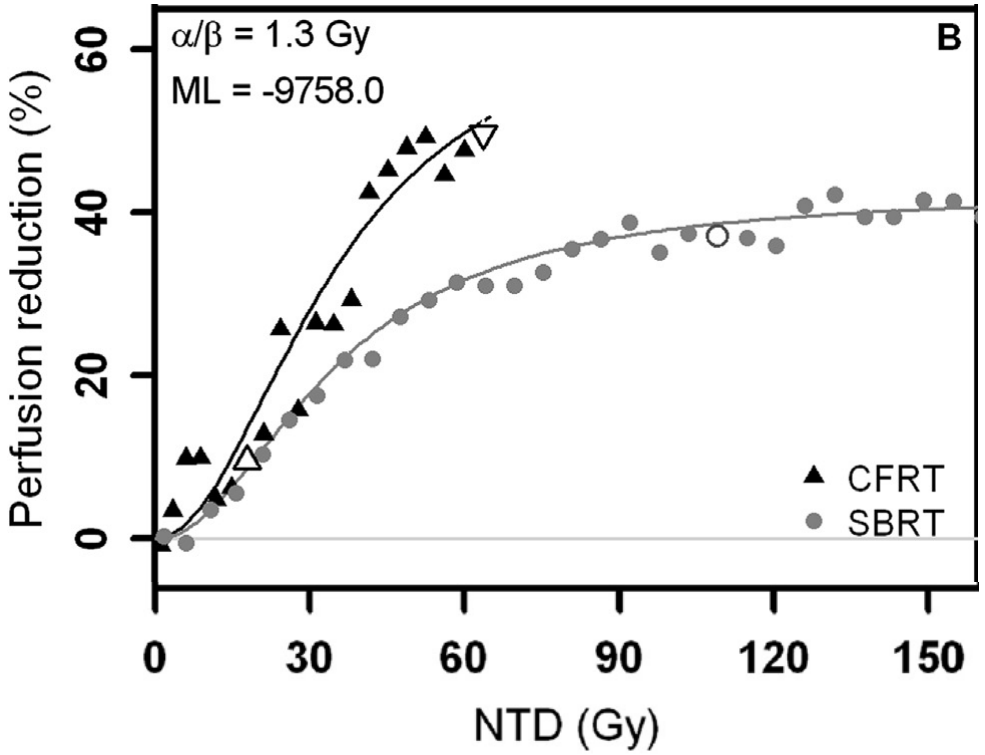


After correction for differences in SFD using the LQ model:

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

Applicability of LQ model in SBRT: NTCP of lung perfusion



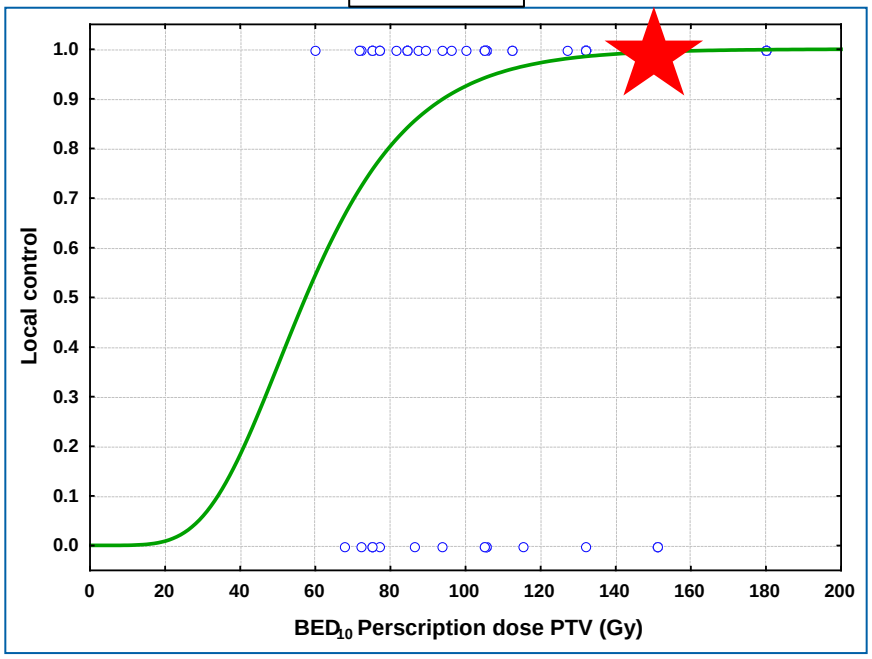


After correction for differences in SFD using the LQ model:

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

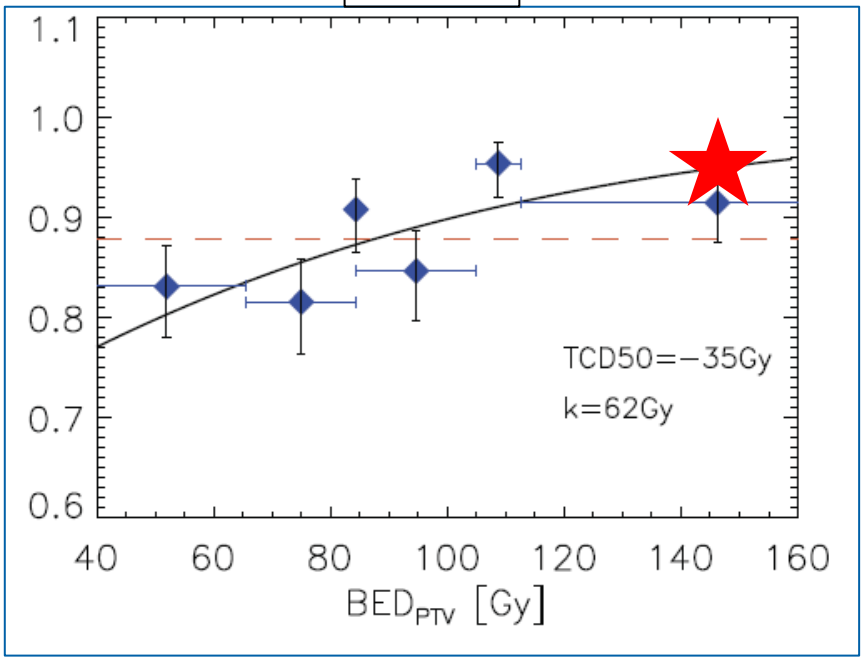
What dose is now actually required?

n=505



Grills JTO 2010; Ohiri IJROBP 2012

n=395

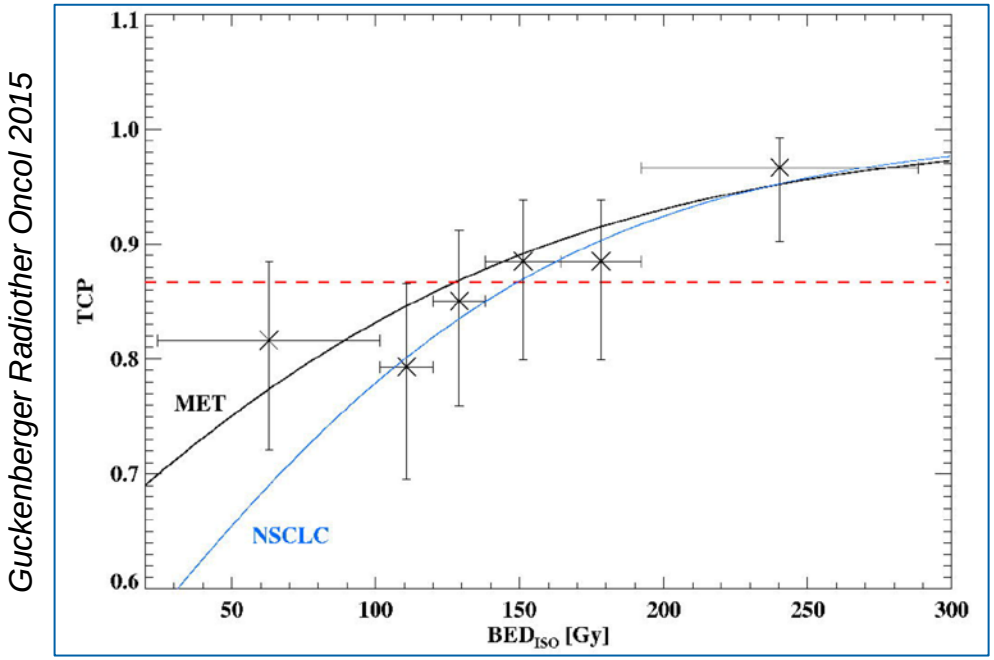


Guckenberger Radiother Oncol 2013

★ **= 3 x 18Gy**

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

Primary NSCLC & lung metastases



NSCLC: n=525

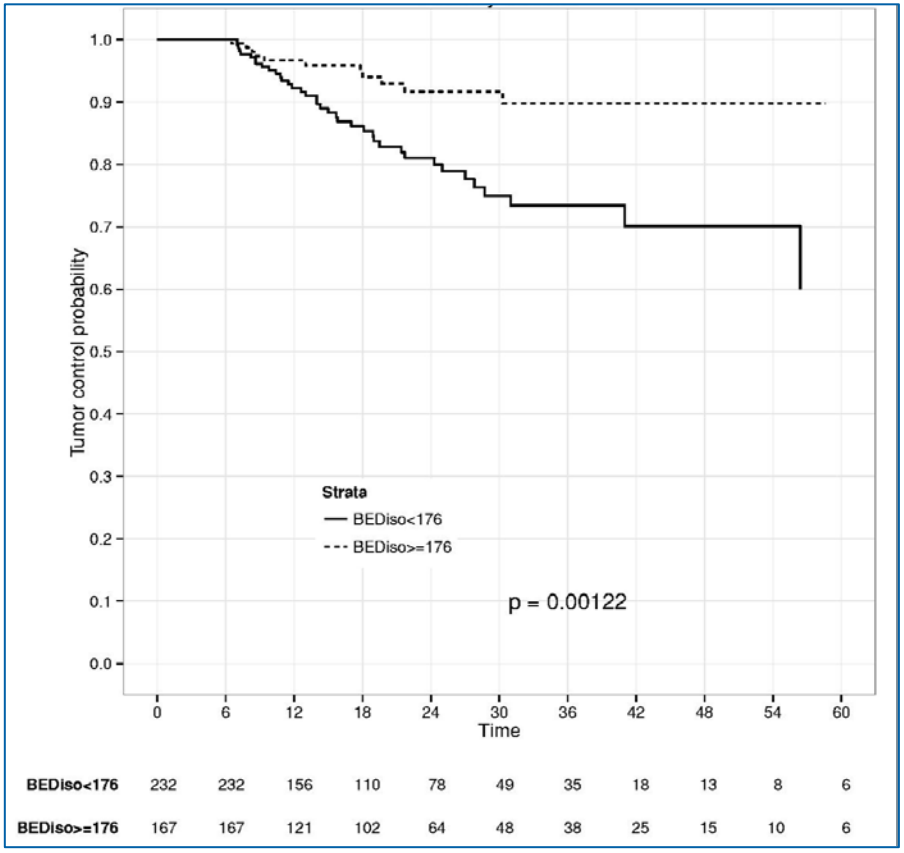
Lung mets: n=399

Dose effect relationship not significantly different between

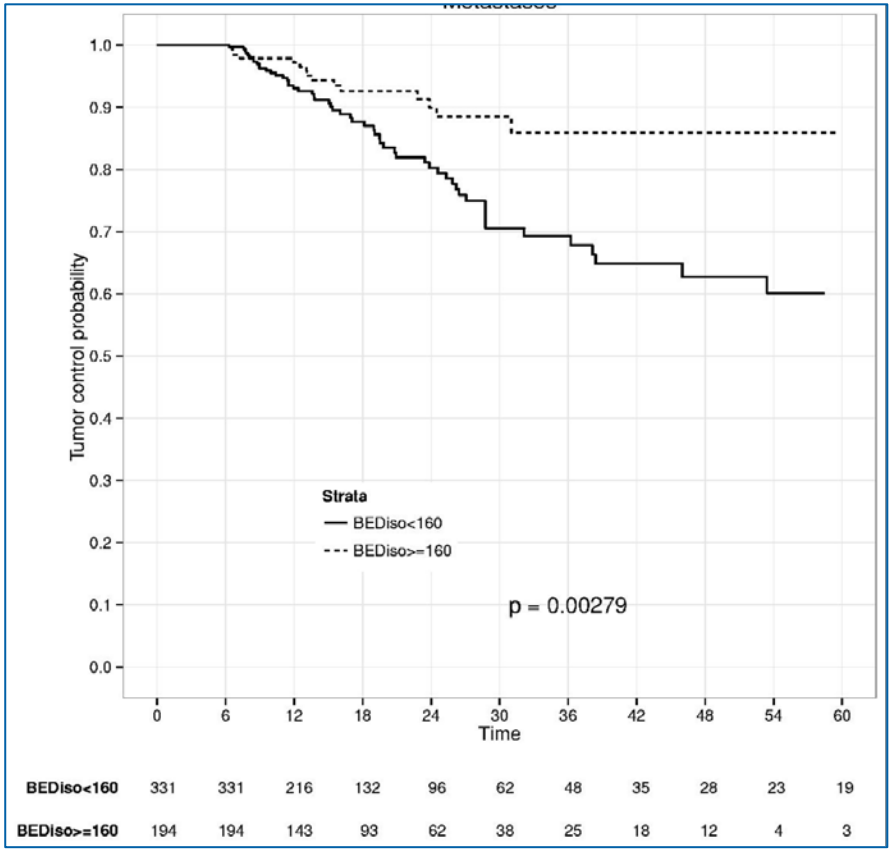
- Primary NSCLC
- Lung metastases of various primary tumor sites

Primary NSCLC & lung metastases

Primary stage I NSCLC

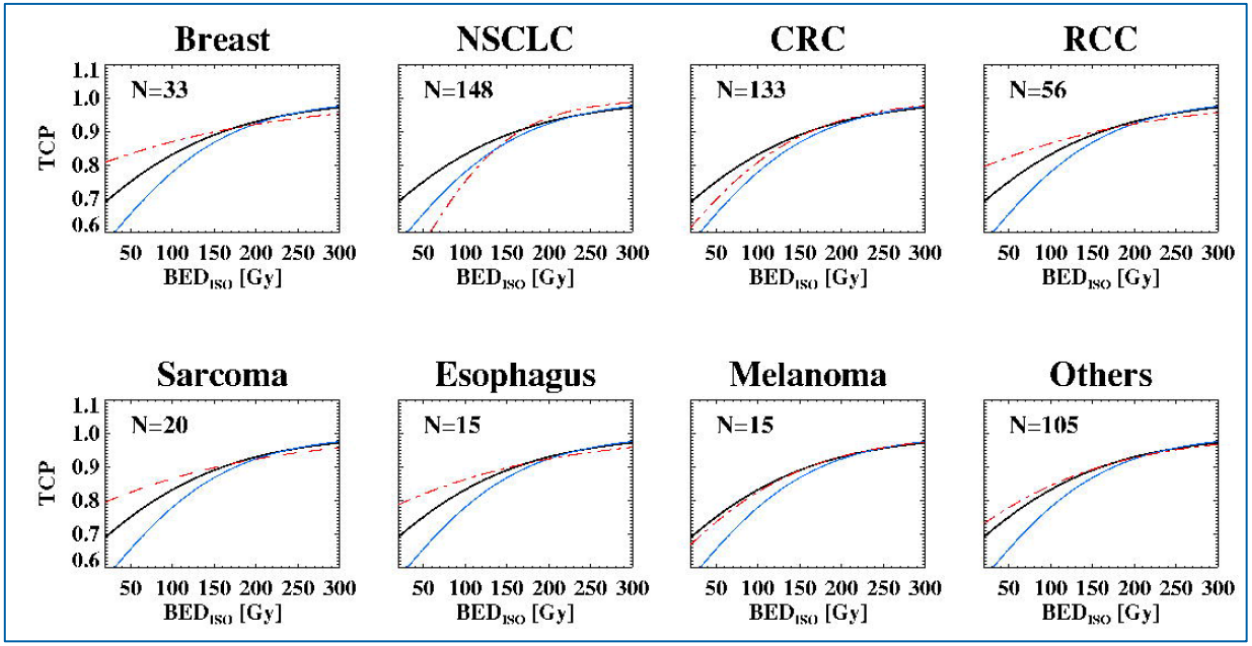


Pulmonary metastases



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**

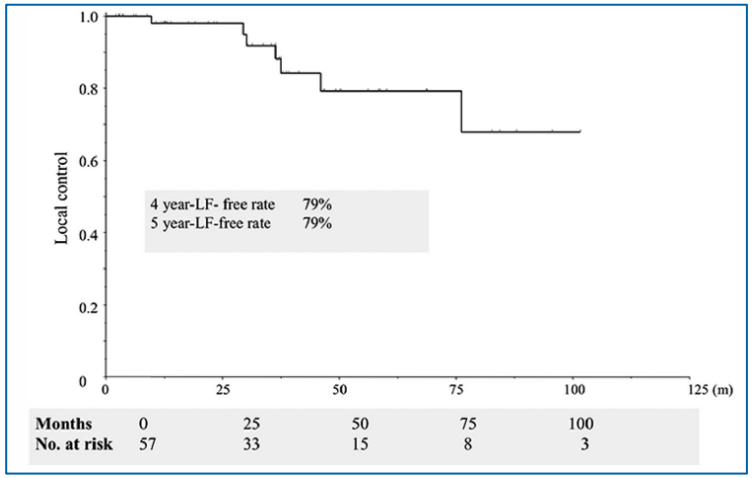
Guckenberger Radiother Oncol 2015

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

Late recurrences in stage I NSCLC

Swedish phase II trial:
N=57

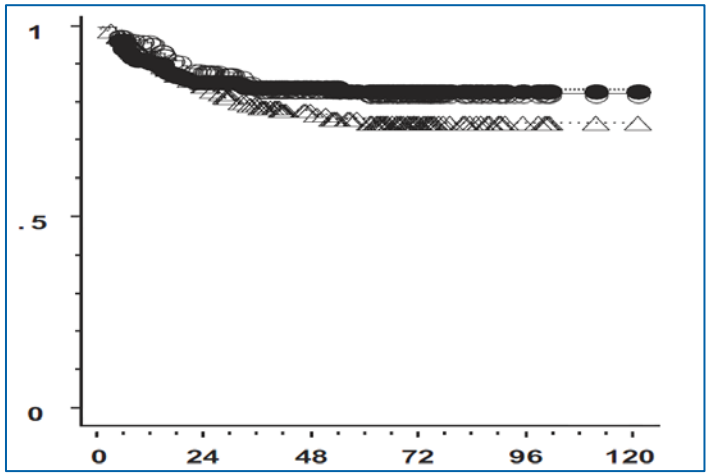
Lindberg Acta Oncol 2015



Median FU 41.5 months
3 x 15Gy @ 67%

Japanese prospective study:
N=180

Shibamoto JTO 2015

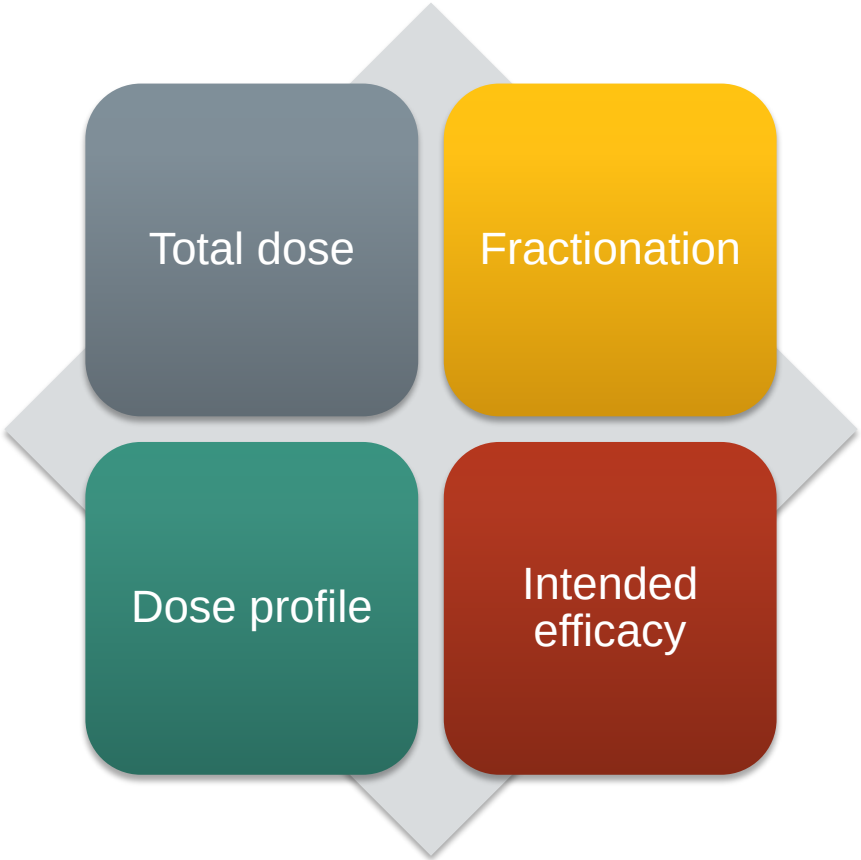


Median FU 52.5 months
4 x 11-13 Gy @ isocenter

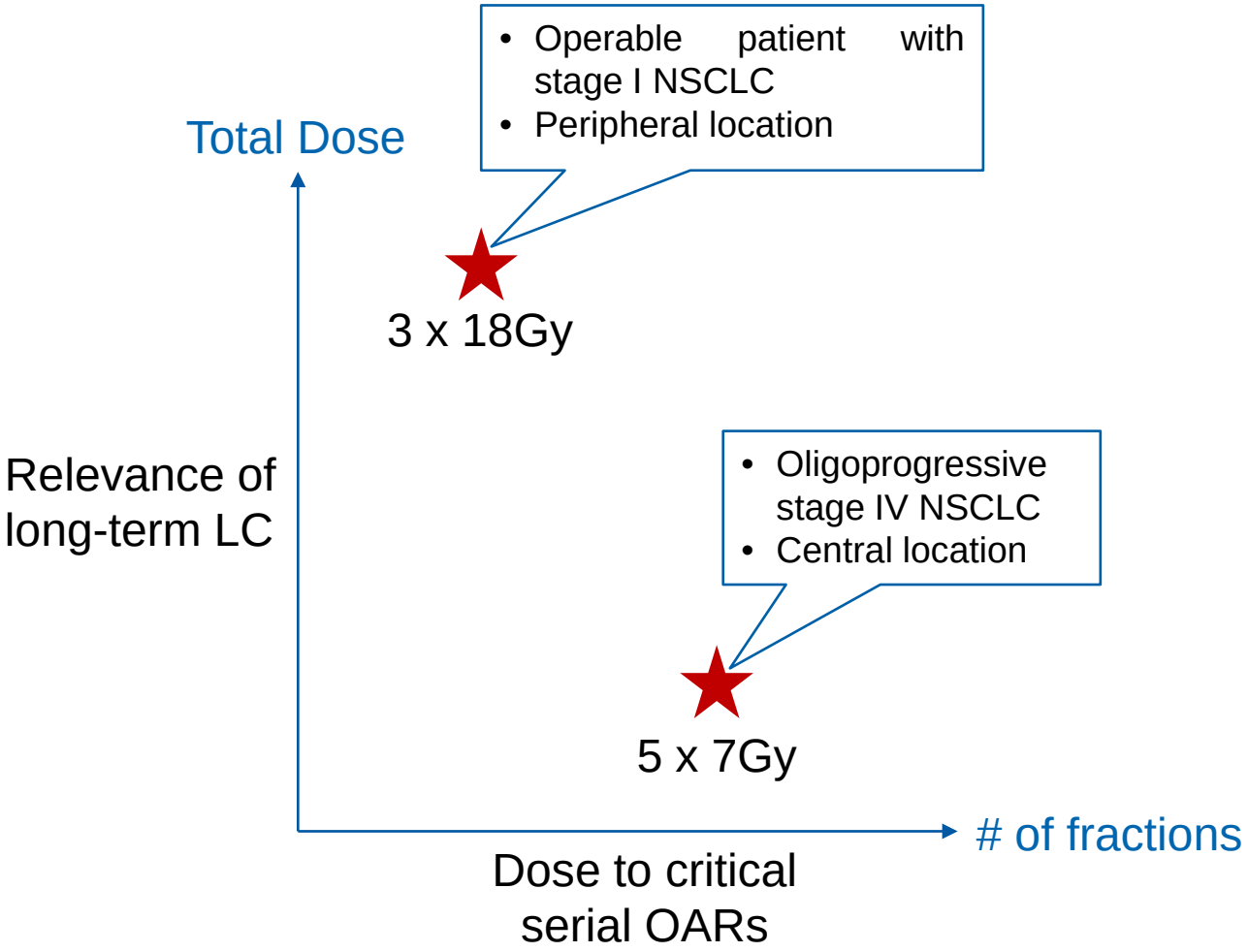
- Very few recurrences after 3 – 5 years

➢ Validity of TCP modelling

Degrees of freedom in SBRT

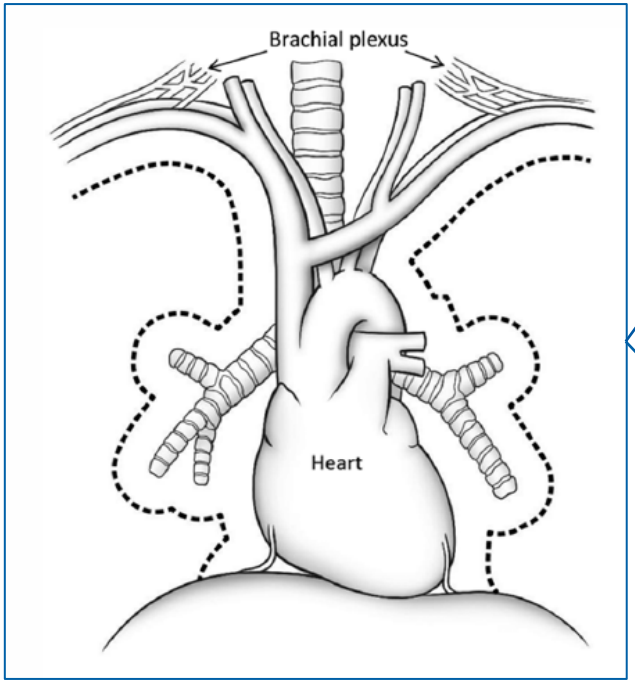


Risk adapted fractionation



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 (Roesch submitted)
- 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

Survival after SBRT in relationship to dose

Dose group	BED
Low	<83.2Gy
Medium	83.2 – 106Gy
Medium – high	106-146Gy
High	>146Gy

Zhang IJROBP 2011

- Decreased CSS after low-dose SBRT
- Decreased OS after low-dose **and high-dose SBRT**
  - ➢ Occult toxicity?

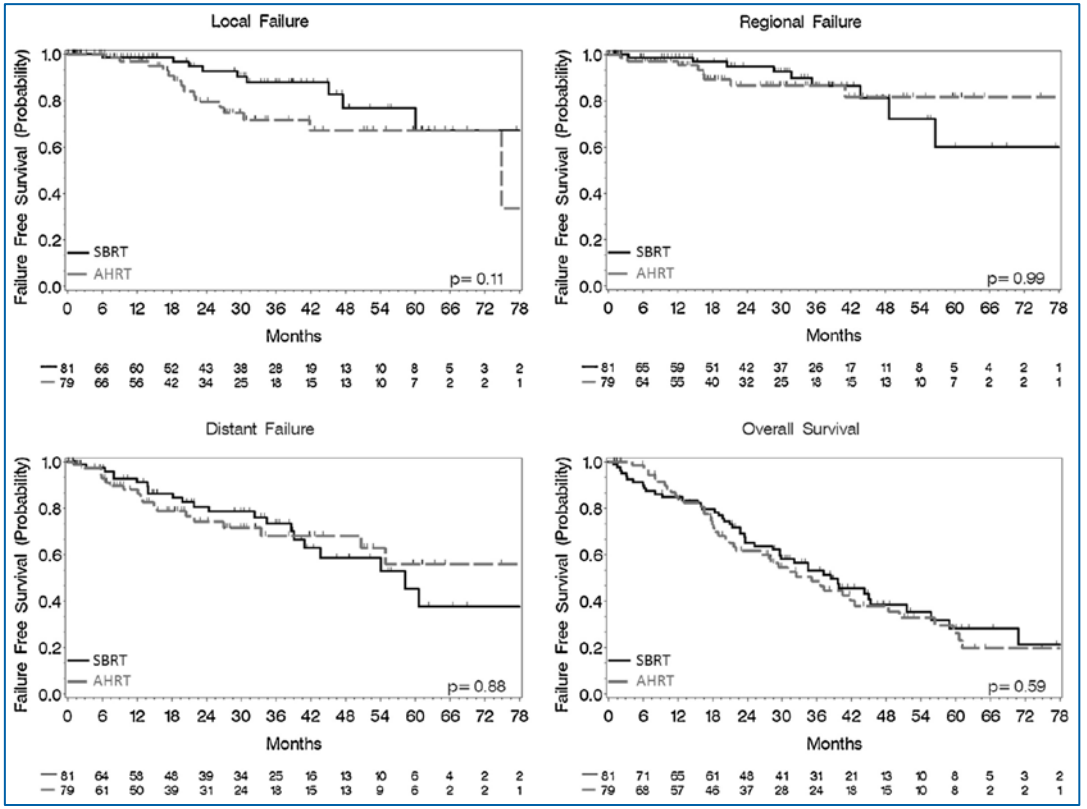
Comparison of accelerated hypofractionation and stereotactic body radiotherapy for Stage 1 and node negative Stage 2 non-small cell lung cancer (NSCLC)

Lucas Lung Cancer 2014

- Retrospective study
- 160 patients
- SBRT: 54Gy in 3F
- AHRT: 70.2Gy in 26Fx

➢ No difference in any in OS, RF, DF, LC

➢ No difference in toxicity



➢ SBRT not fundamentally different, “just” more convenient

CONCLUSIONS

- Clear dose effect relationship in stage I NSCLC and pulmonary metastases
- Dose explains well high rates of local tumor control
- 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

Erasmus MC
University Medical Center Rotterdam

Daniel den Hoed
Cancer Center

Errors and Uncertainties in SBRT

Mischa Hoogeman

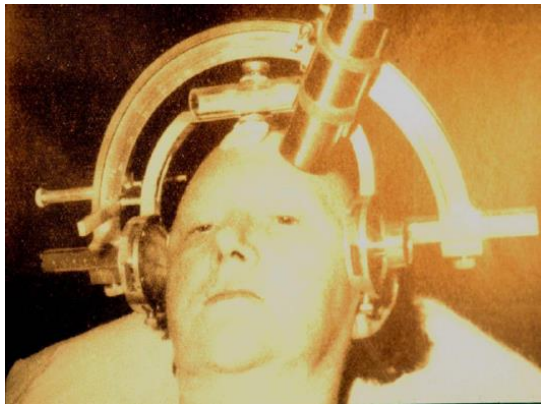
Learning Objectives

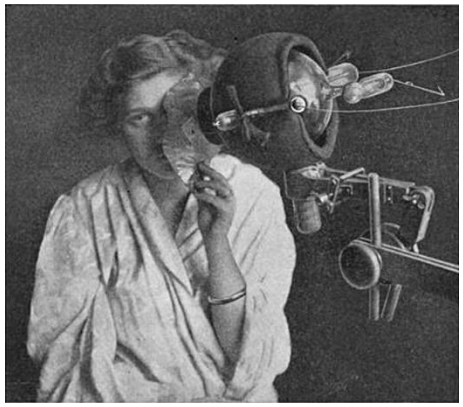
- **To give an overview of errors and uncertainties in stereotactic body radiotherapy**
  - Details on the various errors and uncertainties will be covered in separate lectures

Erasmus MC

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 …"

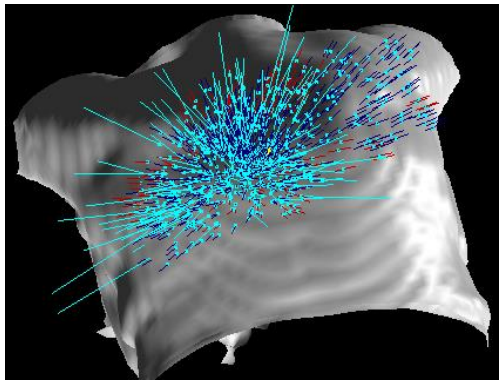


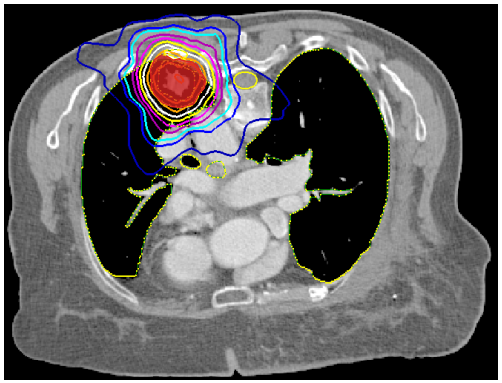


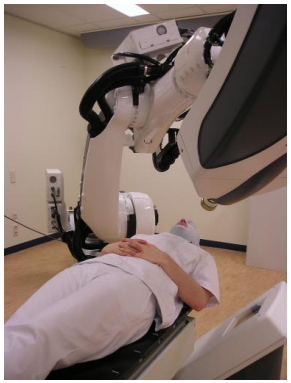
Erasmus MC

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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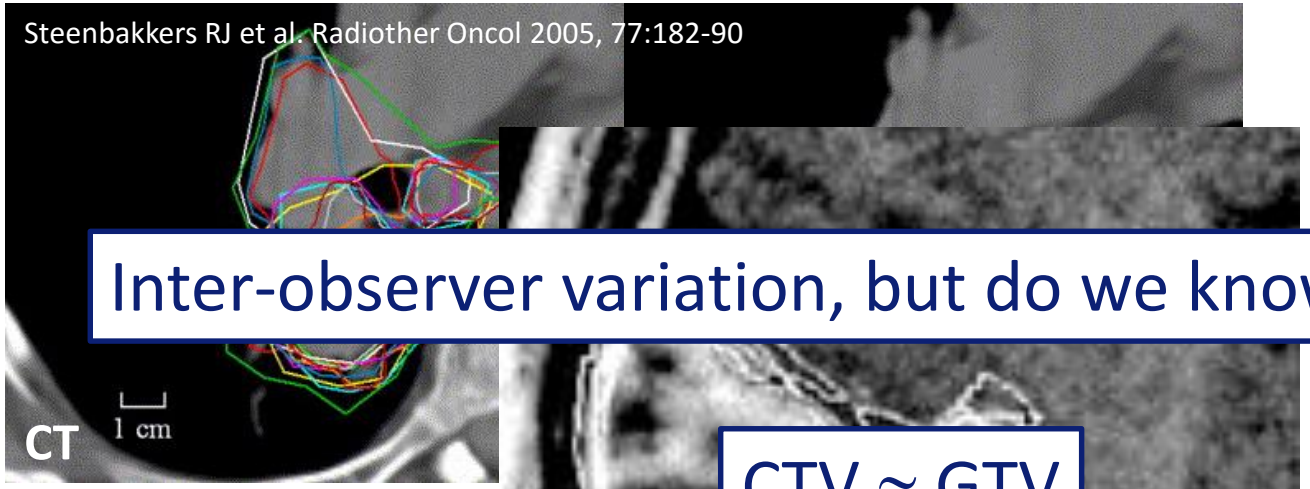
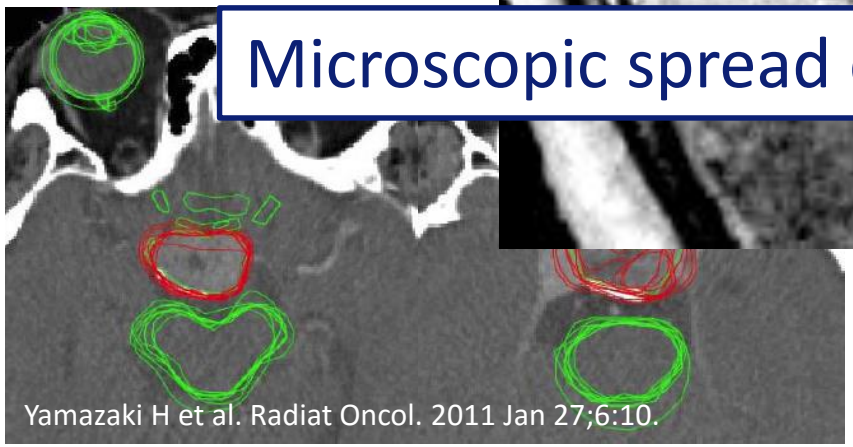
Contouring the Tumor

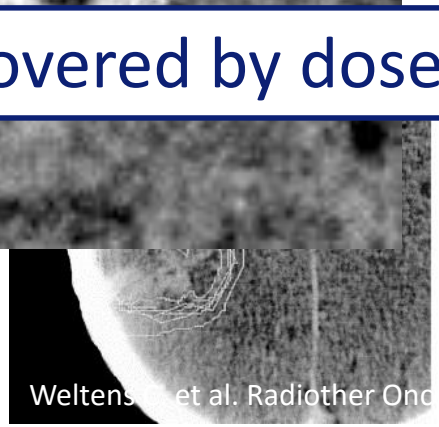


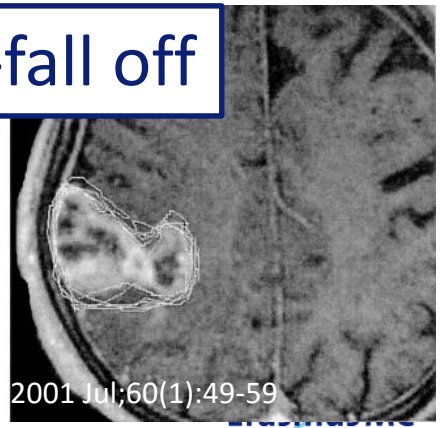
Inter-observer variation, but do we know the truth?

CTV ≈ GTV

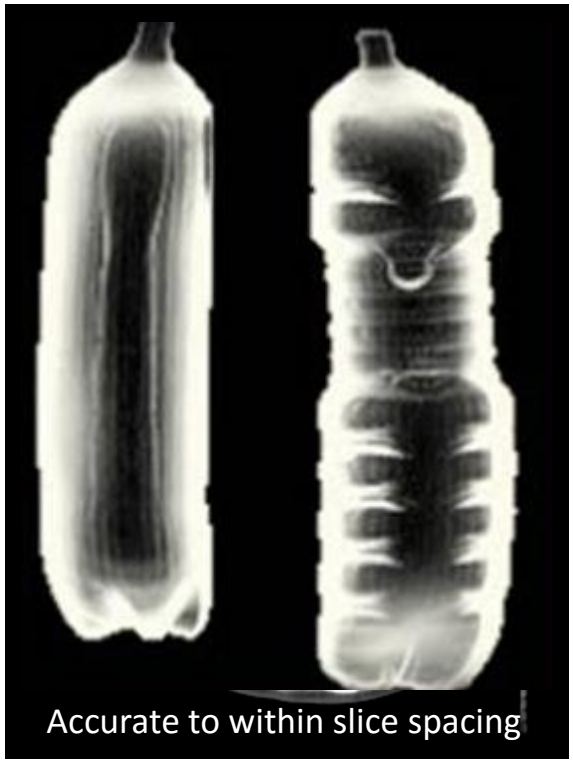


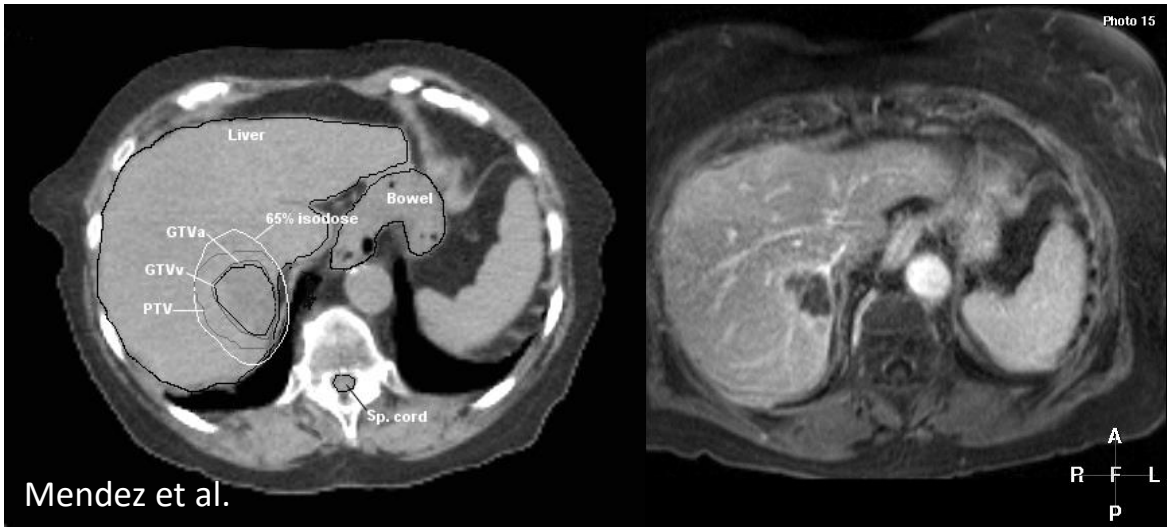
Microscopic spread covered by dose-fall off

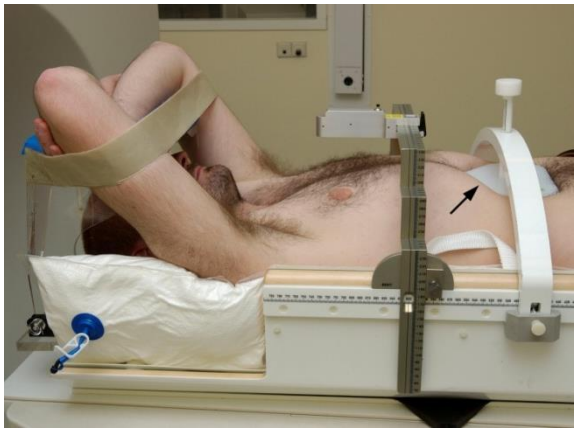




Multimodality Imaging and Registration







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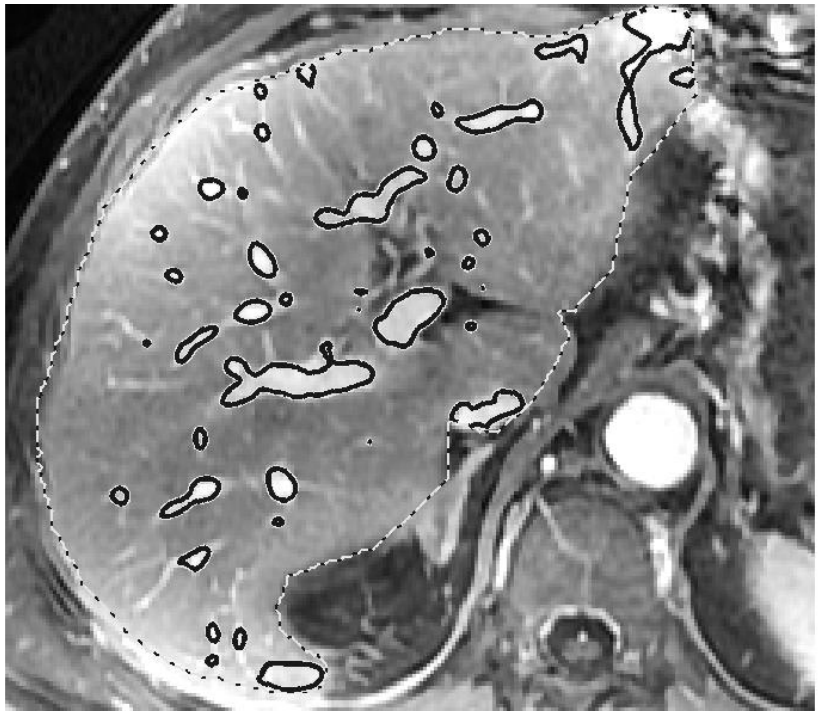
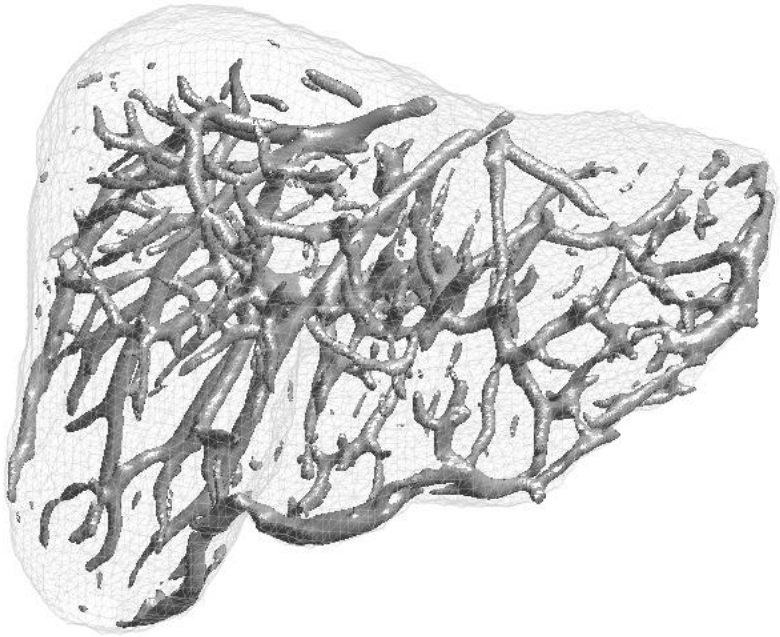
Non-rigid Matching by Vessel Segmentation





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

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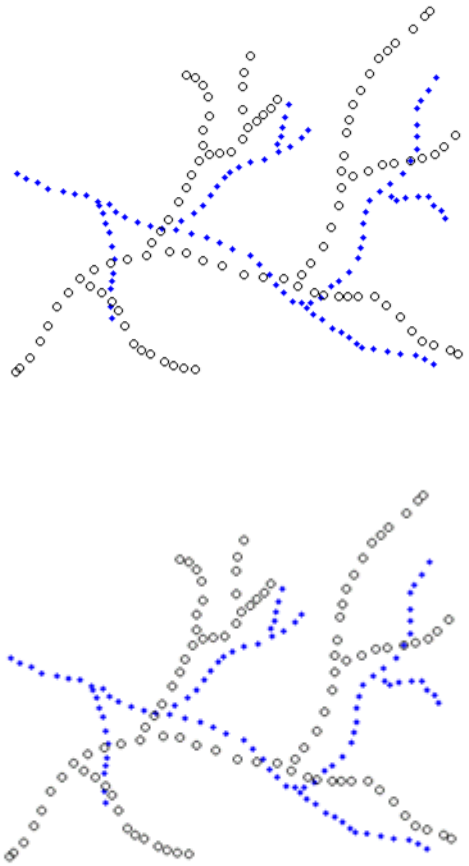
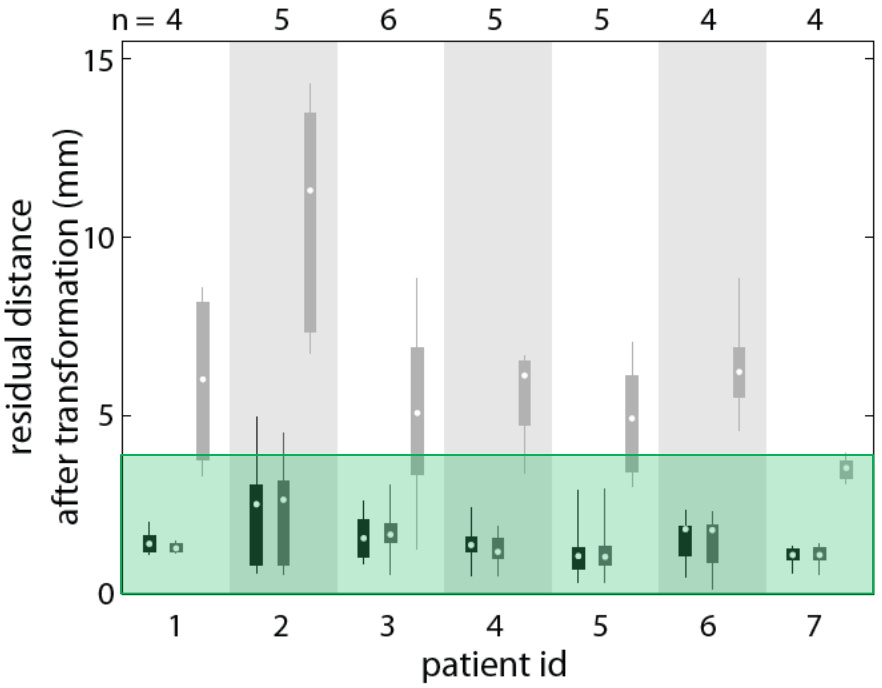
Transformation Error and Anatomical Validation



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

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 583–596, 2010

0360-3016/10/$–see front matter

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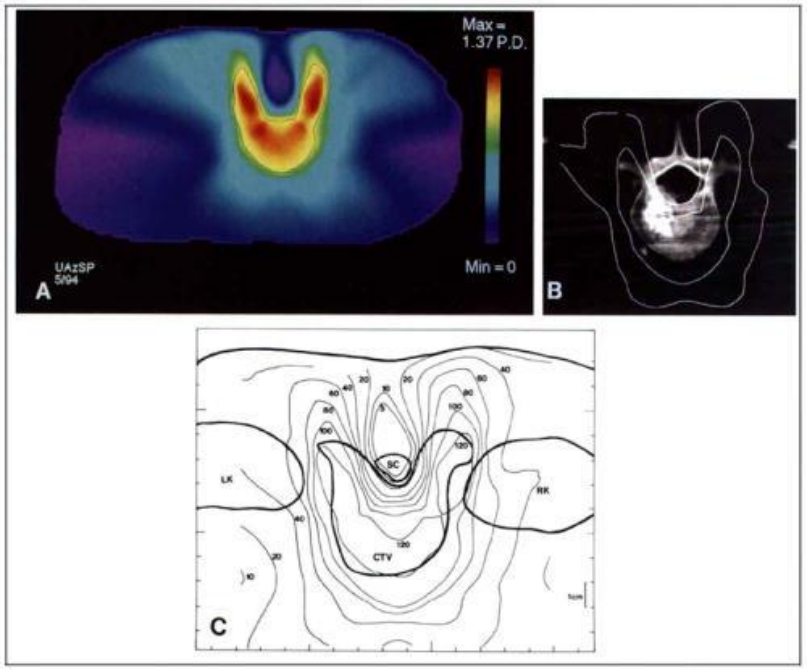
Preliminary Clinical Experience with Linear Accelerator-based Spinal Stereotactic Radiosurgery
Hamilton, Allan J. M.D.; Lulu, Bruce A. Ph.D.; Fosmire, Helen M.D.; Stea, Baldassarre M.D., Ph.D.; Cassady, J. Robert M.D. Volume 36(2), February 1995, p 311–319.



TREATMENT PLANNING

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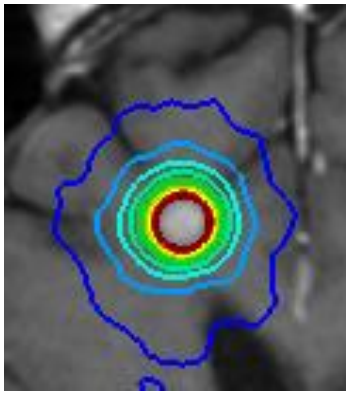
Dose Calculation

- 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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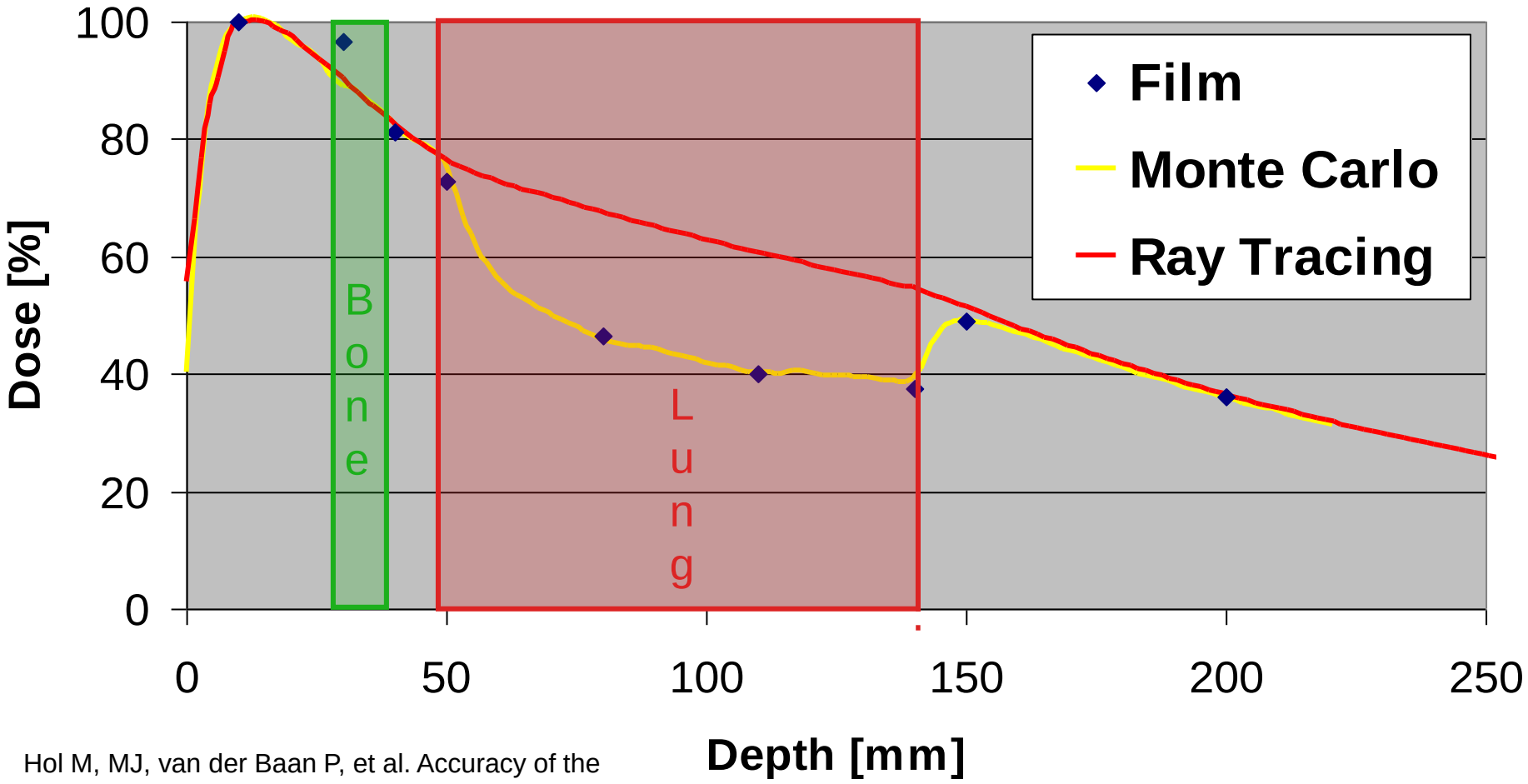
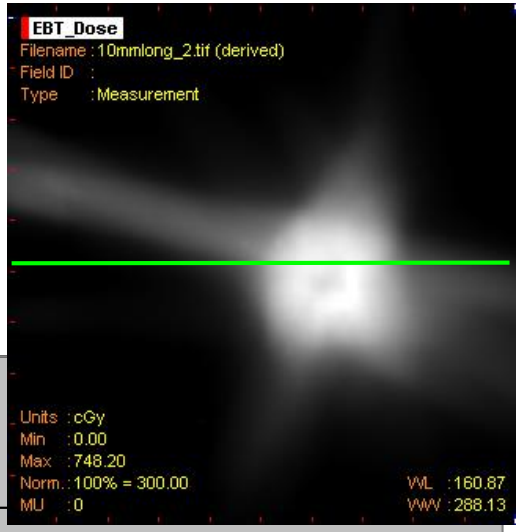
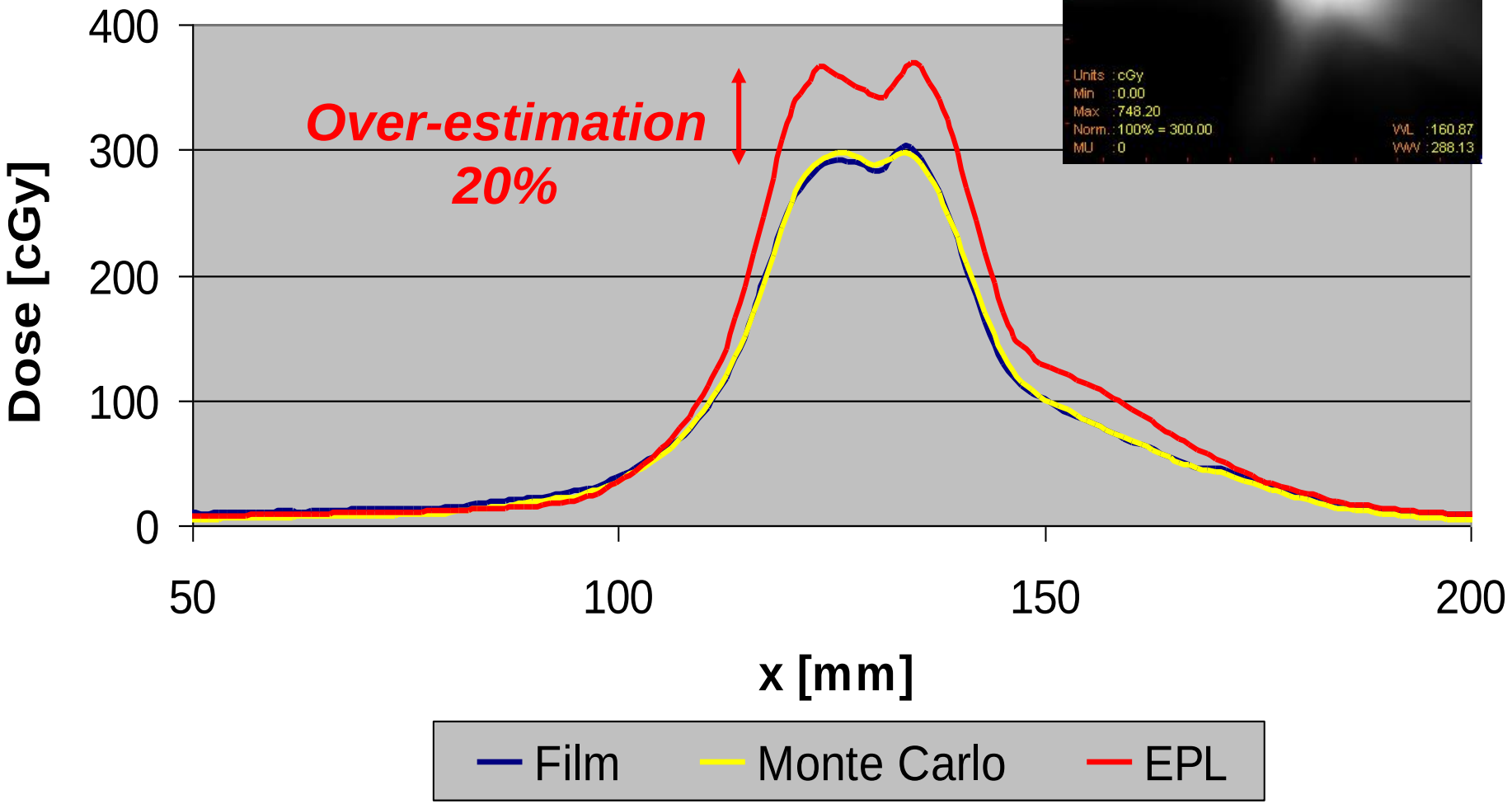
Dose Calculation Algorithm



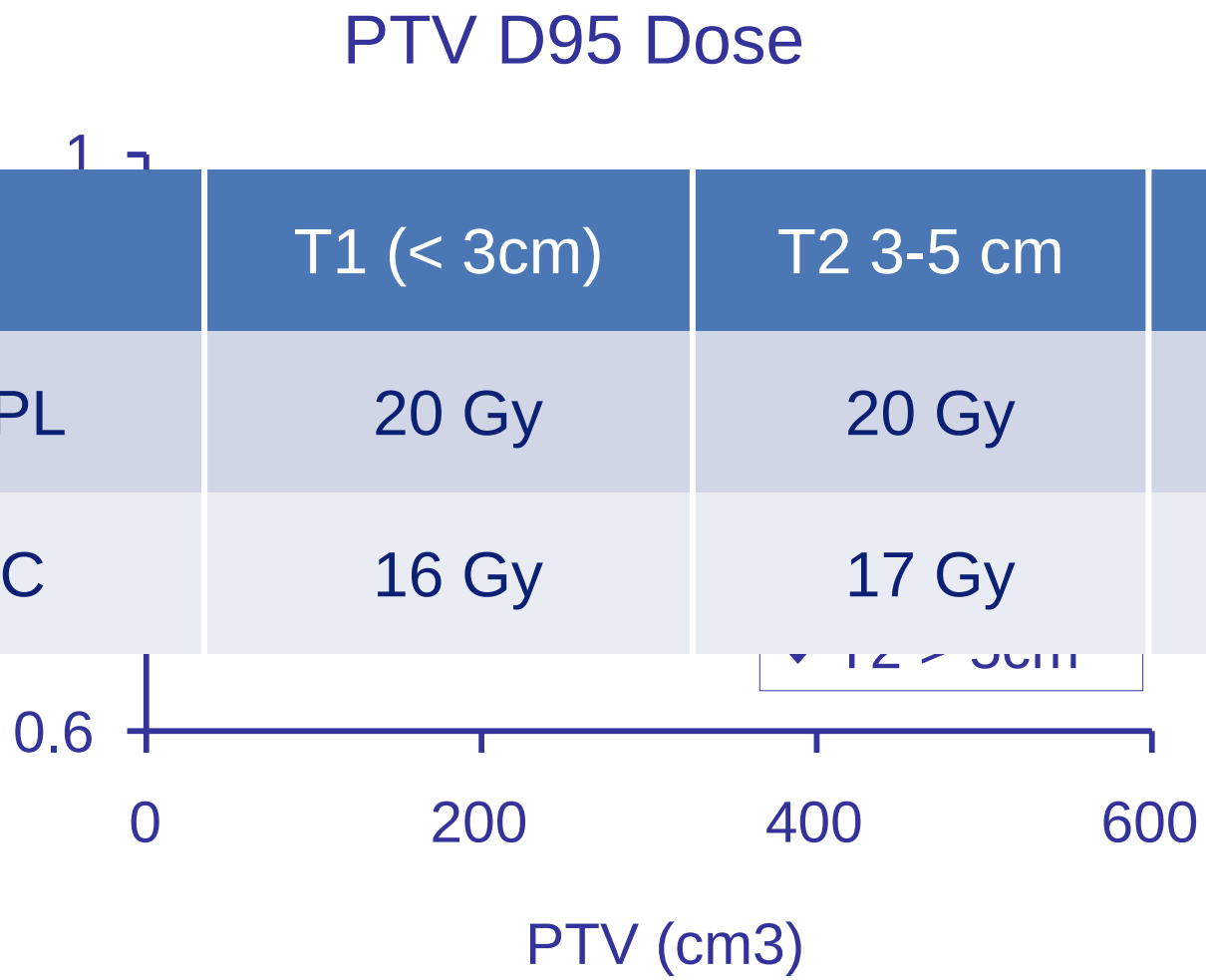
Hol M, MJ, van der Baan P, et al. Accuracy of the Monte Carlo Dose Calculation Algorithm for Cyberknife Treatment of Small Lung Lesions. Med Phys 2008;35:2953

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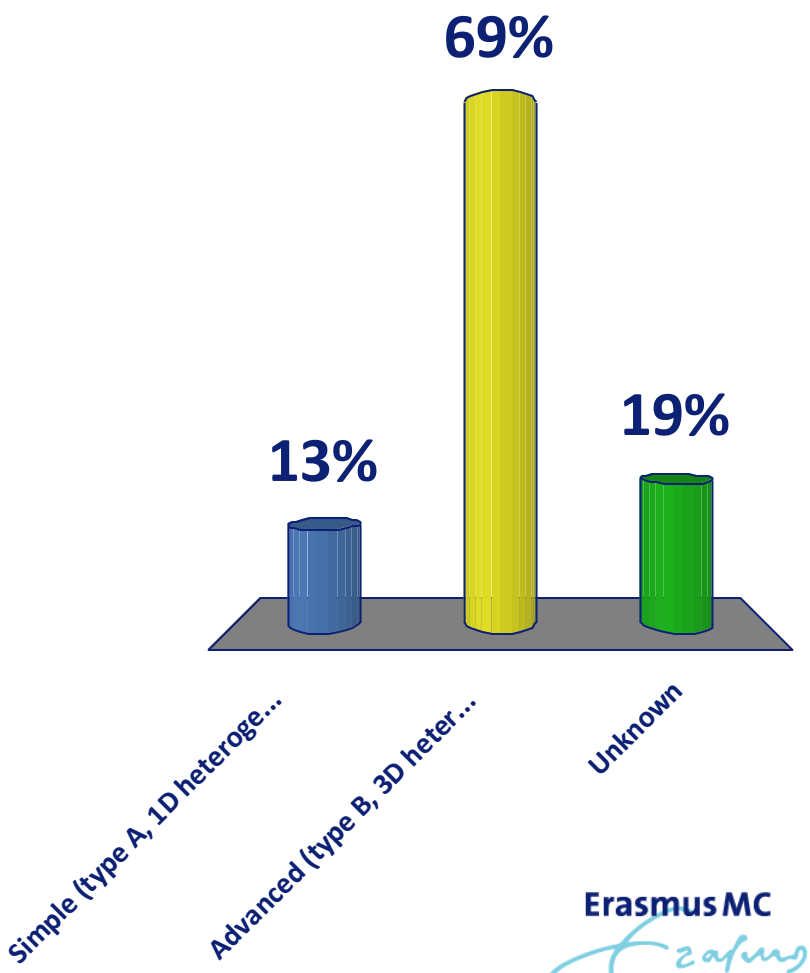
Which dose algorithm will you use (are using) for lung SBRT?

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

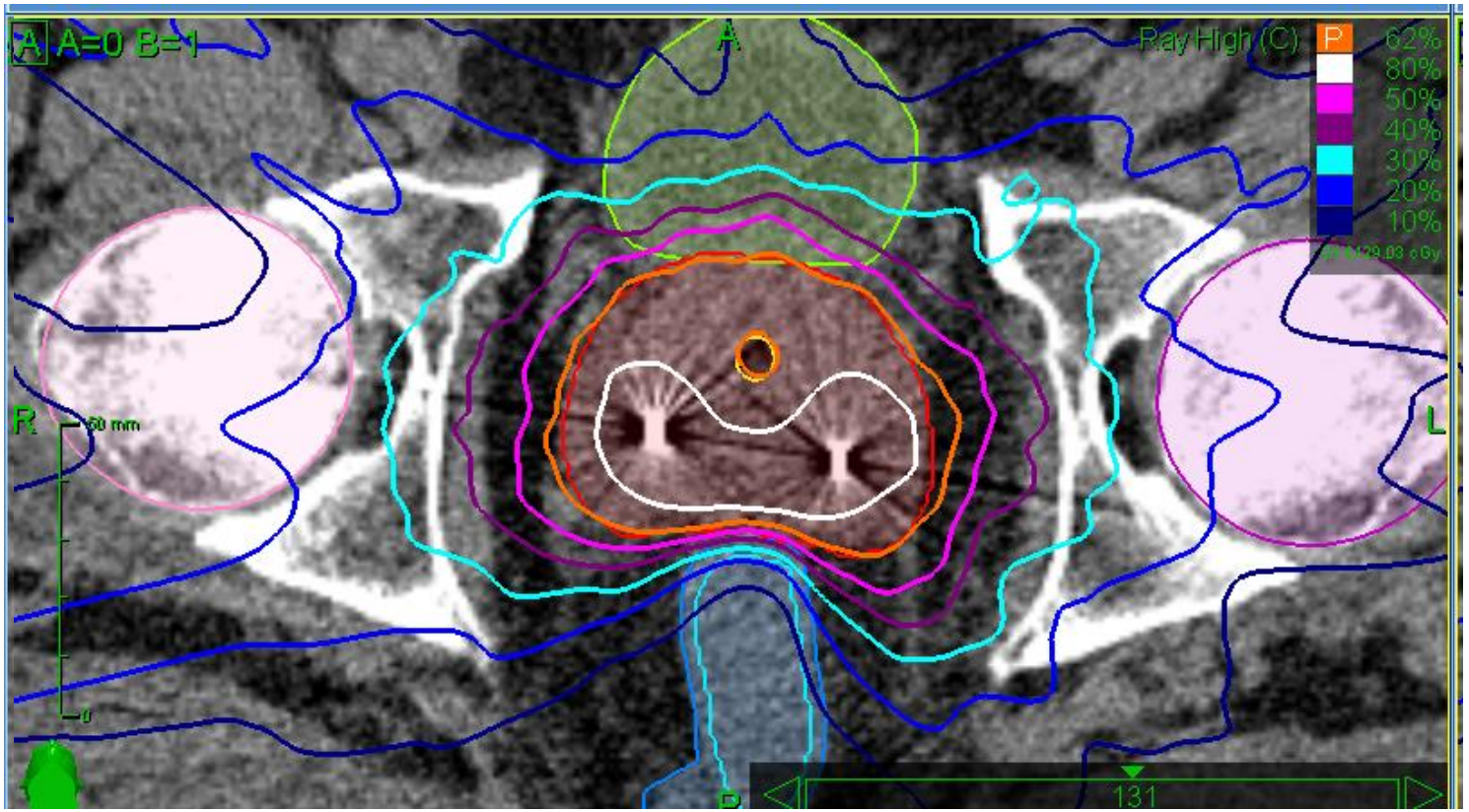
	5 mm	
	Raw $s_{c,p}$	$s^{*}_{c,p}$
A16	0.615	0.675
PinPoint	0.613	0.679
Diode	0.710	0.679
Diamond	0.613	0.677
Mean $s_{c,p}$	0.638	0.677
$\pm 2\sigma$	0.096	0.004

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

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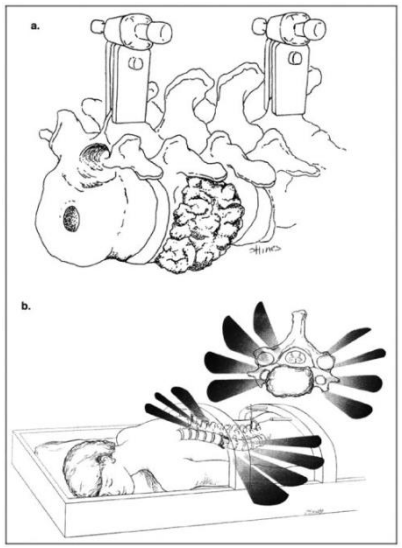

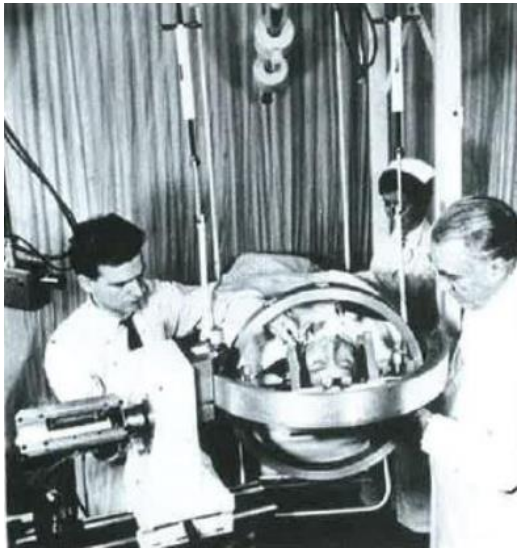

PATIENT SETUP, IMMOBILIZATION, TARGET LOCALIZATION, AND DELIVERY

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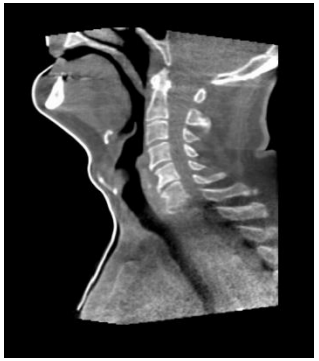
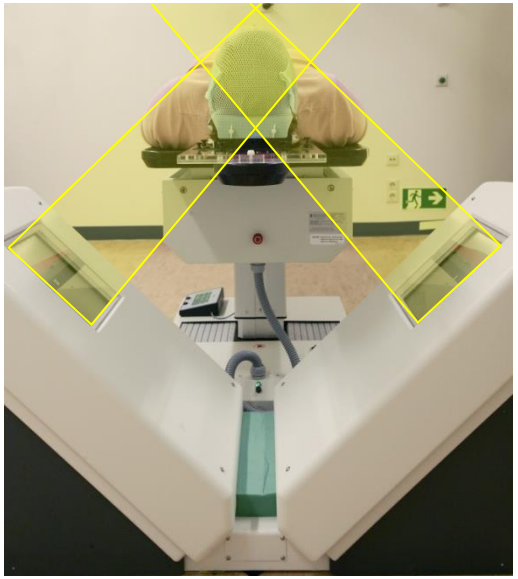
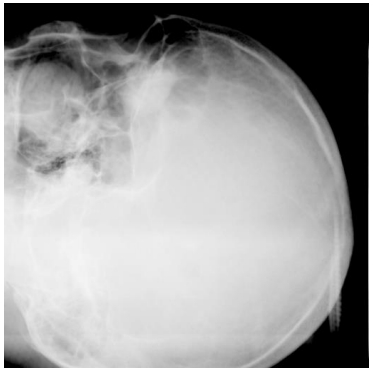
From CT to LINAC: Image-based Alignments (Frameless)



3D to 3D





2D to 3D

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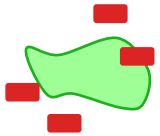

MARKERS AS SURROGATE

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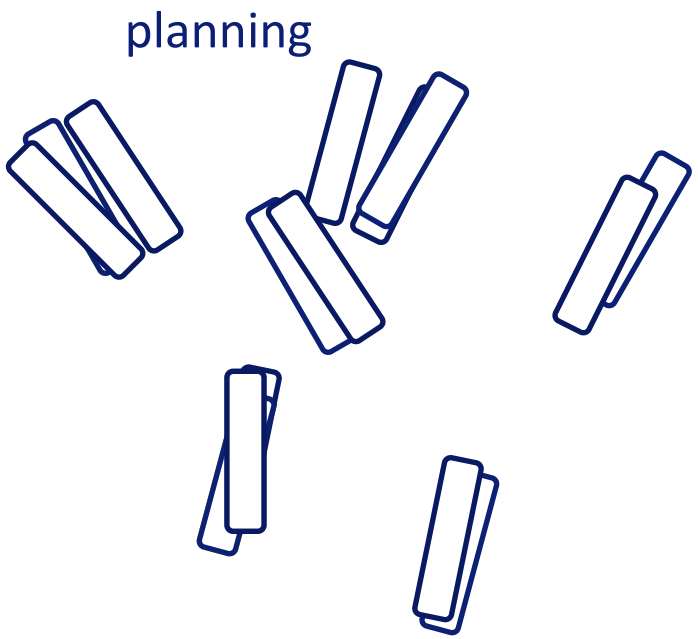
Deformation in Marker Configuration



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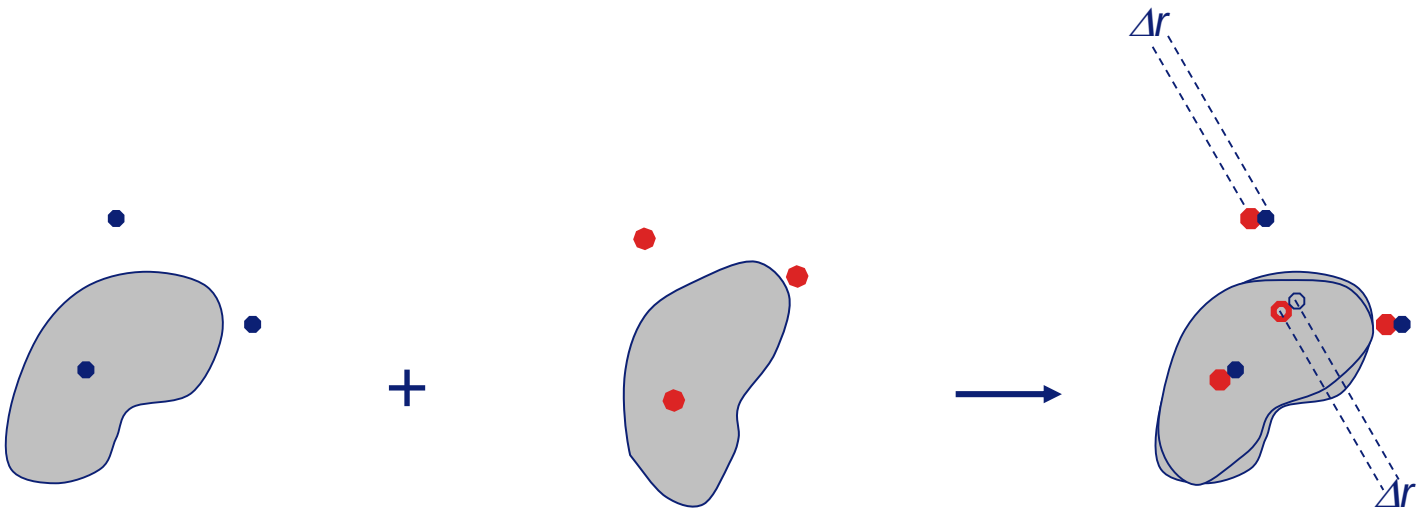
Assessing Marker Stability



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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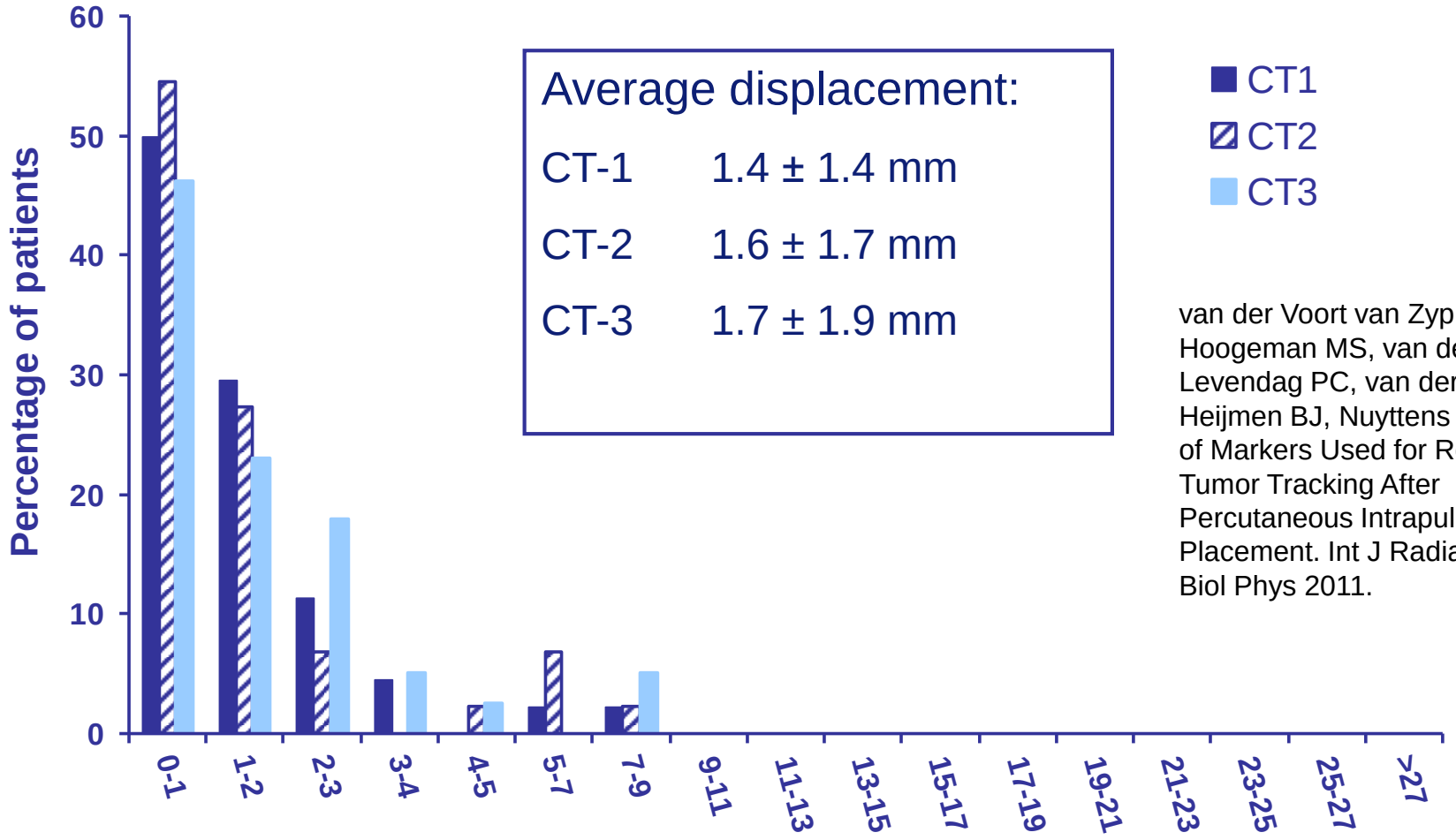
Displacement of the COM of Marker Configurations



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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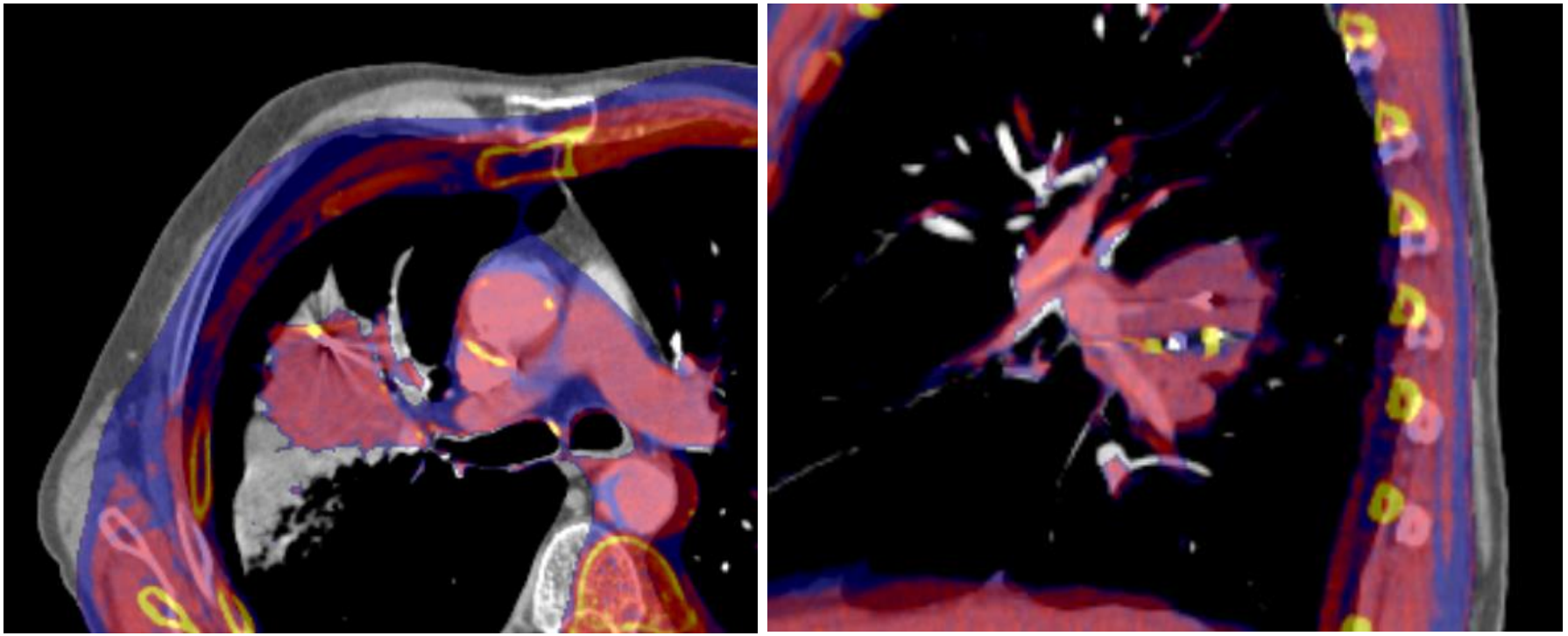
Examples of displacements in COM ≥ 3 mm



Evident migration in 1 patient

Insert 3 markers

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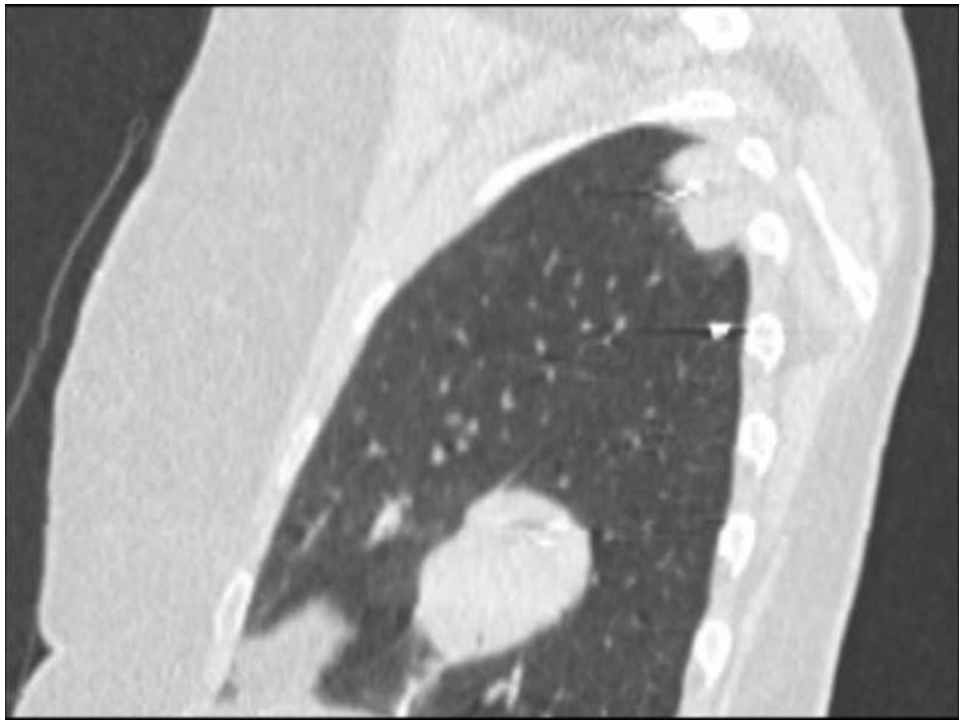
Non-Synchronous Motion Between Markers and Tumor

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



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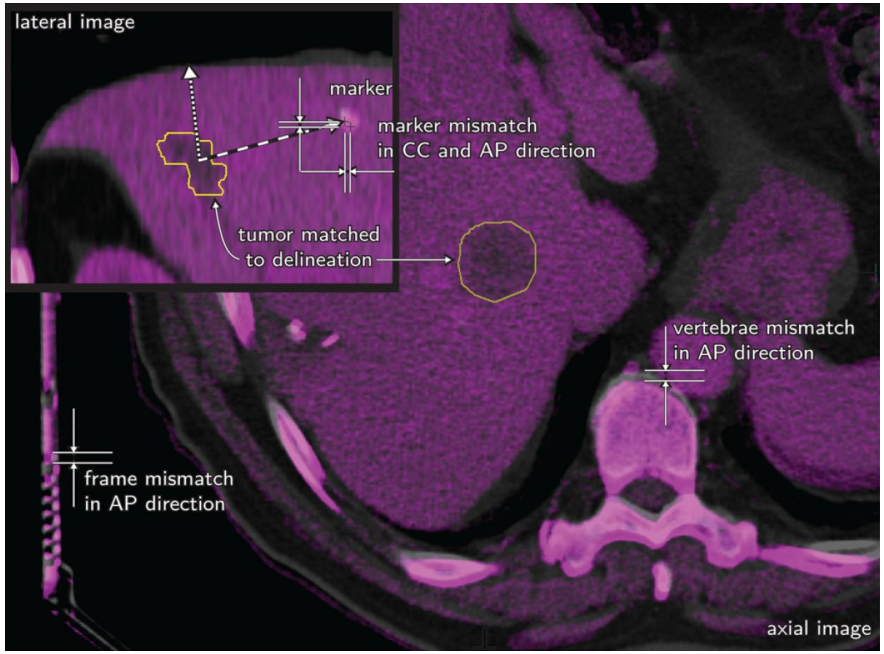
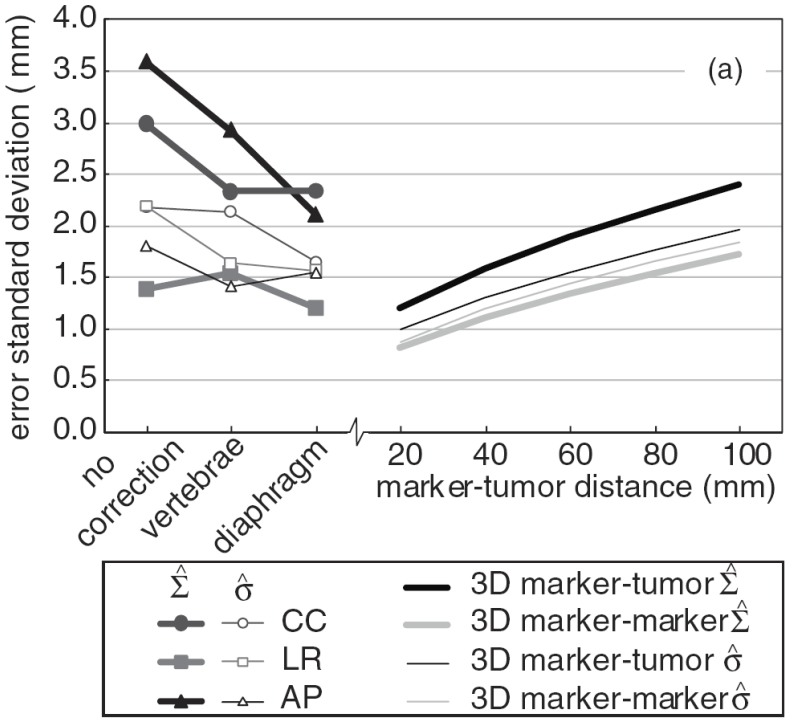
Liver Tumor Surrogates





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

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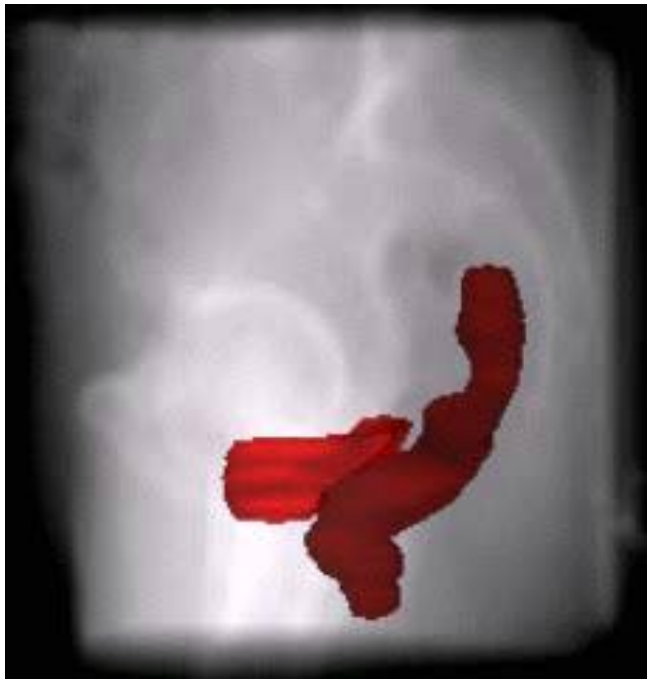
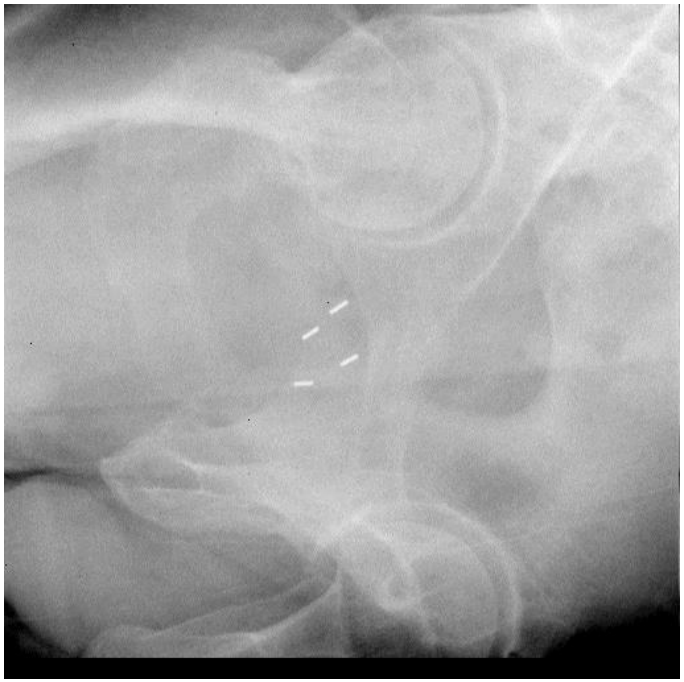
Inter-Fraction and Intra-Fraction Errors

- 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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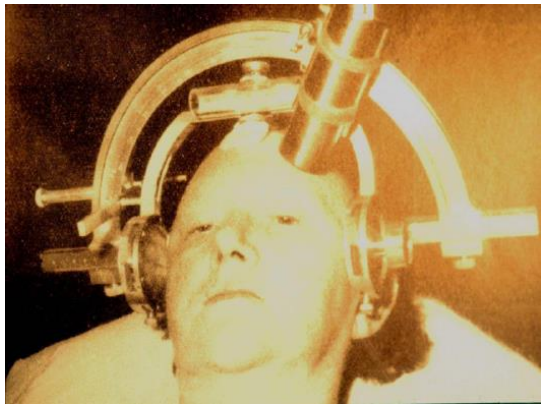
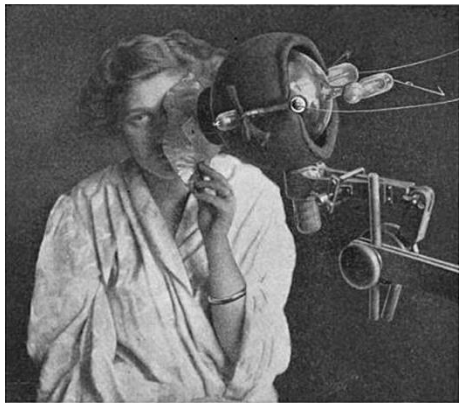
Vendors' Claims of Stereotactic Devices

- "… 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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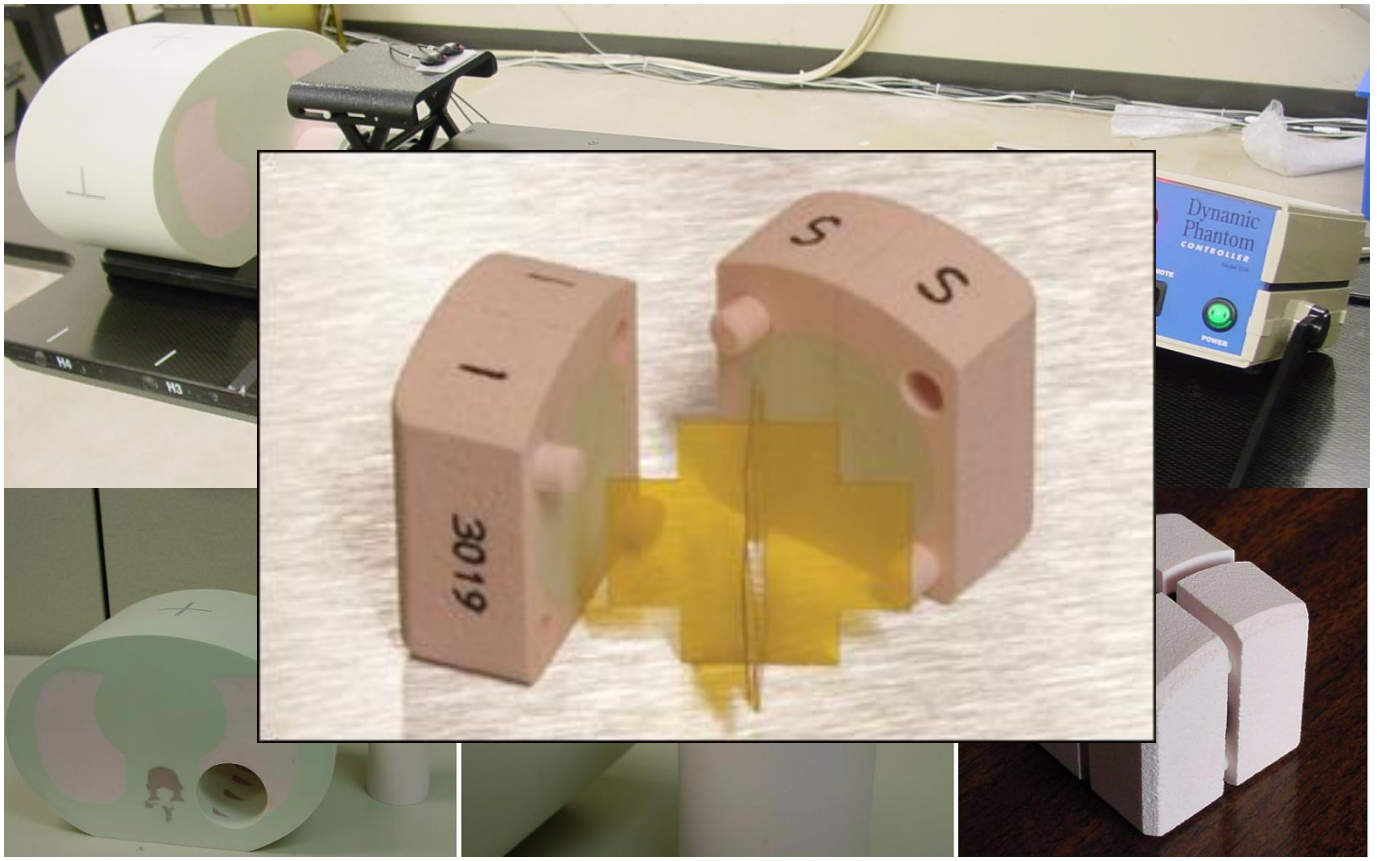
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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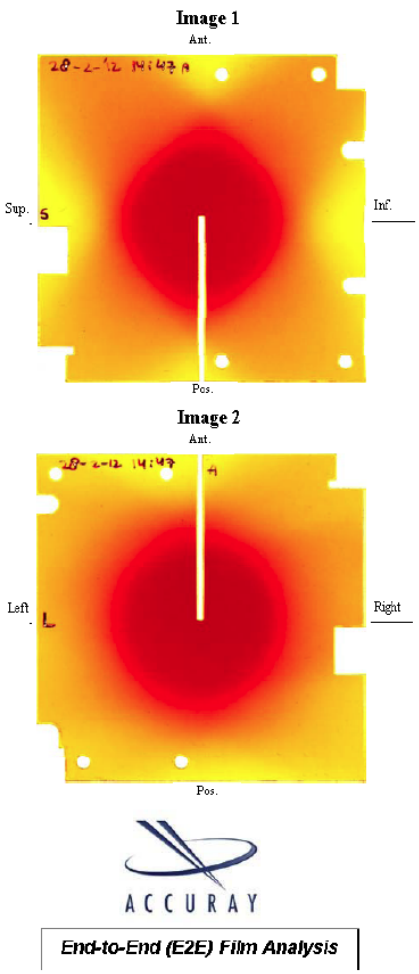
Analysis of Tracking Error



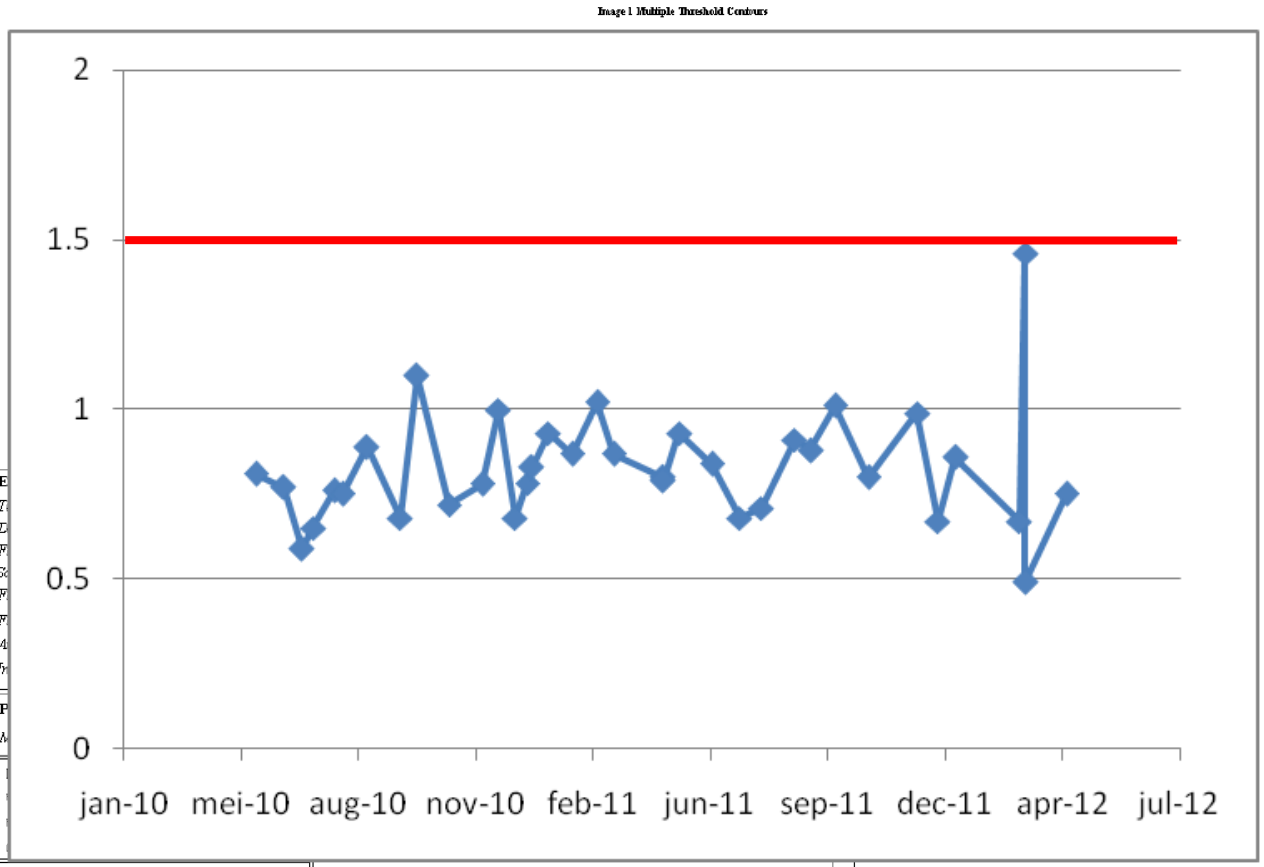


Image 2 (A/L Image)	
mm from left edge:	31.23
mm from anterior edge:	32.09
contour area/ball area:	1.15

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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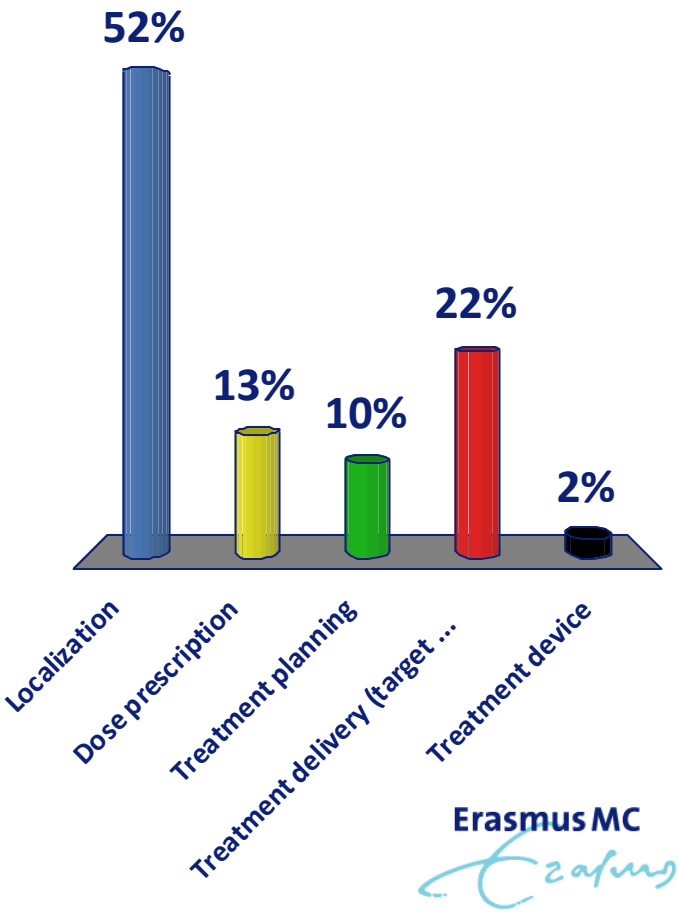
Which type of error is clinically most significant?

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



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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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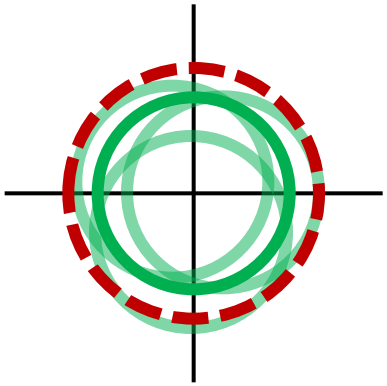
Why do we use margins?

- **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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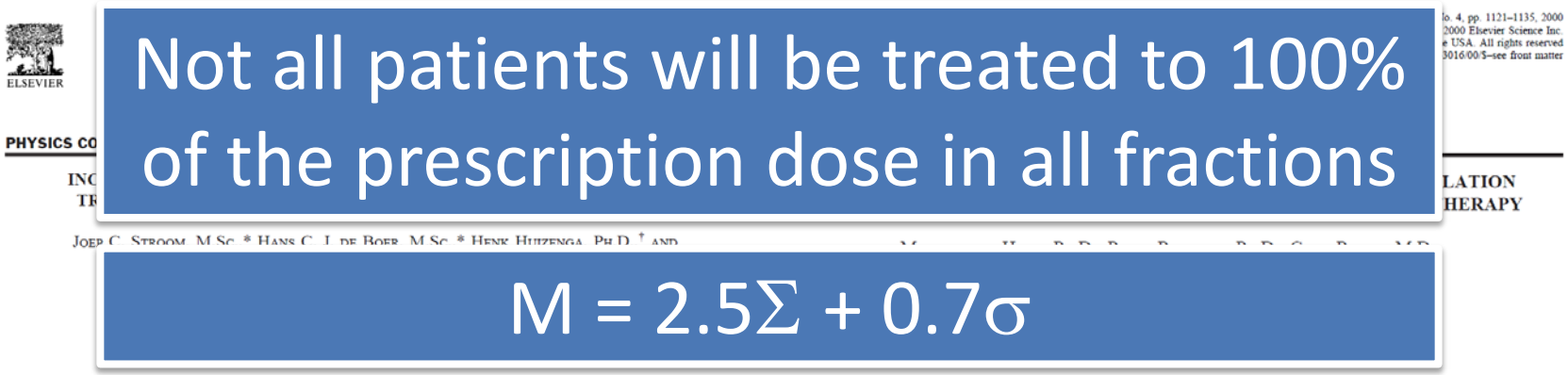
How large should the margin be?

- **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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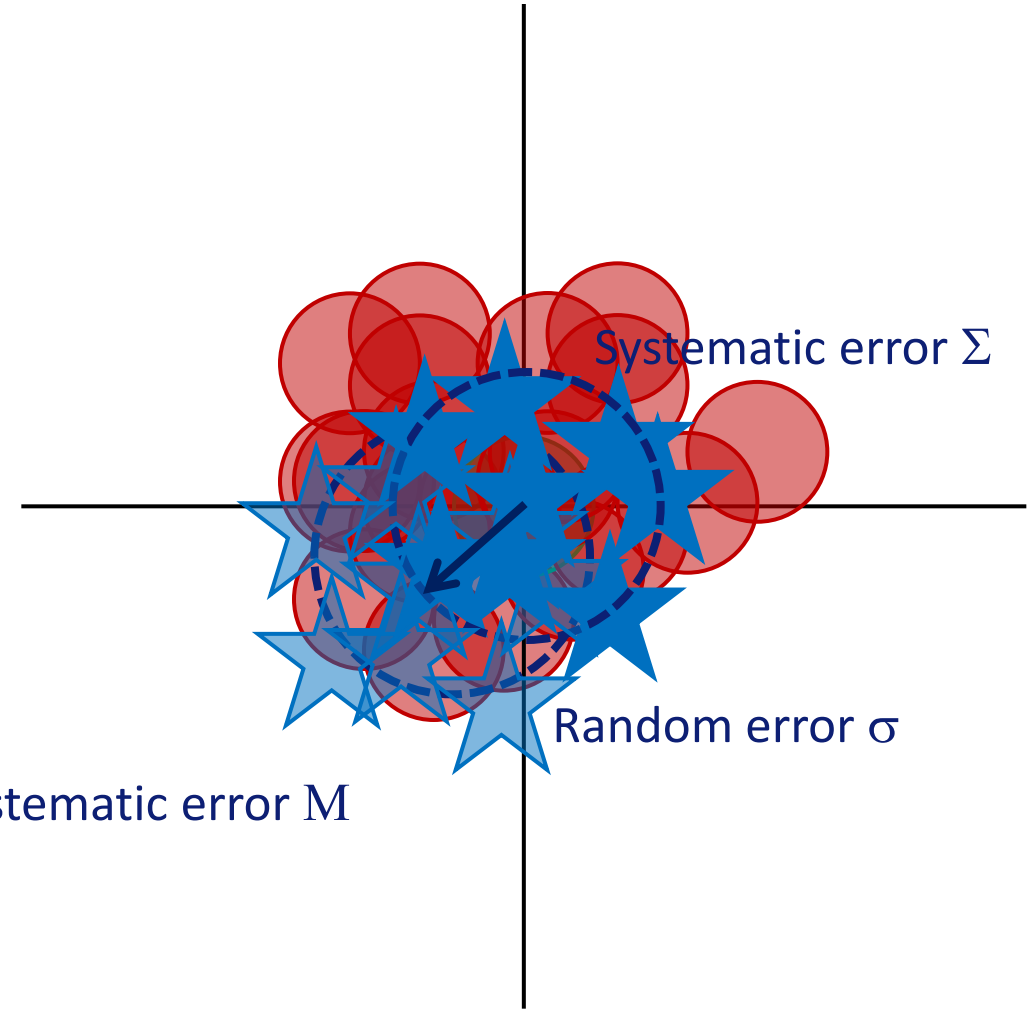
Categorization of Errors: a 2D Example



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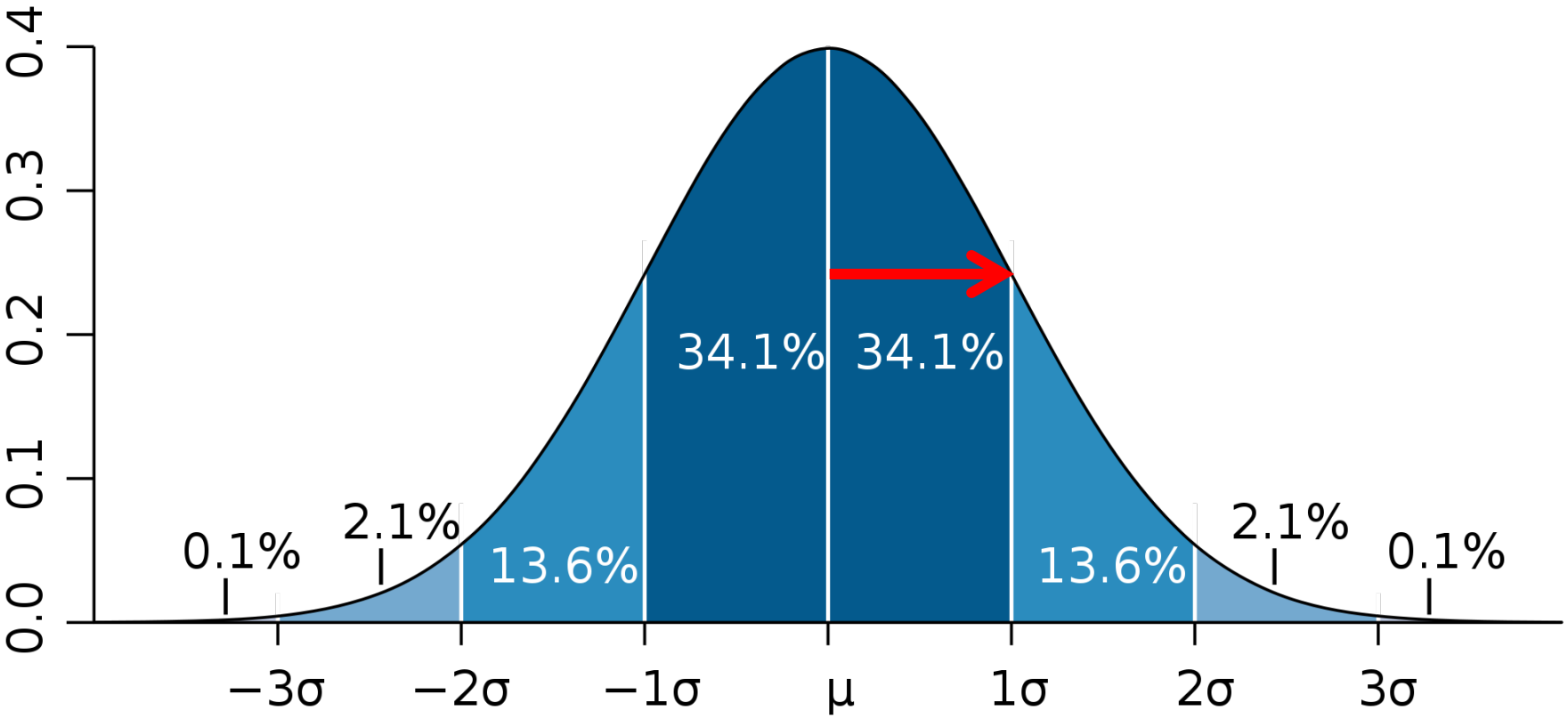
Probability Density Function: Normal Distribution



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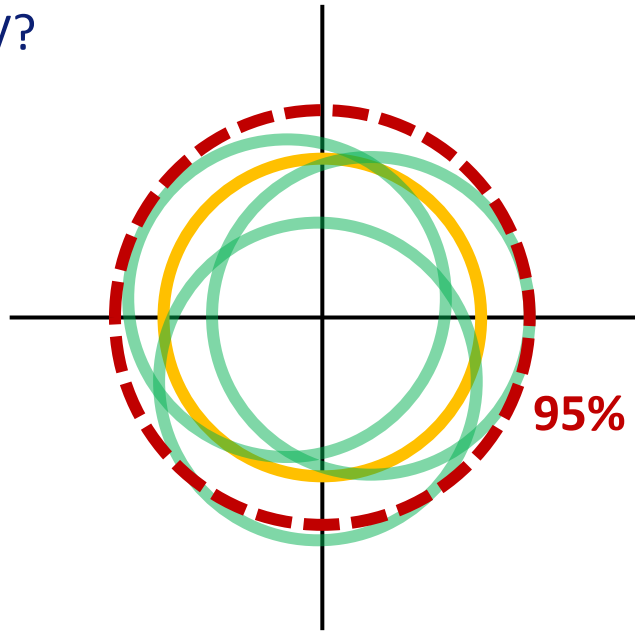
Systematic Errors Only (M_{sys} = 2.5 Σ)

- The systematic set-up errors are described by a 3D Gaussian distribution
- How to choose M_{sys} to ensure a high probability that the prescribed dose is delivered to the CTV?



- **Choice:** for 90% of all possible systematic set-up errors (treatments), the full CTV is within the PTV (=95% isodose)

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Systematic Errors Only (M_{sys} = 2.5 Σ)

- **Spherical Tumor**
  - $\int_0^{M_{sys}} p(\Sigma)dr = 0.9$
  - $\int_0^{M_{sys}} \frac{r^2}{\sqrt{\frac{\pi}{2}}\Sigma^3} e^{-\frac{r^2}{2\Sigma^2}} dr = 0.9$

Population (%)	$\alpha\Sigma$
80	2.16
90	2.50
95	2.79
99	3.36

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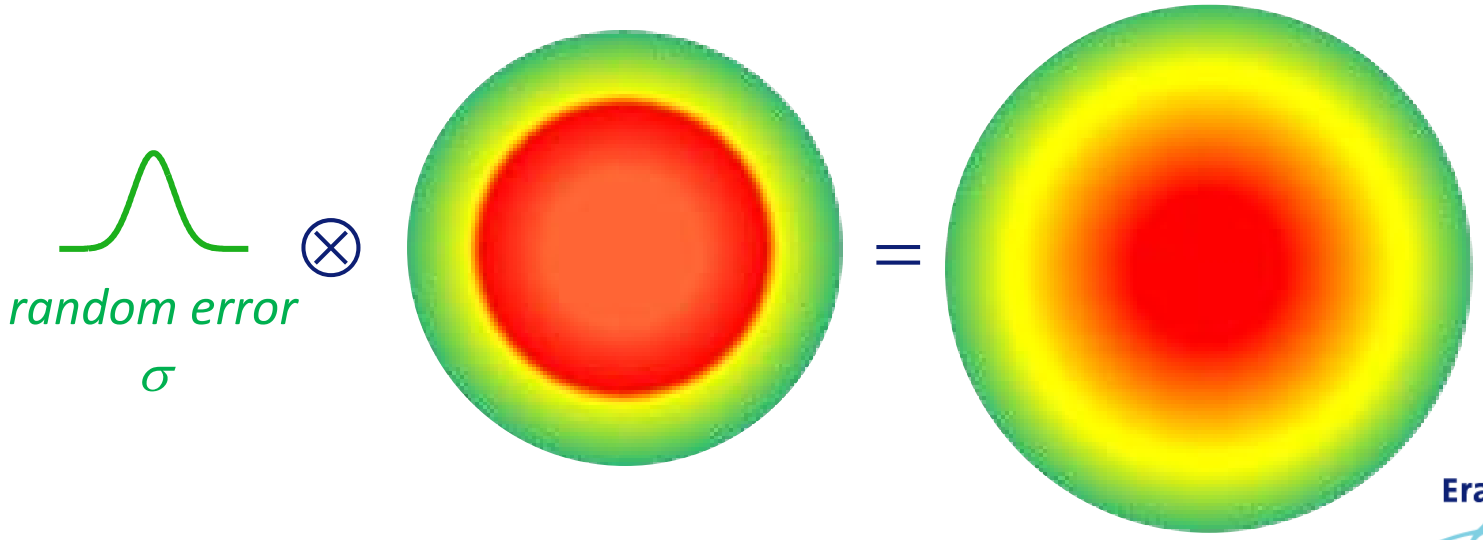
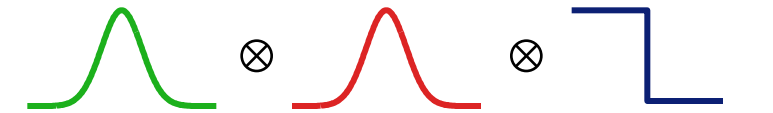
Random Errors Only: $M_{rand}=0.7\sigma$

- 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

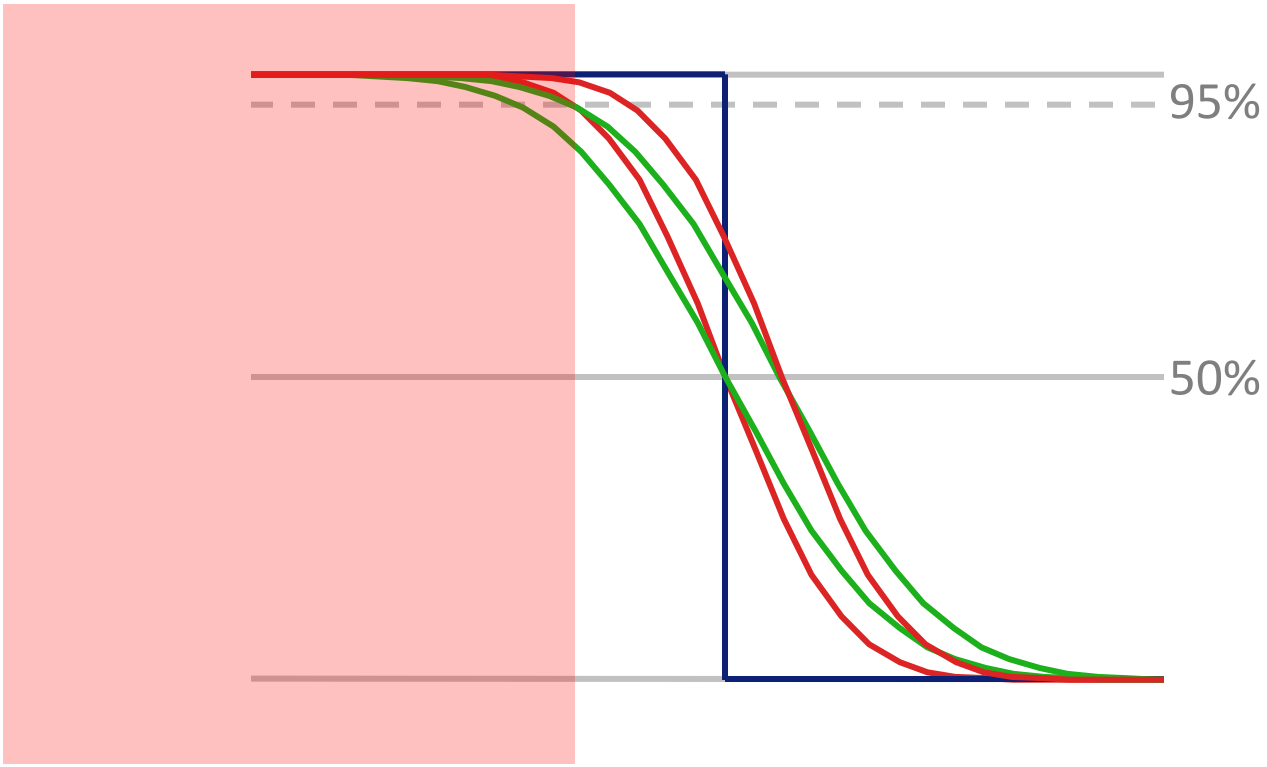


Margin Recipe for Random Error

Water σ_p= 3.2 mm
Lung σ_p = 6.4 mm



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



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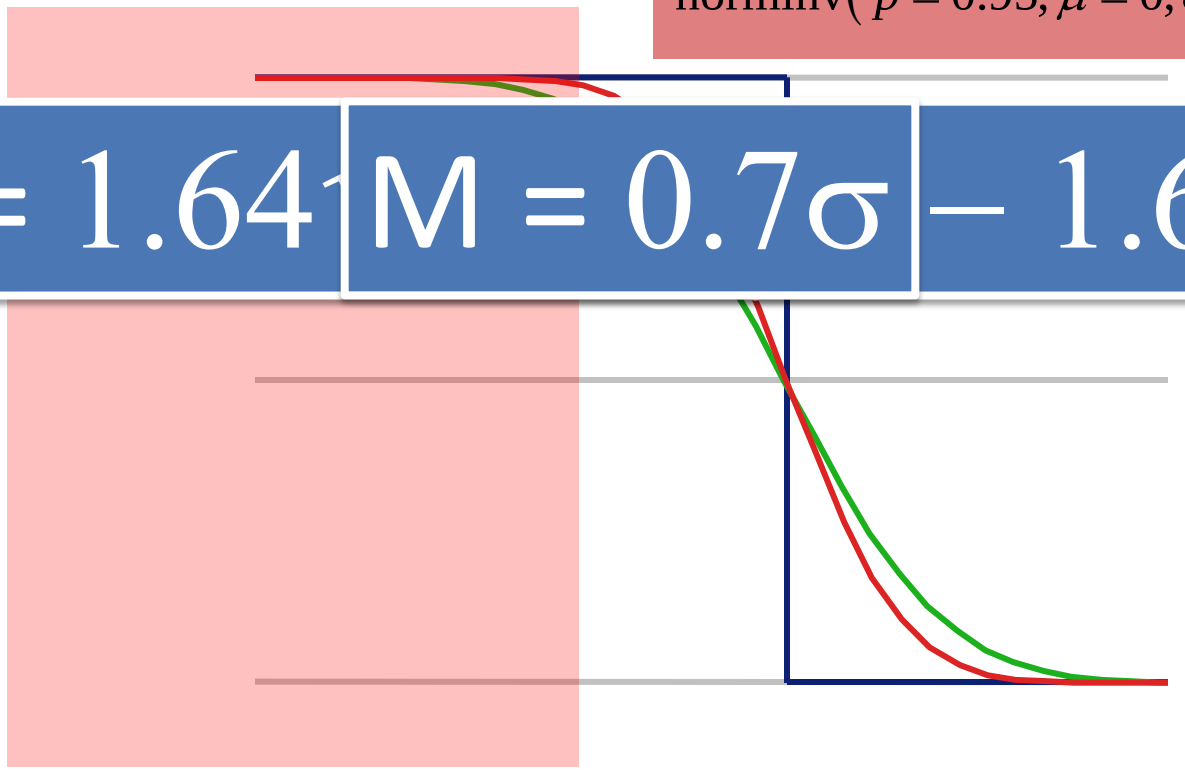
Margin Calculation: Random Component

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

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

$$M = 1.64 \quad M = 0.7\sigma \quad -1.64\sigma_p$$



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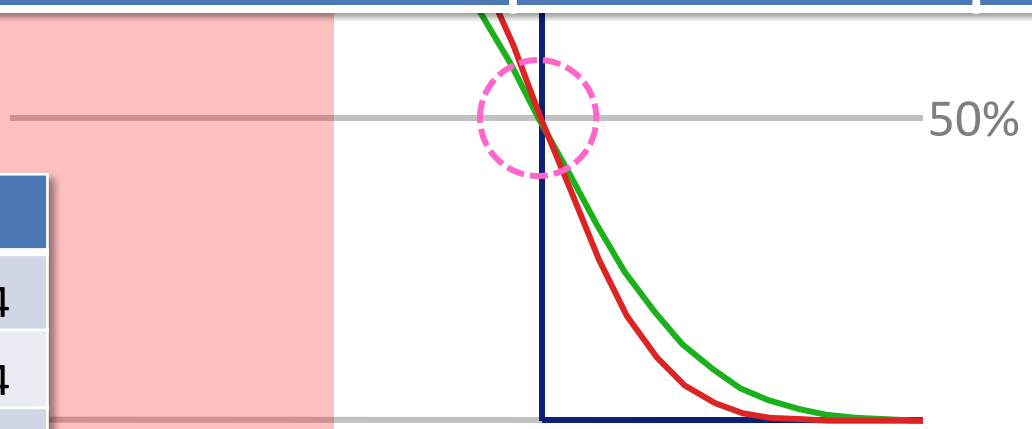
Random Error and Minimum Dose Requirement

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

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



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

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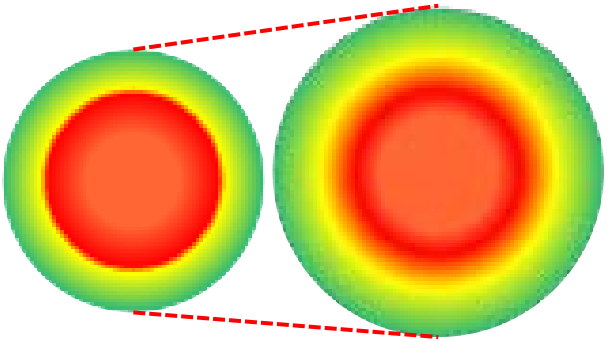
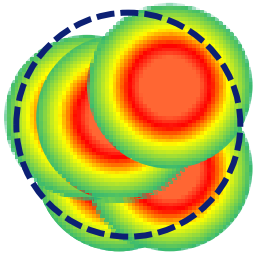
Margin Recipe: Systematic Error and Random Errors



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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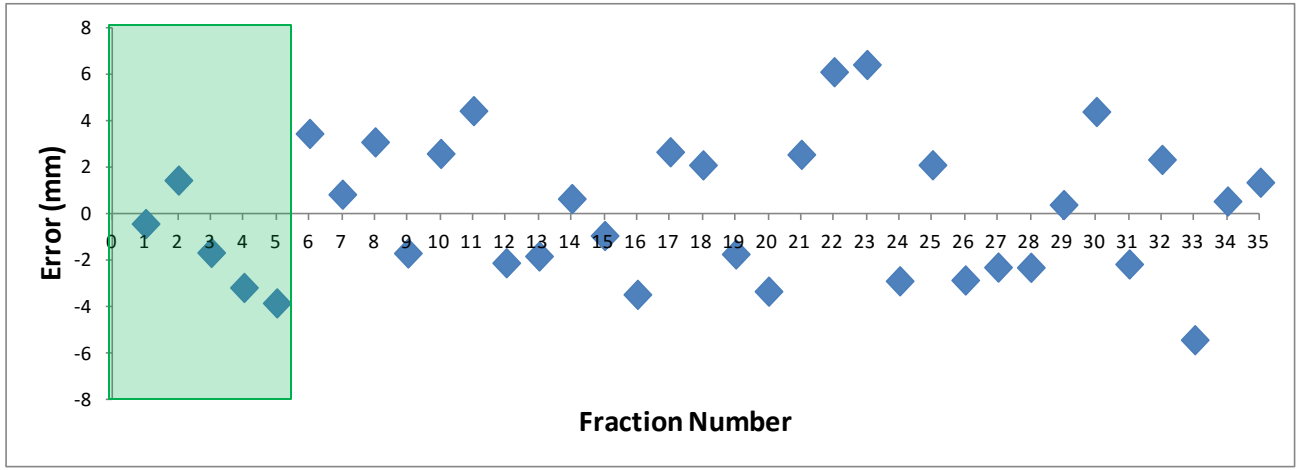
Number of Fractions and Residual Systematic Error

- 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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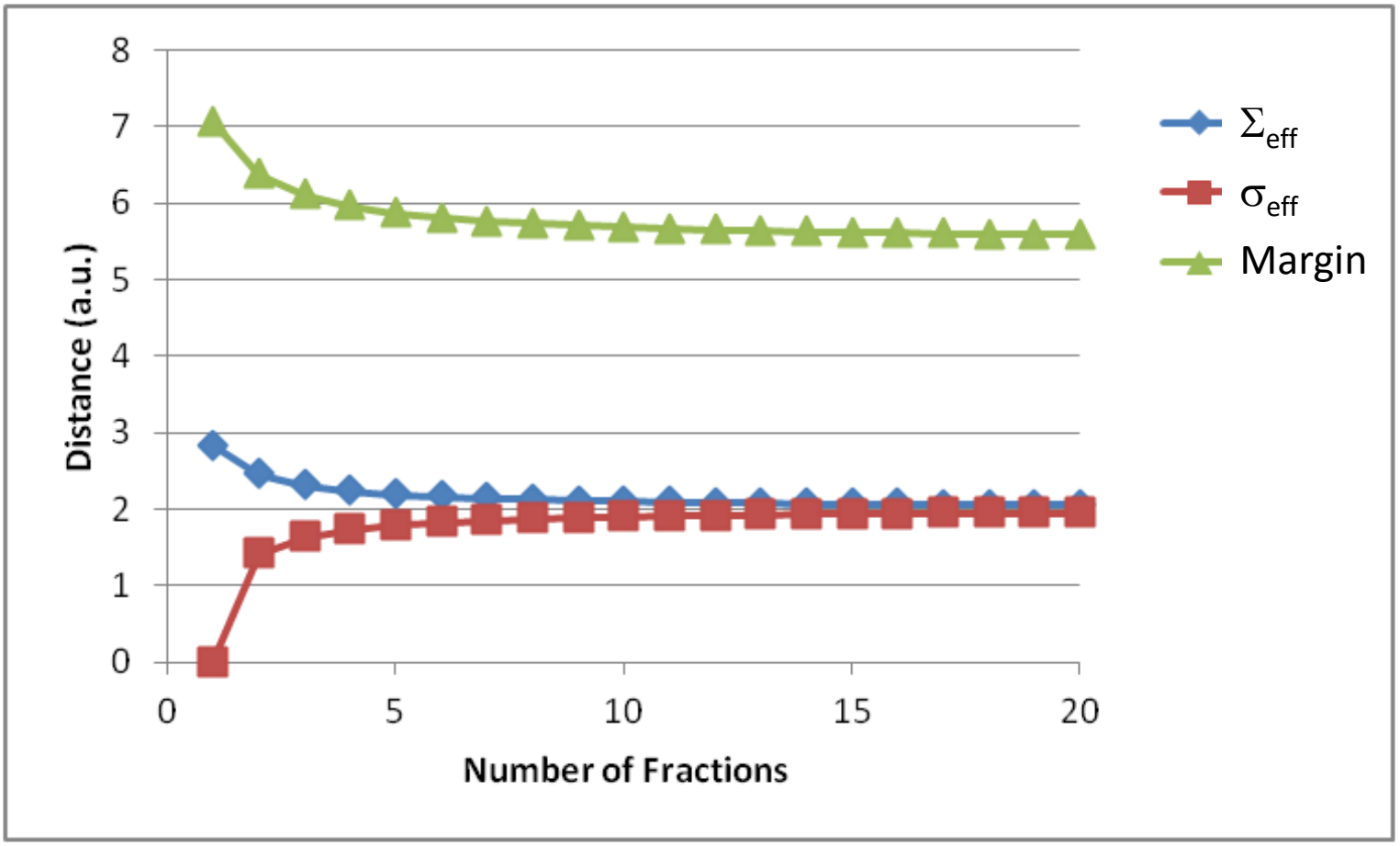
Margin and Number of Fractions



Σ = 2 mm, σ = 2 mm, P=80%

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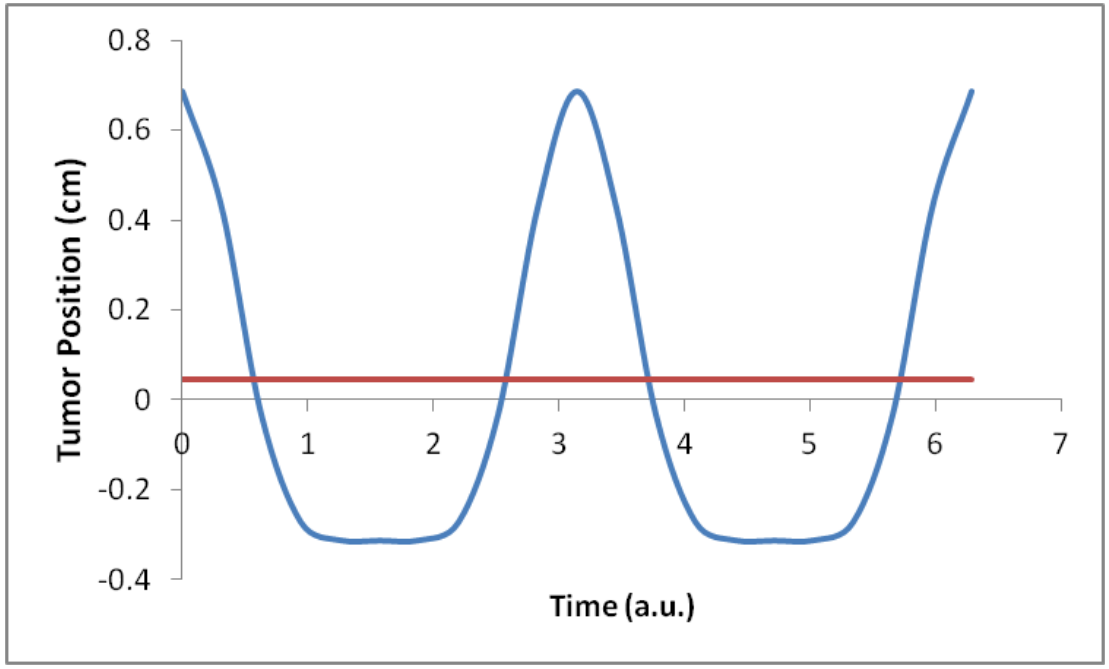
Including Error due to Respiratory Motion

- 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?

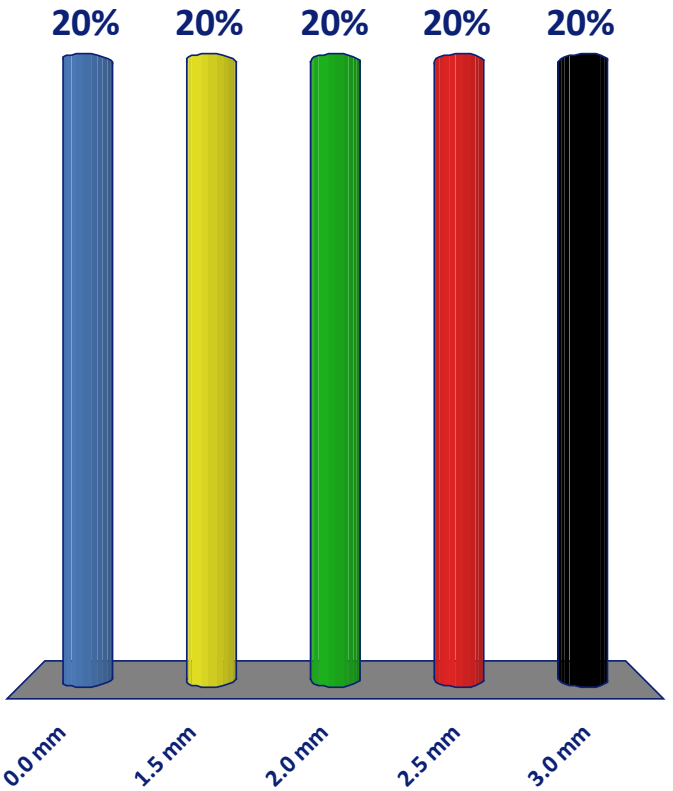
A. 0.0 mm

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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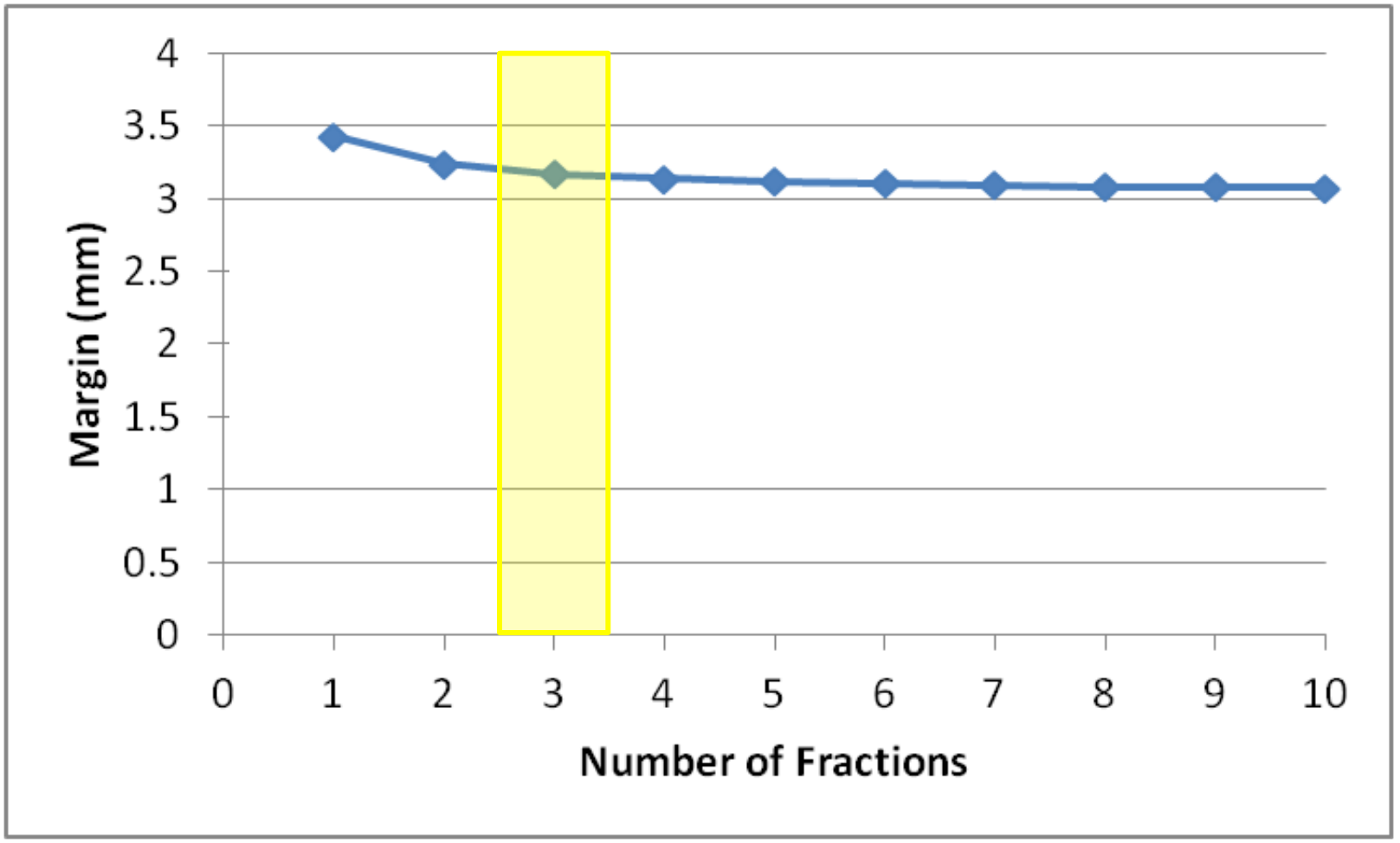
Results SRT Example



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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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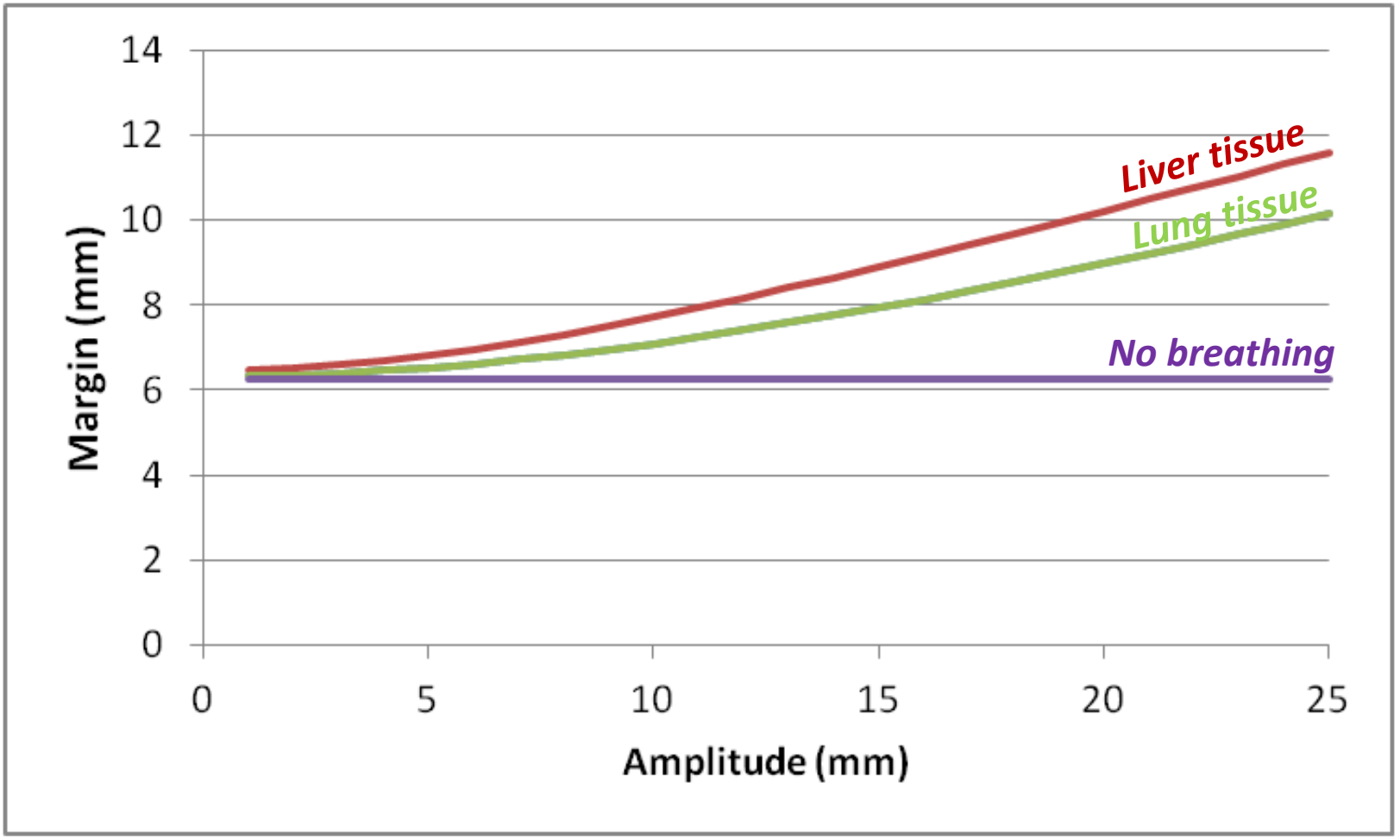
Margins SBRT Lung Case



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INTERNAL TARGET VOLUME

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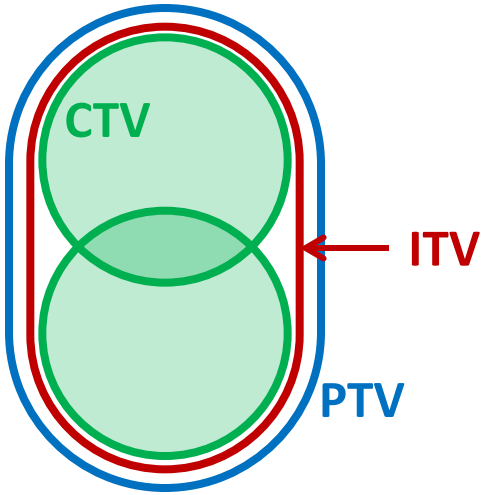
ITV Concept in ICRU-62 Report

- 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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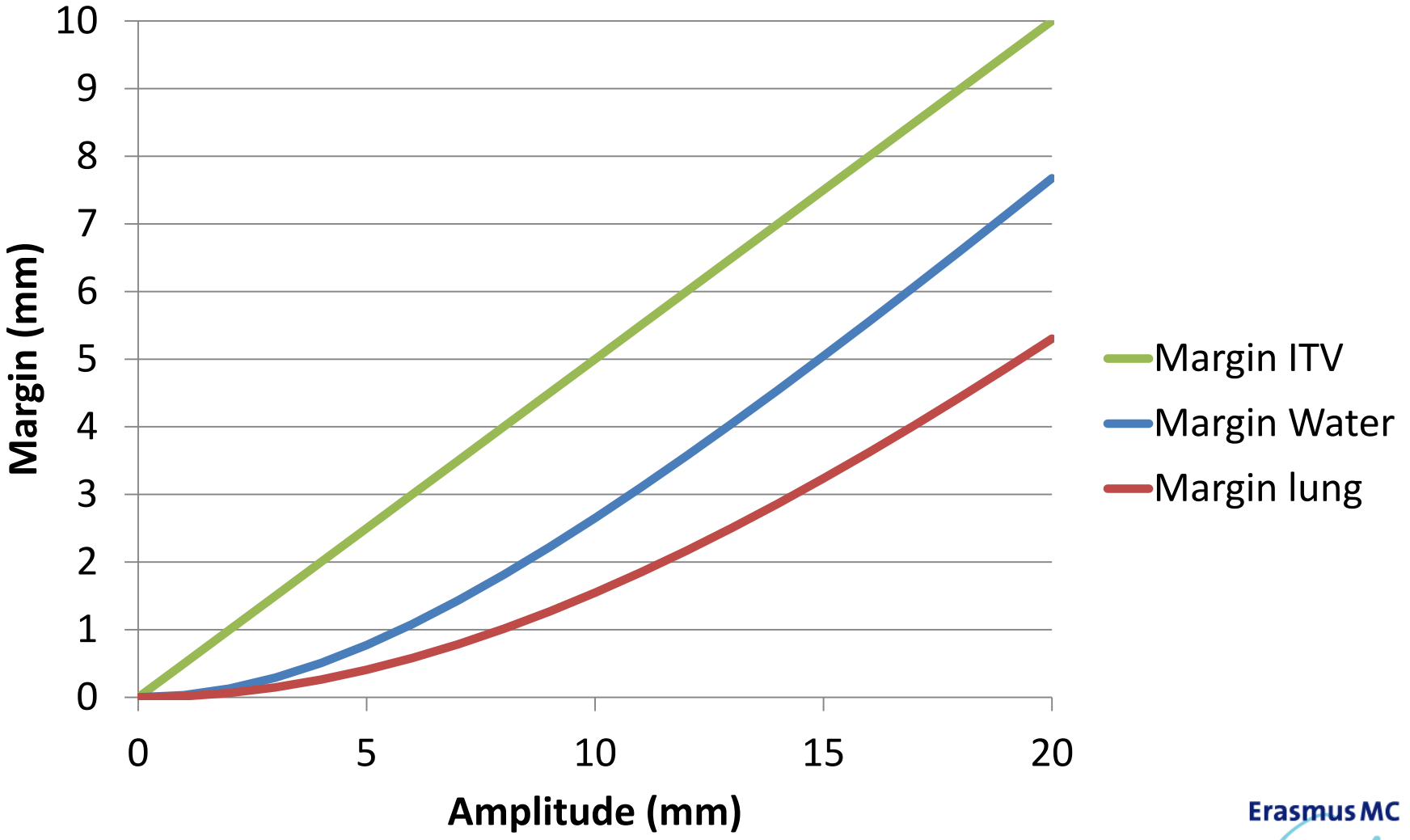
Margin vs ITV for Perfect Inter-fraction Alignment



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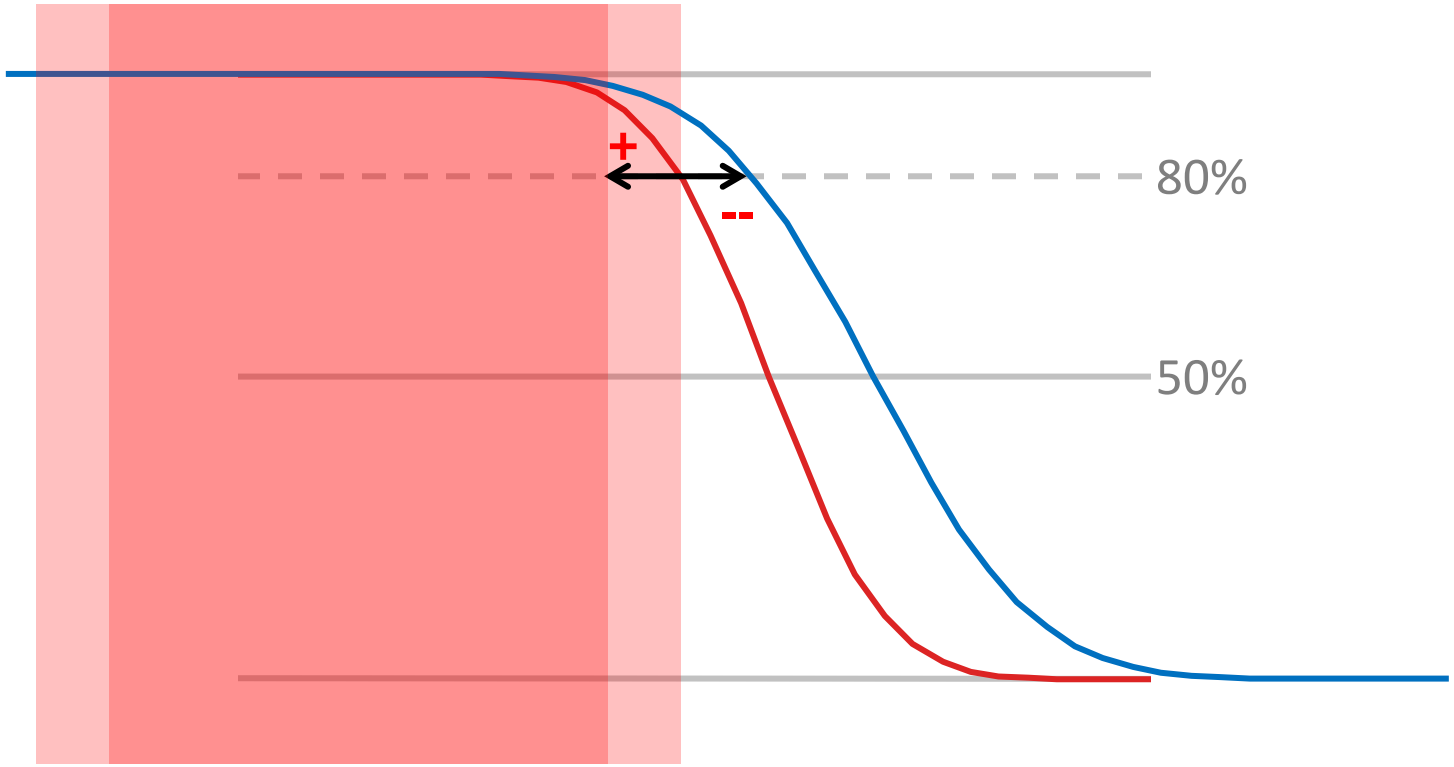
Margin Recipe for Random Error



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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

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Management of brain and spine SBRT: Positioning

Coen Hurkmans, clinical physicist

Catharina Hospital, The Netherlands

catharina hospital

"I want a detailed analysis, your best educated guess, and then round it out with some wild speculation."

Content

- Fixation devices brain
- Set-up accuracy with IGRT
- Fixation devices spine
- Set-up accuracy with IGRT
- IGRT technology
- Brain SBRT: End-t CZE

Less on fixation –
more on "prescribing to isodose"?

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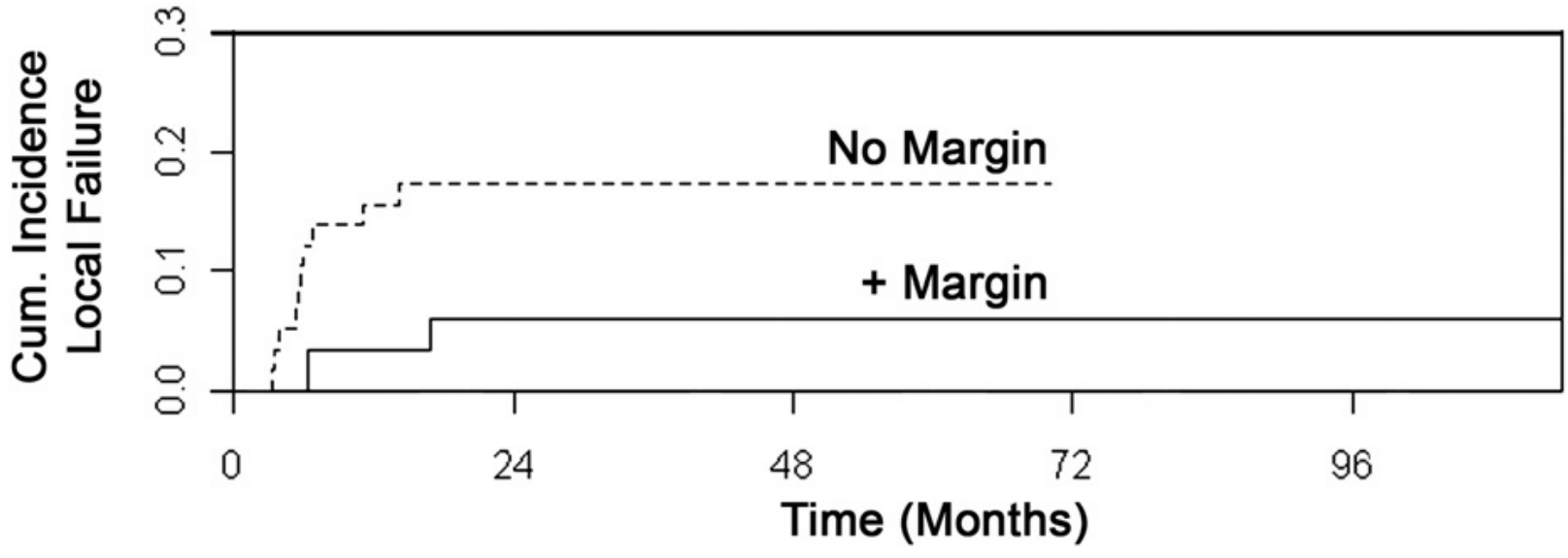
Brain SBRT: required accuracy



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

Choi IJROBP 2012, 84 p336

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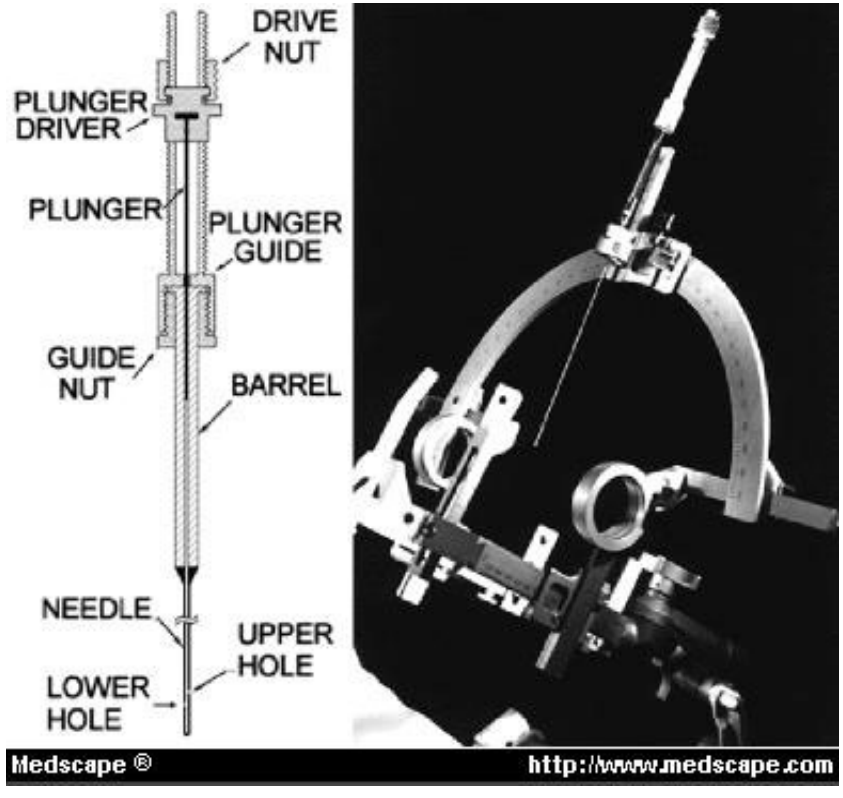
Frames

Lars Leksell, neurosurgeon. Frame developed in 1949



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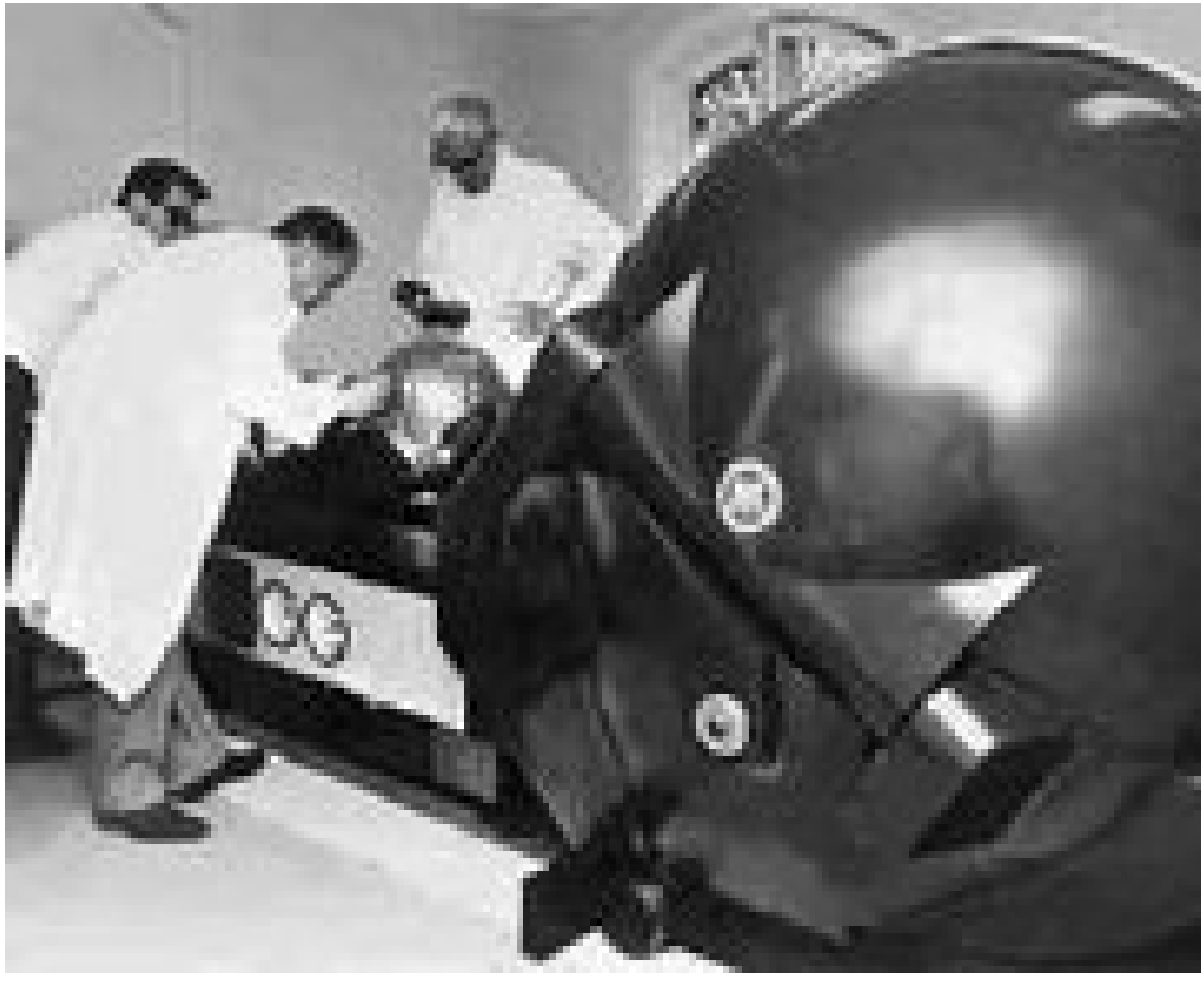
Gamma knife 1968



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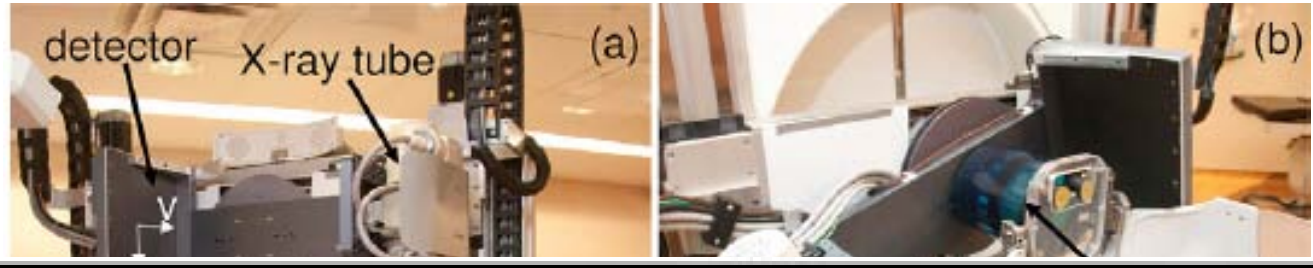
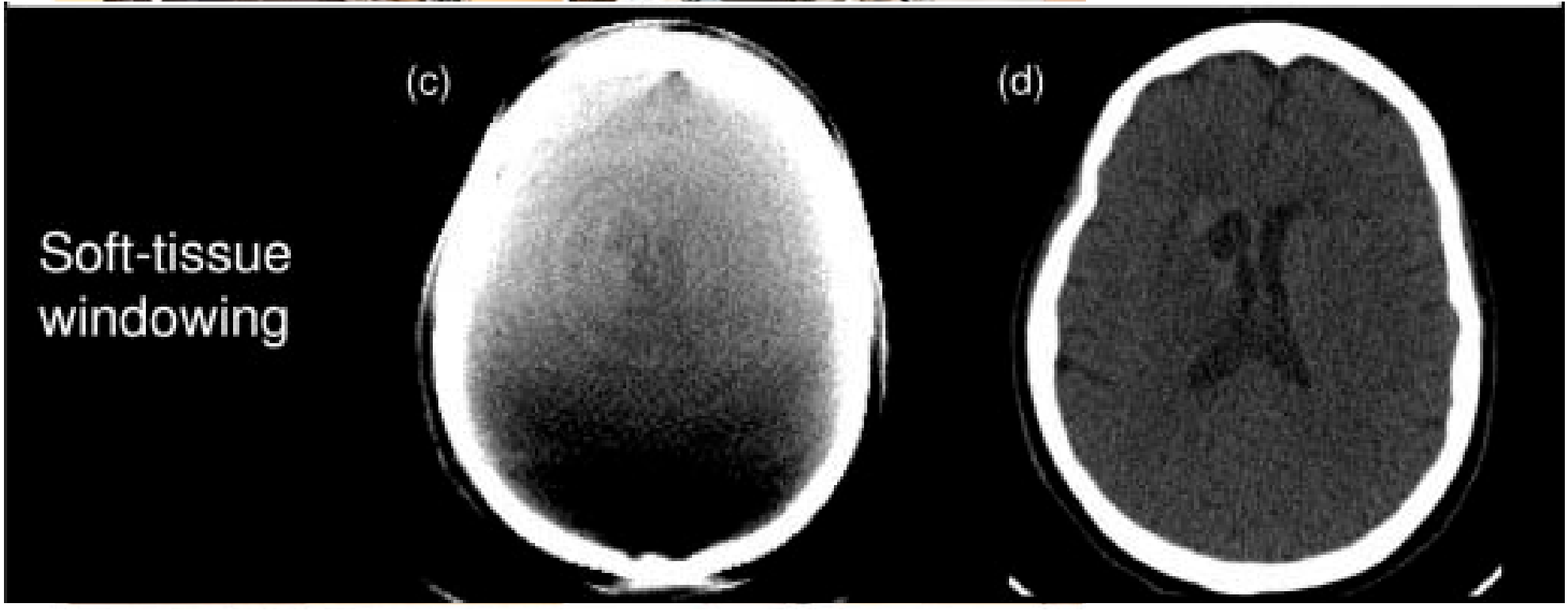
Gamma knife 2013



Frame accuracy:
deflections up to 1.5 mm
due to different load



Ruschin IJROBP 85, 2013 p243

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Gamma knife 2015

Includes CBCT and set-up camera

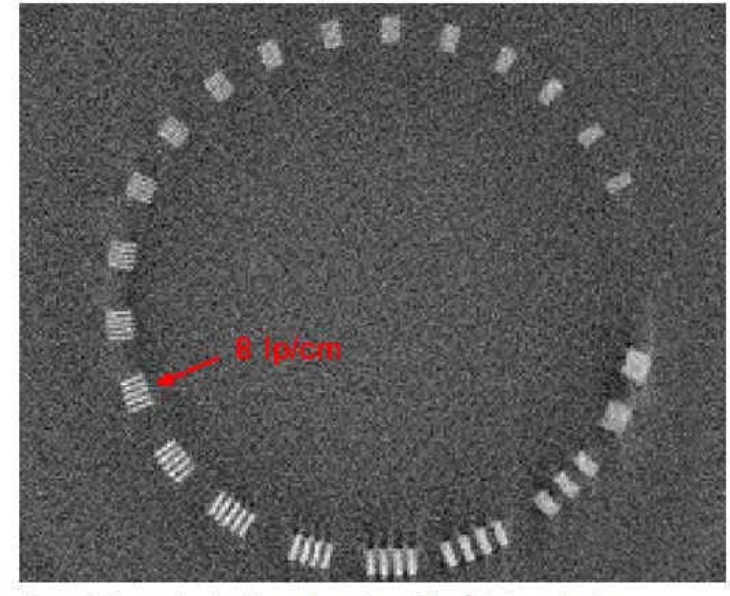

Figure 3. Reconstructed line pair section of the Catphan phantom.

Elekta website white papers, 2015

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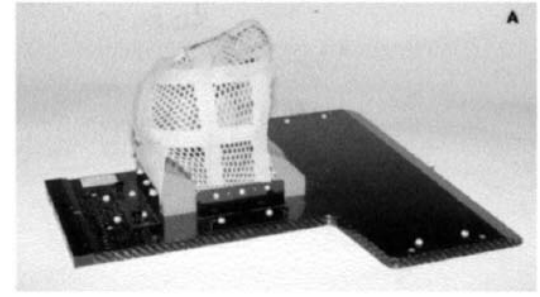
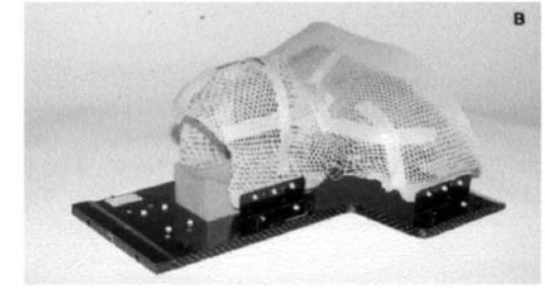
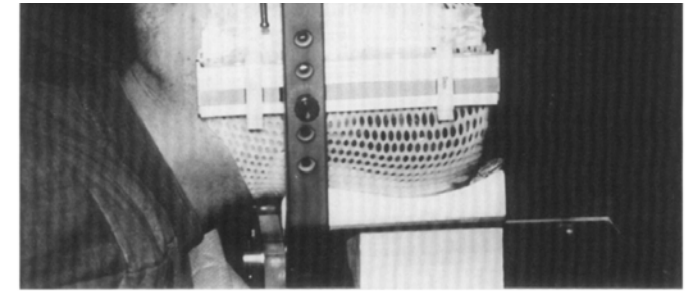
Masks: Literature

- Gilbeau, R&O 58, 2001 p155, Posifix (based on epid, 30 pats):
  1D Σ=1.8 mm, σ=1.8 mm

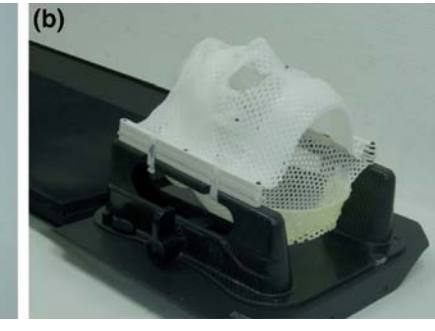




- Willner, R&O 45, 1997 p83, Brainlab (based on CT, 16 pats, 22 images):
  SI:M=0.4±1.5, RL:M=-0.1±1.8,
  AP:M=0.1±1.2

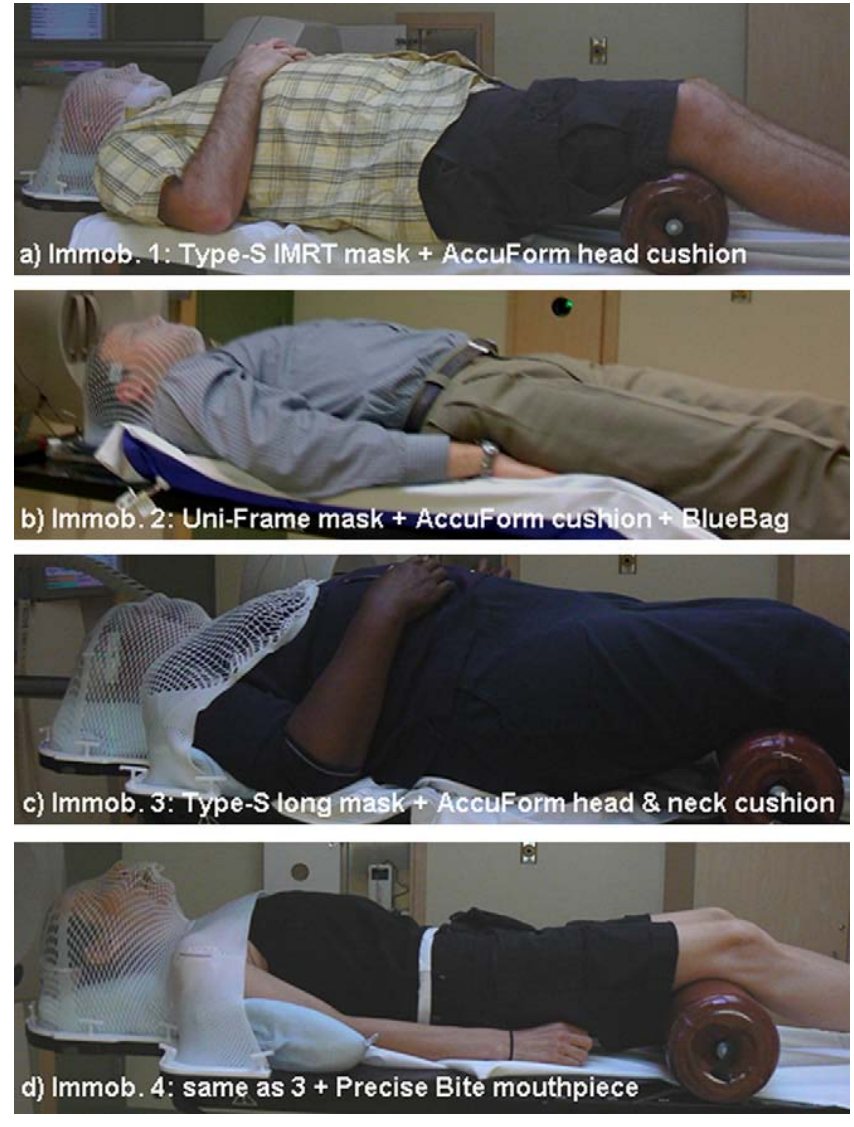


- Georg, IJROBP 66, 2006 s61, Brainlab headmask (based on epid, 10 pats)
  SI: Σ= 1.0, σ= 0.5, RL: Σ=0.7 σ= 0.6,
  AP:Σ=0.6 σ= 0.5



Masks: Literature

- AccuForm head cushion (Civco) and BlueBag indexed body immobilization system (Medical Intelligence) and Precise Bite mouthpiece (Civco), 121 pats
- Mean 3D interfraction motion (mm):
  immob 1: 2.3 (± 1.4)
  immob 2: 2.2 (± 1.1)
  immob 3: 2.7 (± 1.5)
  immob 4: 2.1 (± 1.0)
- Mean 3D intrafraction motion (mm):
  immob 1: 1.1 (± 1.2)
  immob 2: 1.1 (± 1.1)
  immob 3: 0.7 (± 0.9)
  immob 4: 0.7 (± 0.8)
- Rotations: 1° to 1.4° (1D, 1 SD)



Tryggestad, IJROBP 80, 2011 P281

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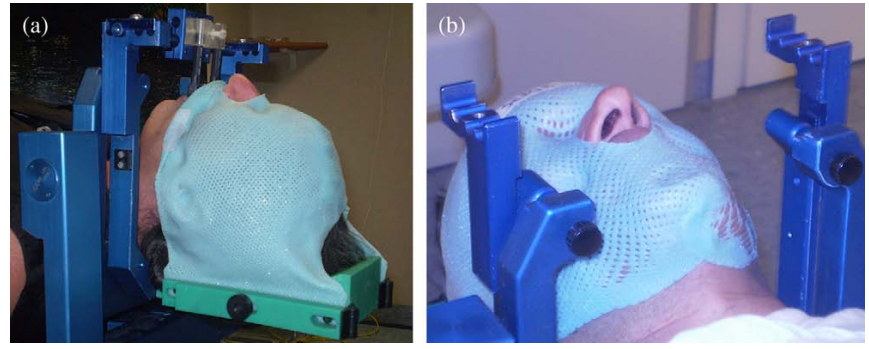
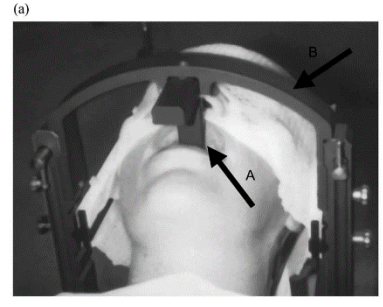
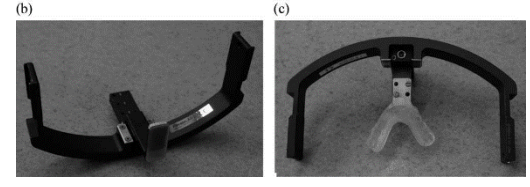
Bite blocks

1. Masi, IJROBP 71, 2008 p926 (Novastereo, Novater) 3D: 3.2 ± 1.5 mm and 2.9 ± 1.3 mm (**with bite block, ns**) 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. Baumert, R&O 74, 2005 p61: 3D: 3.7 ± 2.8 mm and 2.2 ± 1.1 mm **(with customised bite-block, p<0.001**)
3. Santvoort IJROBP 72, 2008 p261 Brainlab average 3D: 2.1 ± 1.2mm and 1.7 ± 0.7mm **with home made bite block, p=s**
4. Ruschin IJROBP 79, 2010 p306 Gamma-Knife bite block accuracy: average 3D: 2.0 mm ±1.1 mm



1





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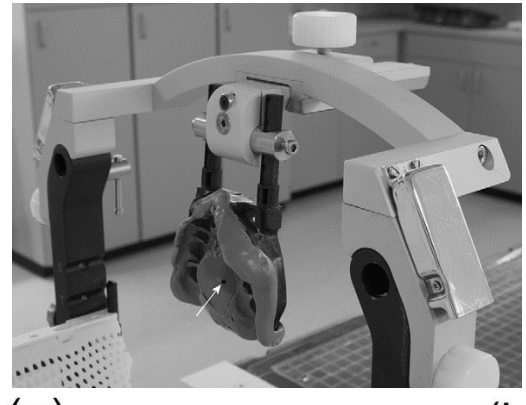

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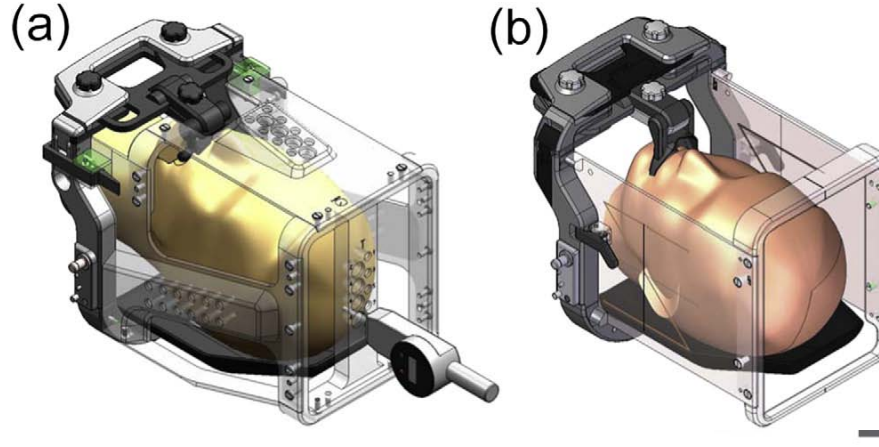

4

Again…..

Masks and bite blocks
are NOT sufficient

for current CTV-PTV margins!

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After correction with IGRT

- **Tryggestad** (civco), IJROBP 80, 2011 P281,
  mean 3D: from approx 1.8 mm to 1.15 mm,
  Residual set-up error (all immobs combined)
  ML:M=0.14 ±0.6, CC:M=0.47±0.8 and
  AP: M=–0.02±0.7
  significant
- **Masi** (novastereo), IJROBP 71, 2008 p926
  from
  X: M=0.5±1.3 Y:M=0.2±2.4 Z:M=0.0±1.7
  to X:M=-0.2±0.6 Y:M=0.1±0.6 Z:M=0.3±0.6
  significant
- **Baumert** (brainlab), R&O 74, 2005 p61, no data
- **Santvoort** (brainlab): 3D from 2.1 ± 1.2mm to 0.7 ±0.6 mm (mask)
  and from 1.7 ± 0.7mm to 0.4 ± 0.4mm (with bite block), **significant**
- **Ruschin** IJROBP 79, 2010 p306 (gammaknife): 3D from 2.0 ±1.1 mm to 0.8 ±0.1 mm,
  significant

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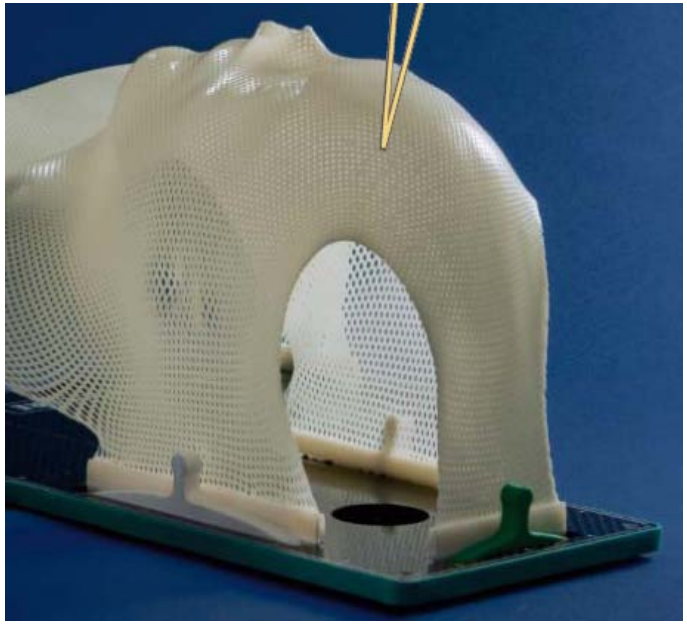
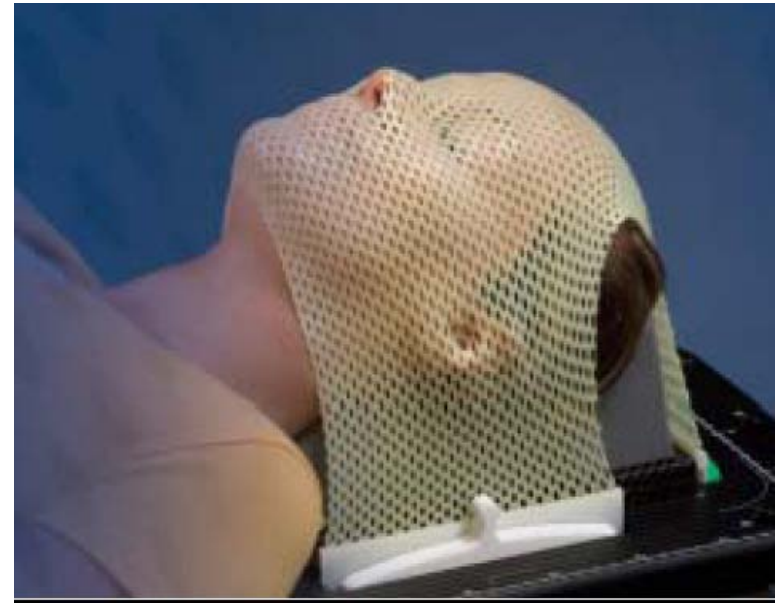
IGRT practical implementation at CZE



Efficast



Raycast

+

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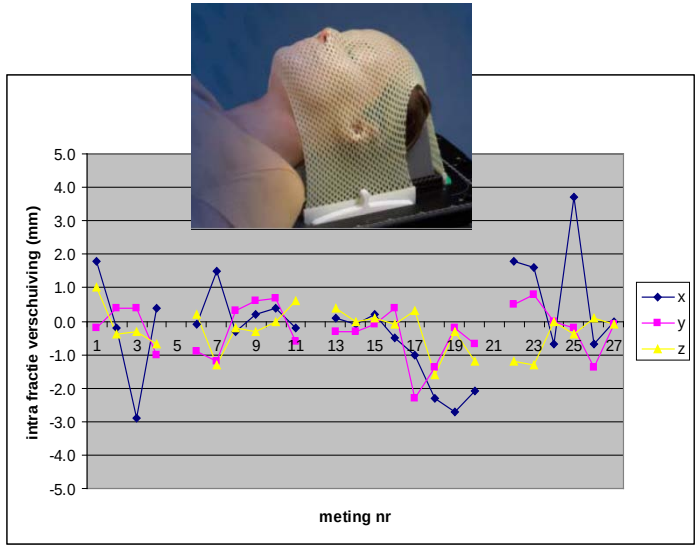
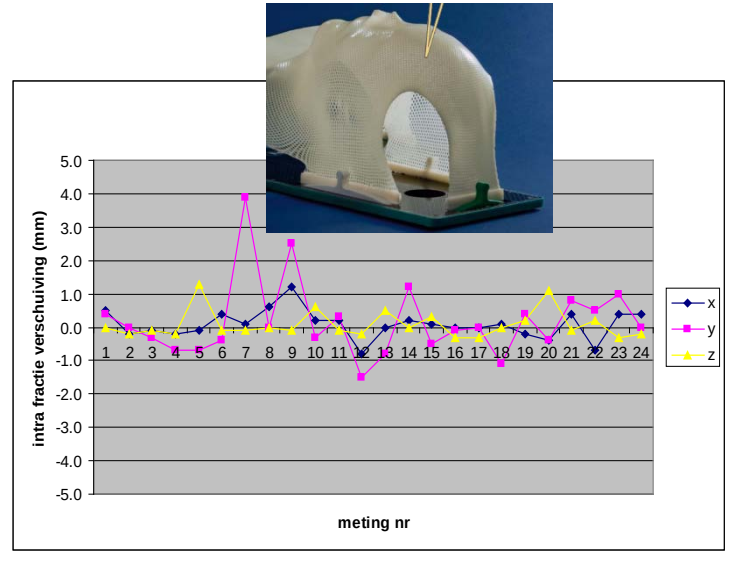
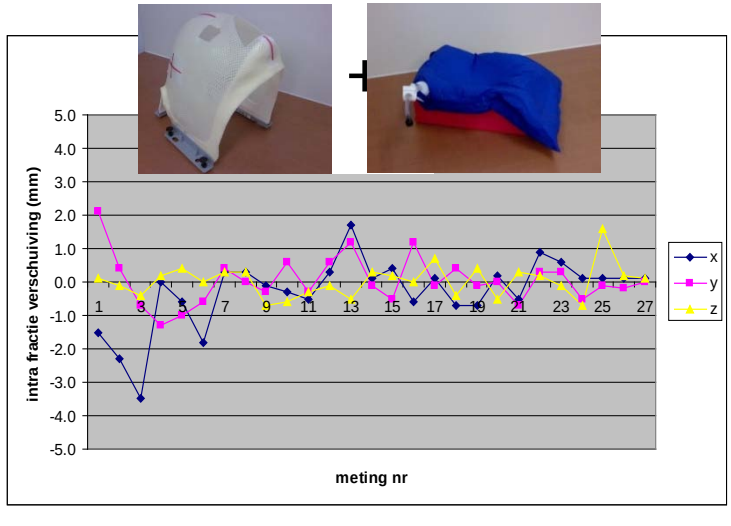
Mask QA study CZE: Translations







Hybrid in general < 1 mm

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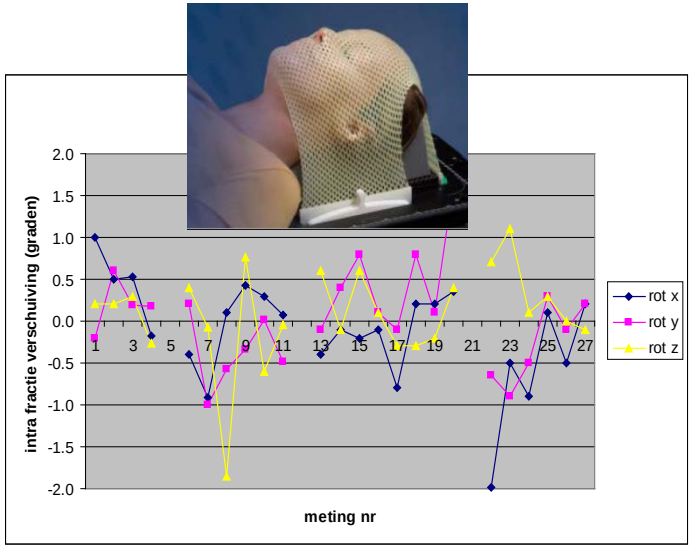
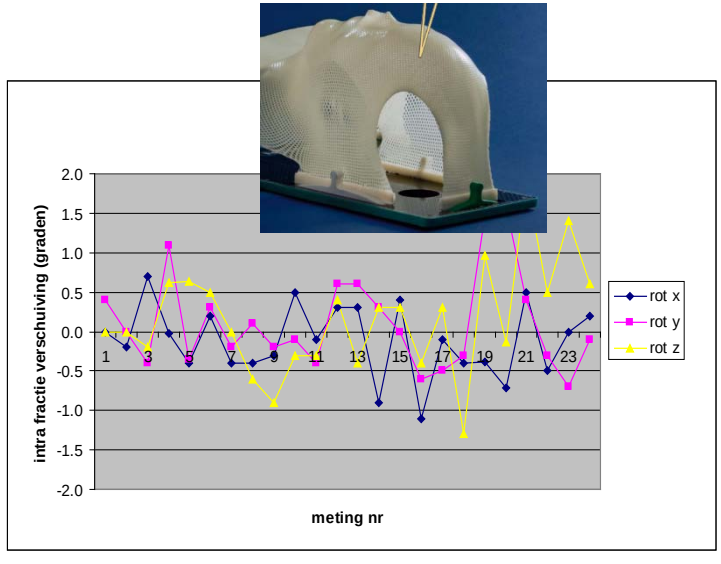
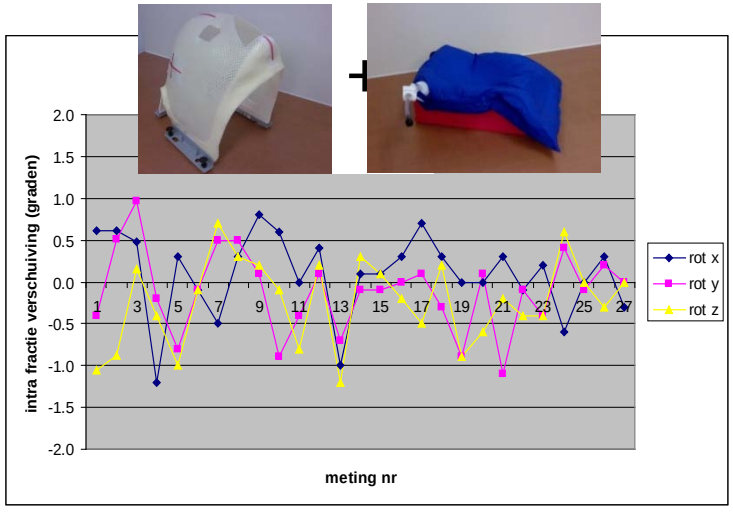
Mask QA study CZE: Rotations







Hybrid in general < 1°

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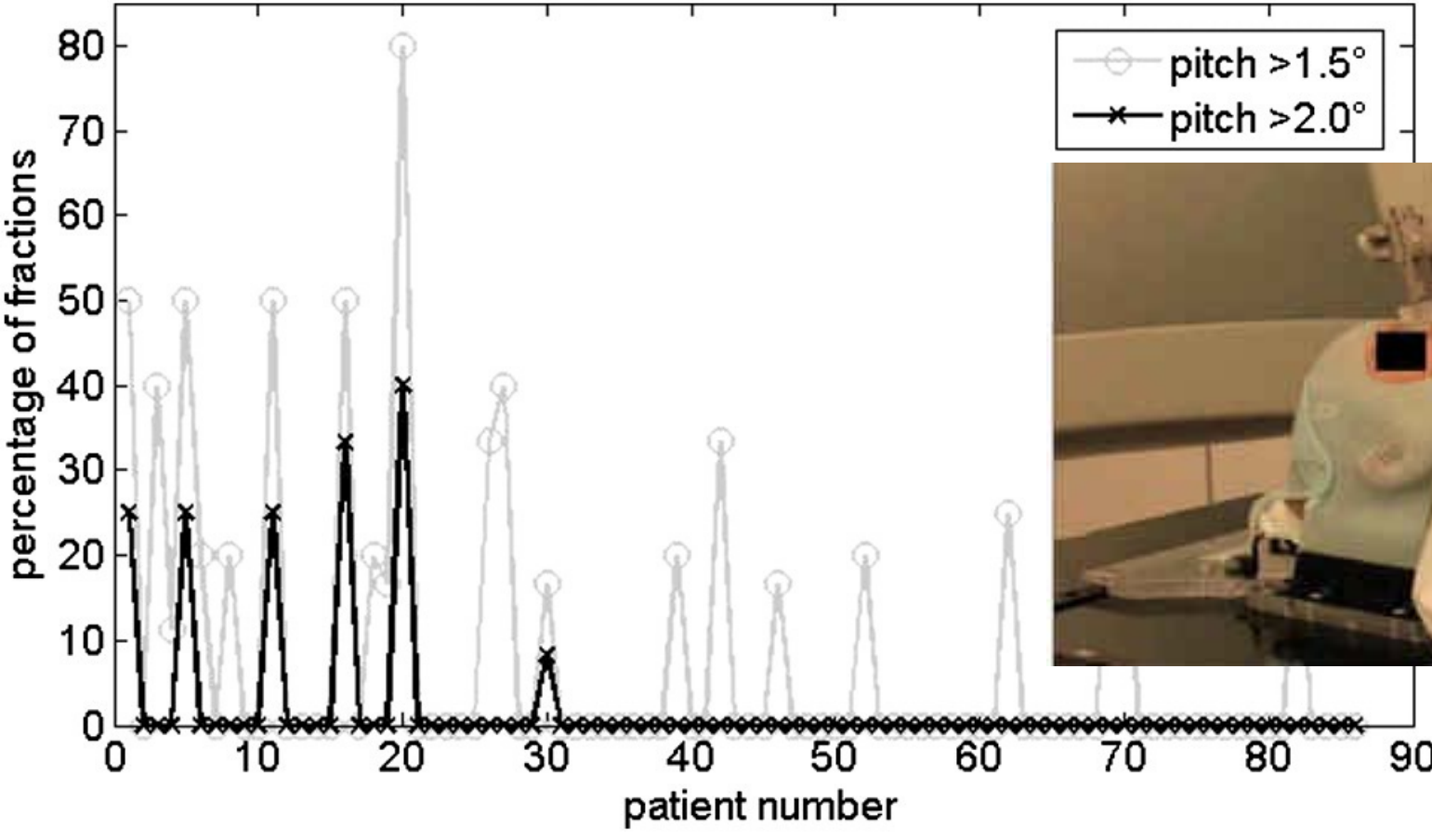
Mask QA: experience with a new system



Lang et al PRO, 2015

73 patients with trUpoint masks on truebeam

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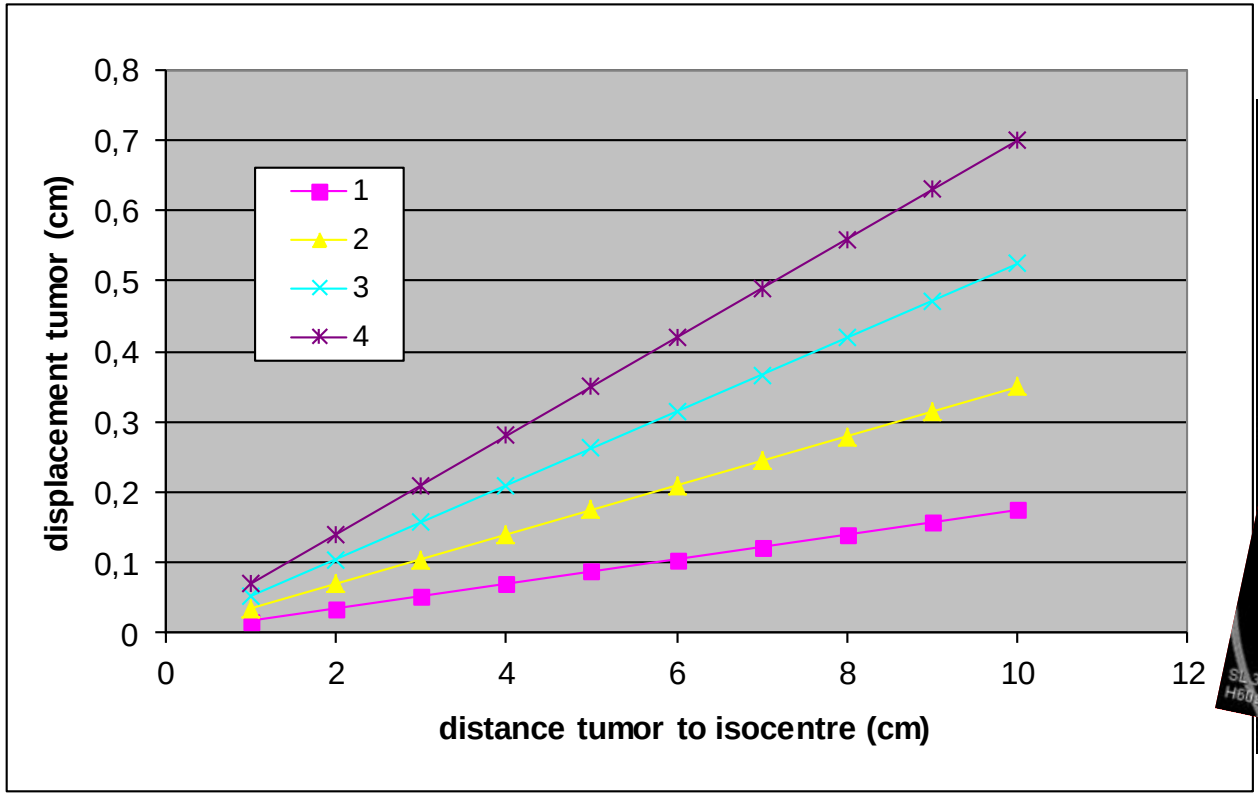
Rotations in single isocentre treatments with multiple lesions



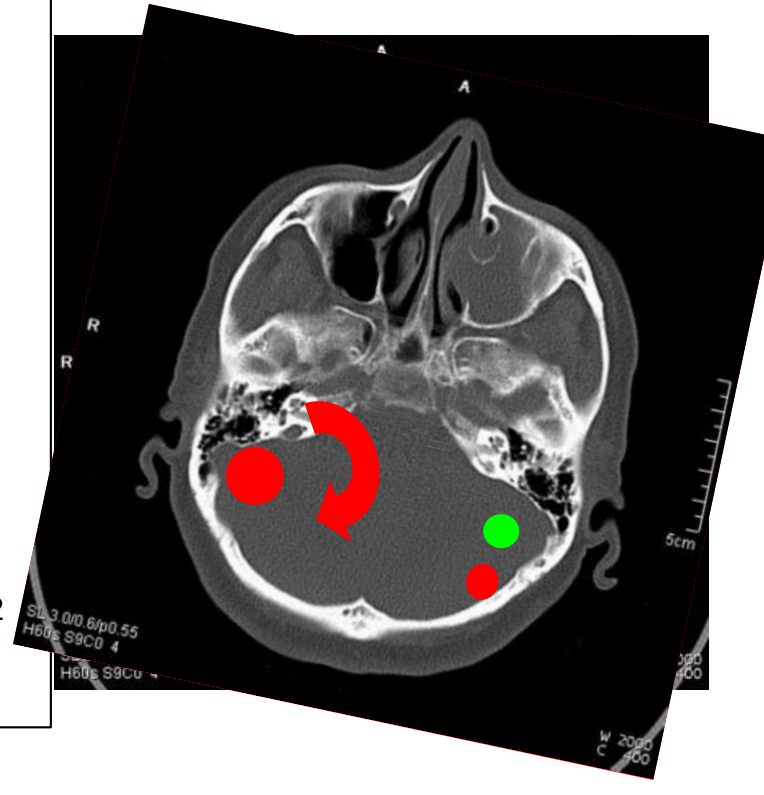
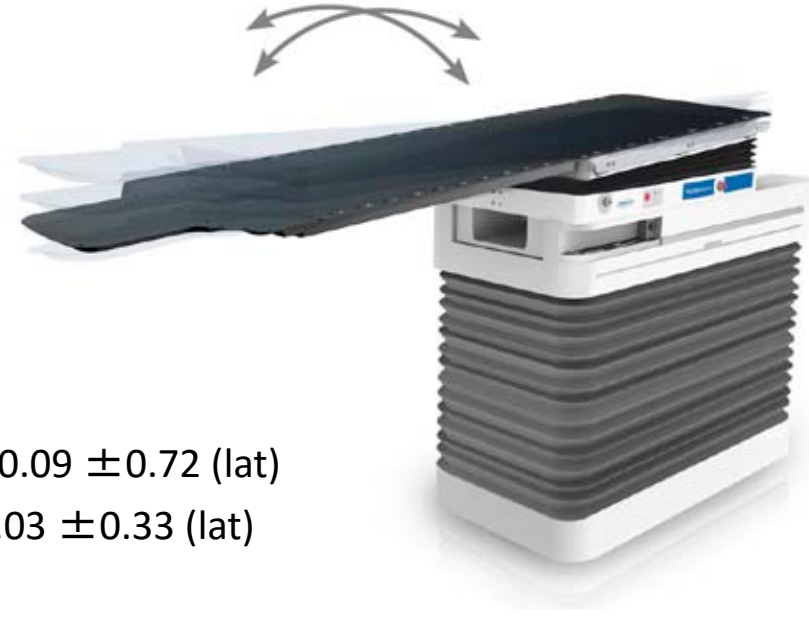


Table assisted rotation correction



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)

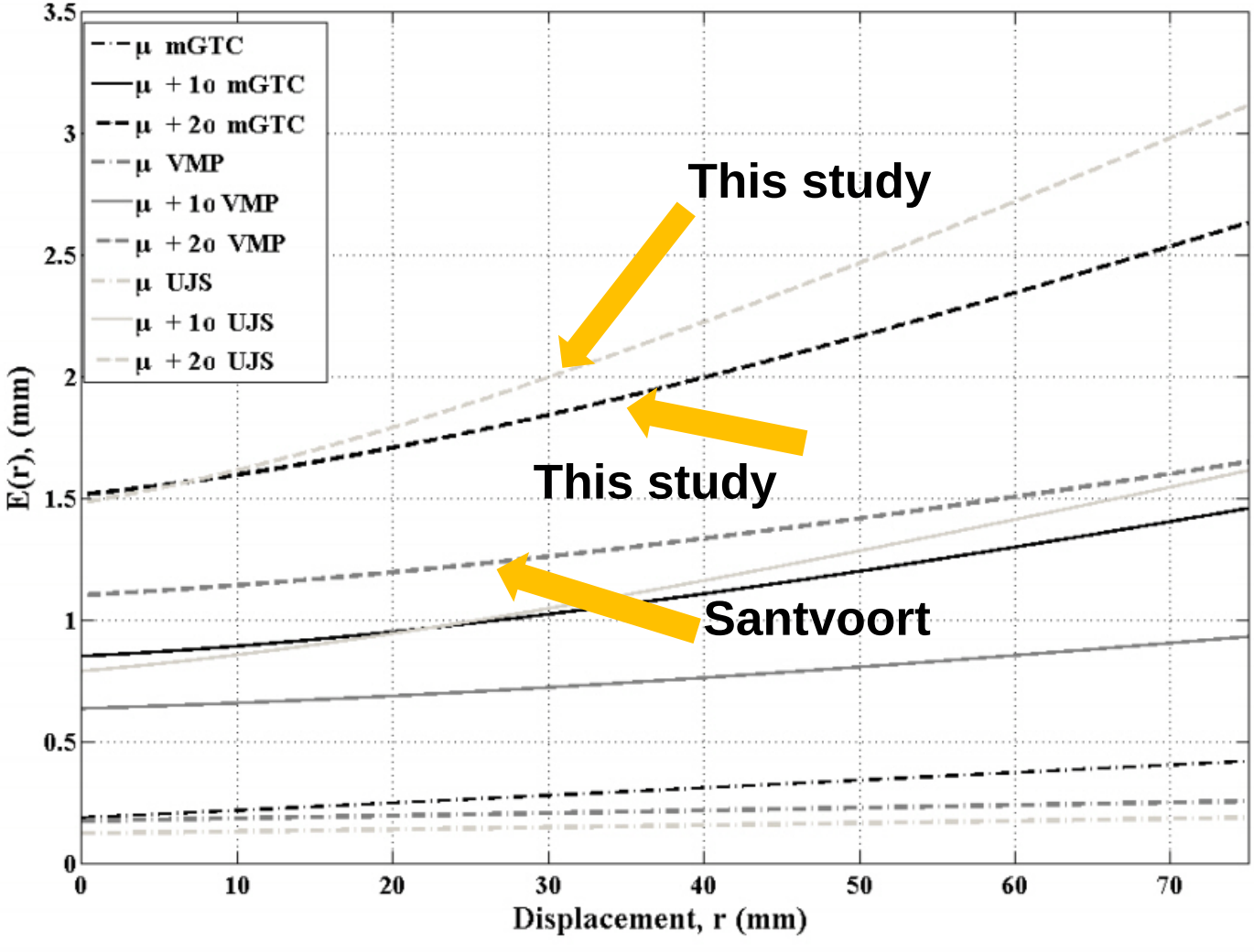
(intrafraction, after approx 15 min)

A ≥0.5° rotation was identified as threshold for coverage loss. (Volume covered by prescription isodose would have decreased by 5% in this population)

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

Rotation correction with multiple lesions

With 6DOF



Winey et al JACMP 15(3)p122 2014

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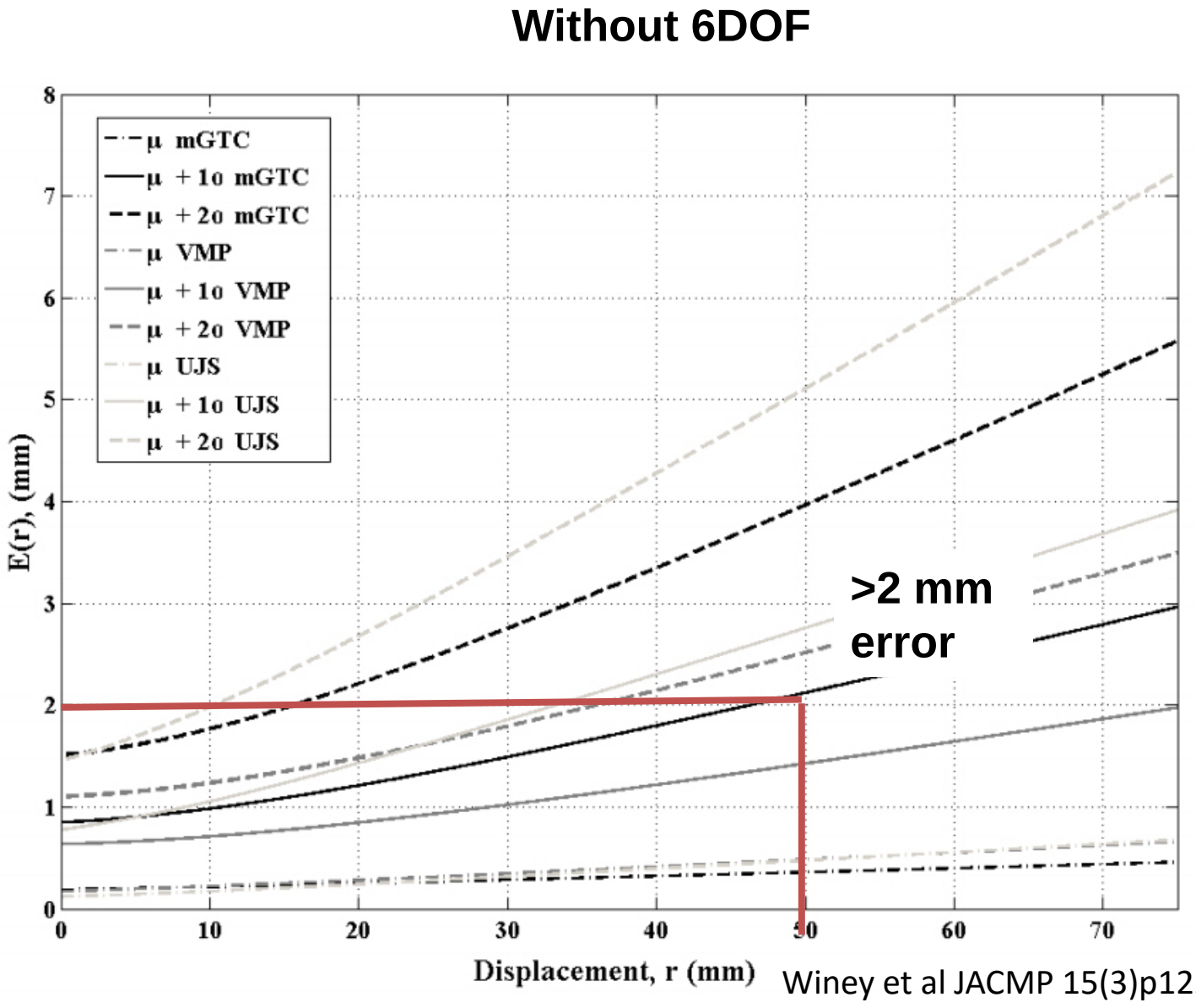
Rotation correction with multiple lesions



So:
use 6DOF couch

OR

multiple
isocentres

Winey et al JACMP 15(3)p122 2014

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Question

When implementing SBRT for brain, one should at least:

1. Use a bite block
2. Use on-line IGRT
3. Use a frame
4. Use a 6DOF couch

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Intra fraction motion: treatment time

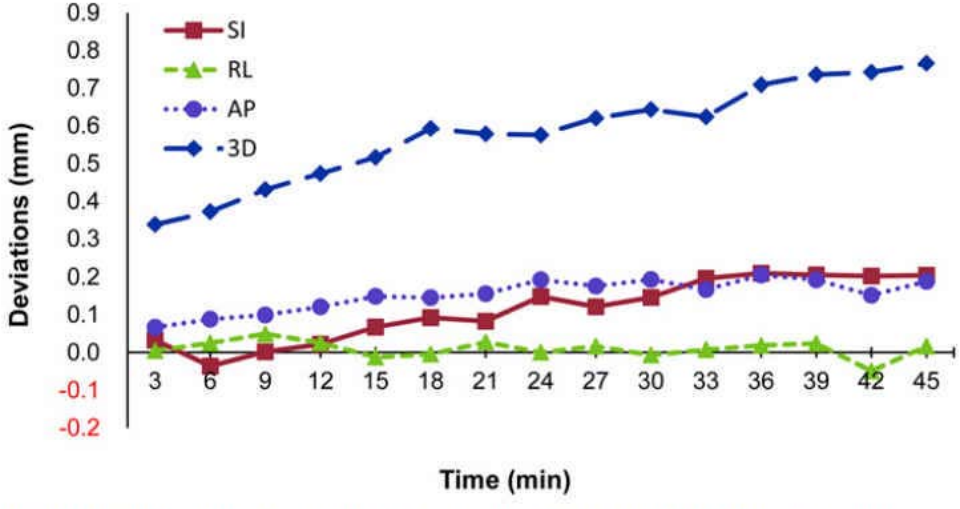
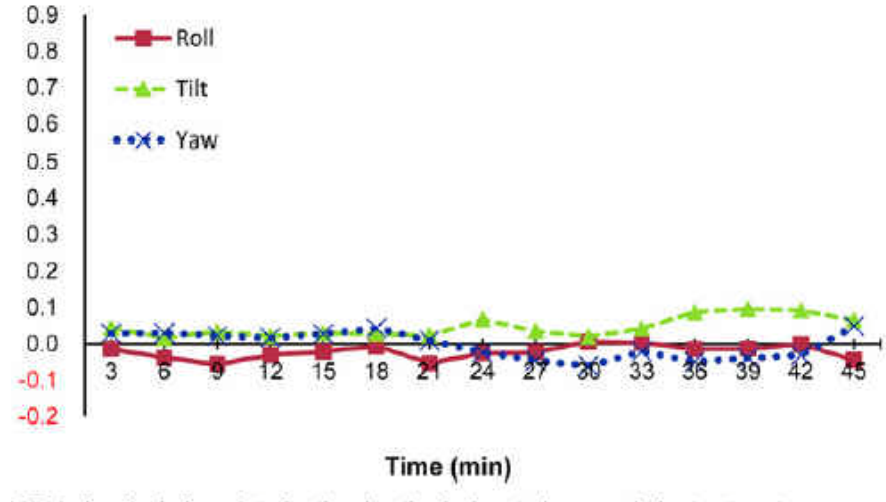


Fig 2. Translational deviations. Intrafractional motion in the translational axes during treatment.



. 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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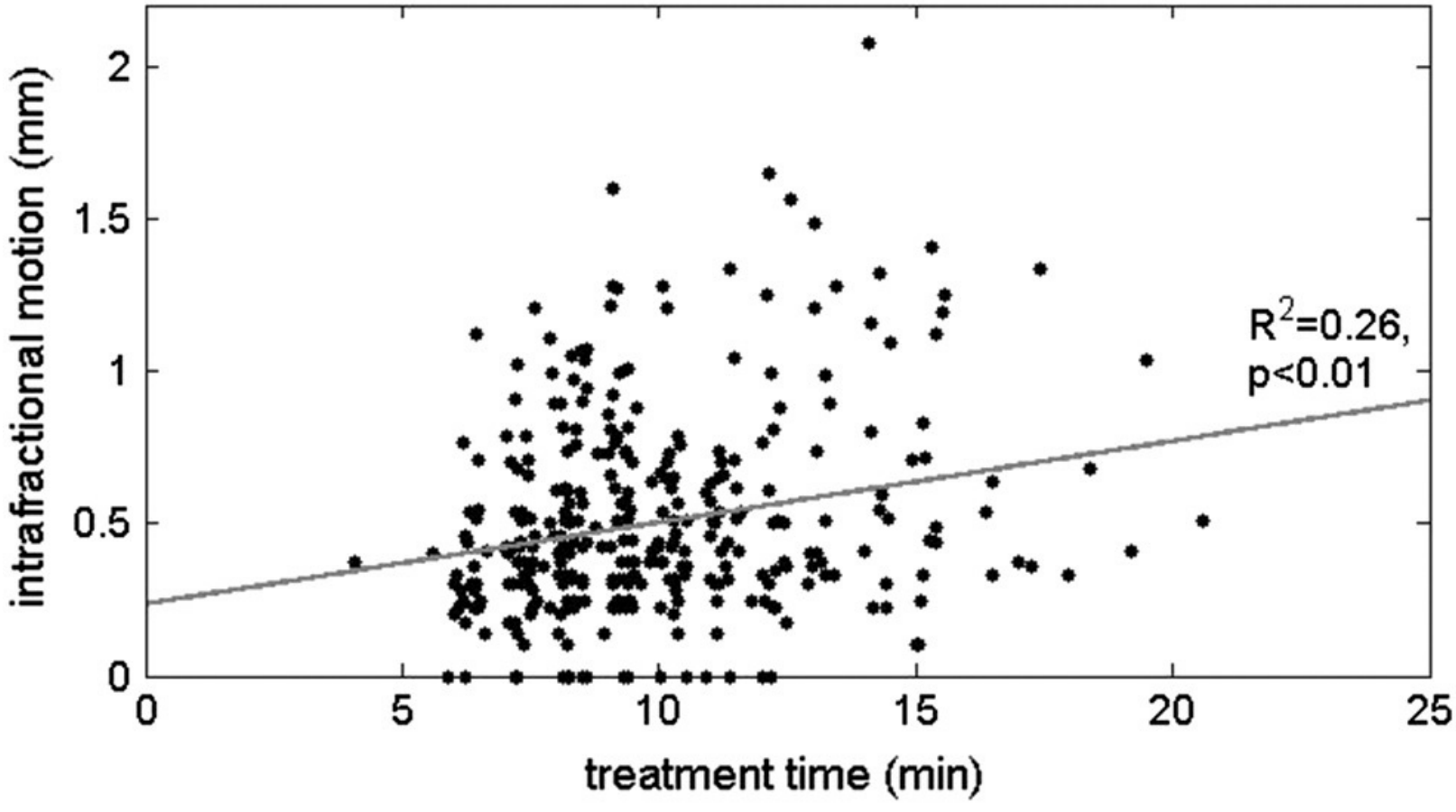
Intra fraction motion: treatment time



Lang et al PRO, 2015

73 patients with trUpoint masks on truebeam

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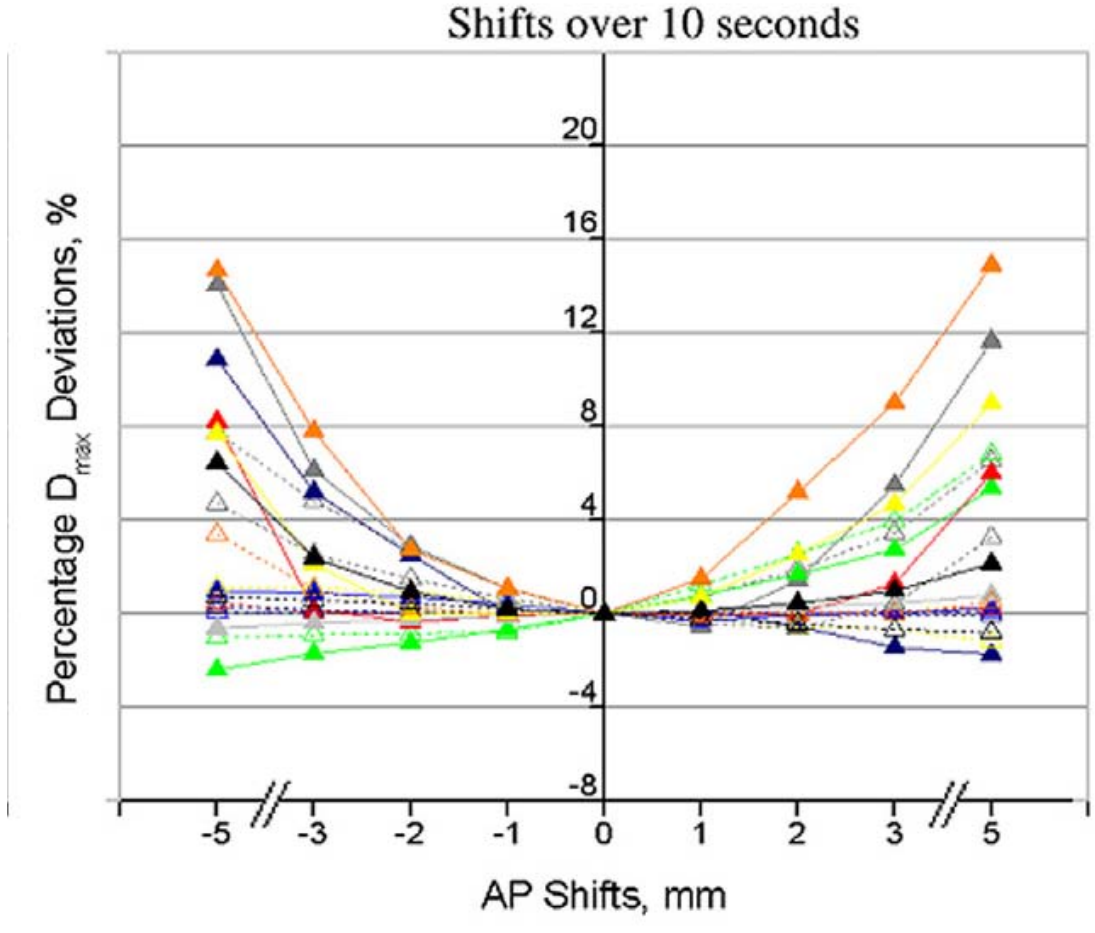
Spine SBRT: Required accuracy

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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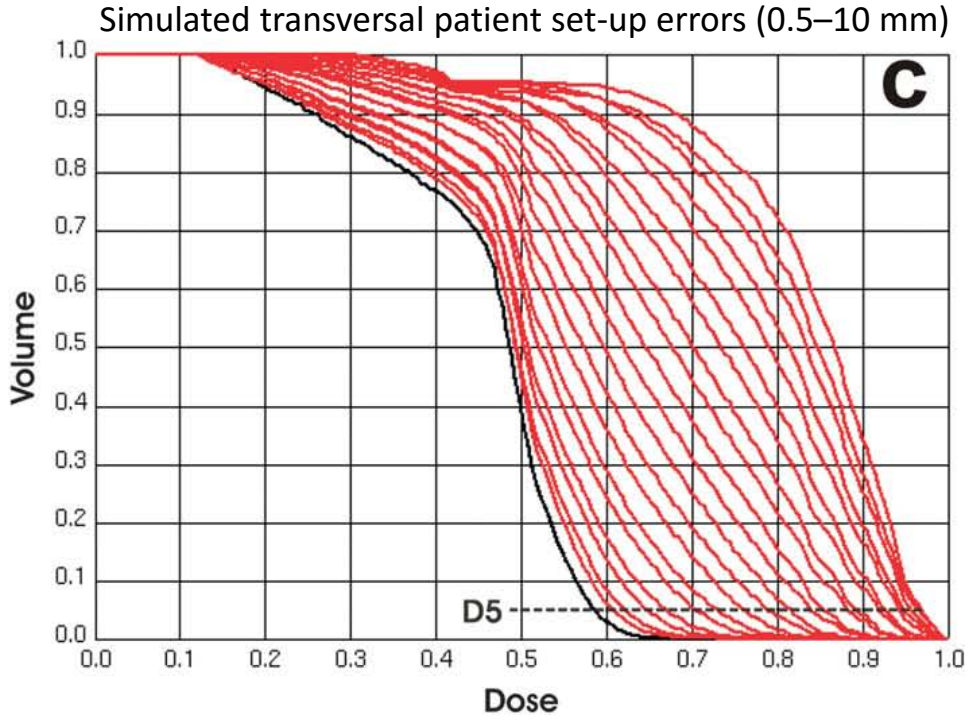
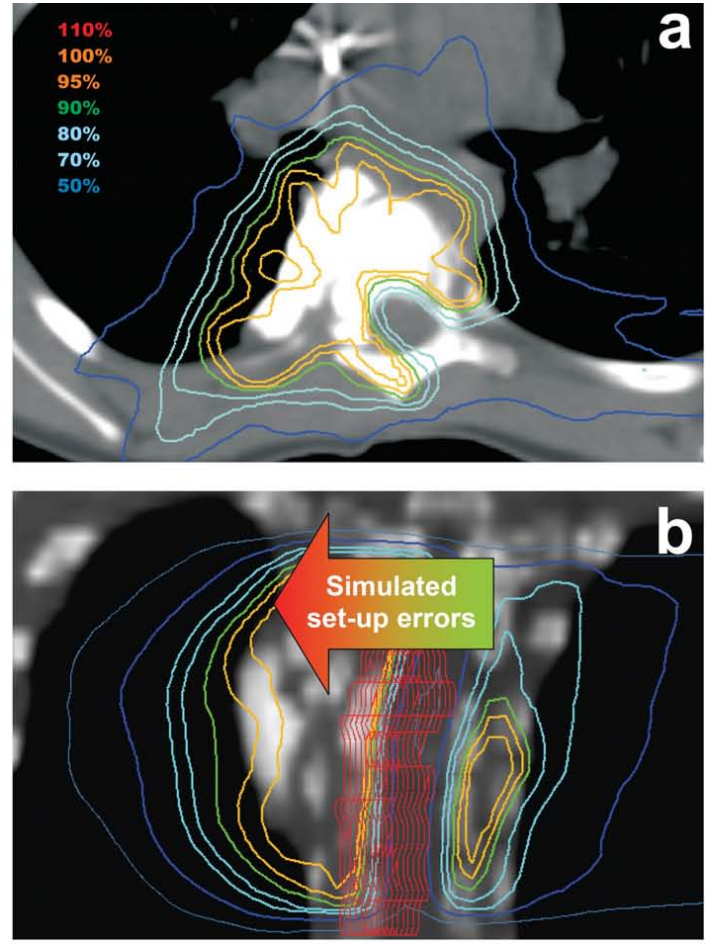
Spine SBRT: Required accuracy





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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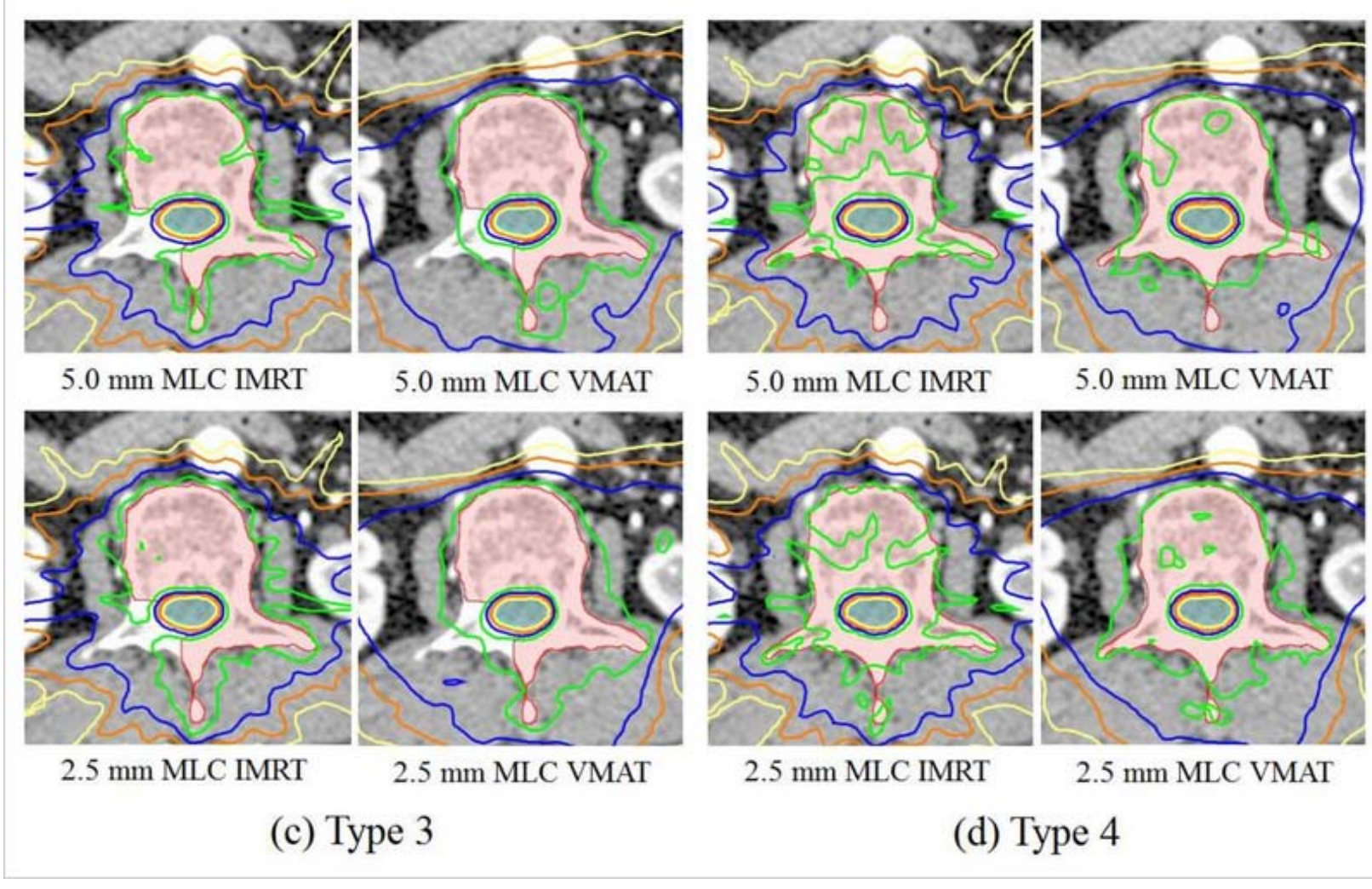
Spine SBRT: Required accuracy MLC



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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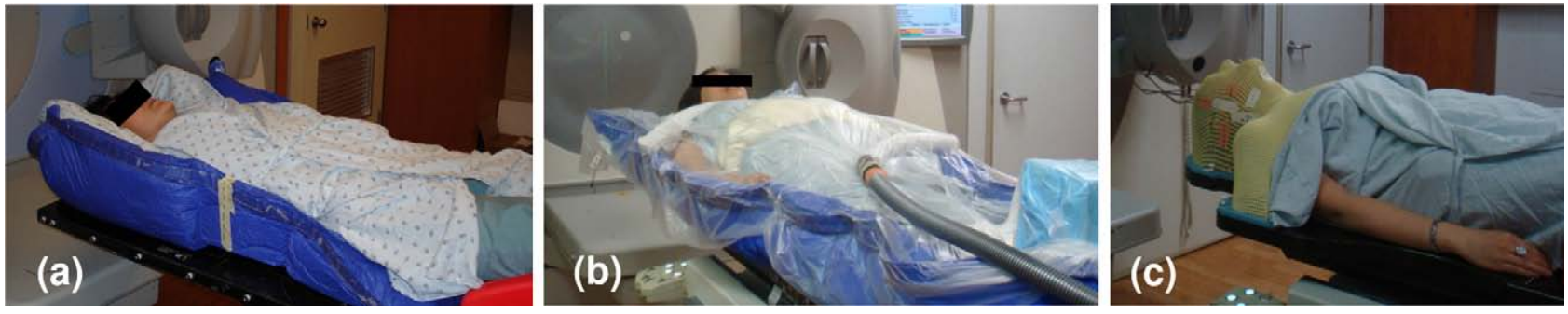
Positioning for spine SBRT

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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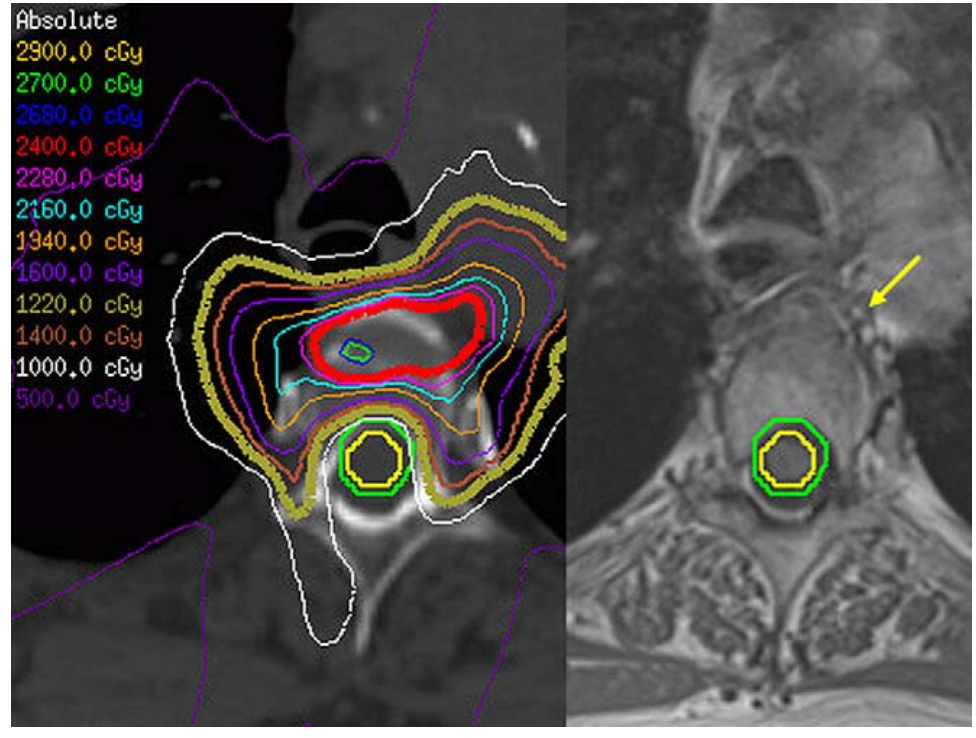
Positioning for spine SBRT

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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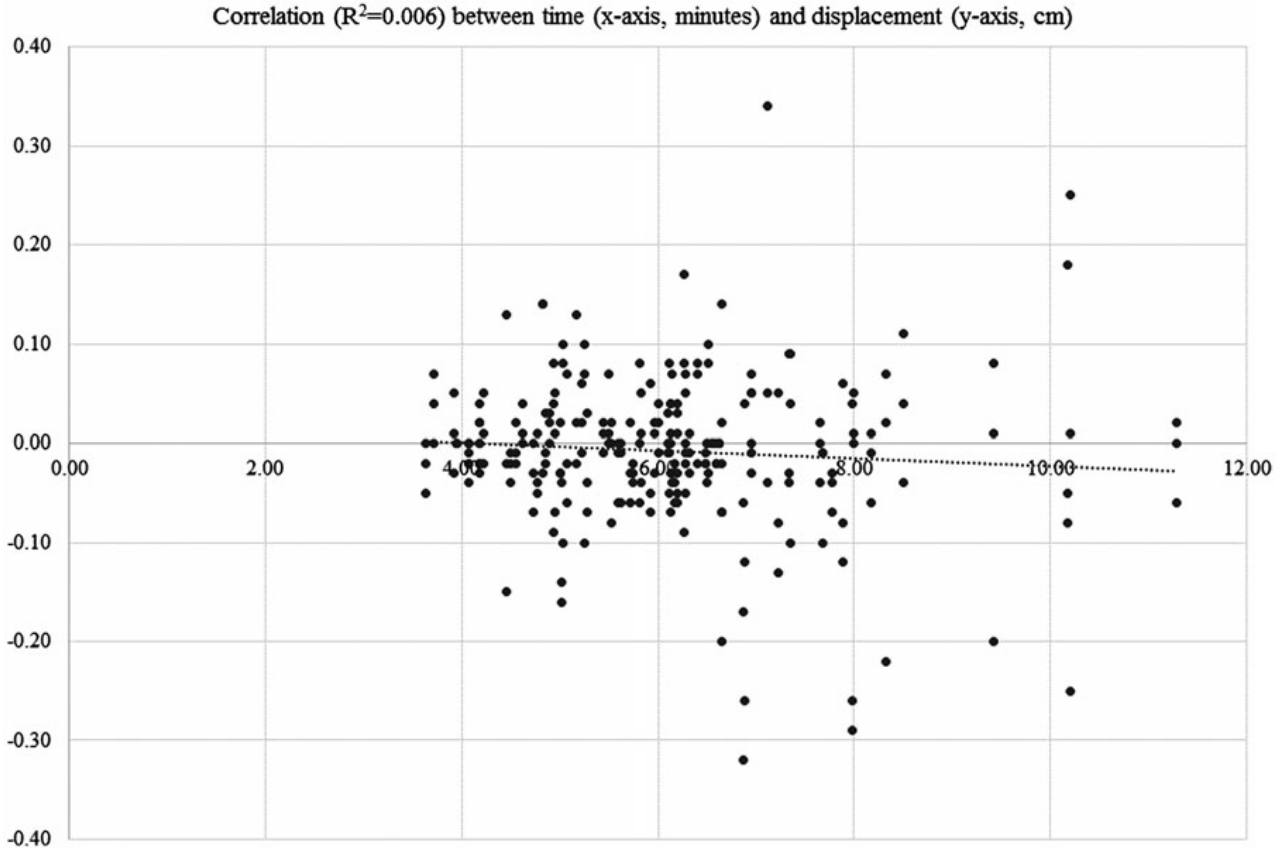
Positioning for spine SBRT



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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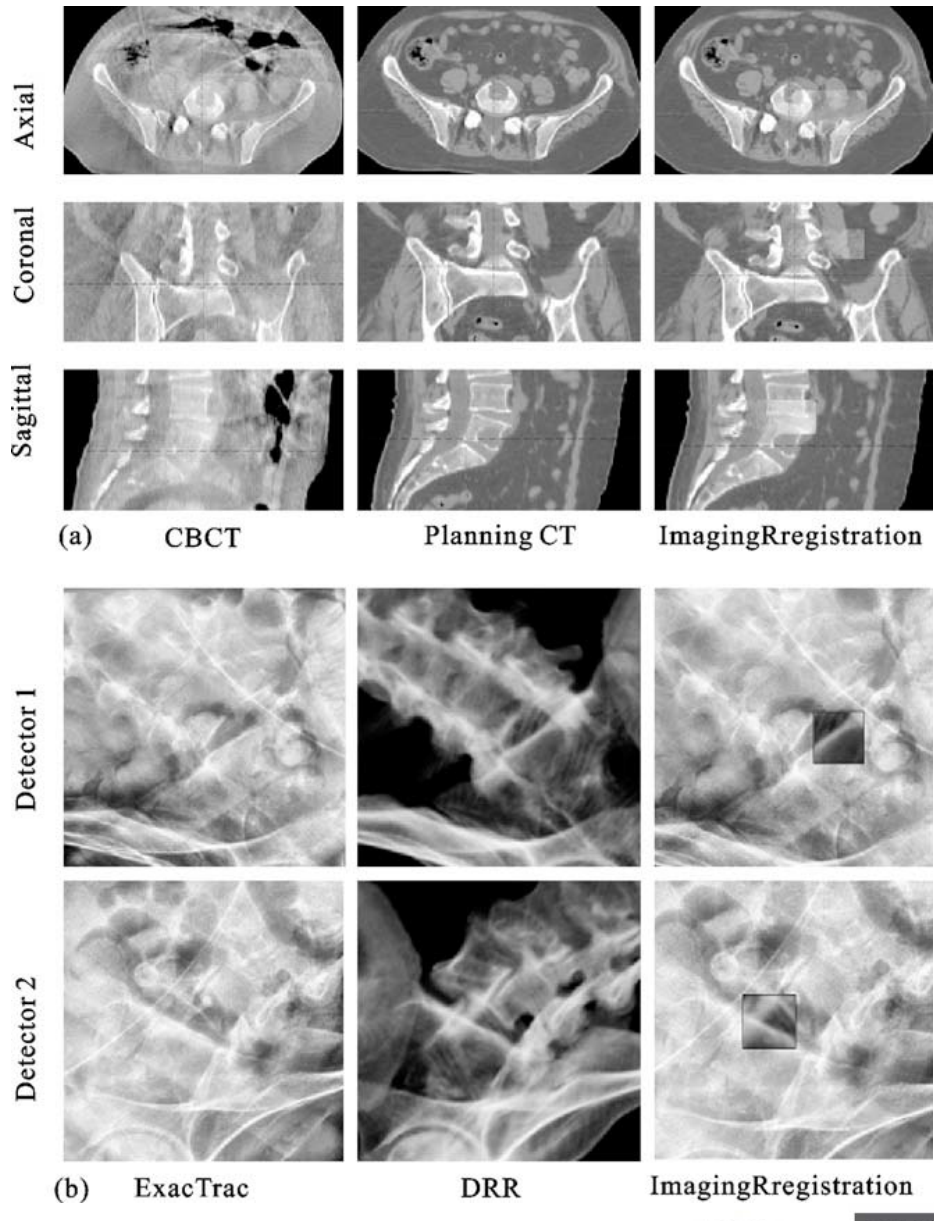
Imaging technology

Comparison of Novalis 6DOF setup measured with ExacTrac or with CBCT:

Phantom experiments RMS <1.0 mm and <1° . 11 spinal SBRT pats: RMS <2.0 mm and <1.5° .

