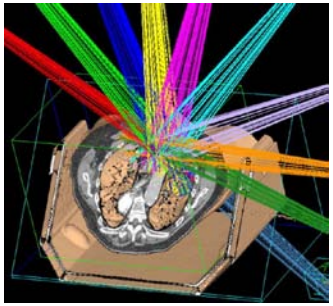
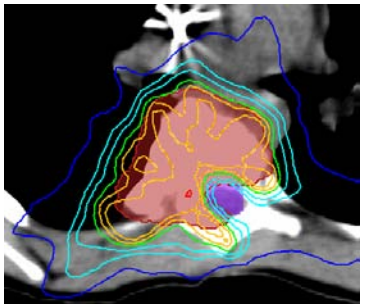
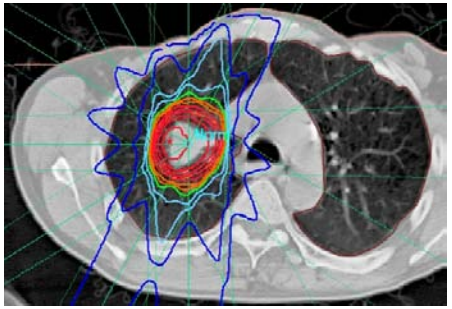
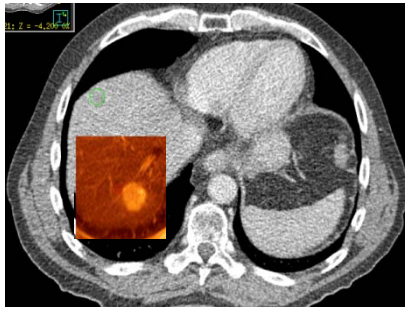
ESTRO

Implementation & Practice of Image-Guided Stereotactic Body Radiotherapy

30.8 – 3.9. 2015 in Dublin, Irland

Matthias Guckenberger, Dirk Verellen

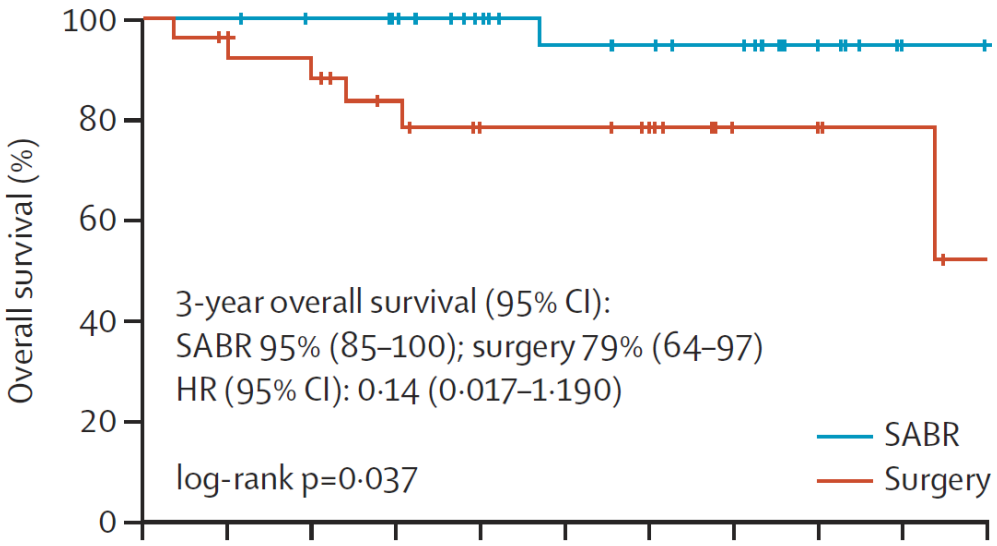
UniversityHospital Zurich

I believe …

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

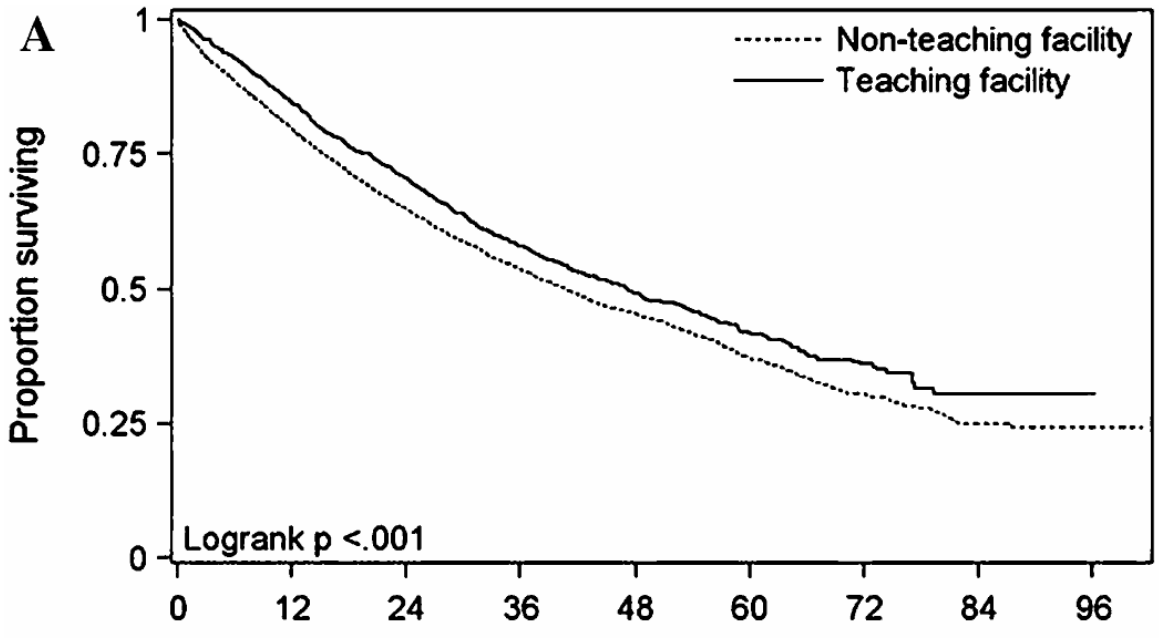
Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

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†*

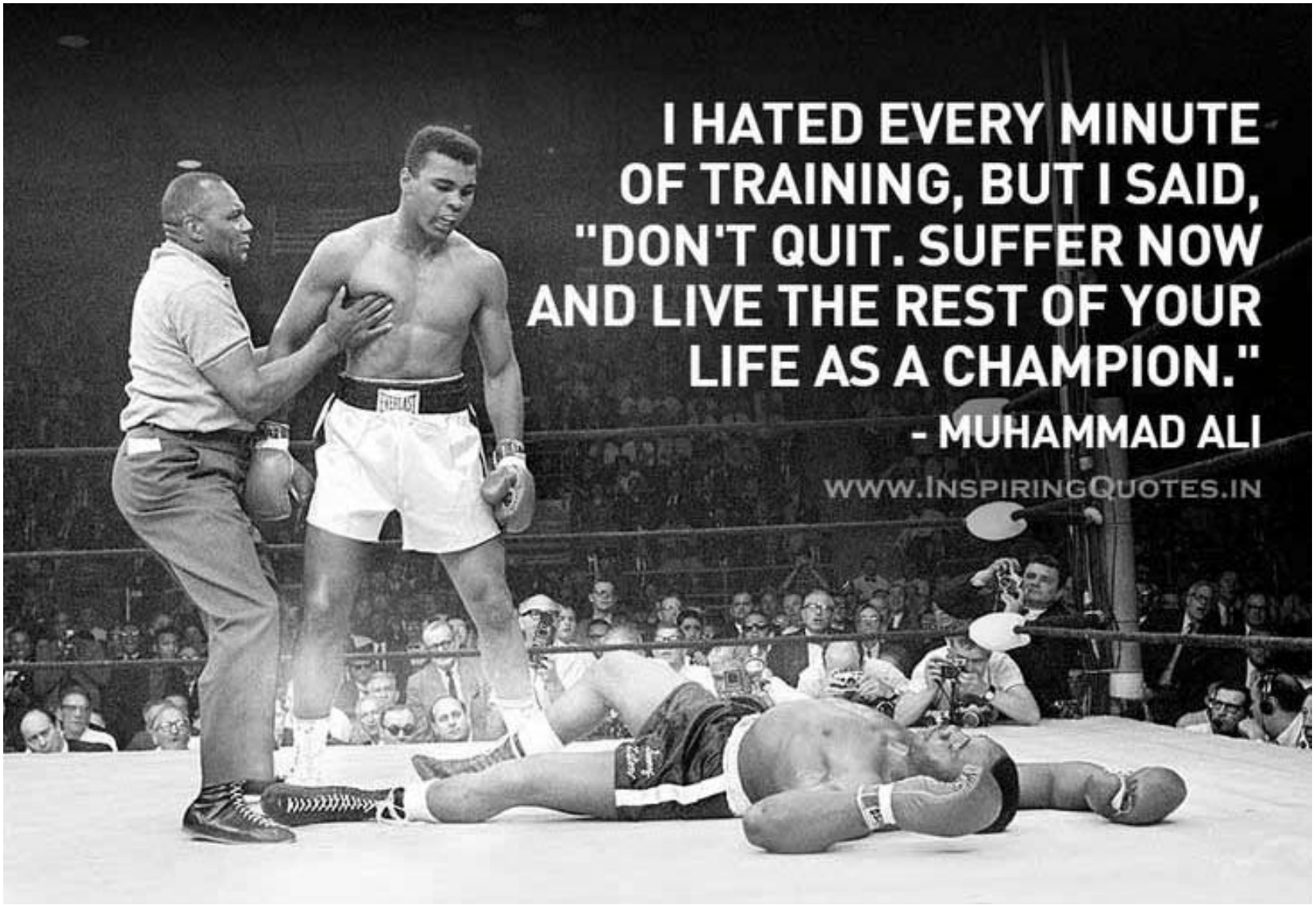


Lessons to be learned from surgery

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


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

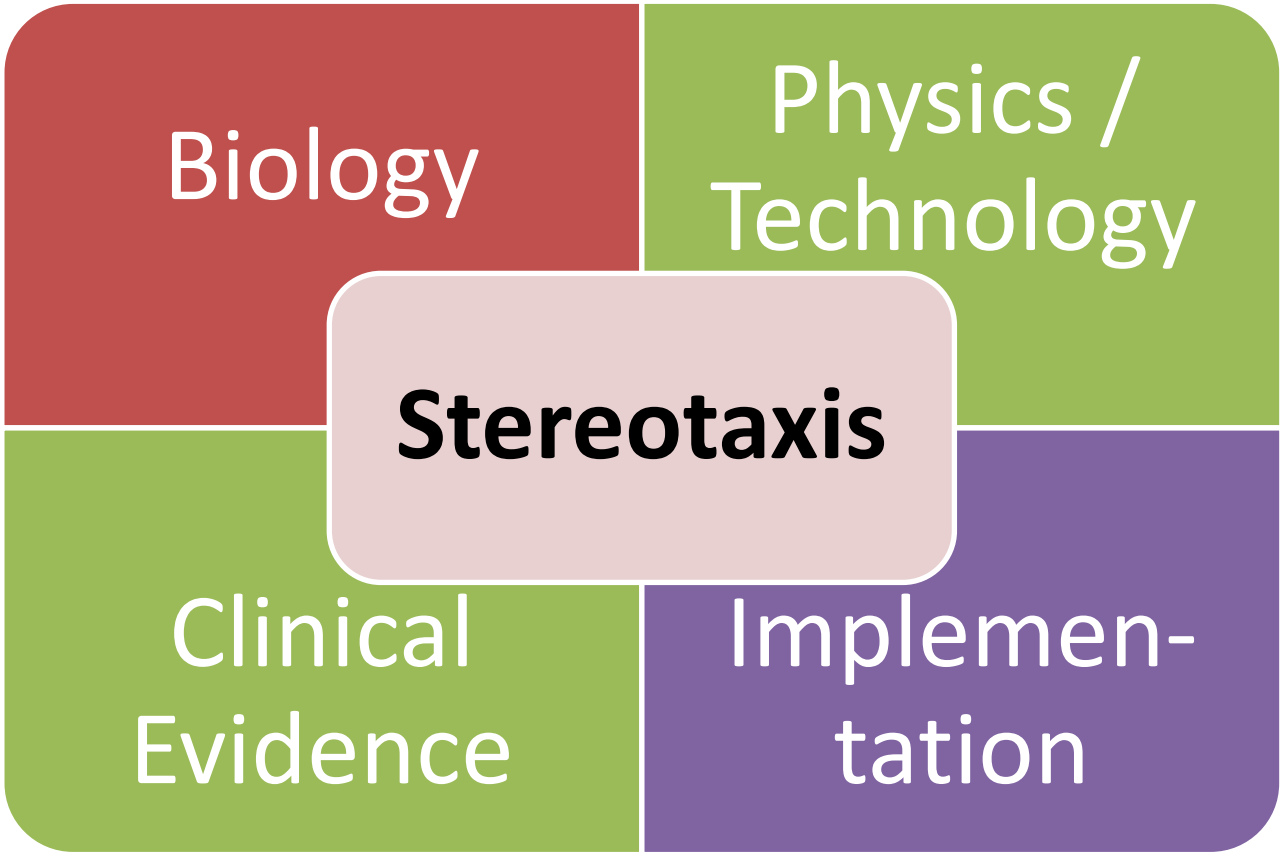
Morten Hoyer

Eric Lartigau

Suresh Senan

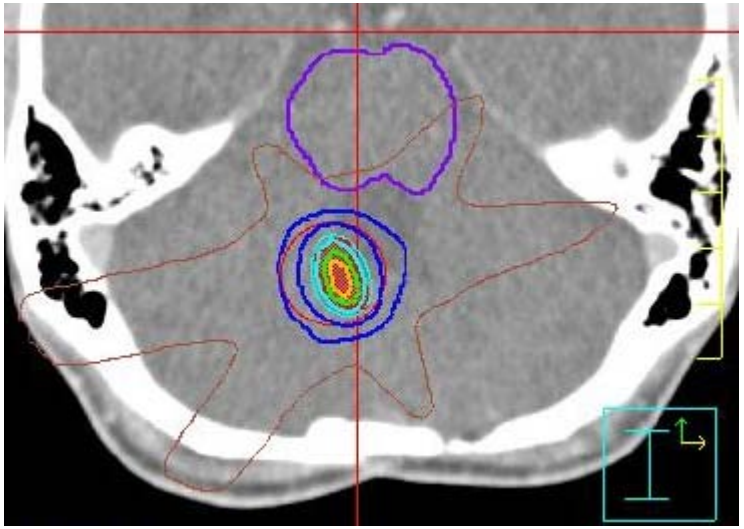
Alejandra Méndez Romero

Our program

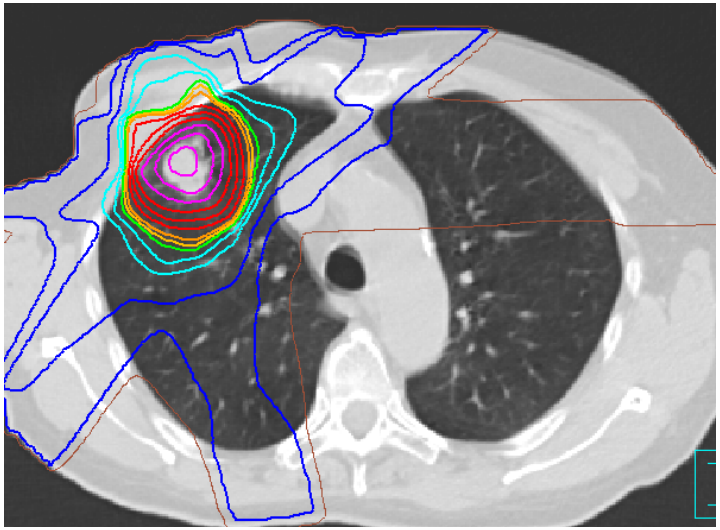

Biology
Physics / Technology
Stereotaxis
Clinical Evidence
Implemen-tation

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
- Re-irradiation
- Emerging indications

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: ***Tracking - Accuray***
		Practical split-session for SBRT lung: ***CBCT Approach-Elekta***
		Practical split-session for SBRT lung: ***CBCT Approach-Varian***

Interactive case demonstration and discussion

Course program

Tuesday and Wednesday afternoon:

Split-up sessions

1. Spine SBRT
2. Brain SRS
3. Liver SBRT
4. Physics in implementation of SBRT
5. RTT session

YOU CAN ATTEND 3 / 5 of these split up sessions

Course program

Thursday: Practical implementation

- Starting a SBRT program: a clinicians view 2x
- Starting a SBRT program: a physicists view 2x
- 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
- Christine Verfaillie

Teachers:

- Stephanie Lang
- Karin Diekmann
- Mischa S. Hoogeman
- Morten Hoyer
- Coen Hurkmans
- Eric Lartigau
- Suresh Senan
- Alejandra Méndez Romero

Lets have a lively course with lots of discussion!

Too quiet !

A bit too much!

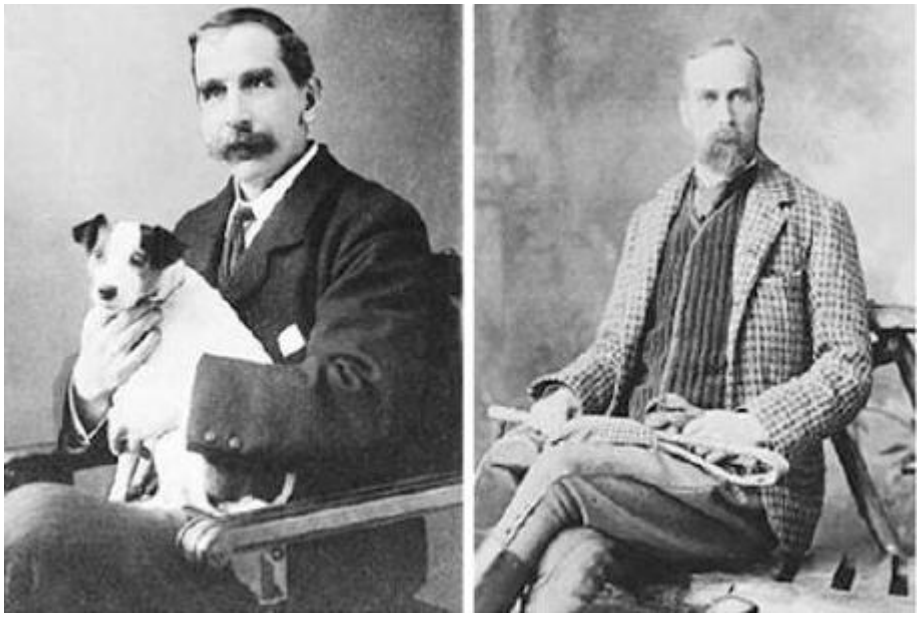
Department of Radiotherapy

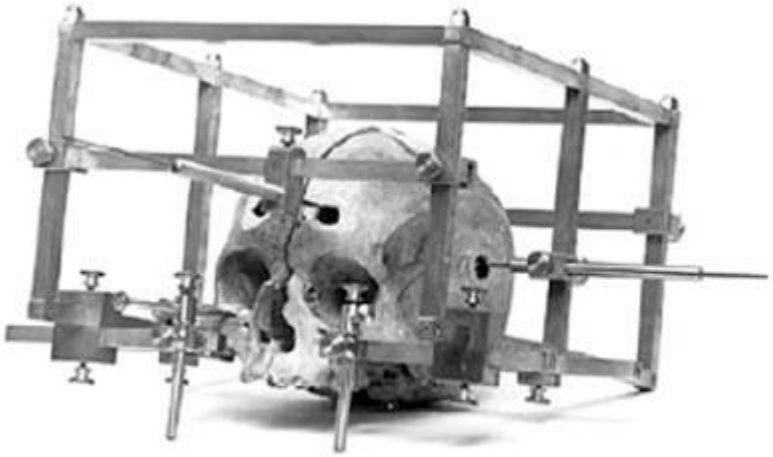
Medical University of Vienna / AKH Vienna

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

Karin Dieckmann

History of Stereotactic Radiotherapy I

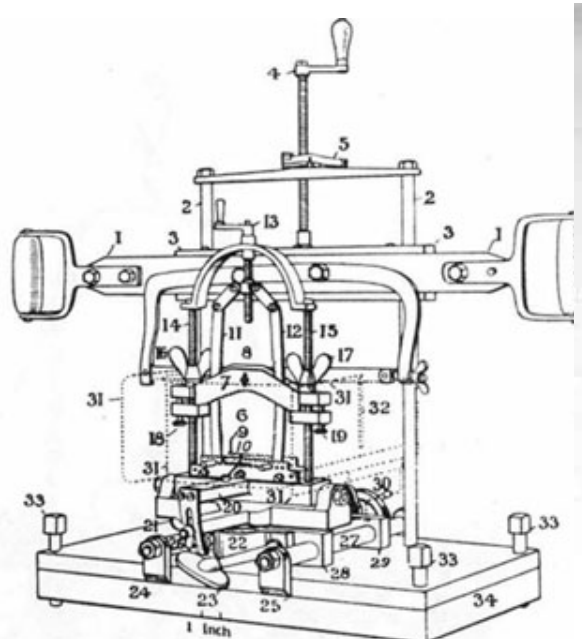


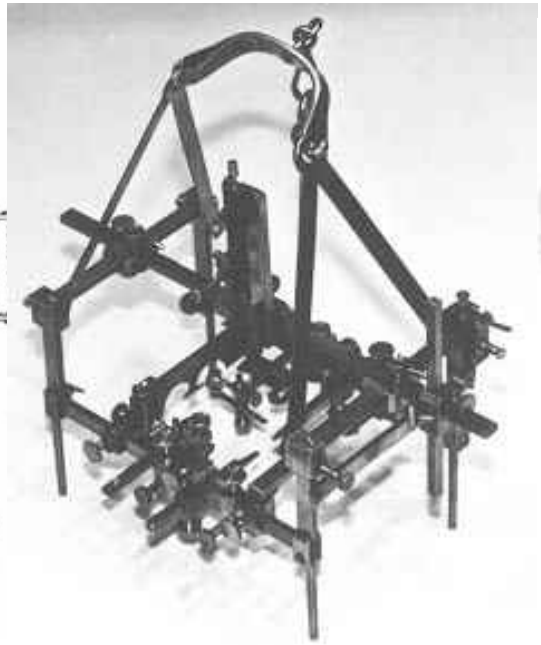


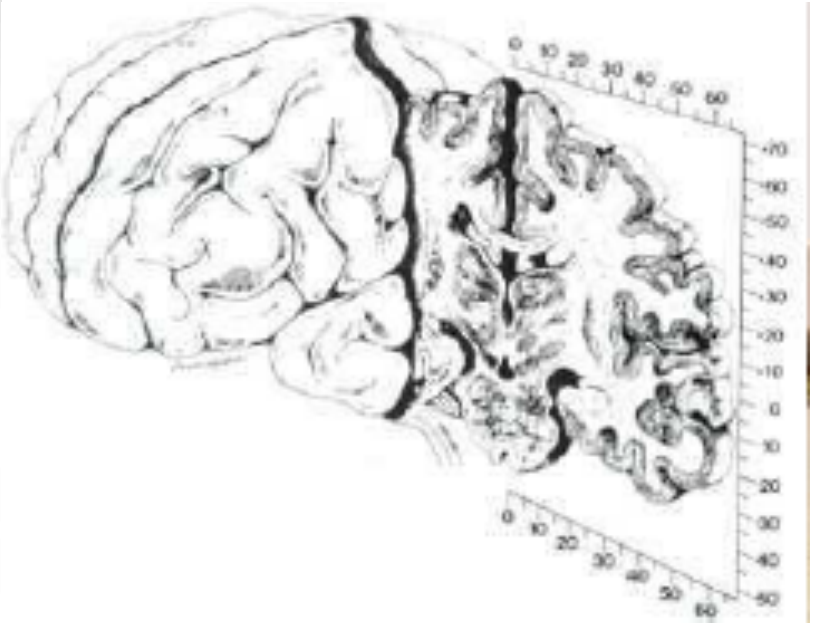
1908: Sir Victory Horsley and Robert H. Clarke

- 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 I





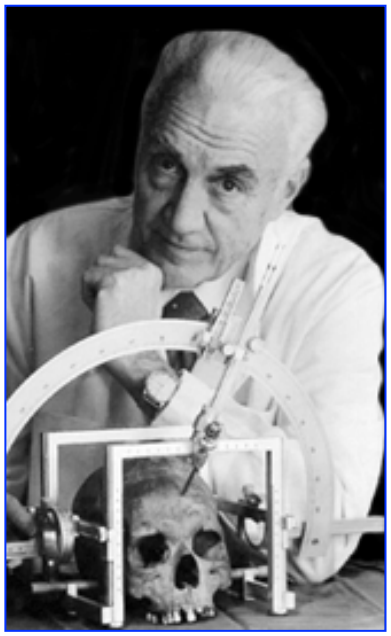


Problem: Relationship between bony landmarks and cerebral structures are unsure

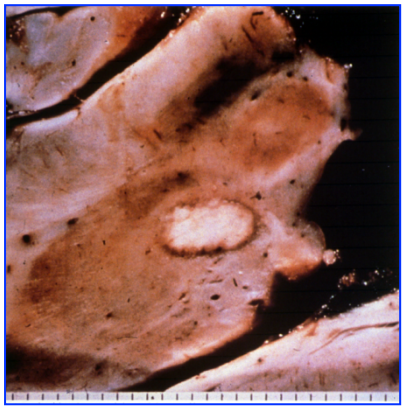
Targeting of **subcortical structures** only e.g. gasserian ganglion with foramen ovale as landmark

Imaging e.g.ventriculography → stereotactic atlas

History of stereotactic Radiotherapy II



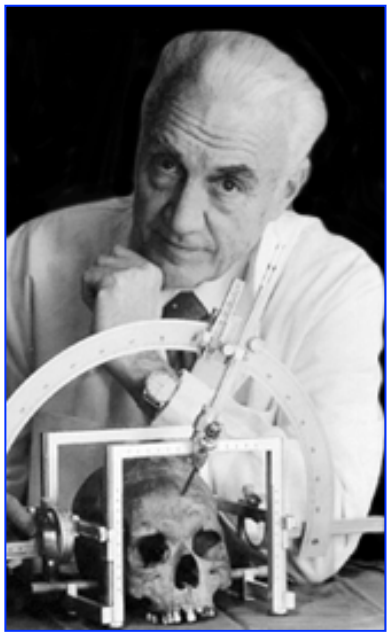
1951, using the **Uppsala University** **cyclotron**, Lars Leksell and the physicist and radiobiologist Borje Larsson, developed the concept of **radiosurgery**.



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.

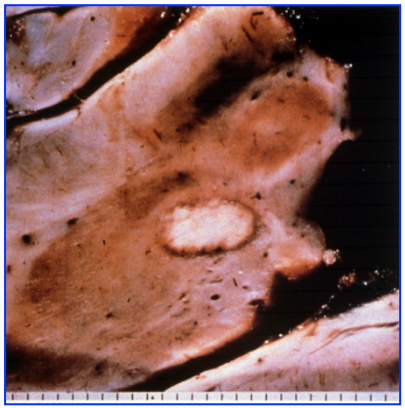
He called this technique **"strålkniven"** (ray knives).

History of stereotactic Radiotherapy II



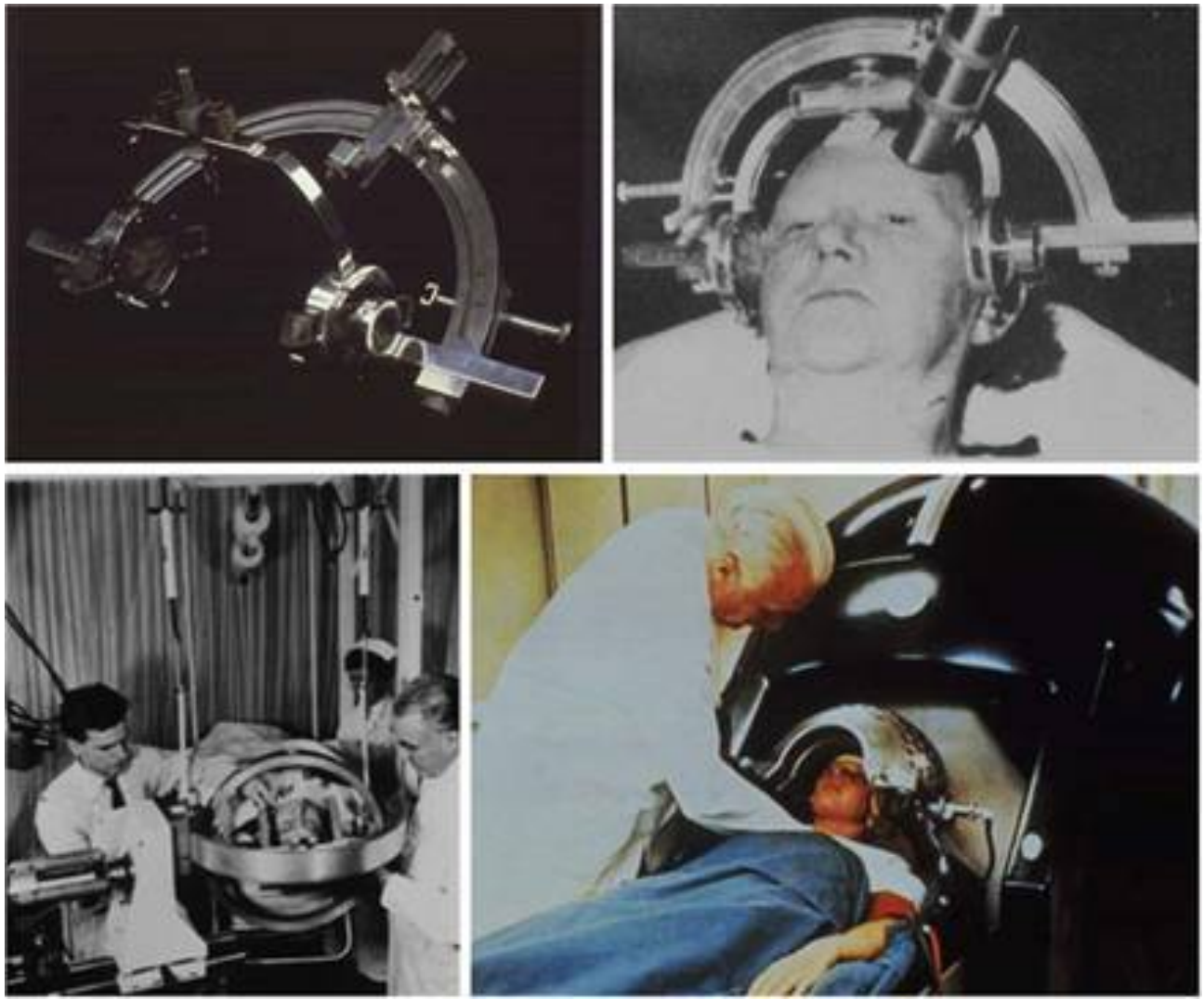
Thus, he achieved a new non-invasive method of destroying discrete anatomical regions within the brain while minimizing the effect on the surrounding tissues.

That 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 disorders.



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)

History of Stereotactic Radiotherapy II



1968: Gamma Knife Radiosurgery using Co-60 for treatment of functional disorders

Definition of stereotactic

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

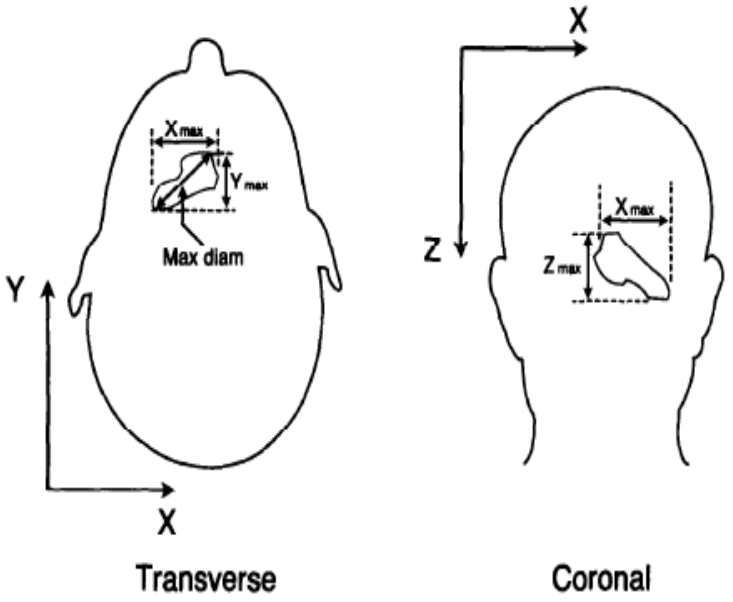
„tact“ (Latin: „To touch“)

Thus the literal meaning: „3-dimensional arangement to touch“

The Philosophy of

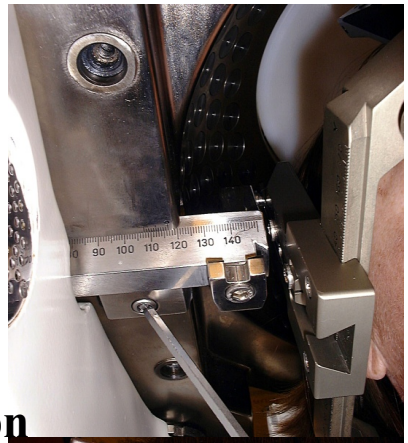
Stereotactic Radiosurgery:

Technique of **delivering high dose radiation** to a specific target while delivering minimal dose to surrounding tissue



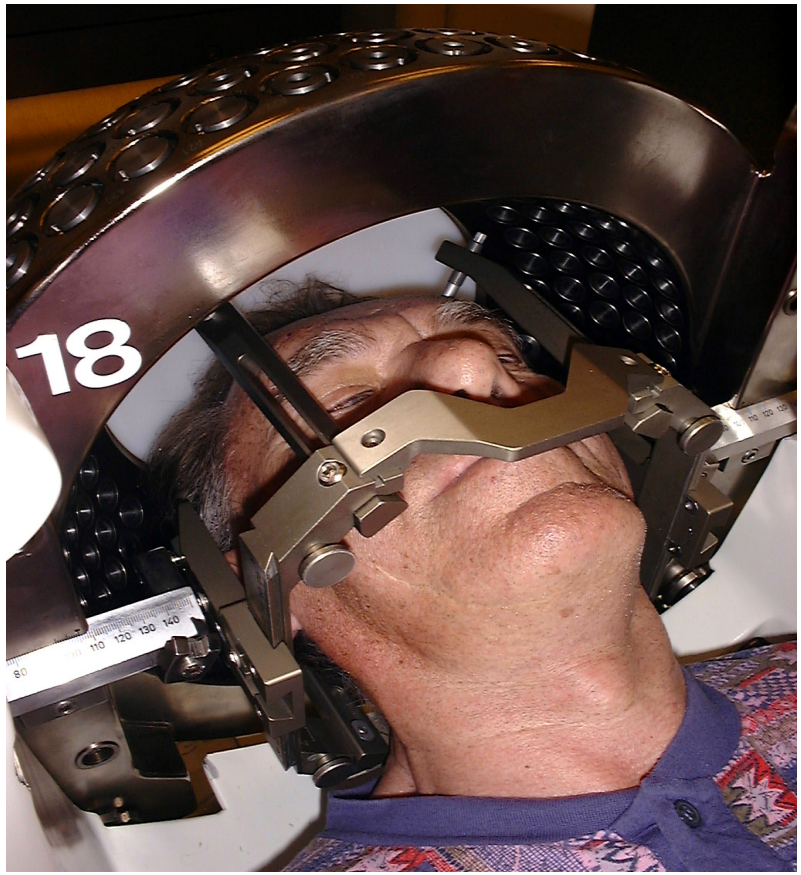
Frame-based stereotactic Radiotherapy

- 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



The target is placed in the center of the converging beams Gamma Knife

201 beams of CO^{60} pass through various sized holes (collimators“) in „helmet“

Frame-based stereotactic Radiotherapy at a LINAC

Since 1980:

LINAC based stereotactic RT brain

- LINAC most widely available

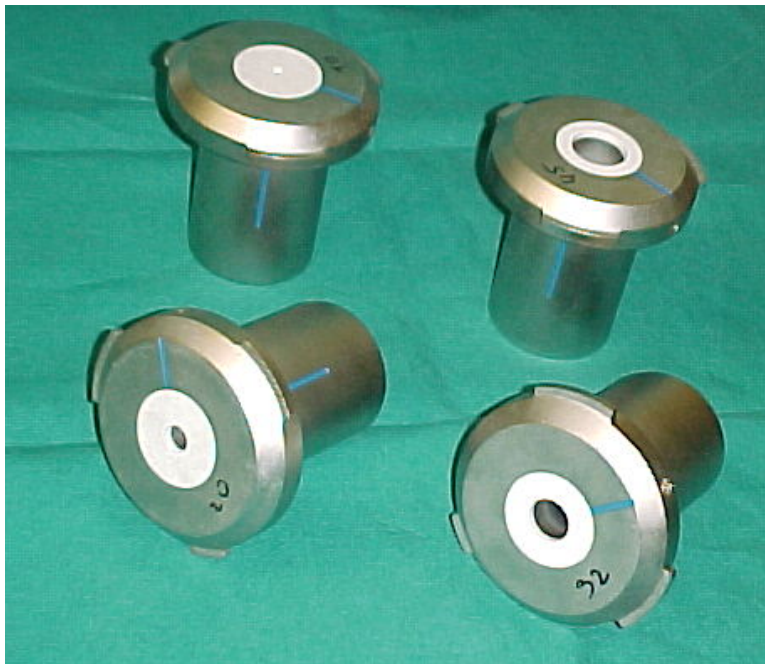
Majority are modified multi-use LINACS

Special soft ware

Special hardware

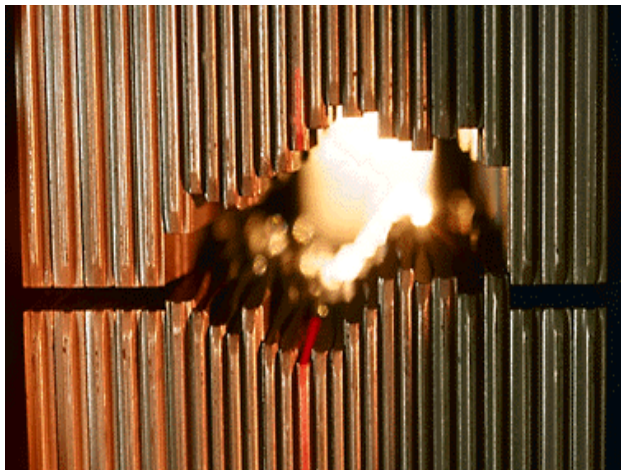
Some are specially designed for SRS

- ***Circular Collimators in several Ø: (10,13,16,20,24,28,32,36,40,45mm @ isocenter)***
- ***Treatment planning time consuming***
- ***Typical treatments: 1-3 isocenters with 4 - 7 arcs per isocenter.***



mMLC features

- *weight appr. 31 kg*
- *max. field size 10x10 cm²*
- *interleave leakage and transmission*
- *26 leaf pairs, 3 - 5.5 mm leaf width @ isocenter*
- Typical treatments encompass 1 isocenter with 8 - 12 static beams
- **Treatment planning process is fast (!)**



Frame-based Stereotactic Radiosurgery Positioning Accuracy

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

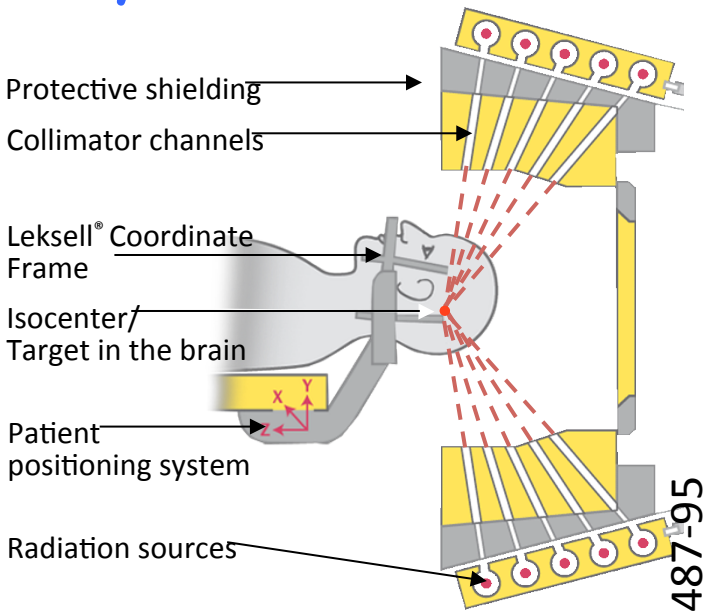
Heck B et al

Graf Chromic films densitometric measurements

X: - 0.014+/- 0.09mm

Y: 0.013+/- 0.09mm

Z: - 0.002+/- 0.06mm

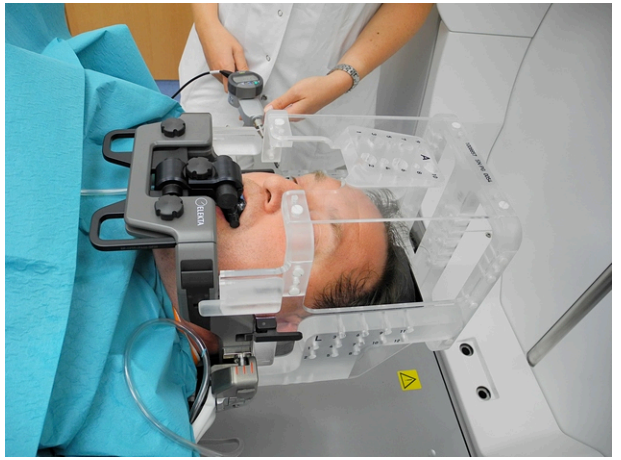


All measured data were within a sphere of 0.2mm radius

MRI-based target definition

X: 0.06+/-0.09mm

Y: 0.04+/-0.09mm



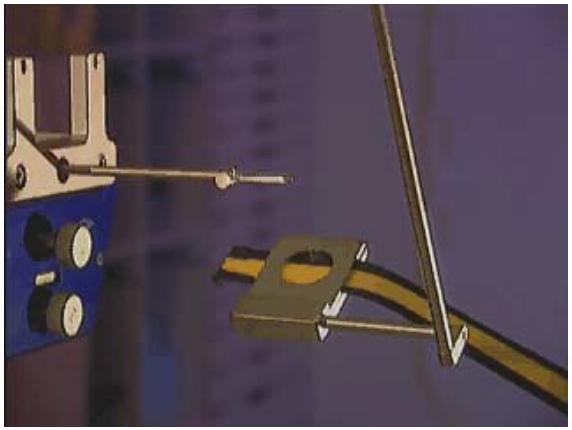
Med Phys 2007 Apr; 34(4): 1487-95

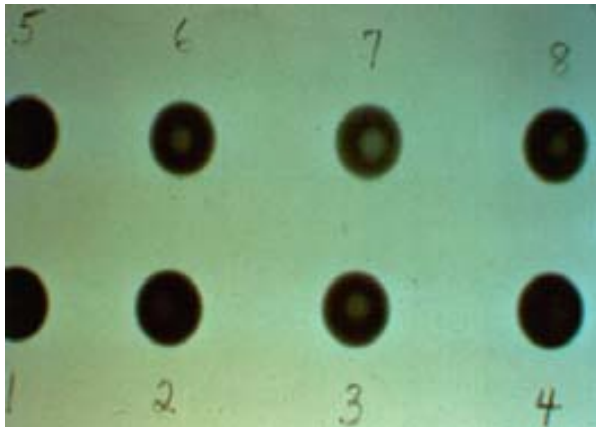
Winston/Lutz Medical Physicist

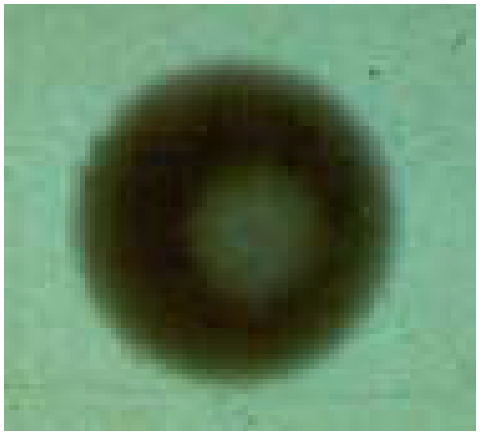
1986

- Published the first systematic study on radiosurgery
- System performance tests that established the localization and treatment delivery accuracies for LINAC radiosurgery treatments.

Projection of the ball centered within the field<0.5mm

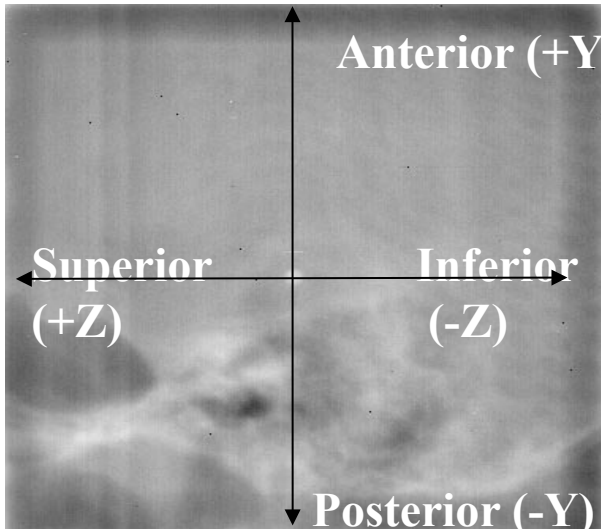


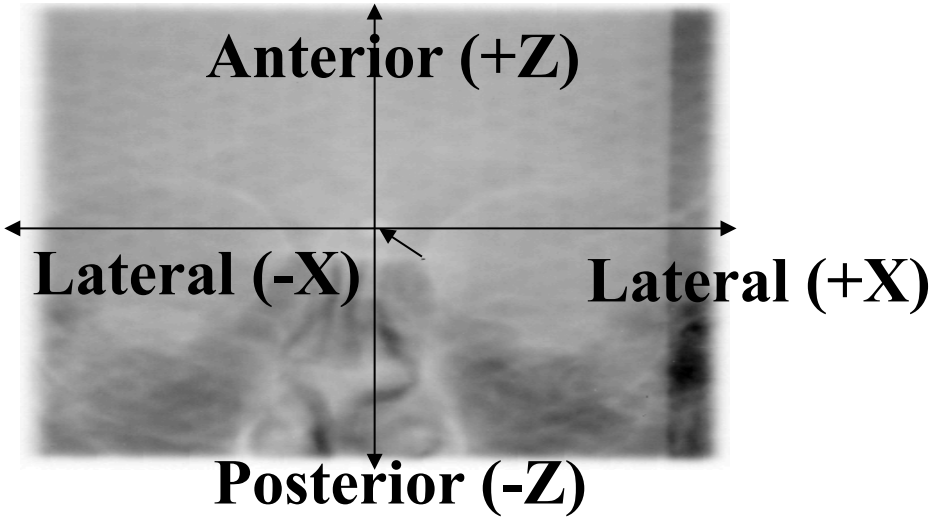




Accuracy of non invasive fixation systems 2D-2D image registration for verification set-up

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



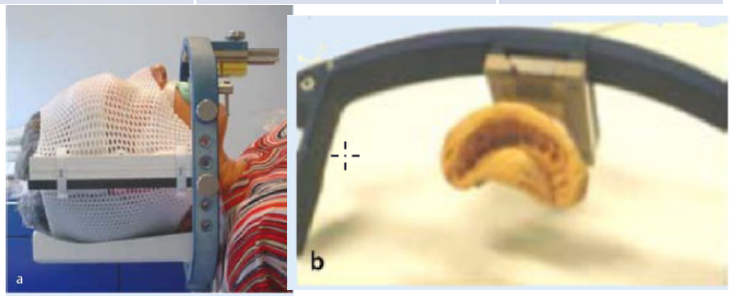


Accuracy of non invasive fixation systems

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

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



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

L = linac; G = Gamma Knife; MPD = median/mean peripheral dose; PD = peripheral dose; MCD = median/mean central dose, Med = median dose, NA = not applicable, RS = radiosurgery.

* When local control rate is actuarial, the 1-year figure is given.

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

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

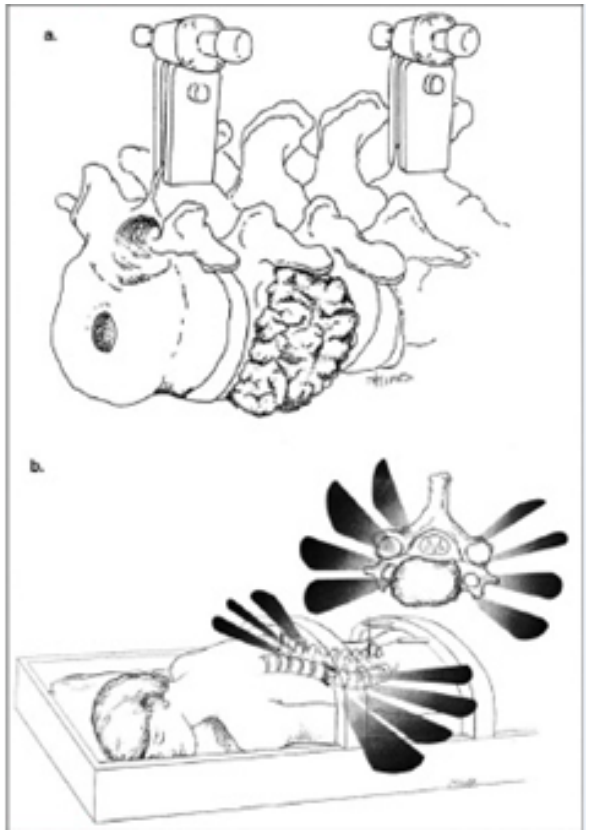
L = linac; G = Gamma Knife; MPD = median/mean peripheral dose; PD = peripheral dose; MCD = median/mean central dose, Med = median dose, NA = not applicable, RS = radiosurgery.

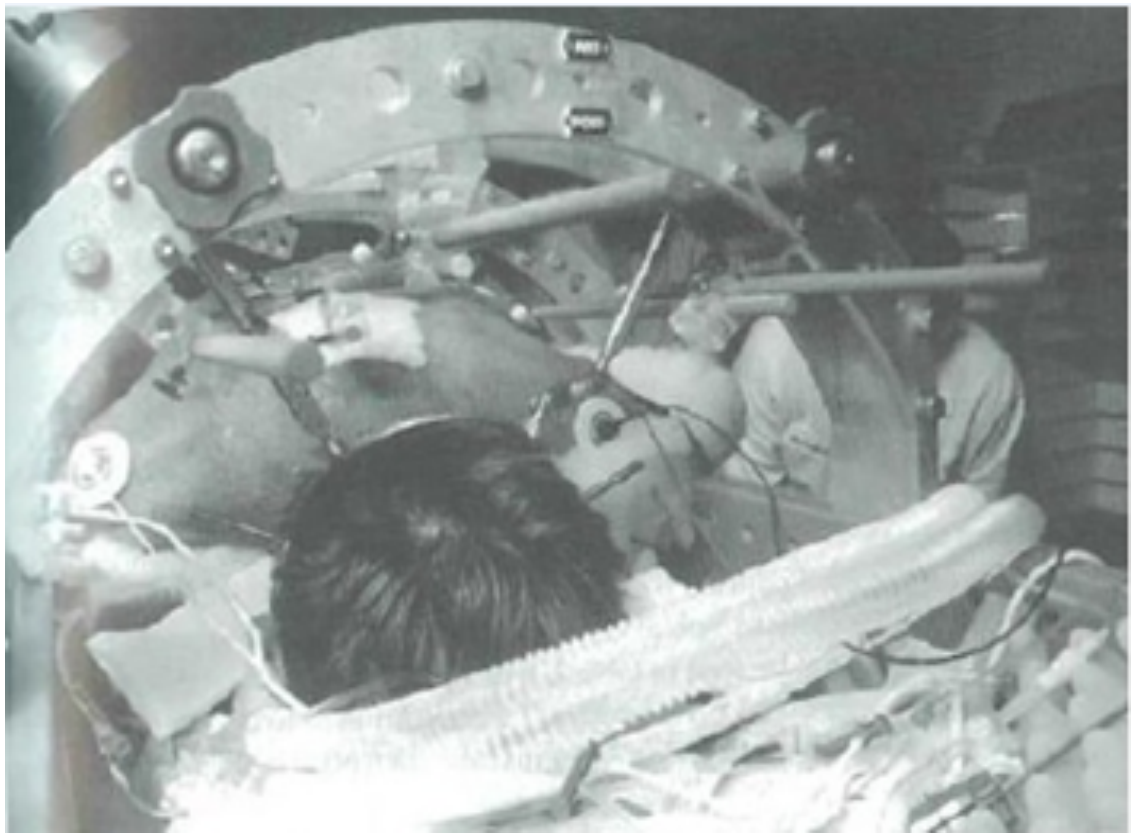
* When local control rate is actuarial, the 1-year figure is used.

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

Frames for fractionated extracranial /body stereotactic radiotherapy III

Hamilton Rigid Stereotactic Spine frame

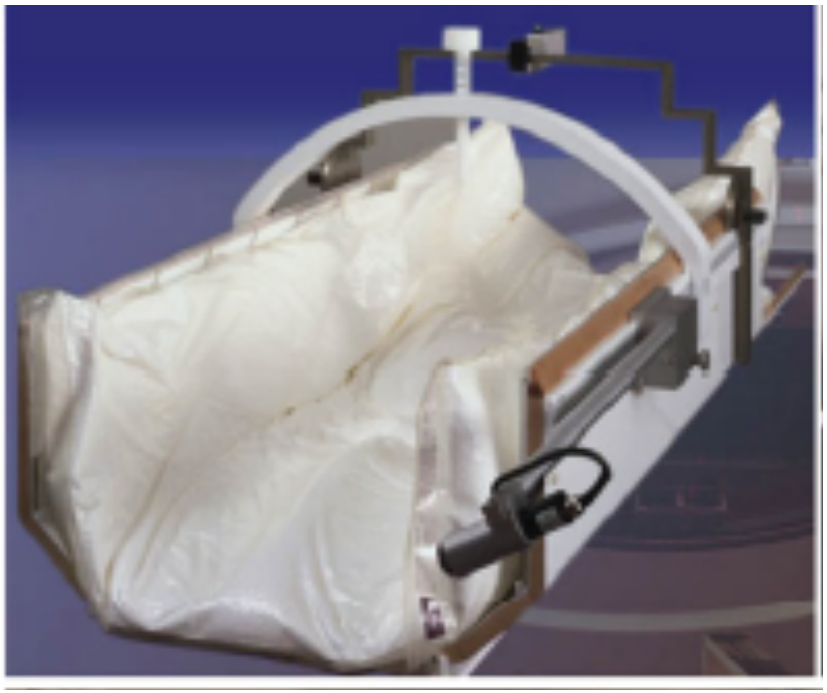


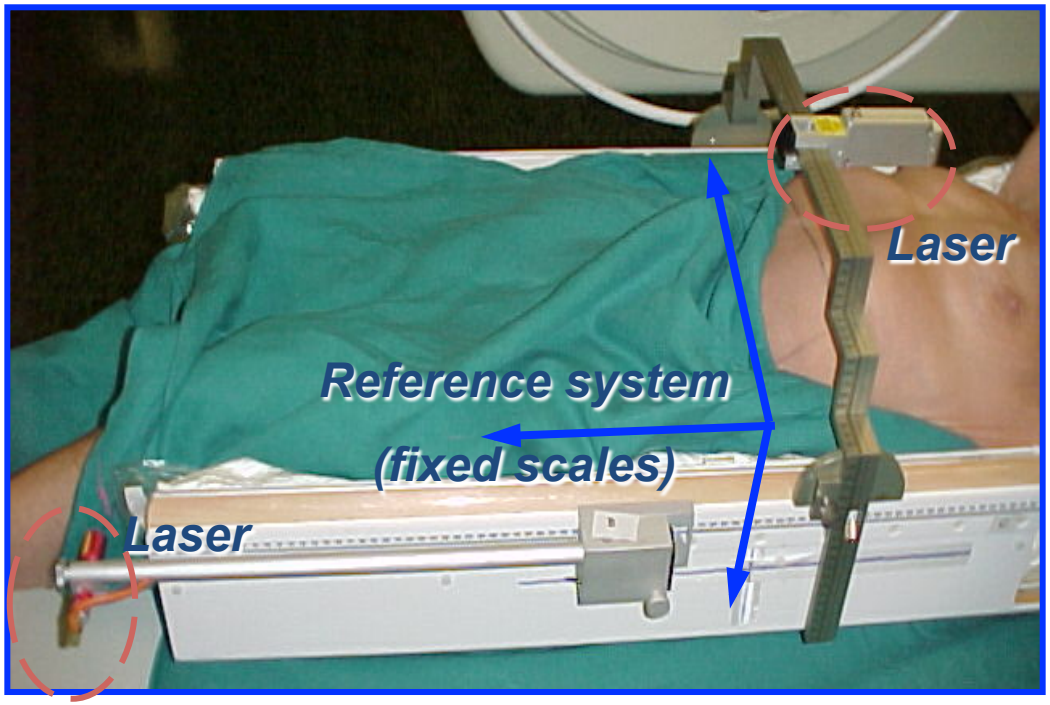


Hamilton et al. Neurosurgery 36 (2): 311-19, 1995
Hamilton et al. Stereotactic Funct NS, 1995

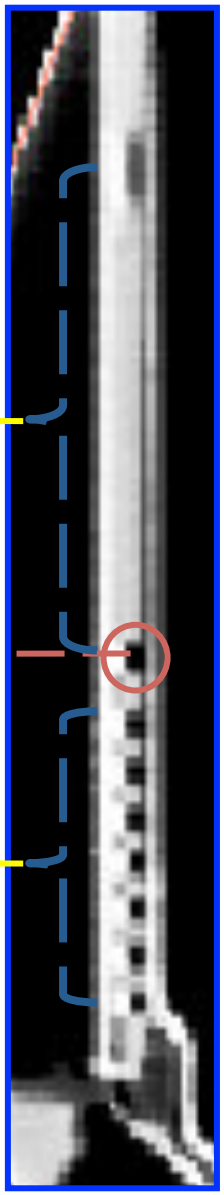
Extracranial Stereotactic Radiotherapy by Lax and Blomgreen

- 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

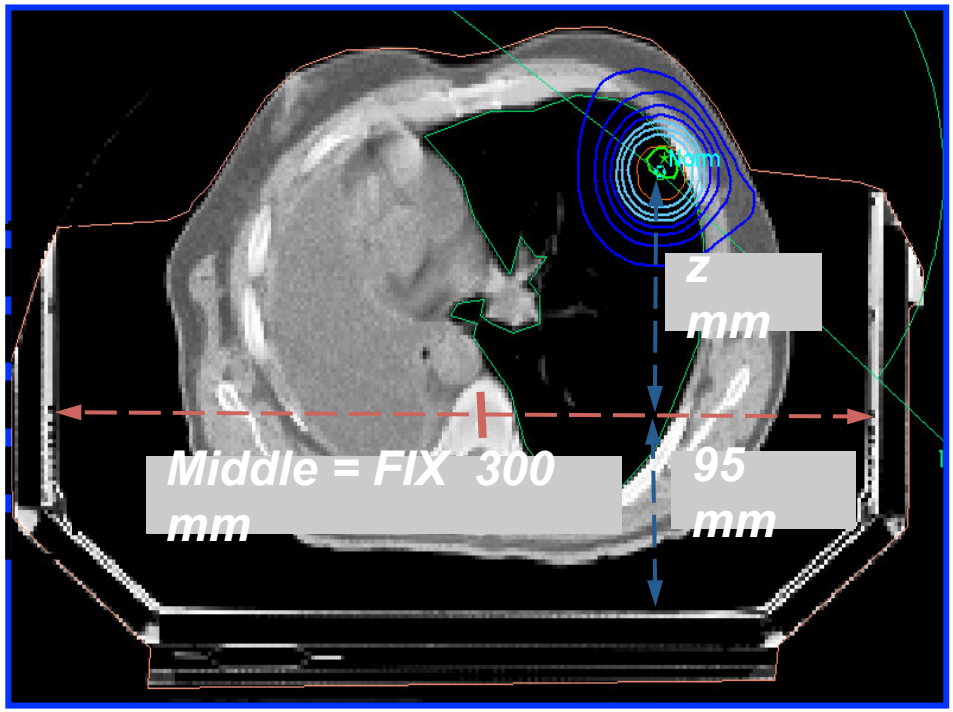
Y + 7 x 100 mm in cranial direction

ISOCENTER POSITION

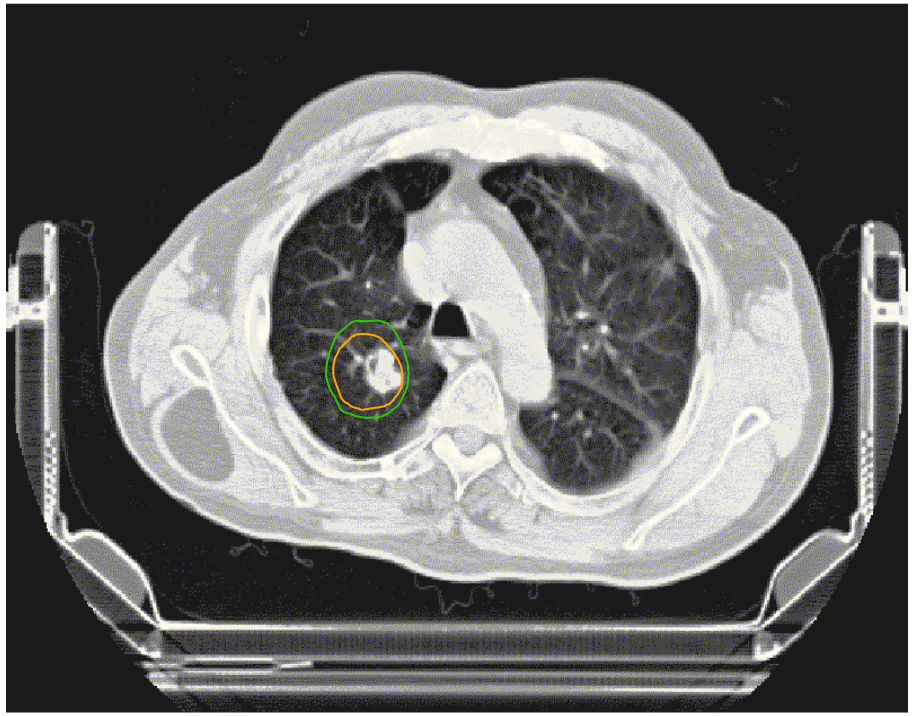
X = 300 ± x [mm]

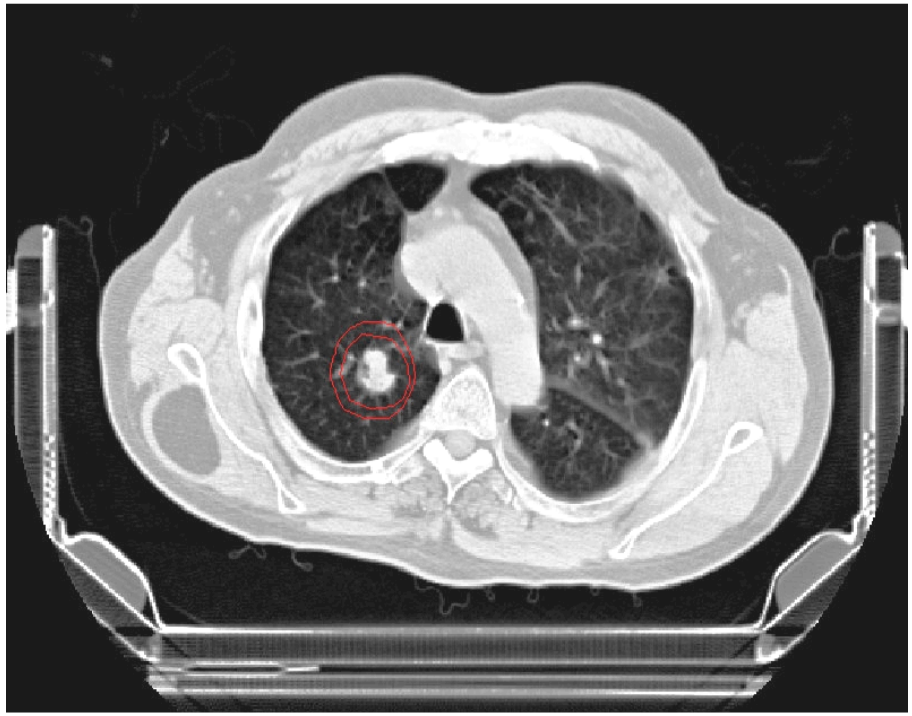
Y = y + (counts) x 100 [mm]

Z = ± z + 95 [mm]



Preliminaries for SBRT





- highly reproducible patient position
- highly reproducible target position
- effective immobilization of the patient
- 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

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

Historical data in Literature for Liver metastasis

Autor	No of Meta	Dose (Gy)	Local control	Median Follow up
Blomgren et al. 1998	21	20-45	95%	9,6 Mo
Sato et al. 1998	5	50-60	100%	10 Mo
Herfarth et al. 2001	56	14-26	76%	5,7 Mo
Wulf et al. 2001	23	28-30	83%	9 Mo
Schefer et al. 2005	22	36-60	K.A.	7 Mo
Katz et al. 2007	174	30-55	86%	14,5 Mo
AKH Wien	62	24-45	84%	13 Mo

Single Fraction Stereotactic Irradiation

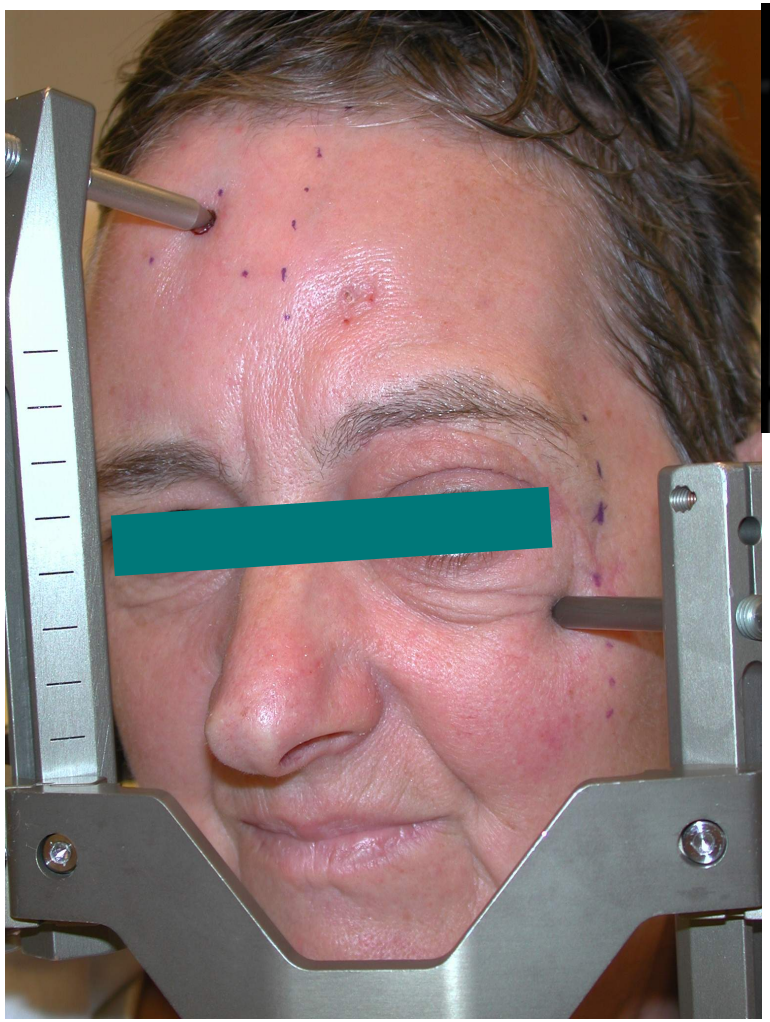
autor	Pts no	Follow up Months (median)	Dose	Results (median)
Nakagawa et al. 2000	22	2-82	18-25	OS 9,8 MO PD:n=1 NC: n=2 PR: n=7 CR: n=12
Hara et al 2002	23	3-24(13)	20-30	LC 13 months 63% < 30 Gy 88% >30Gy
Hof et al 2003	10	8,3-29,9 (14,9)	19-26	PD: n=2 act OS 80%; y act.OS 28%; 2 J act. LC 88,9%;1 J act. LC 71,1%; 2 J
Hof et al 2007	61		12-30	Actuarial OS 12months 78,4% 24 months 65,1% 36 months 47,8%

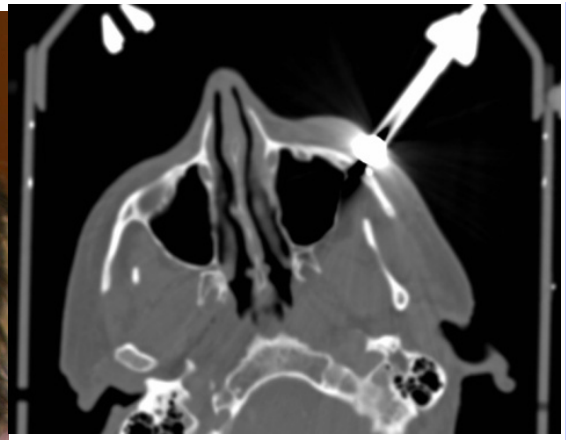
Fractionated Stereotactic Lung Irradiation

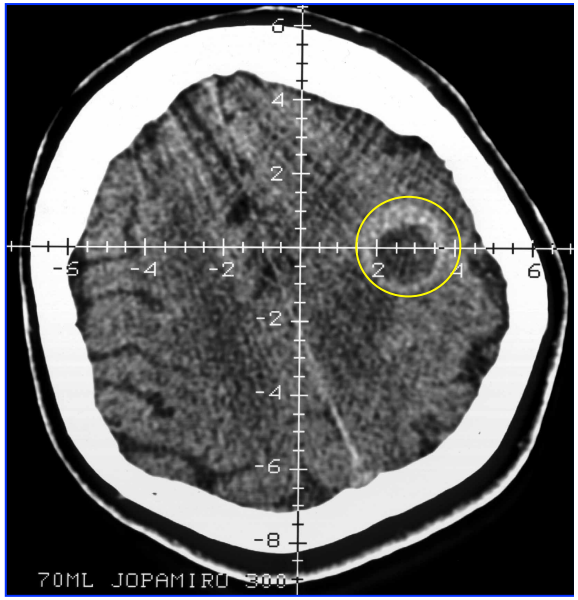
autor	Pts no	Follow up (median) months	Fractions no	Dose Gy	Results
Uematsu et al 2000	66	3-31(11)	5-15	30-75	PD: n=2 SD+CR=64
Wulf et al	27	2-33 (8)	3	30	Act.LC 76% 1y Act. LC 76% 2y
Timmermann et al 2003	27		3	8-20	PR 60% CR 27%
Nagata et al 2003	55Lung Tu T1:n=31 T2:n=15 T3: n=3 Meta: 10 12	2-51 (19)	4 4 5	40-48 48 60	PR 84% CR 12% OS 95%; ½ years OS 92%; 1 year OS 82%; 2 years OS 89% 1 y OS 65% 2 years

Invasive frame based Stereotactic RT

Work-flow



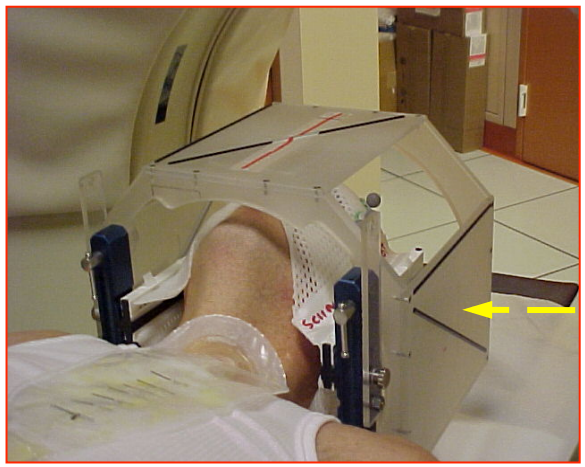


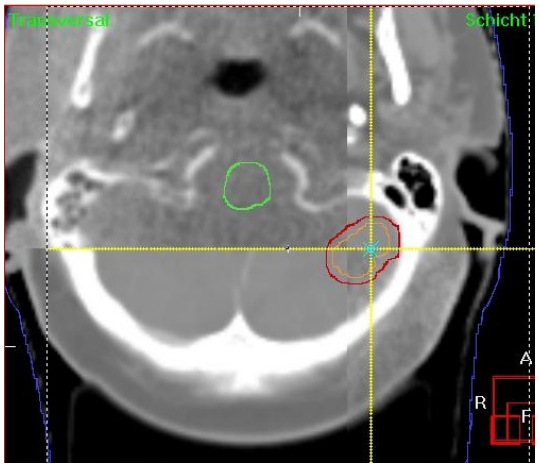


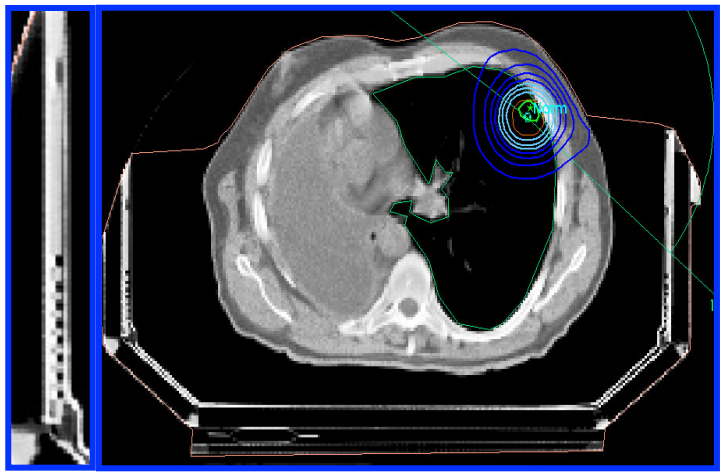
1. **Invasive frame**
2. Imaging (MRI/ MRI plus CT)
3. Target delineation/Treatment planning
4. Isocenter (s) positioning
5. RT-Treatment **„all in one“**

Non invasive frame-based Stereotactic RT

Work-Flow



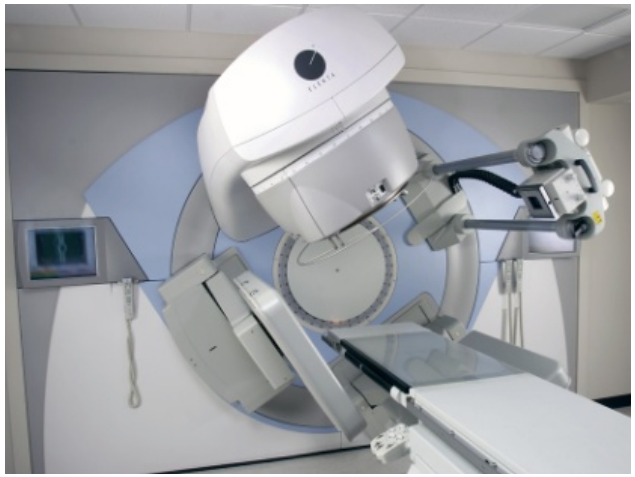


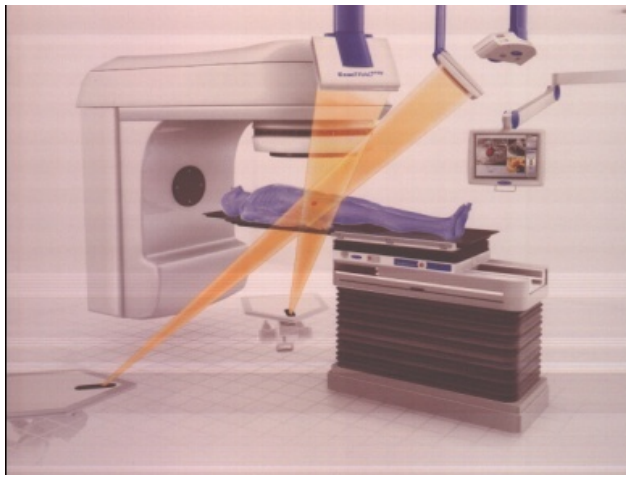


1. **Non Invasive mask/ body frame**
2. Localisation system
3. Imaging (CT/MRI image fusion)
4. Target delineation
5. Isocenter (s) positioning
6. Control CT
6. RT-Treatment a few days after the planning CT/MRI

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

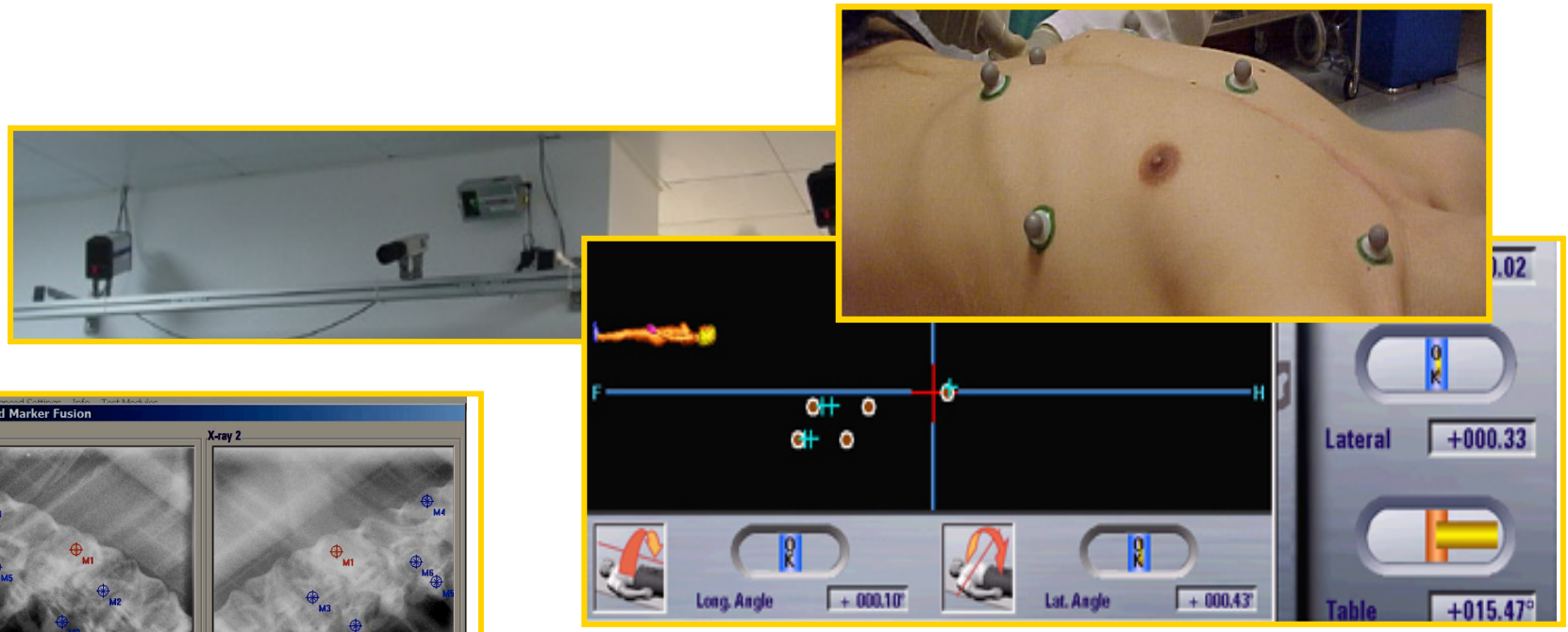
Implementation of IGRT systems for localization at the LINACs





Frame-less Alternatives

- External marker tracking and vacuum fixation



- **Internal marker tracking and vacuum fixation**

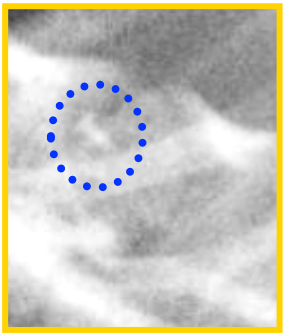
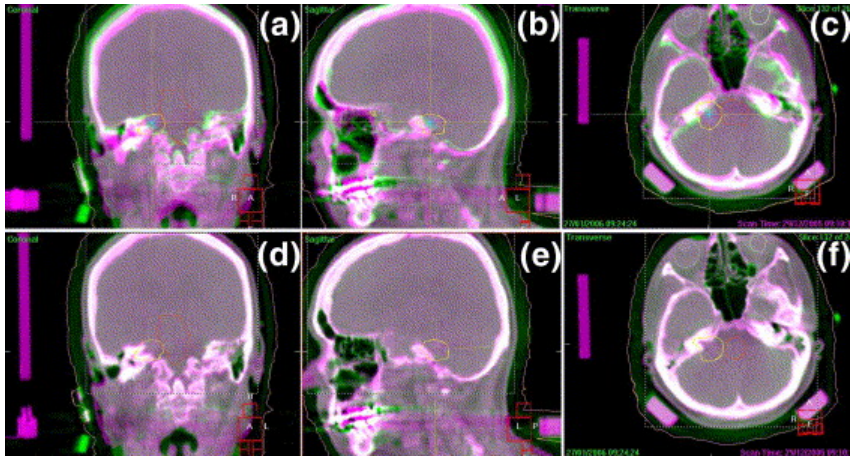


Image guided frame-less Stereotactic Radiotherapy

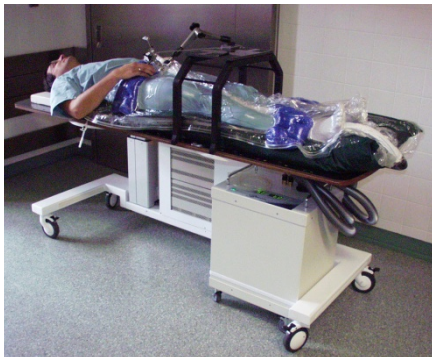
Replacement of the stereotactic systems with external coordinates for patient positioning by **direct imaging** before the treatment and **online correction**



Boda-Heggemann 2006

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

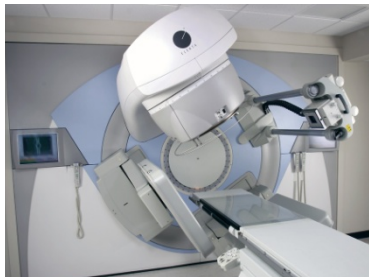
Image Guidance for SBRT

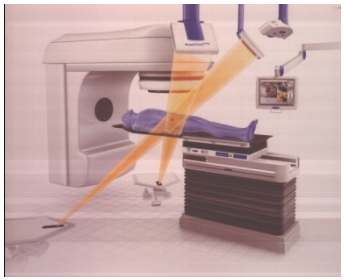


- Challenges for Liver and Lung
  - Small margins vs. respiration

  → **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"
  - ➢ IGRT technology contributed to simplify logistics for SBRT

„get the patient from the CT to the linac"





Indications increased for SBRT

- Lung tumors/ Lung metastasis
- Liver metastasis
- Spinal cord
- Bone metastasis (oligometastasis)
- Paravertebral lesions
- Pancreas
- Adrenal glands
- *Re-irradiations*

A Survey of Stereotactic Body Radiotherapy Use in the United States

Hubert Pan

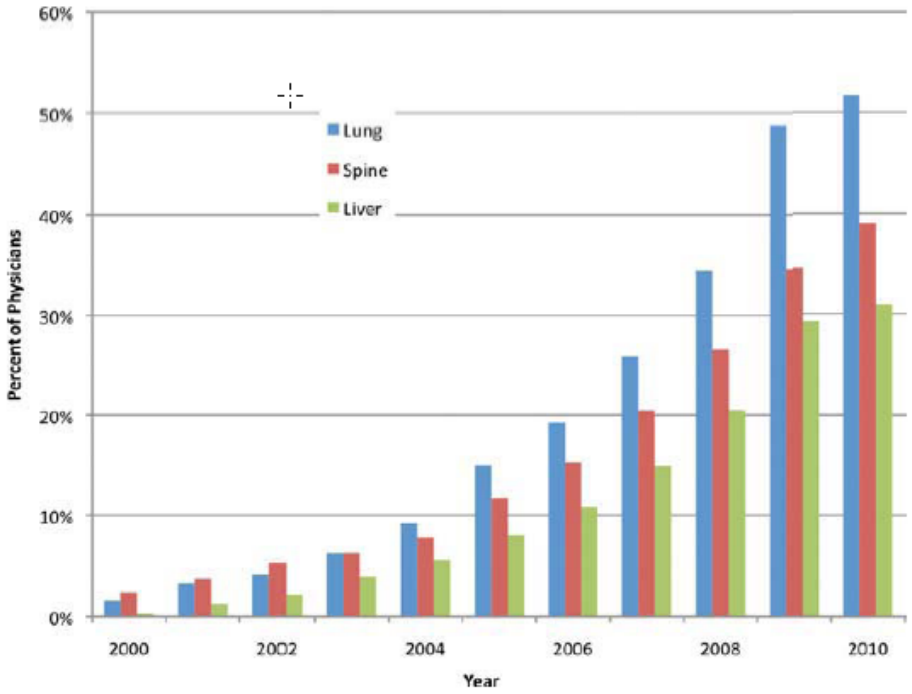


Figure 4. Cumulative adoption of stereotactic body radiotherapy is shown for the 3 most common disease sites treated: lung, spine, and liver.

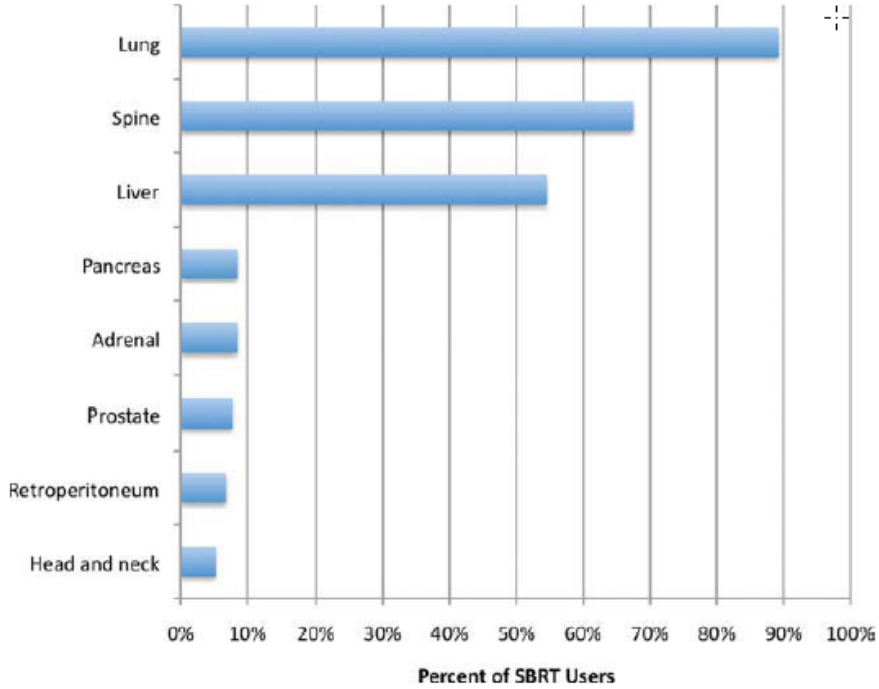
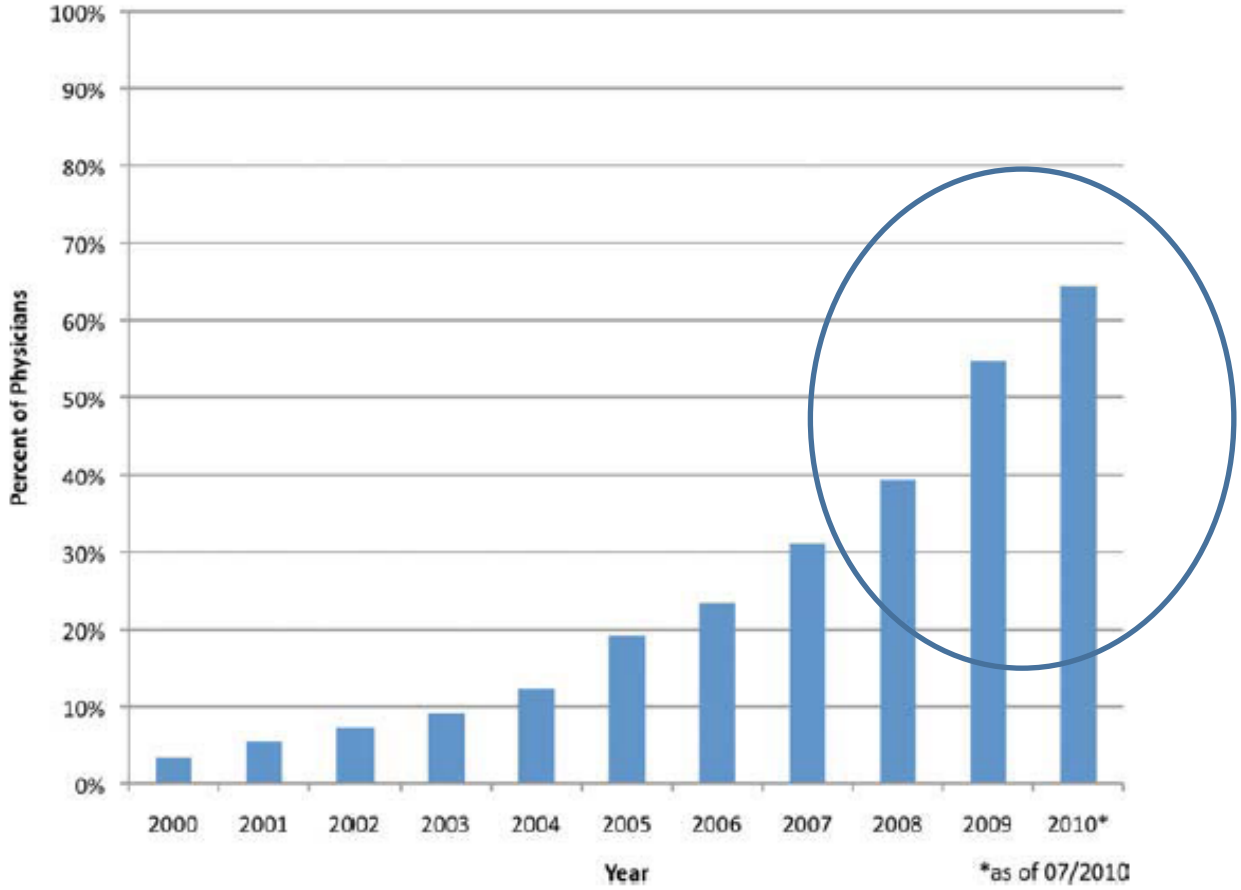


Figure 5. Disease sites treated by stereotactic body radiotherapy (SBRT) users who responded to the survey are shown.

A Survey of Stereotactic Body Radiotherapy Use in the United States

Hubert Pan

> 1300 physicians



Reasons for adopting SBRT are:

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

Cancer October 1, 2011

Workflow for SBRT

Patient positioning

Organ movement

Imaging CT/PET-CT/MRI

Image fusion

Target delineation

Treatment plann

Positi ent

- B
- Tu set-up

Positioning /movement control of the tumor before and during and after RT

Take care of intrafraction motion

Preparation for treatment planning

Planning

RT-Performance

Frame-based vs Frame-less SRS
Invasive vs Non-invasive

- 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**

- Positioning in a mask system with **real time imaging** control before each treatment
- Mask system relocable used **for more than one fraction**

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

- 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 volumes can be treated

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

ESTRO 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

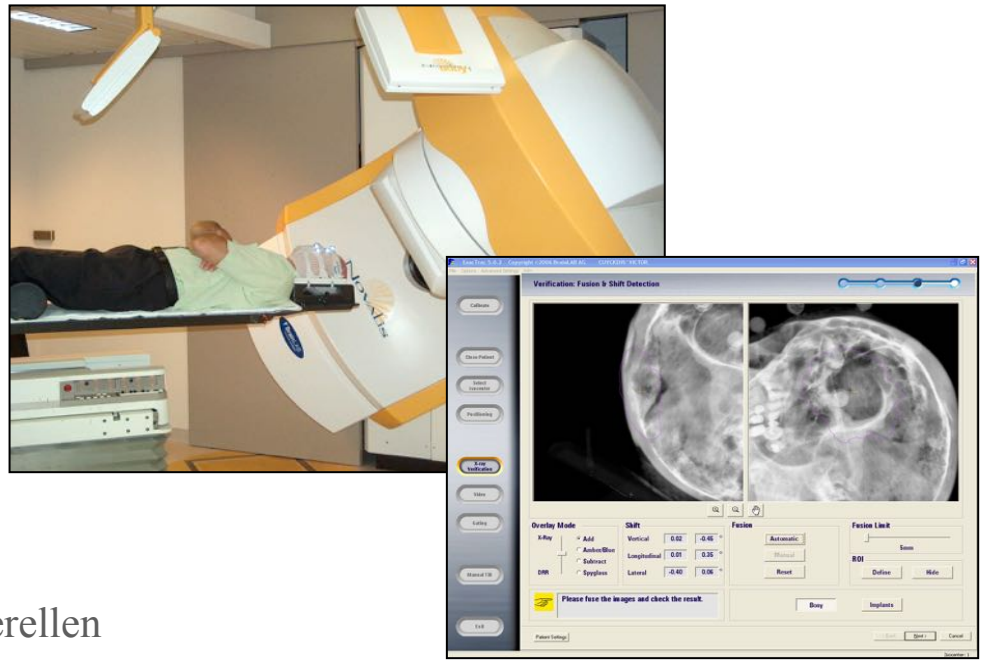
ESTRO School

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.

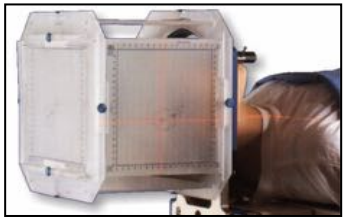
To frame or not to frame …

- 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

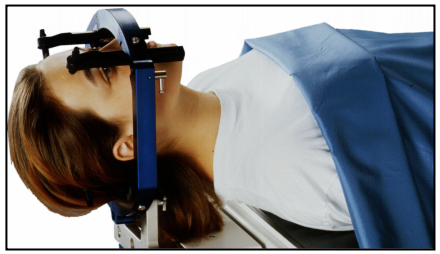
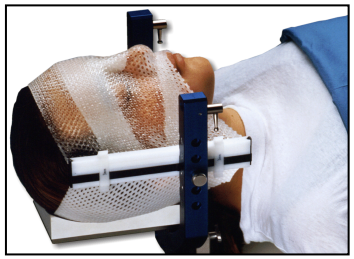


Some definitions

- 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

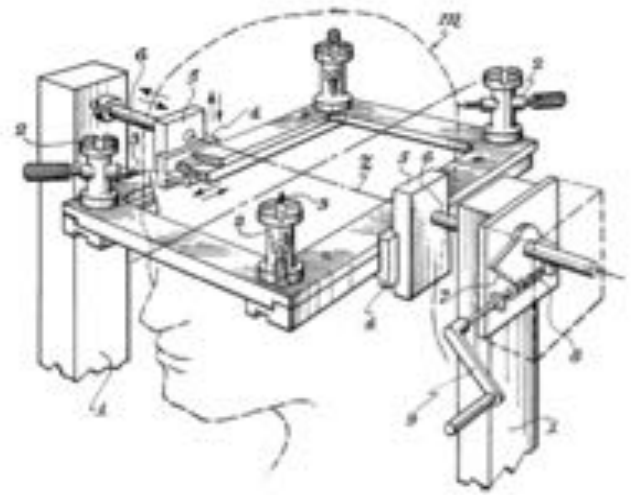



- Invasive versus non-invasive
  - Whether the patient is rigidly fixed to the stereotactic system using invasive techniques or a ‘patient friendly’ immobilization system is used allowing multiple fractions

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

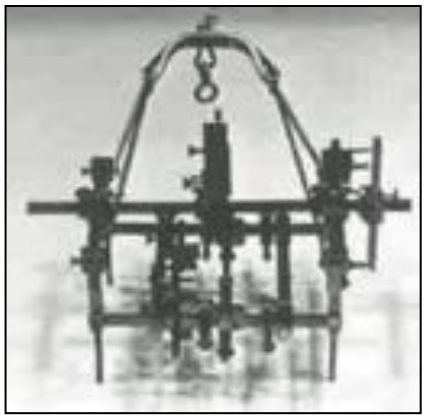
A short history of intracranial SRS

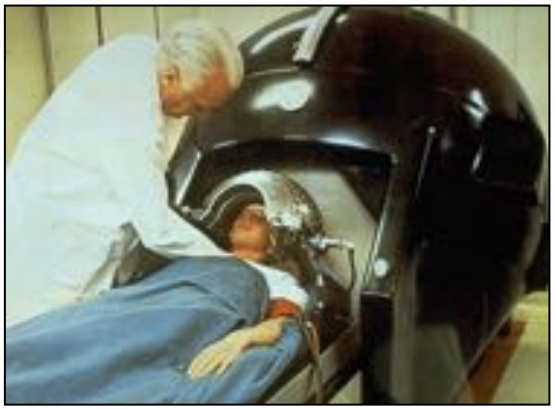
- **1908:**
  - **Robert Henry Clarke and Victory Horsley:** Stereotactic technique based on the reproducibility of the relationships between landmarks on the skull (external auditory canals, midline) and anatomical structures within the brain
- **1950s:**
  - **Lars Leksell:**

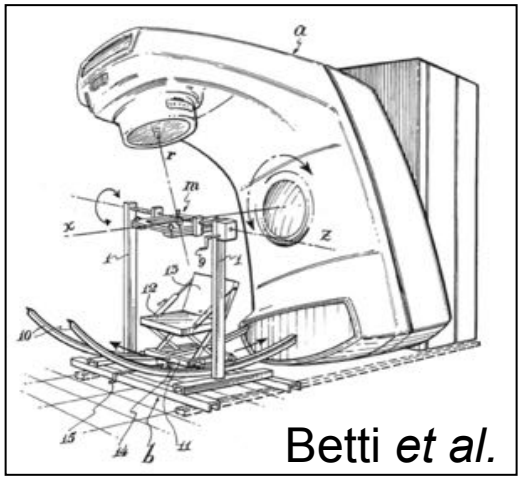
    Experiments with 250 kV rotating X-ray source (1951) and stereotactic proton therapy (1955)
- **1967:**
  - **Lars Leksell:**

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

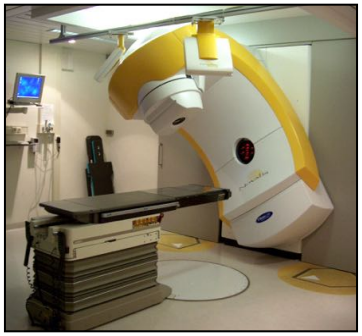
    CT-localization and linac-based SRS







Mechanical accuracy, in phantom!

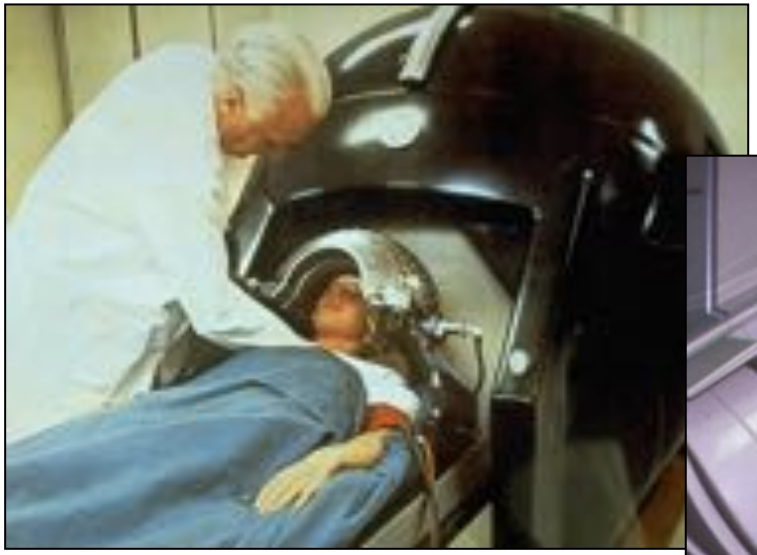


	Mechanical accuracy	Overall treatment accuracy
Gamma Knife Perfexion♮	**0.30 mm**	**0.93 mm**
Dedicated Linac: Novalis	**0.31 mm**	**0.50 – 1.5 mm**
Cyberknife*	**0.50 mm**	**0.85 mm**

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

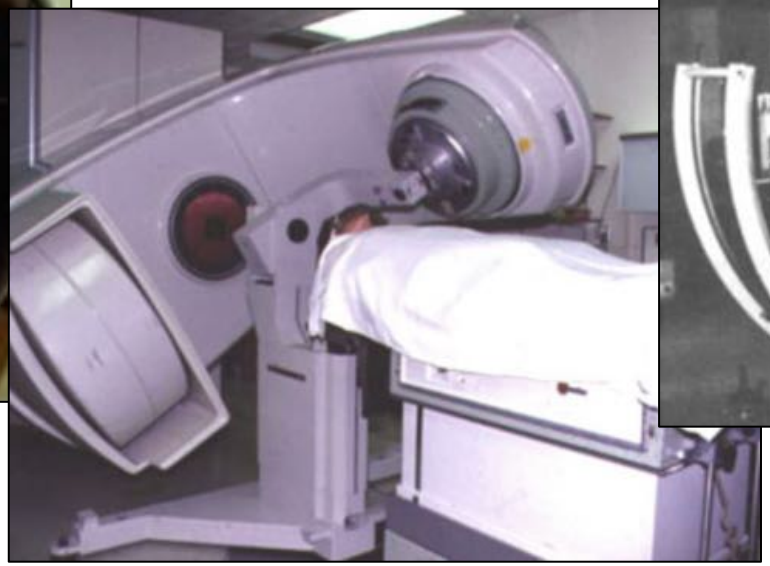
Frame-based SRS

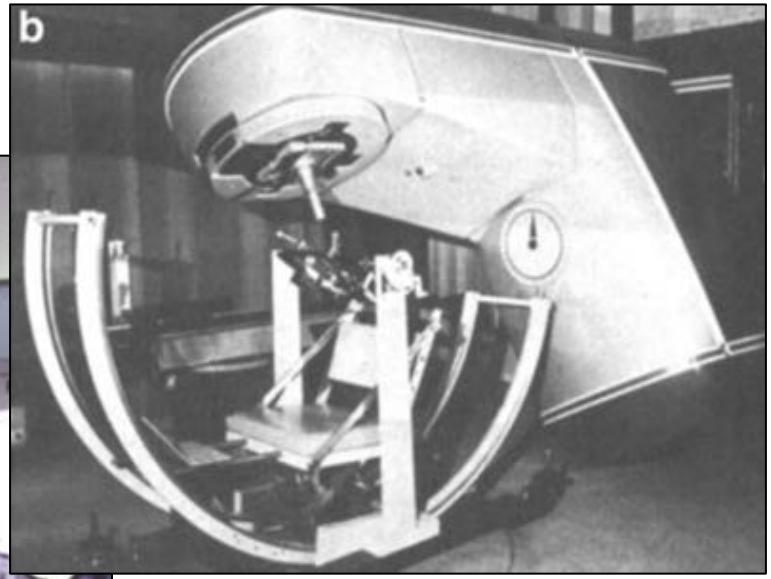
- Frame makes sense in setup with physical-rigid connection between patient and radiation source



Leksell *et al.*

Bova-Friedman *et al.*





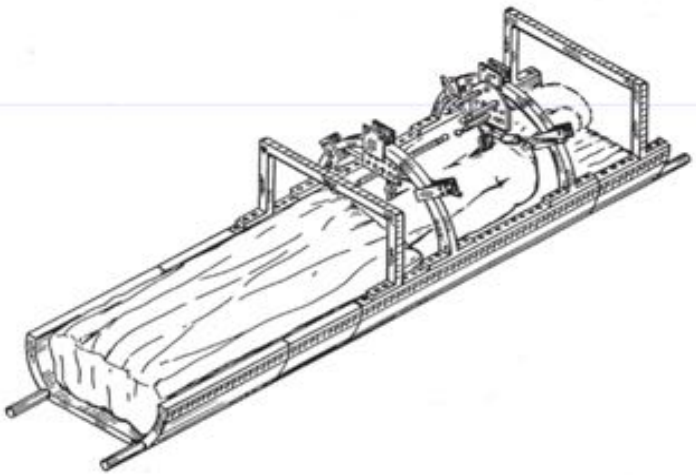
Betti *et al.*

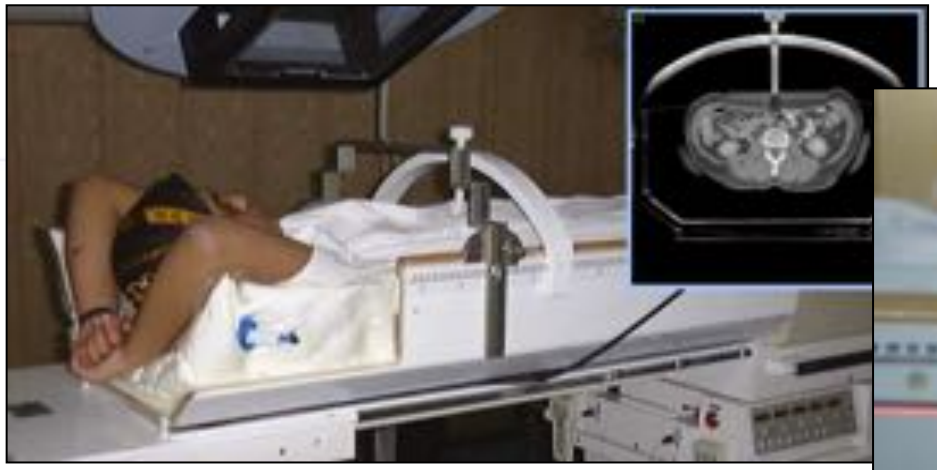
Frame-based SRS

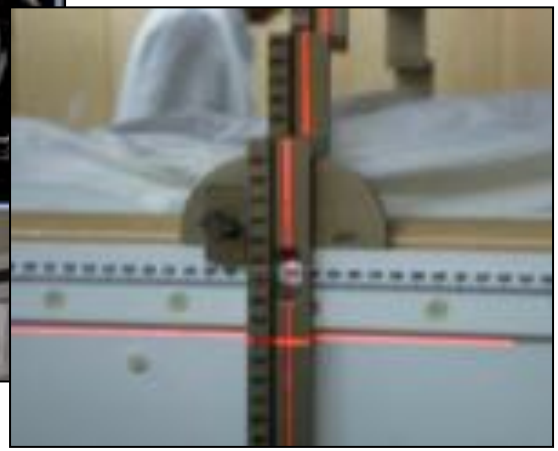
- Frame makes sense in setup with physical-rigid connection between patient and radiation source …
- The treatment couch is probably the weakest link

Towards extracranial SRS: body frames

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







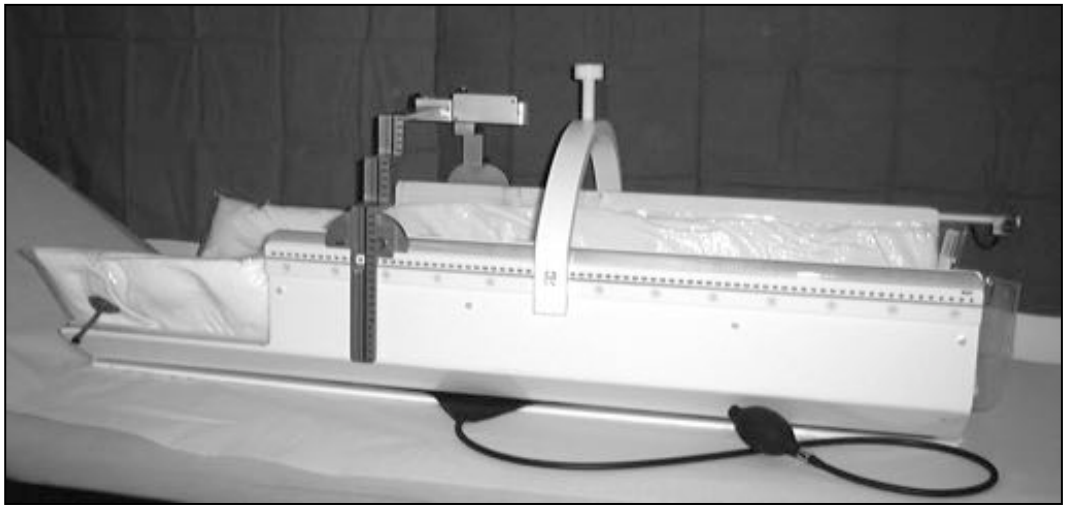
Stereotactic Body Frame, Lax *et al.*

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

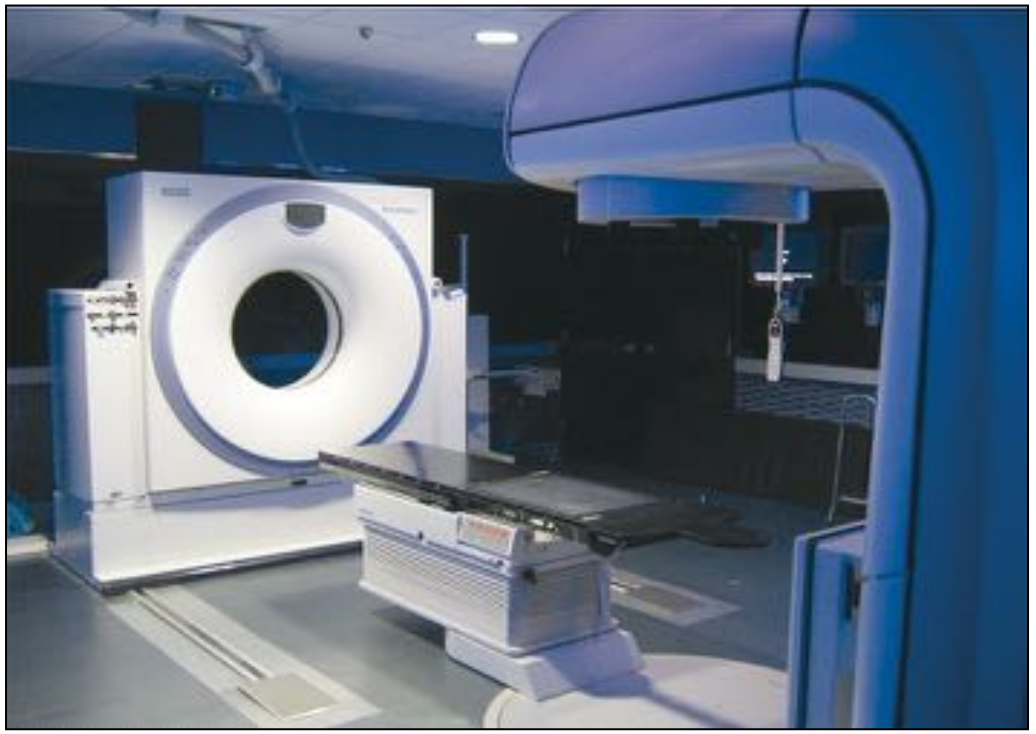
!Pioneers in SBRT!

Towards extracranial SRS: body frames

… still requires IGRT



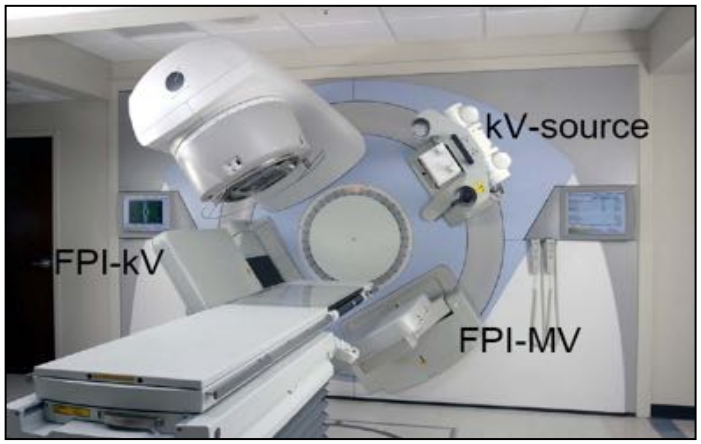
Stereotactic Body Frame, Lax *et al.*



- 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

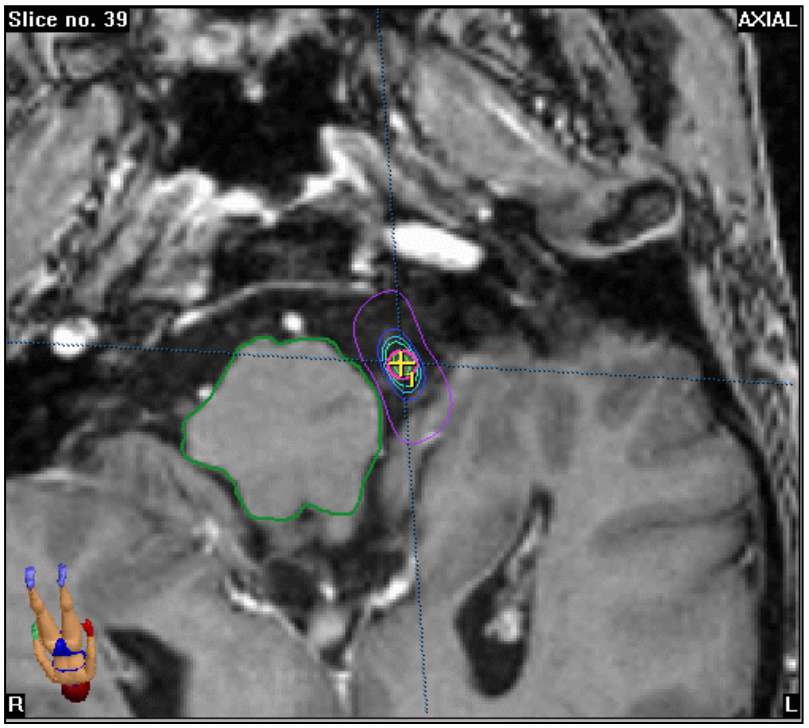
- SBRT and motion management



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

Frameless SRS

- High precision “frameless” stereotactic radiosurgery:

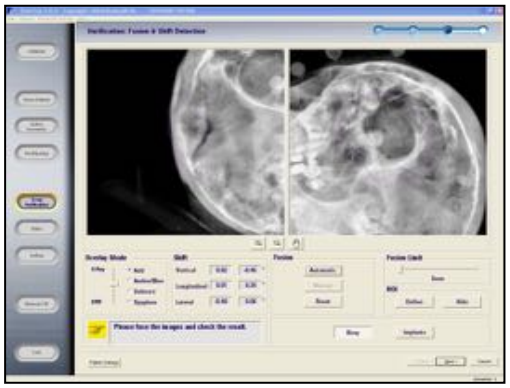


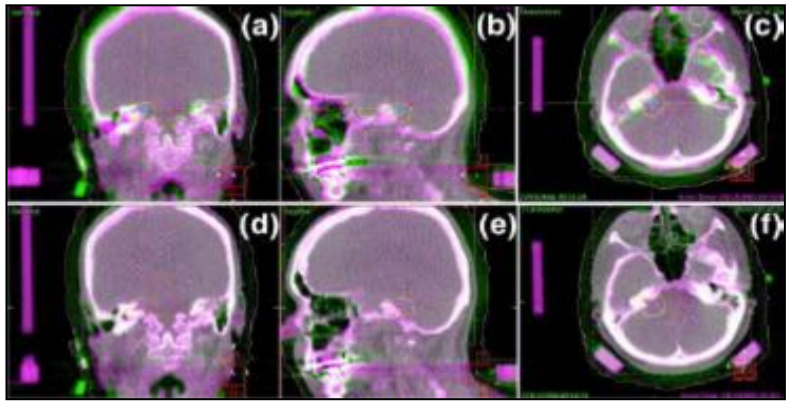
- … also requires implementation of image guided systems for target localization and positioning on the linac!

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**

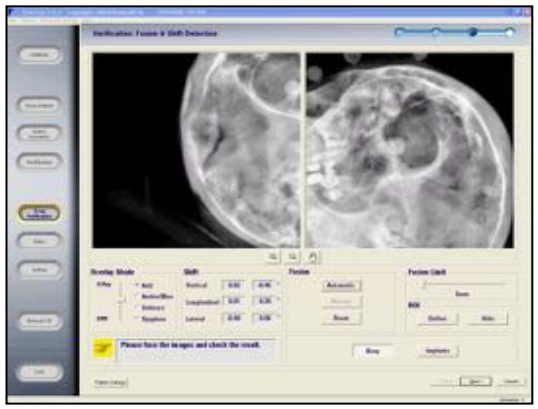


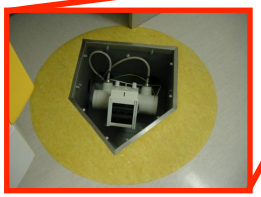


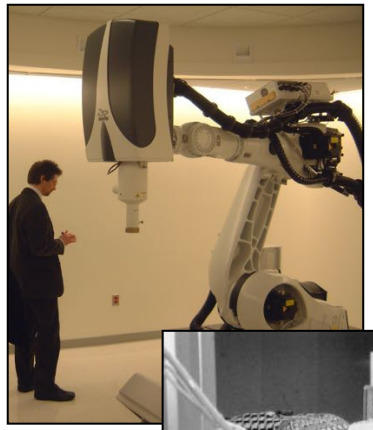
  - Making use of **internal anatomy rather than external landmarks** to localize target, position patient, and avoid geographic miss during treatment.

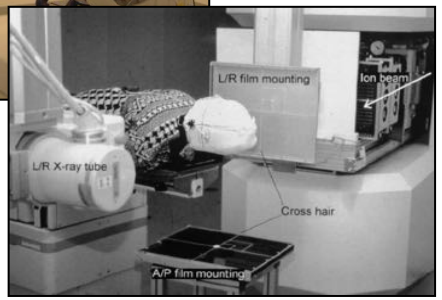
Image-guided frameless SRS

- 2D/3D, planar imaging

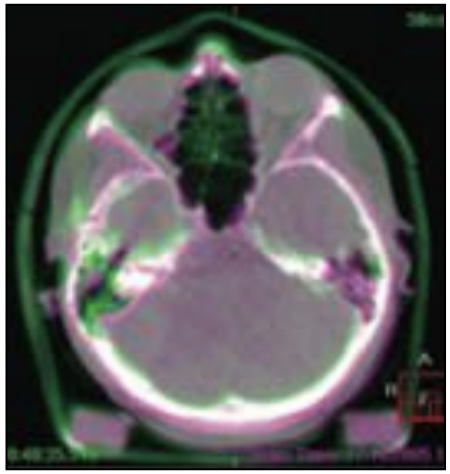


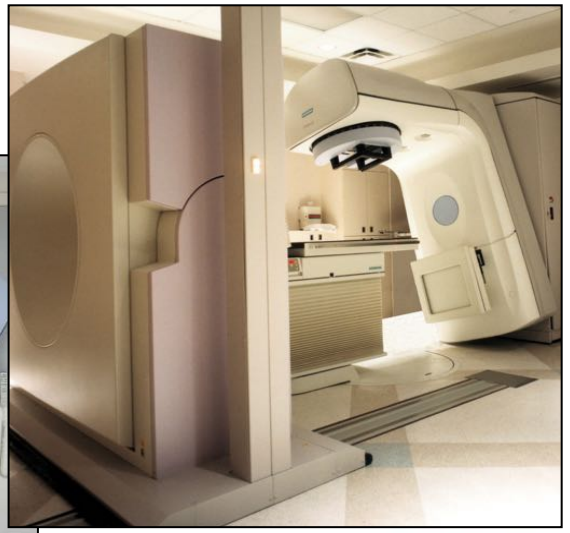






- 3D, volumetric imaging





Outline

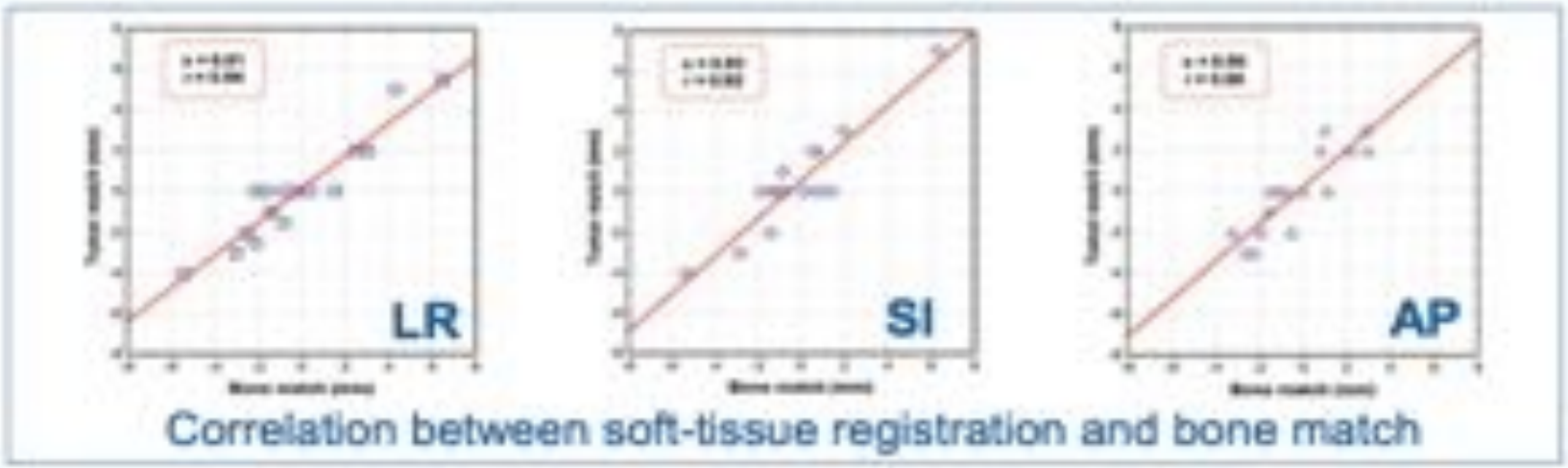
- Can we use bony structures for target localization?
- What accuracy can be achieved?
  - In phantom
  - Clinical validation
- Frame versus frameless
- Some words of caution
- Conclusions and food for thought

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

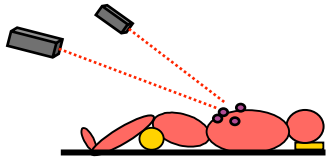
	Differences between bone and tumor match (mm)			
	LR	SI	AP	3D
Mean ± SD	-0.6 ± 1.0	0.0 ± 1.1	-0.2 ± 1.0	1.7 ± 0.7
Maximum	1.8	2.3	2	2.8

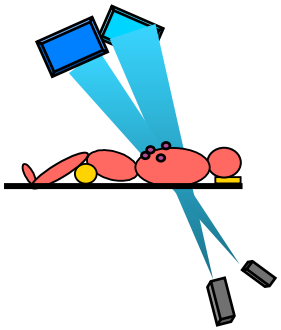
Stable tumor position relative to the skull for one week interval between planning and treatment

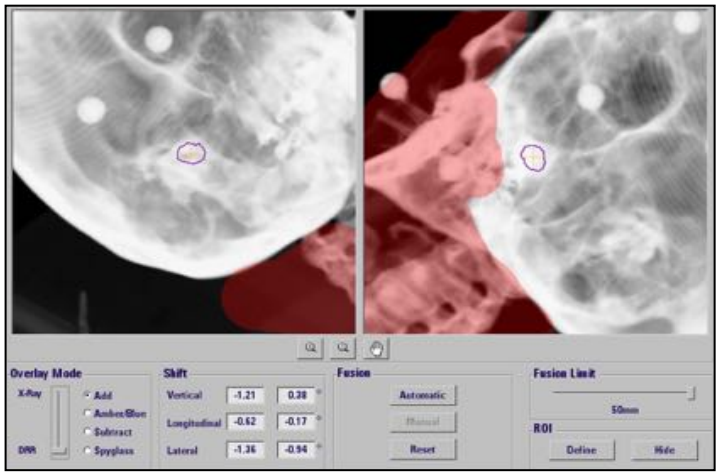
No influence of pre-treatment steroids

M. Guckenberger *et al.* IJROBP 2007

Is the skull a suitable reference?

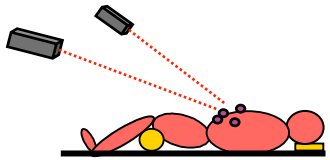


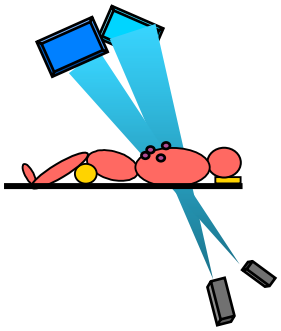


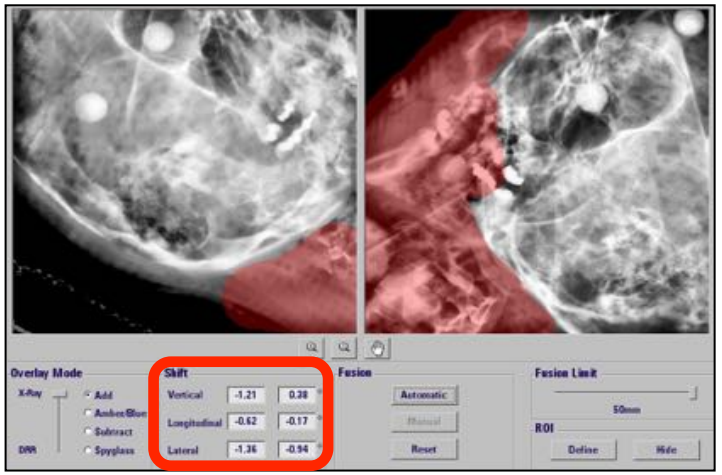


Full 6 DOF automated patient set-up

Is the skull a suitable reference?



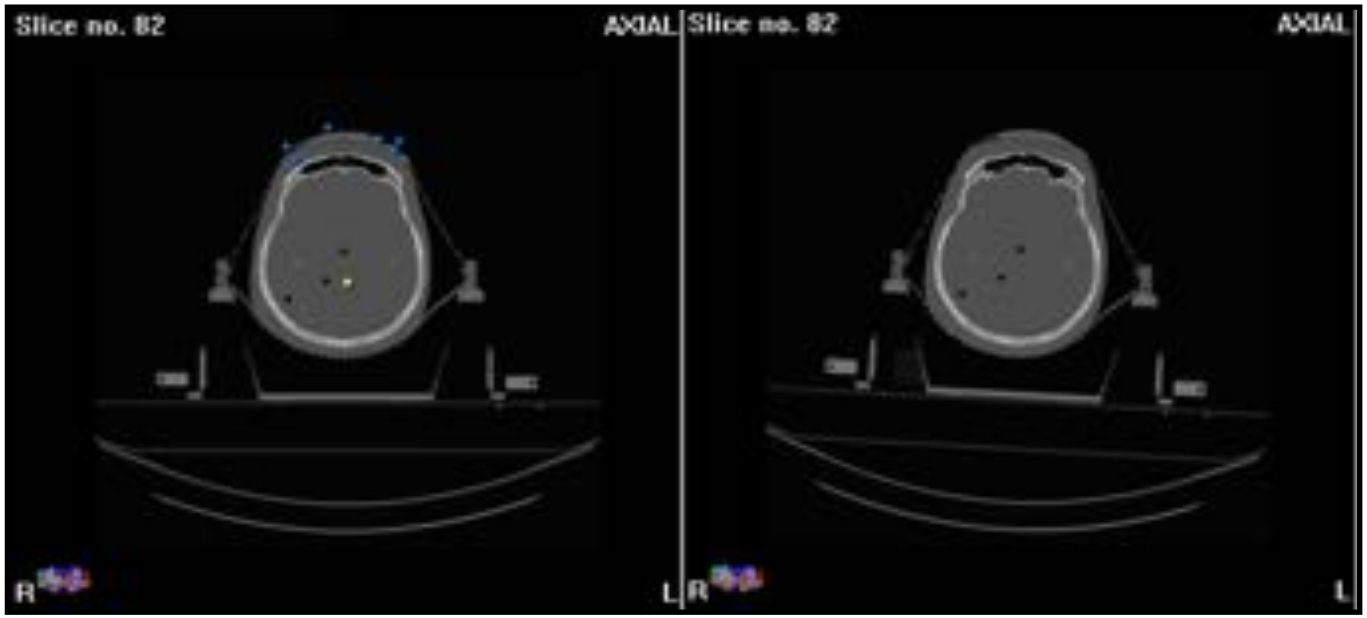


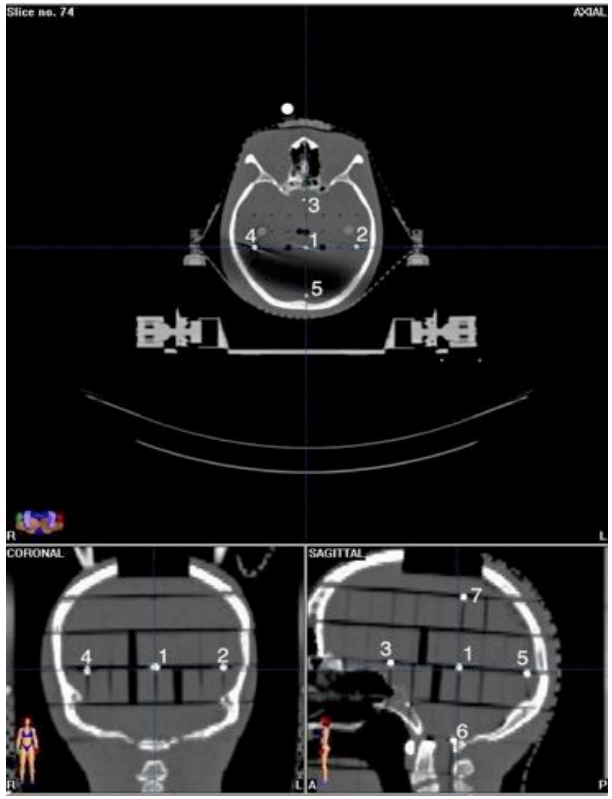


Full 6 DOF automated patient set-up

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

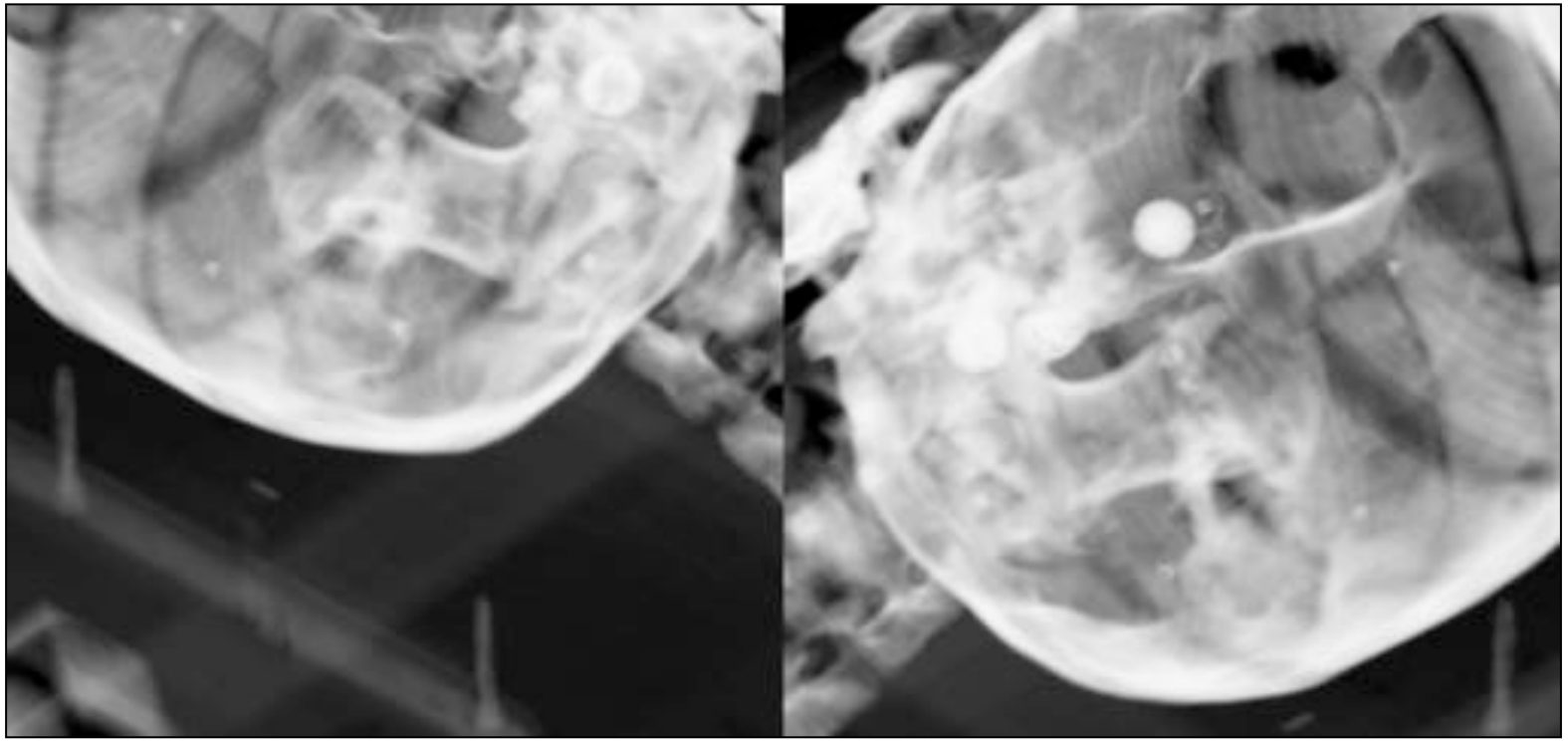




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

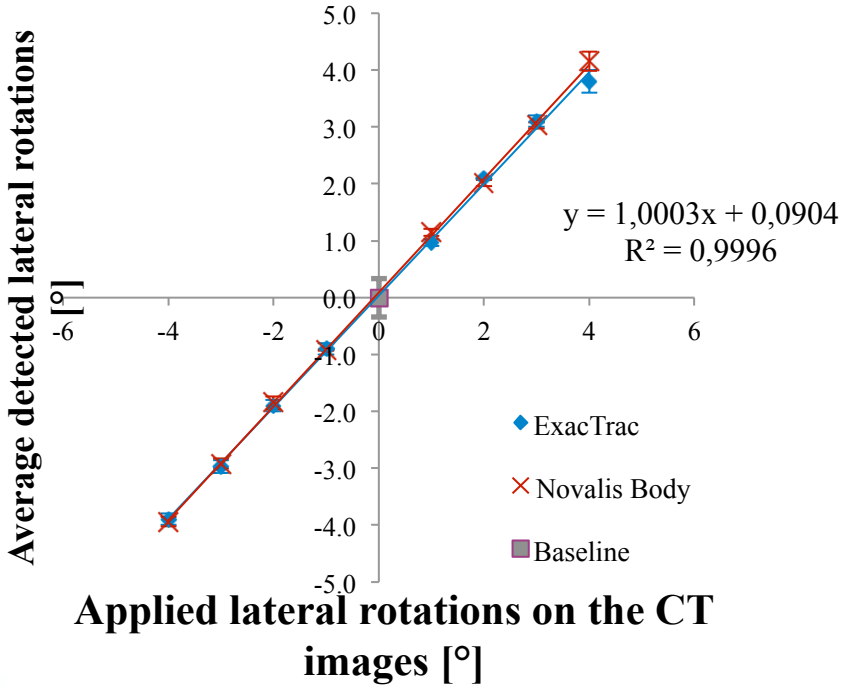
Is the skull a suitable reference?

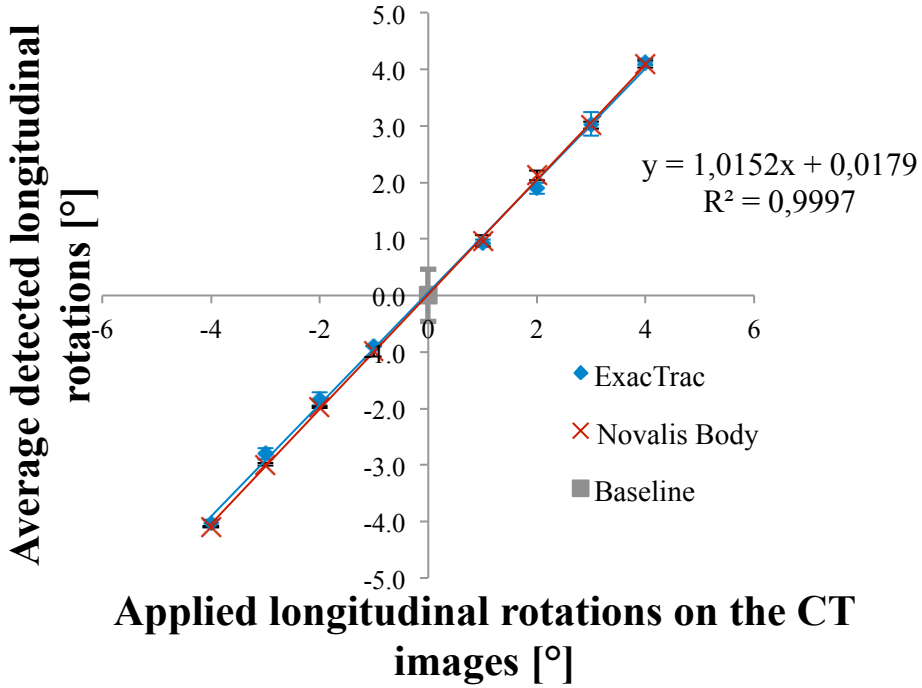
Different locations were chosen to investigate the sensitivity of the registration algorithm on presence/absence of bony fiducials



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

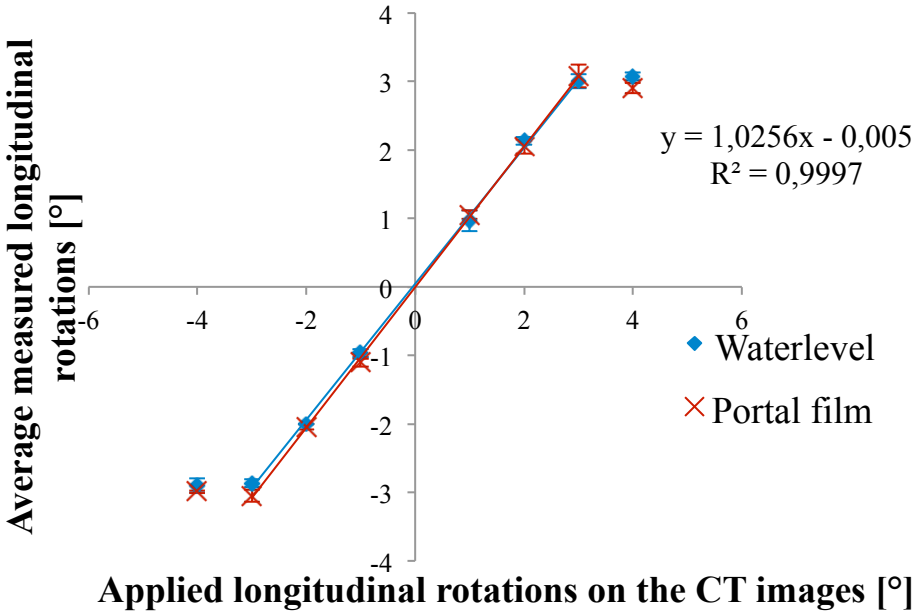
Detection accuracy

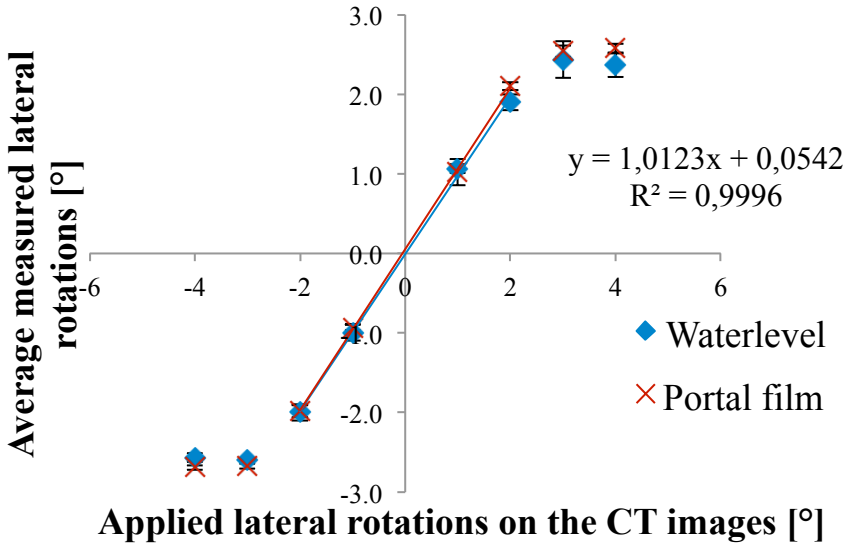




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Positioning accuracy (Robotics)

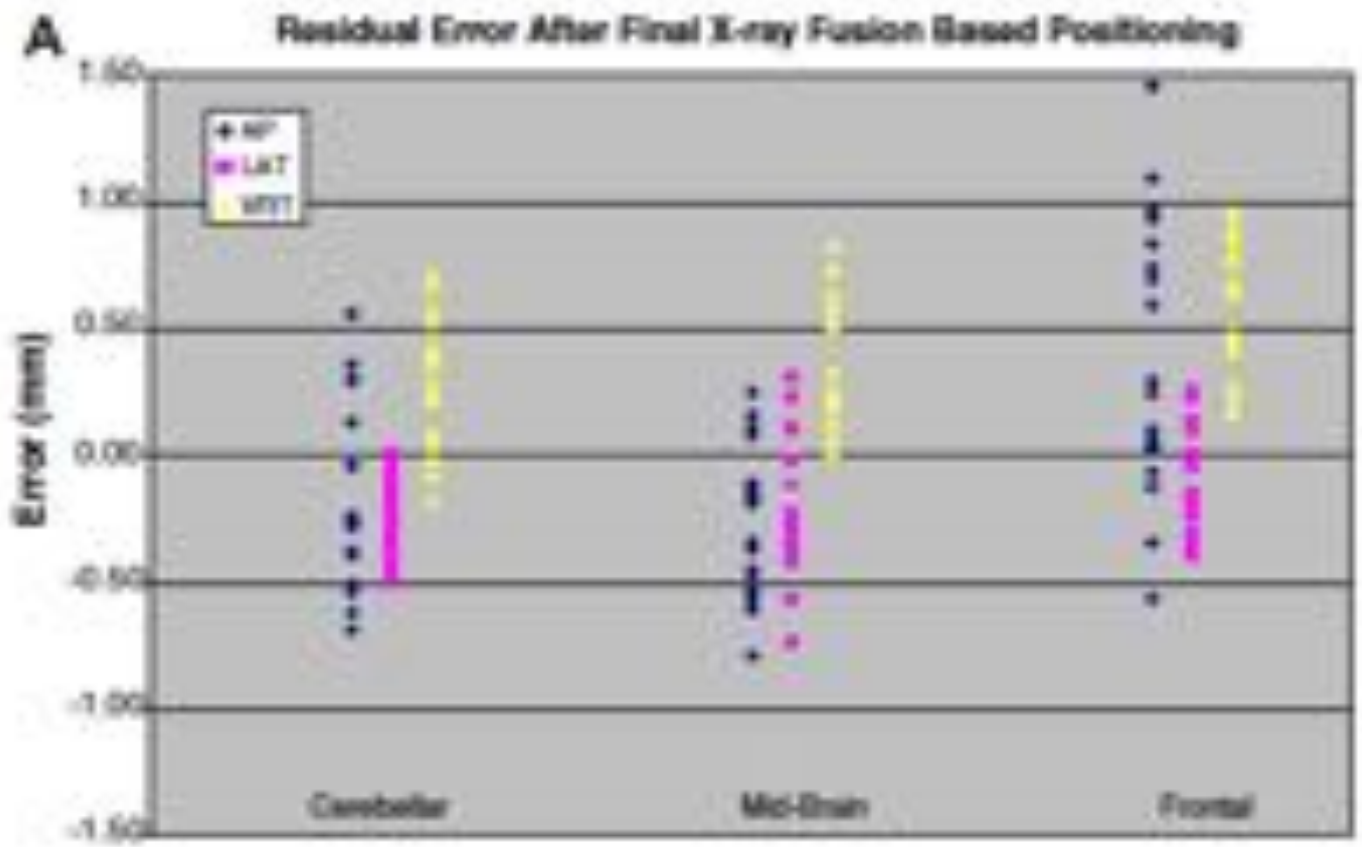




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

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

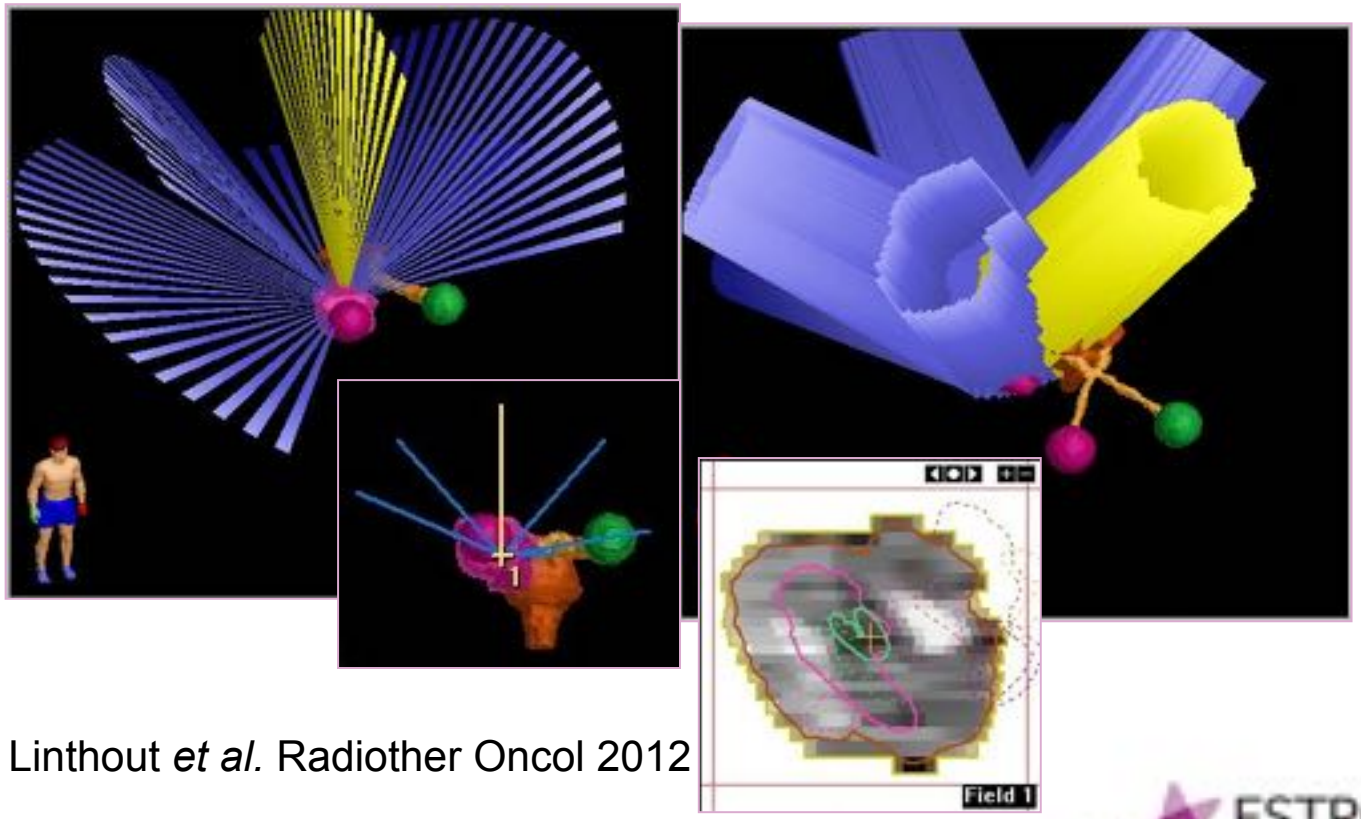
IGRT/frameless: Clinical validation

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

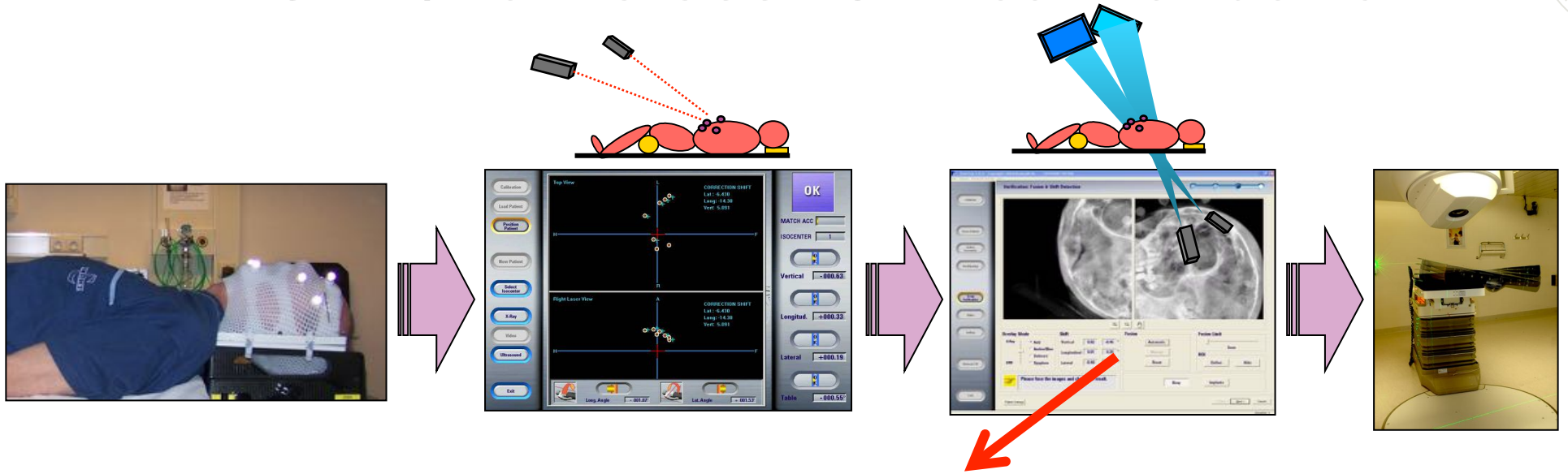
IGRT/frameless: Clinical validation

- 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

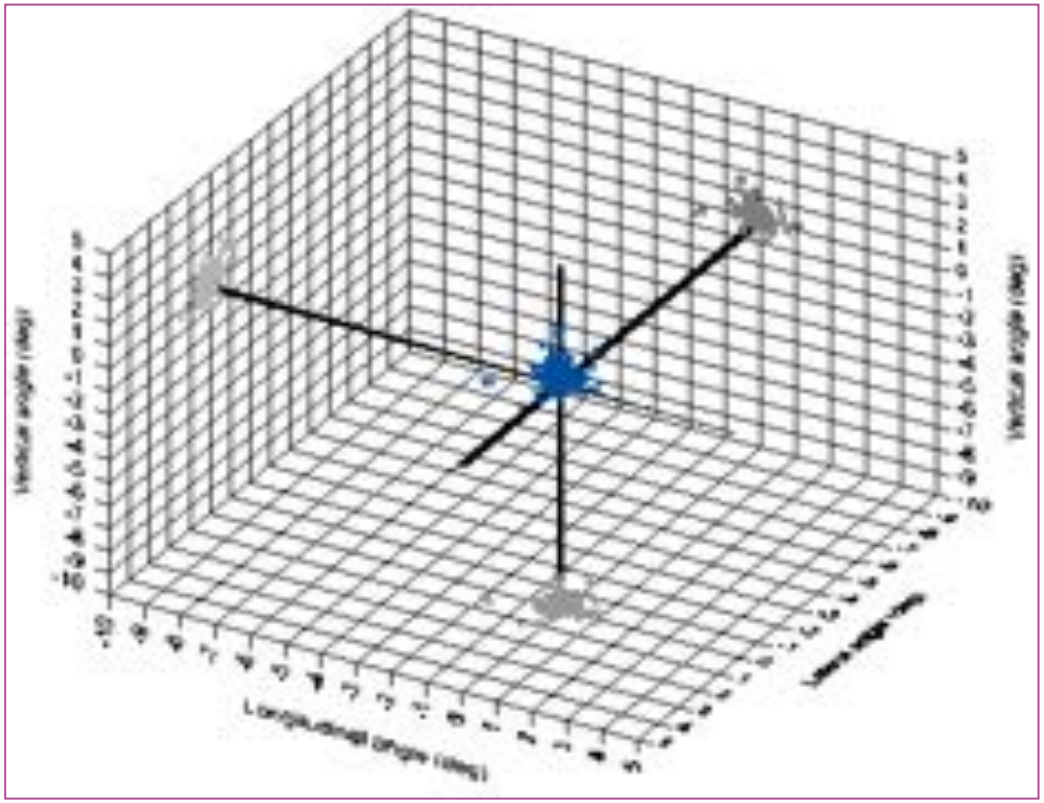


Linthout *et al.* Radiother Oncol 2012

IGRT/frameless: Clinical validation



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°**

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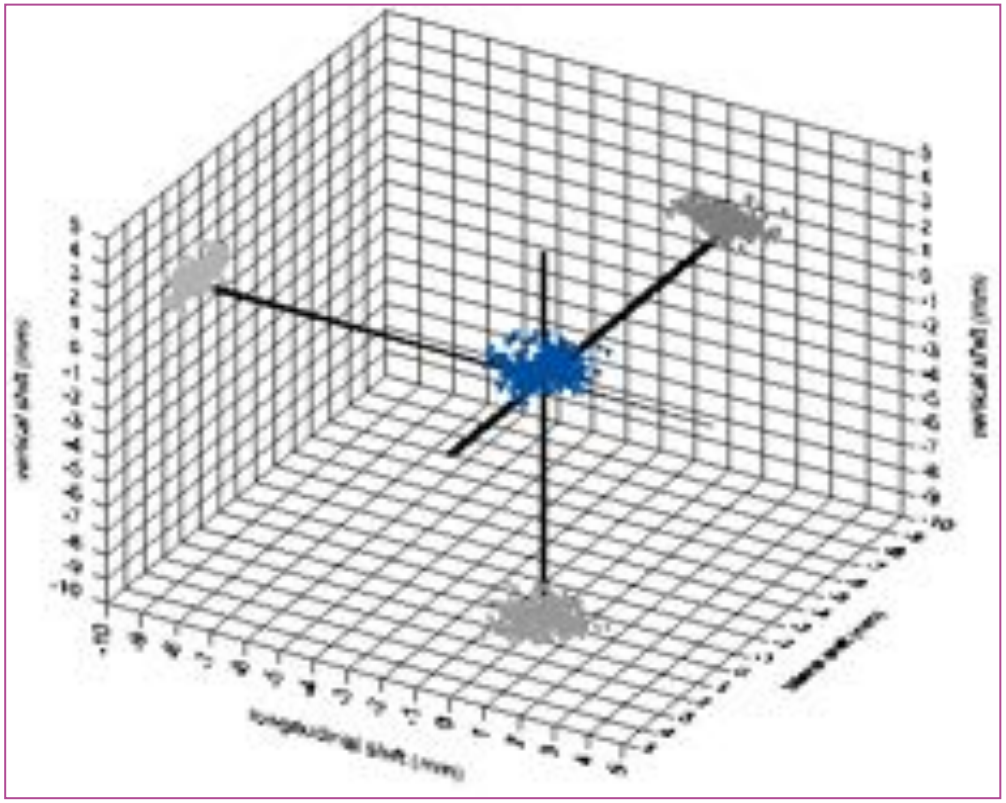
Results: X-ray residual shifts



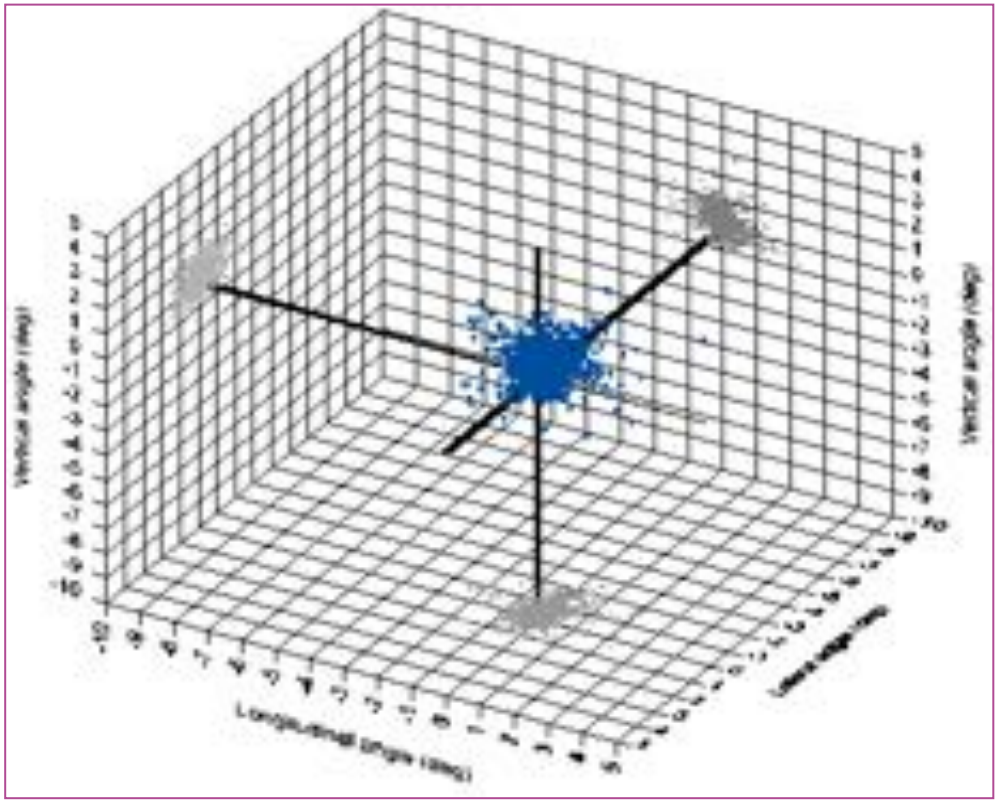
- Lateral
  - Mean: 0.02mm, SD: 0.66mm
  - **-1.59mm – 1.66mm**
- Longitudinal
  - Mean: 0.04mm, SD: 0.53mm
  - **-1.67mm – 1.67mm**
- Vertical
  - Mean: 0.04mm, SD: 0.32mm
  - **-1.11mm – 1.22mm**

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

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

Linthout *et al.* Radiother Oncol 2012

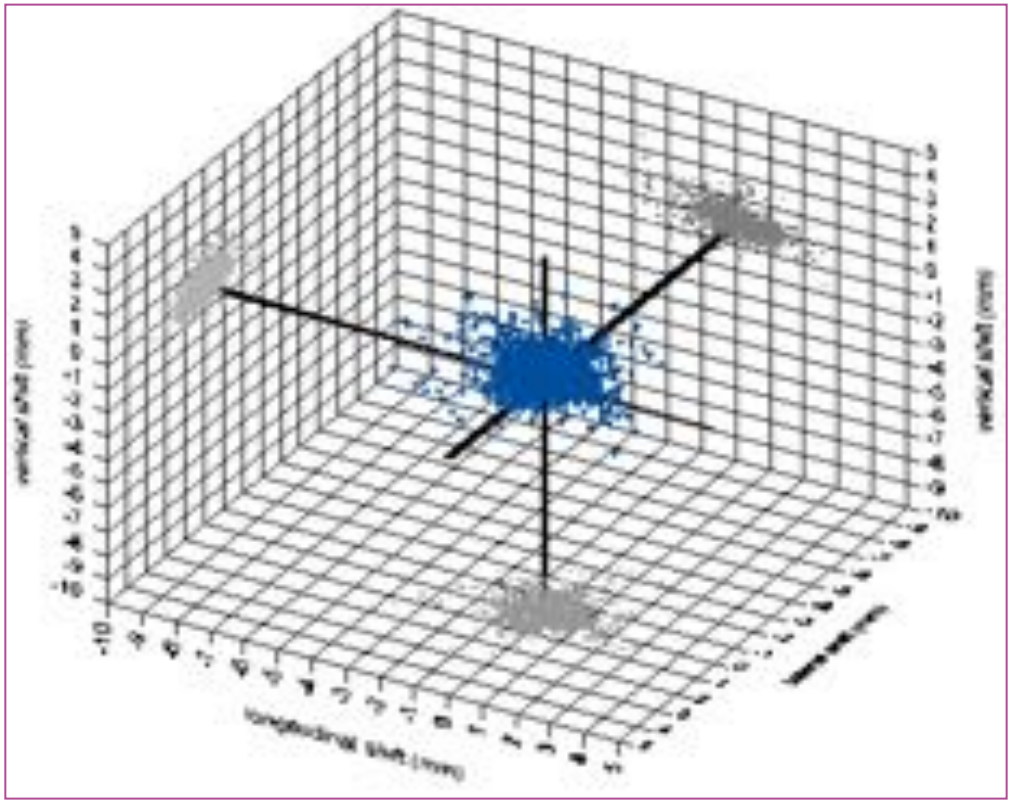
Results: Intrafraction rotations



- 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**

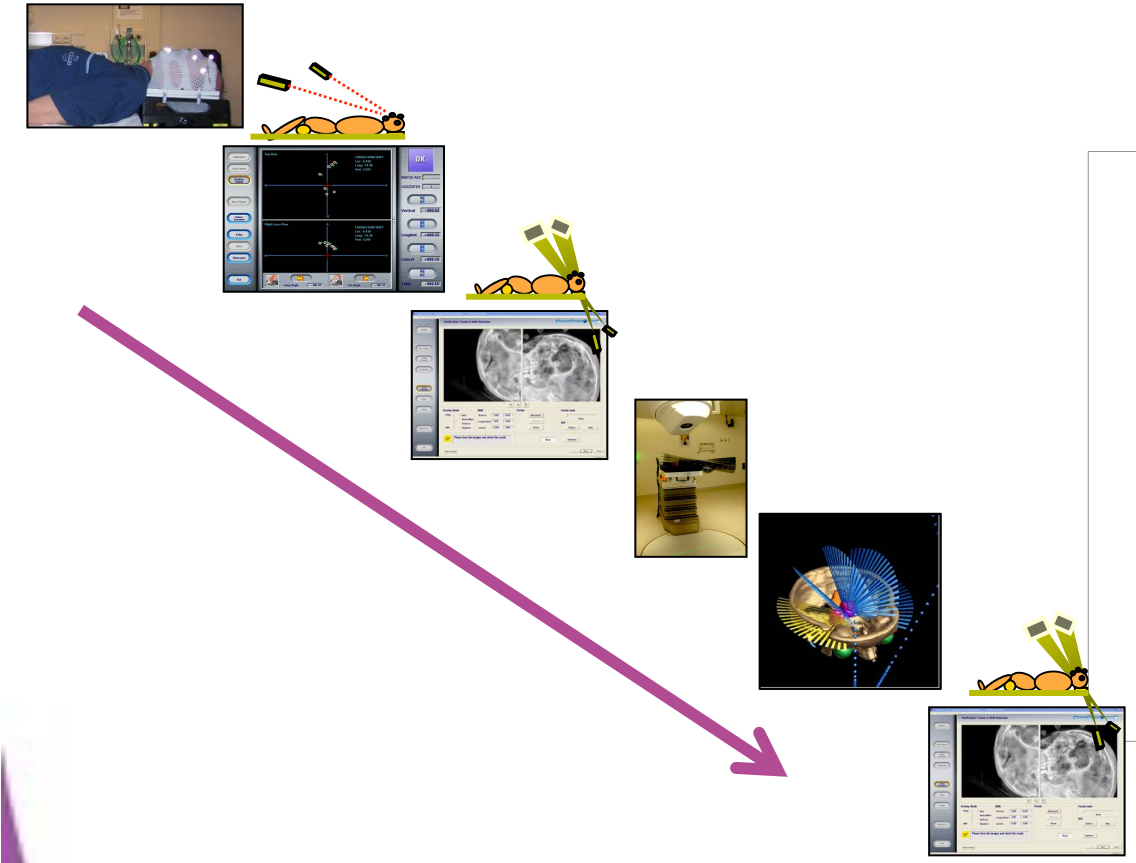
Van Herk formula ($2.5\sum+0.7\sigma$)

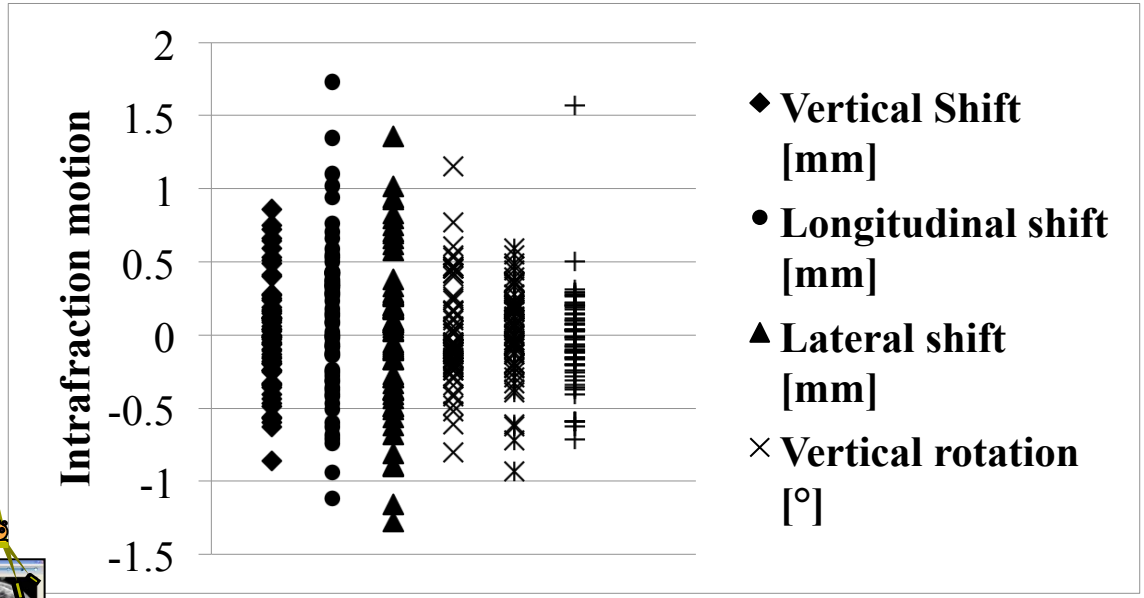
- Lateral **1.37mm**; longitudinal **1.85mm**; vertical **1.00mm**

Linthout *et al.* Radiother Oncol 2012

IGRT/frameless: Intrafraction motion

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





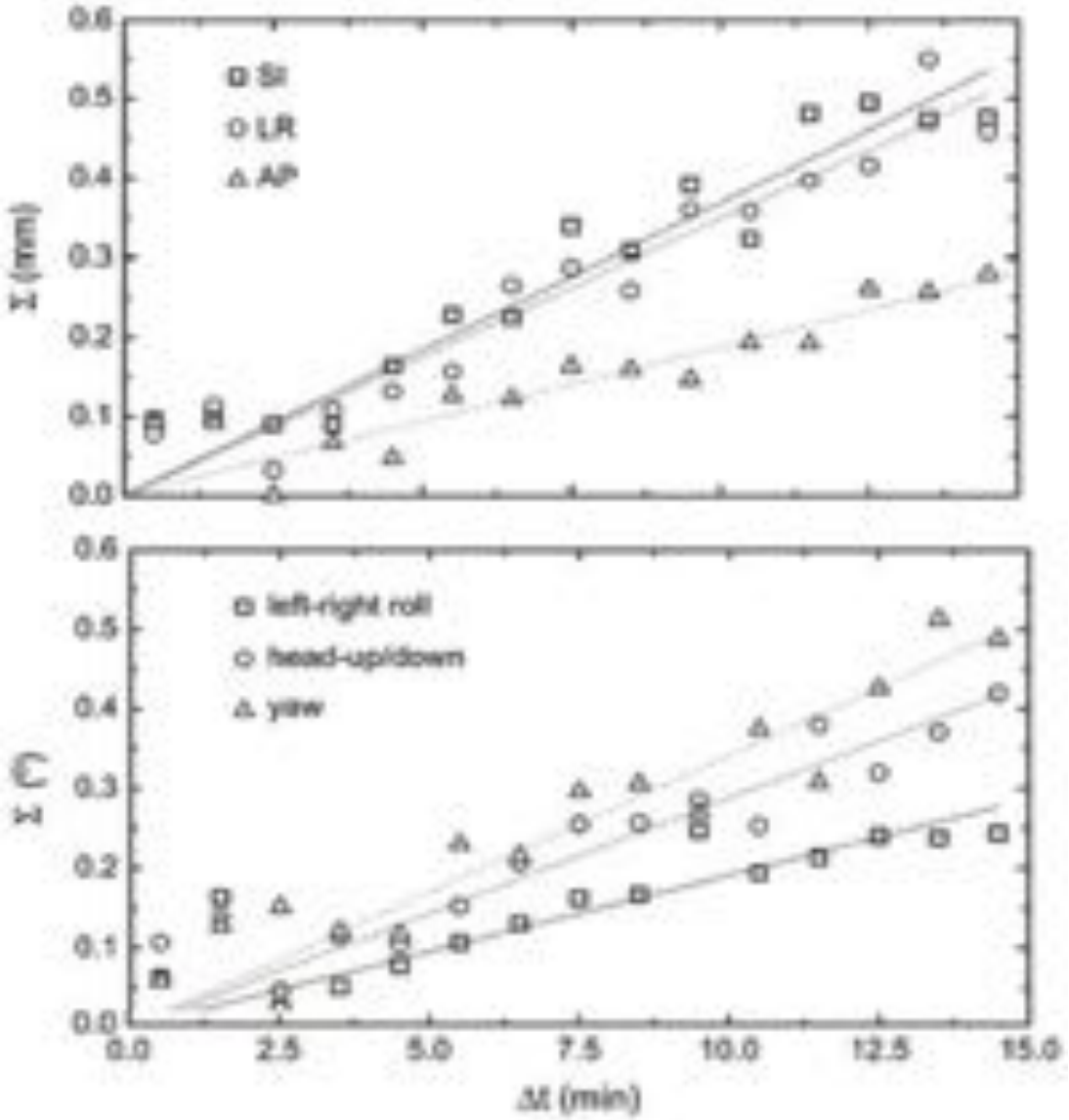
- Intrafraction motion: **mean 3D of 0.58 mm (SD: 0.42 mm)**

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

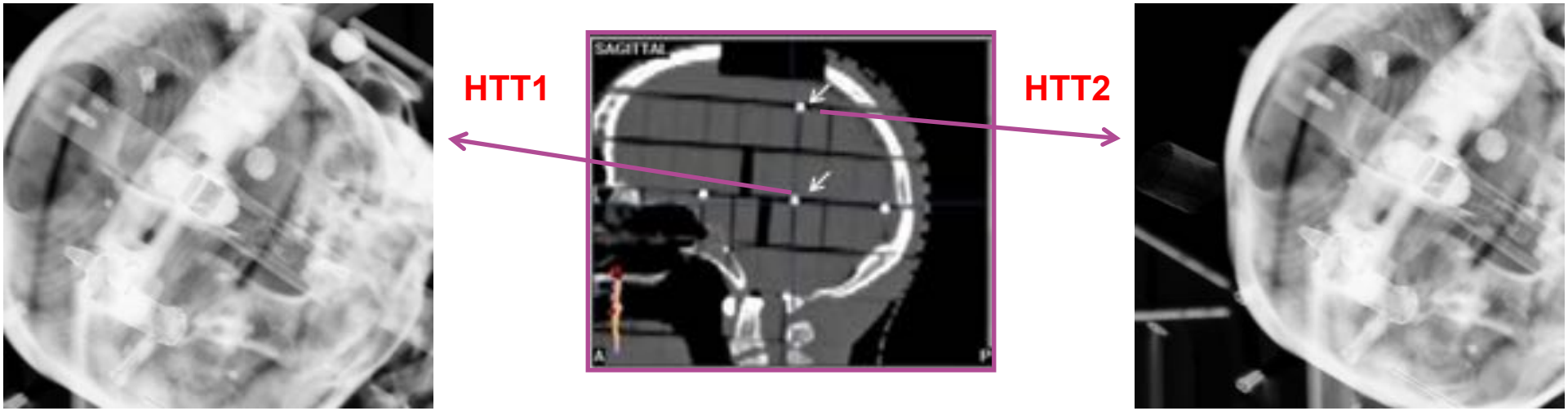
Accuracy: Frame-based versus IGRT-frameless

- 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

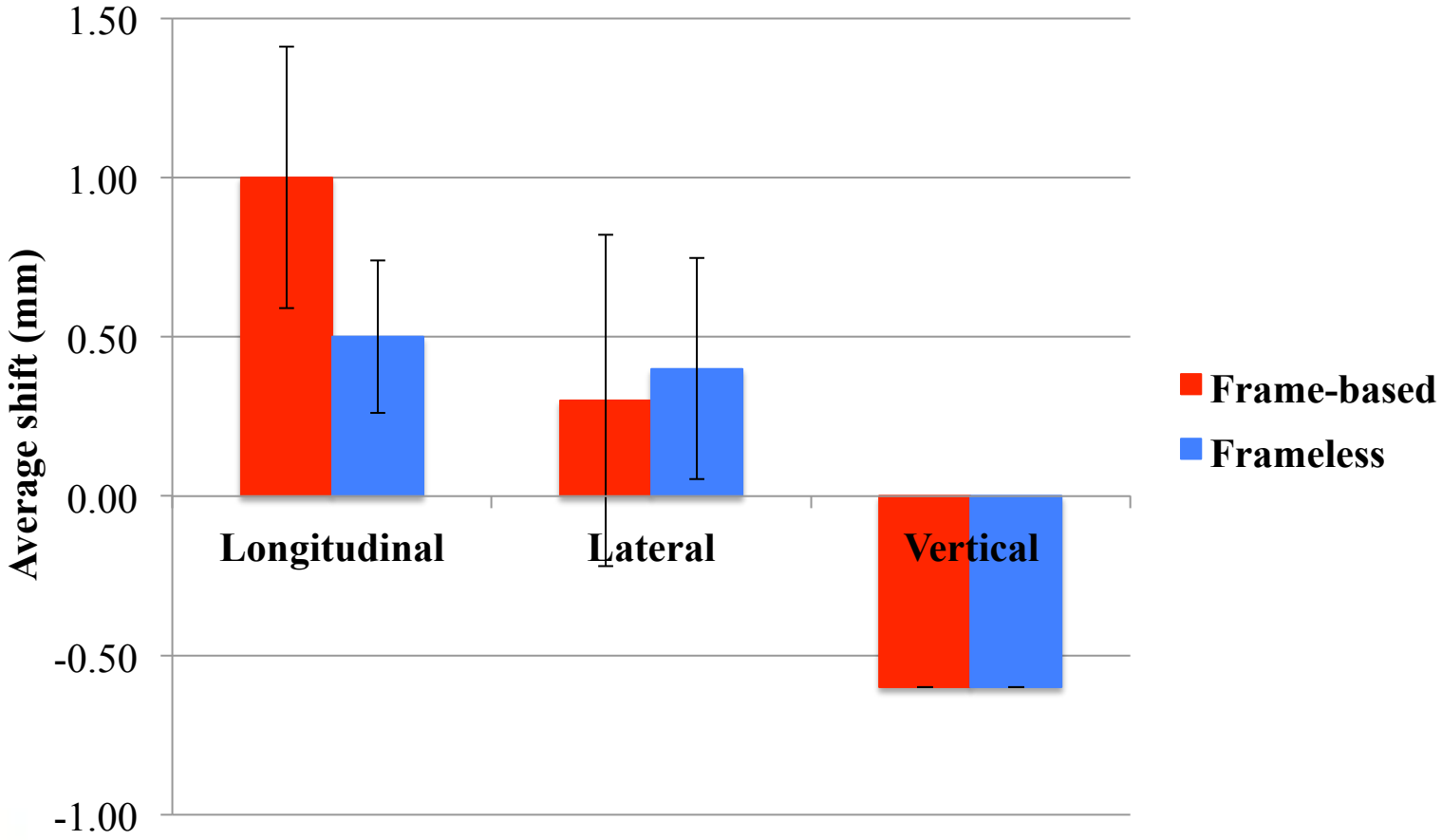
CT Slice Thickness (mm)	Measurement	Leksell (mm)
1	Mean ± 3 SE_M	1.7 ± 0.10
	99% CI for the mean	1.60 to 1.80
1 canted	Mean ± 3 SE_M	N/A
	99% CI for the mean	N/A
4	Mean ± 3 SE_M	2.6 ± 0.14
	99% CI for the mean	2.46 to 2.74
8	Mean ± 3 SE_M	5.4 ± 0.24
	99% CI for the mean	5.16 to 5.64

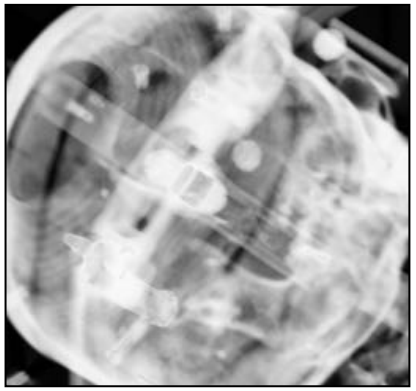
Accuracy: Frame-based versus IGRT-frameless



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

Accuracy: Frame-based versus IGRT-frameless

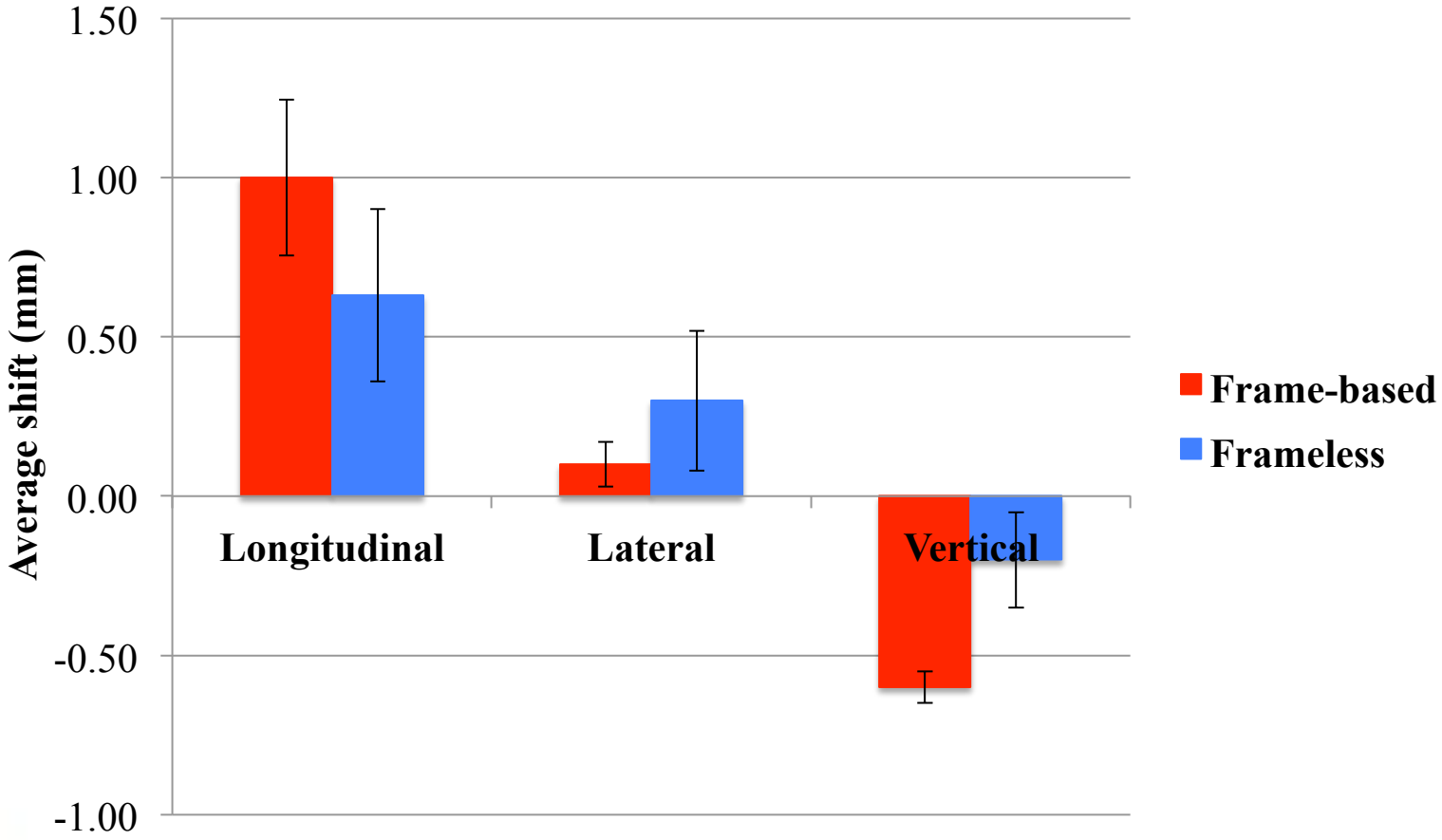


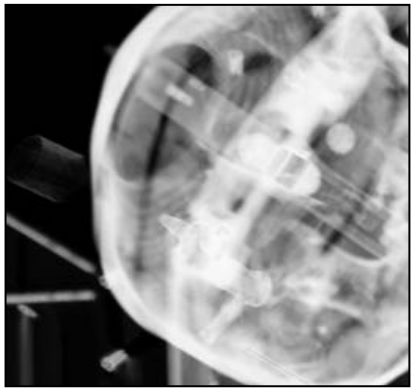


Overall 3D accuracy: 1.20 mm SD 0.66 mm (frame-based)
0.88 mm SD 0.42 mm (frameless)

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

Accuracy: Frame-based versus IGRT-frameless



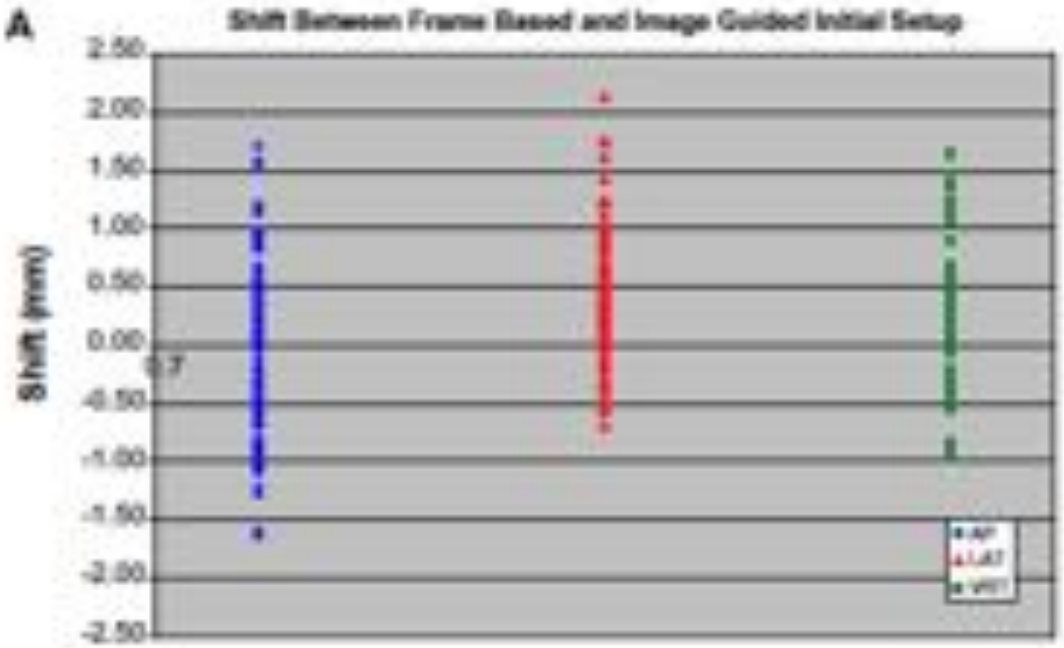


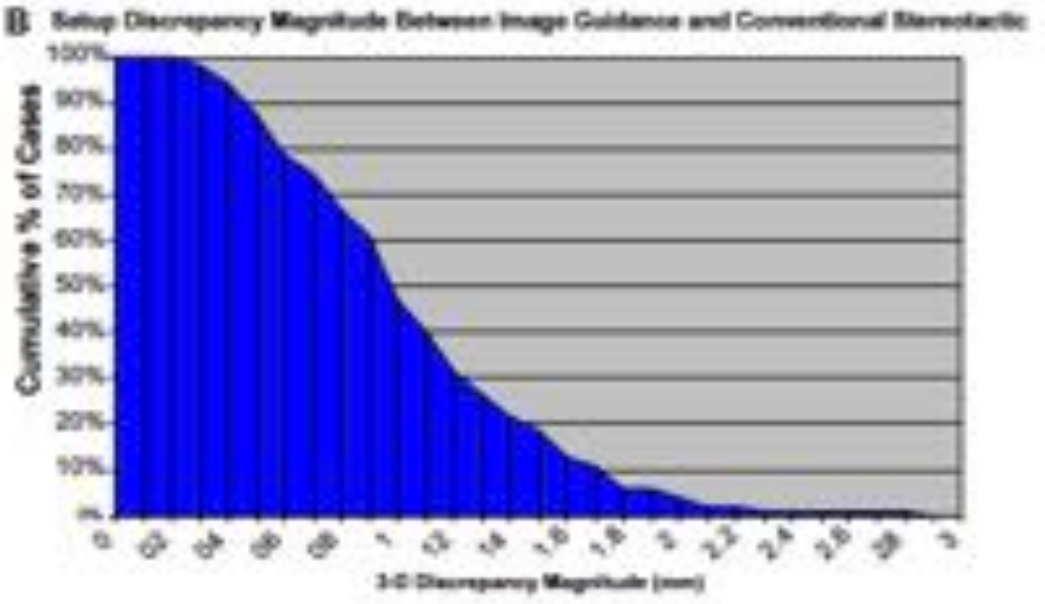
Overall 3D accuracy: 1.17 mm SD 0.24 mm (frame-based)
0.85 mm SD 0.52 mm (frameless)

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

Accuracy: Frame-based versus IGRT-frameless

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

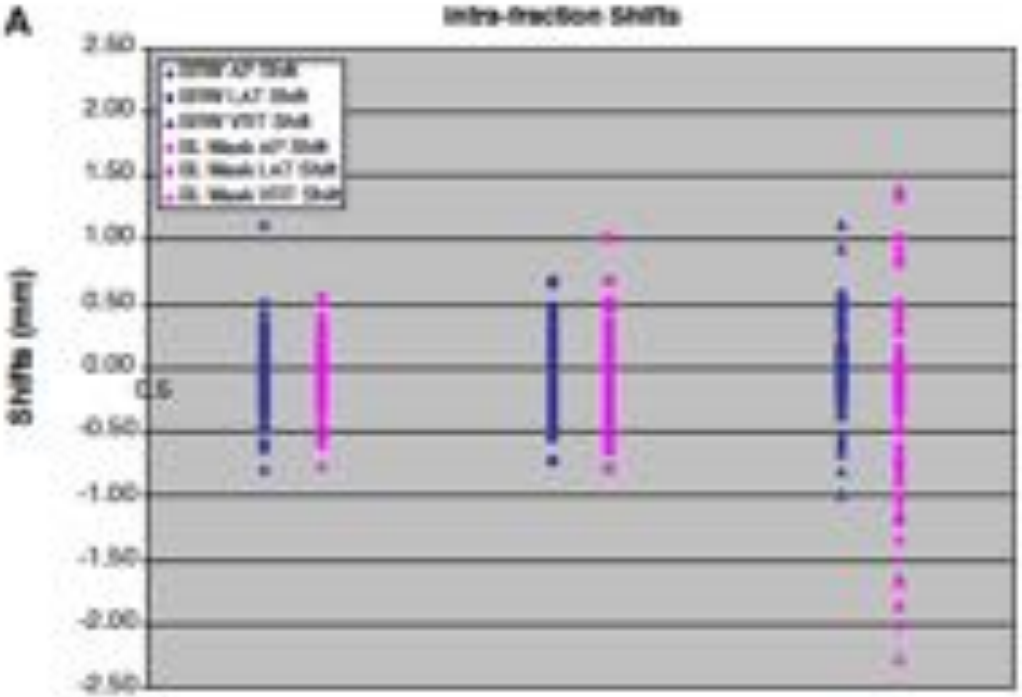


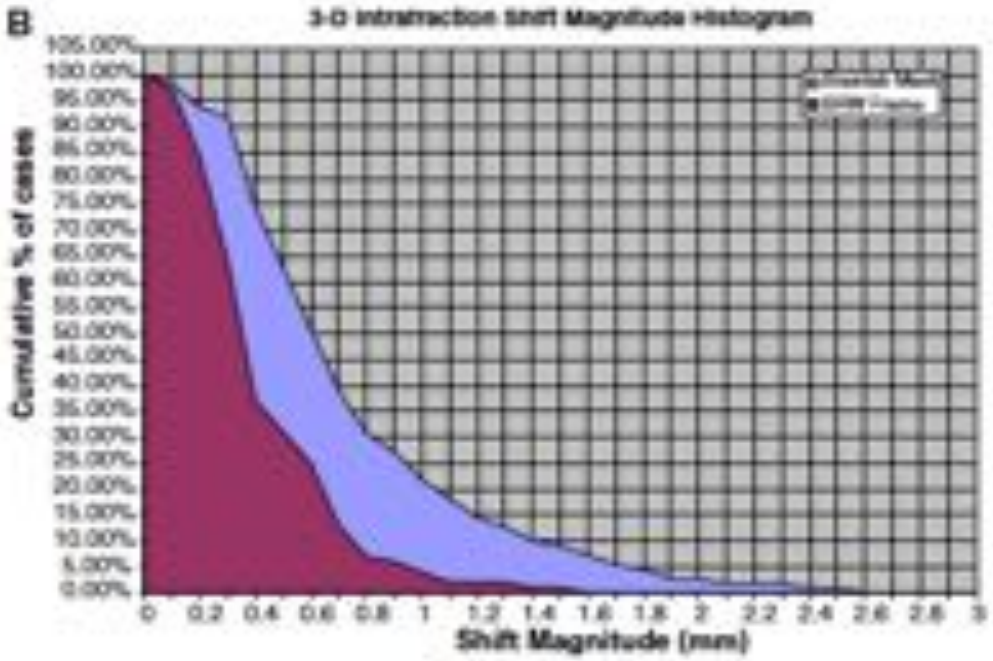


Ramakrishna *et al.* Radiother Oncol 2010

Accuracy: Frame-based versus IGRT-frameless

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





Ramakrishna *et al.* Radiother Oncol 2010

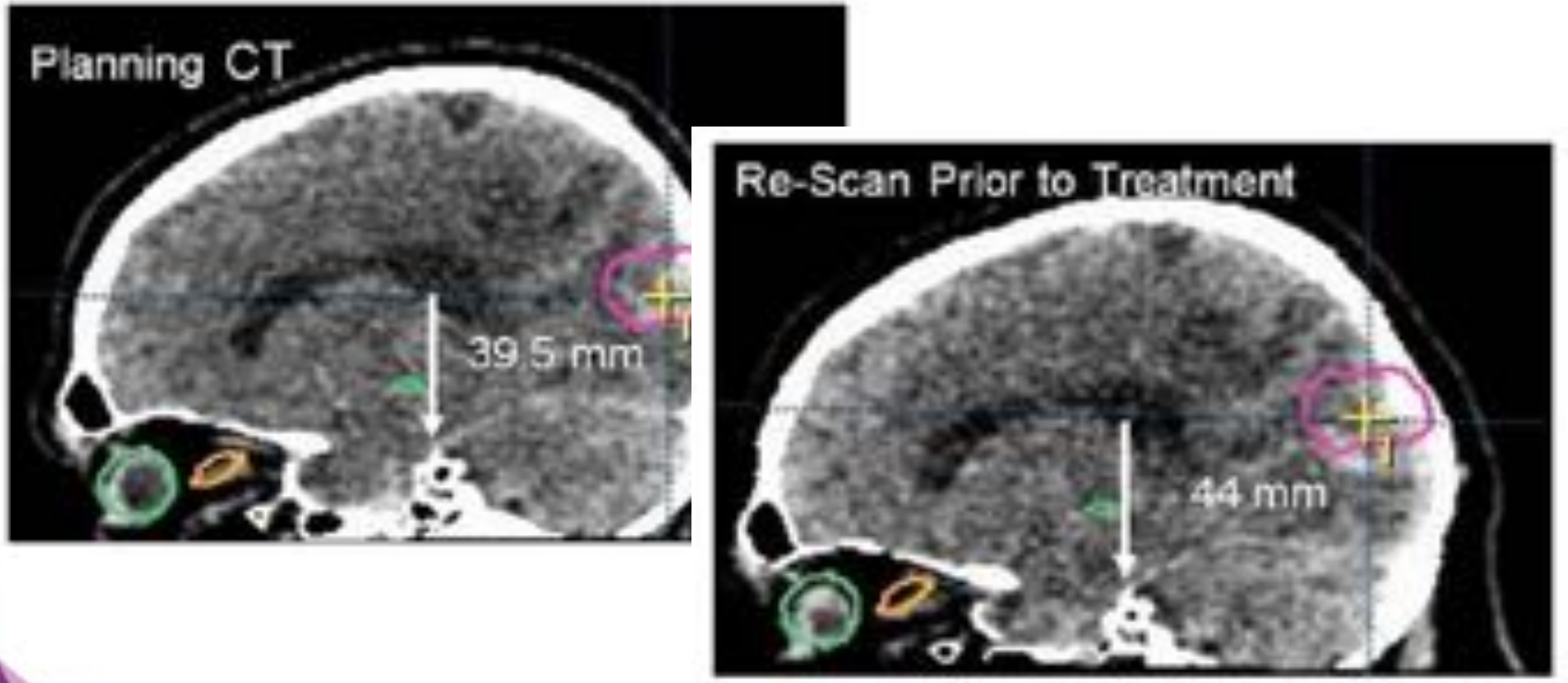
Margins: Frame-based versus IGRT-frameless

- 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

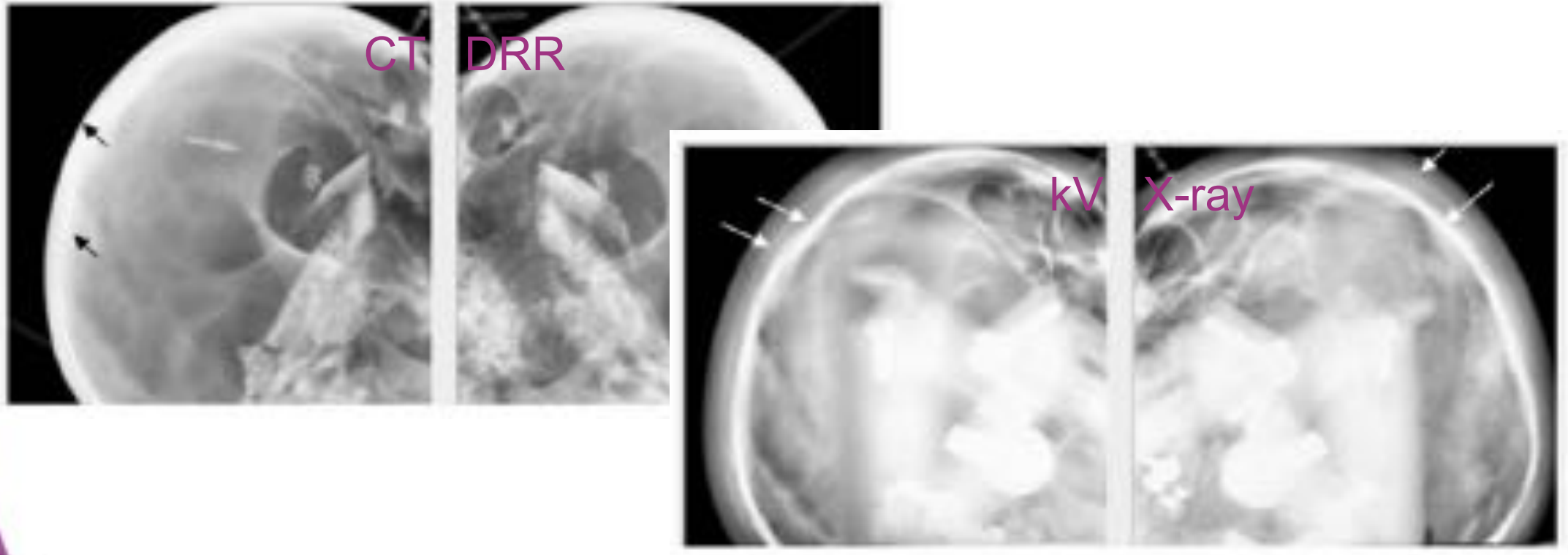
- Frame slippage (4.23 mm) observed with image-guided monitoring of frame-based SRS, confirmed with CT-scan.



Ramakrishna *et al.* Radiother Oncol 2010

IGRT/Frameless: Automated co-registration

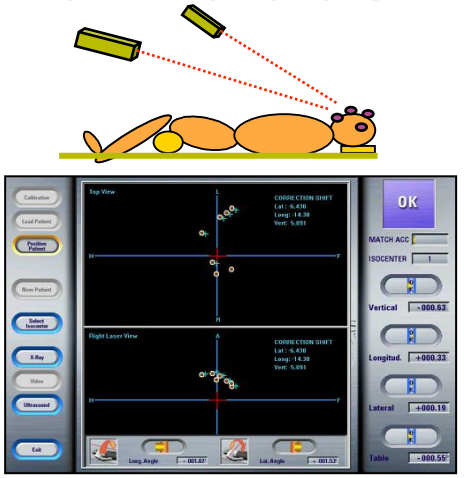
- kV X-ray images might display difference in skull density contours relative to CT-DRR, resulting in erroneous image co-registration.



Ramakrishna *et al.* Radiother Oncol 2010

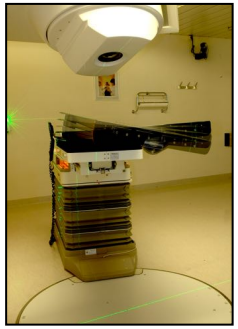
How about table rotations?

Phantom 0°



IR pre-positioning

6DOF registration



6DOF positioning

HTT

Phantom 90°

HTT

Phantom 270°

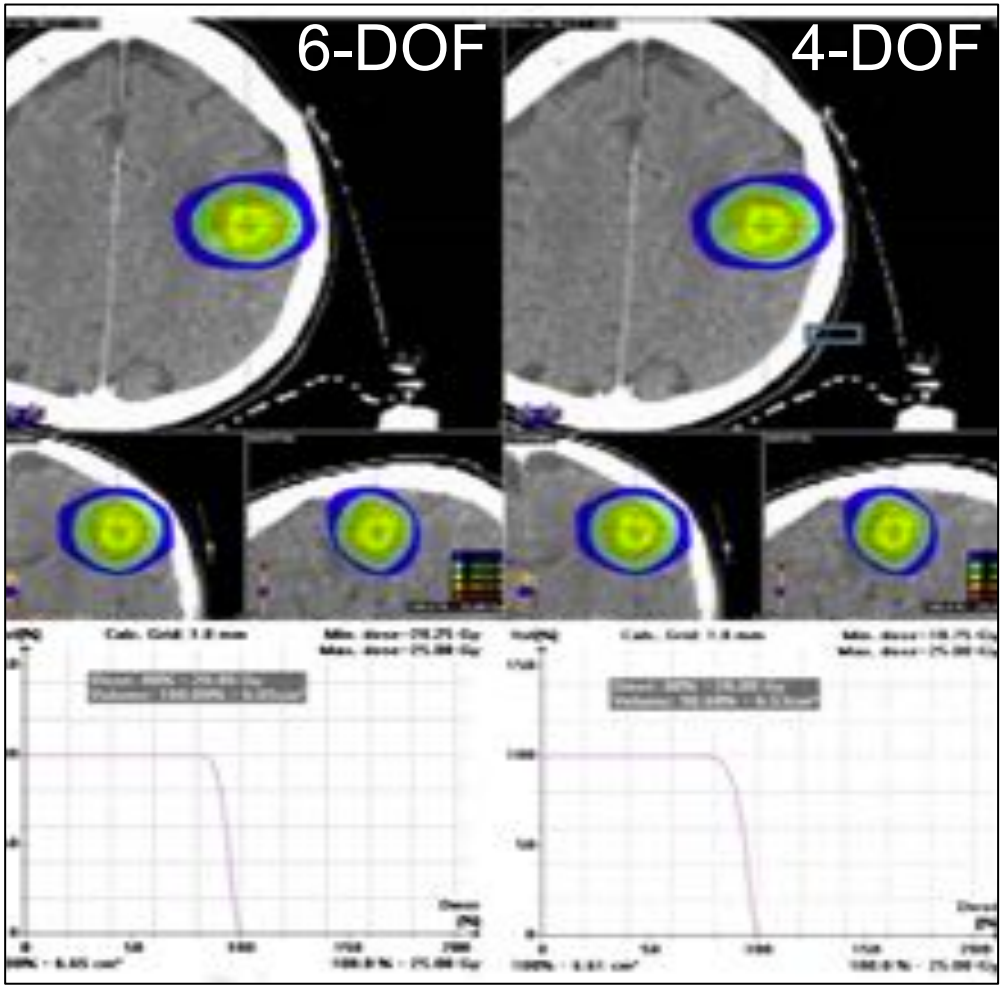
HTT

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)

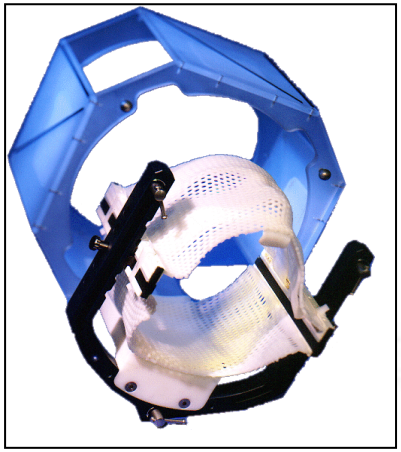
    Mean 3D of 0.89 mm (SD 0.35 mm)
  - Mean rotations:
    - Vertical: -0.08°(SD 0.25°)
    - Longitudinal: 0.09°(SD 0.29°)
    - Lateral: -0.05°(SD 0.20°)

Gevaert *et al.* Radiother Oncol 2012

Non-invasive, frame-based???

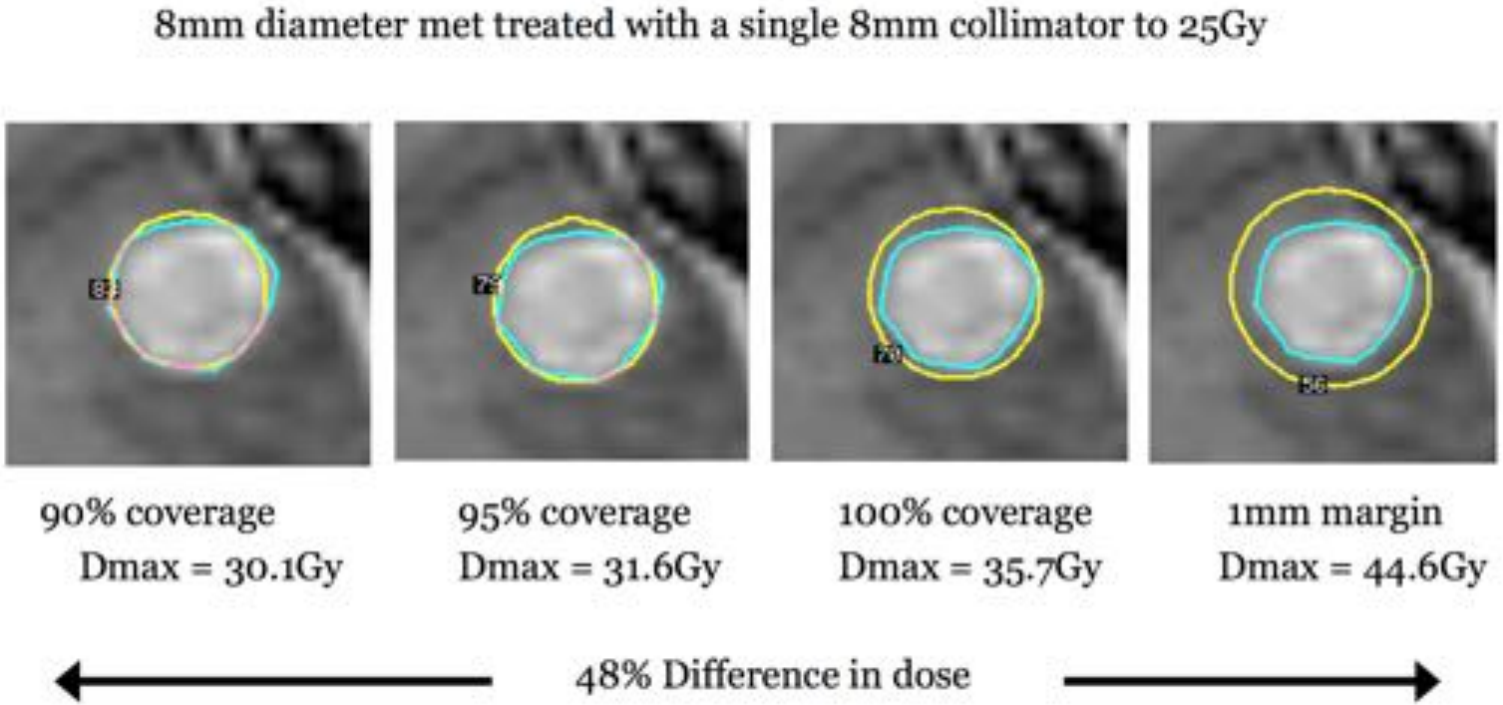
Study	SRT positioning system	Imaging modality	Positioning error
2D-2D image registration for verification of set-up			
Rosenthal 1995	Dental fixation	Orthogonal radiographs	2.3mm ± 1.6mm
Sweeney 2001	Vogele Bale Hohner head holder	Portal imaging	1.9mm ± 1.2mm
Kumar 2005	Gill-Thomas-Cosman	Portal imaging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



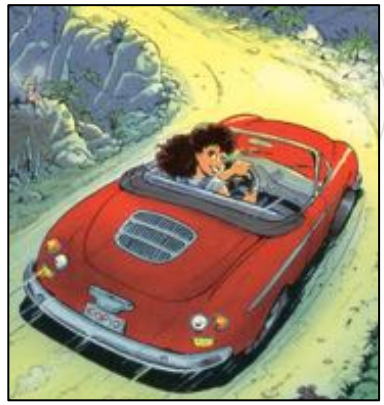
Dose prescription and margins

- 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!!!