Pre-caution should be taken when only ExacTrac X-ray 6D is used to guide SBRT with small setup margins.



Chang R&O 95, 2010 p116-121

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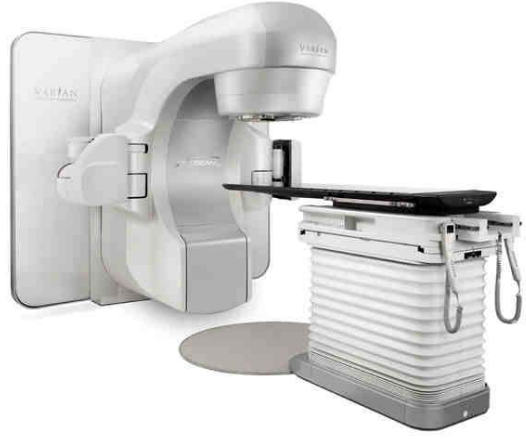
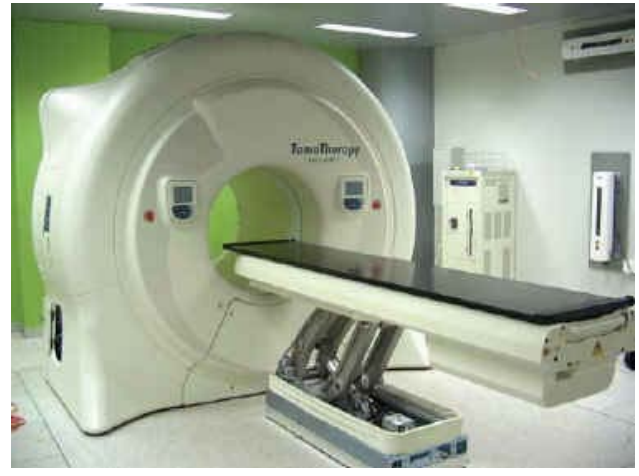
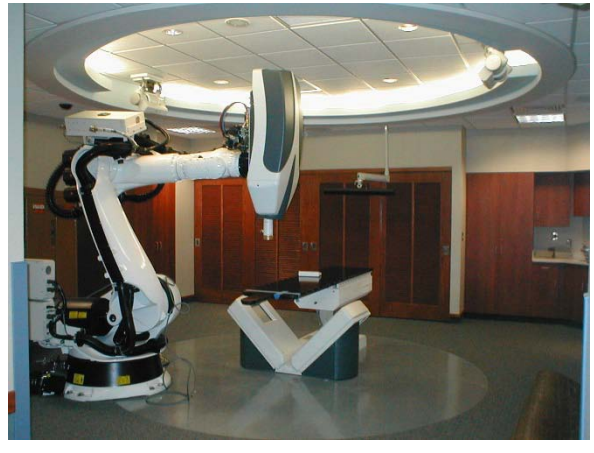
IGRT technology







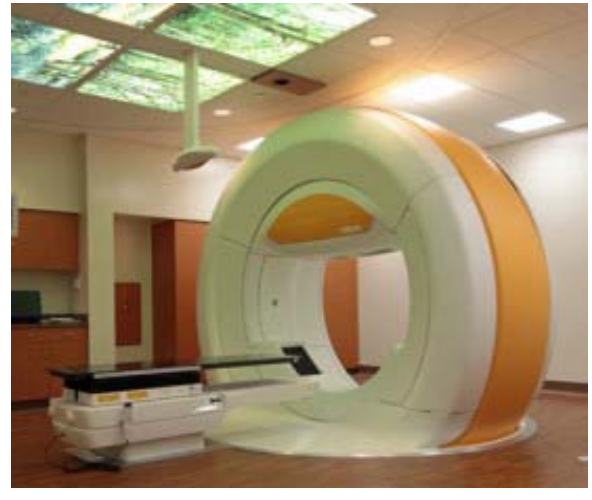


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Table 1 Radiation-based systems for IGRT

Radiation-based systems		Imaging acquisition	Average dose per image*	Geometric accuracy	Functionality and routine clinical use	Examples of sites where technology has been commonly applied	Benefits and caveats
Electronic portal imaging devices (EPIDs)	Examples						
kV or MV 2-D planar	Varian, Siemens, Elekta	2-D	1-3 mGy	1-2 mm	MV or kV "snapshot" planar images; used to acquire portal images for verification of setup based on bony landmarks	Prostate/pelvis Head and neck Lung/thorax Breast Pelvis/gynecologic tumors	Appropriate if bony landmarks serve as a good surrogate for tumor localization; does not acquire 3-D, volumetric information, and is static; kV x-rays will offer better image contrast than MV; kV x-rays will suffer from artifacts in the presence of high-density structures, such as hip prostheses
Stereoscopic kV imaging	Accuracy (Cyberknife)	2-D	0.10-200 mGy	<1 mm	kV-pretreatment planar images and images during treatment to track motion; alignment performed based on implanted markers or marker or bony landmarks; robotic positioning accounts for "6-D," translational and rotational setup corrections	Prostate/pelvis Lung/thorax Gynecologic tumors Brain SBRT/SRS	Appropriate if bony landmarks serve as a good surrogate for tumor localization; does not acquire 3-D, volumetric information

Santos IJROBP 2013 87(1)p33

Brain SBRT: end-to-end accuracy at CZE

- What is the total current accuracy?
- Is the current margin appropriate?

GTV = 5 cm^3

PTV_1= GTV + 3 mm=11.5 cm^3

PTV_2=GTV + 2 mm=9.2 cm^3

With 1 mm smaller margin → 20% reduction in irradiated brain volume

Table 3. Rate of radionecrosis for V10 Gy and V12 Gy volumes

Volume (cm^3)	Radionecrosis (%)
V10 Gy	
<2.2	4.7
2.2–6.3	11.9
6.4–14.5	34.6
>14.5	68.8
V12 Gy	
<1.6	4.7
1.6–4.7	11.9
4.8–10.8	34.6
>10.8	68.8

Abbreviations: V10 Gy, V12 Gy = volume of brain receiving 10 Gy and 12 Gy, respectively.

Blonigen IJROBP 77(4) 2010 p996

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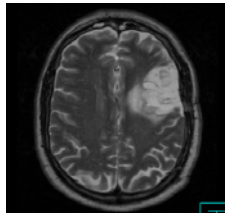
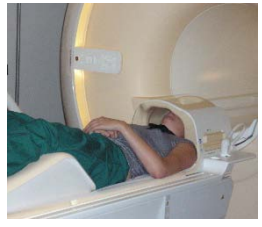
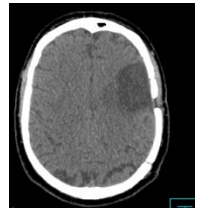
The treatment chain

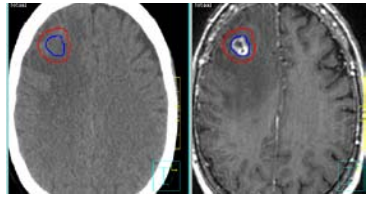
- Imaging
- Image registration
- Delineation
- Treatment planning
- Data transfer
- Patient QA measurement
- Patient immobilization & positioning
- Treatment delivery

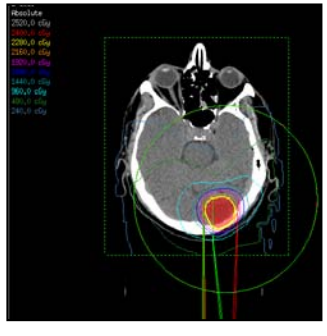
with




+

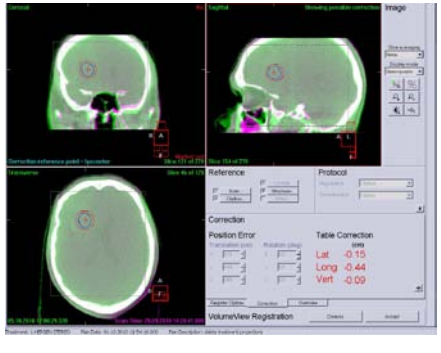


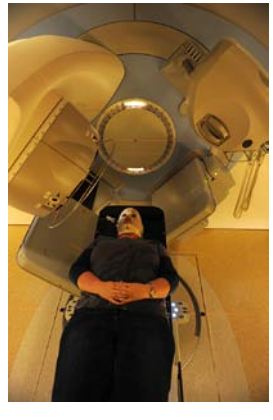
- **Delineation GTV and OAR on MRI**
- **CTV = GTV, PTV = CTV + 3mm**



VMAT planning

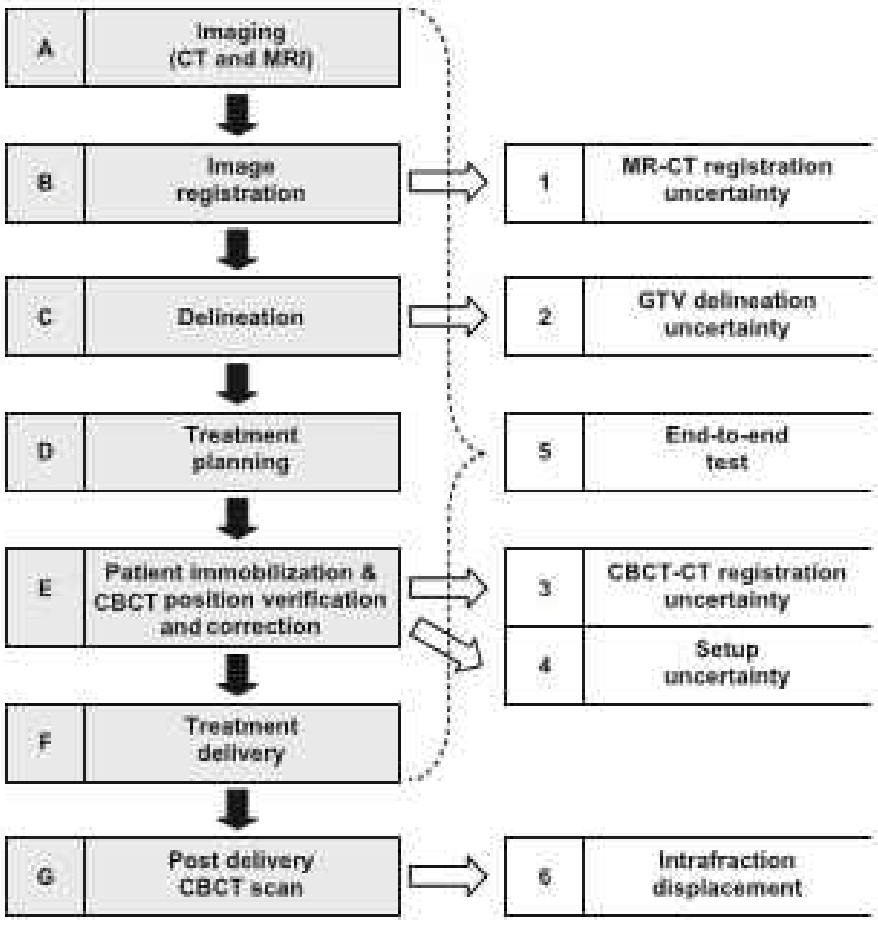
- **1 dual arc per isoc**
- **98% of PTV should get at least 95% of prescribed dose**





Diameter tumour	Dose
≤ 20 mm:	1 x 2200 cGy
21-30 mm:	1 x 1900 cGy
31-35 mm:	1 x 1700 cGy
36-50 mm or close to OAR	3 x 800 cGy

The treatment chain: Measured uncertainties



Error Source	Data based on		Direction		
	# patients	# lesions	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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Take home message

- 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.

- One should perform **complete end-to-end tests** to establish the complete treatment chain accuracy and implement the appropriate CTV-PTV margins accordingly.

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The bridge to Linac based RT: Volumes

GK old	GK new	Linac RT - ICRU
-	-	**PTV**
TV	Target Volume (GTV)	GTV
	Clinical target volume (CTV)	CTV
Planning, Planned or Peripheral Volume	Prescription Isodose Volume (PIV)	Treated Volume e.g. TV_{20Gy}
TVPIV, GTV in PIV, VT ∩ VP PIVTV etc.	Treated Target Volume (TTV)	$GTV_{V100\%}$
Irradiated Volume	Volume of Accepted Tolerance Dose (VATD)	Irradiated Volume
	Organ at Risk Volume	Organ at Risk (OAR) Volume

Torrens et al. J Neurosurg. 2014 Dec;121 Suppl:2-15

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The bridge to Linac based RT: Dose

GK old	GK new	Linac RT
	Absorbed dose DV% (e.g. D95%)	-
	Maximum dose (D2%) (D1mm3)	Maximum dose (D2%)
	Minimum dose (D98%) (D1mm3)	Minimum dose (D98%)
	Mean dose (Dmean)	Mean dose (Dmean)
	Median Dose (D50%)	Median Dose (D50%)
Integral Dose	Total Absorbed Energy (TAE)	

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The bridge to Linac based RT: Dose

GK old	GK new	Linac RT
Planned, Peripheral or Marginal.	**Prescription dose / Prescription isodose**	**Prescription dose Dv% e.g. D100% = 20 Gy or D98% = 20 Gy**
	Absorbed dose DV% (e.g. D95%)	**-**
	Maximum dose (D2%) (D1mm3)	**Maximum dose (D2%)**
	Minimum dose (D98%) (D1mm3)	**Minimum dose (D98%)**
	Mean dose (Dmean)	**Mean dose (Dmean)**
	Median Dose (D50%)	**Median Dose (D50%)**
Integral Dose	**Total Absorbed Energy (TAE)**	

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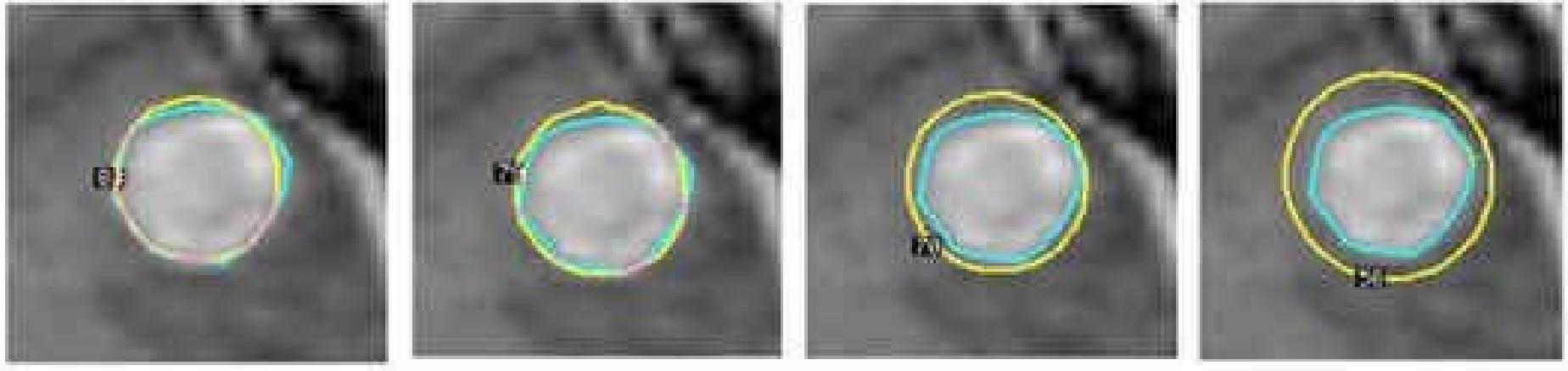
Dose prescription

“I am giving 1 fraction of 25 Gy….”



Isodose line:

83% **79%** **70%** **56%**

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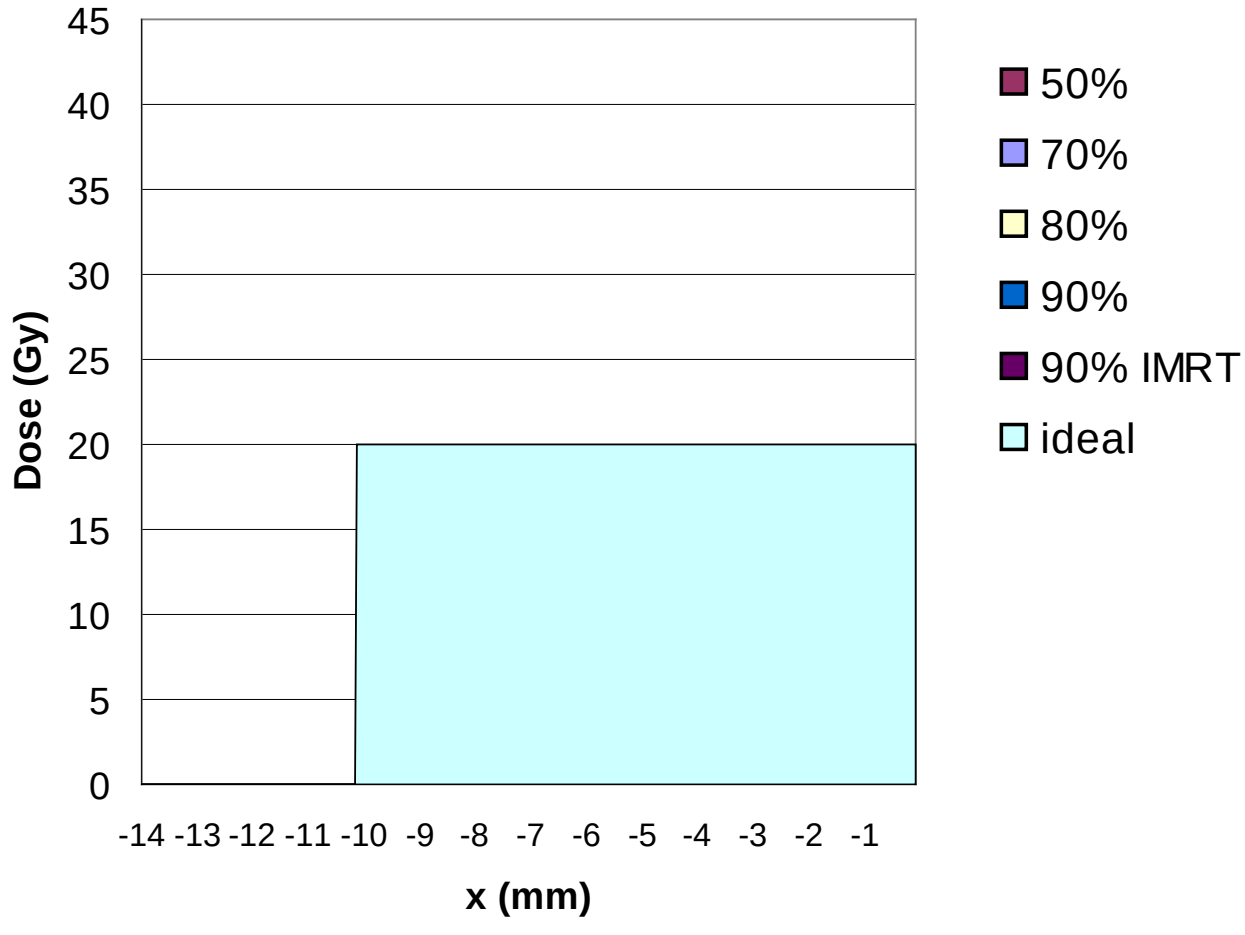
Prescription isodose vs modern linac RT



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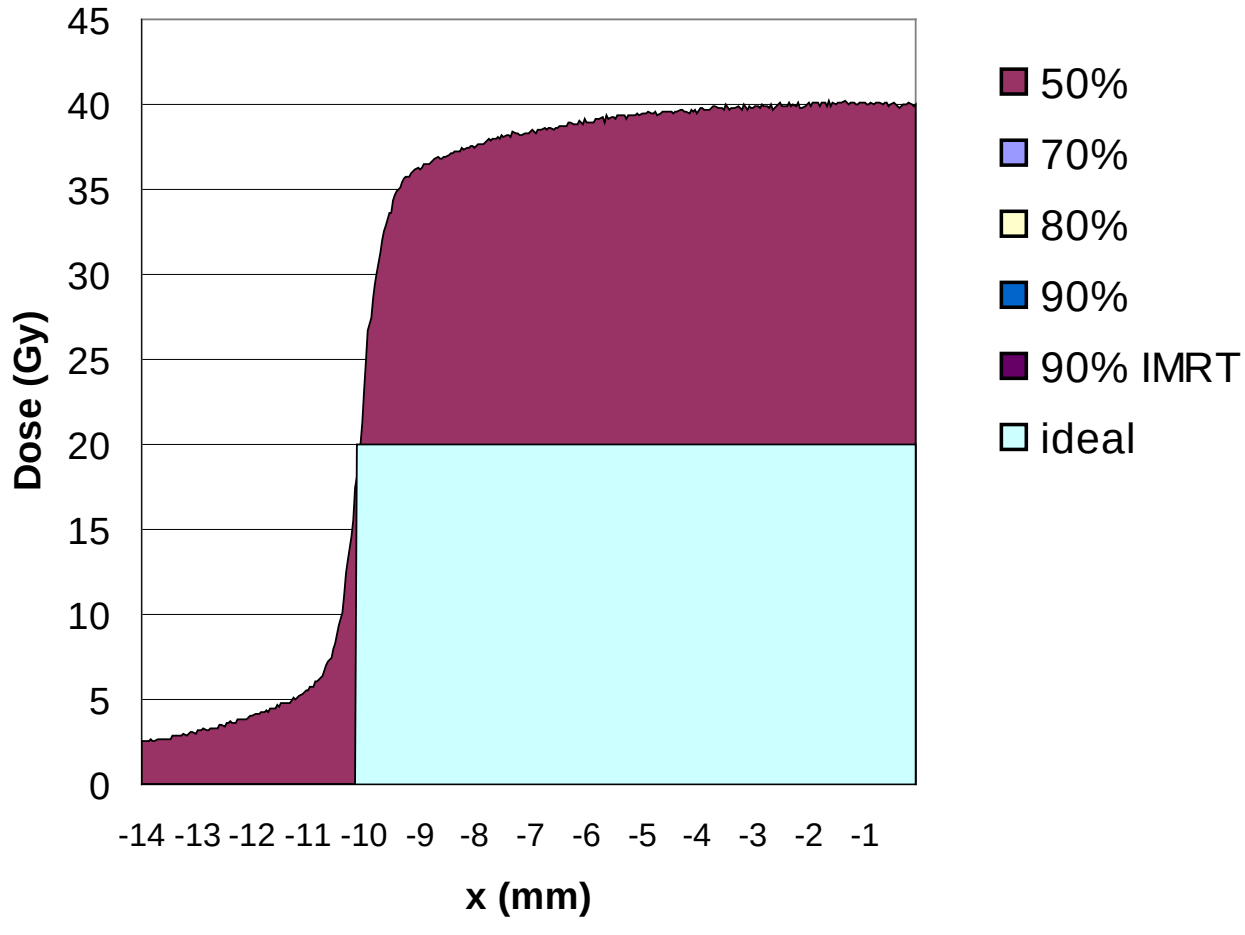
Prescription isodose vs modern linac RT



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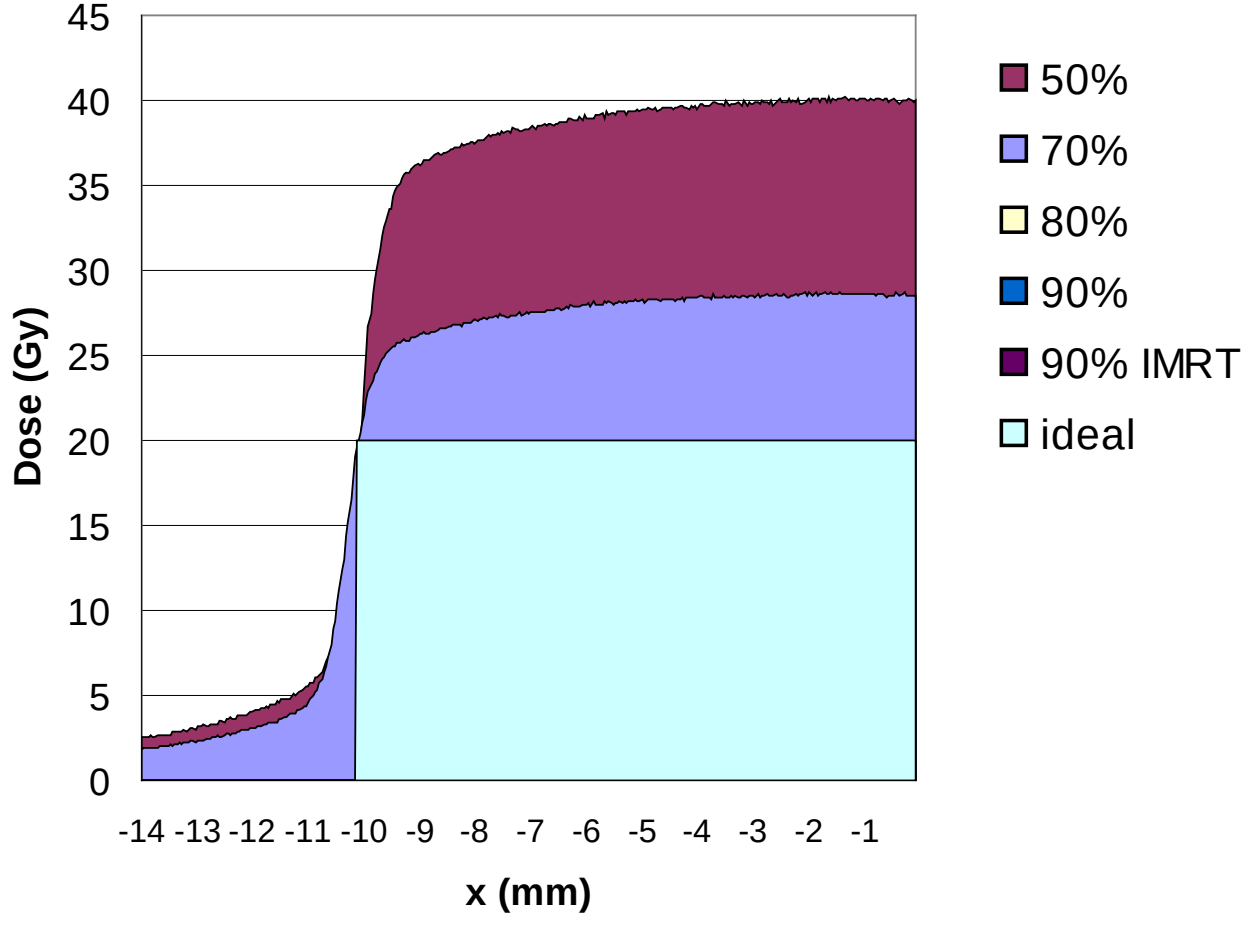
Prescription isodose vs modern linac RT



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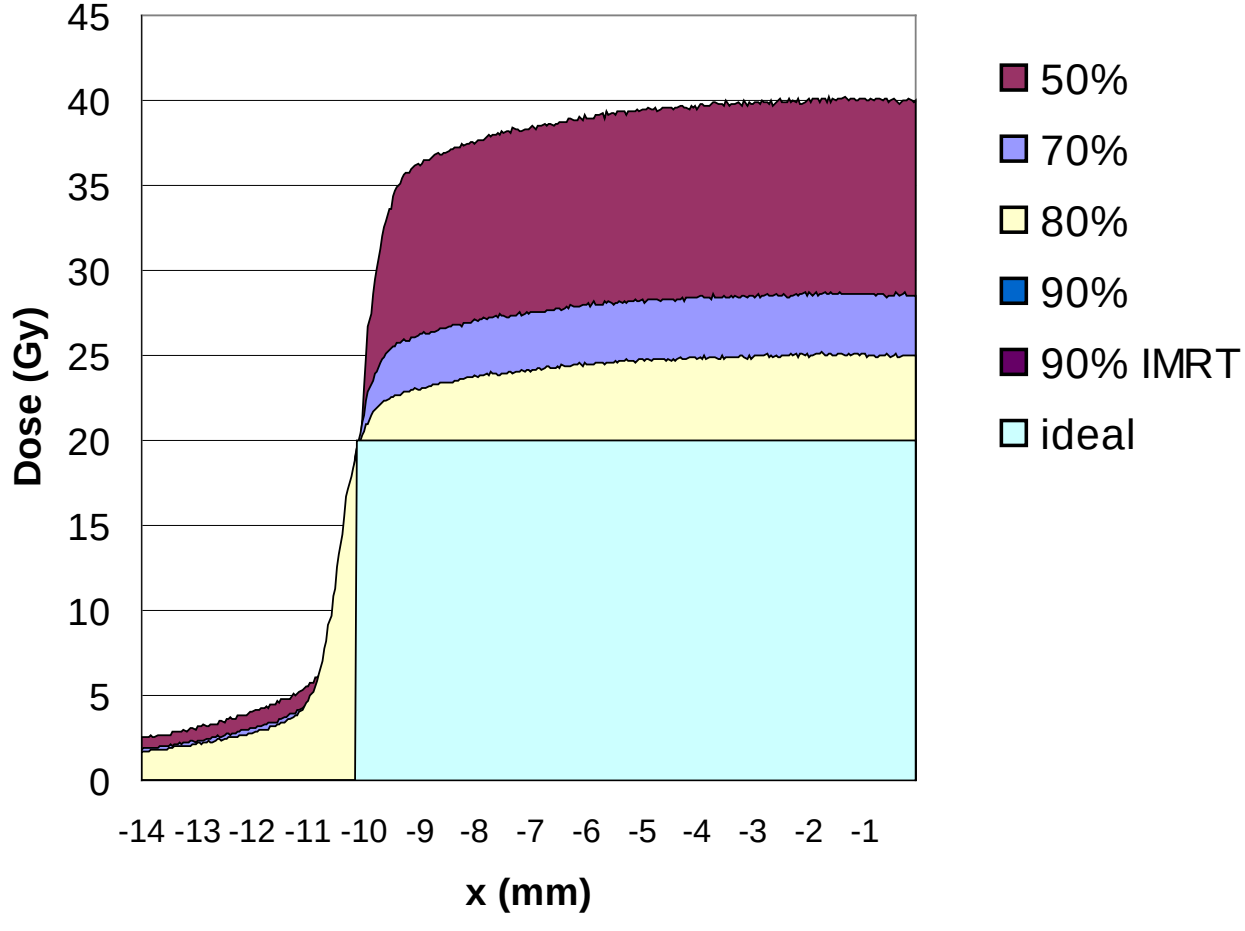
Prescription isodose vs modern linac RT



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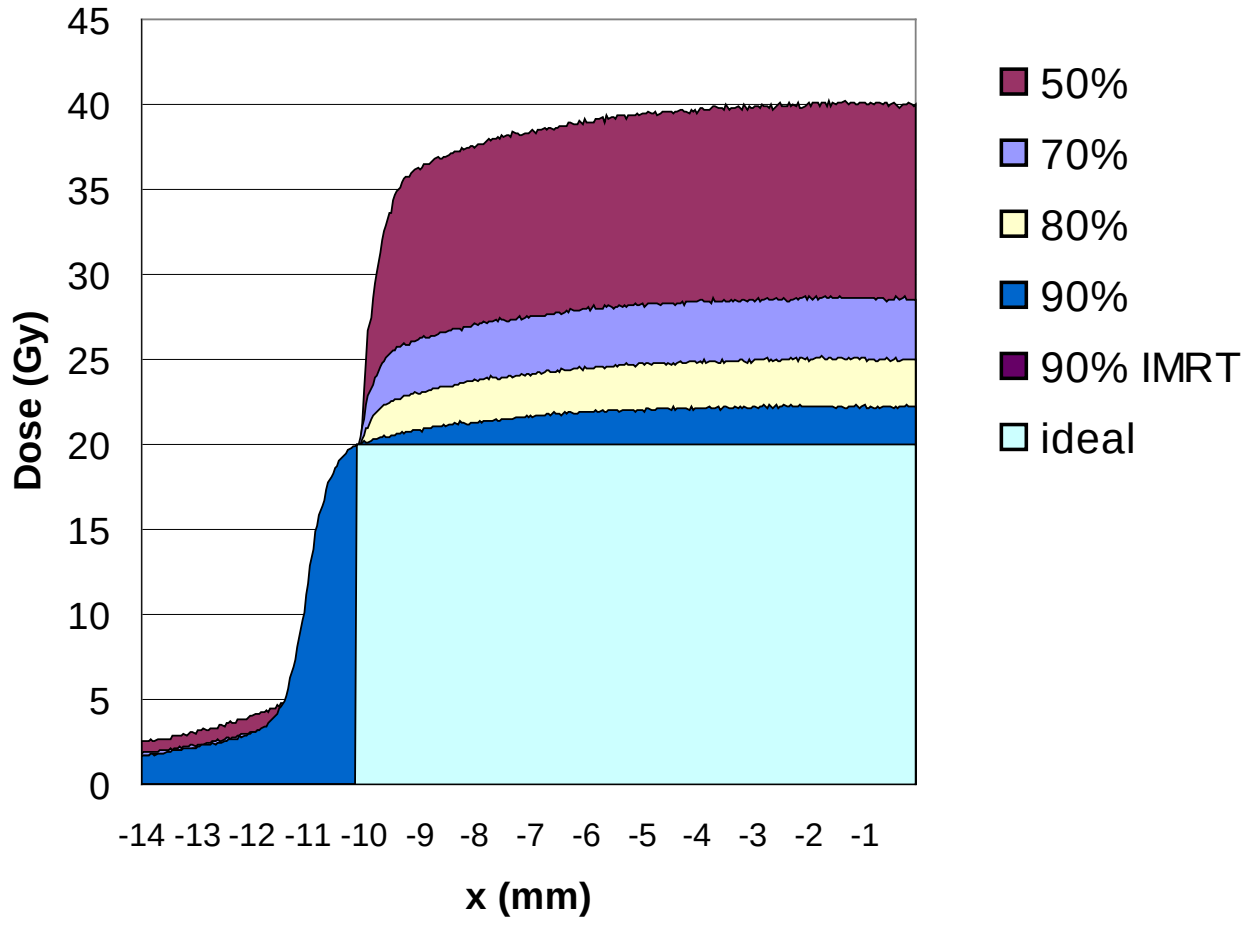
Prescription isodose vs modern linac RT



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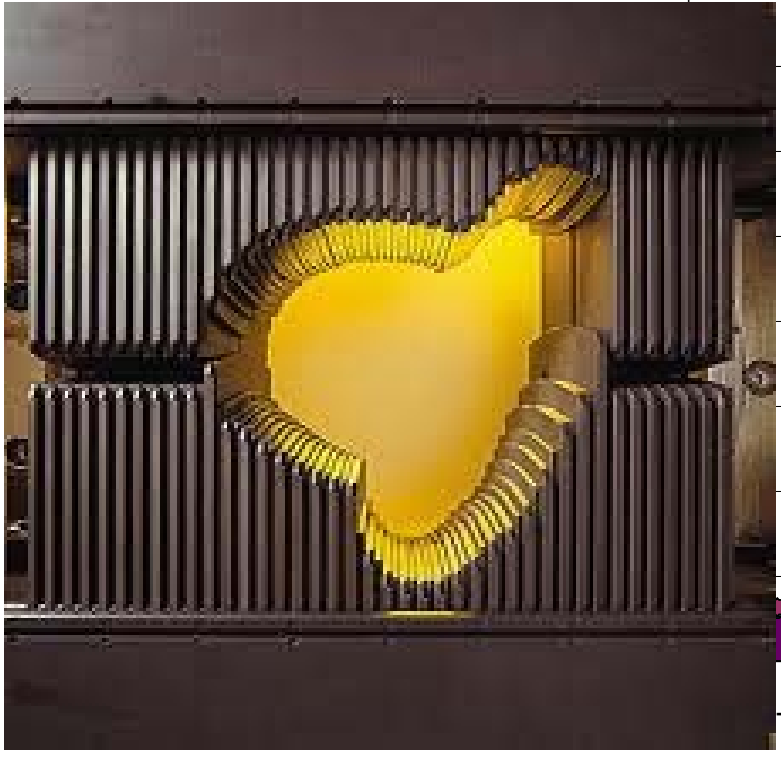
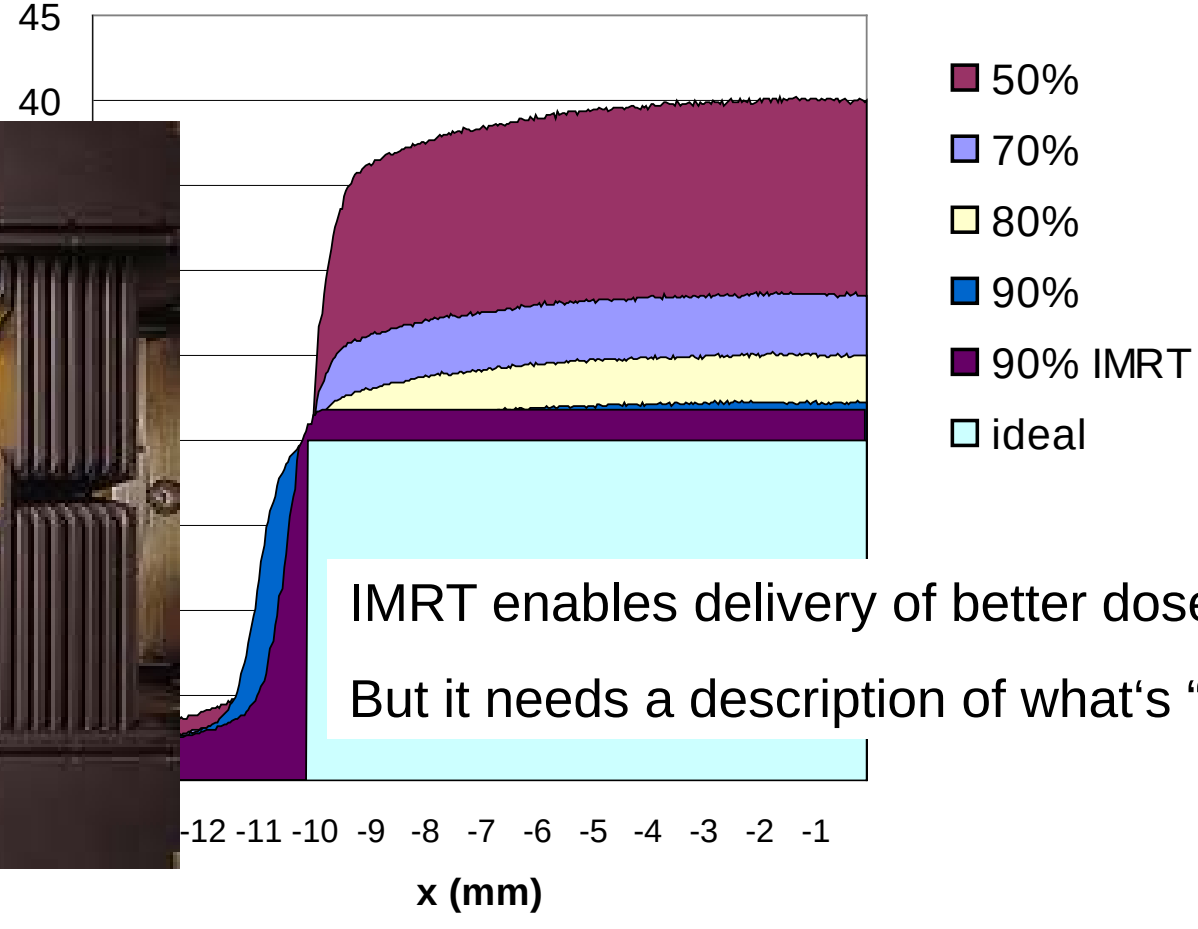
Prescription isodose vs modern linac RT





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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Management of uncertainties in targets w/o respiration motion

Prostate

Stephanie Lang

University Hospital Zürich

UniversityHospital Zurich

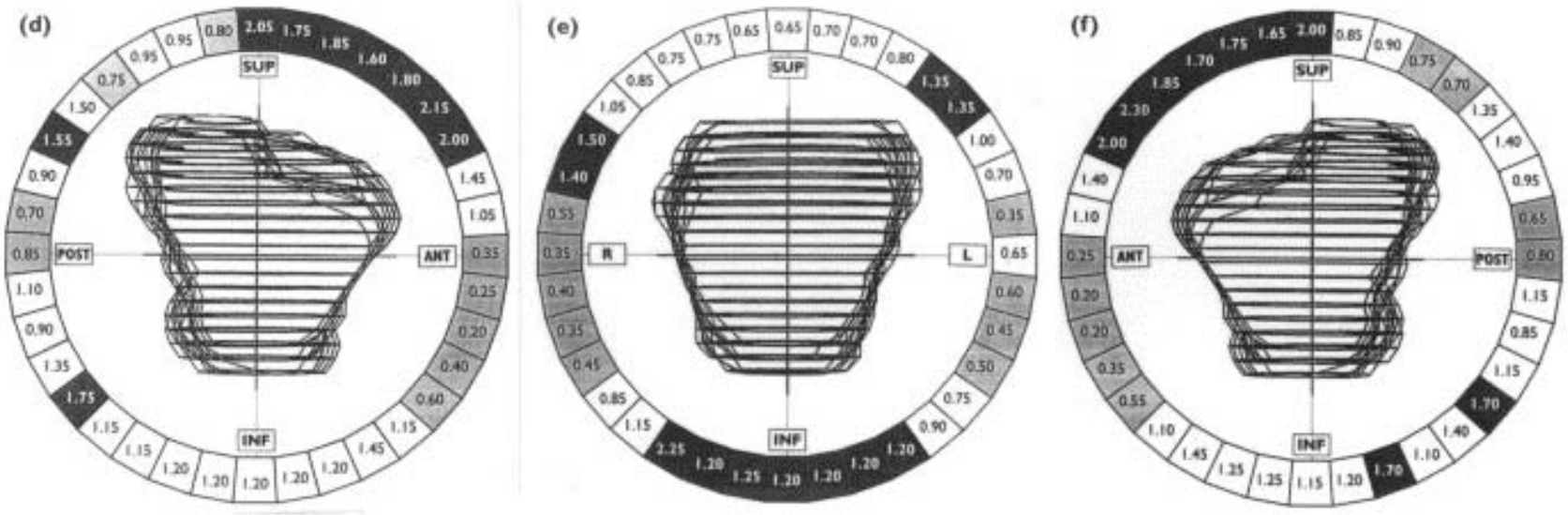
Universität Zürich[UZH]

ESTRO School

Outline

- Contouring 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

Contouring uncertainty

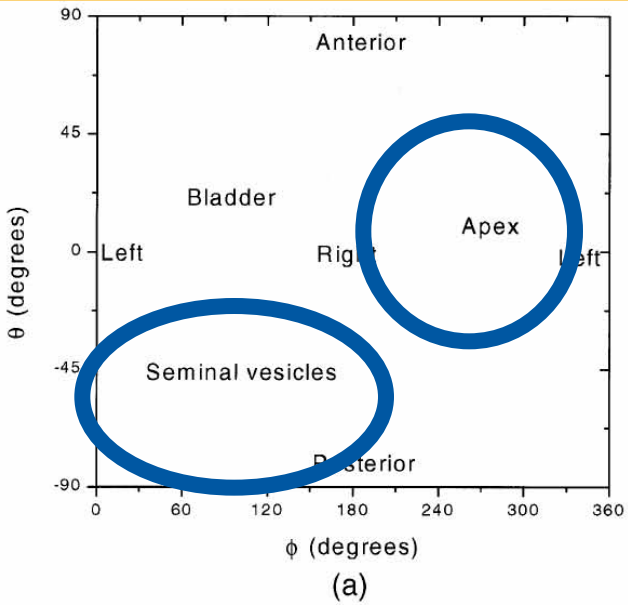


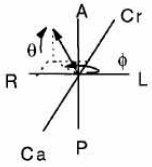
Seddon et al, Radiother Oncol, 2000; 56(1); 73–83

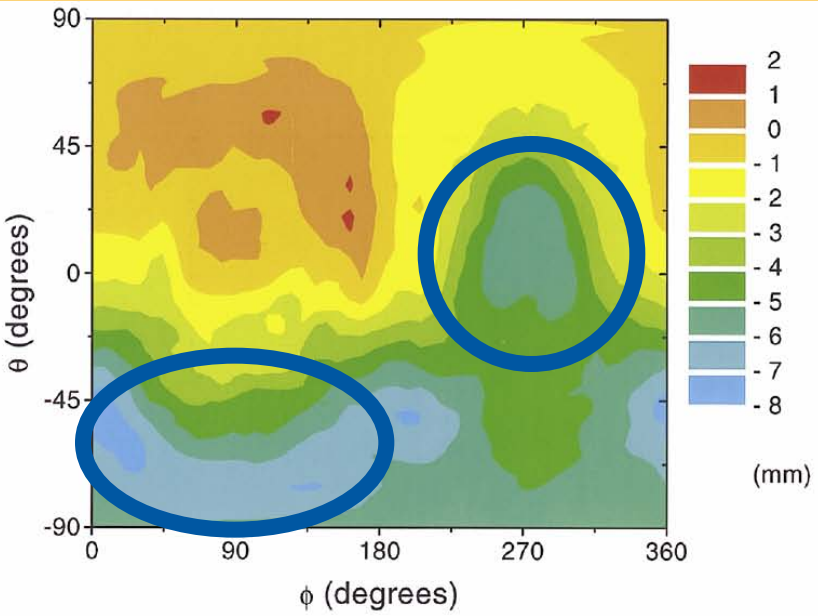
Large interobserver differences in contouring the prostate.

Contouring uncertainty

MRI versus CT





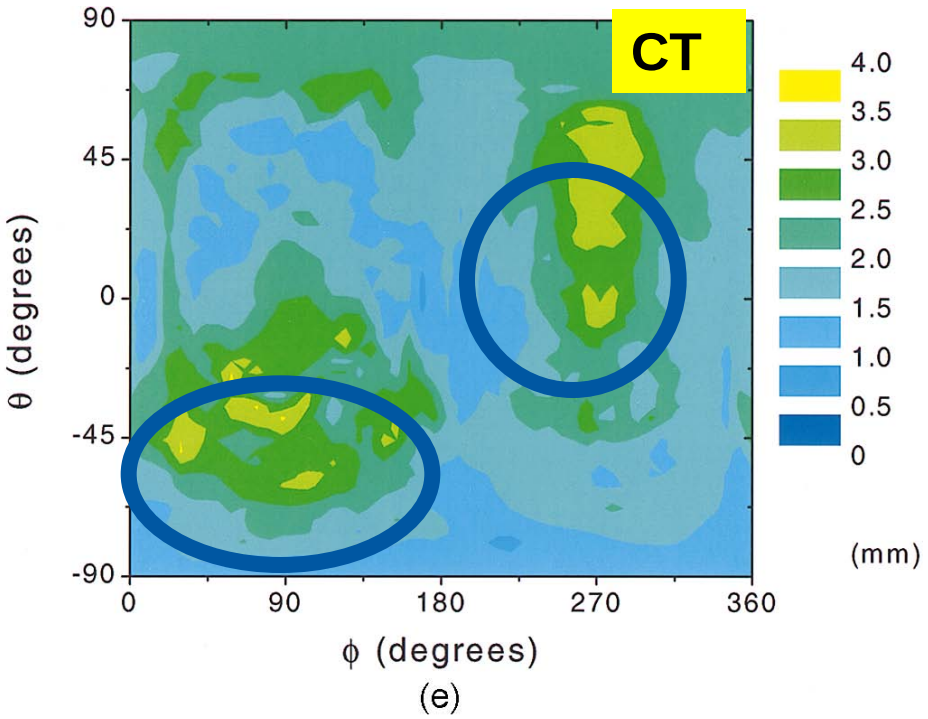


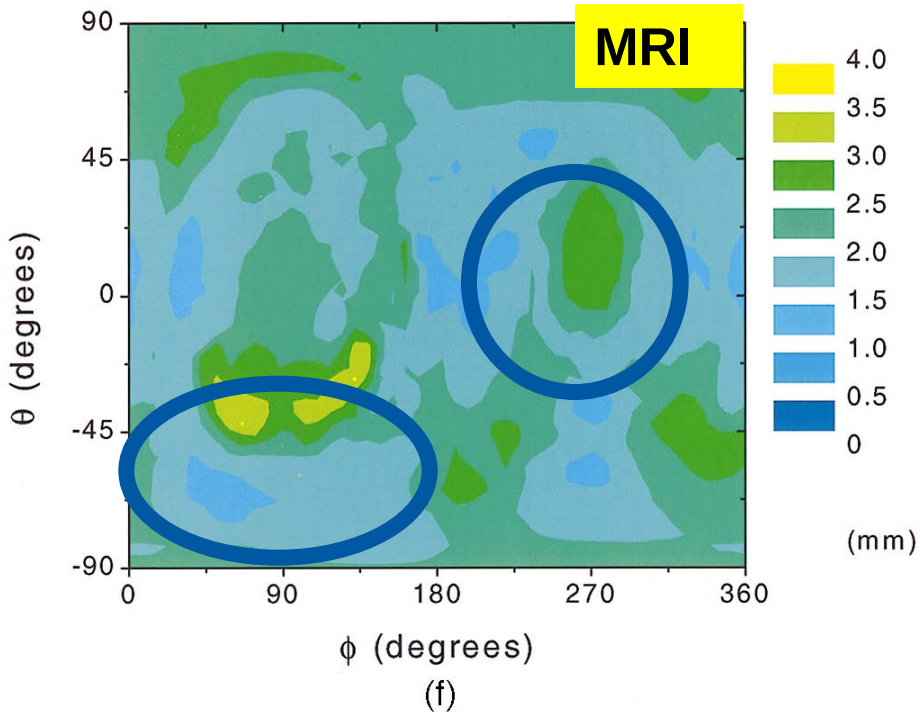
Volume: CT: 64cm^3 MRI: 45cm^3

Rasch et al, IJROBP 1999

Contouring uncertainty

Inter-observer variations



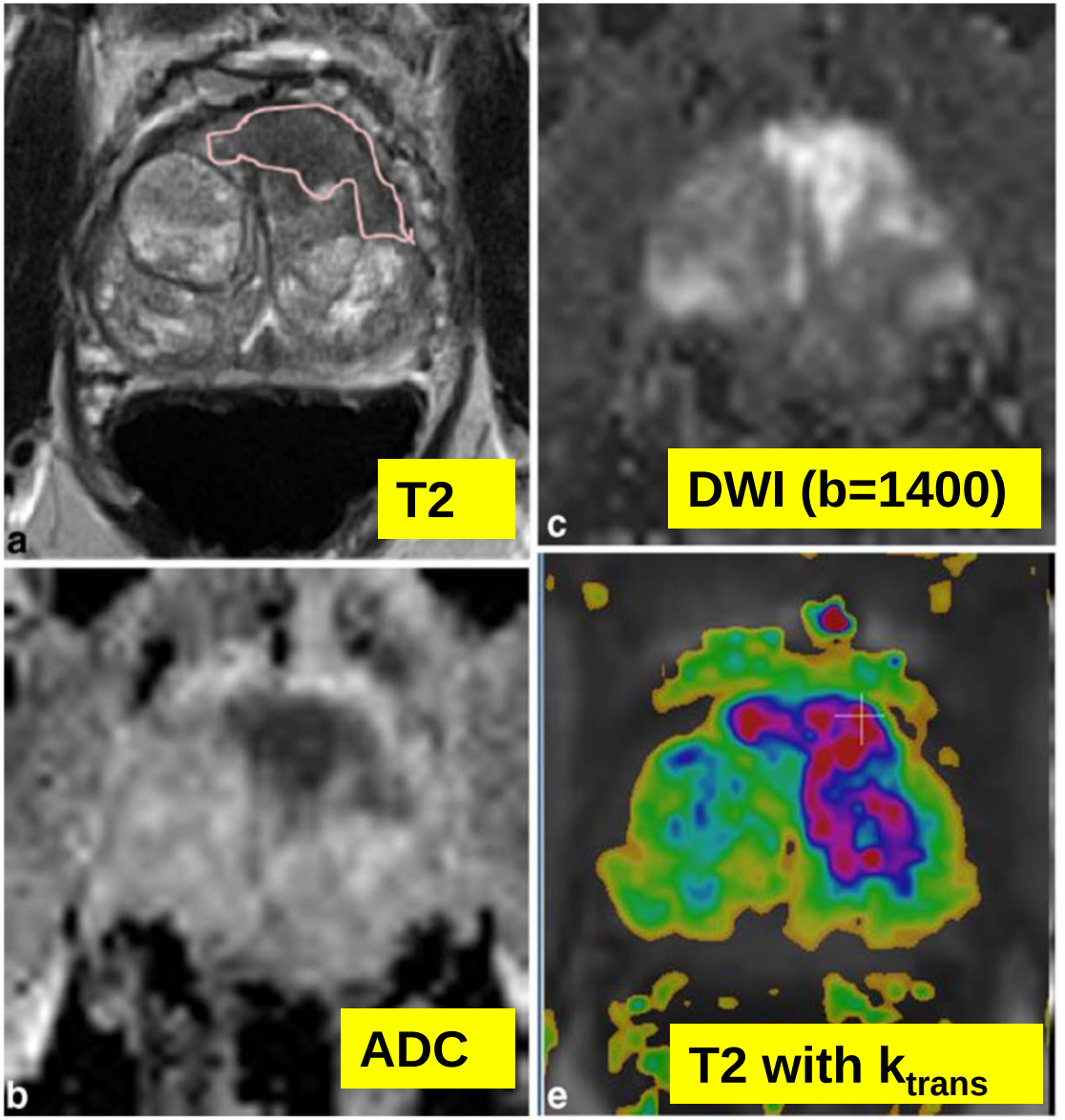


Rasch et al, IJROBP 1999

Reduced inter-observer variations using MRI.

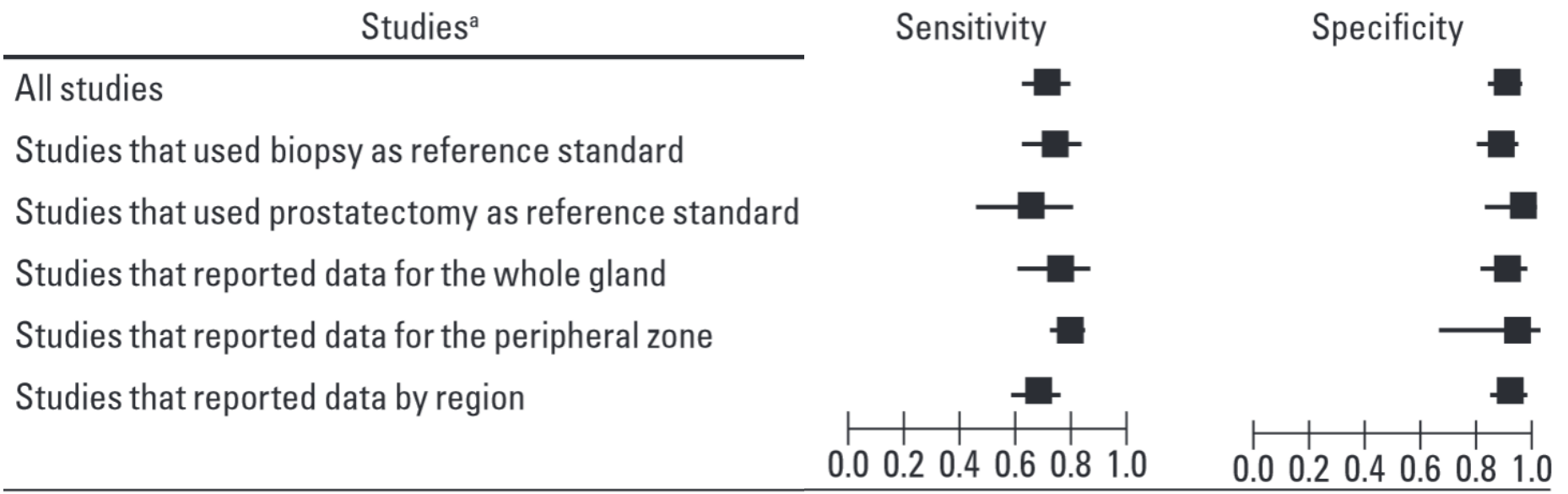
Definition of the tumor lesion

Multiparametric MRI imaging



Barenetst, Eur Radiol (2012), ESUR guidlines

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 Matching

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

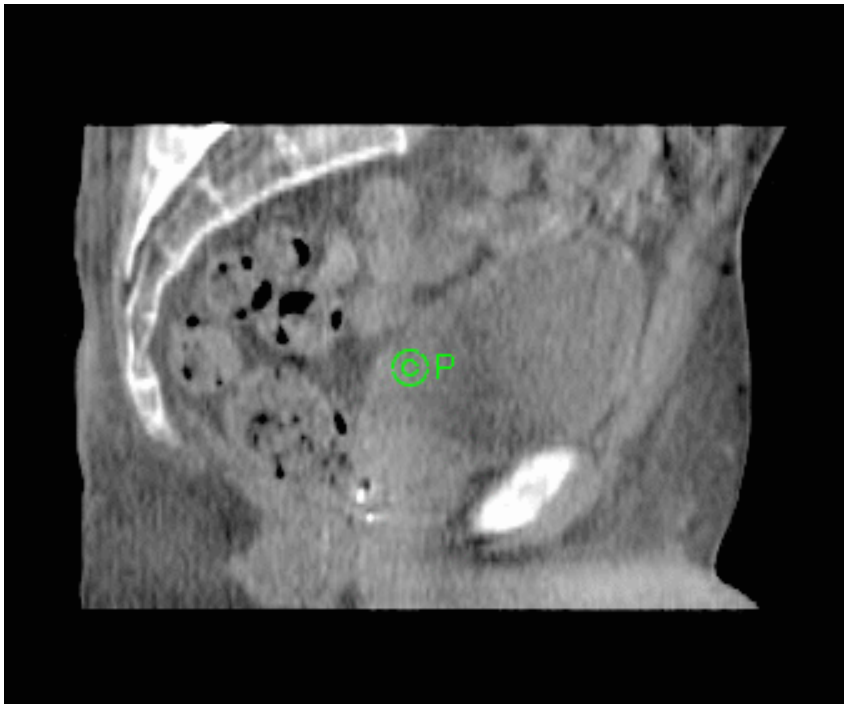
Calypso markers give large artefact in MRI

- 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



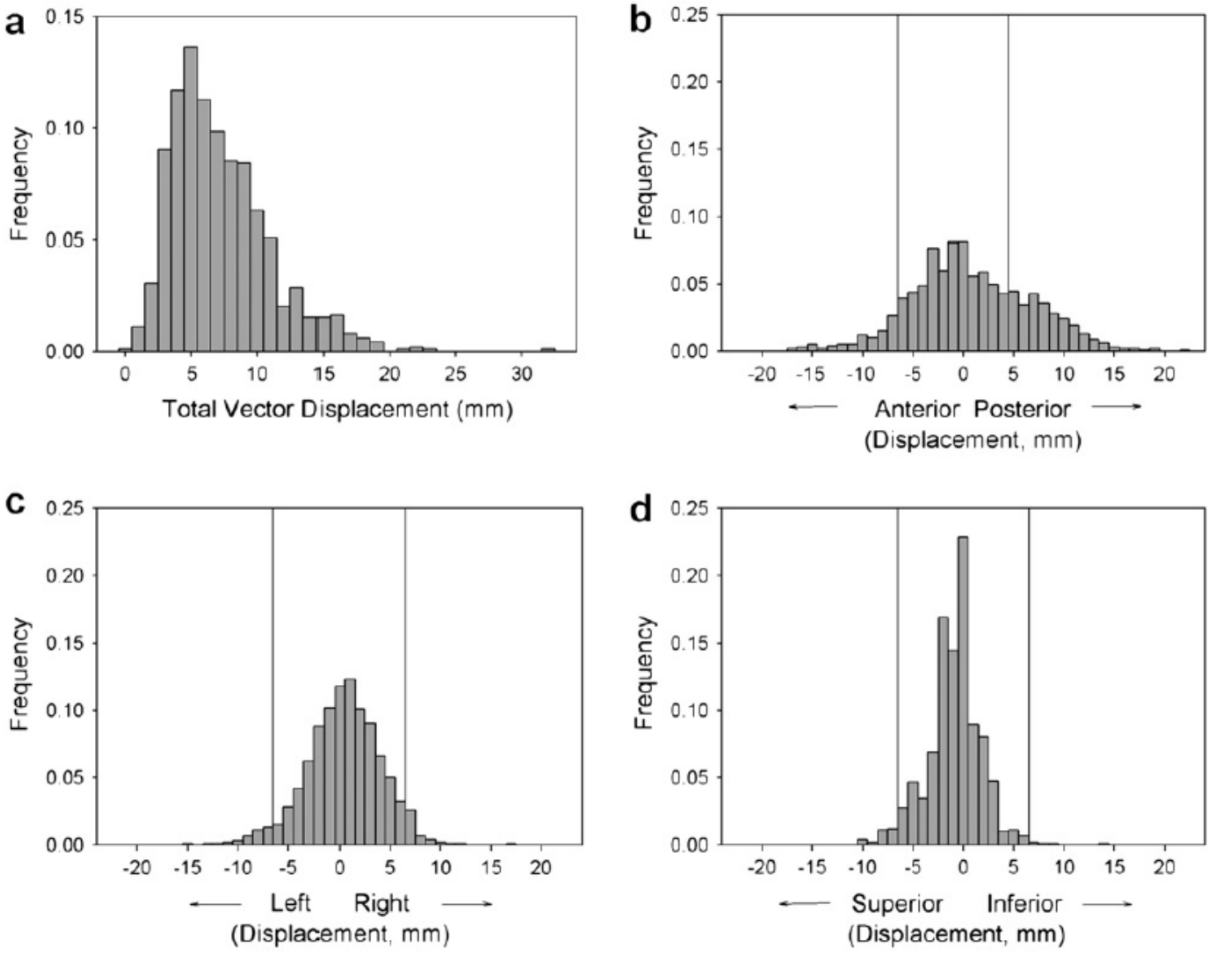
Different bladder filling

Different rectal filling

Different patient positioning

Anatomical changes of the patient

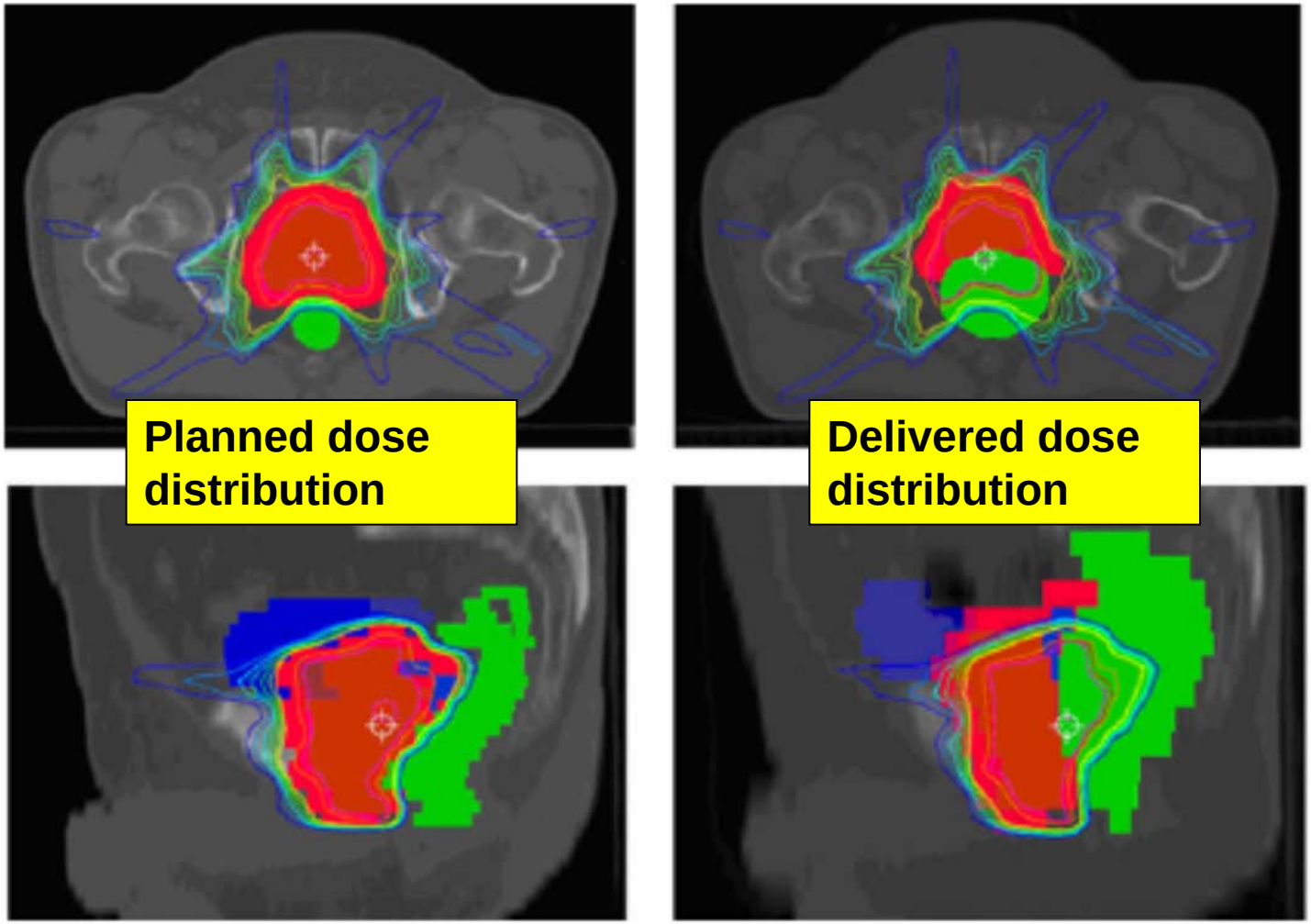
Interfractional motion



→ Up to 3 cm interfractional motion.

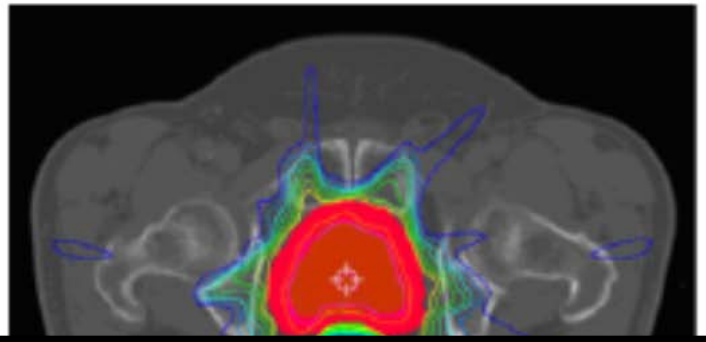
Bylund et al, IJROBP 2008

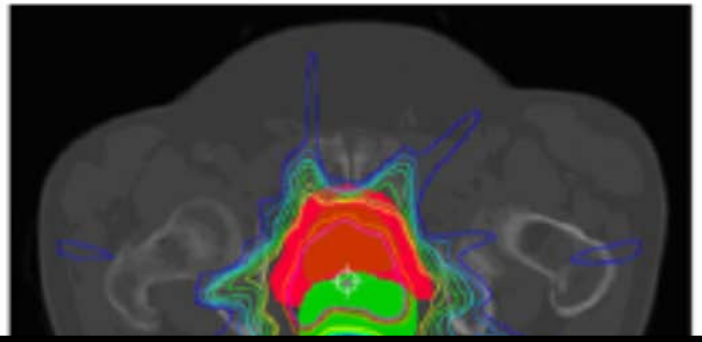
Interfractional motion – Dosimetric impact



Wertz et al, 2007, Phys Med Biol

Interfractional motion – Dosimetric impact



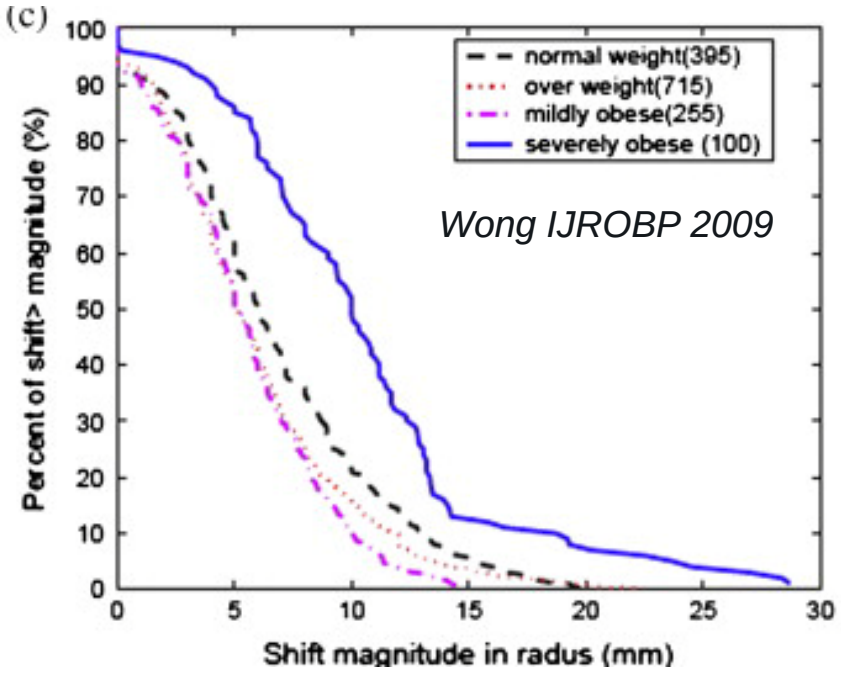


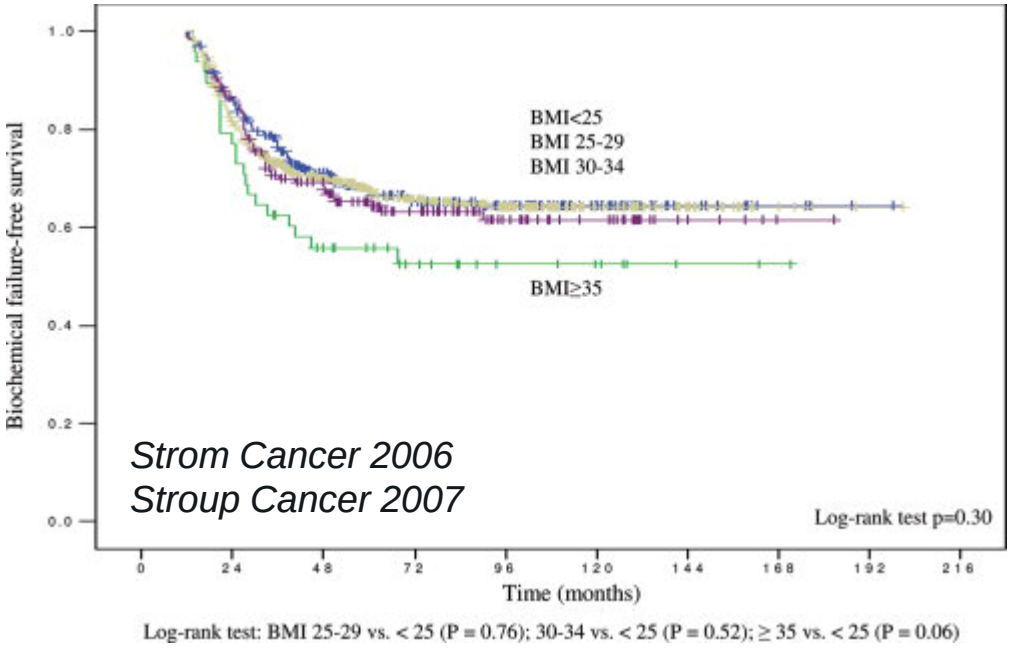
Volume covered by 95% dose	Reference plan [%] mean ± SD	Value deviations uncorrected plan [%-p] mean (min to max)
Prostate	84.5 ± 4.7	−13.3 (−23.6 to −2.1)
Seminal vesicles	67.4 ± 8.7	3.9 (−27.7 to 26.9)

Wertz et al, 2007, Phys Med Biol

Interfractional motion – Impact on outcome

Set-up errors in relationship to the patients` BMI



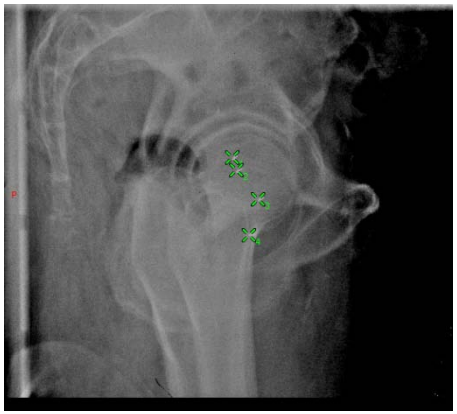


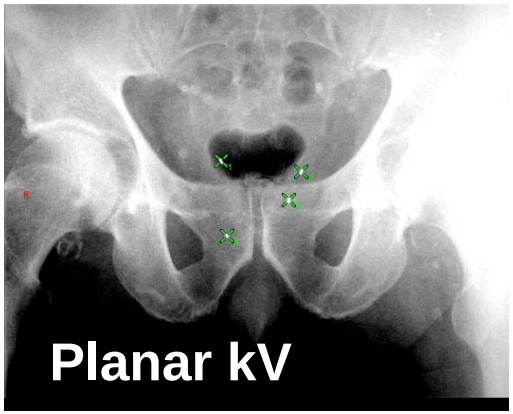
Inaccurate set-up could explain inferior PSA control in obese patients

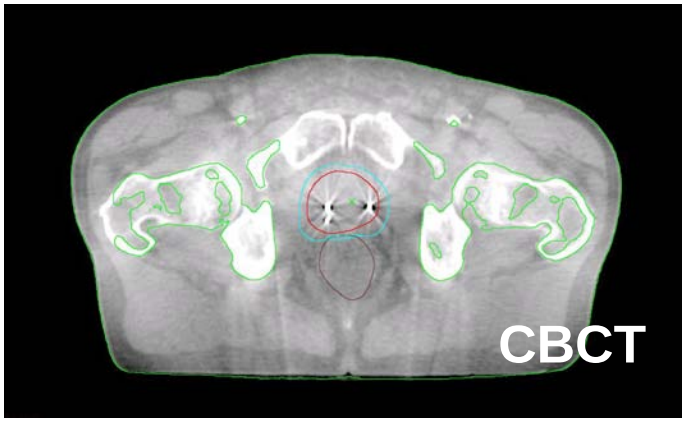
➢Need for image – guidance

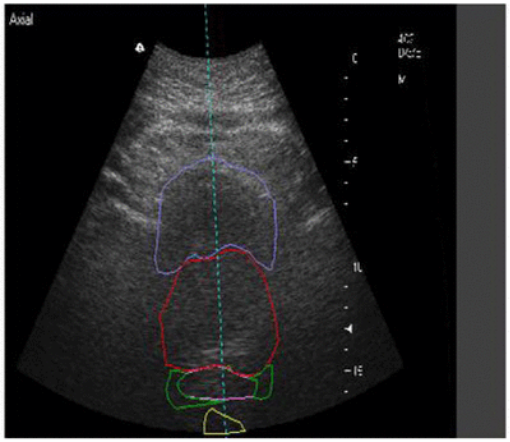
Management of interfraction motion

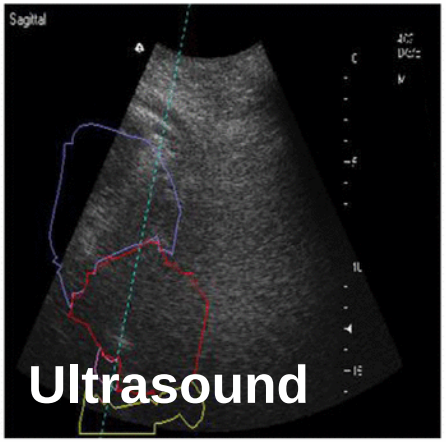
Image guidance

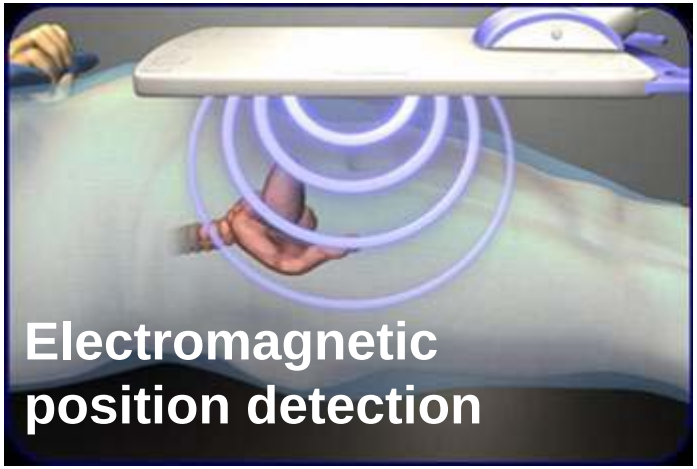






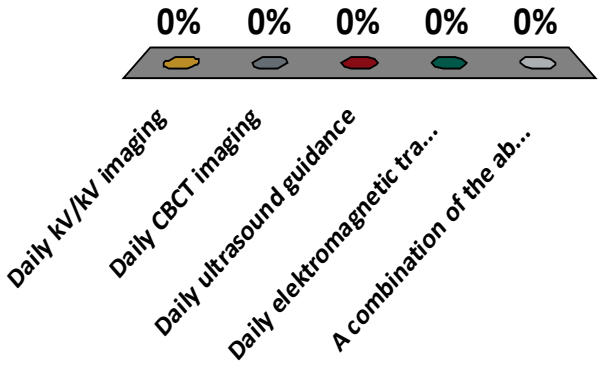






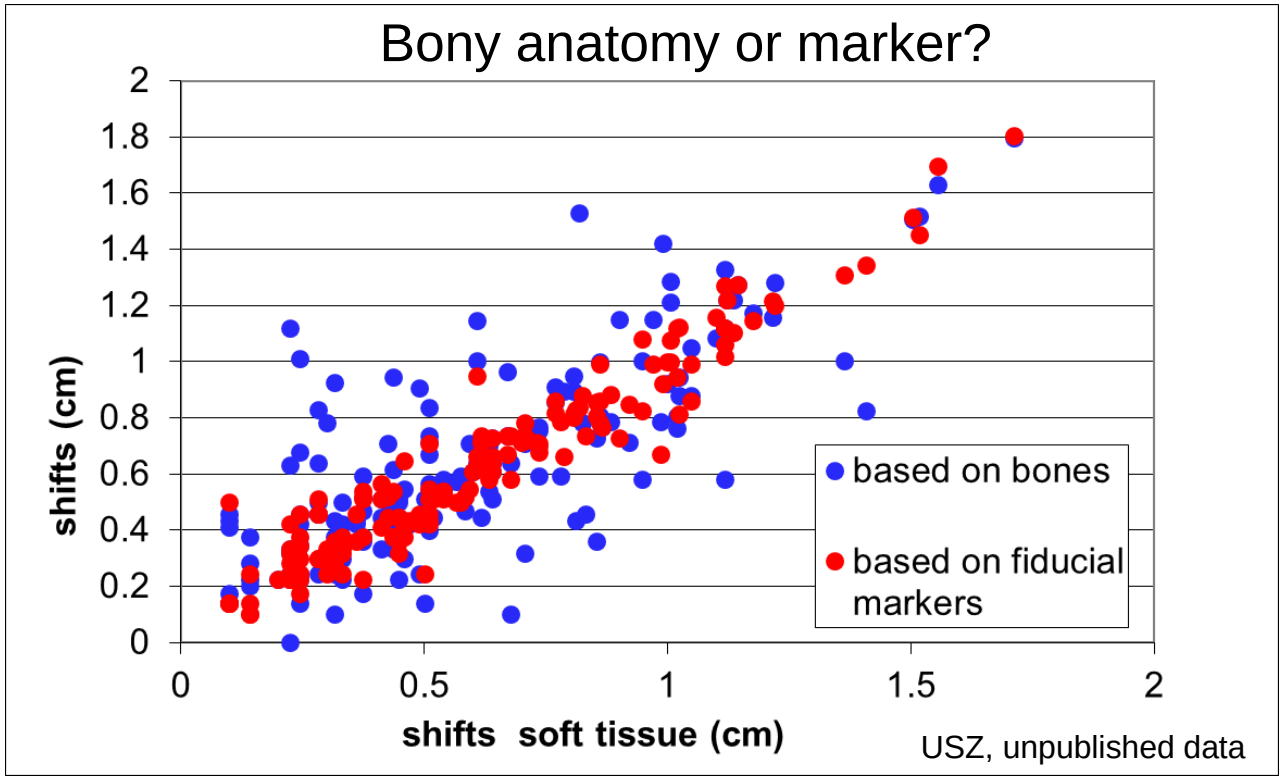
What kind of Image guidance would you use for SBRT prostate cancer?

A. Daily kV/kV imaging
B. Daily CBCT imaging
C. Daily ultrasound guidance
D. Daily elektromagnetic transponder position detection
E. A combination of the above mentioned methods



Management of interfraction motion

Image guidance: On what to match?

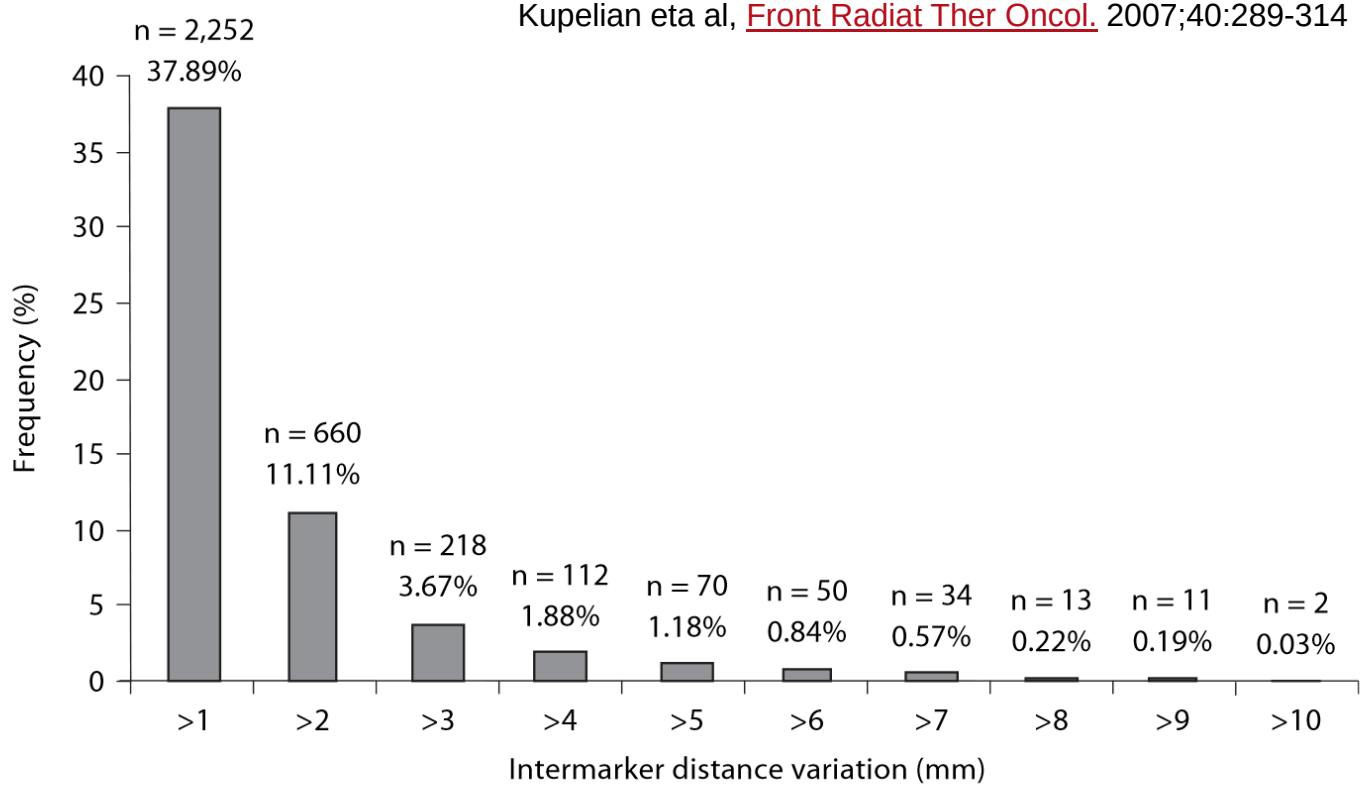


Matching on the bony anatomy leads to large uncertainties and is not recommended for prostate SBRT.

Management of interfraction motion

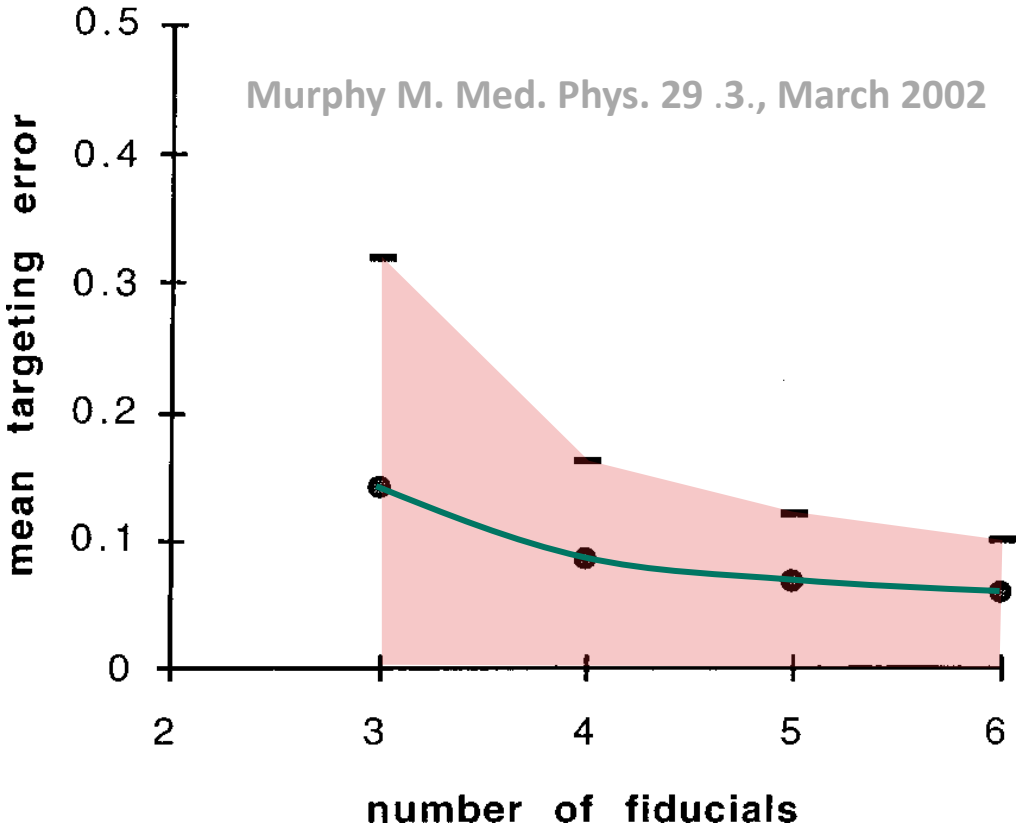
Image guidance: Are the markers stable?

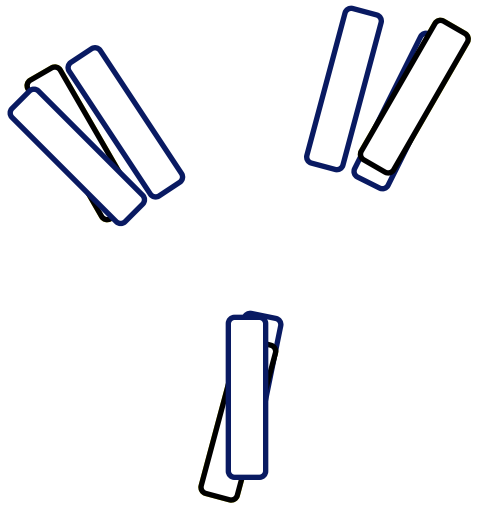
Kupelian eta al, Front Radiat Ther Oncol. 2007;40:289-314



Management of interfraction motion

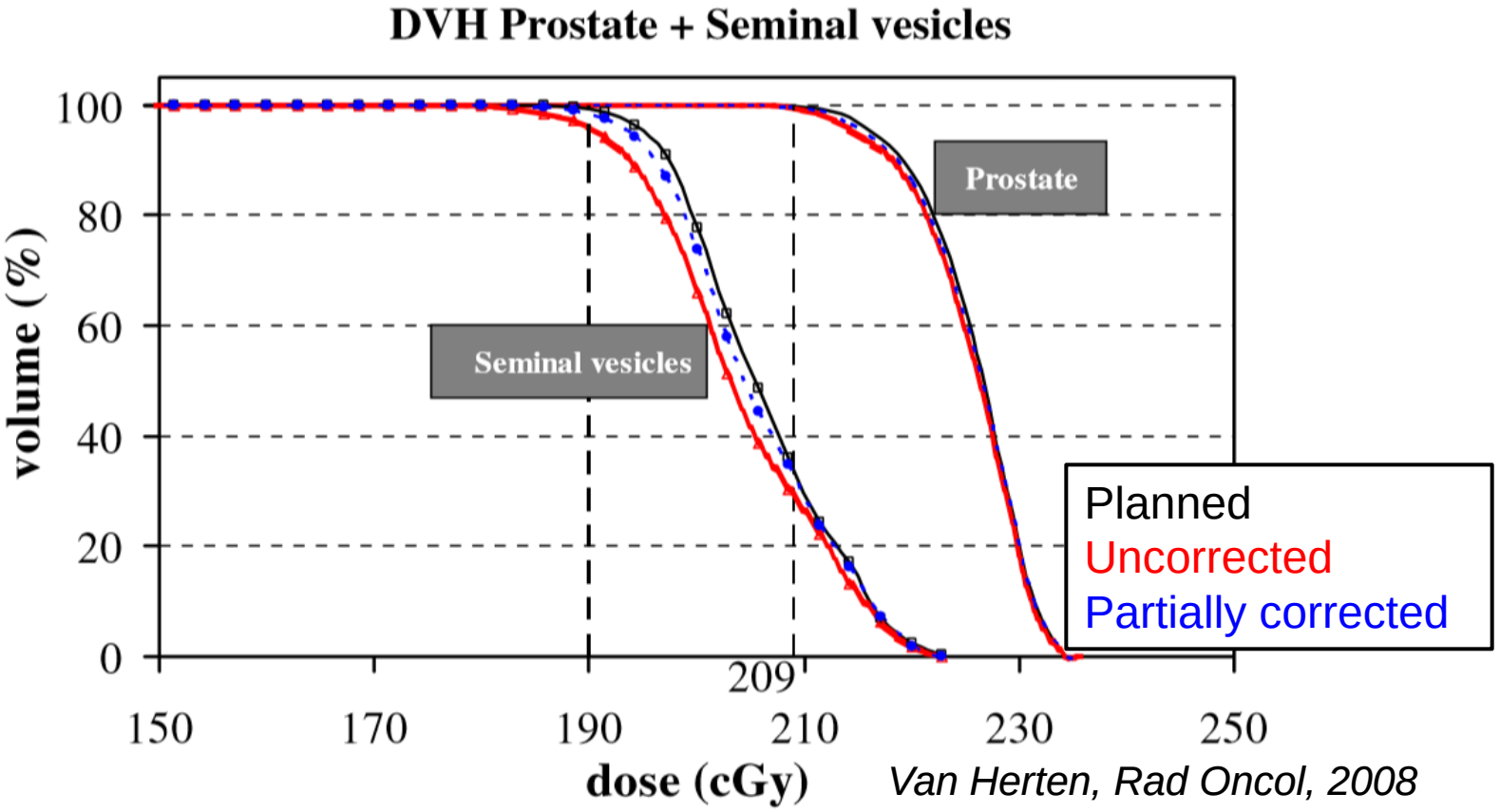
Image guidance: How many markers?





Management of interfraction motion

Image guidance: Importance of rotations

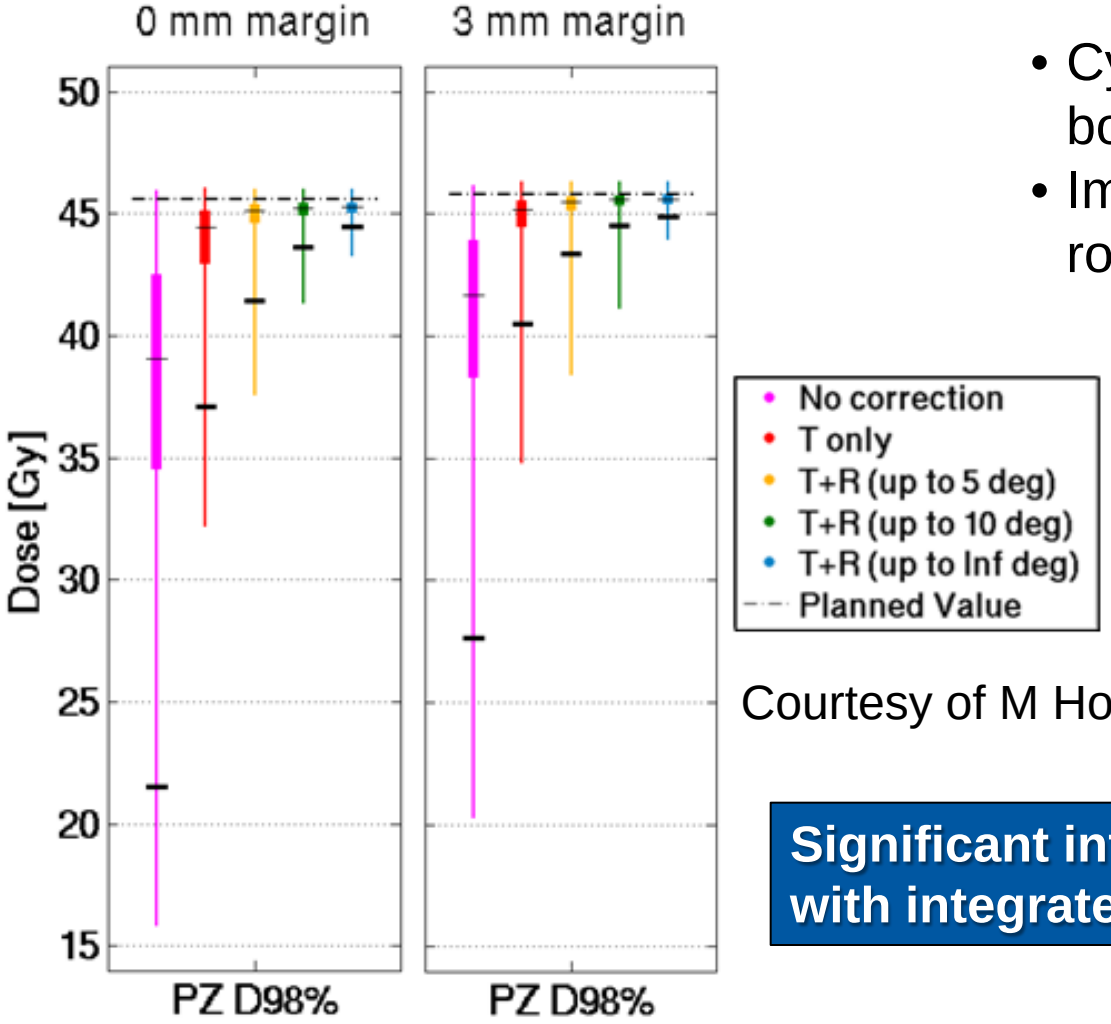


Van Herten, Rad Oncol, 2008

Small influence of rotations on dose distribution for fractionated RT

Management of interfraction motion

Image guidance: Importance of rotations



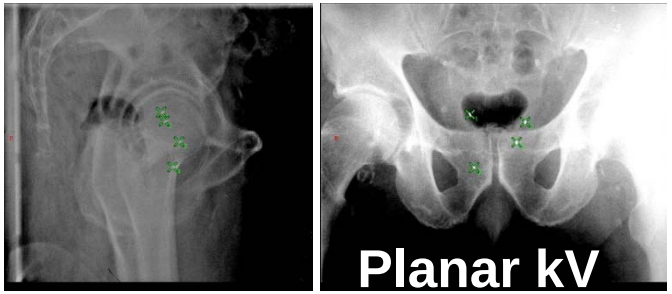
- Cyberknife patients with boost in peripheral zone
- Improved coverage with rotation correction

Courtesy of M Hoogeman

Significant influence for SBRT treatments with integrated boost.

Management of interfraction motion

Image guidance:



Advantages

High accuracy in combination with fiducial markers

Easy and fast matching, therapist indepedent results

Disadvantages

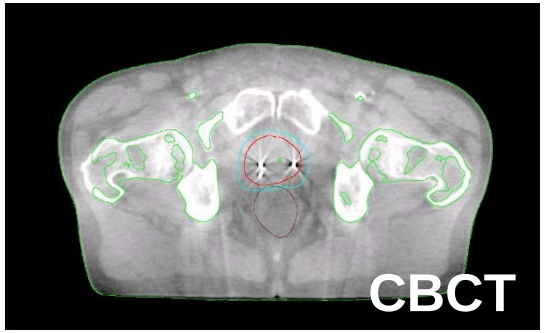
No information on organs at risk (mainly rectum and bladder)

No information on roll of the prostate

Bony match not accurate enough

Management of interfraction motion

Image guidance:



Advantages

Additional information on rectum and bladder filling

Can detect pitch roll and yaw

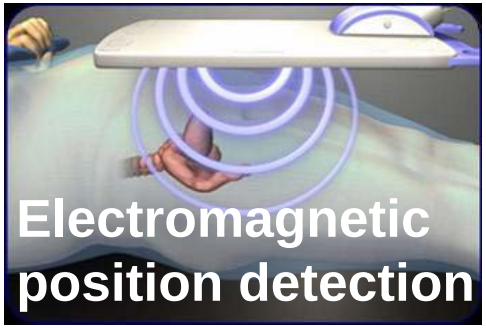
Can detect deformations

Disadvantages

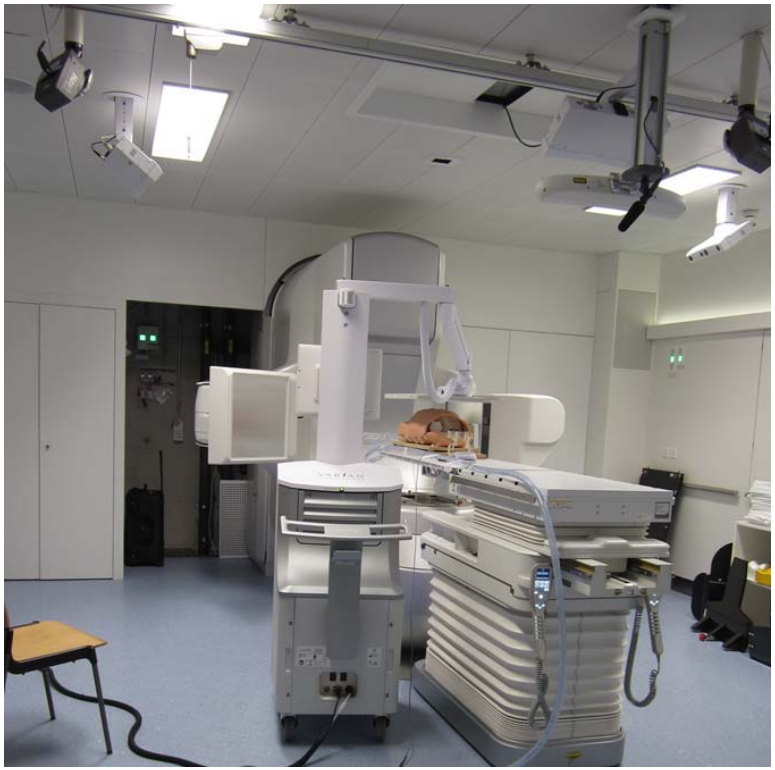
Intrafractional motion might occur during image acquisition

Management of interfraction motion

Image guidance:

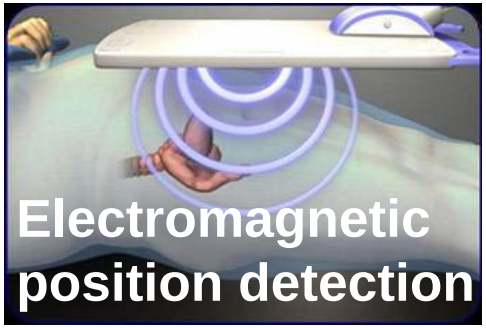


How does it work?



Management of interfraction motion

Image guidance:



Advantages

6D information in real-time

User independet accuracy

High accuracy

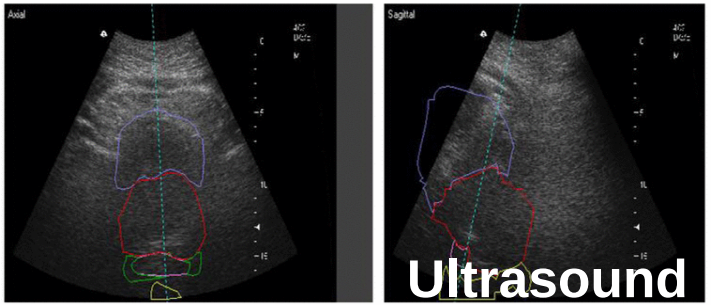
Disadvantages

No information on organs at risk (mainly retum and bladder)

Can detect deformations only to a limited extend

Management of interfraction motion

Image guidance:



Transabdominal ultrasound: comparison with implanted markers

(1) BAT vs. markers (EPID) [5] Langen et al, IJROBP 2003;57:635–644

Evaluation	11 patients, 10 alignments per patient	
Results	Differences (average ± SD)	
	Vertical	−0.7±5.2 mm
	Longitudinal	2.7±4.5 mm
	Lateral	1.8±3.9 mm

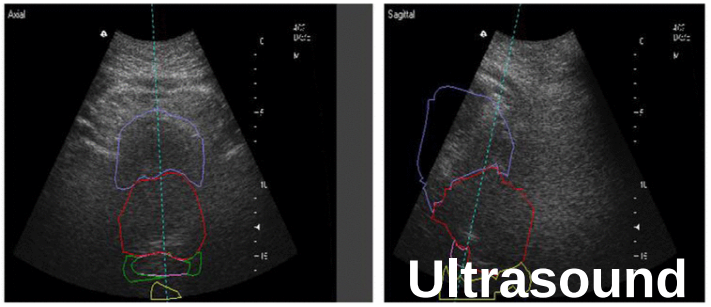
(2) SonArray vs. markers (ExacTrac) [6] Scarborough et al. IJROBP 2005;63:S196.

Evaluation	40 patients, 1,019 alignments, average 25 alignments per patient	
Results	Frequency of misalignments	
	0–5 mm	26%
	5–10 mm	48%
	10–15 mm	17%
	15–20 mm	5%
	>20 mm	4%

Kupelian eta al, Front Radiat Ther Oncol. 2007;40:289-314

Management of interfraction motion

Image guidance:



Advantages

6D information in real-time

Additional information on organs at risk

Disadvantages

Accuracy depends largly on user

Reduced accuracy compared to CBCT or marker matching

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

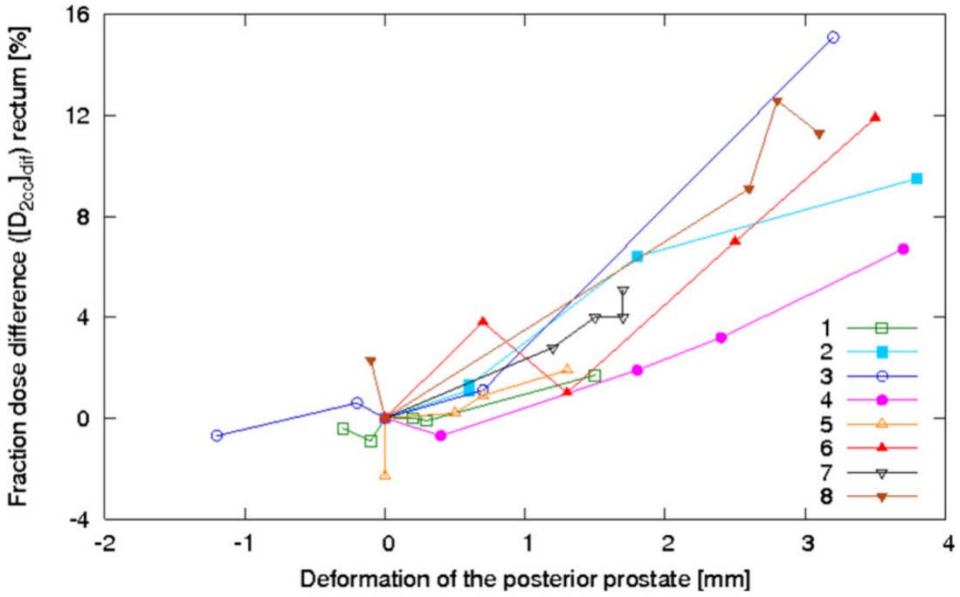
Remaining uncertainty - deformations

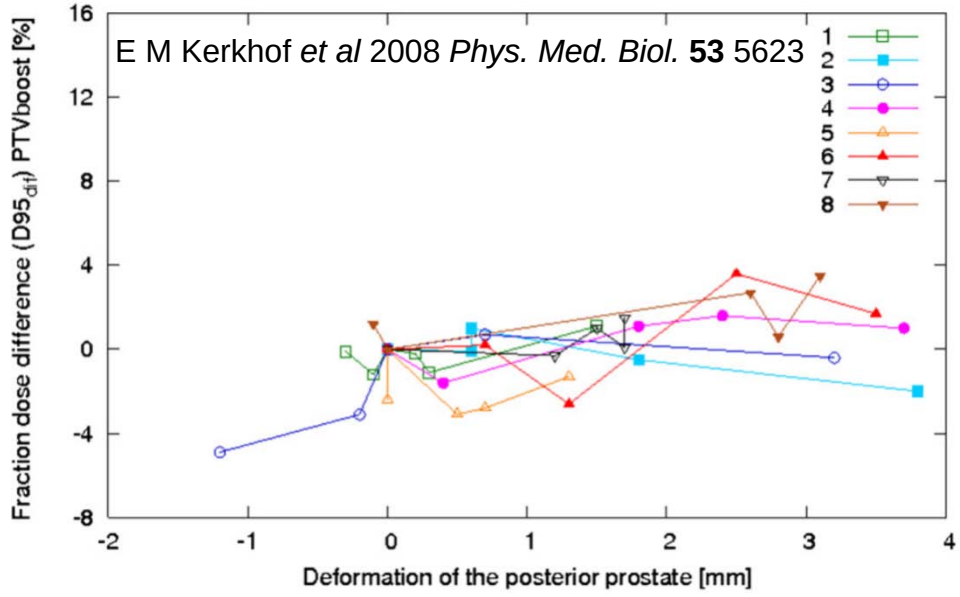
On 8 volunteers, 6MRIs were performed.

IMRT planning on Prostate +4mm was performed.

Plan with the smallest treated rectal volume was taken as reference plan and copied all other scans.

→ Large influence of deformations on dose to the rectum.
→ Only small difference in the dose to the target.





E M Kerkhof *et al* 2008 *Phys. Med. Biol.* **53** 5623

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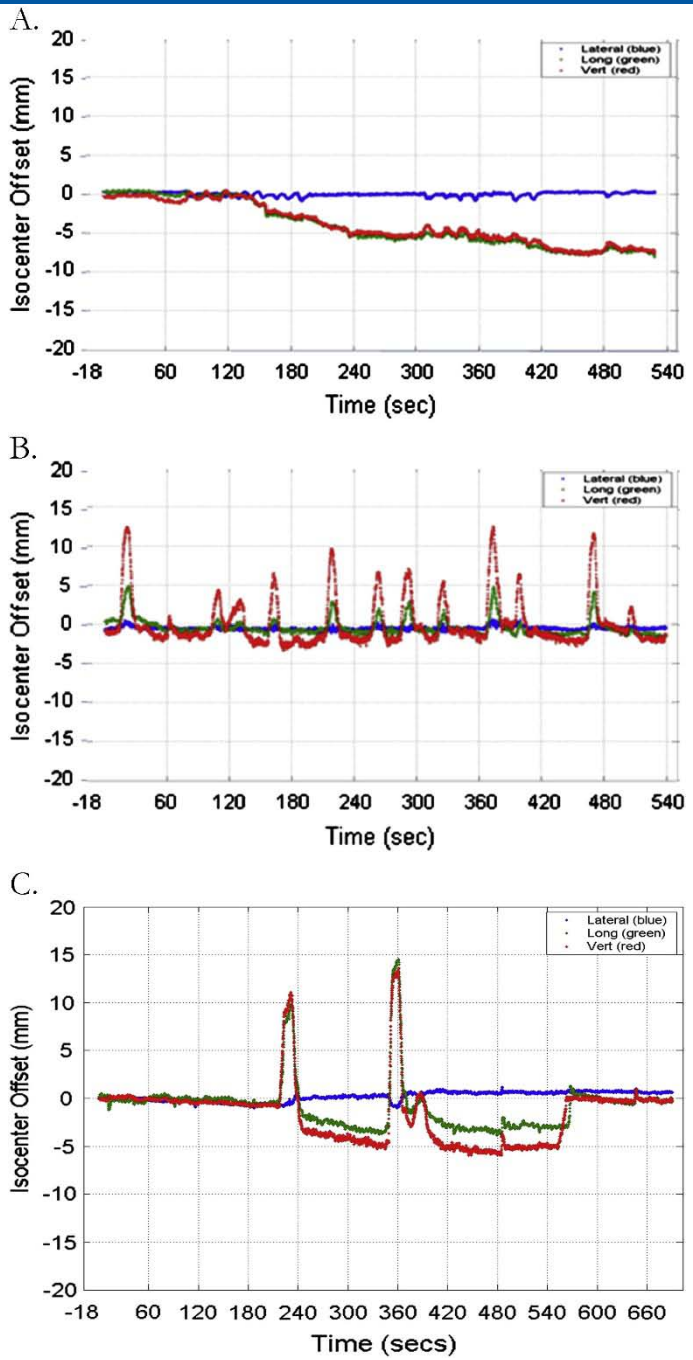
Intrafractional motion

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

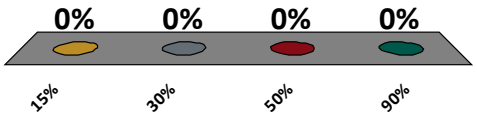


Langen et al, IJROBP, Volume 71, Issue 4, 15 July 2008

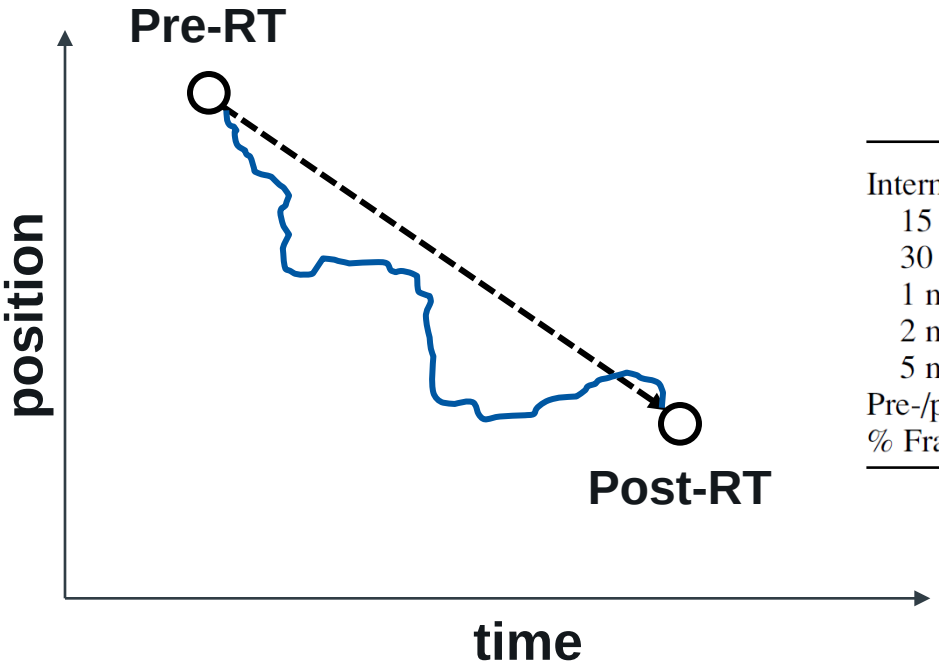
UniversitätsSpital Zürich

During a prostate SBRT treatment fraction, how often does on average the prostate move more than 2mm?

A. 15%
B. 30%
C. 50%
D. 90%



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

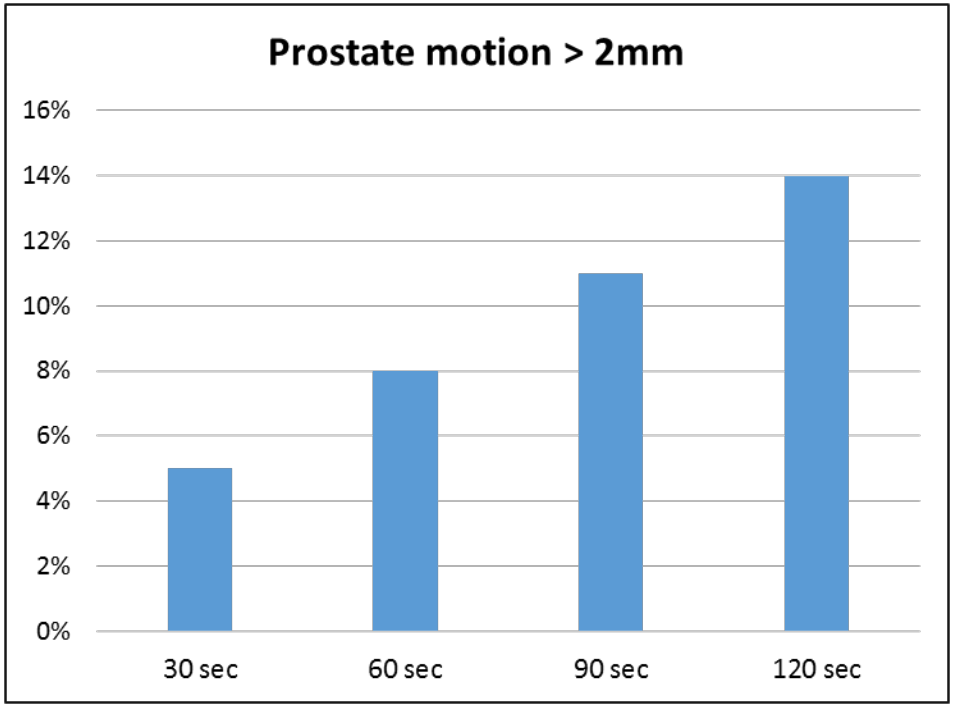
30 sec

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

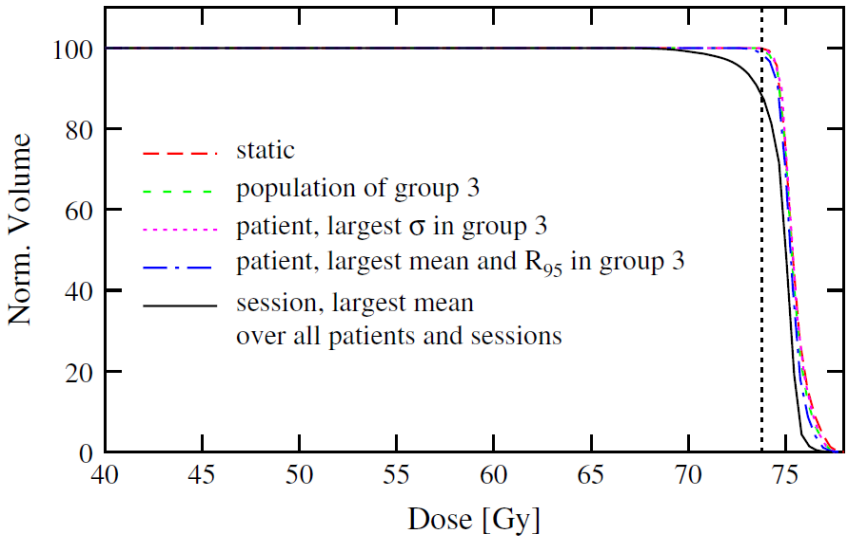
- **Intra-fractional prostate motion „usually“ within 2mm**
- **Intrafractional motion increases with time.**

Dosimetric impact of prostate motion

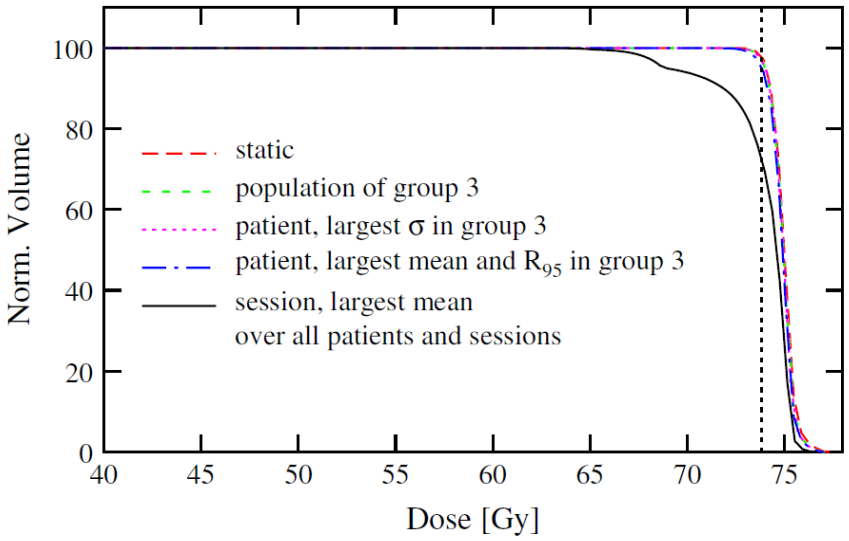
Conventionally fractionated radiotherapy:

Haisen IJROBP 2008

5mm margin



2mm margin



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

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 supprt.

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

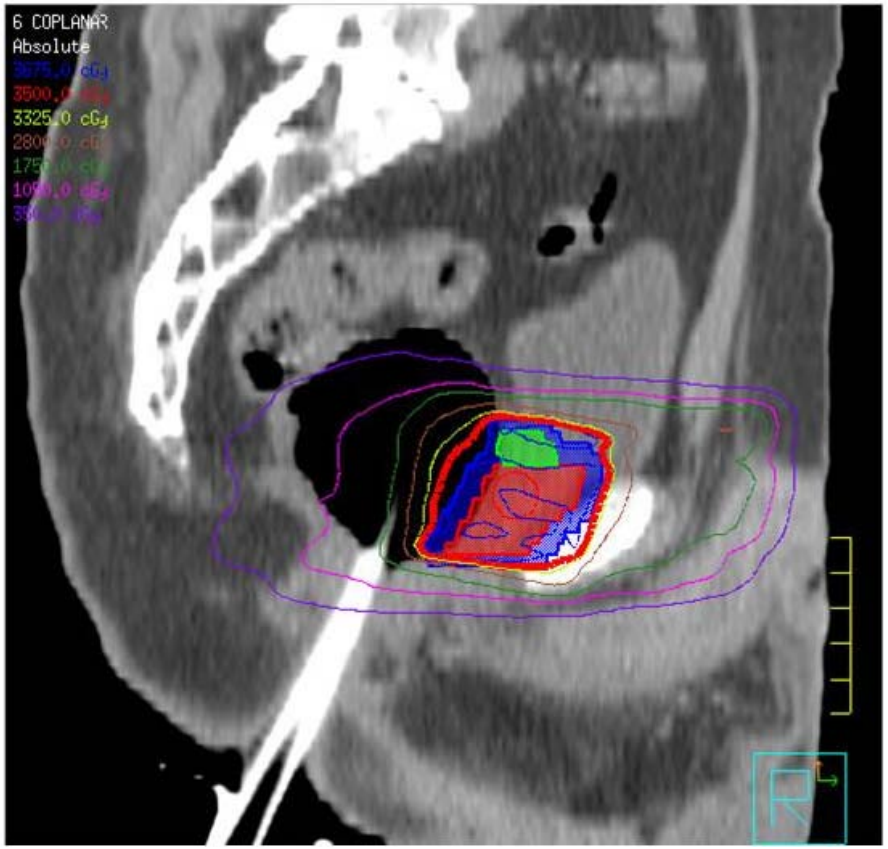
Dietry protocols or magnesiumoxides are not recommended for routine clinical practice.

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

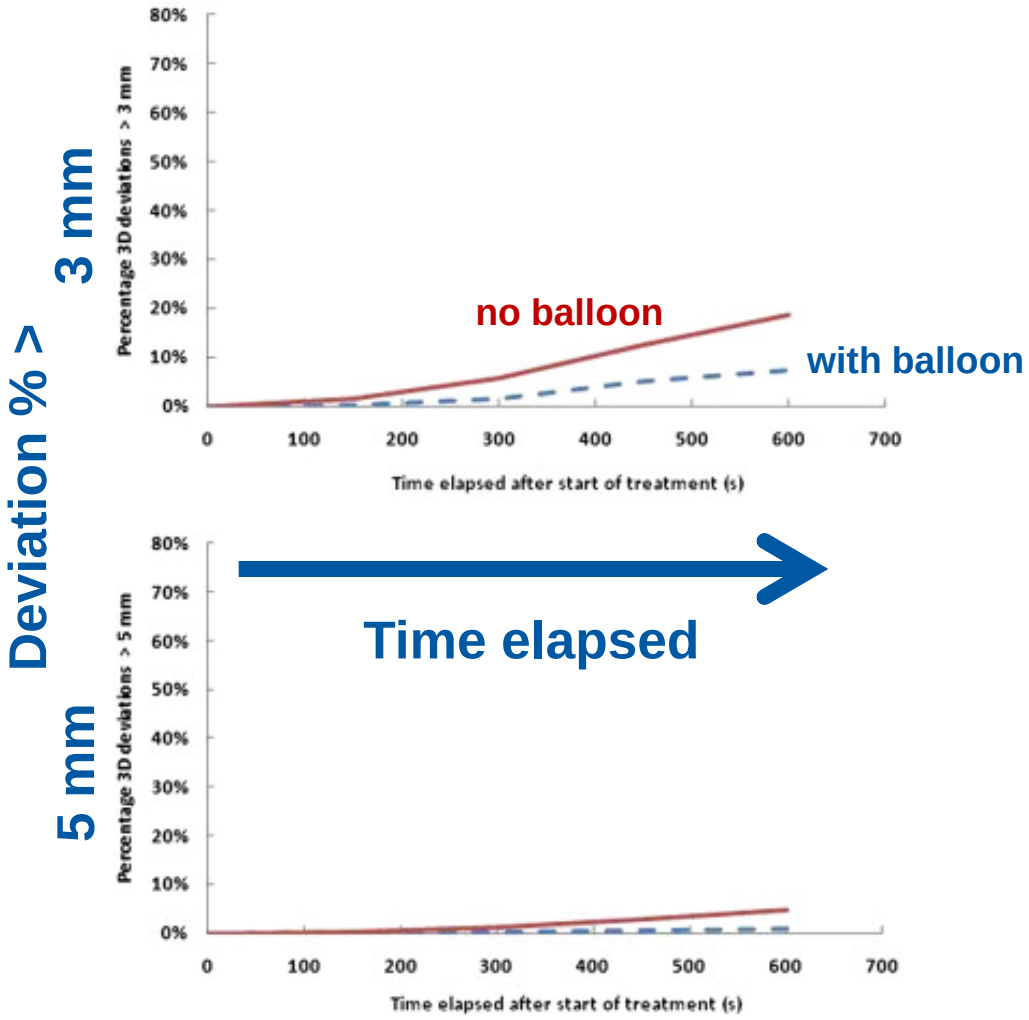
Management of intrafraction motion

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

UniversitätsSpital Zürich

ESTRO School

Management of intrafraction motion

Rectal balloons disadvantages

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

Irritation of the anal canal (hemorroids) Cho KJMS 2009

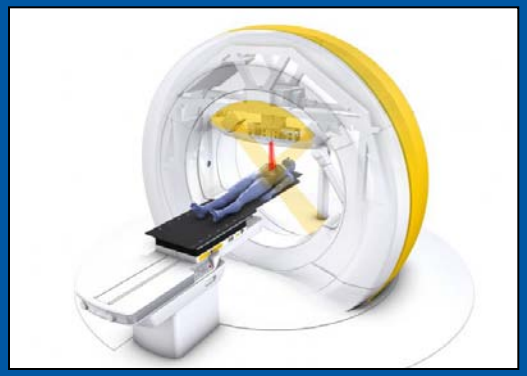
Complex procedure: may require frequent adjustments to avoid systematic errors or deformations (Jones Med Phys 2012, Miralbell IJROBP 2010)

Increases treatment time

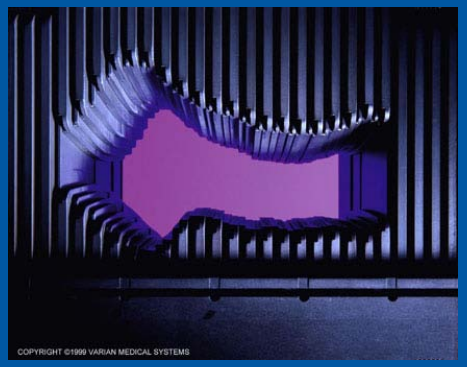
Mixed experience, complex and invasive procedure with questionable benefit.

Tracking – Adaption to the motion

‘Special machines’



‘Add-ons’ Conventional Linacs

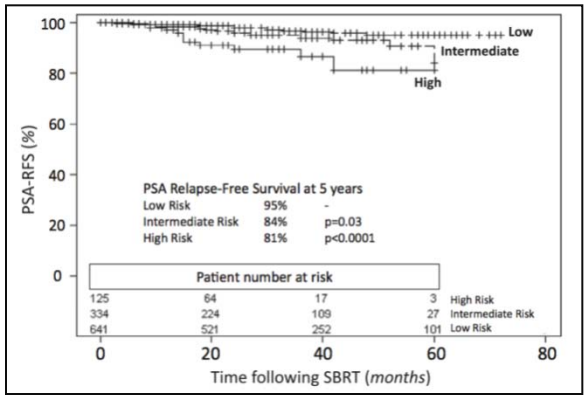


MLC and couch tracking can be performed on conventional linear accelerators, whereas for linac tracking dedicated machines are needed.

Tracking – Adaption to the motion

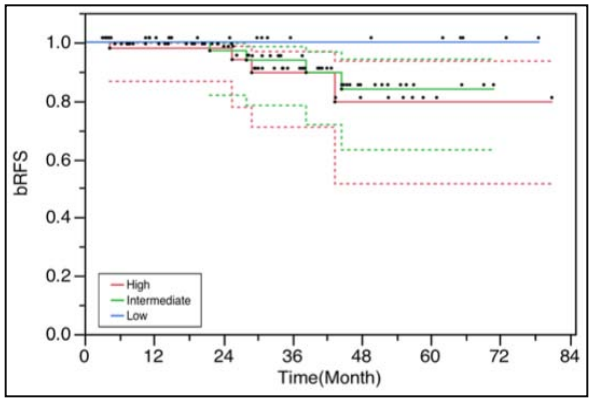
Cyberknife
King 2013

- 1100 patients
- 5 Fx SBRT



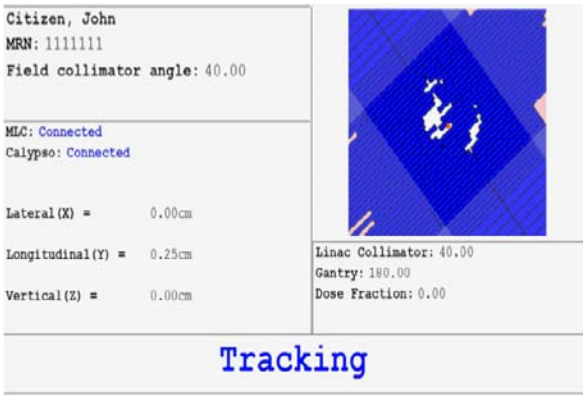
Couch tracking
Shimizu 2014

- 110 patients
- 30 Fx



MLC tracking
Keall 2014

- 10 patients
- 30 Fx



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
Matthias Guckenberger

Thank you for your attention.

Questions?

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Management of targets with respiration induced motion: part II

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

Mischa Hoogeman & Dirk Verellen

DV is involved in an on-going scientific collaboration with BrainLAB AG, RaySearch, MIM

ESTRO School

Learning objectives

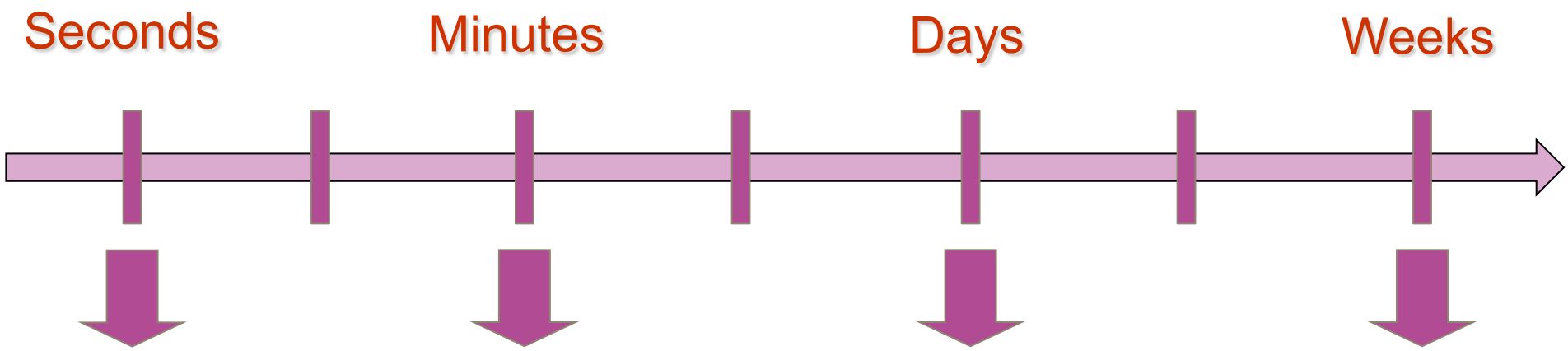
- To give an overview of the magnitude of intra-fractional position errors for patients
- To demonstrate the dosimetric and clinical relevance of these errors
- Sites of interest
  - Intra-cranial
  - Head and neck
  - Spine (supine vs. prone)
  - Prostate
  - Lung
  - Liver

- **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**

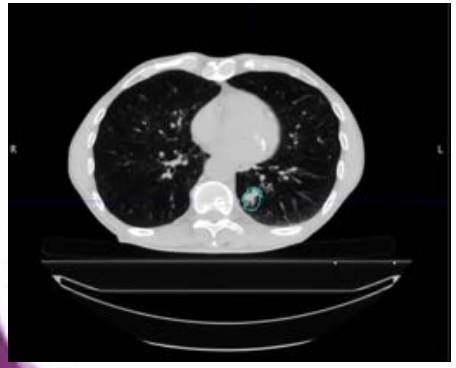
Outline

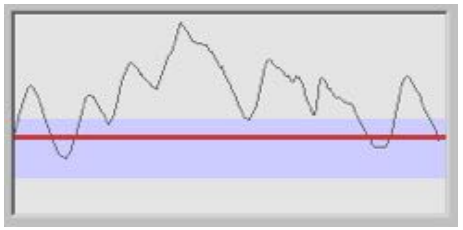
- 4D imaging for treatment preparation
- Motion management during treatment
  - ➢ “**Passive**” versus “**Active**”
- Real-time motion management, what are the options?
- Pitfalls

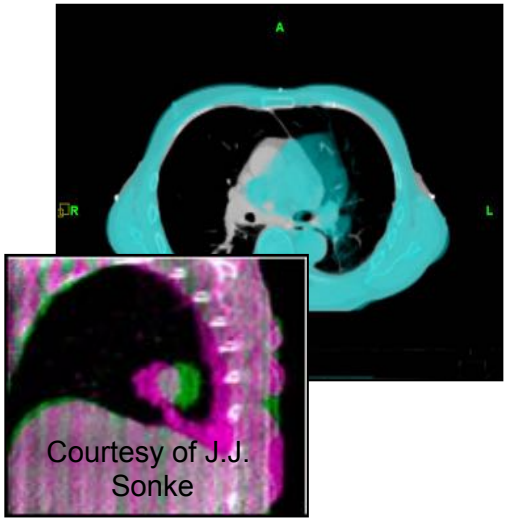
Motion management: the variables

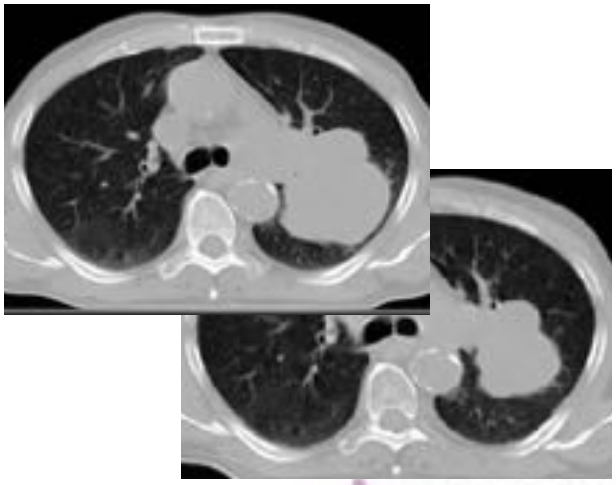


- Seconds
  - Breathing
  - Peristaltic
  - Heart Beat
- Minutes
  - Patient motion
  - Tumor drifts
- Days
  - Breathing pattern
  - Baseline shifts
  - Patient position
- Weeks
  - Shrinkage
  - Progression
  - Weight loss

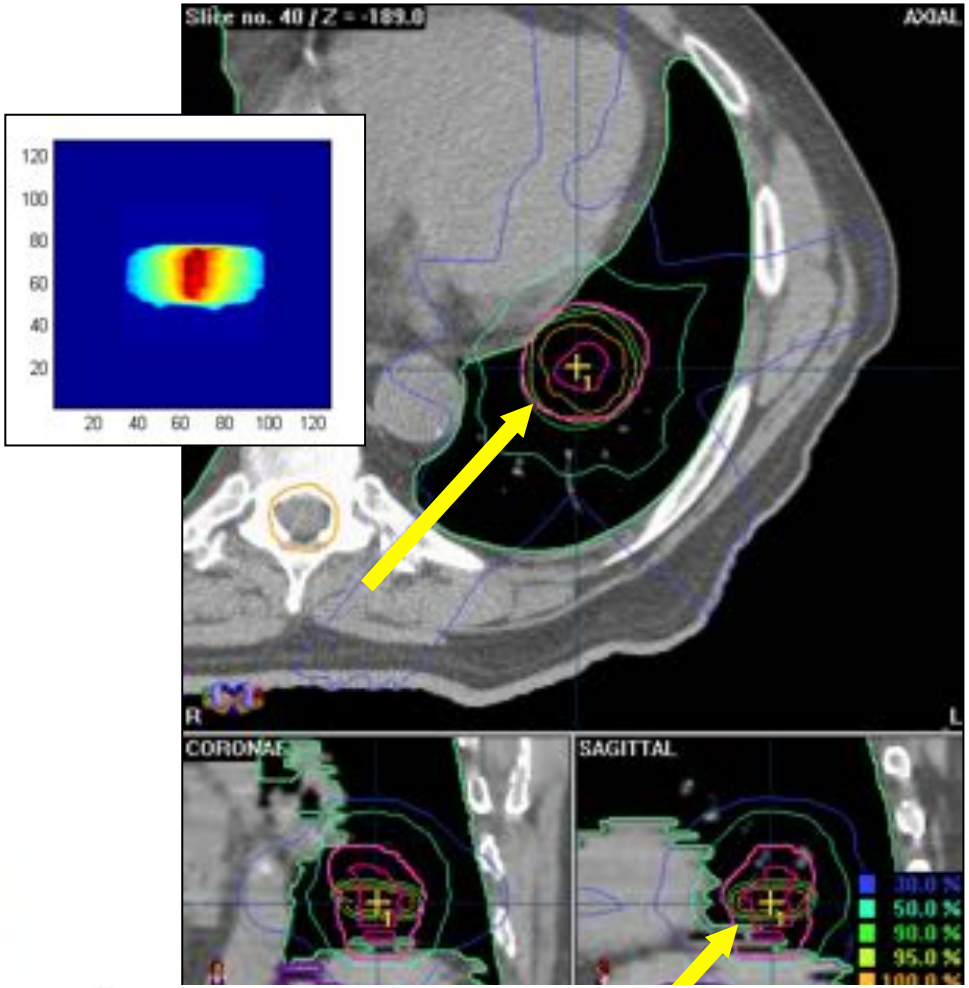


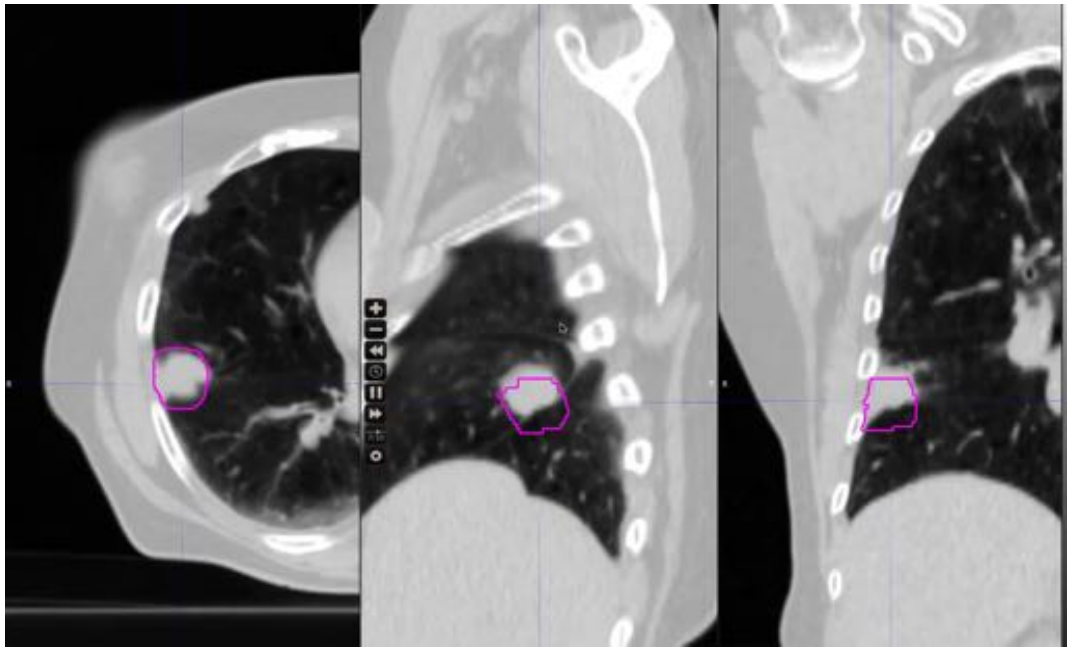


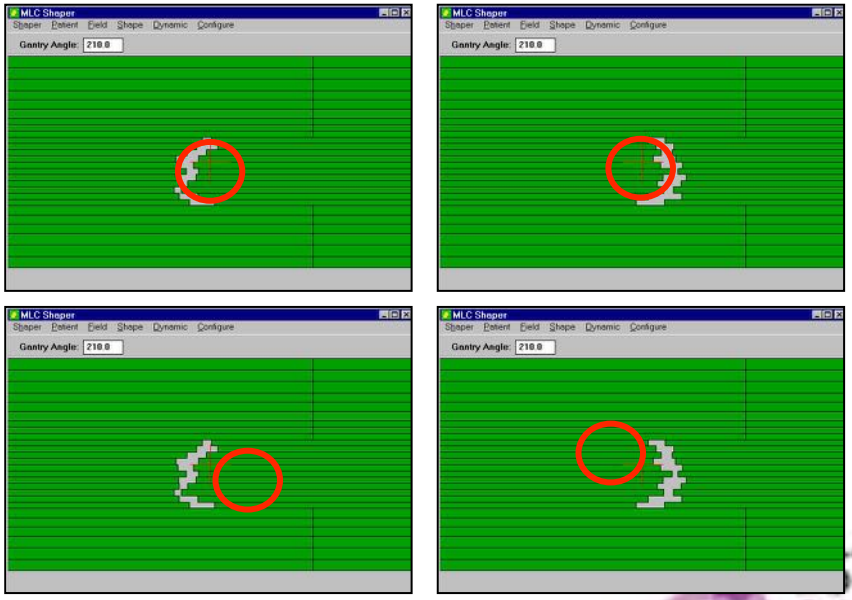


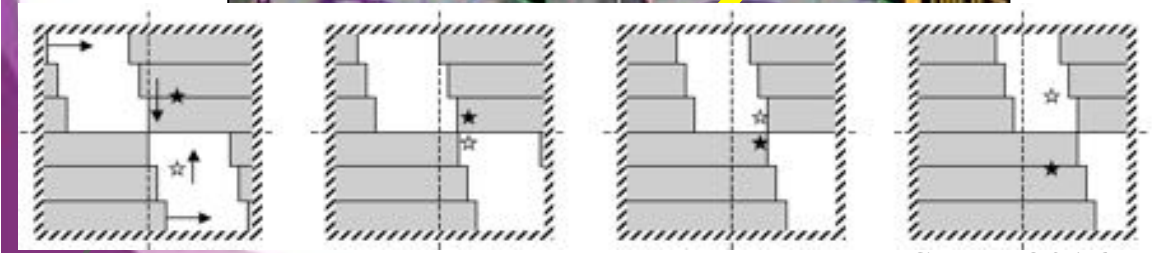


Why motion management?









Bortfeld PMB 2002

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*'

Motion management

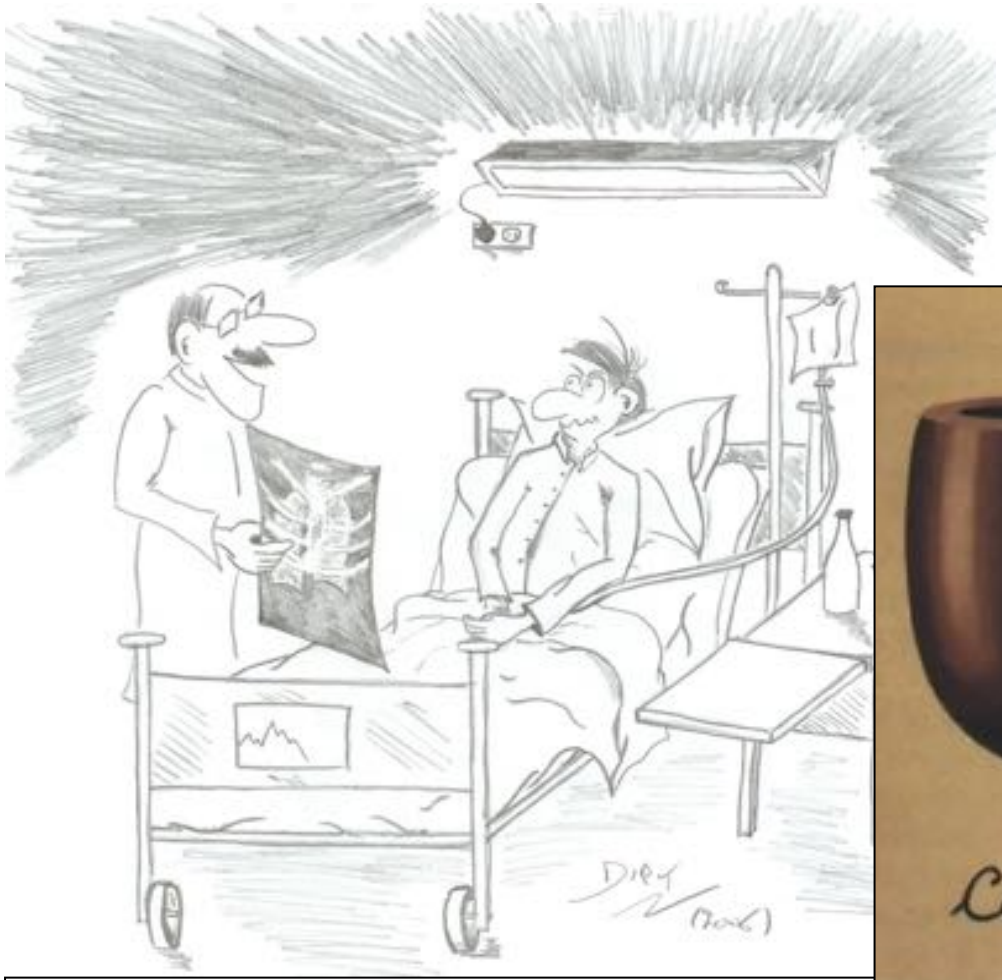
- “passive” motion management
  - Shallow breathing by abdominal compression
  - Motion encompassing techniques
  - Motion compensating in planning optimization

- “Active” motion management
  - Breathhold techniques
  - Gating
  - Tracking using treatment couch
  - Tracking using DMLC
  - Tracking using designer machines

Motion management

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

So, what's the 1st problem?



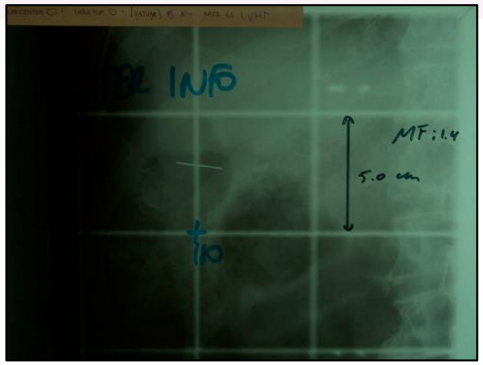
"We discovered a lung tumour,

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

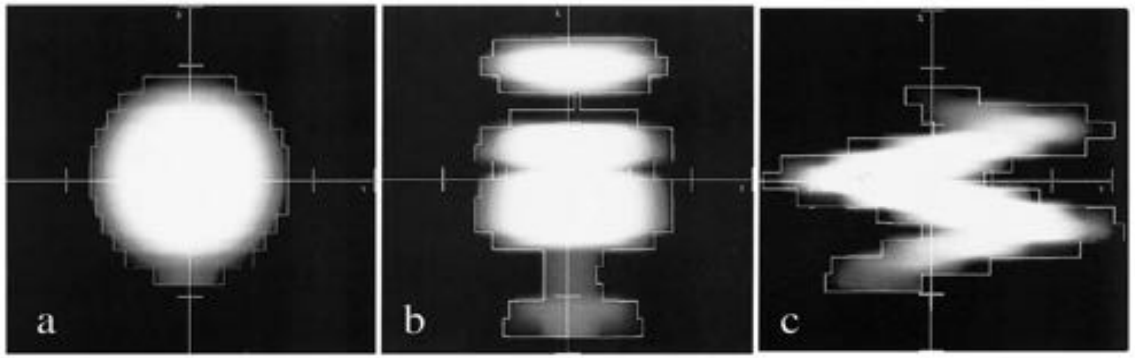


Fig. 3. AP DRRs of a 3.2-cm-diameter sphere generated from spiral CT acquisitions while (a) stationary, and moving 25 mm in the (b) longitudinal and (c) transaxial directions. The period was 4 s. The graphical overlay displays the region localized using a threshold of −875 HU. These images show some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

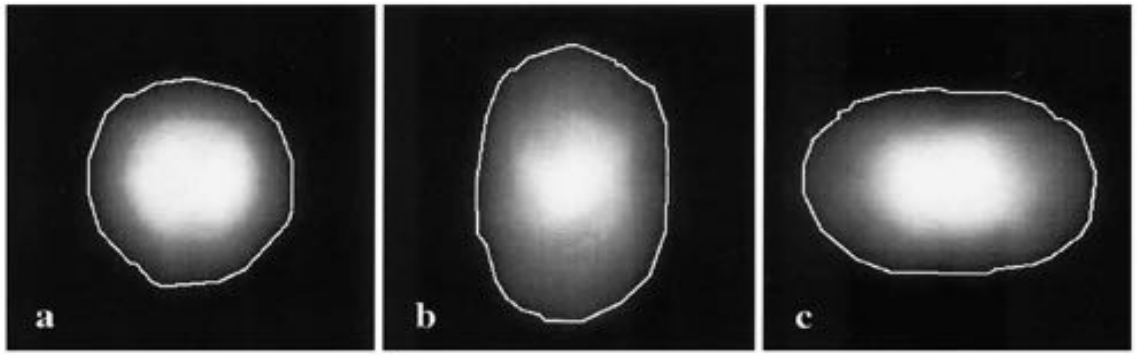
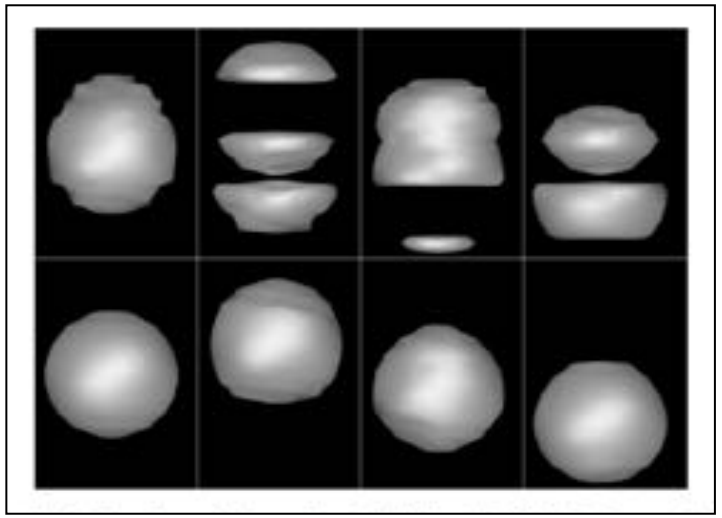


Fig. 4. AP maximum pixel ray trace ^{22}Na-PET images of the same sphere while (a) stationary and moving 25 mm in the (b) longitudinal and (c) transaxial directions. The period was 4 s, and the images were acquired over 20 min. The graphical overlay represents the region localized using a threshold defined 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)"



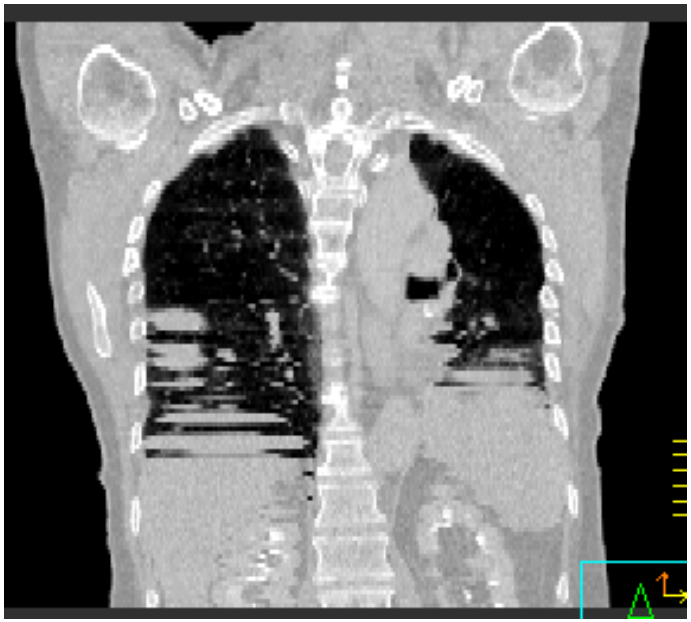
Rietzel *et al.*, Med Phys

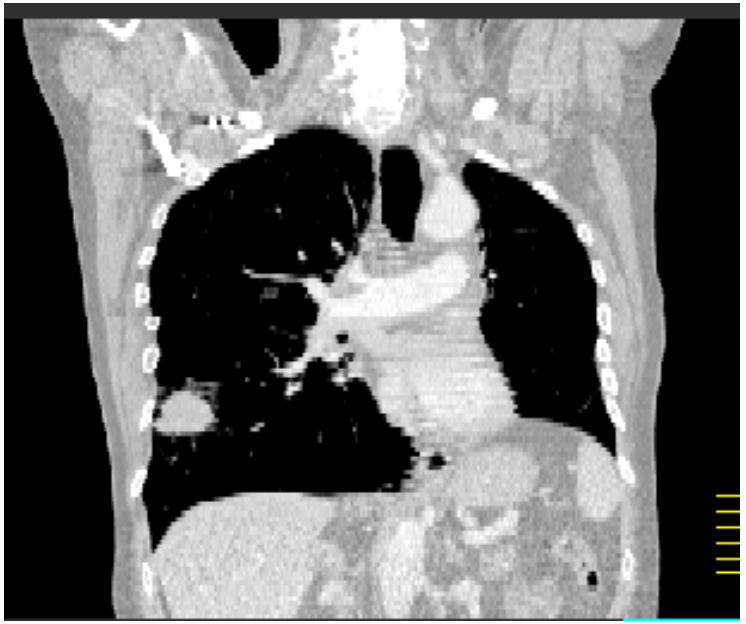
… but, quantitative information is blurred

… strong influence by widowing

Imaging for target definition

- Slow 3D-CT



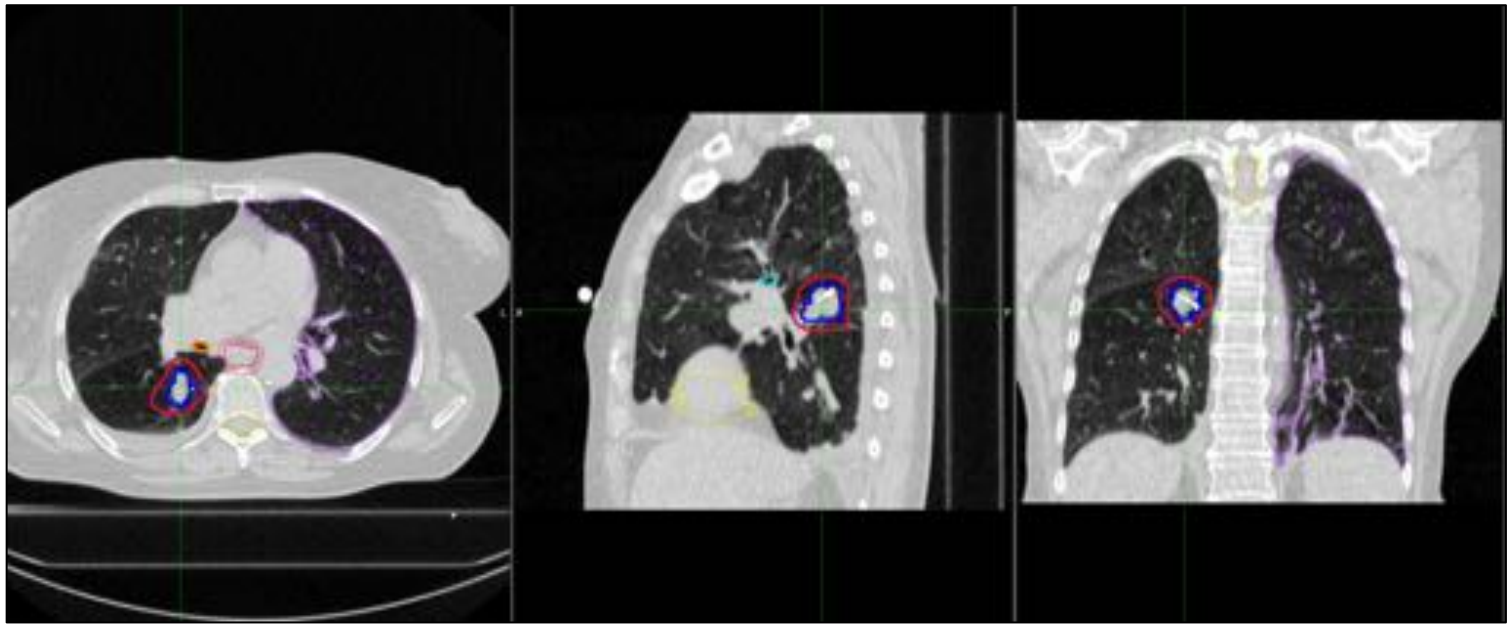


4D-CT image artifact reduction

- 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

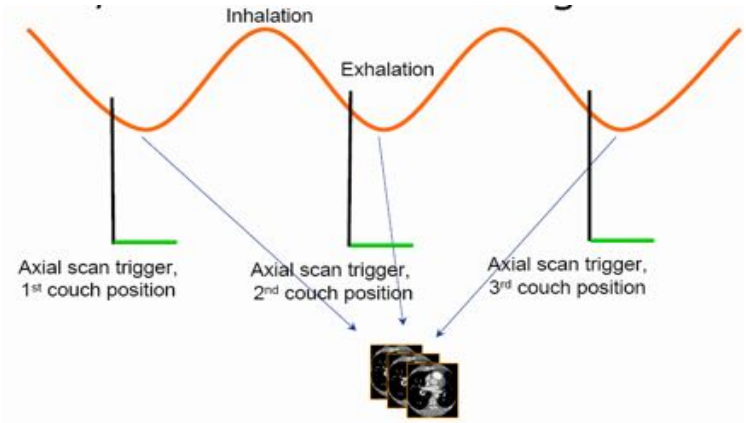
- Fast 3D-CT



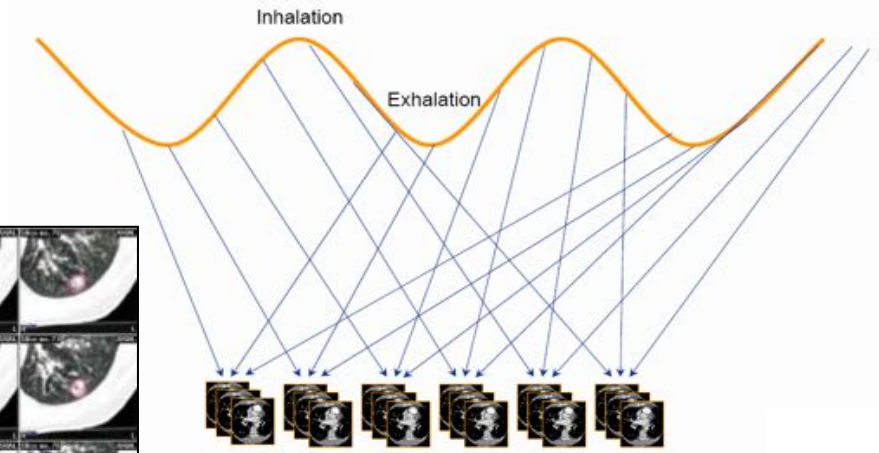
- **Snapshot in time** representing 1 specific target position, again associated with multiple uncertainties:
  - Target position?
  - Target motion?
  - Target trajectory?
  - Baseline?
  - Motion of OAR with respect to target?

Imaging for target definition

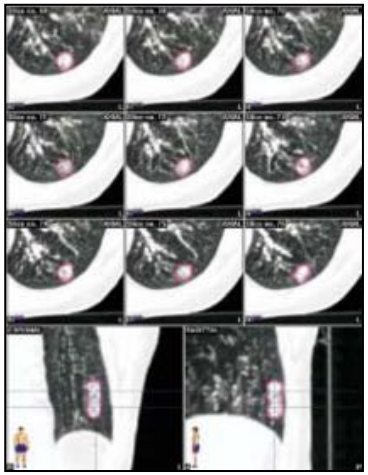
- 4D-CT
  - Gated / breathhold 4D-CT



  - Respiration correlated (RC 4D-CT)

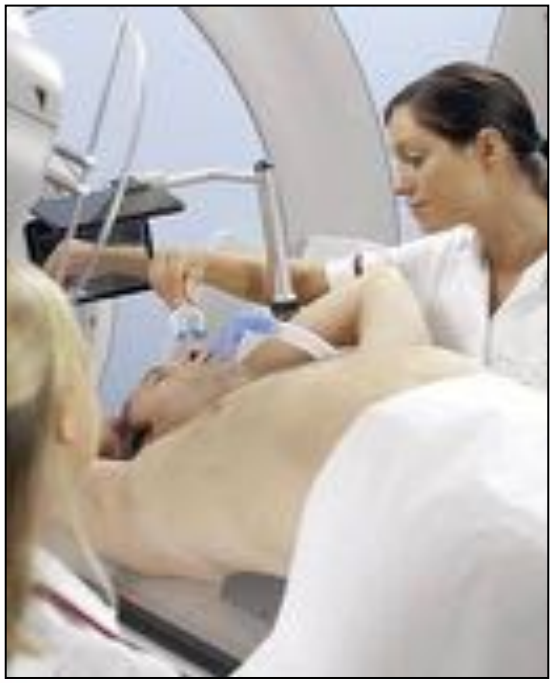


  - Maximum Intensity Profile

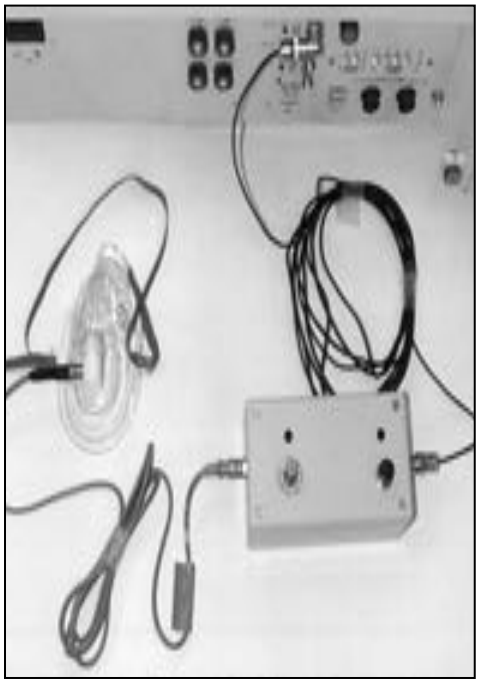


Imaging for target definition: RC-CT

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

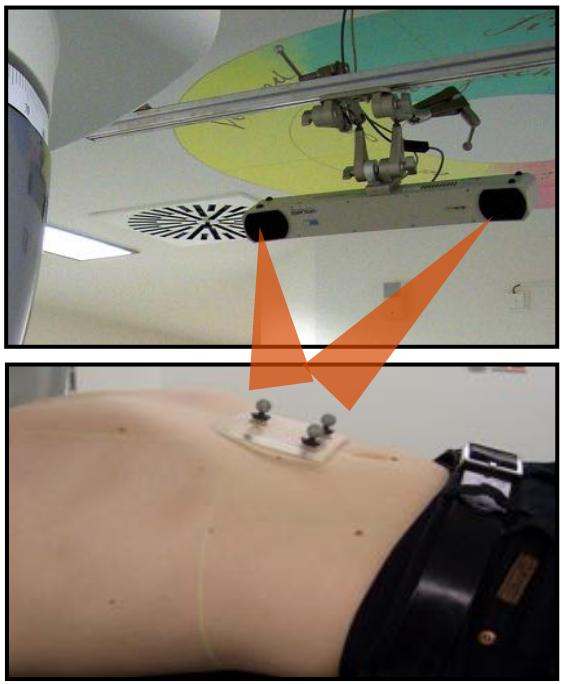


Spirometer



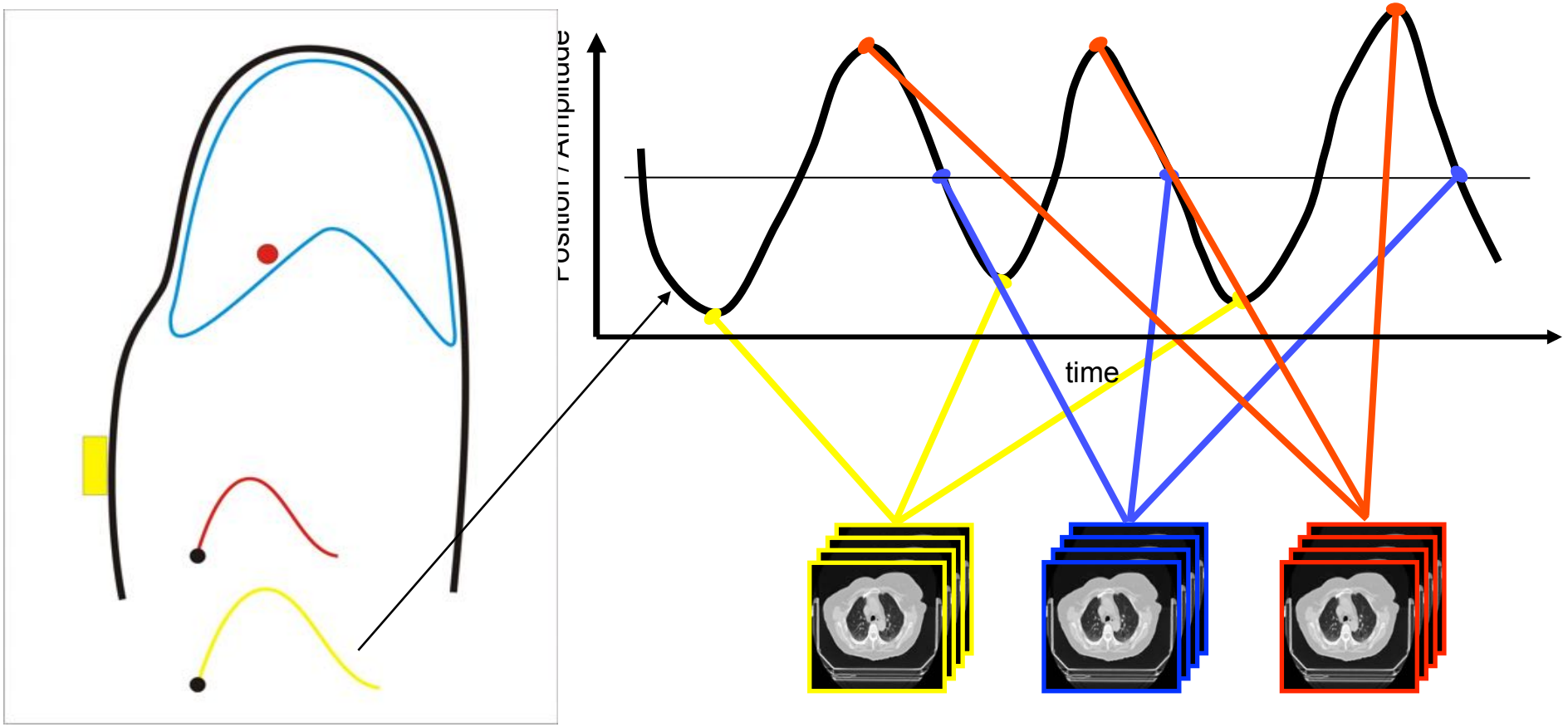
Nasal temperature

Abdominal pressure sensor



Infrared sensor

Imaging for target definition: RC-CT



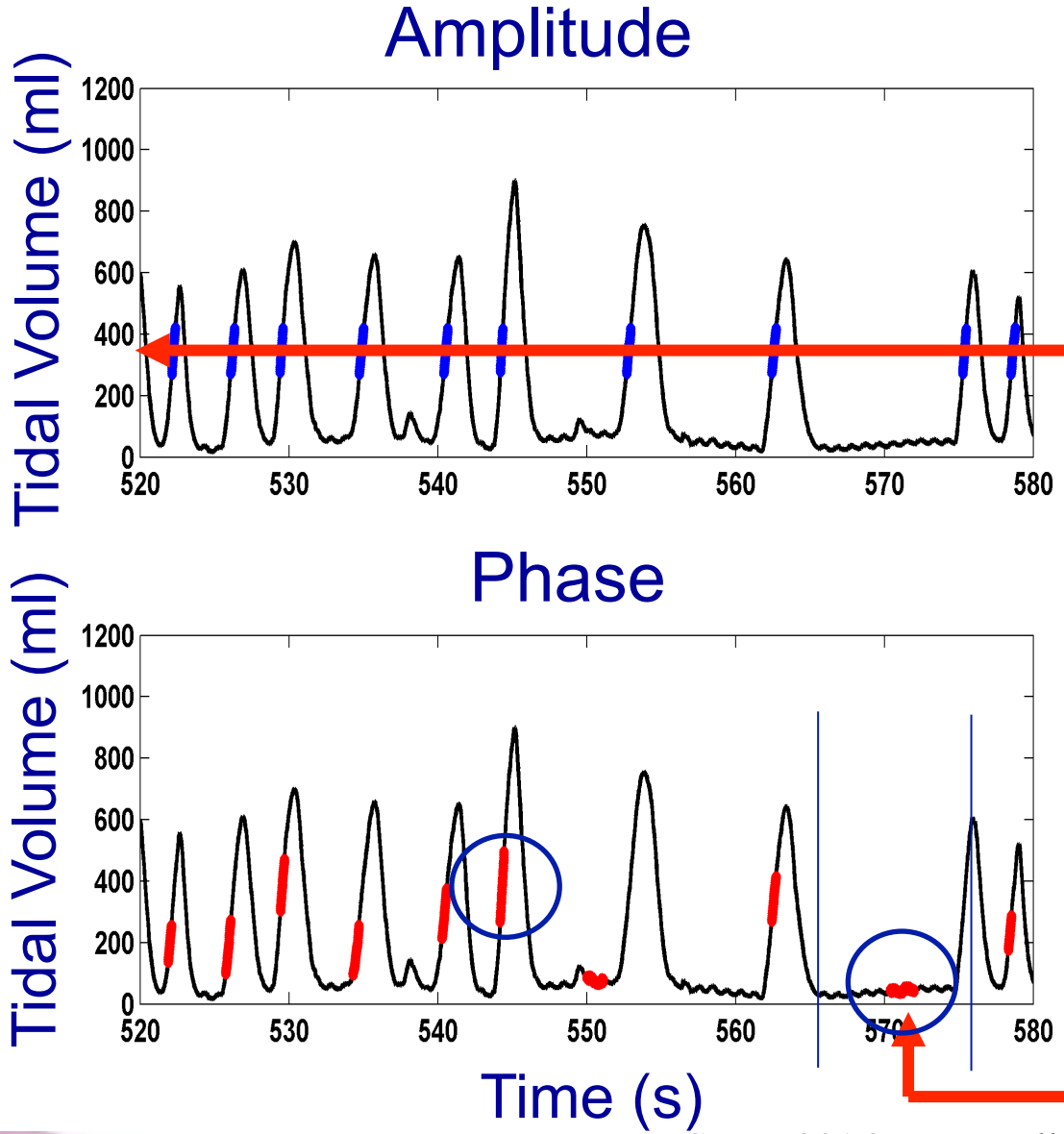
Respiration Correlated CT (4D RC-CT):

- 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

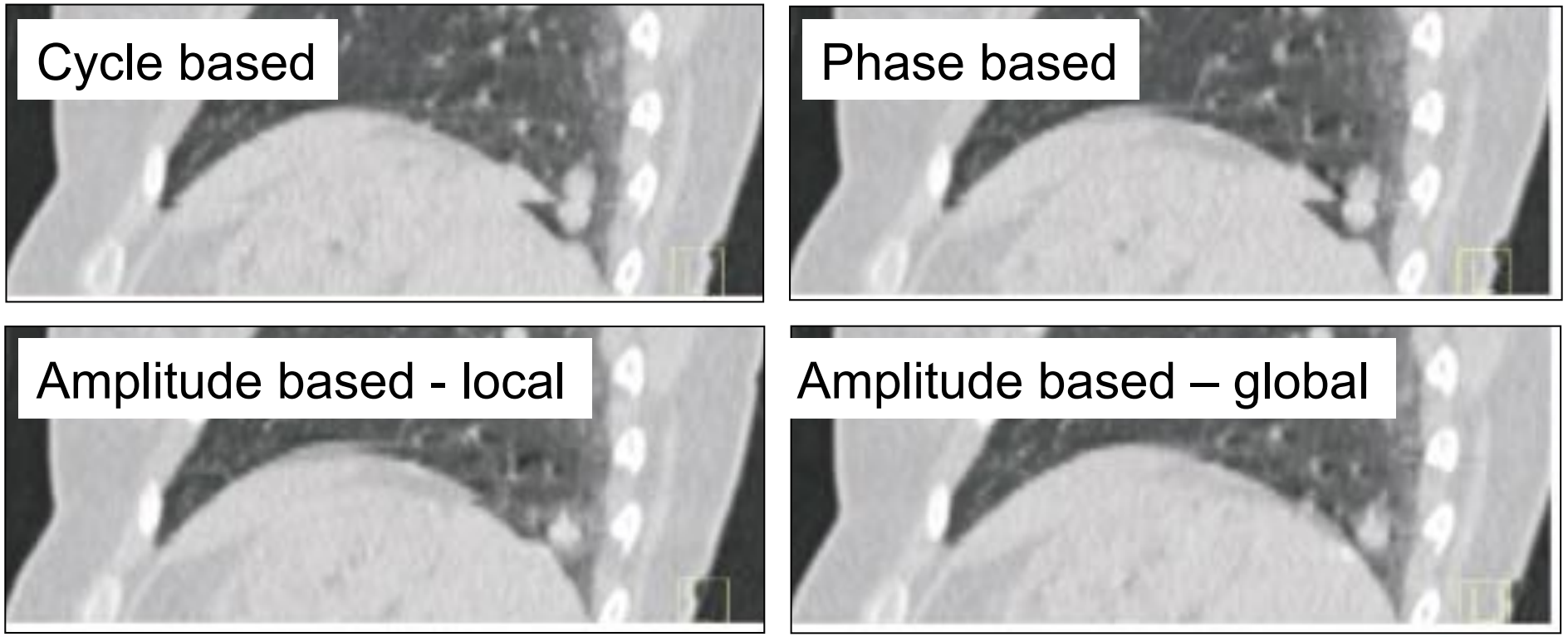
Mid-inspiration defined by percentile tidal volumes

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 …)

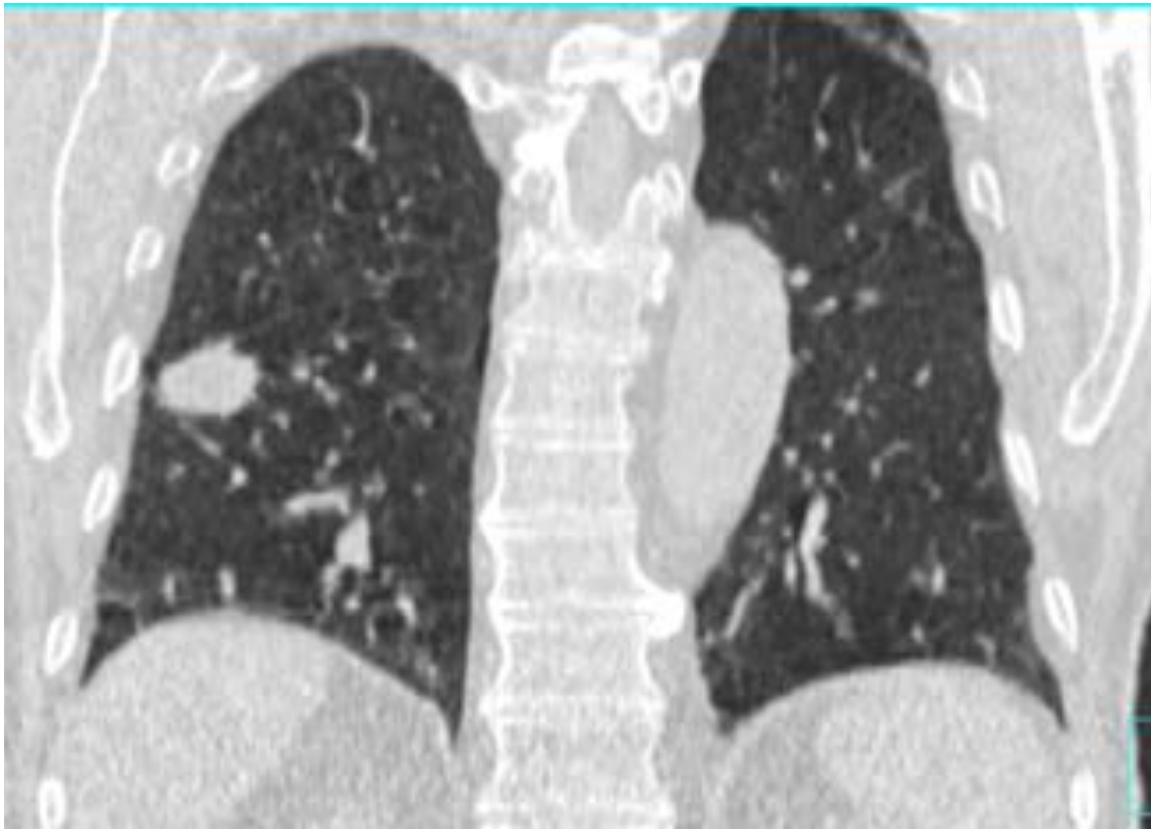


Lu *et al*, Med Phys, 2006 – Guckenberger *et al* Radiother Oncol 2007

Imaging for target definition: RC-CT

Conventional 3D CT

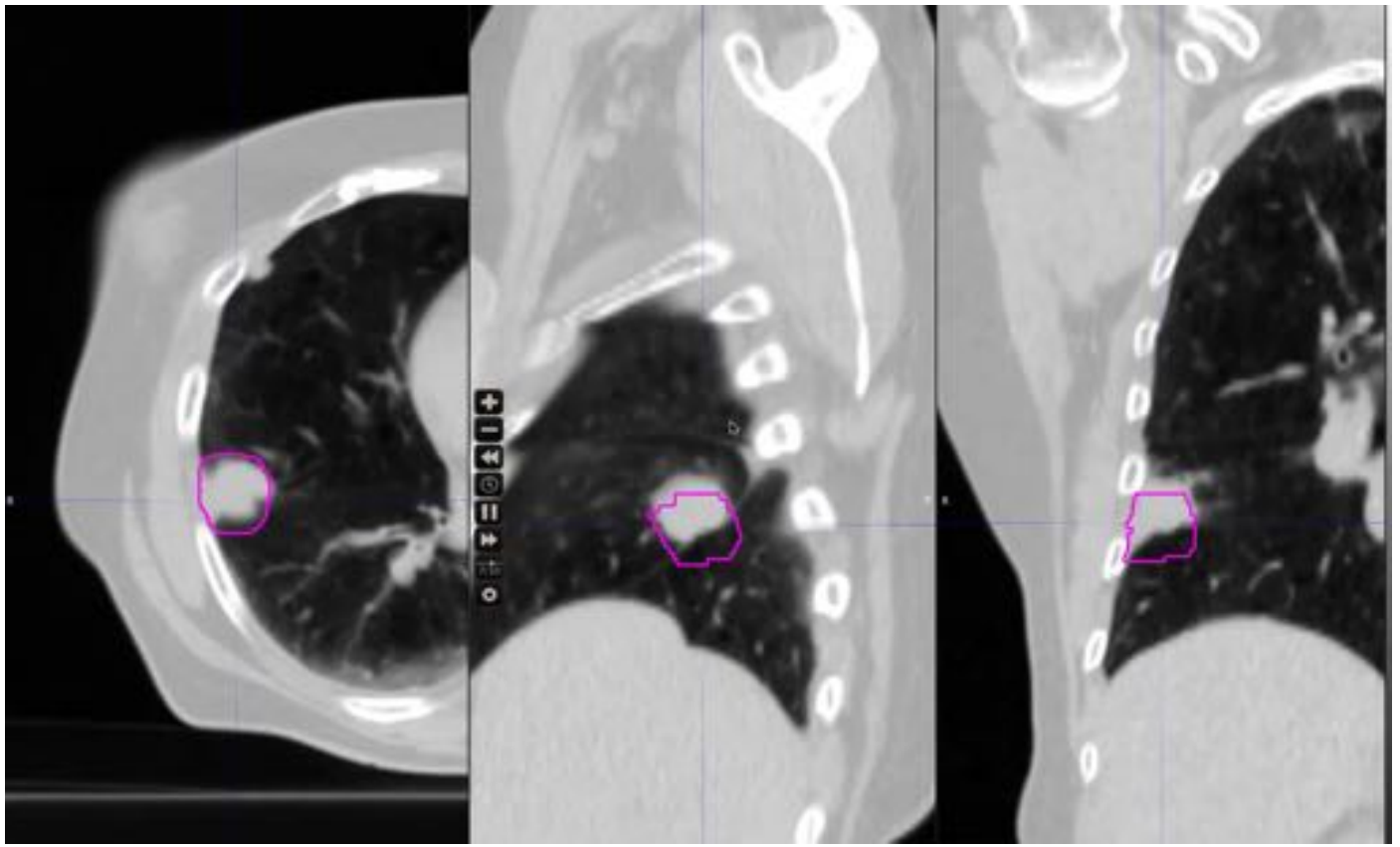
Respiration correlated 4D-CT



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:

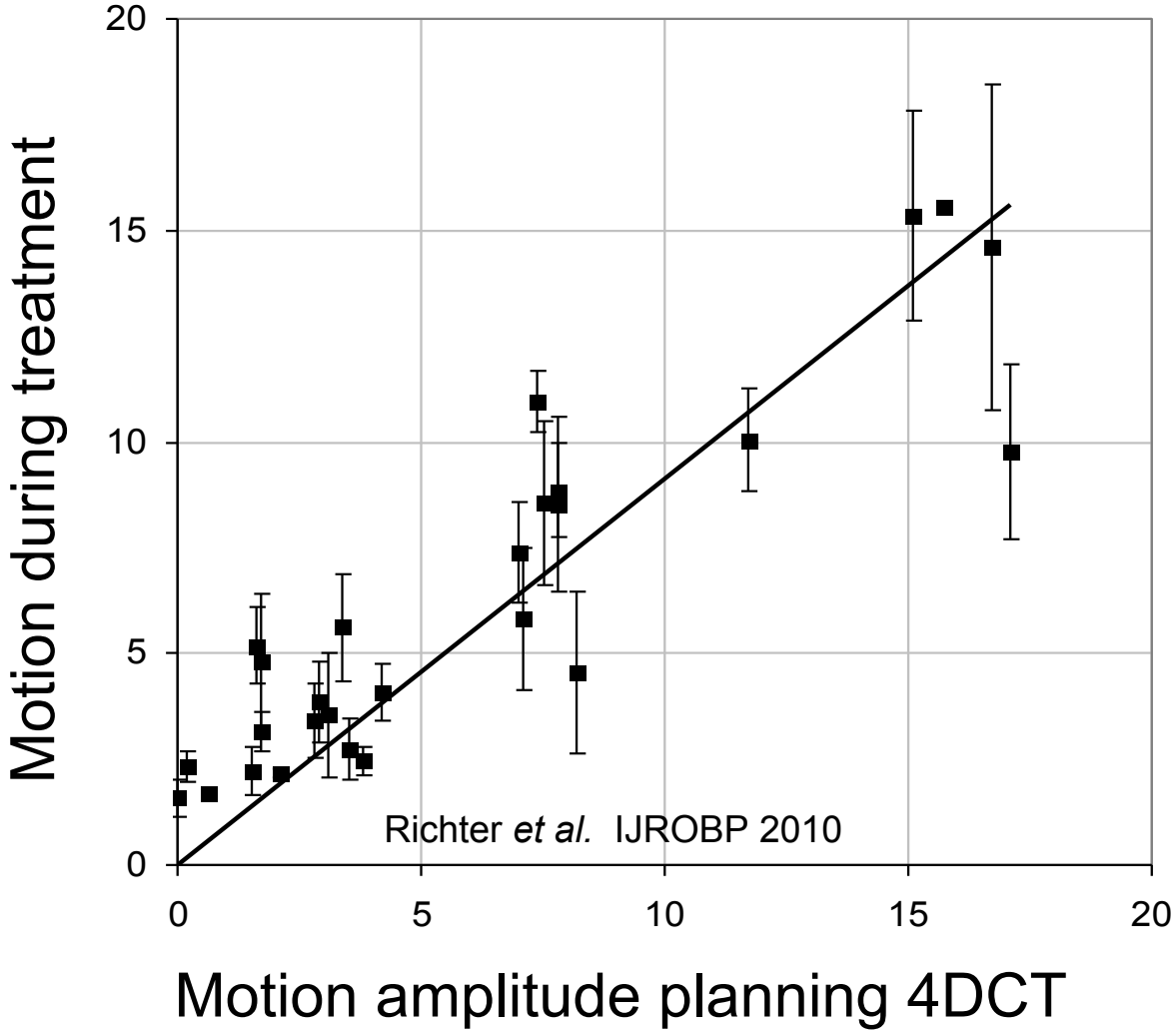
Richter IJROBP 2010

- 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



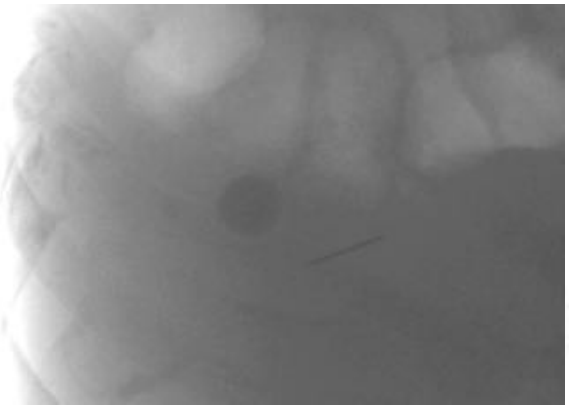
Imaging for target definition: RC-CT

- 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	10.2	6.3	1.6	11.5	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	5.6	2.0	1.3	2.3	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

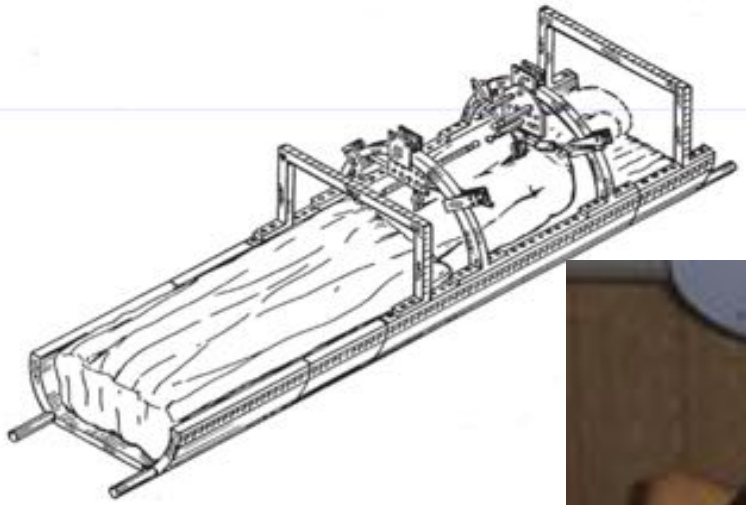
Take home message

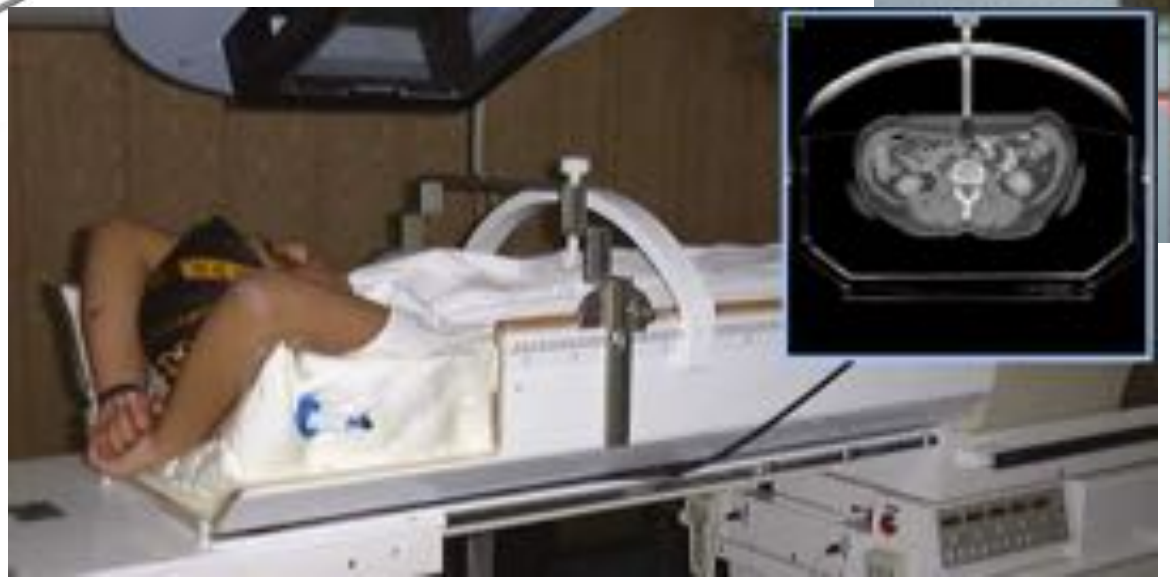
- Fluoroscopy could be used for:
  - Selection of tumors that might require motion management during treatment, or strategy selection.
- FDG-PET should be used for
  - Exclusion of stage IV metastatic disease
  - Staging of nodal status
  - Differentiation of tumor - atelectasis
- Respiration correlated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

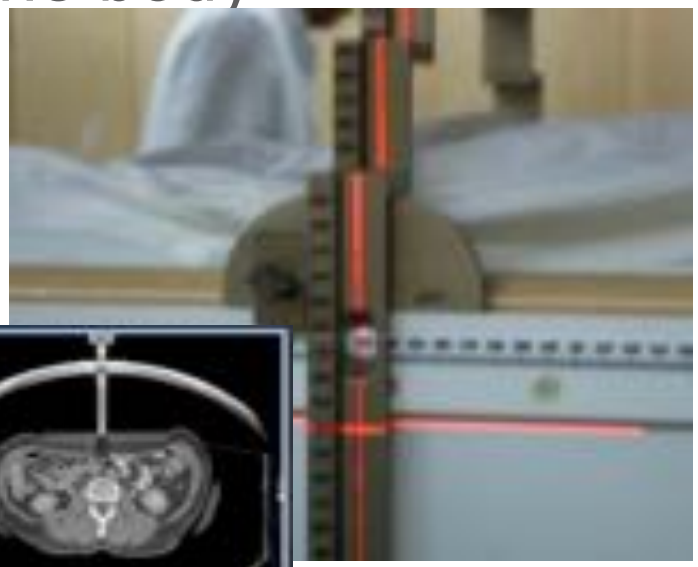
Motion management: Passive

Forced shallow breathing: body frames

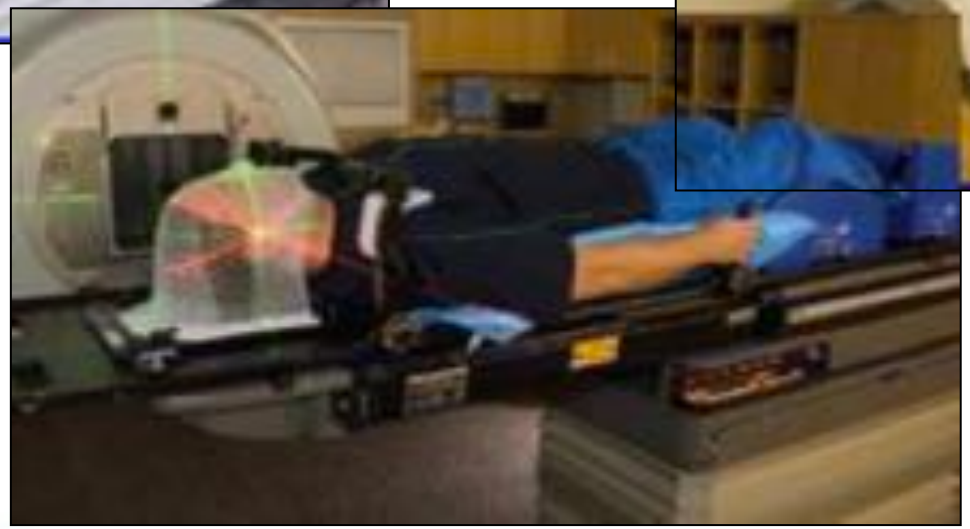
- Challenge:
  - ➢ Creating a rigid external frame that will provide a repeatable reference for sites in the body





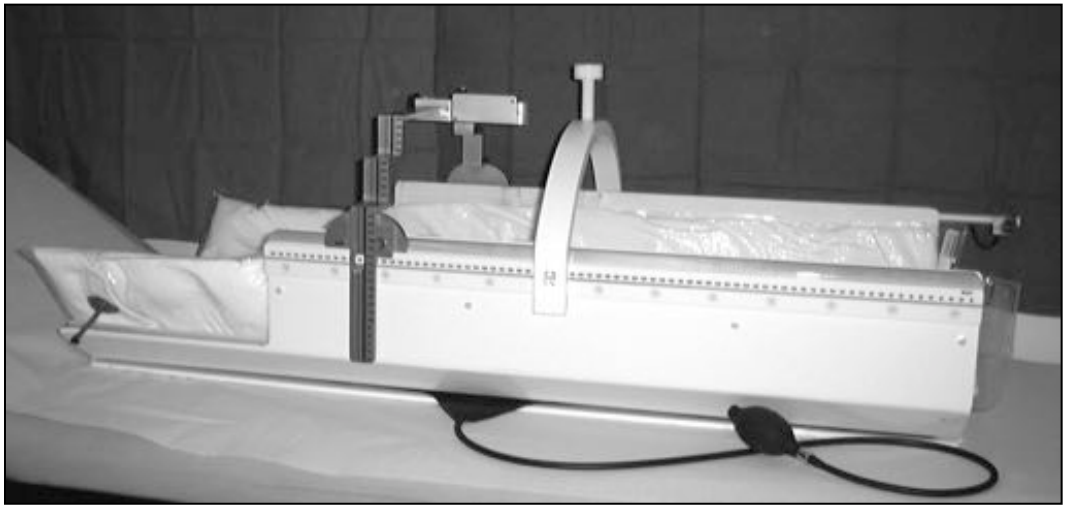


Forced shallow breathing: body frames

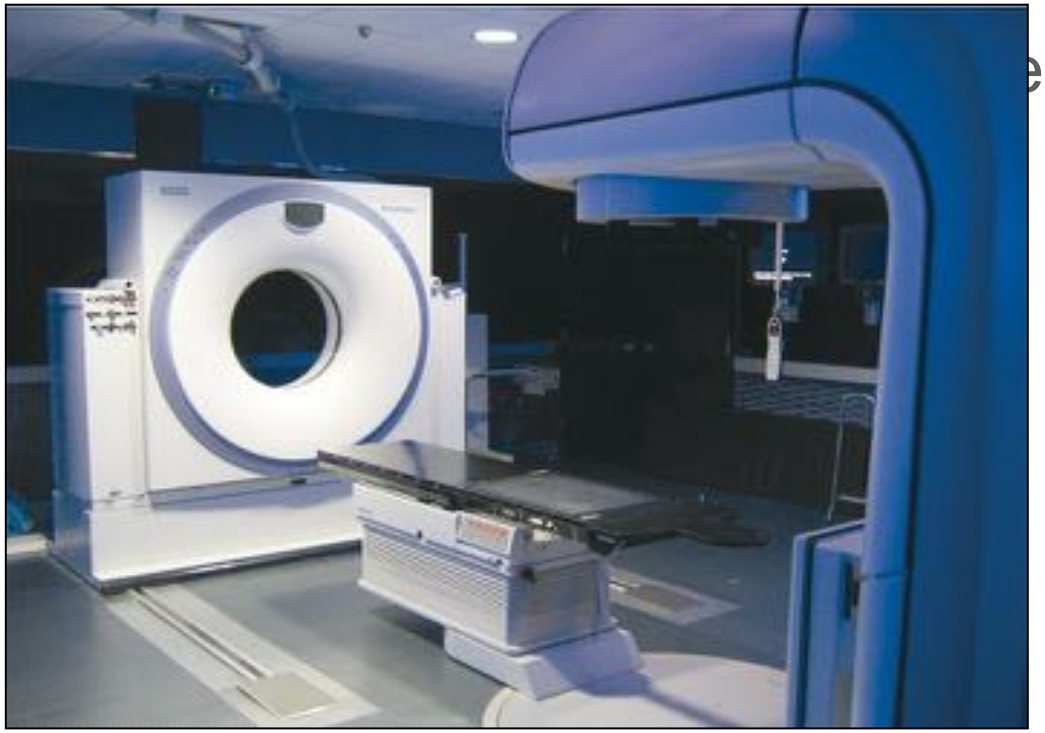


Forced shallow breathing: body frames

… still requires IGRT



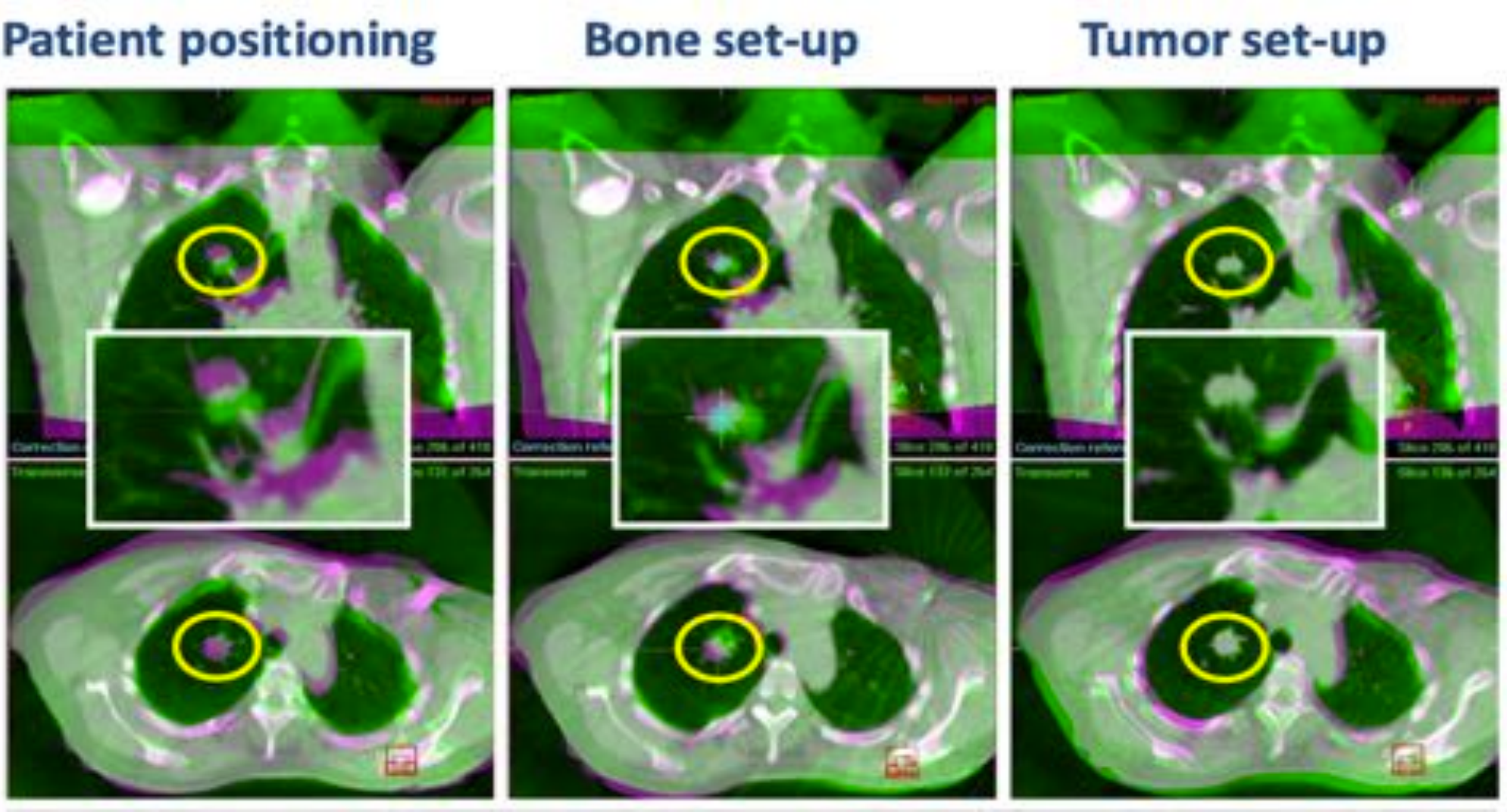
Stereotactic Body Frame, Lax *et al.*



‘Introduced’ for both **immobilization** as well as **target localization** (“stereotactic reference frame”), cf. stereotactic radiosurgery

!Pioneers in SBRT!

Base line shift



Courtesy Guckenberger *et al*

Forced shallow breathing: body frames

- 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"

Motion compensation techniques

- ITV using:
  - PET or slow CT
  - 4D RC-CT or MIP

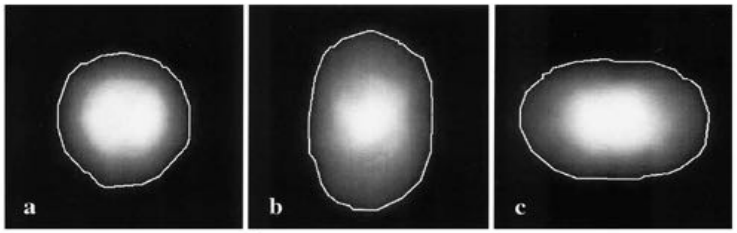
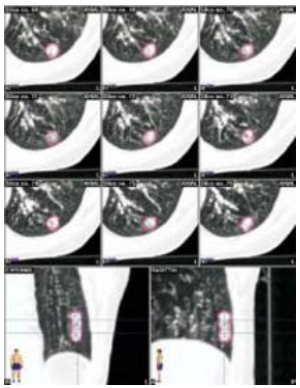
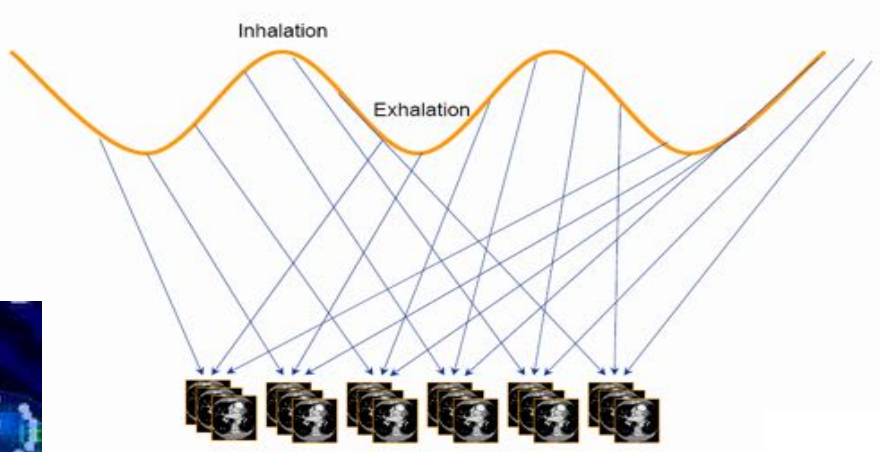
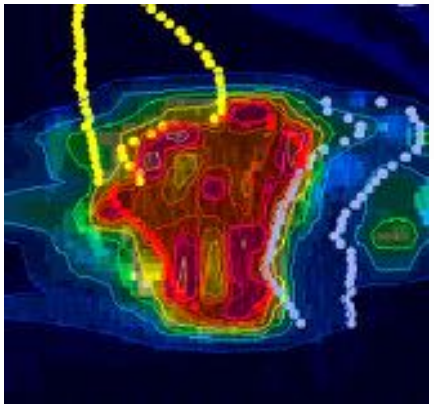


Fig. 4. AP maximum pixel ray trace ^{22}Na-PET images of the same sphere while (a) stationary and moving 25 mm in the (b) longitudinal and (c) transaxial directions. The period was 4 s, and the images were acquired over 20 min. The graphical overlay represents the region localized using a threshold defined 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.

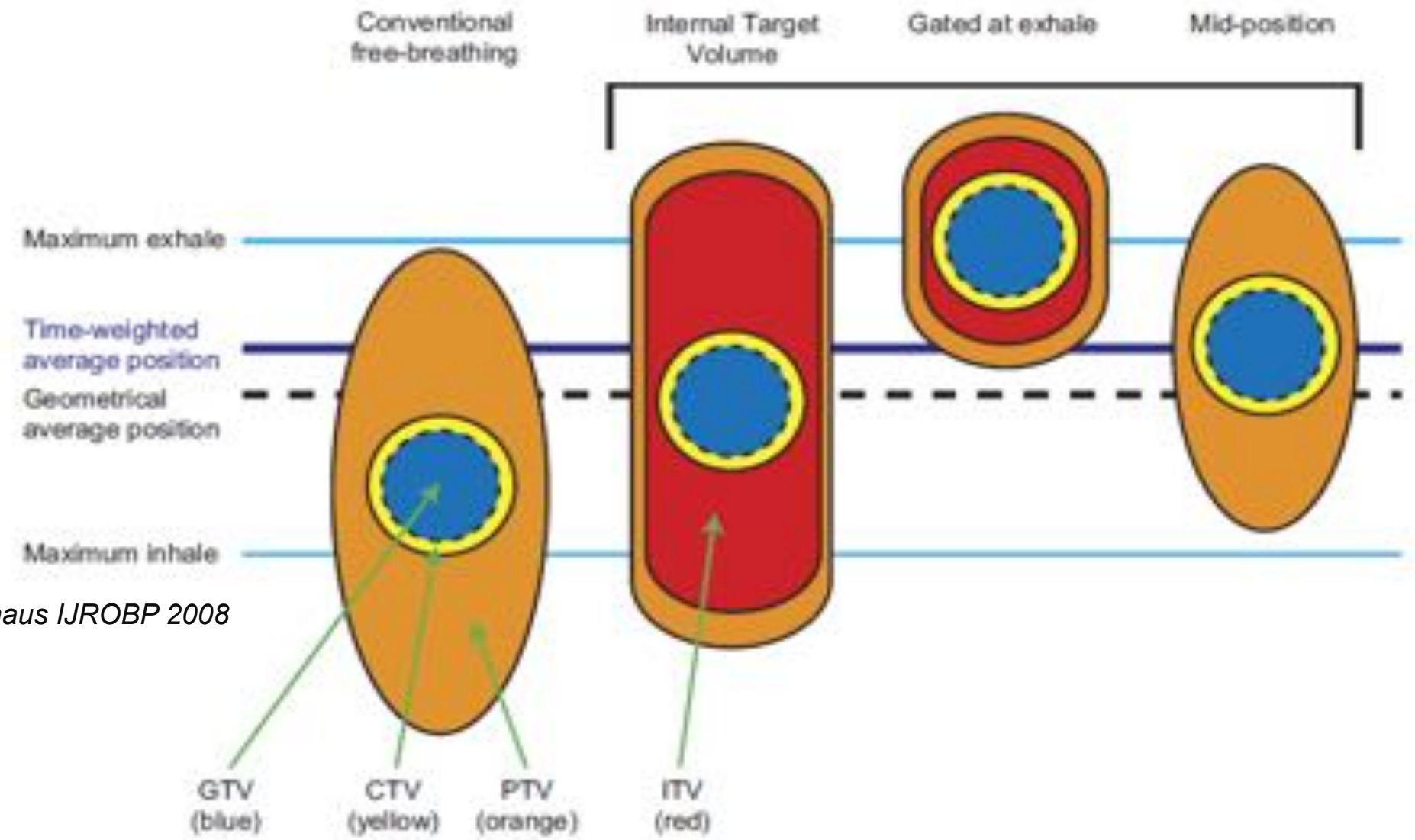




- 4D-CT – 4D-CBCT registration
- Fluence adaptation



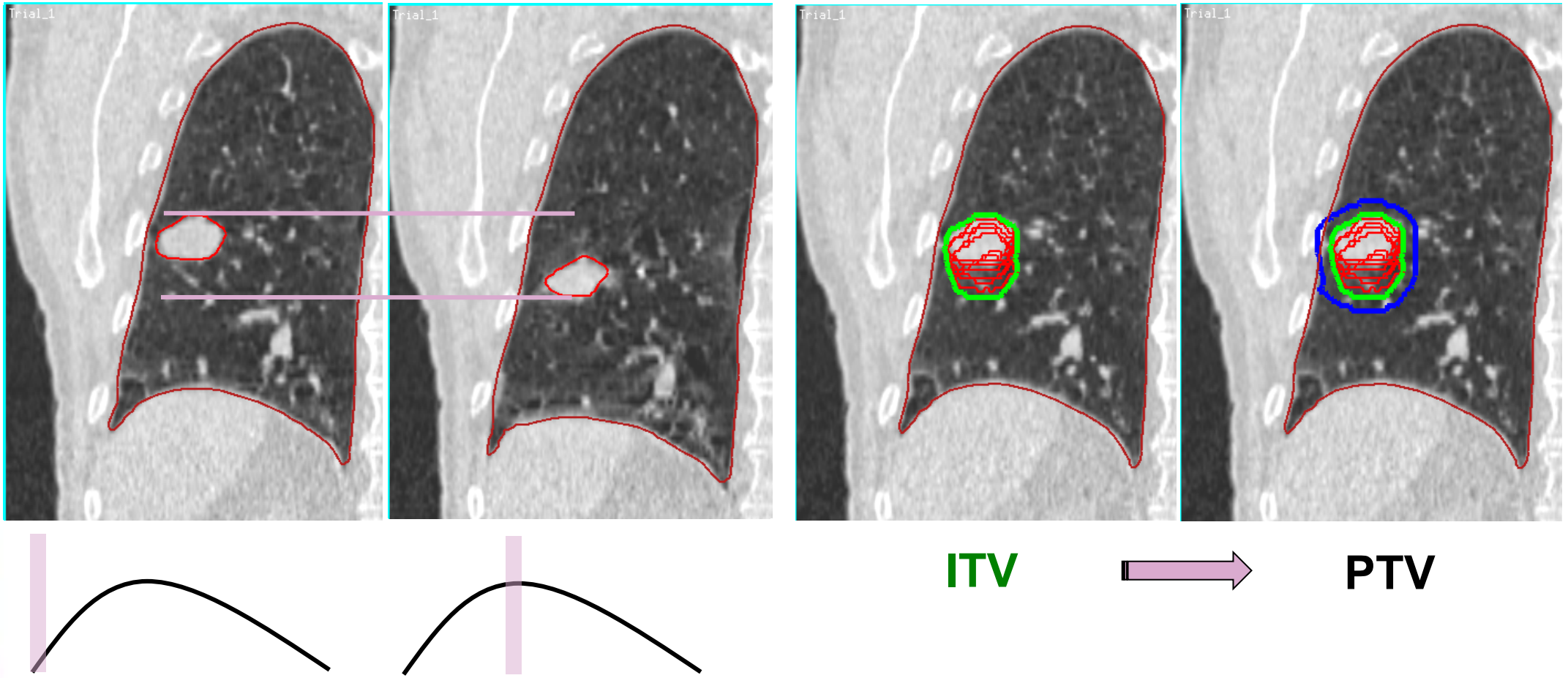
Motion compensation techniques



Wolthaus IJROBP 2008

Motion compensation techniques

Internal target volume (ITV) concept



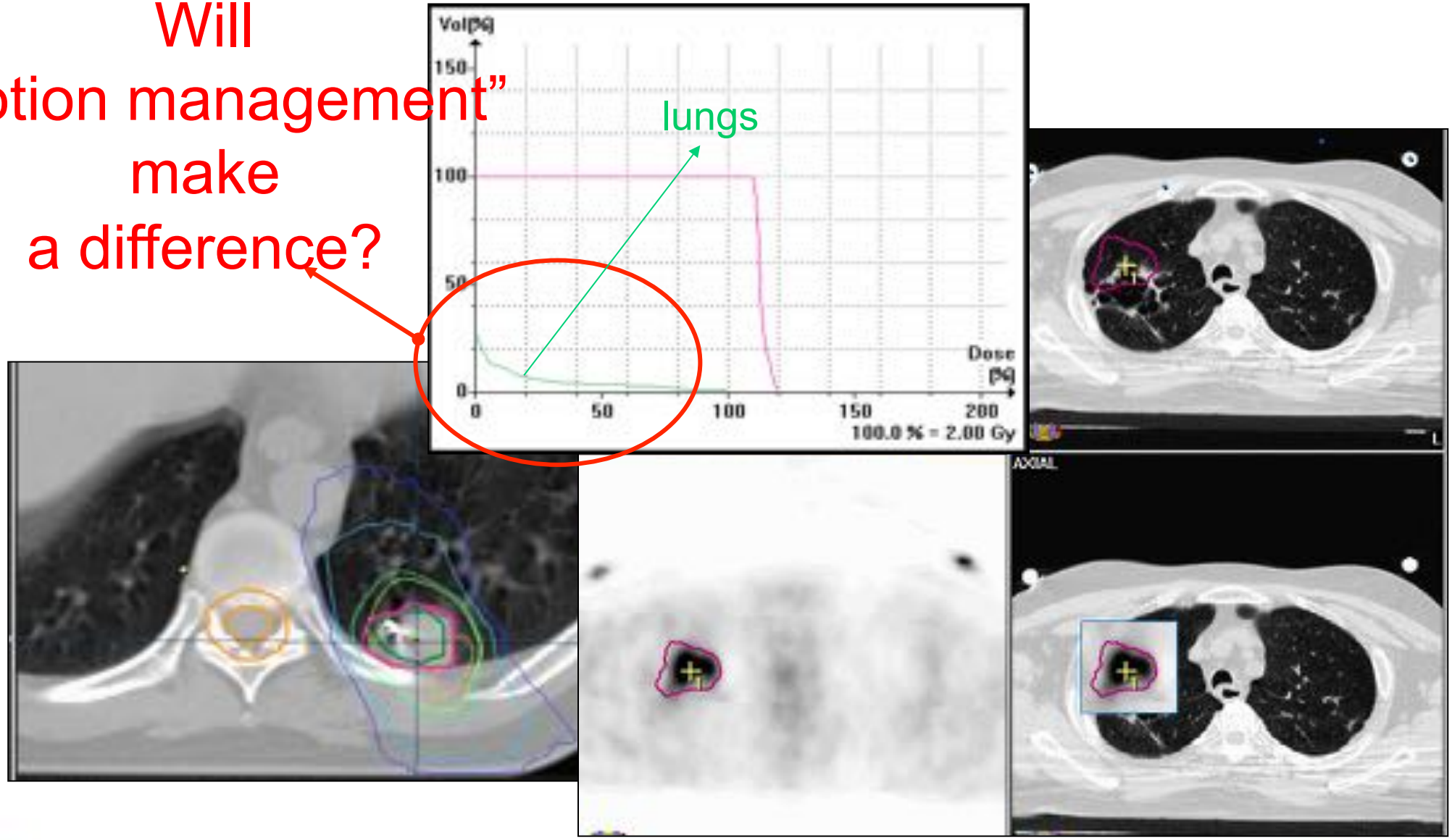
Courtesy Guckenberger *et al*

Motion compensation techniques

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

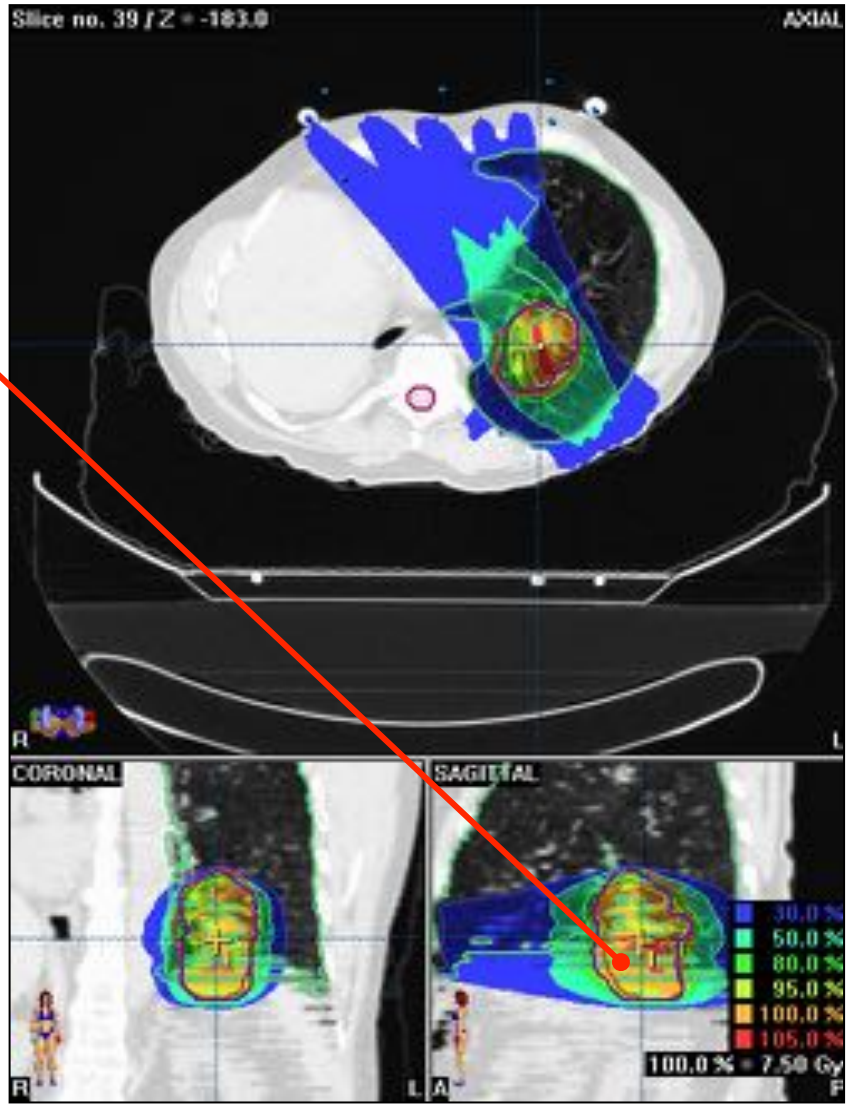
Motion encompassing techniques

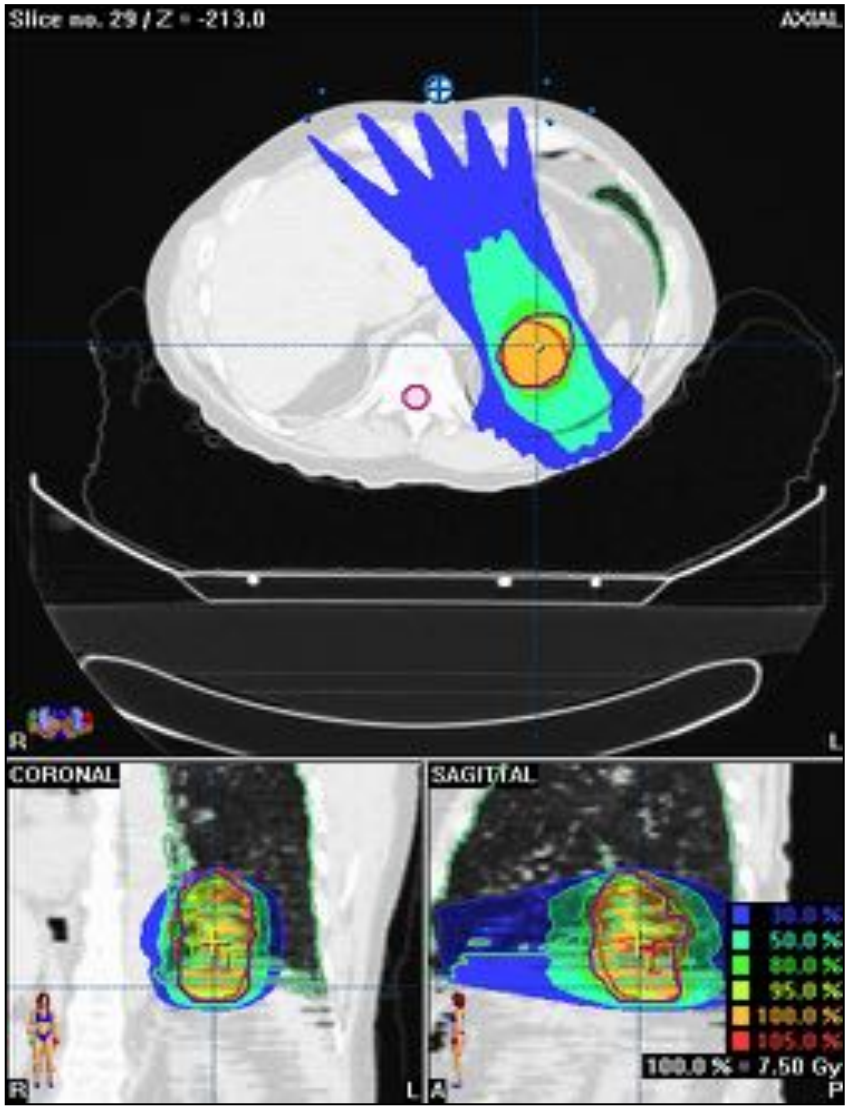
Will
"motion management"
make
a difference?



Motion encompassing techniques

Maybe …

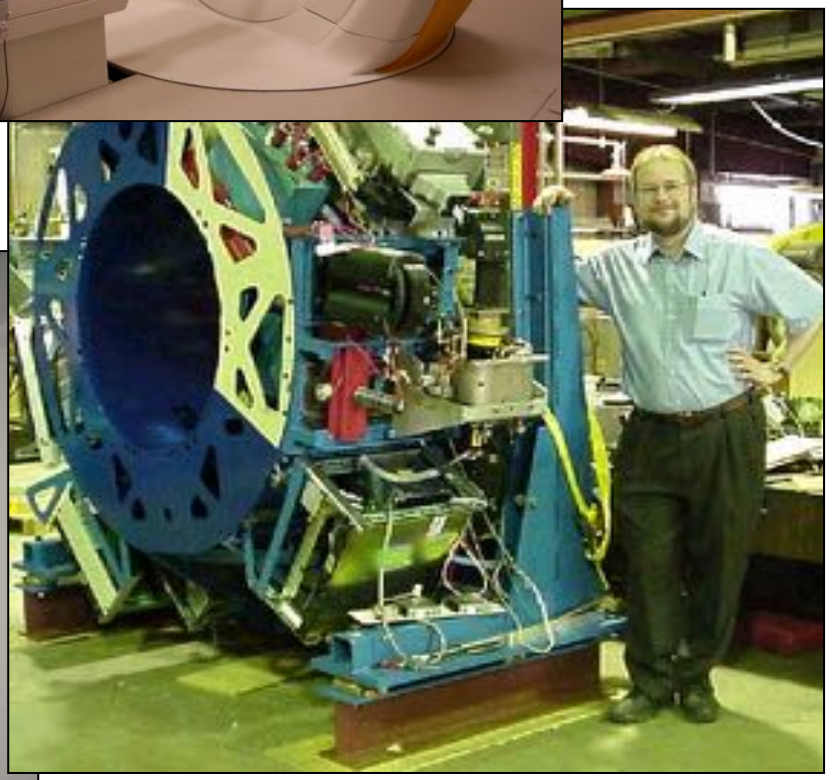


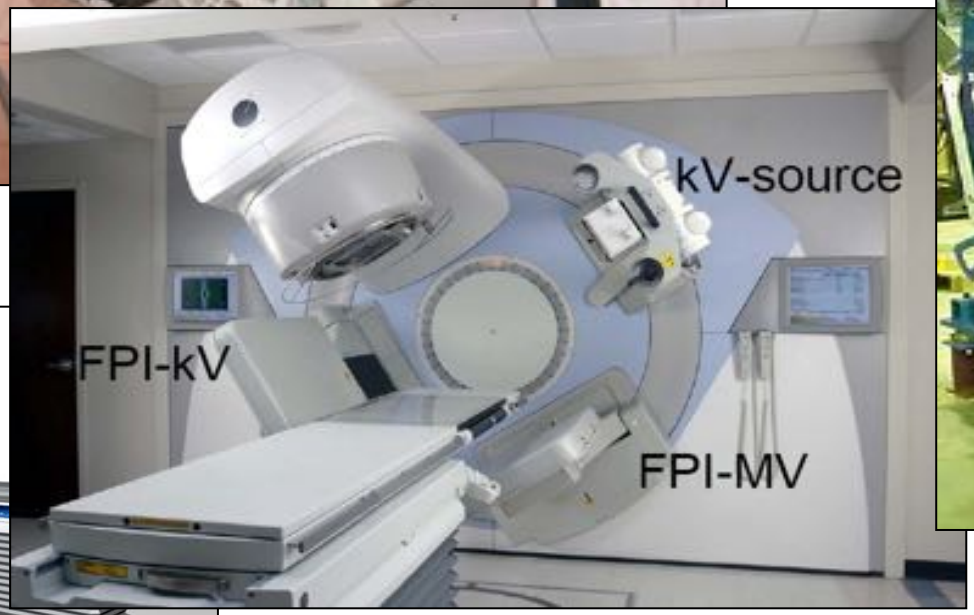


On board volumetric imaging

- So, what can we do with volumetric imaging?

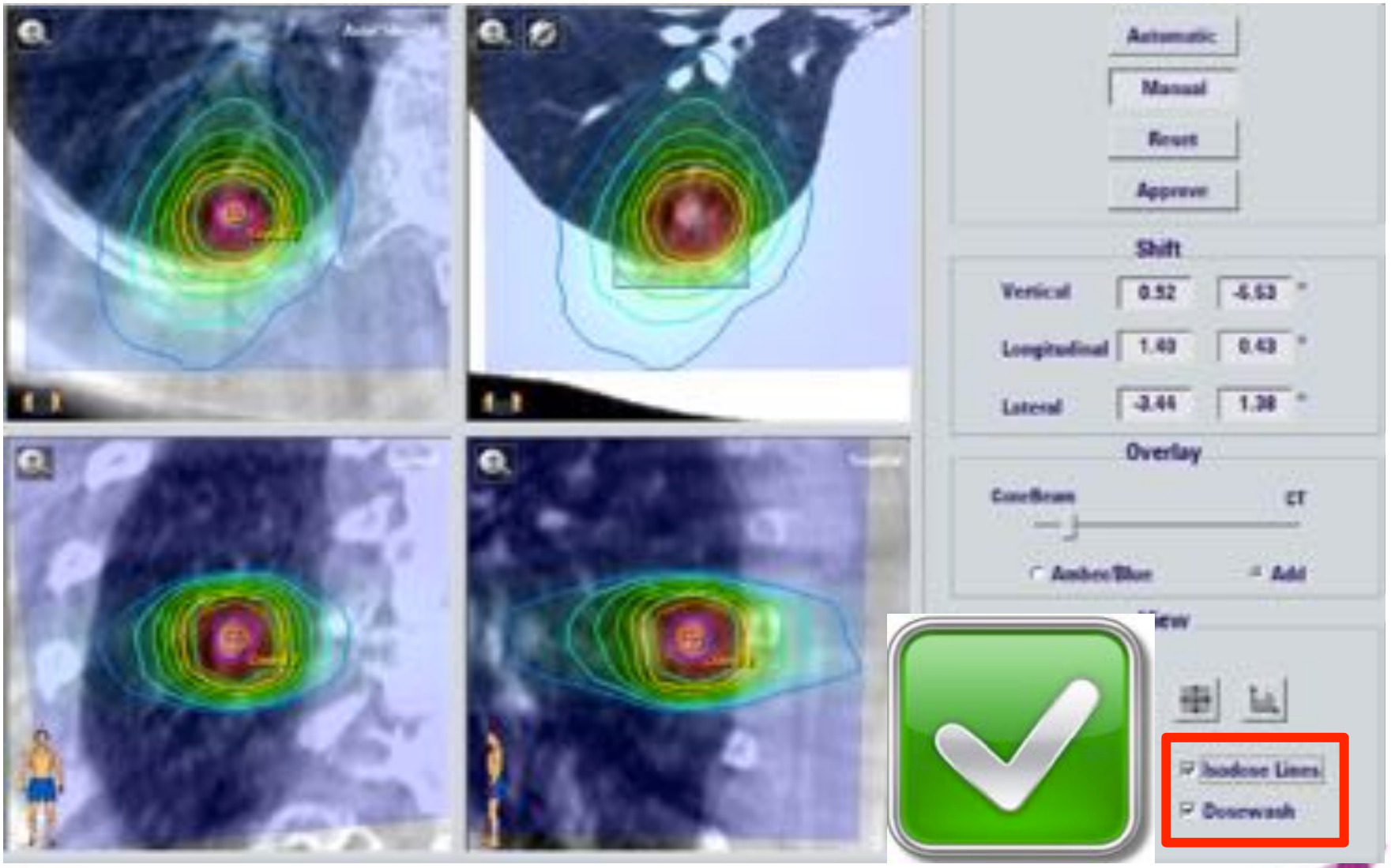
On board volumetric imaging



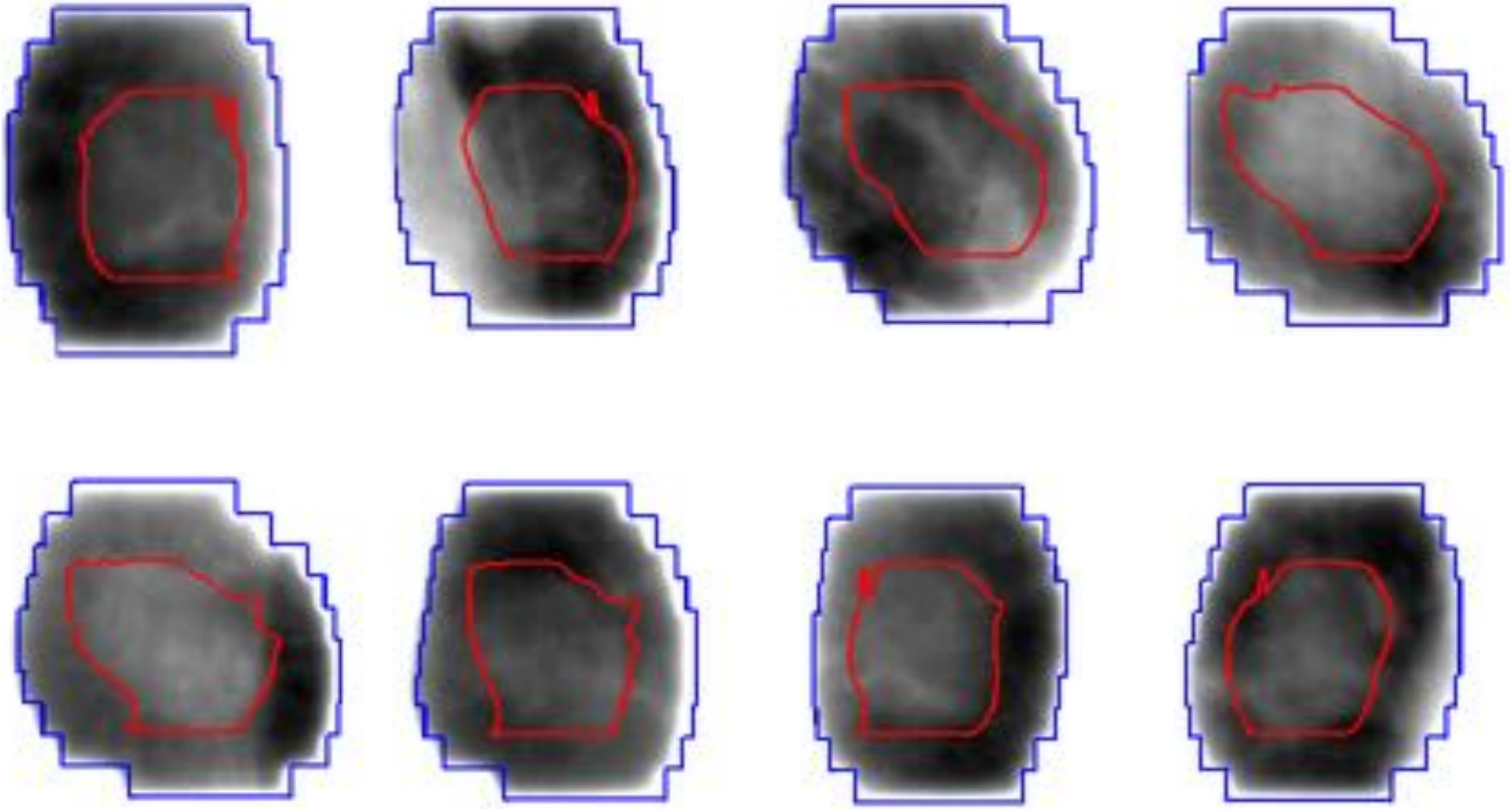


Motion compensation techniques

Registration of blurred target from CBCT with ITV/PTV

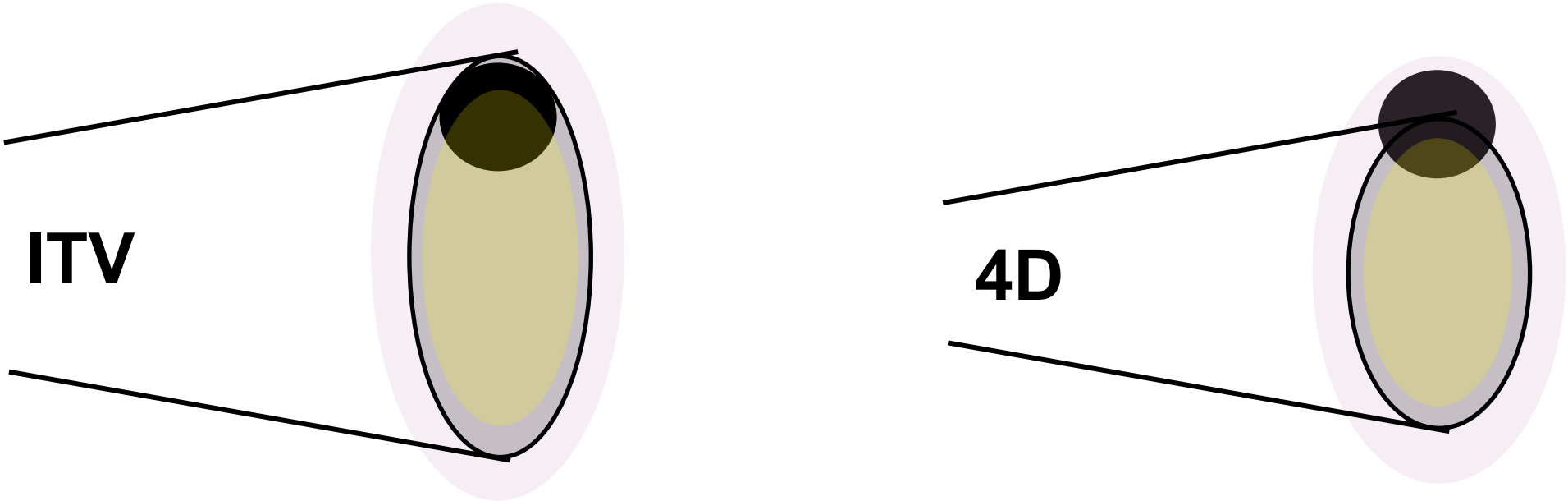


Motion compensation techniques



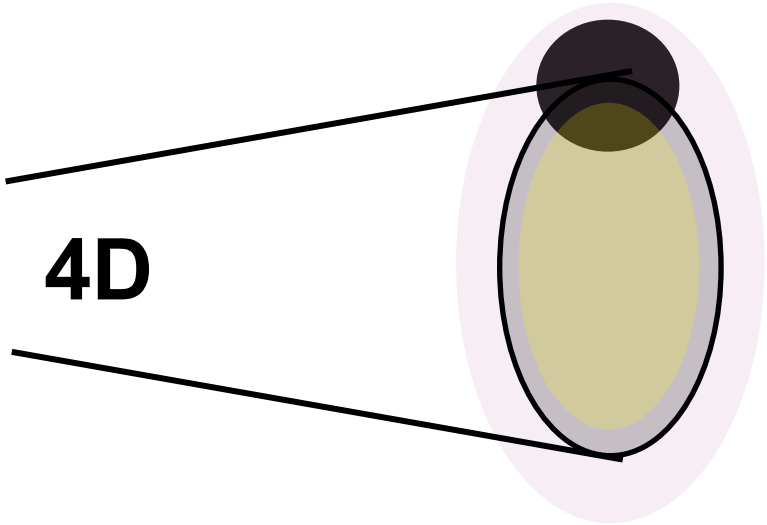
ITV MLC

Motion compensation techniques



Courtesy Guckenberger *et al*

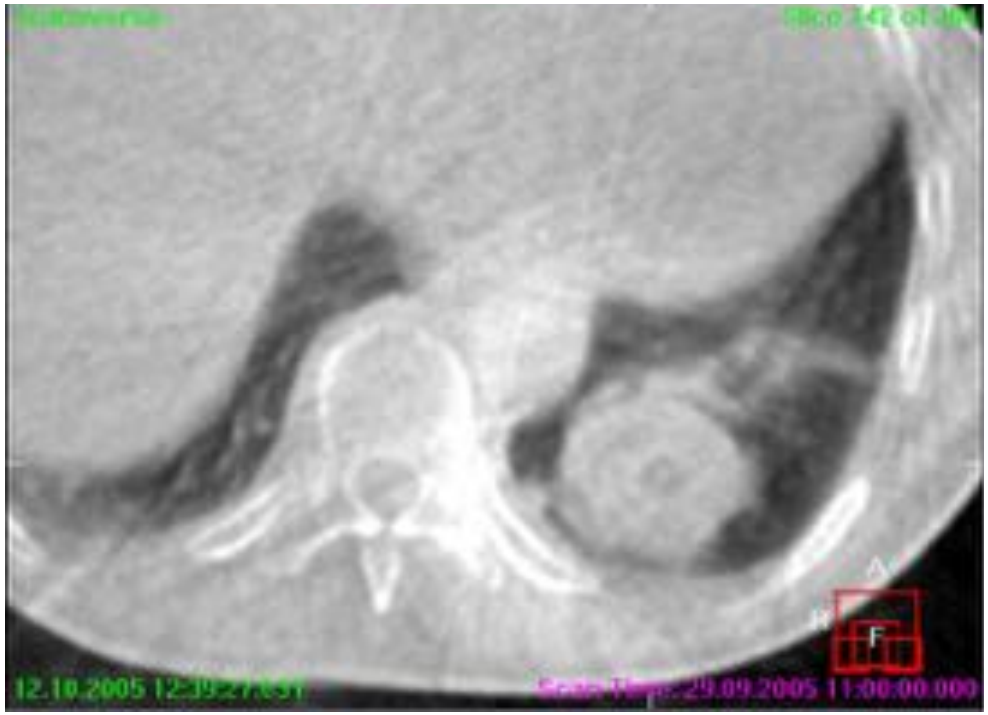
Motion compensation techniques



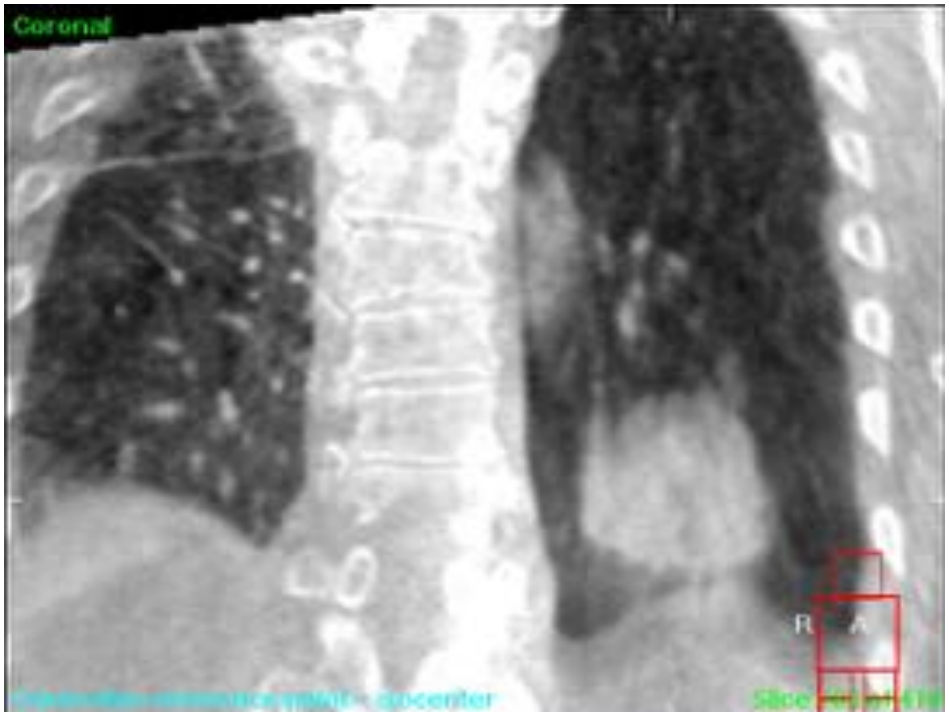
- The tumour is ~10% of the time at 50% of the dose
- This only accounts for about 5% underdose
- Even with large amplitudes, the margin needs not to be large.
- Mid-ventilation or Mid-position approach

- 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



Lower lobe tumor
with large motion amplitude



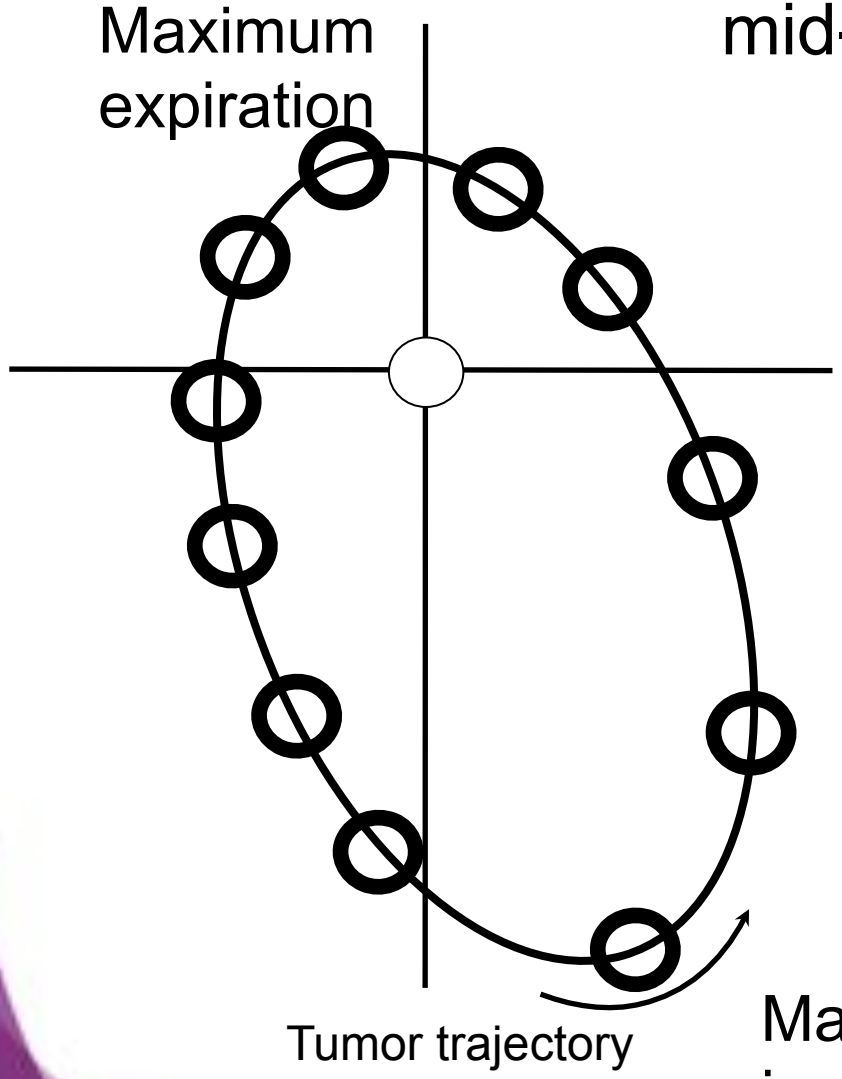
Blurred target because of
long image acquisition time

Integration of breathing motion in CBCT-based IGRT is required: 4D-CBCT

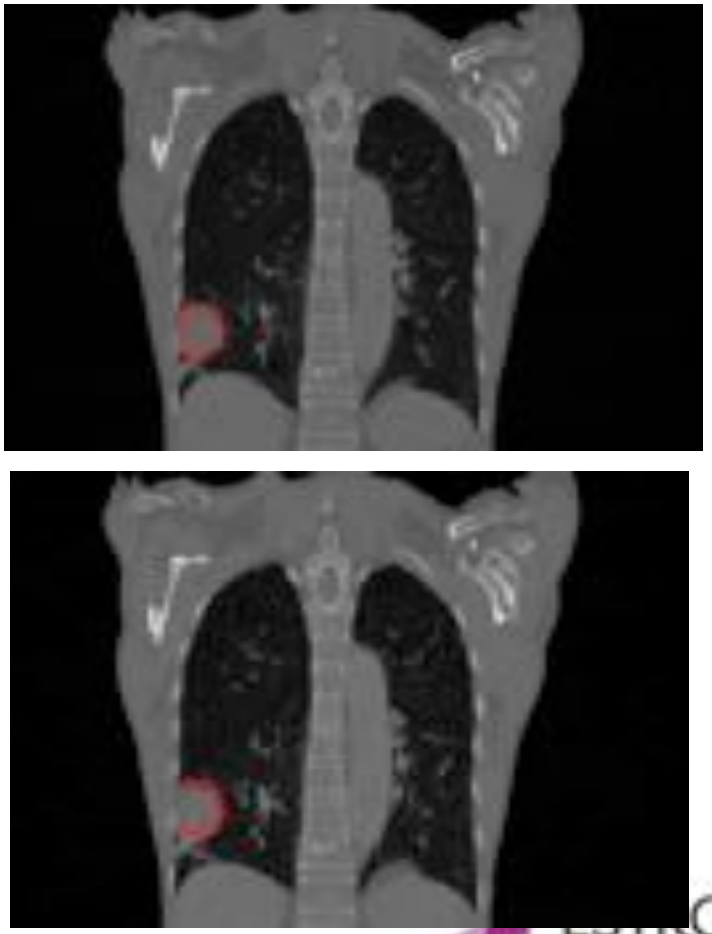
Courtesy Guckenberger *et al*

Motion encompassing techniques

Geometrically most representative 3D scan:
mid-ventilation



Aided by 4D CBCT



Courtesy J-J Sonke

Motion compensation techniques

Treatment planning:
Reference Image

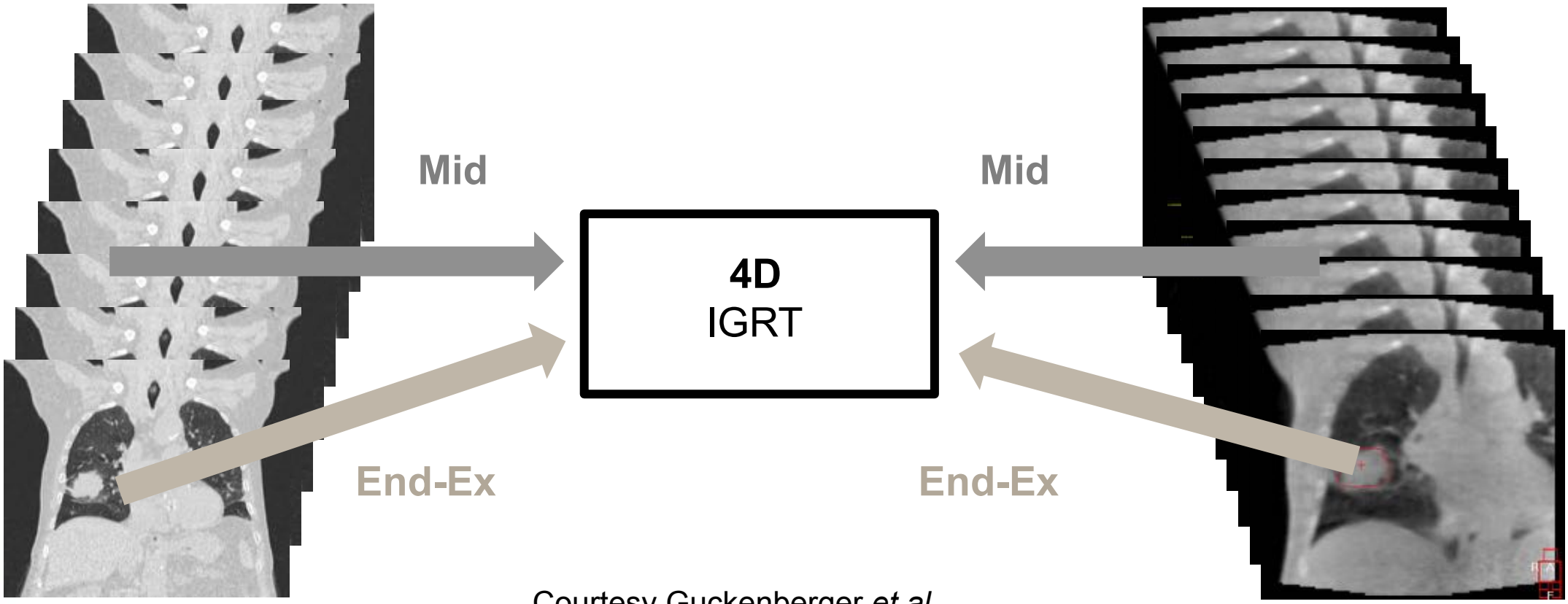
Treatment delivery:
Verification Image

Courtesy Guckenberger *et al*

Motion compensation techniques

Treatment planning:
Reference Image

Treatment delivery:
Verification Image

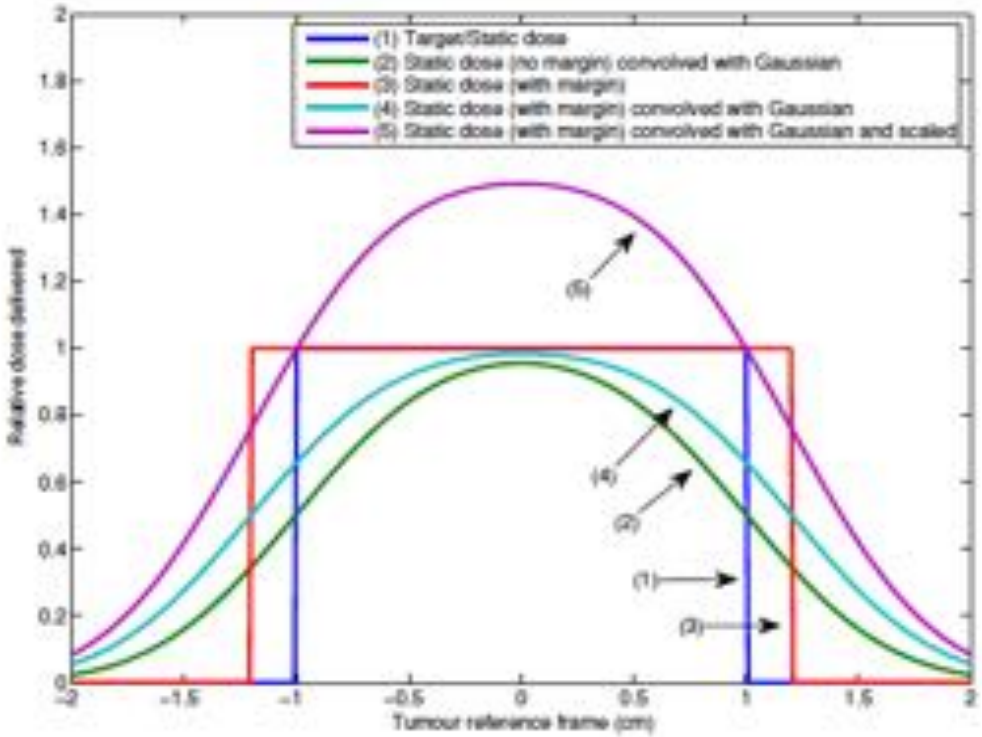


Courtesy Guckenberger *et al*

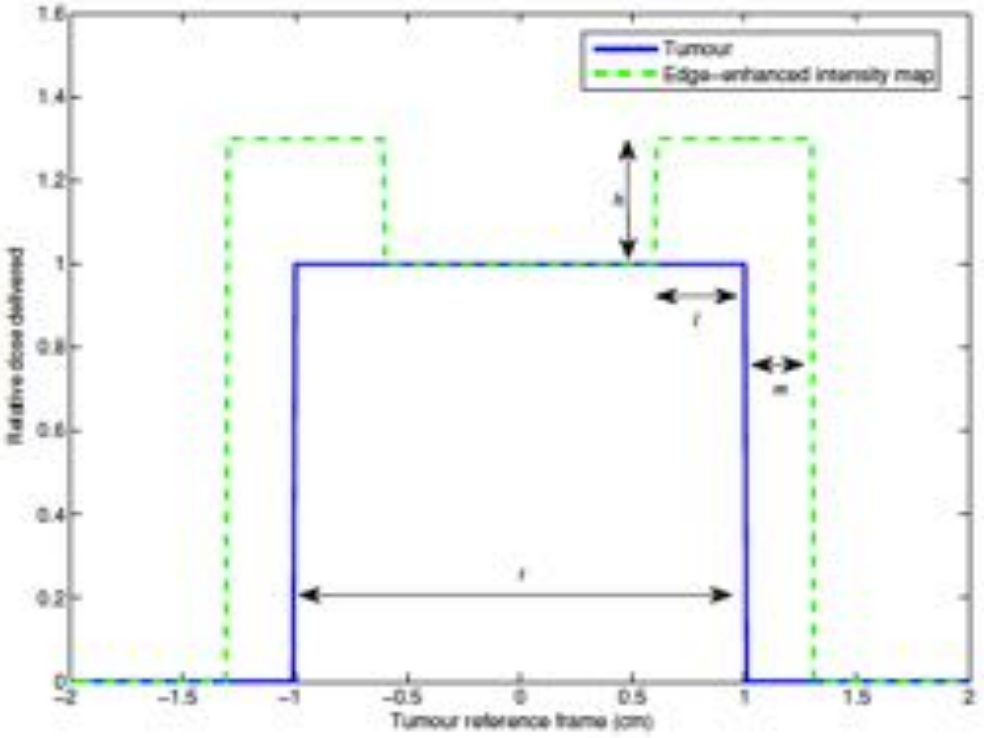
4D CBCT: Registration of corresponding phases

Motion compensation techniques

- Margins versus edge enhancement to compensate for motion blurring in IMRT?



Chan, Bortfeld *et al* PMB 2010

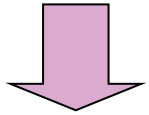


Motion compensation techniques

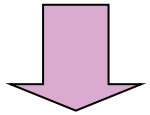
- Margins versus edge enhancement to compensate for motion blurring in IMRT?
- Using margins:
  - Tumor size / SD of tumor motion < 2
    - Optimal intensity map WITHOUT MARGIN, only pure intensity scaling to compensate for blurring created by motion
  - Tumor size / SD of tumor motion > 2
    - Optimal intensity map by combining margin and intensity scaling
- Using edge enhancement
  - Tumor size / SD of tumor motion < 2
    - Again only intensity scaling required
  - Tumor size / SD of tumor motion > 2
    - Edge enhancement is the preferred solution.

Motion compensation techniques

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

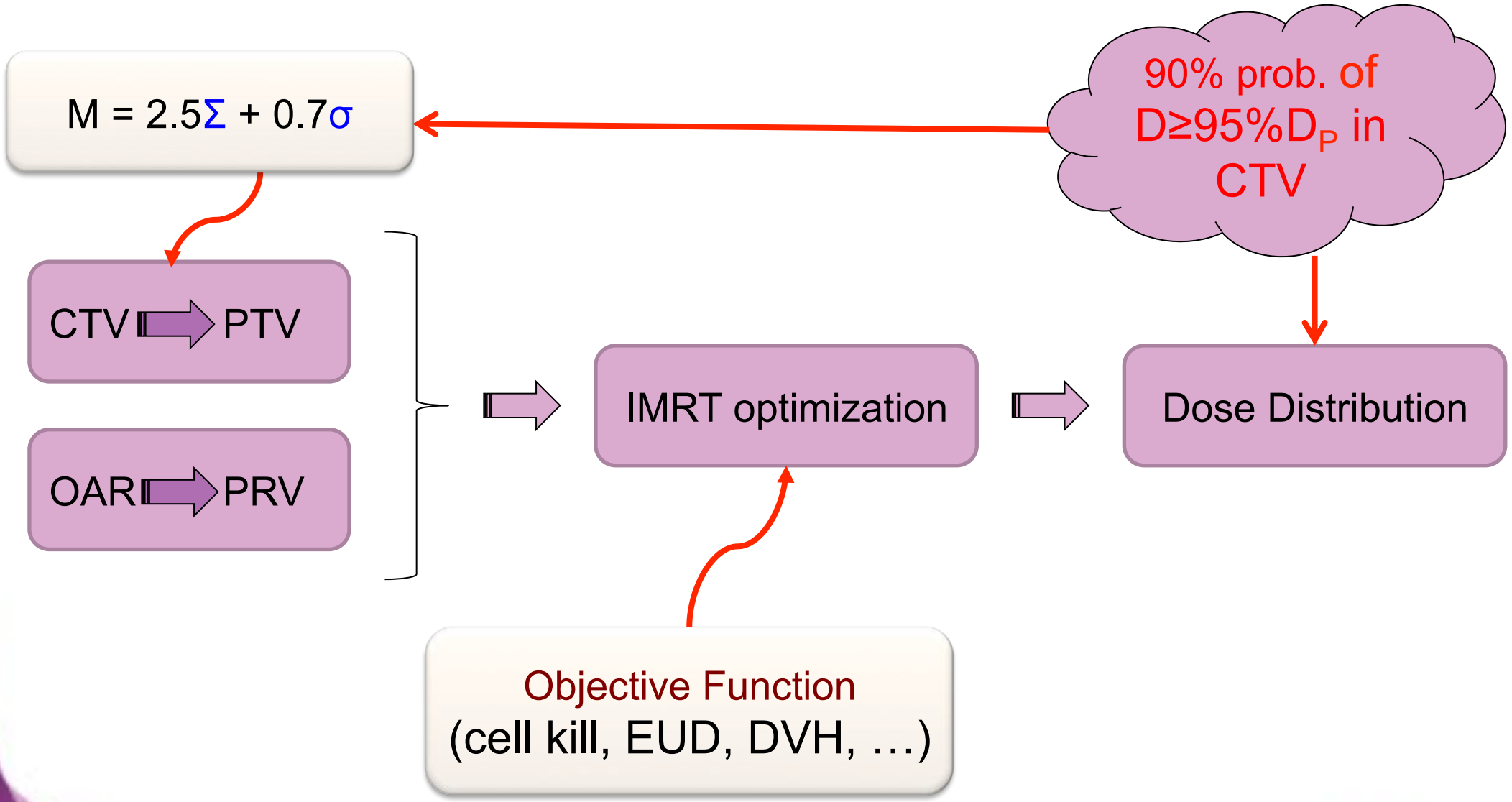


Mathematical model to describe organ motion induced geometric changes
Probability distribution of patient geometries

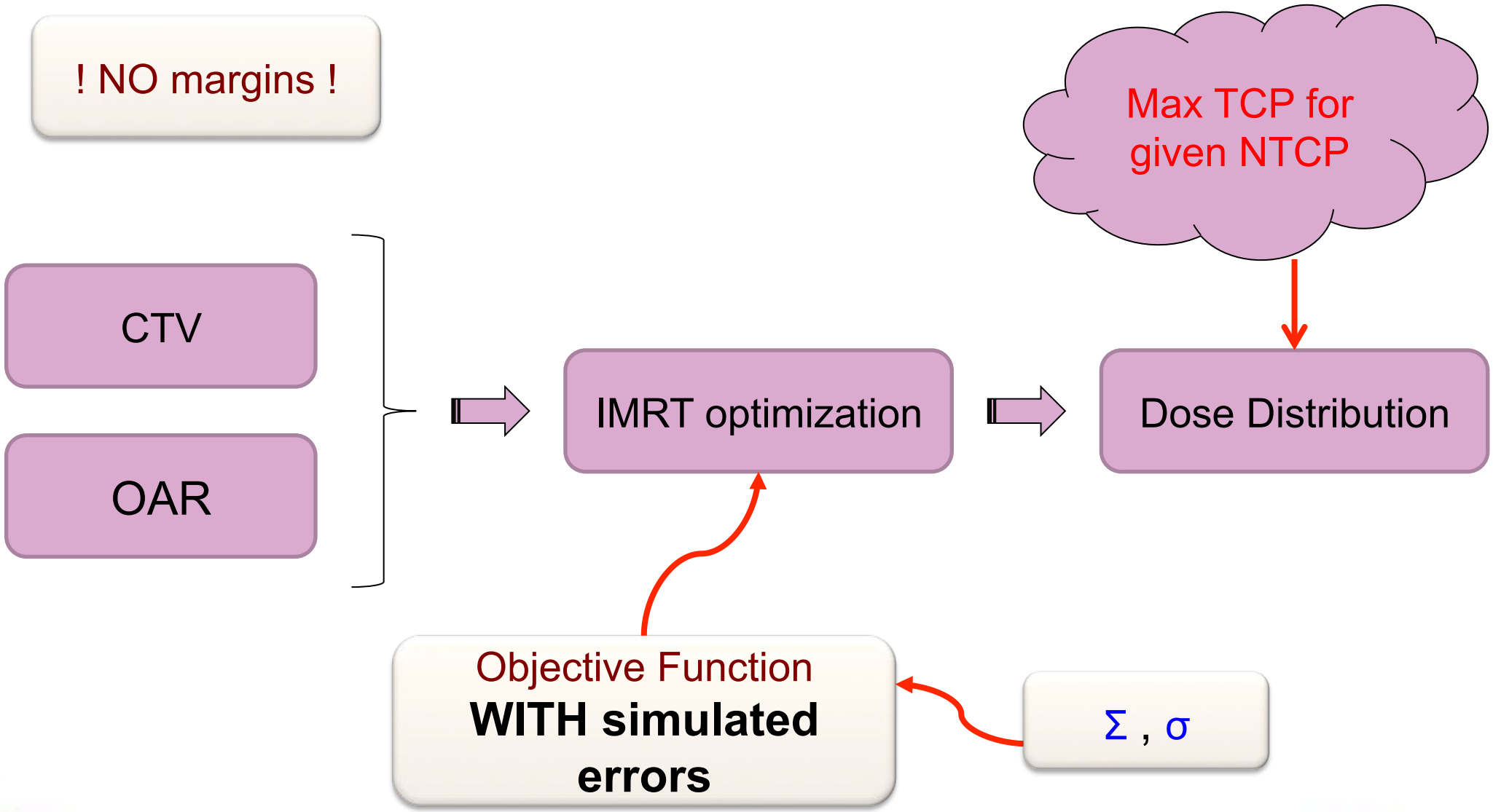


Probabilistic IMRT optimization

“Conventional” IMRT planning

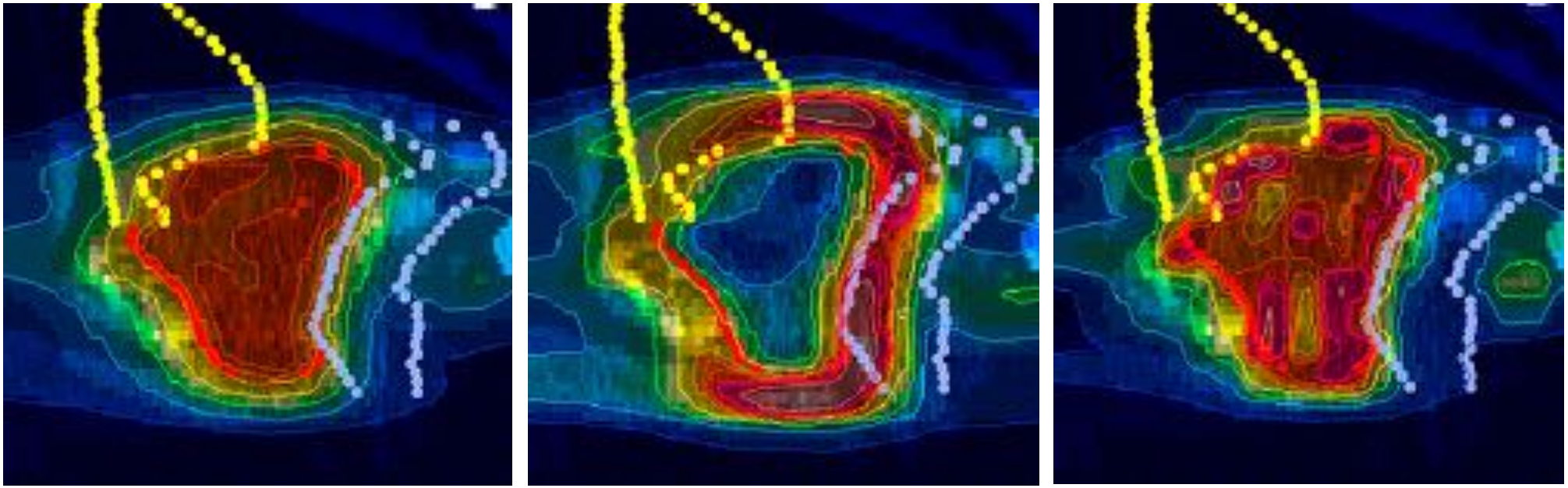


“Probabilistic” IMRT planning



“Probabilistic” IMRT planning

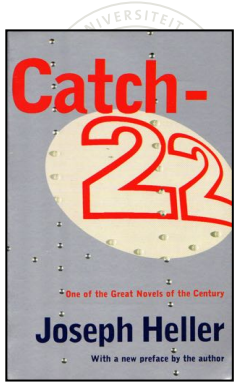
Expectation value | Dose variance per voxel | Risk, ‘static’ dose



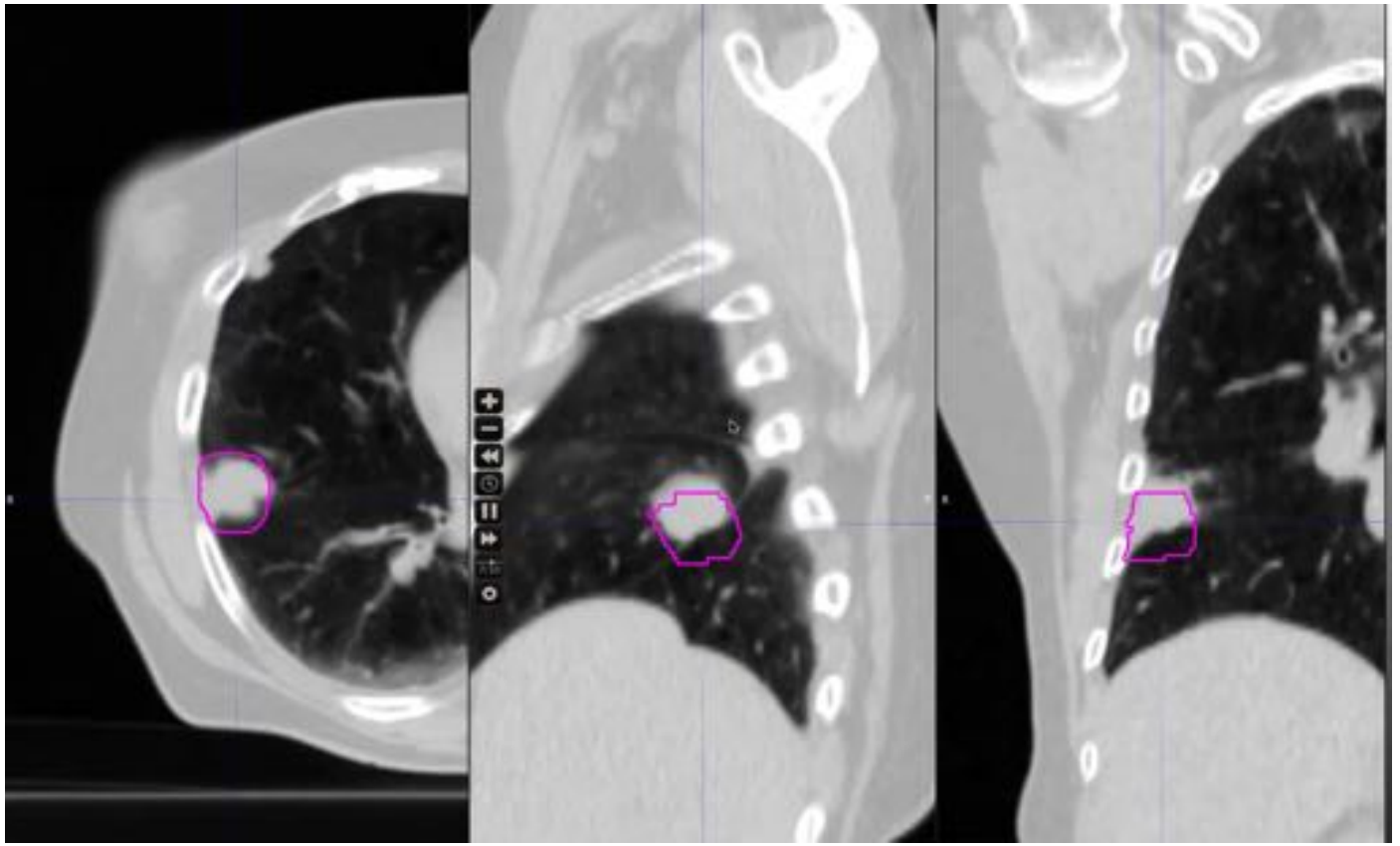
Courtesy U. Oelfke

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

Where's the catch?

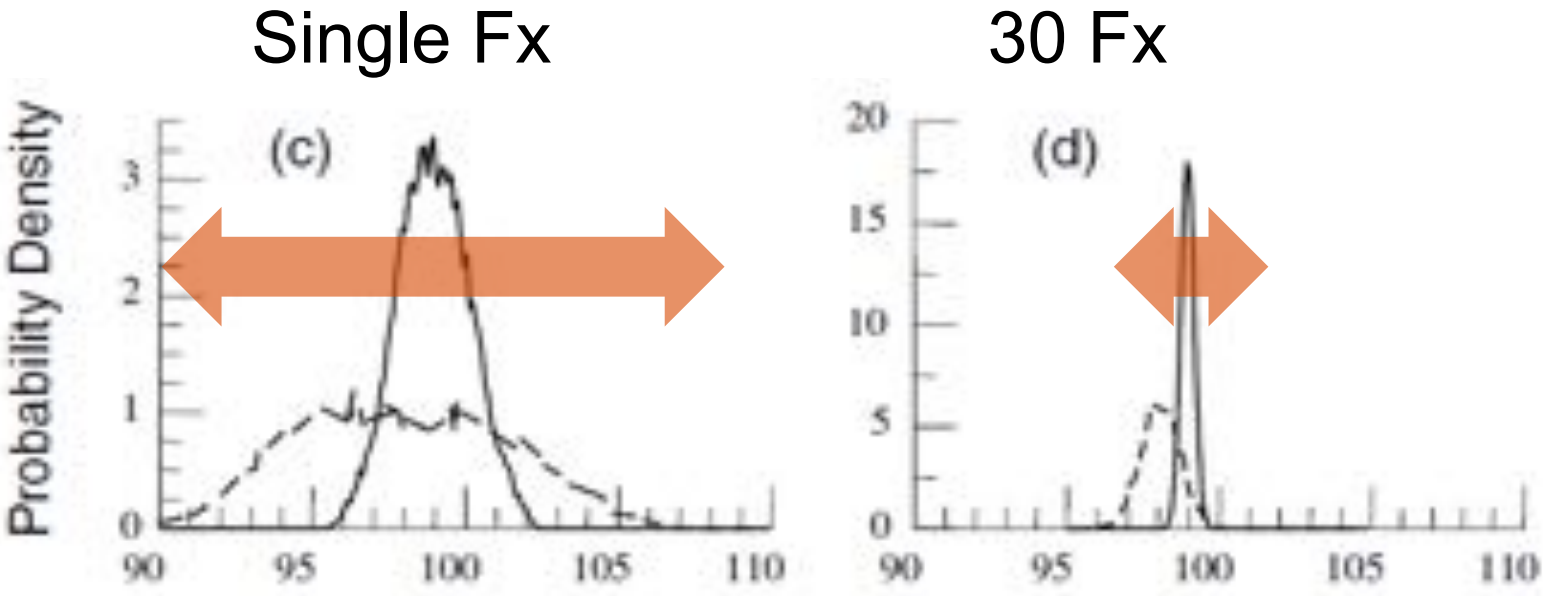


- The so-called 4D CT is nothing but a **continuous movie-loop** and might NOT be representative for the breathing pattern at the time of treatment!!!!



Why motion management in IMRT?

- 1D quantification of the interplay effect in pulmonary IMRT

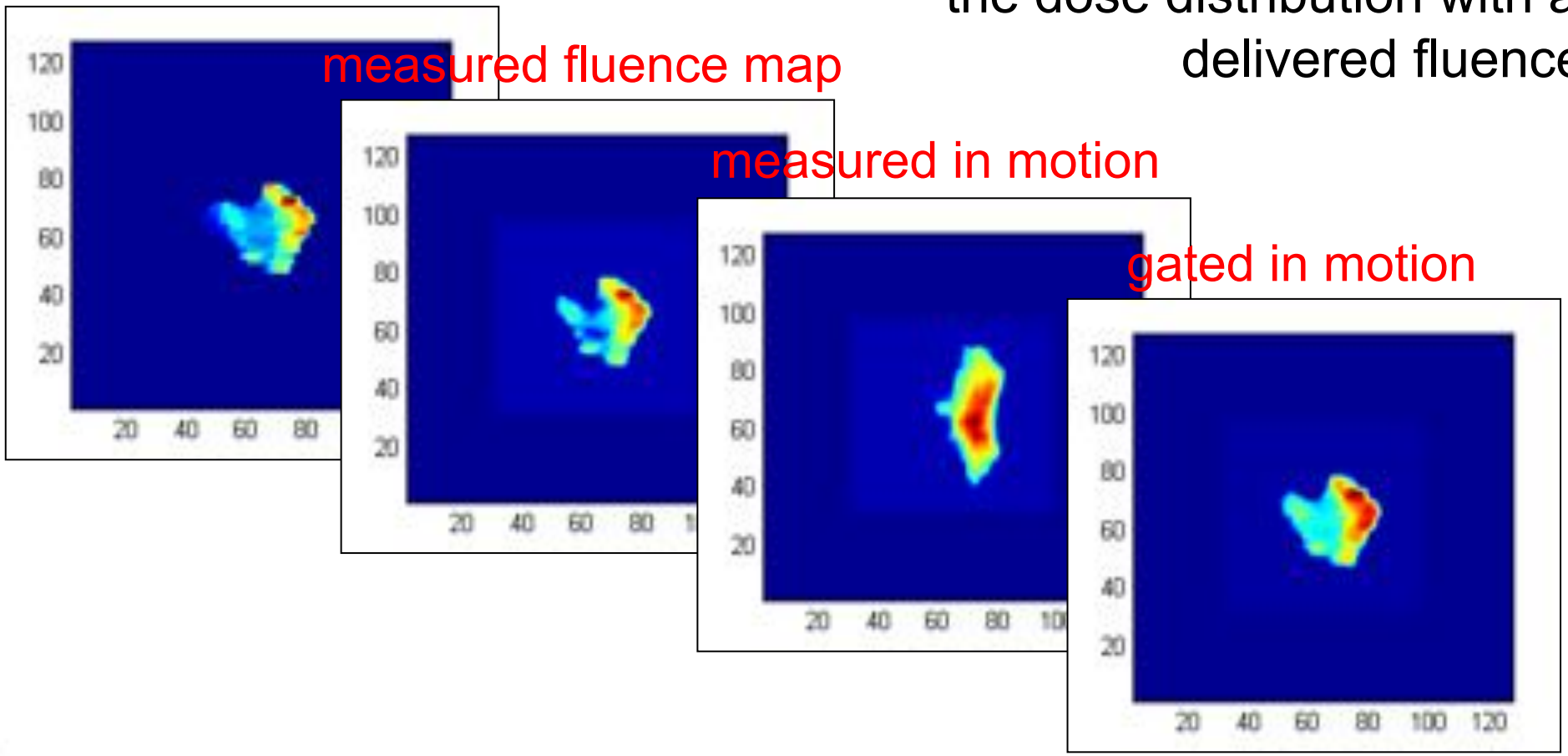


Bortfeld *et al* PMB 2002

- Single fraction: dose variations up to 20%
- 30 fractions: dose variation < 2% … negligible …

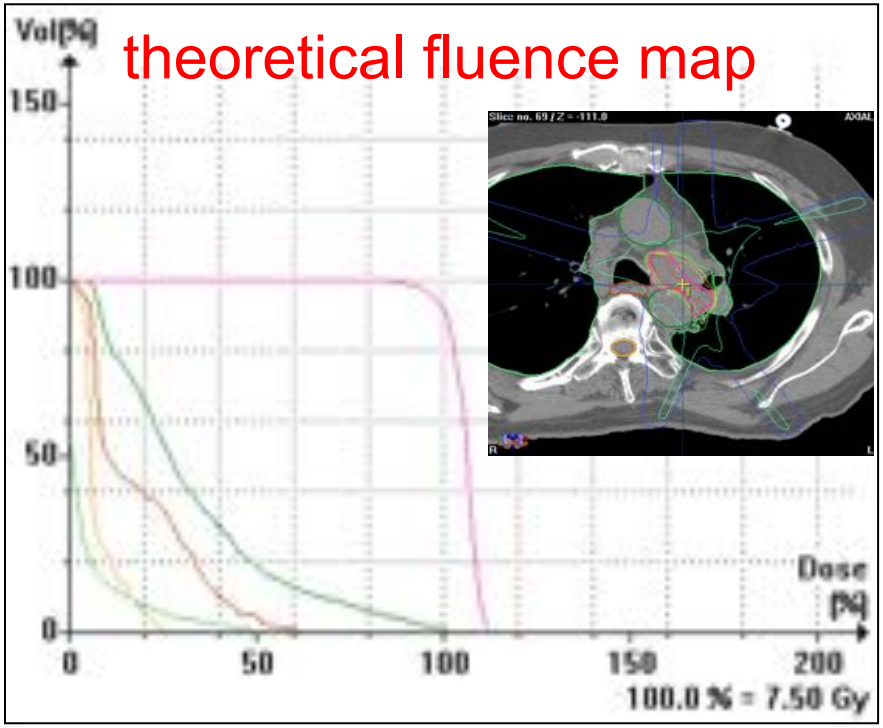
Why motion management in IMRT?

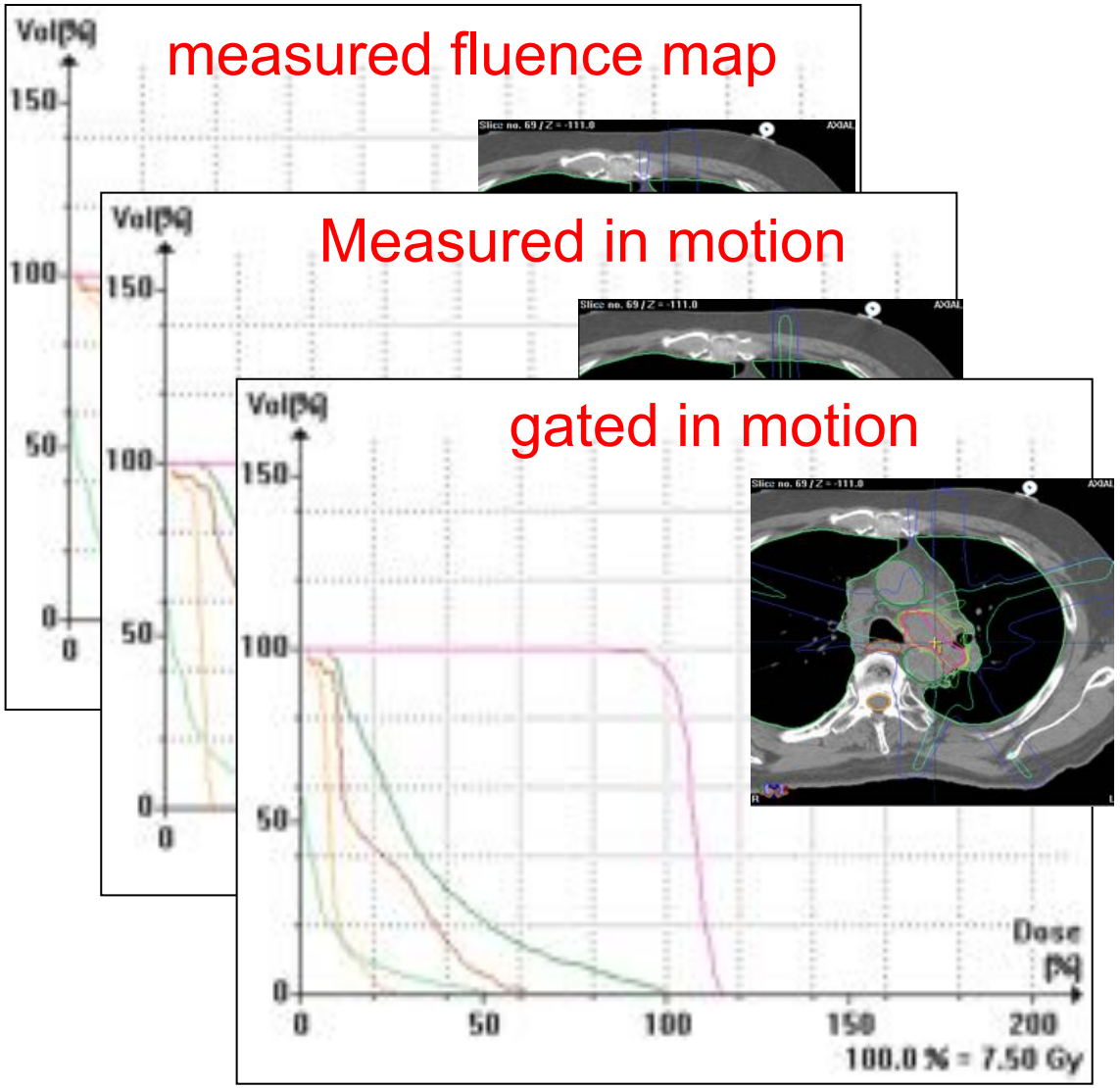
Importing theoretical and measured fluence maps into Treatment Planning System to re-calculate the dose distribution with actually delivered fluence maps



Verellen *et al* Radiother Oncol 2006

Why motion management in IMRT?



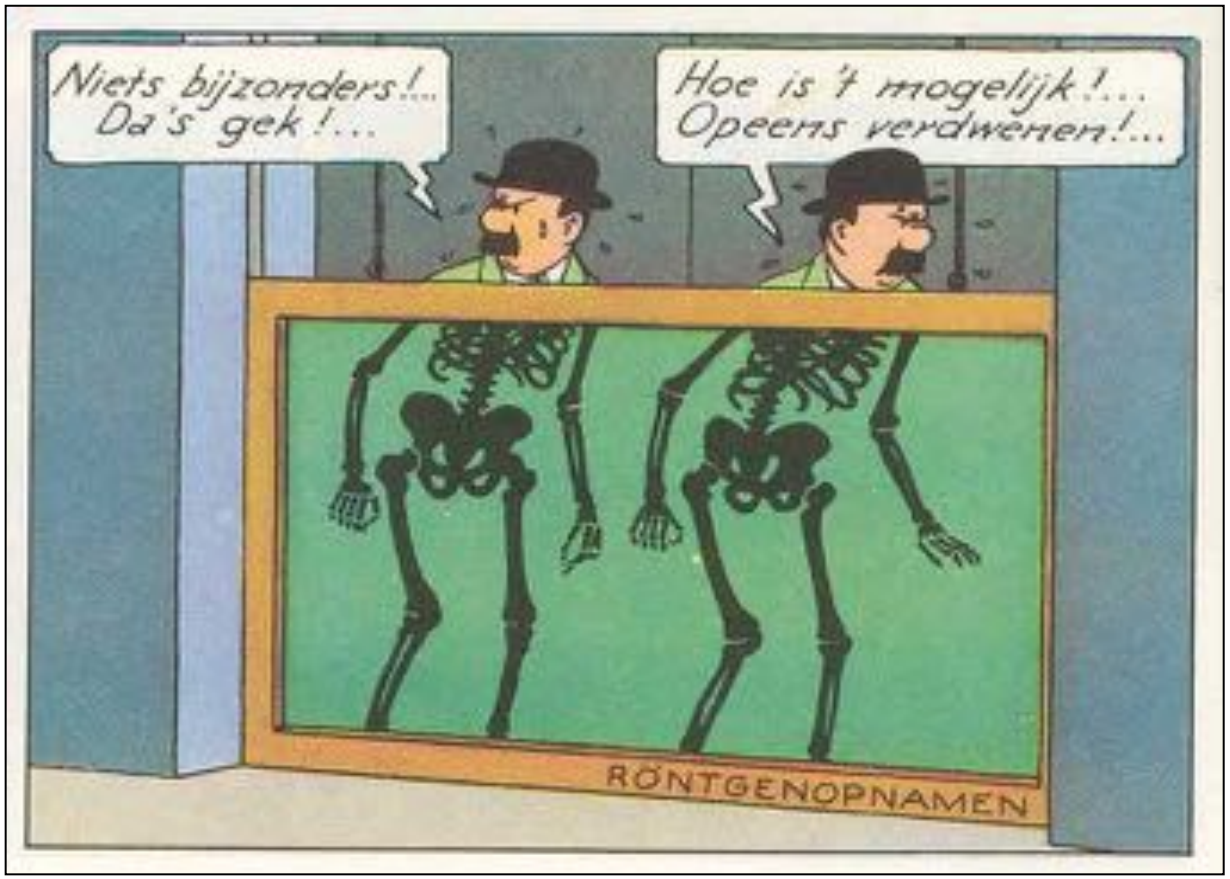


Verellen *et al* Radiother Oncol 2006

Motion management: Active

Planar imaging

- So, what can we do with planar imaging?



Motion management: Active

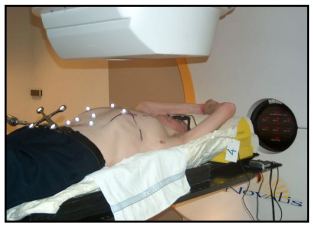
Courtesy Guckenberger *et al*

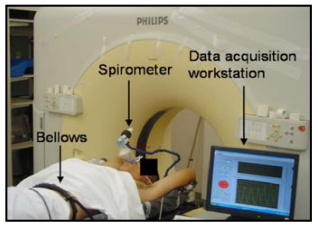
Breathing synchronization

- Requires monitoring respiration (IR markers, spirometers, …)
- Requires correlating external breathing signal with internal tumor motion
- Requires prediction model to compensate for system latency
- Gating
  - *Inefficient use of duty cycle: trade-off between minimizing motion in the gate and beam-on time*
  - *Robust … less depending on 'predicting model'*
  - *Verification during treatment possible*
- Tracking
  - *Efficient use of duty cycle*
  - *Requires accurate 'prediction model' of breathing motion*
  - *Verification during treatment is possible with EPID (VERO)*

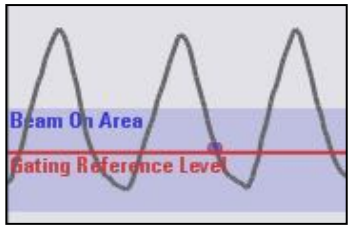
Breathing synchronization: Anticipating unpredictable motion …

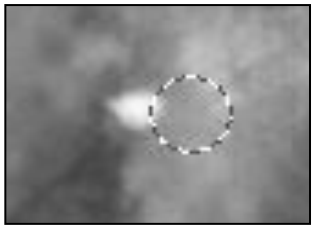
- Monitoring respiration:
  - Requires …



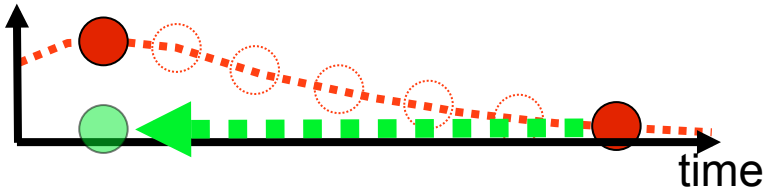


- Correlation model:
  - Requires "stable" correlation between internal and external motion

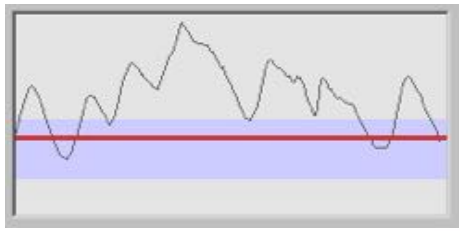




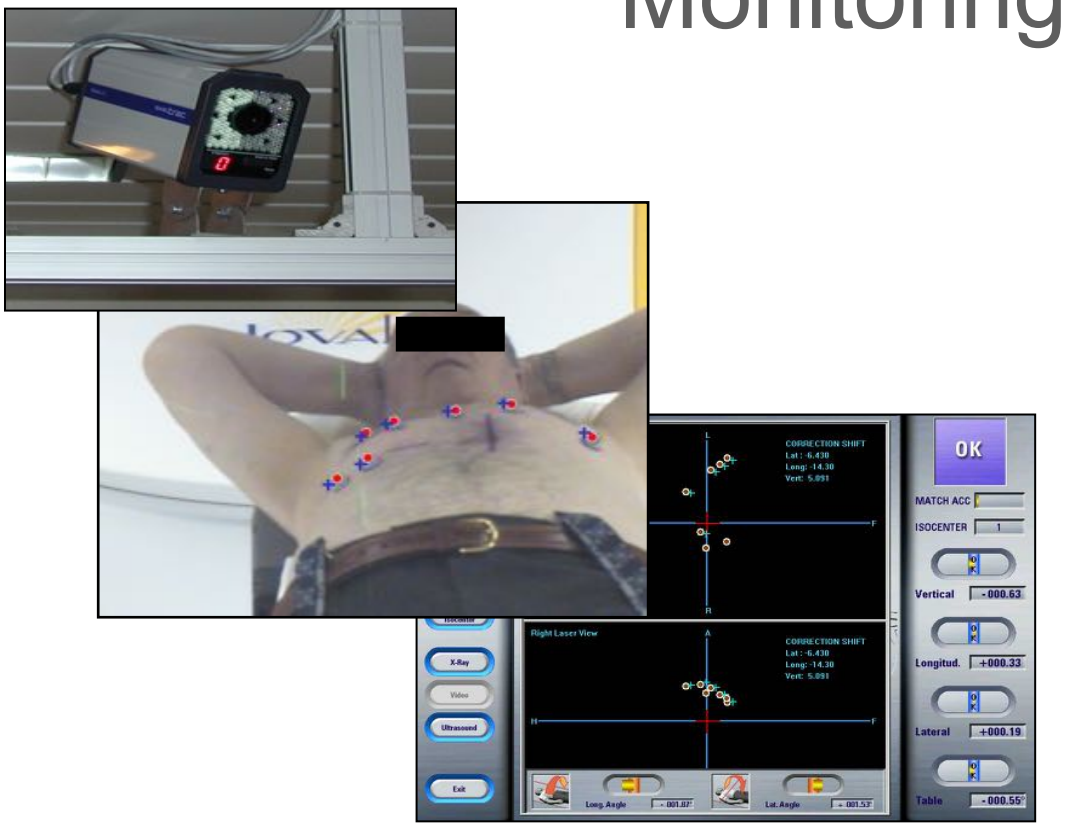
- Prediction model to compensate for system latency:
  - Requires "predictive" (i.e. periodic) motion

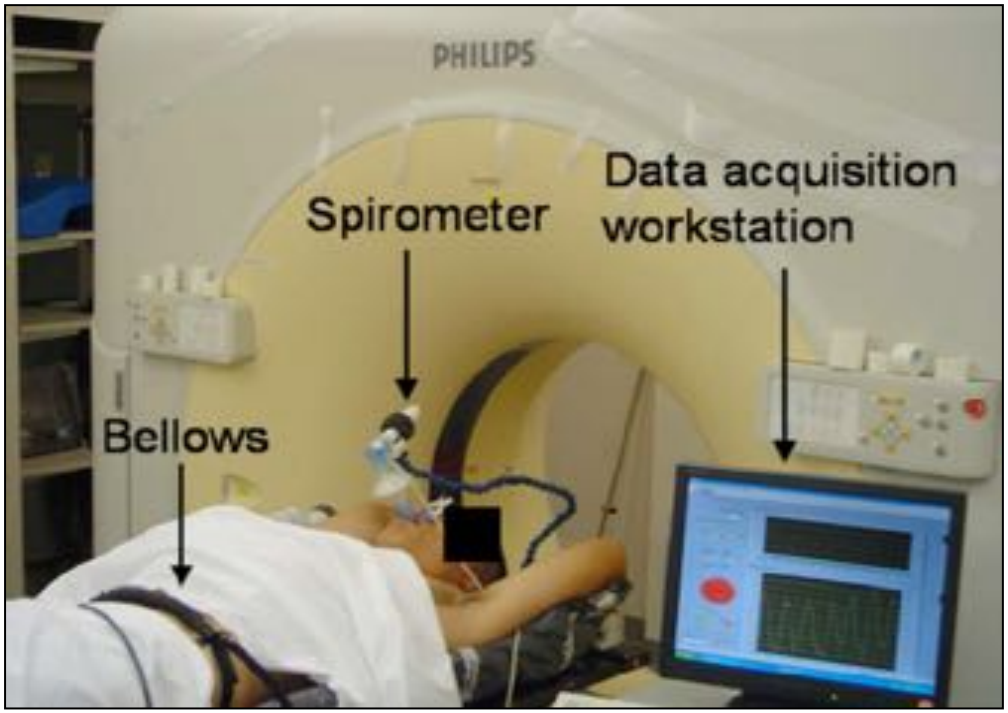


- Interface between machine and man …
  - By definition "unpredictable"?

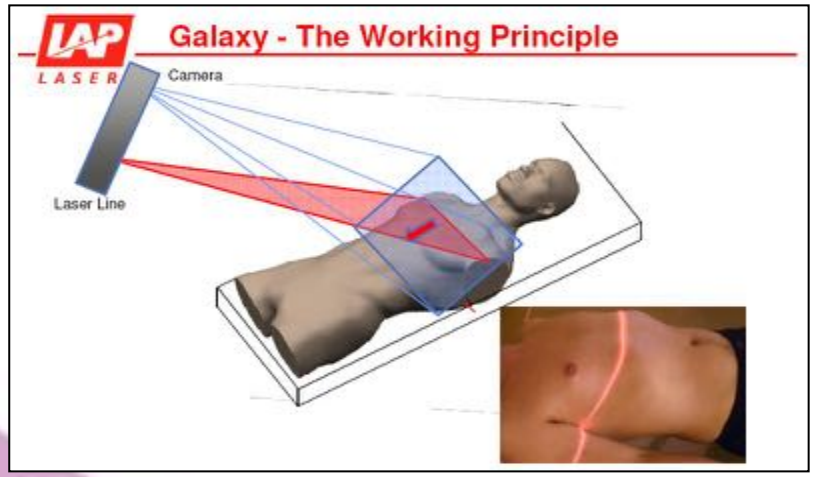


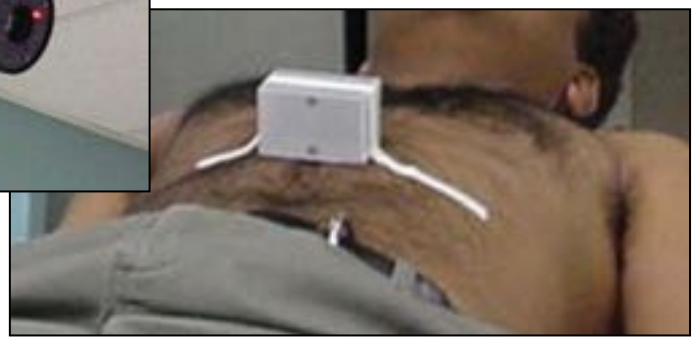
Monitoring respiration





Low *et al.*

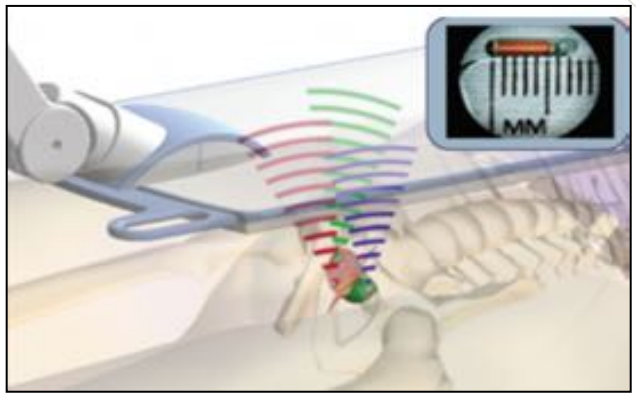




Keall *et al.*

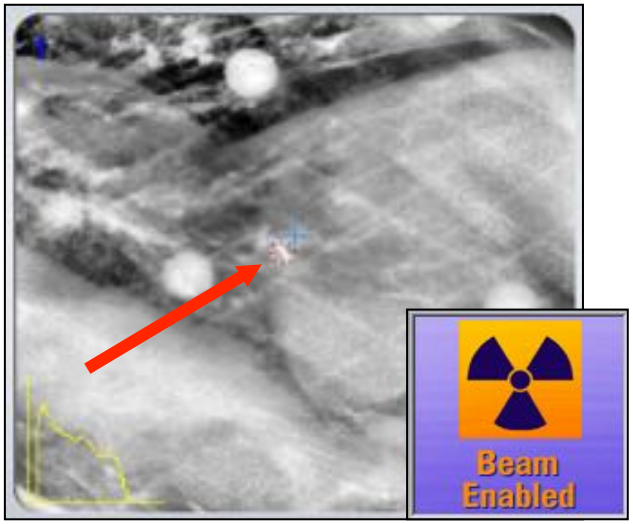
Correlating internal/external motion

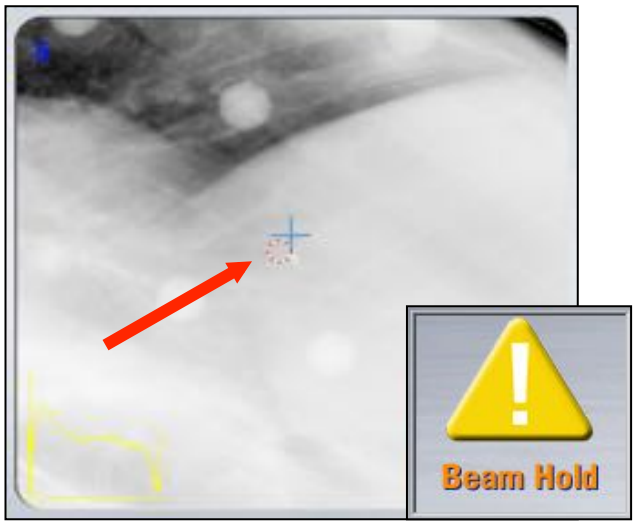
- Real-time tracking of internal marker or direct visualization of tumor



Courtesy Calypso Medical Technologies

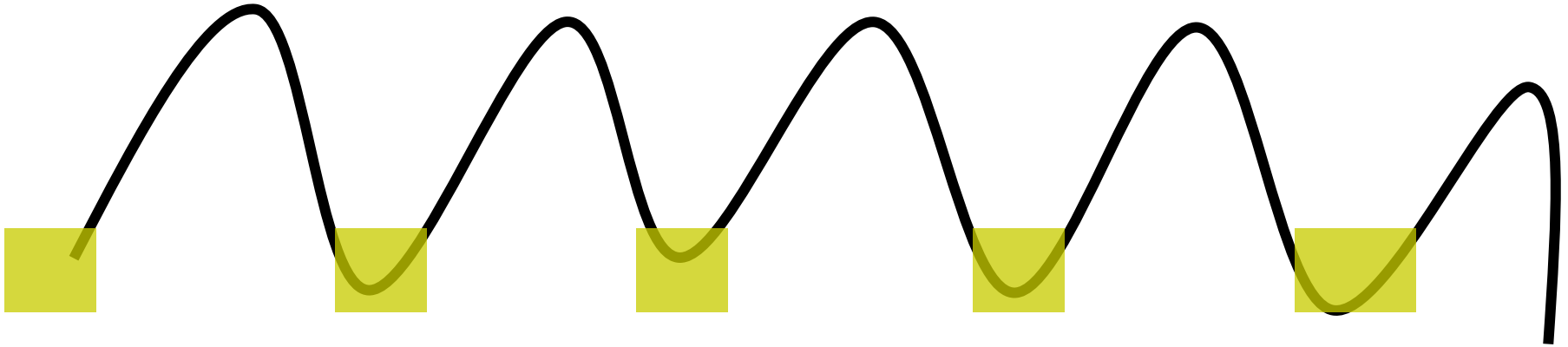
- Correlating external breathing signal with internal tumor motion
  - ➢ Using surrogates (implanted marker, diaphragm, …)



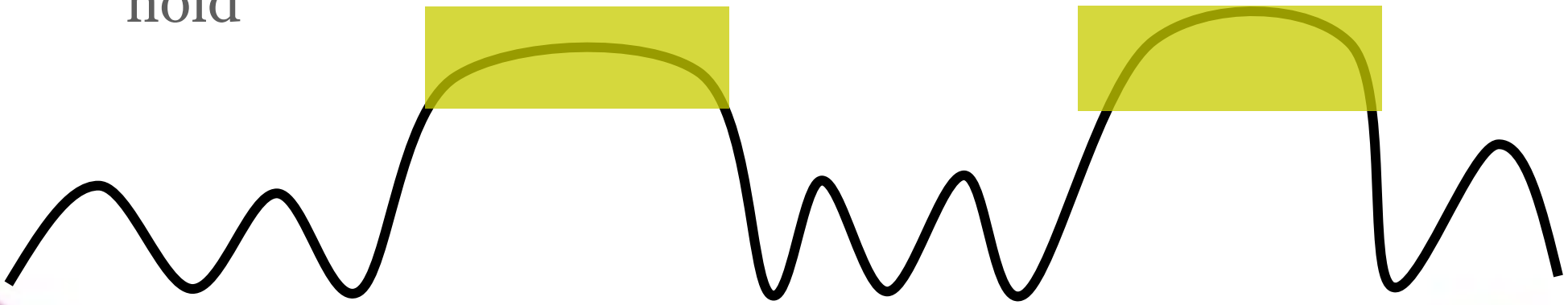


Gating: free breathing / breath hold

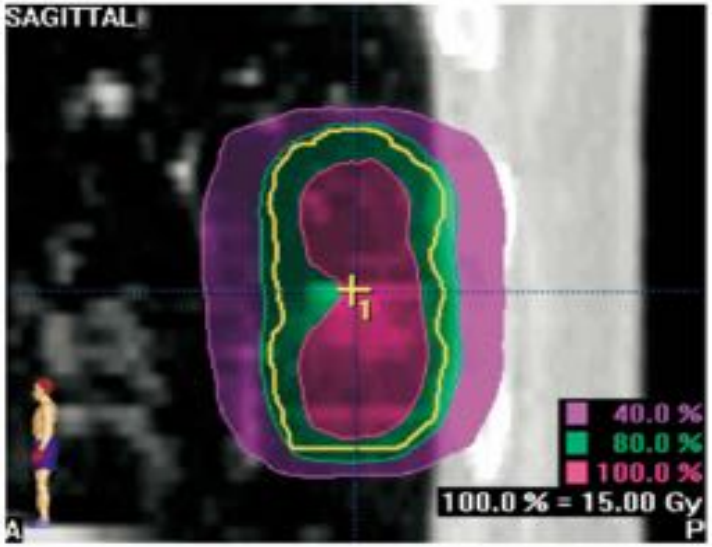
- Free breathing: Beam is switched on during 1 fraction of the breathing cycle

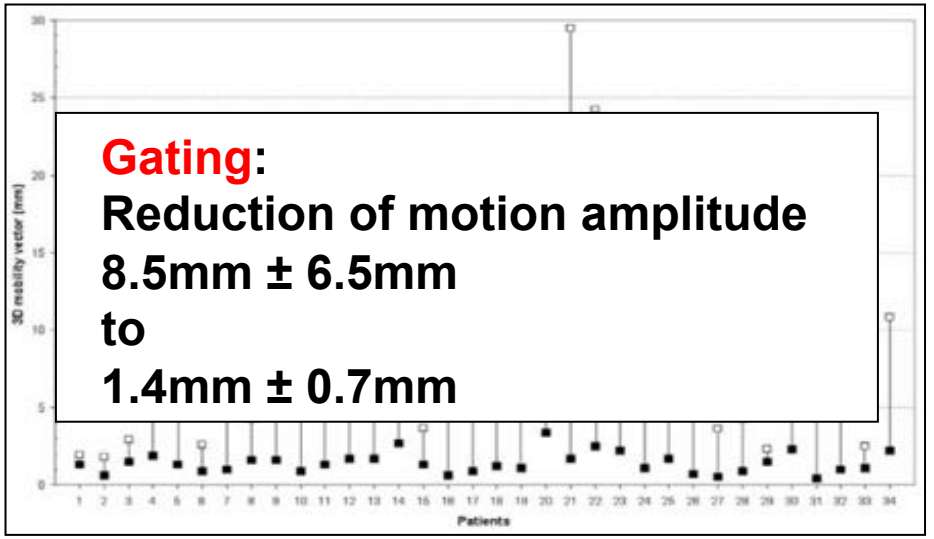


- Breath hold: Beam is switched on only during breath hold



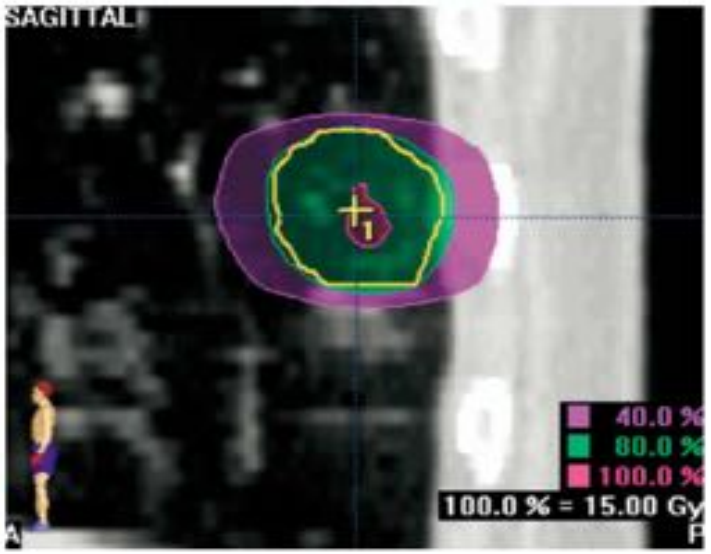
Gating: free breathing / breath hold

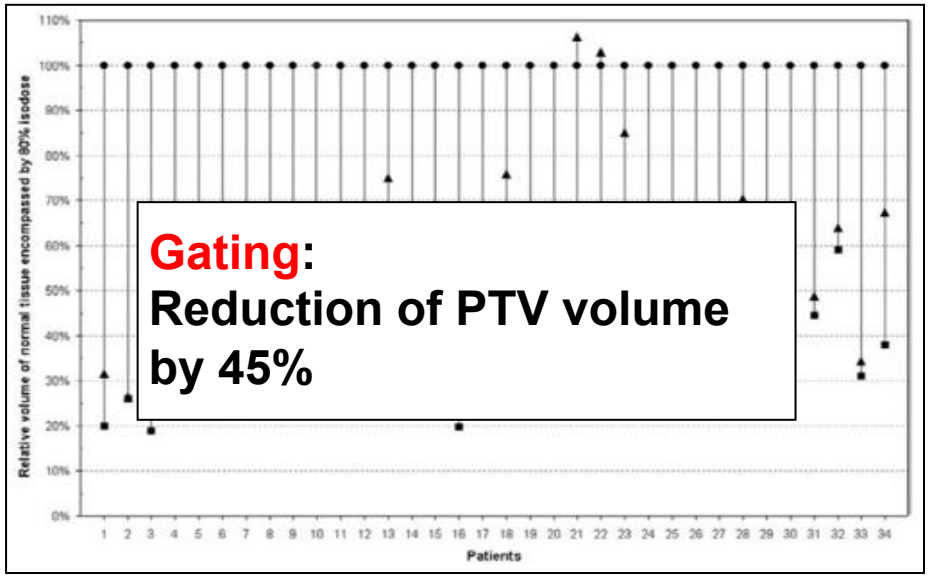




Gating:
Reduction of motion amplitude
8.5mm ± 6.5mm
to
1.4mm ± 0.7mm

Motion amplitude





Gating:
Reduction of PTV volume
by 45%

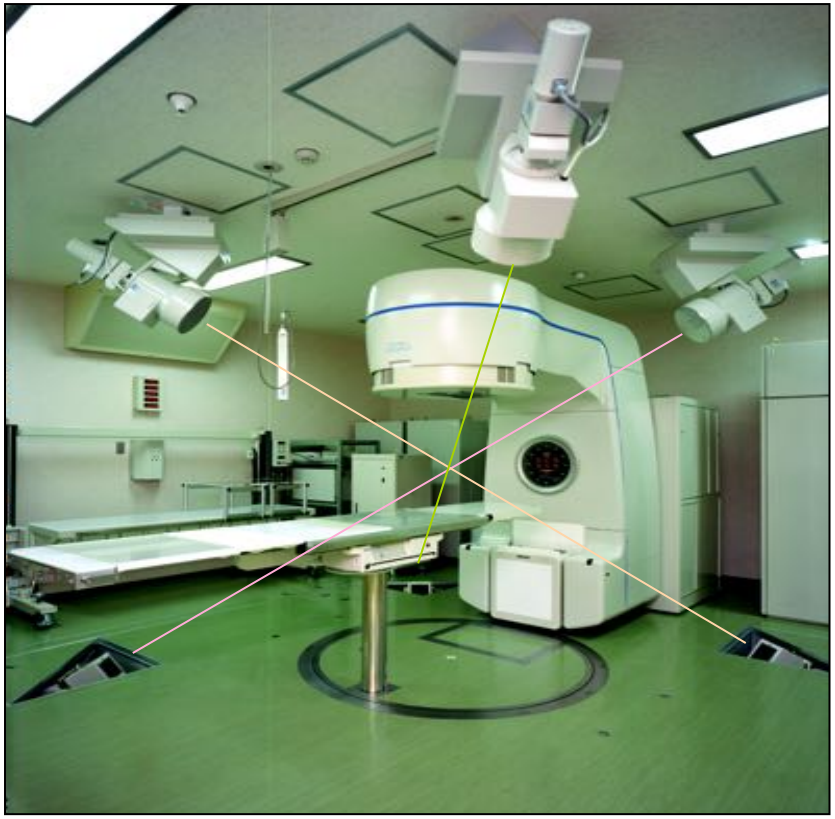
PTV volume

Duty cycle
30 % !

Underberg *et al* IJROBP 2005

1st and 2nd generation RTRT system

- RTRT system @ Hokkaido University



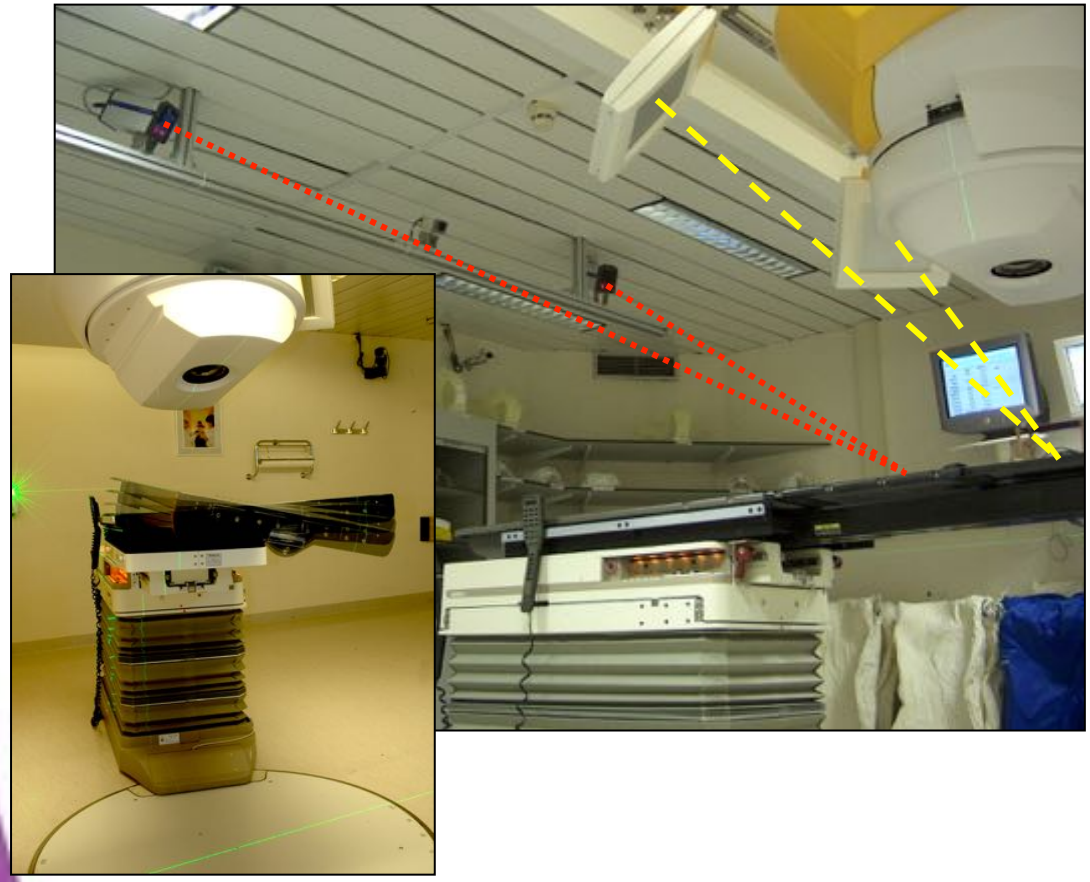
1st Gen: 1999 ~ 2010

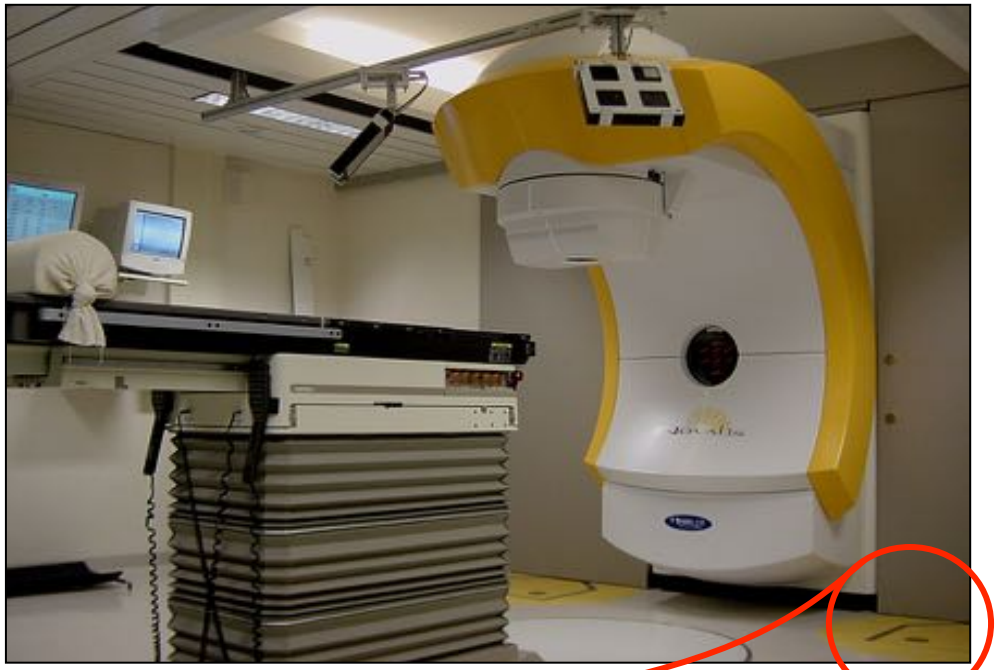
Shirato *et al.*

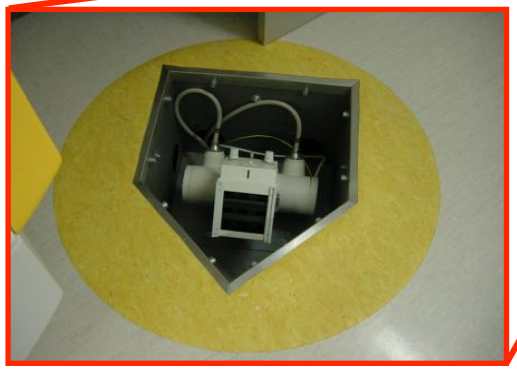
2nd Gen: 2004 ~

Gating: An example

The NOVALIS System





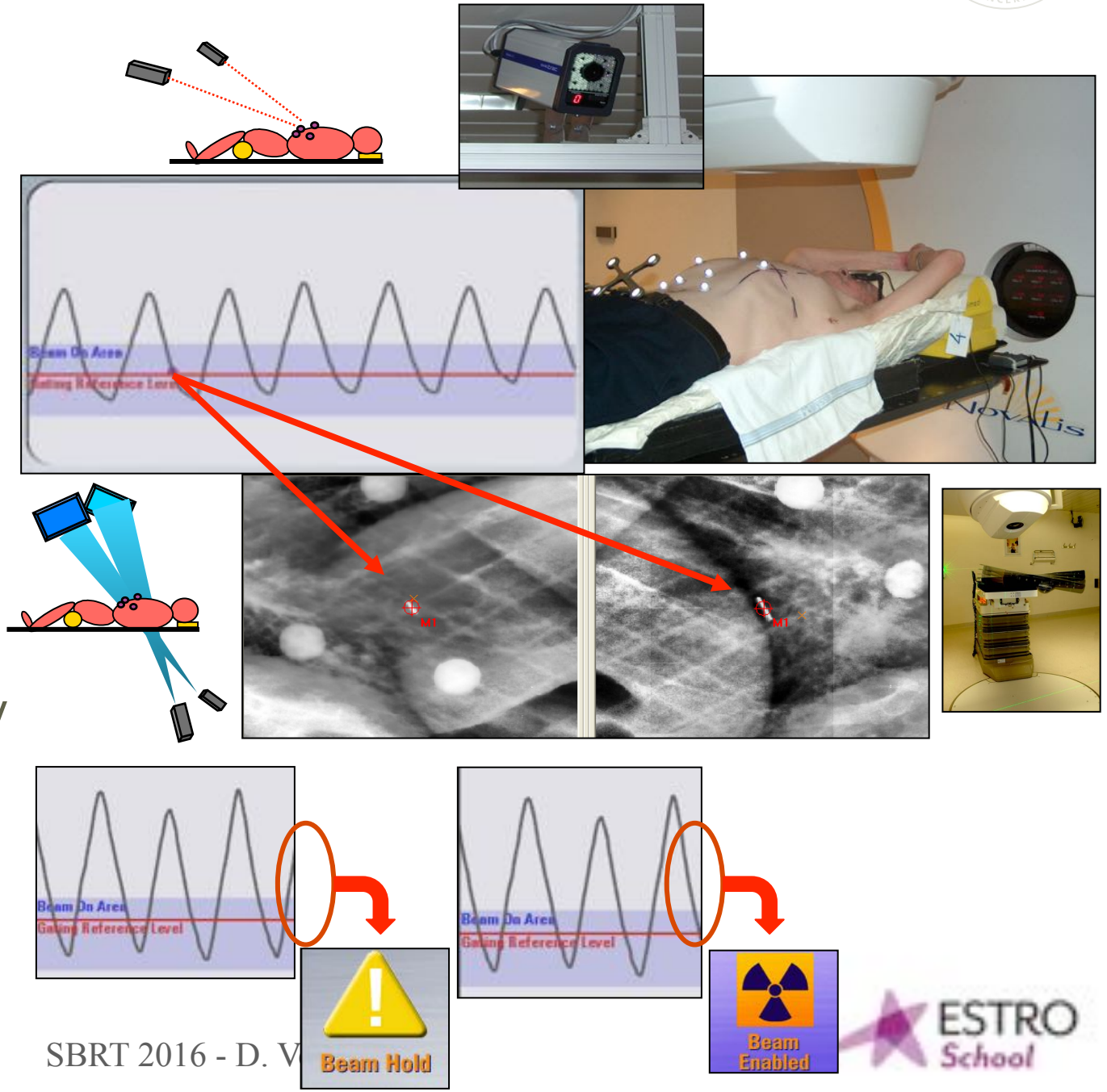


Gating: An example

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

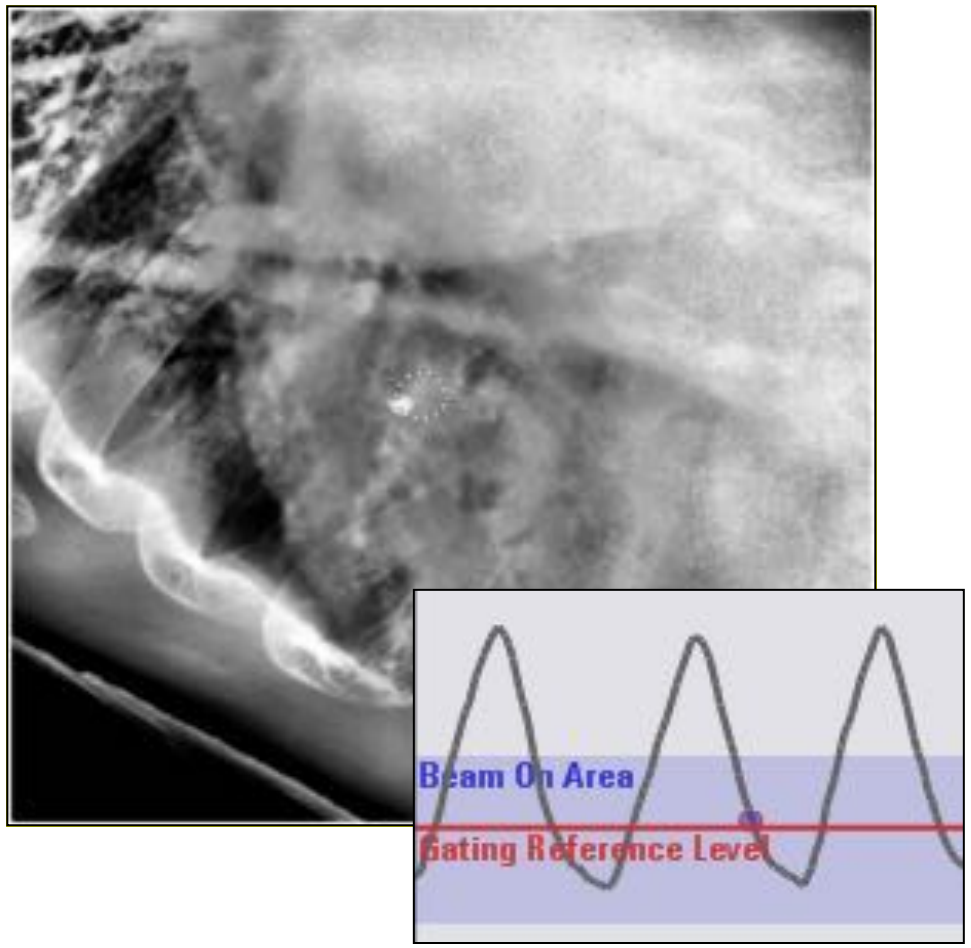


Gating: continuous verification

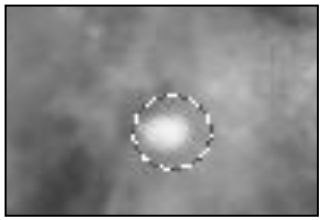
- Target localization verified with repeated on-line verification images
  - 516 verification images
  - Deviation between expected and actual position of internal marker at reference level:

mean 0.8 mm

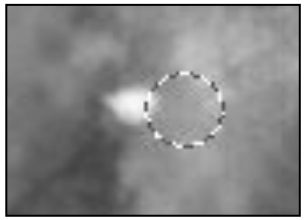
(SD 0.4 mm; max 2.6 mm)



Good correlation



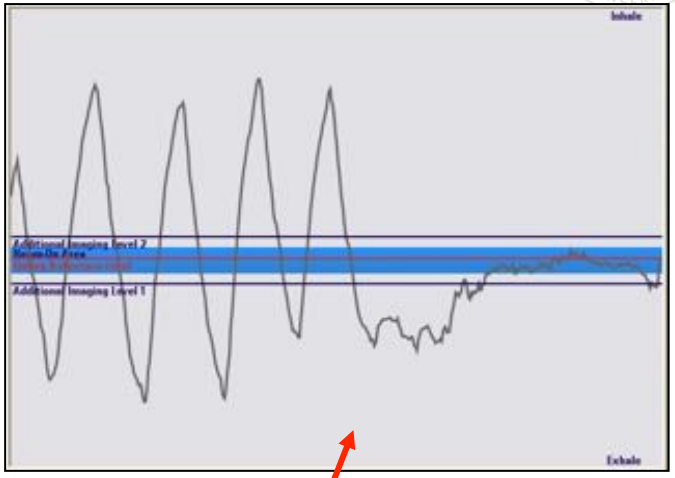
Bad correlation

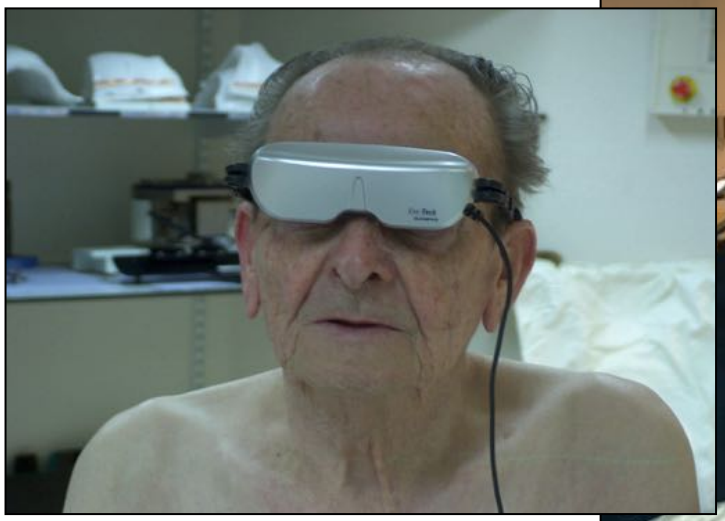


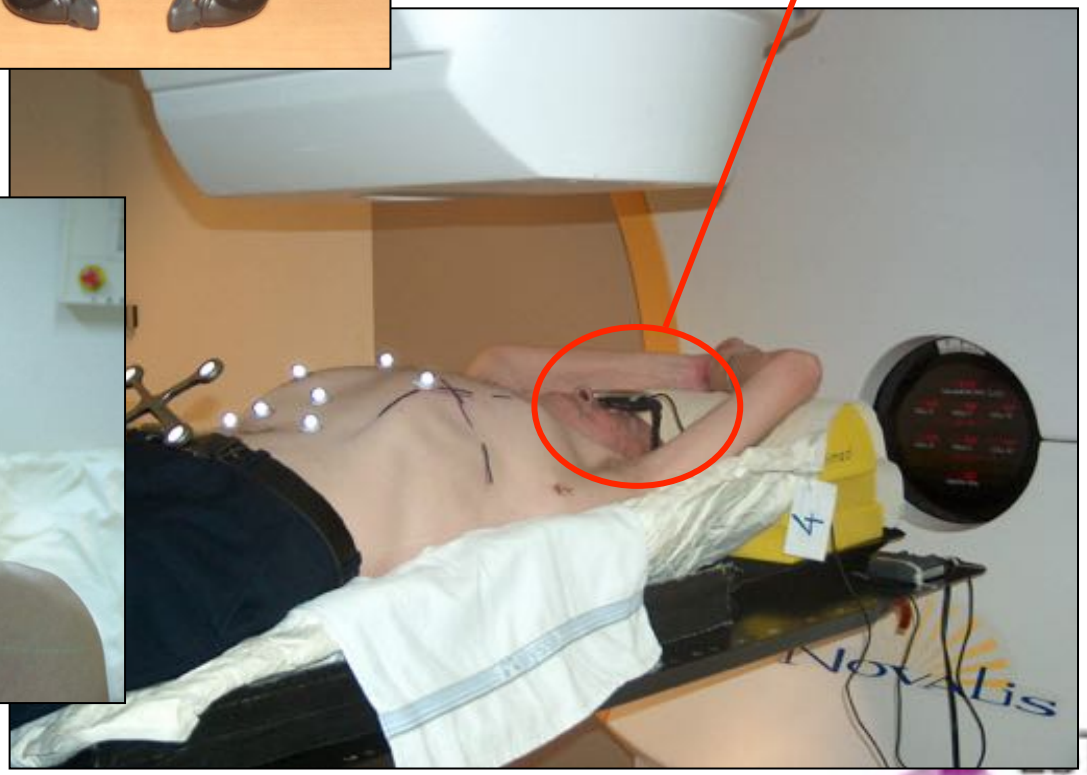
Visually guided voluntary breath-hold

1st patient (Dec 2006):

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



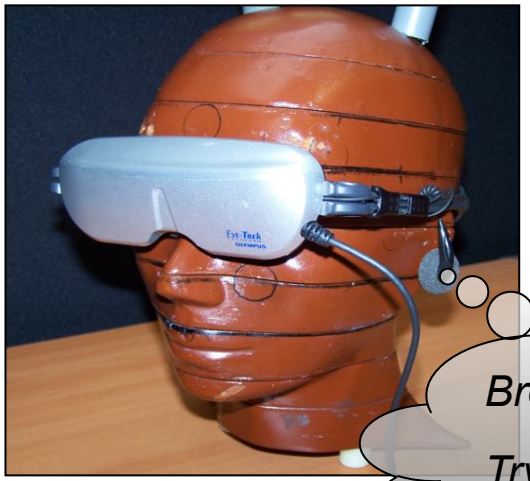




Gating: audio assistance

Breath freely…..

Try to hold your breath in the blue area….



Breath freely…..

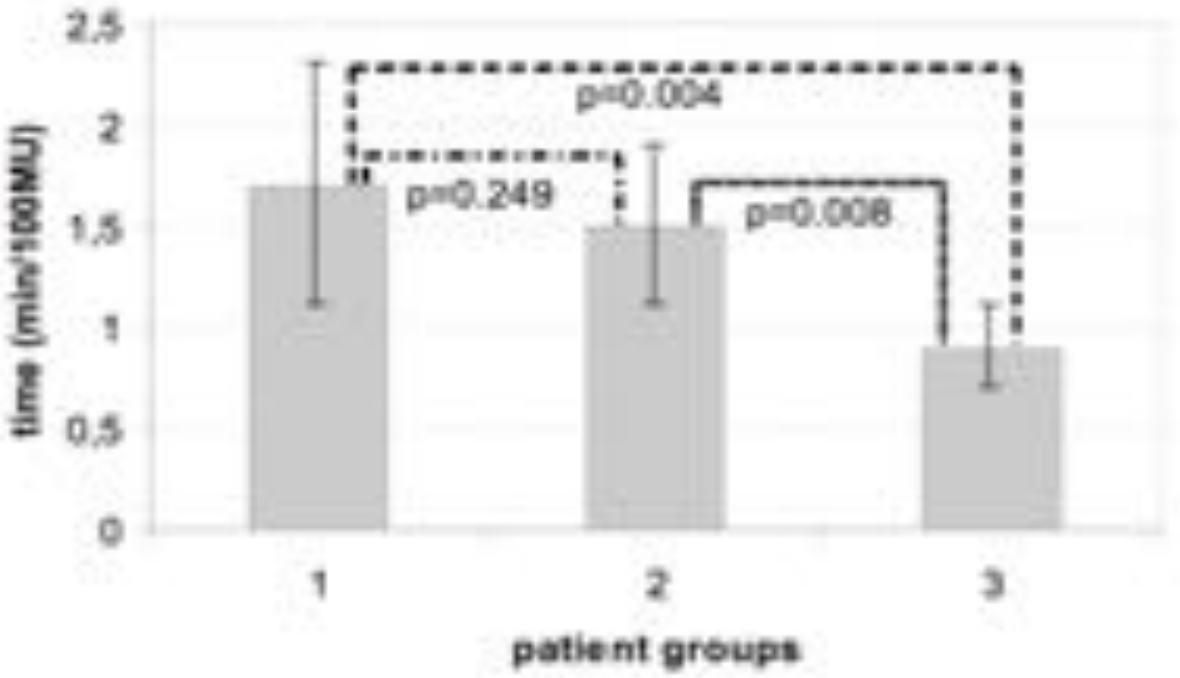
Try to hold your breath in the blue area….

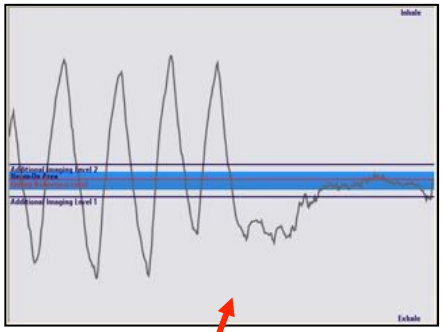
Gating: treatment efficiency

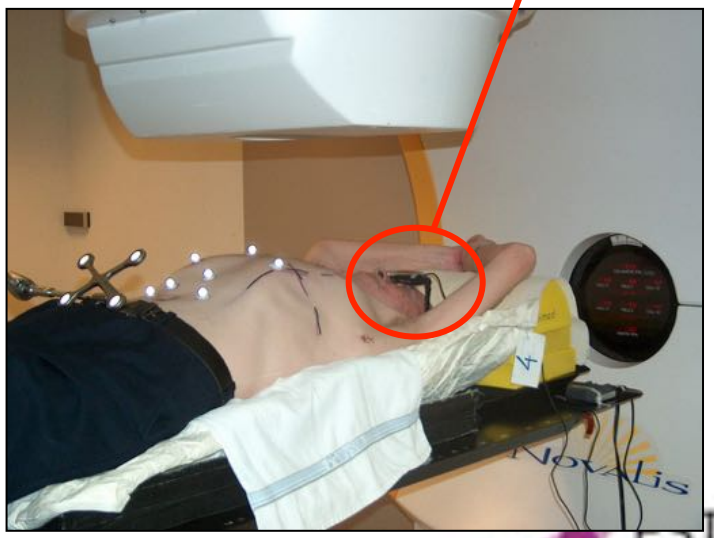
- Gating without video-glasses (9 patients, av. age 67,4y)
  - Average 2,5 min/Gy — SD 0,8 min/Gy
  - Average 1,7 min/100MU — SD 0,6 min/100MU
- Gating with video-glasses (7 patients, av. age 59,7y)
  - Average 1,9 min/Gy — SD 0,6 min/Gy
  - Average 1,4 min/100MU — SD 0,4 min/100MU
- Gating with video-glasses and audio-assistance (9 patients, av. age 75,3y)
  - Average 1,2 min/Gy — SD 0,3 min/Gy
  - Average 0,9 min/100MU — SD 0,2 min/100MU

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.

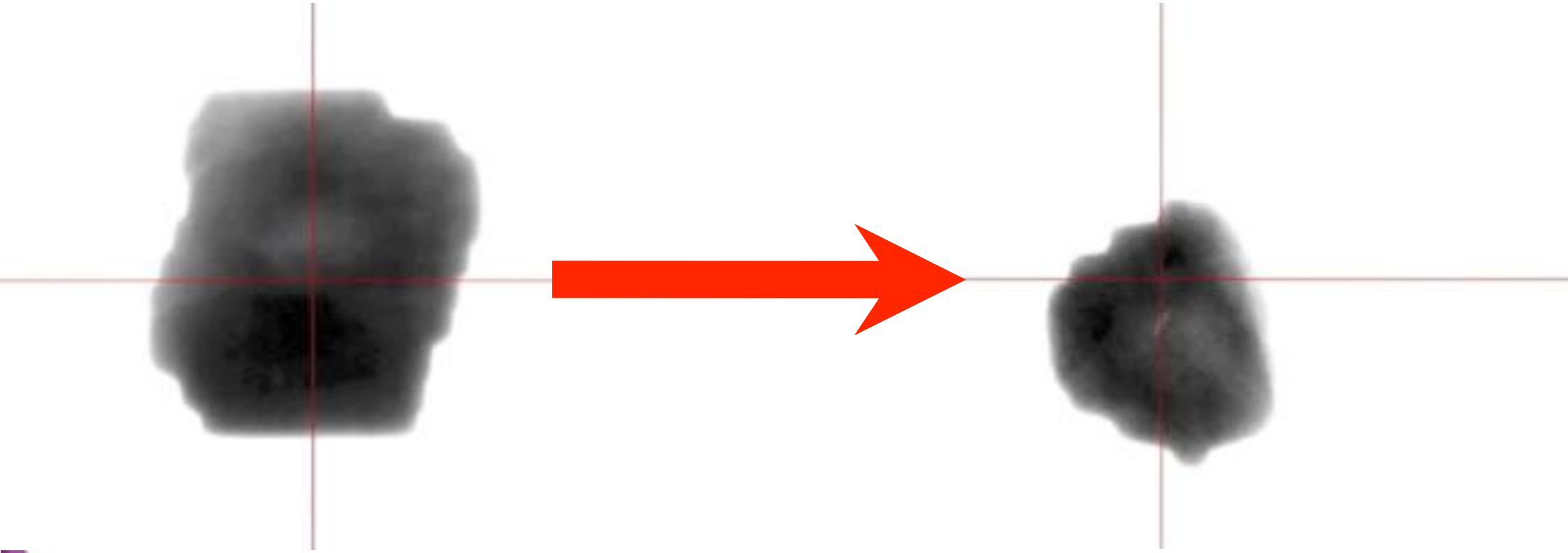






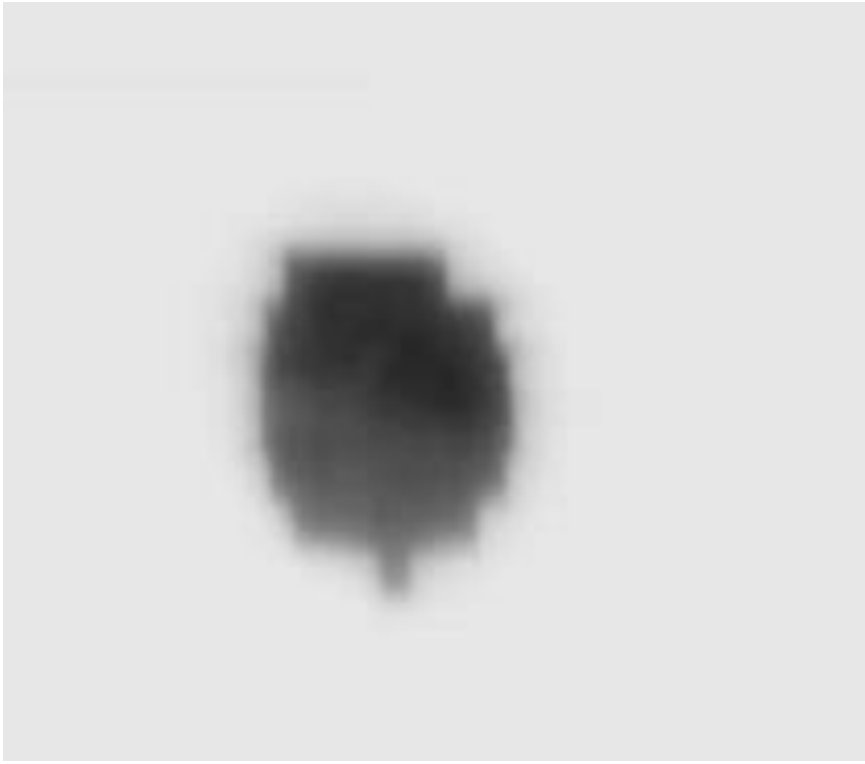
ITV versus tracking

Reduction of high dose volumes

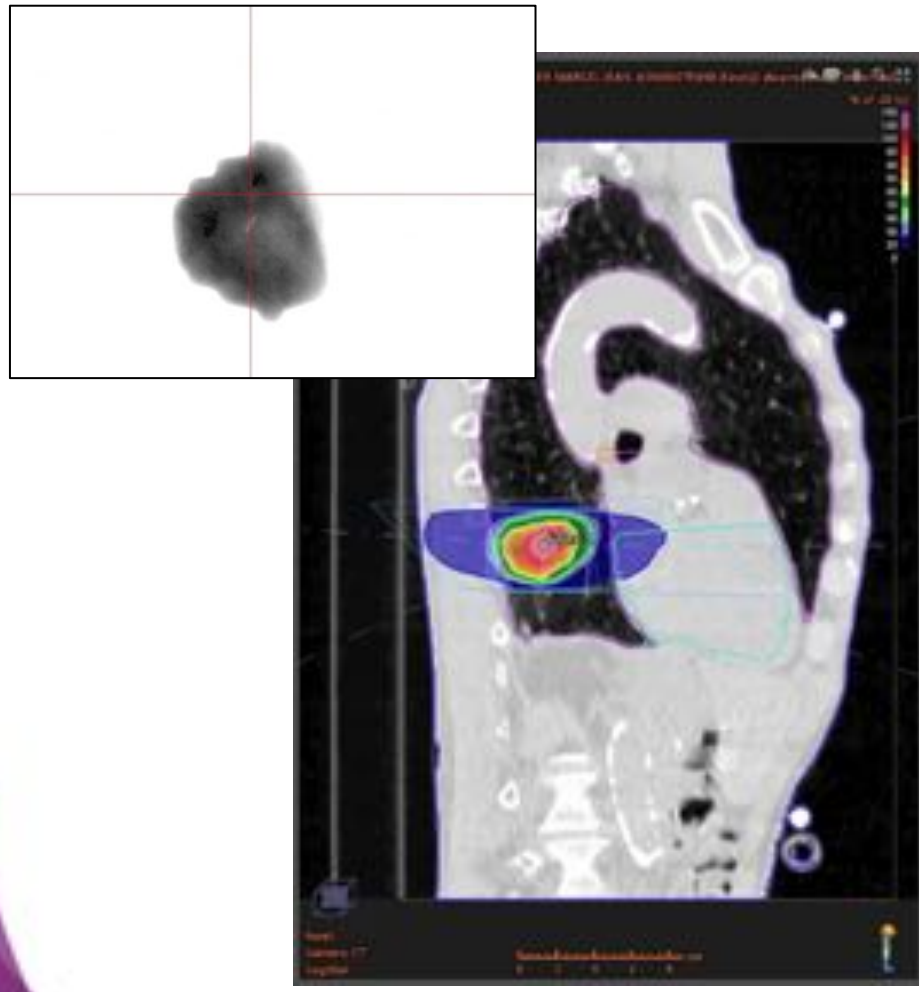


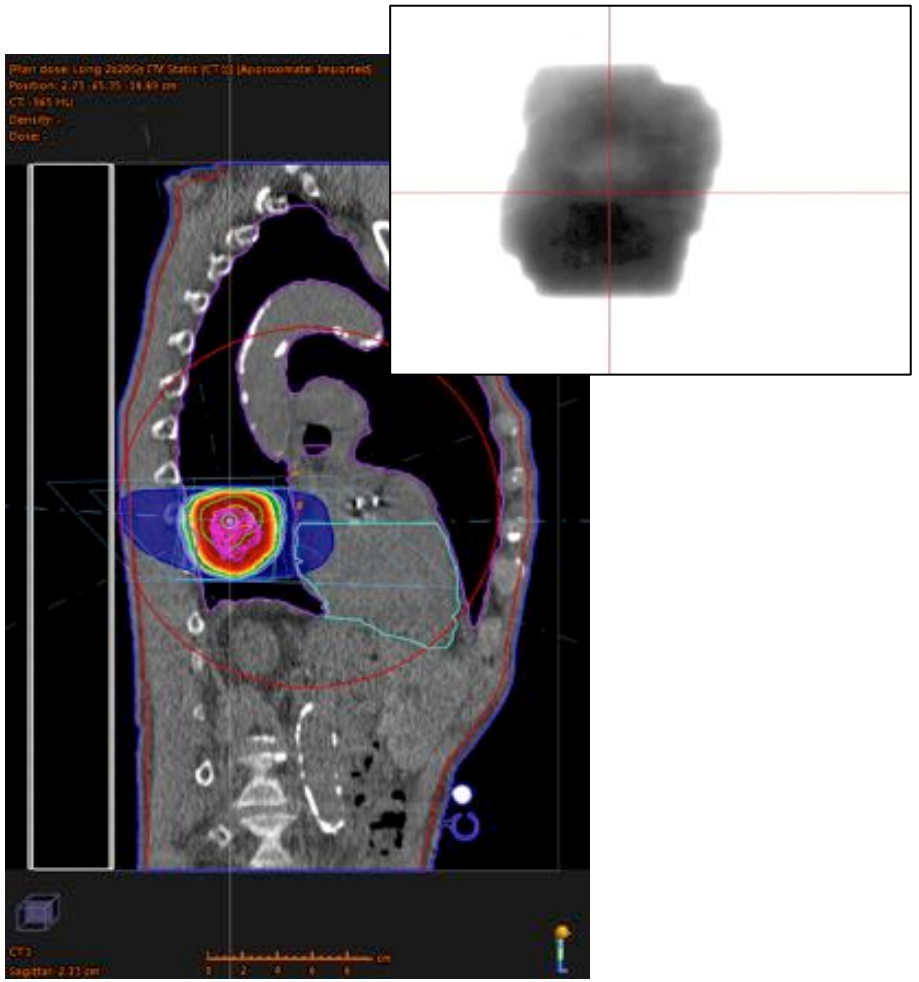
ITV versus tracking

- Real-time adaptation and increased efficiency of respiratory correlated irradiation



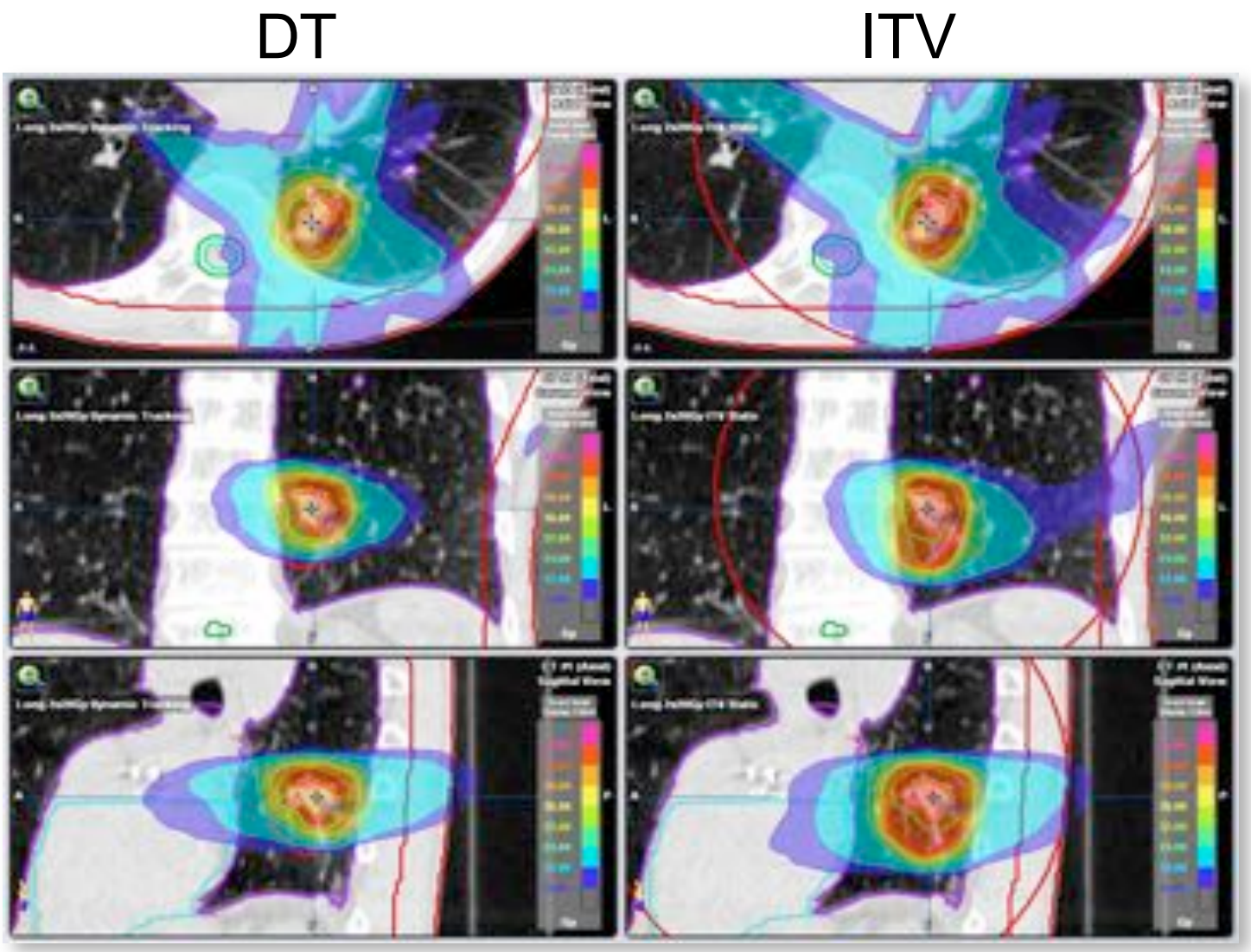
Tracking: “sticky” dose





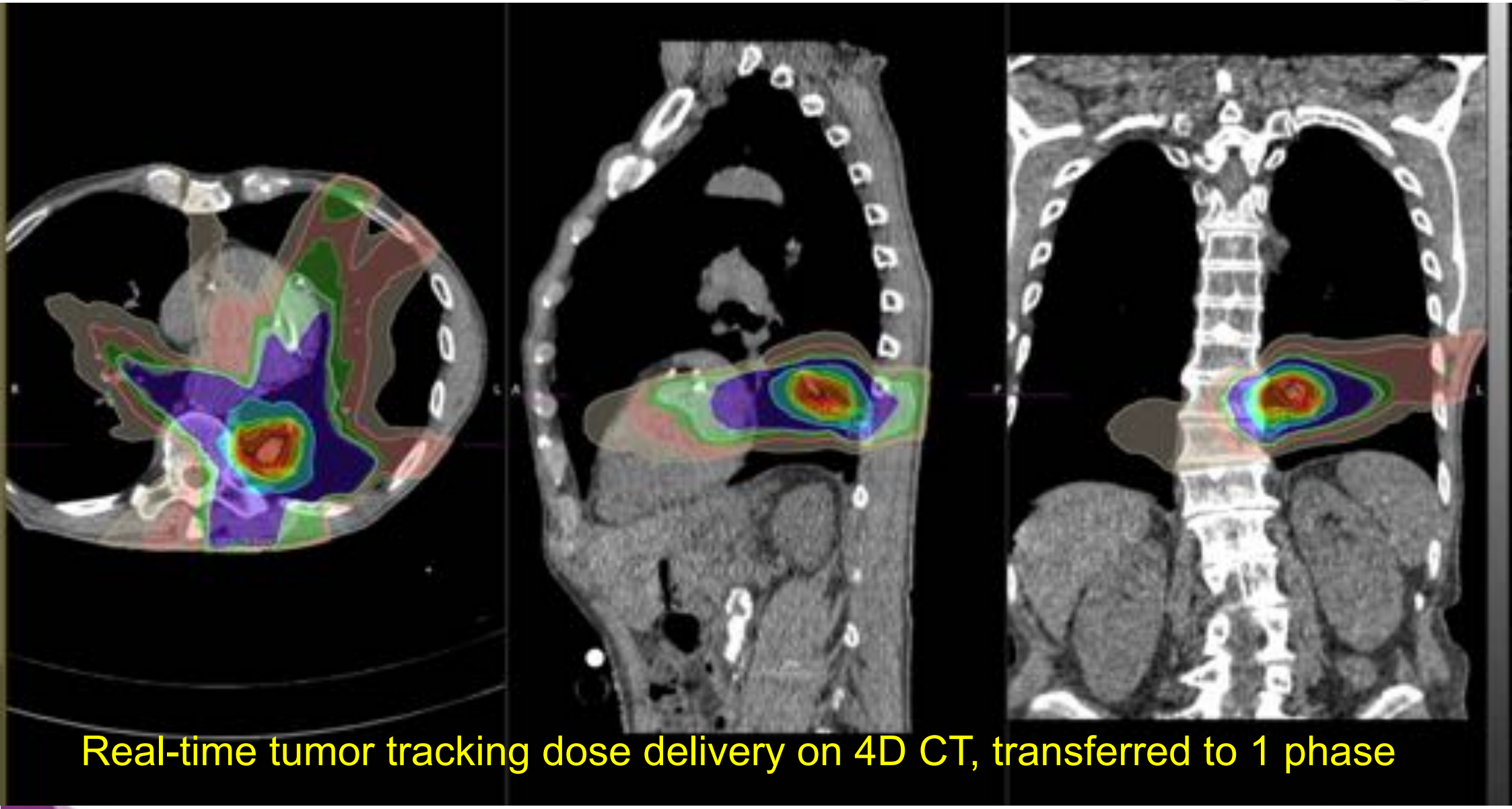
PTV volume reduction

	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**



Dynamic tracking patients @ UZ Brussel (2012-2013)

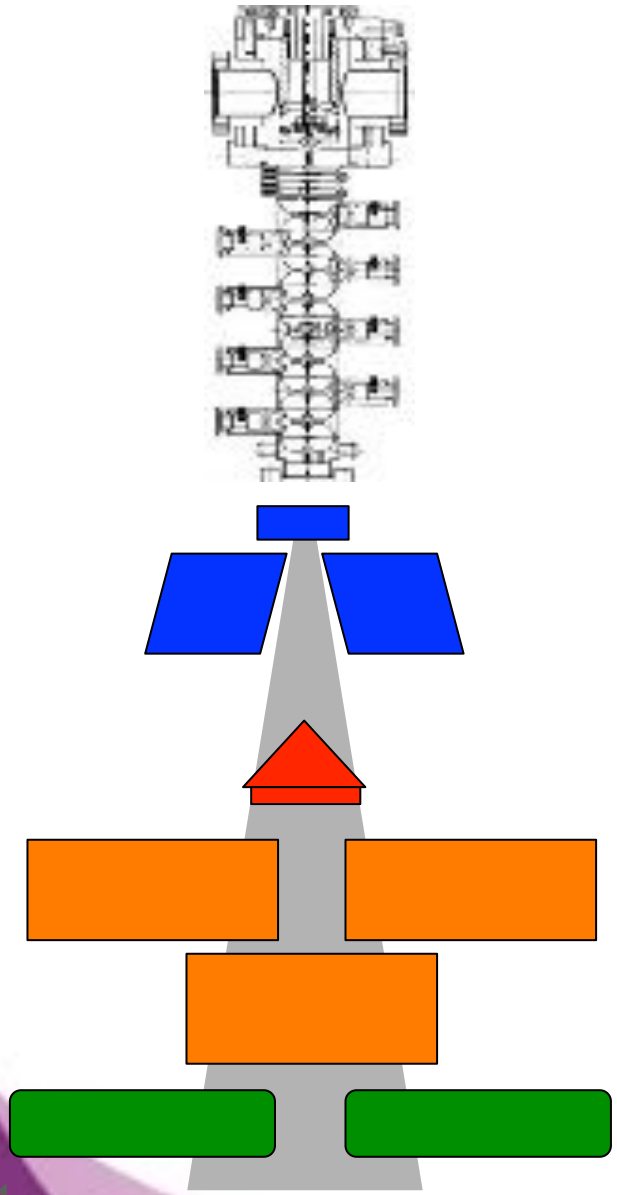
Dose calculation in dynamic anatomy



Real-time tumor tracking dose delivery on 4D CT, transferred to 1 phase

Tumor tracking

Medical linac full beam line



Electron Gun

Accelerator

Target

Primary collimator

Flattening filter

Jaws (X,Y)

MLC

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

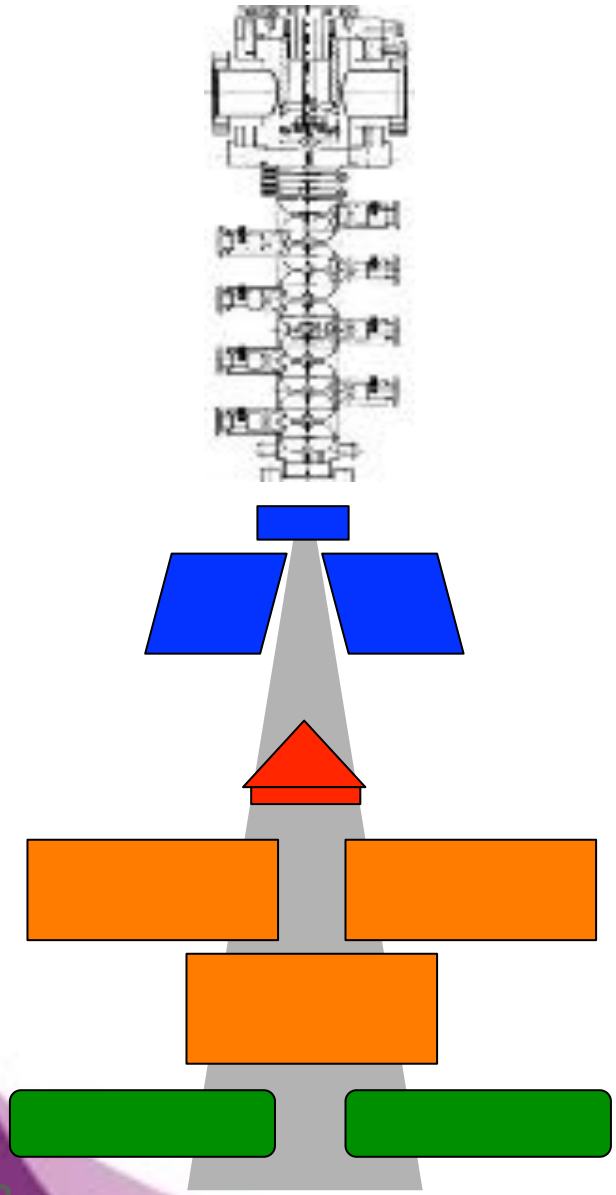
<u>Dynamics of breathing/tracking:</u>
-Frequencies up to 30 Hz
-Amplitudes of a few centimeters
-Sub-millimeter accuracy

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

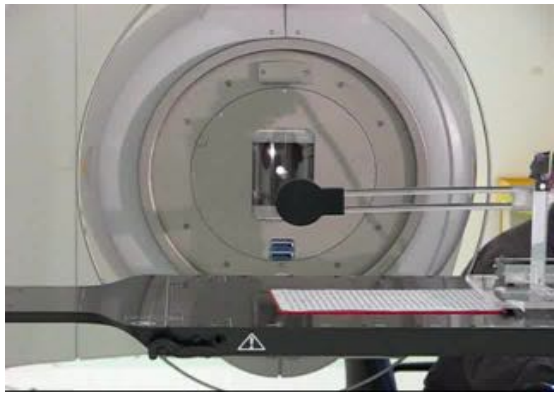
Flattening filter

Jaws (X,Y)

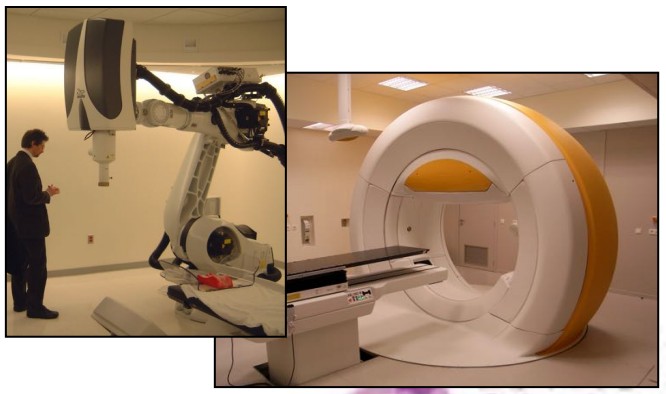
MLC

MLC tracking

Dynamic couch



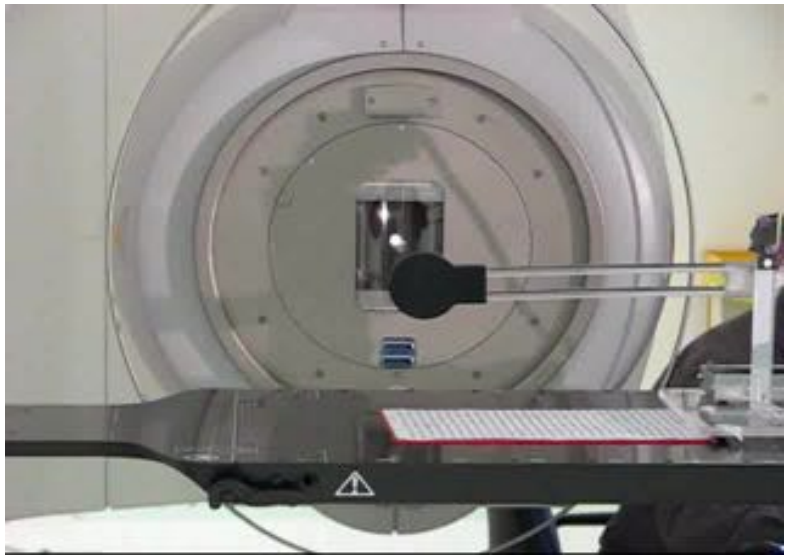
Beam line



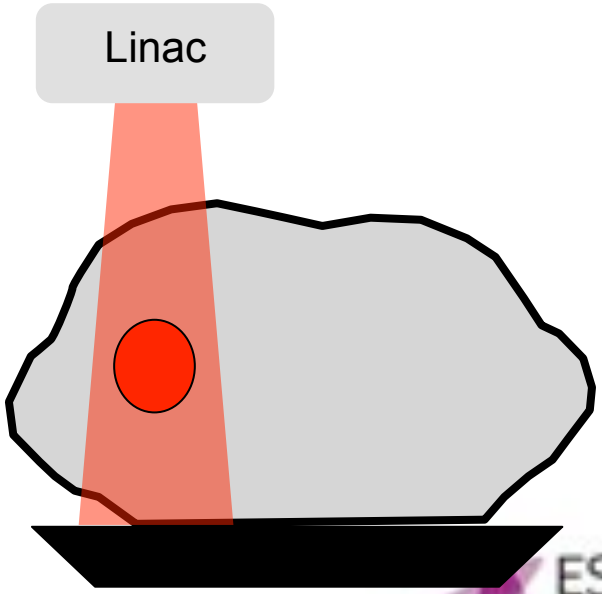
Tumor tracking: couch compensation

Dynamic couch compensation

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

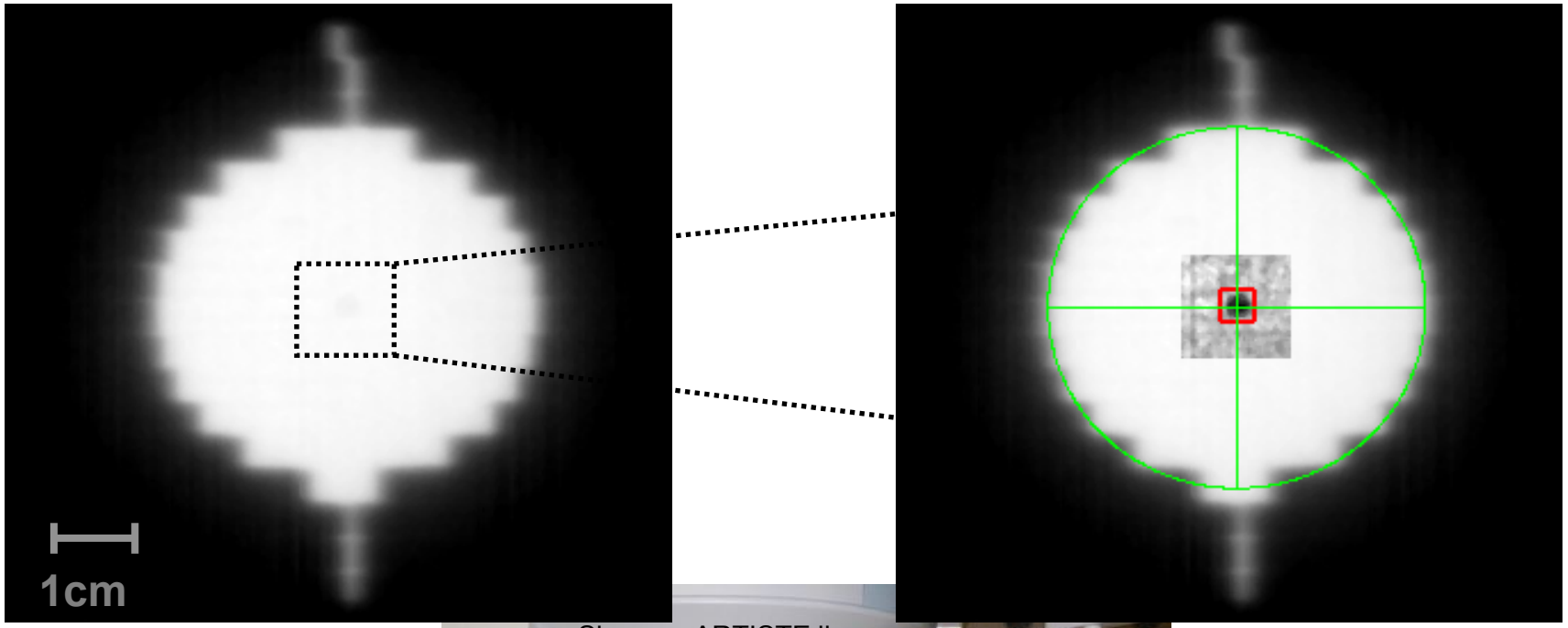


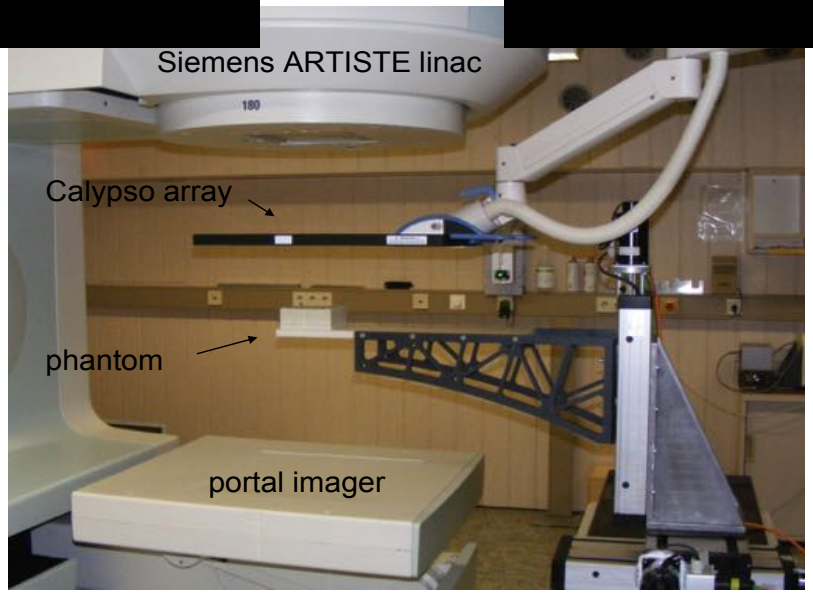
- **Advantages**:
  - Free breathing
  - Linac can operate as in a static situation
- **Drawbacks**:
  - Dynamic behavior of the couch (weight distr.)
  - Complex feedback control system for couch motion
  - Discomfort patient? Relaxing?
  - Impact on tumor motion, patient positioning?
  - Changing position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



Courtesy O. Haas

Tumor tracking: DMLC

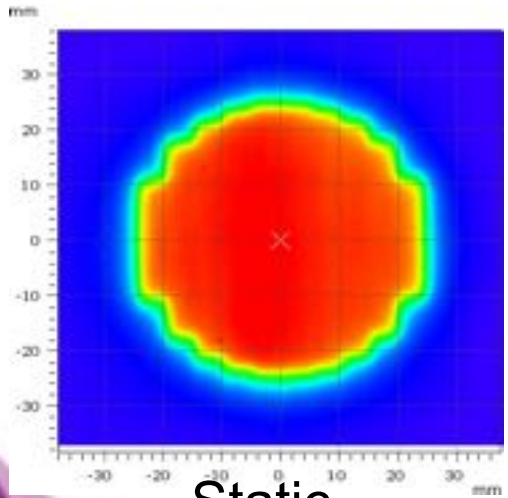


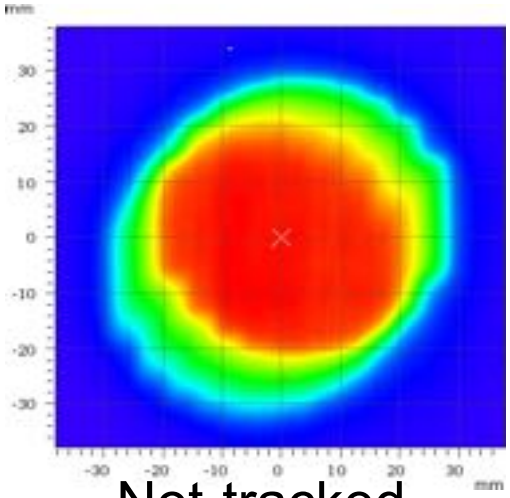


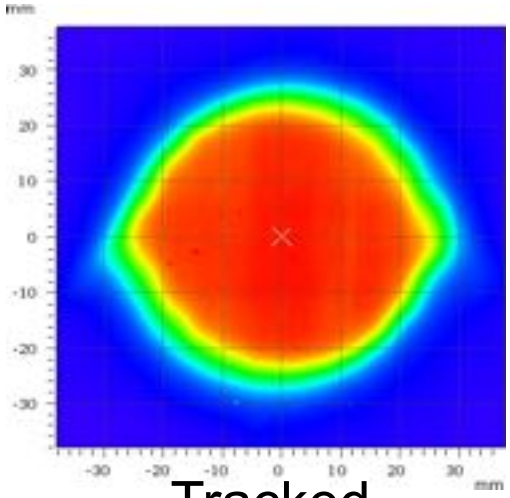
Courtesy U. Oelfke

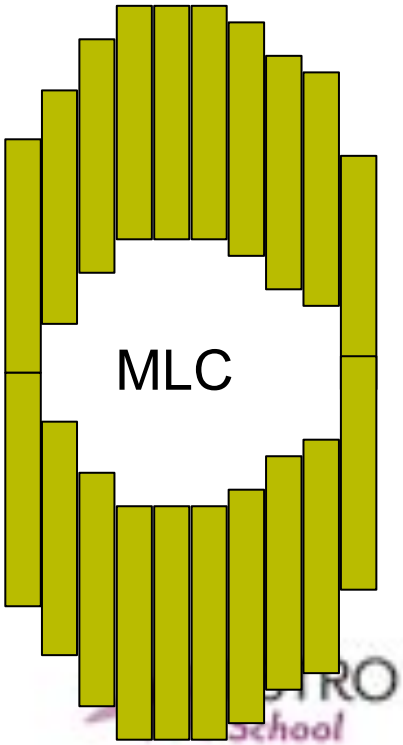
Tumor tracking: DMLC

- **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?

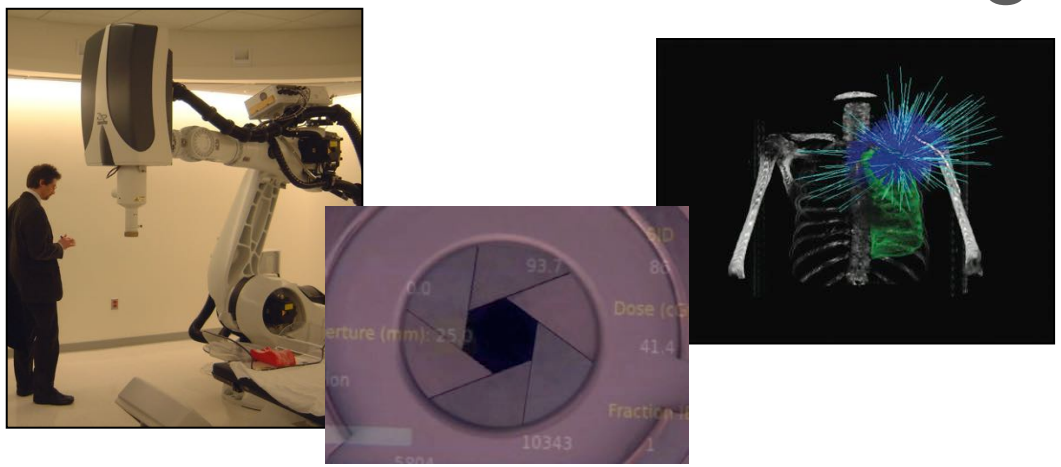

Static

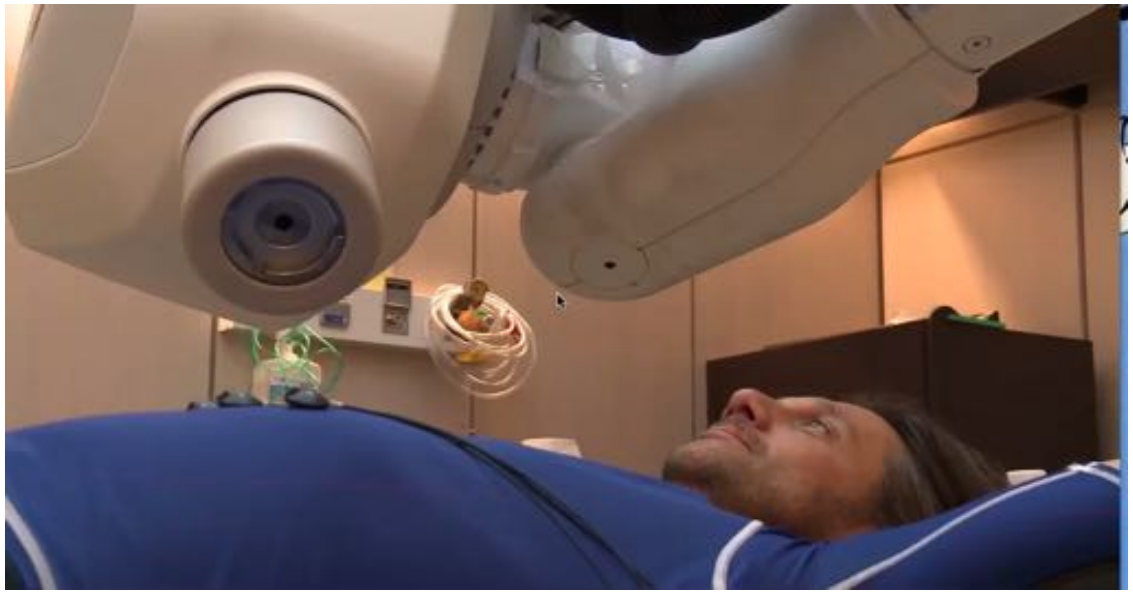

Not-tracked


Tracked



Tumor tracking: Cyberknife





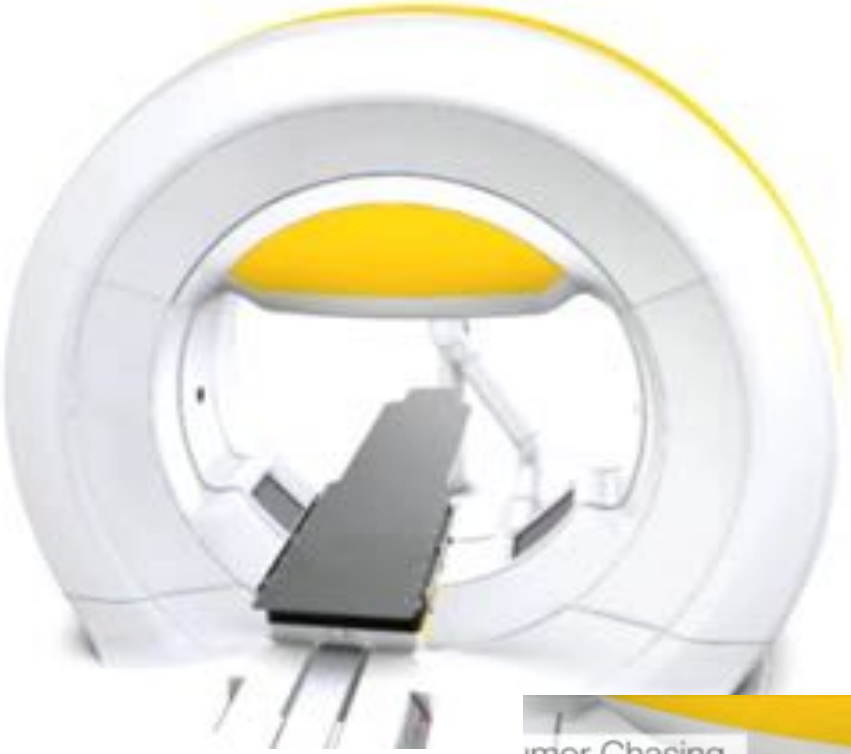
- **Advantages**:
  - High dynamic and geometric accuracy
  - Markerless tracking available for specific cases
- **Drawbacks**:
  - Small circular field sizes (new version comes with MLC)
  - Long treatment times
  - Posterior beams not possible
  - Volumetric imaging not supported
  - Direct verification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

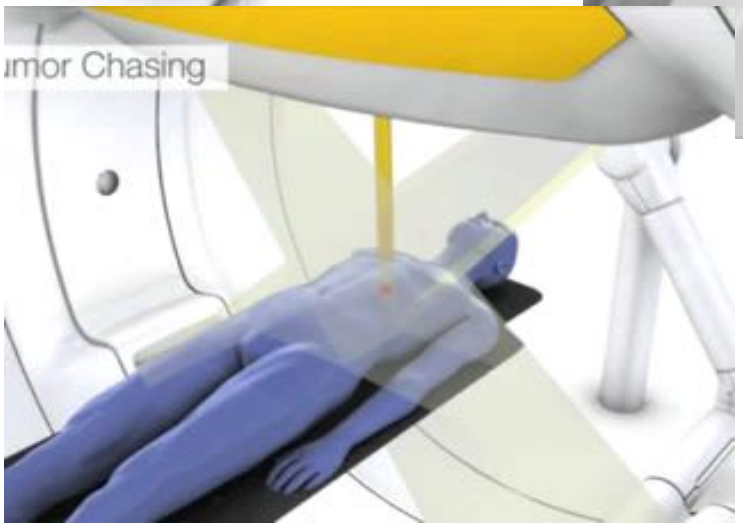
-Light and compact linac (< 300kg)

-Mounted on a robot

Tumor tracking: VERO

… limited edition



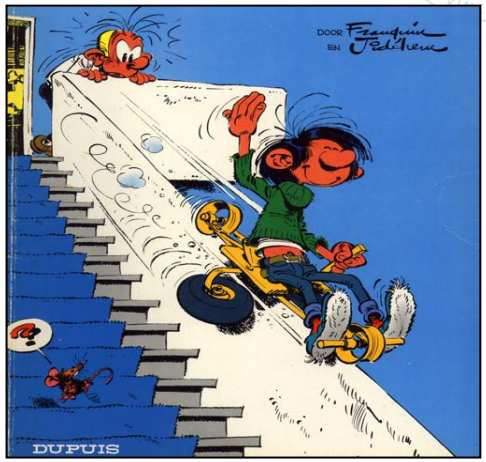


Tumor tracking: VERO

- **Advantages**:
  - High dynamic and geometric accuracy
  - Dual modality tracking verification
  - Both fluoroscopic X-Ray and CBCT volumetric imaging supported
- **Drawbacks**:
  - Decoupling of VMAT/Dynamic arc/IMRT and tracking **not yet clinically available**.
  - 4D-CBCT **clinically not available**.
  - 4D dose calculation of dynamic tracking **clinically not available.**
  - Markerless tracking **not yet clinically available**.

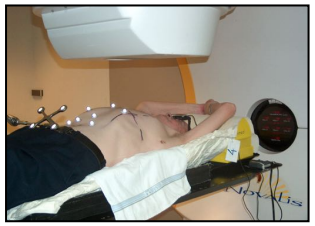
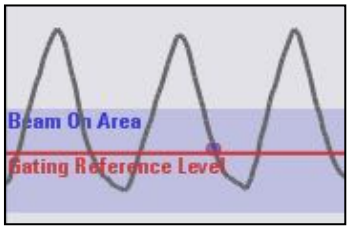
Challenge: patient vs. machine

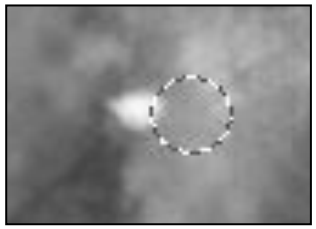
Challenge: patient vs. machine



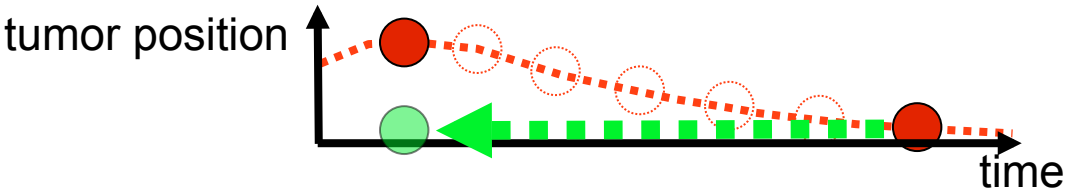
Anticipating unpredictable motion …

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

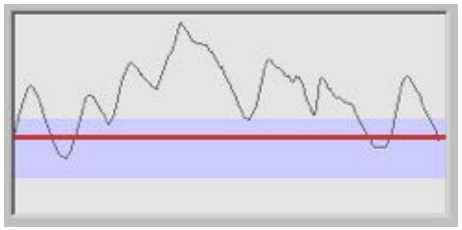





- Prediction model:
  - Requires “predictive” (i.e. periodic) motion



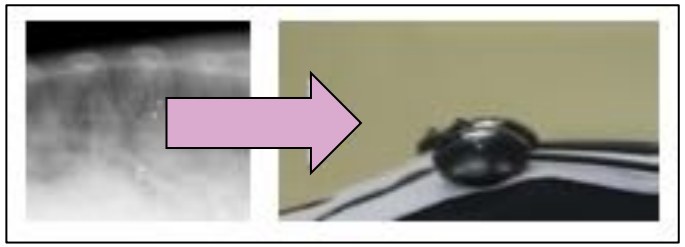
- Interface between machine and man …
  - By definition “unpredictable”?



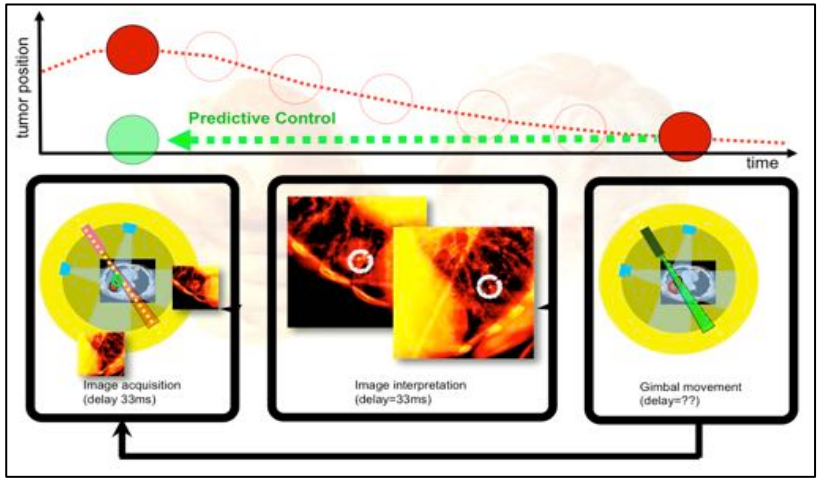
Tracking: error analysis

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

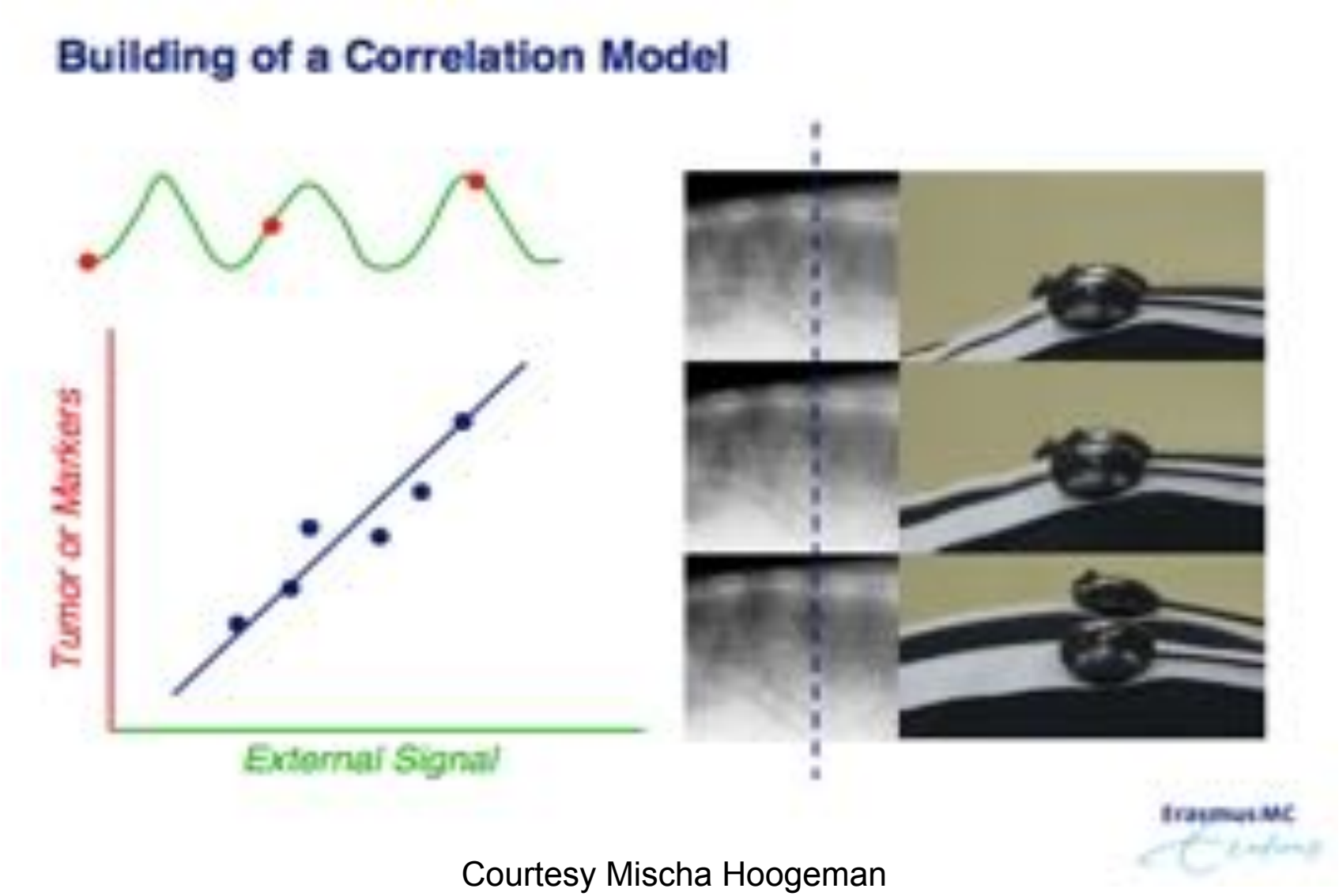
- Correlation model between external markers (chest motion …) and internal tumor motion.



- 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.*)

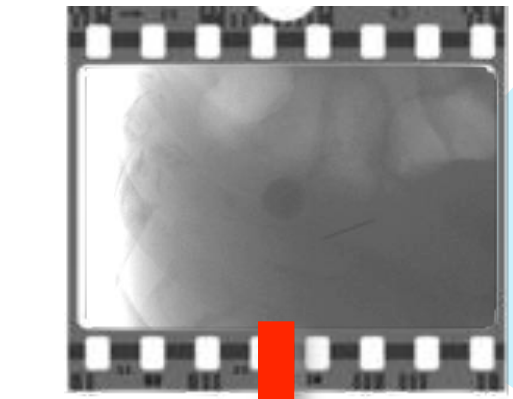


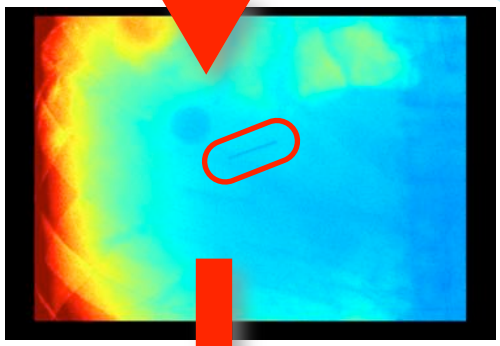
Tracking: Correlation models

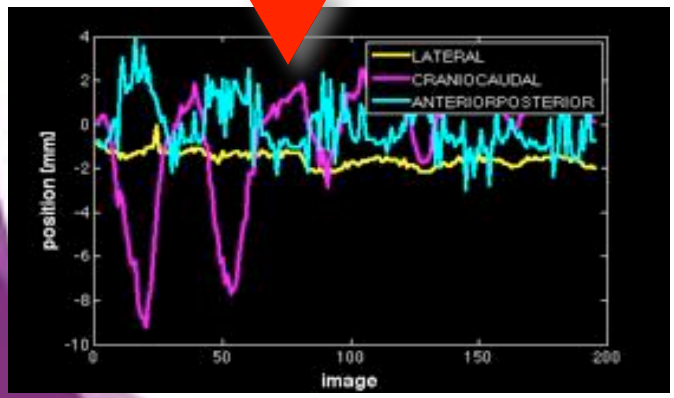


Courtesy Mischa Hoogeman

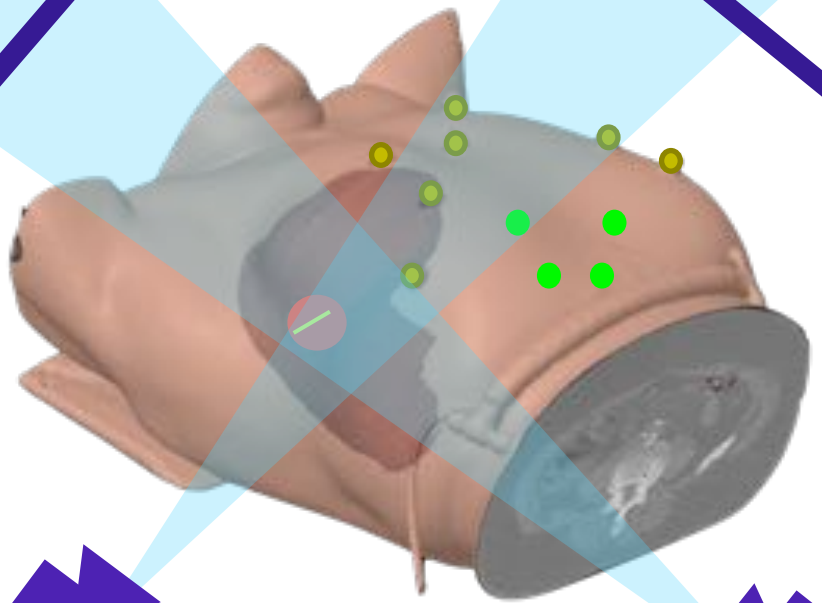
Tracking: Correlation models



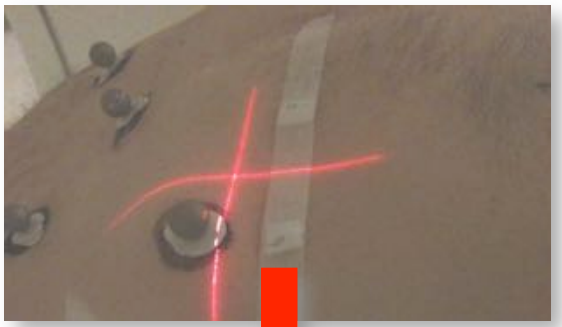


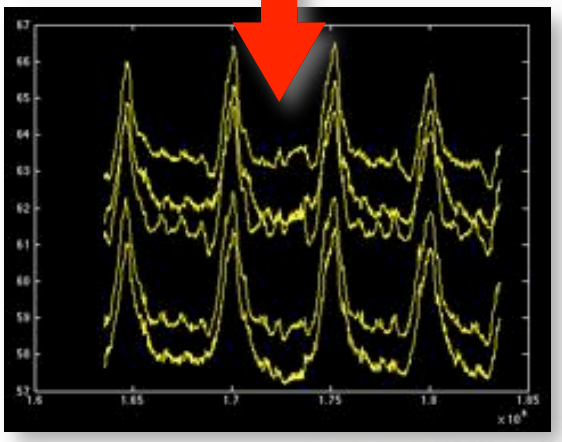


Acquisition of kV fluoro sequence and IR marker motion



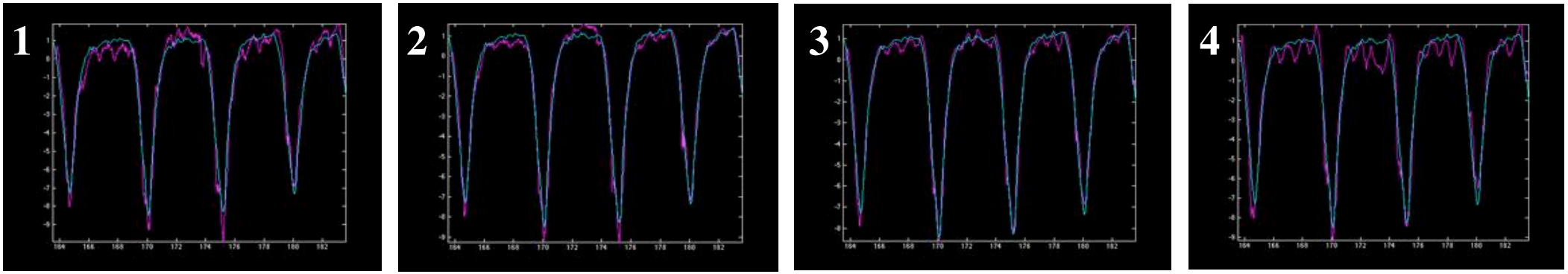
- “stable” IR markers
- “moving” IR markers
- tumor and implanted Visicoil





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

Tracking: Correlation models



Correlation model between external IR skin markers and internal target (marker) motion:

Prediction — from IR marker position and speed

$$f(x,v) = a\,x^2 + b\,x + c + d\,v^2 + e\,v$$

f = X,Y,Z motion of target (marker)

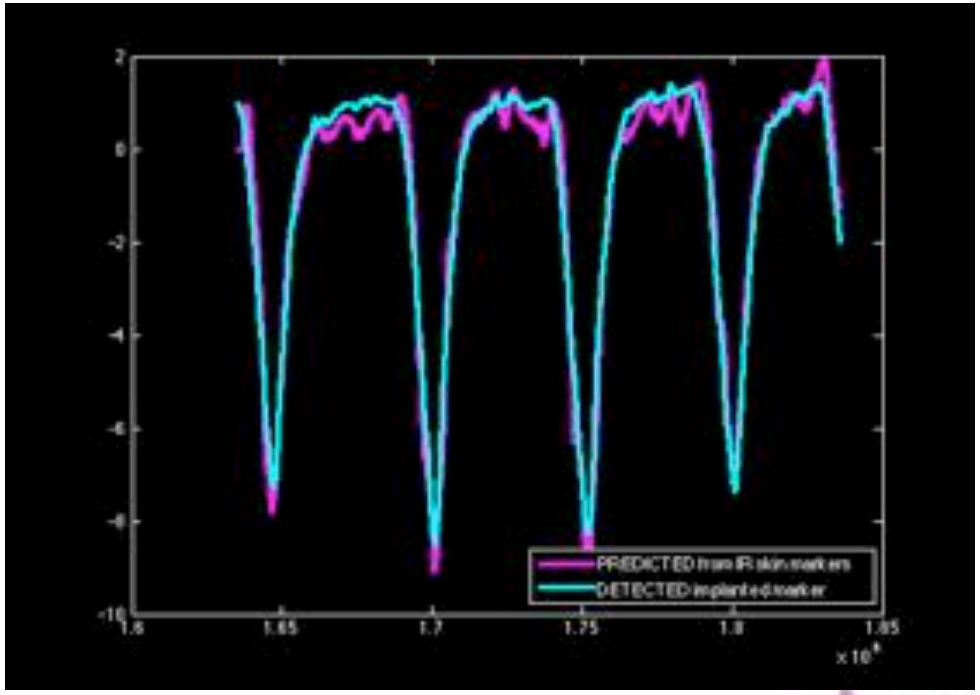
x = Vertical motion IR skin markers

v = 1st derivative of x (speed)

a,b,c,d,e fit, calculated to match predicted with detected target position.

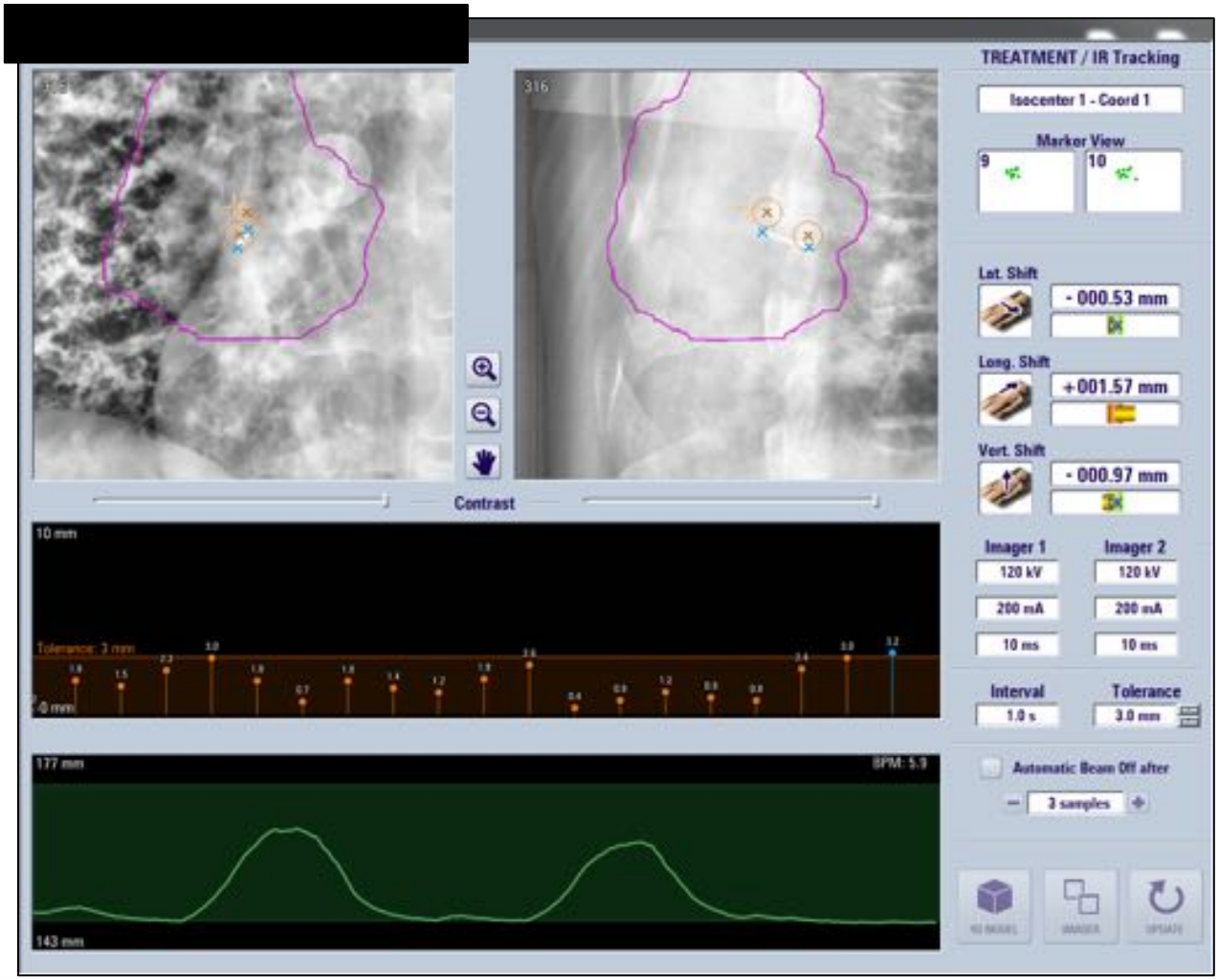
20-40" orthogonal X-ray fluorsocopy (av. 11 img/sec)

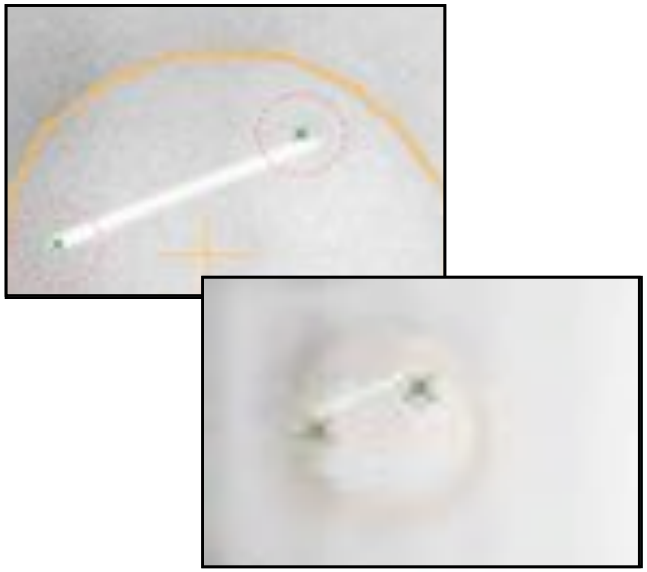
Averaged over 4 IR skin markers



Tracking: verifying corr. model

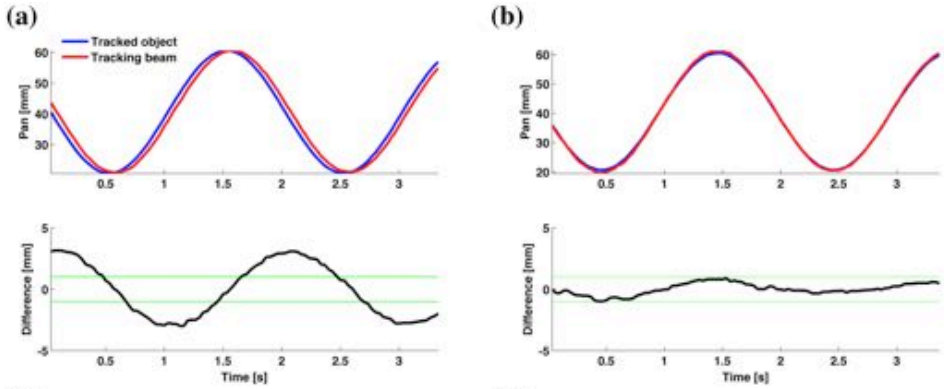
Monitoring imaging during tracking:





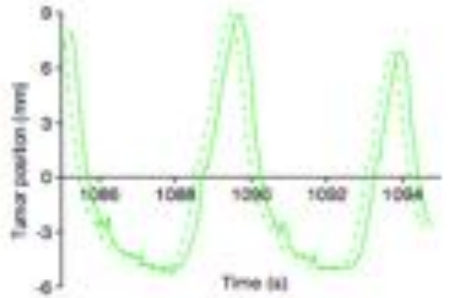
Tracking: system latency

- VERO: system latency = 50ms
  - Depuydt *et al.*

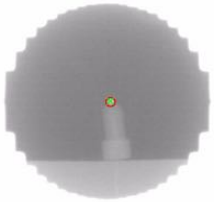


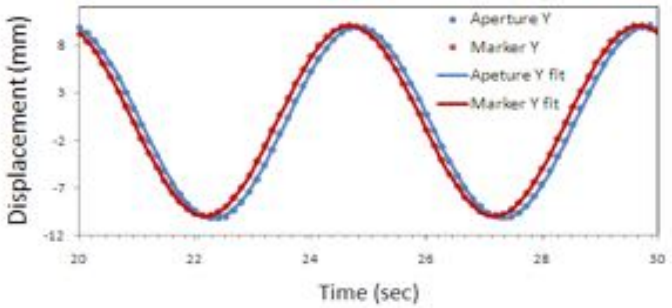
- Cyber Knife: System latency = 115 ms
  - Hoogeman *et al.*

- Data processing
- Communication to robotic controller
- Inertia of robotic manipulator and linear accelerator



- MLC tracking, "breathing leaves": system latency = 140 ms
  - Poulsen *et al.*





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.

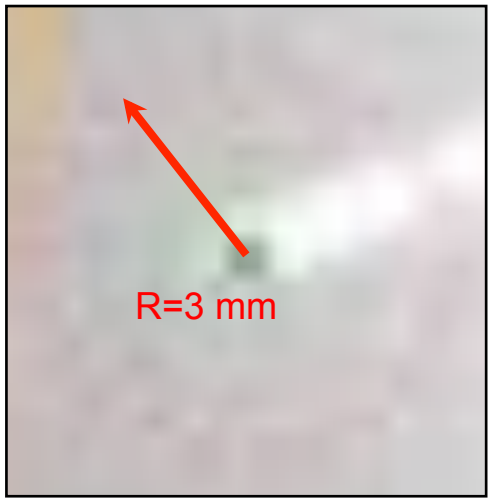
Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distened rectum on the planning CT in spite of image guidance by implanted markers.

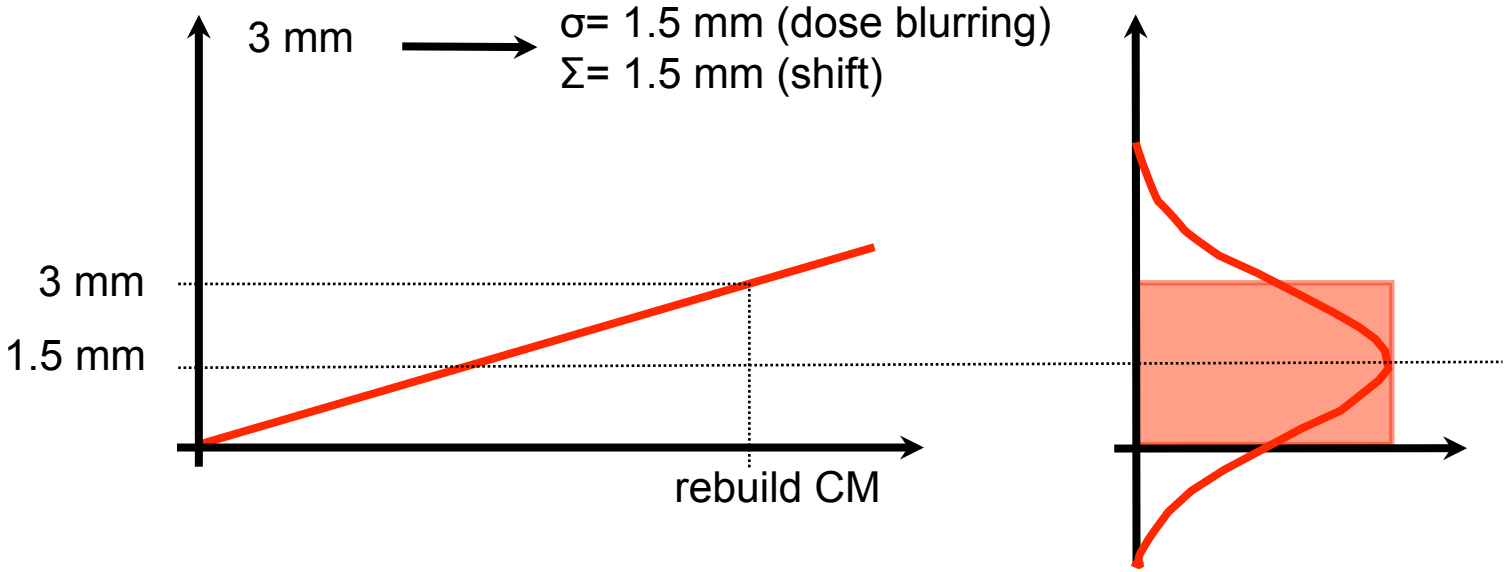
Int J Radiat Oncol Biol Phys 2008; (In Press).

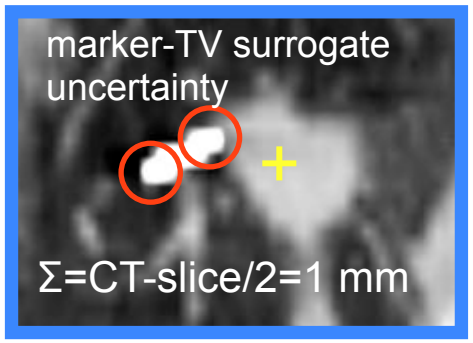
See Mischa's presentation earlier this morning!!

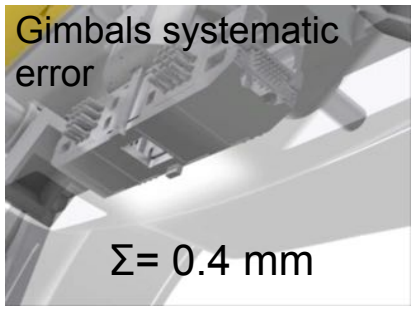
Margin definition DT patients

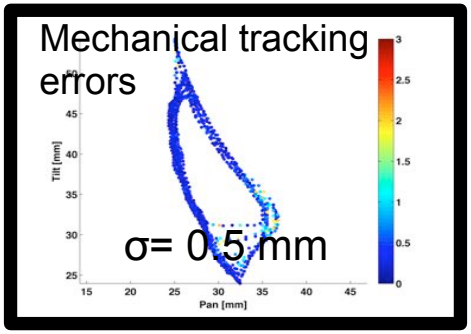
Prediction error tolerance level of 3 mm











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

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

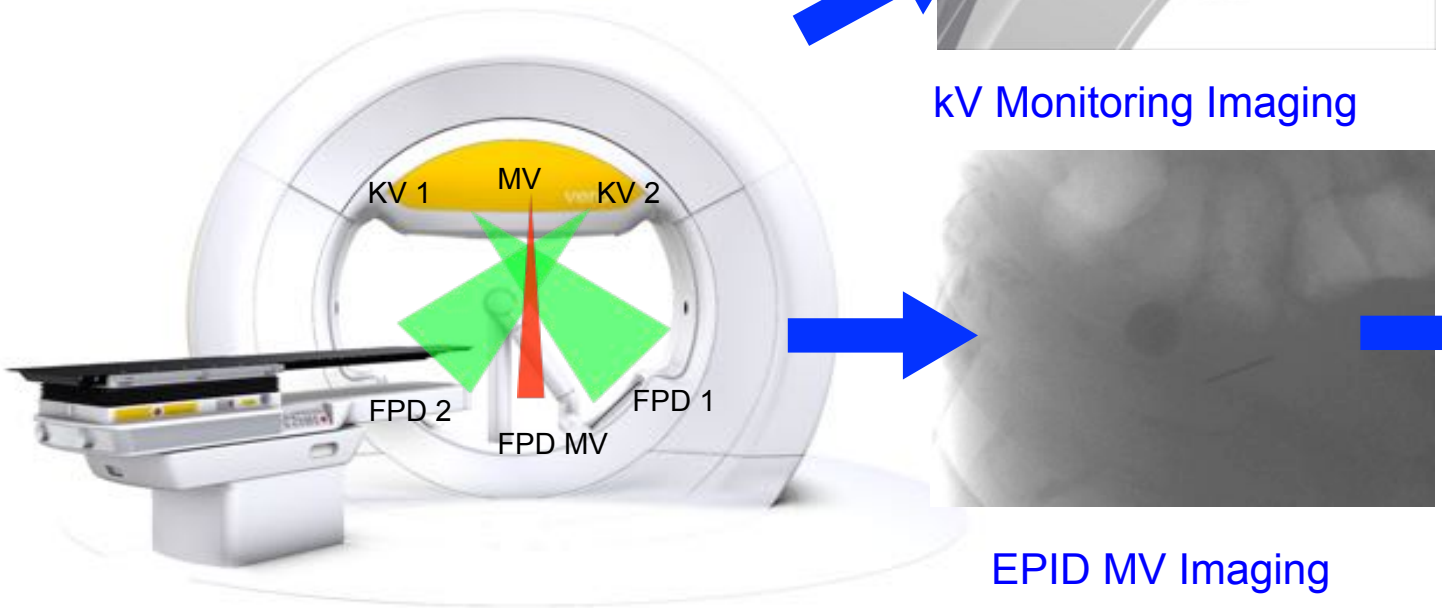
=4.9 mm => 5 mm

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

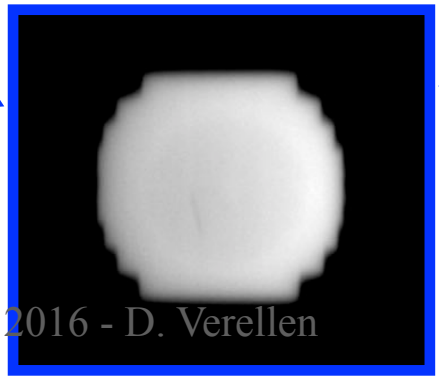
Tumour Tracking Verification

Gimbals position logging

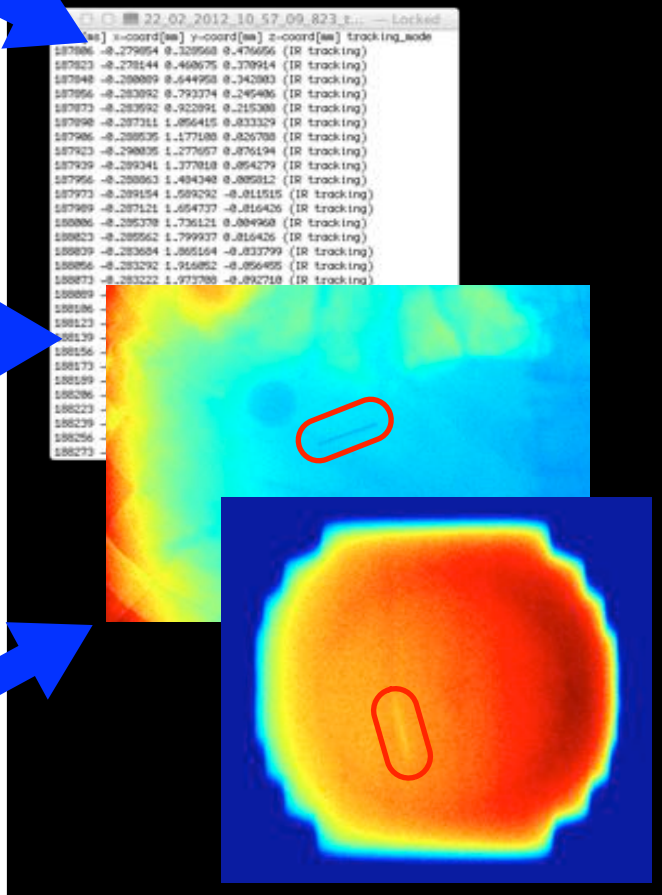
kV Monitoring Imaging



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.

Reducing margins …

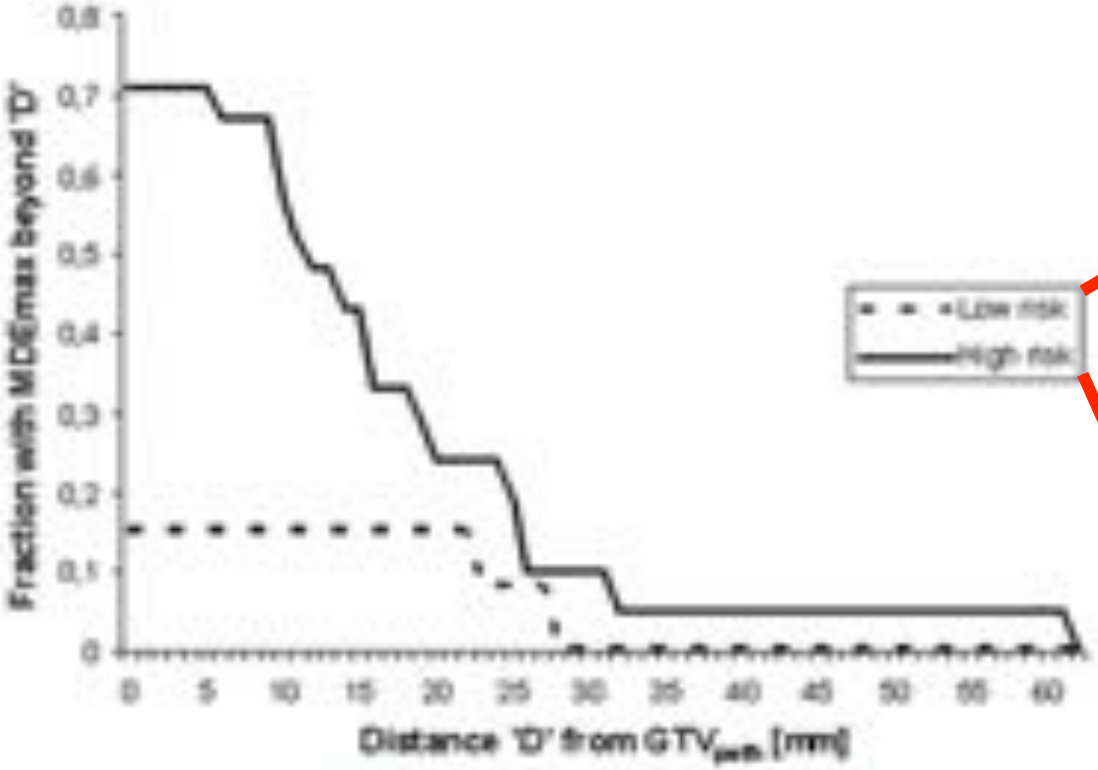
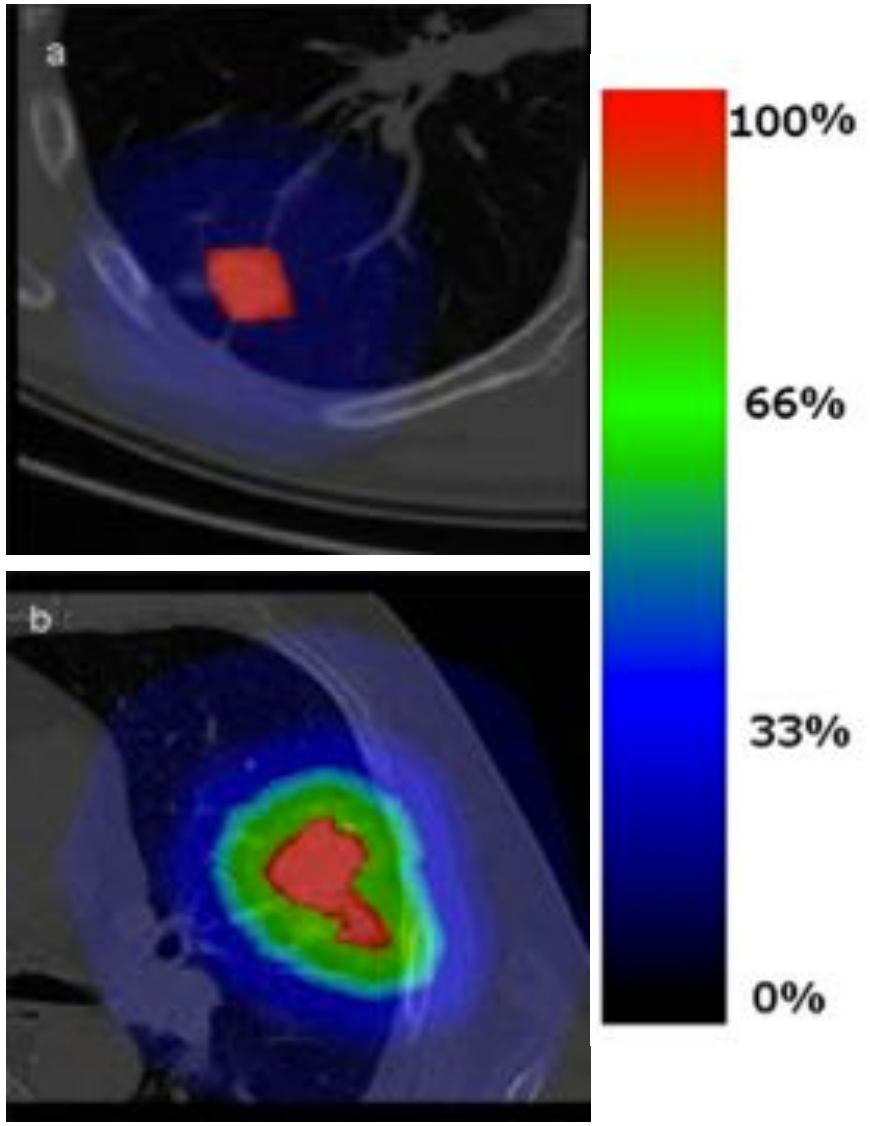


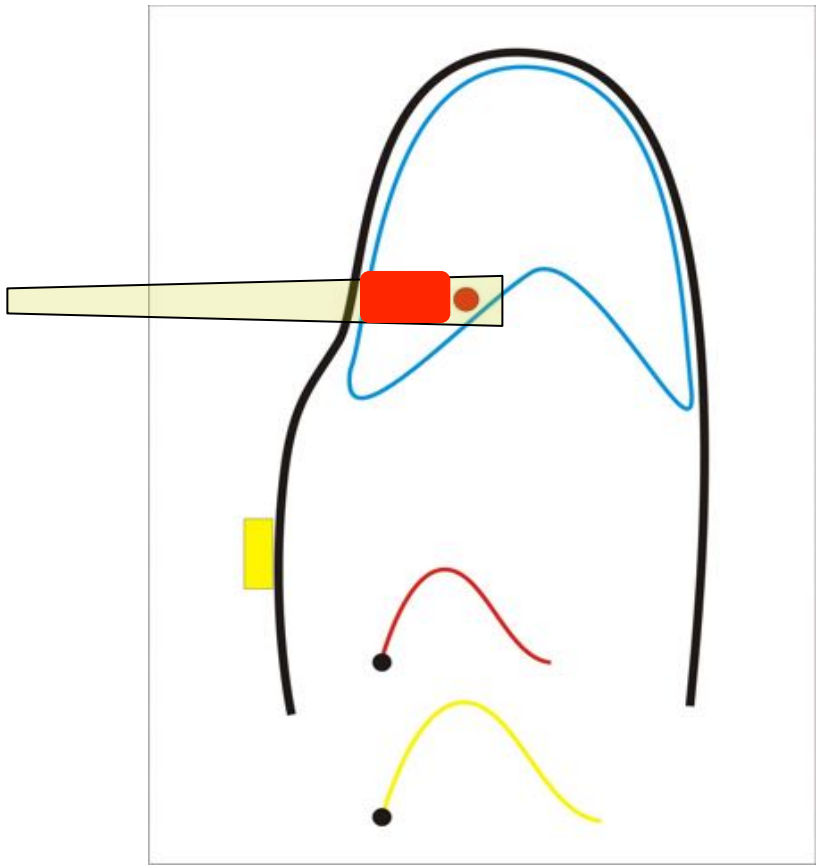
Fig. 3. Cumulative distribution of the maximum distance of microscopic disease extension (MDE_{max}) to the border of the gross tumor volume on pathologic examination (GTV_{path}) according to the risk of MDE. MDE_{max} per patient in the group at low risk of MDE (n = 13) and the group at high risk of MDE (n = 21), as predicted by the linear regression model.



Van Loon *et al.*, IJROBP 2010

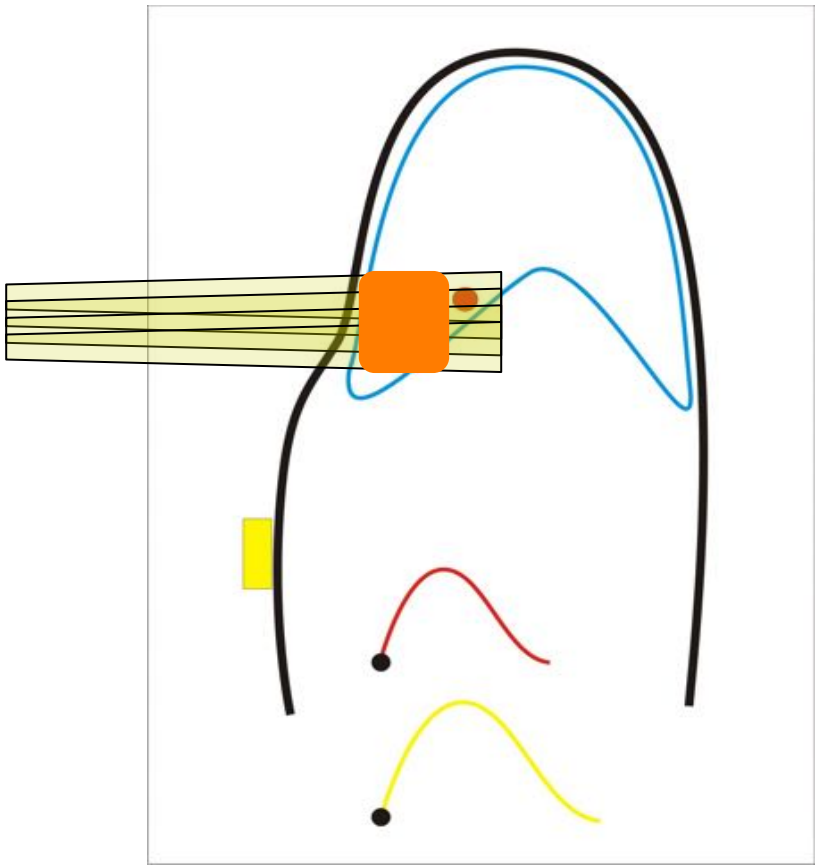
Tracking versus gating

- Gating



➢ Higher dose, concentrated

- Tracking



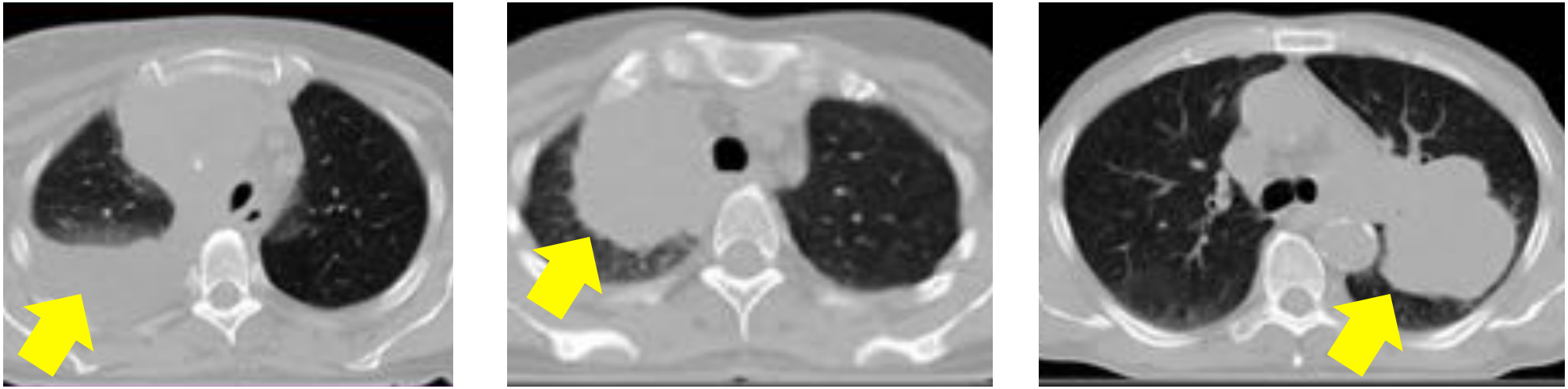
➢ Lower dose, larger volume

Challenges

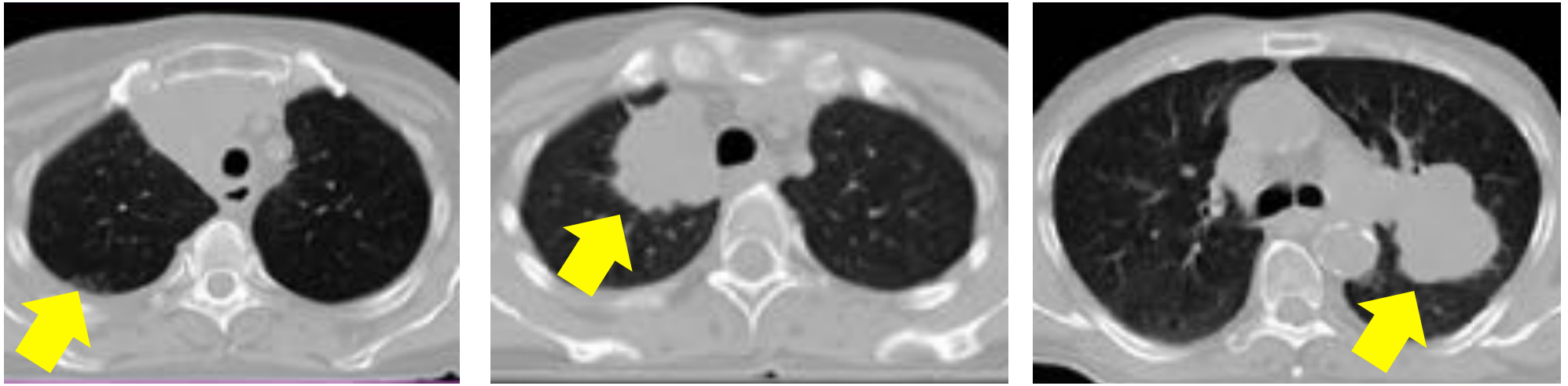
Tumor: shrinkage, progression

Normal tissue: pleural effusions, atelectasis, weight loss

Plan

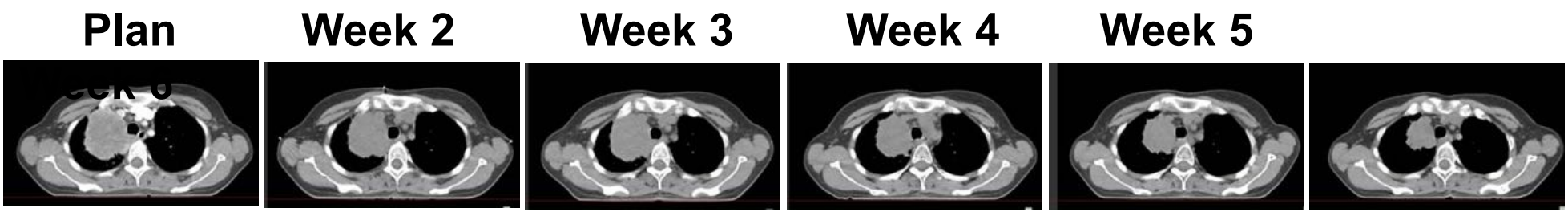


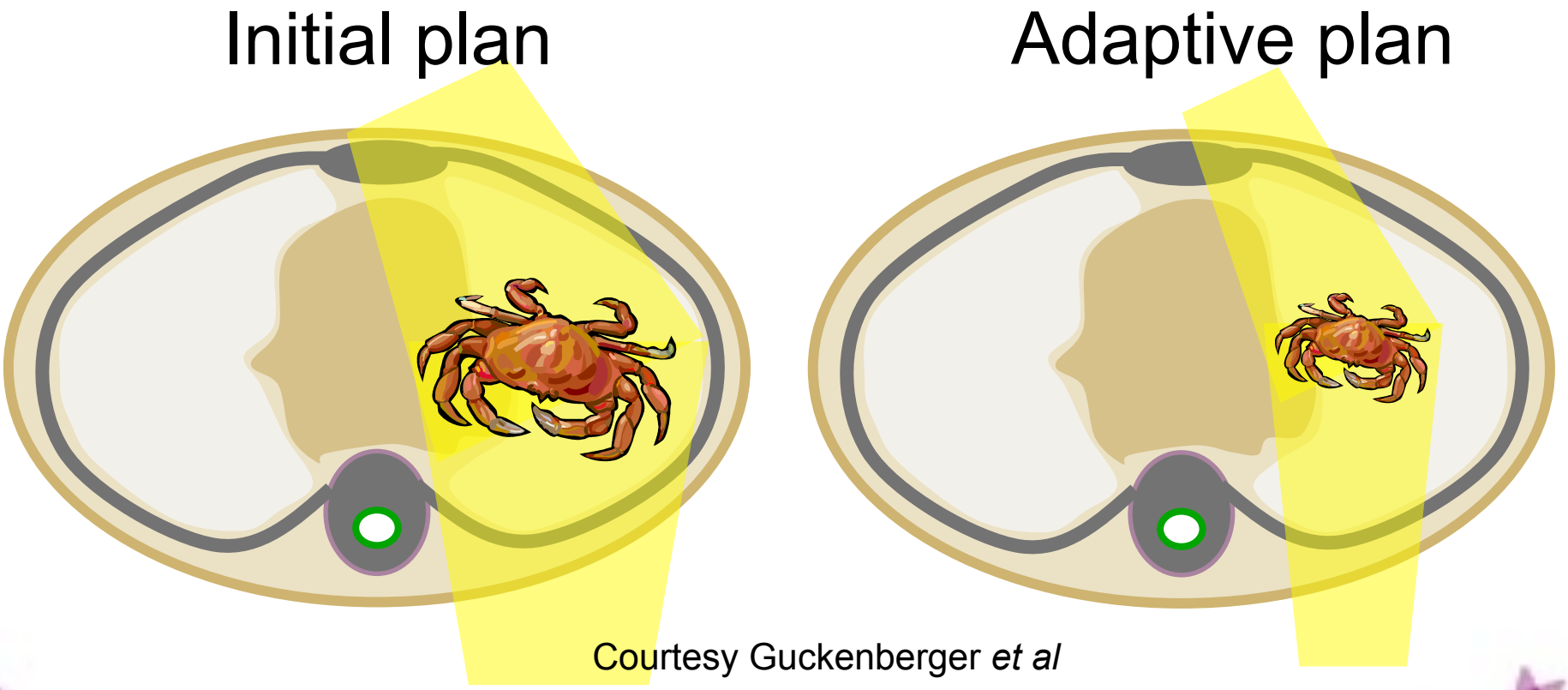
Week 6



Courtesy Guckenberger *et al*

Adaptive radiotherapy …

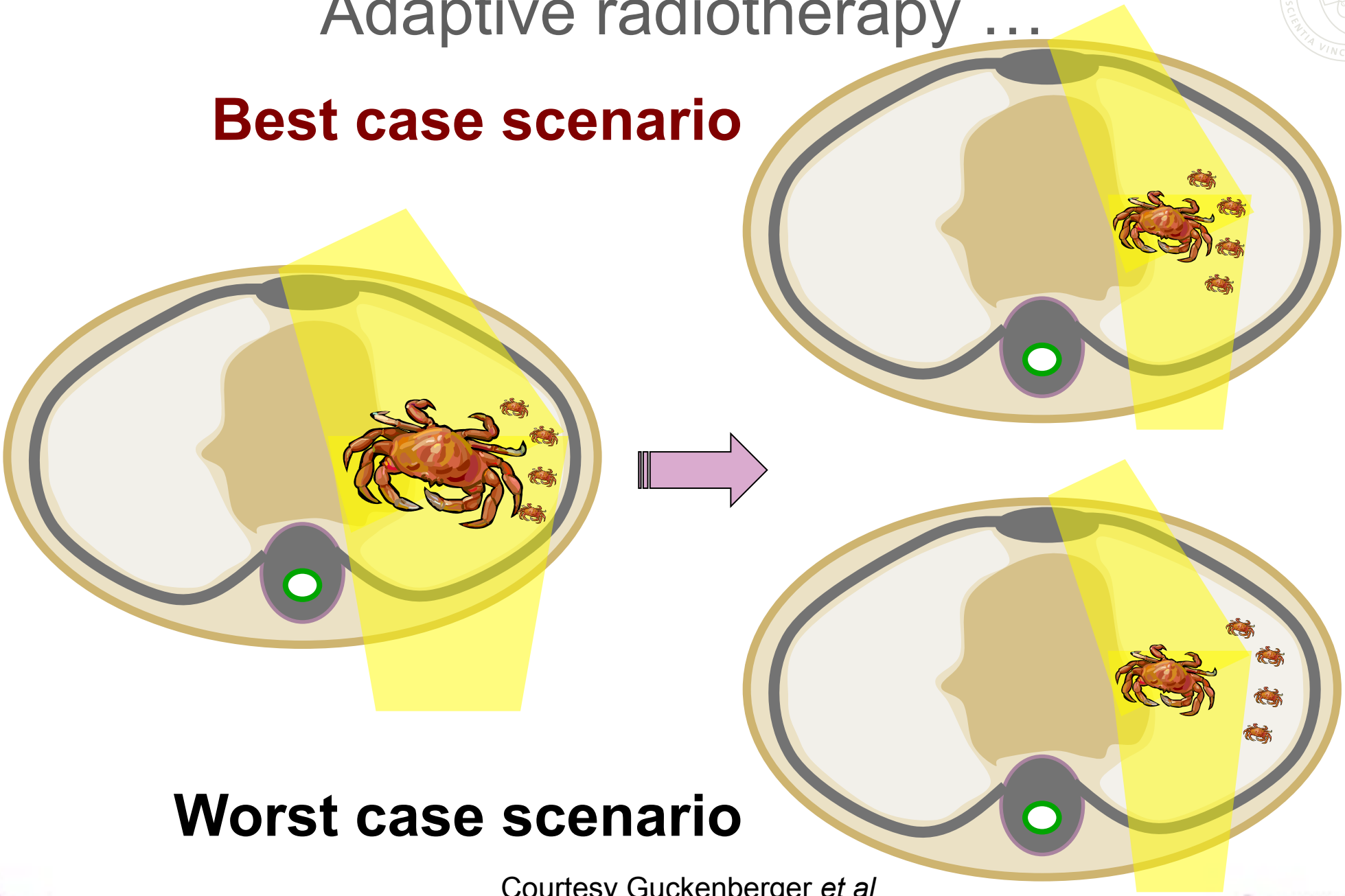




Courtesy Guckenberger *et al*

Adaptive radiotherapy …

Best case scenario

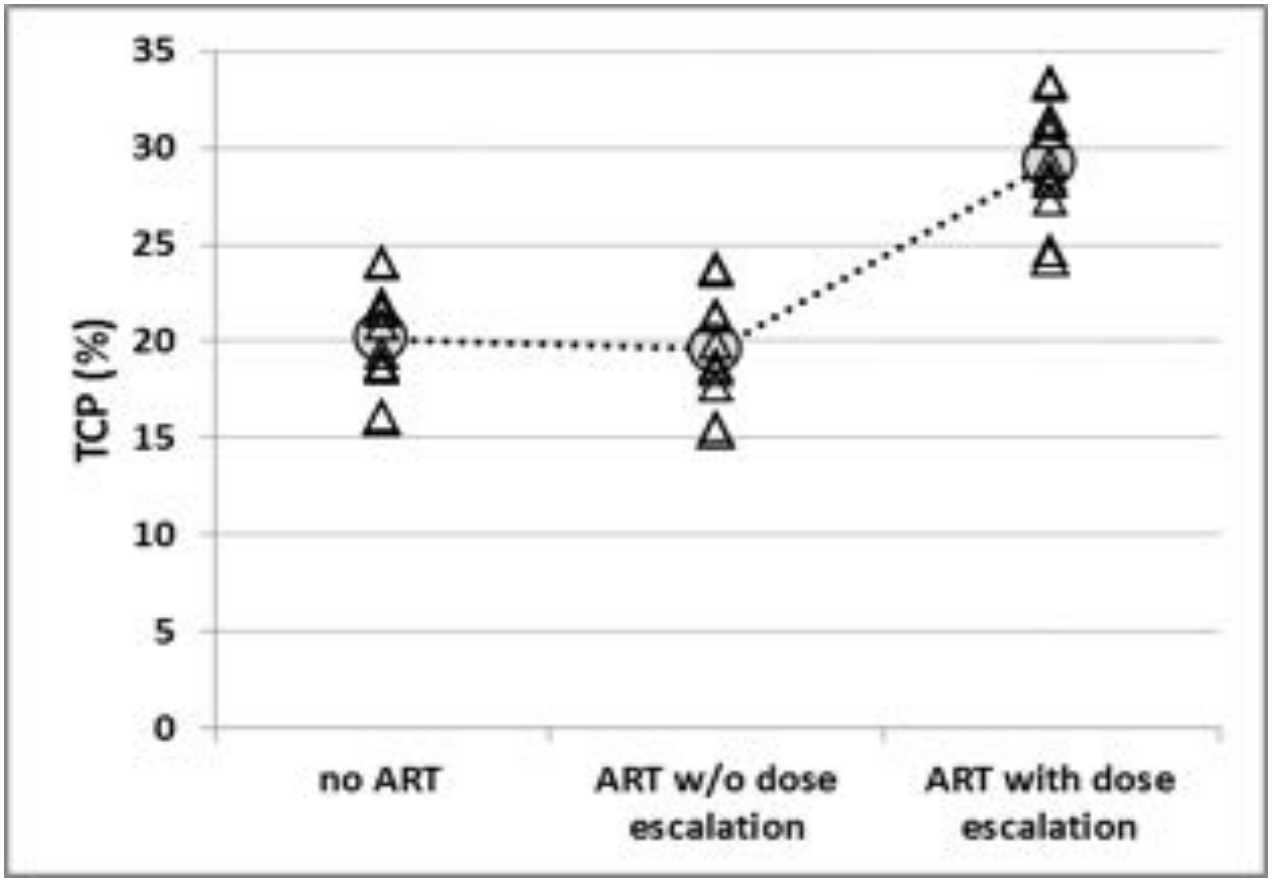


Worst case scenario

Courtesy Guckenberger *et al*

Adaptive radiotherapy …

Calculation of TCP for adaptive RT
considering doses to GTV & microscopic extension



Mean dose GTV

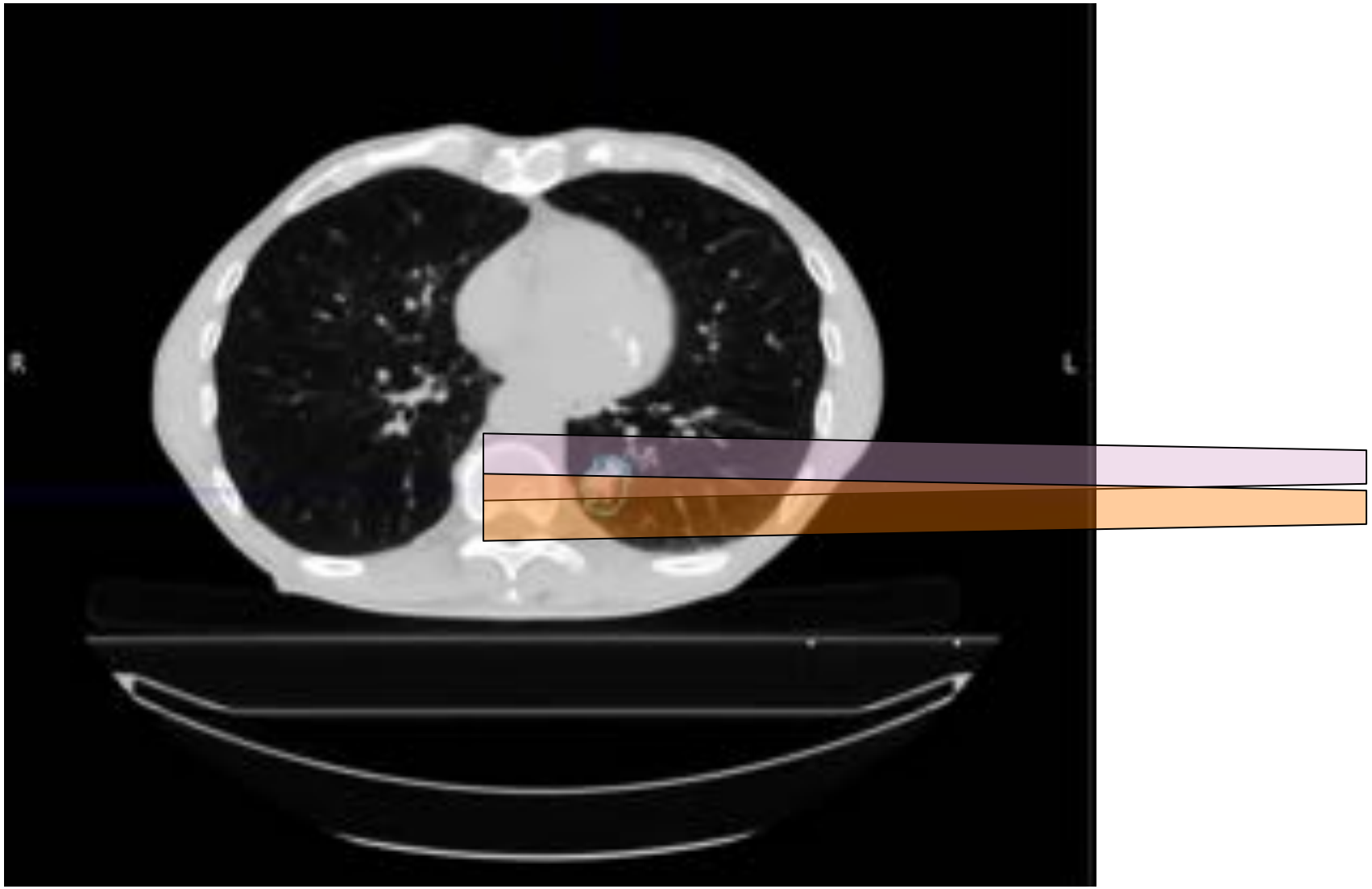
73Gy

68Gy

Guckenberger, *et al.*, IJROBP 2011

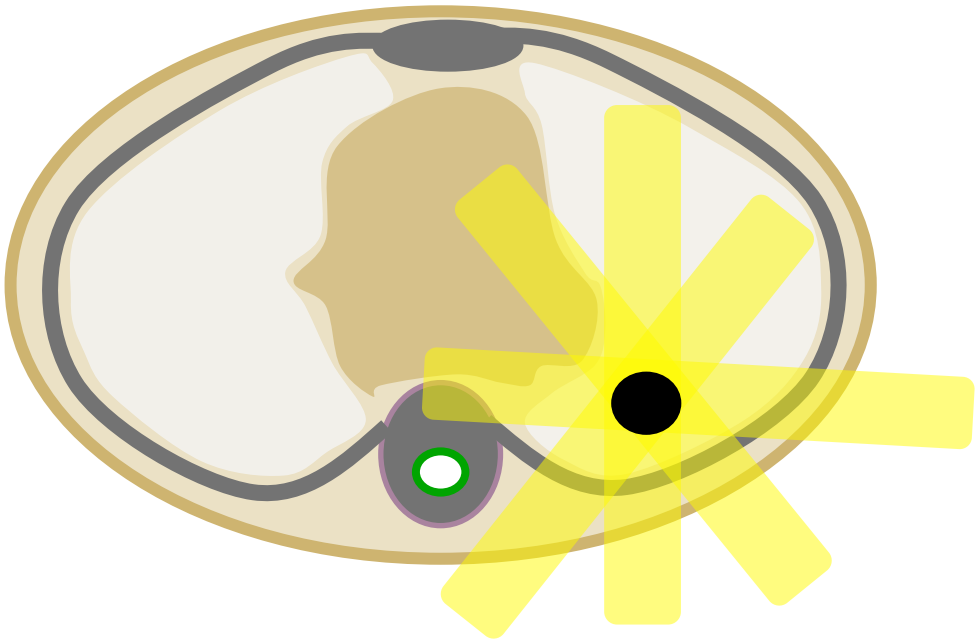
Isotoxic dose escalation

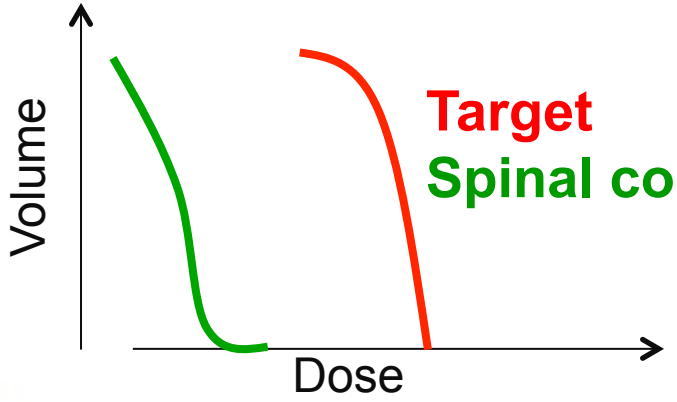
Challenges



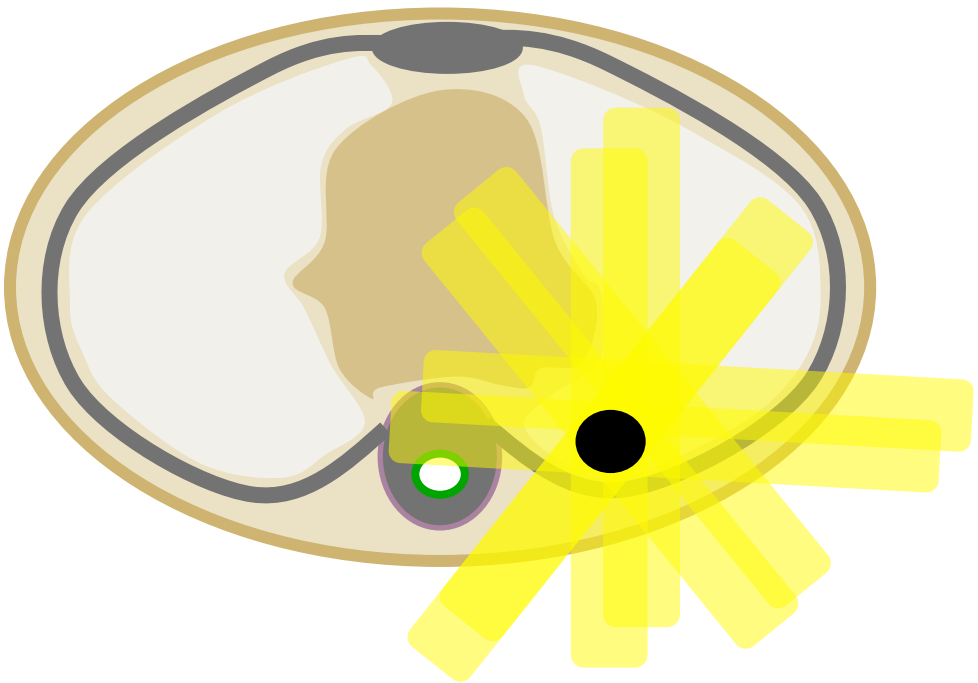
Challenges

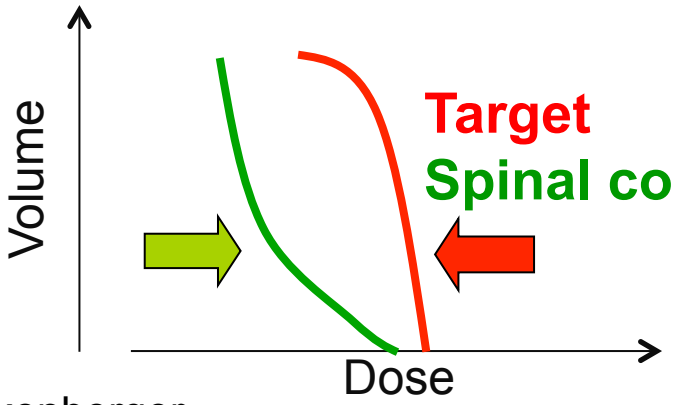
Treatment planning





IGRT treatment

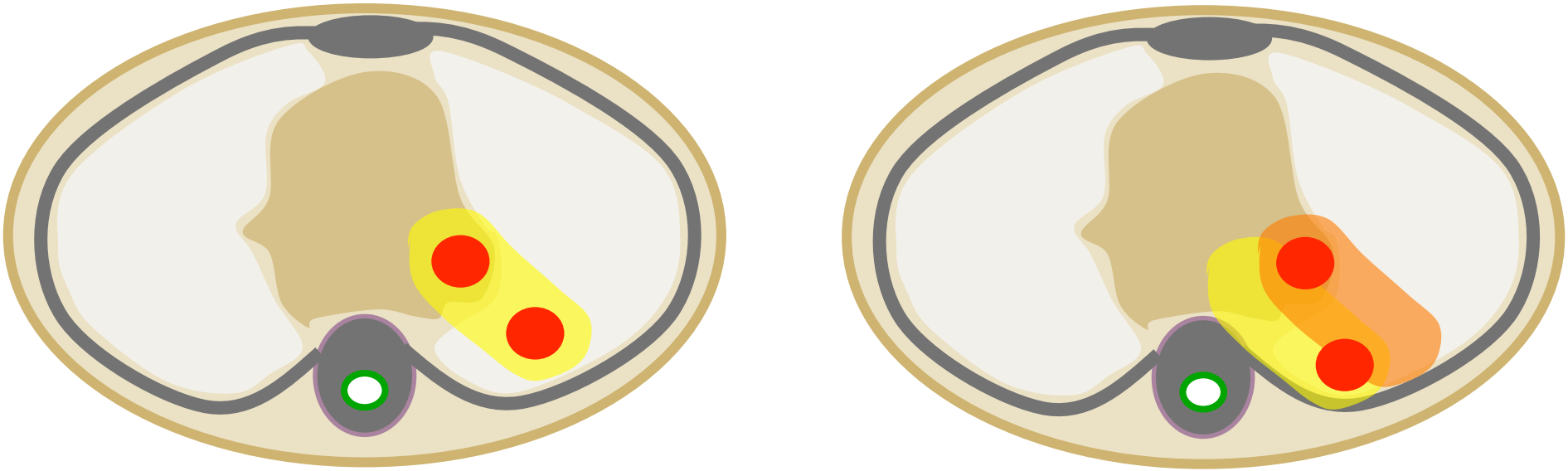




Courtesy M. Guckenberger

Challenges

Treatment planning **IGRT treatment**



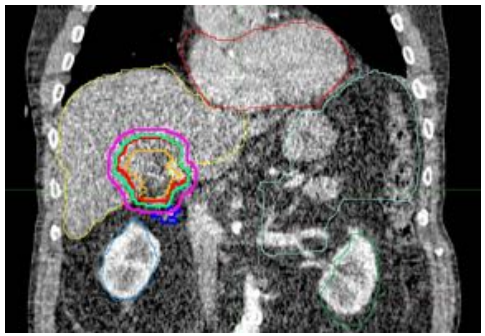
Courtesy M. Guckenberger

Shift of the primary relative to the nodal target

- Volume imaging is required to evaluate these effects
- Shifting the patient or the beam does not solve the problem

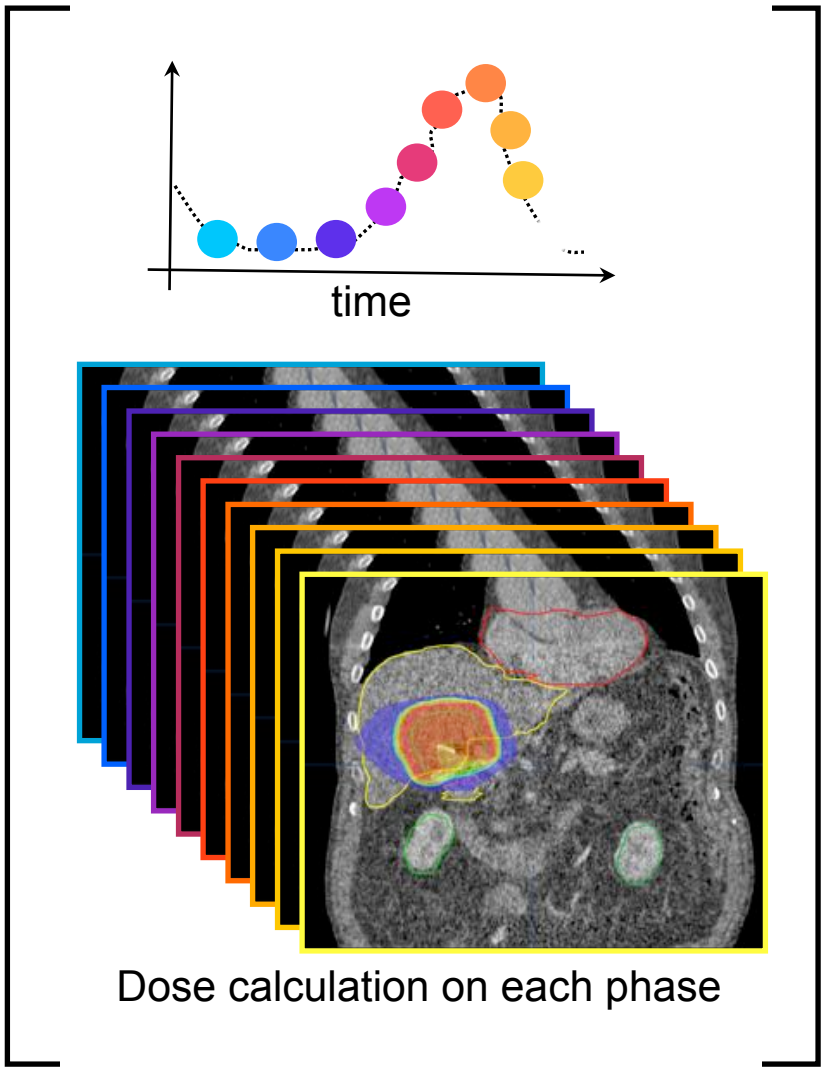
Challenges

4D CT dose accumulation



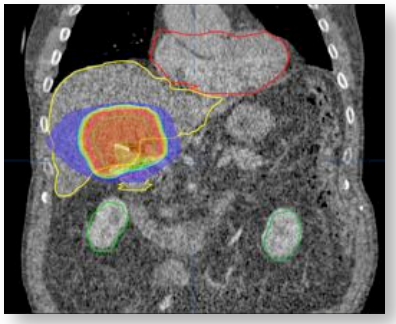
4D CT (10 phases)

$$\sum$$



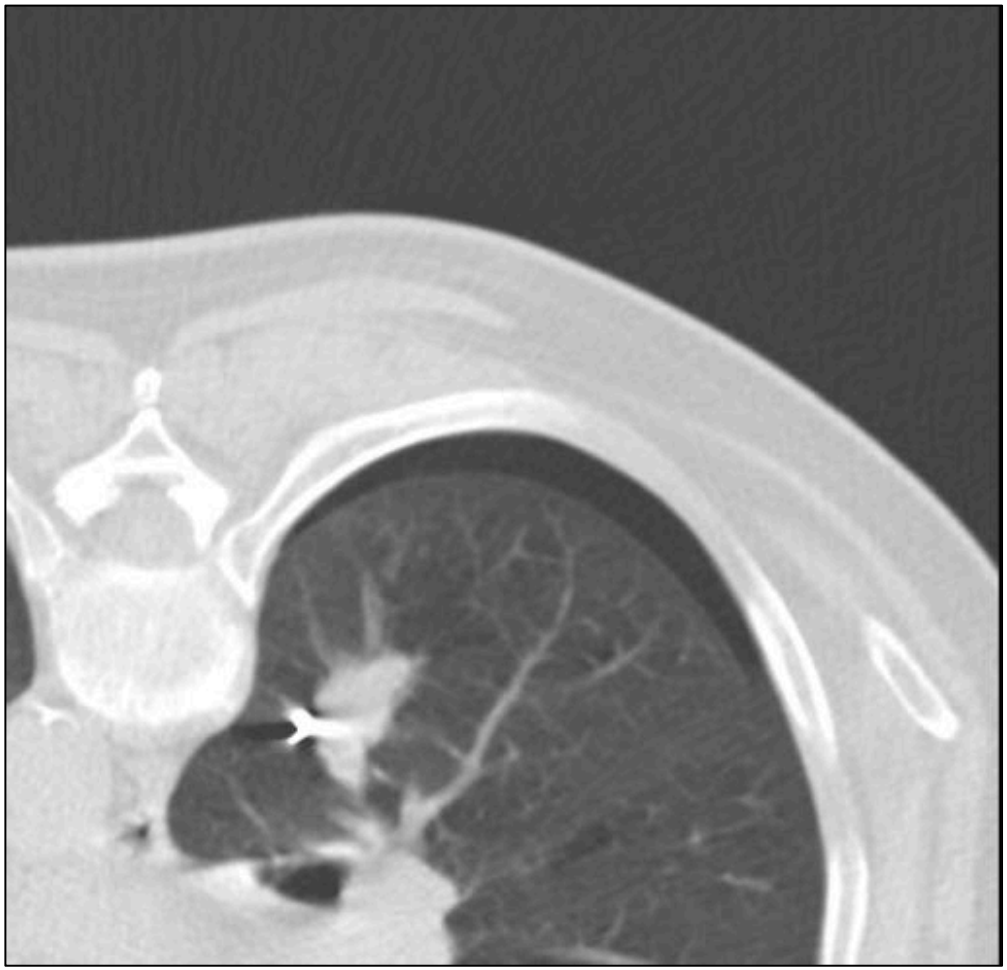
Dose calculation on each phase

$$=$$



Marker placement

- Oops ...