ESTRO

Stereotactic body radiotherapy for stage I NSCLC

Practice in Würzburg using Elekta technology

Matthias Guckenberger

UniversityHospital Zurich

Medical history

72 year old male

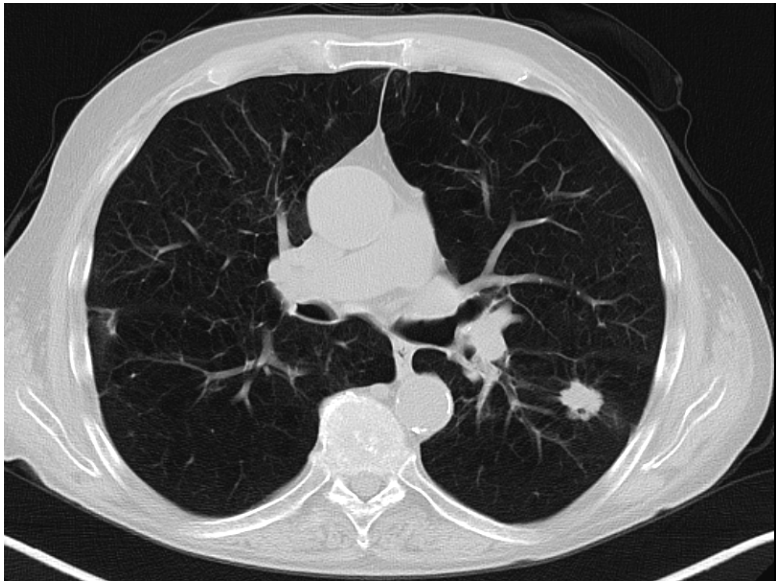
Smoking history with 30 py
O2 supply in rest: 1.5 l/min

Co-morbidities:

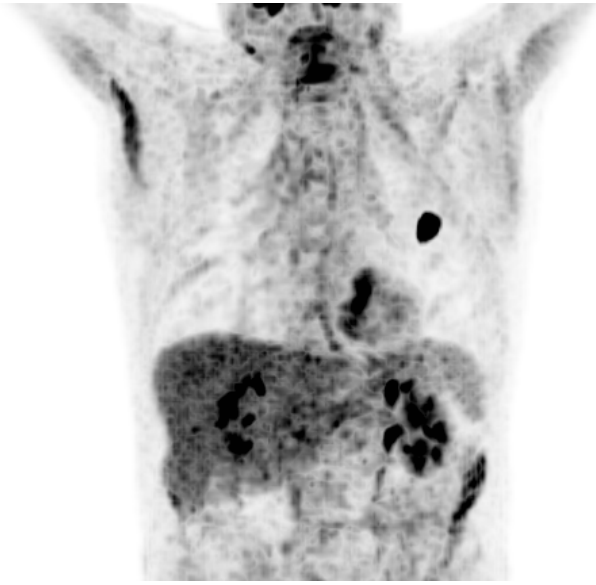
- COPD GOLD IV
- Pulmonary emphysema
- Hypertension
- Osteoporosis

Medical history

- Patient complained increased shortness of breath in May 2012
- Approached his primary physician
- Treatment with antibiotics and steroids
- No improvement after 2 weeks: referred to specialized lung clinic



1.8cm lesion in left lower lobe



FDG-PET positive lesion: SUV_{max} 20.6
No other FDG-PET positive lesions

Interdisciplinary discussion

Histopathological confirmation of cancer:

- Lesion not accessible for transbronchial biopsy
- Increased risk associated with transthoracic biopsy
- High likelihood of primary NSCLC:
  - ➢ Smoking history
  - ➢ New lesion (patient hat chest CT scan 5 years ago)
  - ➢ FDG-PET positive
  - ➢ Typical CT morphological features: spiculation

Treatment:

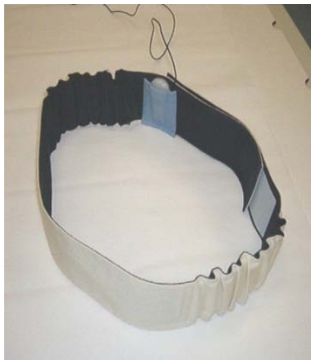
- Pulmonary function not sufficient to undergo lobectomy

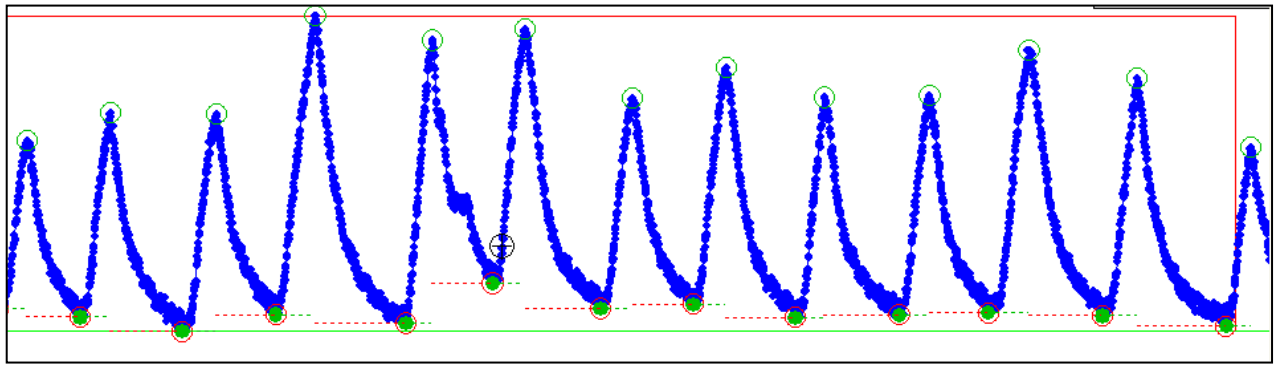
➢ **Radical SBRT**

Treatment planning

Respiration correlated 4D-CT

- Siemens Sensation open 24 slice 4D-CT scanner
- Anzai abdominal pressure belt
  1. Acquisition of a conventional 3D-CT
  2. Acquisition of a respiration correlated 4D-CT
  3. Reconstruction of phases in end-inhalation and end-exhalation





Treatment planning

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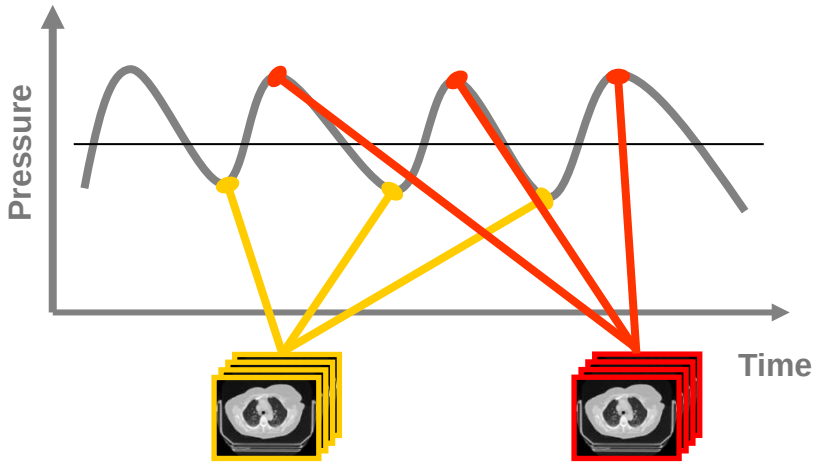


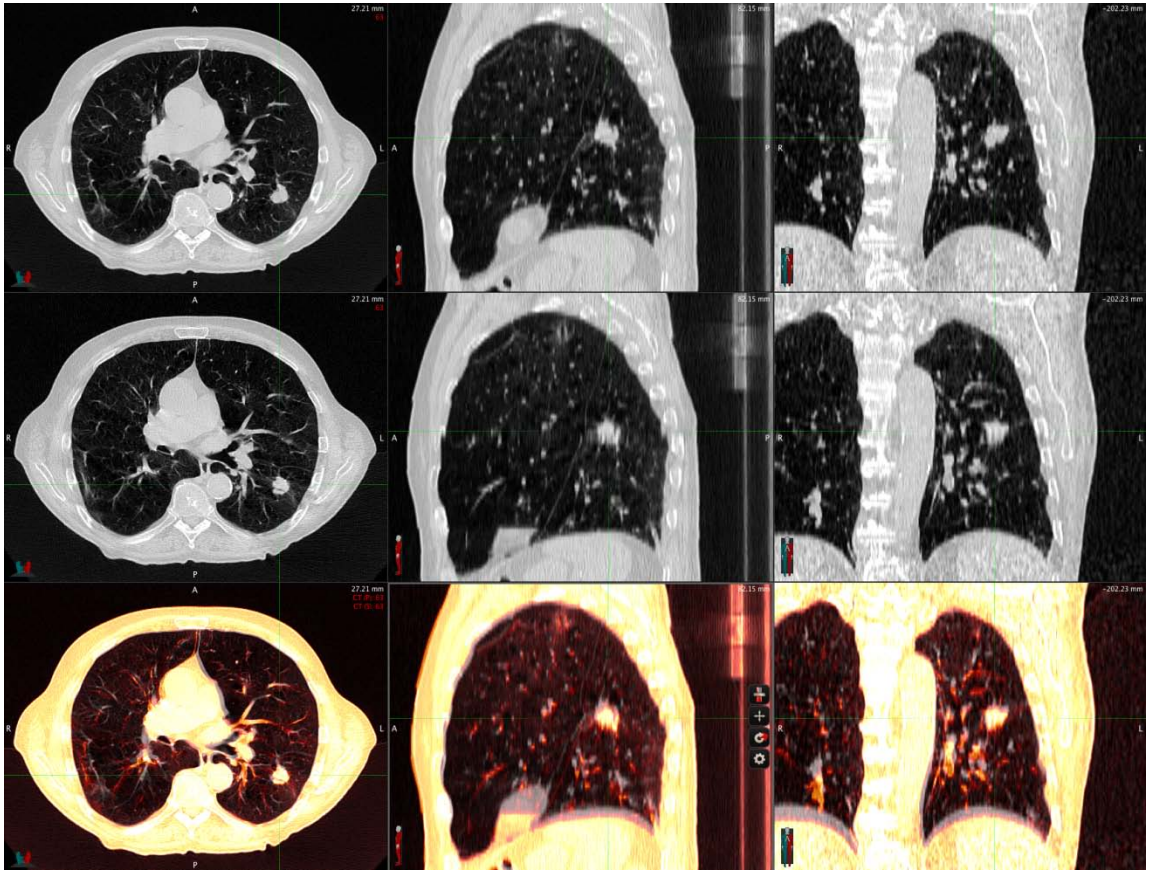
Treatment planning

Target volume definition: respiration correlated 4D-CT

End-exhalation

End-inhalation

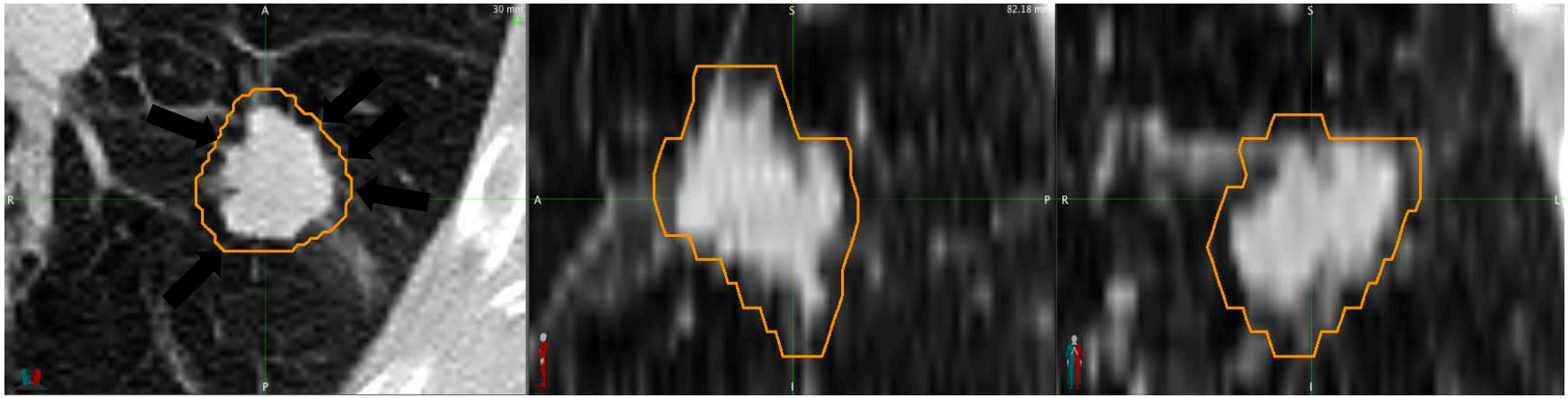
Fusion



Treatment planning

Target volume definition:

GTV = CTV but spiculae included into GTV



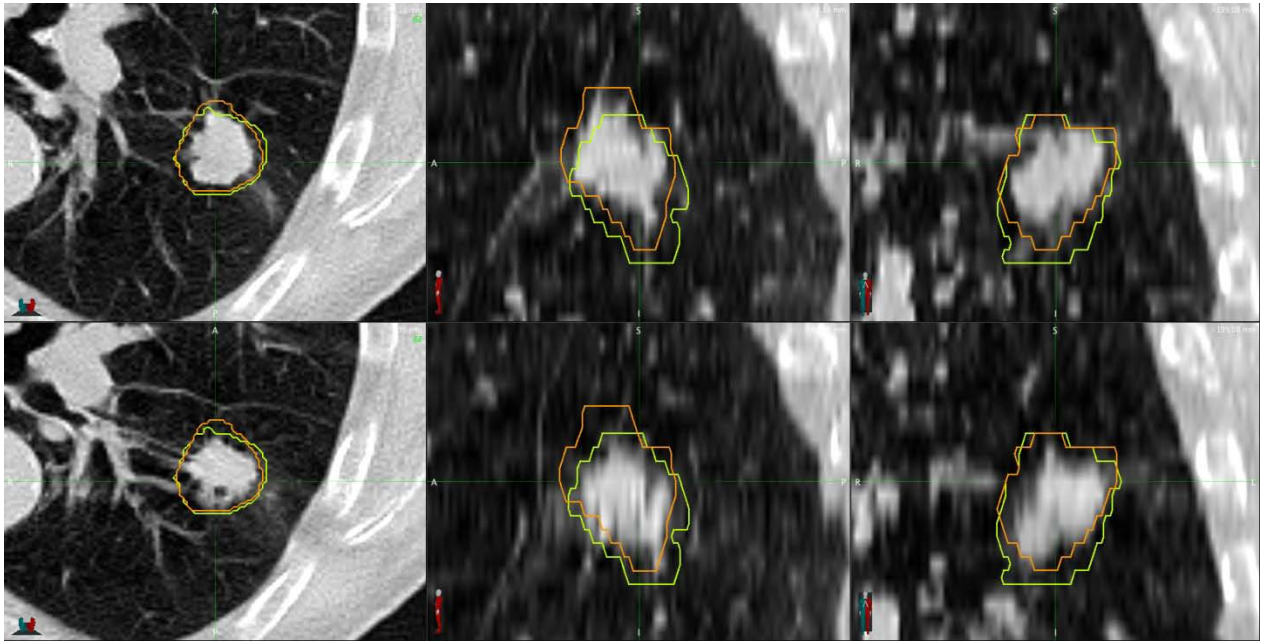
Treatment planning

Target volume definition:

Delineation of the GTV in end-inhalation and end-exhalation CT series

End-exhalation

End-inhalation



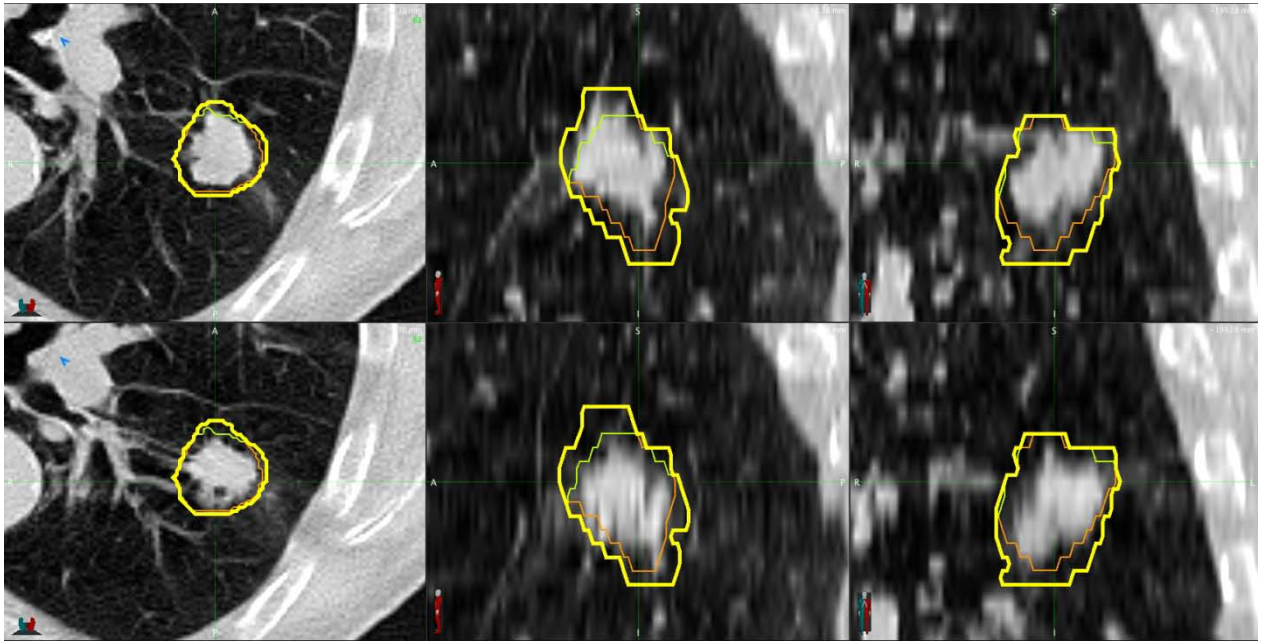
Treatment planning

Target volume definition:

Motion compensation using the internal target volume (ITV) technique

End-exhalation

End-inhalation



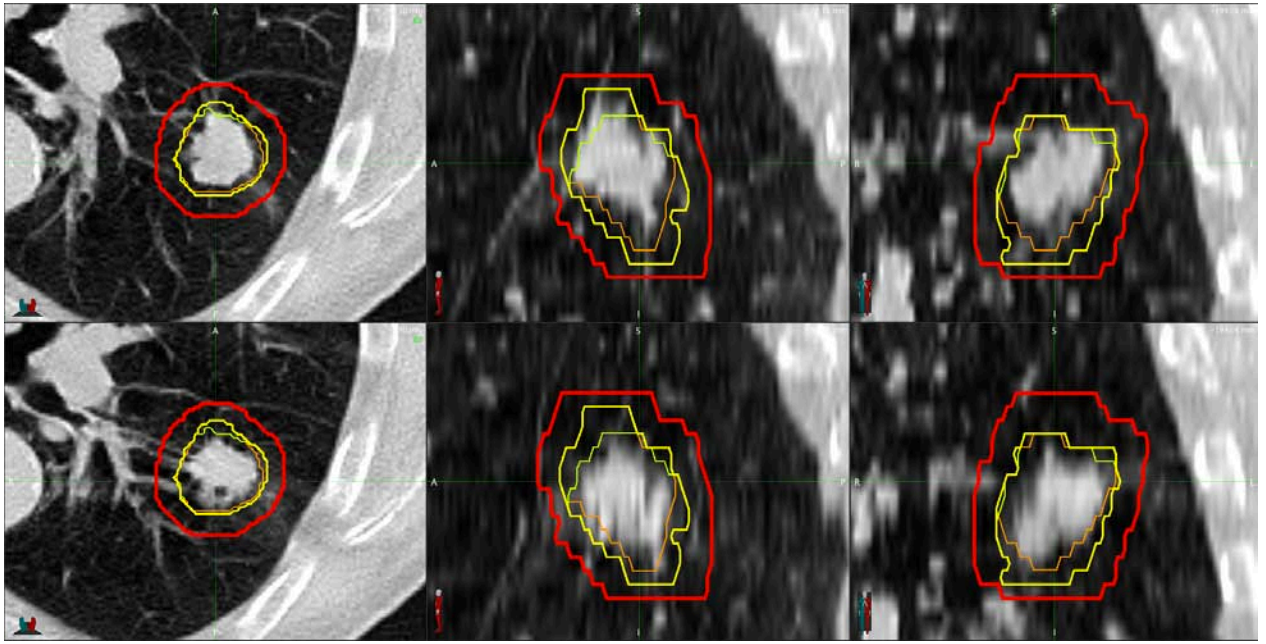
Treatment planning

Target volume definition:

PTV = ITV + 5mm in all directions

End-exhalation

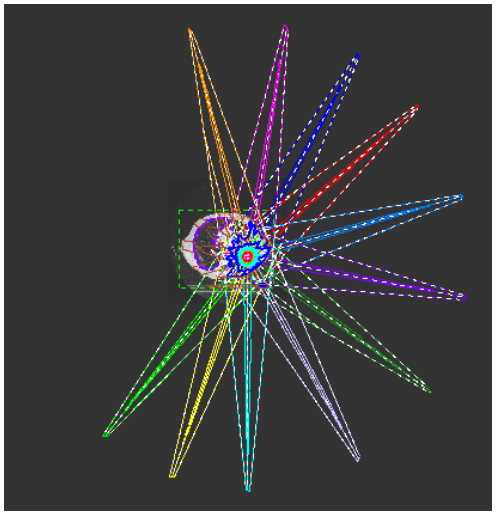
End-inhalation



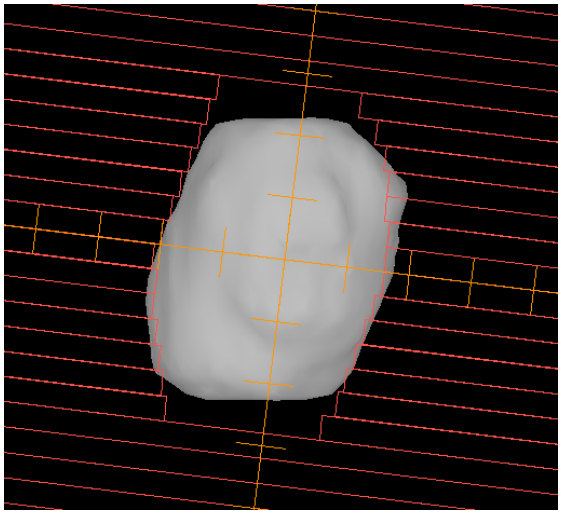
Treatment planning

3D conformal treatment planning:

Inhomogeneous dose distributions by negative “margin” between PTV edge and field size



11 fields
Sparing of contralateral lung

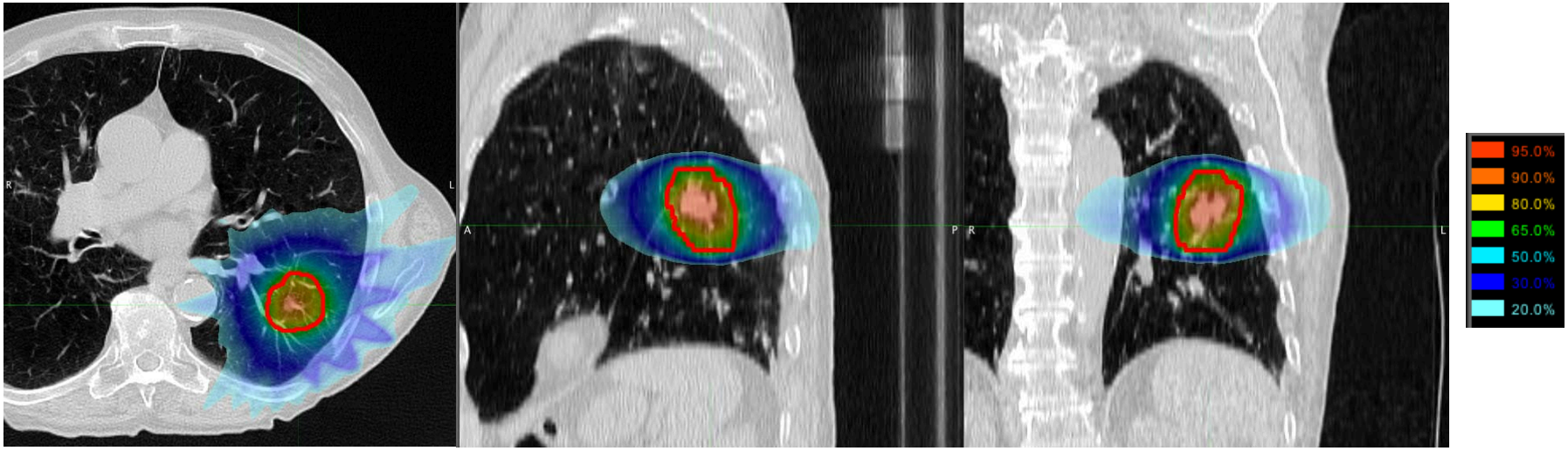


3D conformal beam shaping

Treatment planning

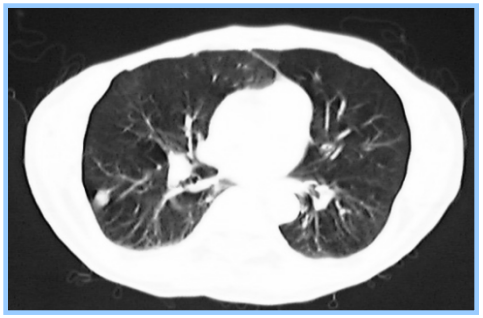
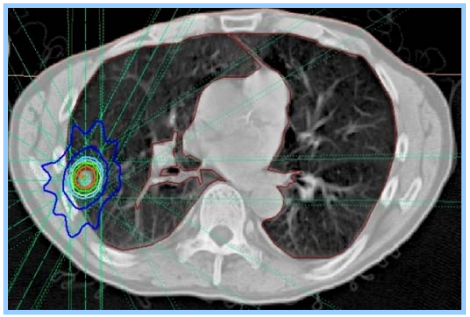
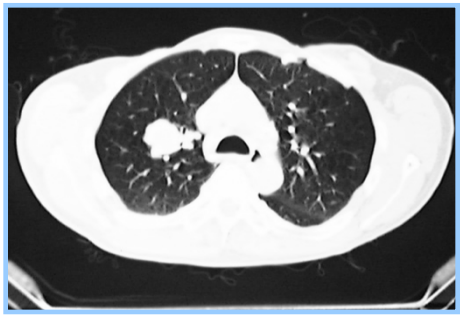
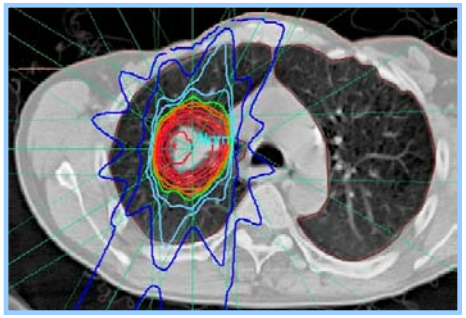
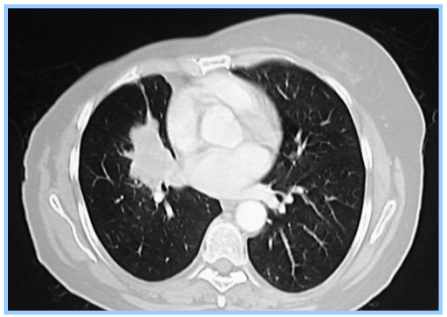
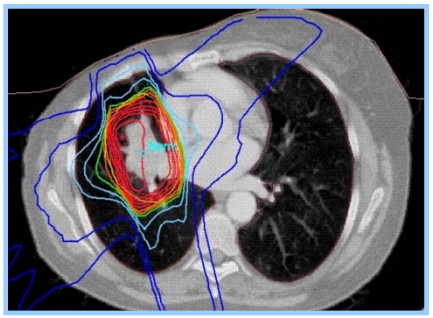
Collapsed cone dose calculation

2mm grid size



Risk adapted fractionation

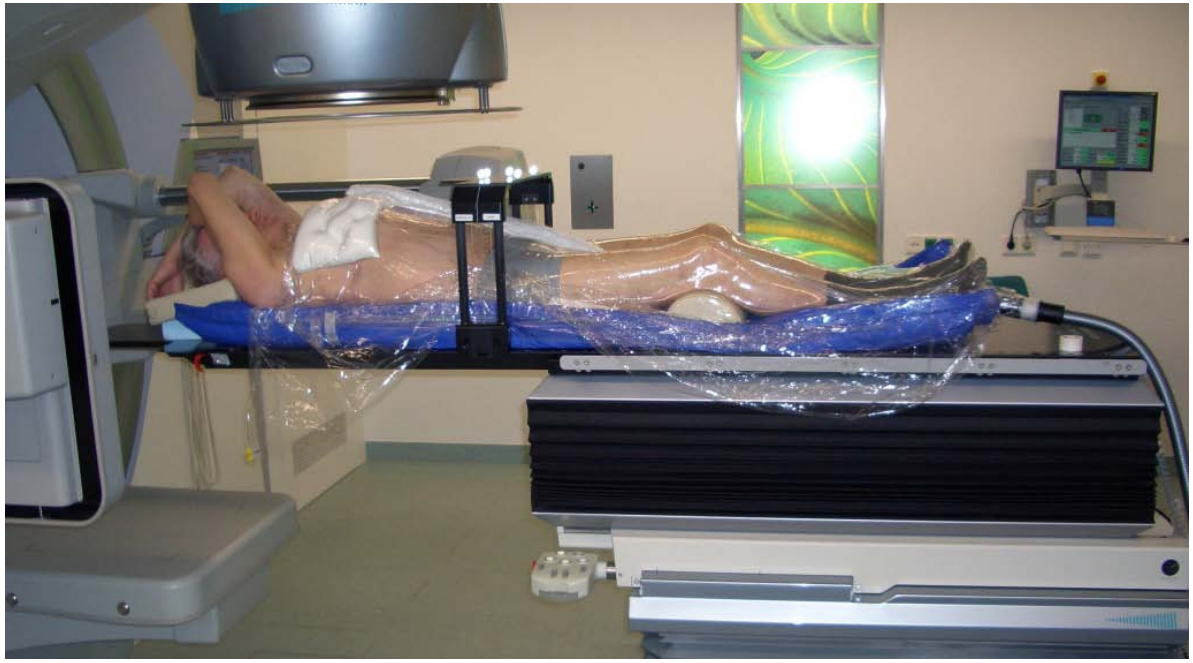
- Peripheral targets (<1-2cm):
  - ***1 x 26Gy to 80% isodose***
- Peripheral targets (<5cm):
  - ***3 x 13.5Gy to 65% isodose***
- Large or central targets (>5cm):
  - ***8 x 6Gy to 65% isodose***

Treatment delivery

Immobilization:

- Encourage using immobilization unless rigorous patient monitoring is performed!
- Only 1 – 5 shots and they must do the job

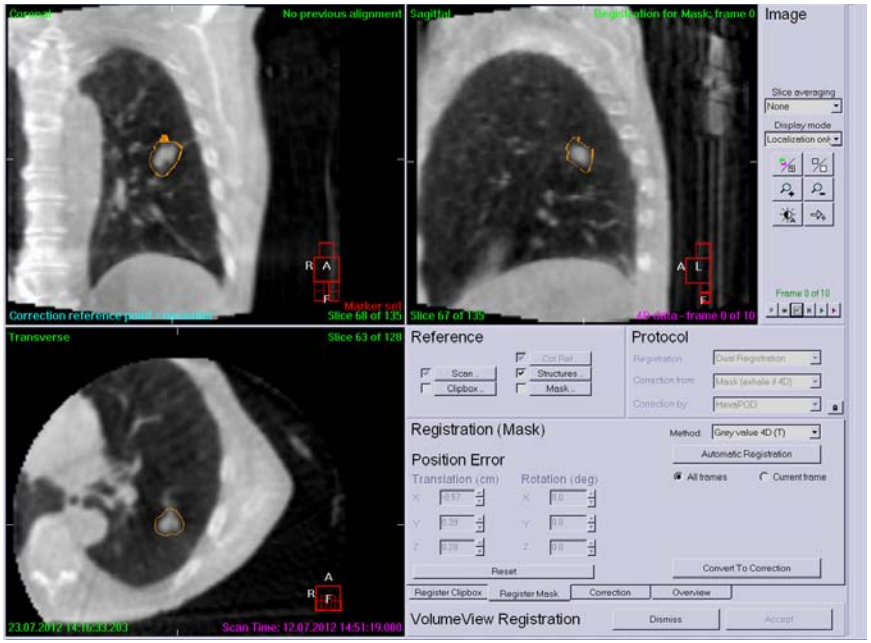


BodyFIX system
with double vacuum

Treatment delivery

Image guidance:

- Performed on a daily basis
- Post-correction and post-treatment imaging should be performed for QA purposes when setting up a SBRT program



Elekta XVI 4.5

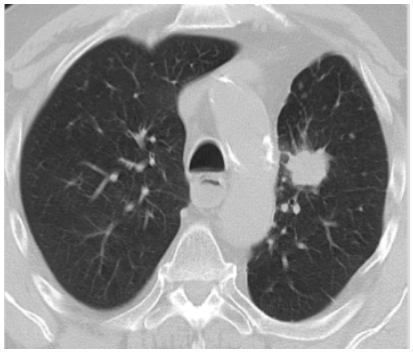
4D ***volumetric*** IGRT

Full integration of breathing motion into the IGRT work-flow

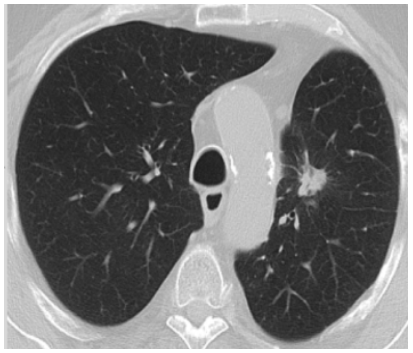
Follow-up

Differentiation post-SBRT fibrosis and local recurrence

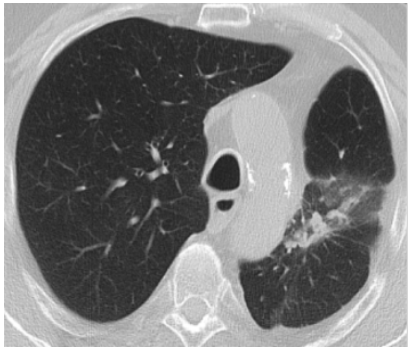
Prior SBRT

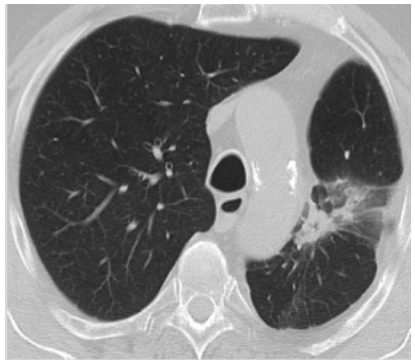


2 months

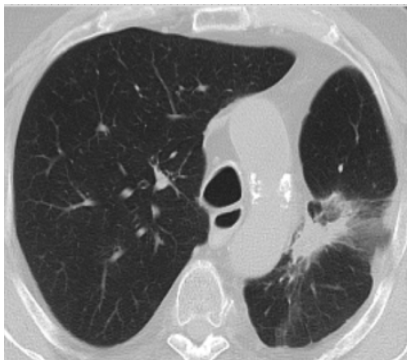


12 months

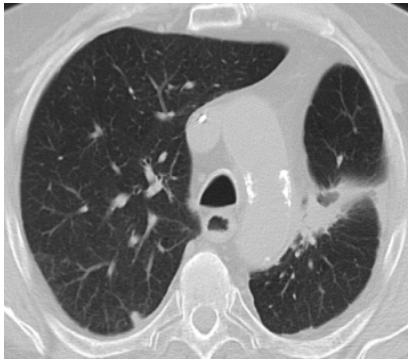




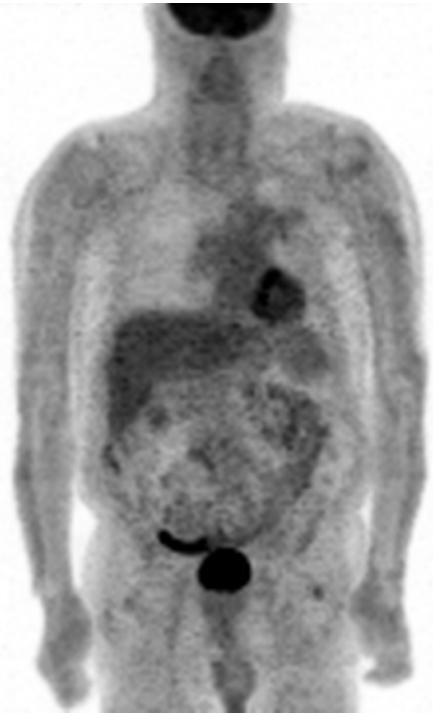
18 months



24 months



30 months



24 months

SBRT in Lung carcinoma:
Oscar lambret with CyberKnife G4

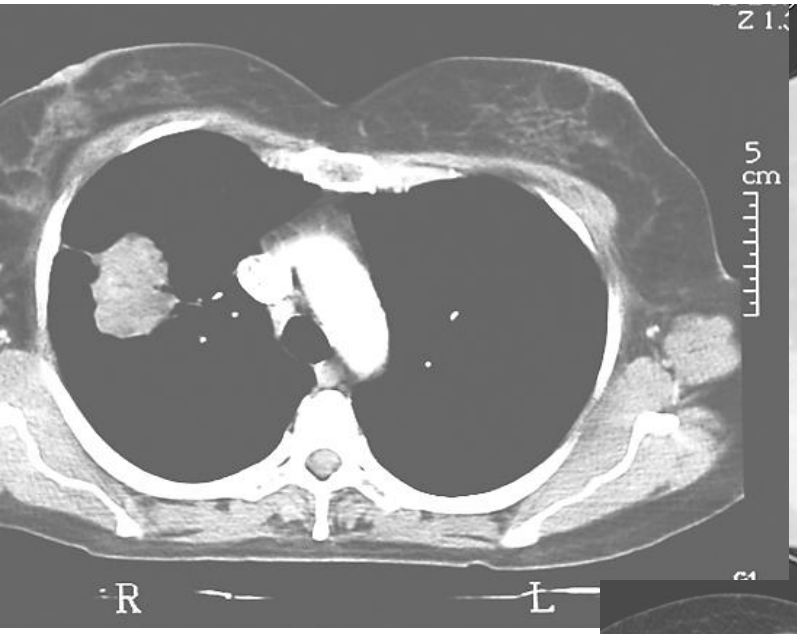
Eric F. LARTIGAU,

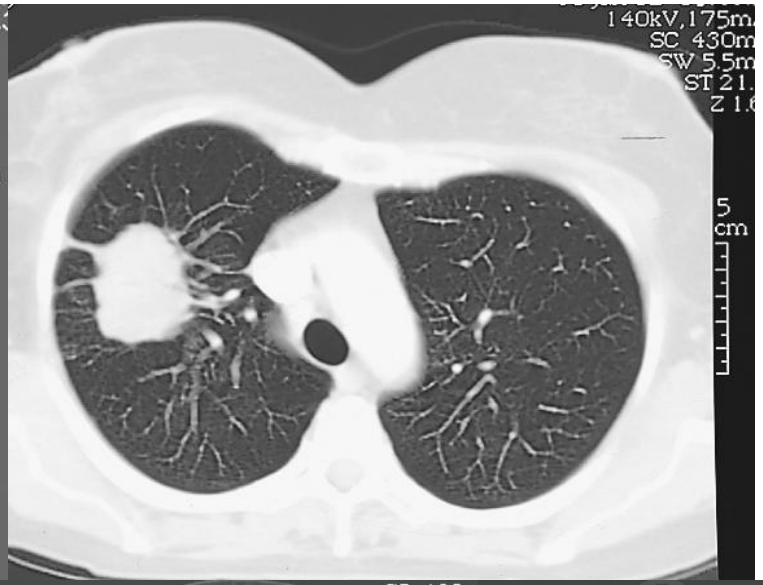
JE BIBAULT & T LACORNERIE

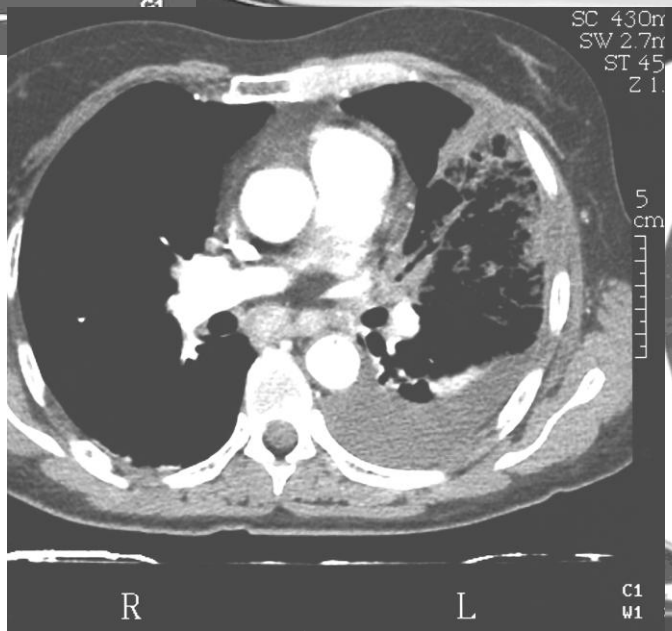
Centre Oscar Lambret &

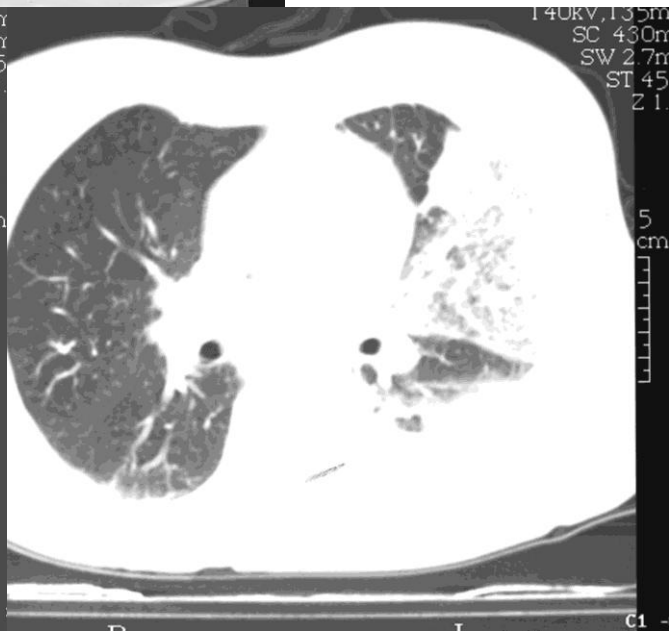
Université Lille Nord de France

Target : Window Width, Reconstruction filters and Level +++





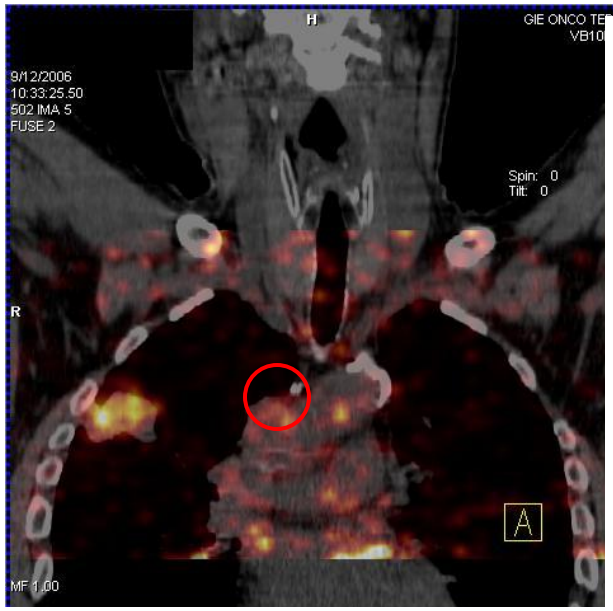


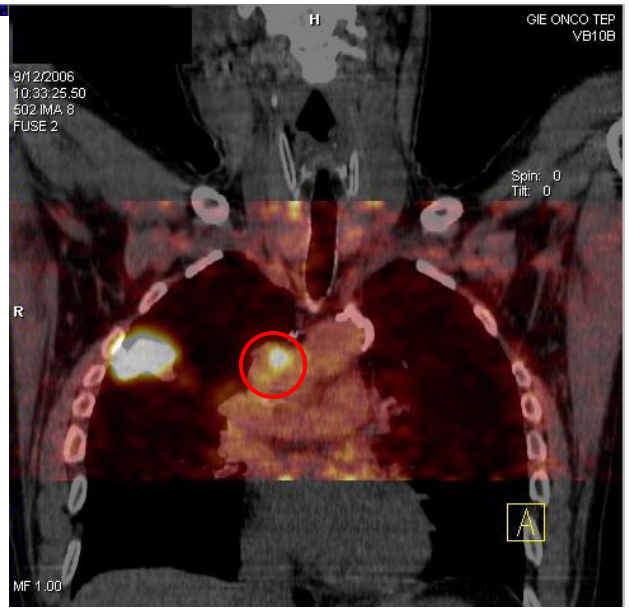


STAGING

CKNO
CyberKnife® Nord Ouest

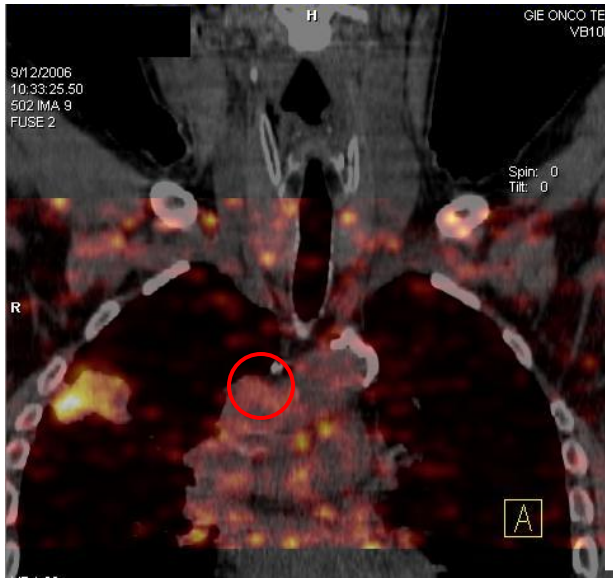
Gate 1 before correction

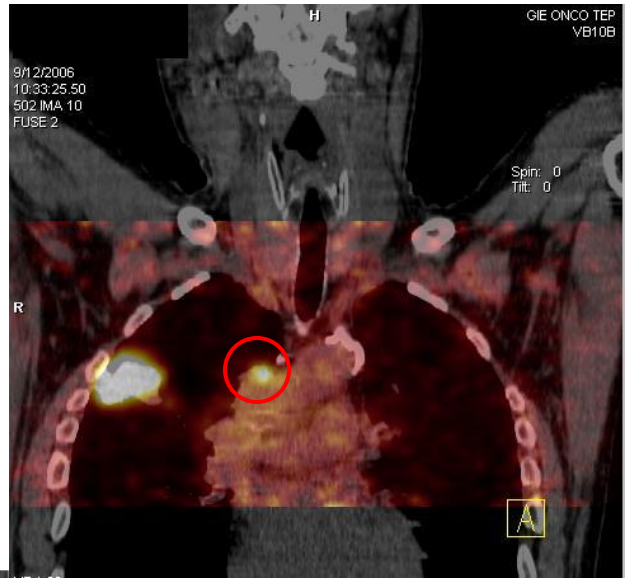




Gate 1 after correction

Gate 3 before correction





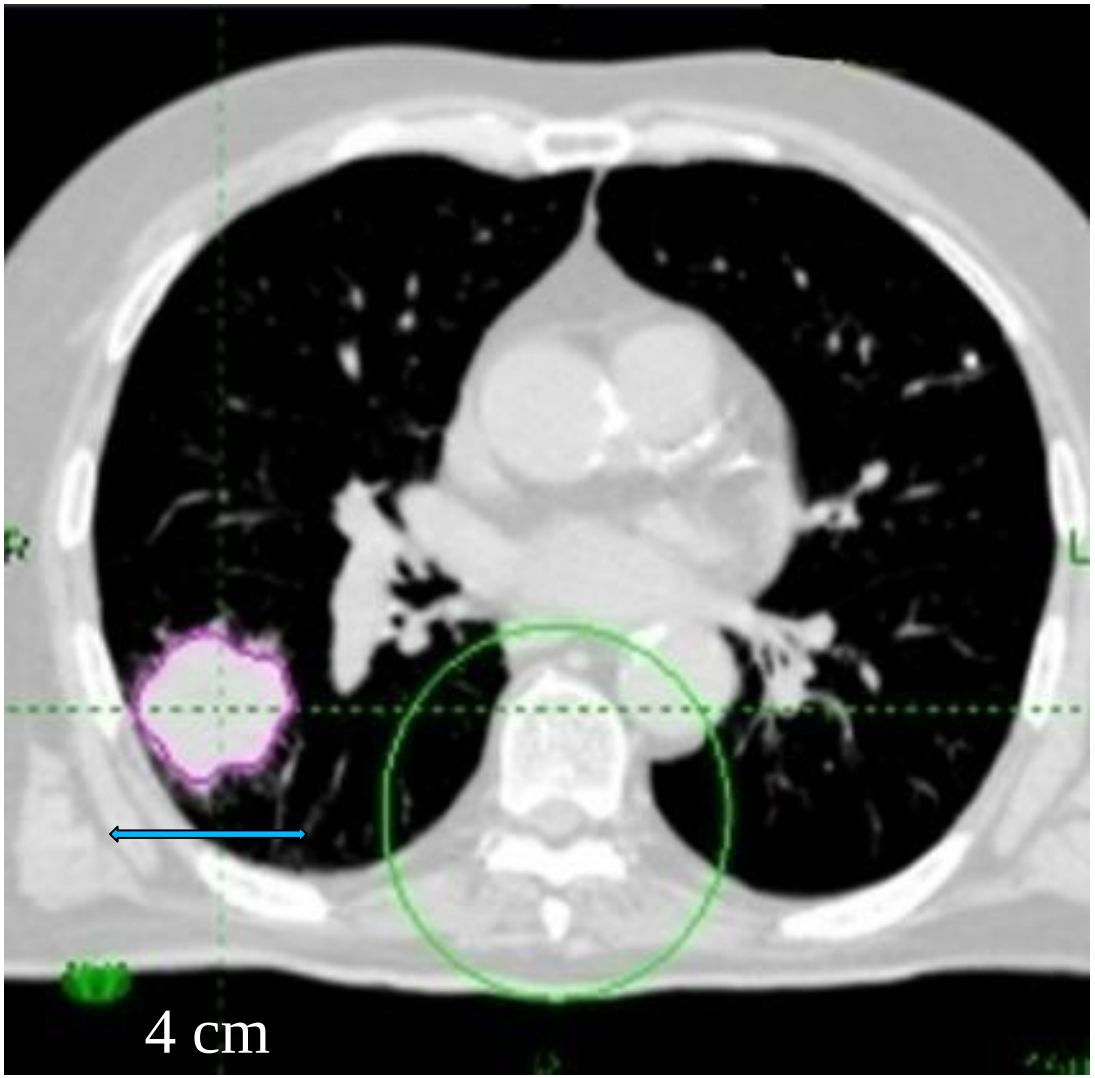
Gate 3 after correction

Man, 72

CKNO
CyberKnife® Nord Ouest

CI to surgery

Multidsciplinary choice : by **law**

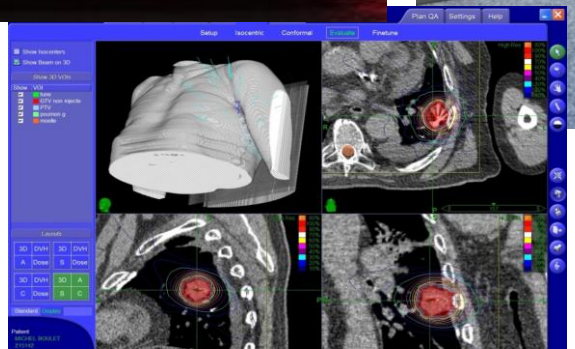


Real Time Dynamic tracking

Free breathing

Internal markers (bone,fiducials)
external markers (diodes)

Couch never moves !!!!



Methods

- Treatment methods :
  - With tumor tracking :
    - Synchrony (fiducials)
    - Xsight Lung (TTV)
  - Without tumor tracking :
    - Xsight Spine + ITV (4D CT-Scan)

Treatment Planning:

- Pre-Treatment evaluation:
  - PET/CT (never used for image fusion)
  - Pulmonary function tests
  - Biopsy proven malignancy (2/3)
- Imaging: CT scan, supine position, arms along torso
- No”strong” immobilization !!
- Contouring:
  - GTV directly contoured in pulmonary CT window
  - GTV to PTV expansion: 5 mm in all directions
  - OARs: lungs, heart, esophagus, trachea, spinal cord, pacemaker

Critical structures
18 Gy X 3

- Spinal cord: max dose 18 Gy (6 Gy per fract.)
- Esophagus: max dose 27 Gy (9 Gy per fract.)
- Trachea / bronchi: 30 Gy (10 Gy per fract.)
- Lungs: V5 < 50%
  V10 < 35 %
  Vtotal-V11 > 1500 cm^3

Contraintes sur les organes à risque v4

Département Universitaire de Radiothérapie - Centre Oscar Lambret - 59020 Lille Cedex

CKNO
CyberKnife® Nord Ouest

Encéphale et œil	> 15 fractions	6 f	5 f	3 f	1 f
Encéphale irradiation totale	max 54 Gy				
Encéphale irradiation partielle	V(encéphale-CTV)60 < 10 cm3			V18 < 1 cm3	V12 < 5 cm3
	max 64 Gy			max 23 Gy	max 15 Gy
Lobes temporaux	max 54 Gy				
Tronc cérébral	max 54 Gy			max 17 Gy	max 12 Gy
Hypophyse	max 50 Gy				
Chiasma		21,5 < 0,2 cm3	V20 < 0,2 cm3	V15 < 0,2 cm3	V8 < 0,2 cm3
	max 54 Gy	max 27 Gy	max 25 Gy		max 10 Gy
Nerf optique et papille	max 54 Gy	V21,5 < 0,2 cm3	V20 < 0,2 cm3	V10 < 0,5 cm3	V8 < 0,2 cm3
		V27 < 0,003 cm3	V25 < 0,003 cm3	V15 < 0,2 cm2	V10 < 0,035 cm3
Rétine	V45 < 50 %				
Œil	V35 < 50 %				
Cristallin	max 6 Gy	max 6,5 Gy	max 6 Gy		
Cornée	max 30 Gy				
Glande lacrymale	V26 < 50 %	V18 < 50 %		V9 < 50 %	
Artère carotide					max 23 Gy

Tête et cou	> 15 fractions	6 f	5 f	3 f	1 f
Cuir chevelu, nuque	max 33 Gy				
Conduit auditif, oreille moyenne	max 50-55 Gy				
Oreille interne	V45 < 50 %	max 30 Gy	max 27,5 Gy	max 20 Gy	max 12 Gy
	max 50 Gy				
Articulation temporo-mandibulaire	max 55 Gy				
Mandibule	max 70 Gy				
Parotides	V15 < 65 %				
	V25 < 50 %				
	V30 < 45 %				
Parotide unique	V20 < 50 %				
Sous-maxillaires	V35 < 50 %				
Cavité buccale	V15 < 80 %				
	V30 < 50 %				
	V45 < 25 %				
	max 50 Gy				
Larynx	V30 < 60 %				V10 < 4 cm3
	V45 < 50 %				V20 < 0,035 cm3
	max 65 Gy				
Pharynx	V50 < 50 %				
Thyroïde	V50 < 50 %				
Peau		V32 < 10 cm3	V30 < 10 cm3	V22 < 10 cm3	V14 < 10 cm3
		max 35 Gy	max 32 Gy	max 24 Gy	max 16 Gy

Moëlle et nerfs	> 15 fractions	6 f	5 f	3 f	1 f
Moëlle épinière	V45 < 10 %	V21,5 < 1.2 cm3	V20 < 1.2 cm3	V16 < 1.2 cm3	V7 < 1,2 cm3
	max 50 Gy	V24 < 0,25 cm3	V22,5 < 0,25 cm3	V18 < 0,25 cm3	V10 < 0,25 cm3
	max 40 Gy - radiochimio	max 32 Gy	max 30 Gy	max 22 Gy	V14 < 0,035 cm3
Plexus brachial	max 55 Gy	V32 < 3 cm3	V30 < 3 cm3	V22,5 < 5 cm3	V14 < 3 cm3
		max 34 Gy	max 32 Gy	max 24 Gy	V18 < 0,035 cm3
Queue de cheval	max 50 Gy	V32 < 5 cm3	V30 < 5 cm3	V22 < 5 cm3	V14 < 5 cm3
		max 37 Gy	max 34 Gy	max 24 Gy	V16 < 0,035 cm3
Plexus sacré	max 54 Gy	V32 < 3 cm3	V30 < 3 cm3	V22 < 3 cm3	V14 < 3 cm3

Thorax	> 15 fractions	6 f	5 f	3 f	1 f
Poumons (D+G) sans PTV	V20 < 35 %	V 13,5 < 1500 cm3	V 12,5 < 1500 cm3	V5 < 50 %	V5 < 50 %
	V30 < 20 %	V14,5 < 1000 cm3	V13,5 < 1000 cm3	V10 < 30 %	V7 < 1500 cm3
		(Vtotal - V13,5) > 1500 cm3	(Vtotal - V12,5) > 1500 cm3	(Vtotal - V11) > 1500 cm3	(Vtotal - V7) > 1500 cm3
Poumon unique	V5 < 60 %			V20Gy < 20%	
	V20 < 10 %				
Poumon homolatéral rt mammaire	V15 < 50 %				
	V20 < 35 %				
	V30 < 20 %				
	V35 < 15 %				
Poumon controlatéral rt mammaire	V10 < 50 %				
	V12 < 35 %				
	V15 < 20 %				
Trachée, grosses bronches	max 80 Gy	V19 < 4 cm3	V18 < 4 cm3	V15 < 4 cm3	V10 < 4 cm3
		max 41 Gy	max 38 Gy	V20 < 1 cm3	
				max 30 Gy	V20 < 0,035 cm3
Cœur	V40 < 50 %	V34 < 15 cm3	V32 < 15 cm3	V24 < 15 cm3	max 22 Gy
	V50 < 15 cm3	V43 < 1 cm3	V40 < 1 cm3	max 30 Gy	V16 < 15 cm3
	max 60 Gy				
Cœur irradiation mammaire gauche	V15 < 20 %				
	V20 < 15 %				
	V25 < 10 %				
Gros vaisseaux		V50 < 10 cm3	V47 < 10 cm3	V39 < 10 cm3	V31 < 10 cm3
		max 57 Gy	max 53 Gy	max 45 Gy	max 37 Gy
Œsophage	V45 < 40 %	V21,5 < 10 cm3	V20 < 10 cm3	V15 < 10 cm3	V8 < 10 cm3
	V55 < 30 %	V29,5 < 5 cm3	V27,5 < 5 cm3	V21 < 5 cm3	V14 < 5cm3
		V32 < 0,5 cm3	V30 < 0,5 cm3	V25 < 0,5 cm2	V20 < 0,5 cm3
Sein (sein controlatéral rt mammaire)	V5 < 50 %				
	V7 < 35 %				
	V10 < 20 %				
	V20 < 15 %				

Abdomen	> 15 fractions	6 f	5 f	3 f	1 f
Foie irradiation totale	max 30 Gy				
Foie irradiation partielle	V30 < 50 %	V21 < 50 %	V20 < 50 %	V15 < 50 %	
		V30 < 33%	V28< 33%	V21 < 33%	
	(Vtotal - V30) > 700 cm3	(Vtotal-V22,5) > 700 cm3	(Vtotal-V21) > 700 cm3	(Vtotal-V17) > 700 cm3	(Vtotal-V9) > 700 cm3
Foie / cirrhose irradiation totale	max 28 Gy				
Foie / cirrhose irradiation partielle	V28 < 50 %				
Estomac	V54 < 10 cm3	V30 < 10 cm3	V28 < 10 cm3	V19 < 10 cm3	V13 < 10 cm3
				V21 < 5 cm3	V14 < 5 cm3
	V64 < 0,5 cc			V25 < 0,5 cm3	V16 < 0,5 cm3
Duodénum	V45 < 10 cm3				V8 < 10 cm3
	V50 < 5 cm3	V19 < 5 cm3	V18 < 5 cm3	V15 < 5 cm3	V9 < 5 cm3
	V64 < 0,5 cc	V35 < 0,5 cm3	V32 < 0,5 cm3	V24 < 0,5 cm3	V16 < 0,5 cm3
Intestin grêle	V40 Gy < 200 cm3	V22,5 < 5 cm3	V21 < 5 cm3	V16 < 5 cm3	V10 < 5 cm3
	V50 < 35 cm3	V38 < 0,5 cm3	V35 < 0,5 cm3	V27 < 0,5 cm3	V15 < 0,5 cm3
Colon	V45 < 20 cm3	V27 < 20 cm3	V25 < 20 cm3	V20 < 20 cm3	V11 < 20 cm3
		V32 < 1 cm3	V30 < 1 cm3	V30 < 1 cm3	V22 < 1 cm3
Reins	V12 < 60 %				
	V20 < 50 %			V10 < 50 %	
	V30 < 20 %	(Vtotal - V19,5) > 200 cm3	(Vtotal - V18) > 200 cm3	(Vtotal - V15) > 200 cm3	(Vtotal - V8) > 200 cm3
Rein unique ou insuffisance rénale	V6 < 30 %				
	V15 < 20 %				
	V20 < 10 %				
Hile rénal		V24,5 < 66 %	V23 < 66 %	V18 < 66 %	V10 < 66 %

Pelvis	> 15 fractions	6 f	5 f	3 f	1 f
Rectum	V50 < 50 %	V27 < 20 cm3	V25 < 20 cm3	V20 < 20 cm3	V11 < 20 cm3
	V60 < 40 %	max 40,5 Gy	max 38 Gy	max 30 Gy	max 22 Gy
	V65 < 25 %				
	V70 < 20 %				
	V75 < 10 %				
Anus	V56 < 50 %				
	V70 < 30 %				
Vessie	V65 < 50 %	V19 < 15 cm3	V18 < 15 cm3	V15 < 15 cm3	V9 < 15 cm3
	V70 < 25%	V40 < 5 cm3	V37,5 < 5 cm3	V30 < 5cm3	V22 < 5 cm3
	V80 < 15 %				
Vagin tiers supérieur	max 120 Gy				
Vagin tiers moyen	max 90 Gy				
Vagin tiers inférieur	max 70 Gy				
Vulve	V30 < 30 %				
Bulbe pénien	V50 < 90 %	V32 < 3 cm3	V30 < 3 cm3	V22 < 3 cm3	V14 < 3 cm3
	V70 < 70 %	V54 < 0,5 cm3	V50 < 0,5 cm3	V42 < 0,5 cm3	V34 < 0,5 cm3
Testicules (fonction de reproduction)	max 1,5 Gy				
Testicules (fonction hormonale)	V30 < 10 %				
Ovaires	max 1,5 Gy				
Moelle osseuse du bassin	V10 < 90 %				
	V20 < 80 %				
	V25 < 70 %				
Cols, têtes fémorales, grand trochanter	V50 < 10 %	V32 < 10 cm3	V30 < 10 cm3	V22 < 10 cm3	V14 < 10 cm3

Os et Membres	> 15 fractions	6 f	5 f	3 f	1 f
Articulations des membres	V45 < 15 cm3				
Tête fémorale		V32 < 10 cm3	V30 < 10 cm3	V22 < 10 cm3	V14 < 10 cm3
Côtes		V37,5 < 1 cm3	V35 < 1 cm3	V29 < 1 cm3	V22 < 1 cm3
		V46 < 0.035 cm3	V43 < 0.035 cm3	V37 < 0.035 cm3	V30 < 0.035 cm3
Os	max 60 Gy				

La dose de tolérance s'exprime de la façon suivante : Vx < Y %
la dose X Gy ne doit pas être délivrée dans plus de Y% du volume de l'OAR
ex : V20 < 30 % = 20 Gy ne doivent pas être délivrés dans plus de 30 % du volume de l'organe

La dose « max » ne doit pas être délivrée sur plus de 2% de l'organe à risque à l'exception de la moëlle où cette contrainte est absolue.

Priorités entre les contraintes :
Organes en série (moelle, grêle, rectum …) : respecter en priorité les contraintes aux fortes doses
Organes en parallèle (foie, poumon, rein …) : respecter en priorité les contraintes aux doses faibles et moyennes

Sauf indication contraire : privilégier la couverture du PTV puis les contraintes aux OAR, puis la réduction de nombre d'UM

« Ces niveaux de dose peuvent éventuellement être dépassés sous réserve d'une justification liée au contrôle local et à la survie du patient,
après information et accord de celui-ci.
Ces dépassements sont notamment possibles lorsqu'ils concernent des organes à risque pour lesquels les lésions radiques n'ont pas de conséquences vitales. »

Consensus 2007 – SFRO - Guide des procédures en radiothérapie externe

Références

IJROBP vol 73 n3 supplément spécial 2010
Consensus 2007 – SFRO – Guide des procédures en radiothérapie externe
Timmerman ; Seminars in Radiation Oncology 2008;18;4:215-222
Grimm ; J App Clin Med Phys 2011
Milano ; Seminars in Radiation Oncology 2007 ; 17;131-140
Emami ; Int J Radiat Oncol Biol Phys 21:109-122, 1991
Cancer Radiothérapie 14 ; 2010 (tout le numéro)

contact : x-mirabel@o-lambret.fr

Document édité le 21/10/2011

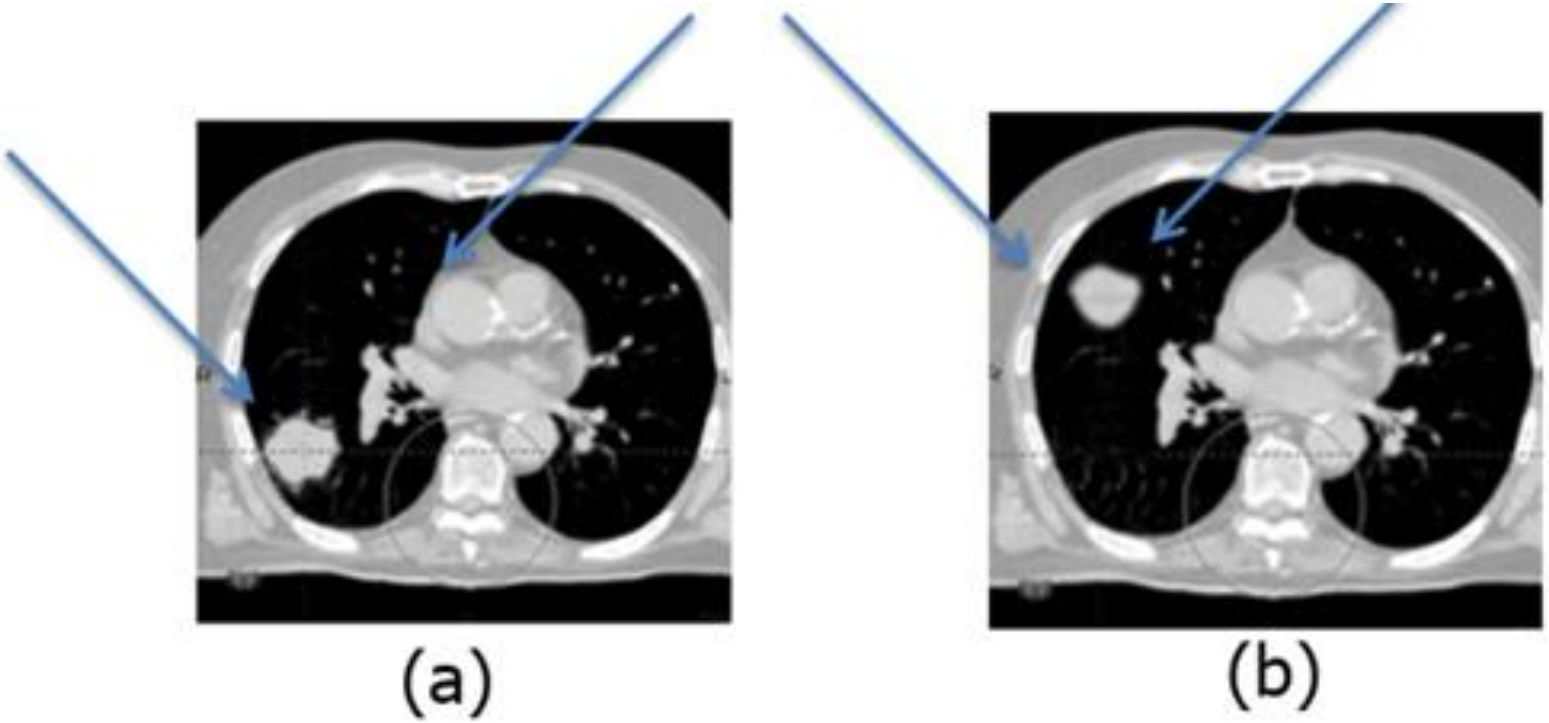
Validation en réunion de dépatement le 17 octobre 2011

Xsight Lung Tracking System

- Does not require any fiducial,
- 15 to 60 mm lesions,
- Tumor’s position is correlated to the position of the external body marker,
- System periodically checks the correlation model,
- 1,5 mm precision.

Patient selection criteria

- 15 to 60 mm lesion,
  - In the lung parenchyma,
  - 15 mm from chest wall,
  - No 45° projection on the spine (⟶ 1view tracking).



Xsight™ Lung Tracking System

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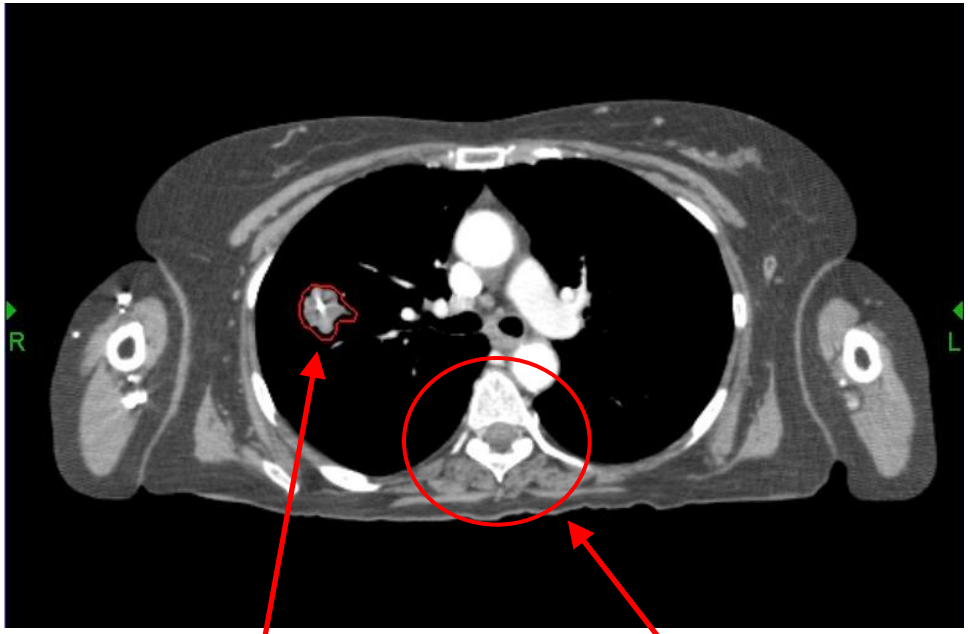
Align Global Patient Position (6D)
Using Xsight™ Spine System

↓

Move Patient from Align Center
to Treatment Center Using AutoCouch

↓

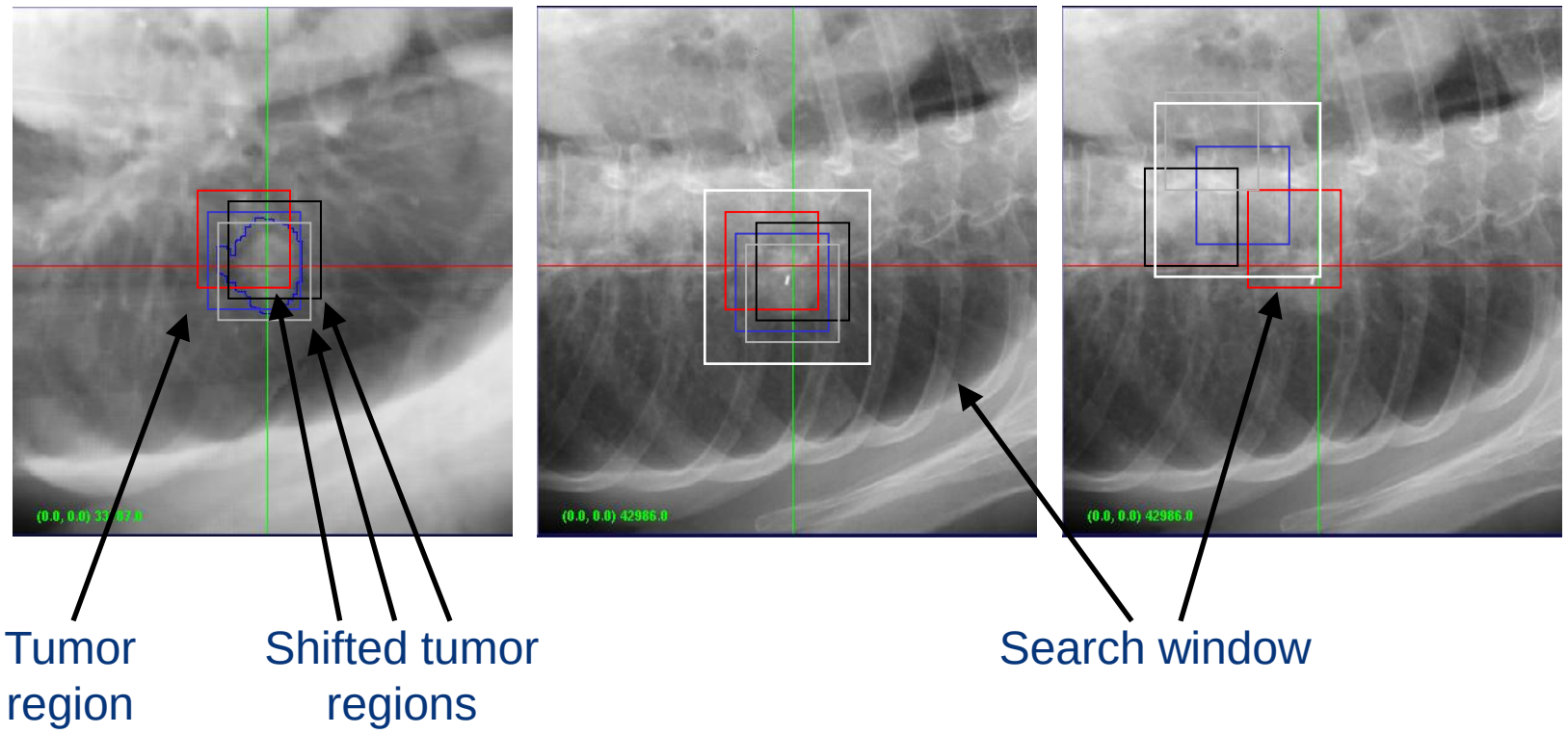
Track Moving Tumor (3D)
Using Direct Tumor Registration



Dynamic lung tumor

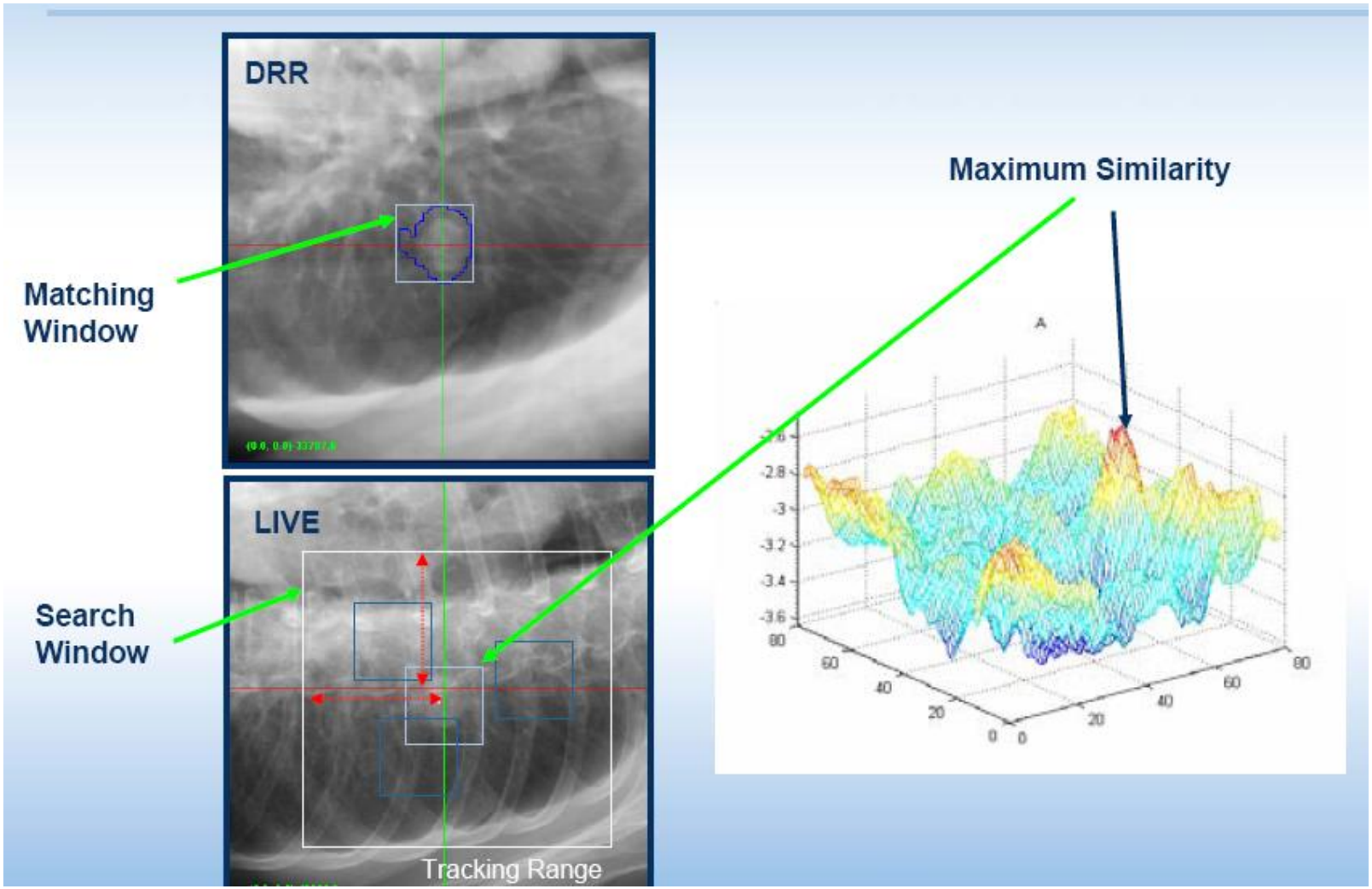
Static spine region

Xsight™ Lung Tracking System

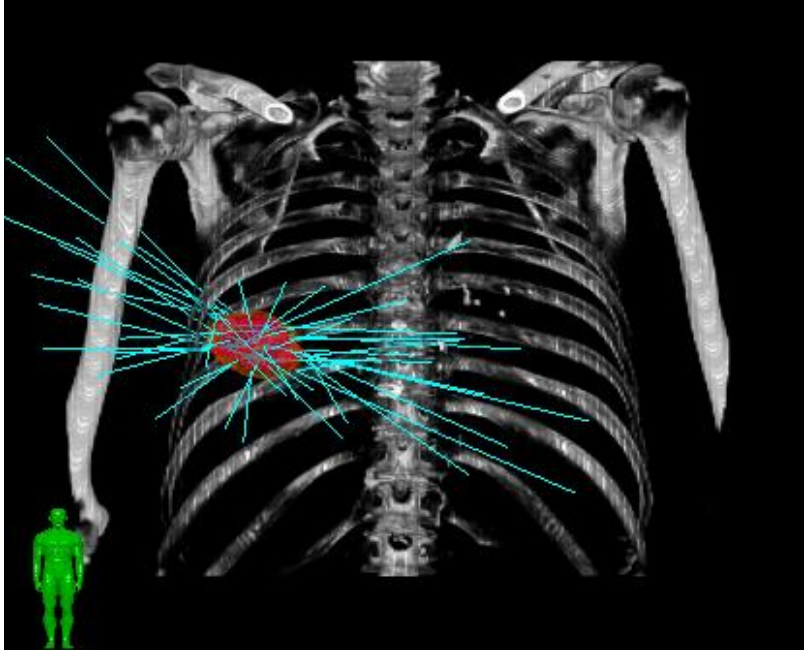


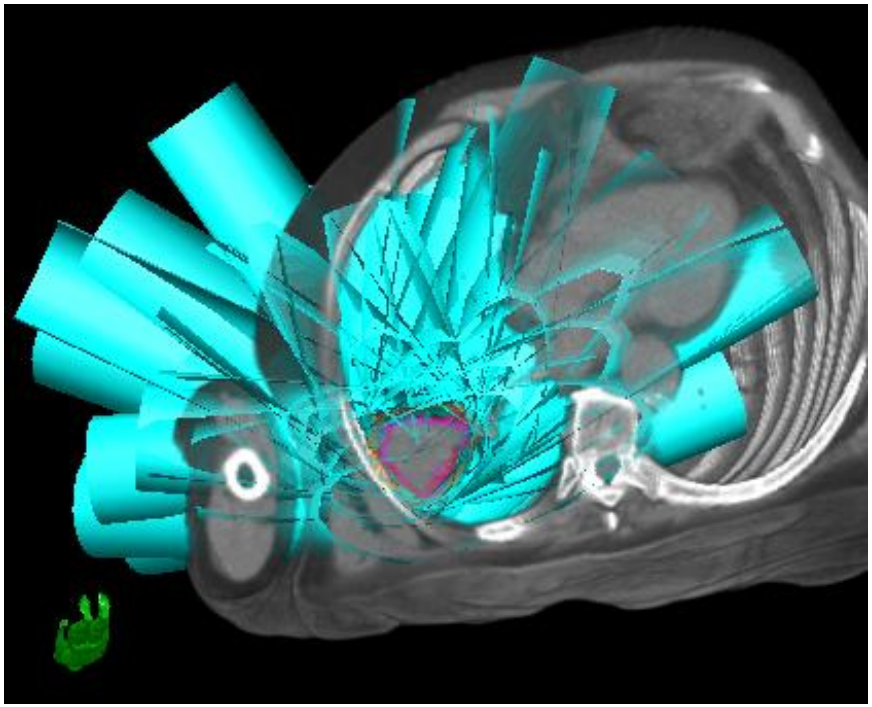
Correct detection: Tumor region and shifted regions match consistently

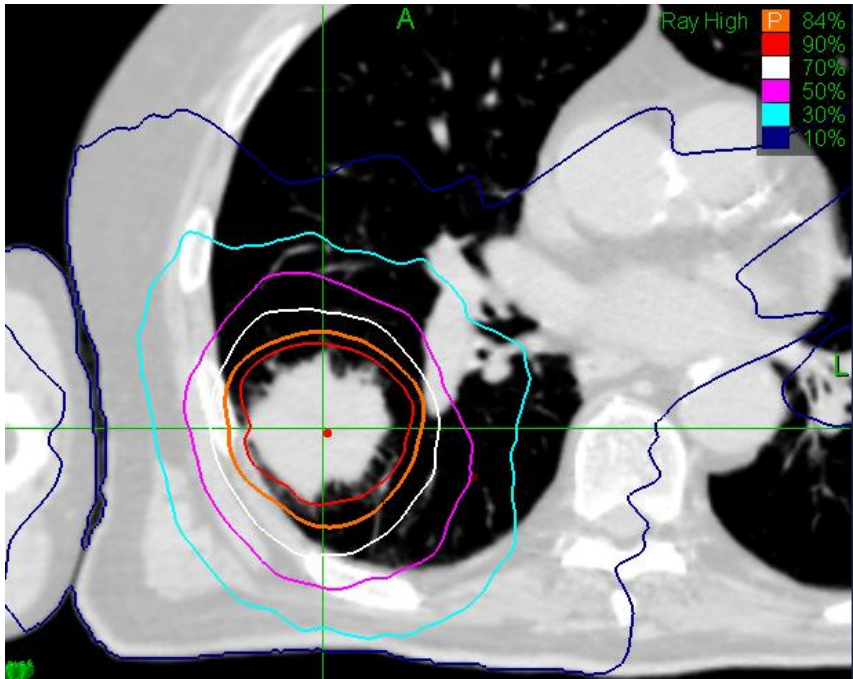
Correlation model



CK: > 100 beams per fraction
Non isocentric
Non coplanar
TT time : 40 to 60 min



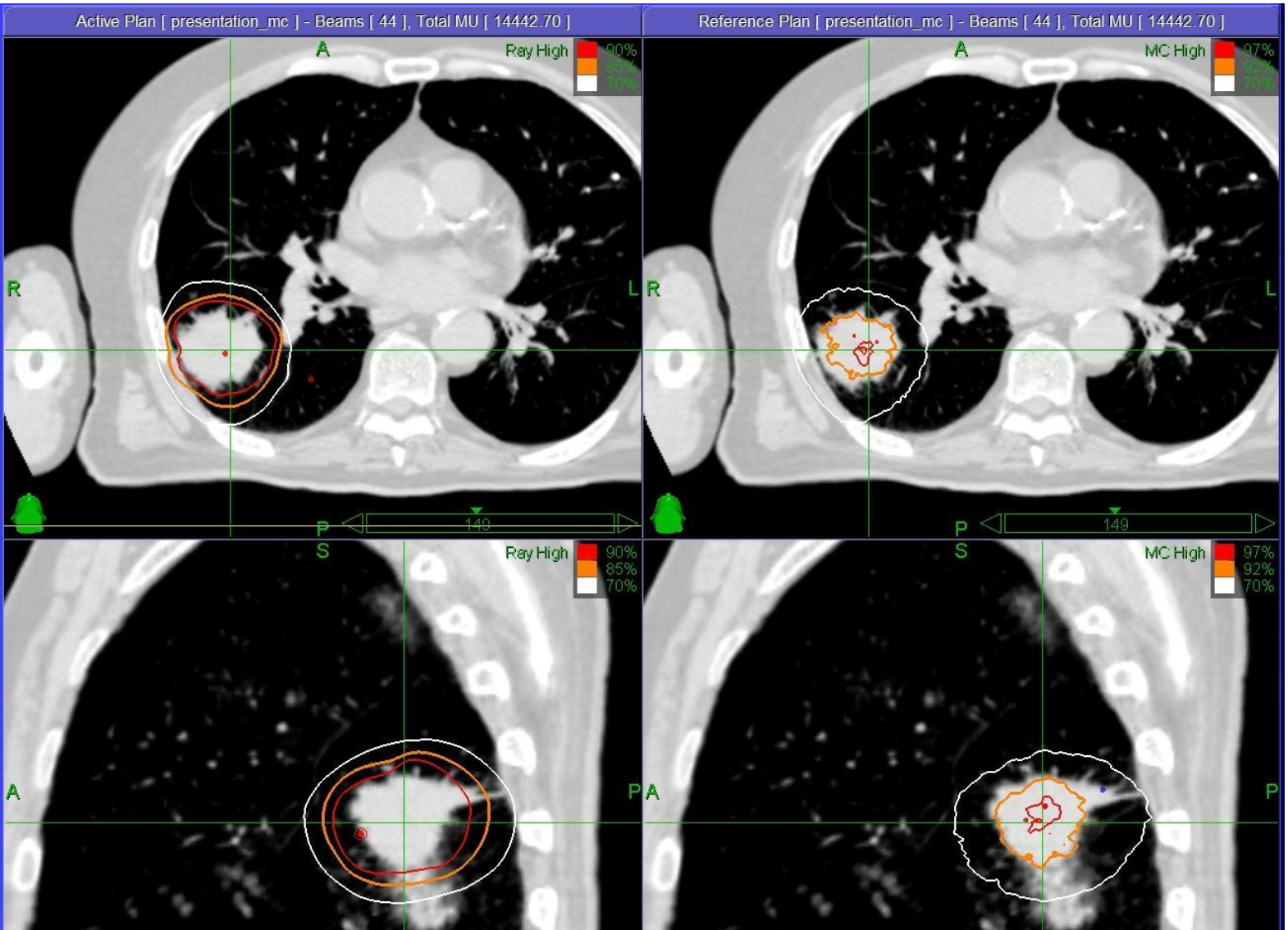




Lung

Ray-Tracing : 3 x 20 Gy

Monte-Carlo :



— **63.5** Gy

— **60.0** Gy

— **50.0** Gy

Role of algorithms

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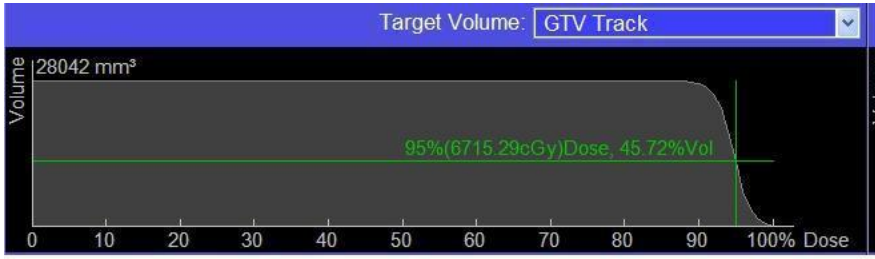
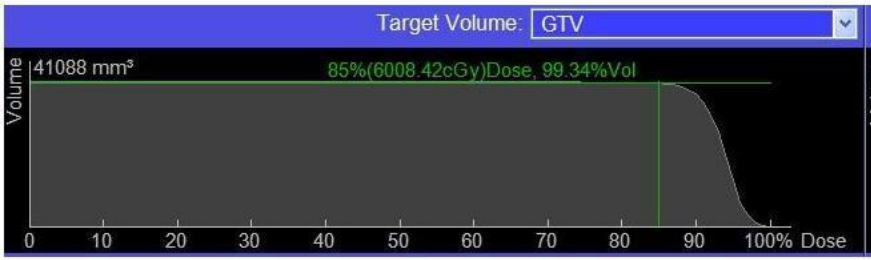
Ray- Tracing :



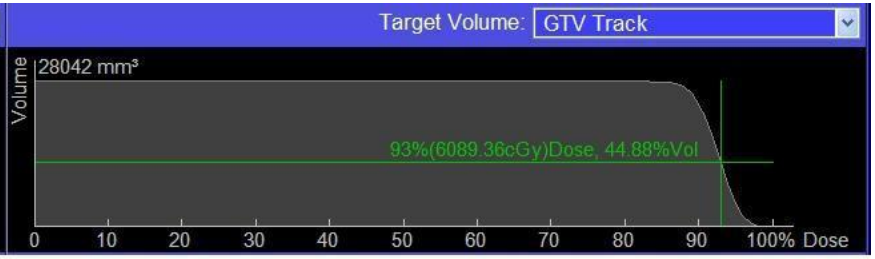
Tracking GTV median dose : 67 Gy



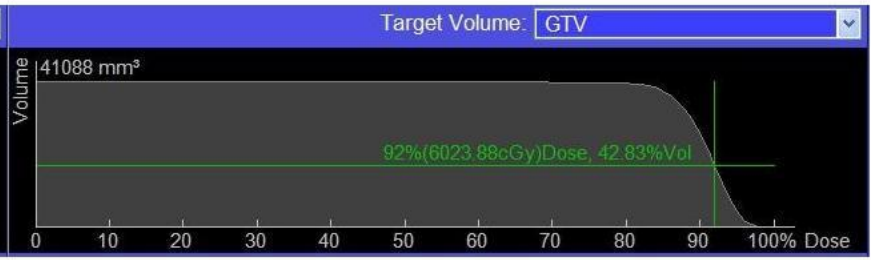
GTV : V60 Gy = 99 %

PTV : V60 Gy = 95 %

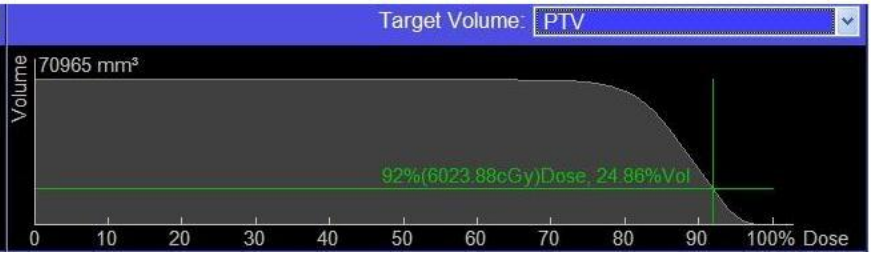
Monte-Carlo :



60.5 Gy



V60 Gy =43 %



V60 Gy = 25 % !!!!

Role of algorithms

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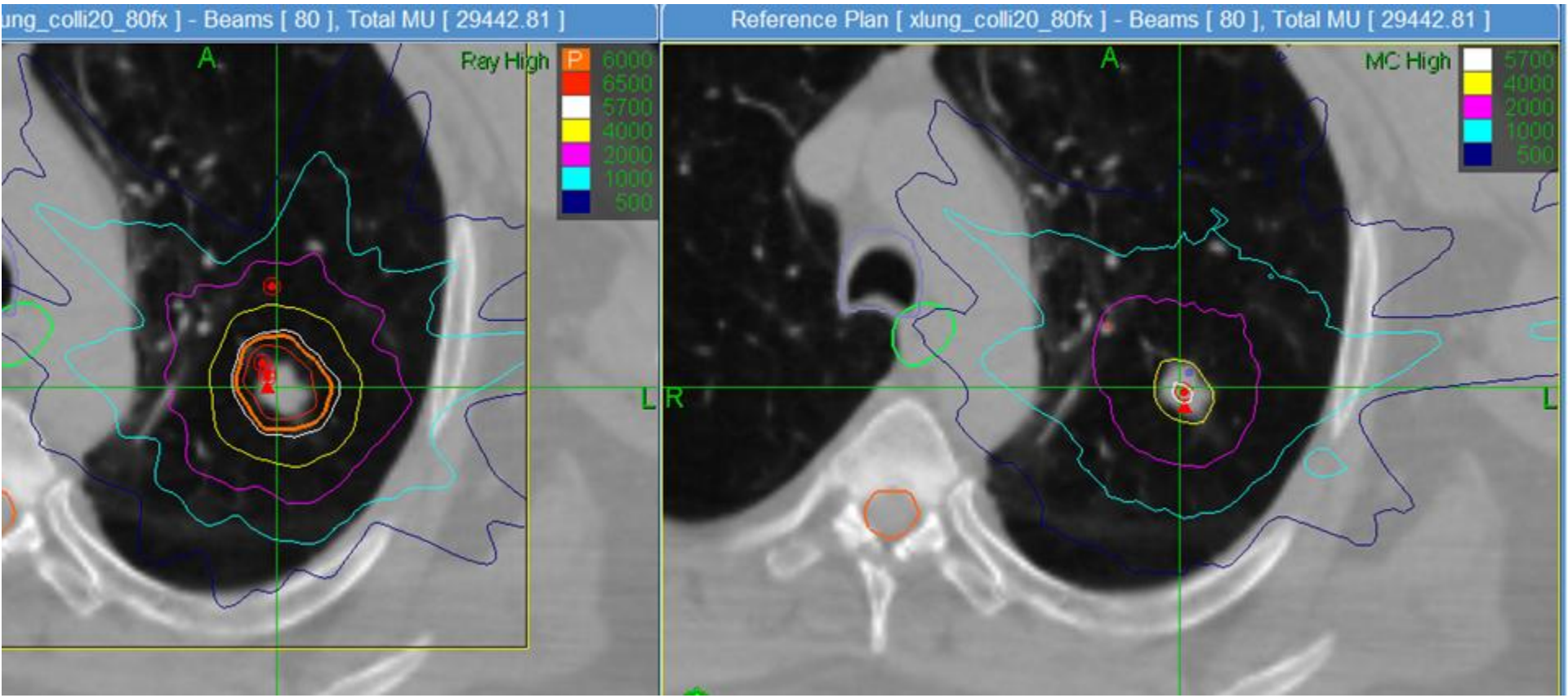
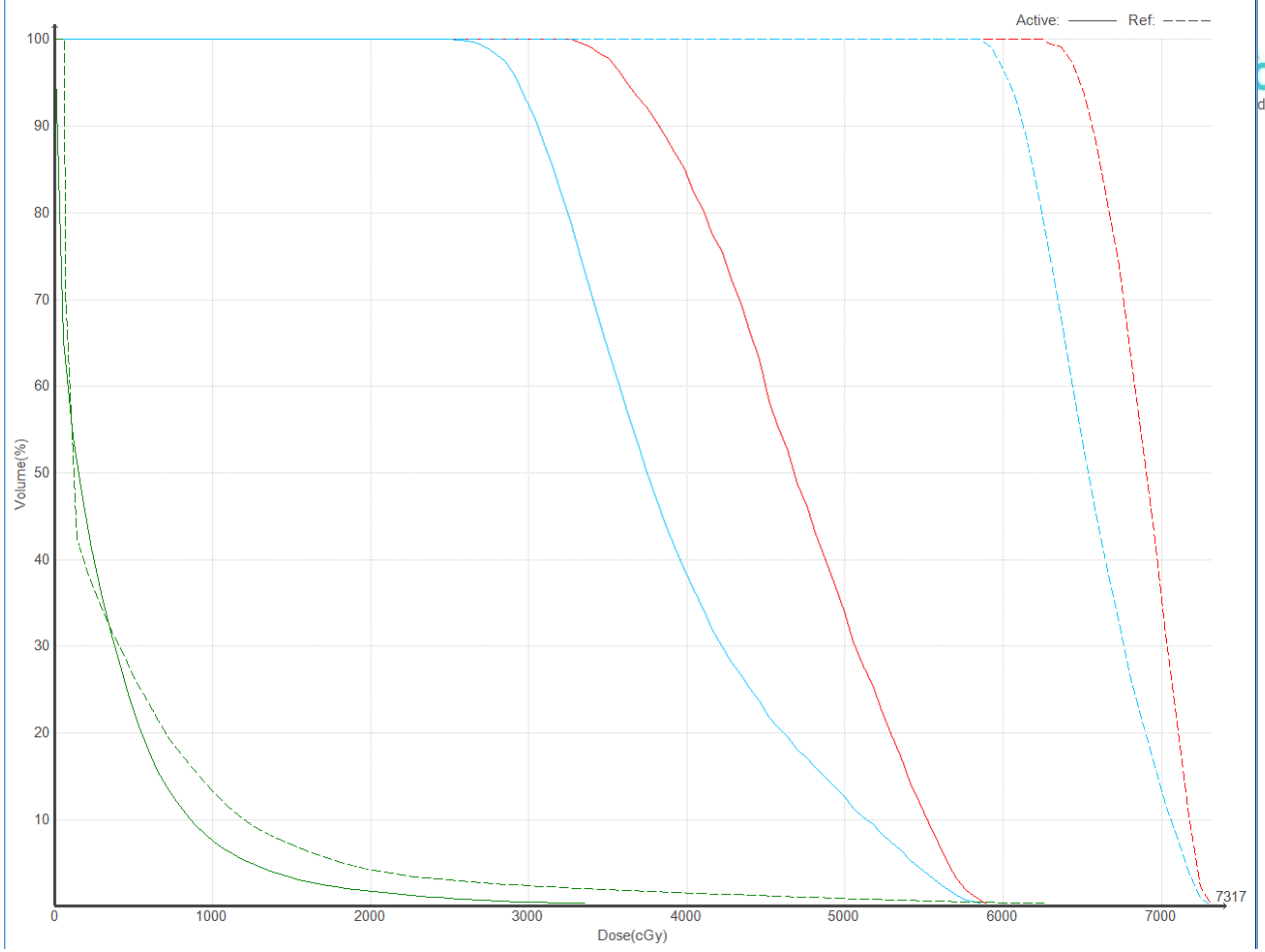
- Small target
- Very low density in the lung
- Respiratory failure

Ray- Tracing : 3 x 20 Gy **Monte-Carlo :**



Role of algorithms



		Dose (Gy)		
	Ray-Tracing	MC	Ray-Tracing	MC
	GTV		PTV	
D2% (near max)	72.4	57.7	72	56
D50%	68.5	45.3	64	36
D98% (near min)	63.6	34.8	59.3	28.9

Role of algorithms

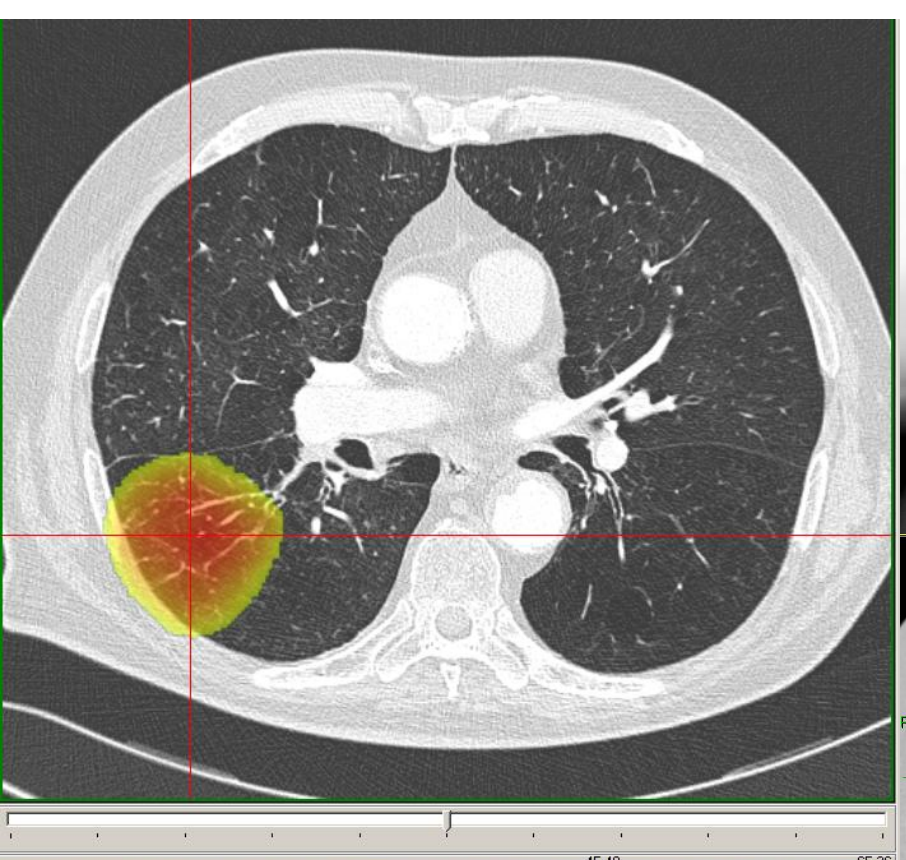
In lung PTV margin has to be used like a "flash" margin in breast treatment

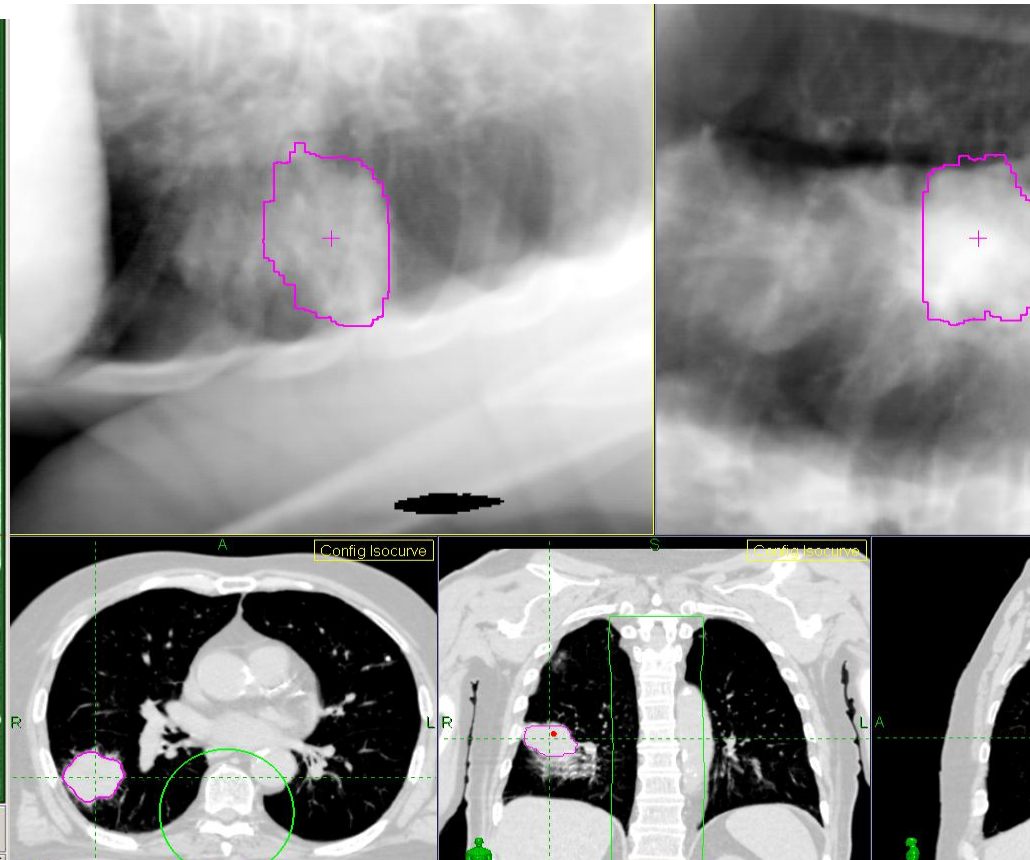
- Use type B algorithms (Monte-Carlo ….)
- At least report GTV D50%, D98%
- To prescribe on **GTV D50%** ???

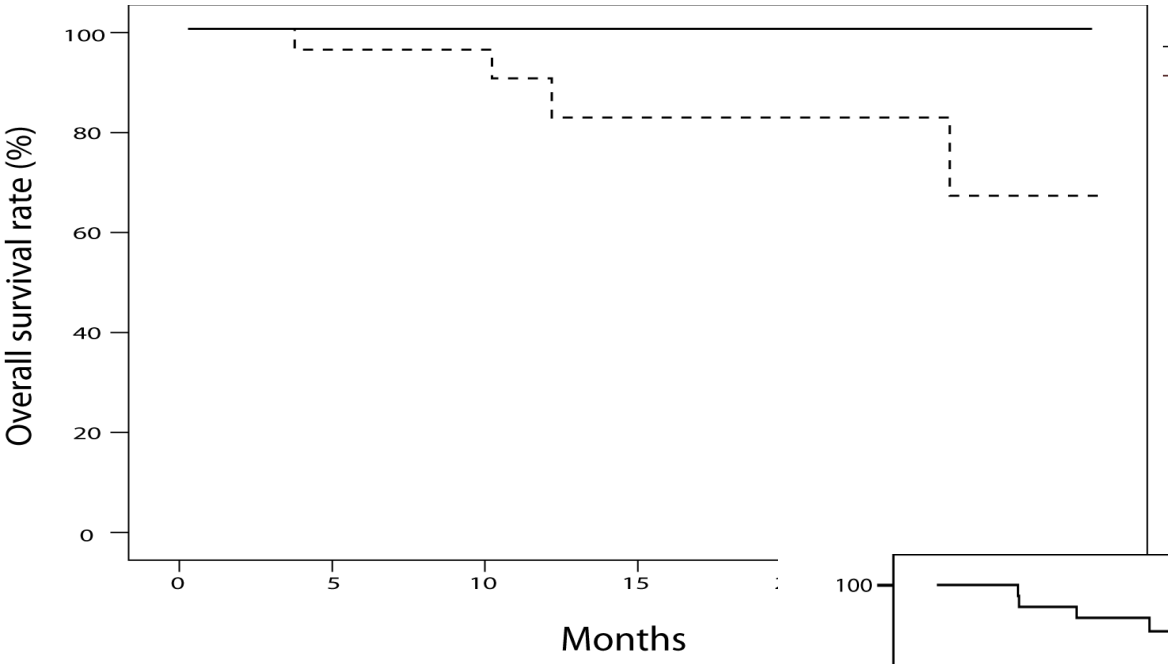
Fiducial less

Between may 2008 and september 2012 : 250 patients

- about 30 % patients with xsight_lung
- about 70 % patients with xsight_spine
- less then 10 patients with fiducial







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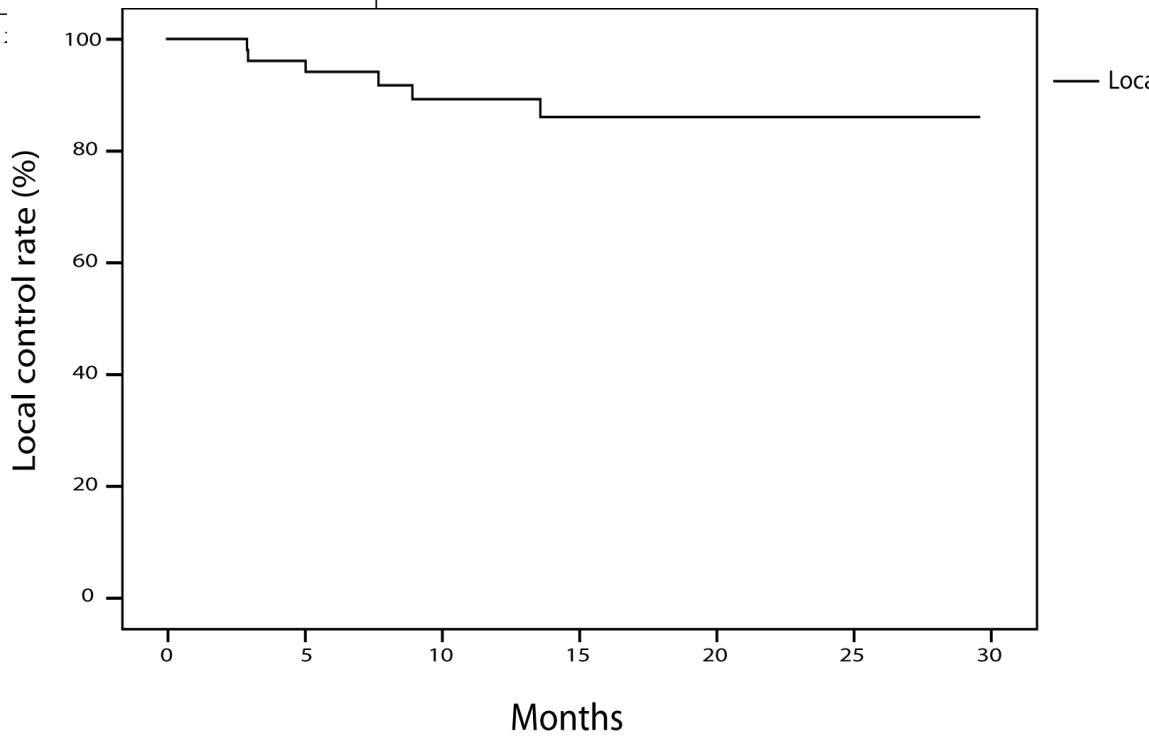

SURVIVAL

Image-Guided Robotic Stereotactic Radiation Therapy with Fiducial-Free Tumor Tracking for Lung Cancer. Radiat Oncol 2012, June 24, Bibault & Lartigau

Toxicity

- Acute :
  - Pneumopathy:
    - 7 grade 1 (14%),
    - 2 grade 2 (14%) at 3 months.

- Late :
  - Fibrosis :
    - 3 grade 1

- No pneumothorax,
- No toxicity grade 3 ou 4.

Result at 6 months

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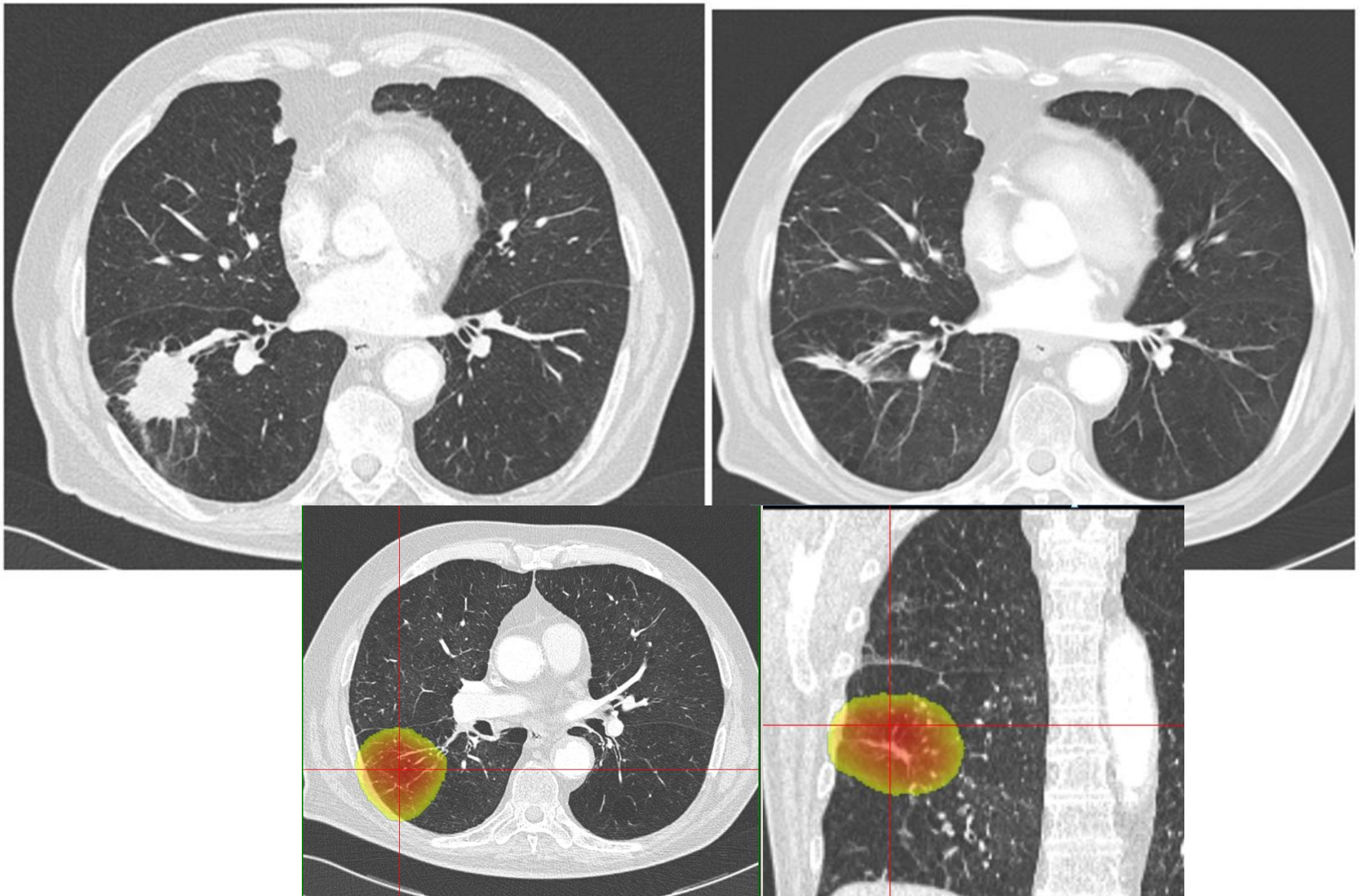
Follow-up CT registered with Planning CT (dose > 45 Gy MC)



June 2008

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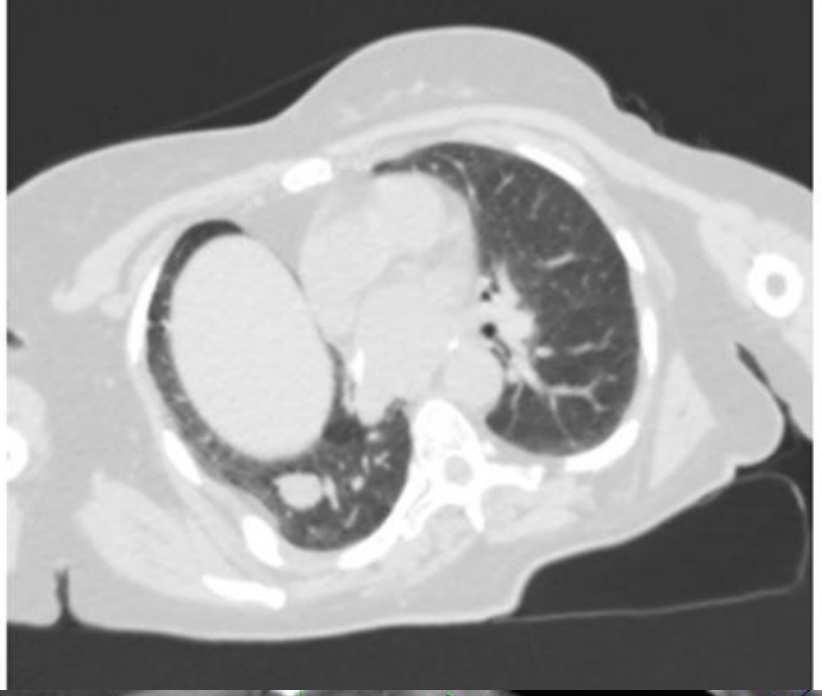
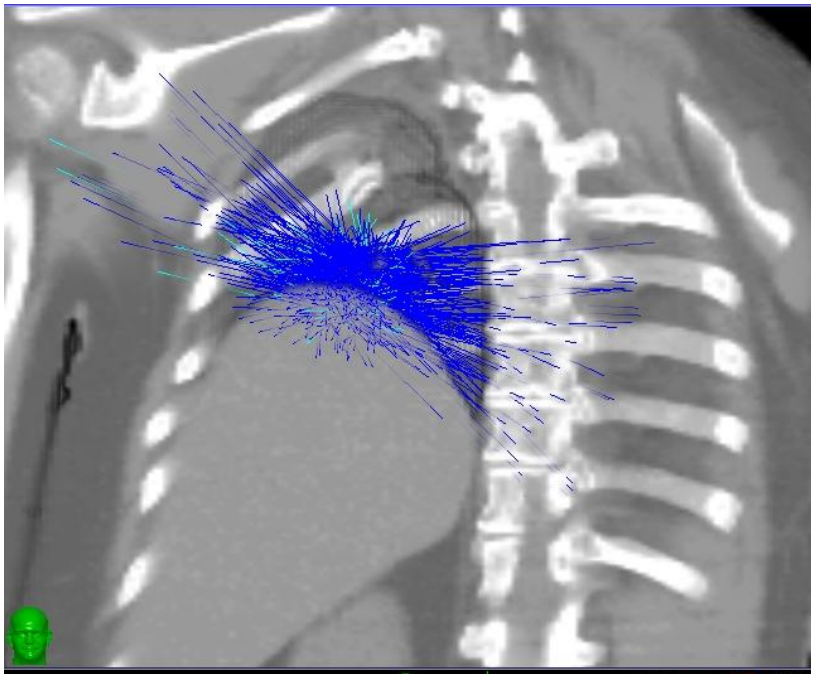
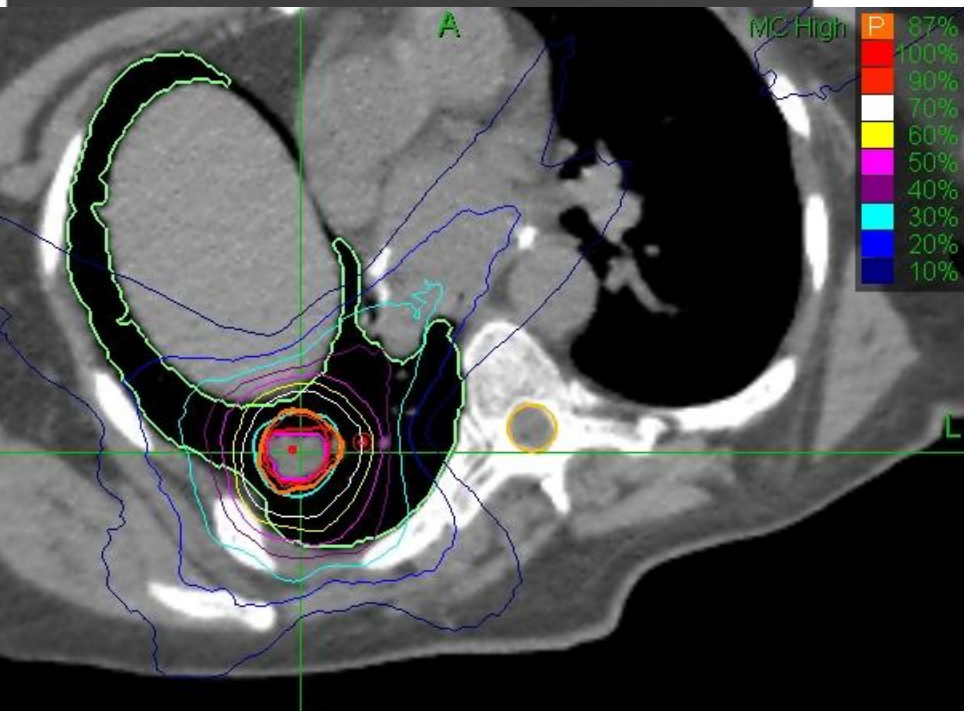
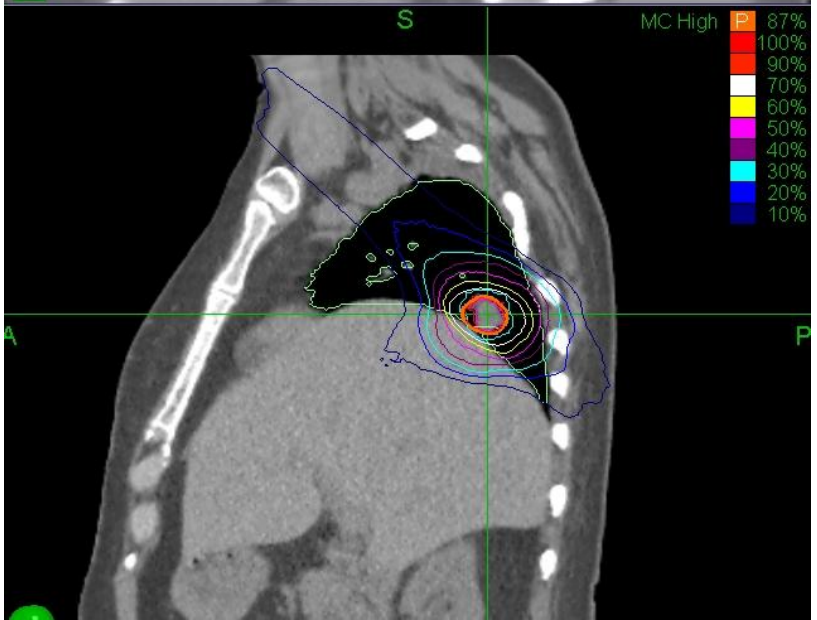


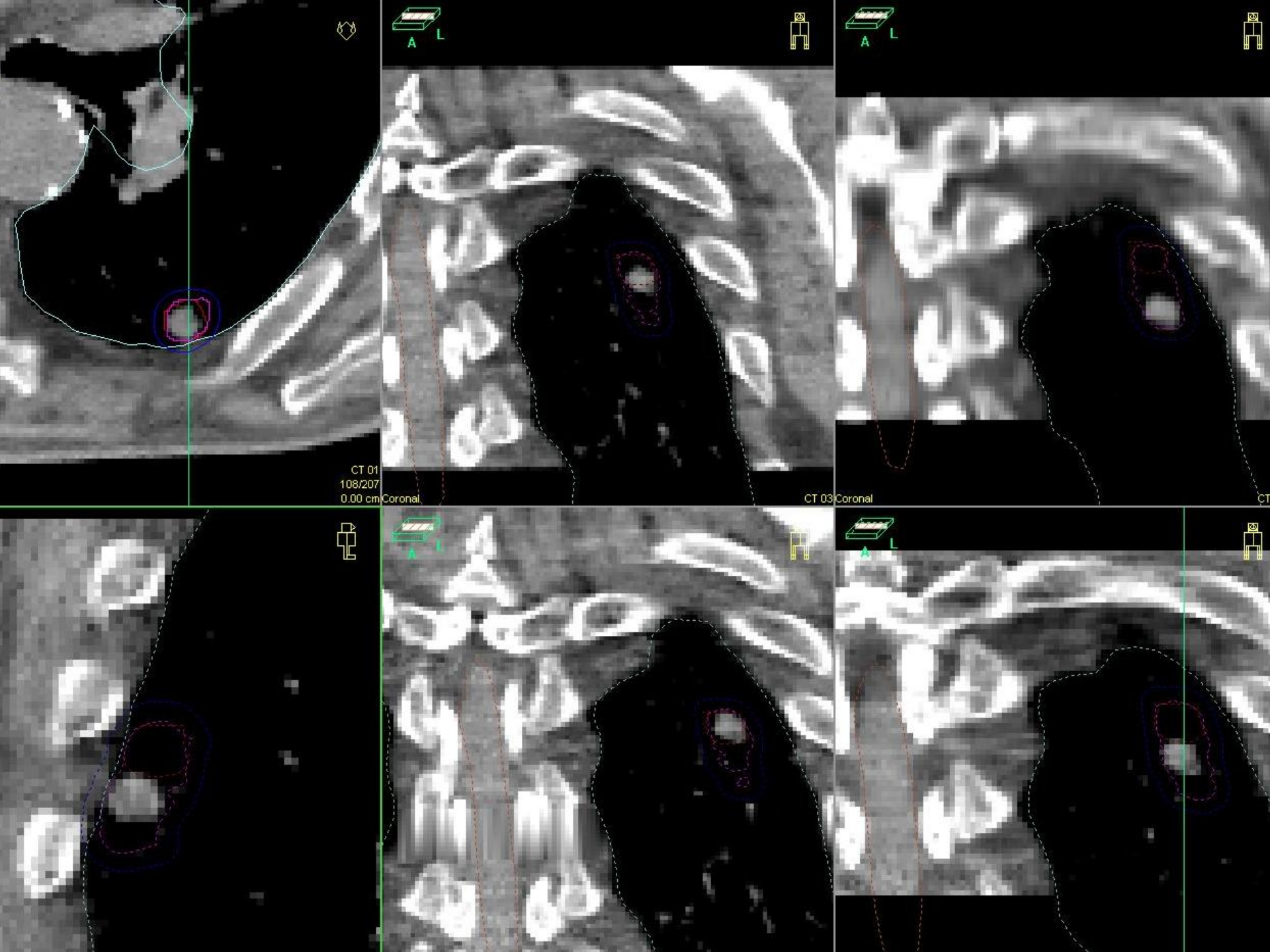






ITV (4D CT)

- When tumour tracking is impossible
- Create an ITV using a 4D CT-Scan
- Less beams (< 70)
- Larger collimators
- Faster TT Time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0.00 cm Coronal
CT 03 Coronal
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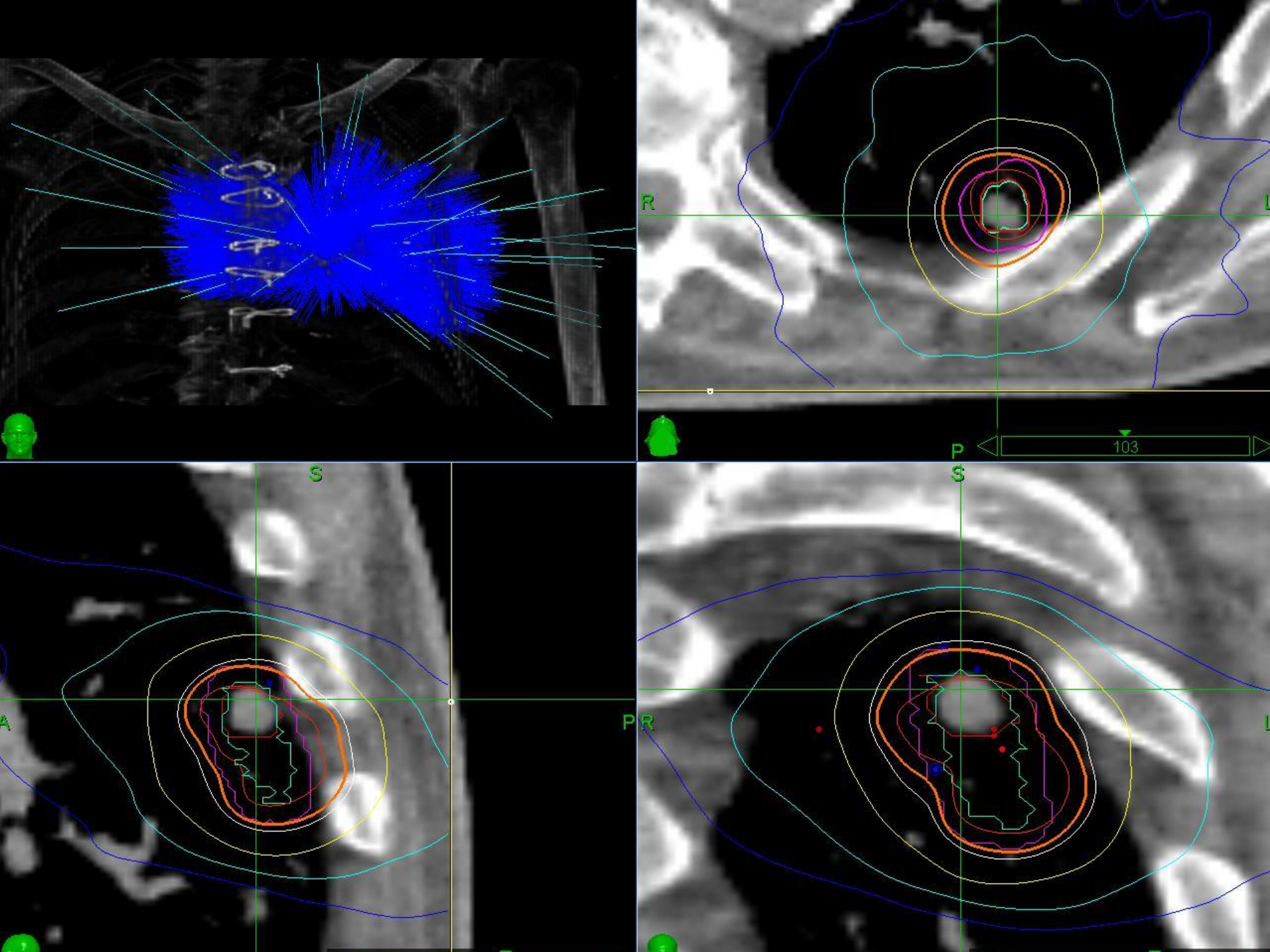
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103
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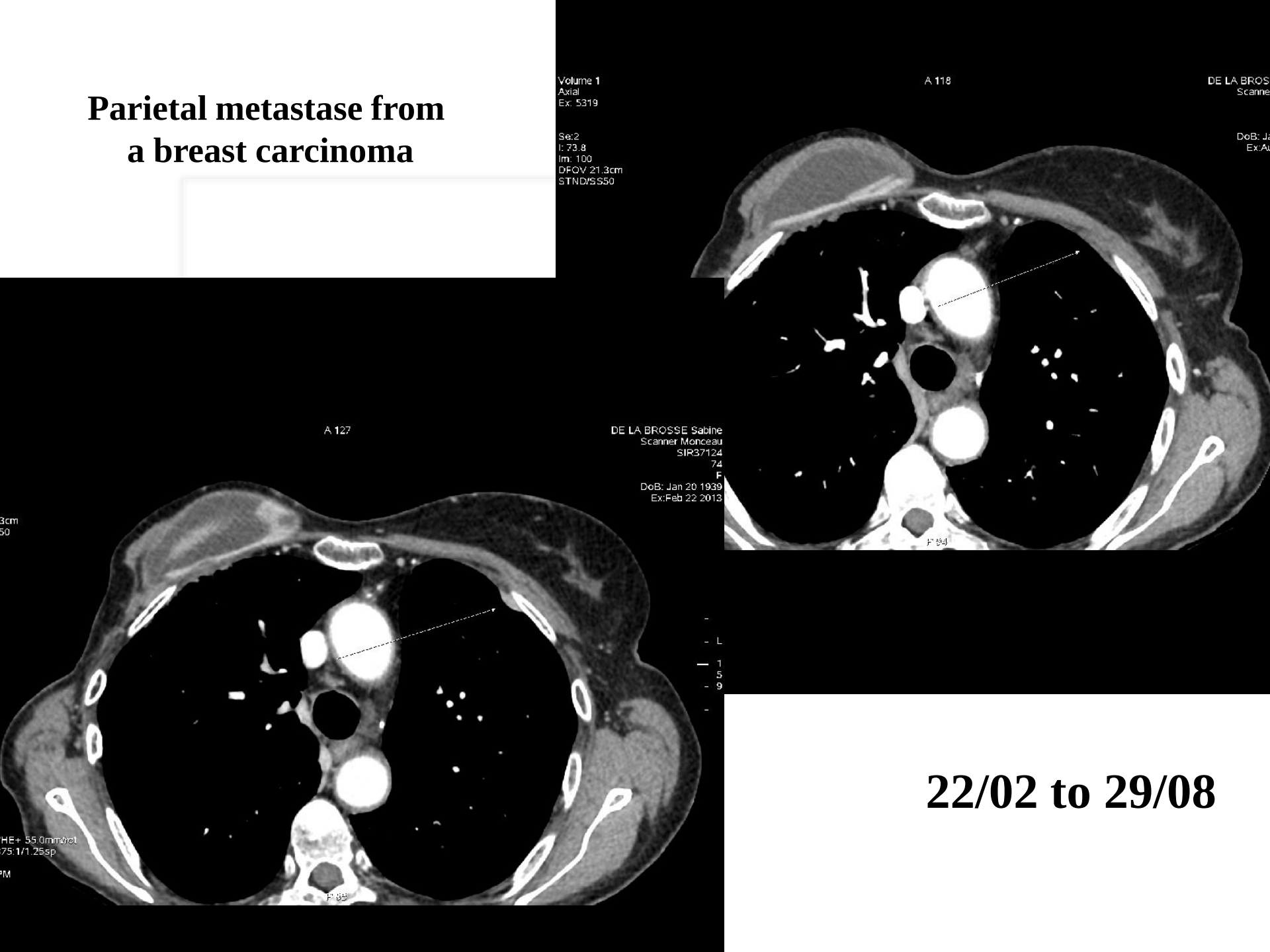
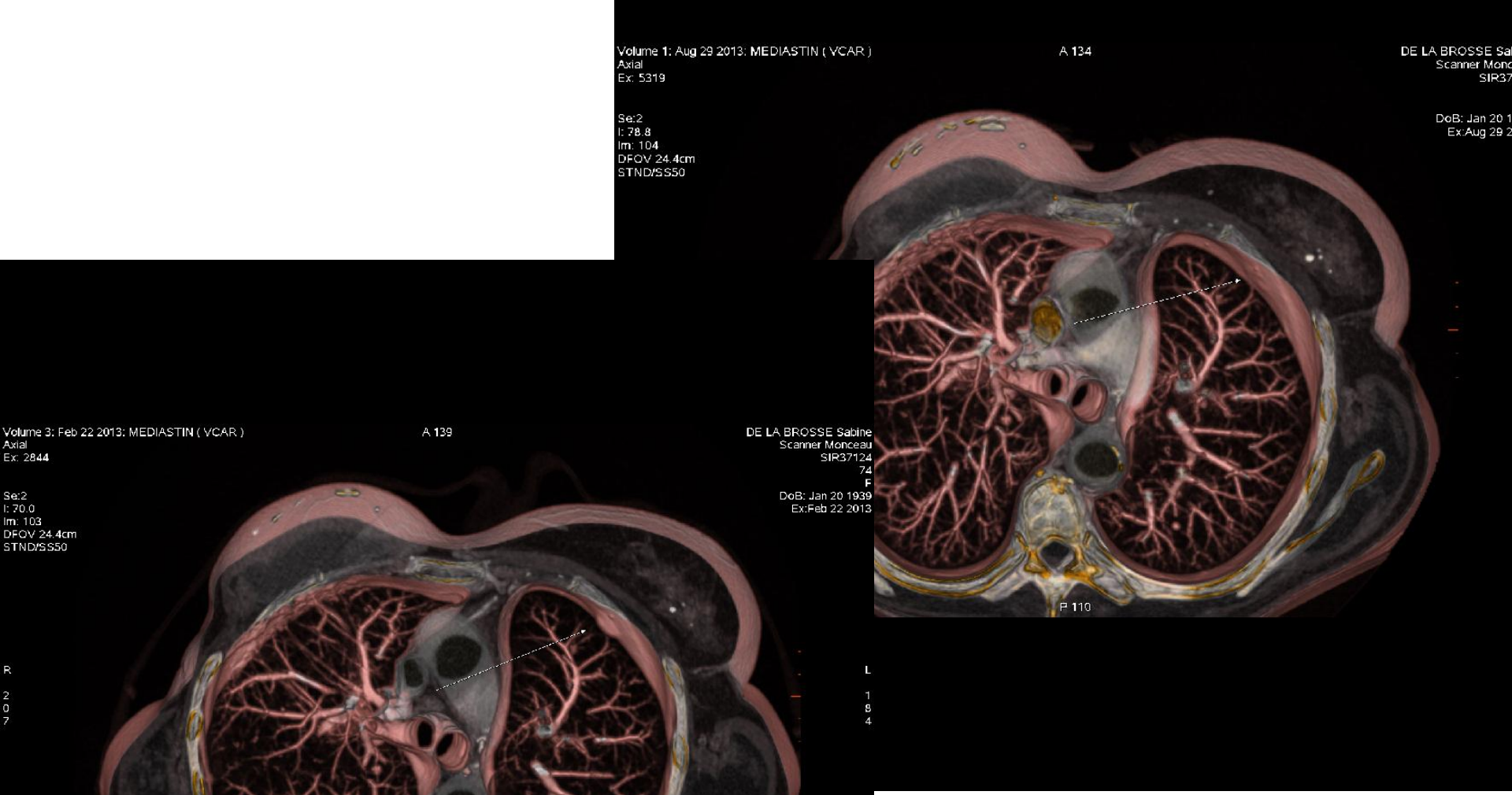
Parietal metastase from a breast carcinoma



22/02 to 29/08


Volume 1: Aug 29 2013: MEDIASTIN (VCAR)
Axial
Ex: 5319
A 134
Se:2
I: 78.8
Im: 104
DFOV 24.4cm
STND/SS50
DE LA BROSSE Sa
Scanner Monc
SIR37
DoB: Jan 20 1
Ex:Aug 29 2
P 110
Volume 3: Feb 22 2013: MEDIASTIN (VCAR)
Axial
Ex: 2844
A 139
Se:2
I: 70.0
Im: 103
DFOV 24.4cm
STND/SS50
DE LA BROSSE Sabine
Scanner Monceau
SIR37124
74
F
DoB: Jan 20 1939
Ex:Feb 22 2013
R
2
0
7
L
1
8
4
DCA:OFF
Vol.Render.
20.3
kV 100
mA 188
Rot 0.40s/HE+ 55.0mm/rot
1.2mm 1.375:1/1.25sp
Tilt: 0.0
03:08:01 PM
W = 1156 L = -532
P 105

22/02 to 29/08

CONCLUSION

- **SBRT is a standard treatment for < 4 cm peripheral NSCLC**
- **Free breathing tracking is routine pratice**

- **Main pattern failure : distant metastases : role of chemo/targeted therapy ?**

- **Toxicity > G3 : centrally located**

Chi *et al.* Systemic review of SBRT, Radiother Oncol, January 2010

ESTRO School

SBRT solutions:
Case demonstration less common solutions

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

Dirk Verellen & Eric Lartigau

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

ESTRO School

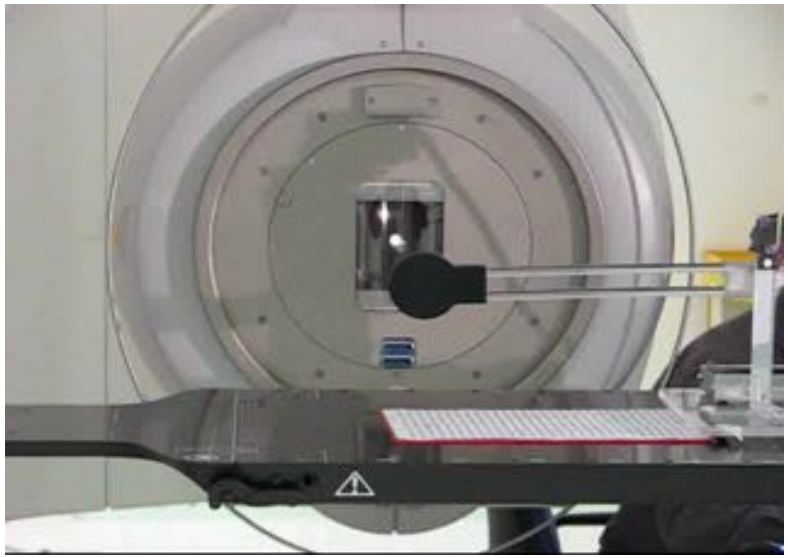
Learning objectives

- To illustrate some promising new kids on the block (unfortunately not yet clinically available for SBRT):
  - Couch tracking
  - D-MLC tracking
- To illustrate potential of Tomotherapy for SBRT
- To demonstrate the workflow related to a real-time tumour tracking (RTTT) treatment using an “extinct” system: VERO
  - From image acquisition and treatment planning to treatment delivery and verification

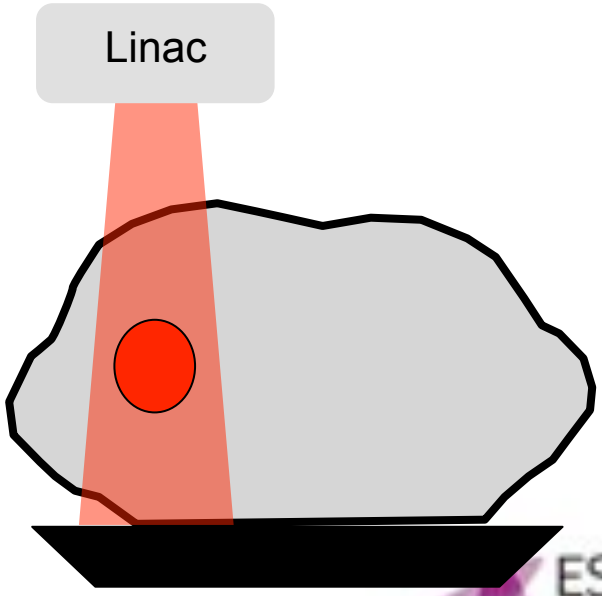
Tumor tracking: couch compensation

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
  - Using a "work horse" linac
- **Drawbacks**:
  - Discomfort patient? Relaxing?
  - Impact on tumor motion, patient positioning?
  - Changing position of beam with respect to patient anatomy

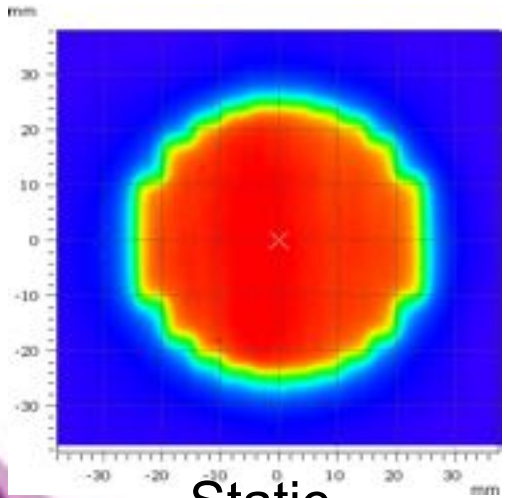


Courtesy O. Haas

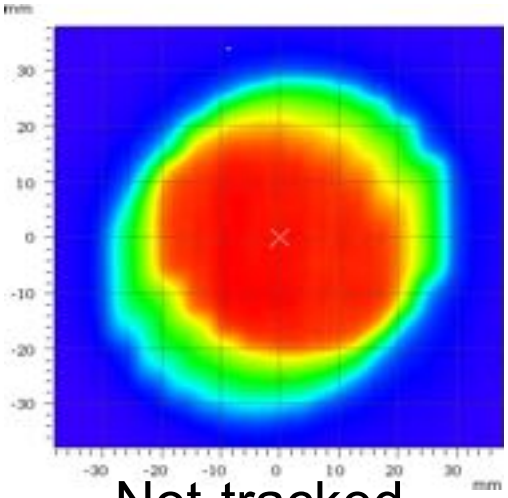
Tumor tracking: DMLC

"Using the MLC to track the tumour: breathing leaves"

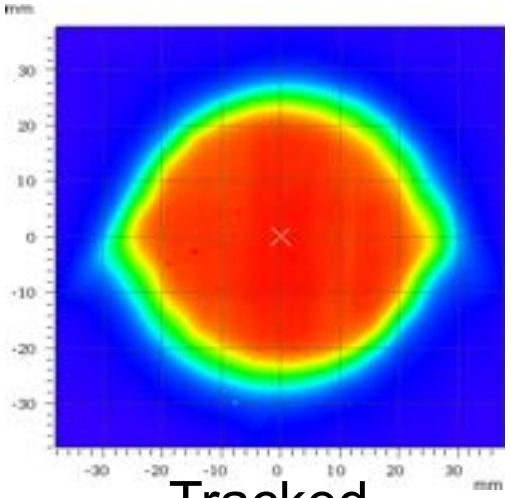
- **Advantages**:
  - Using the available dynamic MLC
  - Using a "work horse" linac
- **Drawbacks**:
  - Only useable with a flattened beam, what with FFF?
  - Tracking and DMLC intensity modulation are coupled: coupled constraints and increased complexity with higher modulation and higher velocities
  - Tracking perpendicular to MLC leaf tracks? Leaf leakage?



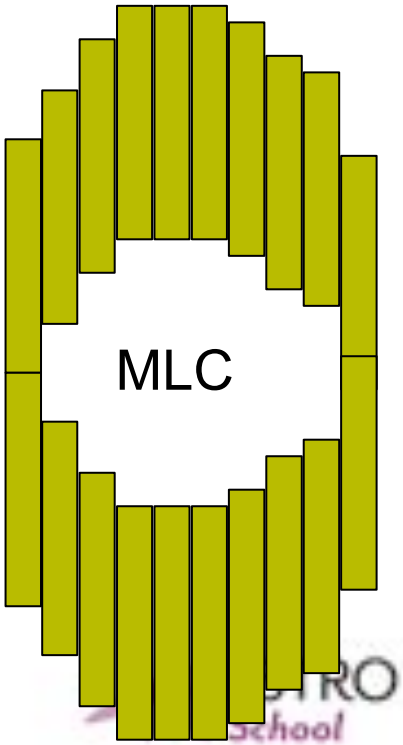
Static



Not-tracked

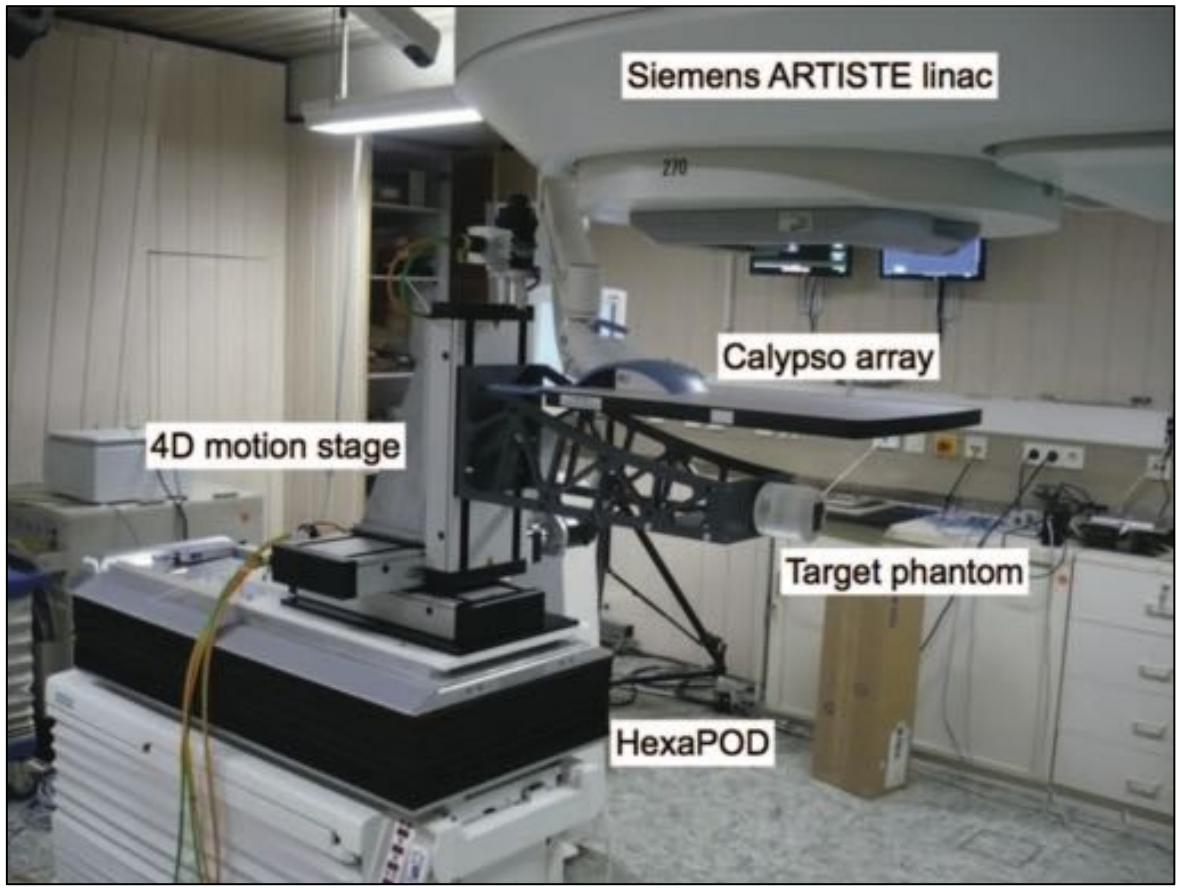


Tracked



A comparative study

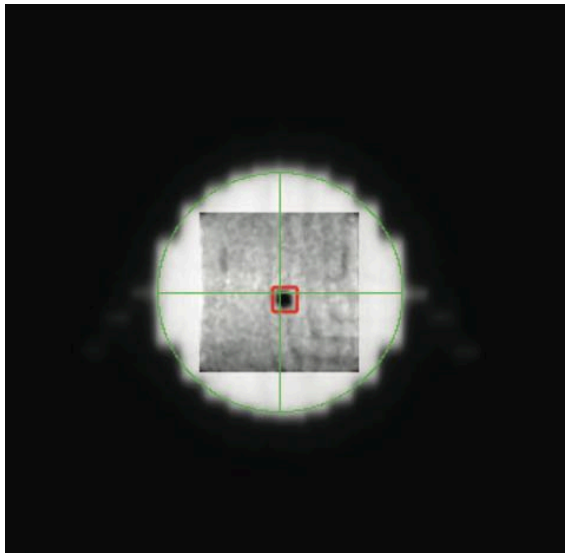
- D-MLC tracking (Siemens 160 MLC) and robotic couch (Elekta HexaPOD)



Menten *et al.* Med Phys 2012

A comparative study

- Respiration patterns from 8 lung patients (Hokaido, Japan)
  - Different amplitudes, and frequencies, including baseline drift
- Prostate motion trajectories from 5 patients (DKFZ, Germany)
  - Slow gradual drifts and fast positional shifts
- Geometric verification using EPID



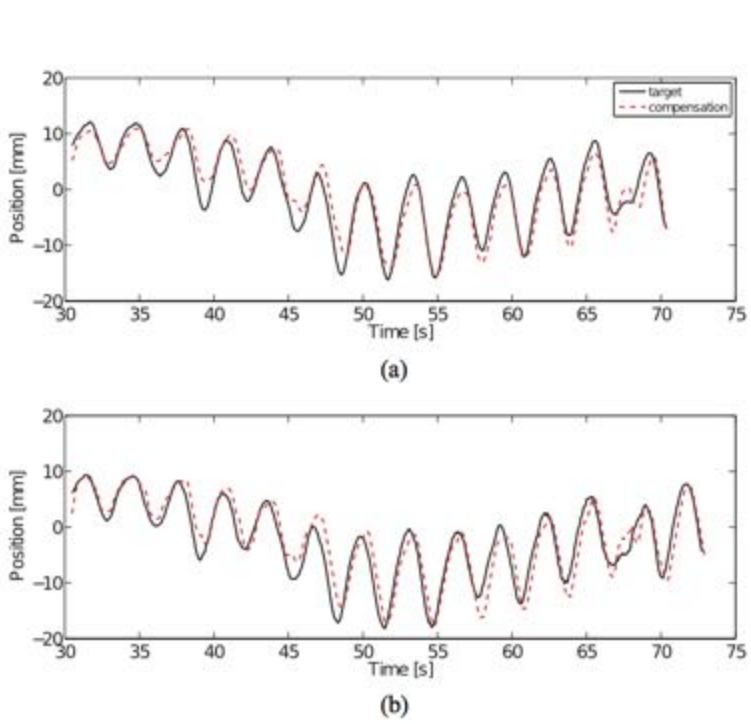
- Dosimetric verification using EDR-2 film dosimetry comparing static dose to moving with and without tracking

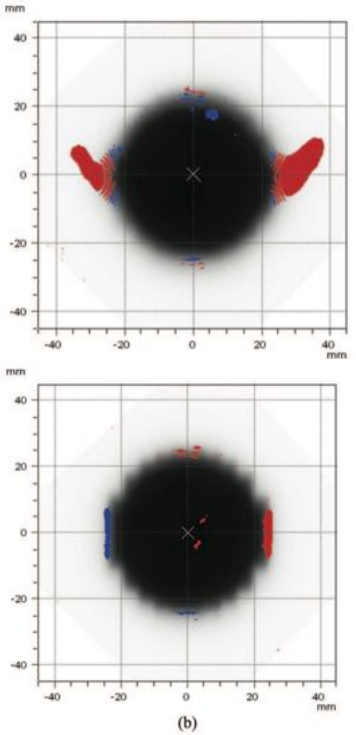
Menten *et al.* Med Phys 2012

A comparative study

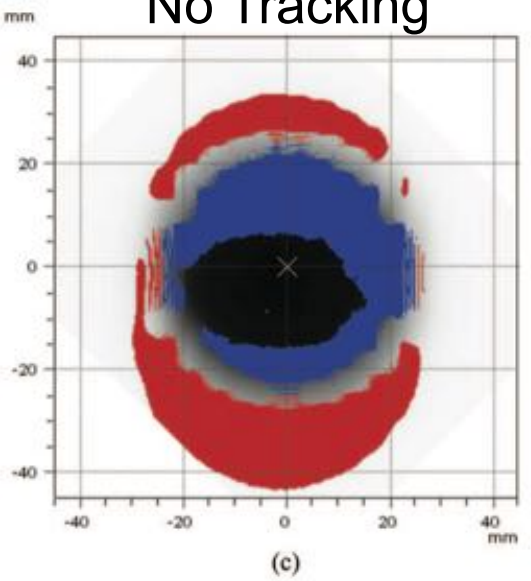
- For lung treatments:
  - Average root mean square tracking error reduced with a factor 2
  - 2%/2mm gamma pass rate increased from 76% to 90% and 95% respectively for DML and couch tracking

- DMLC
- Couch





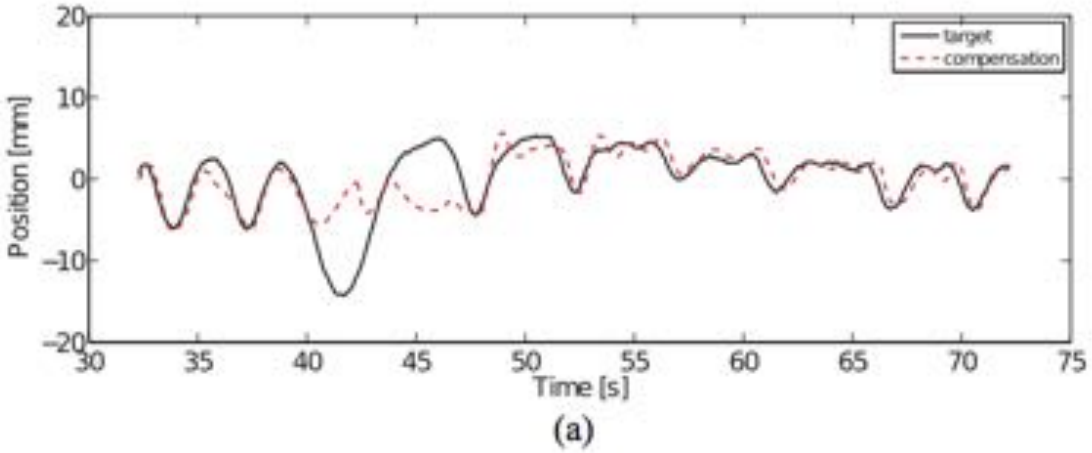
No Tracking



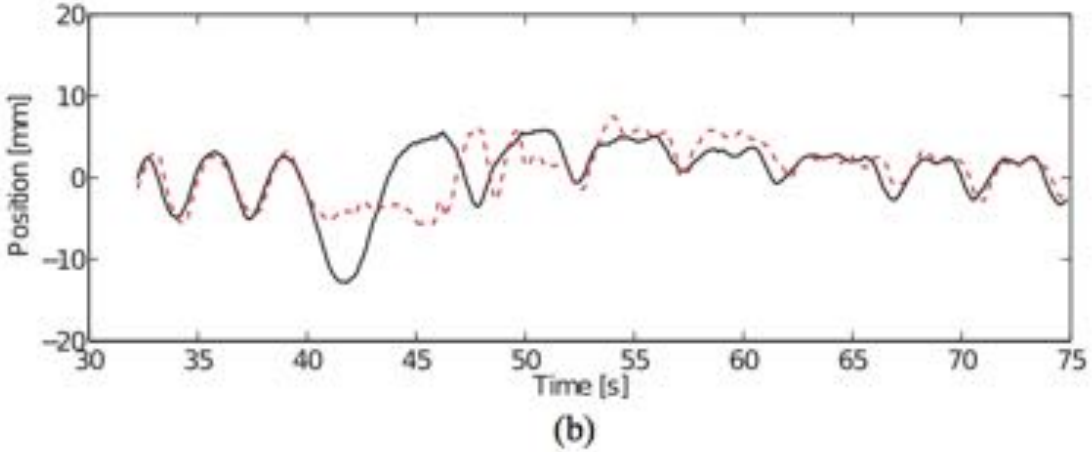
Menten *et al.* Med Phys 2012

A comparative study

- For lung treatments
- D-MLC

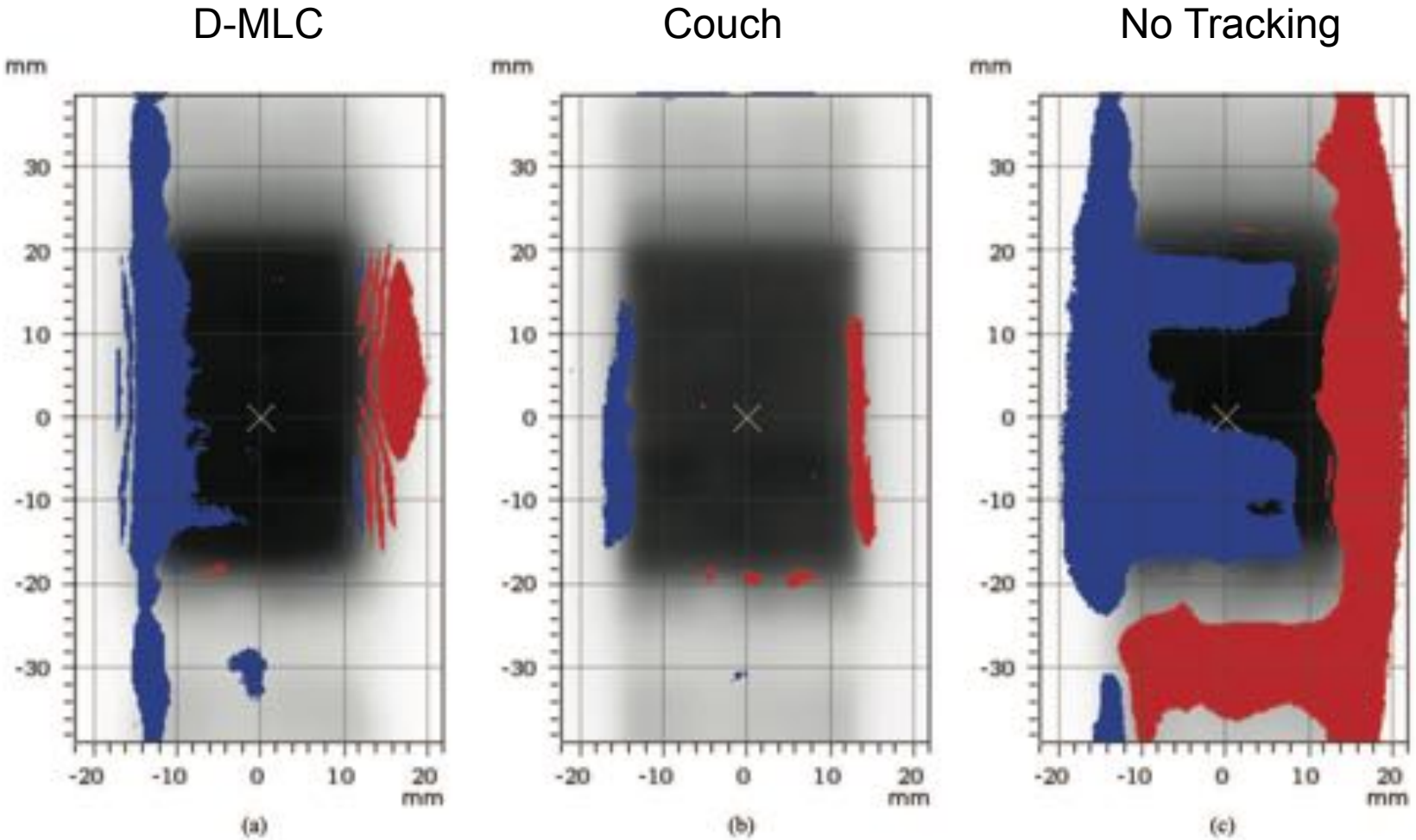


- Couch



A comparative study

- For prostate treatments

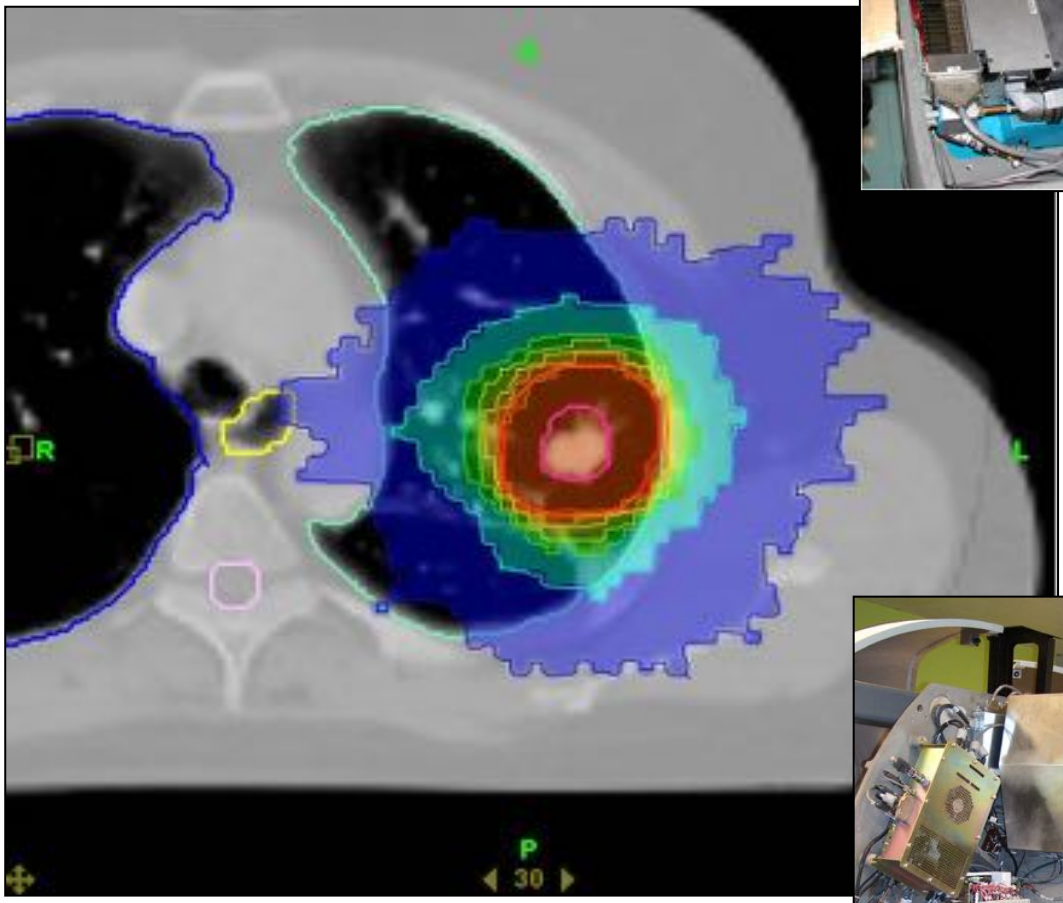


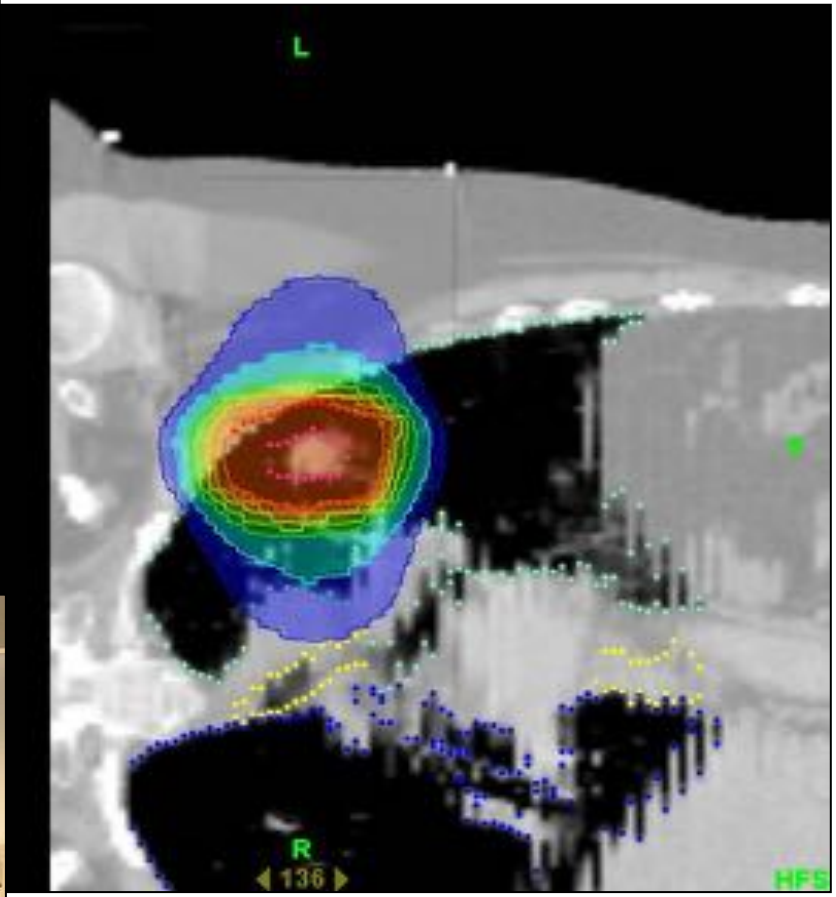
Menten *et al.* Med Phys 2012

Tumor tracking: DMLC

So far only clinically implemented for prostate treatments, not SBRT!

What about tomotherapy?

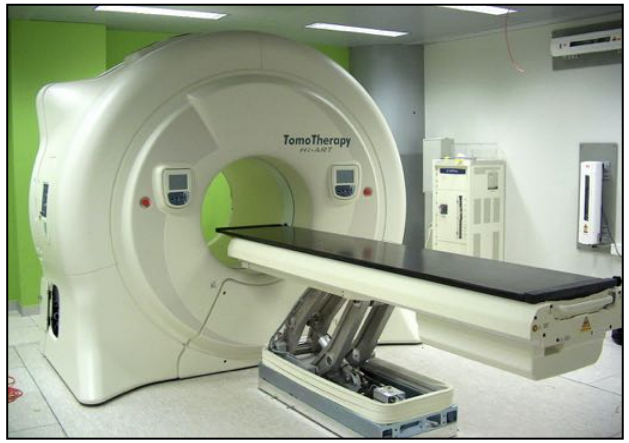


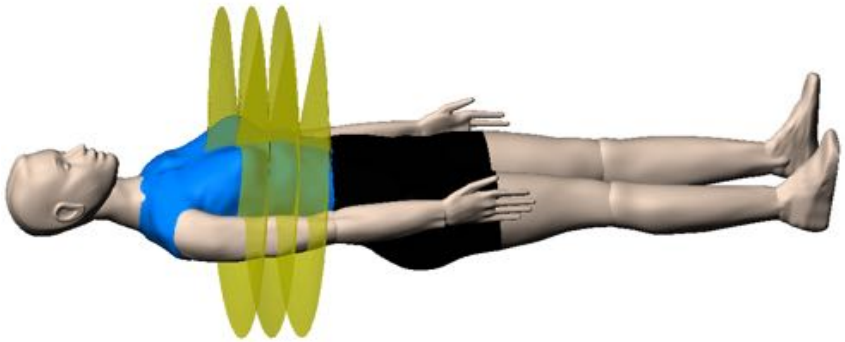


What about tomotherapy?

Pitch: P

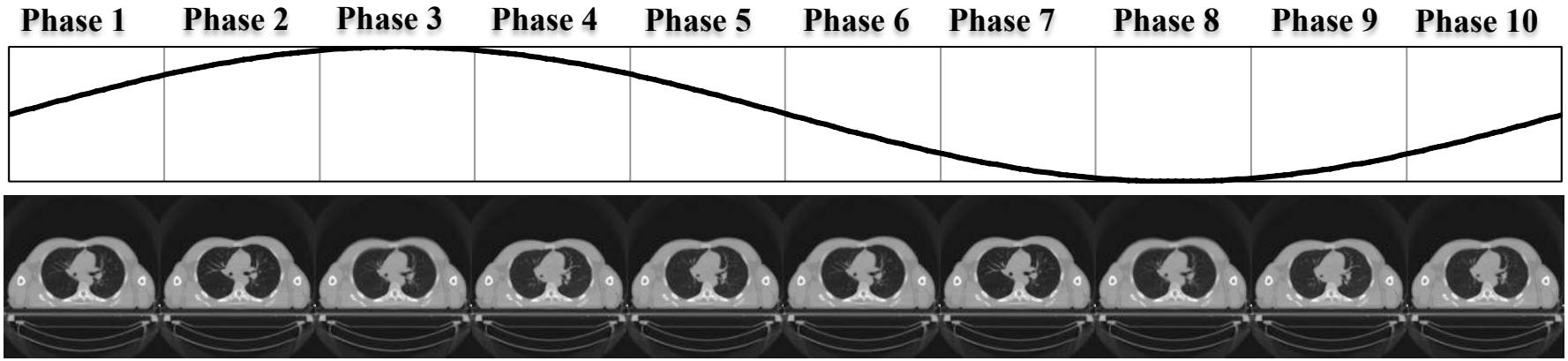
- P = Δy / W
- “loose pitch”: P = 1.0
  (W=2.5 ➔ Δy =2.5 cm per rotation)
- “tight pitch”: P = 0.3
  (W=2.5 ➔ Δy =0.75 cm per rotation)



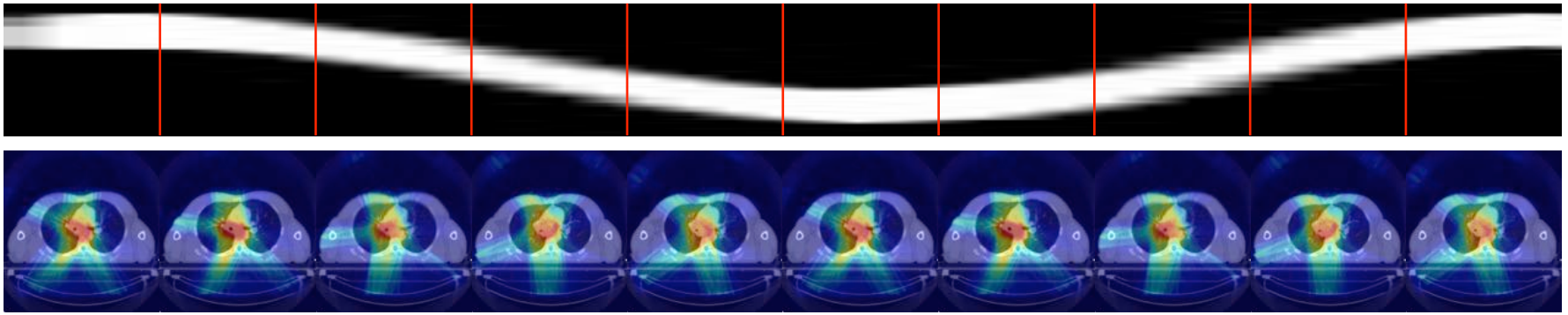


What about tomotherapy?

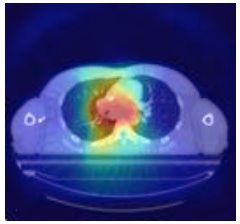
Breathing signal



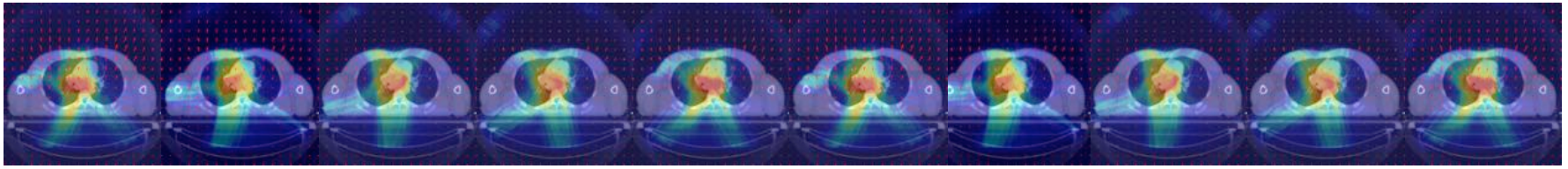
TomoTherapy delivery sinogram



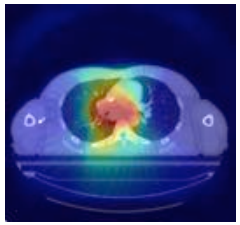
Planned



4DCT-based deformable dose registration



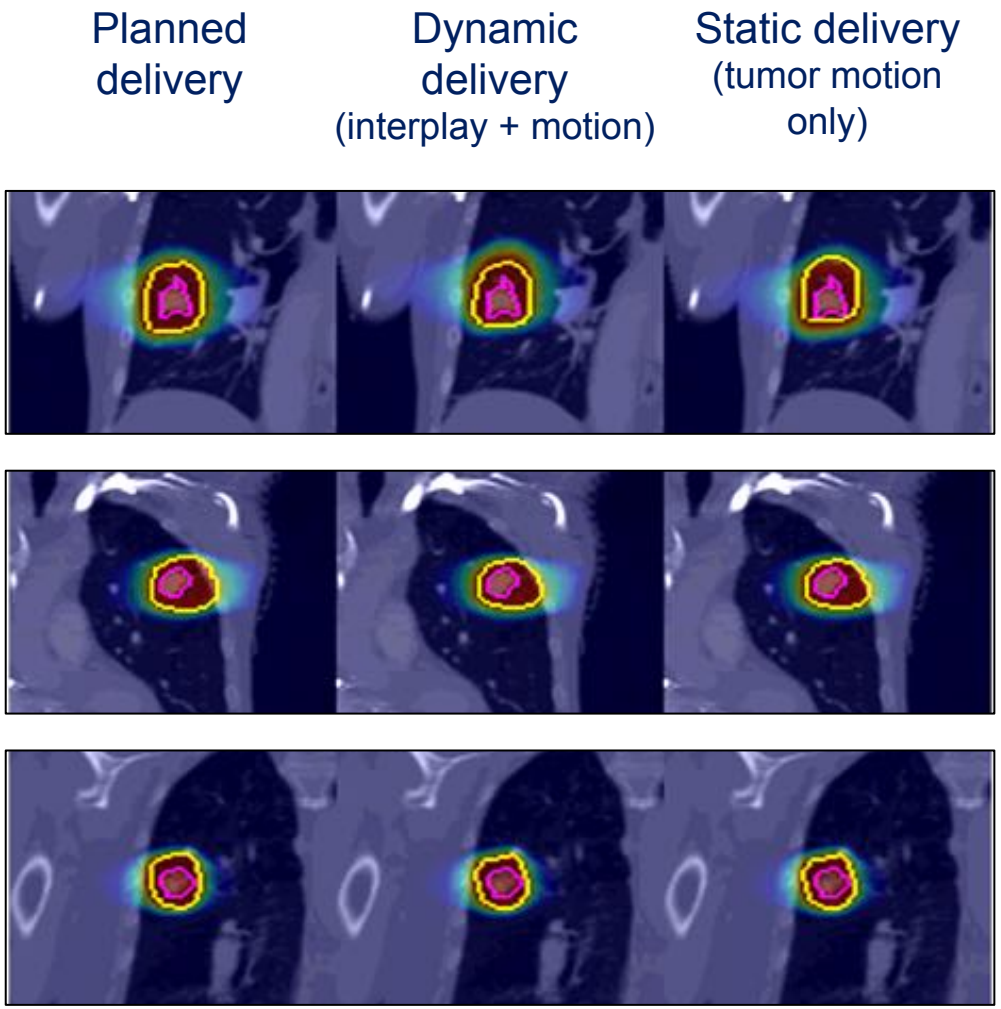
Simulated



Courtesy E. Sterpin *et al.*

What about tomotherapy?

- **Simulation** using 4D-CT, deformable registration and Monte Carlo dose calculation
- All patients were **coached** to ensure regular breathing
- **ITV-based** treatment using helical tomotherapy: good tumor coverage for all patients (95% of the prescribed dose to 95% of the volume)



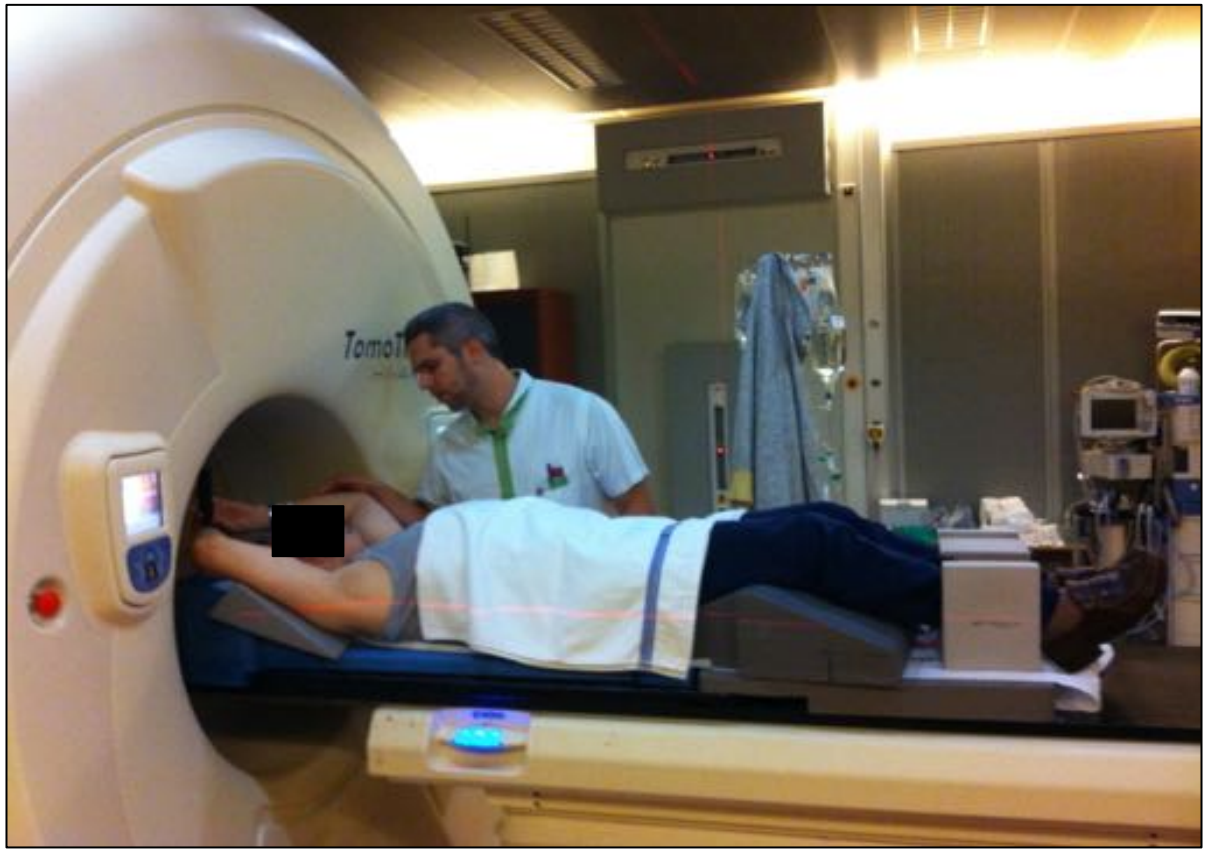
95% iso-dose

GTV_{CT}

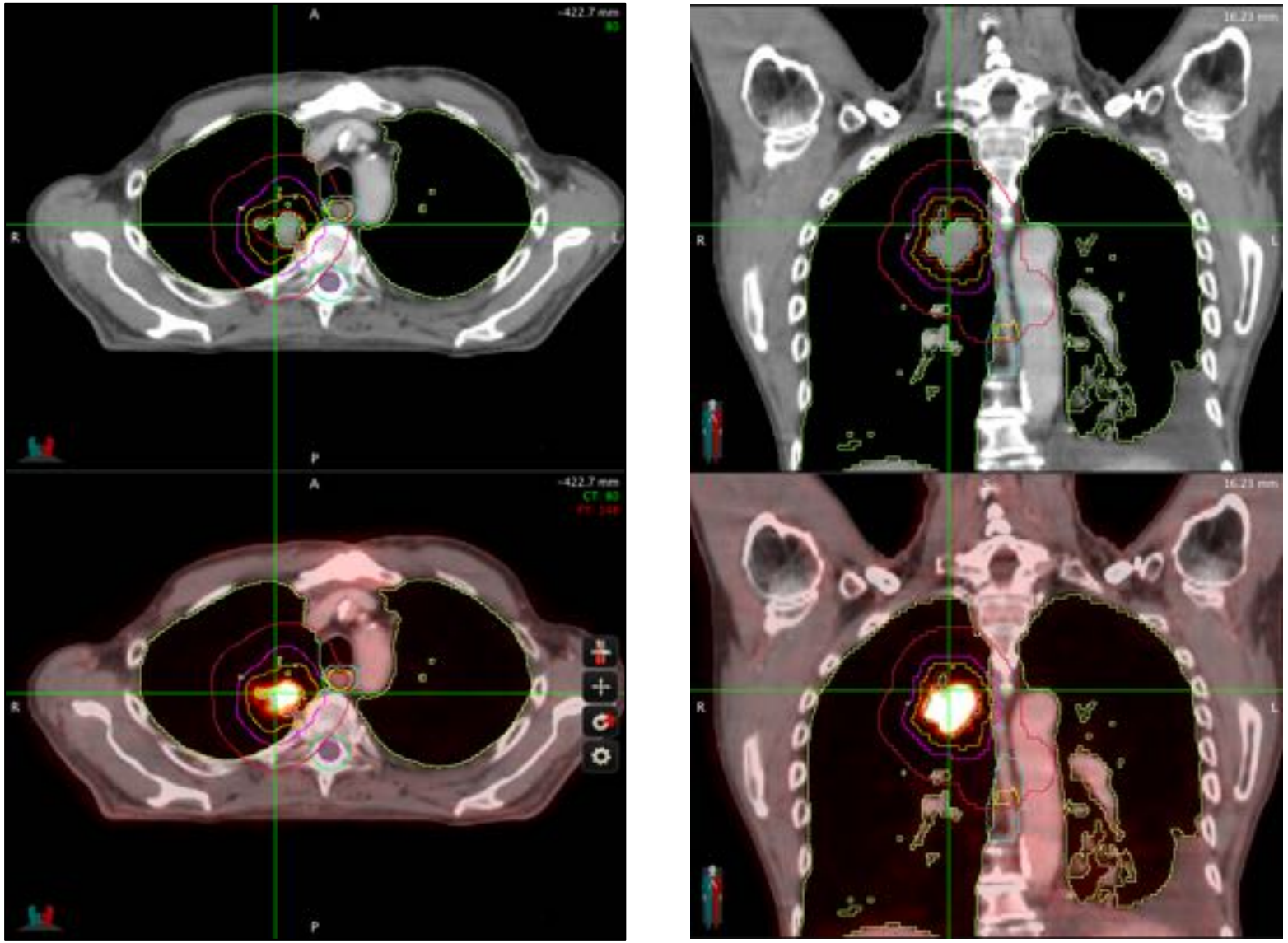
Courtesy E. Sterpin *et al.*

A practical example

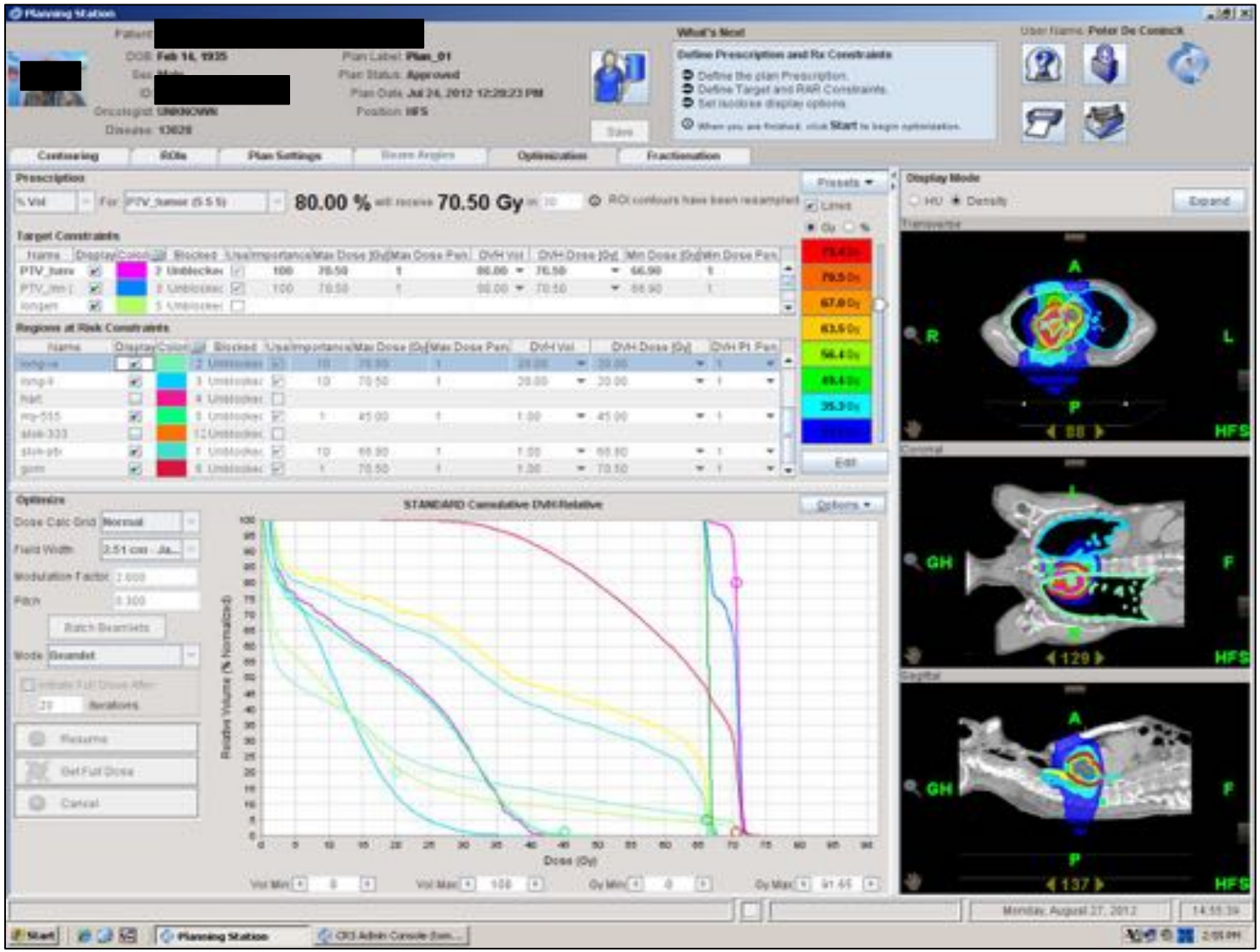
- NSCLC, Stage III, cT4N2M1
  - Primary RT, 30 x 2.35 Gy



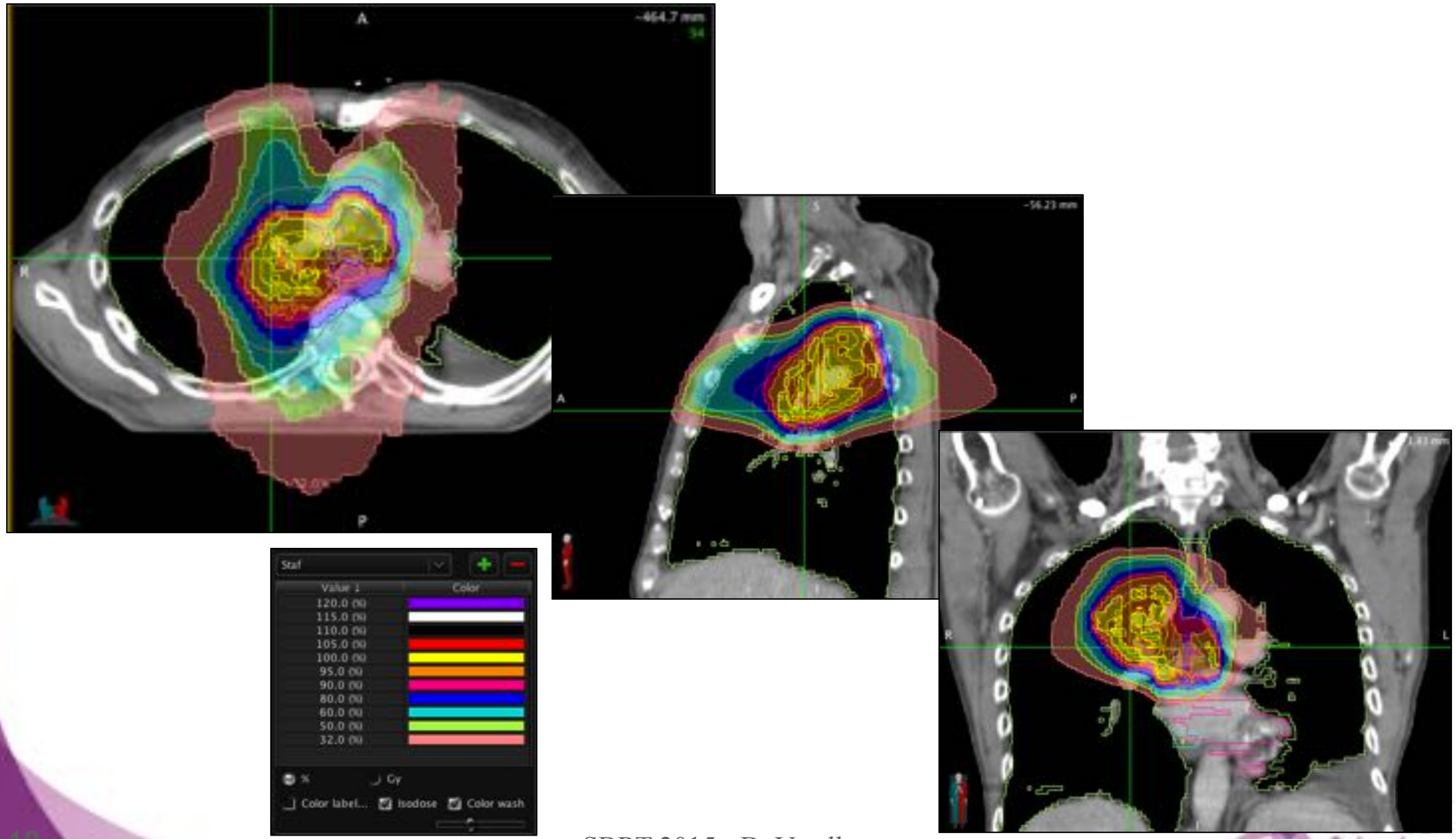
A practical example



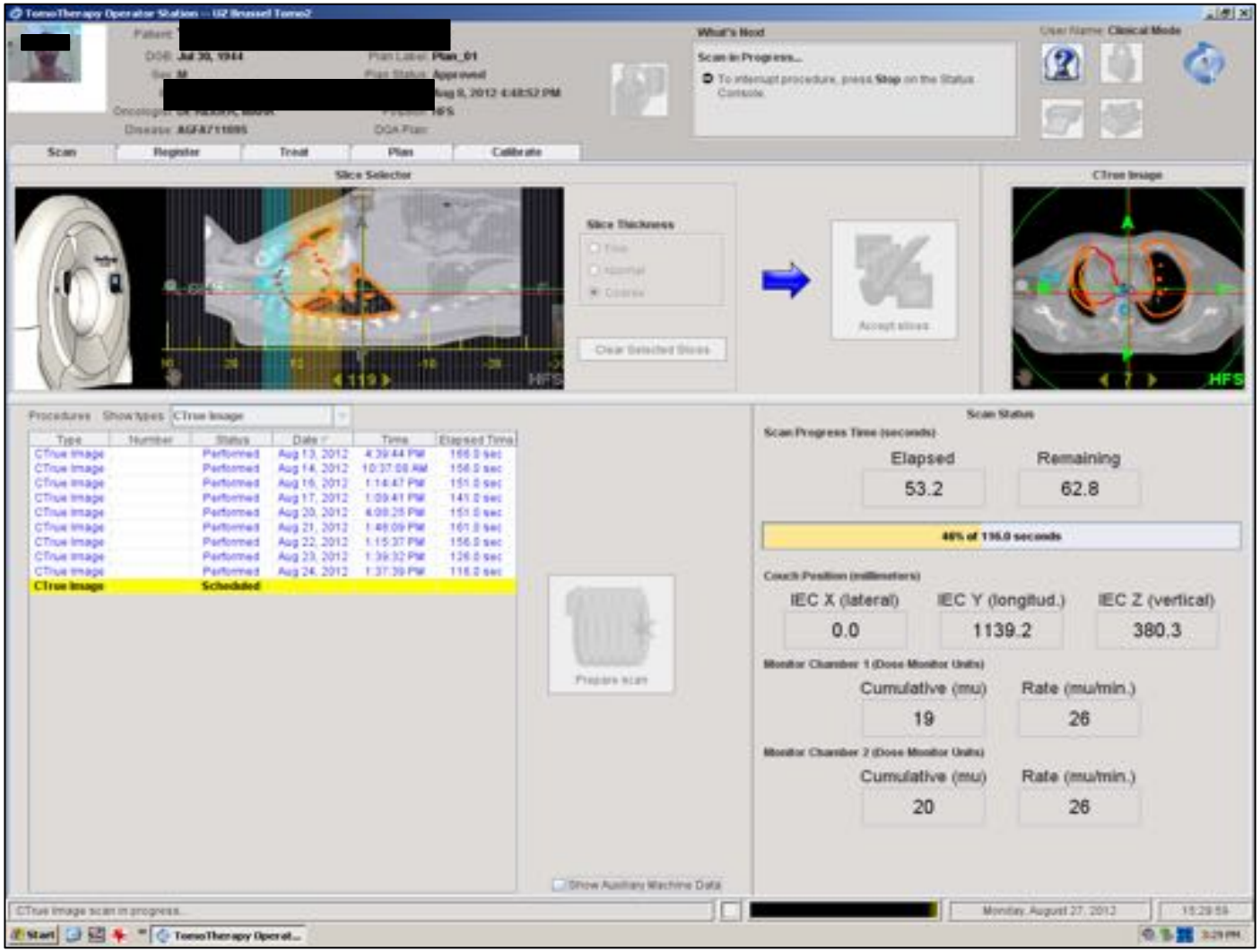
A practical example



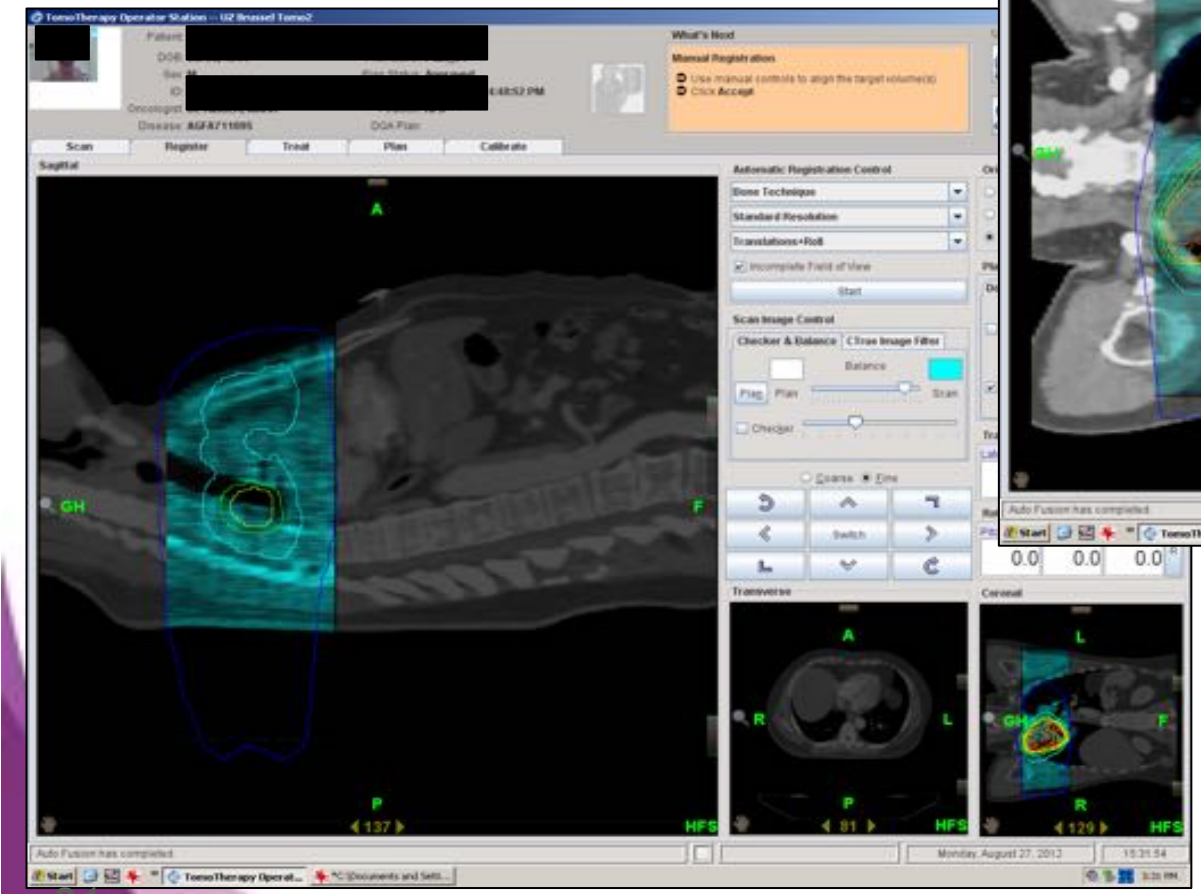
A practical example

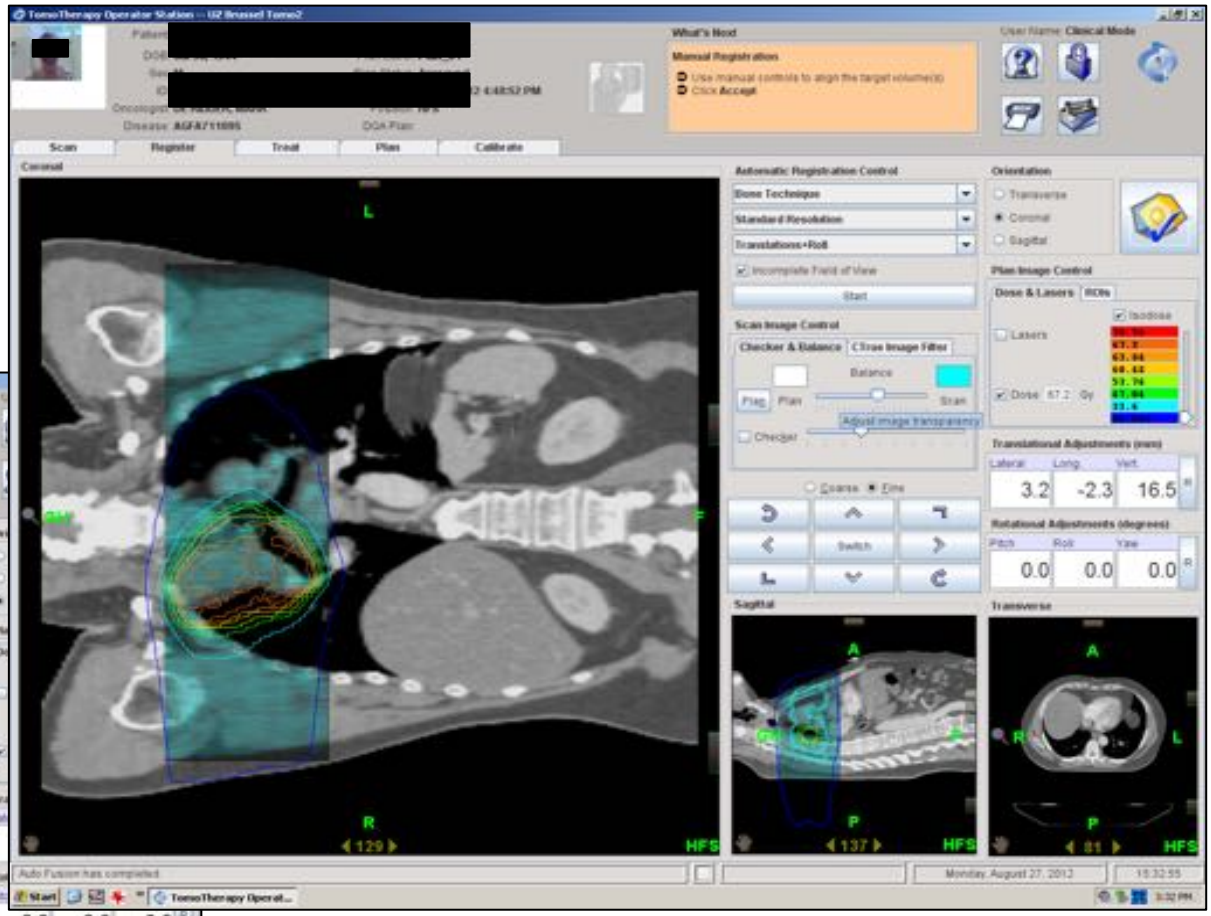


A practical example

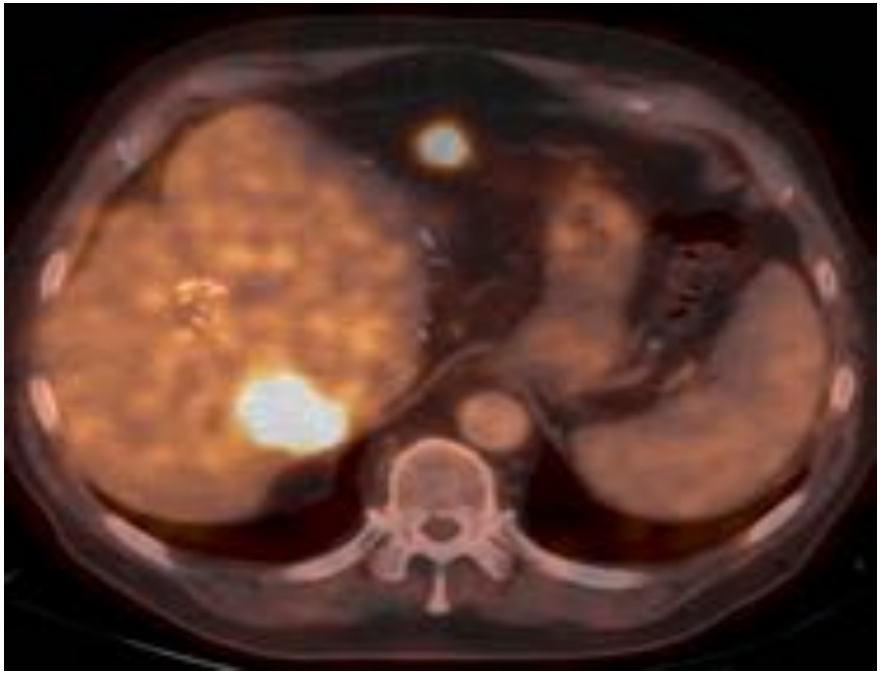


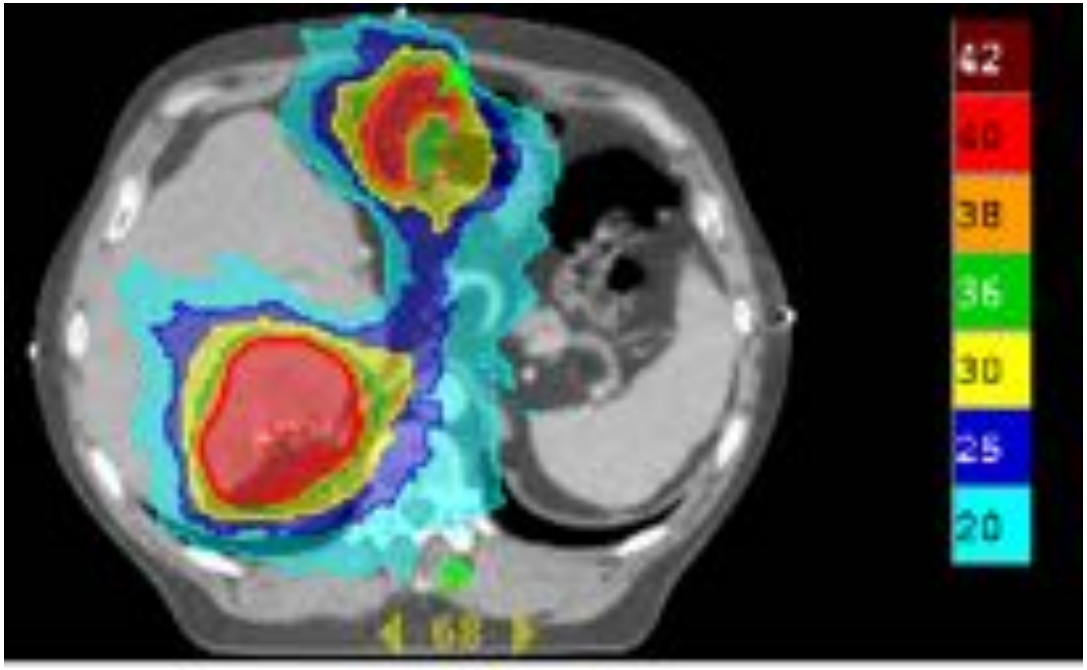
A practical example





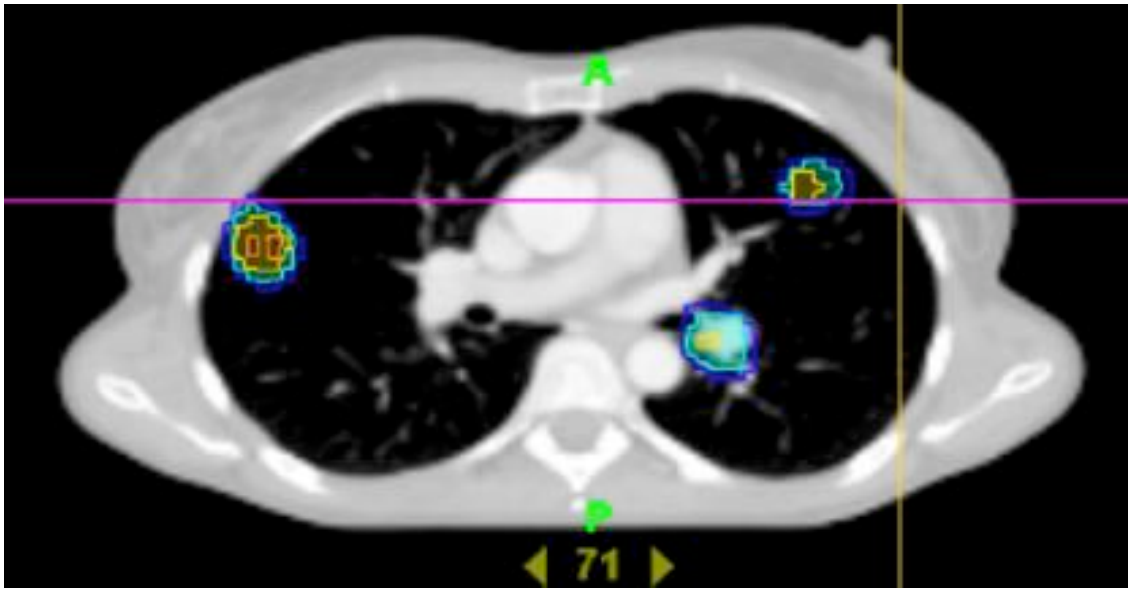
Patient, 63 years





Pre-treatment PET-CT scan (left) and dose distribution of a plan (right) of a patient with a livermetastasis and a perigastric lymph node metastasis.