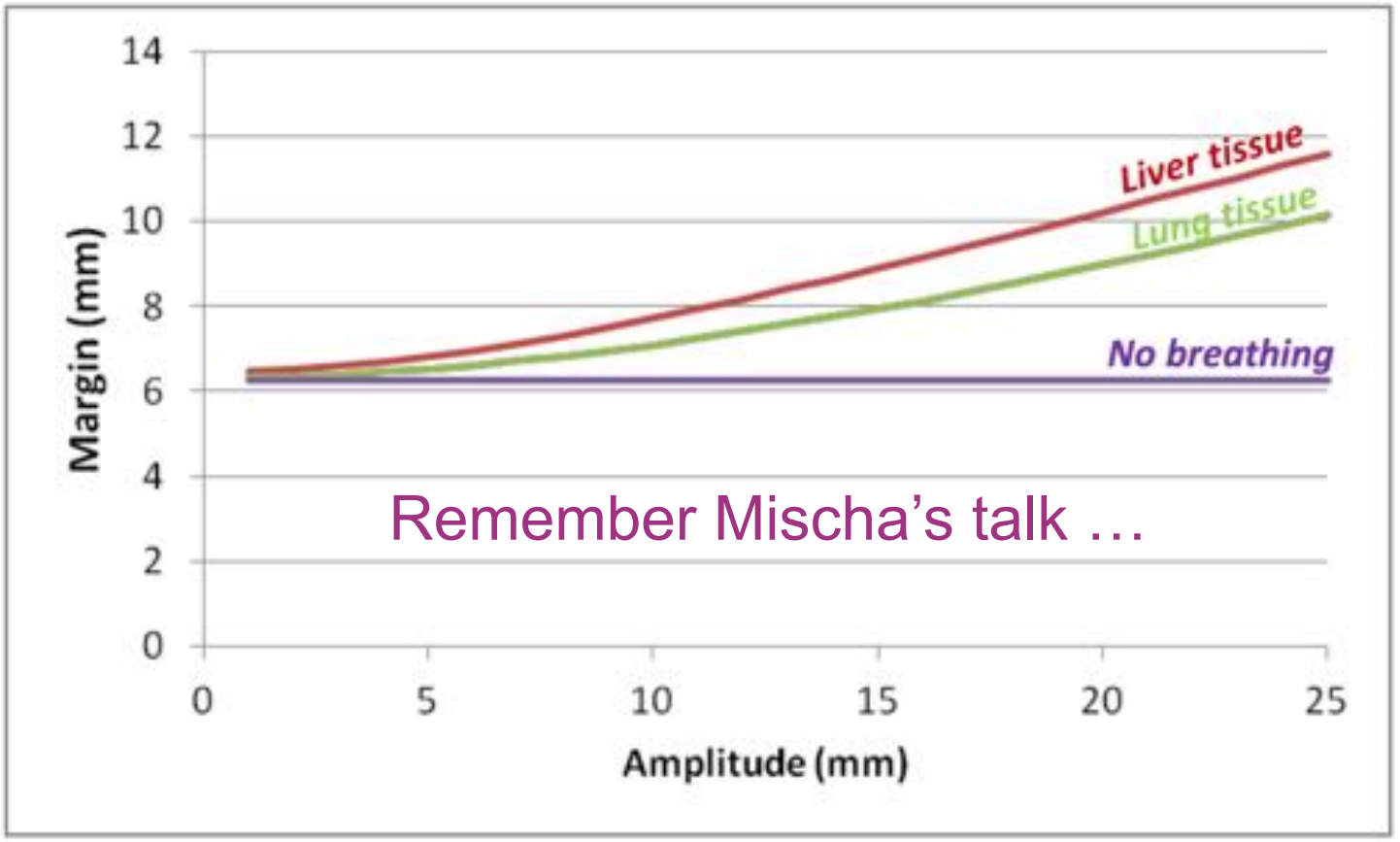


➢ Yes … relative high risk for pneumothorax

So … will we make a difference?

ESTRO School

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

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?).

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

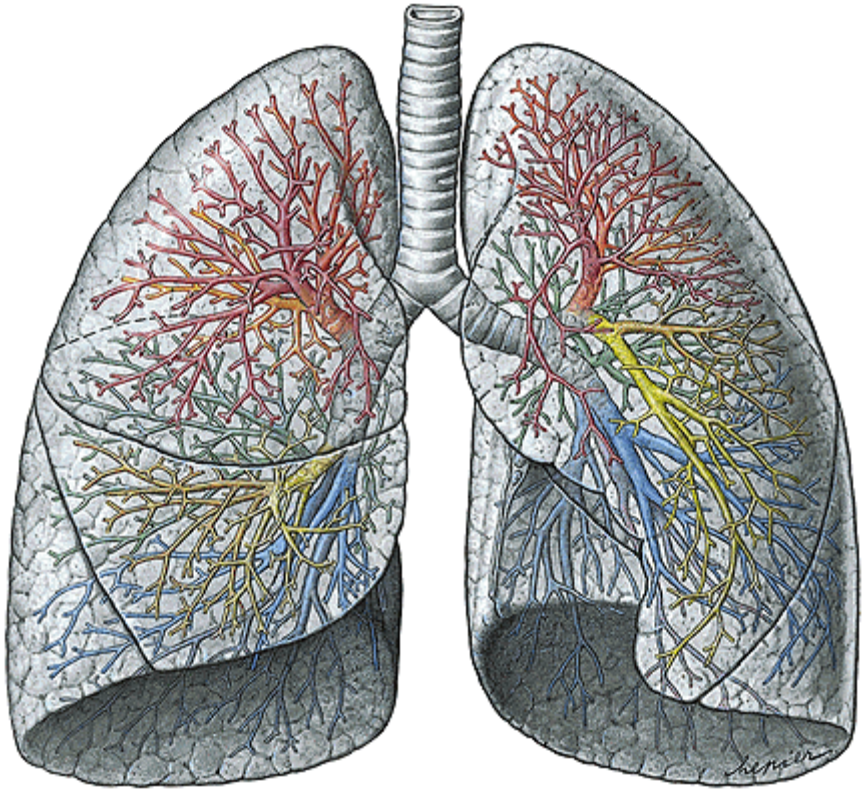
Learning Objectives

- **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



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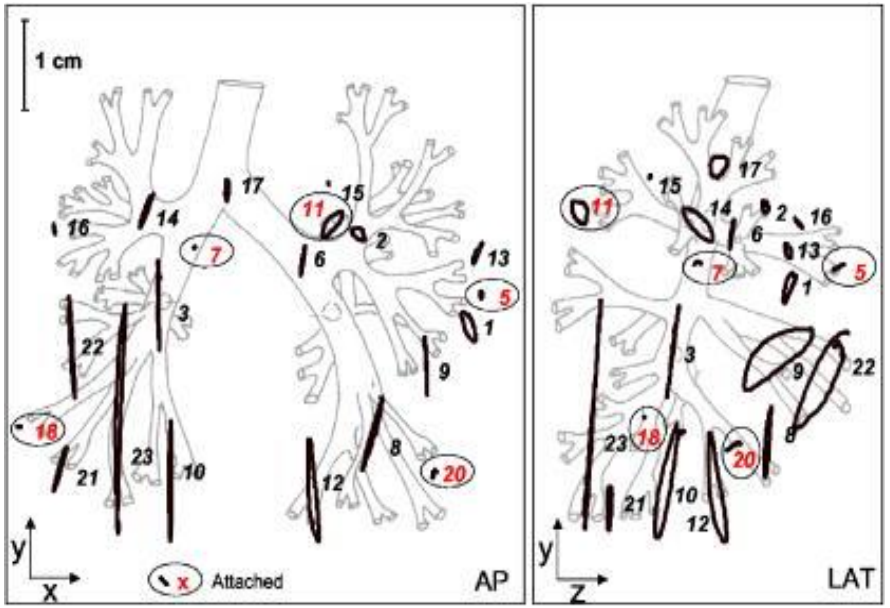
Observation of Motion

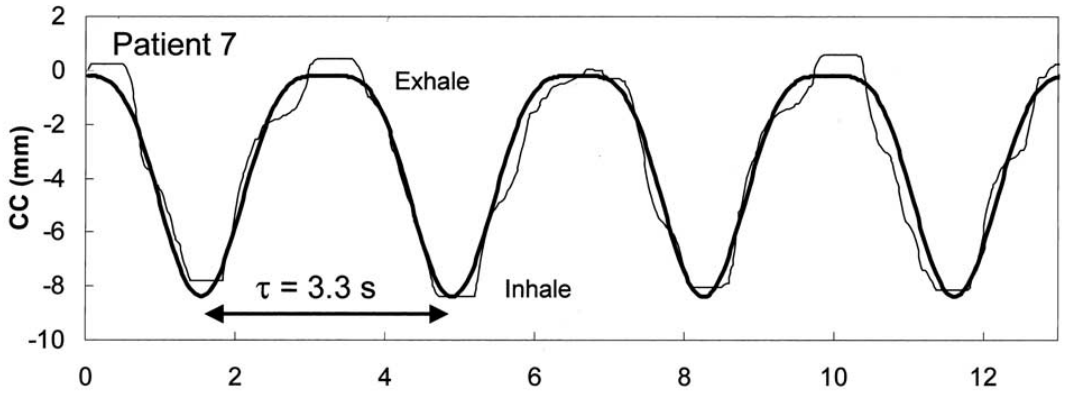
- Fluoroscopy



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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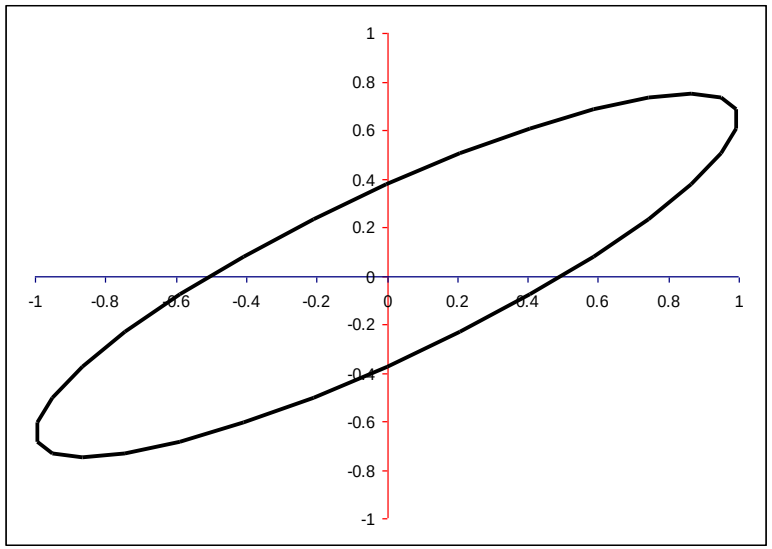
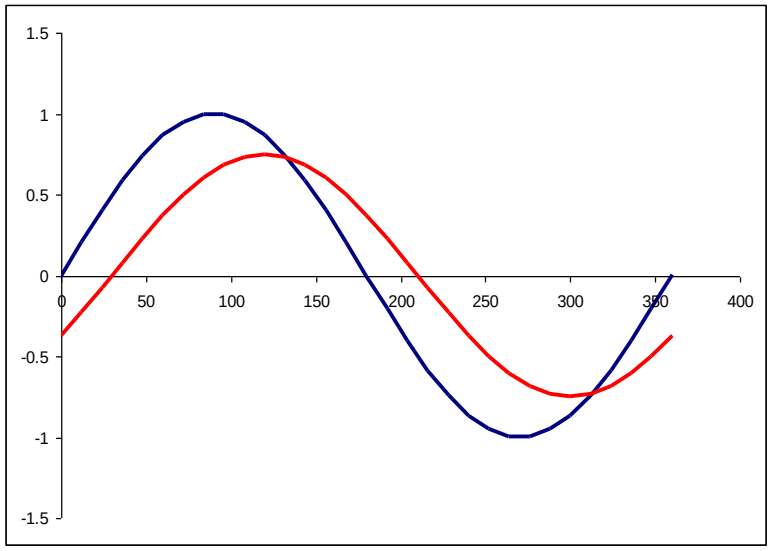
Observation of Motion





- 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

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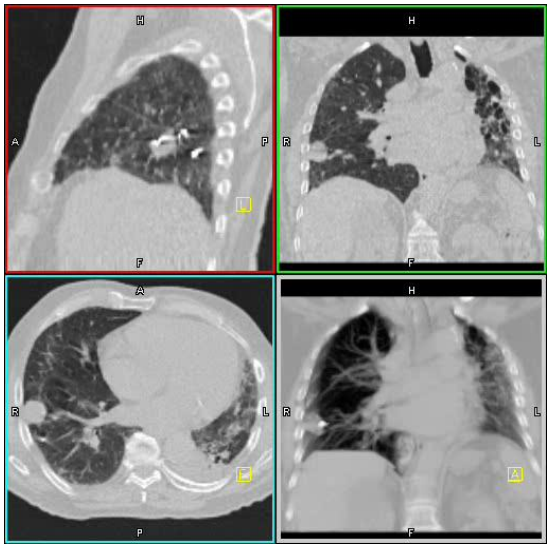
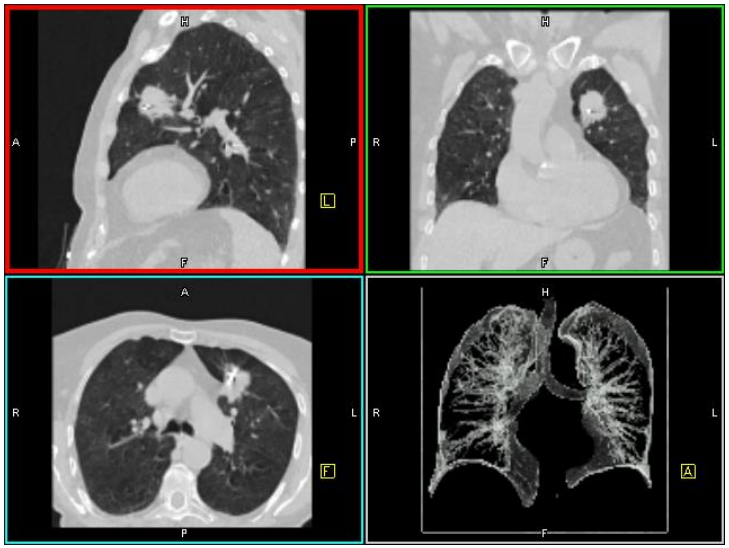
Observation of Motion

- **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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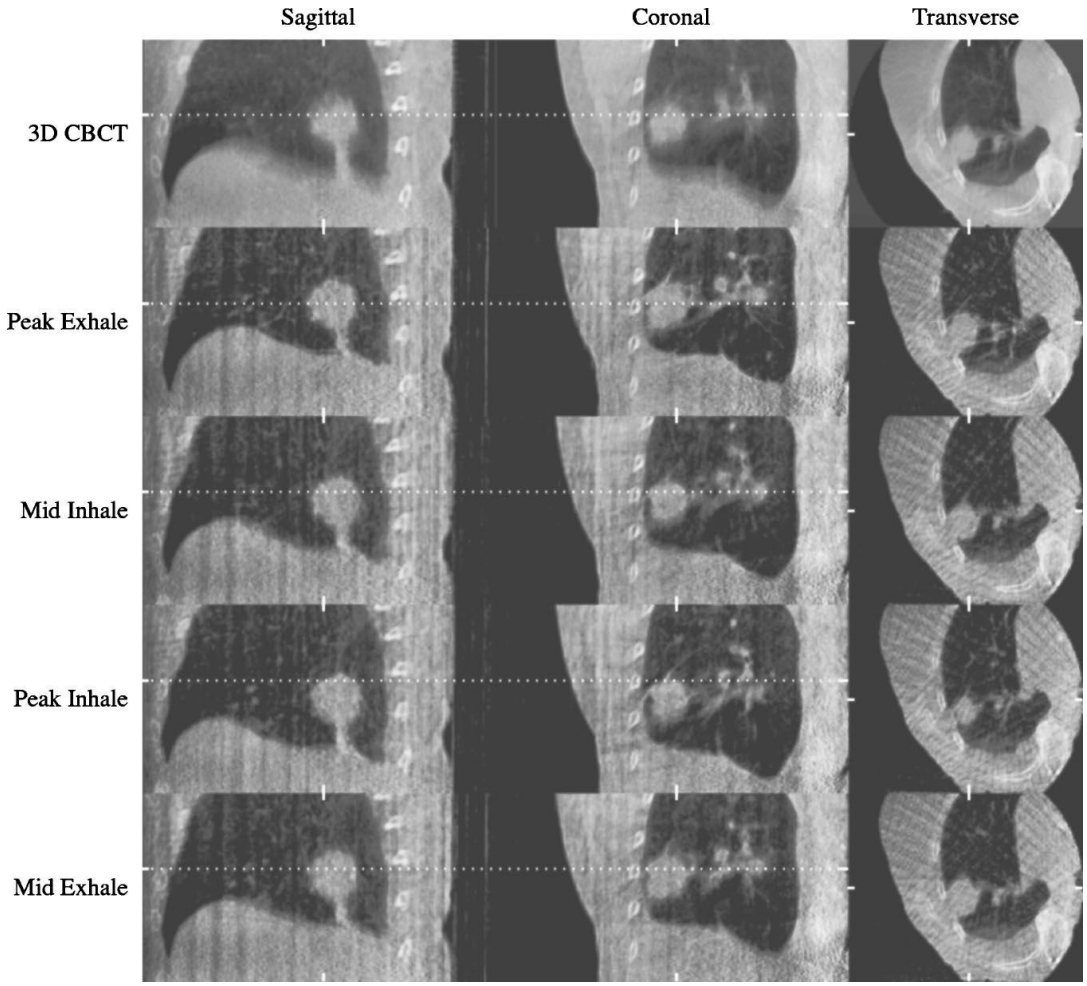
Respiratory Correlated Cone Beam CT Scanning



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

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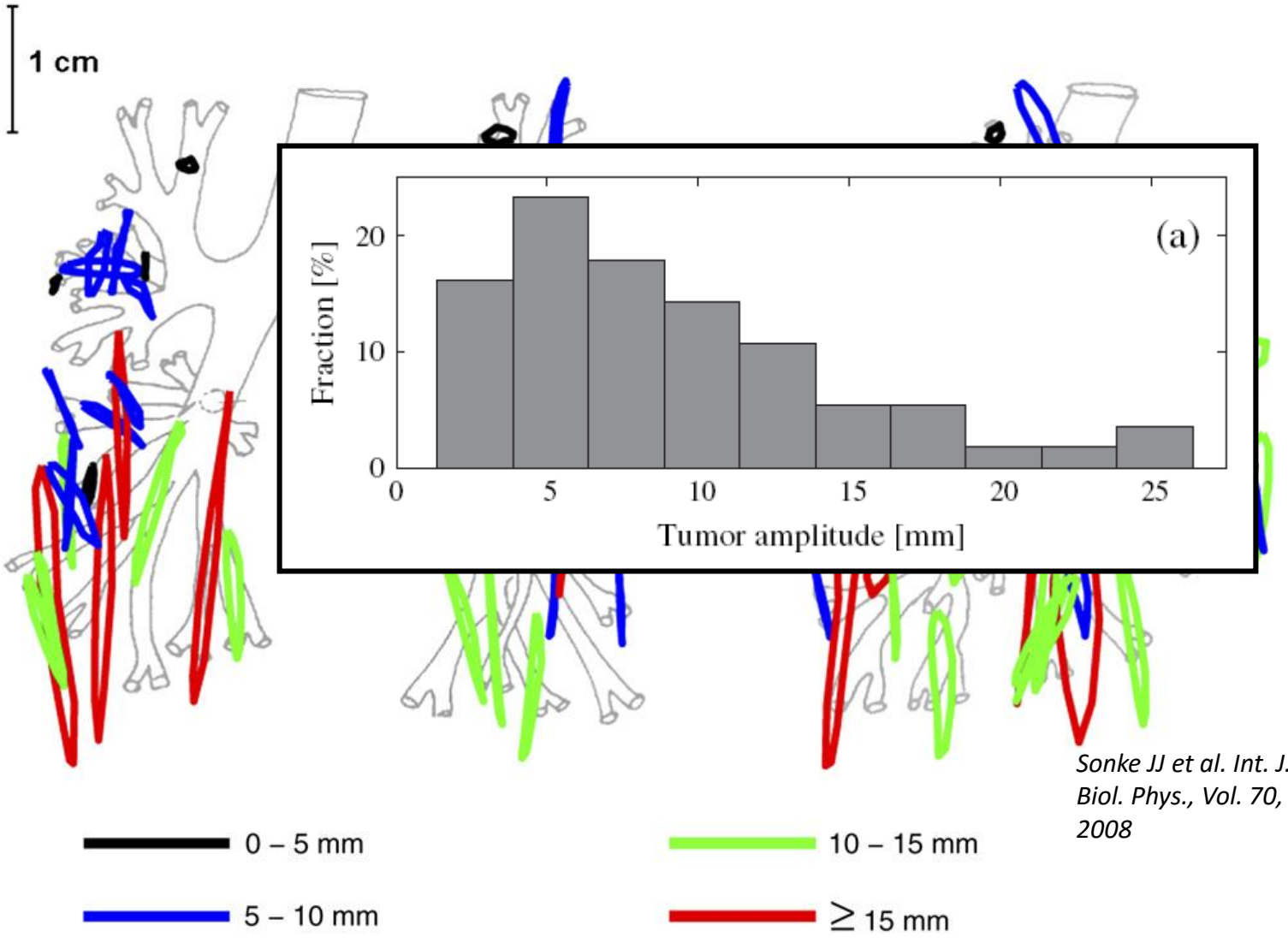
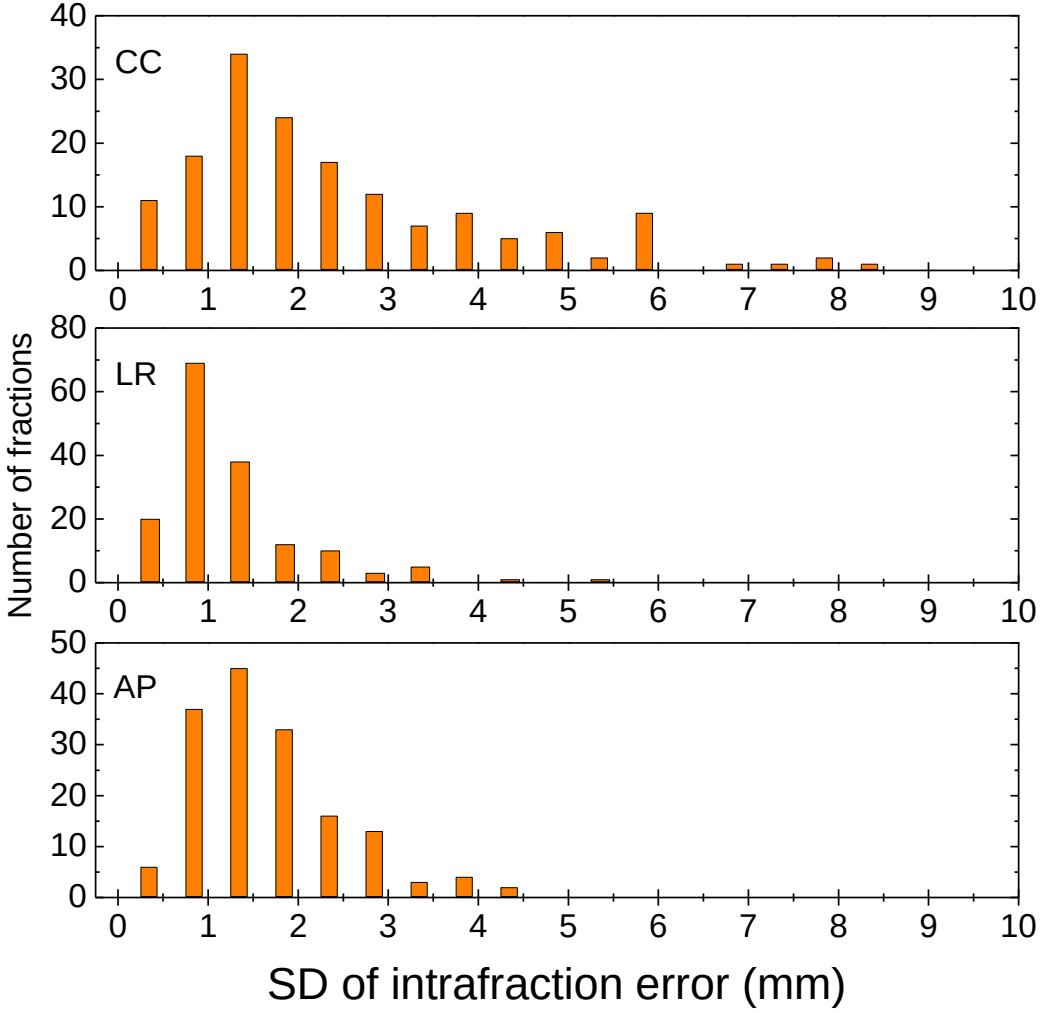
Motion Observations



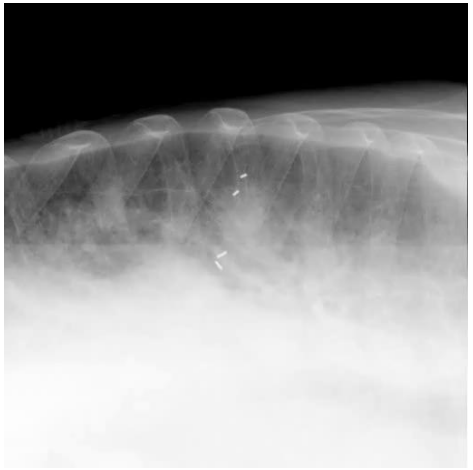
Sonke JJ et al. Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 590–598, 2008

Erasmus MC

Distribution of Intra-fractional Respiratory Motion (1 SD)



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



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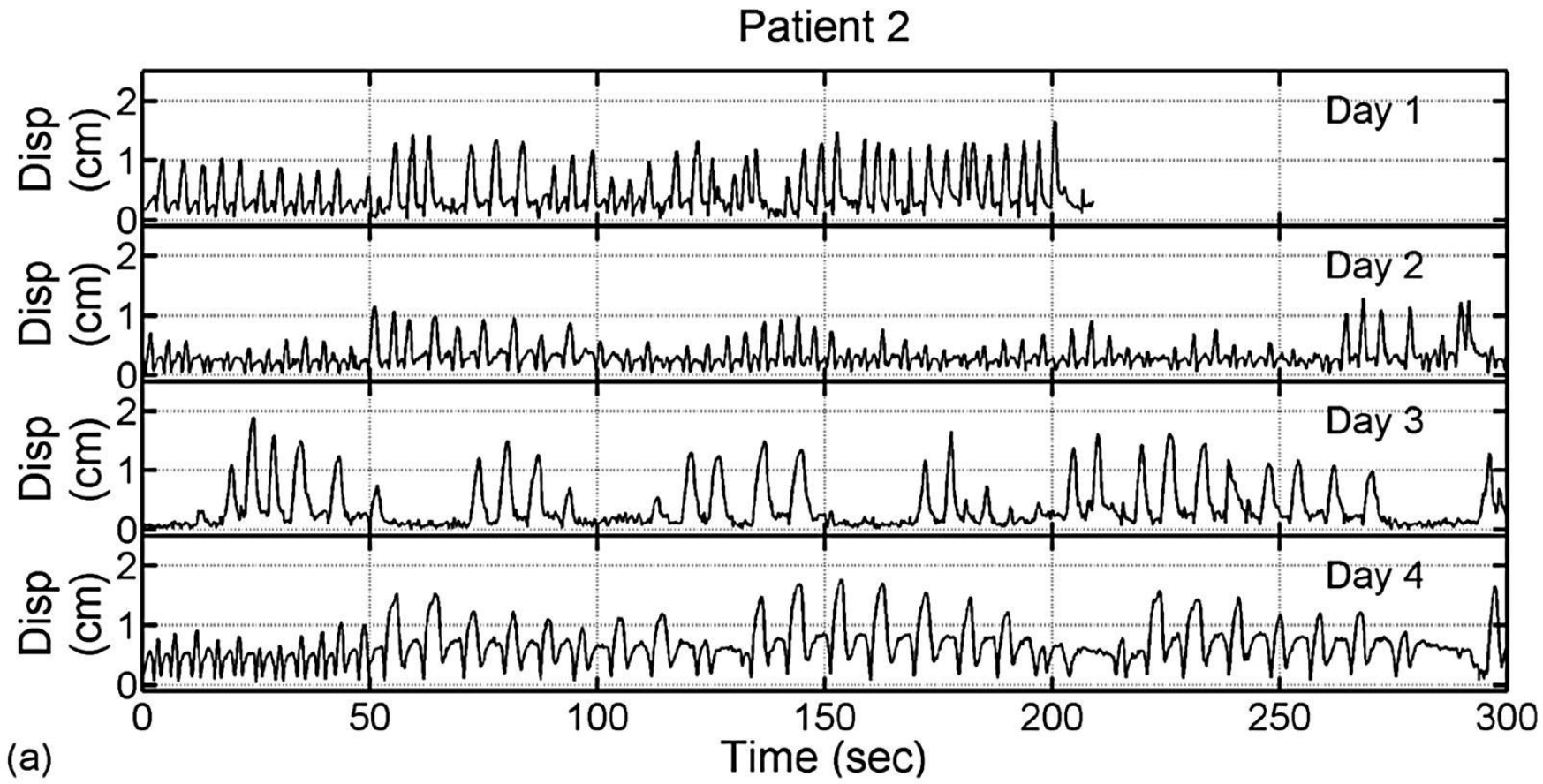
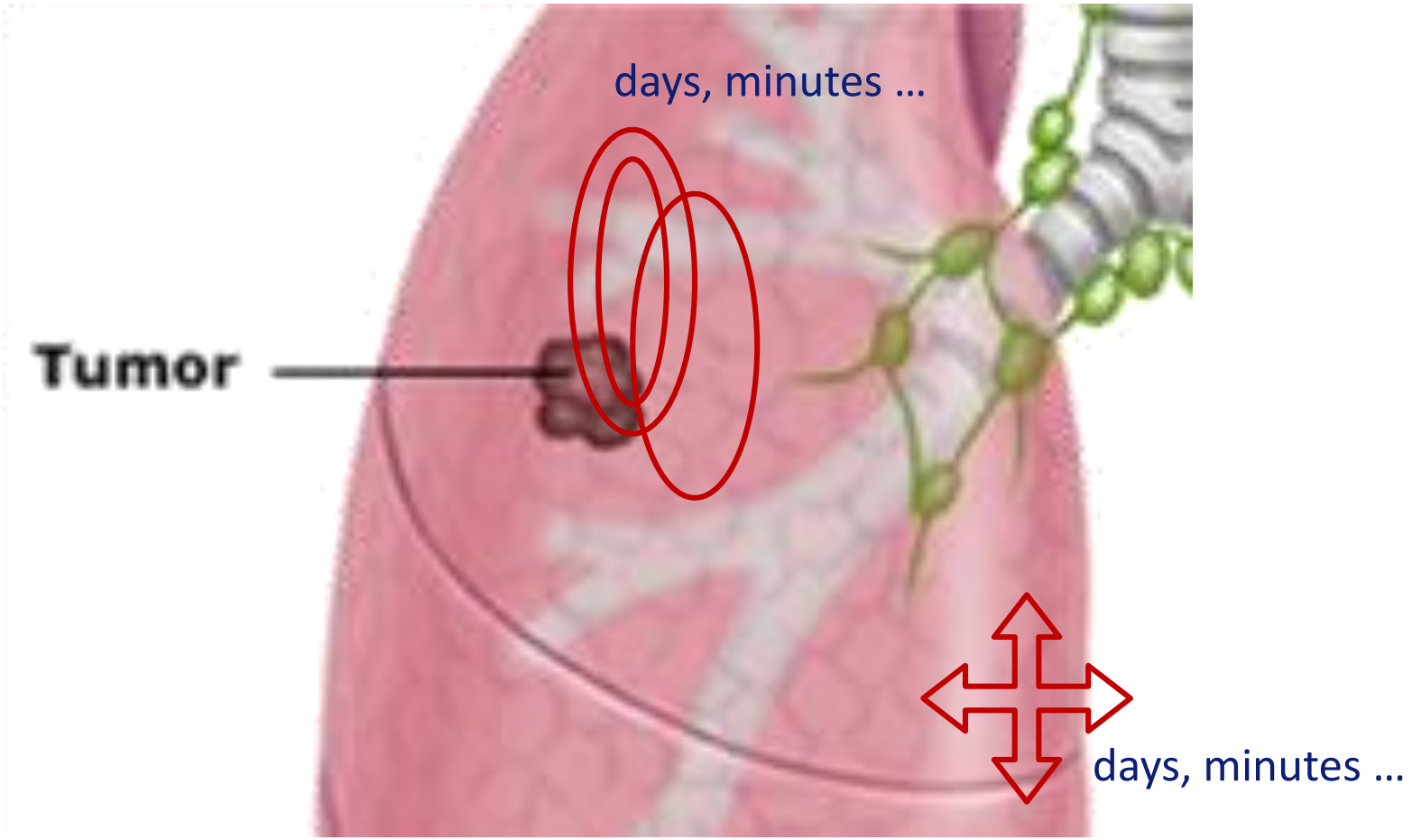
Day-to-Day Variation in Lung Tumor Motion



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.

Erasmus MC

Various Types of Motion



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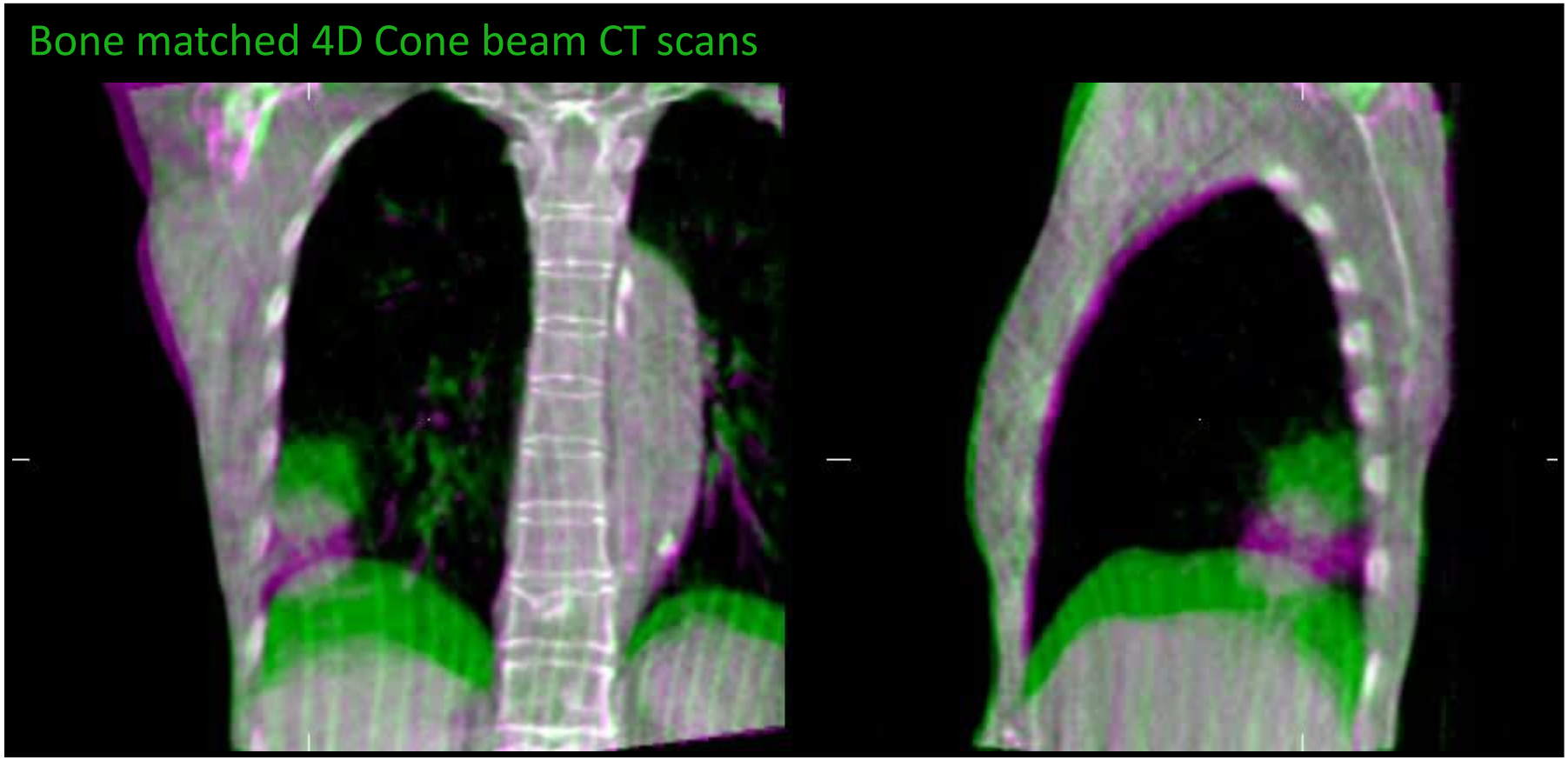
Systematic error and baseline shift



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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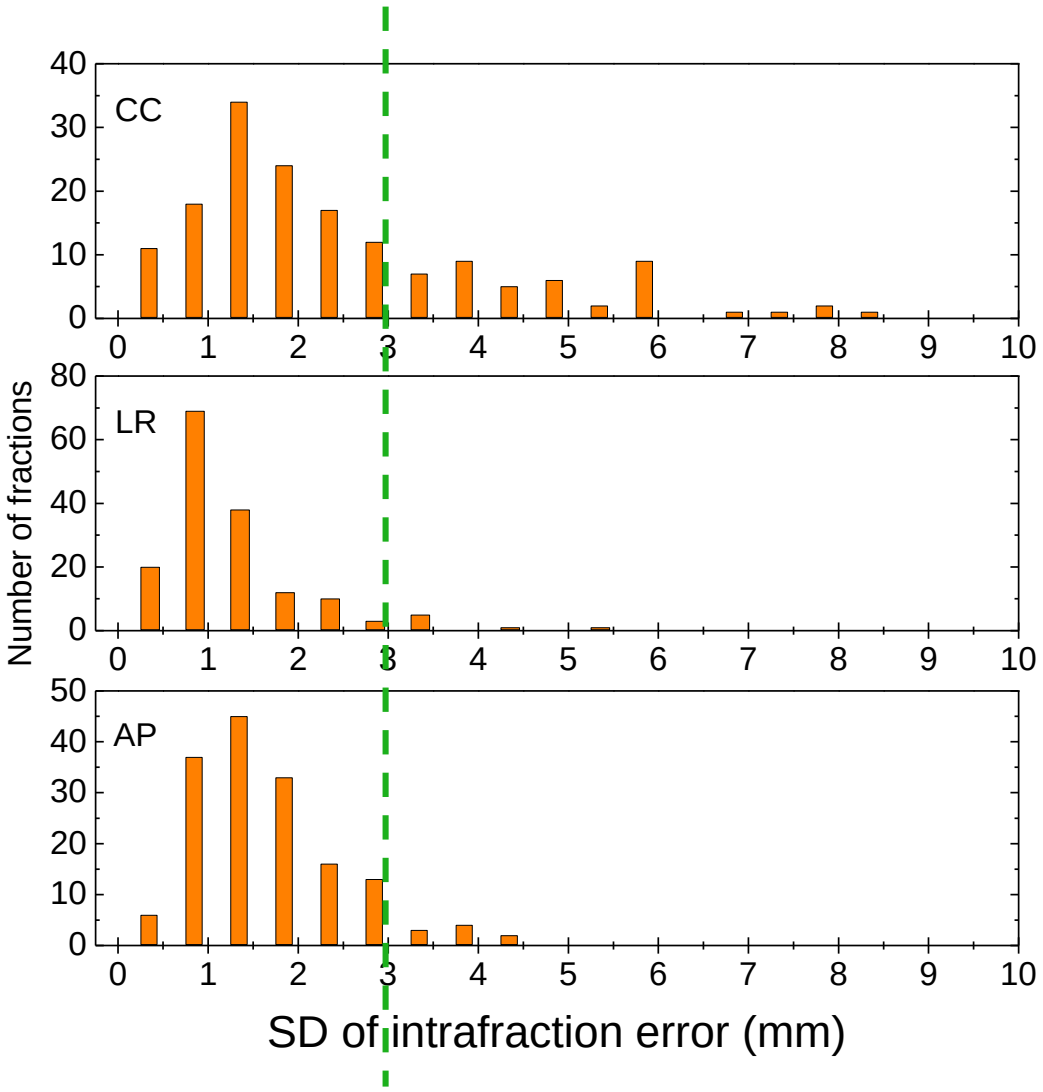
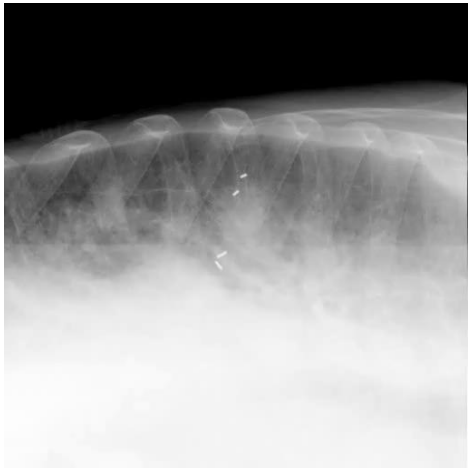
Distribution of Intra-fractional Respiratory Motion (1 SD)



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



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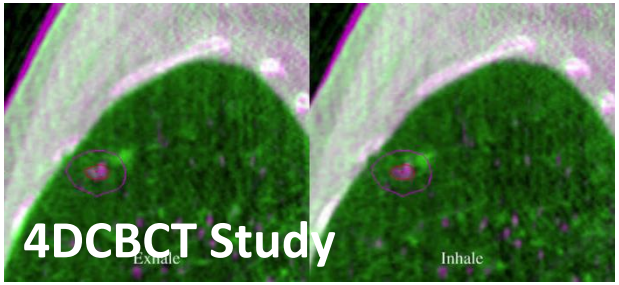
Intra-fraction Variability of Tumor, Bone, and Baseline (Minutes)



Average beam on time 28 ± 5 min

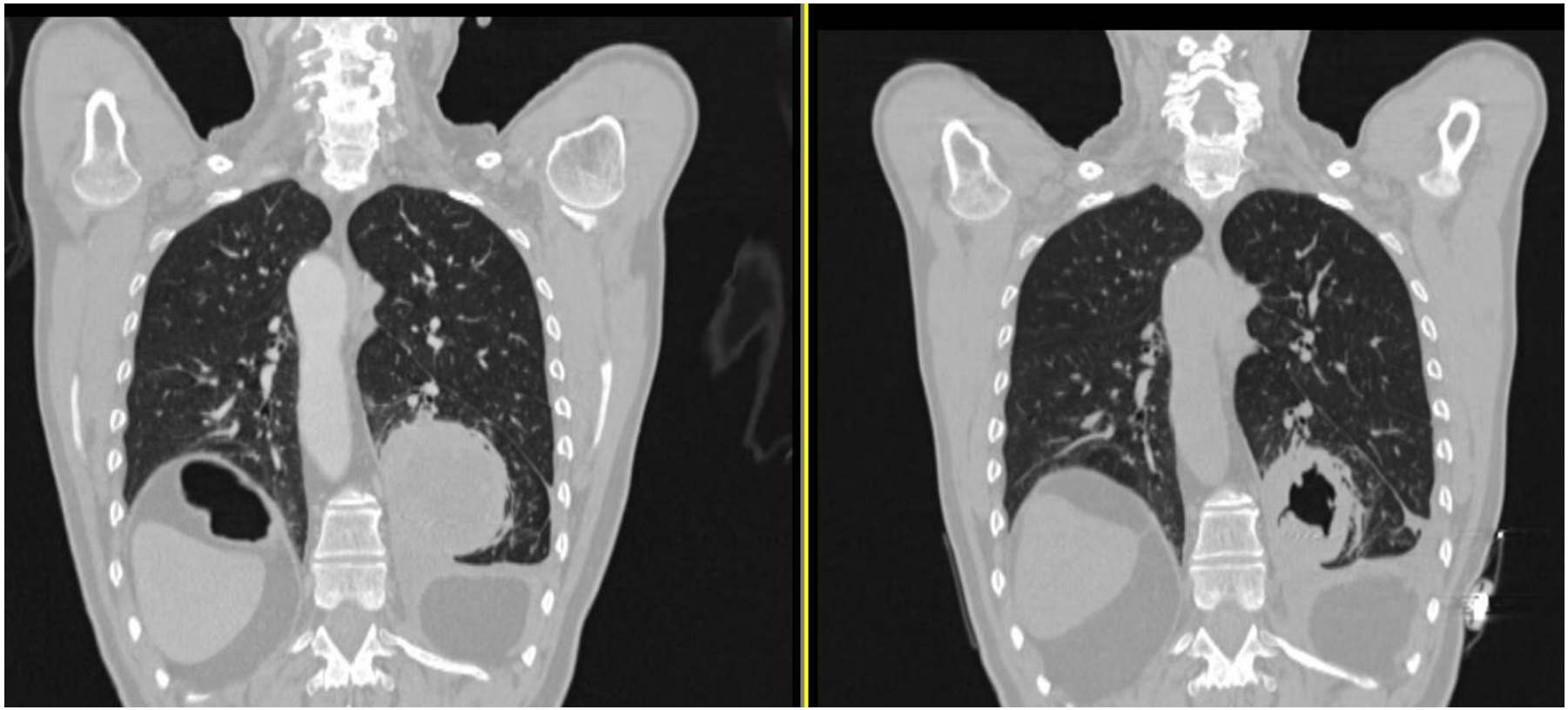
Table 3. Intrafraction variability of tumor, bony anatomy, and baseline in terms of group mean (GM), systematic error (Σ), and random error (σ)

	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

Erasmus MC

Changes in Volume and Shape



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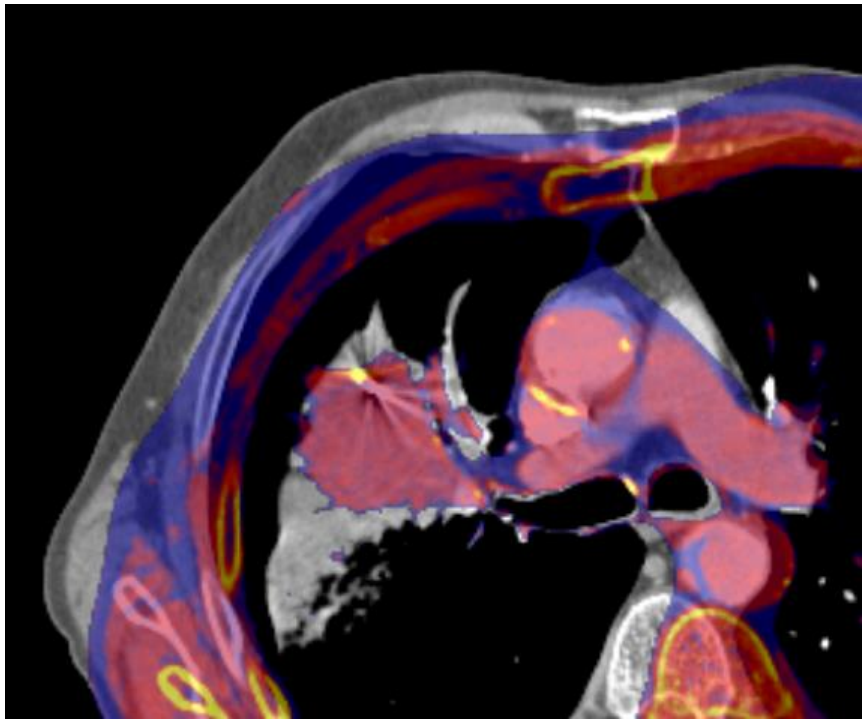
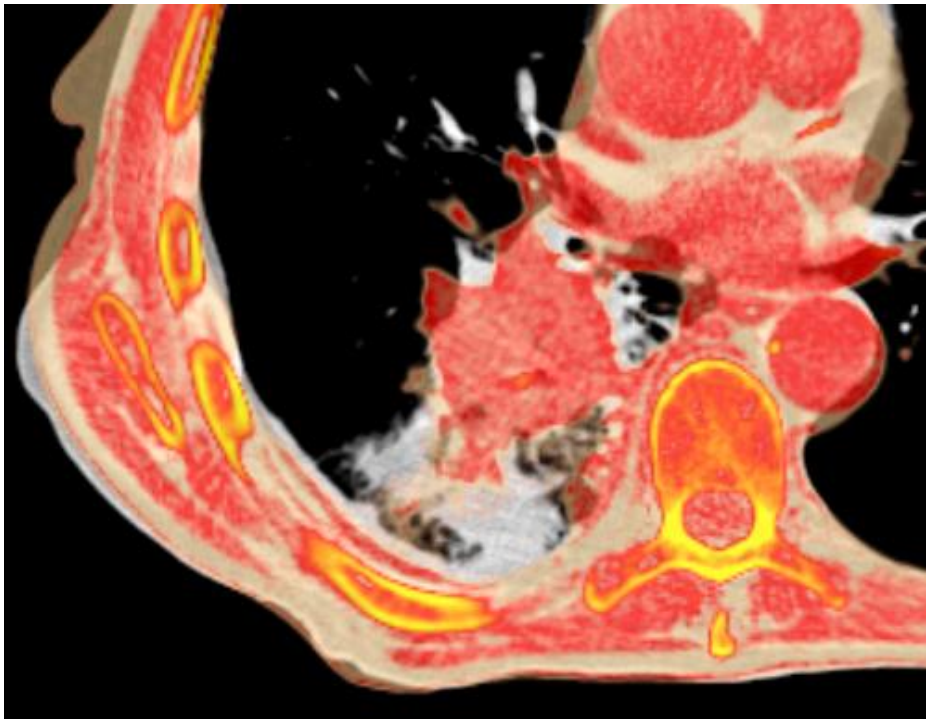
Tumor Changes in Volume and Shape



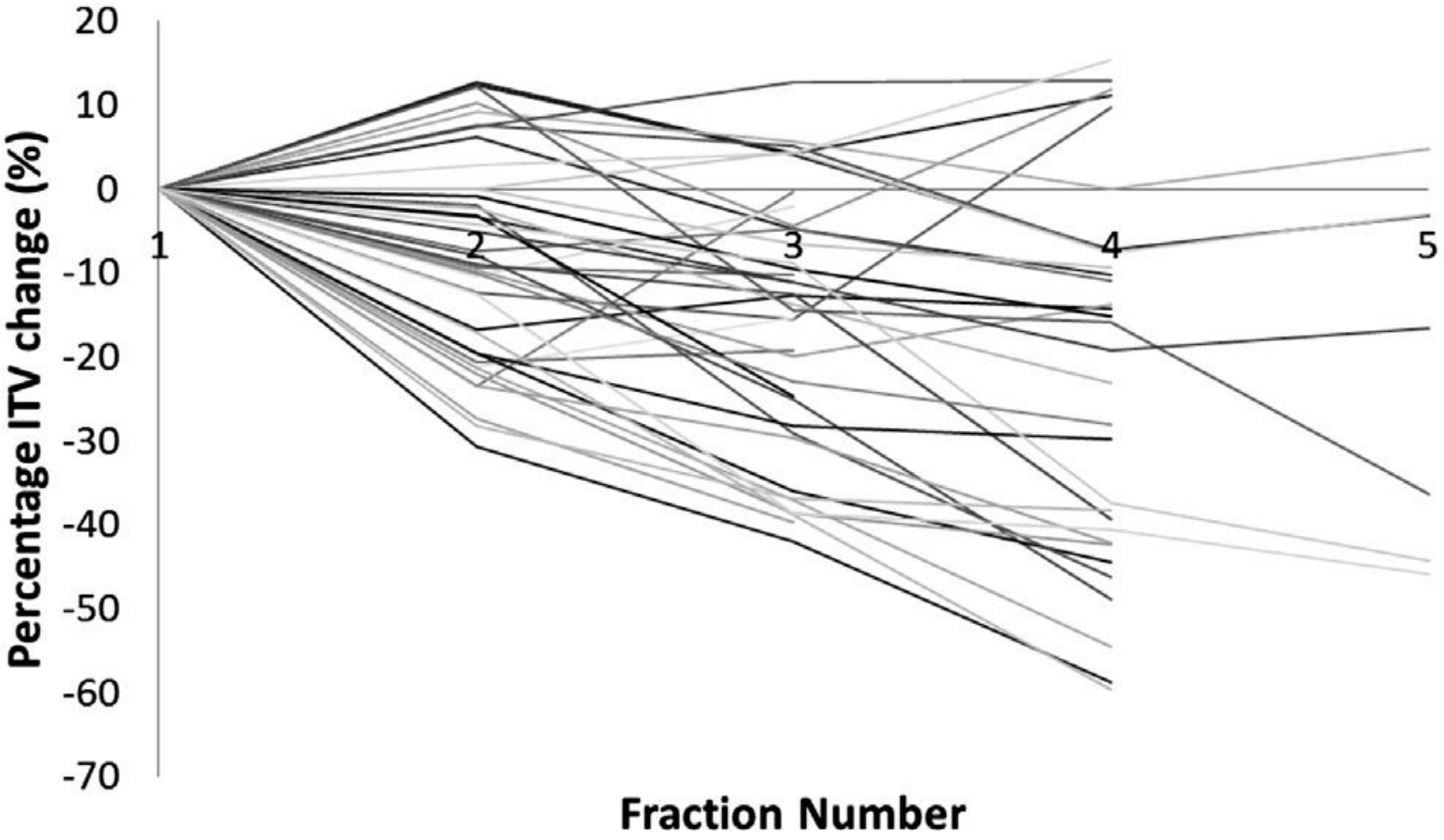


- In 4/44 (42 patients) tumors changes in volume and shape were observed

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

Erasmus MC

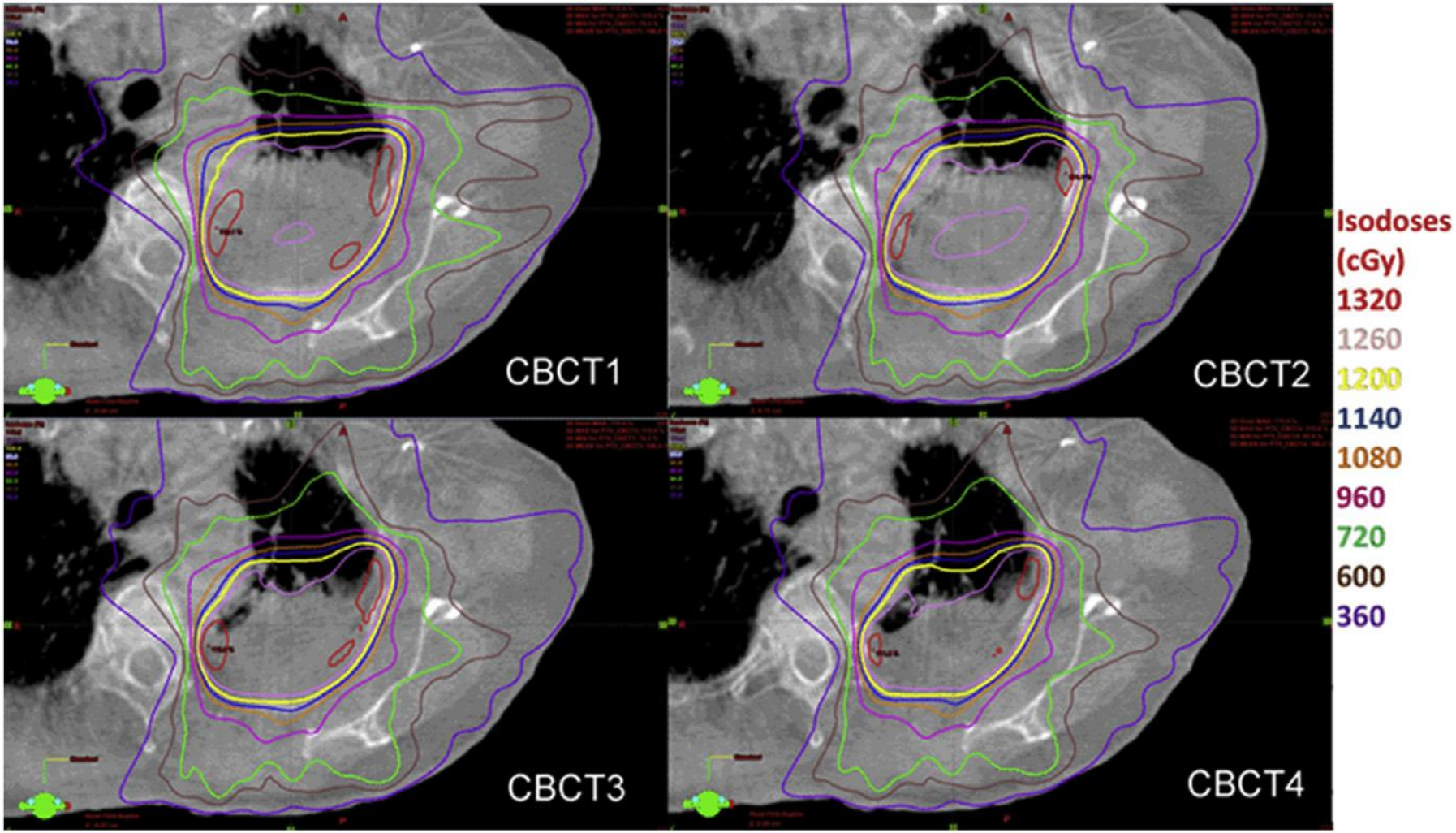
Changes in ITV



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

Erasmus MC

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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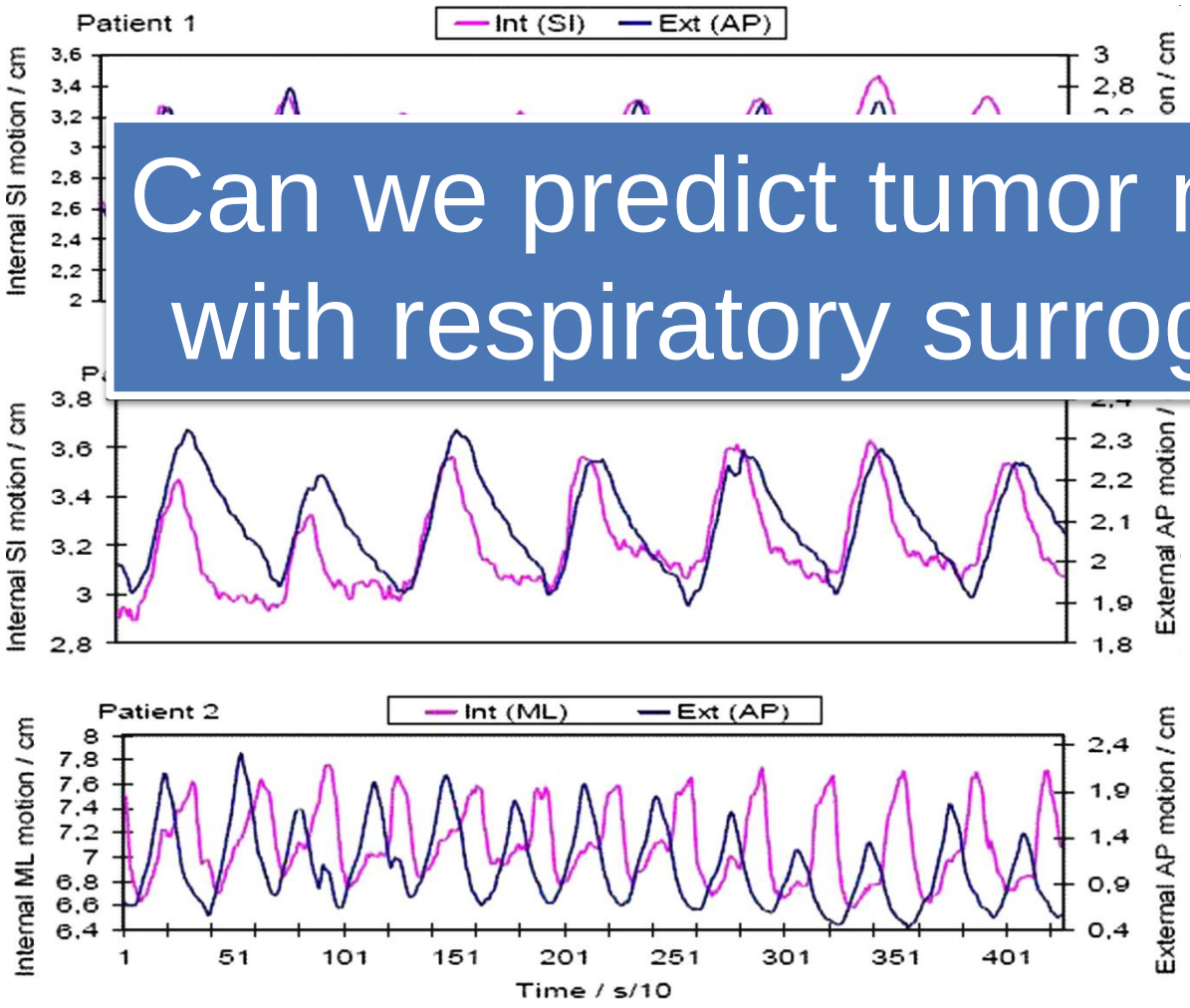
Bad Correlation Internal and External Signal

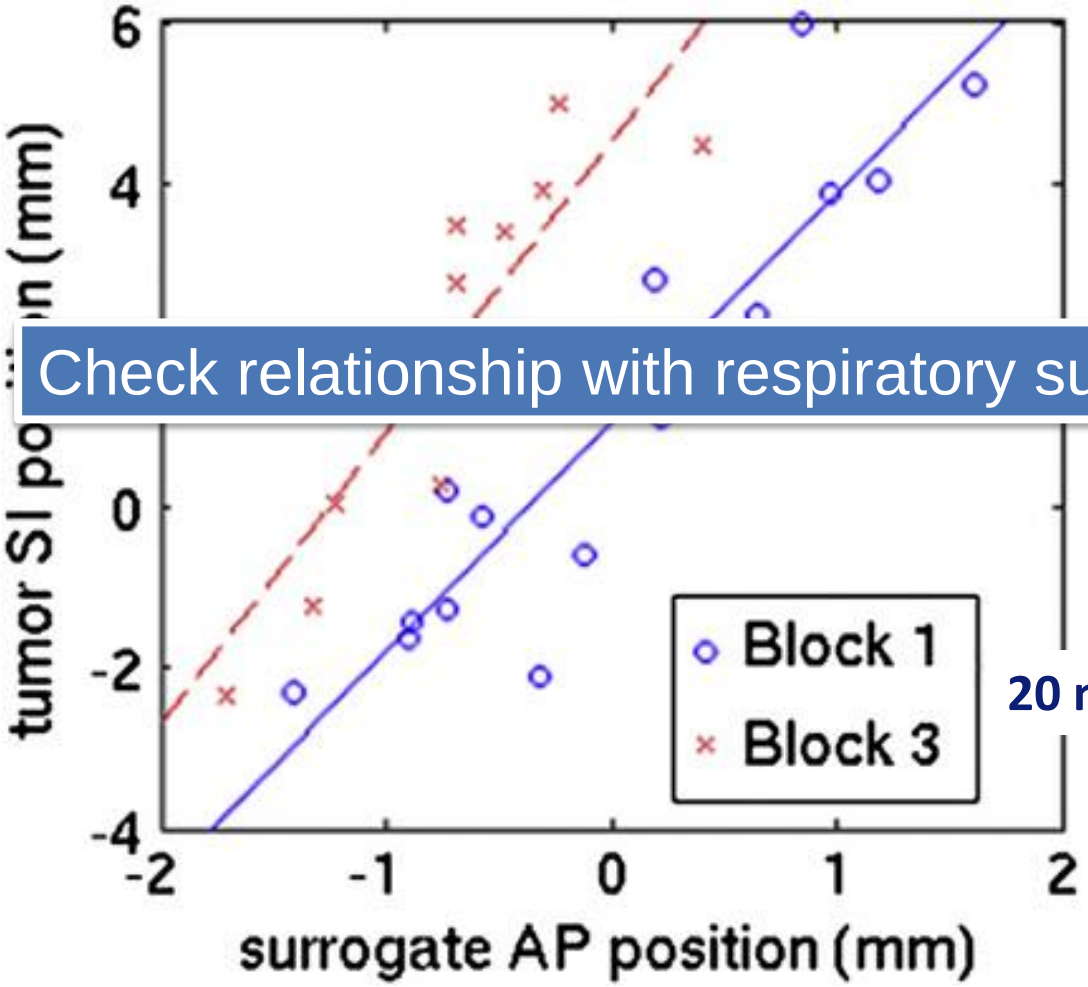


Can we predict tumor motion with respiratory surrogates?

Korreman et al. R&O 2008

Erasmus MC

Changes in Relationship with Respiratory Surrogate



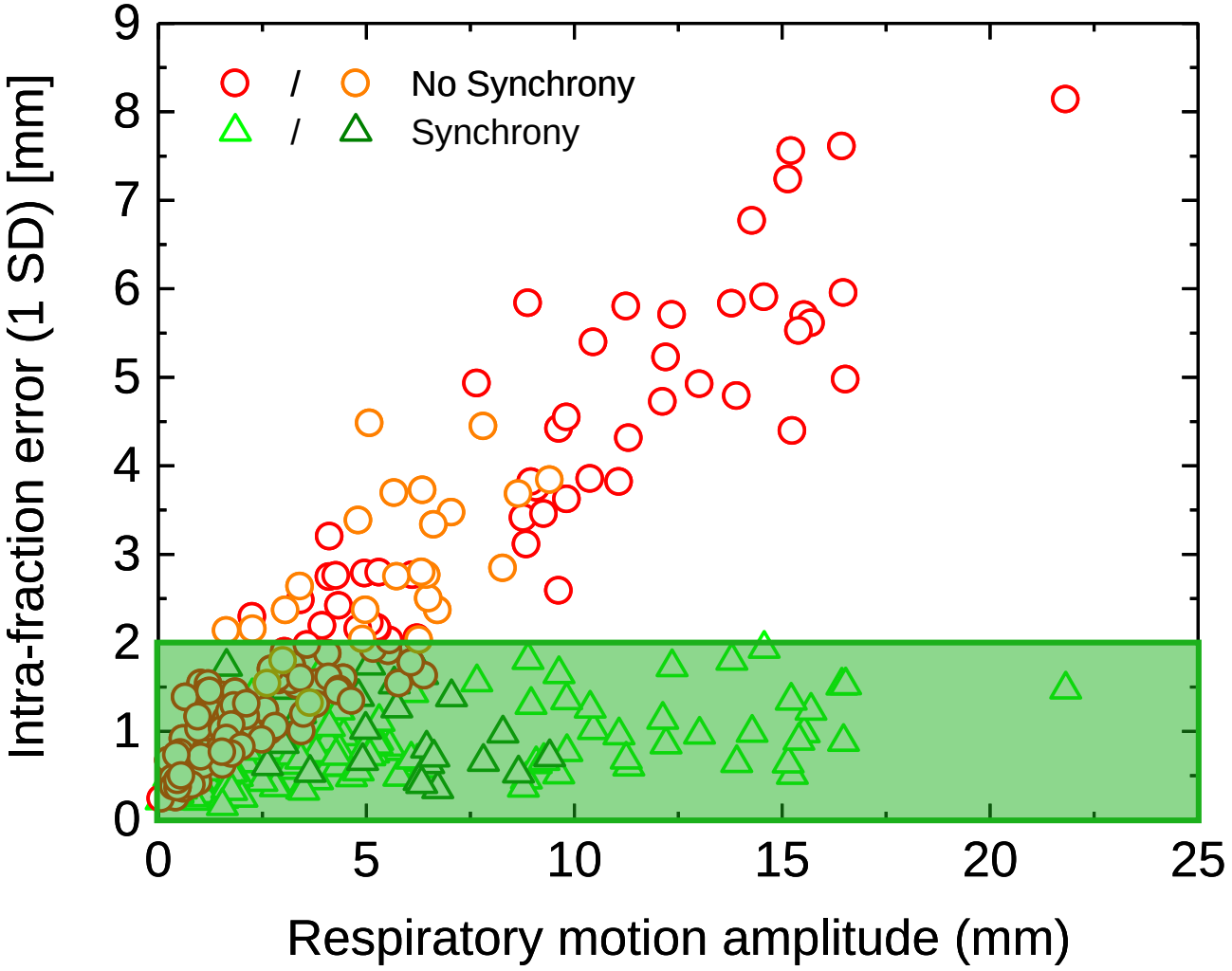
Malinowski K et al. Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1665–1673, 2012

Check relationship with respiratory surrogate after 10 min

20 min difference (+2 mm margin)

Erasmus MC

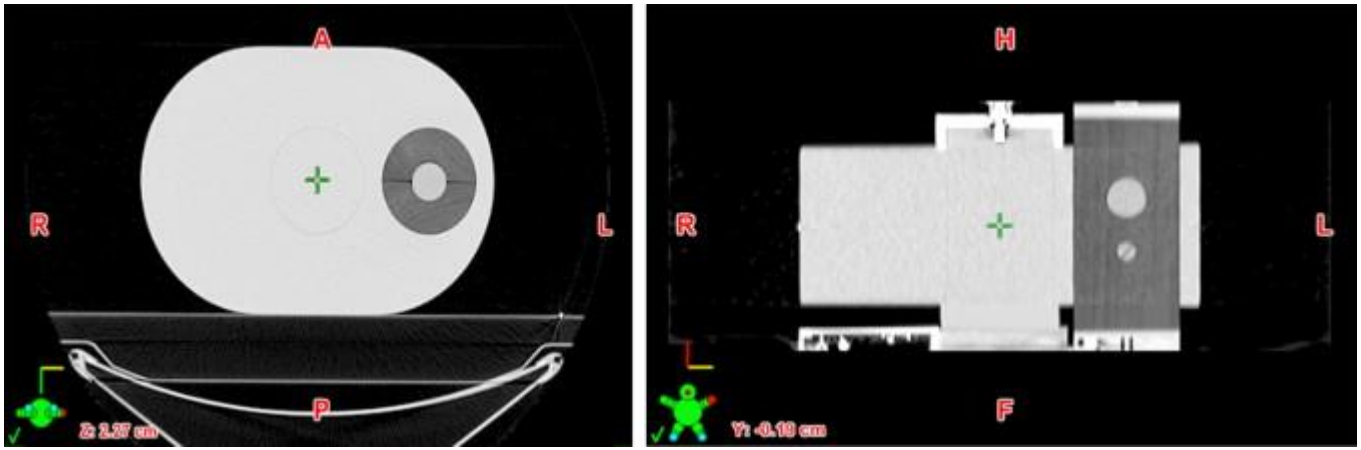
Intra-Fraction Error (167 treatment fractions)



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

Erasmus MC

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

Erasmus MC

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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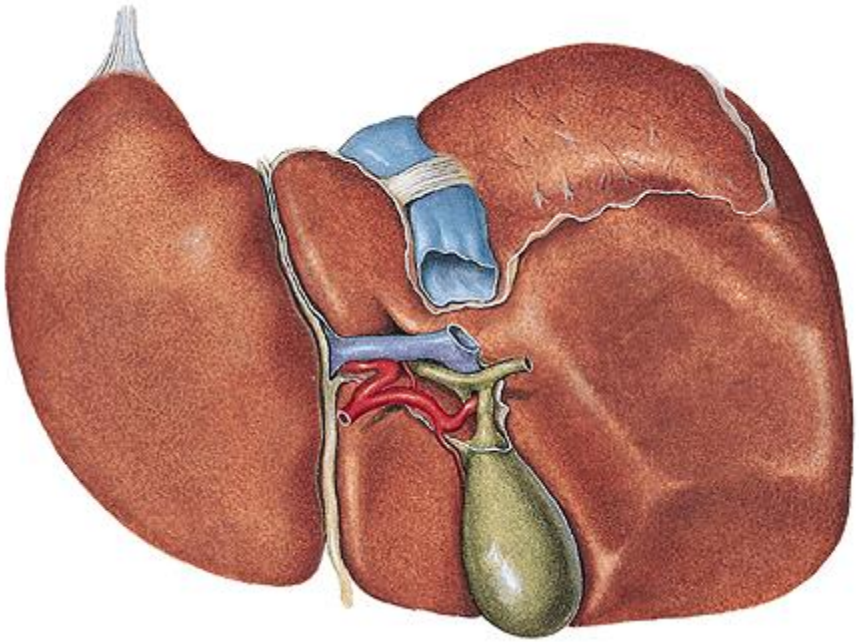
LIVER



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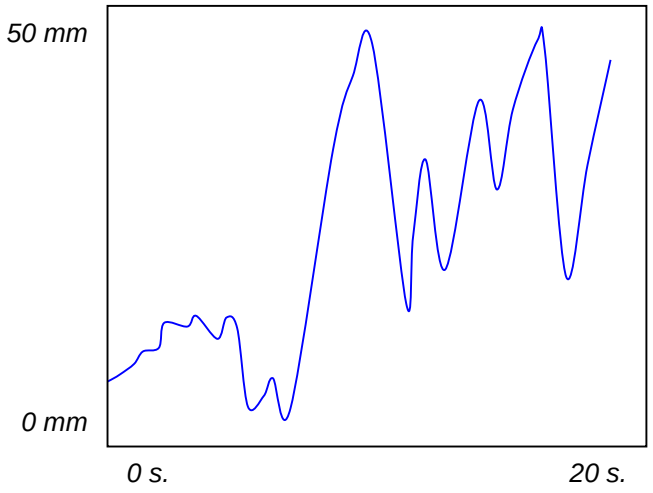
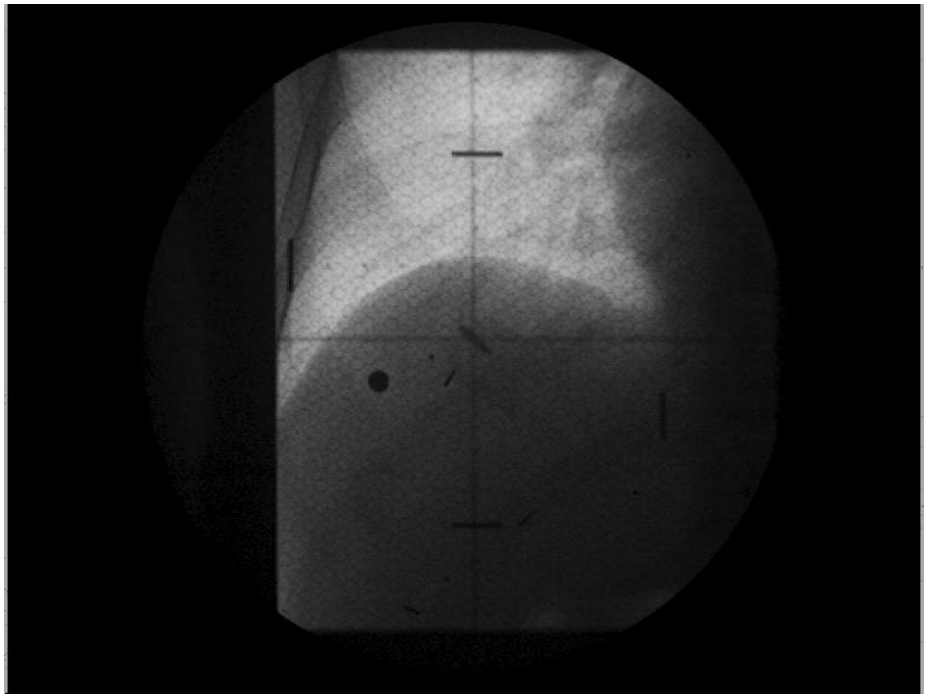
Observation of Motion

- 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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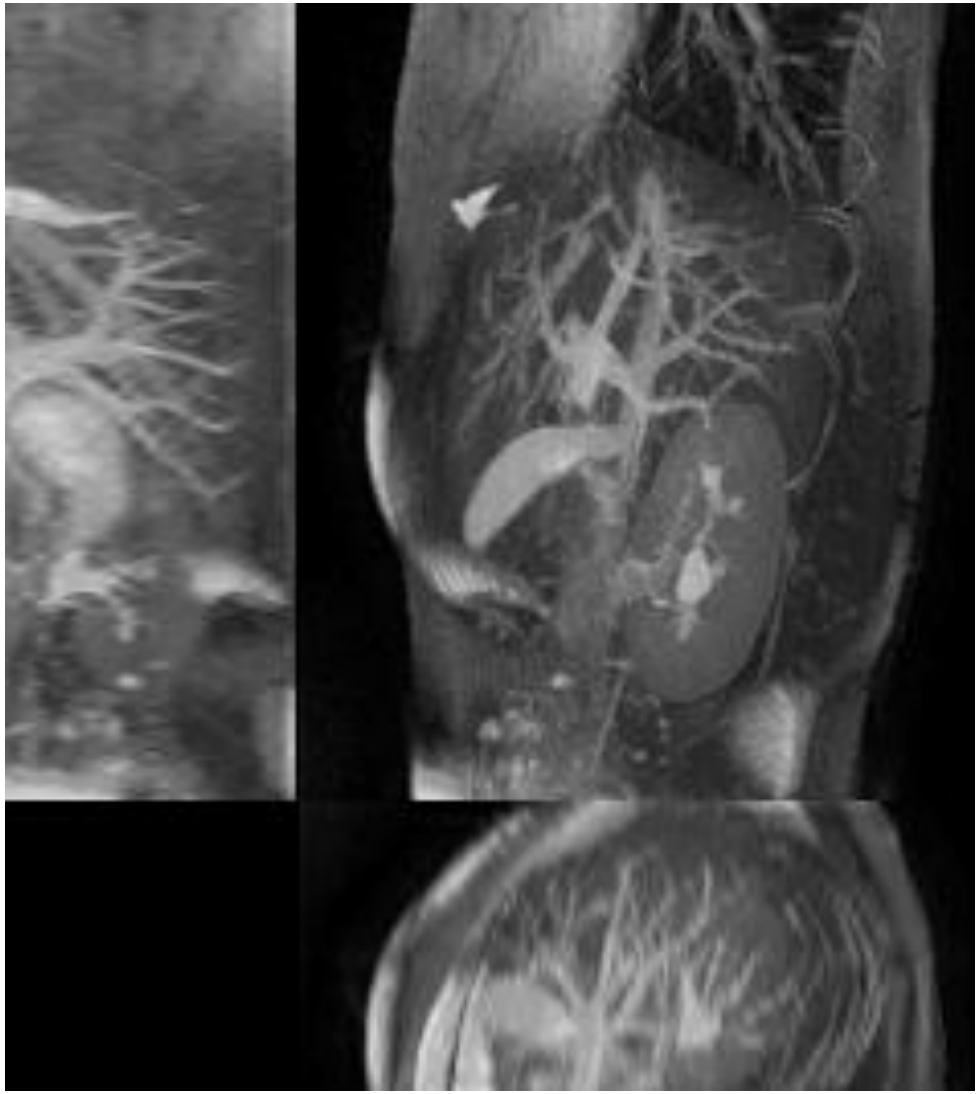
4D MRI Data of Liver



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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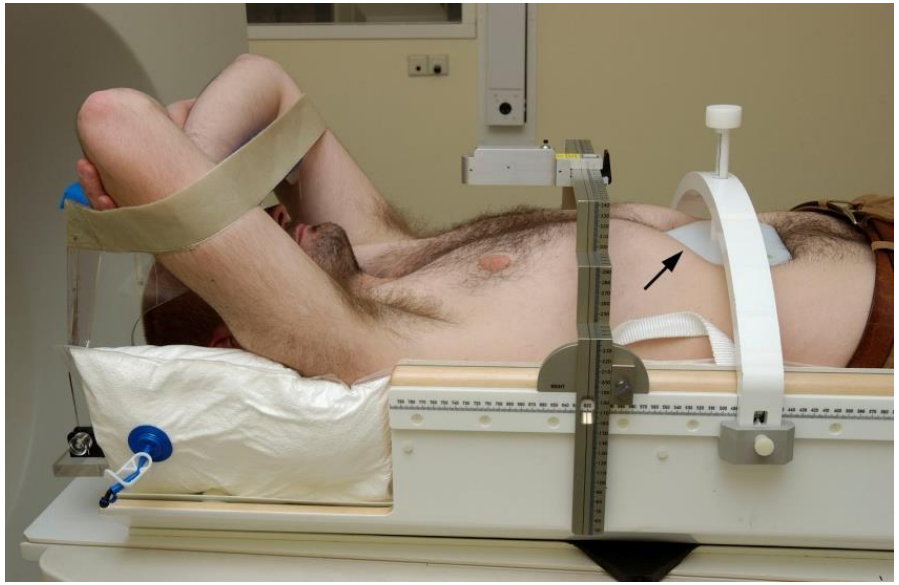
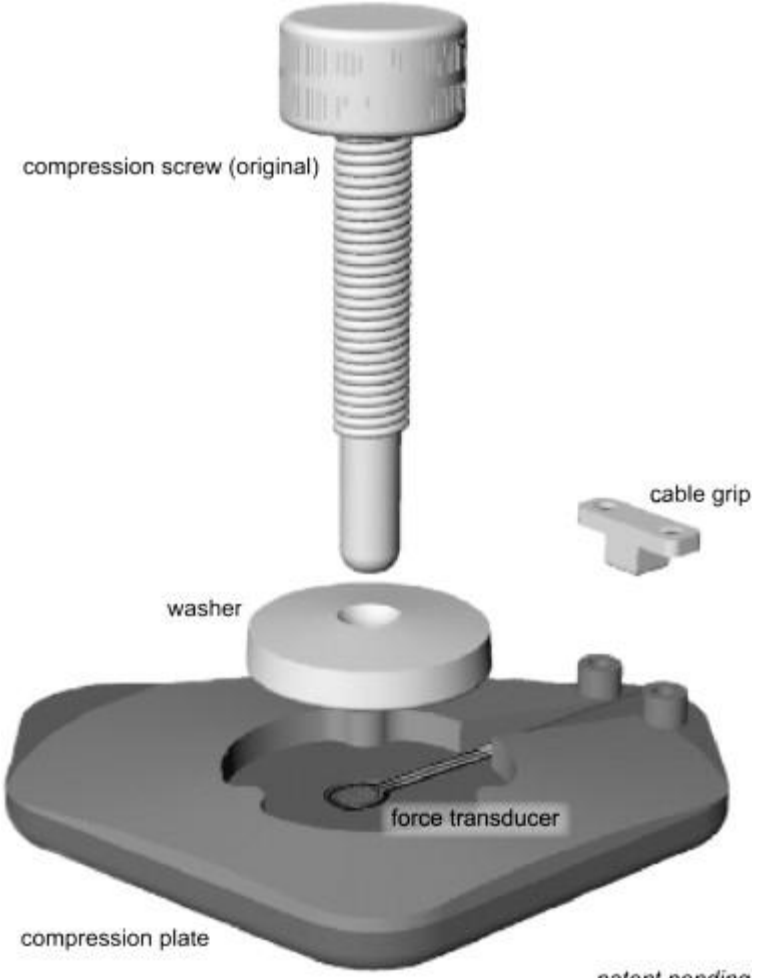
W. Wunderink, A. Méndez Romero et al.

Abdominal Compression





patent pending

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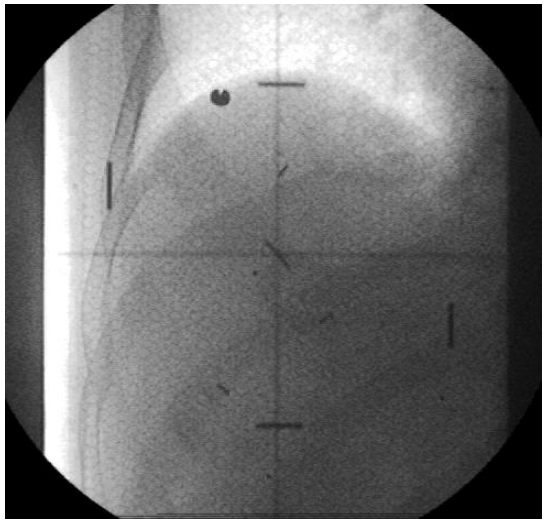
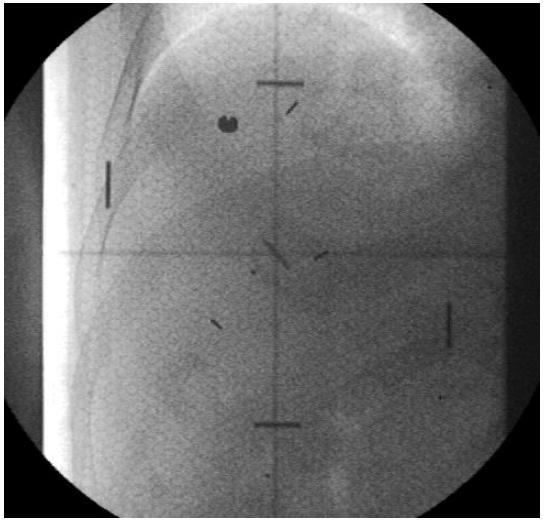
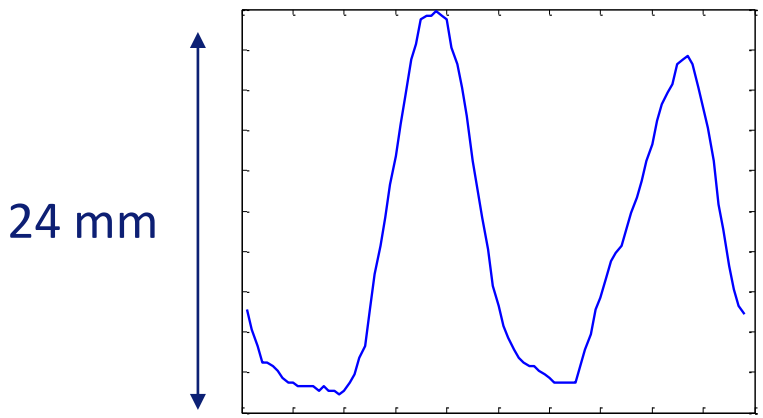
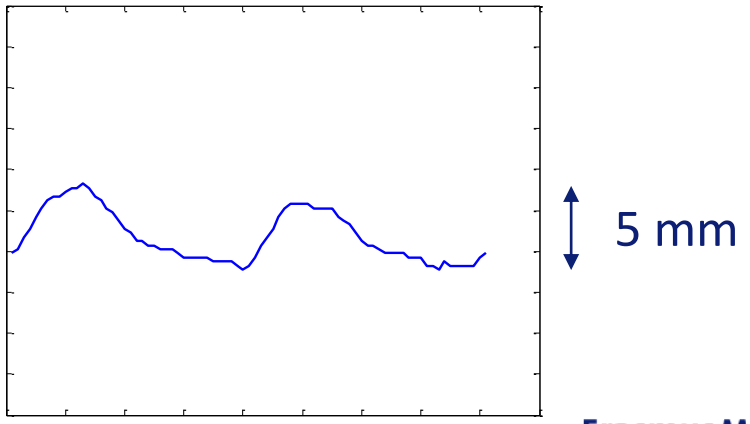
W. Wunderink, A. Méndez Romero et al.

Fluoroscopy









no compression

with compression

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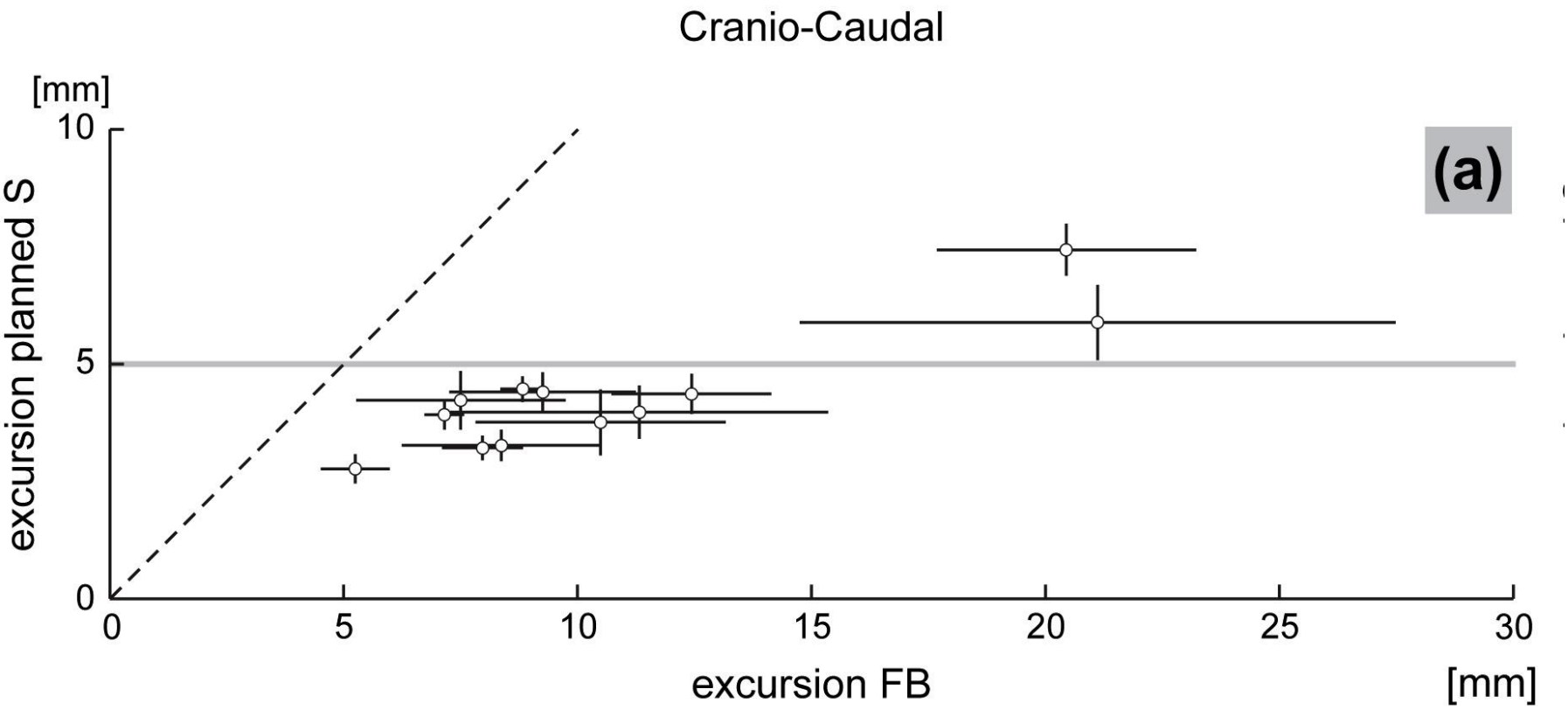
Amplitude Reduction by Abdominal Compression



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

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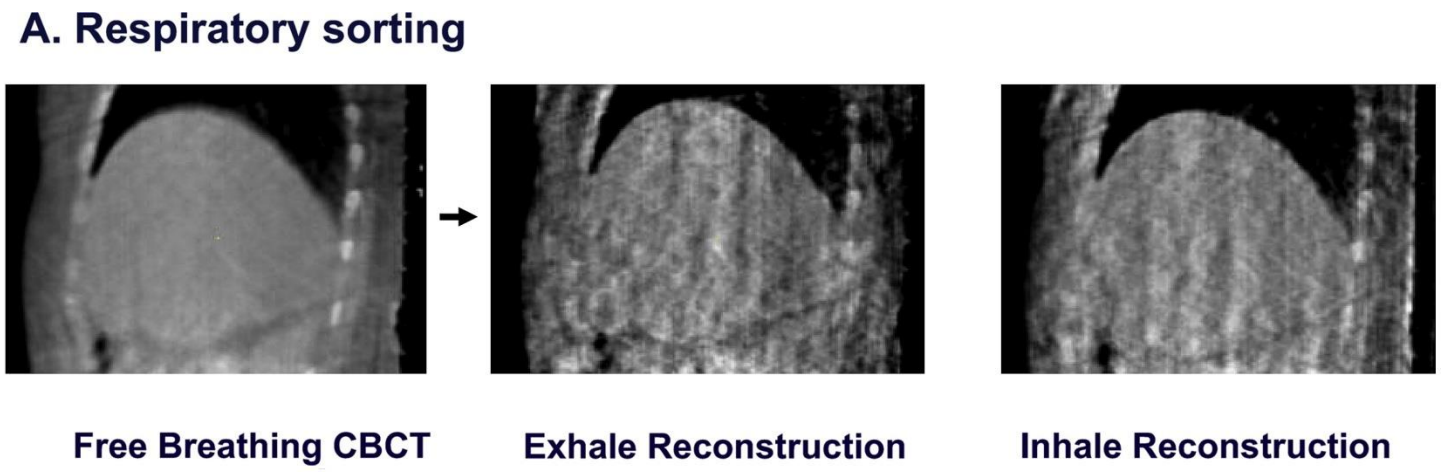
Inter-fraction and Intra-fraction Liver Motion



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

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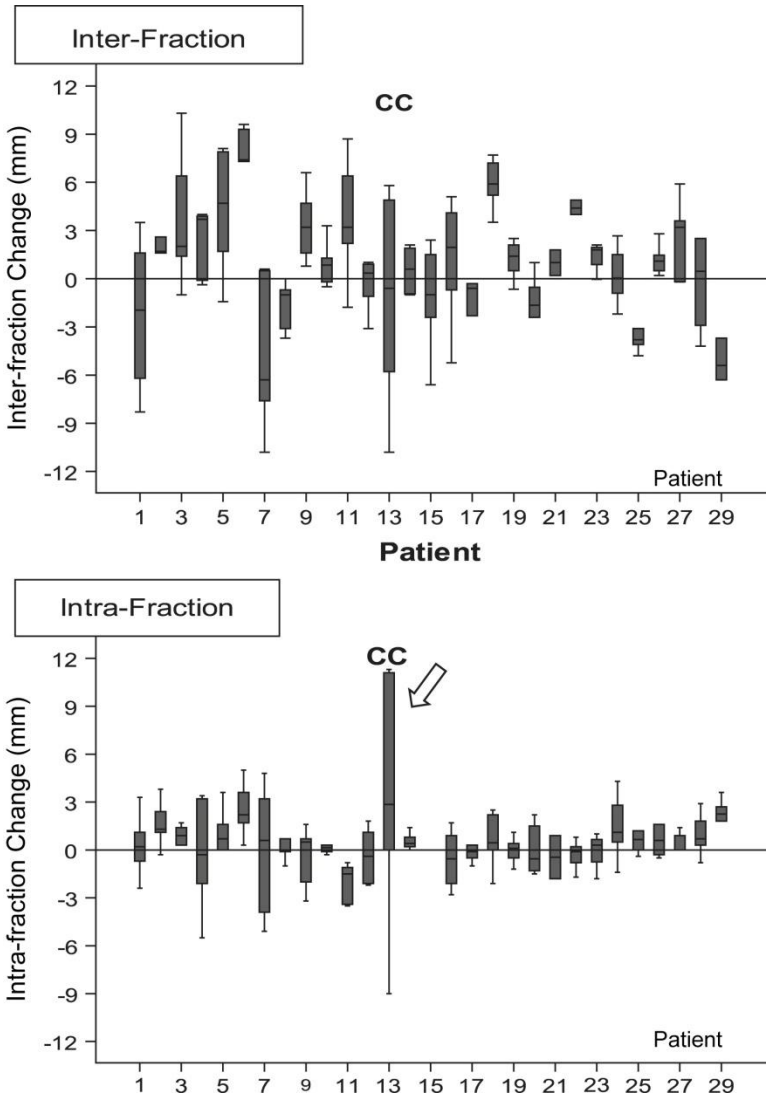
Inter-fraction and Intra-fraction Liver Position Change



- For the majority of liver SBRT patients, the change in liver motion amplitude was minimal over the treatment course and showed no apparent relationships with the magnitude of liver motion and intra-fraction time Case R et al. Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 3, pp. 918–925, 2010

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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

Variable	Intrafraction (mm)			Interfraction (mm)		
	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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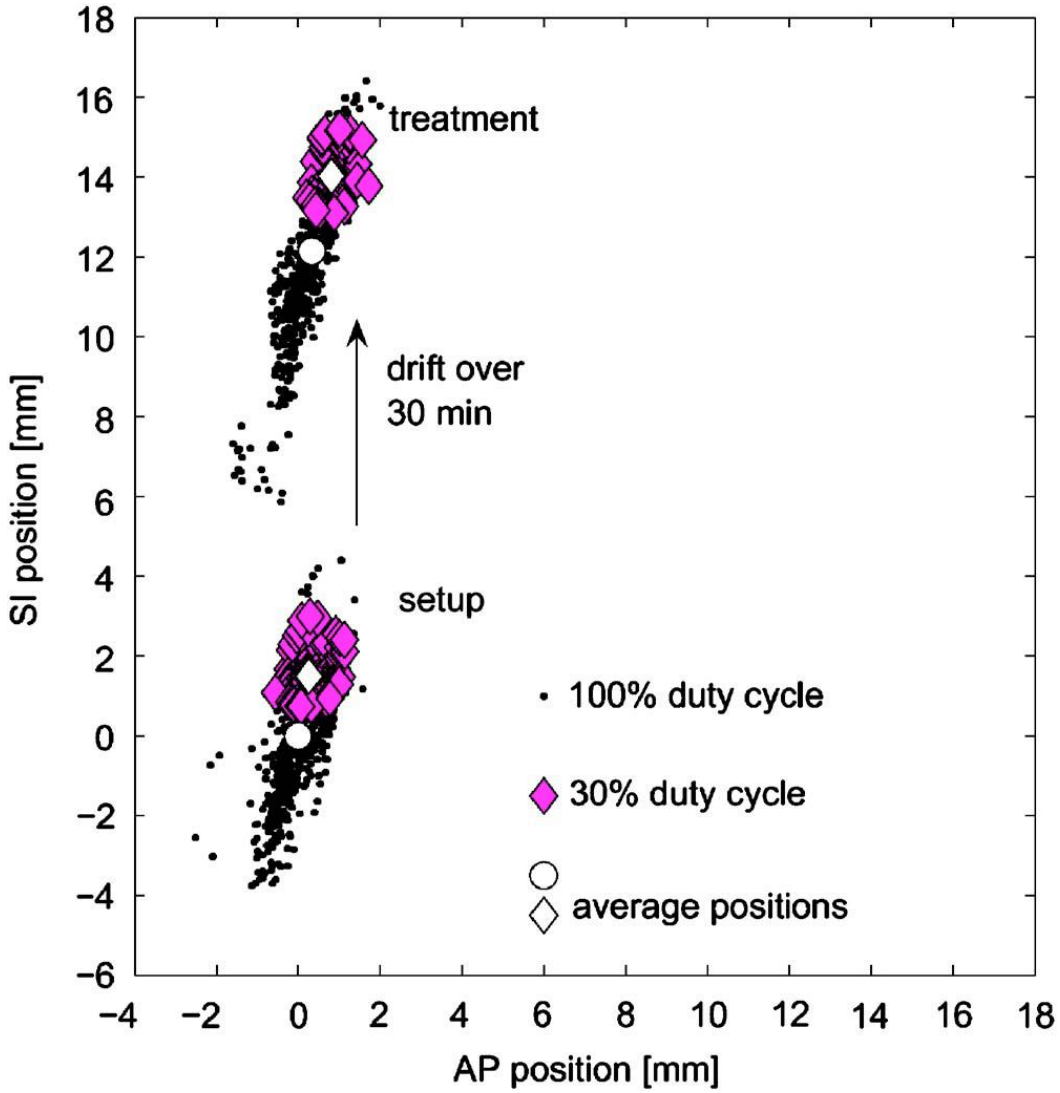
Drift During a Hypothetical 30-min Treatment



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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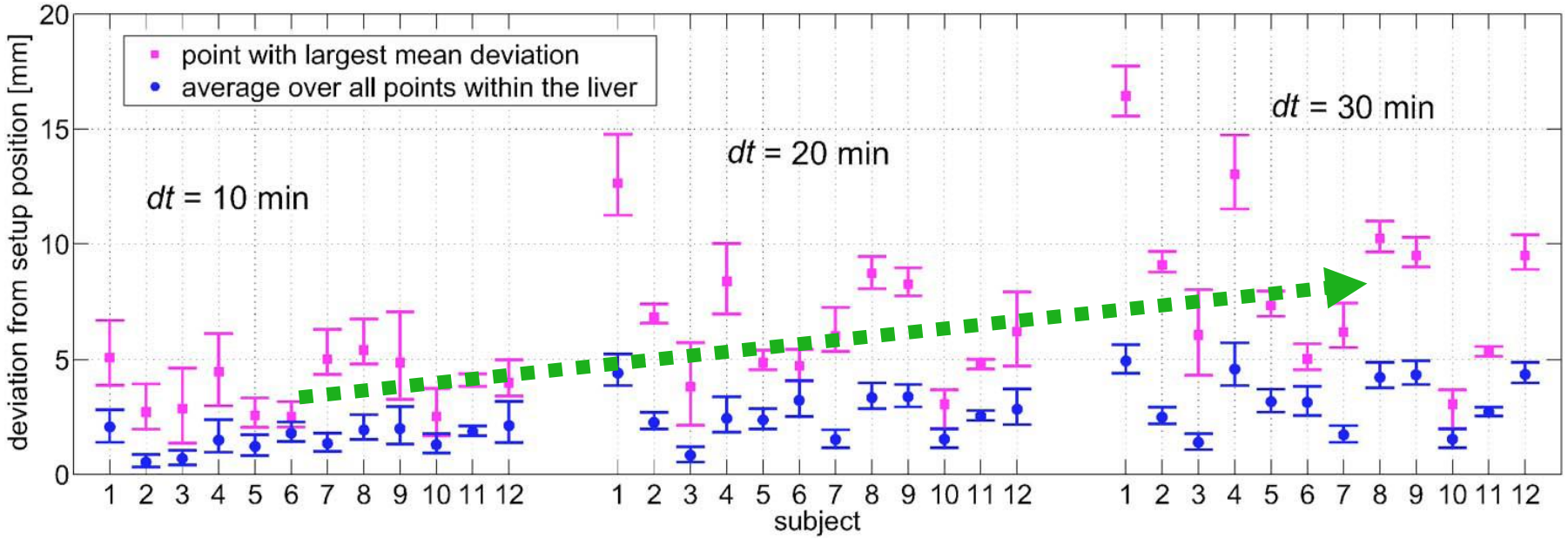
Deviation as a Function of Treatment Time



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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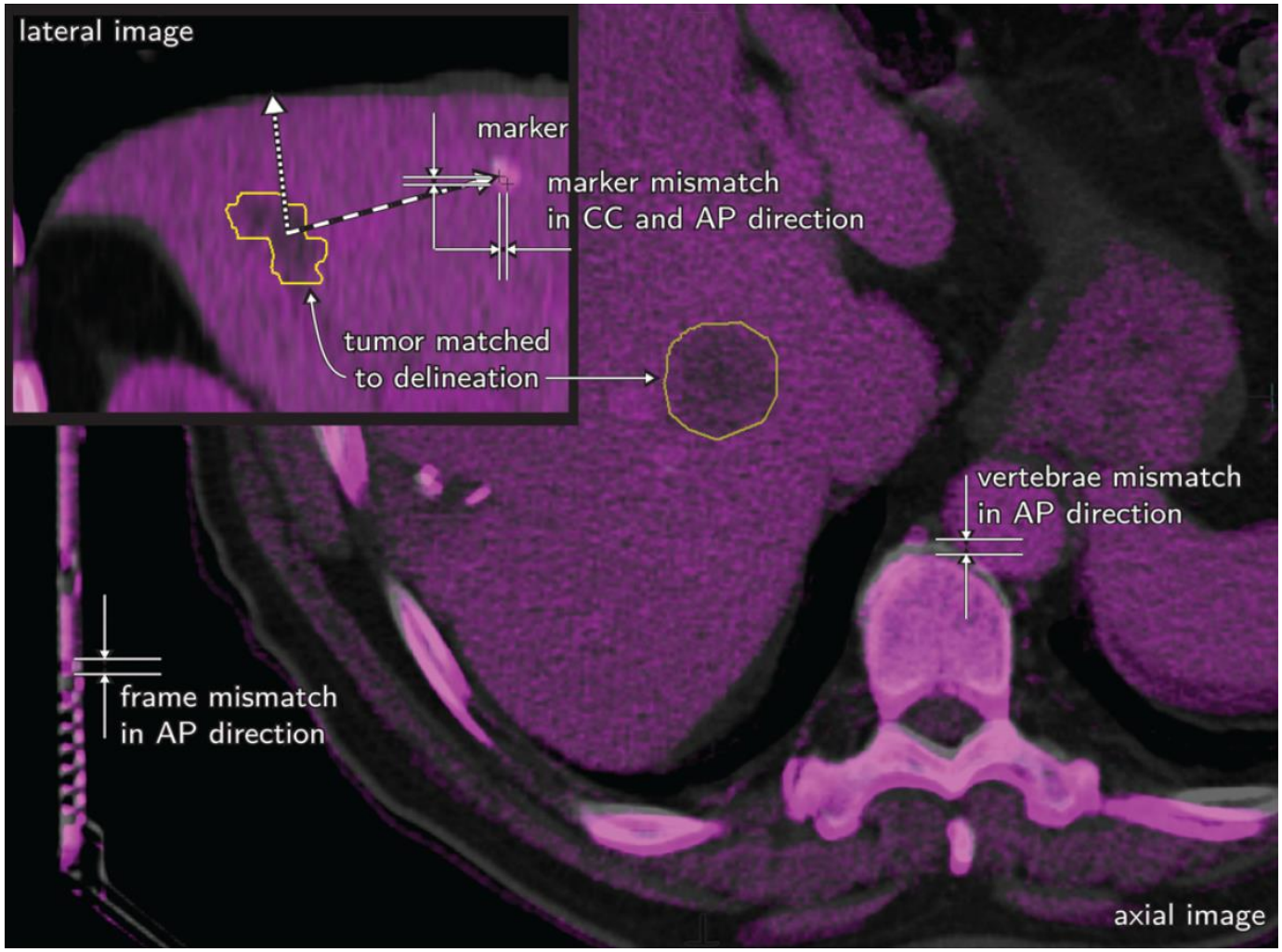
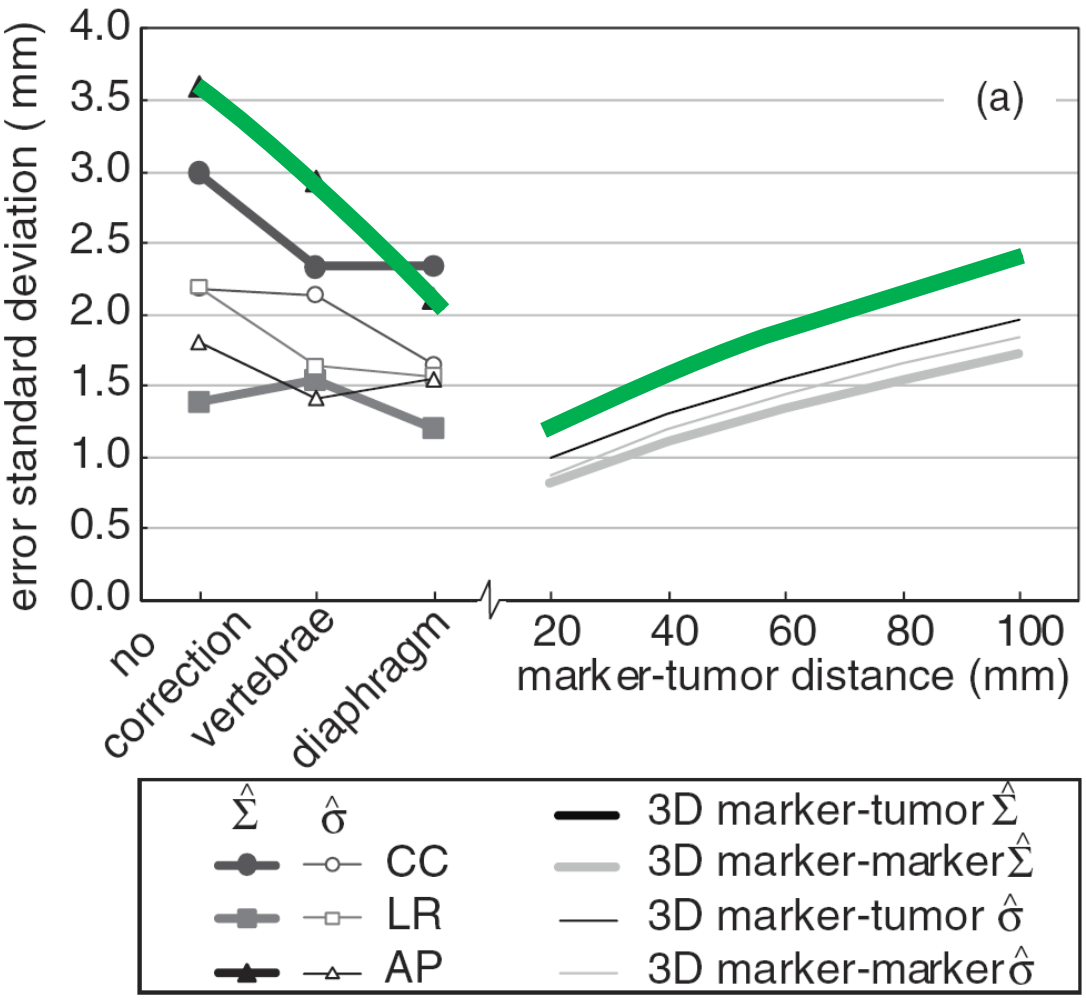
Liver Tumor Surrogates

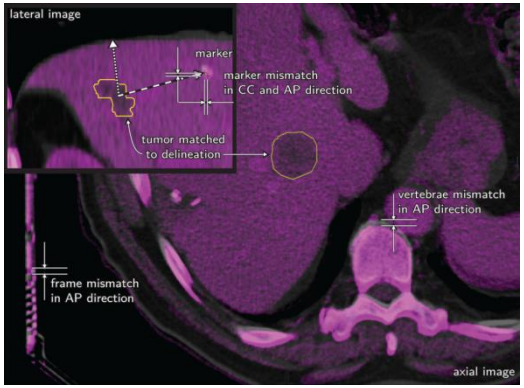


Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

Erasmus MC

Liver Tumor Surrogates

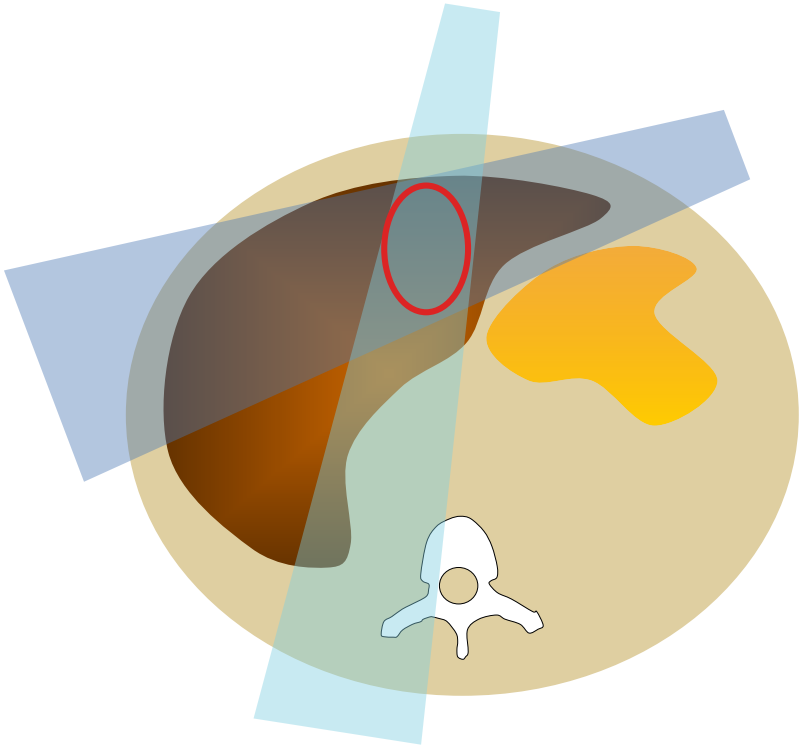




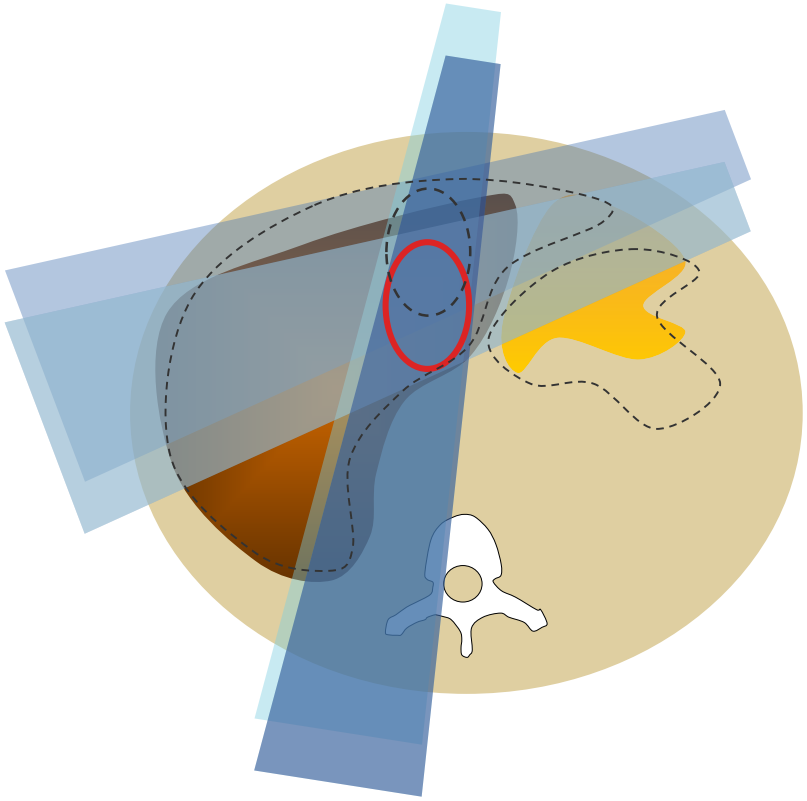
Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

Erasmus MC

Online Adaptive RT for Liver?



Planning



Treatment

Suzanne Leinders IJROBP 2014; slides courtesy of Seppenwoolde

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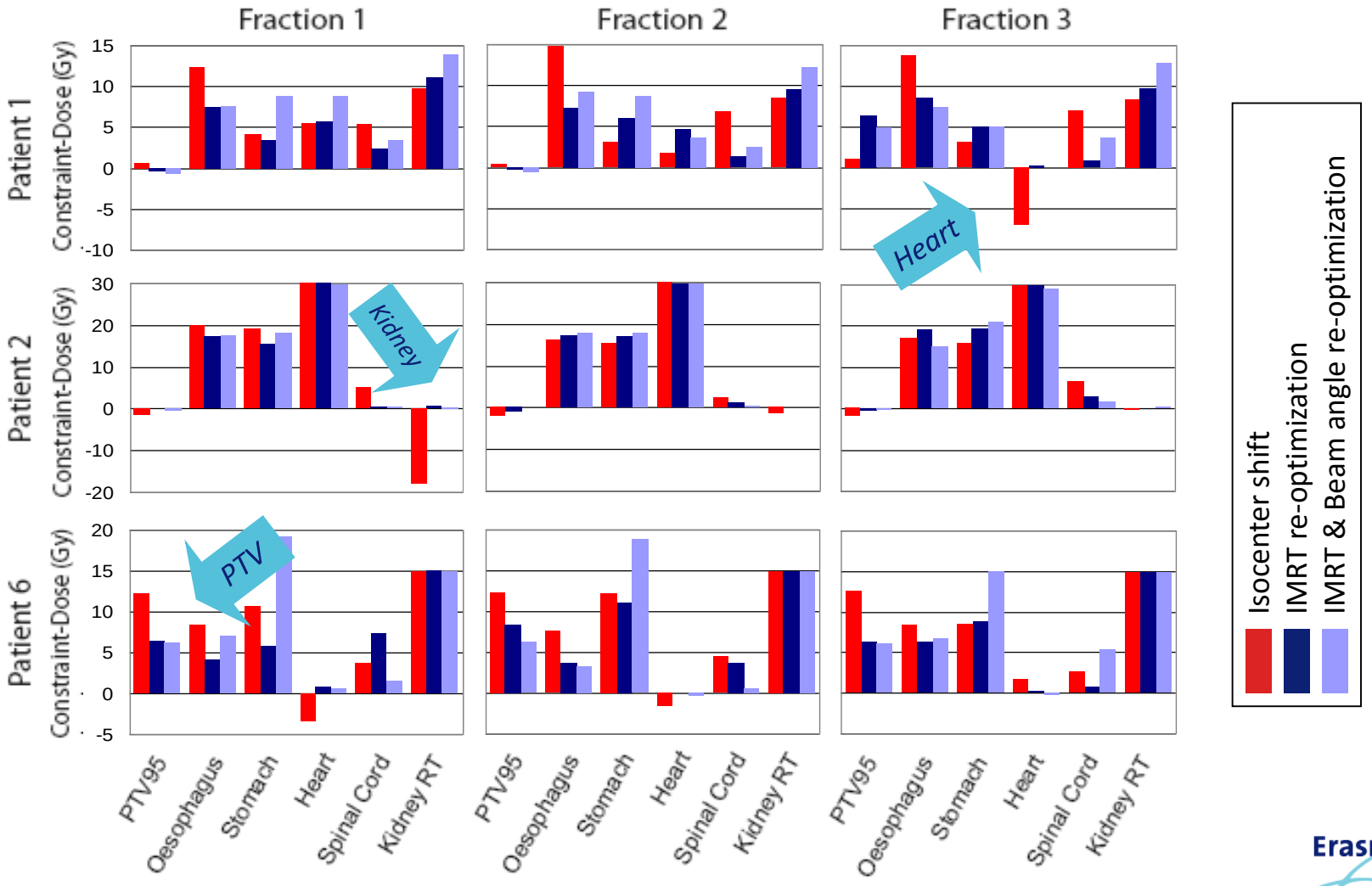
Online Adaptive RT for Liver

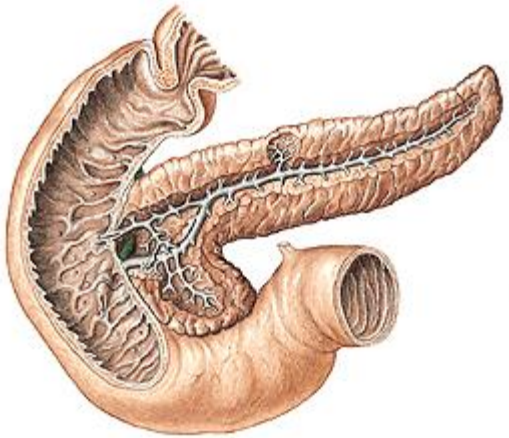


Erasmus MC

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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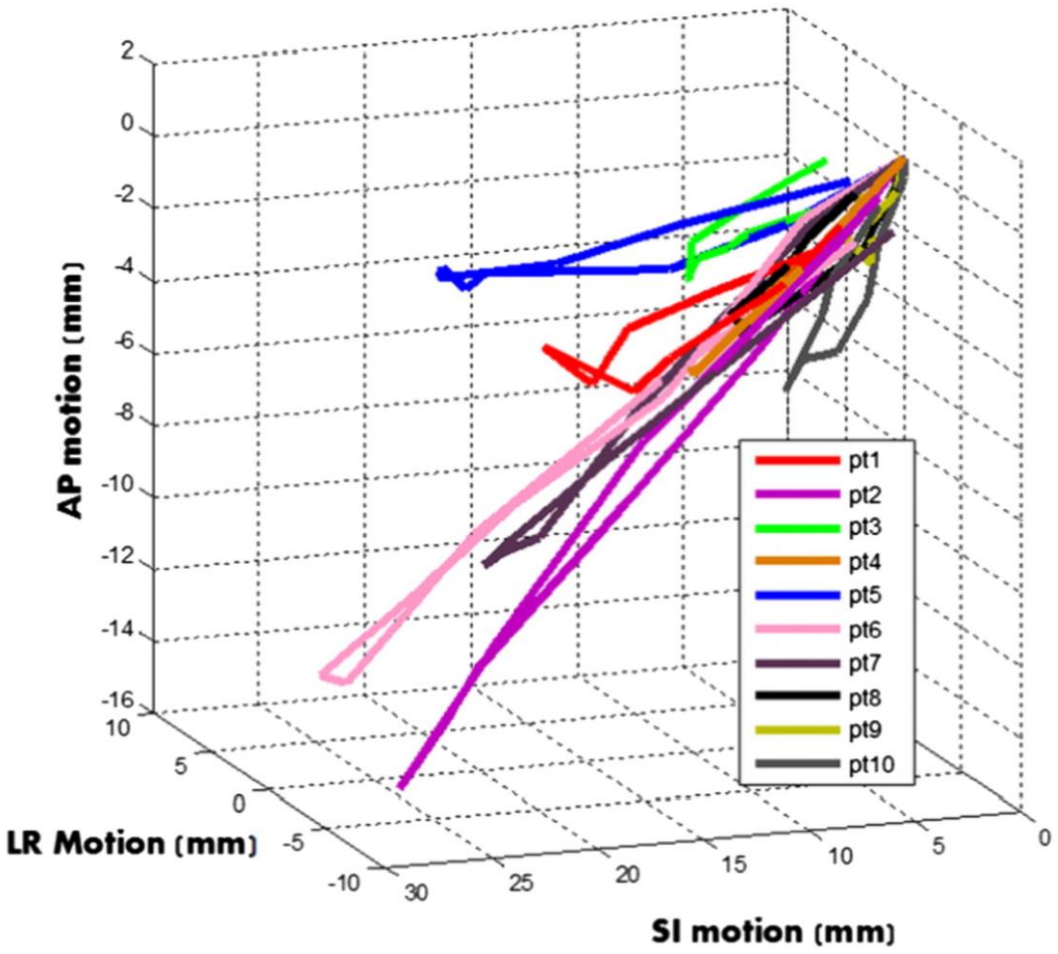
Pancreas Motion Assessed With 4D CT Scanning



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

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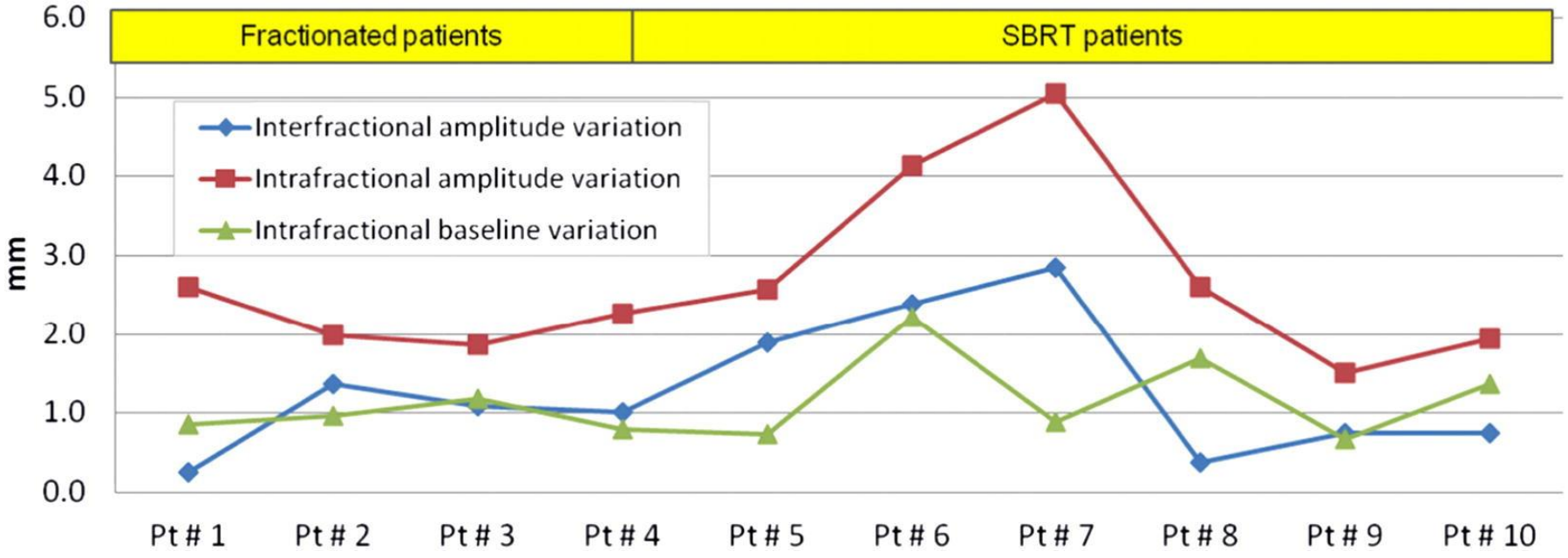
4D CT Cannot Adequately Represent Daily Intrafractional Motion



- Interfractional variation of baseline was not included in this study, with the assumption that it was accounted for using daily image-guided patient setup

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

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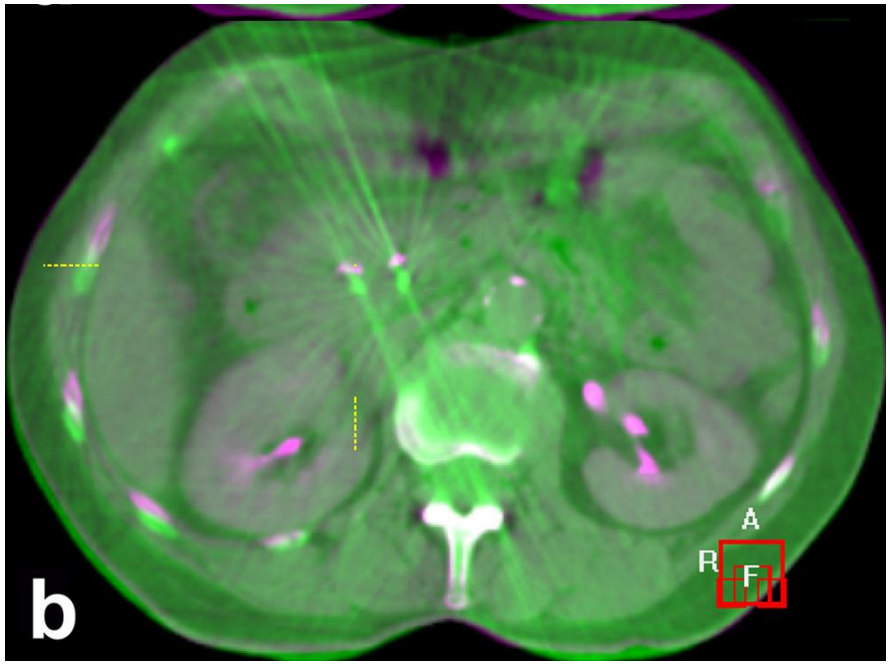
Inter-fraction Variation: Implanted Markers and CBCTs

- 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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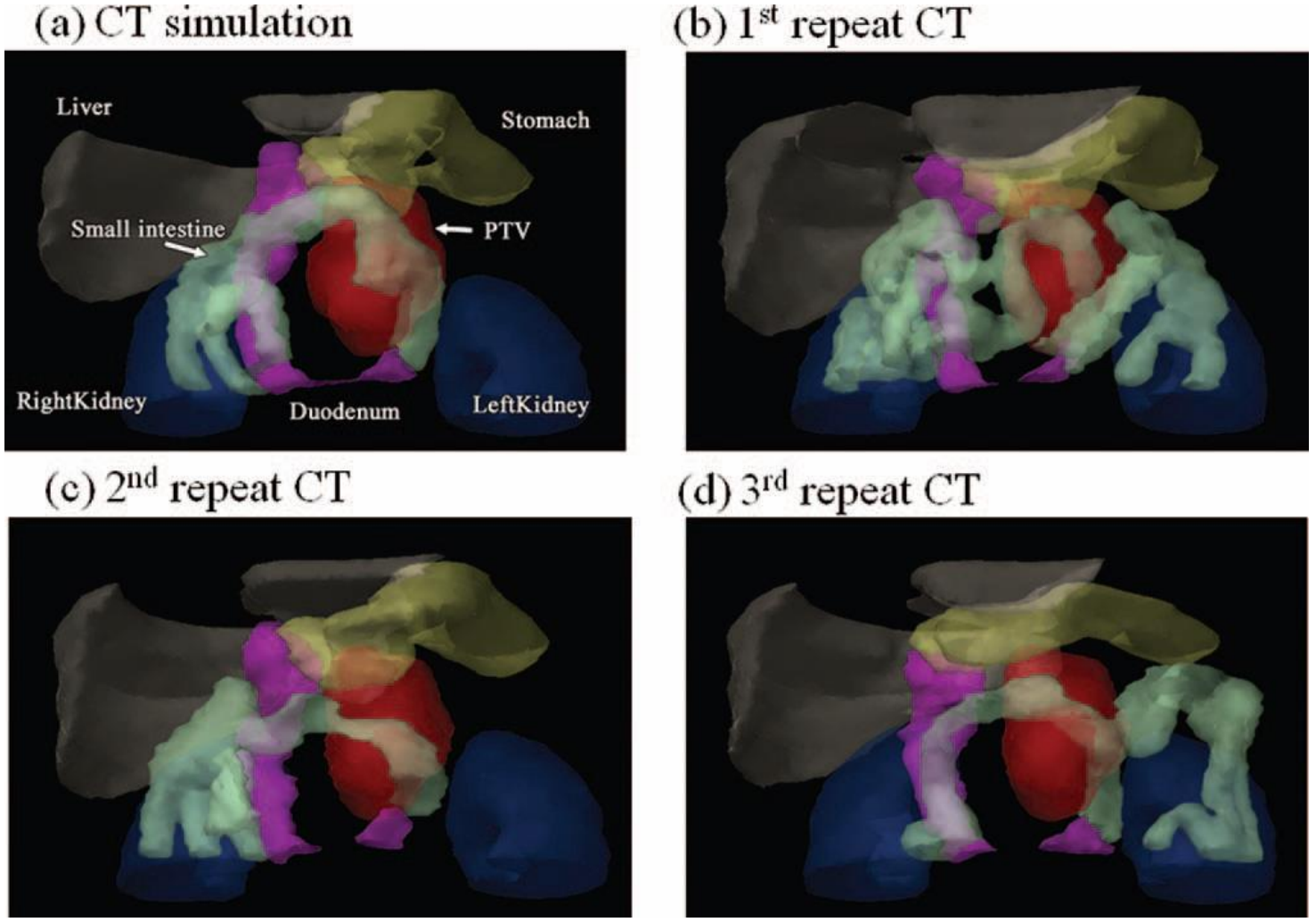
Interfractional Dose Variations in Organs at Risk



Akira Nakamura et al. **Med. Phys. 40 (2), February 2013**

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 abdomen 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

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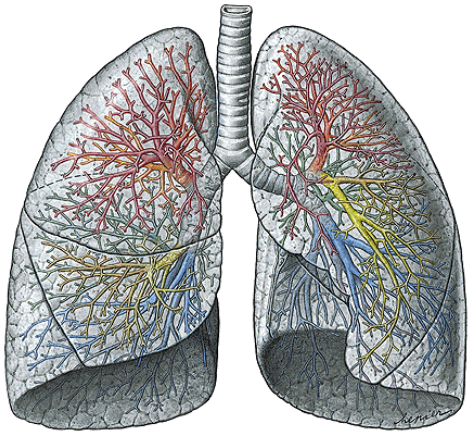
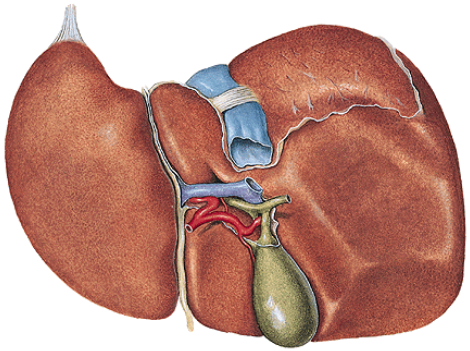
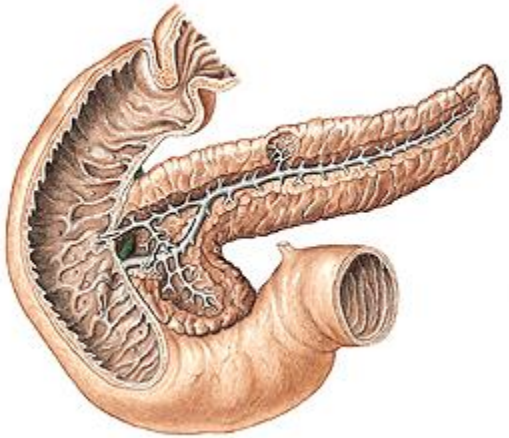
Summary







Treatment planning and evaluation

Coen Hurkmans, clinical physicist

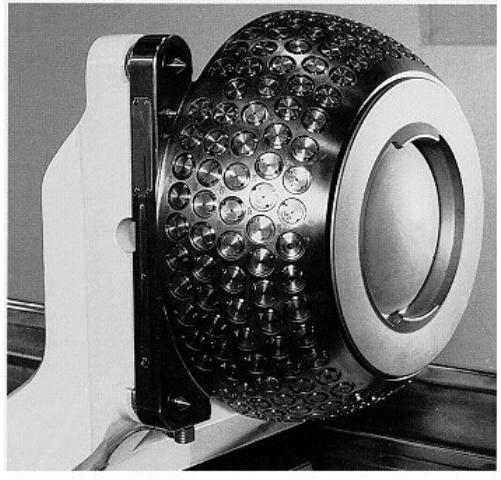
Catharina Hospital, The Netherlands

catharina hospital

First a tough one..

catharina hospital

First SBRT: Gammaknife

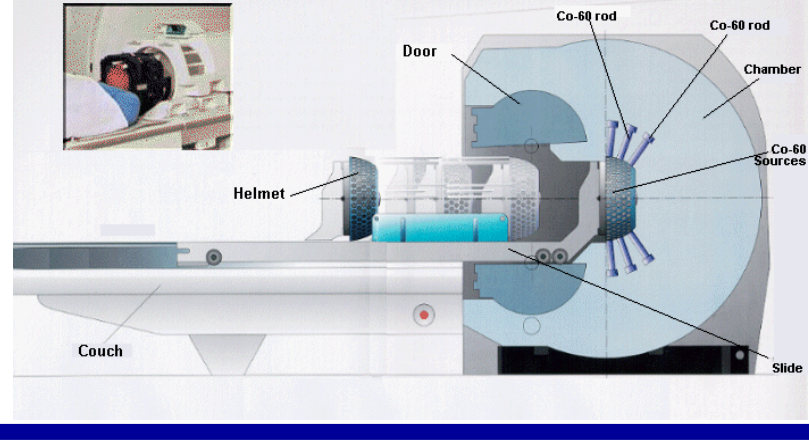


Gamma Knife Radiation Helmet

Isocenter dose = 100%

1st patient treate

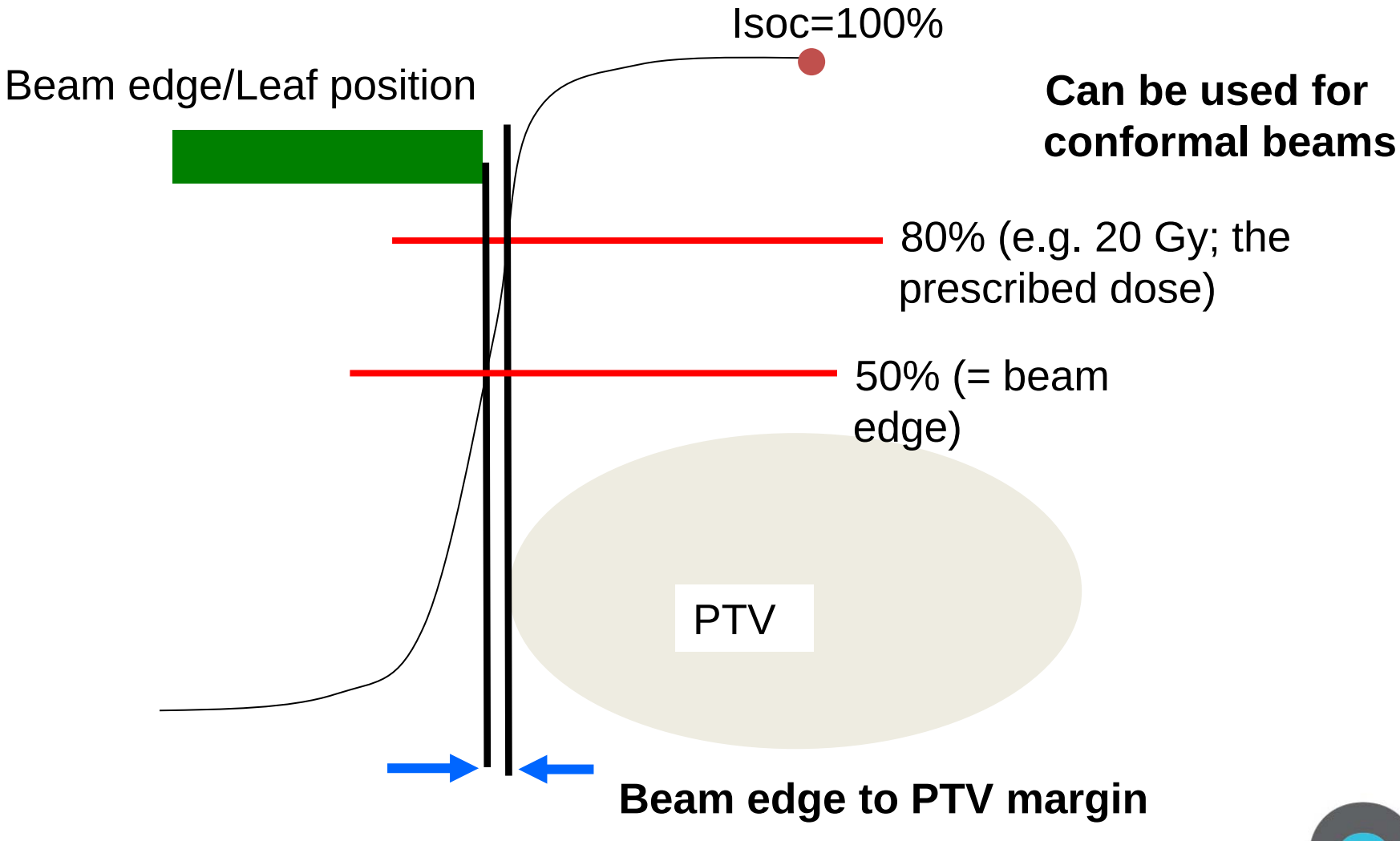
Start at t ...ka, Stockholm, Sweden



1968 1969

catharina hospital

Historical dose prescription: on the xx% isodose



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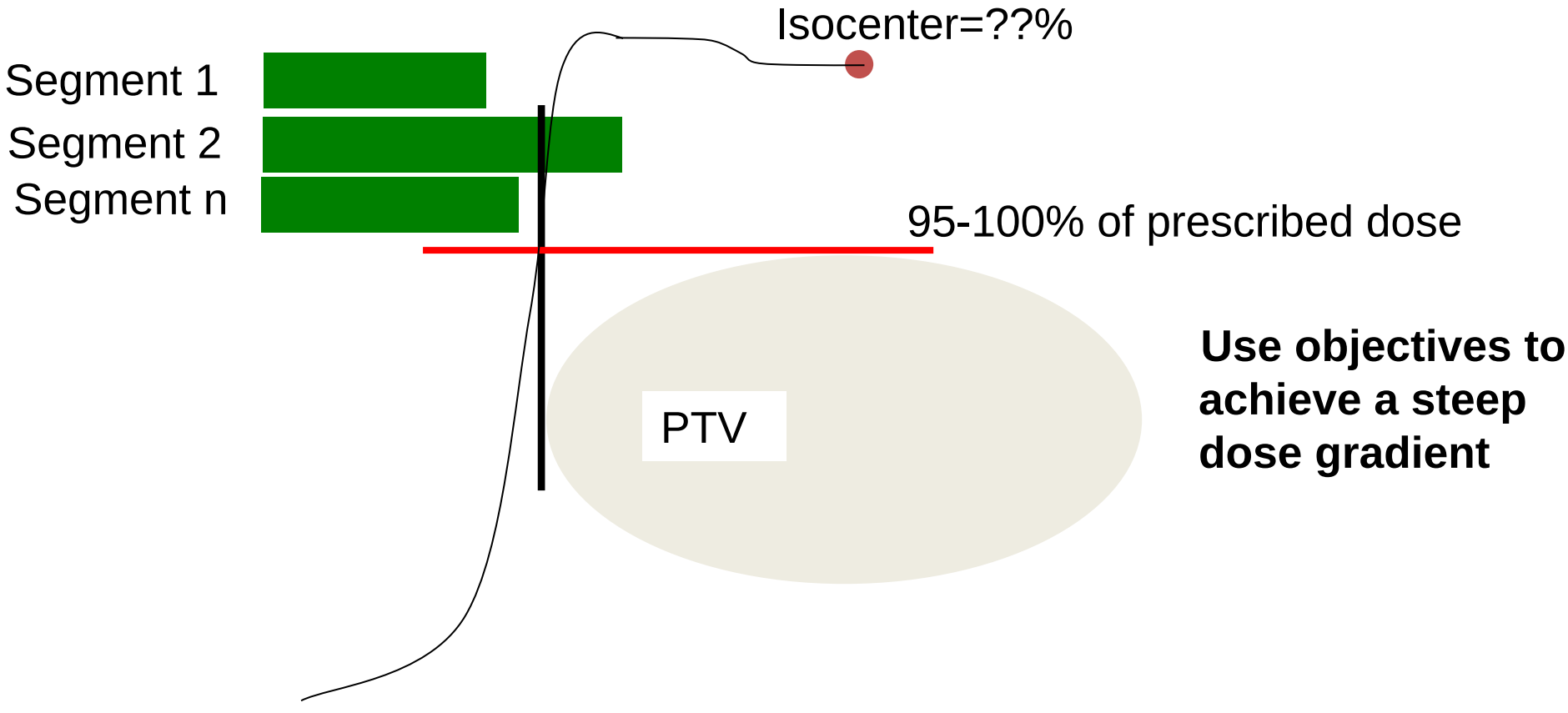
Dose prescription beyond conformal:ICRU



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**
  - 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!

catharina
hospital

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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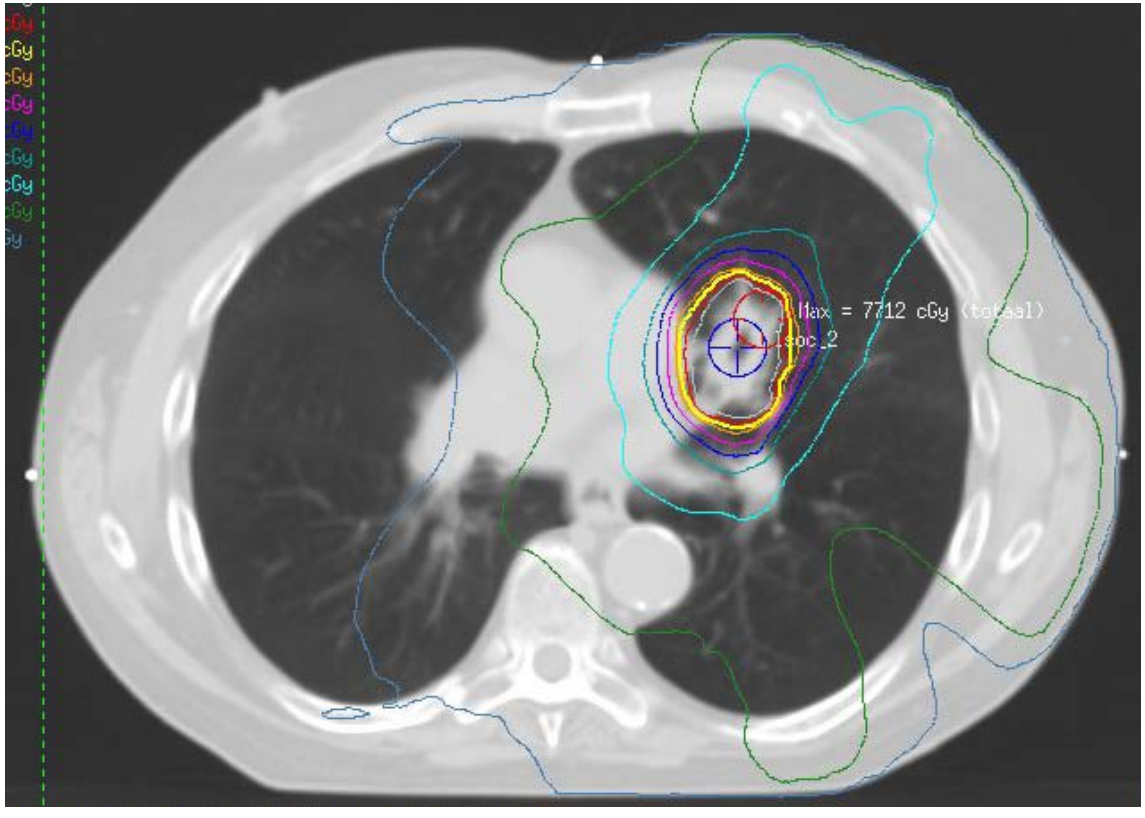
Dose in relation to volume: Target



Lungtech guidelines:

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

N.b. Now discussion if we should prescribe to the GTV instead of PTV (ICRU 100)

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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

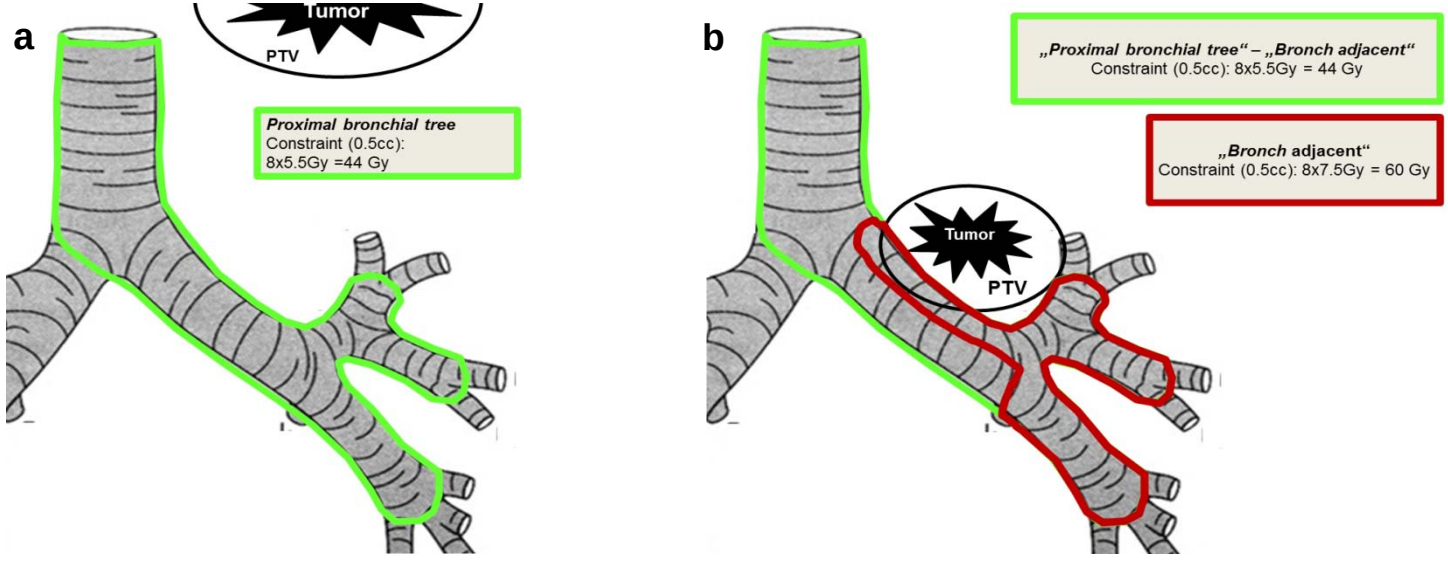

Figure: Dose constraints for the proximal bronchial tree
a) The general dose constraint for the whole structure “proxBT” (green) is 44Gy (<0.5cc) in 8 fractions. For PTVs near or abutting the main bronchus (b) a subvolume “Bronch adjacent” has to be generated (red). The dose constraint for this volume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

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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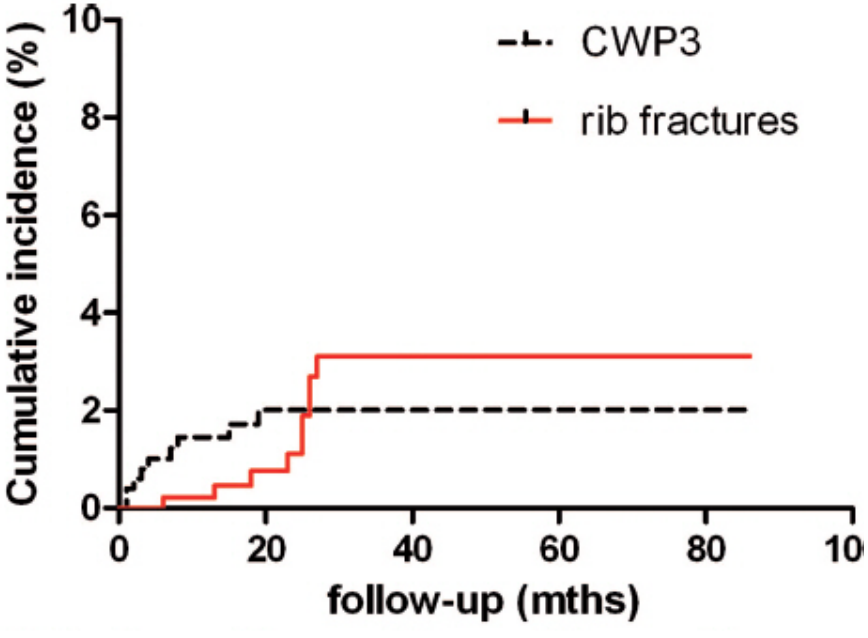
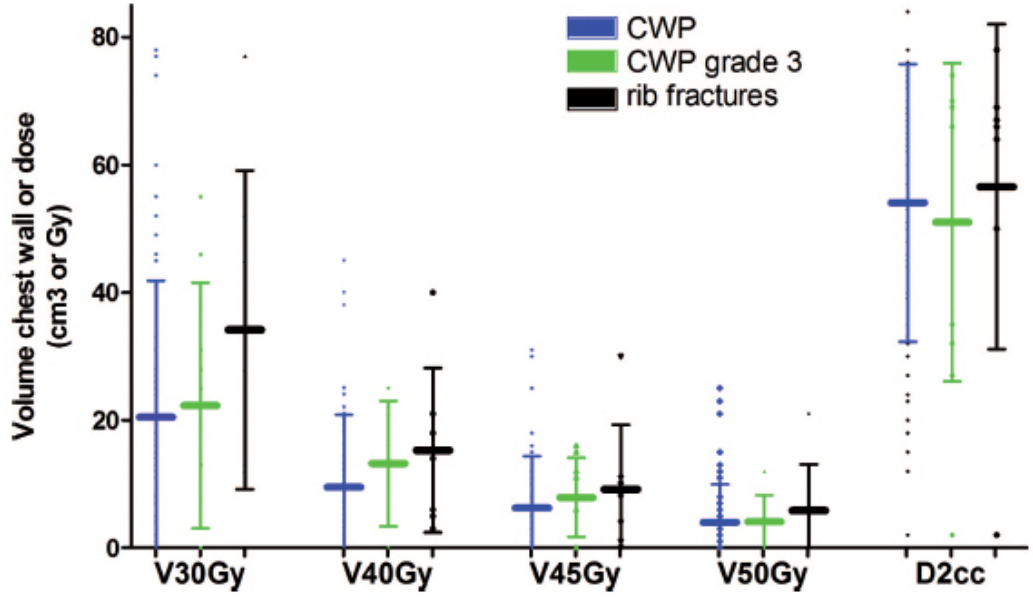
Chest wall /Ribs dose effects





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

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Chest wall /Ribs dose effects

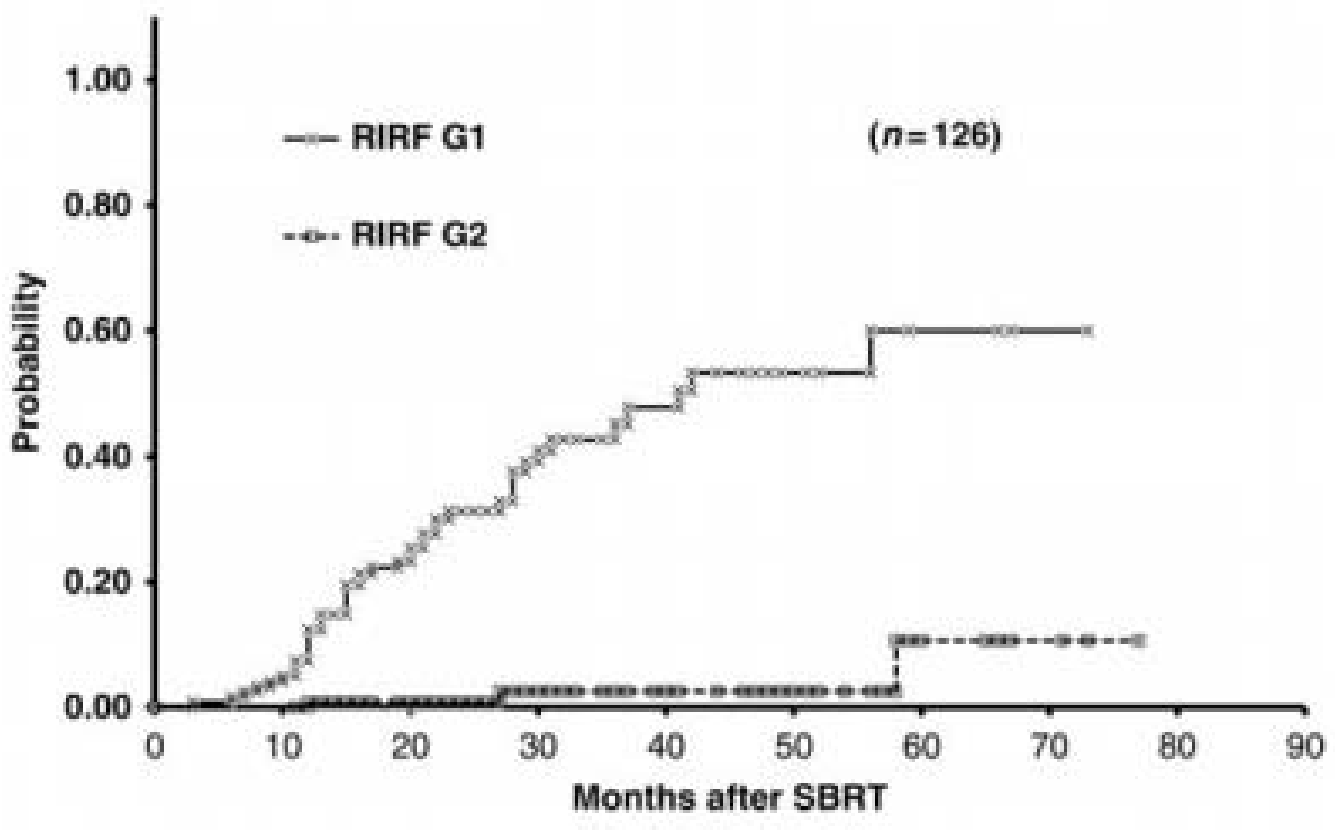

Fig. 2. Cumulative probability of RIRFs after SBRT by symptom grade (NCI–CTCAE). The 3-year cumulative probabilities were 45% and 3% for Grade 1 and 2 RIRFs, respectively.

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

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Chest wall /Ribs dose effects

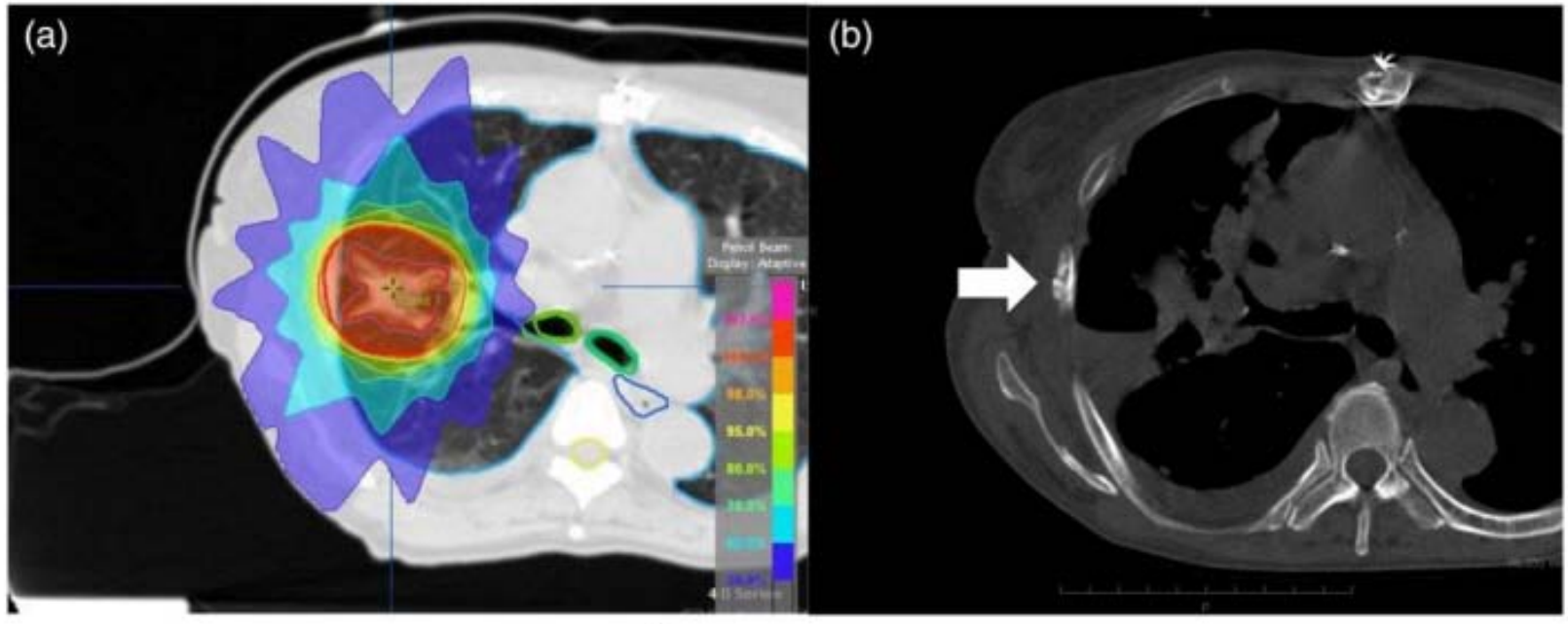

Fig. 1. (**a**) Dose distribution image shows the D (0.5 cm^3) prescribed dose to the rib as 49.6 Gy, with a BED3 of 254.6 Gy. (**b**) Bone window image shows a rib fracture (white arrow) 21 months after completion of SBRT.

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

- Dose prescription
- Dose criteria to be met

} planning algorithm

- 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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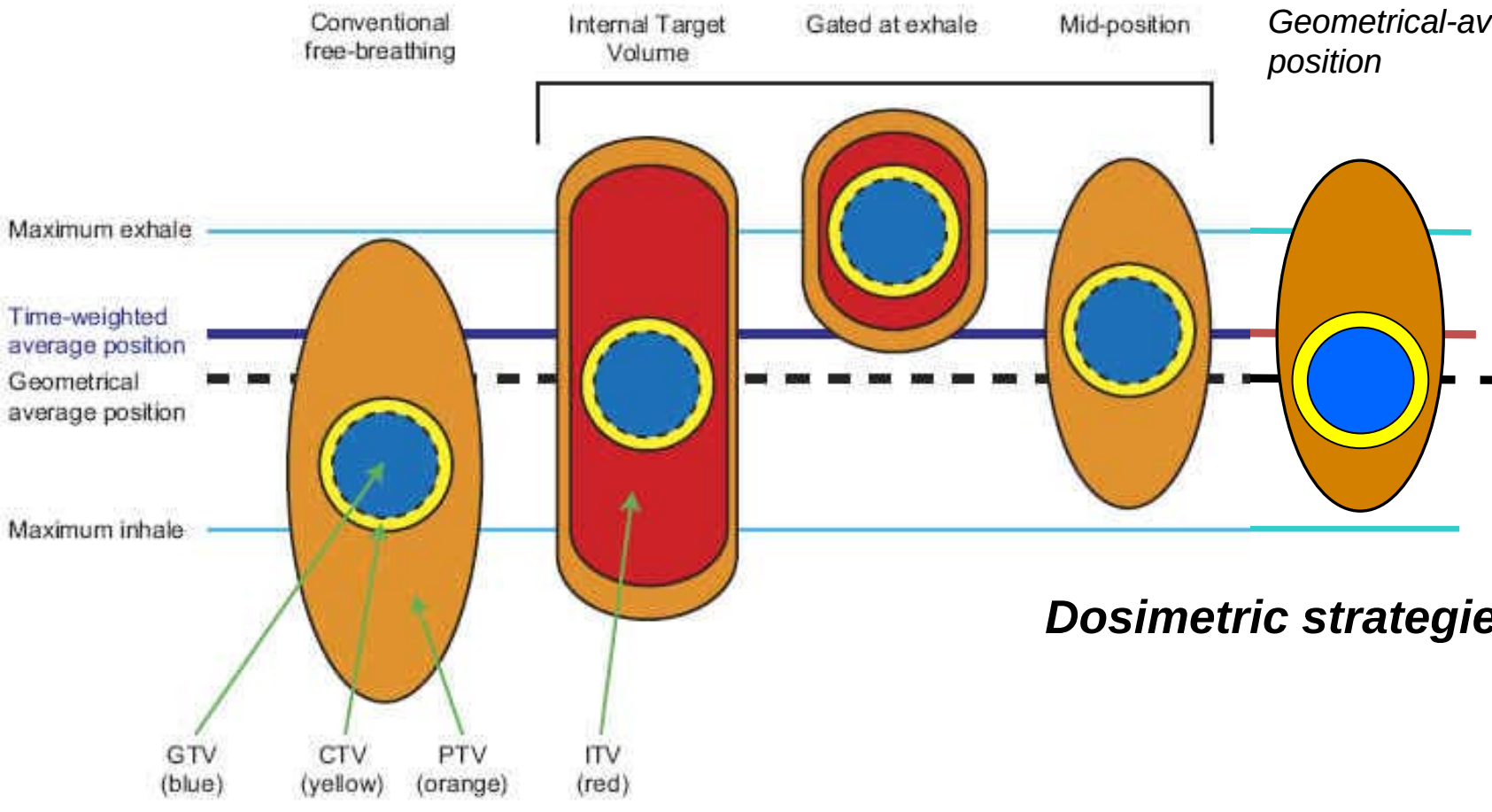
Technique flavours



Dosimetric strategies

Wolthaus, IJROBP 70 (2008) p1229

Cuijpers et al, R&O 97 (2010) p443

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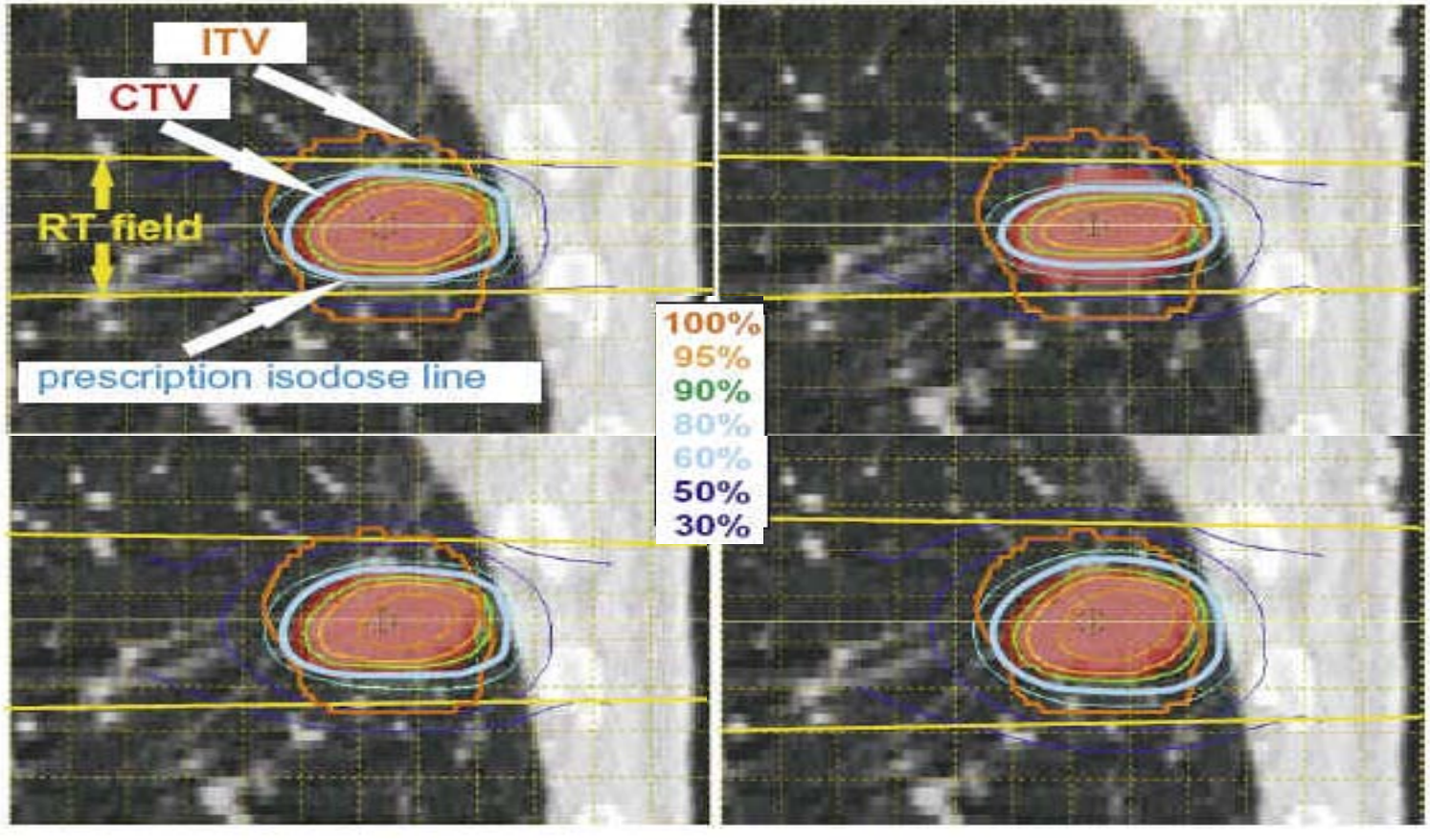
Why dosimetric strategies work

Plan without considering motion; 3D calcs



Plan without considering motion; 4D calcs

Plan based on average position

Plan based on ITV

Guckenberger et al, Radiother Oncol 91(2009) p288

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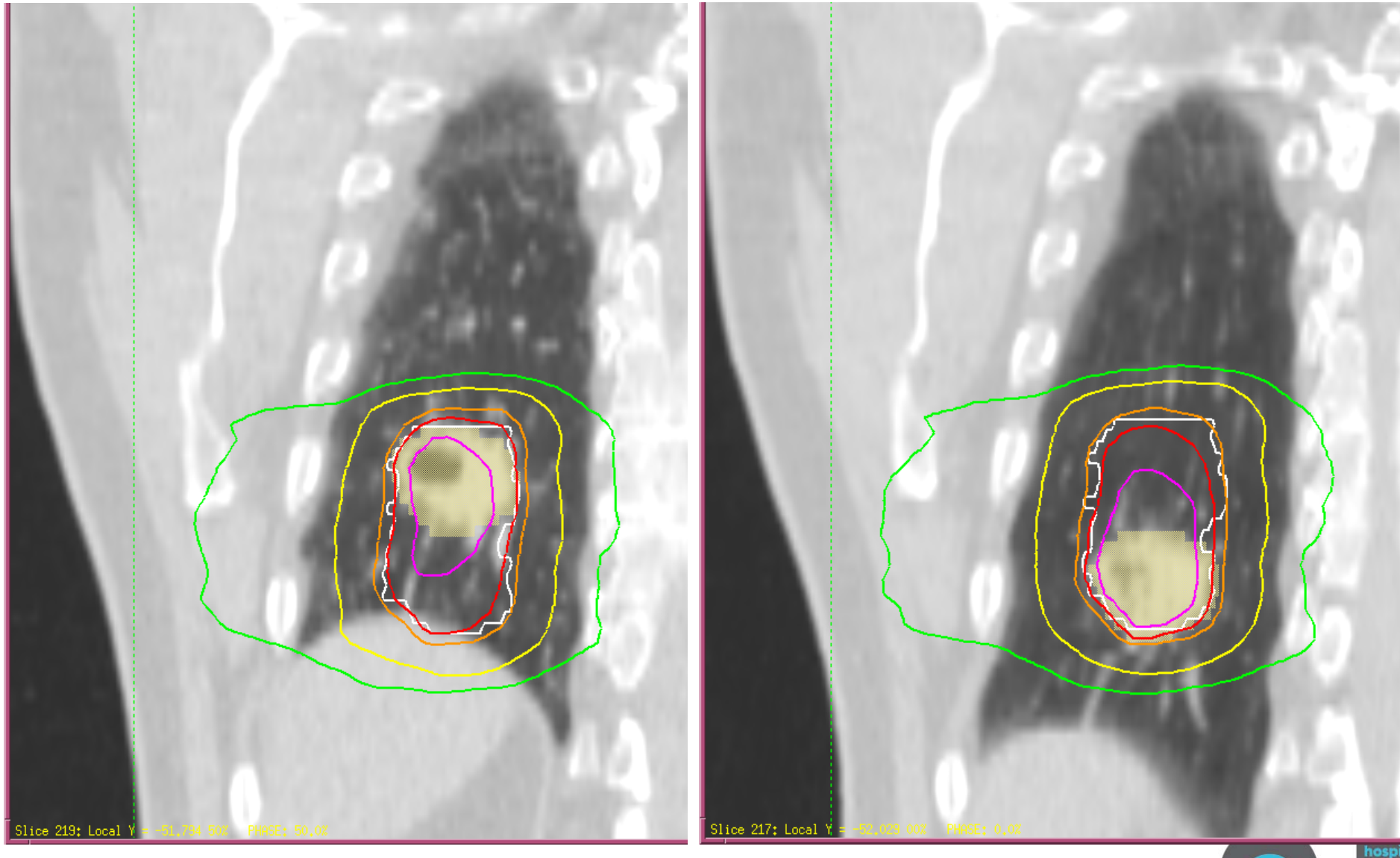
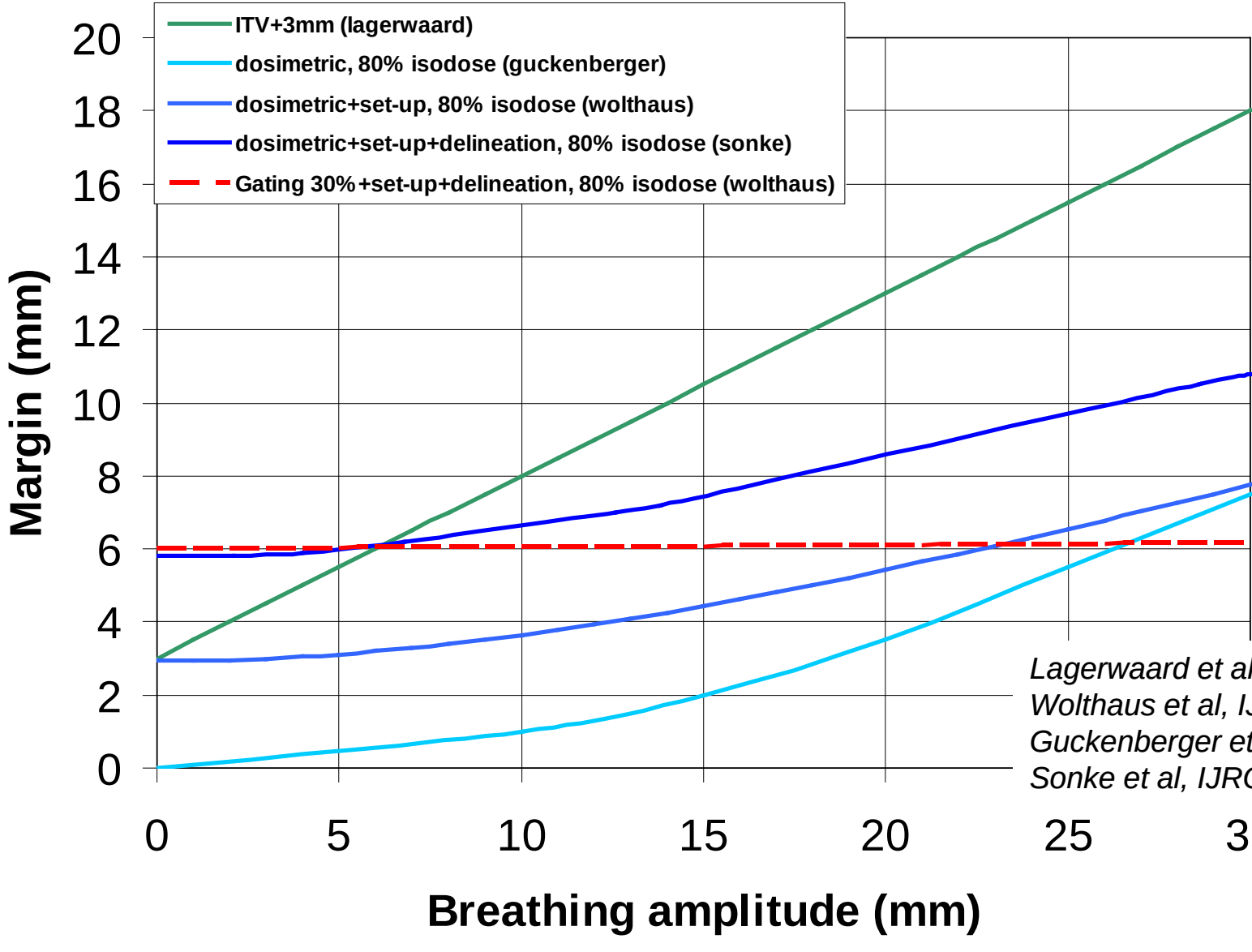
Why it works best in lung



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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Bold statement / Take home message

The ITV concept:

what you see is **NOT** what you get!

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Bold statement / Take home message

The dosimetric concept:

What you see is what you get

only if

proper margins are used!

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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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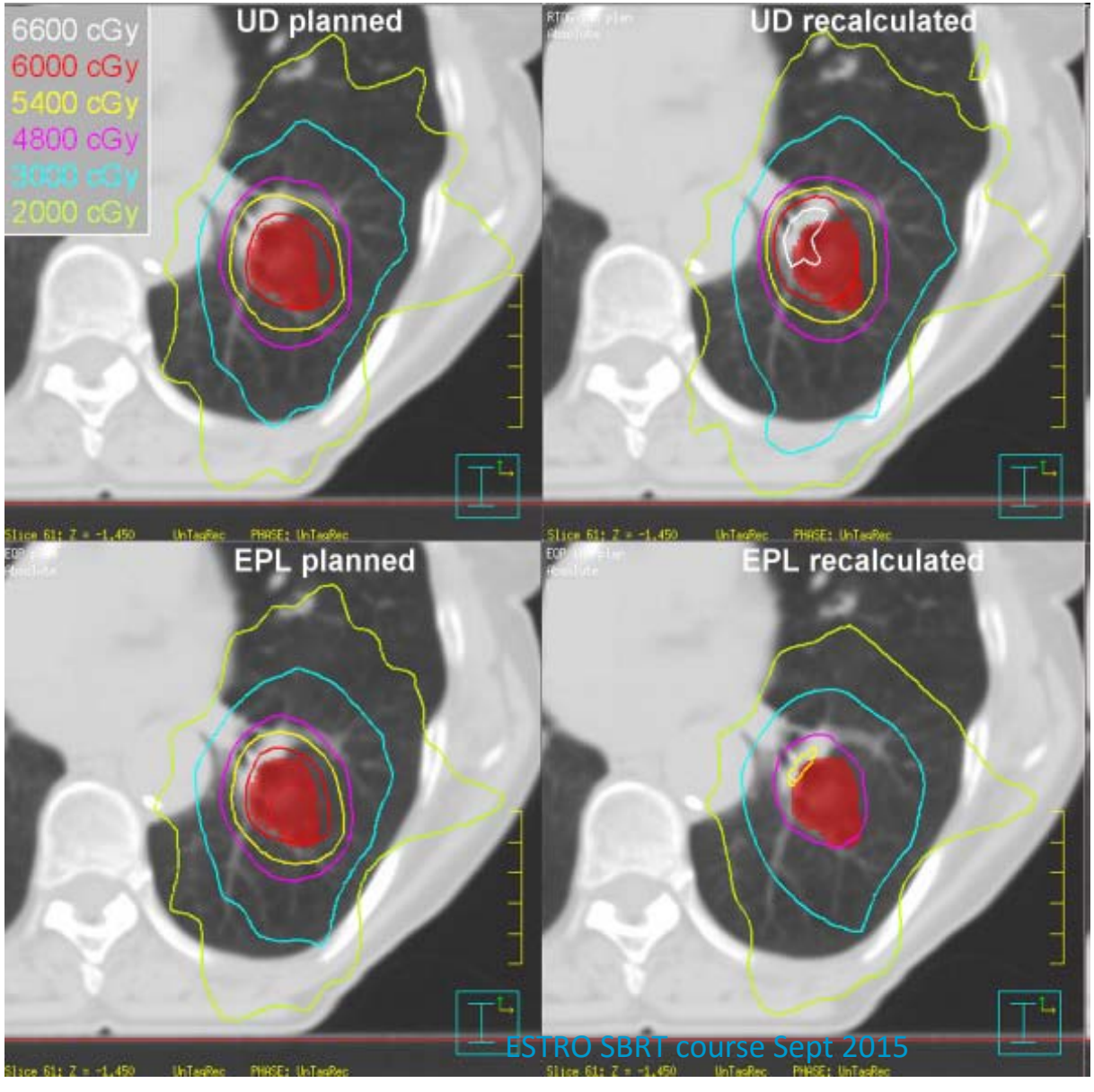
Influence on dose distribution



- 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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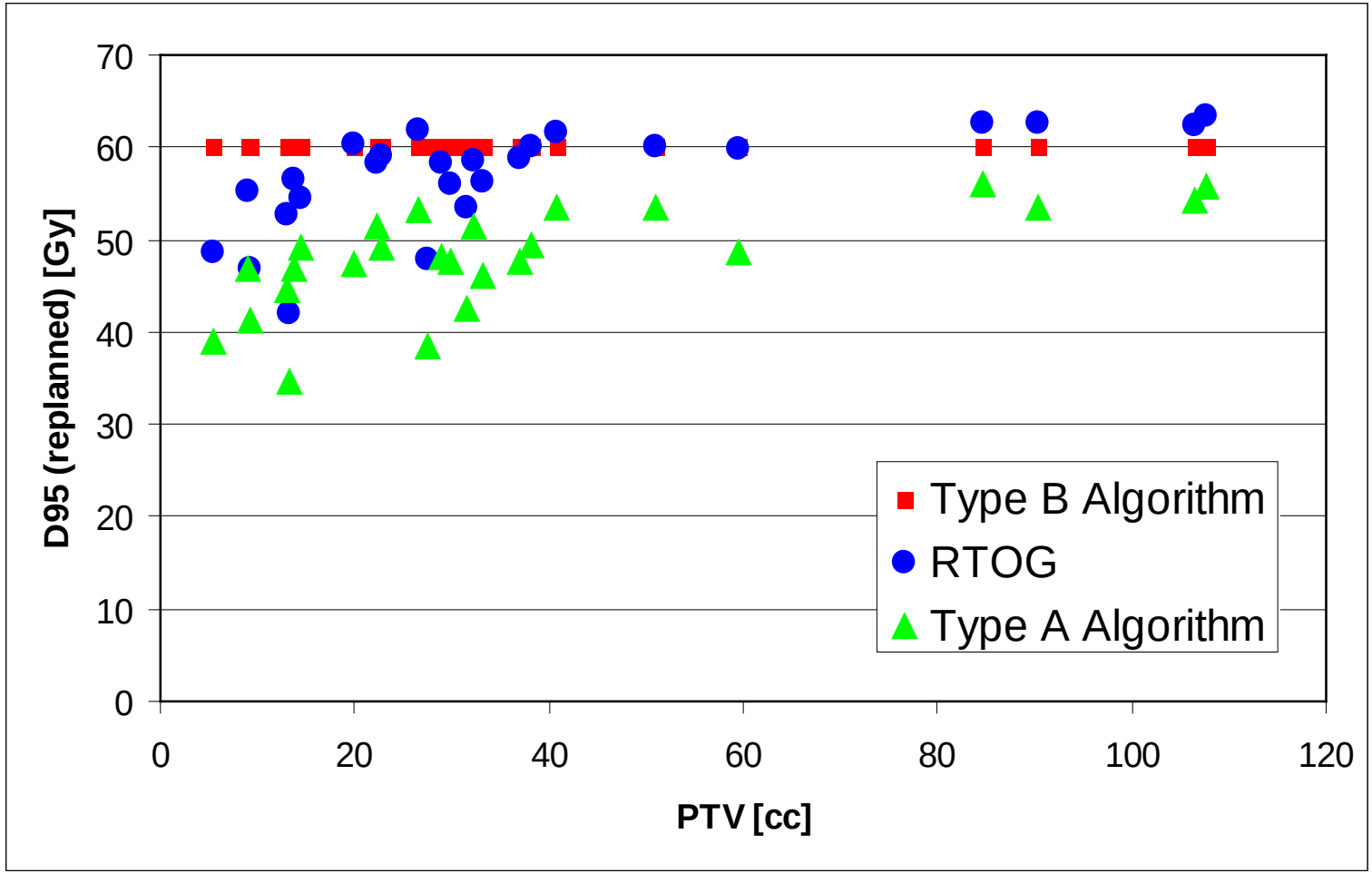
Actual delivered dose – 26 pts



Actual dose lower, depends on PTV Volume

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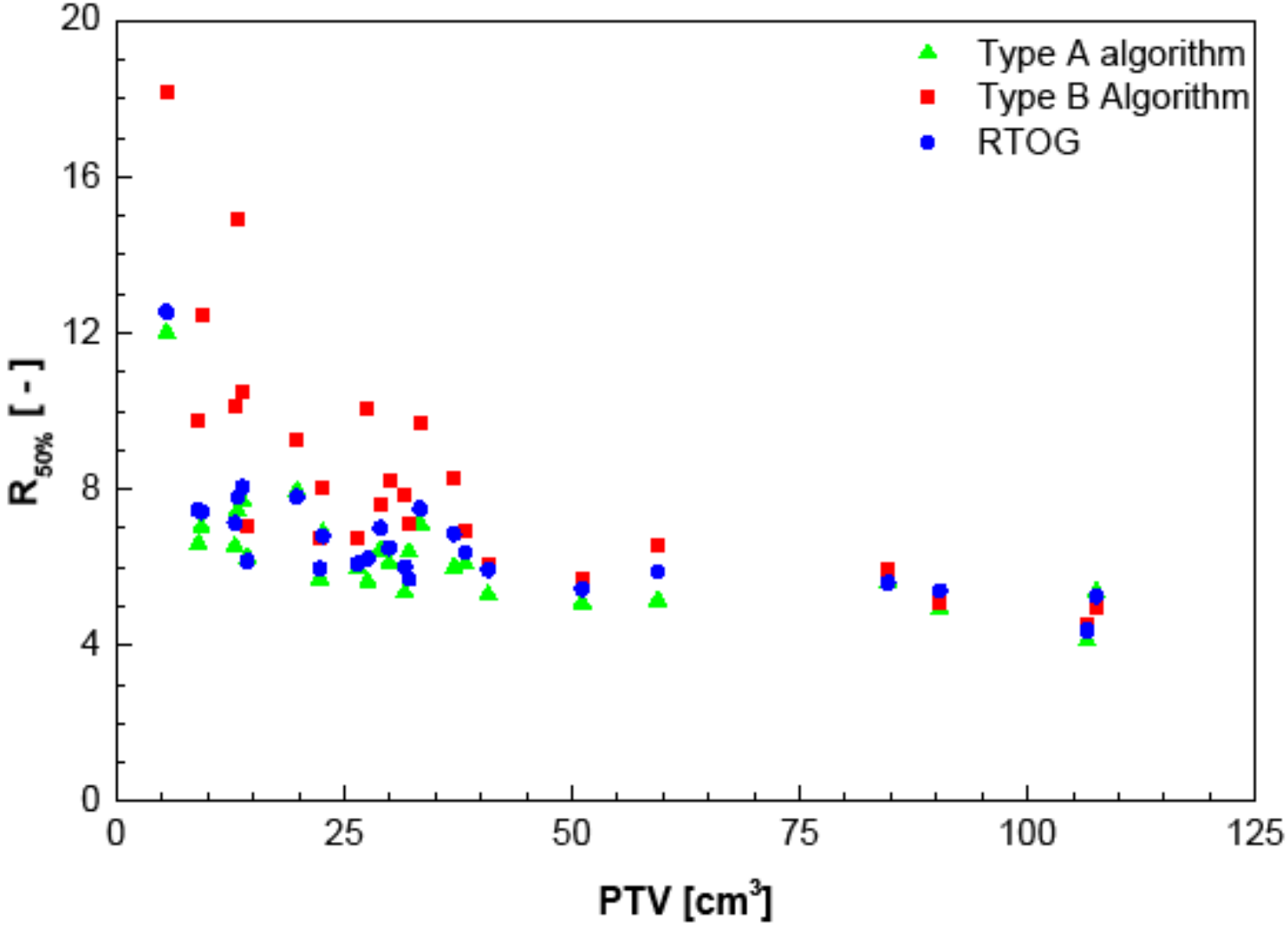
Dose criteria – low-dose conformity



Harder to meet conformity constraints (not recalculated!)

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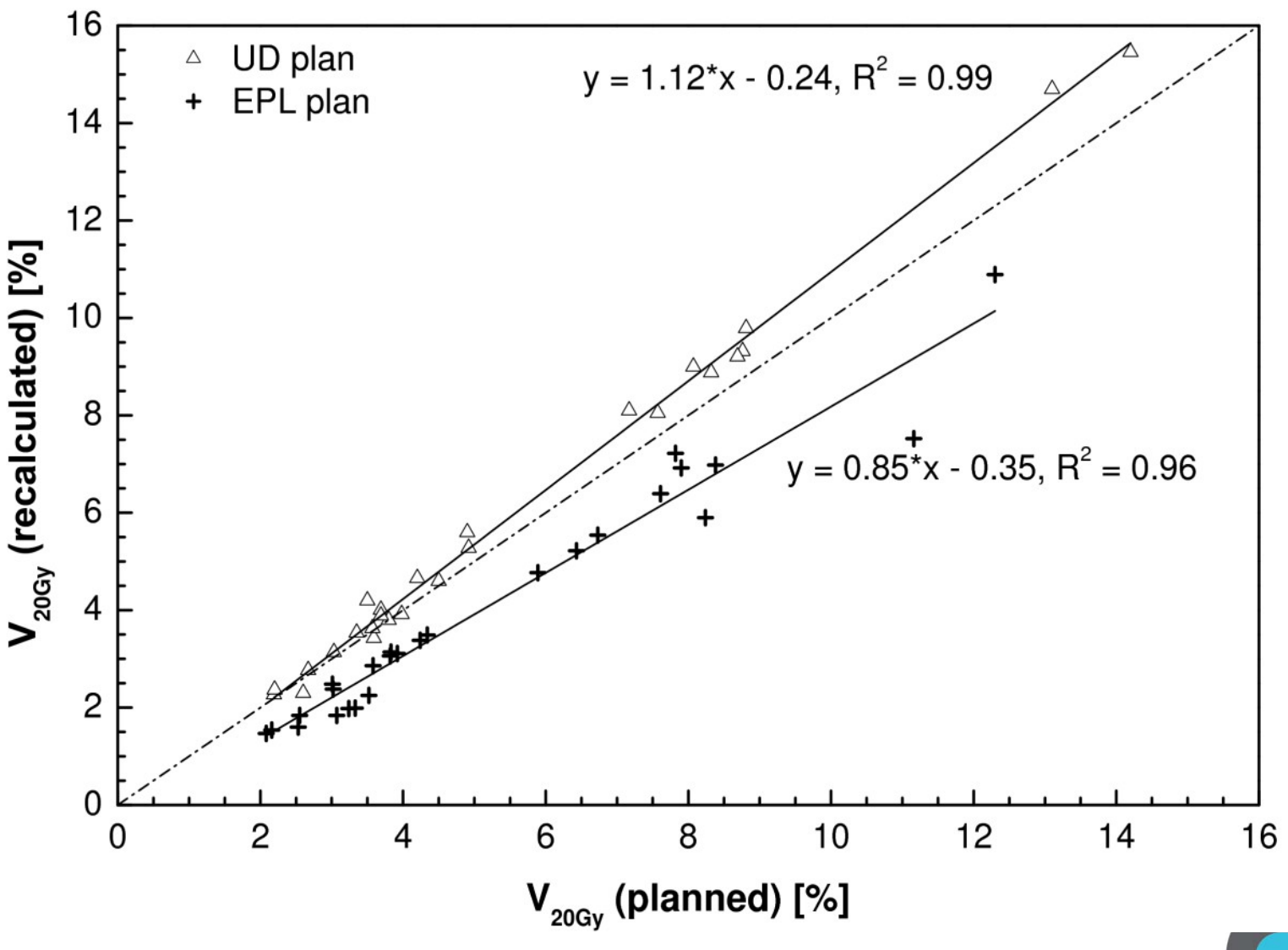
Dose criteria – lung dose



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Dose calculation

- Many clinical data based on type-A algorithms
  - Lower prescription dose
  - Dose to healthy lung overestimated

- Translation needed to own planning system
  - Prescription dose
  - Planning constraints

Prescription dose

ROSEL study	*Radiosurgery Or Surgery for Early Lung Cancer*
For type A models:	Standard fractionation: 3*20 Gy or 3*18 Gy
	Conservative fractionation: 5*12 Gy or 5*11 Gy
For type B models:	Standard fractionation: 3*18 Gy (3*20 Gy is NOT allowed)
	Conservative fractionation: 5*12 Gy or 5*11 Gy

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Algorithm dependent criteria: ROSEL

Type A models

$R_{100\%}$		$R_{50\%}$		D_{2cm} (%)		V_{20Gy} (%)		PTV (cc)
Deviation		Deviation		Deviation		Deviation		
None	Minor	None	Minor	None	Minor	None	Minor	
<1.15	1.15-1.25	<8	8-10	<55	55-60	<4	4-6	0-20
<1.15	1.15-1.25	<7	7-8	<65	65-70	<6	6-8	20-40
<1.10	1.10-1.20	<6	6-6.5	<65	65-75	<8	8-10	>40

Type B models (more advanced)

$R_{100\%}$		$R_{50\%}$		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

Hurkmans *et al,* Radiat Oncol 2009, 4:1

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Revised RTOG criteria: Xiao et al

Table 1. Dosimetric criteria for target coverage

	Ratio of prescription isodose volume to PTV		Ratio of 50% prescription isodose volume to PTV ($R_{50\%}$)		Maximal dose 2 cm from PTV in any direction (% of prescription dose)			
	Major deviation		Major deviation		Major deviation		Percentage of lung receiving ≥20 Gy (%)	
Maximal PTV dimension (cm)	Homo 60 Gy	Hetero 56 Gy	Homo	Hetero	Homo	Hetero	Major deviation	PTV (cm^3)
2	>1.4	>1.4	>4.1	>7.0	>50.2	>55.2	>15	1.8
2.5	>1.4	>1.4	>4.1	>5.8	>50.2	>55.2	>15	3.8
3	>1.4	>1.4	>4.1	>5.4	>50.2	>55.2	>15	7.4
3.5	>1.4	>1.4	>4.1	>5.3	>50.2	>55.2	>15	13.2
4	>1.4	>1.4	>4.0	>5.2	>54.0	>59.7	>15	21.9
4.5	>1.4	>1.4	>3.9	>5.0	>57.8	>62.8	>15	33.8
5	>1.4	>1.4	>3.8	>4.8	>61.8	>75.2	>15	49.6
5.5	>1.4	>1.4	>3.7	>4.5	>69.5	>83.8	>15	69.9
6	>1.4	>1.4	>3.5	>4.1	>69.5	>86.8	>15	95.1
6.5	>1.4	>1.4	>3.3	>3.7	>73.3	>88.7	>15	125.8
7	>1.4	>1.4	>3.1	>3.5	>77.2	>90.7	>15	162.6

Abbreviations: PTV = planning target volume; Homo = unit density; Hetero = suggested adjustments to be used when heterogeneity correction applied.

- Recalculated!
- Criteria do not make optimal use of better optimisation with type B algorithm!

Xiao IJROBP (2009) 1235

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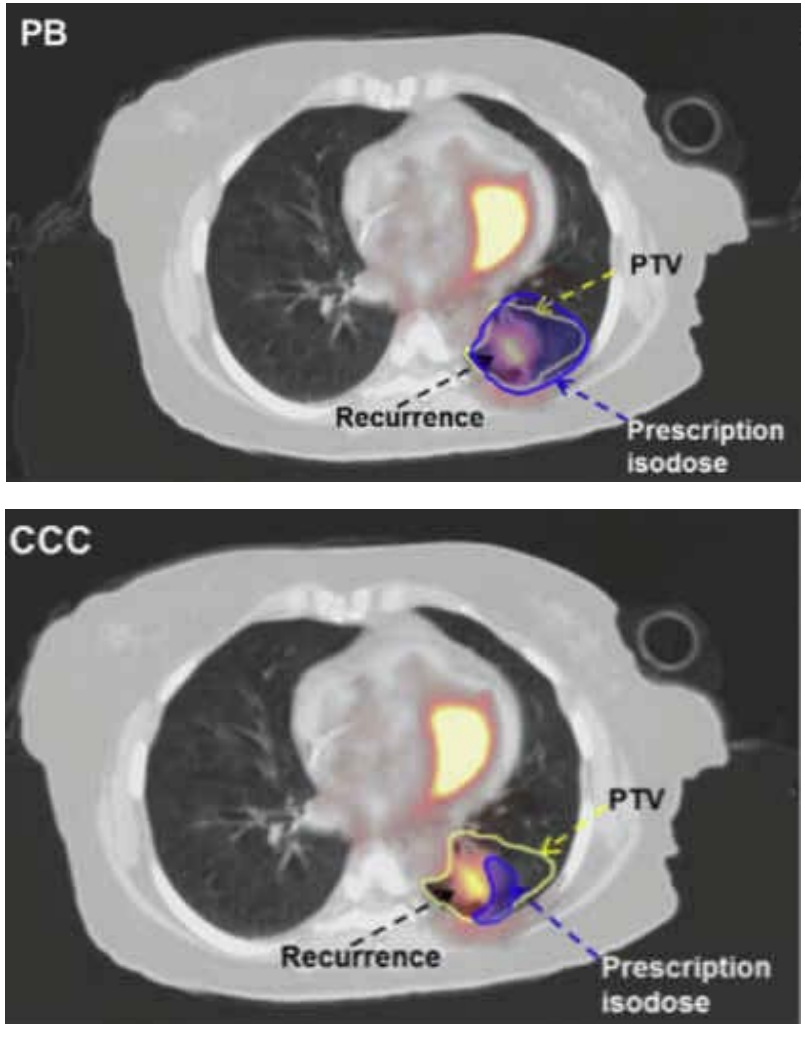
It is clinically relevant!



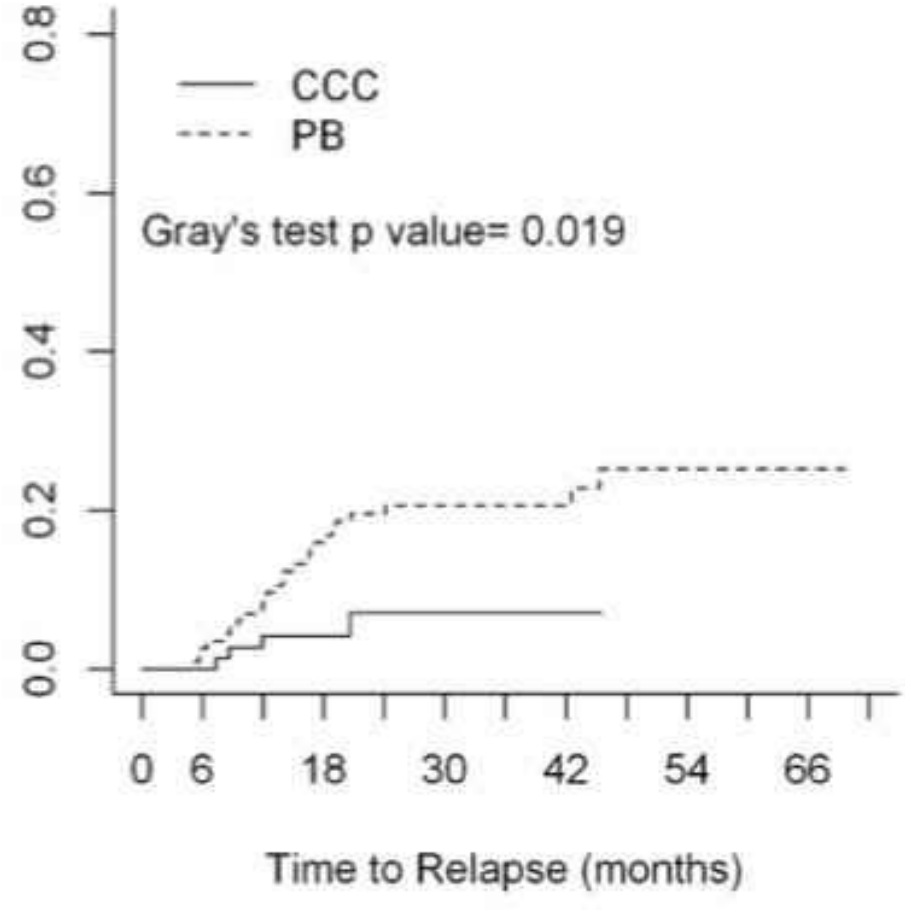


Fig. 1. Cumulative incidence of recurrence by group for all patients (N=201): pencil beam (PB) versus collapsed cone convolution (CCC).

Latifi IJROBP 88 2014

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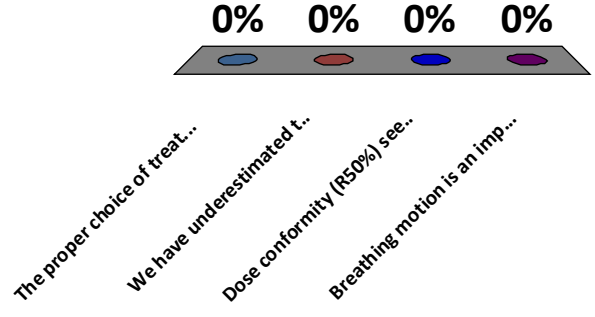
What is true?

A. The proper choice of treatment planning objectives does not depends on your calculation algorithm
B. We have underestimated the dose to small lung tumors in the past
C. Dose conformity (R50%) seems lower using type B algoritms.
D. Breathing motion is an important component of the total CTV-PTV margin needed.



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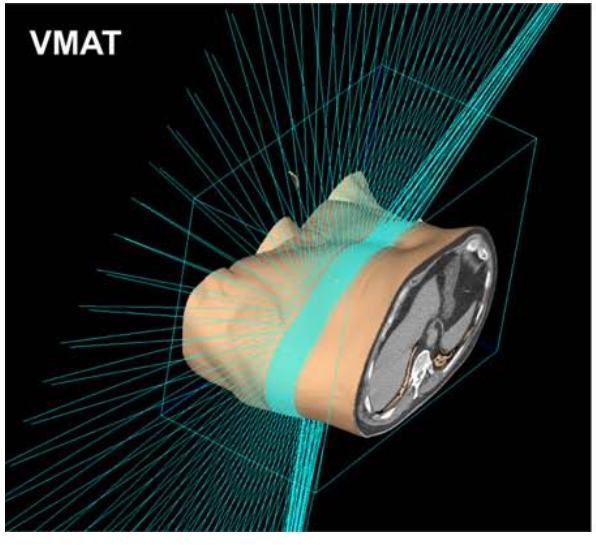
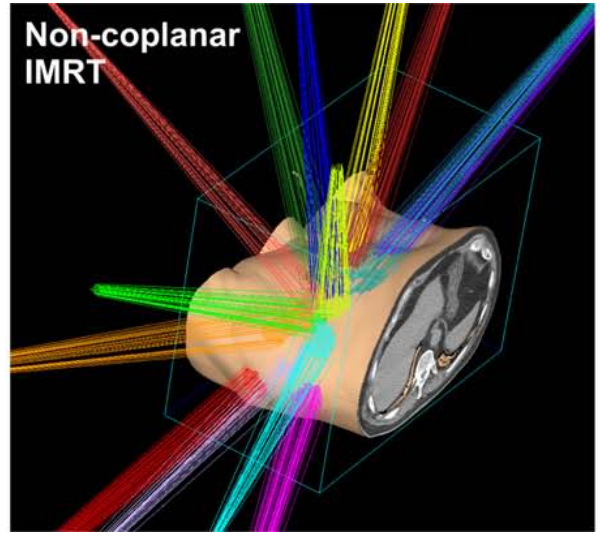
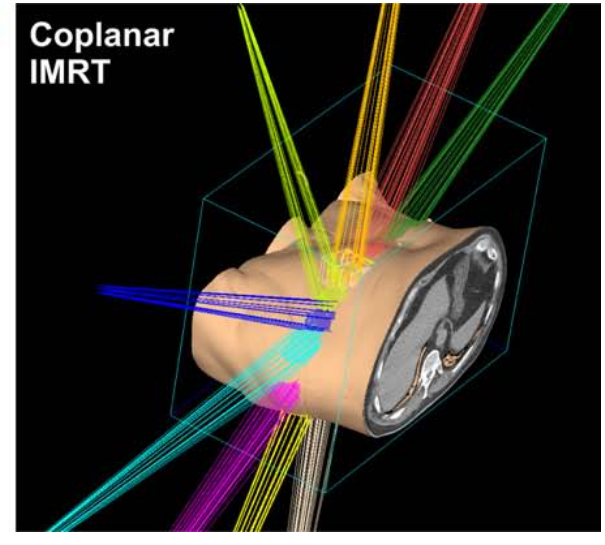
Planning technique







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.*

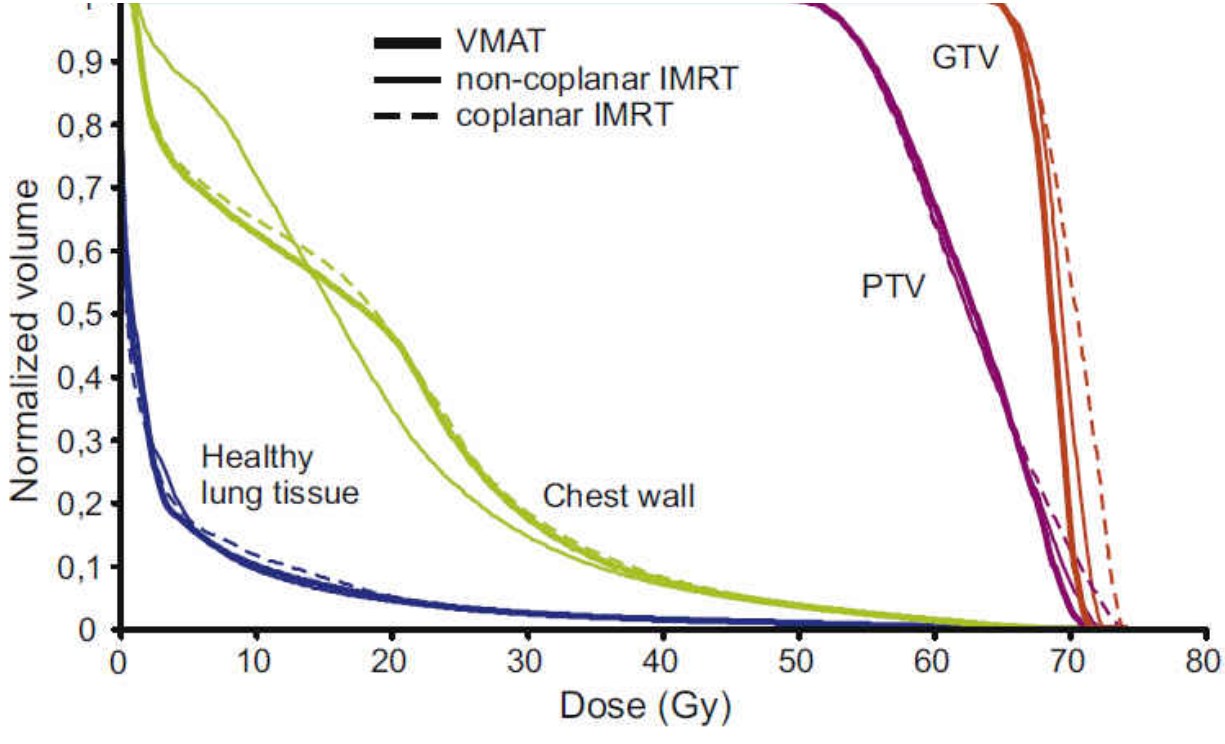


Fig. 3. Dose–volume histograms for example case shown in Fig. 2.

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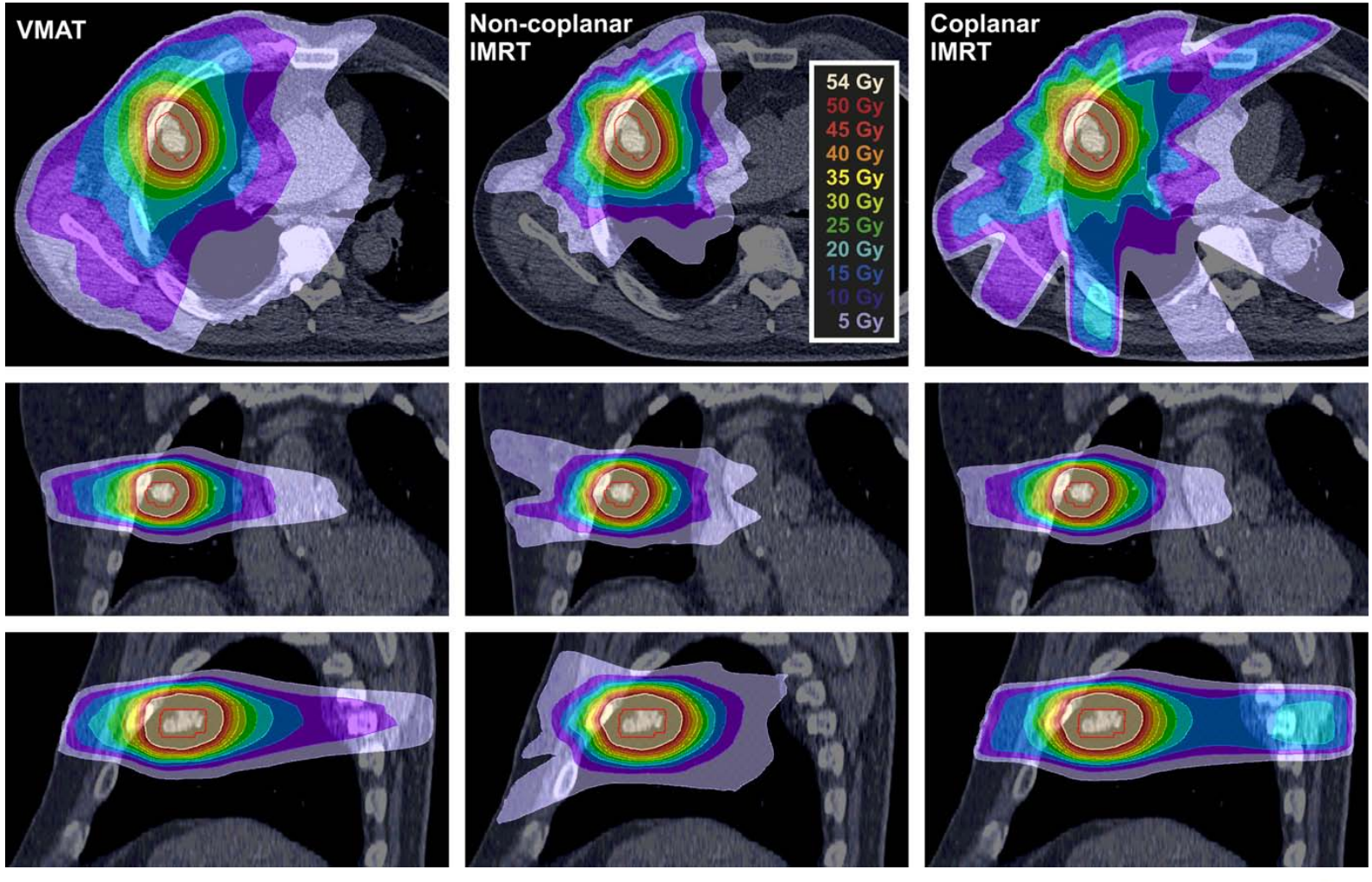
Planning technique



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.

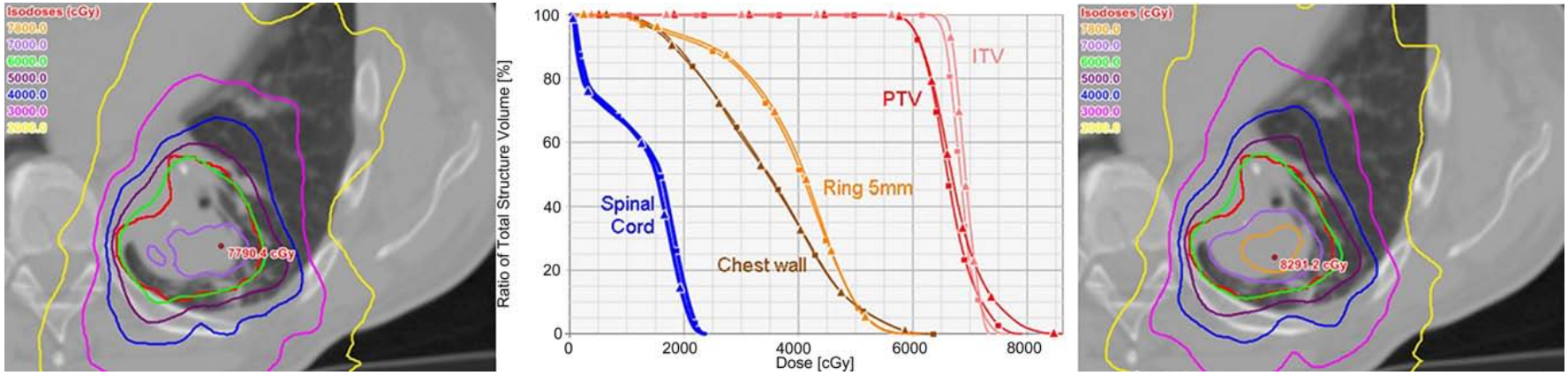

Fig. 2. Comparison of dose distributions in transverse planes for lung flattened beam plan (left) and flattening filterfree plan (right), with planning target volume outlined in red. The dosevolume histogram shows similar planning target volume coverage and organ at risk sparing between 6-MV flattened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

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

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Conclusions

- 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.
- 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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SBRT treatment planning
Liver, Spine and Prostate

Stephanie Lang

University Hospital Zürich

UniversityHospital Zurich

Universität Zürich[UZH]

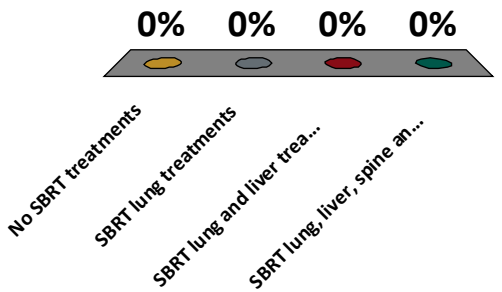
ESTRO School

Outline

- SBRT for Liver cancer
- SBRT for spine
- SBRT for prostate cancer
- FFF beams - a benefit for SBRT treatments?

In your department, do you perform

A. No SBRT treatments
B. SBRT lung treatments
C. SBRT lung and liver treatments
D. SBRT lung, liver, spine and prostate treatments



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?

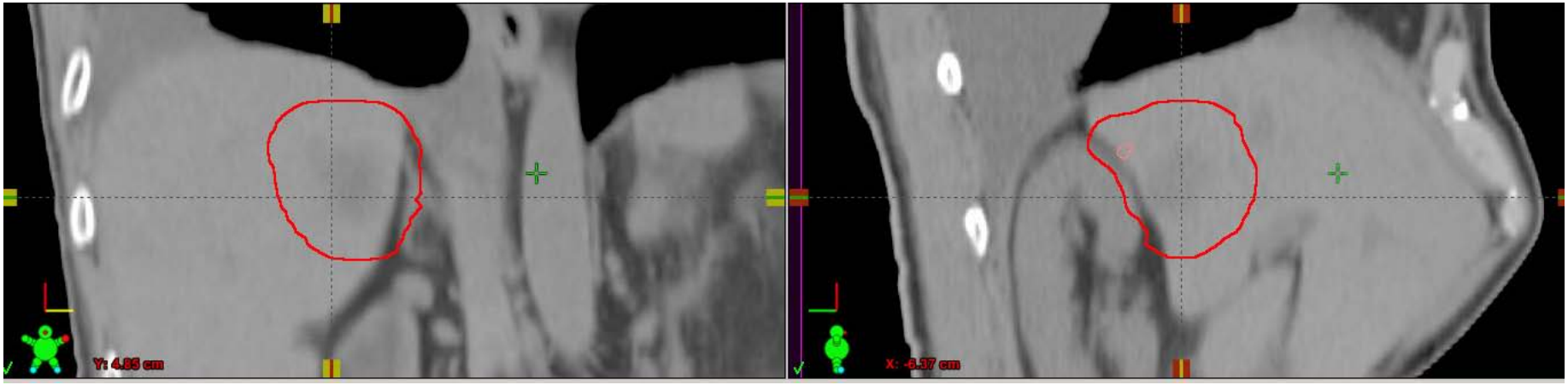
What do we have available?

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

→ Overestimates Liver volume, underestimated dose to the liver

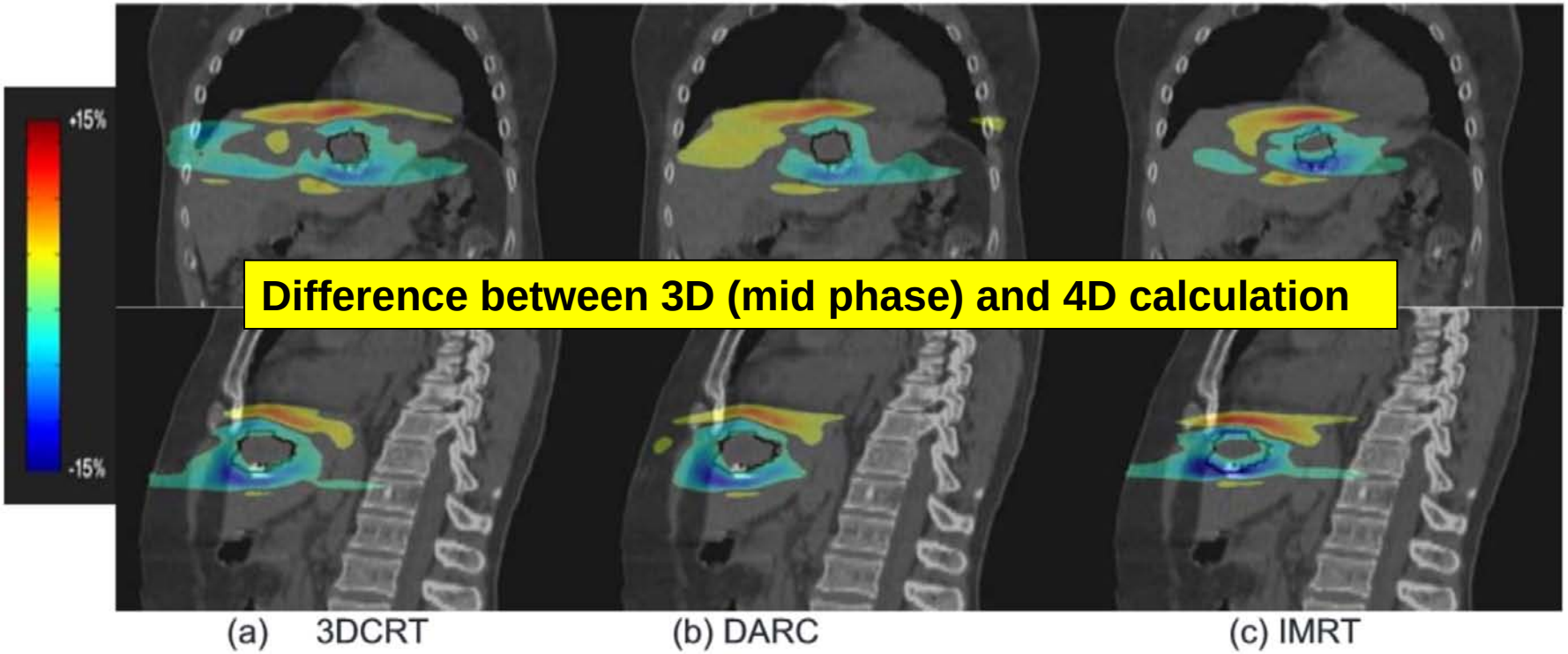
On which CT should we calculate dose?

Tumors in the middle of the liver?



On which CT should we calculate dose?

Tumors in the middle of the liver?

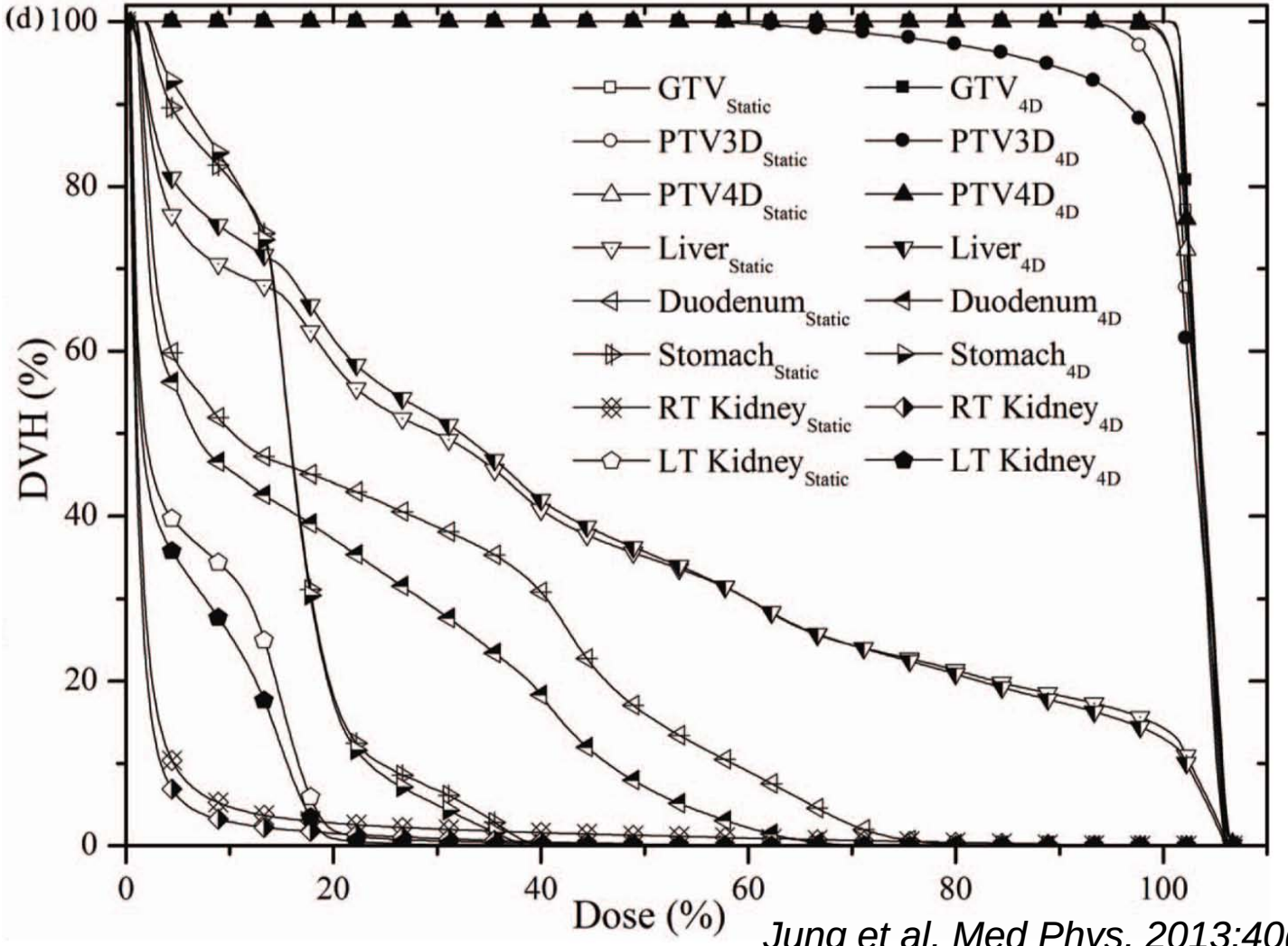


Wu et al, Med Phys,2008;35(4)

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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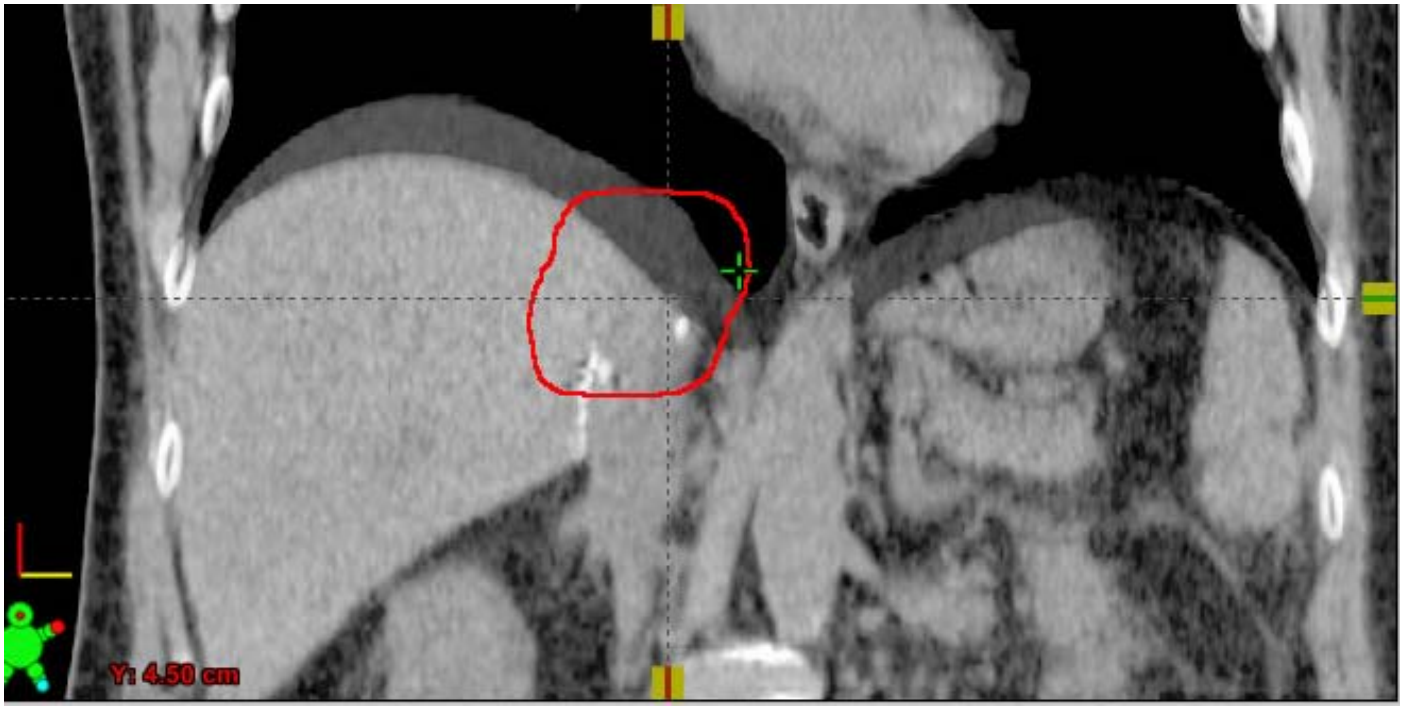
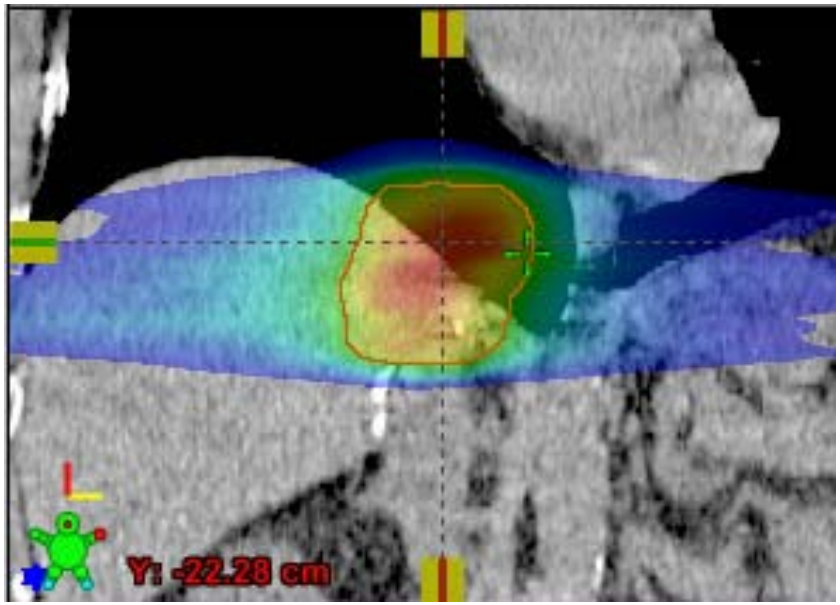
On which CT should we calculate dose?

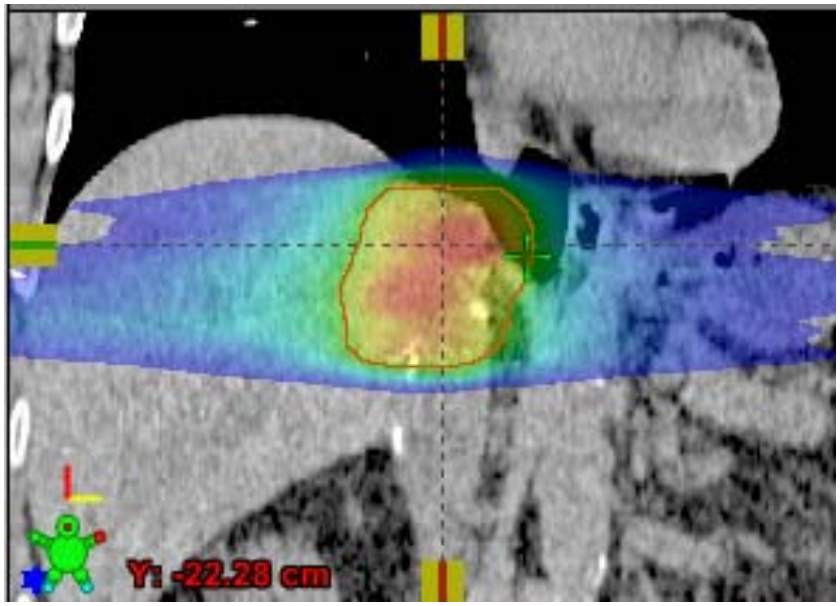
Tumors on the boundary liver - lung?



On which CT should we calculate dose?

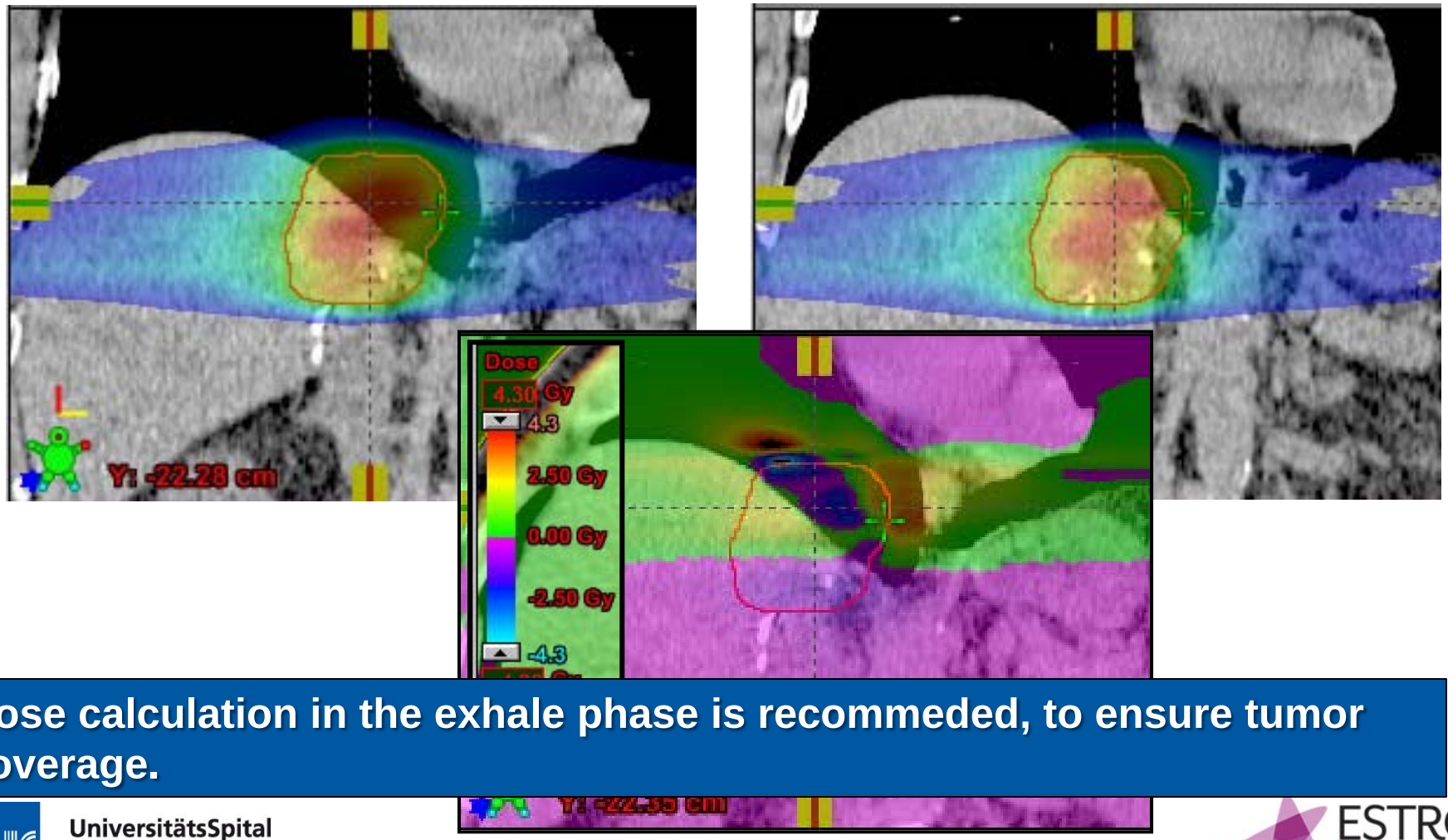
Tumors on the boundary liver - lung?





On which CT should we calculate dose?

Tumors on the boundary liver - lung?



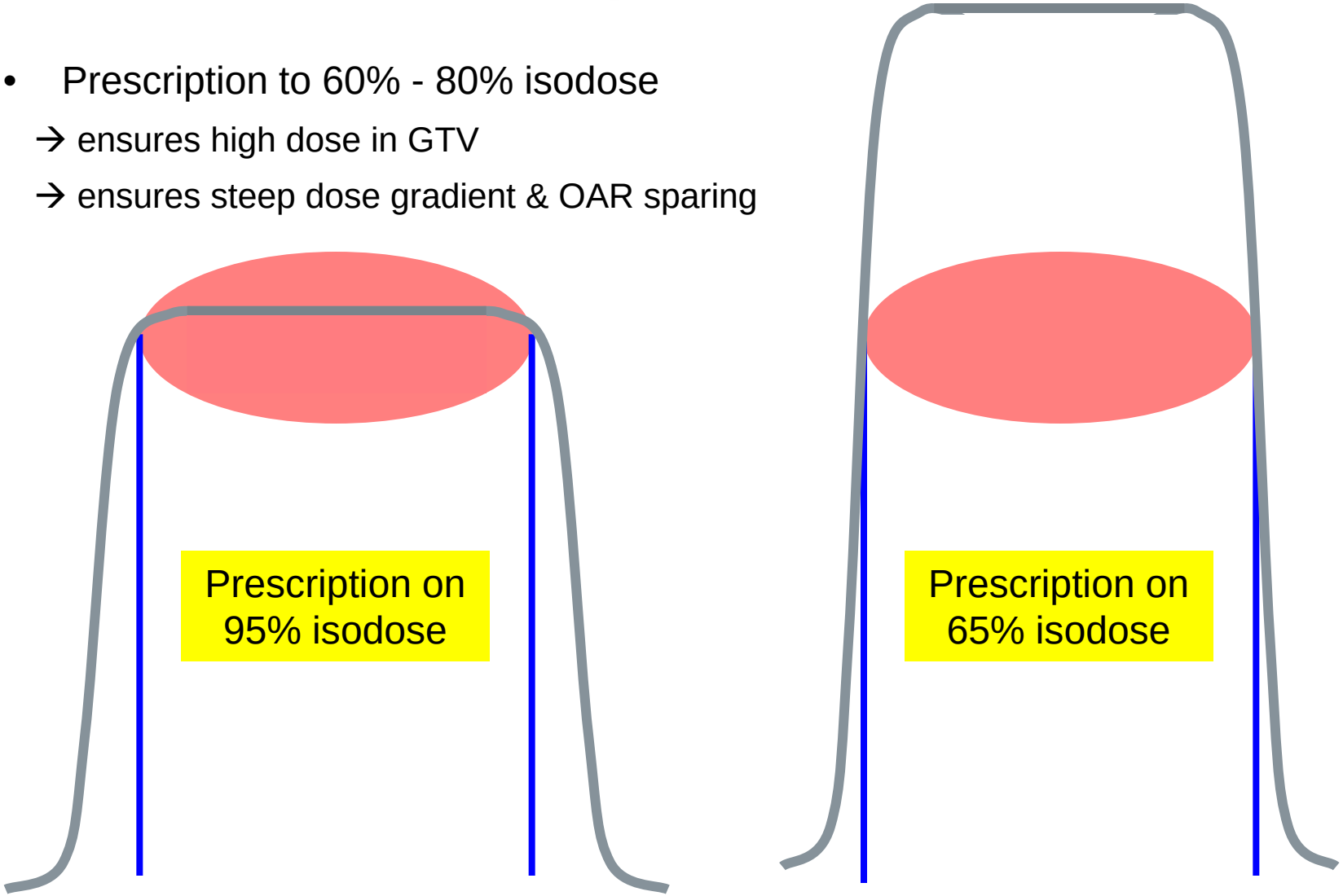
Dose calculation in the exhale phase is recommeded, to ensure tumor coverage.

Treatment planning for liver cancer

- Prescription to 60% - 80% isodose

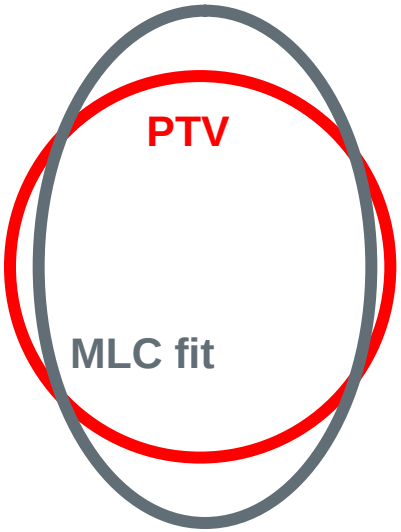
→ ensures high dose in GTV

→ ensures steep dose gradient & OAR sparing



3D conformal treatment planning

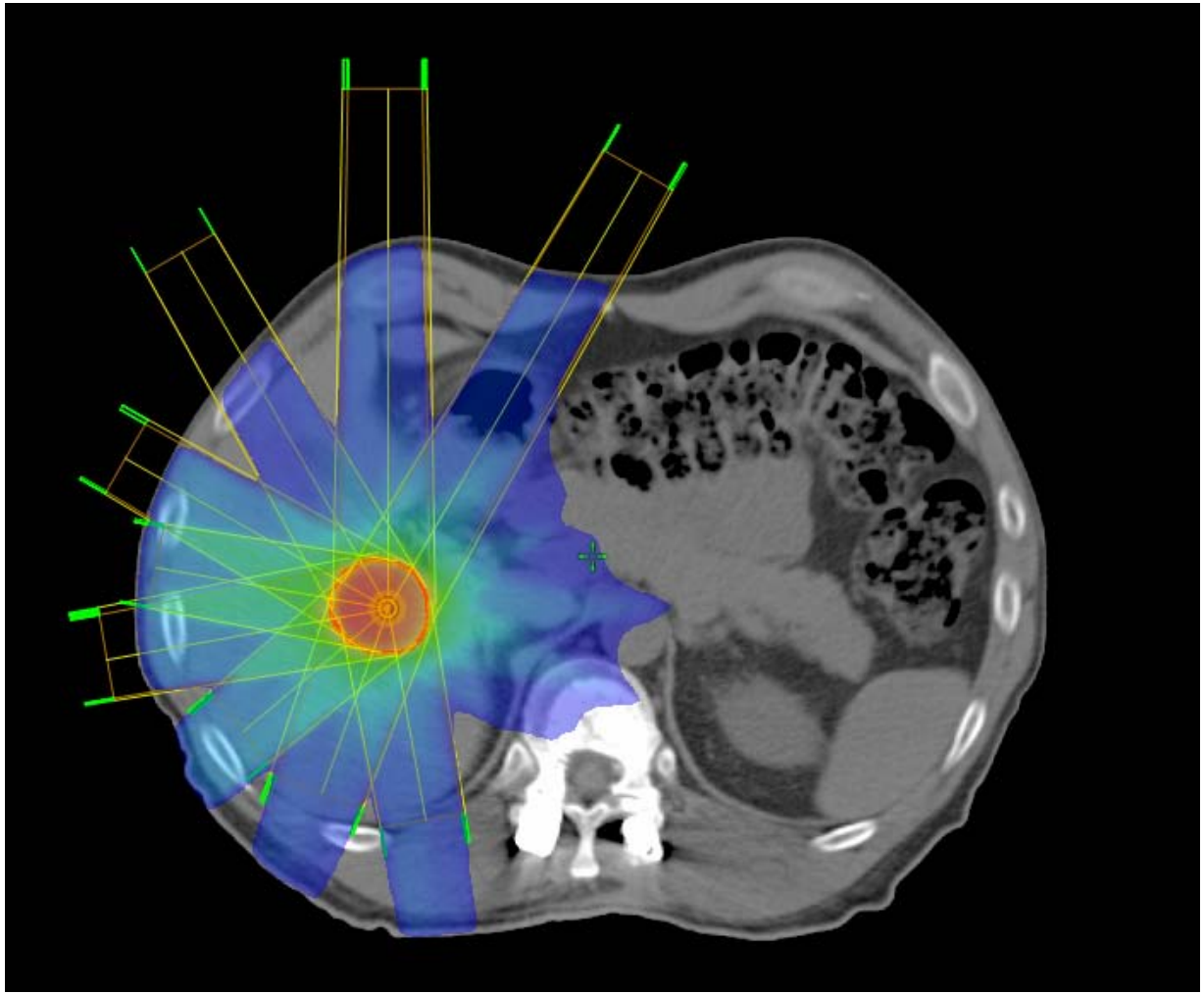
- Isocenter placed in target
- 7-11 fields spread as much as possible
- Avoid directly opposing fields
- Avoid entering a OAR (spinal cod, duodenum, bowel, kidneys).
- Fit MLC to help structure

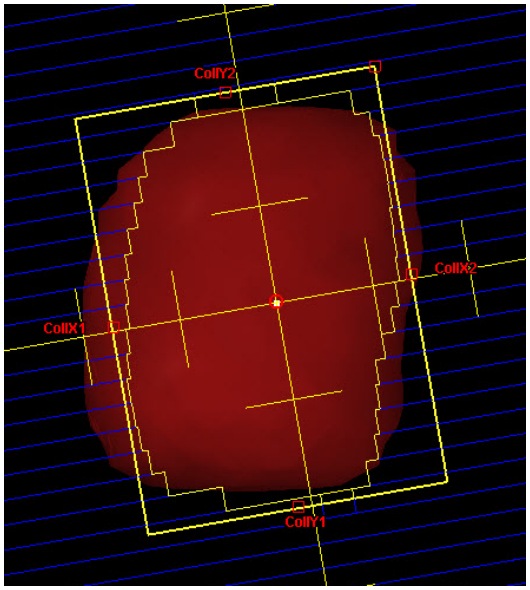


• MLC fit is 2mm longer (sup-inf) and 3 mm tighter (lat and AP) than the PTV

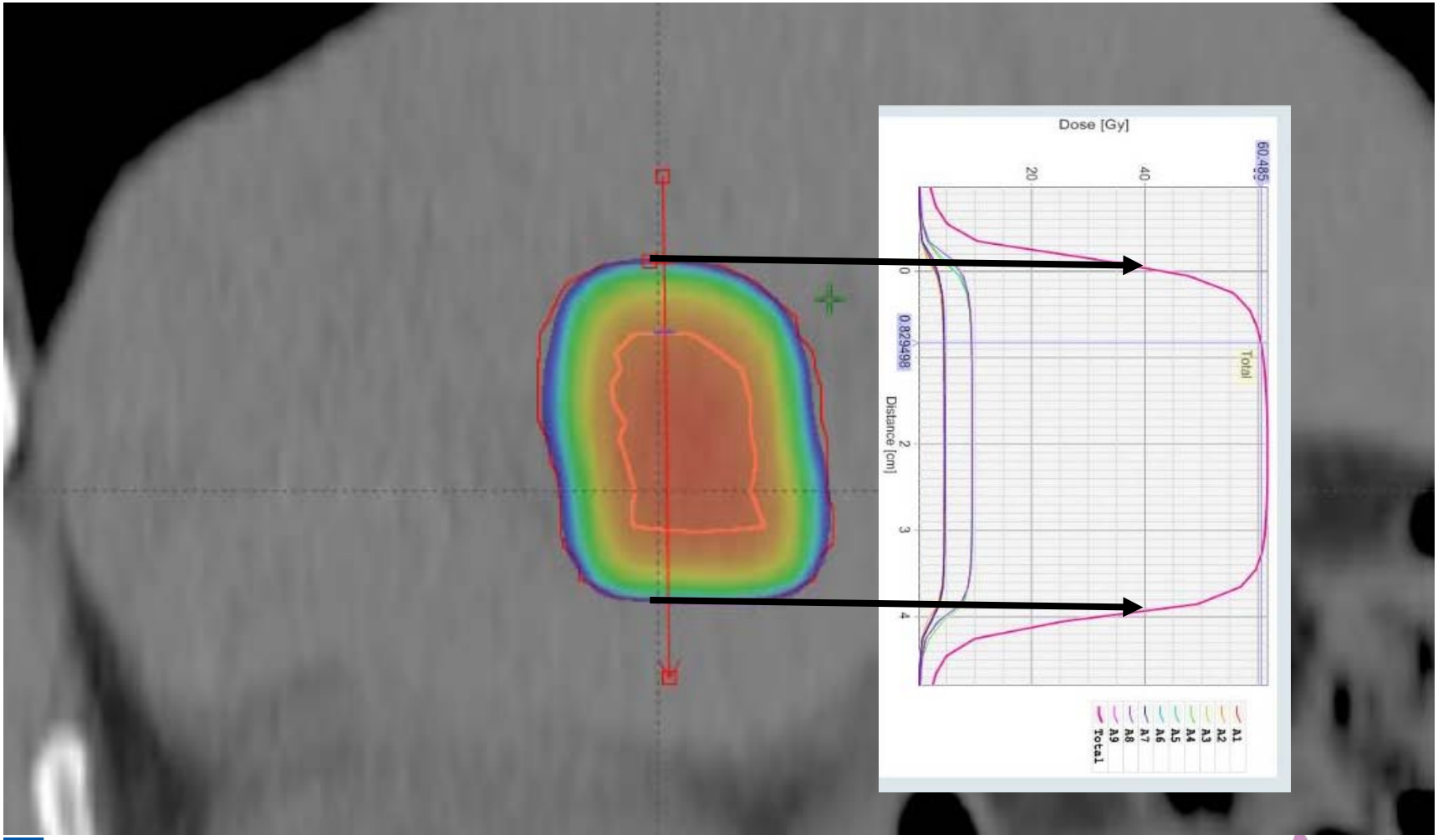
• Manual adjustements may be necessary, for example to sprare thoracic wall better

3D conformal treatment planning

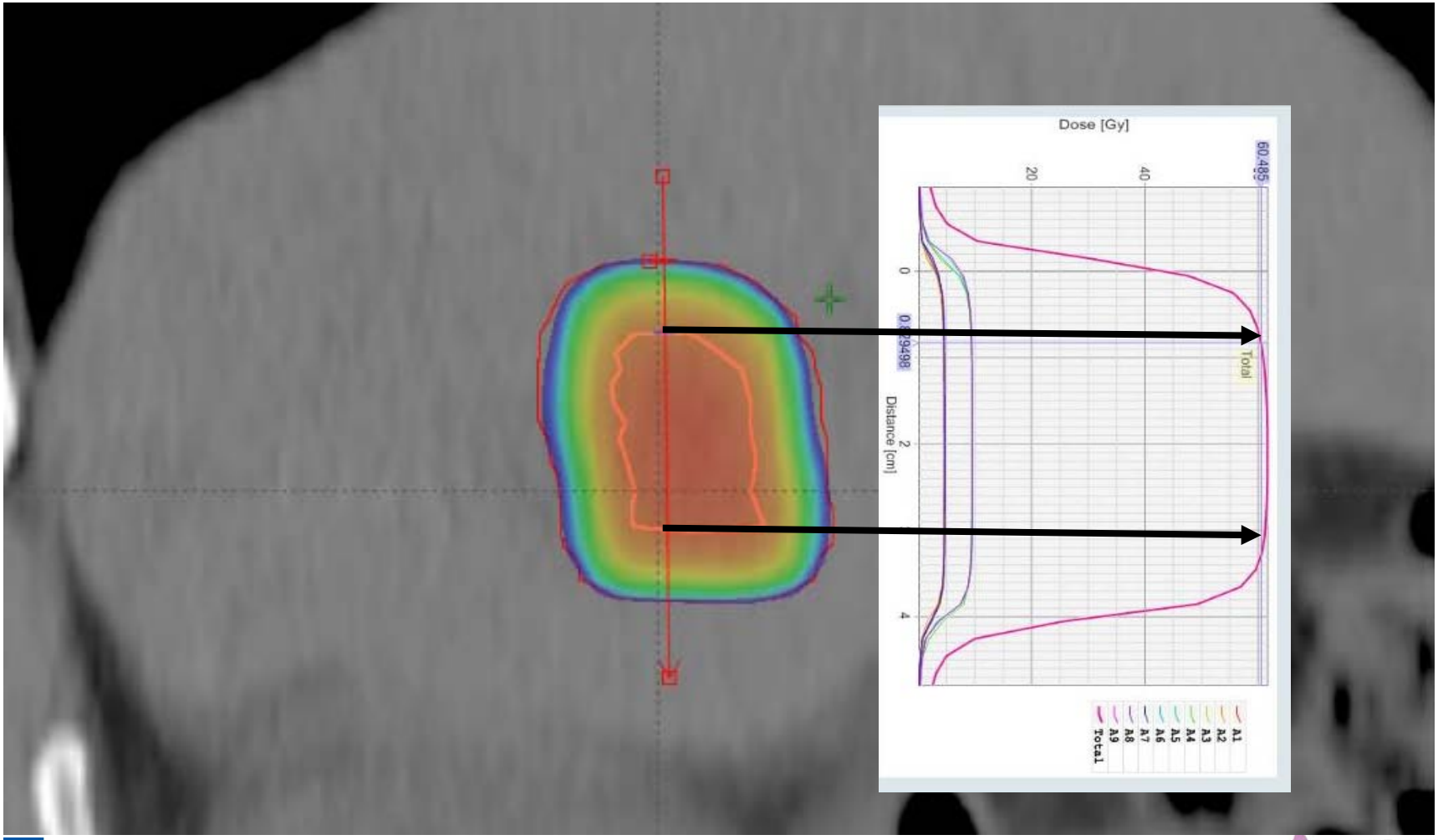




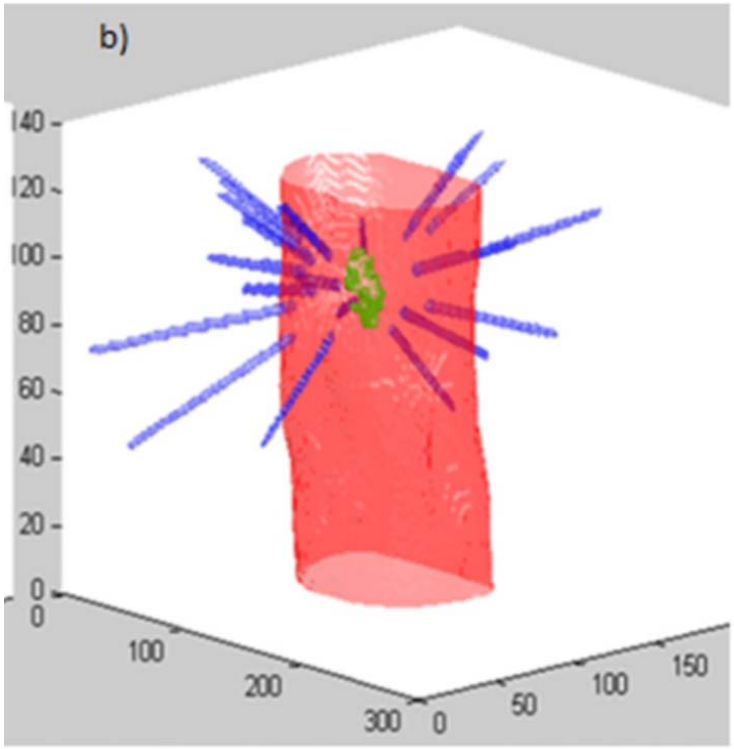
3D conformal treatment planning



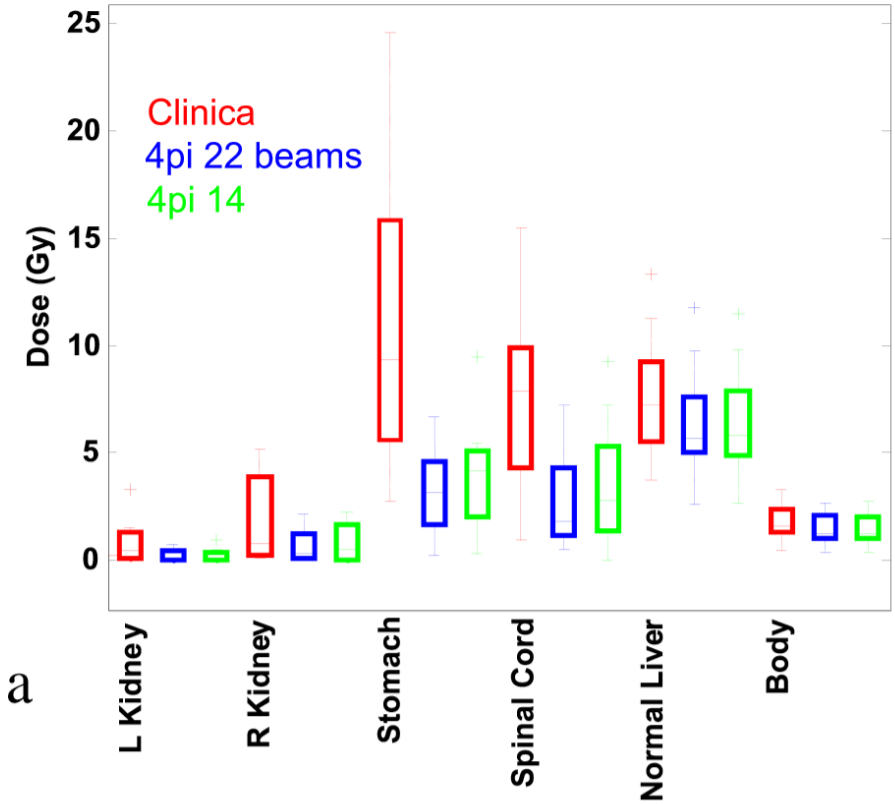
3D conformal treatment planning



Coplanar versus non-coplanar

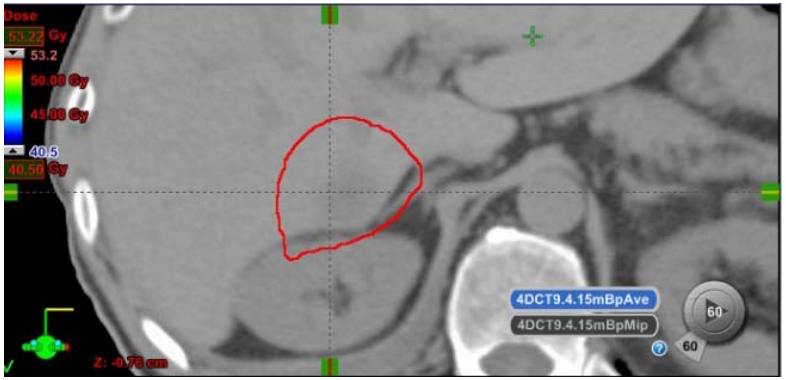


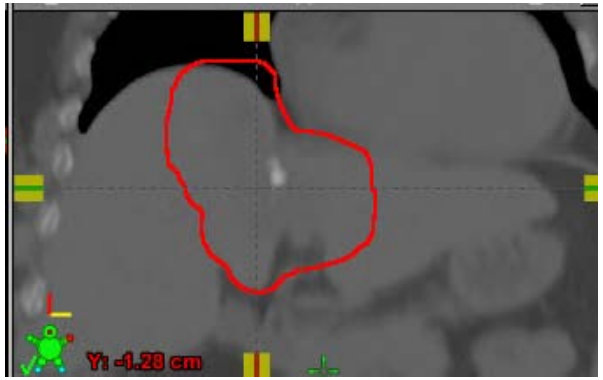
Dong et al, IJROBP 2012

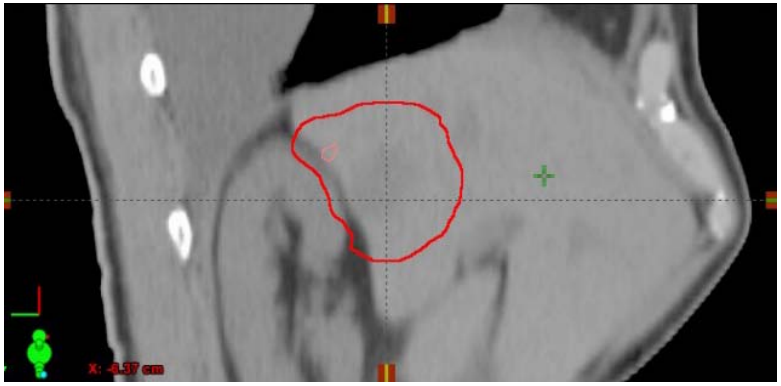


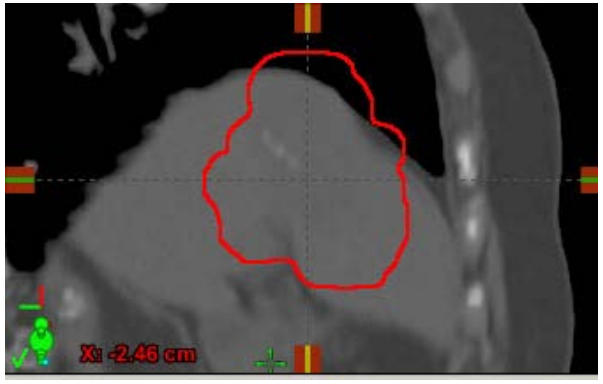
Improved sparing of organs at risk using non-coplanar fields.

Do we need VMAT?





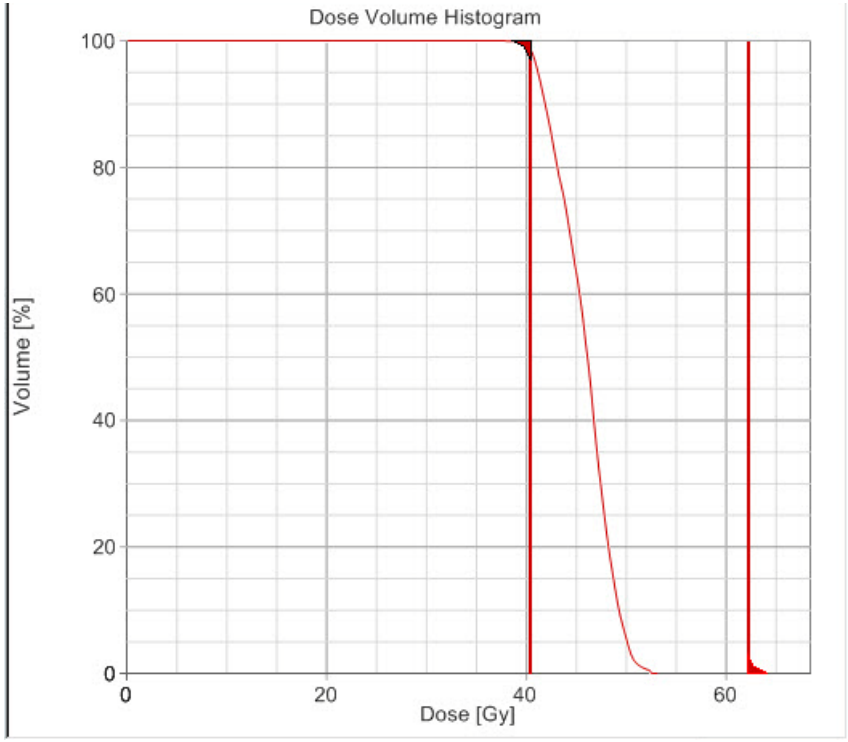


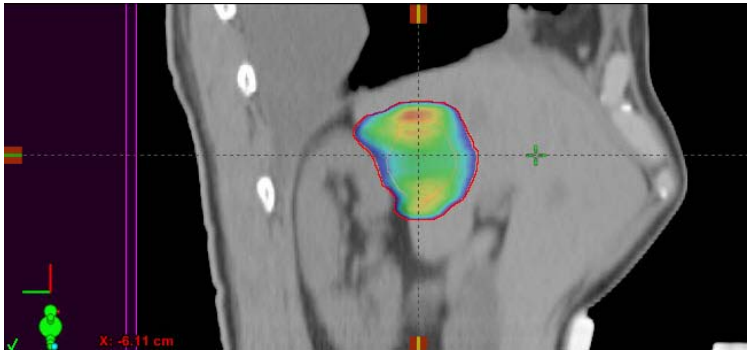


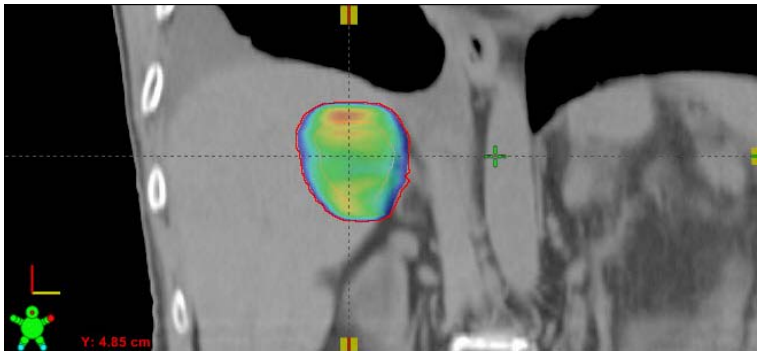
VMAT has advantages when the target volume has a compley shape or an organ at risk is close to the PTV.

VMAT optimisation

How to get the inhomogeneity?

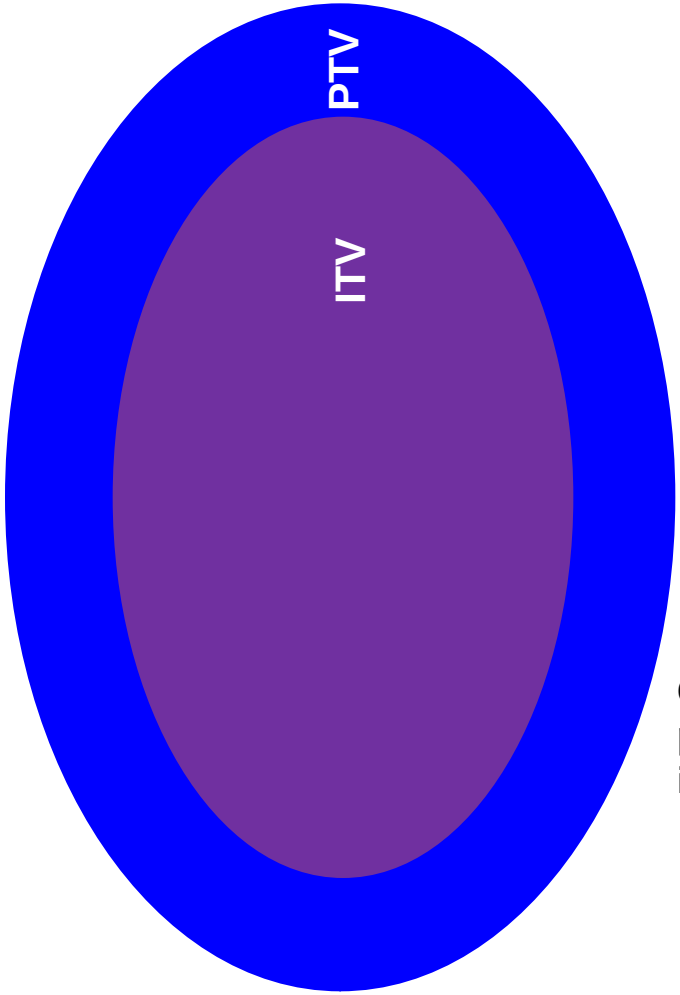






Just an upper and lower constraint lead to an inhomogeneity of about 80% and a hotspot, which is normally not located in the center.

VMAT – how to achieve the inhomogeneity



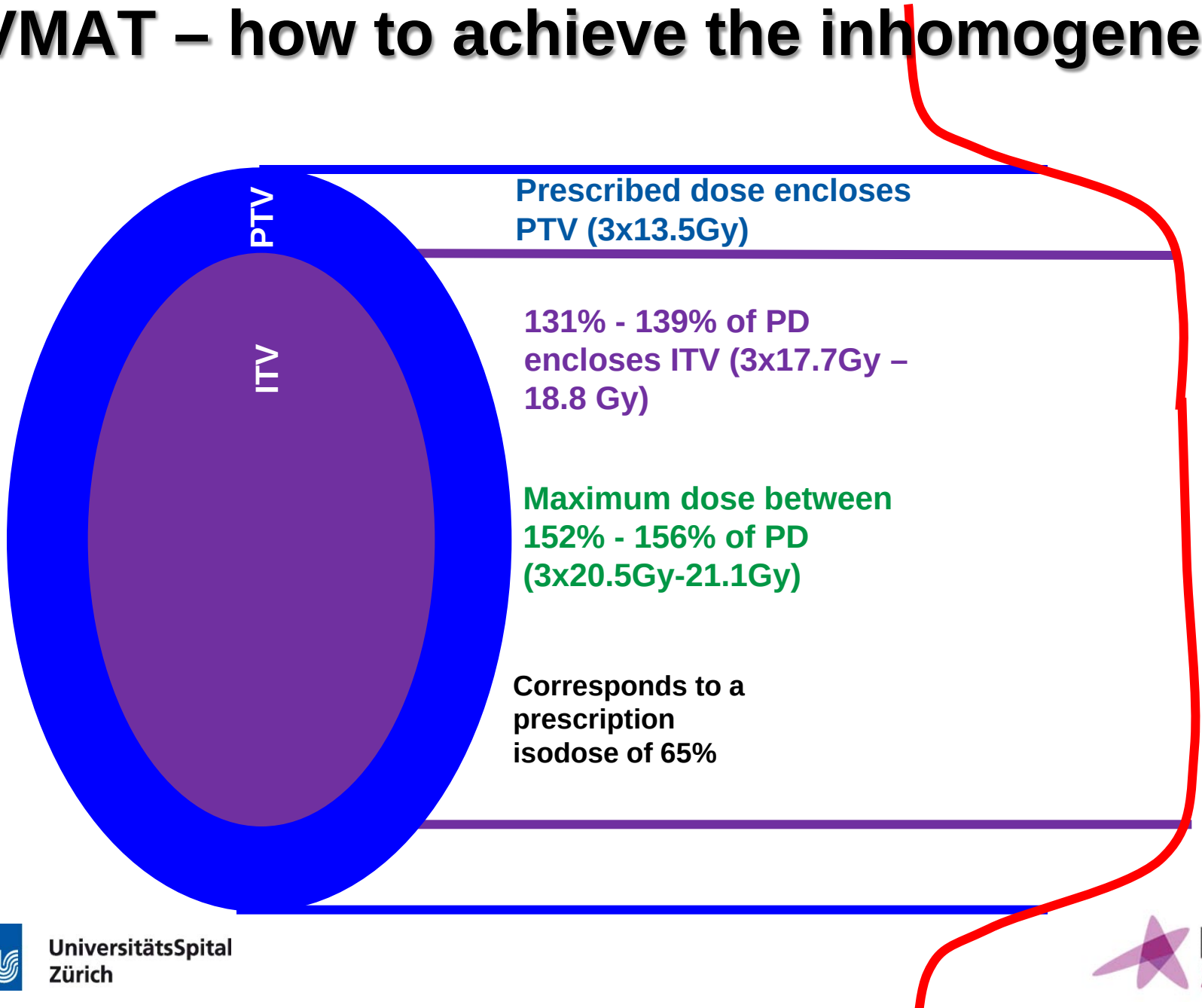
Prescribed dose encloses PTV (3x13.5Gy)

131% - 139% of PD encloses ITV (3x17.7Gy – 18.8 Gy)

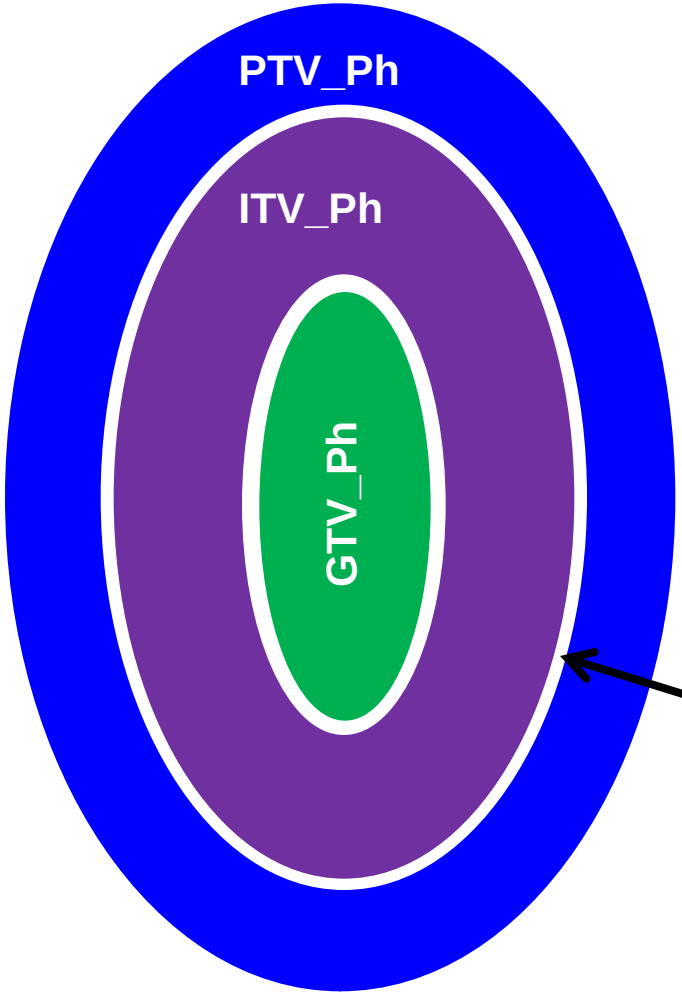
Maximum dose between 152% - 156% of PD (3x20.5Gy-21.1Gy)

Corresponds to a prescription isodose of 65%

VMAT – how to achieve the inhomogeneity



VMAT - Optimisation help structures



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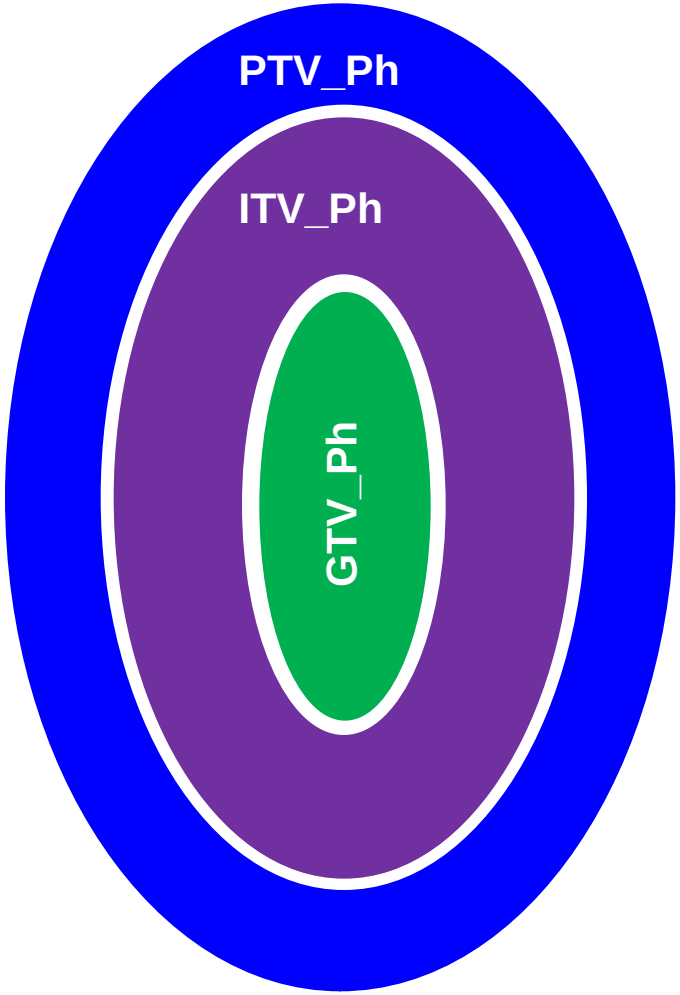
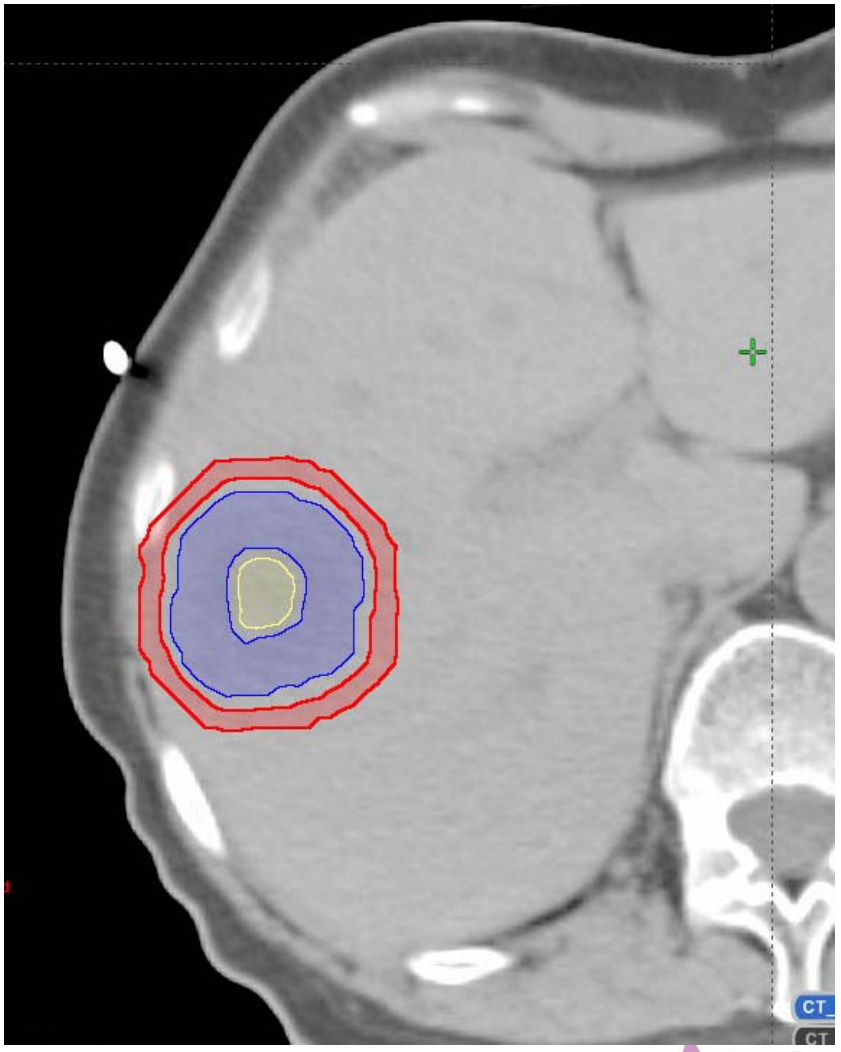
Maximum dose between 152% - 156% of PD (3x20.5Gy-21.1Gy)

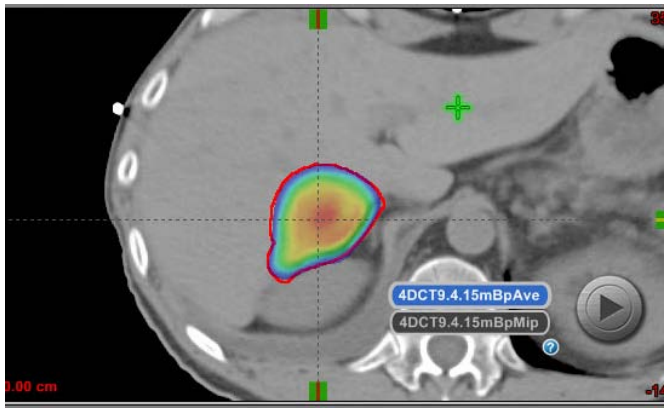
2mm distance

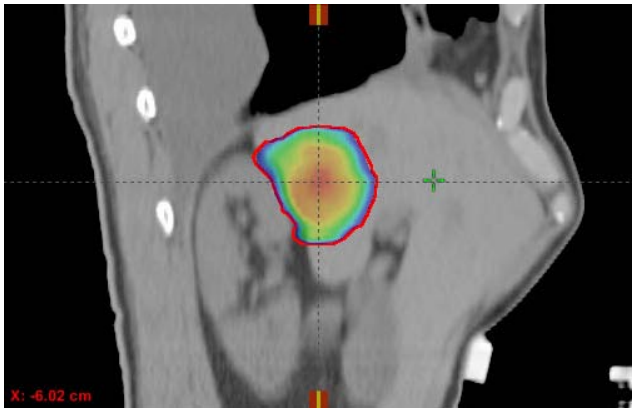
VMAT - Optimisation help structures

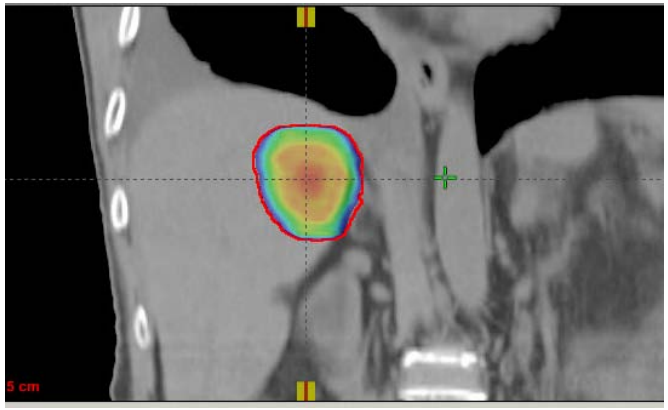




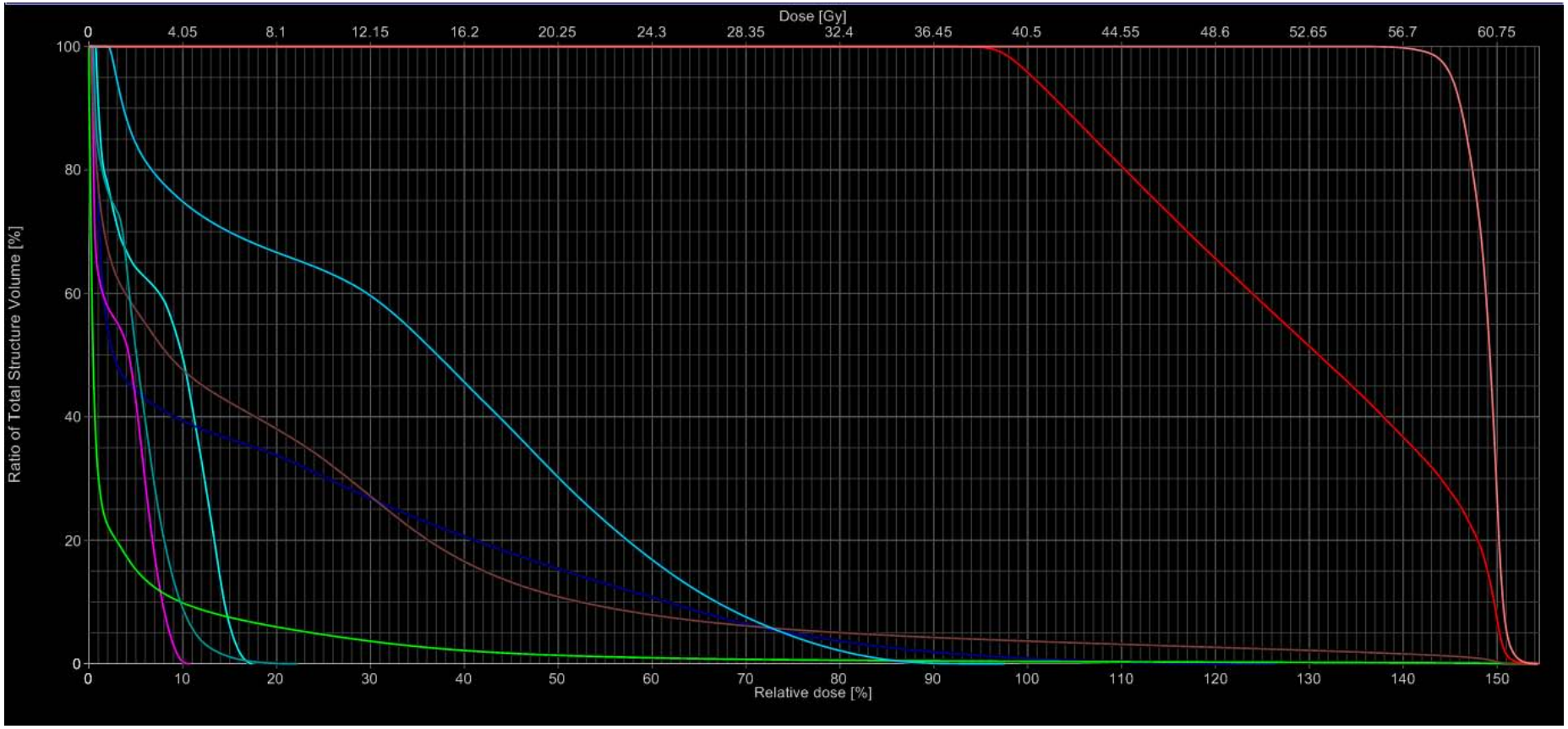
VMAT – dose distribution



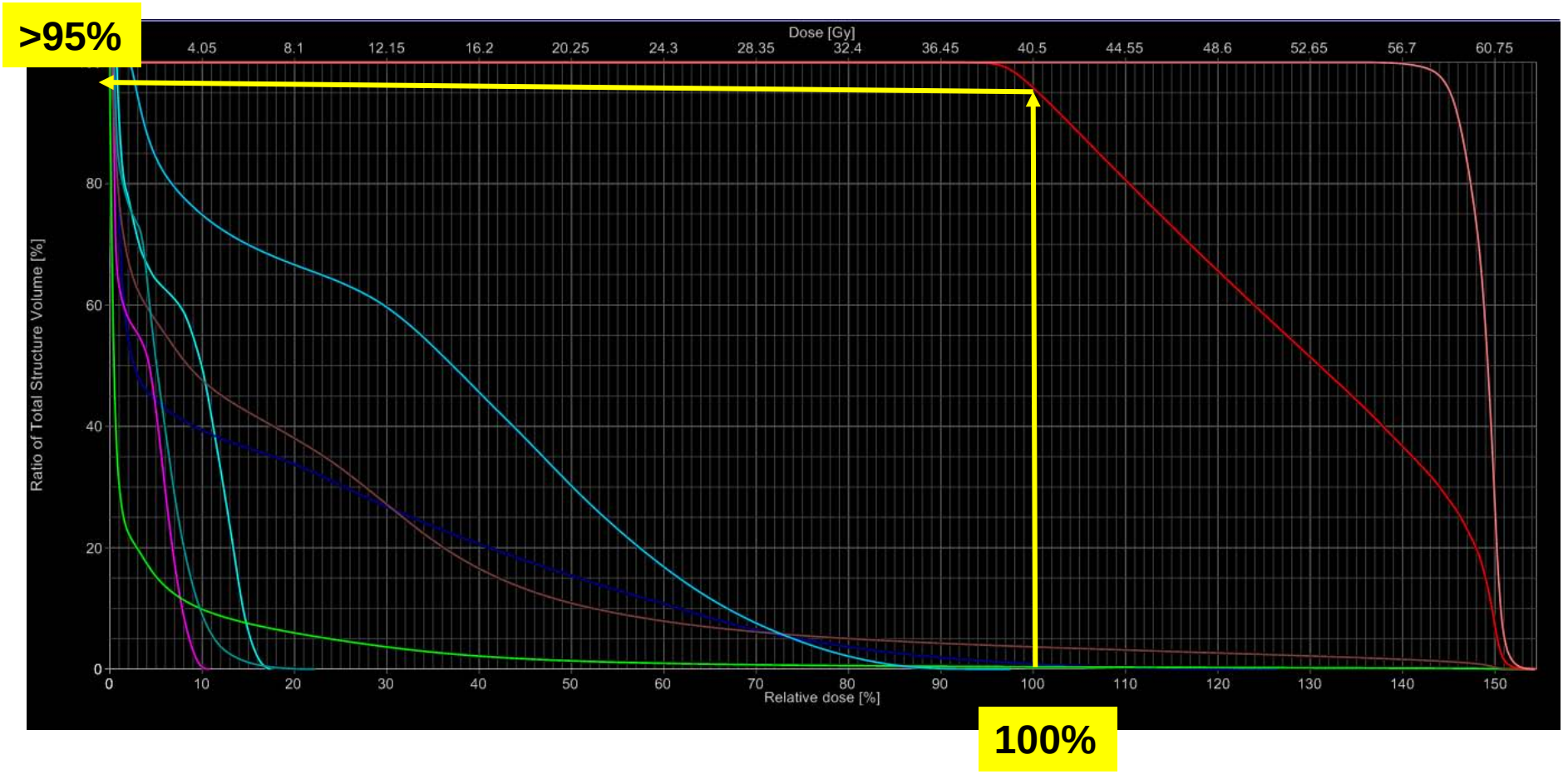




VMAT – dose distribution

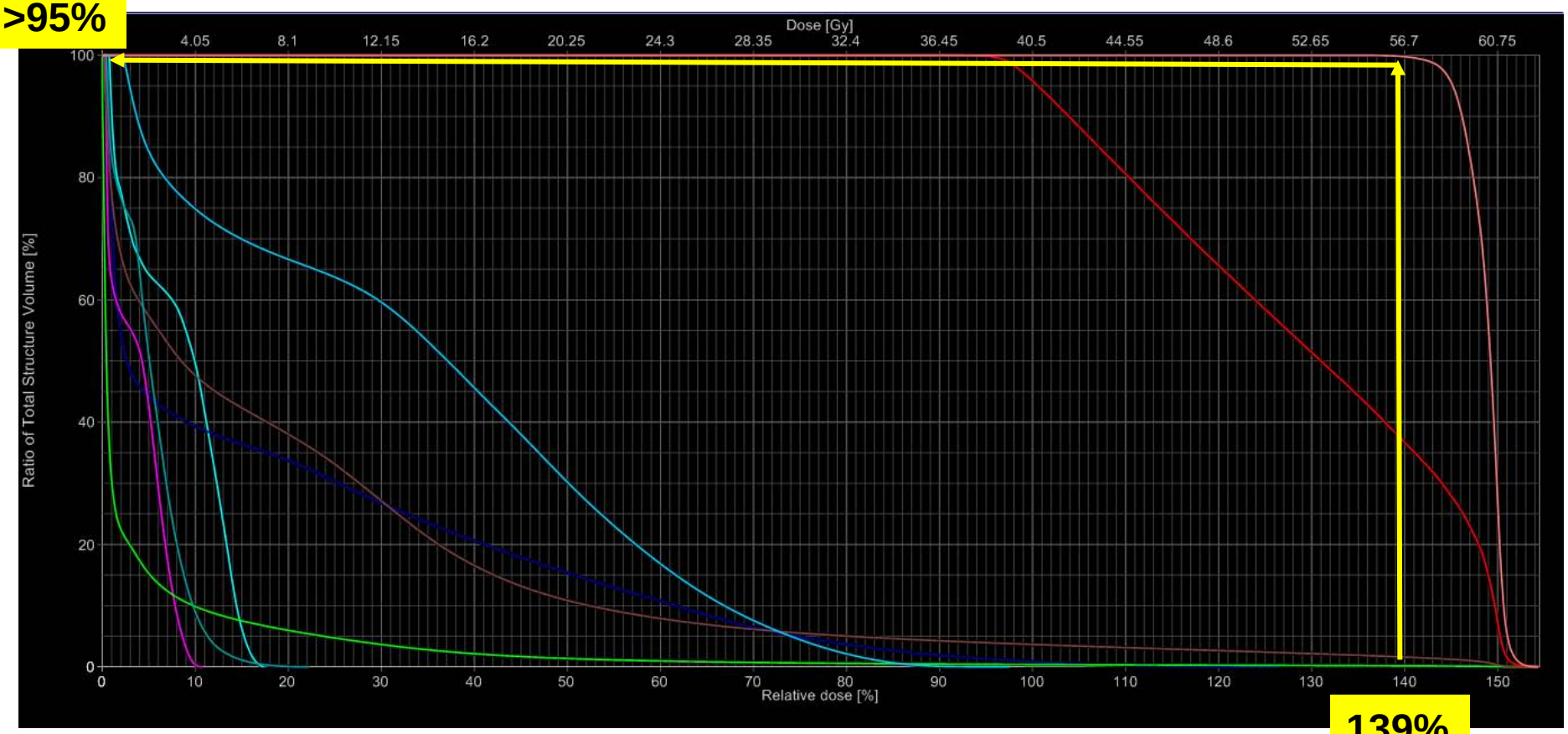


Plan evaluation



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)

UniversitätsSpital Zürich

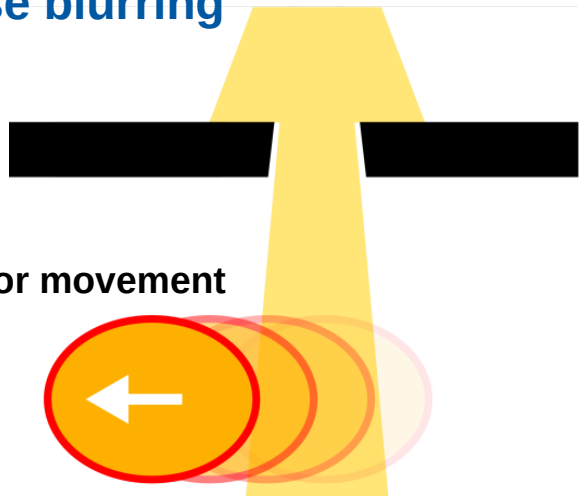
ESTRO School

Plan evaluation

- > 95% of PTV should be covered by 100% of prescribed dose
- > 95% of GTV should be covered by 95% of prescribed dose
- Conformity Index < 1.2 (1.1)

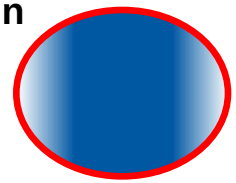
Effects of motion on dose to the GTV dose

Dose blurring



Tumor movement

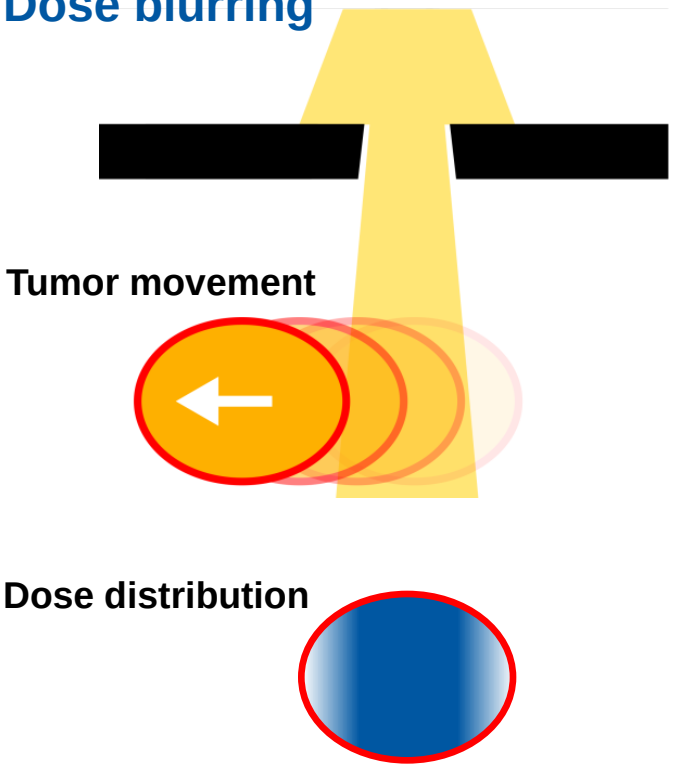
Dose distribution



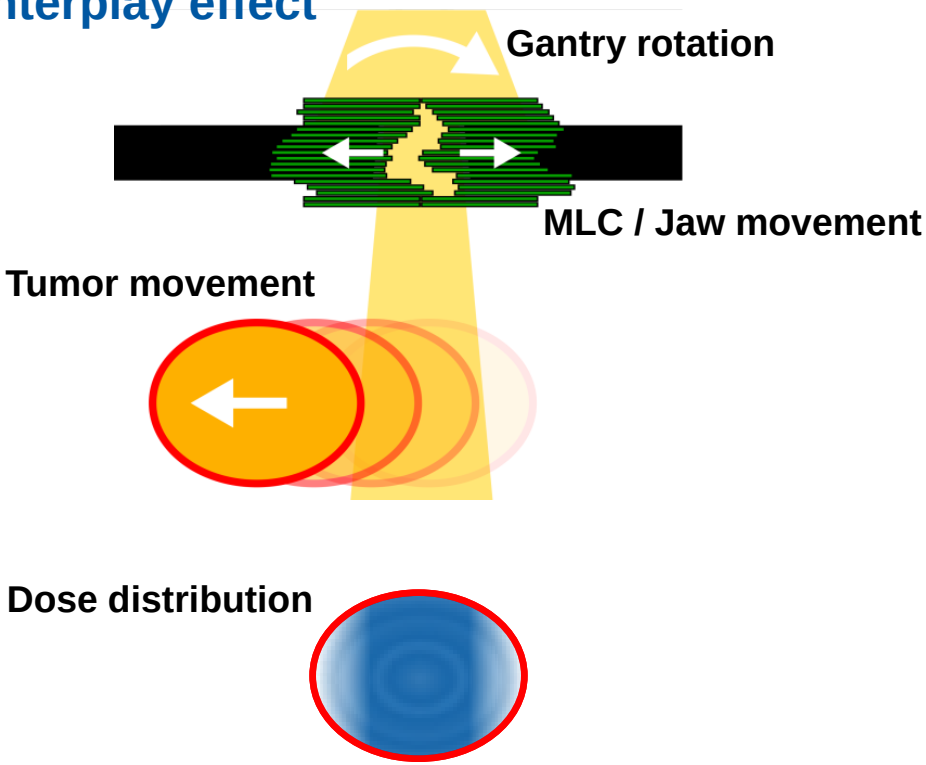
Dose blurring leads to underdosage at the edges of the tumor.

Effects of motion on dose to the GTV

Dose blurring



Interplay effect



Interplay effect leads to inhomogeneities inside the tumor.

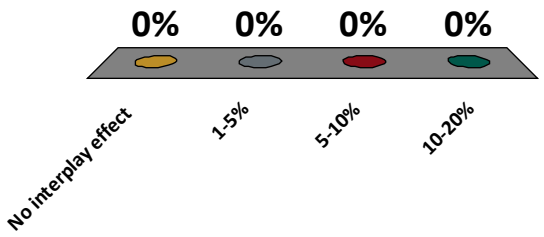
How large is the interplay effect for a VMAT SBRT liver treatment fraction (2 arcs, 13.5Gy, 65% isodose)?

A. No interplay effect

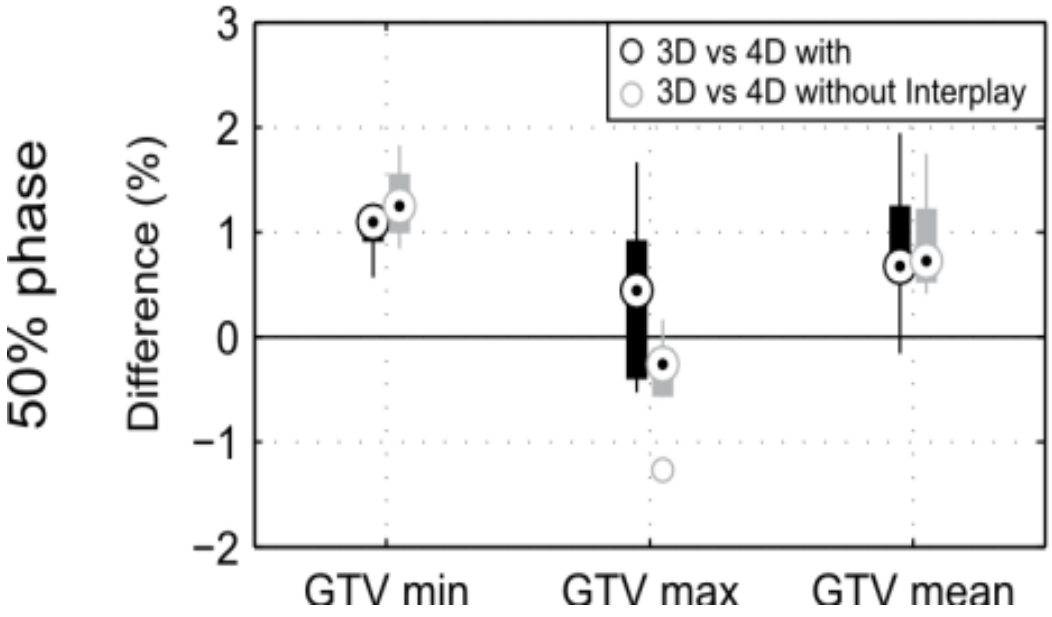
B. 1-5%

C. 5-10%

D. 10-20%



Interplay effect



VMAT SBRT
20%-45% dose inhomogeneity inside the PTV
2-4 arcs
10 clinical patients

Ehrbar et al, ZMP 2015

For VMAT SBRT treatments up to 3% interplay effect .

Interplay effect

study	technique	order of magnitude
Jiang et al, 2003	IMRT, fractionated treatment	30% for a single field, 1%-2% over 30 fractions
Court et al, 2004	IMRT, fractionated treatment	10% if leaf motion is perpendicular or parallele to tumor motion for all fields
Kang et al, 2010	SBRT, IMRT	Small changes in dose to the GTV
Li et al, 2013	SBRT, FFF VMAT	Small changes in the dose to the GTV
Ong et al, 2011	SBRT VMAT	Gamma agreement score >98% for 2 arcs, above 93% for 1 arc
Rao et al, 2011	SBRT VMAT	Changes of less than 1% inside the PTV
Stambaugh, 2011	SBRT VMAT	2-3% @A=2cm, however up 16% for extreme cases (large A and T)

Interplay has to be assessed for department specific irradiation technique.

SBRT spine treatment planning

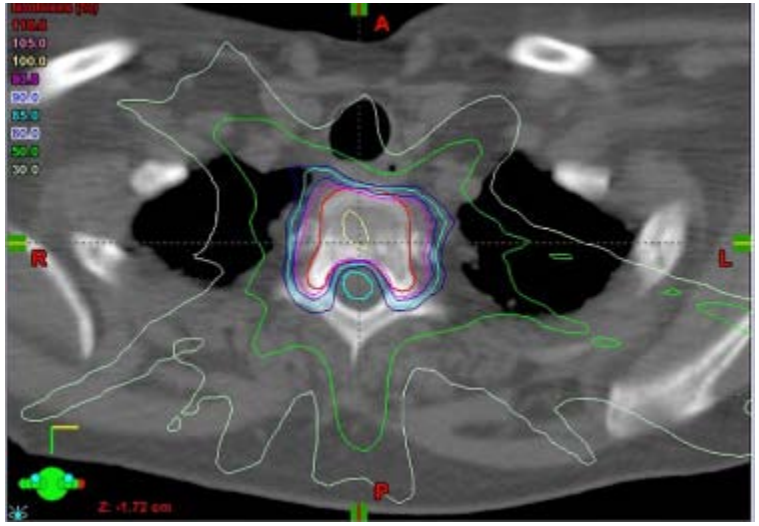
Different concepts

Treatment of the tumor lesion:

1 x 12.5Gy – 25Gy @ 80-95%

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

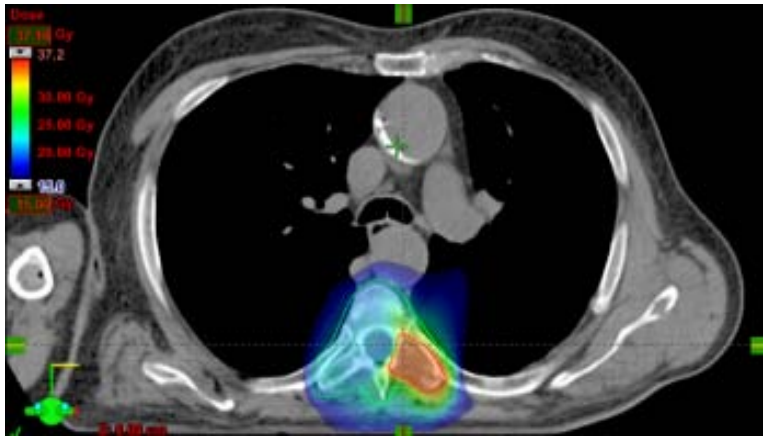
Distance between GTV and spinal cord > 3mm



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

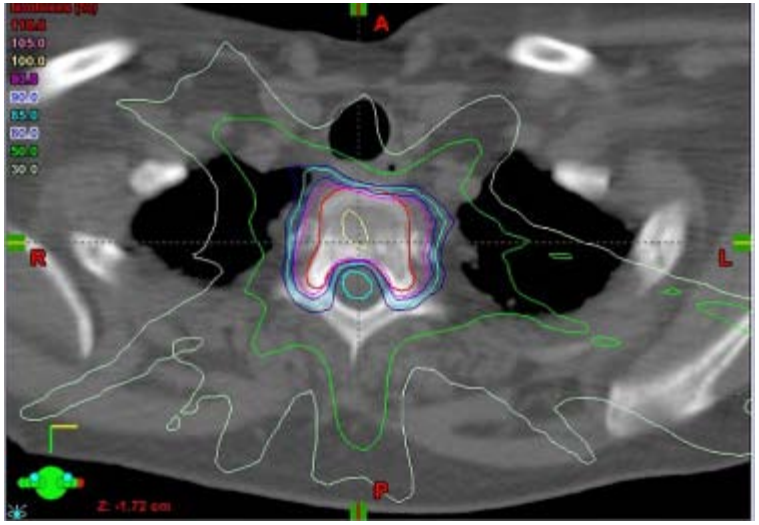


SBRT of spine tumors

Treatment technique:

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

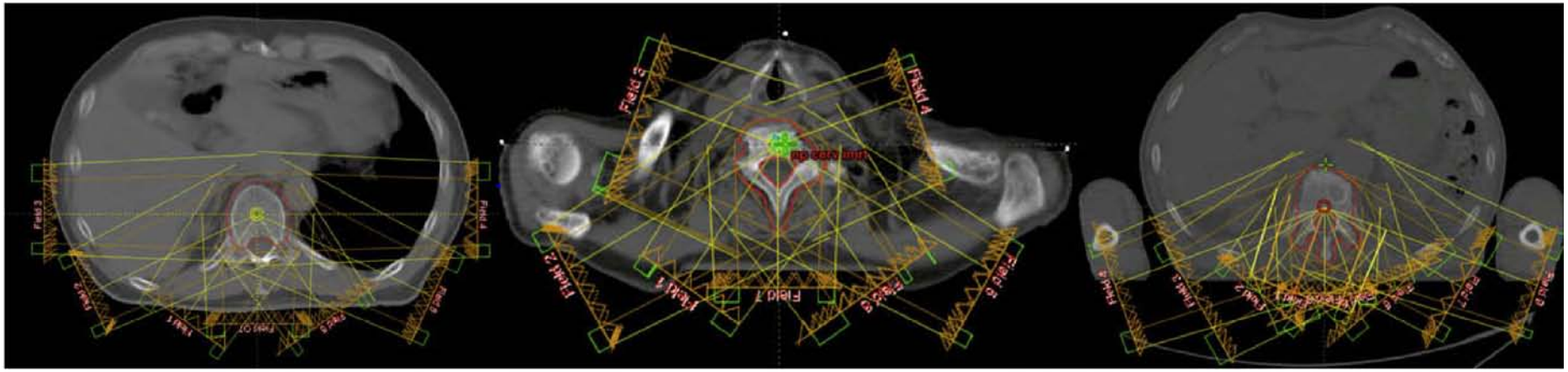
- to shape the dose around the target and
- better spare the spinal cord



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

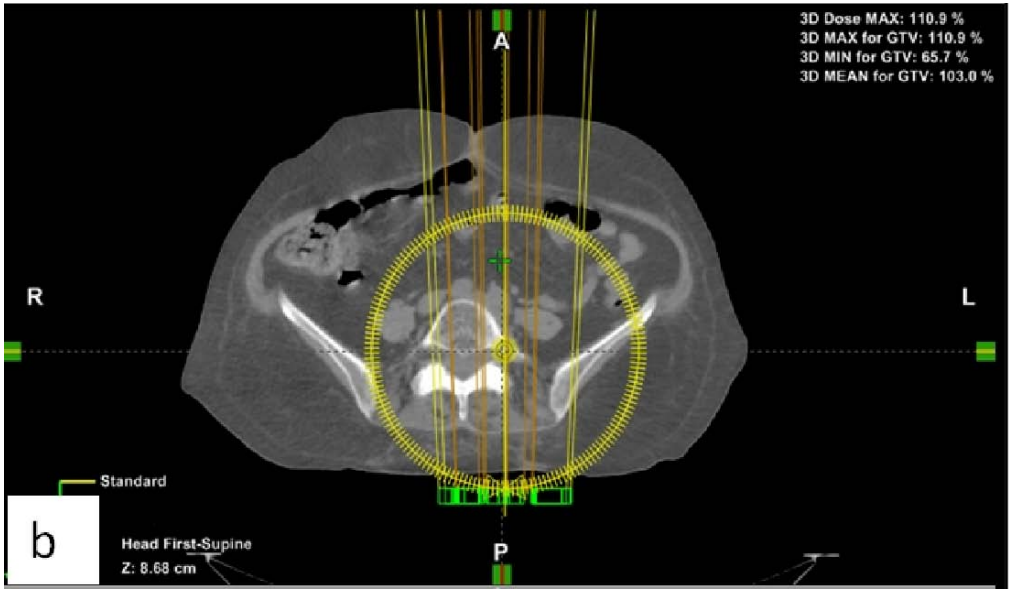


Kuijpers et al, RO, 2010

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

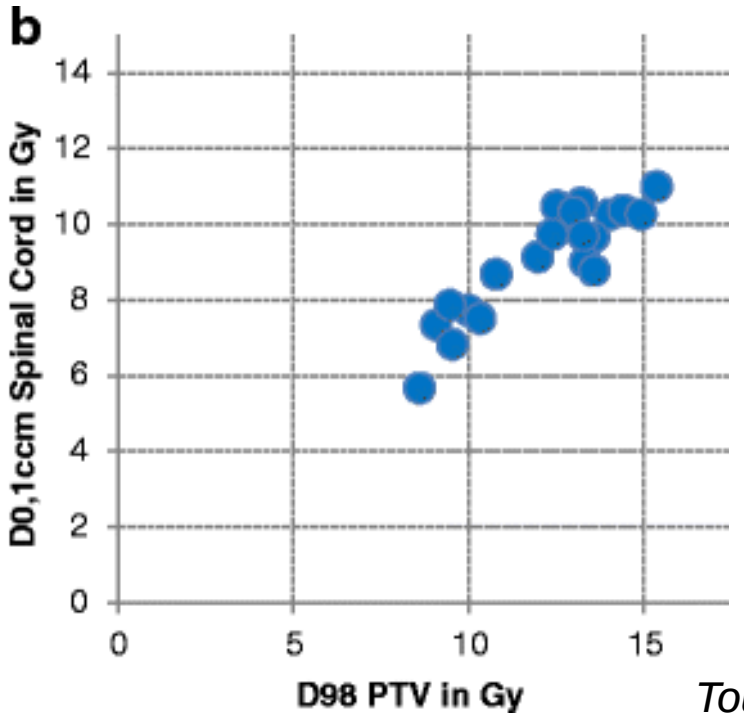
Oh et al, 2013
→Comparable plan quality

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

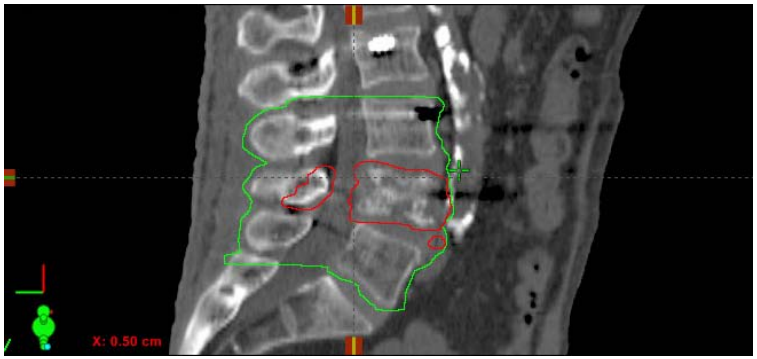
Don’t expect miracles: The smaller the dose to the spinal cord the worse the coverage of the PTV.

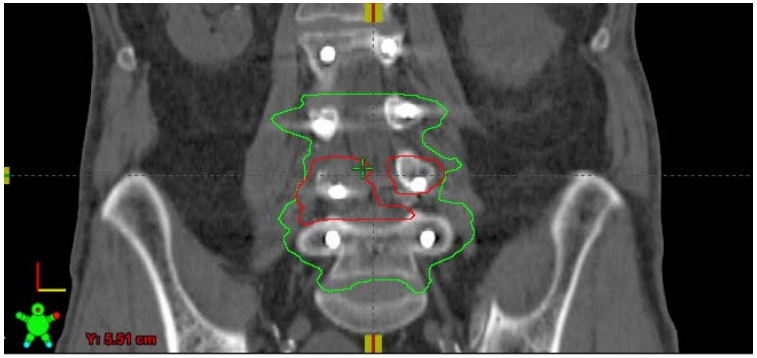
SBRT spine – integrated boost concept

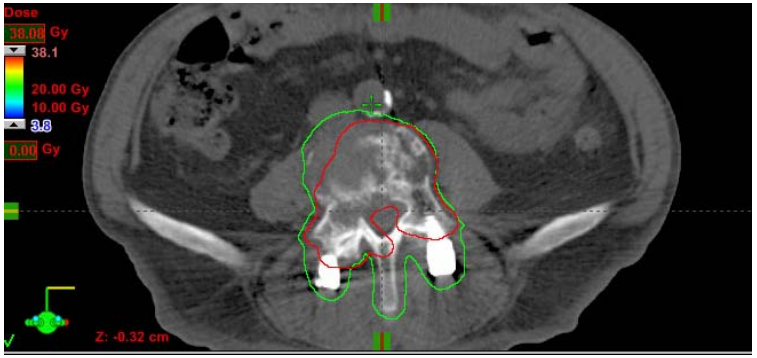
Integrated boost concept:

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)**

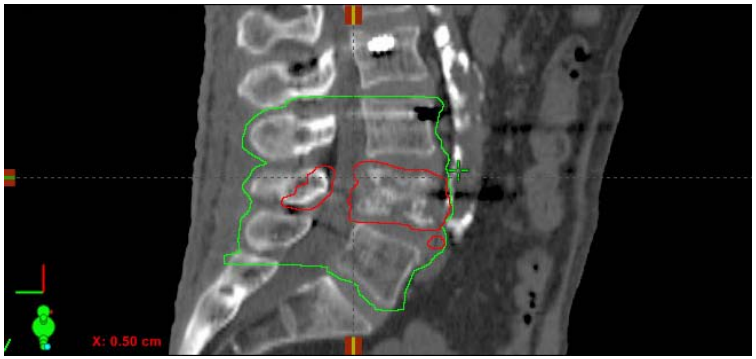
→ Fractionated approach

- **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)**

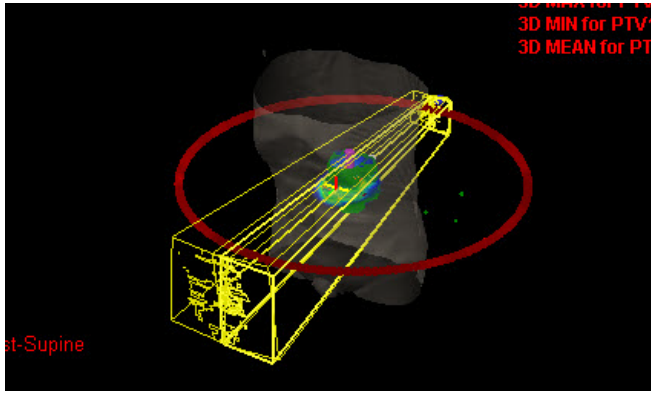
→ Homogeneous prescription

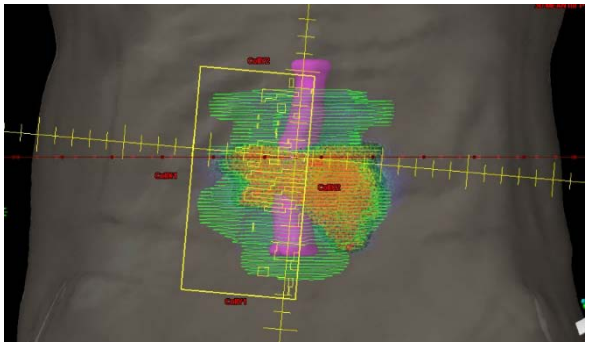


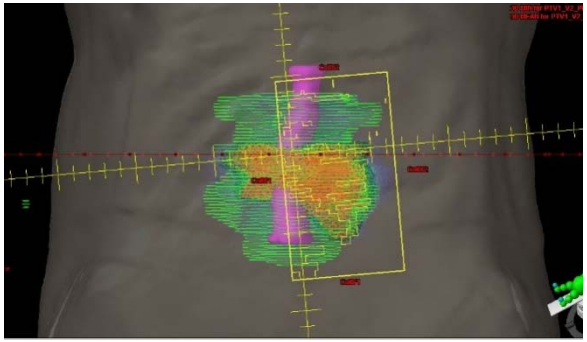
SBRT spine – integrated boost concept

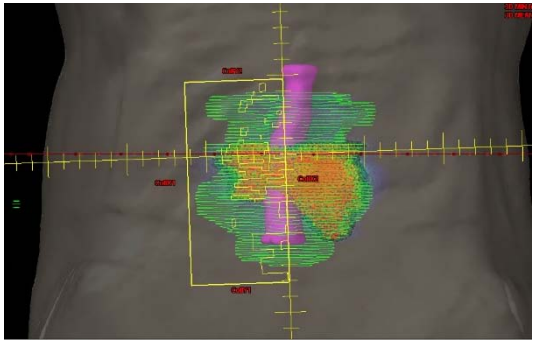
Planning technique:

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



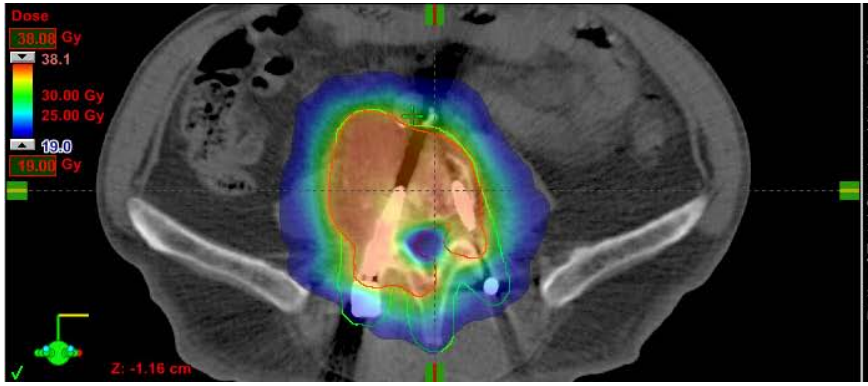


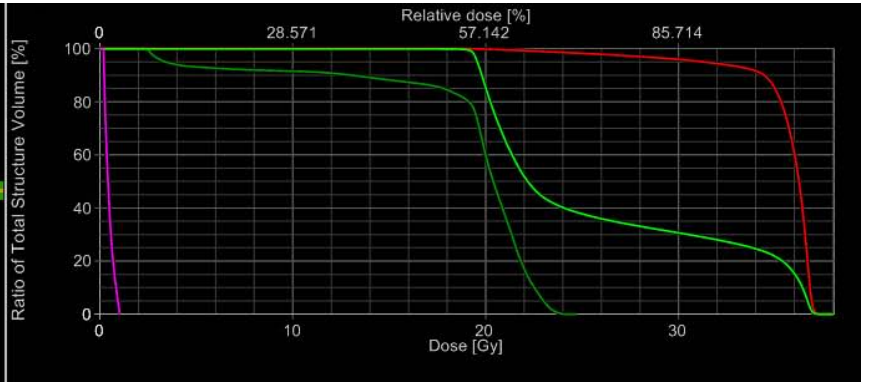


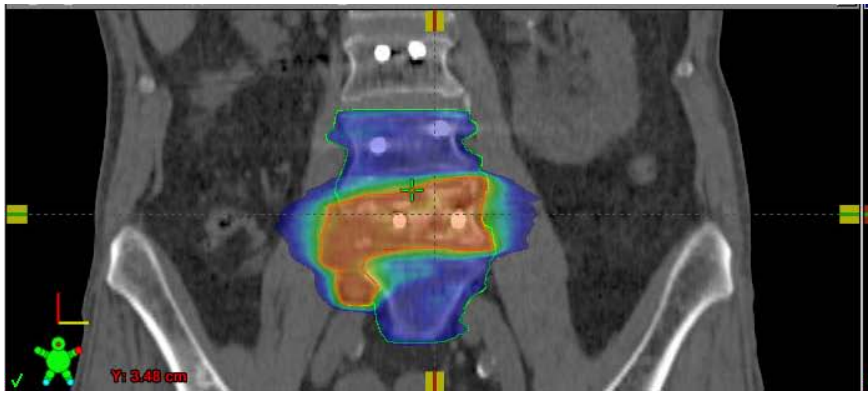


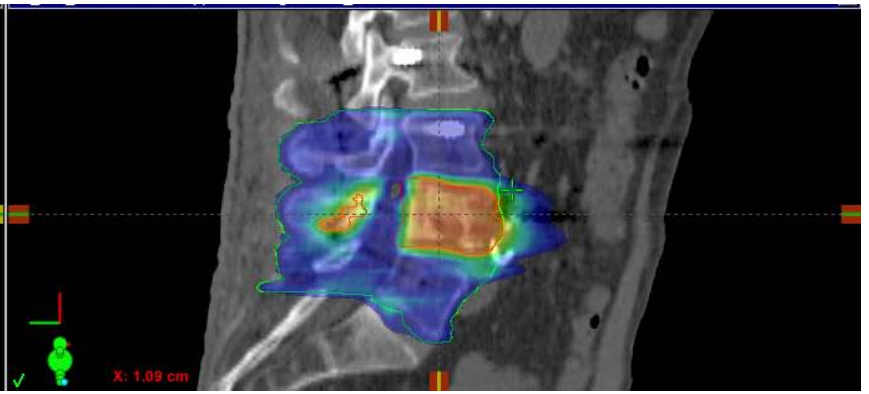
SBRT spine – integrated boost concept

Dose distribution





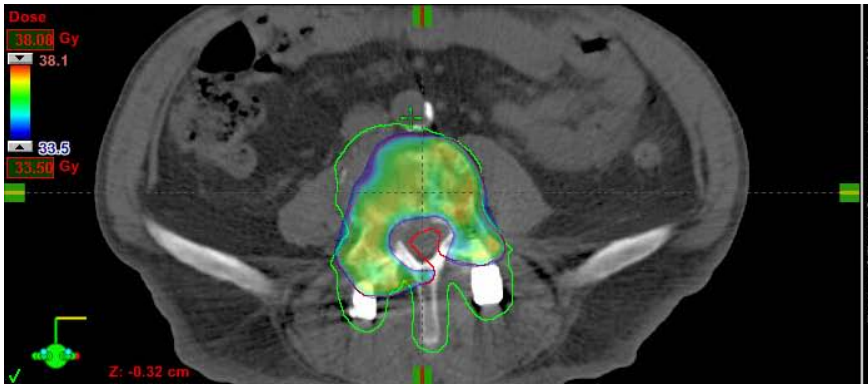


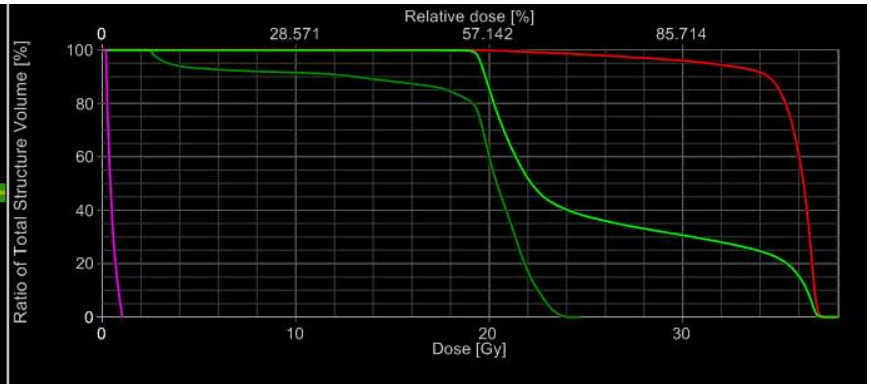


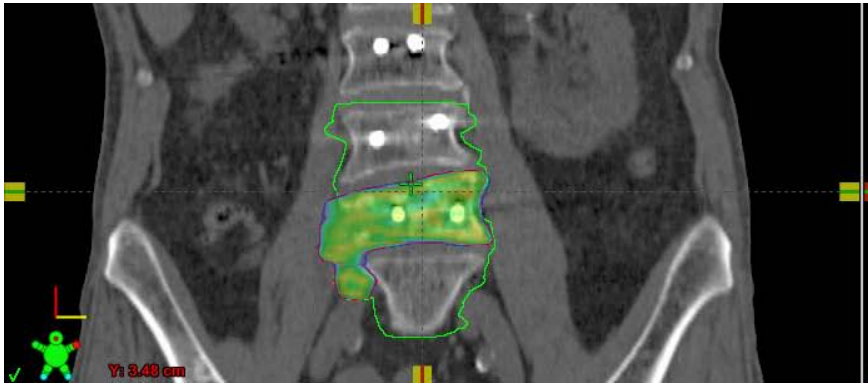
SBRT spine – integrated boost concept

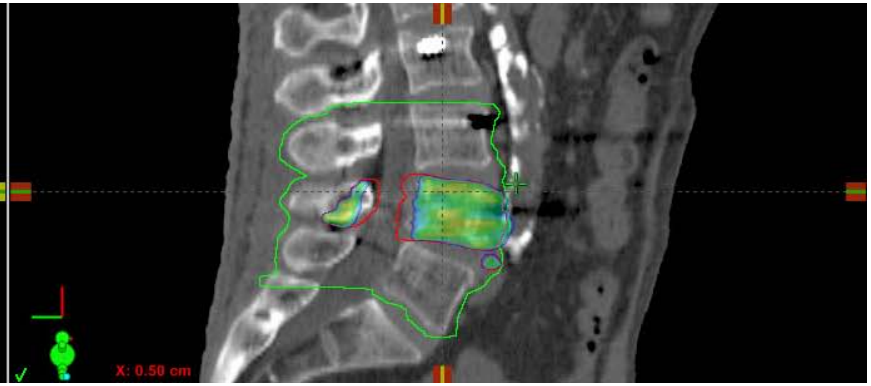
Spinal cord tolerance:

spinal cord max 23.75 Gy → compromise PTV coverage





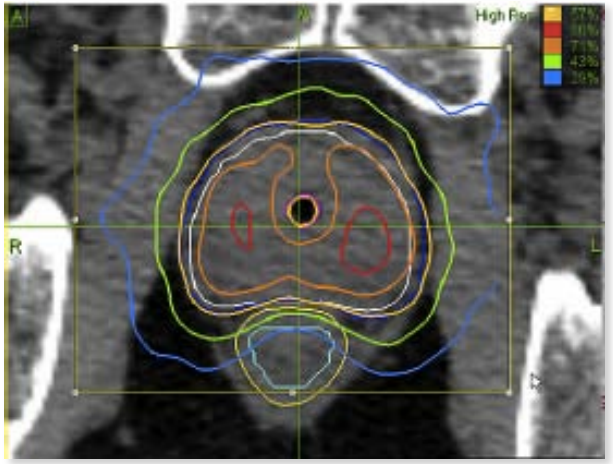




SBRT prostate treatment planning

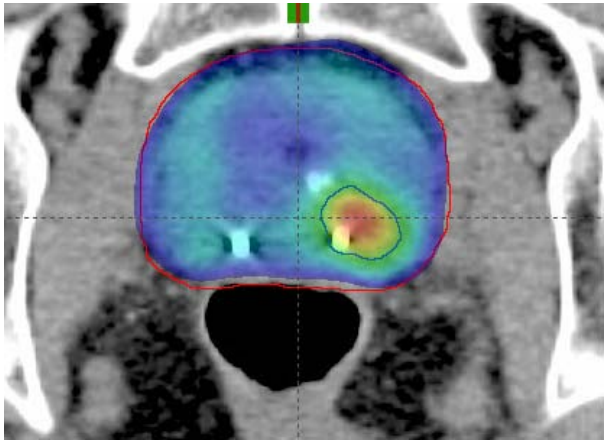
Different concepts

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

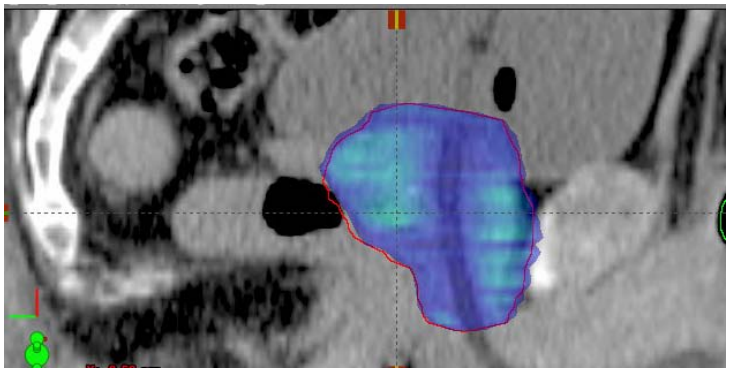
Planning technique:

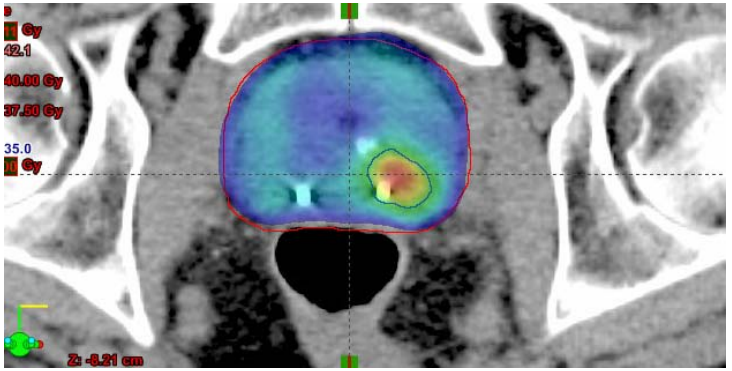
- Same field setup as in conventional fractionated RT of the prostate
- IMRT or VMAT should be used to better spare the rectum and to avoid hotspotts in the urethra

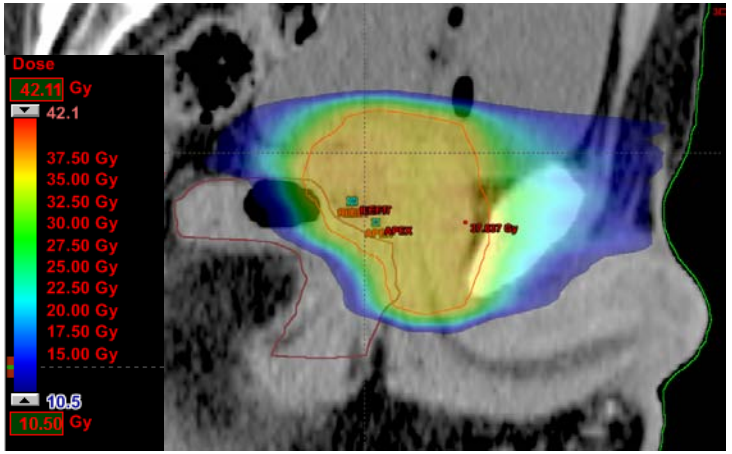
SBRT Prostate - OAR

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

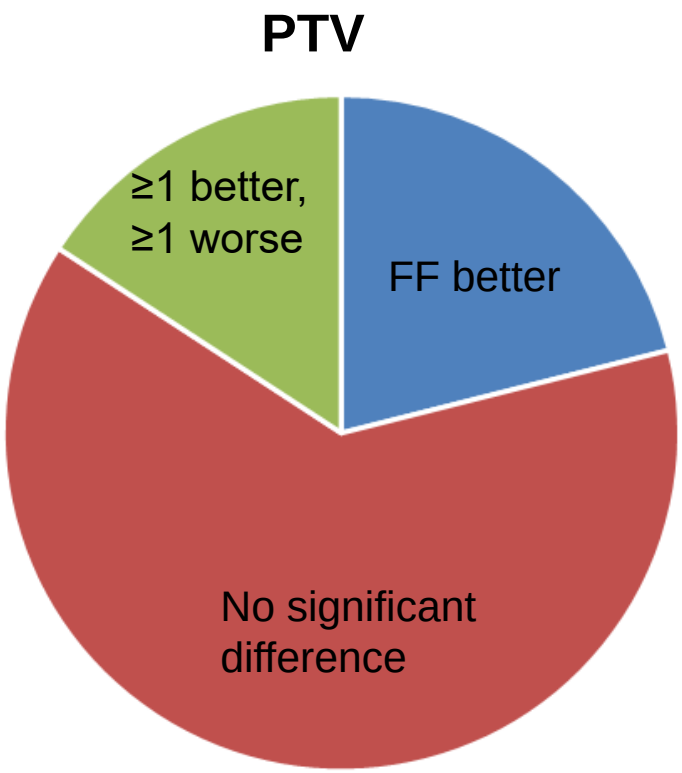


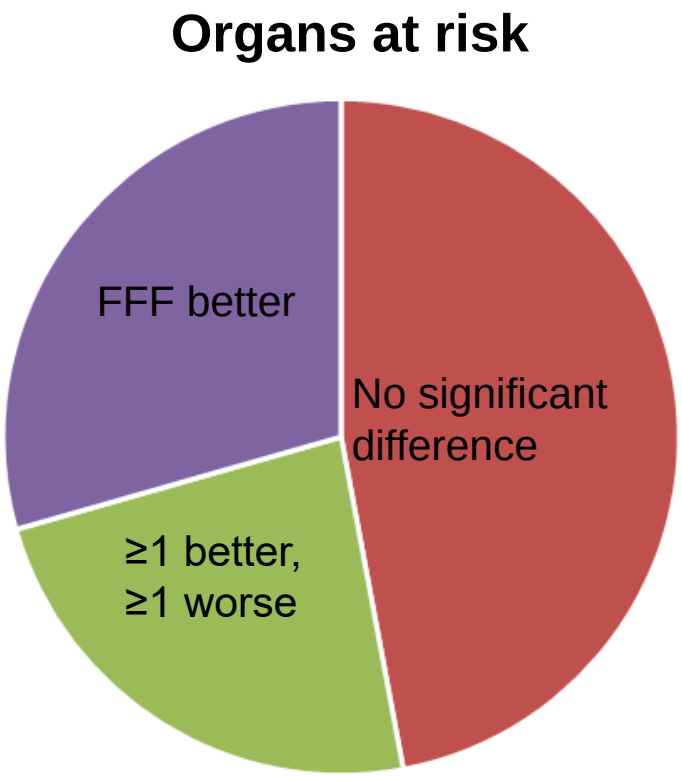




FFF beams – any advantage?

FFF beams – any dosimetric benefit?

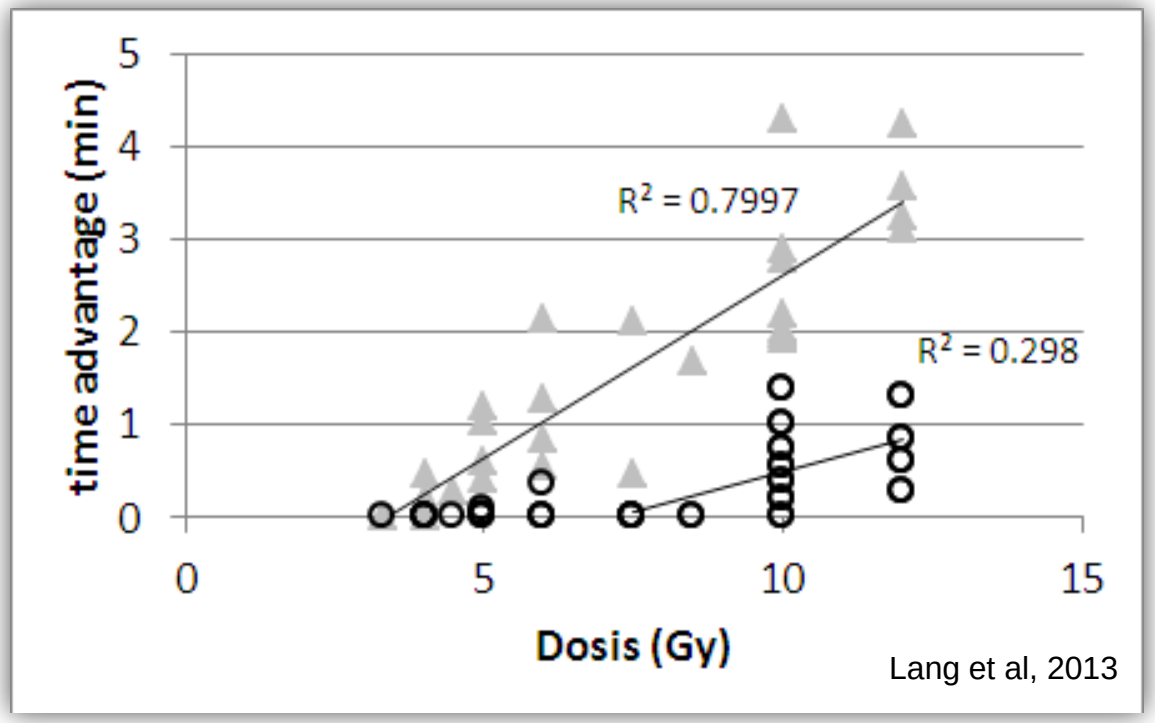




20 studies comparing FFF versus FF:
Lang et al, Ong et al, Reggiori et al, Lechner et al, Alongi et al, Nicolini et al, Lechner et al, Dzierma et al, Kretschmer et al, Lai et al, Wang et al, Stieler et al, Zhuang et al, Hrbacek et al, Shi et al, Gasic et al, Fu et al, Hansen et al, Pruijt et al

FFF beams – faster treatments?

SBRT treatments

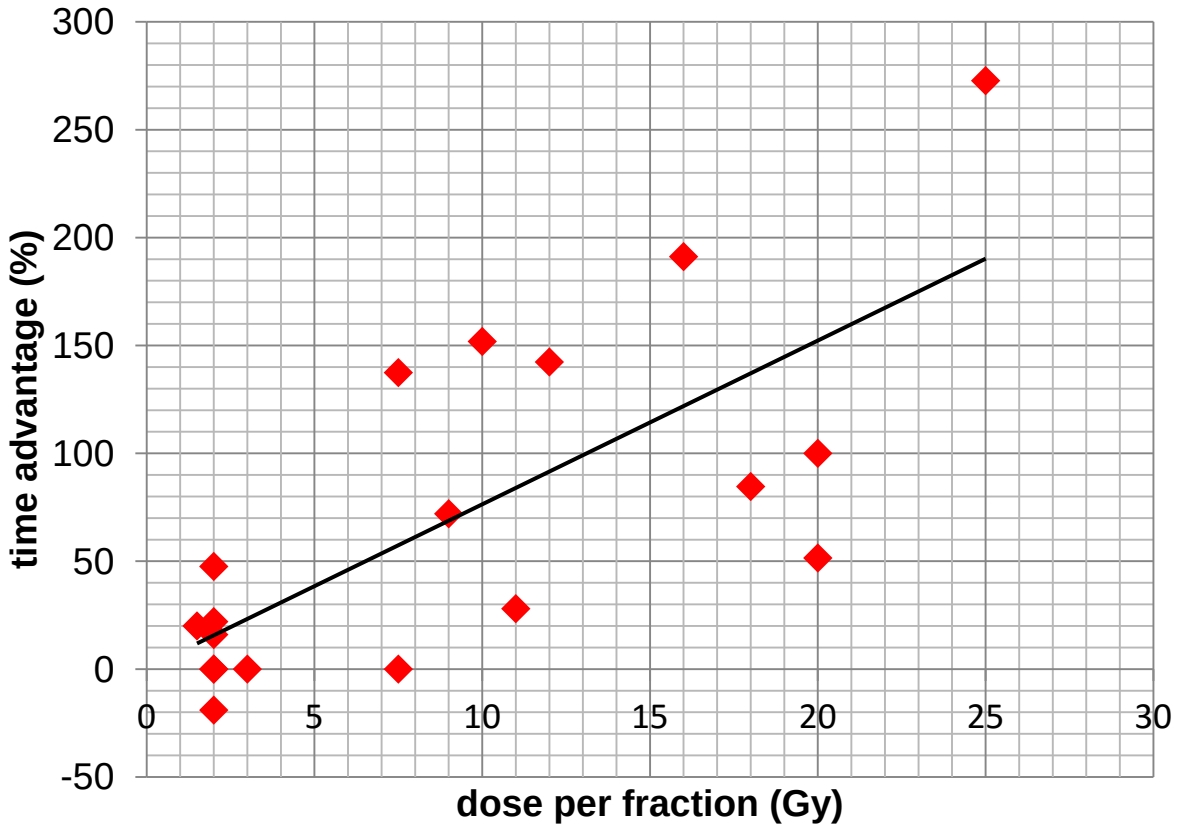


Lang et al, 2013

▲ X6 compared to X6FFF

○ X6FFF compared to X10FFF

FFF beams – faster treatments?



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

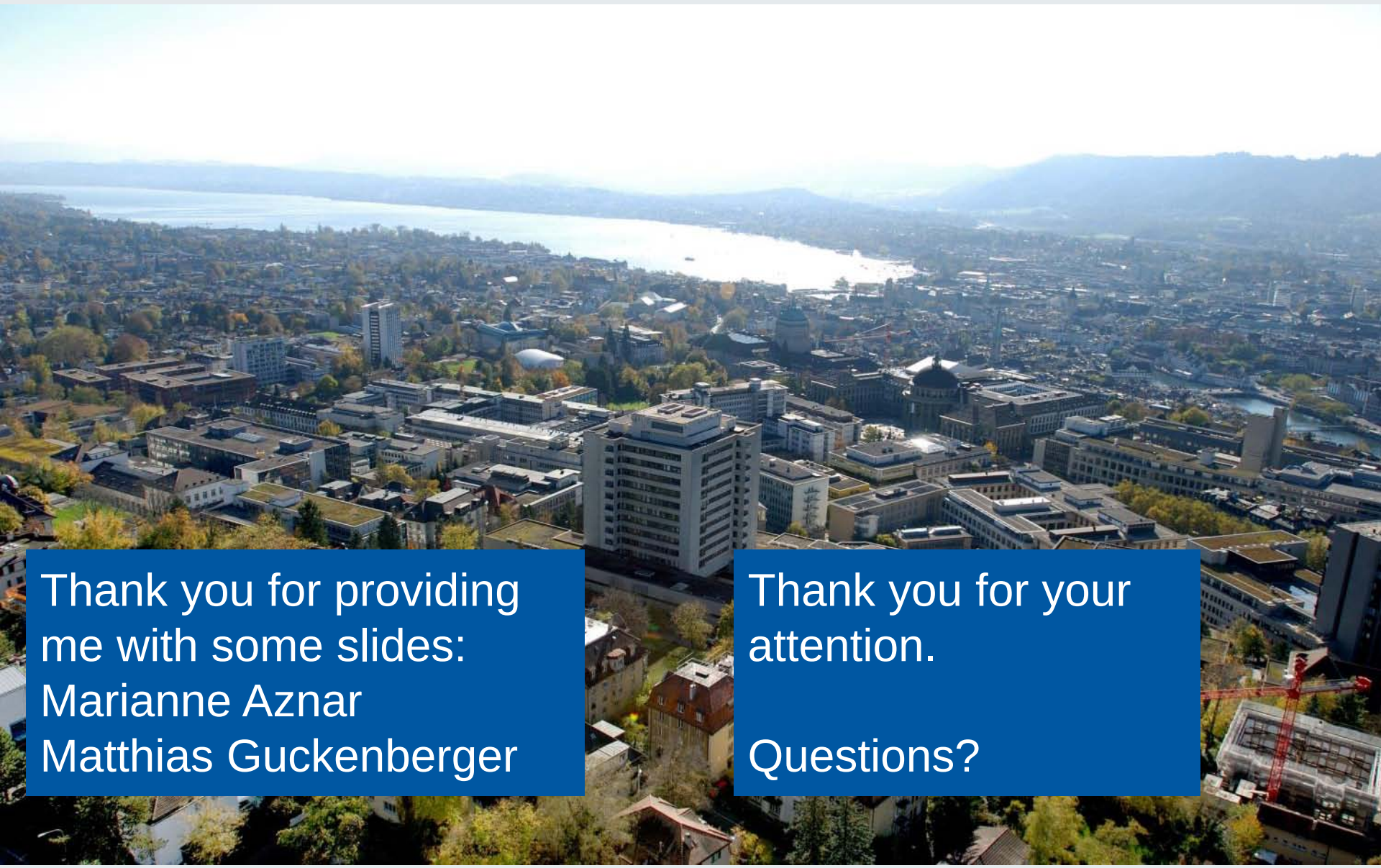
References

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?

QA and safety

Coen Hurkmans, Ph.D., clinical physicist

Catharina Hospital, The Netherlands

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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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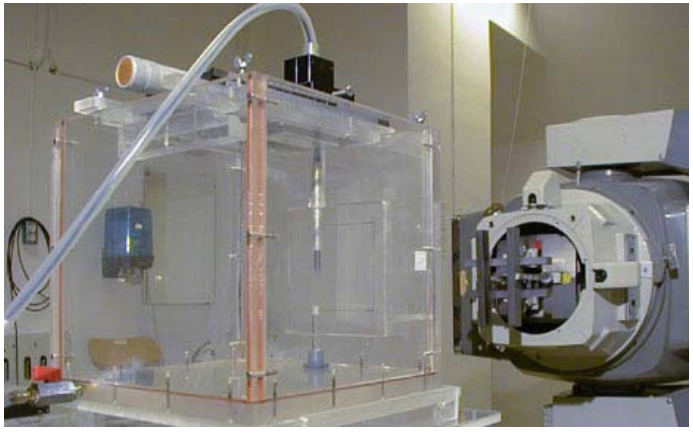
Do Accidents Happen?

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 5.0cm

Water tank outside dimensions (perspex) = 32 × 32 × 21 cm to water surface

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 ↓ units; 7.00)

= 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**

catharina hospital

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

catharina hospital

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

catharina hospital

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

catharina hospital

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:**
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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Jan 2010

- Several articles in NYT early 2010
- Lot's of fuzz in the community
- Hearing in US
- Meetings etc…

The New York Times

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.

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_IzTqhgbMs

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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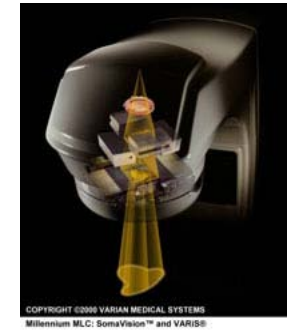
What happened?

- “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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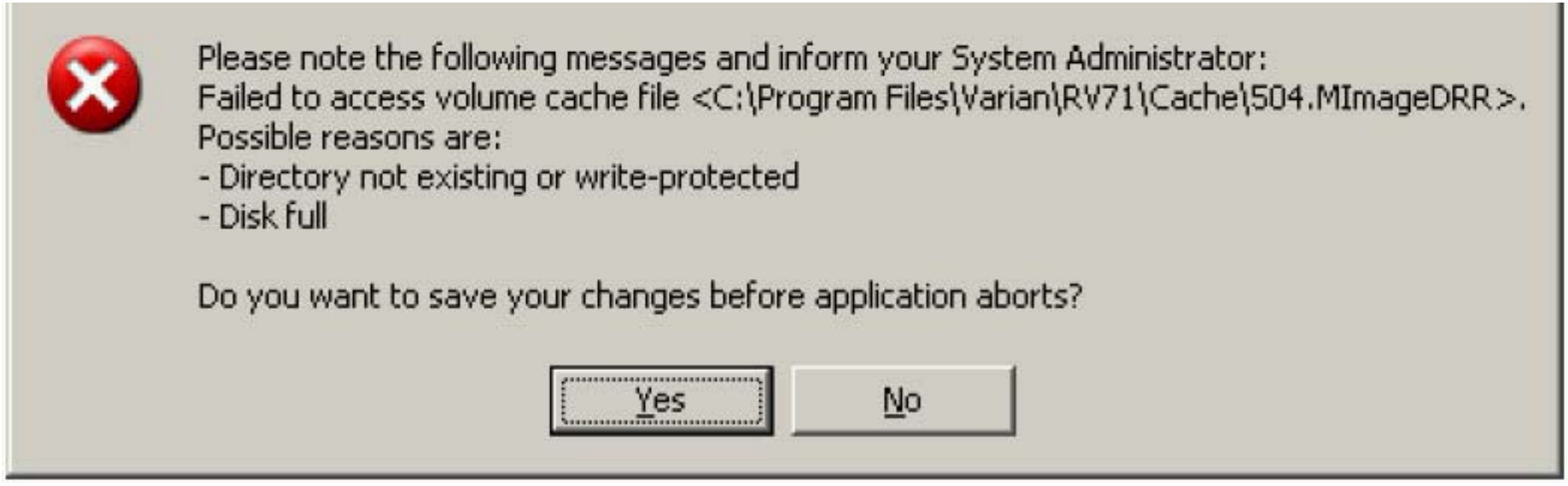
What happened?



The transaction error message displayed

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What happened?

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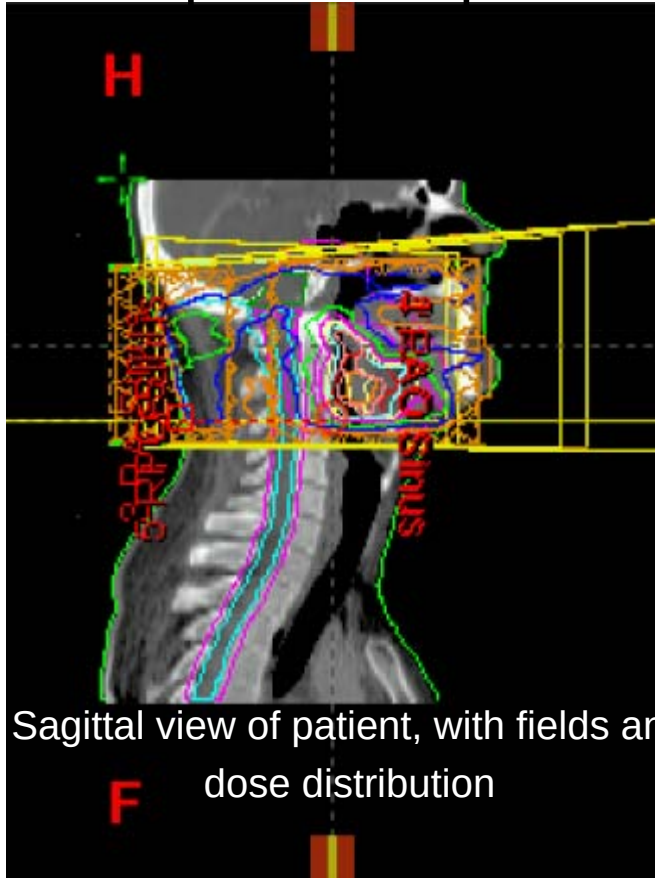
What happened?

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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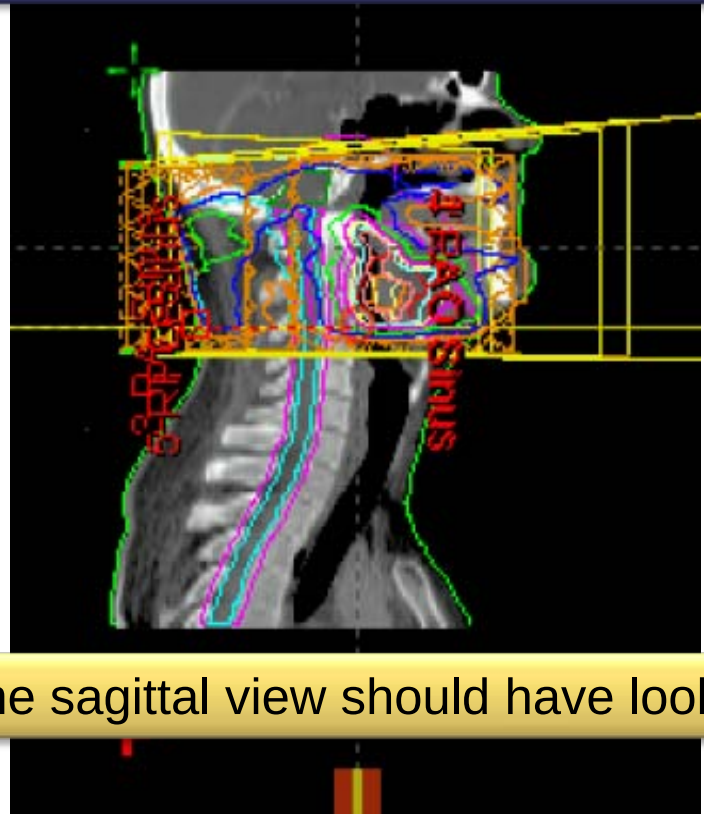
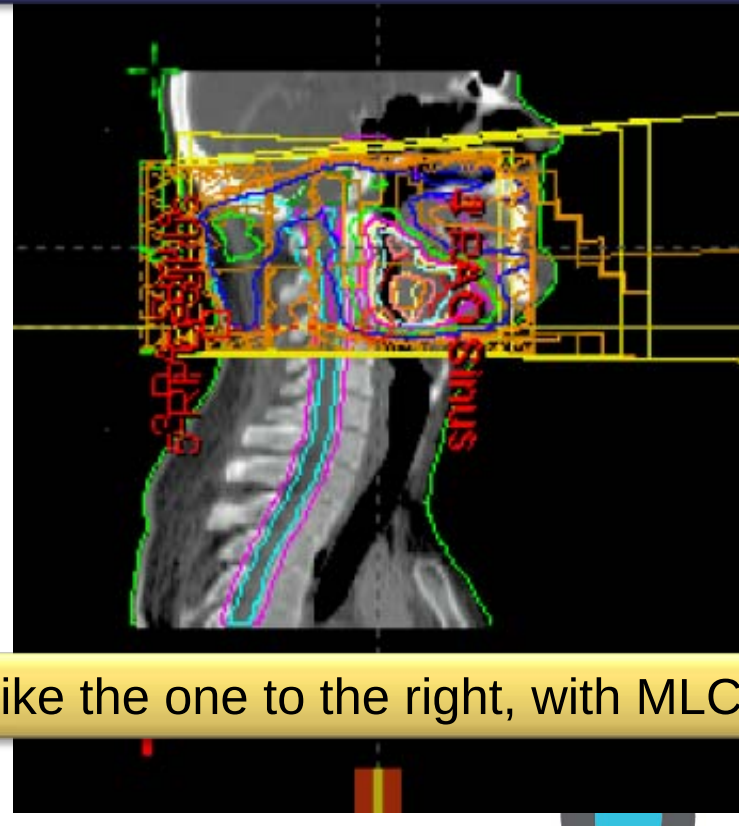
What happened?

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

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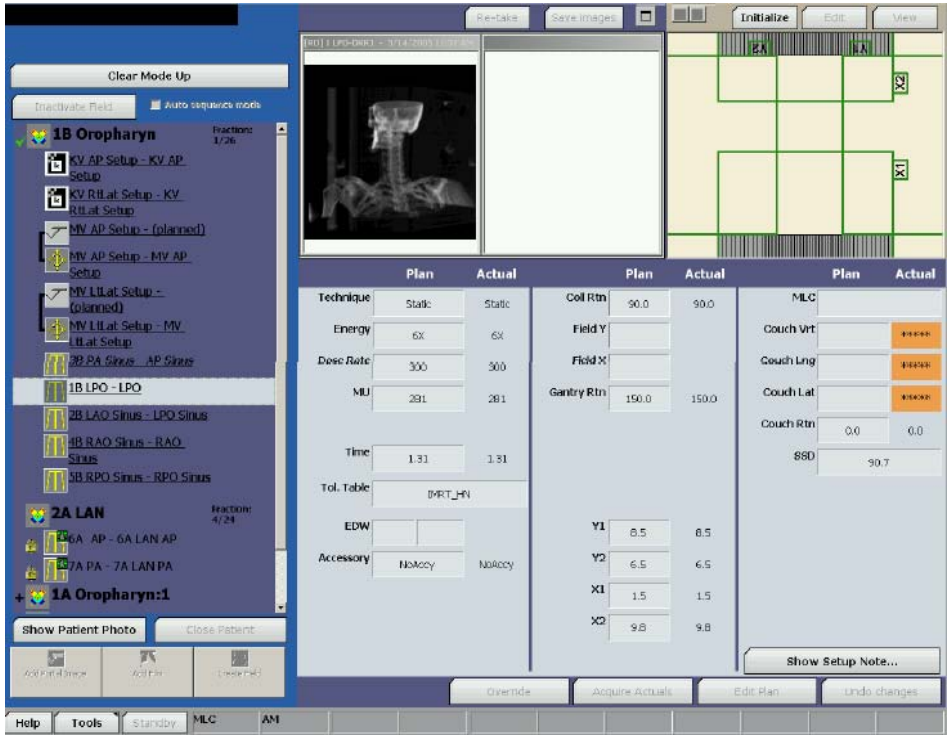
What happened?

- 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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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).

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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 stricktly 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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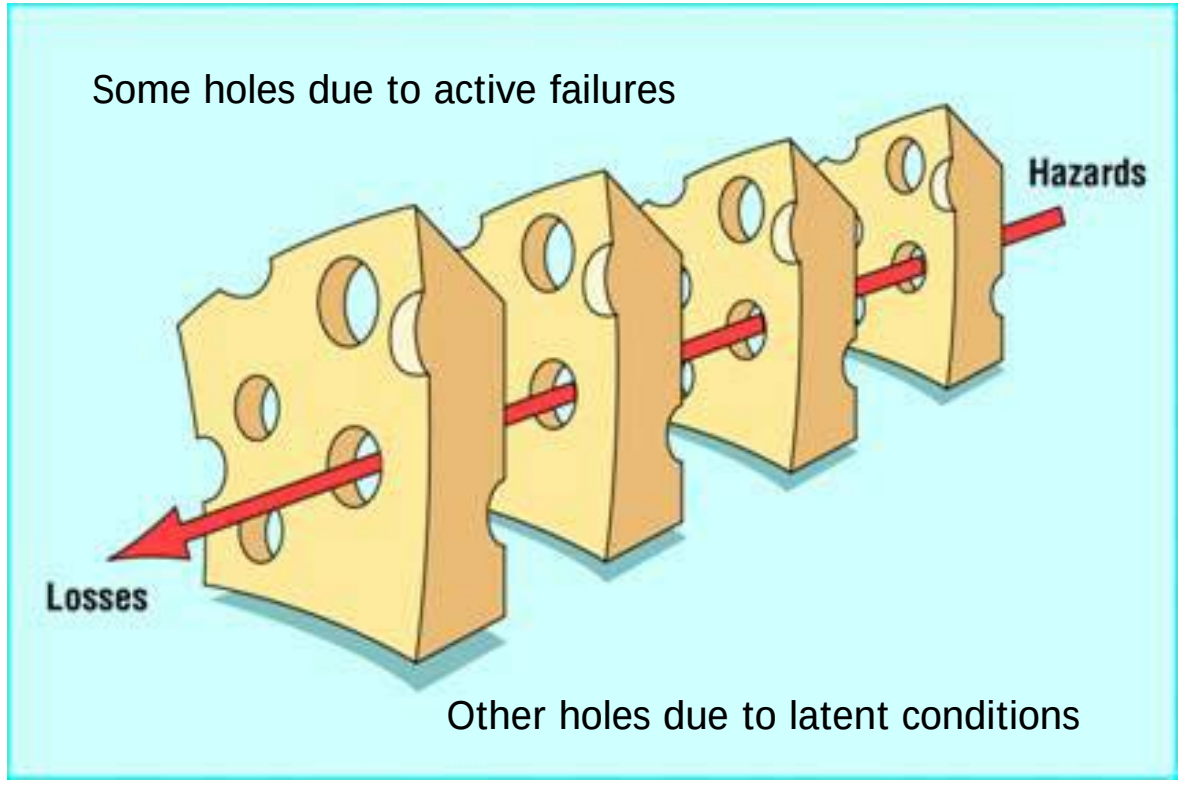
Reason's Swiss Cheese Model of Failure Propagation

Successive layers of defences, barriers, filters and safe guards



When holes line up an error will occur

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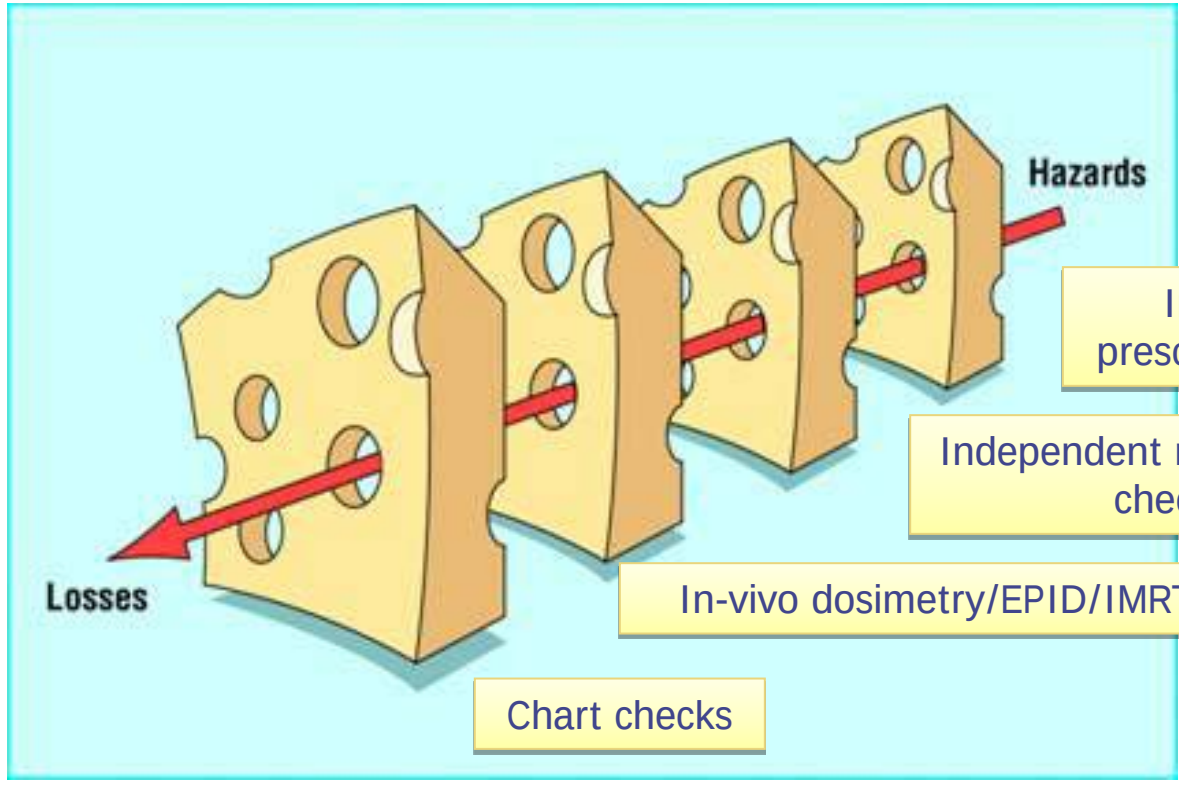
Radiotherapy safety layers

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?

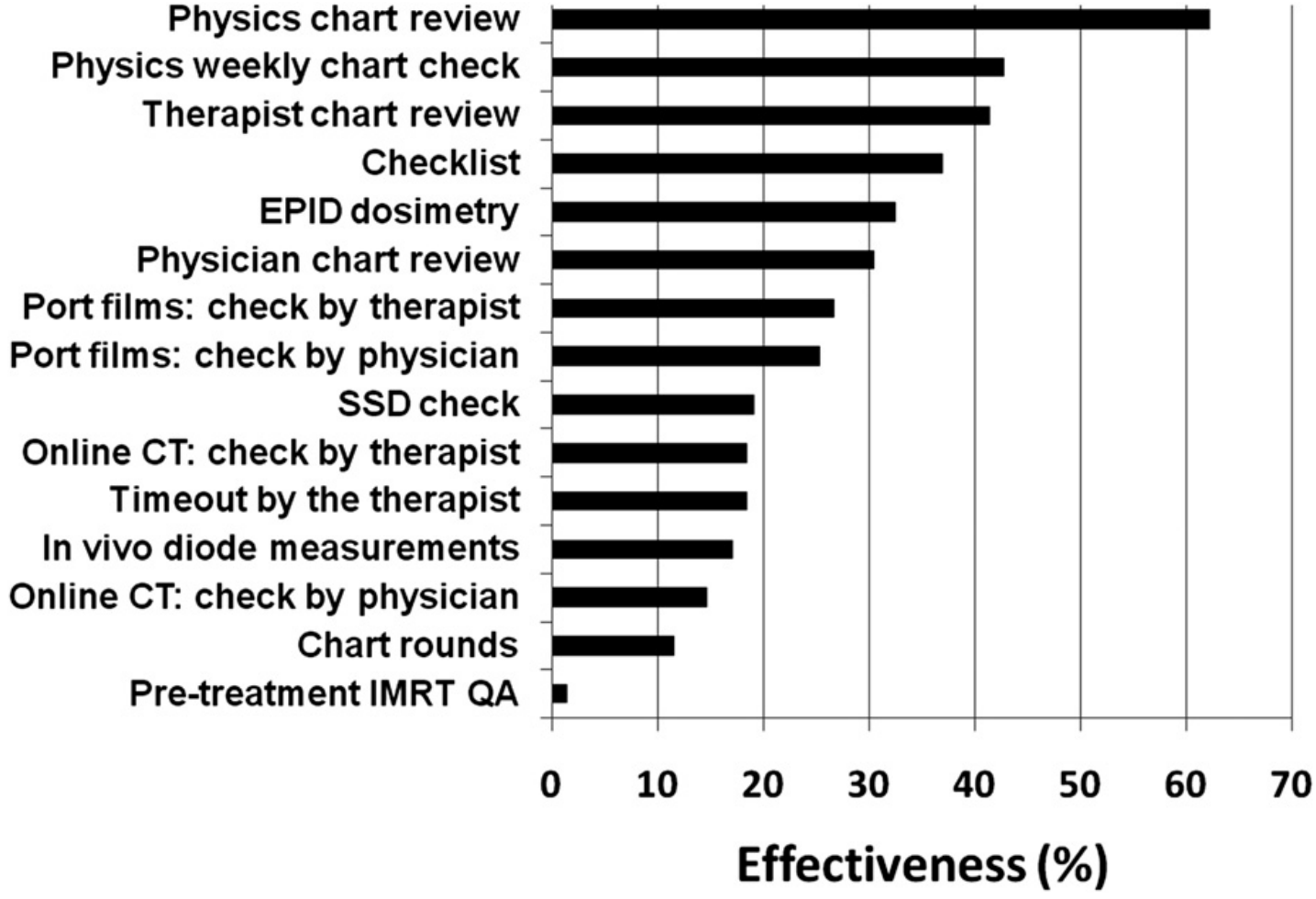

Fig. 2. Effectiveness of each individual quality control (QC) check for detecting the reported high severity incidents.

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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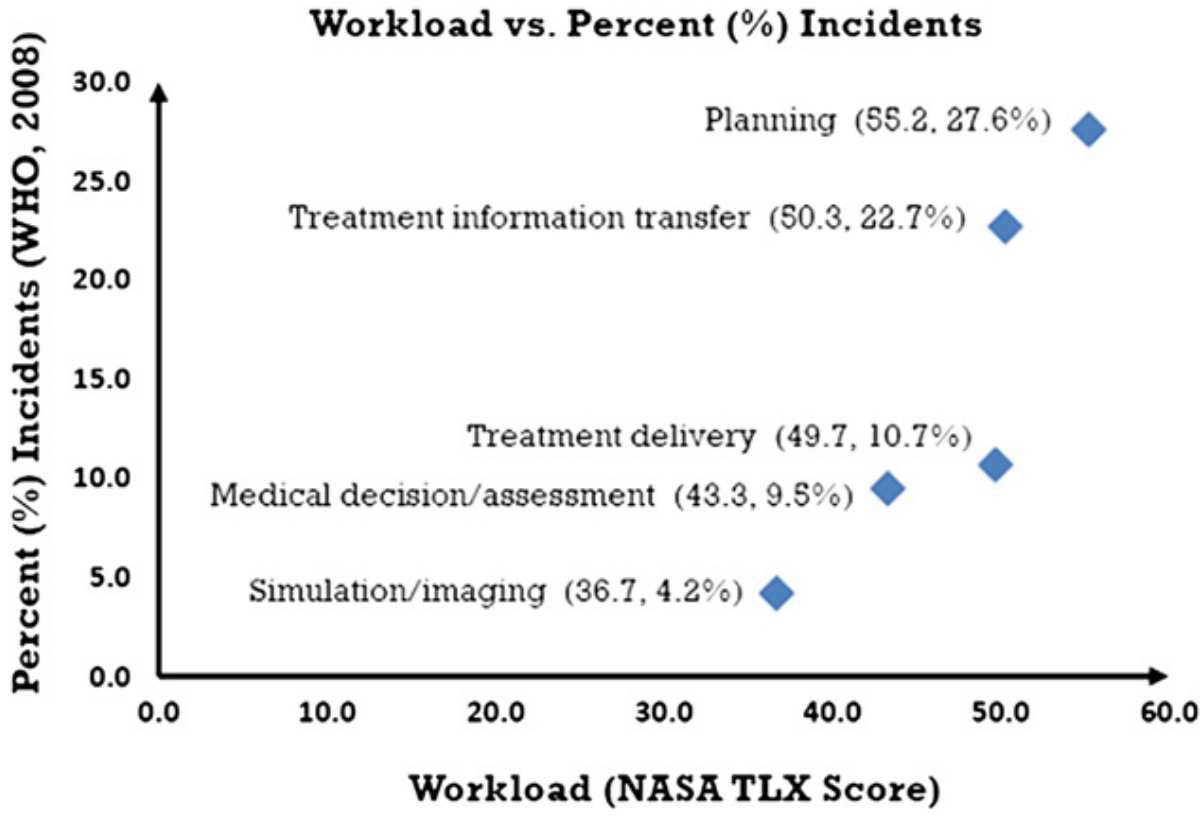
Stress and workload



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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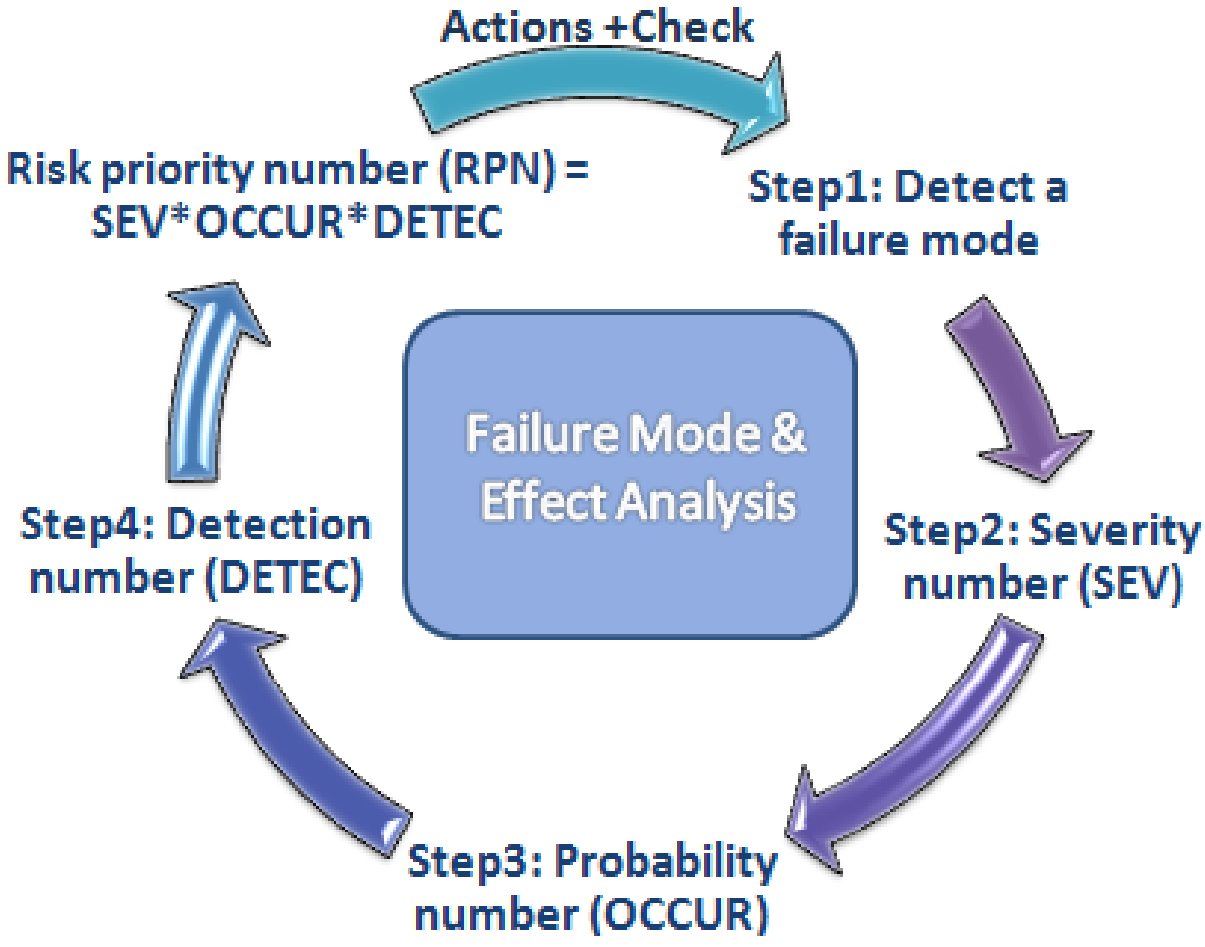
Failure Modes and Effects Analysis



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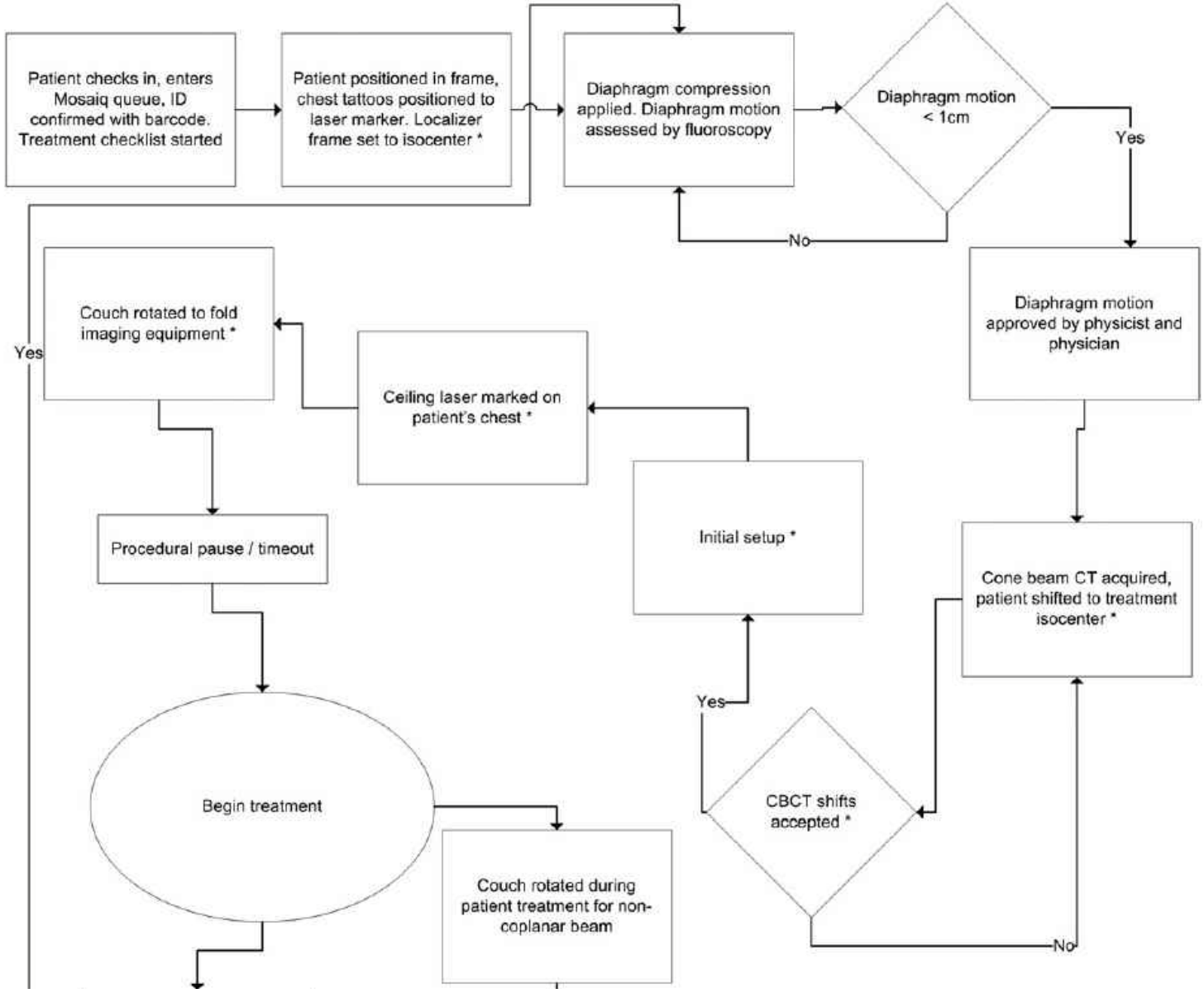
From flow charts



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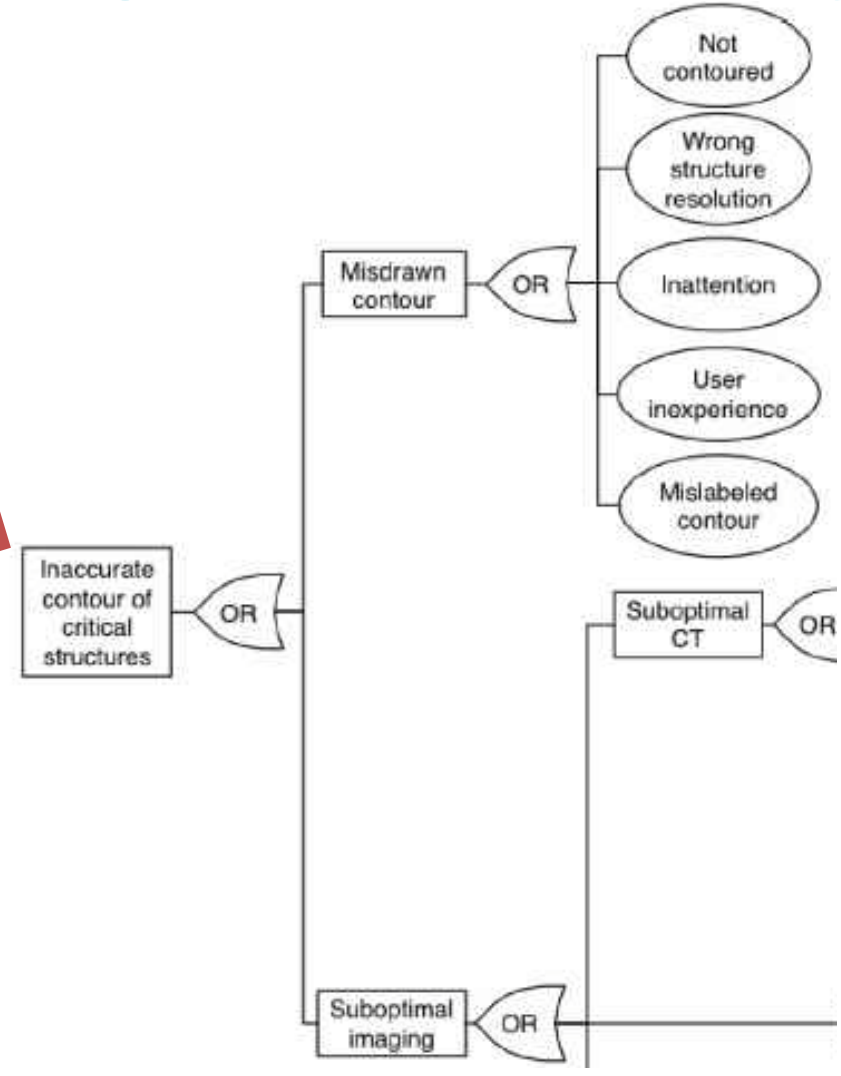
To failure modes using Fault Tree Analysis

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

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

SBRT for stage I NSCLC

UniversityHospital Zurich

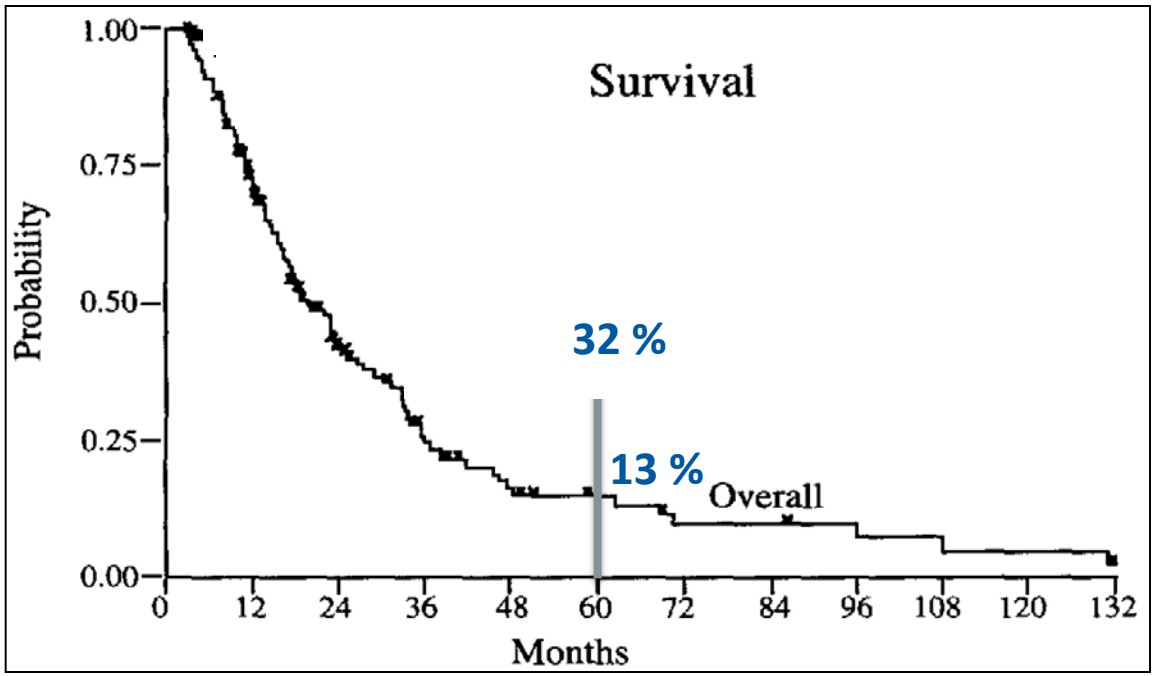
ESTRO

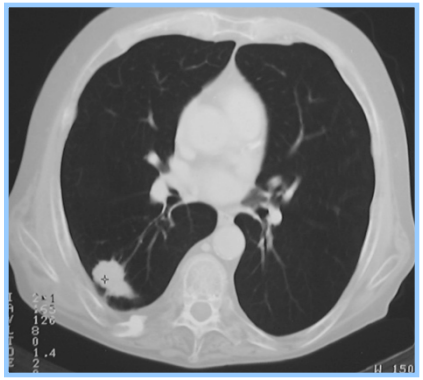
Question

Which of the following questions is **TRUE**

1) SBRT has replaced lobectomy for all patients as standard of care
2) FDG-PET staging is recommended for nodal staging
3) Patient with poor pulmonary function should not be treated with SBRT

RADIOTHERAPY ALONE FOR MEDICALLY INOPERABLE STAGE I NON-SMALL–CELL LUNG CANCER: THE DUKE EXPERIENCE



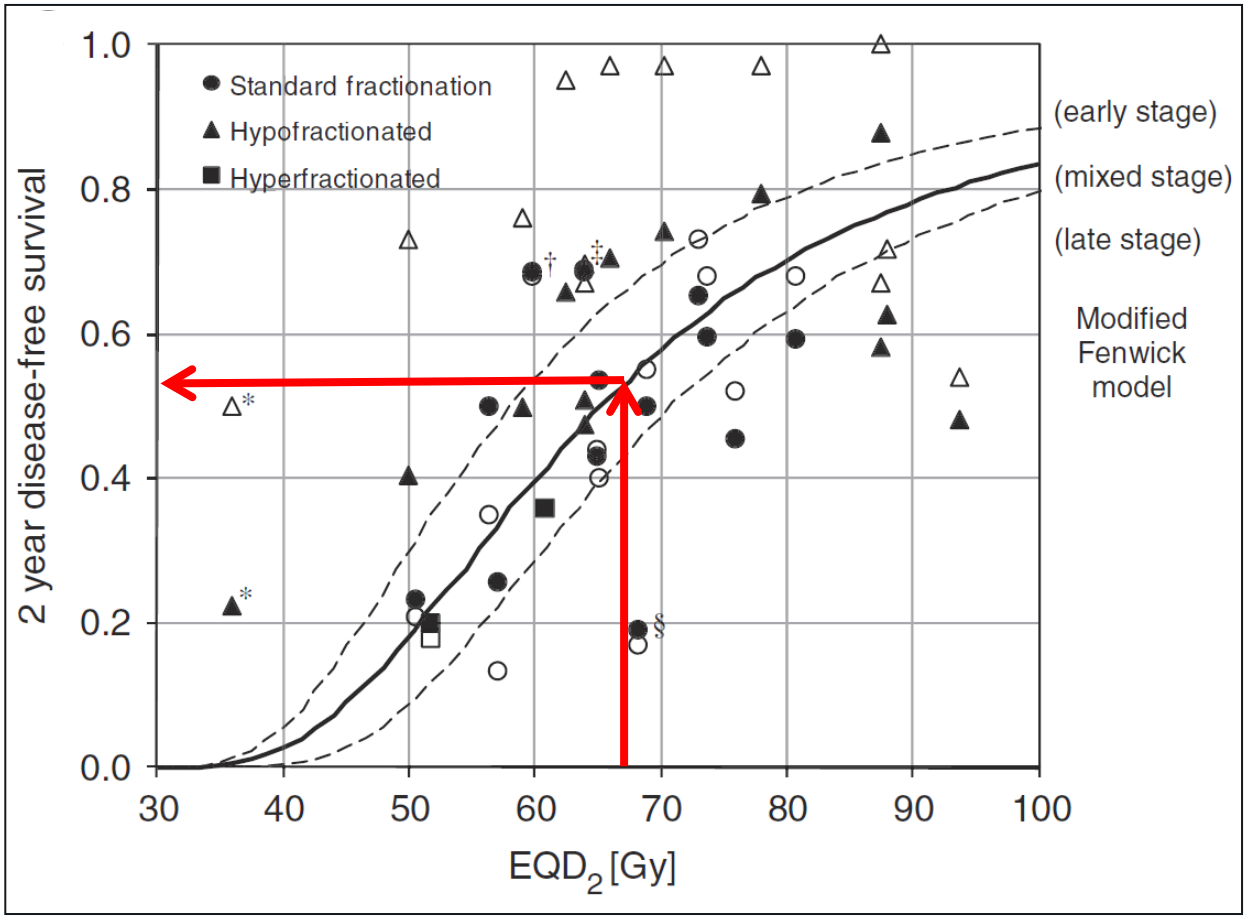


Median dose 64Gy

Sibley (1998)

- NSCLC most frequent cause of death
- Local recurrence most frequent site of failure

Local tumor control after SBRT for stage I NSCLC

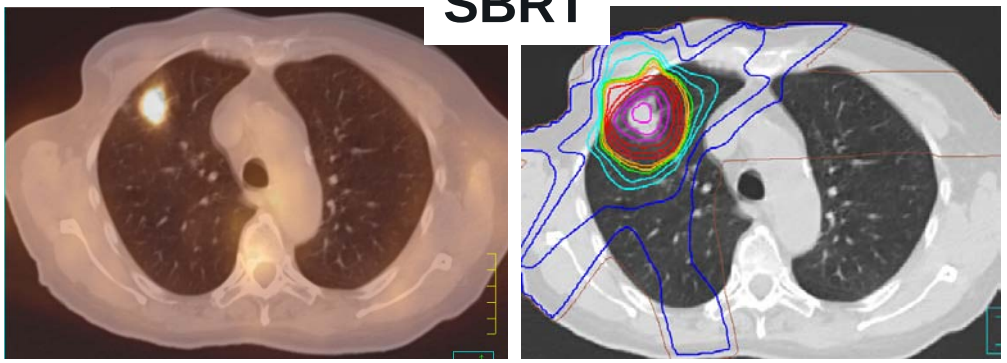


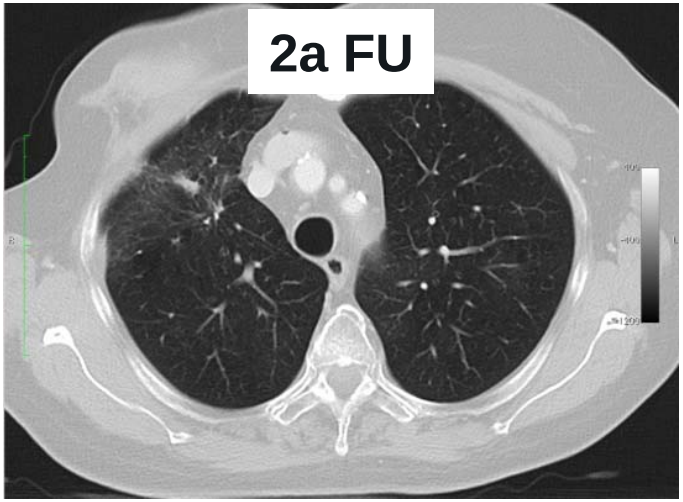
Partridge
Radiother Oncol 2011

Dose response relationship

➢ Rational for dose escalation

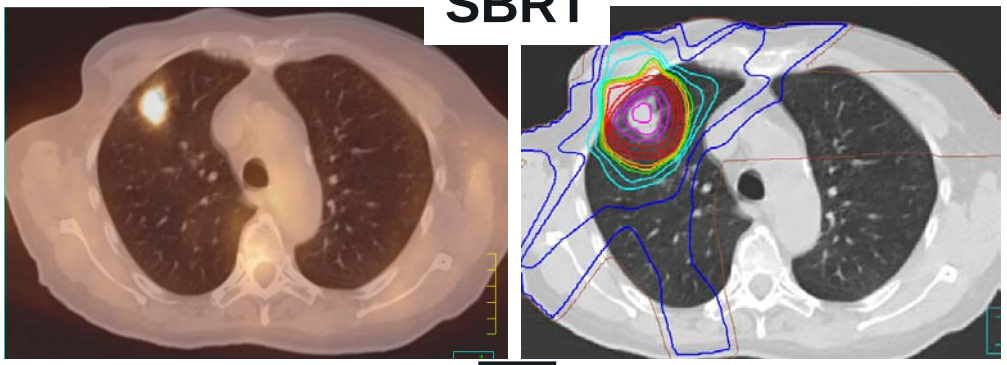
The typical case …

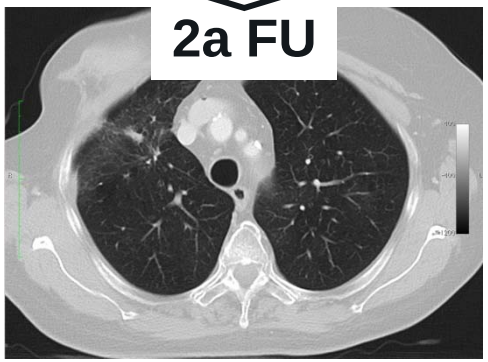




60 pack years
O2 supply in rest: 1.5 l/min
COPD GOLD IV
Pulmonary emphysema

Real world, not a fairy tale …





60 pack years
O2 supply in rest: 1.5 l/min
COPD GOLD IV
Pulmonary emphysema

Dead after 2.5a bacterial pneumonia

Spectrum of stage I NSCLC patients

SBRT

No treatment — **Conv. RT** — **Sublobar resection** — **Lobar resection**

Health / Fitness of the patients

Outcome of SBRT in inoperable patients

Study	Year	# patients	OS @ 2-3a	LC @ 2-3a
Nagata	2005	45	75%	98%
Baumann	2009	57	60%	92%
Fakiris	2009	70	43%	88%
Ricardi	2010	62	51%	88%
Bral	2010	40	52%	84%
Timmerman	2010	55	55.8%	98%
Prospective studies		**328**	**56.2%**	**91.2%**

- Highly consistent results in prospective and retrospective studies

SBRT compared to CF-RT

CF-RT

Study	Year	Local control
Hayakawa	1999	76%
Jeremic	1997	37%
Kaskowitz	1993	50%
Krol	1996	32%
Morita	1997	56%
Nguyen-Tan	1998	59%
Sandler	1990	57%
Sibley	1998	78%
Slotman	1996	94%

60%

SBRT

Study	Year	Local control
Nagata	2005	98%
Baumann	2009	92%
Fakiris	2009	88%
Ricardi	2010	88%
Bral	2010	84%
Timmerman	2010	98%

90%

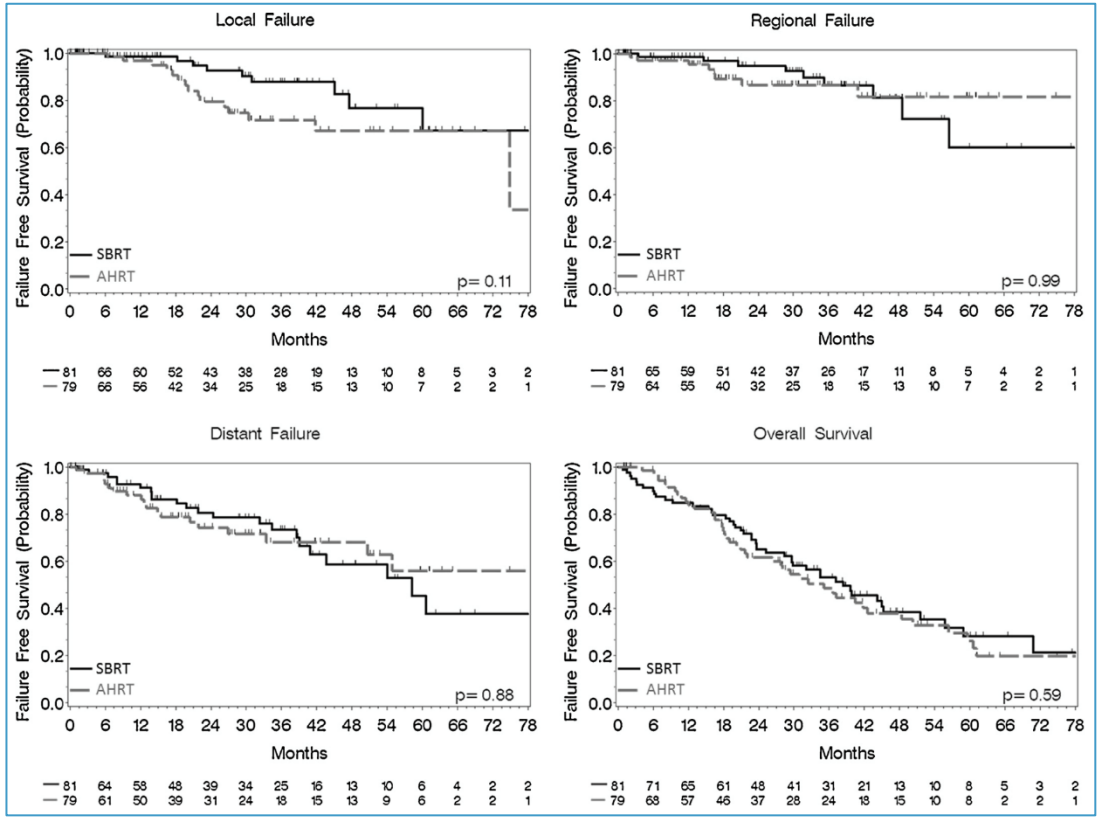
➢ Improved LC & OS of SBRT compared to CF-RT

SBRT compared to MODERN CF-RT

- Retrospective study
- 160 patients

- SBRT: 54Gy in 3F
- AHRT: 70.2Gy in 26Fx

➢ No difference in any in OS, RF, DF, LC
➢ No difference in toxicity



Lucas Lung Cancer 2014

➢ No obvious differences in oncological outcome

SBRT compared to MODERN CF-RT

Randomized **SPACE** trial in 102 patients with stage I NSCLC

Tx	Dose	Margin
SBRT	3 x 22Gy	5-10mm
CF-RT	35 x 2Gy	20mm

Nyman ESTRO 2014

Tx	3a OS	FFP	Pneumonitis	Esophagitis
SBRT	34%	61%	16%	9%
CF-RT	34%	57%	34%	32%

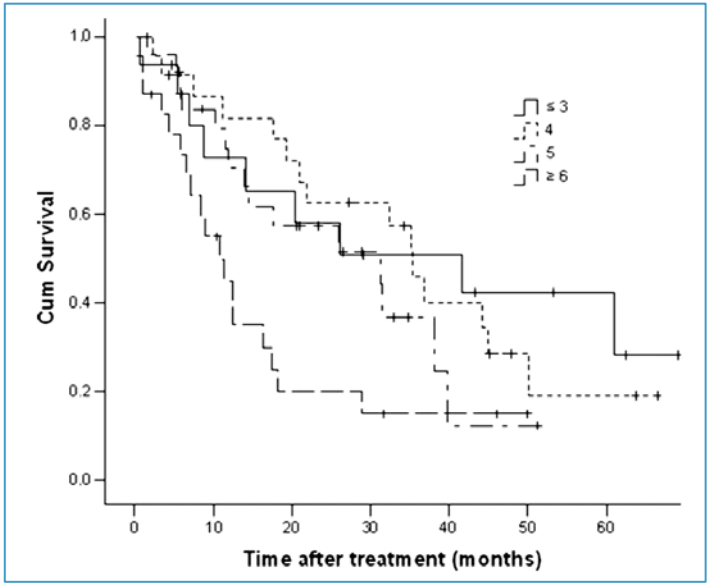
- No difference in oncological outcome
- Smaller margins -> reduced toxicity

Survival after SBRT

Factors influencing OS

- Tumor stage
- Tumor volume / diameter
- Preformance status
- Pulmonary function
- Co-morbidities

Charlson Co-morbidity

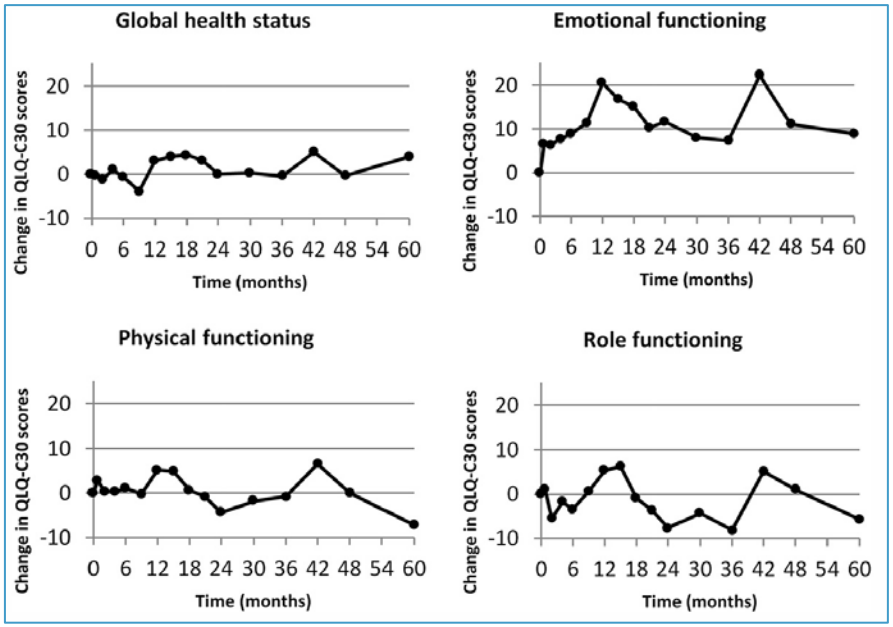


Kopec Radiother Aoncol 2009

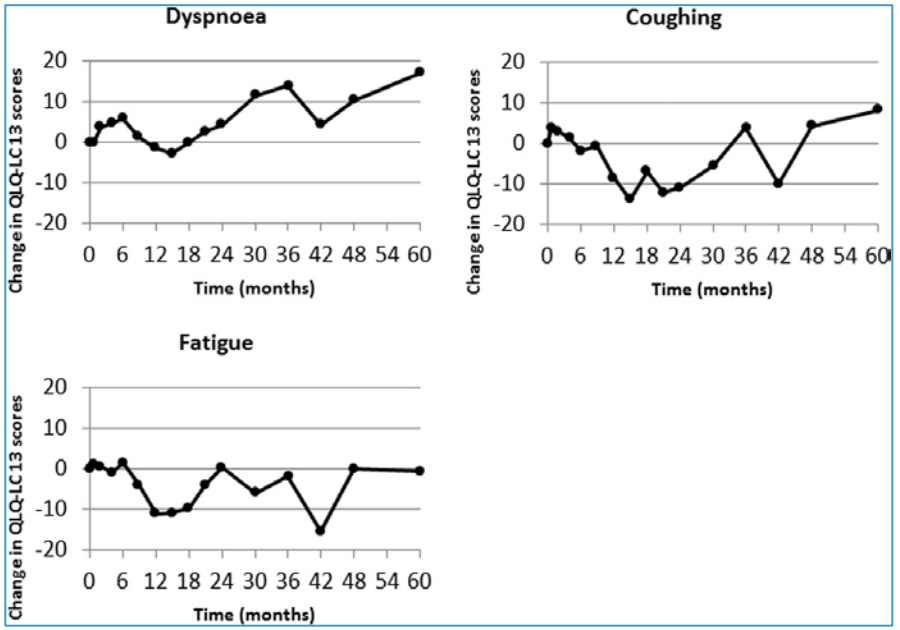
➢ OS highly influenced by patient characteristics

Quality of life

EORTC QLQ-C30



EORTC QLQ-LC13



n=39; SBRT with mostly 3 x 20Gy *(Ubels Radiat Oncol 2015)*

- Stable overall QoL
- Increasing dyspnoea – comorbidities or SBRT?

Toxicity of lung SBRT

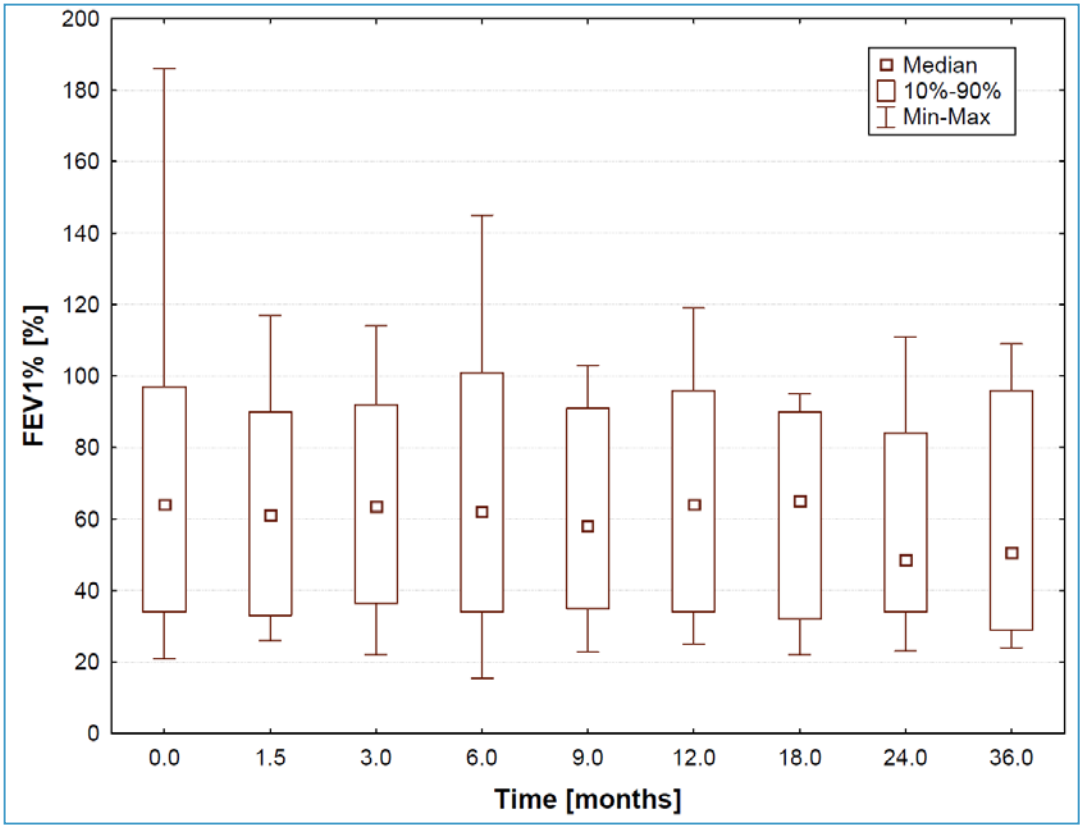
- Chest wall pain
- Rip fracture
- Brachial plexopathy
- Pneumonitis
- Decreased pulmonary function
- Bronchial stenosis / necrosis
- Bleeding

- ➢ Grade V toxicity < 1%
- ➢ Grade III-IV toxicity <10%

➢ Favorable toxicity profile despite high-risk population

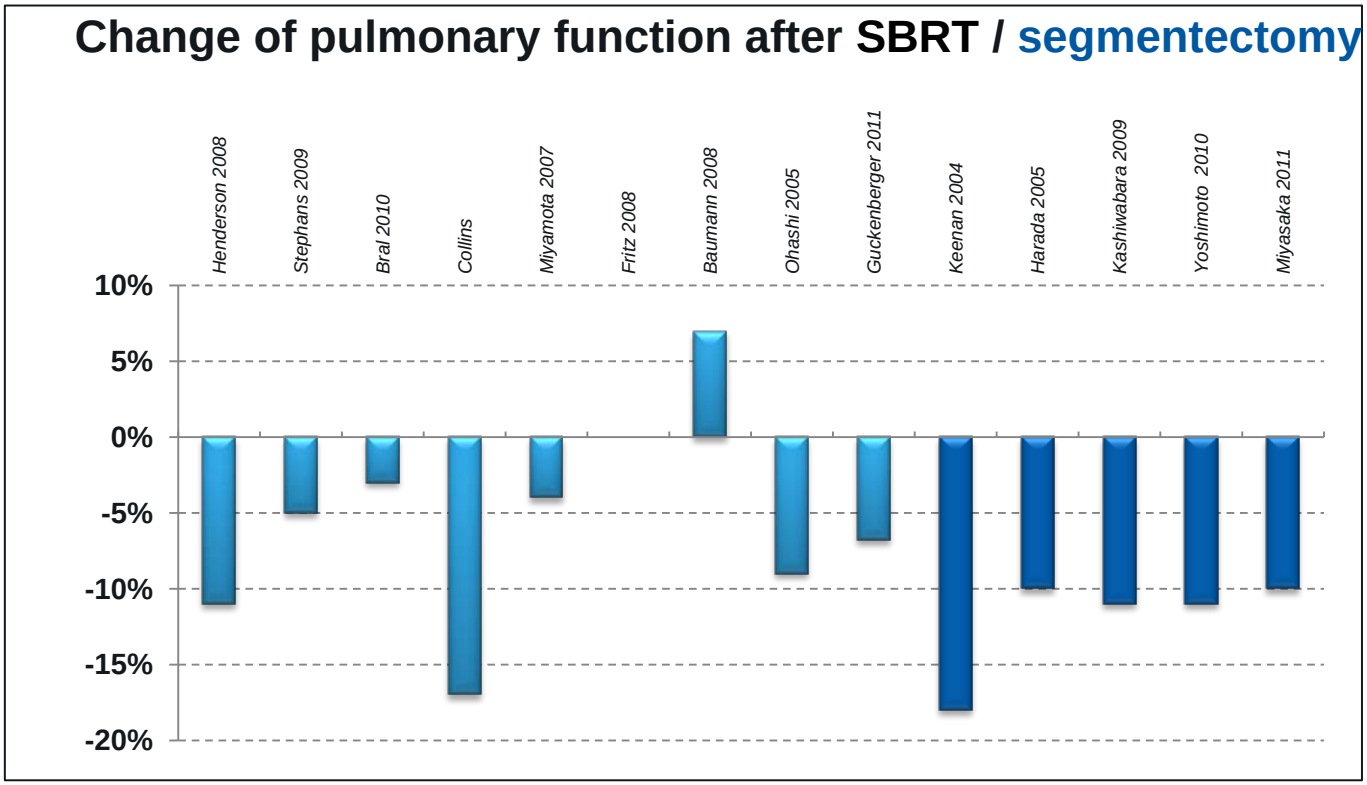
Pulmonary toxicity

Guckenberger JTO 2012



- Small loss of PF after SBRT
- No increased risk for patients with (very) poor PF

Pulomonary toxicity



Averaged PF Changes:

-4%

-12%

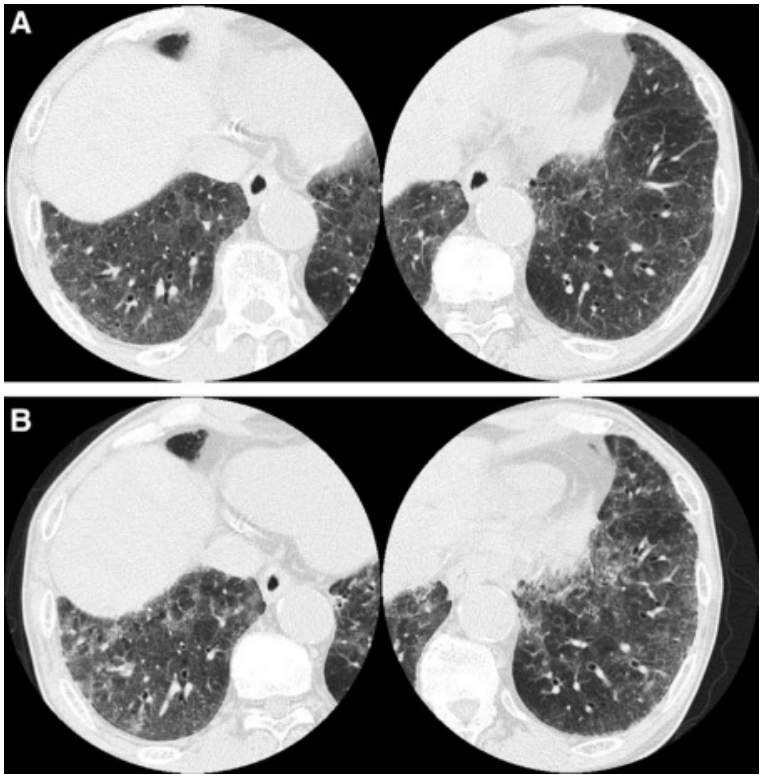
- Only small loss of PF after SBRT
- Loss of PF appears smaller compared to segmentectomy

Interstitial lung disease

Study	Interstitial lung disease Overall patients / % patients with ILD	SBRT dose	Radiation penumonitis
Takeda Lung cancer 2015	124 – **16%**	4 x 12Gy	G2-5 19%
Ueki JTO 2015	157 – **13%**	4 x 12Gy	**G3+ 55%**
Bahig PRO 2016	504 – **6%**		**G3+ 32%** **G5 21%**
Yoshitake Anticancer Res 2015	260 – **8%**		**G2+ 50%** **G5 17%**

➢ ILD as exclusion criteria for SBRT

Interstitial lung disease



Ueki JTO 2015

Clinical Classification

Pulmonary Fibrosis

Exposure-related:
- Occupational
- Environmental
- Avocational
- Medication

Idiopathic interstitial pneumonia (IIP)

Idiopathic pulmonary fibrosis (IPF)

- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis interstitial lung dis. (RBILD)
- Acute interstitial pneumonia (AIP)
- Cryptogenic organizing pneumonia (COP)
- Nonspecific interstitial pneumonia (NSIP)
- Lymphocytic interstitial pneumonia (LIP)

Connective tissue disease:
- Scleroderma
- Rheum. arthritis
- Sjogrens
- UCTD

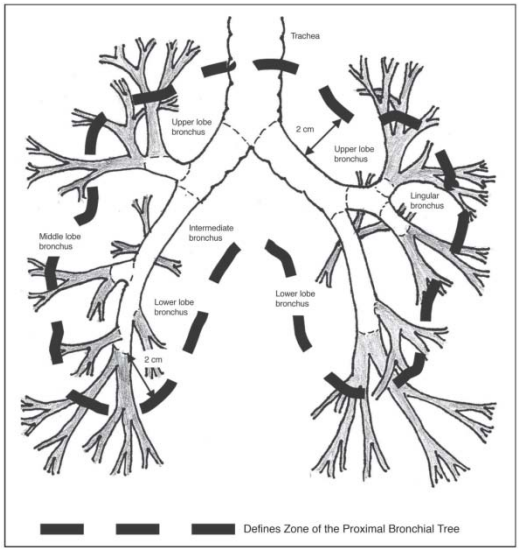
Other:
- Sarcoidosis
- Vasculitis/Diffuse alveolar hemorrhage (DAH)
- Langherhans cell histiocytosis (LCH)
- Lymphagioleiomyomatosis (LAM)
- Pulmonary alveolar proteinosis (PAP)
- Eosinophilic pneumonias
- Neurofibromatosis
- Inherited disorders
- Chronic aspiration
- Inflammatory bowel disease

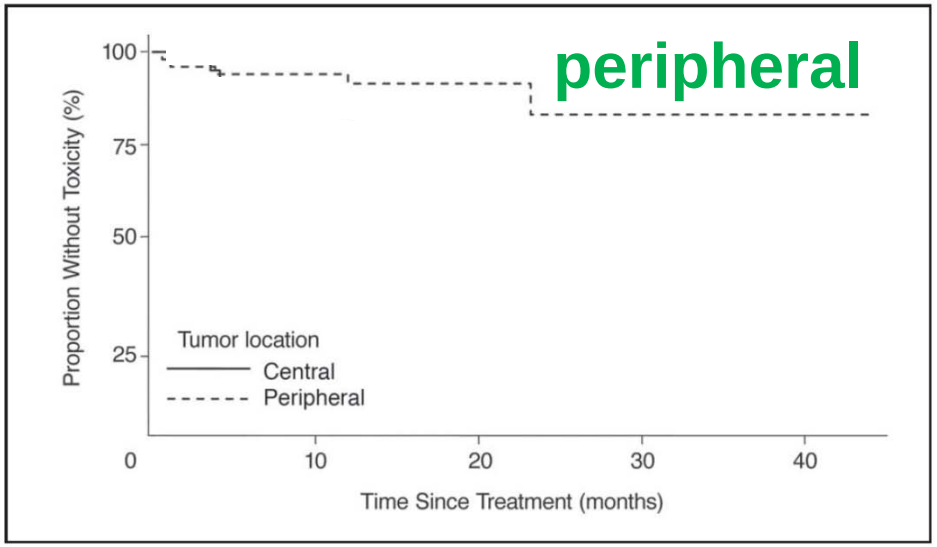
Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

JCO 2008

Prospective phase II study with 70 patients
SBRT with very high irradiation doses of up to 3 x 22Gy





Freedom from ≥ grade 3 toxicity

Is this „EXCESSIVE TOXCITY“ really unexpected after RT with EXCESSIVE DOSES?

Risk adapted fractionation

Increased toxicity		No increased toxicity	
Timmerman 2008	**3** x 20 / 22 Gy	Joyner 2006	**3** x 12 Gy **6** x 6 Gy
Song 2009	**3-4** x 10-20 Gy	Senan 2007	**8** x 7.5 Gy
		Chang 2008	**4** x 12.5 Gy
		Guckenberger 2009	**8** x 6 Gy
		Milano 2009	**10** x 3-5 Gy
		Oshiro 2010	**5** x 10 Gy

Systematic review of SBRT for centrally located NSCLC

Publications	22
Centrally located tumors	563
Stage I NSCLC	315

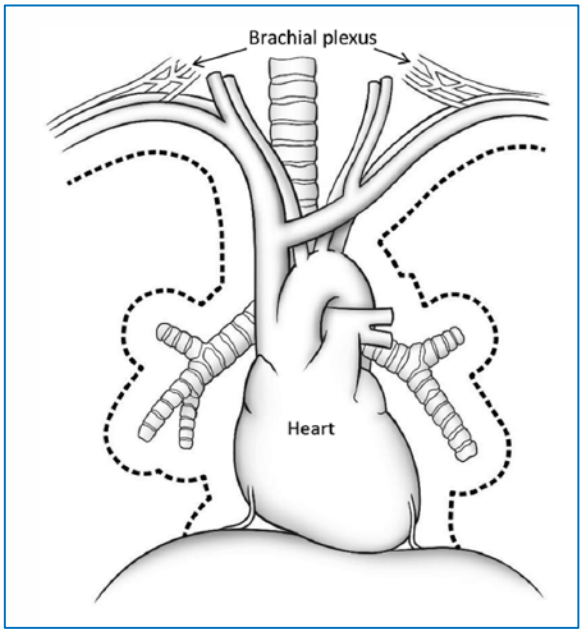
➢ LC for BED ≧ 100 Gy	≧85%
➢ G 3 / 4 toxicity	9%
➢ Overall Tx related mortality	2.7%
➢ Tx related mortality BED <210Gy	1.0%

8 x 7.5Gy	5 x 10Gy	3 x 13Gy

- Acceptable therapeutic ratio of more fractionated SBRT

Systematic review of SBRT for centrally located NSCLC

Central location



Chang JTO 2015

RTOG 0813

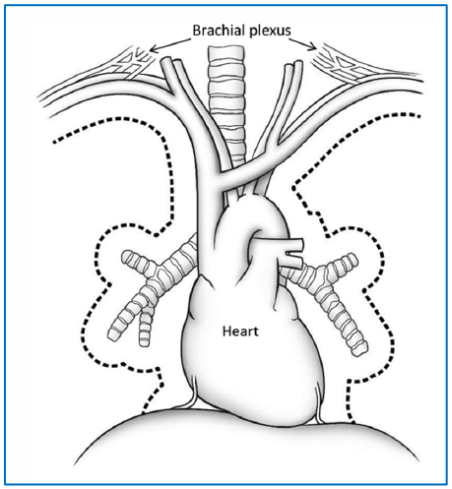
Dose level	Pts accrued (n)	Pts eligible (n)	Pts evaluable for DLT (n)	Number and type of DLT	Worst treatment-related AE at any time		
					Grade 3 (n)	Grade 4 (n)	Grade 5 (n)
10 Gy/fr	8	8	8	0	0	0	0
10.5 Gy/fr	8	7	6	1 (death)	0	0	1
11.0 Gy/fr	18	14	13	1 (bradycardia)	1	0	0
11.5 Gy/fr	43	38	32	2 (hypoxia)	4	0	2
12.0 Gy/fr	43	33	30	1 (pneumonitis)	5	1	1

Bezjak IJROBP Supp 2015

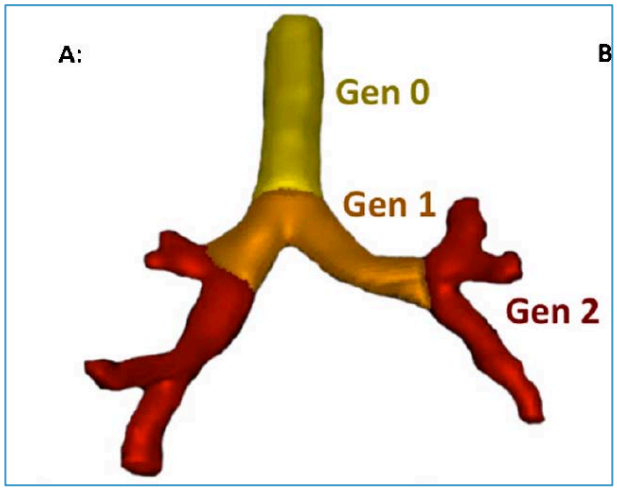
- Overall acceptable toxicity
- Toxicity appears to increase from 5 x 11.5Gy

Peripheral – Central – Ultra-central

Central



Ultra-Central



Chaudhuri Lung Cancer 2015

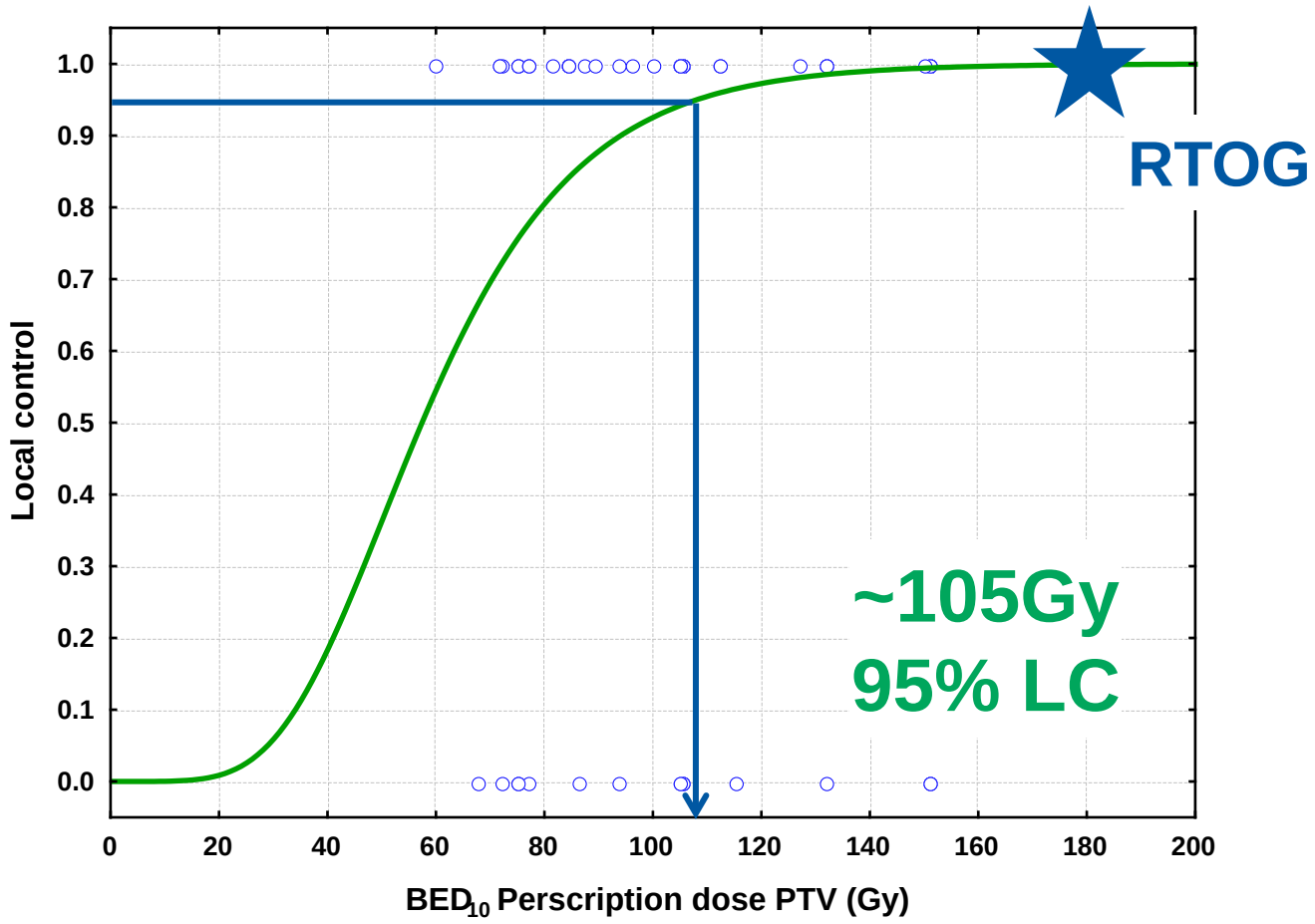
Peripheral	Central	Ultra-central
34	27	7

All treated with 50Gy in 4-5 Fx

- Location did not influence outcome
- No G2+ toxicity in ultra-centrally located NSCLC

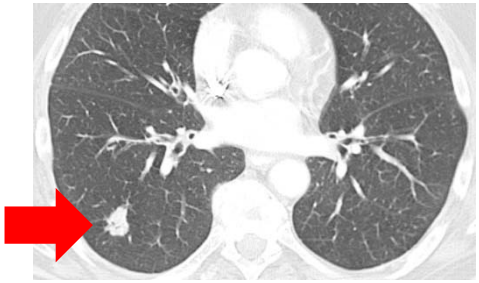
Dose required to achieve local tumor control

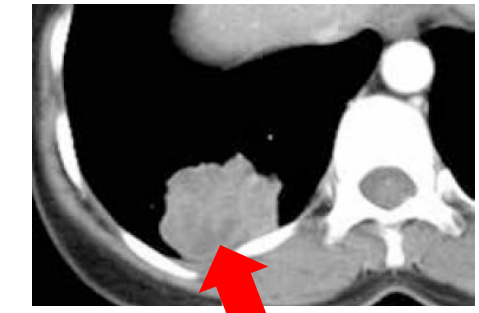
Guckenberger IJROBP 2008
Kerstin ASTRO Meeting 2010

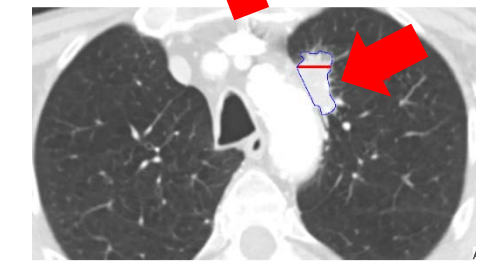


Plateau of dose-response relationship at ~100Gy BED

ESTRO ACROP recommendation







	Consensus fractionation	BED10
Peripheral location	**3 x 15Gy**	**113Gy BED10**
Broad chest wall contact	**4 x 12Gy**	**107 Gy BED10**
Central location	**8 x 7.5Gy**	**105 Gy BED10**

Controversy: Histophathological confirmation

Do we predominantly treat and “cure” benign nodules?

Study		Biopsy
Nagata	2005	100%
Baumann	2009	67%
Fakiris	2009	100%
Ricardi	2010	65%
Bral	2010	100%
Timmerman	2010	100%
Prospective studies		**87.6%**
Senthi	2012	35%
Guckenberger	2013	85%
Grills	2013	59%
Retrospective studies		**57.6%**

- Highly variable patterns of practice
- No obvious differences in outcome

Controversy: Histophathological confirmation

Do we predominantly treat and “cure” benign nodules?

Proportion of benign disease after clinical **CT and FDG-PET** diagnosis:

Operable NSCLC	**0%**
Stage I NSCLC	**8 – 10%**

Fischer 2009, Herder 2006
Meyers 2006, Kozower 2008

- High PPV of CT and FDG-PET based staging
- Accuracy decreased in regions with high incidence of granulomatous diseases

Controversy: Histophathological confirmation

Swensen et al.:

Probability of malignancy = $1/(1 + e^{-a})$

In which e is the base of natural logarithms and a is the sum of all coefficients;

Factor	Coefficient
Constant	−6.8272
Age	years × 0.0391
Diameter	mm × 0.1274
Smoking	
-Current or former smoker	0.7917
-Never smoked	0
Extrathoracic cancer >5 years ago	
-Yes	1.3388
-No	0
Spiculated lesion	
-Yes	1.0407
-No	0
Location	
-Upper lobe	0.7838
-Other lobe	0

Herder et al.:

Probability of malignancy = $1/(1 + e^{-a})$

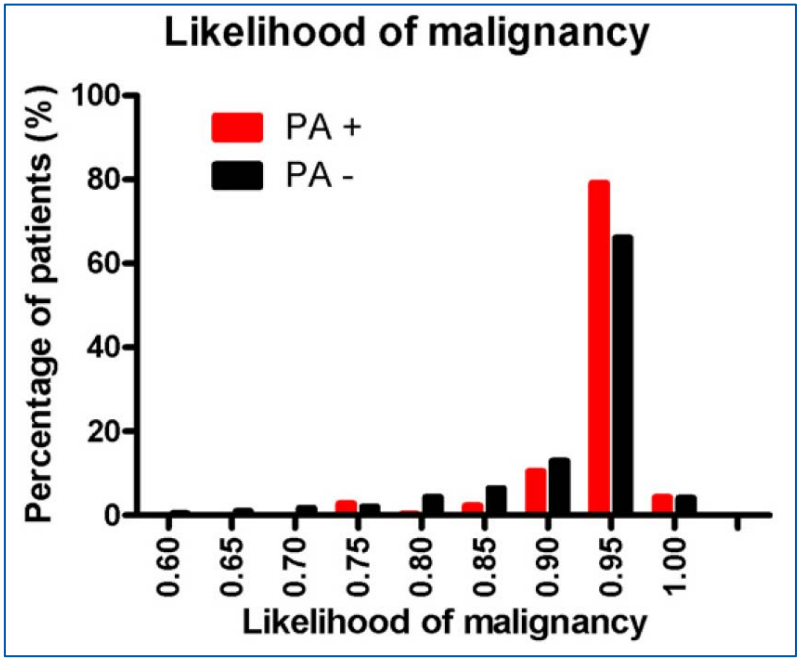
In which e is the base of natural logarithms and a is the sum of all coefficients;

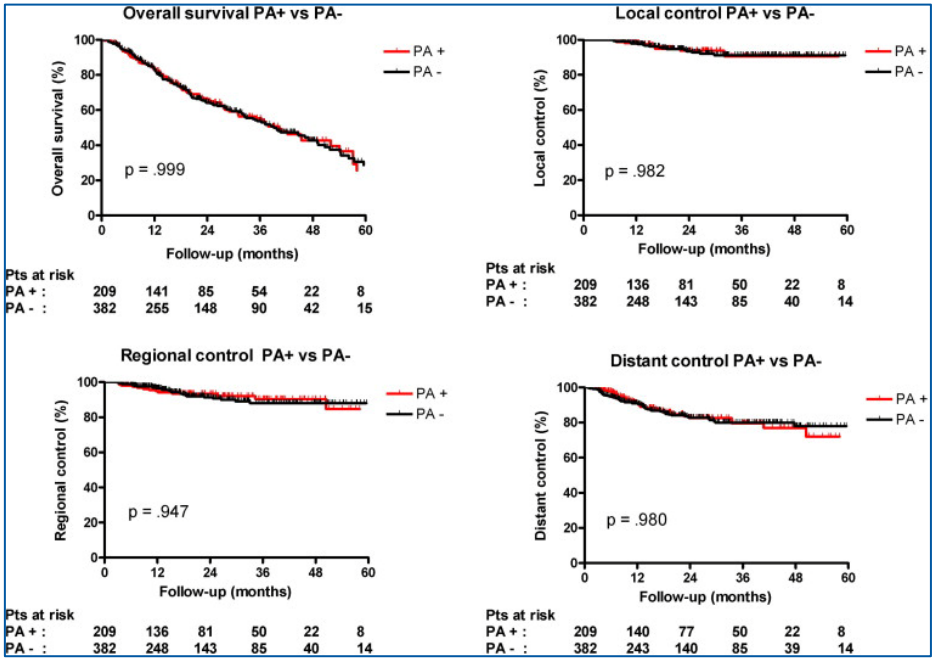
Factor	Coefficient
Constant	−4.739
Probability by Swensen	probability × 3.691
PET uptake (SUV)	
-Faint uptake	2.322
-Moderate uptake	4.617
-Intense uptake	4.771

- Age
- Diameter
- Smoking
- Extrathoracic cancer
- Location
- Spiculation
- FDG-Uptake11

- Calculation of probability of malignancy

Controversy: Histophathological confirmation





Biopsy proven	**209**
Clinical diagnosis	**382**

Verstegen Radiother Oncol 2014

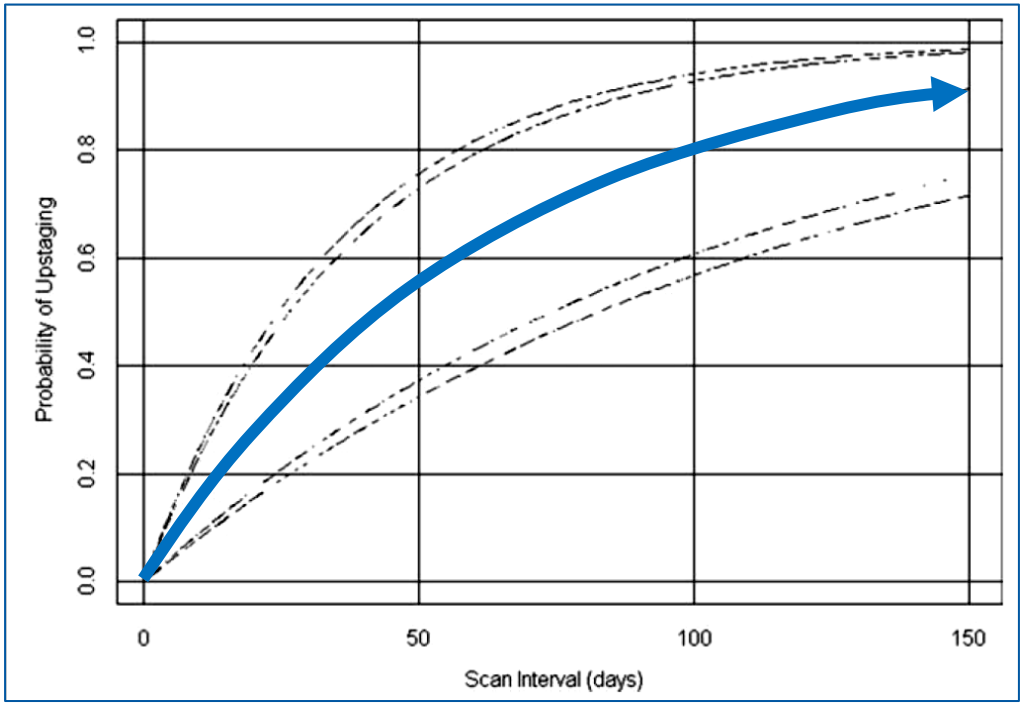
- No differences in outcome between biopsy-proven and non biopsy proven patients

UniversityHospital Zurich

ESTRO

Controversy: Histophathological confirmation Waiting for growth ?

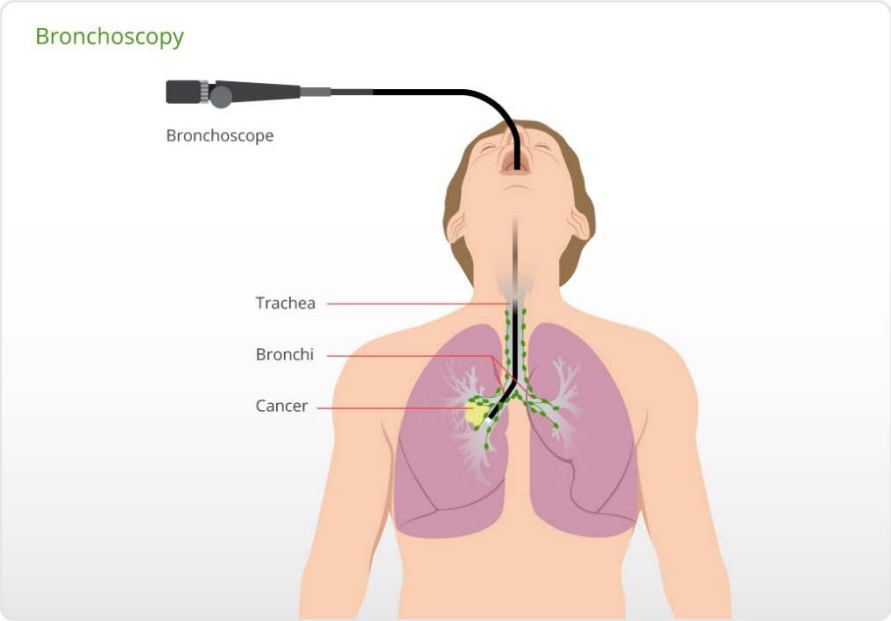
- N=28
- Stage I 21%
- 2x FDG-PET
- Interval median 24 days (8 – 176)



Everitt Cancer 2010

➢ Relevant risk of disease progression

Controversy: Histophathological confirmation



- Histo-pathological confirmation of malignancy is goal
- Feasibility & safety
  - patient and tumor characteristics
  - skills of interventional radiologist and pulmonologist
- Clinical diagnosis only no contraindication for SBRT

Controversy: No treatment of lymph nodes

How good is clinical nodal staging ?

Surgical series

	CT
False negative	~ 25%
References	*D'Cunha 2005*

SBRT series

	CT & FDG-PET
Nodal recurrences	~ 10%
References	*Chi 2010*

Consistent rate of 10% regional recurrences after PET staging

- Further improvement with EBUS / EUS ?
  - NPV of 98.9% in clinical stage I NSCLC *Herth 2008*

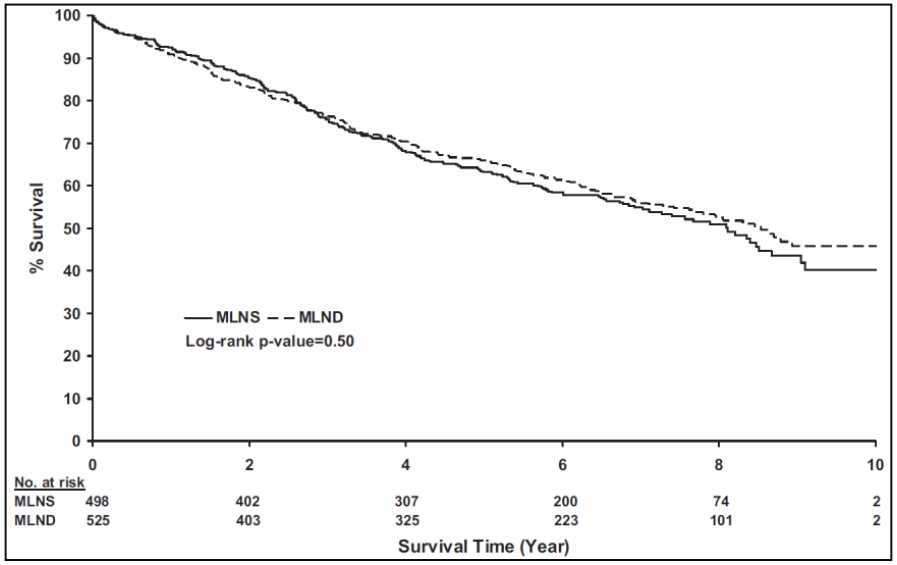
Controversy: No treatment of lymph nodes

What is the clinical benefit of LN sampling / dissection?

ACOSOC Z0030

cN0, nonhilar cN1,cT1, cT2
Randomization:

- MLN sampling (n=498)
- MLN dissection (n=525)



Darling 2011

- Value of Lymph node sampling / dissection:
  - ➢ **Diagnostic or Therapeutic?**

Controversy: No treatment of lymph nodes

What is the theoretical benefit of LN sampling / dissection?

100%	Patient with cNo in FDG-PET
⇩	
12%	(12%) N+
⇩	
4%	(33%) N2
⇩	
0.2%	(5%) OS due to adjuvant CT

- Despite accurate LN staging appears logical, it`s theoretical benefit is very small

Spectrum of stage I NSCLC patients

SBRT

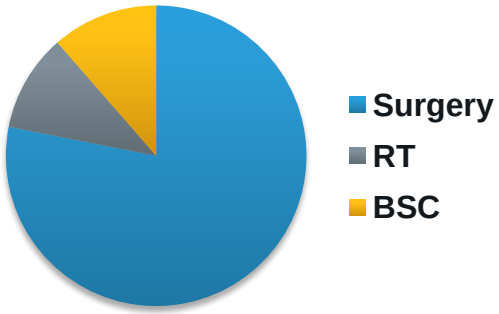
No treatment **Conv. RT** **Sublobar resection** **Lobar resection**

Health / Fitness of the patients

Proportion of patients remaining untreated

Total population

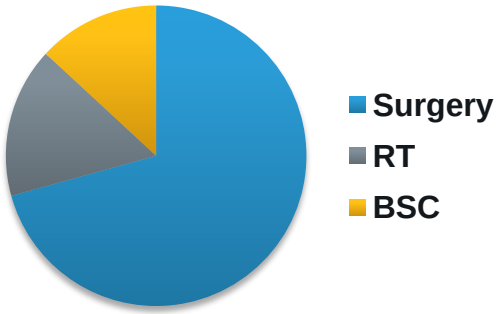
11%



Raz Chest 2007

SEER > 65 years

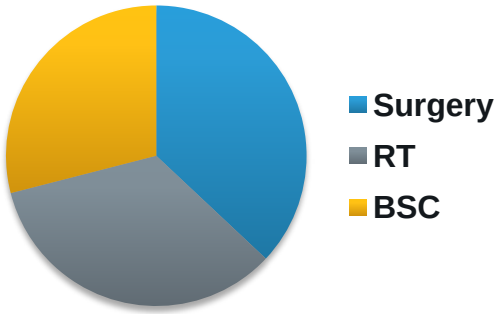
13%



Shirvani IJROBP 2012

Netherlands >75a

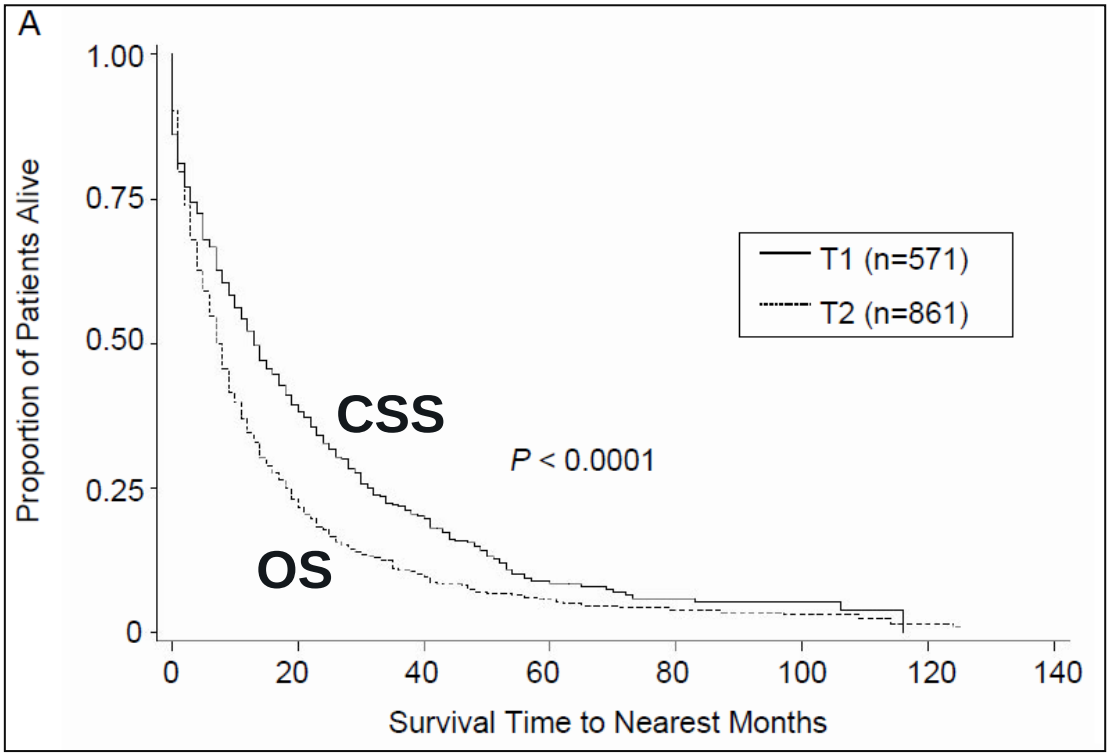
29%



Haasbeek Ann Oncol 2012

- Large proportion of elderly patients remaining untreated
- Proportion of patients will increase with aging societies

Prognosis of UNTREATED stage I NSCLC



5a OS	**9%**
5a CSS	16%

Raz Chest 2007

- Limited long-term OS in this poor prognostic patient cohort
- Short CSS indicating need for curative treatment option

Safety & efficacy in elderly patients

	Patients	Median Age
Takeda 2013	109	83
Sandhu 2013	24	85
Haasebeek 2010	193	79

- Low mortality and morbidity despite very old age

➢ Excellent safety profile

Safety & efficacy in elderly patients

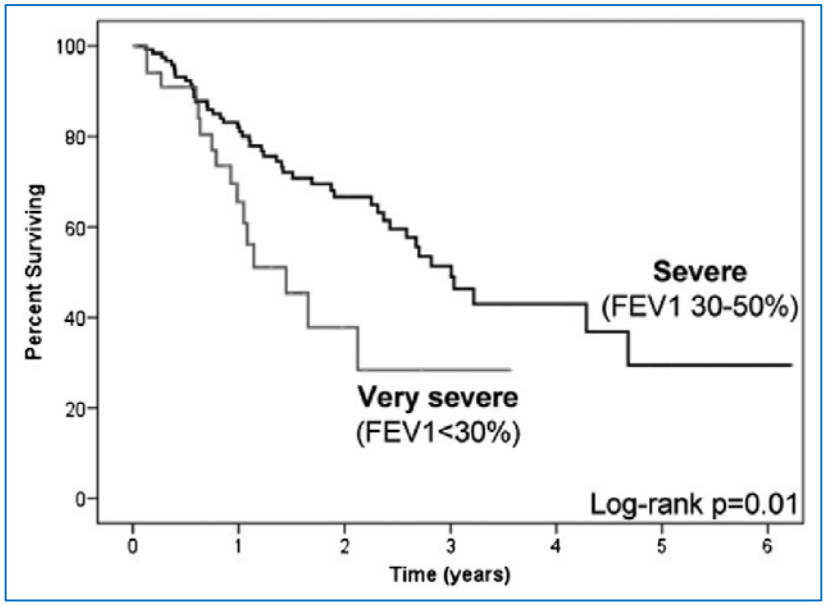
	OS
Takeda 2013	54 % @ 3a
Sandhu 2013	74 % @ 2a
Haasebeek 2010	45 % @ 3a

- Promising OS considering very advanced age and malignant disease

Safety & efficacy in severe COPD patients

176 patients with COPD GOLD III-IV

Toxicity	
30 day mortality	• 0%
Acute toxicity	• G3 RP n=1
Late toxicity	• G3 RP n=2 • Rip fracture n=2 • hemoptysis requiring transfusion n=1



Palma IJROBP 2011

- SBRT is safe but OS is worse in patients with very severe COPD

Which patients do NOT have a benefit of SBRT as a curative treatment approach?