Palliation and QoL: a case study



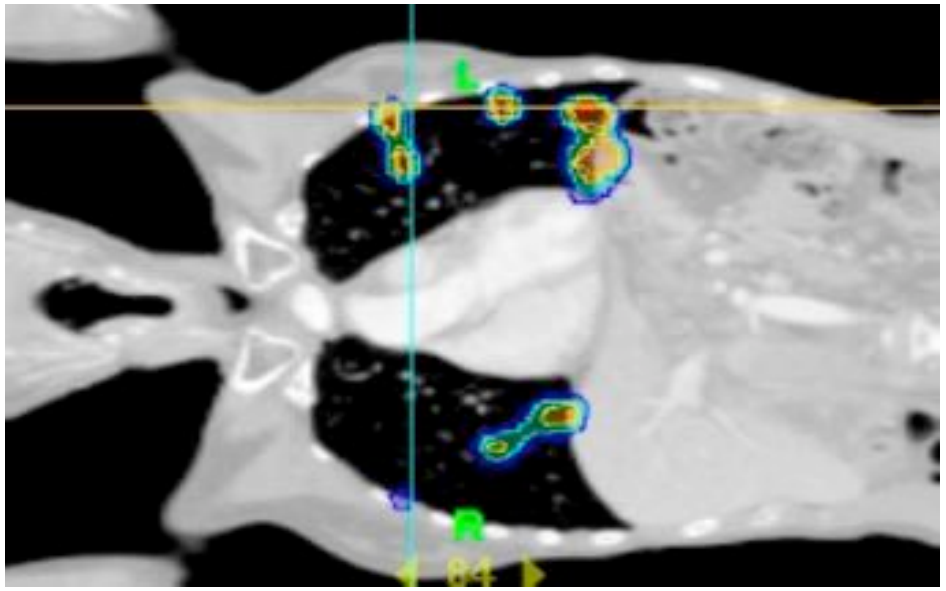
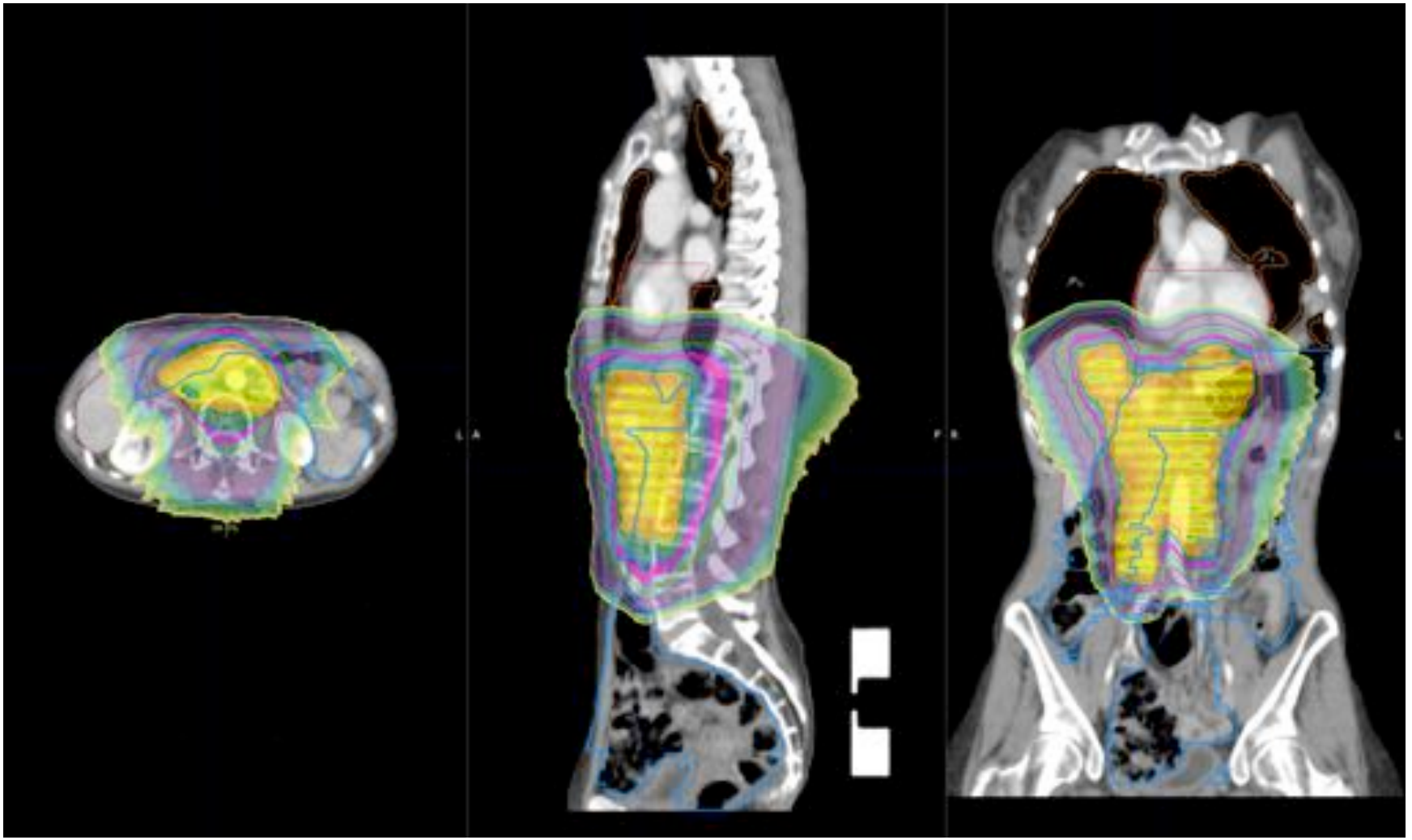


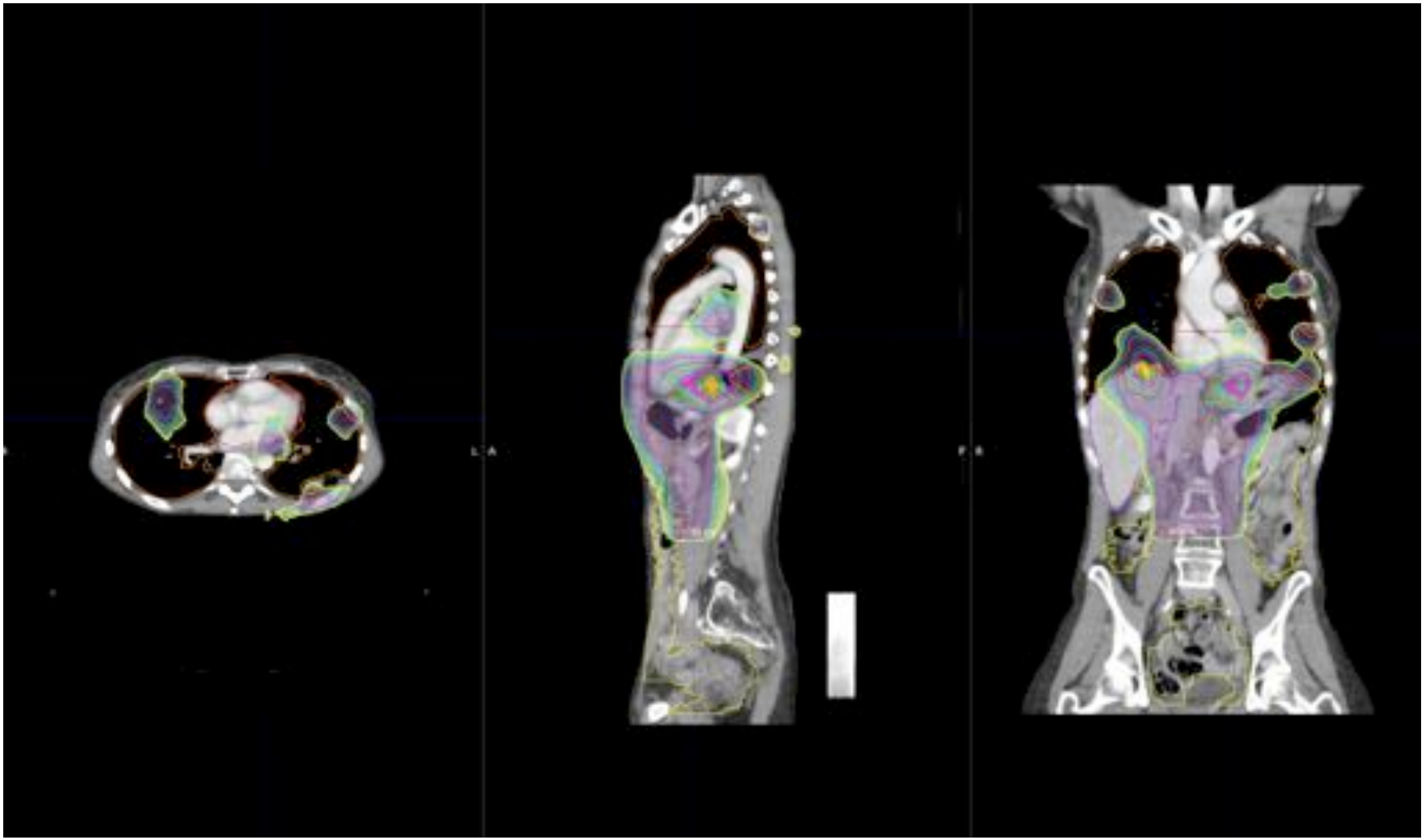
Illustration of a palliative setting in radiotherapy. The patient previously treated for a nasopharyngeal carcinoma presented multiple (17) metastasis not responding after several cycles of chemotherapy, and was treated on all lesions with 10 times 4 Gy with helical tomotherapy in **July 2008**, early 2012 the patient was still in good overall condition.

Accumulated dose: 2007



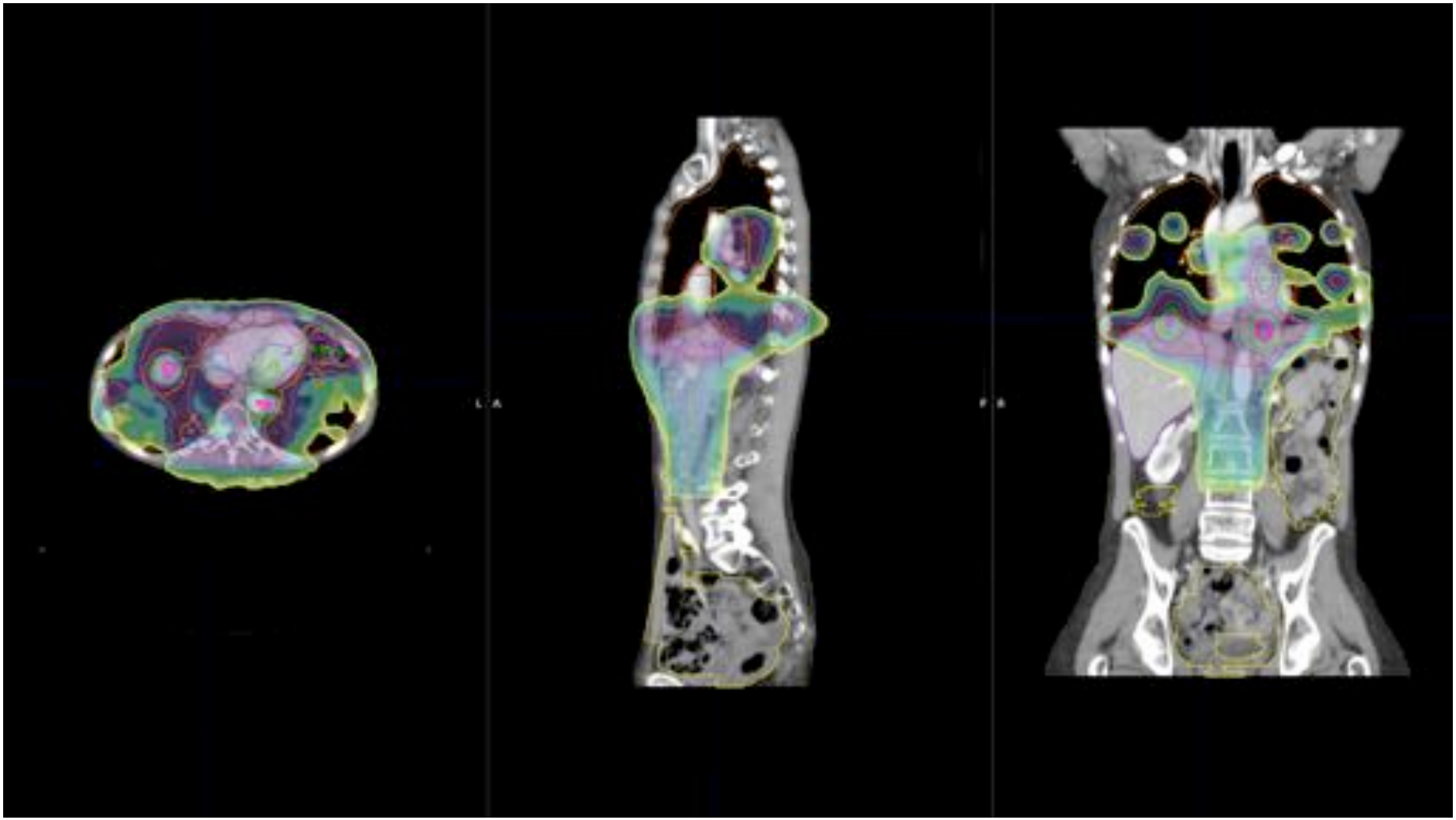
Total Acc Dose 40Gy

Accumulated dose: 2007-2008



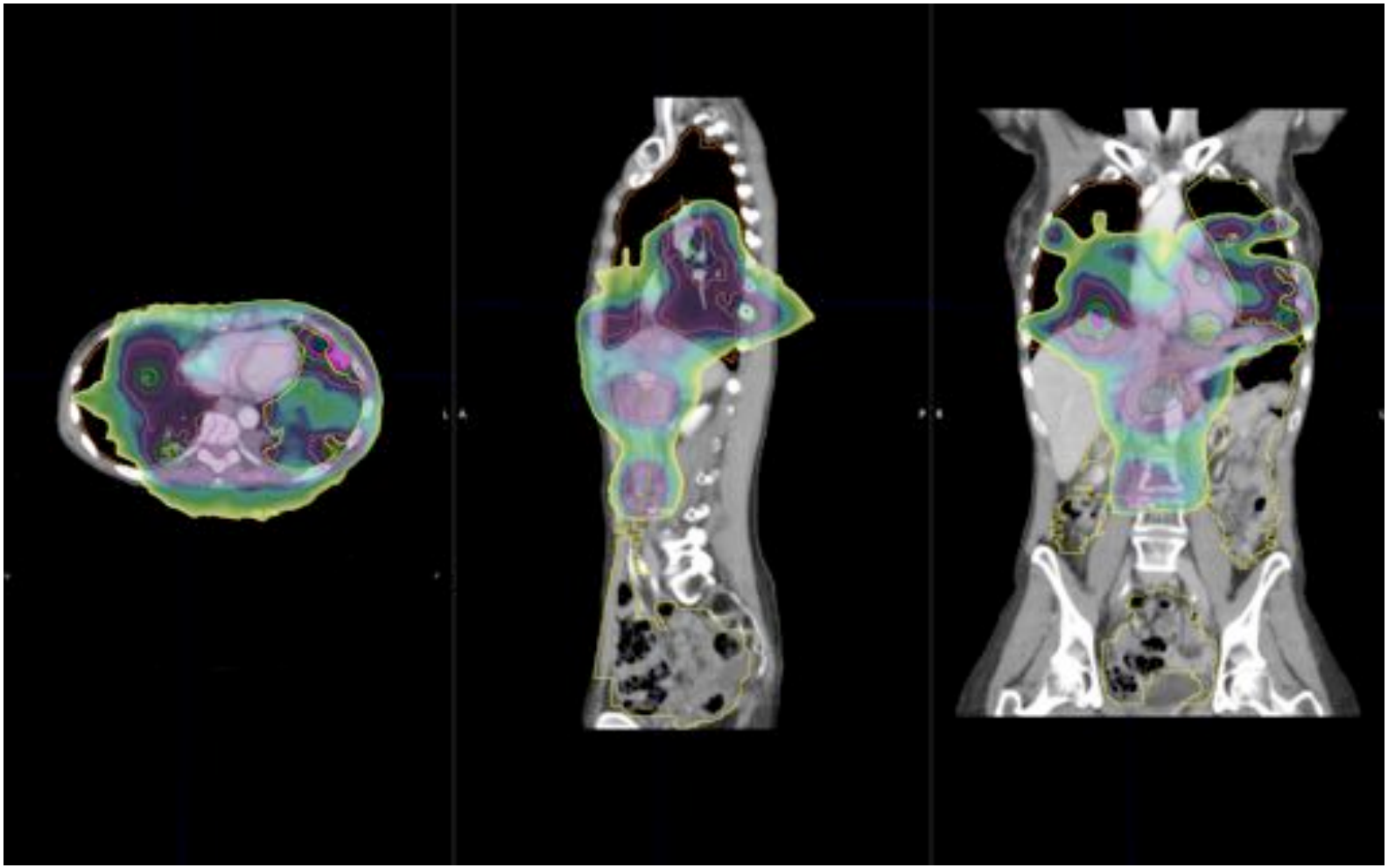
Total Acc Dose 76Gy

Accumulated dose: 2007-2009



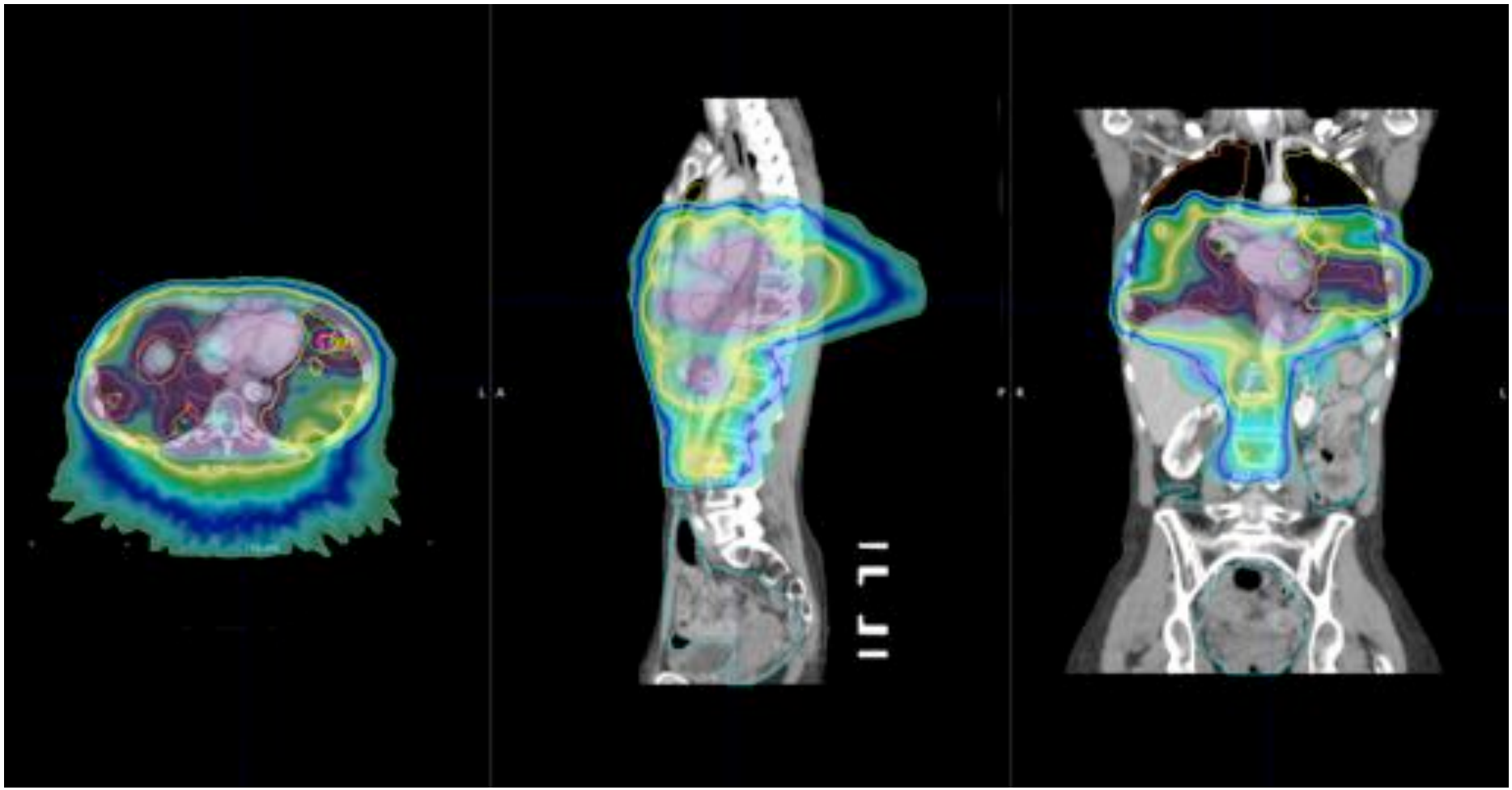
Total Acc Dose 102Gy

Accumulated dose: 2007-2010



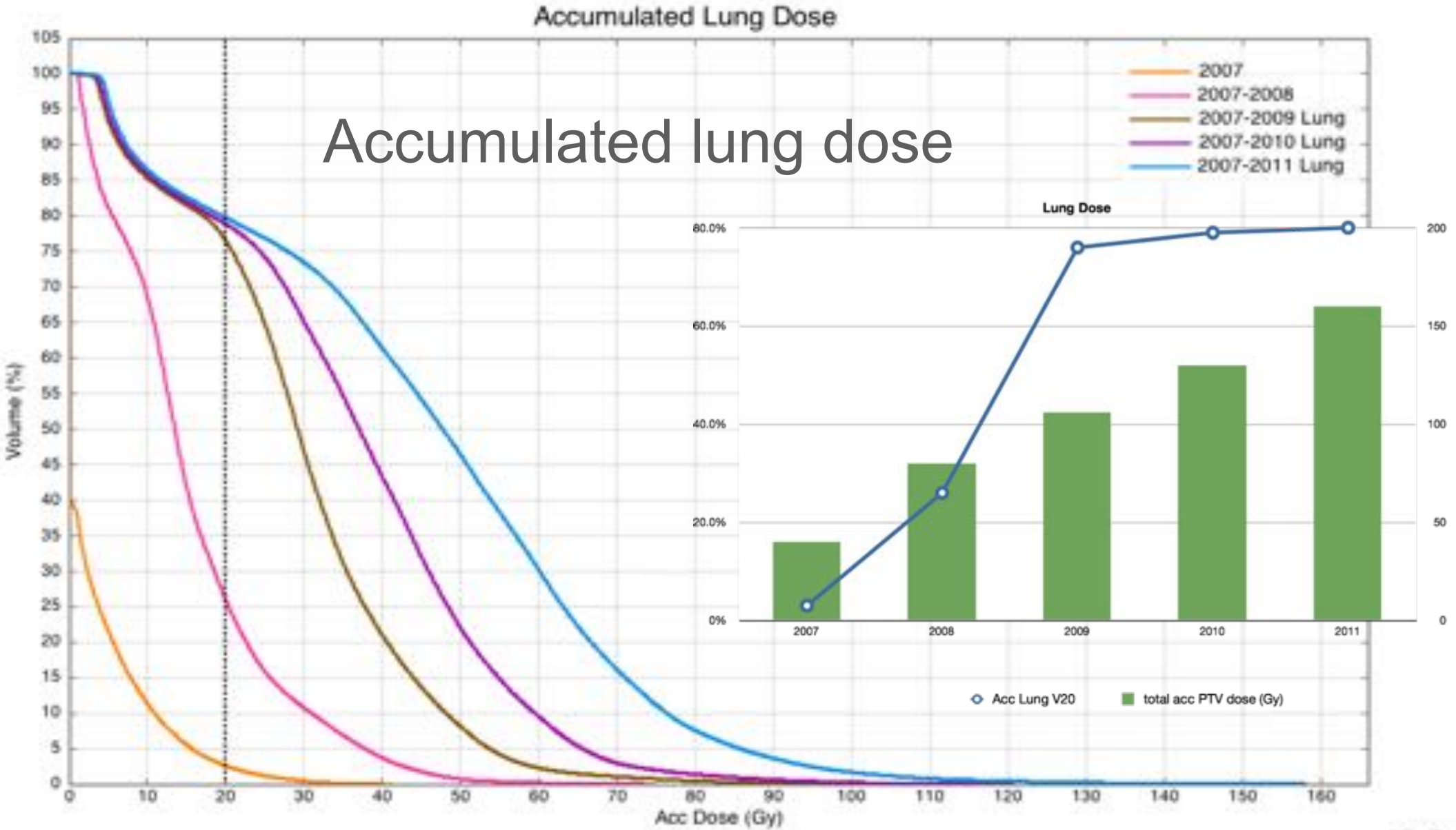
Total Acc Dose 120Gy

Accumulated dose: 2007-2011



Total Accumulated Dose 160Gy

Accumulated lung dose

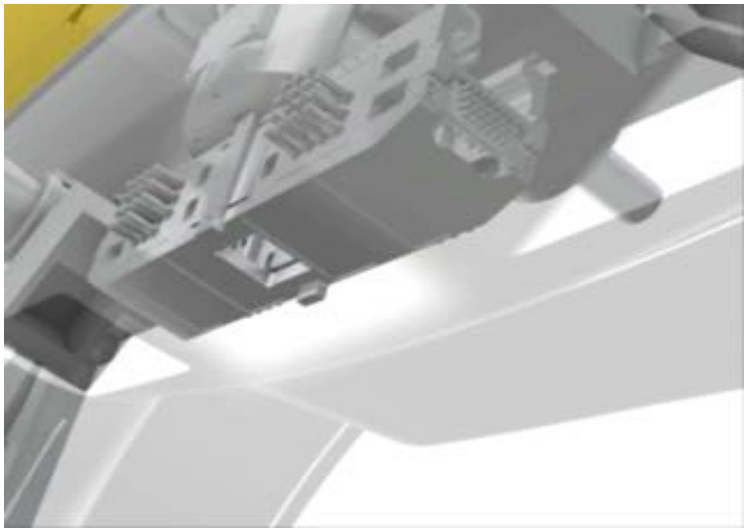


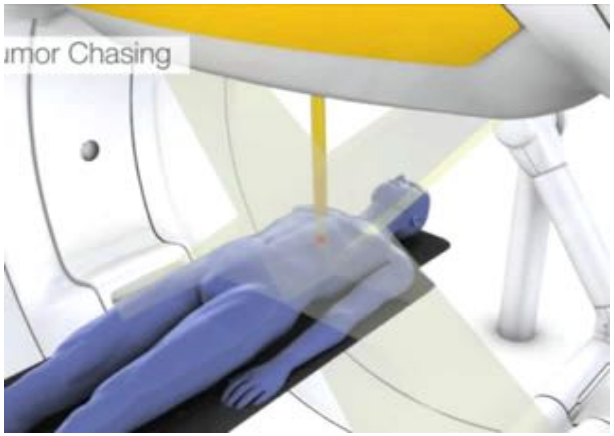
04 Januari 2011

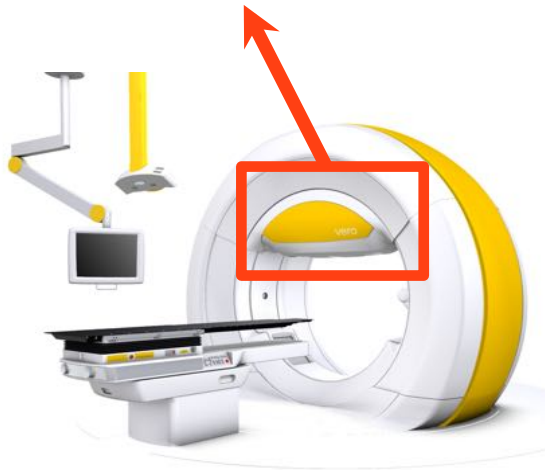
“En guise de carte de voeux, je vous adresse la photo de l'une de vos patientes à J + 50 du dernier traitement.....et les 2500m d'altitude ne m'ont posé aucun trouble particulier au plan respiratoire ni cardiaque, juste quelques courbatures aux mollets le lendemain.....”

Real-time tumour tracking

- VERO as an example

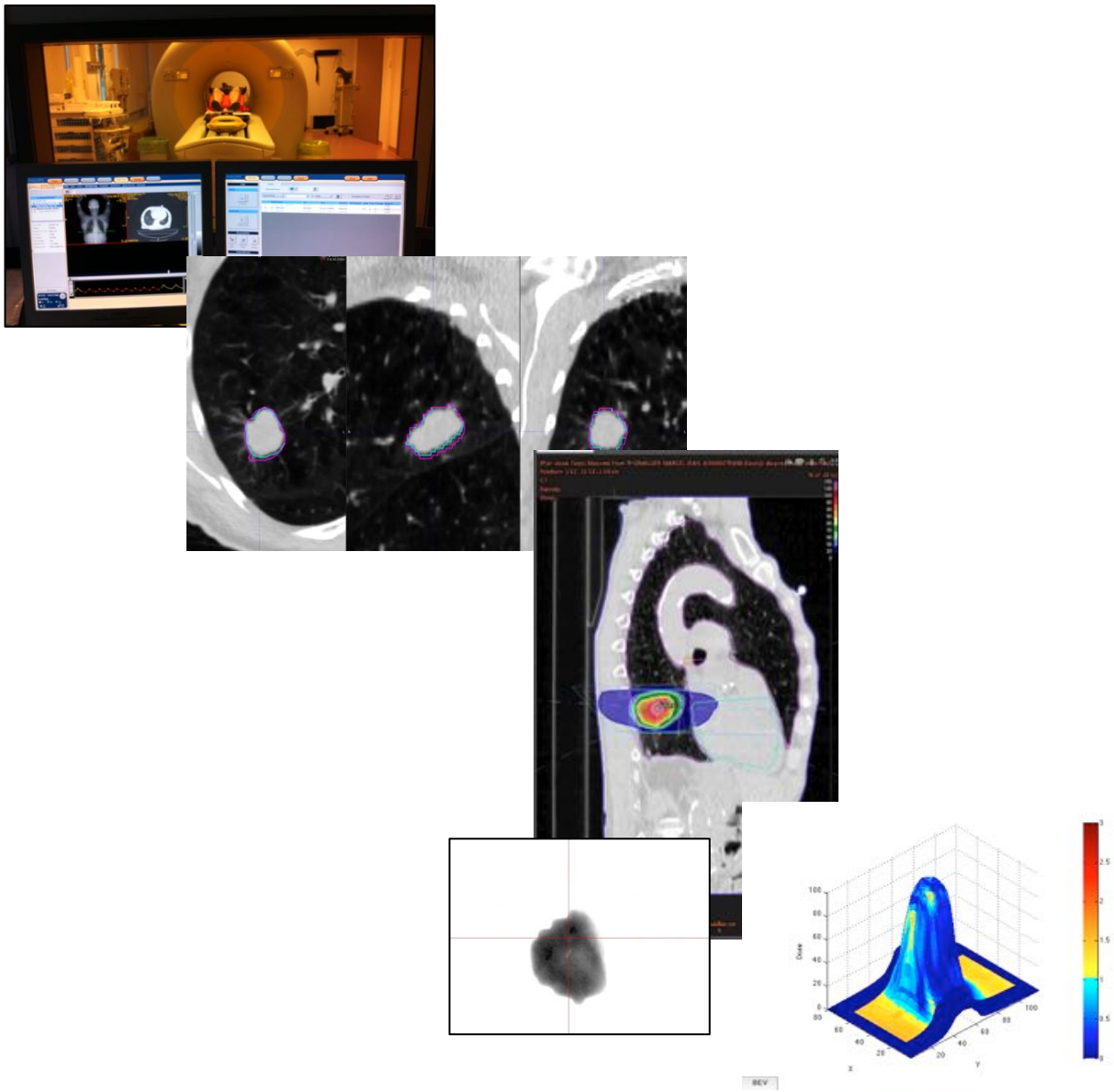






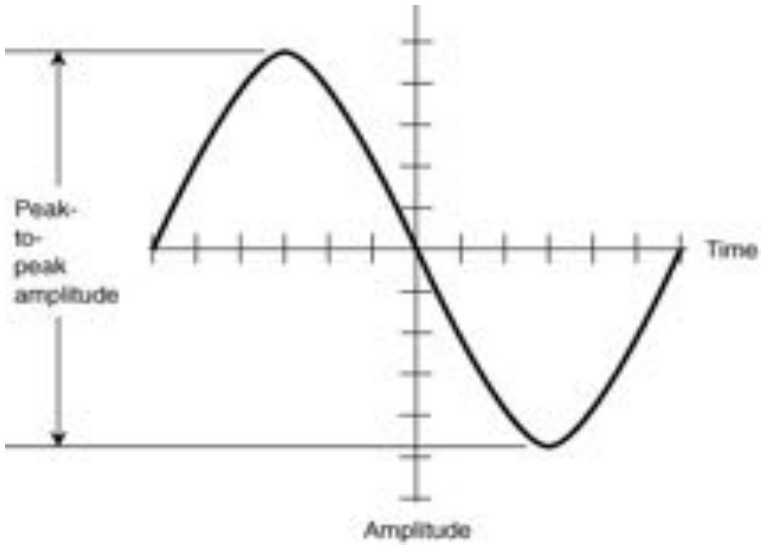
Outline

- Imaging
- Treatment decision
- Volume delineation
- Treatment planning
- Dry run
- Patient specific QA
- Treatment
- *In vivo* treatment verification



Treatment decision
“to track or not to track?”

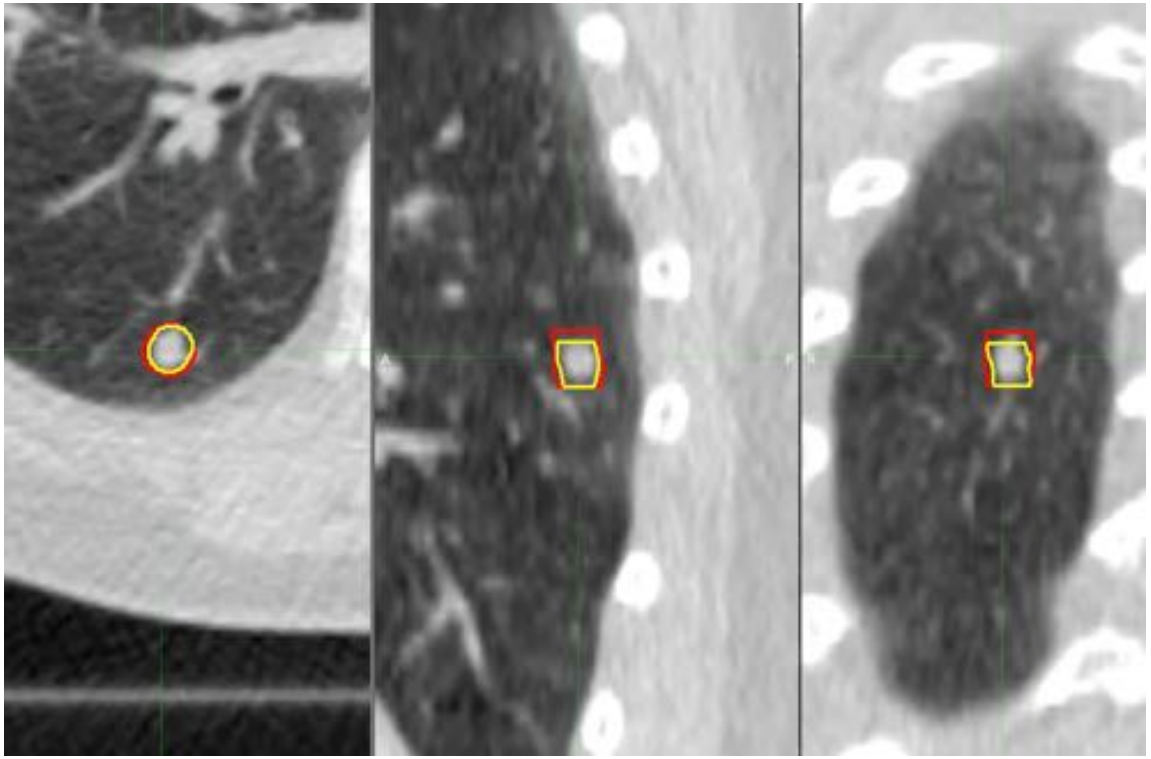
- Decision based on motion amplitude assessed from 4D-CT:



  - **< 7 mm ➔ ITV Approach**
  - PTV = ITV + 5 mm
  - PTV = ITV + 8mm (if lesion < 10 mm)

  - **≥ 7 mm ➔ Real-time tracking**
  - Internal marker if no contra-indication
  - PTV = GTV + 5 mm

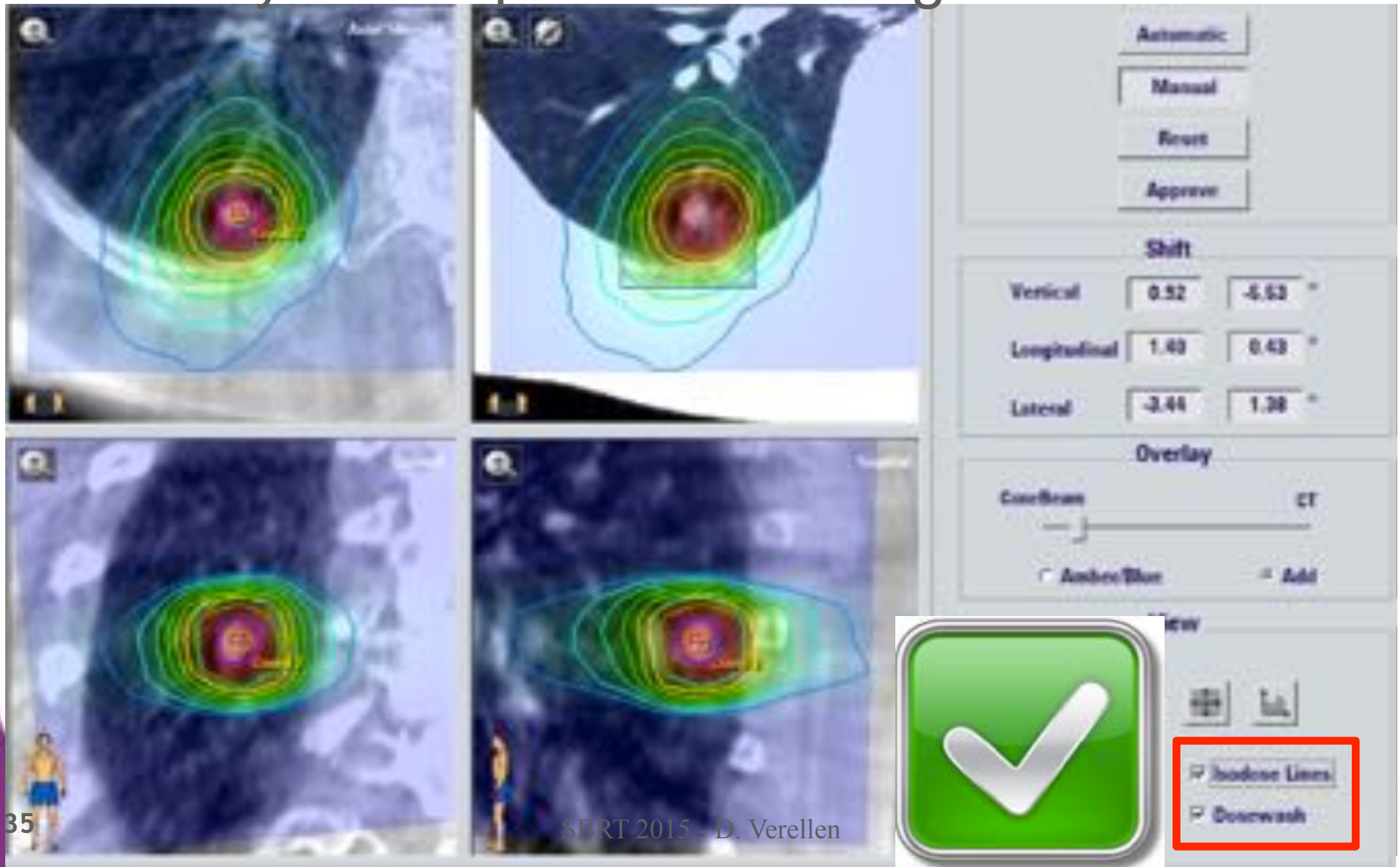
ITV case:
54 year old patient with lungmetastasis



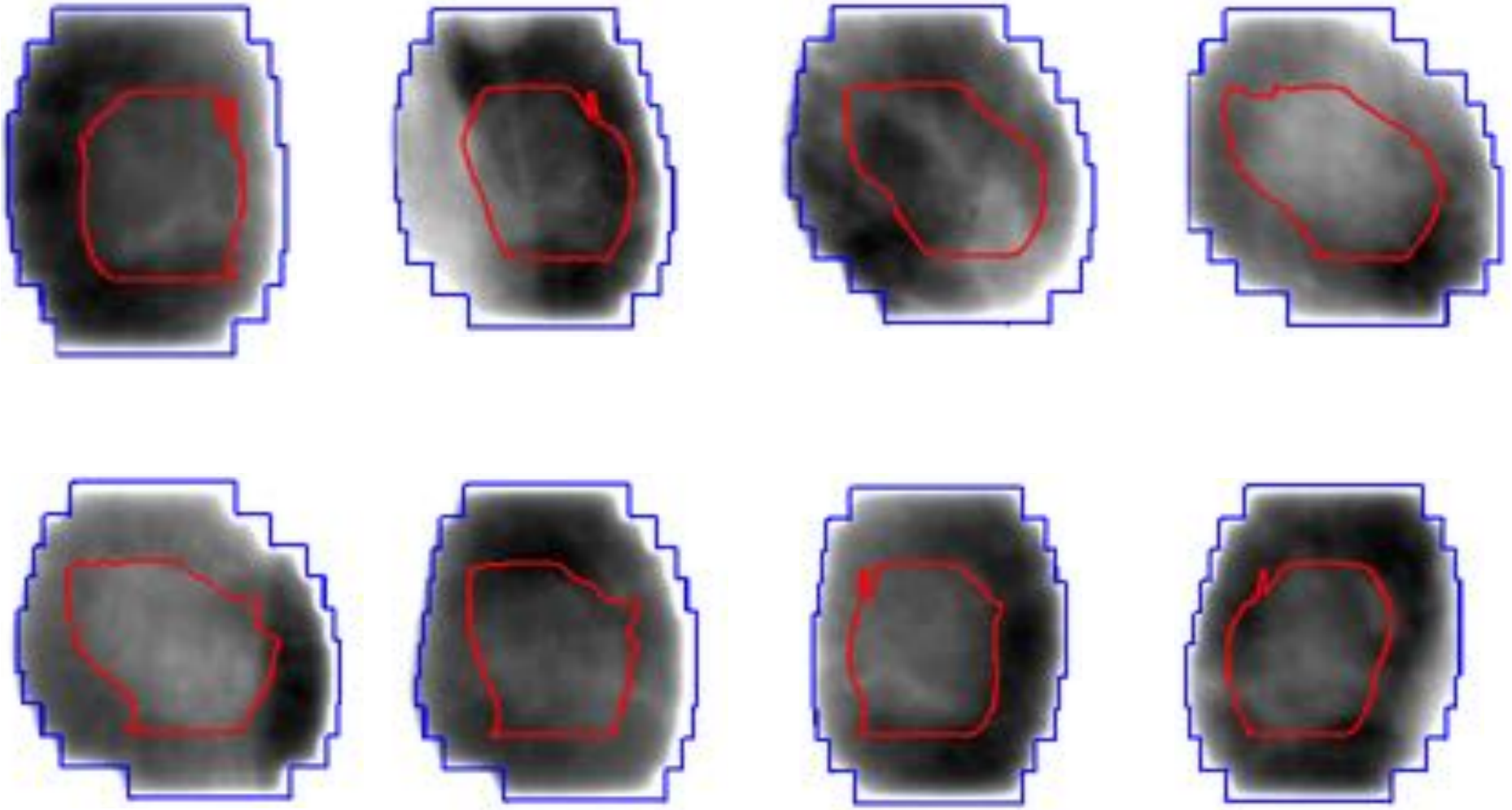
2007: Primary sigmoid cancer
2010: lung + livermetastasis => chemotherapy
2011: resection liver + lungmetastasis
2011: RT 42 Gy (15x 2.8 Gy) thoracic wall
2012: lungmetastasis in right inferior lobe, referred for SBRT 10 x 5 Gy

Motion amplitude: **CC of 4 mm** in 4D CT

ITV case:
54 year old patient with lungmetastasis

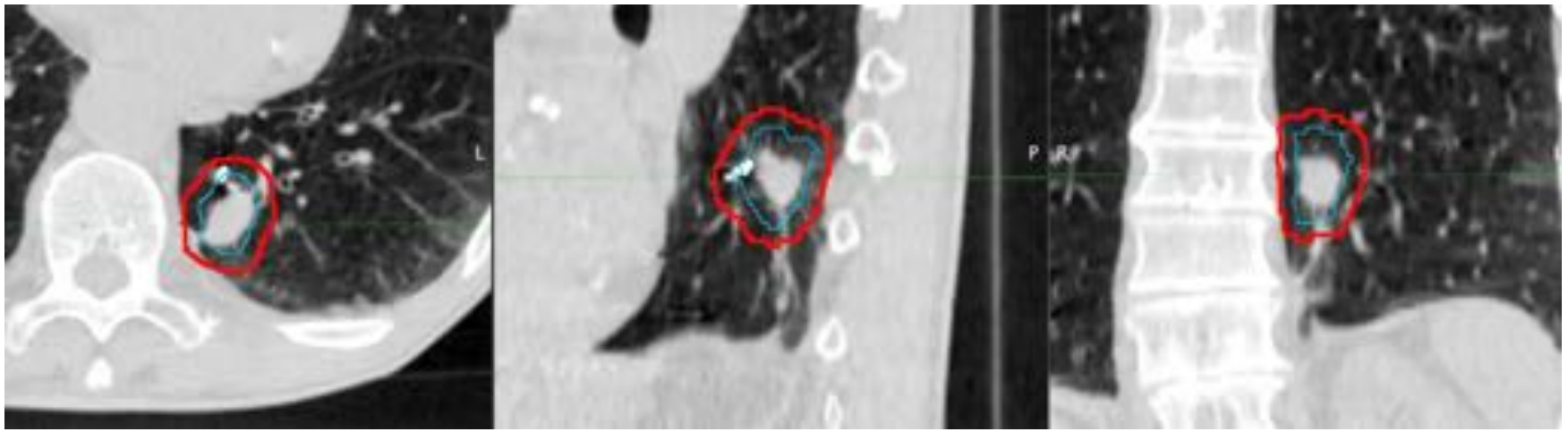


ITV case:
54 year old patient with lungmetastasis



ITV MLC

RTTT case: requires implanted markers

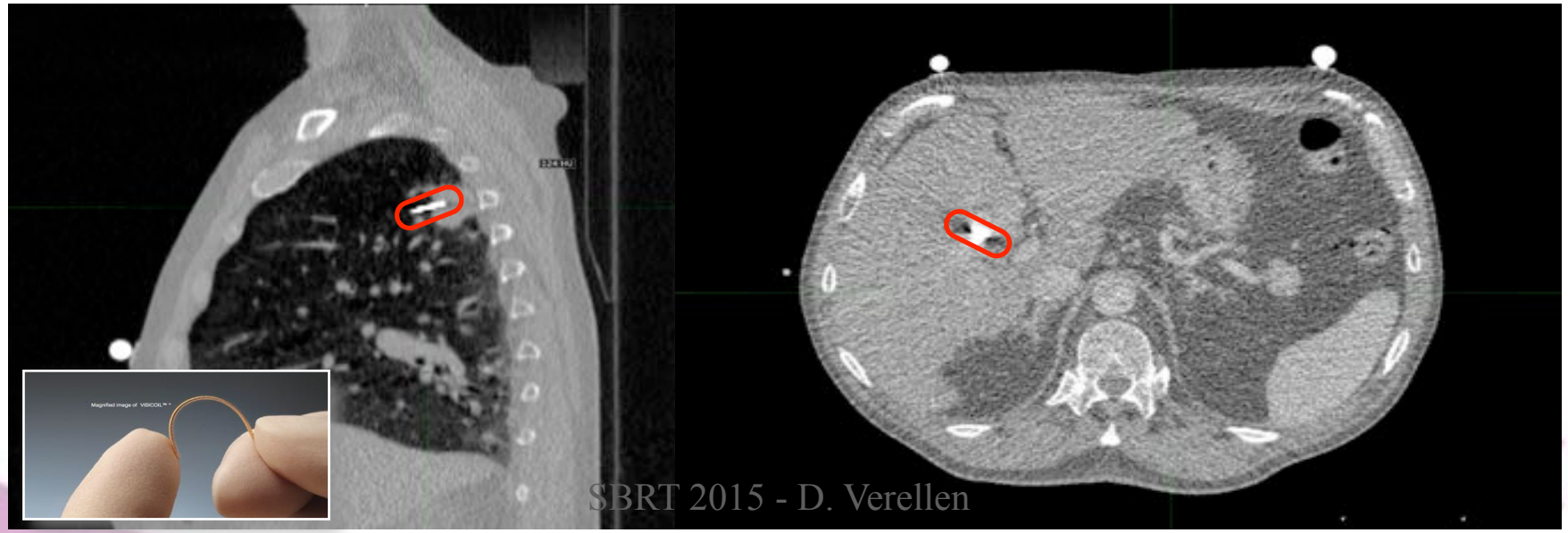


10 mm

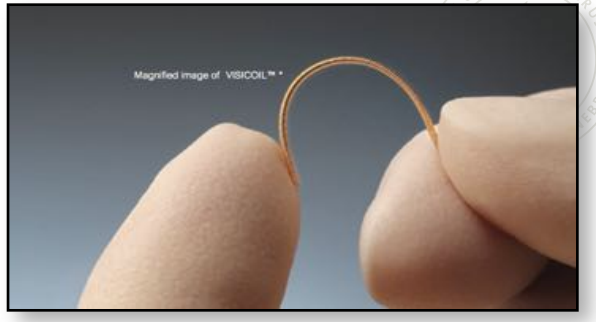
OR

20 mm

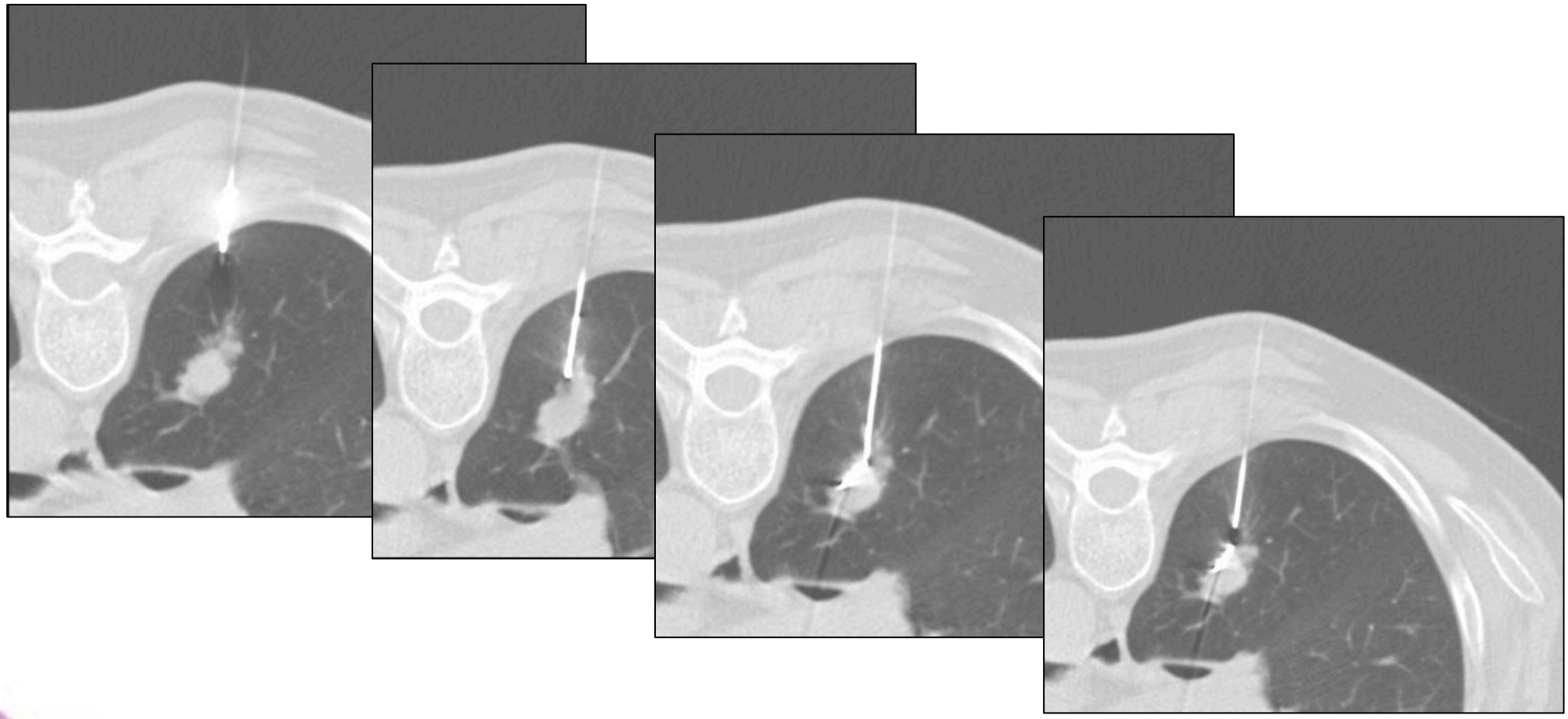
0.75 mm ⌀



Marker placement

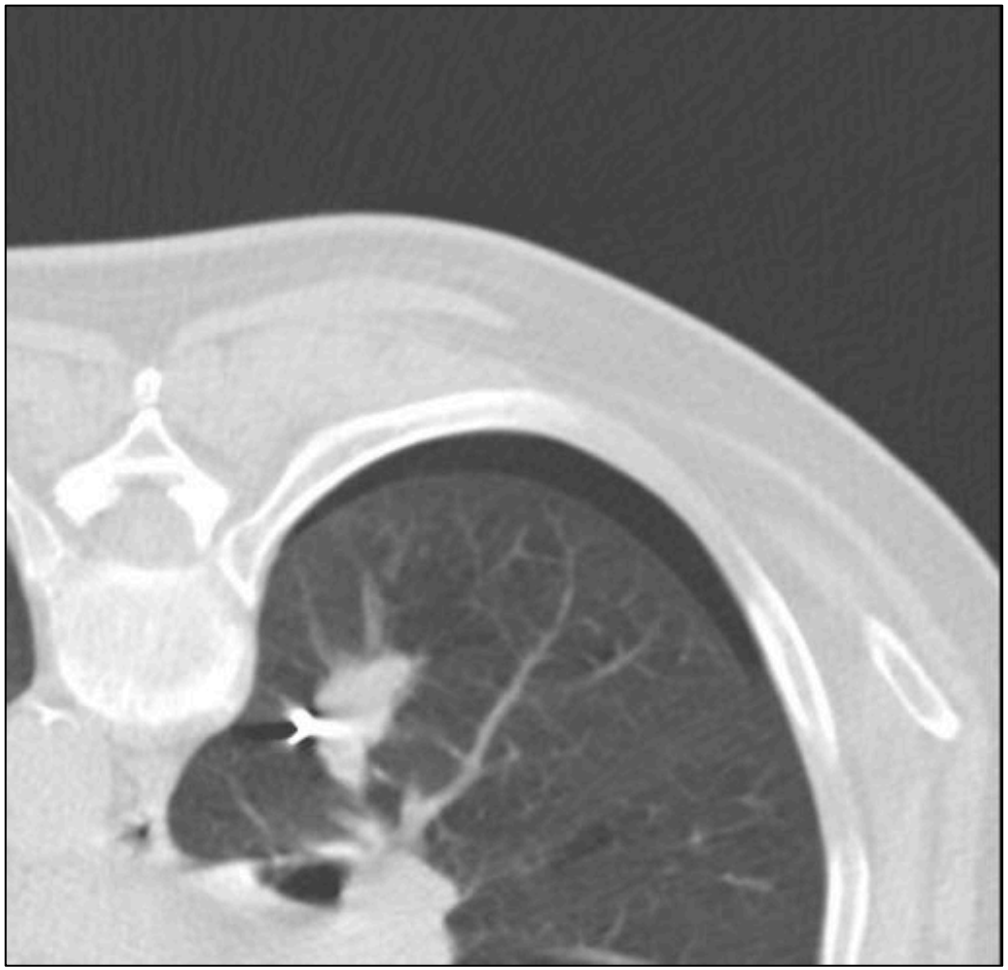


- Visicoil marker (1-2 cm):
  - Implanted percutanuously using CT-fluoroscopic guidance



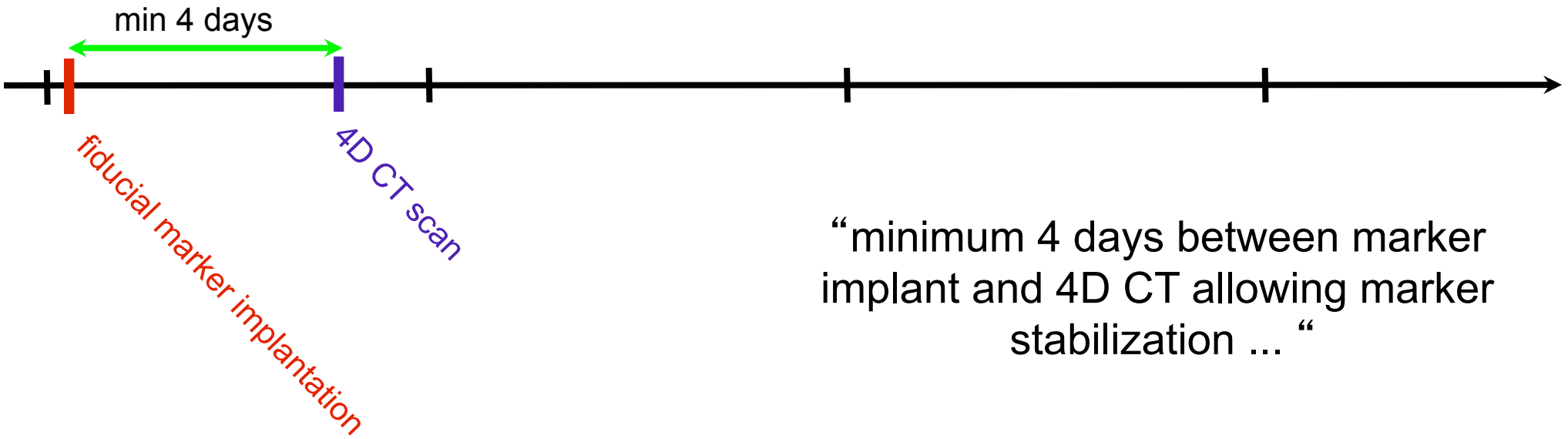
Marker placement

- Oops ...



➢ Yes … relative high risk for pneumothorax

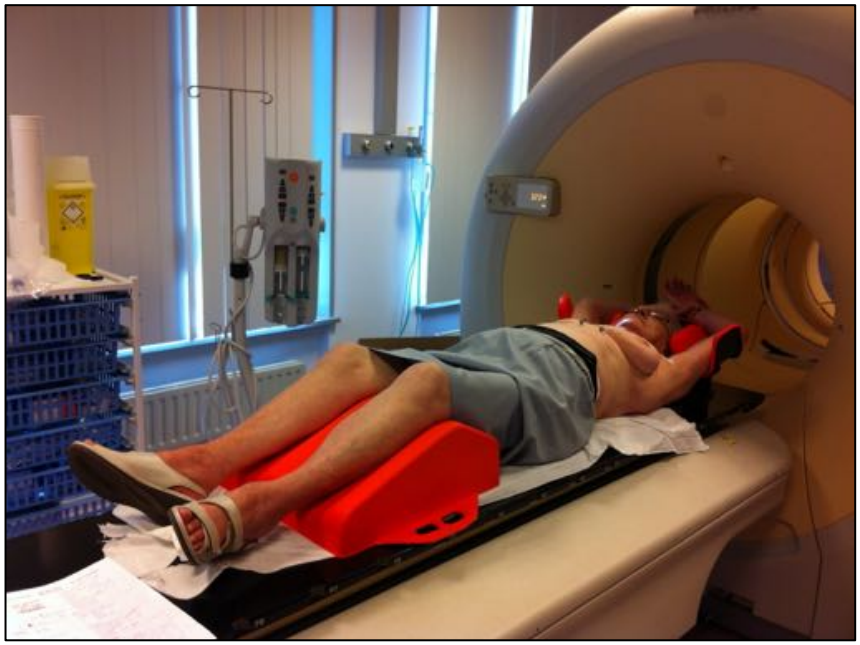
Clinical workflow

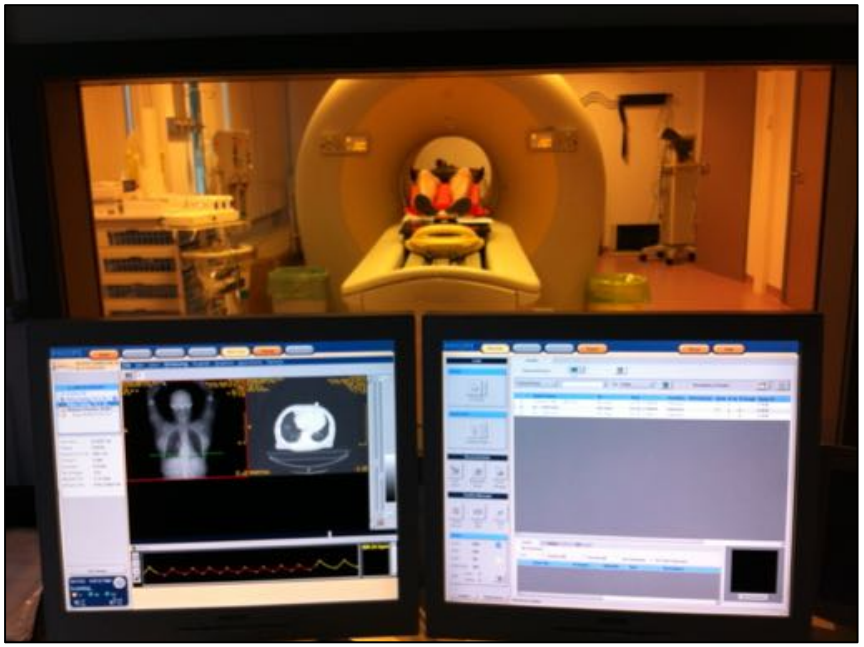


"minimum 4 days between marker implant and 4D CT allowing marker stabilization ... "

Imaging

- 4D-CT and free breathing PET-CT
- Mayo Clinic Respiratory Belt
  - Phase-based binning
  - Different respiration signal compared to respiration signal acquired for dynamic tracking (recently replaced by Varian RPM system)



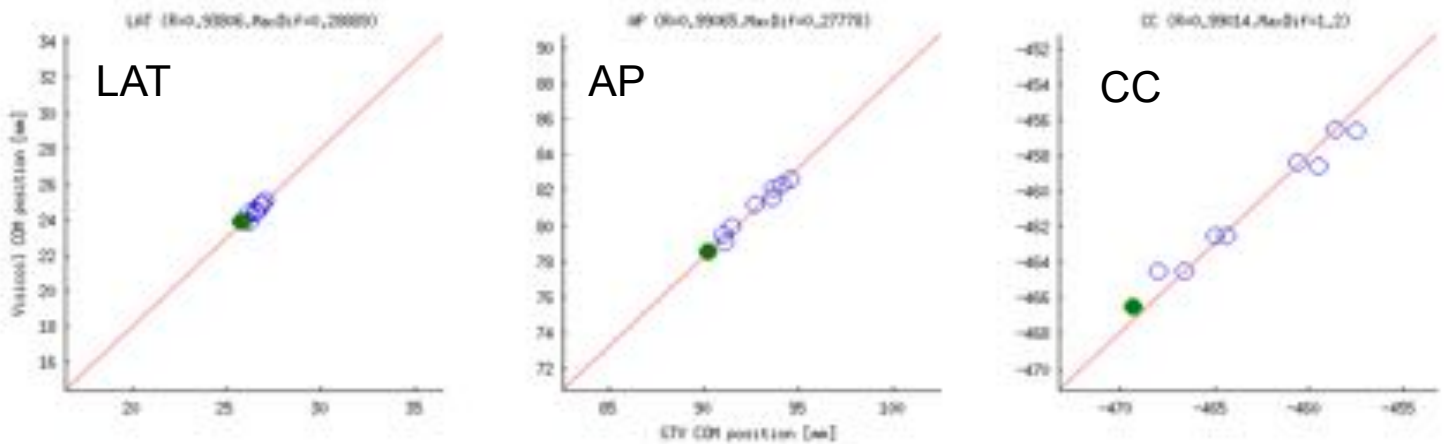


Patient specific pre-treatment QA

- Verifying if marker motion is appropriate surrogate of tumour motion

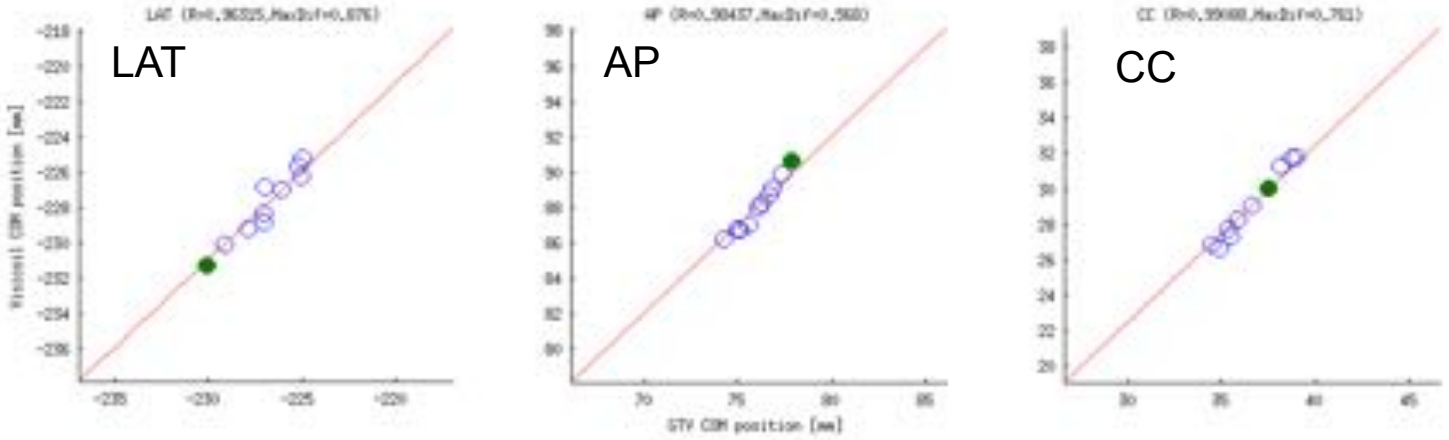
Surrogate value: COM Single Visicoil marker vs. COM GTV

Ex. 1



$(x,y,z)_{COM,Visicoil}=(x,y,z)_{COM,GTV}+Cte$

Ex. 2

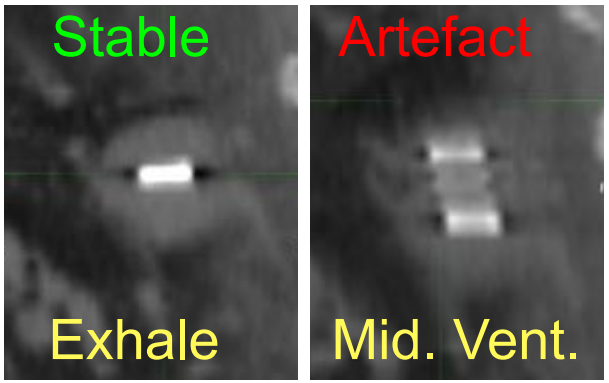


"Max deviation"

1.2 mm in CC

(CT slice 2 mm)

For large amplitudes (> 15 mm p2p):



4D CT Artefacts

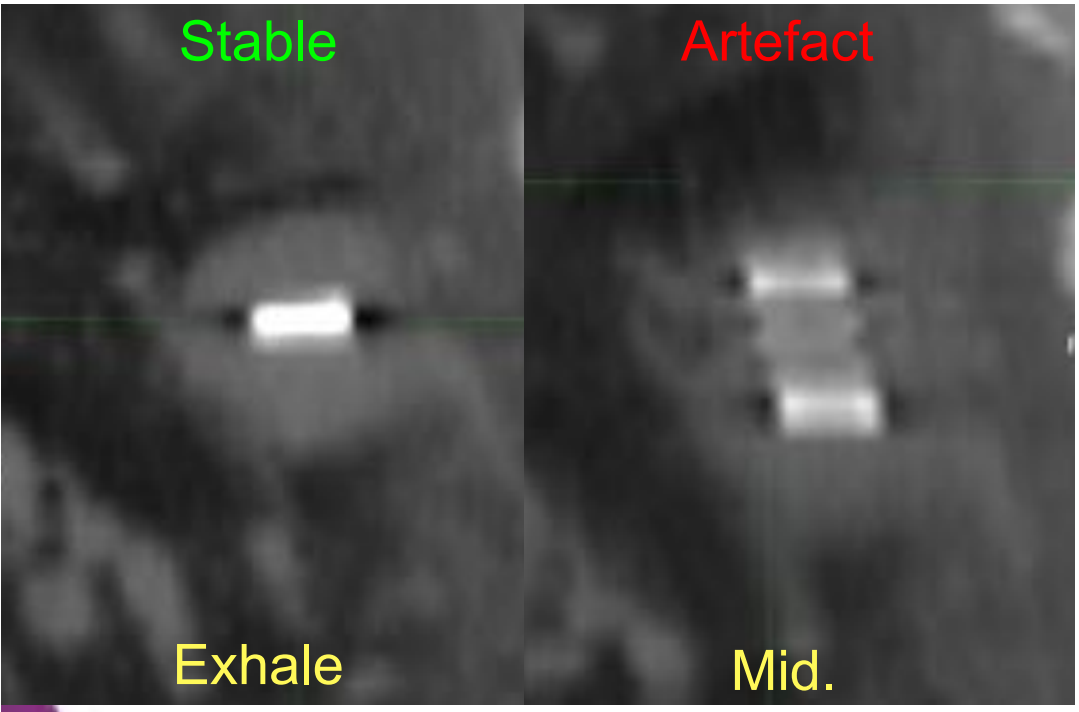
Patient specific pre-treatment QA

- Verifying if marker motion is appropriate surrogate of tumour motion

Surrogate value: COM Single Visicoil marker vs. COM GTV

Lung

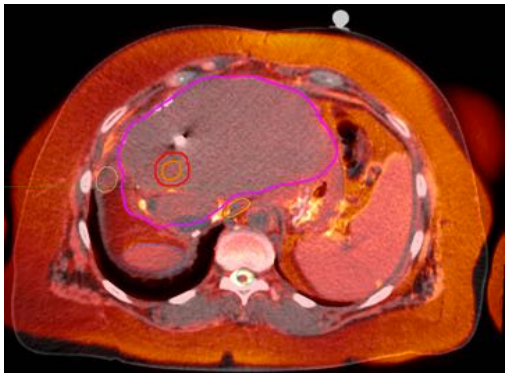
In Lung, for large amplitudes (> 15 mm p2p):



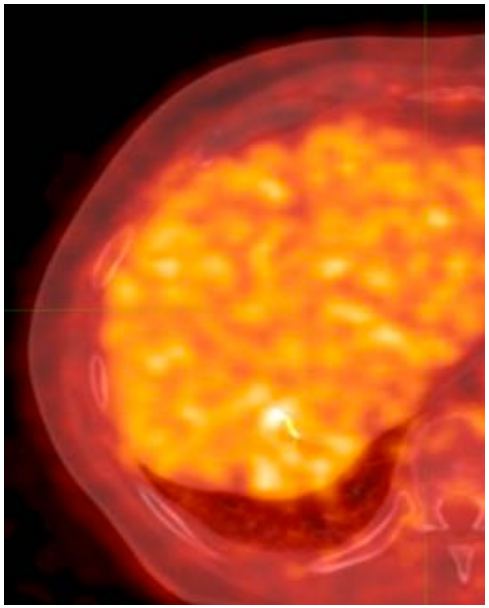
4D CT Artefacts

Liver

Multi-modal delineation
on one 4D CT phase
+ RIGID propagation
based on fiducial marker

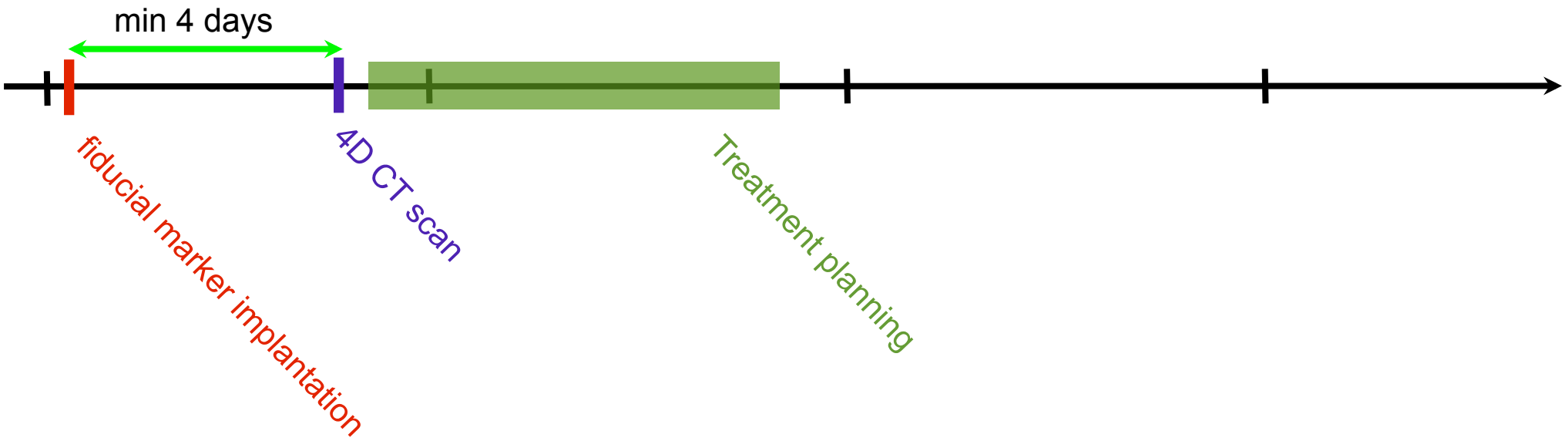


MR fusion



PET-CT fusion

Clinical workflow

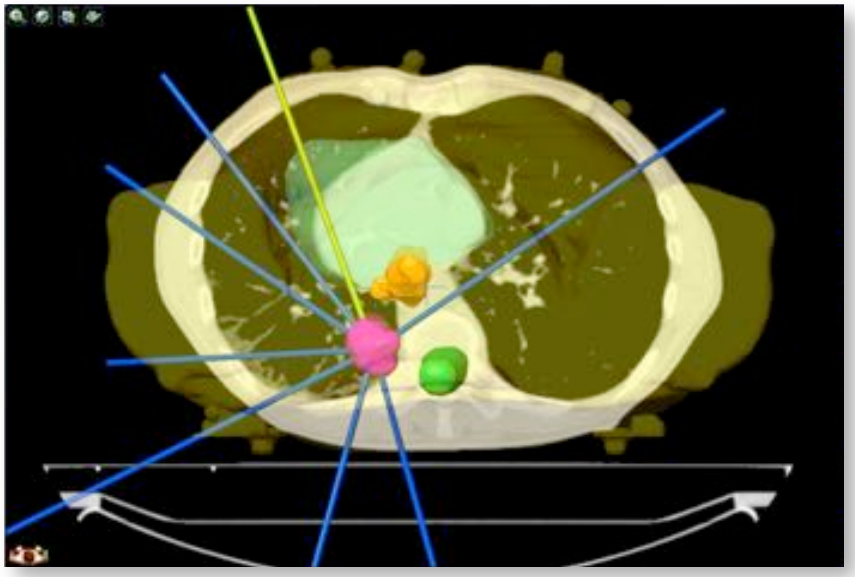


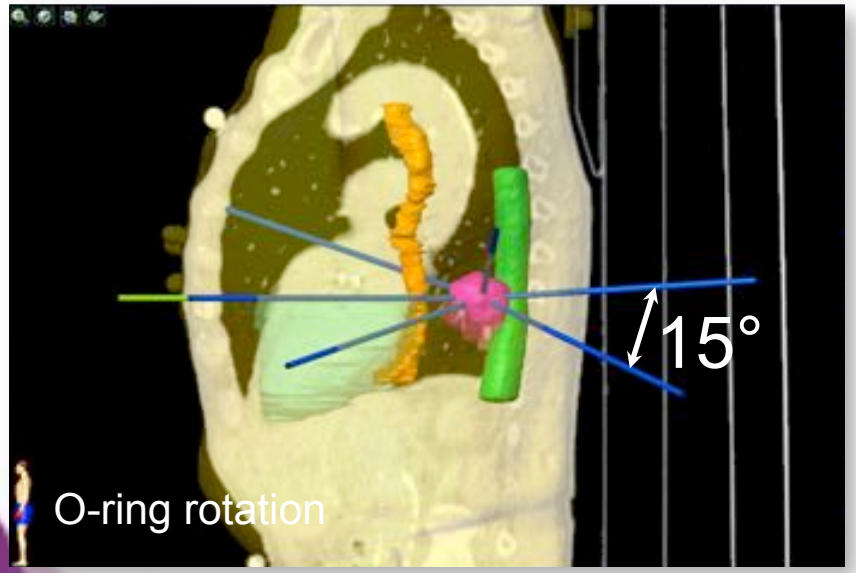
Delineation

- Tracking plan & ITV plan as backup

Modality	Images	Date	Series De
CT	134	29 Jul 2013	TX.2_.0.0%
CT	134	29 Jul 2013	TX.2_.10.0%
CT	134	29 Jul 2013	TX.2_.20.0%
CT	134	29 Jul 2013	TX.2_.30.0%
CT	134	29 Jul 2013	TX.2_.40.0%
CT	**134**	**29 Jul 2013**	**TX.2_.50.0%**
RTst	1	05 Aug 2013	2013-08-05.10.28.kt..forvero
CT	134	29 Jul 2013	TX.2_.60.0%
CT	134	29 Jul 2013	TX.2_.70.0%
CT	134	29 Jul 2013	TX.2_.80.0%
CT	134	29 Jul 2013	TX.2_.90.0%

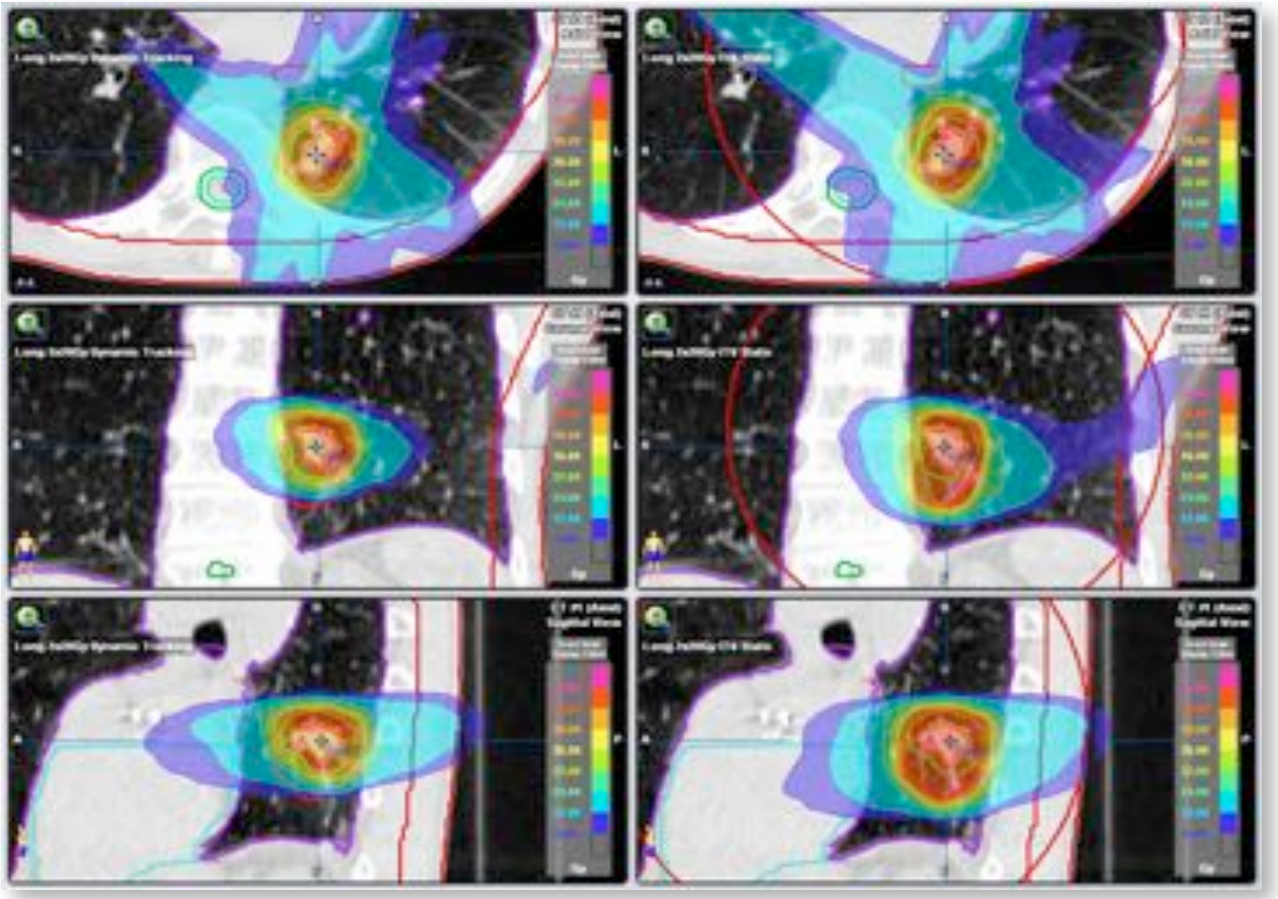
Treatment Planning





Tracking

ITV



8 beam non-coplanar conformal SBRT plan

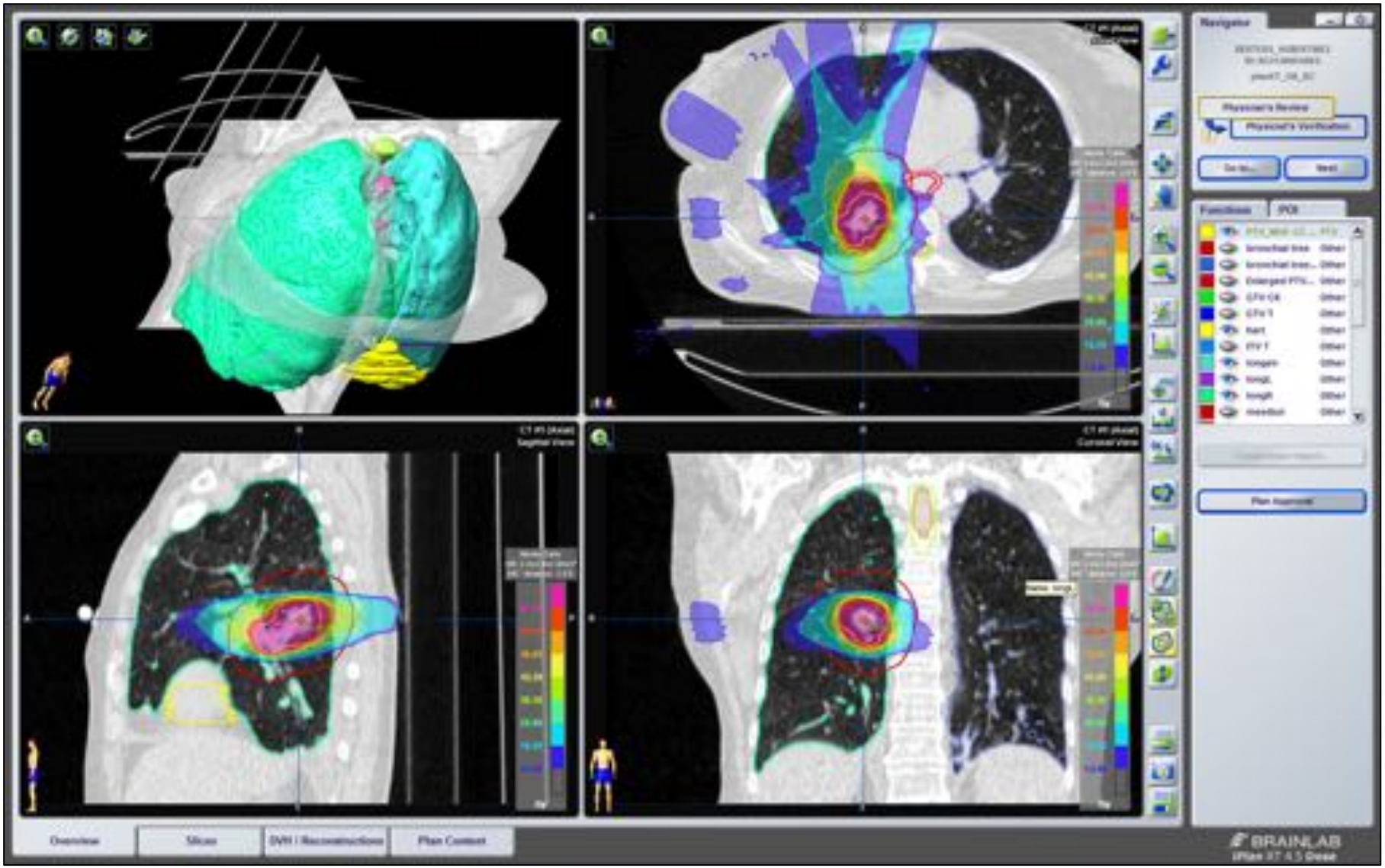
Treatment Planning

- Type B dose calculation algorithm
- For details on plan acceptance see lecture Tuesday
- Treatment constraints:
  - PTV = GTV + 5mm
  - Dose prescription
    - Centrally located lesions
    - Lesions < 1cm from thoracic wall

    ⇒ **4 x 12 Gy (Monte Carlo)**
    - Peripheral lesions

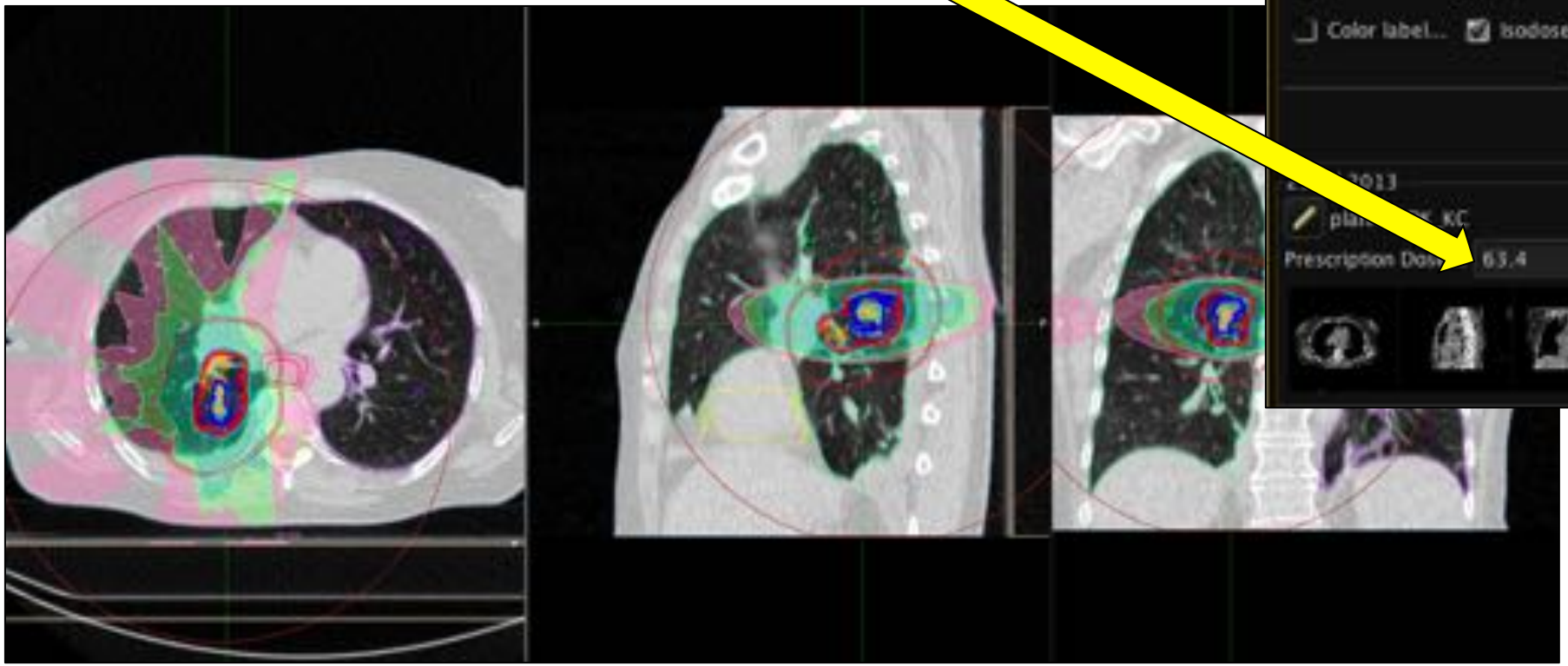
    ⇒ **3 x 17 Gy (Monte Carlo)**
  - Dose prescription
    - Normalization: 100% @ **isocentre**, $D_{1\%}$ < 105%
    - 95% of PTV covered by **prescription isodose** surface (i.e. 12 or 17Gy)
    - 99% of PTV covered by 90% of **prescription isodose** surface
  - Dose constraints:
    - Conformity, low and high dose spillage …
    - Normal tissues …

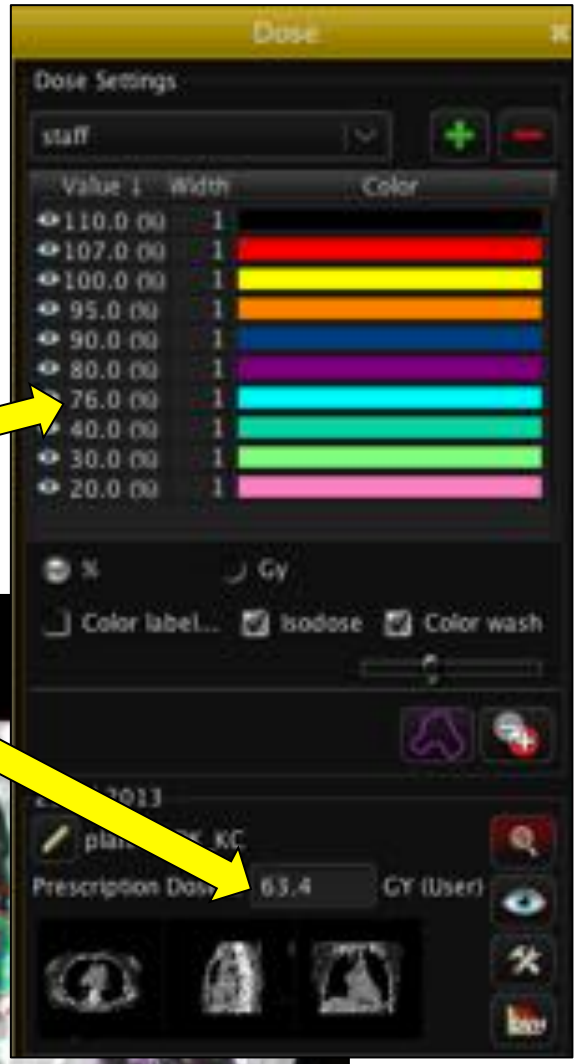
Treatment Planning



Treatment Planning

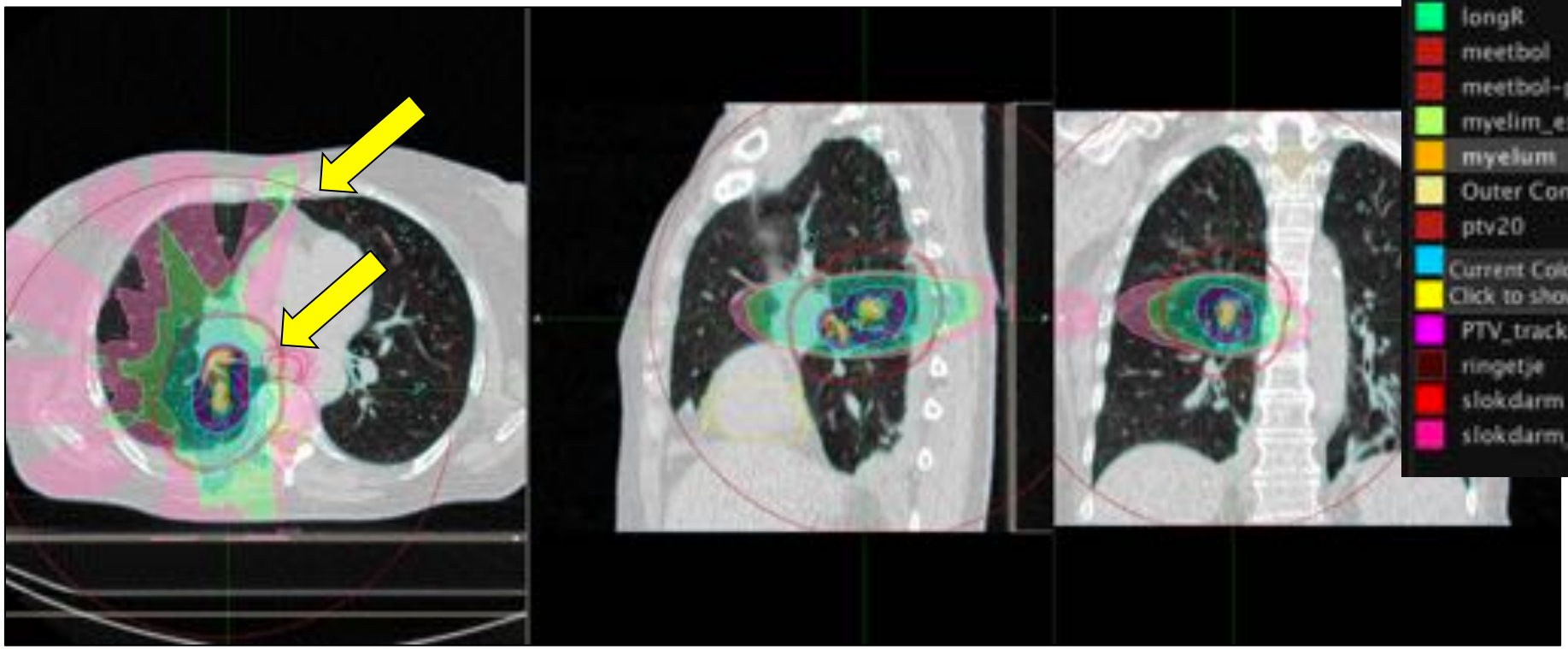
- Isocentre dose = 100%
- Prescription isodose = 48 Gy (76% in this case)



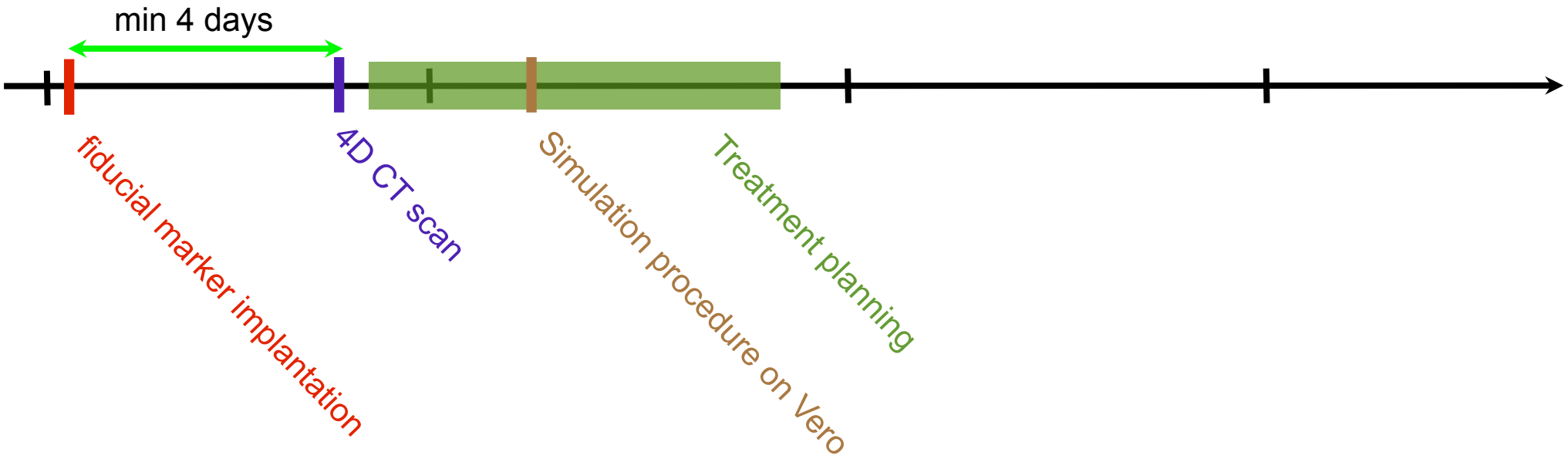


Treatment Planning

- Constraints based on conformity, low and high dose spil, …
- See lecture Tuesday!

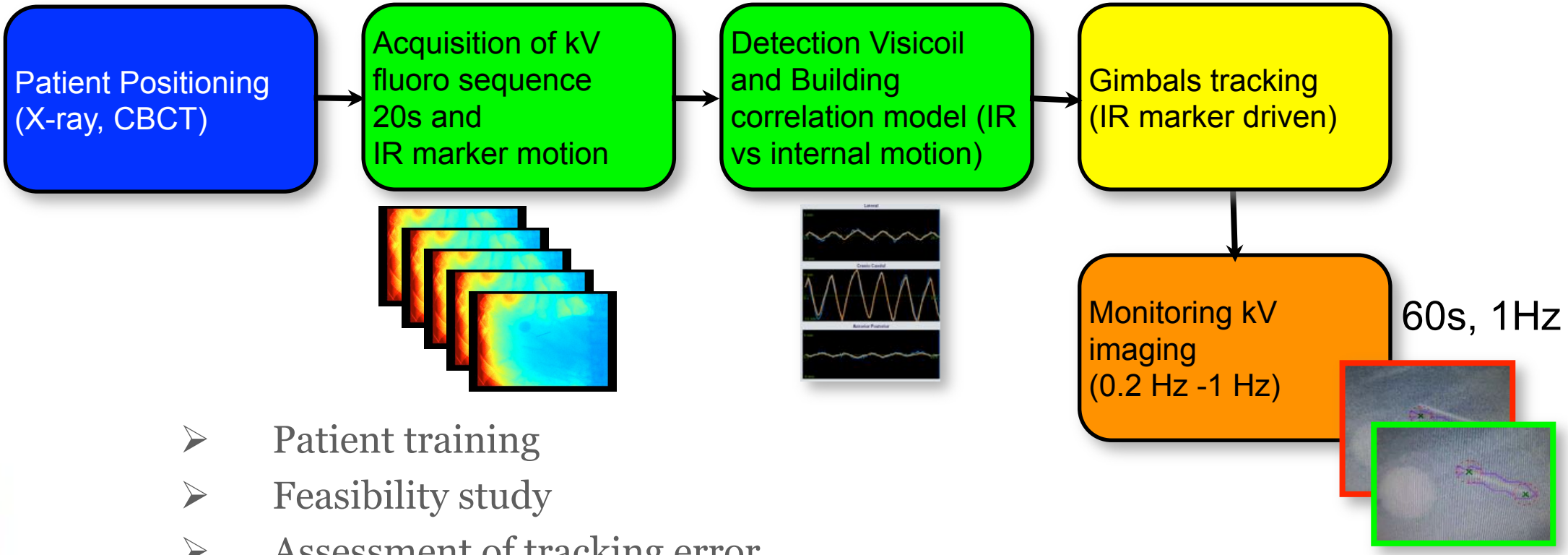


Clinical workflow



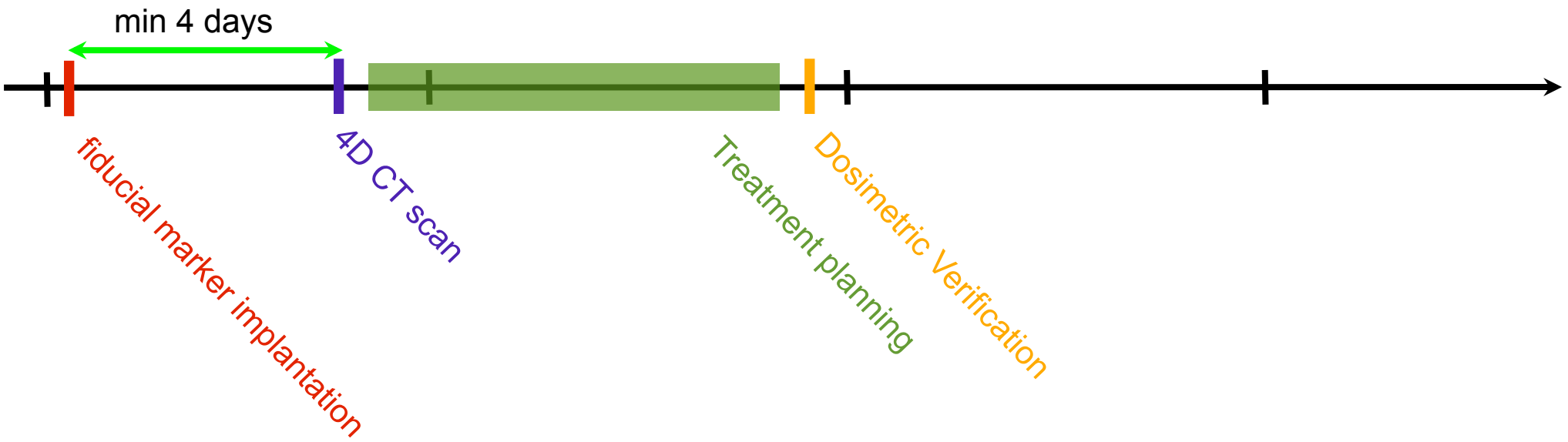
Dry run

- Dry run or simulation on the treatment machine

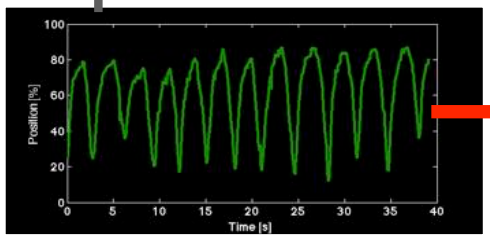


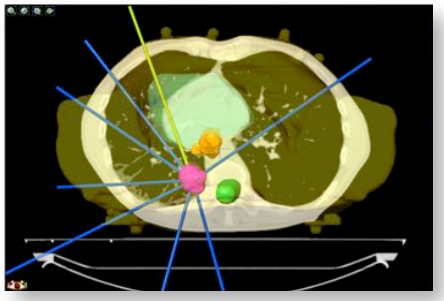
- Patient training
- Feasibility study
- Assessment of tracking error
- Acquiring patient specific respiration signal for QA

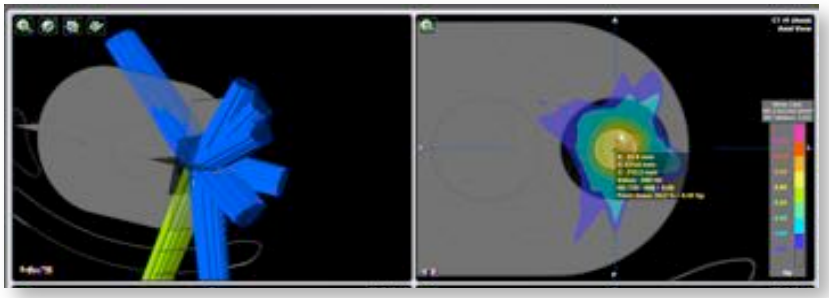
Clinical workflow

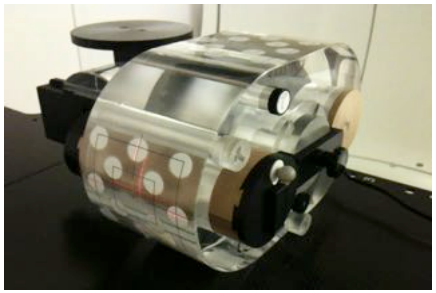


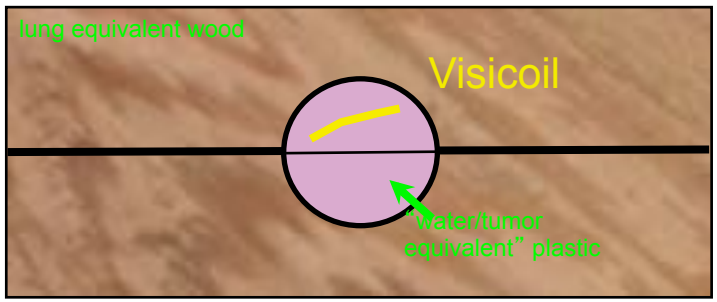
Patient specific QA



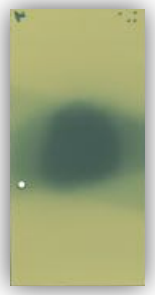


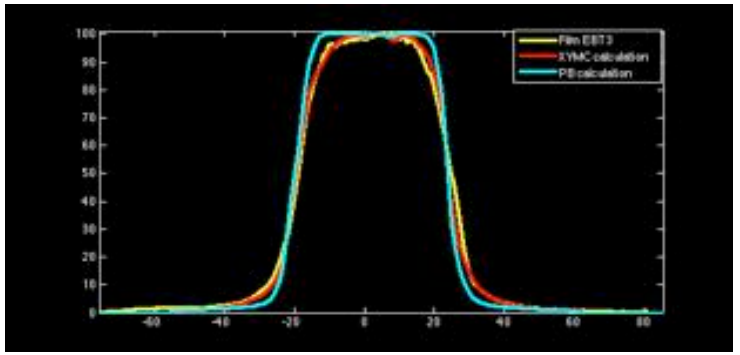


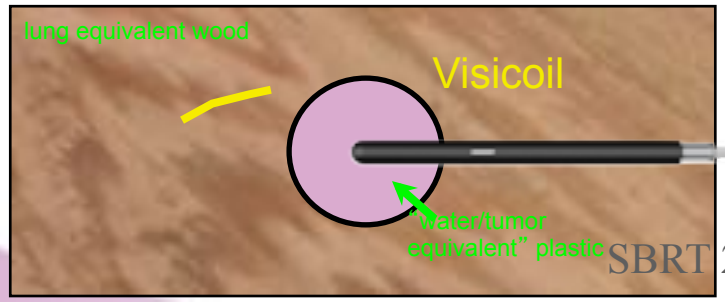




EBT3 film



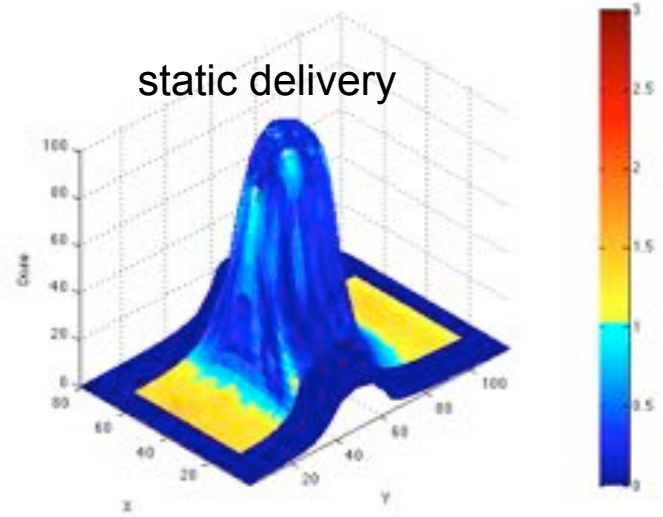




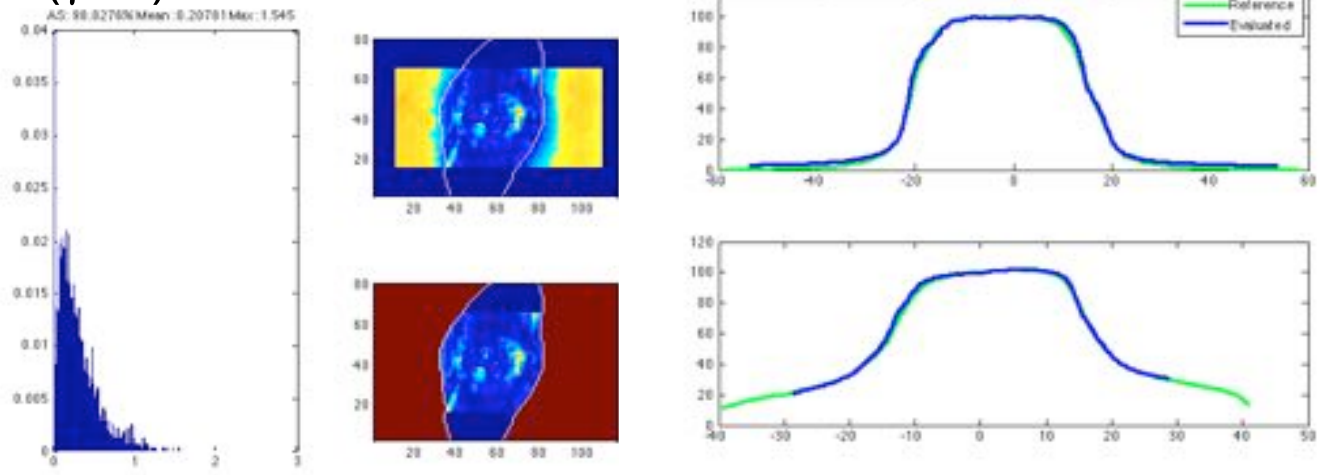
Absolute dose

Patient specific QA

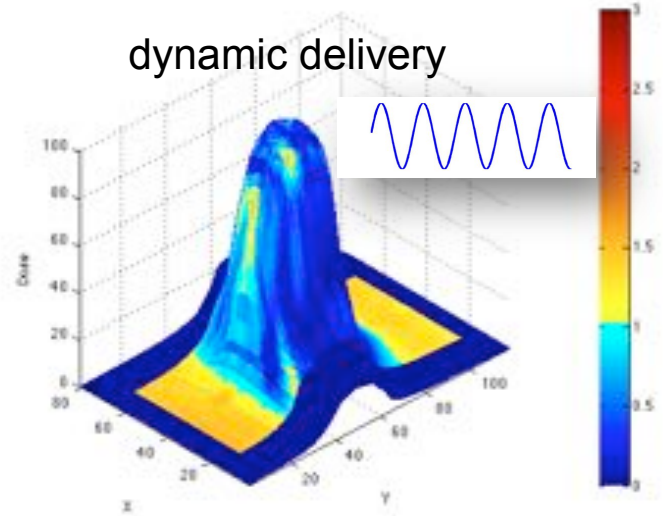
static delivery



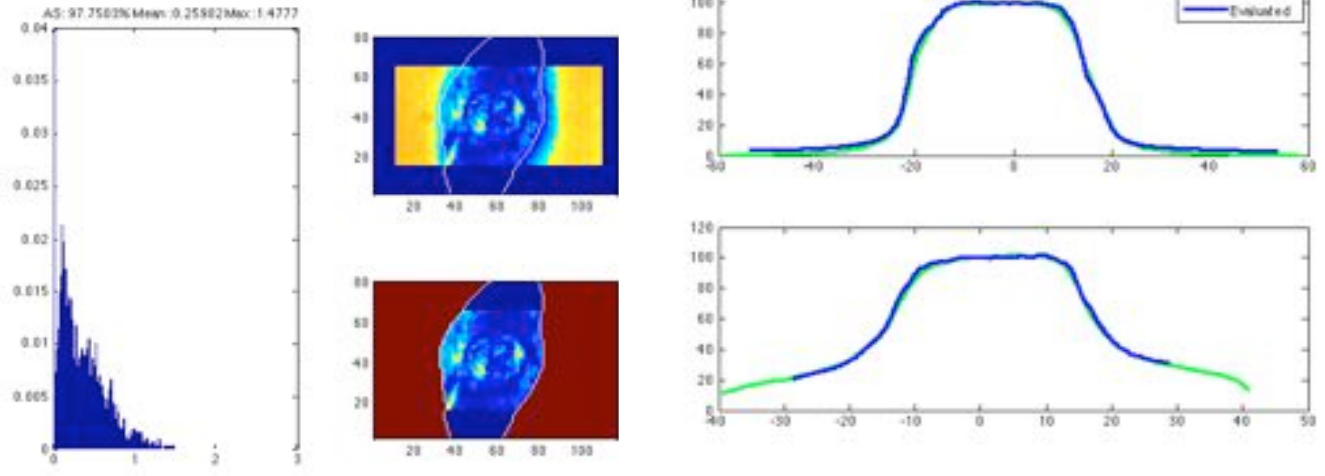
P(γ<1)=99%



dynamic delivery

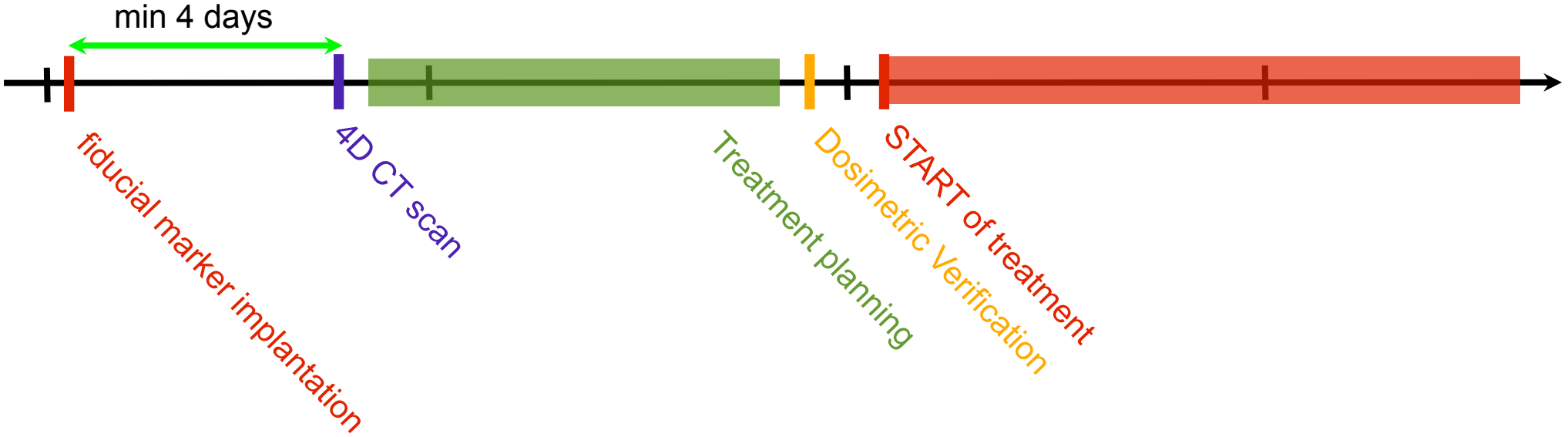


P(γ<1)=98%



gamma 2%, 2mm (normalized in iso, 2% of isocenter dose)

Clinical workflow



Primary NSCLC:
4 x 12 Gy or 3 x 17Gy

Oligometastatic disease
10 x 5Gy

Treatment

Patient Positioning

Acquiring breathing signal

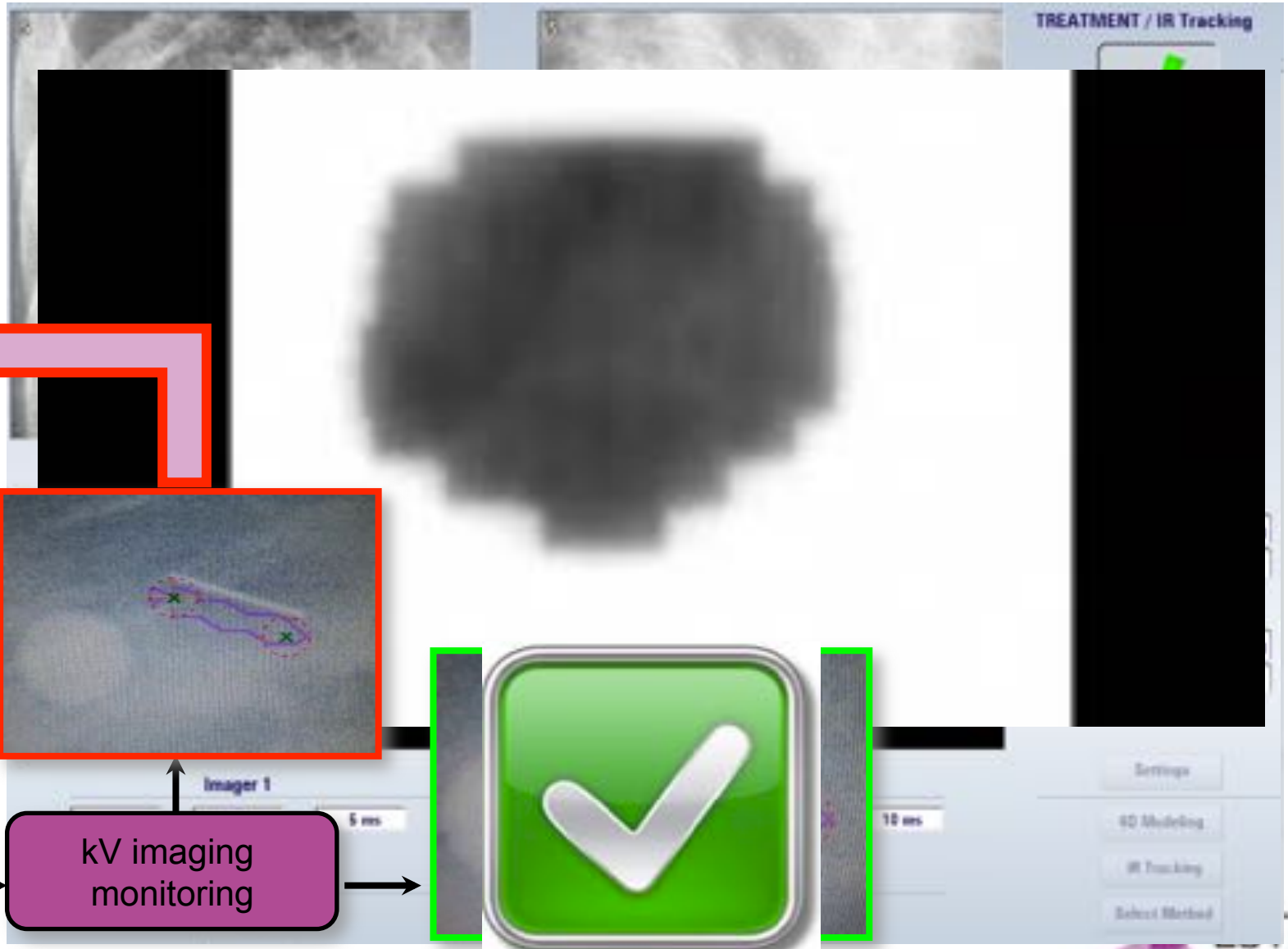
20-40 sec kV fluoro sequence + infra-red marker motion

Visicoil detection + building correlation model

kV imaging monitoring

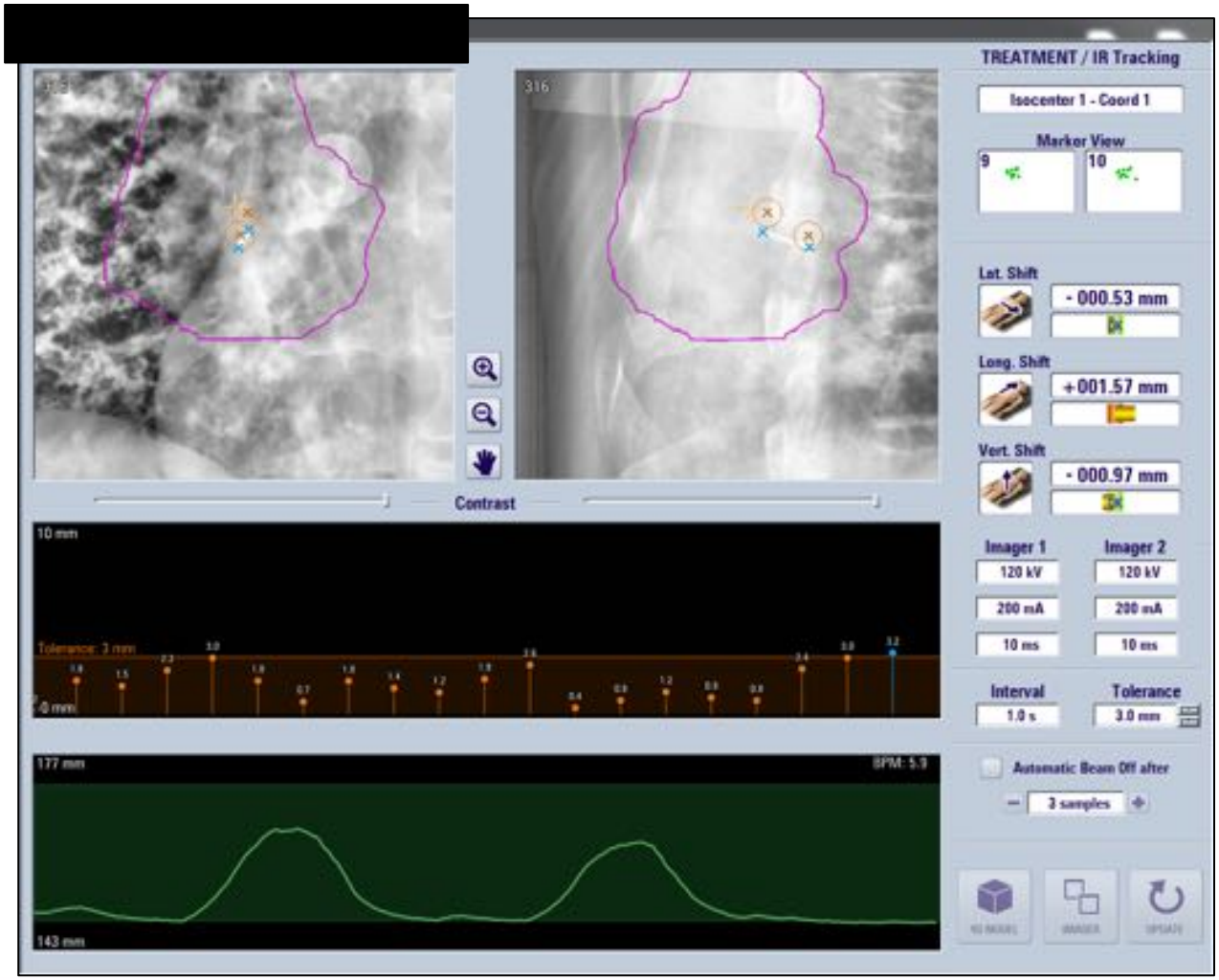
Beam on

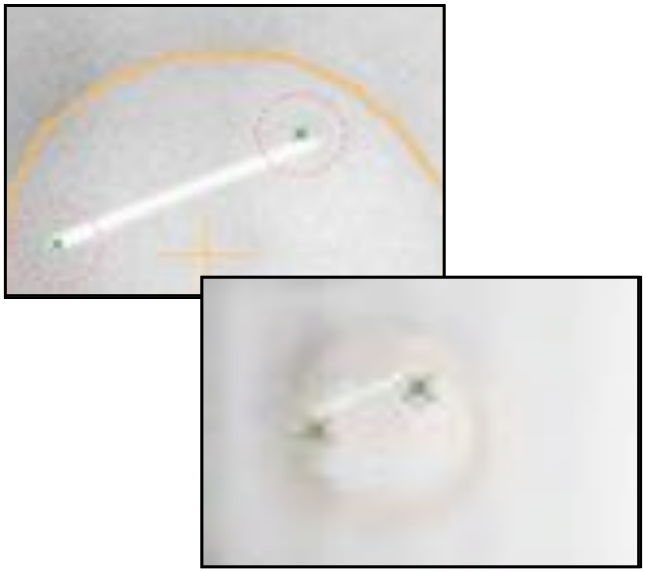
kV imaging monitoring



Treatment: verifying corr. model

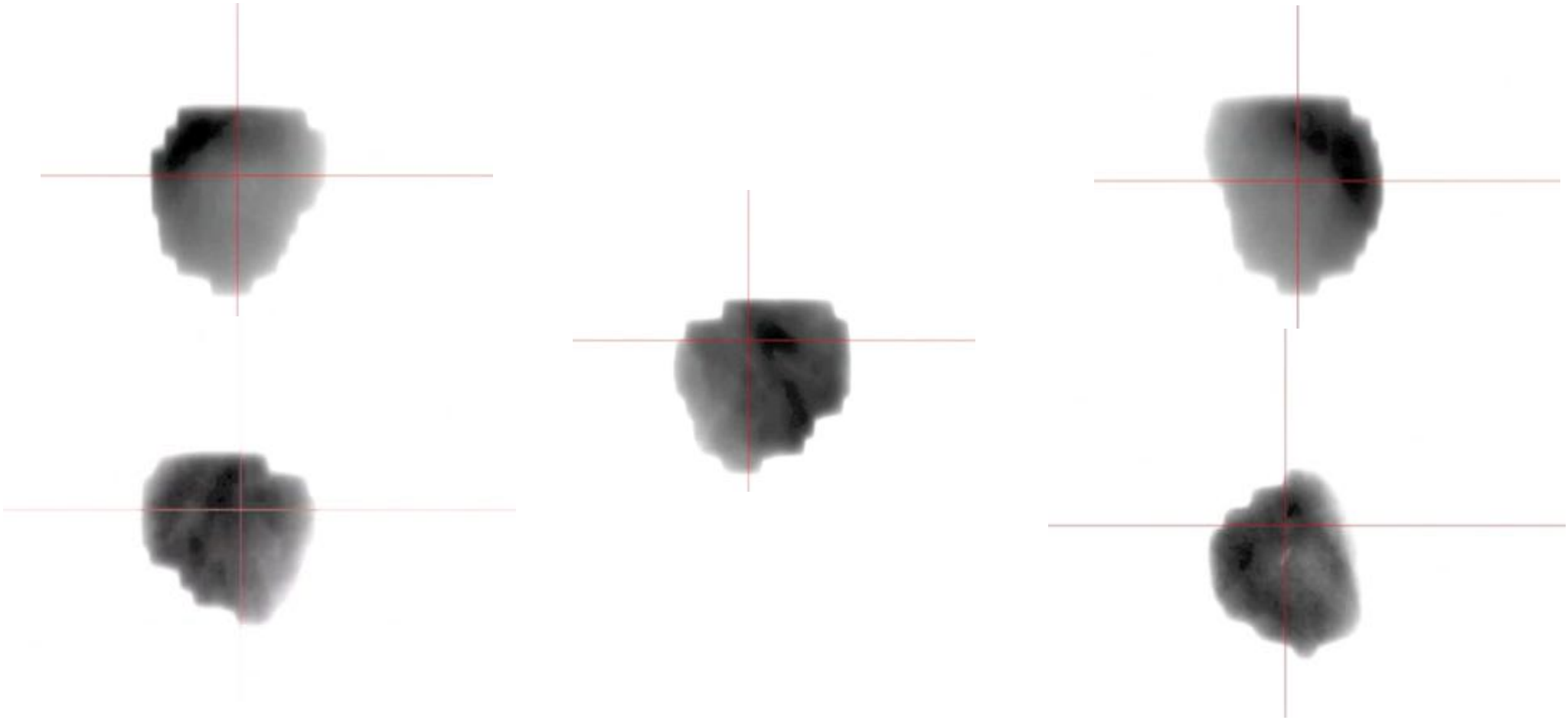
Monitoring imaging during tracking:





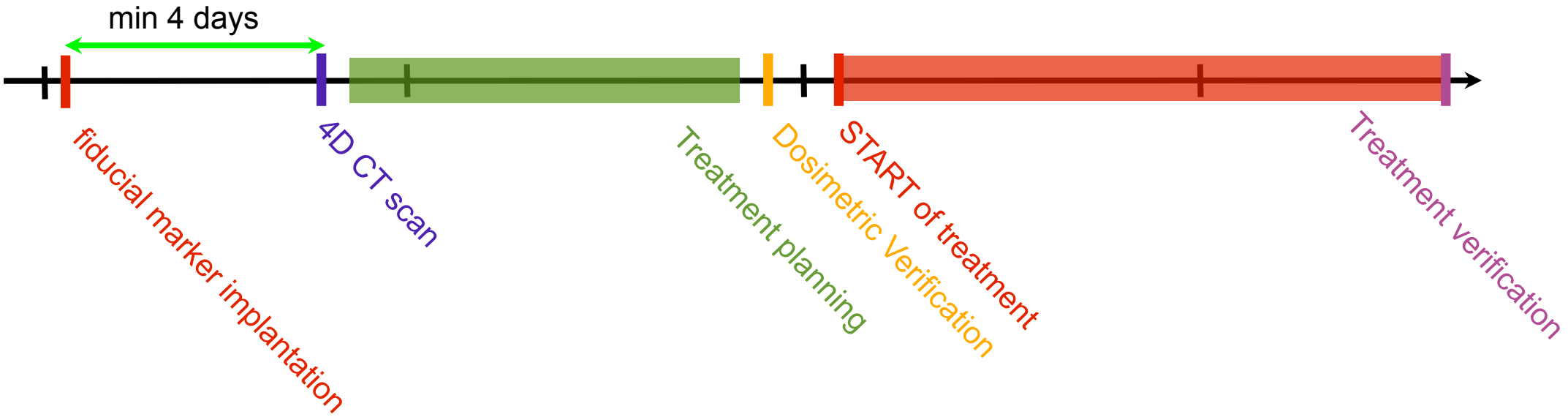
Tumour Tracking Verification (intra)

Visibility in some frames of tumour and of implanted fiducial marker



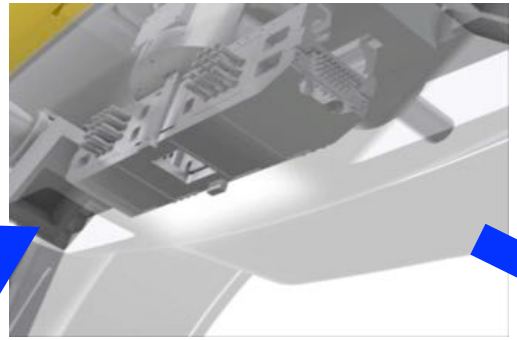
EPID: “The proof is in the pudding ...”

Clinical workflow

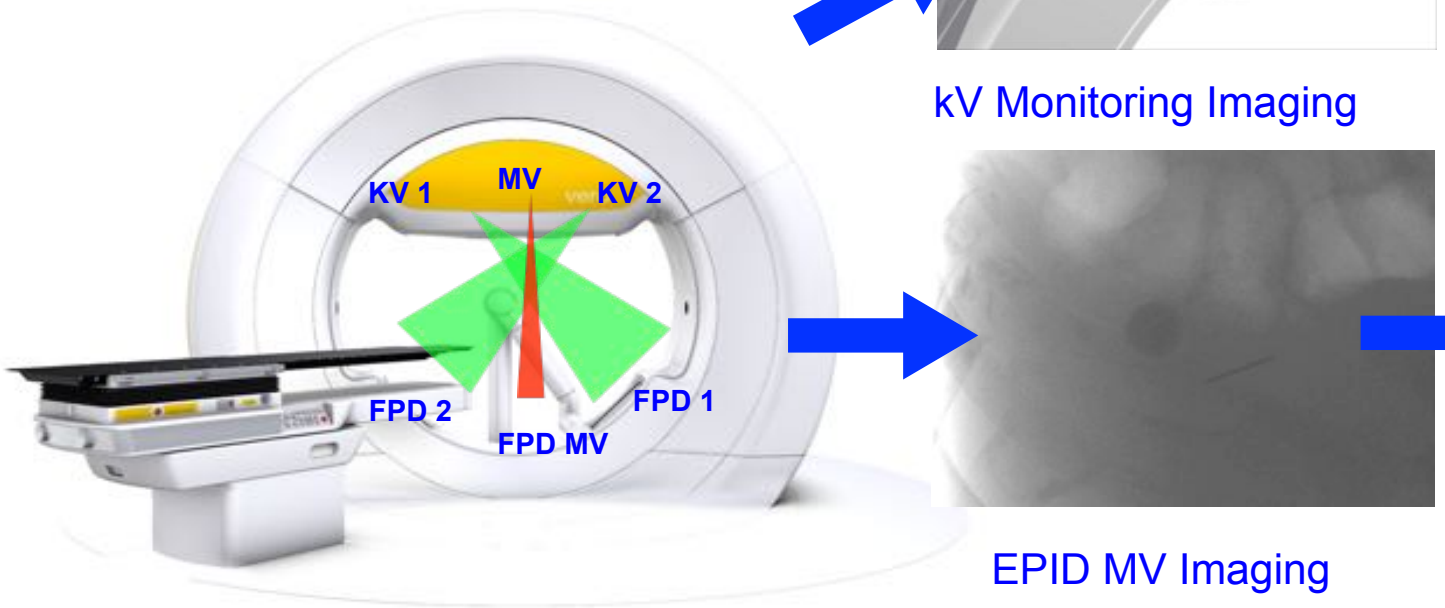


Tumour Tracking Verification (post)

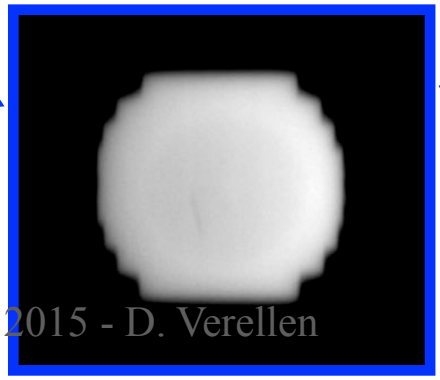
Gimbals position logging



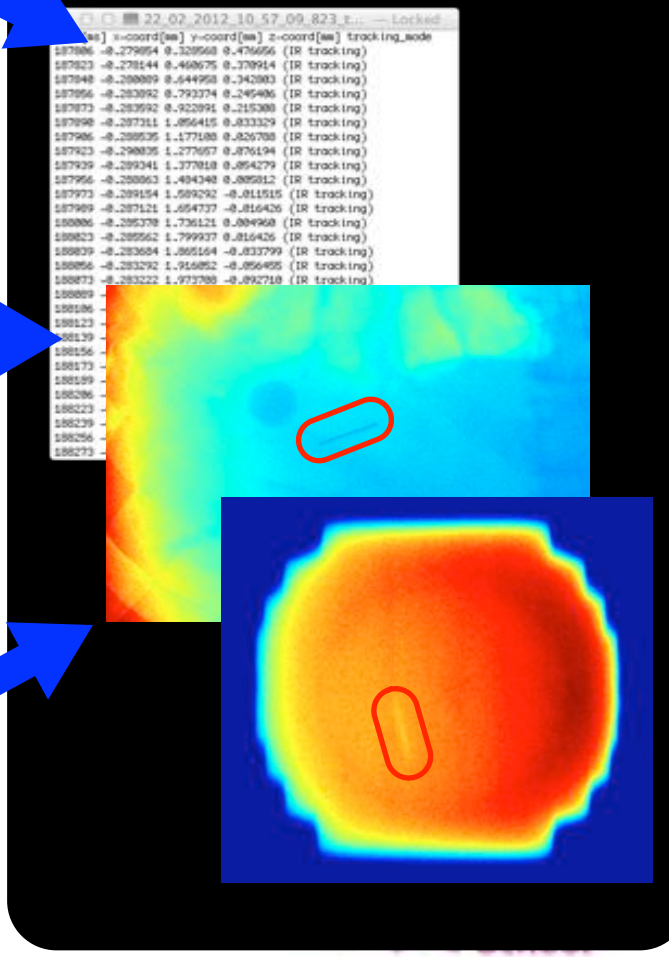
kV Monitoring Imaging



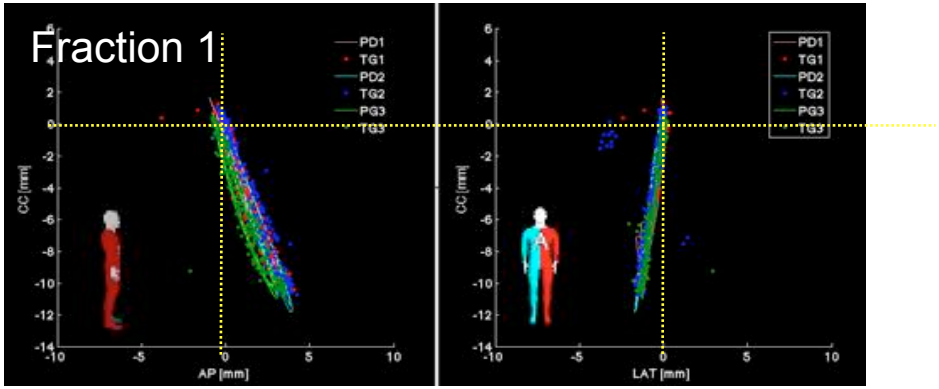
EPID MV Imaging

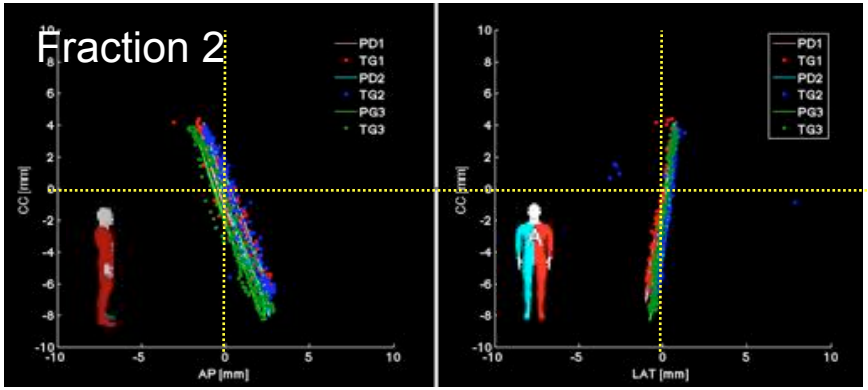


Per fraction QA through combination of different information sources



Tumour Tracking Verification (post)





Fraction 1

	1+2+3 [mm]	4+5+6 [mm]	7+8 [mm]	total (1-8) [mm]
Mean tracking error	1.43	1.84	1.50	1.58
E90% tracking error	2.62	2.60	3.32	2.82
Pan Error	0.59 +/- 0.84	0.59 +/- 0.84	0.89 +/- 2.08	0.66 +/- 1.26
Tilt Error	1.21 +/- 1.60	1.56 +/- 1.95	1.08 +/- 1.76	1.29 +/- 1.80

Fraction 2

	1+2+3 [mm]	4+5+6 [mm]	7+8 [mm]	total (1-8) [mm]
Mean tracking error	2.10 +/- 1.4 (2SD)	0.98 +/- 0.9	1.52 +/- 1.2	1.61 +/- 1.54
E90% tracking error	2.99	1.51	2.39	2.76
Pan Error	0.58 +/- 0.92 (2SD)	0.54 +/- 0.65	0.50 +/- 0.70	0.55 +/- 0.79
Tilt Error	1.95 +/- 1.48 (2SD)	0.43 +/- 1.53	1.34 +/- 1.45	1.33 +/- 1.96

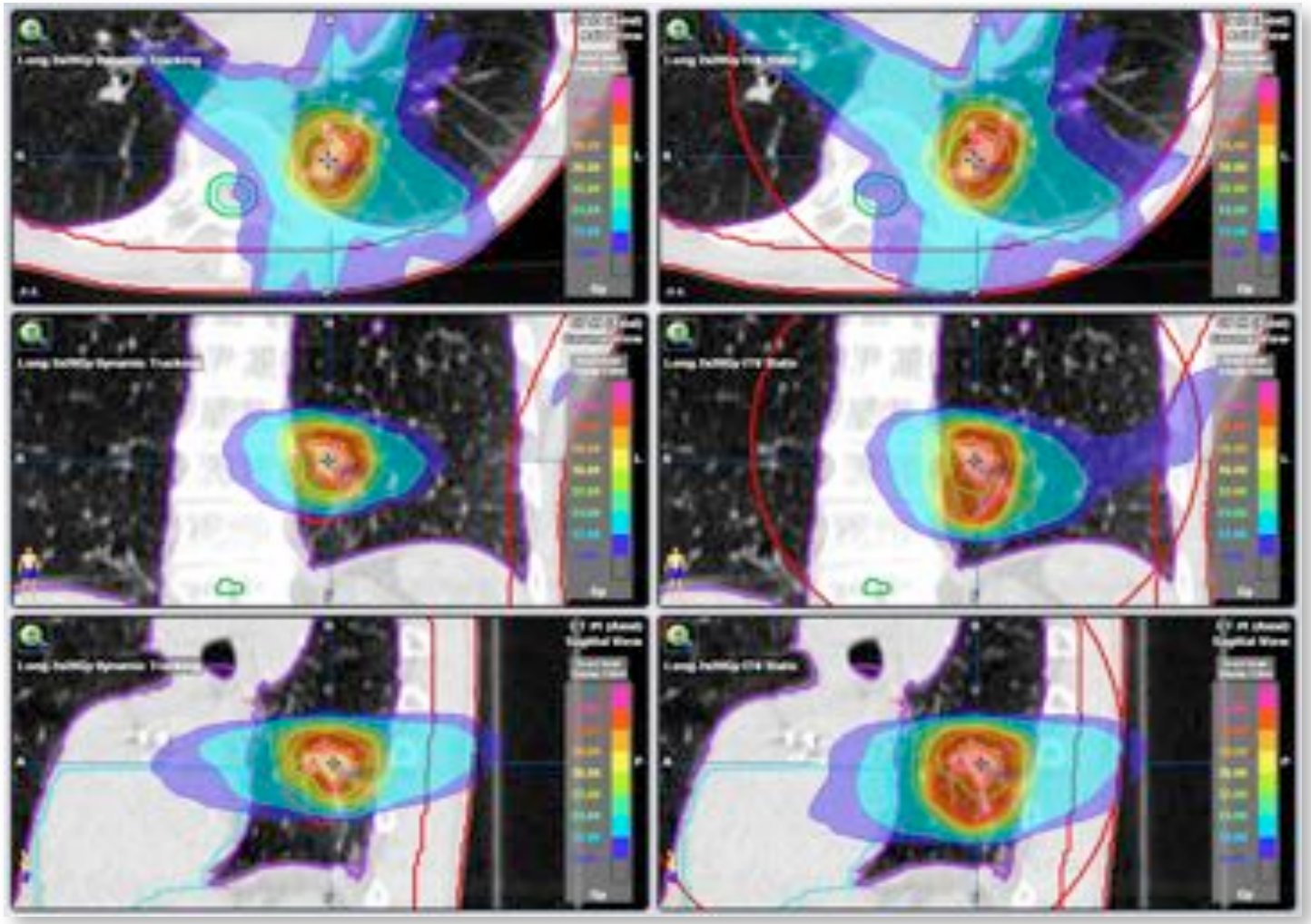
Average $E_{90\%}$= 2.63 mm, Mean Tracking error = 1.57mm

Total treatment time for a 20 Gy fraction ≈ 40 min

PTV volume reduction

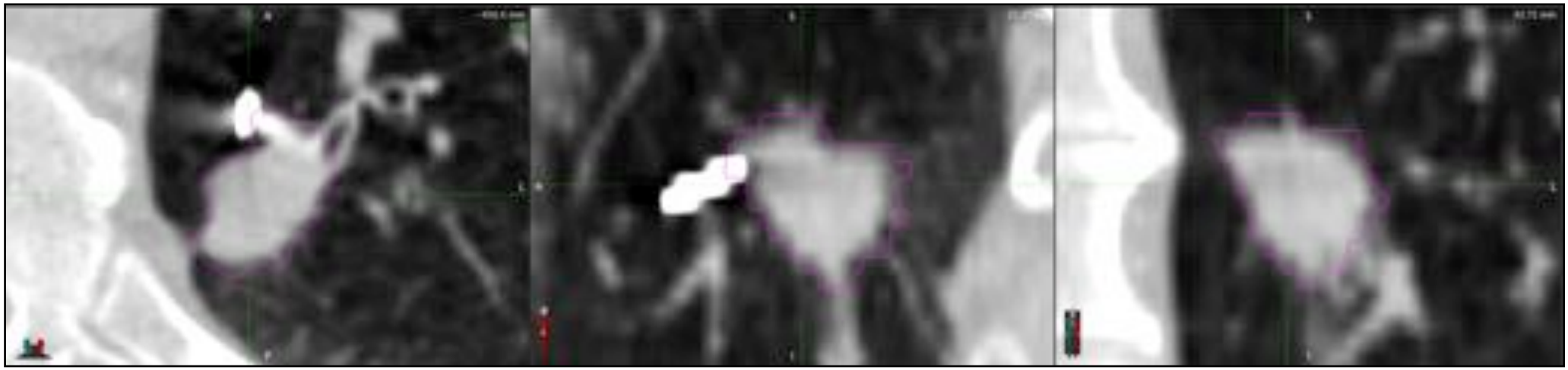
	Site	PTV volume reduction [%]
Patient 1	lung	-39,50
Patient 2	lung	-37,59
Patient 3	liver	-16,21
Patient 4	liver	-46,00
Patient 5	liver	-37,75
Patient 6	lung	-52,72
Patient 7	lung	-44,37
Patient 8	lung	-29,47
Average		**-38,0**

RTTT ITV

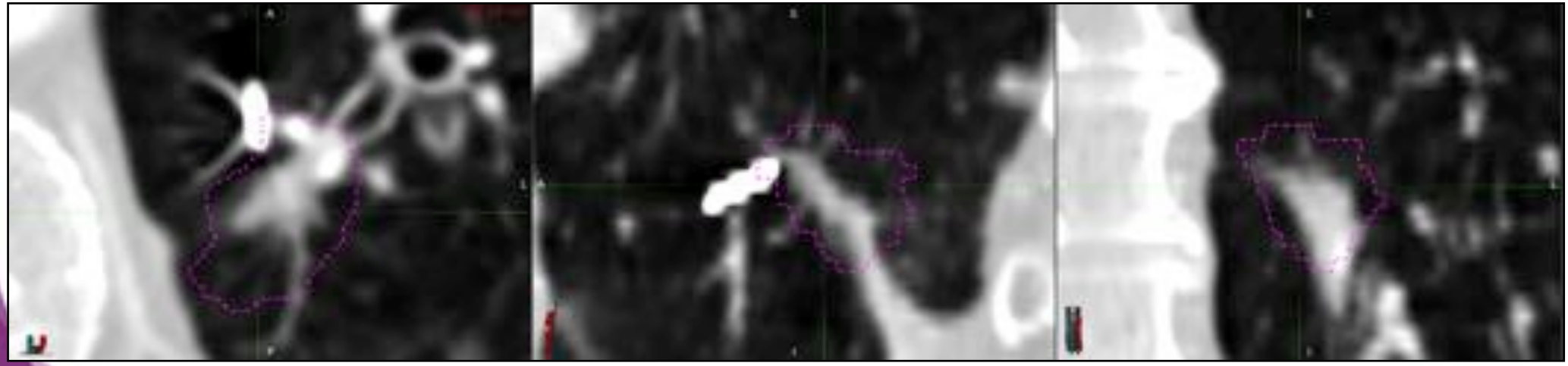


Follow-up

May 7, 2012



August 8, 2012



SBRT in the context of current developments in oncology

Suresh Senan
VU University Medical Center
Amsterdam, The Netherlands


Disclosure Statement

- The Department of Radiation Oncology at VUMC has a research agreement with Varian Medical Systems.
- Speakers honoraria from Varian Medical Systems.

Teaching goals

Understand comparative effectiveness research (CER), and how it led to SBRT becoming a guideline-recommended standard of care.

Know why aging populations and comorbidity are both likely to lead to SBRT being used in operable patients with Stage I NSCLC.

Understand why advances in systemic therapy will lead to increasing clinical demands for SBRT in metastatic disease.

Be aware of the focus on '**value**' in healthcare, and the role of patient reported outcomes, in determining reimbursements.

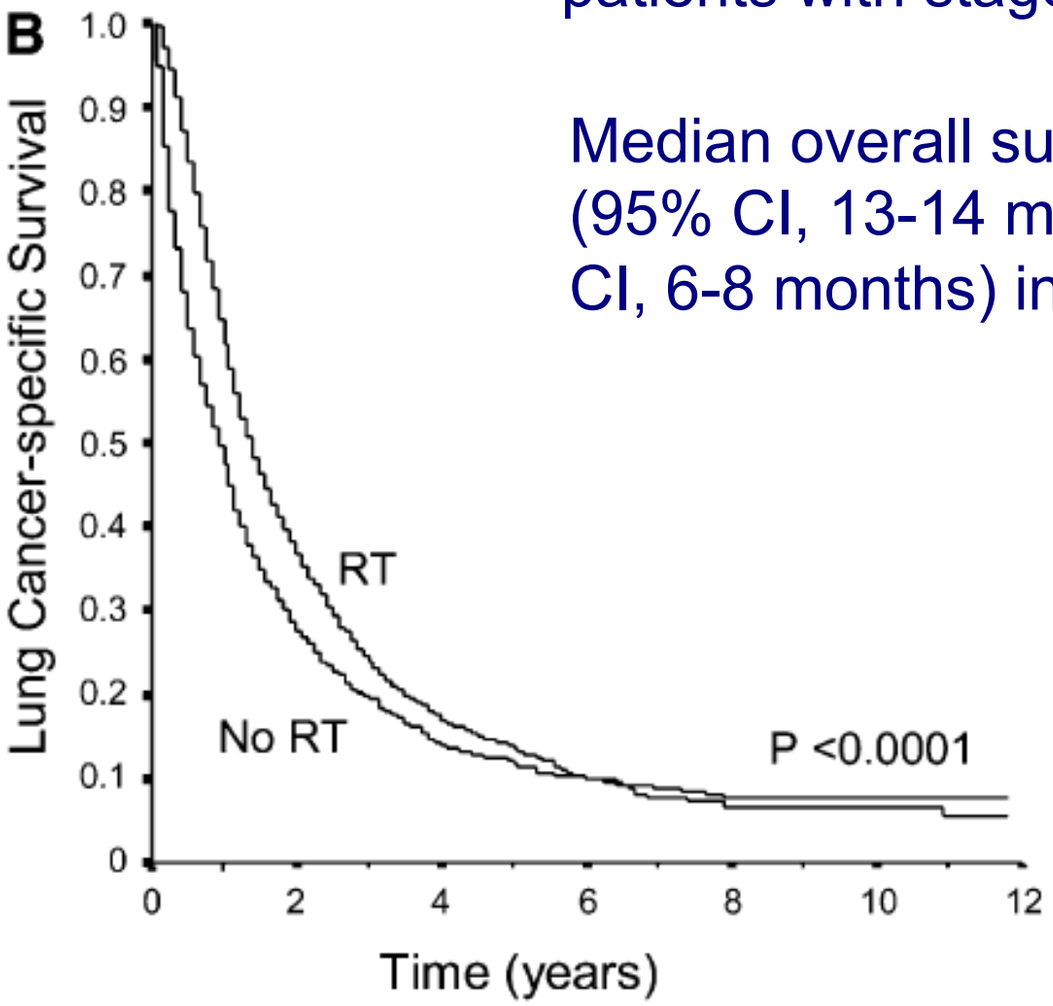
Stage I NSCLC:

Why conventional radiotherapy failed to impress

Conventional radiotherapy

SEER database (1992-2002): 6065 unresected patients with stage I-II NSCLC

Median overall survival post-RT was 13 months (95% CI, 13-14 months) versus 7 months (95% CI, 6-8 months) in untreated pts



Wisnivesky JP, 2010

Few referrals for conventional RT

- Single Dutch institution
- **113 patients** for curative 3D CRT (1991 - 1999)
- T1N0M0 = 58%; T2N0M0 = 42%
- Local progression as a cause of death in **30%**
- Median actuarial cause-specific survival (CSS) was 19 months; 1- and 3-year CSS rates were 72 and 30% (*pre-FDG PET era*)

Lagerwaard FJ, Radioth Oncol 2001

Hypofractionated, Conventional delivery

- Phase NCIC CTG BR.25 II study
- 80 biopsy-proven, peripherally located, T1-3 N0 M0 NSCLC
- (2006 to 2008, 17 Canadian institutions)
- 60 Gy in 15 fractions, using 3DCRT. No inhomogeneity correction or IMRT use, with fluoroscopy for motion evaluation
- GTV= primary tumor only; PTV margin = 1.0 to 1.5 cm.
- Primary endpoint: 2-year primary tumor control rate.

Cheung PC, JNCI 2014

Hypofractionated, Conventional delivery

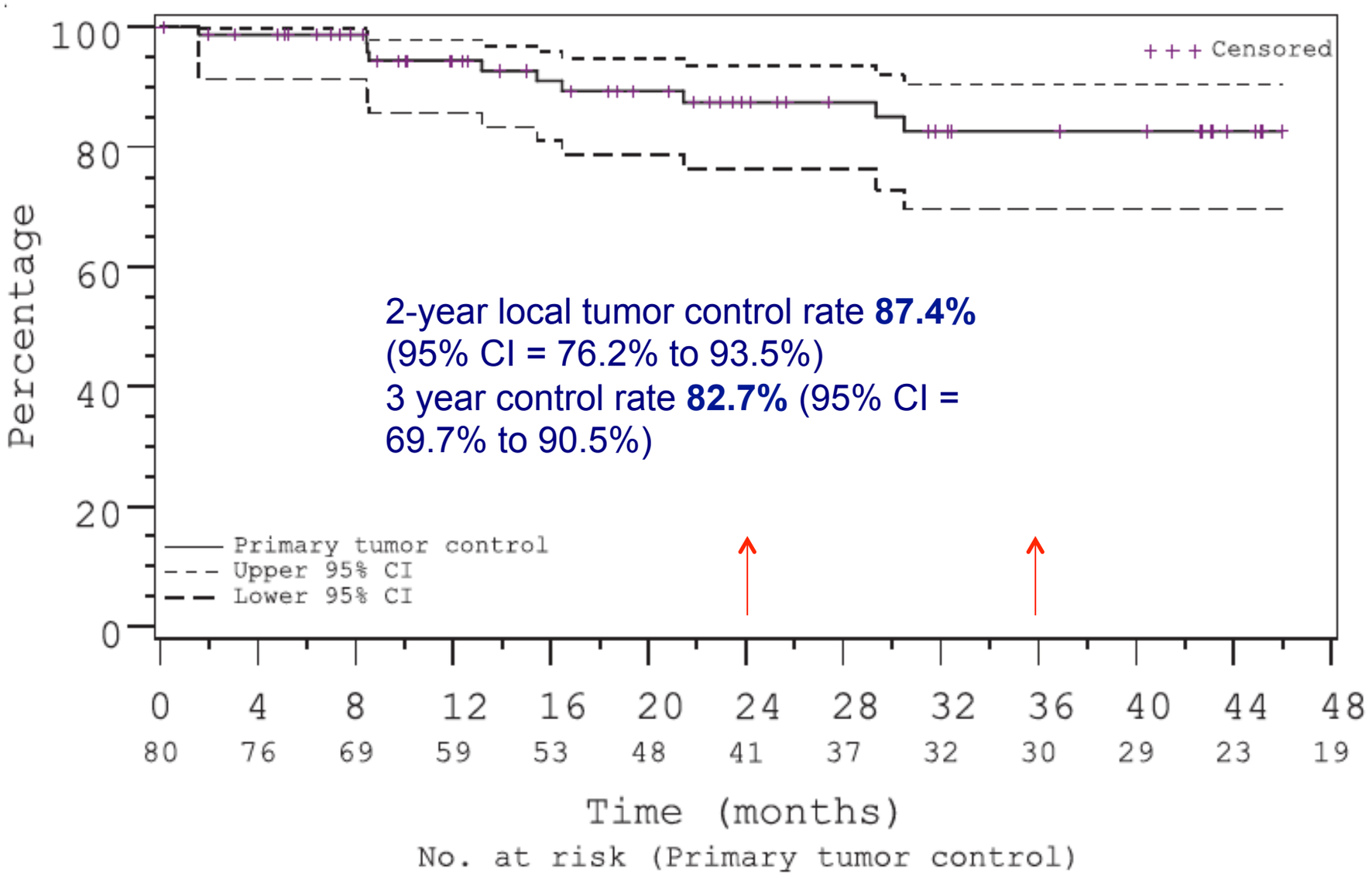
Phase NCIC CTG BR.25 II study

Commonest grade 3+ toxicities

- dyspnea 13.8%
- pneumonitis **10%**
- fatigue 6.5%
- cough **7.5%**
- Grade 5 hemoptysis in 1 patient

Cheung PC, JNCI 2014

Hypofractionated, Conventional delivery



Cheung PC, JNCI 2014

SABR: Guidelines & evidence

SABR is the preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.

[ESMO Clinical Practice Guidelines [Vansteenkiste J, Ann Oncol 2013; Guidelines of National Comprehensive Cancer Network [NCCN v3.2014]

Comparative effectiveness research suggests that survival is similar after either surgery or SABR for early-stage NSCLC

[reviewed in Louie AV, Radiotherapy Oncol 2015]

Hierarchy of research design

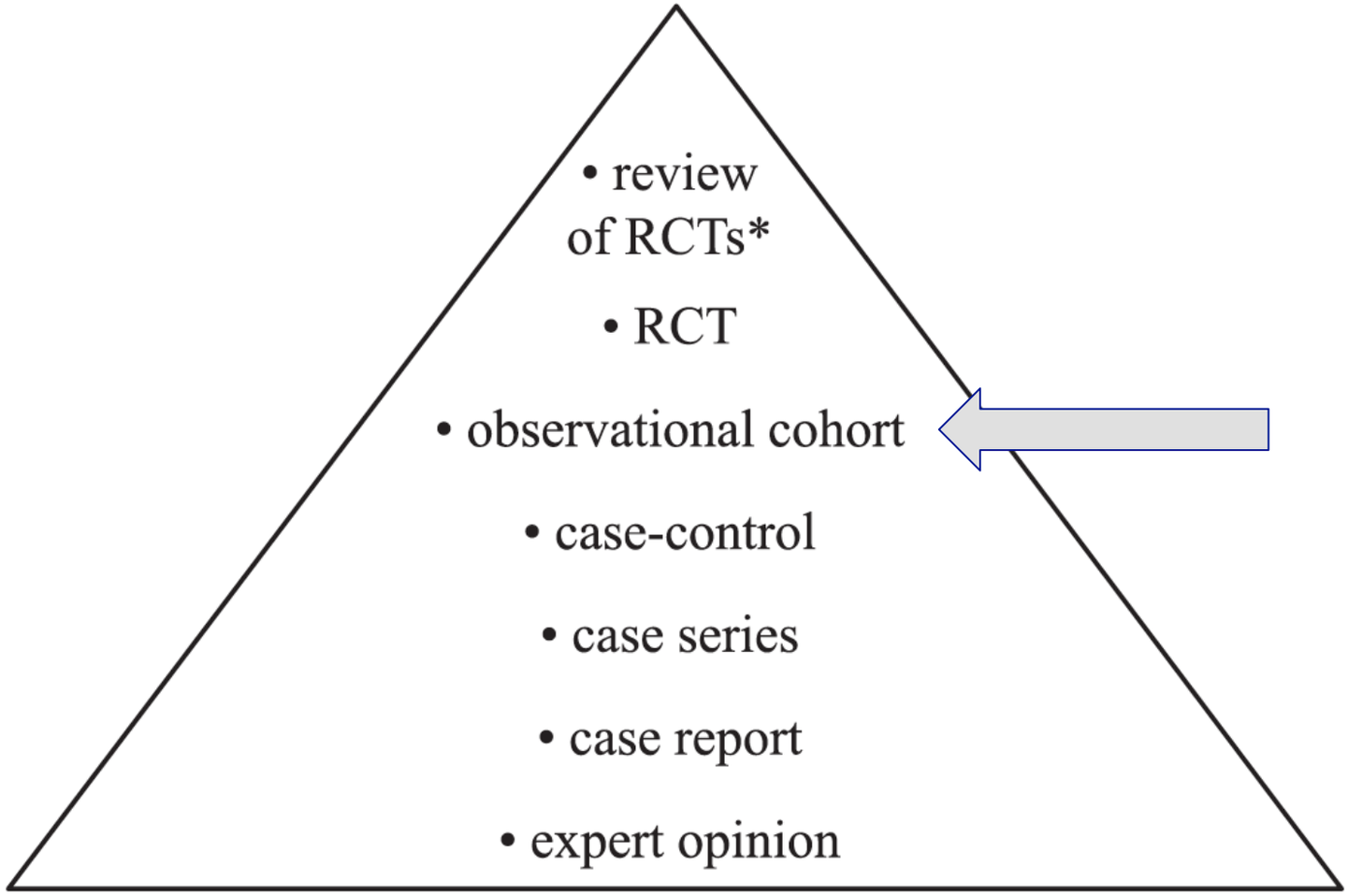


Figure 1. Example of hierarchy of research design as per evidence-based medicine; *review of randomized controlled trials includes systematic reviews with or without meta-analysis. RCT = randomized controlled trial.

Concato J, AJRCCM 2013

Prospective RCT's of SABR vs conventional RT

	SPACE NCT01920789	CHISEL NCT01014130
Study arms	SABR: 66 Gy in 3 frac (isocenter) CFRT: 66 Gy (2Gy frac)	54 Gy in 3 frac CFRT: 60-66Gy (2Gy frac)
Primary End-point	Freedom from tumor progression at 36 mo.	Time to Local Failure at 24 mo
Secondary end-points	OS at 36 mo. Toxicity, QoL	OS, CSS, Toxicity QoL
Total enrolled	102 pts (completed)	100 pts (ongoing)

Is conventional radiotherapy inferior?

Randomised SPACE trial of conventional radiotherapy (CFRT) vs SABR (NCT019207)

Study arms	**SABR: 66 Gy in 3 fractions** (to isocenter) **CFRT: 70 Gy in 35 fractions**
Primary End-point	Freedom from tumor progression at 36 months
Secondary end-points	OS at 36 months Toxicity, QoL
Total enrolled	102 patients (completed)

Similar local failure rates (11% SABR vs 13% CFRT), regional recurrences (7% vs 8%, distant metastases (24% vs 23%)

Fewer cases of pneumonitis (16 vs 34%) and esophagitis (9 vs 32%) seen in SABR arm. Any G3-5 toxicity seen in 16 versus 18%

Nyman J, ESTRO 2014

Comparative effectiveness research

- CER is the generation of evidence comparing **benefits and harms** of interventions for a clinical condition [Sox HC, Ann Int Med 2009].

- CER assists in making informed decisions to improve outcomes at the individual and population levels.

- **Observational studies** offer insights to specific challenges in oncology such as **rising costs** and **rapidly evolving technology**

Louie AV, Radioth Oncol 2015

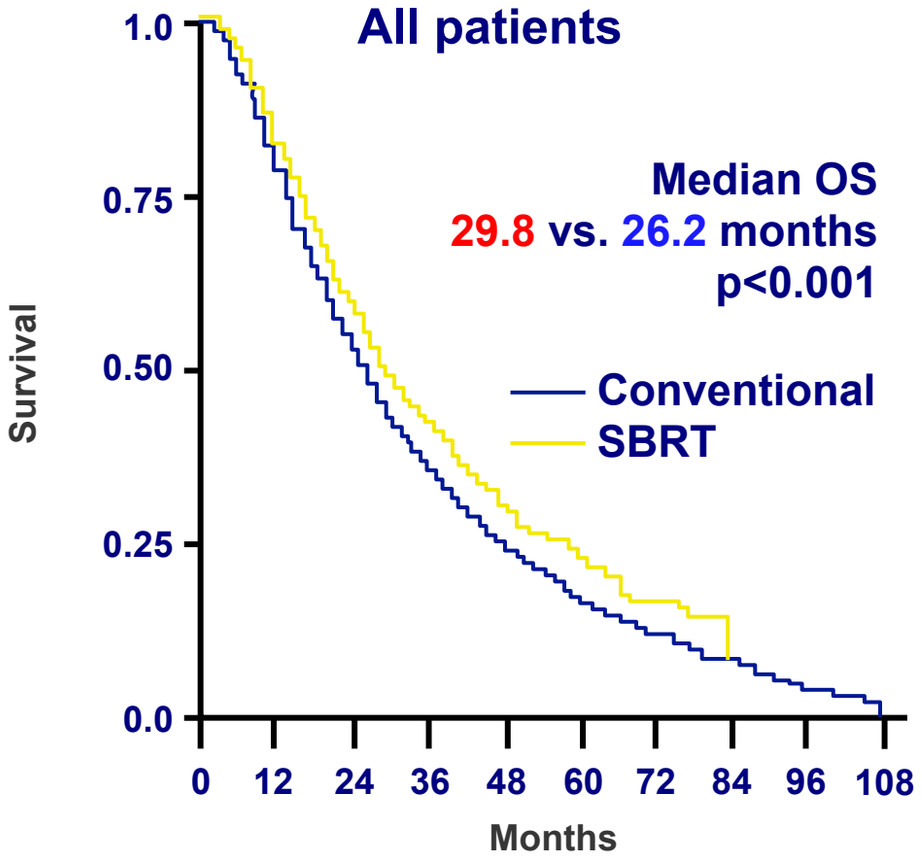
CER of conventional radiotherapy vs SABR

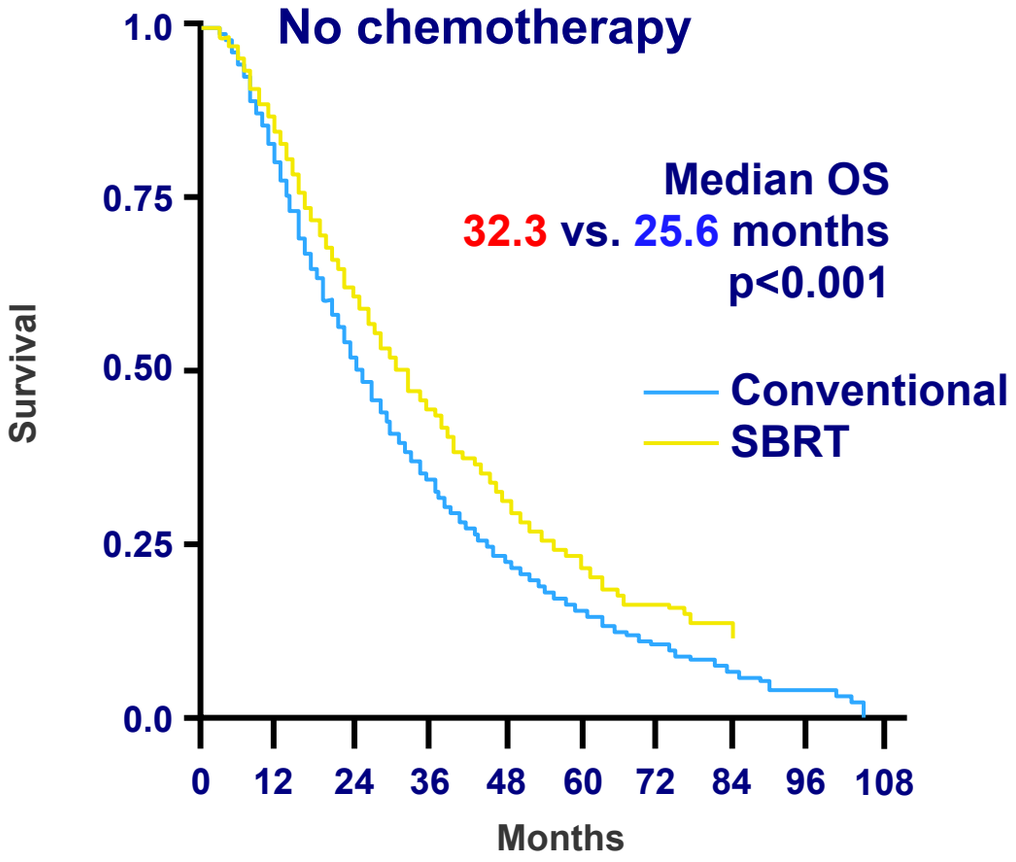
- US National Cancer Database
- Propensity-matched analysis of **1502 patients**, 50% of whom received SBRT and others conventional radiotherapy
- **3-year overall survival** in matched cohort was **40% versus 48%** for conventional radiotherapy vs SABR (p = 0.001)
- Hazard ratio for SABR from a univariate Cox regression was **0.82** (95% CI: **0.73–0.92**, p = 0.001)

Koshy M, Radioth Oncol 2015

National Cancer Database (1998-2010)

Stage I NSCLC (5,944 SBRT, 13,429 CFRT)





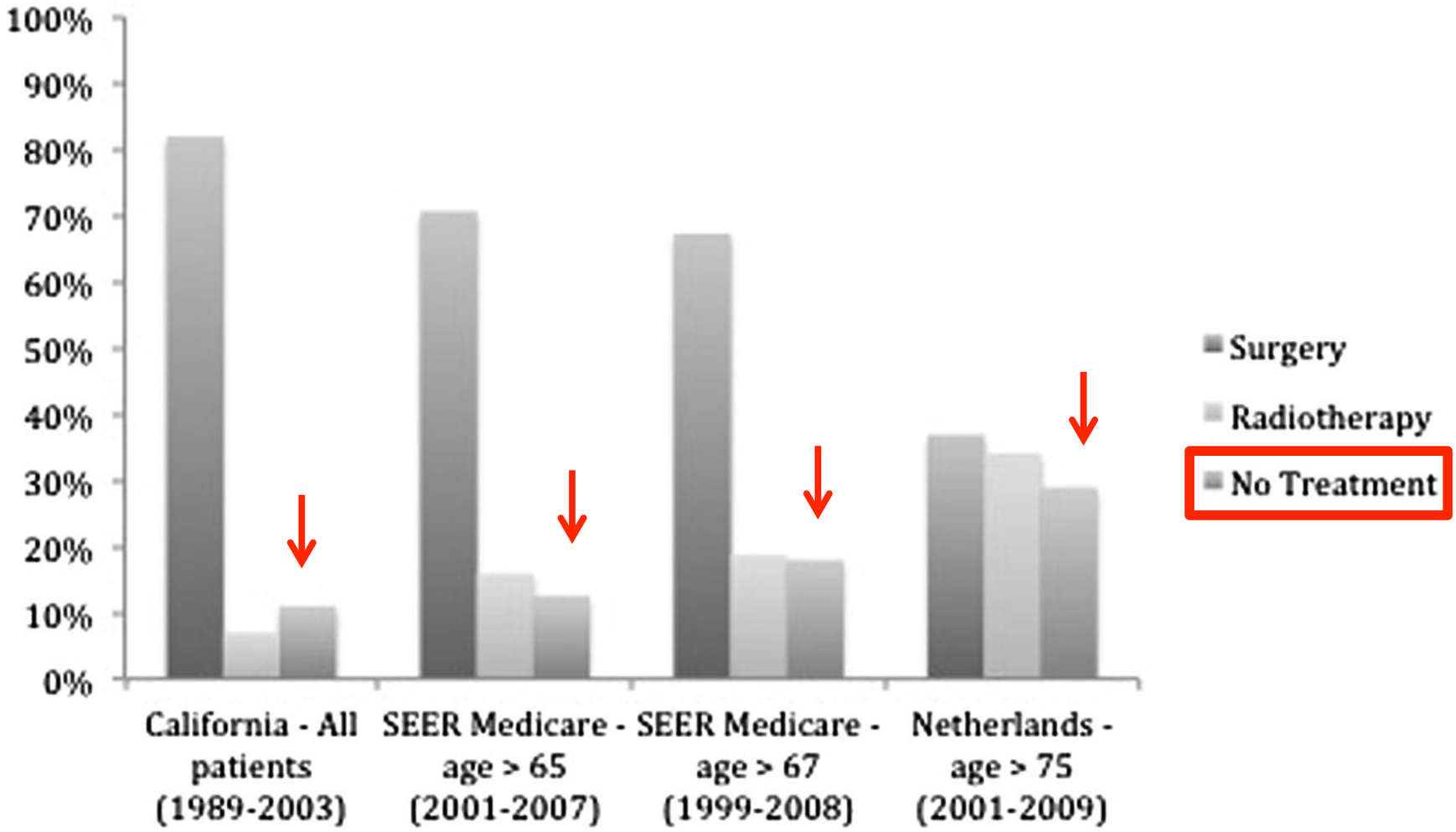
SBRT improved OS compared with CFRT regardless of chemotherapy use in this population-based analysis of clinical stage I NSCLC

Robinson C. proc ASCO 2015 abstr 7513

Stage I NSCLC:

Will conventional radiotherapy make a comeback?

Population trends in treatment utilization

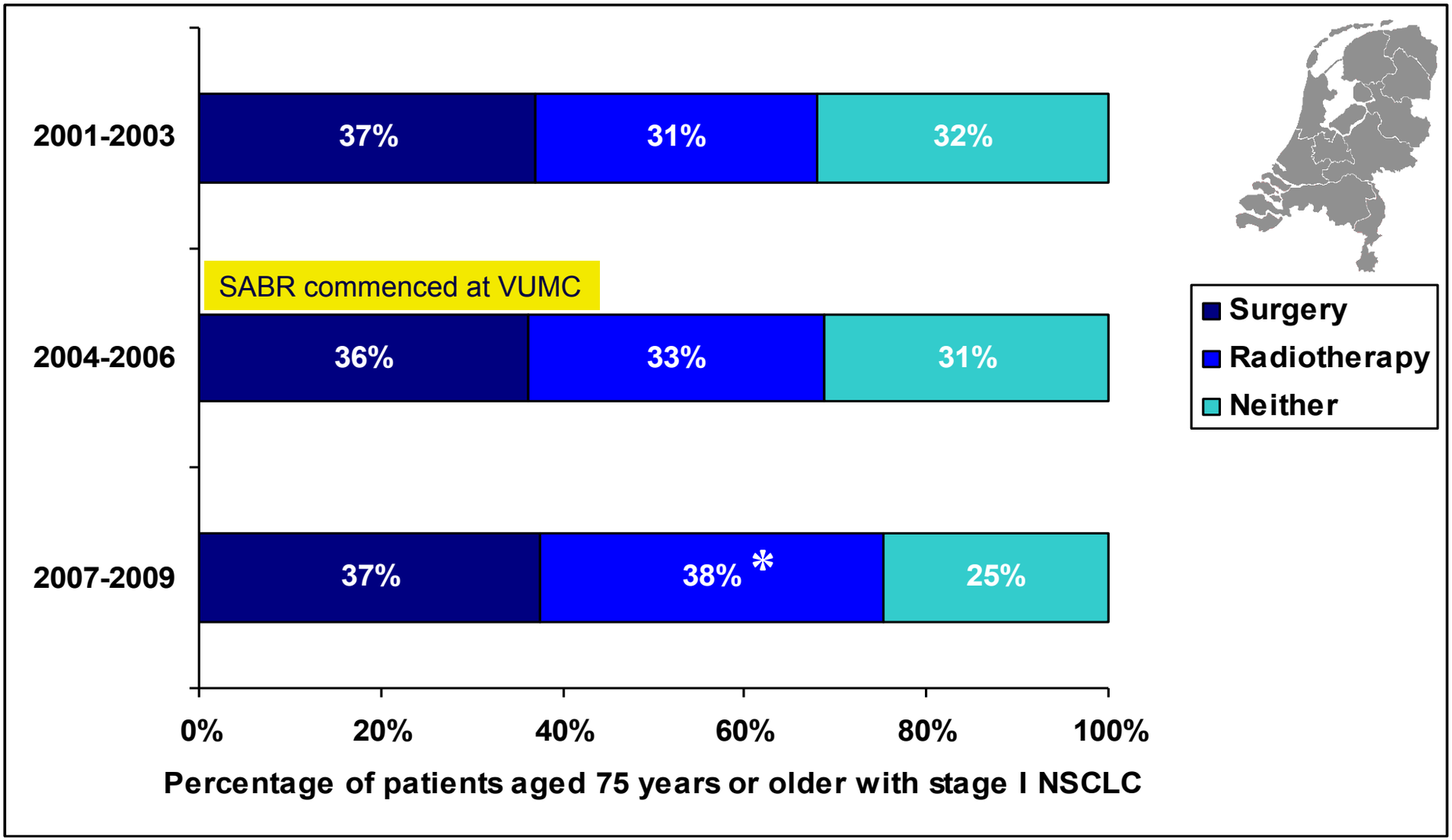


Increased proportion of untreated patients with increasing age. Median overall survival of untreated patients ranged from 6.6 – 12 months

Louie AV, Radioth Oncol 2015

Dutch population study (2001-2009)

4605 stage I NSCLC patients aged ≥75 years

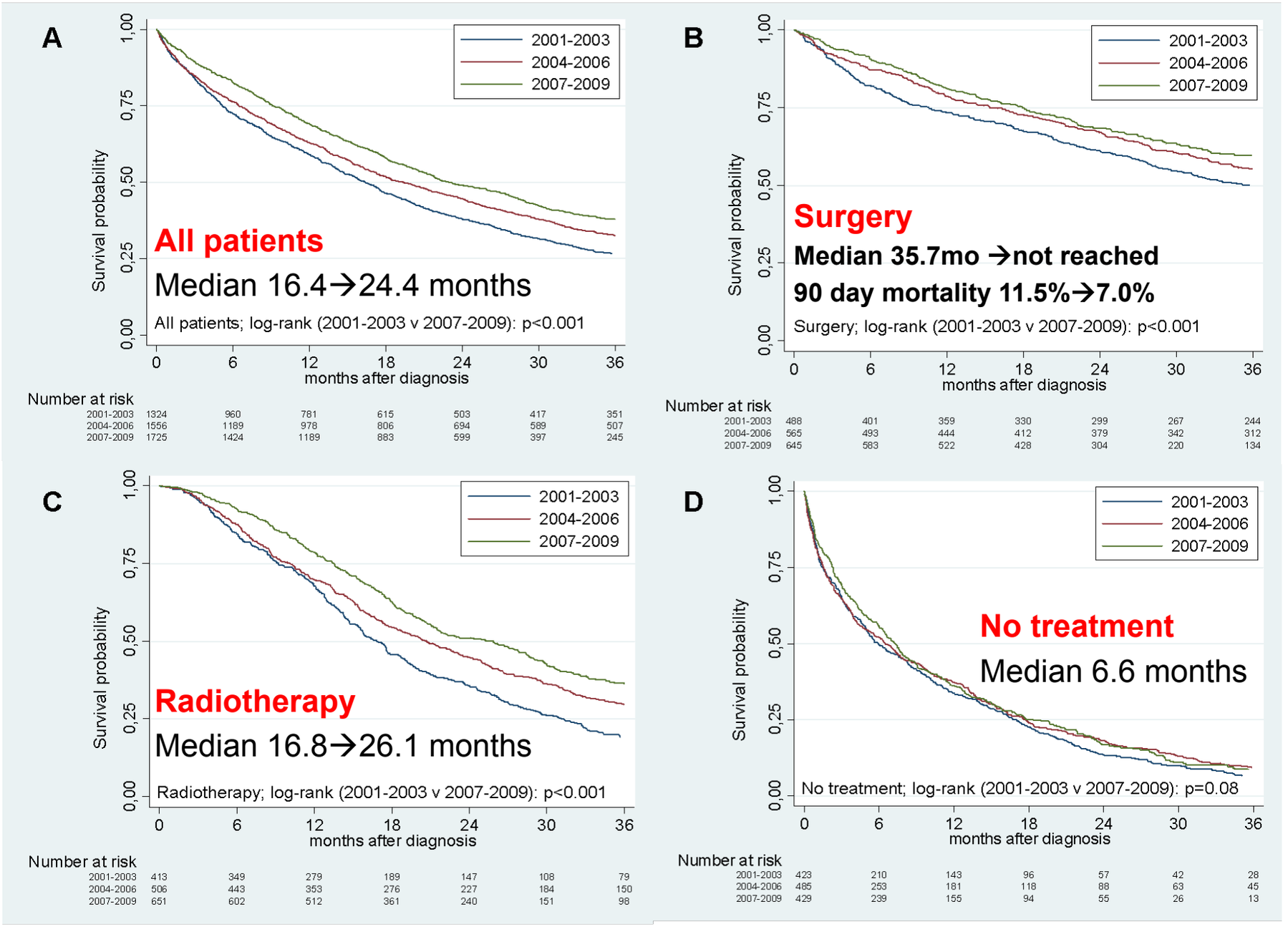


* estimated utilization of SABR in radiotherapy group was >75%,

Haasbeek C, Ann Oncol 2012

Dutch population study (2001-2009)

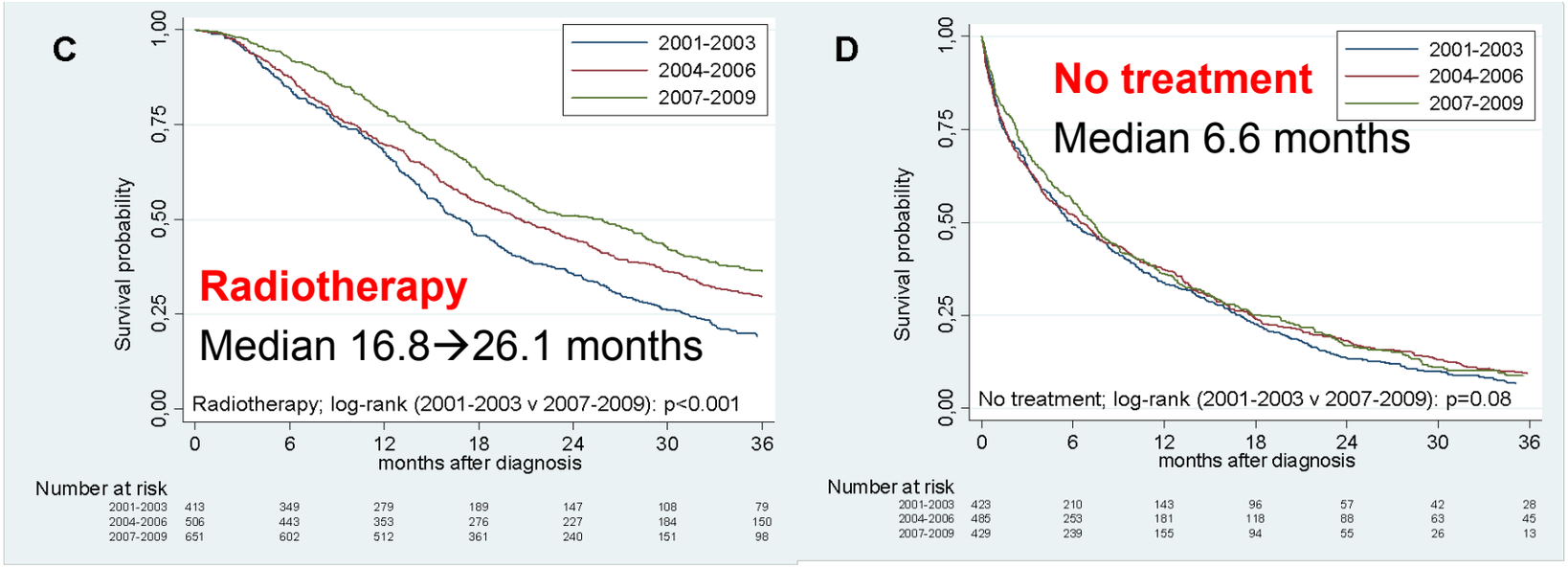
Survival in 4605 patients aged ≥75 years



Haasbeek C, Ann Oncol 2012

Dutch population data ('involuntary data')

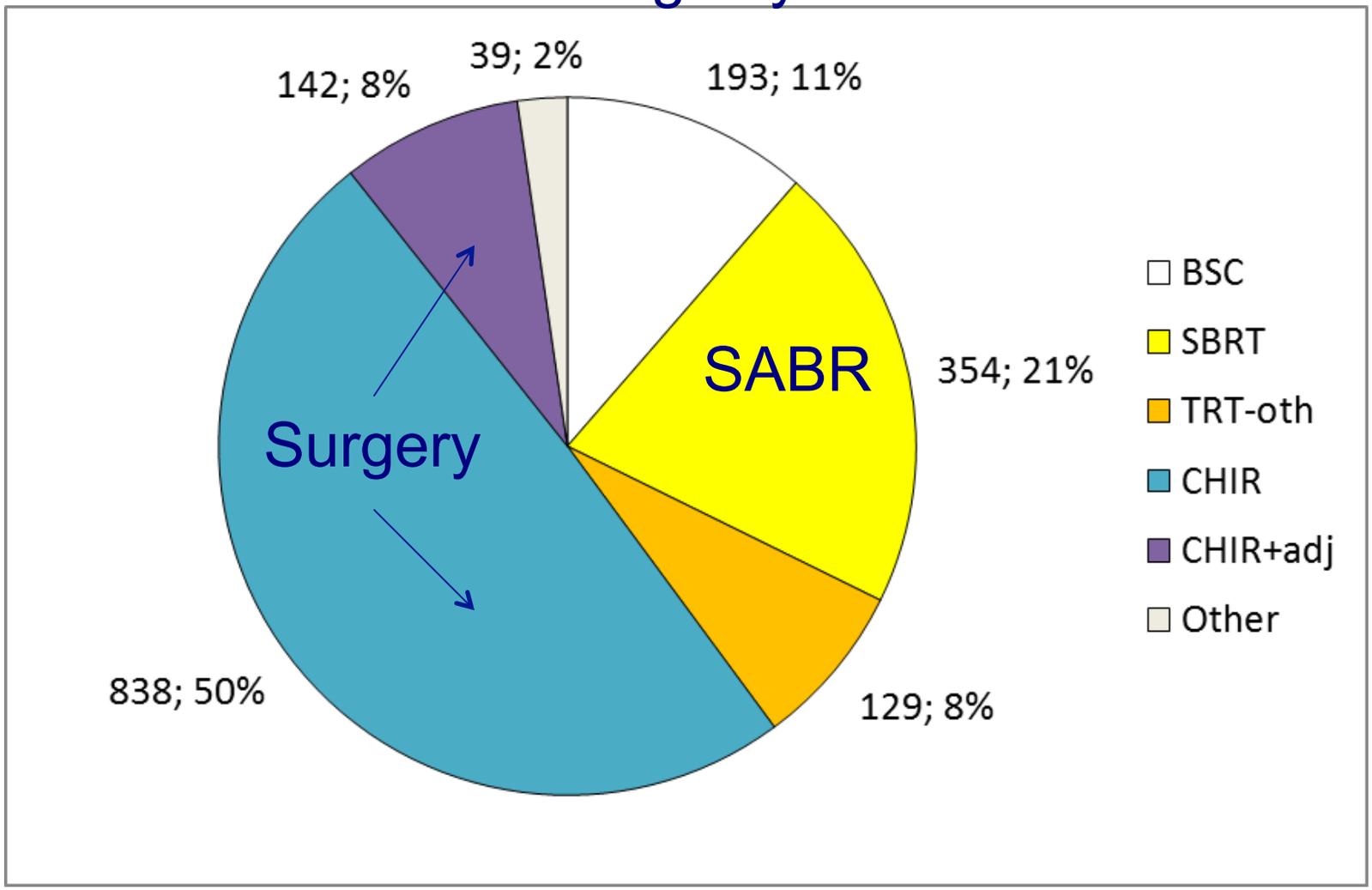
Haasbeek C,2012



- SABR can be rapidly implemented at a national level
- Survival gains of 9.3 months attained in the unfit elderly
- No significant decline in quality of life after lung SABR (*Systematic review, Chen H submitted*)

Dutch stage I NSCLC data (2012)

Netherlands Cancer Registry



(courtesy of Dr R Damhuis, IKNL)

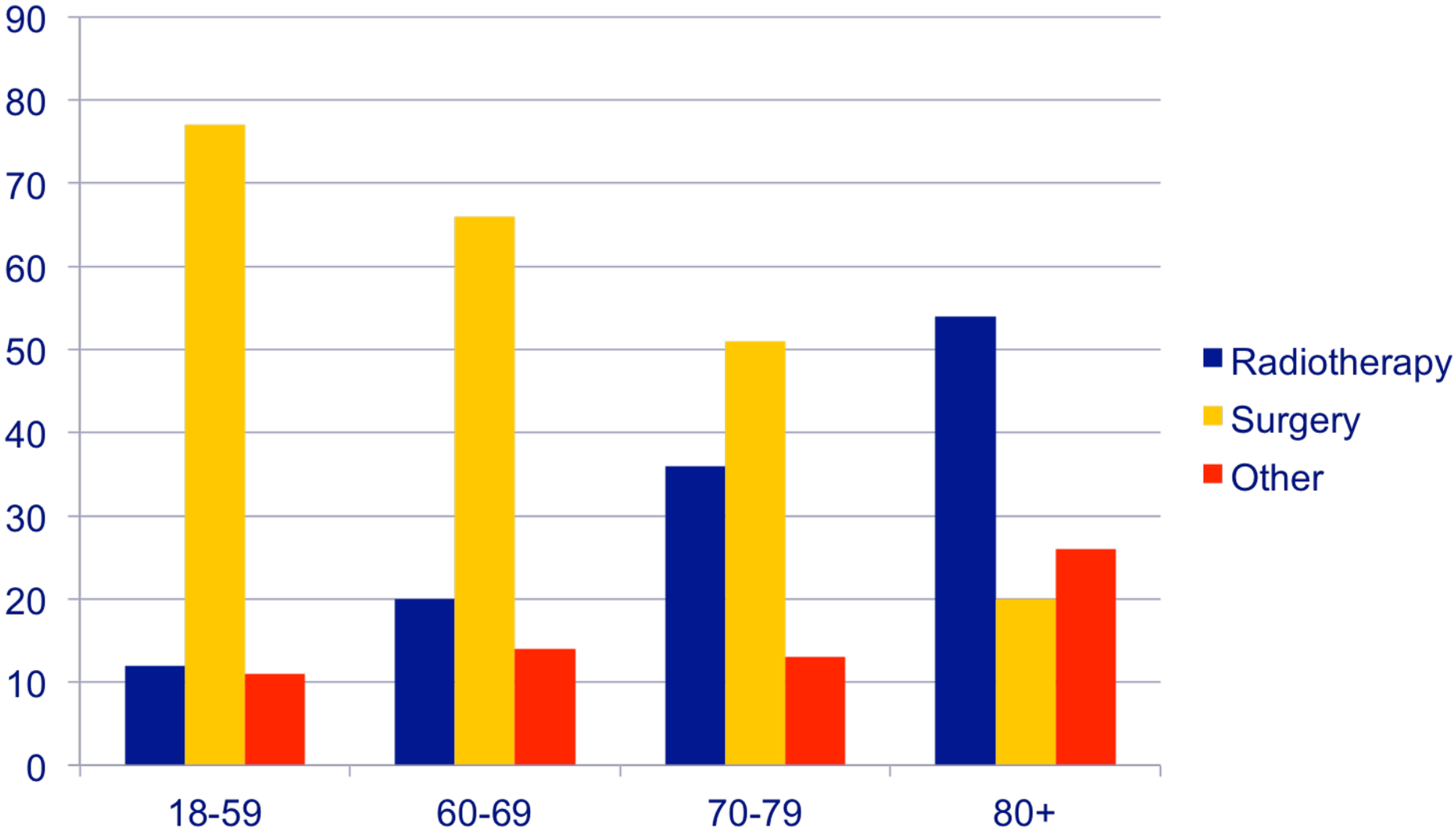
65% of Dutch lung resections performed using a VATS (2013)

WWW.CLINICALAUDIT.NL/JAARRAPPORTAGE

Dutch stage I NSCLC treatment patterns

VUmc

Netherlands Cancer Registry 2010-2012



Courtesy of dr R Damhuis

Comparative effectiveness research: surgery vs. SABR

Study	Study design	Number of patients	Surgical procedure	Overall survival		Conclusions/comments
				Surgery	SABR	
Crabtree [126]	Propensity-score matching	Unmatched: surgery = 458, SABR = 151 matched: 112/ group	(Bi) lobectomy, 78% sublobar, 19% pneumonectomy, 4%	78%, 3 yrs 68%, 3 yrs	47%, 3 yrs 52%, 3 yrs	Although surgical resection seems to result in better OS versus SABR, matching these patients remains challenging
Matsuo [127]	Propensity-score matching	Unmatched: surgery = 65, SABR = 115 matched: 53/	Sublobar resection	56%, 5 yrs	40%, 5 yrs	SABR is an alternative to sublobar resection in high-risk patients who cannot tolerate lobectomy due to comorbidities
S						R is
S						perable
V						tly usting for
V						e the two
G						e older
L						ifferences
				benefit in OS		
Shah [37]	Markov model	Lobectomy, wedge resection and SABR outcomes modeled from various sources		Not reported, model validated based on recurrence patterns		SABR is the dominant strategy compared to wedge resection. In patients eligible for lobectomy, surgery is most cost-effective
Zheng [131]	Meta-analysis	Forty SABR studies (n = 4850) and 23 surgery studies (n = 7071)		~80%, 3 yrs	57%, 3 yrs	When adjusting for potential operability in SABR patients, no difference found in OS

yrs = year, m = months, OS = overall survival, SA = sensitivity analyses.

Most studies suggested that local control / disease-free survival after SABR is at least equivalent, if not better, than post-surgery

Most suggest that overall survival after SABR is either equivalent or worse than surgery cohorts (*patient factors*)

Louie AV, Radioth Oncol 2015

Stage I NSCLC

Impact of co-morbidity

Co-morbidity and survival

3152 resected cases from Danish Cancer registry (2005-2010)

5-year survival by co-morbidity score

Stage	Charlson score 0			Charlson score 3+		
	5-year survival	95% CI		5-year survival	95% CI	
pT1	0.69	0.62	0.75	0.38	0.23	0.53
pT2	0.50	0.45	0.55	0.30	0.20	0.41
pT3	0.40	0.31	0.50			
pT4	0.23	0.09	0.40			
pN0	0.61	0.57	0.65	0.38	0.27	0.49
pN1	0.46	0.37	0.55			
pN2	0.24	0.17	0.33	0.12	0.03	0.29

CI: confidence interval.

Luchtenborg M, EJC 2012

Post-surgical outcomes vs comorbidity

Nationwide Inpatient Sample (1994 to 2003) & SEER

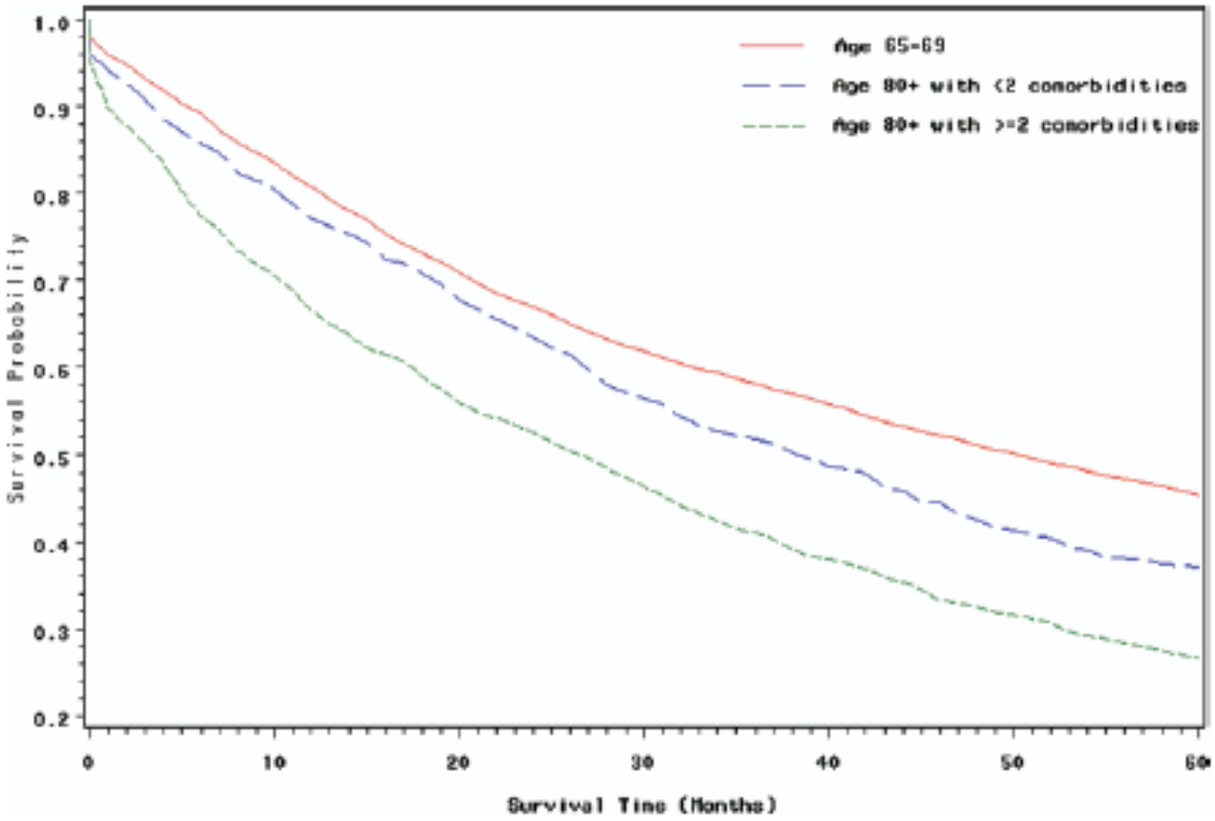


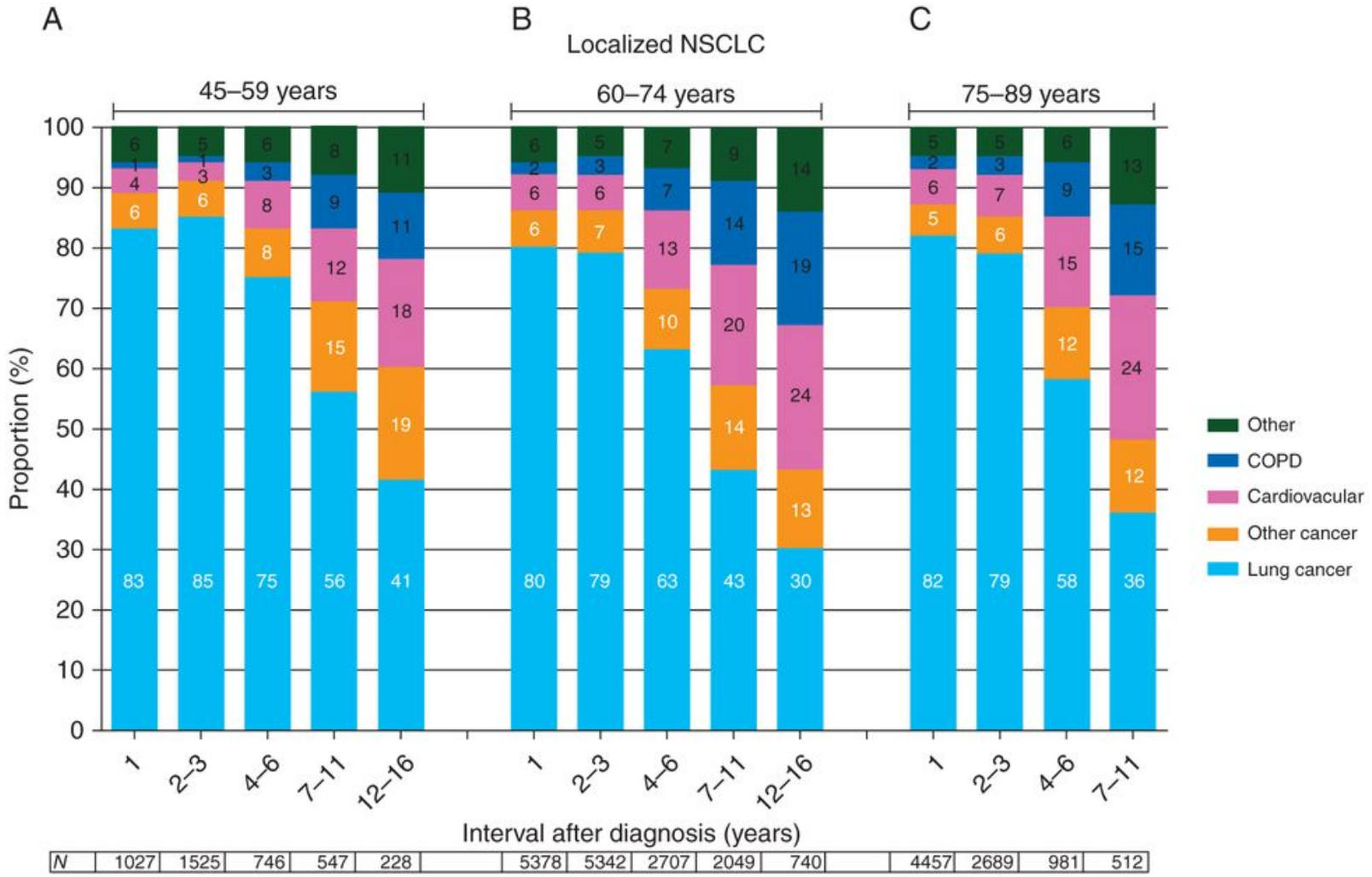
Figure 3. Five-year survival after lung operation, by age and comorbidity count.

Elderly lung cancer patients had a 10% decrease in 5-year survival if ≥2 comorbidities were present

Finlayson E, 2007

Co-morbidity and survival - NSCLC

Proportional distribution of causes of death for **NSCLC patients** by disease stage, age and interval after diagnosis.



Janssen-Heijnen M, Ann Oncol 2015

COPD and sudden cardiac death

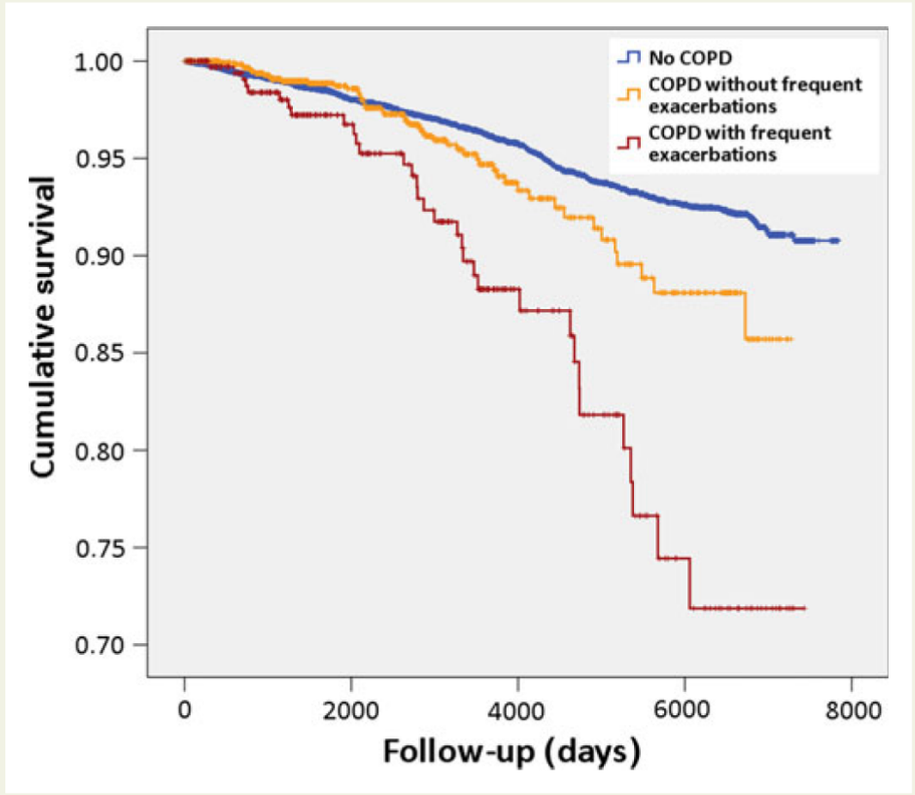


Figure 3 Kaplan–Meier curve of sudden cardiac death according to chronic obstructive pulmonary disease status with or without frequent exacerbations (log-rank $P < 0.001$).

- Population-based cohort study
- 13 471 persons aged ≥45 years, and up to 24 years follow-up
- Age- and sex-adjusted HR for sudden cardiac death was 2.12 (95% CI 1.6-2.8) after 5.5 years of COPD diagnosis

Lahousse L, Eur Heart J 2015

Causes of death in COPD

981 deaths in a trial of COPD medication **(no cancer at inclusion)**

Table 2 Summary of adjudicated cause of death classified by GOLD stage.

Cause of death (%)	GOLD stage		
	II $N = 298$	III $N = 496$	IV $N = 166$
Respiratory	16.8	37.5	59.0
Cancer	37.6	24.6	12.0
CV	14.4	8.3	5.4
Sudden cardiac death	5.7	4.0	1.8
Sudden death	2.3	4.6	1.8
Other causes	12.8	7.3	4.8
Unknown	9.7	13.5	14.5

CV: cardiovascular, GOLD: Global Initiative for Chronic Obstructive Lung Disease.

- GOLD II - cancer/cardiac deaths more common
- GOLD III-IV - respiratory deaths more common

McGarvery L, 2011

Stage I NSCLC

A patient's right to know

Challenges facing survivors

Patient's right to know

VUmc

The Oncologist®

European Perspectives

A Catalyst for Change: The European Cancer Patient's Bill of Rights

Mark Lawler,[a] Thierry Le Chevalier,[b] Martin J. Murphy, Jr.,[c] Ian Banks,[d] Pierfranco Conte,[e] Francesco De Lorenzo,[f,g] Françoise Meunier,[h] H.M. Pinedo,[i] Peter Selby,[j] Jean-Pierre Armand,[k] Mariano Barbacid,[l] Michèle Barzach,[m] Jonas Bergh,[n] Gerlind Bode,[o] David A. Cameron,[p] Filippo de Braud,[q] Aimery de Gramont,[r] Volker Diehl,[s] Sarper Diler,[t] Sema Erdem,[u] John M. Fitzpatrick,[v,w] Jan Geissler,[x,y] Donal Hollywood,[z,†] Liselotte Højgaard,[aa,bb] Denis Horgan,[cc] Jacek Jassem,[dd] Peter W. Johnson,[ee,ff] Peter Kapitein,[gg] Joan Kelly,[v,hh] Sandra Kloezen,[ii] Carlo La Vecchia,[jj] Bob Löwenberg,[kk] Kathy Oliver,[ll] Richard Sullivan,[mm] Josep Tabernero,[nn] Cornelis J. Van de Velde,[oo] Nils Wilking,[pp] Roger Wilson,[qq] Christoph Zielinski,[rr] Harald zur Hausen,[ss] Patrick G. Johnston[a,tt]

Article 1: The **right** of every European citizen to receive **the most accurate information** and to be **proactively involved in his/her care**.

Article 2: The right of every European citizen to optimal and timely access to appropriate specialized care, underpinned by research and innovation.

Article 3: The right of every European citizen to receive care in health systems that ensure improved outcomes, patient rehabilitation, **best quality of life and affordable health care**.