779 patients treated at 5 institutions
No exclusion criteria for SBRT

- 6 months death rate 50 / 779 patients

Prediction of 6 months death:

- ECOG performance status
- AUC maximal 0.70
- 10% high risk population: 6 months death rate 8.8%

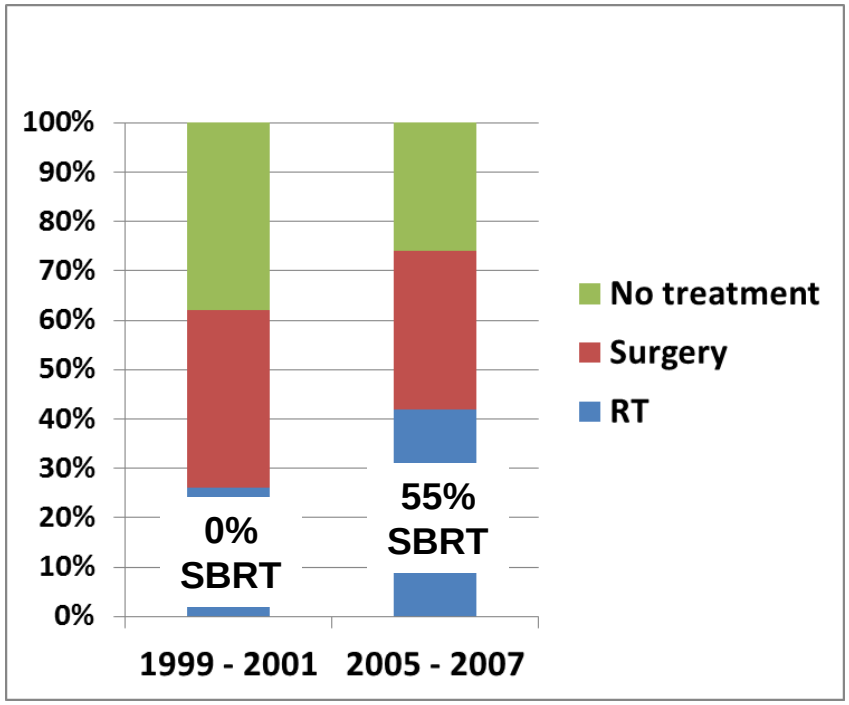
Klement JTO 2016

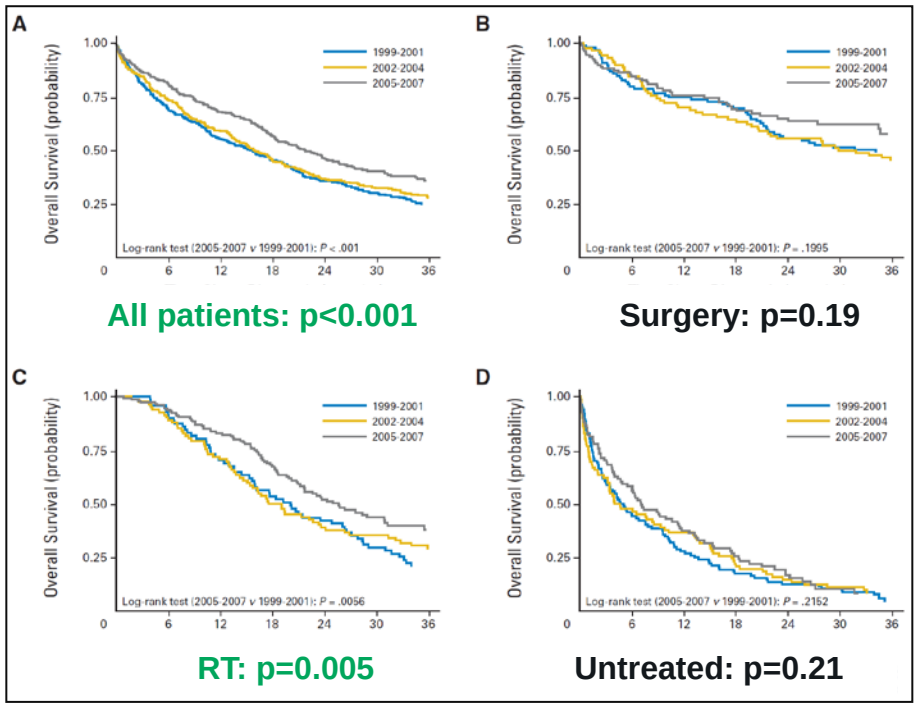
- Age, sex, ECOG, FEV1, CCI shall not be used to exclude patients from SBRT

SBRT for previously untreated elderly patients

Cancer registry northern Netherlands stage I NSCLC, age ≥75a

Palma JCO 2010





- Significant ↓ of untreated patients after introduction of SBRT

➢ Significant improved OS in the total population

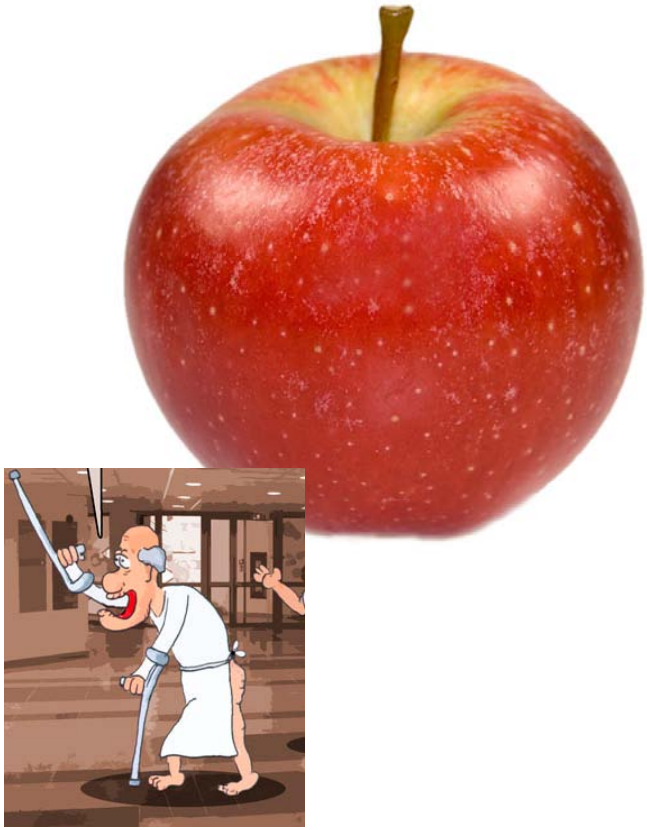
Spectrum of stage I NSCLC patients

SBRT ⇨

No treatment **Conv. RT** **Sublobar resection** **Lobar resection**

Health / Fitness of the patients

SBRT



Surgery

There is not one single thing as INOPERABLE

From a surgical perspective:

Risk factor	No surgery	Sublobar resection	Lobectomy
Functional reserve	-	-	+
Anesthesia	-	+	+

- Functional reserve: pulmonary function testing
- Anesthesia: e.g. ASA

High-risk population not suitable for lobectomy

ACOSOG Z4099 / RTOG 1021:

Randomized trial comparing SBRT and sublobar resection

Inclusion criteria:

Major criteria

FEV1 ≤ 50% predicted
DLCO ≤ 50% predicted

Minor criteria

Age ≥ 75 years
FEV1 51-60% predicted
DLCO 51-60% predicted

- Defintion of a high-risk patient population not suitable for THE standard of lobectomy

The evidence:
randomized trials comparing lobectomy and SBRT

Rosel

STAR

RTOG 1021

Enrollment: 68 / 2410 (2.8%)

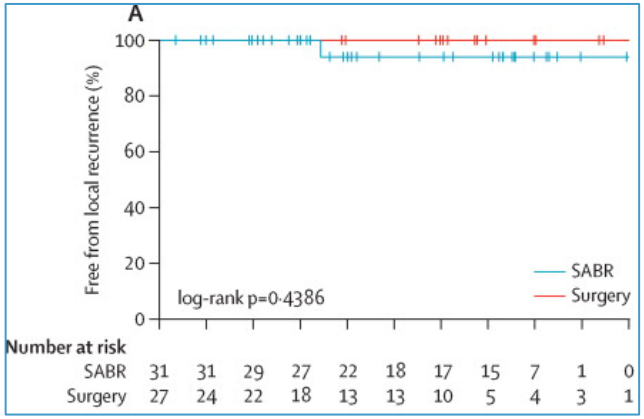
- Was it successfull — certainly no !!!
- Was it for nothing — certainly no !!!

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

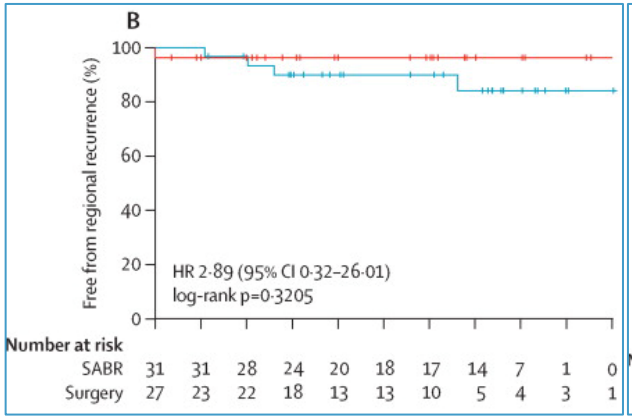
Chang *Lancet Oncol 2015*

	Grade 3	Grade 4	Grade 5
SBRT n=31	10%	0%	0%
Lobectomy n=27	44%		4%

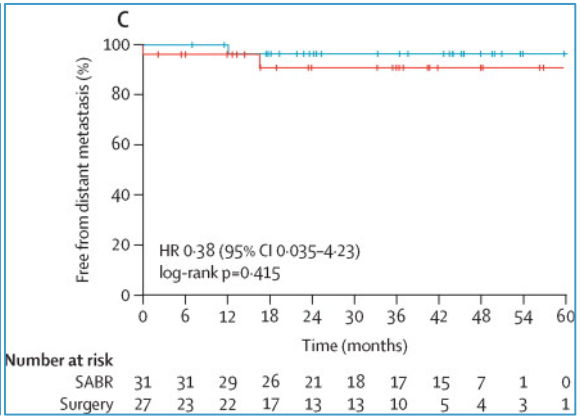
Freedom from local progresion



Freedom from regional recurrence

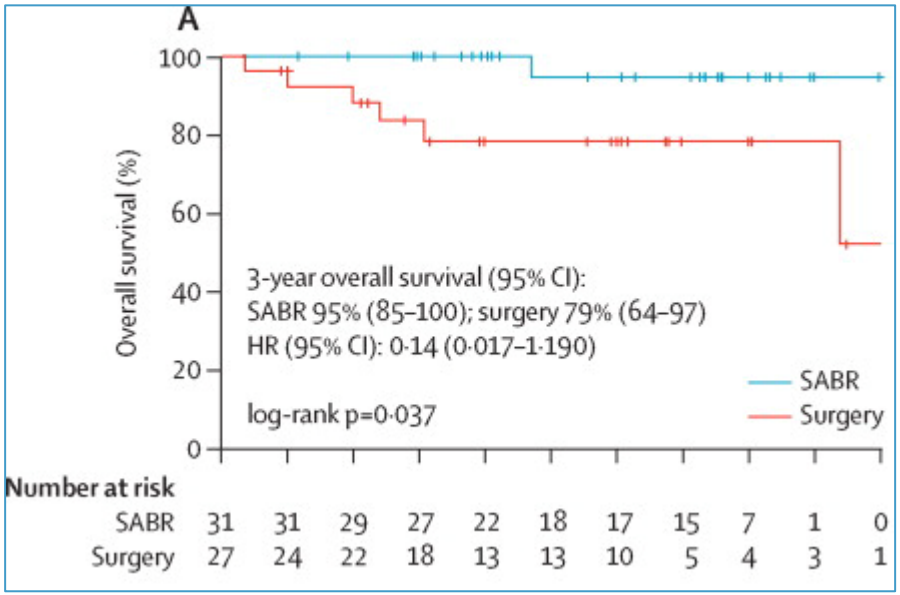


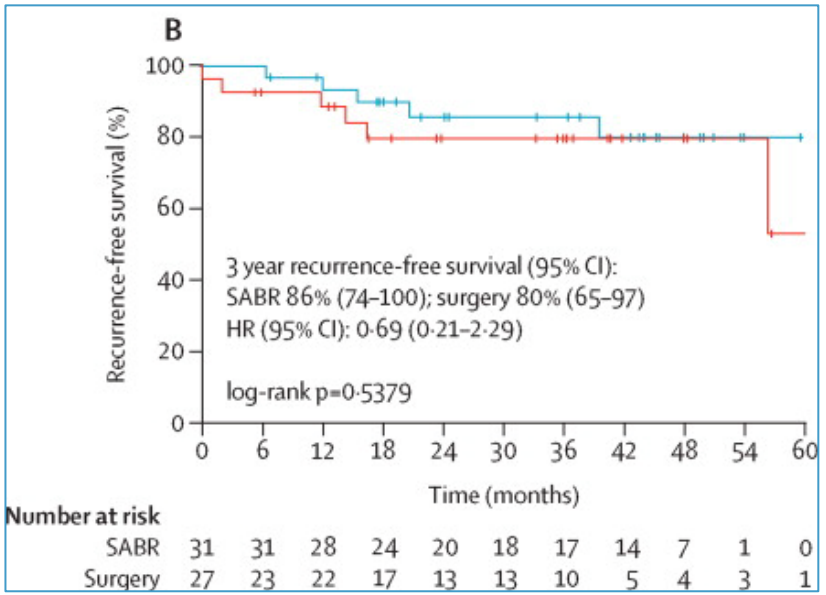
Freedom from Distant metastases



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

Chang *Lancet Oncol 2015*





- Higher rates of adverse events after surgery
- No significant differences in recurrence pattern
- (Improved) at least equivalent OS

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

Chang *Lancet Oncol 2015*

Discussion of this study:

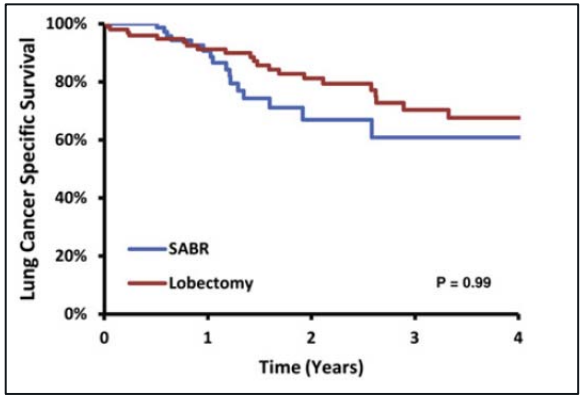
Opponent	Supporter
Only 58 centers	Two high quality studies
Overall 38 centres	Best of-ist-time Tx in both studies
Differences in study design	Interpretation considering statistical limitations
Surgical OS 67% in STARS and 100% in ROSEL	Best evidence available until today

- SBRT is better tolerated treatment resulting is most likely identical overall survival
- Higher toxicity versus higher rates of locoreginal recurrence

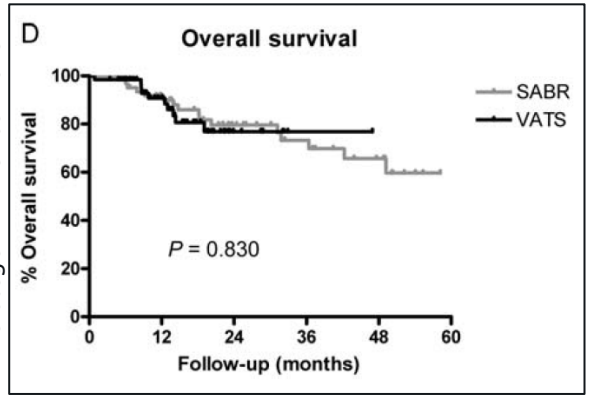
The evidence:
there is more that RCT

Propensity Score Matched Analyses, systematic reviews

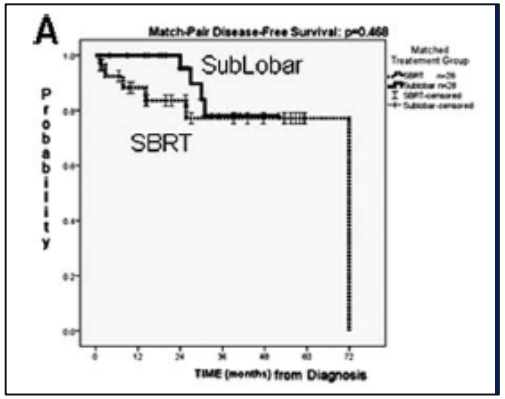
Shirvani IJROBP 2012



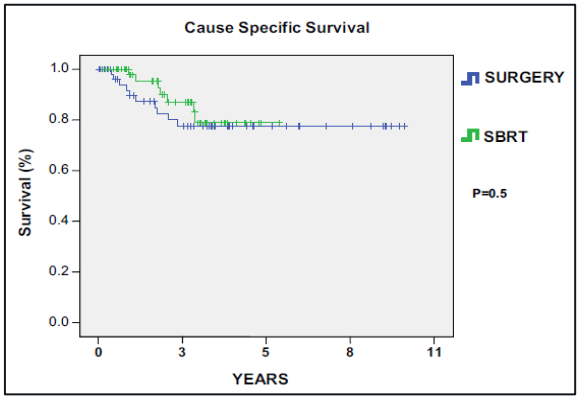
Verstegen Ann Oncol 2013



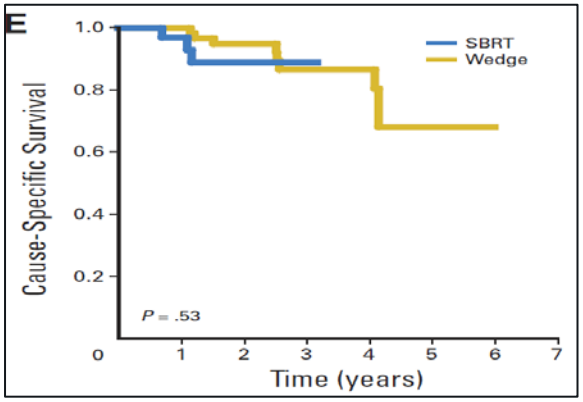
Varlotto Cacner 2013



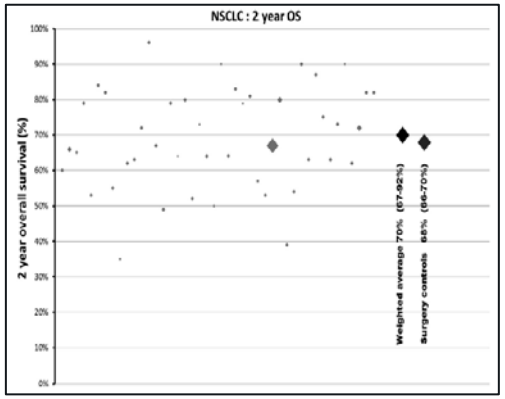
Puri JTCS 2012



Grills JCO 2010



Solda Rediother Oncol 2013



- Differences in study methodology > differences in outcome

SBRT: results of population based studies

SEER database: stage I NSCLC, age ≥65a: n=10.923

Safety **Efficacy**

OS **CSS**

Shirvani IJROBP 2012

	90 day death rate
SBRT	**0.8 %**
SLR	**5.6 %**
LE	**4.1 %**

SLR

LE

- SBRT as low-risk option for patients >65 years old

Multicenter comparison of SBRT and VATS LE

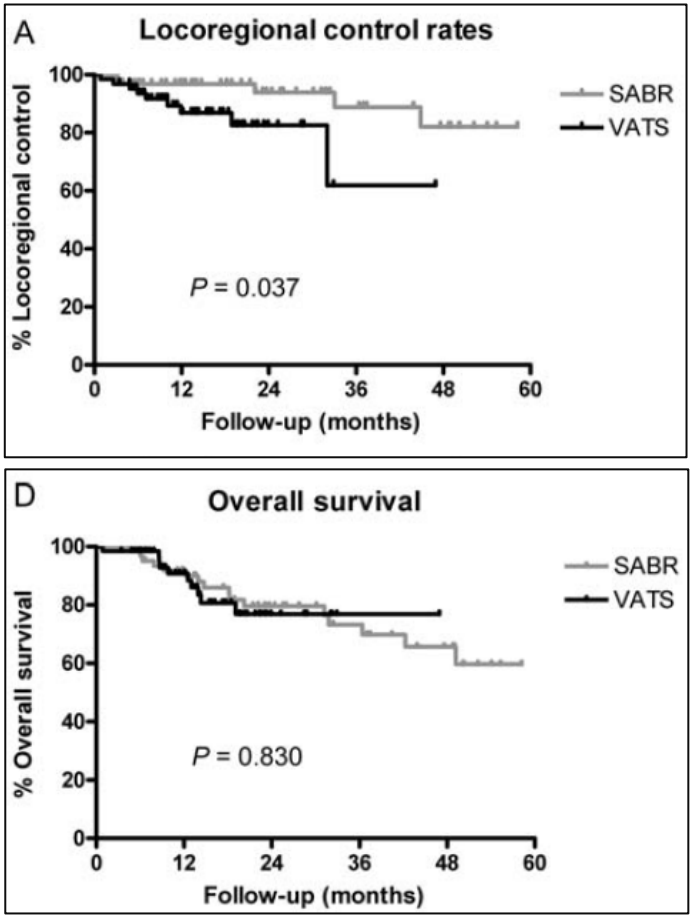
SBRT: n=64

Propensity Score matched:

- cTNM stage
- Age
- Gender
- Charlson comorbidity score
- Lung function
- Performance score

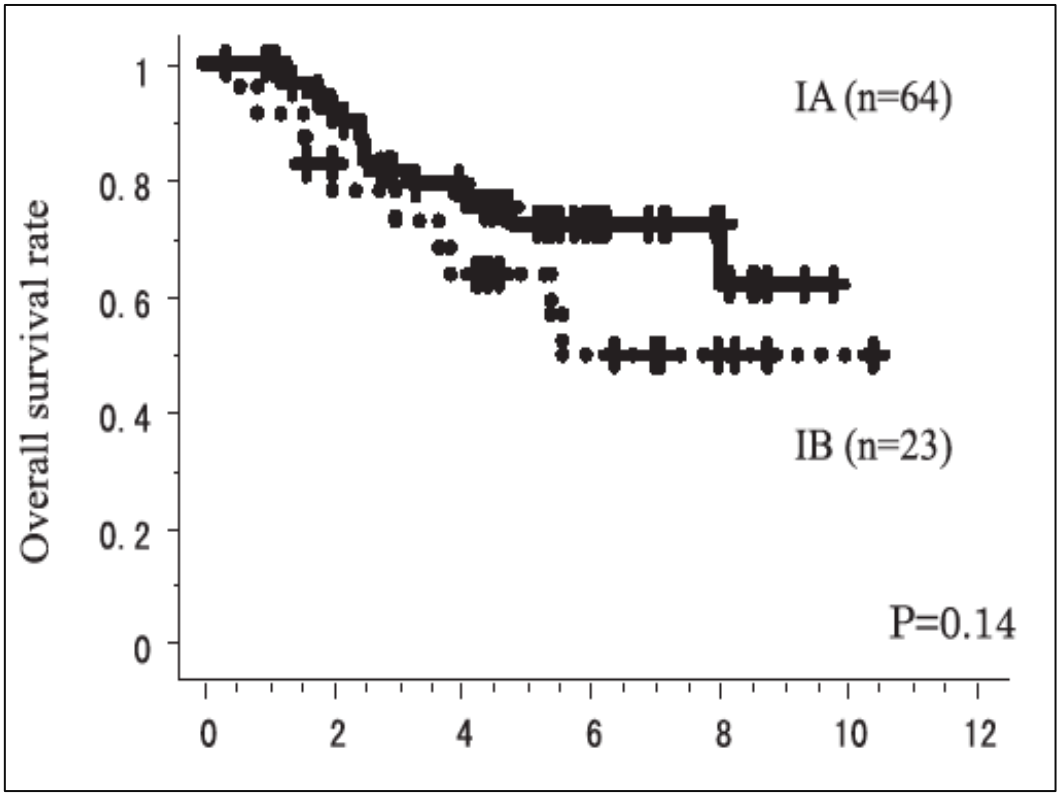
VATS LE: n=64

Verstegen Ann Oncol 2013



➢ Superior LRC and equivalent OS after SBRT compared to VATS LE

SBRT in patients who refused surgery



5a OS	IA	IB
SBRT	72%	62%

Onishi IJROBP 2011

- No apparent difference in OS between SBRT and IASLC data

Salvage RT options after SBRT failure

Isolated ***local*** failure	Isolated ***regional*** failure

Surgery:
Chen JTO 2010
Neri JTO 2010

Re-SBRT:
Peulen Radiother Oncol 2011
Valakh J Cancer Res Ther 2013

Mediastinal RT:
Ward JTO 2016

- All rare events after SBRT, distant progression is > frequent
- Individualized & multi-disciplinary savage strategy required

SUMMARY

- Mature methodology of SBRT
  - ➢ NCCN & ESMO recommended treatment
- Value of SBRT compared to previous Tx options: inoperable patients
  - ➢ BSC -> all patients unless very short OS expectancy & SBRT technically not feasible
  - ➢ CRT -> SBRT standard of care
- SBRT treatment of choice in patients refusing risk of surgical procedure
- SBRT equivalent to sublobar resection
- Lobectomy recommended treatment of choice

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

ESTRO ACROP Guideline on implementation and practice of SBRT for early stage NSCLC

UniversityHospital Zurich

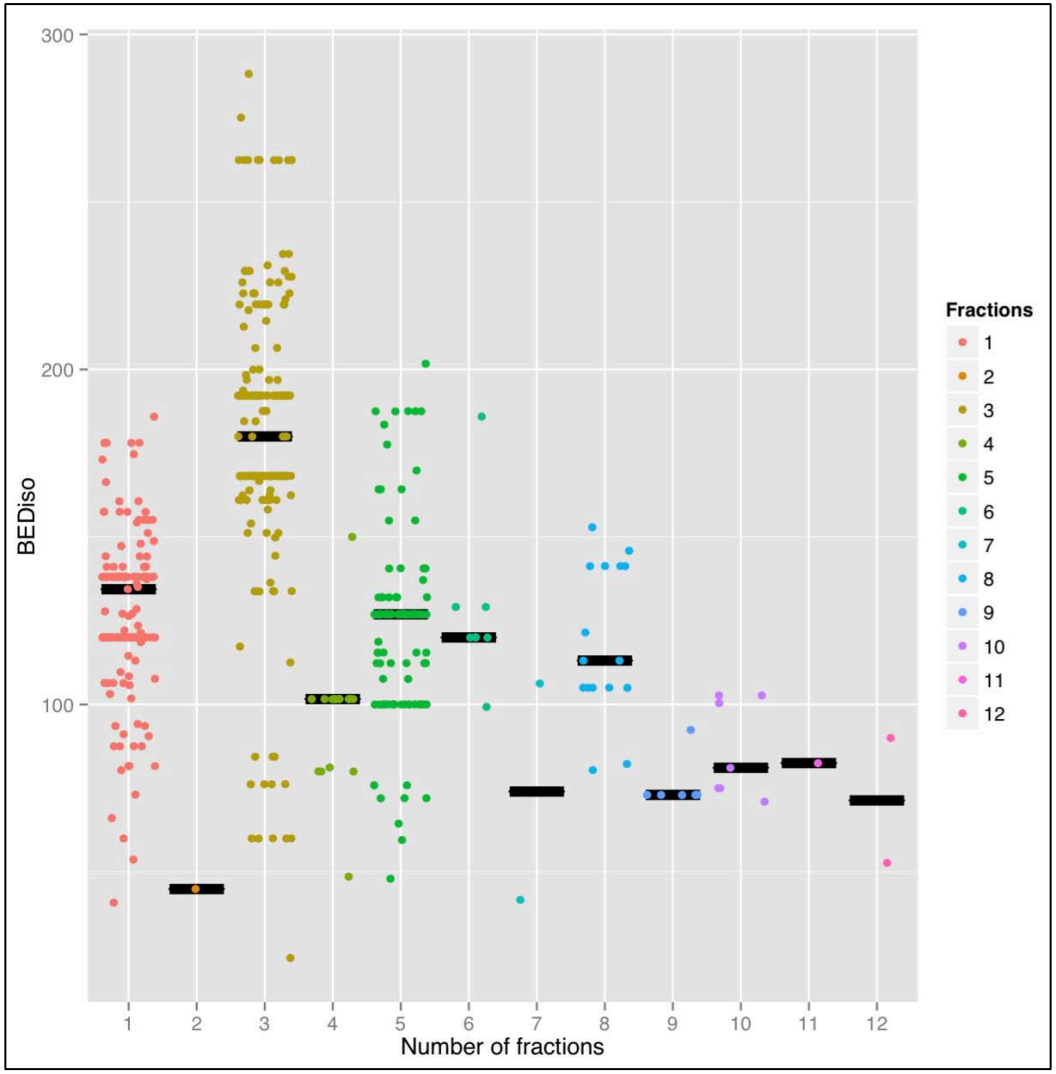
ESTRO

Question

Which of the following questions is TRUE

1) SBRT should always be performed with the latest technology only
2) SBRT requires thorough quality control
3) SBRT should preferably be performed using tracking technology

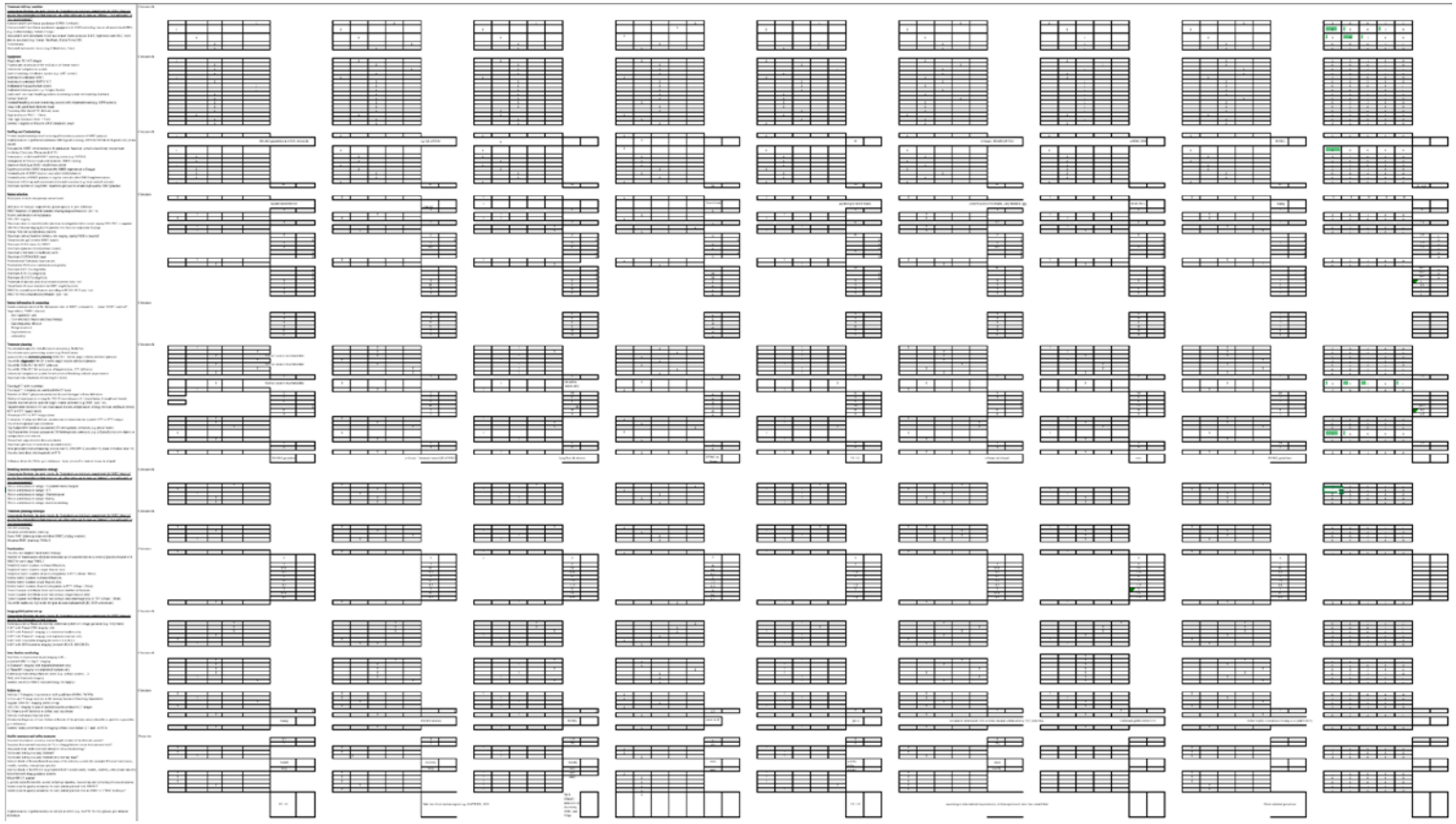
Variability in lung SBRT doses in Germany



Teachers discussing details of SBRT practice ...

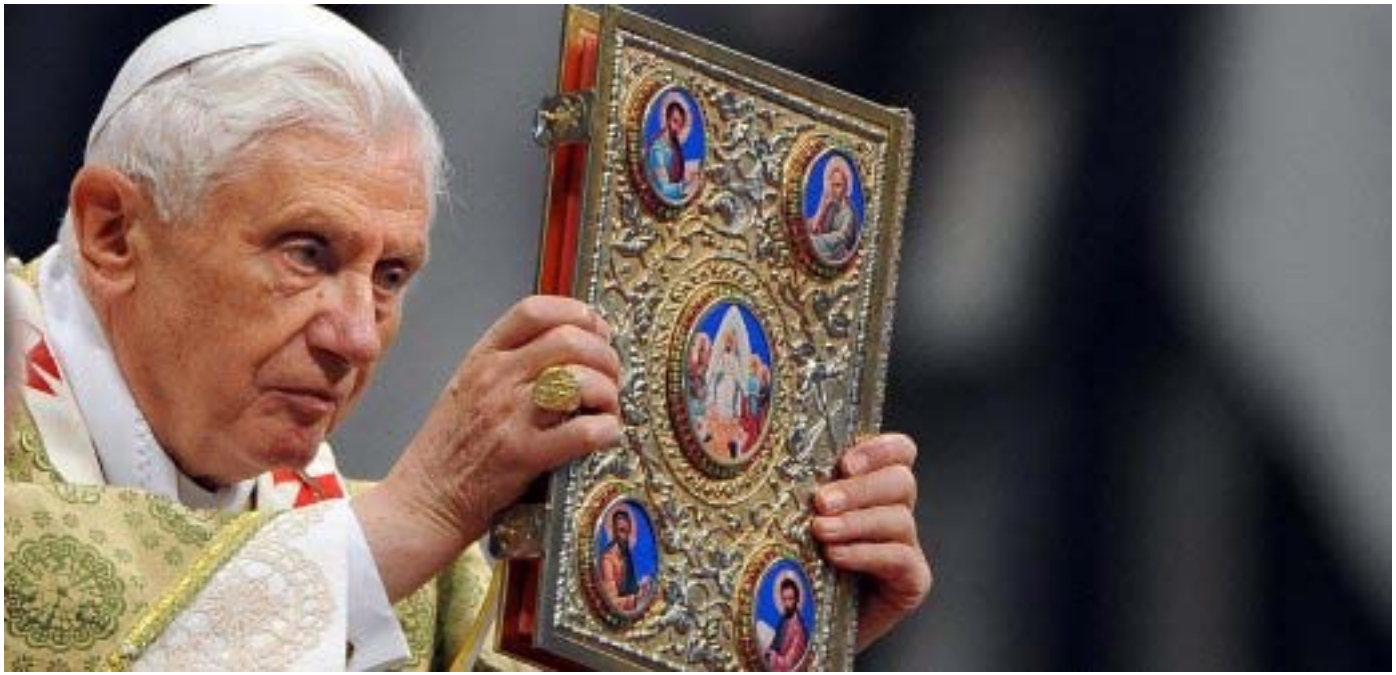

ME WANT ANSWERS
ME WANT EXPLANTIONS.
NOW!!!!!!!!
memegenerator.net

Questionnaire within ESTRO Course Faculty



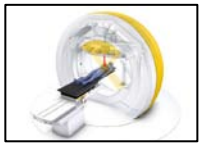
- Questionnaire of 140 items
- Covering all aspects of SBRT for stage I NSCLC

Questionnaire within ESTRO Course Faculty



Opinion from a bunch of ESTRO teachers !

Linac / device for lung SBRT



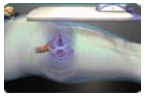
?

Device	*Mandatory*	*Recommended*	*Optional*	*Not sufficient*	*Not recommended*
Conventional C-arm linac (EPID, 1cm leafs)	1	0	0	**5**	2
Conventional C-arm linac with IGRT technology (more advanced than EPID)					
Dedicated C-arm stereotactic linac (more advanced IGRT, high-resolution MLC, better accuracy)					
Tomotherapy					
Dedicated stereotactic device					

Additional devices ...

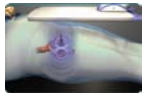
Mandatory

Recommended



Additional devices ...

Optional



	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**

Additional devices ...

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

Staffing and Credentialing

	Mandatory	*Recommended*	*Optional*
Participation in dedicated SBRT teaching course (e.g. **ESTRO**)	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

Patient selection for SBRT: Patient characteristics

Relevant!

Not relevant!

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

Patient selection for SBRT: Tumor characteristics

Maximum target size

Patient selection for SBRT: Procedures

Mandatory

Mandatory ***Recommended***

Recommended

Patient selection for SBRT: Procedures

Optional or not recommended

- EBUS/EUS nodal staging in cN0 patients who have no suspicious findings
- Pre-tratment Perfusion-ventilation scintigraphy

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	**3**	4

Treatment planning

Recommended

	Mandatory	*Recommended*	*Optional*
Use of a fixed dose inhomogeneity in PTV	1	**5**	1

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 the diagnostic FDG-PET in the target volume definition process
- Use of stereotactic positioning system (e.g. BodyFrame)
- Acquisition of a dedicated planning FDG-PET for the target volume definition process
- Use of the FDG-PET for evaluation of target motion, ITV definition
- Use of patient-specific immobilization device (e.g. BodyFix)
- Abdominal compression system for reduction of breathing induced target motion

Treatment planning

"Just work till midnight, you need to relax too"

Treatment planning

Median

Maximum slice thickness of planning CT

Maximum gird size for dose dose calculation

Median

GTV - CTV margin

Minimum CTV - PTV margin

Treatment planning: Breathing motion compensation

	Mandatory	*Recommended*	*Optional*	*Not sufficient*
Population-based margins				
ITV				
Midventilation				
Gating				
Real-time tracking				

Treatment planning: Planning technique

	Mandatory	*Recommended*	*Optional*
3D CRT planning			
Dynamic conformal arc planning			
Static IMRT planning			
Dynamic IMRT planning			

Treatment planning: Fractionation

Mandatory:

Risk adapted fractionation 7

	Institutional specific fractionations	Consensus fractionation	BED10 of consensus fractionation
Peripheral location	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 location	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**

Image guidance

	Mandatory	*Recommended*	*Optional*	Not recommended / sufficient
Stereotactic set-up based on external coordinate system w/o image guidance				
IGRT with Planar EPID imaging only				
IGRT with Planar kV imaging w/o implanted markers only				
IGRT with Planar kV imaging with implanted markers only				
IGRT with Volumetric imaging (in-room CT, CBCT)				
IGRT with 4D Volumetric imaging (in-room 4D-CT, 4D-CBCT)				

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

Follow-up

Recommended & optional

	Mandatory	*Recommended*	*Optional*
Follow-up CT image analysis at the treating Radiation Oncology department			
Routine biopsy confirmation of imaging-defined local failure			
Regular FDG-PET imaging for follow-up			
Periodic pulmonary function tests			

Accuracy of the treatment device

Required mechanical accuracy of the delivery system?
(vector length in mm)

1.7

Required dosimetrical accuracy in a lung phantom inside the treatment field?
(in %)

2.3

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**

Overview

SBRT workflow or equipment items	Mandatory (minimum) requirements	Recommended for best practice
Equipment		
	C-arm linear accelerator with volumetric in-room image guidance	Dedicated C-arm stereotactic linear accelerator (more advanced IGRT, more precise accuracy)
	Respiration correlated 4D-CT	High-resolution MLC < 10mm
Staff teaching, training and credentialing		
	Written departmental protocols	Participation in dedicated SBRT teaching course (e.g. ESTRO)
	Multi-disciplinary project team for SBRT implementation and application	Participation in Vendor-organized dedicated SBRT training
	Structured follow-up for clinical outcome assessment	Hands-on training at SBRT-experienced centre
		Supervision of first SBRT treatments by SBRT-experienced colleague
Patient selection for SBRT		
	Discussion in interdisciplinary tumor board	Biopsy confirmation of malignancy
	Minimum ECOG 3	
	Minimum life expectancy of 1 year	
Treatment planning		
	3D conformal treatment planning	Dynamic IMRT planning (VMAT)
	Type B algorithms	Use of a fixed dose inhomogeneity in PTV
	Respiration correlated 4D-CT imaging	
	ITV based motion management strategy	
Dose and fractionation		
	Risk adapted fractionation schemes for peripheral and central tumors and tumor for 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)
Follow-up		
	Follow-up according to published guidelines	Routine biopsy confirmation of imaging-defined local failure
	FDG-PET imaging in case of suspected local recurrence	
Quality assurance		
	Intensified quality assurance (mechanical accuracy of 1.25 mm and a dosimetric accuracy of 3% in a lung phantom inside the treatment field)	End-to-end testing in a moving 4D lung phantom
	Small field dosimetry detectors for commissioning	
	End-to-end testing in a lung phantom	
	Quality assurance of in-room image-guidance systems and of the 4D-CT scanner	
	Weekly checks of the mechanical accuracy of the delivery system	
	Daily quality checks of the alignment of the IGRT system with the MV treatment beam	

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

SBRT, CZE experience

Coen Hurkmans, Ph.D., clinical physicist

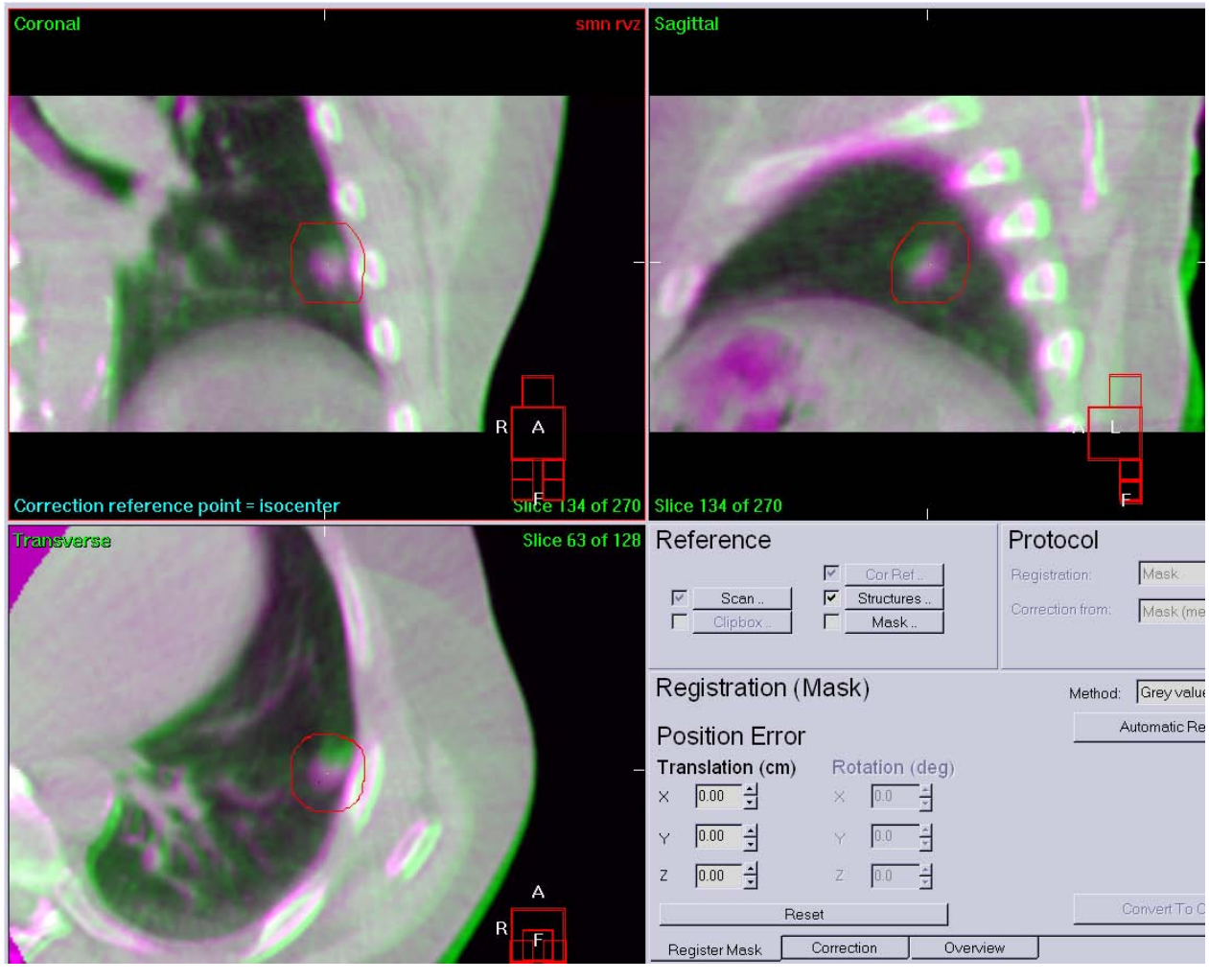
Catharina Hospital, The Netherlands

catharina hospital

Content

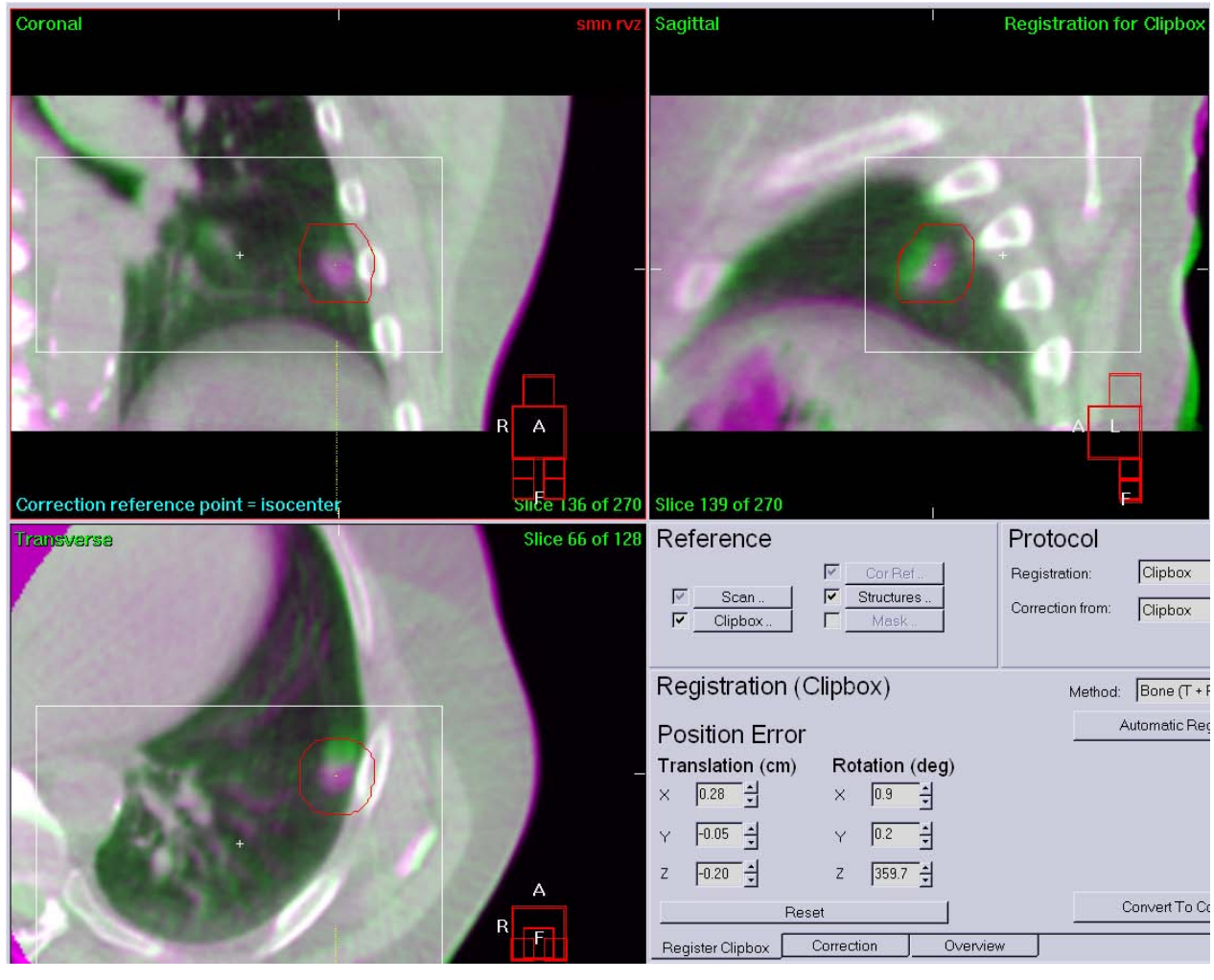
- Lung Intrafraction motion
- CVDR
- Online 4D CBCT
- CZE results on set-up and dose verification
- Lungtech trial guidelines
- Brainmets trial guidelines
- Brainmets guidelines

Clinical casus: intra-fraction motion



Fraction 1
unmatched

catharina hospital



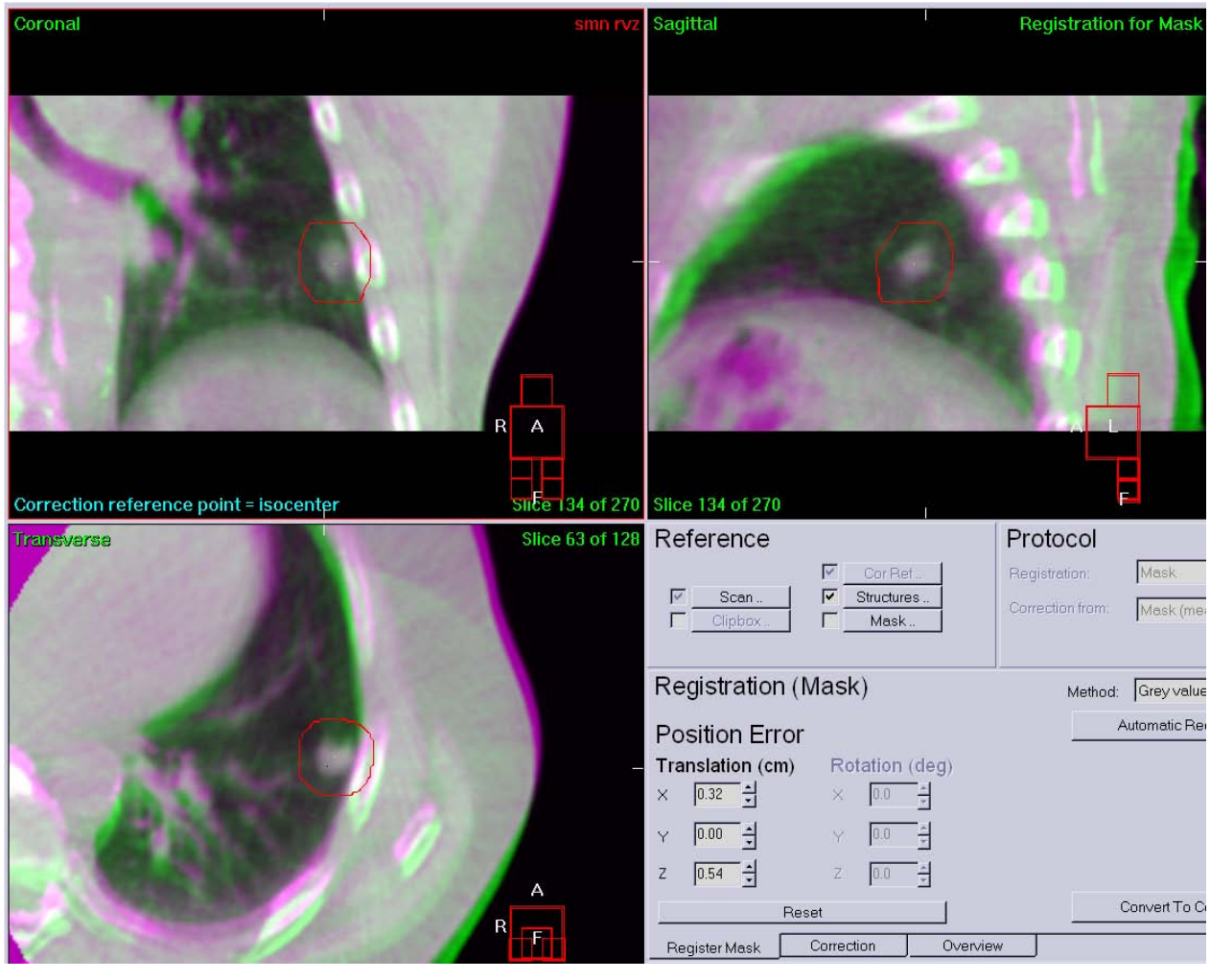
Fraction 1 bone match

X= 0.28

Y=-0.05

Z=-0.20

catharina hospital



Fraction 1 tumormatch

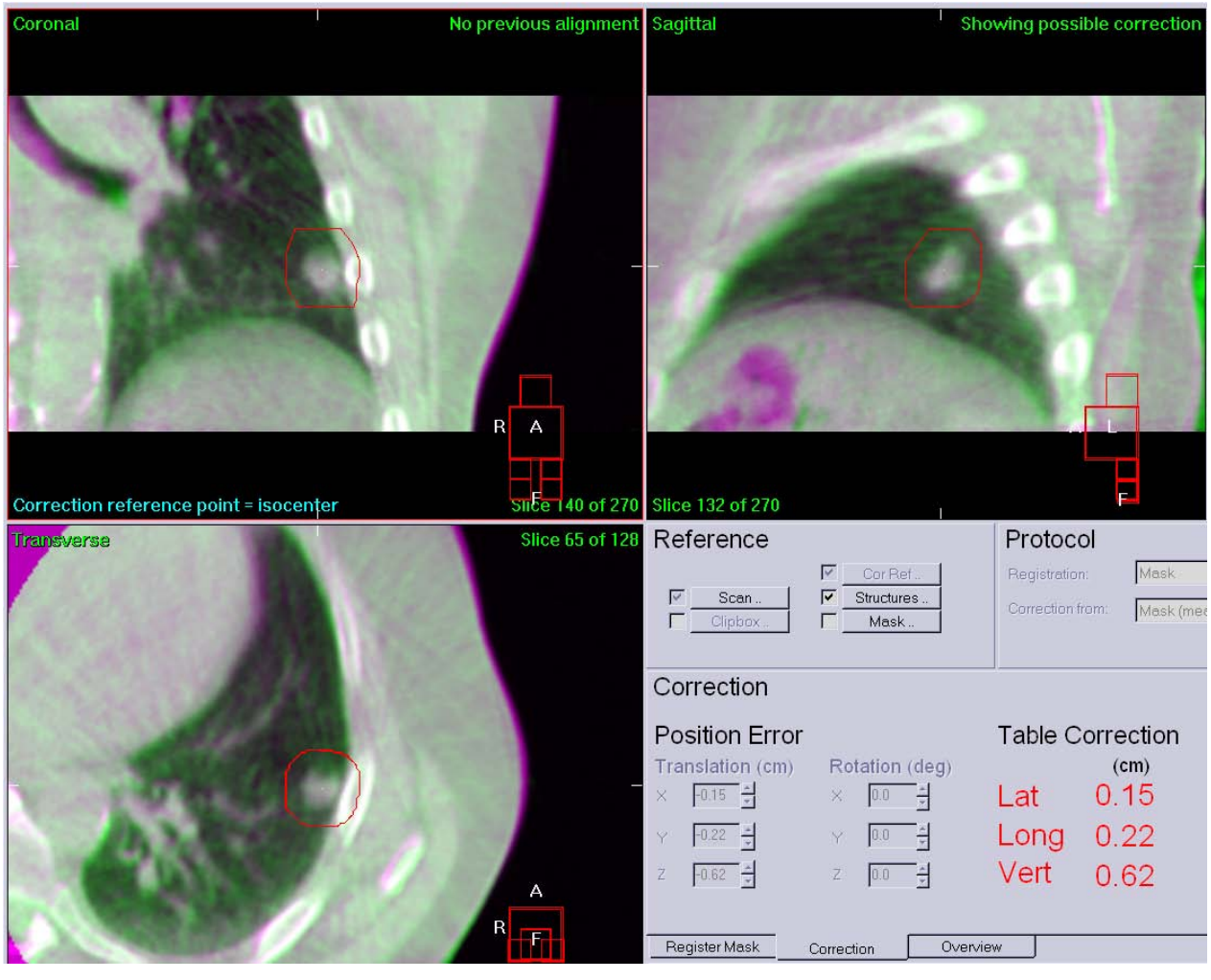
X= 0.32 (0.28)

Y=0.00 (-0.05)

Z=0.54 (-0.20)

Tumor shift of >7 mm!

catharina hospital



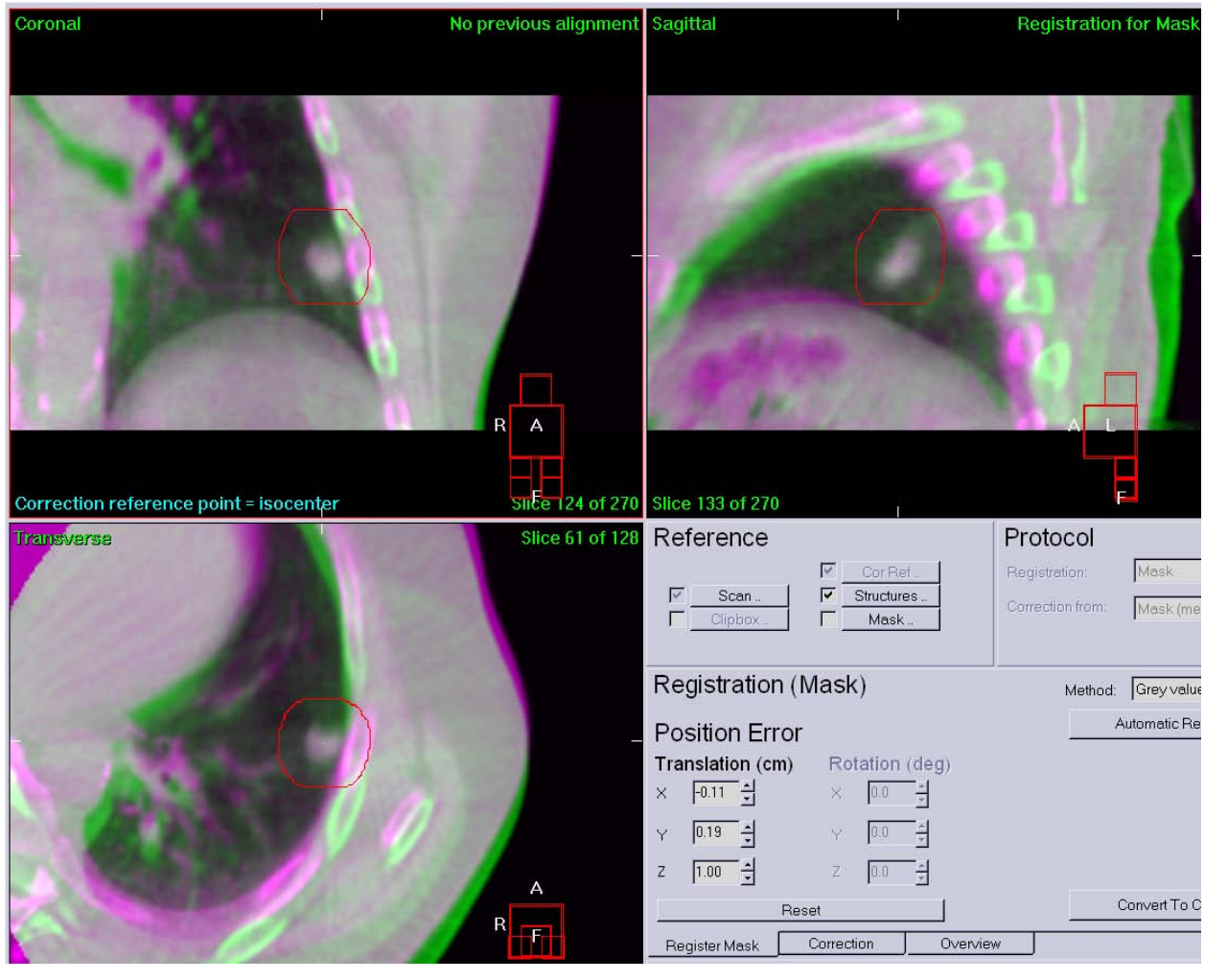
After Fraction 1 tumormatch

X=0.15

Y=0.22

Z=0.62

catharina hospital



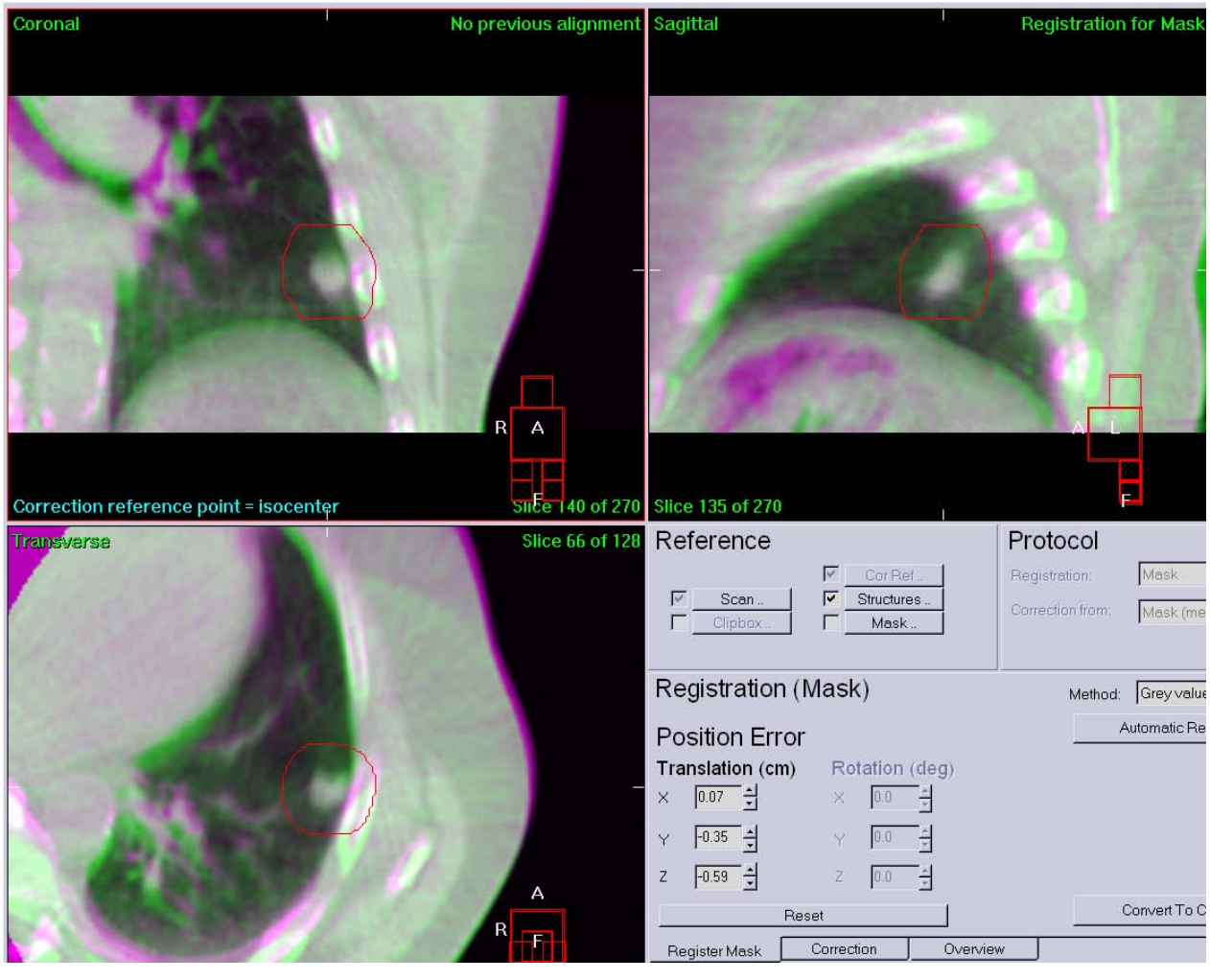
Fraction 3
tumormatch

X=-0.11

Y=0.19

Z=1.00

catharina
hospital



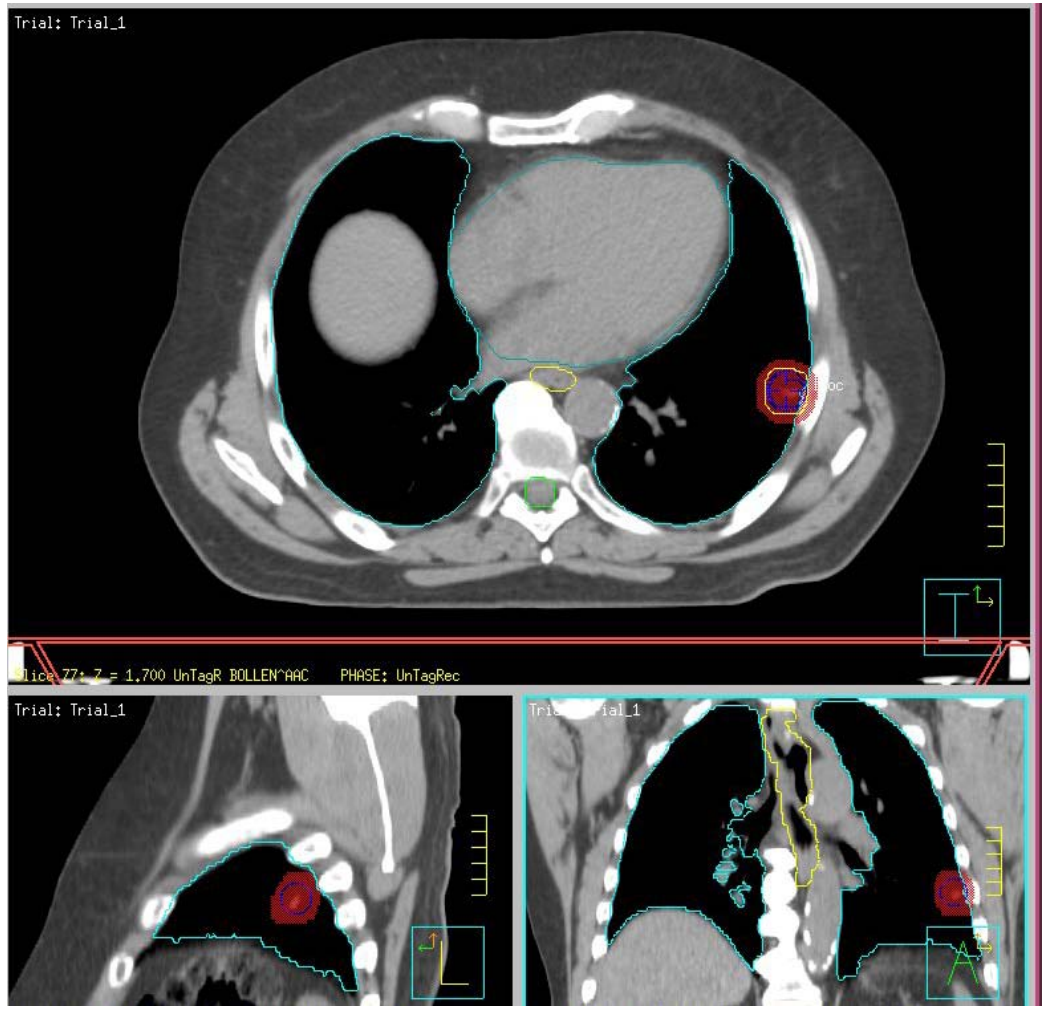
Fraction 3 after 1 arc tumormatch

X=0.07

Y=-0.35

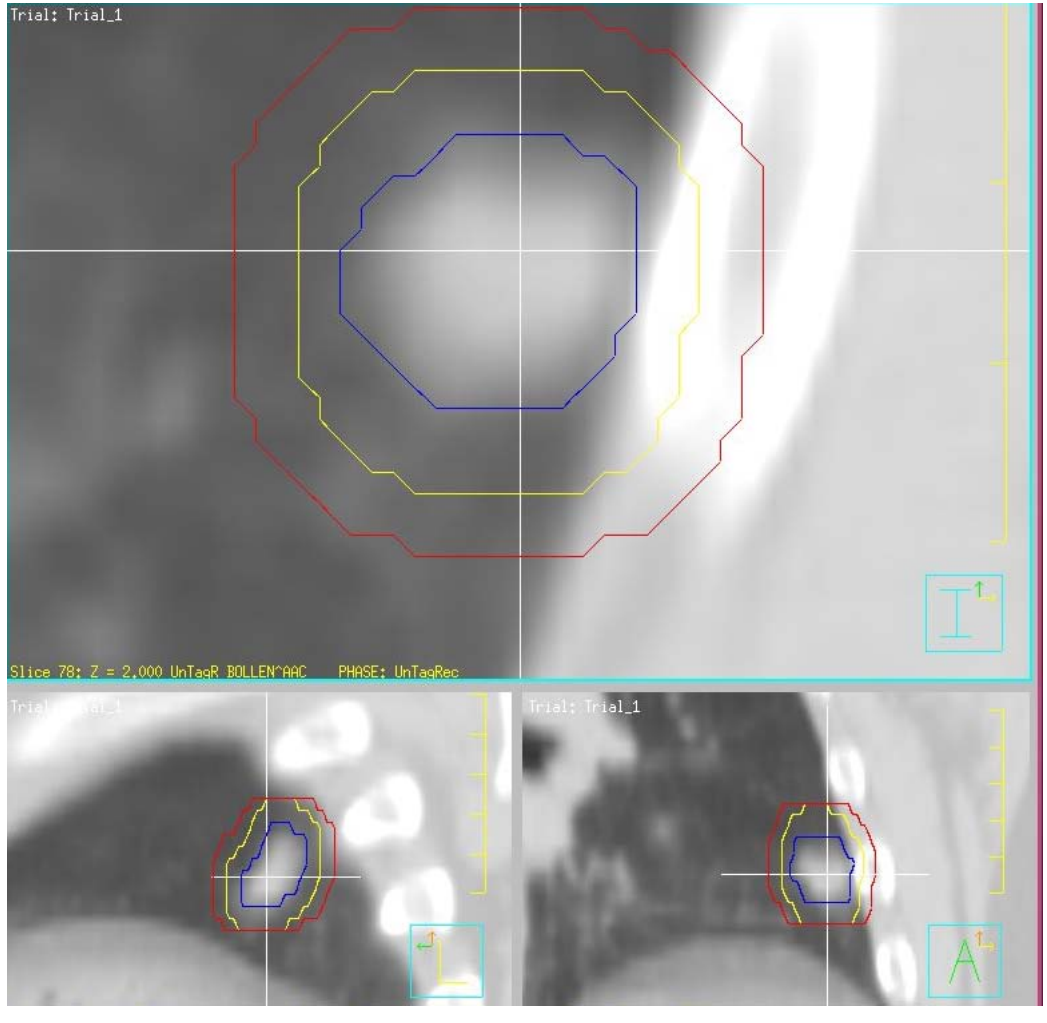
Z=-0.59

catharina hospital



Original plan
5 x 11 Gy

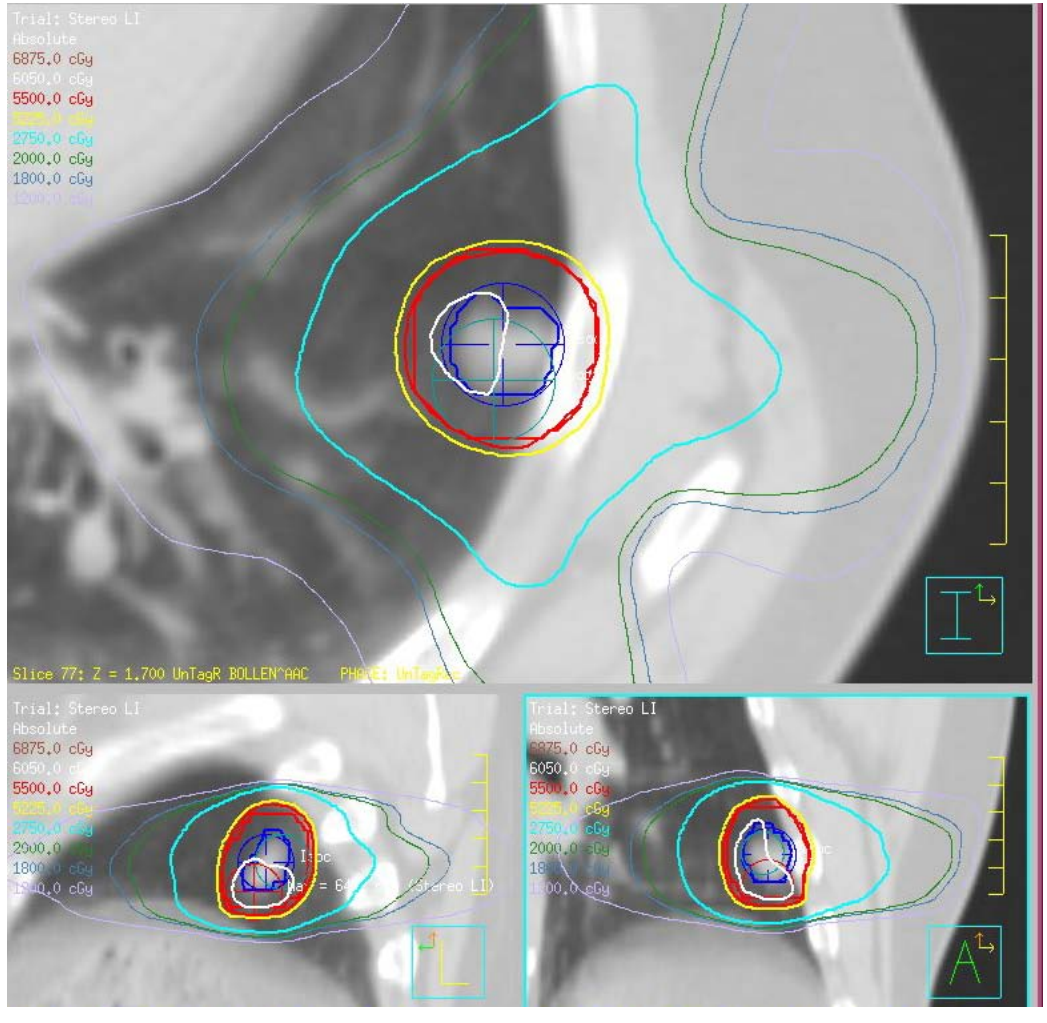
catharina hospital



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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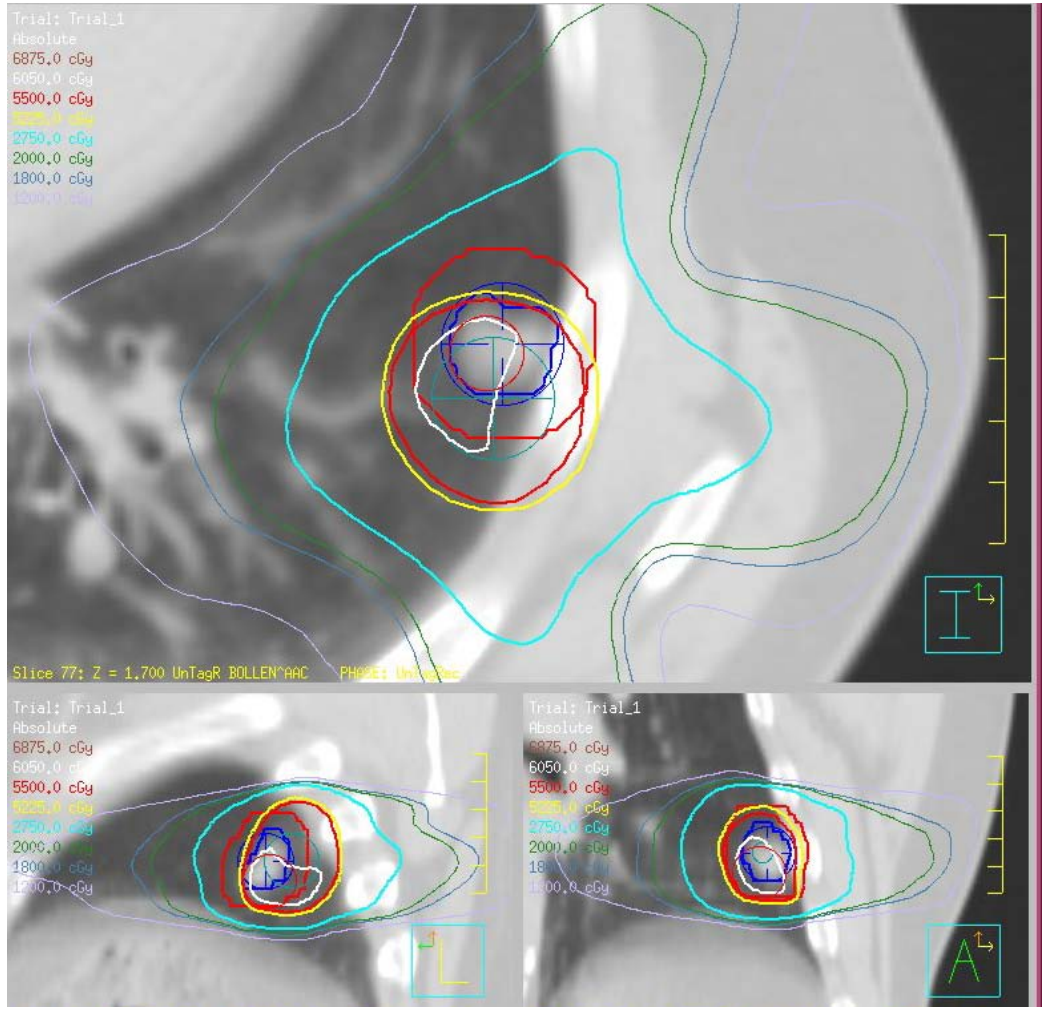
Original plan with shift



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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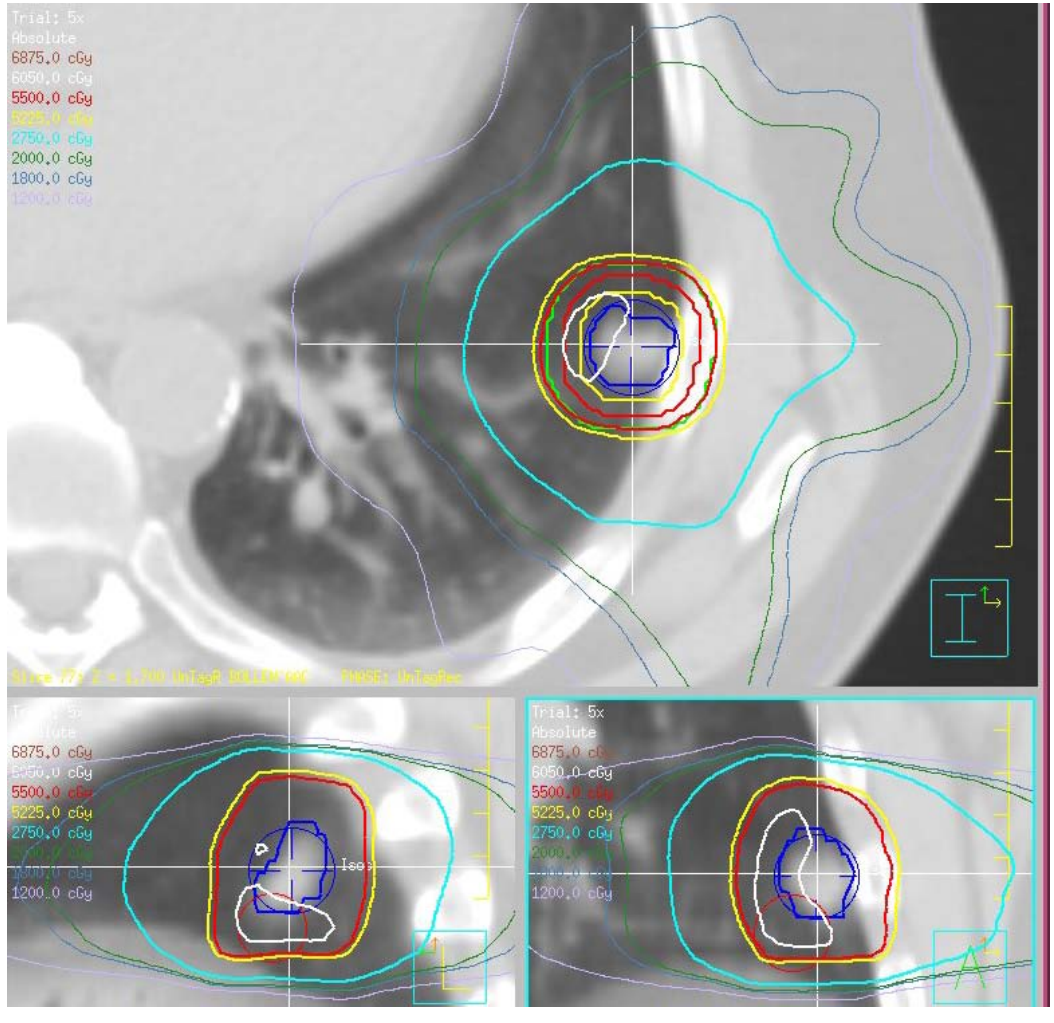
New plan with 3mm extra margin



PTVnew

V100% = 97.2%

PTV

V100% = 100%

Thorax

V37Gy = 26.8cc

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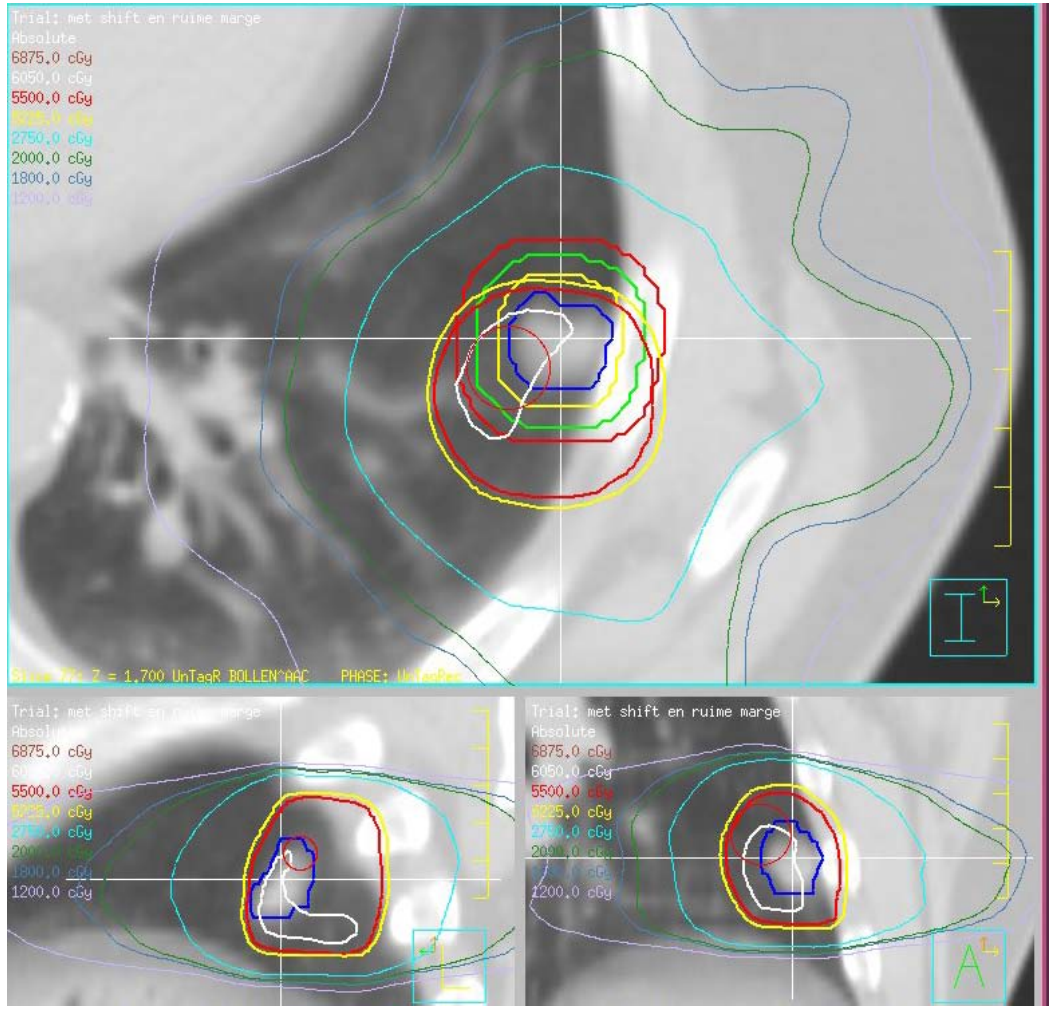
New plan with shift: robust?



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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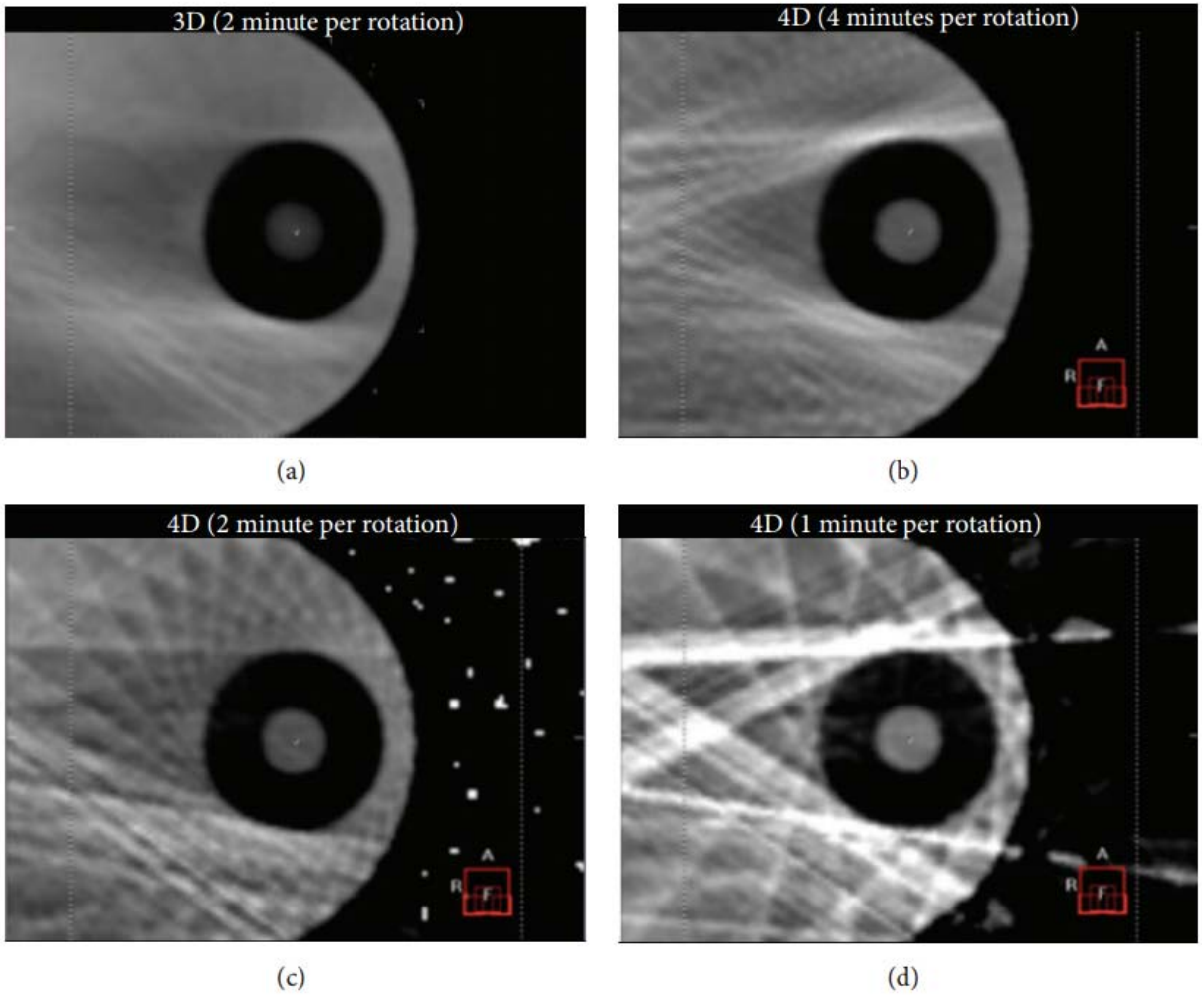
Online 4D CBCT



mages (axial view) for a moving phantom (QUASAR; Modus Medical Devices, Inc.): (a) 3D (2 minut
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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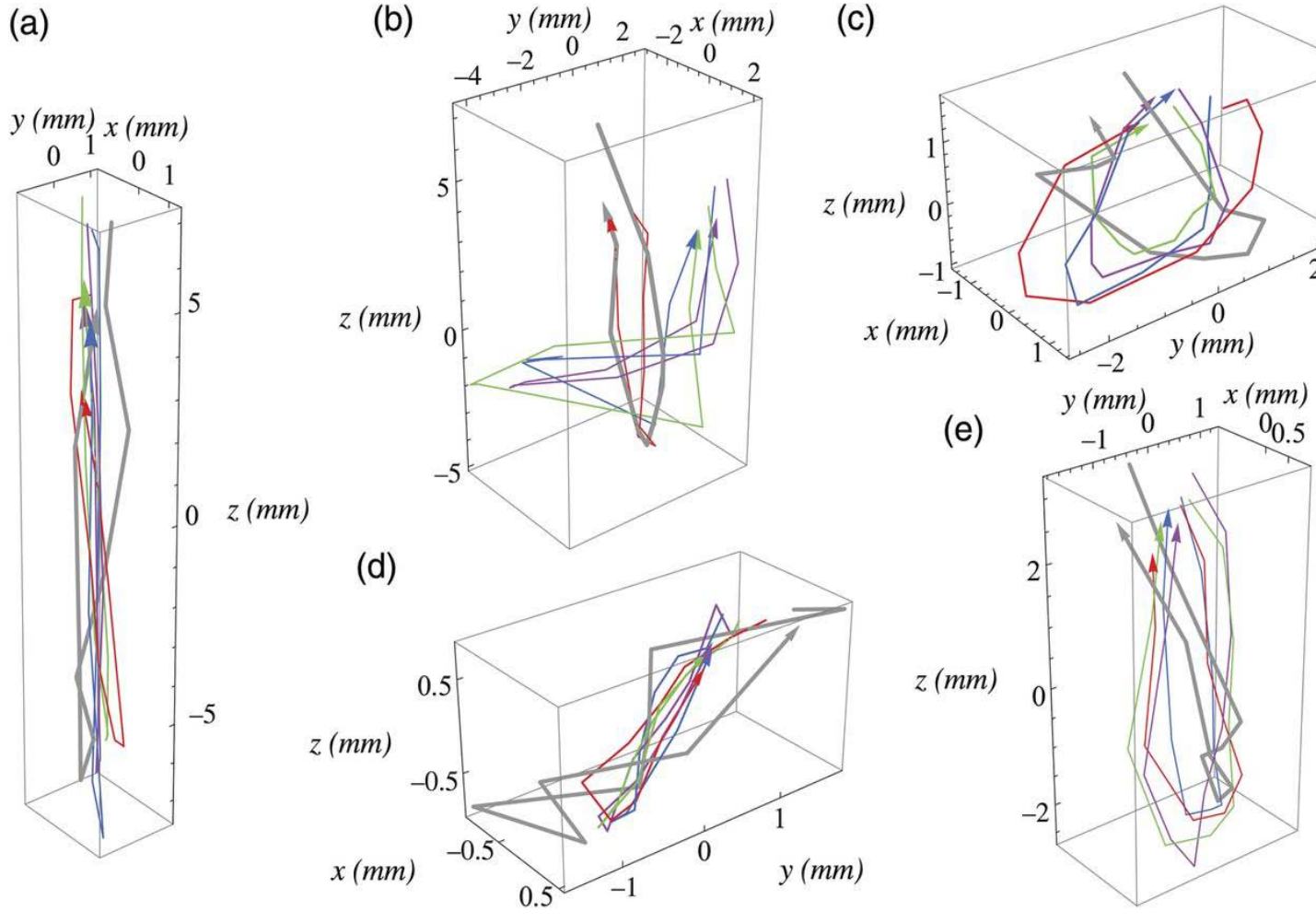
Online 4D CBCT

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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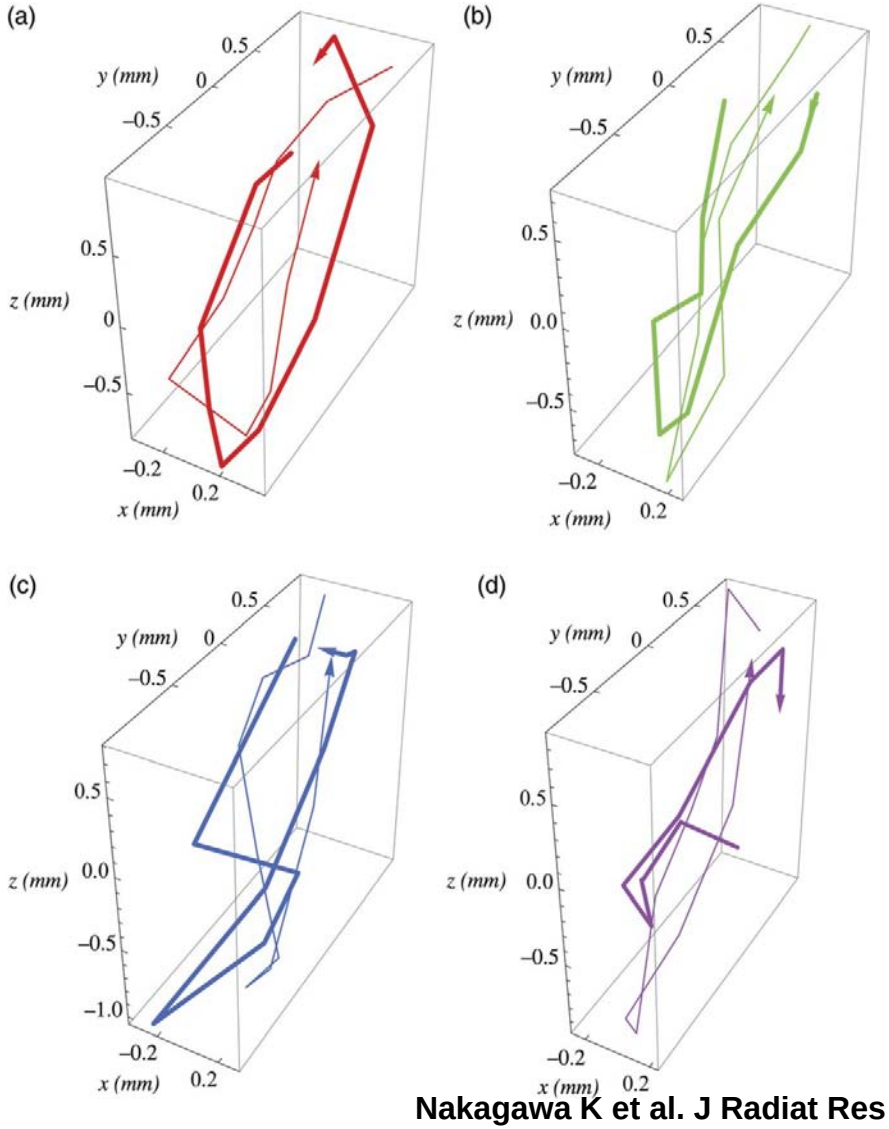
Online 4D CBCT



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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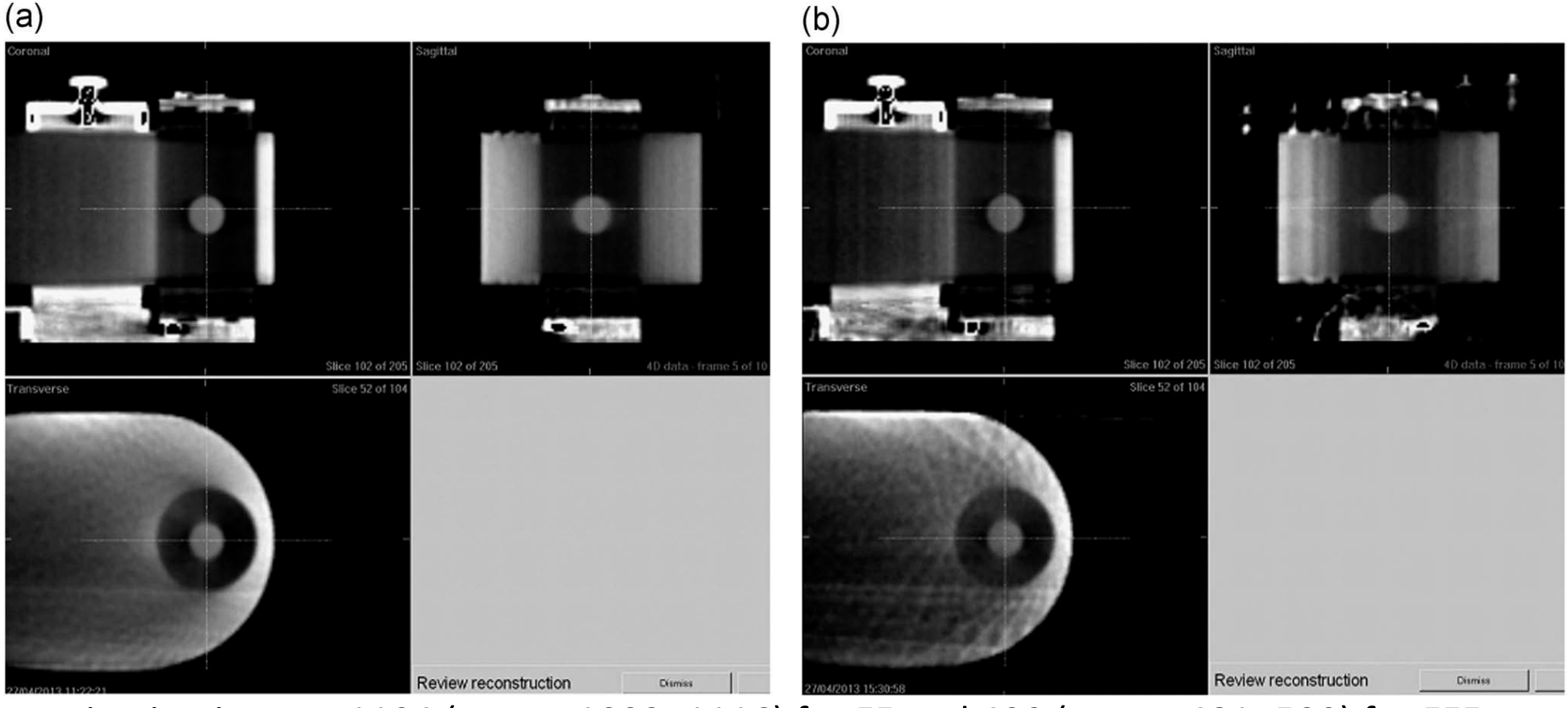
Online 4D CBCT

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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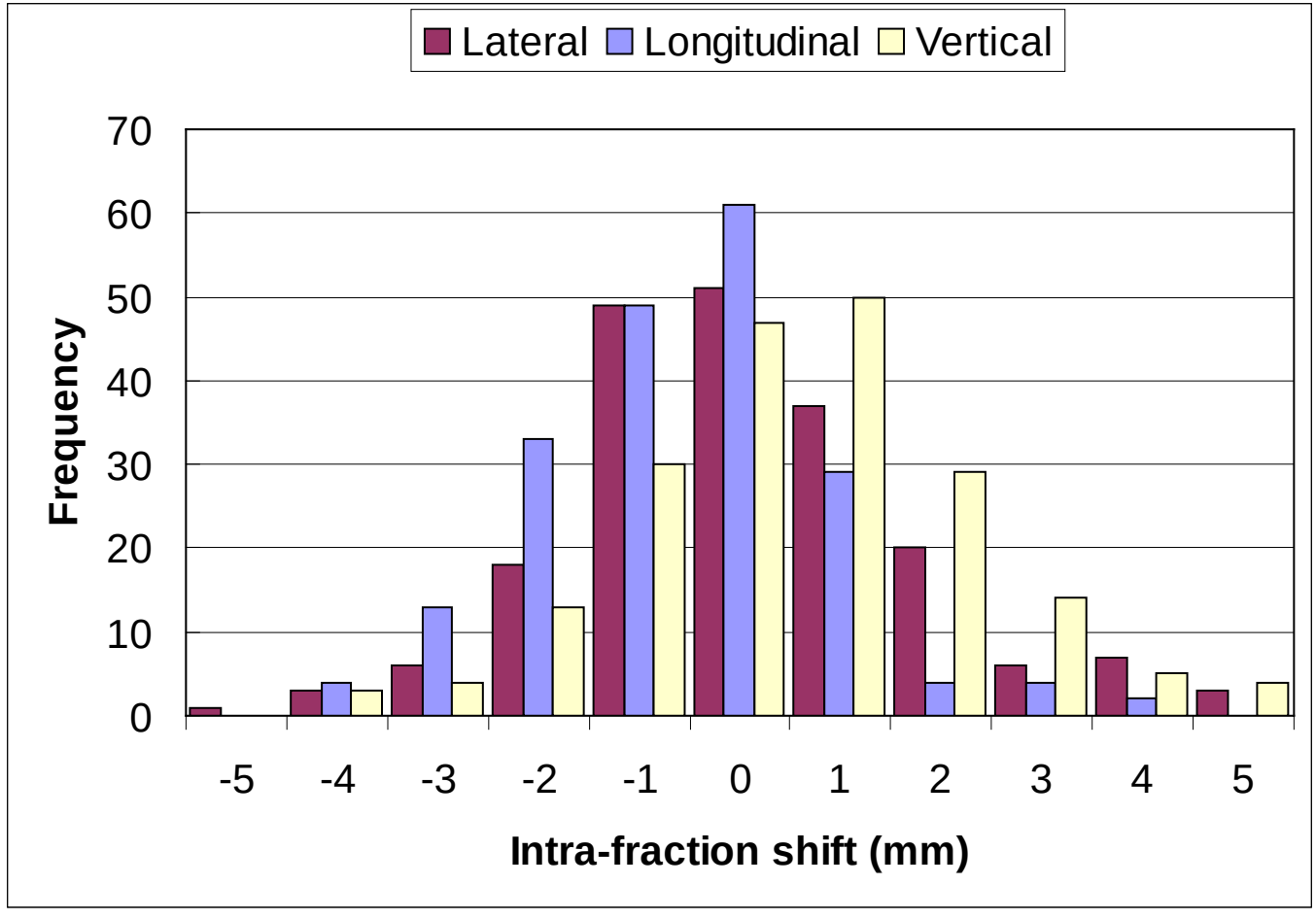
Journal of Radiation Research

Intra fraction stability CZE



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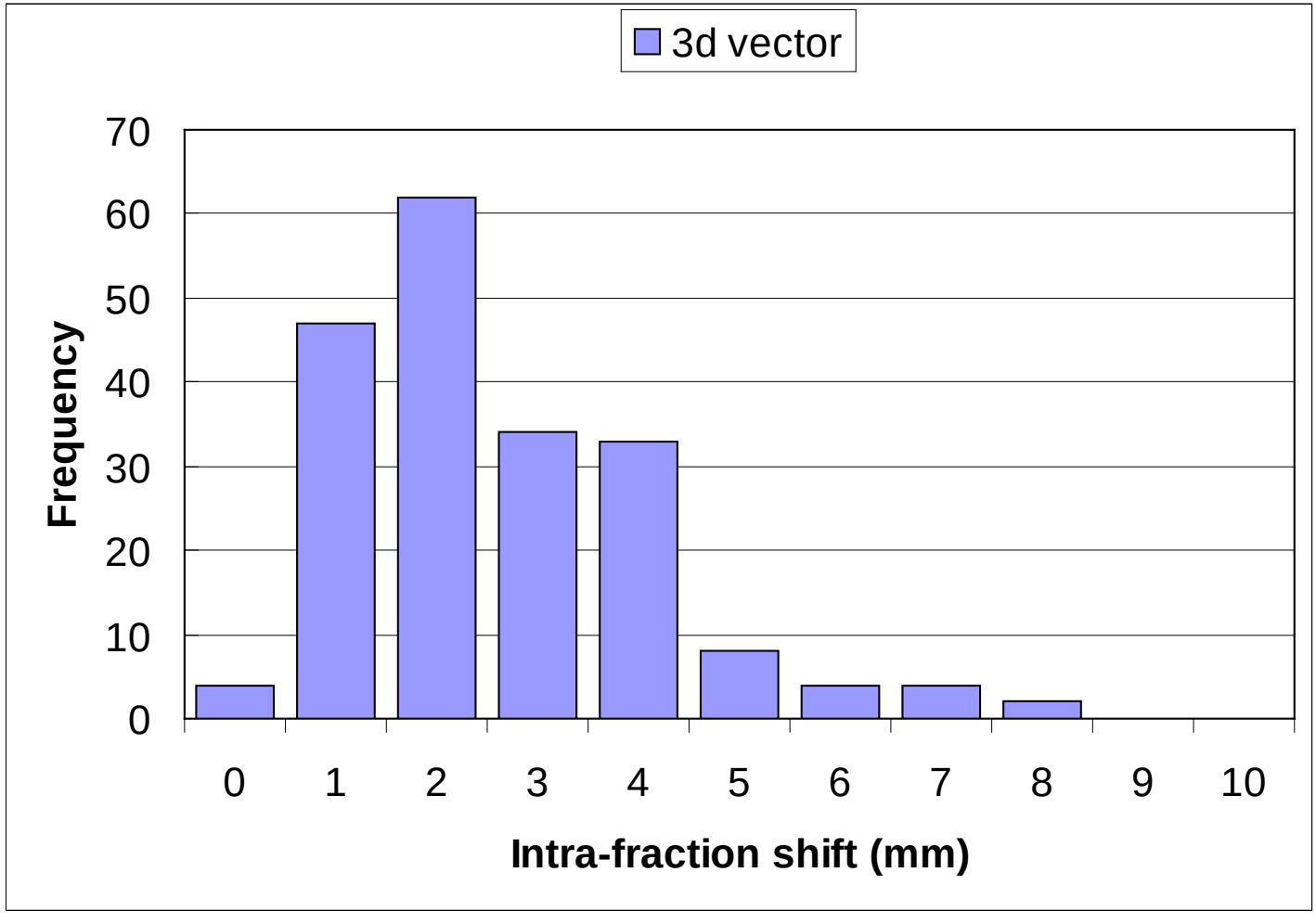
Intra fraction stability CZE



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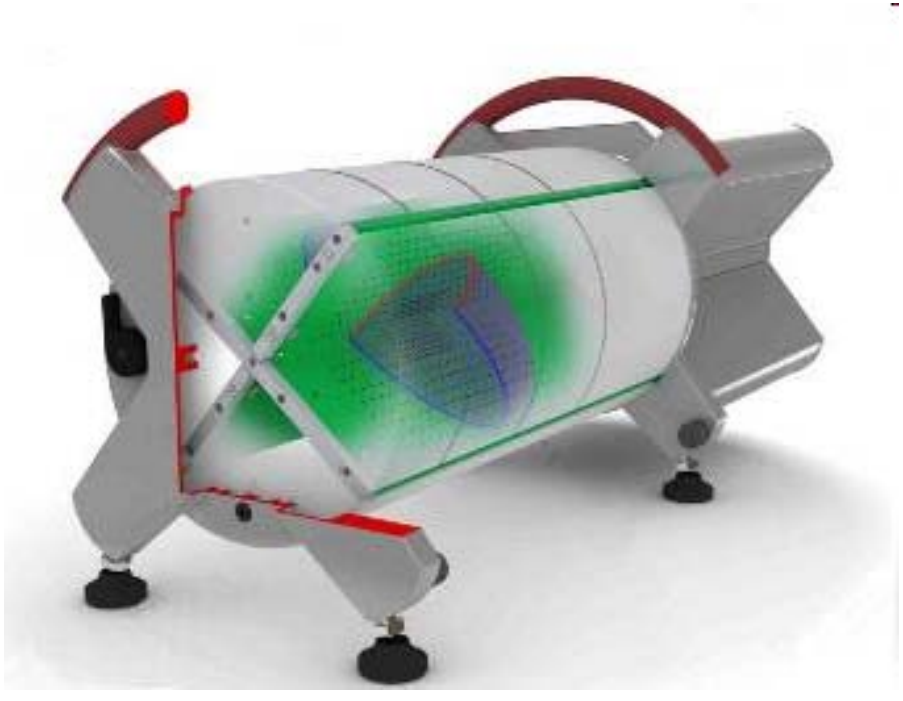
Patient specific dosimetry CZE



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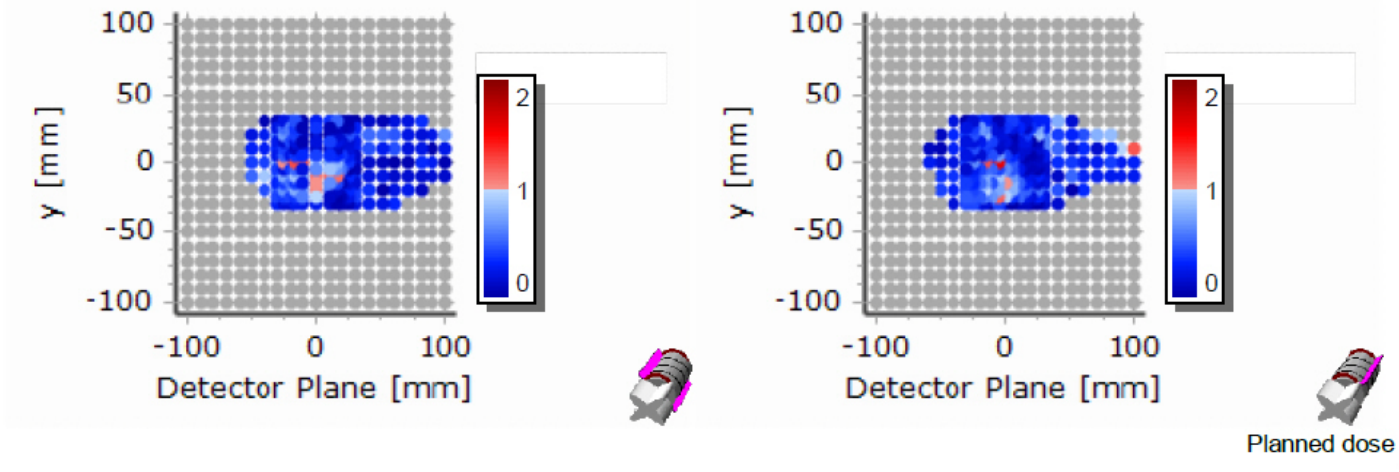
Gamma analysis

Parameter Definitions & Acceptance Criteria, Detectors

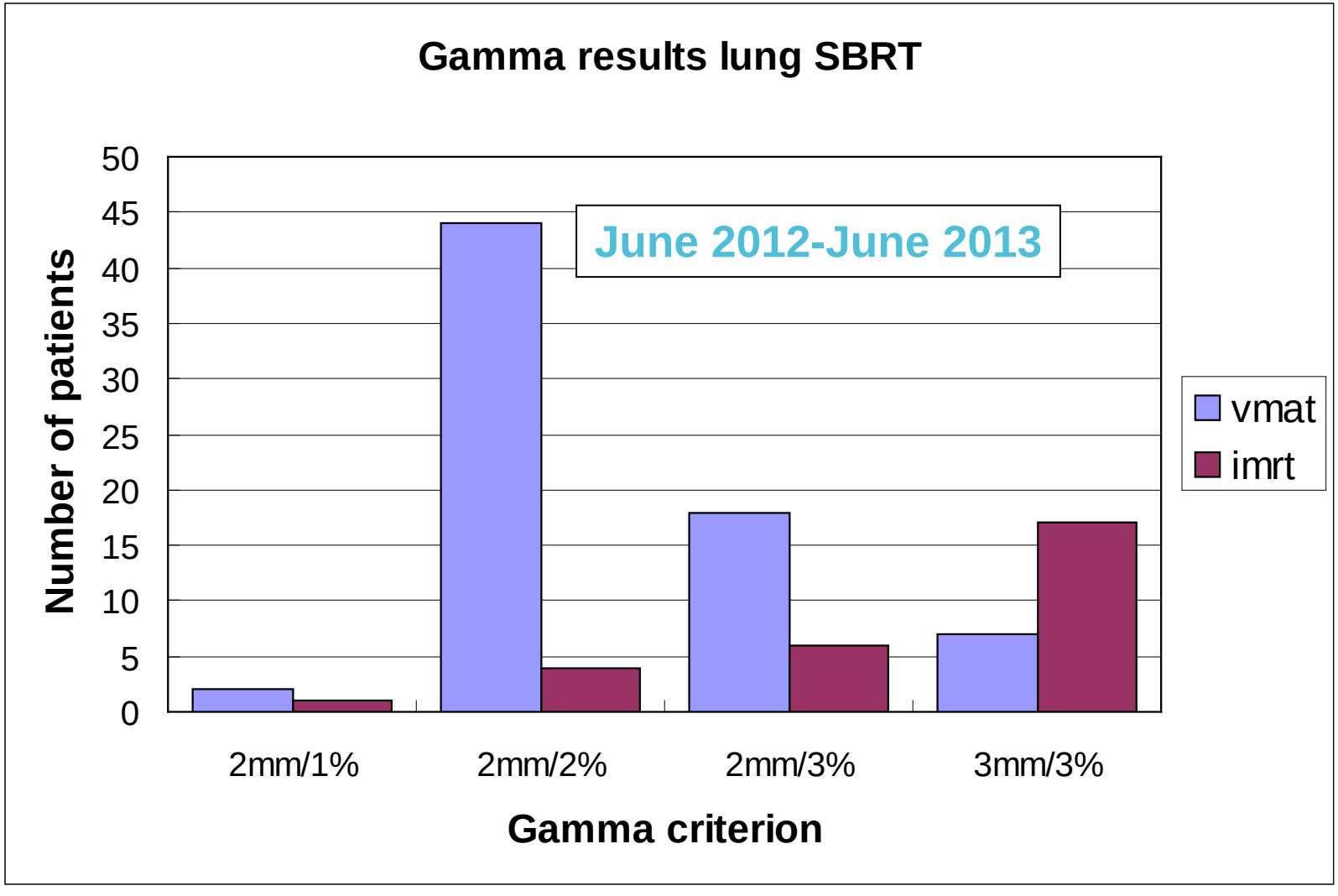
Parameter	Selected Detectors	Δ Dose	Δ Dist	Acceptance Limits
Dose Deviation	Dose from 20% to 500%	n.a.	n.a.	90% within ±3.0%
Dist to Agreement	Gradient >= 1%/mm	n.a.	n.a.	90% with DTA <= 2.0 mm
Gamma Index	Dose from 20% to 500%	±3.0%	2.0 mm	95% with gamma < 1

Gamma index, Fraction



Planned dose

Gamma results



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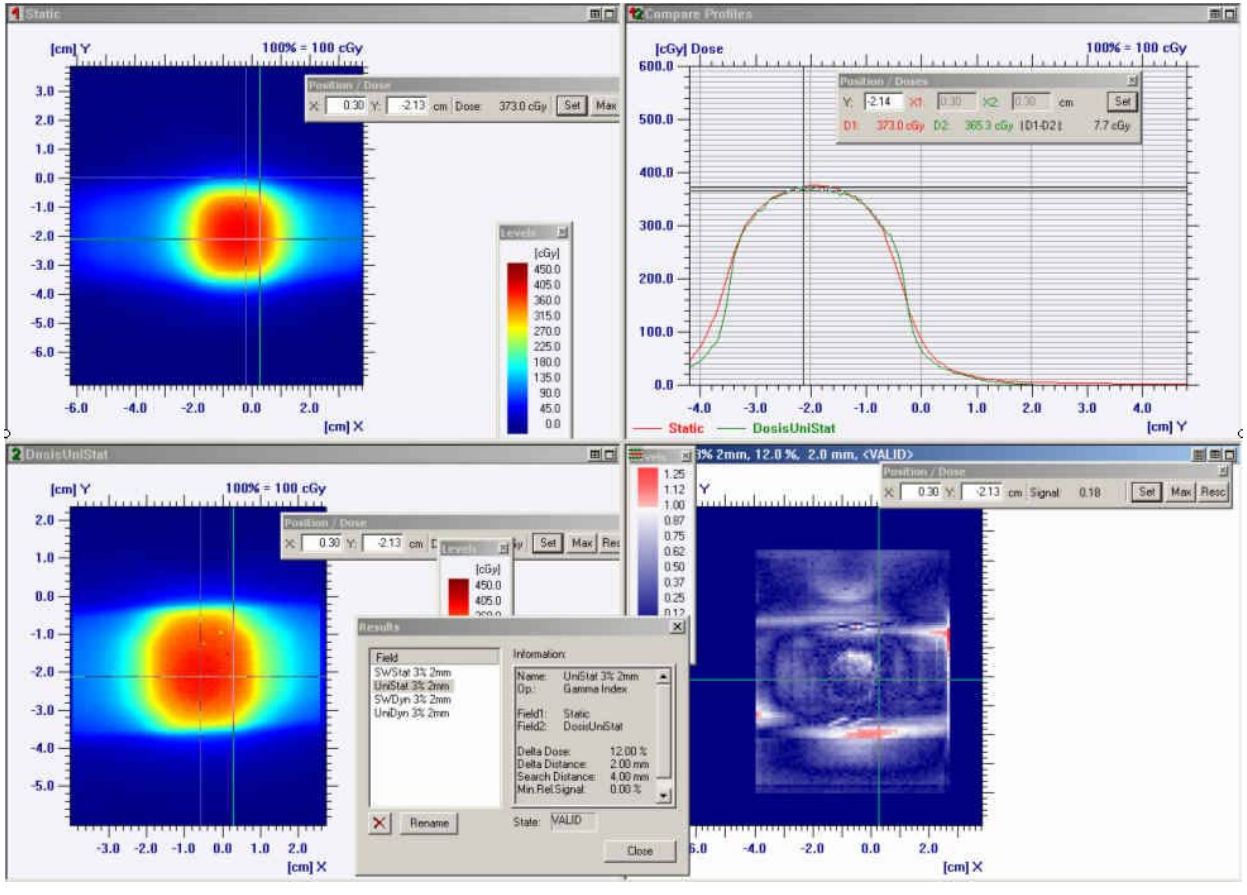
4D Dosimetry QA

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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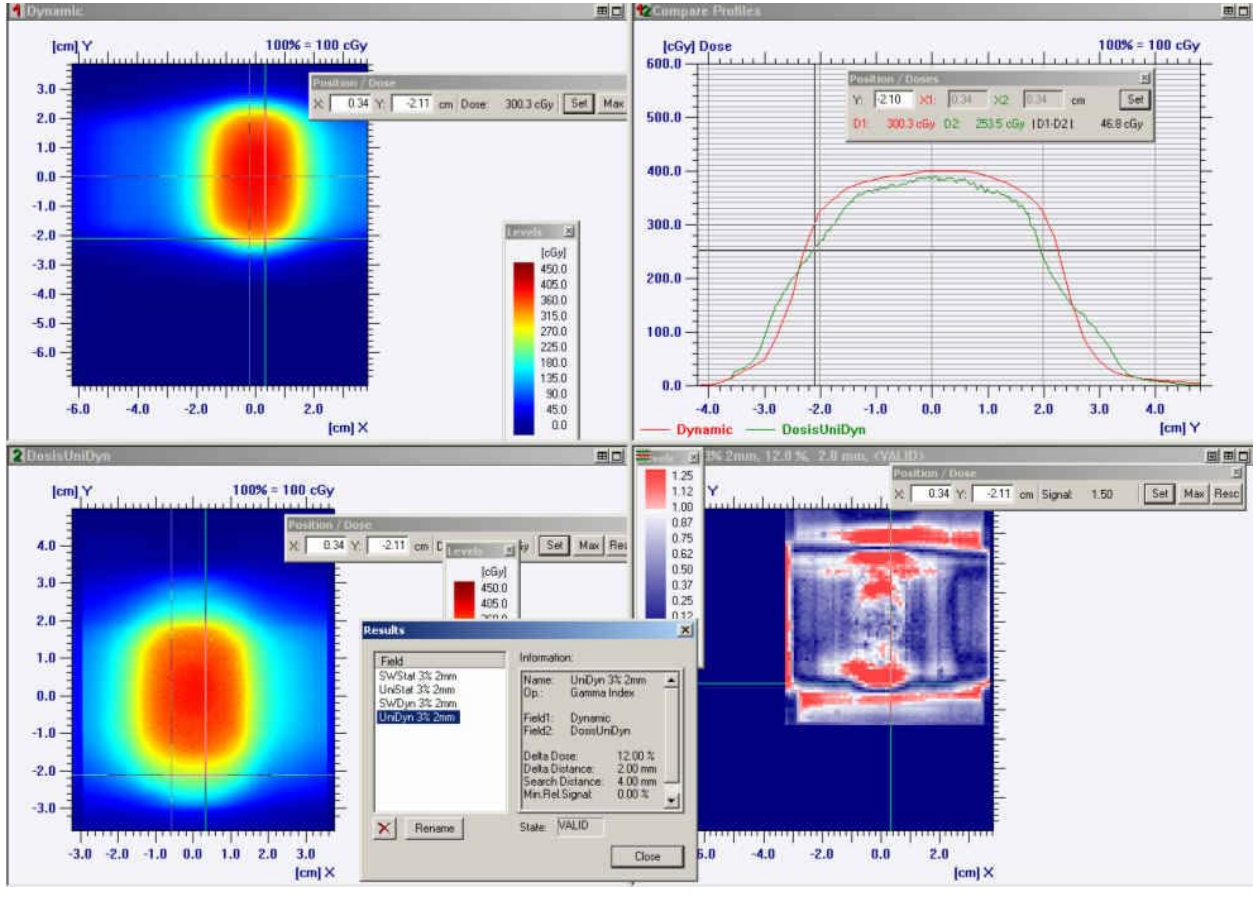
4D Dosimetry QA

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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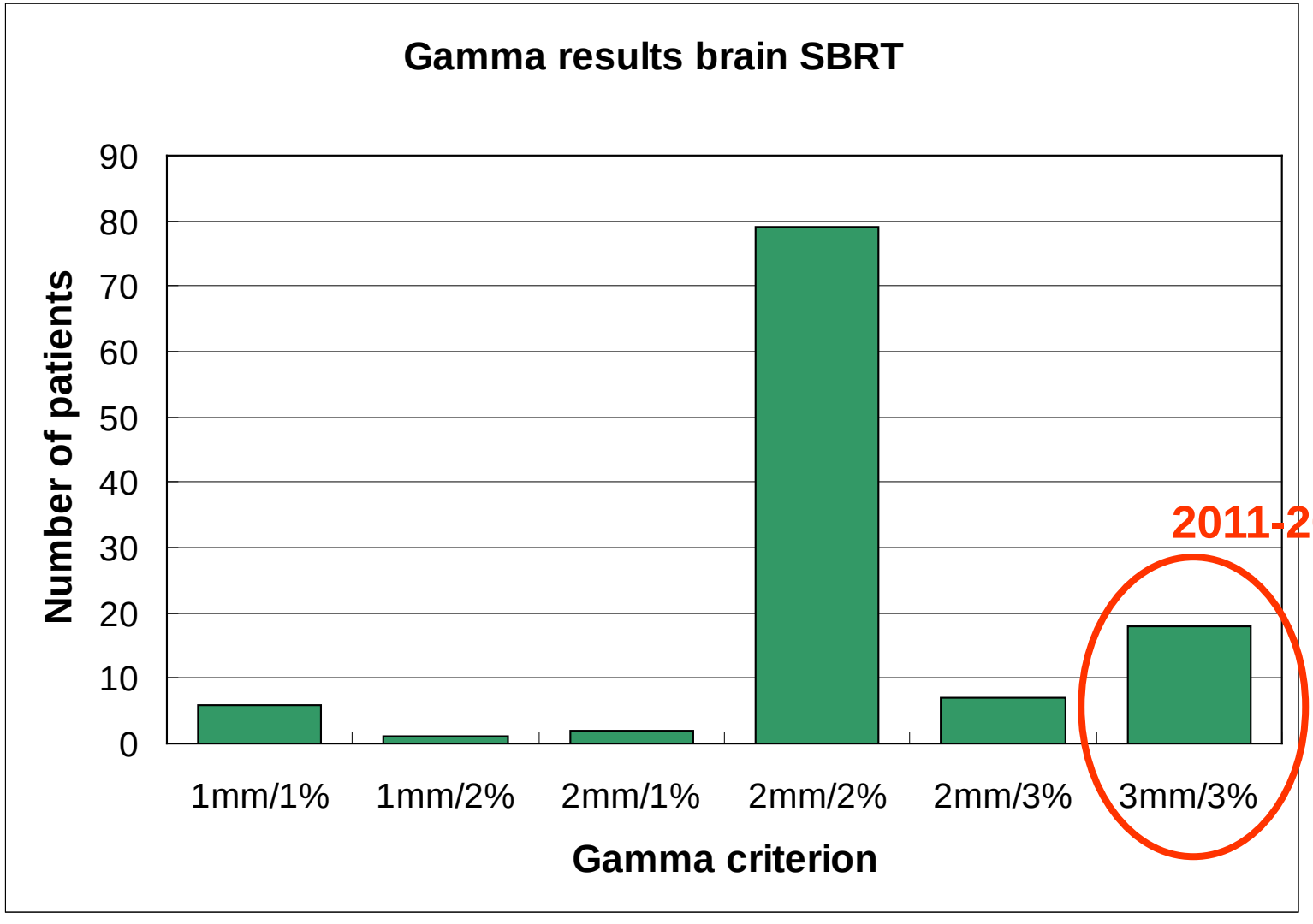
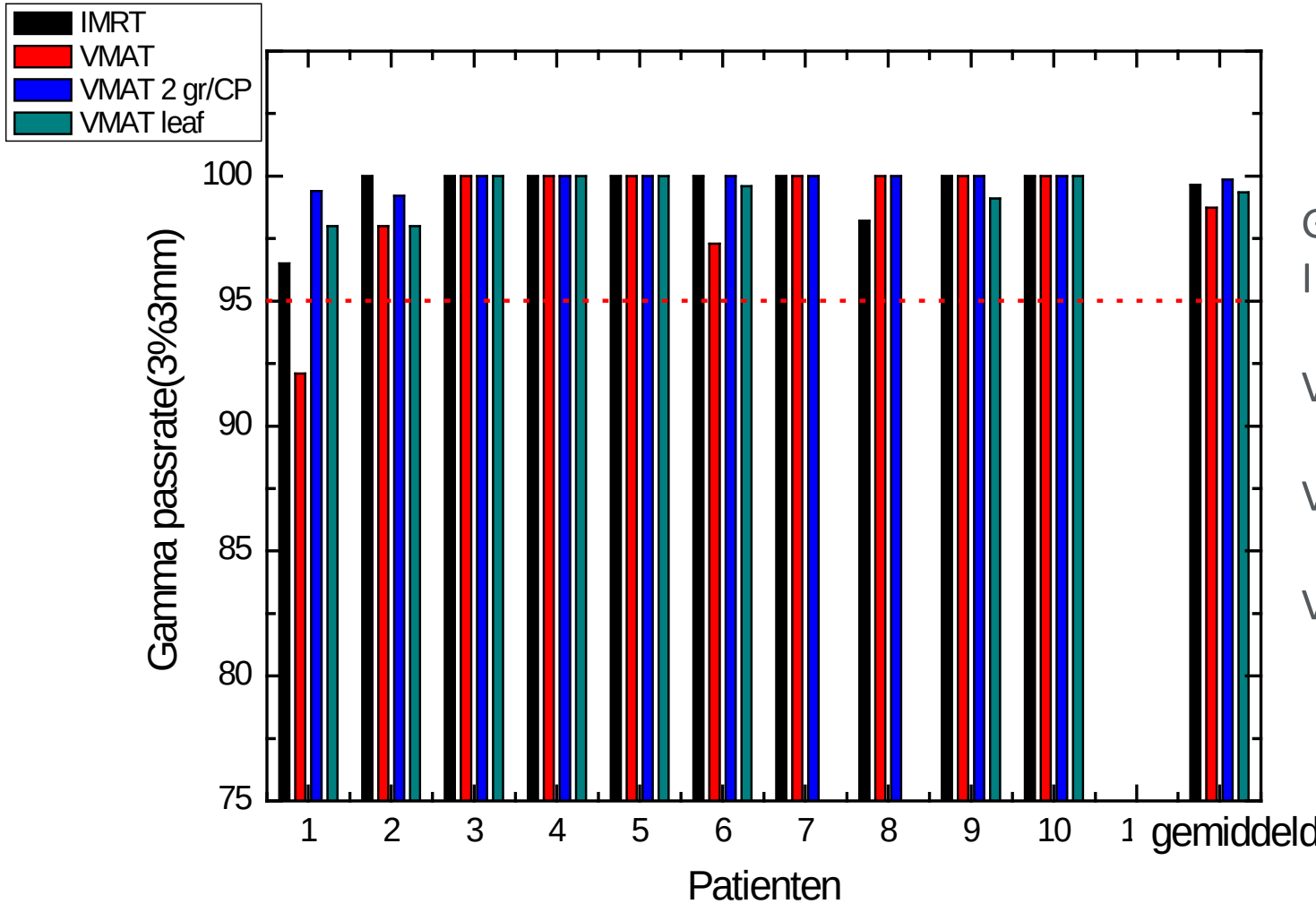
Gamma results brain VMAT



QA VMAT – 3% 3mm



Gemiddeld:

IMRT	99.65%
VMAT	98.74%
VMAT 2°/CP	99.86%
VMAT leaf	99.34%

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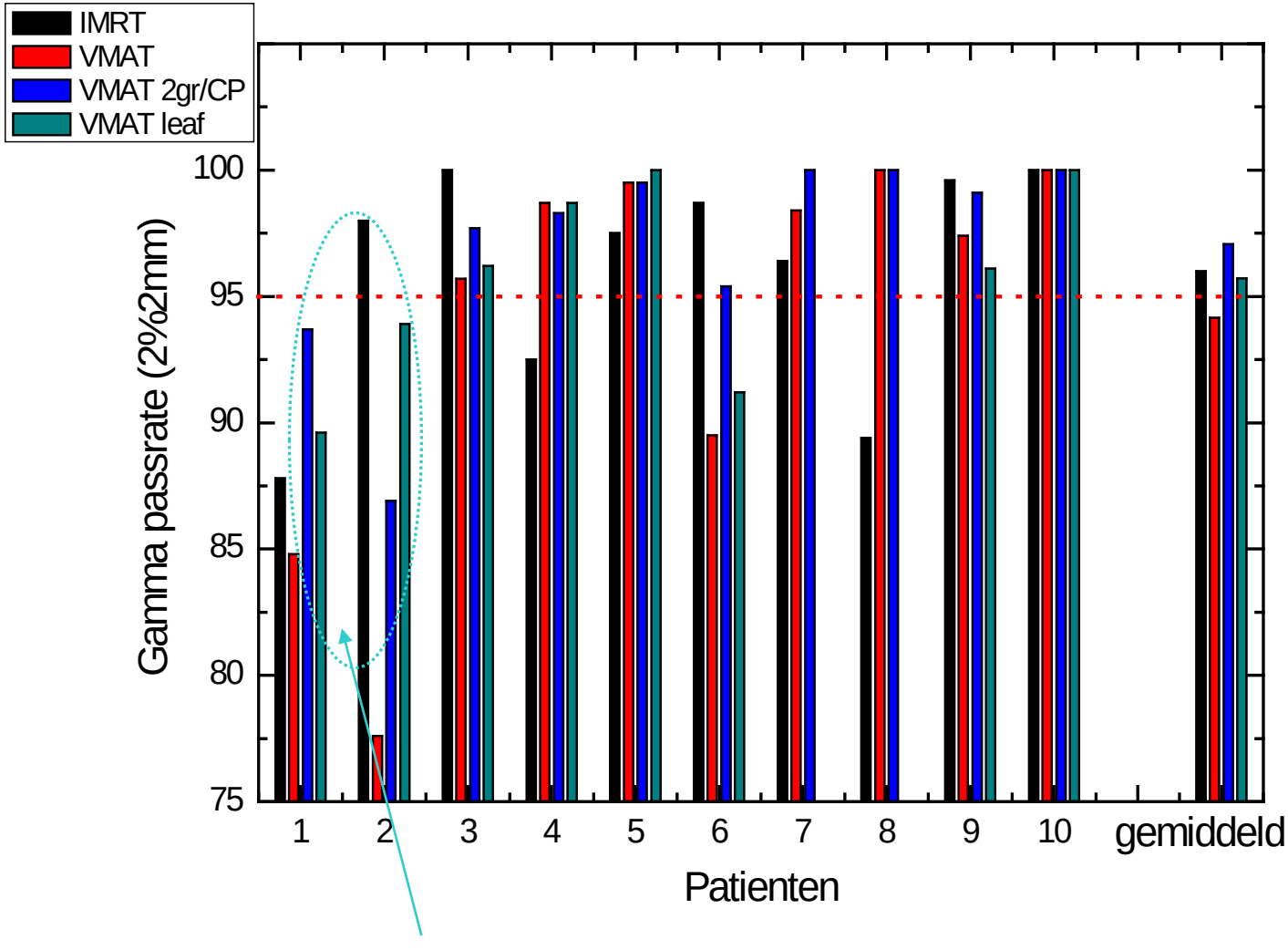
QA VMAT – 2% 2mm



- 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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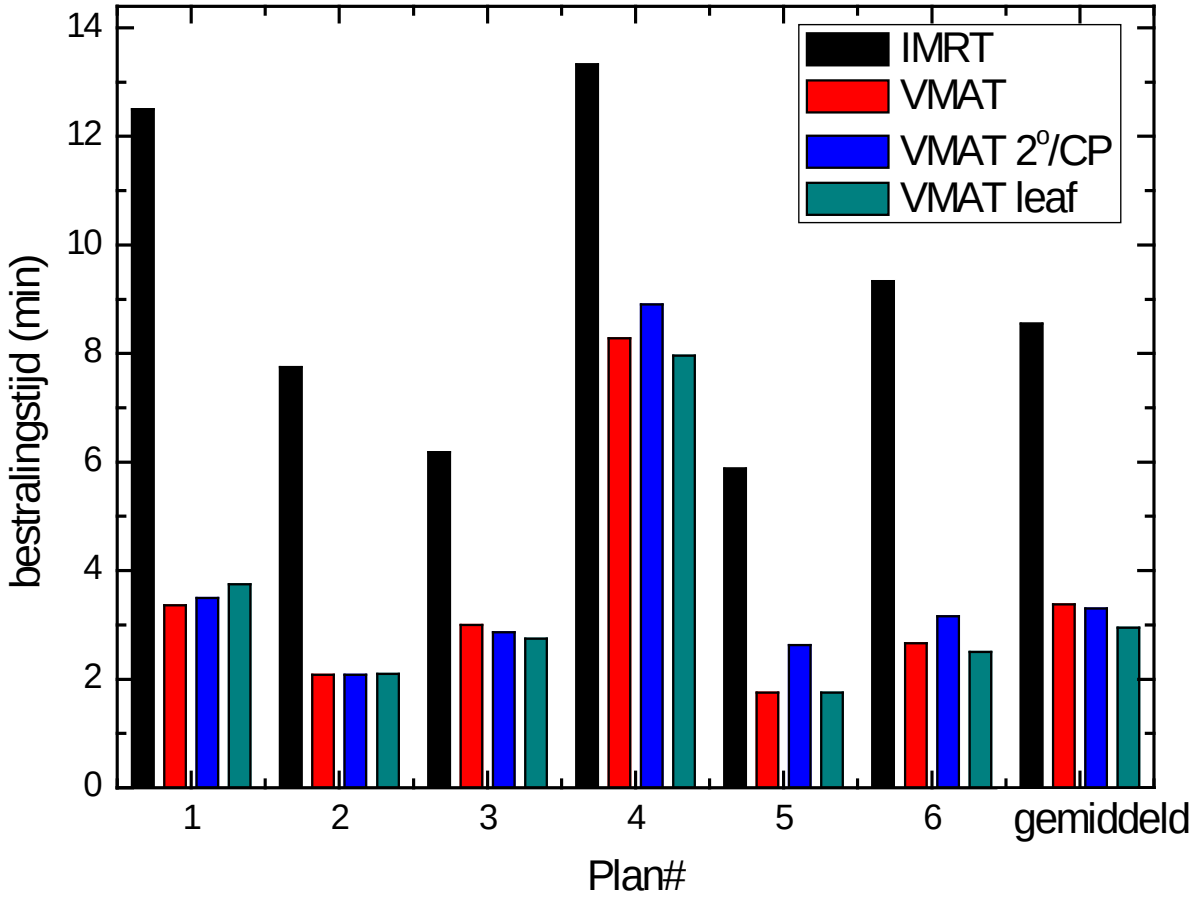
IMRT vs VMAT – irradiation time



- 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

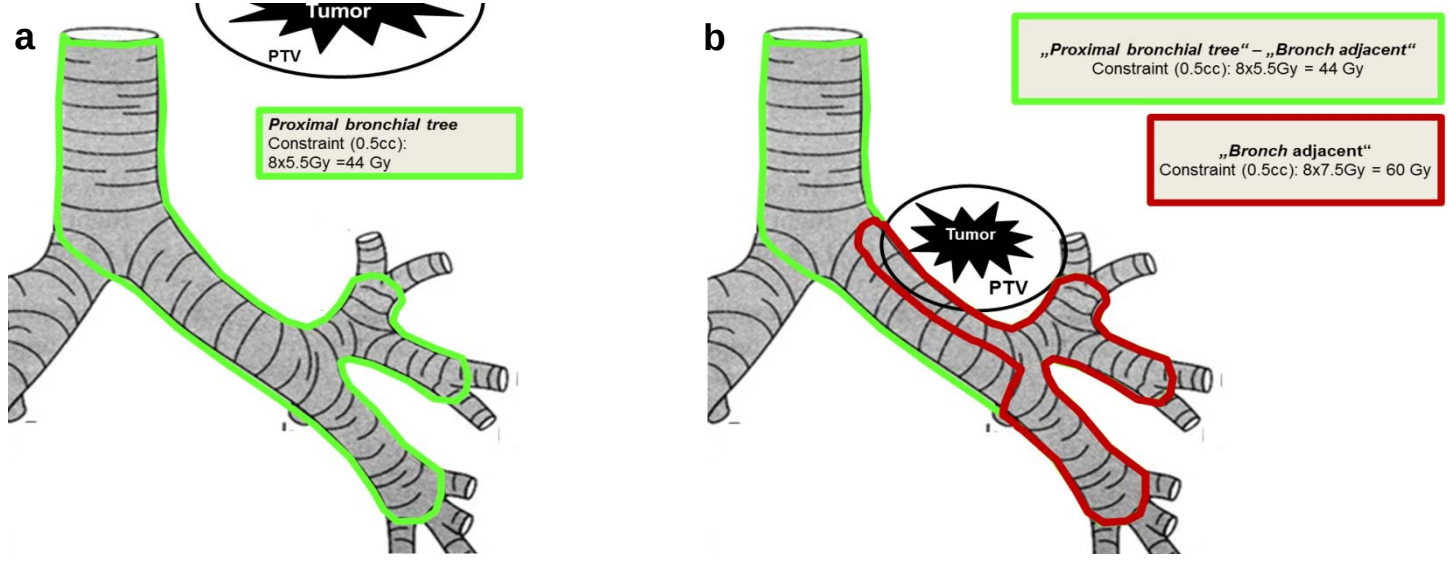

Figure 3: Dose constraints for the proximal bronchial tree
a) The general dose constraint for the whole structure “proxBT” (green) is 44Gy (<0.5cc) in 8 fractions. For PTVs near or abutting the main bronchus (b) a subvolume “Bronch adjacent” has to be generated (red). The dose constraint for this volume (<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.

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.

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

SBRT for pancreatic cancer

UniversityHospital Zurich

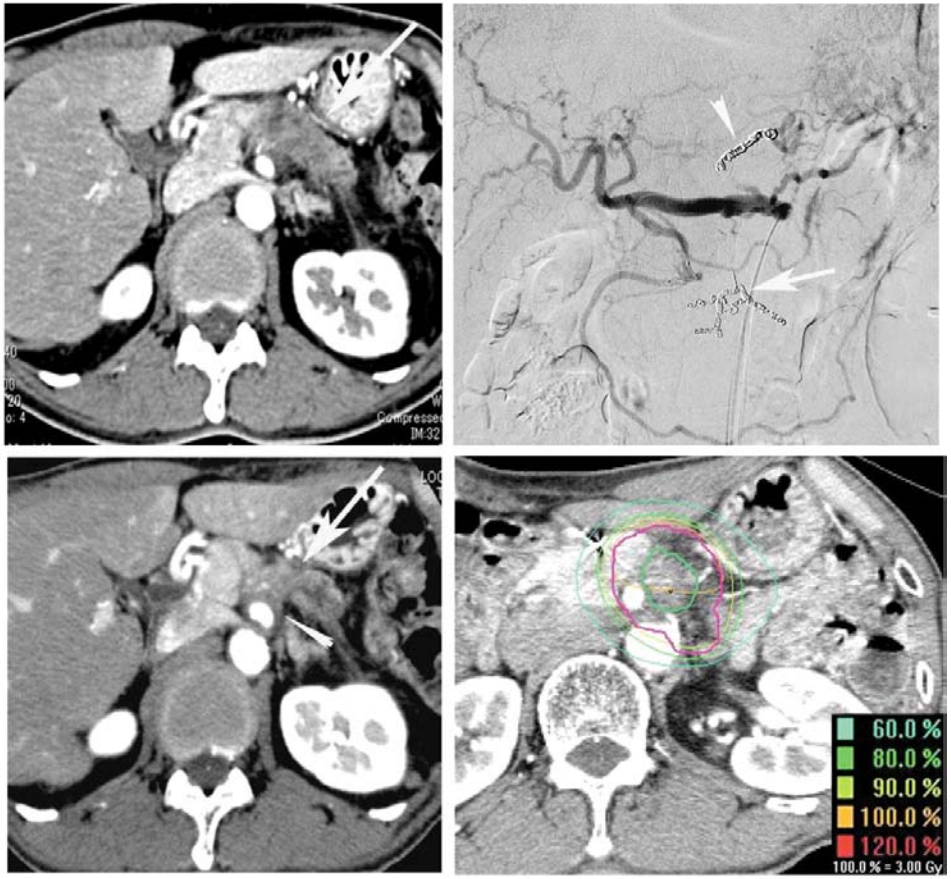
ESTRO

Question 1

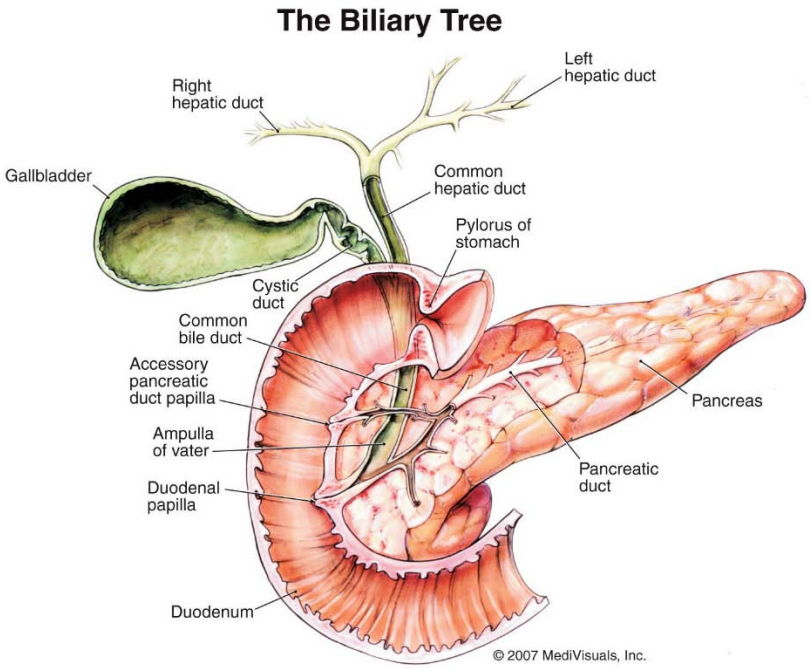
Which answer is correct in pancreatic SBRT?

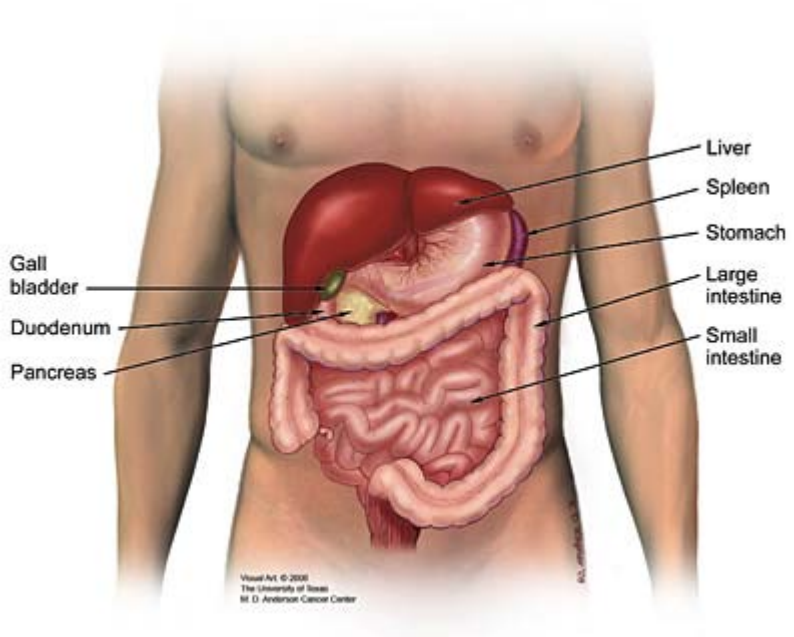
1. SBRT should not be performed outside of clinical trials due to the risk of duodenal toxicity
2. Single fraction SRS is preferred compared to fractionated SBRT.
3. SBRT has replace the need for systemic treatment.

Pancreatic cancer



Pancreatic cancer

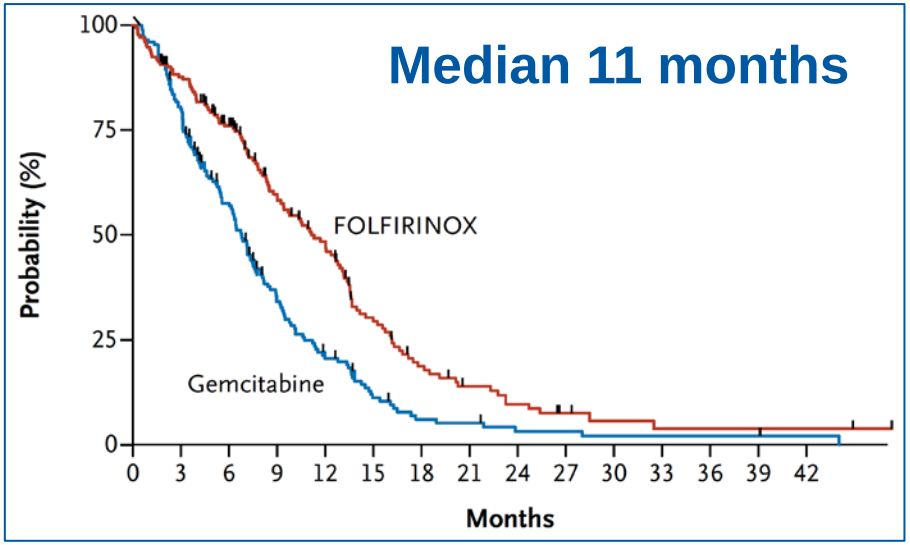




- Location: head 75% tail 25%
- Critical OARs VERY close to target: duodenum, stomach, small bowel

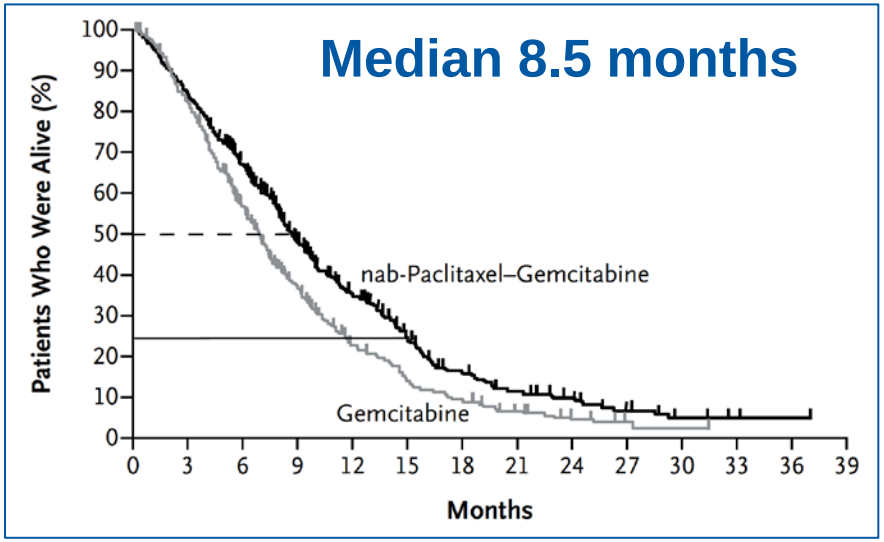
Pancreatic cancer – CT only

FOLFIRINOX



Conroy NEJM 2011

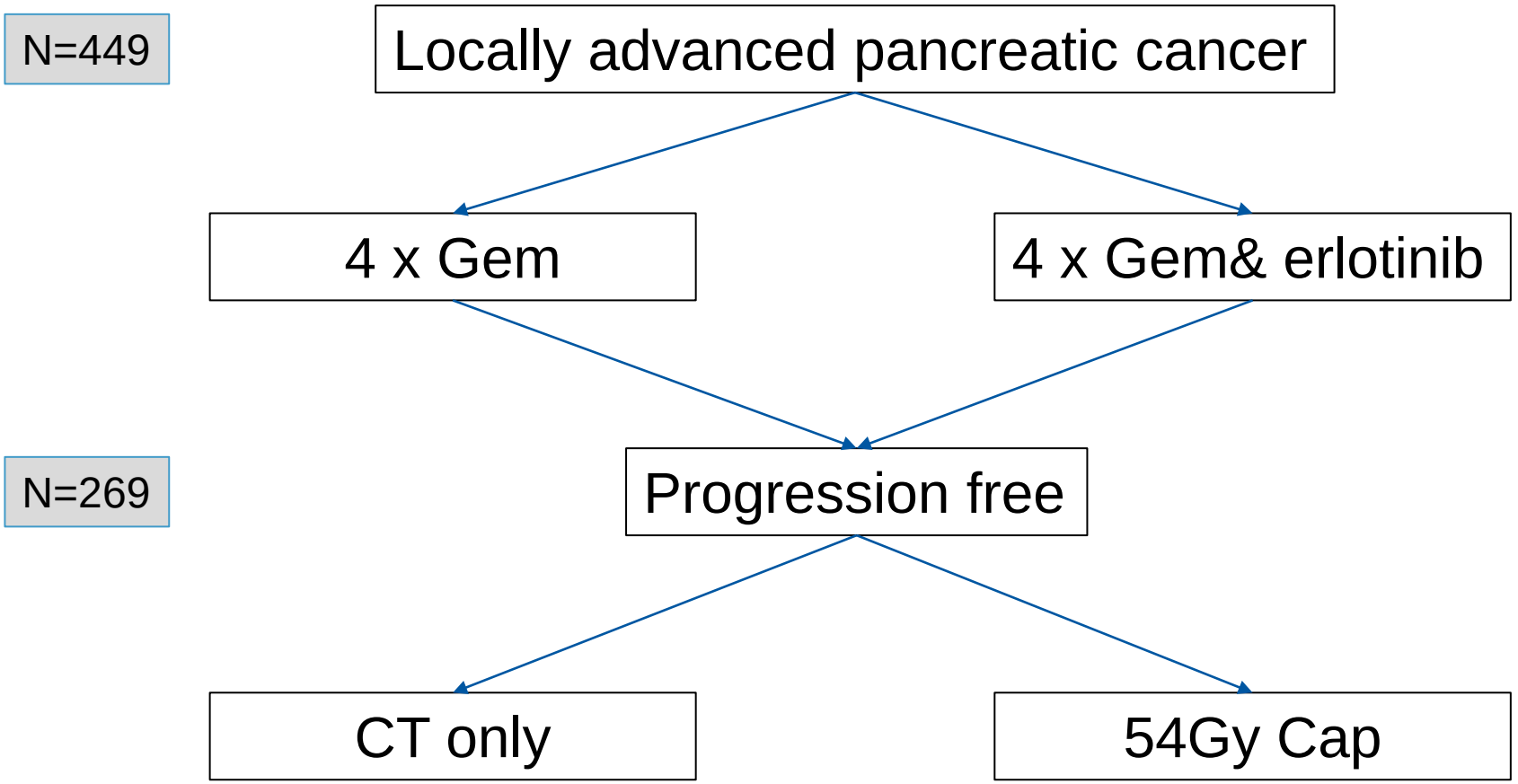
Nab-Paclitaxel



Von Hoff NEJM 2013

- Median OS of 9 – 11 months in metastatic pancreatic cancer with CT alone

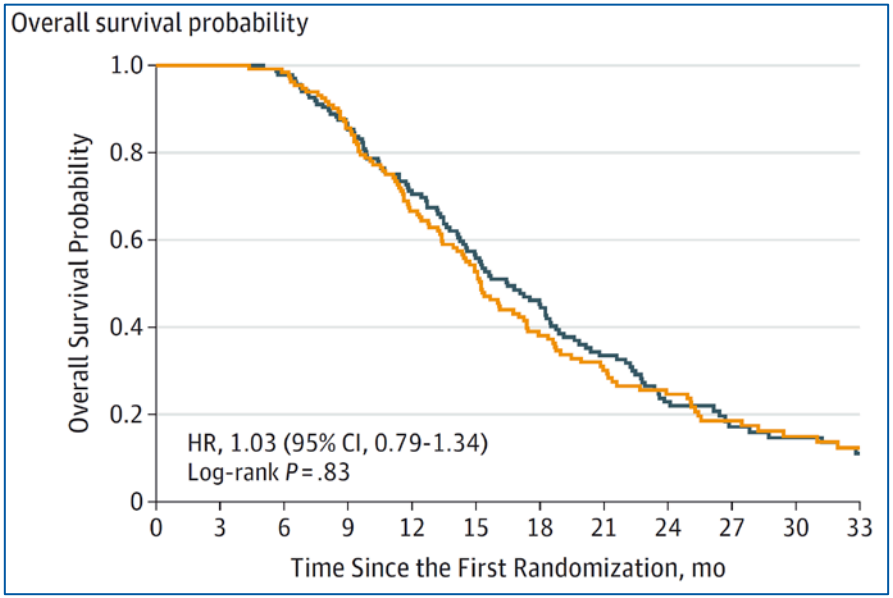
Pancreatic cancer – PAP 007



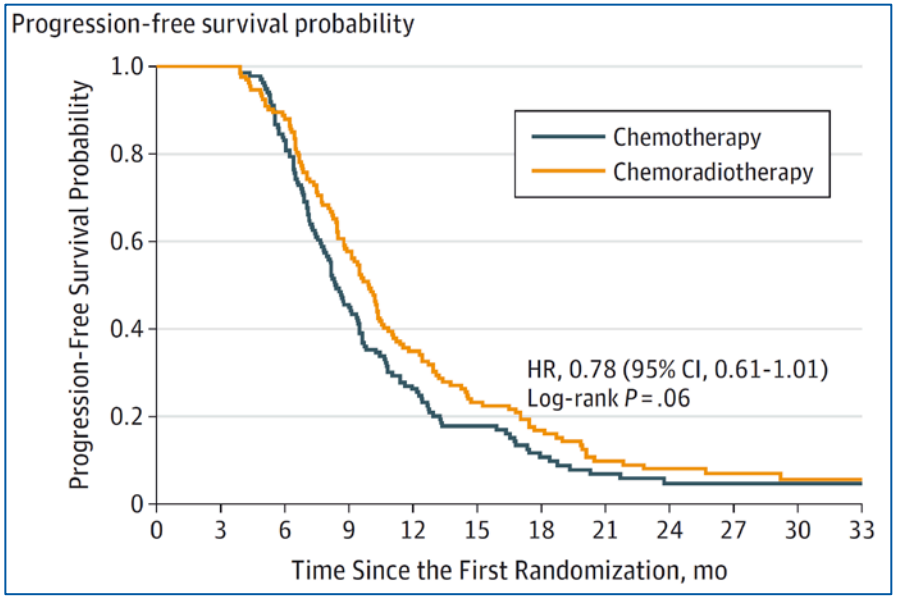
- Rapid progression of 1/3 of the patients

Pancreatic cancer – PAP 007

Overall survival



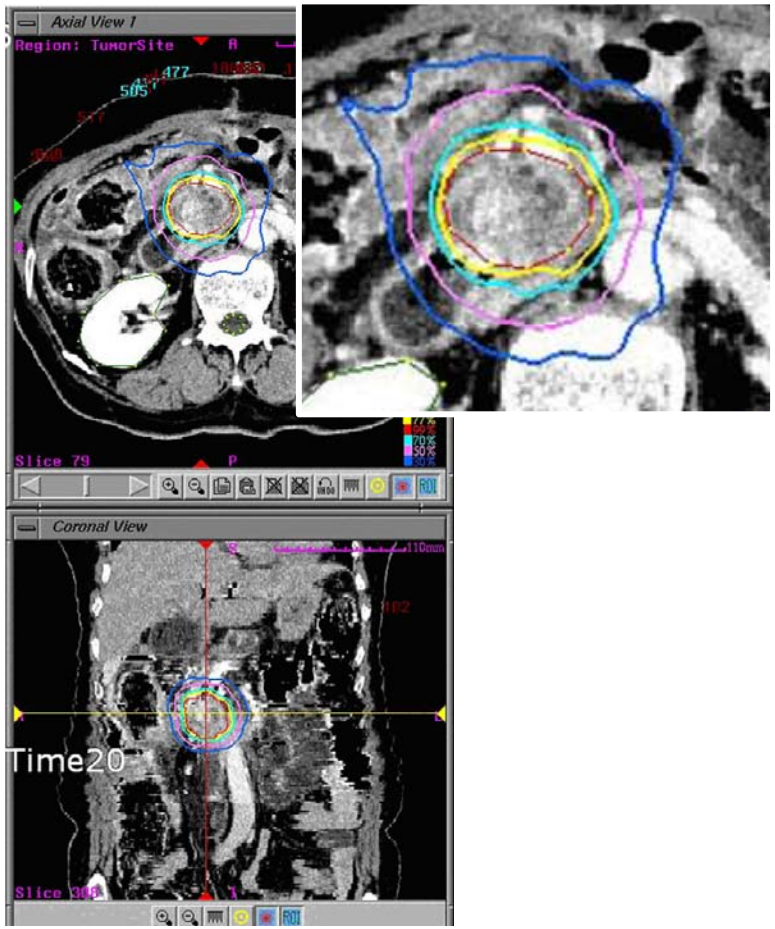
PF survival



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 ?

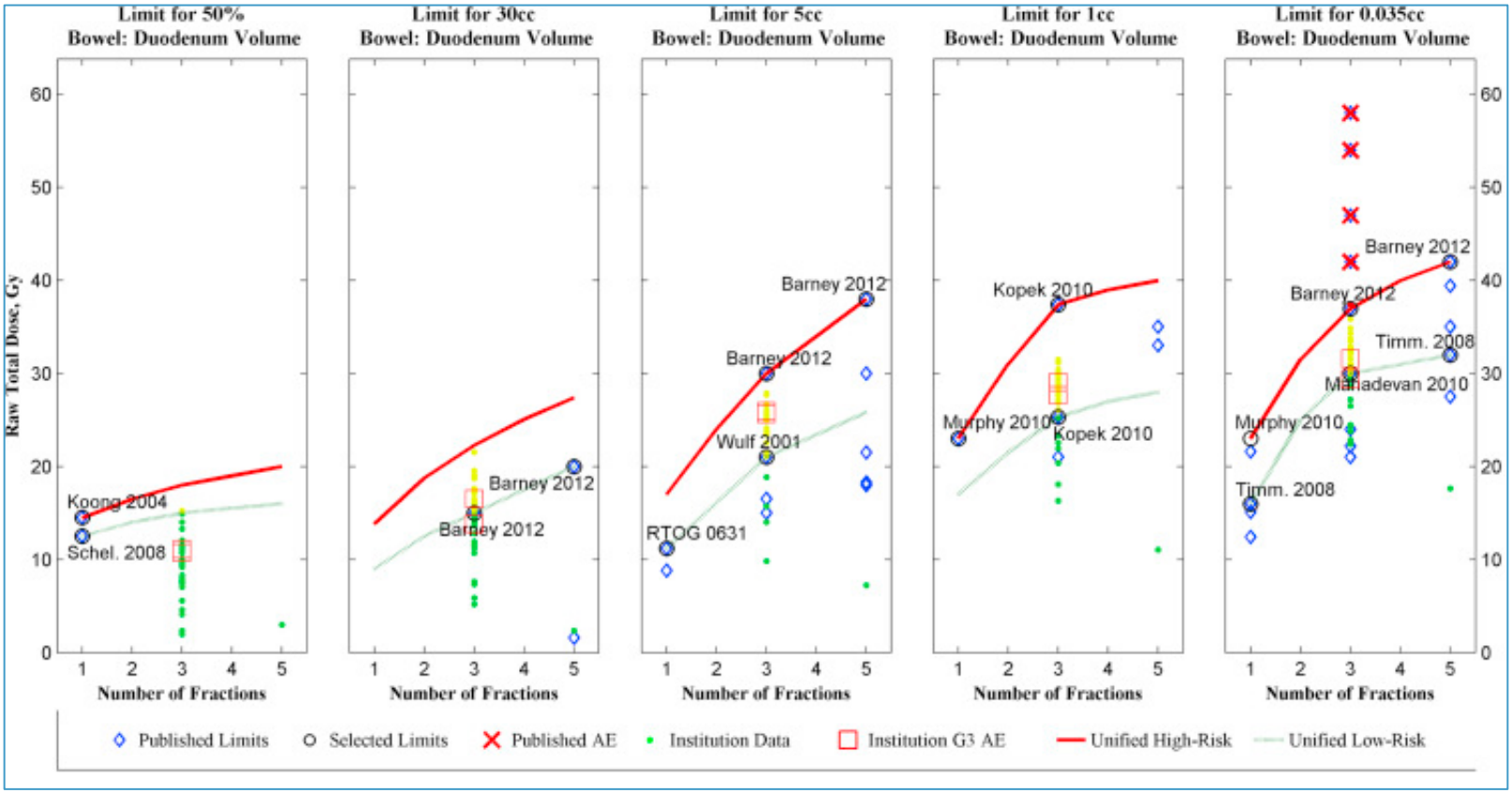
SBRT for locally advanced pancreatic cancer

	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



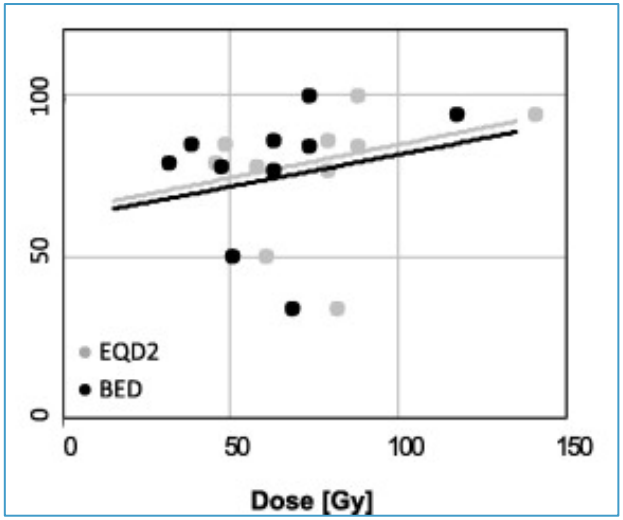
Issues:

- Validation, motion, short FU, chemotherapy, …

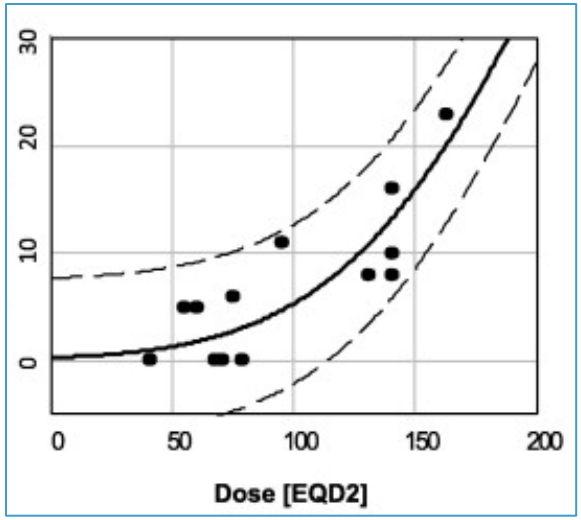
SBRT for locally advanced pancreatic cancer

Systematic literature review: 20 trials / 721 patients

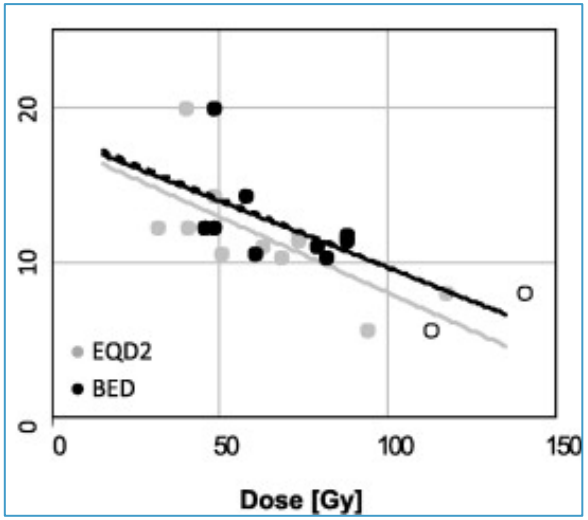
Local control



> G2 toxicity



Overall survival



More SBRT dose results in …

- Slightly better local control
- Substantially incerased toxicity
- Worse overall survival

Brunner Radiother Oncol 2015


GAME OVER
INSERT COIN

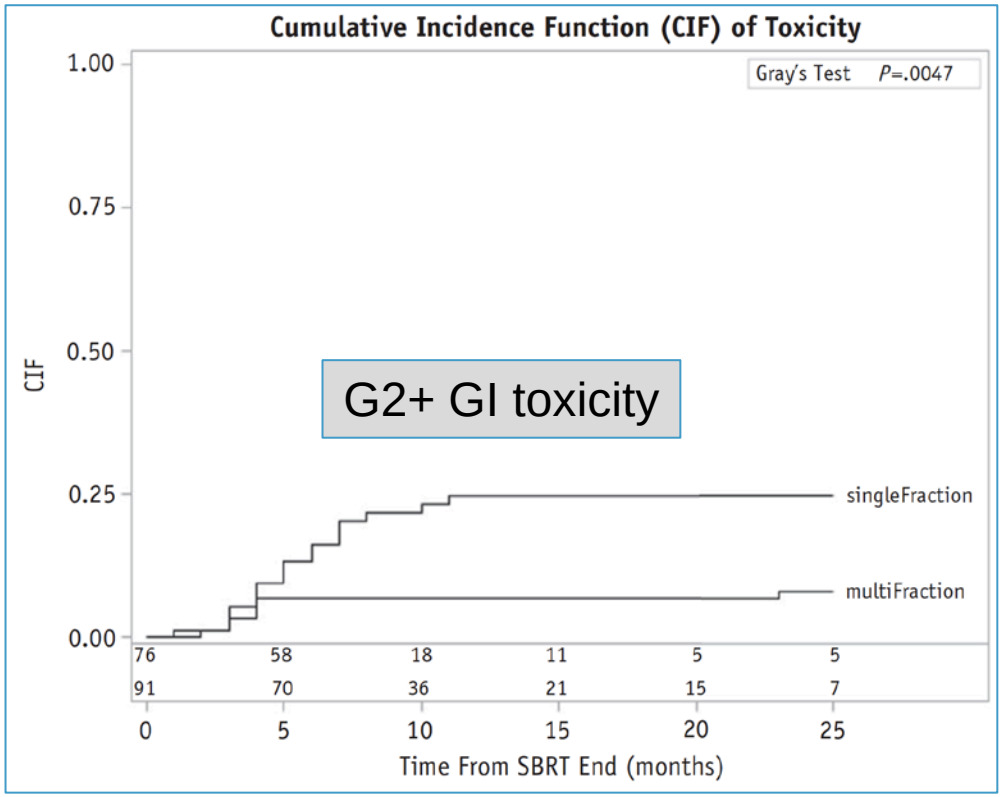
Duodenal toxicity – fractionation

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 comared to MF SBRT
- Toxicity risk factor for reduced OS

SBRT for locally advanced pancreatic cancer

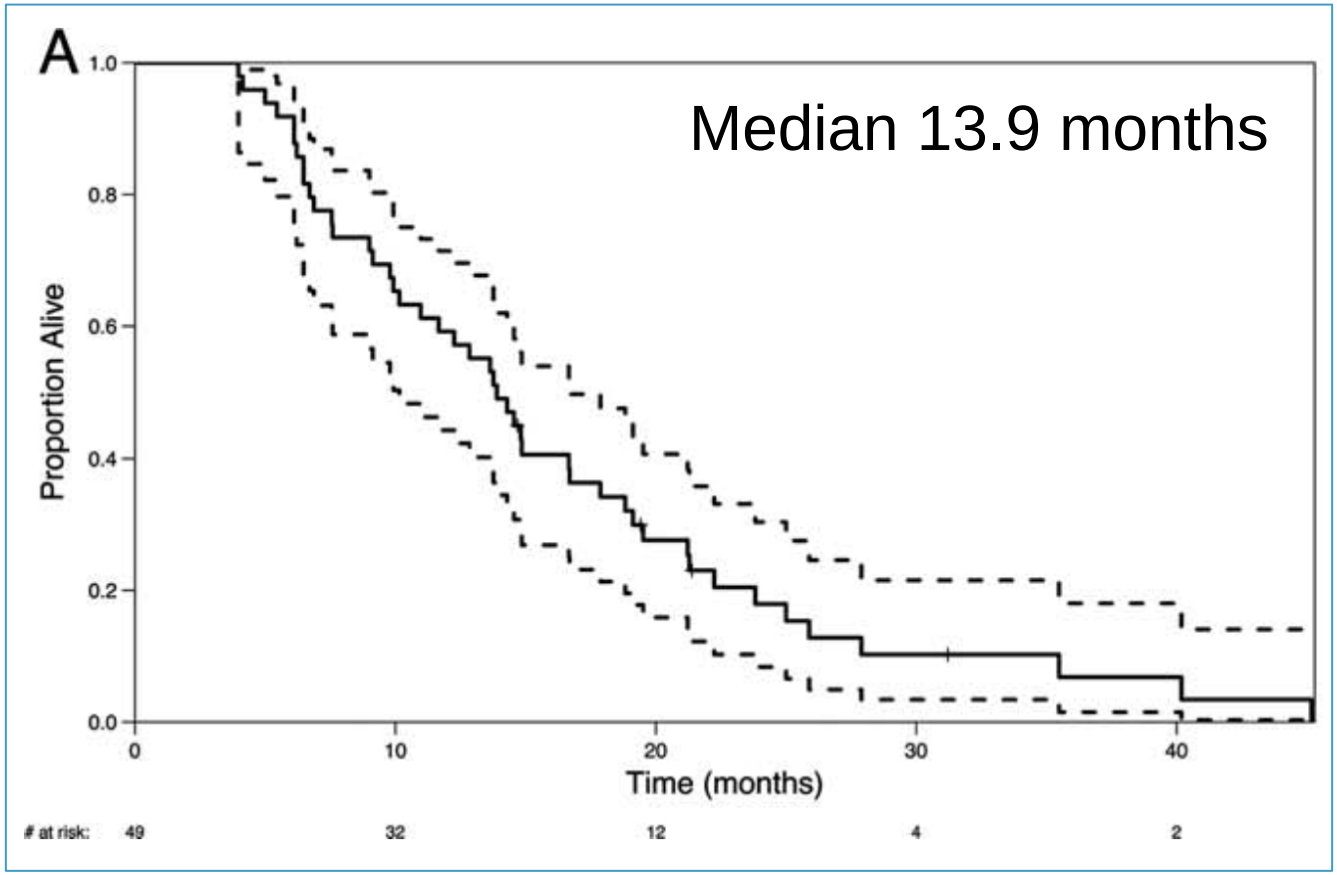
- Phase 2 multi-institutional study
- 49 pat. with locally advanced PC
  - 3 x Gem (1000mg/m2)
  - 1 week break
  - SBRT with 5 x 6.6Gy
- Median FU 14 months

Acute GI Tox G >=2	Late GI Tox G >=2
2%	11%

➢Fractionated SBRT with lower SFD well tolerated

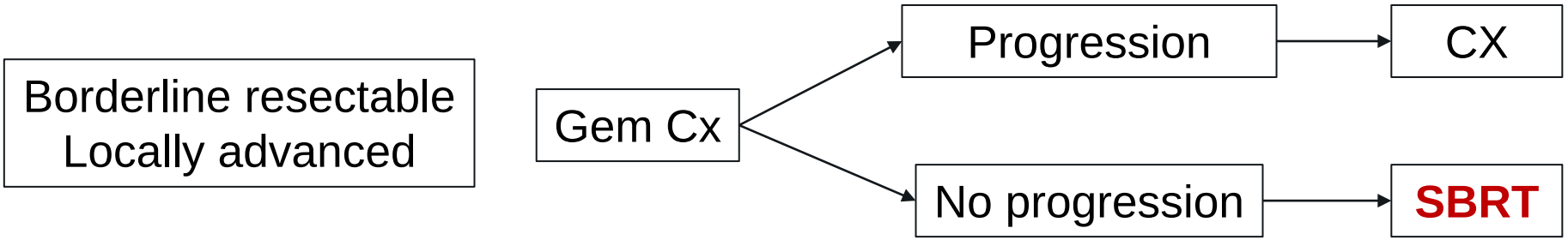
SBRT for locally advanced pancreatic cancer

Herman Cancer 2015



- Reasonable OS, despite not being overwhelming
- OS the only relevant endpoint?

SBRT to achieve resectability



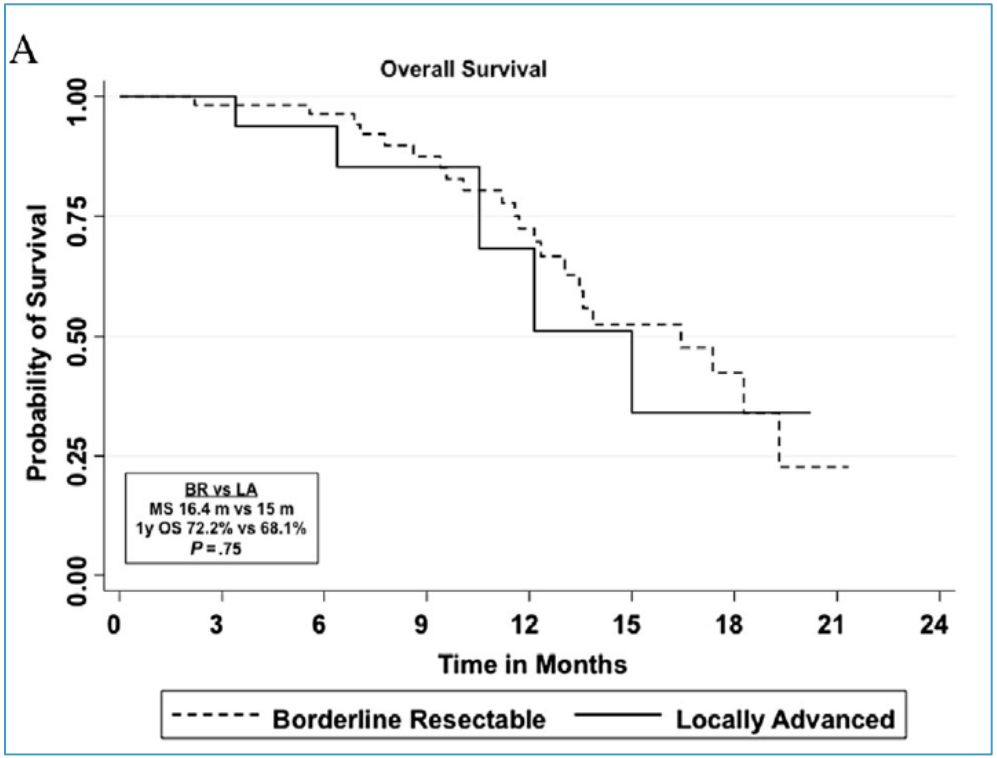
SBRT: 5 x 7Gy to vessle abutting region
5 x 5Gy to remaining tumor

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

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?

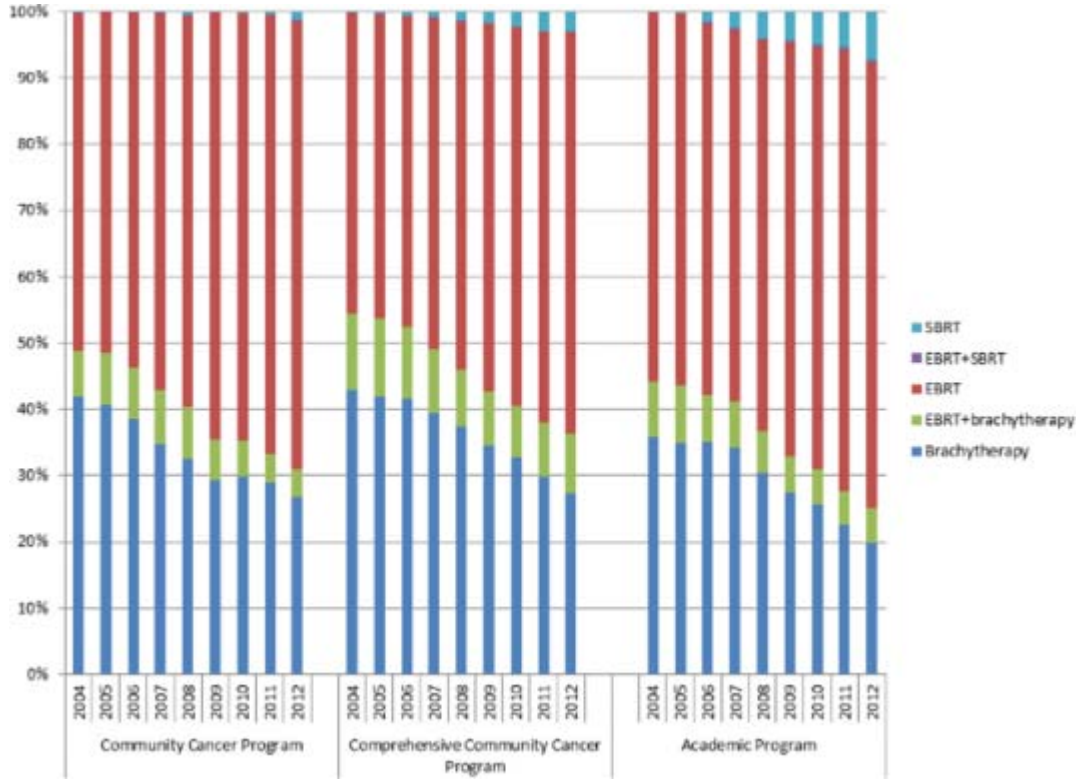
1. SBRT for prostate cancer is especially well evaluated in high-risk disease.
2. Especially GI and not GU toxicity is an issue of concern in SBRT for prostate cancer.
3. SBRT is using most frequently 5 fraction of doses between 35 – 40Gy.

SBRT for prostate cancer

Why SBRT
Small well circumscribed target
Low alpha / beta ratio
Benefit of dose escalation
Technical solutions available
Strong competition

Use of SBRT for prostate cancer

National Cancer Data Base covering 70% of US cancer patients



➢ SBRT for Prostate cancer in 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

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

Dose and fractionation

	5 x 7Gy, once weekly pHART3	5 x 8Gy, once weekly pHART6
Risk	Low risk	Low-intermediate risk
Follow-up	74 mo	36 mo
Median PSA nadir	0.4 ng/ml	0.3 ng/ml
2a bRFS-2+nadir	98.7%	100%
GU G2 tox	5%	24.2%
GI G2 tox	7.6%	26.2%
GU & GI G3 tox	No differencs	

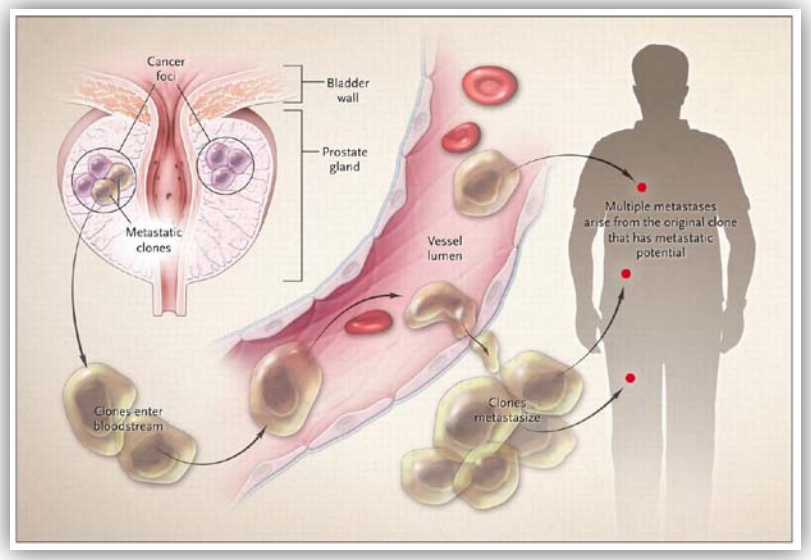
➢ Increase in G2 but not in G3 toxicity

Prostate SBRT

1. Dose and fractionation
2. **Target volume concept**
3. Treatment delivery
4. Outcome

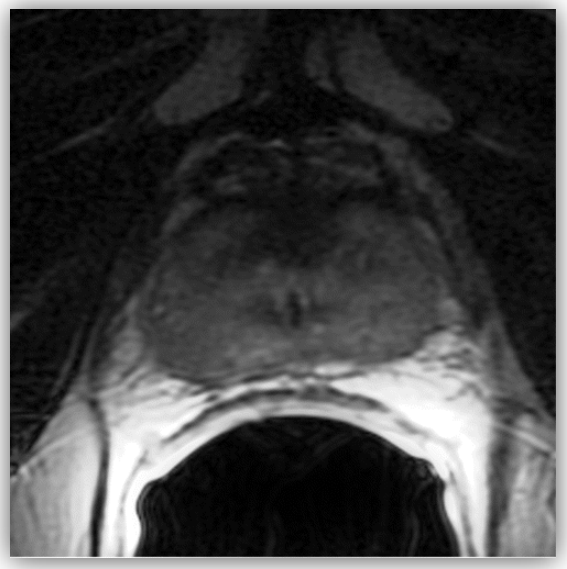
Metastatic spreat of prostate cancer

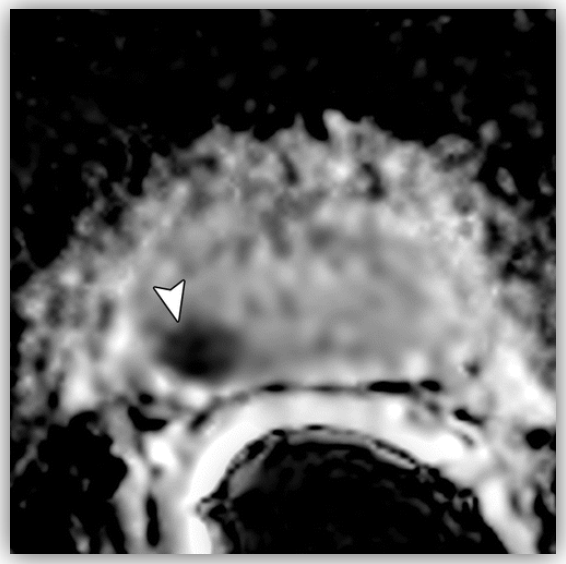
Liu Nat Med 2009
Ahmend NEJM 2009

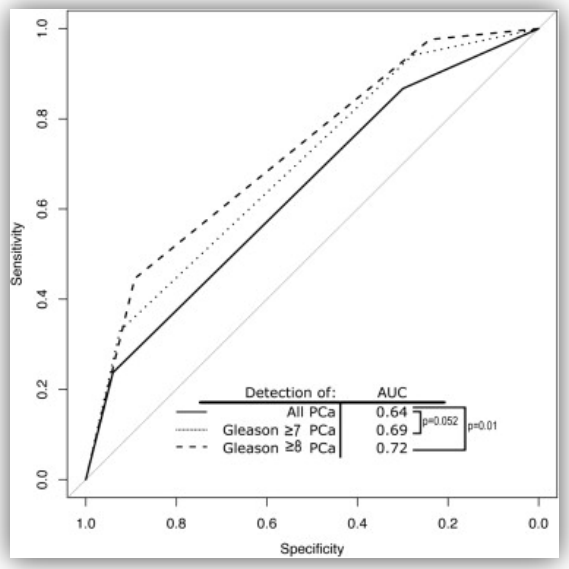


- Prostate Cancer: Multi-focal and poly-clonal disease
- HOWEVER: mono-clonal origin of metastatic spreat
- Clinically significant cancer
  - GS ≤ 6 w/o G pattern 4 or 5
  - Organ-confined disease
  - Tumour volume <0.5 cm^3

Multiparametric MRI for detection of clinically significant cancer





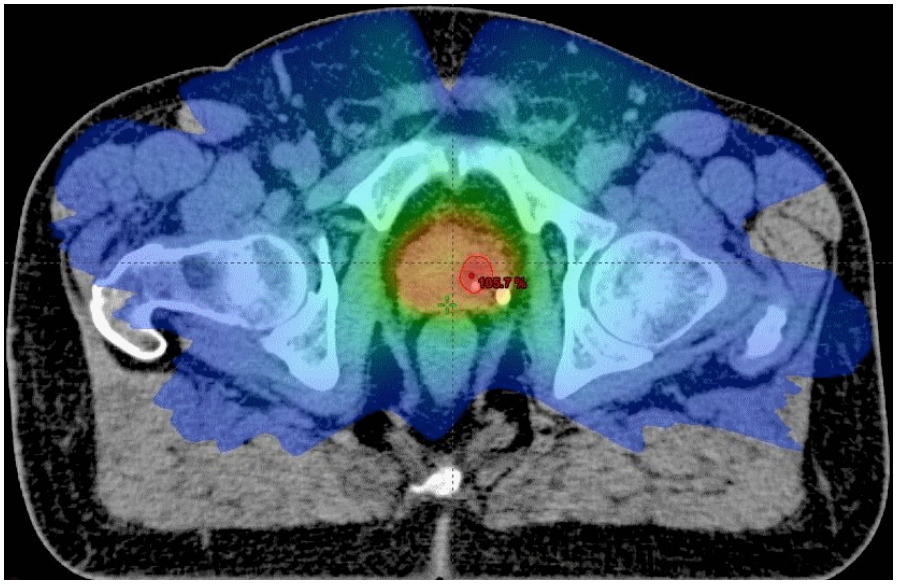


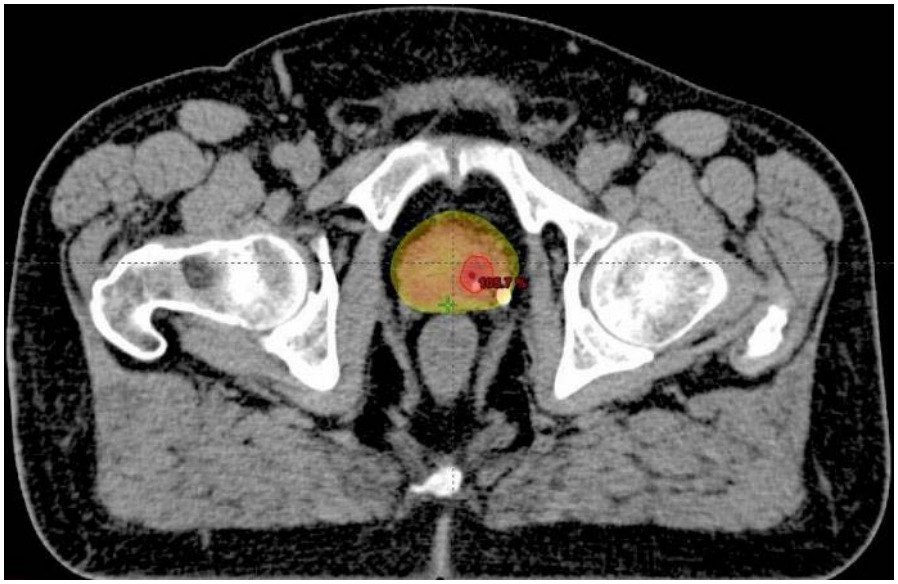
Donati Radiology 2013

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

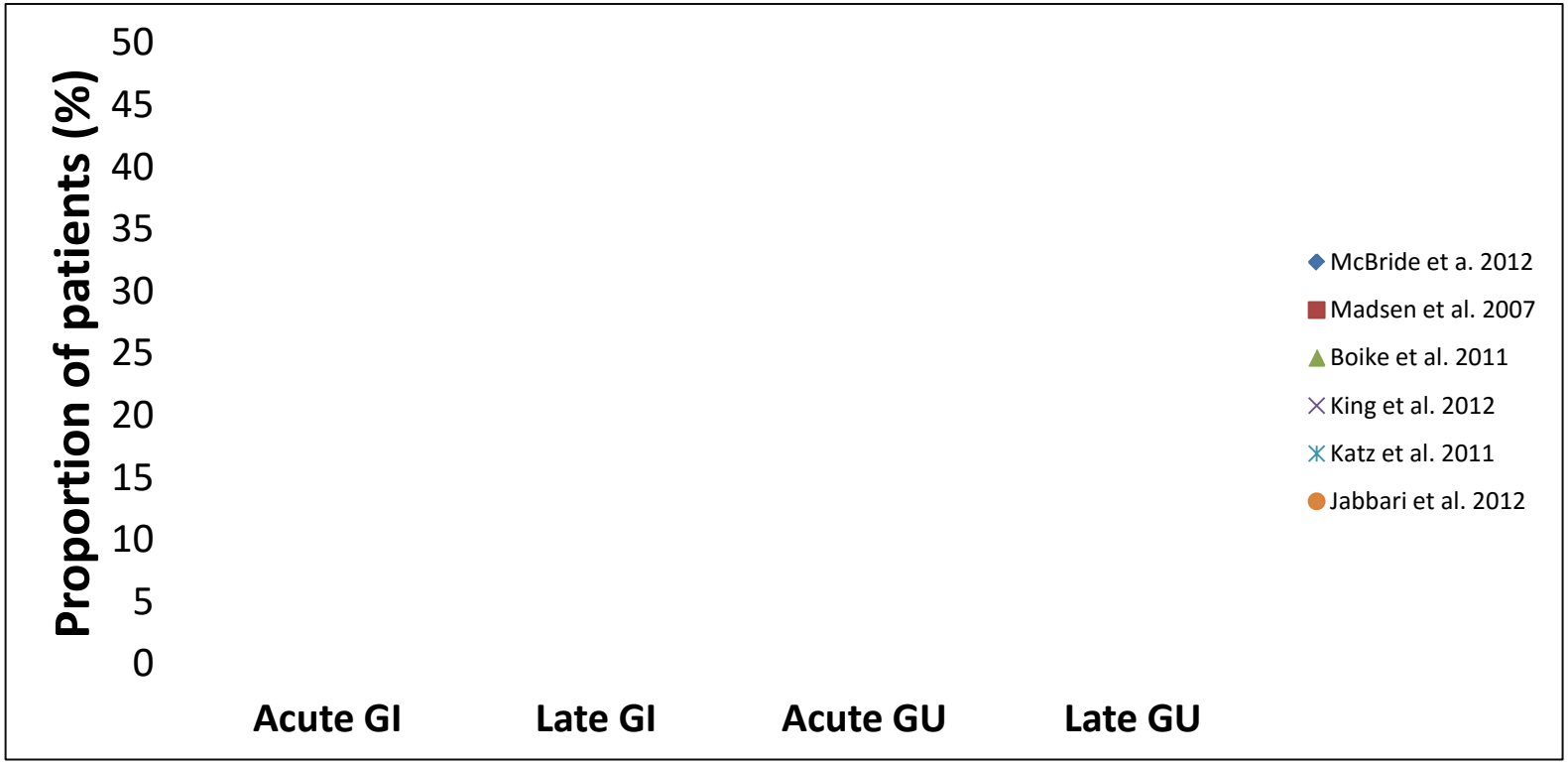
Series	Median Follow-Up
Robotic SABR	
King	2.7 years
Katz	72 months
Chen	28 months
Friedland	24 months
Oliai	Low-dose 27 months High-dose 37 months
Meier	30 months
Gantry-Based SABR	
Kim	24.5 months as per dose group
Menkarios	33 months
Loblaw	55 months
Mantz	Minimum 5 years

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

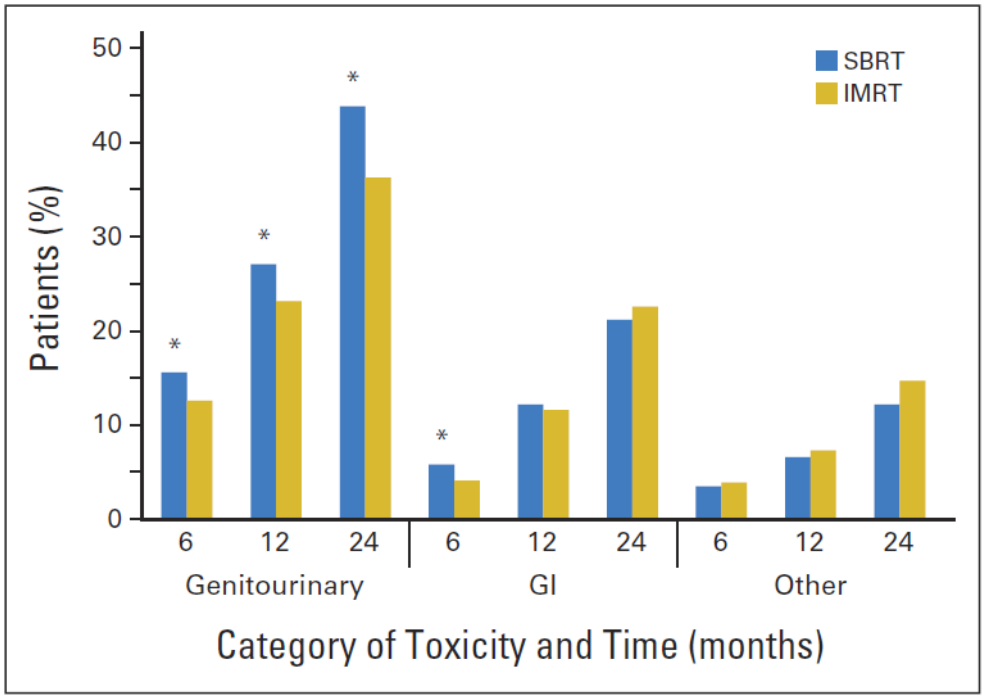
Population based analysis

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%)

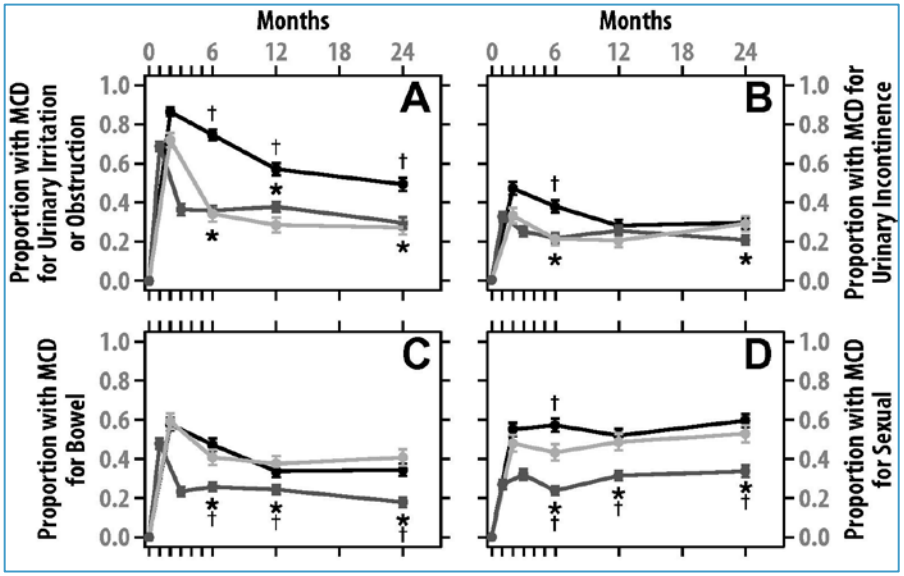
Halpern Cancer 2016

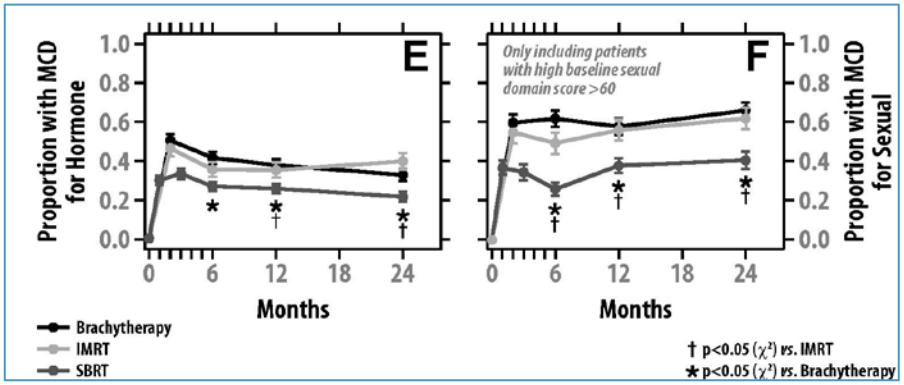
- Incontinece increased compared to IMRT
- Highest erectile dysfunction rate

QoL analysis

Multi-center retrospective analysis

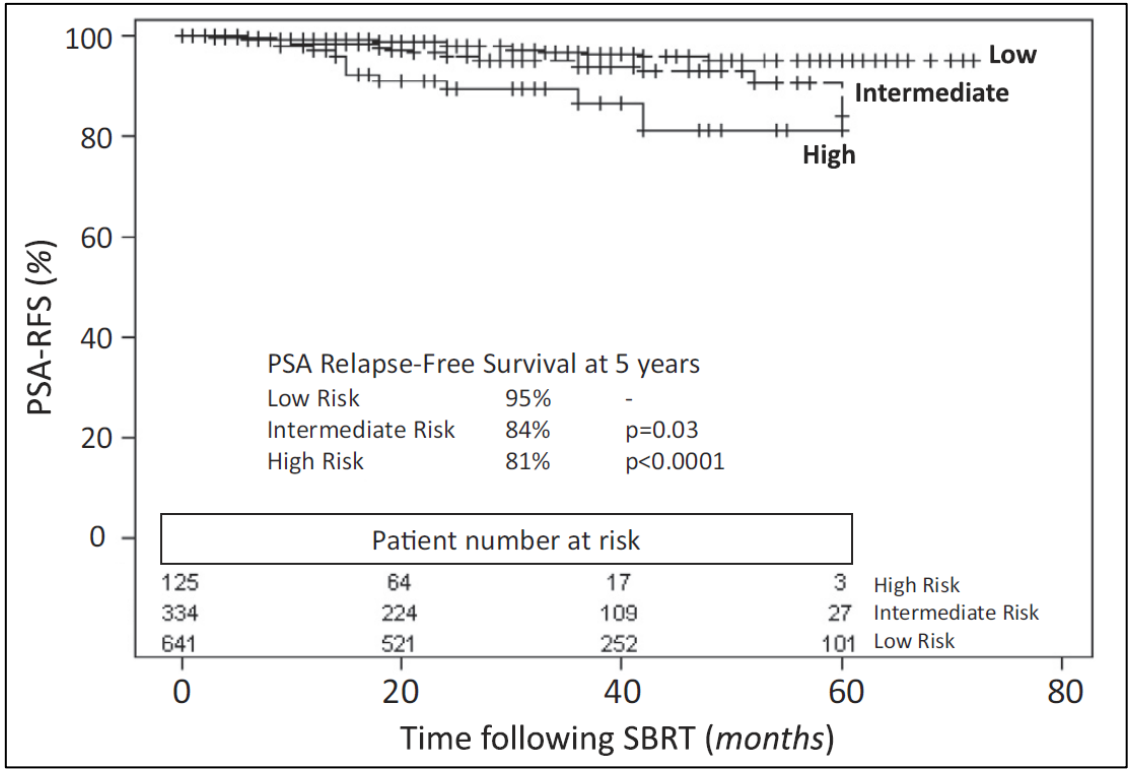
IMRT	SBRT	Brachytherapy
N=160	N=381	N=261
75.6–79.2 Gy	35 – 40Gy in 5Fx	^{125}I or ^{103}Pd





- „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

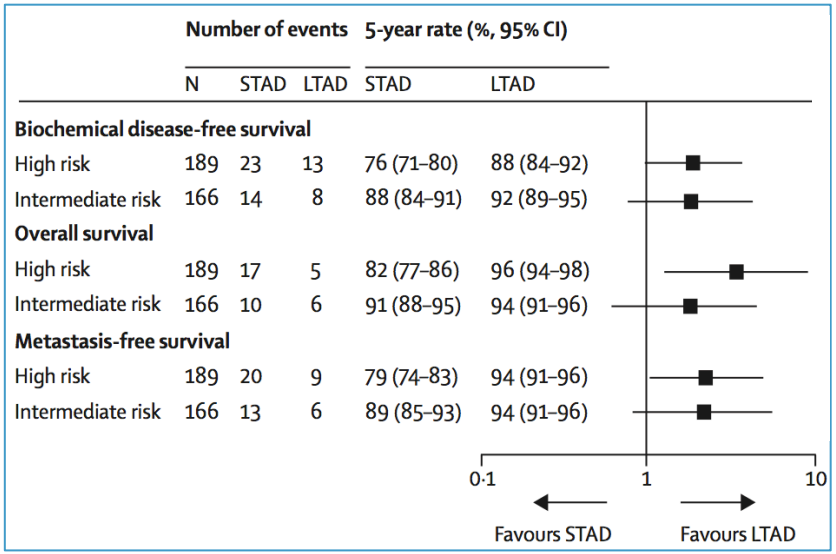
All patients enrolled in phase II studies

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

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

Stereotactic body radiotherapy for vertebral metastases

Matthias Guckenberger

UniversityHospital Zurich

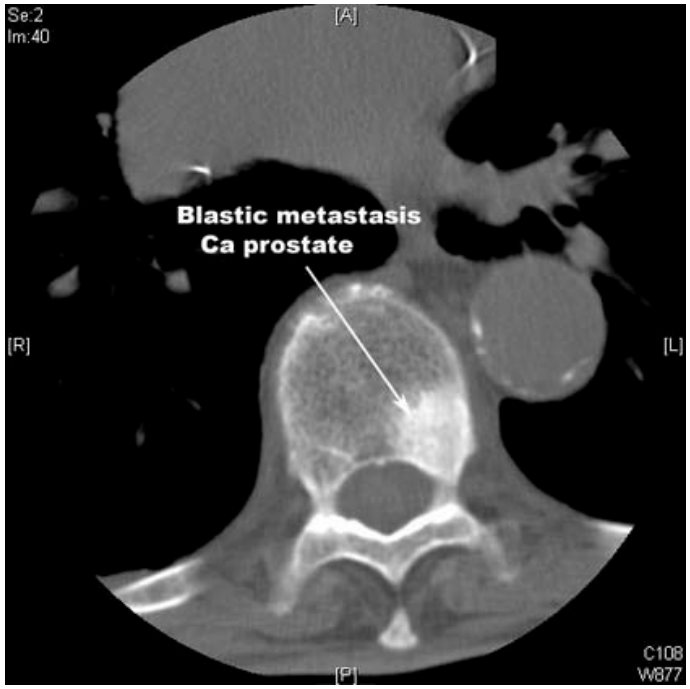
ESTRO

Question:

Which statement is correct about conventional RT (1 x 8Gy; 10 x 3Gy)?

1. Overall pain response is achievd in about 2/3 of the patients
2. Complete pain respone is achieved in the majority of the patients
3. Duration of pain response is minimum 6 months

Conventional radiotherapy techniques for treatment of spine metastases



Uncomplicated bone metastases

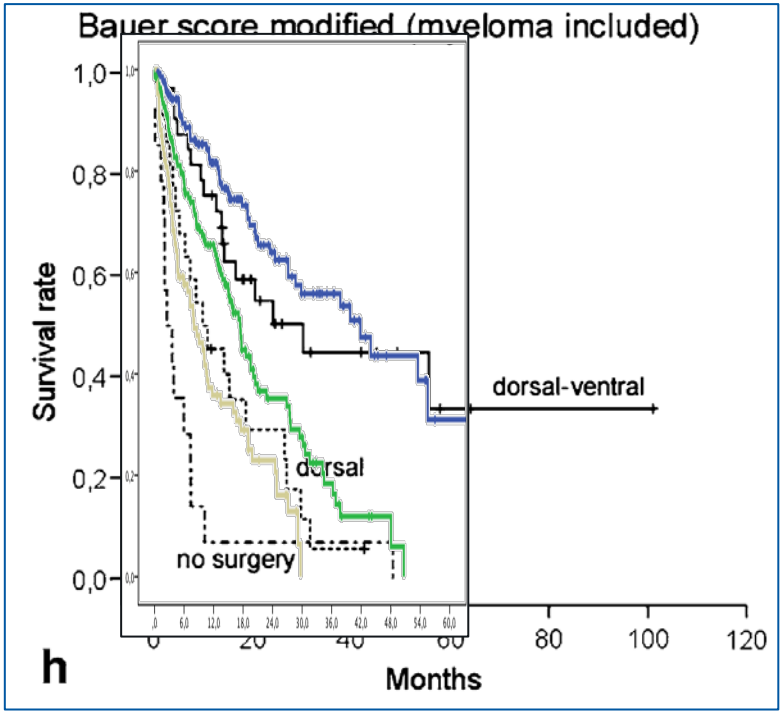
Pain control with conventional radiotherapy for bone metastases

	# 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%

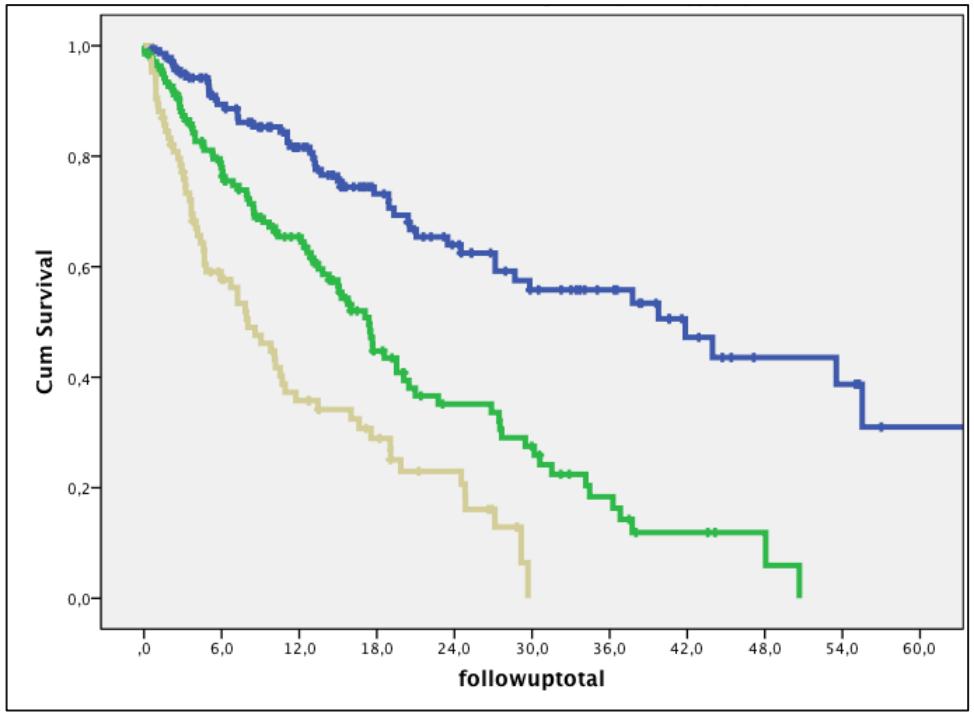
OS in patients with vertebral metastases

Conventional radiotherapy



Leithner Eur Spine J

SBRT



Guckenberger submitted

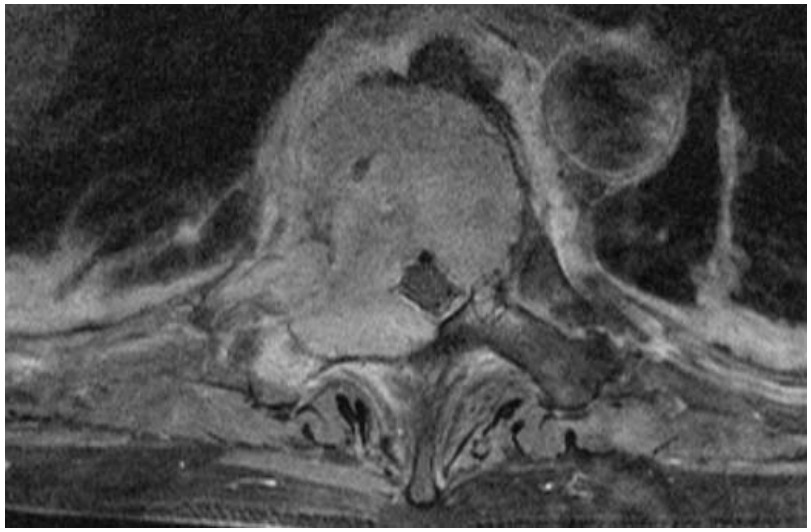
- Favorable OS in selected patients
- Contribution of SBRT?