The Oncologist 2014

Models of decision making about treatment

Analytical stages		Paternalistic model	Intermediate approaches	Shared model	Intermediate approaches	Informed model
Information exchange	Flow	One way (largely)		Two way		One way (largely)
	Direction	Doctor ↓ patient		Doctor ↓ ↑ patient		Doctor ↓ patient
	Type	Medical		Medical and personal		Medical
	Minimum amount	Legal requirement		Anything relevant for decision making		Anything relevant for decision making
Deliberation		Doctor alone or with other doctors		Doctor and patient (plus potential others)		Patient (plus potential others)
Who decides what treatment to implement?		Doctors		Doctor and patient		Patient

Charles C. BMJ 1999

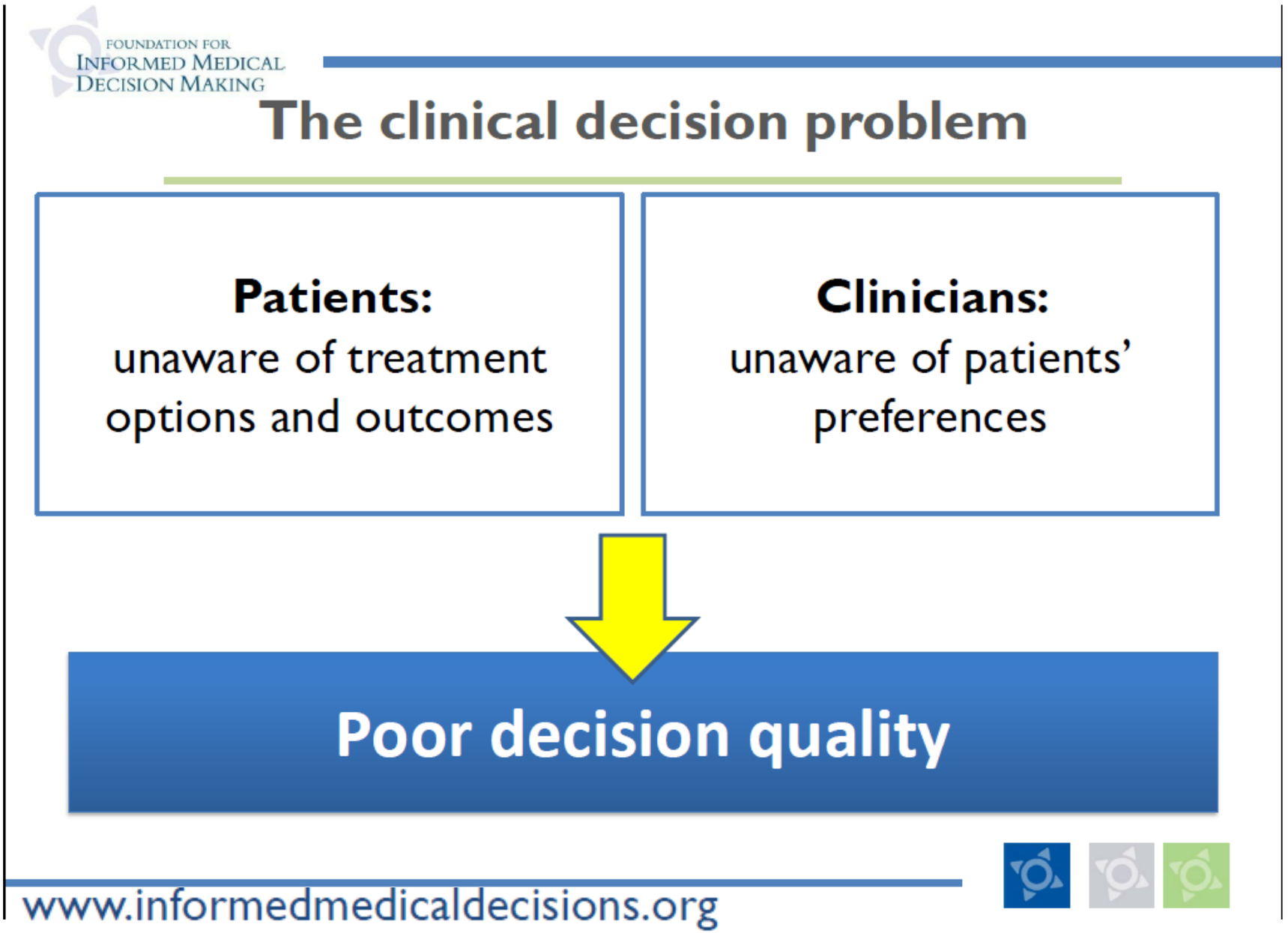
Preference-sensitive conditions

- Conditions where two or more medically acceptable options exist, and choice should depend on **patient preferences**.

- ..trials of decision support systems designed to help patients understand their treatment options that informed patient choice (**shared decision making**) results in different patterns of practice than that found with patients experiencing usual care.

Wennberg JE, BMJ 2002

Shared decision making



ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)

Table 1. Potential benefits of a new treatment

Living longer
Improved OS
Improved surrogate of OS
DFS (when OS data are immature in adjuvant setting)
Improved PFS
Living better *
Improved quality of life *
Improved surrogate of quality of life
Improved PFS
Reduced toxicity *

Cherny NI, Ann Oncol 2015

ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)

- Cure takes precedence over deferral of death.
- **Direct endpoints** such as **survival** and **quality of life** take precedence over surrogates such as progression-free survival or response rate.
- Disease-free survival in curative disease is a more valid surrogate than progression-free survival or response rate in noncurative disease.
- Interpretation of the evidence of benefit derived from surrogate outcomes (such as progression-free survival) may be influenced by secondary outcome data.

Cherny NI, Ann Oncol 2015

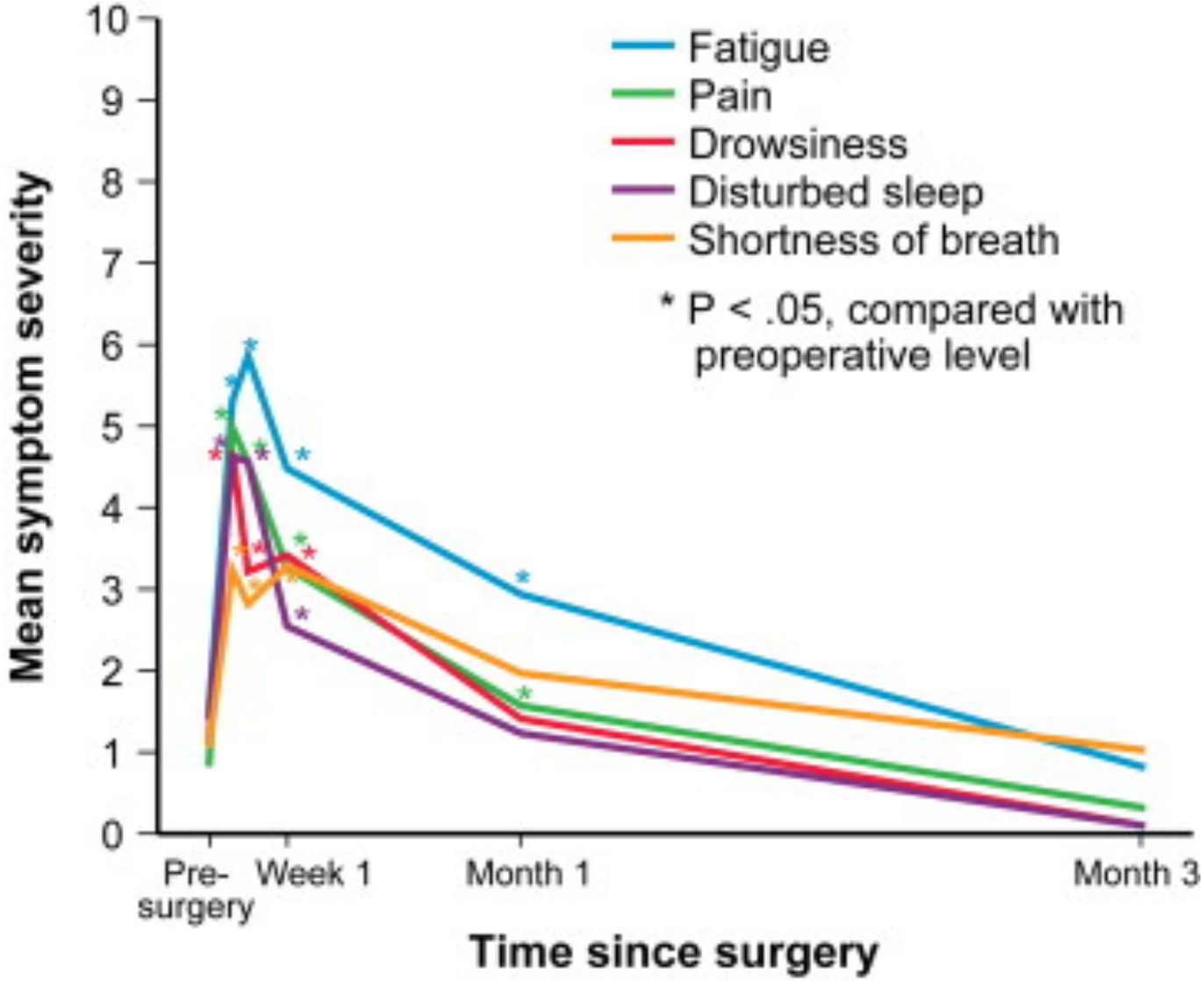
ASCO Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options

- Patients are increasingly responsible for a greater proportion of the cost of their health care.
- To ensure informed decision making, patients need access to both **clinical and cost information** about their **treatment options**.
- Patients need a clear understanding of the **possible clinical benefits and harms** of **treatment options** available to them, along with an appreciation of how these options differ with respect to the relative financial consequences they will face.

Schnipper LE, JCO 2015

Patient-reported symptom recovery after surgery

Severity levels over time for 5 most-severe symptoms after thoracic surgery (n = 60 patients)



Fagundes CP, JTCVS 2015

Patient-reported symptom recovery post-surgery

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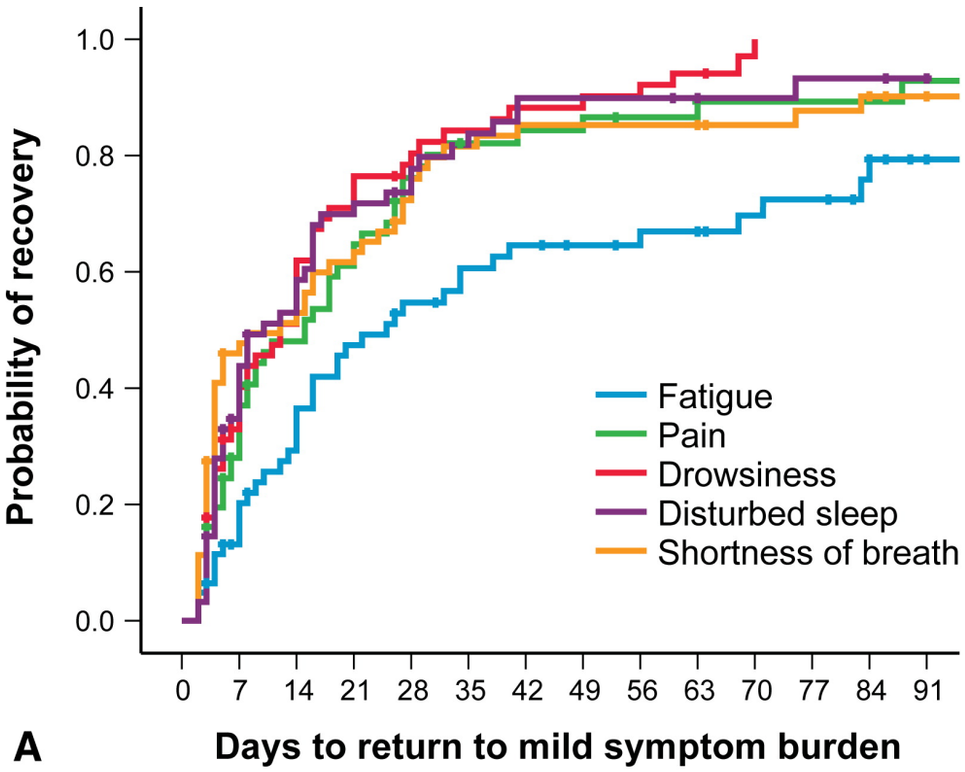
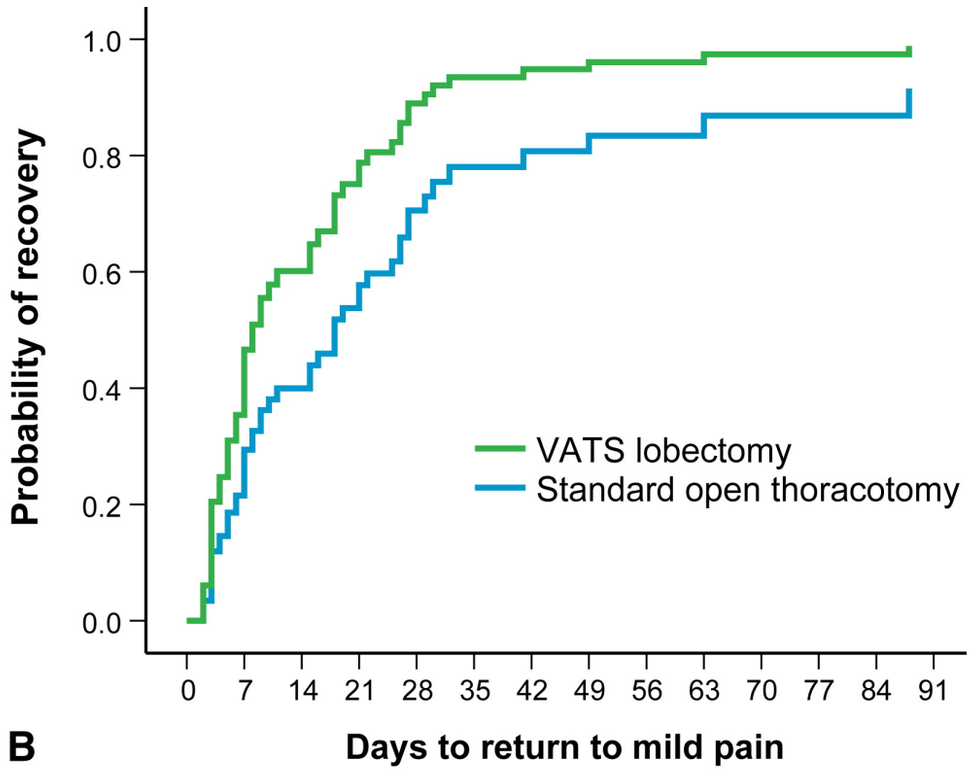
Measures using MD Anderson Symptom Inventory (n = 60 patients)



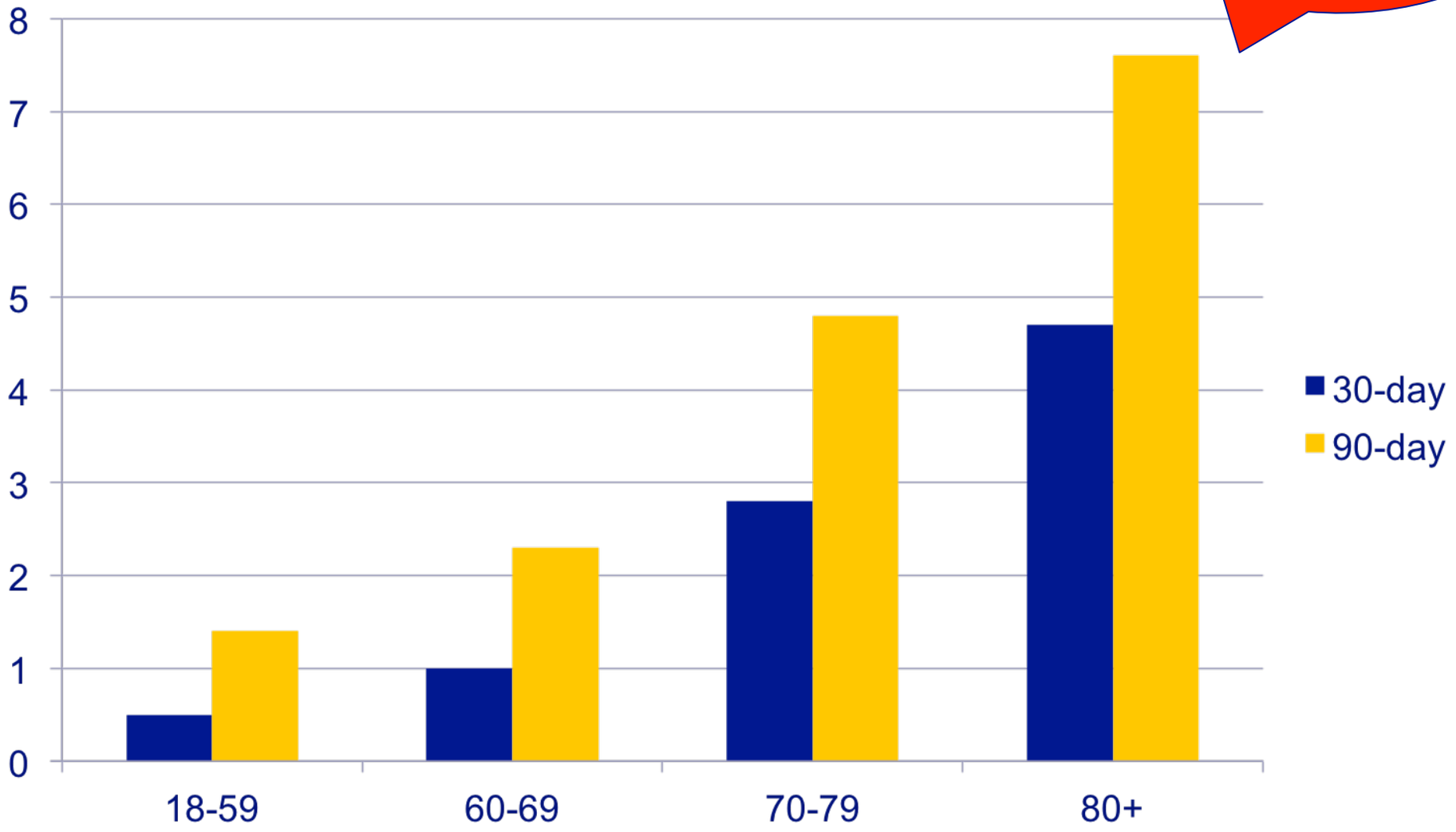


Fagundes CP, JTCVS 2015

Postoperative mortality after lobectomy

Did patients know about the 90-day mortality rates, QoL decreases, and SABR?

Netherlands Cancer Registry 2010-2012



Courtesy of dr R Damhuis

Recurrence patterns following surgery (n - 1294 pts)

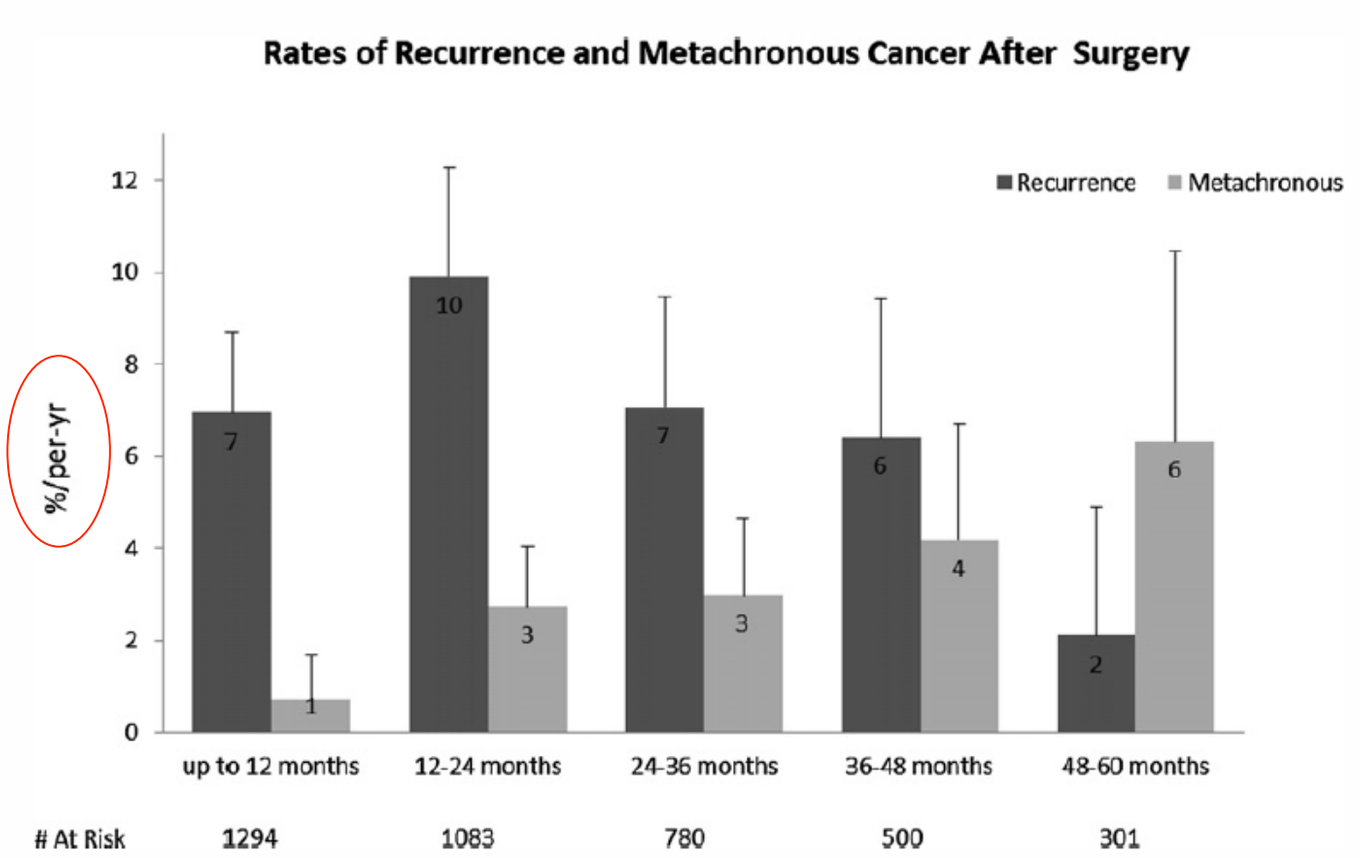


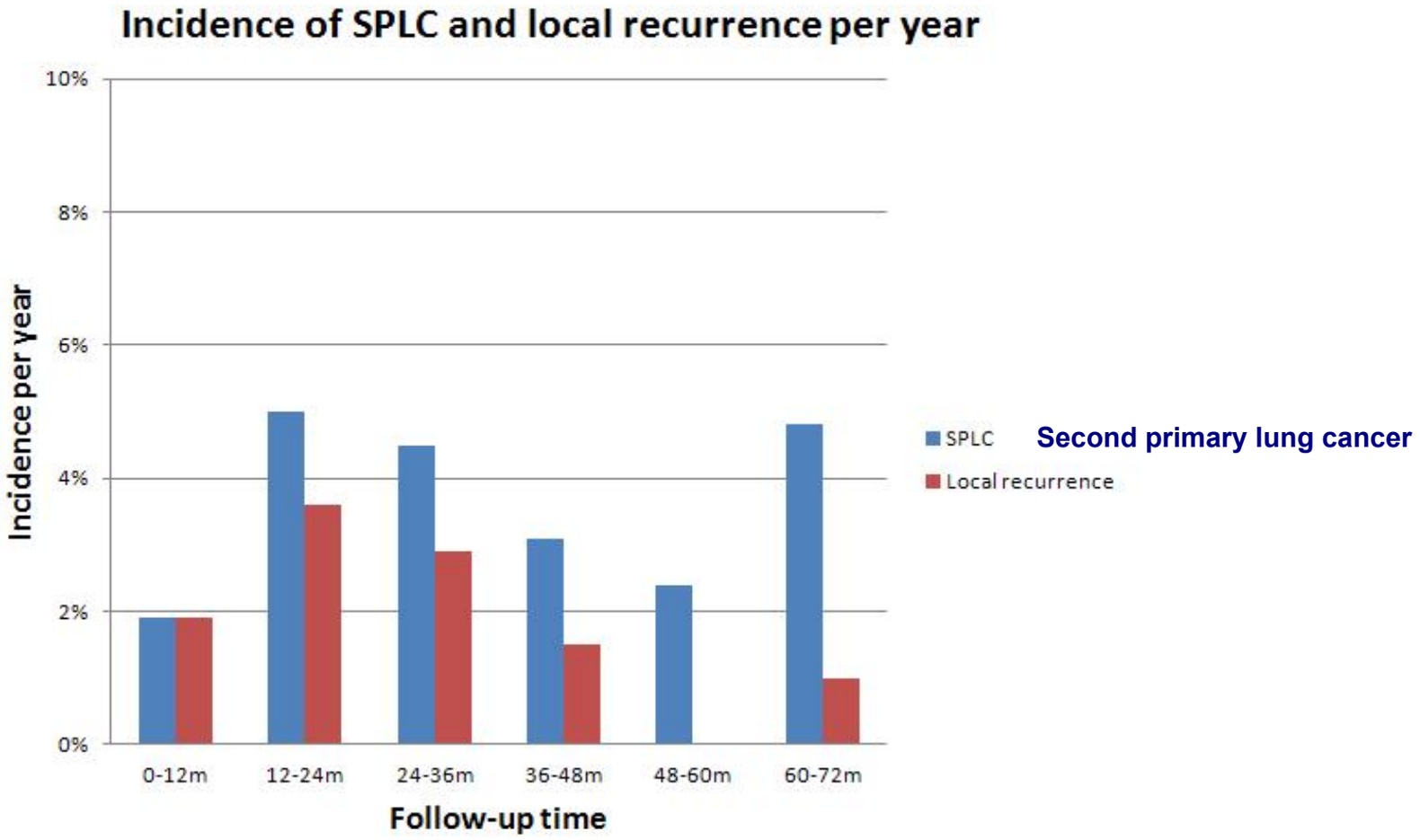
FIGURE 1. Hazard rates of recurrent and second primary lung cancer after resection over time.

Early risk of recurrence post-surgery ranged from 6-10% per person-year (years 1-4), but decreased thereafter to 2%.

Risk of 2nd primary lung cancer ranged from 3-6% per person-year and did not diminish over time.

Lou F, JTCVS 2012

Recurrence patterns after SABR (855 pts)



BED_{10} >100 Gy, median follow-up 52 months

Actuarial local control rate at 5 years was 91%

Actuarial cumulative incidence of SPLC at **3- and 5-years** were **11.7% and 16.7%**, respectively.

Verstegen NE, JTO 2015

Reporting and Grading financial toxicity

Table 1. Proposed Financial Toxicity Grading Criteria

Grade	Description
1	Lifestyle modification (deferral of large purchases or reduced spending on vacation and leisure activities) because of medical expenditure
	Use of charity grants/fundraising/copayment program mechanisms to meet costs of care
2	Temporary loss of employment resulting from medical treatment
	Need to sell stocks/investments for medical expenditure
	Use of savings accounts, disability income, or retirement funds for medical expenditure
3	Need to mortgage/refinance home to pay medical bills
	Permanent loss of job as a result of medical treatment
	Current debts > household income
	Inability to pay for necessities such as food or utilities
4	Need to sell home to pay for medical bills
	Declaration of bankruptcy because of medical treatment
	Need to stop treatment because of financial burden
	Consideration of suicide because of financial burden of care

Khera N, JCO 2014

Financial toxicity of cancer treatment

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Washington Cancer Patients Found To Be At Greater Risk For Bankruptcy Than People Without A Cancer Diagnosis

Scott D. Ramsey, MD, PhD[a], David K. Blough, PhD[b], Anne C. Kirchhoff, PhD, MPH[c], Catherine R. Fedorenko, MMSc[a], Kyle S. Snell, MS[a], Karma L. Kreizenbeck, BA[a], Polly Newcomb, PhD[a], William Hollingworth, PhD[d], and Karen A. Overstreet, JD[e]

Health Aff (Millwood) 2013

Economic Hardship of Minority and Non-Minority Cancer Survivors 1 Year After Diagnosis: Another Long-Term Effect of Cancer?

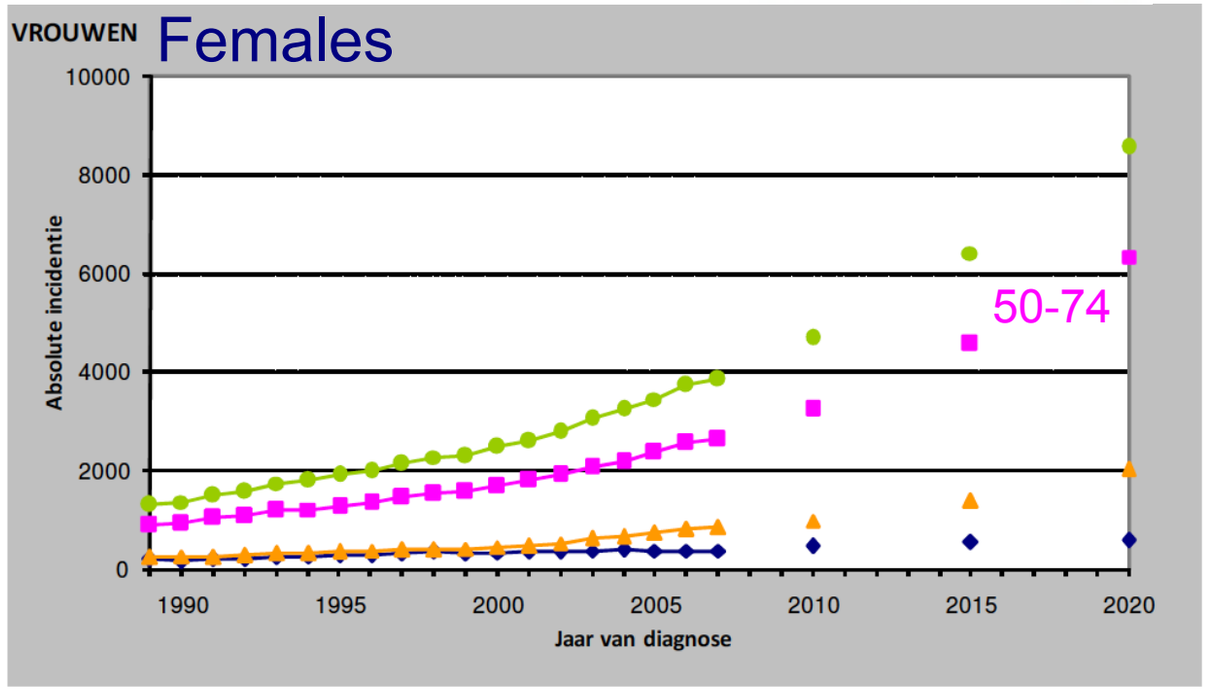
Maria Pisu, PhD[1]; Kelly M. Kenzik, PhD[2]; Robert A. Oster, PhD[1]; Patricia Drentea, PhD[3]; Kimlin T. Ashing, PhD[4]; Mona Fouad, MD, MPH[1]; and Michelle Y. Martin, PhD[1]

Cancer 2015

Population-Based Assessment of Cancer Survivors' Financial Burden and Quality of Life: A Prospective Cohort Study

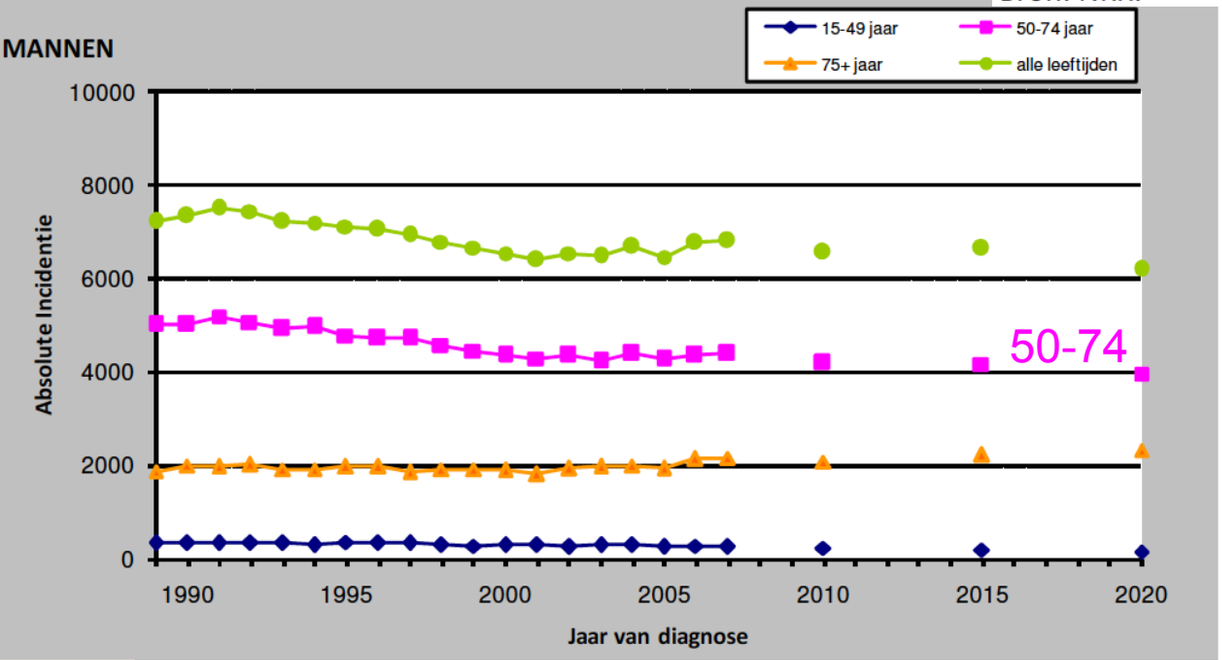
By S. Yousuf Zafar, MD, MHS, Rebecca B. McNeil, Catherine M. Thomas, ScM, Christopher S. Lathan, MD, John Z. Ayanian, MD, MPP, and Dawn Provenzale, MD

JOP 2015



Figuur 7-1: Longkanker – Absolute incidentiecijfers 1989-2007 met prognoses tot 2020.
Bron: NKR.

Males



PRO's analyses in ROSEL study (n = 22)

- PRO tools administered at baseline, and 3, 6, 12, 18, and 24 months post-treatment (SABR or surgery)

- EORTC Quality of life Core questionnaire (**EORTC QLQ-C30**)
- EORTC 13-item lung cancer supplement (**LC-13**)
- EuroQol disease-generic questionnaire (**EQ-5D**)
- Short form health and labor questionnaire (**SF-HLQ**) used for indirect costs of productivity loss, which includes work absences, reduced efficiency at work, and substitution for unpaid work

Louie AV, Radioth Oncol 2015 *in press*

PRO's analyses in ROSEL study (n = 22)

- In all comparisons, only global health status was found to be significantly worse on univariable cox proportional hazard modeling for surgical patients when compared to SABR (HR 0.19, p=0.038).

- SF-HLQ analysis: lower **total productivity cost** to society for SABR compared to surgery. The mean total productivity cost for **SABR was €95** and **€3,513 for surgery** (p=0.044).

- Patients reported a lower total degree of hindrance in paid and unpaid work for SABR compared to surgery (mean hindrance scores for SABR: 1.9, for surgery: 6.0, p=0.010).

Louie AV, Radioth Oncol 2015 *in press*

Hilary Term
[2015] UKSC 11
On appeal from: [2013] CSIH 3; [2010] CSIH 104

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JUDGMENT

Montgomery (Appellant) *v* Lanarkshire Health Board (Respondent) (Scotland)

- The Supreme Court's ruling has confirmed that a doctor must make the patient aware of any risks that a reasonable patient would think were material.

- The shift in focus from that of a **reasonable doctor** to that of a **reasonable patient** reflects a change in public attitudes to the doctor-patient relationship and a move away from **medical paternalism towards patient autonomy** in making decisions about their medical treatment.

- www.kennedyslaw.com/.../informed-consent-following-**montgomery-v-l**... June 26 2015

The patient's right to know

BMJ 2015;350:h1481 doi: 10.1136/bmj.h1481 (Published 16 March 2015)

OBSERVATIONS

ETHICS MAN

Update on the UK law on consent

Last week's case of Montgomery *v* Lanarkshire Health Board has important implications for doctors

Daniel K Sokol *practising barrister and medical ethicist, 12 King's Bench Walk, London*

News

Doctors should not cherry pick what information to give patients, court rules

BMJ 2015 ; 350 doi: http://dx.doi.org/10.1136/bmj.h1414 (Published 13 March 2015)
Cite this as: *BMJ* 2015;350:h1414

Clare Dyer

Author affiliations

Overview of talk - 1

- How SABR became established as the standard of care in Stage I NSCLC; future developments

- Evolving role of SABR for oligometastases in the era of personalized medicine

Oligometastatic paradigm

- Patients developing a small number of metastatic lesions might achieve long-term survival if all these lesions are ablated with surgery or stereotactic radiotherapy [Hellman and Weichselbaum, JCO 1995]

- The number of patients with oligometastatic disease receiving aggressive treatment is increasing rapidly.

Palma DA, Nat Rev Clin Oncol 2014

Oligometastases

Oligometastatic
A malignancy that has progressed to a limited number of haematogenous metastases, defined in most studies as 1–3 or 1–5 metastatic lesions.

Synchronous oligometastasis
A clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour.[111]

Metachronous oligometastasis
The development of oligometastatic disease after treatment of the primary tumour. The interval for classification of 'metachronous' versus 'synchronous' is not standardized.[111]

Oligorecurrence
Oligometastasis in the setting of a controlled primary tumour.[111]

Oligoprogression
Progression of a limited number of metastatic deposits, while all other metastases are controlled with systemic therapy.

Palma D, Nat Rev Clin Oncol 2014

The evidence from randomized trials

- Patients with a **single brain metastasis**, the addition of surgical resection to WBRT improved median overall survival from 15 weeks to 40 weeks [Patchell RA, NEJM 1990]

- For patients with **1-3 brain metastases**, radiosurgery in addition to WBRT improved median overall survival from 4.9 months to 6.5 months [Andrews DW, Lancet 2004]

- In non-resectable **colorectal liver metastases**, radiofrequency ablation (RFA) combined with systemic treatment was not superior to systemic treatment alone [Ruers T, Ann Oncol 2012]

Approaches to Oligometastases

VUmc

- OLD: treat according to clinical presentation (e.g. solitary late recurrence)

- NEW: molecular characteristics of tumor

Oligometastases

- **Colorectal cancer with lung metastases**
- Metastatic malignant melanoma
- Non-small cell lung cancer (NSCLC)

Pulmonary oligometastases: metastasectomy or SABR?

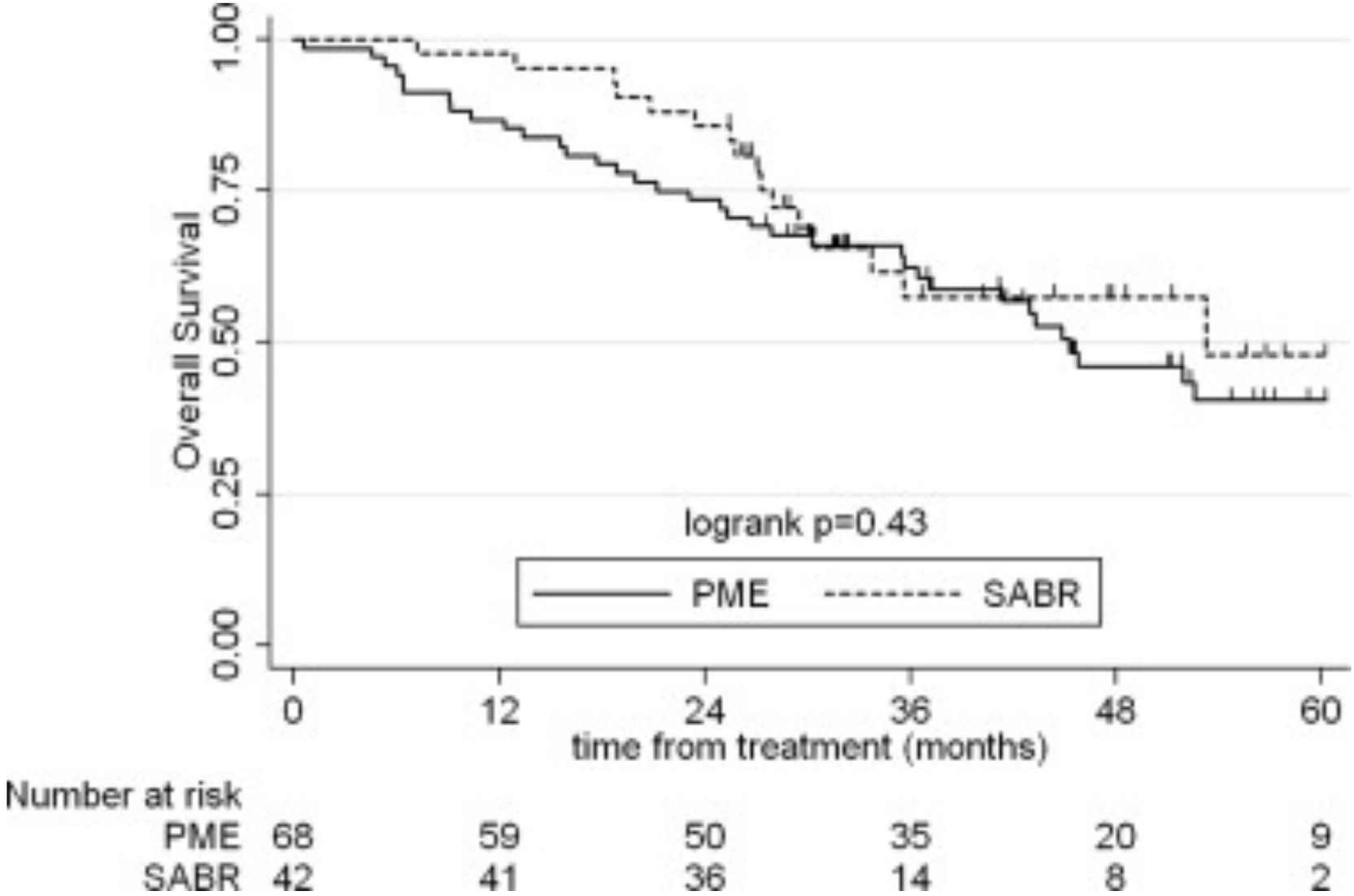
- Consecutive patients at university-hospital (2007-2010)
- Tumor board policy - surgery preferred therapy before SABR
- 110 patients (surgery, n=68; SABR, n=42)

- Estimated OS rates at 1, 3 and 5 years:
- 87%, 62%, and 41% for surgery, versus
- 98%, 60%, and 49% for SABR, respectively (logrank-test, p=0.43).

- 2-year local control rates of 94% (SABR) and 90% (surgery)
- Progression-free survival was 17% at three years

Widder J, Radioth Oncol 2013

Pulmonary oligometastases: metastasectomy or SABR?



Overall survival, **PME** (pulmonary metastasectomy) versus **SABR** (stereotactic ablative radiotherapy).

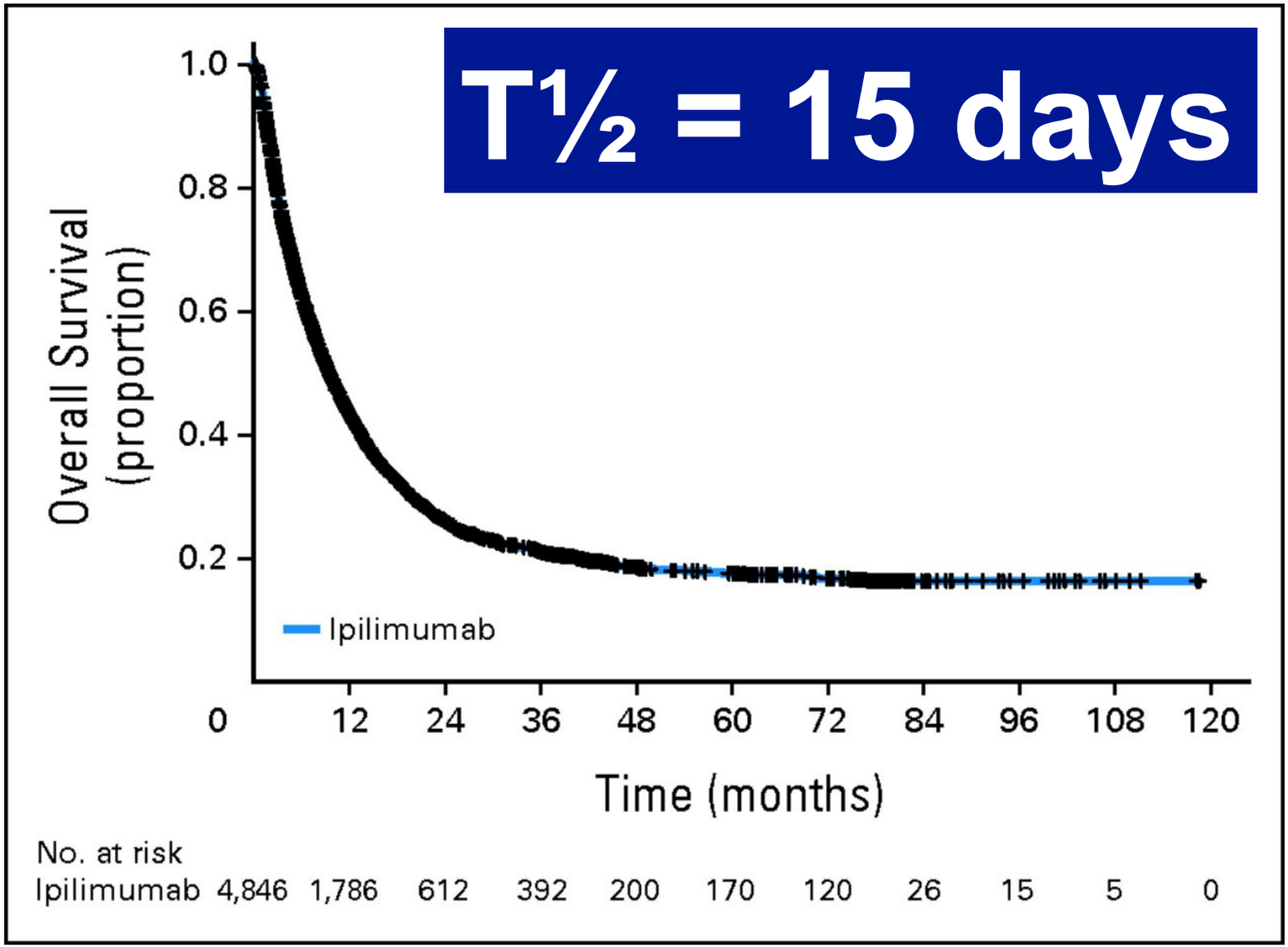
Widder J, Radioth Oncol 2013

Oligometastases

- Colorectal cancer with lung metastases
- **Metastatic malignant melanoma**
- Non-small cell lung cancer (NSCLC)

Advances in systemic therapy: **Melanoma**

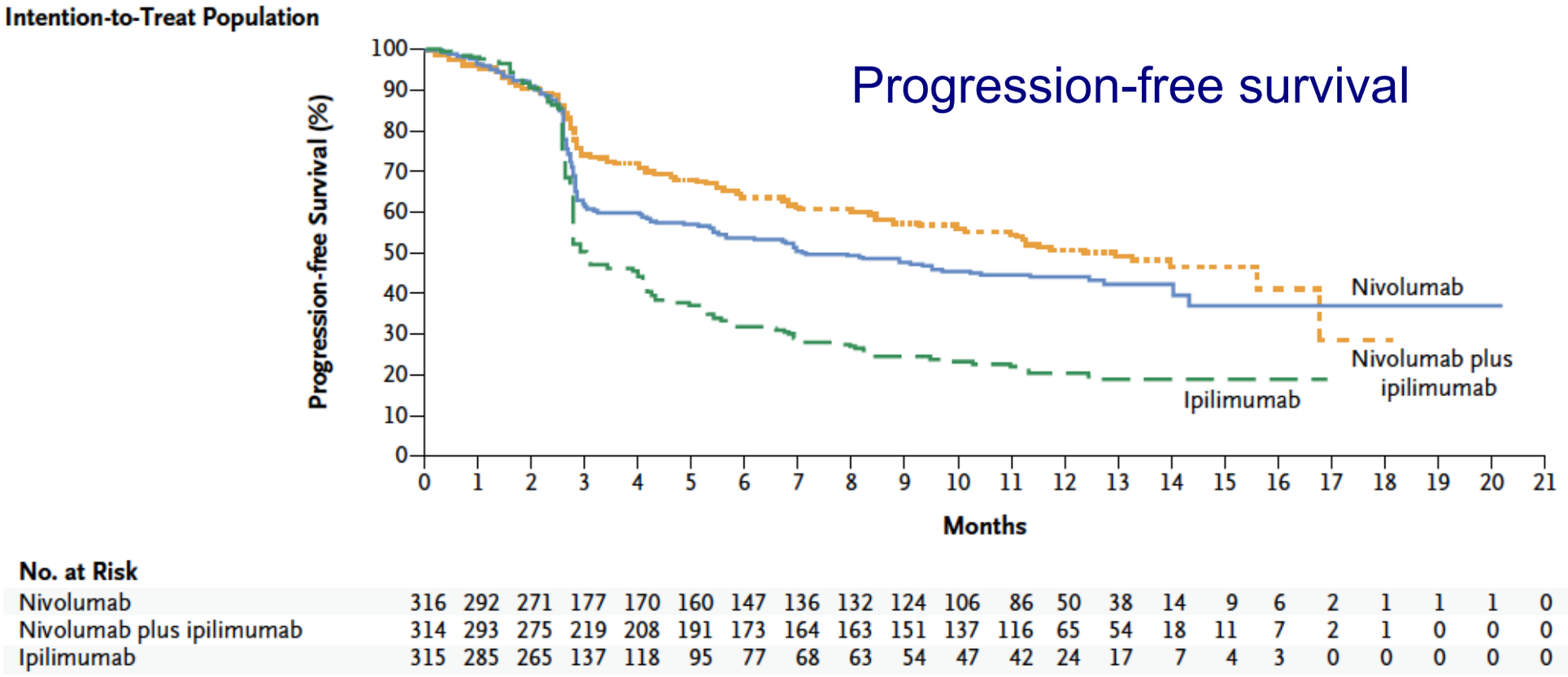
Pooled overall survival (OS) analysis with expanded access protocol (EAP) data.



Schadendorf D. JCO 2014

Metastatic melanoma – phase III trial

Median PFS **11.5** months with nivolumab plus ipilimumab, as compared with **2.9** months with ipilimumab and **6.9** months with nivolumab (HR for comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; P<0.001)



Larkin J, NEJM 2015

Financial toxicity

Medscape Medical News > Conference News

Another Sea Change in Melanoma: Immune Combo Triumphs

Nick Mulcahy

May 31, 2015

Medscape Medical News > Conference News

New Immunotherapy Costing $1 Million a Year

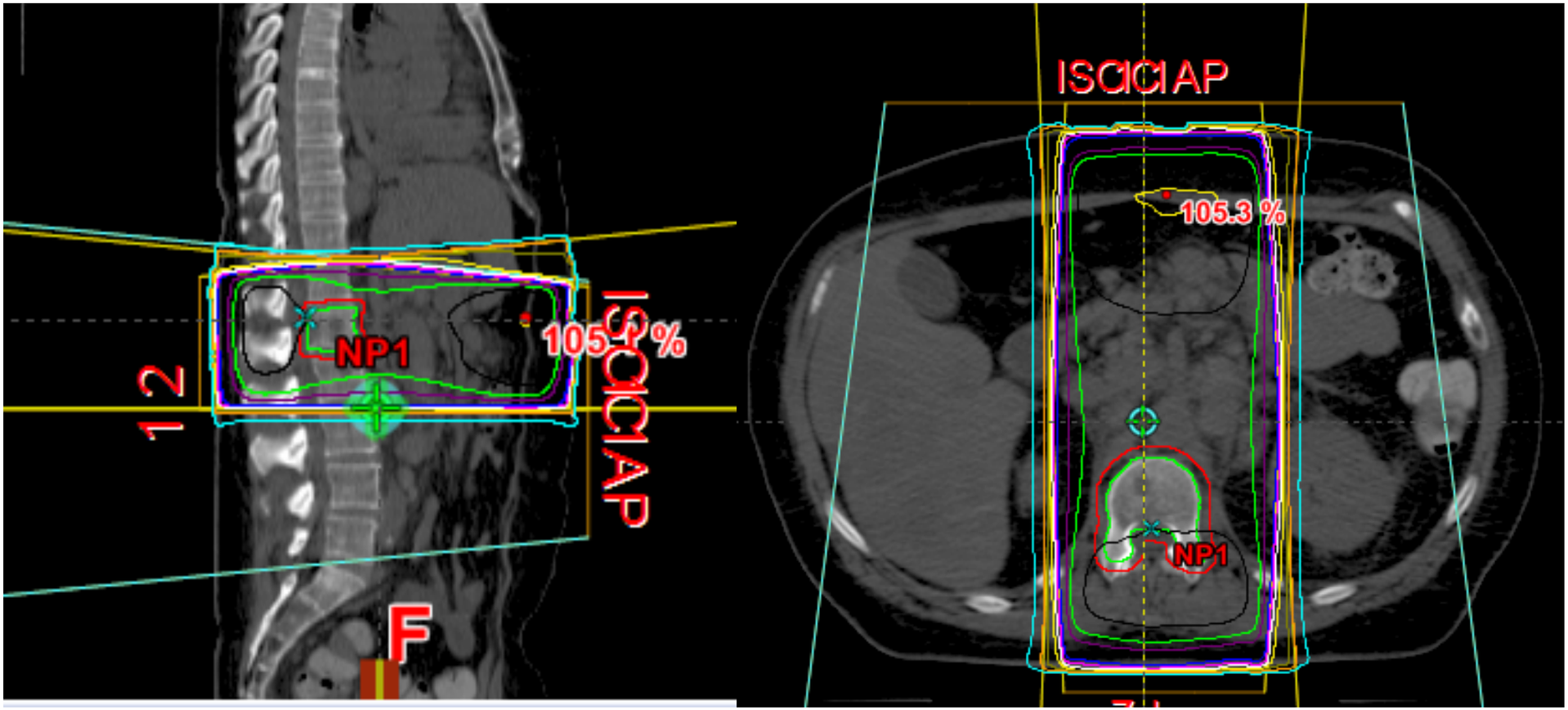
Gooder Than Gold

Zosia Chustecka

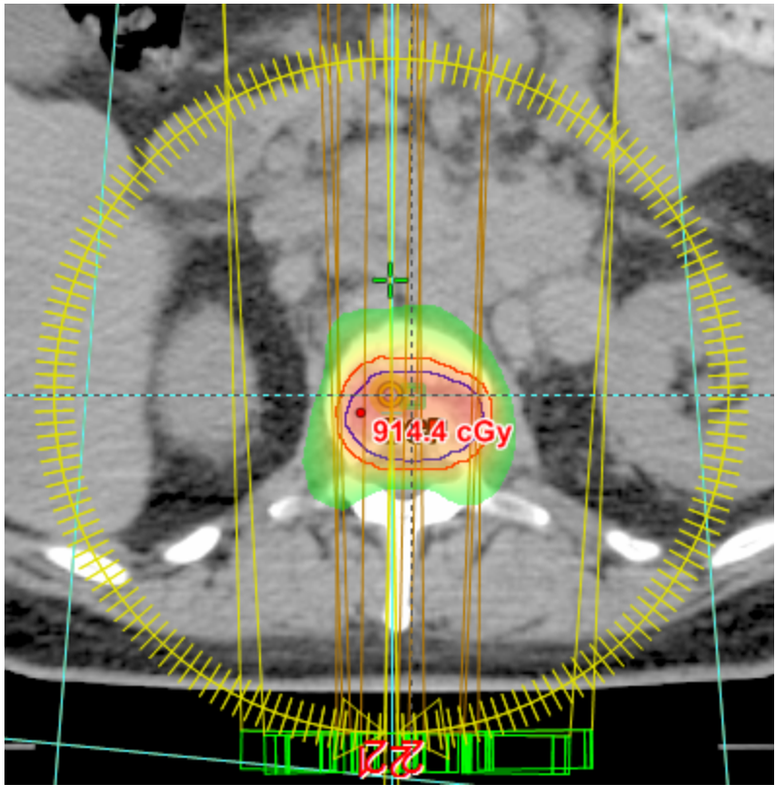
June 01, 2015

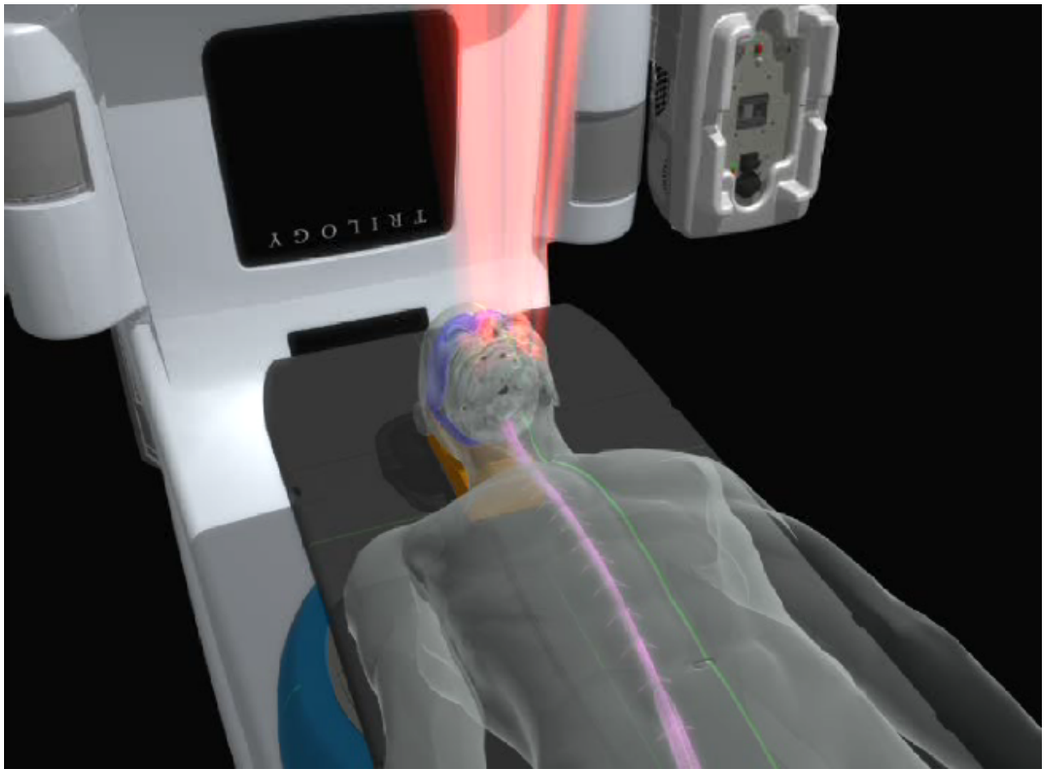
Vertebral metastases: standard fields

Single-fraction of 8 Gy, using anterior-posterior fields



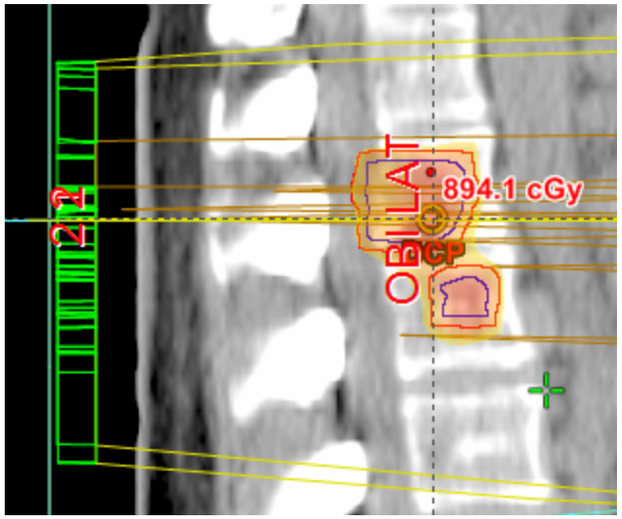
Melanoma vertebral metastases: VMAT



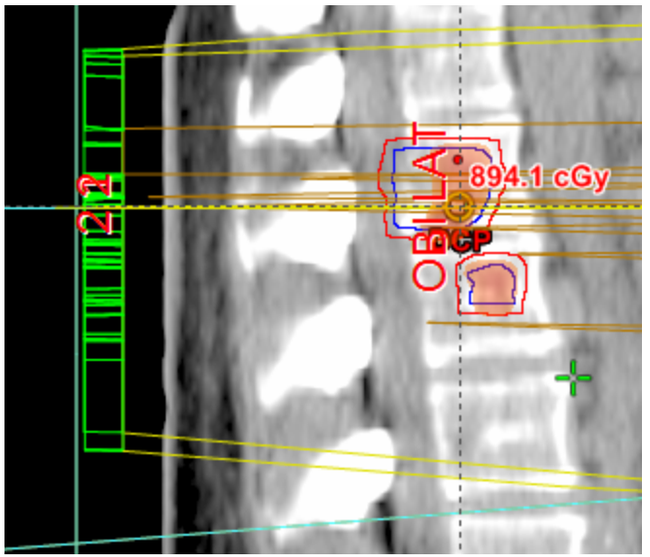


VMAT = volumetric modulated radiotherapy

7 Gy



8 Gy



Oligometastases

- Colorectal cancer with lung metastases
- Metastatic malignant melanoma
- **Non-small cell lung cancer (NSCLC)**

Oligometastases in era of targeted therapy

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Driver mutations

MEK <1%
AKT <1%
PI3KCA 1%

Adenocarcinomas of the lung

Median OS (months)
30.5 versus 23.6 (p = 0.31)
36 versus 39 HR 1.19
HR = 1.065 (p = 0.65)
19.3 versus 19.5 (p = 0.87)
Not reported
HR = 0.95 (p = 0.76)

TABLE 7. Chemotherapy versus EGFR TKIs in Patients with

Study	Treatment	N
Maemondo	Gefitinib versus carboplatin/paclitaxel	230
Mitsudomi	Gefitinib versus cisplatin/docetaxel	177
OPTIMAL	Erlotinib versus carboplatin/gemcitabine	165
EURTAC	Erlotinib versus platinum-based chemotherapy	174
LUX-Lung 3	Afatanib versus CDDP/Pemetrexed	345
LUX-Lung 6	Afatanib versus gemcitabine/CDDP	364

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progressio

Rociletinib in T790 EGFR-mutant NSCLC

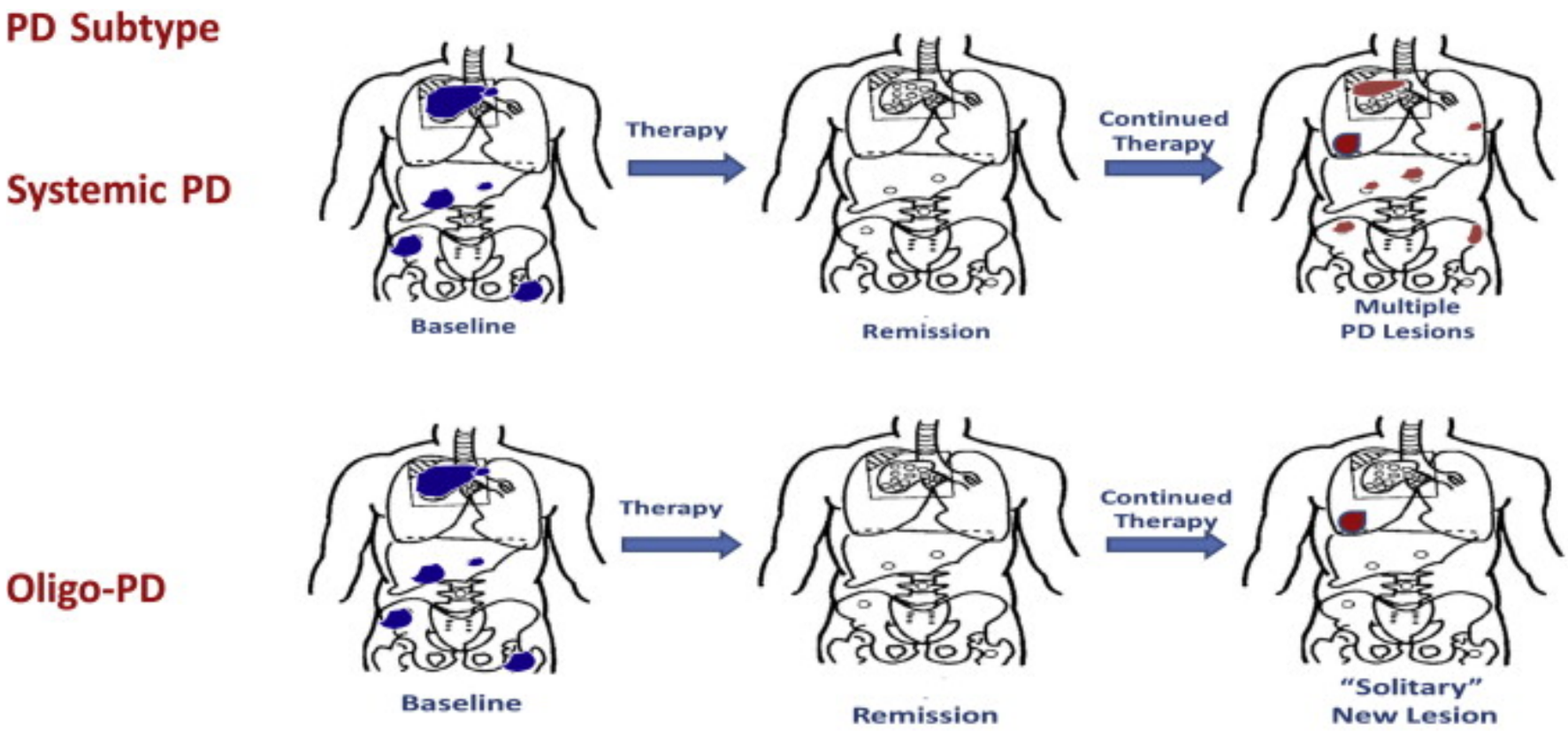
VUmc

Rociletinib is an irreversible, highly selective TKI of mutations of EGFR (activating and T790M)

- 72 patients, median age 59; 14% Asian
- Objective response rate in 46 patients with T790M-positive disease was **59%** (95% CI 45 to 73)
- Median PFS not reached, estimated >12 months

Sequist L, NEJM 201

Acquired Resistance to Targeted Therapies



Gandara D, Clin Lung Cancer 2014

Changing approach (ESMO)

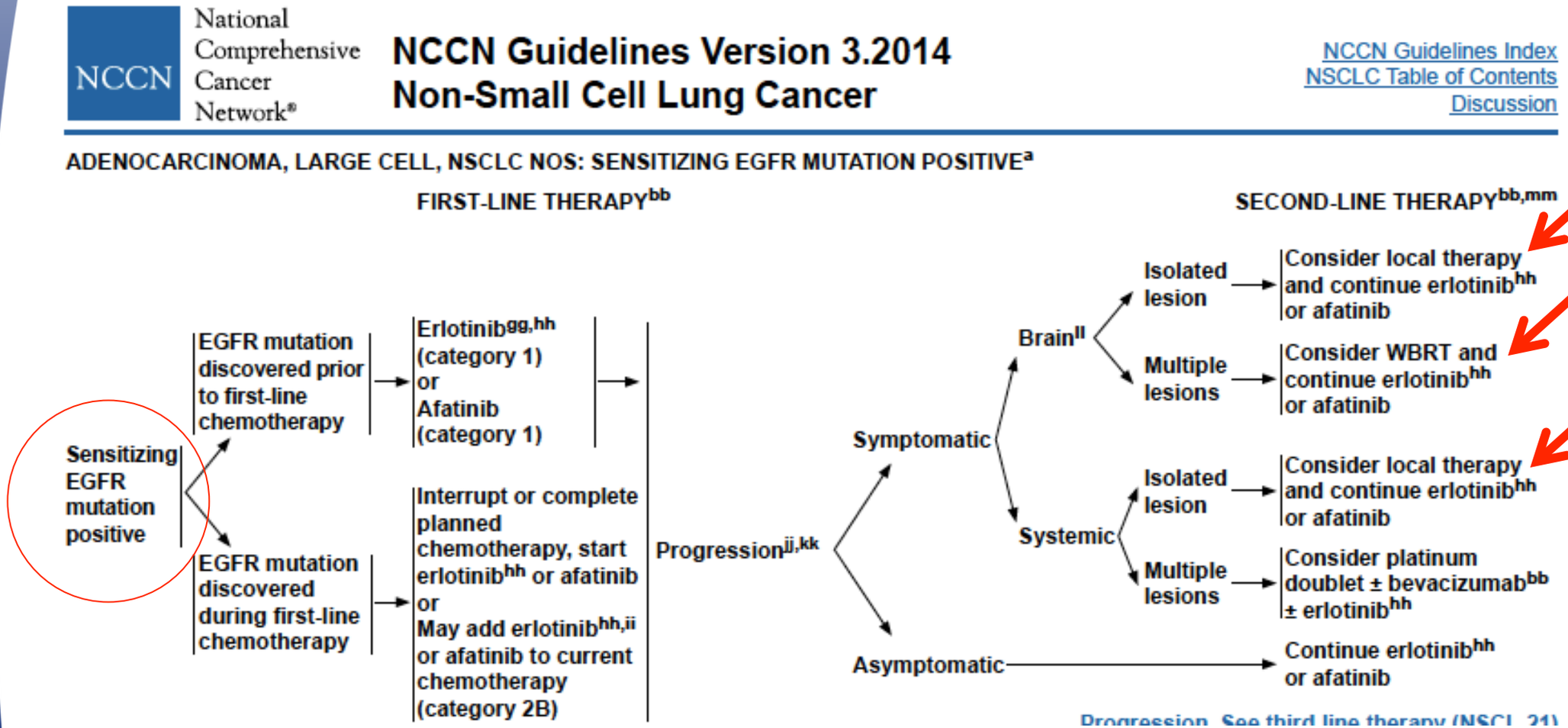
How should oligometastatic progression during TKI be managed?

Local therapies including radiation, radiofrequency ablation, and metastasectomy are established treatment strategies in certain cancers including renal cell carcinoma, sarcoma, and colorectal cancer. Several experiences also support the use of local therapies (surgery, stereotactic radiation) with continued EGFR or ALK inhibition in cases of oligometastatic progression, resulting in minimal toxicity and in months to years of disease control [65].
Prior to proceeding with local therapy, patients should have a full evaluation of the extent of disease, including CNS imaging.

Recommendation 27: In case of oligometastatic progression during TKI treatment, use a local treatment (such as surgery or radiotherapy) and continue/resume TKI
Strength of recommendation: C
Level of evidence: V

Besse B, 2nd ESMO Consensus, Ann Oncol 2014

Changing approach (NCCN)



Radiaton oncologists & risk of ‘bystander effect’

We have a continuous need to reflect on:

- Clinical need for improved treatments?
- Evidence for efficacy (clinical trials, CER)?
- Treatment toxicities, especially use of patient reported outcomes (PRO’s)
- Cost-effectiveness (incentives and hurdles)

Thank you for listening

Radiobiology of hypofractionation

Part I

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Professor, MD, PhD

Department of Oncology, Aarhus University Hospital

AARHUS UNIVERSITET

Aarhus Universitetshospital

CIRRO

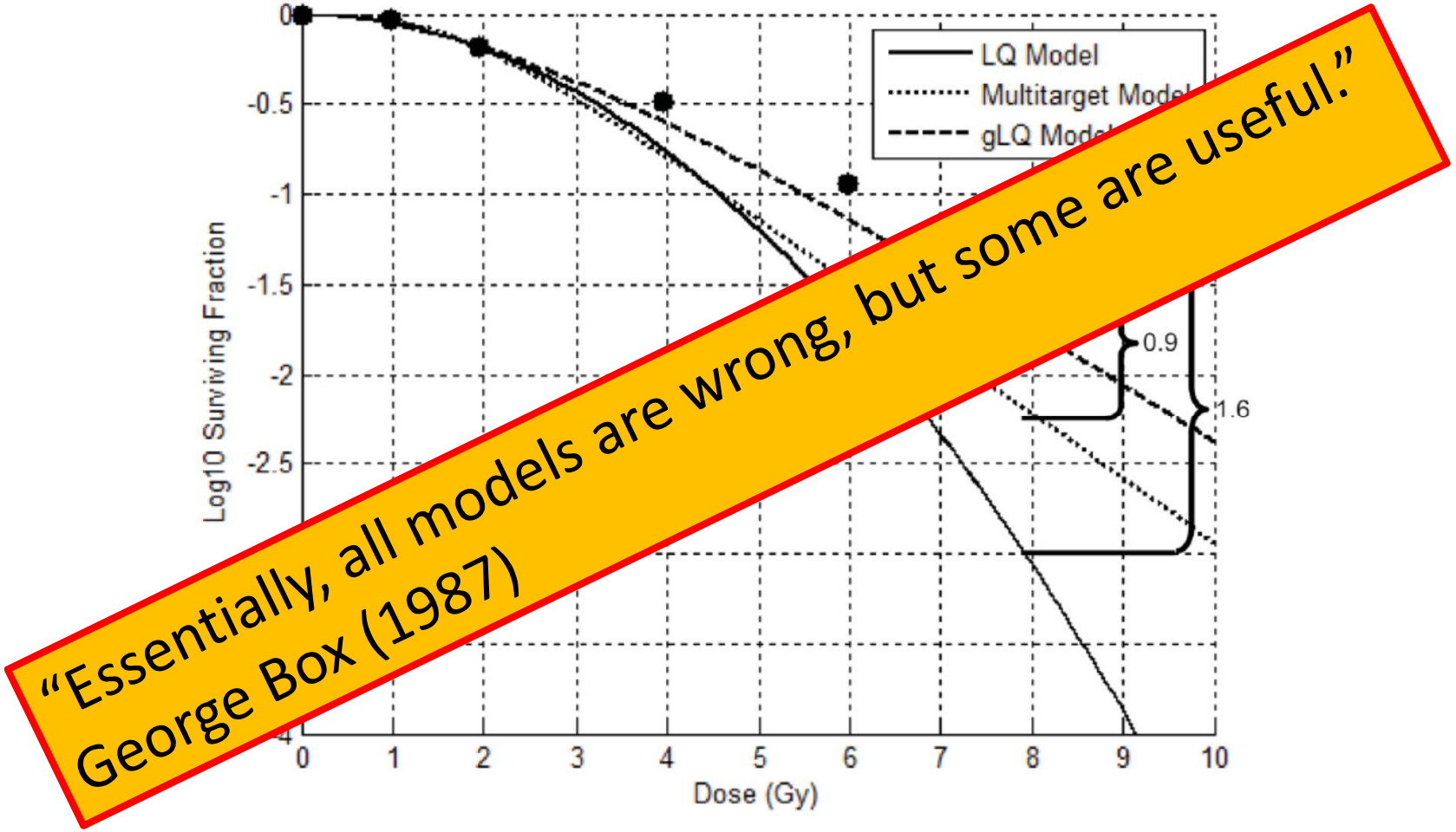
ESTRO School

How to prescribe *'a treatment'*

- We prescribe dose in Gray
- Dose is a surrogate of cell kill
- We do not prescribe XX% cancer cell kill
- We expect close relationship between dose and cancer cell kill (due to DNA-strand break)

Modeling survival after radiation therapy

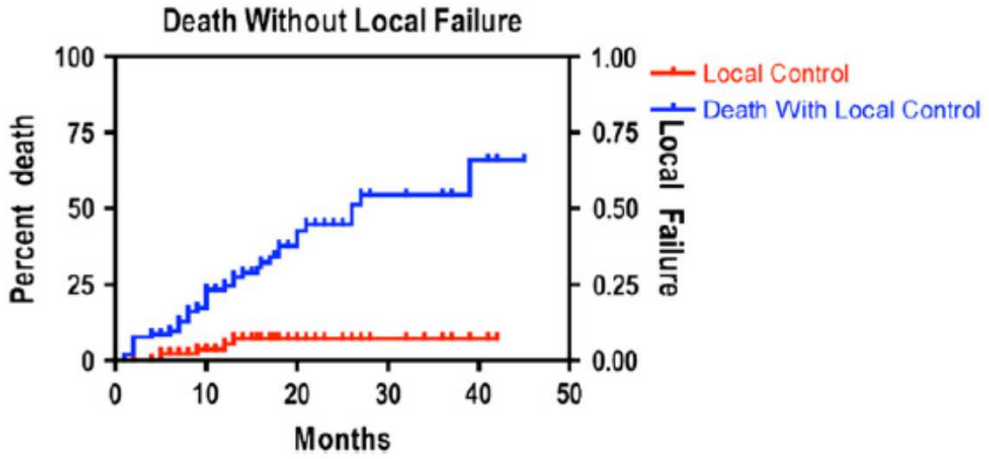
Linear-quadratic-, multitarget- and generalized linear quadratic models



"Essentially, all models are wrong, but some are useful."
George Box (1987)

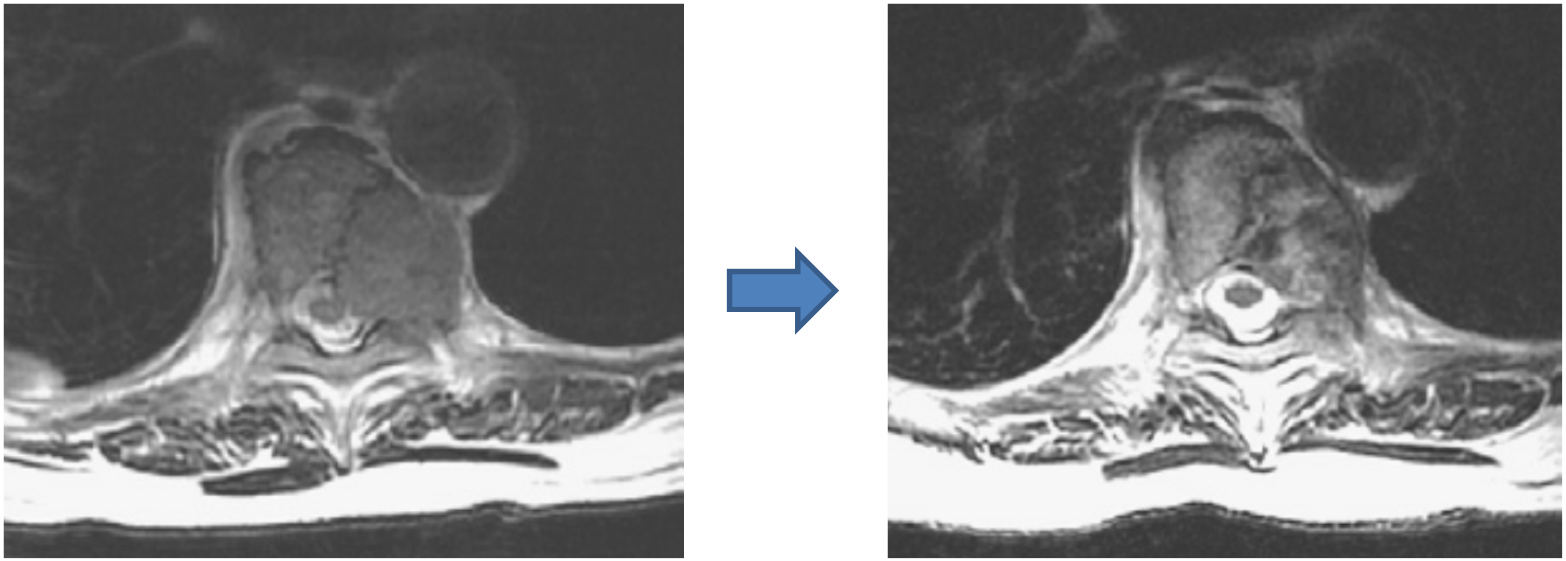
Ohri et al: IJROBP 2012; 83 (1): 385

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.

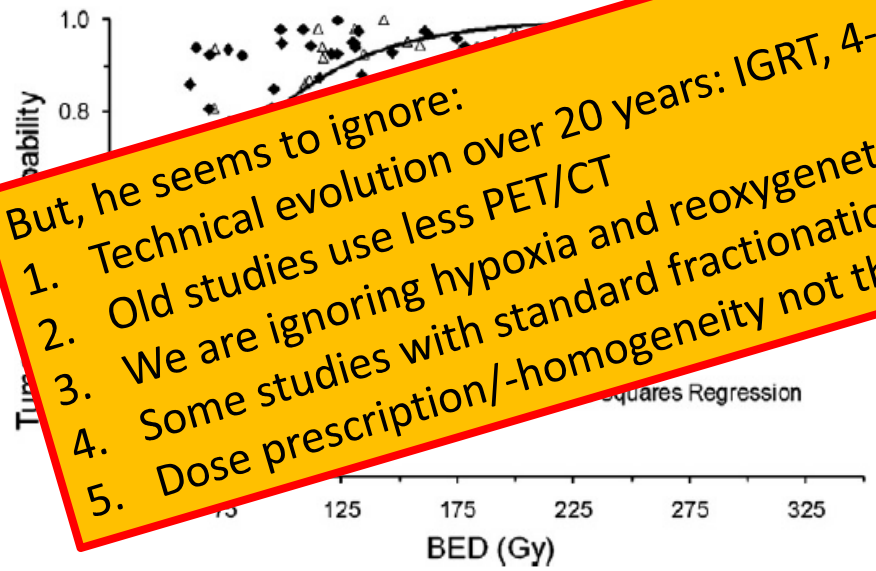
Brown et al. IJROBP 2008; 71(2): 324

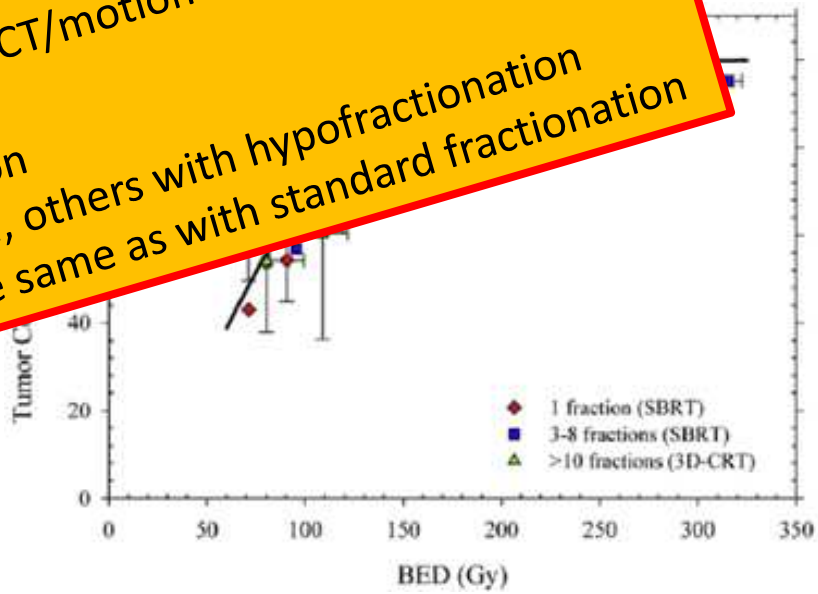
Matthias Guckenberger:

"The efficacy of SBRT can be explained by the LQ-model"

"….and there is a dose-response relati…"

Early stage NSC…





But, he seems to ignore:

1. Technical evolution over 20 years: IGRT, 4-DCT/motion management
2. Old studies use less PET/CT
3. We are ignoring hypoxia and reoxygenetion
4. Some studies with standard fractionation, others with hypofractionation
5. Dose prescription/-homogeneity not the same as with standard fractionation

Mehta et al PRO 2012; 2: 288

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

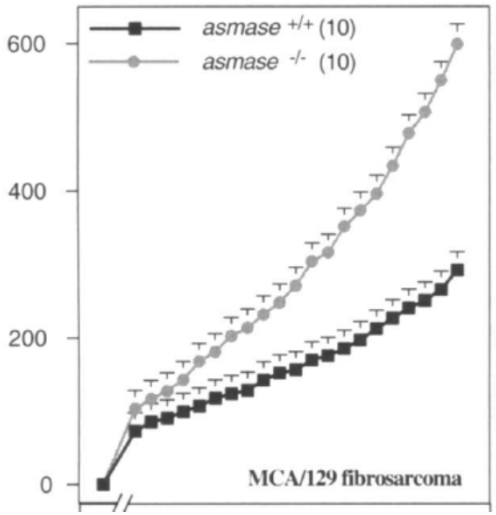
Endothelial response to high RT doses

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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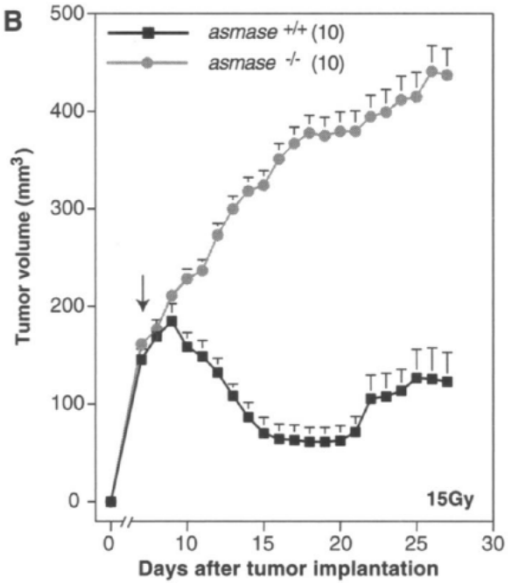
Tumors with apoptosis-resistent vascular endothelium were resistant to radiation



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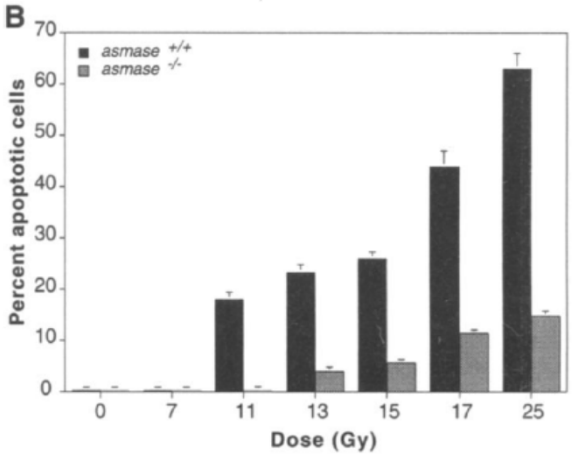
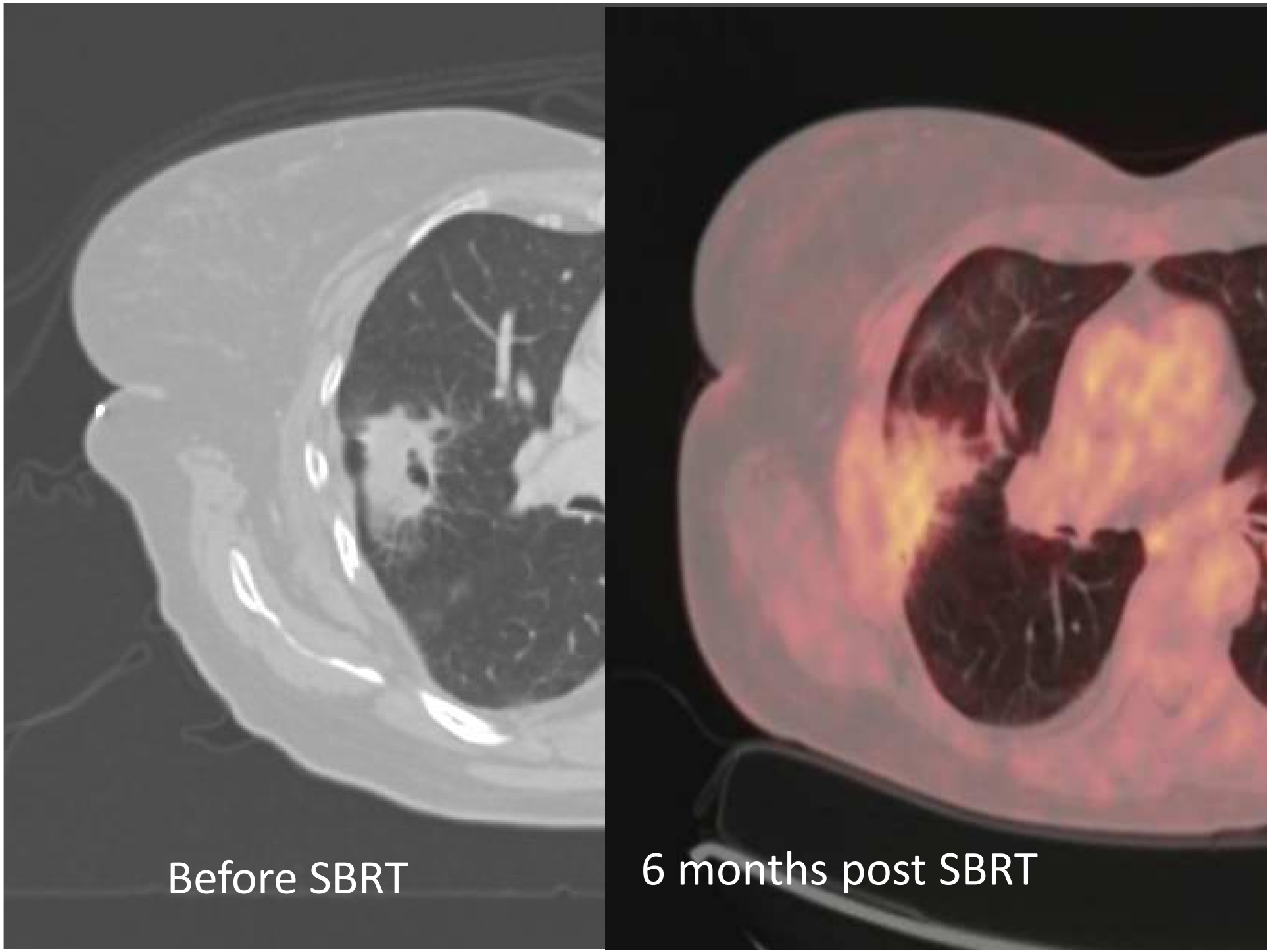


Tumors with apoptosis-resistent vascular endothelium Were resistant to radiation

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

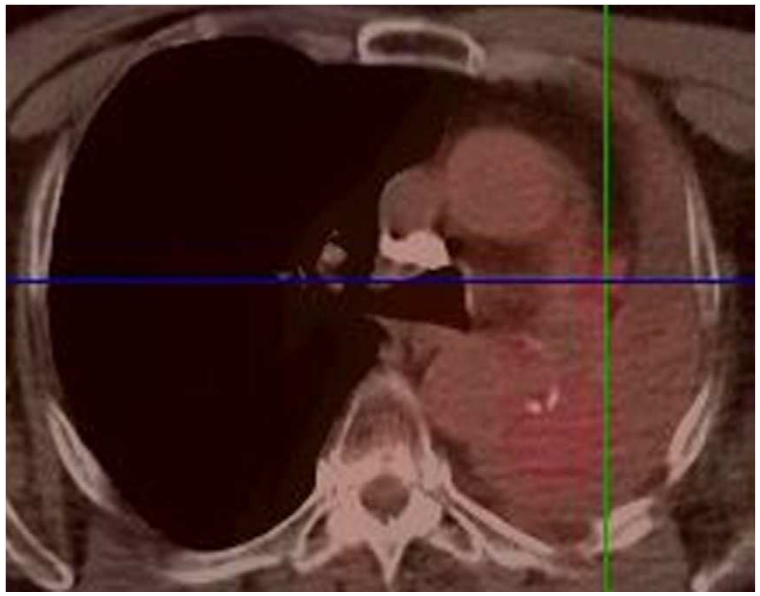
Science 300: 1155; 2003

Immune effects


Before SBRT
6 months post SBRT

FDG-PET response following SBRT

23 months post-SBRT



SUV = 5.87

39 months post-SBRT

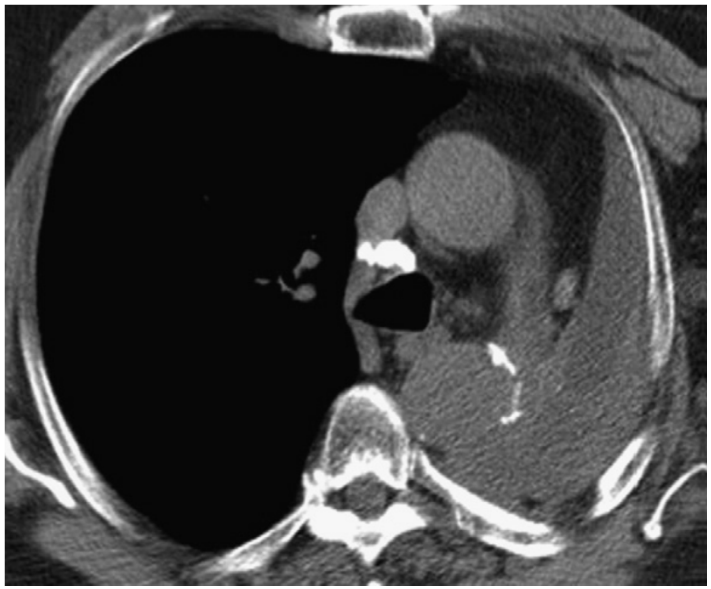
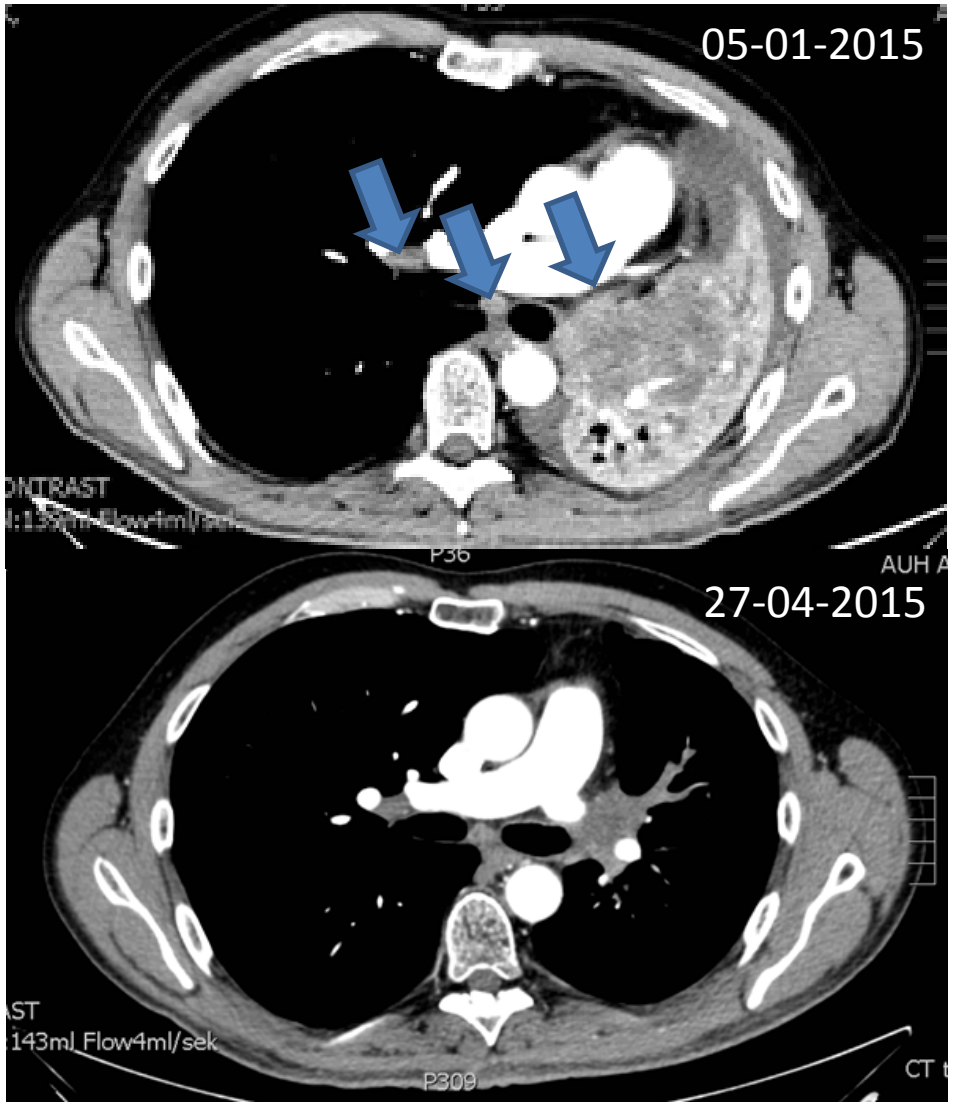


Table 4 Patients with concerning SUVs without evidence of failure

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

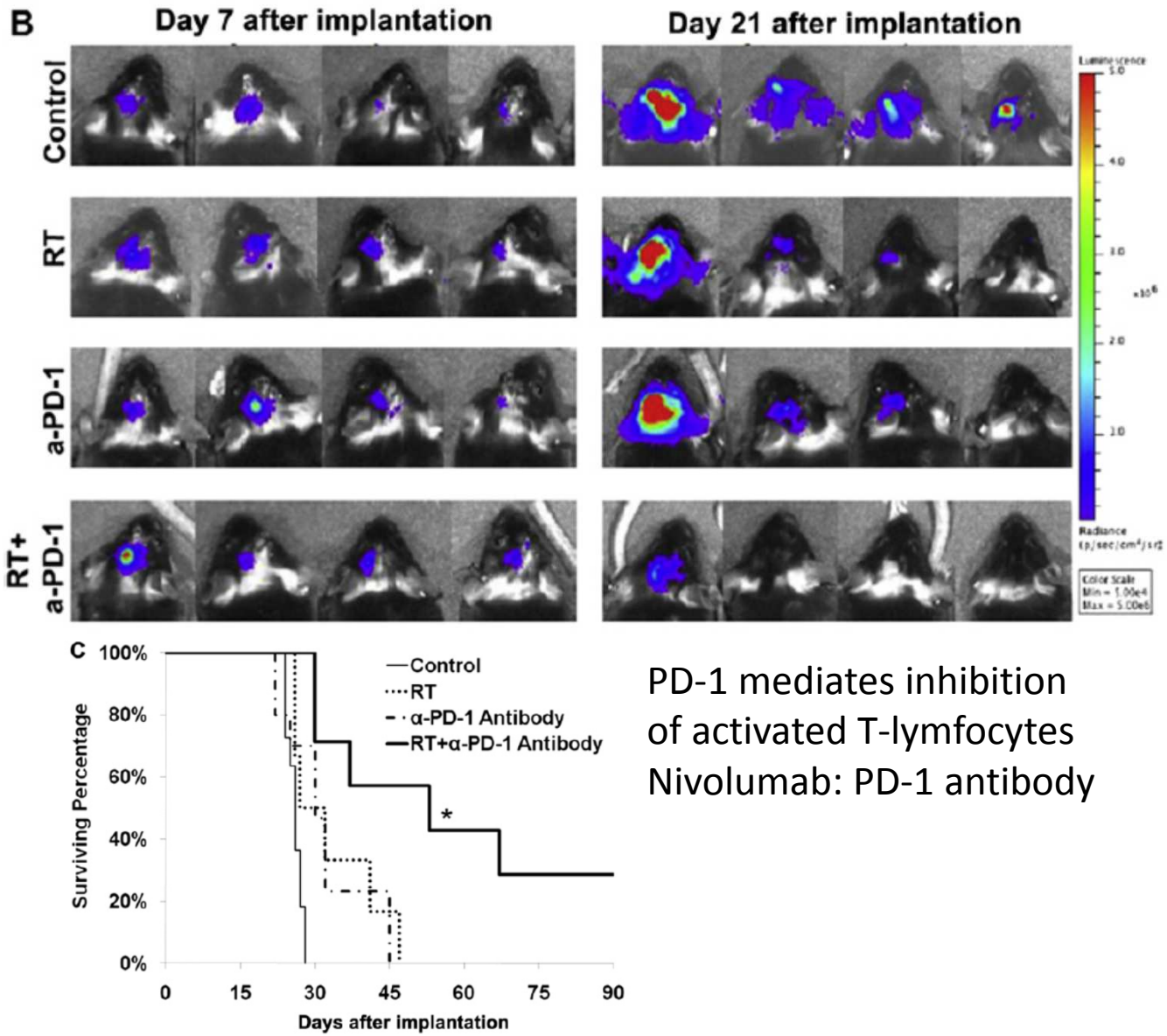
A recent case from AUH



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

PD-1 antibody and radiation

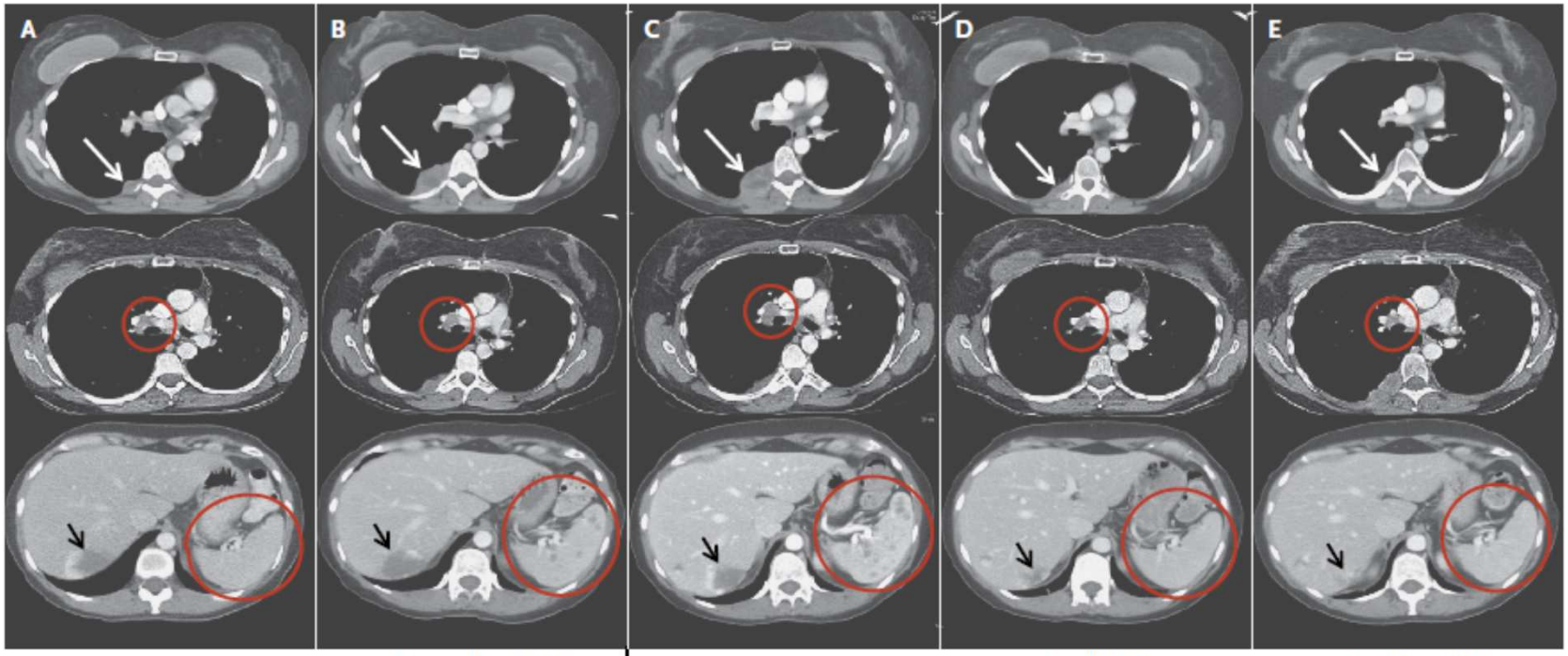


PD-1 mediates inhibition
of activated T-lymfocytes
Nivolumab: PD-1 antibody

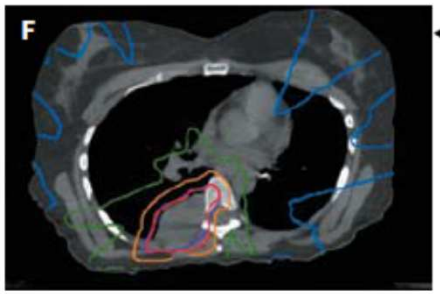
Zeng et al. IJROBP 2012; 86(2): 343

- Hettich and Niedermann
- OC-0487 estro forum
- Experimental studies on immune markers after hypofractionation 2x12 Gy

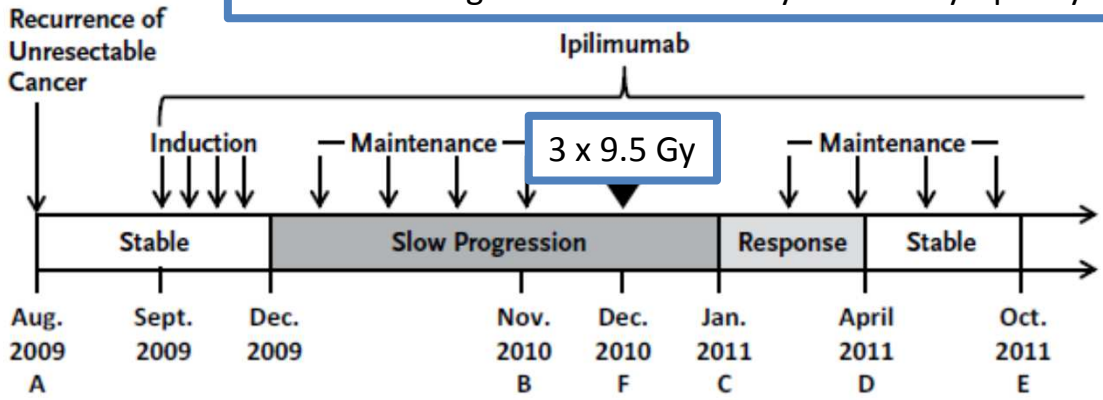
Abscopal immune effects



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



December 2010



Postow et al:
NEJM 2012;366:925

Publications on abscopal effects

W 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/o 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

How often?

- 1 in 10.000
- In most cases

Effect of immune stimulation?

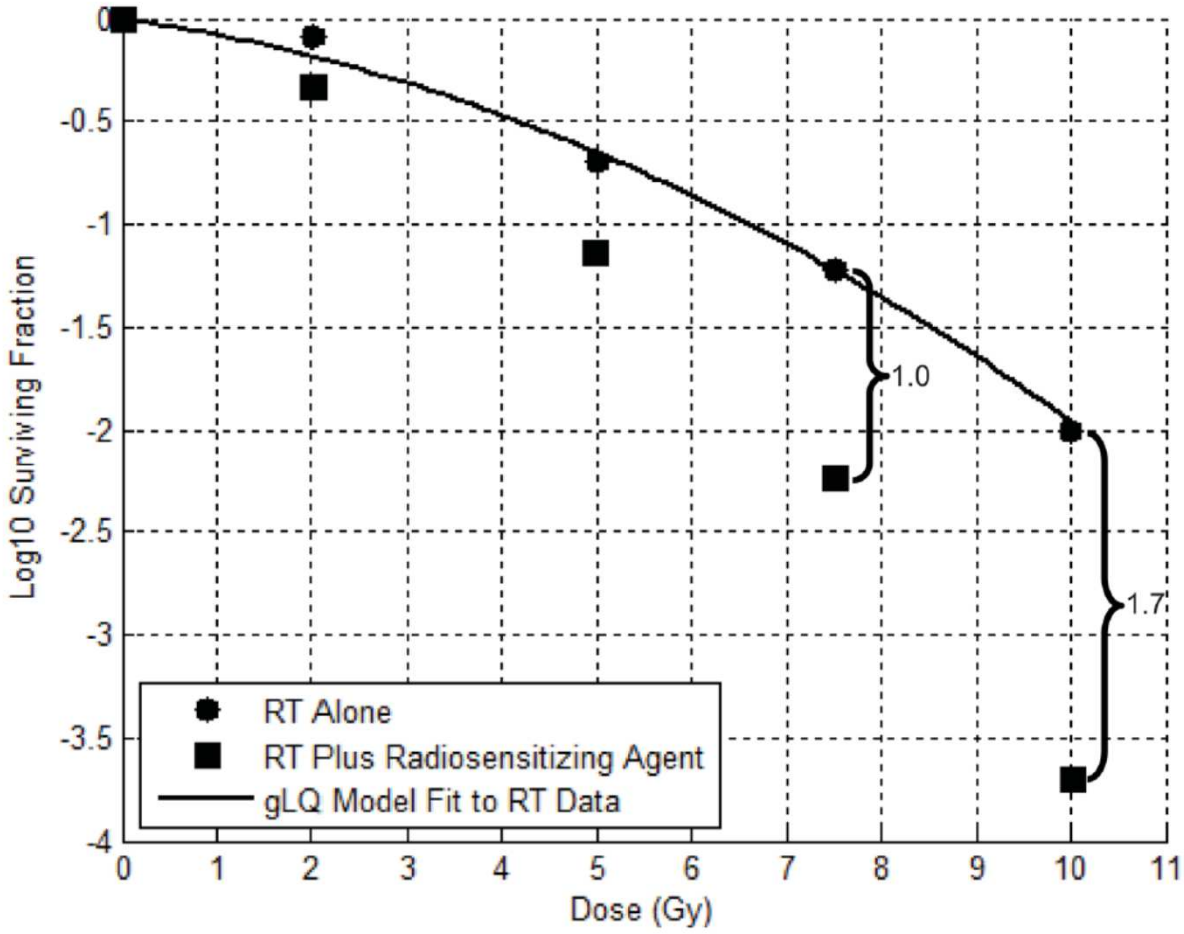
- Only works with immune stimulating agents
- Also works without immune stimulating agents

Effect of dose per fraction?

- Only works with doses greater than 8 Gy
- Also works with normofractionation?

Concommittant chemotherapy

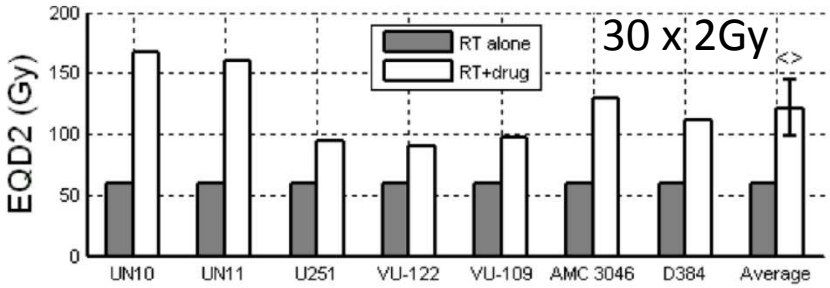
Radiosensitizing chemotherapy

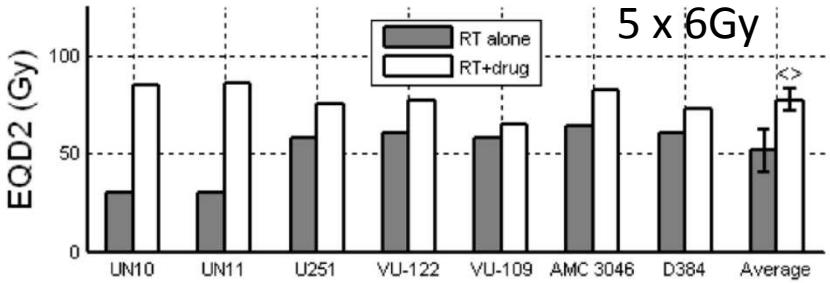


Ohri et al: IJROBP 2012; 83 (1): 385

Radiosensitizing chemotherapy

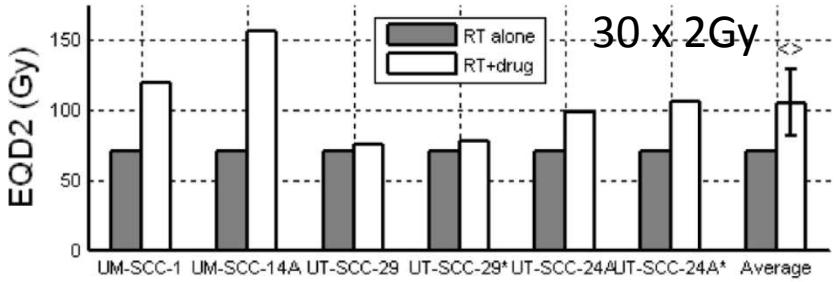
GBM

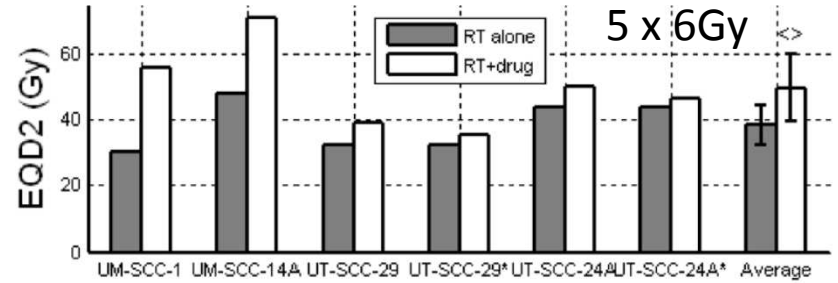




RT +/- concurrent temozolomide

HNC

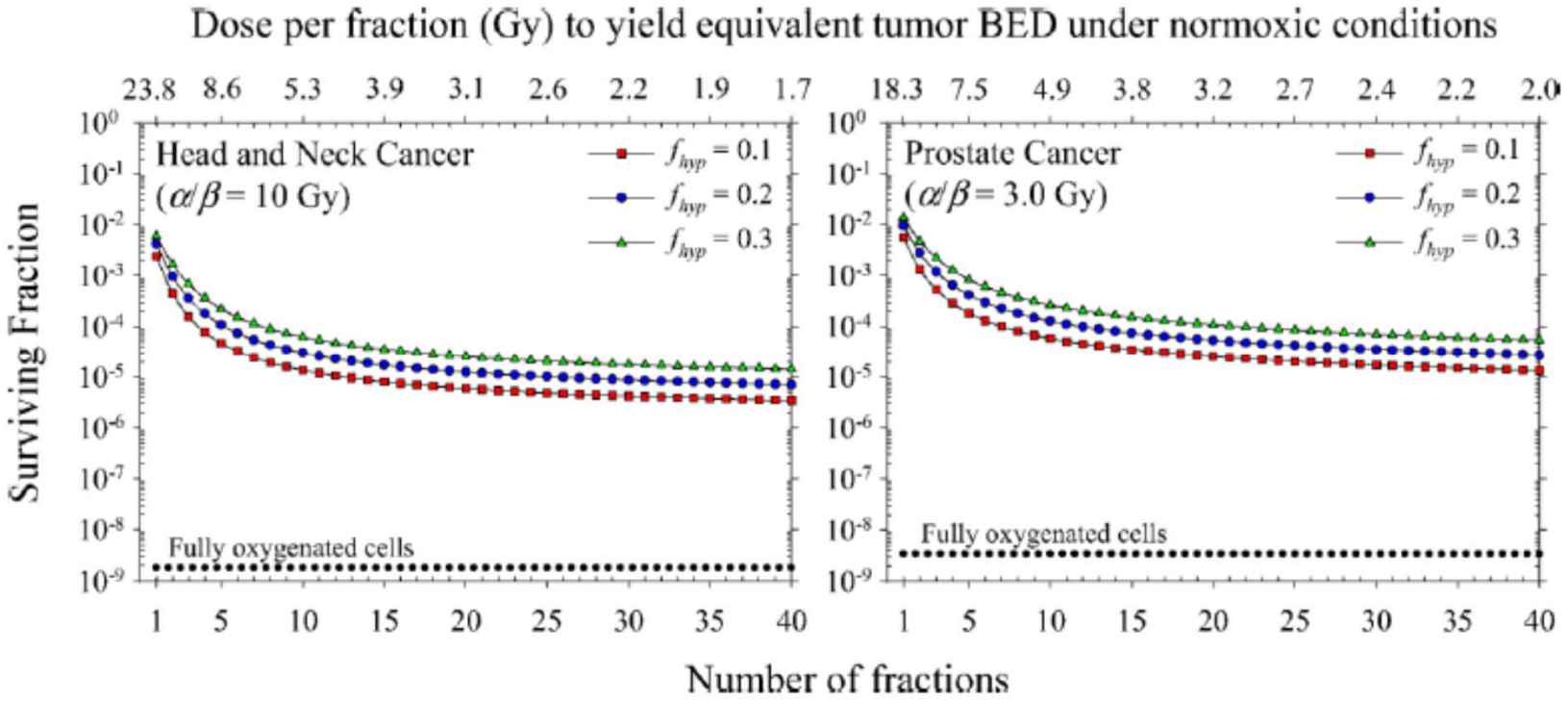




RT +/- concurrent cisplatin

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

The effect of hypoxia is dependent of the number of fractions



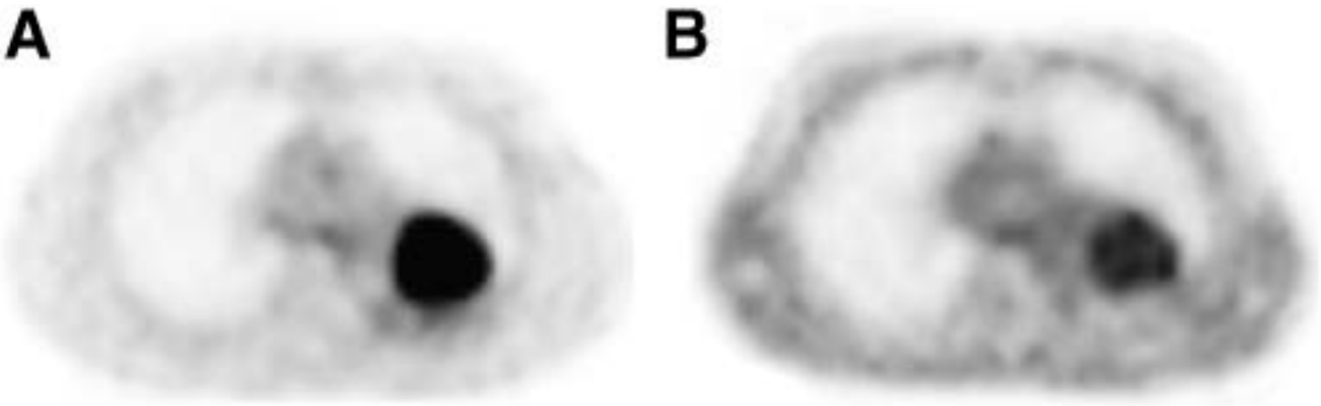
Carlson et al. IJROBP 2011; 79: 1188

FAZA-PET in lung cancer

Hypoxia

11/17 patients with hypoxic tumors

FDG-PET F-MISO-PET



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

Conclusions

Based on experimental observations:

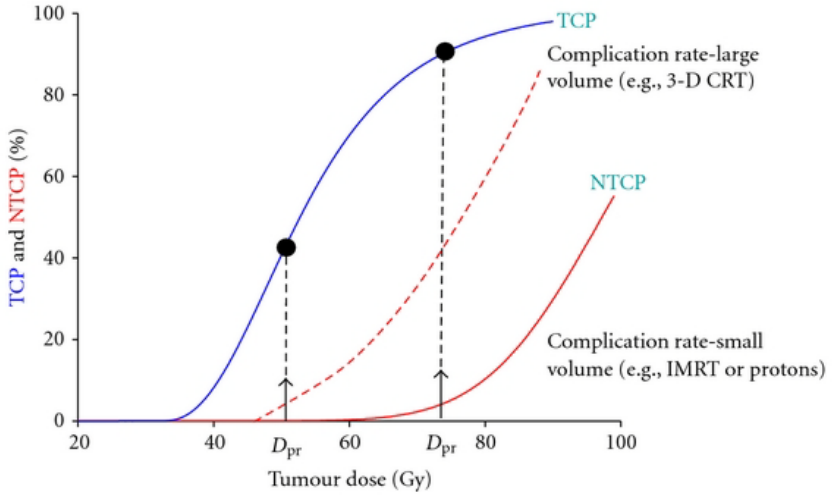
- Traditional models for cell survival after radiation may overestimate the cell kill (especially with high dose per fraction)
- In addition to direct radiation cell kill, there may be indirect cell kill related to
  - Vascular effects and
  - Immune effects
- Chemotherapy may enhance SBRT induced cell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

AARHUS UNIVERSITY

CIRRO

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

Dose effect modeling in SBRT



Dose effect modeling

Dose effect modeling:

- Multi-step process

Question 1

What explains excellent local control rates > 90% in SBRT for stage I NSCLC?

1. **Endothelial damage**
2. **Vascular damage**
3. **Immune effects**
4. **The damn high irradiation dose**

Question 2

The linear quadratic model is reliable for conversion of SBRT doses into 2Gy-equivalent doses?

1. **Only for modeling of local tumor control?**
2. **In fractionated SBRT only until a SFD of 10Gy?**
3. **In fractionated SBRT w/o an upper SFD limit?**
4. **Only for modeling of normal complication probability modeling?**

Question 3

Which statement is <u>wrong</u>:

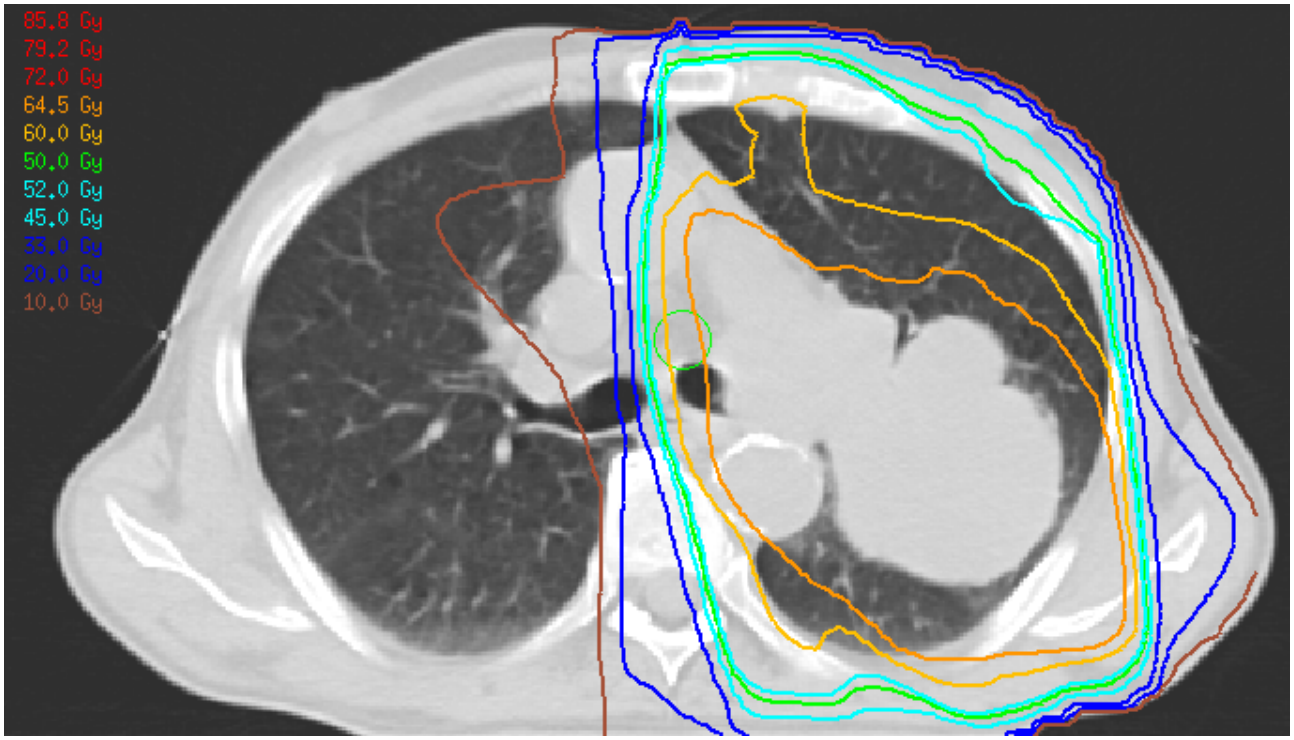
1. **Lung metastases require similar doses to achieve local tumor control compared to primary NSCLC**
2. **Durable local control may not be necessary in all patients treated with SBRT for metastatic diease**
3. **The PTV encomassing dose is sufficient to describe the SBRT treatment dose**
4. **Breathing motion has only small effects on the delivered dose in lung SBRT**

Outcome of lung SBRT

	# of fractions	Single fraction dose	Dose perscription	Local control
Nagata 2005	4	12Gy	@ isocenter	**98%**
Baumann 2009 Lindberg 2015	3	15Gy	@ 65%	**92%** @ 3 a **79%** @ **5 a**
Fakiris 2009	3	20-22Gy	@ 80%	**88%** @ 3 a
Ricardi 2010	3	15Gy	@ 80%	**88%** @ 3 a
Bral 2010	3-4	13 – 20Gy		**84%** @ 2a
Timmerman 2010	3	18Gy	@ 80%	**98%** @ 3a

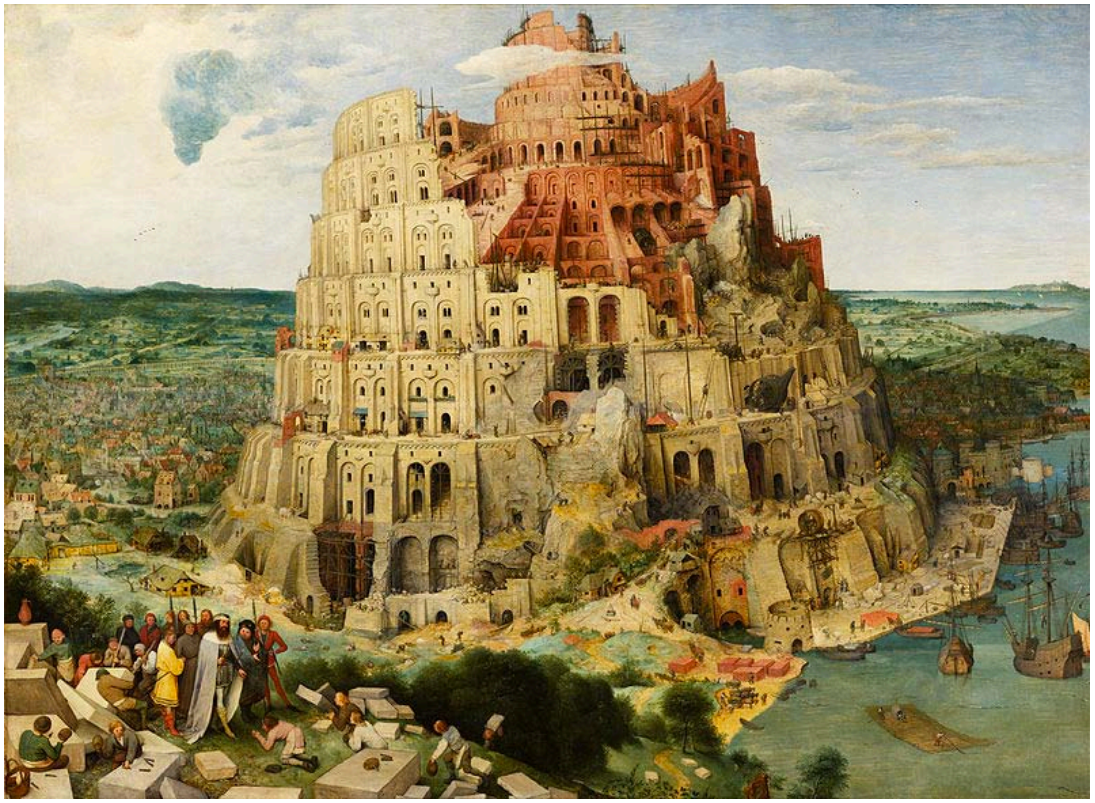
➢ Huge differences in single fraction dose & total dose

Dose in lung 3D-CRT



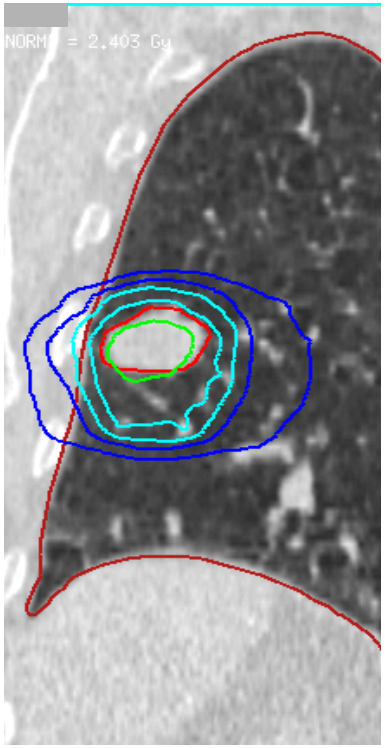
We had a common language: IRCU

Dose in lung SBRT



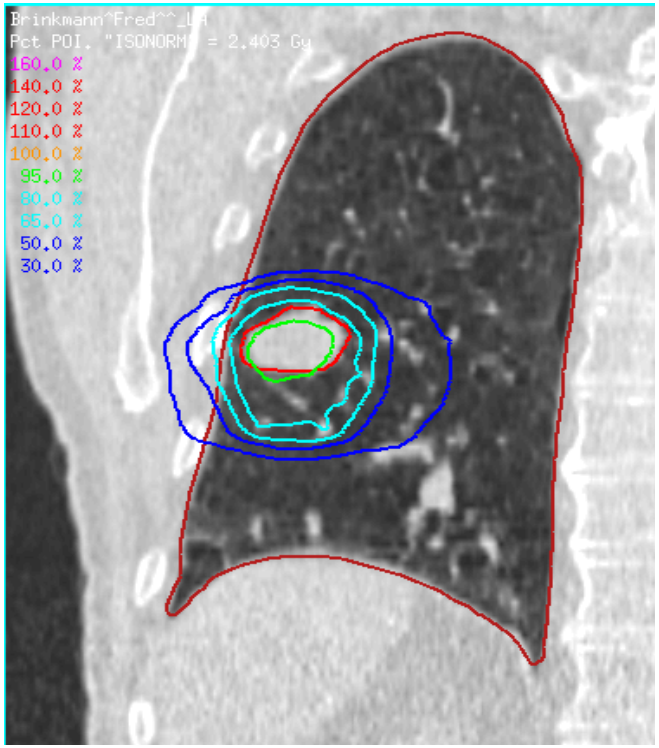
We had a common language before, but now?

Dose in lung SBRT – what dose ?

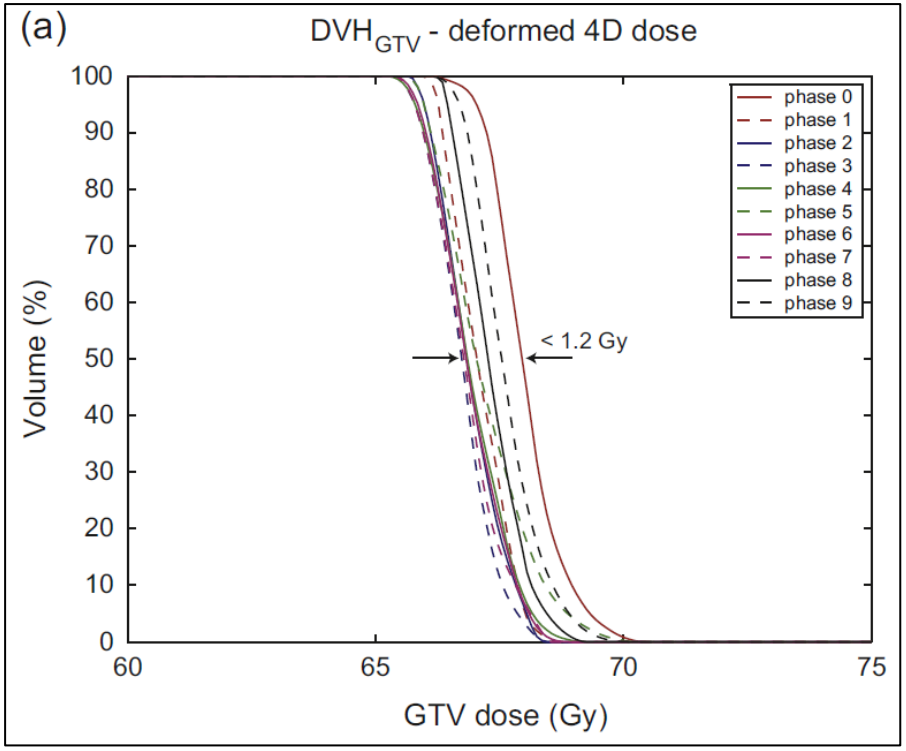


- Differences in dose inhomogeneity
- Moving tumors in inhomogeneous dose distribution
- Dose to PTV / CTV / GTV
- Accuracy of dose calculation algorithms
- Physical doses in context of variable hypo-fractionation
- Validity of LQ model for BED calculation
- No standardized dose reporting

Dose in lung SBRT: prescription and reporting



Mexner IJROBP 2009



- Limited variation in **GTV dose** between all breathing phases, even end-inhalation and end-exhalation

Dose in lung SBRT: prescription and reporting

Dose BED	PTV Min. dose	PTV Max. dose
Prescription 80%	100	153

Guckenberger IJROBP 2007

- PTV max. dose (isocentric) closely correlated with effective GTV dose

Dose in lung SBRT: prescription and reporting

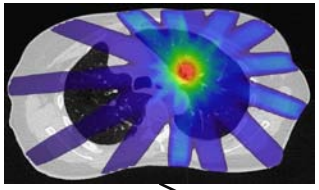
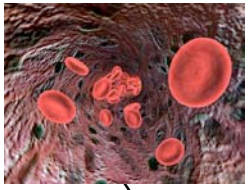
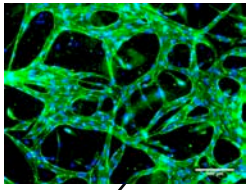
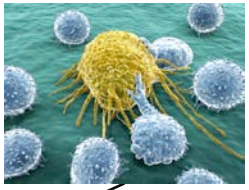
	PTV Min. dose - BED
Prescription 80%	100
Prescription 65%	100

Guckenberger IJROBP 2007

- Huge influence of PTV dose inhomogeneity on effective GTV dose

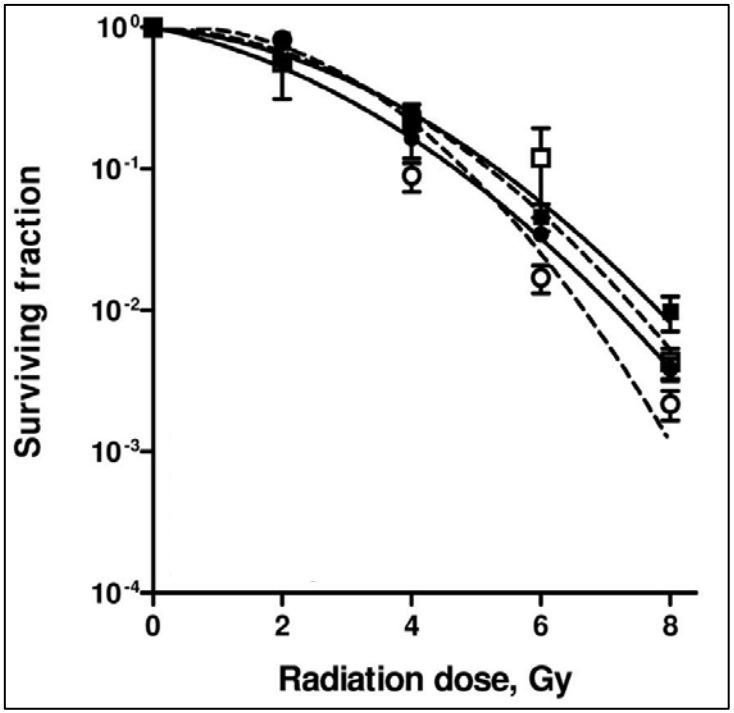
Biology of Stereotactic Body radiotherapy

Ablative RT dose	Endothelial damage	Anti-vascular effect	Immune effect

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

The linear quadratic model



$$SF = e^{-(\alpha D + \beta D2)}$$

$$BED = nD\,(1 + (D/(\alpha/\beta)))$$

- α: cell kill per Gy of the initial linear component (on a log-linear plot)
- β: cell kill per Gy^2 of the quadratic component of the survival curve

The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery

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Colin G. Orton, Ph.D., Moderator

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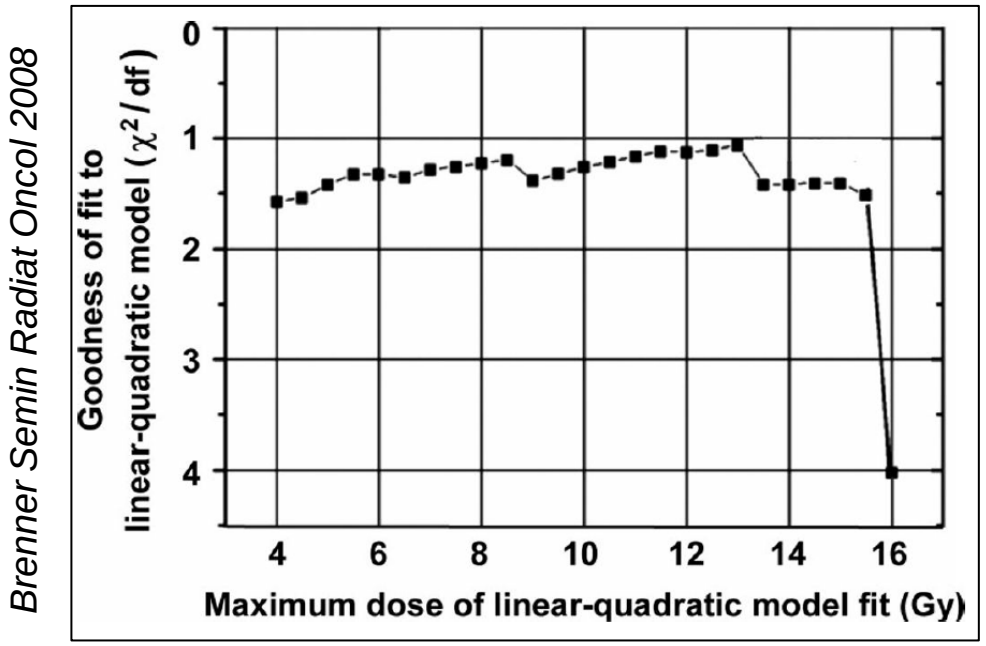
Semin Radiat Oncol. 2008 October ; 18(4): 234–239. doi:10.1016/j.semradonc.2008.04.004.

Point: The linear-quadratic model is an appropriate methodology for determining iso-effective doses at large doses per fraction

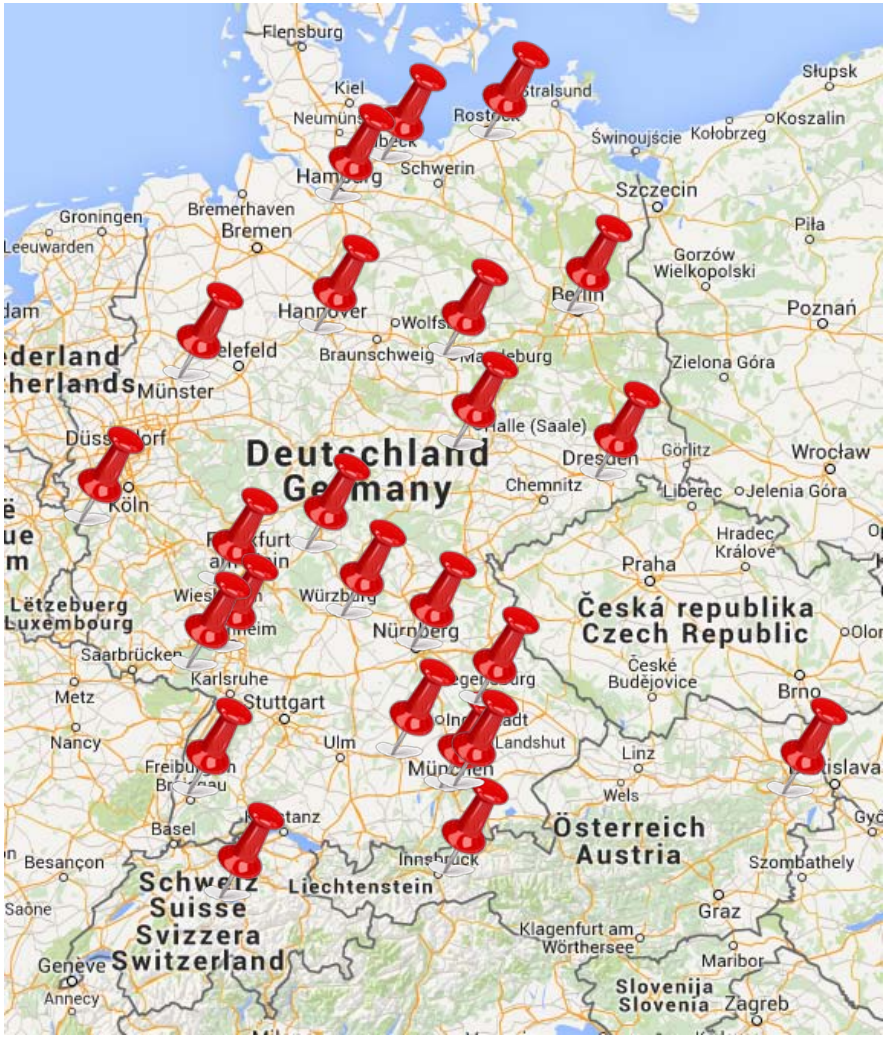
David J. Brenner, Ph.D., D.Sc.
From the Center for Radiological Research, Columbia University Medical Center, 630 West 168th Street, New York, NY.

The linear quadratic model: use for extreme hypofractionation



- Brenner: „*reasonably well validated, experimentally and theoretically, up to about 10 Gy / fraction, and would be reasonable for use up to about 18 Gy per fraction*"

Dose response in lung SBRT



Study Design

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

Study inclusion criteria

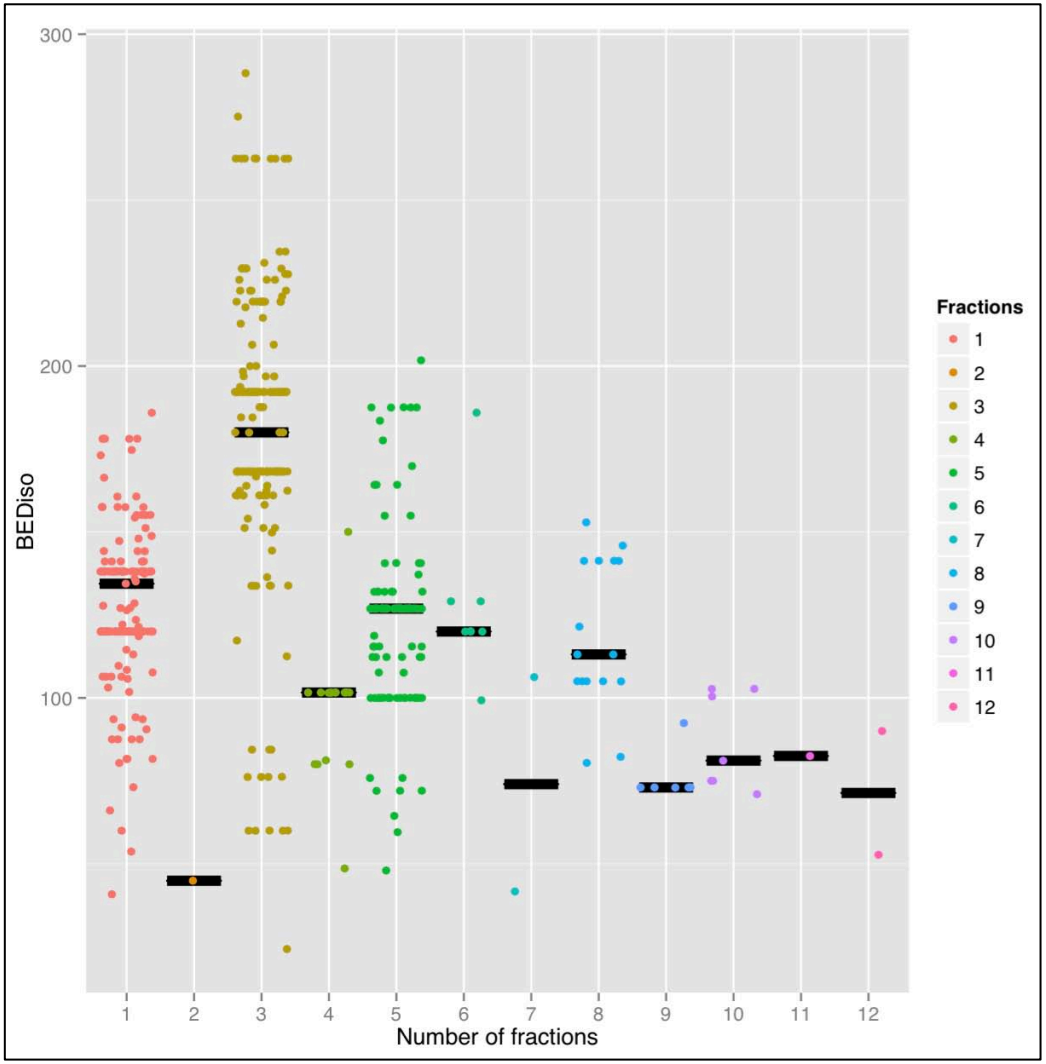
- Minimum follow-up 6 months
- Complete physical planning data

DEGRO AG Stereotactic Radiotherapy

UniversityHospital Zurich

ESTRO

Variability in treatment doses



Huge variability

- Clinical mess
- Modeling paradise

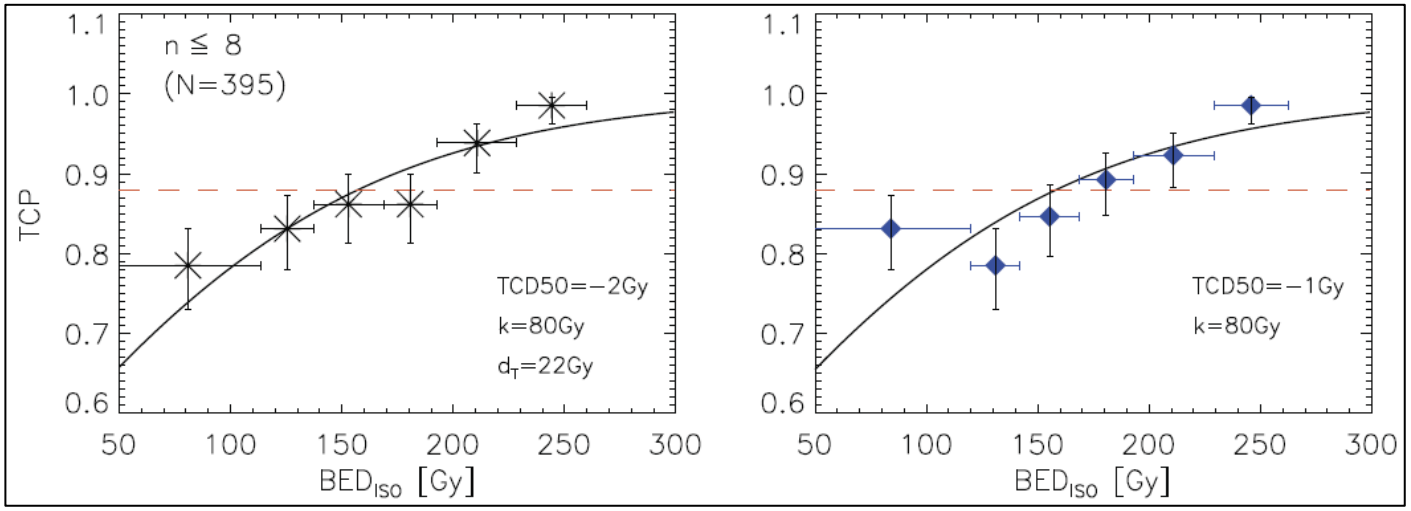
Applicability of LQ model for modeling TCP

Endpoint: local tumor control in stage I NSCLC

LQ model

LQ-L model

Guckenberger Radiother Oncol 2013



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

Applicability of LQ model for modeling TCP

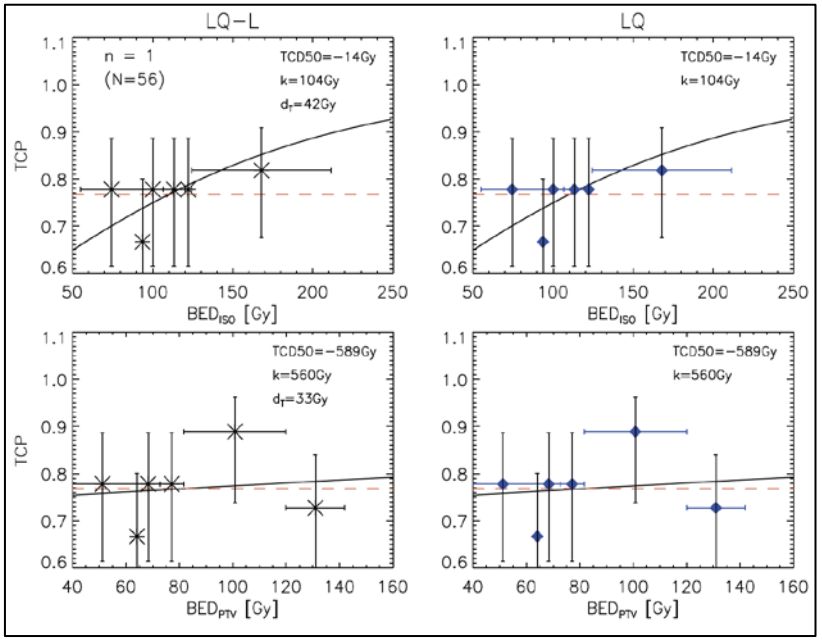
Guckenberger Radiother Oncol 2013

Single fraction radiosurgery (n=56):

PTV D_{min} 15 – 33Gy
PTV D_{max} 18 – 41Gy

No dose effect independent of

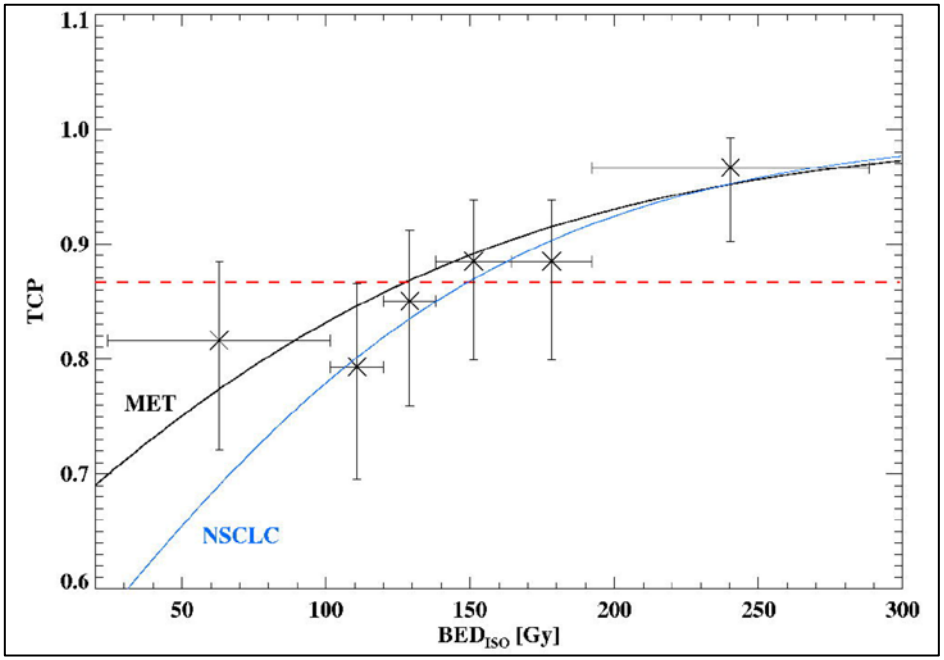
LQ vs LQL
PTV D_{min} vs PTV D_{max}



➢ Hypoxic tumor condition in 20% of the patients as explanation for lack of dose response in SF radiosurgery?

Primary NSCLC vs NSCLC mets vs lung mets

Dose effect relationship different between primay NSCLC and pul metastases?



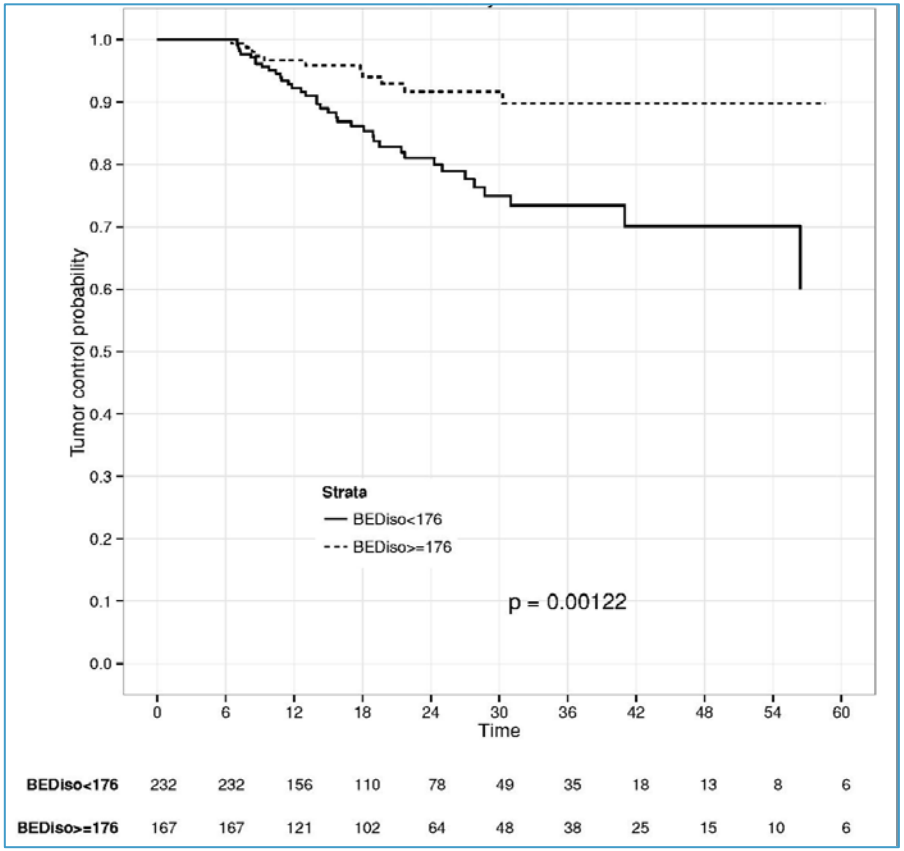
Cohort of patients	TCD90 (BED Iso)
Primary stage I NSCLC	176Gy (+45 / - 25)
NSCLC pul. Metstases	167Gy (+82 / -67)
All pul. metastases	160 (+77 / -37)

Guckenberger submitted

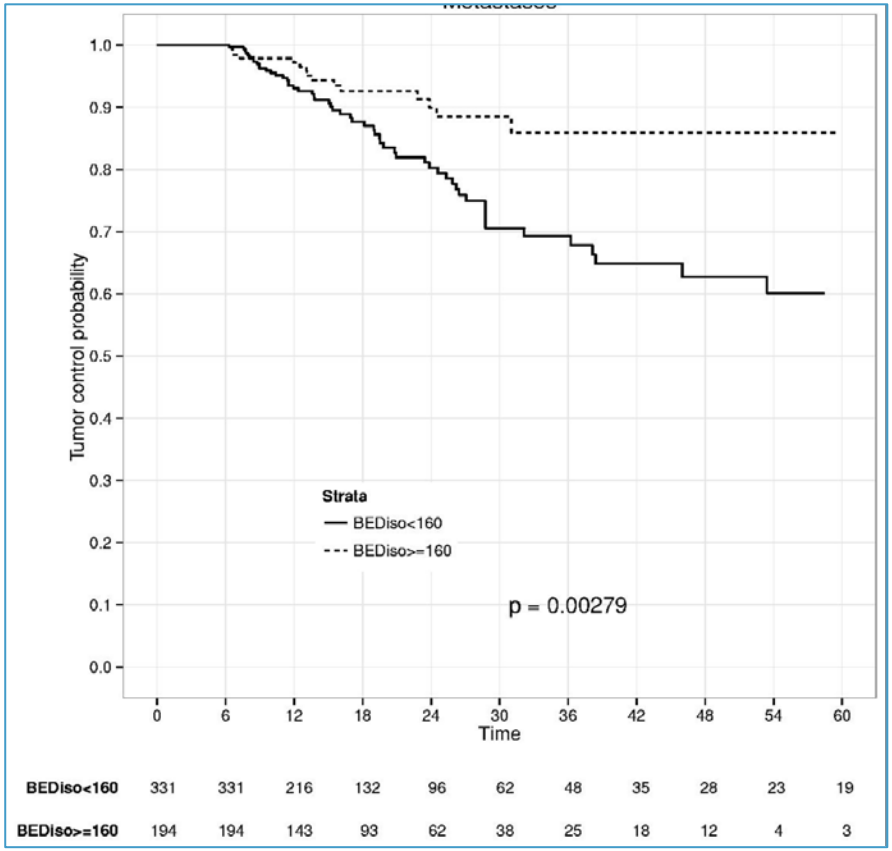
- Dose effect relationship for all patient sub-cohorts
- Radiosensitivity not significantly different between primary NSCLC, NSCLC lung metastases and all lung metastases

Primary NSCLC vs lung mets

Primary stage I NSCLC



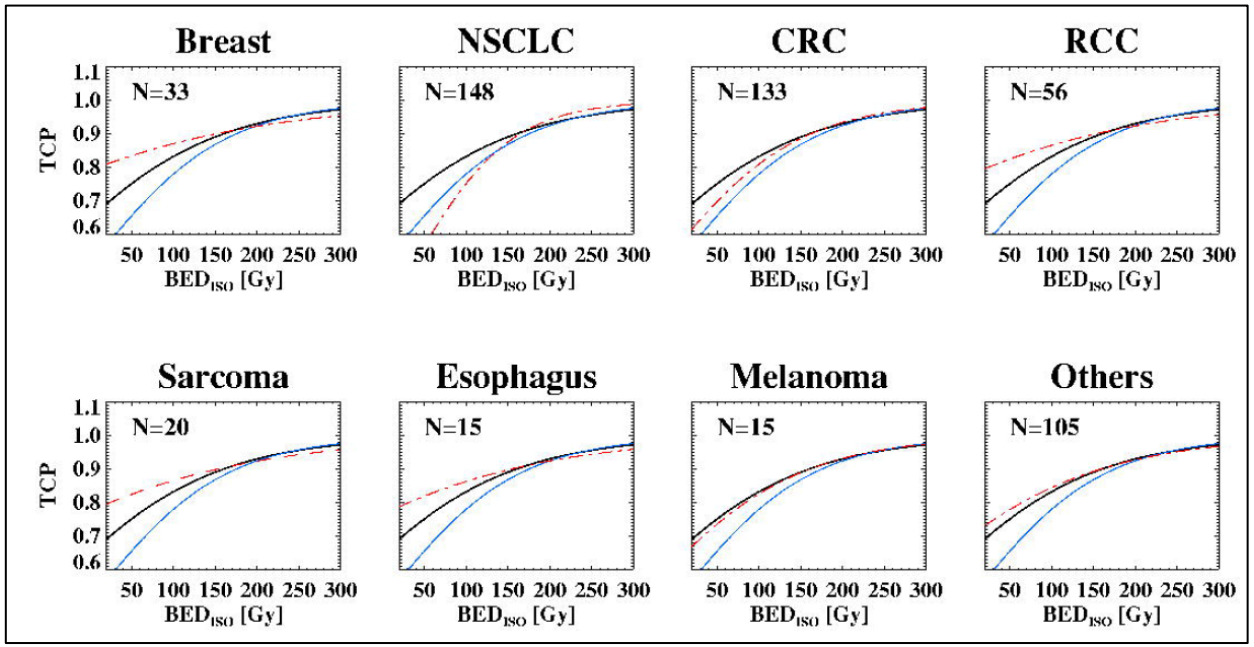
Pulmonary metastases



Guckenberger submitted

Influence of primary tumor on radiosensitivity

Dose effect relationship influenced by primary cancer site ?



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

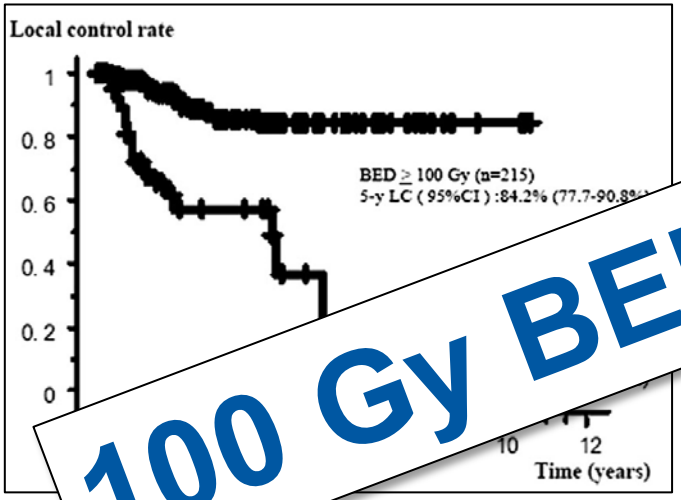
Guckenberger submitted

- Dose response models very similar and TCD90 not significantly different
- Results do not exclude different radiosensitivity in the low-dose region

The „magic“ dose

100 Gy BED

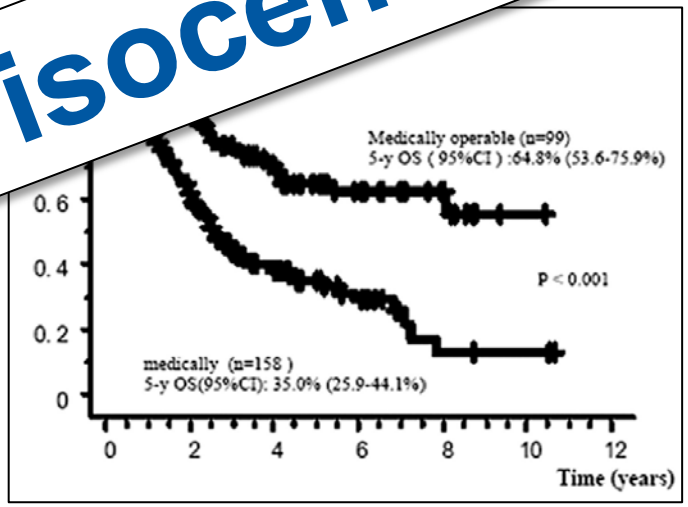
100 Gy BED at the isocenter!



Japan

tumor control

Overall survival



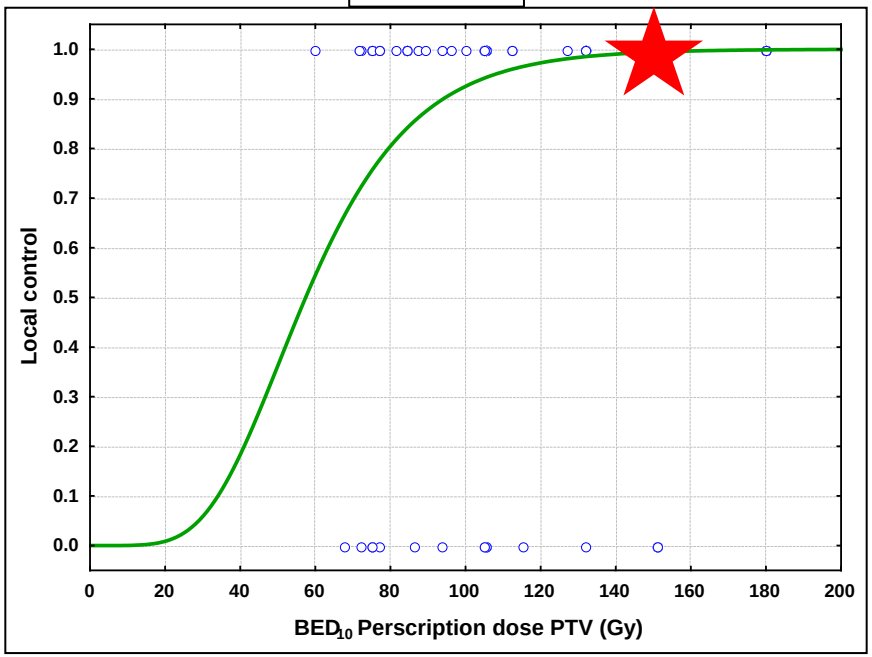
≥ [illegible]Gy BED	84%
<100Gy BED	37%

≥ 100Gy BED	65%
<100Gy BED	35%

Substantial dose effect relationship with excellent results for doses ≥ 100Gy BED

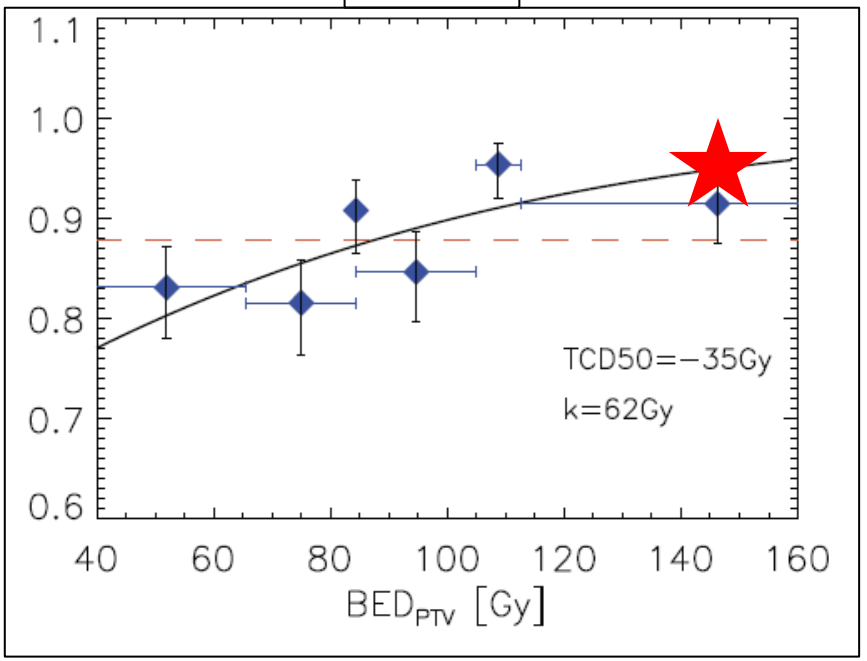
Dose effect modelling – individual patient data

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

Survival after SBRT in relationship to dose

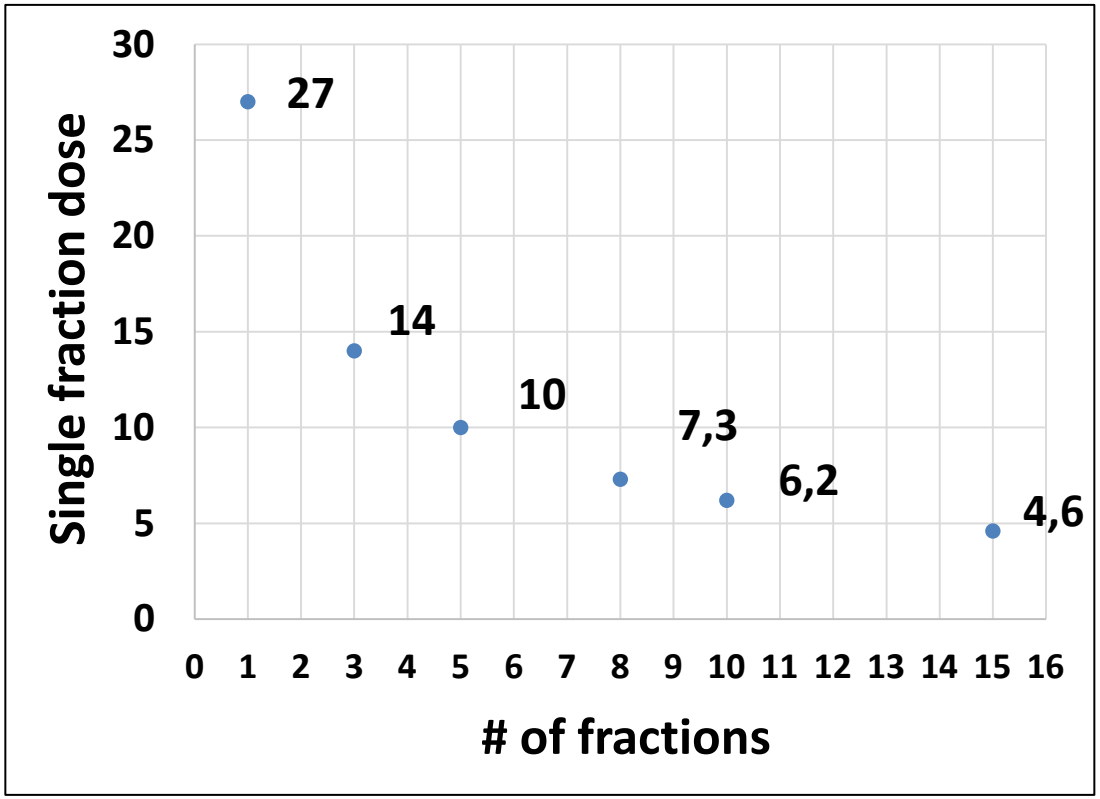
Dose group	BED
Low	<83.2Gy
Medium	83.2 – 106Gy
Medium – high	106-146Gy
High	>146Gy

Zhang IJROBP 2011

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

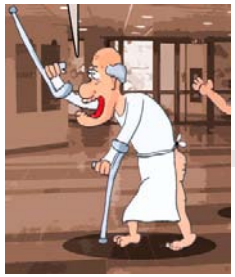
Dose required / sufficient to achieve 90% TCP

100Gy BED



➢ >100Gy BED delivered in 3 – 8 fractions

No treatment



SBRT

Sublobar resection

Lobar resection

Competing risk of death

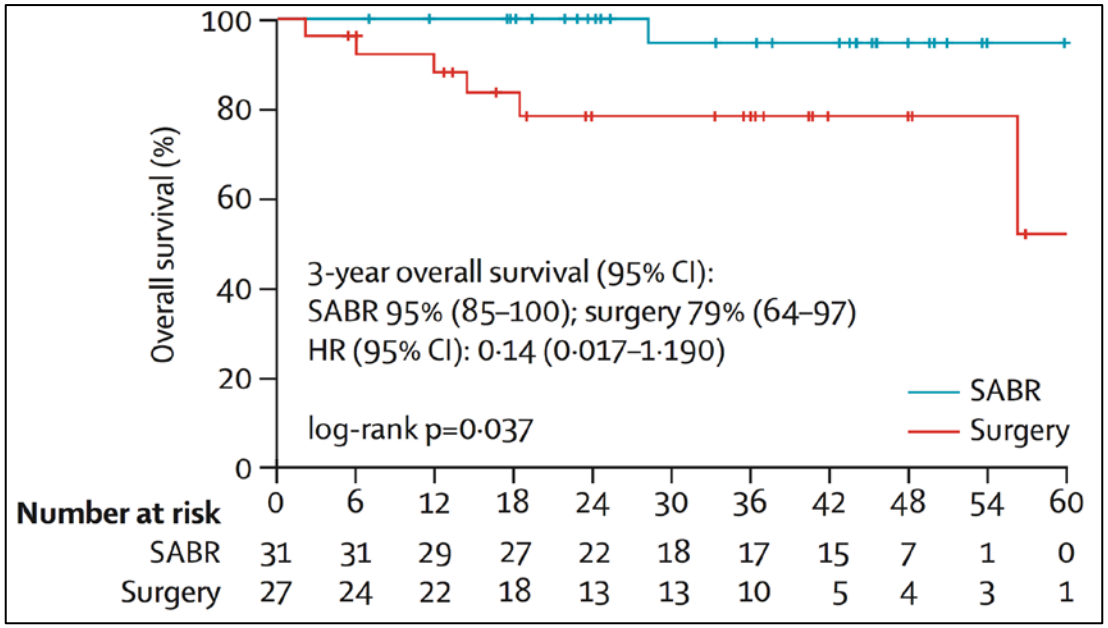
Vulnerability

Relevance of long term LC

Intensity of radiotherapy

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



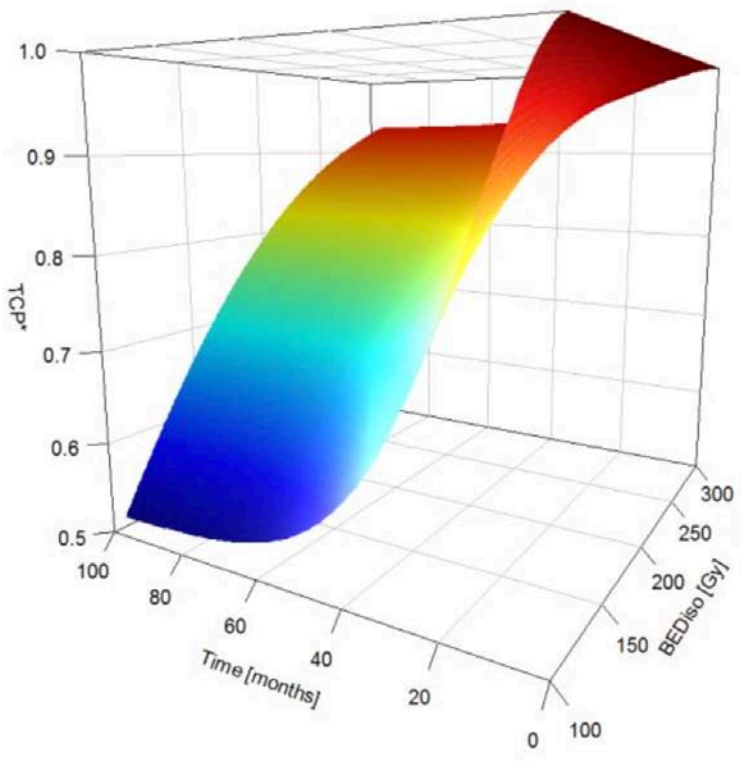
n=31

n=27

➢ Long-term survivors are (hopefully) ahead

Dose – response and time

Klement submitted



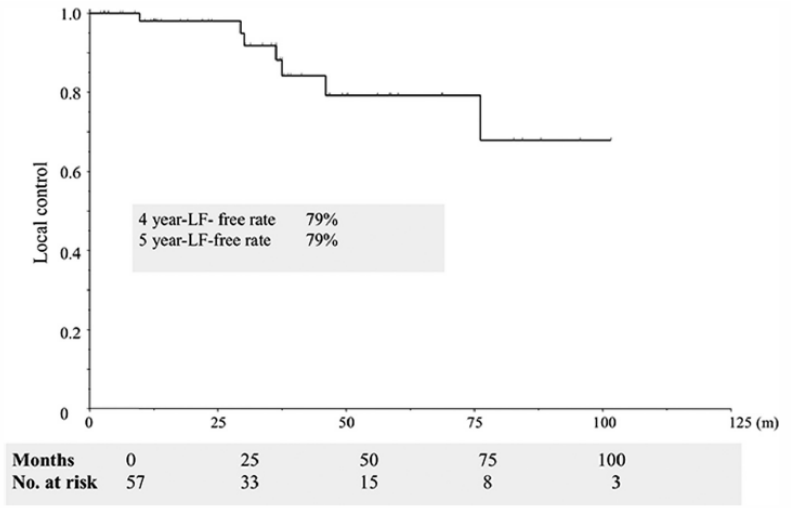
Cure rate model:
One model including

- Dose
- Time of event
- Dose

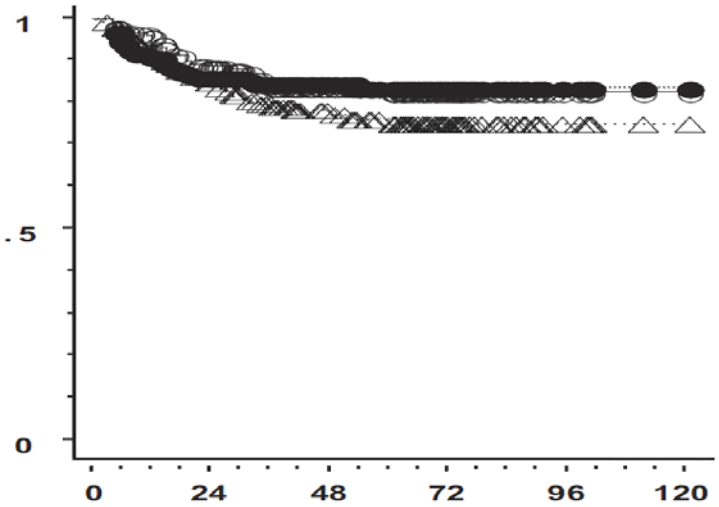
➢ Adaptation of radiotherapy based on clinical relevance of achieving freedom from local tumor progression

Late recurrences in stage I NSCLC

Swedish phase II trial:
N=57
Median FU 41.5 months
3 x 15Gy @ 67%



Japanese prospective study:
N=180
Median FU 52.5 months
4 x 12Gy @ isocenter



➢ Large majority of recurrences within 3 (max. 5) years

Dose de-escalation

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 of 20.4 months in Platinum-resistant stage NSCLC DESPITE lower irradiation doses

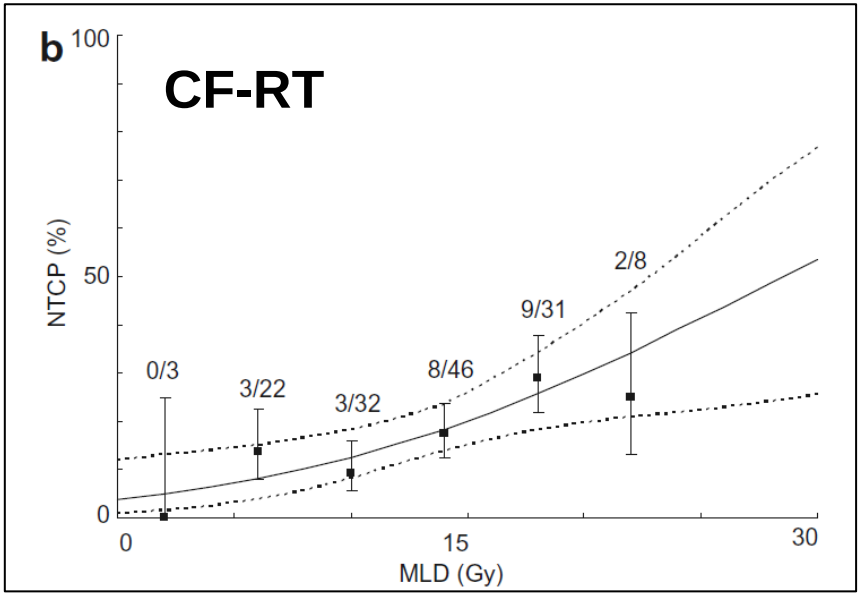
Tolerance of OARs

Organ at risk	1 fx (RTOG 0915)	3 fx (RTOG 0618 / 1021)	5 fx (RTOG 0815)	8 fx Haasbeck et al. 2011)
Trachea and large bronchus	D_{max} 20.2 Gy	D_{max} 30 Gy	D_{max} 105 % * 18 Gy < 5cc **	D_{max} 44 Gy ---
Heart	D_{max} 22 Gy 16 Gy < 15cc	D_{max} 30 Gy ---	D_{max} 105% * 32 Gy < 15cc	---
Esophagus	D_{max} 15.4 Gy 11.9 Gy < 5cc	D_{max} 25.2 Gy 17.7 G< 5cc	D_{max} 105% * 27.5 Gy < 5cc **	D_{max} 40 Gy ---
Brachial plexus	D_{max} 17.5 Gy 14 Gy < 3cc	D_{max} 24 Gy 20.4 Gy < 3cc	D_{max} 32 Gy 30 Gy < 3cc	D_{max} 36 Gy ---
Chest wall	D_{max} 30 Gy 22 Gy < 1cc	--- 30 Gy < 30cc 60 Gy < 3 cc	--- 30 Gy < 30cc 60 Gy < 3 cc	---
Spinal cord	D_{max} 14 Gy 10 Gy < 0.35cc	D_{max} 18 Gy (RTOG 0236)	D_{max} 30 Gy 22.5 Gy <0.25cc	---

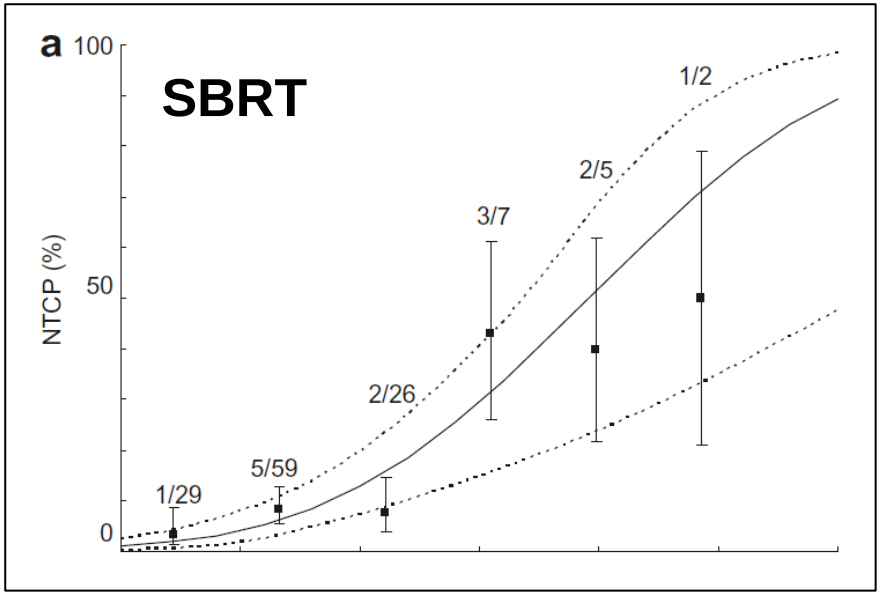
Guckenberger Strahlentherapie 2013

- Extrapolation from experiences in conventionally fractionated RT
- Lack of validation

Dose effect relationship for OARs: Radiation induced pneumonitis



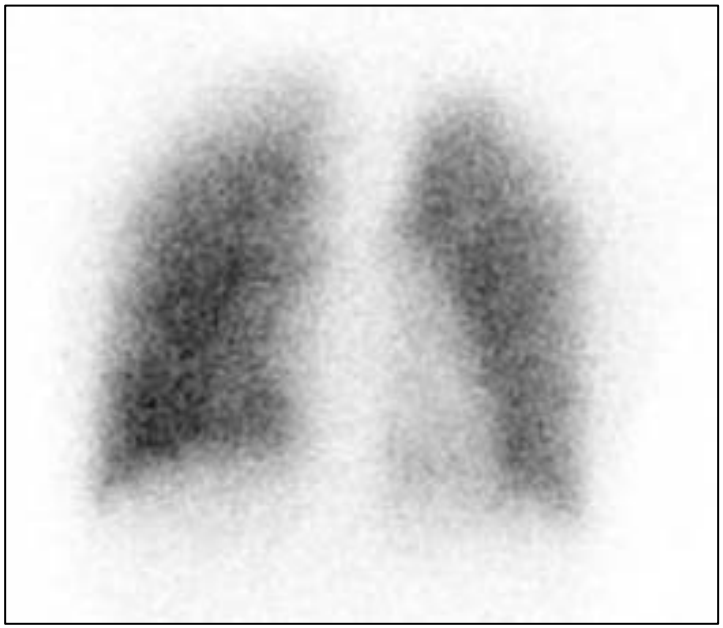
Borst Radiother Oncol 2009

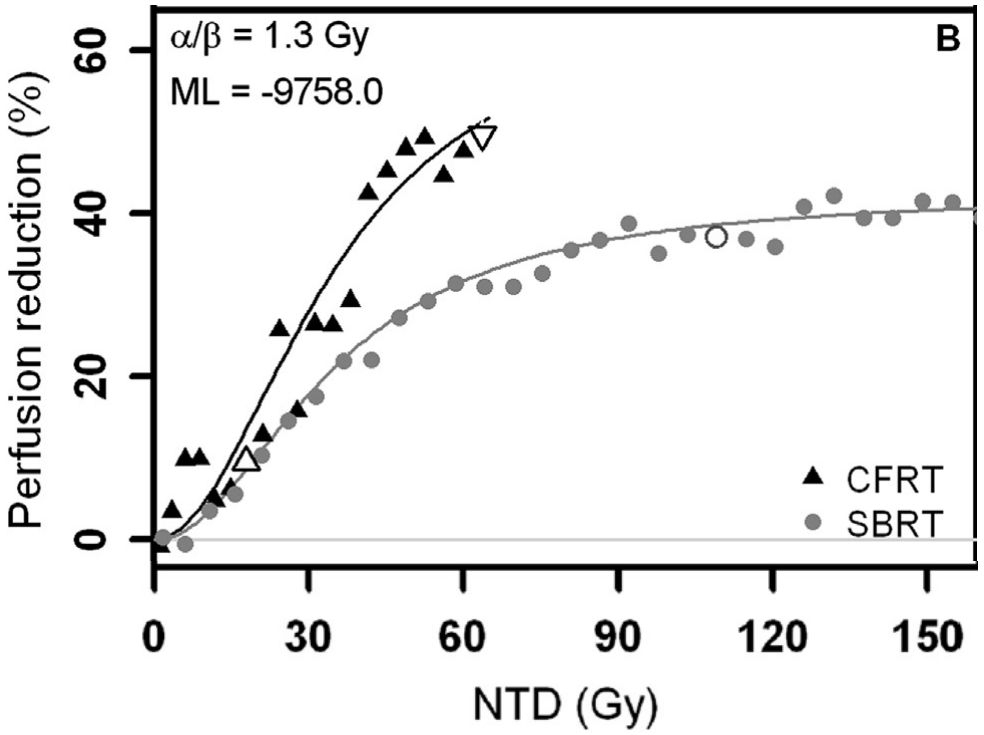


After correction for differences in SFD using the LQ model:

- No difference in dose-effect relationship between CF-RT and SBRT

Dose effect relationship for OARs: Lung perfusion





Lung perfusion changes not different between SBRT and CF-RT

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 / 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

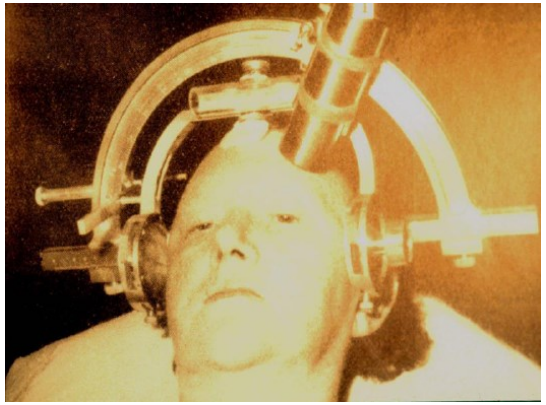
Learning Objectives

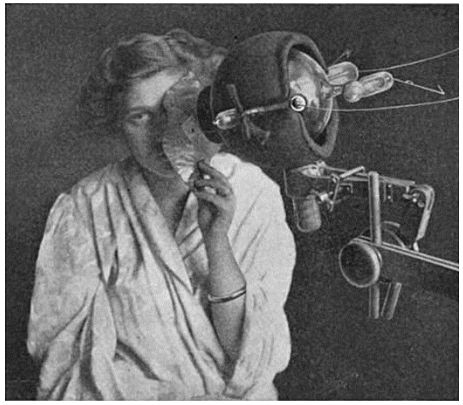
- **To give an overview of errors and uncertainties in stereotactic body radiotherapy**
  - Details on the various errors and uncertainties will be covered in separate lectures

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 …"

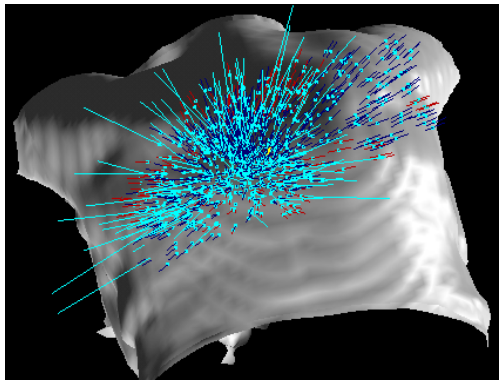


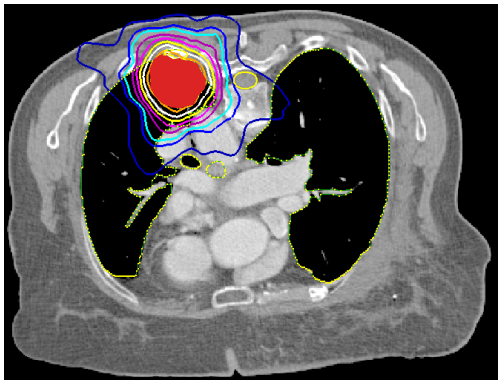


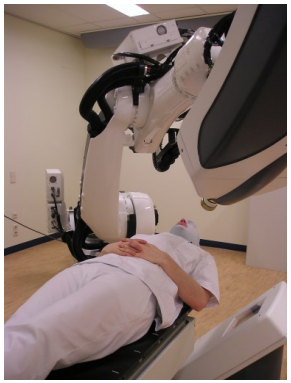
Erasmus MC

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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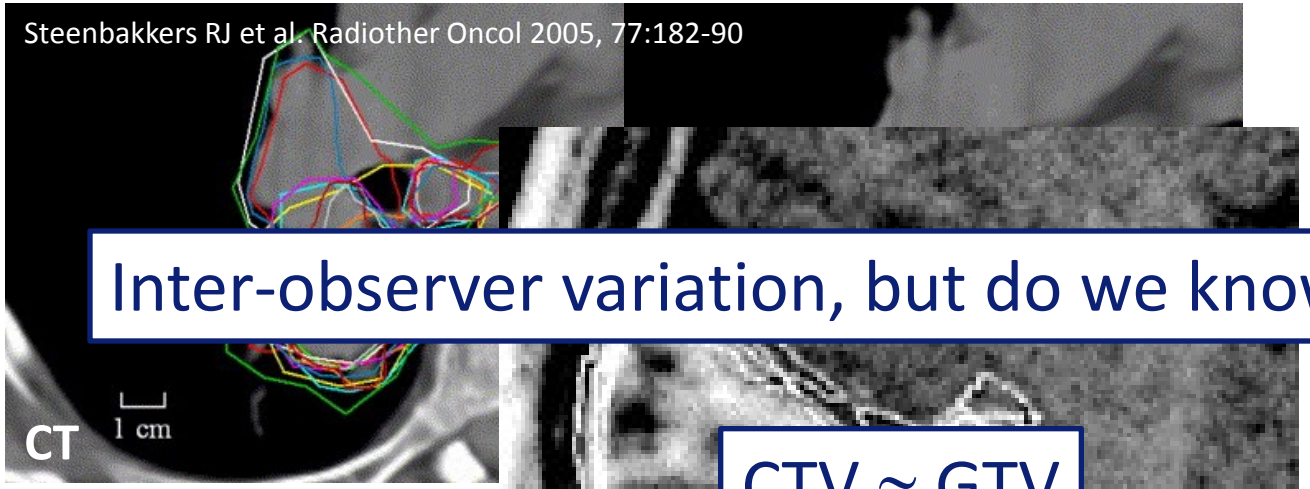
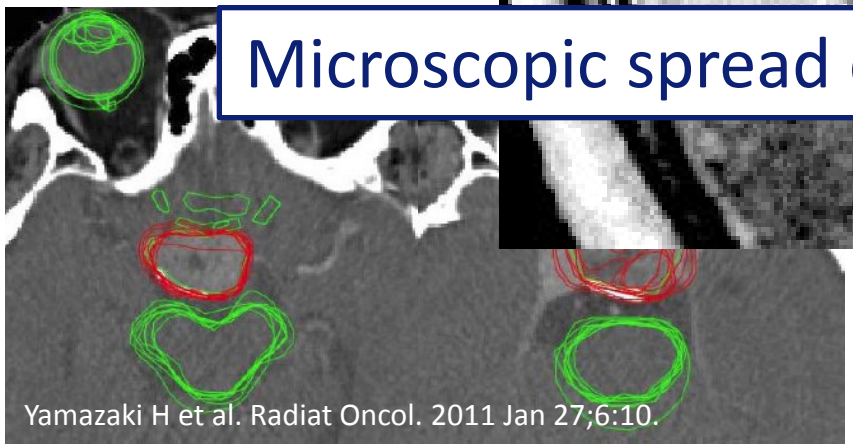
Contouring the Tumor

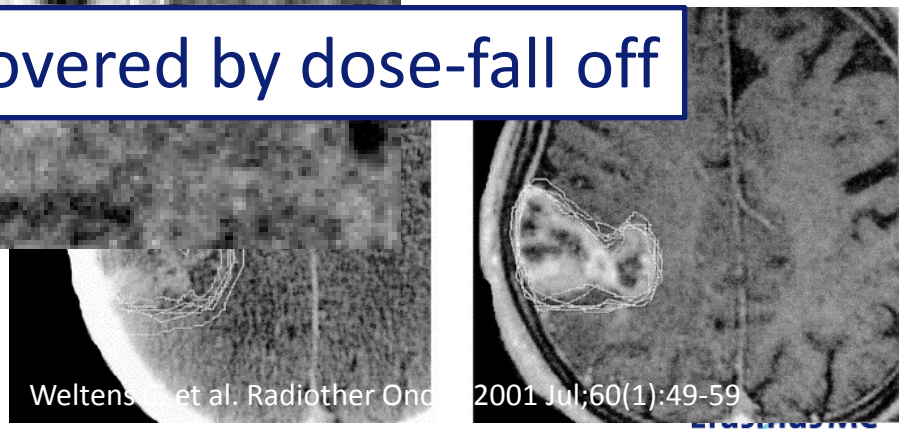


Inter-observer variation, but do we know the truth?

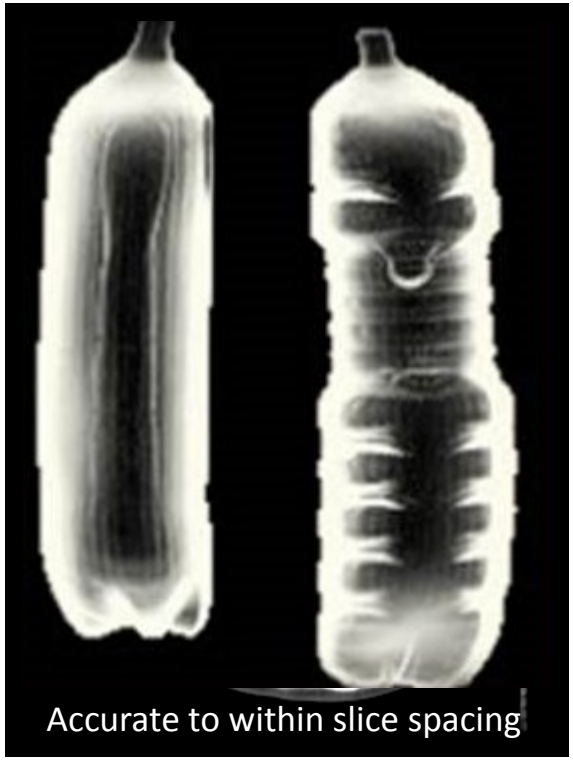
CTV ≈ GTV

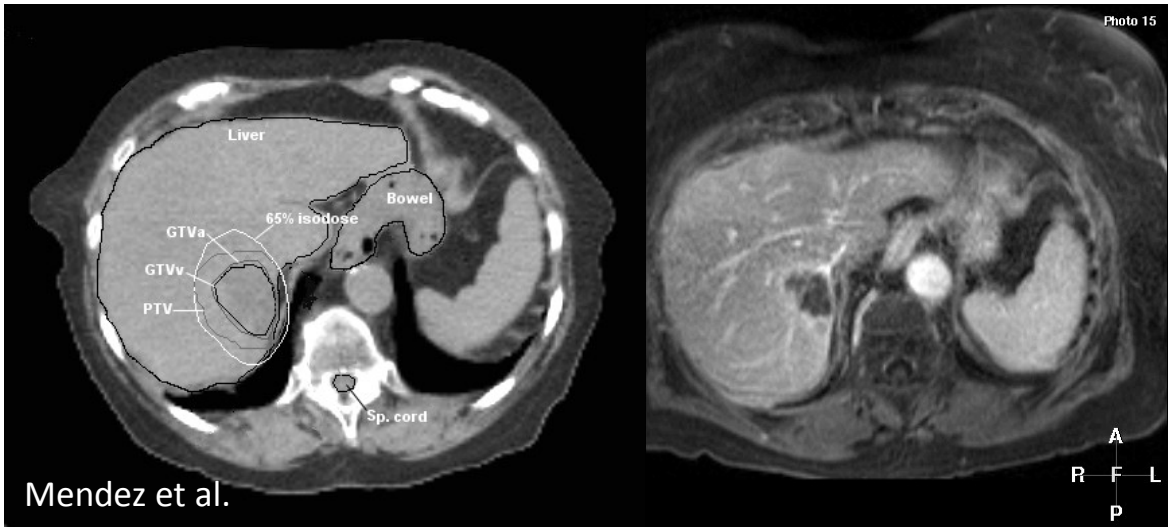
Microscopic spread covered by dose-fall off

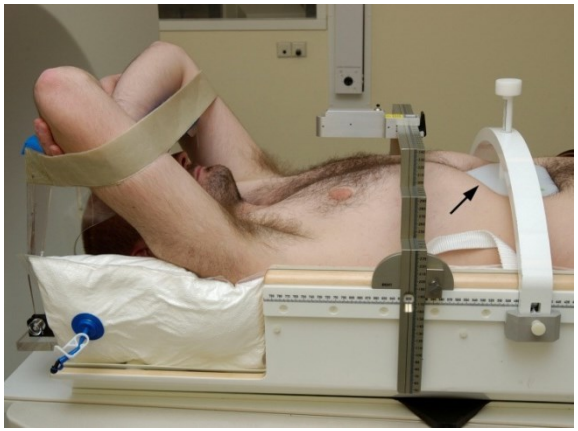




Multimodality Imaging and Registration







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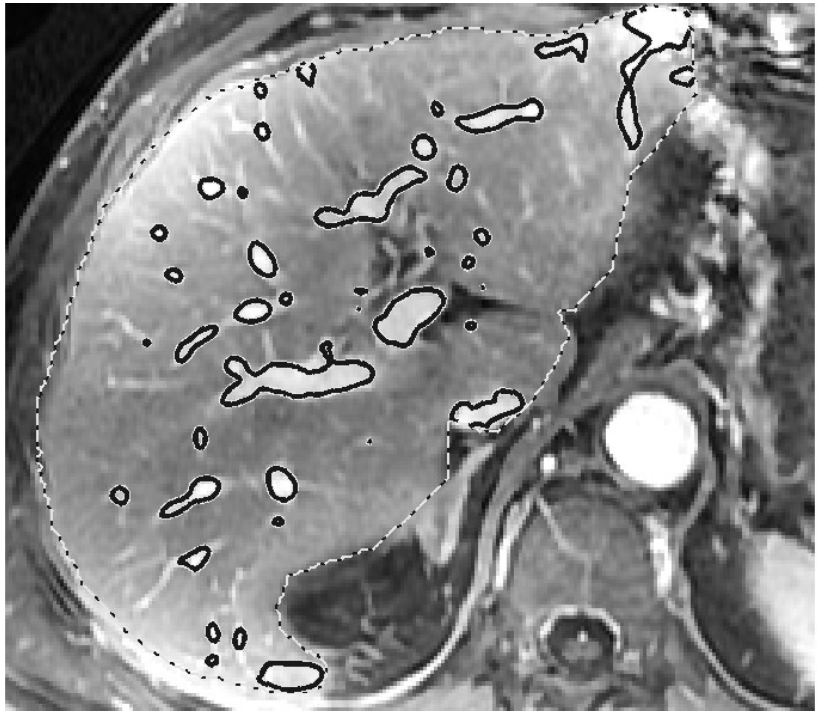
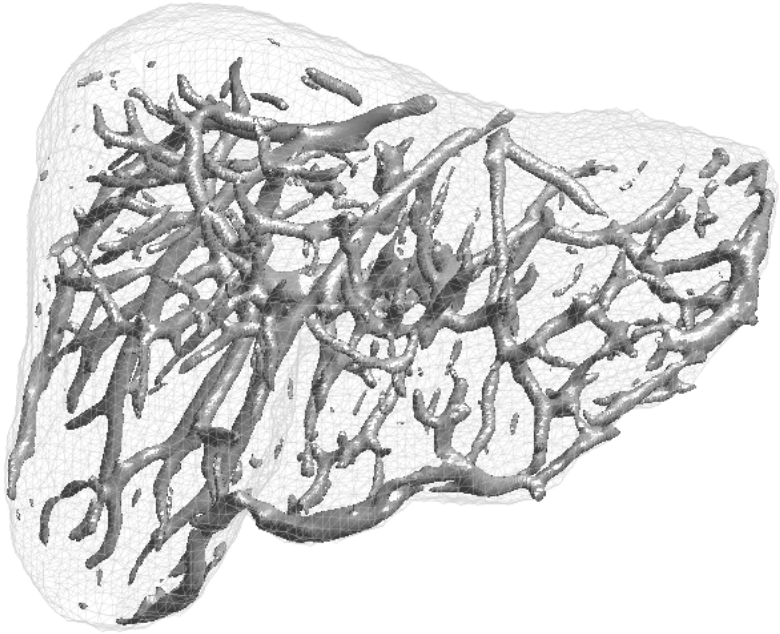
Non-rigid Matching by Vessel Segmentation

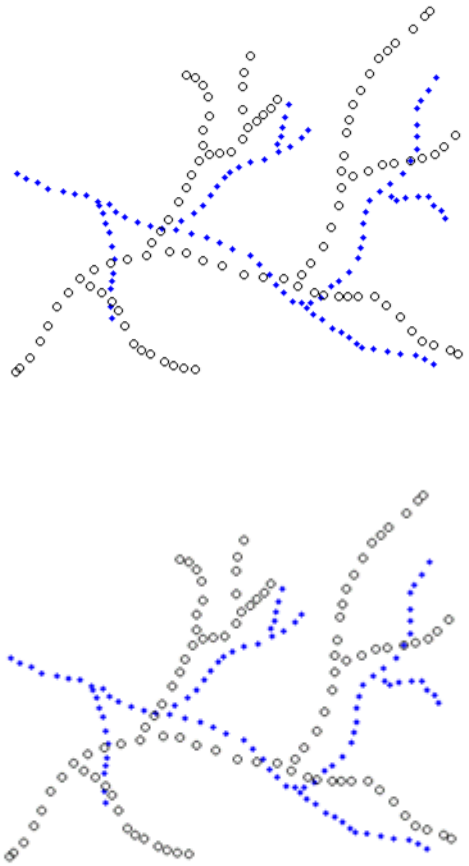




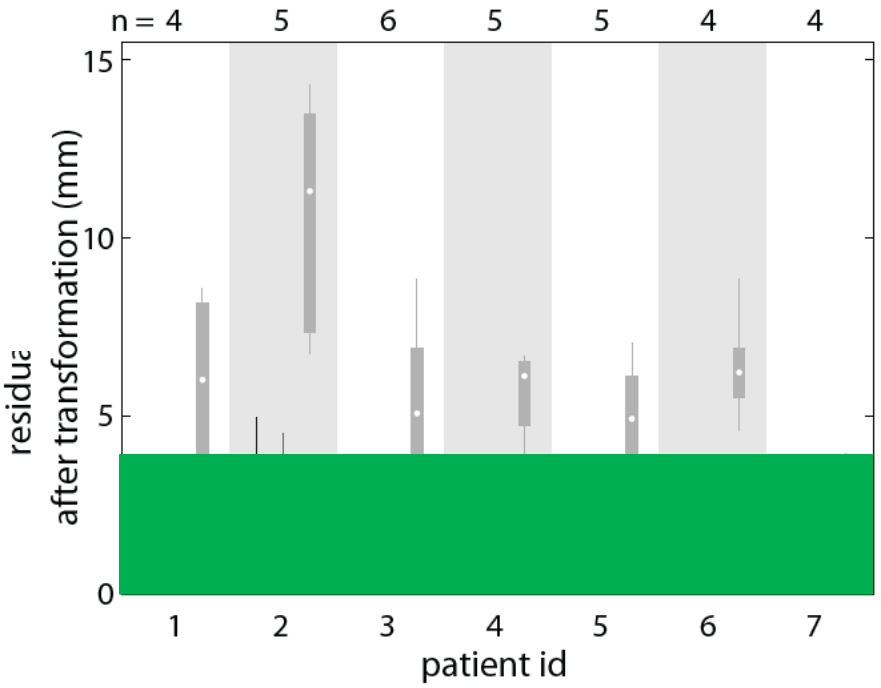
Vasquez Osorio E et al. Med Phys. 2012 May;39(5):2463-77

Erasmus MC

Transformation Error and Anatomical Validation



Anatomical landmarks



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

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A Multi-institution Deformable Registration Accuracy Study

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

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.06.031

PHYSICS CONTRIBUTION

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

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

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

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

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DOSE PRESCRIPTION

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Radiobiology

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

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

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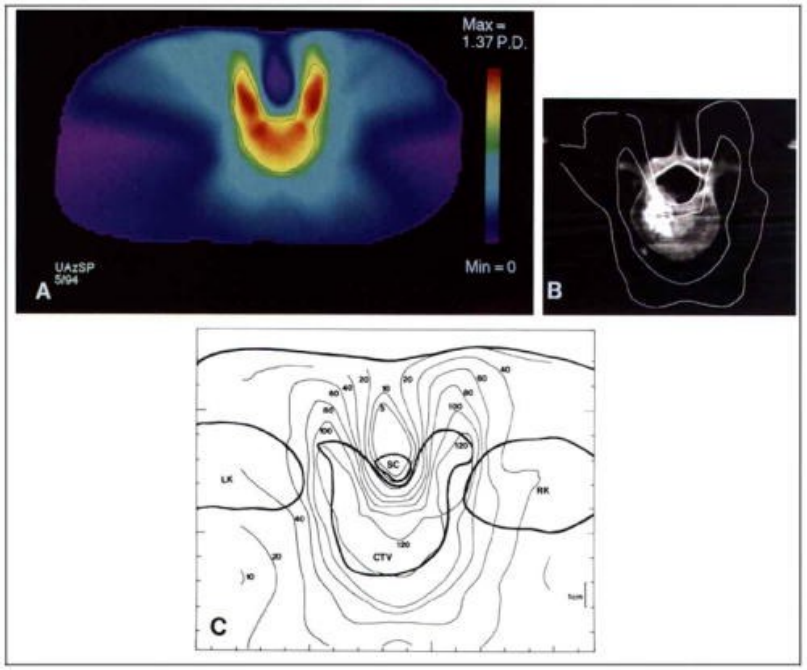
Preliminary Clinical Experience with Linear Accelerator-based Spinal Stereotactic Radiosurgery
Hamilton, Allan J. M.D.; Lulu, Bruce A. Ph.D.; Fosmire, Helen M.D.; Stea, Baldassarre M.D., Ph.D.; Cassady, J. Robert M.D. Volume 36(2), February 1995, p 311–319.



TREATMENT PLANNING

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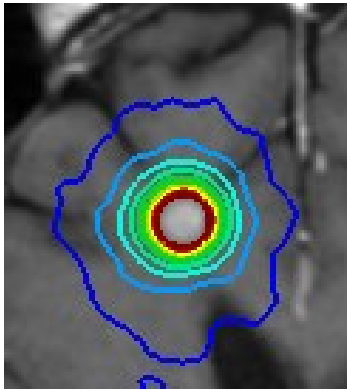
Dose Calculation

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



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

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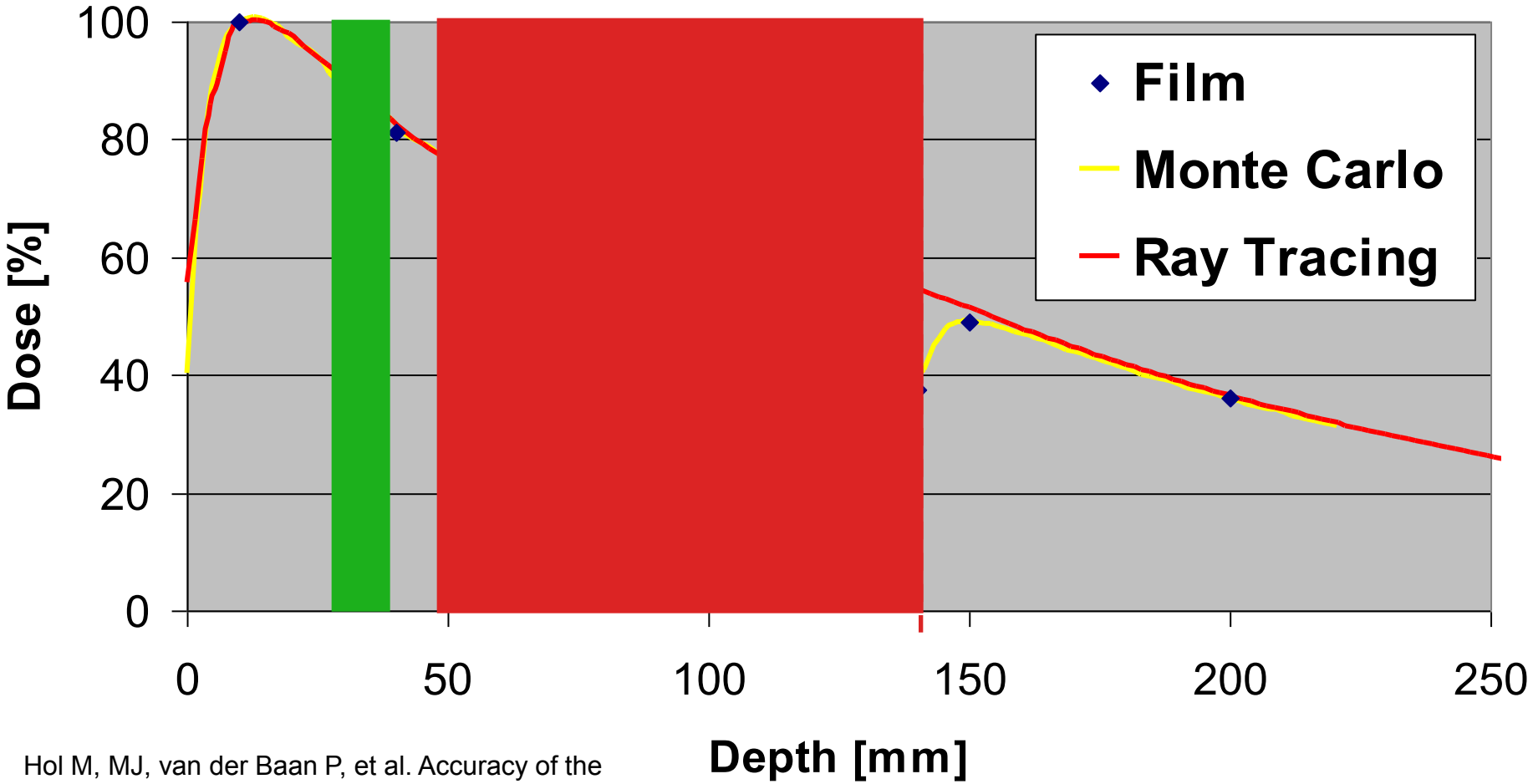
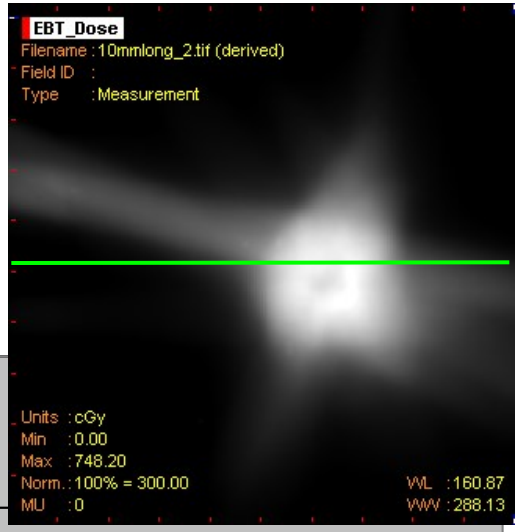
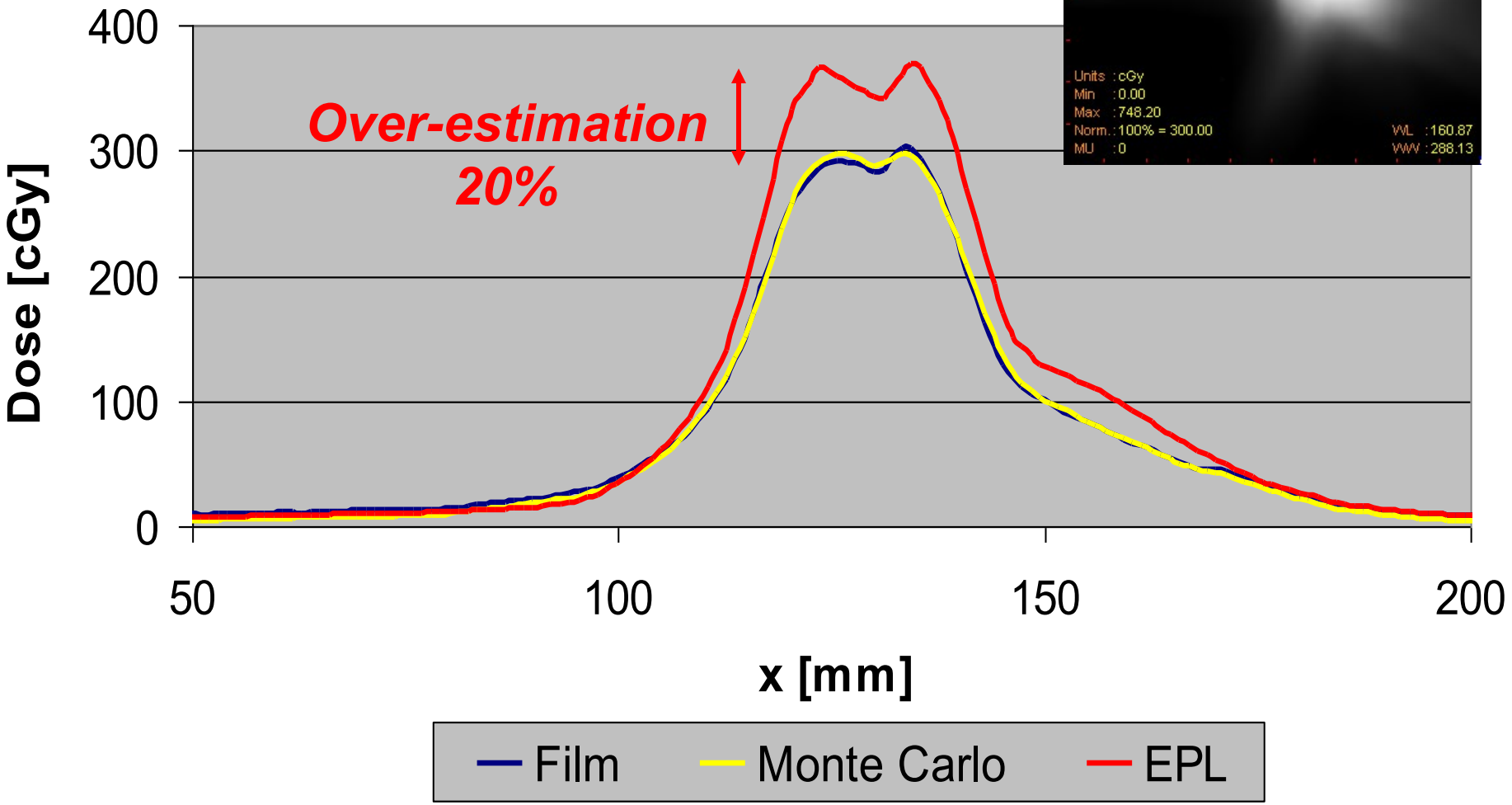
Dose Calculation Algorithm



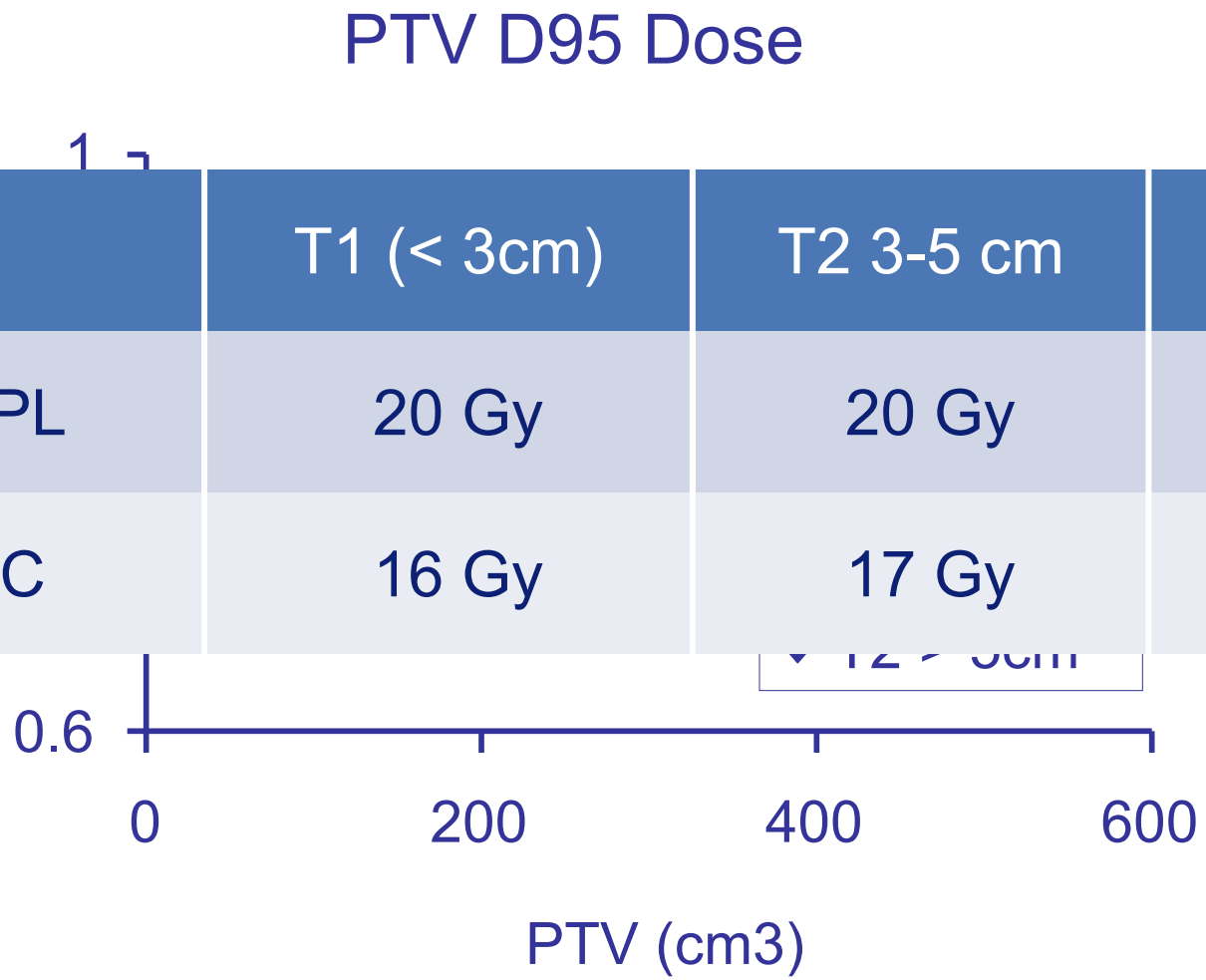
Hol M, MJ, van der Baan P, et al. Accuracy of the Monte Carlo Dose Calculation Algorithm for Cyberknife Treatment of Small Lung Lesions. Med Phys 2008;35:2953

Peripheral 10-mm tumor





Prescription MC/EPL as a Function of PTV



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

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

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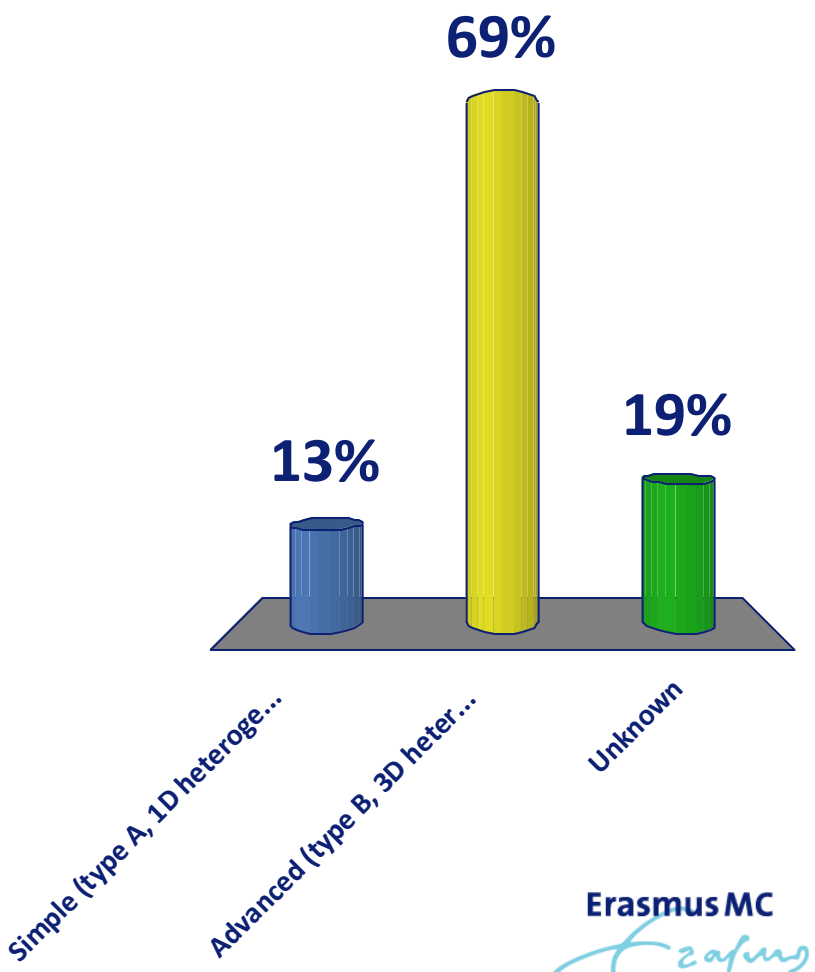
Which dose algorithm will you use (are using) for lung SBRT?

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

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

C. **Unknown**



Erasmus MC

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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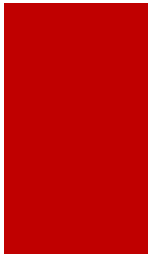
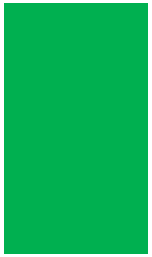
Output Factor Correction

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

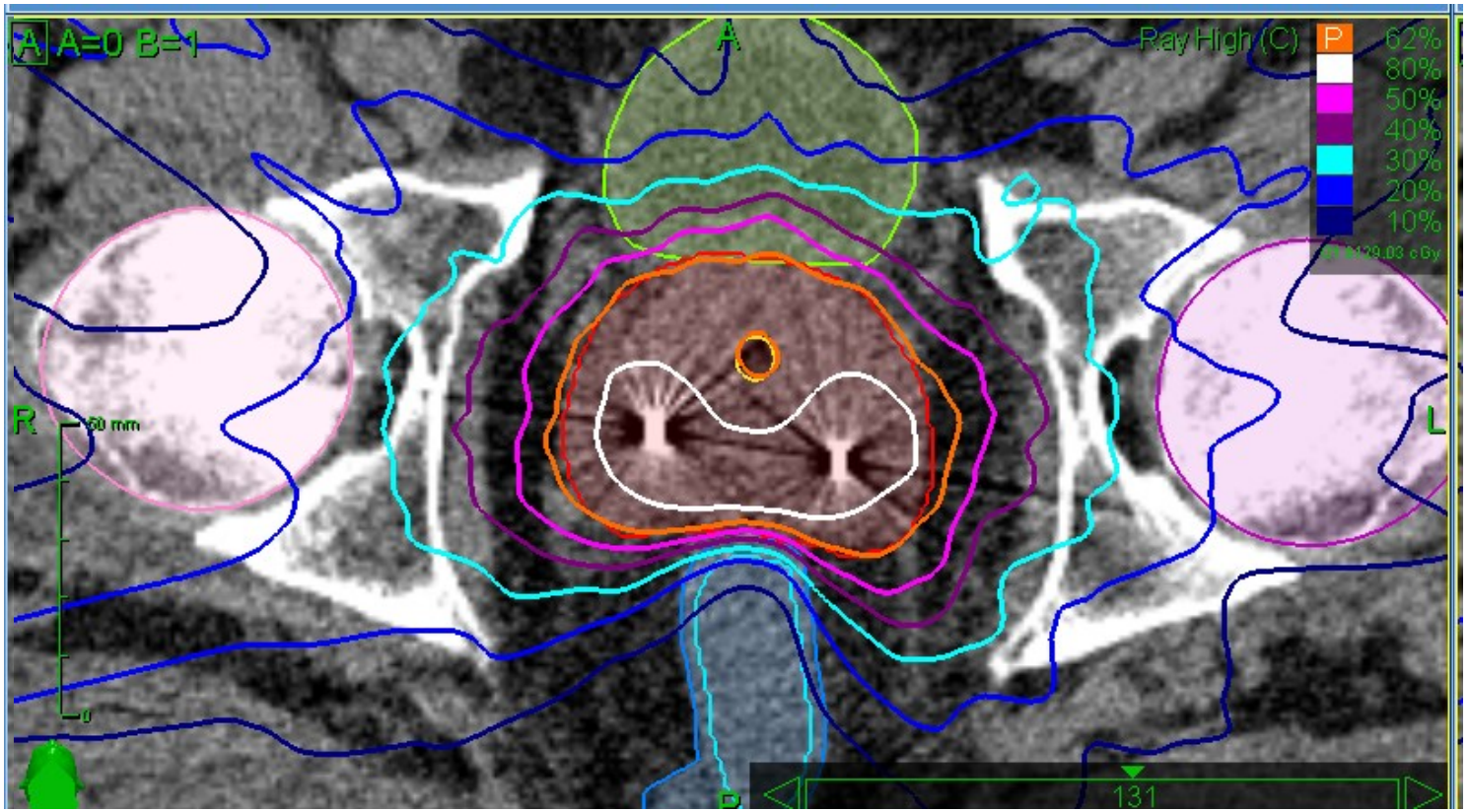
	5 mm	
	Raw $s_{c,p}$	$s^{*}_{c,p}$
A16		
PinPoint		
Diode		
Diamond		
Mean $s_{c,p}$	0.638	0.677
$\pm 2\sigma$	0.096	0.004

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

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

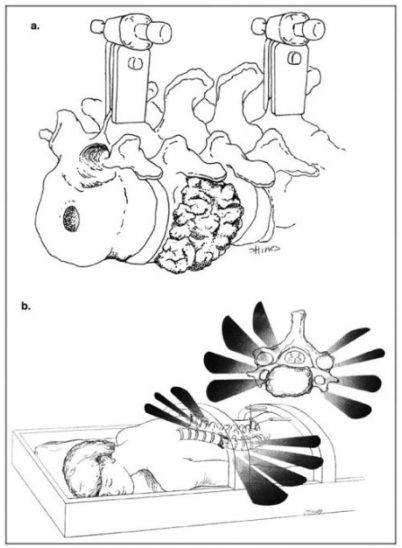
Francescon P, Cora S, Satariano N. Calculation of k(Q(clin),Q(msr)) (f(clin),f(msr)) for several small detectors and for two linear accelerators using Monte Carlo simulations. Med Phys. 2011 Dec;38(12):6513-27

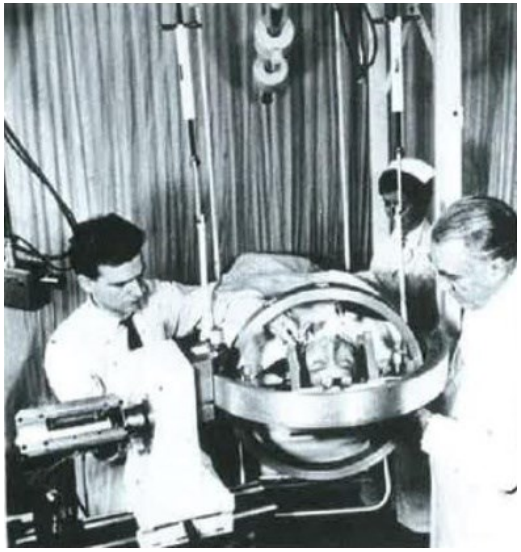
Treatment Plan Quality



Courtesy of Linda Rossi

Erasmus MC





PATIENT SETUP, IMMOBILIZATION, TARGET LOCALIZATION, AND DELIVERY

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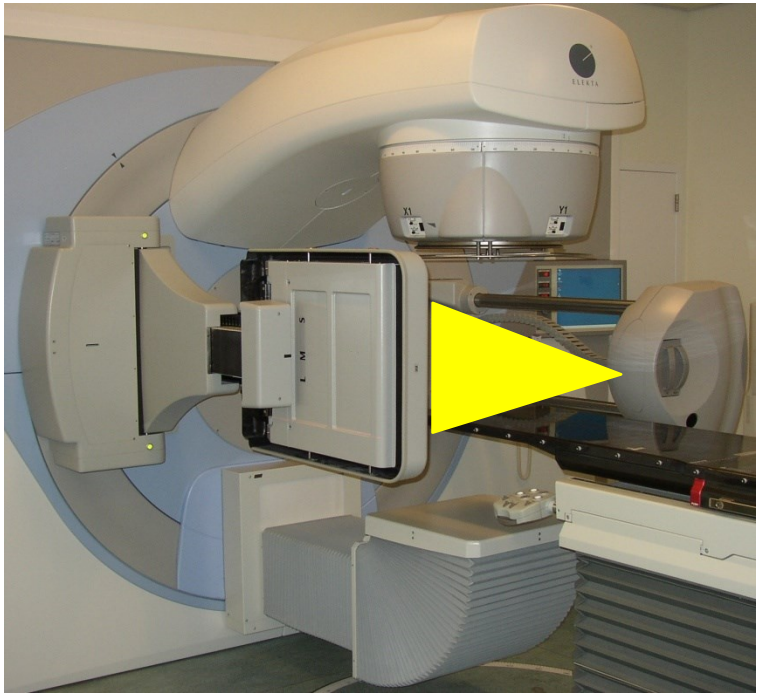
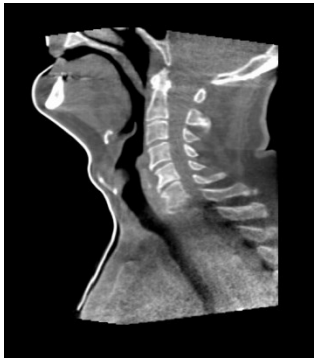
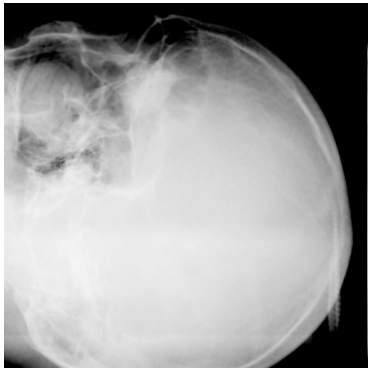
From CT to LINAC: Image-based Alignments (Frameless)





3D to 3D



2D to 3D

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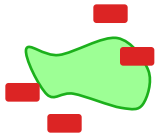

MARKERS AS SURROGATE

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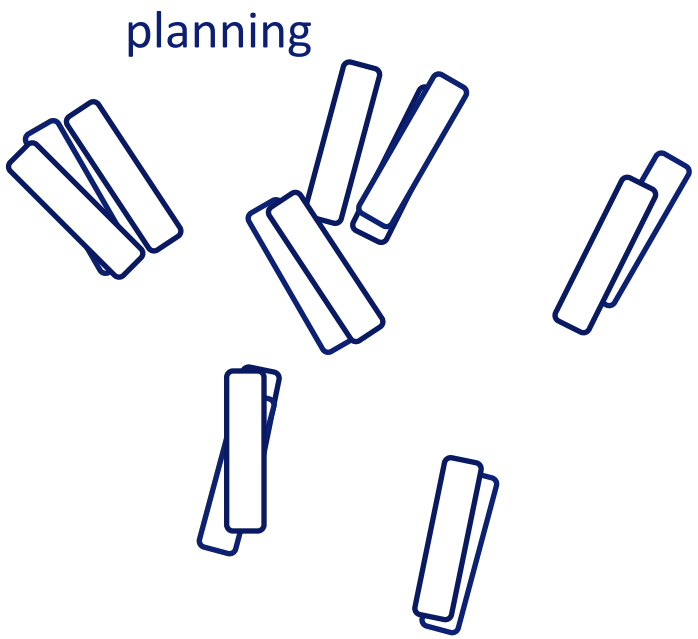
Deformation in Marker Configuration



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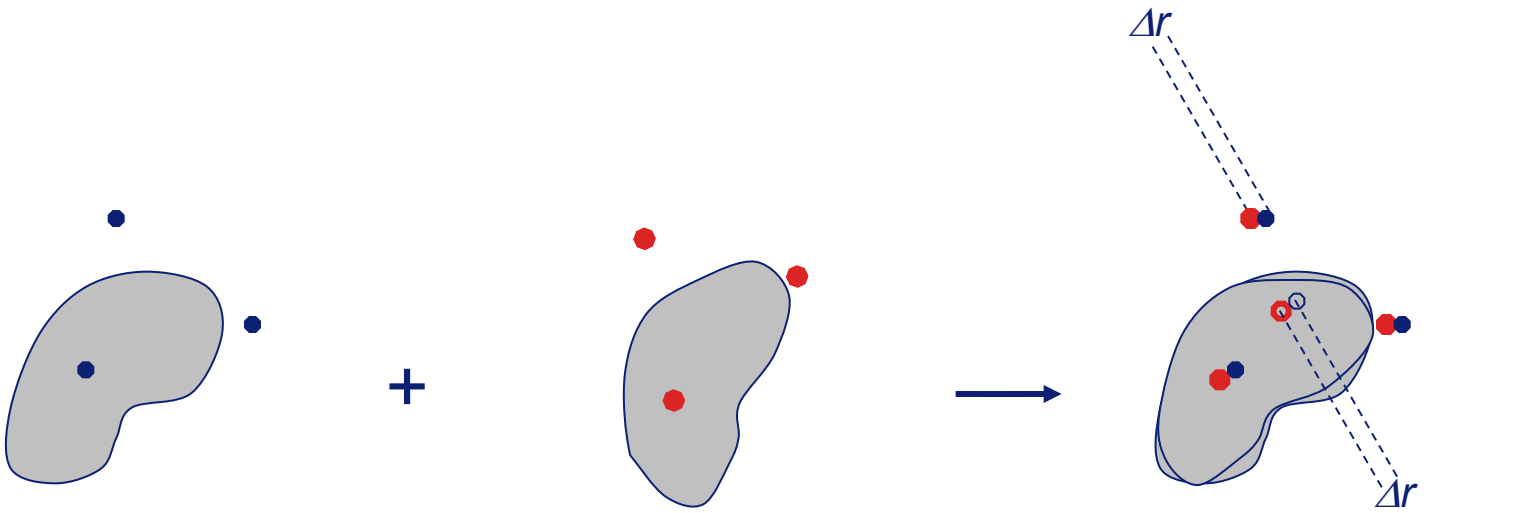
Assessing Marker Stability



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

→ Distance between the COM of marker configurations

→ Change in distance between pairs of markers

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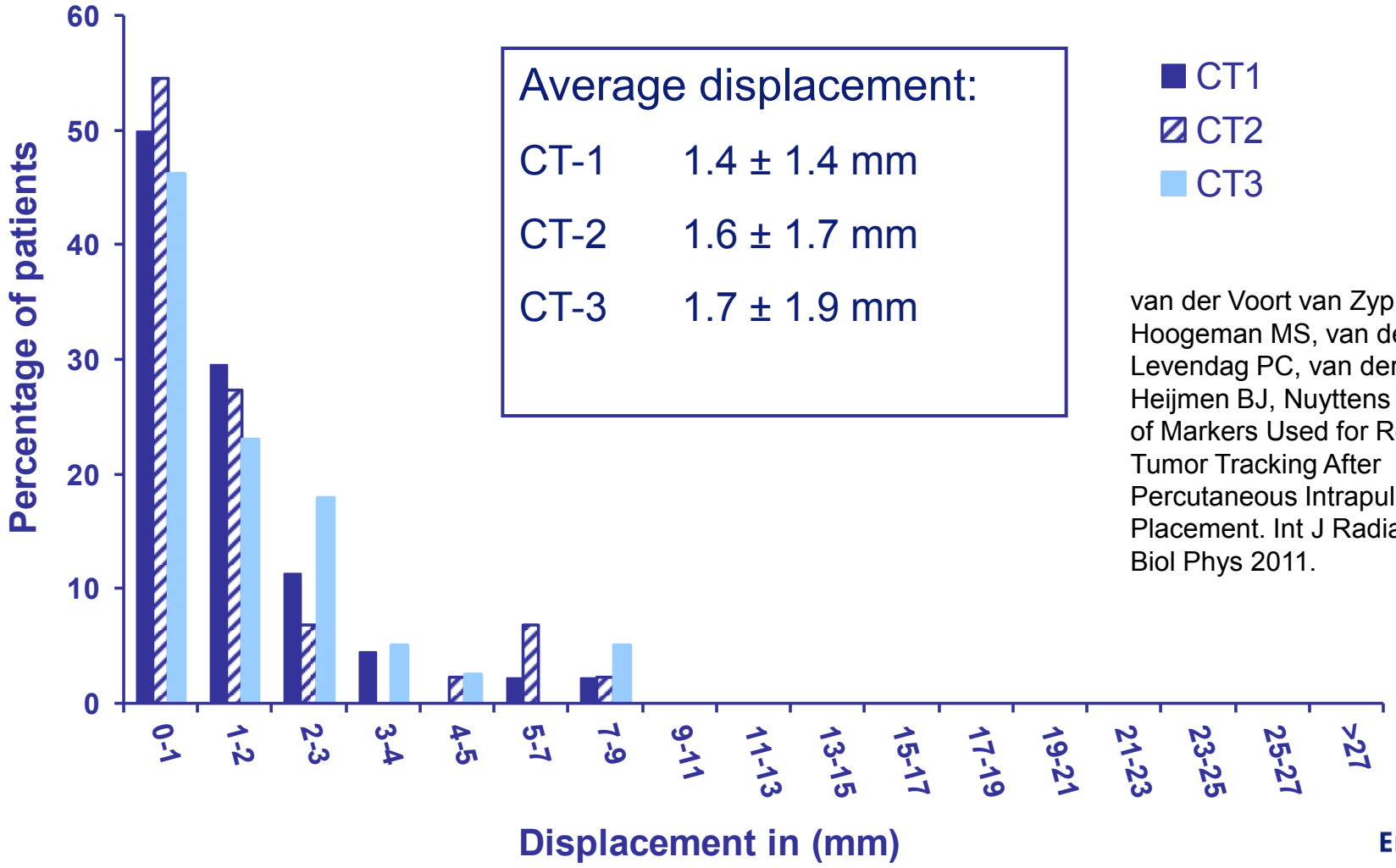
Displacement of the COM of Marker Configurations



Average displacement:

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

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

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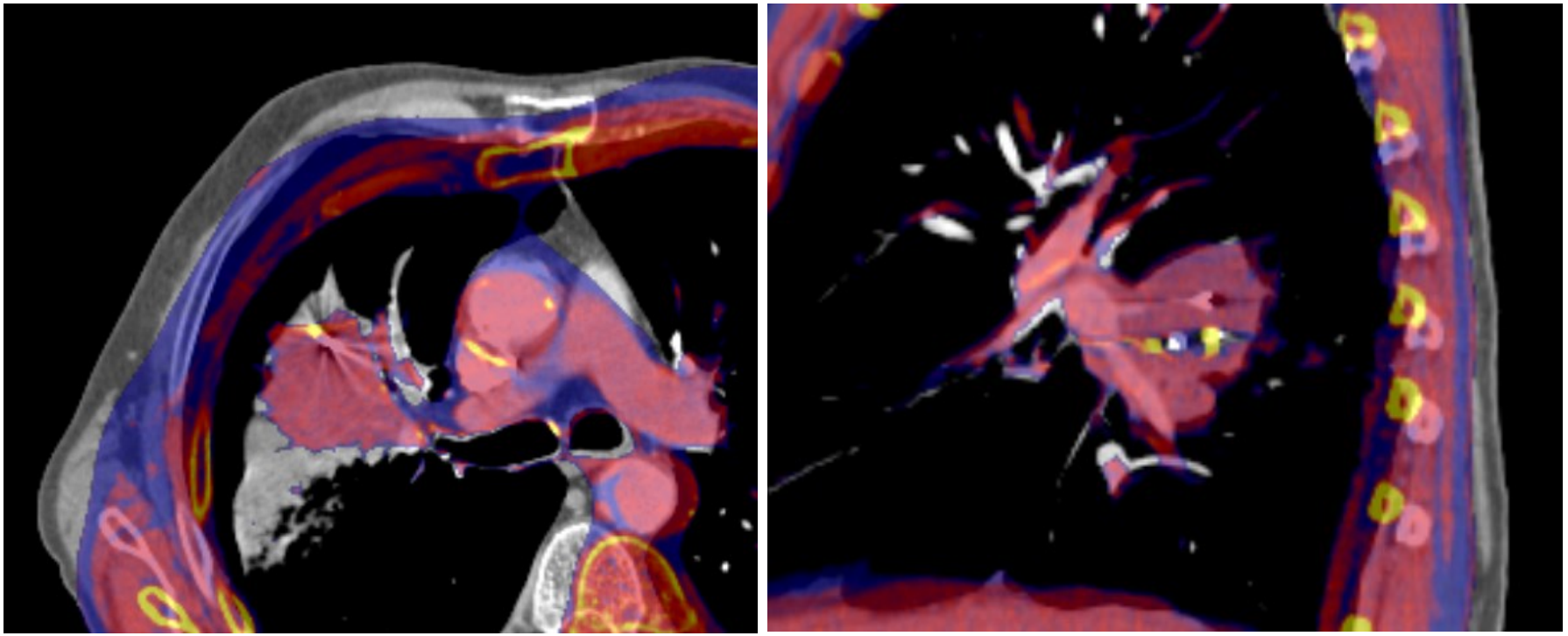
Examples of displacements in COM ≥ 3 mm



Evident migration in 1 patient

Insert 3 markers

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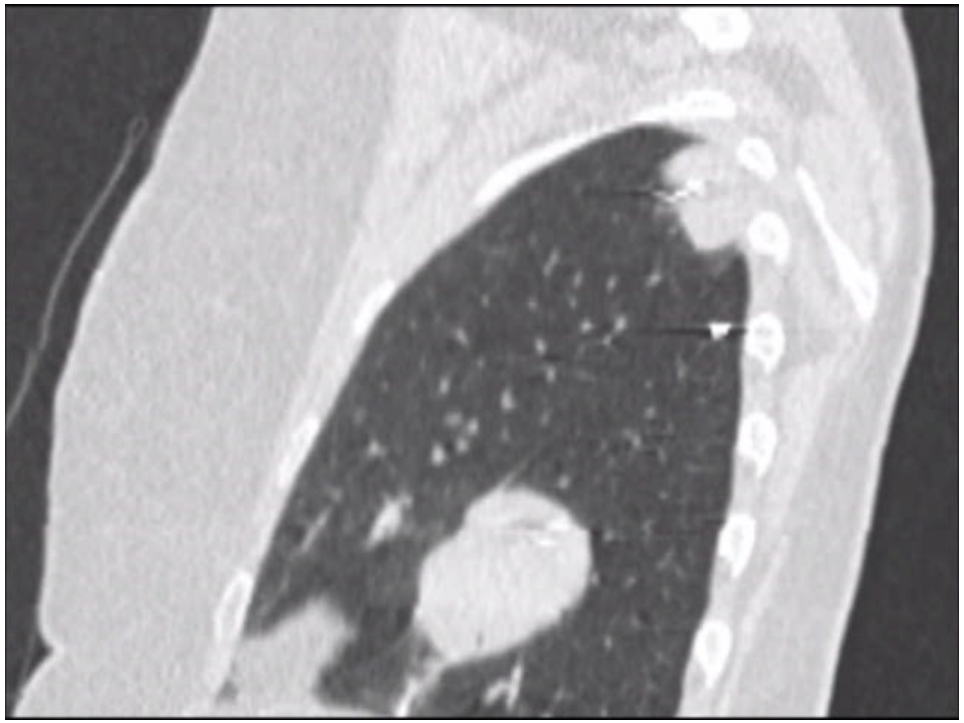
Non-Synchronous Motion Between Markers and Tumor

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



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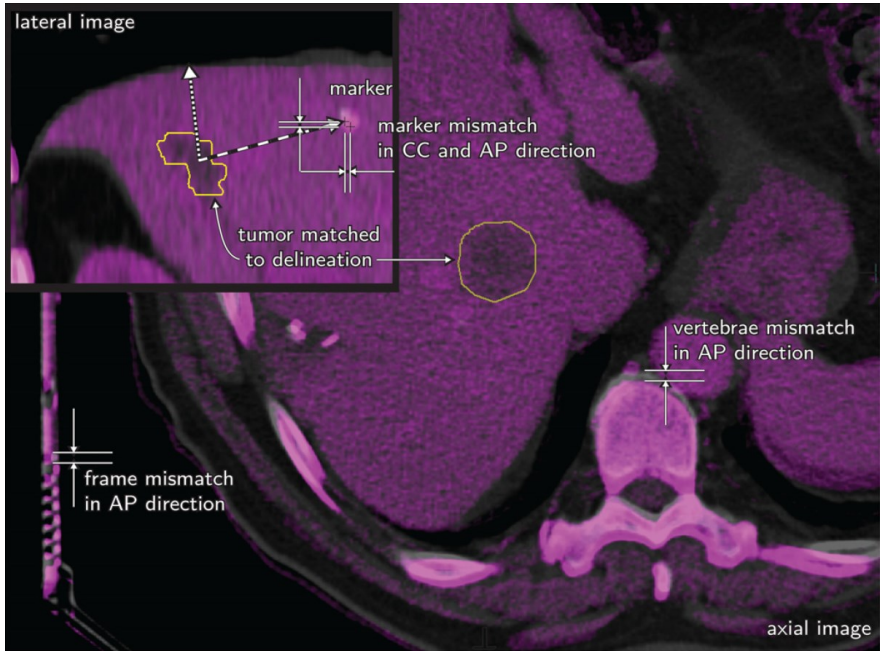
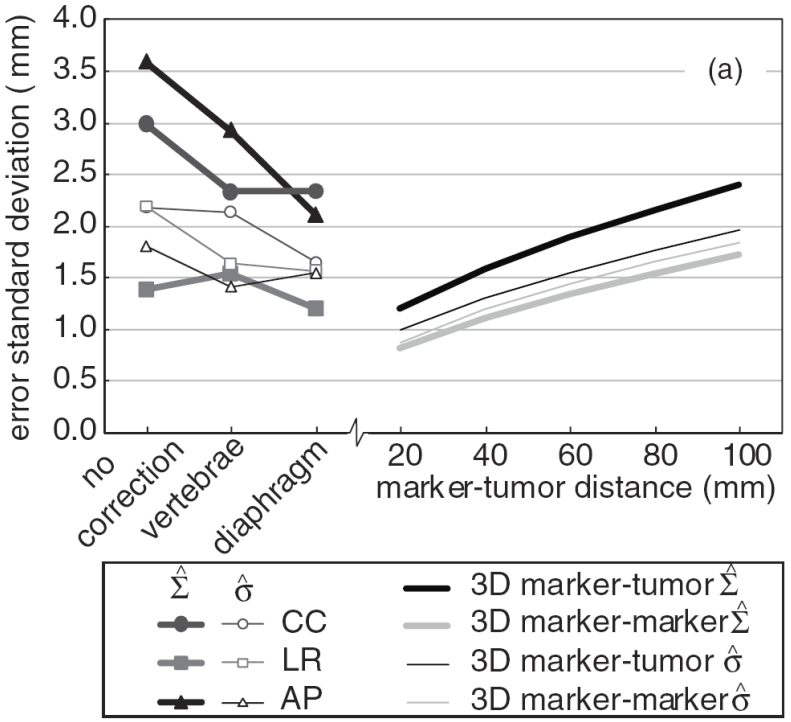
Liver Tumor Surrogates





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

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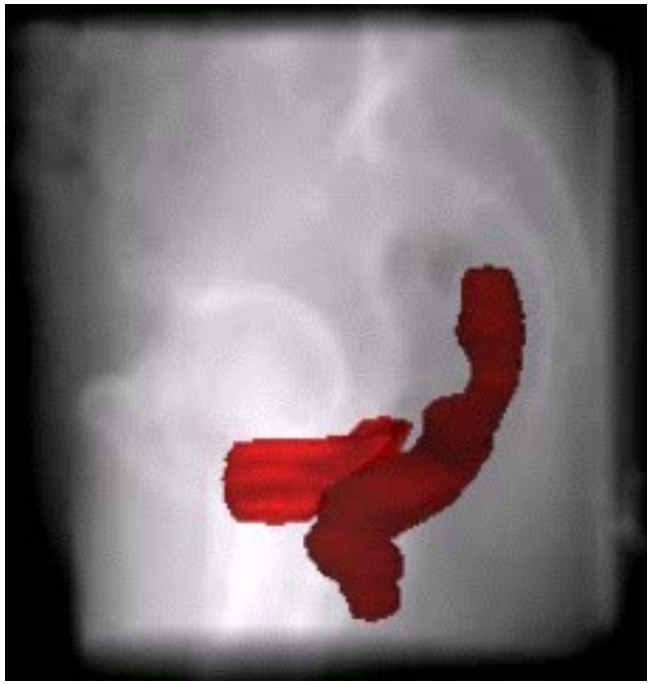
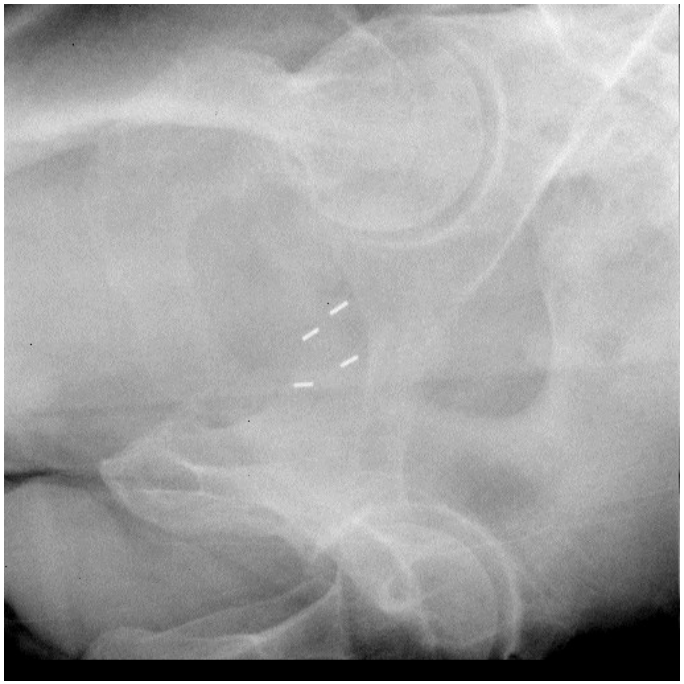
Inter-Fraction and Intra-Fraction Errors

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





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

=> Monday morning talks

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TREATMENT DEVICES

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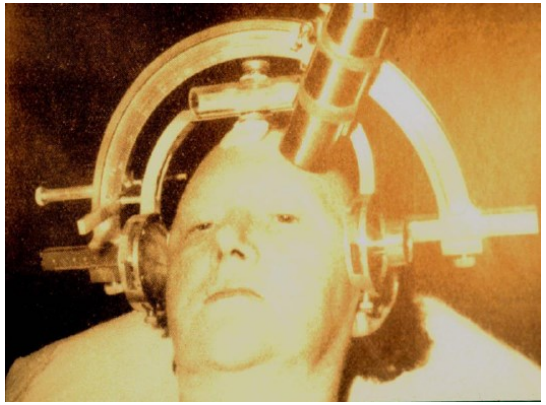
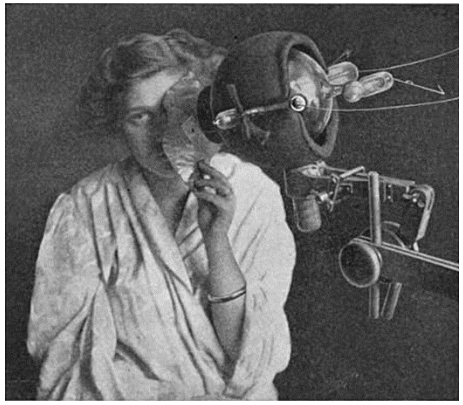
Vendors' Claims of Stereotactic Devices

- "… system capable of delivering high doses of radiation with sub-millimeter accuracy anywhere in the body …"
- "… doctors are able to focus radiation directly, and very precisely, on the target in the brain …"
- "… It combines imaging, beam delivery and sophisticated technology to accurately and precisely target tumors …"
- " … designed for precision …"





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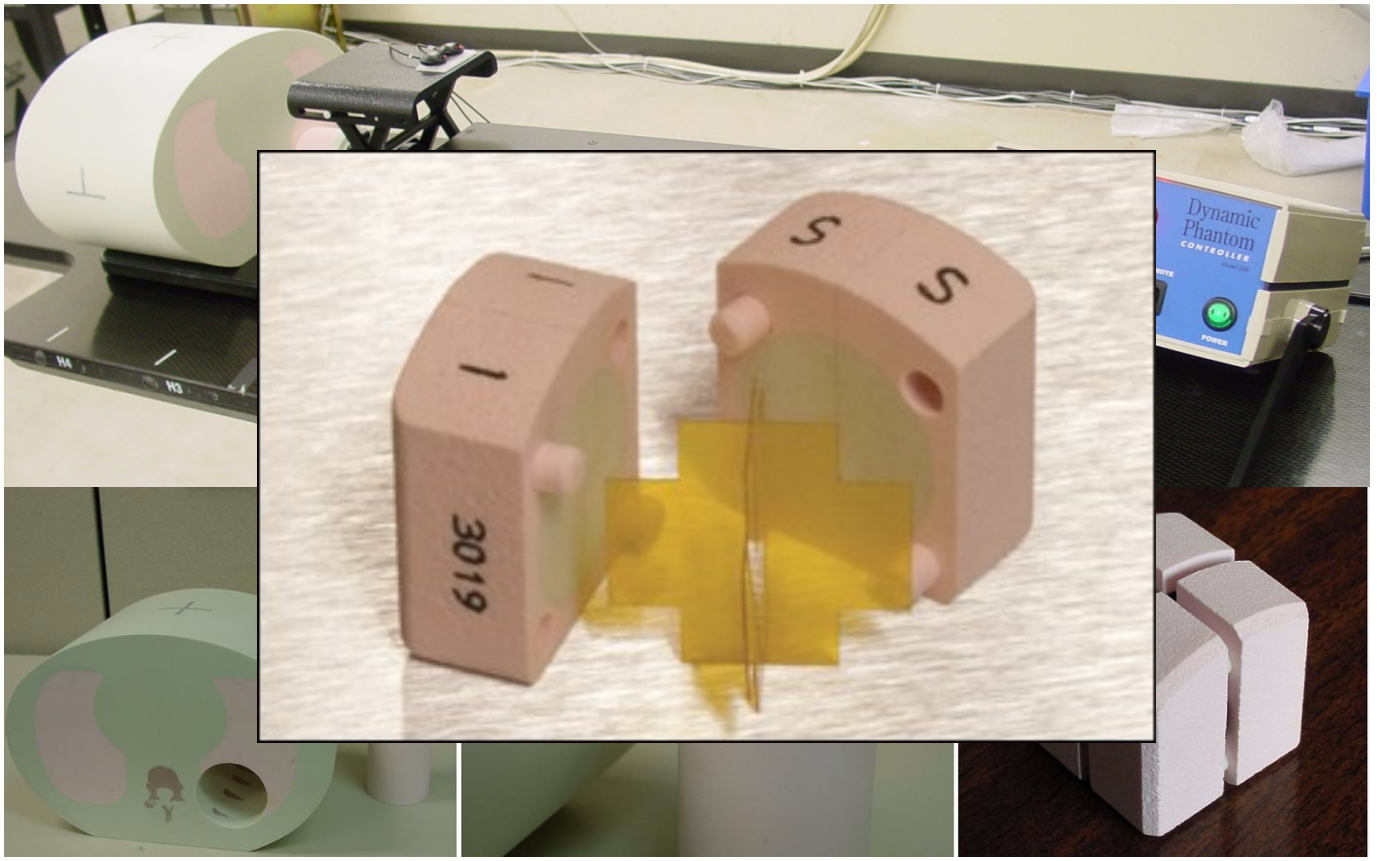
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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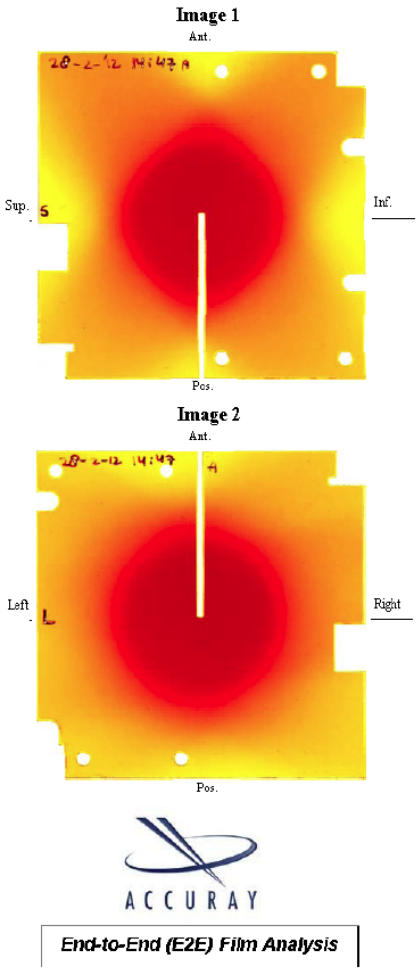
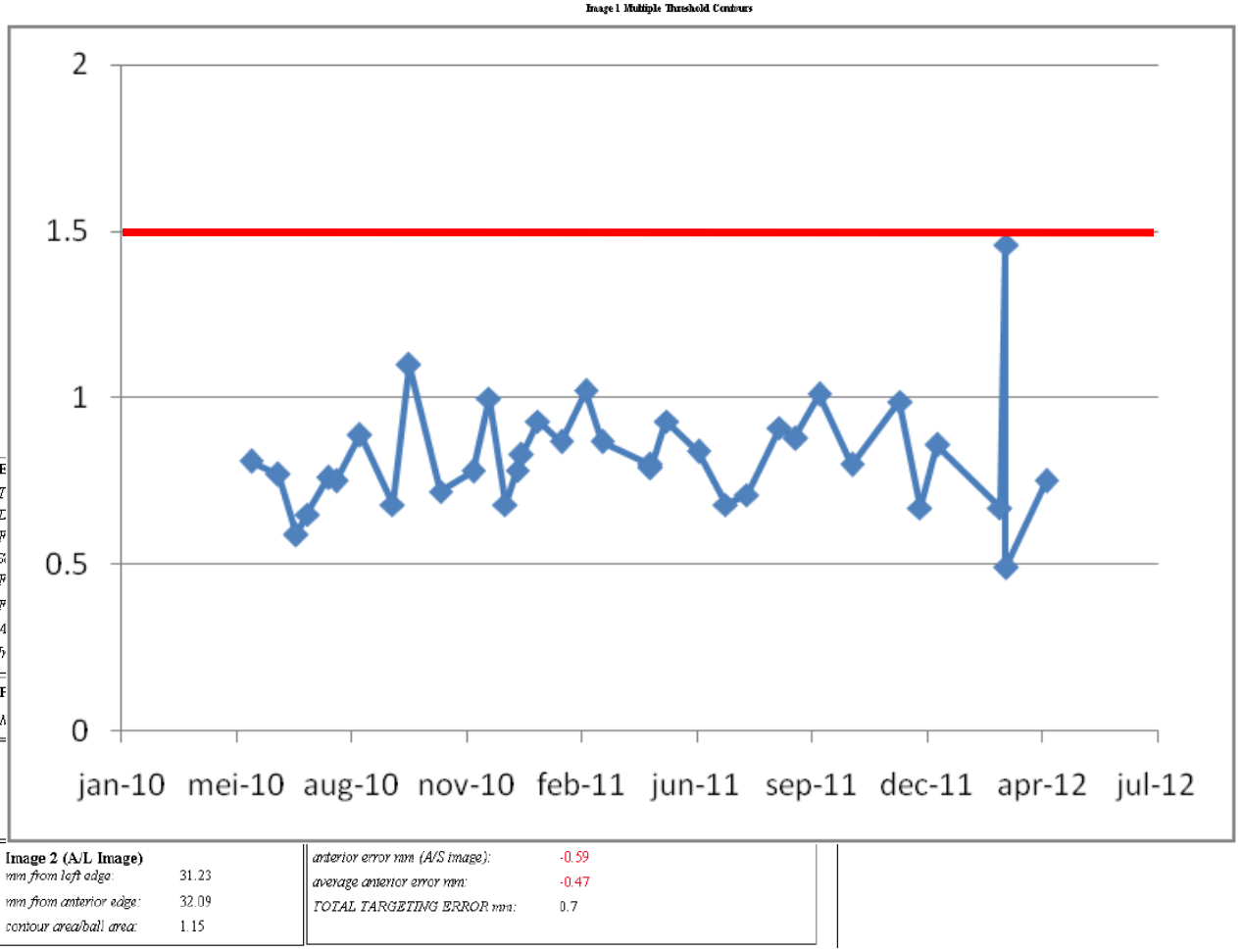
Analysis of Tracking Error





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CONCLUSIONS

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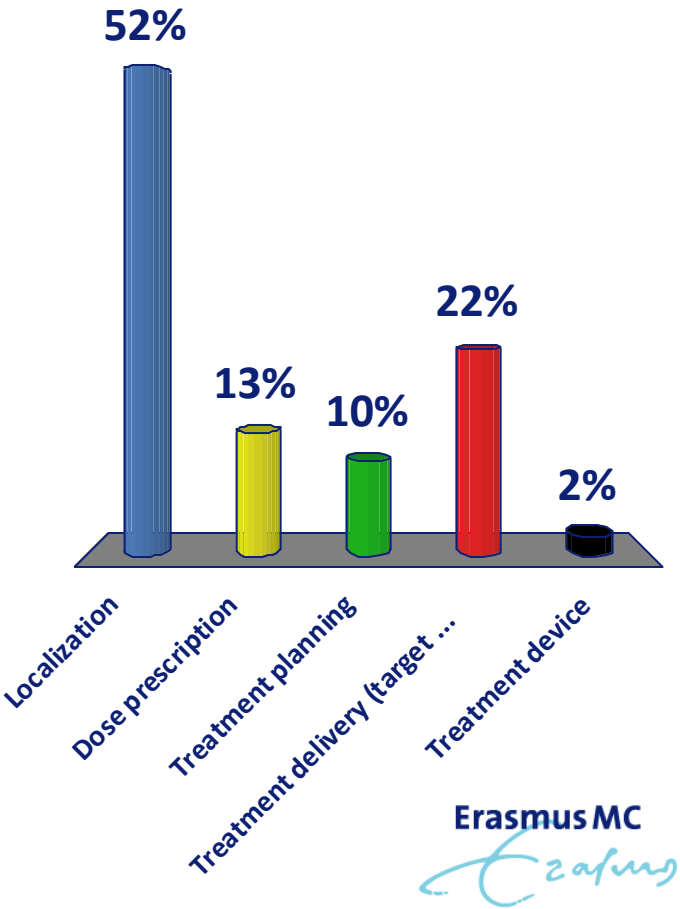
Which type of error is clinically most significant?

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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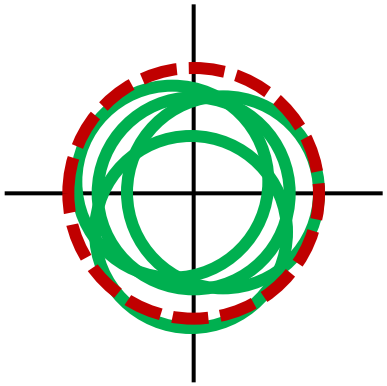
Why do we use margins?

- **Target / tumor**
  - To **a-priori** compensate for (unknown) 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)



- **Healthy tissue**
  - To avoid unintended dose to critical organs after aligning the beam to the displaced target (in case of differential motion between target and OAR)

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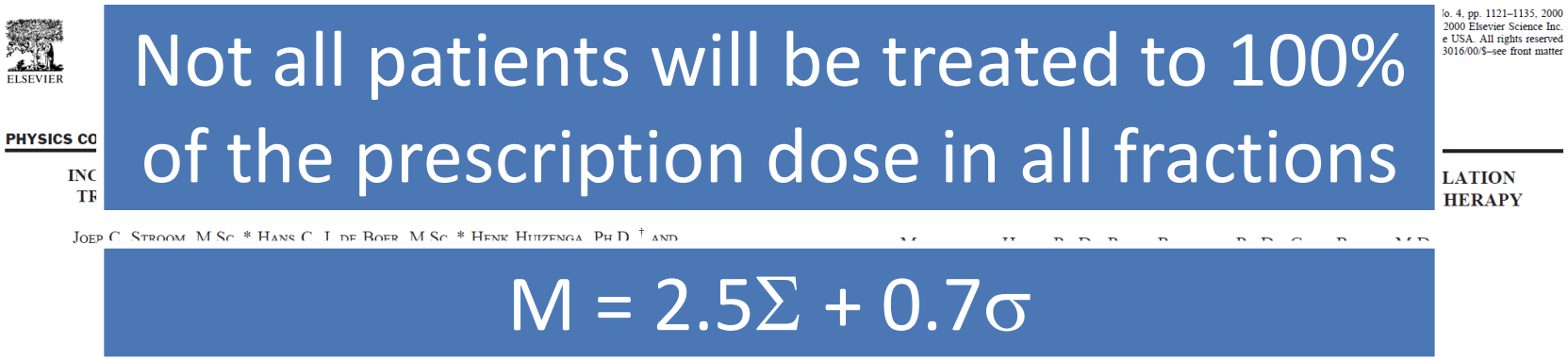
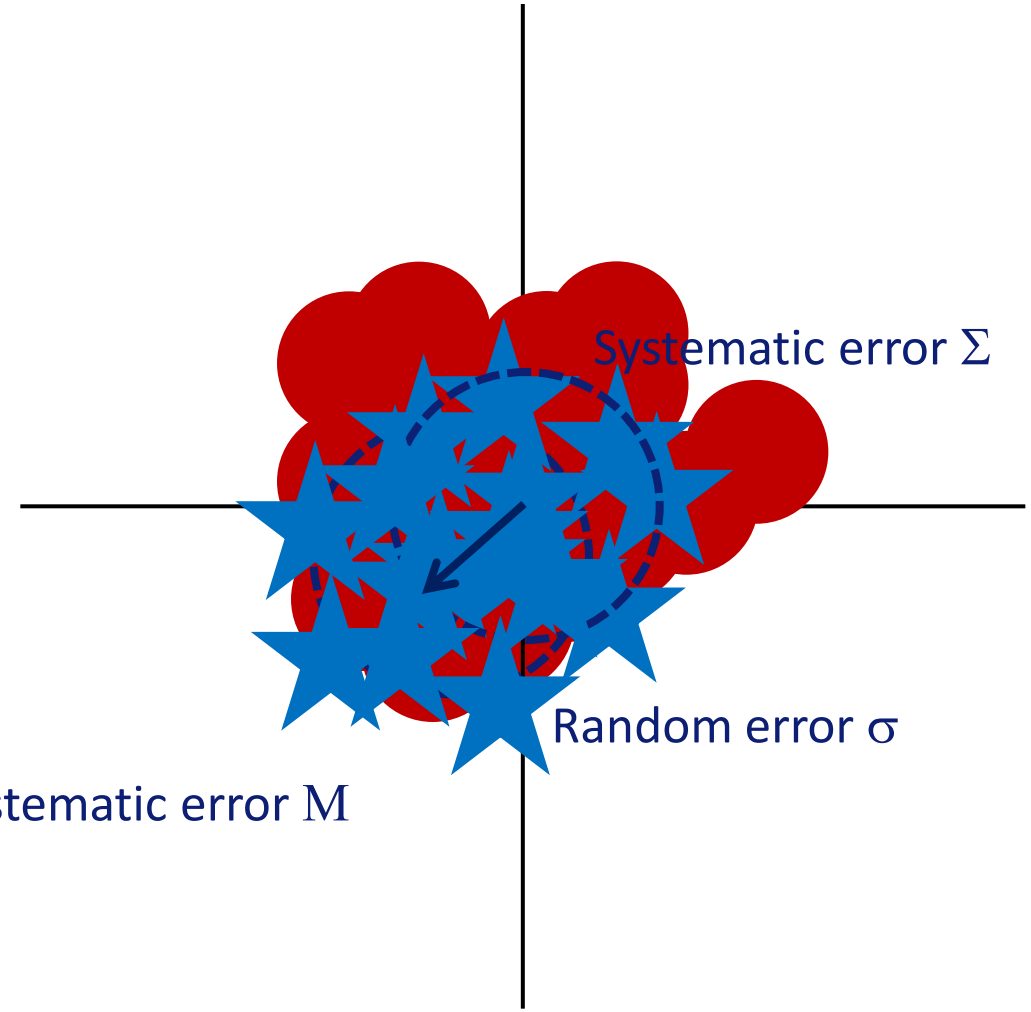
How large should the margin be?

- **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.**



Categorization of Errors: a 2D Example



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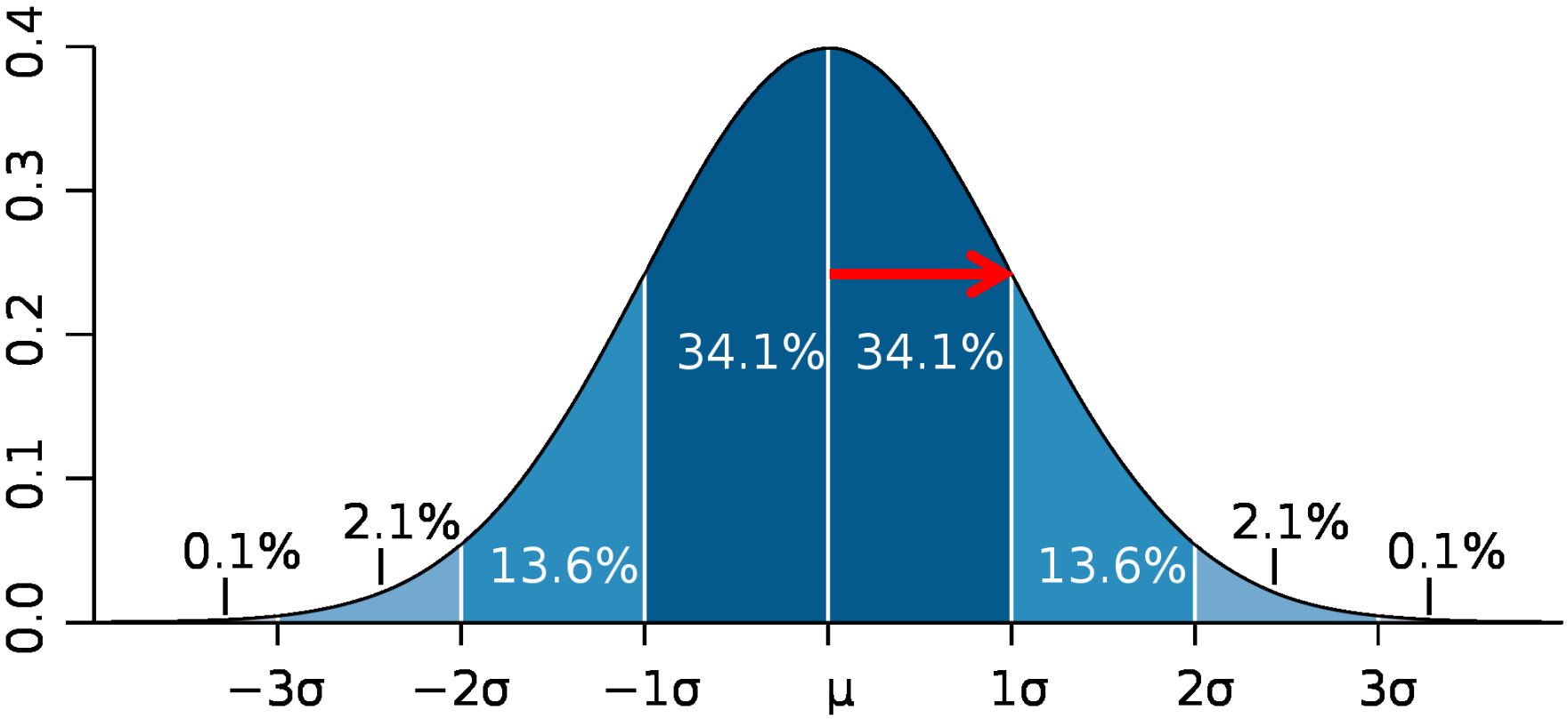
Probability Density Function: Normal Distribution



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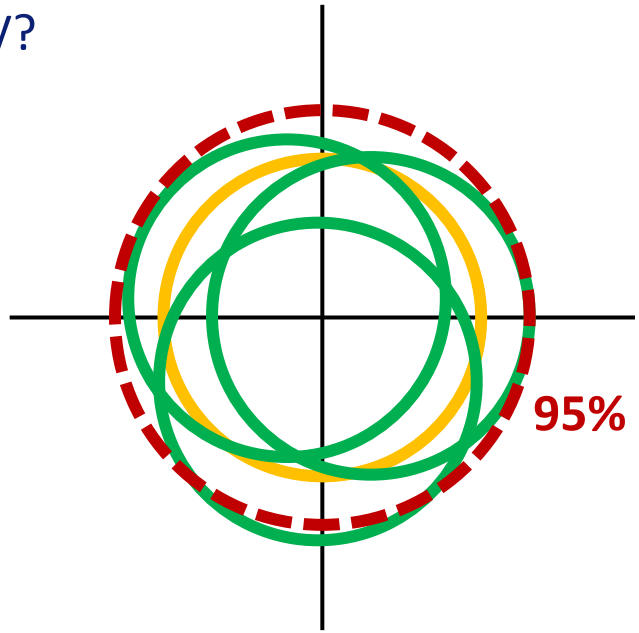
Systematic Errors Only (M_{sys} = 2.5 Σ)

- 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, 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 (%)	x.xxΣ
80	2.16
90	2.50
95	2.79
99	3.36

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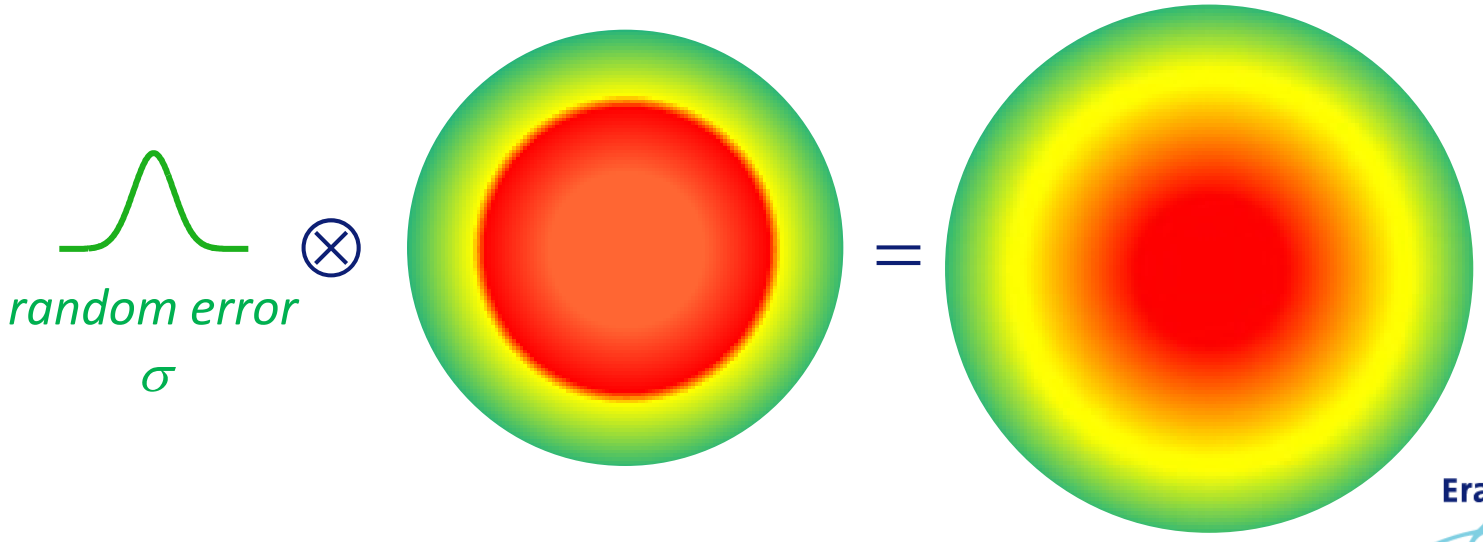
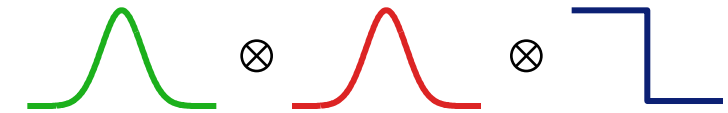
Random Errors Only: $M_{rand}=0.7\sigma$

- 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 appeared 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

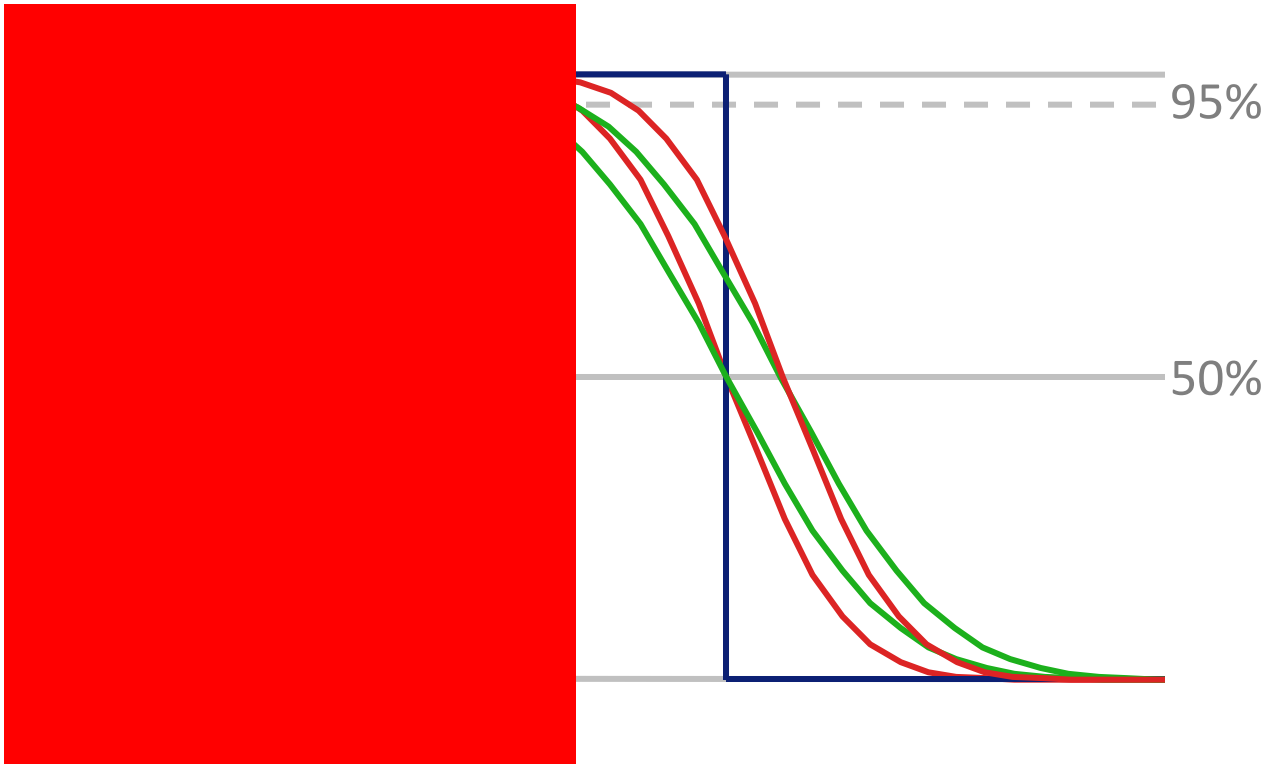


Margin Recipe for Random Error

Water σ_p= 3.2 mm
Lung σ_p = 6.4 mm



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



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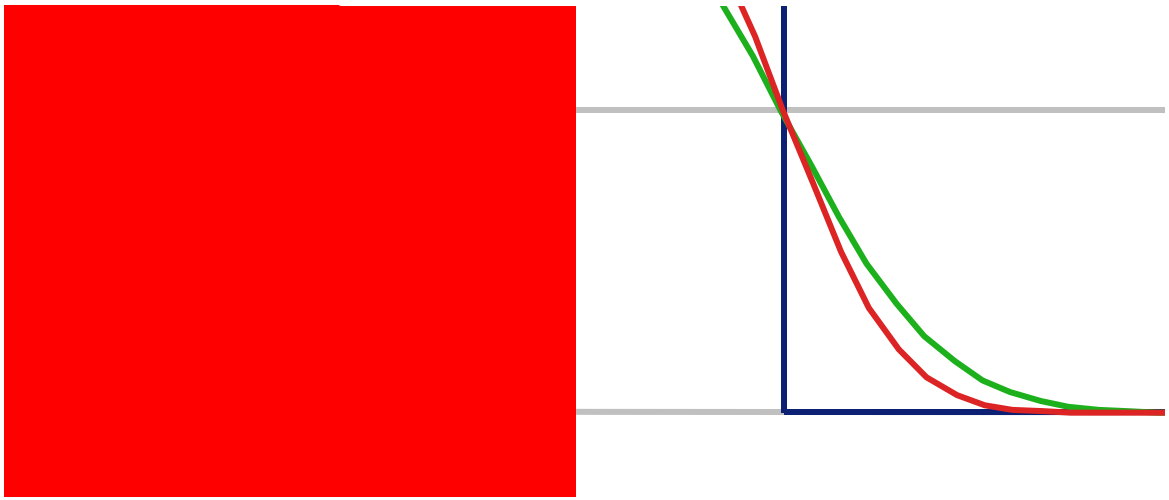
Margin Calculation: Random Component

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

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

$$M = 1.64 \quad M = 0.7\sigma \quad -1.64\sigma_p \quad \overline{\ \ }_{nd})$$



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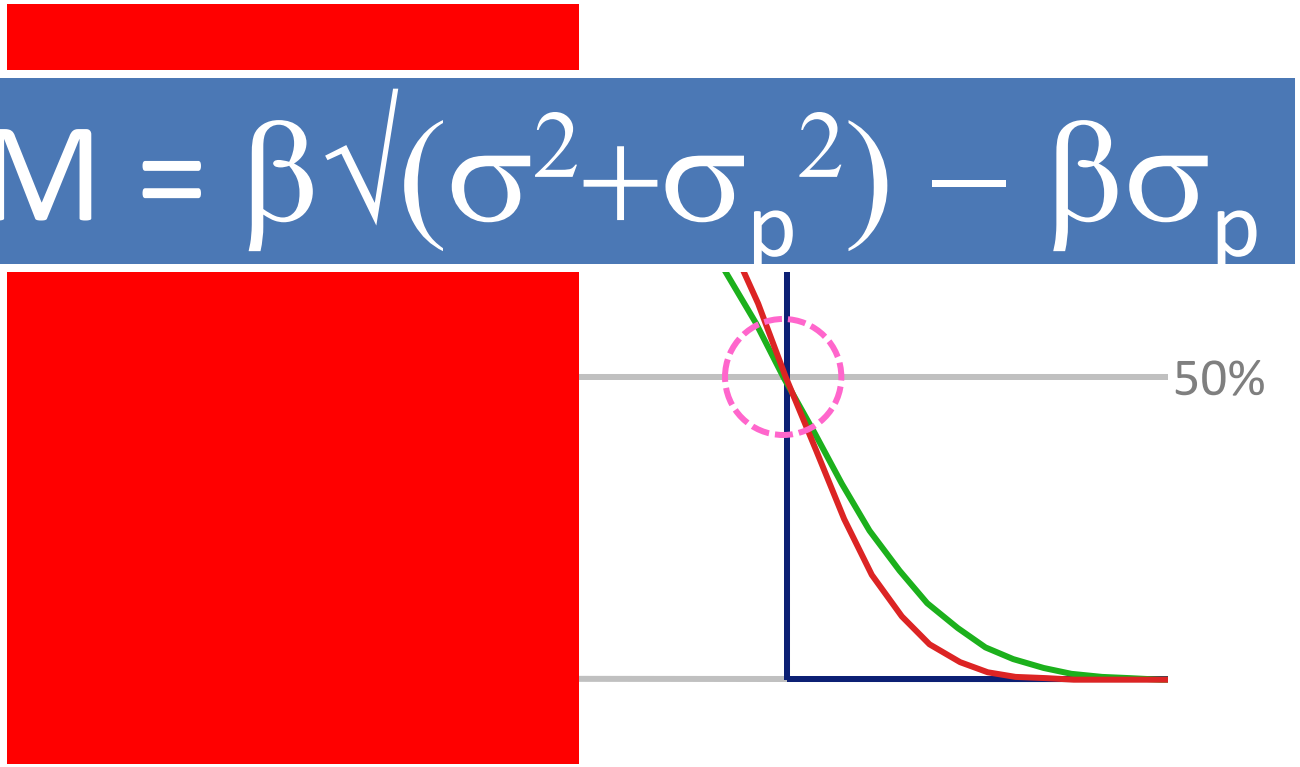
Random Error and Minimum Dose Requirement

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

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



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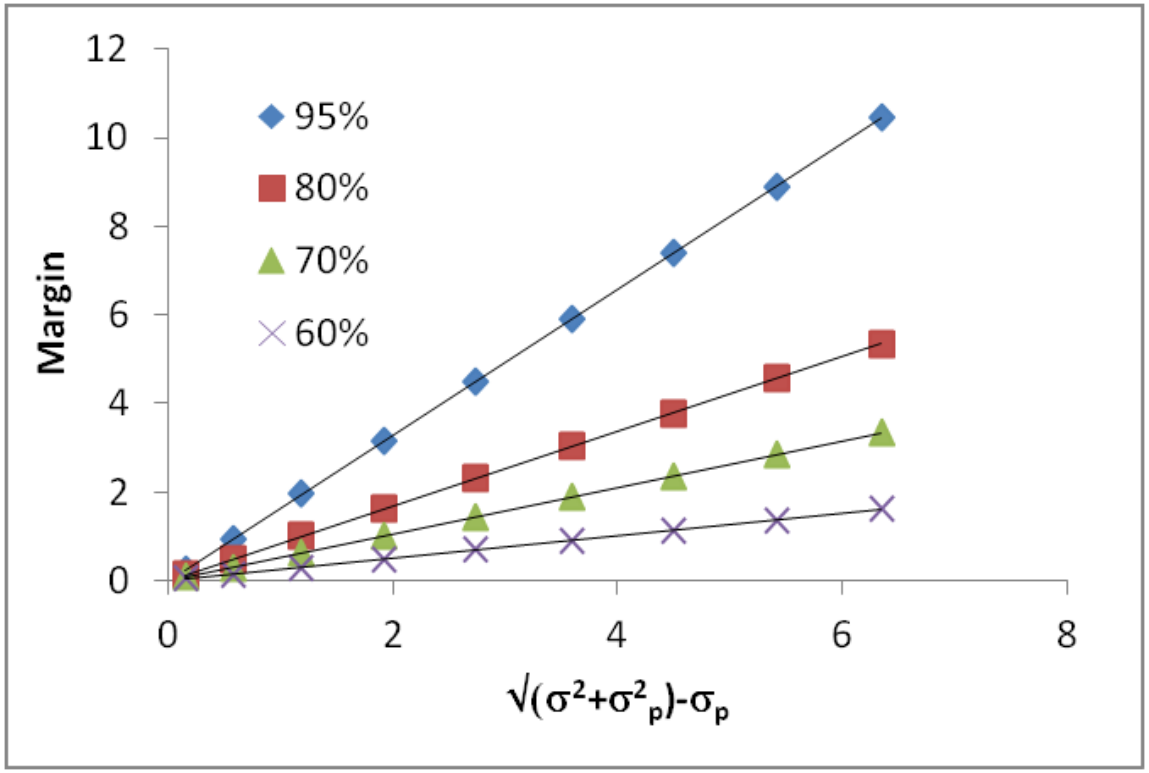
Random Margin and Prescription Level



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

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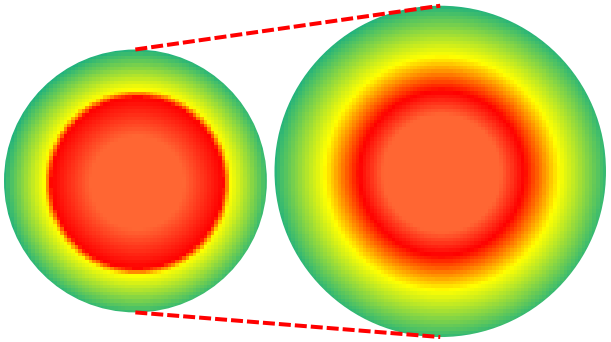
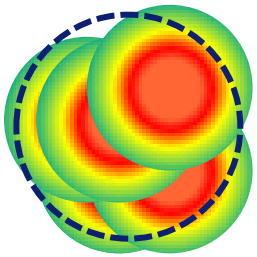
Margin Recipe: Systematic Error and Random Errors



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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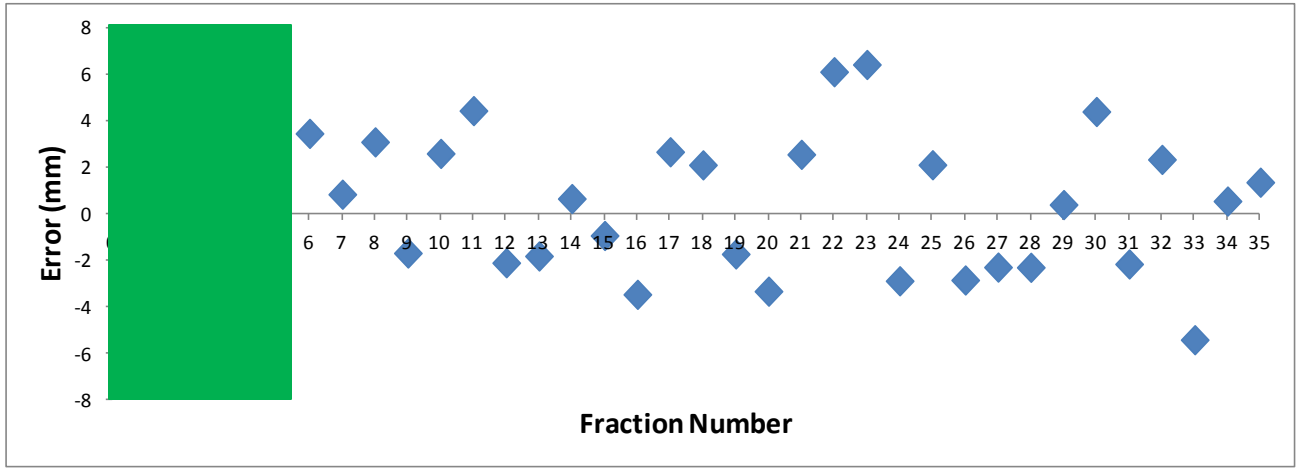
Number of Fractions and Residual Systematic Error

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



- Residual error
  - Error after 5 fractions = -1.6 mm
  - Error after 35 fractions = 0.1 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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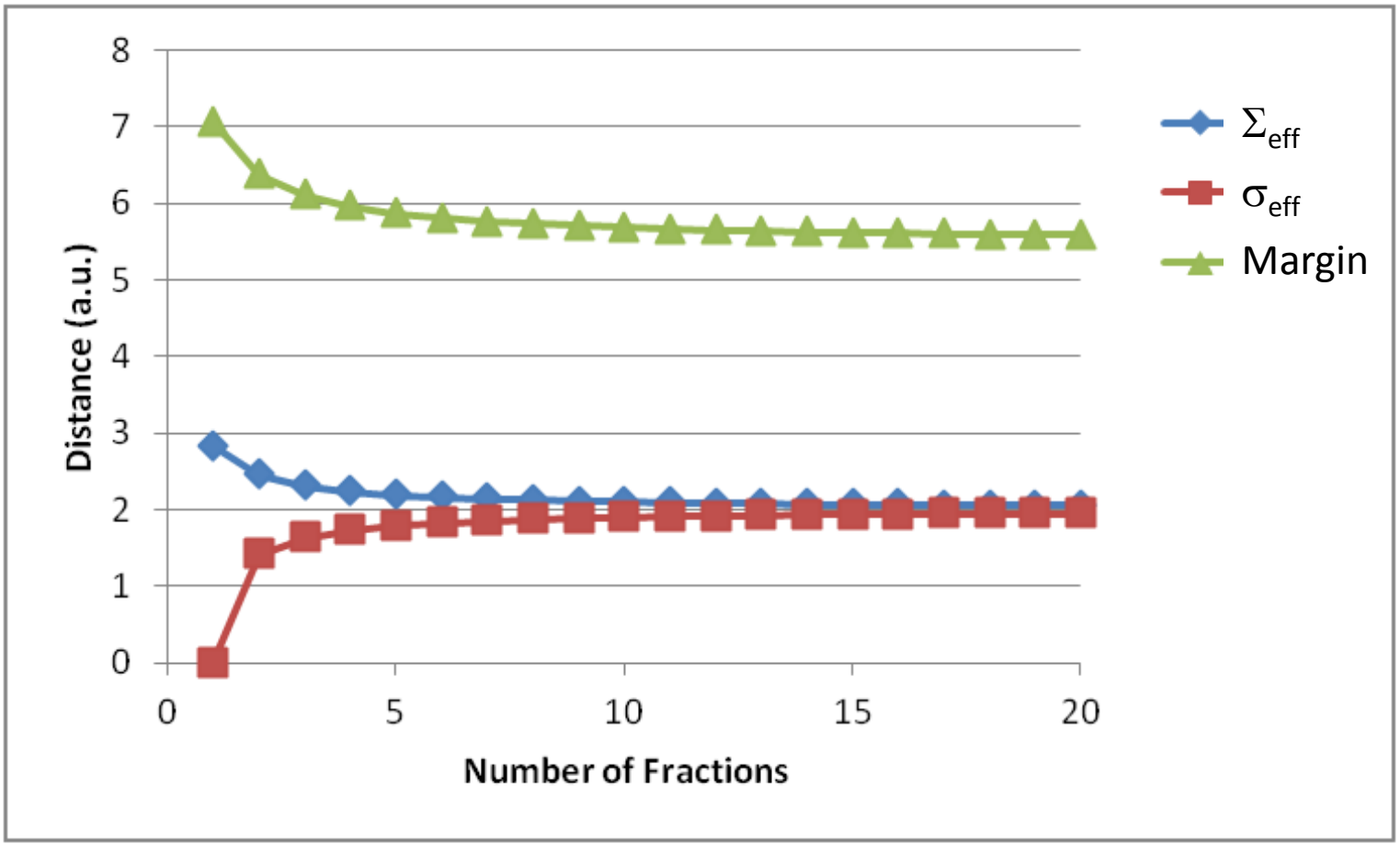
Margin and Number of Fractions



Σ = 2 mm, σ = 2 mm, P=80%

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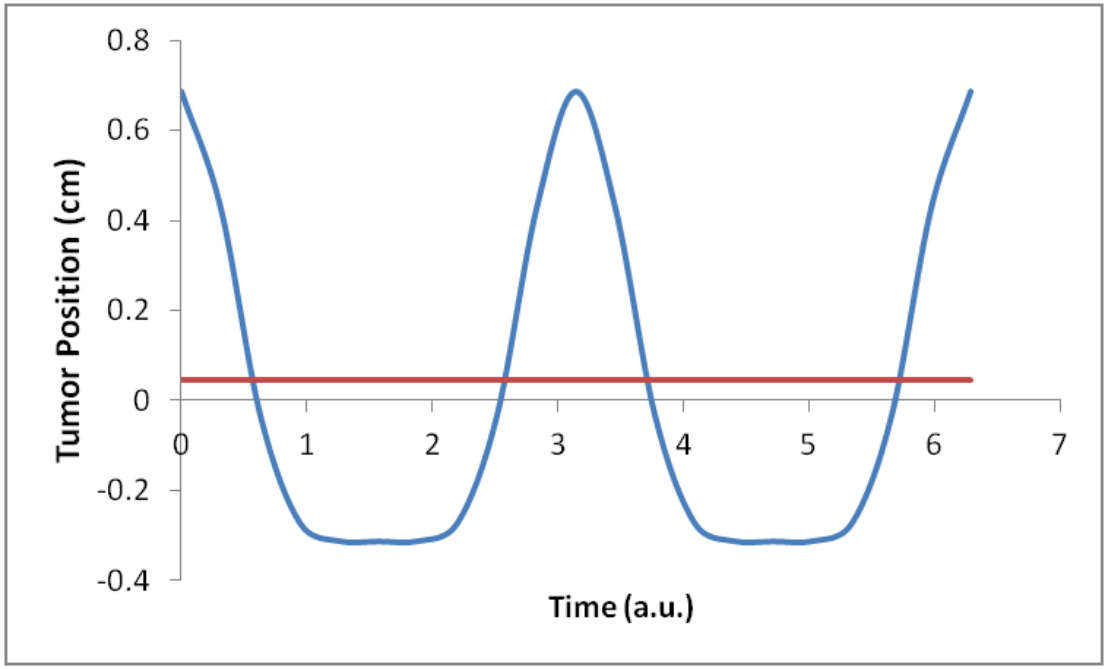
Including Error due to Respiratory Motion

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



- For blurring one needs the SD of the respiratory motion
  - $\sigma = 0.358A$

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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?

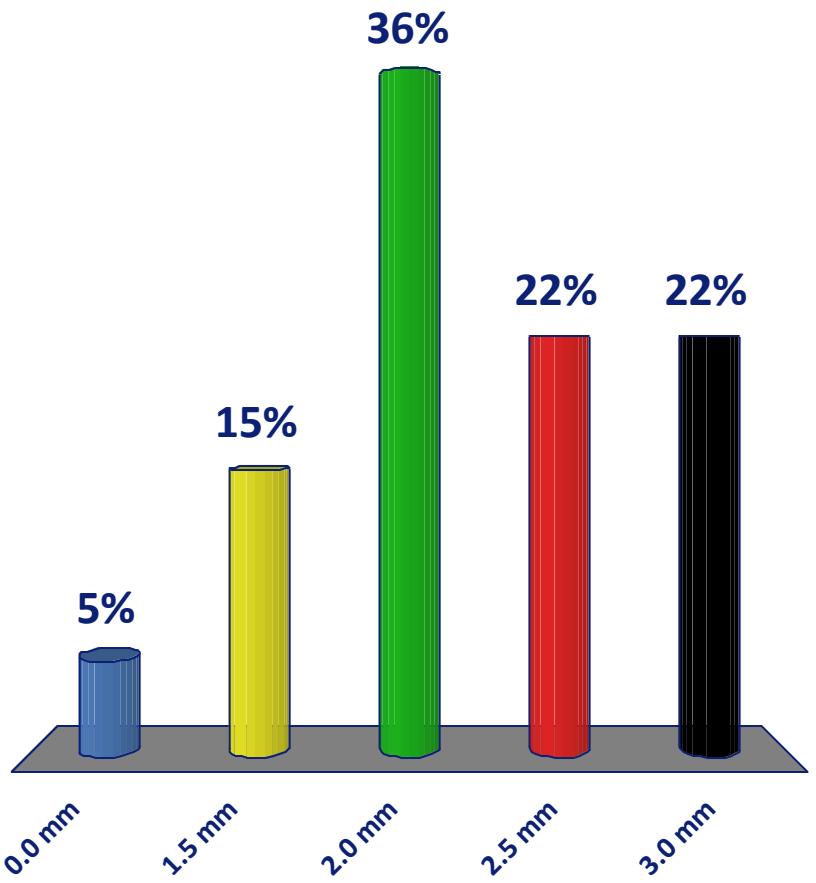
A. 0.0 mm

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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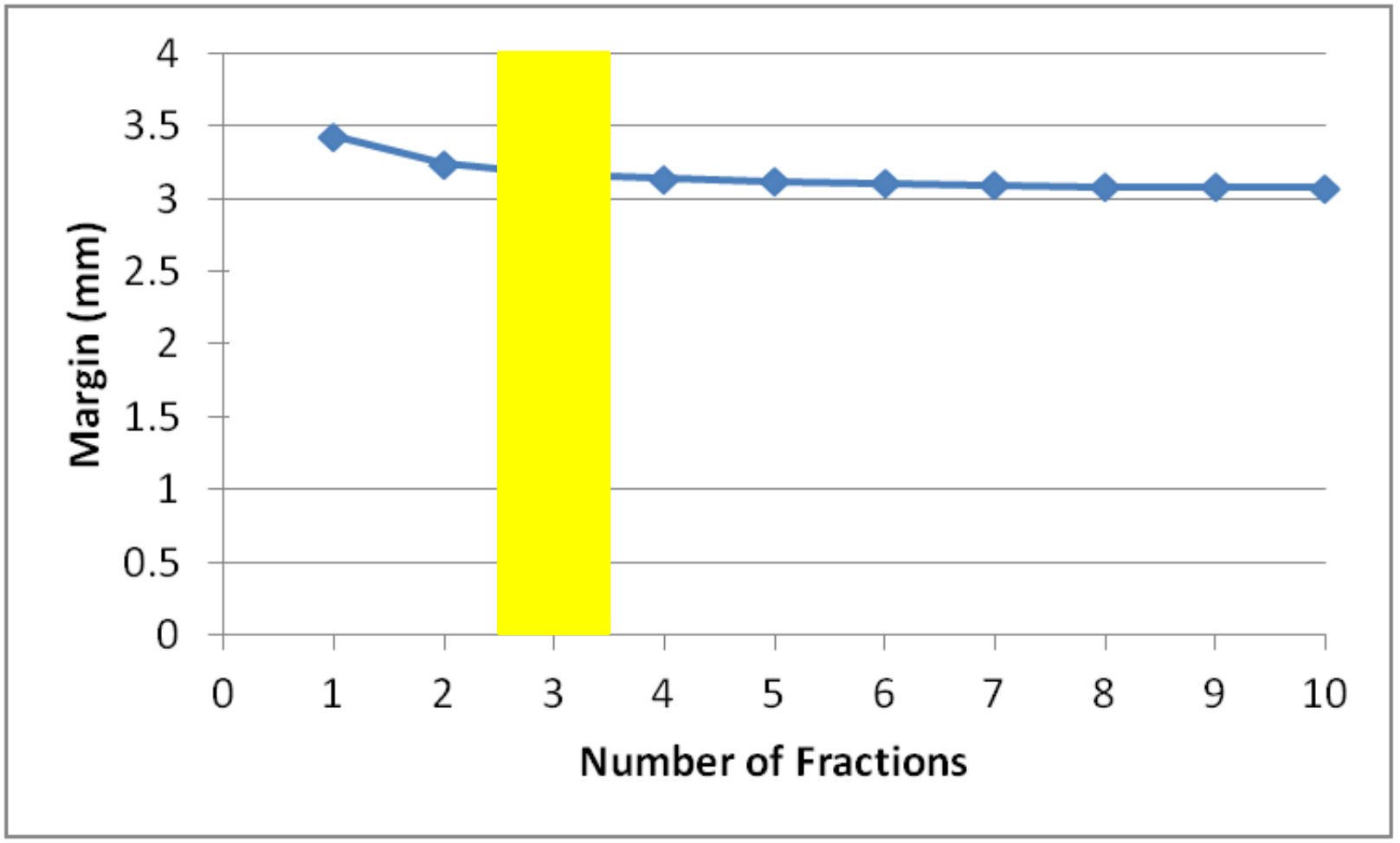
Results SRT Example



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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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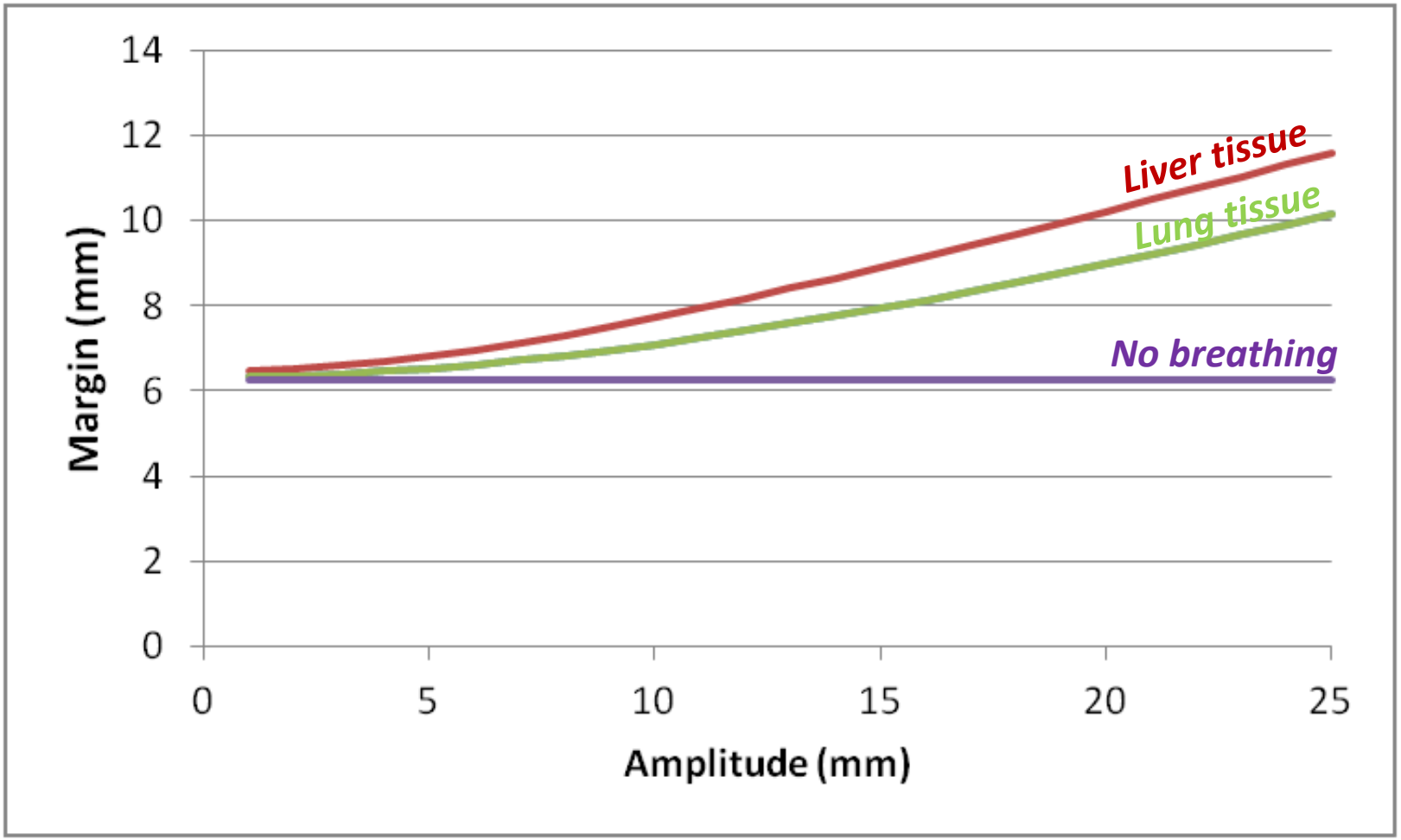
Margins SBRT Lung Case



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INTERNAL TARGET VOLUME

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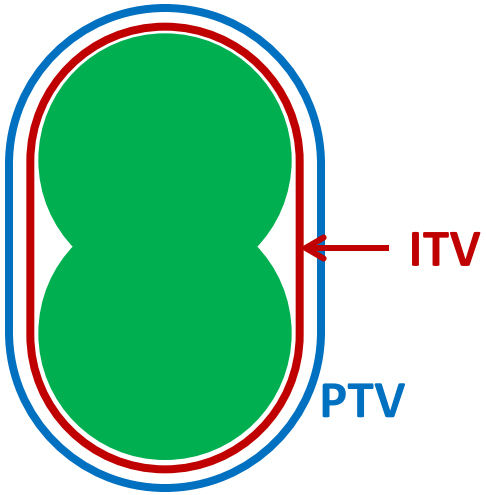
ITV Concept in ICRU-62 Report

- 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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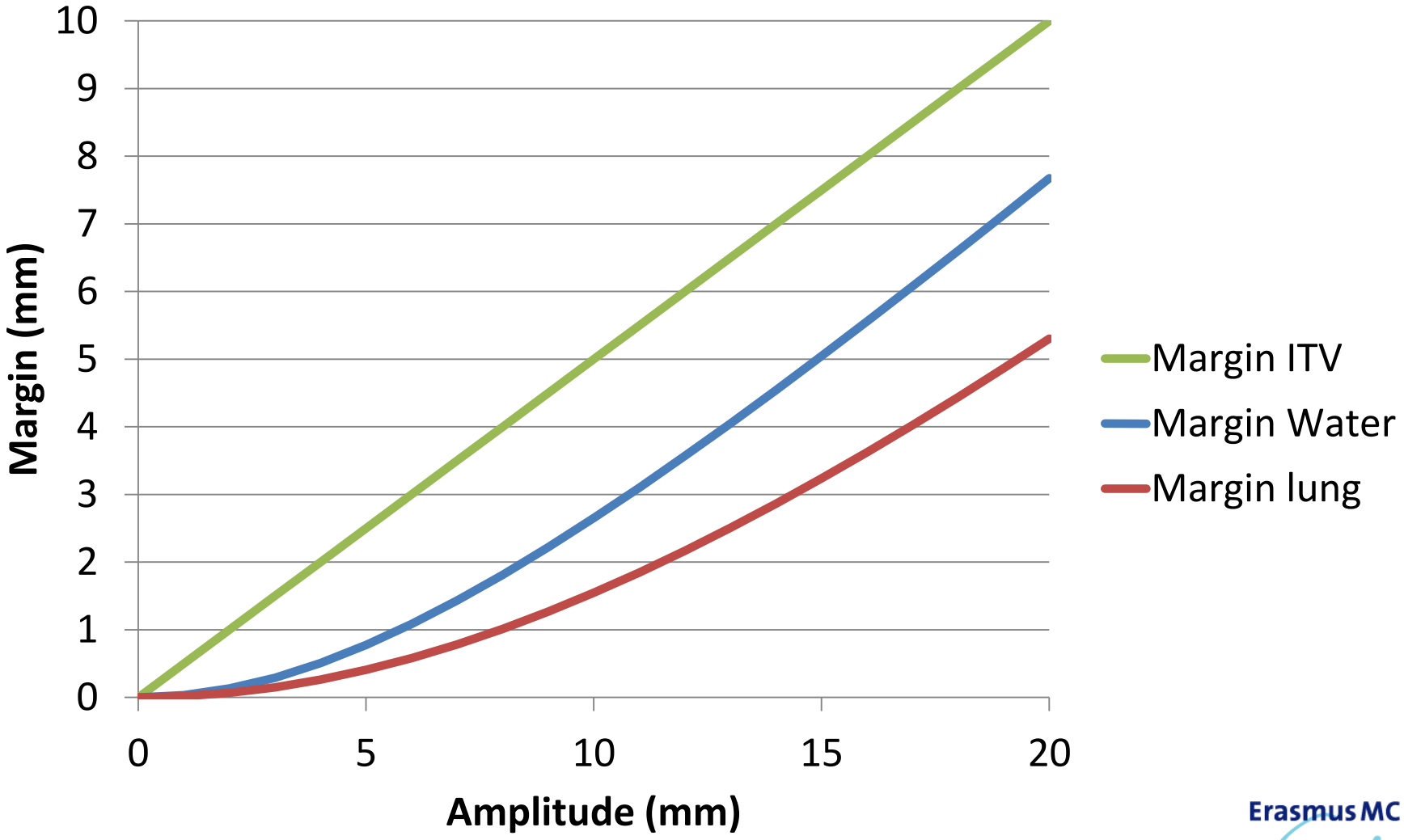
Margin vs ITV for Perfect Inter-fraction Alignment



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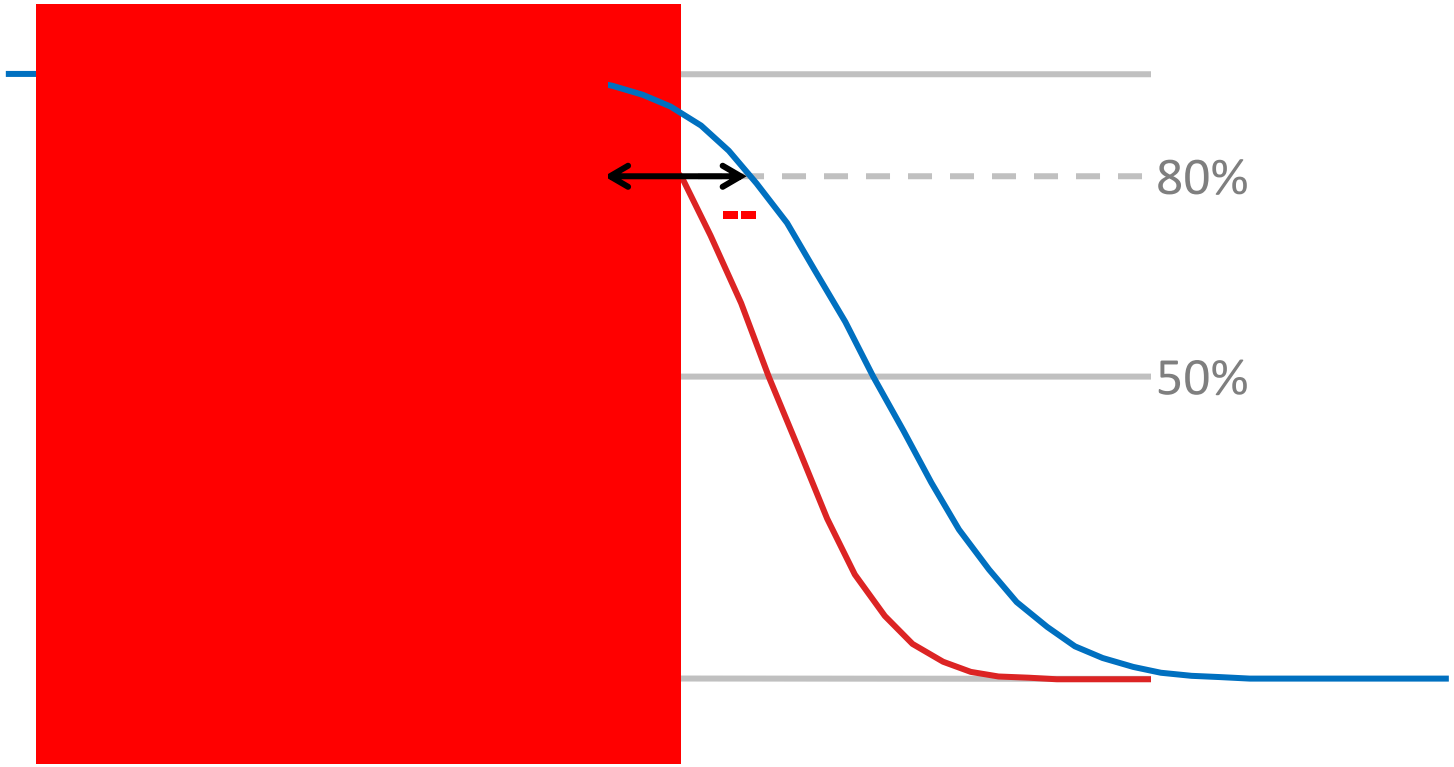
Margin Recipe for Random Error



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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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Erasmus MC

Management of uncertainties in targets w/o respiration motion

Prostate

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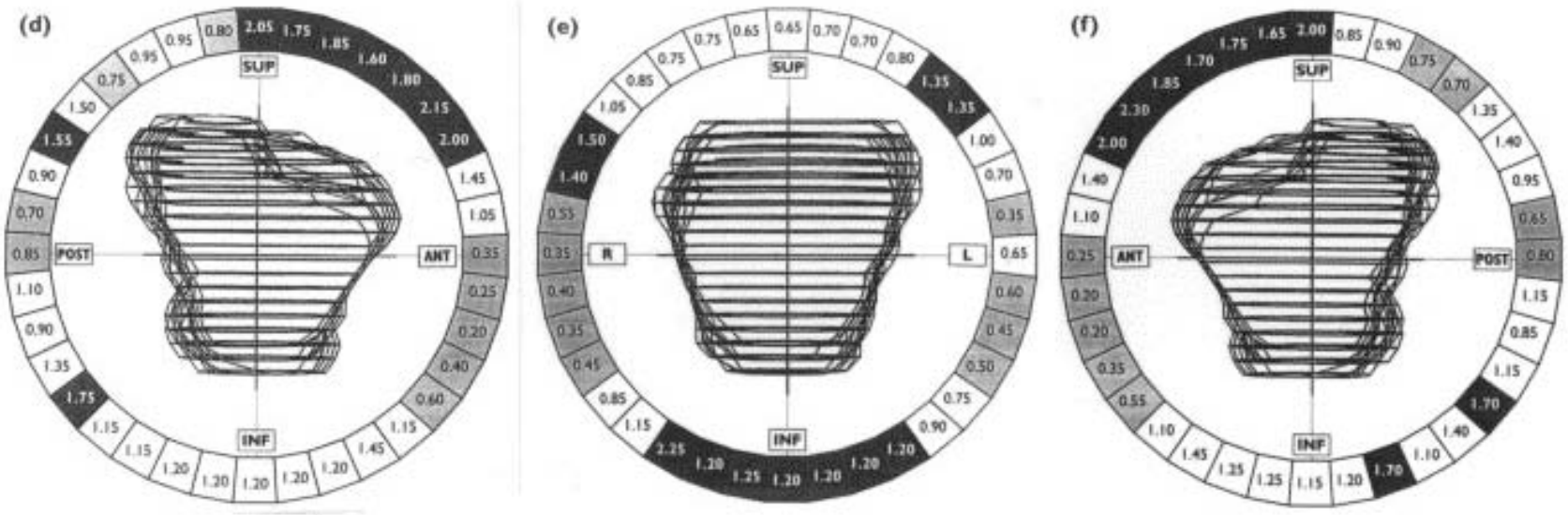
ESTRO School

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

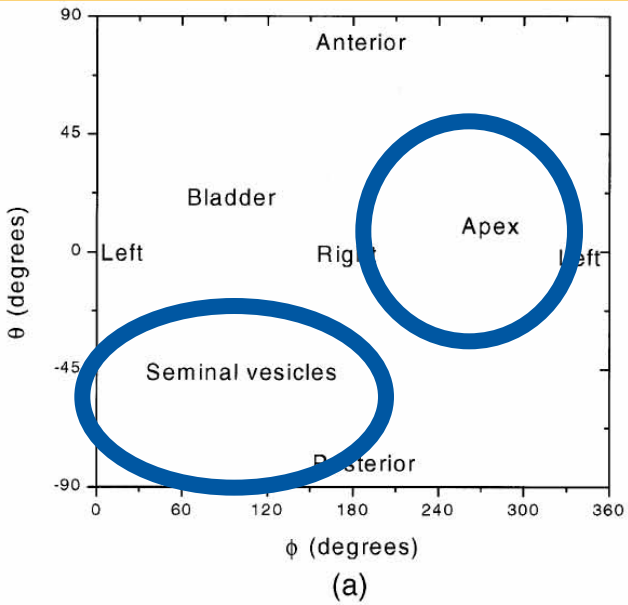


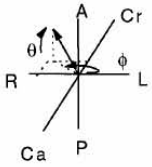
Seddon et al, Radiother Oncol, 2000; 56(1); 73–83

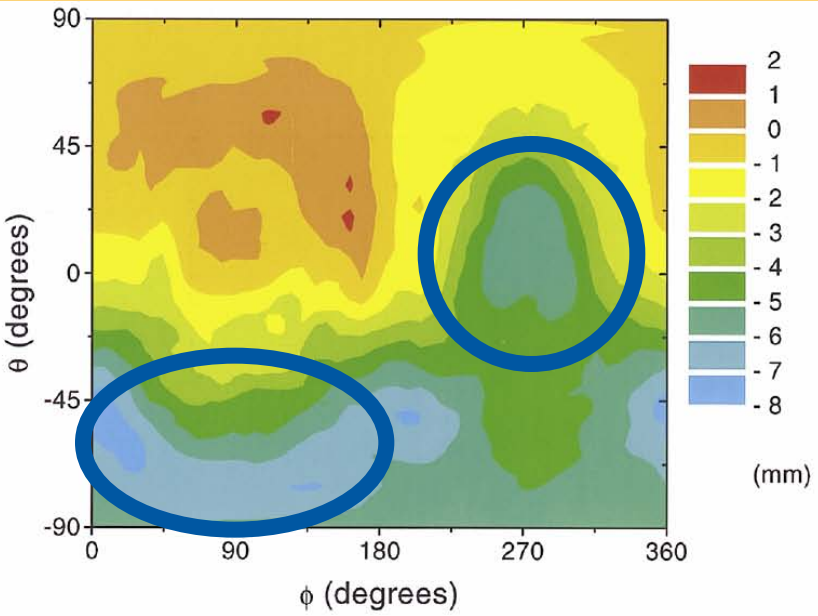
Large interobserver differences in contouring the prostate.

Contouring uncertainty

MRI versus CT





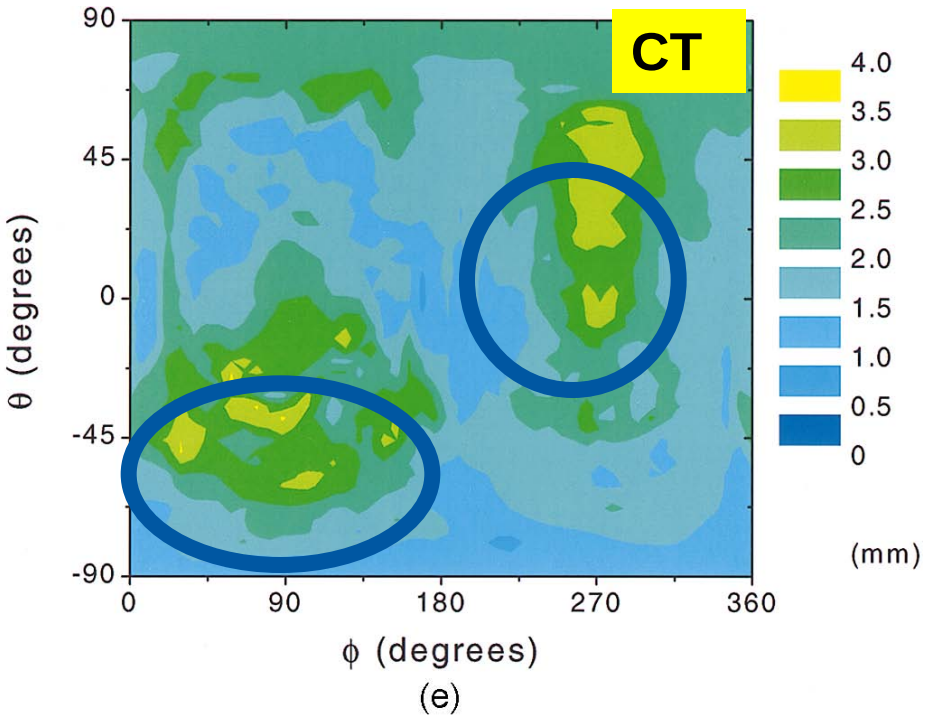


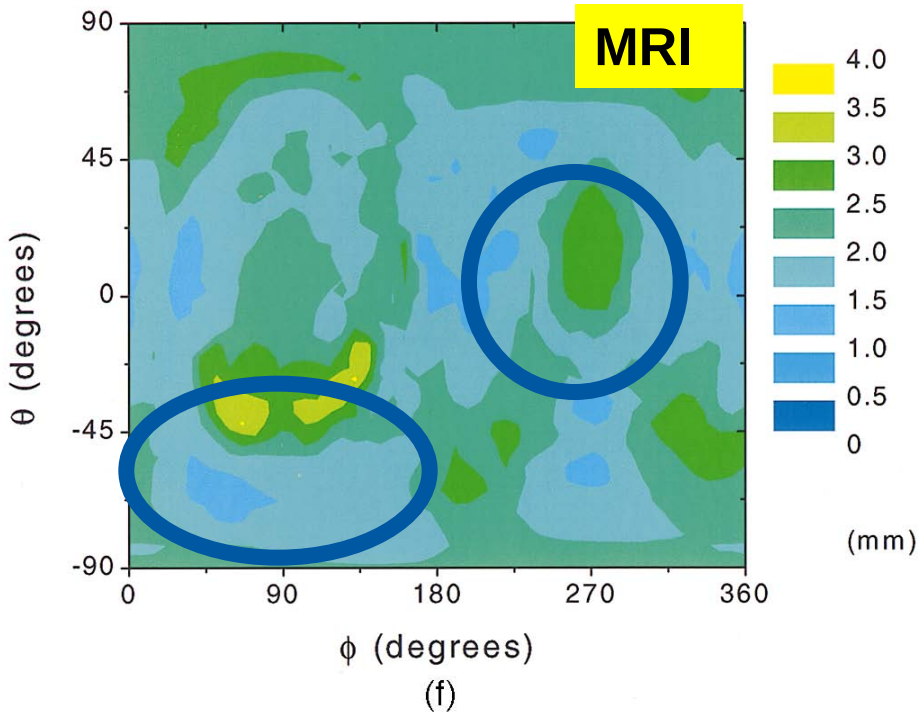
Volume: CT: 64cm^3 MRI: 45cm^3

Rasch et al, IJROBP 1999

Contouring uncertainty

Inter-observer variations



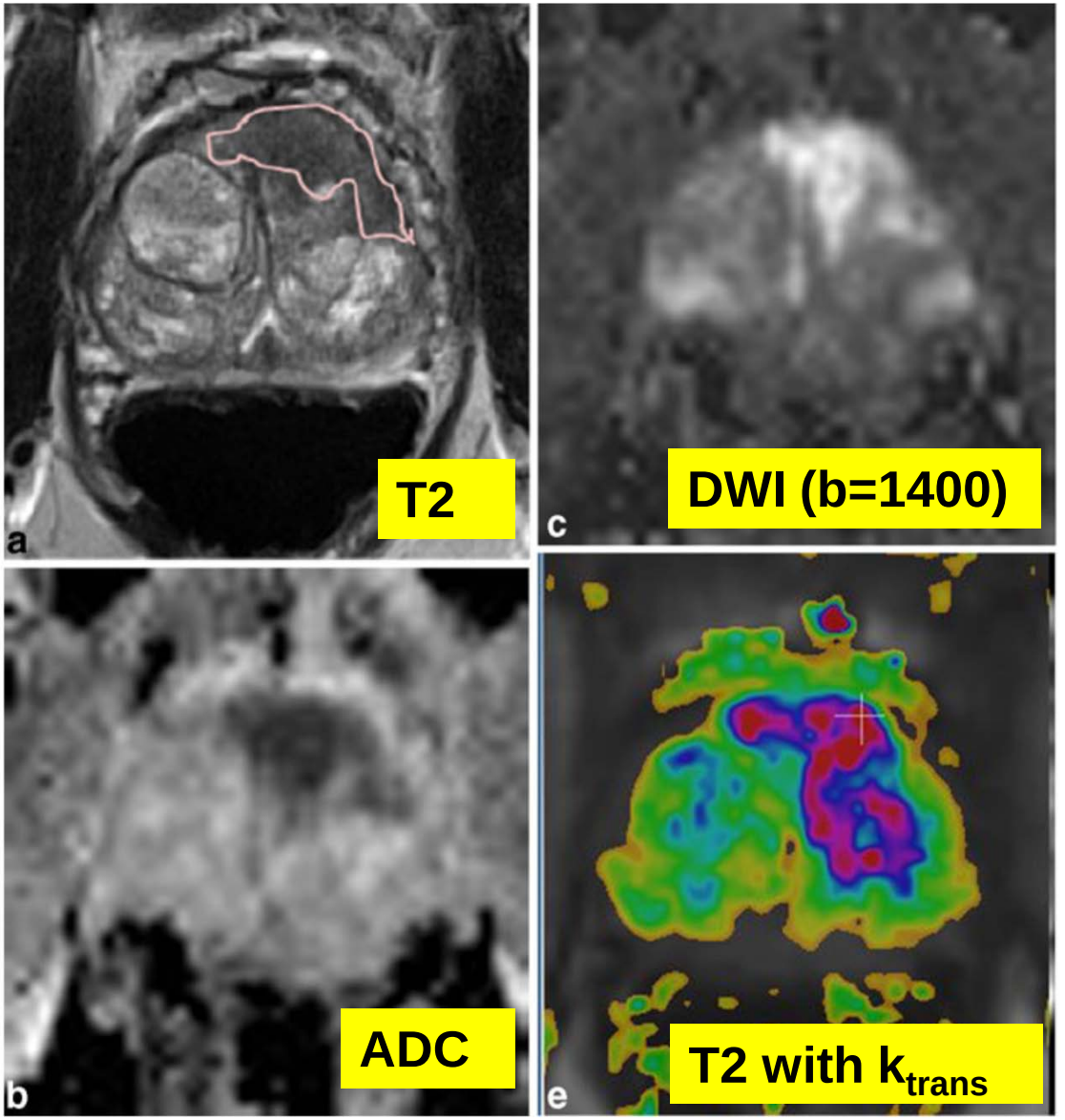


Rasch et al, IJROBP 1999

Reduced inter-observer variations using MRI.

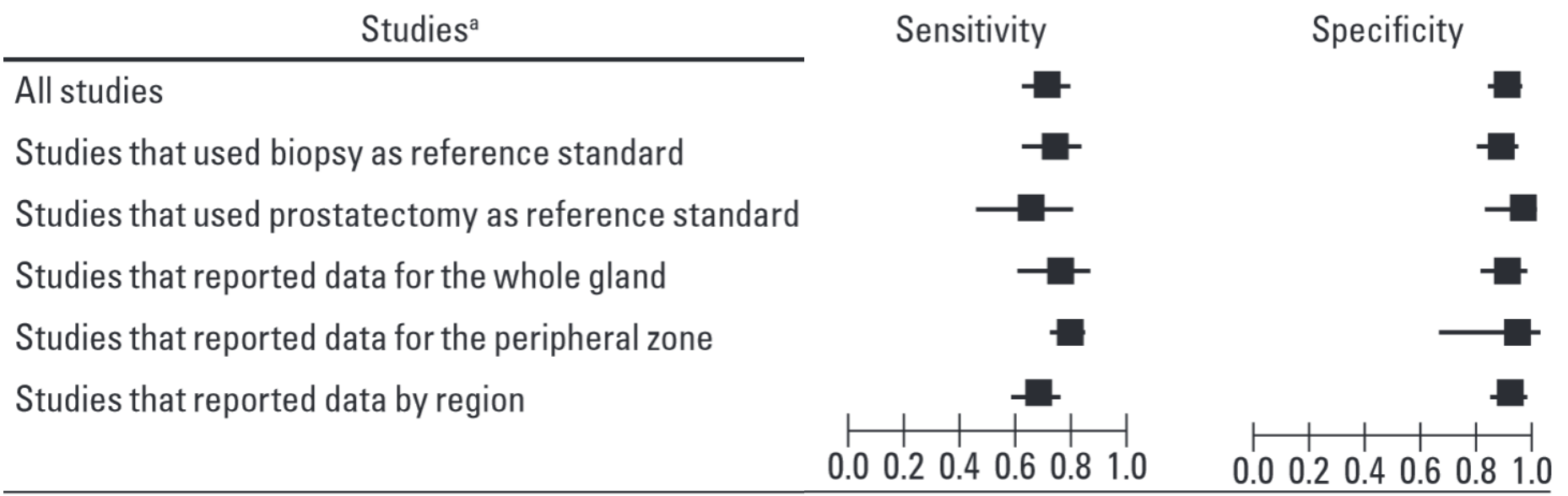
Definition of the tumor lesion

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

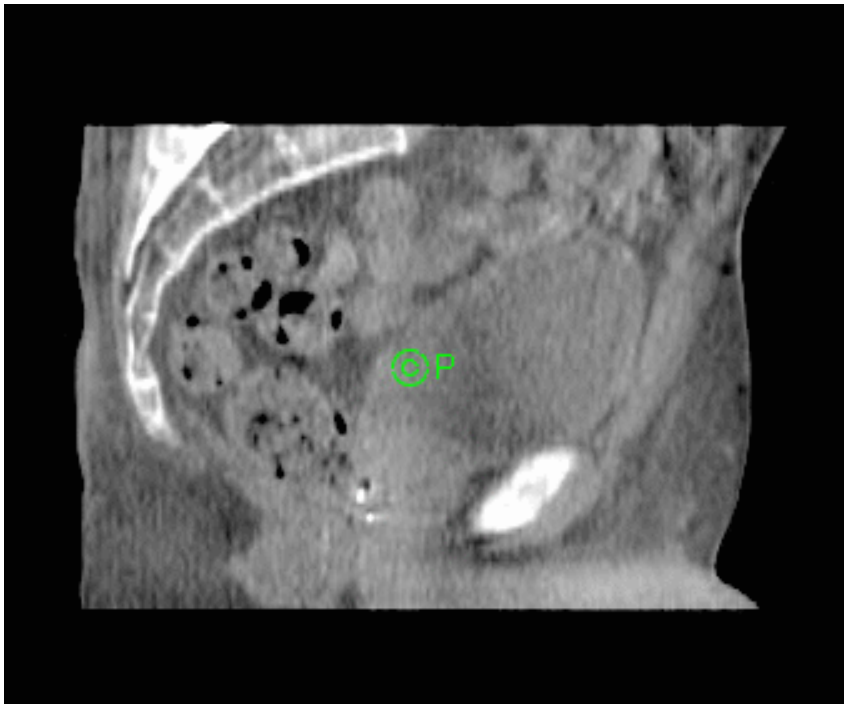
Calypso markers give large artefact in MRI

- 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



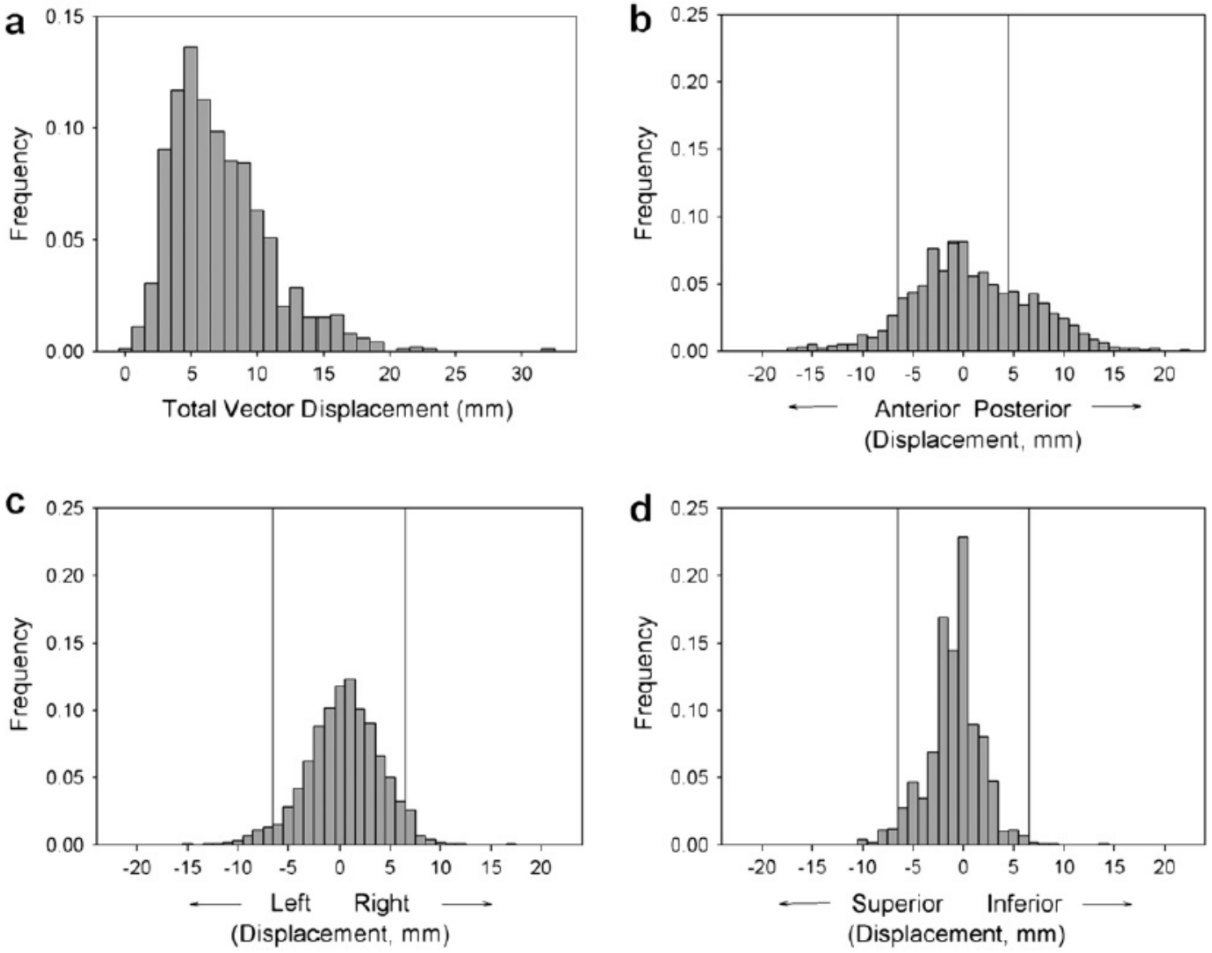
Different bladder filling

Different rectal filling

Different patient positioning

Anatomical changes of the patient

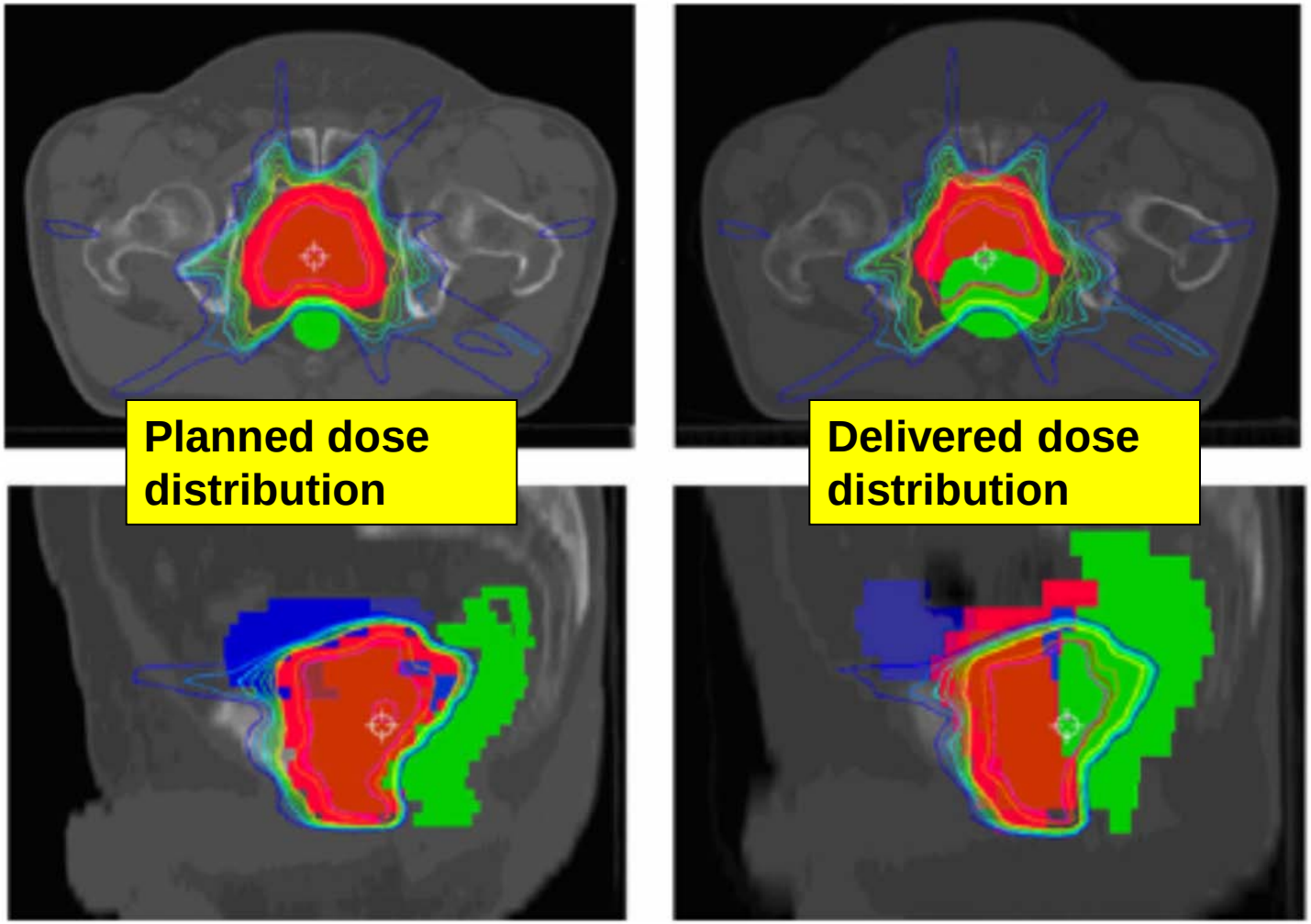
Interfractional motion



→ Up to 3 cm interfractional motion.

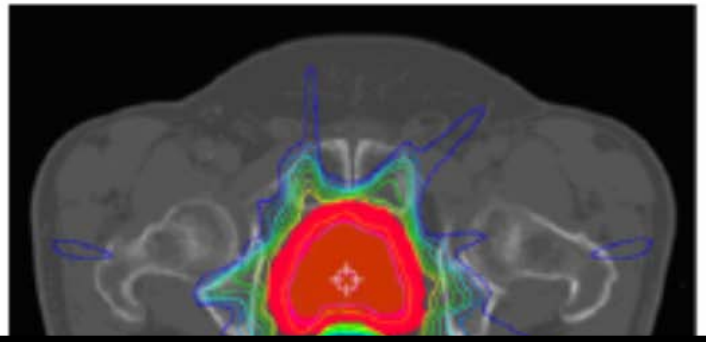
Bylund et al, IJROBP 2008

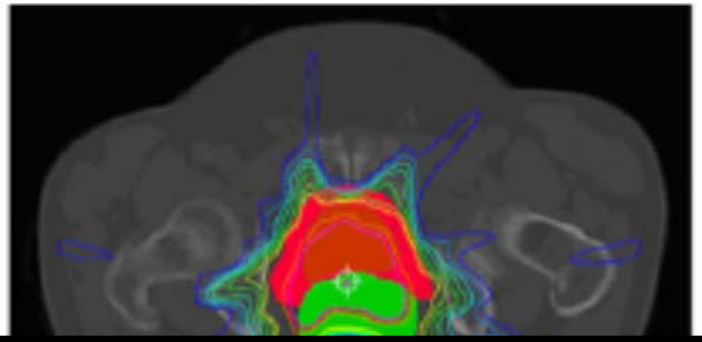
Interfractional motion – Dosimetric impact



Wertz et al, 2007, Phys Med Biol

Interfractional motion – Dosimetric impact



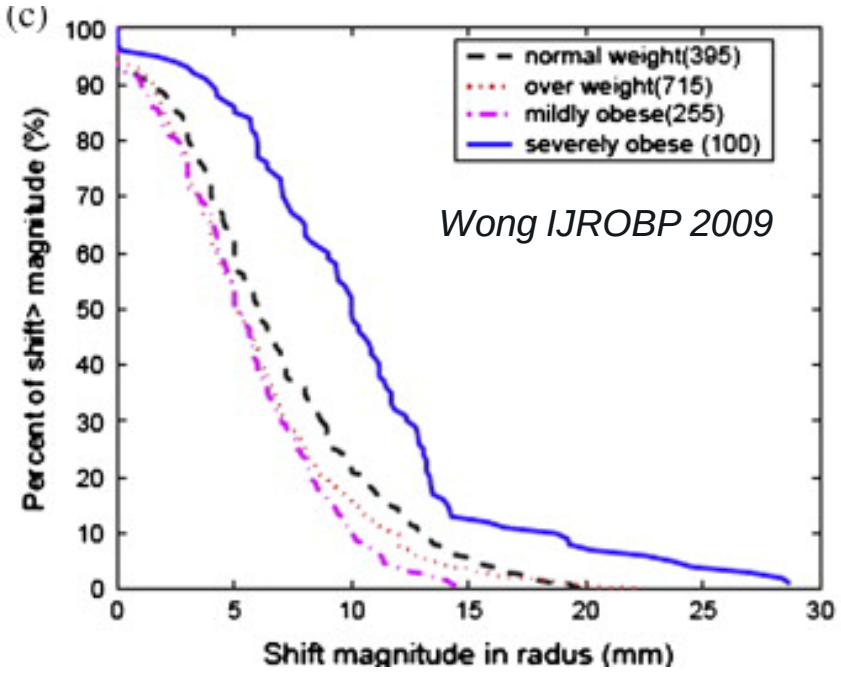


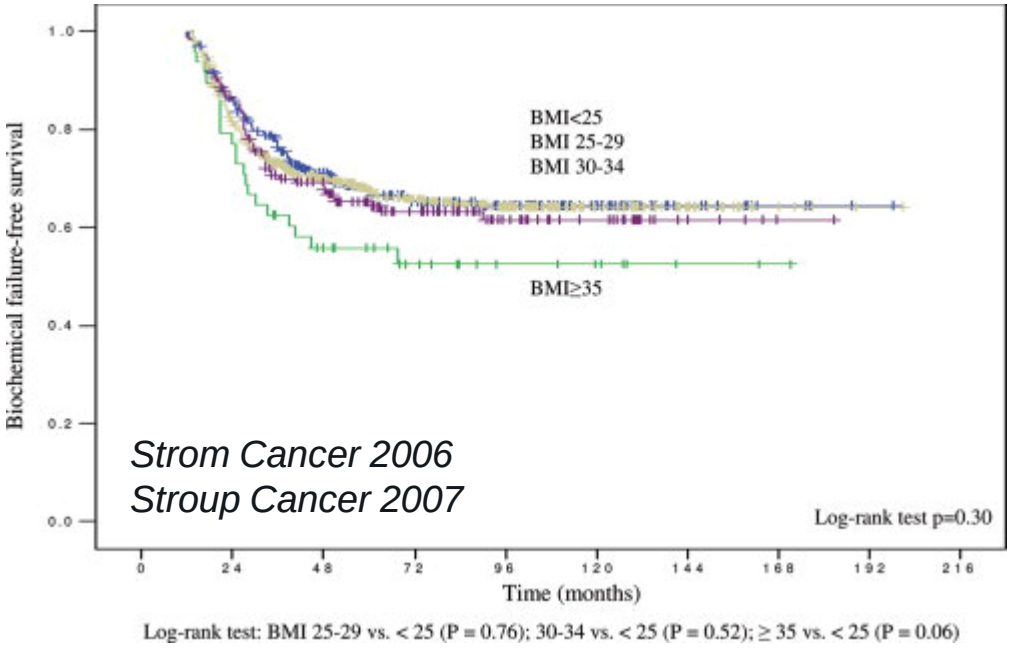
Volume covered by 95% dose	Reference plan [%] mean ± SD	Value deviations uncorrected plan [%-p] mean (min to max)
Prostate	84.5 ± 4.7	−13.3 (−23.6 to −2.1)
Seminal vesicles	67.4 ± 8.7	3.9 (−27.7 to 26.9)

Wertz et al, 2007, Phys Med Biol

Interfractional motion – Impact on outcome

Set-up errors in relationship to the patients` BMI



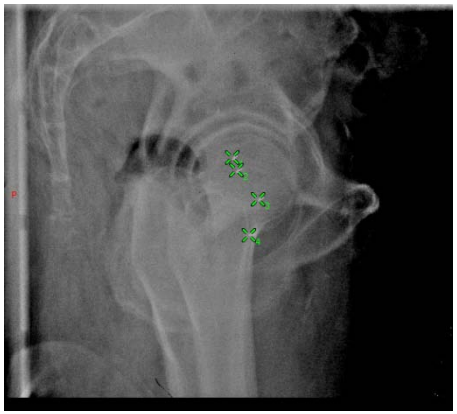


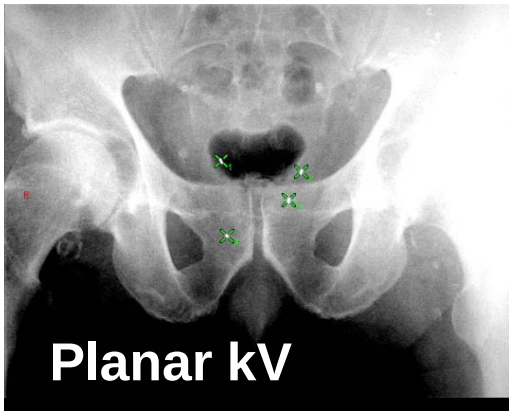
Inaccurate set-up could explain inferior PSA control in obese patients

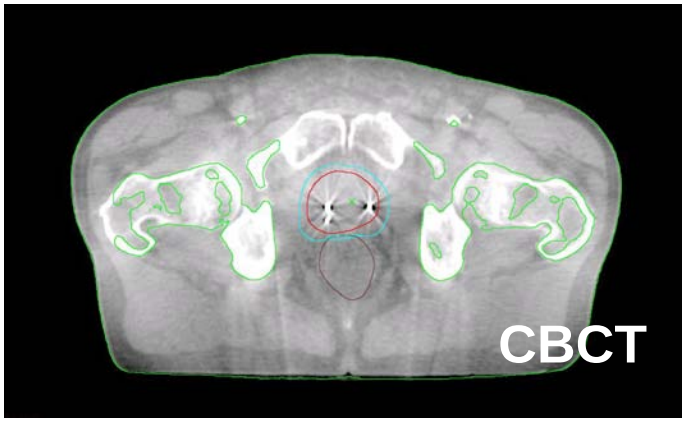
➢Need for image – guidance

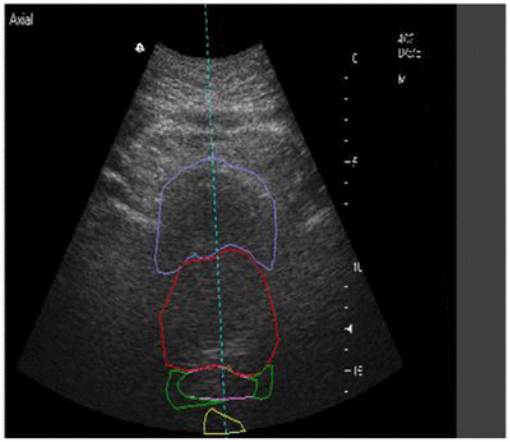
Management of interfraction motion

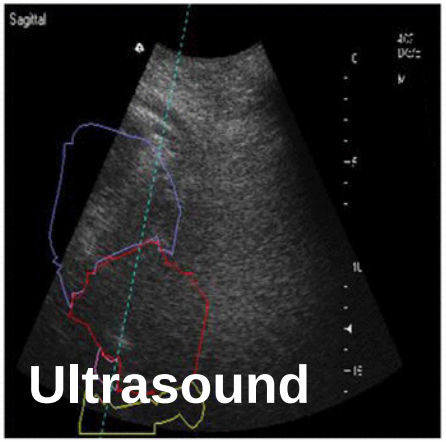
Image guidance

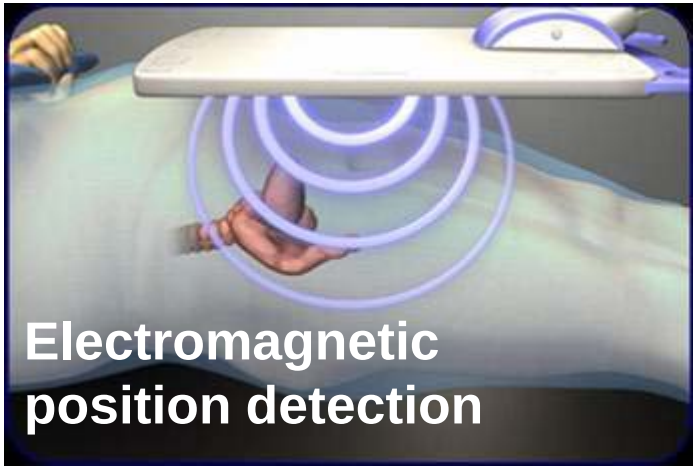






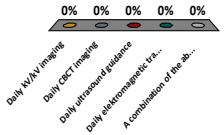






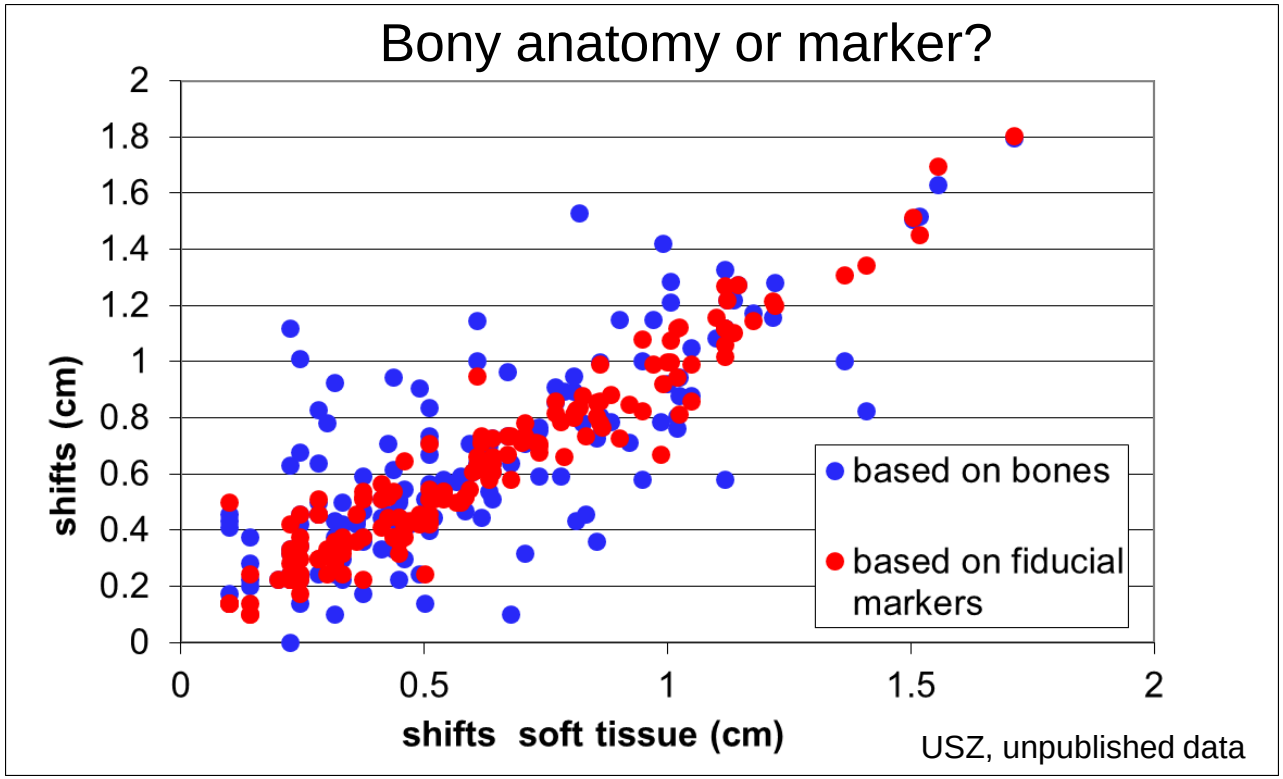
What kind of Image guidance would you use for SBRT prostate cancer?

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?

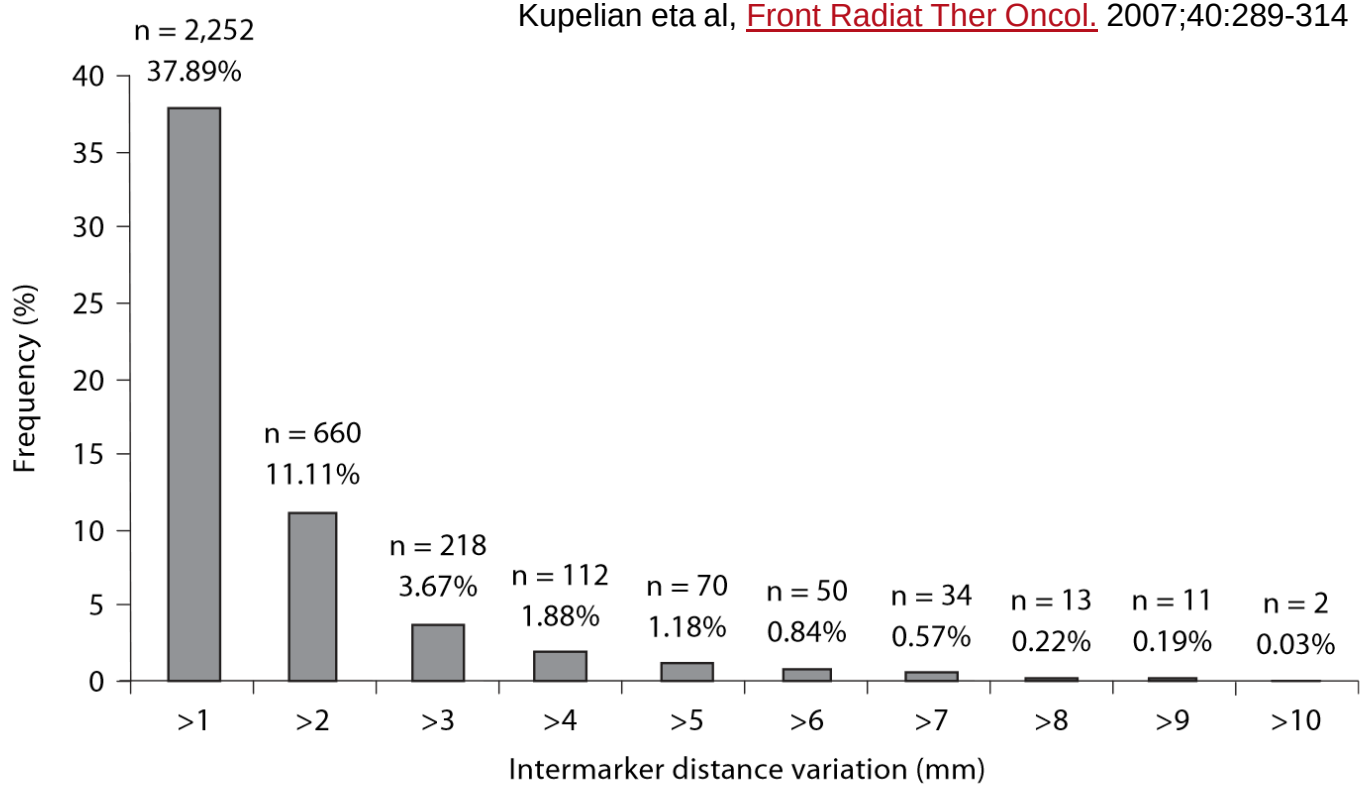


Matching on the bony anatomy leads to large uncertainties and is not recommended for prostate SBRT.

Management of interfraction motion

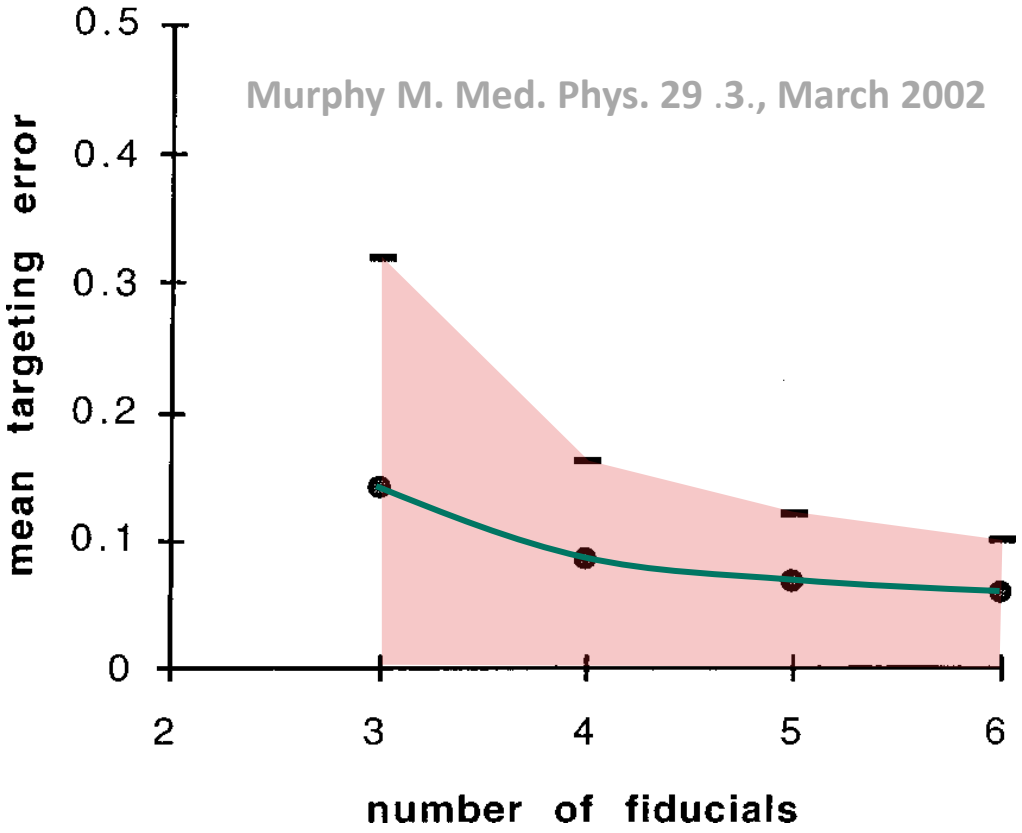
Image guidance: Are the markers stable?

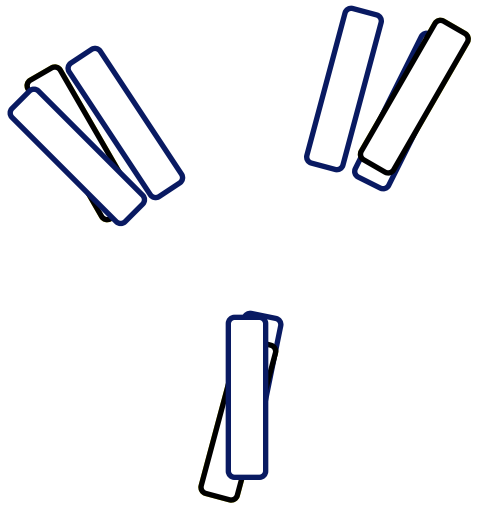
Kupelian eta al, Front Radiat Ther Oncol. 2007;40:289-314



Management of interfraction motion

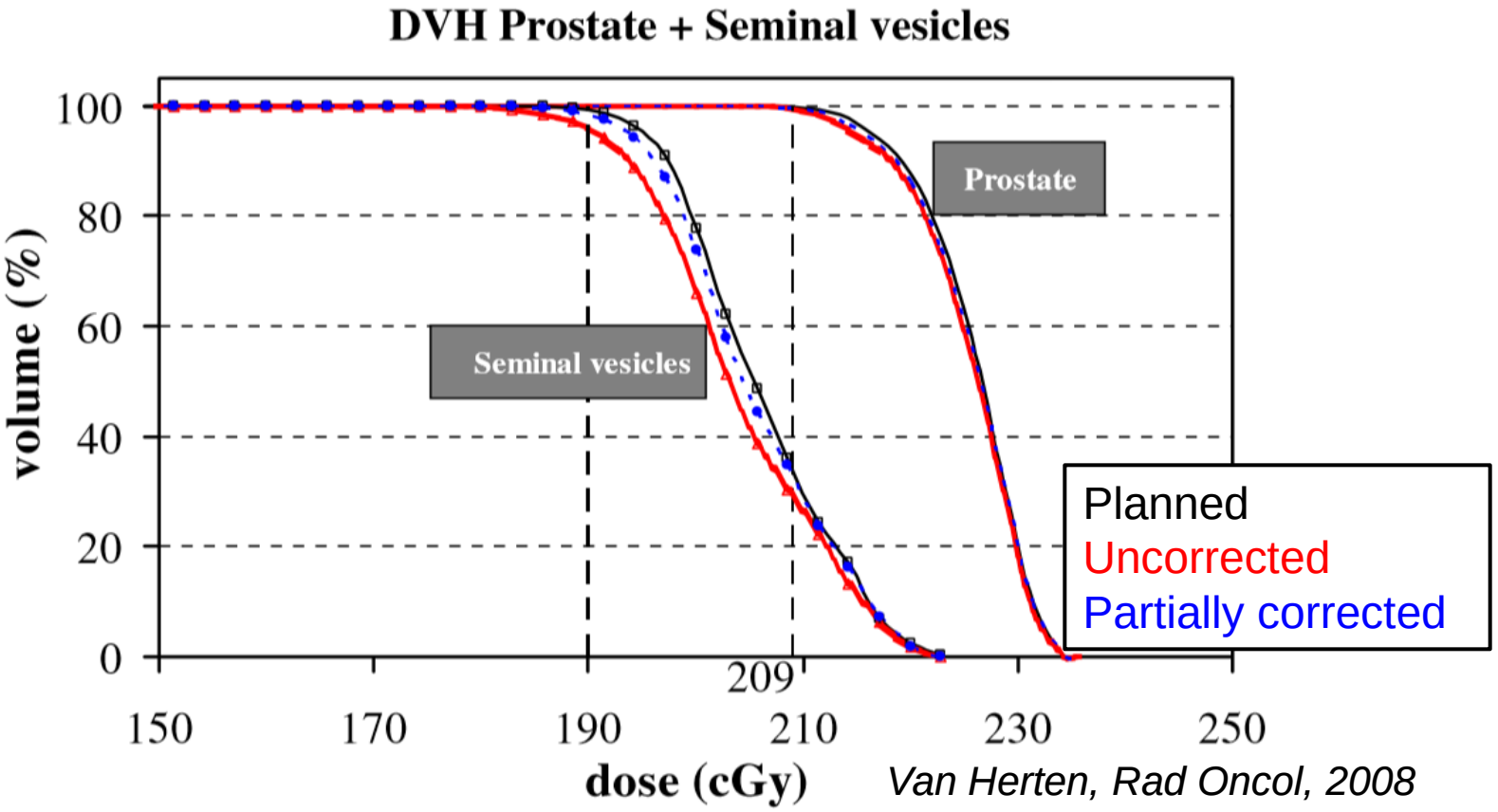
Image guidance: How many markers?





Management of interfraction motion

Image guidance: Importance of rotations

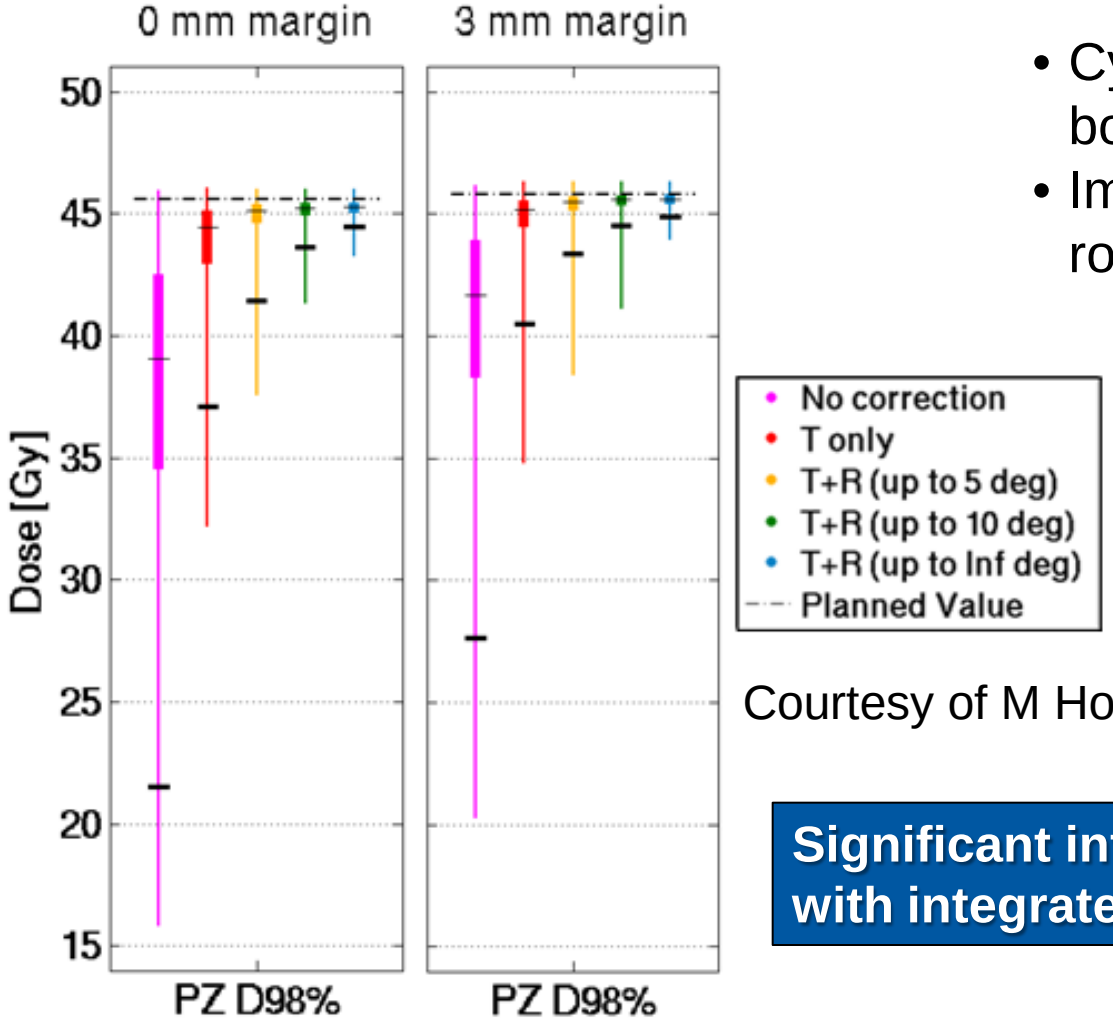


Van Herten, Rad Oncol, 2008

Small influence of rotations on dose distribution for fractionated RT

Management of interfraction motion

Image guidance: Importance of rotations



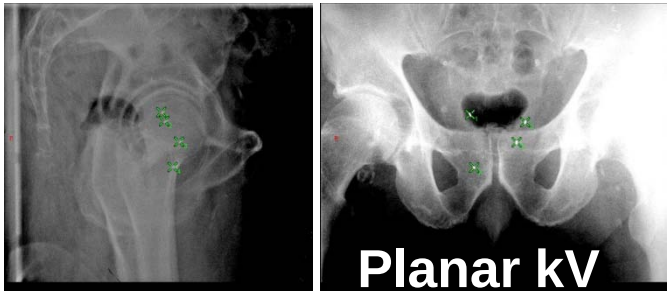
- Cyberknife patients with boost in peripheral zone
- Improved coverage with rotation correction

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

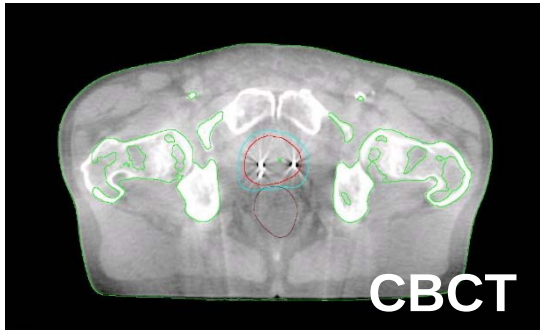
No information on organs at risk (mainly rectum and bladder)

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

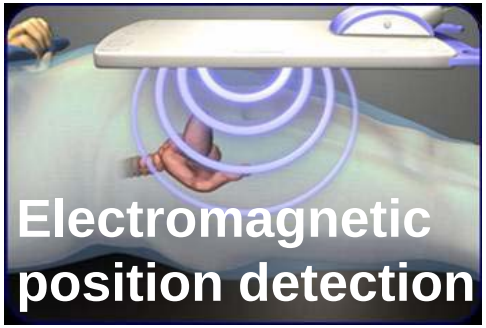
Can detect deformations

Disadvantages

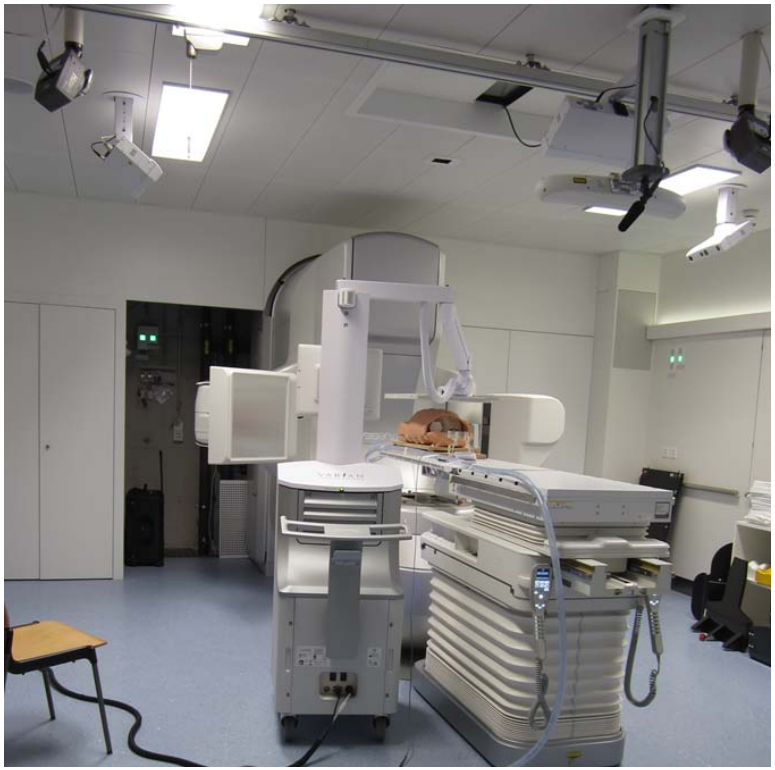
Intrafractional motion might occur during image acquisition

Management of interfraction motion

Image guidance:

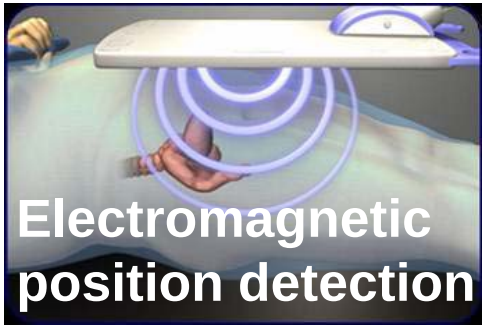


How does it work?



Management of interfraction motion

Image guidance:



Advantages

6D information in real-time

User independet accuracy

High accuracy

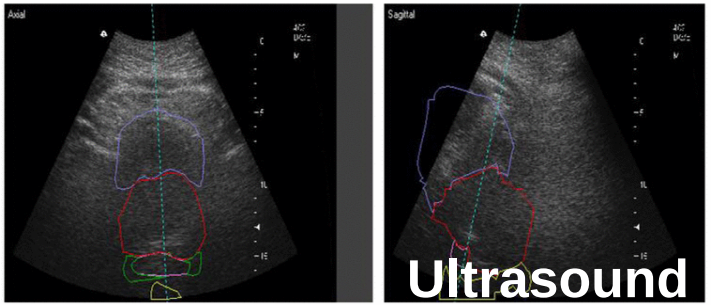
Disadvantages

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

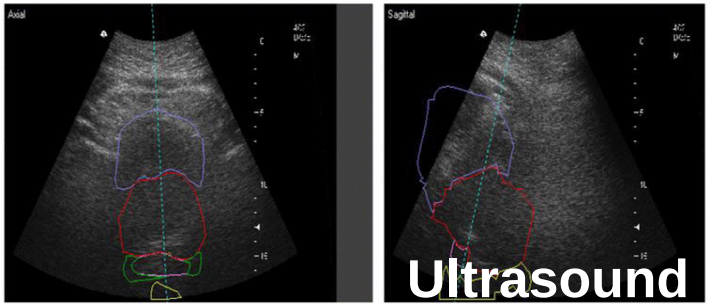
(2) SonArray vs. markers (ExacTrac) [6] Scarborough et al. IJROBP 2005;63:S196.

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

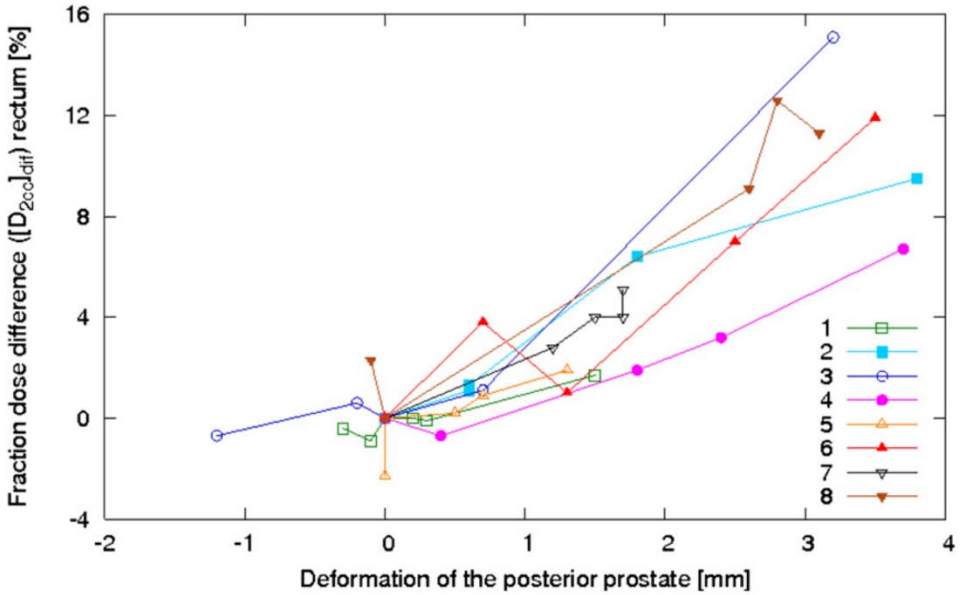
Remaining uncertainty - deformations

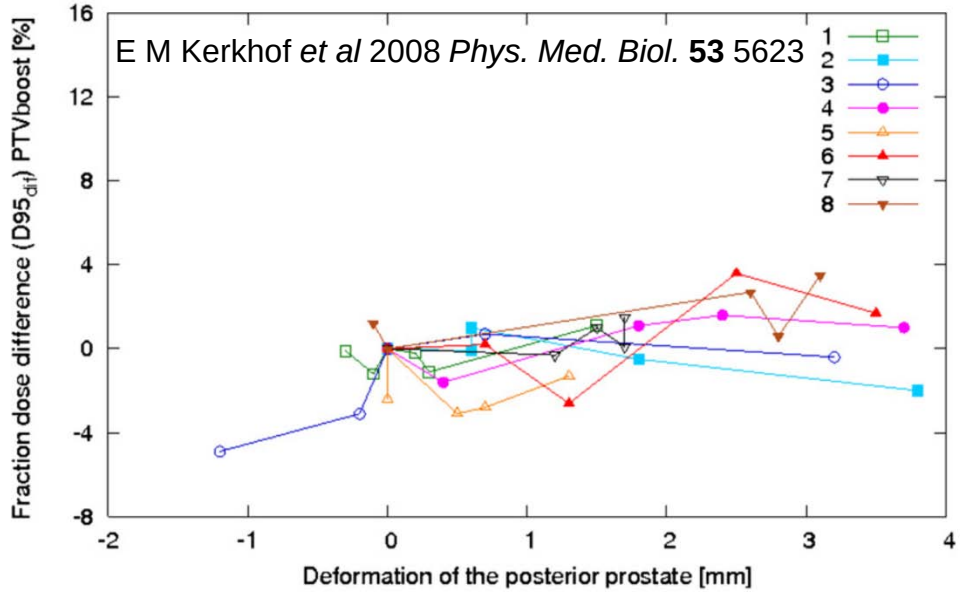
On 8 volunteers, 6MRIs were performed.

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

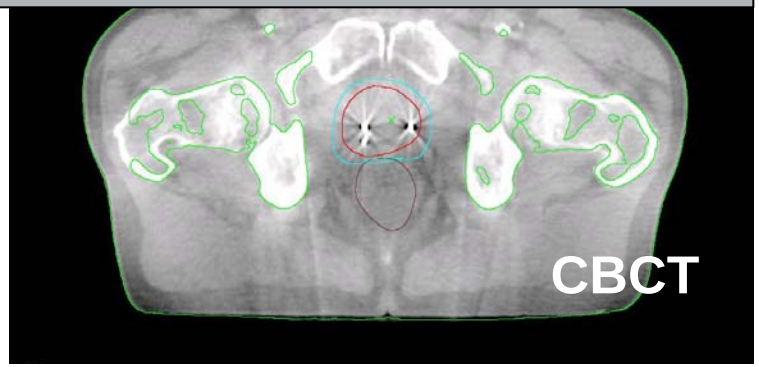
UniversitätsSpital Zürich

Image guidance for prostate SBRT @ USZ

Positioning based on Calypso

Intrafractional motion monitoring using Calypso, position correction for shifts larger 2mm

CBCT imaging to check bladder and rectum filling as well as deformations



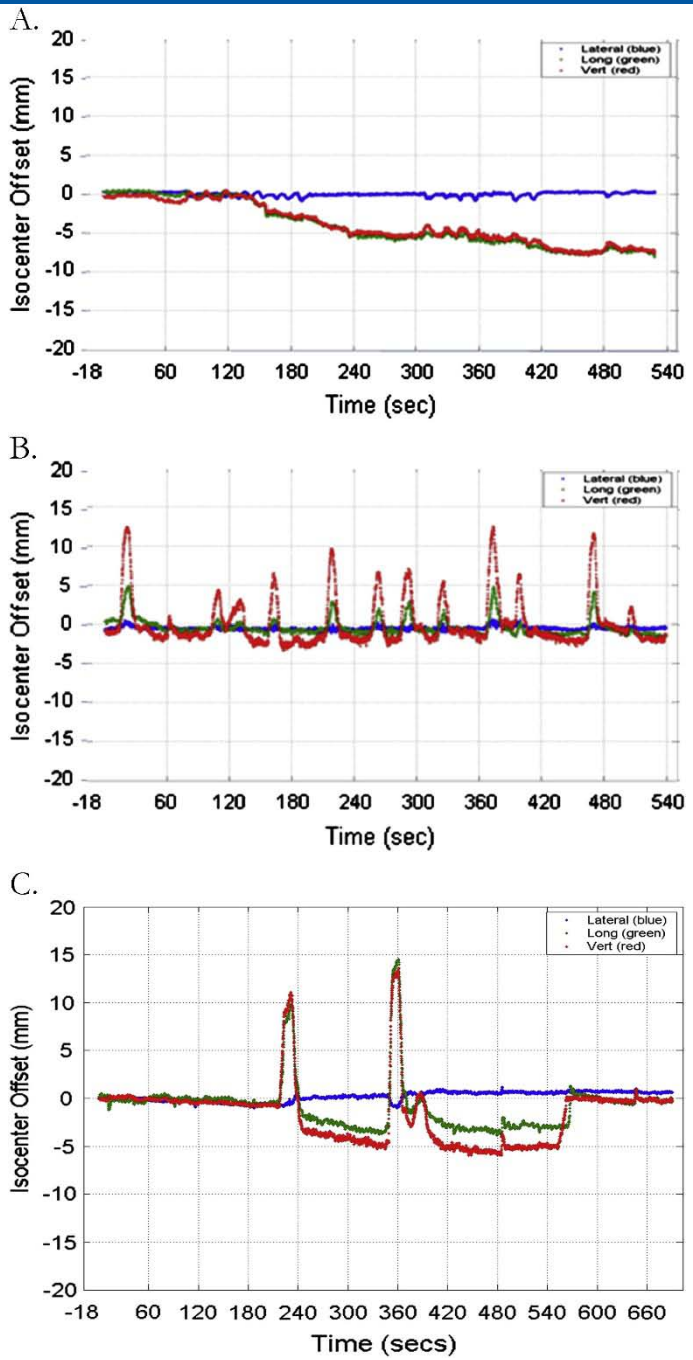
Intrafractional motion

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

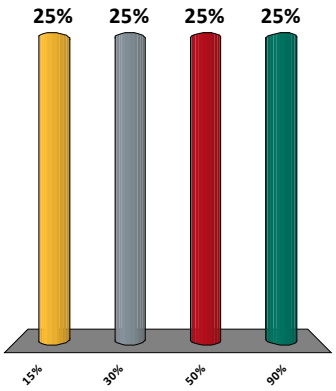
During a prostate SBRT treatment fraction, how often does on average the prostate move more than 2mm?

A. 15%

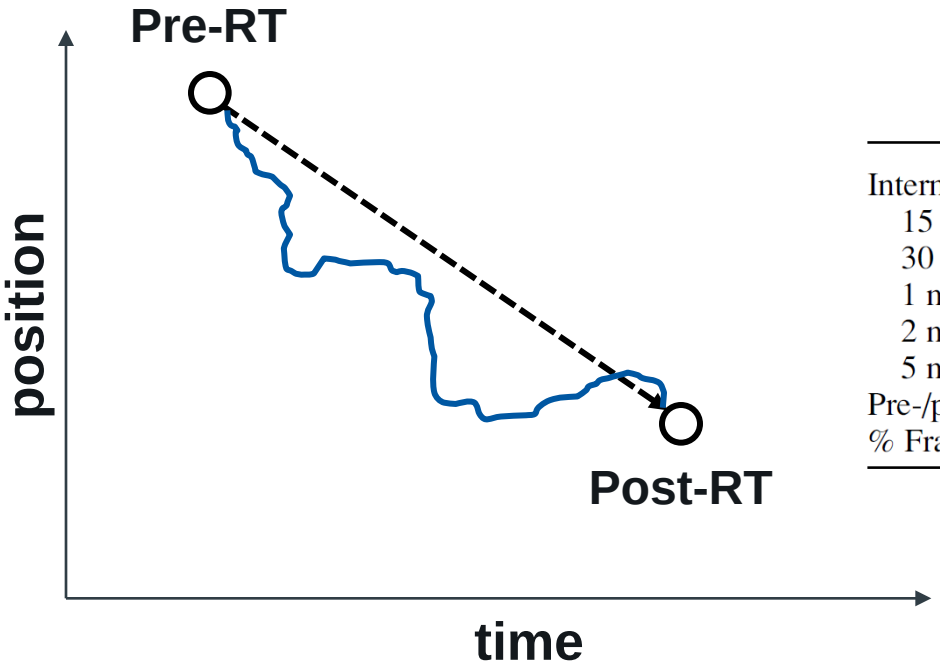
B. 30%

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

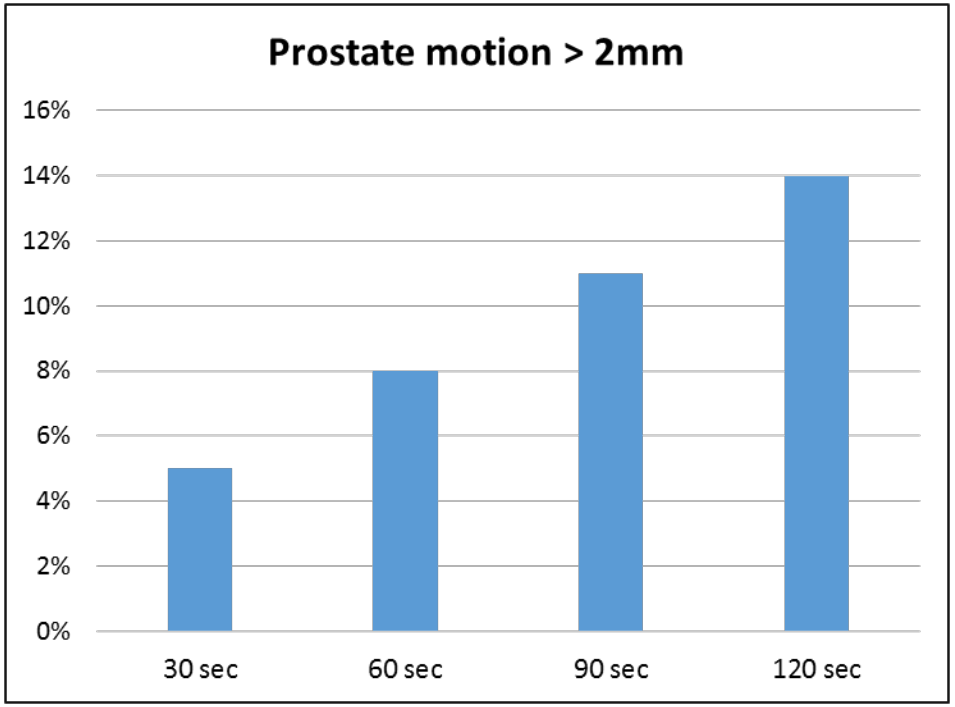
30 sec

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

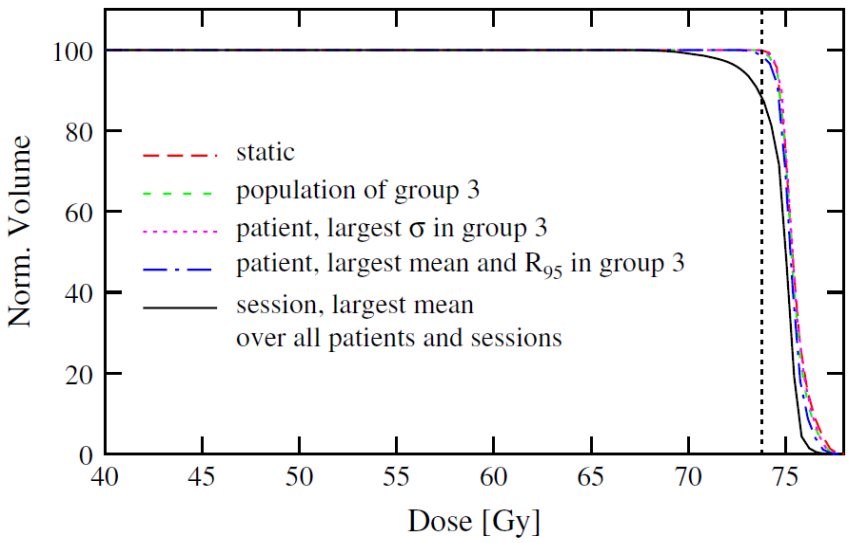
- **Intra-fractional prostate motion „usually“ within 2mm**
- **Intrafractional motion increases with time.**

Dosimetric impact of prostate motion

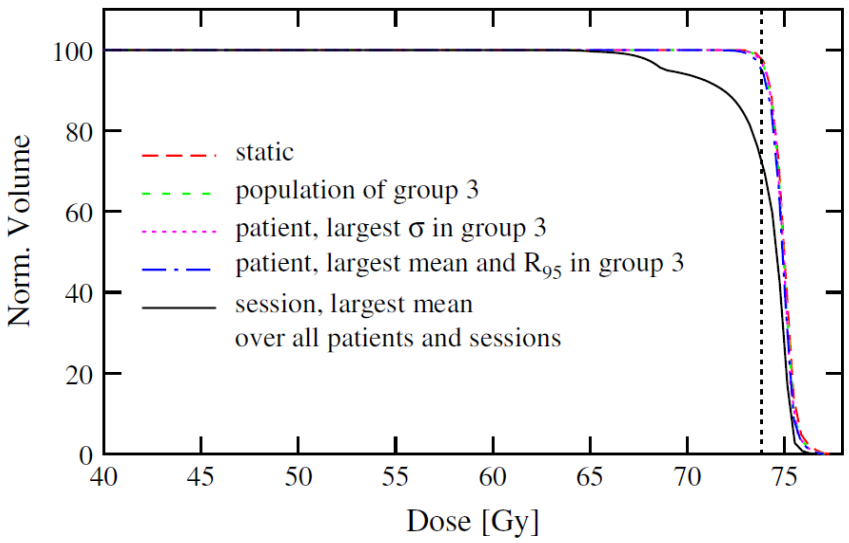
Conventionally fractionated radiotherapy:

Haisen IJROBP 2008

5mm margin



2mm margin



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

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ESTRO School

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

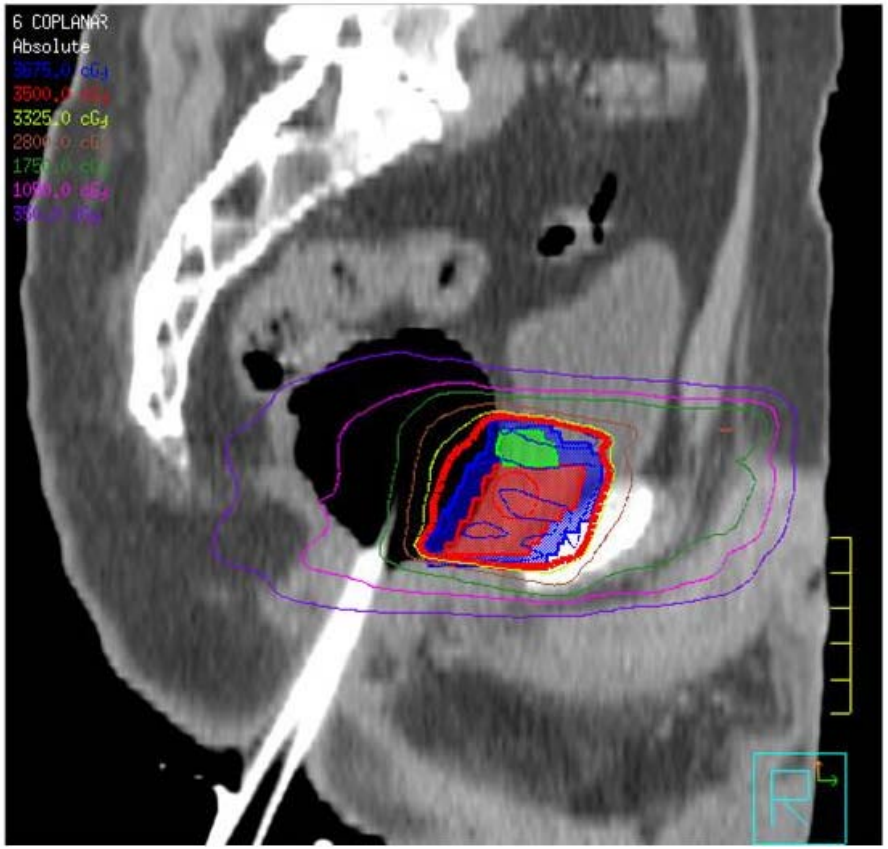
Dietry protocols or magnesiumoxides are not recommended for routine clinical practice.

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

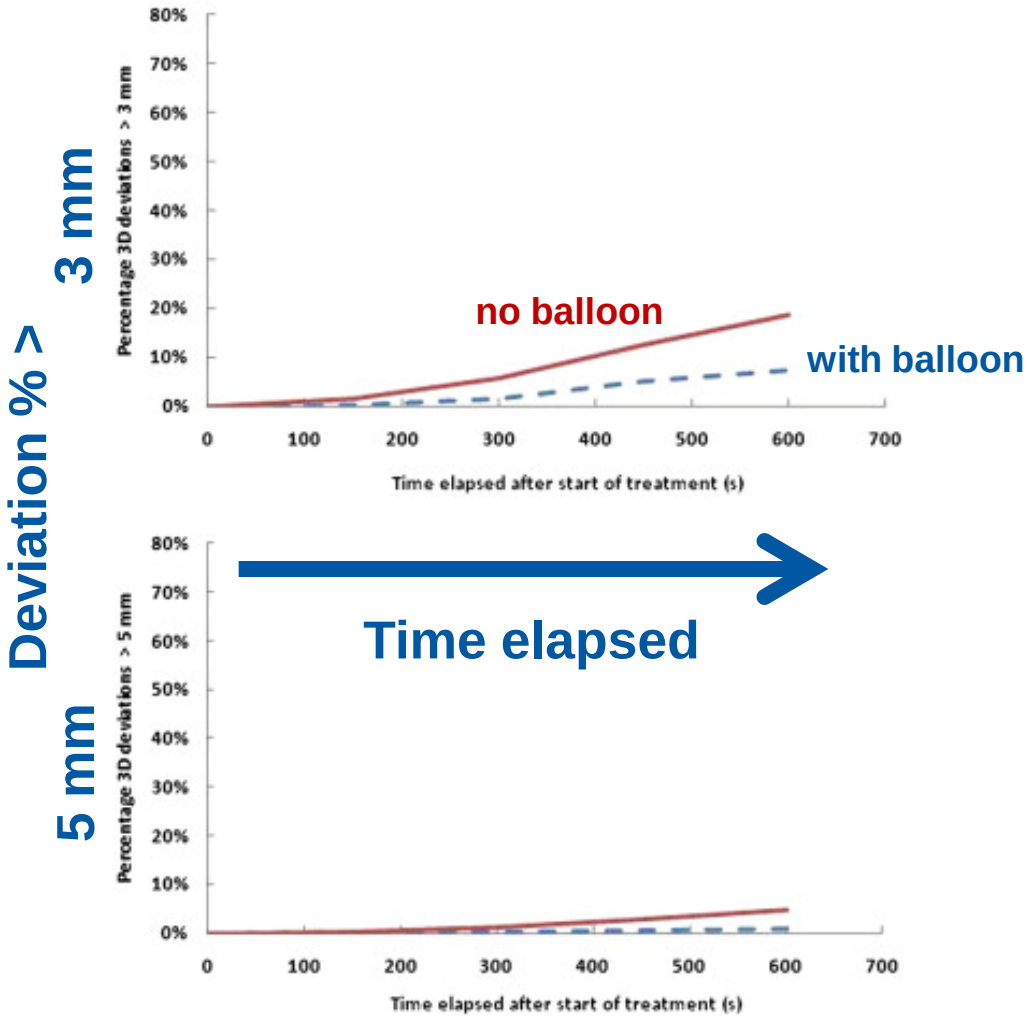
Management of intrafraction motion

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

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

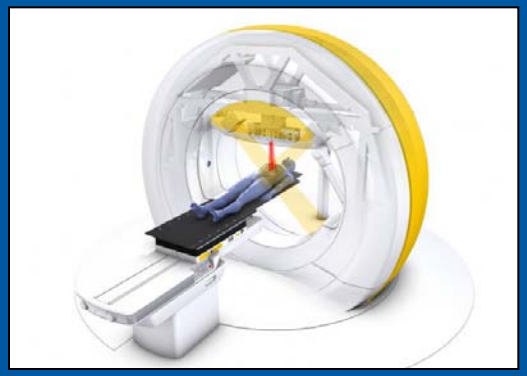
Complex procedure: may require frequent adjustments to avoid systematic errors or deformations (Jones Med Phys 2012, Miralbell IJROBP 2010)

Increases treatment time

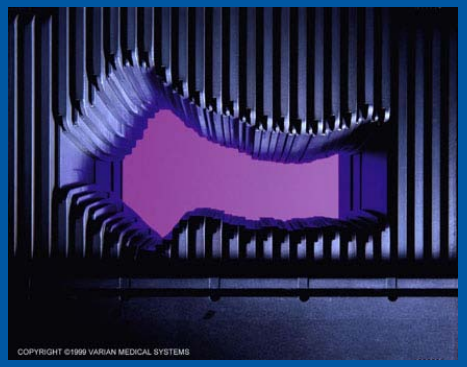
Conclusion: mixed experiences, complex and invasive procedure, questionable benefits

Tracking – Adaption to the motion

‘Special machines’



‘Add-ons’ Conventional Linacs

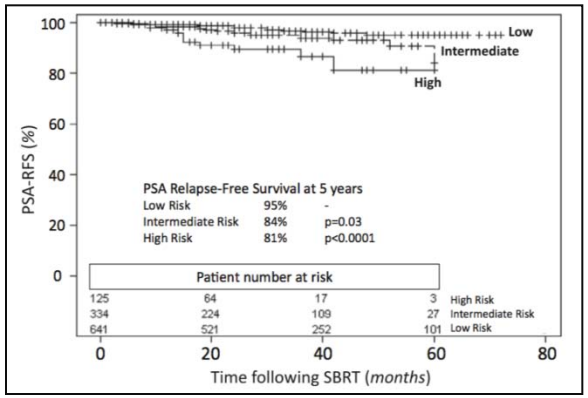


MLC and couch tracking can be performed on conventional linear accelerators, whereas for linac tracking dedicated machines are needed.

Tracking – Adaption to the motion

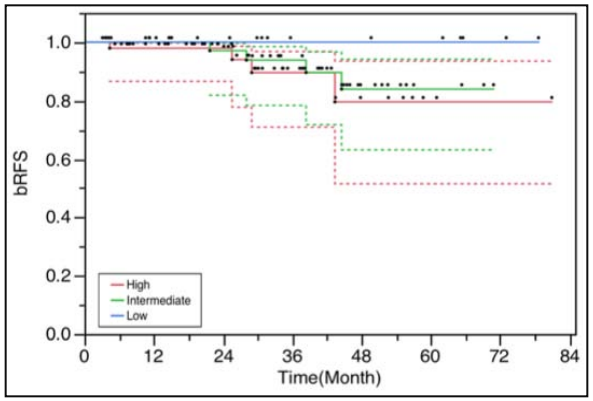
Cyberknife
King 2013

- 1100 patients
- 5 Fx SBRT



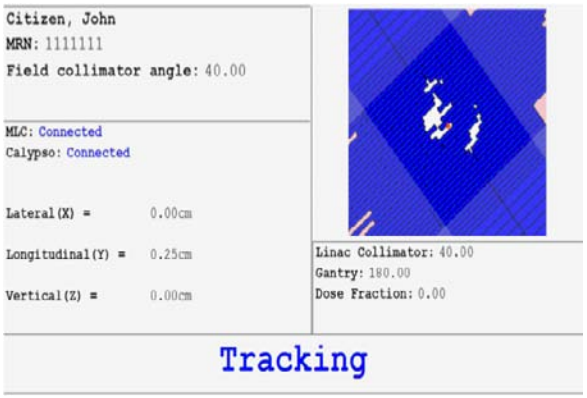
Couch tracking
Shimizu 2014

- 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?

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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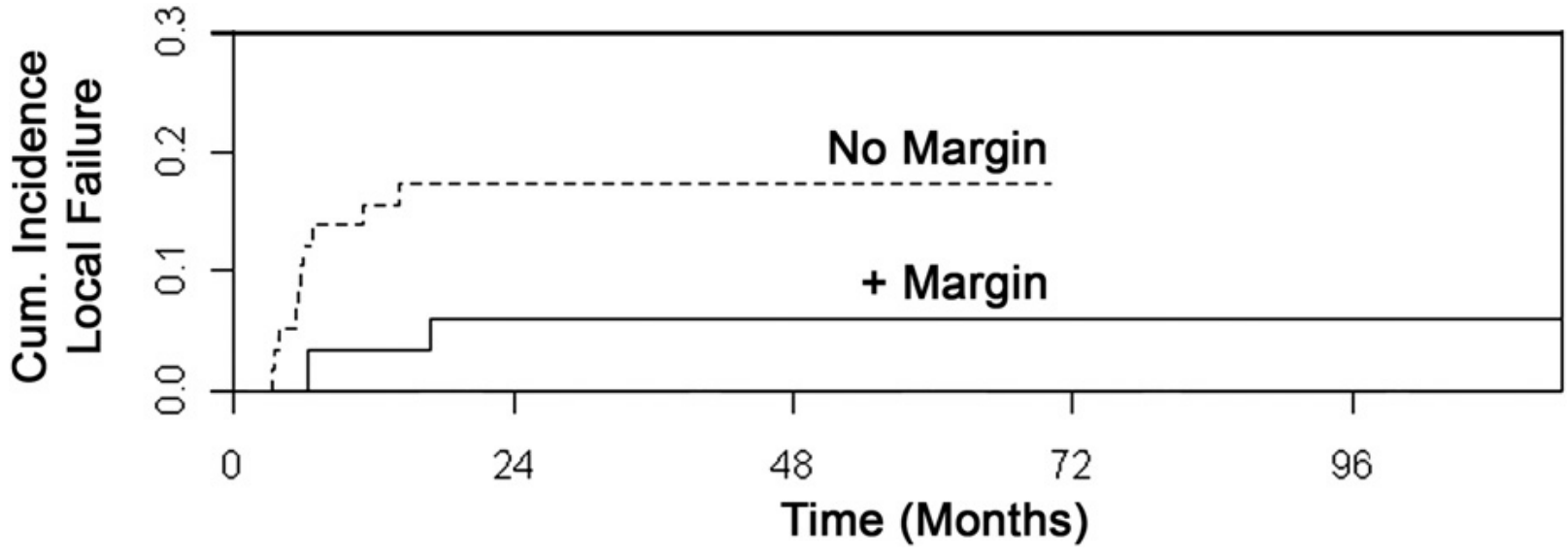
Brain SBRT: required accuracy



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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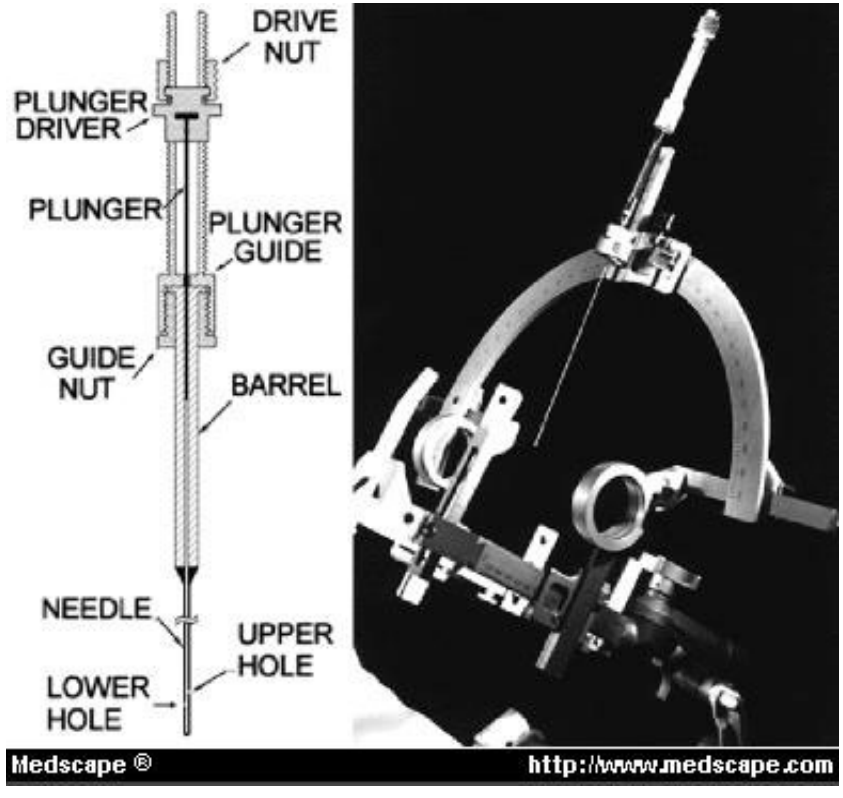
Frames

Lars Leksell, neurosurgeon. Frame developed in 1949



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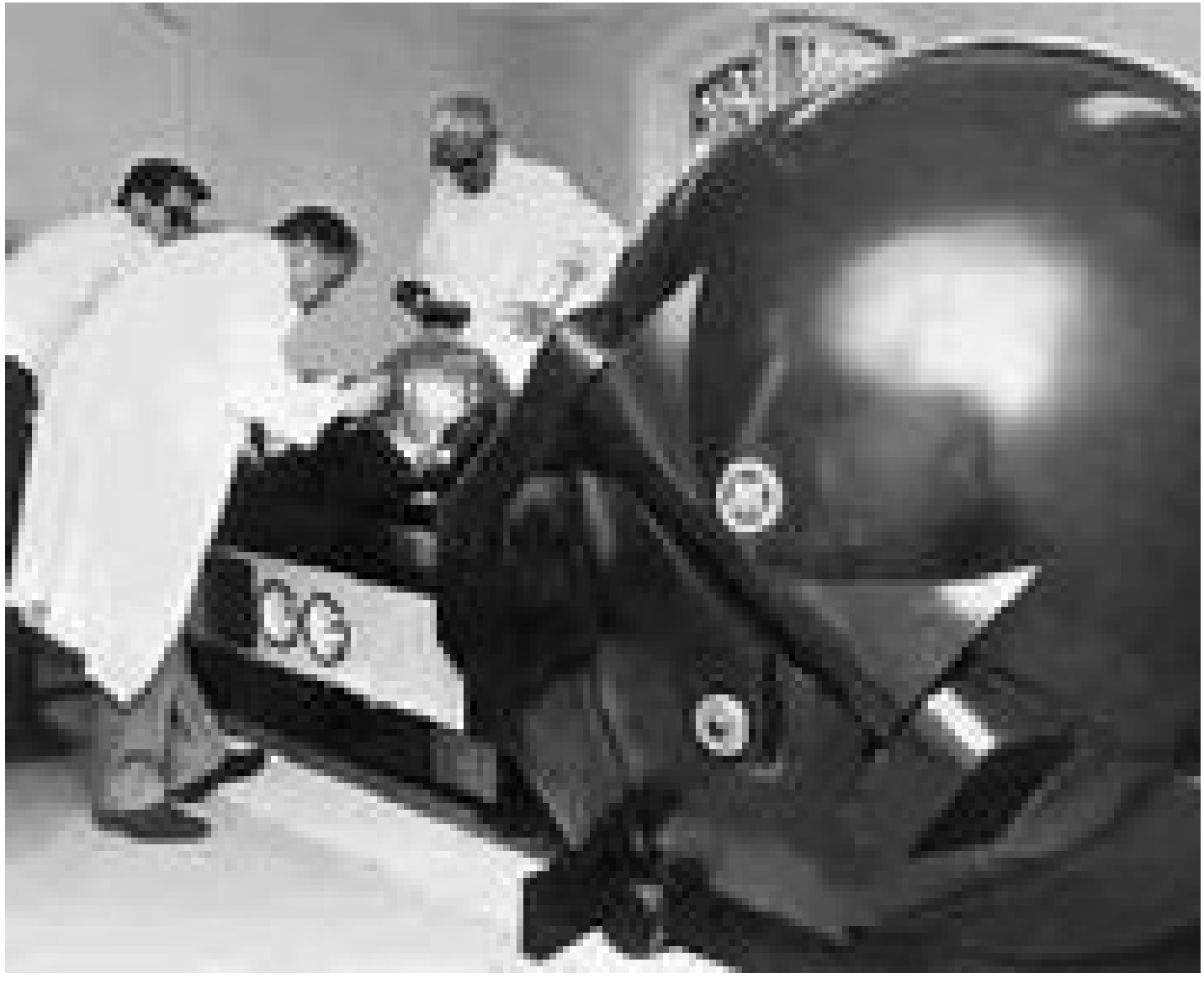
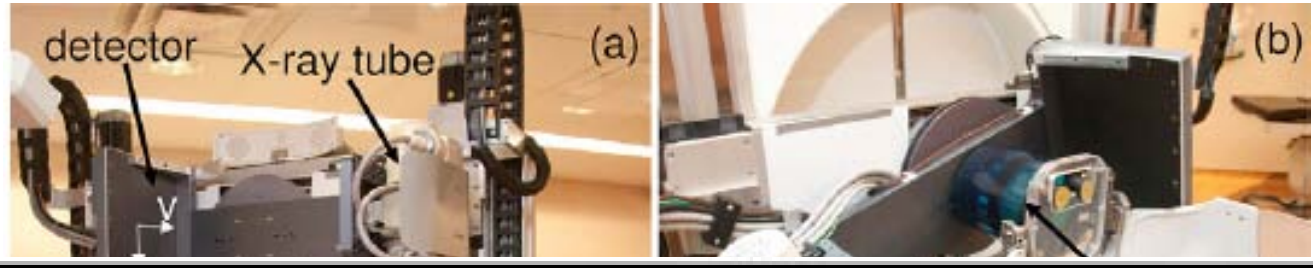
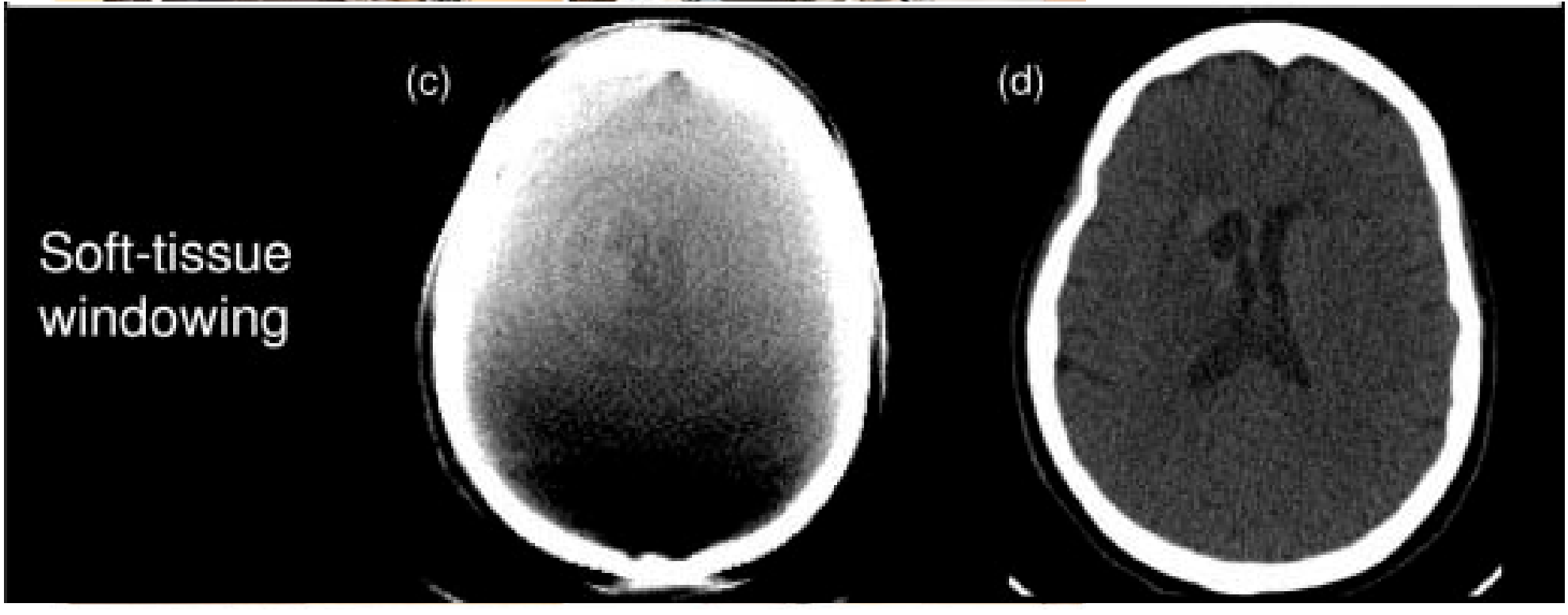
Gamma knife 1968



Gamma knife 2013



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



Ruschin IJROBP 85, 2013 p243

Gamma knife 2015

Includes CBCT and set-up camera

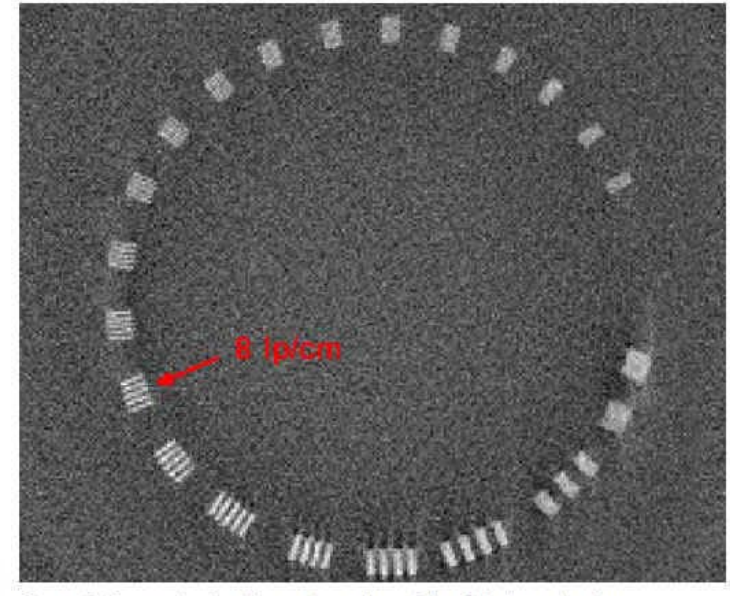
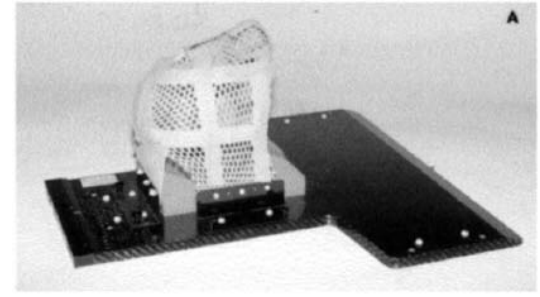


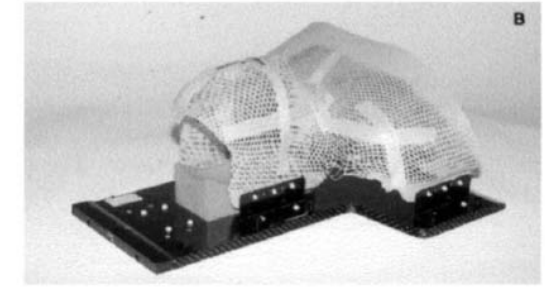
Figure 3. Reconstructed line pair section of the Catphan phantom.