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

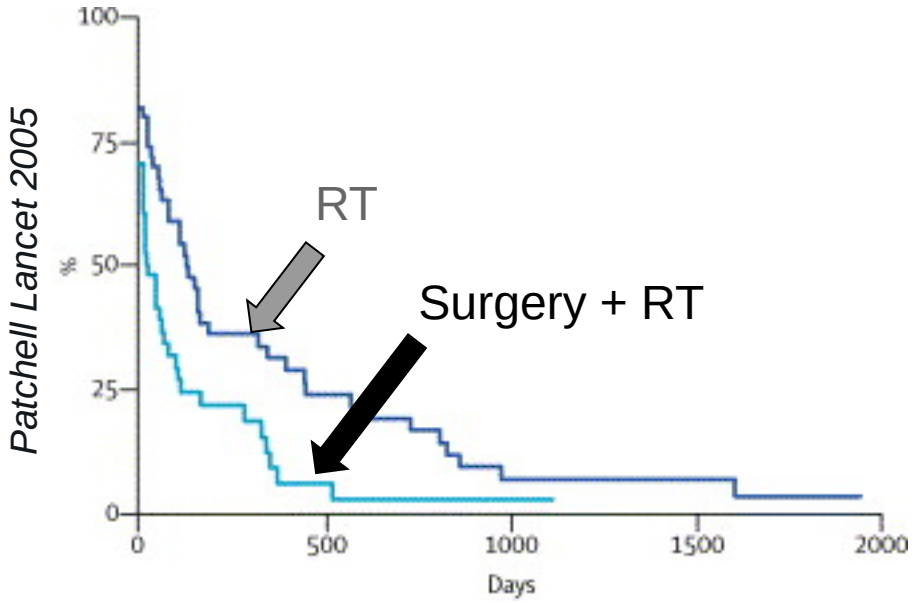
Mizumoto IJROBP 2011

	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


SAFETY
FIRST
FAA
Bennett
THE CHRISTIAN SCIENCE MONITOR

Safety of spine SBRT: myelopathy

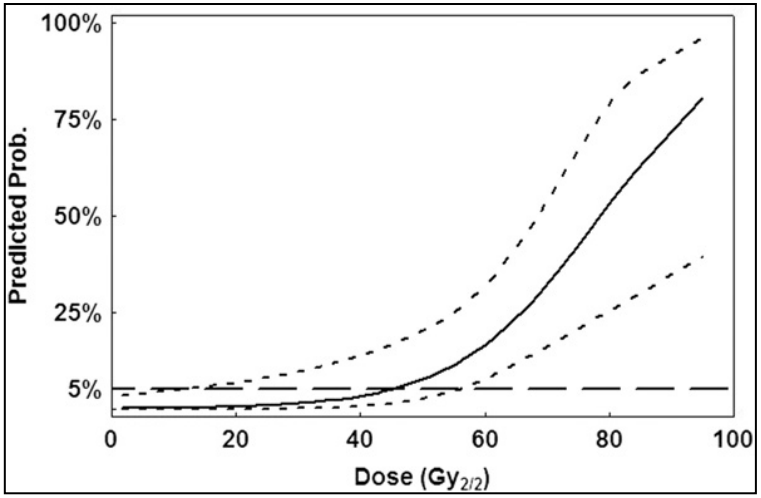
Study	# events	OAR definition	Dose in patients with radiation myelopathy	Conclusion
Ryu 2006	**1 / 177**	SC 6mm CC of TV	9.6Gy to 10%	10% < 10Gy
Gibbs 2009	**6 / 1075**	NS	D_{max} 8.5 – 26.2Gy	$1cm^3$ < 8Gy
Sahgal 2010	**5 / 24** case control study	Thecal sack	D_{max} median 59Gy ($nBED_{2/2}$)	D_{max} below thresholds using LQ model

- (Very) Few patients developed radiation induced myelopathy
- Dose – response inconclusive
- However: follow-up short in majority of patients

Safety of spine SBRT: myelopathy

Multi-institutional analysis:

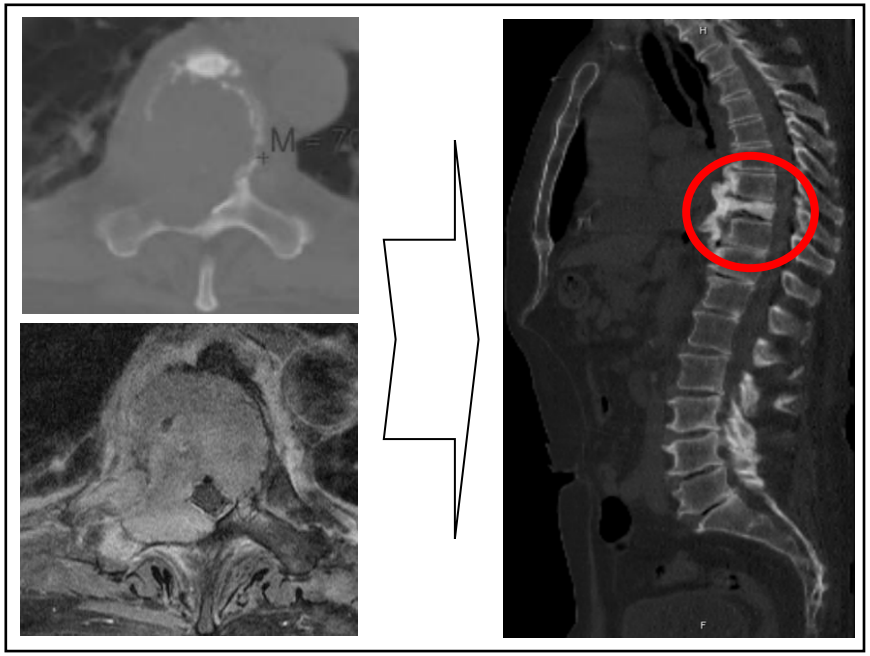
- 9 cases with radiation induced myelopathy
- 66 cases w/o radiation induced myelopathy *Sahgal IJROBP 2012*



	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

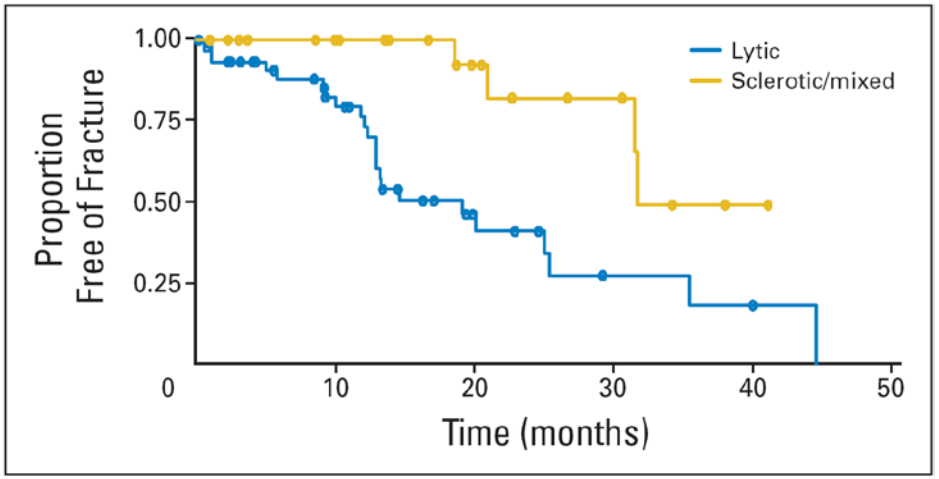
Vertebral compression fractures



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

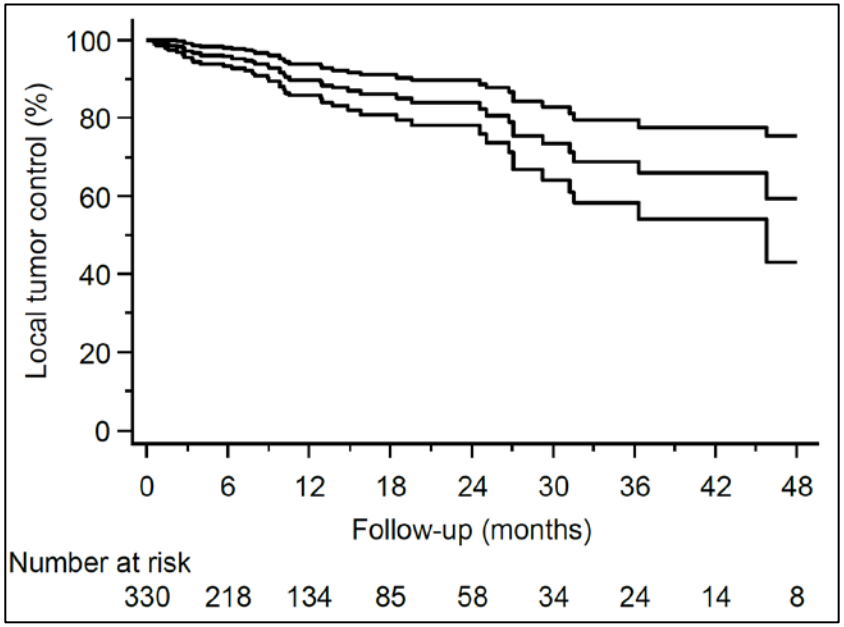
- Osteolytic metastases
- Kyphotic/scoliotic deformity

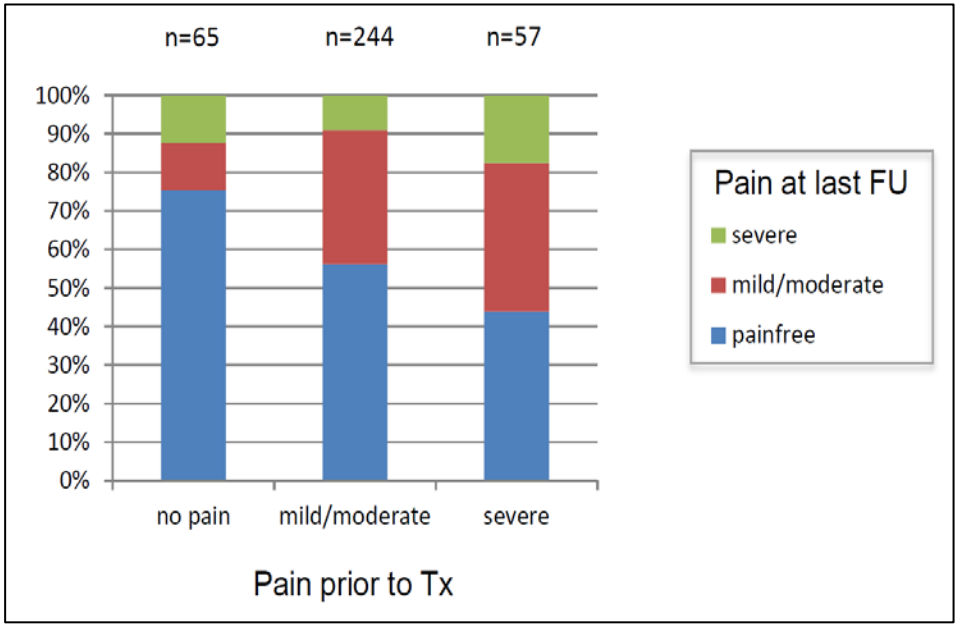
Local tumor control after spine SBRT

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	

Local tumor control and pain control

Guckenberger Radiat Oncol 2014





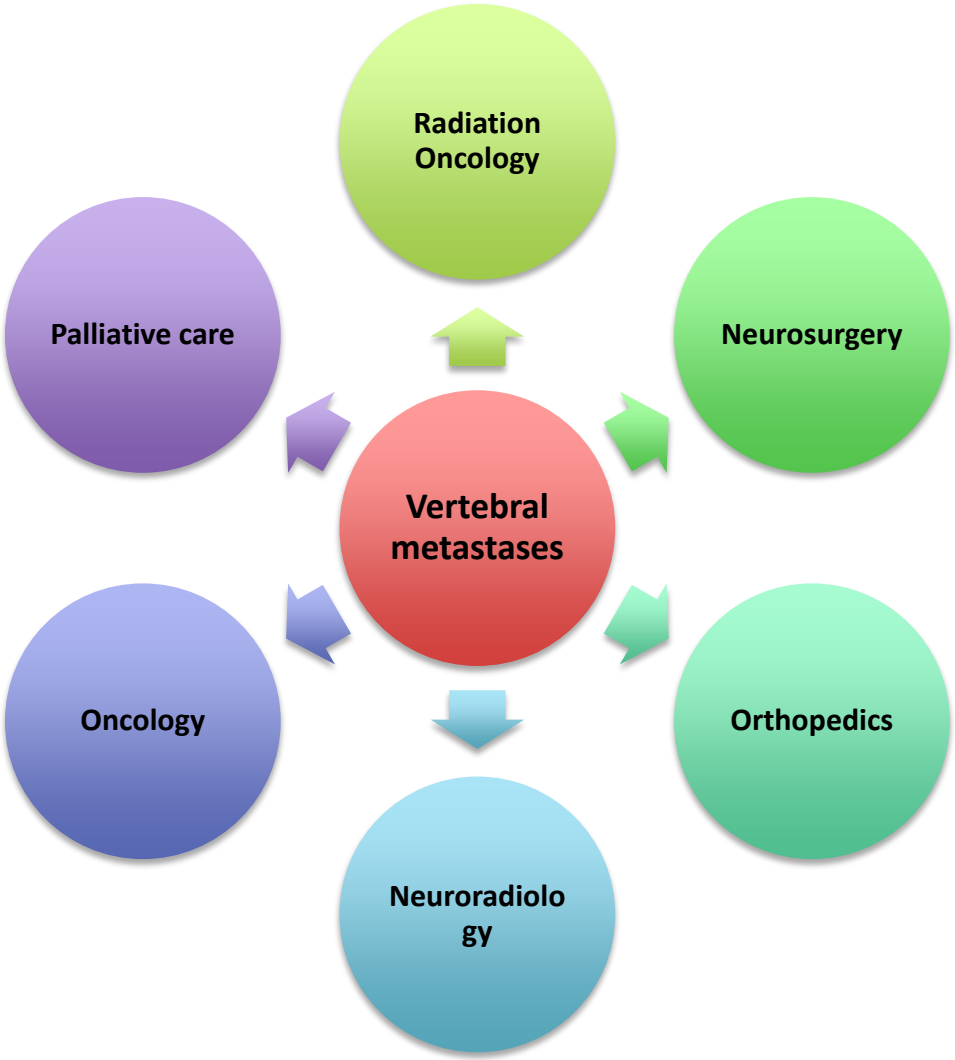
Long-term **local tumor** control

Long-term **pain** control

Long-term local tumor control -> Long term pain control

CONCLUSIONS

INTERDISCIPLINARY



CHALLENGE

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

Stereotactic body radiotherapy for vertebral metastases

Matthias Guckenberger

UniversityHospital Zurich

ESTRO

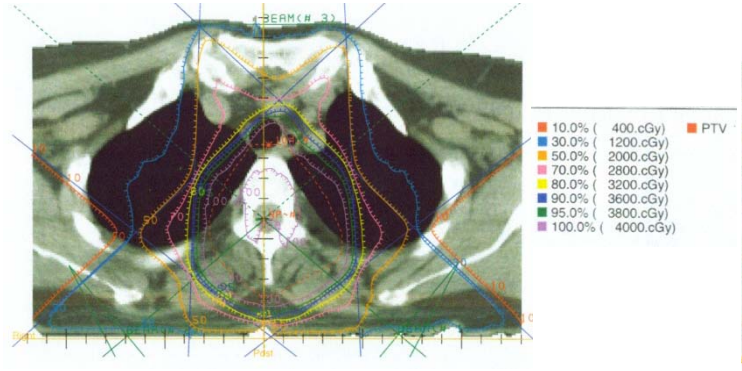
Case example: re-irradiation for verterbral metastasis

- 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

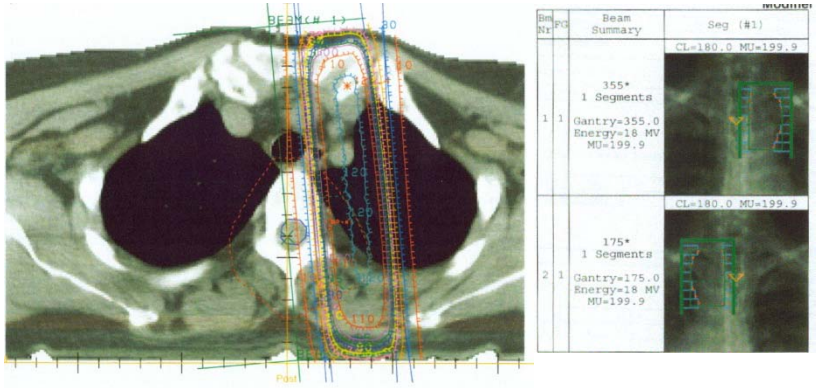
- Developed breast cancer in 2002 and bone metastases in 2007
- In 2008, a palliative radiotherapy of thoracic vertebras 2-4 was performed with a total dose of 40Gy
  - 20 Gy were delivered using posterior wedged fields
  - 20 Gy were delivered using AP/PA fields with sparing of the spinal cord

Case example: re-irradiation for verterbral metastasis

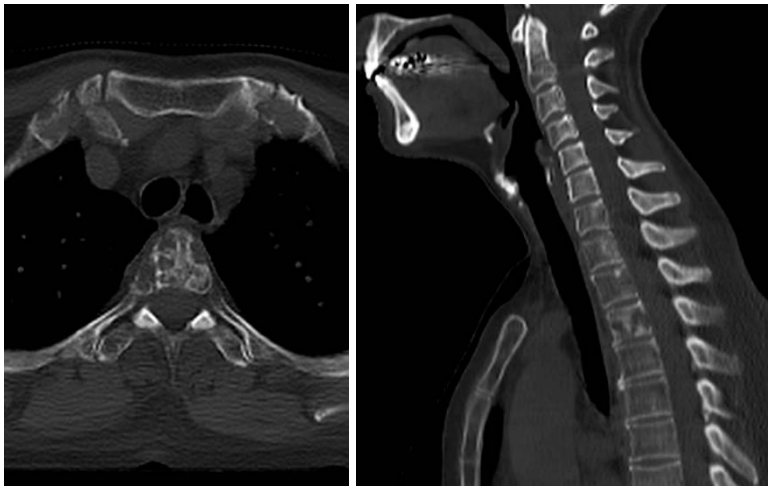
20 Gy wedged fields



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

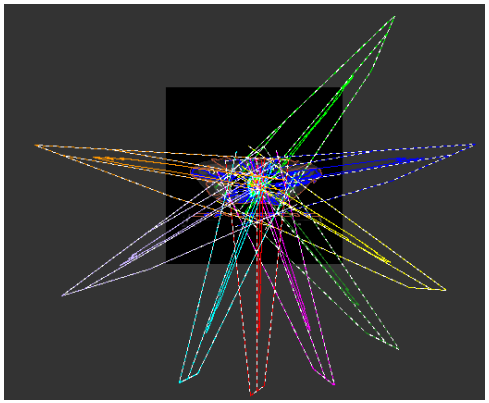
Assumption of spinal cord tolerance:

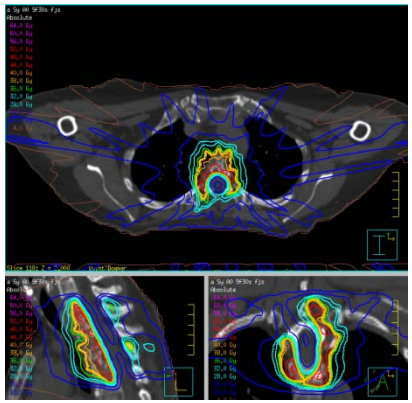
40Gy	-31 years
20 + 2 Gy	-2 years
62Gy	physical dose ->
30Gy	**residual „damage“**

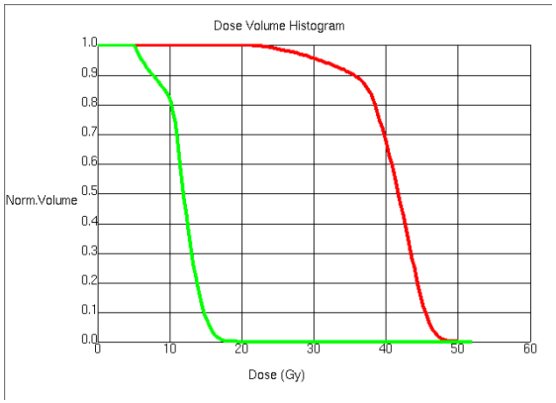
- **Maximum dose of 20Gy in 15 fractions**

- Worst case scenario
- 50% recovery because of (very) long interval

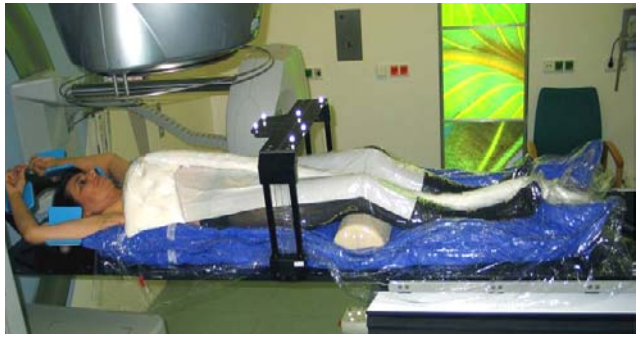
Case example: re-irradiation for verterbral metastasis

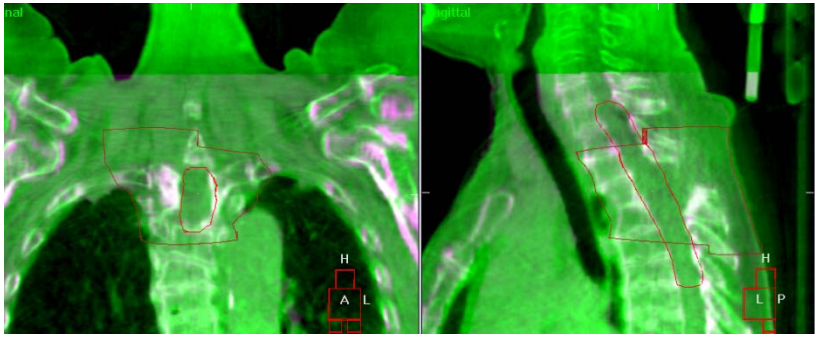






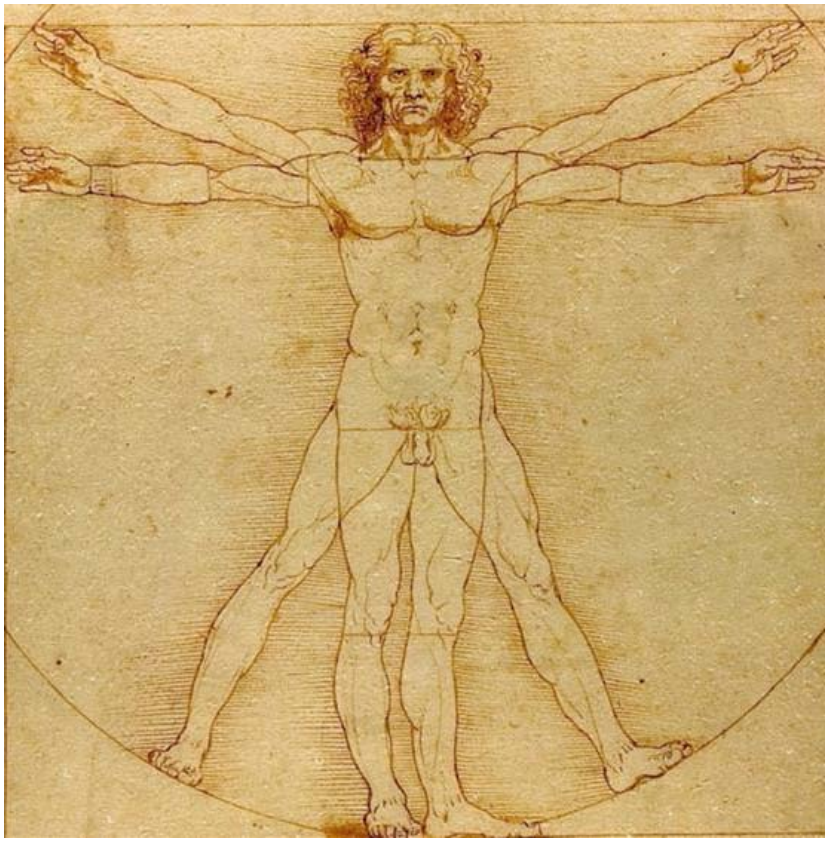
Target definition: only affected parts of the vertebrae included into TV
IMRT planning: 40Gy in 15 Fx with SC_{max} 20Gy





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-irradiation

- 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

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

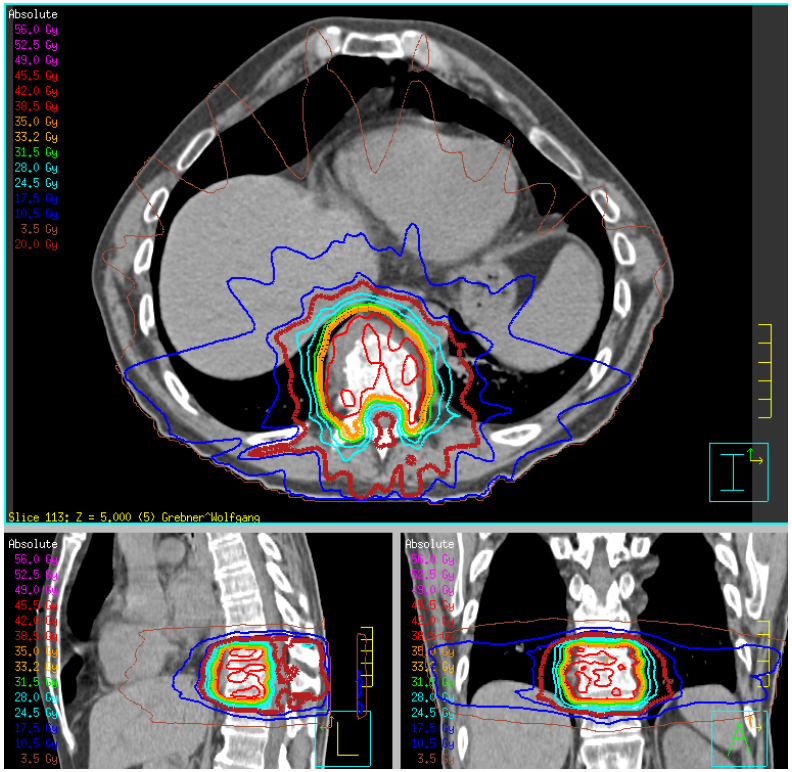
Skin & mucosa	Small intestine	Mesechymal	Bone
Full – partial	Partial	Partial	Partial

Lung pneumonitis	Lung fibrosis	Heart	Bladder	Kidney
Full – partial	No	No	No	No

Factors associated with recovery:

- Initial biological dose in relationship to tolerance dose
- Initial volume irradiated
- Time interval between treatment courses

Re-irradiation for spinal metastases

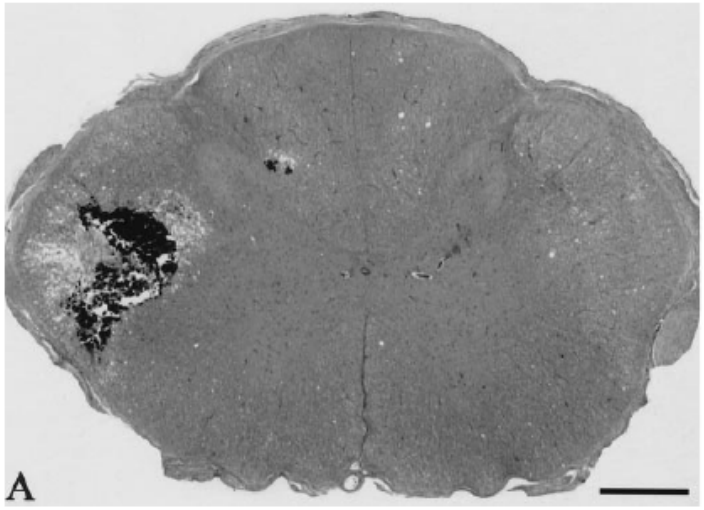


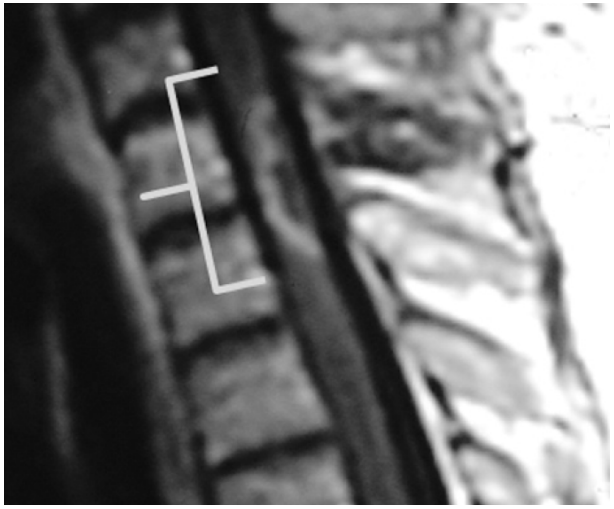
Clinical practice of SBRT for re-irradiation of spinal metastases

1. Spinal cord tolerance

2. Dose and fractionation

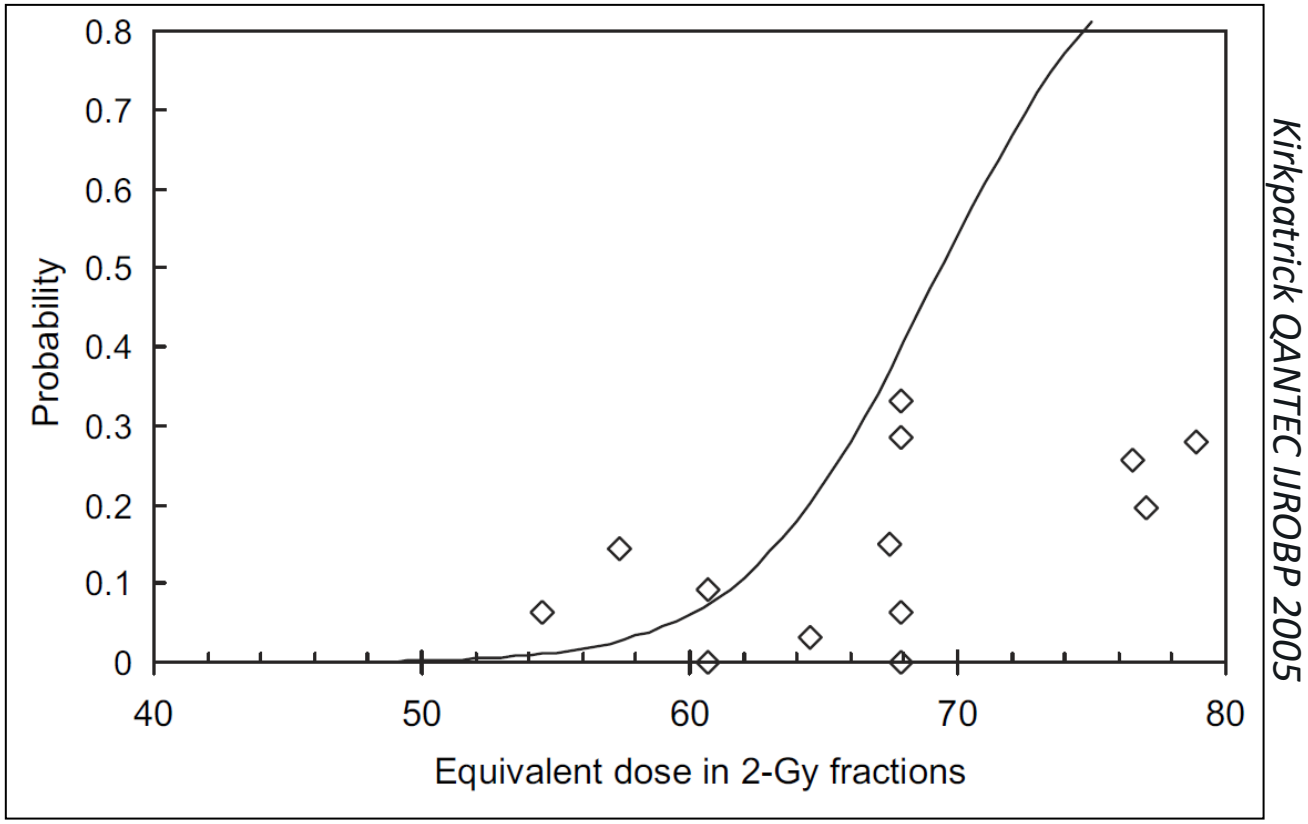
Radiation induced myelopathy





- Appearance of signs/symptoms of sensory or motor deficits, loss of function or pain
- Confirmed by magnetic resonance imaging
- Occurs less between 6 months and 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**

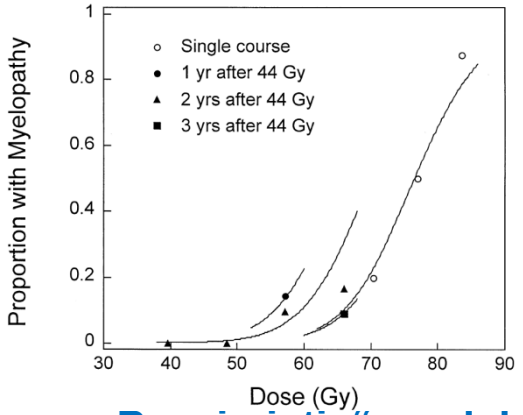
Optimistic model:

➢ Recovery of 76%, 85% and 101% after 1, 2 and 3 years

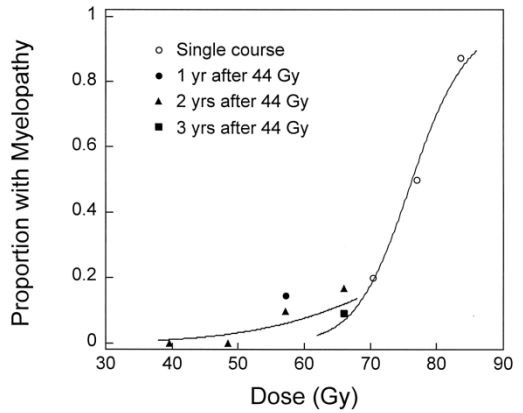
Conservative model:

➢ Recovery of 61%

„Optimistic“ model



„Pessimistic“ model



Ang IJROBP 2001

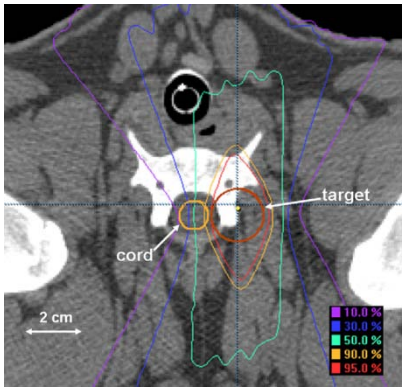
Spinal cord tolerance – reirradiation: Animal studies

26 minipigs, uniform 30Gy in 10 Fx

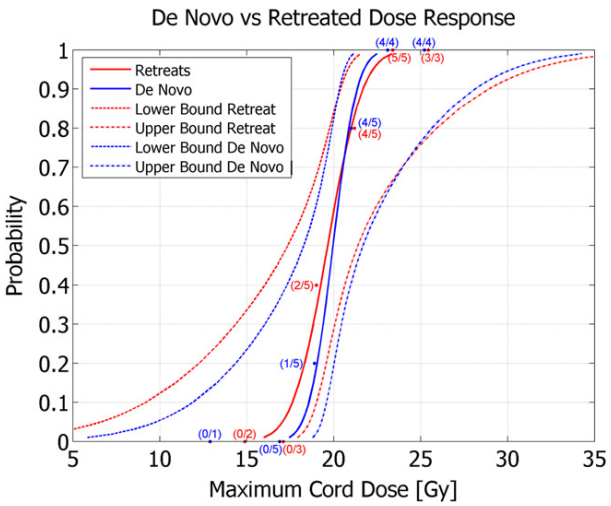
Reirradiation after 1 year:

- Inhomogeneous (10-90%) SRS
- 14.9Gy – 25.4Gy

➢ **ED_{50} of 19.7Gy**



Medin IJROBP 2011



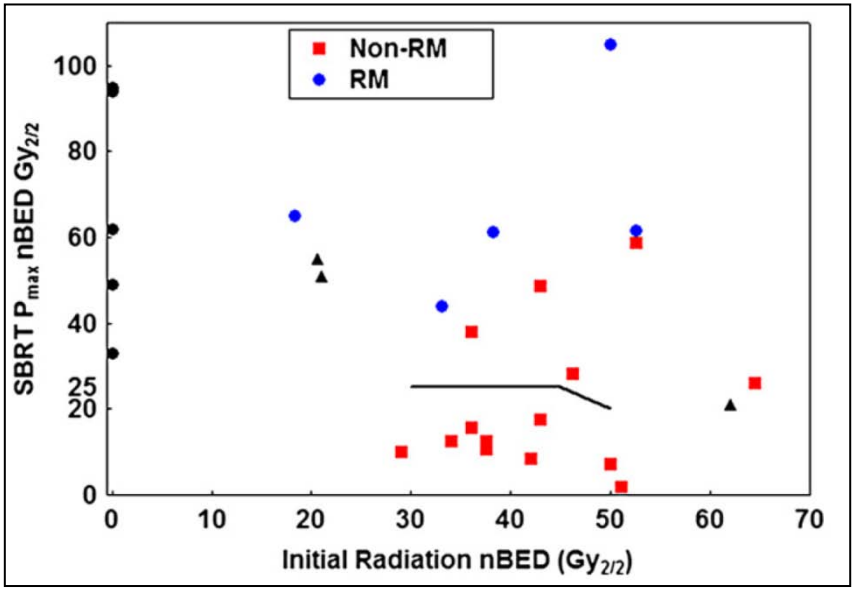
➢ Identical SRS tolerance as in the primary situation

➢ Full recovery of 30Gy in 10 Fx within 1 year

UniversityHospital Zurich

ESTRO

Spinal cord tolerance: re-irradiation with hypofractionation (SBRT)



Sahgal IJROBP 2010:

Case-control study:

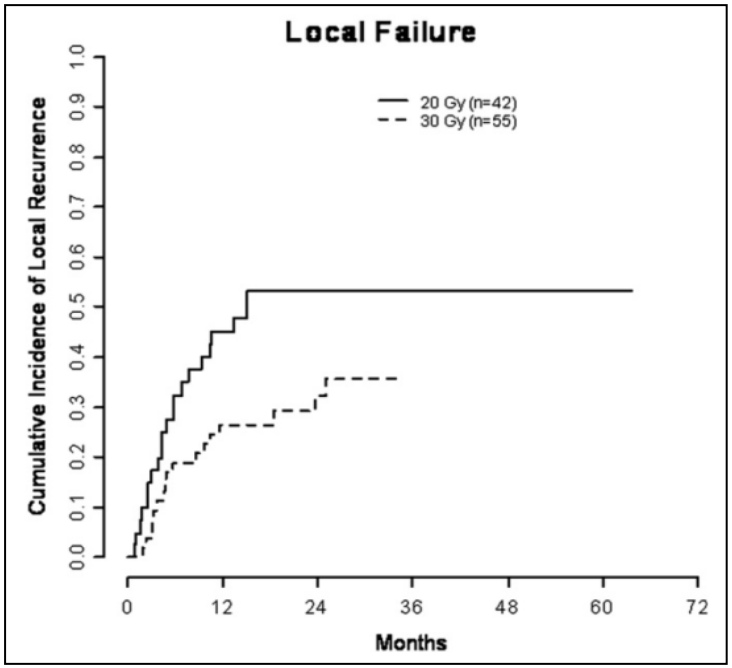
- 5 cases of RM after SBRT
- Thecal sack as OAR
- Maximum dose to thecal sack
- 2Gy equivalent with α/β=2Gy

Clinical Practice: **0% risk of myelopathy if**

- Initial course <50Gy (EQD2/2)
- SBRT course <25Gy (EQD2/2)
- Interval >5 months

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

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

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

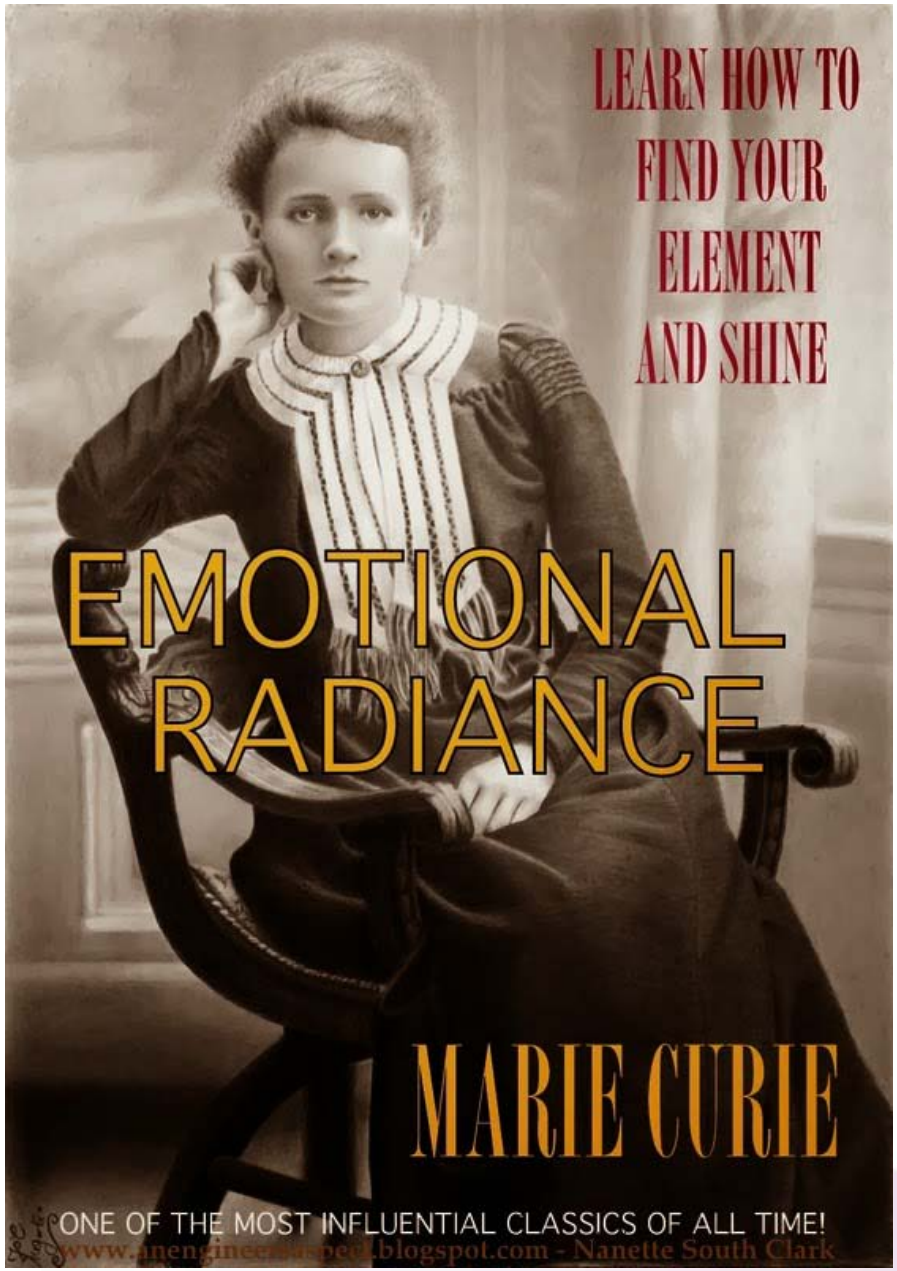
Study	# patients / cases	Follow-up (months)	Myelopathy	Lcoal / pain control
Milker-Zabel 2003	18 / 19	12.3	0%	95%
Mahan 2005	8 / 8	15.2	0%	100%
Sahgal 2009	25 / 37	7	0%	70%
Choi 2010	42 / 51	7	n=1 G4	73%
Sterzing 2010	36 / 36	7.5	0%	63%
Damast 2010	94 / 97	12.1	0%	66%
Garg 2011	59 / 63	13	n=2 G3 peripheral 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

- Despiste week level of evidence, there appears to be spnal cord recovery
- Spinal cord recovery reaches **50** – 100%
- Spinal cord 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



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CLINICAL PRACTICE LIVER SBRT

A. Méndez Romero , M. Hoogeman

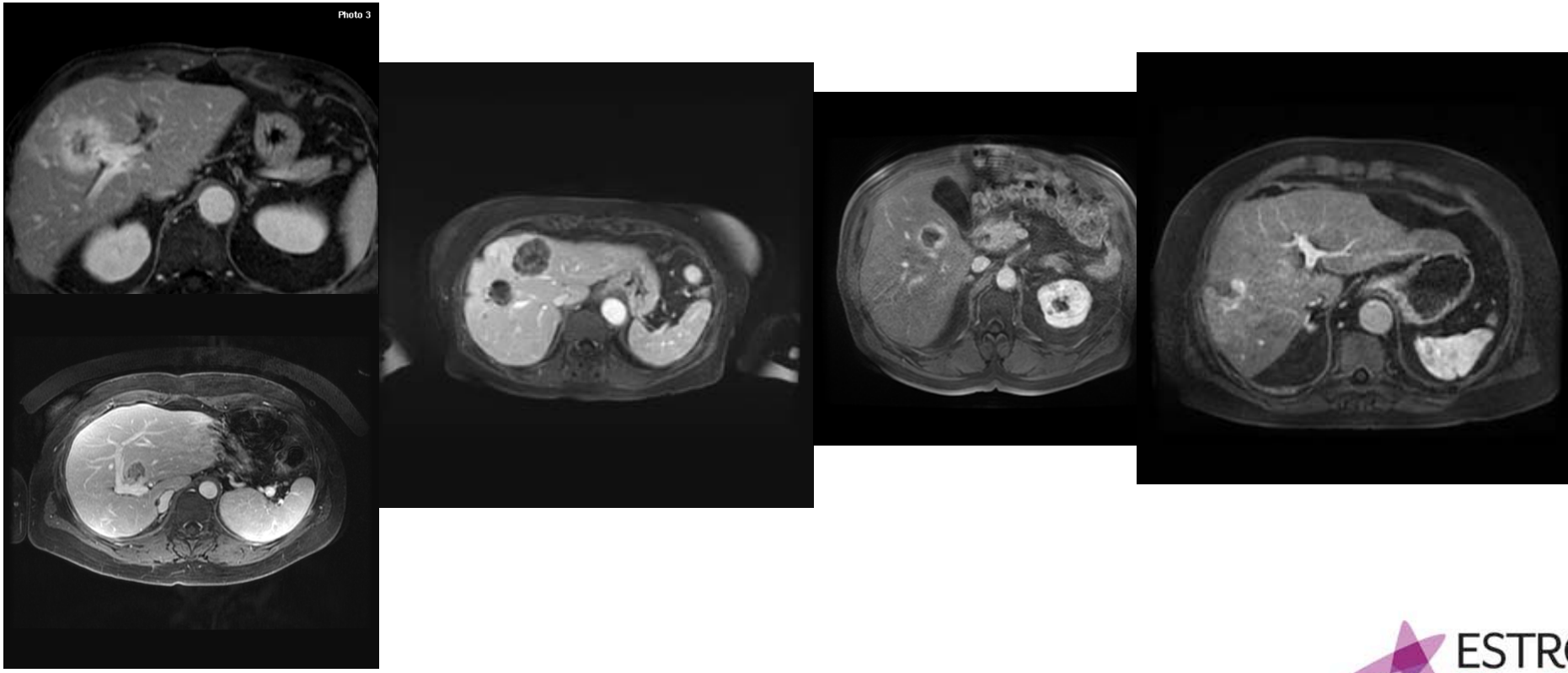
LEARNING OBJECTIVES

Considerations to treat a liver patient with SBRT:

- Immobilization
- Respiratory management
- Fiducials
- Imaging
- Planning
- Daily setup repositioning

INDICATIONS LIVER METASTASES

- No strict criteria
- 1 - 3 metastases (although 5 reported) and ≤ 6 cm
- Adequate liver function
- If present, limited and potentially treatable systemic disease



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IMMOBILIZATION

RESPIRATORY MANAGEMENT

Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer. R. van den Begin. Radioth and Onc.

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BREATHING MANAGEMENT

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Impact of inadequate respiratory motion management in SBRT for oligometastatic colorectal cancer

Robbe Van den Begin, Benedikt Engels *, Thierry Gevaert, Michaël Duchateau, Koen Tournel, Dirk Verellen, Guy Storme, Mark De Ridder

Department of Radiotherapy, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Belgium

ARTICLE INFO

Article history:
Received 11 August 2014
Received in revised form 3 November 2014
Accepted 3 November 2014
Available online xxxx

Keywords:
SBRT
Oligometastases
Colorectal cancer
Local control
Local failure
Motion management

ABSTRACT

Purpose: Stereotactic body radiotherapy (SBRT) in oligometastatic colorectal cancer (CRC) resulted in a disappointing 1-year local control rate of 54% in our experience. We aimed to determine the root cause(s).
Methods: 47 oligometastatic CRC patients were treated with SBRT by helical tomotherapy to a dose of 40 or 50 Gy in 10 fractions, without specific respiratory motion management and PTV-margins of 10–10–12 mm in all patients. The local recurrences (LRs) were delineated on diagnostic PET–CT scans and co-registered with initial planning CTs. LRs were classified as in-field or marginal with respect to the initial dose distribution, and predictors for LR were determined.
Results: Out of 105 irradiated metastases, LR modeling yielded 15 in-field and 15 marginal failures. Metastases in moving organs (liver and lung) exhibited a local control of 53% at 1-year (95% confidence interval (CI): 38–67%), compared to 79% for lymph nodes (95% CI: 32–95%). The first group exhibited a sixfold increased risk compared to the latter on multivariate analysis ($p = 0.01$).
Conclusions: The nature and locations of LR indicated that dose prescription and methodology were both inadequate for liver and lung metastases. This study demonstrates the need for individual respiratory motion management and a biological effective dose of >75 Gy.
 Radiotherapy and Oncology xxx (2014) xxx–xxx

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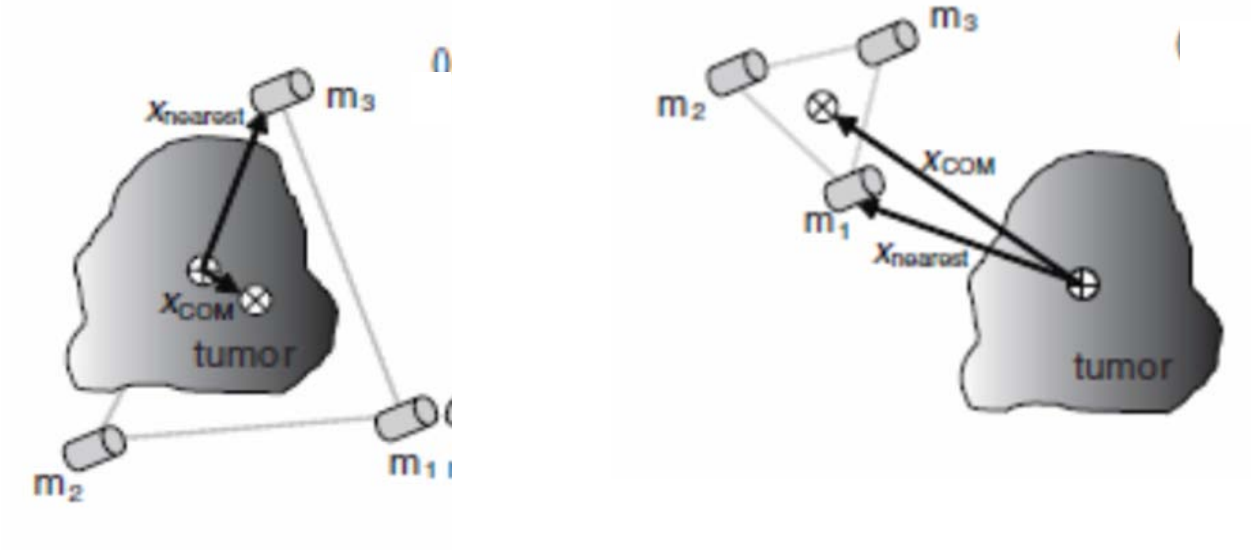
FIDUCIAL IMPLANT

- Ultrasound – guided (less spatial accuracy)

- CT – guided



Seppenwoolde Y. Physics in Medicine and Biology 2011.
Treatment precision of image-guided liver SBRT using implanted fiducial markers depends on marker tumor distance

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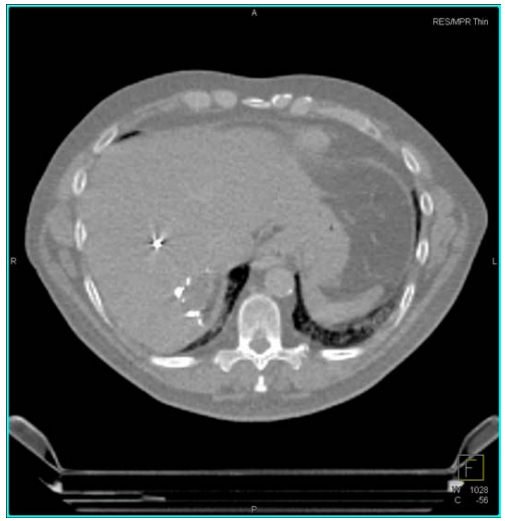
COMPLICATIONS

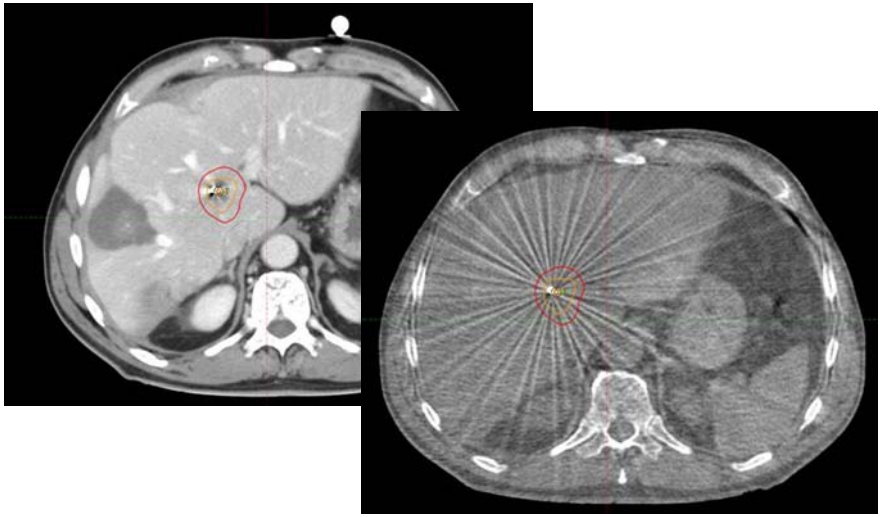
- Abdominal pain
- Migration (cardiac embolization/ hepatic infarct)
- Biloma
- Pleural effusion
- Bleeding (minor)
- Tumor implant along the needle tract

PURPOSE FIDUCIAL IMPLANT

- Breathing motion measurement



- Daily evaluation tumor position assessment



Courtesy Dr Haasbeek VUMC

Tracking CK Erasmus MC

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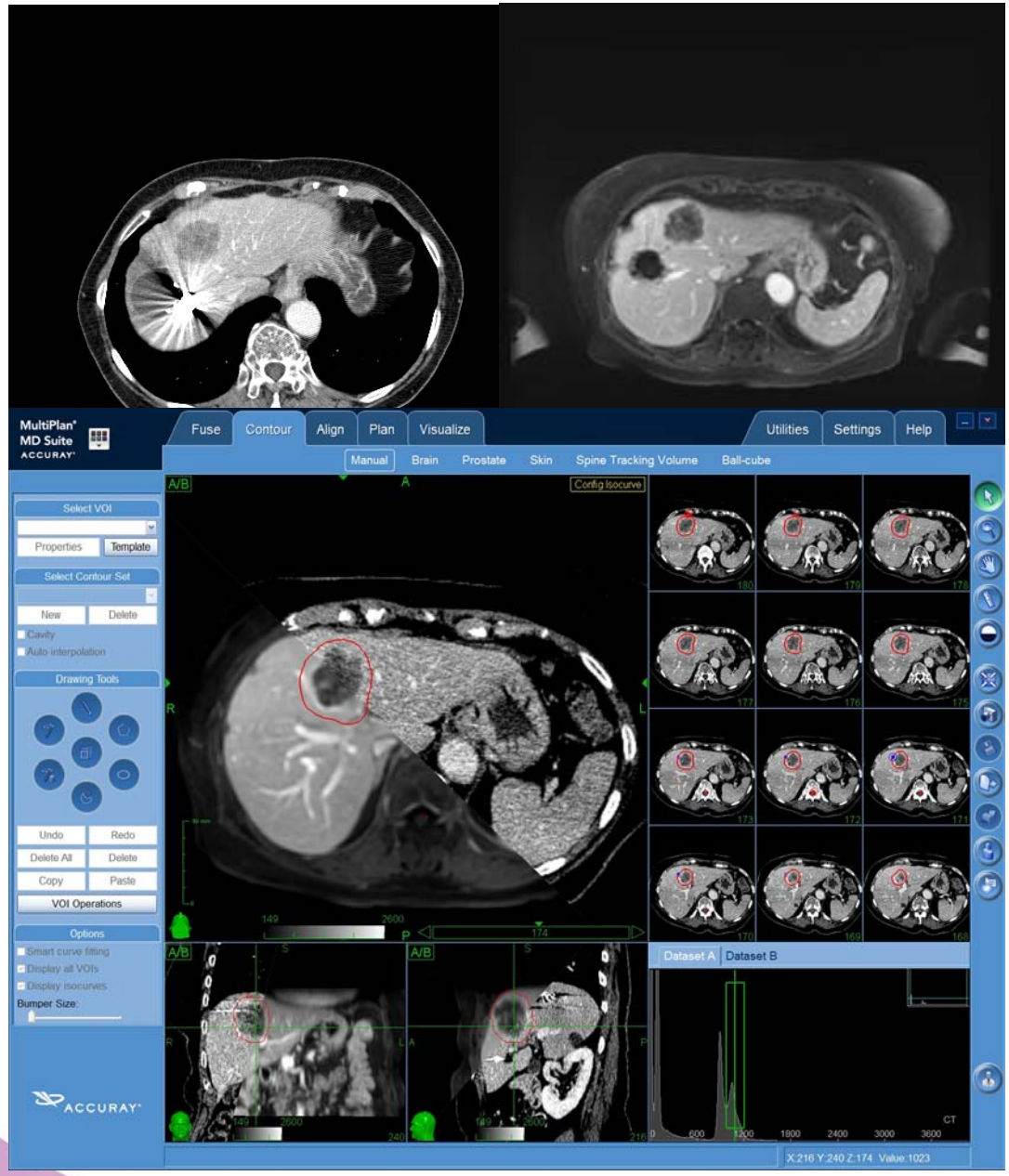
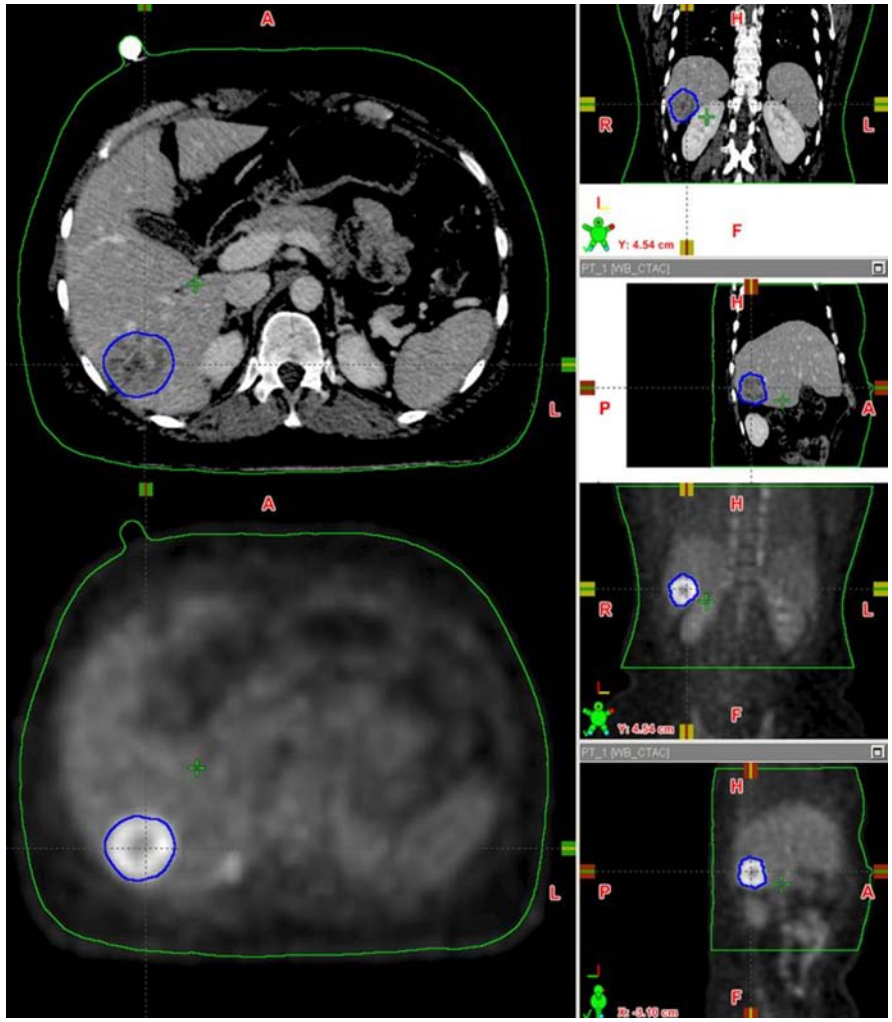
IMAGING FOR DELINEATION





Courtesy Dr Haasbeek VUMC

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CT PLANNING

- In Erasmus MC use of CK technology:

-Fiducials

-CT planning arterial or venous phase in expiration

-4D CT without contrast

-GTV=CTV

- Institutions with other linac technology:

-Not always fiducials

-Breath hold CT or 4D CT with contrast for planning

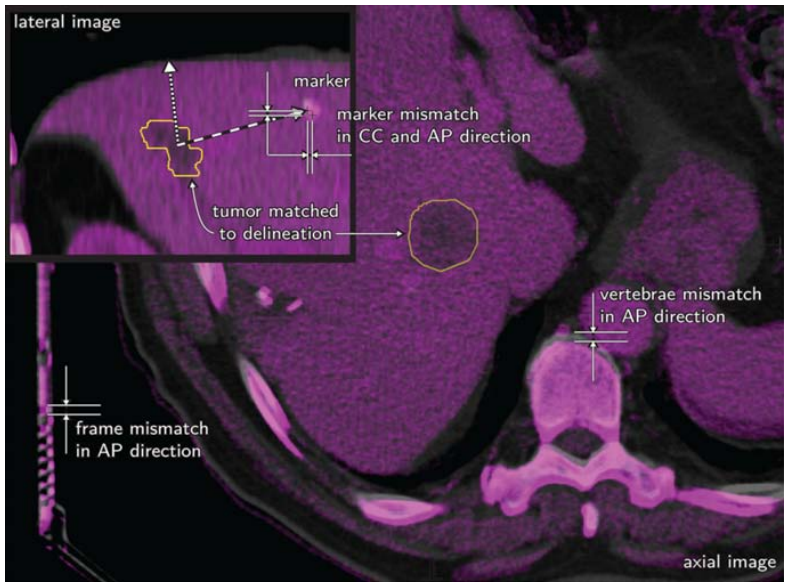
-4D CT

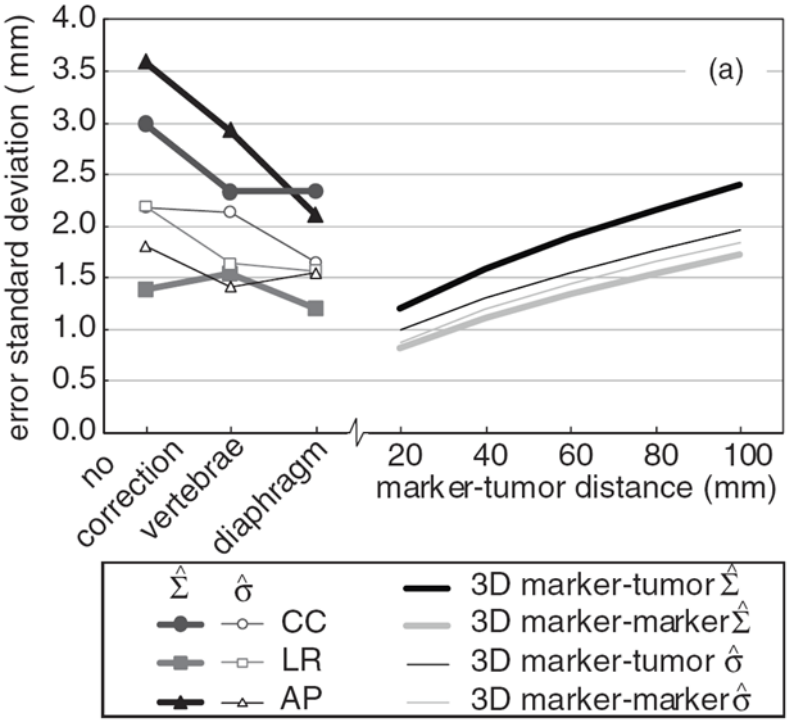
-Frequently GTV=CTV

MARGINS AND IGRT SOLUTIONS

Margins at Erasmus MC

- Patient specific margins are used for CyberKnife treatments that use fiducial marker tracking





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

Margins at Erasmus MC using CK

- Distance between COM of marker configuration and the tumor
- Motion amplitude of the tumor assessed by the markers

Afstand marker COM-tumor COM (cm)

	2 cm			3 cm			4 cm			5 cm			6 cm		
Breathing motion (cm)	CC	AP	LR	CC	AP	LR	CC	AP	LR	CC	AP	LR	CC	AP	LR
0.5	4.7	4.7	4.7	5.2	5.2	5.2	5.6	5.6	5.6	6	6	6	6.4	6.4	6.4
1	4.8	4.7	4.7	5.2	5.2	5.2	5.7	5.7	5.7	6.1	6.1	6.1	6.5	6.5	6.5
1.5	4.8	4.8	4.8	5.3	5.3	5.3	5.8	5.8	5.8	6.2	6.2	6.2	6.6	6.6	6.6
2	5			5.4			5.9			6.3			6.7		
2.5	5.1			5.6			6			6.4			6.7		
3	5.3			5.7			6.2			6.6			7		

Marges in mm

- Table is valid for prescription iso-dose lines of 60-70%. For prescription at 80% add 0.3 mm.

- Disclaimer: for tracking only!

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Distribution of Margins Used Clinically

	Margin (mm)	Number of patients
Isotropic	5	4
Isotropic	5.5	1
Isotropic	6	10
Isotropic	7	3
Anisotropic		1

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Solutions for IGRT

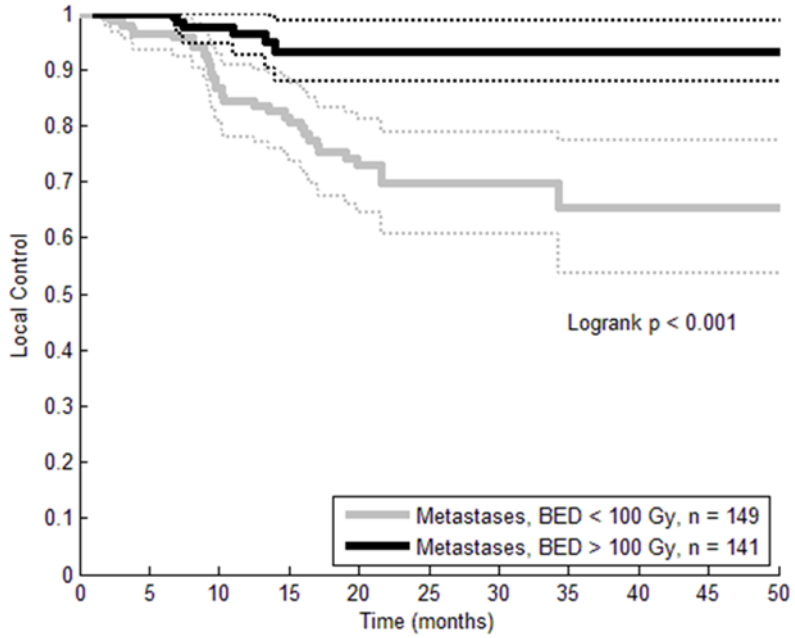
- Localize the tumor for perfect daily alignment
  - Implanted markers
  - Liver contour
  - Bony setup
- Respiratory motion managements strategy
  - Tracking
  - Gating
  - Patient specific margin based on an alignment on average tumor position
  - ITV and on tumor (surrogate)

Solution for IGRT

	Technique	Localization	IGRT	Margins
A	CyberKnife	Fiducials	Respiratory motion tracking; free breathing	CTV + 5-7 mm
B	Linac with CBCT	Liver contour	CBCT match on liver contour; free breathing	ITV + 3 mm
C	Novalis Exactrac	Fiducials	Gating using kV planar images	ITVg + 5-7 mm
D	Linac with CBCT	Liver contour	CBCT match on liver contour; free breathing (breath hold if needed)	ITV + 5-10 mm
E	Linac with CBCT	Fiducials	Mid-ventilation; free breathing	CTV + 10 mm

LOCAL CONTROL LIVER METASTASES

BED ≤ 100 Gy_{10}: 70% at 2 years
BED > 100 Gy_{10}: 93% at 2 years
Logrank p < 0.001



Kaplan-Meier curves for local control following SBRT after grouping patients by BED

Local Control following Stereotactic Body Radiotherapy for Liver Tumors: A Preliminary Report of the AAPM Working Group for SBRT . N. Ohri, A. Jackson, A. Mendez Romero, M. Miften, R. K. Ten Haken, L. A. Dawson, J. Grimm, E. D. Yorke, W. A. Tomé

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CONSTRAINTS

	3x20Gy	5x12Gy	8x7,5Gy
Liver - GTV (α/ß=3) (Liver metastases)	≥700ml <15Gy	≥700ml <18Gy	≥700ml <21.6Gy
Spinal cord (α/ß=2)	≤18Gy	≤22.5Gy	≤27.2Gy
Esophagus (α/ß=3)	≤27Gy	≤33Gy	≤40Gy
Stomach (α/ß=3)	<30Gy and ≤5ml ≤22.5Gy	<36.5Gy and ≤5ml ≤26Gy	<44Gy and ≤5ml ≤32.8Gy
Small bowel (α/ß=3)	<30Gy	<36.5Gy	<44Gy
Kidney (α/ß=3)	67% volume r kidney<15Gy	67% volume r kidney<18Gy	67% volume r kidney <21.6Gy

Liver metastases: BED >100Gy (α/ß=10)

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MESSAGE TO TAKE HOME

- Different technologies are available to deliver SBRT for liver
- Select within your team which system suits you better
- Imaging is an important issue for liver SBR
- Fiducials are a helpful tool
- Published constraints make your life easier!

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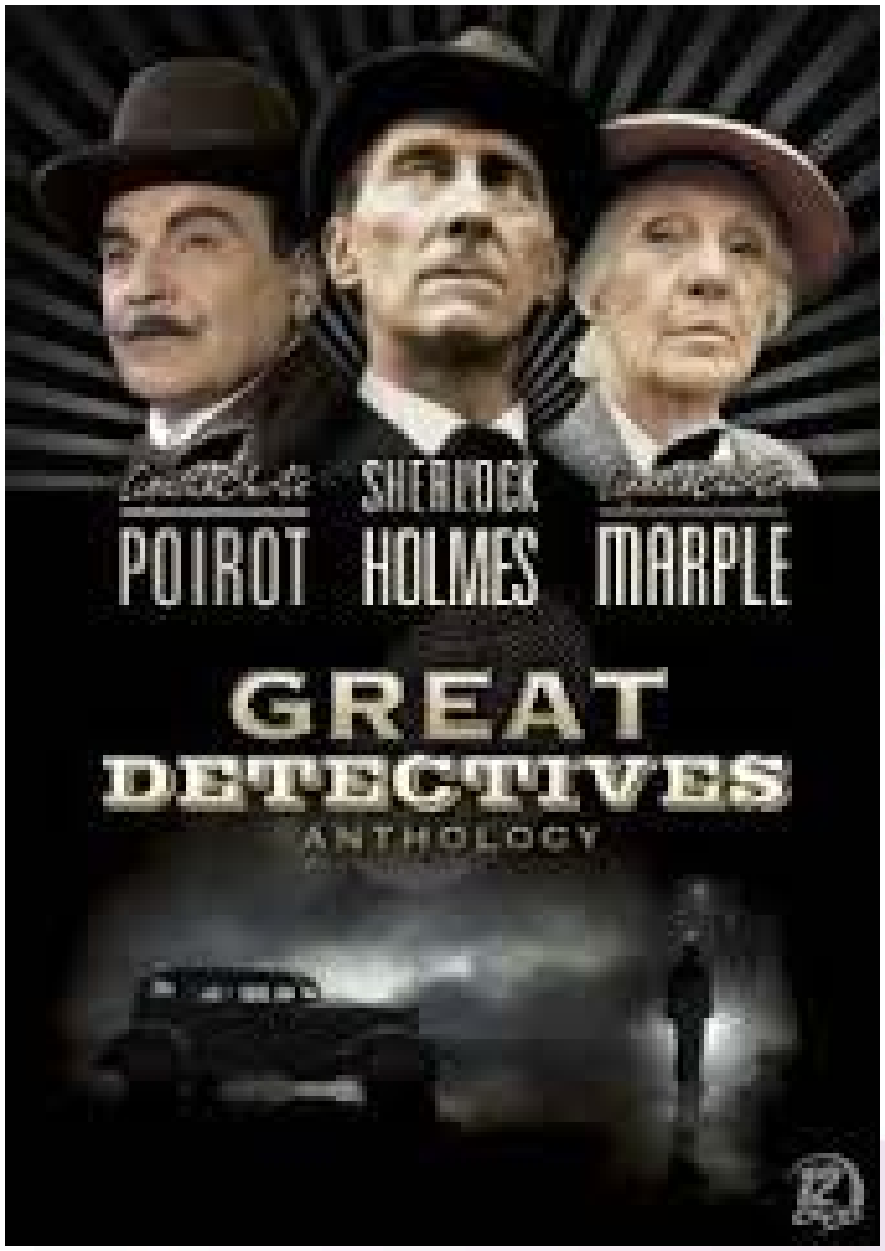

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IS THERE A ROLE FOR SBRT IN THE TREATMENT OF PRIMARY LIVER TUMORS ?

A. Méndez Romero

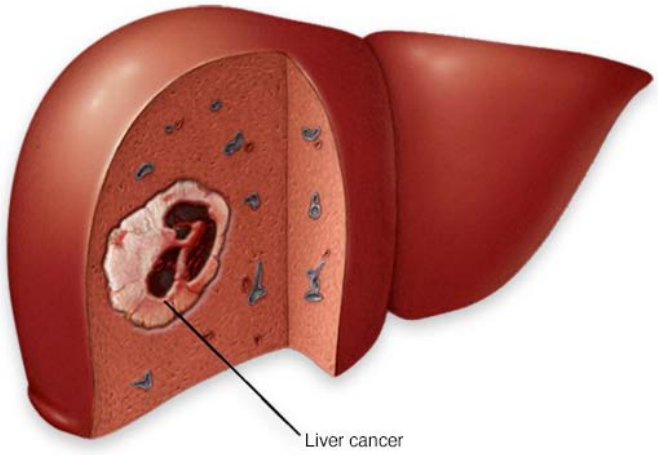
LEARNING OBJECTIVES

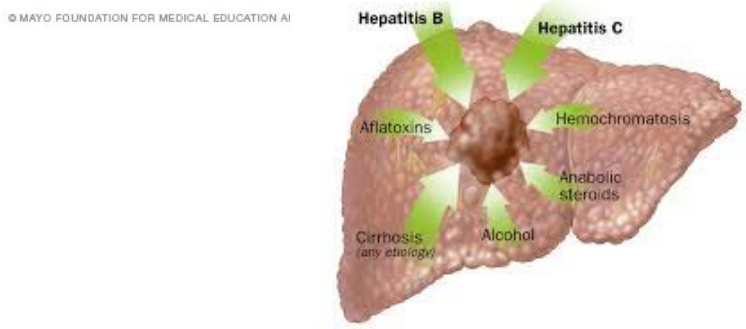
- Primary liver tumors
- Treatment strategies
- SBRT as a radical treatment option or a pre-transplant approach
- Toxicity
- Dose volume recommendations

PRIMARY LIVER TUMORS

Hepatocellular ca (hepatocytes)

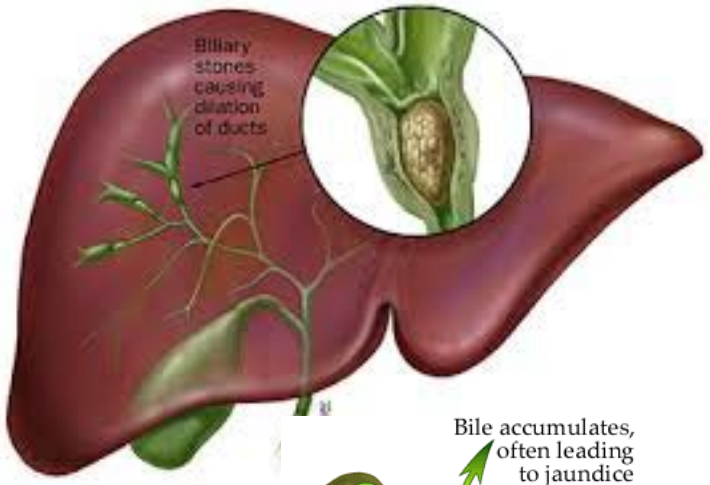
HCC

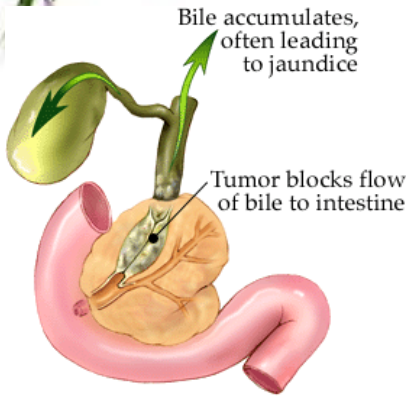




Cholangio ca (bile duct cells)

CCA





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IS THERE A ROLE FOR SBRT IN HCC?

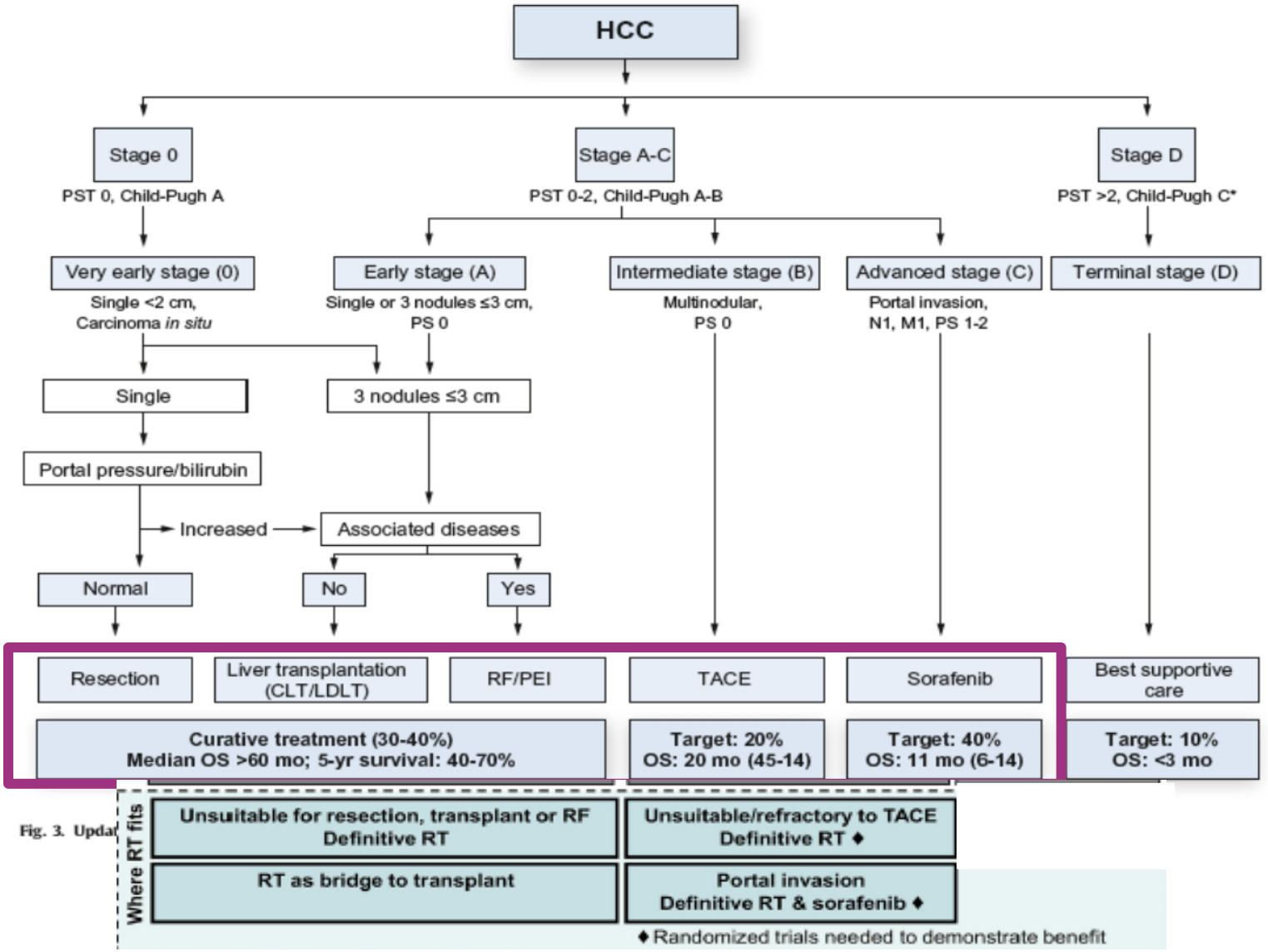

Fig. 3. Updat

EASL-EORTC Clinical Practice Guidelines: Management of HCC, EJC 2012, and Klein J IJROBP 2012

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HCC TREATED RADICALLY

- No clear limit in tumor size/number/ BCLC

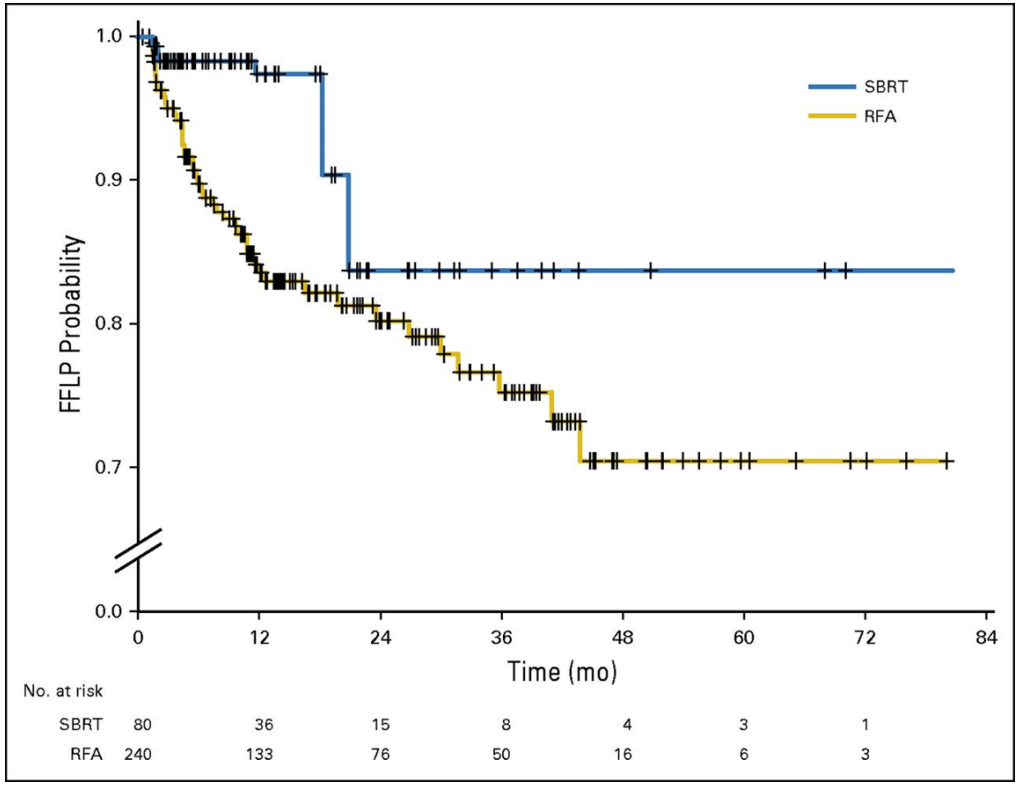
- Frequently:
  - Not eligible for resection and often not for RFA or for TACE
  - ≤ 5-<10cm
  - 1-3 tumors
  - Most experience gained in Child A
  - BCLC: A-B-C

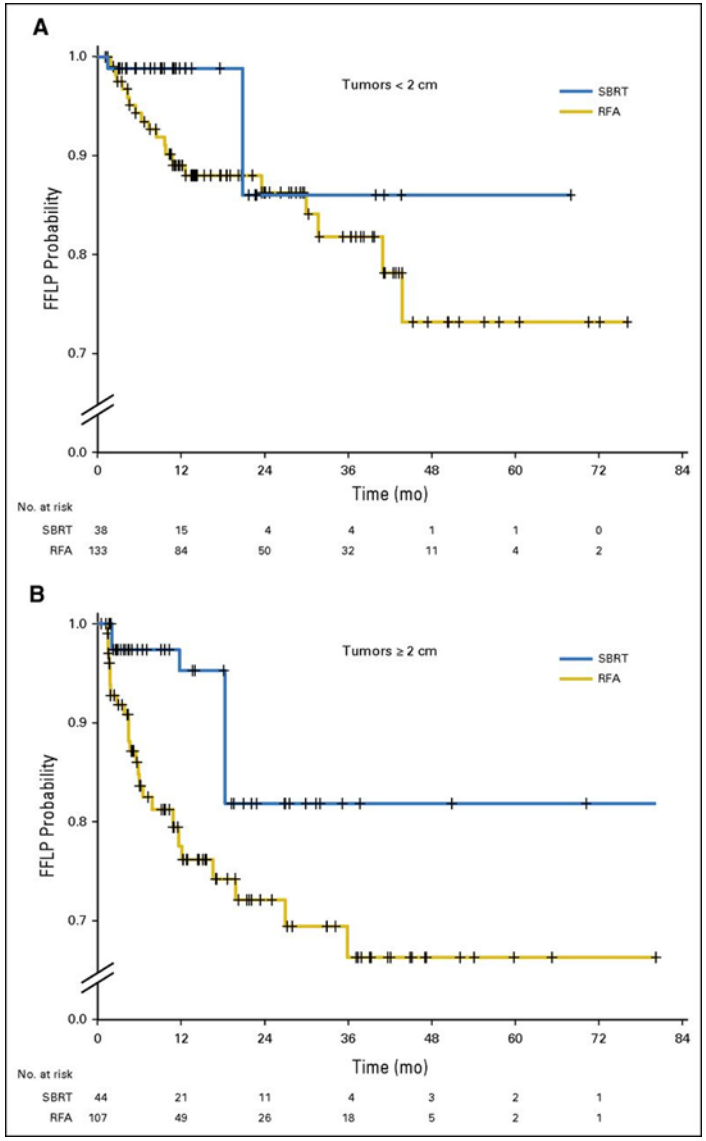
HCC TREATED RADICALLY

AUTHOR	DESIGN	CHILD-PUGH / BCLC GRADE	NUMBER OF PATIENTS	DOSE FRACTIONATION SCHEME	2 y LOCAL CONTROL	2y /MEDIAN SURVIVAL
Andolino (No transplant) 2010	Retrospective	A B /A-C	24 13	3x12-16Gy 5x8Gy	87%	47%/ 20 Months
Kang 2012	Phase II	A B7 /A-C	41 6	3x14-20Gy	95%	69%/ Not reported
Bujold 2013	Phase I-II	A /A-C	102	6x4-9Gy	87% at 1 y	34%/ 17 Months
Bibault 2013	Retrospective	A B /A-C	67 8	3x8-15Gy	90%	50%/ 15 Months
Sanuki 2013	Retrospective	A B /A	158 27	5x8Gy 5x7Gy	93%	83%/ Not re
Park 2013	Retrospective	A B /A-B	19 7	10x4-5Gy	88%	eported
Kimura 2015	Retrospective	A B /A-B	56 9	4x12Gy (peripherally loca tumor		76%/ 41 Months
Su 2016	Retrospective	A B /A-B	114 18	42-46 28- 1 fraction	84%	82%/ Not reported

LOCAL CONTROL 2y 84 – 100 %

SBRT vs. RFA





Wahl DR. Outcomes after SBRT or RFA for HCC. JCO 2016

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TACE COMBINED WITH RT

Abstract

Background: In previous randomized trials, transarterial chemoembolization (TACE) has shown an improvement of survival rate in hepatocellular carcinoma (HCC) when combined with radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) or other therapies. The aim of this meta-analysis was to evaluate the effectiveness of combination therapy of TACE with RFA, PEI, radiotherapy (RT), three-dimensional conformal radiation therapy (3D-CRT) or High-Intensity Focused Ultrasound (HIFU).

Methods: Randomized or nonrandomized studies comparing TACE combined with RFA, PEI, RT, 3D-CRT or HIFU with TACE alone for HCC were included. Meta-analysis was performed using a fix-effects model in RCTs and a random-effects model among the observational studies.

Conclusions: This meta-analysis demonstrated that TACE combined with local treatments, especially PEI, HIFU or 3D-CRT could improve the overall survival status than performing TACE alone. Importantly, these results need to be validated in further high-quality clinical trials.

Liao M. TACE in combination with local therapies for HCC: A Meta-Analysis. PLOS one 2013

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SBRT COMBINED WITH SORAFENIB

- Phase I trial
- Child-Pugh A cirrhosis
- Not candidates for other standard local-regional treatments
- Sorafenib 400mg/daily 12 weeks and after that full dose
- SBRT 6 fractions (5-8.5Gy) weeks 2 and 3
- 16 evaluable patients
- Dose limiting toxicity gastrointestinal 3-4 (bleed/obstruction)
- Not recommended concurrent use SBRT-Sorafenib

Brade AM. Phase 1 Trial of Sorafenib and SBRT for HCC. IJROBP 2016

HCC TREATED PRE-TRASPLANT

- No clear limit in tumor size/number

- Frequently
  - Not candidates for RFA or TACE
  - Milan criteria (One tumor ≤5cm or 3 ≤3cm)
  - BCLC: A-B (sometimes D in Child C cirrhosis)

HCC TREATED PRE-TRASPLANT

AUTHOR	DESIGN	CHILD-PUGH/ BCLC GRADE	NUMBER OF PATIENTS	DOSE FRACTIONATION SCHEME	LOCAL CONTROL UNTIL TRANSPLANT	MEDIAN SURVIVAL
Sandroussi 2010	Retrospective	A B C /A-B,D	4 5 1	23-54Gy in 5-6 fractions	100% (2 delisted)	Not reported
Andolino (Transplant) 2011	Retrospective	A B /A-B	12 11	3x12-16Gy 5x8Gy	10[illegible] [illegible]ed	
Facciuto 2011	Retrospective	A,B /A	27		100% (10 delisted)	32 Months
Katz 2011	Retrospective	A B C Unknown /A-B,D	4 3	10x5Gy	100% (6 delisted)	Not reported
O'Connor 2012	Retrospective	A B C /A-B, D	7 2 1	3x11-18Gy	100%	Not reached

LOCAL CONTROL 100% UNTIL TRANSPLANT

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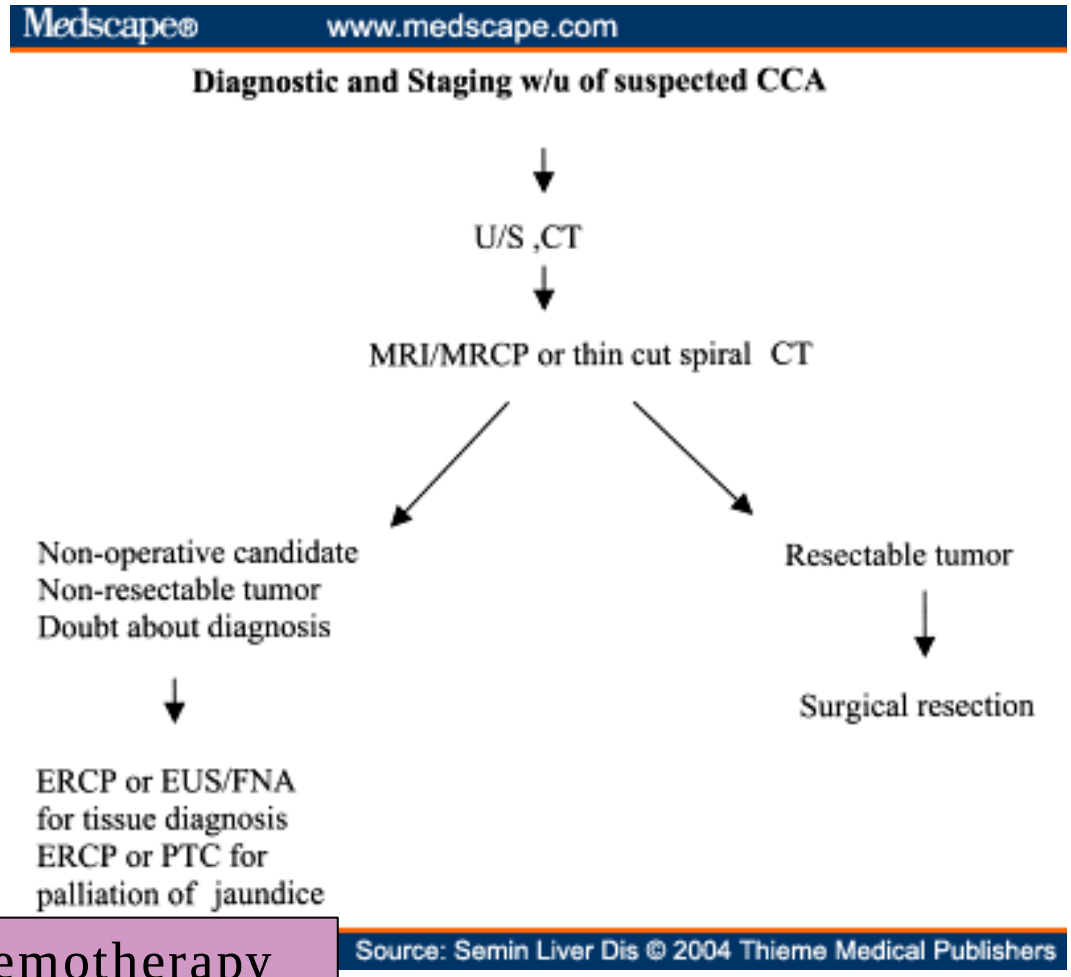
IS THERE A ROLE FOR SBRT IN CCA?



Chemotherapy

+ SBRT

Radical setting
or also pretransplant for perihilar CCA

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CCA TREATED RADICALLY

- No strict criteria regarding stage, tumor size or number
- Ineligible for resection
- Frequently
  - Intrahepatic but also perihilar
  - Chemotherapy
  - ECOG O-2

CCA TREATED RADICALLY

AUTHOR	DESIGN	LOCATION	NUMBER OF PATIENTS	RT DOSE SCHEME± CHEMOTHERAPY	2y LOCAL CONTROL	2y /MEDIAN SURVIVAL
Tse 2008	Phase I	Intra-hepatic	10	6x4-9Gy No chemo	65%* at 1 y	58% at 1y 15 Months
Momm 2010	Retrospective	Perihilar	13	32-56Gy in 3-4Gy per fraction 6/13 Chemo	Not reported	67% 23.6 Months
Kopek 2010	Retrospective	Intra-hepatic Perihilar	1 26	3x15Gy (at isocenter) No chemo	84% at 1 y	15% 10.6 Months
Polistina 2011	Prospective	Perihilar	10	3x10Gy 10/10 chemo	ted	80% 35.5 Months
Barney 2012	Retrospective	Intra-hepatic Perihilar **Extrahepatic: Adrenal gland	6 3 1	45-60Gy in 3-5 fractions 8 chemo	100%	Not re
Mahadevan) 2015	Retrospective	Intra-hepatic Perihilar Intra-+extra-hepatic	31 2 9	10-45Gy in 3-5 fractions 18 chemo	79%	31% 17 Months
Tao 2016	Retrospective	Intra-hepatic	79	50.4-75Gy in 15-30 fractions 75 chemo	BED≤80.5Gy 3y 45% >80.5Gy 3y 78%	61% 30 Months

LOCAL CONTROL 65-100%

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CCA TREATED PRE-TRANSPLANT

- Retrospective, 12 patients
- Unresectable perihilar CCA ≤3cm with negative lymph nodes
- Pre-transplant:
  - SBRT 3-5 fractions of 10-20Gy (Total: 50-60Gy)
  - Capecitabine: 1330mg/m2/day until transplant
- 6 patients transplanted, 5 partial response, 1 no responder
- 1y OS after transplant 83%
- No vascular, biliary or hepatic insufficiency

Welling Th. Neoadjuvant SBRT, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. Liver Transpl 2014

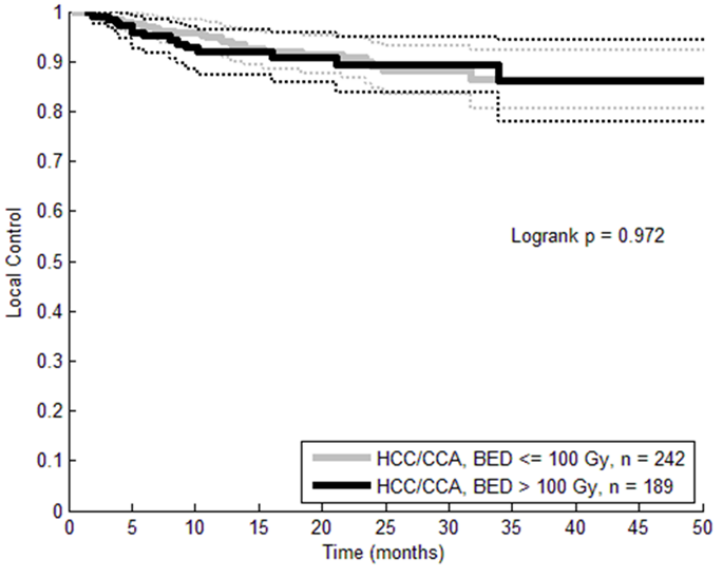
RELATION DOSE/LOCAL CONTROL

- Not clear

- AAPM-SBRT liver working group

  Mainly HCC

  (Ohri N IJROBP 2014 abstract)



- CCA Intrahepatic: BED> 80.5Gy (Tao R, JCO 2016)

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SUSCEPTIBILITY HEPATIC TOXICITY

- Main issue for HCC
- Biological factors:
  - Preexisting/ severity liver cirrhosis (Child Pugh B > A)
  - Hepatitis virus B carrier status
- Physical factors:
  - Mean liver dose
  - Liver volume receiving <18 Gy in 3 fractions (>800cc)
  - Low dose-volumes in Child B patients
- Tumor factors: ≥ 35mm

HEPATIC TOXICITY SBRT STUDIES

- Reported CTC grade ≥ 3 hepatic:
  - Elevation liver enzymes
  - Hyperbilirubinemia/Hypoalbuminemia/Elevation INR
  - Child Pugh decline
  - Death due to decompensation

- Hepatic toxicity influences prognosis:
  - Greater risk of death (Lasley FD. PRO 2015)
  - 2 year survival (Sanuki N. Hepat Research 2015)

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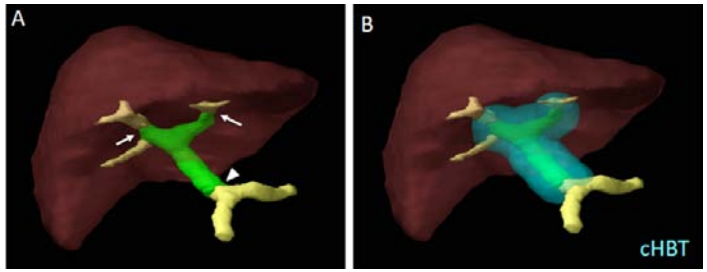
PREDICTORS BILIARY TRACT TOXICITY

- Retrospective 96 liver patients
- Median dose 40Gy in 5 fractions (25-54Gy in 1-5 fractions)

- CCA:
  - biliary obstruction/stricture
  - hepatobiliary infections



- Toxicity associated with SBRT dose-parameters
- V BED_{10} 72Gy< 21cc V BED_{10} 66Gy< 24cc

Osmudson EC. Predictors of toxicity associated with SBRT to the central hepatobiliary tract. IJROBP 2014

DOSE VOLUME RECOMMENDATIONS

QUANTEC

- Child-Pugh A:
  - 6 fractions: mean liver dose (liver-GTV) < 18 Gy
  - 3 fractions: mean liver dose (liver-GTV) <13 Gy
  - 3 fractions: >800 ml of normal liver < 18 Gy

- Child-Pugh B:
  Mean liver dose (liver-GTV) ≤ 6 Gy, in 4-6 Gy per fraction

MESSAGE TO TAKE HOME

- SBRT offers high local control in selected patients with primary liver tumors
- SBRT can be delivered as a definitive treatment but also as a pre-transplant therapy
- Toxicity is acceptable in most studies, however patients with advanced cirrhosis have a higher risk of toxicity
- Randomized trials are needed to define the role of SBRT in the treatment of primary liver tumors

MEDICAL UNIVERSITY OF VIENNA

COMPREHENSIVE CANCER CENTER VIENNA

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

Oligometastases
Rational for stereotactic radiotherapy

Karin Dieckmann

Department of Radiation Oncology,

General Hospital Vienna

Medical University of Vienna, Austria

Questions

- Is there a definition of oligometastases?

  A: ≤ 5

  B: < 10

Questions

- Is there enough evidence for practicing SBRT for oligometastases?

  A: no

  B: yes

Questions

- In which type SBRT will be most favorable

  A: Colon

  B: Lung

  C: Prostate

  D: Kidney

  E: Breast

Questions

- What is the maximum number of metastases for SBRT in one session?

  A: 1

  B: 3

  C: only technical limitations

Questions

- Would you treat oligometastases in more than one organ?

  A: yes

  B: no

Questions

- Would you irradiate a new metastases detected at the three months follow up?

  A: yes

  B: no

One Definition of Oligometastases

Oligometastases can be defined clinically as a limited number of metastatic lesions **≤ 5** in a limited number of organs **≤ 3**, generally identified by imaging.

Oligometastases (1-<3 ≤ 5)

Synchronous and Metachronous

- Primary tumor can be controlled or not controlled

Oligorecurrence

- Primary tumor controlled
- One to several new metastases after locoregional treatment

Oligoprogression

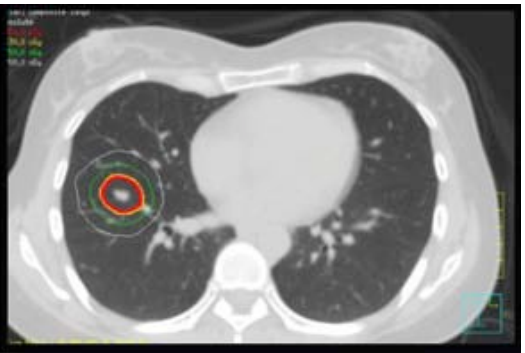
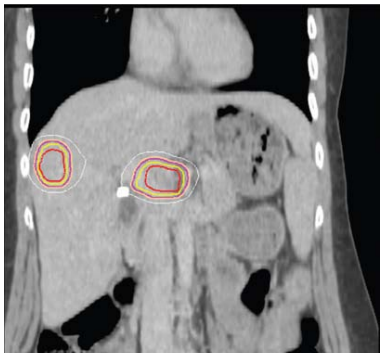
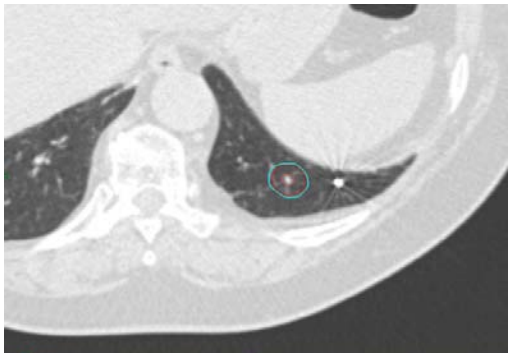
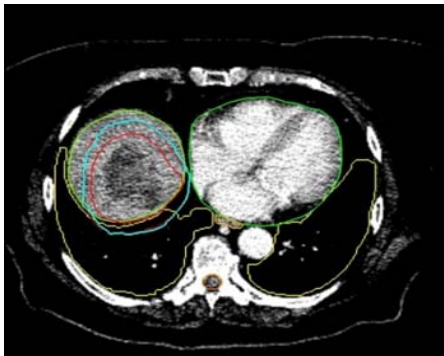
- Primary tumor controlled
- One to few metastases may progress after cytoreductive medication (new biologically Targeted agence)
- heterogeneity of metastases

Presentation and Definition of Oligometastases

Synchronous oligometastases a clinical scenario in which oligometastatic disease is detected **at the time of diagnosis** of the primary tumour

Metachronous oligometastasis the development of oligometastatic disease **after treatment of the primary tumour**.

The interval for classification of metachronous versus synchronous is not standardized

Oligometastases and Oligo-Recurrence Oligo-Progression

Oligometastases: primary tumor status has to be controlled before treatment

Intention: prolong survival not to persue cure

Oligo-Recurrence: Curative SBRT-treatment of the metastasis local tumor controlled

Intention: Cure the patient

Oligo Progression: Curative SBRT-treatment of the progressive metastasis

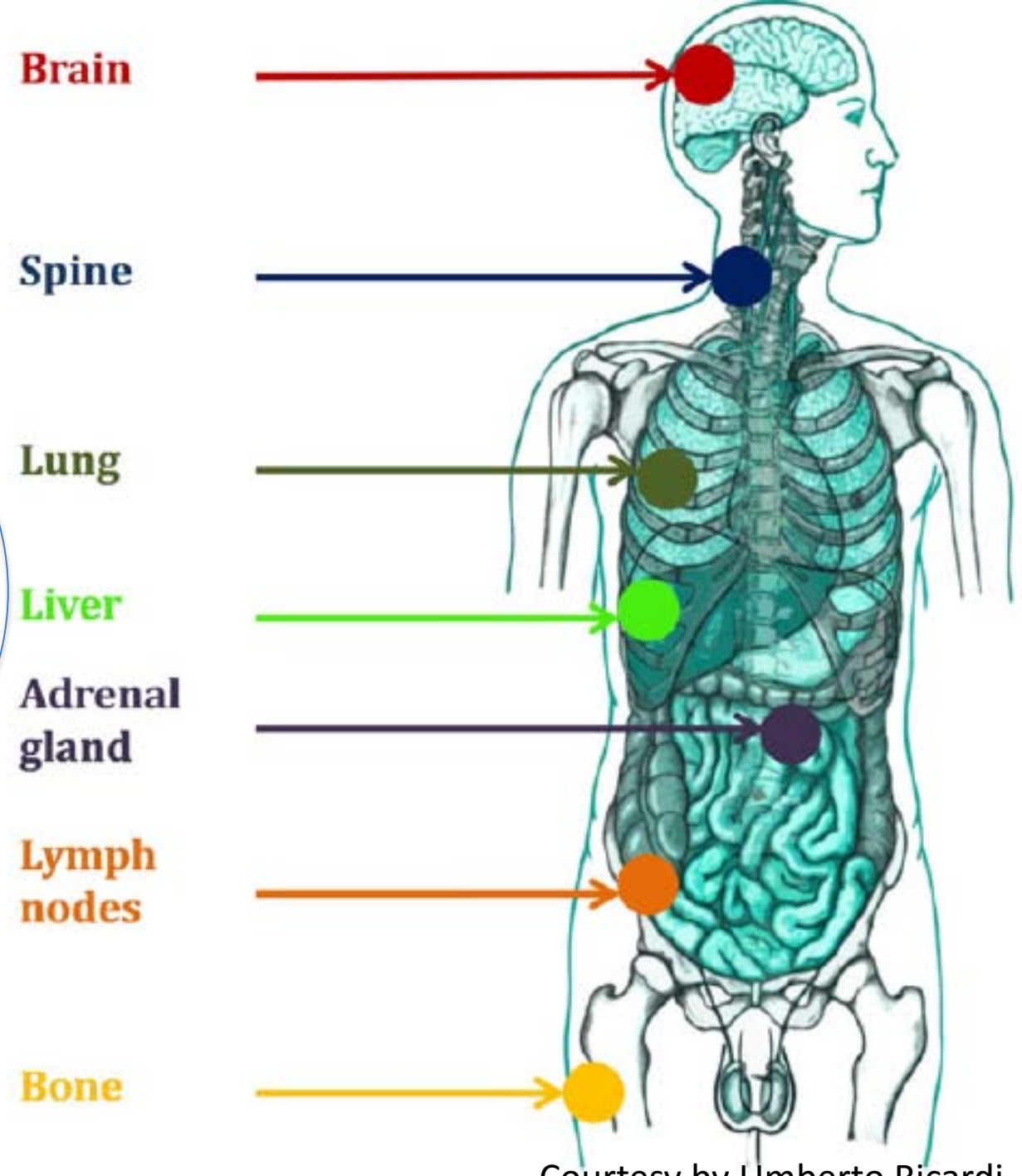
Intention: To control the growing metastasis

Treatment options:

Surgery
RFA
SBRT

in combination with
or without systemic
Treatment

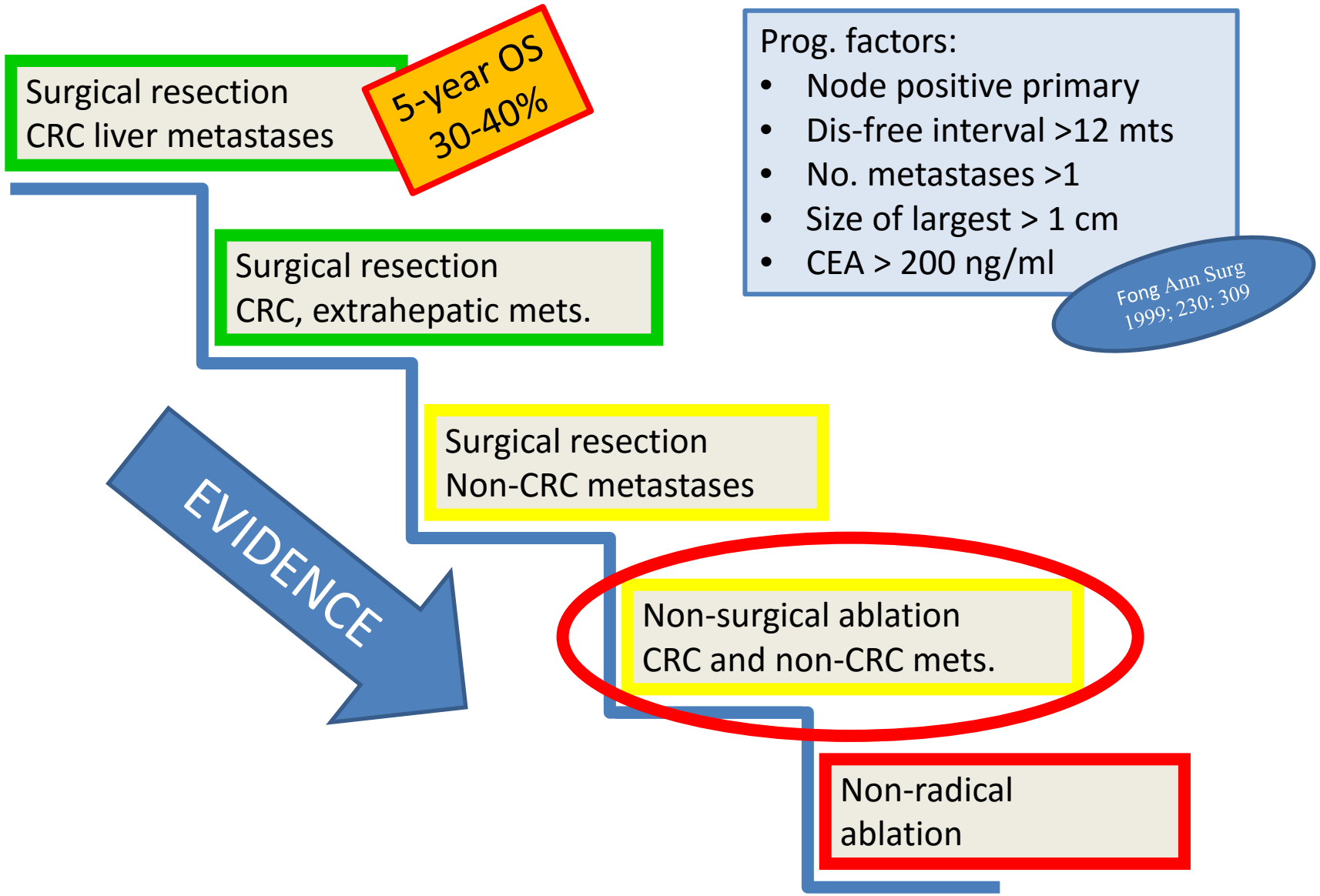
Goal:
Increasing PFS
Increasing OS



Courtesy by Umberto Ricardi

Clinical evidence

Surgery and ablation for CRC oligo-metastases



Oligometastasis and oligo-recurrence: more than a mirage

Histology

Pulmonary **Metastasectomy** from selected studies

Primary tumor type	*Year*	*No. patients*	*5-year survival (%)*	*10-year survival (%)*	*References*
Melanoma	2007	1720	21	/	Petersen et al. 2007
Many types	2011	575	46	/	Casiraghi et al. 2011
Colorectal carcinoma	2002	165	39.6	37.2	Saito et al. 2002
Colorectal carcinoma	2007	175	53.8	20.6	Welter et al 2007
Renal cell carcinoma	2002	191	41.5	/	Pfannschmidt et al. 2002
Renal cell carcinoma	2011	202	39	/	Meimarakis et al. 2011
Testicular germ cell tumors	1998	157	68	/	Liu et al. 1998
Malignant fibrous histiocytoma	2005	103	21	/	Suir et al. 2005
Gynecologic cancers	2006	103	46.8	34.3	Suri et al. 2005
Bone sarcoma	2010	52	31	/	Garcia Franco et al. 2011

- 5 Years **OS 21-54%** according to histology
- > 50% of the metastases are unresectable

Prospective studies with oligometastases of Lung treated with **SBRT**

Oligo metastases: new paradigm and options for radiotherapy

Badakhshi et al

Study	Number, design	Local control	Survival	Dose prescription
Yoon et al. [34]	53, perospective	At 14 months: 70–100%	2 years: 51%	30–48 Gy in 3–4 fractions
Okunieff et al. [33]	50, perospective	3 years: 91%	3 years: 25% for BED 100 Gy	48–57 Gy in 3–10 fractions
Norihisa et al. [50]	34, perospective	2 years: 90%	2 years: 84%	48–60 Gy in 4–5 fractions
Brown et al. [49]	35, perospective	At median 18 months: 71%	At median 18 months: 77%	5–60 Gy in 1–4 fractions
Rusthoven et al. [30]	38, perospective	2 years: 96%	2 years: 39%	60 Gy in 3 fractions
Ricardi et al. [35]	61, perospective	2 years: 89%	2 years: 66.5%	45 Gy in 3 fractions 26 Gy in 1 fraction

BED biological equivalent dose.

SBRT:

- 2 Years local control rates of **50-~ 90-96% / Survival 40-84%**
- Limited Toxicity; Mostly not grade 3-4
- Contra indications for SBRT are limited

SBRT in lung metastases is a good alternative for metastasectomy

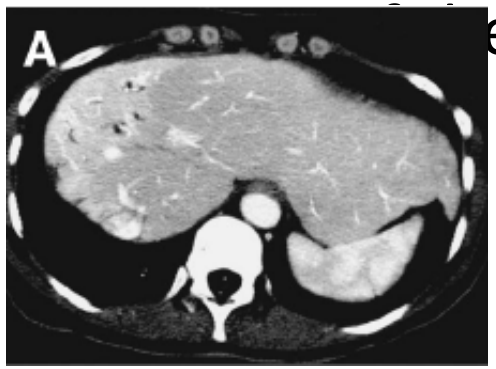
Strahlentherapie und Onkologie 5 · 2013

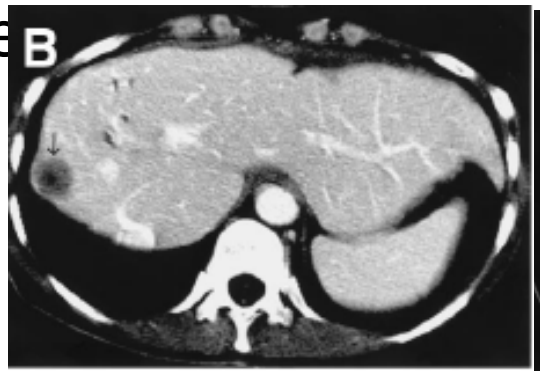
Oligometastasis and oligo-recurrence: more than a mirage

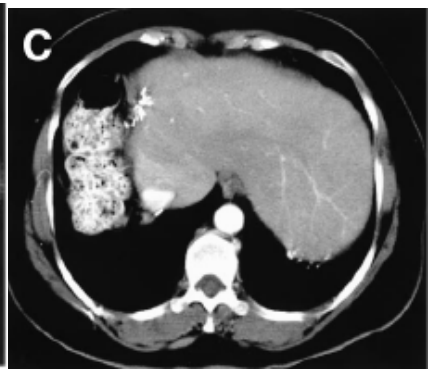
Liver **Metastasectomy** from selected studies

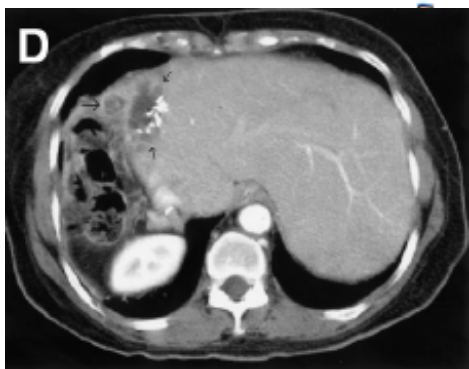
Primary tumor type	*Year*	*No. patients*	*5-year survival (%)*	*10-year survival (%)*	*References*
Noncolorectal	2005	142	26	/	Ercolani et al 2005
Noncolorectal Nonendocrine liver metastases	2006	1452	36	23	Adam et al 2006
Noncolorectal nonneuroendocrine liver metastases	2007	360	37	/	Reddy et al 2007
Breast cancer	2010	41	48	/	Hoffmann et al 2010
Soft-tissue sarcoma	2009	45	49	/	Rehders et al 2009

- 5 Years **OS 26-49%** according to histology
- High number of metastases are unresectable
- RFA are limited to the size and location









Oncology 2014, 9:230

Prospective studies with oligometastases of the liver treated with SBRT

Oligo metastases: new paradigm and options for radiotherapy

Study	Number, design	Local control	Survival	Dose prescription
Herfarth et al. [53]	33, prospective	6 month: 75% 12 month: 71%	1 year: 72%	14–26 Gy in 1 fraction
Méndez-Romero [37]	14, prospective	1 year: 100% 2 year: 86%	1 year: 85% 2 year: 62%	12.5 Gy in 3 fractions
Ambrosino et al. [52]	27, prospective	74%	–	25–60 Gy in 3 fractions
Lee et al. [51]	140, prospective	71%		24 Gy in 6 fractions
Rusthoven et al. [38]	47, prospective	1 year: 95% 2 year: 92%	2 year: 30%	12–20 Gy in 3 fractions
Rule et al. [54]	27, prospective	24 month: 50 Gy: 89% 60 Gy: 100%	–	10 Gy in 3–5 fractions 12 Gy in 5 fractions

- 2 years Local control of 70-100% ; **OS 30-62%**
- SBRT of oligometastases is an alternative to surgery

Strahlentherapie und Onkologie 5 · 2013

Stereotactic Body Radiotherapy in the Management of Oligometastatic Disease *Kamran A. Ahmed,*

SBRT for mixed oligometastatic sides

Study	No. of Lesions	Dose	Rate of Local Control	Rate of Toxicity
Greco[23]	126	18–24 Gy in 1 fraction	64% at 2 y	Grade 3 (< 4%)
Kang[25]	78	42 Gy in 3 fractions	66% at 3 y	Grade 4 (3%)
Milano[5]	293	Median 50 Gy in 10 fractions	77% at 2 y	Grade 3 (1%)
Salama[4]	113	24–48 Gy in 3 fractions	67% at 2 y	Grade 3 Acute: 3% Late: 10%
Stinauer[26]	53	40–50 Gy in 5 fractions or 42–60 Gy in 3 fractions	88% at 18 mo	Grade 3 (3%)
Wersall[24]	162	30–40 Gy in 3 fractions	Crude (90%)	Grade ≥ 1 toxicity (40%)

- Toxicity rate Grade 3 and 4 is low (3 and 10%)

Cancer Control 21 January 2016, Vol. 23, No. 1

Stereotactic Body Radiotherapy in the Management of Oligometastatic Disease *Kamran A. Ahmed,*

Retrospective and prospective experiences for **Lung metastases** treated with SBRT

Study	No. of Lesions	Dose	Rate of Local Control	Rate of Toxicity
Okunieff[37]	125	50 Gy in 10 fractions (most common)	91% at 3 y	Grade 2 (6.1%) Grade 3 (2%)
Onimaru[38]	57	48–60 Gy in 8 fractions	70% at 3 y for 48 Gy 100% for 60 Gy	Grade 5 (2.2%)
Ricardi[34]	77	26 Gy in 1 fraction to 45 Gy in 3 fractions	89% at 2 y	Grade 3 (1.6%)
Rusthoven[36]	63	60 Gy in 3 fractions	96% at 2 y	Grade 3 (8%)
Yoon[35]	101	30 Gy in 3 fractions to 48 Gy in 4 fractions	70% for 30 Gy 77% for 40 Gy 100% for 48 Gy	No cases of grade ≥2

Cancer Control 21 January 2016, Vol. 23, No. 1

Stereotactic Body Radiotherapy in the Management of Oligometastatic Disease *Kamran A. Ahmed,*

Phase 1 Phase 2 Trails assessing **Liver metastases** with SBRT

Study	No. of Lesions	Dose	Rate of Local Control	Rate of Toxicity
Herfarth[28]	60	14–26 Gy in 1 fraction	81% at 18 mo	No major adverse events reported
Hoyer[29]	44	45 Gy in 3 fractions	86% at 2 y	1 death from hepatic failure Grade 4 (1) Grade 3 (2)
Lee[30]	68	Median 41.8 Gy in 6 fractions	71% at 12 mo	Grade 3 (6) Grade 4 (1)
Rusthoven[27]	63	60 Gy in 3 fractions	92% at 2 y	No grade 4/5
Scorsetti[31]	76	Majority 75 Gy in 3 fractions	94% at 12 mo	No grade ≥ 3

Toxicity after liver irradiation Grade 3 /4 1-6%

Cancer Control 21 January 2016, Vol. 23, No. 1

Who is the right patient for SBRT

Patient selection

- Good Performance status
- Primary rate of disease control
  - Locally controlled or potentially treatable primary tumor
- Life expectancy
- Number of visible metastases (1-3/1-5)
- Number of involved organs
- Limited tumor diameter

Lung Metastases Eligibility Criteria

No strict criteria

- **Number** of metastases:
  - 1 - 3 or 1 - 5 metastases
- **Size** of metastases:
  - < 5cm or < 7cm
- **Location**:
  Most institutions either exclude or reduce dose to centrally located tumors
- **Lung function:**
  FEV1 not clear >0.75 l ?

Liver Metastases Eligibility Criteria

No strict criteria

- Number of metastases:
  - 1 - 3 metastases (although 1 - 5 reported)

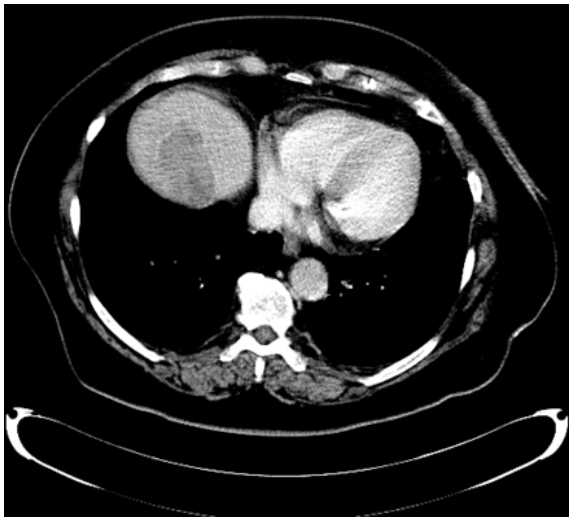
- Size of metastases:
  - ≤ 6 cm

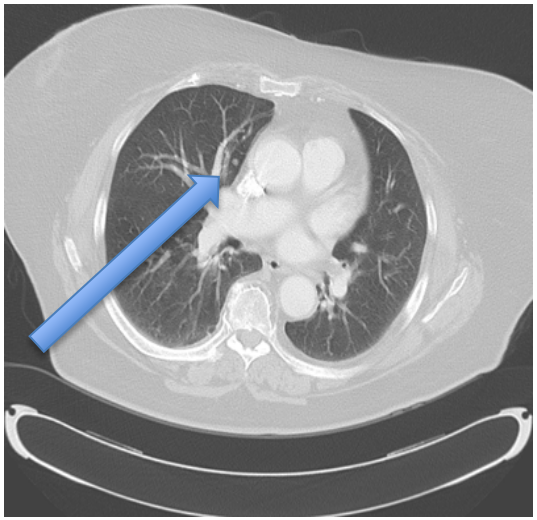
- Adequate liver function

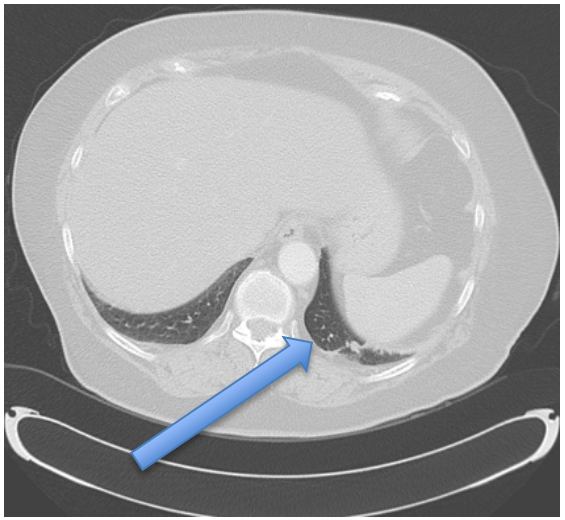
Case

Patient 83 years old with comorbidity

- 2012: Right hemicolectomy due to adenoca pT3N1M0
- No postoperative chemotherapy due to age
- 2013: Liver metastases segment 8 of 6cm and 2 lung metastases



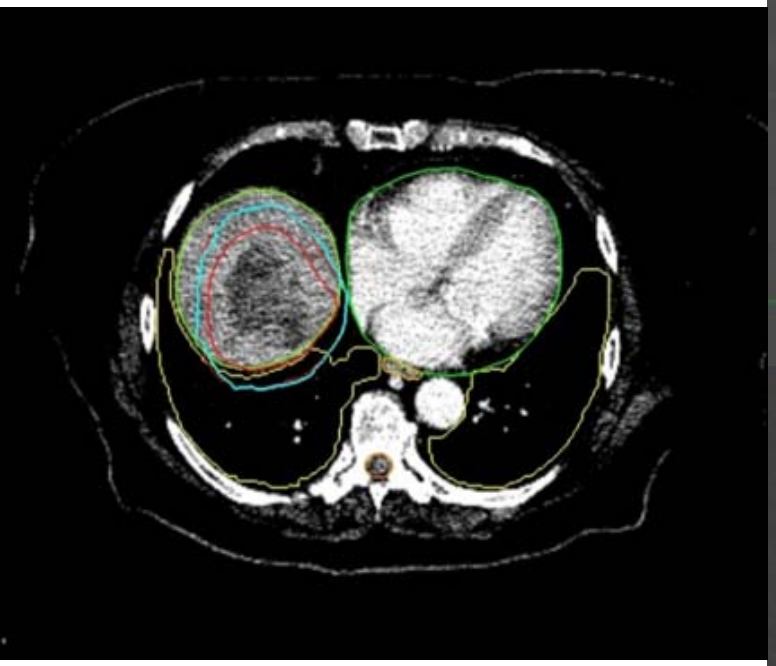


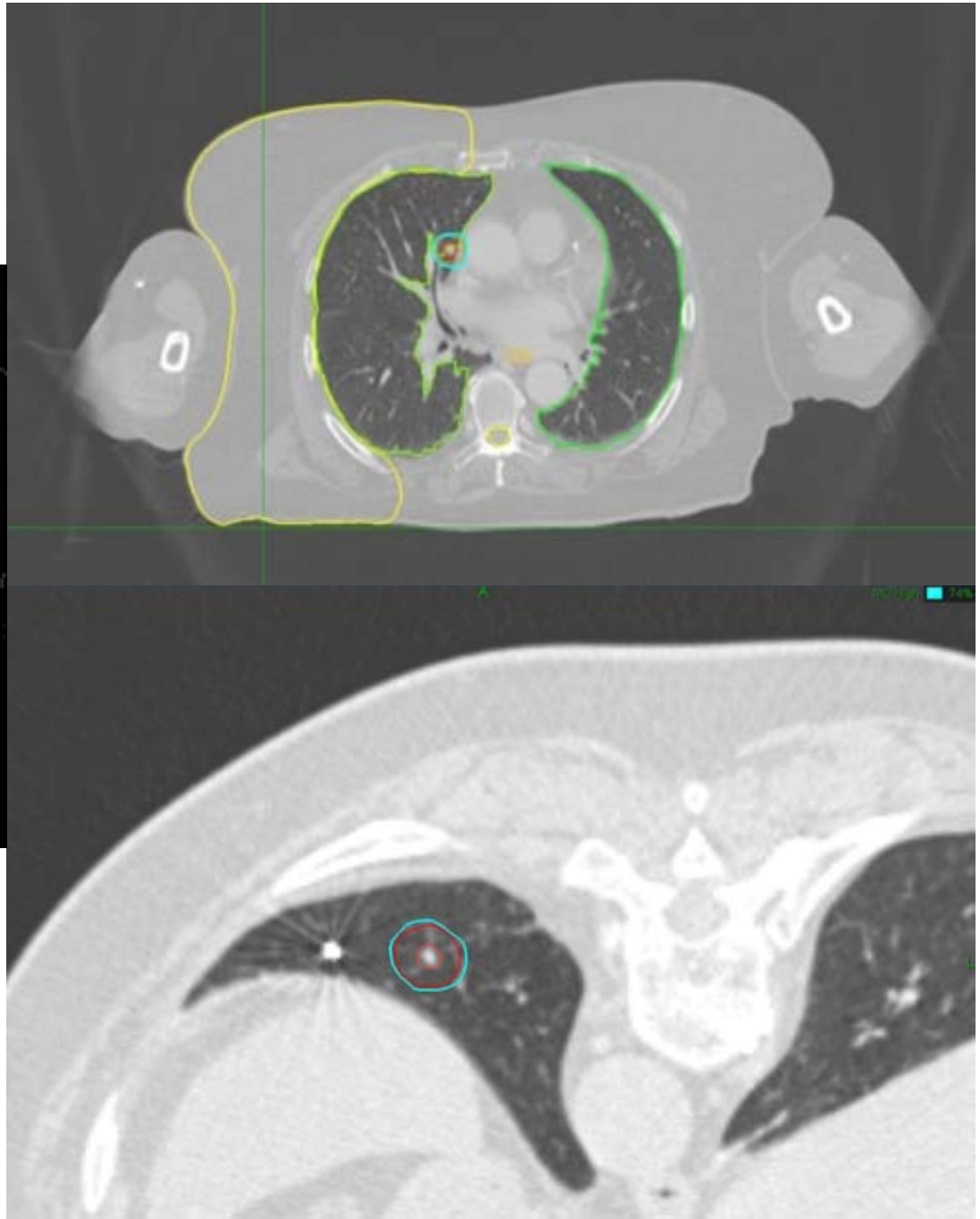


What would you advice? Surgery, RFA, SBRT?

What would you advice?

A. Surgery
B. RFA
C. SBRT
D. Non of these





Factors who might influence local control (survival s; local control c)

Favorable:

- Histology: breast, prostate, kidney, adenocarcinoma (s)

- Metachronous metastases (s)

- Disease-free interval: > 12 m, >24m (s)

- Location of the metastases: extracranial, bone (s)

- Number of metastases: 1-3 (s)

- Size of metastases: ≤ 3cm (c), <5cm (c), GTV ≤23 ml (s/c)

Drugs, SBRT and Oligometastases

- Ongoing studies with VEGFI, TKI, Interleukin ..... are evaluating
  - increase therapeutic efficacy
  - Pattern of failure
  - Fractionation schedules / target volumes
  - Treatment response
  - Side effects

- No clear data
- Good experience with conventional fractionation in combination with Chemo or new biological agences have to be analysed carefull with SBRT
- Studies have to be performed

Conclusion

Evidence based practice for extracranial oligometastases

- SBRT results in a high control rate of treated metastases (~80%)
- About 20% of patients are progression free at 2-3 years after SBRT
- Toxicity is low
- SBRT should be considered in patients with isolated metastases, especially if the disease-free survival is longer than 6 months

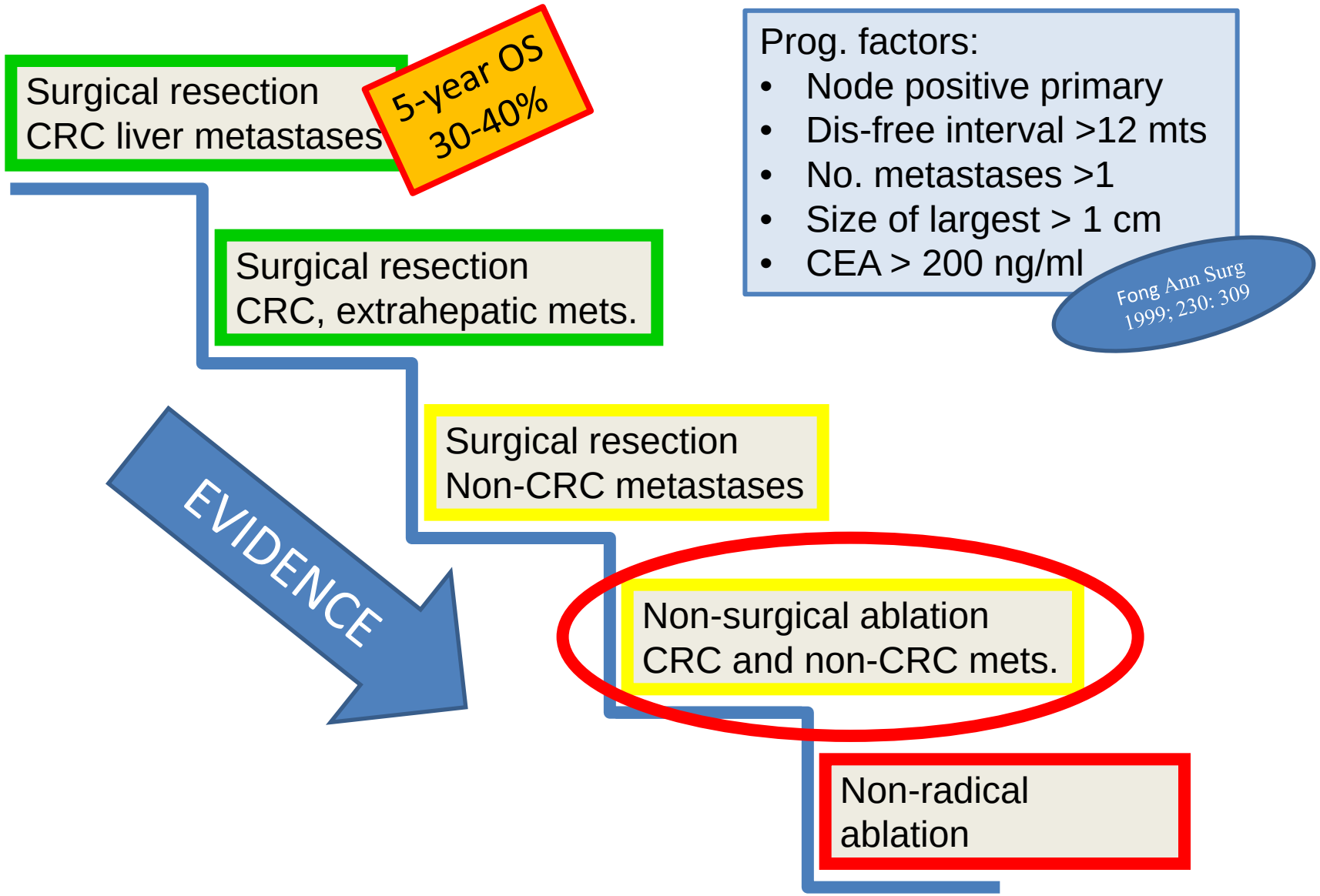
Stereotactic body radiation therapy for oligo-metastases

Morten Høyer
Danish Center for Particle Therapy
Aarhus University Hospital, Denmark

CIRRO AARHUS UNIVERSITET

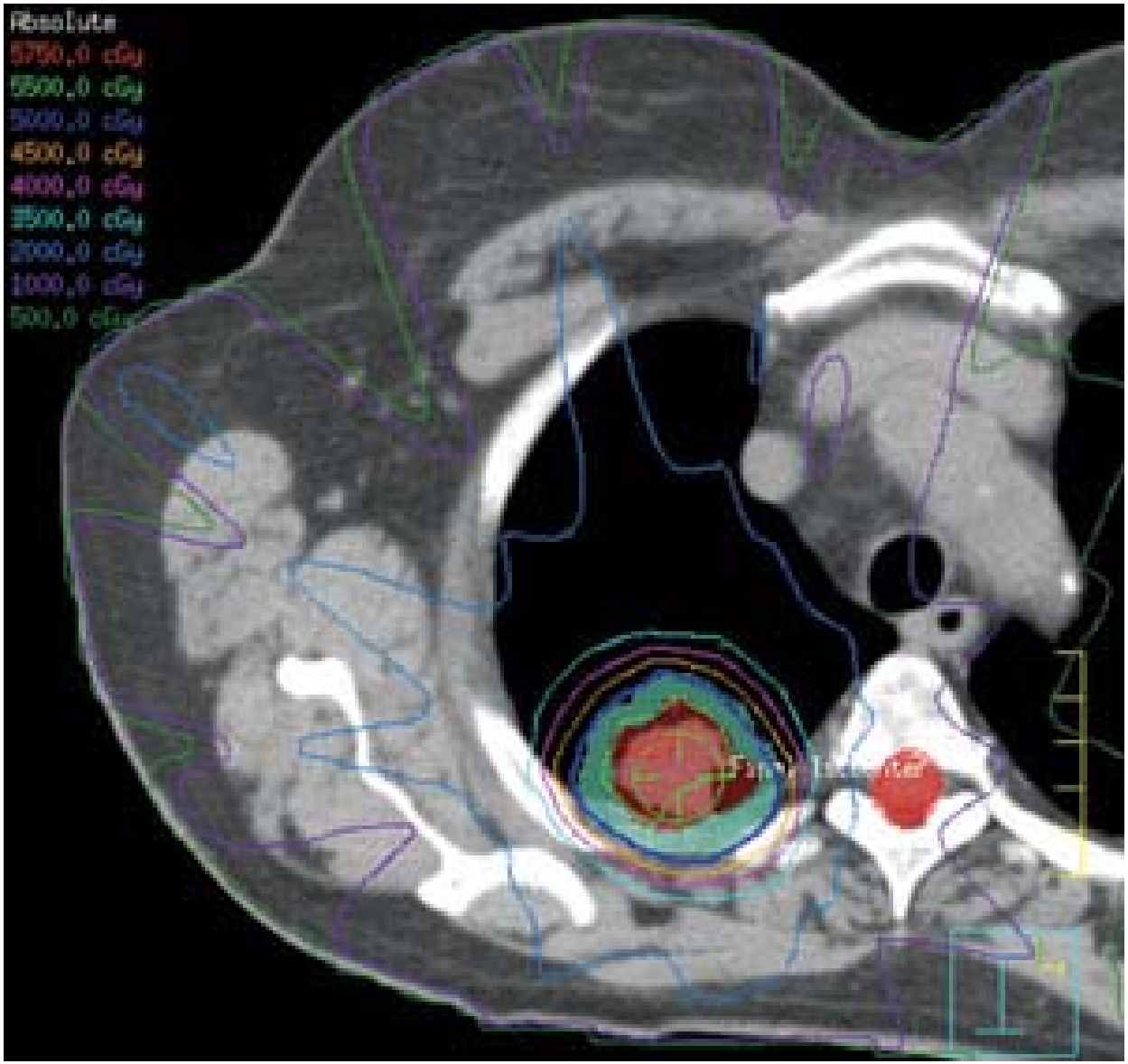
Clinical evidence

Surgery and ablation for CRC oligo-metastases



Lung metastases

SBRT of oligometastases to the **lung**



SBRT of oligometastases to the **lung**

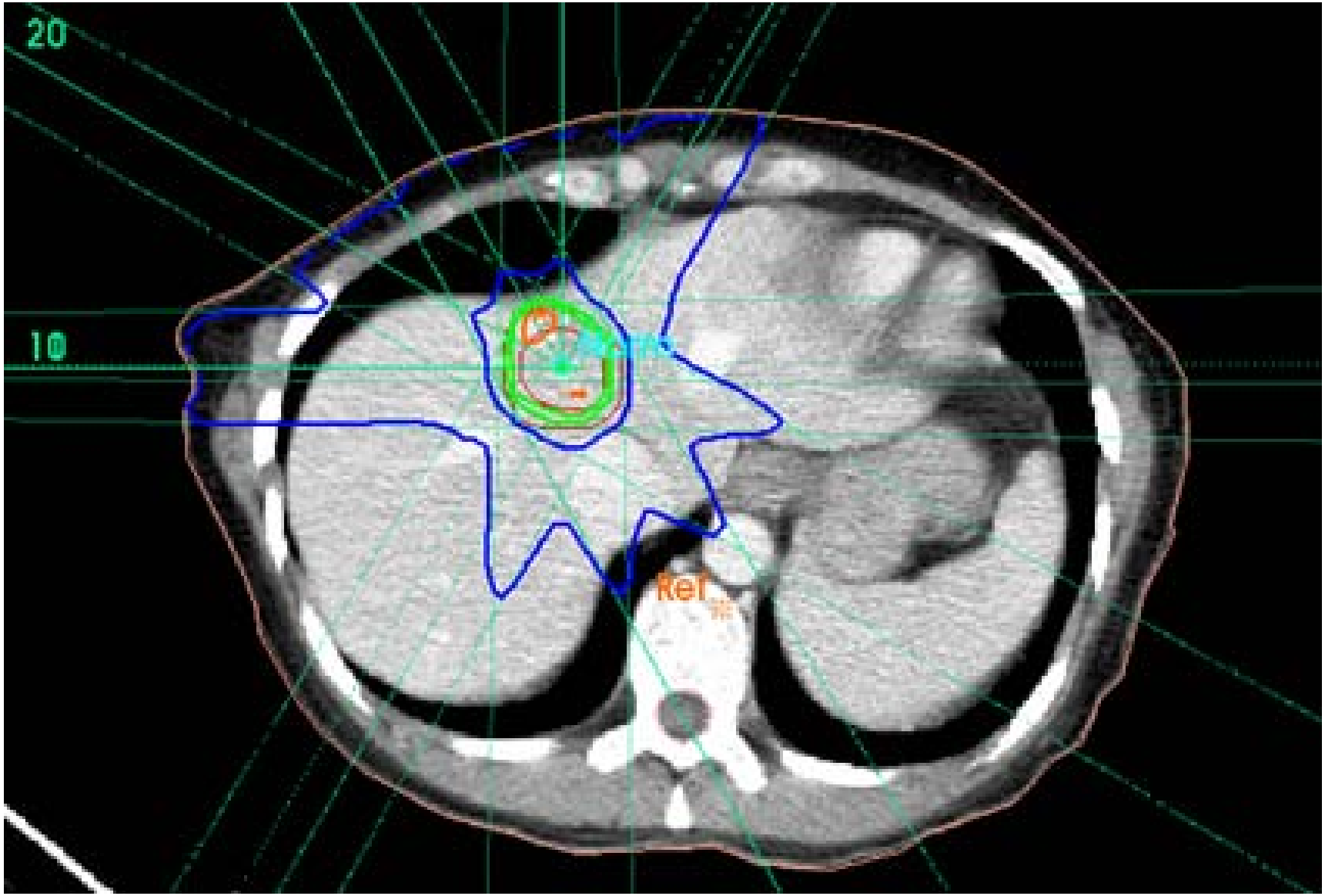
Phase II or retrospective cohorts

Author; year	Design	Pts	Dose/frx	m-FU	Locol control (%)	Survival 1,2 years 1, 2 years (%)
Wulf 2004	Dose esc.	41	3x10-12.5 Gy 1x26 Gy	9 mts	80	85, 33
Hof 2007	Phase I/II	61	1x12-30 Gy	14 mts	83 (>26 Gy and <10cc)	78, 65
Rusthoven 2009	Phase I/II	38	3x16-20 Gy			
Zhang 2011	Retrospect				97, 89	79, 41 (3 yr)
Ric[illegible]			3x15 Gy, 4x9 Gy	20 mts	89	79, 67
C[illegible] 2014	Phase II	40	4x12 – 3x25 Gy	24	80	80, 65
DeVin 2014	Retrospect	56	10x4-5 Gy	12 mts	33 (incl brain)	55 (2 yr)
Takahachi 2014	Carbon ions Feasibility	34	12x5 Gy 1x44 Gy	24 mts	85	90, 65
Fode 2015	Retrospect	92	3x15-22.5 Gy	29	LR: 13	80, 58
Guckenberger/ DEGRO (abstract)	Retrospect Multi-inst	715	NA	NA	NA	53 (2 yr) 24 (5 yr)

Lung mets: Local control rates 80-96%

Liver metastases

SBRT of oligometastases to the **liver**



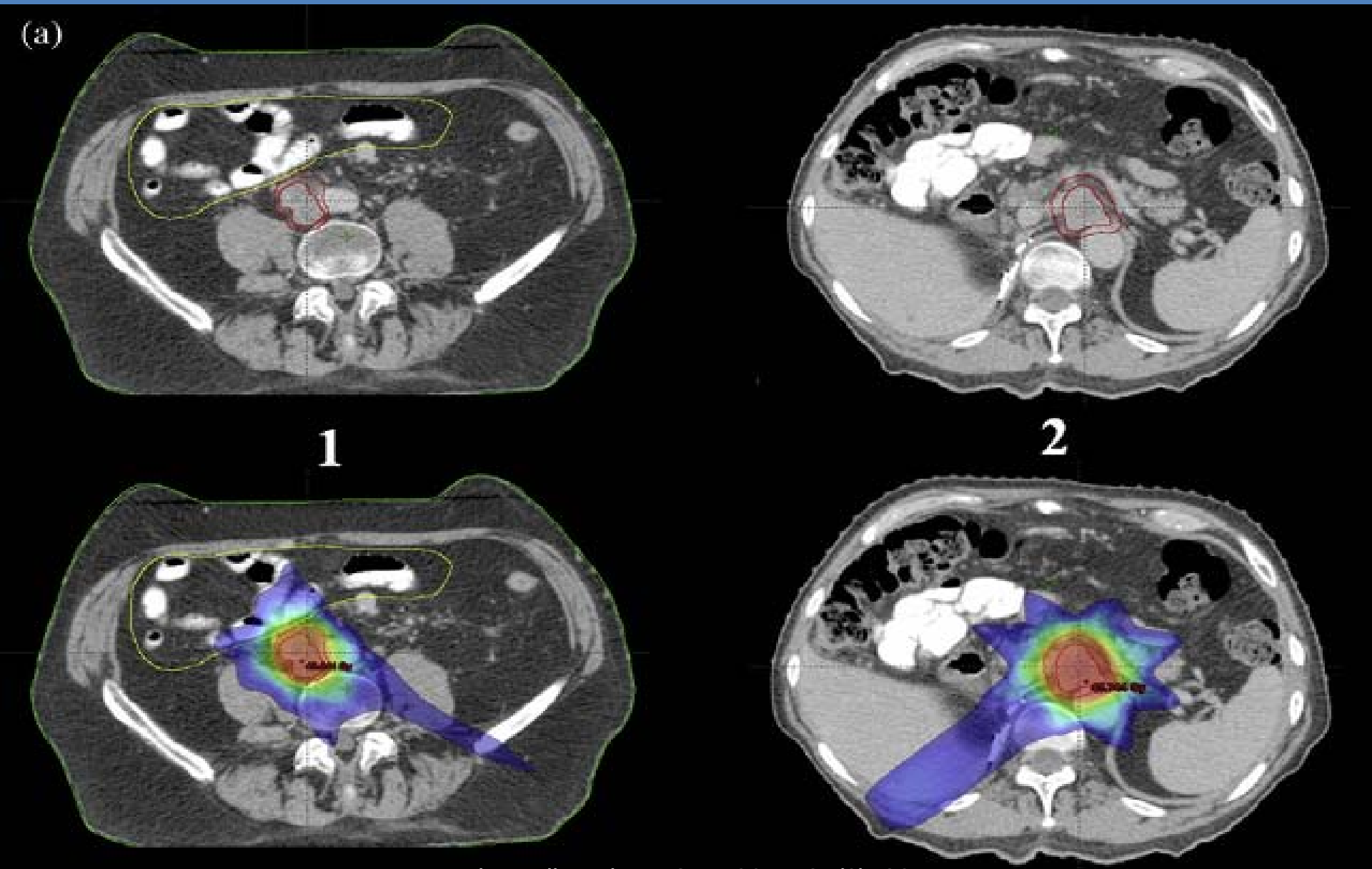
SBRT of oligometastases to the **liver**
Phase II or retrospective cohorts

Author; year	Design	Pts	Dose/frx	m-FU	Local control 2-years (%)	Survival 1-, 2- years (%)
Mendez-Romero 2006	Phase I/II	17	3x10-12.5 Gy	13 mts	86	85, 62
Rusthoven 2009	Phase I/II	47	3x12-20 Gy	16 mts	92	77, 30
Lee 2009	Phase I	68	6x4.6-10 Gy	11 mts		
Goodman 2010	Phase I	19				62, 49
Rule [illegible]			5x10 Gy, 5x12 Gy	20 mts	56 89 100	90, 50 78, 67 75, 56
Cha[illegible]	Retrospect	65	2-3x20 Gy	55	38 (2-yr)	77,45
Scorsetti 2013	Phase II	61	3x25 Gy	12	91	83,38
Comito 2014	Phase II	42	4x12 – 3x25 Gy	24	80	80, 65
DeVin 2014	Retrospect	77	10x4-5 Gy	12	33	32 (3-yr)
Fode	Retrospect	225	3x15-22.5	29	LR: 13	80, 58

Liver mets: Local control rates 80-100%

Lymph node metastases

Examples: SBRT for abd. lymph node mets.



Bignardi et al. IJROBP 2011; 81(3): 831

SBRT of abdomino-pelvic lymph node metastases
Retrospective cohorts

Author/year	# pts. LNmet/total	Primary	Fract x dose	Local control 2-years	Survival 2-years	Severe morbidity
Kang 2010	26/59	CRC	3 x 12-17Gy	66%	66%	Grade
Bignardi 2011	19	Mixed	6 x 7.5Gy	78		
Petrongari 2011	12/12	Prostate				
Bae 2012				years)	60% (3-years)	Grade≥3 (n=3)
		cancer	3 x 10Gy	14/14	65%	No
Be 013	11/24	Prostate cancer	10 x 5Gy	11/11	NA	No
De Vin 2014	88/309	Mixed	10 x 4-5Gy; 3 x 12Gy; 5 x 8.5Gy	33%	32% (3-years)	NR
Fode 2015	6/201	Mixed (CRC)	3 x 15Gy (isocenter)	6/6	58%*	No
Ost 2016	77/119	Prostate	Varying	93%	48%*	No

Favorable local control, but lymph node metastasis patients not reported separately

Adrenal metastases

SBRT of adrenal metastases
Retrospective cohorts

Author/year	# pts. LNmet/ total	Primary	Fract x dose	Local control 2-years	Survival 2-years	
Chawla 2009	30	Mixed		(1-year)	44% (1-year)	No
H	13 (18)	NSCLC	5 x 4-8Gy	77%	50%	Grade 3 (n=2)
Casamassima 2012	48	Mixed (lung; n=24)	3 x 12Gy	90%	40%	No

Adrenal metastases: Local control rates 55-90 %

Metastatic colorectal cancer

SBRT of colo-rectal oligometastases

Phase II or retrospective cohorts

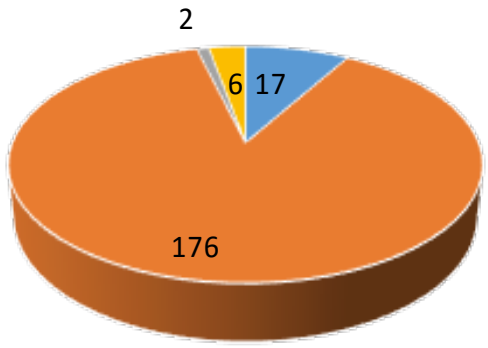
Author/year	Design	# mCRC pts.	Lung/liver/LN	Fract x dose	Local control 2 years	Survival 2 years
Lee 2009	Phase I	40/68	0/40/0	3 x 9.2-20Gy (NTCP-based)	(-)	35%
Van der Pool 2010	Phase I/II	20	0/20/0	3 x 12.5Gy	74%	83%
Kang 2010	Retrospect	59	13/10/31	3 x 12-17Gy	65%	65%
Chang 2011	Phase I/II	65	0/65/0	1		38%
Bae 2012	Retrospect	41			76%	68%
Van den Begin 2014				x 10 Gy (isocenter)	53%(lung/liver) 79% (LN) 1-year	65%*
Filippi 20		40	40/0/0	1 x 26-4 x 12 Gy	NA	73%
Comito 20	Phase II	82	60/52/0	4 x 12-3 x 25Gy	80%	65%
Thibault 2014	Retrospect	45/83		4 x 12-20 Gy	76%	72%*
De Vin 2014	Retrospect	103/309	56/77/176	10 x 4-5 Gy	33%	32% (3-year)
Takahachi 2014 Carbon ions	Feasibility	34	34/0/0	4 x 13.2-15 GyE	85%	65%
Qiu 2015	Retrospect	64	42/NA/NA	10x5Gy or 5x10Gy	31%	43%
Fode 2015	Retrospect	201	30/165/6	3 x 15-22.5 Gy (isocenter)	LR: 13%	58%

mCRC: Local control rates 31-85%

The Aarhus experience

Patient characteristics		
CRC/non-CRC	201	
Median number of metastases	1 (range 1-6)	
Median size of largest metastasis	30 mm (5-88 mm)	
Dead/alive	62 (31%)	139(69%)
Prior resection or RFA: yes/no	98 (49%)	103 (51%)
Prior systemic therapy yes/no	132 (66%)	69 (34%)

Metastatic organ

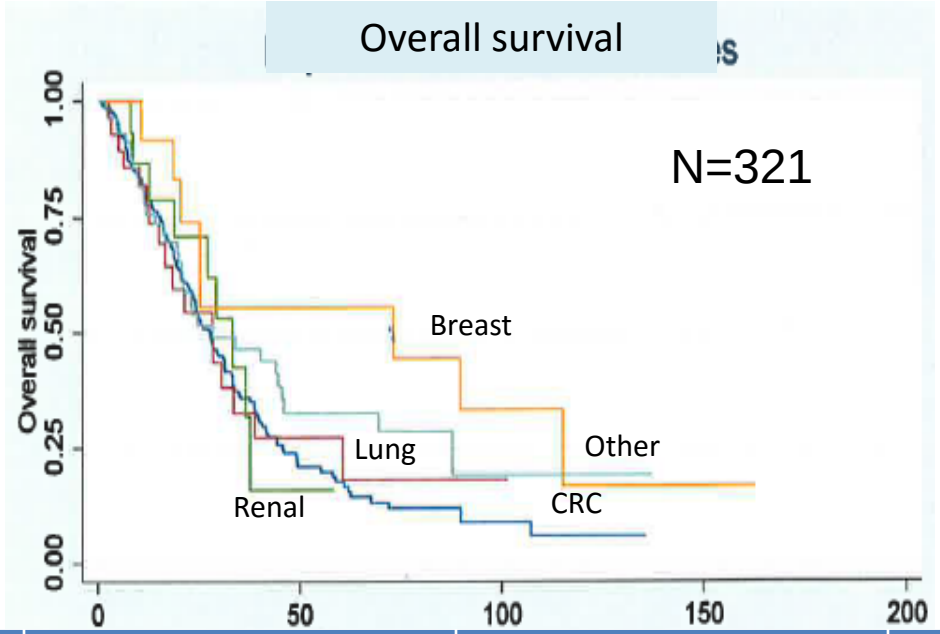


2000-2014:
N=201 pts.

Ineligible for surgery or RFA

MM Fode et al. Radiother Oncol 2015; 114(2):155

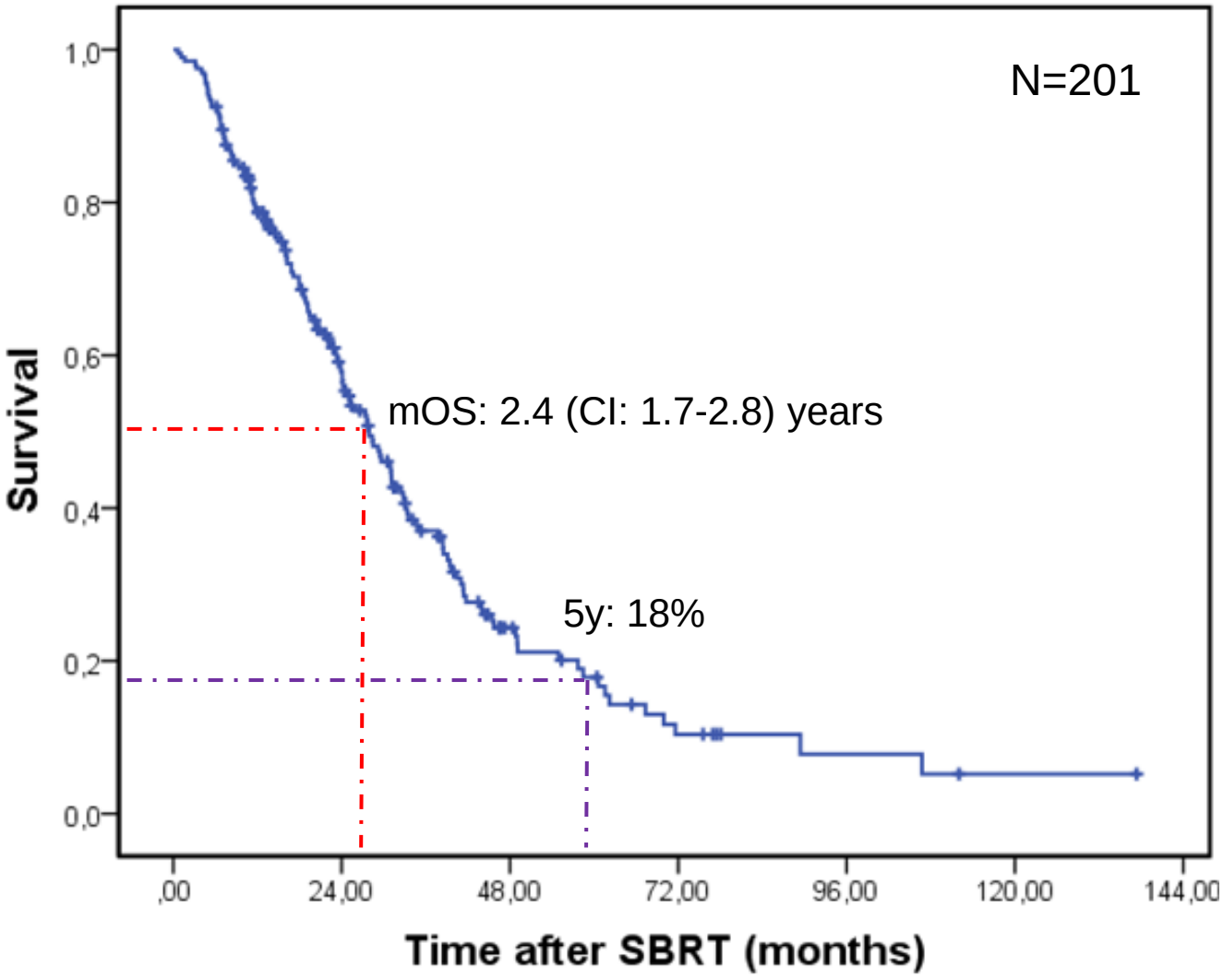
Survival by histological type



	No.	Med. OS (years)	95% C.I. (years)
Colorectal	201	2.4	1.7-2.8
Lung	31	1.5	1.2-2.5
Renal	17	2.4	1.1-3.1
Breast	12	6.1	1.5-9.6

MM Fode et al. Radiother Oncol 2015; 114(2):155

Overall survival after SBRT for mCRC



MM Fode et al. Radiother Oncol 2015; 114(2):155

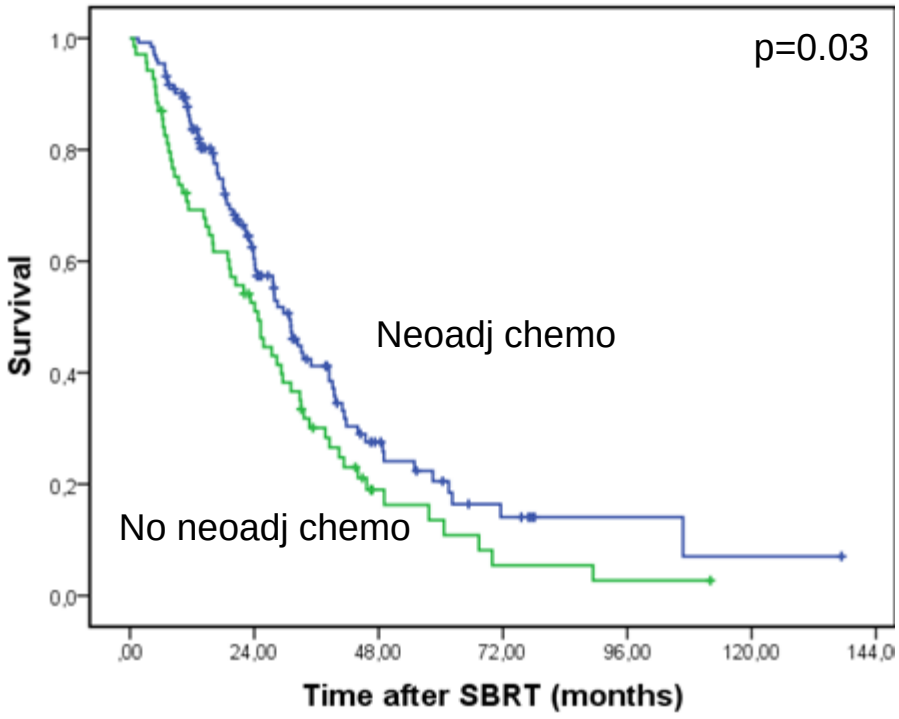
Prognostic factors related to survival after SBRT for mCRC

Covariate	Categories (n)	Median OS years (95 % CI)	HR	P- value
Performance status	0-1 (187) 2-3 (14)	2.5 (2.1 – 2.8) 1.2 (0.3- 1.9)	2.54	<0.01
Gender	Males (136) Females (65)	3.0 (2.4-3.6) 3.5 (2.8-4.2)	0.65	0.03
Age	<71 (101) ≥72 (100)	3.2 (2.6-3.8) 2.9 (2.6-3.6)	1.10	0.38
Size of largest metastases	≤ 30 mm (102) >30 mm (98)	2.8 (2.5 – 3.4) 1.9 (1.5 – 2.1)	1.67	<0.01
Number of metastases	1 metastasis (86) 2-6 metastases (115)	2.8 (2.3 – 3.4) 2.0 (1.8 – 2.5)	1.49	0.02
Treatment site	Lung (30) Liver, other (171)	3.4 (2.3 – 5.1) 2.1 (1.9– 2.6)	1.74	0.03
Prior chemotherapy	Yes (132) No (69)	2.6 (2.0 – 3.2) 2.1 (1.3 – 2.5)	1.44	0.03
Prior local therapy	Yes (98) No (103)	2.6 (2.0- 2.8) 2.1 (1.9- 2.8)	1.16	0.39
Timing of metastasis	Metachronous (70) Synchronous (131)	2.5 (2.0 – 3.3) 2.3 (1.8 – 2.7)	1.14	0.48

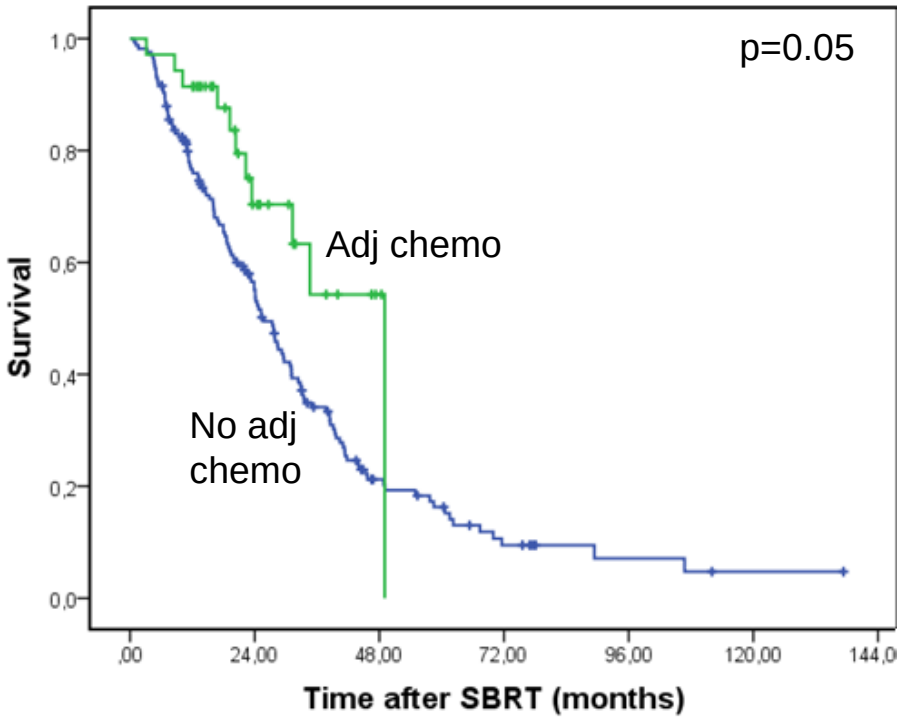
MM Fode et al. Radiother Oncol 2015; 114(2):155

SBRT and chemotherapy for mCRC

Chemotherapy before SBRT



Chemotherapy after SBRT



MM Fode et al. Radiother Oncol 2015; 114(2):155

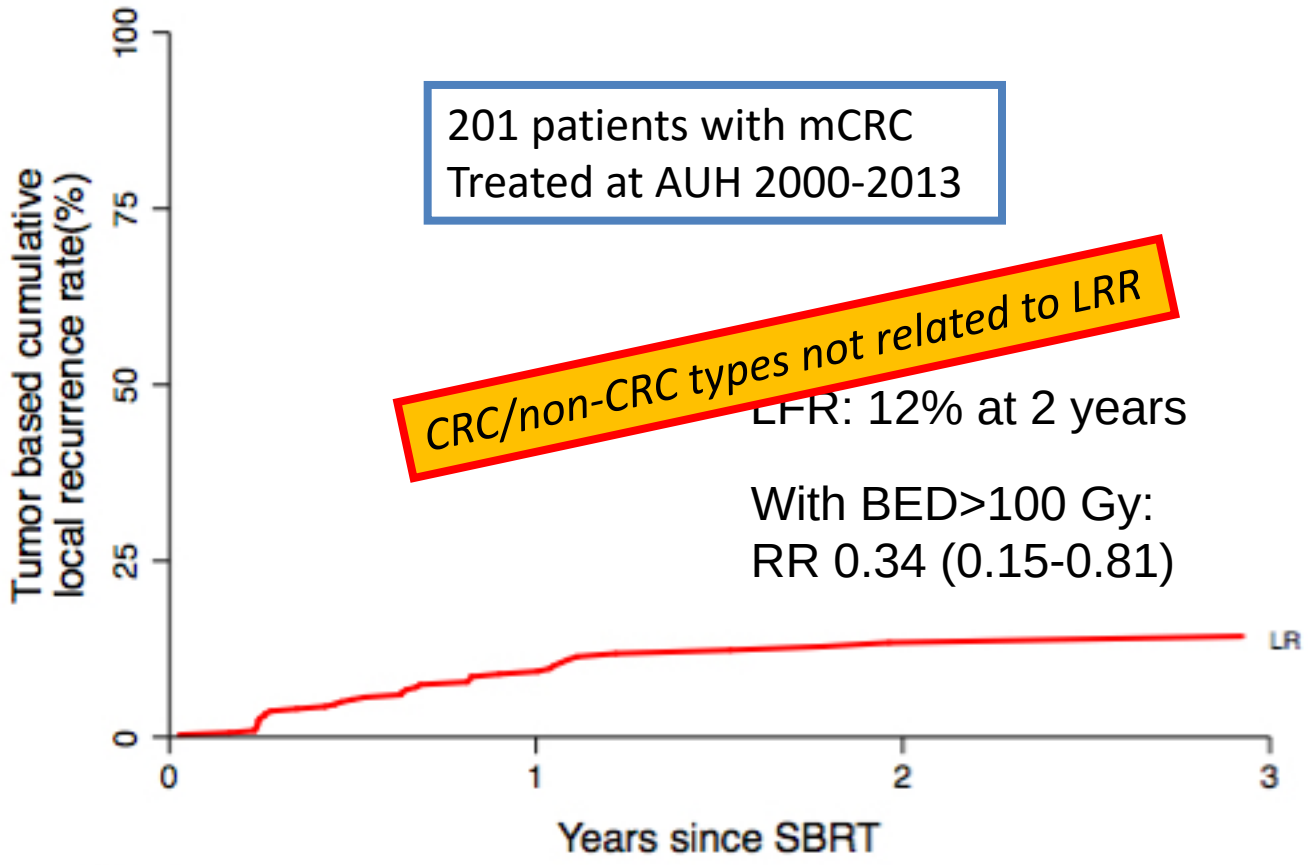
Overall survival after SBRT for mCRC

Multivariate analysis

Covariate	HR (95% CI)	P-value
Performance status **0-1** **2-3**	2.63 (1.45 – 4.77)	<0.01
Size of largest metastasis **≤ 30 mm** **>30 mm**	1.66 (1.18 - 2.34)	<0.01
Number of metastases **1** **2-6**	1.71 (1.19 – 2.45)	<0.01

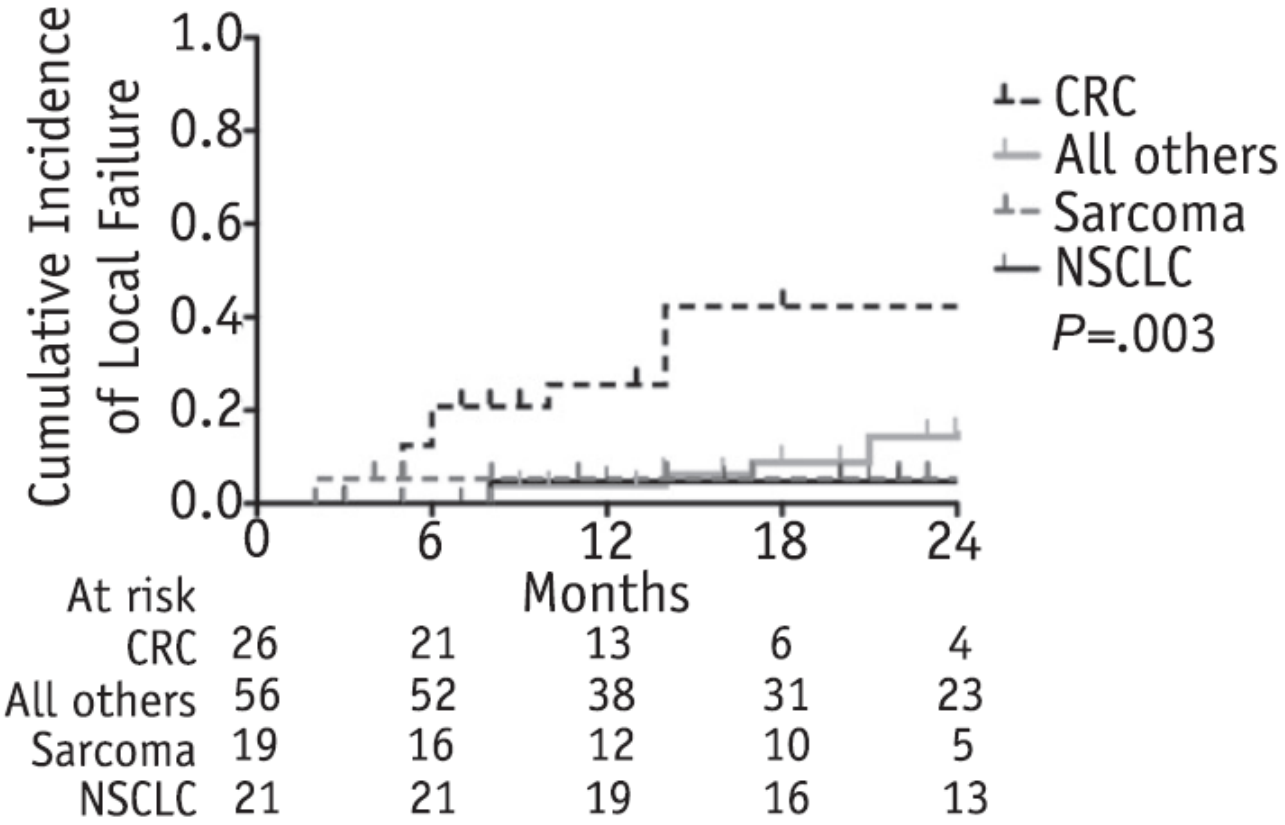
MM Fode et al. Radiother Oncol 2015; 114(2):155

Local failure after SBRT for mCRC



MM Fode et al. Radiother Oncol 2015; 114(2):155c

Histology versus local failure

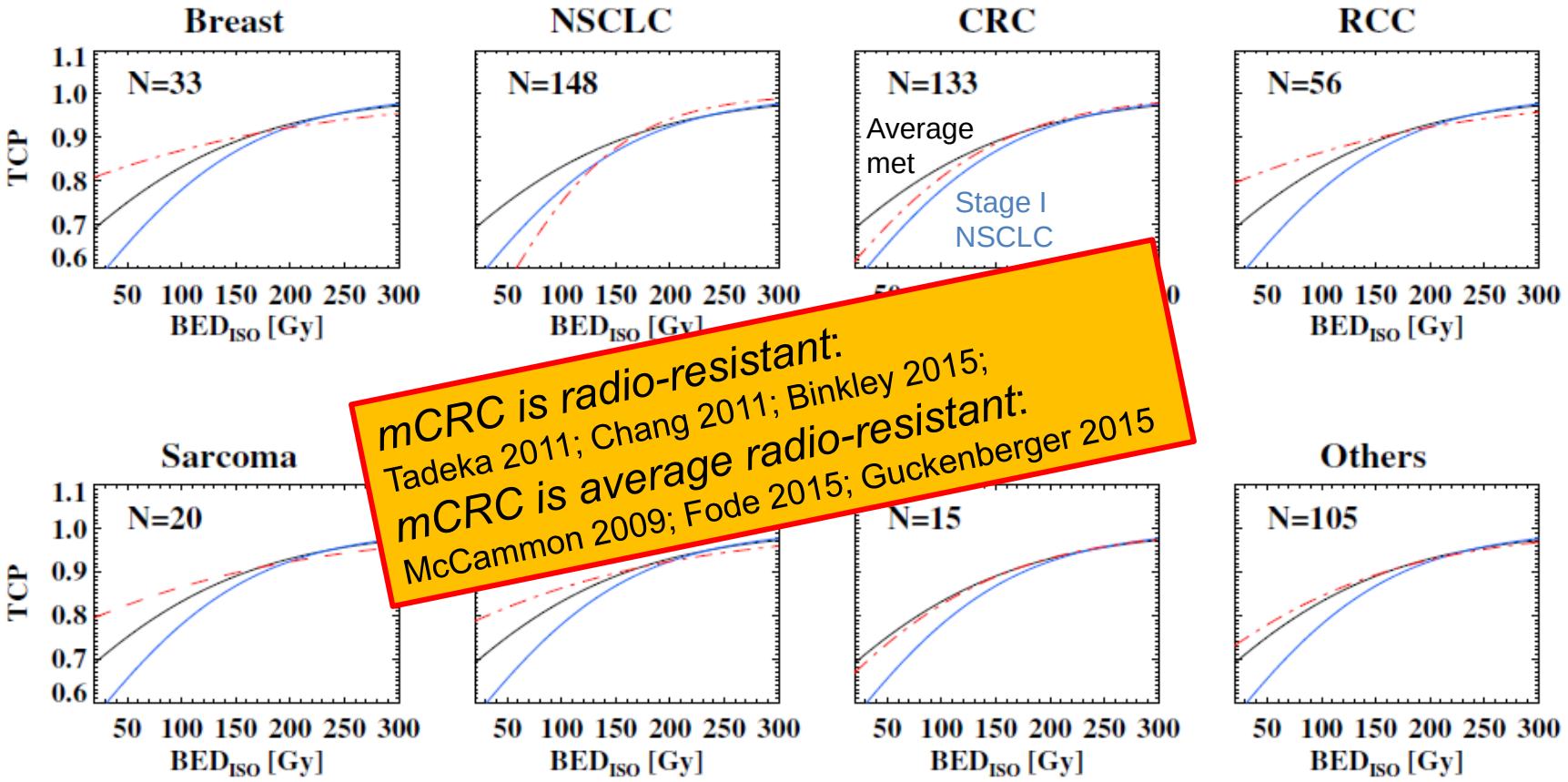


Competing risk analysis

Binkley et al. IJROBP 2015; 92(5): 1044

Radiation dose and local control

Best fit regression of dose-response relationships for lung metastases from various primaries



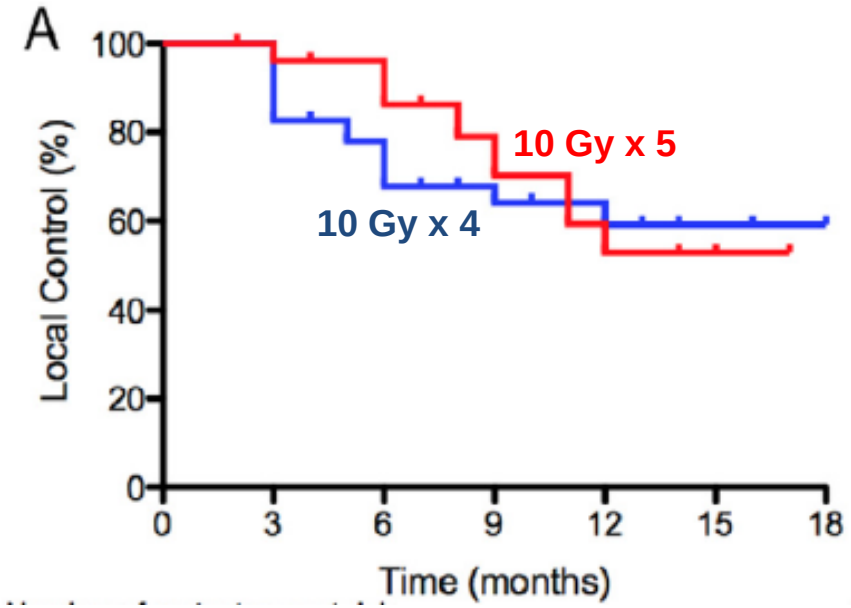
mCRC is radio-resistant:
Tadeka 2011; Chang 2011; Binkley 2015;
mCRC is average radio-resistant:
McCammon 2009; Fode 2015; Guckenberger 2015

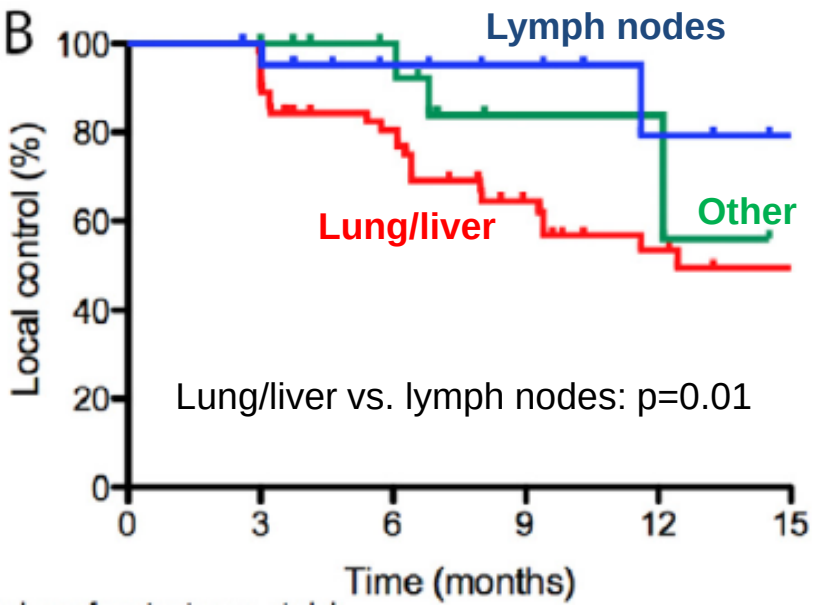
German-Austrian database
399 stage I NSCLC patients
397 metastasis patients

Guckenberger et al. Radiother Oncol 2015 *in press*

Radiation dose and local control in mCRC

47 patients with mCRC
Effect of motion?



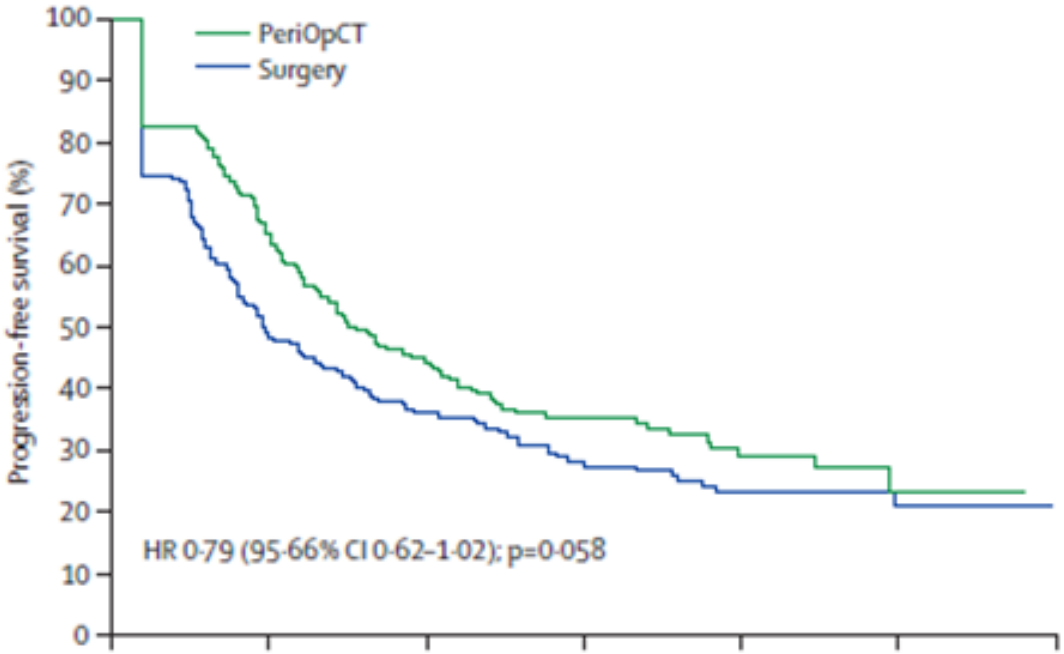


Tomo-therapy without fiducial markers
Standard population-based margins

Van den Begin et al. Radiother Oncol 2014; 113: 235

Combining local and systemic therapies

Progression free survival after resection +/- FOLFOX4

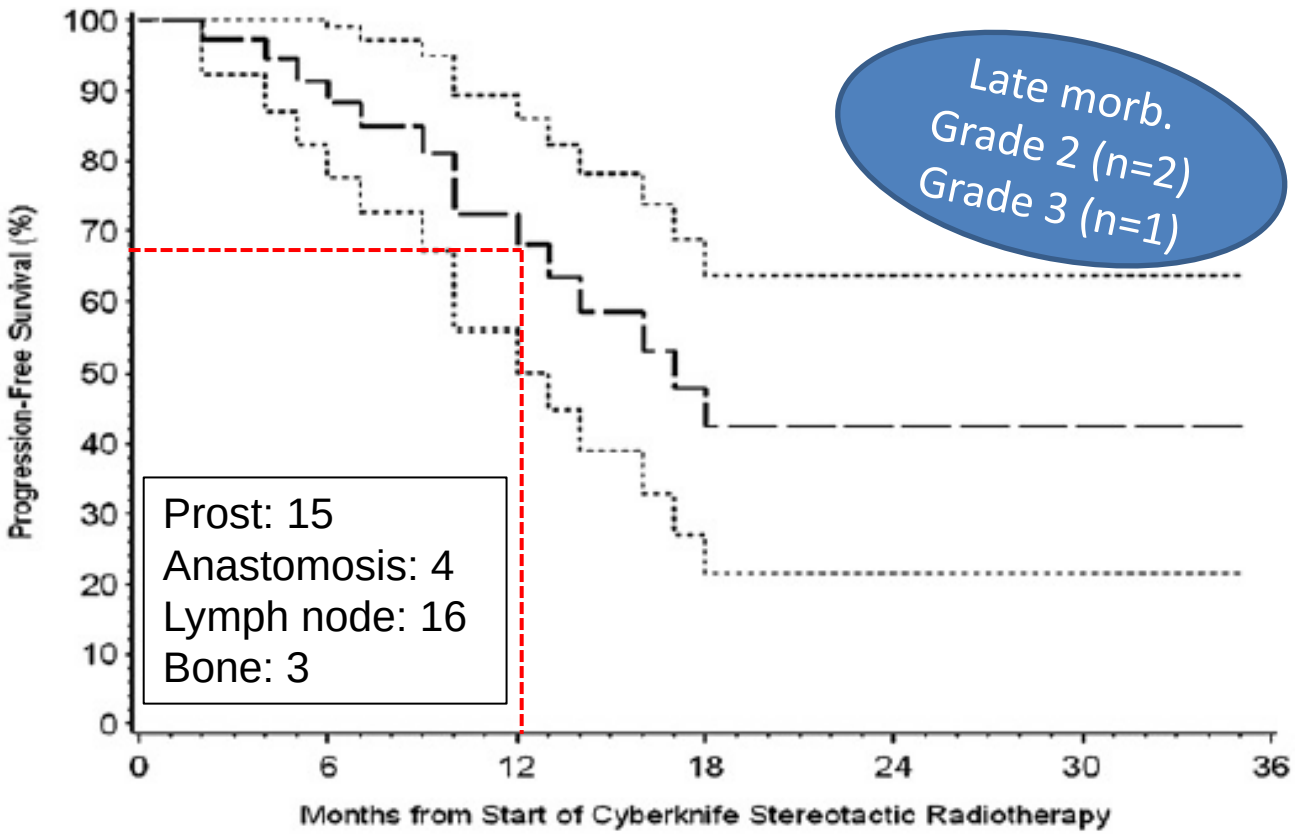


HR: 0.79 (CI 0.622–1.02; p=0.058)
in all randomly assigned patients

EORTC 40983
Nordlinger et al: Lancet (2008) 371:1007

Metastatic prostate cancer

SBRT for recurrent prostate cancer



LN-mets: 3 x 11 Gy Cyber-Knife

Jereczek-Fossa et al IJROBP 2012; 82(2): 889

SBRT for prostate cancer metastases

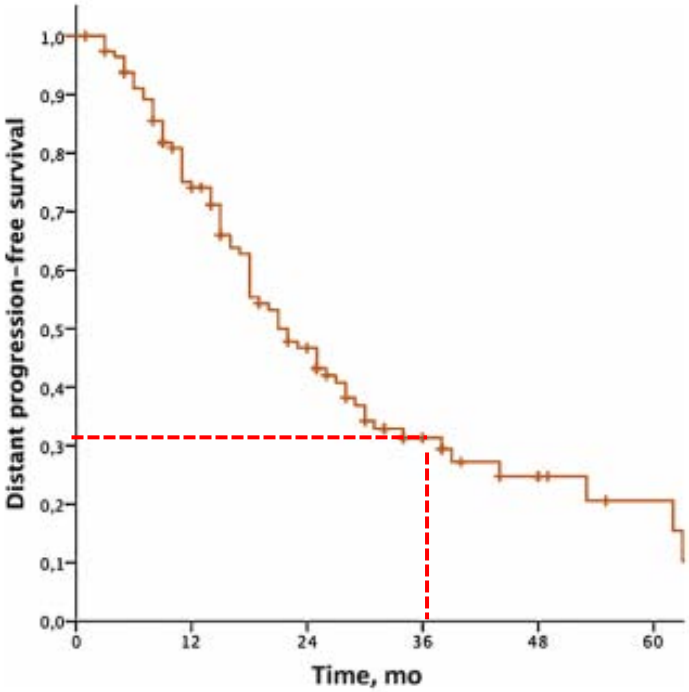


Fig. 1 – Kaplan-Meier analysis depicting time to distant progression.

- Multi-institutional database (n=119)
- Hormone naïve with metastases in:
  - Lymph nodes (n=72)
  - Bone (n=43)
  - Viscera (n=2)
- Number of metastases (1-3; 1 met.: 72%)
- LPFS 79% (BED<100 Gy) and 99% (BED≥100 Gy)
- The median time to start of palliative ADT was 28 months (95% CI, 16.2–69.7)
- The 3- and 5-yr OS was 95% and 88%, respectively

P. Ost et al. Eur Urol 2016; 69(1): 9-12

SBRT of prostate cancer and systemic therapies

- *Is SBRT replacing systemic therapy?*
- *Or should they be combined?*

- ***TOAD trial*** *(Duchesne et al, ASCO 2015): immediate versus delayed ADT at PSA relapse after definitive therapy*
  - *HR=0.55 (CI: 0.30-1.00)*
- ***CHAARTED-*** *(Sweeney et al NEJM 2015): ADT+docetaxel versus ADT alone in advanced stage hormone sensitive PCa*
  - *HR=0.61 (CI: 0.47-0.80)*
  - *m-OS: 58 and 44 months, respectively*
- ***STAMPEDE*** *(James et al Lancet 2016): SOC+docetaxel versus SOC in advanced stage hormone sensitive PCa*
  - *HR=0·78 (CI: 0·66–0·93)*
- *Combination with immune stimulating agents*

Prognostic factors

Overall survival after SBRT for oligometastases

Brain (n=107), lung (n=56), liver (n=77), lymph node (n=88), bone (n=24), adrenal gland=14) and other (n=15)

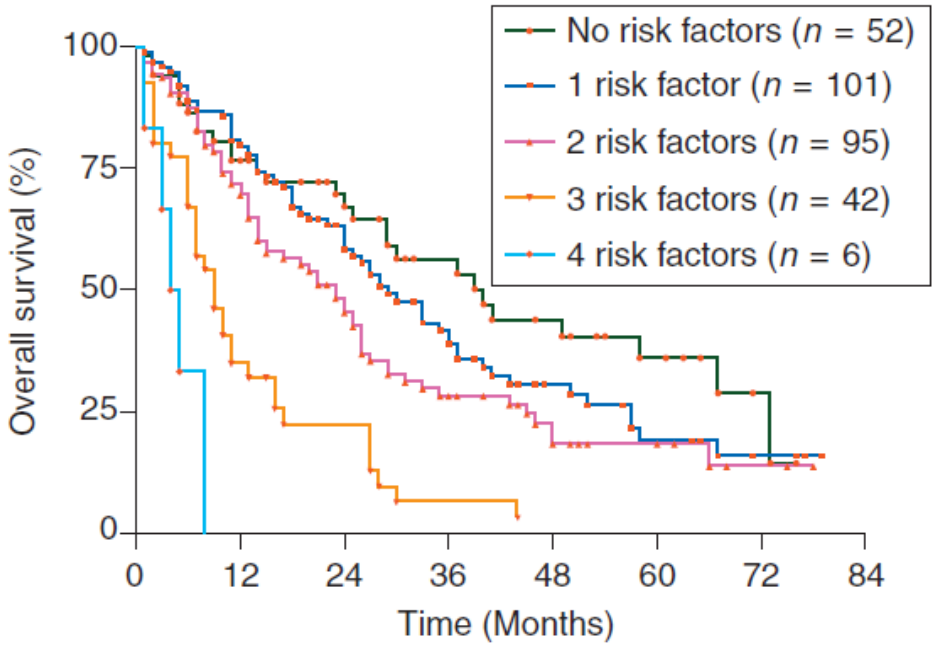


Table 2. Multivariate analysis: prognostic factors for survival

Significant variables	Hazard ratio (95% CI)	*P*-value (cox regression)
Gender		
Female versus male	1.401 (1.046–1.877)	0.024
Histology of primary		
Adenocarcinoma versus nonadenocarcinoma	0.430 (0.309–0.597)	<0.001
Oligometastatic disease		
Metachronous versus synchronous	1.491 (1.113–1.996)	0.007
Oligometastatic site		
Extracranial versus intracranial	1.819 (1.344–2.463)	<0.001
BED ≥75 versus <75 Gy	1.626 (1.058–2.500)	0.023

CI, confidence interval; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; BED, biologically effective dose.

DeVin et al. Annals of Oncology 2014; 25: 467

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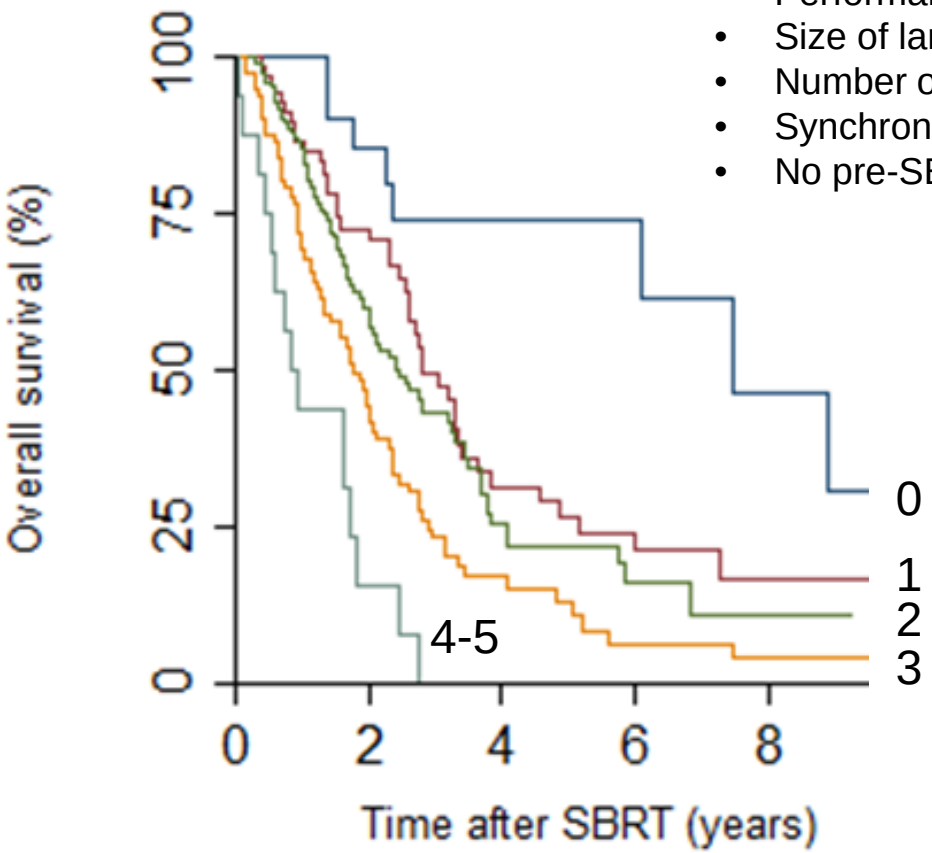
Aarhus University Hospital

Overall survival

According to prognostic factors

- Performance status 2+
- Size of largest metastasis ≥ 3cm
- Number of metastases 2+
- Synchronous metastases
- No pre-SBRT chemotherapy



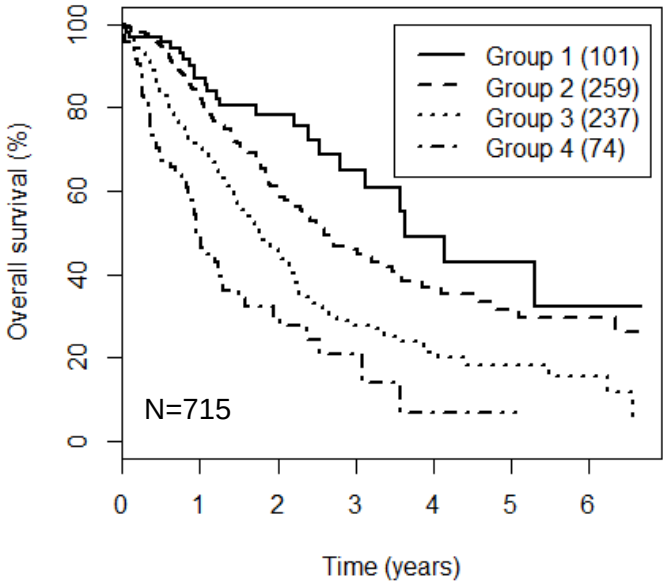
MM Fode et al. Radiother Oncol 2015; 114(2):155

CIRRO

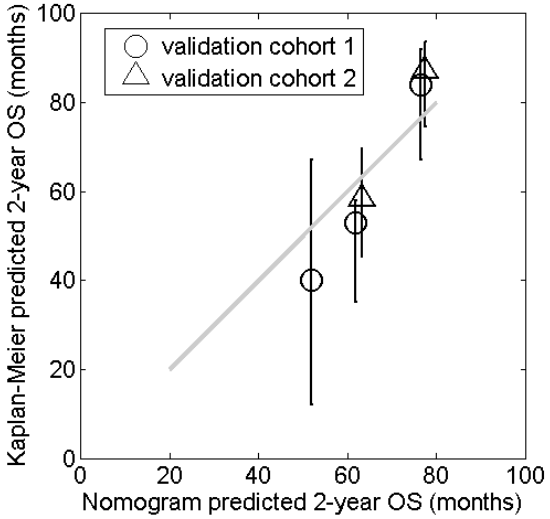
Aarhus University Hospital

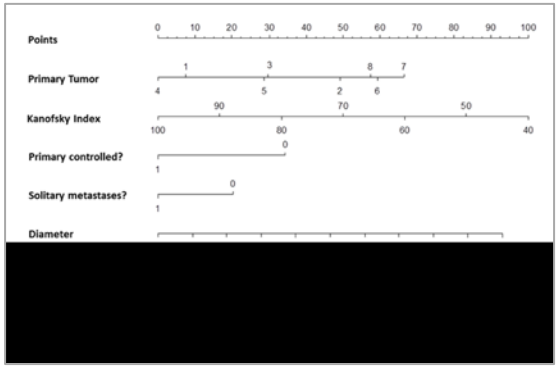
Overall survival after SBRT for lung metastases

Training set (DEGRO)



Validation sets (Aarhus and Turin)





Prognostic factors:

Karnofsky performance index

Type of the primary tumor
(Kidney, CRC, sarcoma and breast best)

Control of the primary tumor

Maximum diameter of metastasis

Number metastases (1 versus >1)

M Guckenberger et al. European Lung Cancer Conference 2016

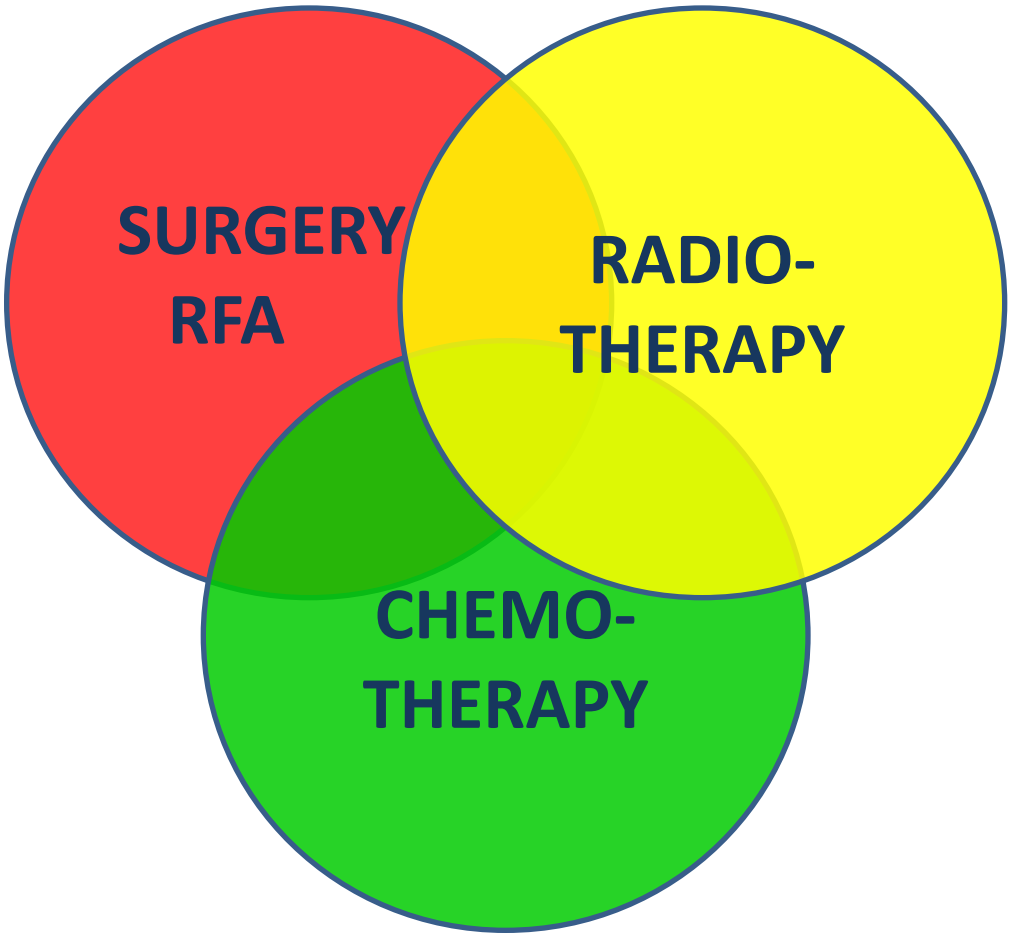
CIRRO

Aarhus University Hospital

The four aces

- Young age
- Good performance status √
- Slowly progressing cancer √
- Low tumor burden √

Treatment of cancer in a Multidisciplinary Team



Conclusions – SBRT of oligometastases

- Long-term survival after SBRT may be achieved in patients with favorable prognostic factors:
  - Colorectal and prostate primaries
  - Good performance status
  - Small size of the metastases
  - Low number of metastases
- Few patients with grade $\geq$ 3 morbidities
- Candidates for SBRT should enter phase III trials

Experience based on selected patients

AARHUS UNIVERSITET

CIRRO

Practice of SBRT :
RTT perspective

Lineke Berkelaar- van der Weide (MSc)
RTT research
VU University Medical Center
l.vanderweide@vumc.nl


AMSTERDAM

HOORN

~3.500 new patients / year

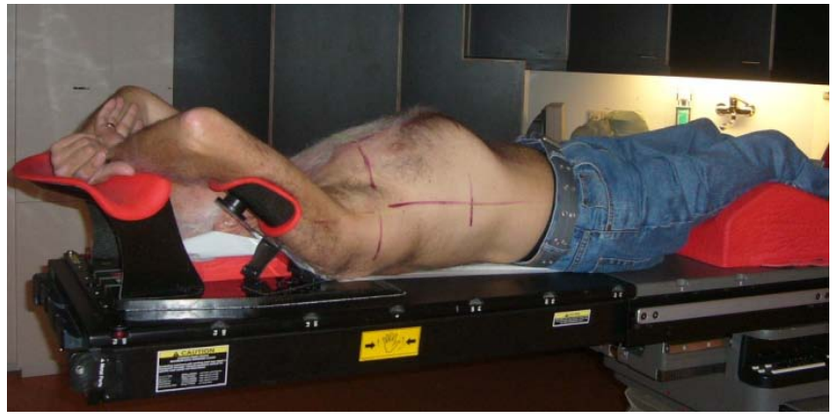
~1.600+ SBRT patients

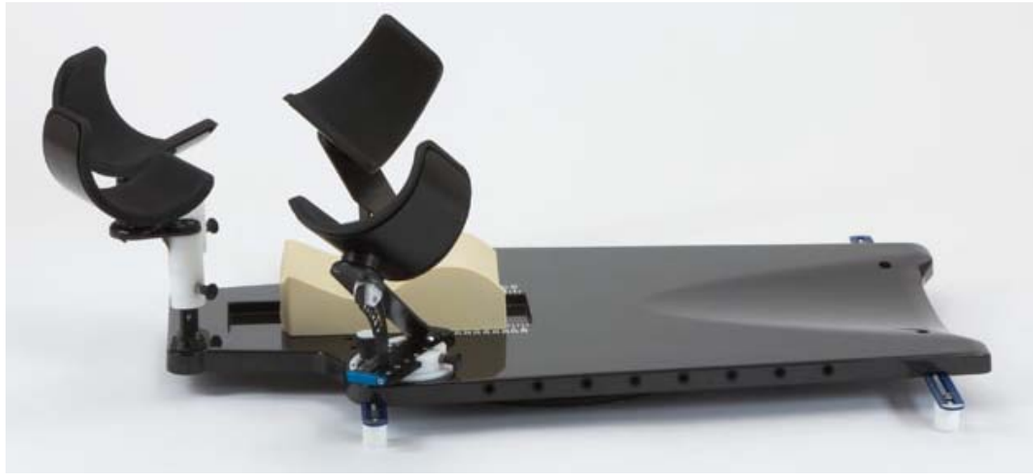
RTTs role in treatment

- Patient positioning
- IGRT-protocols:
  - Orthogonal kV images
  - CBCT (PTV match)
  - ExacTrac (bone match)
- Motion Management
- Online intrafraction monitoring
  - Real-time Positioning Management (RPM)
  - ExacTrac
  - Auto Beam Hold package
- Offline intrafraction monitoring
  - Continuous acquired kV-images during treatment (3fps-15fps)
- In between and possible at the end of the arcs : CBCT (depends on tumorsite)

Patient positioning (Lung, Spine, Liver)

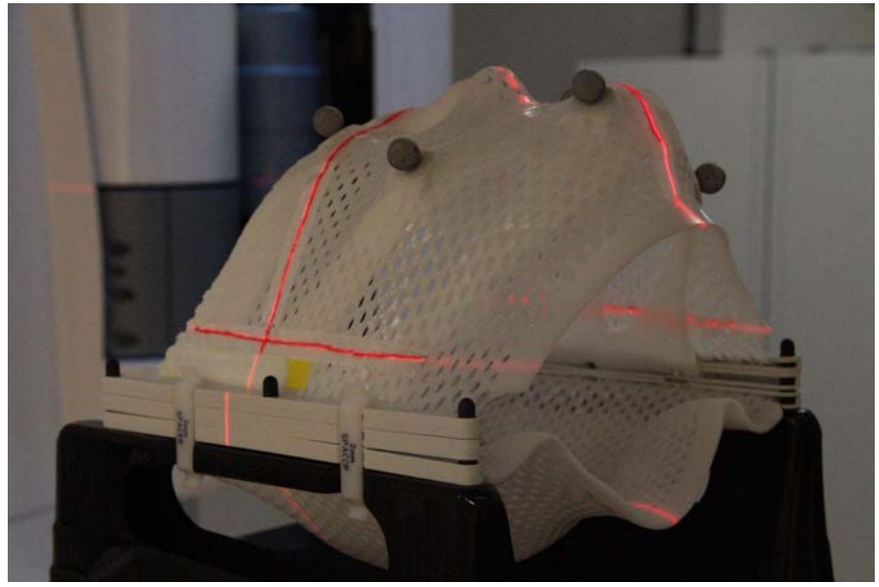
- Thoraxsupport (Macromedics)
- Posirest lung board
- Knee cushion



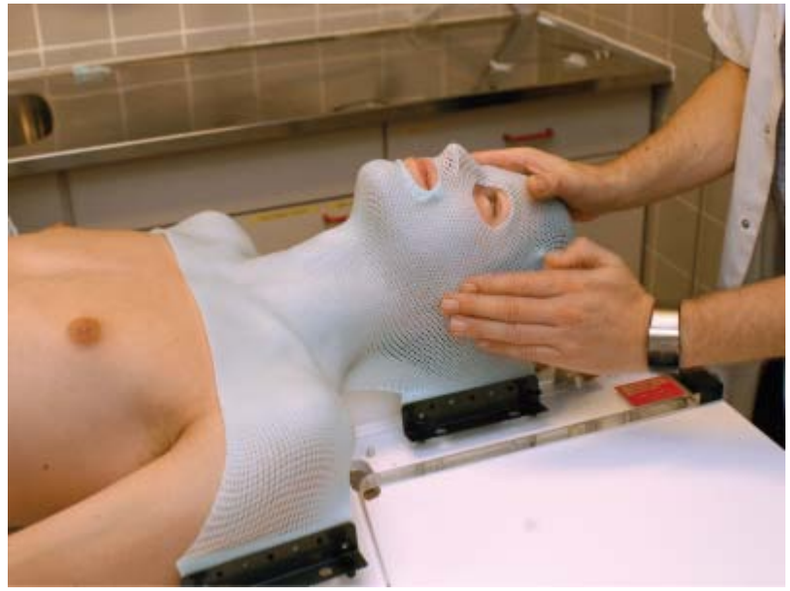


Patient positioning (brain, spine (above T4))

- Mask brain



- Mask spine



IGRT-options in your department

- MV imaging alone
- MVCT
- In-room CT/ CT on rails
- (kV-kV and) CBCT
- Exac trac

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

IGRT-protocols

Depends on tumorsite

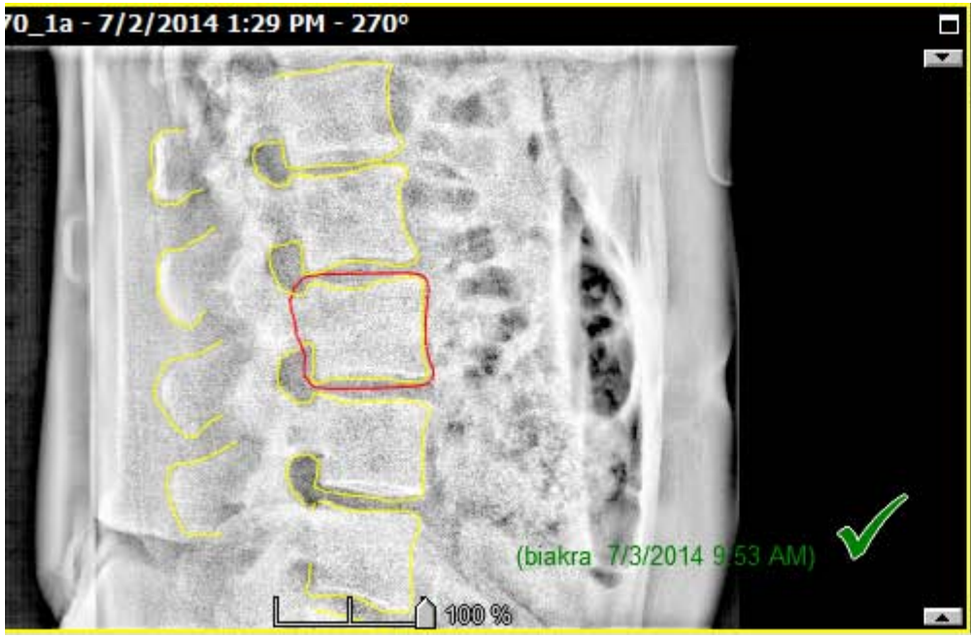
For setup:

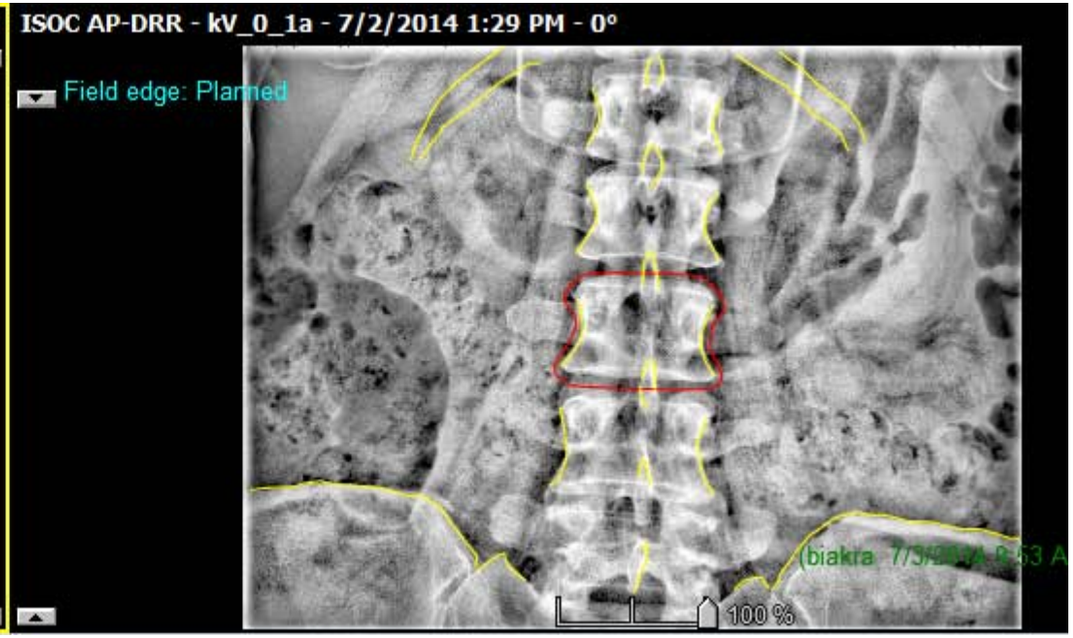
- Orthogonal kV-images
- CBCT:
  - PTV match, when necessary 6D couch
- Exac-Trac (in combination with CBCT)

During treatment:

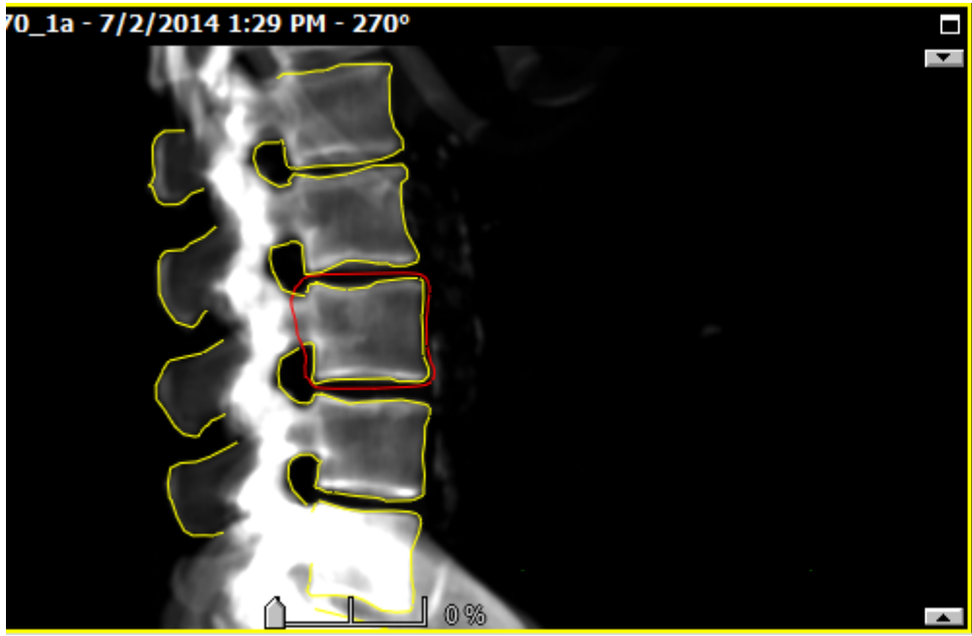
- CBCT halfway treatment
- CBCT post-treatment

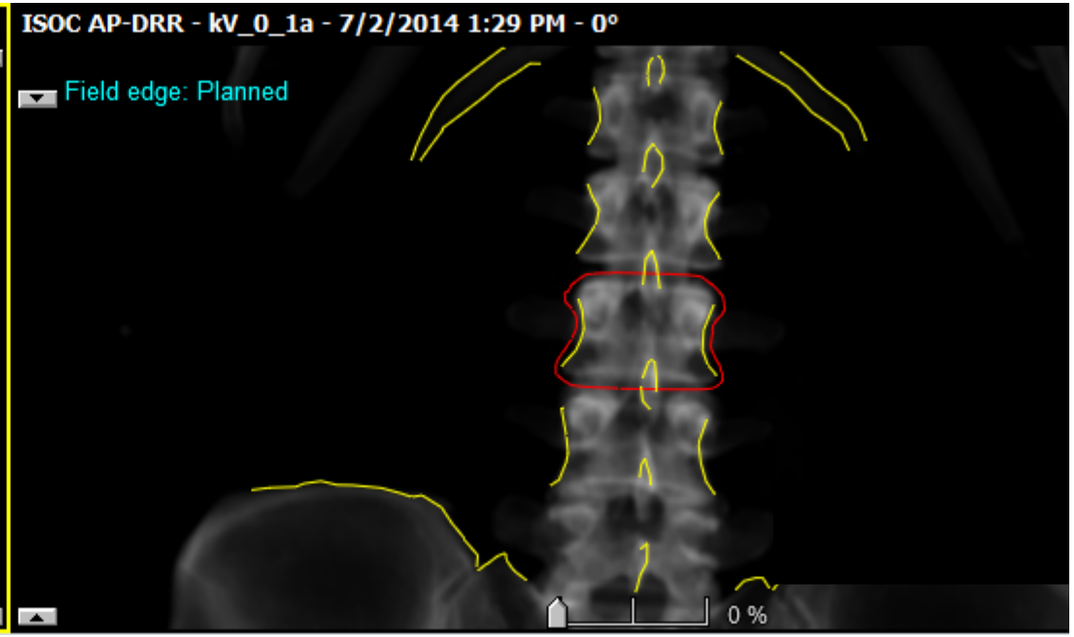
Orthogonal kV-images

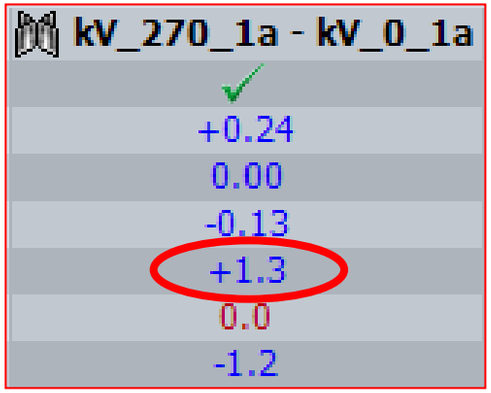




Orthogonal kV-images

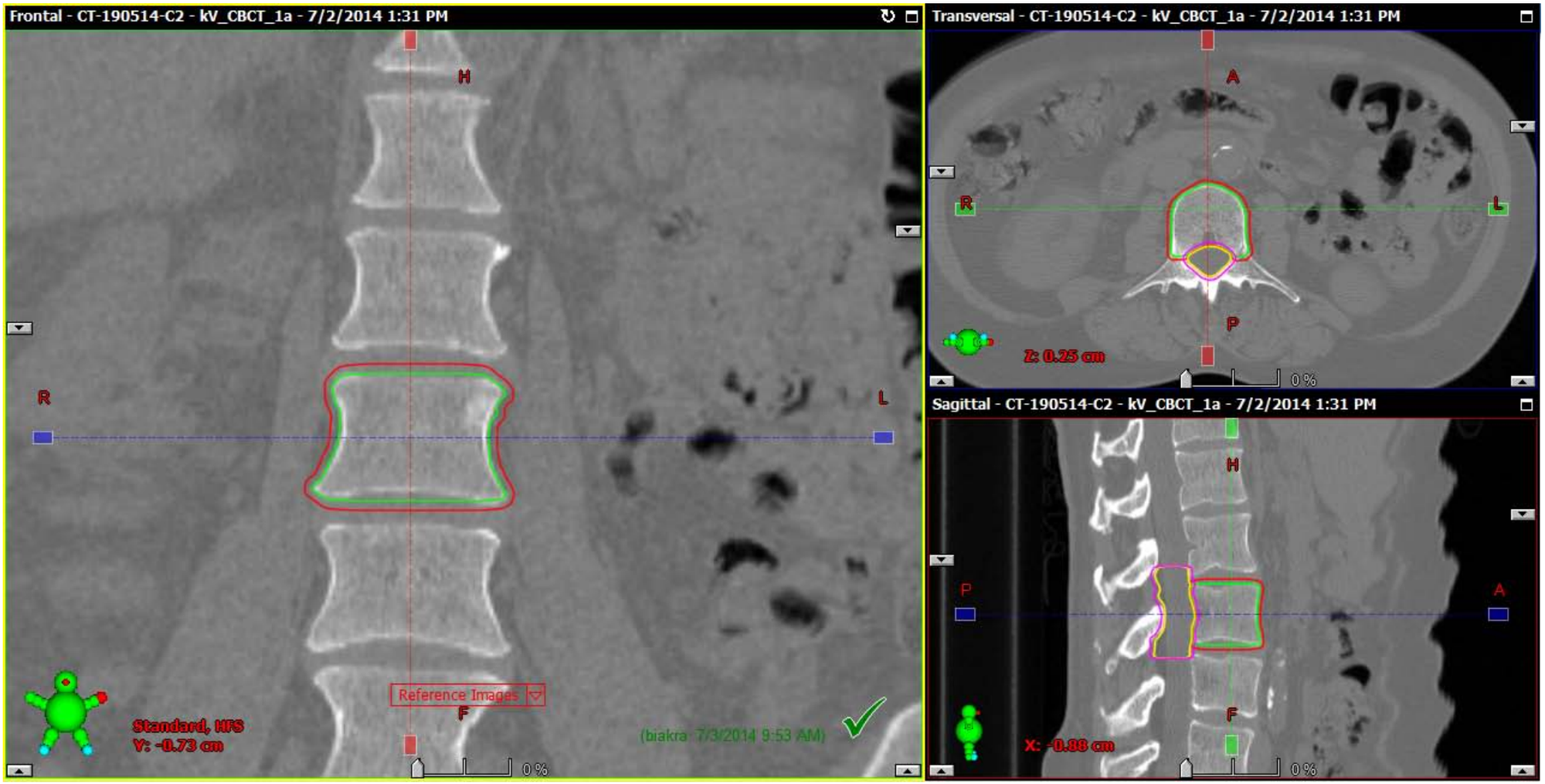




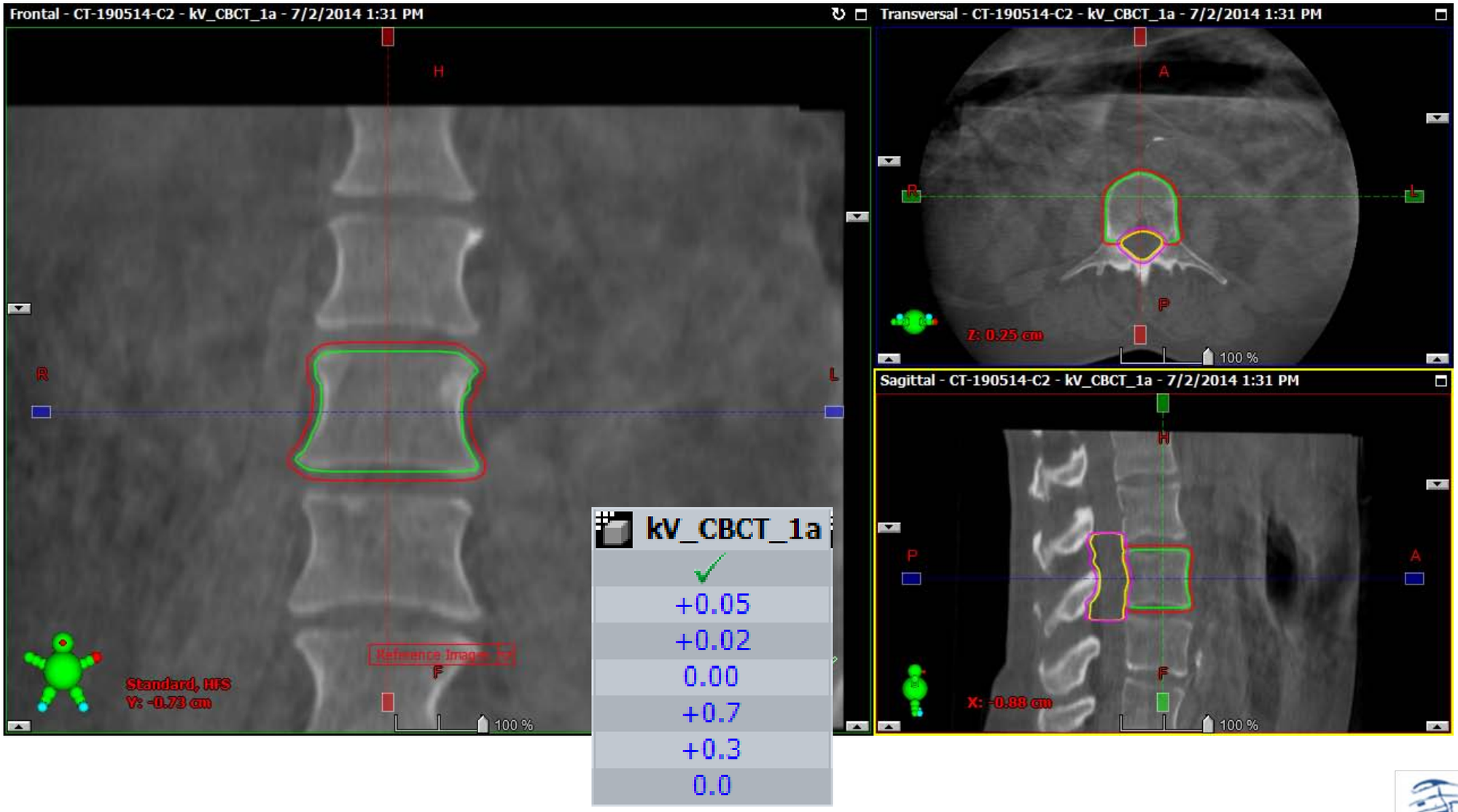


Advantage of use kV-kV first:
- Pitch and roll > 1.0° extra CBCT to ensure if patients are not counteracting

CT, normal spine case

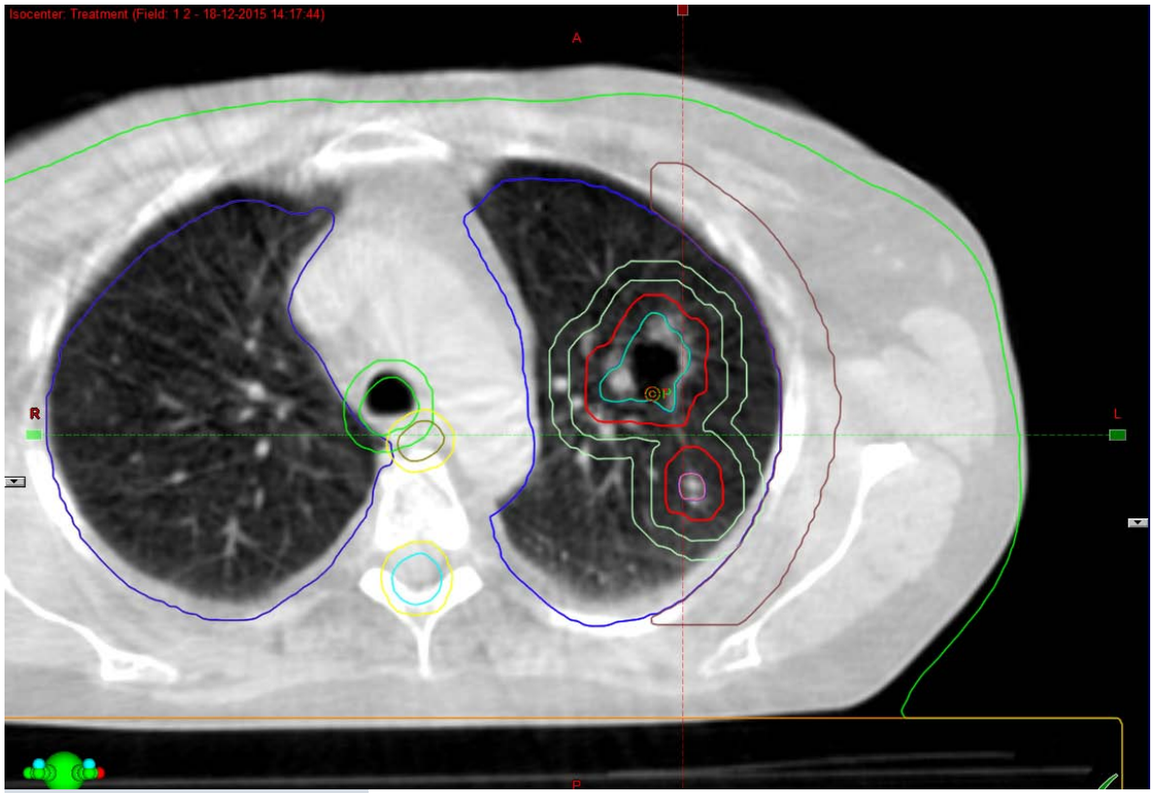


CBCT, normal spine case



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

IGRT-protocols

Depends on tumorsite

For setup:

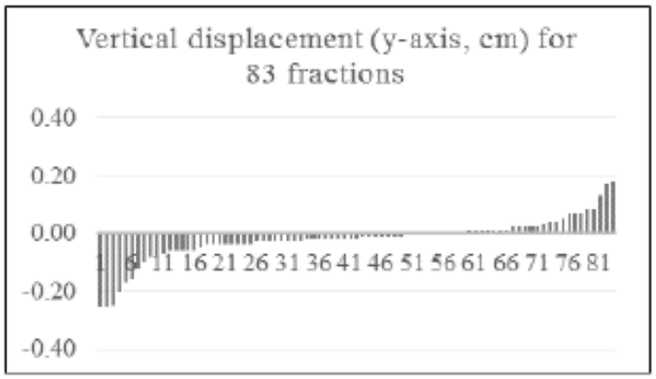
- Orthogonal kV-images
- CBCT:
  - PTV match, when necessary 6D couch
- Exac-Trac (in combination with CBCT)

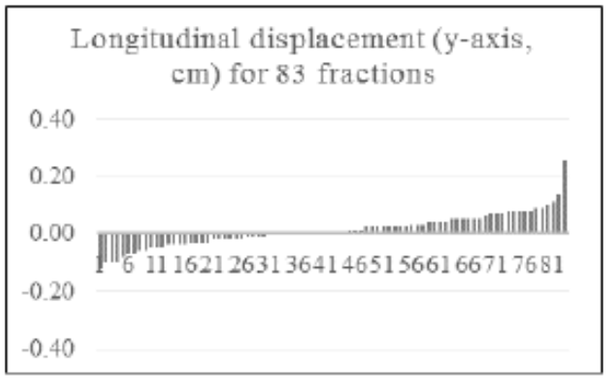
During treatment:

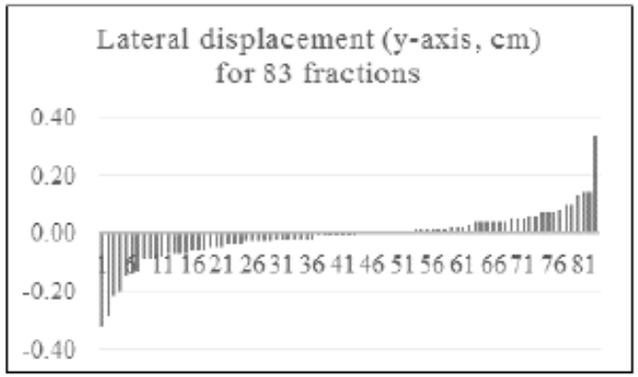
- CBCT halfway treatment
- CBCT post-treatment

Spine and bony pelvis: 6Dcouch, FFF
(83 fractions; Dahele et al in press Acta Oncologica)

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 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.

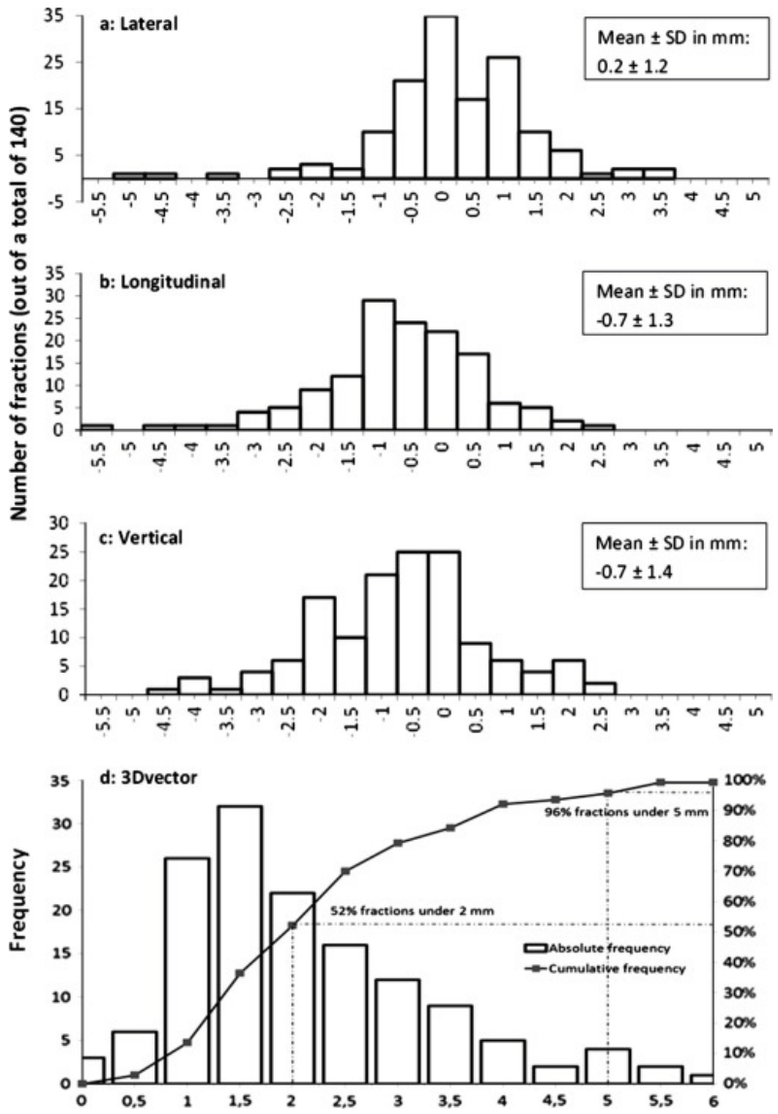
Post-treatment CBCT, SBRT lung

- 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 (1)

A strategy for motion management is essential in SBRT for anatomical indications effected by breathing motion (e.g. lung, liver, adrenal gland, lymph node)

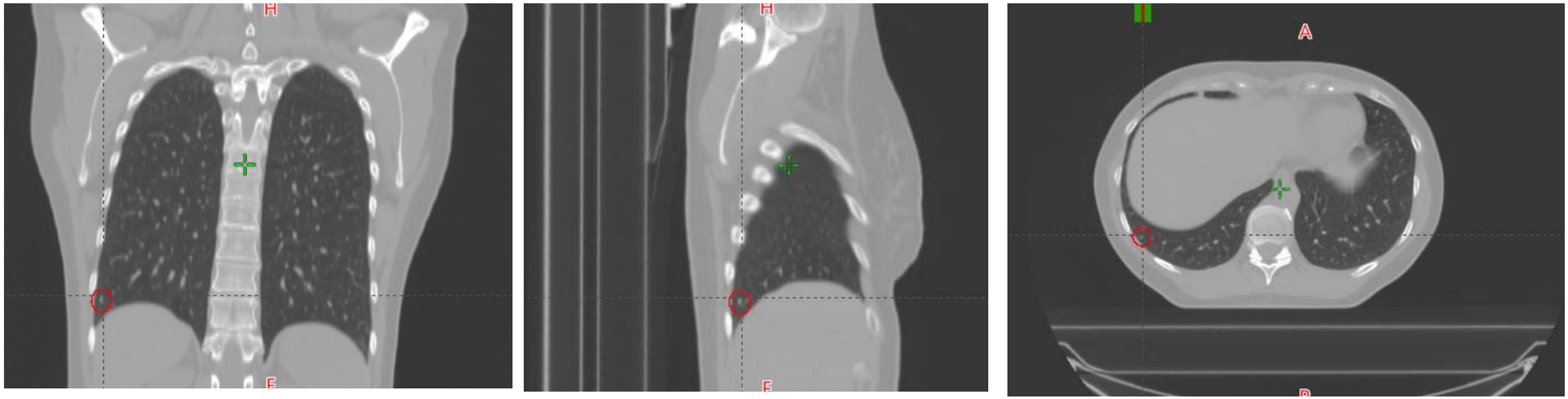
- Dependant on departmental availability of kit
- Role in coaching / training patient
- Additional considerations when these techniques are used e.g. longer on treatment couch

Motion management (2)

- Stop / reduce tumour movement
  - Deep Inspiration BreathHold
    - Lung
  - Expiration BreathHold
    - Liver

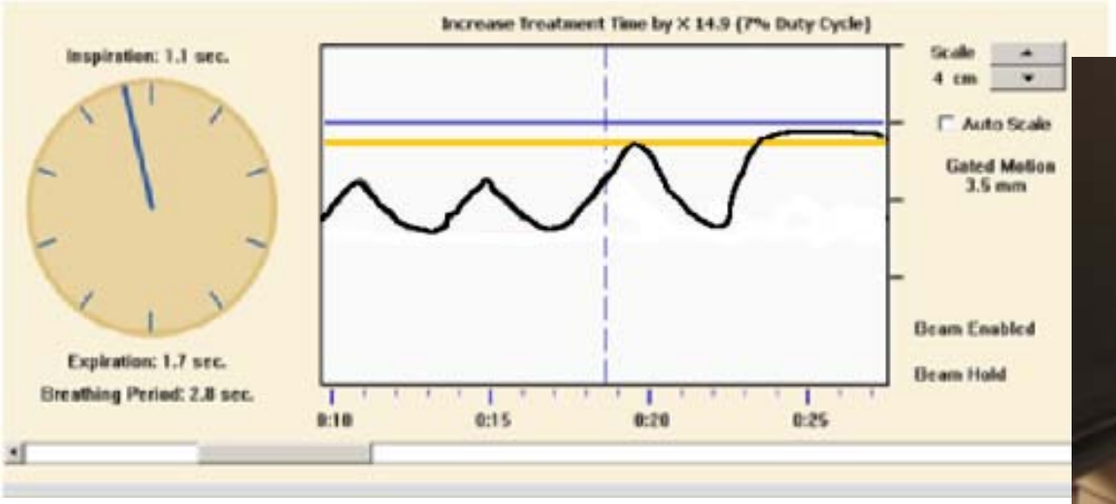
Deep Inspiration Breath Hold (DIBH)

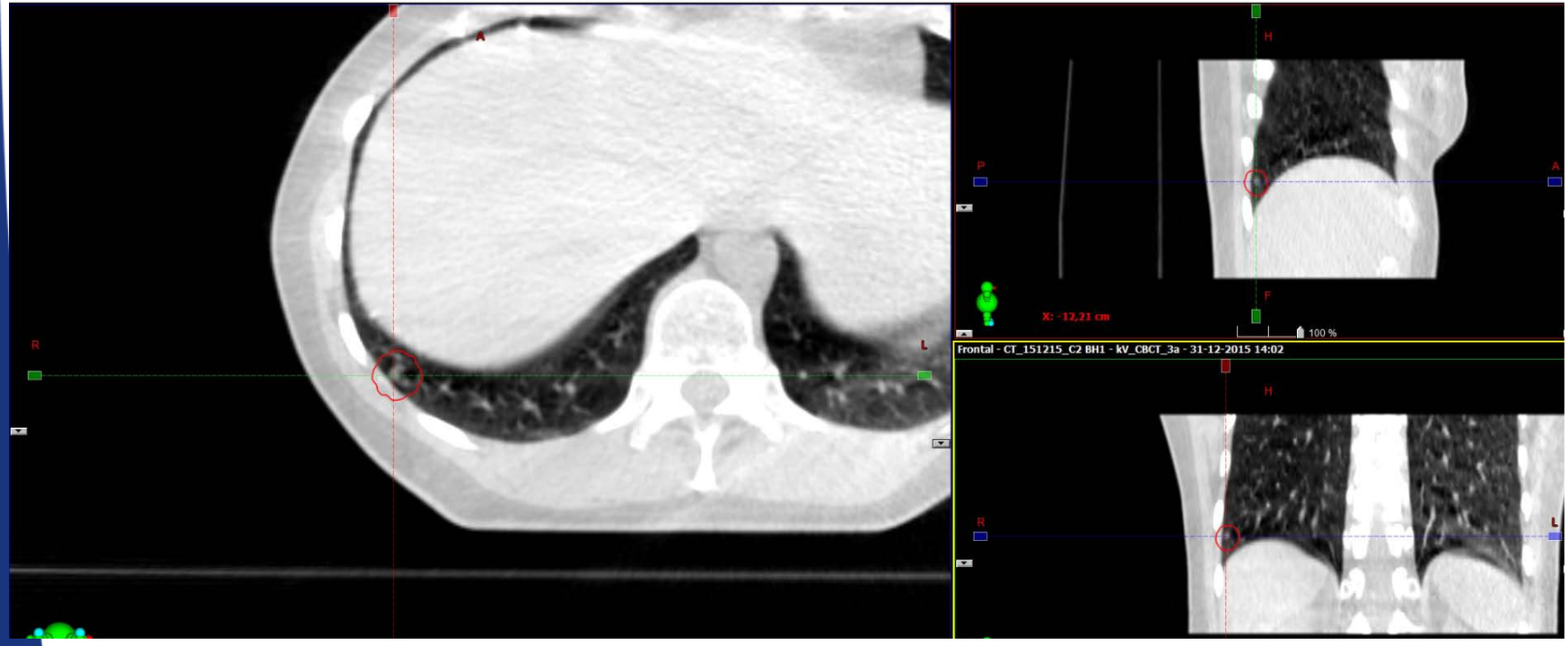
46-yr old patient
4 lesions in lung
1 lesion close to diaphragm



Tumorshift on planning-CT >3cm

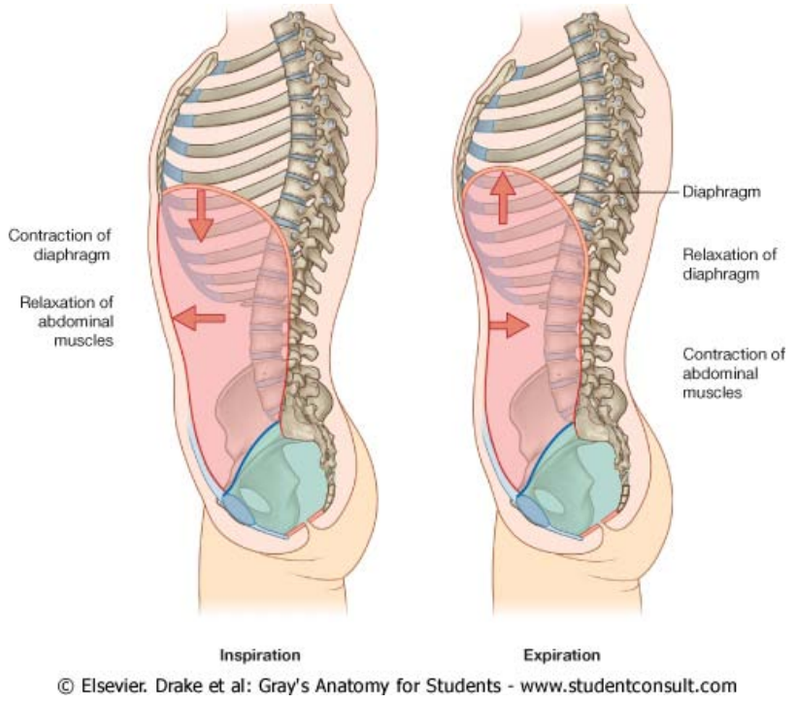
Deep Inspiration Breath Hold (DIBH)



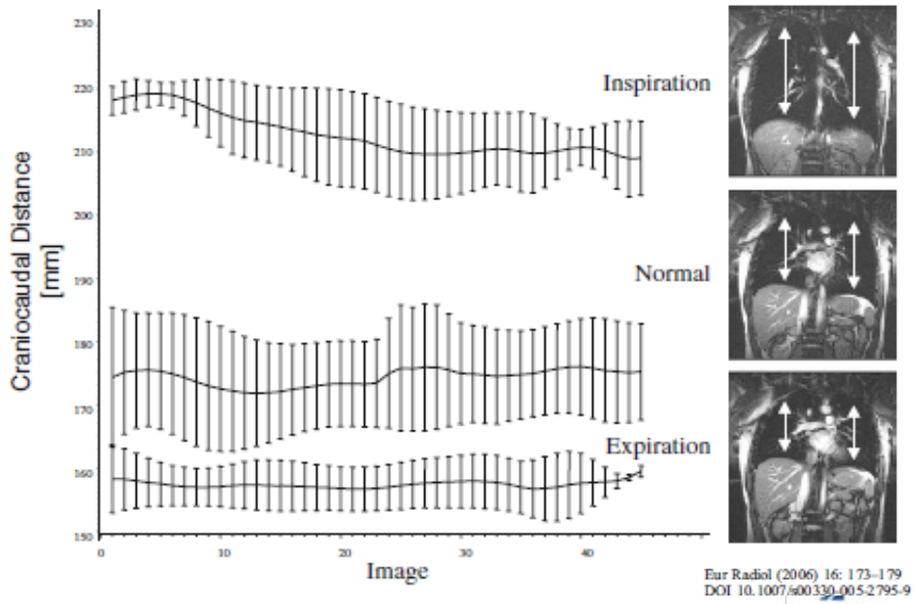


Expiration Breathhold: why & where?