Elekta website white papers, 2015

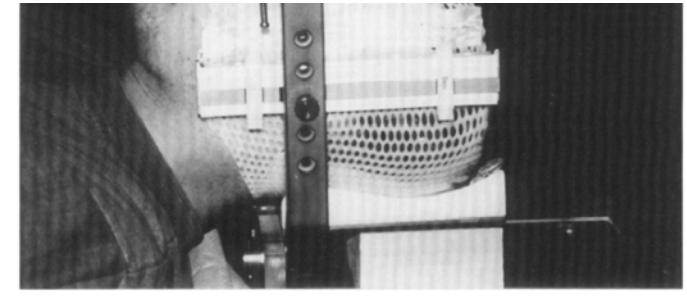
Masks: Literature

- 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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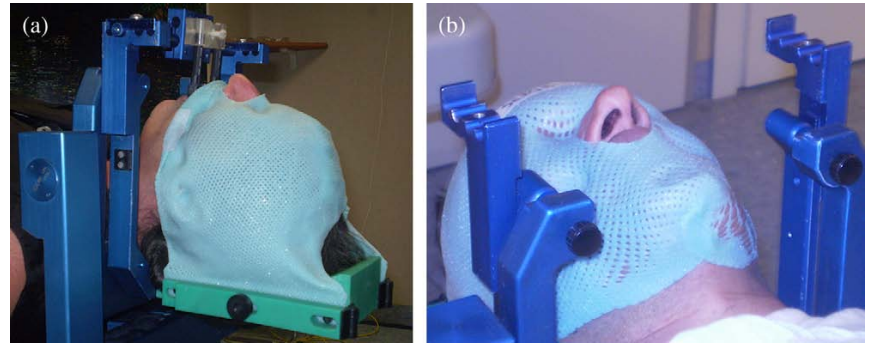
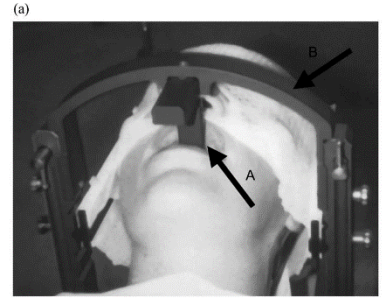
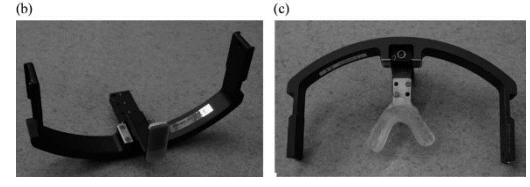
Bite blocks

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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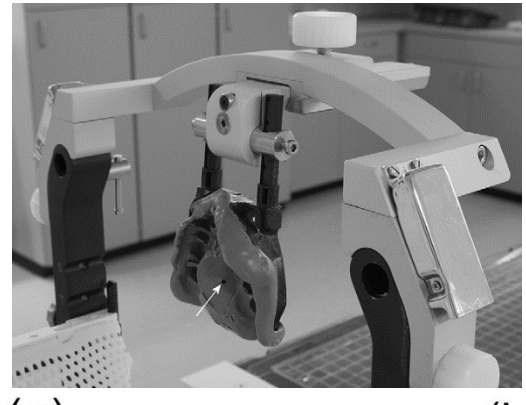
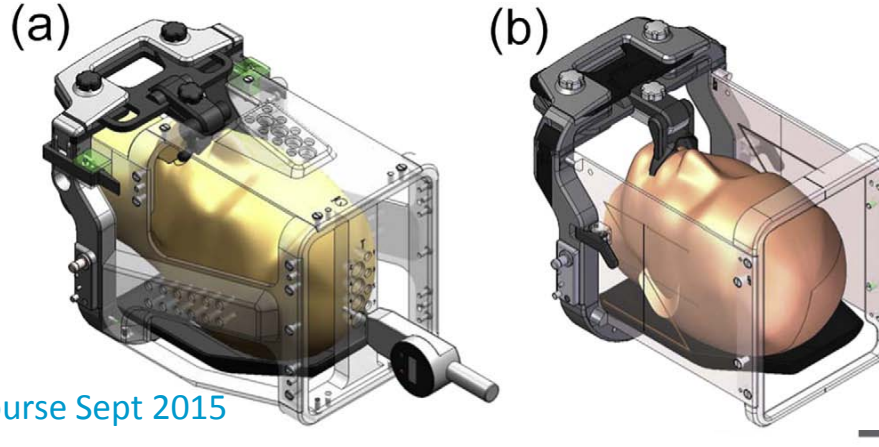


3



4

Again…..

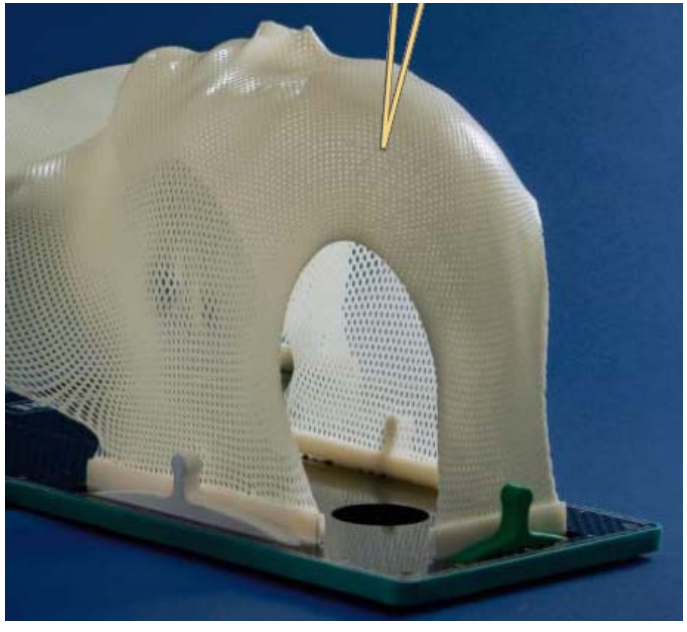
Masks and bite blocks
are NOT sufficient

for current CTV-PTV margins!

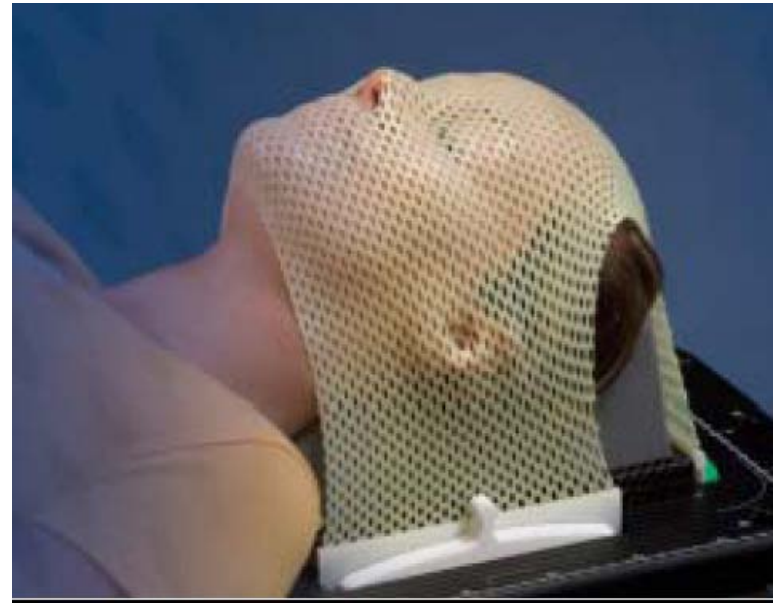
After correction with IGRT

- **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

IGRT practical implementation at CZE



Efficast



Raycast

+

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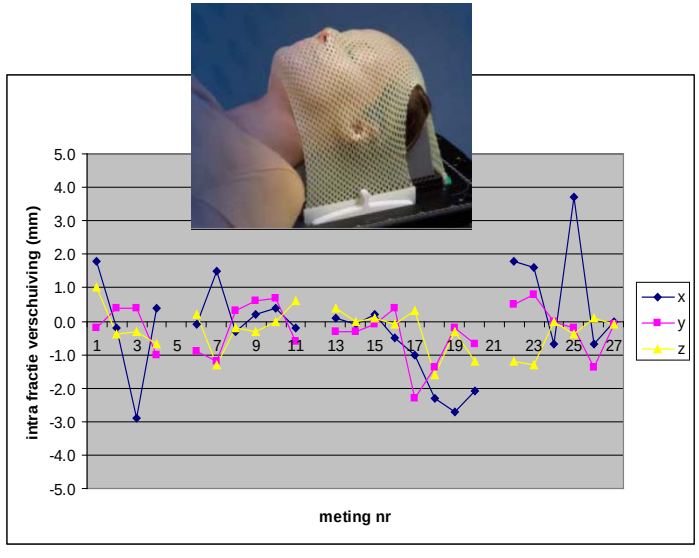
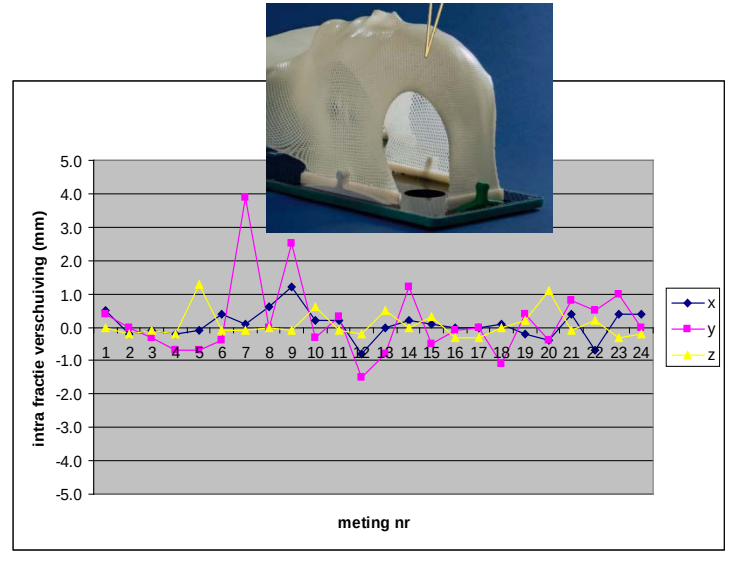
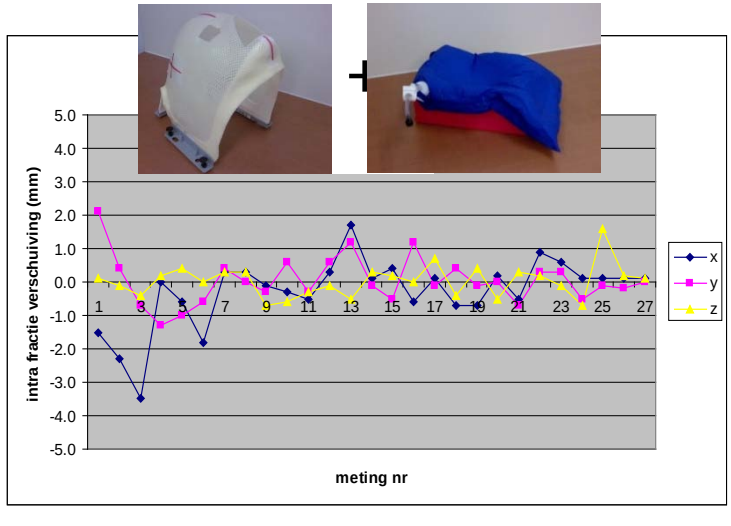
Mask QA study CZE: Translations







Hybrid in general < 1 mm

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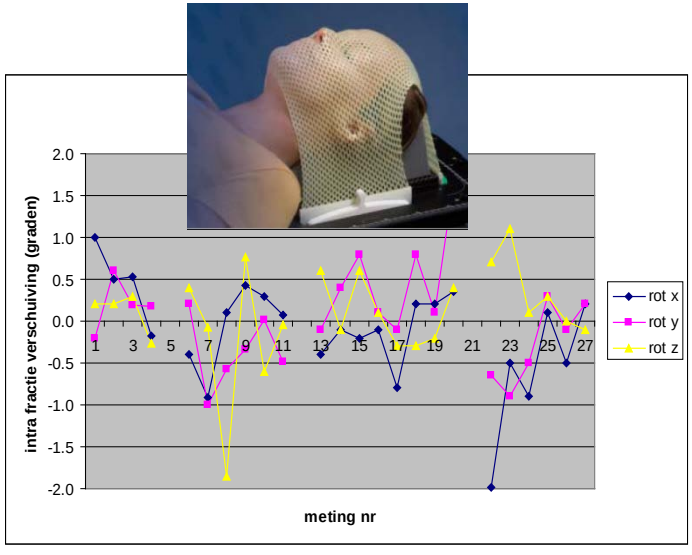
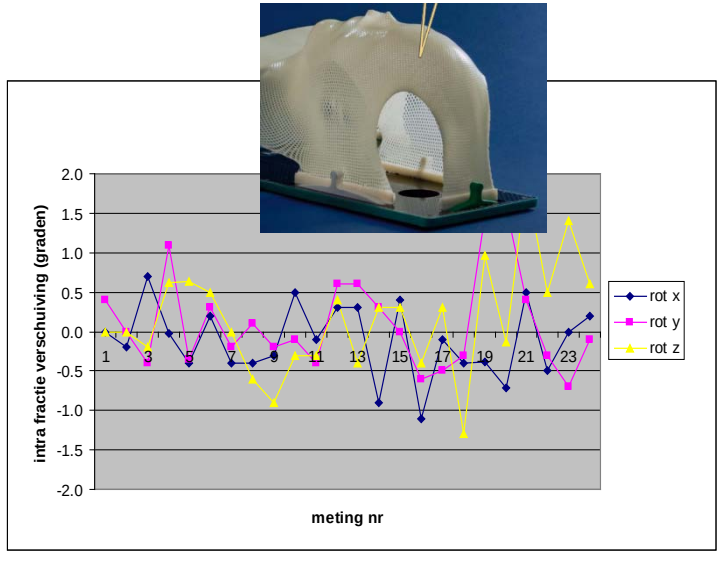
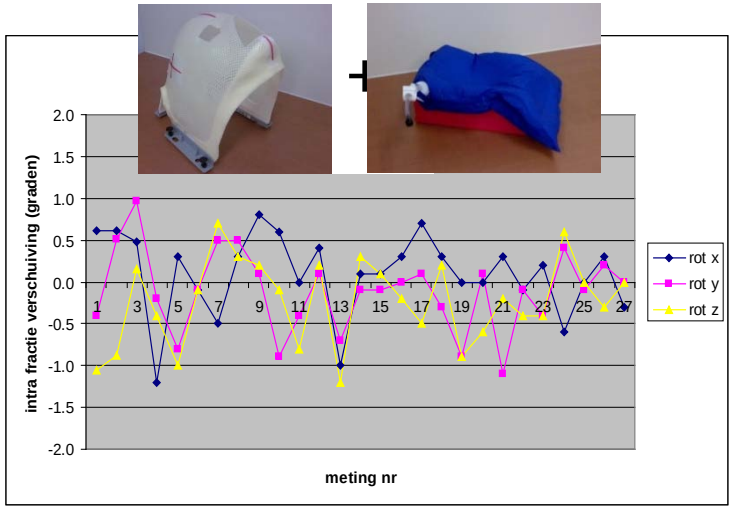
Mask QA study CZE: Rotations







Hybrid in general < 1°

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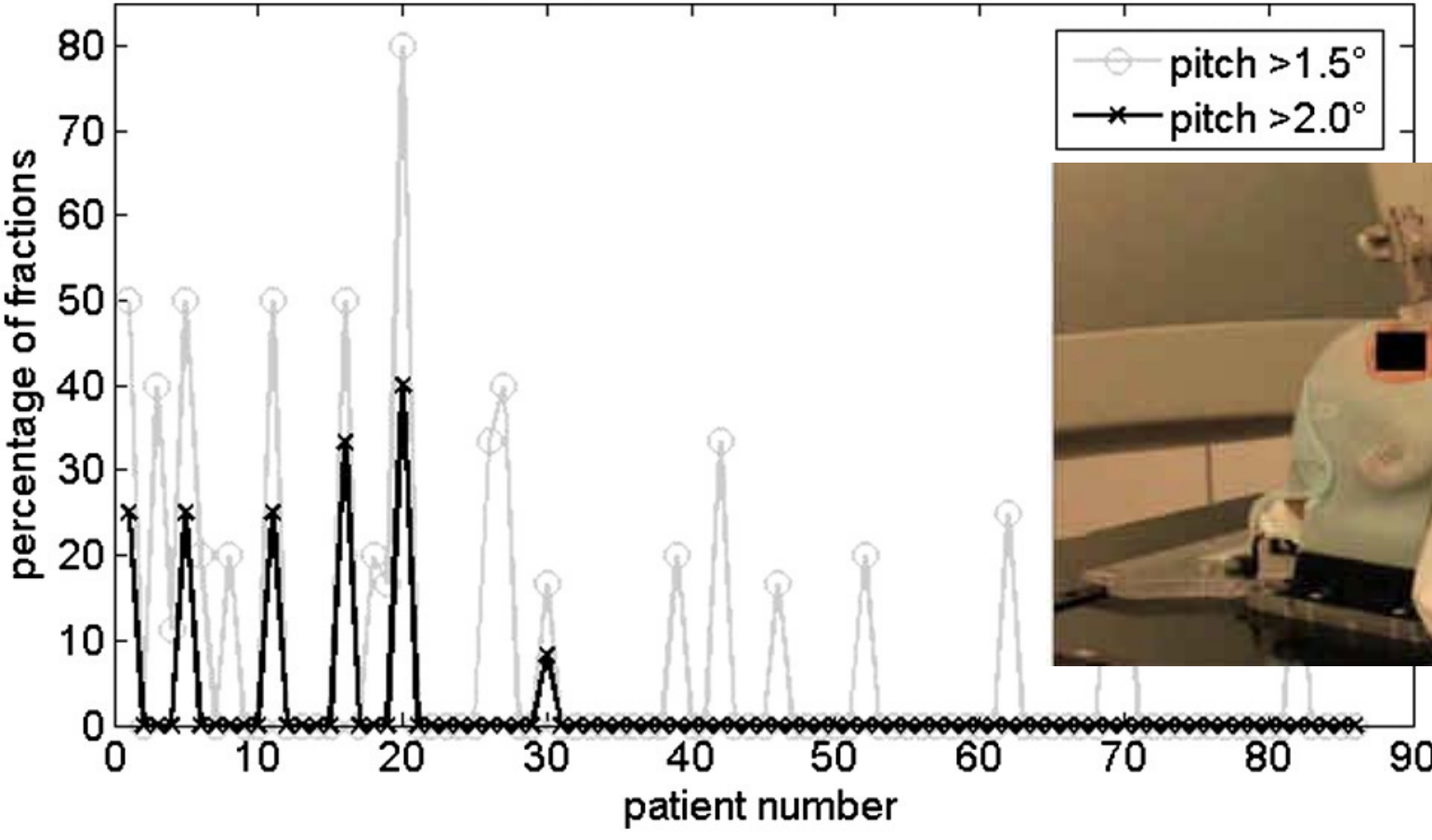
Mask QA: experience with a new system



Lang et al PRO, 2015

73 patients with trUpoint masks on truebeam

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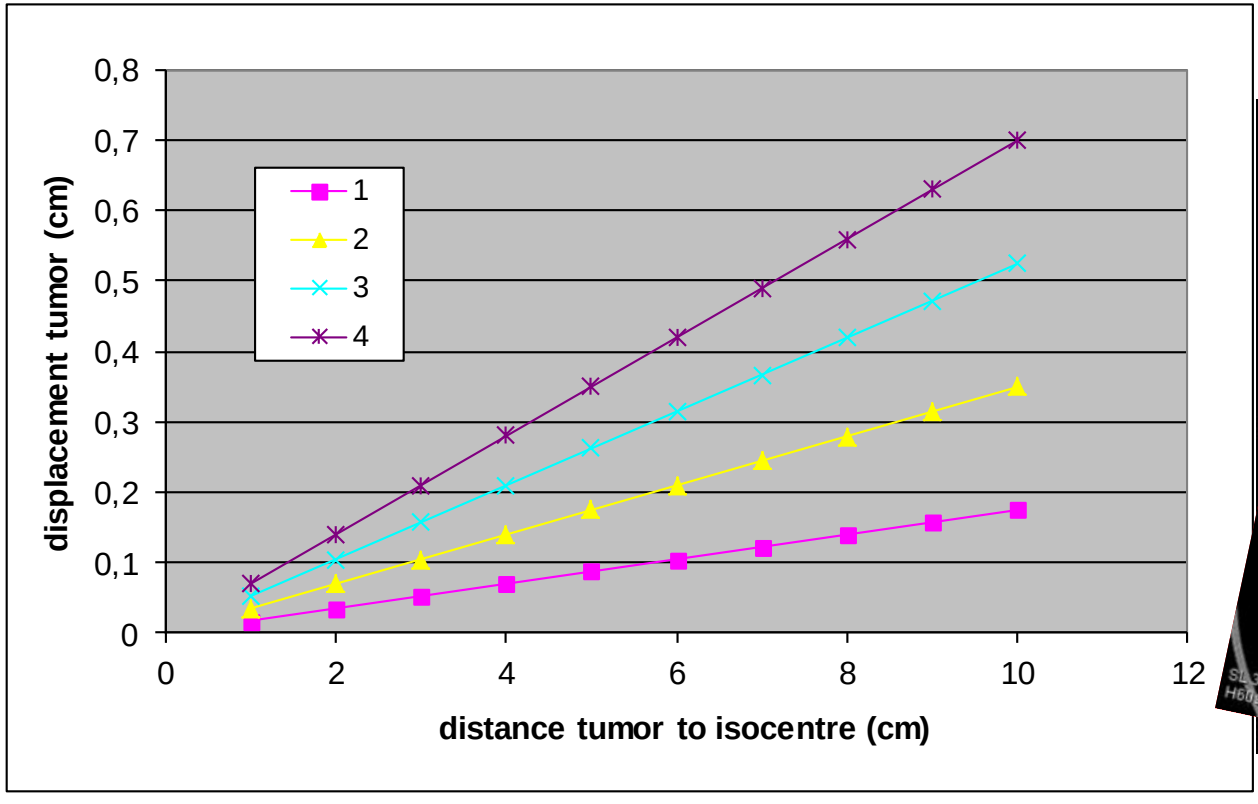
Rotations in single isocentre treatments with multiple lesions



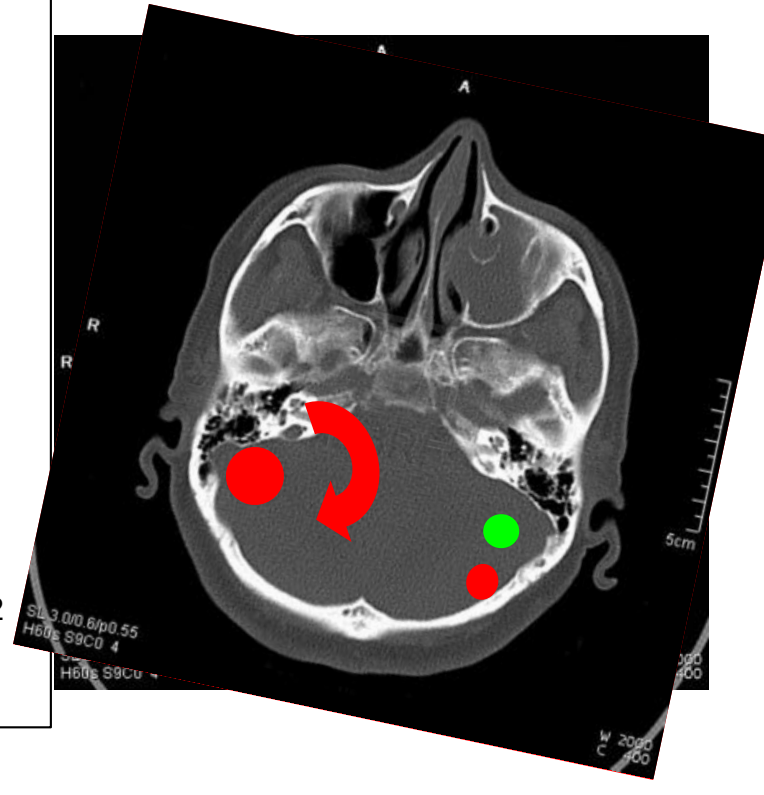


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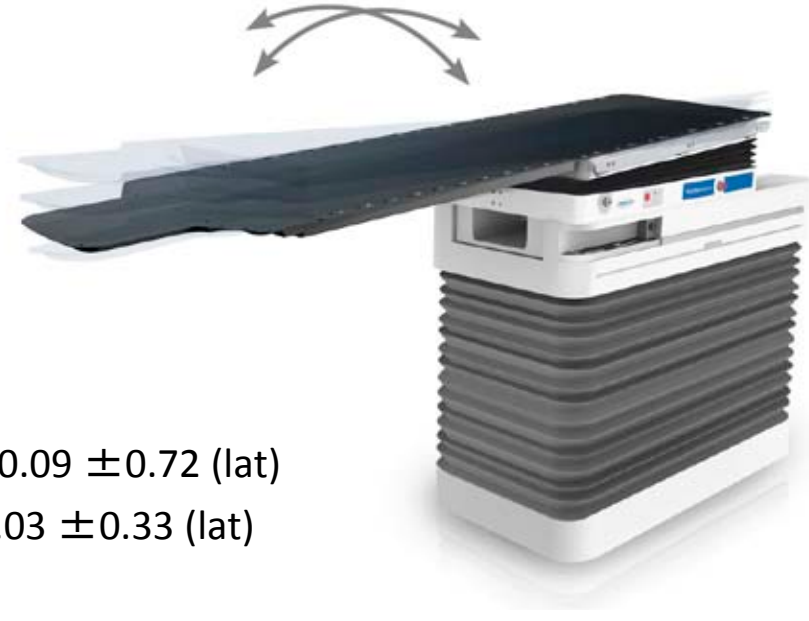
Table assisted rotation correction



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)

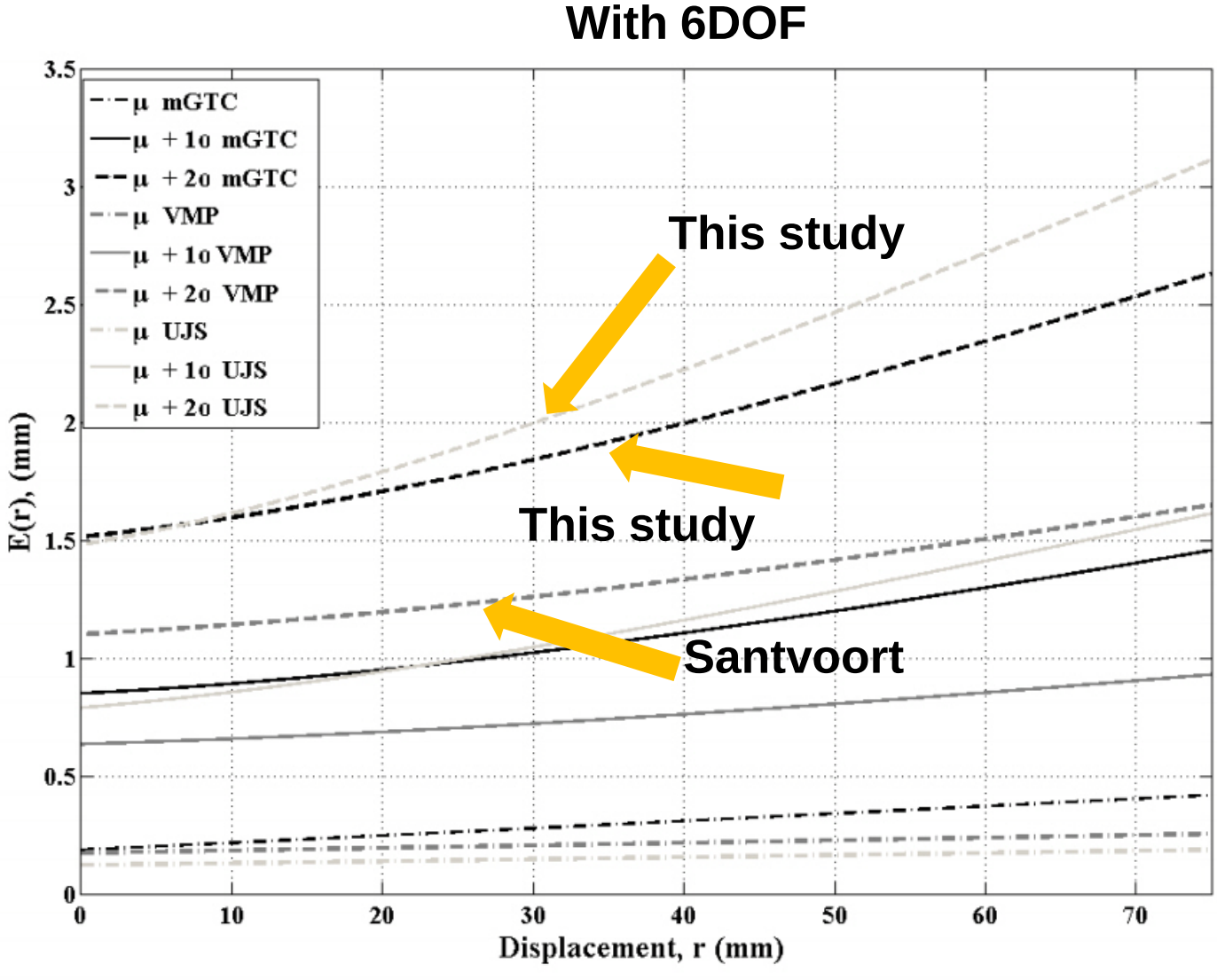
After: 0.01 ±0.35 (vert),0.03 ±0.31 (long) and 0.03 ±0.33 (lat)

(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



Winey et al JACMP 15(3)p122 2014

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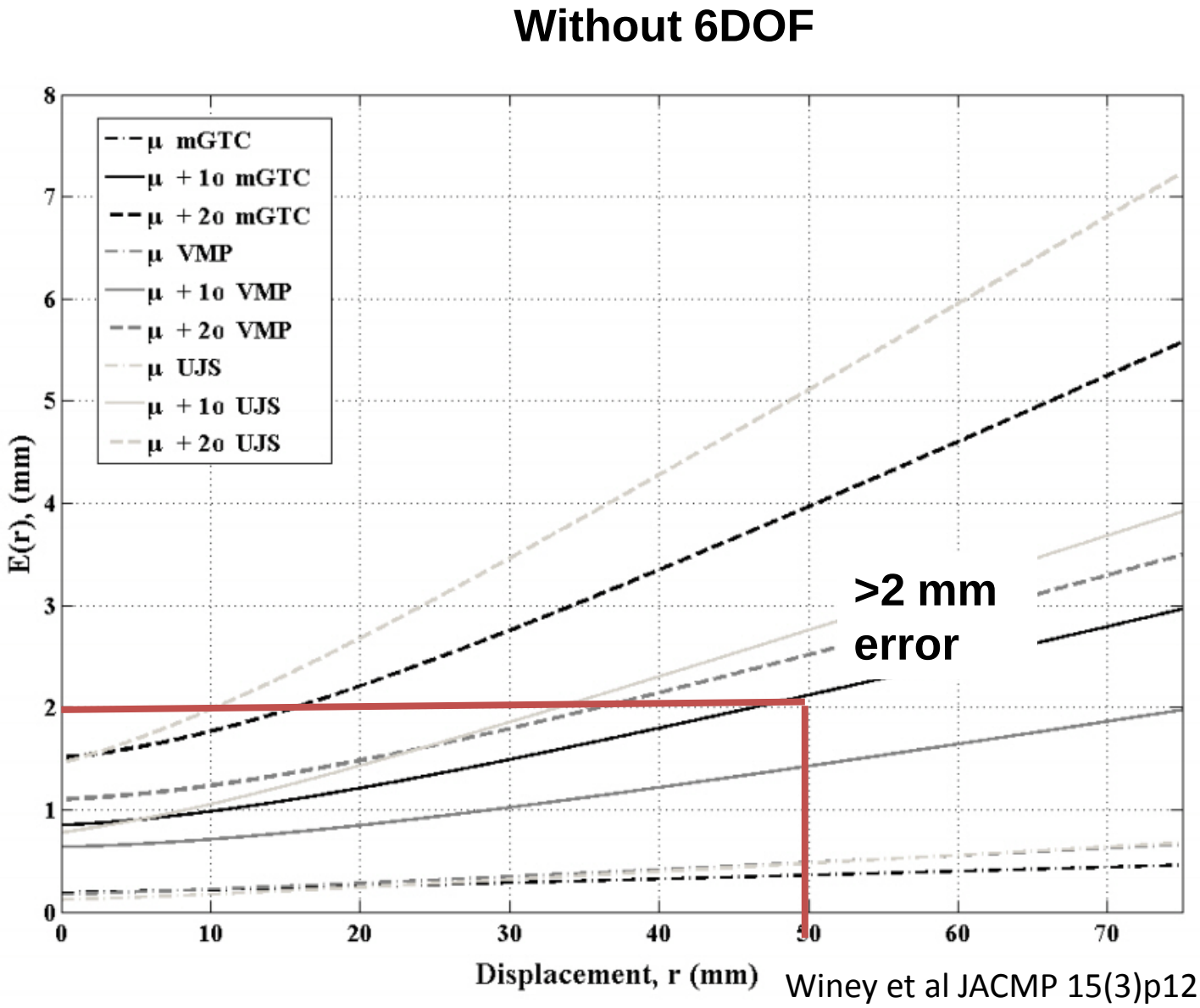
Rotation correction with multiple lesions



So:
use 6DOF couch

OR

multiple isocentres

Winey et al JACMP 15(3)p122 2014

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

Intra fraction motion: treatment time

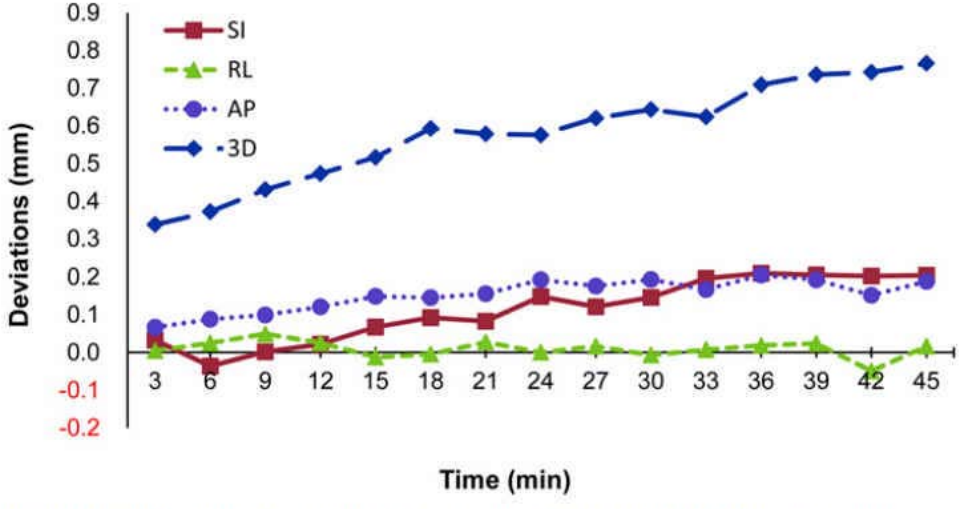
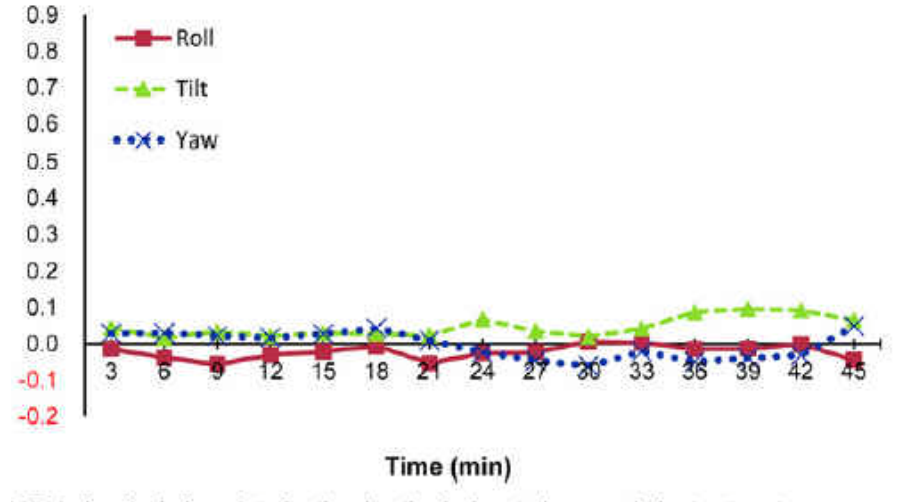


Fig 2. Translational deviations. Intrafractional motion in the translational axes during treatment.



. 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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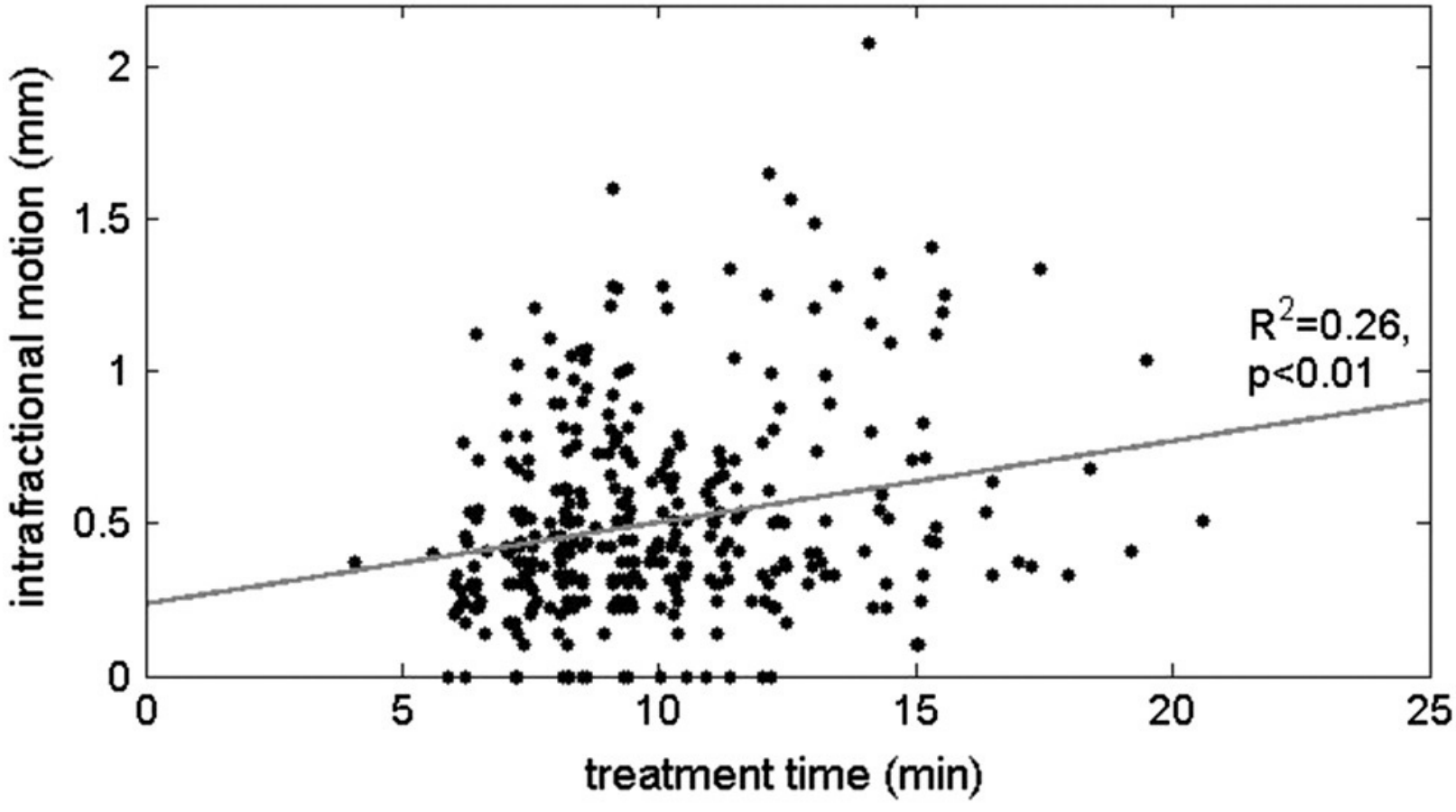
Intra fraction motion: treatment time



Lang et al PRO, 2015

73 patients with trUpoint masks on truebeam

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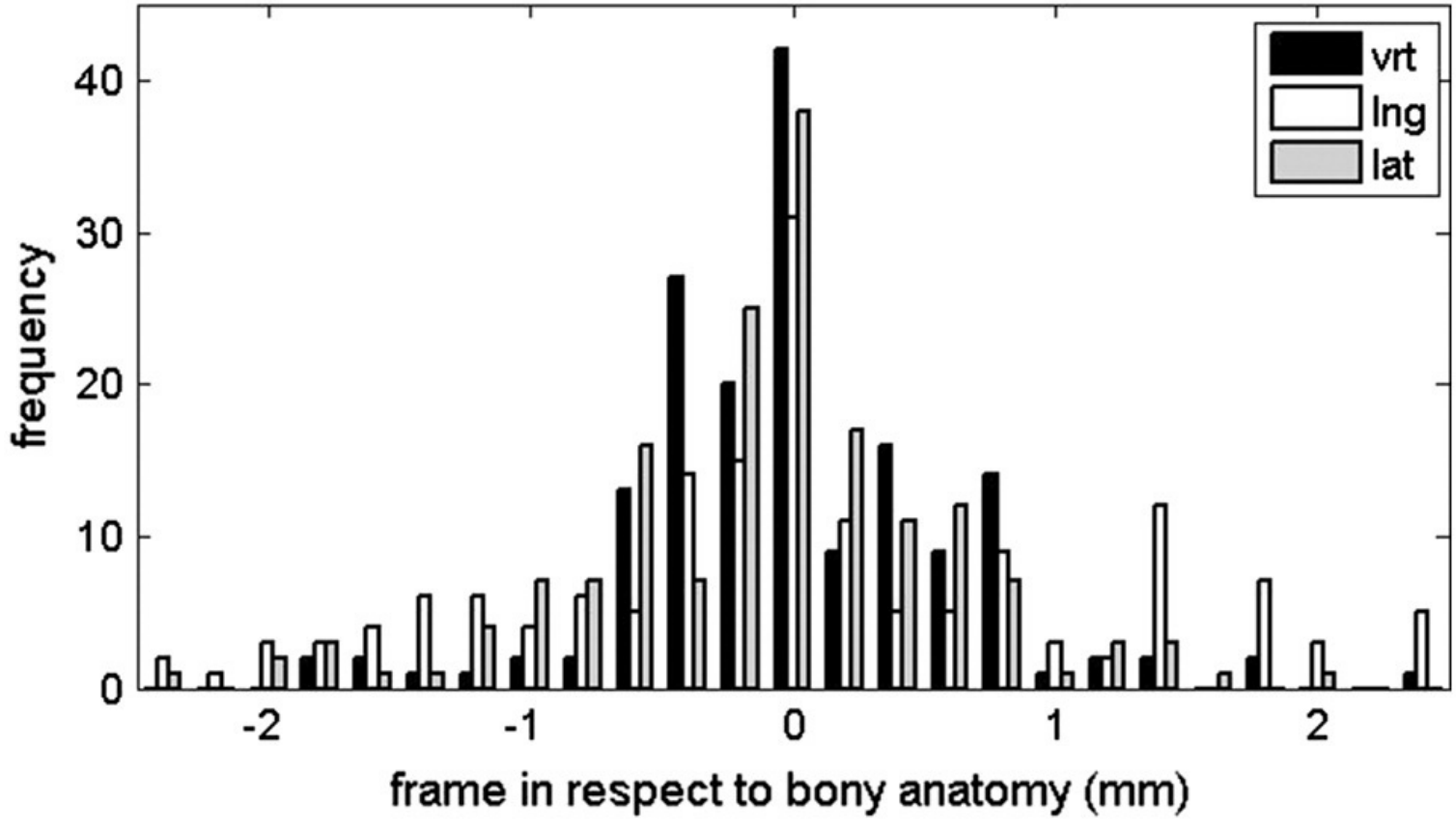
Intra fraction motion: match structure



Lang et al PRO, 2015 73 patients with trUpoint masks on truebeam

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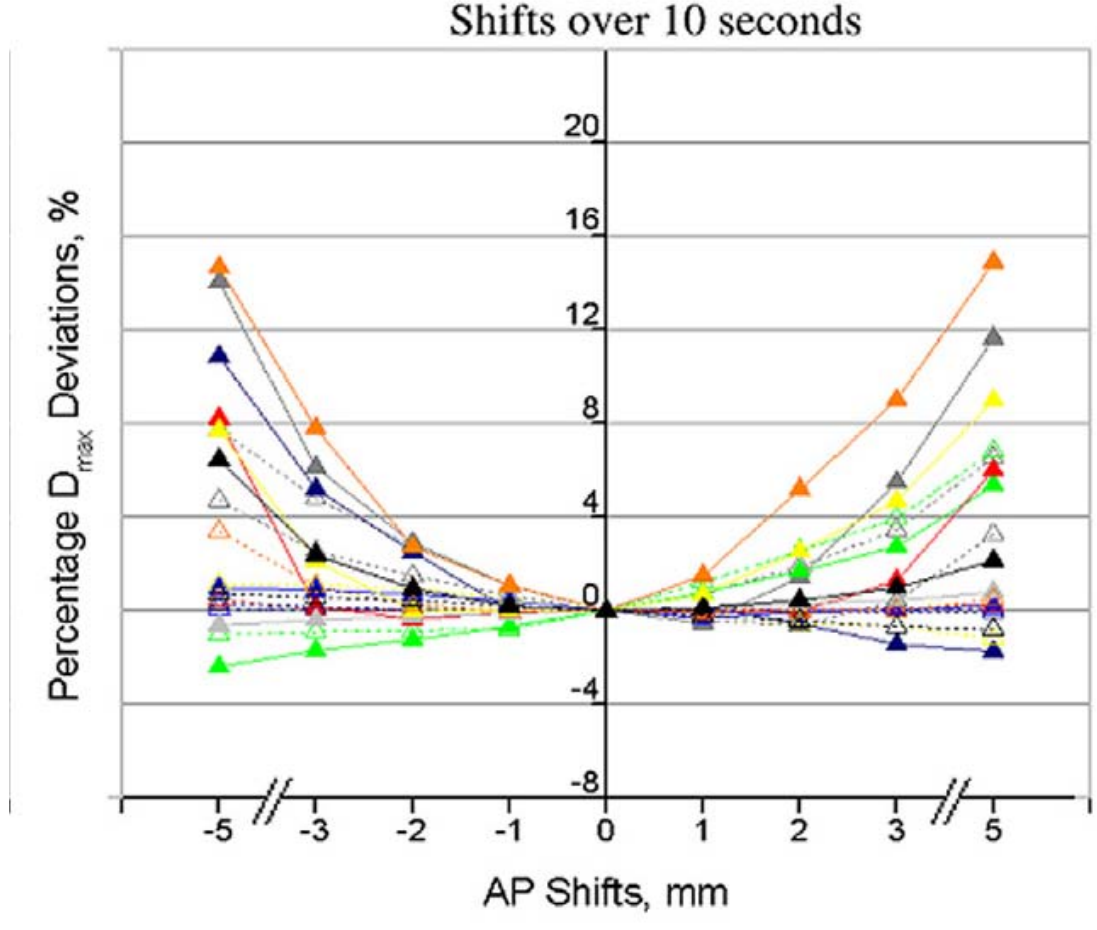
Spine SBRT: Required accuracy

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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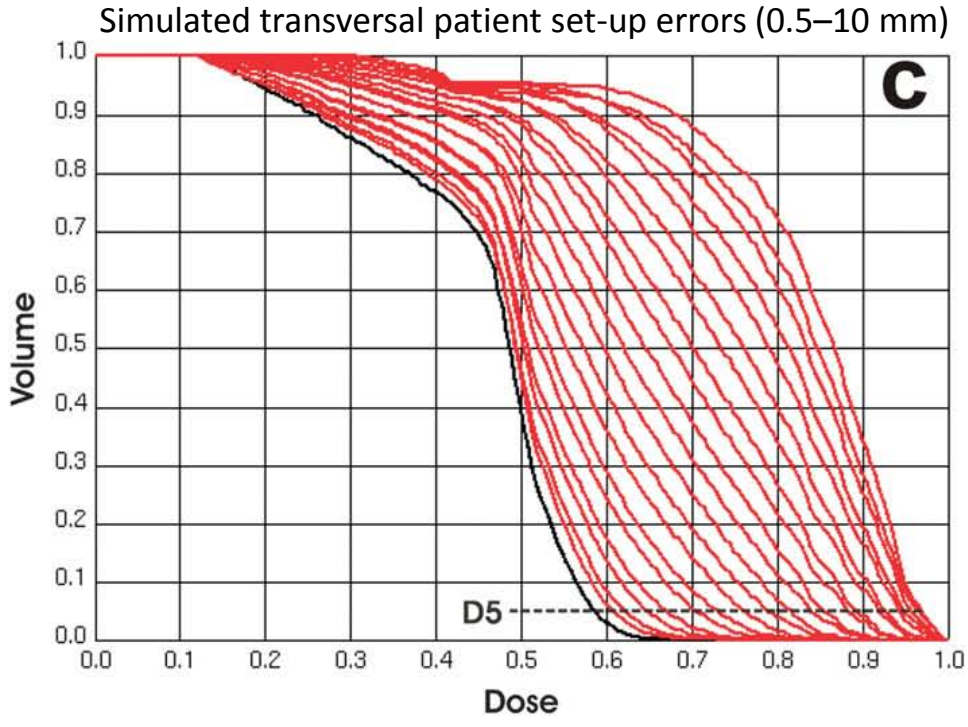
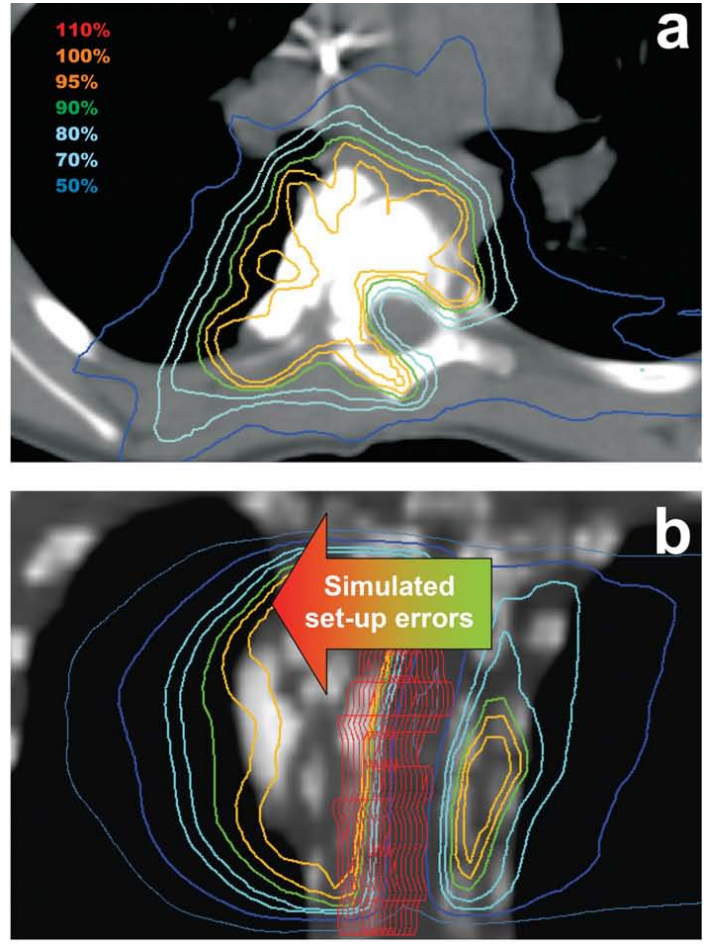
Spine SBRT: Required accuracy





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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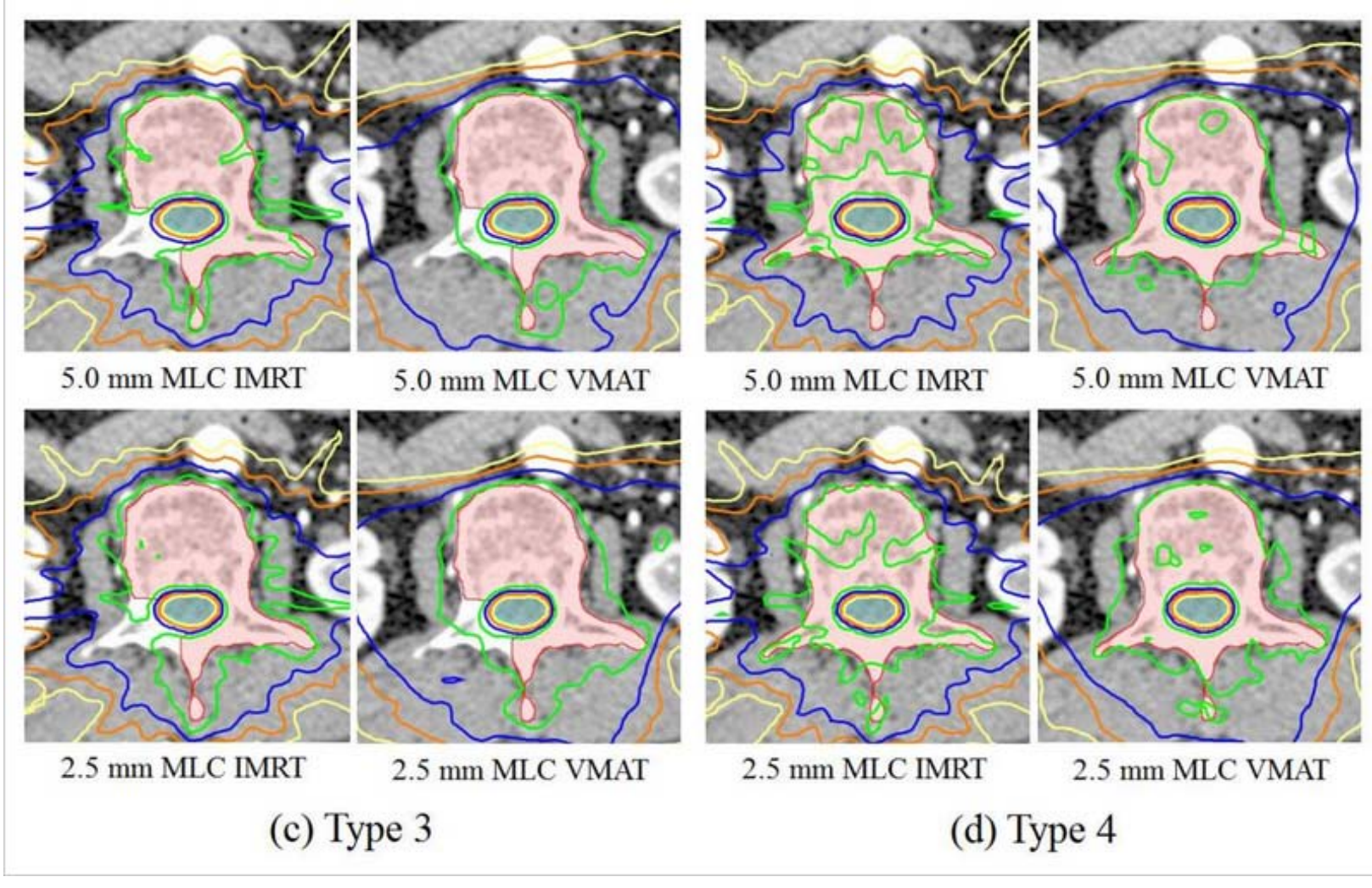
Spine SBRT: Required accuracy MLC



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

Spine SBRT: Required accuracy MLC

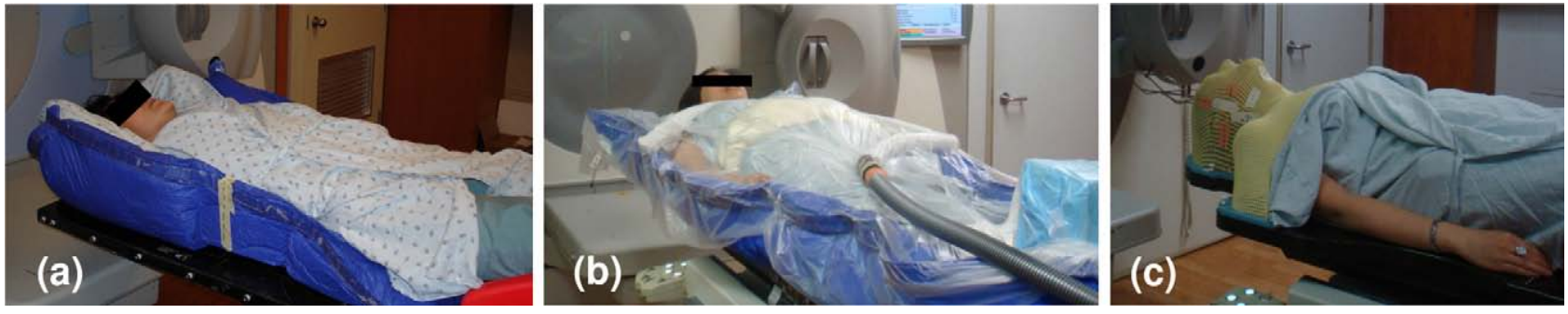
		2.5-mm MLC	5-mm MLC	Improvement ratio (%)	*p* value
IMRT	TVC	88.40 ± 15.62	83.55 ± 20.24	8.38 ± 13.66	0.042
	CI	2.03 ± 0.67	2.24 ± 1.06	−4.86 ± 13.00	0.119
	GI	9.30 ± 2.06	10.98 ± 3.34	−13.79 ± 7.38	0.003
VMAT	TVC	95.26 ± 3.12	92.65 ± 5.48	2.97 ± 3.10	0.005
	CI	1.85 ± 0.34	1.88 ± 0.41	0.02 ± 11.48	0.689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

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

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

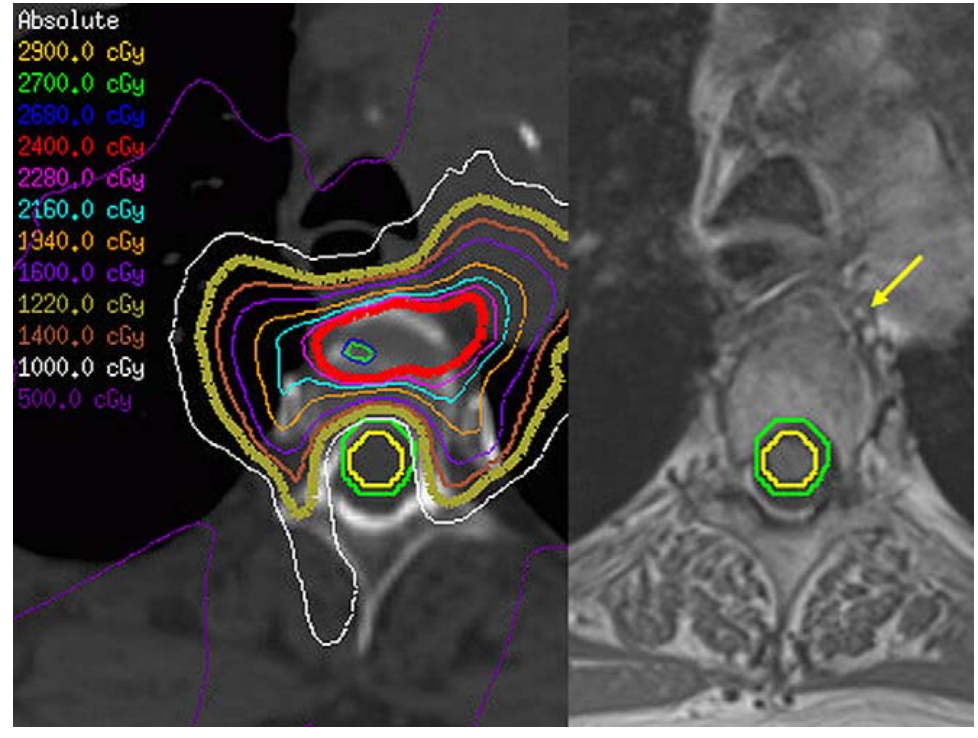
Positioning for spine SBRT

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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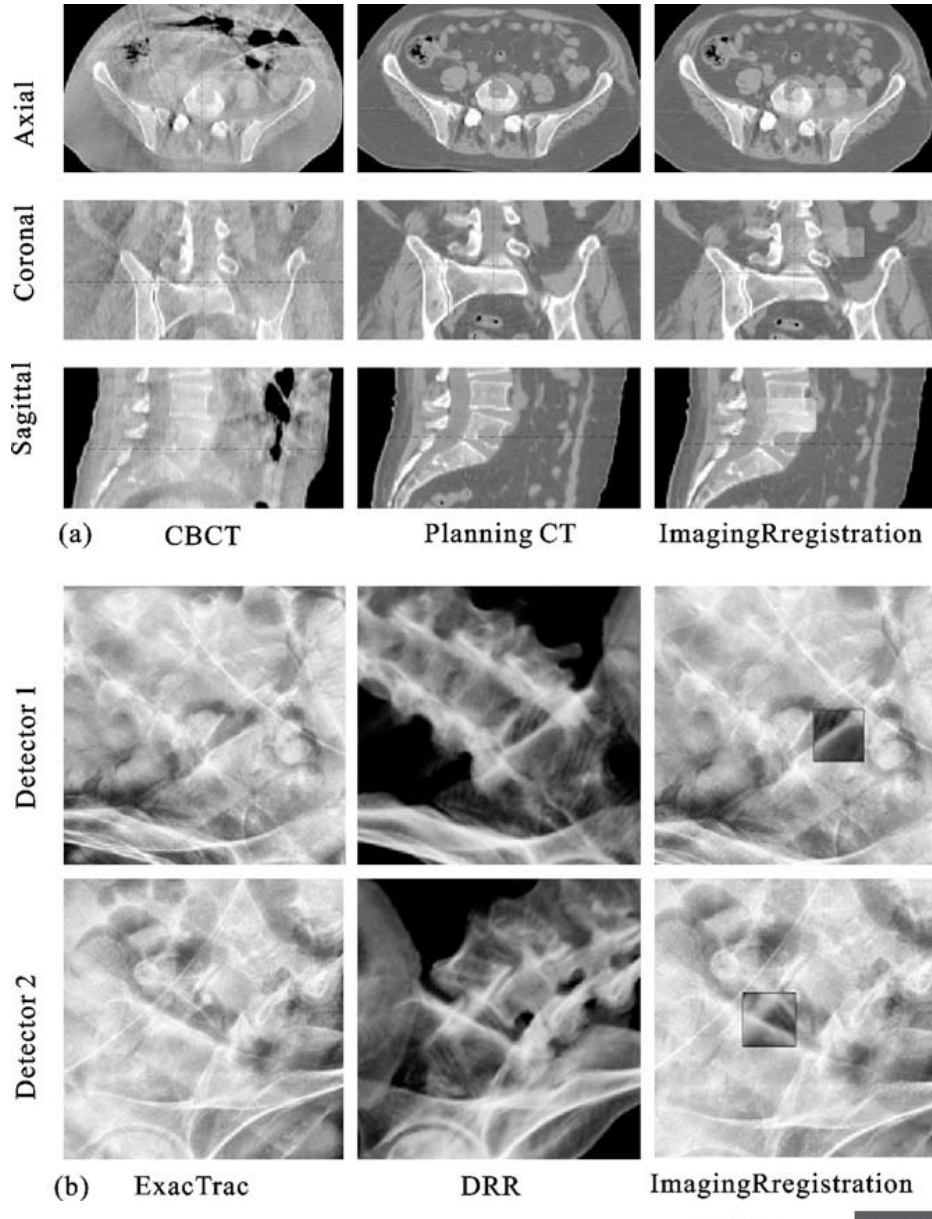
Imaging technology

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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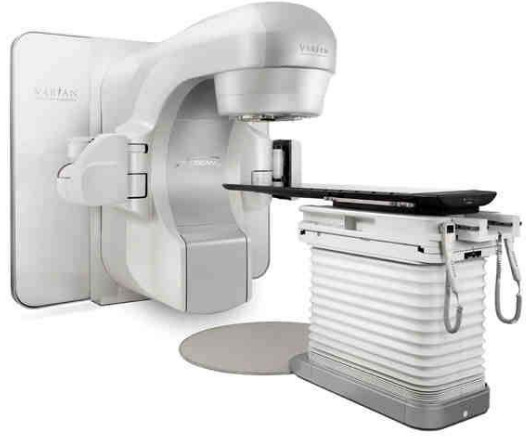
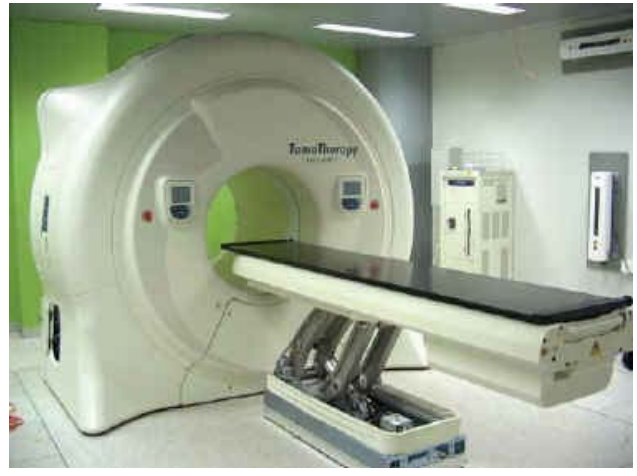
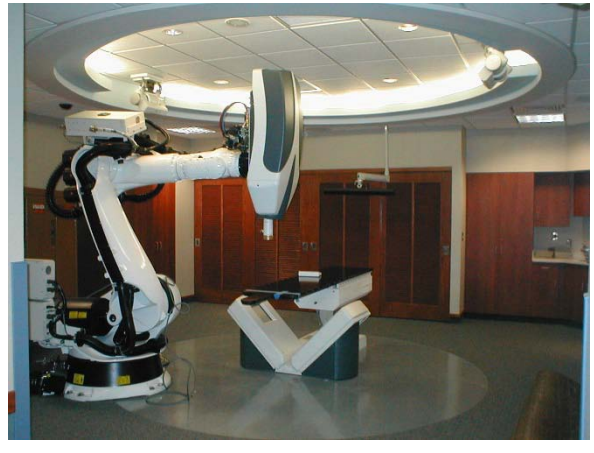
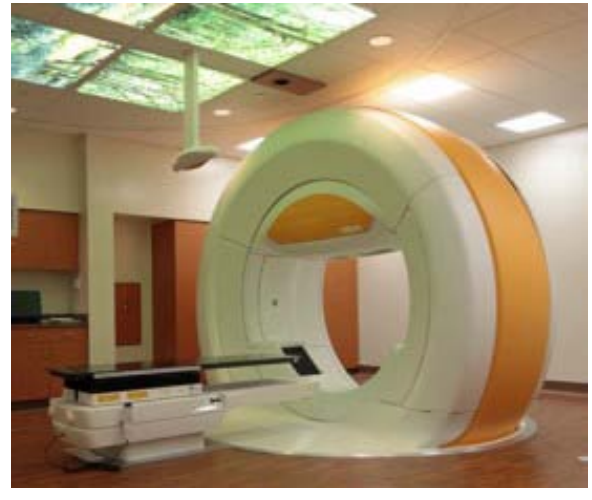
IGRT technology









ESTRO SBRT course Sept 2015

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Table 1 Radiation-based systems for IGRT

Radiation-based systems	Examples	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)							
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

BrainLAB (Novalis)	2-D	0.33-0.55 mGy	<1 mm	An optical guidance system in conjunction with stereoscopic, planar kV images and "snapshot" images during treatment to detect patient motion; used for bony alignment and to compensate for patient motion during treatment; uses a "6-D" treatment couch to compensate for translational and rotational setup corrections	SBRT/SRS Brain Spine Lung Liver Head and neck Gynecologic tumors	Appropriate if bony landmarks serve as a good surrogate for target localization; does not acquire 3-D, volumetric information, and is static. "Snapshot" imaging evaluates movement of bony landmarks during treatment, and subsequent termination of the beam and realignment of the patient, if necessary
BrainLAB/MHI (VERO)	2-D	0.33-0.55 mGy	0.1 mm	A pair of x-rays and couch motion used for initial alignment; for patient motion during treatment; subsequently, the on-board imaging system acquires x-rays and correction of "6-D" setup errors is performed by translating and rotating the x-ray, mounted on gimbals		Appropriate if bony landmarks serve as a good surrogate for target localization; includes volumetric data acquisition (see CBCT section)

Table 1 (*continued*)

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
X-ray real-time tracking systems	Examples						
Combined infrared and 2-D orthogonal kV imaging localization	BrainLAB (ExacTrac)	4-D		An optical, infrared camera system, along with 2 x-ray imagers located obliquely in the treatment room for stereoscopic imaging	Tumor tracking, using x-ray images and based on correlation between tumor position and external markers, updated during treatment using kV orthogonal imaging	SBRT/SRS Brain Spine Lung Liver Head and neck Gynecologic tumors	Correlation between external markers and internal tumor motion helps circumvent possible phase offsets; implantation of markers, if required, is an invasive procedure
	Accuray (CyberKnife)	4-D		A robot capable of movement around the patient except from angles posterior to the couch	Tumor tracking, using x-ray images and based on correlation between tumor position and external markers using an adaptive model, updated during treatment using kV orthogonal imaging	SBRT/SRS Brain Spine Lung Liver	Correlation between external markers and internal tumor motion helps circumvent possible phase offsets; implantation of markers, if required, is an invasive procedure
	BrainLAB/MHI (VERO)	4-D			Tumor motion compensation performed by fluoroscopic imaging during treatment, target delineation on the images, and tracking of the center of mass of the target		Target delineation on fluoroscopic images is confounded by lack of soft-tissue contrast
	RTRT (Hokkaido, Mitsubishi)	4-D	0.20-20 mGy Estimated skin dose from 1 fluoroscope: 29-1182 mGy/h	<1 mm static accuracy; <1.5 mm for a target moving up to 40 mm/s	Implanted artificial fiducials are located and continuously tracked by 2 of the 4 orthogonal imaging systems during treatment	Lung Liver Prostate Spinal tumors	Real-time imaging of implanted fiducials can result in very high skin doses, up to 1200 mGy/h from 1 fluoroscopic procedure of the RTRT systems

* Dose to the patient is mainly determined by imaging quality, attenuation characteristics of imaged anatomy, and the imaging duty cycle (duration/frequency).

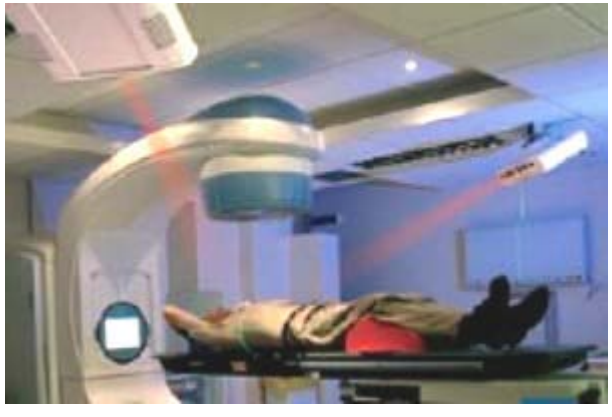
CT-on-rails	Examples Siemens CT-on-rails	3-D	10-50 mGy	≤1 mm	Fan-beam kV CT; used for routine volumetric imaging to ensure accurate targeting of the radiation \beam	Prostate Head and neck Lung/thorax Paraspinal tumors	Can be used for monitoring patient setup (interfraction motion) and changes in anatomy that have occurred possibly during treatment, by performing imaging immediately after treatment; has the ability to monitor tumor response through the course of therapy
MVCT	Examples Tomotherapy	3-D	10-30 mGy	≤1 mm	Fan-beam MV CT; used for routine volumetric imaging to ensure accurate targeting of the radiation beam	Prostate Lung/thorax Breast Gynecologic tumors Head and neck Paraspinal tumors Esophagus Sarcomas GI malignancies	Has the ability to monitor tumor response through course of therapy

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
Cone-beam CT (CBCT)	Examples						
	Varian, Elekta, Siemens, BrainLab (VERO)	3-D	30-50 mGy	≤1 mm	kV or MV cone beam CT (CBCT); localization based on volumetric image acquisition and 3-D−3-D matching with treatment planning CT; for the x-ray source/detector arms for CBCT, volumetric CBCT data acquisition is performed by rotating the O-ring (x-ray source) and the flat panel detector 200°	SBRT/SRS Lung/thorax Liver Brain Head and neck Spine	Is a slow scan, which tends to acquire the "average" position of organs undergoing respiratory-induced motion; can be used for monitoring patient setup (interfraction motion) and changes in anatomy that have occurred possibly during treatment, by performing imaging immediately after treatment; has the ability to monitor tumor response through course of therapy; kV CBCT has better contrast resolution than MV CBCT; kV CBCT suffers from artifacts in the presence of high density materials (eg, hip prostheses); patient scatter (especially for larger patients) can degrade image quality for kV CBCT

Non-ionizing imaging

Calypso

Nomos BAT



Align RT

Elekta MRI linac

Table 2 Non-radiation-based systems for IGRT

Non-radiation-based systems		Imaging acquisition	Geometric accuracy	Functionality/ technical abilities
Ultrasound	Examples			
	BAT, SonArray, iBEAM, RESTITU/Clarity	3-D	3-5 mm	Used for ultrasound-based alignment of target to decrease interfraction setup errors
Camera-based	Examples			
	AlignRT	3-D	1-2 mm	Used for surface-based localization
	Galaxy 3D laser, LAP, Moser IJROBP 85, 2013 p846			
Magnetic resonance imaging	Examples			
	Viewray	3-D	1-2 mm	Used for localization based on MRI
Non-x-ray 4-D tracking systems	Examples			
Electromagnetic	Calypso	<2 mm	System is independent from the linac	Electromagnetic transponders implanted in the prostate gland, used for improving setup accuracy and for accounting for intrafraction motion of the prostate gland

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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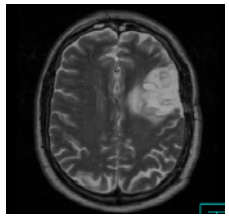
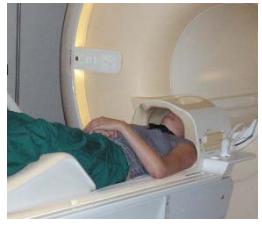
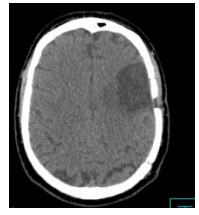
The treatment chain

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

with

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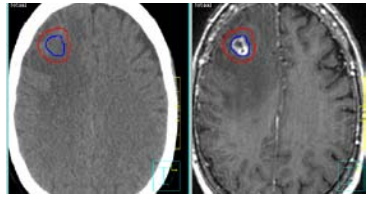
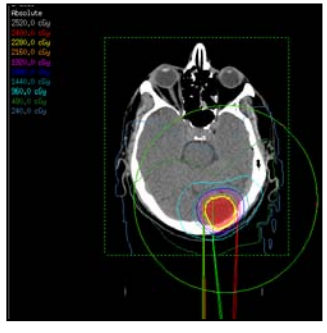
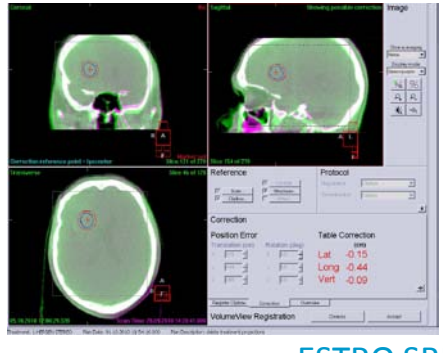


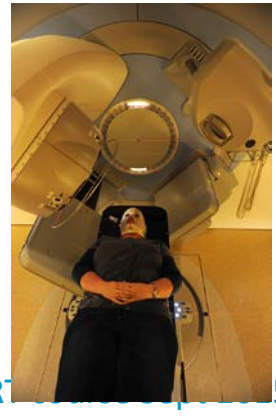
- **Delineation GTV and OAR on MRI**
- **CTV = GTV, PTV = CTV + 3mm**



VMAT planning

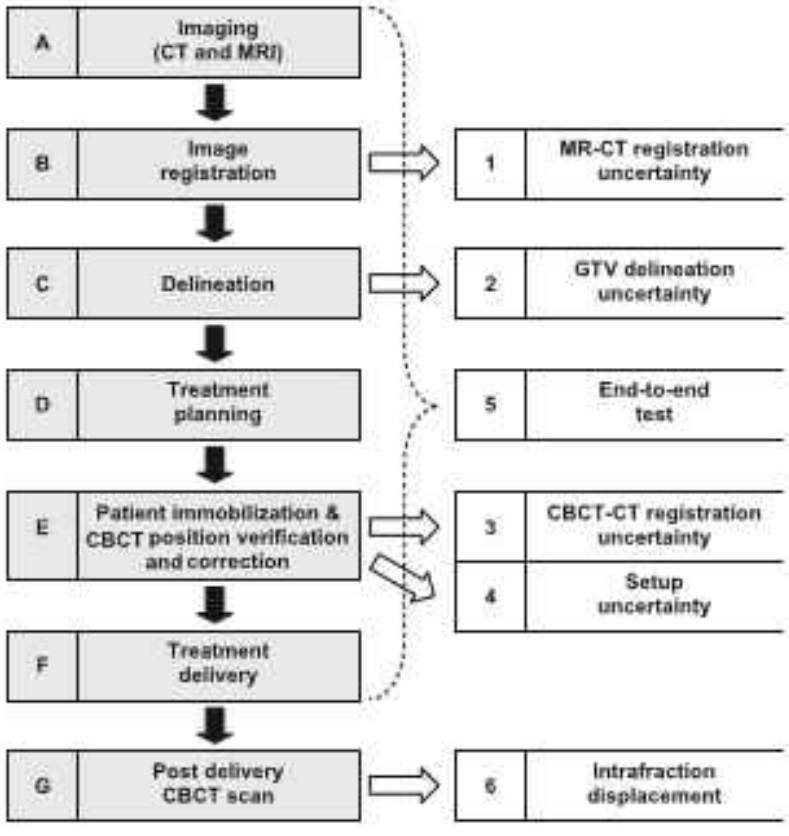
- **1 dual arc per isoc**
- **98% of PTV should get at least 95% of prescribed dose**





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[b])	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

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.

The bridge to Linac based RT: Volumes

GK now	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

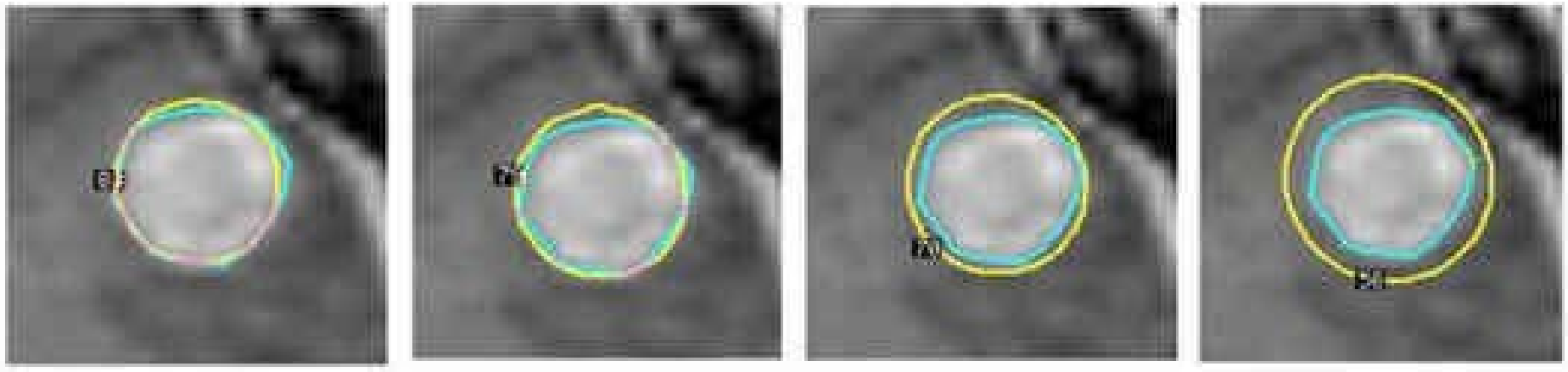
The bridge to Linac based RT: Dose

now	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)	

The bridge to Linac based RT: Dose

now	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)	

Dose prescription and margins



90% coverage
Dmax = 30.1Gy

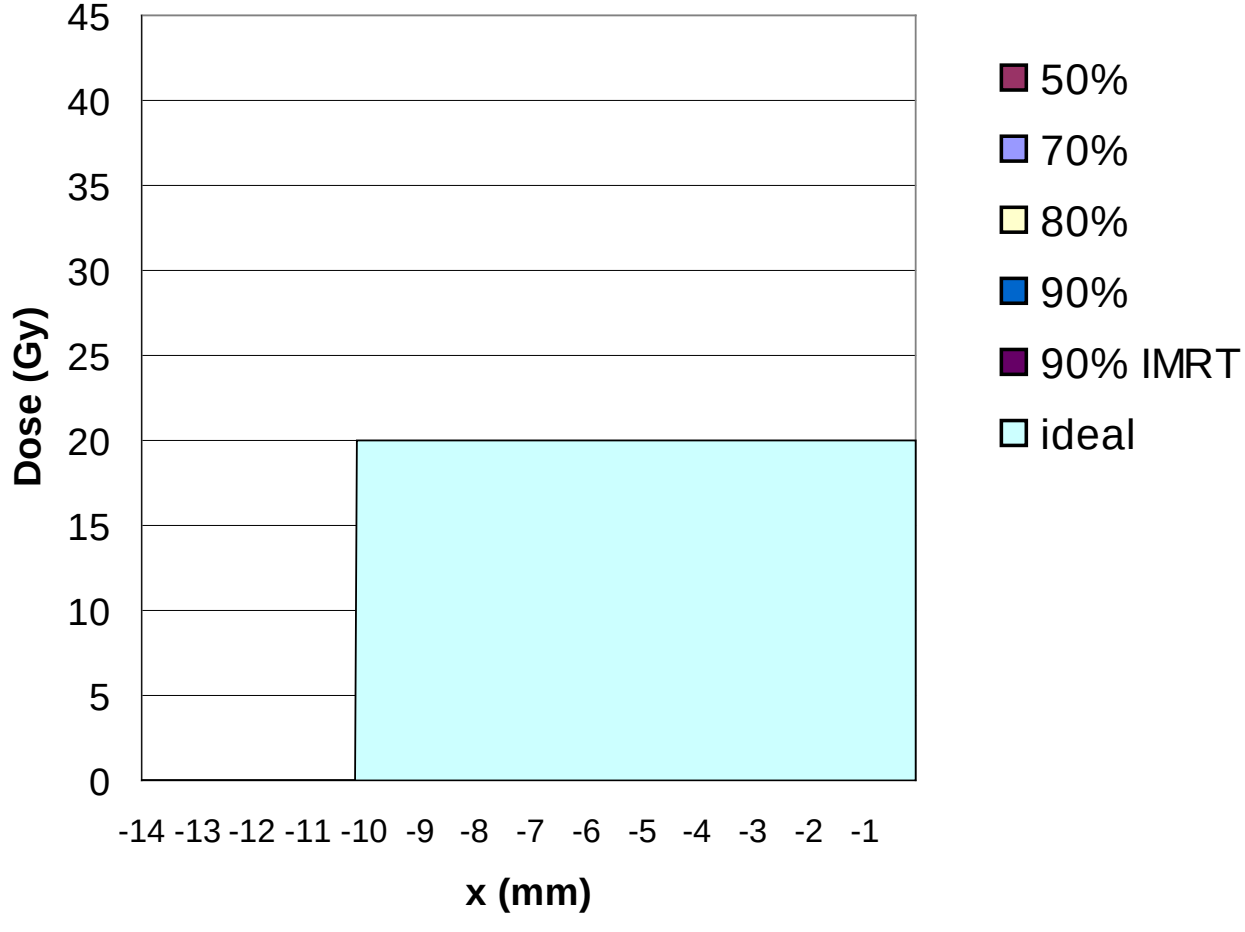
95% coverage
Dmax = 31.6Gy

100% coverage
Dmax = 35.7Gy

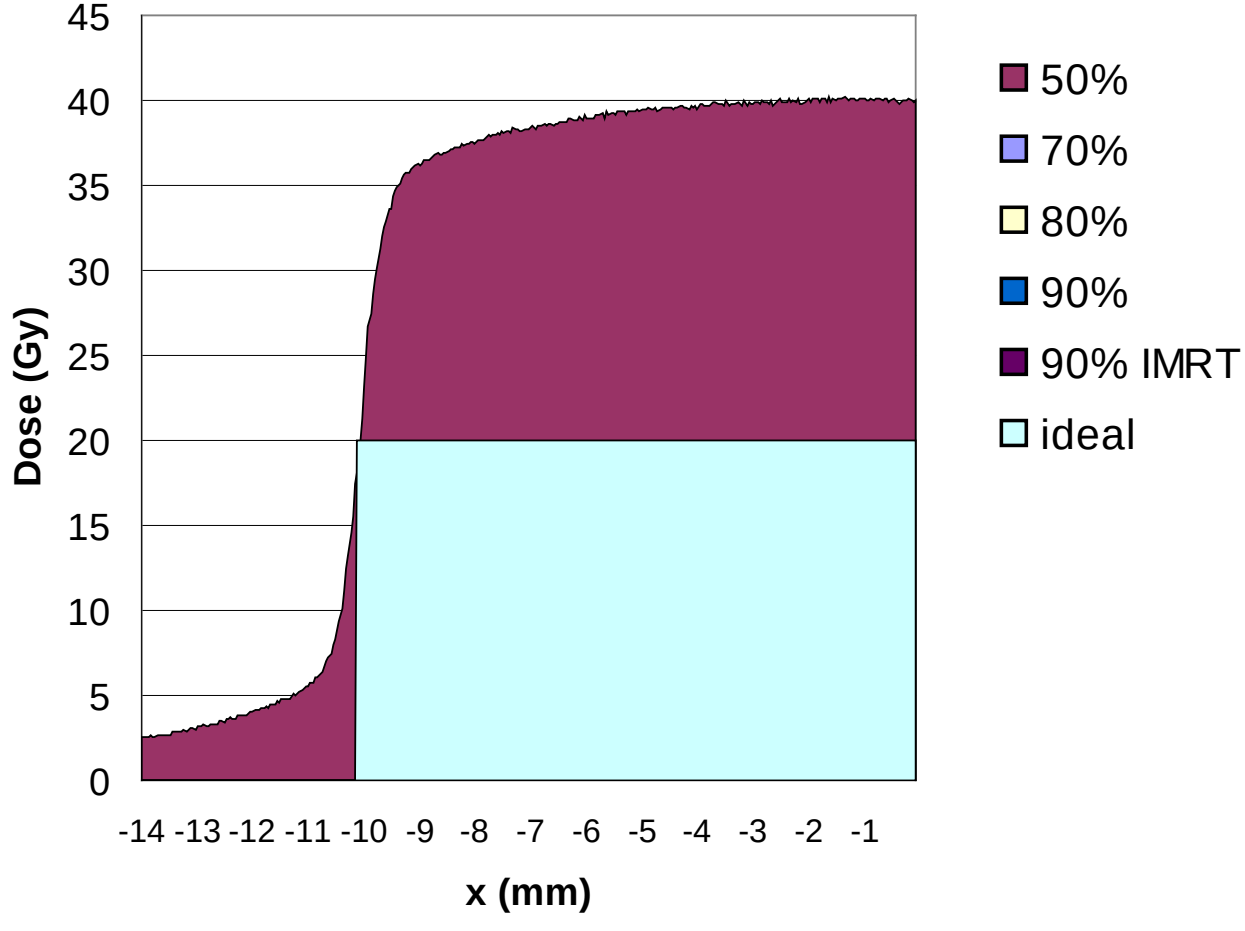
1mm margin
Dmax = 44.6Gy

48% Difference in dose

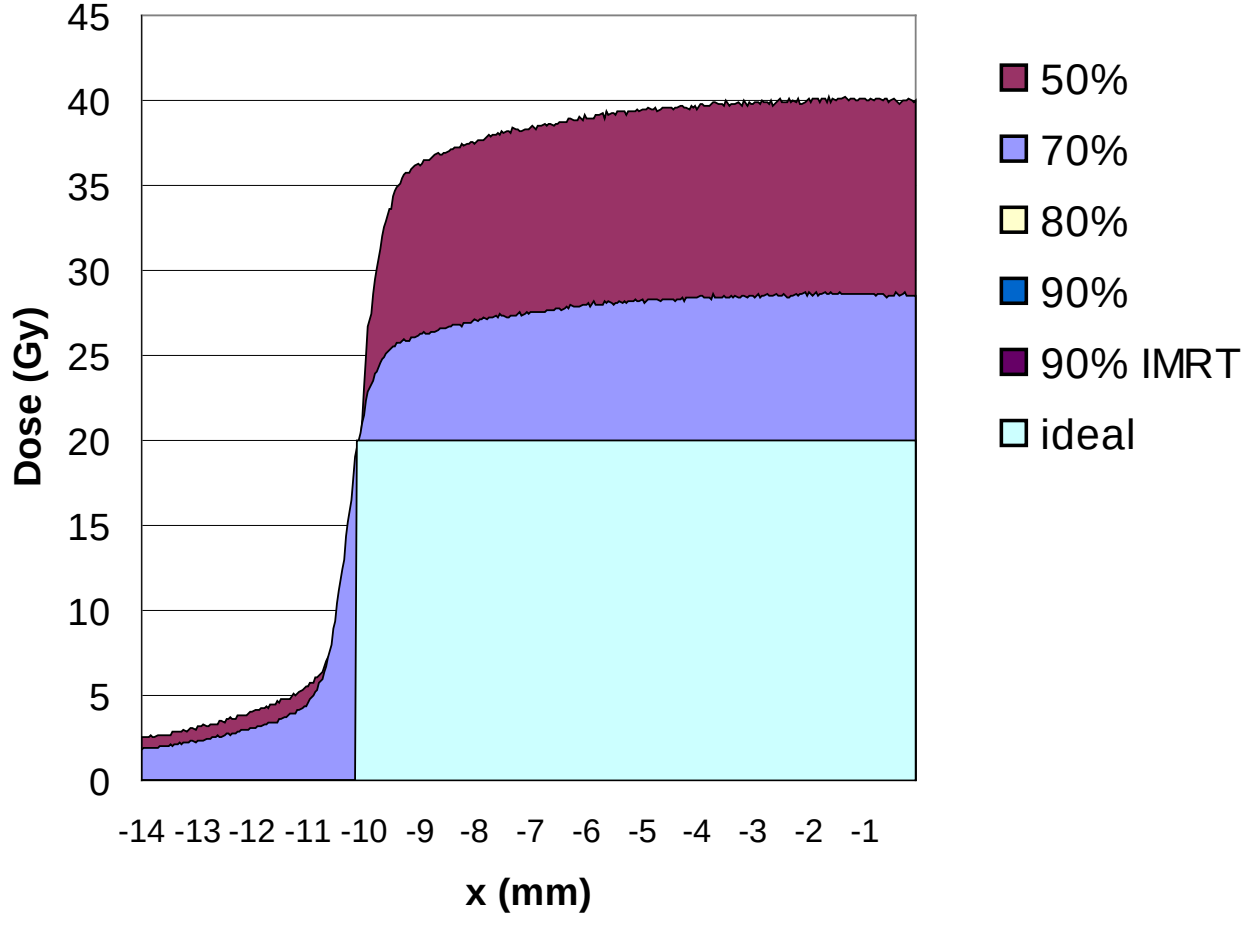
Prescription isodose vs modern linac RT



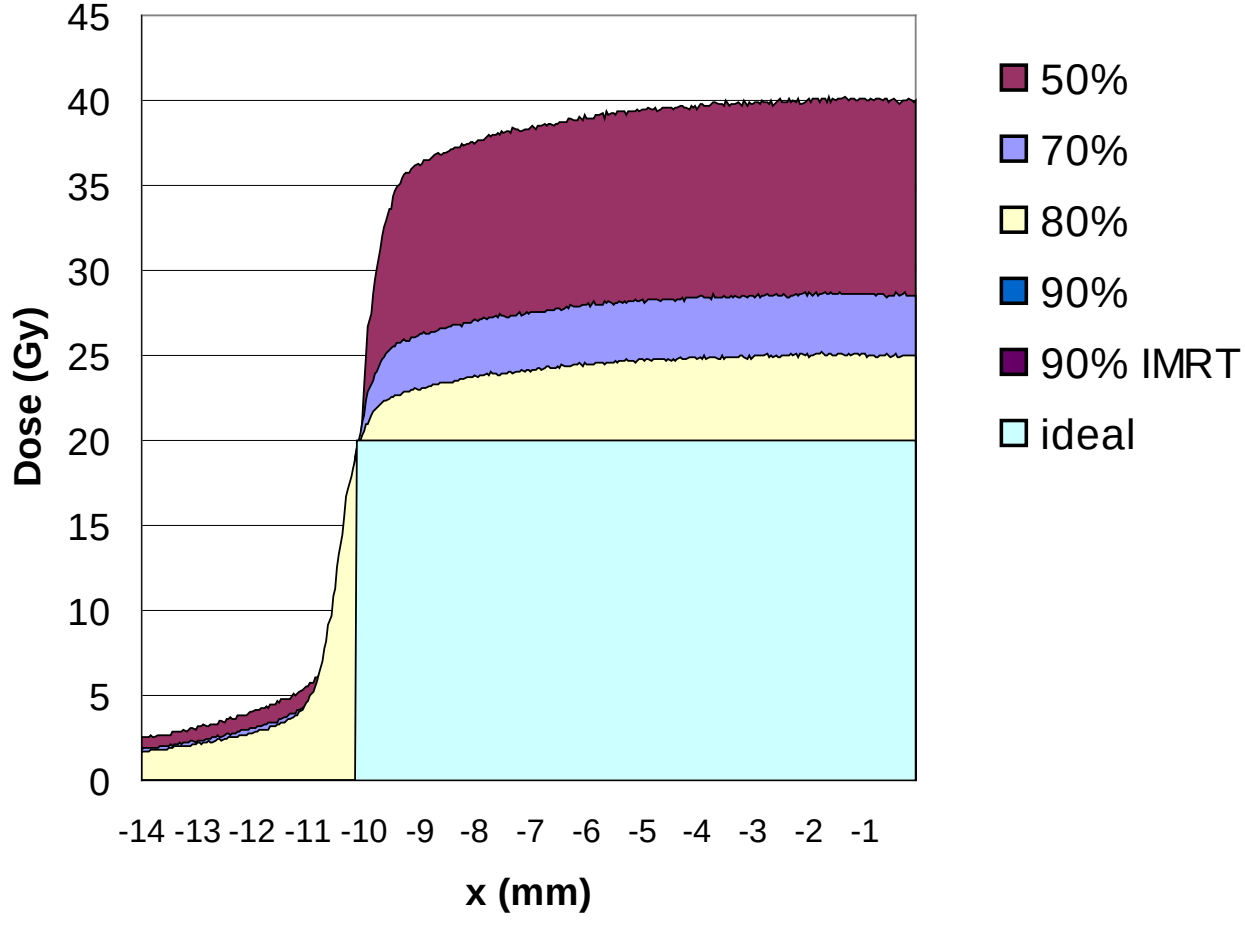
Prescription isodose vs modern linac RT



Prescription isodose vs modern linac RT



Prescription isodose vs modern linac RT



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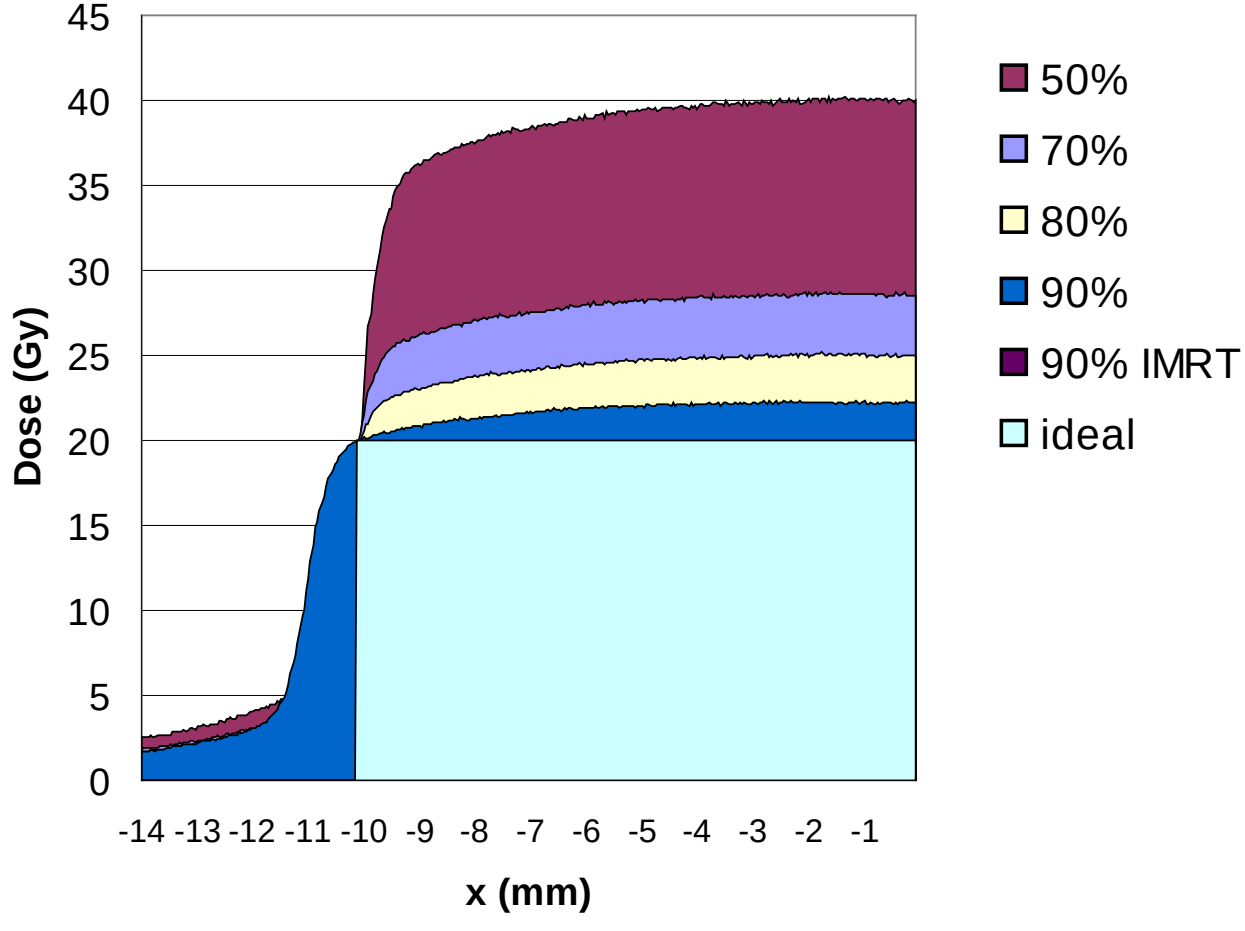
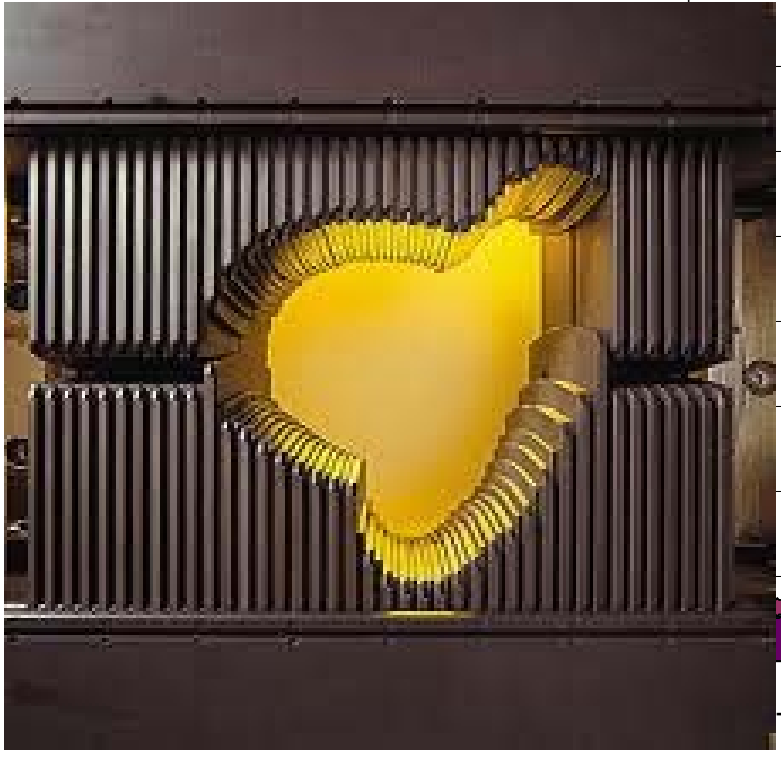
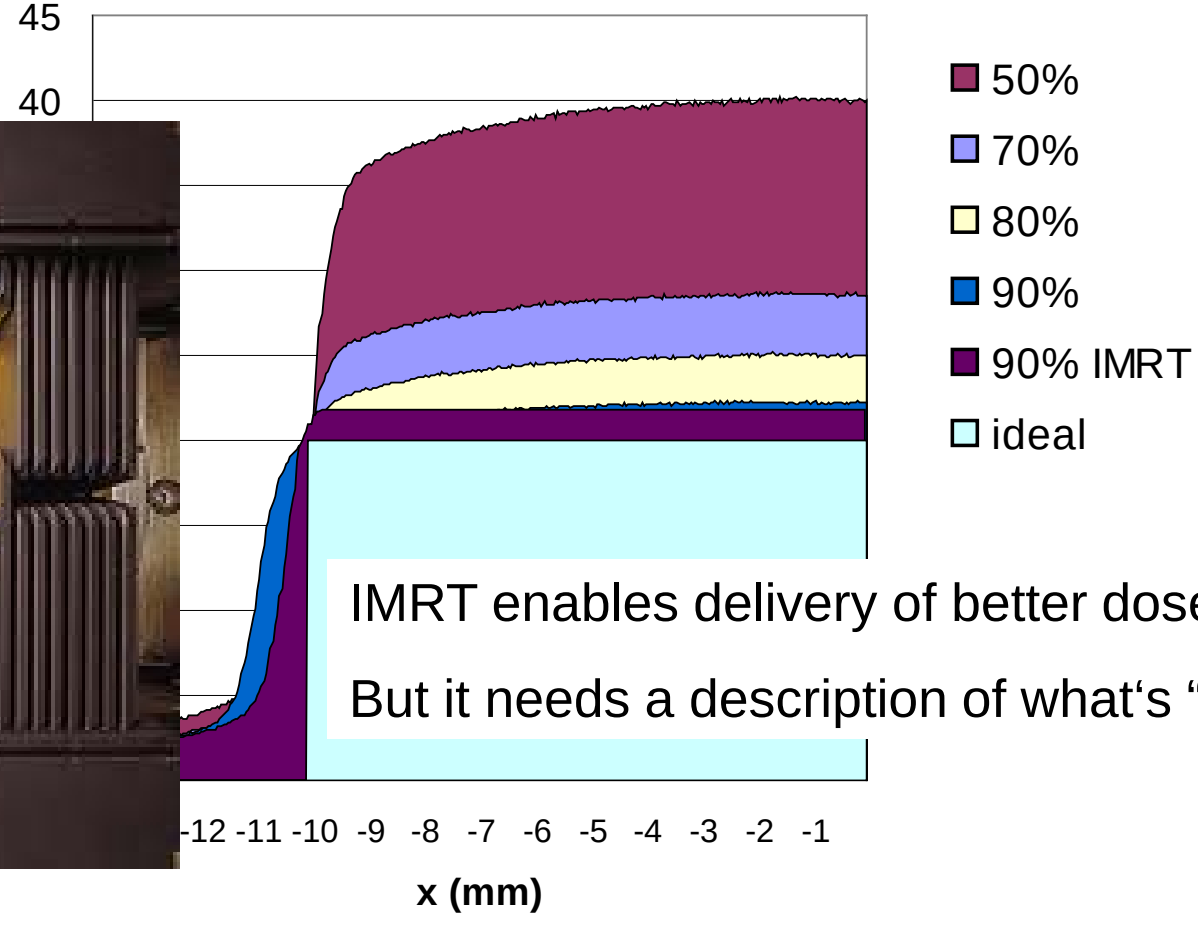
Prescription isodose vs modern linac RT



catharina hospital

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 / Prescription isodose

+ Mean / Median dose and Dose to Organs at risk

catharina hospital

Conclusion

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

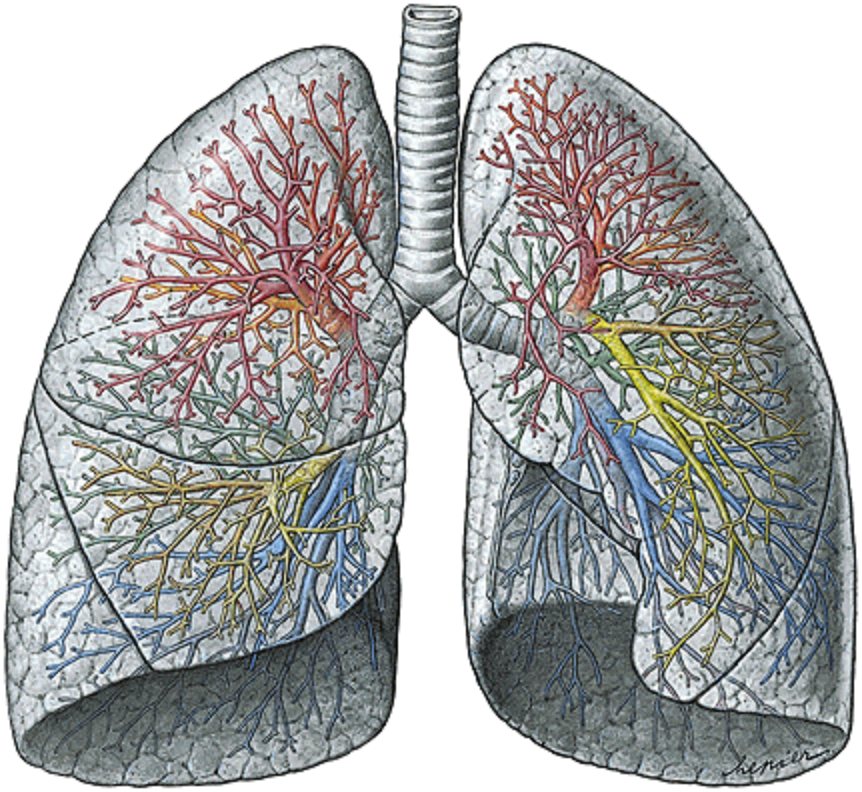
Learning Objectives

- **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**

- **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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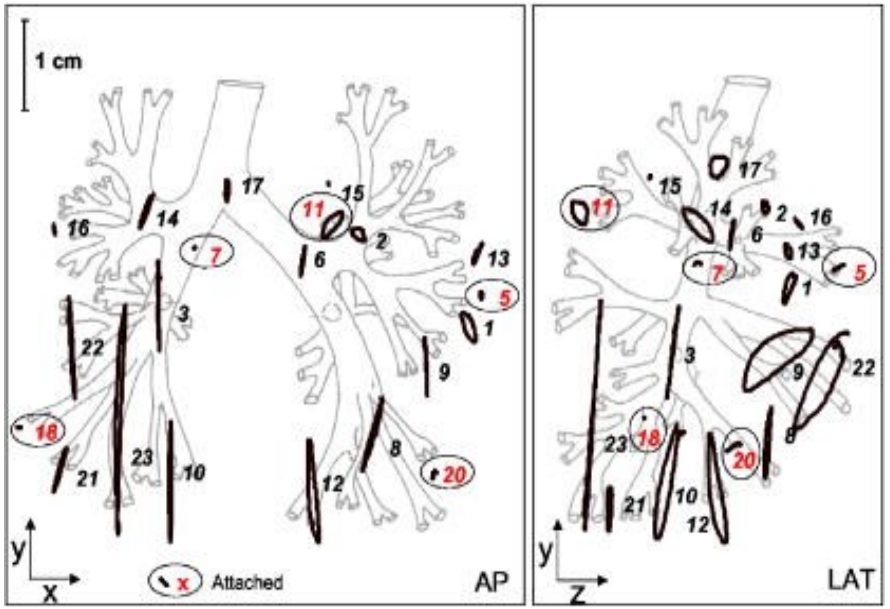
Observation of Motion

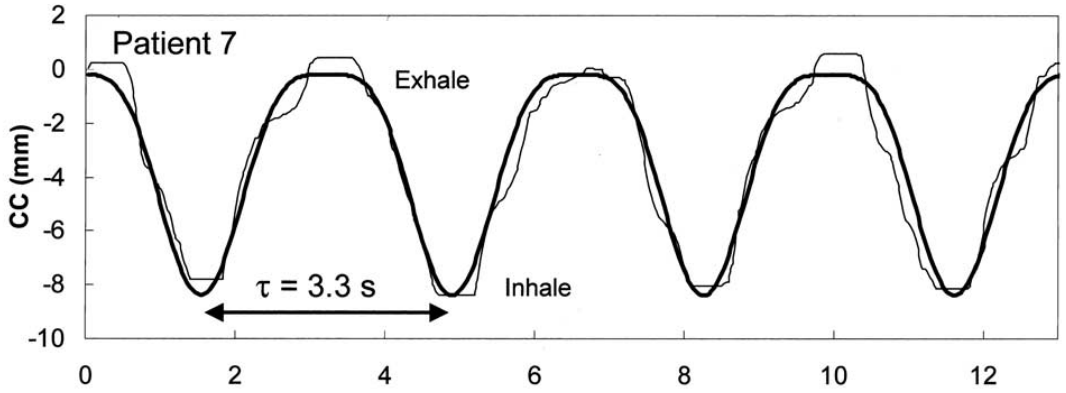
- Fluoroscopy



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

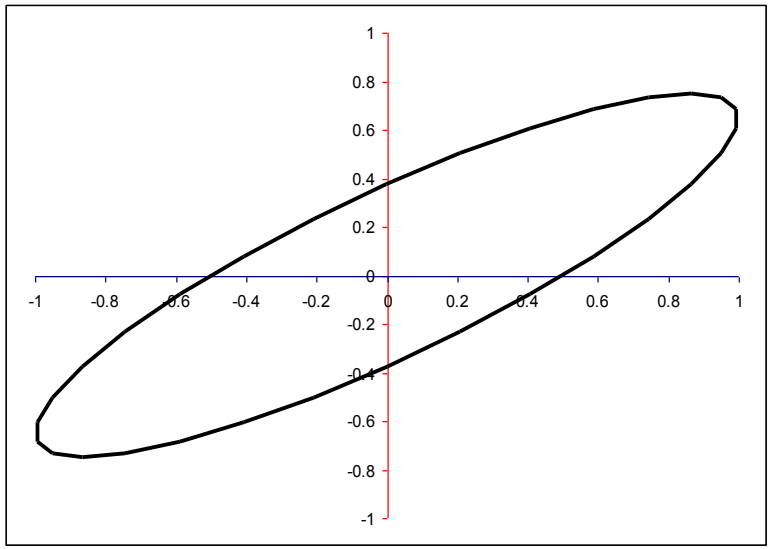


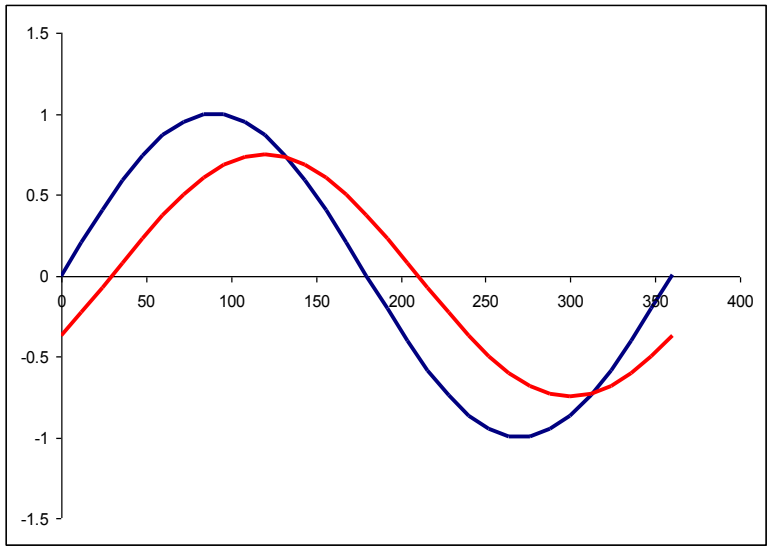
$$y = y_0 - A\cos^{2n}\left(\frac{\pi t}{\tau} - \phi\right)$$

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

Erasmus MC

Observation of Motion



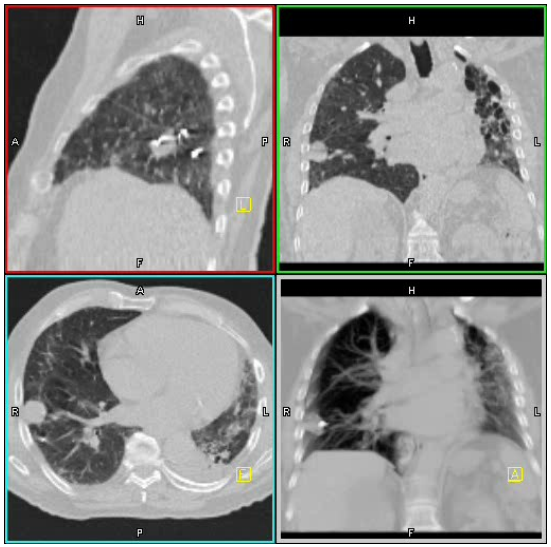


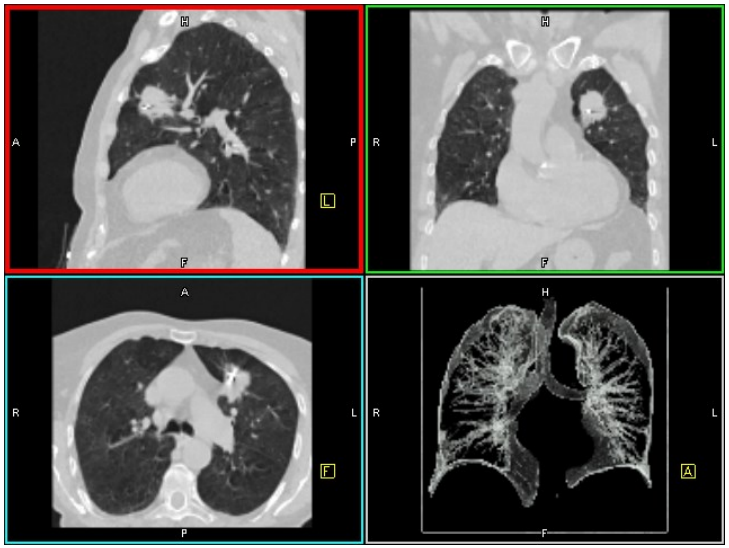
- Hysteresis in half of the patients (1-5 mm separation of trajectories)
- The extent of hysteresis and the amplitude of the tumor motion remains fairly constant during the entire treatment
- However, in many patients, shifts in the exhale tumor position were observed intra- and interfractionally

Erasmus MC

Observation of Motion

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





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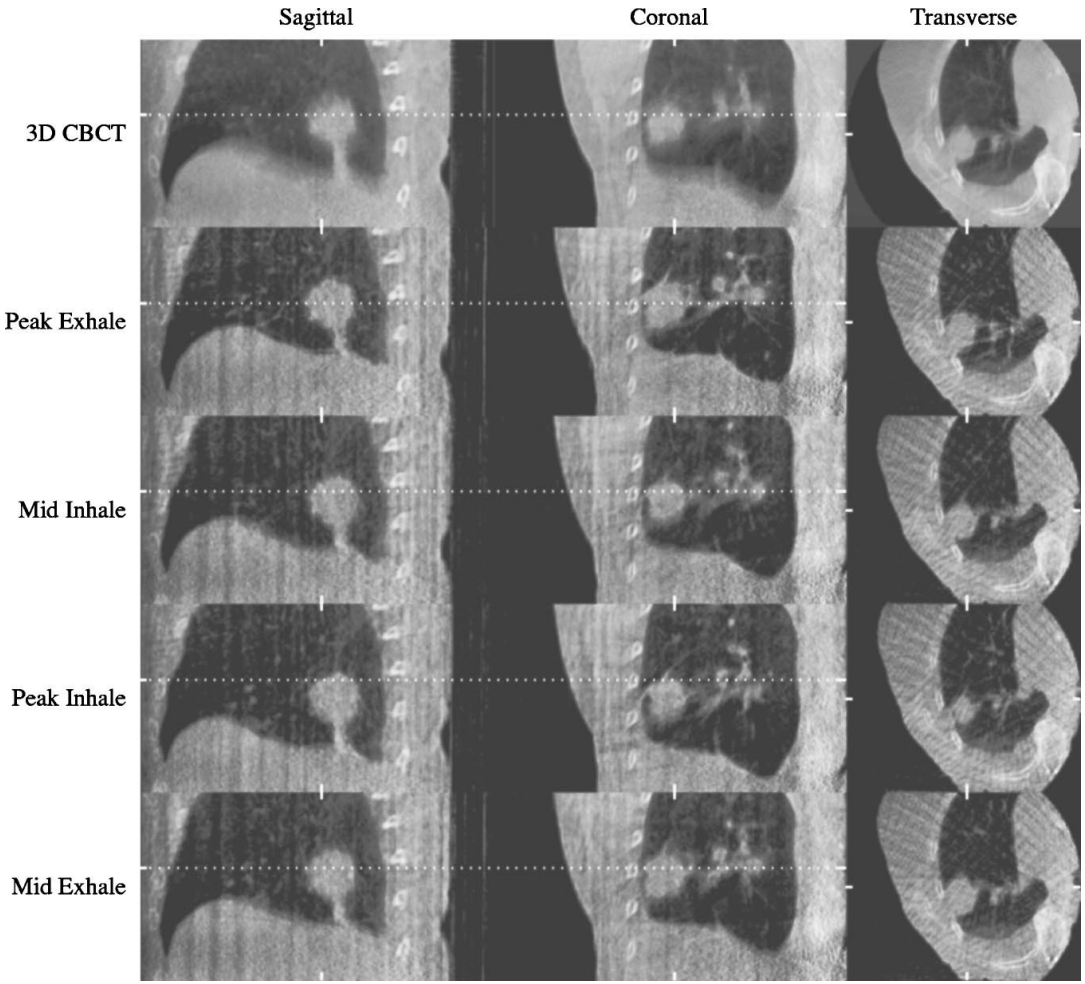
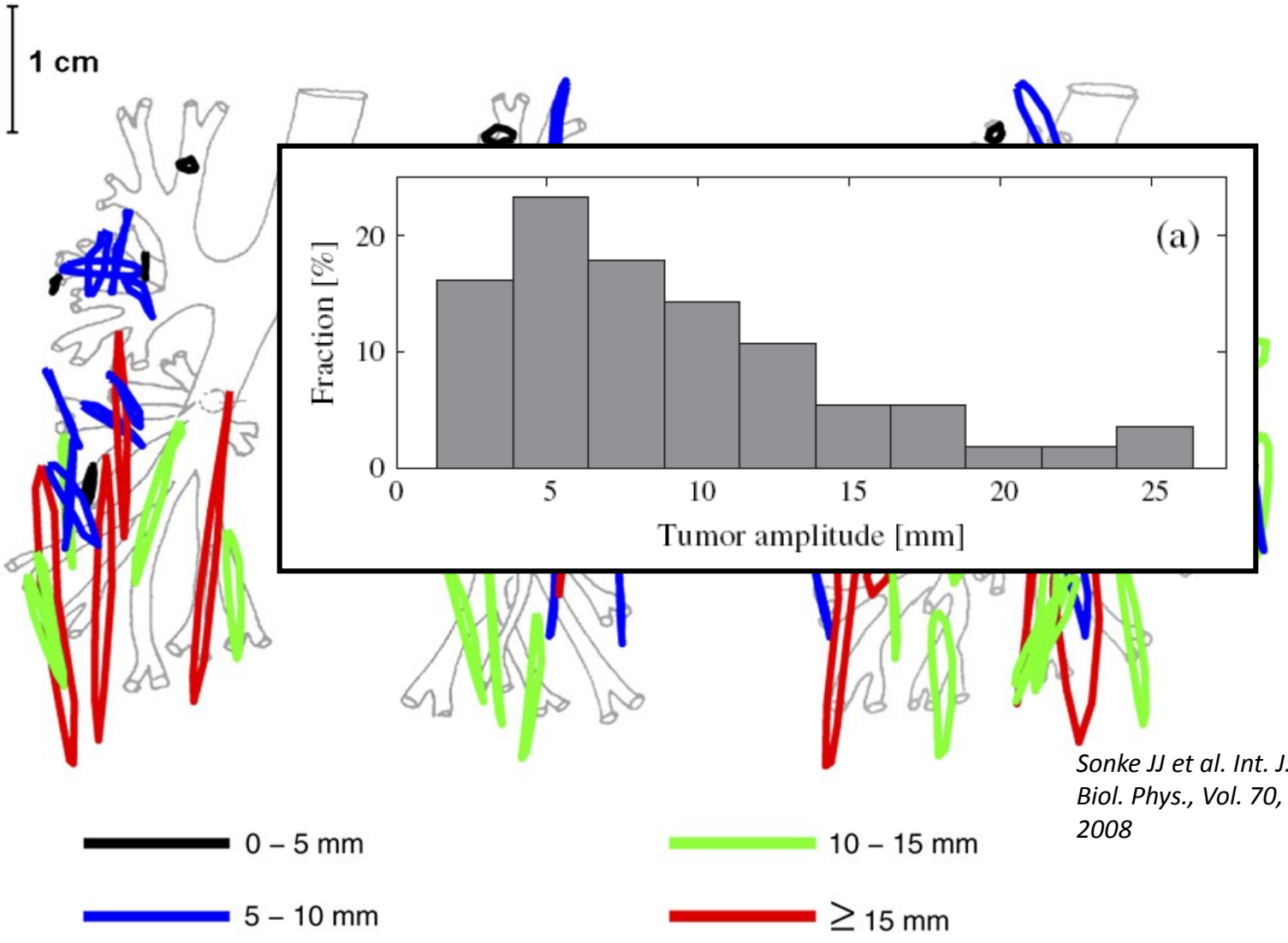
Respiratory Correlated Cone Beam CT Scanning



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

Erasmus MC

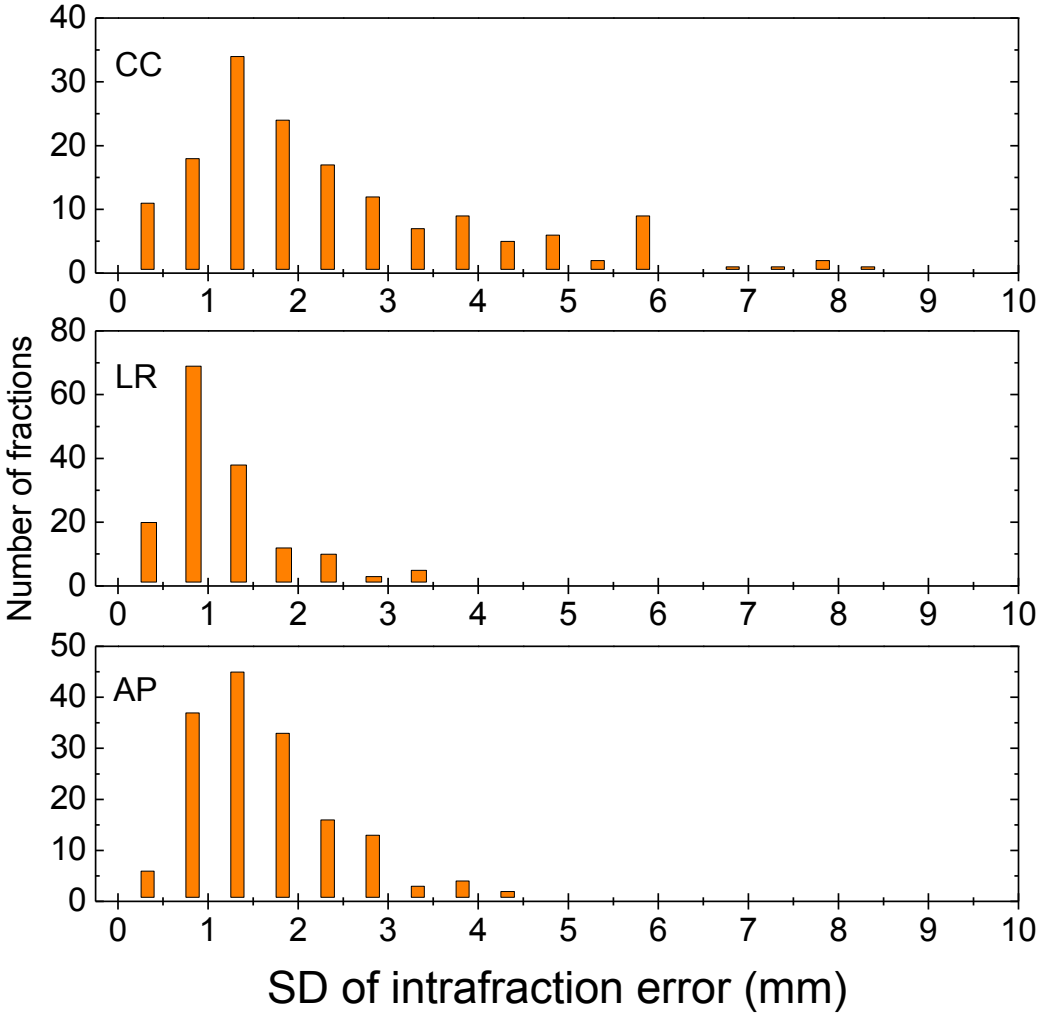
Motion Observations



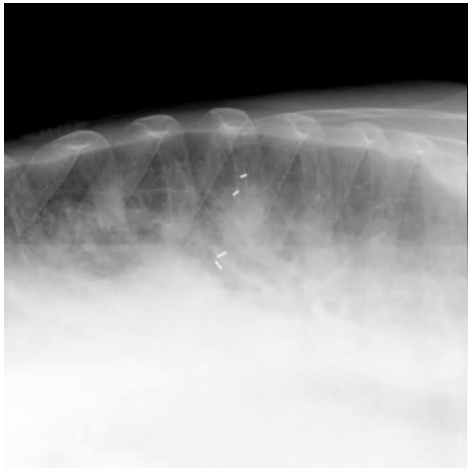
Sonke JJ et al. Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 590–598, 2008

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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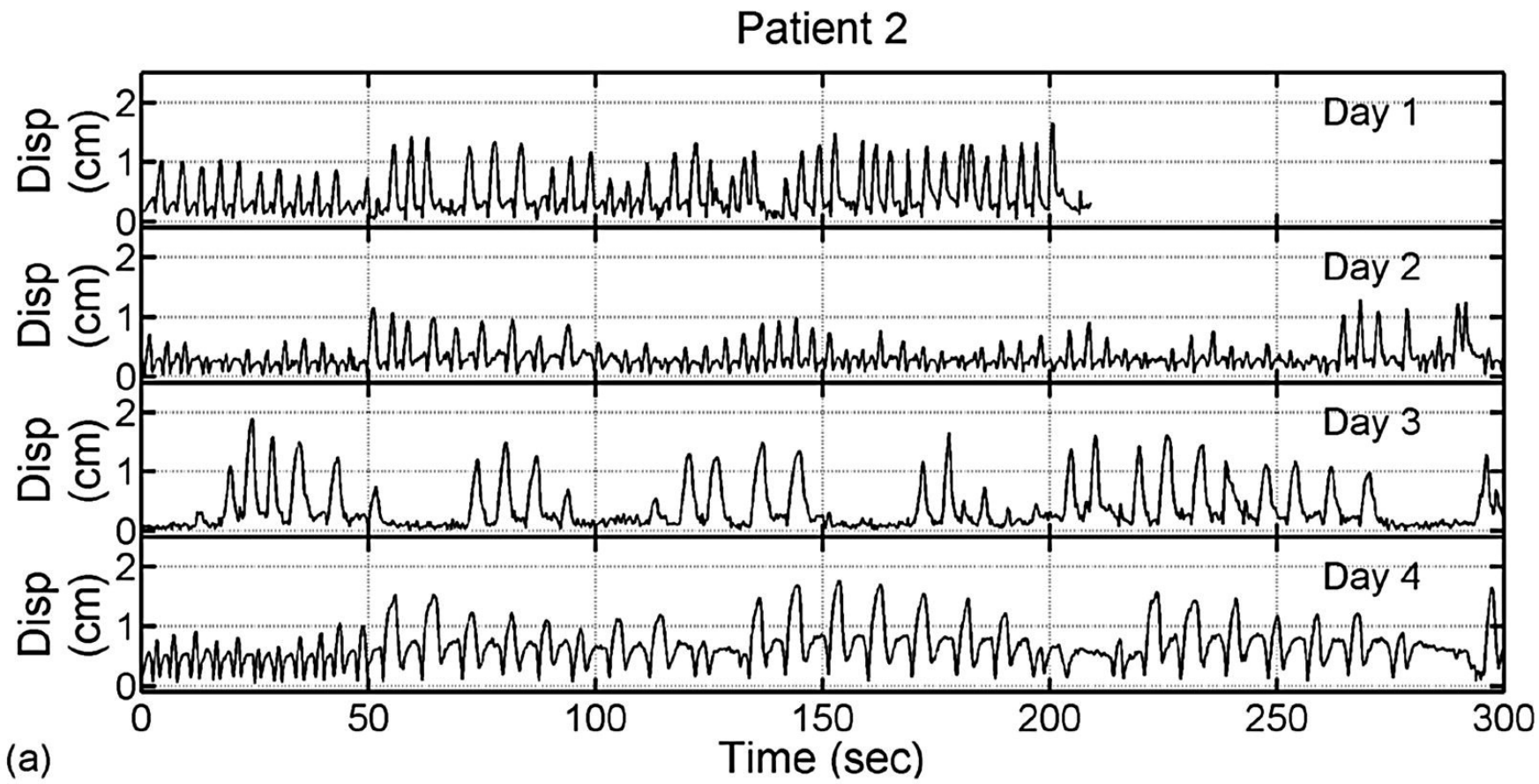
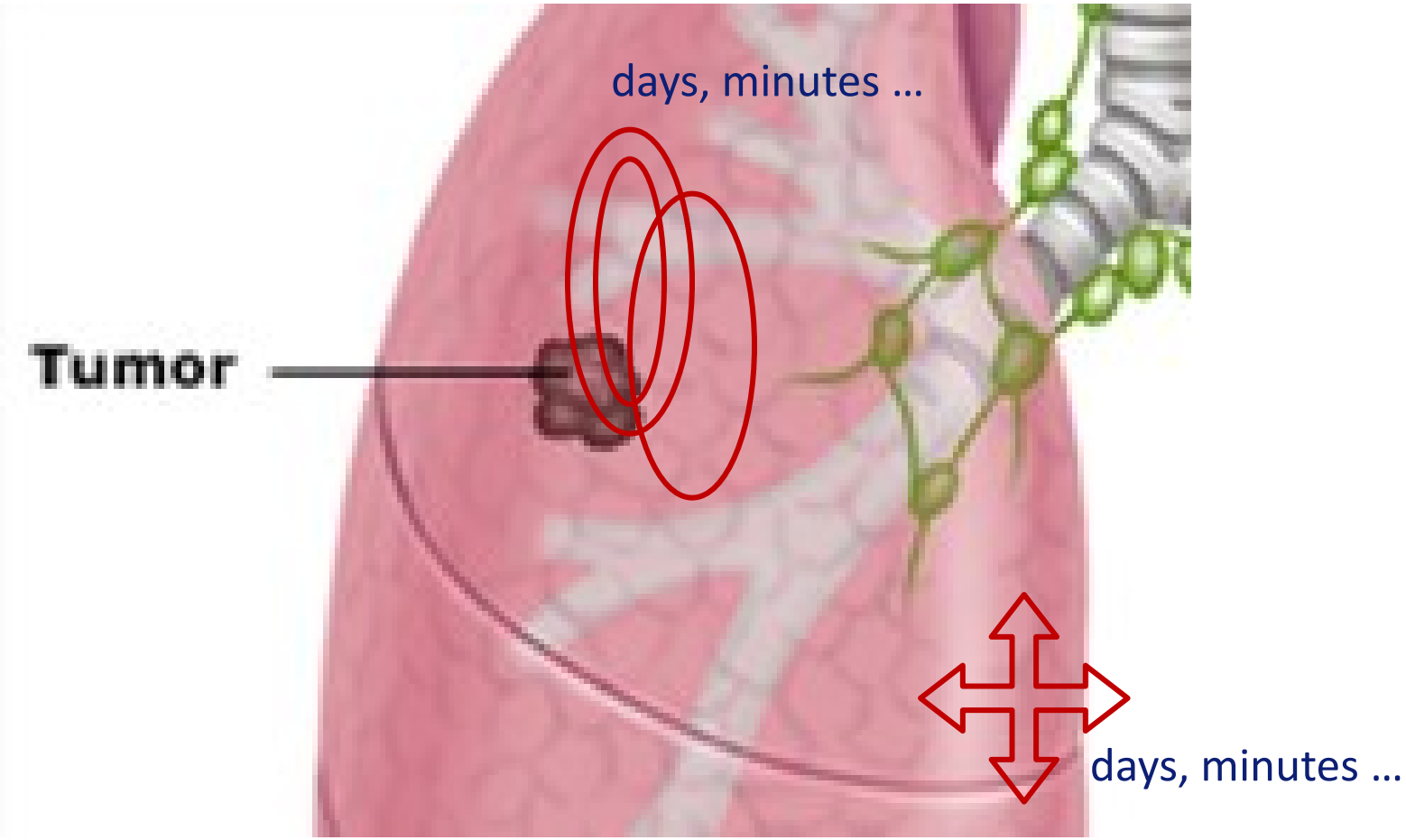
Day-to-Day Variation in Lung Tumor Motion



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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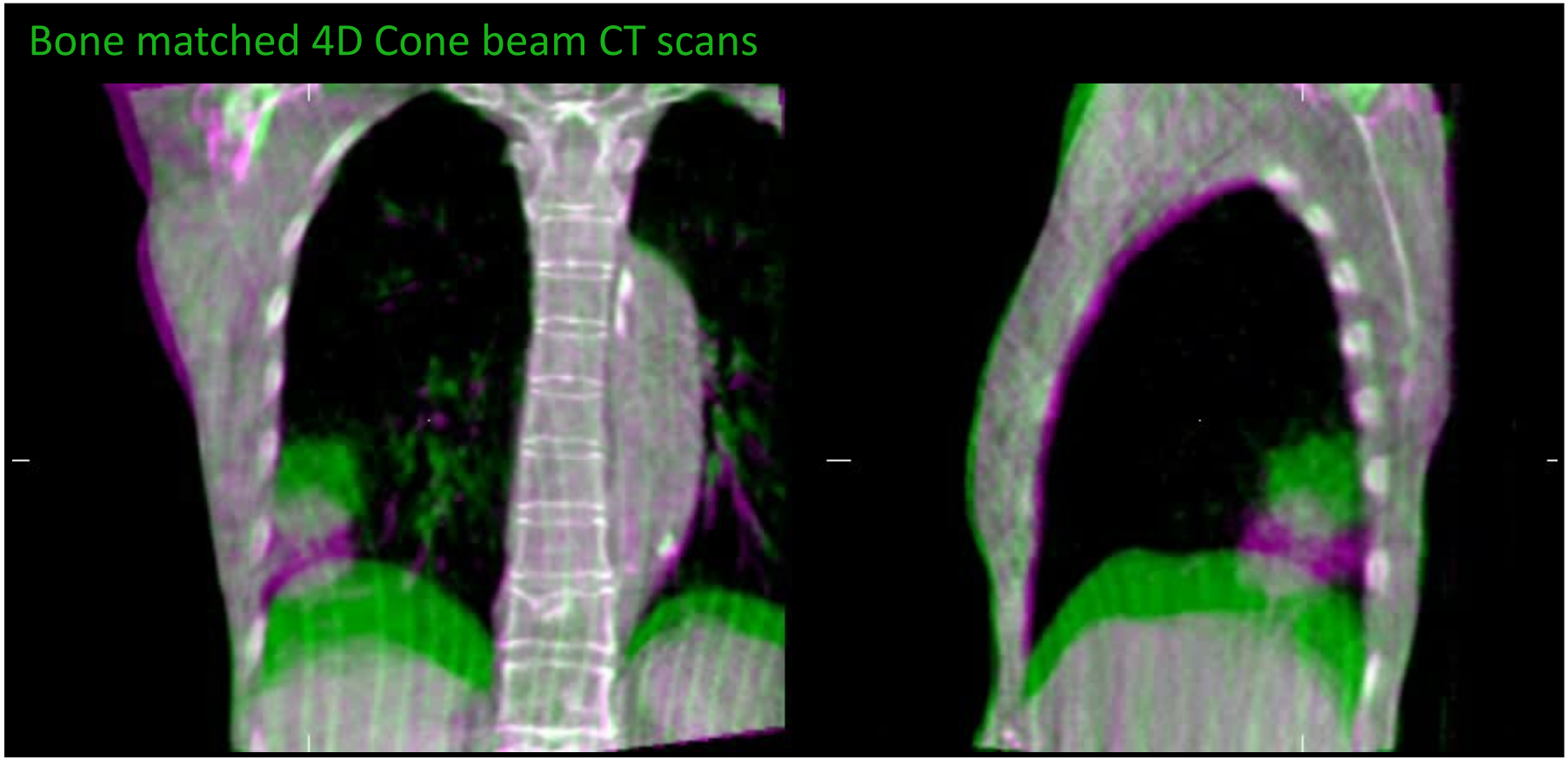
Systematic error and baseline shift



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

Erasmus MC

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	1.1	1.5	2.0

Sonke et al. IJROBP 2007 Nov 23, Epub

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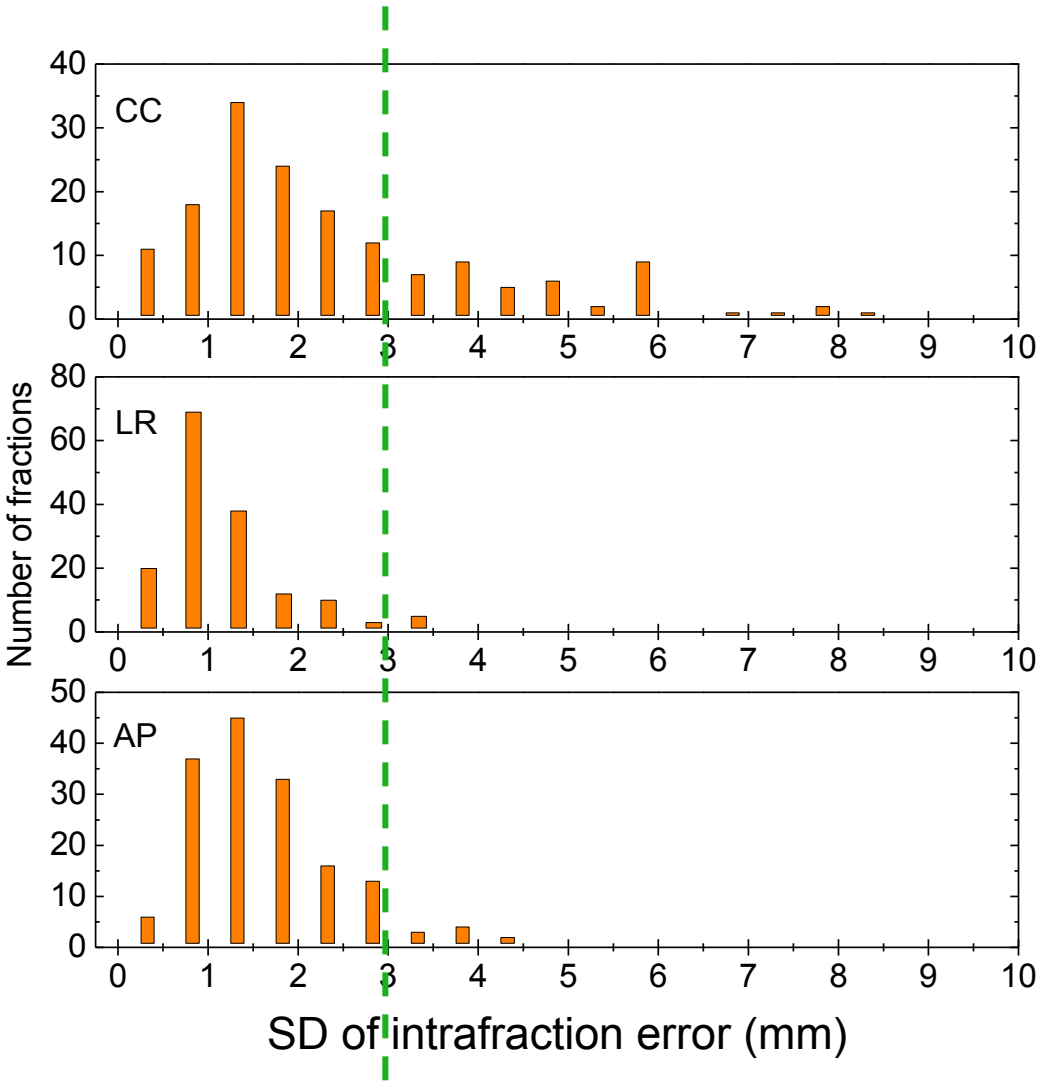
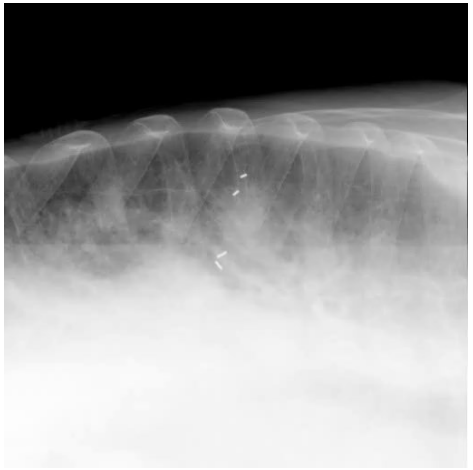
Distribution of Intra-fractional Respiratory Motion (1 SD)



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



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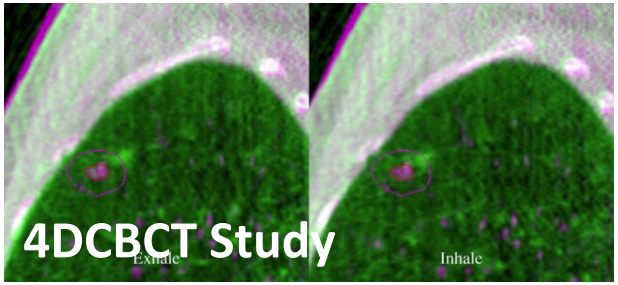
Intra-fraction Variability of Tumor, Bone, and Baseline (Minutes)



Average beam on time 28 ± 5 min

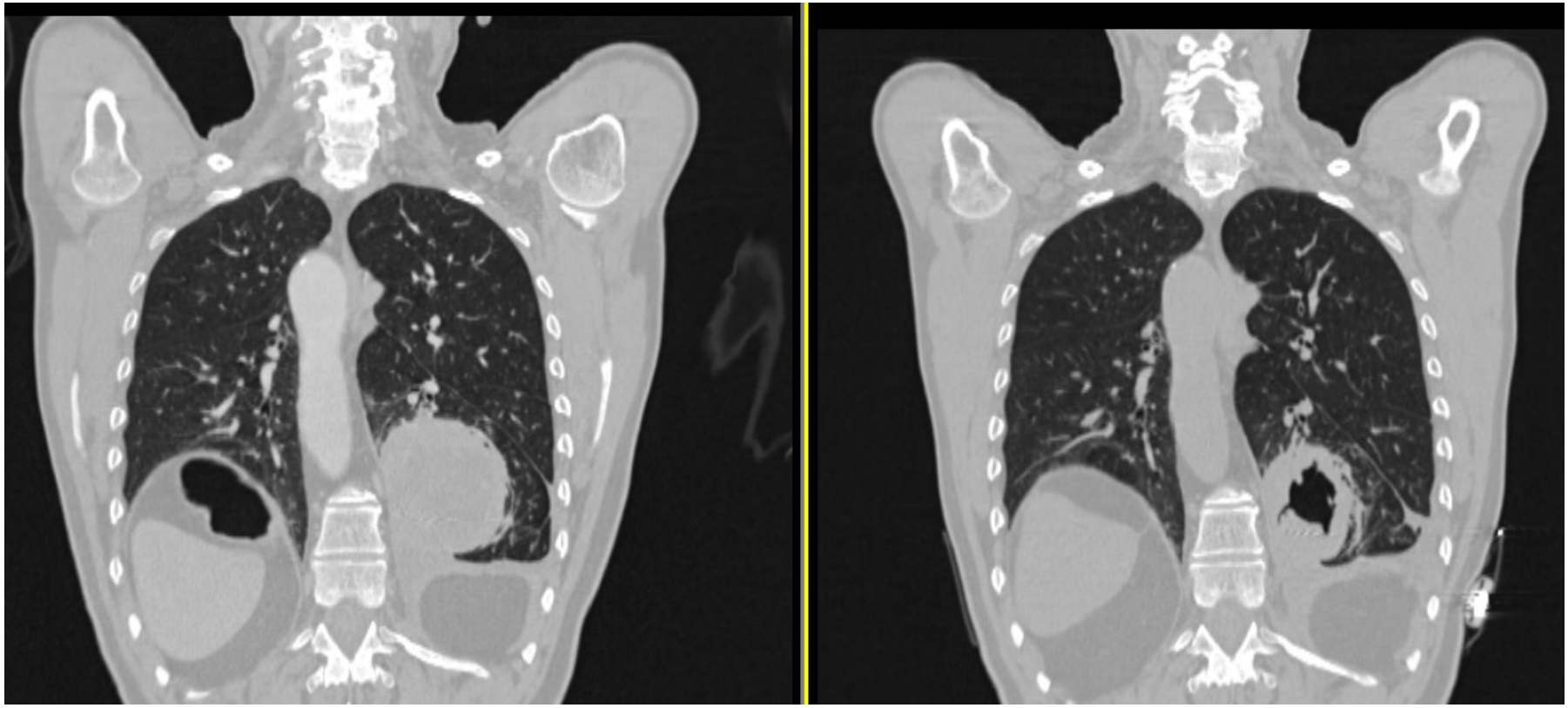
Table 3. Intrafraction variability of tumor, bony anatomy, and baseline in terms of group mean (GM), systematic error (Σ), and random error (σ)

	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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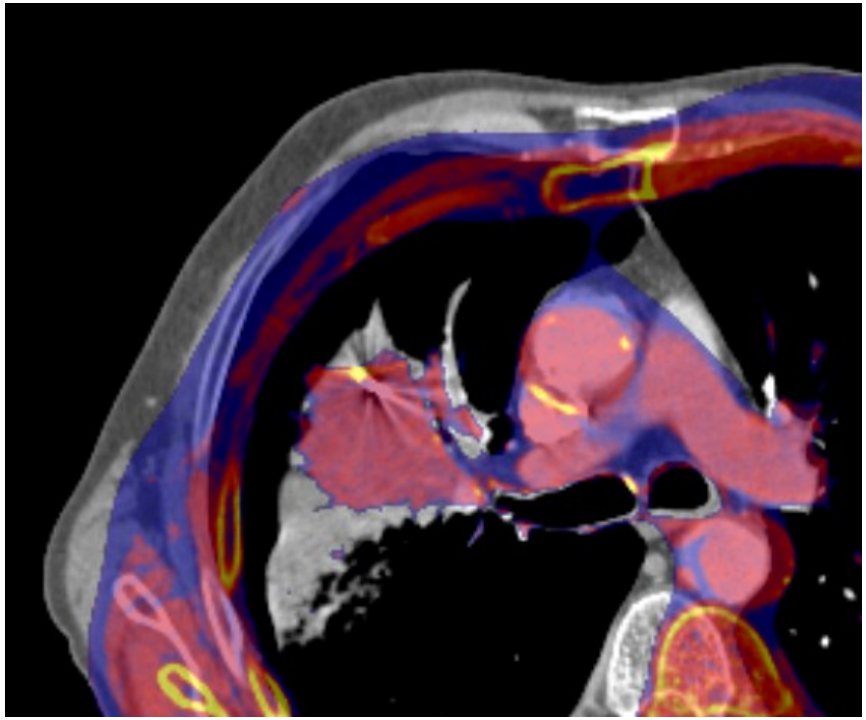
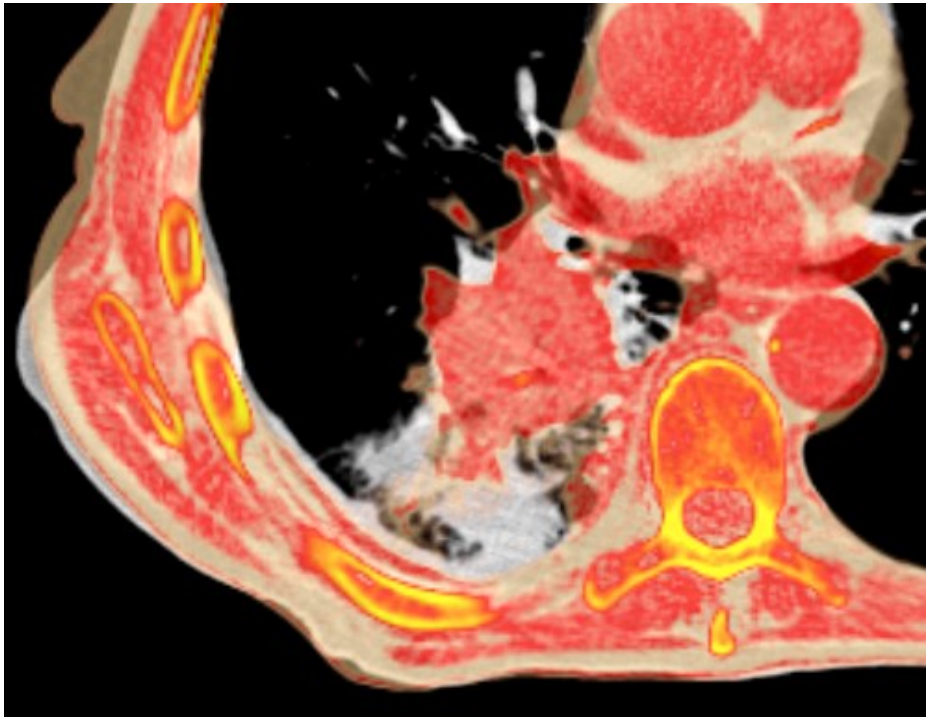
Tumor Changes in Volume and Shape





- 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

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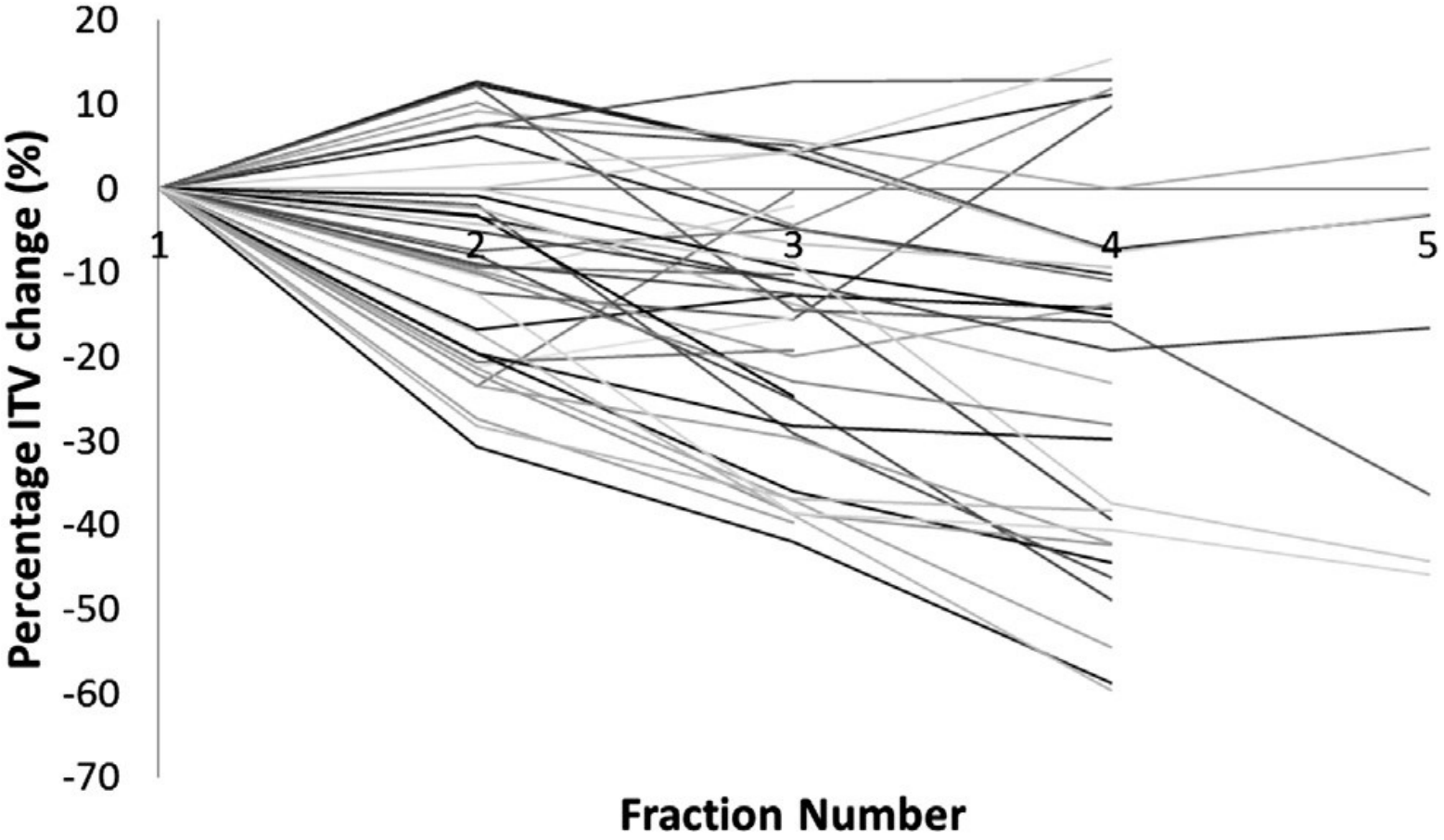
Changes in ITV



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

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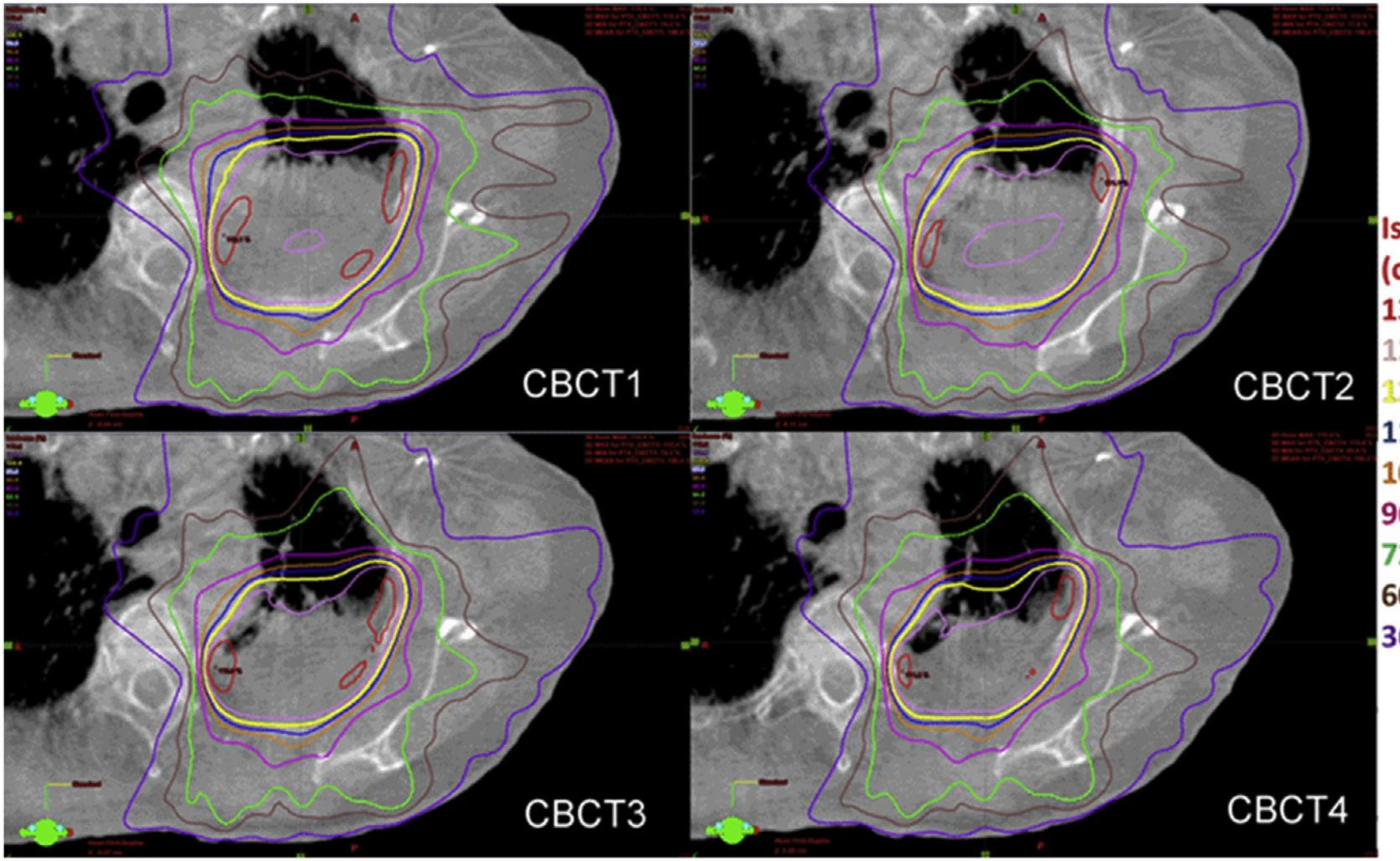
Replanning Example



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

Discussion: Clinical Relevance

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

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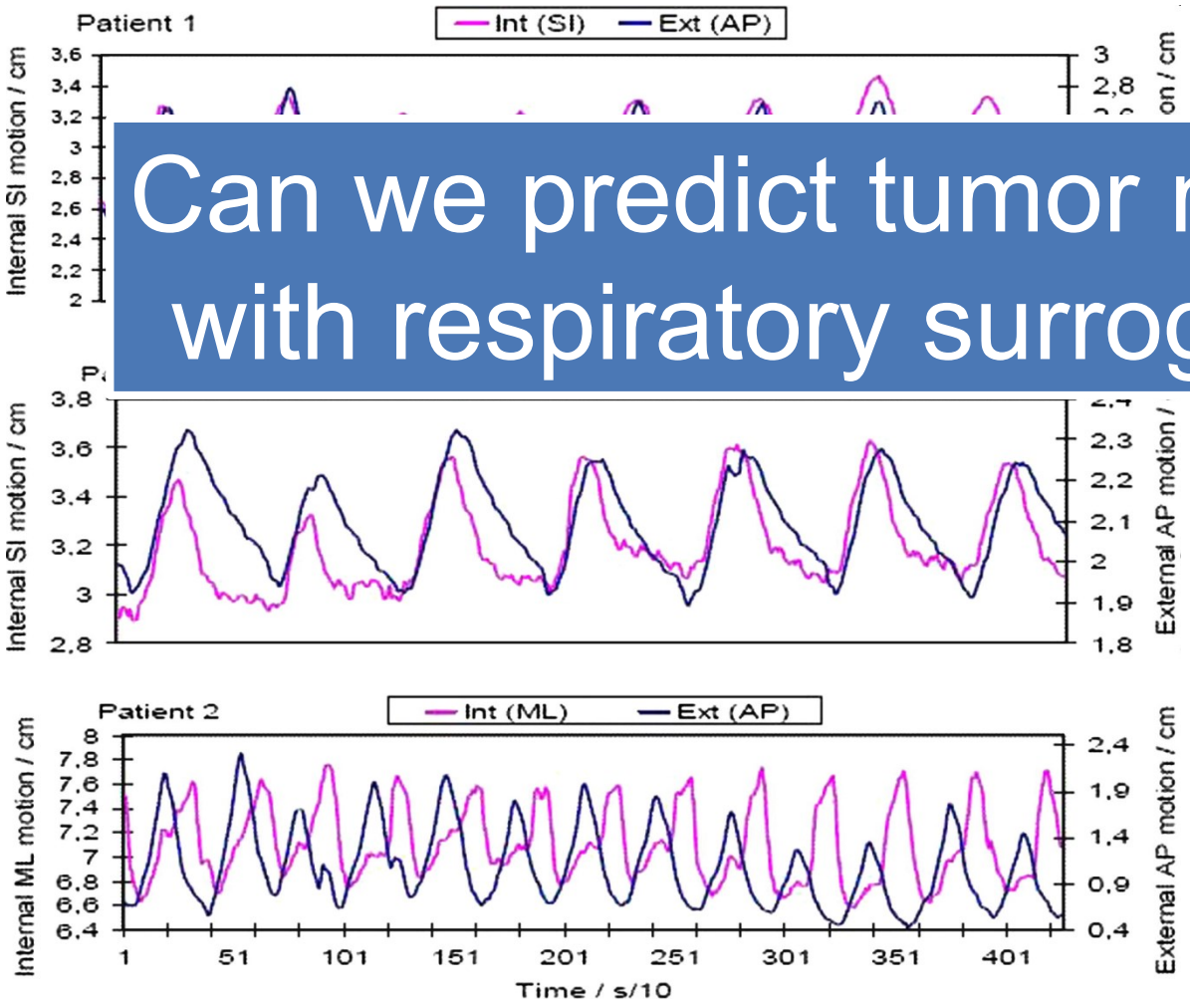
Bad Correlation Internal and External Signal



Can we predict tumor motion with respiratory surrogates?

Korreman et al. R&O 2008

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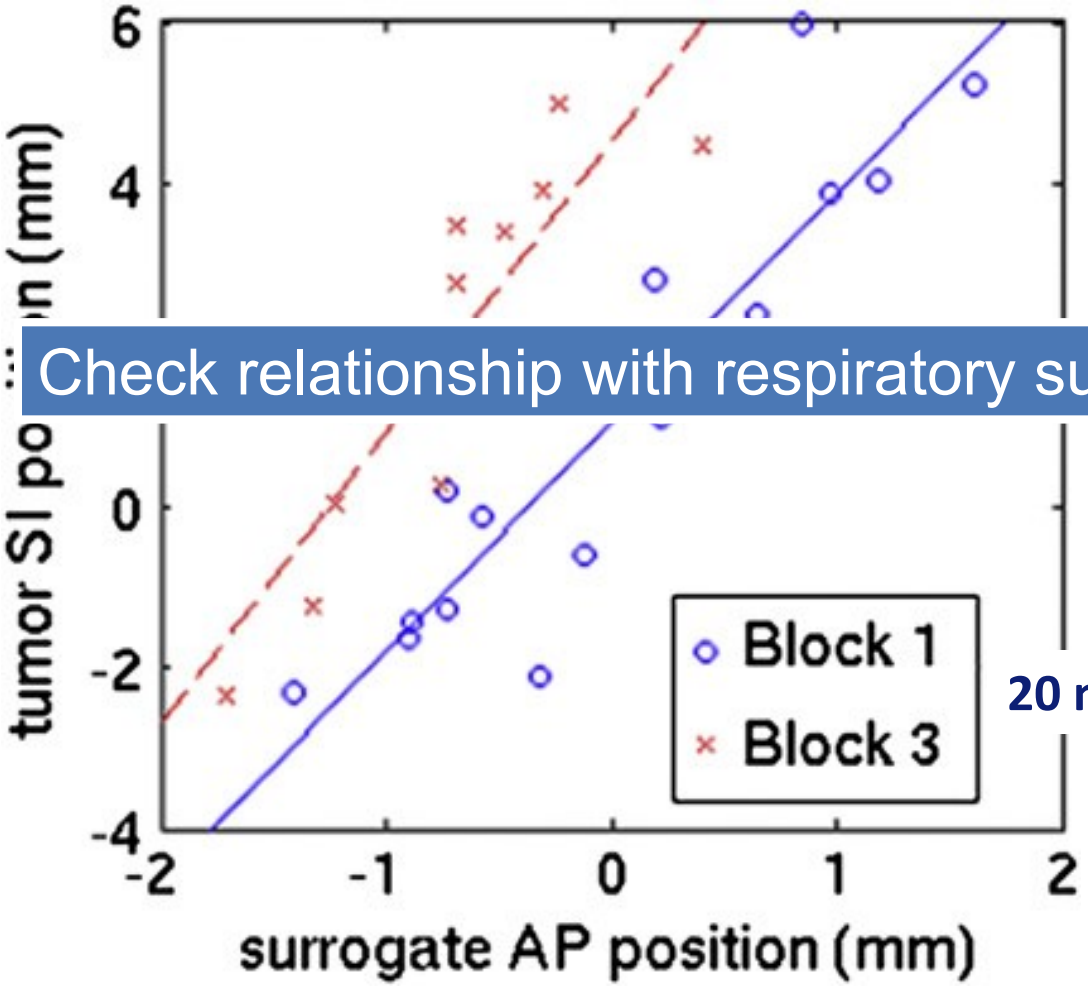
Changes in Relationship with Respiratory Surrogate



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

Check relationship with respiratory surrogate after 10 min

20 min difference (+2 mm margin)

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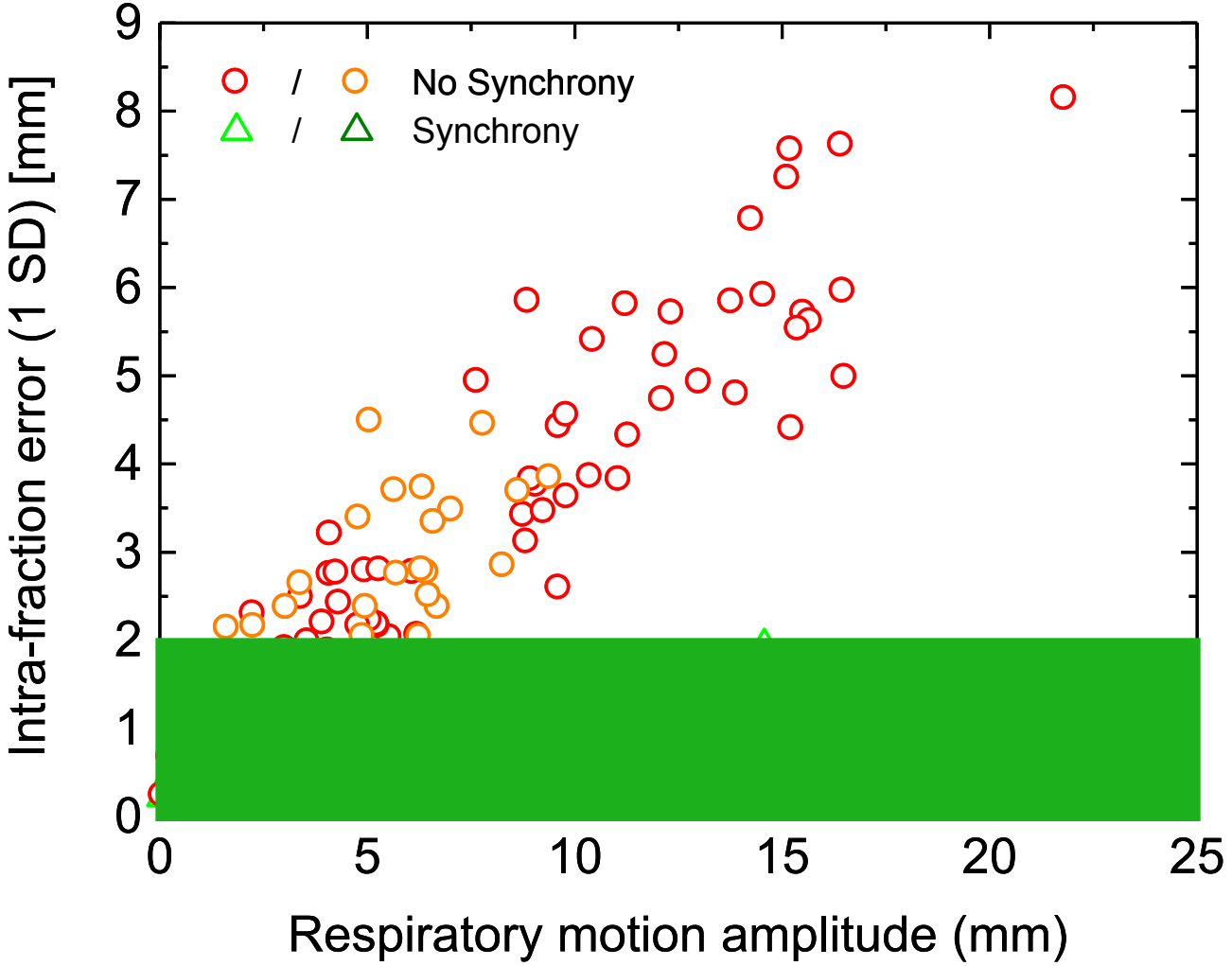
Intra-Fraction Error (167 treatment fractions)



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

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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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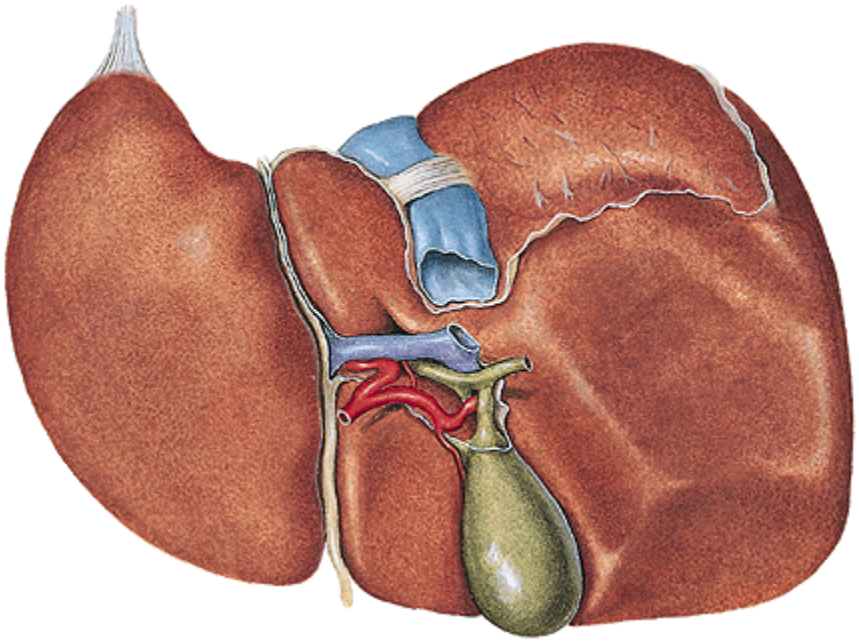
LIVER



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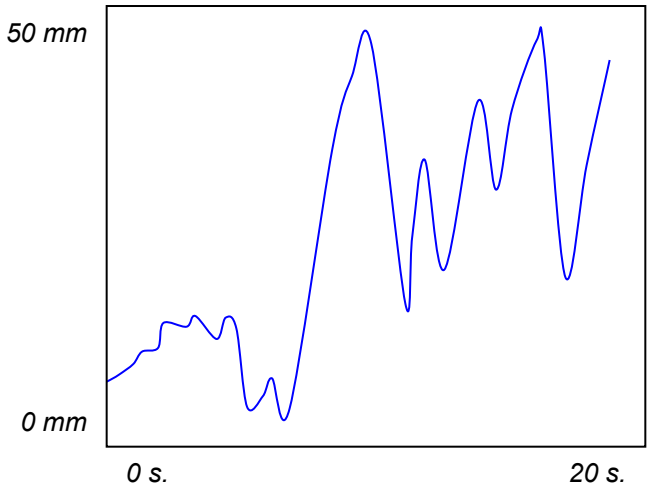
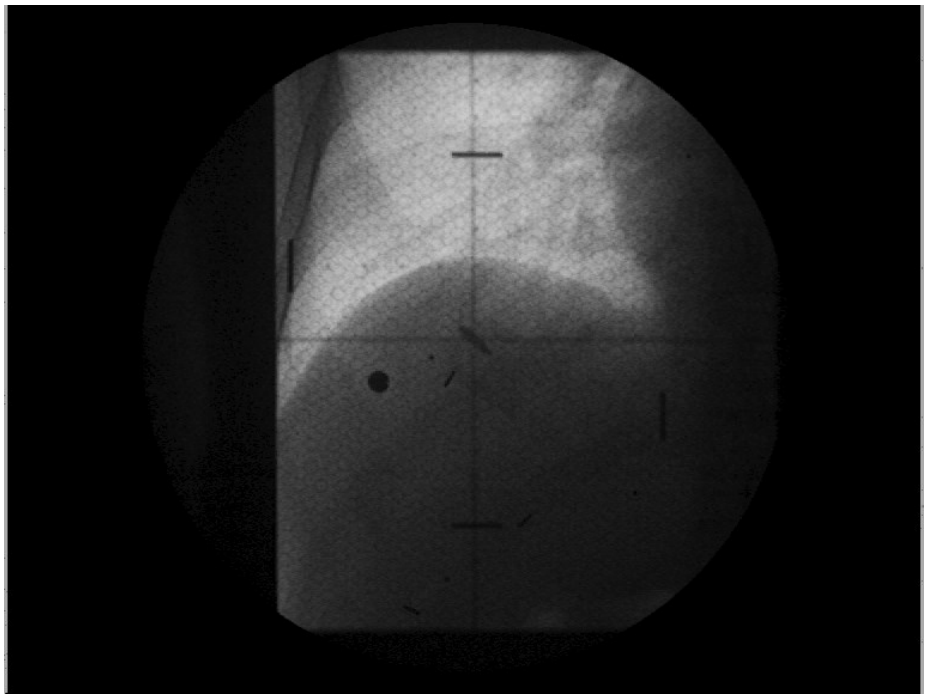
Observation of Motion

- 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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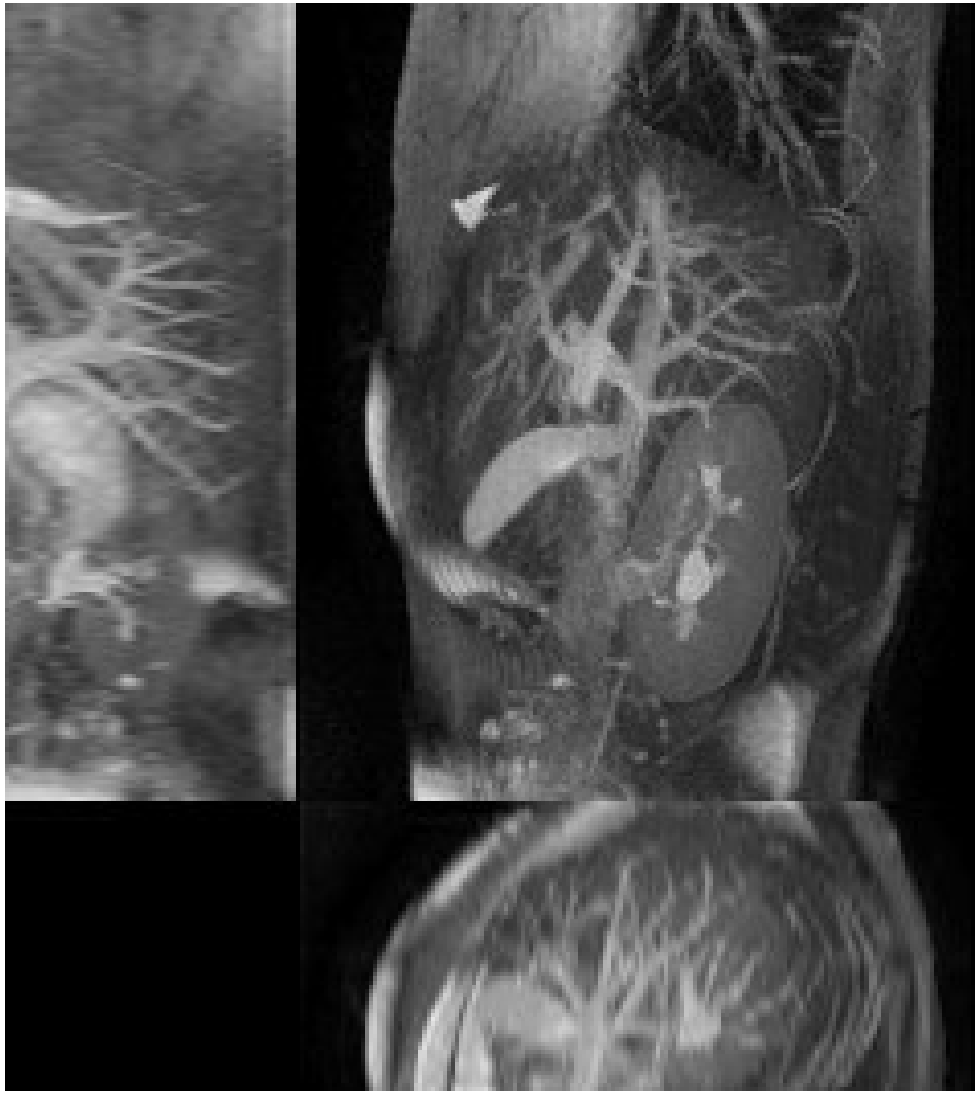
4D MRI Data of Liver



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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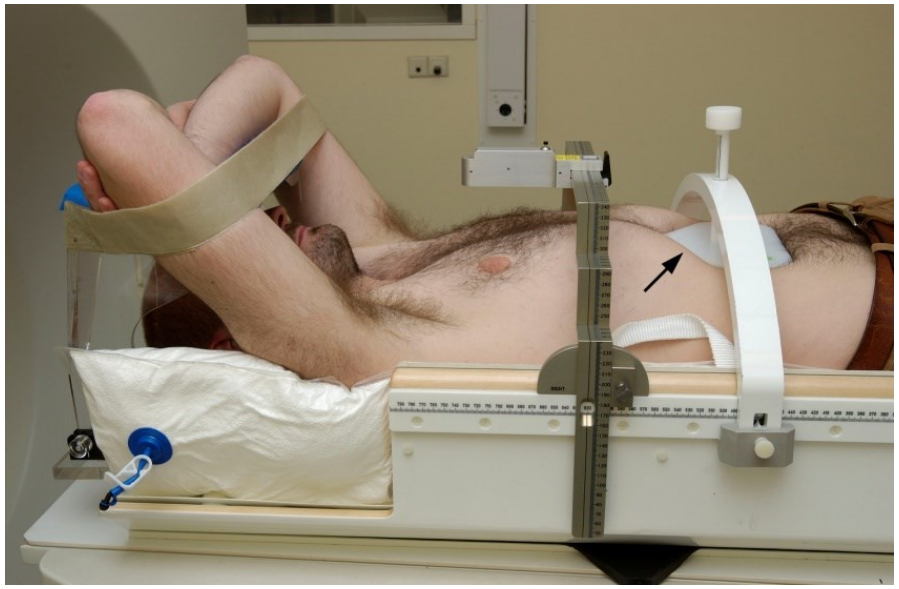
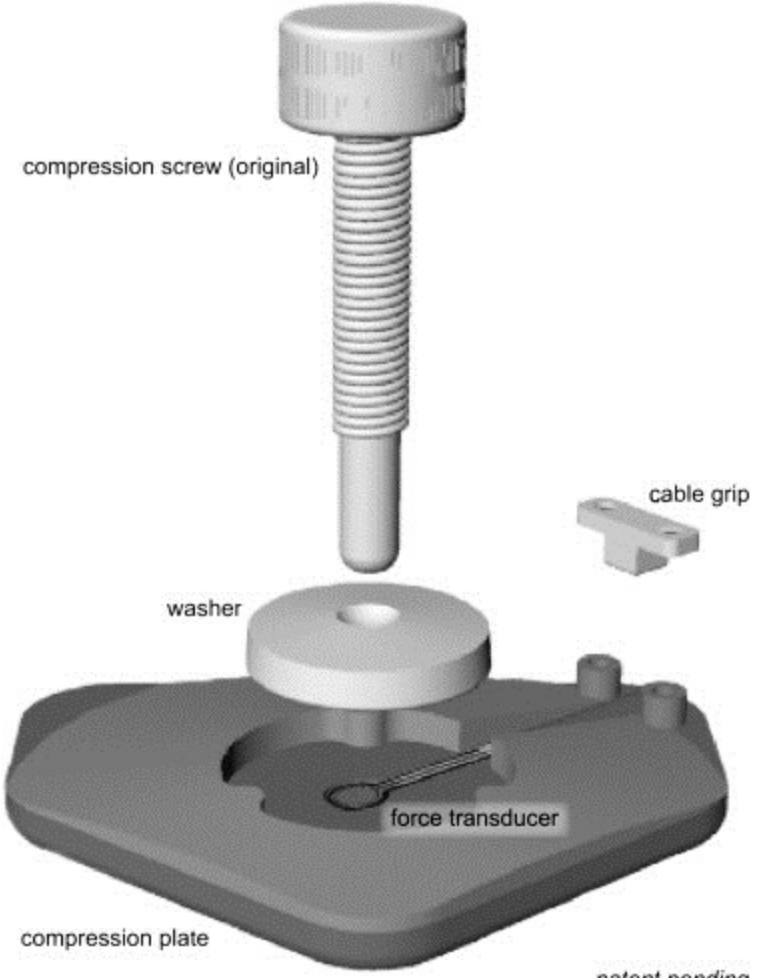
W. Wunderink, A. Méndez Romero et al.

Abdominal Compression





patent pending

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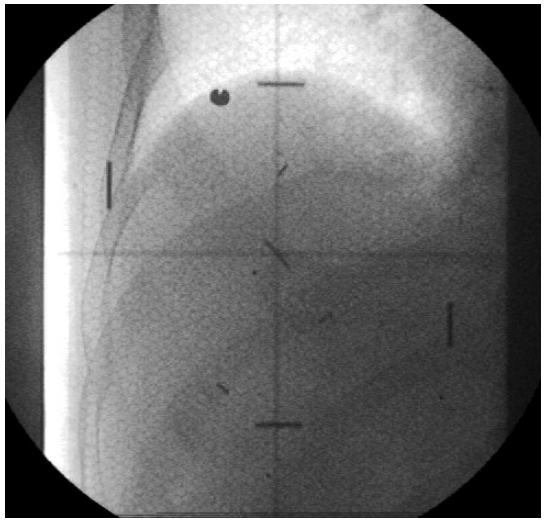
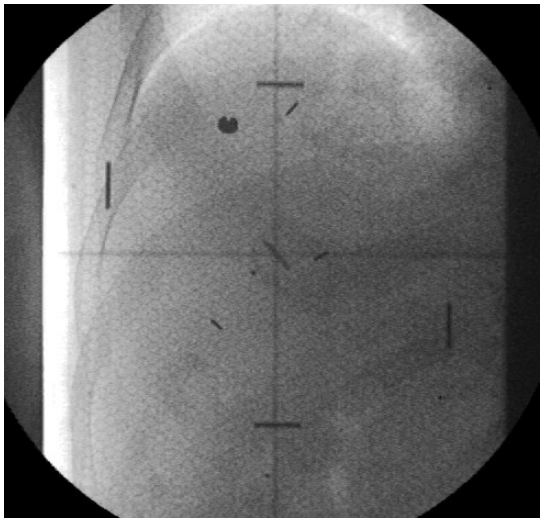
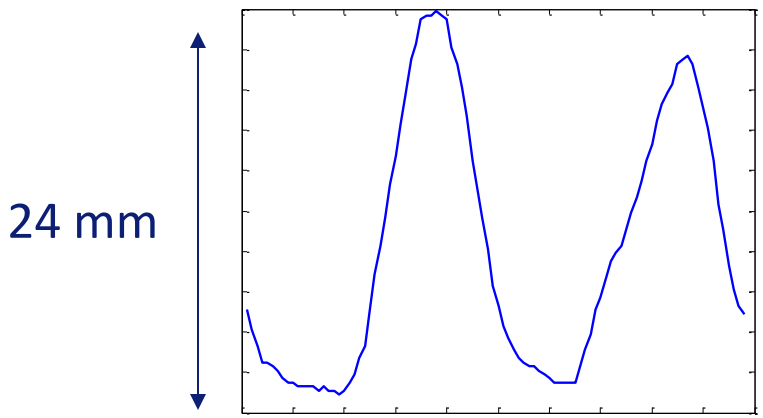
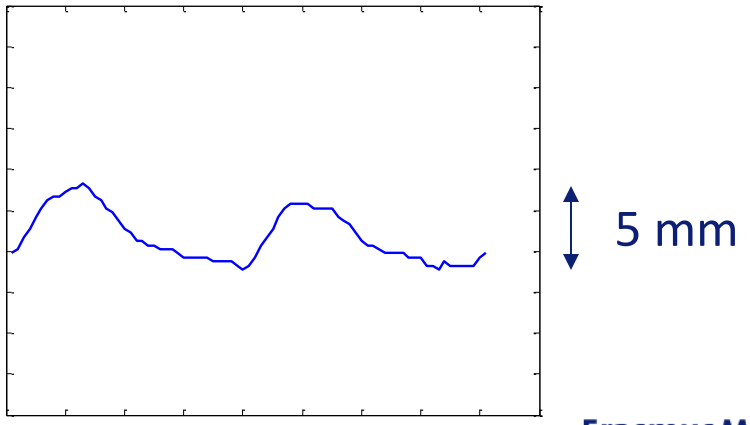
W. Wunderink, A. Méndez Romero et al.

Fluoroscopy









no compression

with compression

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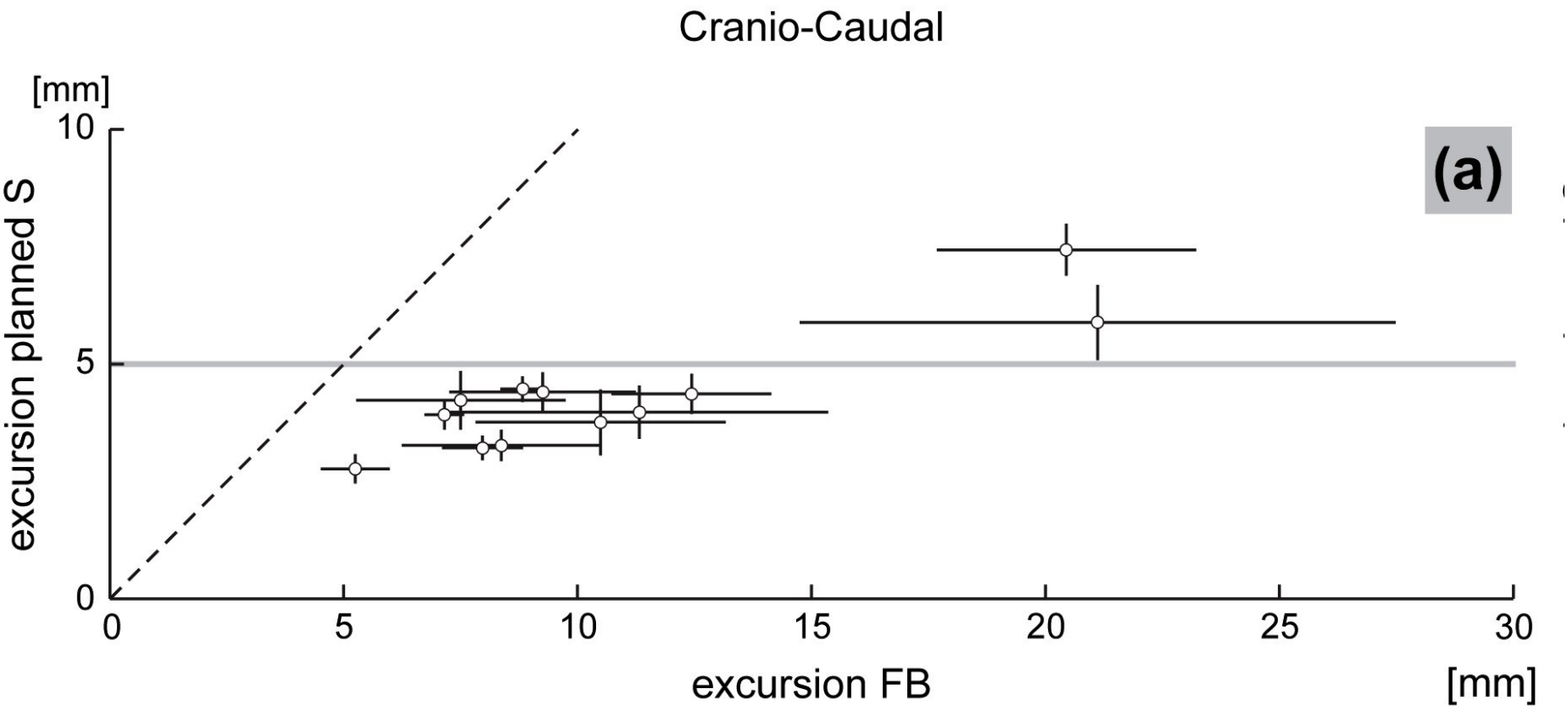
Amplitude Reduction by Abdominal Compression



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

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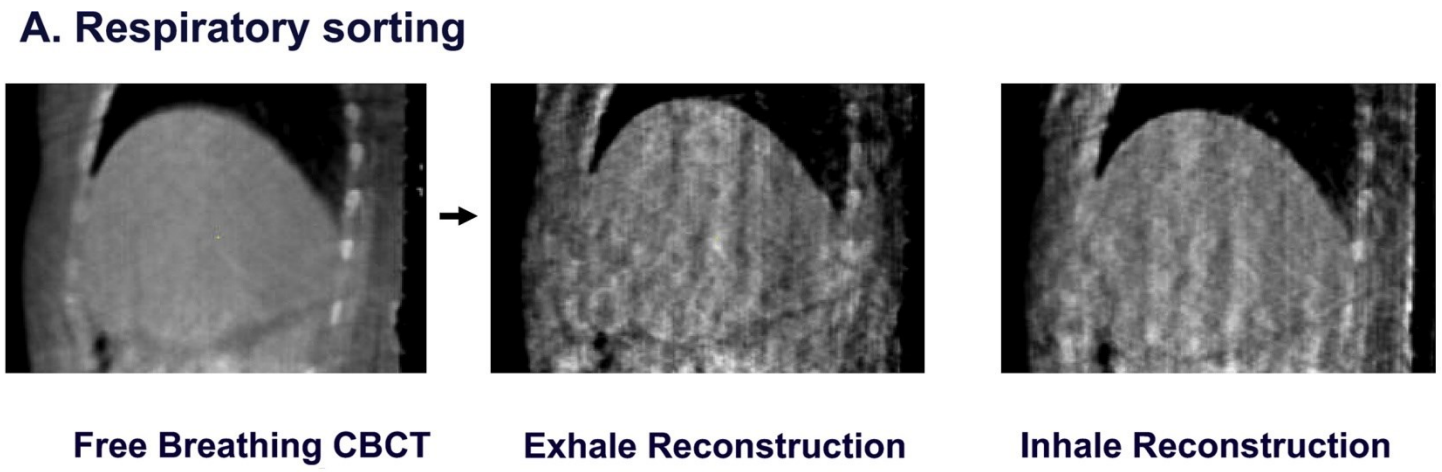
Inter-fraction and Intra-fraction Liver Motion



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

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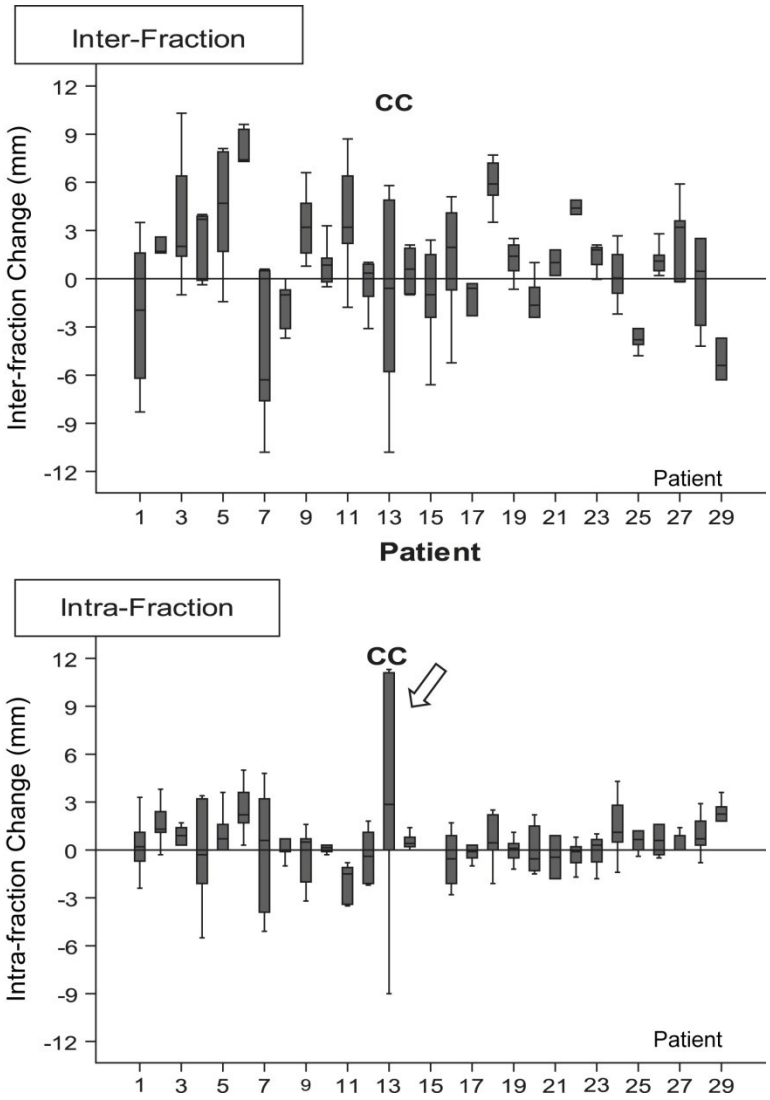
Inter-fraction and Intra-fraction Liver Position Change



- 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

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

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

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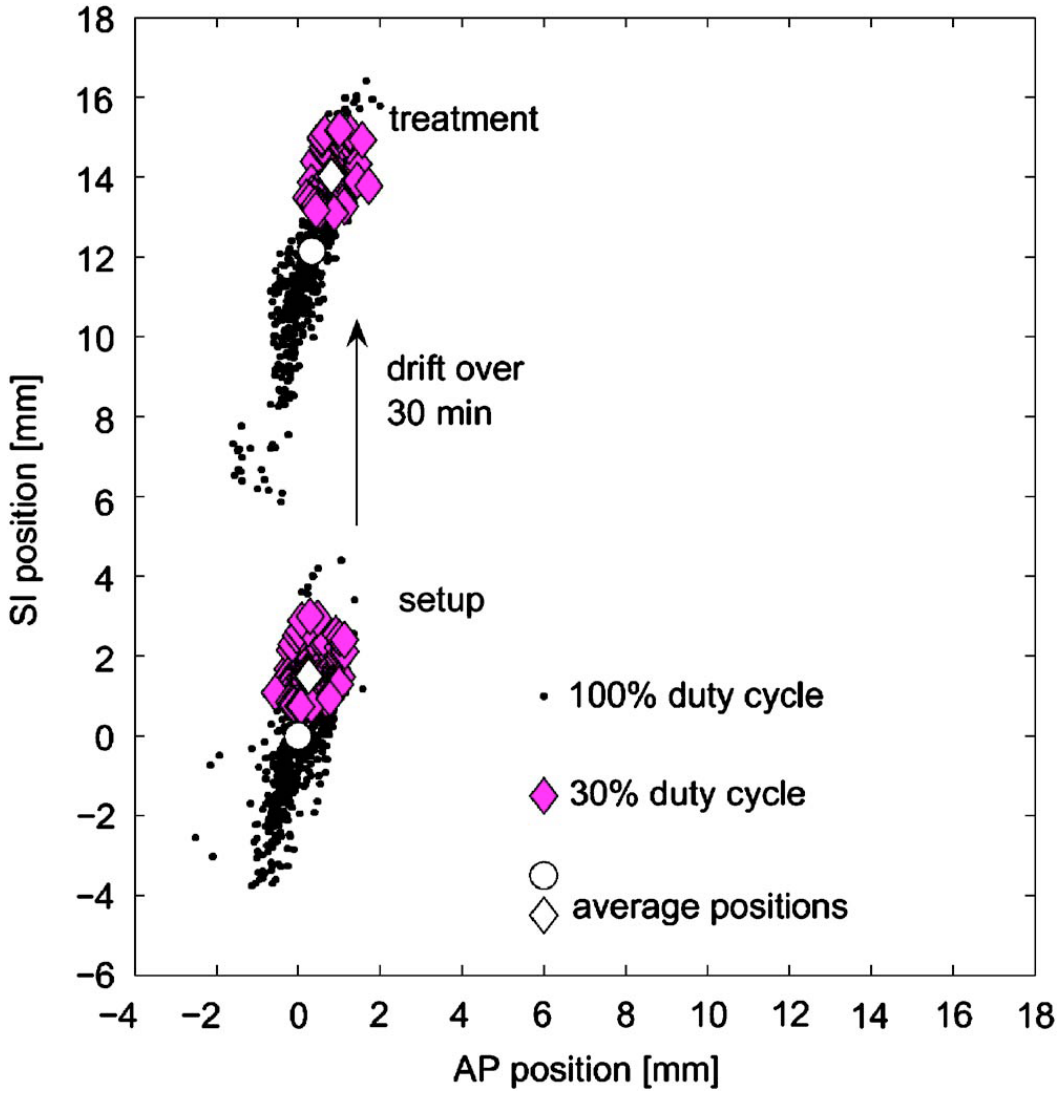
Drift During a Hypothetical 30-min Treatment



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

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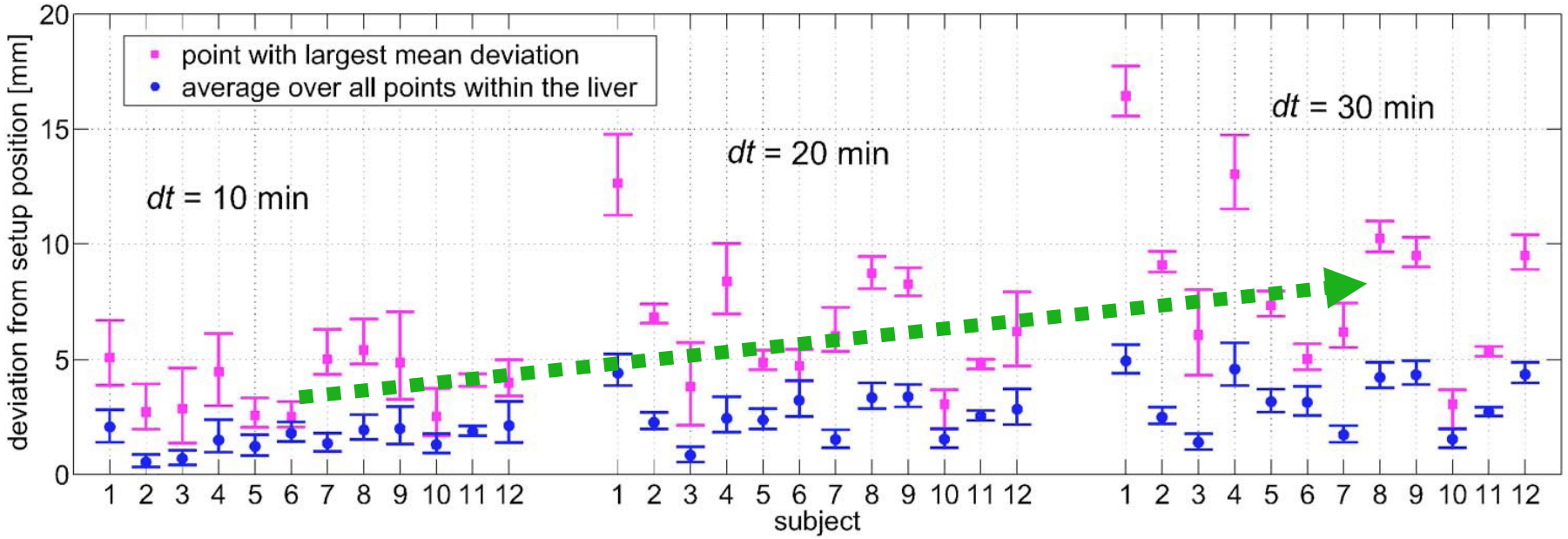
Deviation as a Function of Treatment Time



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

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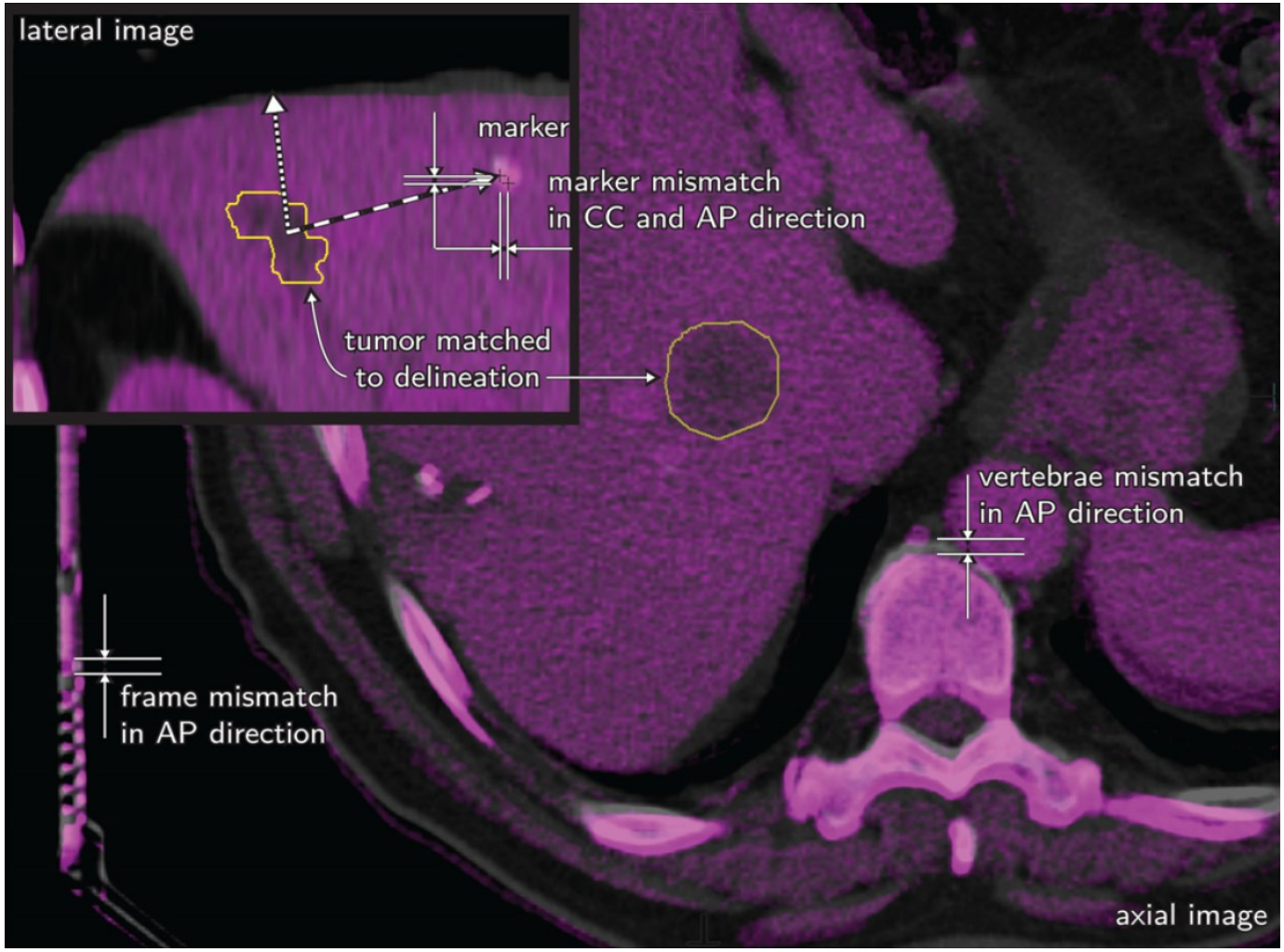
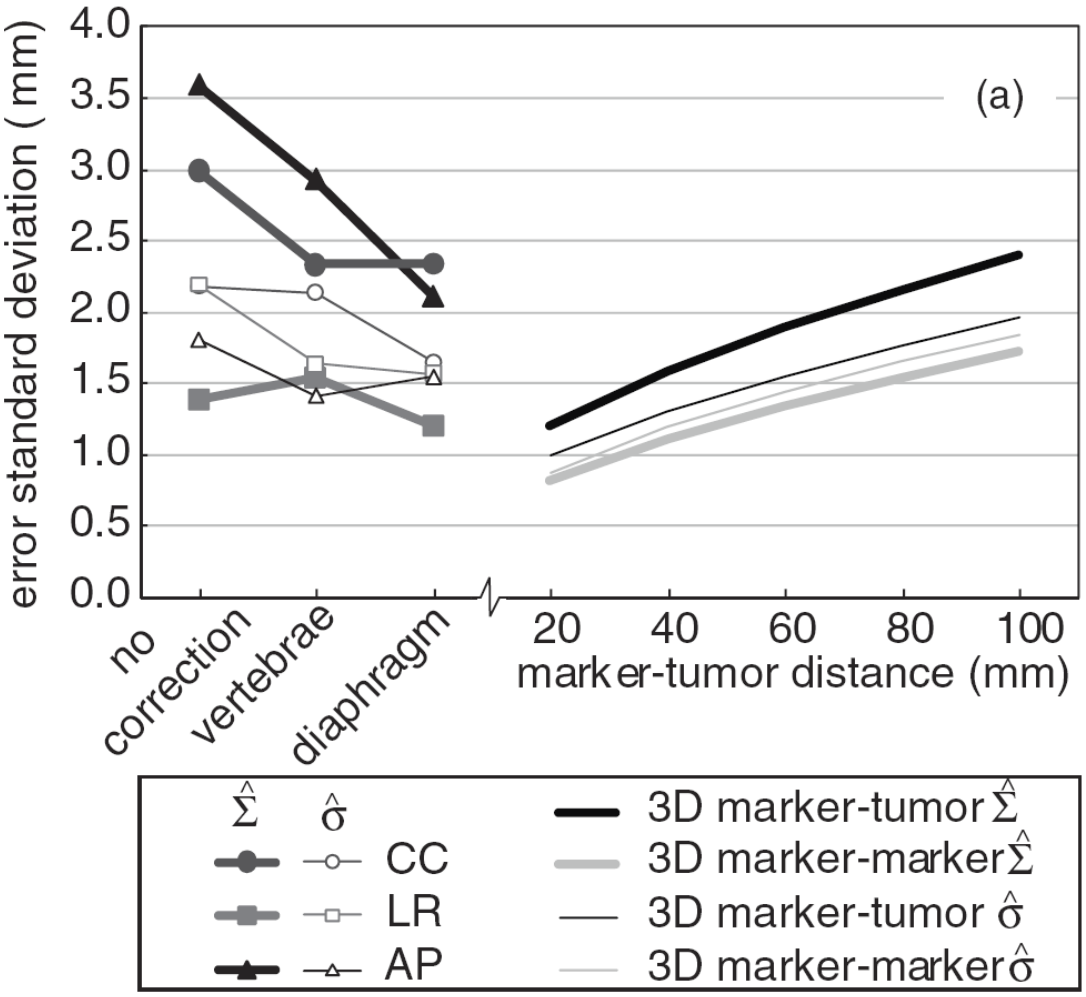
Liver Tumor Surrogates

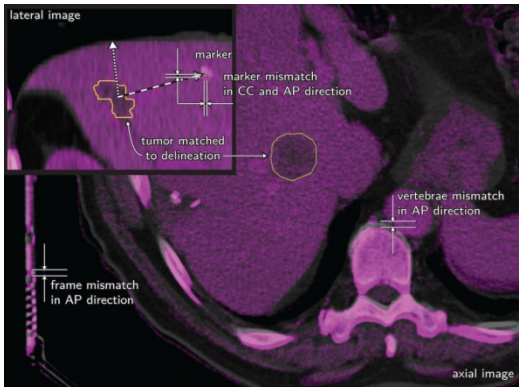


Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

Erasmus MC

Liver Tumor Surrogates

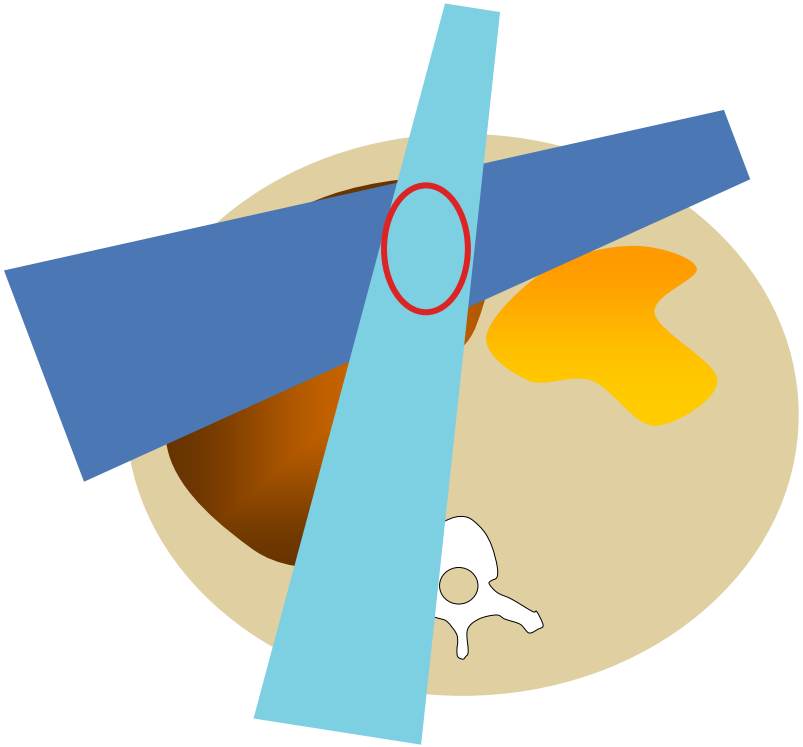




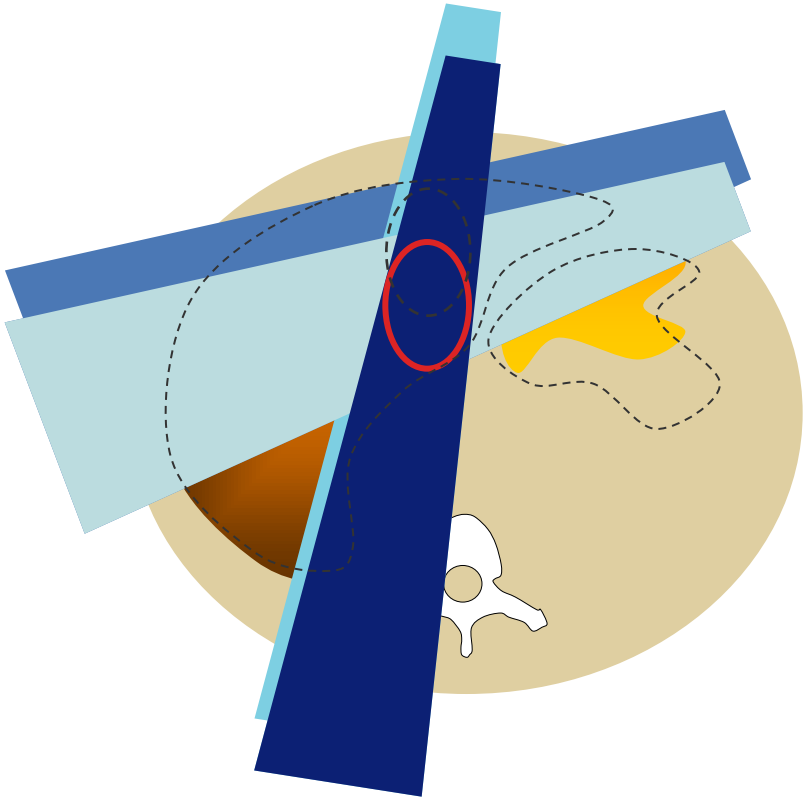
Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

Erasmus MC

Online Adaptive RT for Liver?



Planning

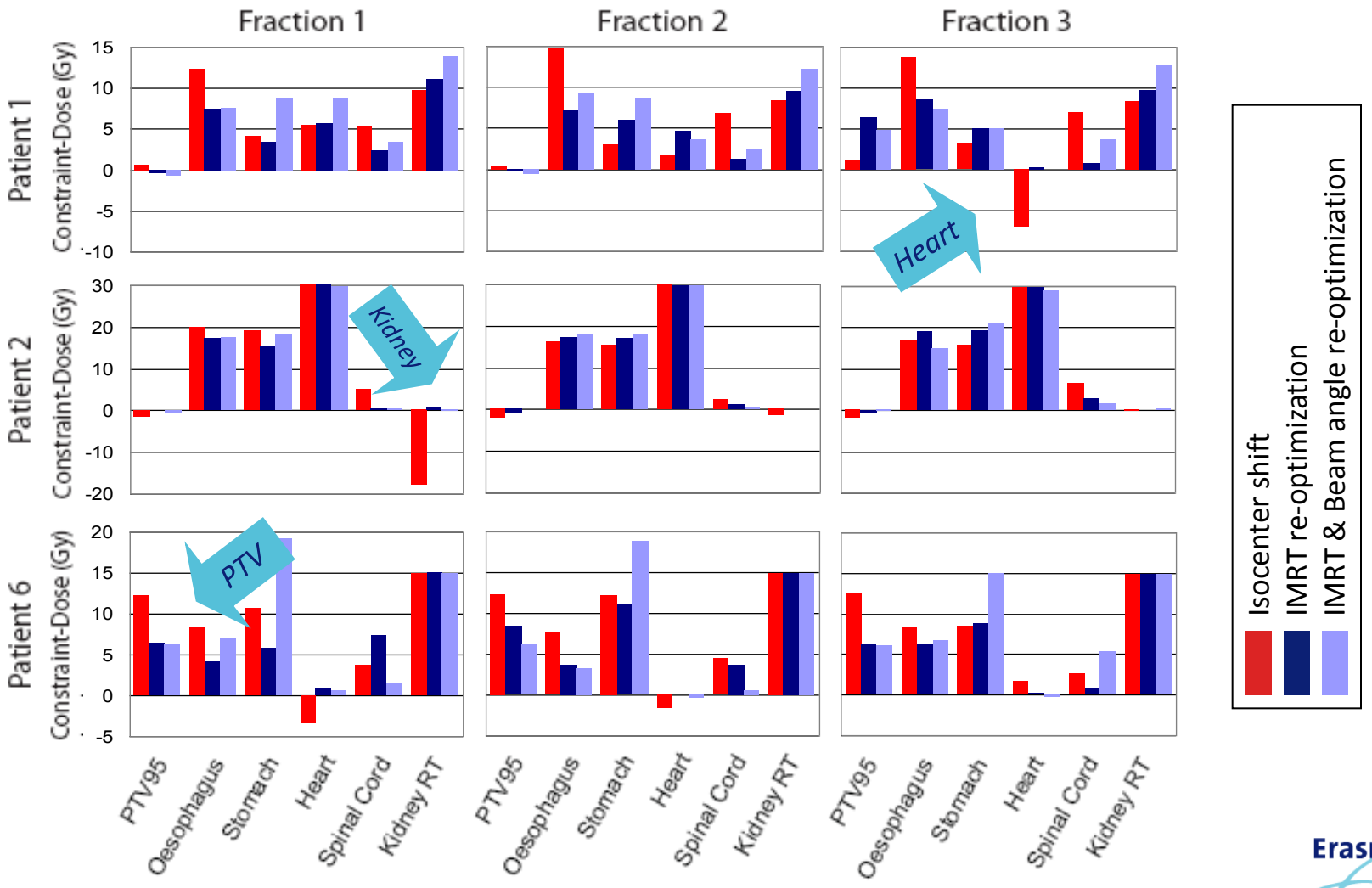


Treatment

Suzanne Leinders IJROBP 2014; slides courtesy of Seppenwoolde

Erasmus MC

Online Adaptive RT for Liver



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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

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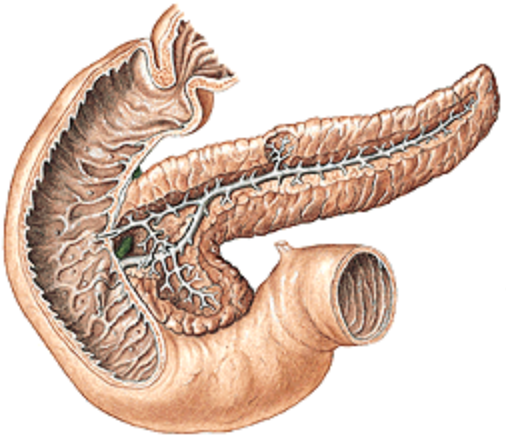

PANCREAS

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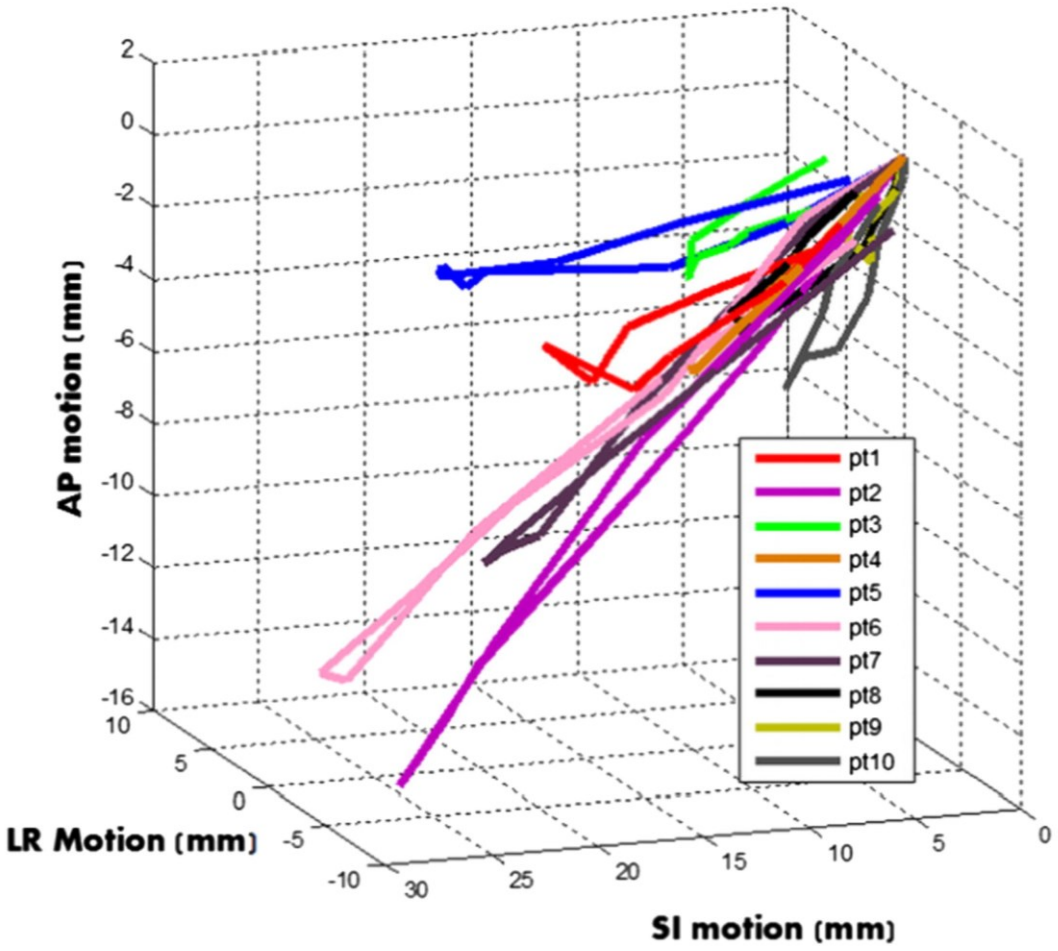
Pancreas Motion Assessed With 4D CT Scanning



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

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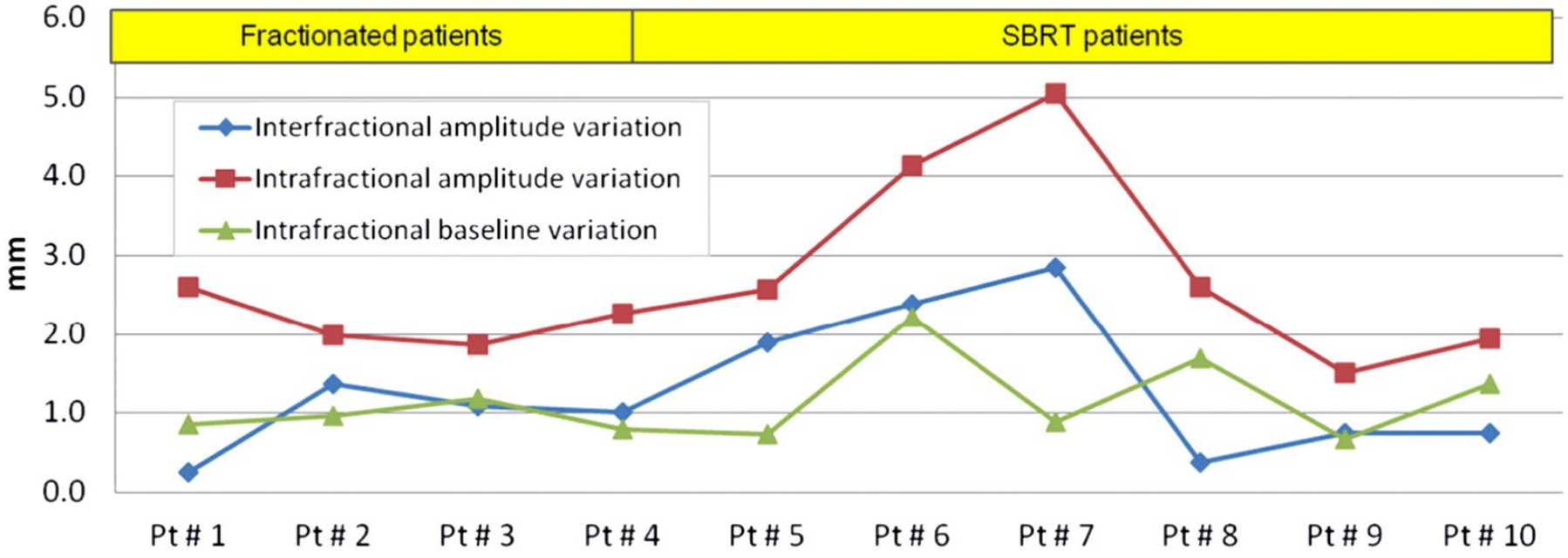
4D CT Cannot Adequately Represent Daily Intrafractional Motion



- 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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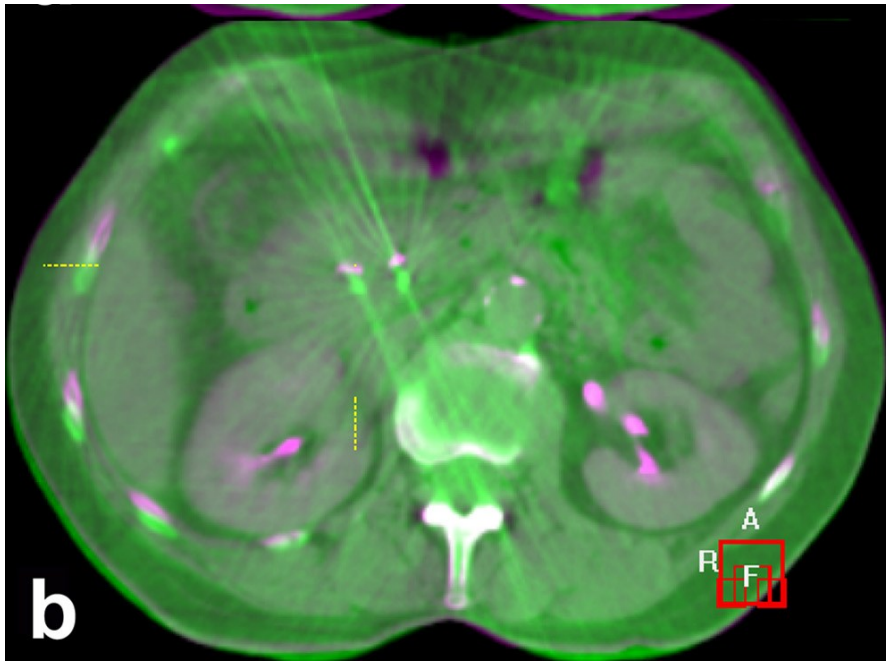
Inter-fraction Variation: Implanted Markers and CBCTs

- 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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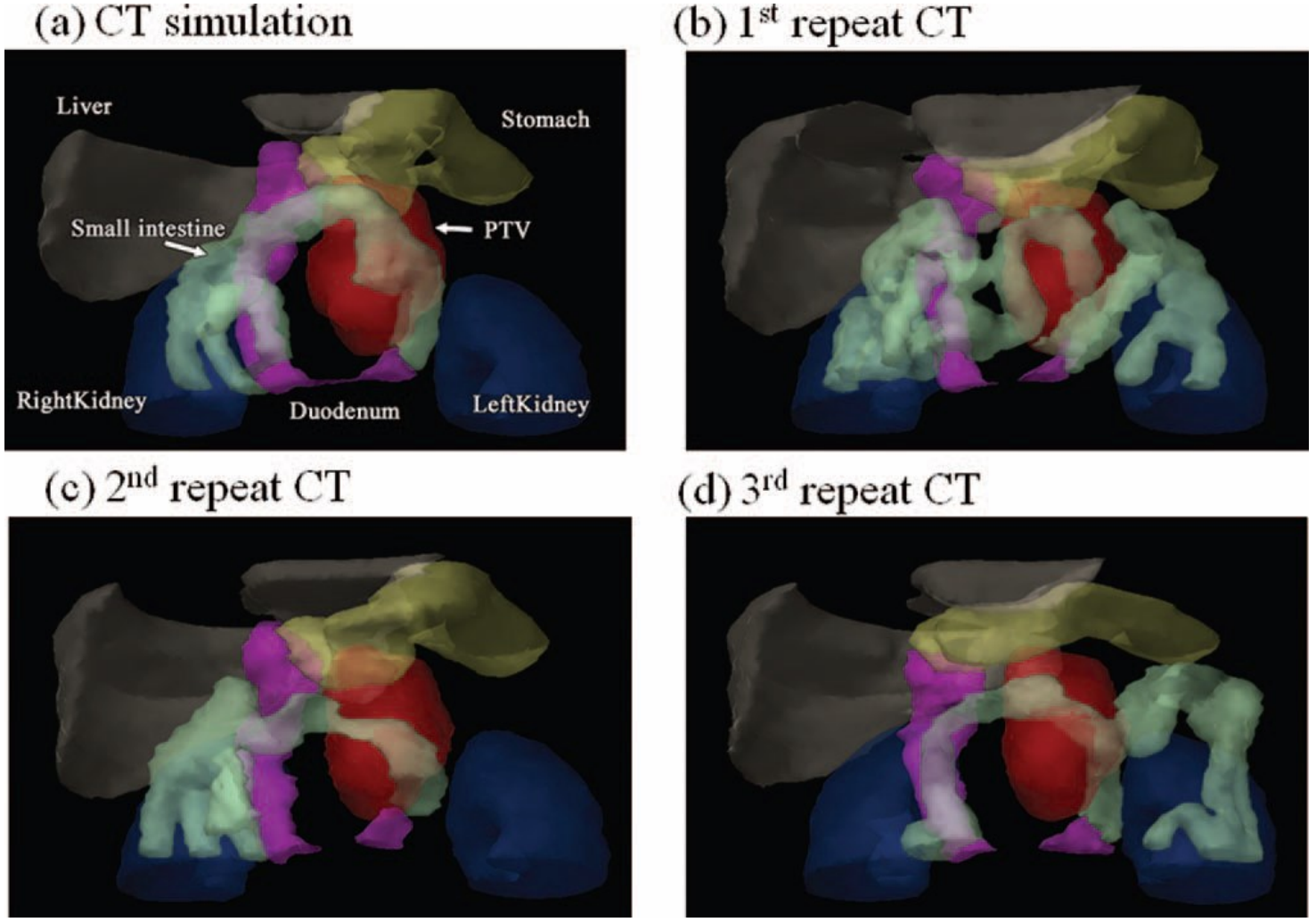
Interfractional Dose Variations in Organs at Risk



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

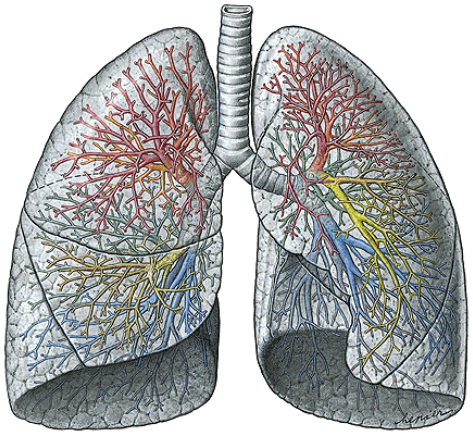
Erasmus MC

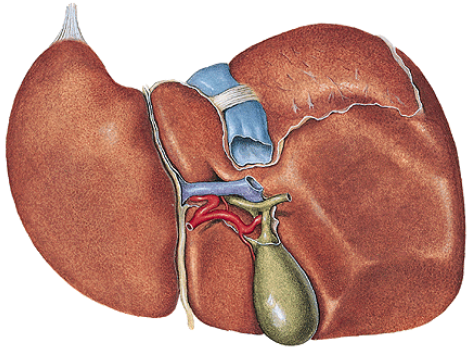
Discussion: Clinical Relevance

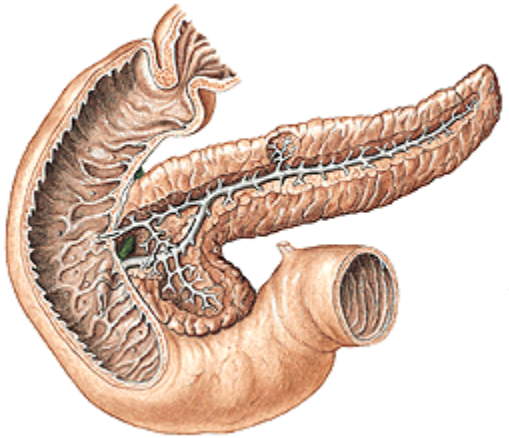
- **Should we measure intra-fraction motion?**
  - Yes, at planning in order to individualize the safety margin**??**
  - And if necessary to reduce the motion amplitude with compression
- **Should we correct for intra-fraction motion?**
  - The penumbra is more sharp in abdomen than in lung
  - Amplitude 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

Erasmus MC

Summary







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?

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?

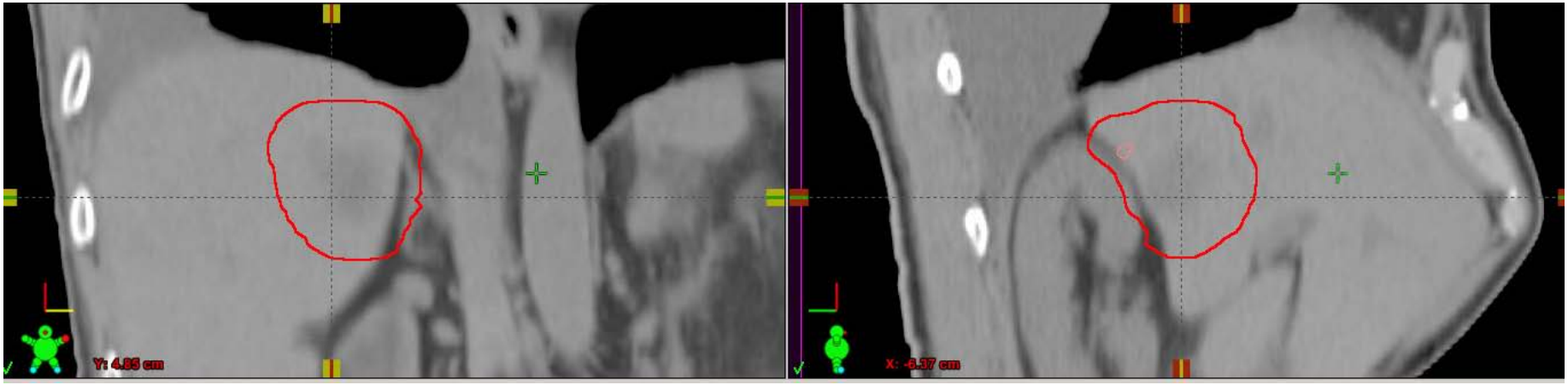
What do we have available?

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

→ Overestimates Liver volume, underestimated dose to the liver

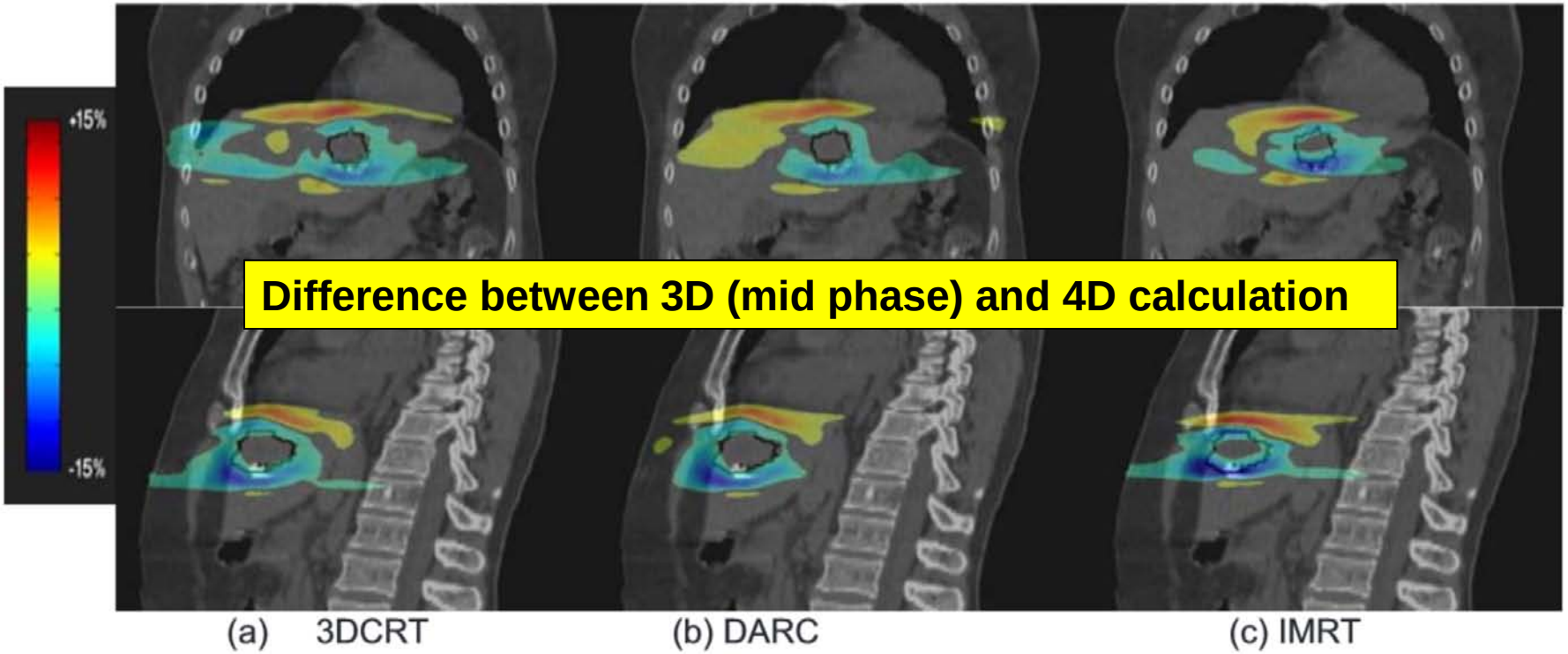
On which CT should we calculate dose?

Tumors in the middle of the liver?



On which CT should we calculate dose?

Tumors in the middle of the liver?

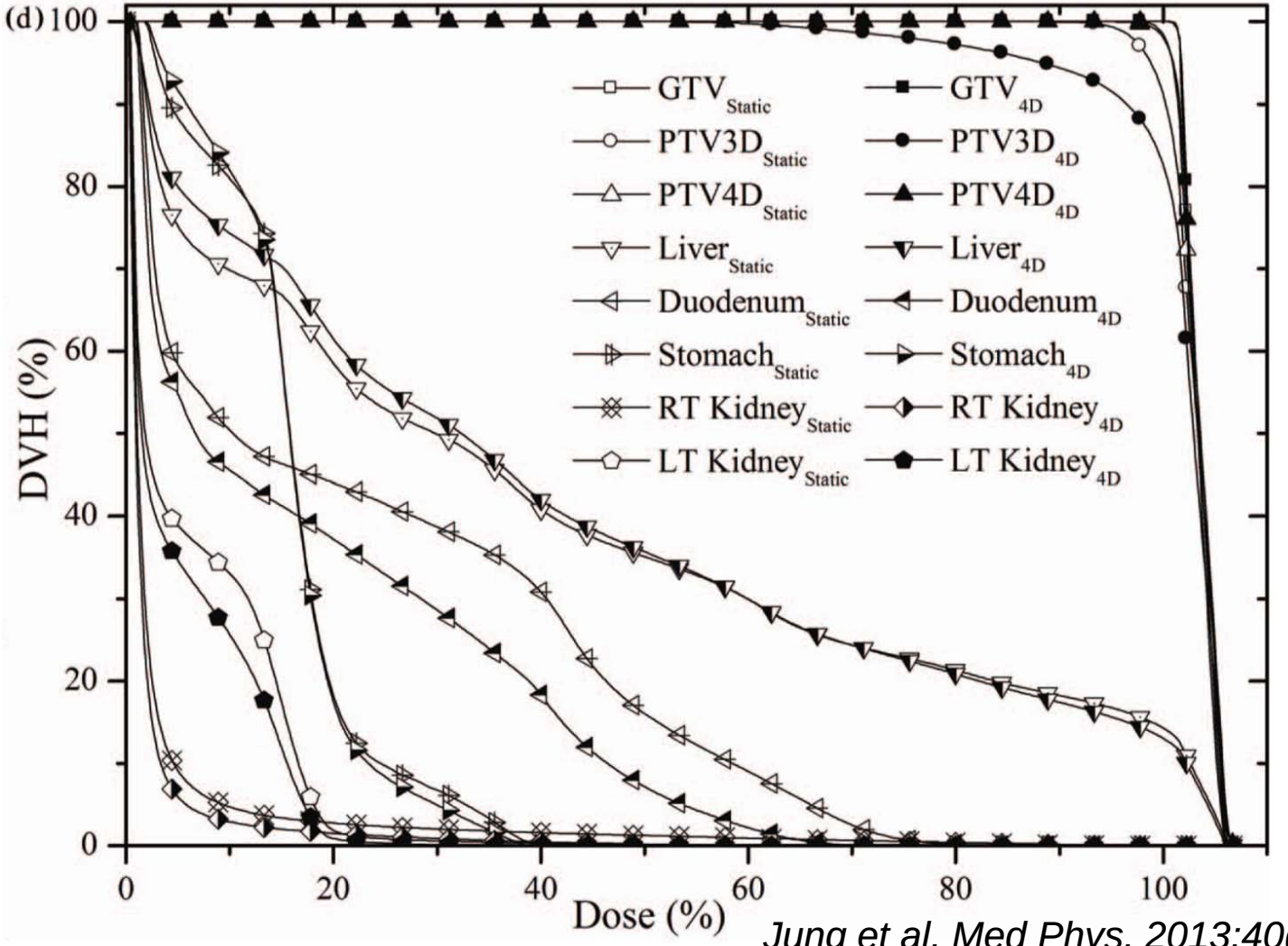


Wu et al, Med Phys,2008;35(4)

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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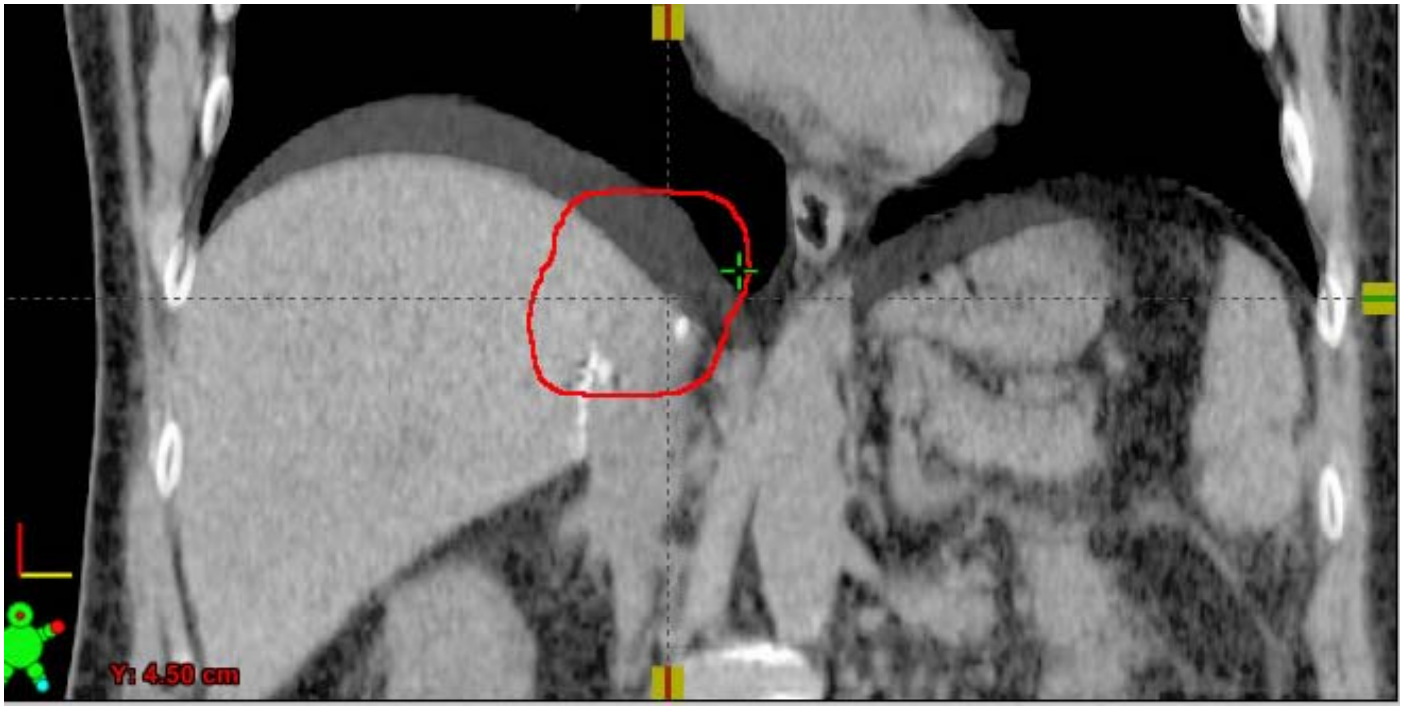
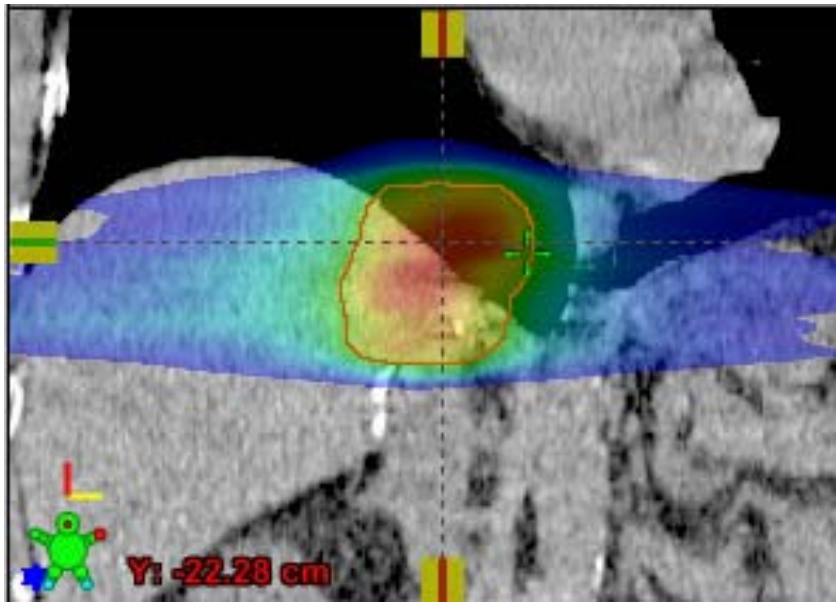
On which CT should we calculate dose?

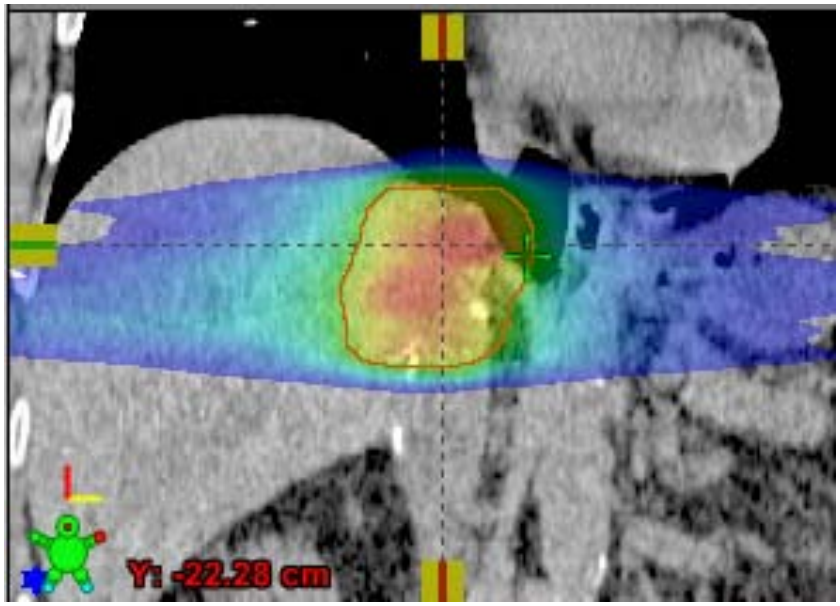
Tumors on the boundary liver - lung?



On which CT should we calculate dose?

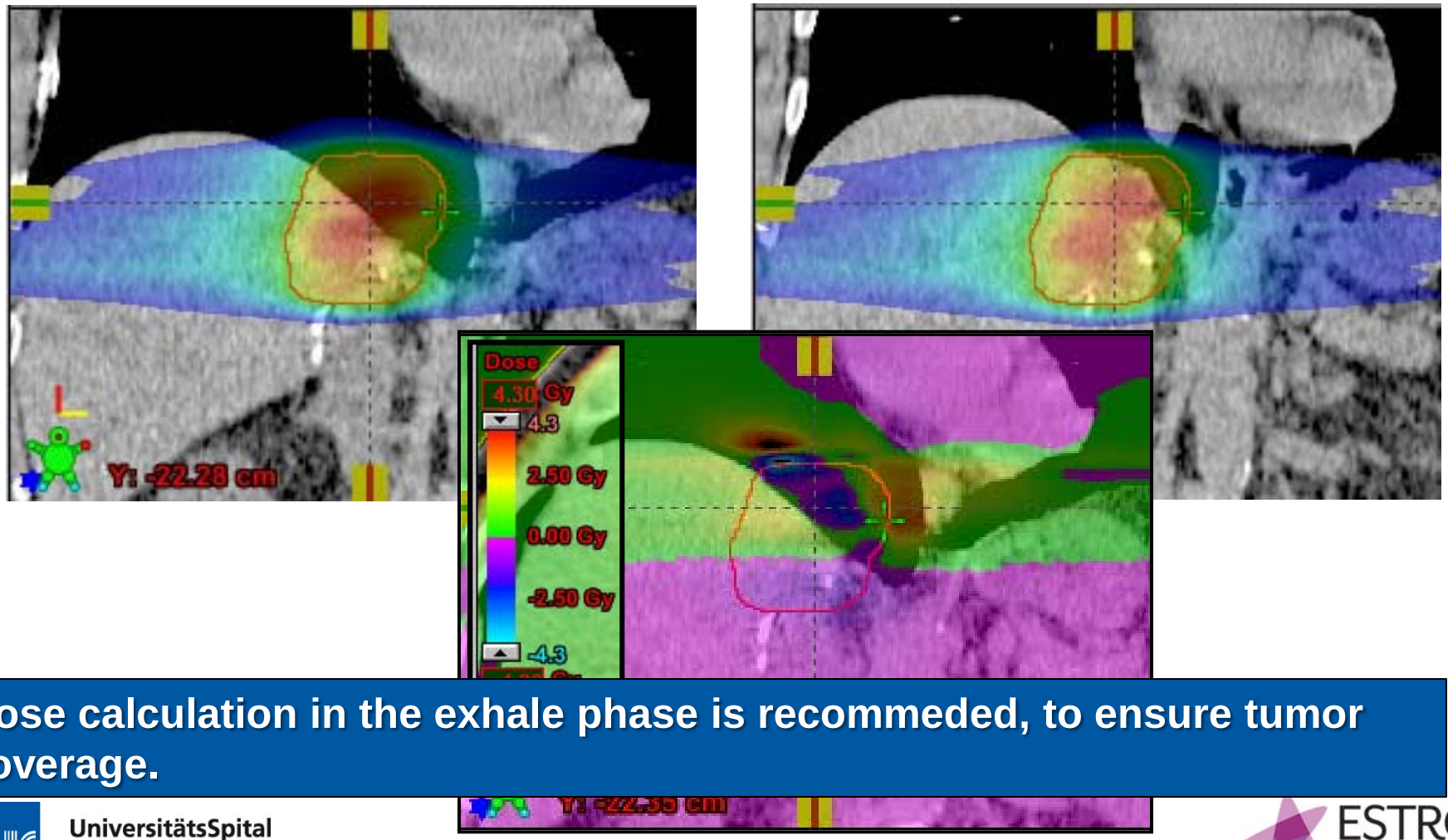
Tumors on the boundary liver - lung?





On which CT should we calculate dose?

Tumors on the boundary liver - lung?



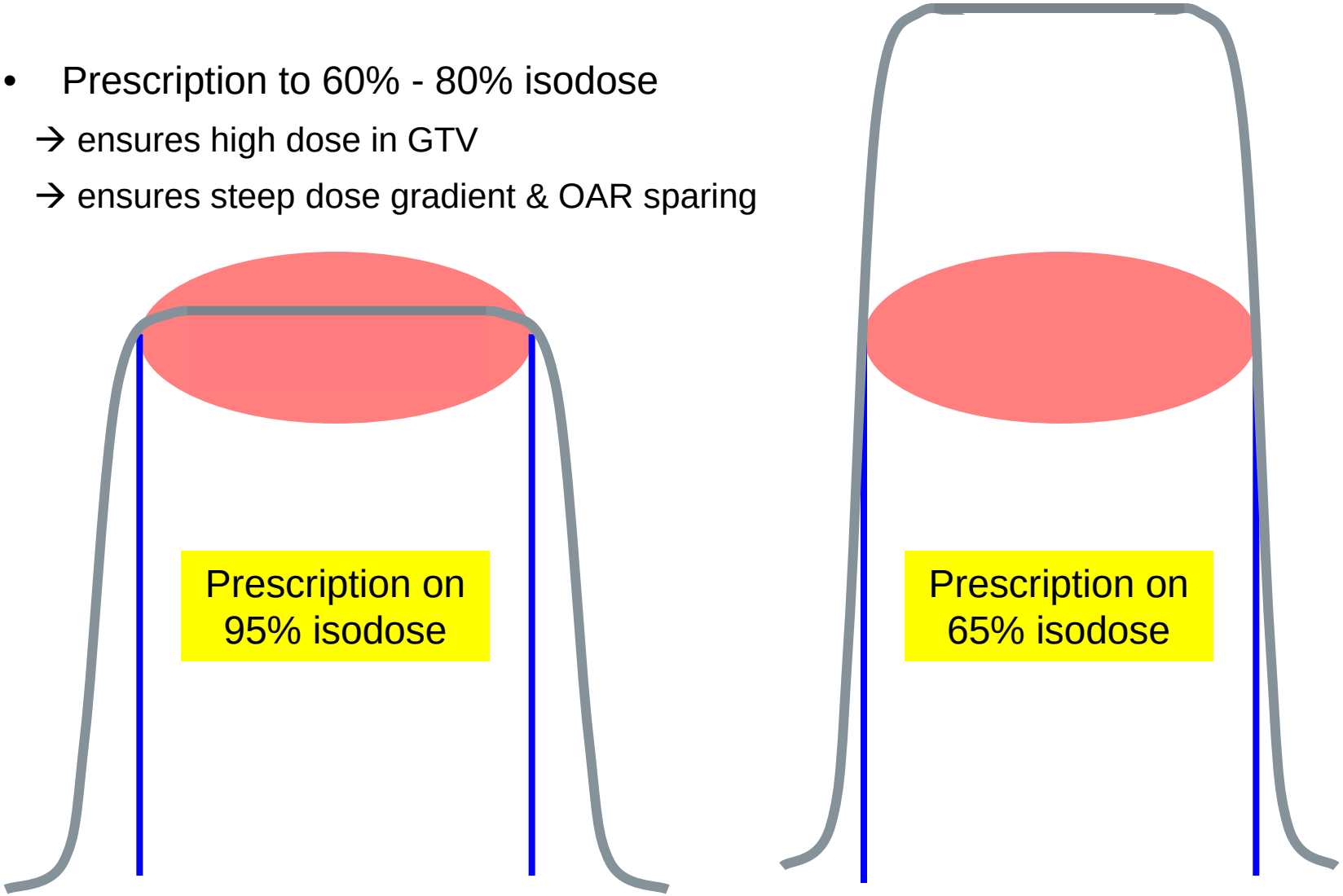
Dose calculation in the exhale phase is recommeded, to ensure tumor coverage.

Treatment planning for liver cancer

- Prescription to 60% - 80% isodose

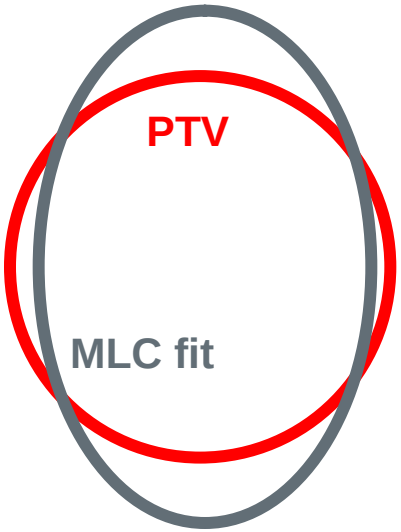
→ ensures high dose in GTV

→ ensures steep dose gradient & OAR sparing



3D conformal treatment planning

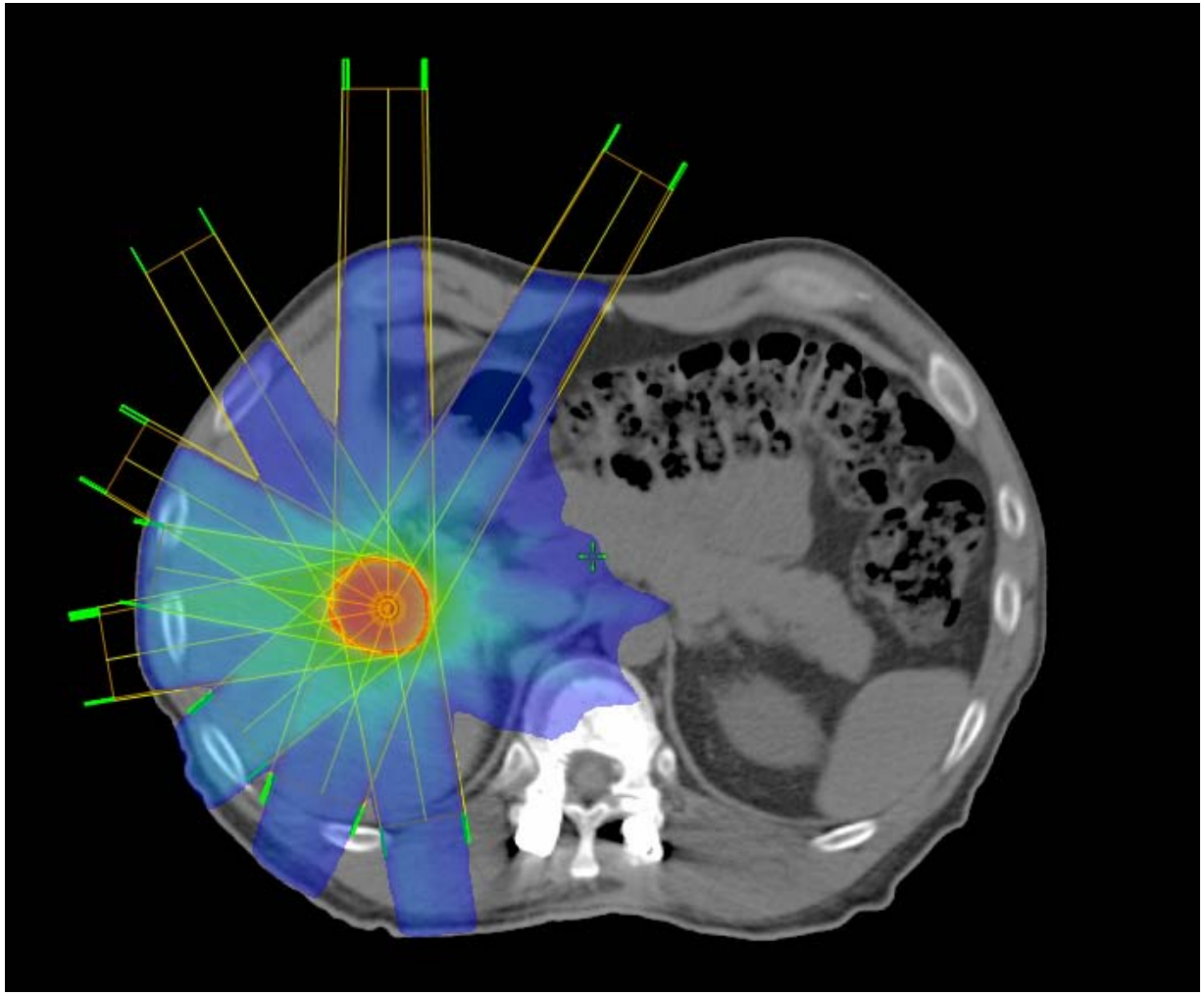
- Isocenter placed in target
- 7-11 fields spread as much as possible
- Avoid directly opposing fields
- Avoid entering a OAR (spinal cod, duodenum, bowel, kidneys).
- Fit MLC to help structure

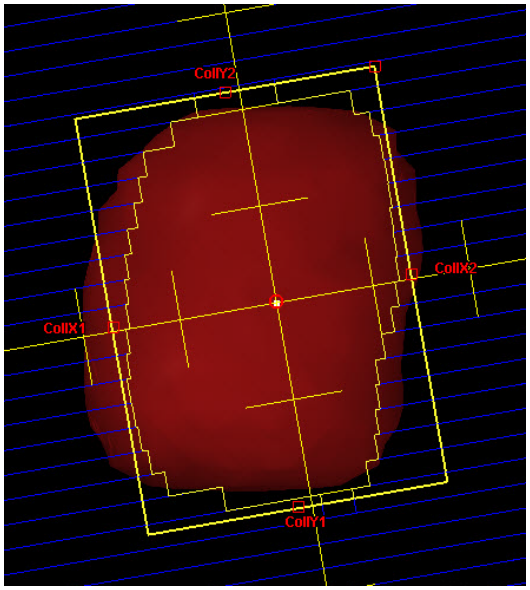


• MLC fit is 2mm longer (sup-inf) and 3 mm tighter (lat and AP) than the PTV

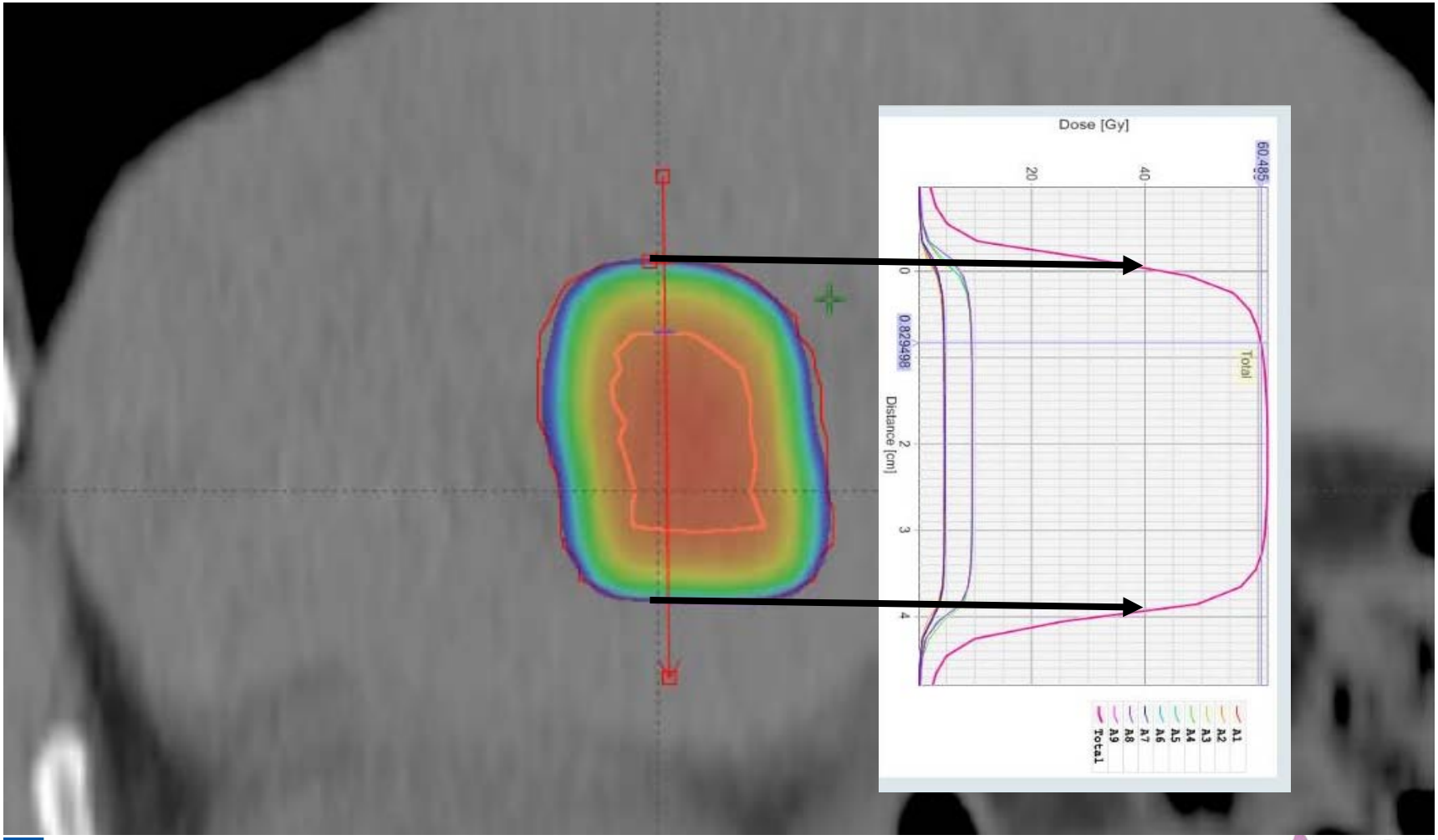
• Manual adjustements may be necessary, for example to sprare thoracic wall better

3D conformal treatment planning

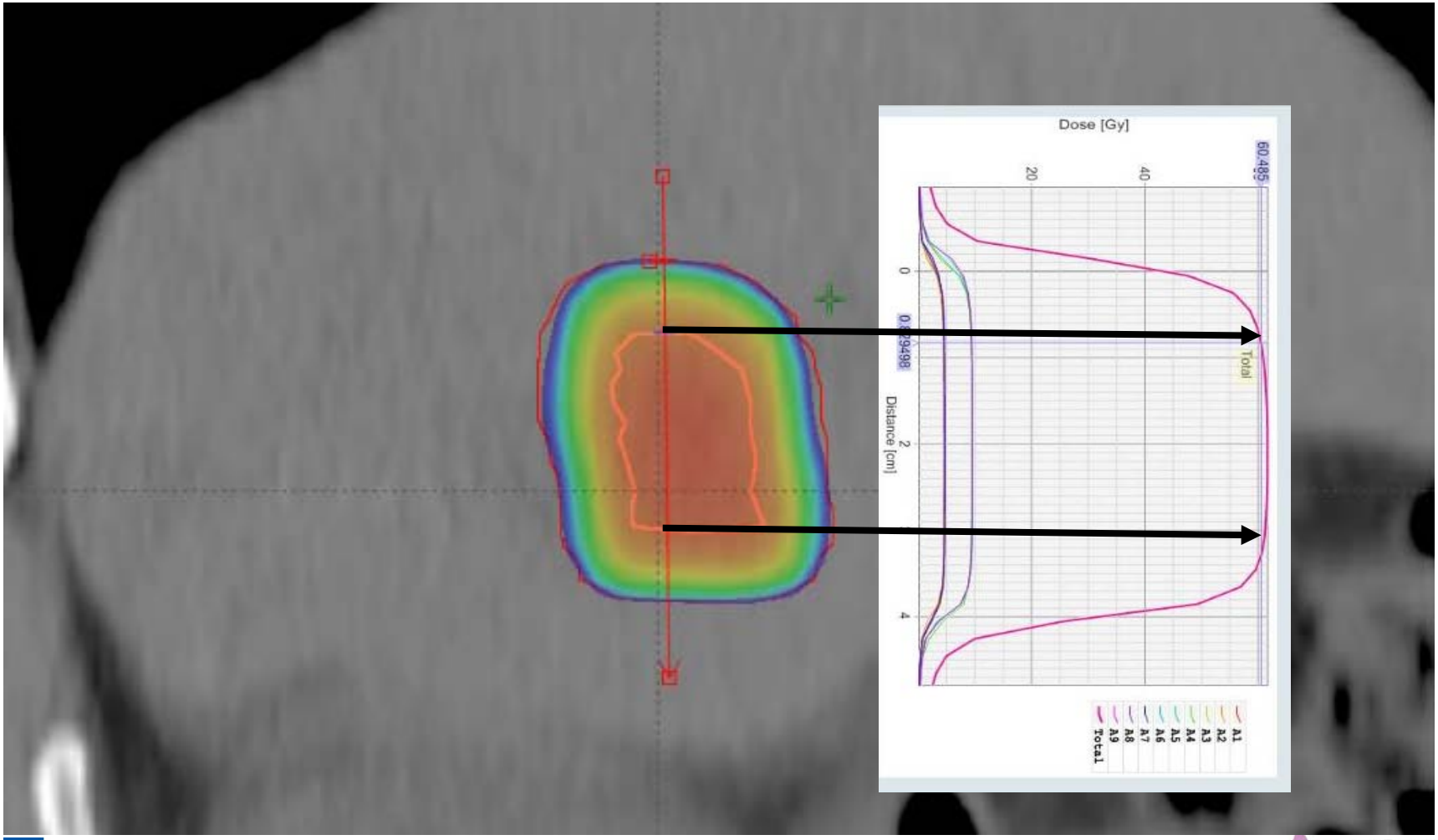




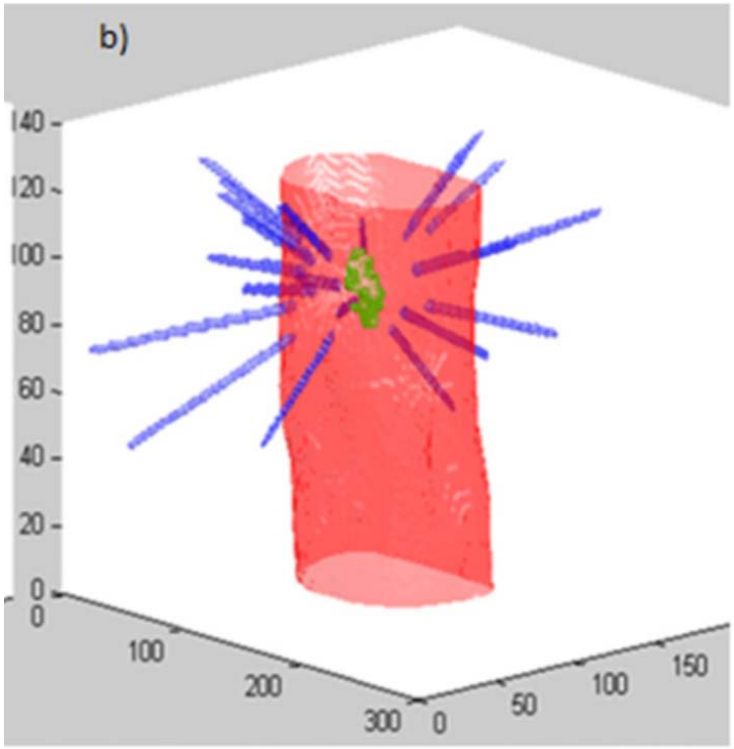
3D conformal treatment planning



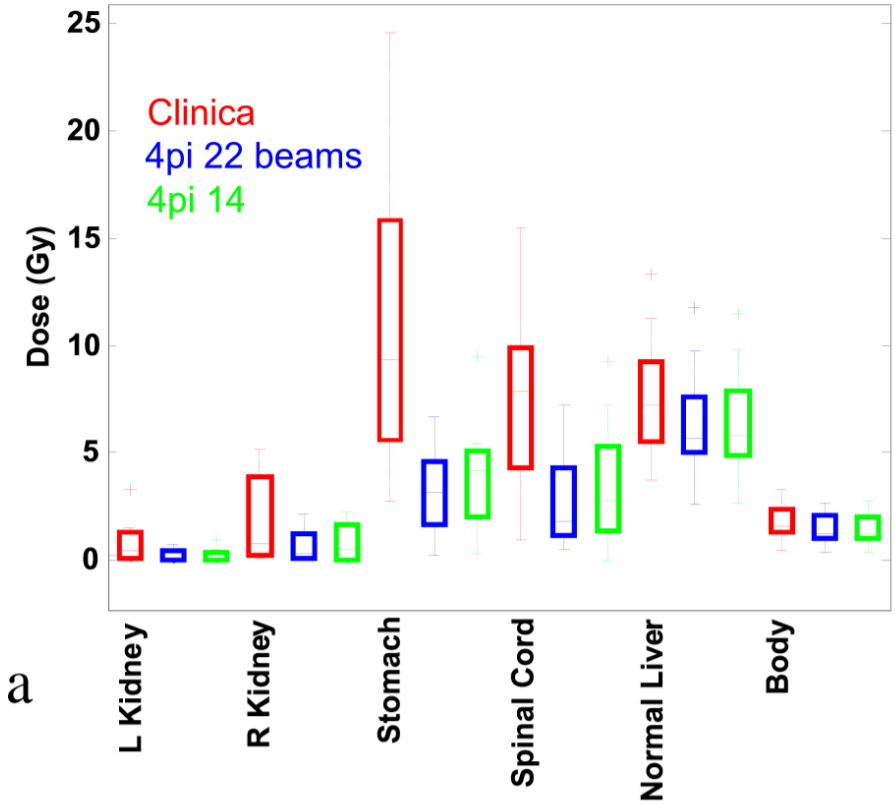
3D conformal treatment planning



Coplanar versus non-coplanar

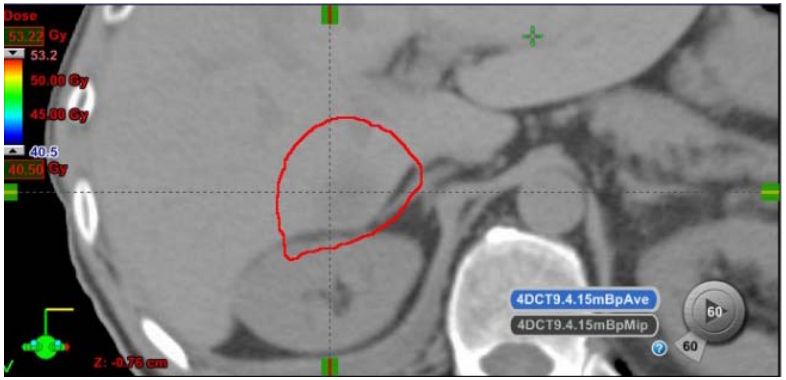


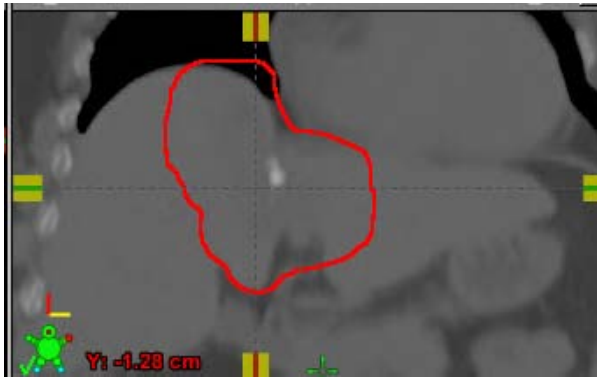
Dong et al, IJROBP 2012

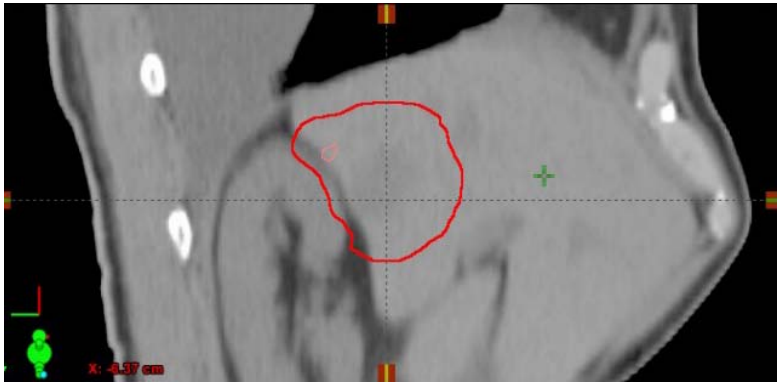


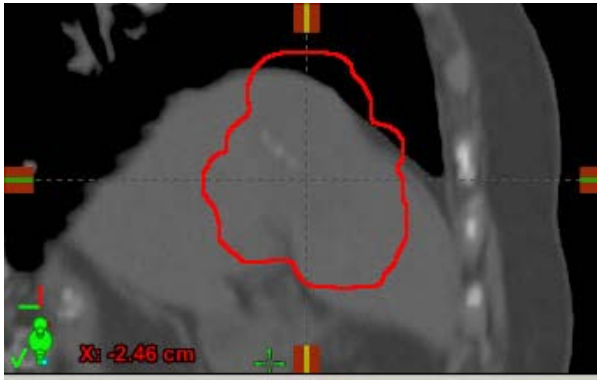
Improved sparing of organs at risk using non-coplanar fields.

Do we need VMAT?





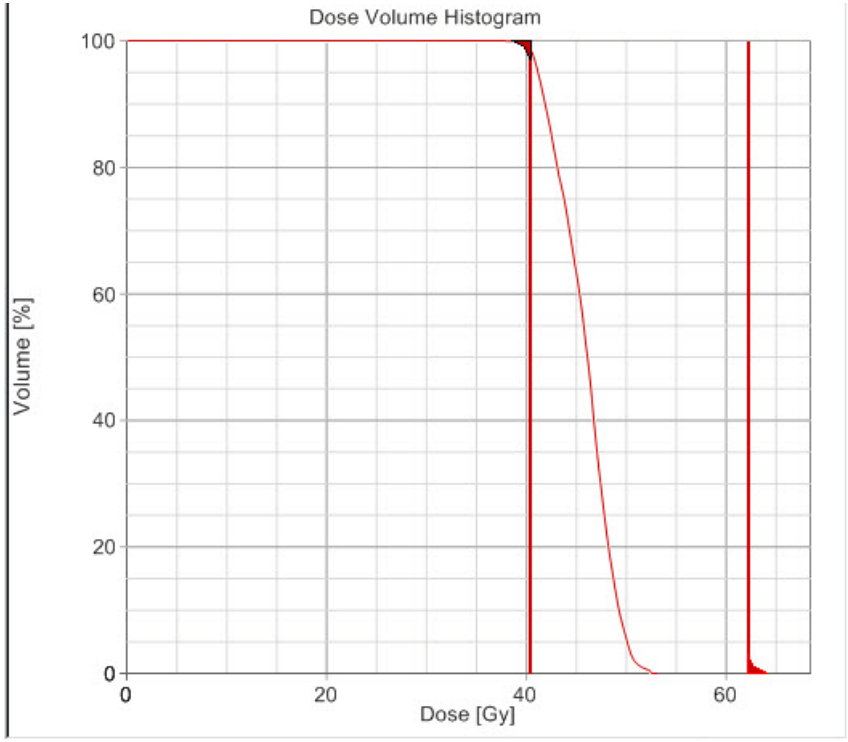


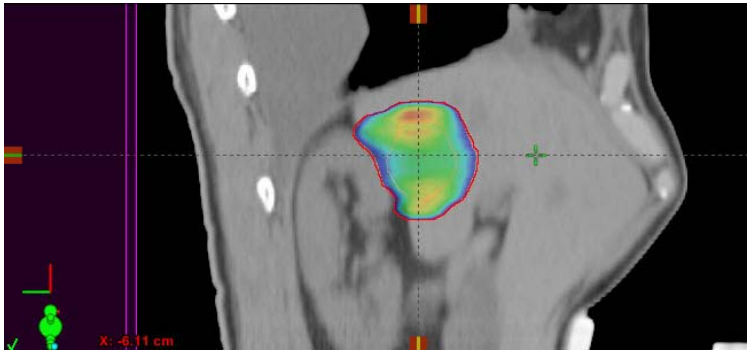


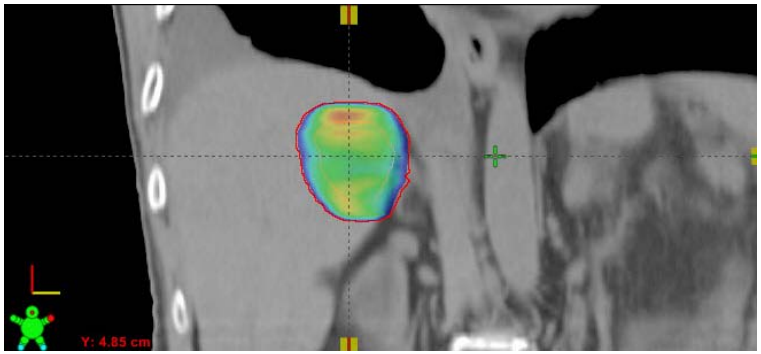
VMAT has advantages when the target volume has a compley shape or an organ at risk is close to the PTV.

VMAT optimisation

How to get the inhomogeneity?

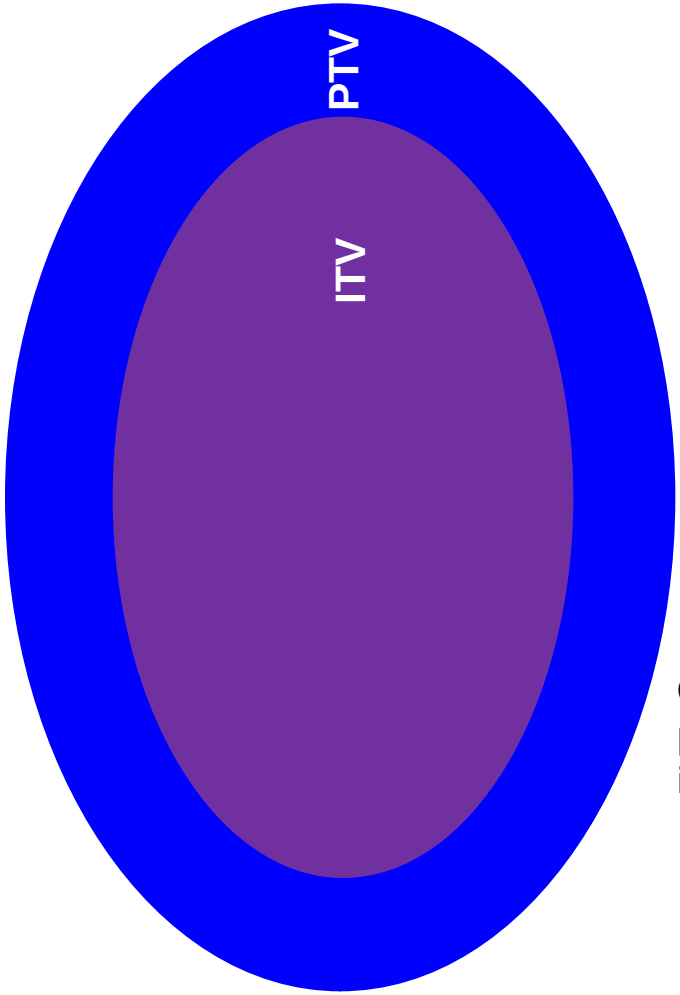






Just an upper and lower constraint lead to an inhomogeneity of about 80% and a hotspot, which is normally not located in the center.

VMAT – how to achieve the inhomogeneity



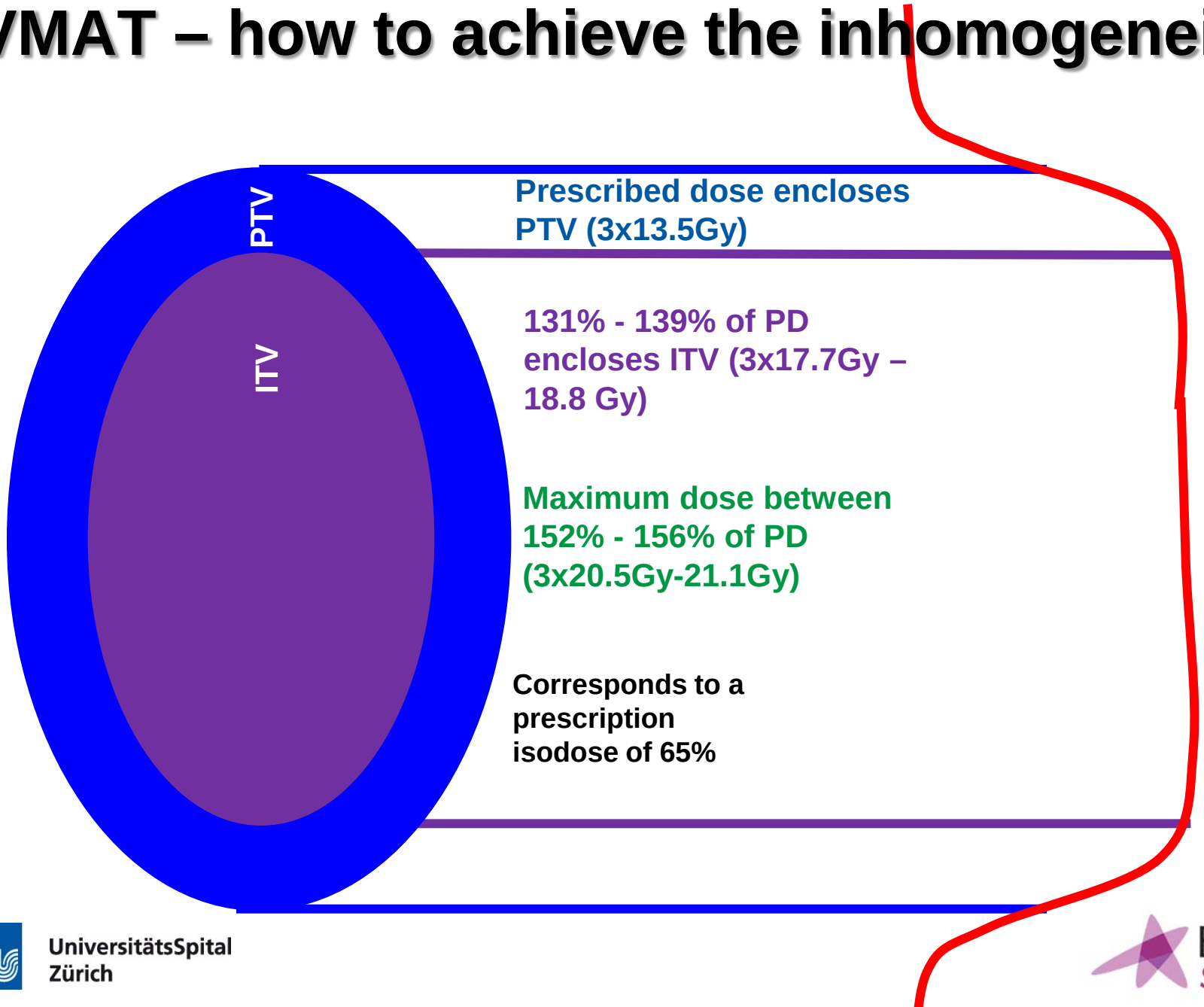
Prescribed dose encloses PTV (3x13.5Gy)

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

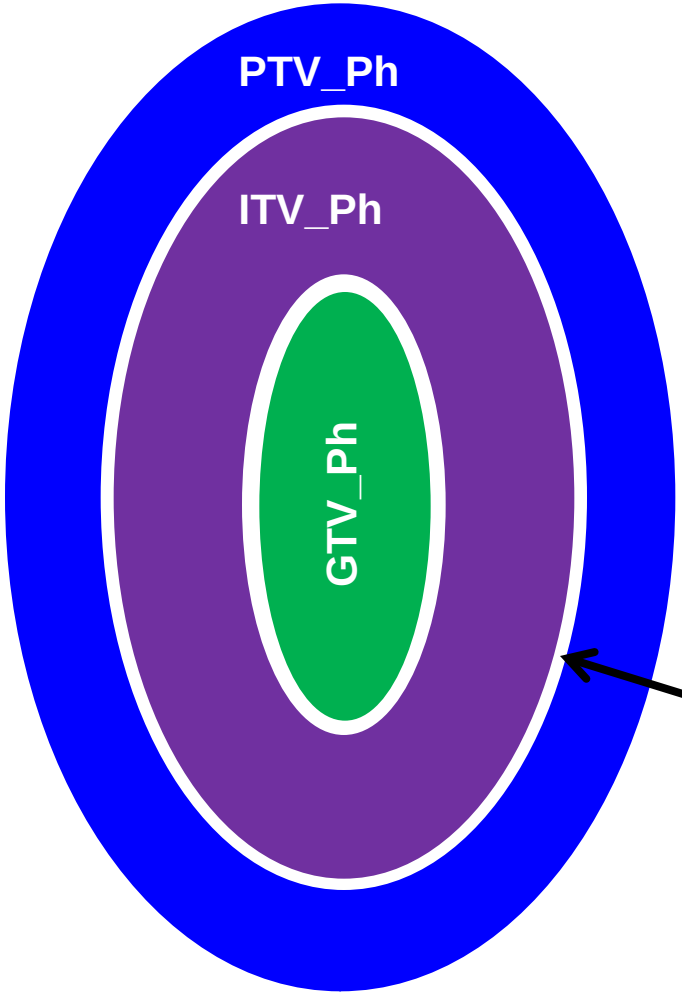
Maximum dose between 152% - 156% of PD (3x20.5Gy-21.1Gy)

Corresponds to a prescription isodose of 65%

VMAT – how to achieve the inhomogeneity



VMAT - Optimisation help structures



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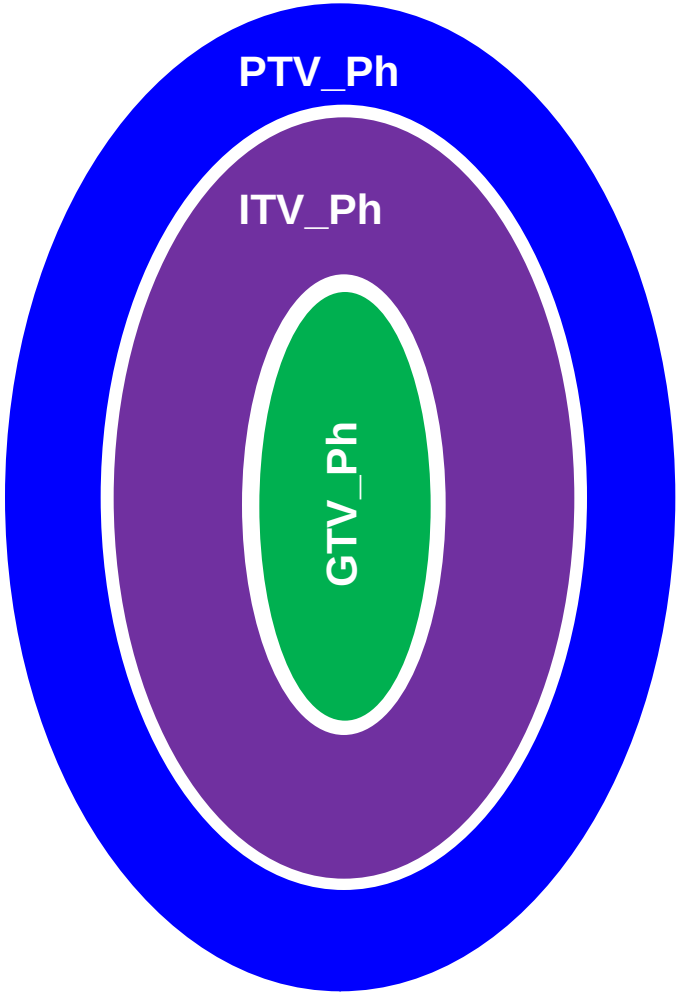
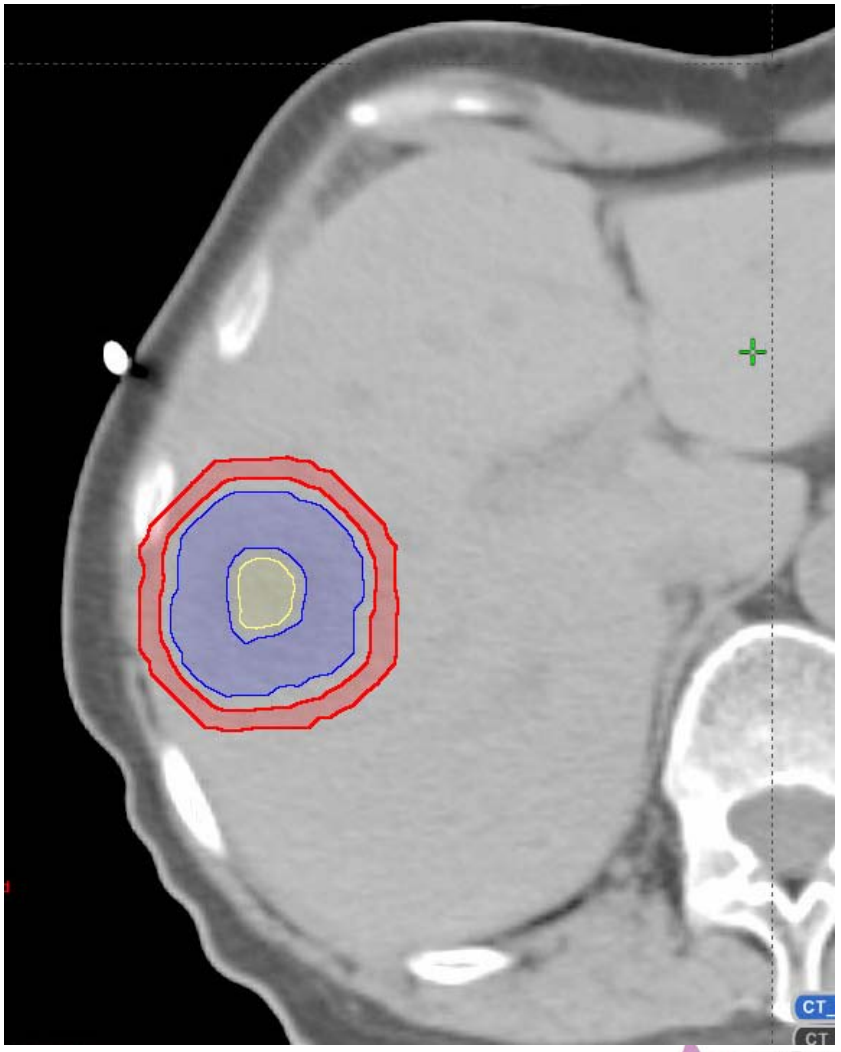
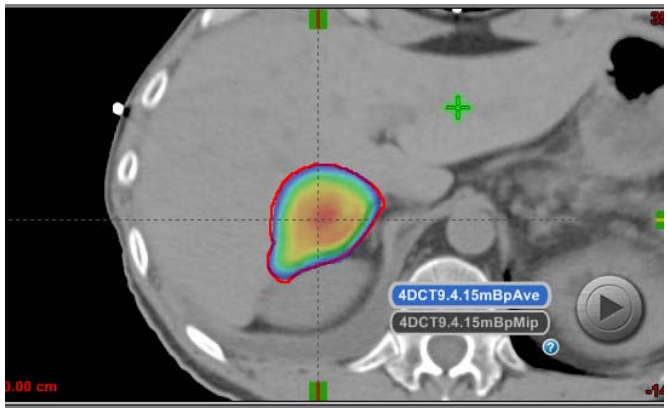
2mm distance

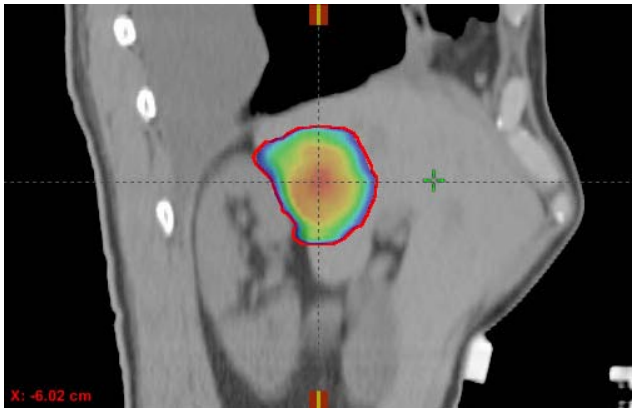
VMAT - Optimisation help structures

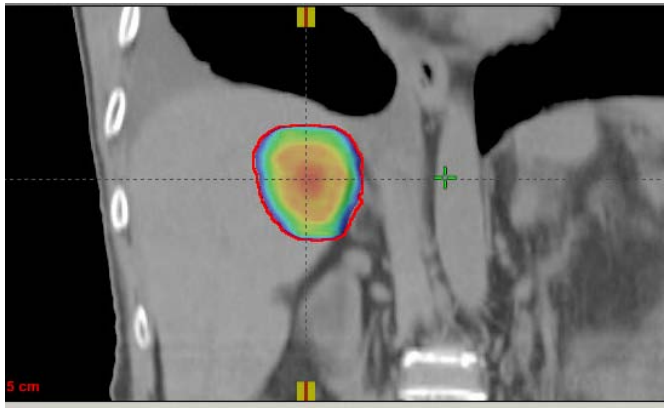




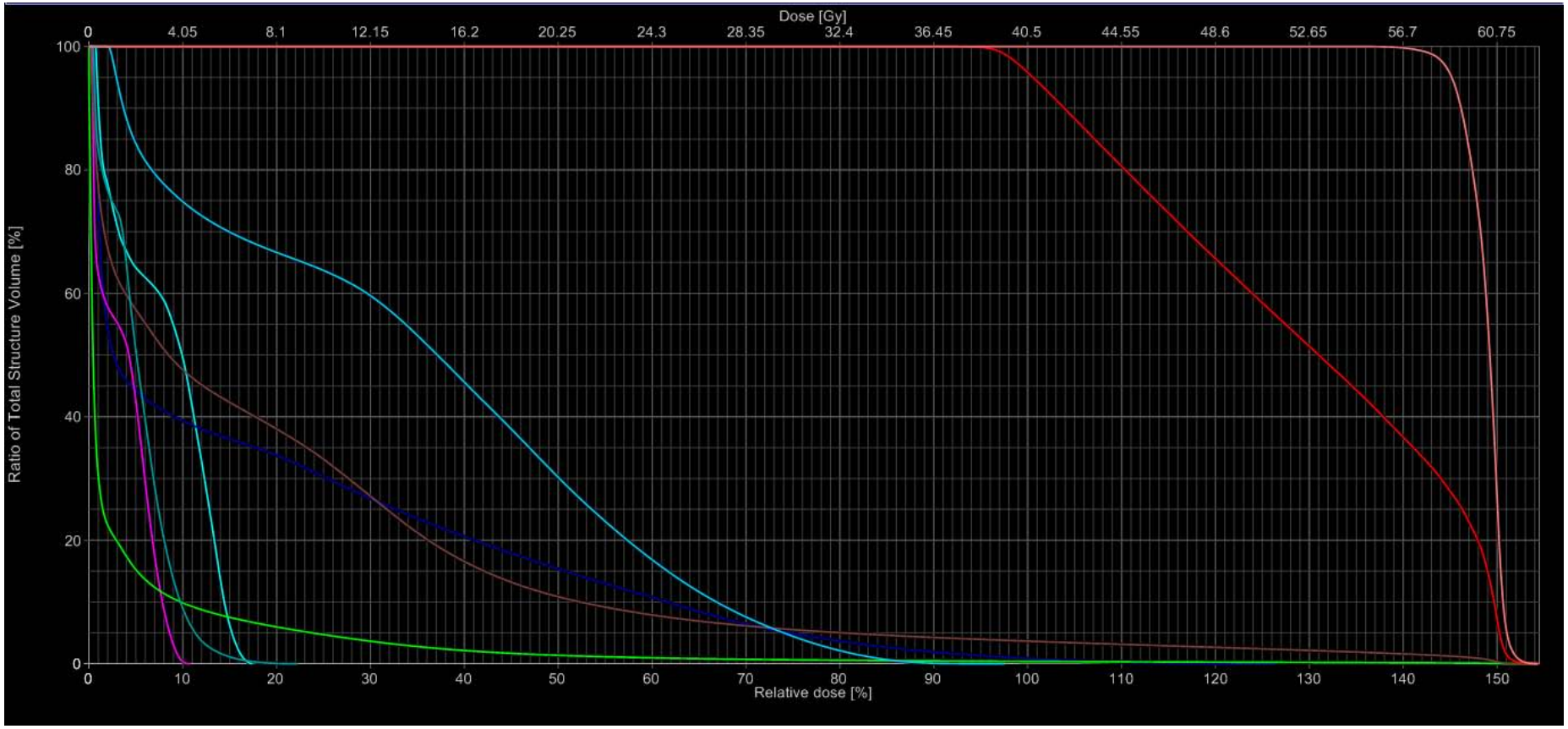
VMAT – dose distribution



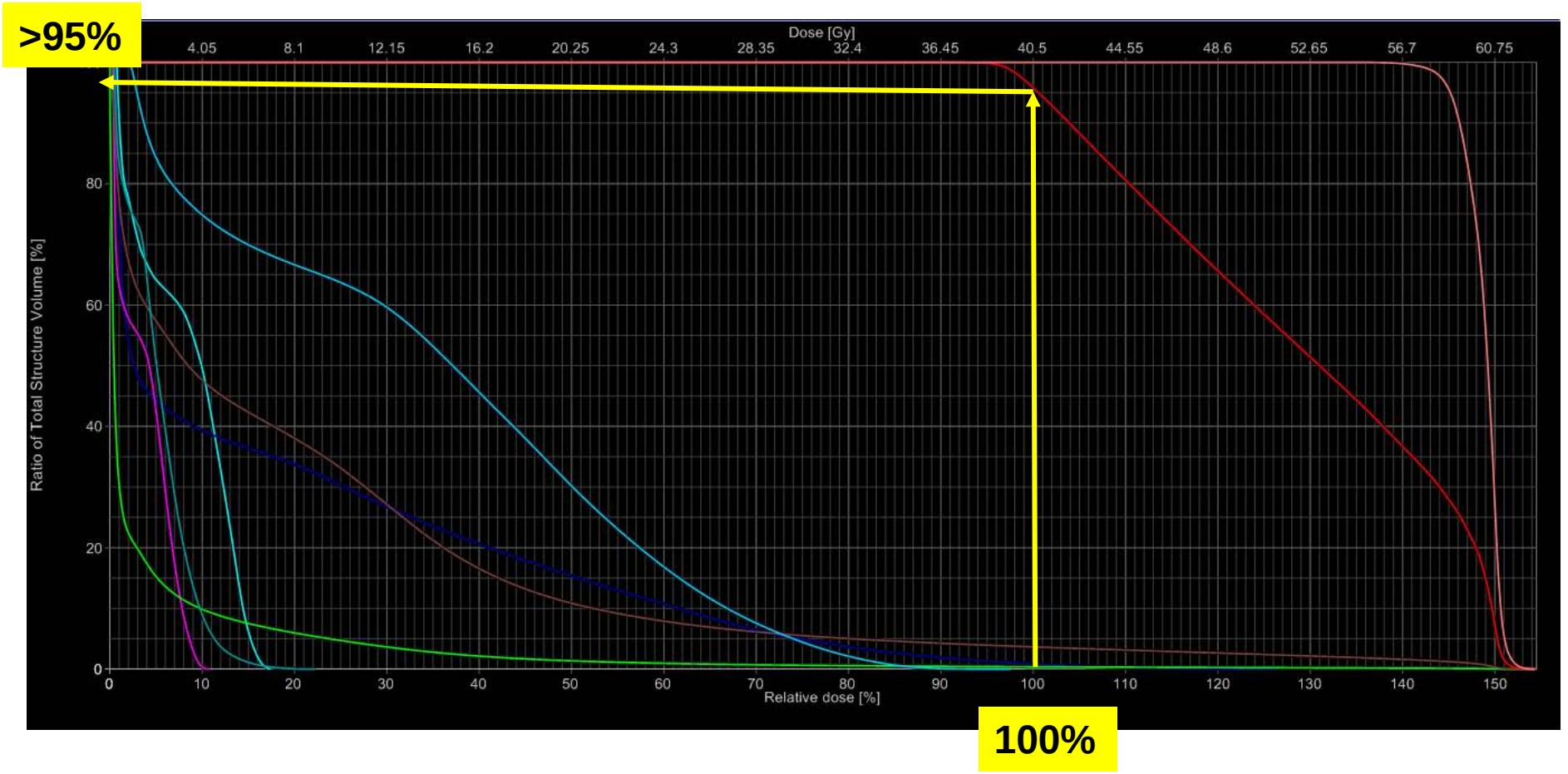




VMAT – dose distribution

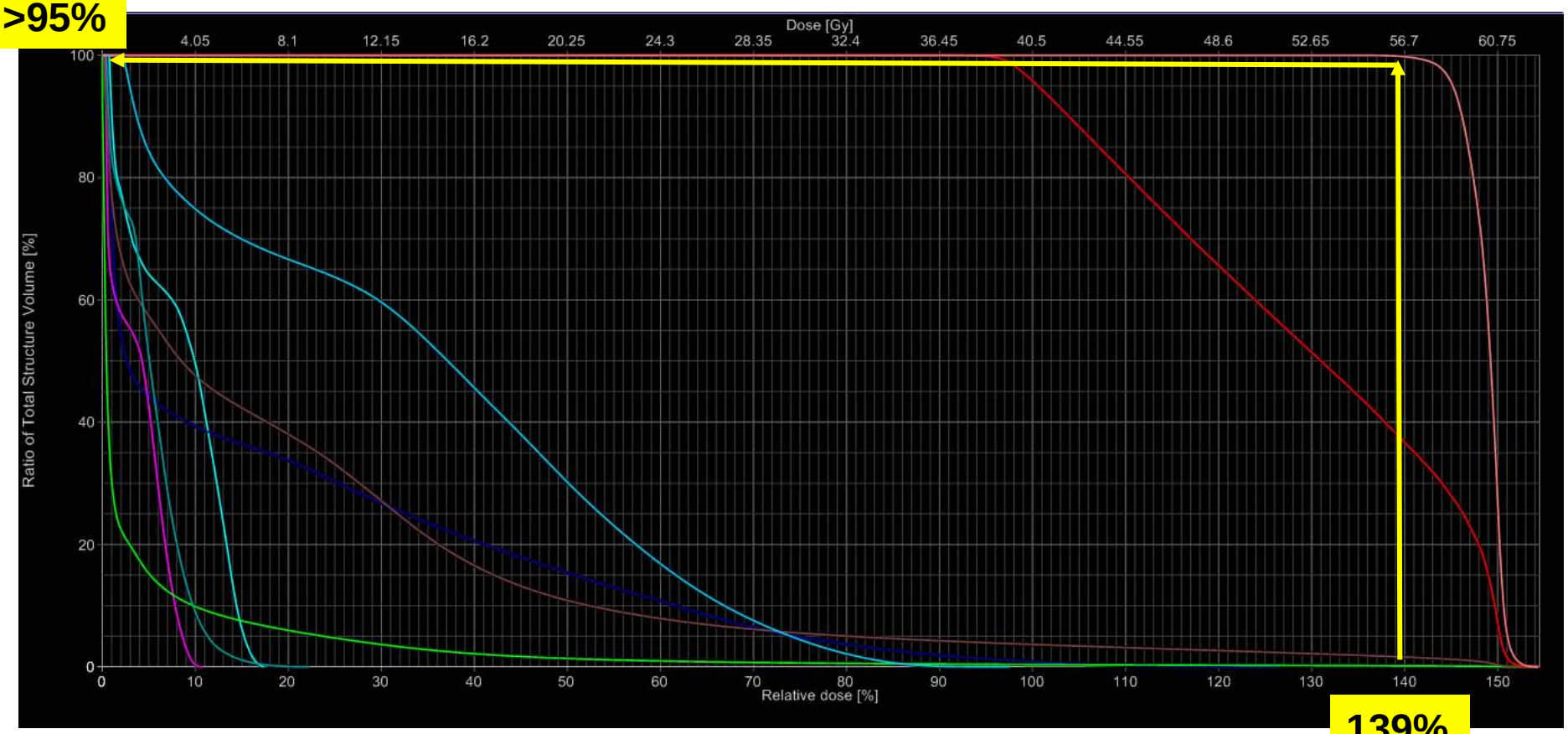


Plan evaluation



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

Plan evaluation



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

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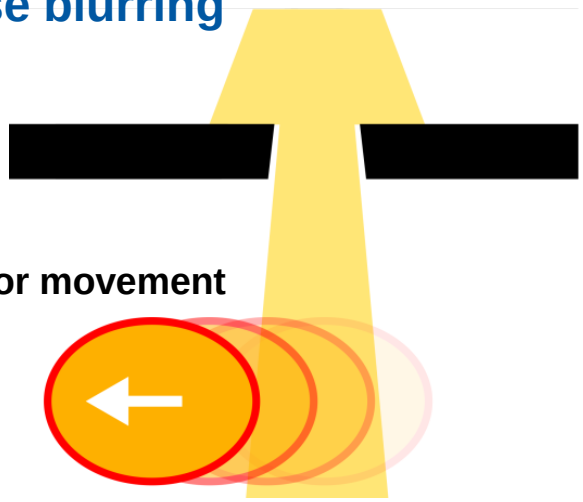
ESTRO School

Plan evaluation

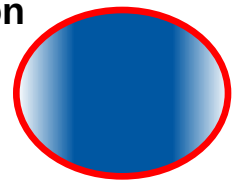
- > 95% of PTV should be covered by 100% of prescribed dose
- > 95% of GTV should be covered by 95% of prescribed dose
- Conformity Index < 1.2 (1.1)

Effects of motion on dose to the GTV dose

Dose blurring



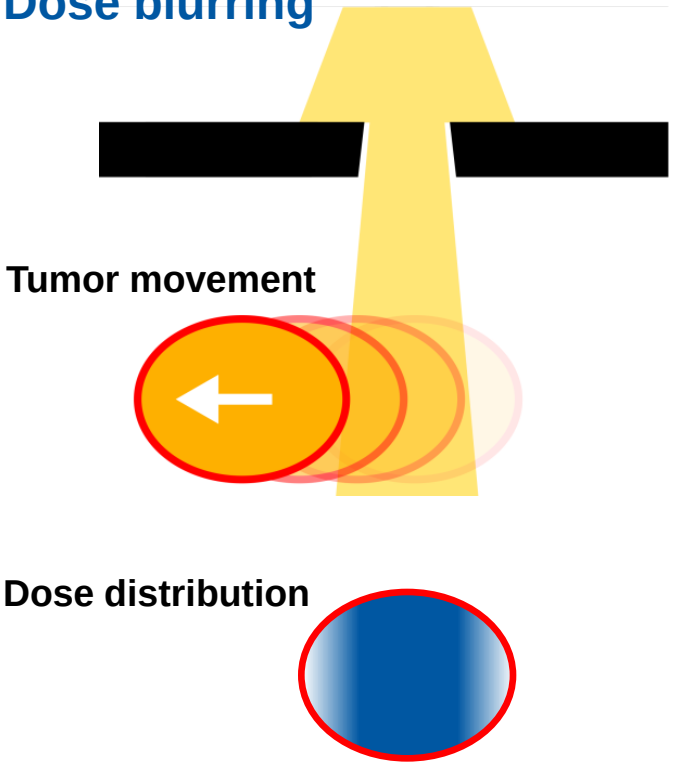
Dose distribution



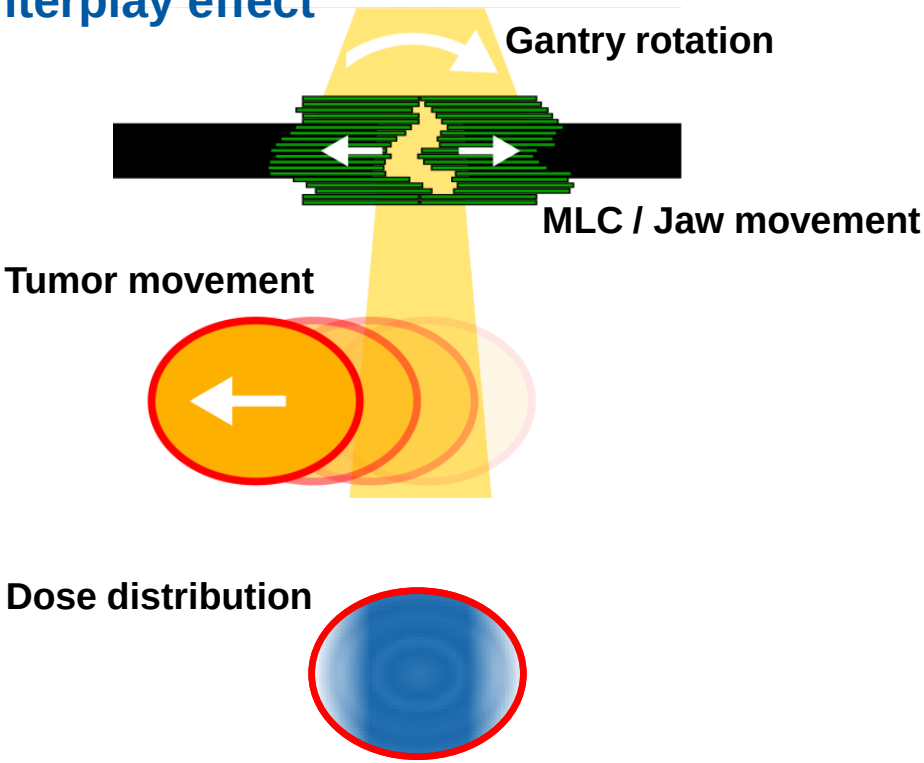
Dose blurring leads to underdosage at the edges of the tumor.

Effects of motion on dose to the GTV

Dose blurring

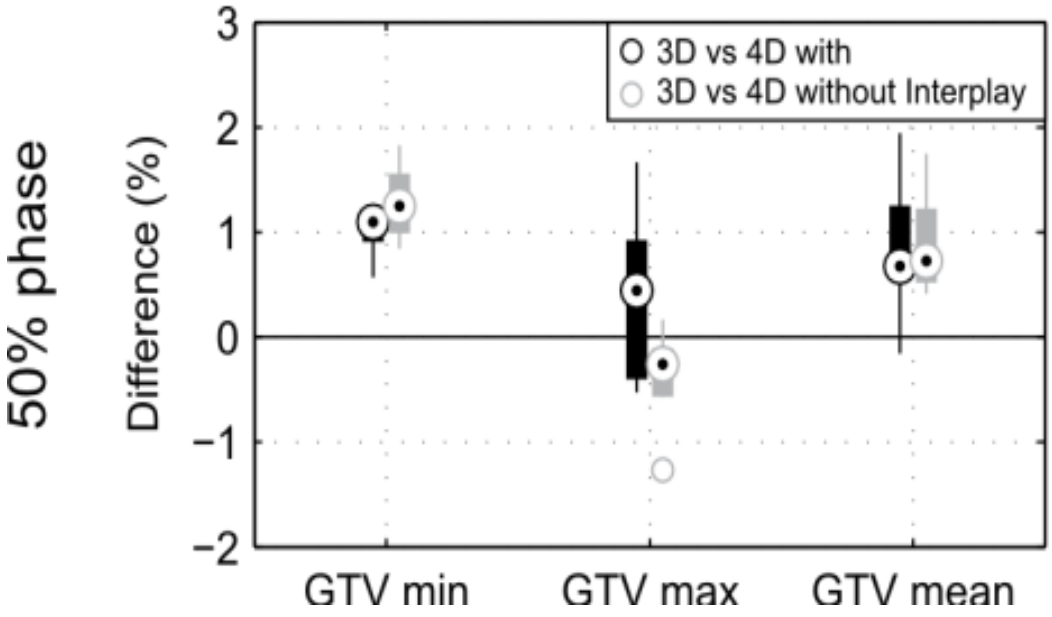


Interplay effect



Interplay effect leads to inhomogeneities inside the tumor.

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

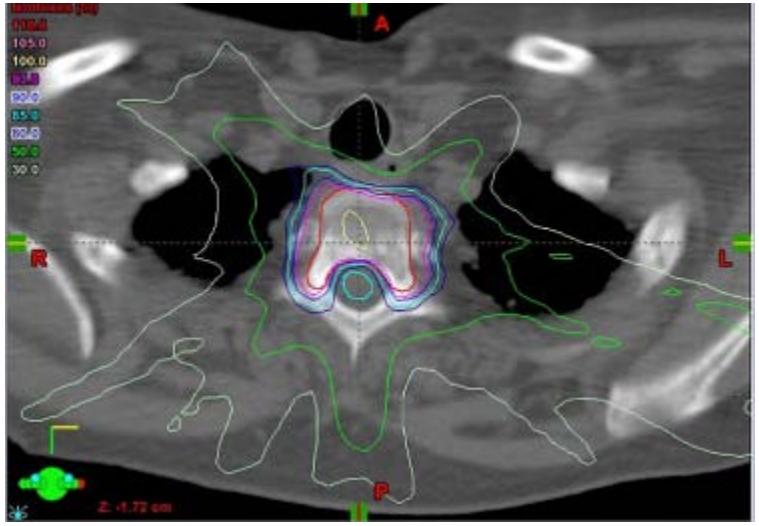
Different concepts

Treatment of the tumor lesion:

1 x 12.5Gy – 25Gy @ 80-95%

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

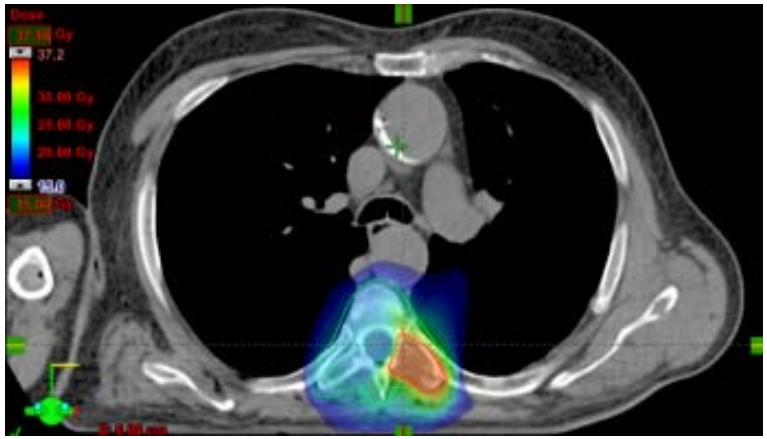
Distance between GTV and spinal cord > 3mm



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

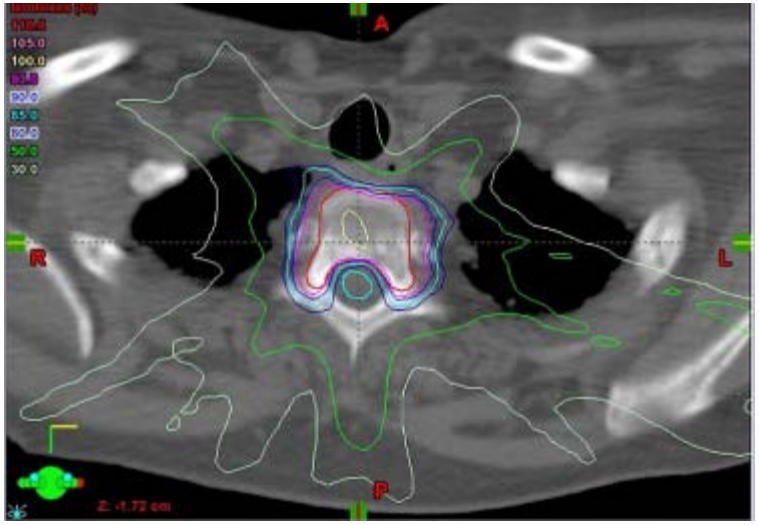


SBRT of spine tumors

Treatment technique:

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

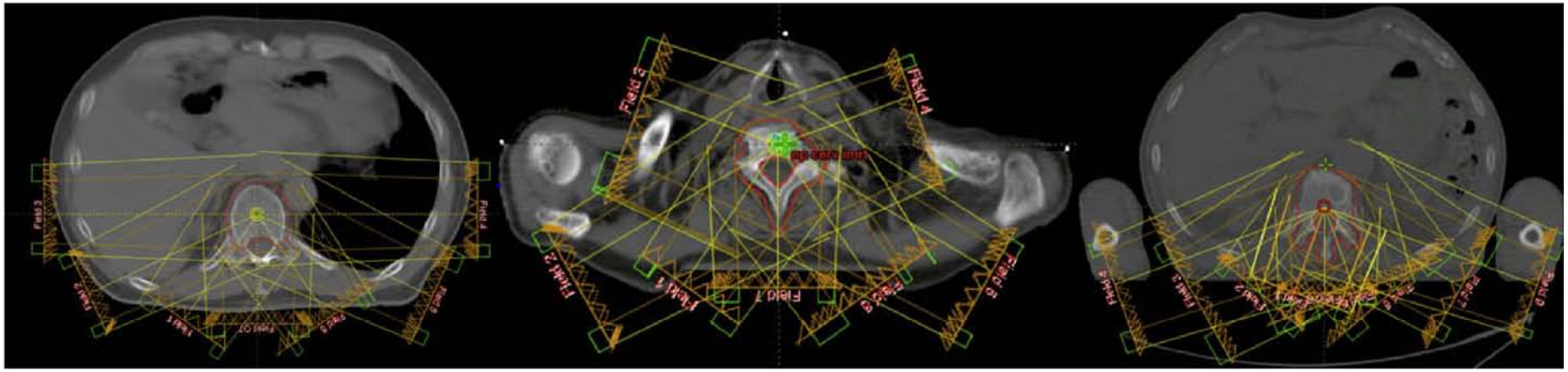
- to shape the dose around the target and
- better spare the spinal cord



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

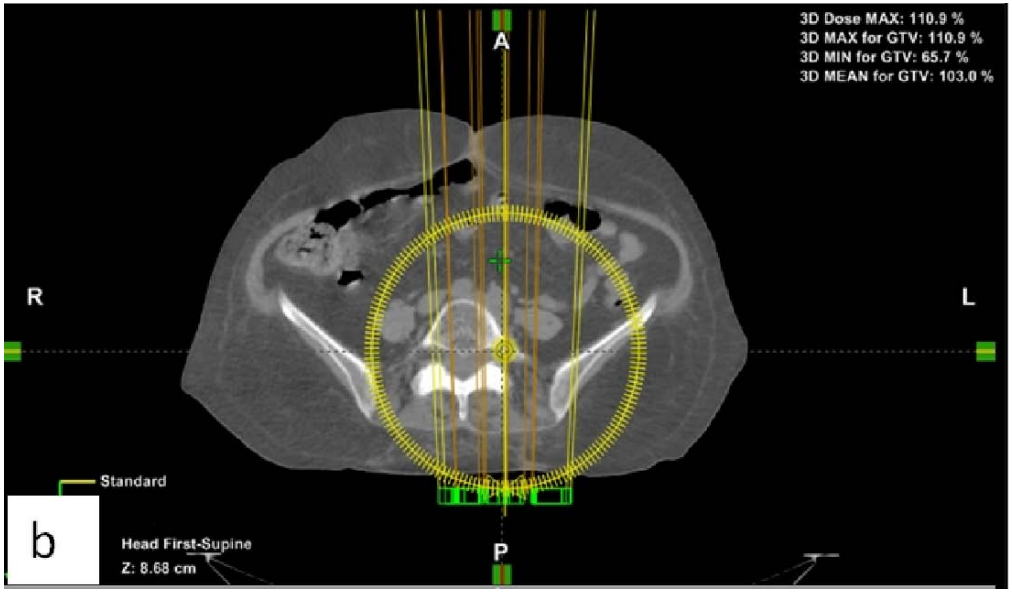


Kuijpers et al, RO, 2010

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

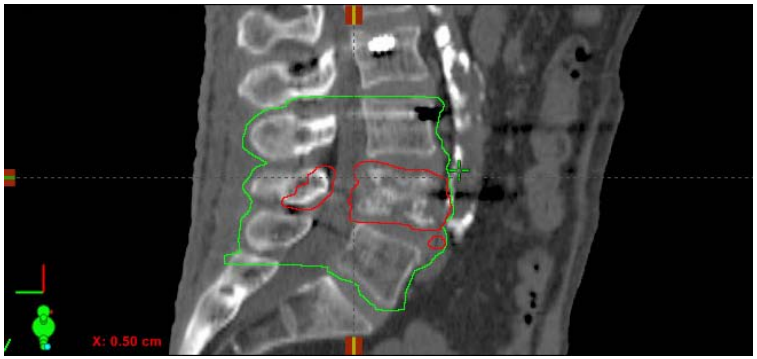
No difference between VMAT and IMRT in plan quality, however reduced treatment time with VMAT.

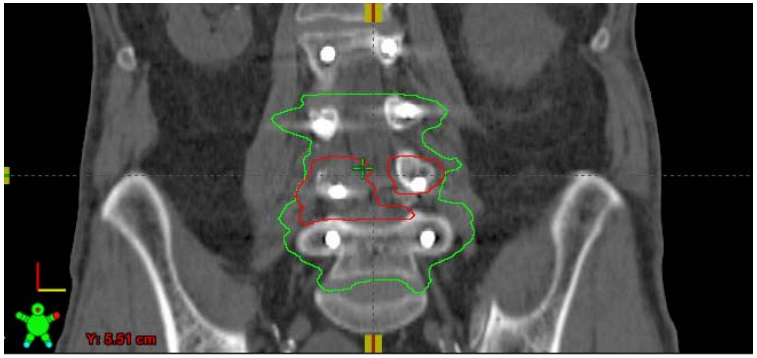
SBRT spine – integrated boost concept

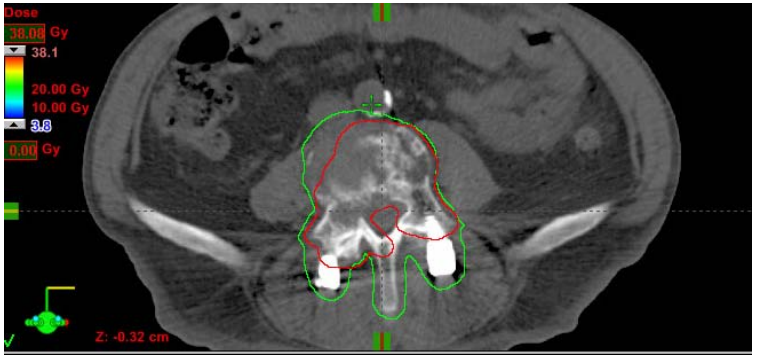
Integrated boost concept:

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)**

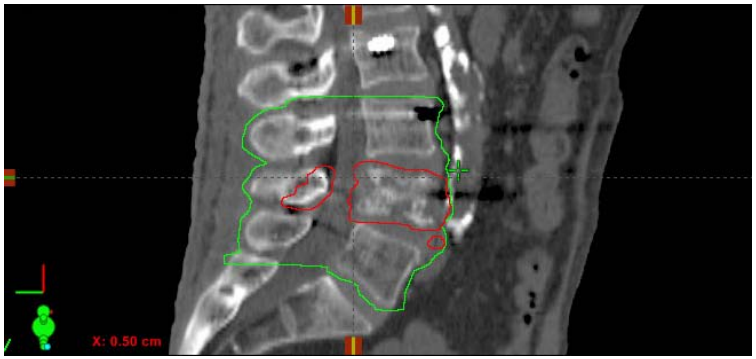
→ Fractionated approach

- **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)**

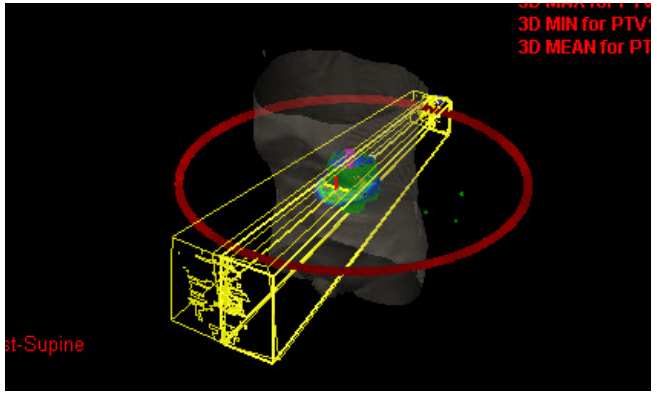
→ Homogeneous prescription

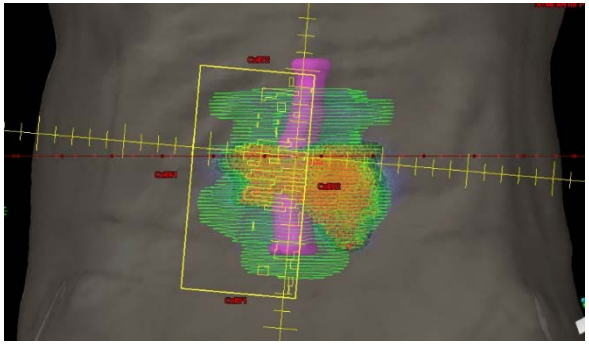


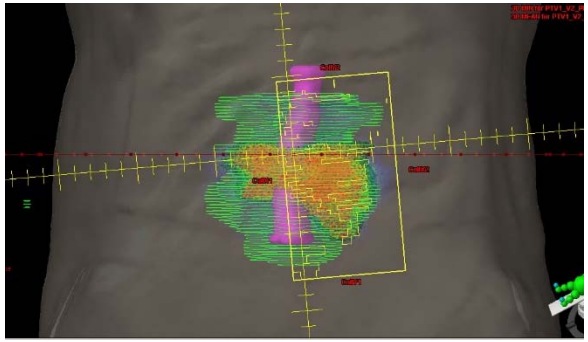
SBRT spine – integrated boost concept

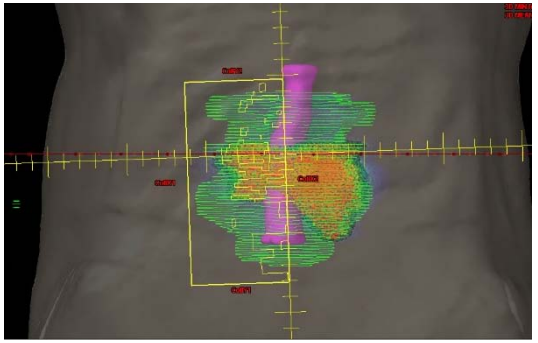
Planning technique:

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



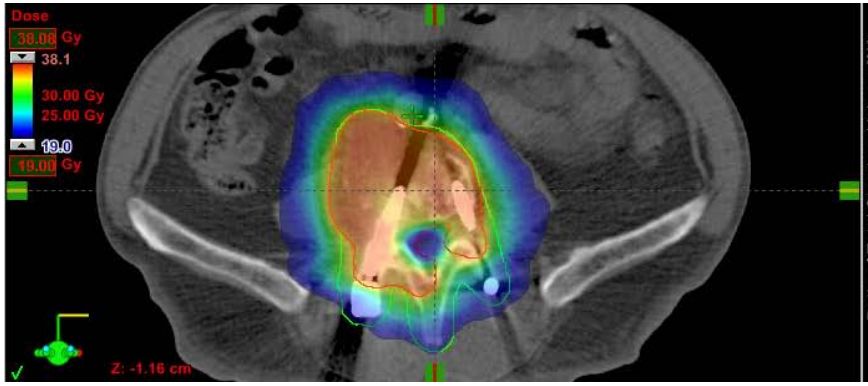


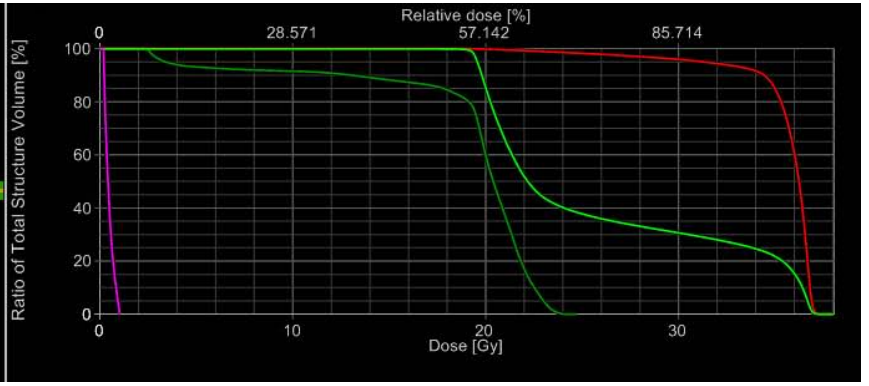


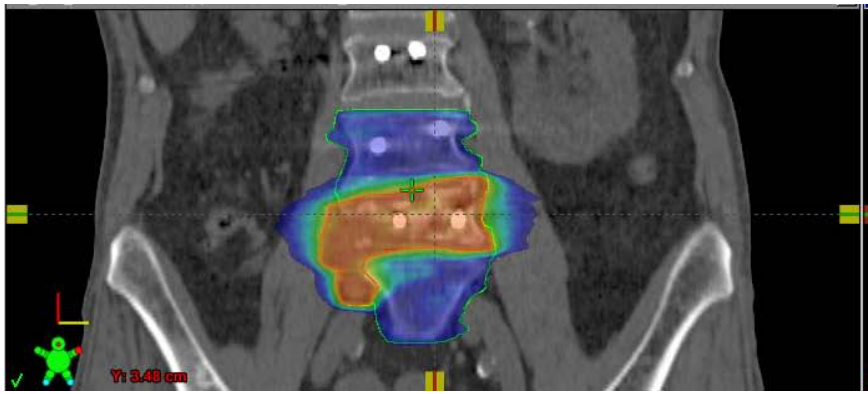


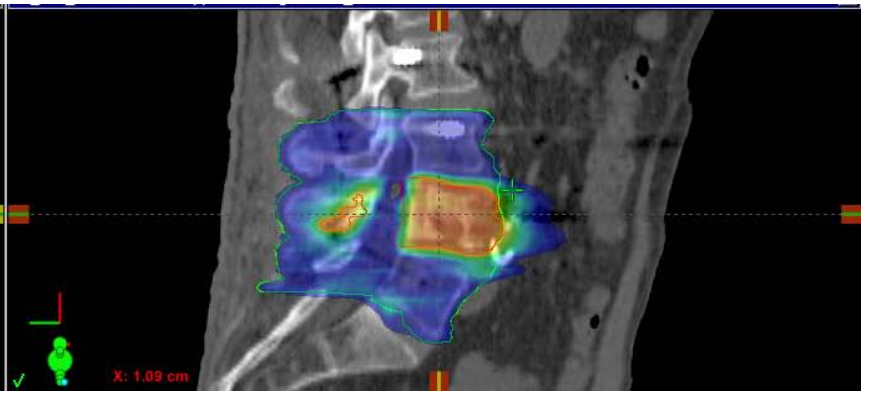
SBRT spine – integrated boost concept

Dose distribution





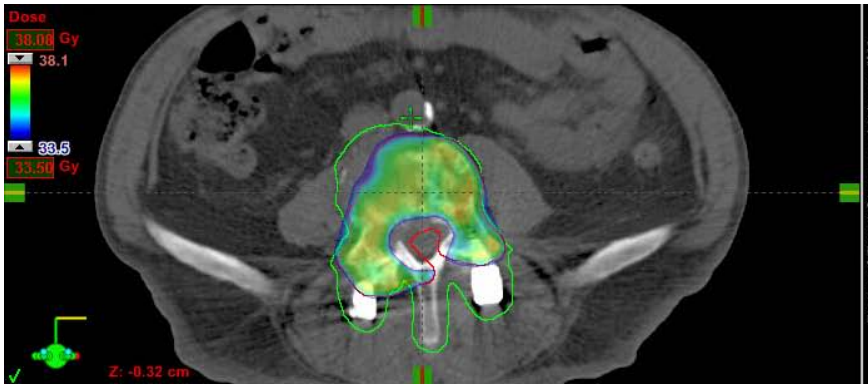


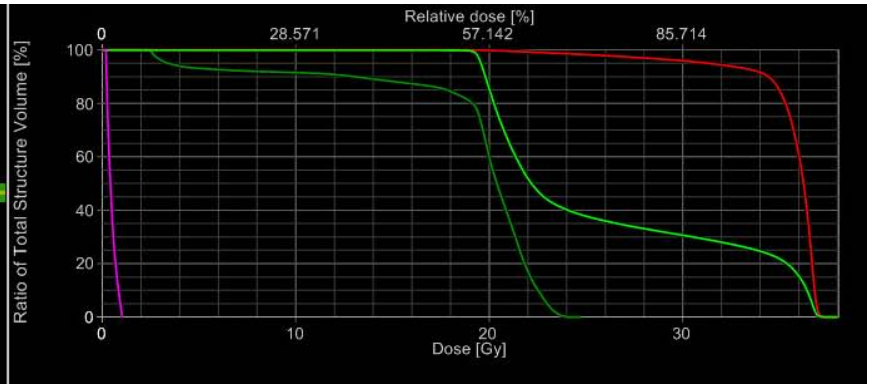


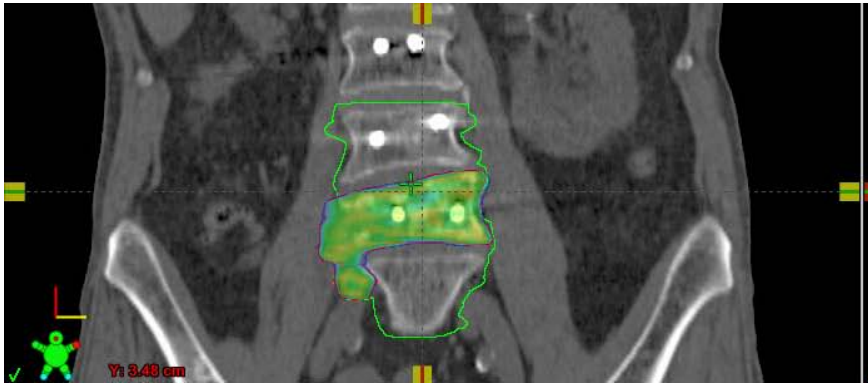
SBRT spine – integrated boost concept

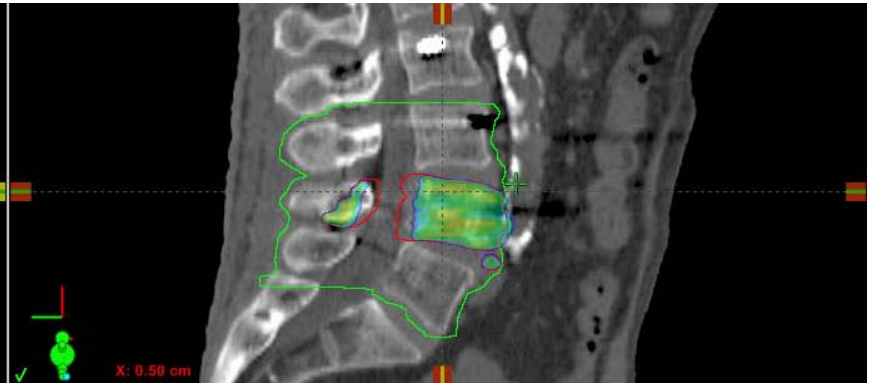
Spinal cord tolerance:

spinal cord max 23.75 Gy → compromise PTV coverage





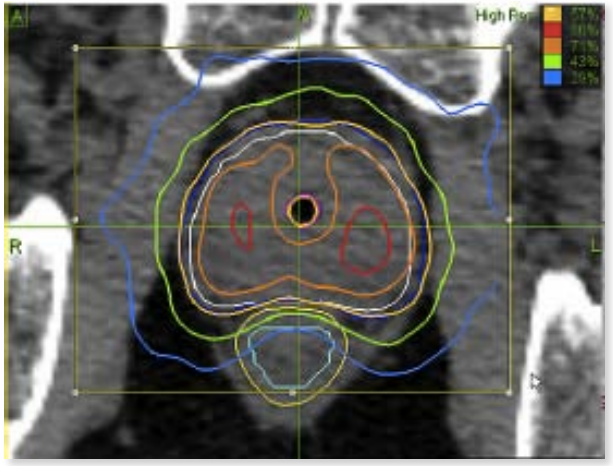




SBRT prostate treatment planning

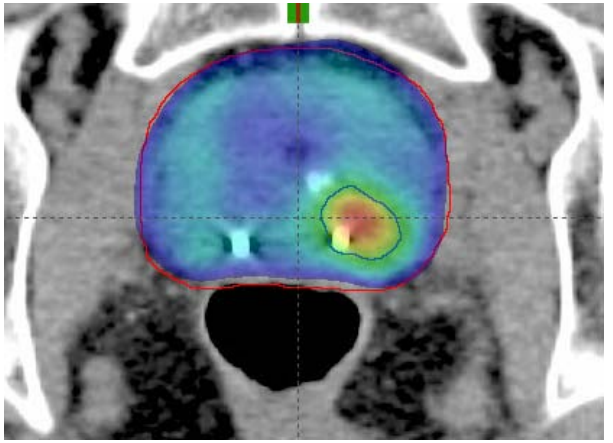
Different concepts

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

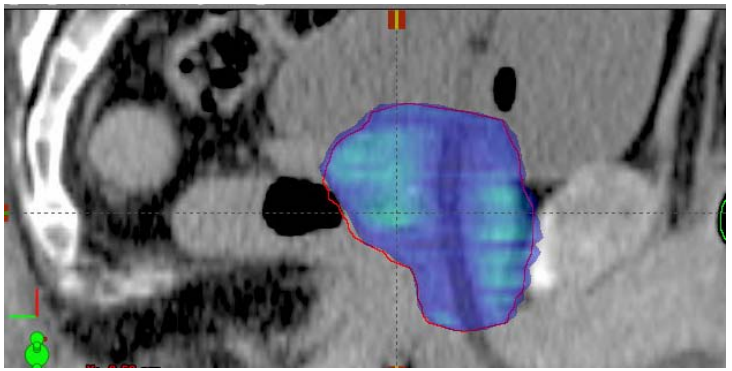
Planning technique:

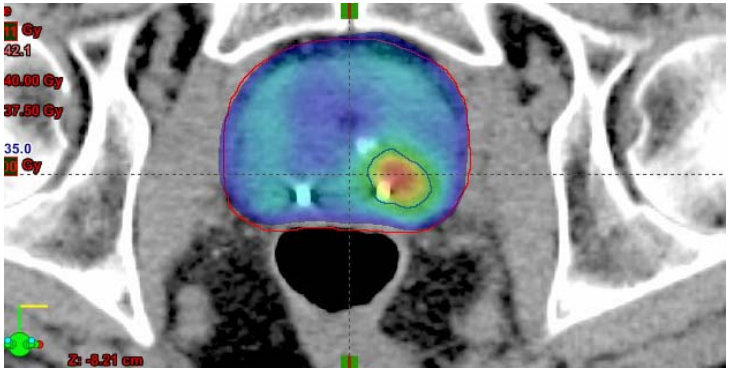
- Same field setup as in conventional fractionated RT of the prostate
- IMRT or VMAT should be used to better spare the rectum and to avoid hotspotts in the urethra

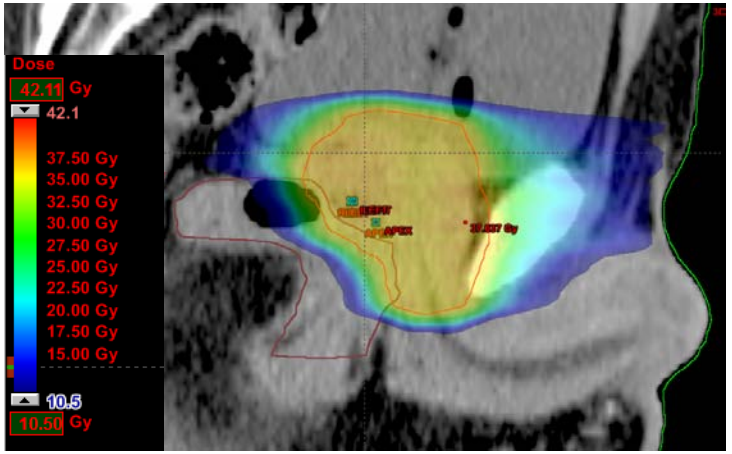
SBRT Prostate - OAR

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

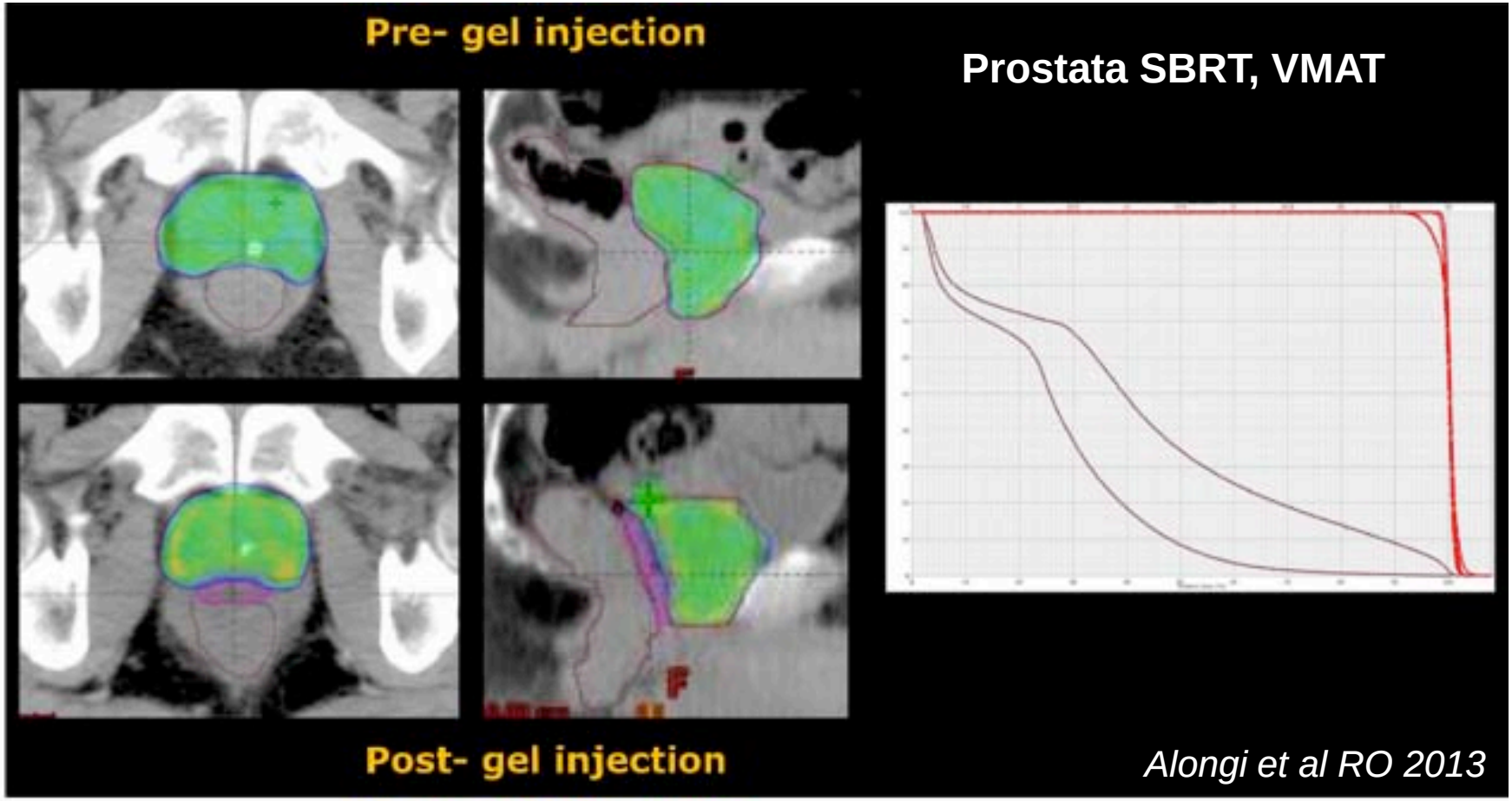
The anterior part of the rectum should receive less than 30% of the prescribed dose







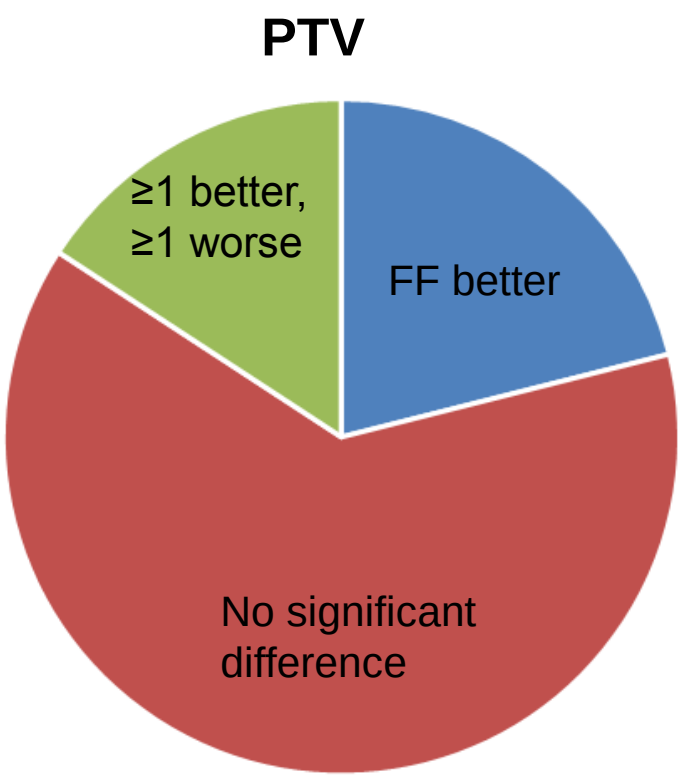
Rectal spacer

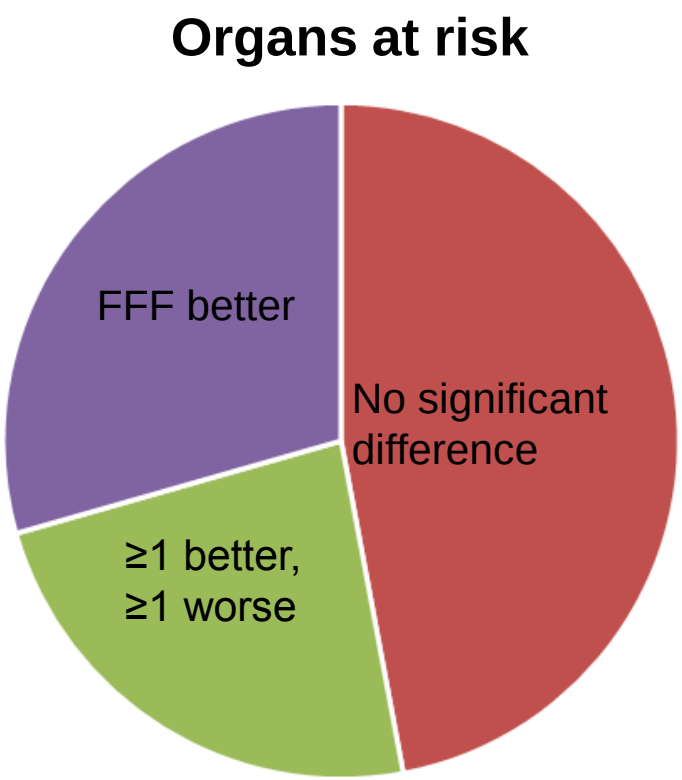


SpaceOAR™ was implanted in 8 patients with a single case of rectal fascia infection resolved with antibiotics.

FFF beams – any advantage?

FFF beams – any dosimetric benefit?

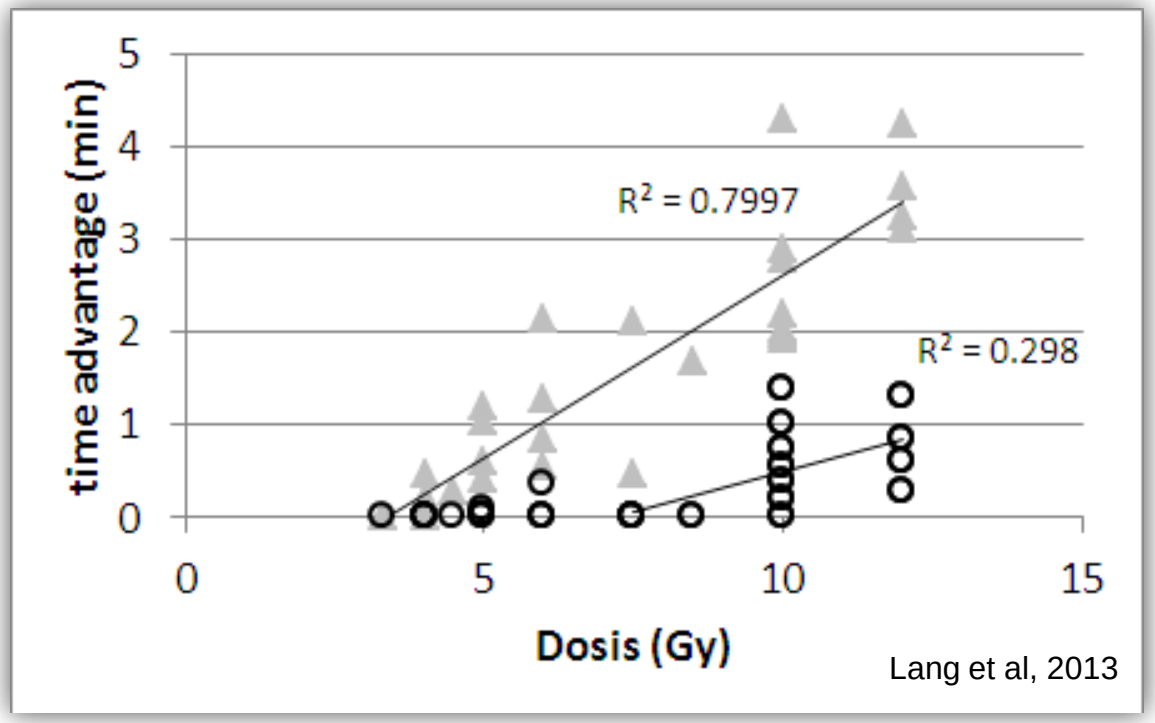




20 studies comparing FFF versus FF:
Lang et al, Ong et al, Reggiori et al, Lechner et al, Alongi et al, Nicolini et al, Lechner et al, Dzierma et al, Kretschmer et al, Lai et al, Wang et al, Stieler et al, Zhuang et al, Hrbacek et al, Shi et al, Gasic et al, Fu et al, Hansen et al, Pruijt et al

FFF beams – faster treatments?

SBRT treatments

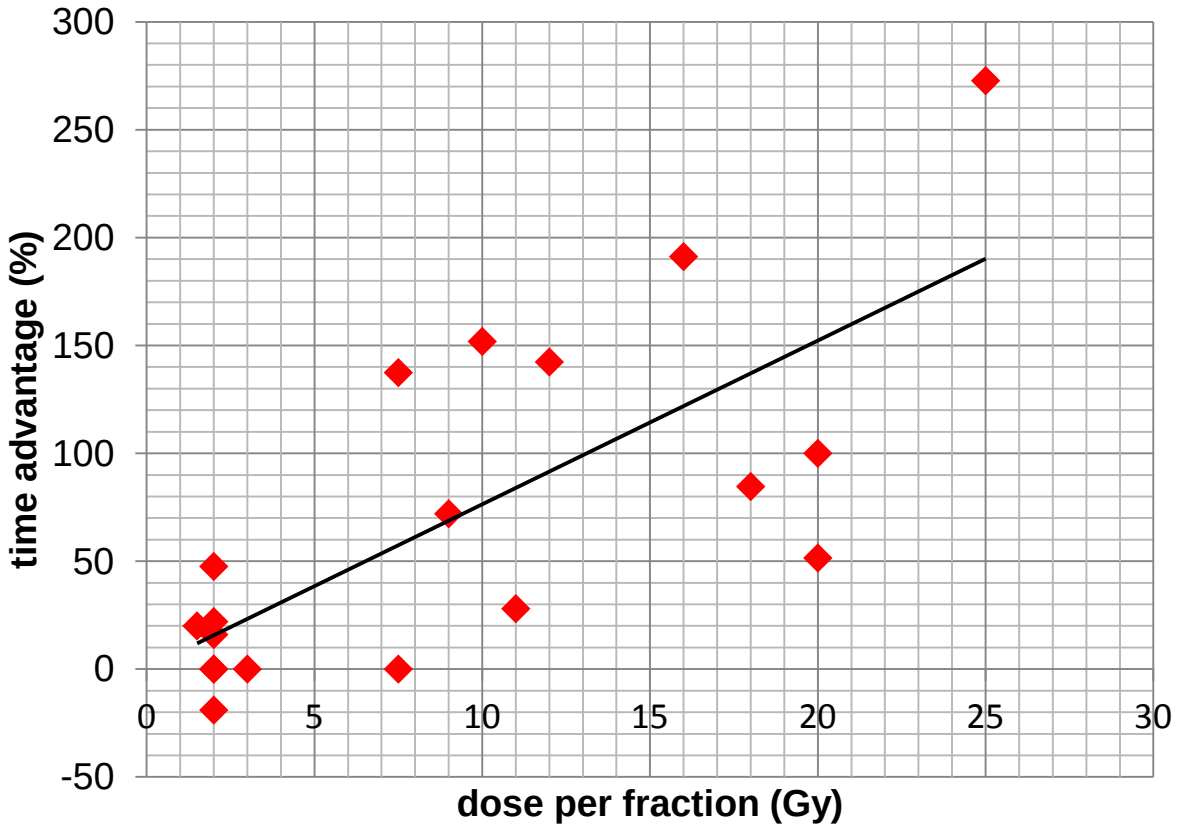


Lang et al, 2013

▲ 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,
Lechner et al,
Alongi et al,
Nicolini et al,
Dzierma et al,
Lai et al,
Wang et al,
Stieler et al,
Zhuang et al,
Hrbacek et al

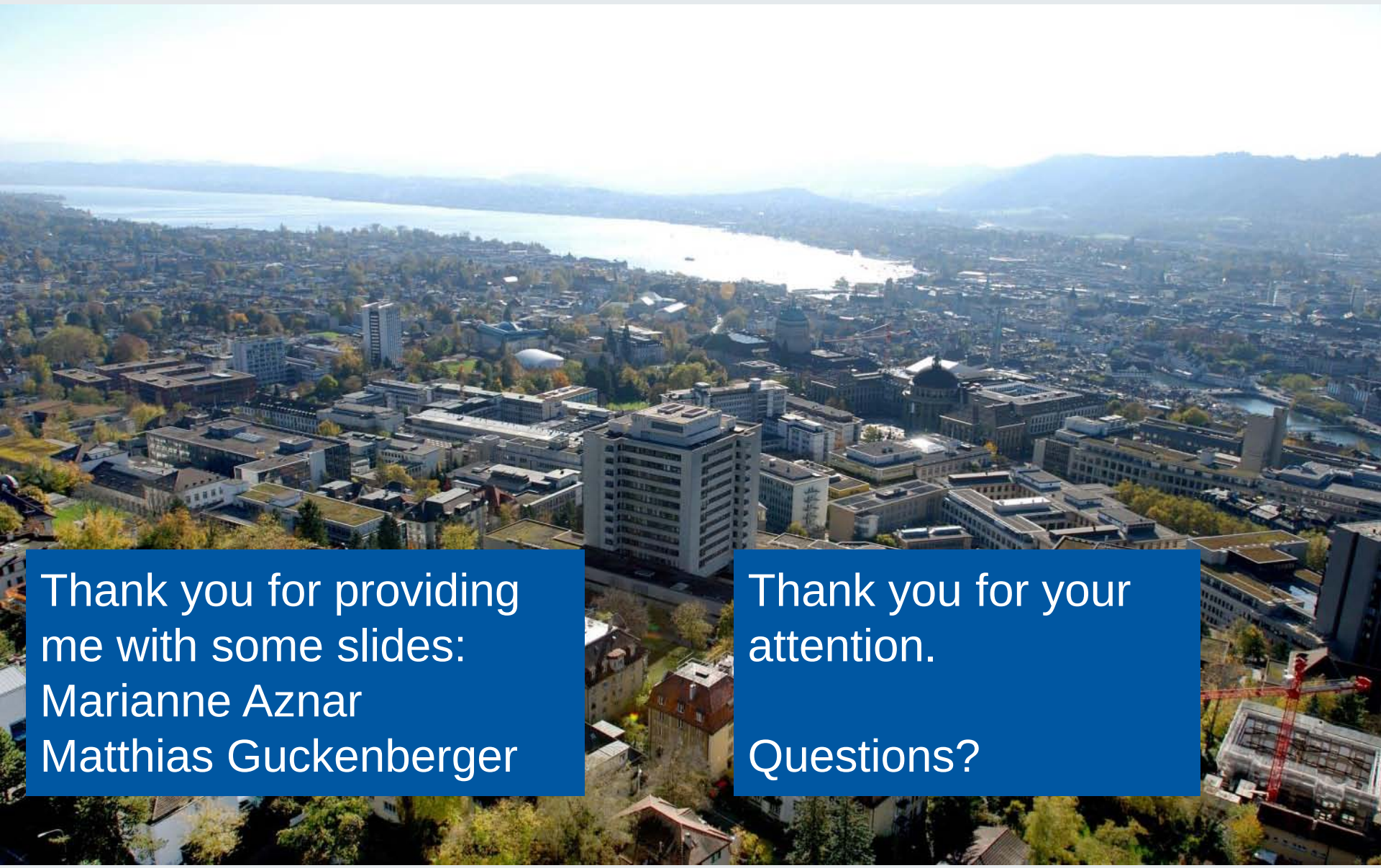
References

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

catharina hospital

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?

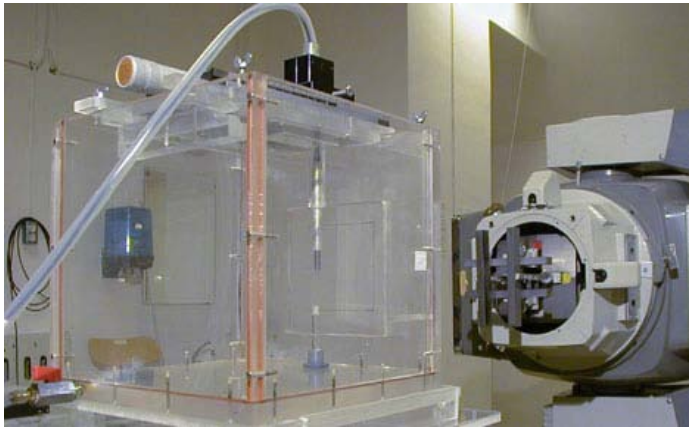
To know how to effectively reduce (potential) errors

Do Accidents Happen?

atharina
ospital

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

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**

North Staffordshire Royal Infirmary, 1982-1991

- Until 1982, a hospital relied on manual calculations for the correct dose to be delivered to the tumour
  - Treatments were generally performed at standard SSD (100 cm) (very few SAD)
- A computerized treatment planning system was acquired in 1981- clinical use in autumn of 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 computer planning system was installed and **a discrepancy was discovered between the new plans and those from the previous system**
  - Further investigation revealed that 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

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

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

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**

Table from: "Report of an investigation by the Inspector appointed by the Scottish Ministers for The Ionising Radiation (Medical Exposures) Regulations 2000"

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)

catharina hospital

Jan 2010

The New York Times

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

THE RADIATION BOOM

Radiation Offers New Cures, and Ways to Do Harm

By WALT BOGDANICH
Published: January 23, 2010

SIGN IN TO RECOMMEND
TWITTER
SIGN IN TO E-MAIL
PRINT
REPRINTS
SHARE

GOLDEN GLOBE® WINNER

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.

catharina hospital

Energy and Commerce - Subcommittee on Health held a hearing entitled "Medical Radiation: An Overview of the Issues" on Friday, February 26, 2010

Panel I
Mr. James Parks
Dr. Rebecca Smith-Bindman M.D.
Mr. Eric E. Klein Ph.D.
Ms. Cynthia H. McCollough Ph.D.
Ms. Suzanne Lindley

Panel II
Mr. Michael G. Herman Ph.D.
Ms. Sandra Hayden B.S.
Dr. E. Stephan Amis Jr.
Dr. Tim Williams
Mr. David N. Fisher
Mr. Kenneth Mizrach

Chairman Mr Pallone, NJ

Available at:

http://www.youtube.com/watch?v=NcqRgVqeQSg

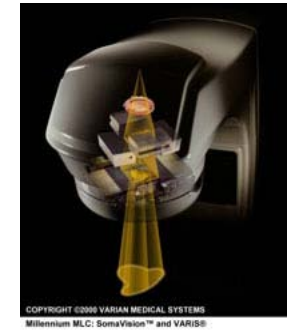
http://www.youtube.com/watch?v=L_IzTqhghMs

Let's have the story

- Tuesday - March 8, 2005
  - The patient begins an IMRT treatment at St Vincent's Hospital, Manhattan, NY.
  - The plan had passed the QC process according to the local protocol
  - 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
  - Fractionation is changed. Existing fluences are deleted and re-optimized. New optimal fluences are saved to DB.
  - Final calculations are started, where MLC motion control points for IMRT are generated.

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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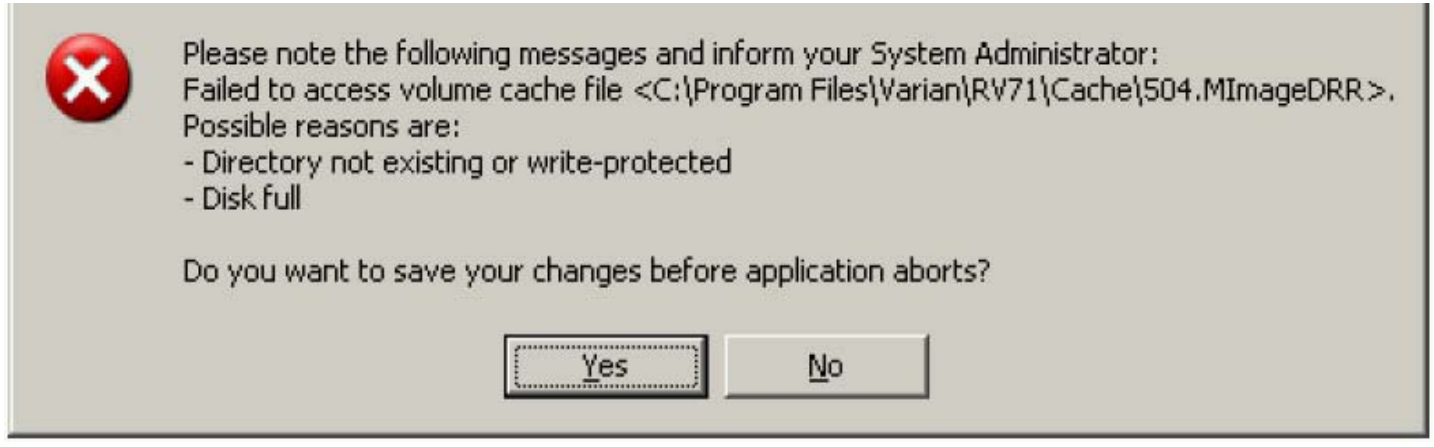
What happened?



The transaction error message displayed

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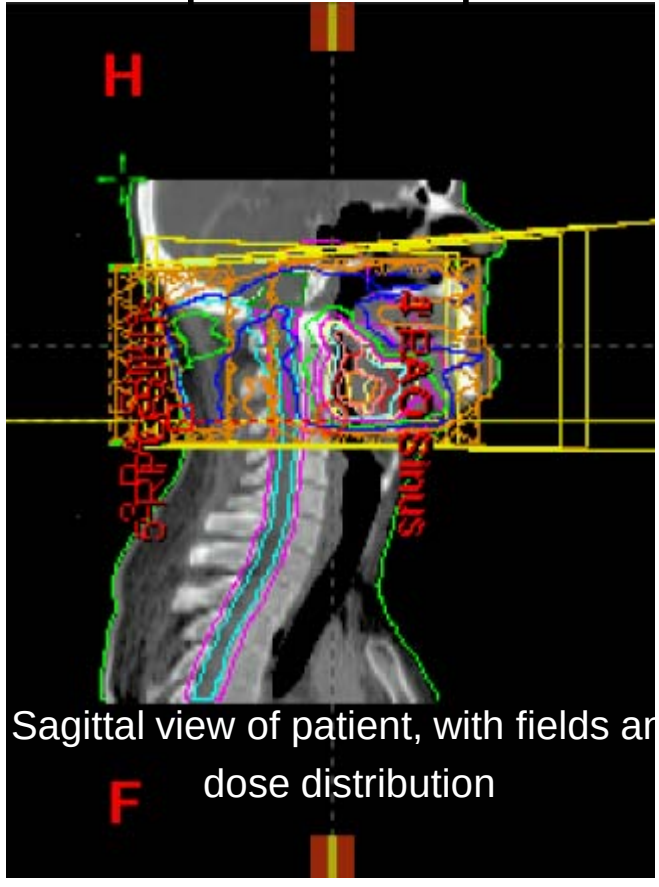
What happened?

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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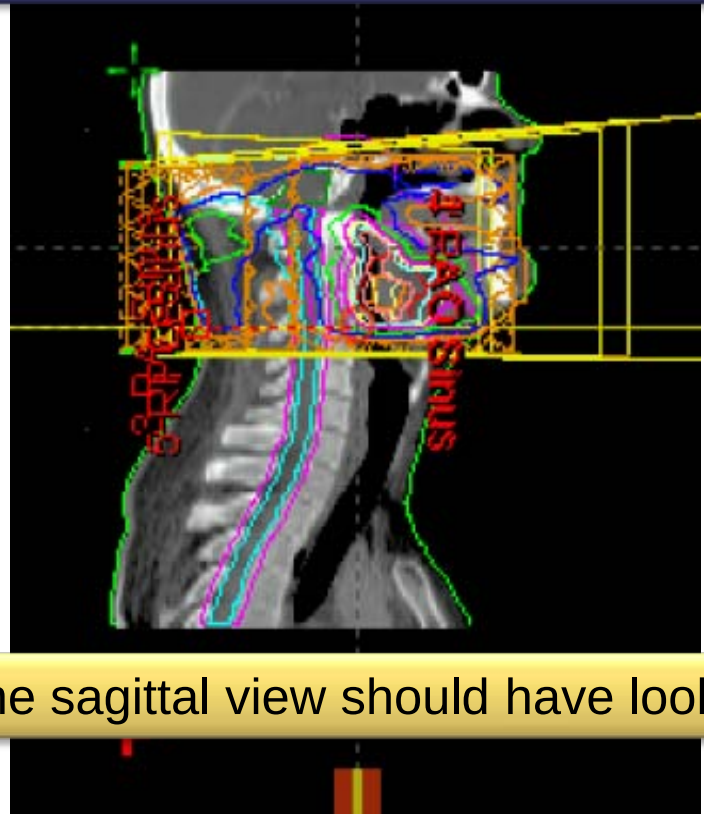
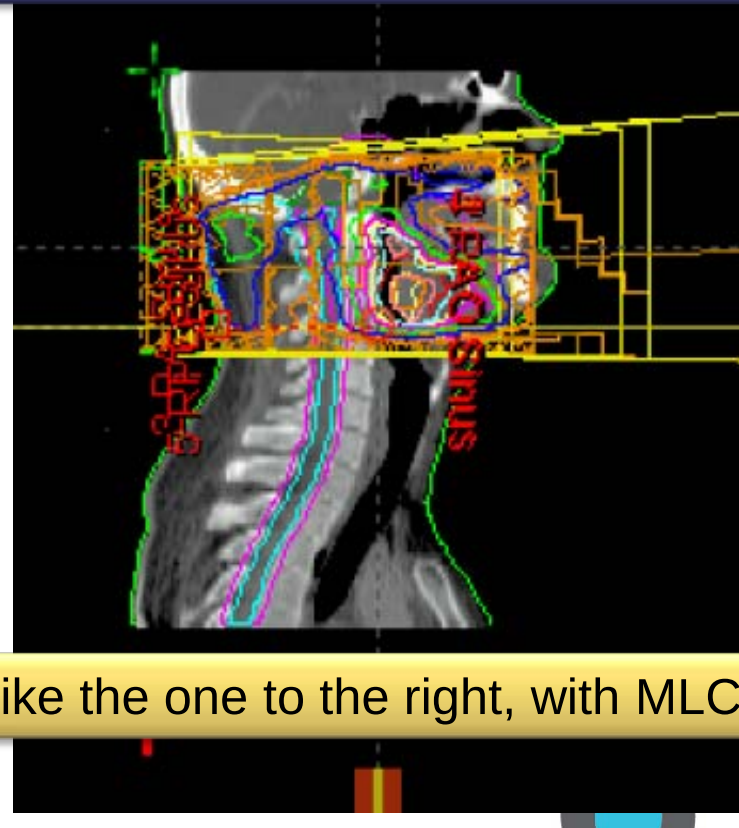
What happened?

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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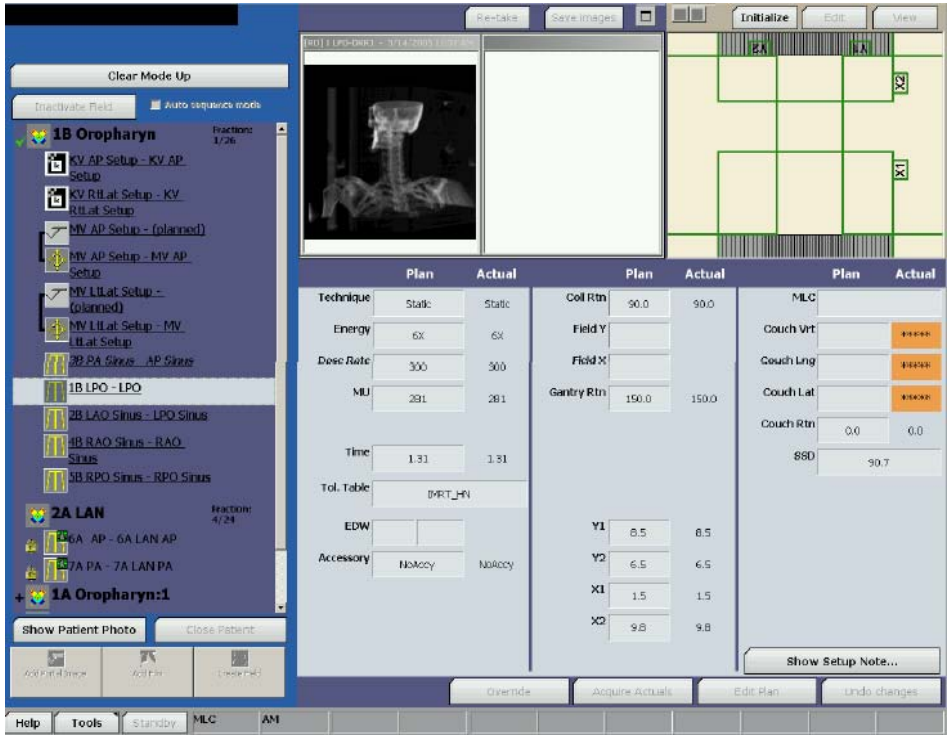
What happened?

- 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

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!

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%.

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. The calculations were performed using the existing Linac model in the TPS.
- Routinely EPID patient dosimetry QA is performed at this institution. 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. However, on the new linac only small fields were used. (HD 2.5 mm MLC)
- Also weekly Matrix measurements are performed. However, 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.

Recently… New identical Linac…

Why did QART fail?

- The institution stated 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. However, the MU's needed were based on the measurements, not on the TPS calculation. (not mandatory for RPC check).

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.

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!

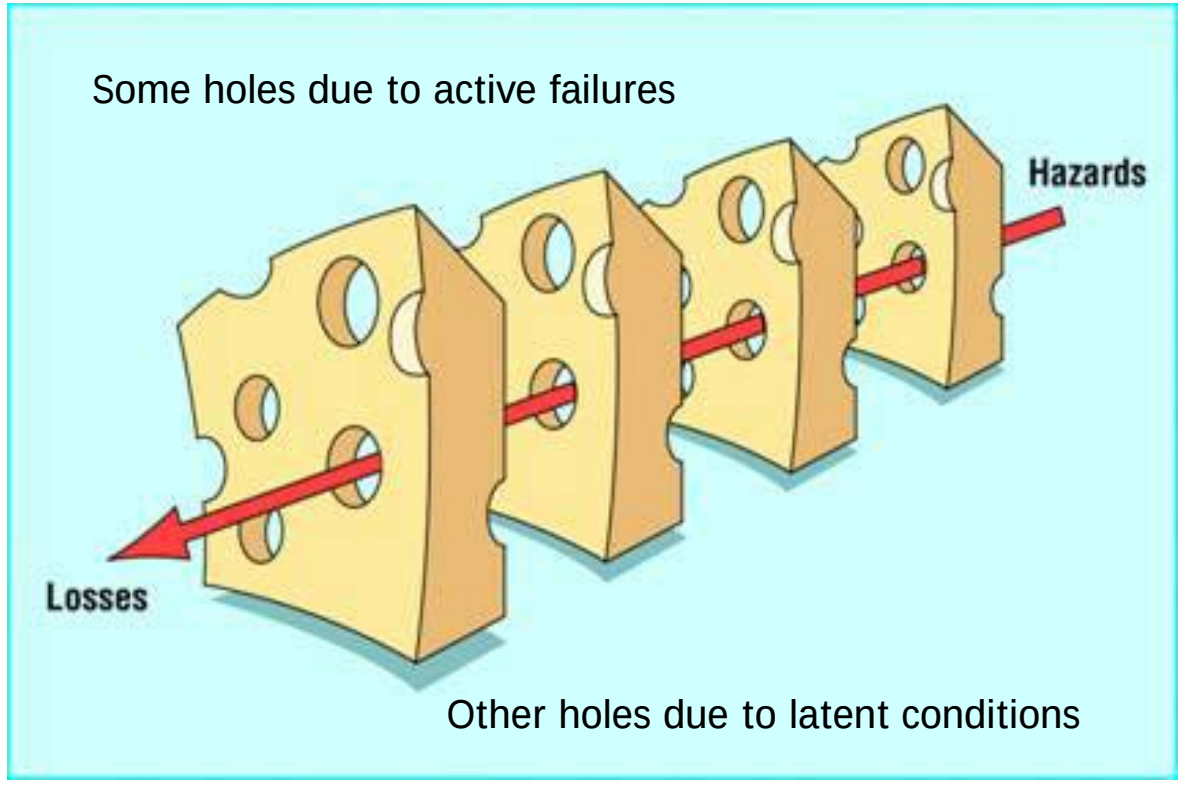
- **Perform external reference dosimetry audits / trial audits based on TPS calculations**

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.**

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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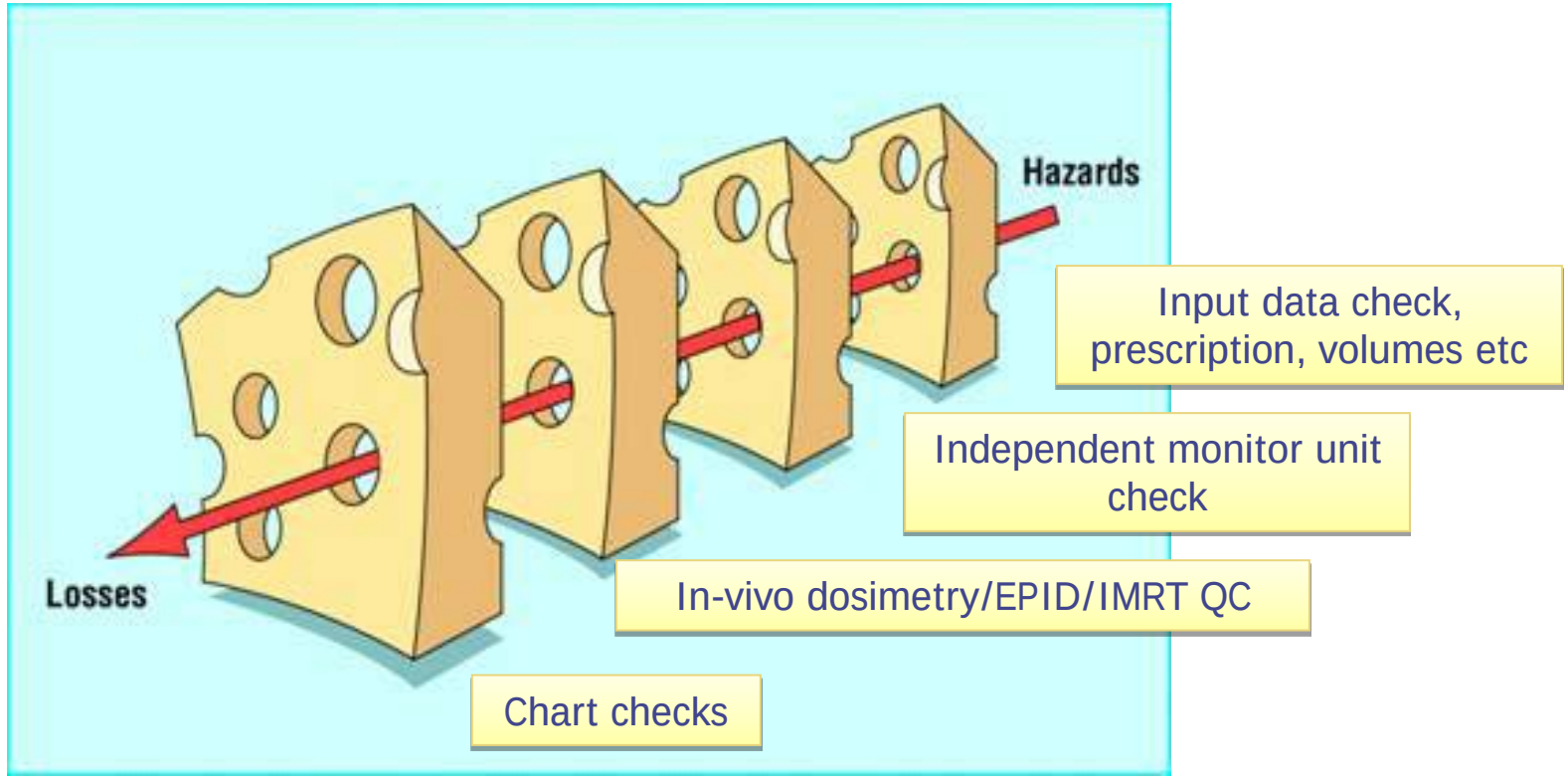
Radiotherapy safety layers

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?

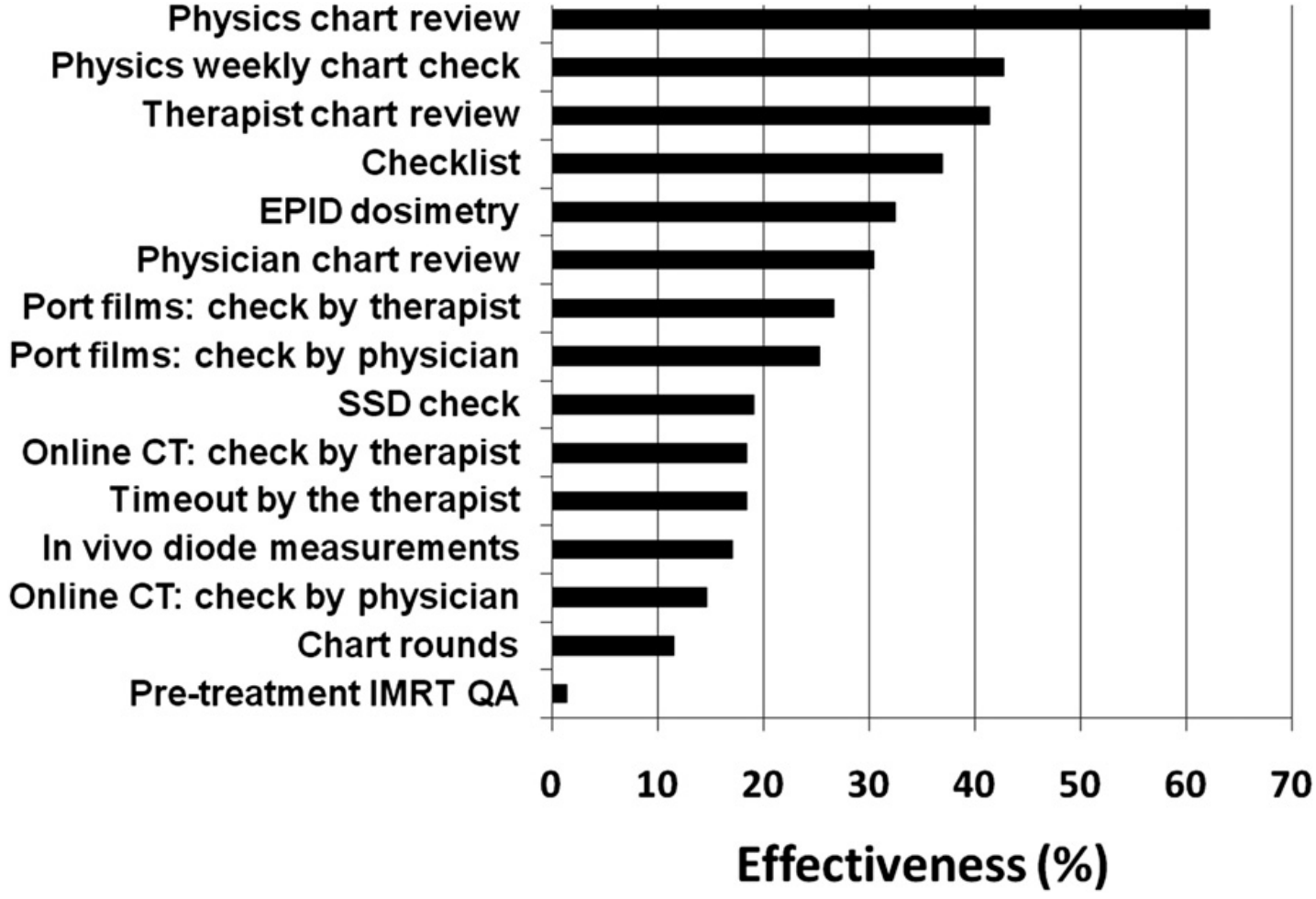


Fig. 2. Effectiveness of each individual quality control (QC) check for detecting the reported high severity incidents.

Ford et al, IJROBP 2012 84(3) e263-269

Which combination of QA tools are effective?

Table 3 Combinations of QC checks and associated error-detection effectiveness for high severity incidents

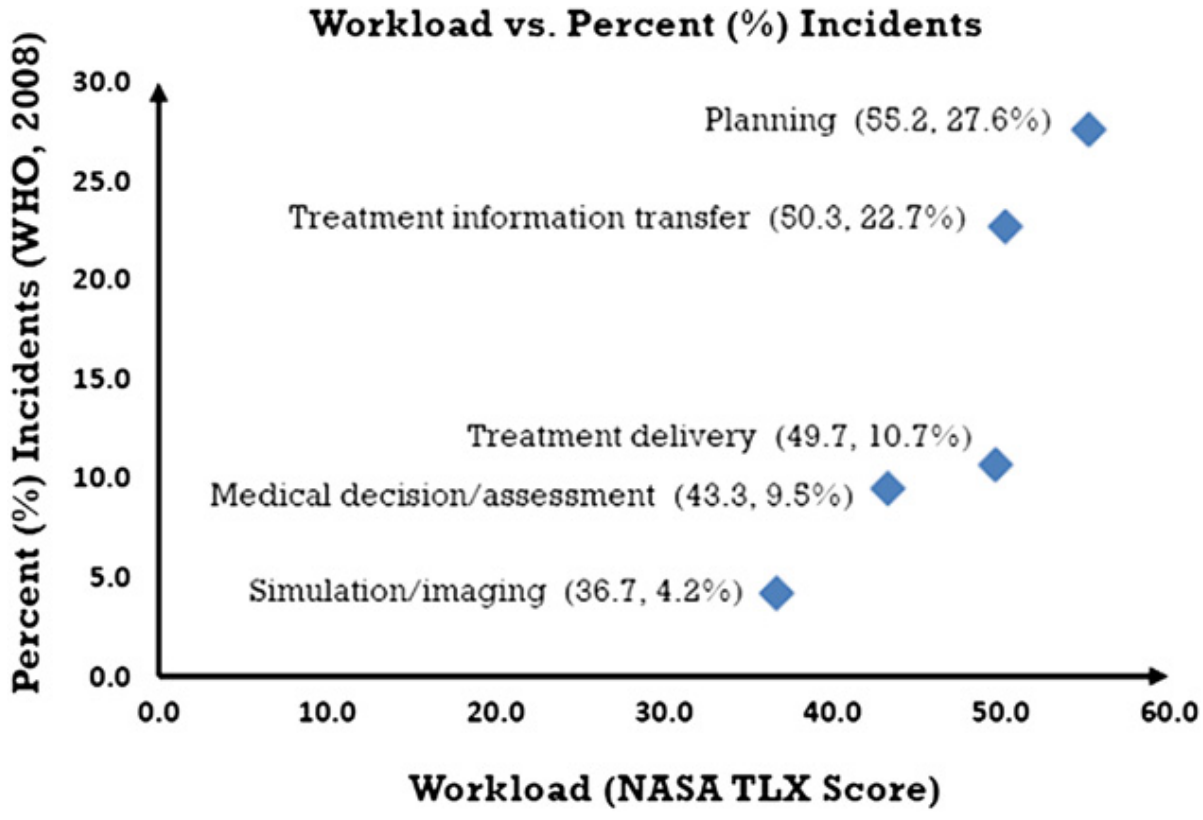
	No. of checks in combination							
	1	2	3	4	5	6	7	Common
1. Physician chart review				x	x	x	x	x
2. Physics chart review	x	x	x	x	x	x	x	x
3. Therapist chart review								
4. Pretreatment IMRT QA								x
5. Chart rounds								x
6. Timeout by therapist			x	x	x	x	x	
7. SSD check							o	
8. Port films: 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

Stress and workload



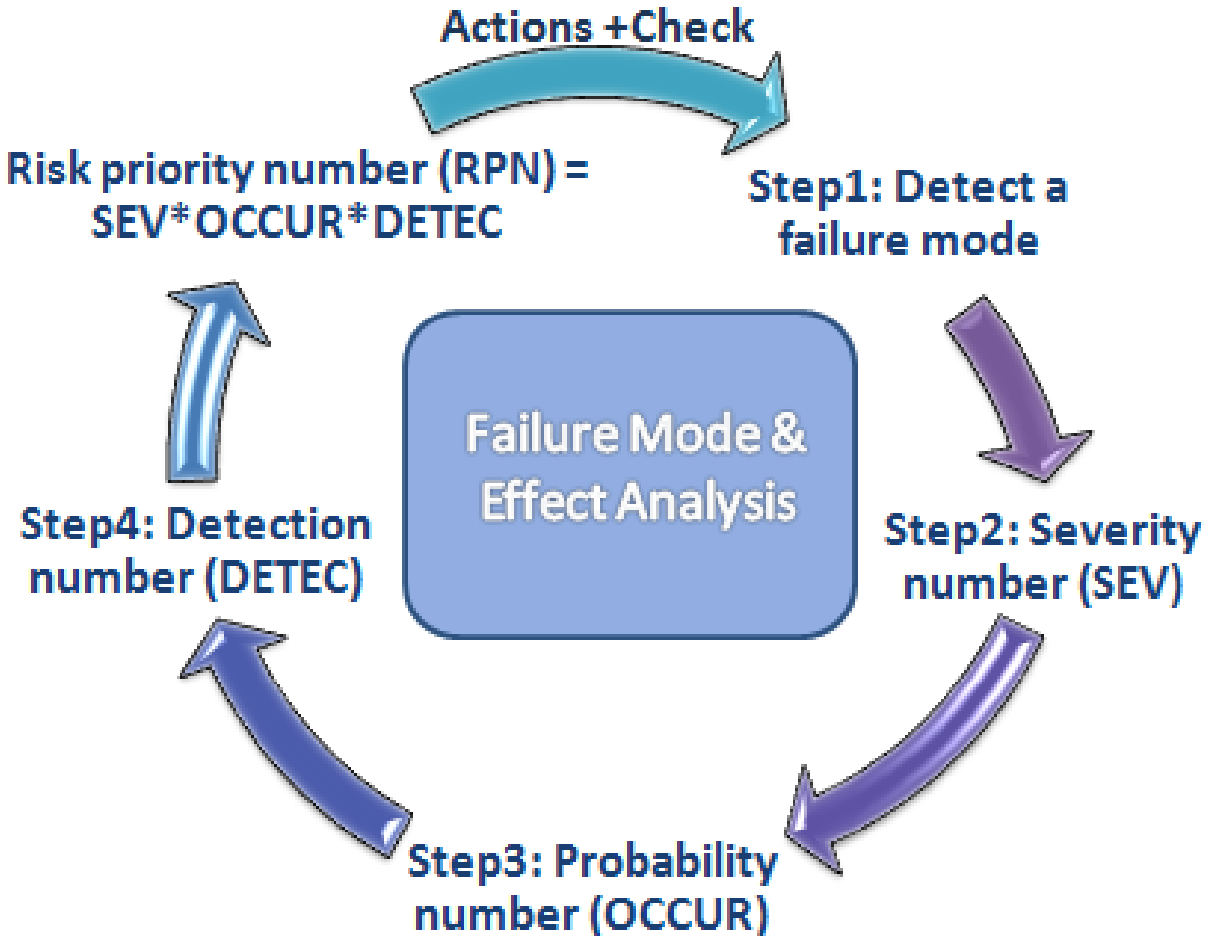
Quantitative Assessment of Workload and Stressors in Clinical Radiation Oncology

Mazur et al IJROBP 2012 83 (5) e571-576

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.

Failure Modes and Effects Analysis



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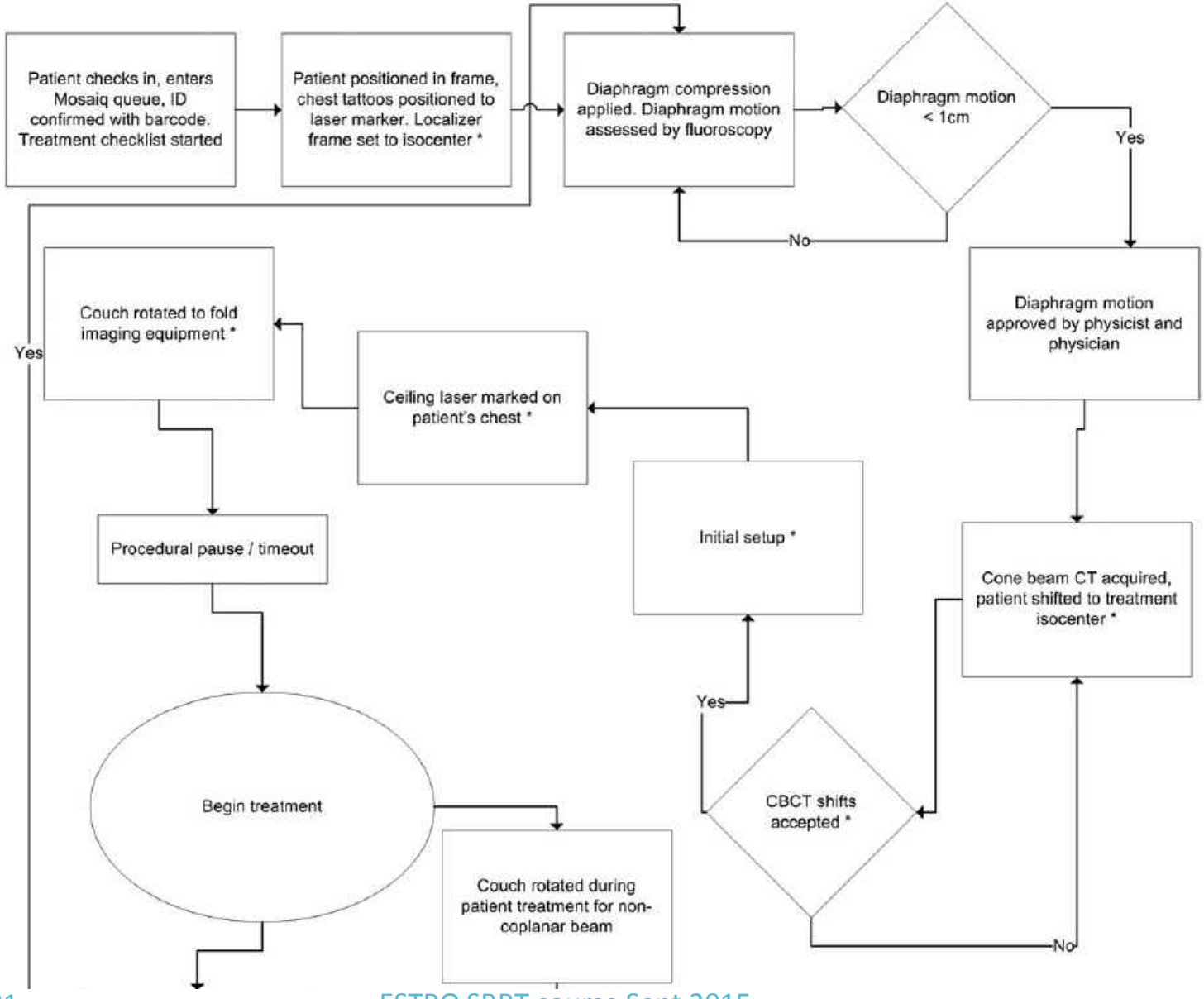
From flow charts



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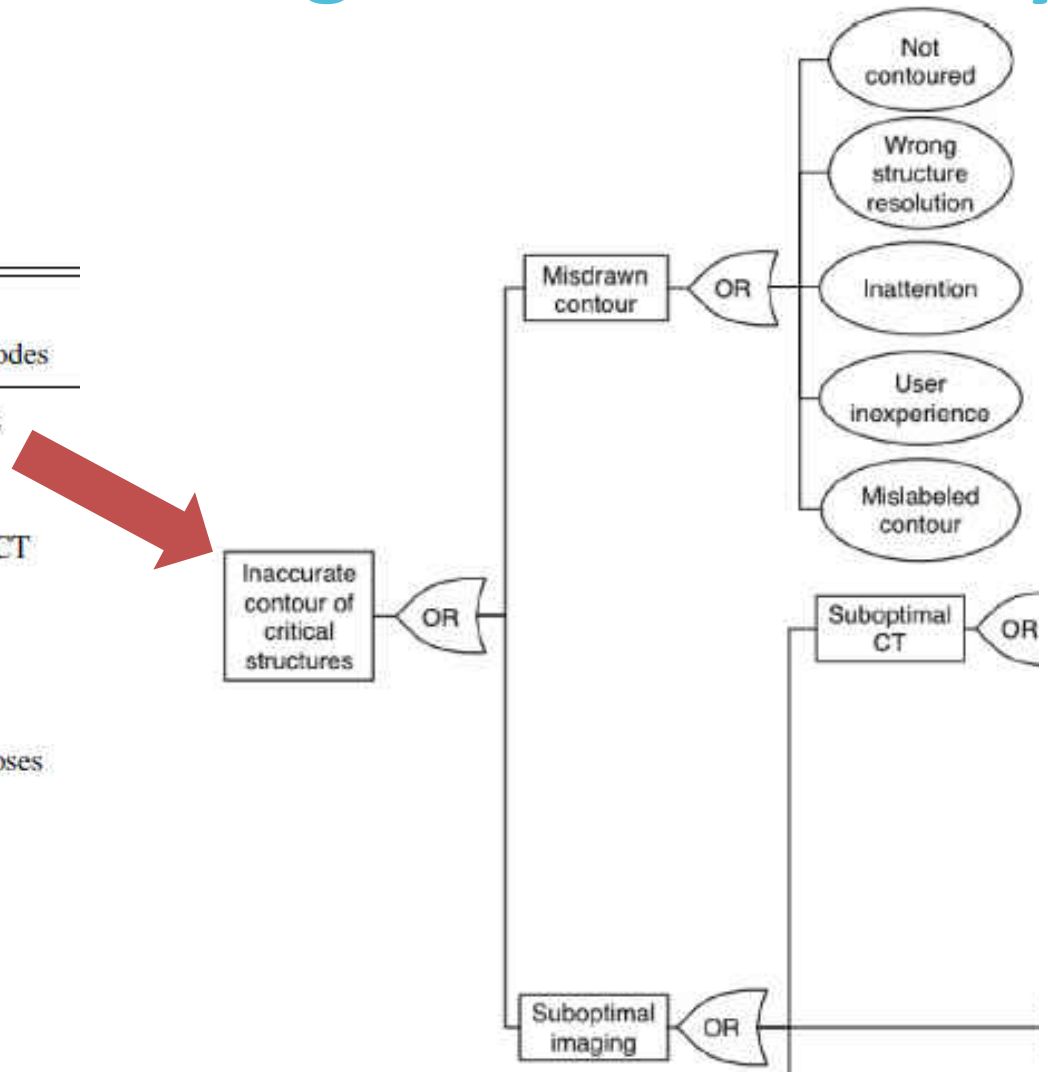
To failure modes using Fault Tree Analysis

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

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!!

Acknowledgements

Tommy Knoos, Lund University and Skåne University Hospital, Sweden

Julian Perk, University of California Davis Medical Center, Sacramento, CA, USA

Evidence-based practice of SBRT for stage I NSCLC:

Patient selection and outcomes

Professor Suresh Senan
VU University Medical Center


Disclosures

- Speakers honoraria from Varian Medical Systems.
- Department of Radiation Oncology at VUMC, Amsterdam has a research agreement with Varian Medical Systems.
- Faculty member of ESMO

Definition of SABR / SBRT

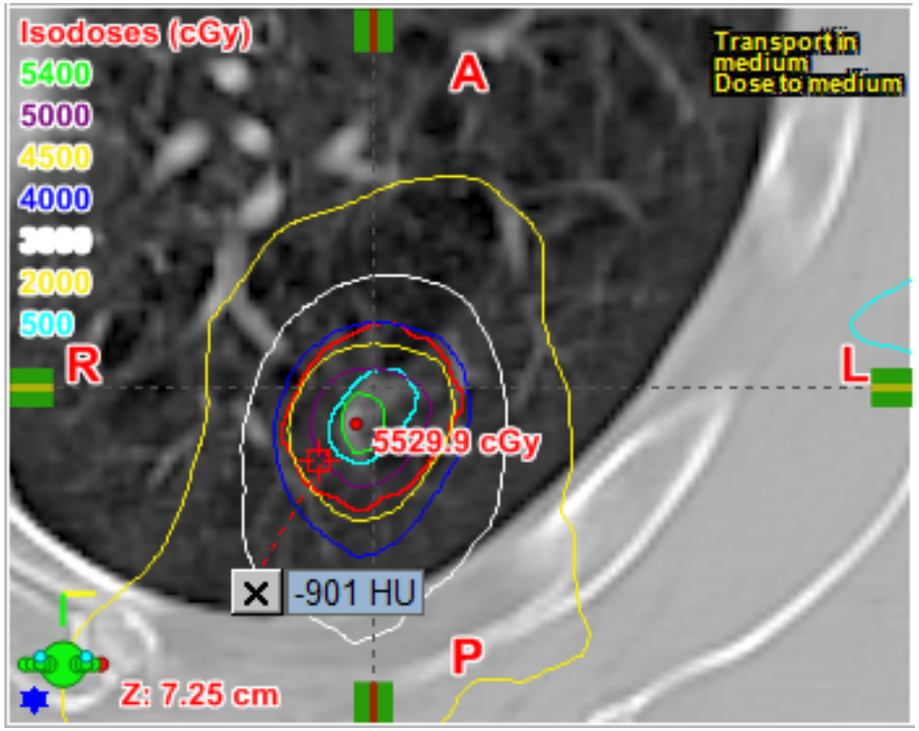
Senan, Guckenberger, Ricardi, IASLC Multidisciplinary Approach to Thoracic Oncology 2014

A technique for delivering external beam radiotherapy

(i) high degree of accuracy to an extra-cranial target,

(ii) using high doses of irradiation,

(iii) in 1-8 treatment fractions.



Overview of talk

- Multi-disciplinary tumor board (ESMO guidelines)
- SABR guidelines (technical)
- Patient selection (operable, pathology, PET –ve cases)
- Toxicity and local control (peripheral tumors)
- Controversies: central tumors, tumors <1 cm
- Follow up: Recurrence or fibrosis
- Second Primary Lung Cancer (SPLC)

Role of multi-disciplinary team

- Patient selection
- Additional staging (hilar nodes, review PET)
- Identifying high-risk cases (interstitial fibrosis)
- Complex cases (GGO, multple tumors)
- Suspicious post-SABR radiological changes
- Salvage therapies

Can you treat without a tissue diagnosis?

- “pre-treatment pathological diagnosis strongly recommended for all patients before any curative treatment for early stage NSCLC, unless a multidisciplinary tumour board (MDT) is of the opinion that the risk-benefit ratio of the procedure is unacceptable.

- Expert MDT’s may be best placed to assess the likelihood of benign disease in their own populations including, where available, algorithms that have been validated for the population in question [Herder G, Chest 2005]. In case of the latter, a likelihood of malignancy exceeding 85% may be preferred”.

ESMO Early stage NSCLC: consensus on diagnosis, treatment and follow-up [Vansteenkiste J, Ann Oncol 2014].

Treatment without a tissue diagnosis

Of 21,648 cases of stage I NSCLC in the Dutch Cancer Registry between 1997-2011, a pathological diagnosis was obtained in 90%.

(Louie AV, Damhuis R, et al, *submitted*)

Dutch surgical data from the FDG-PET era show a ≤6% likelihood of benign lesions in resected specimens

(Van Tinteren, H, Lancet 2002; Herder G, JCO 2006; Verstegen N, Ann Oncol 2013; van den Berg LL, JTO 2015)

SABR without a tissue diagnosis

VUmc

Stage I NSCLC results at VUMC

3 year endpoints	**Pathology proven** (n=209)	**Pathology –ve** (n=393)	
Overall survival	55.4%	54.4%	P = .93
Local control	**90.4%**	**91.5%**	**P = .92**
Regional control	90.3%	87.9%	P = .83
Distant control	79.6%	79.8%	P = .95
Disease free survival	**72.1%**	**73.2%**	**P = .98**

Calculated mean probability of malignancy [Herder G, CHEST 2005]	94.8% (95% CI 94.3-95.4%)	92.5% (95% CI 91.8-93.3%

Verstegen NE, 2011

Decision-making for SABR

Example: 8 mm spiculated lesion in the upper lobe in a 65 year old smoker without a history of malignancy

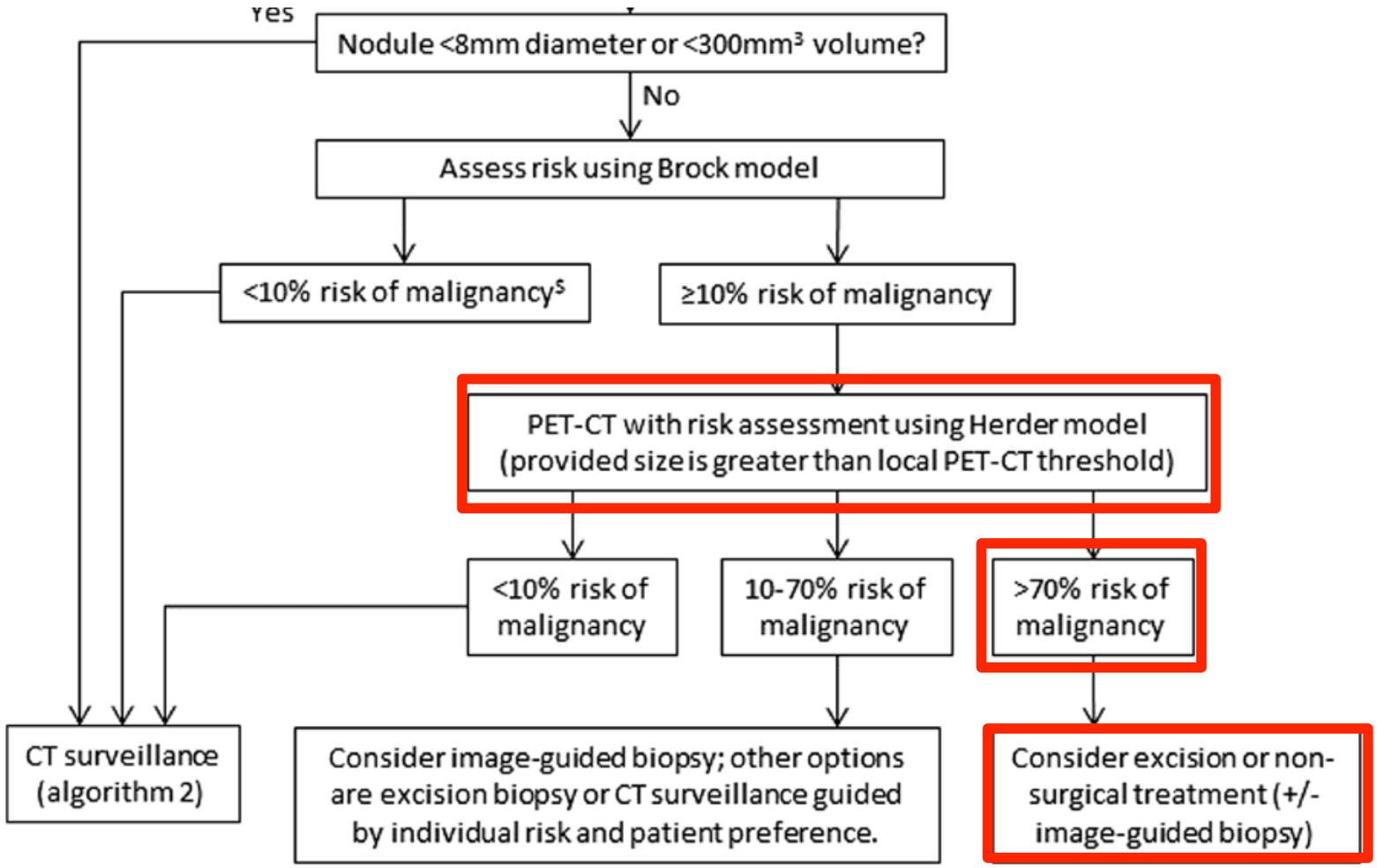
Algorithm [Swensen SJ, 1997; Gould MK, 2007]: 34-40% probability of malignancy

Even if lesion shows intense FDG uptake on a PET scan, the probability of malignancy would still be only 79%

Recommendation: Follow-up imaging to establish growth

Senan S, Lancet Oncol 2013

British Thoracic Society guidelines 2015



In an UK population, “use of a 70% threshold led to a small increase in risk of benign disease, but reduced chance of treatment delay”

Callister MEJ, Thorax 2015

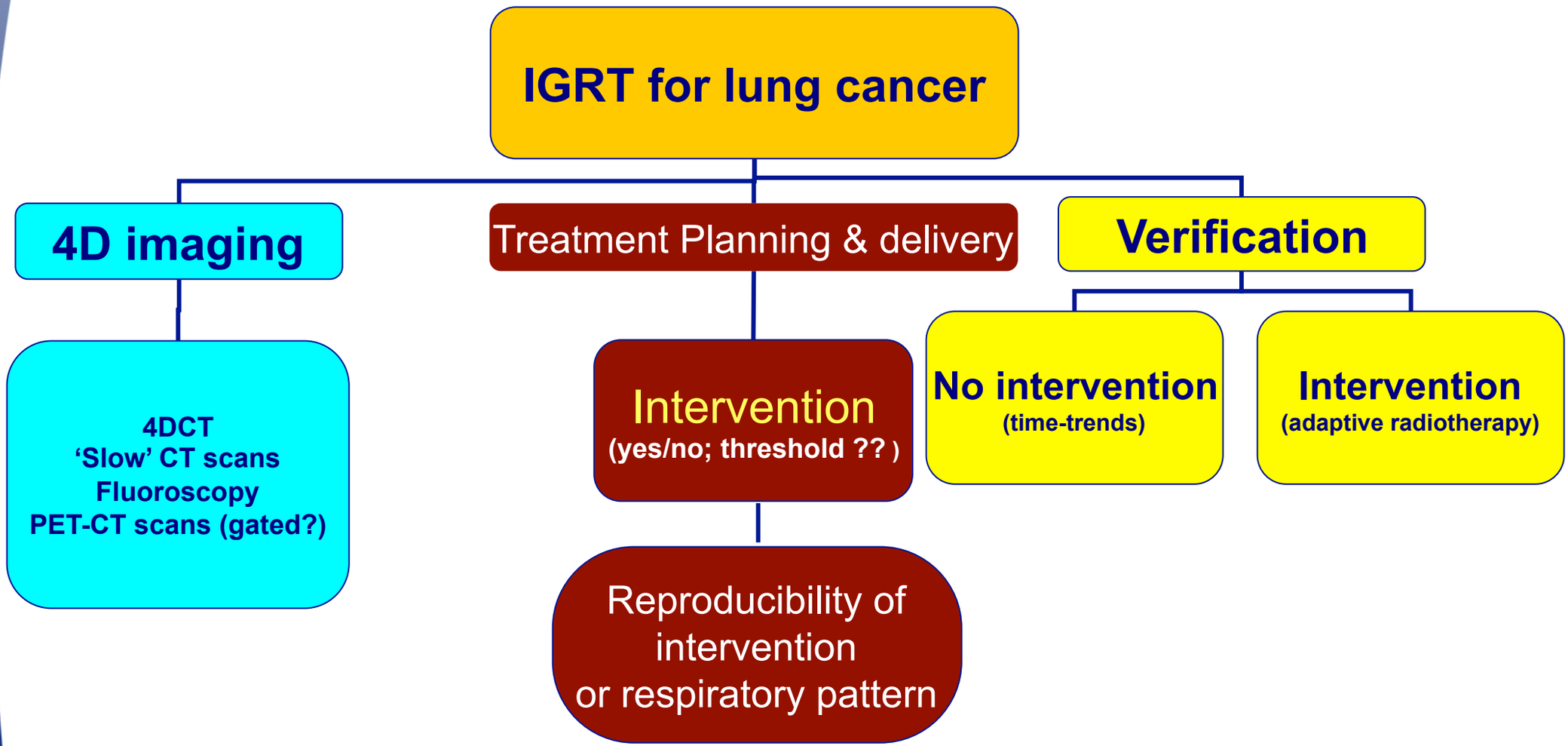
Radiotherapy Guidelines for SABR

- **ROSEL Guidelines [Hurkmans C, 2009]**

- **Guidelines by professional groups**:

- American Association of Physics in Medicine Task Group 101 [Benedict SH, 2010]
- ASTRO & American College of Radiology [Potters L, 2010]
- National Radiotherapy Implementation Group of the UK [Kirkbride P, 2012]
- Canadian Association of Radiation Oncology - Stereotactic Body Radiotherapy [Saghal A, 2012]
- Working group Stereotactic Radiotherapy of Germany Society of Radiation Oncology (DEGRO) [Guckenberger M, 2013]

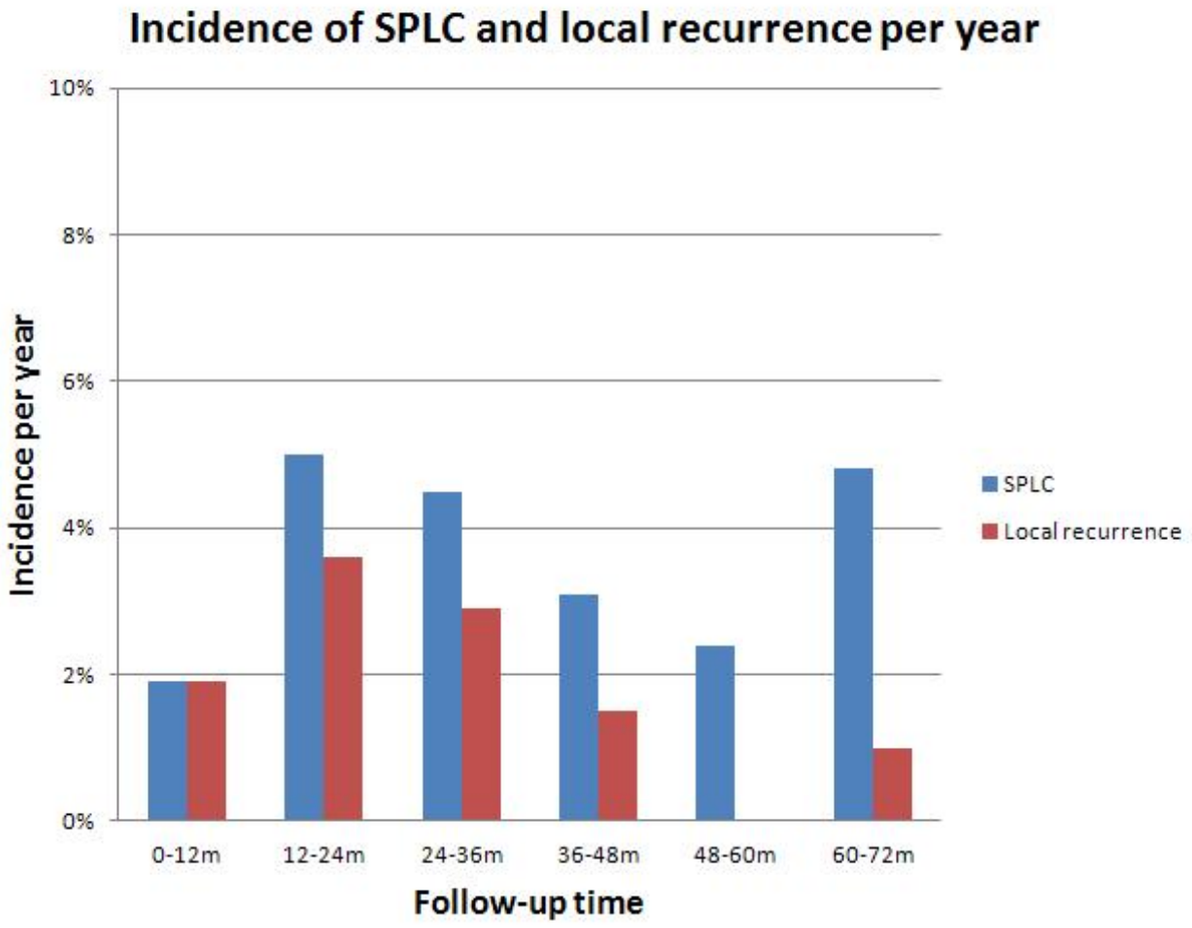
4D radiotherapy for lung cancer



Lagerwaard F, 2007

SABR without motion management

- **ITV-based** SABR in 855 patients (Median follow-up: 52 months)
- Actuarial local control rates at 3 and 5 years were 92.4% & 90.9%



Verstegen NE, JTO 2015

PET scans in target definition?