- Breath-holding in expiration
- Fit patients
- Minimize mobility
- Stability through expiration
- Upper abdomen
- Imaging optimization

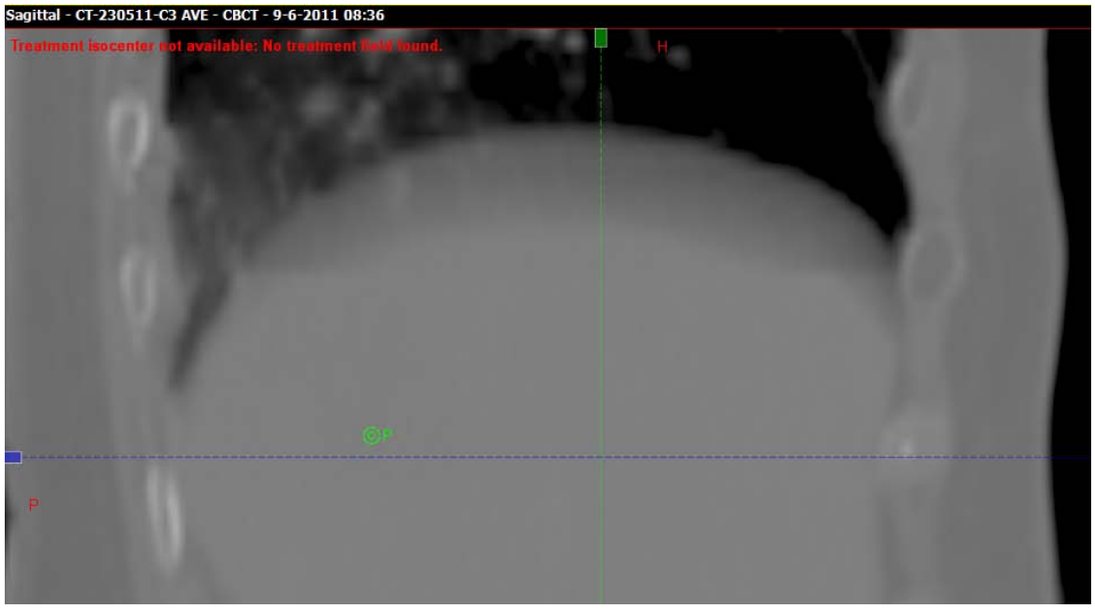


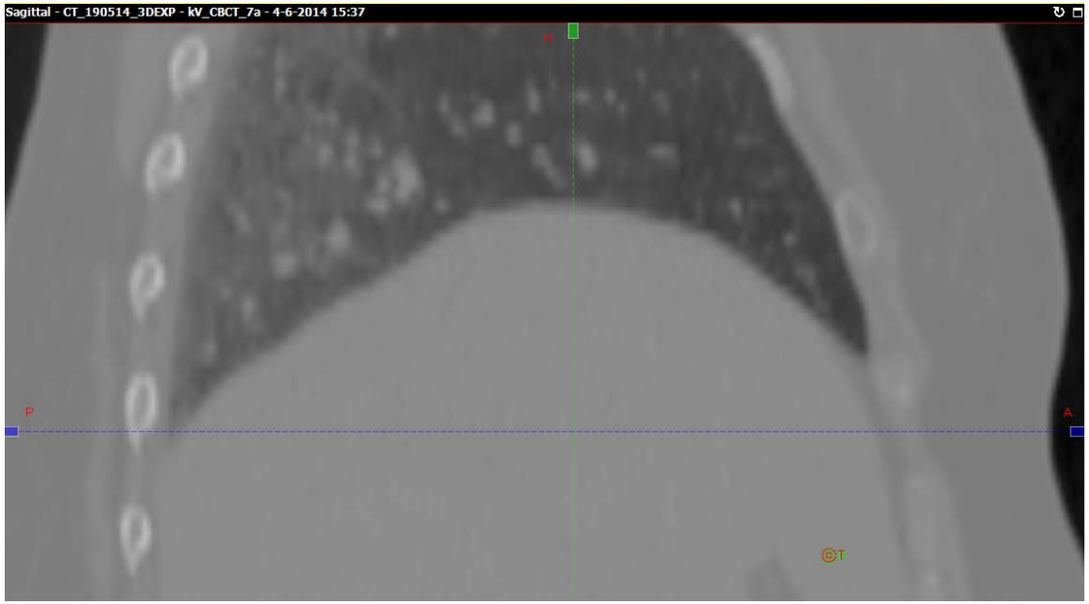
© Elsevier. Drake et al: Gray's Anatomy for Students - www.studentconsult.com



Eur Radiol (2006) 16: 173–179
DOI 10.1007/s00330-005-2795-9

Imaging optimization





Imaging:
Freebreathing
vs
Expiration
Breathhold

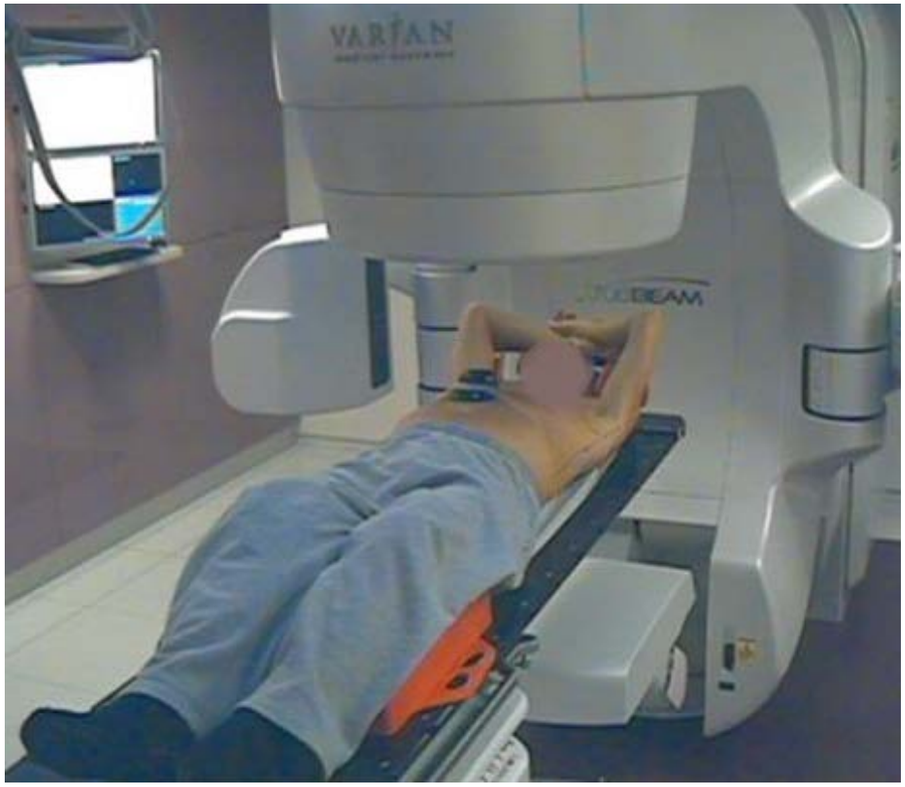
Intrafraction monitoring devices

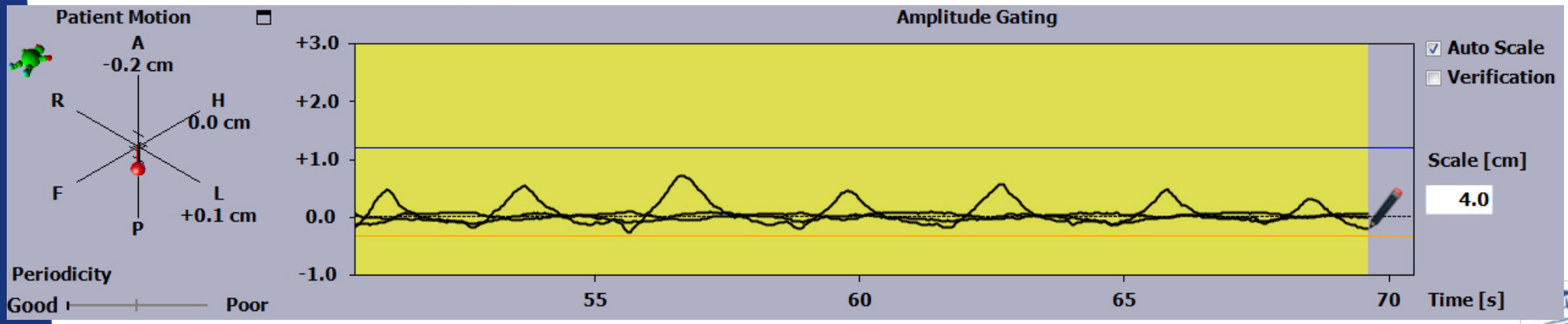
- RPM system
- Exac Trac
- Auto Beam Hold
- Calypso
- Surface scanning system
- Ultrasound package
- MRI possibilities

Intrafraction monitoring

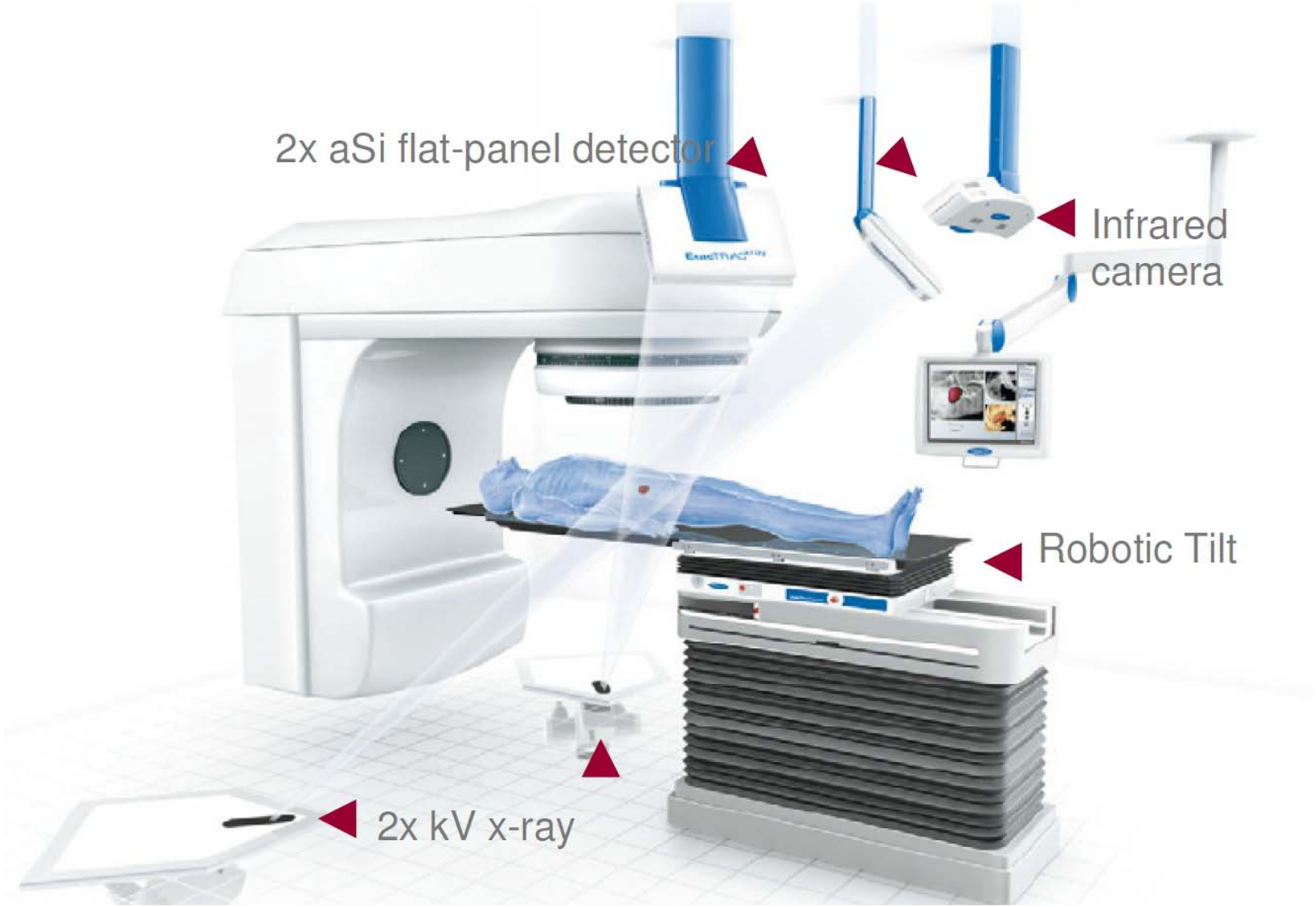
- RPM system
- Exac Trac
- Auto Beam Hold withTriggered Imaging

RPM-system

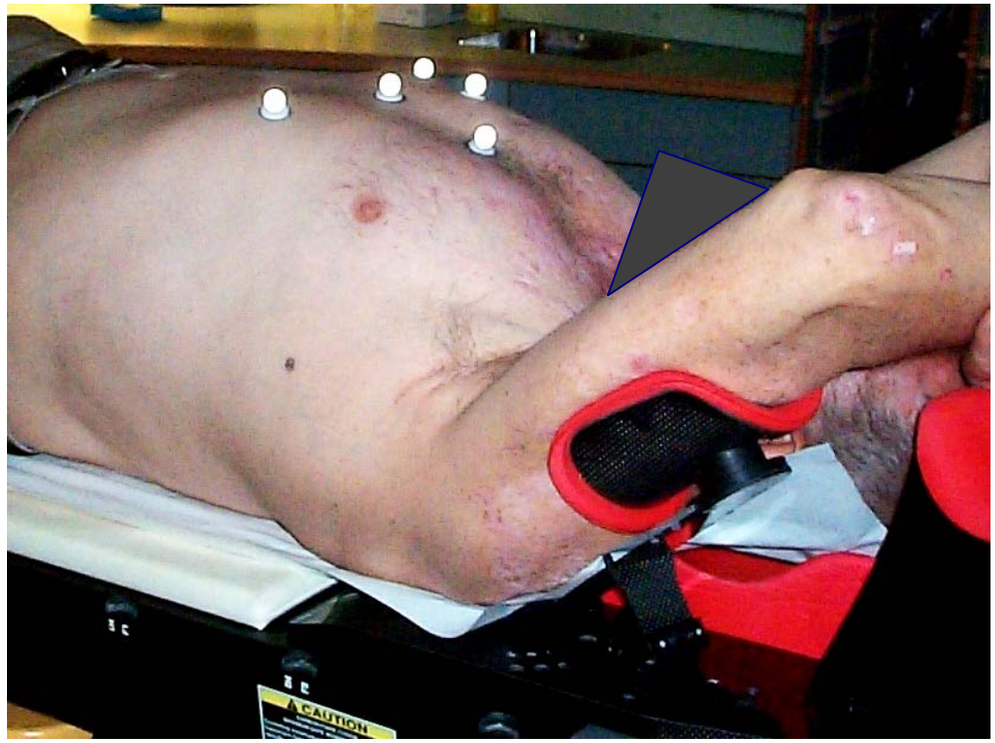

VARIAN


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

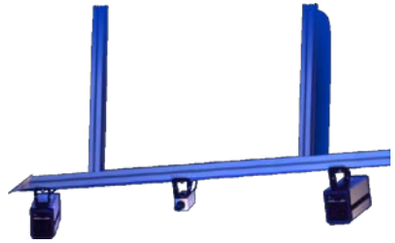


ET infrared positioning

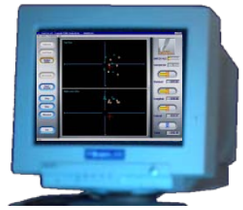
VUmc

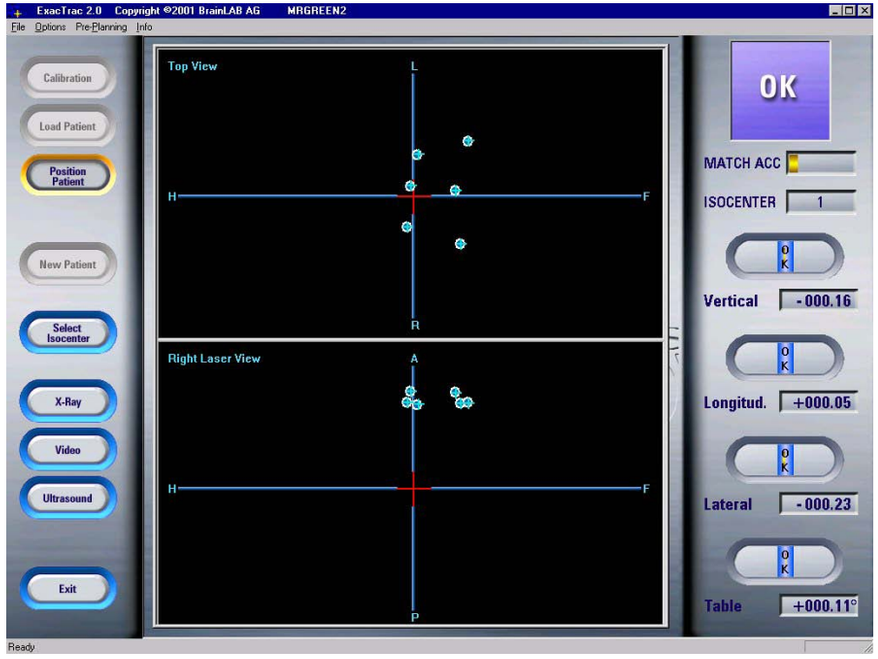
ExacTrac markers

ExacTrac camera's

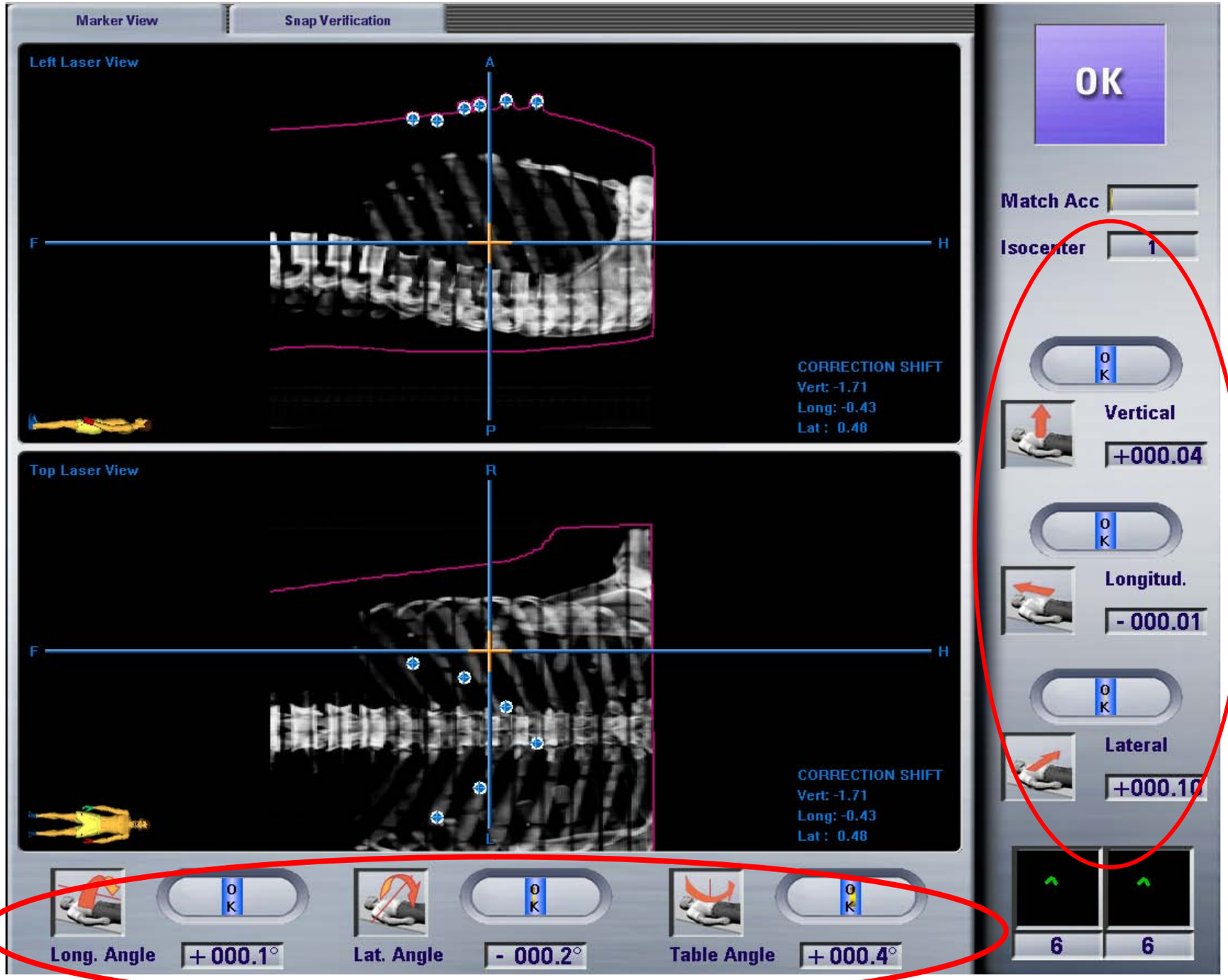


Procedure





Monitoring ExacTrac markers



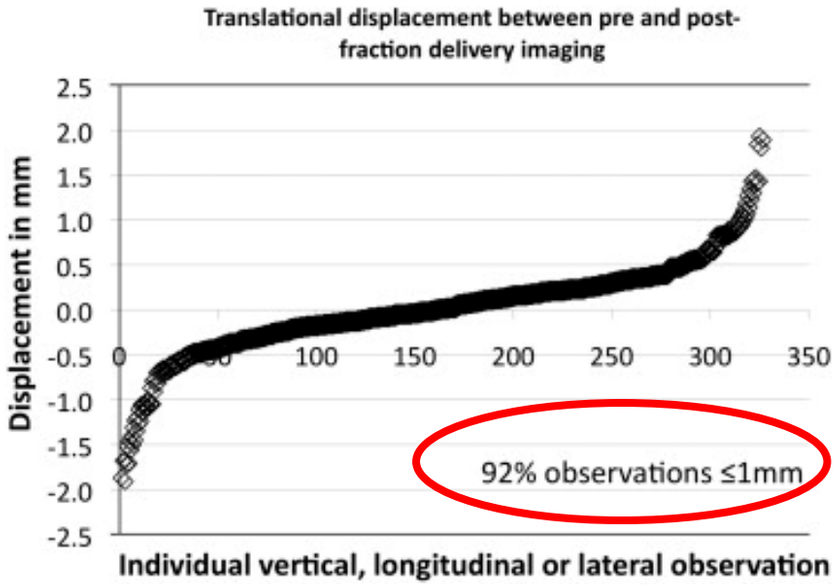
Stability based on ExacTrac

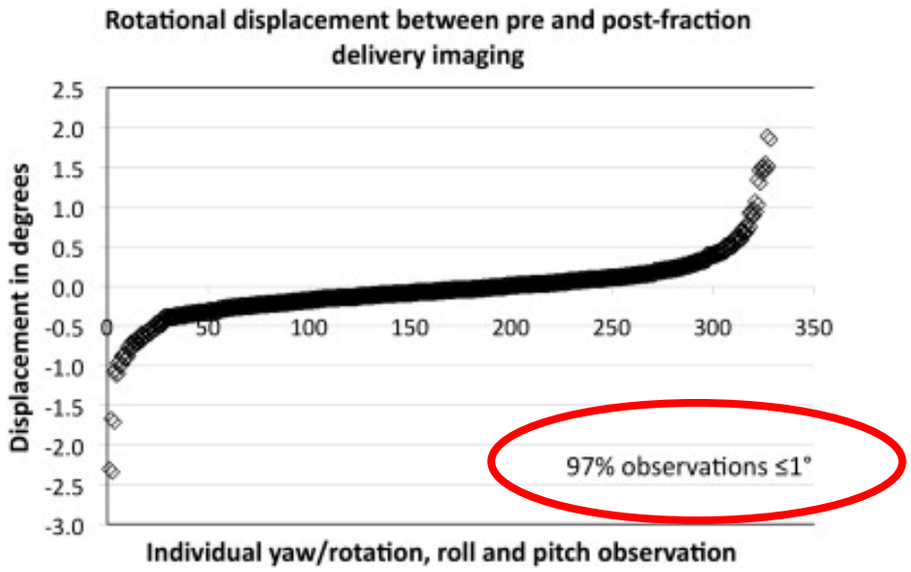
Radiotherapy and Oncology
Volume 104, Issue 1, July 2012, Pages 28–32

SBRT of lung cancer

An analysis of patient positioning during stereotactic lung radiotherapy performed without rigid external immobilization

Max Dahele[a], Wilko Verbakel[a, b], Johan Cuijpers[a, b], Ben Slotman[a], Suresh Senan[a]





Results: Images from 109 fractions in 30 patients resulted in 327 translational and 327 rotational pre- and post-fraction comparisons. Mean RapidArc® delivery time for variable fraction dose was 4.2 min (SD = 1.4). 92% and 97% of translational and rotational differences were ⩽1 mm and ⩽1° in any direction and 98% of translational differences were ⩽1.5 mm. Mean vertical, longitudinal and lateral motion was 0 mm (SD = 0.4), 0 mm (0.6) and 0 mm (0.6). 84% and 94% of the 109 fractions were delivered with ⩽1 and ⩽1.5 mm translation in all three directions and 93% with ⩽1° of rotation. Two patients accounted

Auto Beam Hold package

- Part of TrueBeam ® (TB) 2.0 and onwards

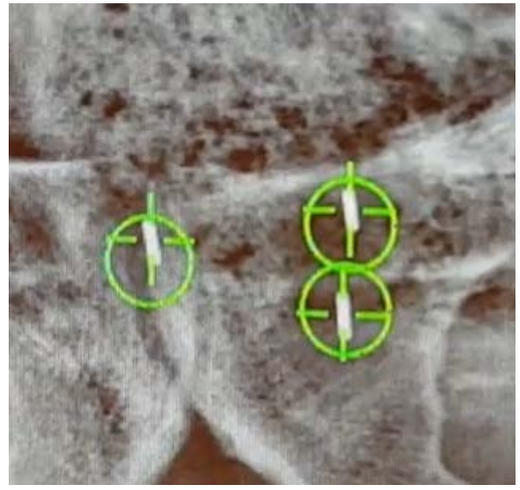
- ABH consists of the following steps:
  1. Triggered Imaging (TI):
     - Respiratory gating, at beam on/off
     - MU
     - Gantry angle (only for RA)
     - Time, minimum interval = 3 sec
  2. Auto detection of fiducially markers on TI (AD)
  3. Beam hold (BH) option to control state of treatment beam based on AD

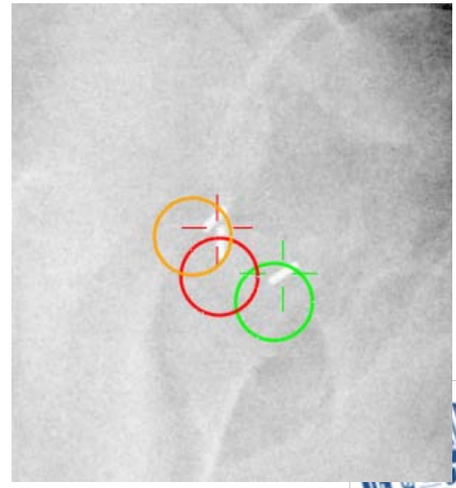
Auto detection and Beam Hold

- **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

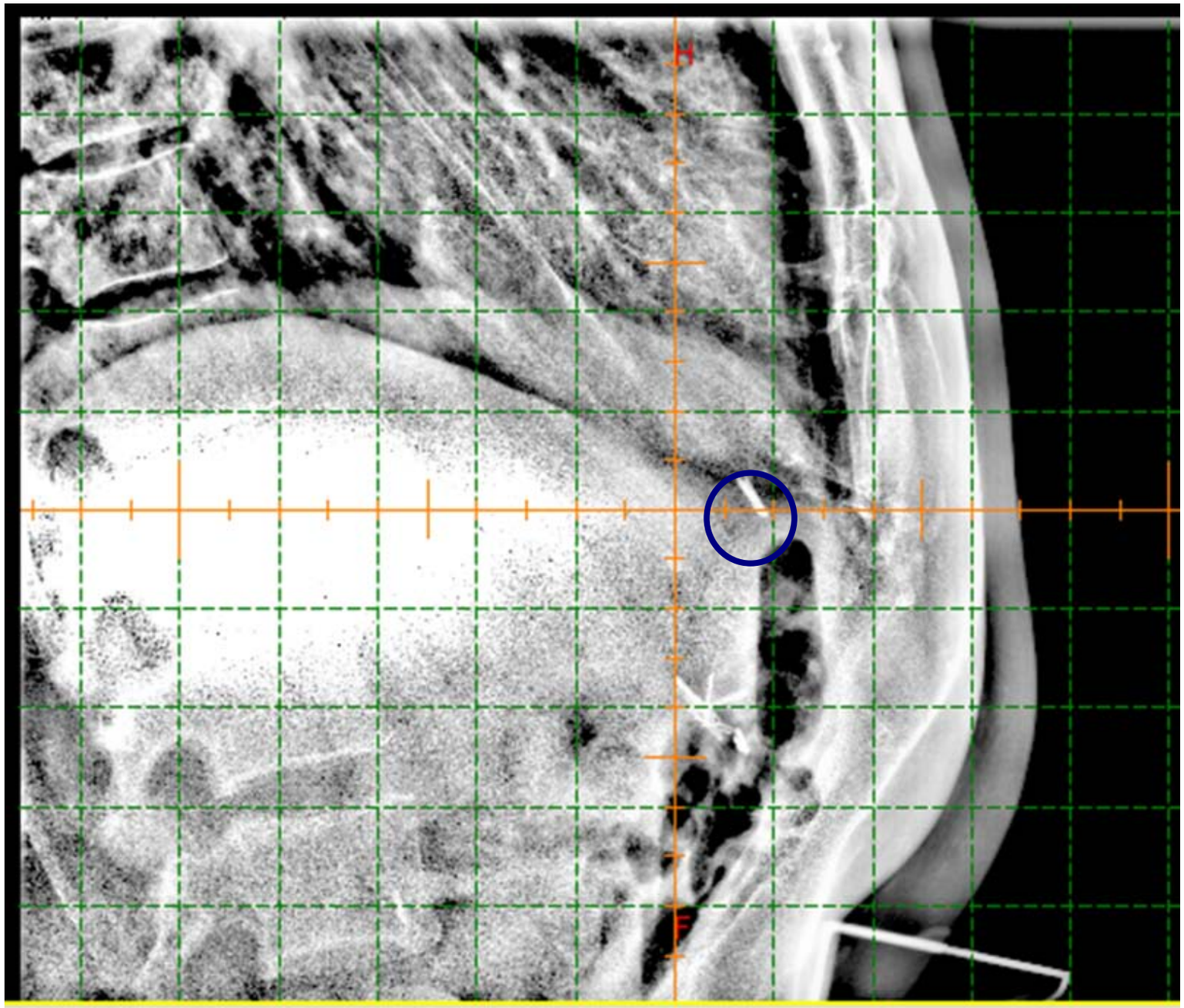
- **If >=1 markers outside TI limit treatment system can *hold (pause)* the treatment beam: beam hold (BH)**
  - If time is chosen as trigger and beam is held the system keeps shooting TI
  - If all markers return within TI limit system continues beam automatically

- **ABH can act in passive or active mode**

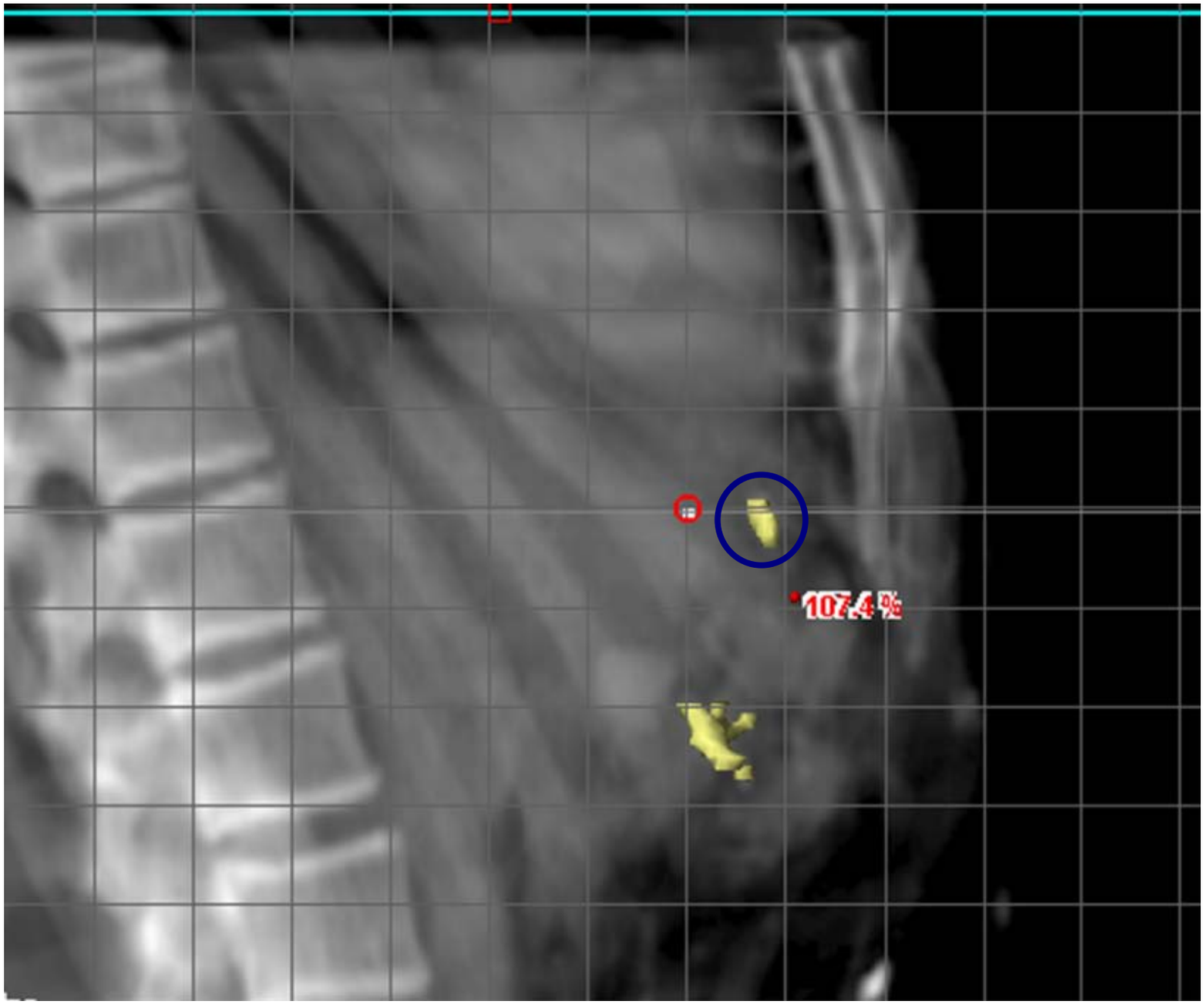




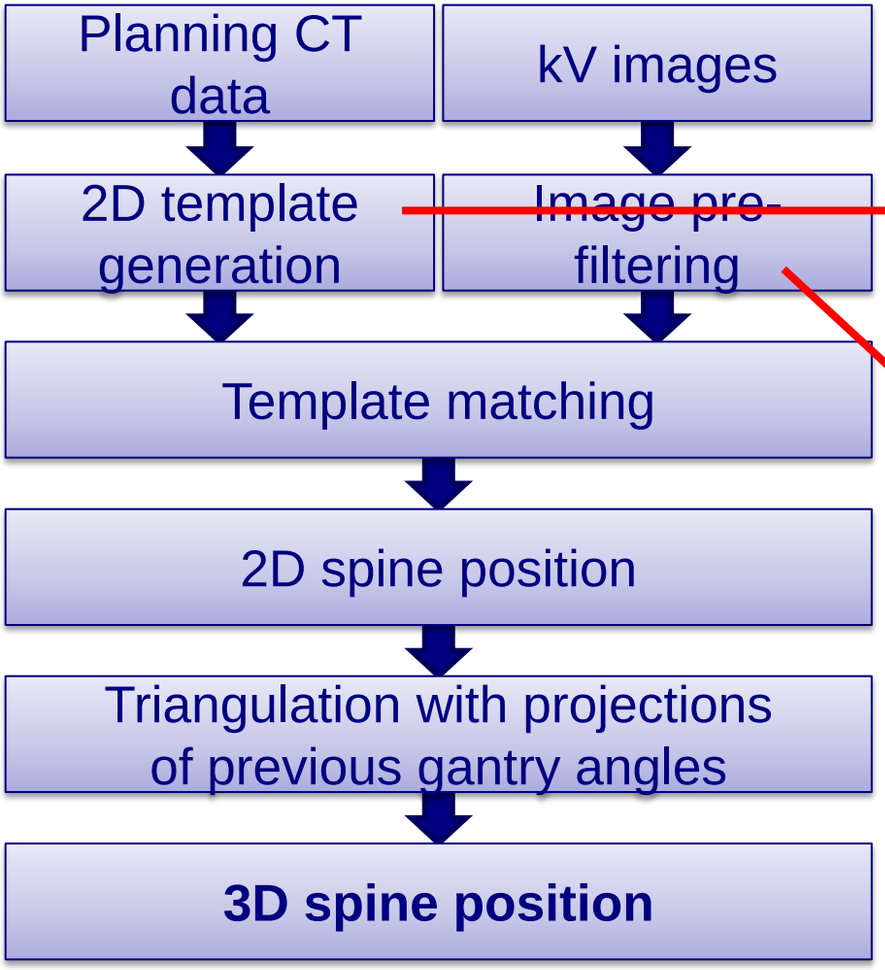
Triggered Imaging

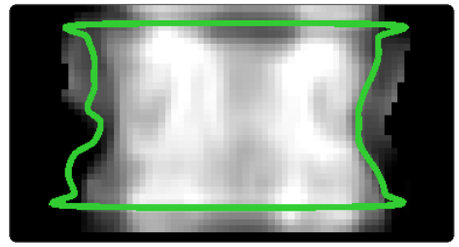


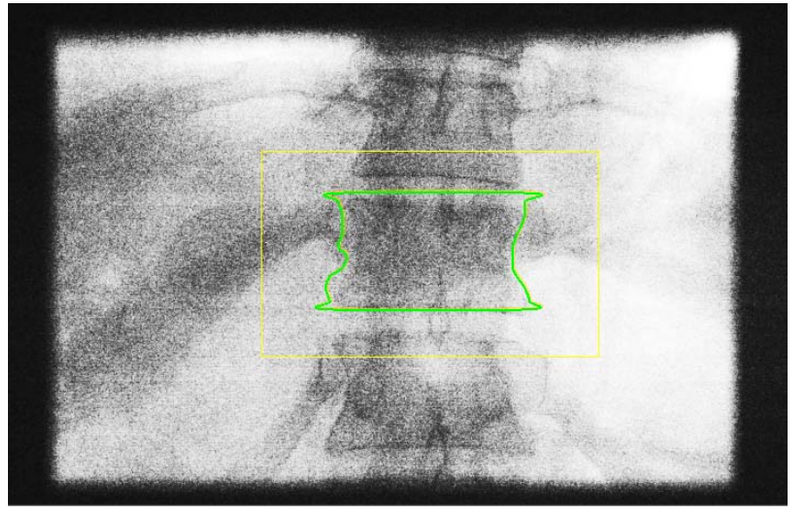
Triggered Imaging



Offline intrafraction monitoring





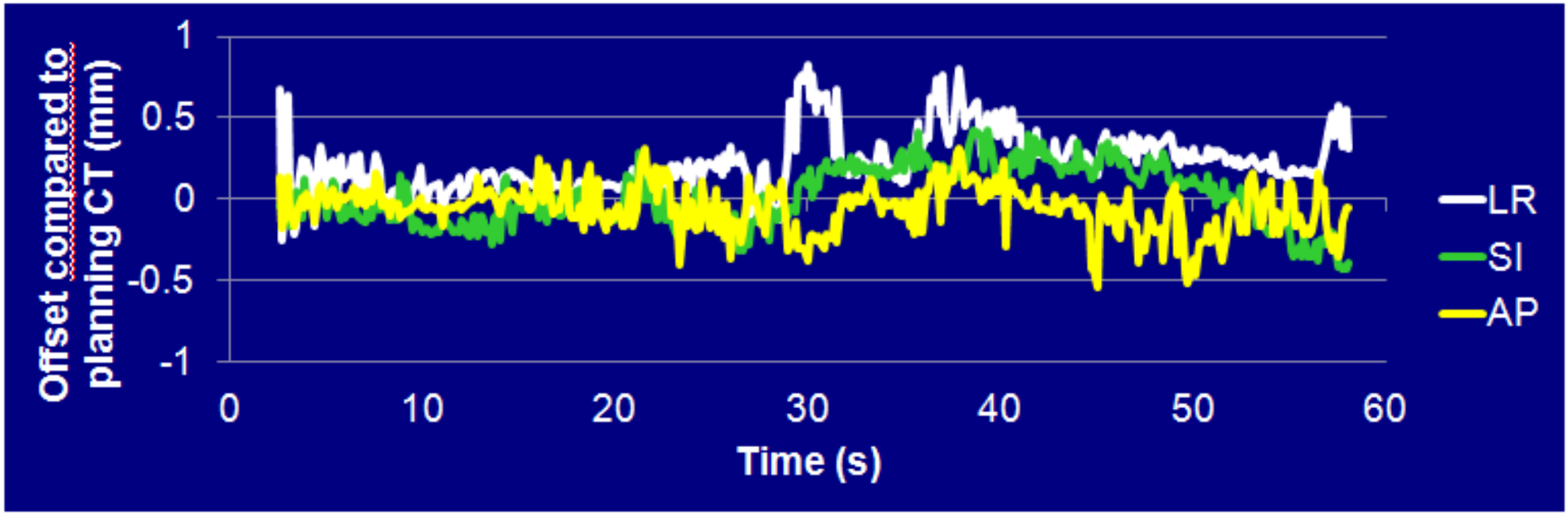


Int J Radiat Oncol Biol Phys. 2016 Apr 1;94(5):1154-62. doi: 10.1016/j.ijrobp.2016.01.006. Epub 2016 Jan 12.

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

Acknowledgments

- Max Dahele
- Femke Spoelstra
- Bianca Kraan
- Ingrid Kuijper
- Colien Hazelaar
- Tezontl Rosario
- Stereoteam

Questions?

l.vanderweide@vumc.nl

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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

Jean-Pierre Bissonnette[a)]
Task Group 179, Department of Radiation Physics, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada, M5G 2M9

Peter A. Balter and Lei Dong
Department of Radiation Physics, The University of Texas M.D. Anderson Cancer Center, Houston, Texas 77030

Katja M. Langen
Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, Florida 32806

D. Michael Lovelock
Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Moyed Miften
Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado 80045

Douglas J. Moseley
Department of Radiation Physics, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada, M5G 2M9

Jean Pouliot
Department of Radiation Oncology, UCSF Comprehensive Cancer Center, 1600 Divisadero St., Suite H 1031, San Francisco, California 94143–1708

Jan-Jakob Sonke
Department of Radiation Oncology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

Sua Yoo
Department of Radiation Oncology, Duke University, Durham, North Carolina 27710

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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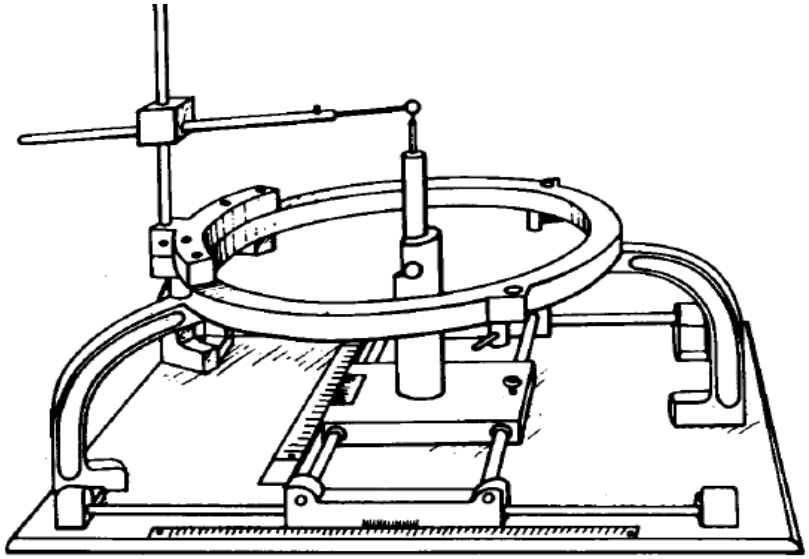
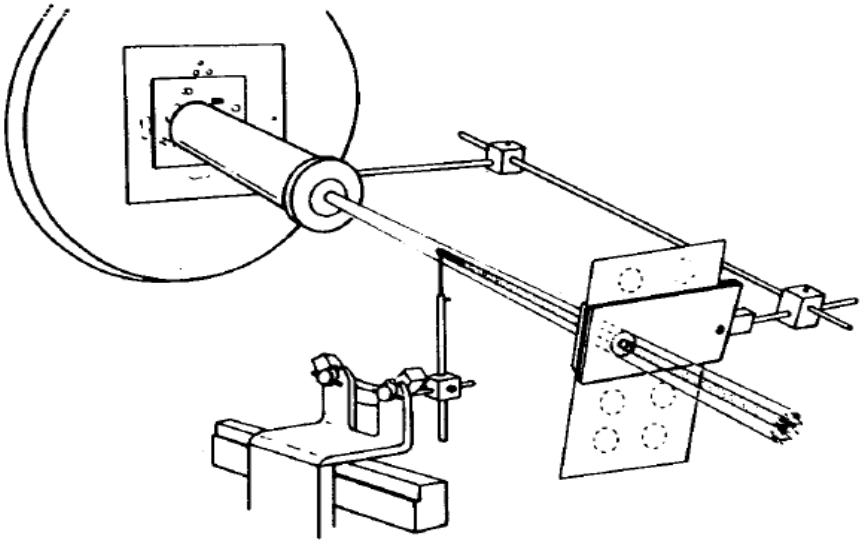
Lutz – Winston Test





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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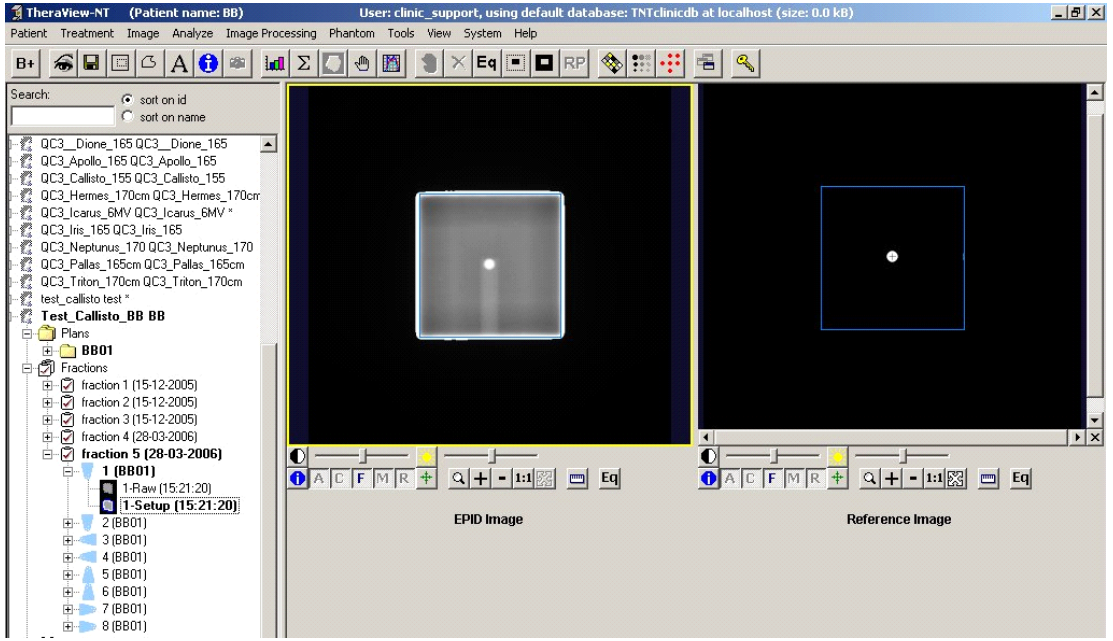
Imaging System and Radiation Isocenter Alignment

- The alignment is done as a function of gantry angle since the components may flex during gantry rotation



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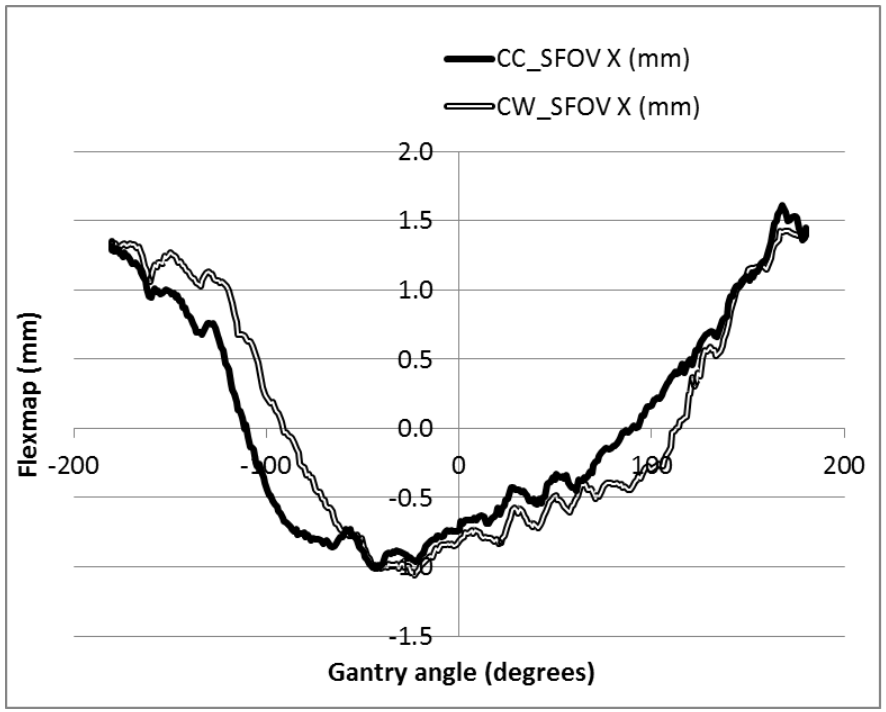
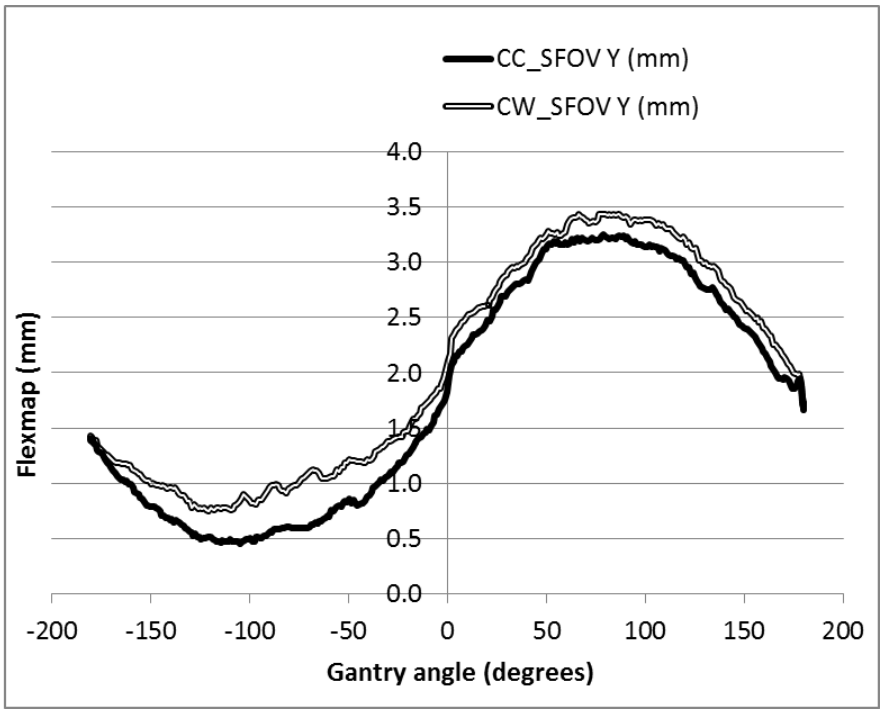
Example Flexmaps





- Varian system compensates flexes by moving the robotic arm

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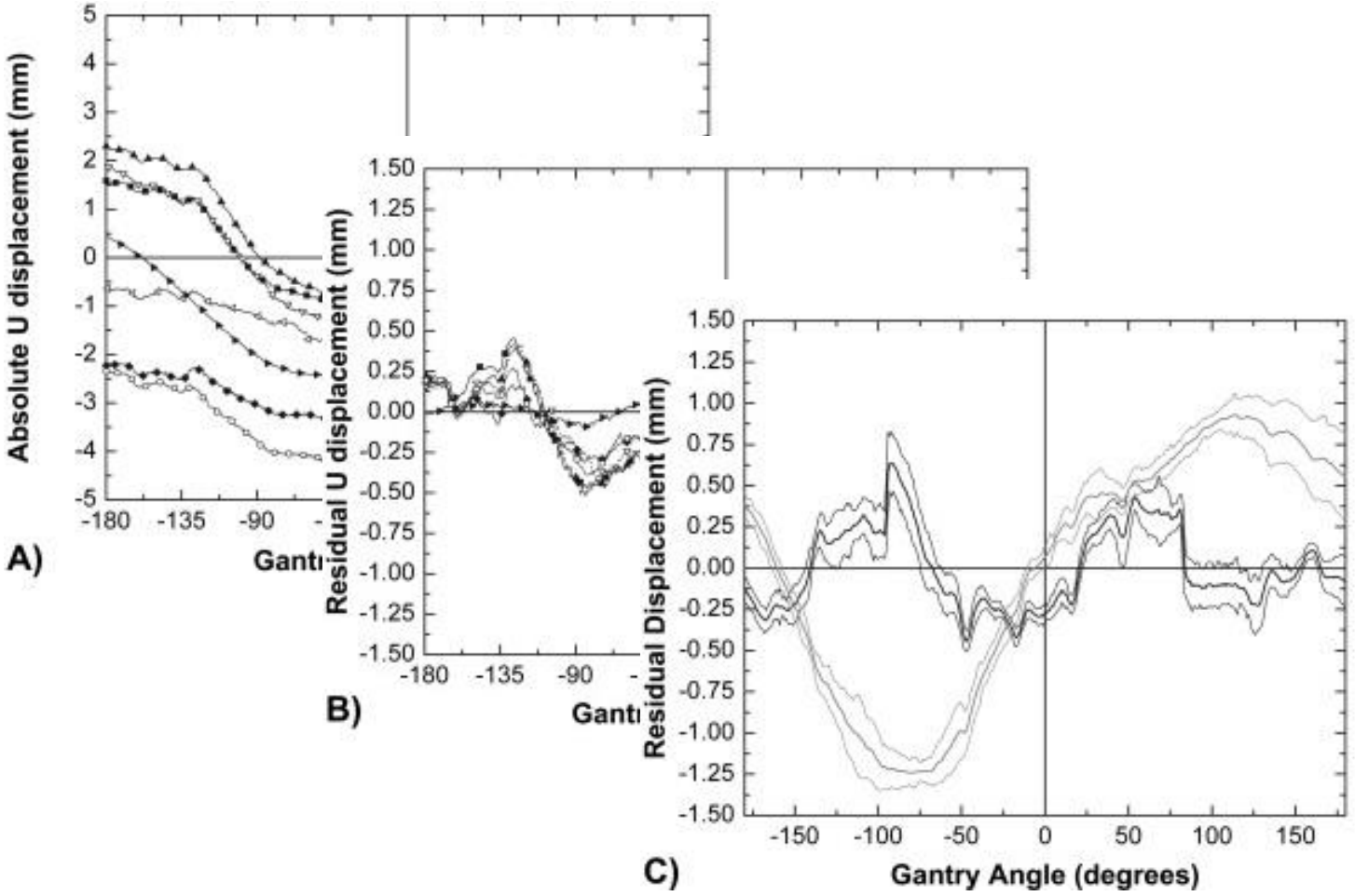
Stability of Flexmaps



[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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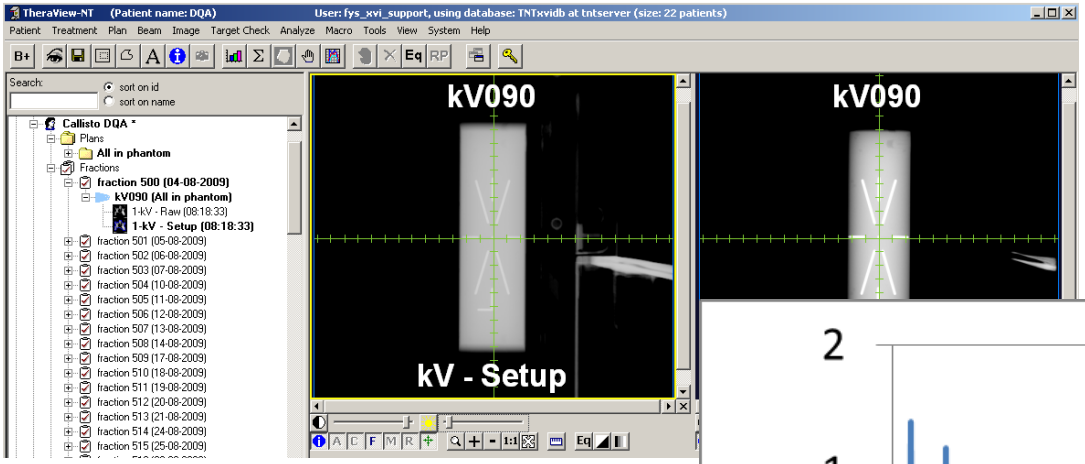
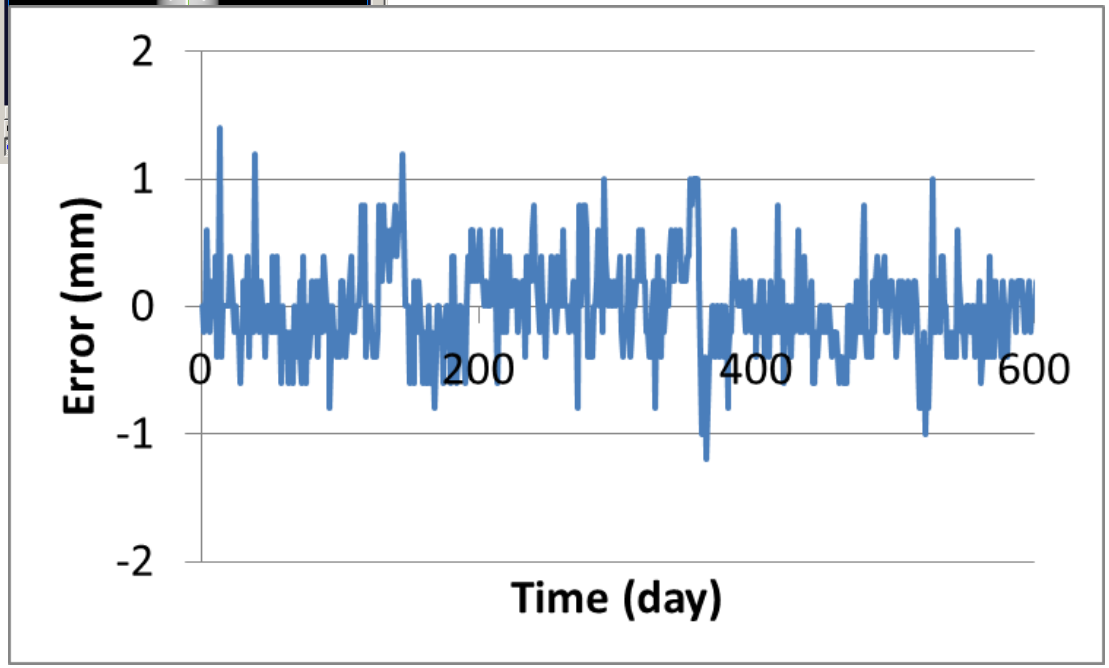
Daily QA Phantom





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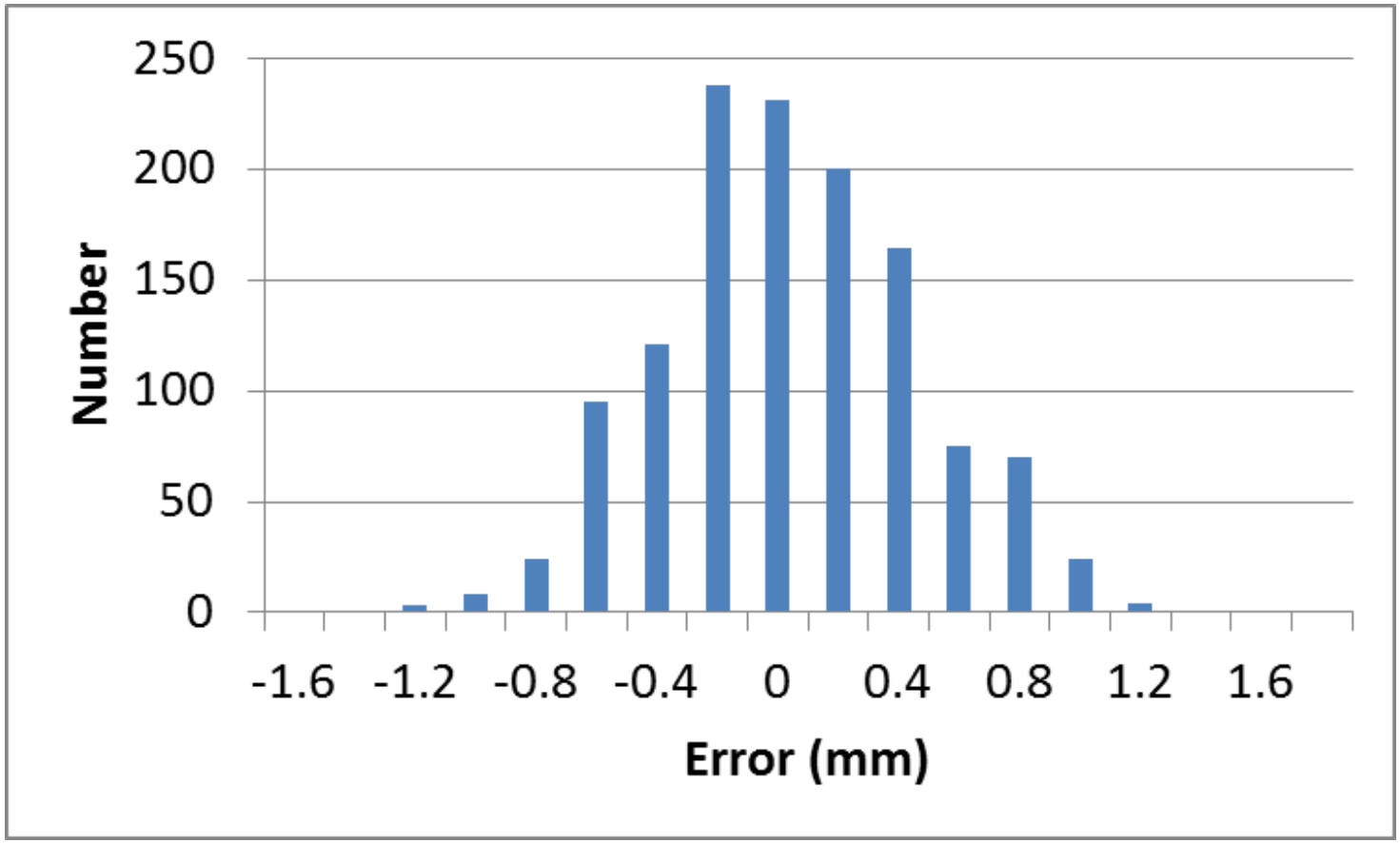
Imaging System - Radiation Isocenter Alignment Error



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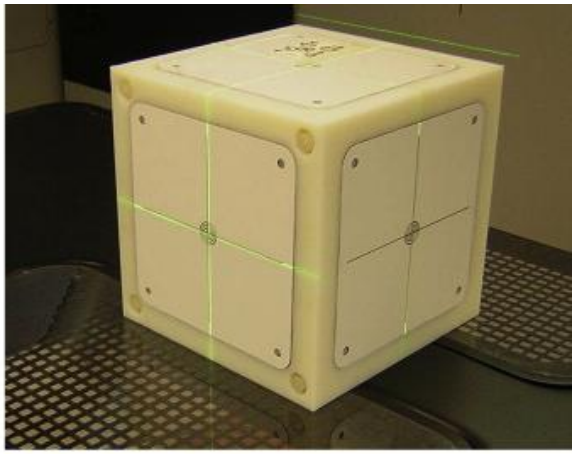
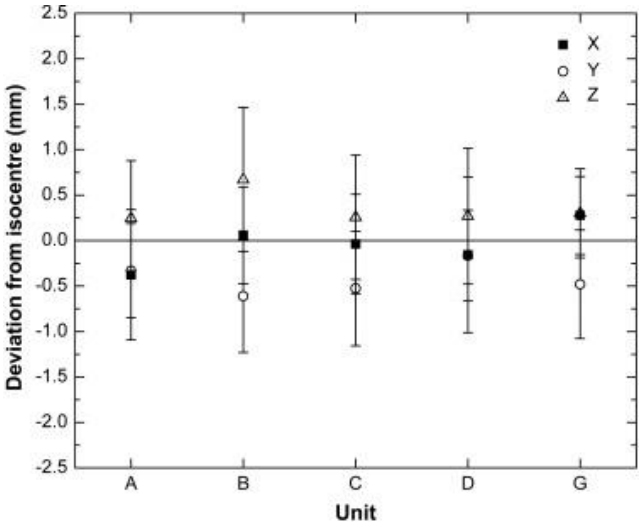
Imaging System and Radiation Isocenter Alignment





- 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 isocenter1

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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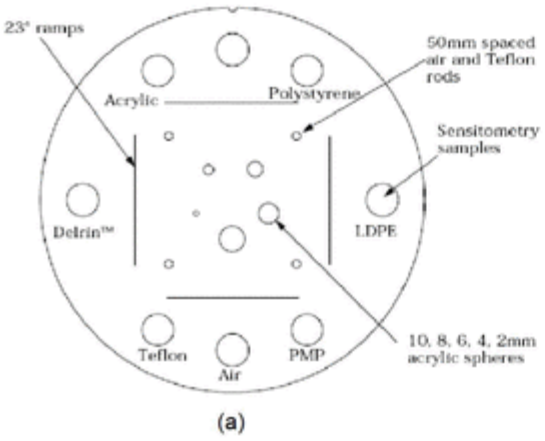
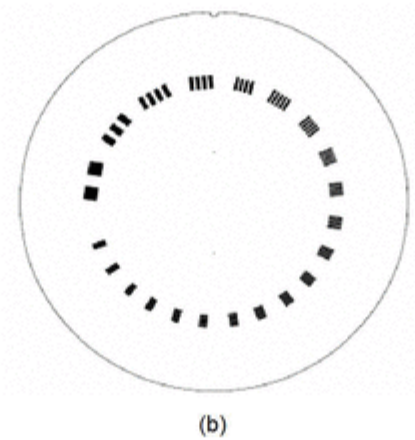
Accuracy of a Remotely Controlled Couch

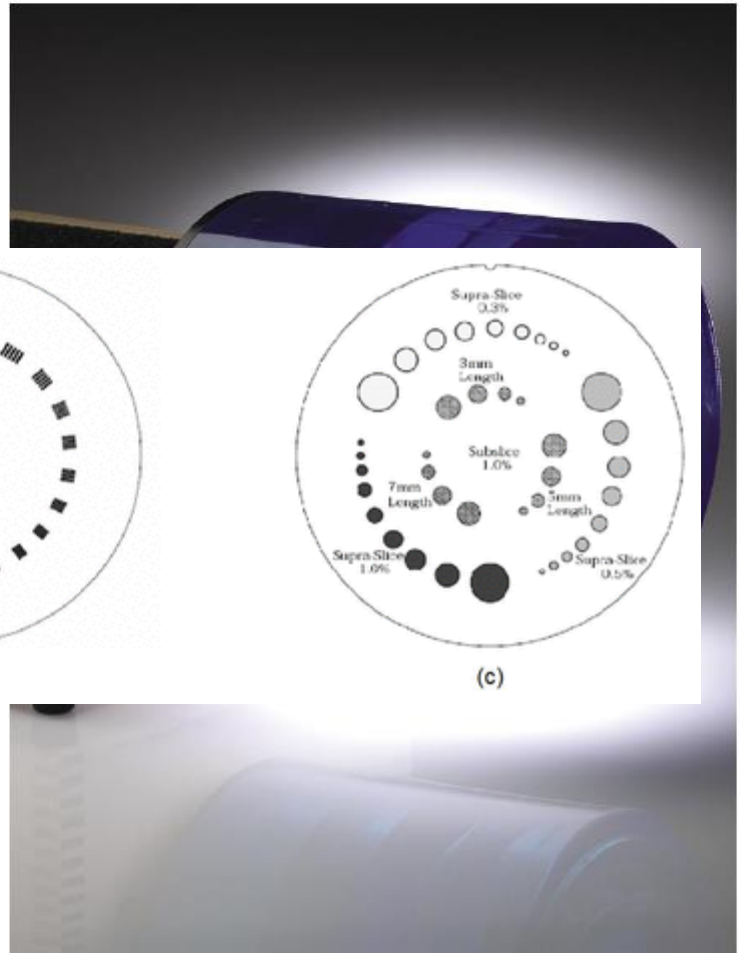
- Remotely controlled couches are available to correct translations or both translations and rotations
- Submillimeter couch position accuracy has been demonstrated (commissioning)
- For daily QA incorporate couch test in imaging system - radiation isocenter test

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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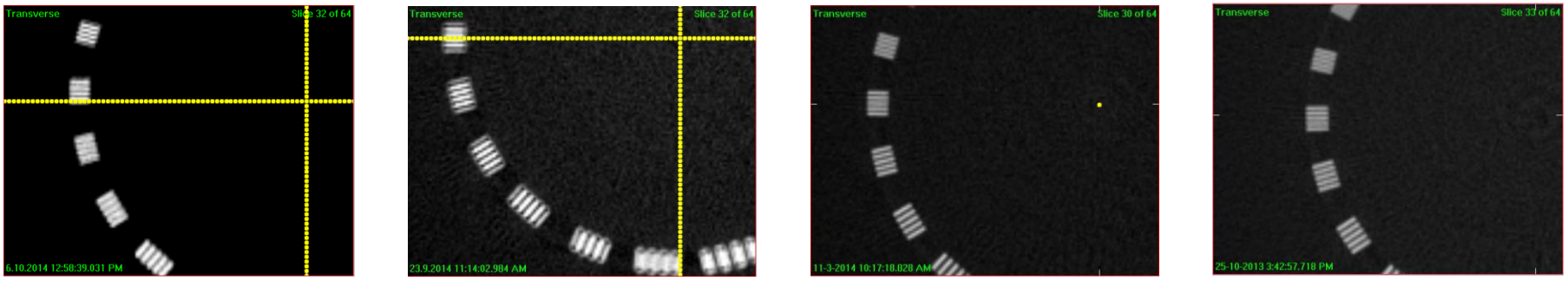
Image Quality Example



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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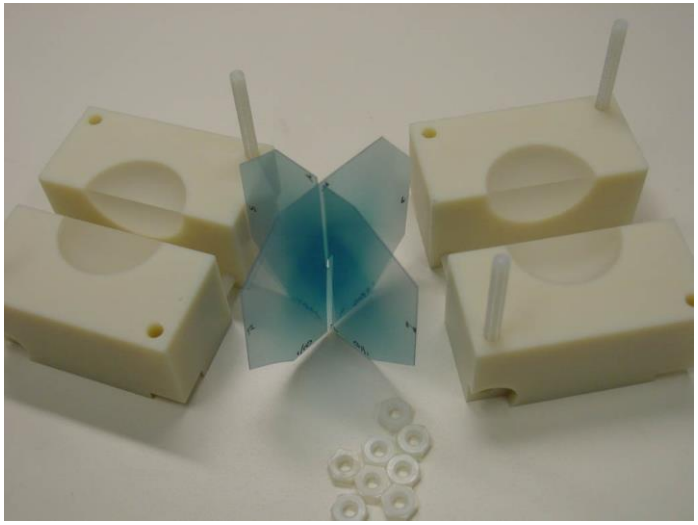
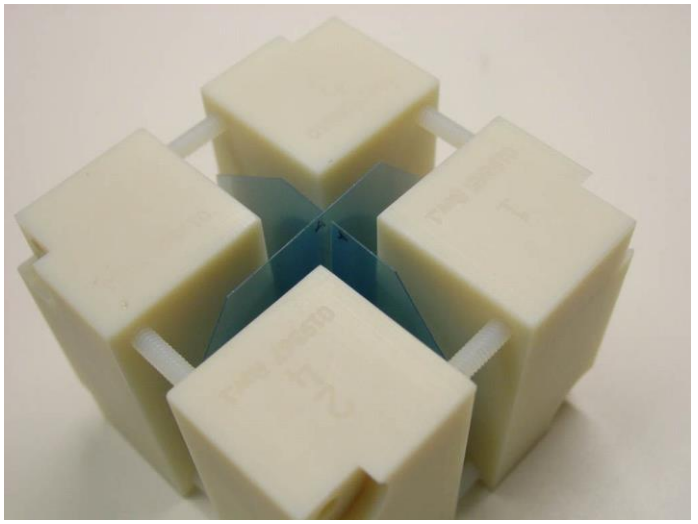
QA OF PLANAR KV SYSTEMS

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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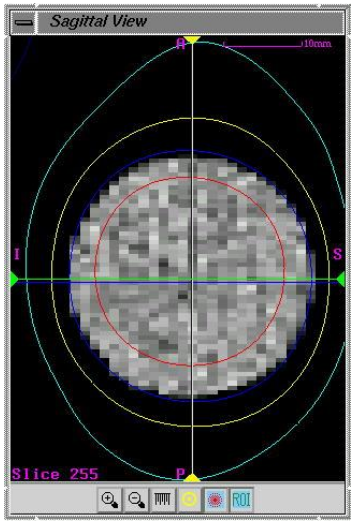
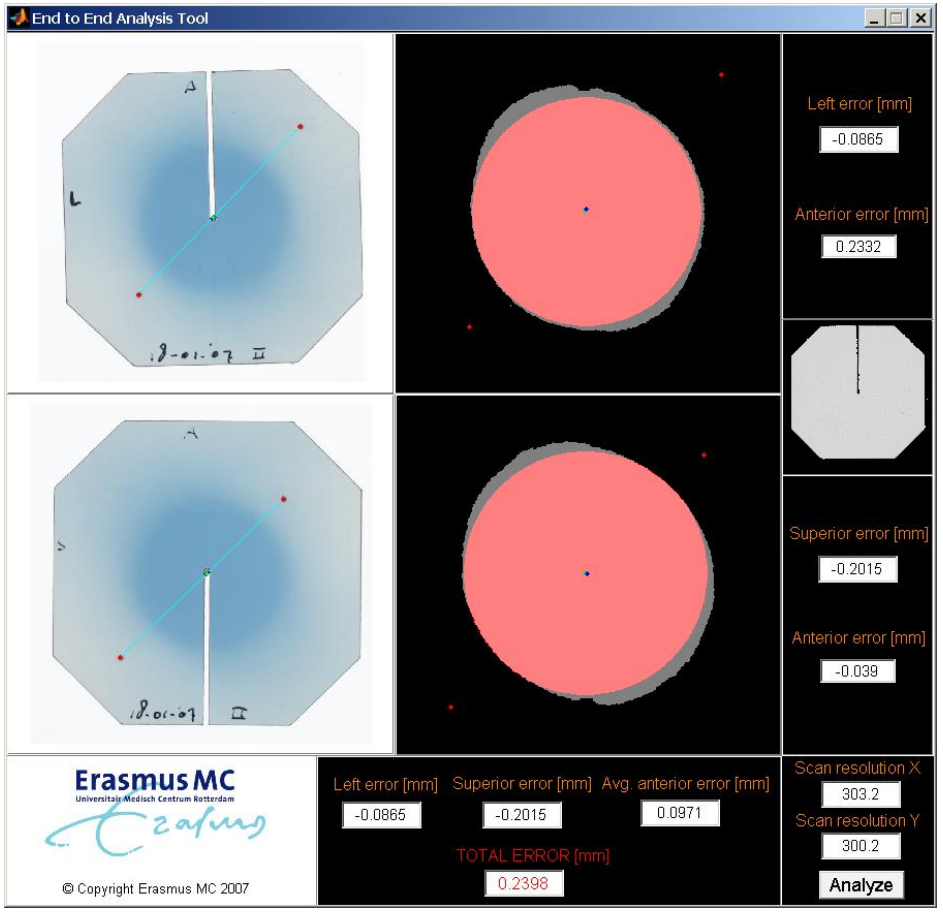
DeltaMan Analysis





Test out of imaging center

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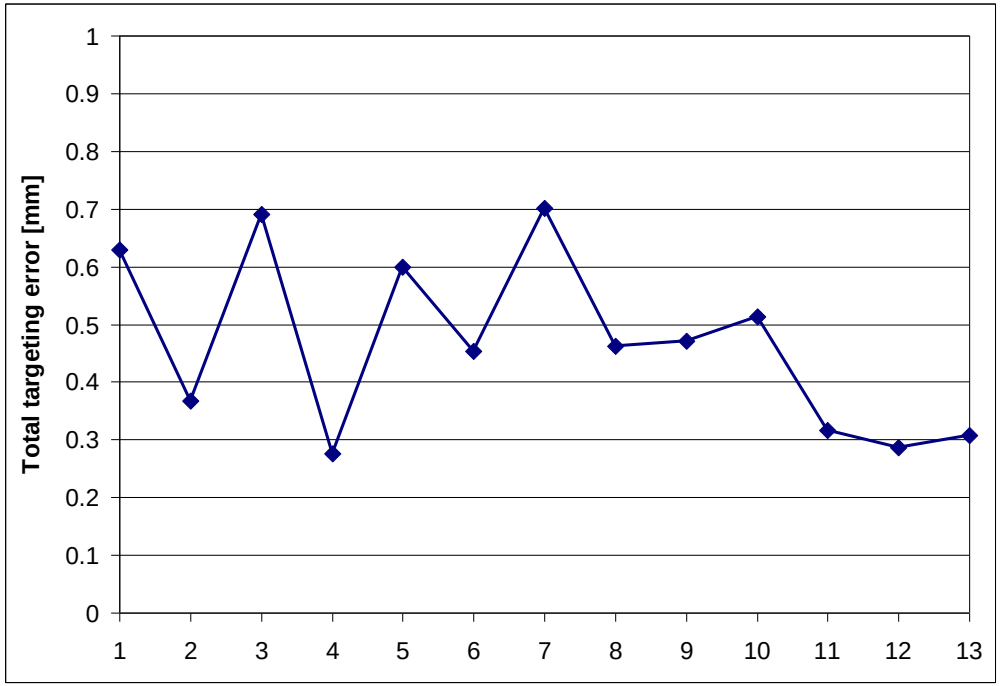
E2E Test Results

- 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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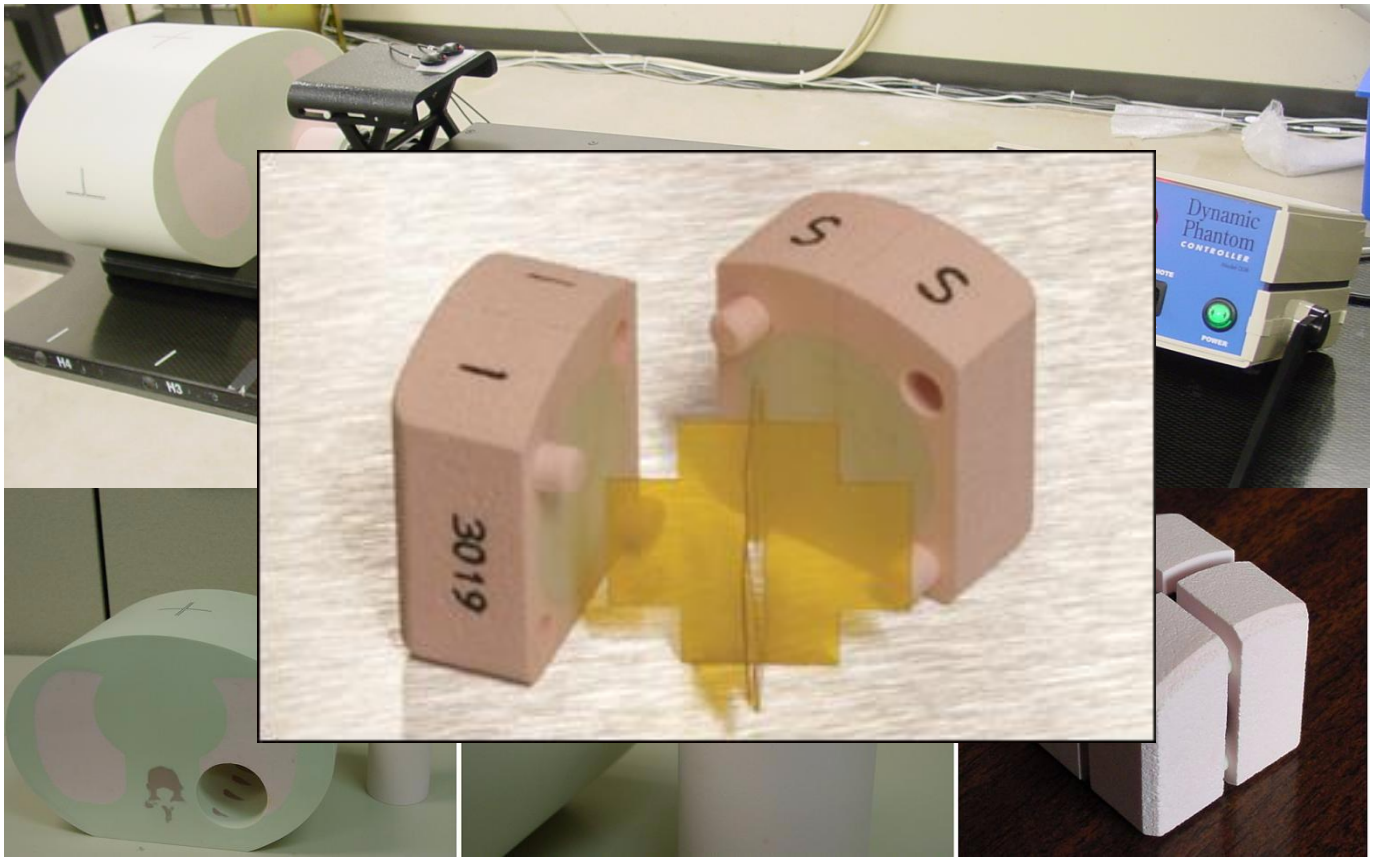
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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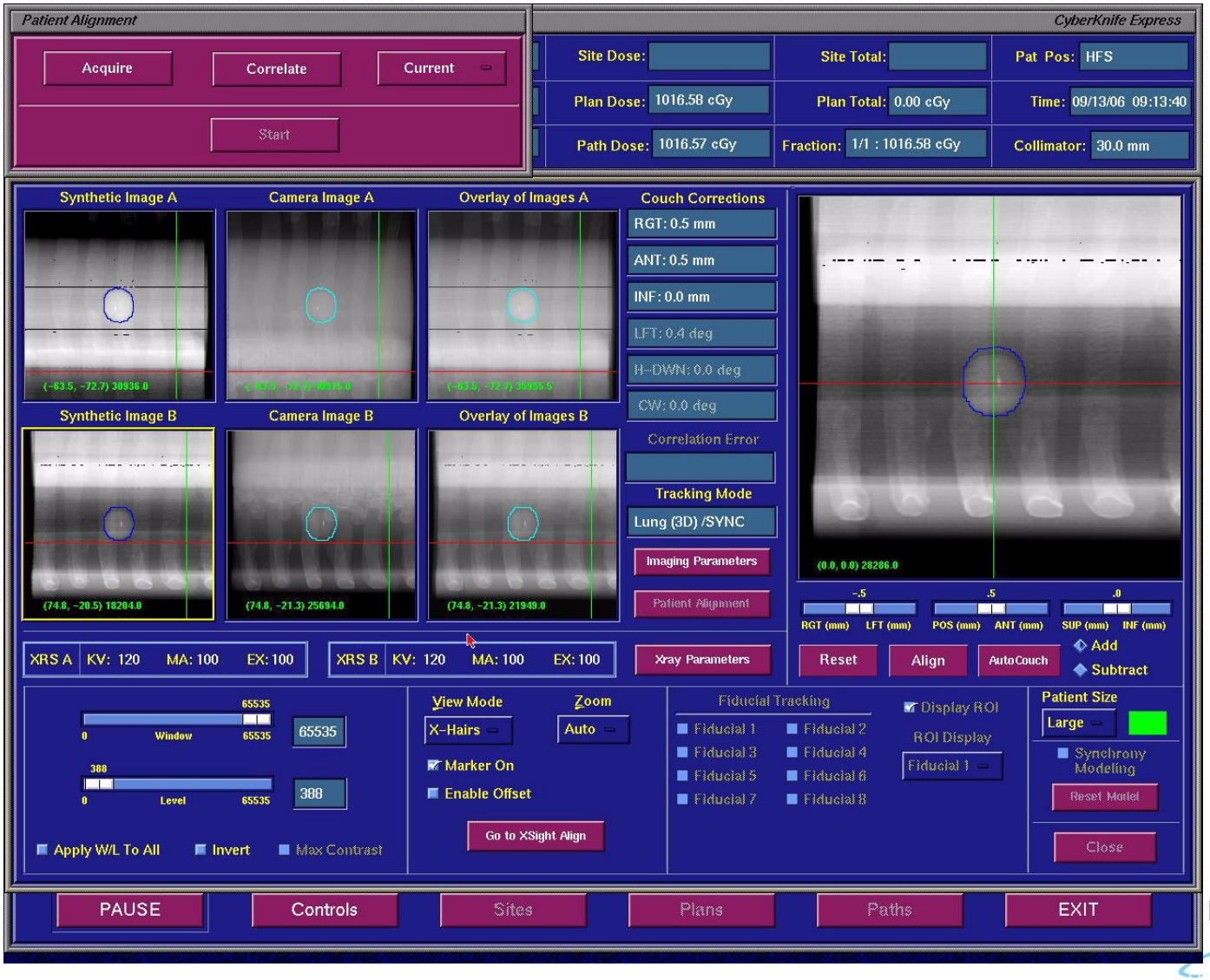
Treatment Delivery



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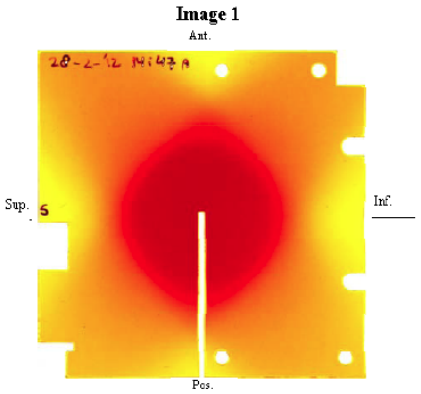
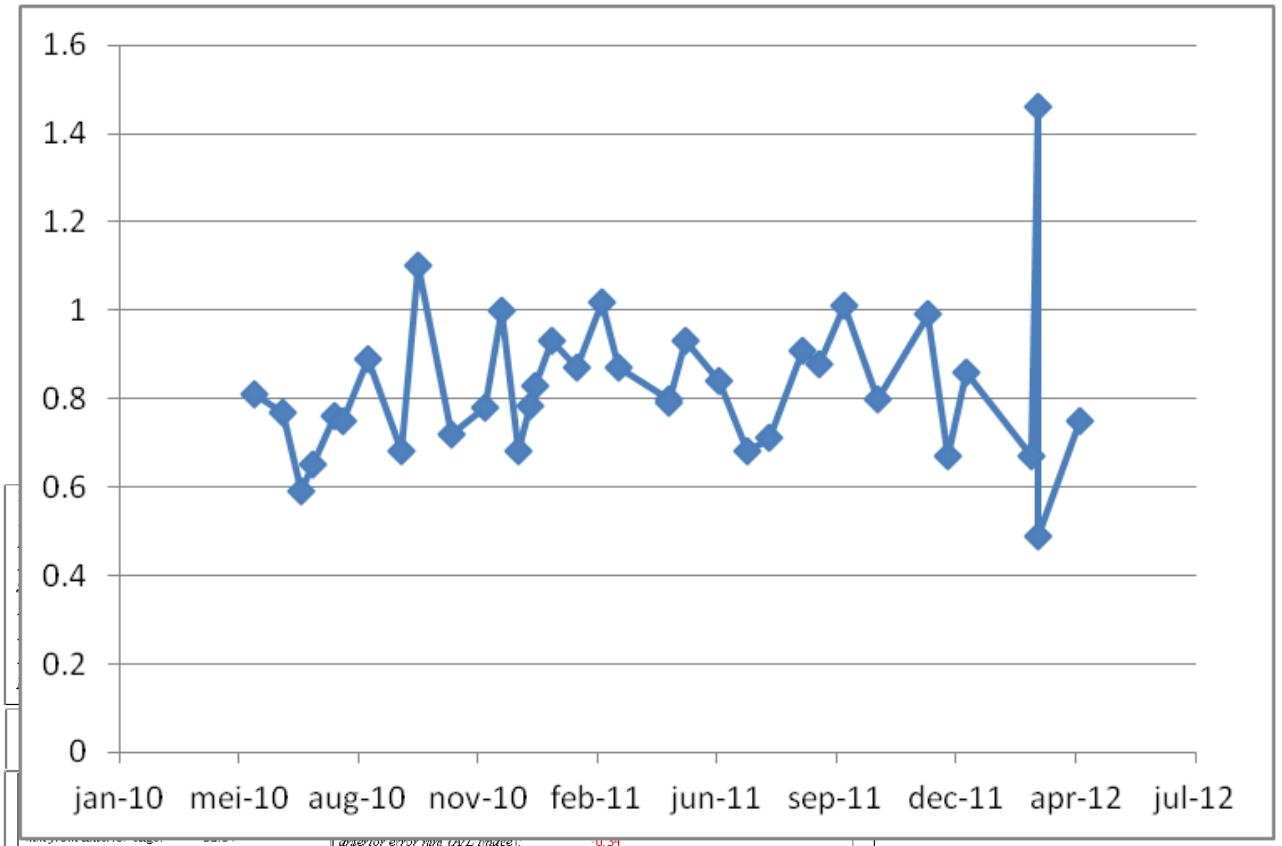
Analysis of Tracking Error





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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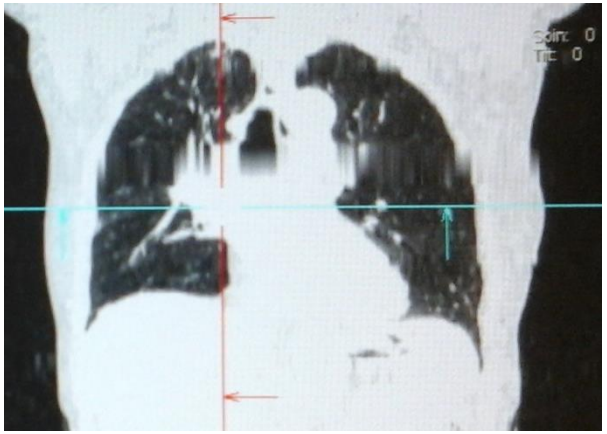
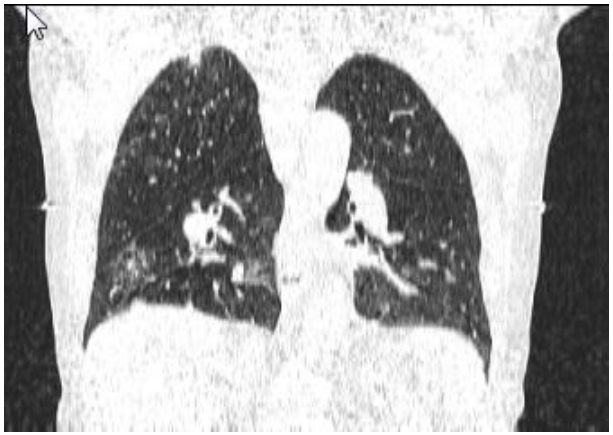
4D CT

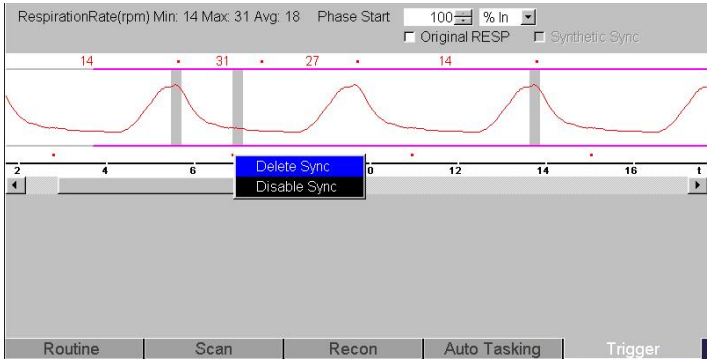
Checklist Reconstruction Improvement

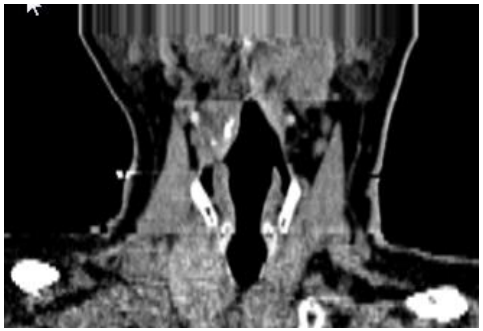
- Correct scan protocol (slow vs. normal breathing protocol)





- Correct placement of synchronization points





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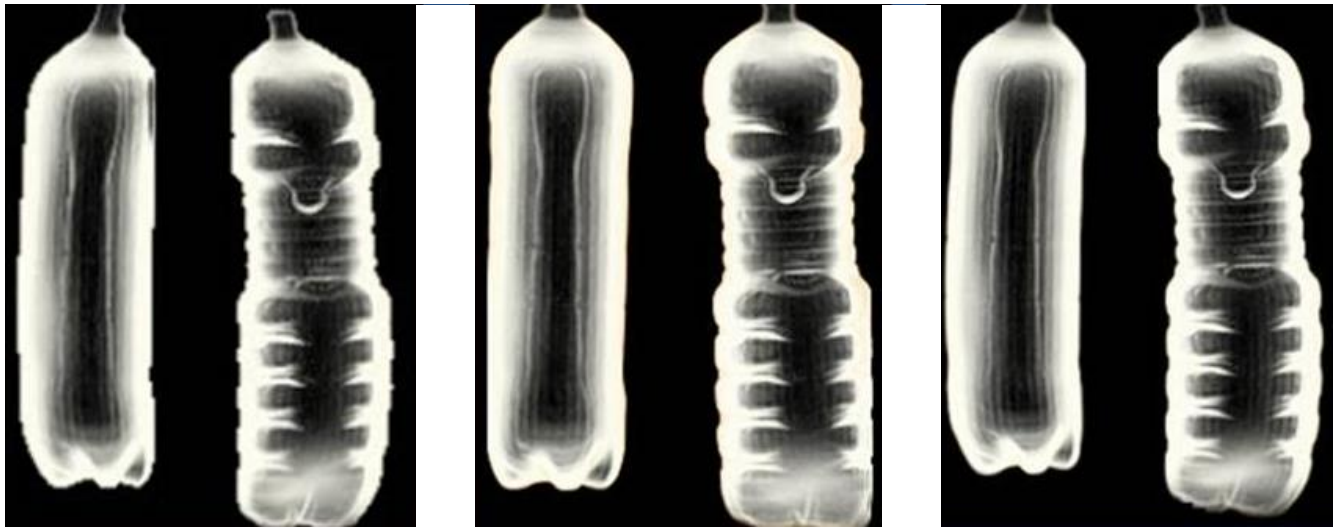
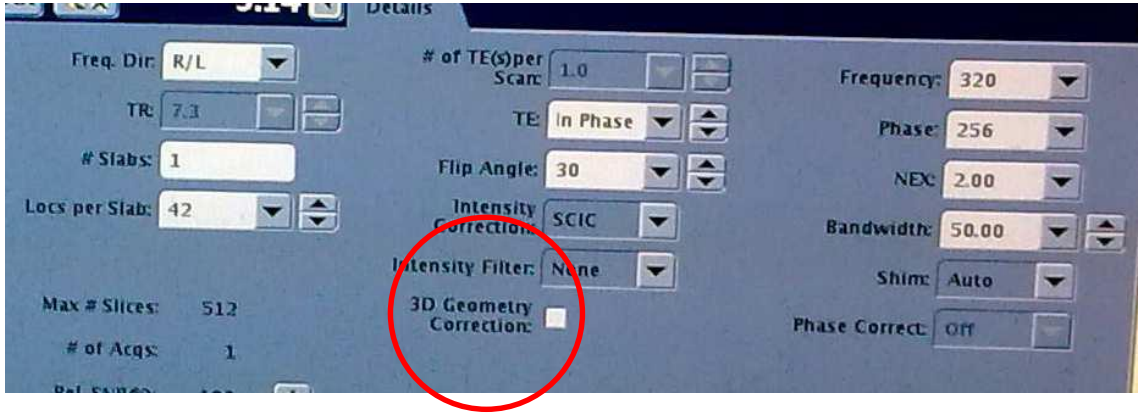
MRI

3D Geometrical Correction





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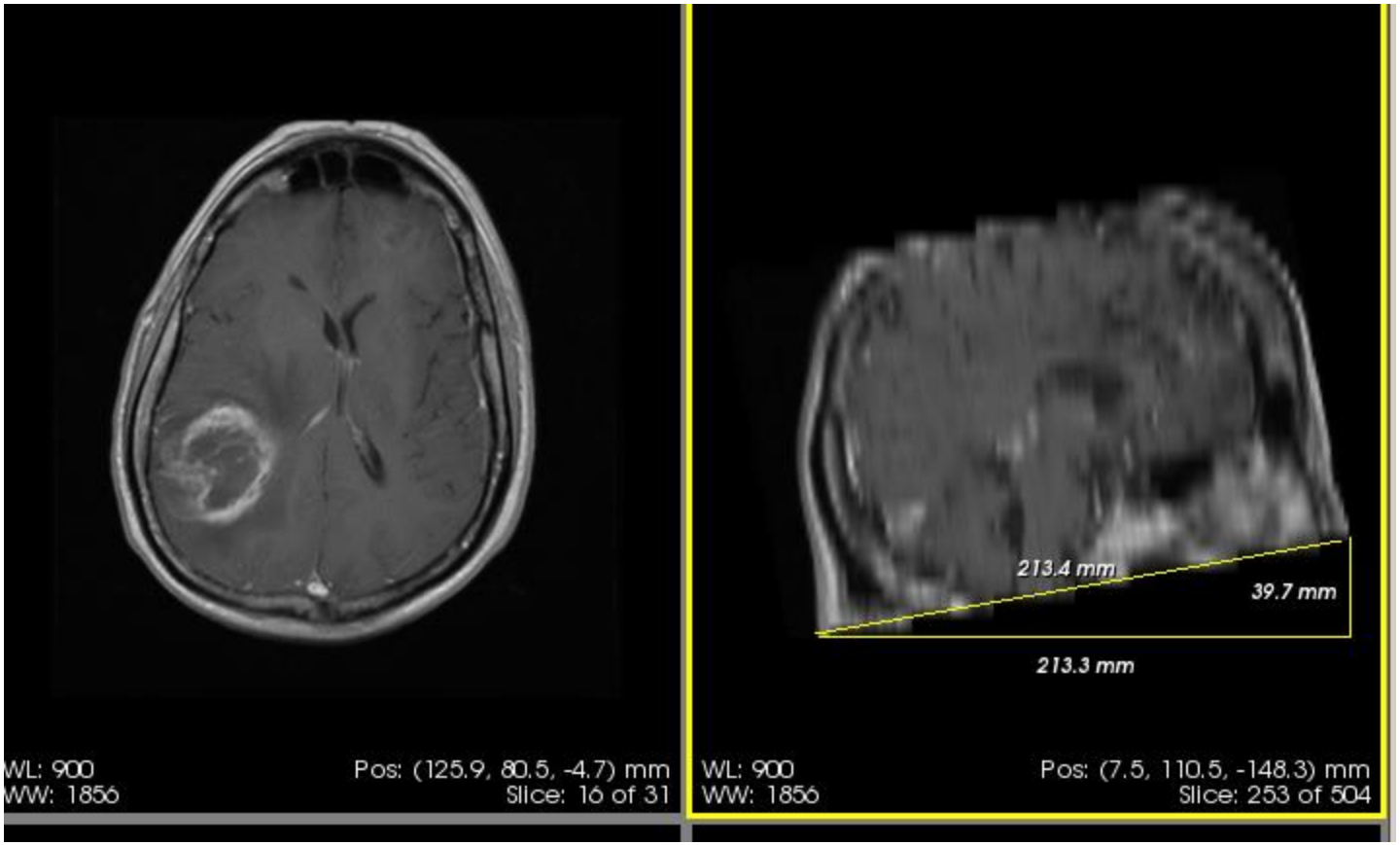
Observations

- 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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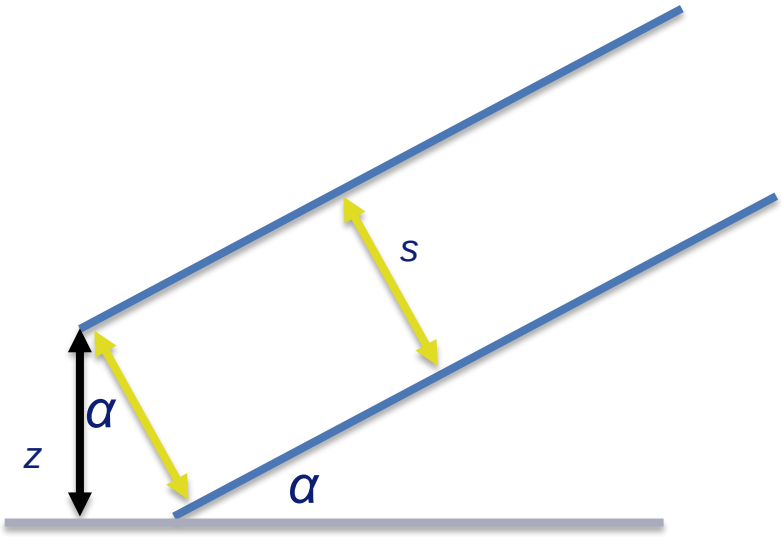
Tilted MRIs



- 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

Starting a SRT Program for Brain and Body: Clinicians perspective

- Karin Dieckmann
- Matthias Guckenberger

Motivation for SRS / SBRT

- Cli to improve outcome
- Researc
- Financial purposes
- Differentiation from other RT depa

Be honest to yourself !

Outline

- Staff
- QA
- Workflow planning

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
  - Surgeon
  - …….
- Number of **expected patients**

Low number of patients a day
More than 5-10 patients a day

To do`s: planning of program

Protocol and “business plan” generation

- Referring partners
- Equipment
- Staffing
  - Hiring
  - Education

Protocol generation

- Equipment:
  - Linac: MLC, Couch, IGRT, IMRT, VMAT
  - Cyber Knife
  - Imaging:(4D)-CT, MRI, PET
  - TPS
  - Positioning and immobilization
  - QA : CBCT, Exactrac,Linac -MRI

Team building

Team: Build a dedicated team of interested people who will start the program

- Clinician
- Physicist
- RTT

➢ **All three are required and act as a TEAM !**

Staffing-Building a SRT team
Training

- **READ THE LITERATURE**

- Training programs by manufacturer
- Longer training visit in experienced center
- National teaching courses
- ESTRO Courses
- Nat. & internat. conferences

Visit an experienced center

- Experience for several years
- Similar equipment
- Cover indications you are interested in

- ➢ Staffing
- ➢ Equipment
- ➢ Protocols
- ➢ Work-flow management
- ➢ Costs & reimbursement

Points of discussion

Staffing-Building a SRT Team

Minimum stuff requirements

- Radiographers n=3/1 main responsible
- Physicists n=2/1 main responsible
- Medical doctors n=2/1 main responsible

Based on the Number of expected Patients you have to decide:

One / two patients per day

Much more than one patient per day

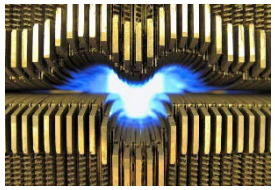
Good logistic

- LINAC
- Tomotherapy

Stereotactic Unit

- Dedicated LINAC
- CyberKnife
- GammaKnife

Equipment demands



Linac

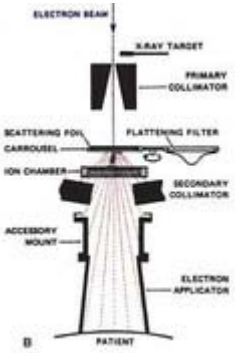
≤ 5 mm leafs
circular collimators

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

[Bodyframe: for smaller individuums]

Respiration management

Deep inspiration
Tracking
Abd. compression
Full 4 D planning

Fully optimized 4D planning and IGRT work-flow

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,.....)

Guidelines for safe practice of stereotactic body (ablative) radiation therapy

Matthew Foote,[1] Michael Bailey,[2] Leigh Smith,[3] Shankar Siva,[4] Fiona Hegi-Johnson,[5] Anna Seeley,[3] Tamara Barry,[1] Jeremy Booth,[6,7] David Ball[4,8] and David Thwaites[7]

Journal of Medical Imaging and Radiation Oncology **59** (2015) 646–653

Stereotactic body radiotherapy for liver tumors

Principles and practical guidelines of the DEGRO Working Group on Stereotactic Radiotherapy

Strahlenther Onkol 2014 · 190:872–881

Spanish Society of Radiation Oncology clinical guidelines for stereotactic body radiation therapy in lymph node oligometastases

Clin Transl Oncol (2016) 18:342–351

Practical Considerations Arising from the Implementation of Lung Stereotactic Body Radiation Therapy (SBRT) at a Comprehensive Cancer Center

J Thorac Oncol. 2008;3: 1332–1341

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.

Reimbursement

Reimbursement of planning and delivery for **in-** or **out-**patient

<u>Discussion with</u>

- medical centre administration
- Insurances
- Health Care Organisations

Thank you for your attention and Good Luck for you and your patients

Starting your SBRT program: RTT perspective

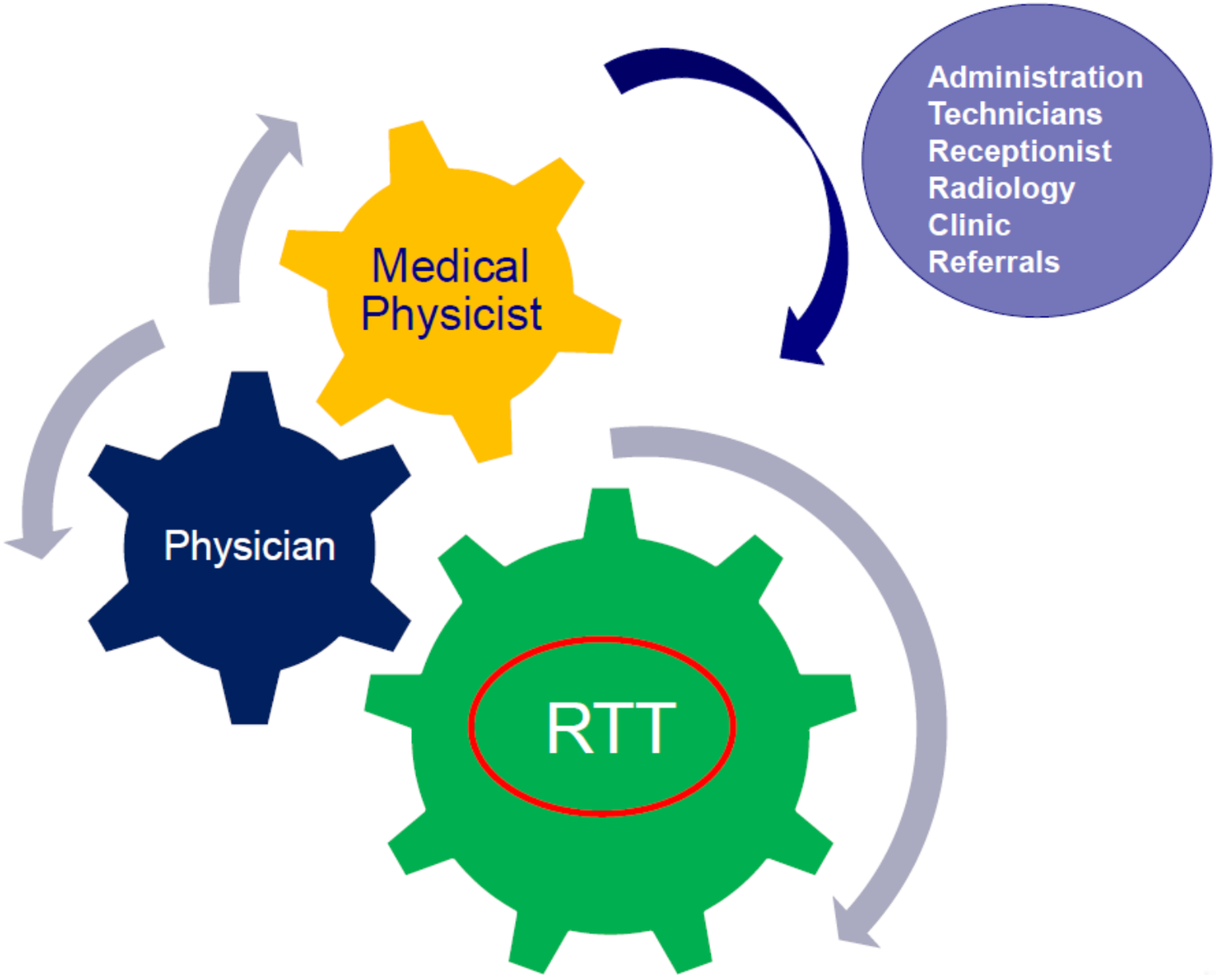
Lineke Berkelaar- van der Weide (MSc)
RTT research
VU University Medical Center
l.vanderweide@vumc.nl


Treatment

A clinician in our department said:

Be aware of the responsibility you have as RTT. In surgery, the surgeon plan to treat the patient and is doing it by him/herself, but in radiotherapy the clinician plan to treat a patient, but the RTT is doing the job on the linac.

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 tumorsides 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
- Common remarks

RTTs role

- Immobilisation
- (4D)CT
- Planning
- Treatment:
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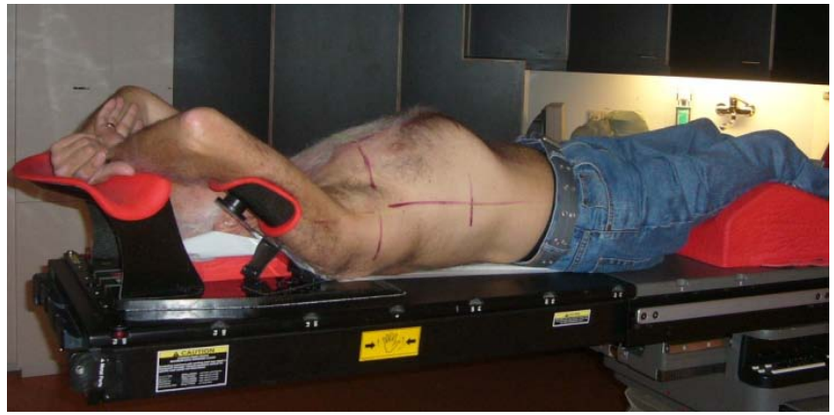
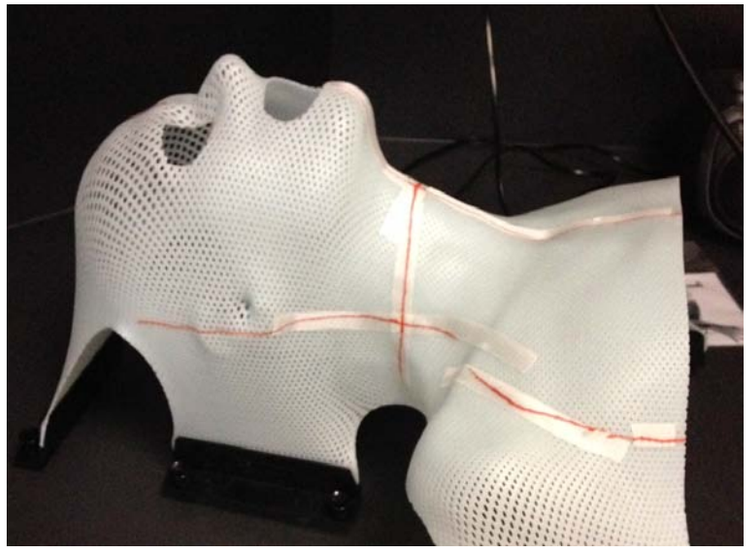
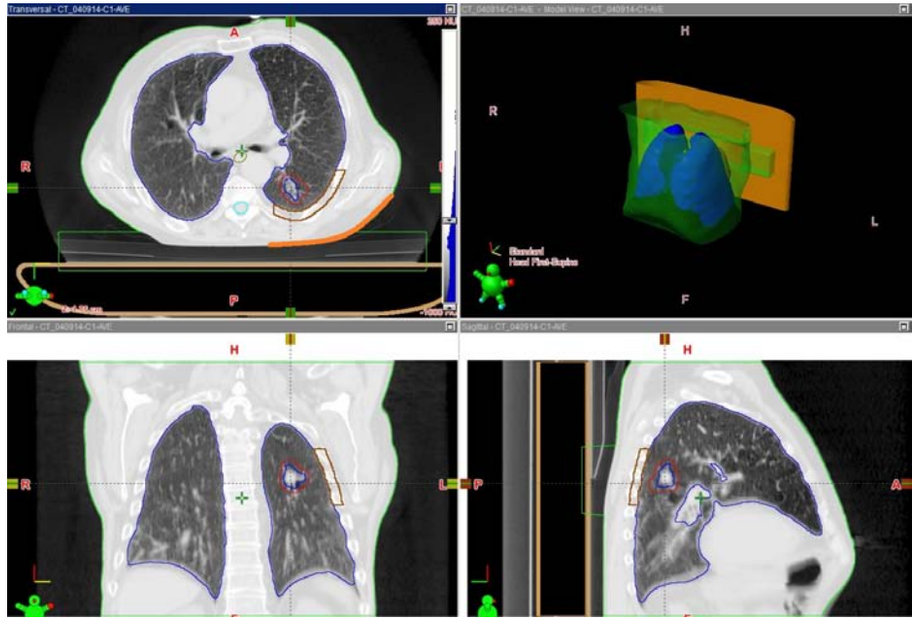




RTTs role

- Immobilisation
- (4D)CT
- Planning
- Treatment:
  - Patient positioning
  - IGRT-protocols
  - Intrafraction monitoring
- Common remarks



RTTs role

- Immobilisation
- (4D)CT
- Planning
- Treatment:
  - Patiënt positioning
  - IGRT-protocols
  - Motion management
  - Intrafraction monitoring
- Common remarks

Who is essential on the linac by starting up a new tumorside?

- RTT alone
- RTT and physicists
- RTT and clinician
- RTT, physicists and clinician

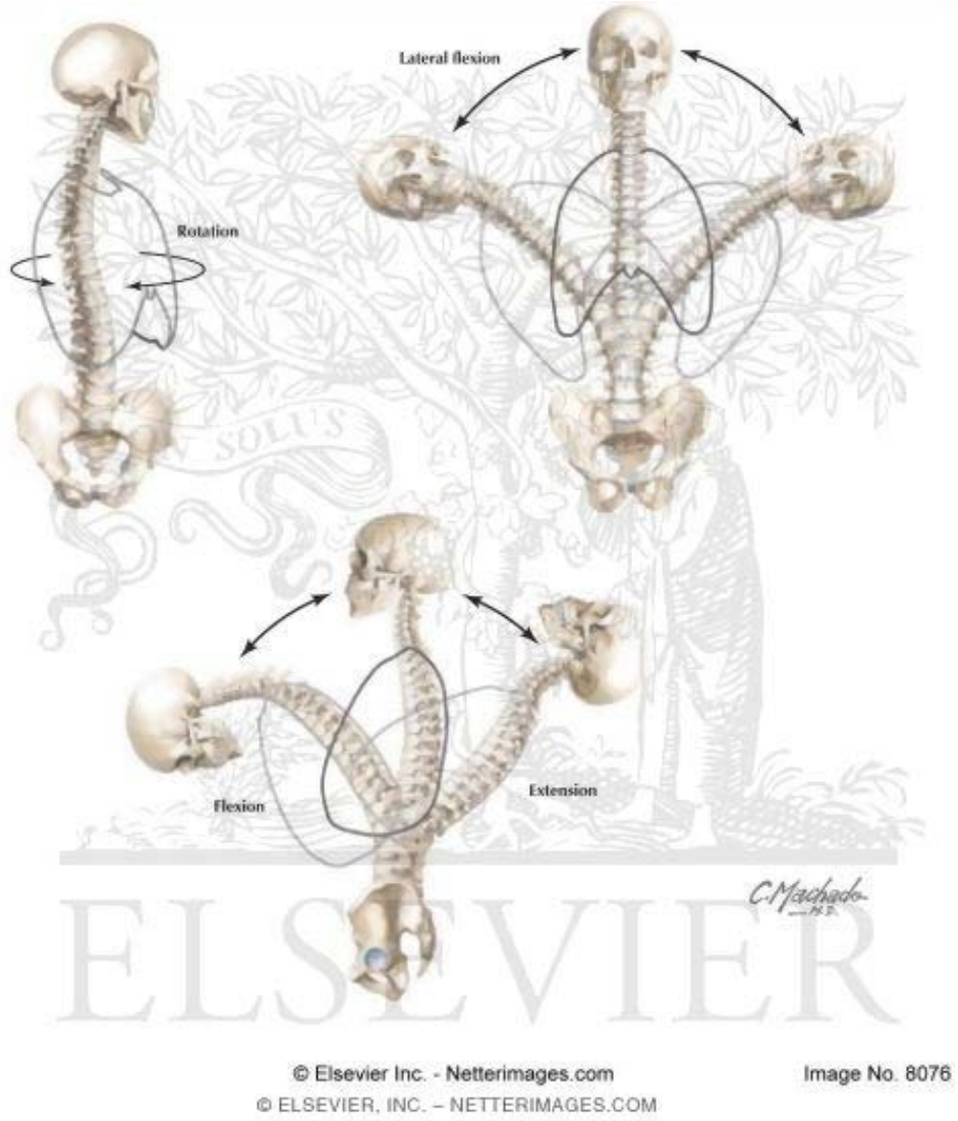
Who is essential on the linac when you have experience with the SBRT treatment?

- RTT alone
- RTT and physicists
- RTT and clinician
- RTT, physicists and clinician

Treatment

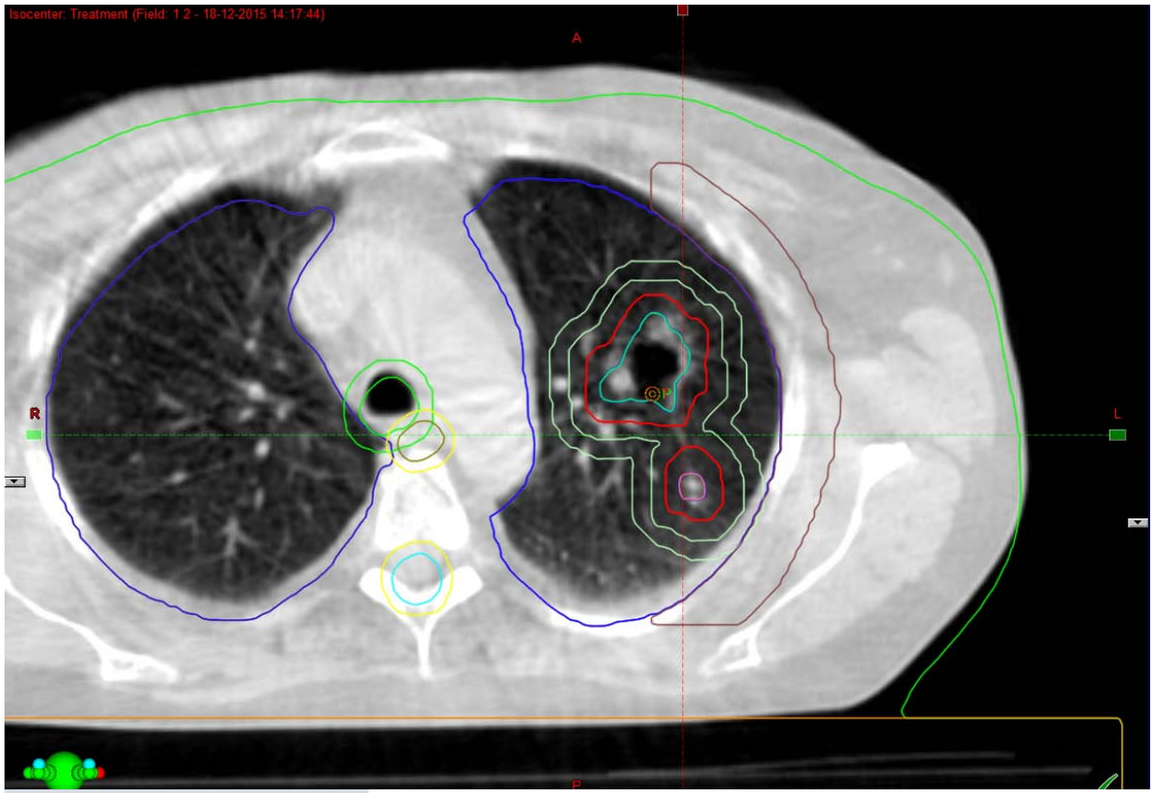
- Positioning
- IGRT
  - CBCT
  - 6D-couch
  - CBCT halfway treatment
  - CBCT post-treatment

  - Offline check of the CBCT



Use of 6D-couch

55-yr old patient
Multiple lesions left lung
2 lesions in 1 PTV
8 x 7,5 Gy



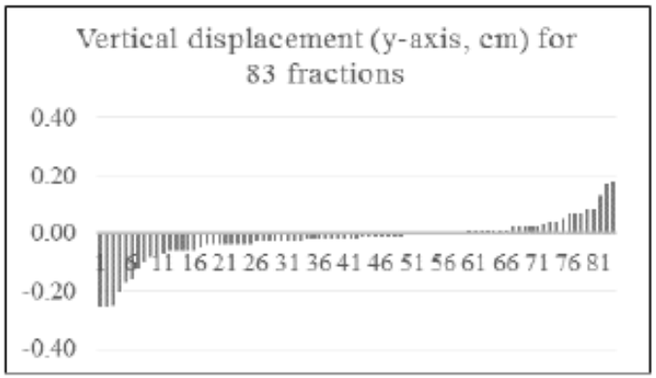
	kV_CBCT_3a
Status	✓
Vrt [cm]	-0,49
Lng [cm]	+0,76
Lat [cm]	+0,53
Pitch [°]	0,0
Roll [°]	-0,8
Rtn [°]	0,0

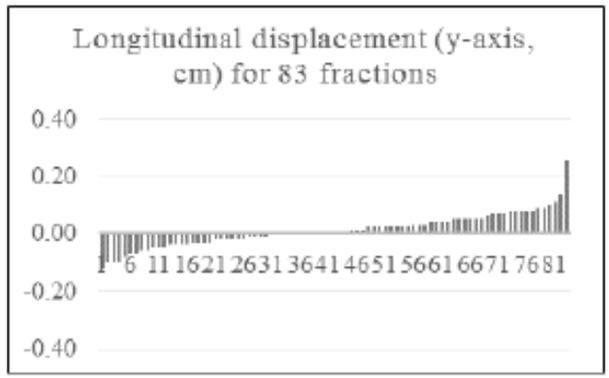
Treatment

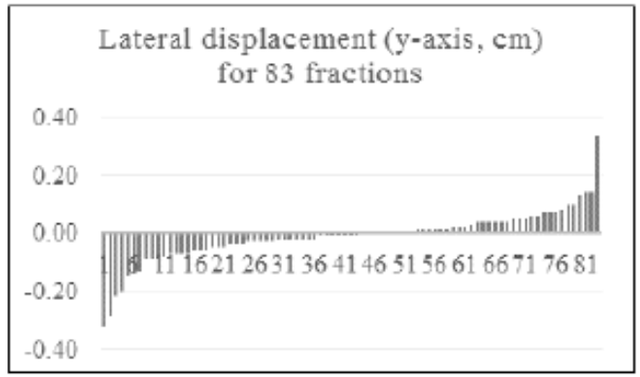
- Positioning
- IGRT
  - CBCT
  - 6D-couch
  - CBCT halfway treatment
  - CBCT post-treatment

Spine and bony pelvis: 6Dcouch, FFF
(83 fractions; Dahele et al in press Acta Oncologica)

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 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.

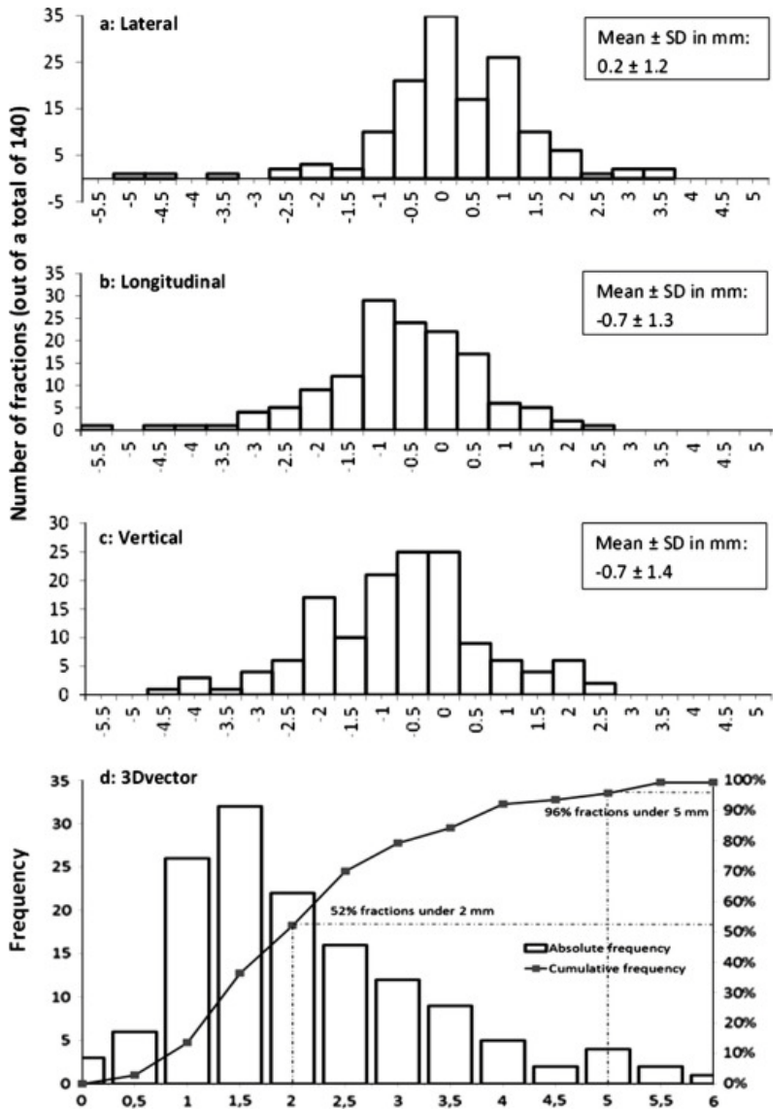
Post-treatment CBCT, SBRT lung

- 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 (1)

A strategy for motion management is essential in SBRT for anatomical indications effected by breathing motion (e.g. lung, liver, adrenal gland, lymph node)

- Dependant on departmental availability of kit
- Role in coaching / training patient
- Additional considerations when these techniques are used e.g. longer on treatment couch

Intrafraction monitoring

- RPM system
- Exac Trac
- Auto Beam Hold withTriggered Imaging
- Continuous acquired kV-images during treatment (3fps-15fps)

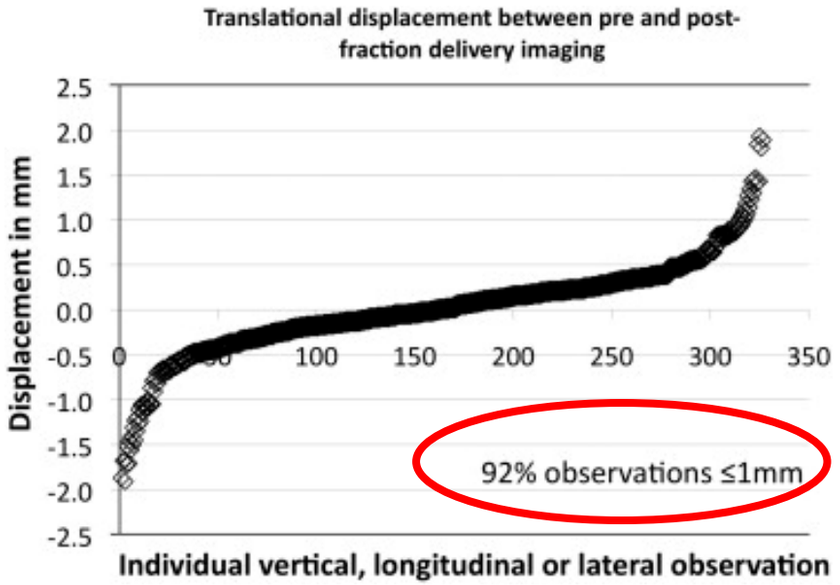
Stability based on ExacTrac

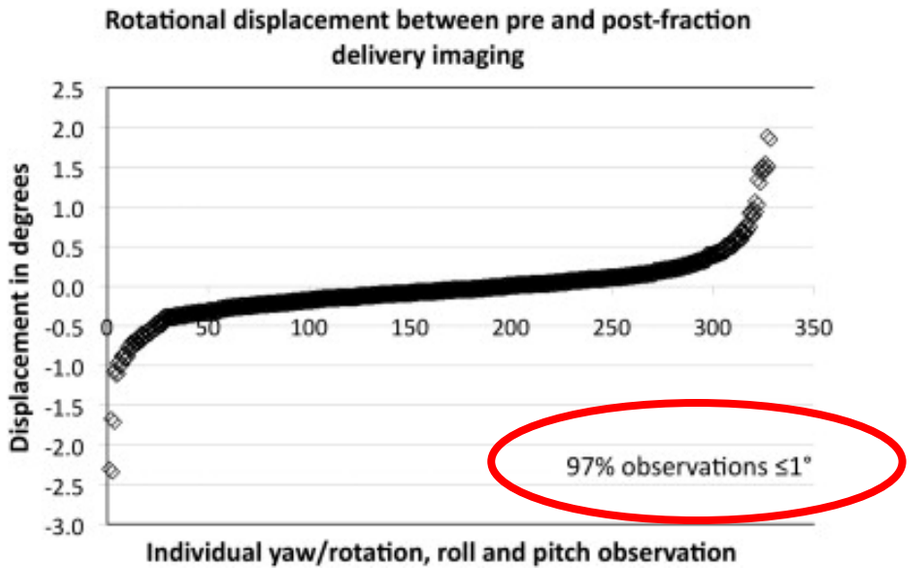
Radiotherapy and Oncology
Volume 104, Issue 1, July 2012, Pages 28–32

SBRT of lung cancer

An analysis of patient positioning during stereotactic lung radiotherapy performed without rigid external immobilization

Max Dahele[a], Wilko Verbakel[a, b], Johan Cuijpers[a, b], Ben Slotman[a], Suresh Senan[a]





Results: Images from 109 fractions in 30 patients resulted in 327 translational and 327 rotational pre- and post-fraction comparisons. Mean RapidArc® delivery time for variable fraction dose was 4.2 min (SD = 1.4). 92% and 97% of translational and rotational differences were ⩽1 mm and ⩽1° in any direction and 98% of translational differences were ⩽1.5 mm. Mean vertical, longitudinal and lateral motion was 0 mm (SD = 0.4), 0 mm (0.6) and 0 mm (0.6). 84% and 94% of the 109 fractions were delivered with ⩽1 and ⩽1.5 mm translation in all three directions and 93% with ⩽1° of rotation. Two patients accounted

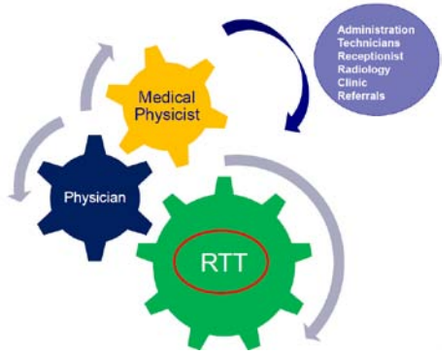
Common remarks

RTTs are the central persons in a treatment of patient

RTTs:

- contact person for patient
- patient experience
- quality of treatment

Some key notes



- RTTs are an important wheel within the whole proces
- 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

Questions?

l.vanderweide@vumc.nl

Erasmus MC
University Medical Center Rotterdam

Daniel den Hoed
Cancer Center

Starting a SBRT program

Mischa Hoogeman

DOSE MEASUREMENTS

Erasmus MC

Commissioning: Pre-Measurement Preparation

- Sometimes it is the only time that physicists can **extensively** measure ra
- Al
  ac

Consider specific requirements for SRS and SBRT

- **Errors in these phases may affect many patients!**

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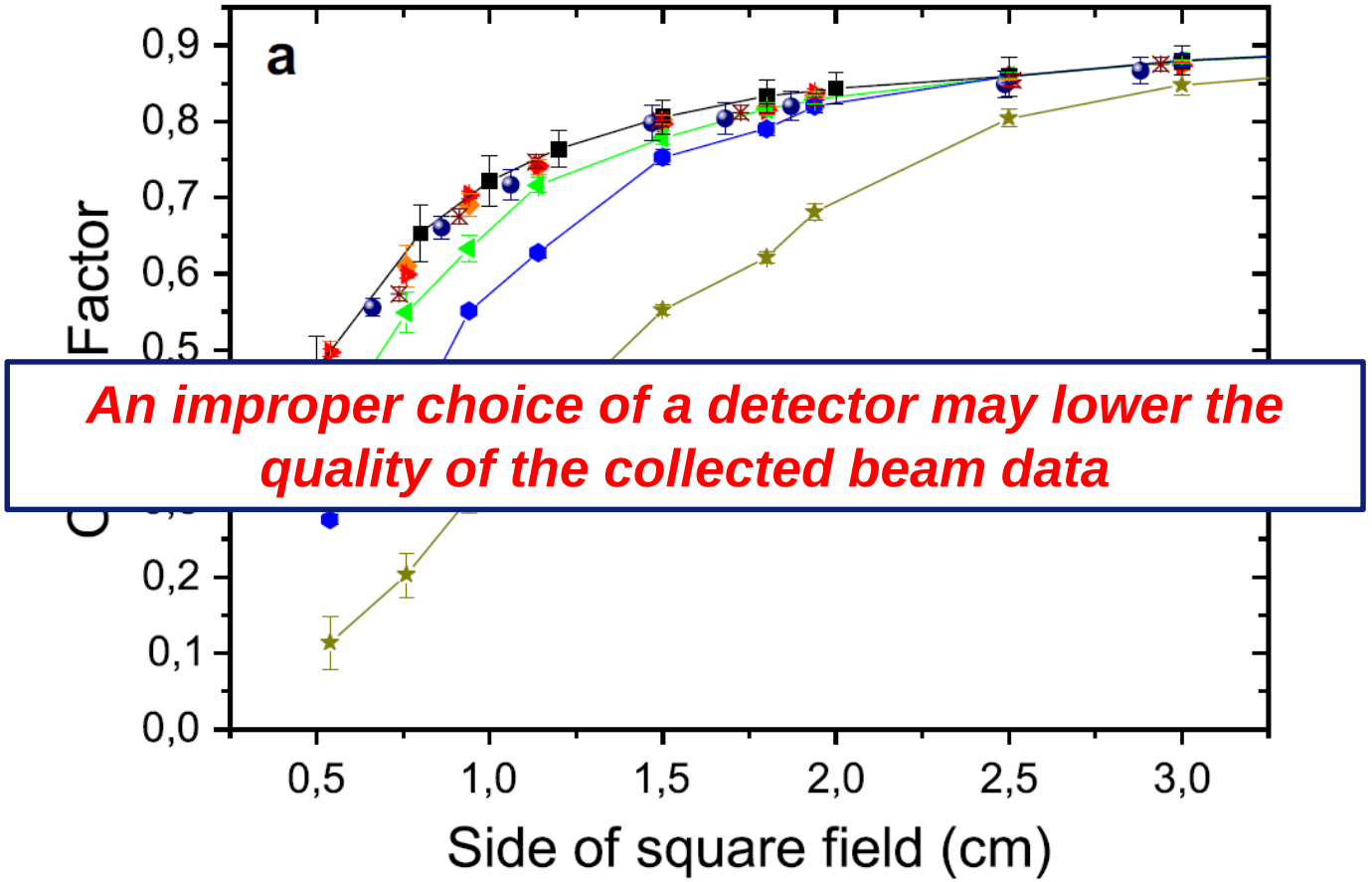
Output Factor for Various Detectors



An improper choice of a detector may lower the quality of the collected beam data

Sánchez-Doblado F, Hartmann GH, Pena J, Roselló JV, Russiello G, Gonzalez-Castaño DM. Phys Med. 2007 Jun;23(2):58-66. Epub 2007 May 2.

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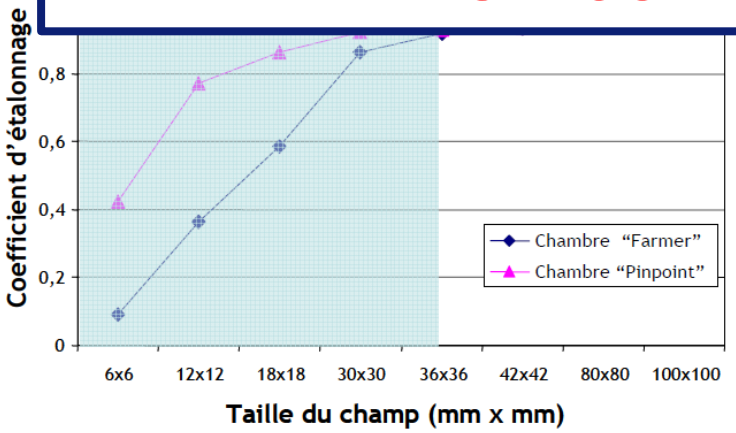
Measurement for dosimetric data input in TPS

- France 2006-2007
- 145 patients
- Non-adequate detector for small beams measurements
- Detected by the company 1 year after
- Neu

Importance of the choice of detectors when commissioning !



IRSN: Note de synthese sur les surexpositions au Centre Hospitalier Universitaire de Toulouse

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Dosimetry of Small Fields

- **Comfortable with measurements of small fields**
  - Not only output factors but also the correct measurements of profiles are challenging
  - Use published codes of practice
    - Read literature (e.g. Stereotactic body radiation therapy: The report of AAPM Task Group 101, and other Task Groups)
  - Communicate with other users
  - Check the measured data with reference data

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TRAINING

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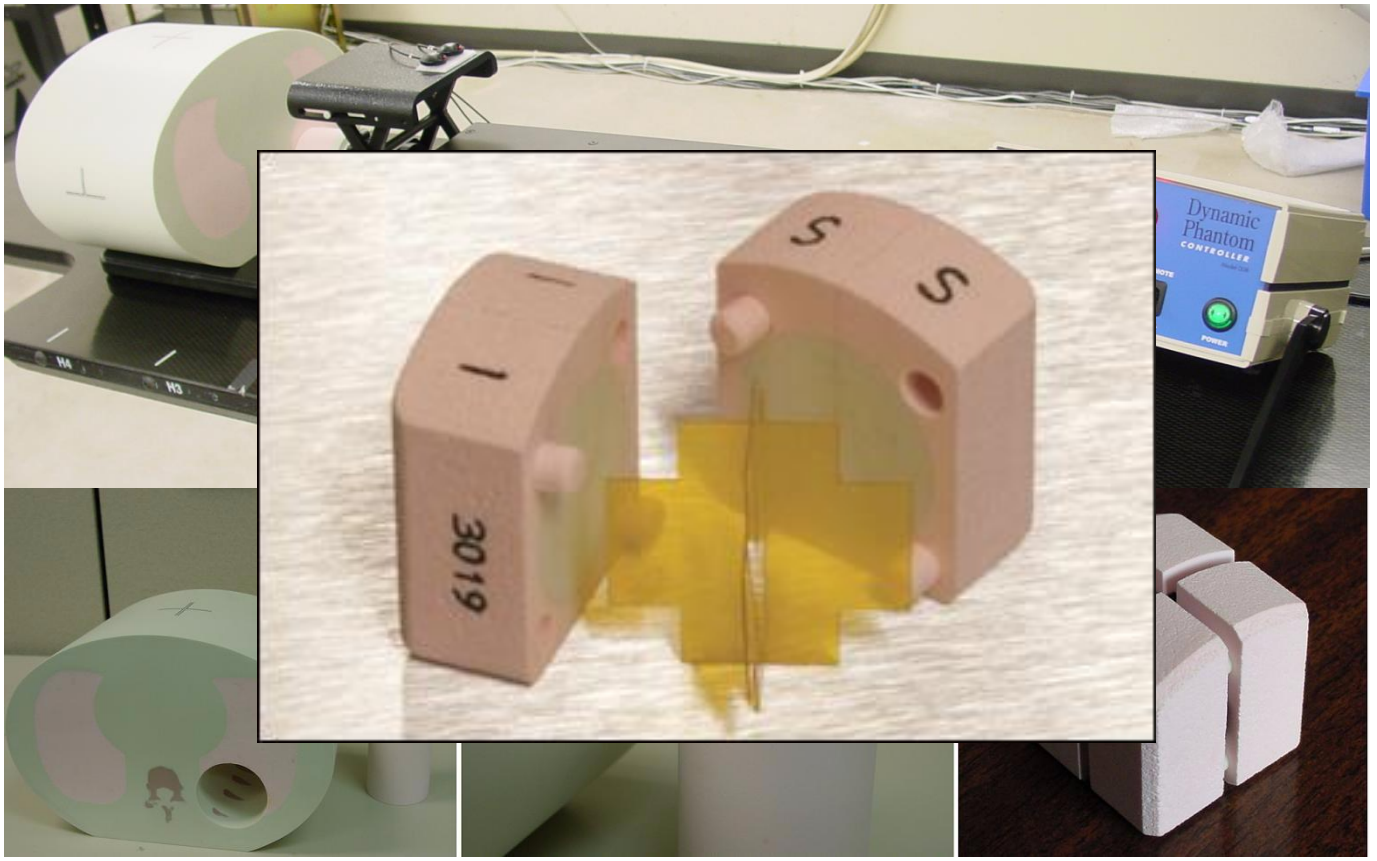
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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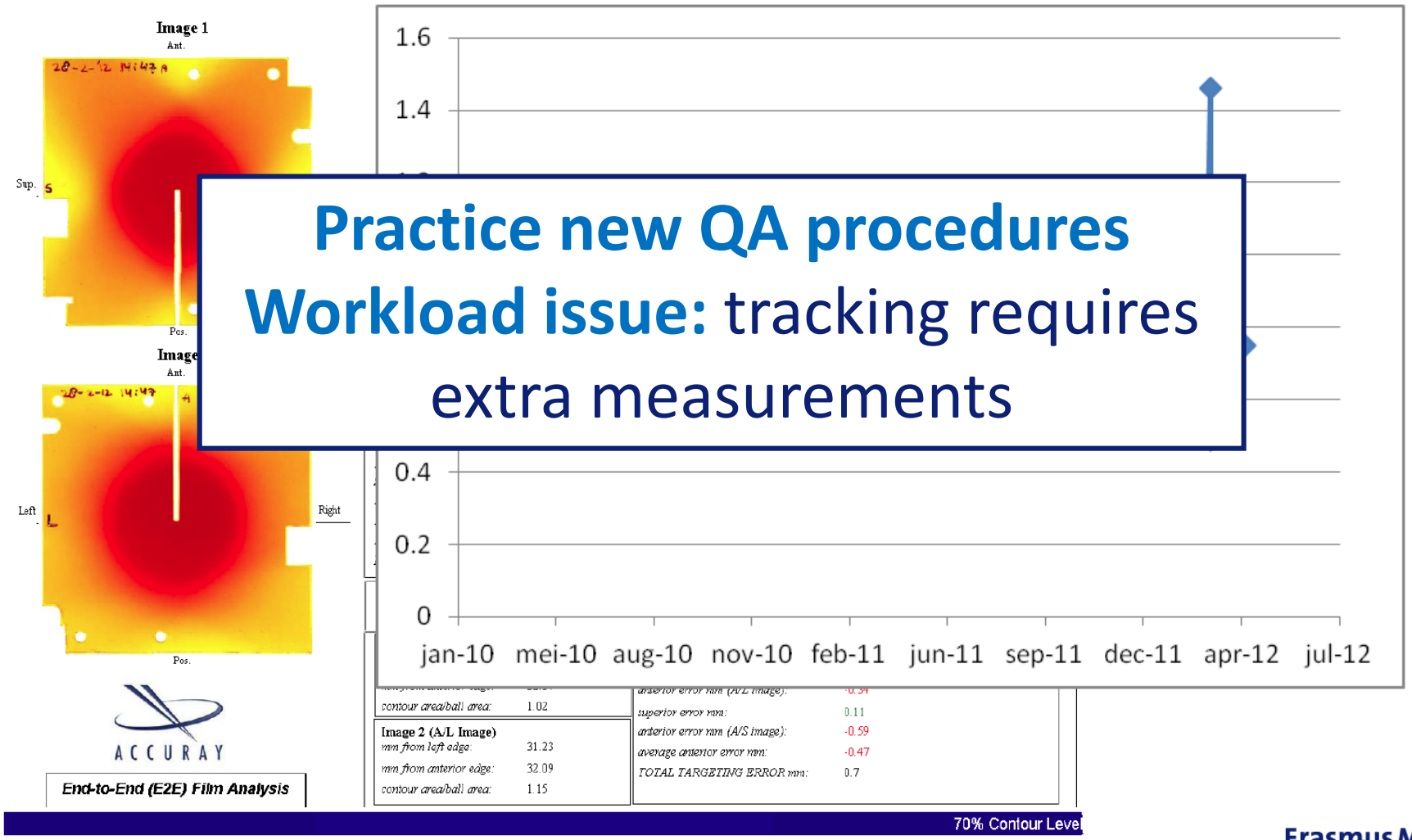
Analysis of Tracking Error



Practice new QA procedures

Workload issue: tracking requires extra measurements

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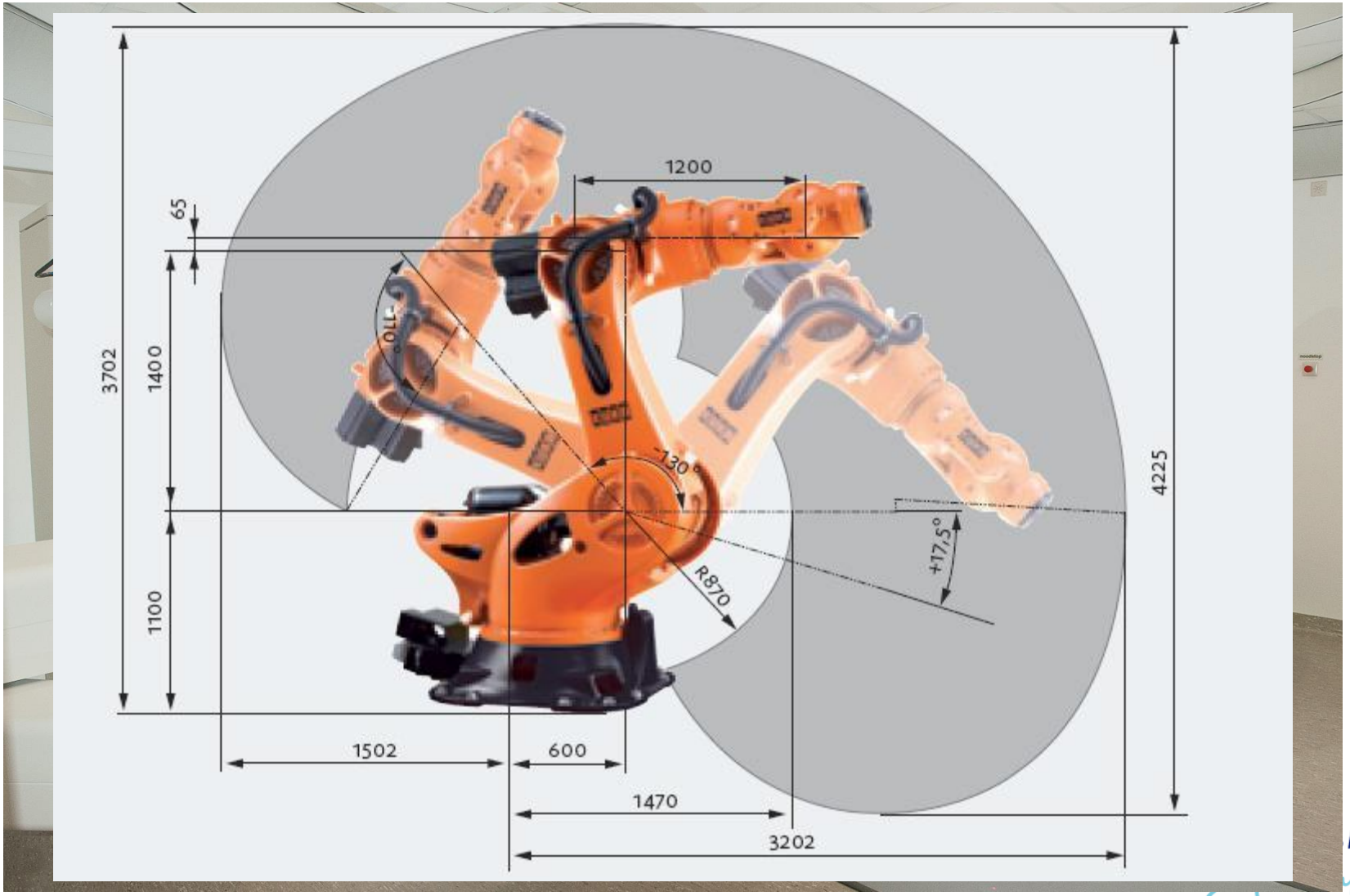
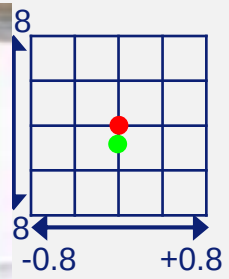
New Technology



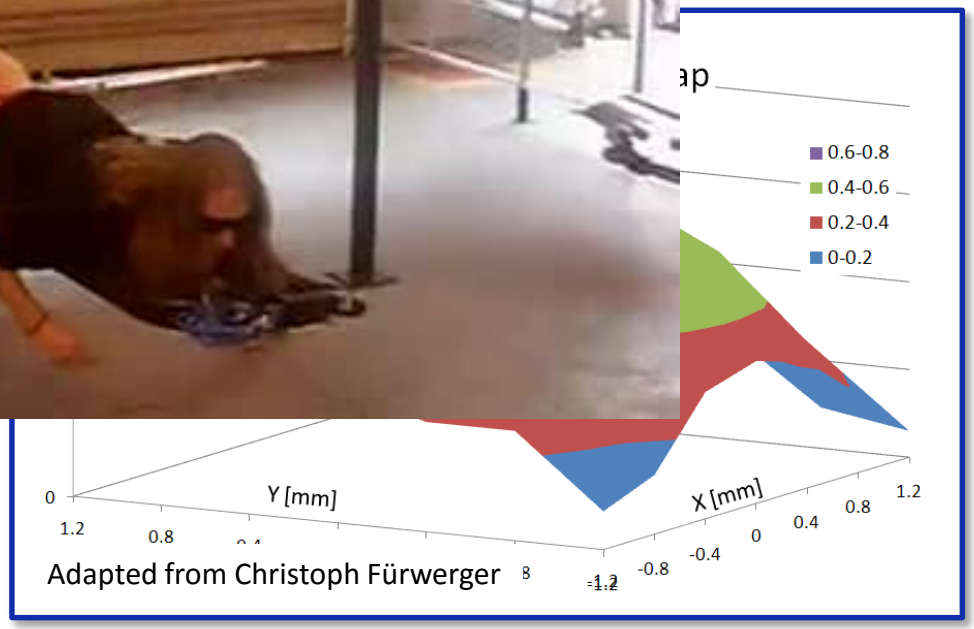
New Skills and New Knowledge: Training

Calibrate pc

- At each r
  scanned
  perpendi
  beam
- Light inte
- Two 5 x 5
- The calib
  to the ce
  map
- Must be
  fixed con
- Result: N

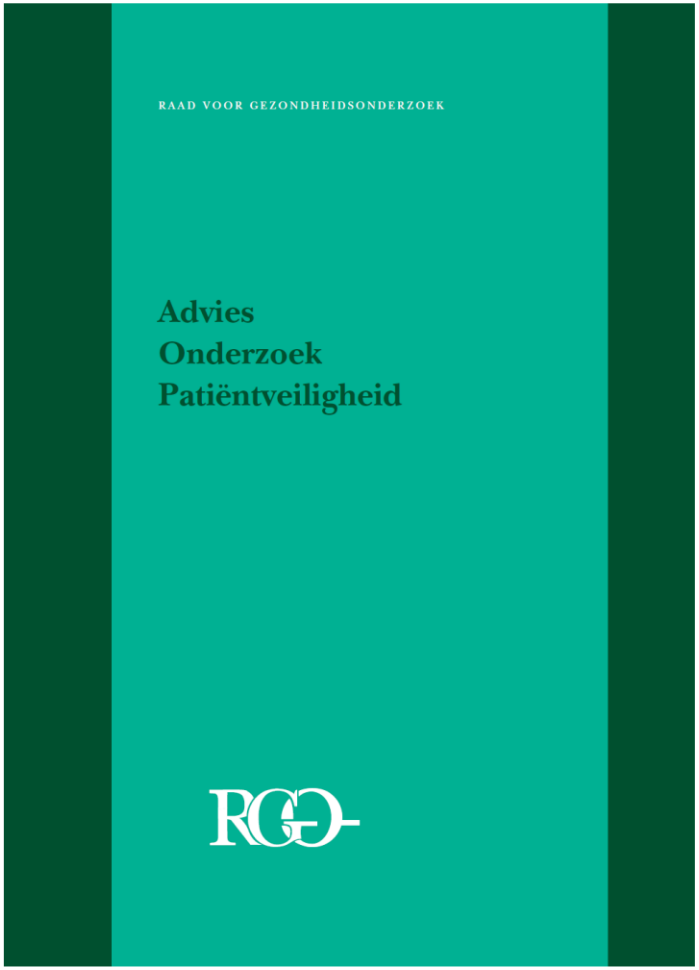


inal node
eration (coarse)
rated node



Adapted from Christoph Fürwerger

Since the publication of “To err is human” (Institute of Medicine – 2000) and a few reports shortly afterwards, suggesting that in the Netherlands **at least one thousand patients die each year due to medical errors**, ‘patient safety’ has become an important issue in Dutch healthcare.



RISK ANALYSIS

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HFMEA

- **HFMEA= Healthcare Failure Mode and Effect Analysis**
  - It is a predictive risk analysis method
  - It is a systematic approach to identify and prevent unsafe situations

- **For each project that involves a change in treatment technique a project plan is required including**
  - Plan of approach
  - Resources needed
  - Risk analysis **DOCUMENTED!**
  - Documentation (e.g. test results and manuals)
  - Education

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Perform Risk Analysis with the Whole Team

- A multidisciplinary **team has to be assembled** including experts and an advisor

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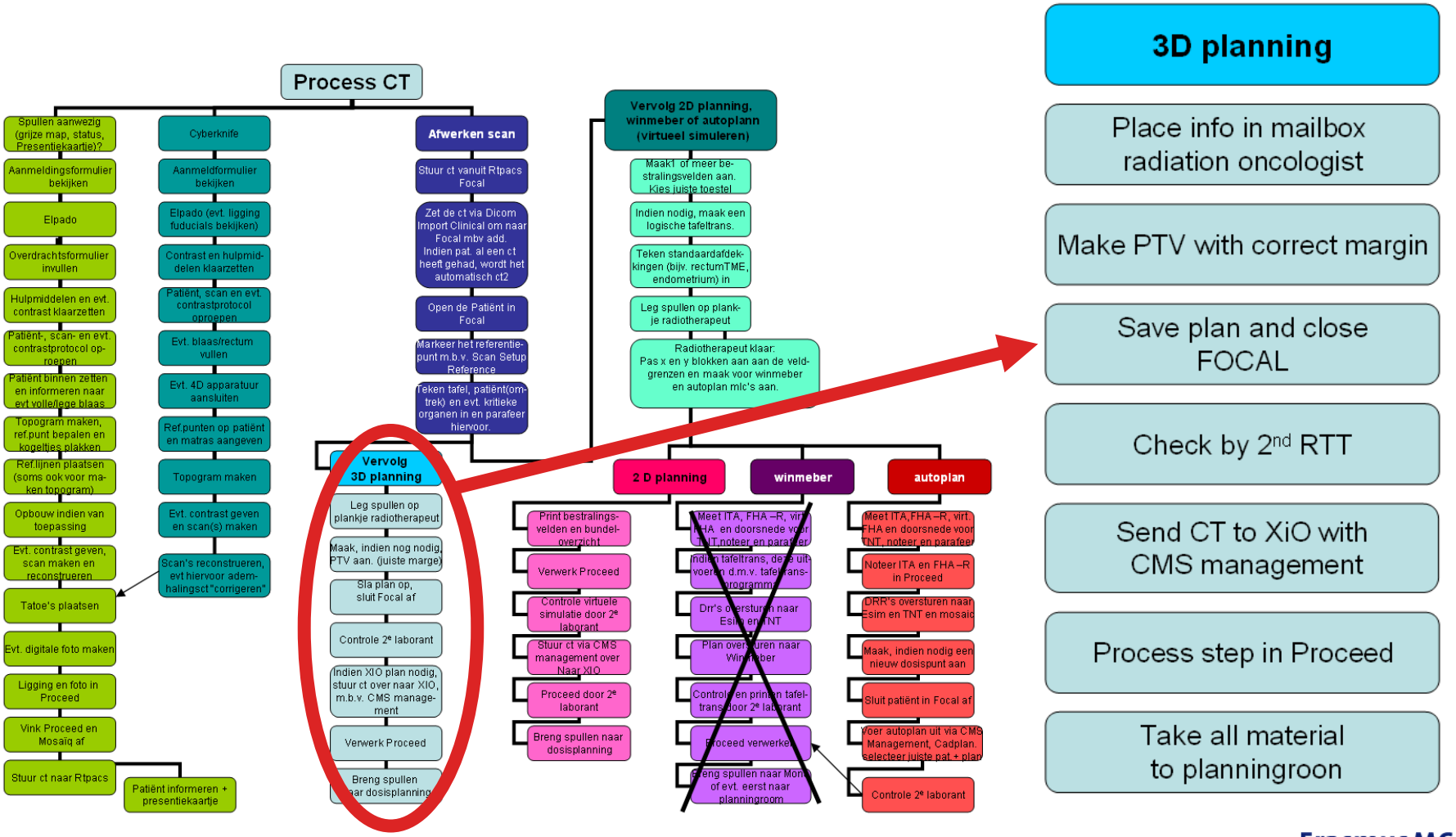
Graphically Describe the Process



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Hazard Score

Severity	Frequency	Detectability	Score
None	>Yearly	Almost certain	1
Low	Yearly	Very likely	2
Medium	Monthly	Likely	3
High	Weekly	Not likely	4
Catastrophic	Daily	Not	5

$$Hazard\ Score = Severity\ x\ Frequency\ x\ Detectability$$

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Hazard Table

Hazard Score	Conclusion
<11	Risk is acceptable and mitigated by standard procedures
11-21	Risk is unacceptable and not always mitigated by standard procedures. Measures are needed.
>21	Risk is unacceptable and counter measures are required with active surveillance.

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HFMEA in Standardized Spreadsheet

Processtap	Mogelijke faalwijze	Mogelijk gevolg	nst (apparaat/proces/patiënt)	Mogelijke oorzaak					Actie of beheersmaatregel	Verantwoordelijke
			0							
Voorlichting patient										
Patient komt op mouldroom			0							
Patient krijgt CT										
Controle kwaliteit 4DCT dir	2	2	12		CT protocollen duidelijk op KIS				scans voor	MM
Proefligging plan maken										
Proefligging op toestel	2	2	8		Maaike legt nogmaals probleem aan Joc planning				MM	
Overnemen resultaat proefl									aat estel. Resultaat	RR
	1	1	2		hier is een duidelijk protocol op KIS voor					
Intekenen arts			0		zie rij 17				en bij fysica	GK
Aanmaken ITV en PTV					Pop-up in Multiplan die weggeklikt moet worden bij afwijking van resultaat				TV en 2 view.	MM
MONO intekening	2	3	24		proefligging. Zoveel mogelijk proefligging proefligging opslaan in Proceed.				MONO stap	
	2	4	32		laboranten checken, maar protocol ma placo?					
	2	5	40		Voor 1 view kunnen we dit controleren i Wie controleert PTV marges?					
	2	2	12		afspraak bij wijziging op MONO, arts communiceert naar planning en MONO stap niet verwerkt.					

CT protocols should be published in protocol database

Add quality control on the applied PTV margins

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DURING TREATMENT DELIVERY

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During Treatment Delivery (CyberKnife as Example)

- **Treatments with tight safety margins**
  - No lock on the target => no treatment
    - Tumor cannot be localized (Xsight Lung Tracking)
    - Marker distances changed (Marker Tracking)

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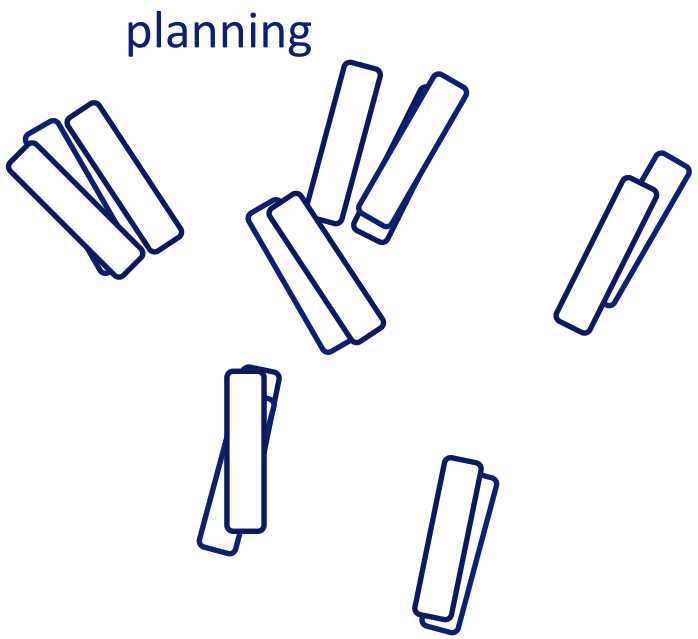
Deformation in Marker Configuration

- Rigid-body threshold exceeded => increase rigid-body threshold



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During Treatment Delivery

- **Well-trained staff is required**
  - Recognize failures in targeting
    - Understands metrics displayed by the system
    - Understands consequences of adjusting an imaging parameter
    - Visual verification (independent)

- **Attendance of medical physicist and radiation oncologist**
  - Medical physicist present during first patient treatments
  - Radiation oncologist on site
  - Clear protocols and/or decision trees

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Analyze the Treatment Data

Continued Quality Assurance
… stay alert!

Coen Hurkmans, Ph.D., clinical physicist
Catharina Hospital, The Netherlands

catharina hospital

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

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

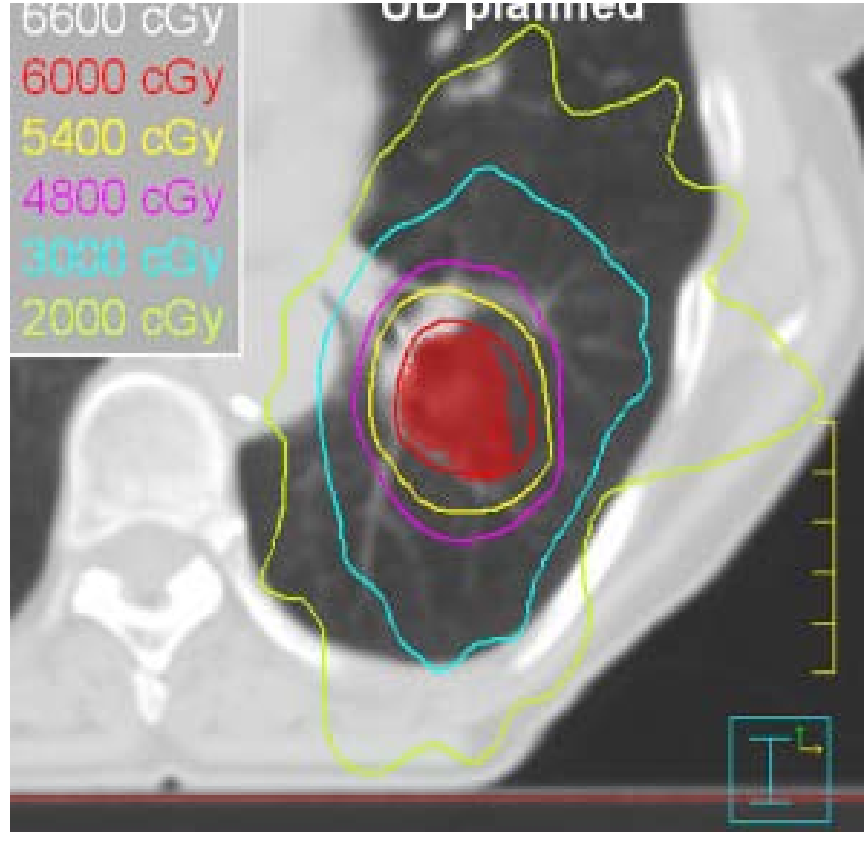
Initial plan and prescription:

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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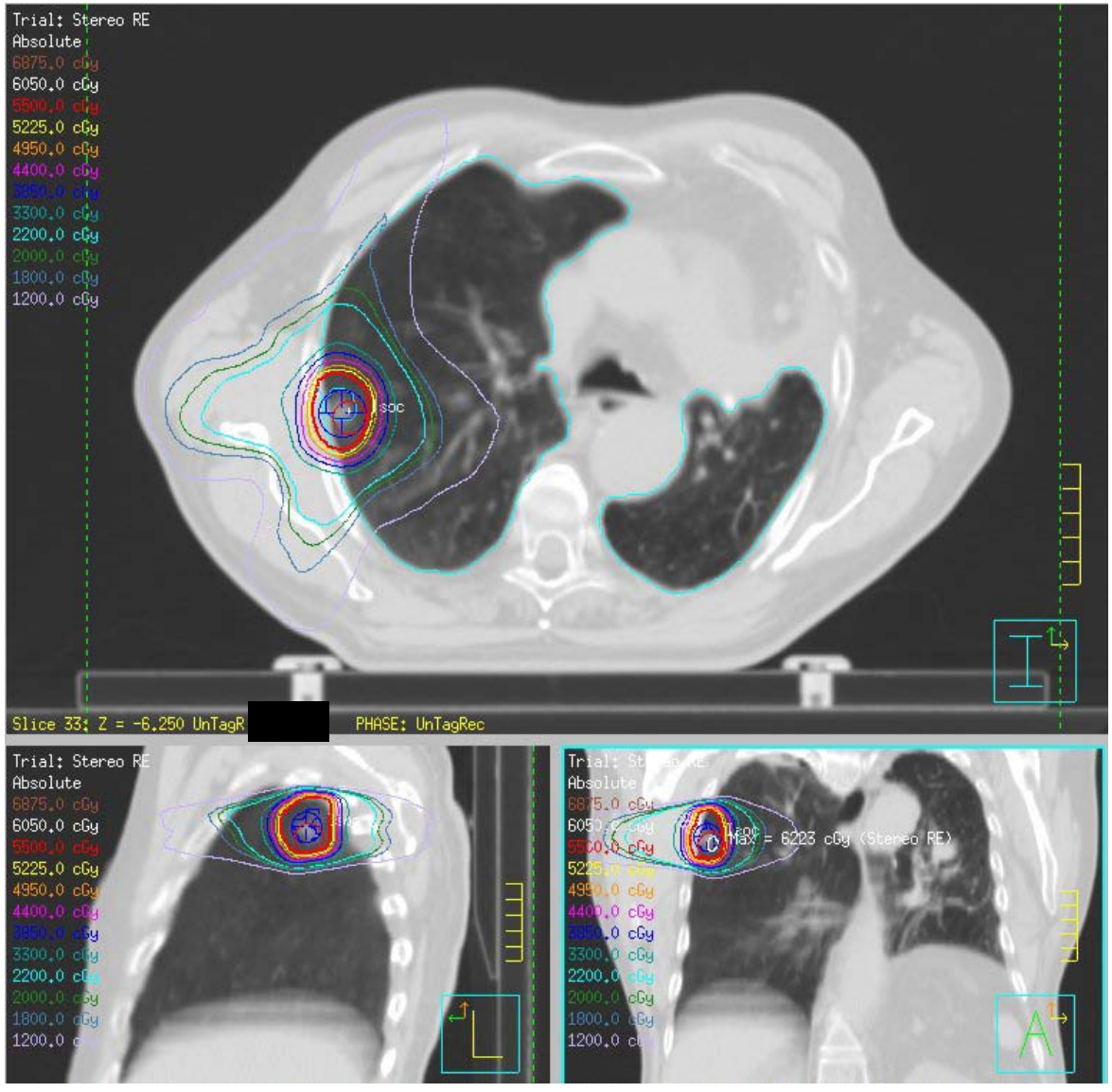
Unexpected shifts



- 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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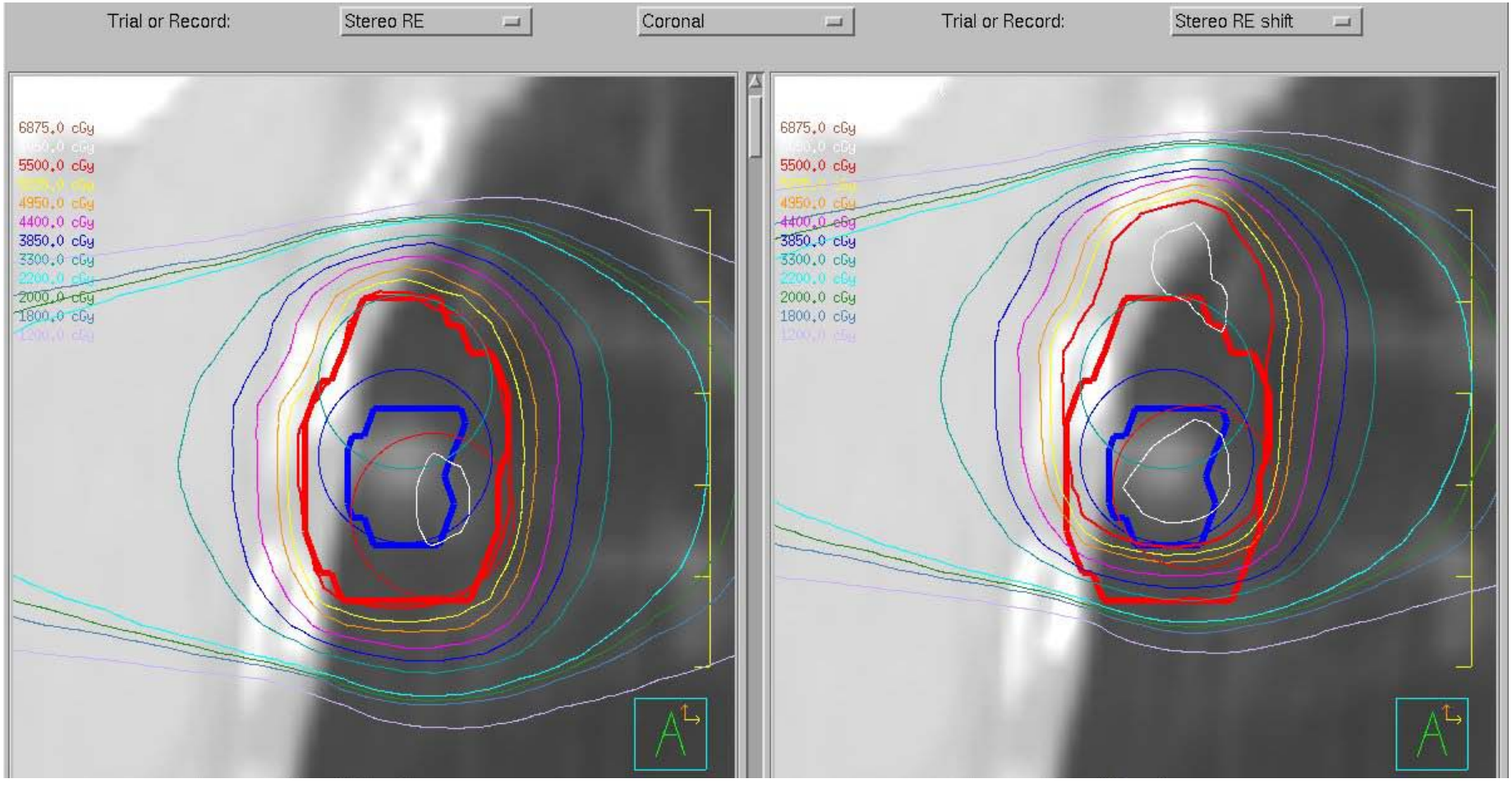
Unexpected shifts: Dose shift



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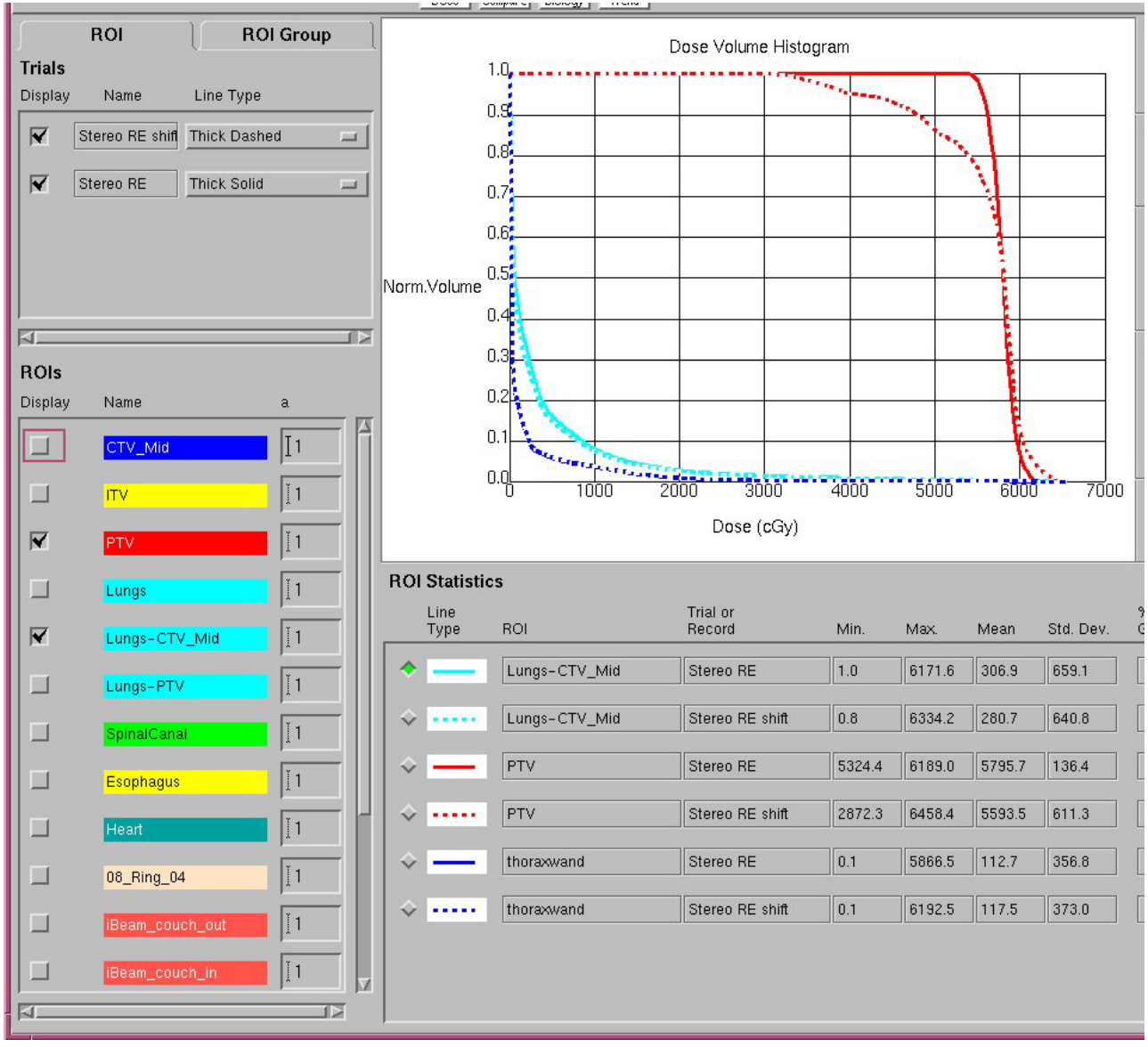
Unexpected shifts: Dose shift



- 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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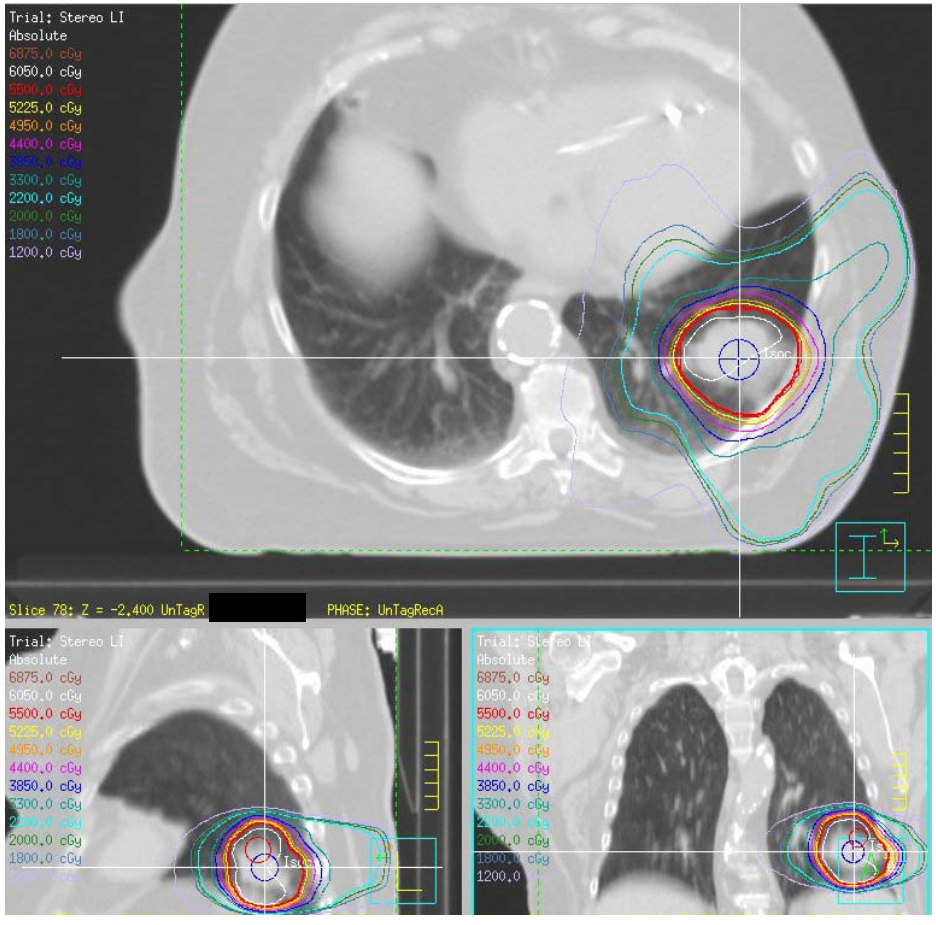
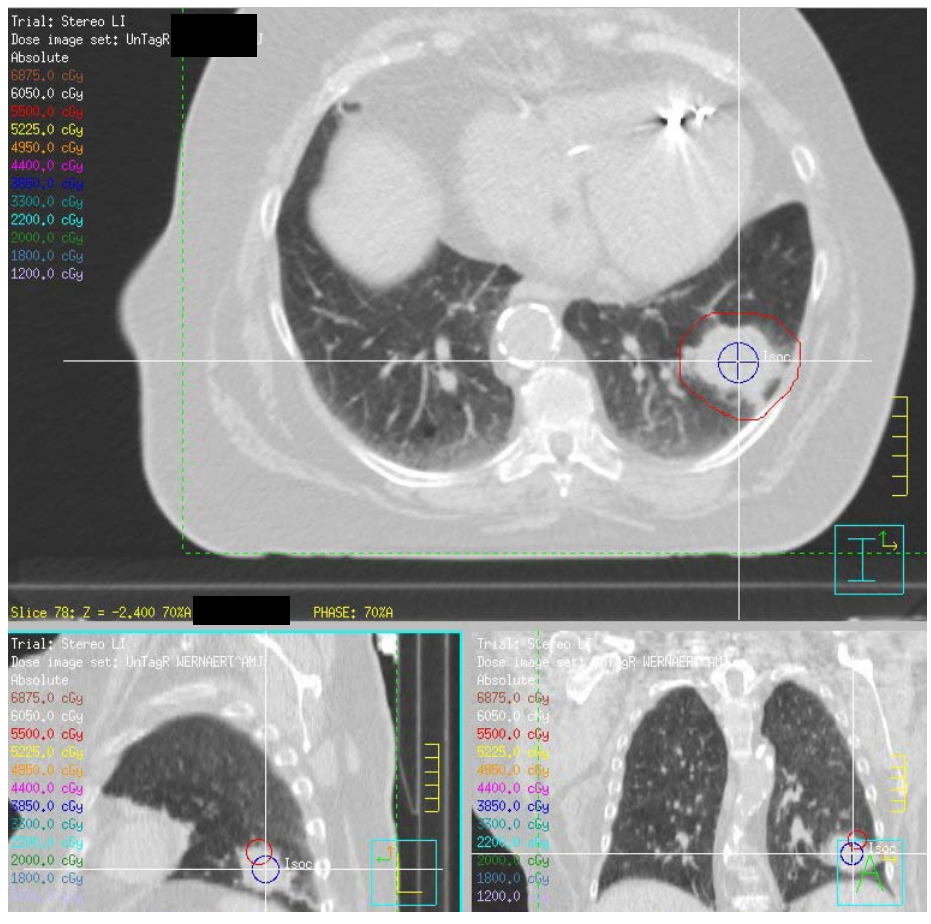
Wrong CT for matching with CBCT

Average CT



Midvent phase



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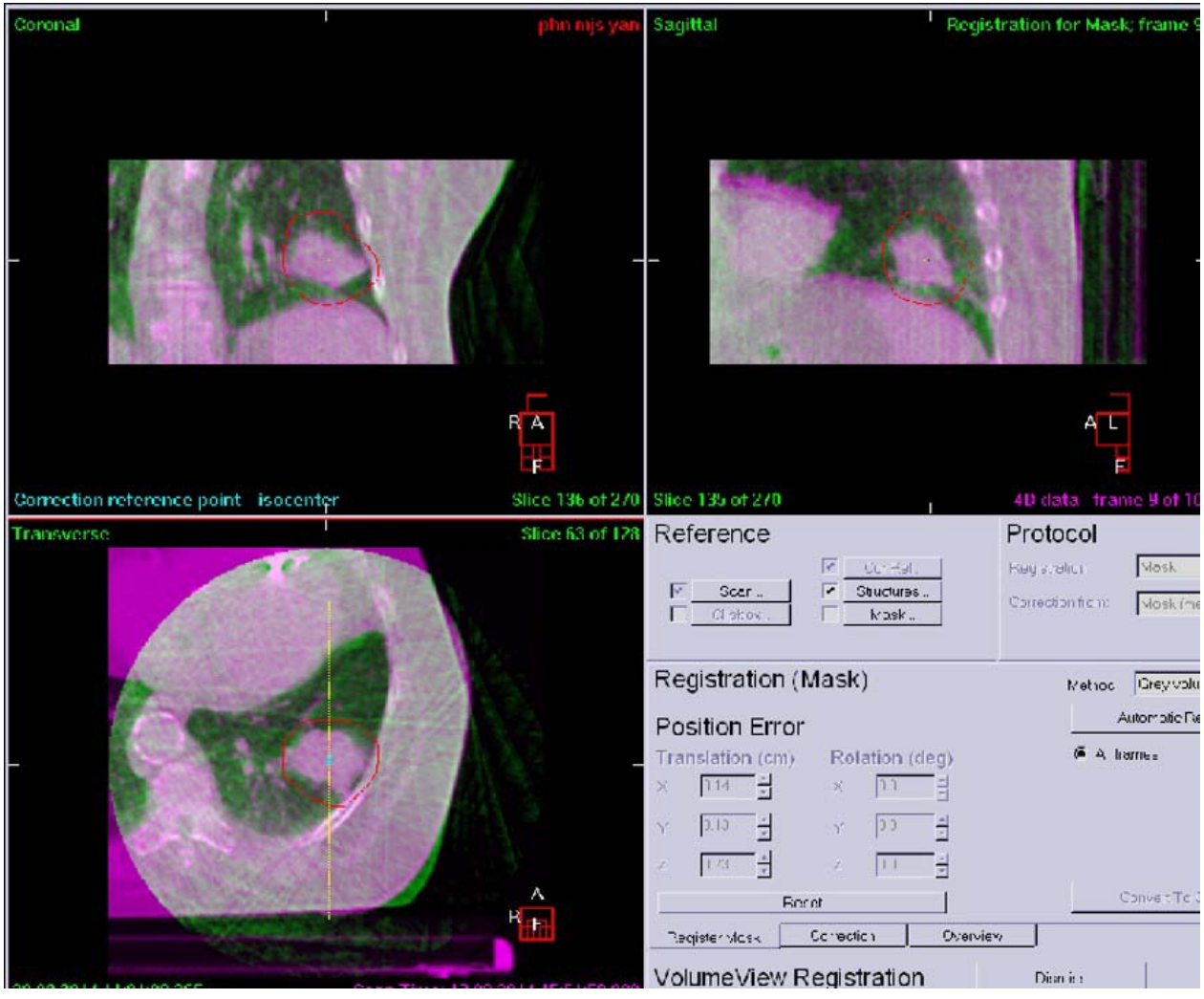
Wrong CT for matching: 4D-CT



- 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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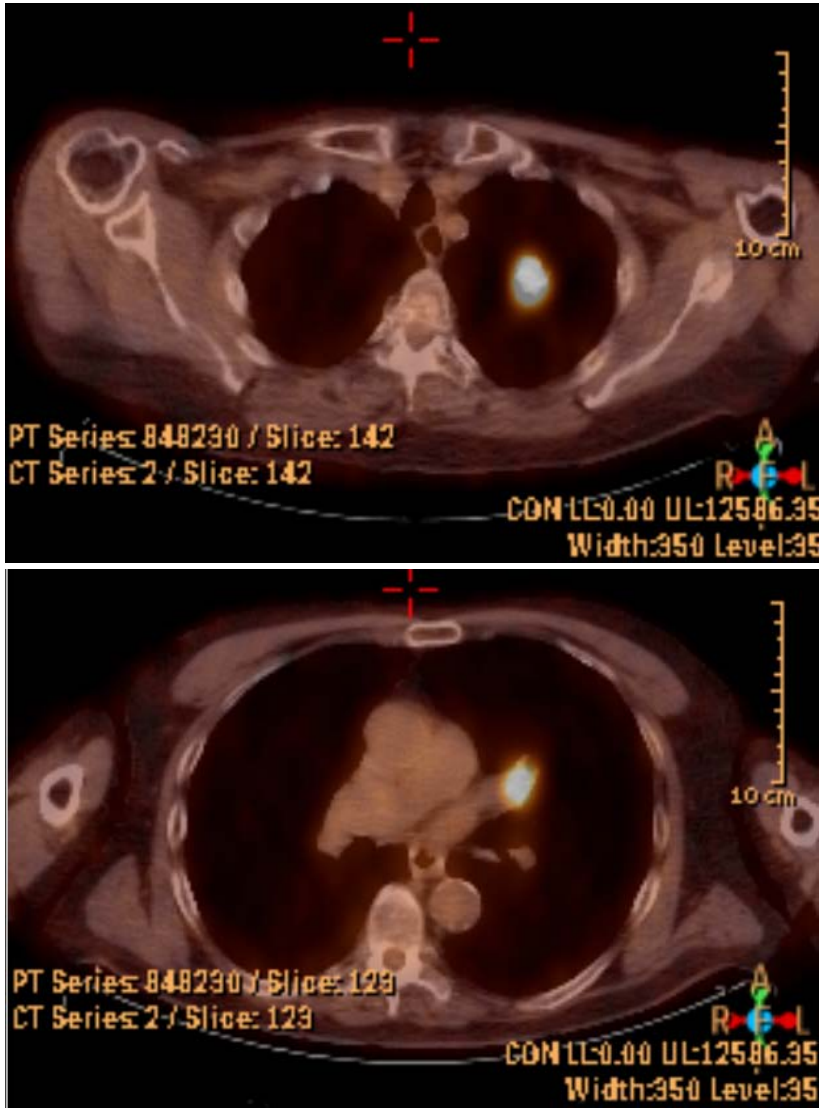
Too low dose due to proximity of OAR



PET-CT diagnosis March 2013

Two lesions

- Upper lesion 3 x 18 Gy
- Central lesions 8 x 7.5 Gy

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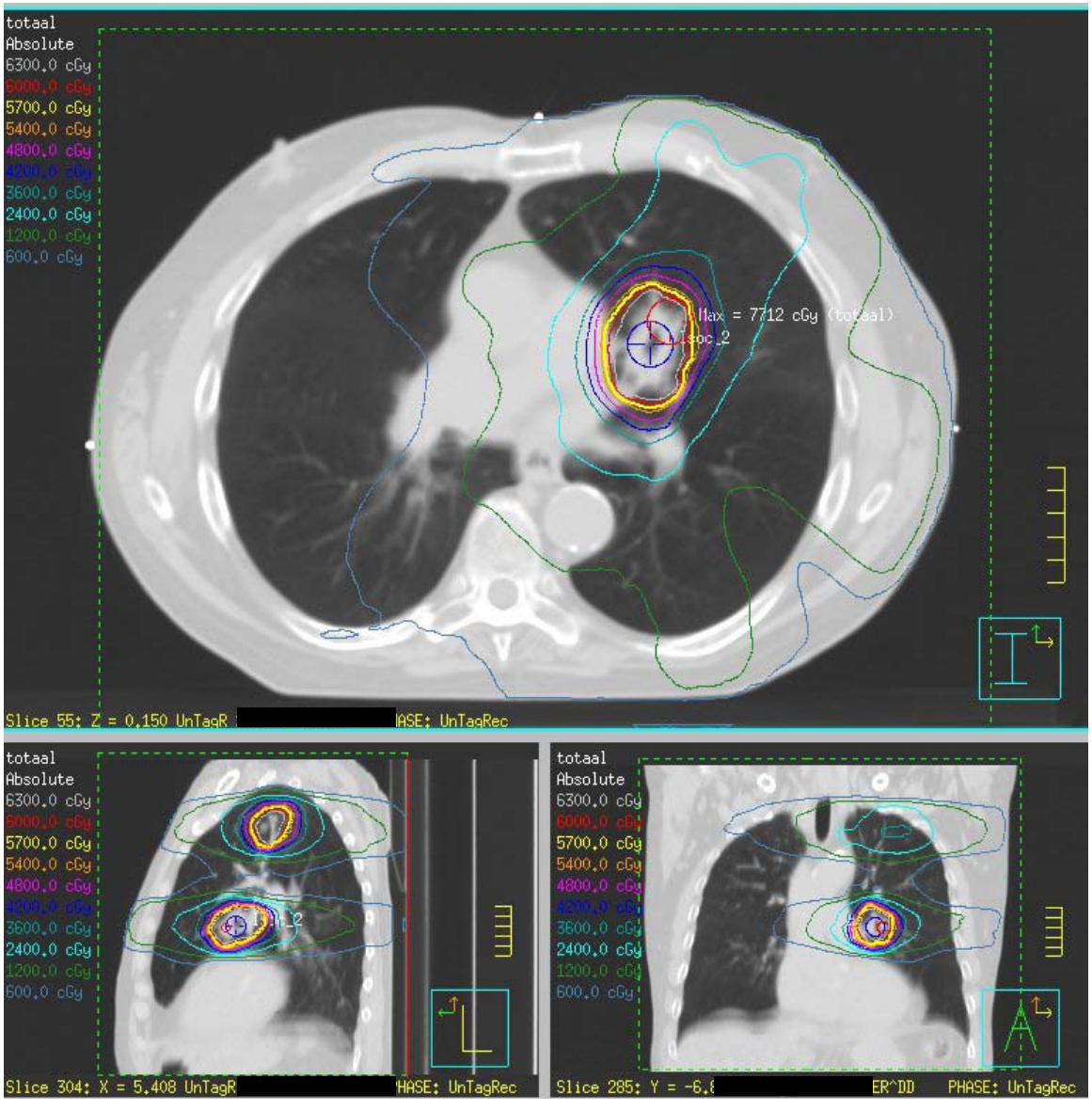
Too low dose due to proximity of OAR



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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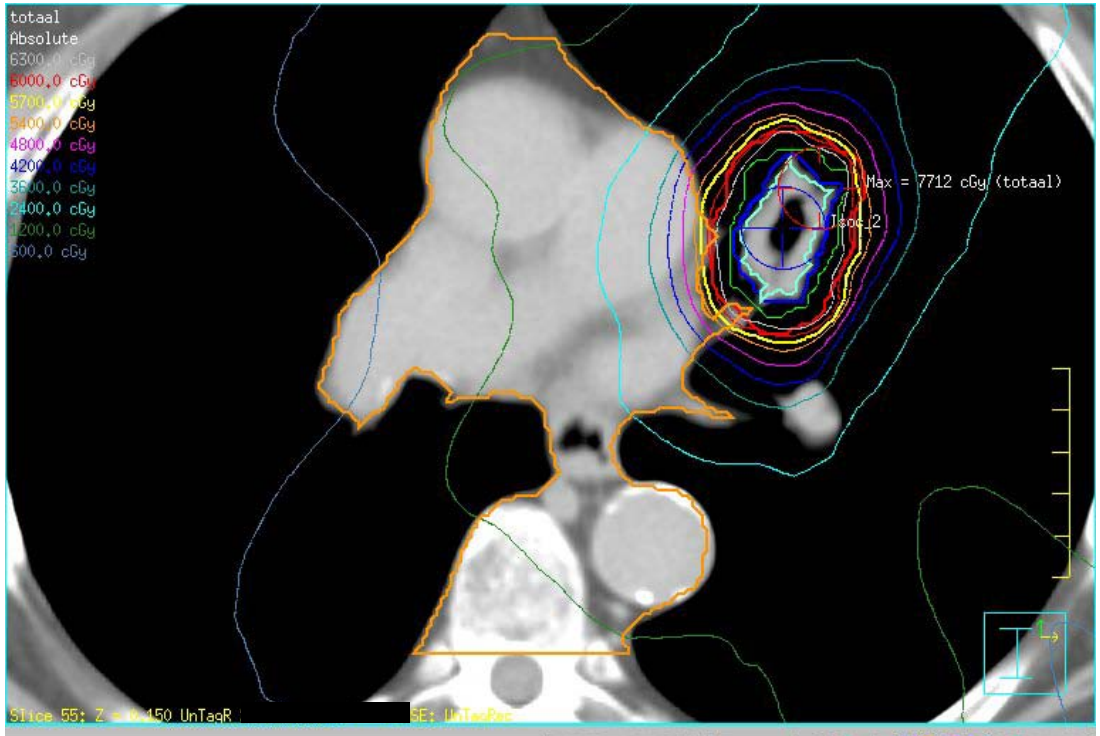
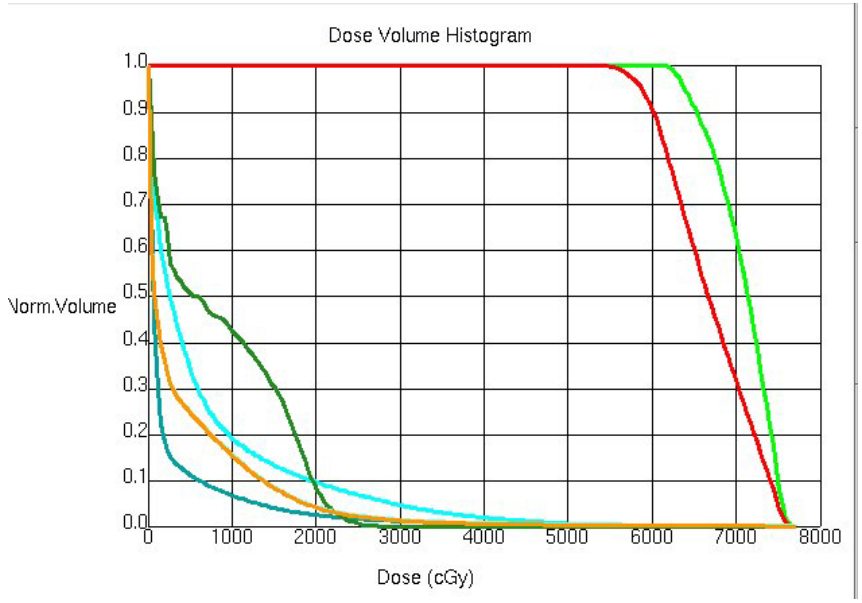
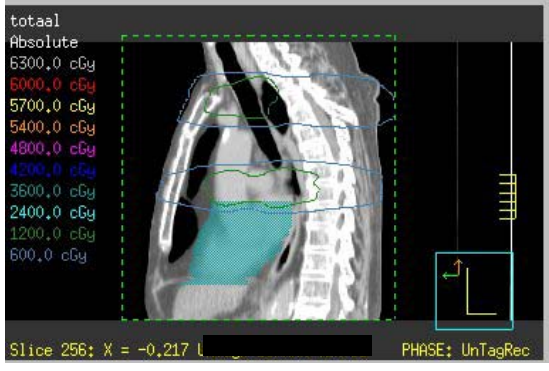
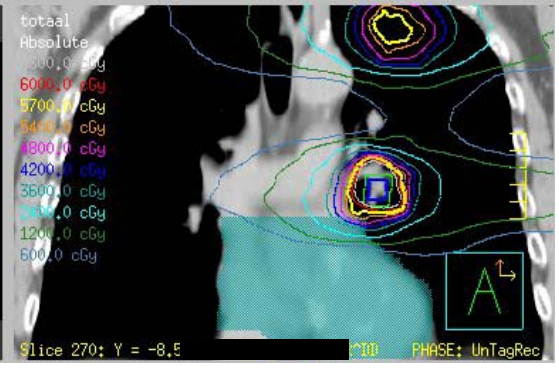
Too low dose due to proximity of OAR









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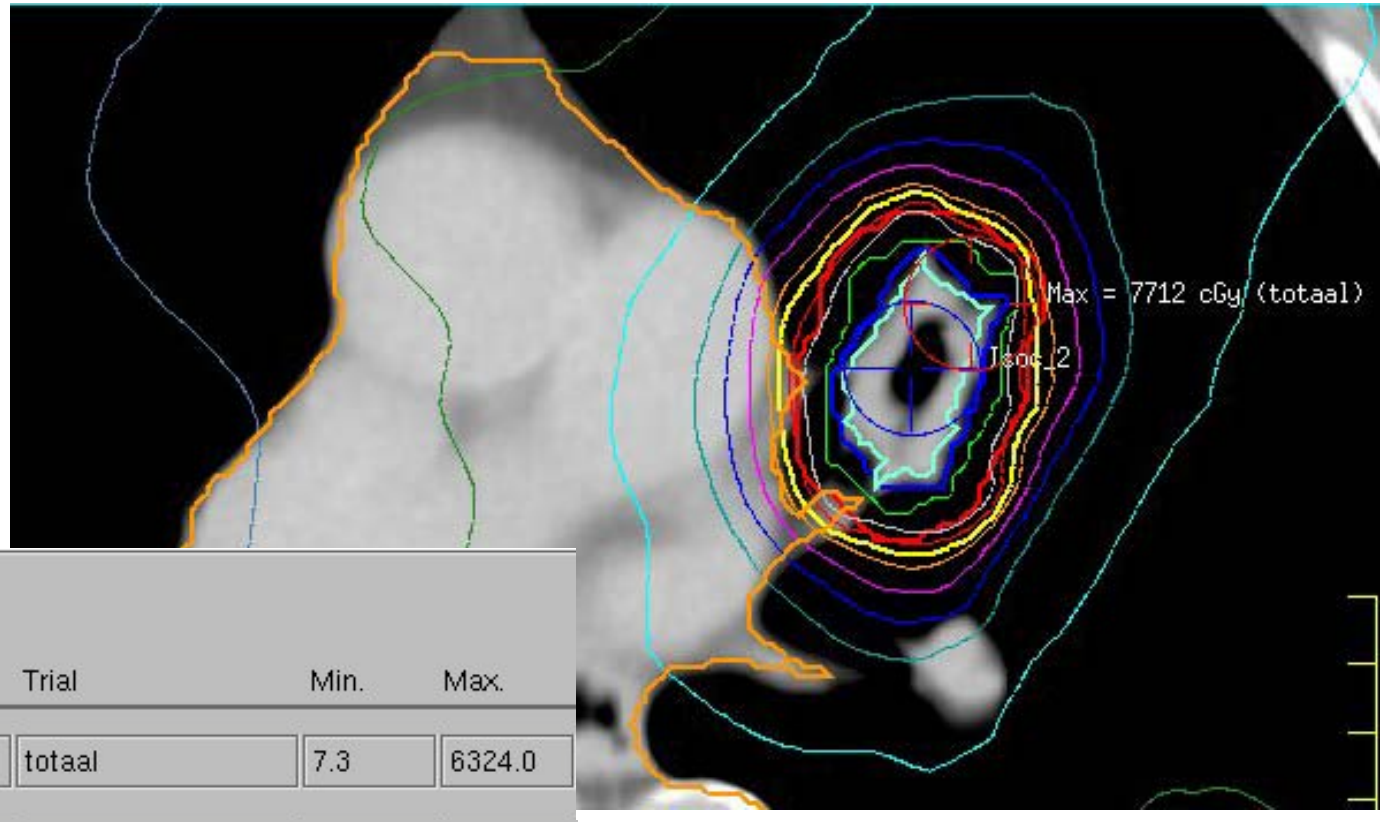
+ Wrong OAR auto-delineation..

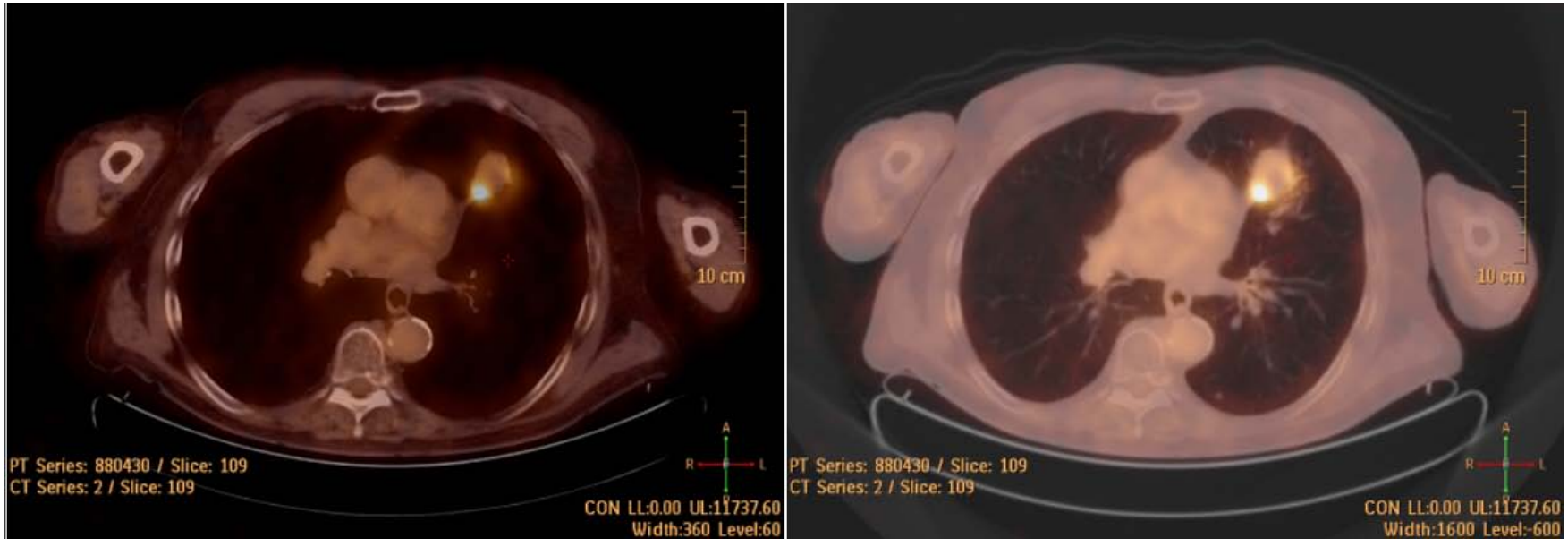


ROI Statistics

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

Too low dose due to proximity of OAR?

June 2014 FDG uptake. Recurrence?



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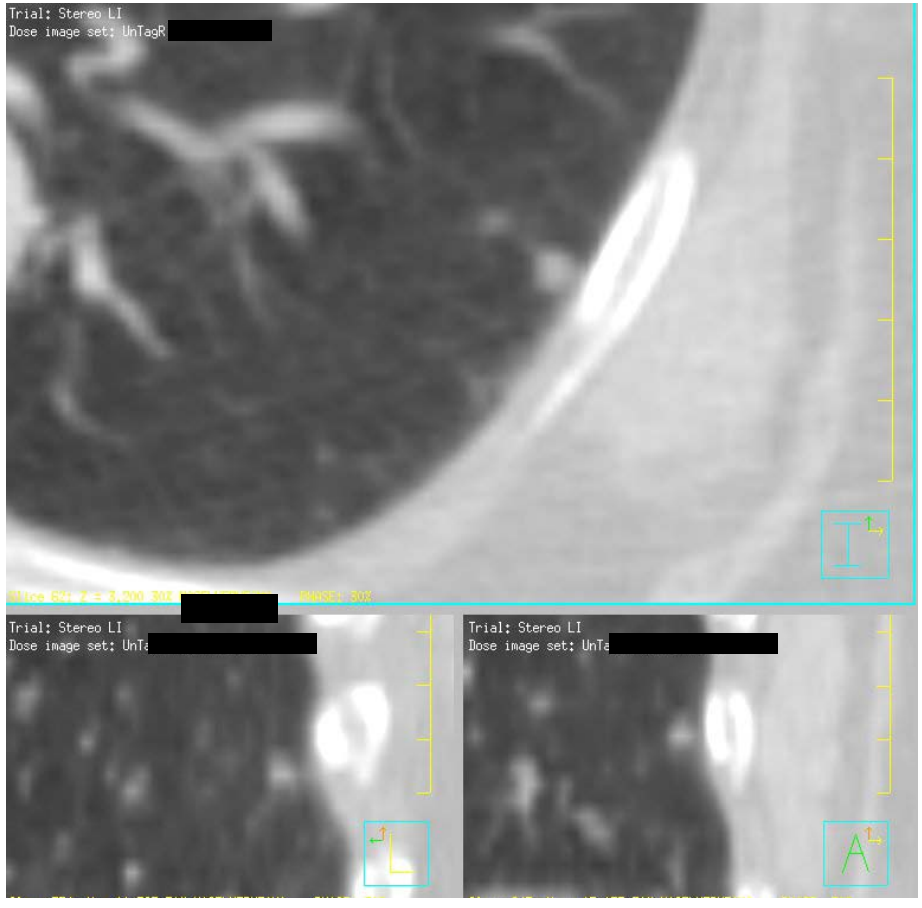
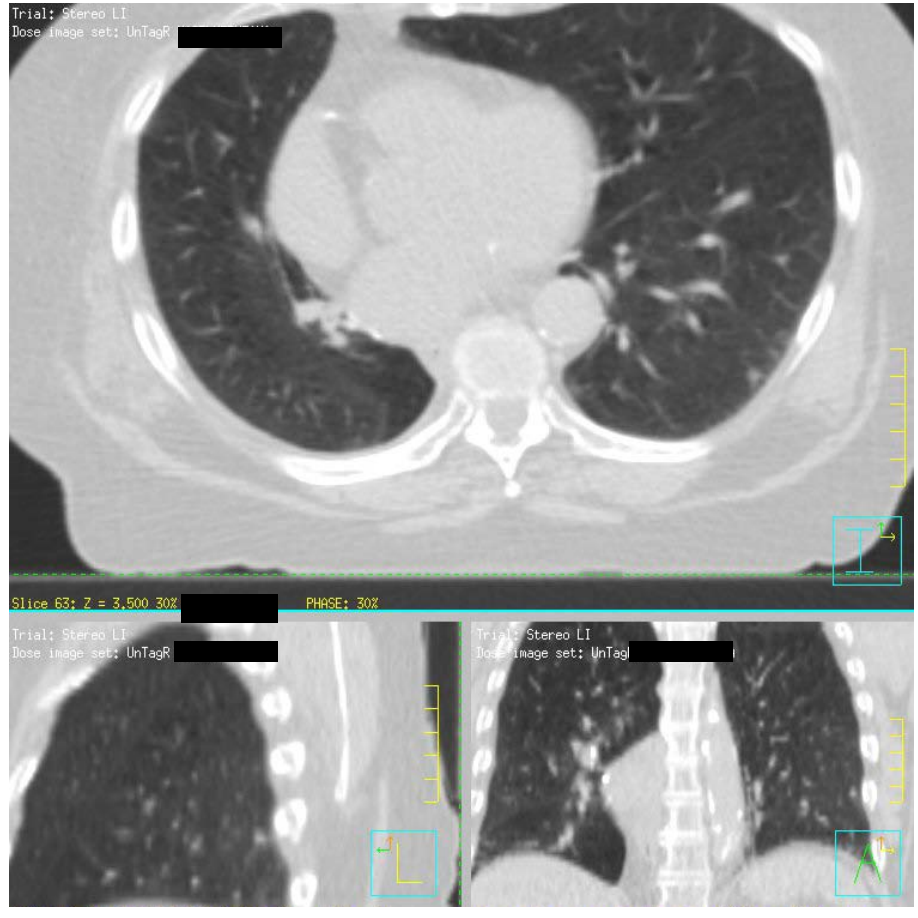
Too small lesions to detect on CBCT





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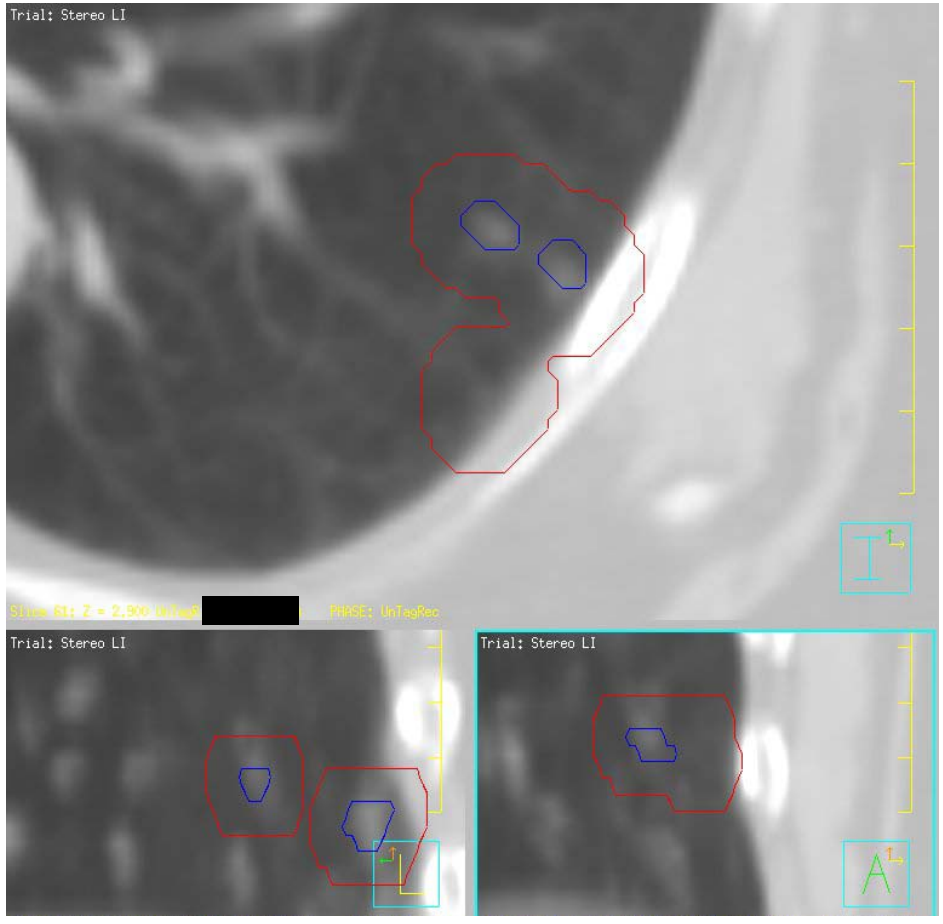
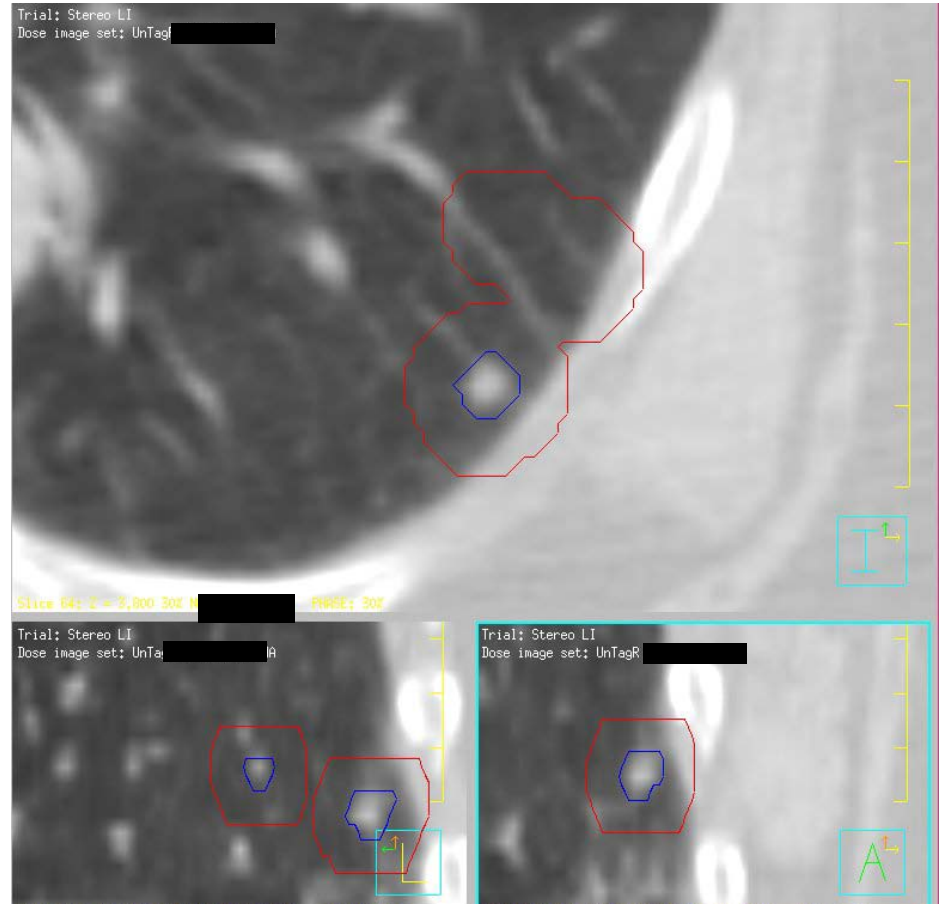
Too small lesions to detect on CBCT

Average



Midvent



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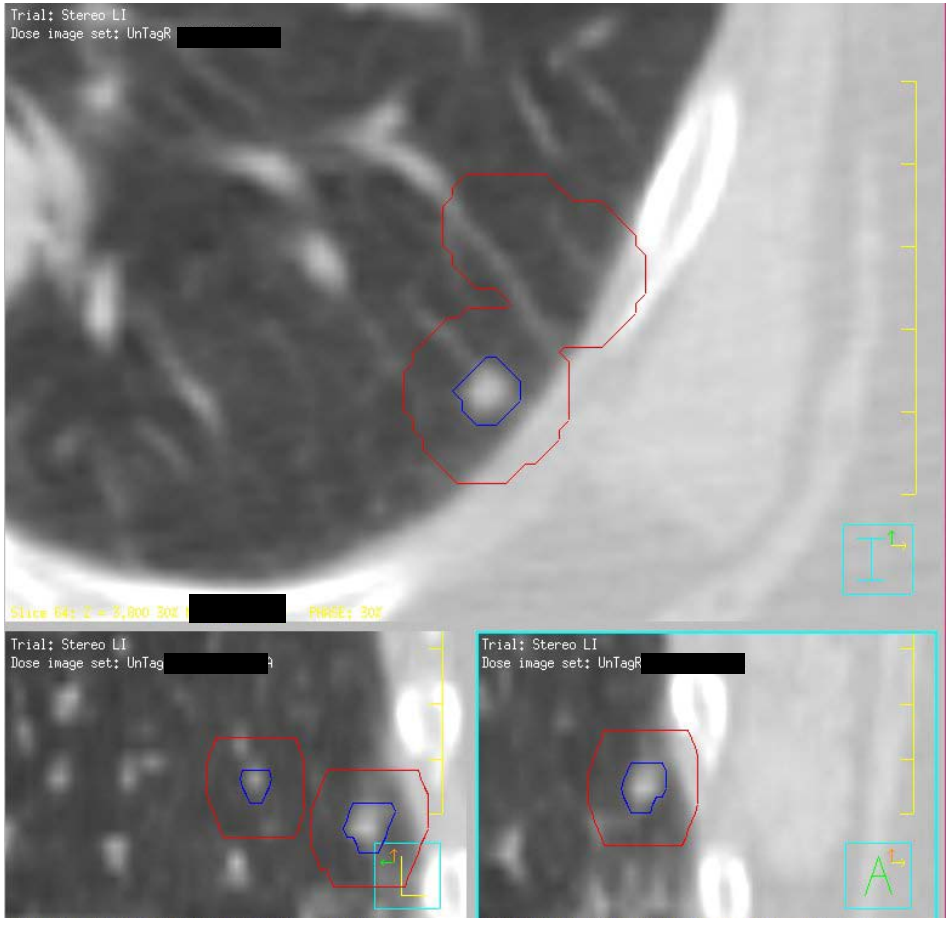
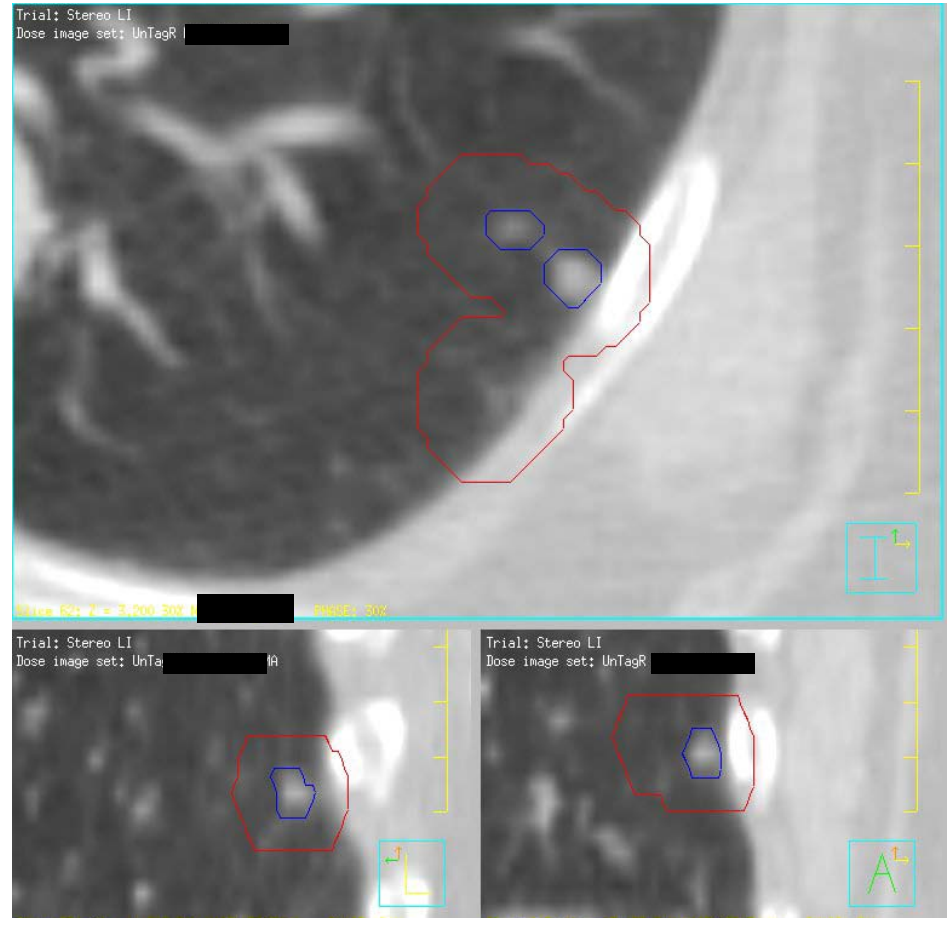
midvent





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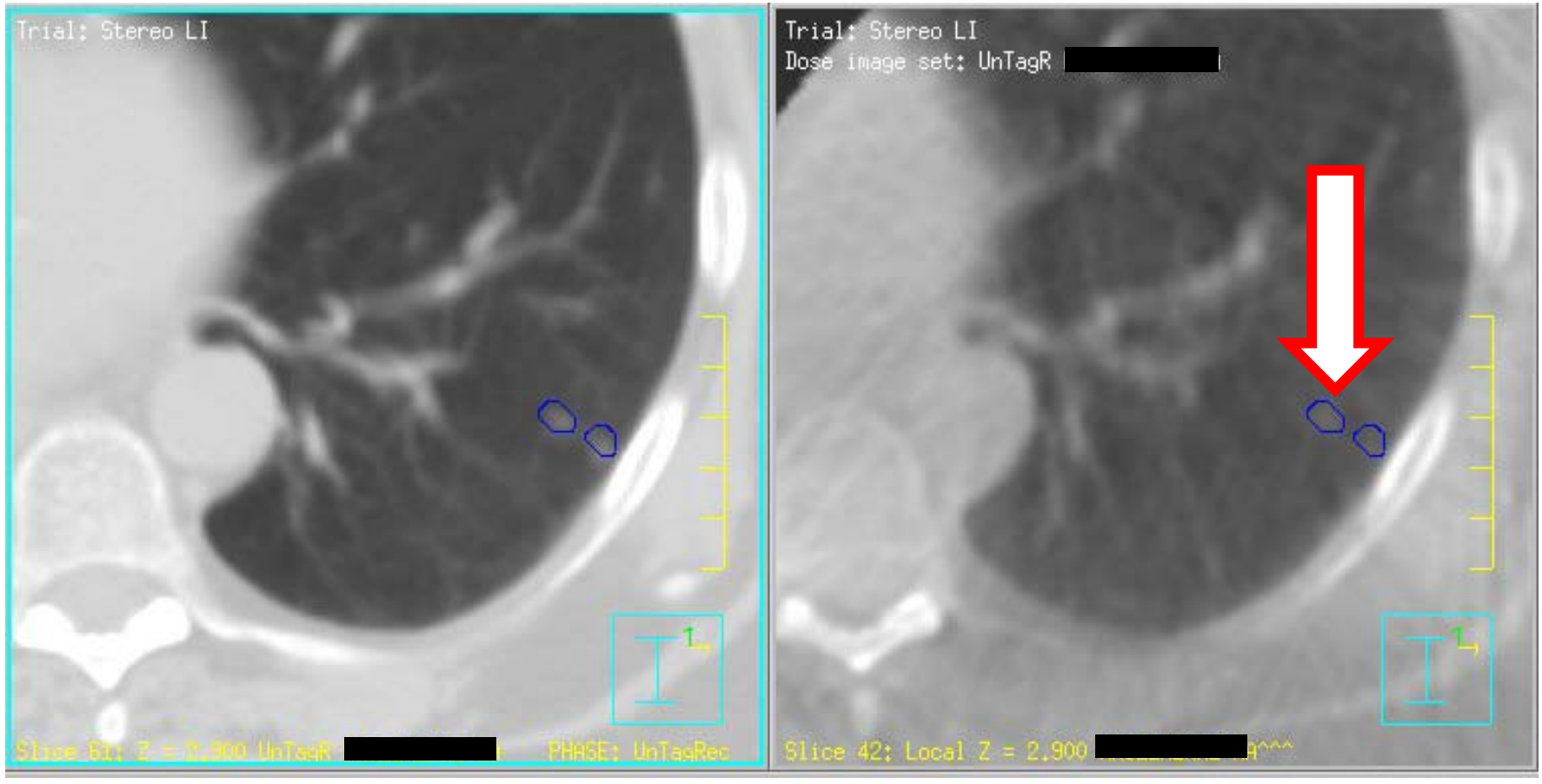
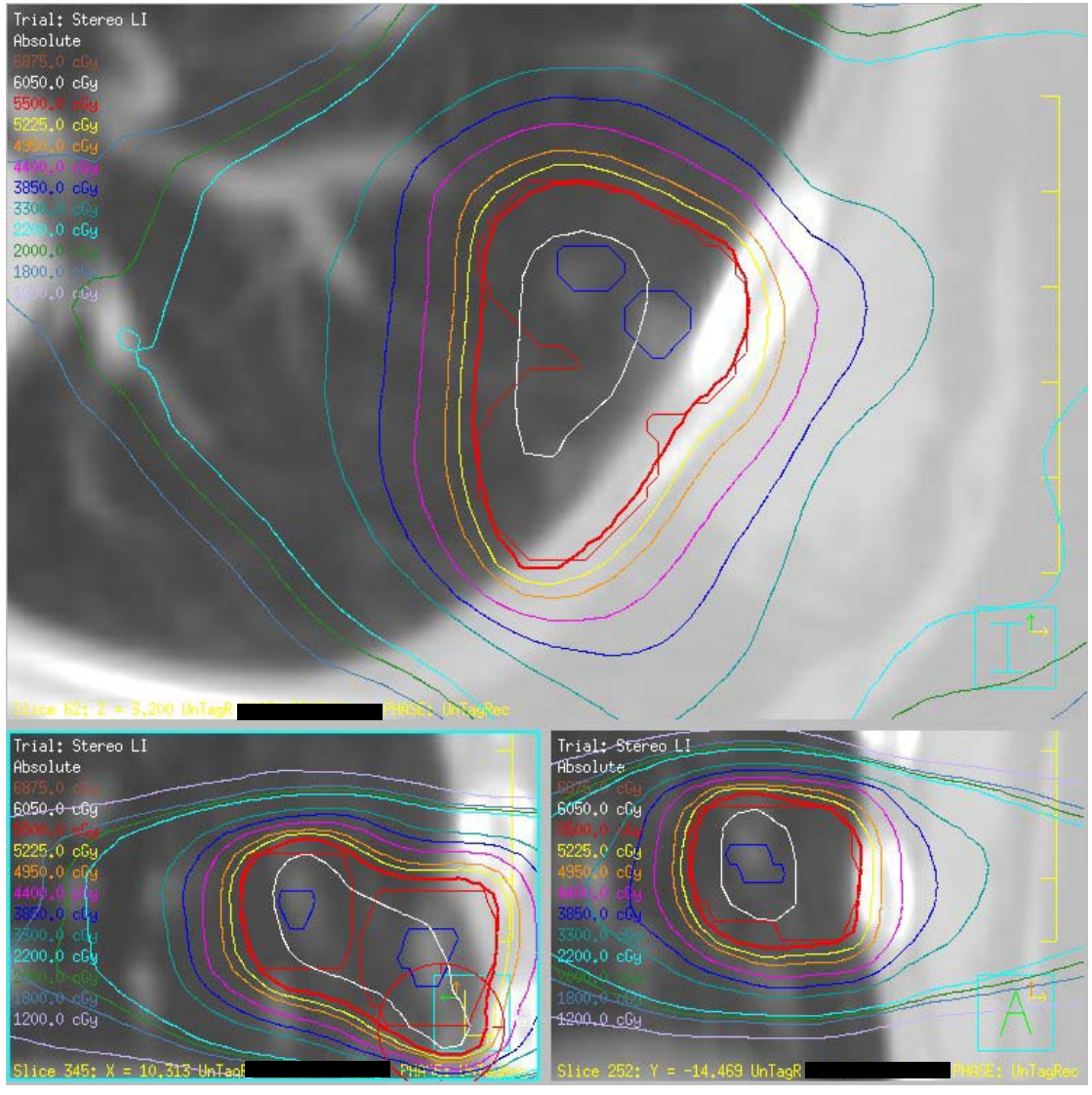
Too small lesions to detect on CBCT

CT

CBCT



Too small lesions…for dose calculation?



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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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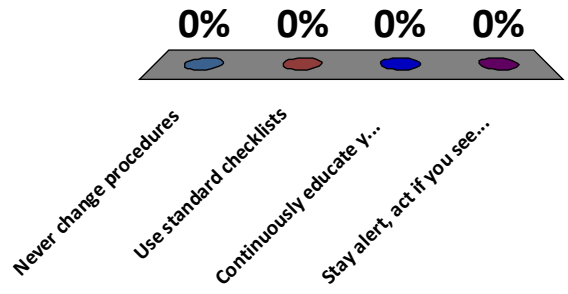
What is most important to keep your SBRT program safe?

A. Never change procedures
B. Use standard checklists
C. Continuously educate yourself
D. Stay alert, act if you see something strange and adopt procedures if needed



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Take home message

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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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