In 9 (of 10) lung tumors, the planned prescription isodose did not cover the 4D-PET/CT derived ITV

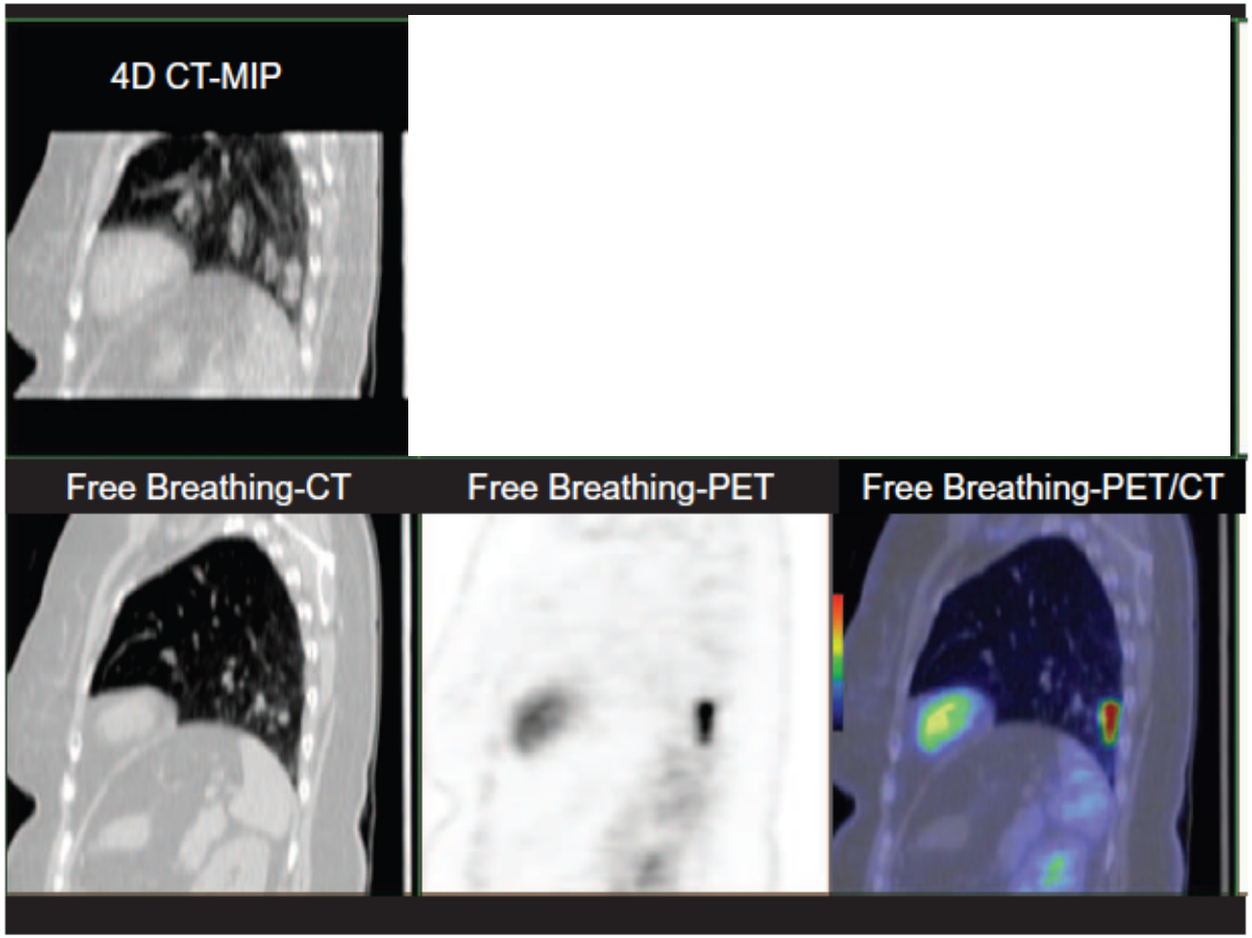


FIGURE 1. The 4D positron emission tomography (PET)/computed tomography (CT) acquisition (above) and 3D PET/CT acquisition (below) in a patient with a lower lobe tumor, demonstrating CT images (left), PET images (middle), and coregistered PET/CT images (right).

Siva S, JTO 2015

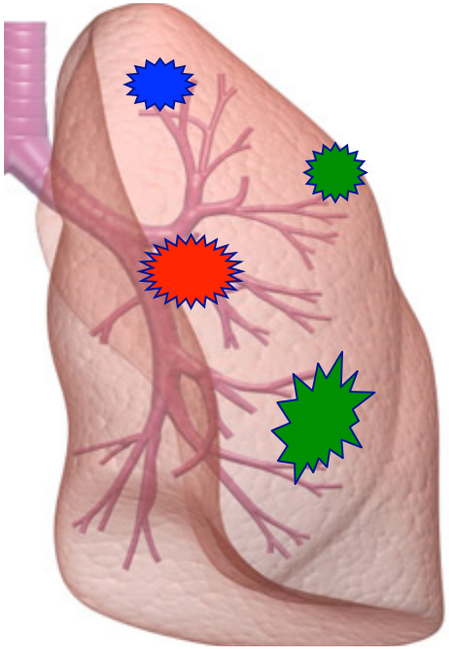
SABR for stage I NSCLC

Dose and **outcomes**

‘Risk-adapted’ SABR delivery

Fractionation** schemes used in Netherlands

** Prescribed to the encompassing isodose



- **3 fractions of 18Gy**: T1 lesions, not adjacent to chest wall
- **5 fractions of 11Gy**: T1 lesions with broad chest wall contact, and T2 lesions
- **8 fractions of 7.5Gy**: central lesions with limited overlap with mediastinum

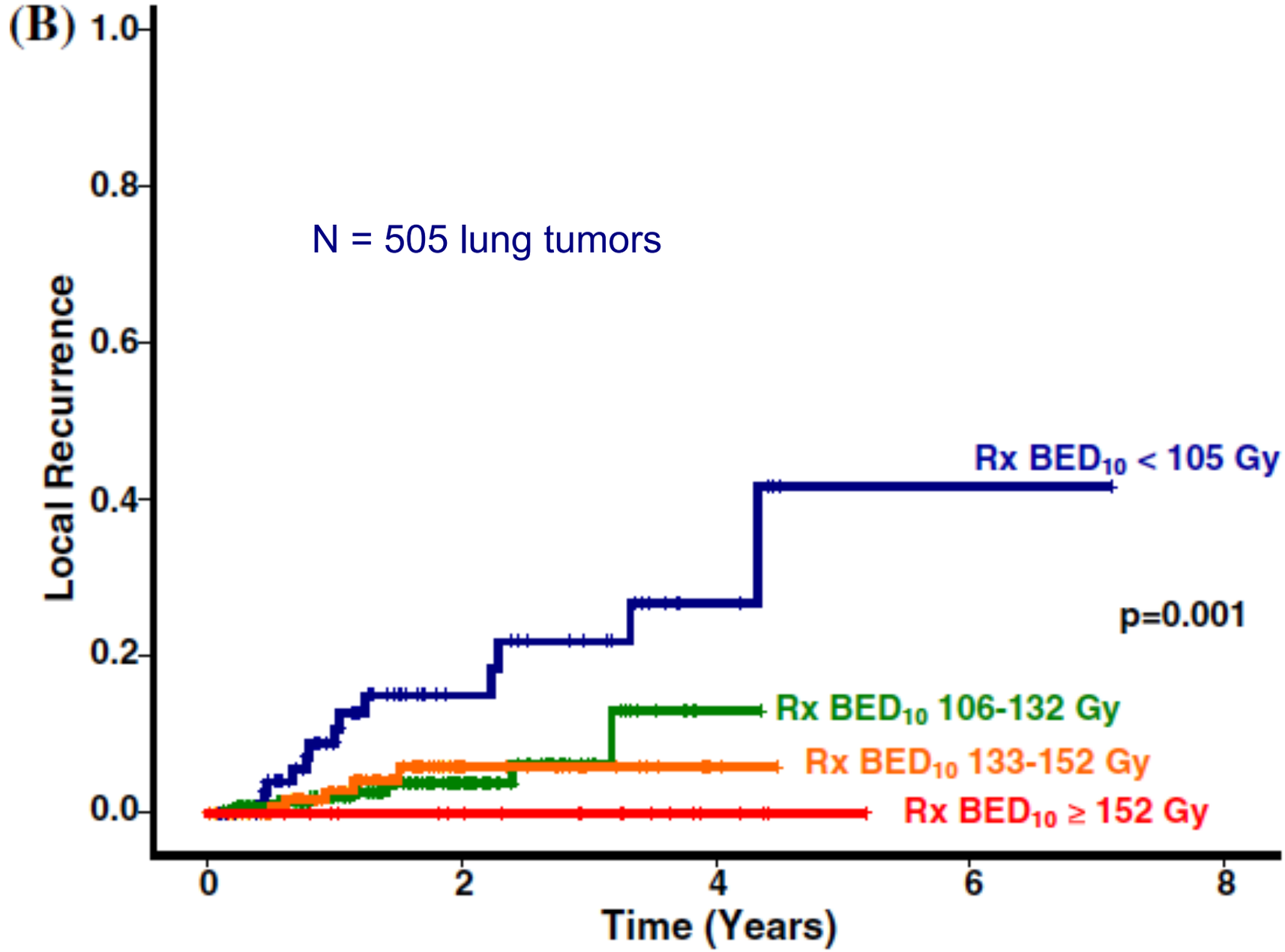
Louie AV, 2014

Achieving a BED_{10} ≥100 Gy

- Fractionation schedules which may, or may closely, achieve a BED_{10} ≥100 Gy and BED_3 ≤210 Gy:
  - 50 Gy in 5 fractions
  - 54 Gy in 6 fractions
  - 56 Gy in 7 fractions
  - 60 Gy in 8 fractions

Senthi S, Radioth Oncol 2013

Recommended BED_{10} >100 Gy



Kestin L, Radioth Oncol 2014

Results of SABR

Table 37.2. Overview of Results of Sterotactic Ablative Radiotherapy after Delivery of Radiation at More than 106 Gy Biologic Effective Dose

Author (Year)	No. of Patients	Patients with Histopathologic Confirmation of NSCLC (%)	Overall Survival at 2-3 Years (%)	Freedom from Local Progression at 2-3 Years (%)
Prospective Phase II Trials				
Nagata et al. (2005)[71]	45	100	75	98
Baumann et al. (2009)[72]	57	67	60	92
Fakiris et al. (2009)[73]	70	100	43	88
Ricardi et al. (2010)[74]	62	65	51	88
Bral et al. (2010)[75]	40	100	52	84
Timmerman et al. (2010)[76]	54	100	56	98
All prospective studies[a]	*328*	*87.6*	*55.1*	*91.2*
Large Retrospective Series				
Grills et al. (2010)[77]	434	64	60	94
Senthi et al. (2012)[78]	676	35	55	95
Guckenberger et al. (2013)[79]	514	85	46 62[b]	80 93[b]
All retrospective studies[a]	*1,624*	*58.8*	*53.5*	*90.0*

[a]The weighted average values are calculated for the summary of all prospective and retrospective studies.
[b]Subgroup of 164 patients treated with ≥106 Gy biologically effective dose.

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

Estimated 3-year OS was **95%** (95% CI 85-100) for SABR vs. **79%** (64-97) for surgery

3-year recurrence-free survival of **86%** (95% CI 74-100) in SABR group vs. **80%** (65-97) in surgery group (HR 0.69, 95% CI 0.21-2.29, log-rank *P*=0.54)

Chang J, Senan S, Lancet Oncol 2015

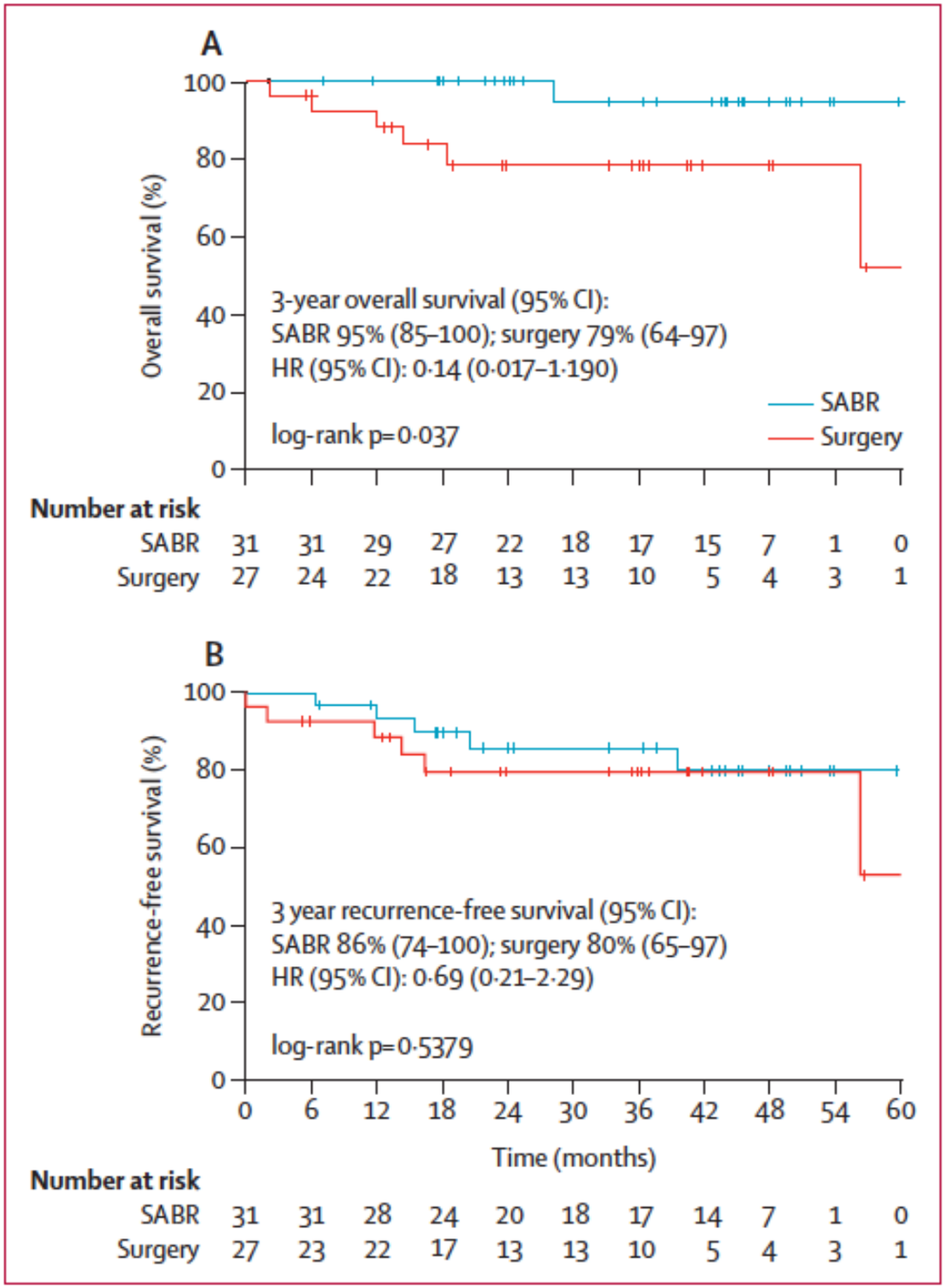


Figure 2: **Overall survival (A) and recurrence-free survival (B)**
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

ROSEL-STARS analysis: operable cases

- **Interpretation**: SABR could be an option for treating operable stage I NSCLC. Because of the small patient sample size and short follow-up, additional randomised studies comparing SABR with surgery in operable patients are warranted.

Chang JY, Senan S, et. al. Lancet Oncol 2015

SABR outcomes in operable patients

Table 1 Comparison of Chang *et al.* (1) data with SABR results for medically-operable patients with esNSCLC

Study	N	Eligible	Treatment	Age	Median follow-up (months)	Local or lobar failure	Regional failures	Distant failures	PFS	OS	Toxicity
Chang (1), Lobectomy Cohort Phase III	27	Operable T1-2a N0	Lobectomy	67	35.4	3-year 0%	3-year 4%	3-year 9%	3-year 80%	3-year 79%	Grade ≥3 (48%) 1 Grade 5
Chang (1), SABR Cohort Phase III	31	Operable T1-2a N0	54 Gy (3 fractions); 50 Gy (3 fractions); 60 Gy (3 fractions)	67	40.2	3-year 4%	3-year 10%	3-year 3%	3-year 86%	3-year 95%	Grade 3 (10%)
Timmerman (6), RTOG 0618 Phase II	26	Operable T1-2 N0	54 Gy (3 fractions)	72	25	2-year 20%	2-year 12%	2-year 15%	2-year 65%	2-year 84%	Grade 3 (16%)
Lagerwaard (7), Retrospective	177	Operable T1-T2 N0	60 Gy (risk-adapted to 3, 5, or 8 fractions)	76	31.5	3-year 7%	3-year 10%	3-year 10%	3-year 81%	3-year 85%	Grade ≥3 pneumonitis in 2% and rib fracture 3%
Onishi (8), Retrospective	87	Operable T1-2 N0	45-72.5 Gy at isocenter (3-10 fractions)	74	55	5-year 13%	5-year 15%	5-year 25%	NR	5-year 70%	Grade 3 (8.2%)

SABR, stereotactic ablative radiotherapy; esNSCLC, early stage non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; NR, not reported.

Rusthoven CG, Ann Transl Med 2015

Size of trials and their impact …..

VUmc

A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. Rosell R, NEJM 1994

60 pts

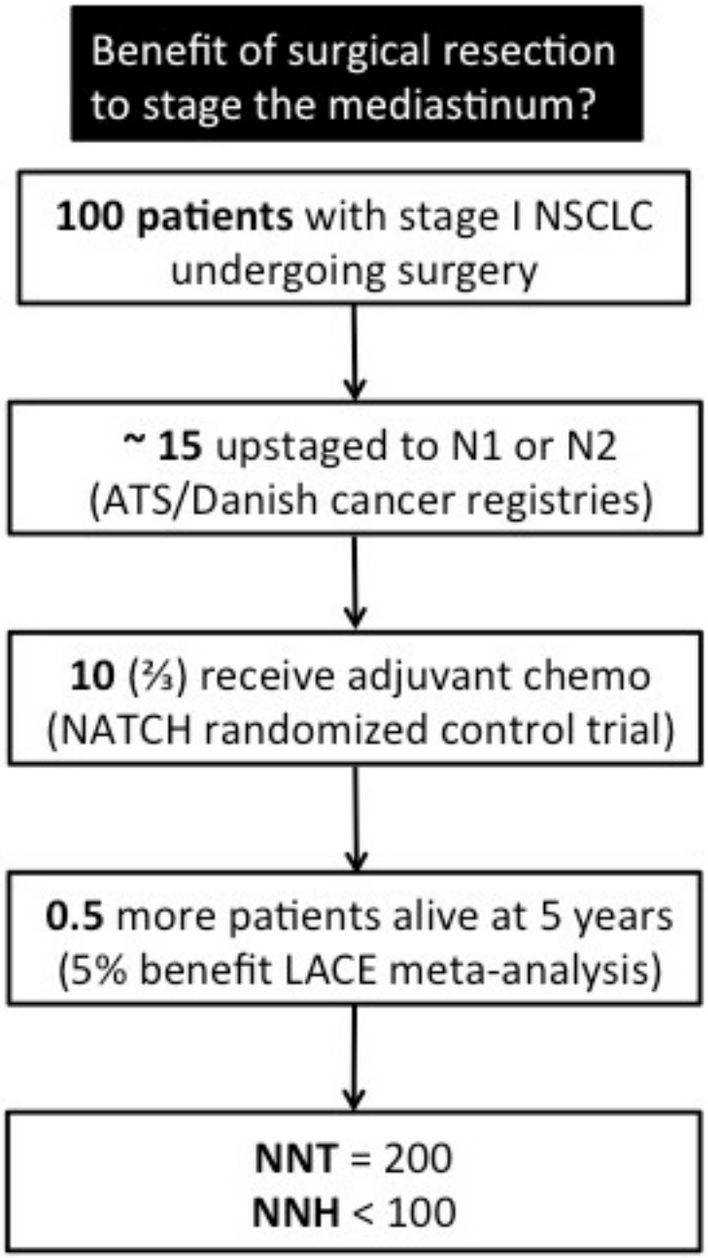
Median survival was 26 months in patients treated with chemotherapy plus surgery, as compared with 8 months after surgery alone

A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. Roth JA JNCI 1994

60 pts

Estimated 2- and 3-year survival rates were 60% and 56% for perioperative chemotherapy patients, and 25% and 15% after surgery alone, respectively.

Benefits of surgical nodal staging



NNT: Number needed to treat when considering surgery to guide decision-making for adjuvant chemotherapy for stage I NSCLC at 5 years.

NNH: Number needed to harm when considering a post-operative mortality rate of at least 1%, is 100 or less.

Louie AV, Radioth Oncol 2015

SABR and immunity

Kwilas AR, 2012

Low dose

SABR doses

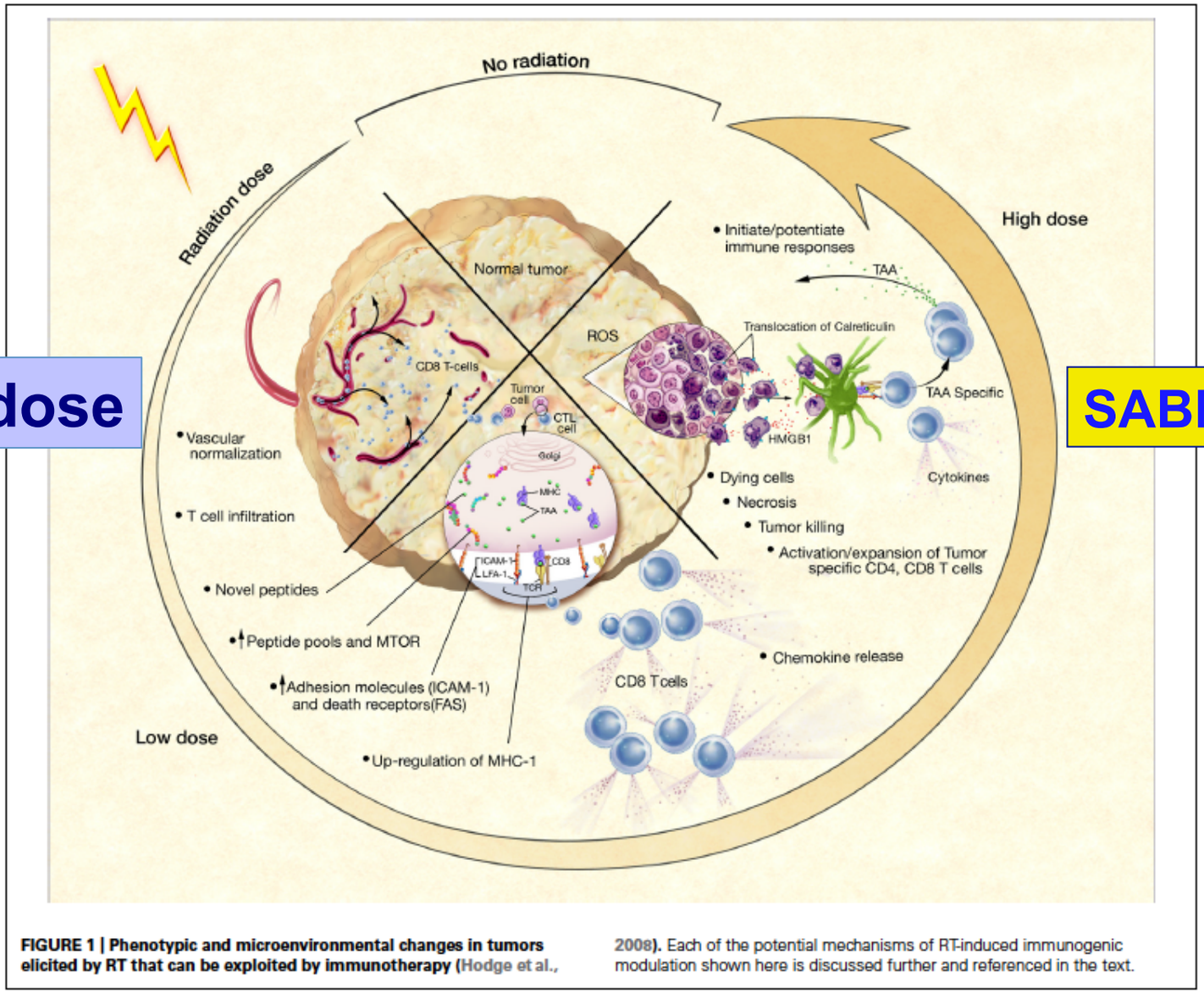


FIGURE 1 | Phenotypic and microenvironmental changes in tumors elicited by RT that can be exploited by immunotherapy (Hodge et al., 2008). Each of the potential mechanisms of RT-induced immunogenic modulation shown here is discussed further and referenced in the text.

Radiation Therapy to Convert the Tumor into an in situ Vaccine [Formenti SC, IJROBP 2012]

SABR for stage I NSCLC

toxicity

Dose constraints in SBRT trials

Table 1
Dose constraints used in major trials of SBRT

Organ	RTOG 0618 (3 Fractions)	Dutch ROSEL[a] Trial (3 Fractions)	Dutch ROSEL Trial (5 Fractions)	International STARS[b] Trial (4 Fractions)	JCOG 0403
Spinal cord	≤18 Gy	≤18 Gy	≤25 Gy	20 Gy ≤1 mL 15 Gy ≤10 mL	≤25 Gy
Esophagus	≤27 Gy	≤24 Gy	≤27 Gy	35 Gy ≤1 mL 30 Gy ≤10 mL	40 Gy ≤1 mL 35 Gy ≤10 mL
Lung	V20 ≤10%	V20 ≤5%–10%	V20 ≤5%–10%	V20 ≤20% V10 ≤30% V5 ≤50%	V15 ≤25% 40 Gy ≤100 mL MLD ≤18 mL
Brachial plexus	≤24 Gy	≤24 Gy	≤27 Gy	Point ≤40 Gy 35 Gy ≤1 mL 30 Gy ≤10 mL	Not limited
Heart	≤30 Gy	≤24 Gy	≤27 Gy	40 Gy ≤1 mL 35 Gy ≤10 mL	48 Gy ≤1 mL 40 Gy ≤10 mL
Trachea	≤30 Gy	≤30 Gy	≤32 Gy	35 Gy ≤1 mL 30 Gy ≤10 mL	40 Gy ≤10 mL
Bronchi	≤30 Gy	≤30 Gy	≤32 Gy	40 Gy ≤1 mL 35 Gy ≤10 mL	40 Gy ≤10 mL
Skin	≤24 Gy	Not limited	Not limited	40 Gy ≤1 mL 35 Gy ≤10 mL	Not limited

Doses represent limits at any point in the organ at risk unless otherwise specified.
Abbreviations: JCOG, Japanese Clinical Oncology Group; MLD, Mean Lung Dose.
[a] Randomized clinical trial of surgery versus radiosurgery in patients with stage IA NSCLC who are fit to undergo primary resection.
[b] Randomized study of lobectomy versus CyberKnife (Accuray, Sunnyvale, CA, USA) for operable lung cancer.

Shervani S, Thorac Surg Clin 2013

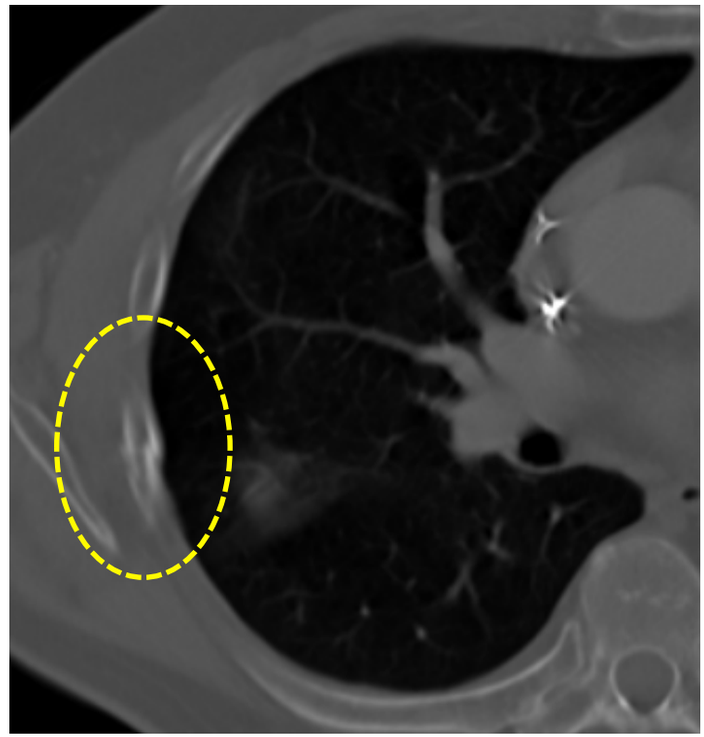
Normal tissue constraints (VUmc)

OARs	Point D_{max} for 8x7.5Gy	Total $EQD_{2,LQ}$
Esophagus (α/β = 3)	40Gy	64Gy
Heart (α/β = 3)	44Gy, no dose limits if PTV is adjacent	74.8Gy
Trachea/PBT (α/β = 3)	44Gy, no dose limits if PTV is adjacent	74.8Gy
Great vessels (α/β = 3)	No dose limits	N.A.
Spinal cord (α/β = 2)	28Gy	38.5Gy

Dose compromises to PTV were only allowed when exceeding the point D_{max} for the esophagus or spinal cord

SABR toxicity: chest wall

- 500 patients with T1-2N0 tumors (2003-2009)
- Median follow-up 33 months (13-86 months)
- Severe chest wall toxicity uncommon
  - severe pain in 2.2%,
  - rib fractures in 2.7%



Bongers E, JTO 2011

Chest-wall toxicity: Fractures

Rib fracture in **17%** (50/289) but only 44% (n=22) were symptomatic
Median follow-up 21.0 months (6.2–52.1); median time to fracture 16.4 months

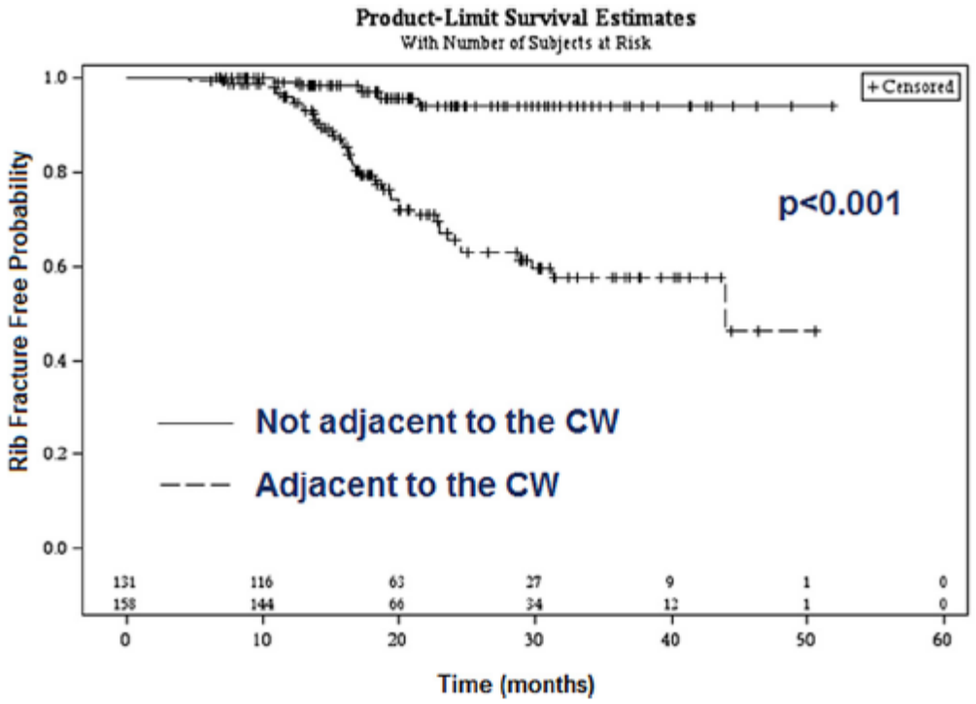


Fig 1. Incidence of rib fracture after lung stereotactic ablative radiotherapy in 158 tumours adjacent to the chest wall versus 131 tumours not adjacent to the chest wall ($P < 0.001$).

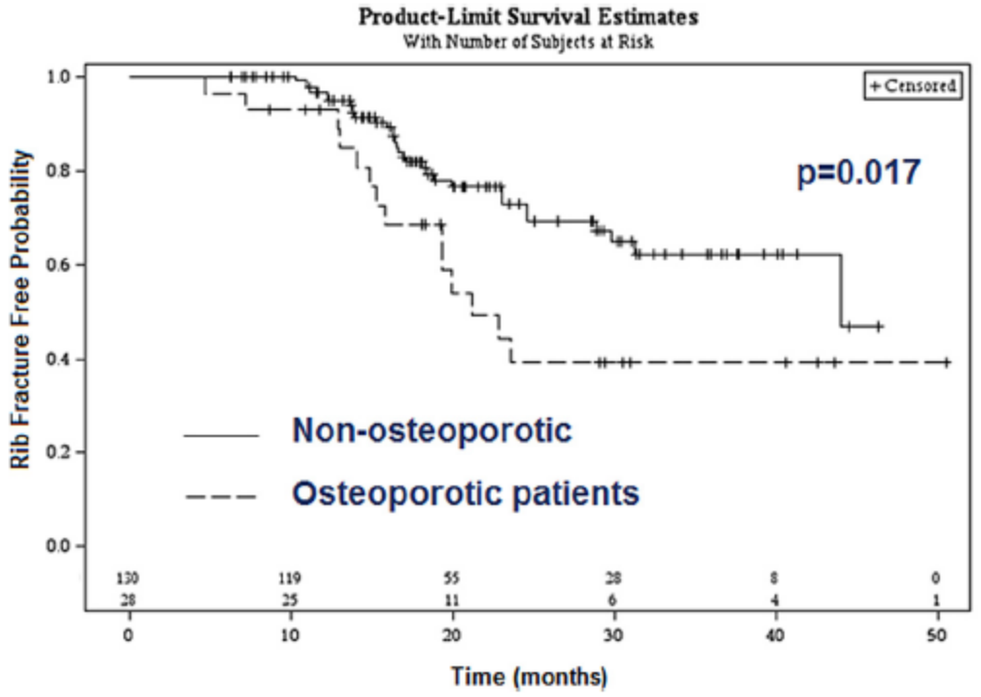


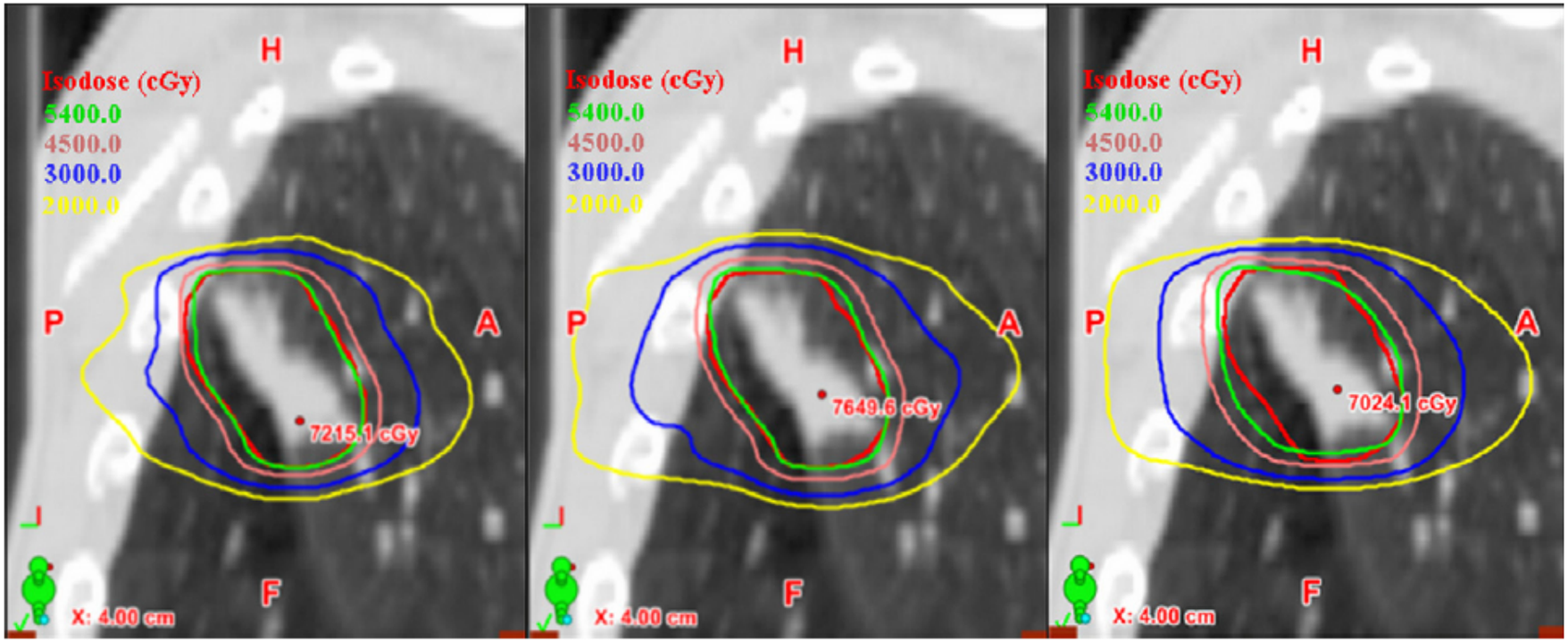
Fig 2. Incidence of rib fracture after stereotactic ablative radiotherapy in 158 tumours adjacent to the chest wall for osteoporotic versus non-osteoporotic patients.

Thibault I, Clin Oncol 2015

SABR: Limiting chest wall doses

EORTC recommendations [De Ruysscher D, JCO 2010]:
Chest wall doses are preferably <30 Gy in 3-5 fractions, to a volume of <30 mL.

RapidArc™ | 10 beam conformal | Dynamic conformal arc



—— 30 Gy isodose

Ong CL, Radioth Oncol 2010

SABR and radiation pneumonitis

VUmc

Japanese multi-institution analysis
Radiation pneumonitis ≥Grade 3 (CTCAE V3.0)

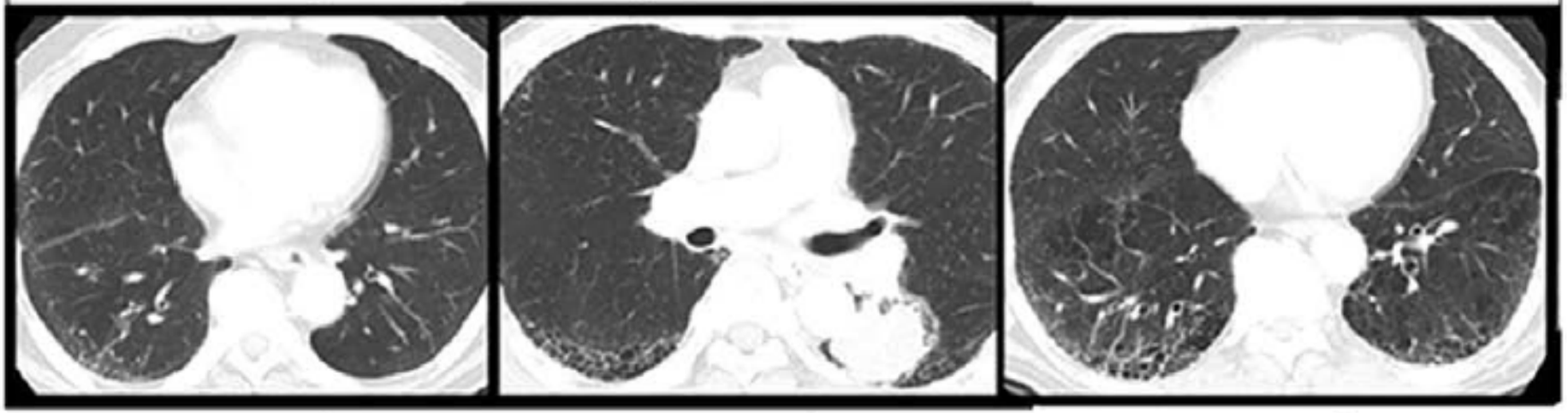
subgroup		Grade 3,4,5	Grade 5
All patients (n= 2278 pts)		3.3%	0.6%
Operable patients (n= 683 pts)		1.9%	0.4%
Pulmonary emphysema (+) (n= 449 pts)		4.4%	1.1%
Pulmonary fibrosis (+) (n= 243 pts)		11.9%	5.9%

No pathological diagnosis: 606 pts

Onishi H, Proc ASTRO 2013

Pulmonary fibrosis score

score	Pulmonary Fibrosis Score (PFS)
0	No fibrosis
1	Interlobular septal thickening; no descrete honeycombing
2	Honeycombing (with or without septal thickening) involving <25% of the lobe
3	Honeycombing involving 25 - 49% of the lobe
4	Honeycombing involving 50 - 75% of the lobe
5	Honeycombing involving > 75% of the lobe



score 1 score 2 score 3

Tsujino K, JTO 2014

Eur Radiol
DOI 10.1007/s00330-015-3617-3

CHEST

Prevalence and progression of combined pulmonary fibrosis and emphysema in asymptomatic smokers: A case-control study

Kum Ju Chae · Gong Yong Jin · Young Min Han · Yong Seek Kim · Su Bin Chon · Young Sun Lee · Keun Sang Kwon · Hye Mi Choi · David Lynch

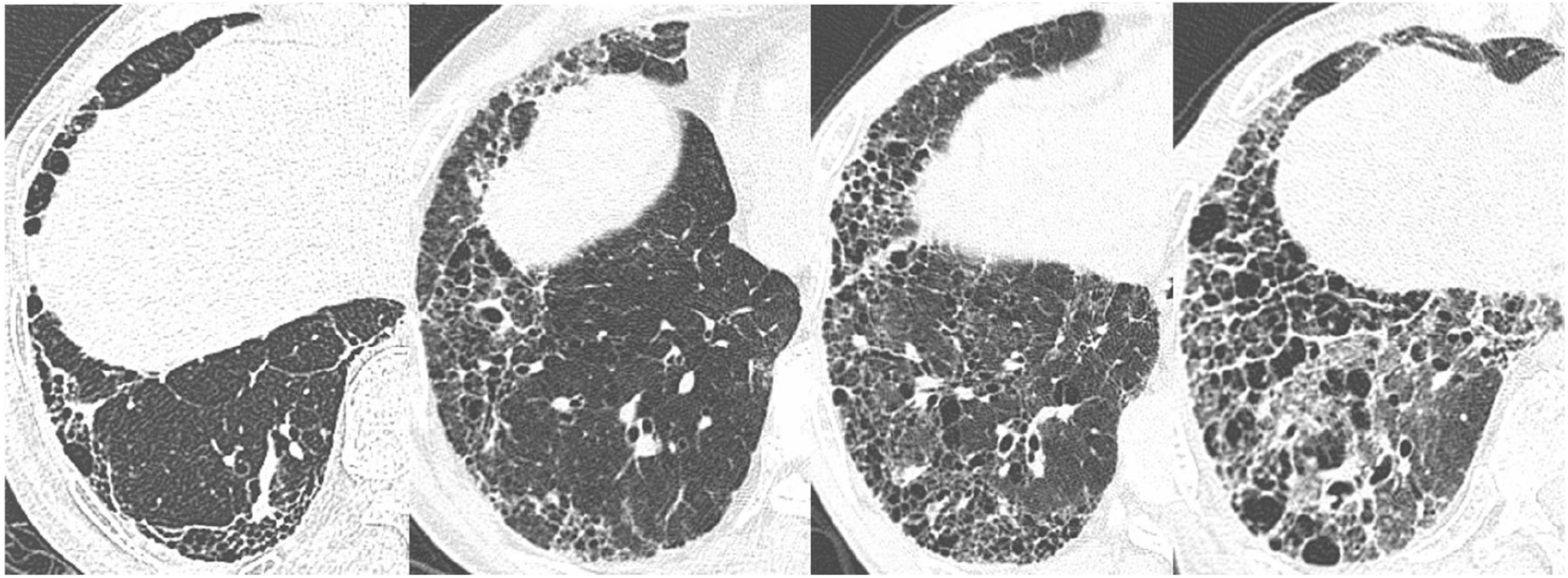


Fig. 1 CT images of standard reference cases of honeycombing. Extent of honeycombing in lower lobes scored as 1 (mild, 1–25 %), 2 (moderate, 26–50 %), 3 (marked, 51–75 %), or 4 (severe, > 75 %)

SABR & pulmonary interstitial changes

- 260 consecutive SABR cases with primary lung cancer
- Pre-treatment pulmonary interstitial fibrosis (PIF) group (n=18); non-PIF group (n=242)
- Grade ≥2 radiation pneumonitis in 9 (**50.0%**) of PIF group versus 14 (**6.7%**) in non-PIF group
- 3 patients with grade 5 RP were all in PIF group.

CONCLUSION:

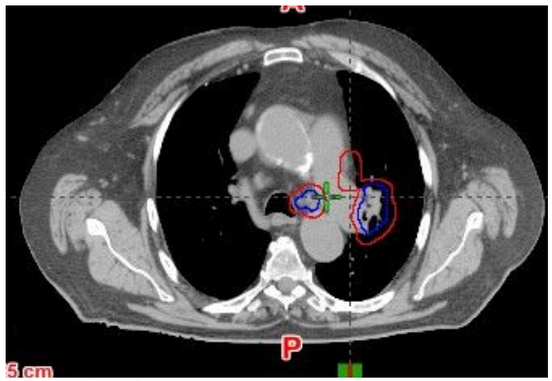
On multivariate analysis, the presence of PIF was the only significant predictive factor of ≥grade 2 pneumonitis

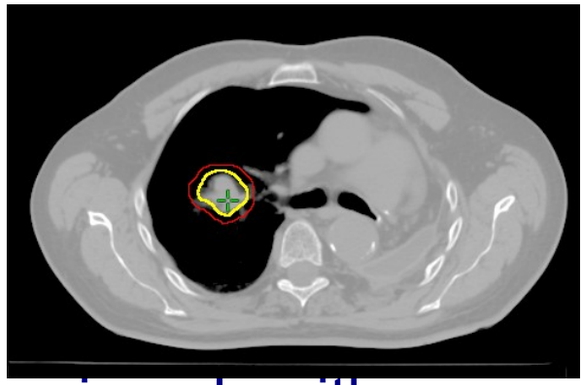
Yoshitake T, Anticancer Res 2015

Risks of Grade 3 radiation pneumonitis

Aim: Identify dosimetric predictors for pneumonitis (RP)

- 79 patients at high-risk of RP (2008-2011)
  - PTV > 100cc 70 pts
  - Previous pneumectomy / bi-lobectomy 13 pts (10 / 3)
- Reasons for ineligiblity for standard treatment options
  - Co-morbidity 84.3%
  - Patients refusal 15.7%



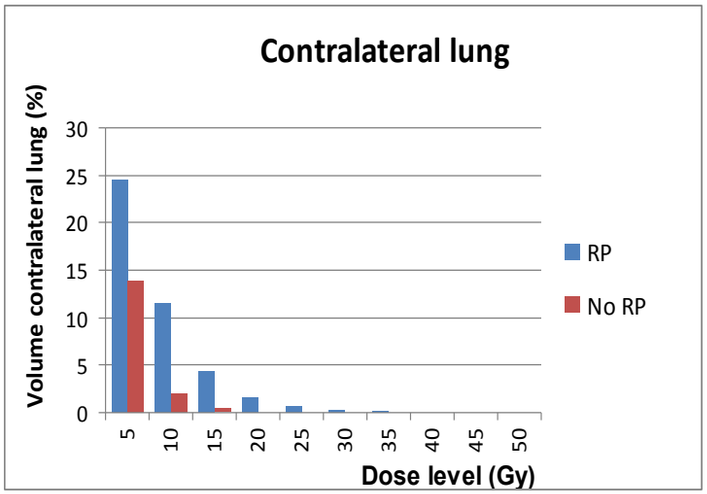


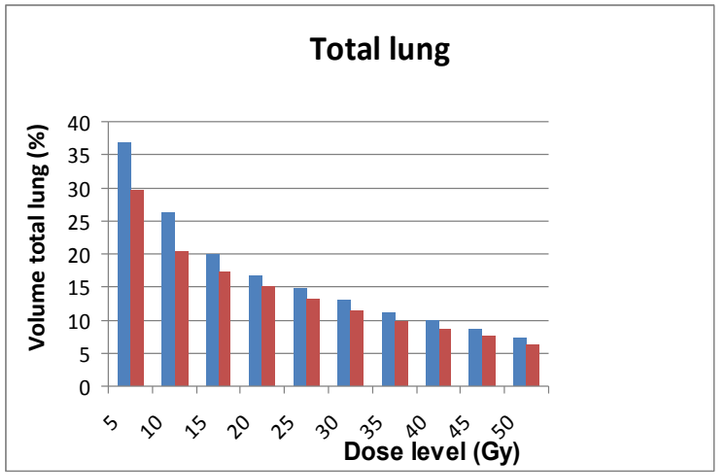
- Use of RapidArc and AAA planning algorithm

Bongers E, Radioth Oncol 2013

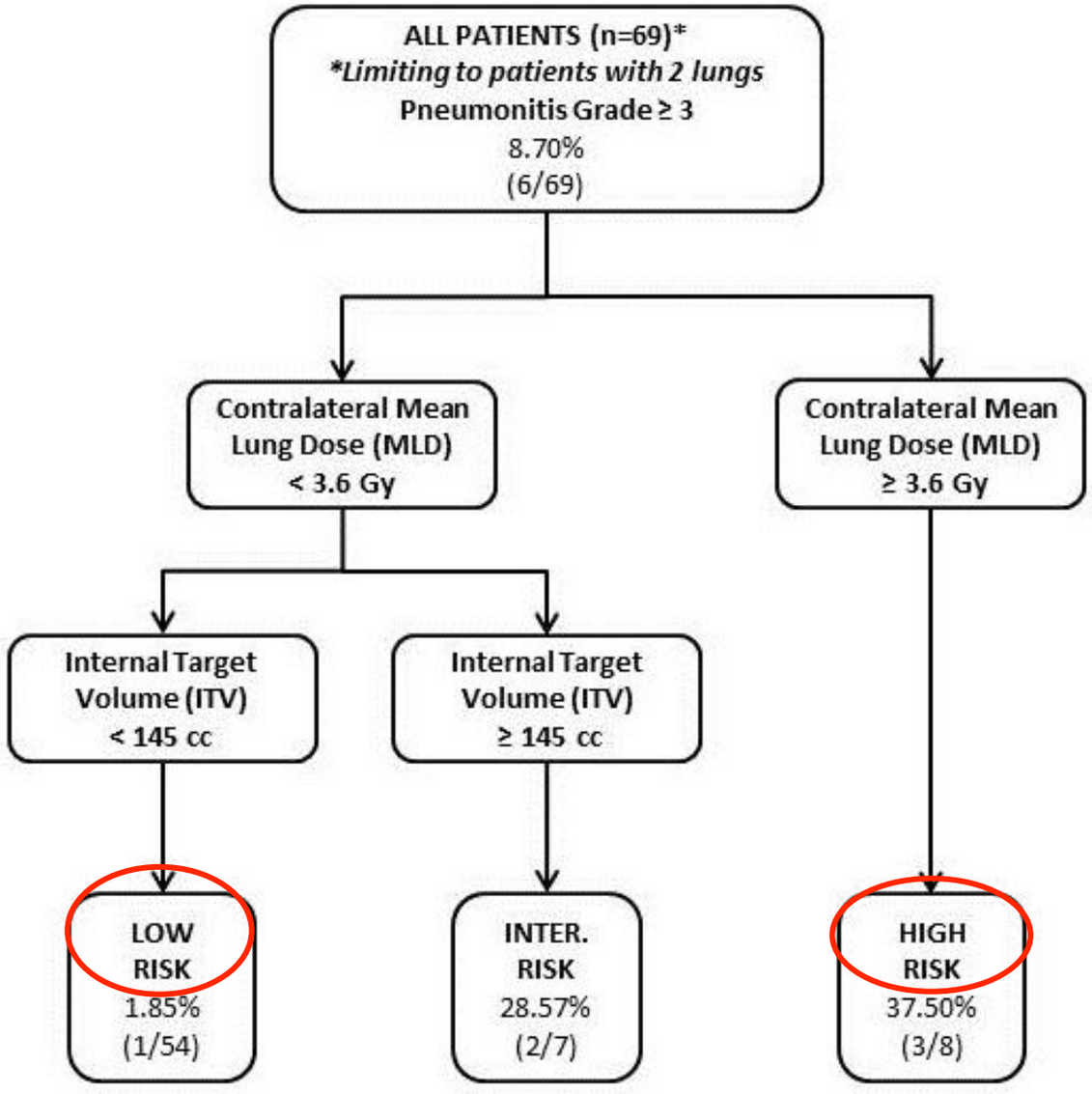
SABR: predictors of G3 radiation pneumonitis

79 consecutive patients treated with either a PTV >100 cm^3 (n=69) or previous pneumonectomy or bi-lobectomy (n=13).





Recursive Partitioning Analysis



Bongers E, Radioth Oncol 2013

Gold 'seed' versus platinum embolization coils

- 270 markers (129 seeds, 141 coils) implanted percutaneously under CT-guidance in 54 consecutive patients

- Retention directly after implantation: 99.3% of coils versus 85% of seeds ($p < 0.0001$)

- Pneumothorax, and pneumothorax requiring chest tube: less frequent with **coils** (23% and 3%, respectively) versus **seeds** (54% and 29%, respectively; $p = 0.02$ and 0.01).

Hong JC, 2011

Reply by authors of RFA paper

de Baere T, Ann Oncol 2015

Concerning SABR, it has been reported that placement of fiducial needed for SABR have resulted in 33.3 % pneumothoraces (Major : 13.3% ; Minor : 20%) with 30.5% of small peri- tumoral alveolar hemorrhage, and 2.9% of major bleeding in 105 patients with tumors to the lung [5], which makes SBRT invasiveness close to the one of RFA.

Ref 5. Trumm CG, J Vasc Interv Radiol 2014

Population-based use of trans-thoracic needle biopsies (TTNB)

- Approximately 80 000 cancer patients underwent a TTNB
- After outpatient TTNB, 12% developed a pneumothorax, of which 2.3 % were hospitalized

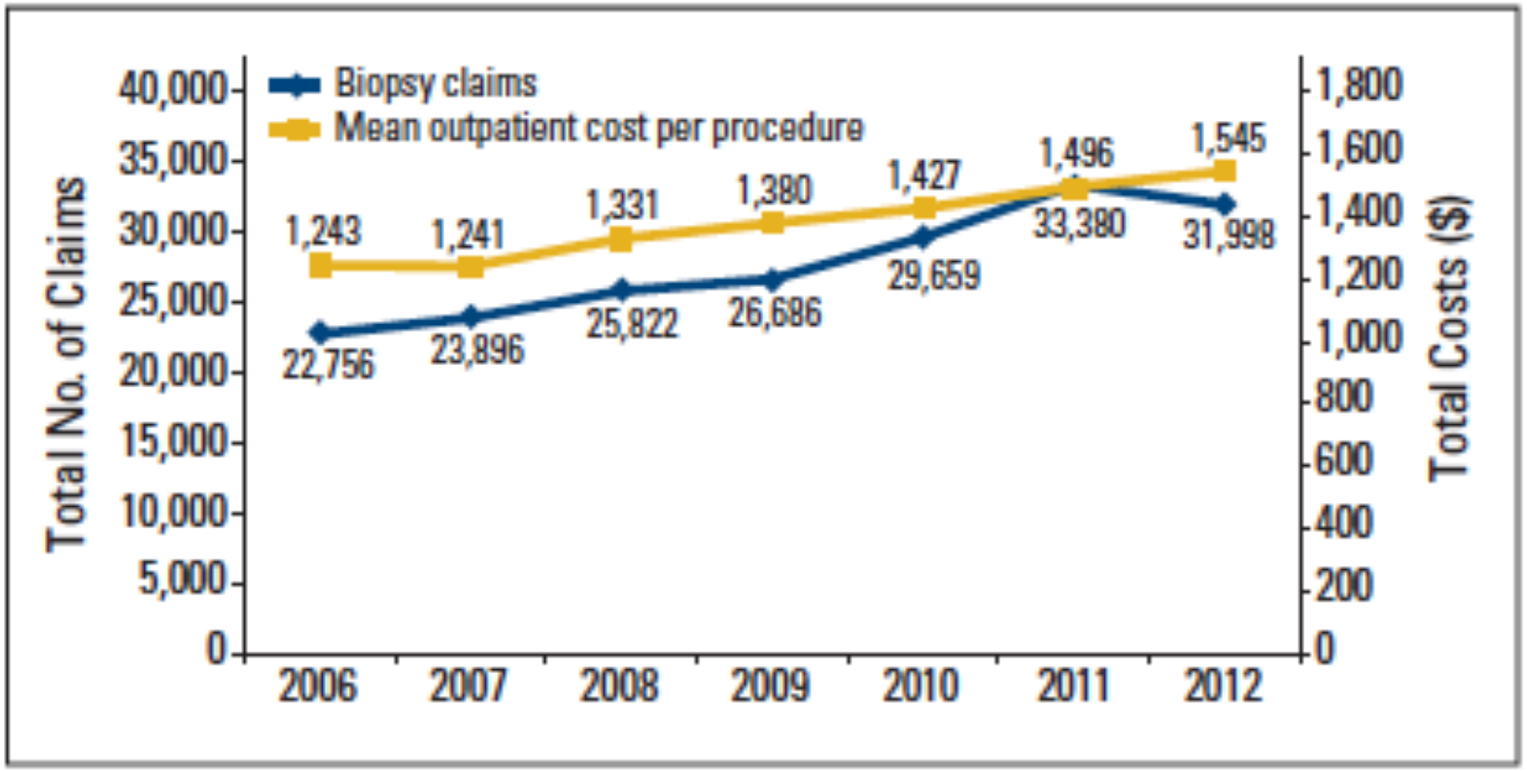


Figure 2. Trends in use and cost of image-guided transthoracic needle biopsy in patients with cancer from 2006 to 2012.

Accordino MK, JOP 2015

Overview of talk

- Multi-disciplinary tumor board (ESMO guidelines)
- SABR guidelines (technical)
- Patient selection (operable, pathology, PET –ve cases)
- Toxicity and local control (peripheral tumors)
- Controversies: central tumors, tumors <1 cm
- Follow up: Recurrence or fibrosis
- Second Primary Lung Cancer (SPLC)

SABR for central tumors

VUmc

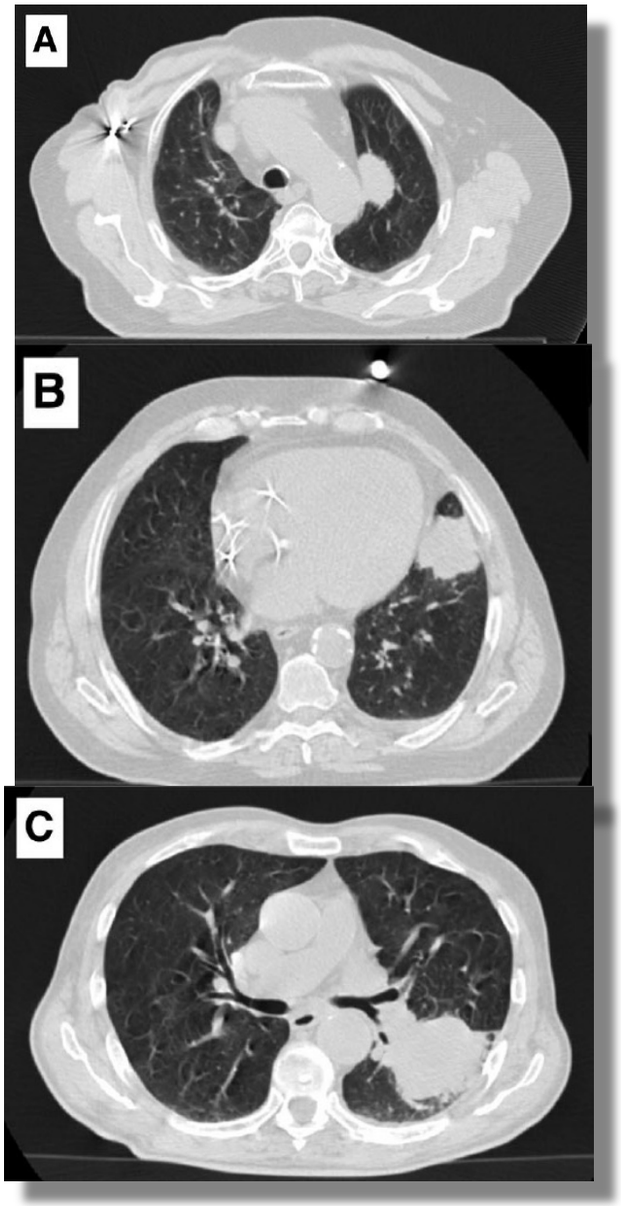
Systematic review of SABR for central tumors

20 publications: 563 central lung tumours (315 were early-stage NSCLC)

Local control rates **≥85%** when prescribed dose (BED_{10}) was **≥100 Gy**.

Treatment-related mortality **2.7%** overall versus **1.0%** when normal tissue dose (BED_3) was ≤210 Gy

Grades 3-4 toxicities appear commoner following SABR for central tumours, but occurred in less than **9%** of patients.



Senthi S, Radioth Oncol 2013

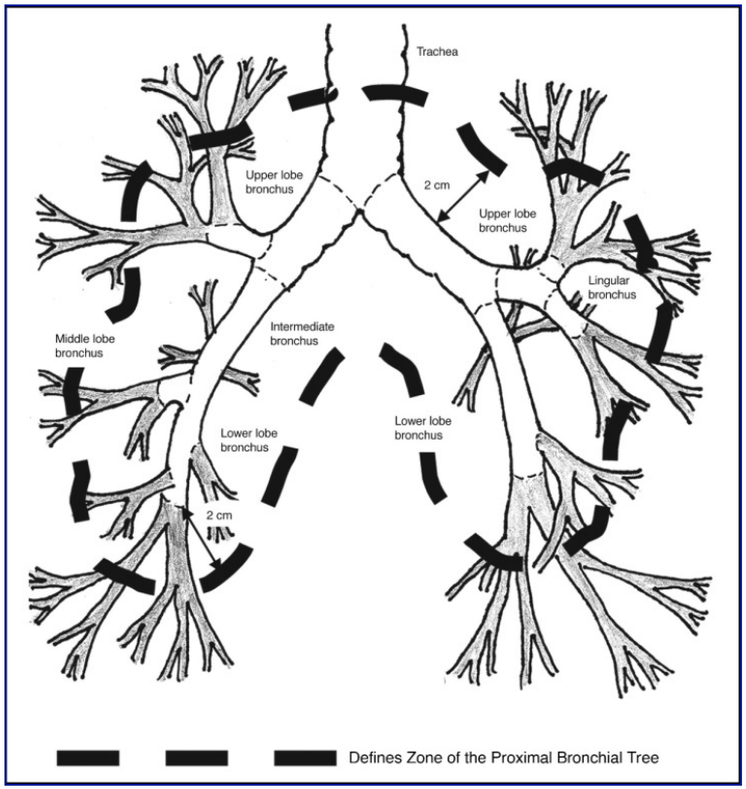
Central tumors: newer data

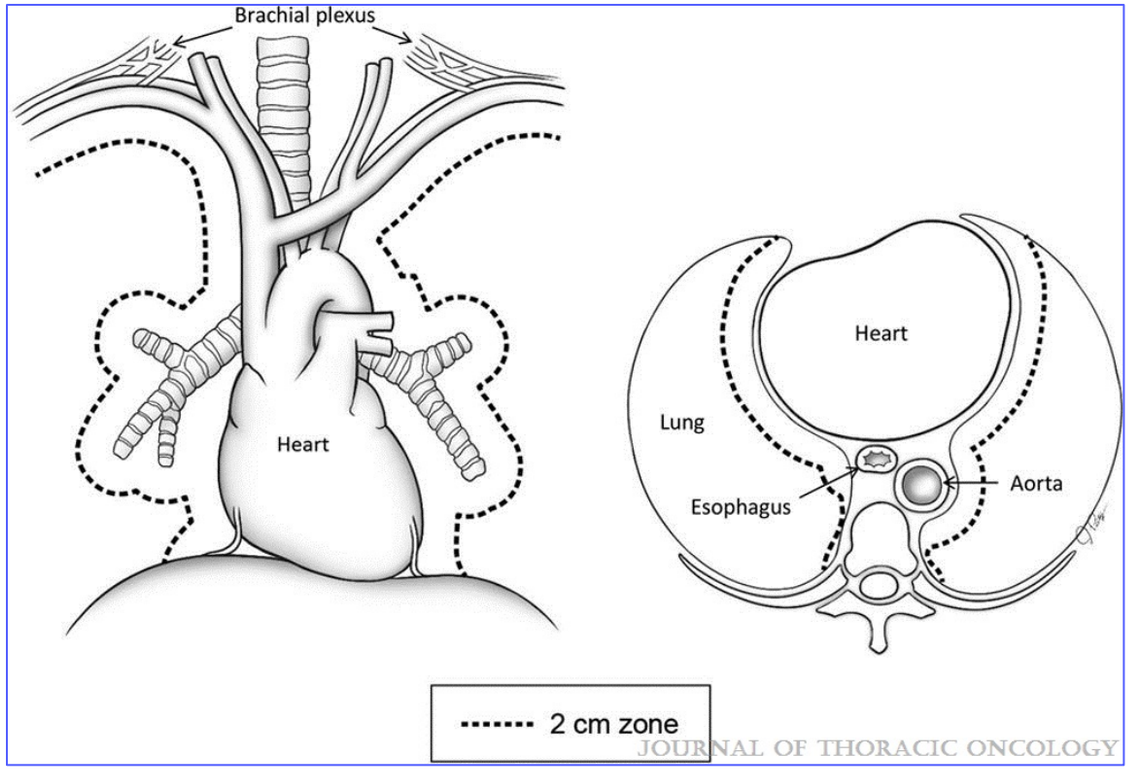
- Mangona VS, IJROBP 2014
- Modh A, IJROBP 2014
- Schanne DH, Strahlenther Onkol 2014
- Stephans KJ, IJROBP 2014
- Nishimura S, J Thorac Oncol 2014
- Chang JY, IJROBP 2014
- Li Q, Radiation Oncol 2014
- Park HS, JTO 2015
- Chaudhuri AA, Lung Cancer 2015
- Davis JN, Radiation Oncol 2015

- RTOG 0813 – closed September 2013, accrued 120 patients

"Seamless Phase I/II Study of SBRT for Early Stage, Centrally Located NSCLC in Medically Inoperable Patients"

Defining central tumors





RTOG trials

IASLC-ARTC [Chang JY, JTO 2015]

A tumor within 2 cm in all directions of any mediastinal critical structure, including bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve.

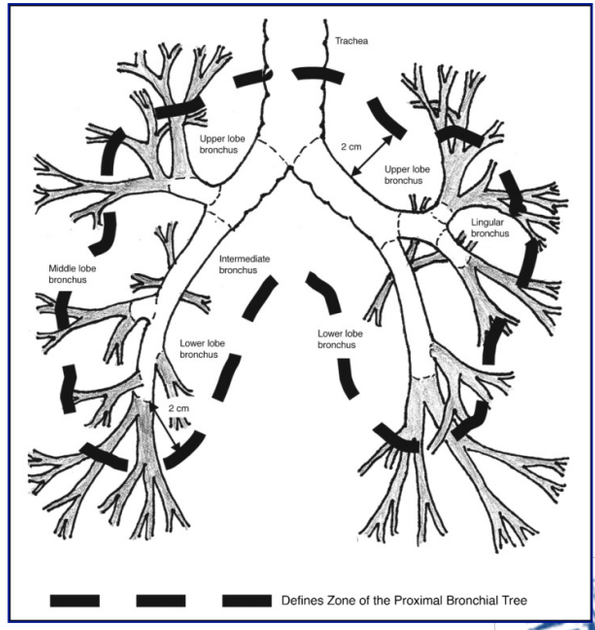
RTOG 0813 Trial for central tumors

- Medically inoperable patients with biopsy proven, PET staged T1-2N0M0 NSCLC, ≤ 5 cm centrally located tumors

- 100 evaluable patients from 43 centers (2009-2013)
- Of the 12 excluded patients, 8 did not meet eligibility criteria.

- Median age 72 years (range 52- 89), 45% squamous cell carcinoma, **65% had T1 tumors**.

- Median follow up was 26.6 months.



Bezjak A, WCLC Denver (Oral 19.03, 8th September 2015)

RTOG 0813 Trial: Adverse events

- G2+ pulmonary toxicity in **4/8** at10.0 Gy/fr, **5/14** at 11.0 Gy/fr, **15/38** at 11.5 Gy/fr, and **10/33** at 12.0 Gy/fr pts.

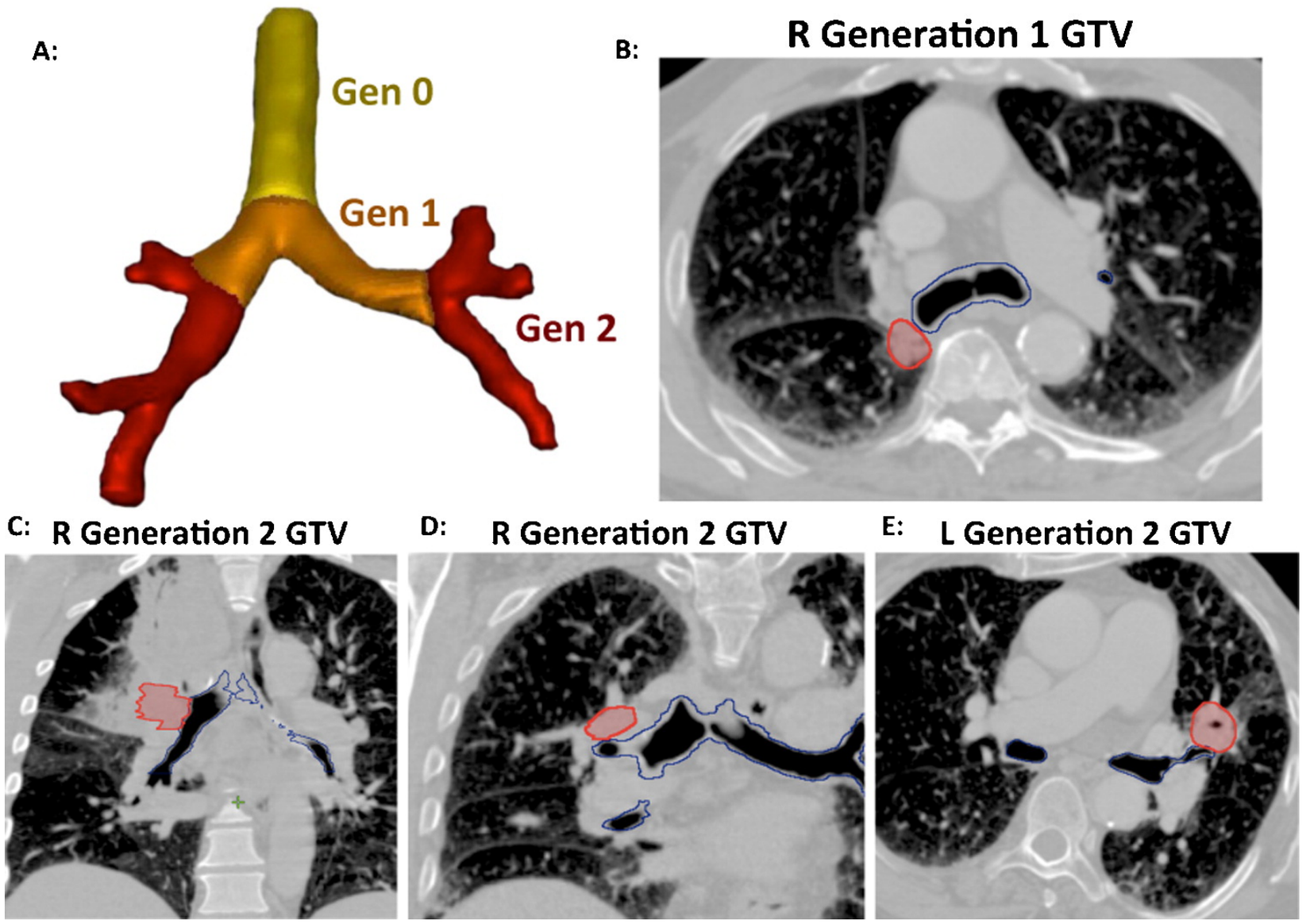
- 4/100 (4%) had fatal hemoptysis potentially attributable to SBRT

Dose/fraction (total = 5 fr)	Patient numbers	Grades 3-5 toxicity (CTCAE v4.0)		
		G3	G4	G5*
10 Gy	8			
10.5 Gy	7			1
11 Gy	14	1		
11.5 Gy	38	4		2
12 Gy	33	5	1	1

* Gr 5 all due to hemoptysis; mean 13 months post-SBRT

Bezjak A, WCLC Denver (Oral 19.03, 8th September 2015)

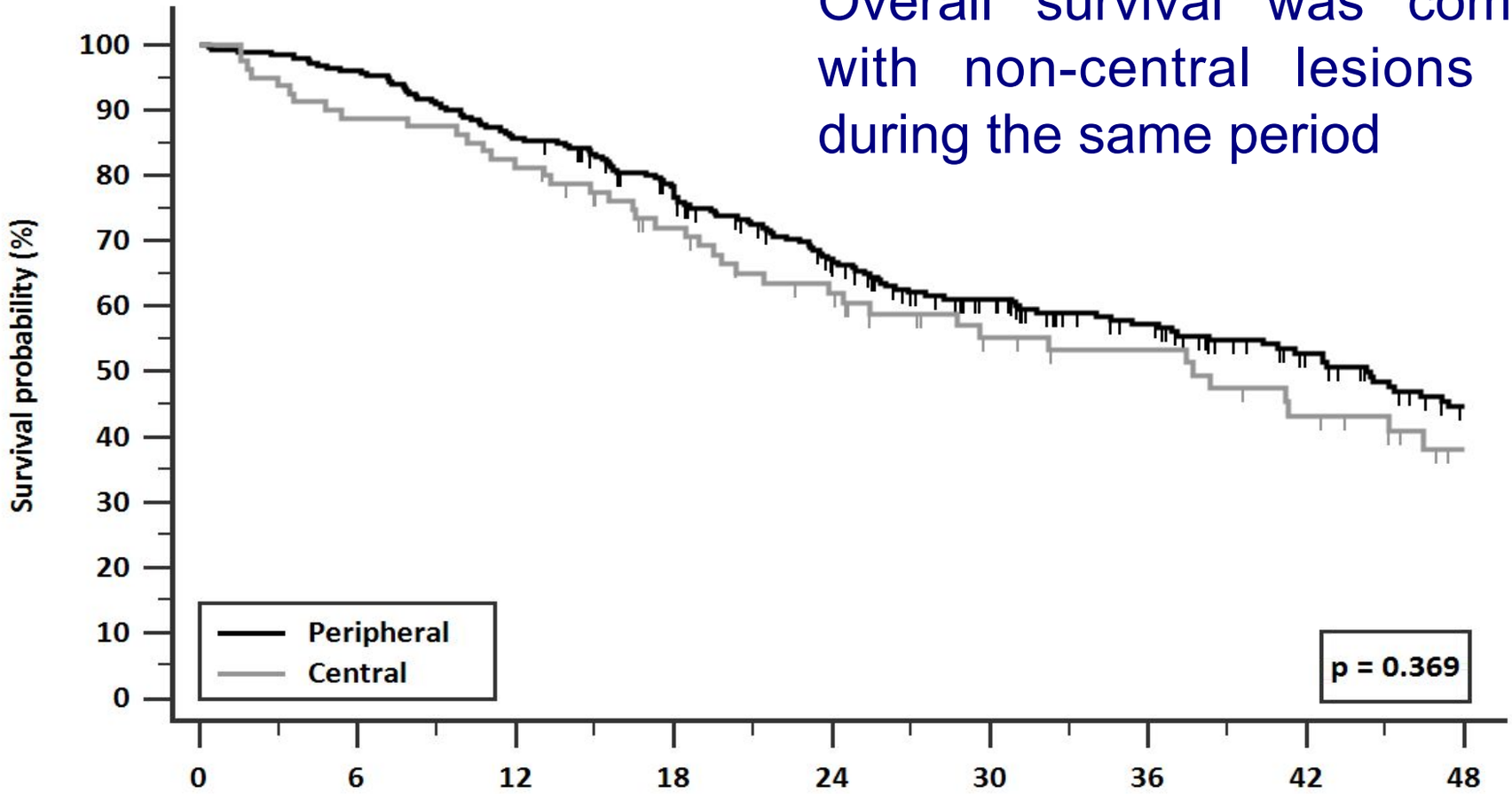
Central tumors: ‘ultracentral’ subgroup



Chaudhuri AA, Lung Cancer 2015

Central tumors treated at VUMC

Overall survival was comparable with non-central lesions treated during the same period



Number at risk									
Peripheral	252	242	216	184	150	120	98	75	55
Central	80	71	65	52	41	30	27	20	12

Tekatli H, *submitted*

Surgery for early-stage NSCLC

VUmc

Chemotherapy for Early Stage Trial (CHEST)

- Phase III study in 270 patients (only 1 case with N2 disease) randomized to either 3 cycles of chemotherapy followed by surgery, or surgery alone

- Median age: 62; 72% had ECOG performance score 0

	Chemo + surgery	surgery
Perioperative mortality rate	3%	4%
Complete resection rates	88%	84%
Failure at primary site	9.3%	10.6%
Lymph node relapses	13.2%	6.4%

Scagliotti G, JCO 2012

SABR for central tumors?

For tumours with a size >5 cm and/or central location, far less data are available for SABR. These patients are preferentially treated with radical radiotherapy using more conventional daily or accelerated schedules [38] [III, A].

Clinical Practice Guidelines of the European Society for Medical Oncology [Vansteenkiste J, Ann Oncol 2013]

Can you perform SABR in tumors with a diameter ≤1 cm?

SABR in tumors with diameter ≤1 cm

Baseline Patient Characteristics		Baseline Tumor Characteristics	
Characteristic	**N (%)**	**Characteristic**	**N (%)**
Sex		**Pathology**	
Male	18 (51.4)	Yes	6 (17.1)
Female	17 (48.6)	No	29 (82.9)
Planning algorithm		**PET avidity**	
AAA	22 (62.9)	Yes	33 (94.3)
PBC	13 (37.1)	No	2 (5.7)
Prior malignancy		**Pathology**	
Yes	25 (71.4)	Yes	6 (17.1)
No	10 (28.6)	No	29 (82.9)
WHO performance		**Growing lesion**	
0-1	11 (31.4)	Yes	19 (54.3)
2-3	24 (68.6)	No	16 (45.7)
Treatment indication		**Tumor diameter**	
Metastasis	11 (31.4)	8 mm	9 (24.3)
Double lung tumor	13 (37.1)	9 mm	10 (27.0)
Primary lung tumor	9 (25.7)	10 mm	18 (48.6)
Recurrent lung tumor	2 (5.7)		
Fractionation scheme			
1 fraction	1 (2.9)		
3 fractions	20 (57.1)		
5 fractions	12 (34.3)		
8 fractions	2 (5.7)		

Louie AV, IJROBP 2014

SABR in tumors with diameter ≤1 cm

- AAA plans were recalculated using Acuros XB
  - Mean ITV/PTV dose
  - D95 ITV/PTV
  - % Rx dose in GTV in the 0 and 50% respiratory phases

- Local control calculated using the K-M method

- <u>RESULTS</u>
- 35 patients with 37 sub-centimeter tumors analysed
- 2-year local progression-free survival was 100%.
- 22 AAA plans recalculated using Acuros (AXB)

Louie AV, IJROBP 2014

SABR in tumors with diameter ≤1 cm

- **D95** (mean ± SD) was lower: 2.2±4.4% (to ITV) and 2.5±4.8% (to PTV) when AXB used
- **Mean doses** were lower: 2.9±4.9% (ITV) and 3.7±5.1% (PTV)
- Calculated AXB doses were significantly lower in 1 patient (difference in ITV and PTV mean dose, as well as ITV and PTV D95 ranged from 22% to 24%). However, the **end respiratory phase GTV received at least 95% of the prescription dose**.
- SABR is feasible for lung tumours ≤ 1 cm, with excellent local control

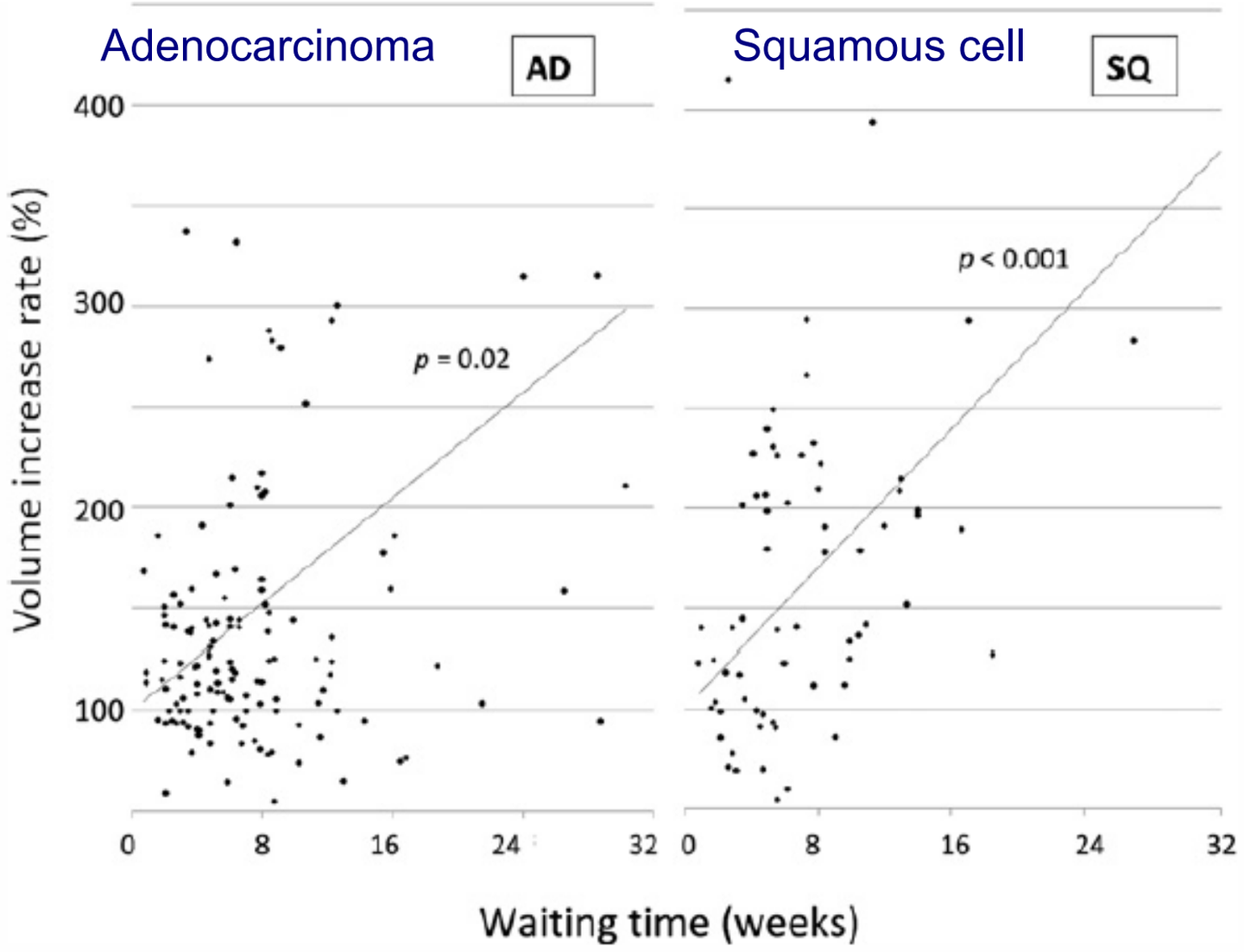
Louie AV, IJROBP 2014

Risk of delayed treatment of lung cancer

CLINICAL INVESTIGATION IJROBP 2011

PROGRESSION OF NON–SMALL-CELL LUNG CANCER DURING THE INTERVAL BEFORE STEREOTACTIC BODY RADIOTHERAPY

TARO MURAI, M.D.,* YUTA SHIBAMOTO, M.D.,* FUMIYA BABA, M.D.,* CHISA HASHIZUME, M.D.,†

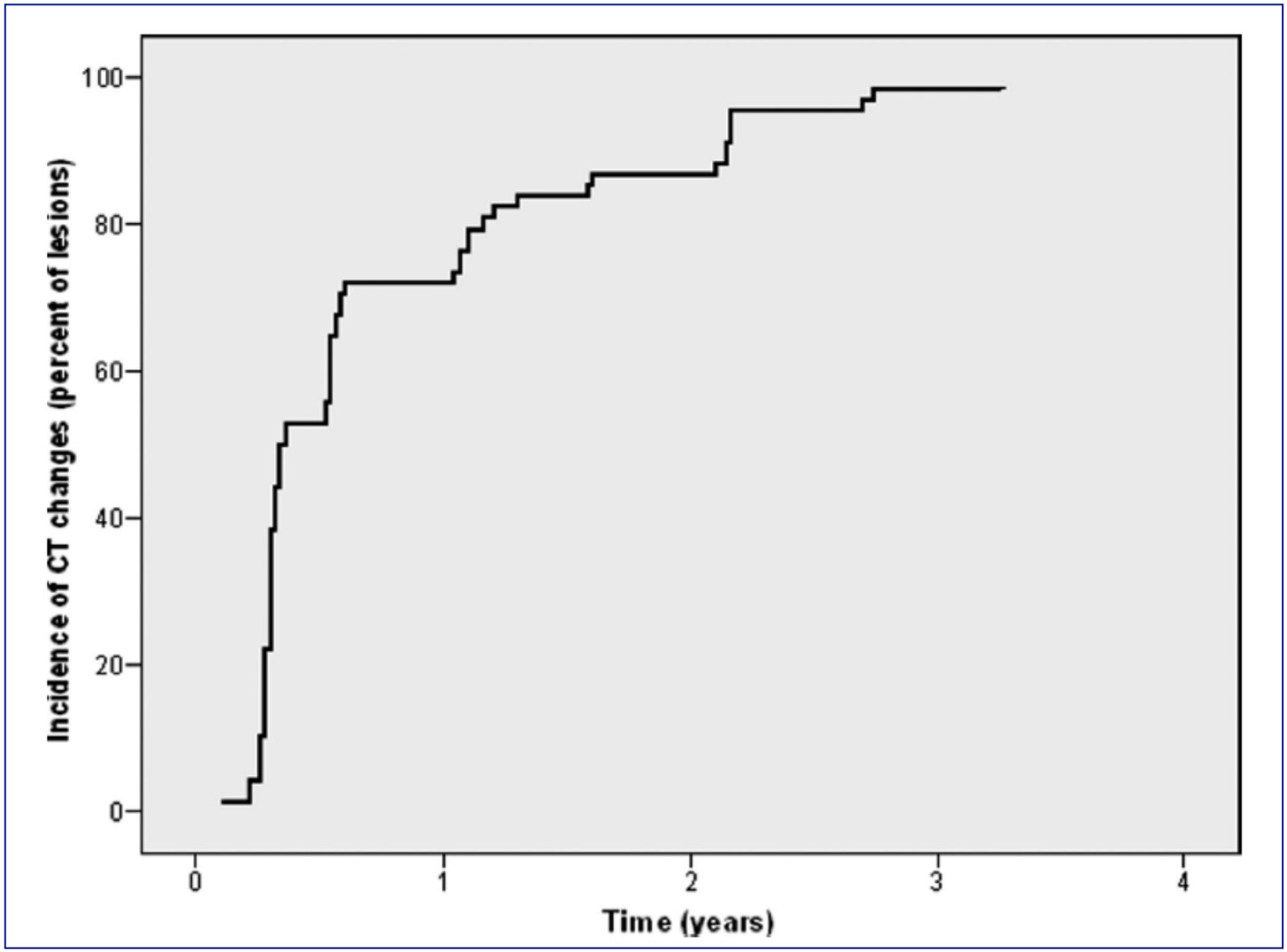


Why make follow-up CT scans?

- Detect Local Recurrence (~10% at 5 years)
- Detect Salvageable Regional Recurrence
- New Lung Primaries (3-6% per year)

- ESMO recommendations: CT scans every 3-6 months for 2-3 years, annually thereafter, especially in patients suitable for salvage
- NCCN guidelines: CT q6-12 months for two years than annually
- AATS guidelines –patients should have annual low dose CT as per result of NLST

Non-tumor CT changes post-SABR

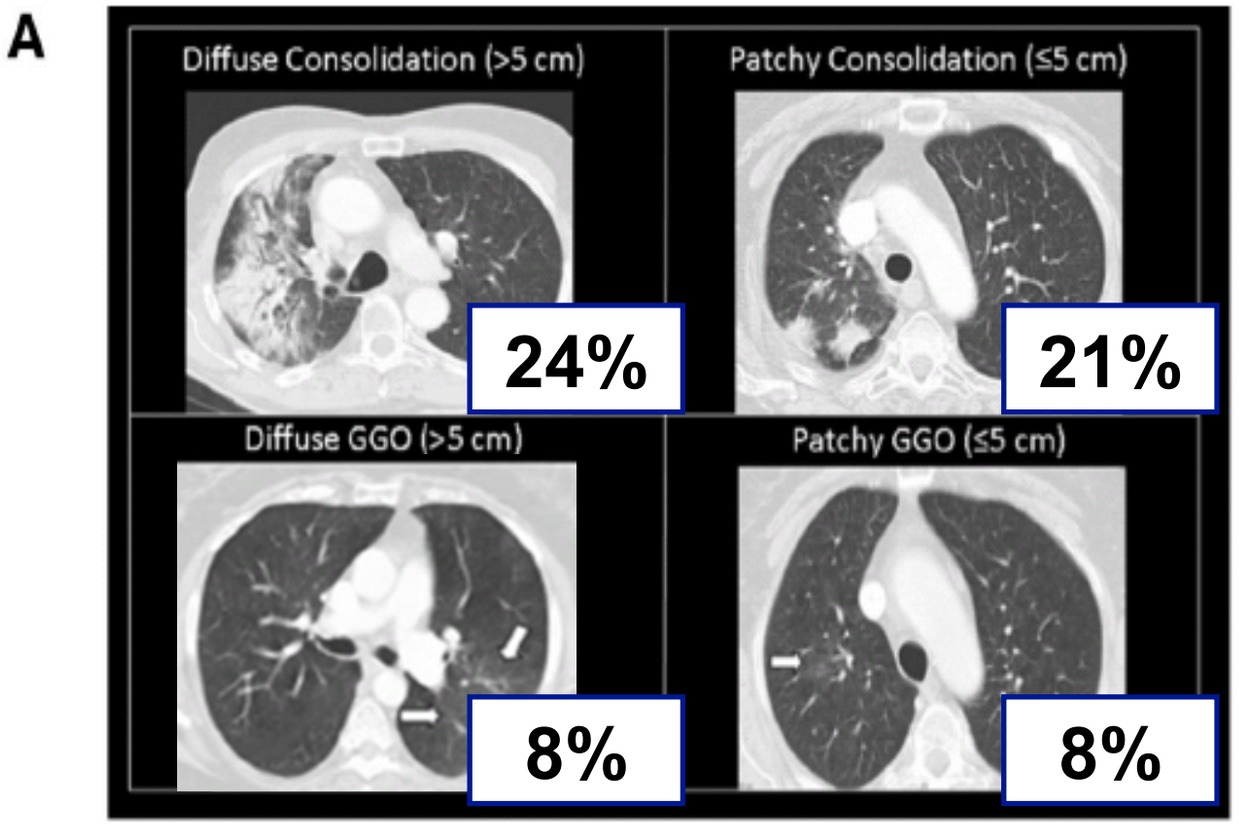


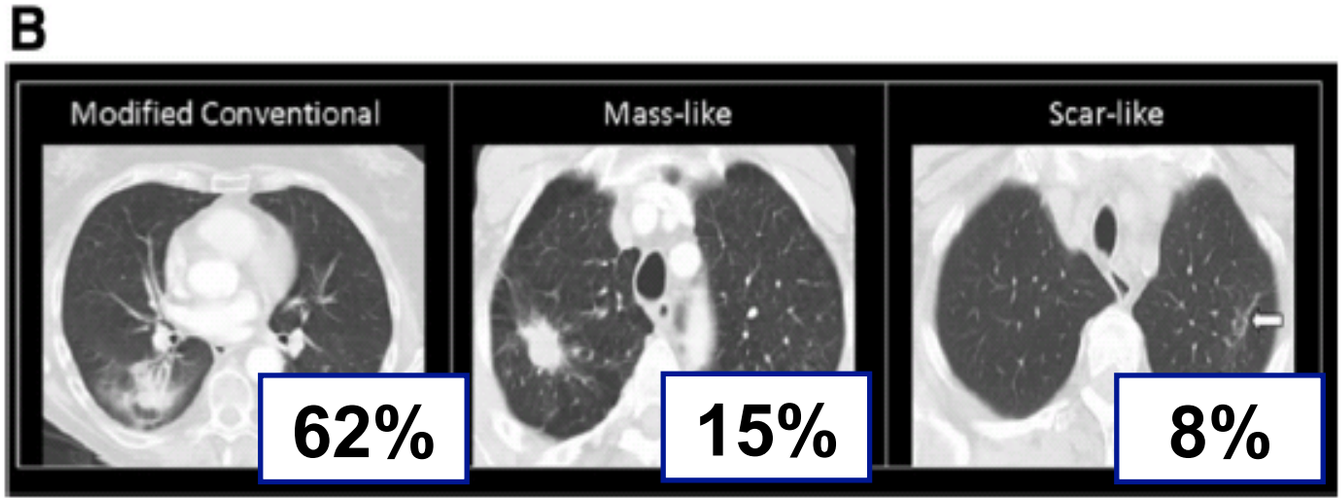
Dahele M, JTO 2011

Post-SABR lung changes (fixed beams)

Acute:
≤6 months

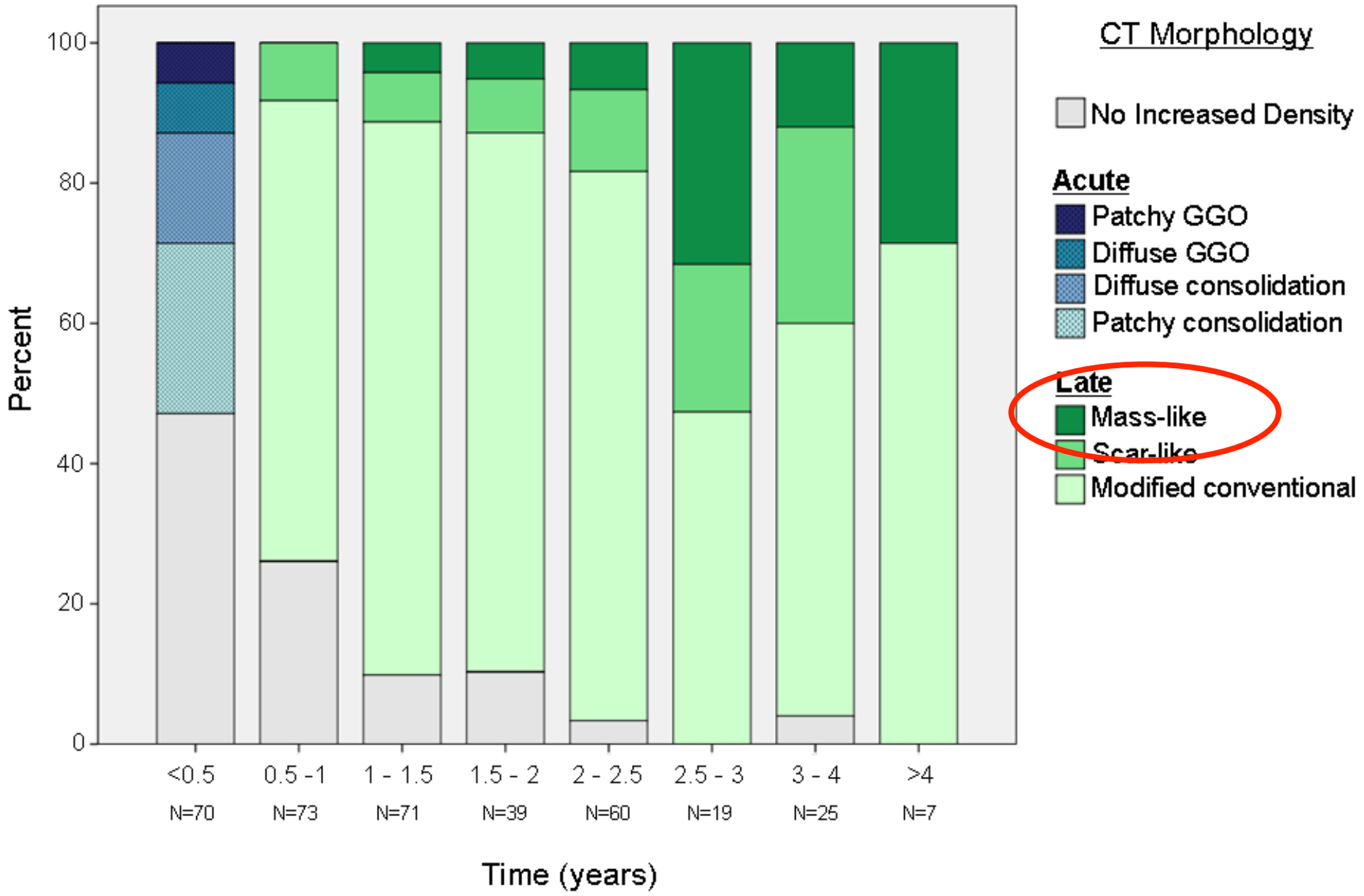
Late:
>6 months





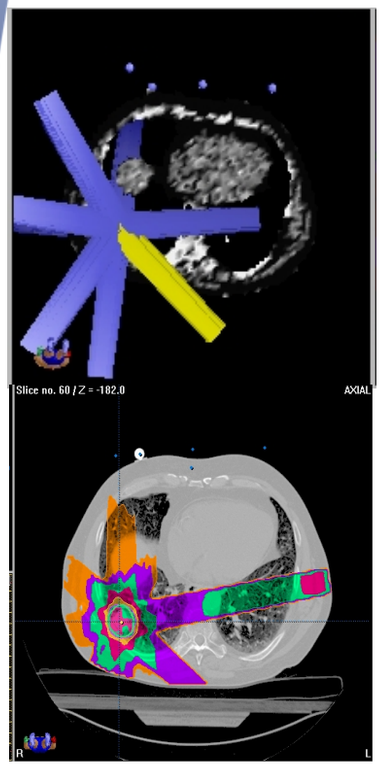
Dahele M, JTO 2011

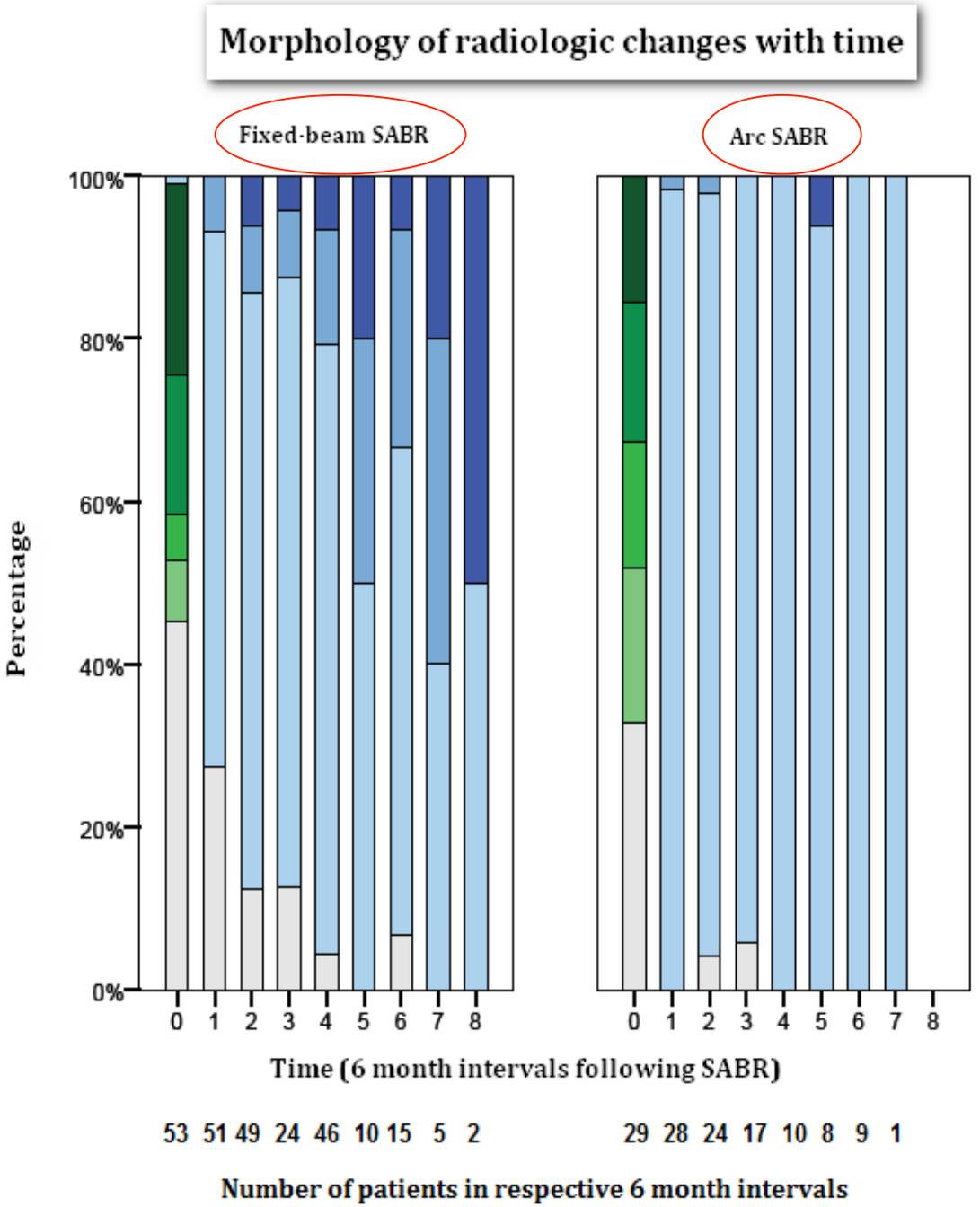
Post-SABR radiological changes

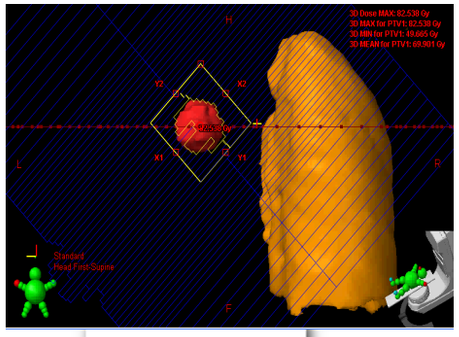


Dahele M, JTO 2011

SABR technique and patterns of fibrosis







Morphology

- Mass-like
- Scar-like
- Modified-conventional
- Patchy consolidation
- Diffuse consolidation
- Patchy ground glass opacity
- Diffuse ground glass opacity
- No increased density

Senthi S, Radioth Oncol 2013

Fibrosis vs. recurrence after SABR

VUmc

Systematic review of literature on recurrences

High-risk features (HRF):

- enlargement of mass
- sequential enlargement on CT
- growing mass after 12 months

- bulging margin
- linear margin disappears

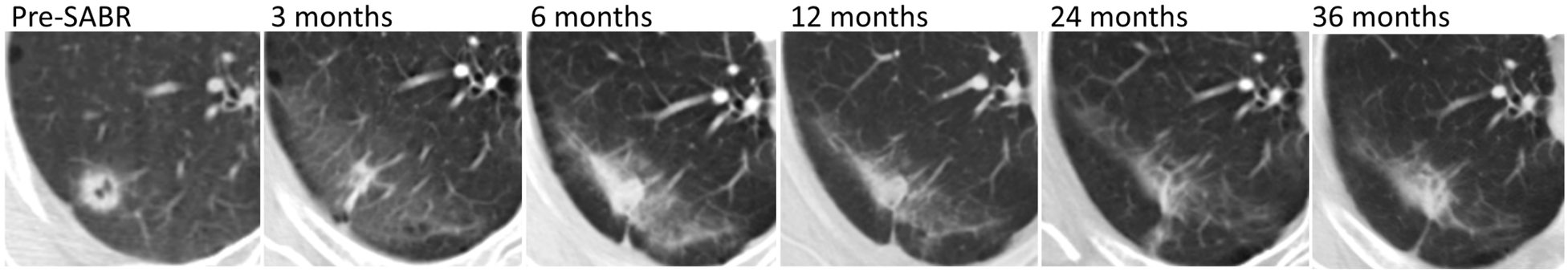
- air bronchograms disappear

Huang K, Radioth Oncol 2012

Fibrosis or recurrence after SABR?

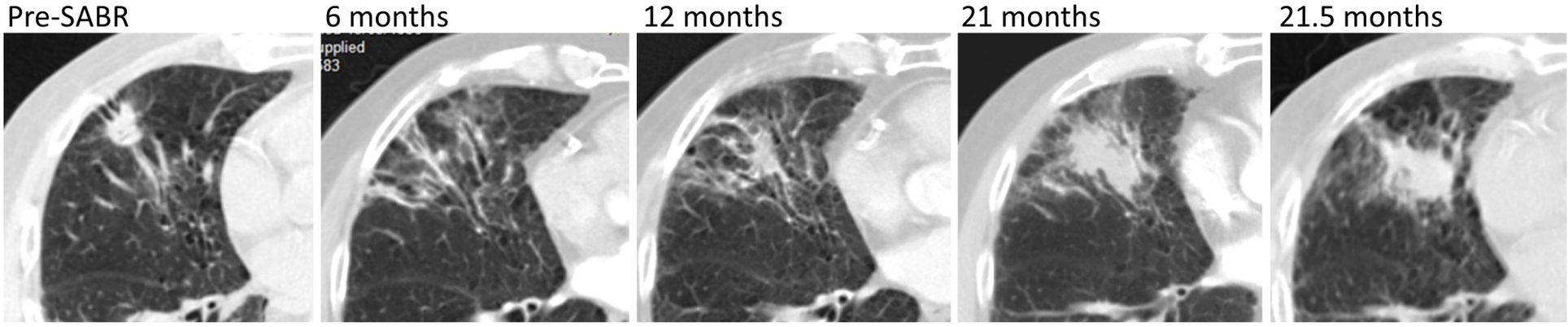
Blinded scoring of 12 path. proven recurrences matched with 24 non-reccurences

A. No Recurrence



HRF: Enlarging Opacity

B. Recurrence



HRFs: Enlarging Opacity
Craniocaudal Growth

Sequential Enlargement
Enlargement after 12 months
Linear Margin Disappearance
Bulging Margin

Loss of Air Bronchogram

Huang K, Radioth Oncol 2013

High-risk CT Factors: validation

High-Risk Feature	Sensitivity	Specificity	p-value
Enlarging Opacity	92	67	< 0.001
Sequential Enlargement	67	100	< 0.001
Enlargement after 12 months	100	83	< 0.001
Bulging Margin	83	83	< 0.001
Linear Margin Disappearance	42	100	0.002
Loss of Air Bronchogram	67	96	< 0.001
Cranio-Caudal Growth	92	83	< 0.001

Huang K, Radiother Oncol 2013

Fibrosis or recurrence after SABR?

VUmc

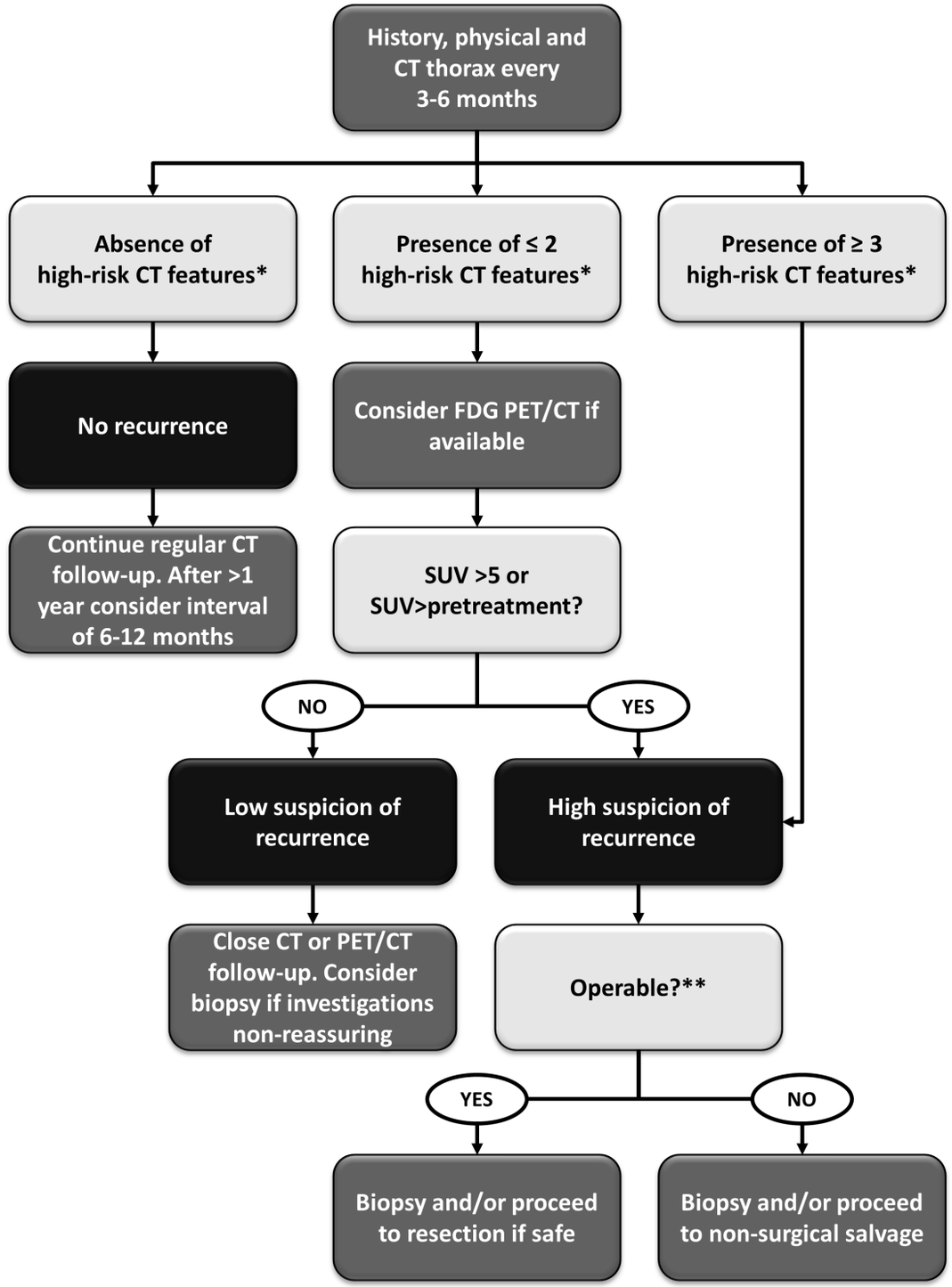
- All HRF's associated with local recurrence ($p<0.01$). Best individual predictor was opacity enlargement after 12-months (100% sensitivity, 83% specificity, $p<0.001$).

- Odds of recurrence increased 4-fold for each additional HRF detected.

- Presence of ≥3 HRFs highly sensitive and specific for recurrence (both >90%).

Huang K, Radioth Oncol 2013

Fibrosis or recurrence after SABR?



Huang K, Radioth Oncol 2013

Overview of talk

- **Multi-disciplinary tumor board** (ESMO guidelines)
- SABR guidelines (technical)
- Patient selection (operable, pathology, PET –ve cases)
- Toxicity and local control (peripheral tumors)
- Controversies: central tumors, tumors <1 cm
- **Follow up: Recurrence or fibrosis**
- **Second Primary Lung Cancer (SPLC)**

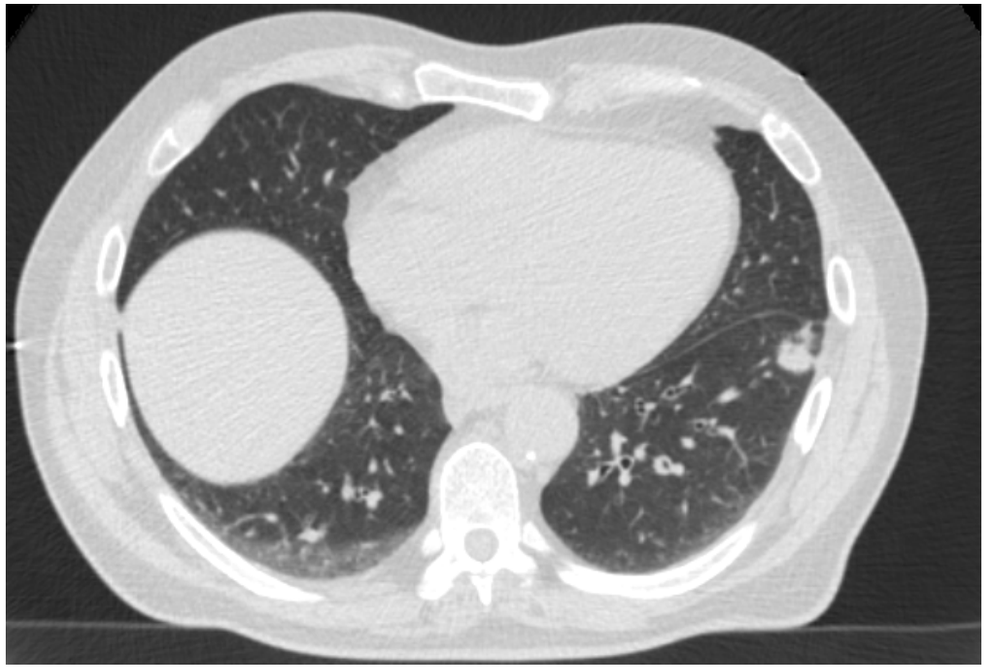
Patient V, current age 68 years

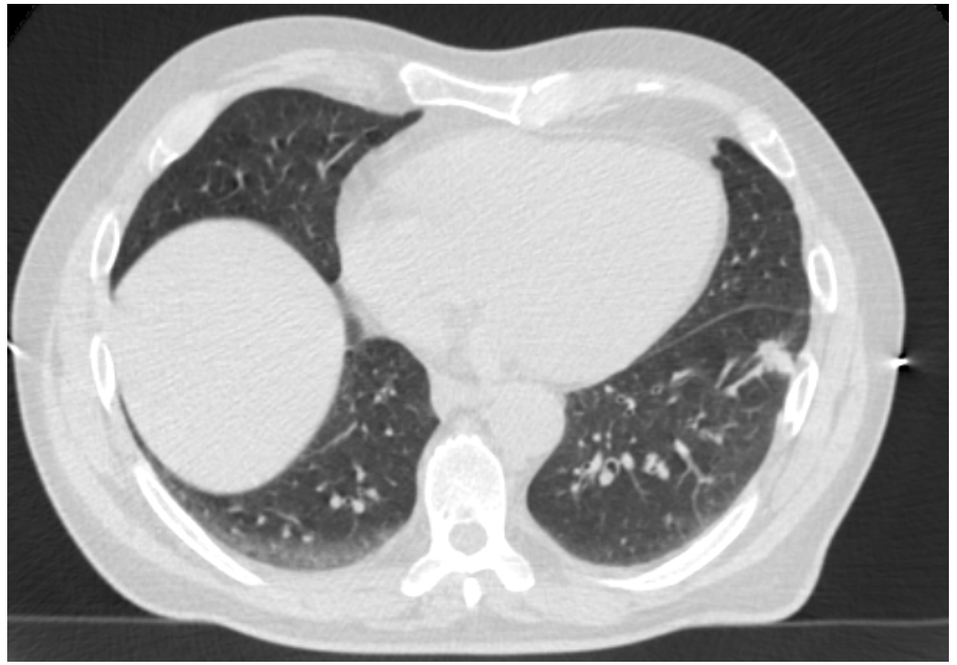
1995: larynx carcinoma treated with radiotherapie.

2008: Growing FDG-PET nodule in left lower lobe; moderate FDG uptake in mediastinal and hilar lymph nodes

Cervical mediastinoscopy: no nodal metastases

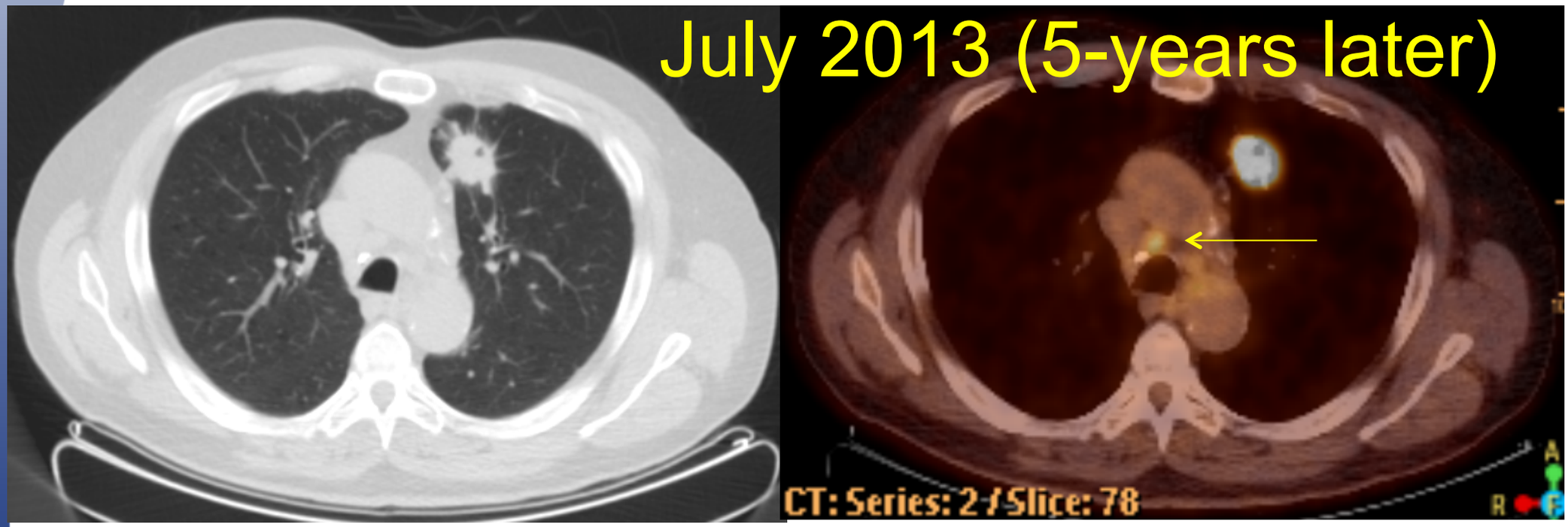
Treated in randomised trial of surgery versus SABR (ROSEL study)





Van Iersel M, Lung Cancer 2015

Patient V, current age 68 years



Transthoracic needle biopsy: squamous cell malignancy (primary)

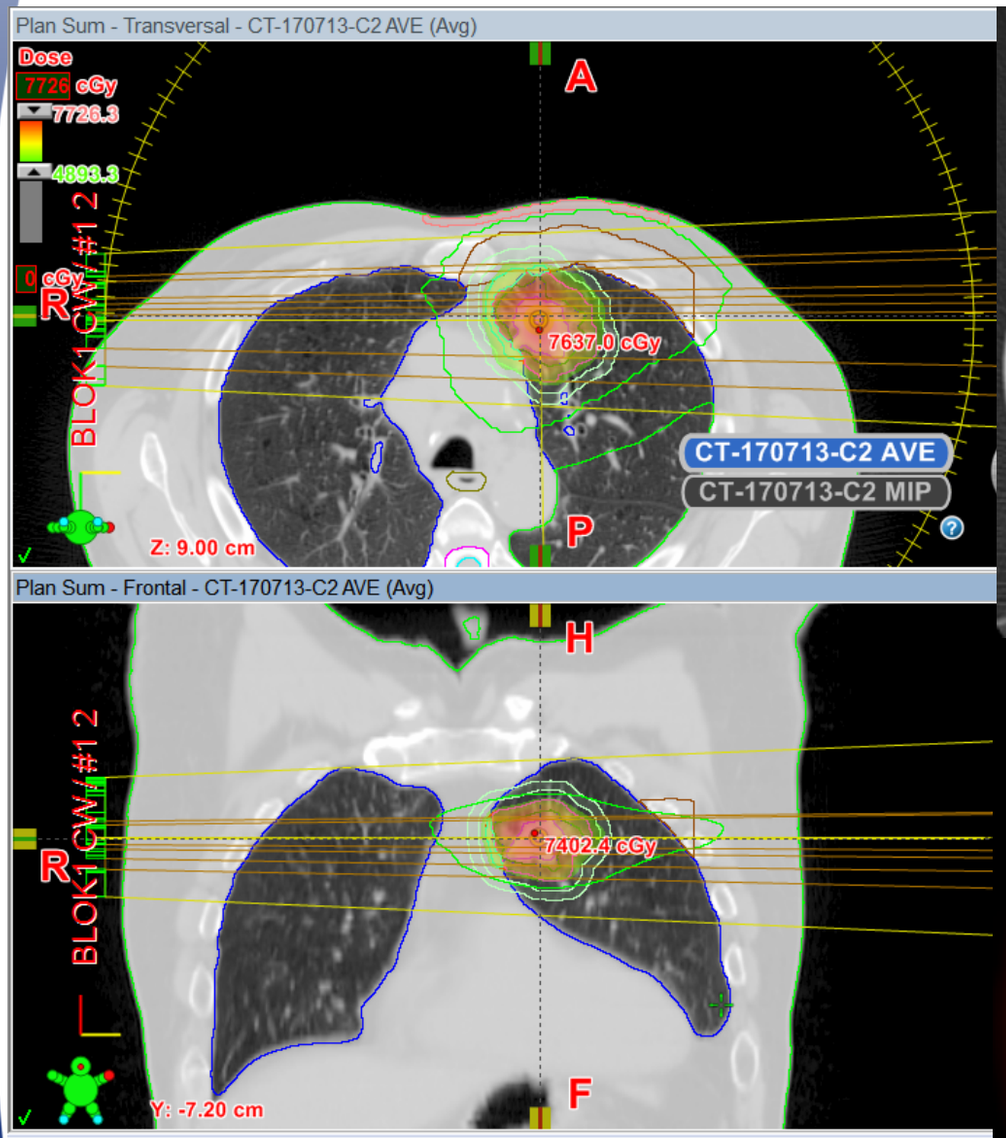
EBUS showed reactive nodes at locations 4R, 7, 4 left and 11L

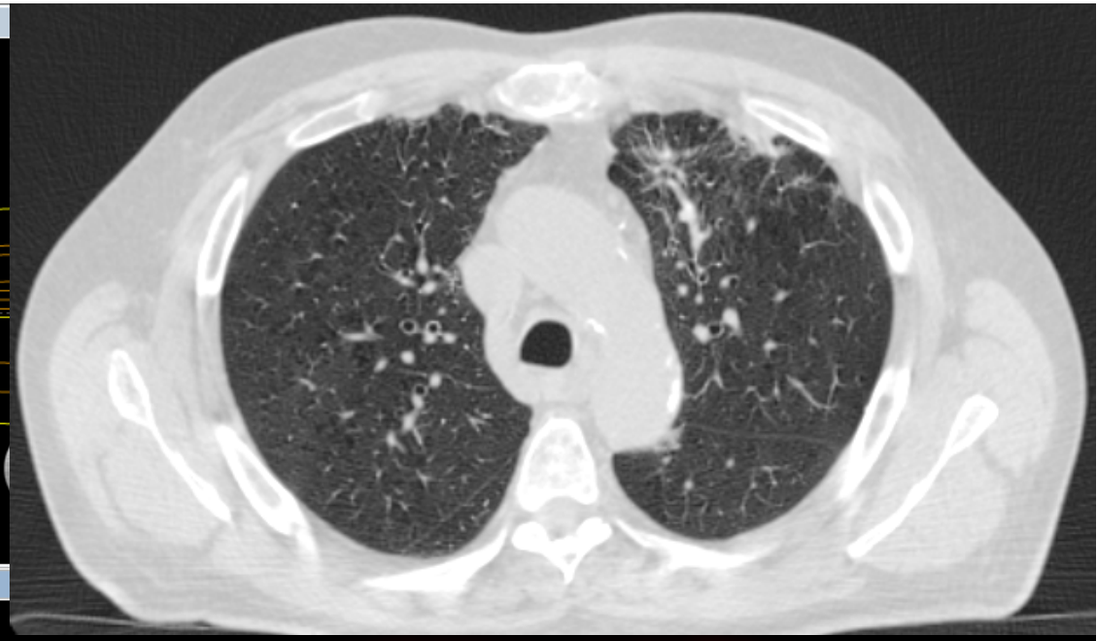
Van Iersel M, Lung Cancer 2015

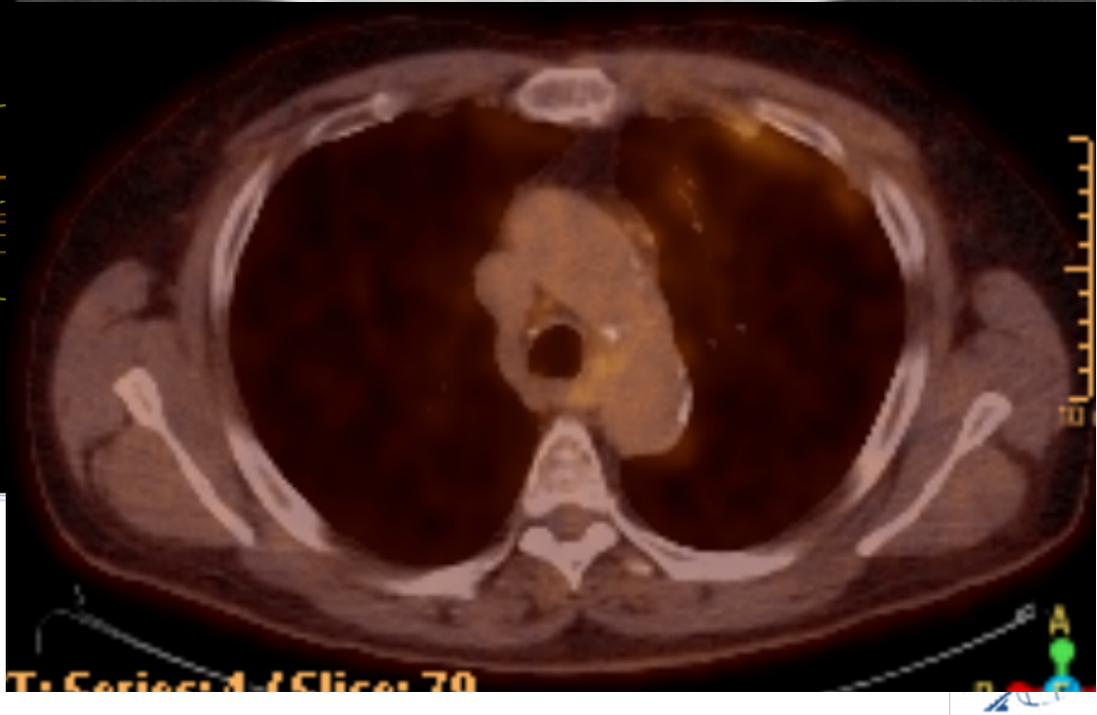
Patient V, current age 68 years

July 2013

November 2013



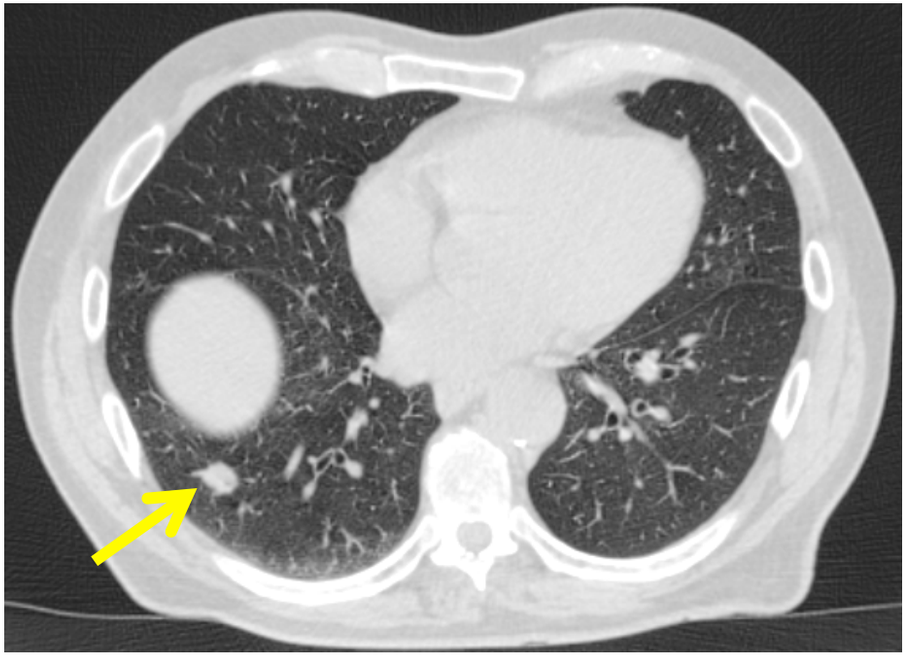


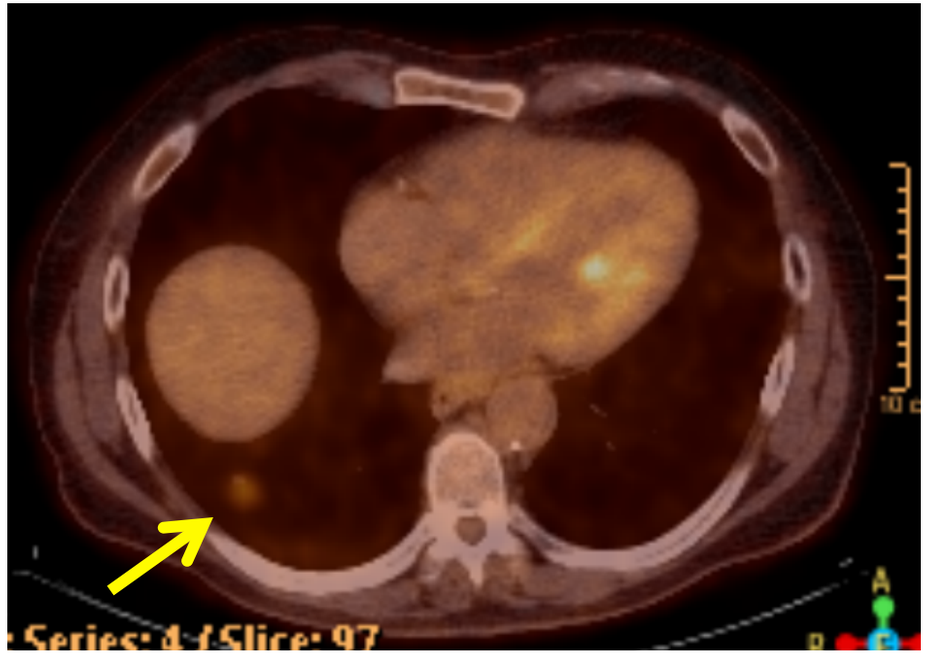


Van Iersel M, Lung Cancer 2015

Patient V, current age 68 years

November 2013





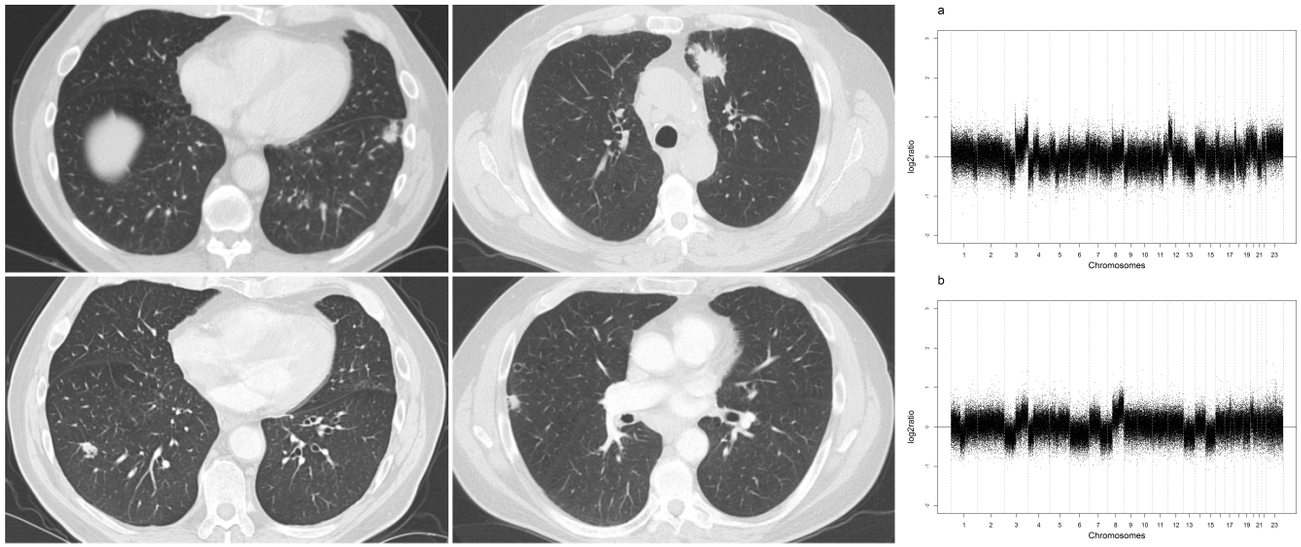
- Transthoracic needle biopsy: squamous carcinoma
- Array CGH analysis: clonal relationship unlikely. Differences as well from the previous larynx carcinoma (1995)

- November 2013: SABR to right lower-lobe
- November 2014: No evidence of disease

Van Iersel M, Lung Cancer 2015

Metastases or new primary

Panel showing serial CT scans and array CGH in patient

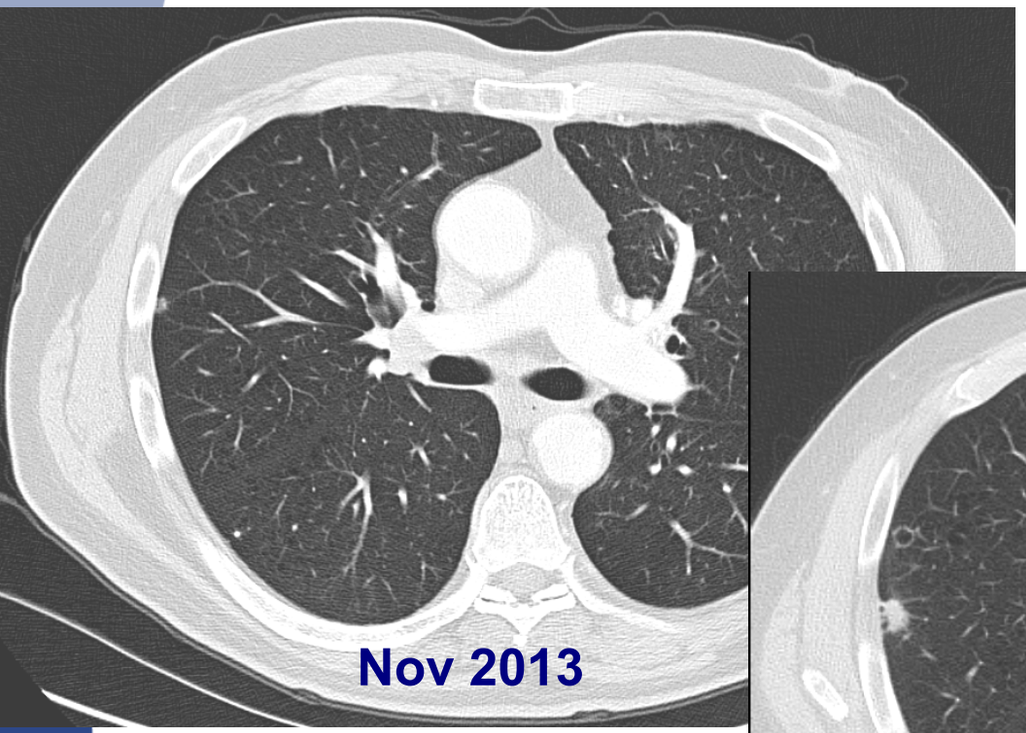


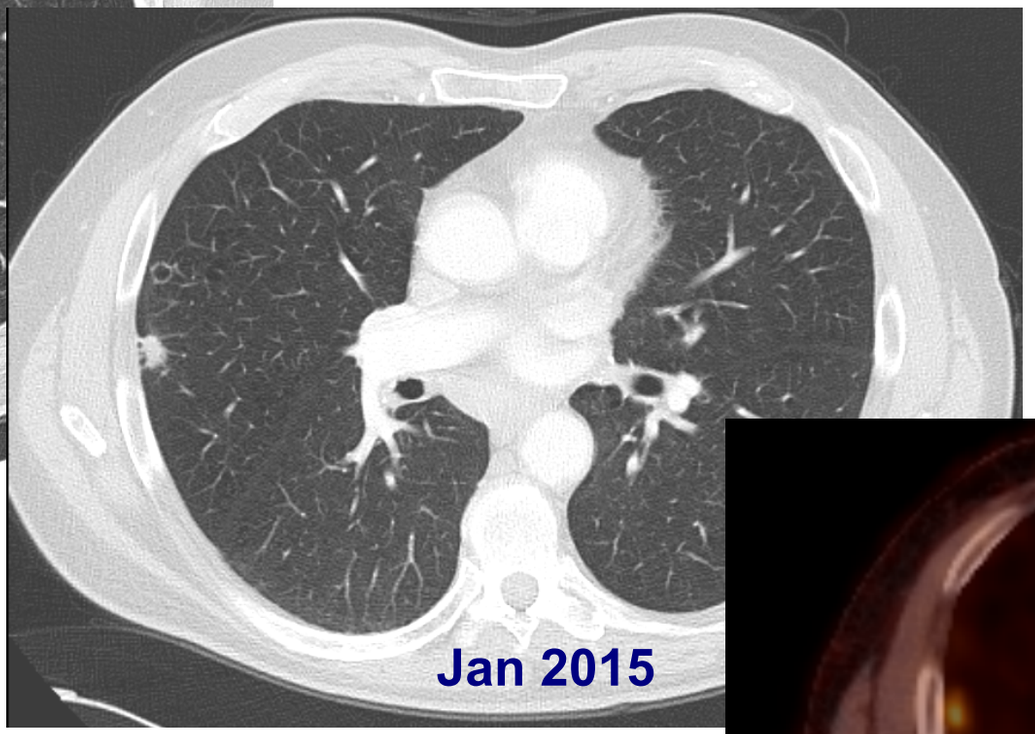
Array CGH: Tumor DNA is differentially labeled to reference (wild type) DNA, resulting in a gains and losses pattern for each tumor. 50 nanograms of DNA/sample is sufficient.

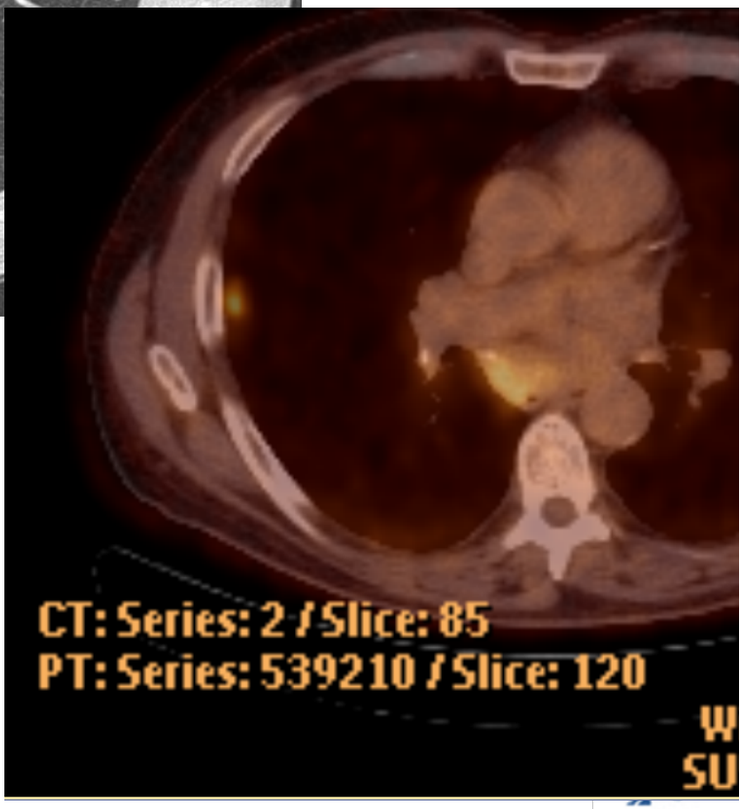
Different CGH patterns prove **lack of clonality**; similar CGH patterns denote clonality; up to 10% have inconclusive findings

Van Iersel M, Lung Cancer 2015

Patient V, current age 68 years







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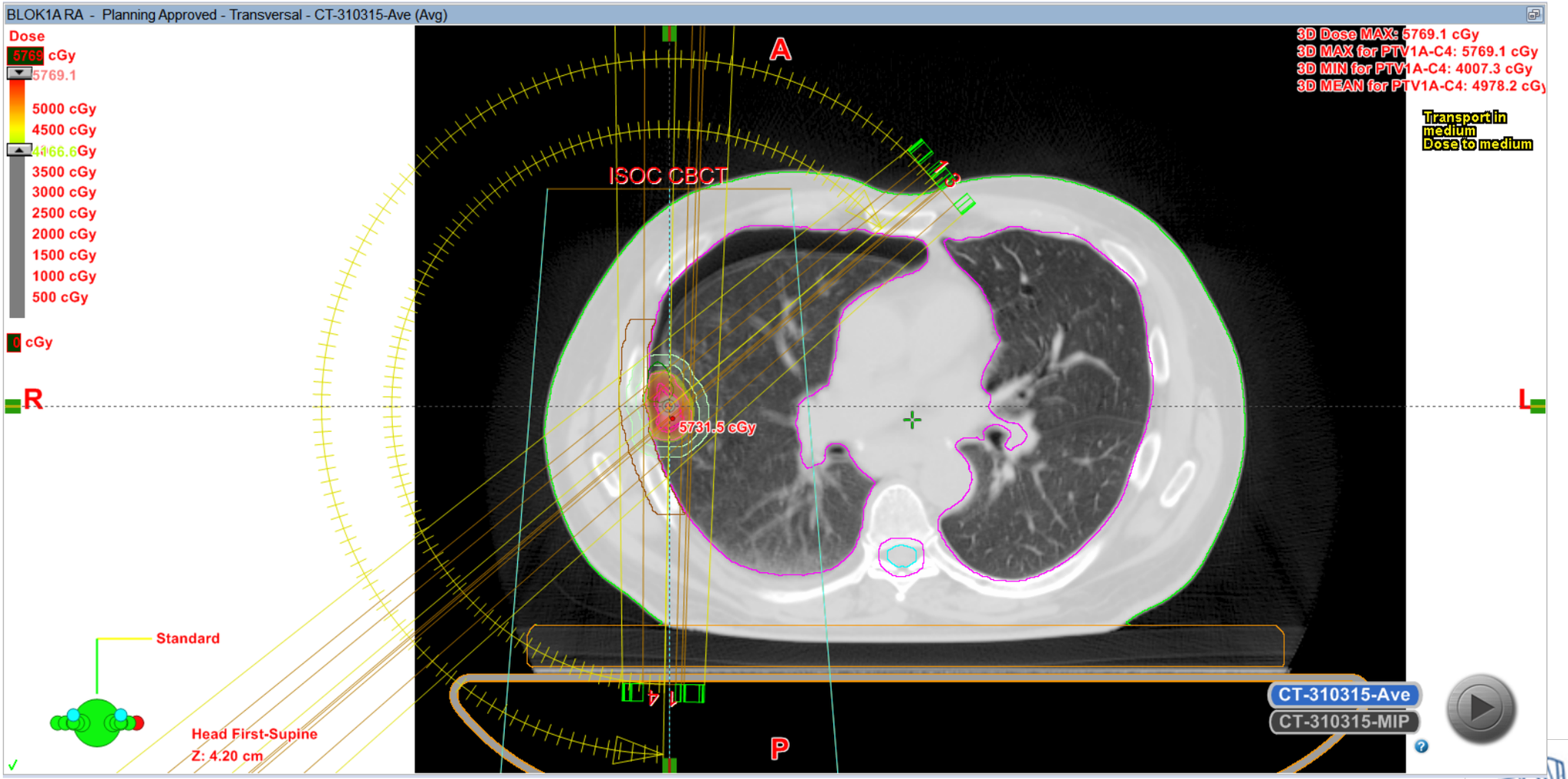
Pneumothorax complicating needle biopsy – ‘malignant cells’

2015: SABR (55 Gy) to 4th lung tumor



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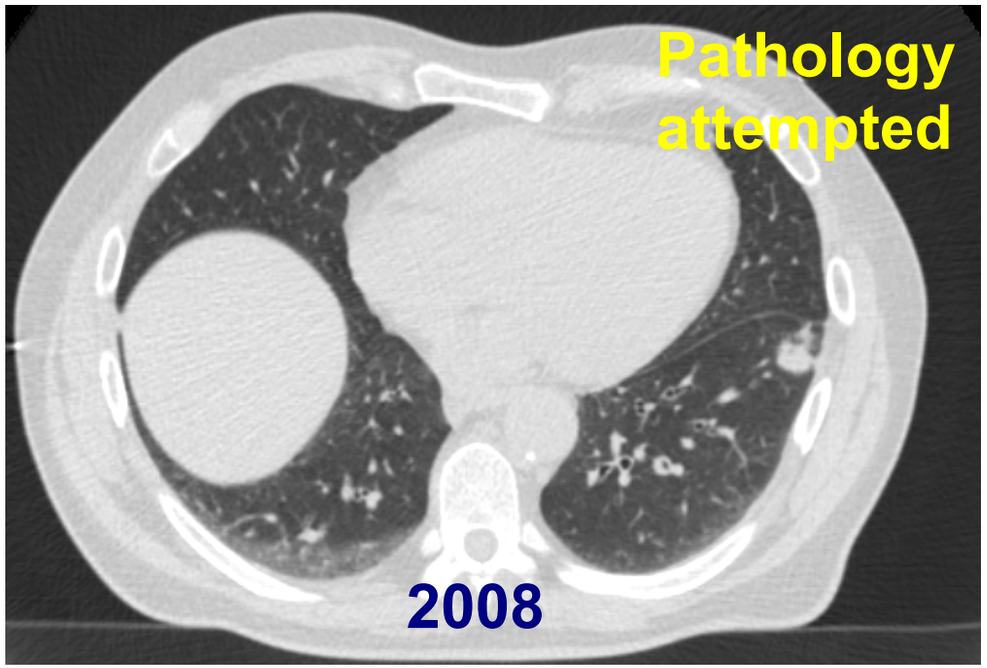
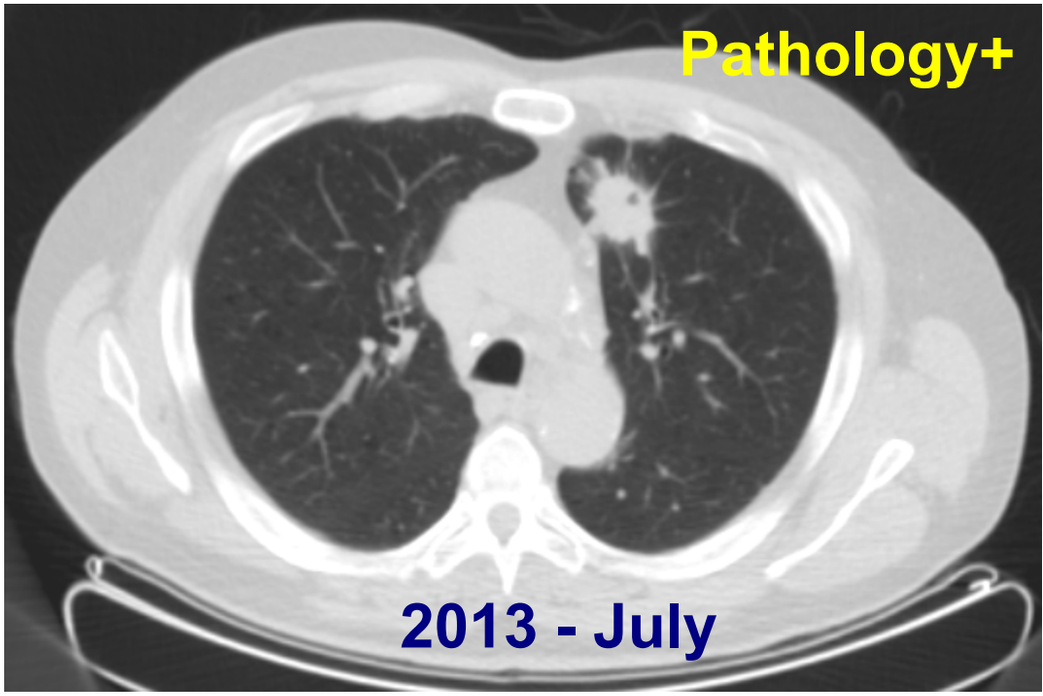
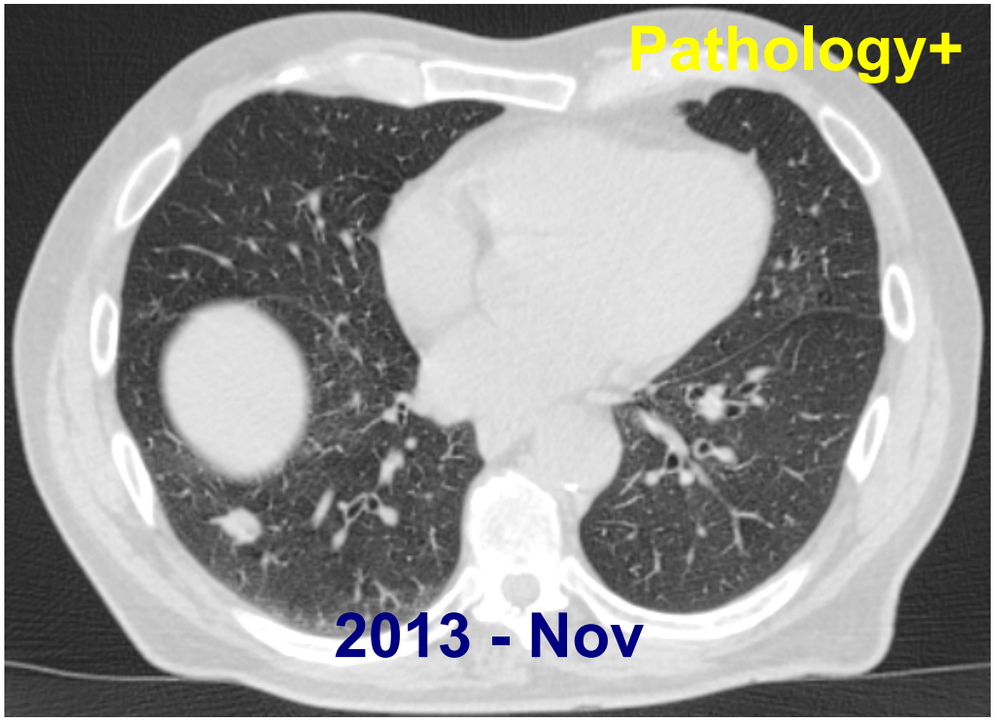
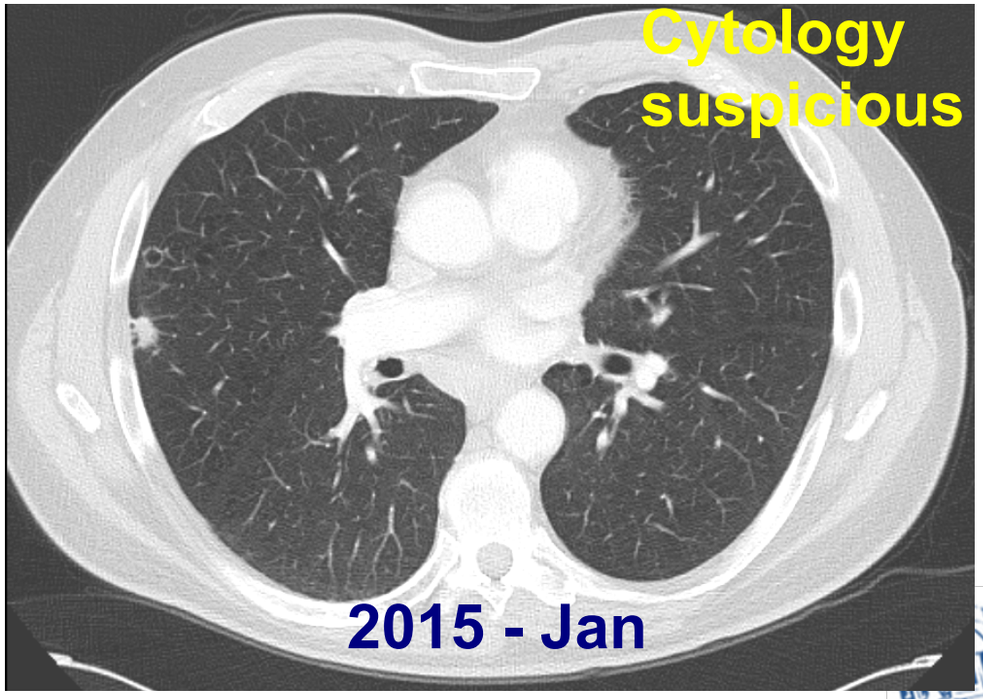
Patient V, current age 68 years









Is surgery following SABR feasible, and safe?

Surgical salvage after SABR

- Dutch institutional database review
- Complications classified with the Dindo-Clavien classification
- 17 patients who underwent a total of 21 resections identified
  - 9 patients treated for recurrence of early stage NSCLC
  - 8 patients treated for recurrence of solitary metastasis
- 4 patients, all treated for oligo-metastasis, underwent 2 resections for separate local recurrences

Verstegen NE, ELCC 2015

Surgical salvage after SABR

- Median time to recurrence range15.6 months (6-48 months)

- Type of resection:
  - Lobectomy (N = 15)
  - Sleeve-lobectomy (N=1)
  - Pneumonectomy (N=1)
  - Segment resection (N = 1)
  - Wedge resection (N = 3)

- Intra-operative findings:
  - No adhesions (N = 8)
  - Limited adhesions (N = 7)
  - Extensive adhesions (N = 5)

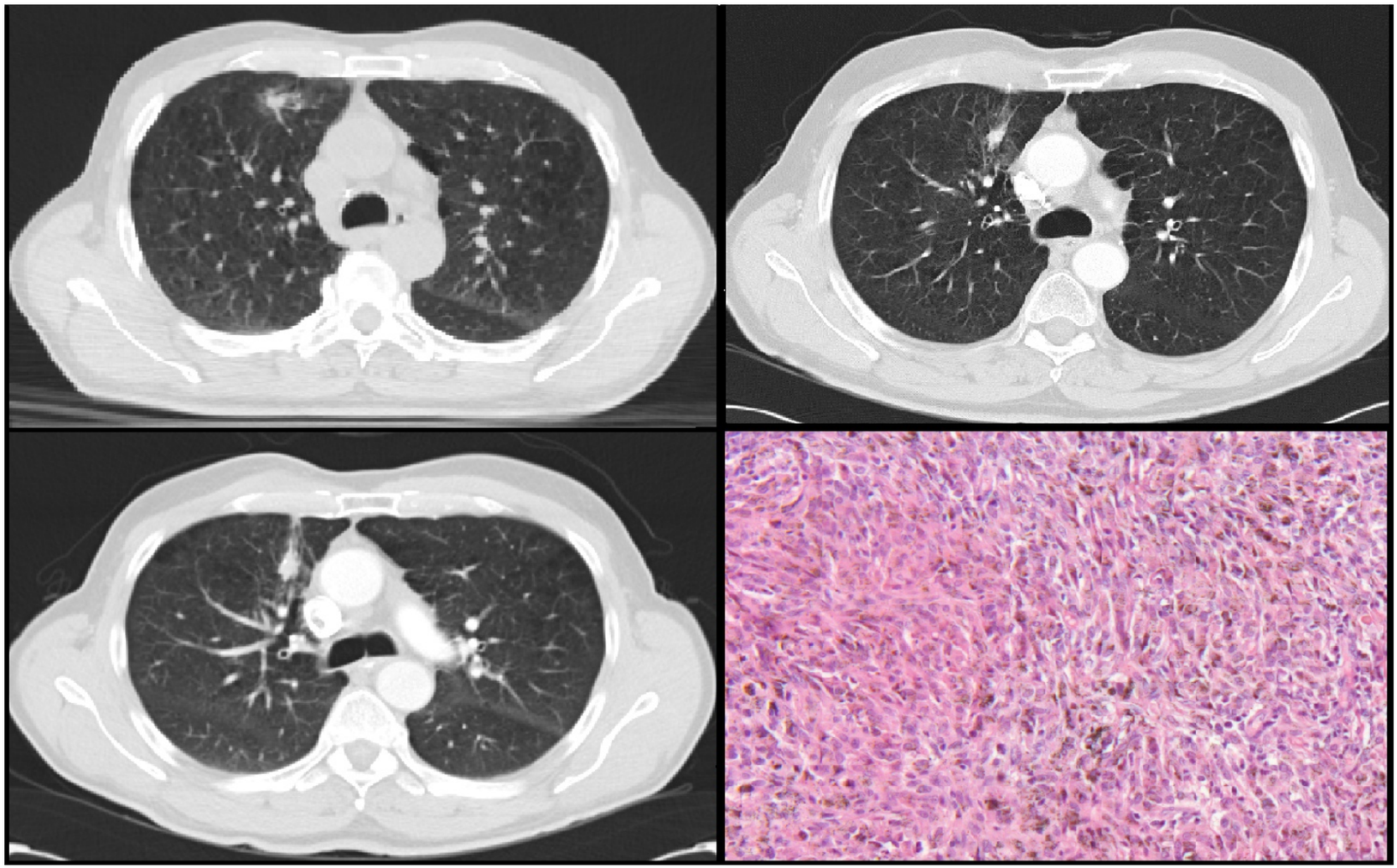
Verstegen NE, ELCC 2015

Surgical salvage after SABR

- 8 surgeries commenced as VATS – 4 converted to thoracotomy
- 4 patients with complications:
  - 2 patients with grade 2 complications
  - 2 patients with persistent airway leakage treated with now thoracic tube (grade 3a complication)
- Median length of hospital stay: 7 days (range 4-15 days)
- 30-day mortality: 0%

Verstegen NE, ELCC 2015

Salvage surgery post-SABR



Upper-left: CT-scan at diagnosis of primary tumor
Upper-right: CT-scan one year post SABR
Lower-left: CT-scan at the time of local recurrence
Lower-right: histological specimen showing poorly differentiated tumor cells (100x enlarged)

Surgical salvage after SABR

- 5 patients upstaged:
  - N2-disease (N=3)
  - T3 tumor (N=1)
  - T4 tumor (N=1)
- All upstaged patients received adjuvant treatment
- Median follow-up after surgery: 40.6 months
- Median overall survival after surgery: 38 months
  - 1-year survival: 100%
  - 2-year survival: 80%

Verstegen NE, ELCC 2015

Stage I NSCLC

Invasive nodal staging before SABR?

SABR with endoscopic mediastinal staging

STAGE study: **ST**ereotactic **A**blative radiotherapy for lung cancer after sta**G**ing with **E**ndosonography

Prof J.T.Annema,
Email: j.t.annema@amc.uva.nl

Prof S. Senan

(suspected) NSCLC and possible SABR candidate

↓

One of the following features based on CT-PET imaging:
Centrally located clinical T1-T2
Peripheral located T2
Suspicion of N1 or N2 disease
Non-FDG avid primary lung tumor and lymph nodes

↓

Determine loco-regional nodal status (N0-N3) based on CT-PET imaging

↓

INTERVENTION:
Single scope complete mediastinal and hilar staging procedure:
EBUS followed by EUS-B
Optional:
Sputum collection and bronchoscopy with minimal lavage

↓

Determine change of loco-regional nodal status (N0-N3) based on endosonographic staging

Priority areas for research

PATIENT SELECTION

- If a RCT is not feasible in medically operable ES-NSCLC patients, investigate the role of SABR through CER using detailed prospective registration of comorbidity and toxicity data
- Establish the risks and benefits of SABR in CT-screened ES-NSCLC lung cancer patients
- Develop robust prediction models for distant metastasis risk in order to guide adjuvant treatment
- Establish the safety and appropriate administration of adjuvant systemic therapy
- Identify patients in whom SABR should not be offered, due to high risk of early mortality from competing causes

Louie AV, Radioth Oncol 2015

Priority areas for research

QUALITY ASSURANCE

- Monitor outcomes of SABR in community practice, as well as salvage surgery due to misclassification of benign fibrosis
- Establish optimal SABR doses for central tumors
- Determine safe dose-toxicity criteria for critical normal organs

DIAGNOSTIC MANAGEMENT

- Establish the role of biopsy in the FDG-PET era in different global populations
- Determine the role of EBUS/EUS for staging subgroups of FDG-PET staged patients

SURVIVORSHIP

- Develop SDM modules for patients with ES-NSCLC
- Explore the safety and role of surgical or re-SABR salvage

Louie AV, Radioth Oncol 2015

Conclusions

- Keeping up with changes in developments in diagnosis, staging and follow-up of early-stage NSCLC is essential in order to influence members of your MDT.
- We need improvements in treatment workflow, including non-invasive volumetric imaging.
- Be critical when evaluating ‘new’ developments as late recurrences are possible.
- Ensure continuous training and education for all members of your tumor board MDT.

UniversityHospital Zurich

Stereotactic body radiotherapy for stage I NSCLC:

Practice using Elekta technology

Matthias Guckenberger, Coen Hurkmans

ESTRO

UniversityHospital Zurich

OAR definition

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. 1442–1457, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.07.1977

CLINICAL INVESTIGATION **Normal Tissue**

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

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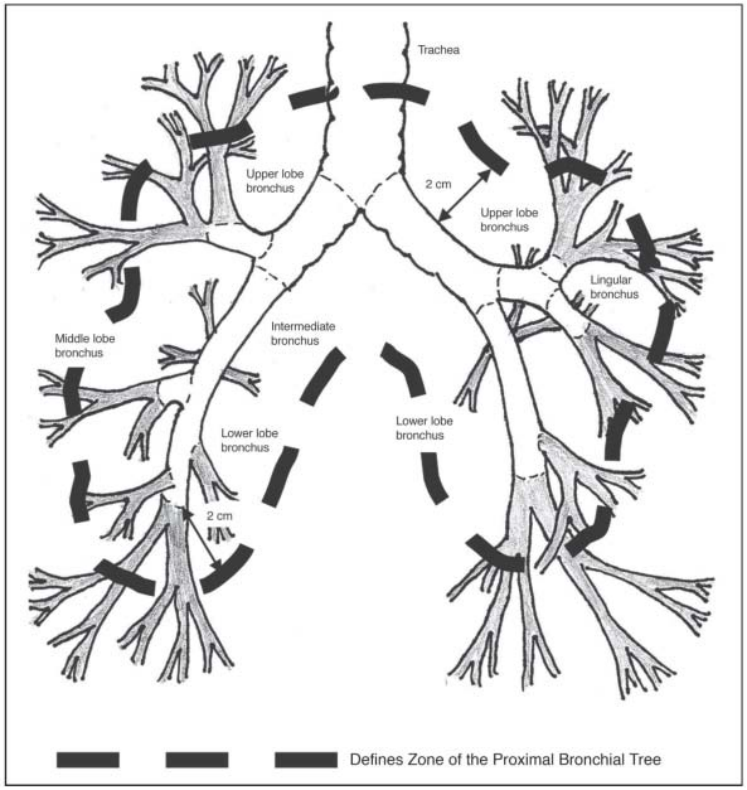
ESTRO

OAR definition

Proximal bronchial tree



OAR definition

Proximal bronchial tree

- Delineated on the mediastinal CT window
- Includes mucosa, submucosa, cartillage rings, and airway channels associated with these structures
- Starts 2 cm above carina and ends at the site of segmental bifurcation of the bronchi

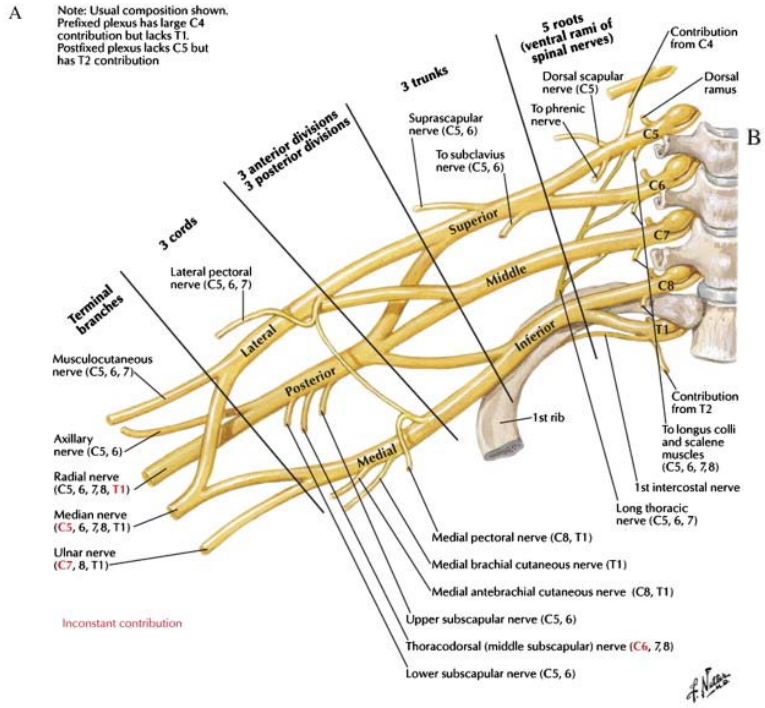
OAR definition

Central tumor location according to RTOG 0813

Tumors that are **immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura)** also are considered central tumors and are eligible for this protocol.

OAR definition

Brachial plexus



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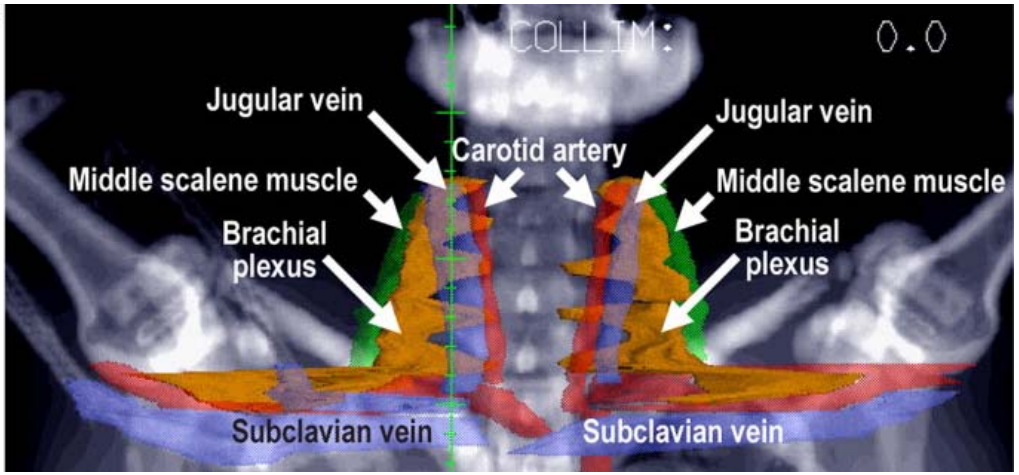

Hall IJROBP 2008, Kong IJROBP 2011

OAR definition

Brachial plexus

1. Identify and contour C5, T1, and T2.
2. Identify and contour the subclavian and axillary neurovascular bundle.
3. Identify and contour anterior and middle scalene muscles from C5 to insertion onto the first rib.
4. To contour the brachial plexus OAR use a 5-mm diameter paint tool.
5. Start at the neural foramina from C5 to T1; this should extend from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles.
6. For CT slices, where no neural foramen is present, contour only the space between the anterior and middle scalene muscles.
7. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle.
8. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head.
9. The first and second ribs serve as the medial limit of the OAR contour.

Hall IJROBP 2008, Kong IJROBP 2011

OAR definition

Chest wall

Different CLINICAL endpoints:

- Rip fracture
- Intercostal neuralgia
- Myositis
- Fibrosis
- Skin ulceration

OAR definition

Chest wall

Study	CW definition
Dunlap (IJROBP, 2010)	3 cm expansion of ipsilateral lung – [lung, Mediastinum and vertebral body]
Creach (R&O, 2012)	As in Dunlap
Andolino (IJROBP, 2011)	3 cm expansion of ipsilateral lung/liver – [lung/liver, mediastinum and vertebral body] + ribs separately
Bongers (IJROBP 2011)	expansion of the lungs with 2 cm in lateral, posterior, and anterior directions except in the direction of the mediastinum, with inclusion of intercostal muscles but excluding other muscles and skin
Stephans (IJROBP 2012)	arc of all ipsilateral soft tissue outside of lung tissue from the edge of the sternum cir- cumferentially to the edge of the vertebral body including the spinal nerve root exit site

UniversityHospital Zurich

SBRT tolerance doses

Organ at risk	One fraction (RTOG 0915)	Three fractions (RTOG 0618 / 1021)	Four fractions (RTOG 0915)	Five fractions (RTOG 0813)	Eight fractions (Haasbeck et al. 2011)
Trachea and large bronchus	D_{max} 20.2 Gy	D_{max} 30 Gy	D_{max} 34.8 Gy 15.6 Gy <4cc	D_{max} 105% * 18 Gy < 5cc **	D_{max} 44 Gy
Heart	D_{max} 22 Gy 16 Gy < 15cc	D_{max} 30 Gy	D_{max} 34Gy 28 Gy <15cc	D_{max} 105% * 32 Gy < 15cc	---
Esophagus	D_{max} 15.4 Gy 11.9 Gy < 5cc	D_{max} 25.2 Gy 17.7 G< 5cc	D_{max} 30Gy 18.8 Gy<5cc	D_{max} 105% * 27.5 Gy < 5cc **	D_{max} 40 Gy
Brachial plexus	D_{max} 17.5 Gy 14 Gy < 3cc	D_{max} 24 Gy 20.4 Gy < 3cc	D_{max} 27.2 Gy 23.6Gy < 3cc	D_{max} 32 Gy 30 Gy < 3cc	D_{max} 36 Gy
Chest wall	D_{max} 30 Gy 22 Gy < 1cc	30 Gy < 30cc 60 Gy < 3 cc	D_{max} 27.2 Gy 32Gy<1cc	30 Gy < 30cc 60 Gy < 3 cc	---
Spinal cord	D_{max} 14 Gy 10 Gy < 0.35cc	D_{max} 18 Gy (RTOG 0236)	D_{max} 26Gy 20.8Gy < 0.35cc	D_{max} 30 Gy 22.5 Gy <0.25cc	D_{max} 28 Gy

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Radiographic follow-up

Acute changes after SBRT:

- diffuse consolidation
- patchy consolidation
- diffuse ground-glass opacities (GGO)
- patchy GGO
- no change

Late changes after SBRT:

- modified conventional (consolidation, volume loss, and bronchiectasis similar to but less extensive than conventional radiation fibrosis)
- scar-like fibrosis (linear opacity in the region of the original tumor)
- mass-like fibrosis
- no change

Radiographic follow-up

Acute changes after SBRT: Late changes after SBRT:

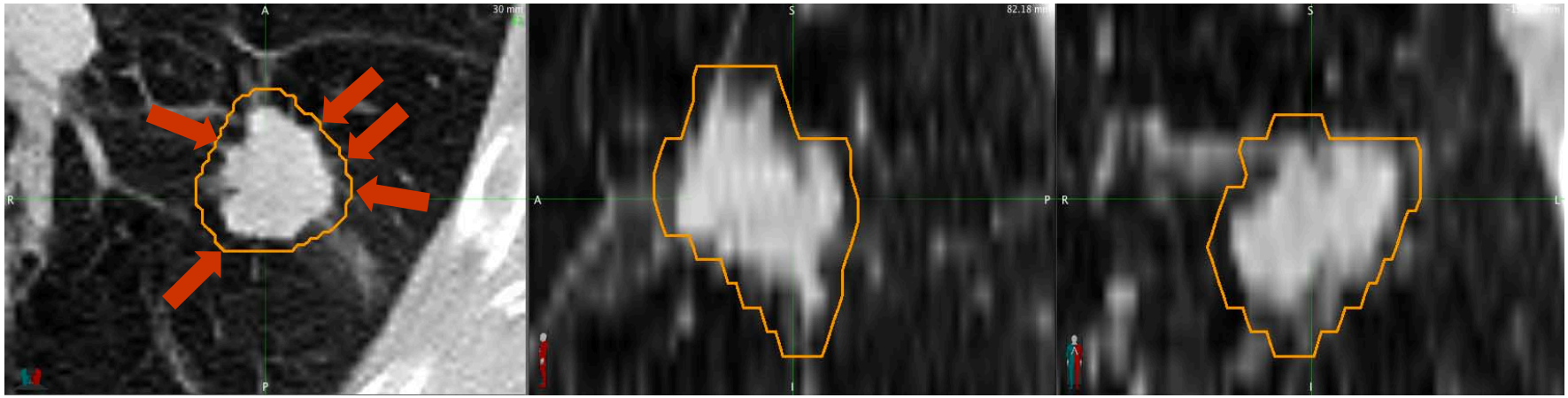
Hung Radiother Oncol 2012

Study		Benign acute CT changes (%)					Benign late CT changes (%)				Recurrence features
		Diffuse consolidation	Patchy consolidation	Diffuse GGO	Patchy GGO	No evidence of increasing density	Modified conventional	Scar-like fibrosis	Mass-like fibrosis	No evidence of increasing density	
Dahele et al. [9]	Acute $n = 67$ lesions Late $n = 68$ lesions	16	24	7	6	46	71	11	7	11	Recurrences excluded from study
Kimura et al. [17]	$n = 52$ lesions	38	15	12	2	33	62	22	17	0	Four based on CT enlargement, evolved from scar-like ($n = 2$) and mass-like ($n = 2$) fibrosis
Palma et al. [18]	3DCRT $n = 50$ patients	14	22	4	16	44					Excluded from study
	RA $n = 25$ patients	32	8	4	16	40					
Trovo et al. [19]	6 months $n = 33$ patients 12 months $n = 35$ patients	27	33	12	6	21	46	14	20	20	Three based on CT enlargement and increased SUV, evolved from diffuse GGO ($n = 1$) patchy consolidation and GGO ($n = 2$)
Weighted Averages	Acute $n = 227$ Late $n = 155$	24	21	8	8	38	62	15	14	9	

Target volume definition

Target volume definition:

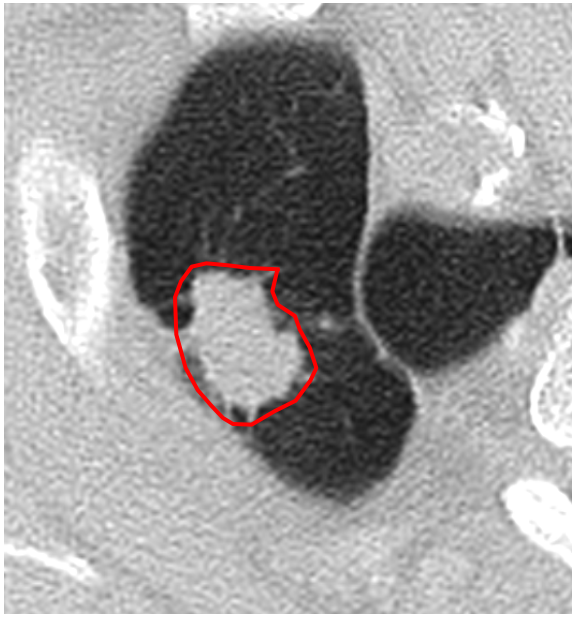
GTV = CTV but spiculae included into GTV

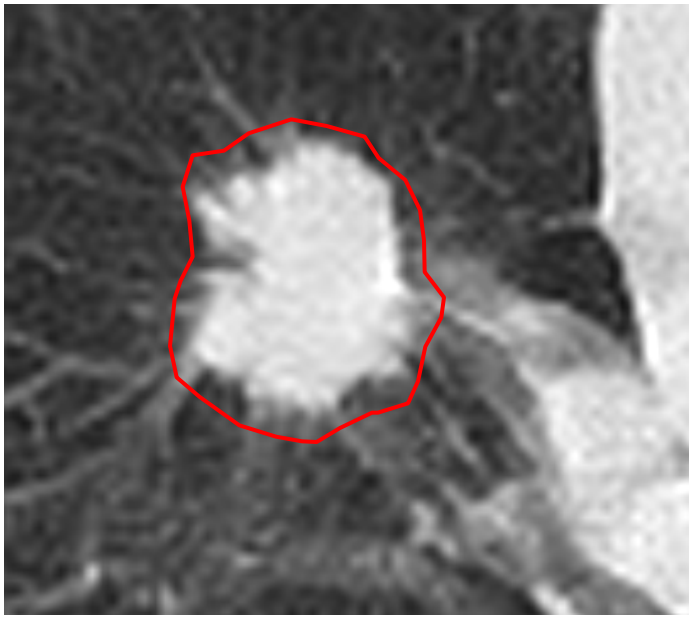


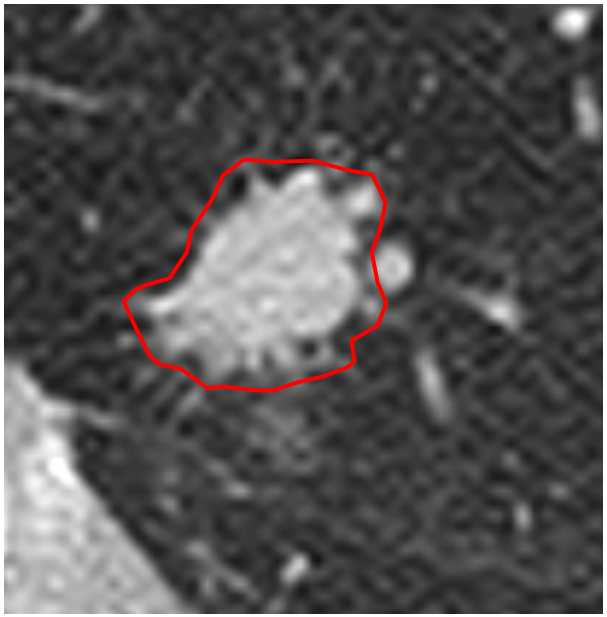
Target volume definition

Target volume definition:

GTV = CTV but spiculae included into GTV

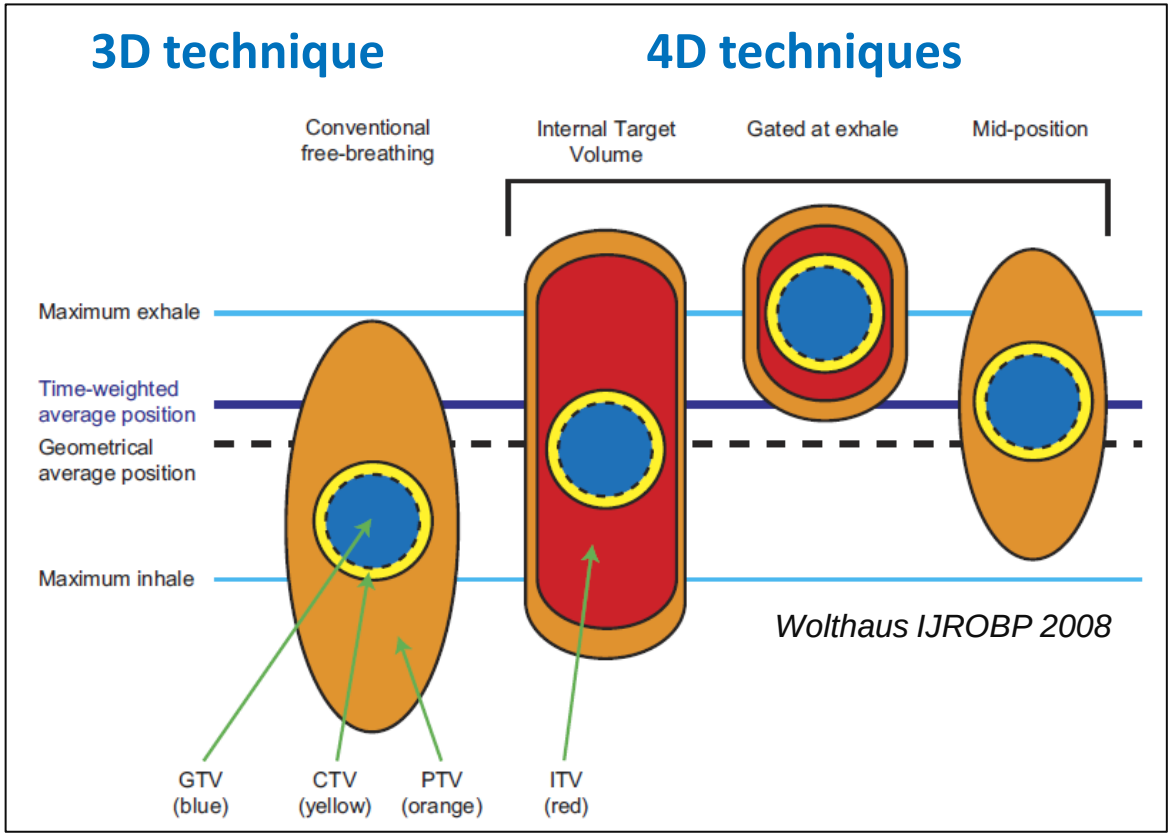




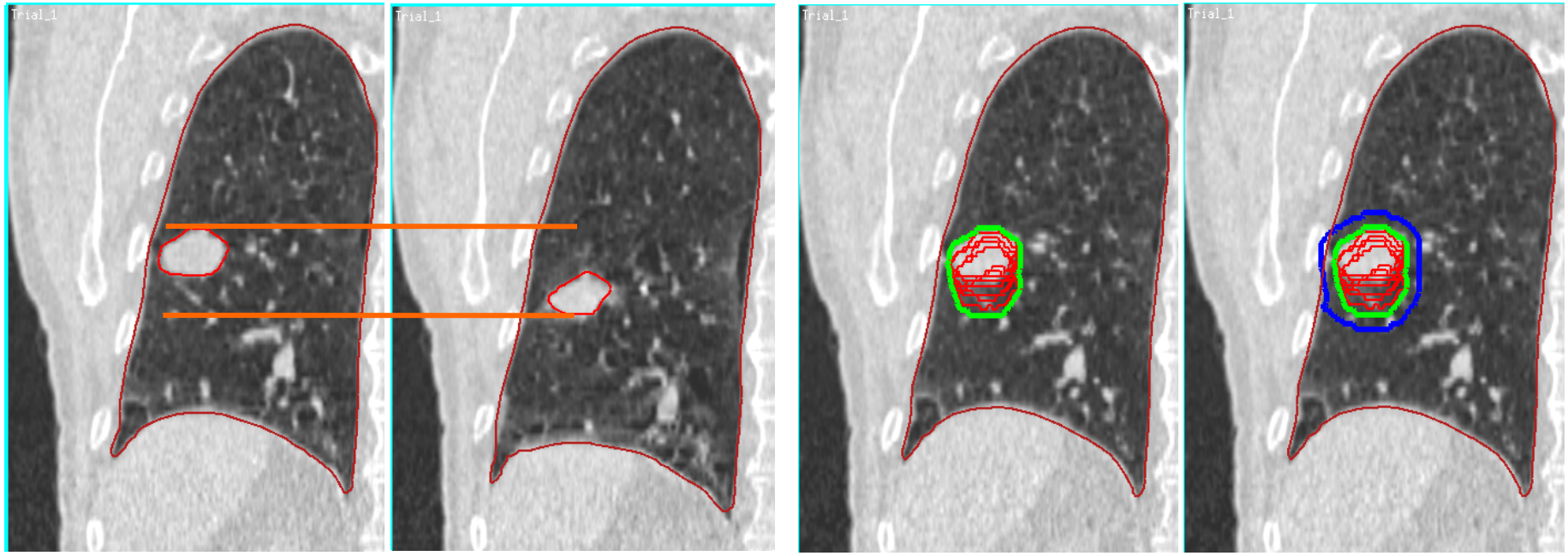


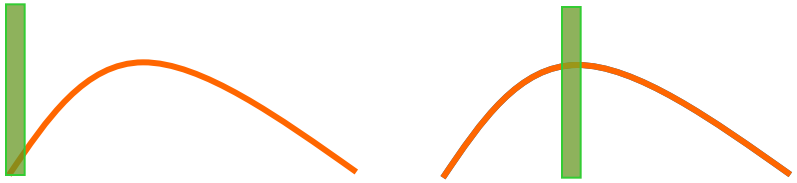
Motion compensation strategy

3D versus 4D target volume concepts



Internal target volume concept





ITV → X mm → PTV

Internal target volume concept

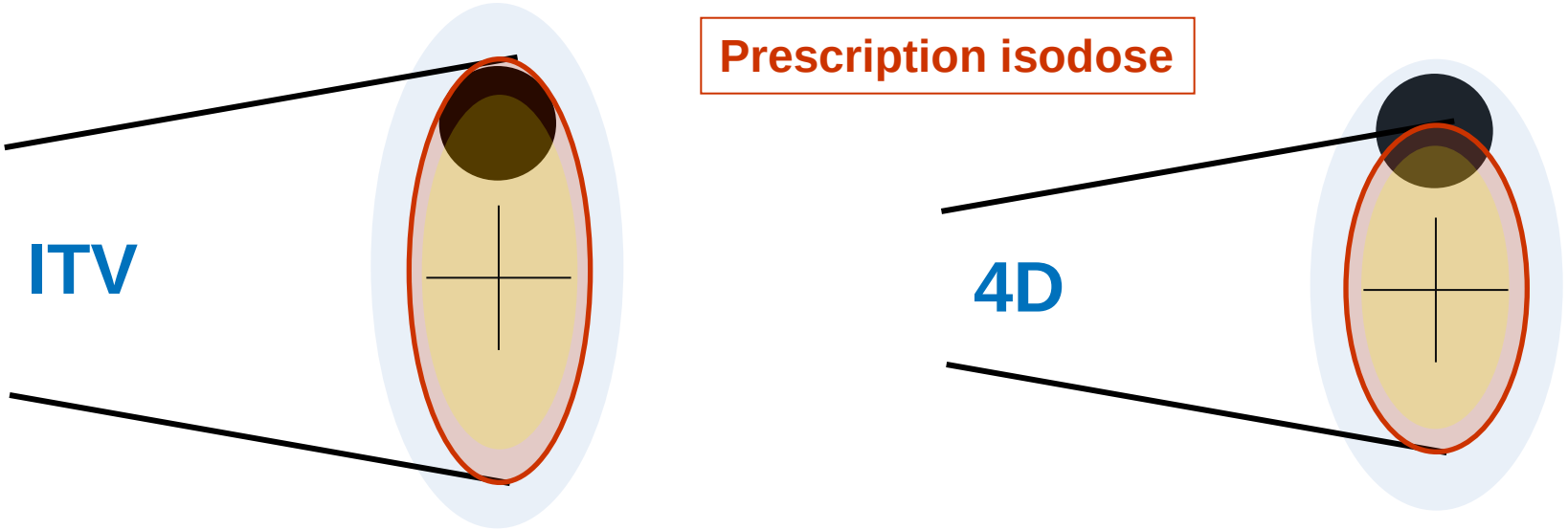
Pro:

- Large clinical experience
  - Low toxicity
  - High rates of LC
- Short RT delivery times
- Straight work-flow

Cons:

- Larger target volumes

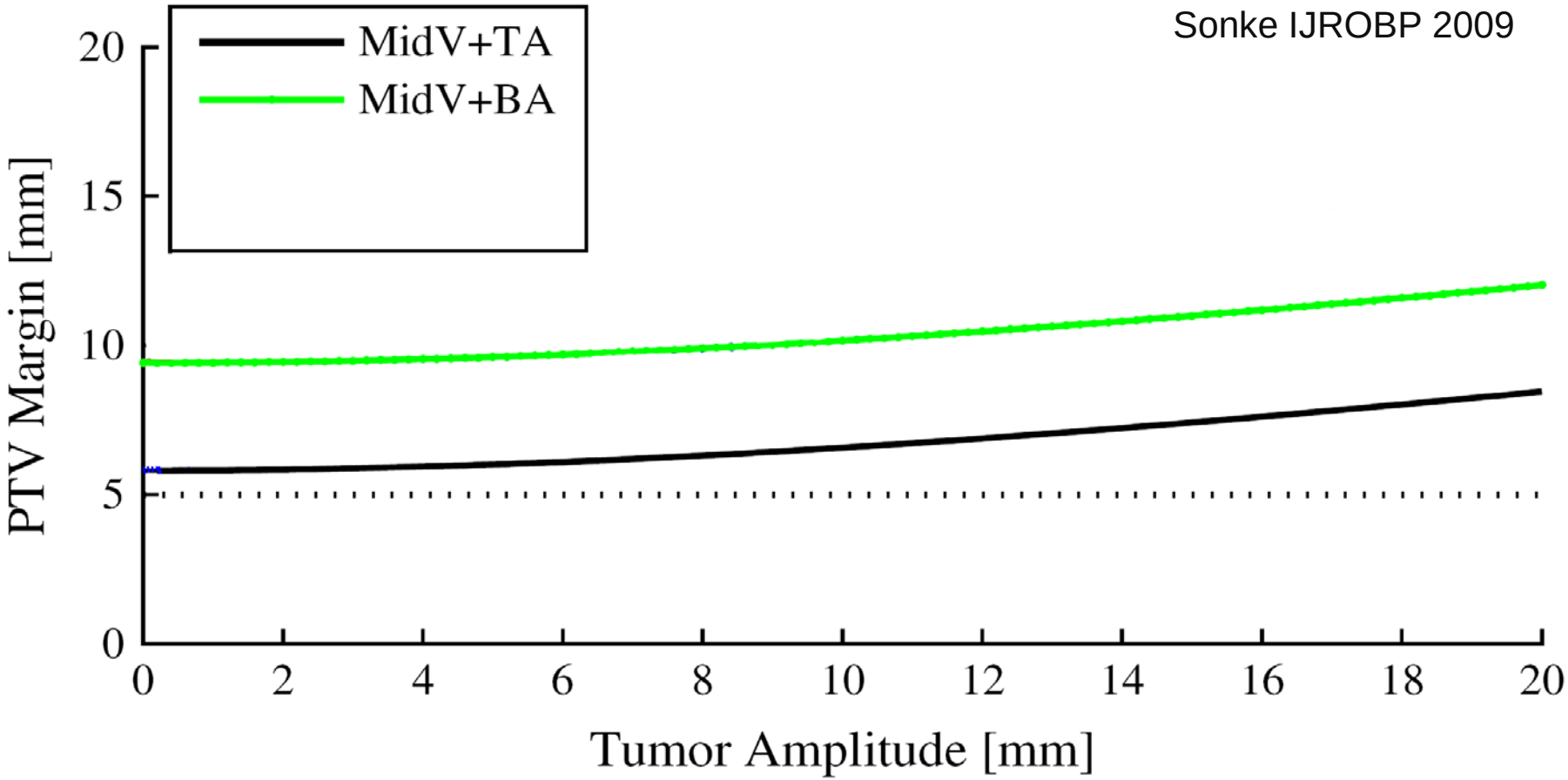
Mid-ventilation concept



- Periodical tumor motion around the mean tumor position
- Radiation beams do not need to encompass the whole breathing amplitude
  - Dose “outside” the beams
  - Short probability of tumor “outside” the beams
  - Compensation of dose loss with higher doses in the beam centre

Mid-ventilation concept

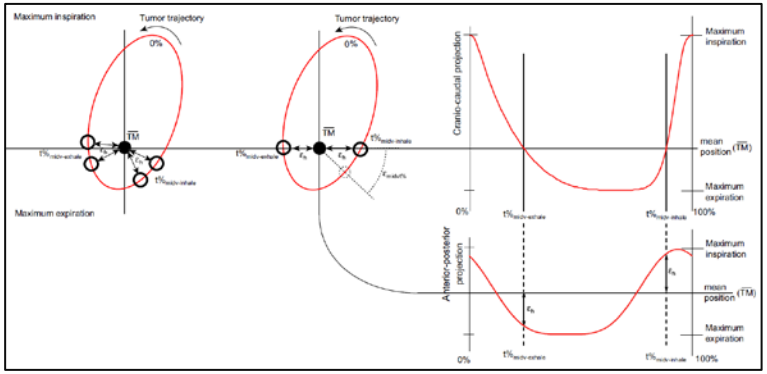
Sonke IJROBP 2009



Small benefit of gating and tracking for motion amplitudes < 20mm

Midventilation concept: how does it work

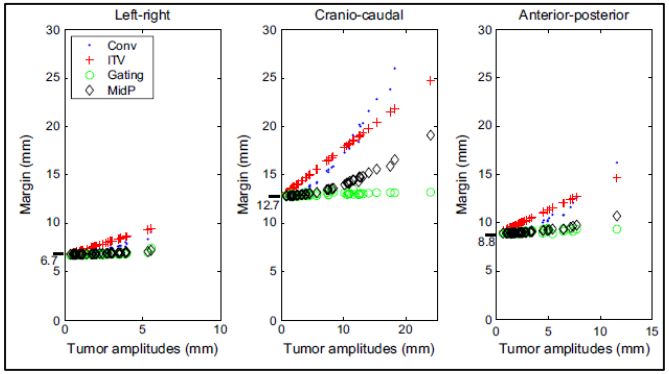
Step 1: Mid ventilation Scan



Re-construction of mid-ventilation phase for treatment planning and IGRT

Wolthaus IJROPB 2006

Step 2: Margins



Margin evaluation depeding on motion magnitude, separately for AP, LA and CC direction

Wolthaus IJROPB 2008

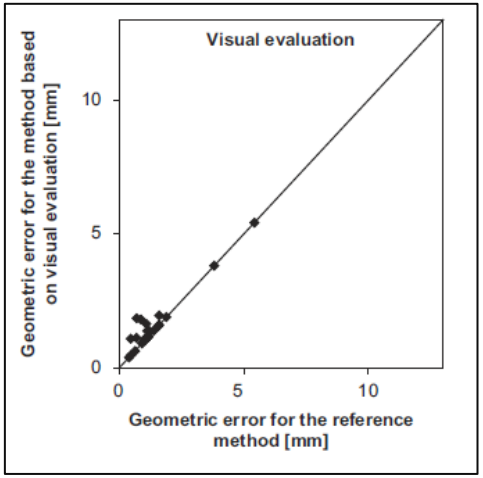
➢ **Not implemented into commercial software**

Midventilation concept: the pitfalls

„Too complex“

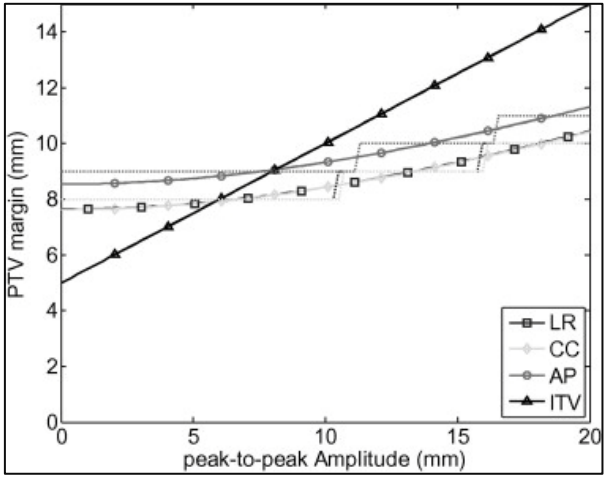
- Used by only few specialized centers

Visual identification of midventilation position



Nygaard Acta Oncol 2013

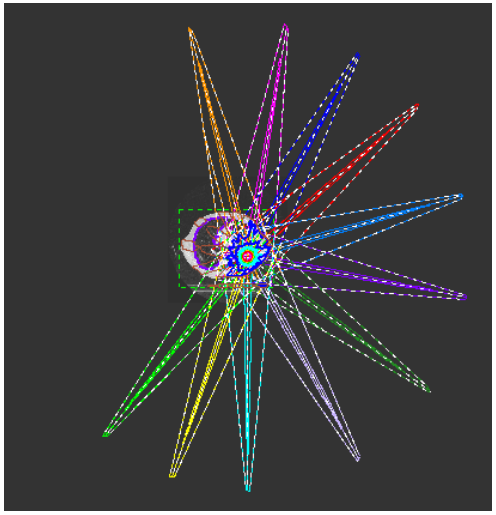
Step-wise margins



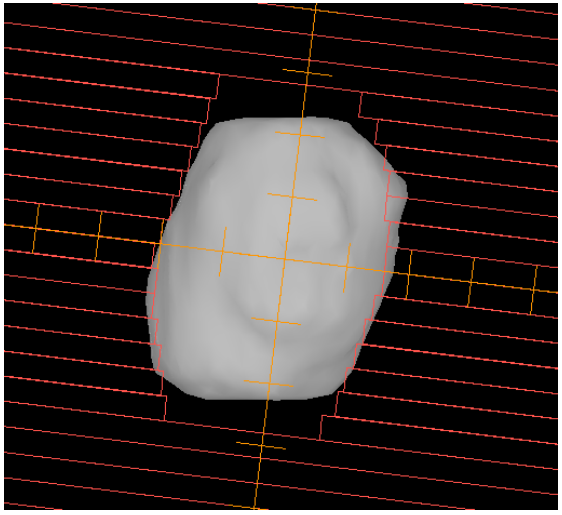
Peulen Radiother Oncol 2014

Treatment planning

3D conformal treatment planning:



11 coplanar fields



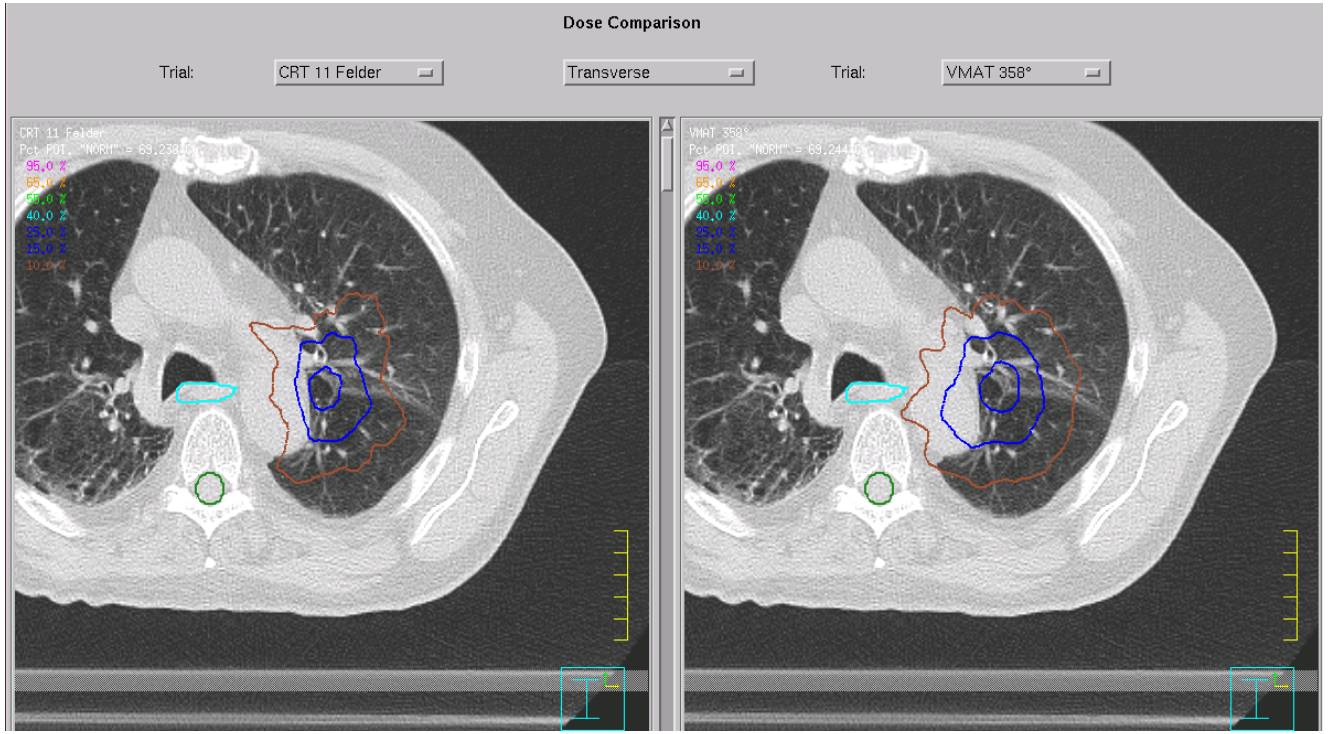
3D conformal beam shaping

- Particular focus on sparing of contralateral lung
- Inhomogeneous dose distributions by negative “margin” between PTV edge and field size

UniversityHospital Zurich

Treatment planning

3D conformal treatment planning: VMAT



VMAT:

- different, not better dose distributions
- Delivery times - 1min

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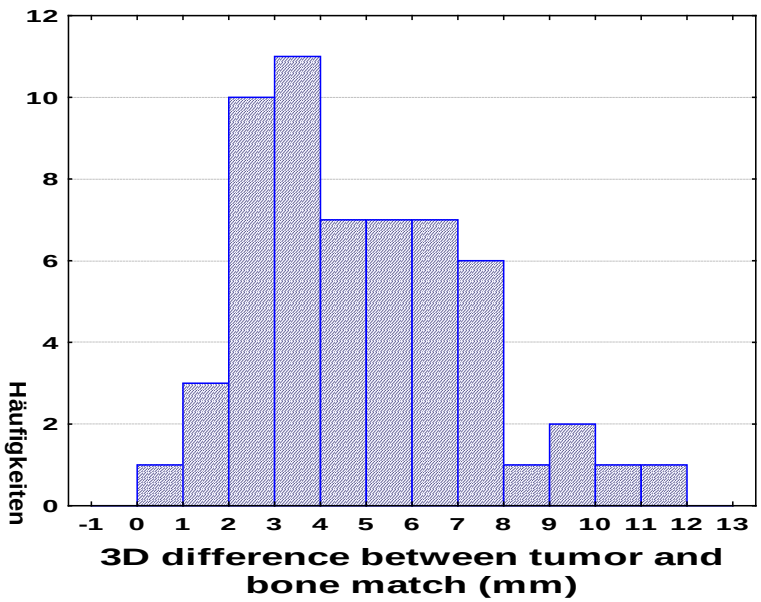
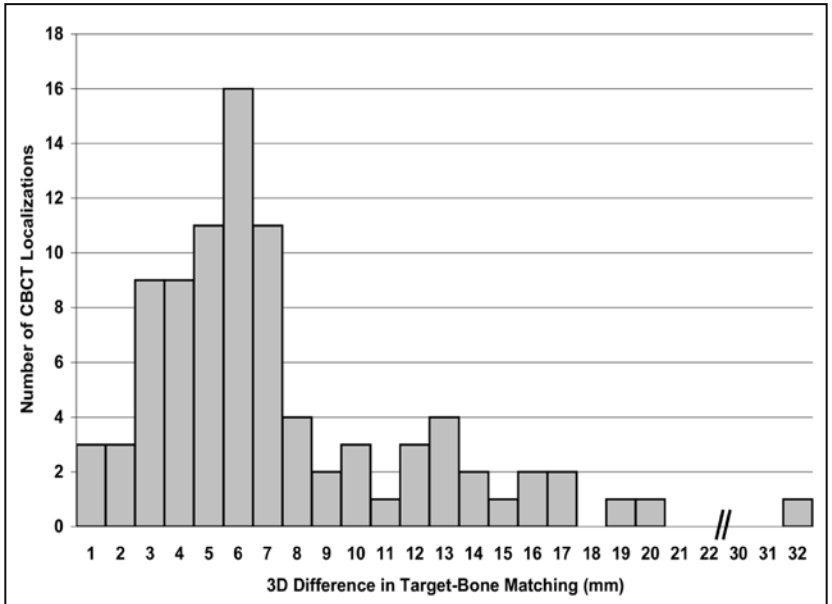
Treatment delivery: IGRT



Mean: 5.3mm

90th percentile: 8mm

Guckenberger et al. 2006



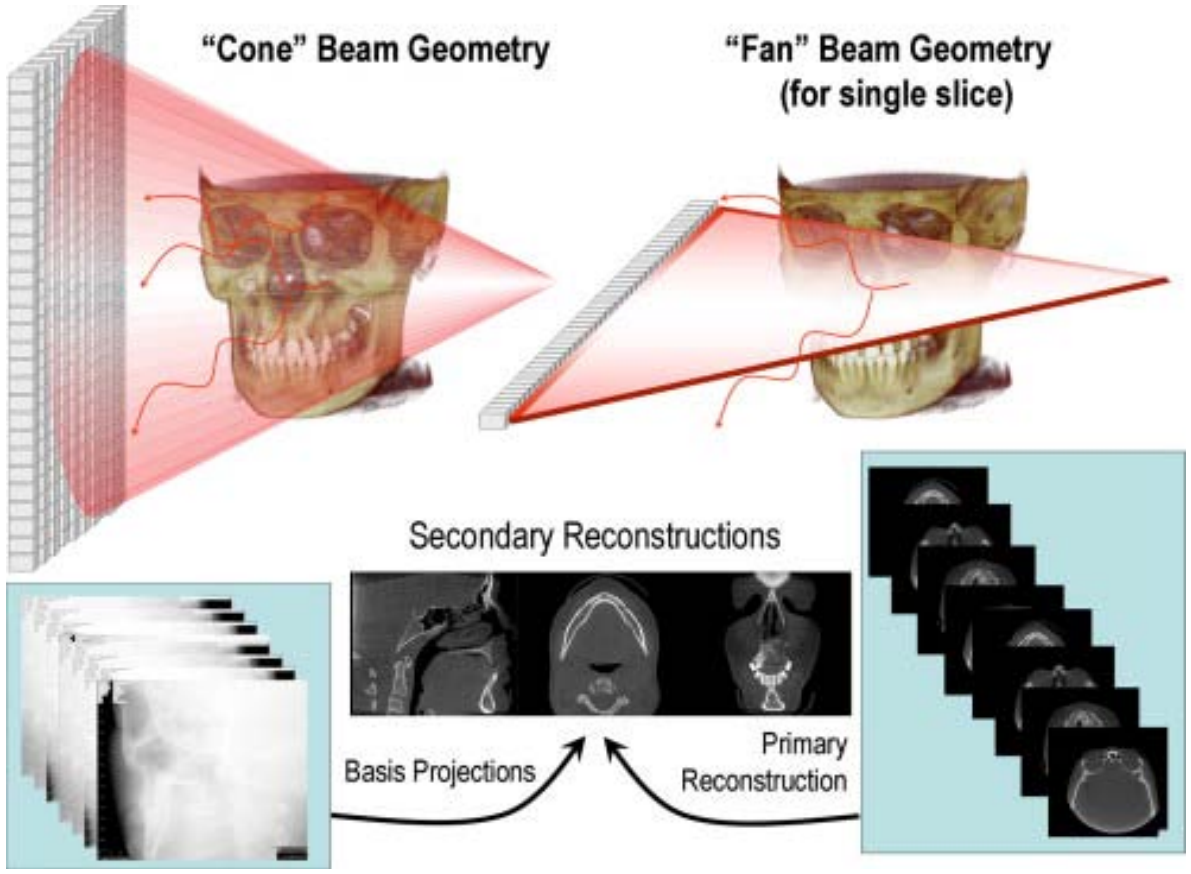
Mean: 6.8mm

90th percentile: 13.9mm

Prudie et al. 2007

- DAILY pre-SBRT IGRT required
- Post-correction and intra/post-treatment imaging for QA

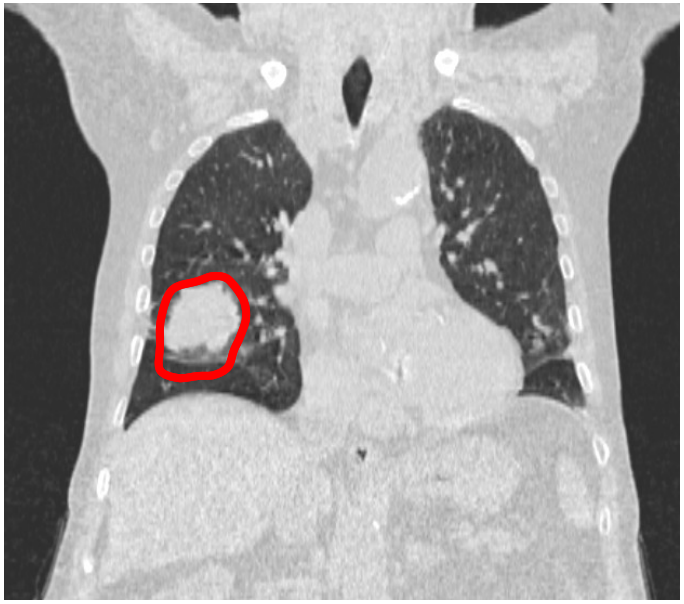
CT: Cone & Fan beam imaging



Scarfe 2008

IGRT using CBCT technology

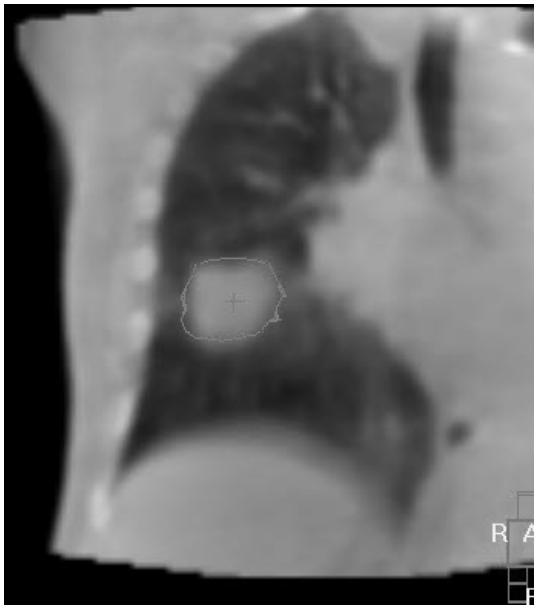
Treatment planning



Respiration correlated CT

Manual contour registration

Treatment delivery

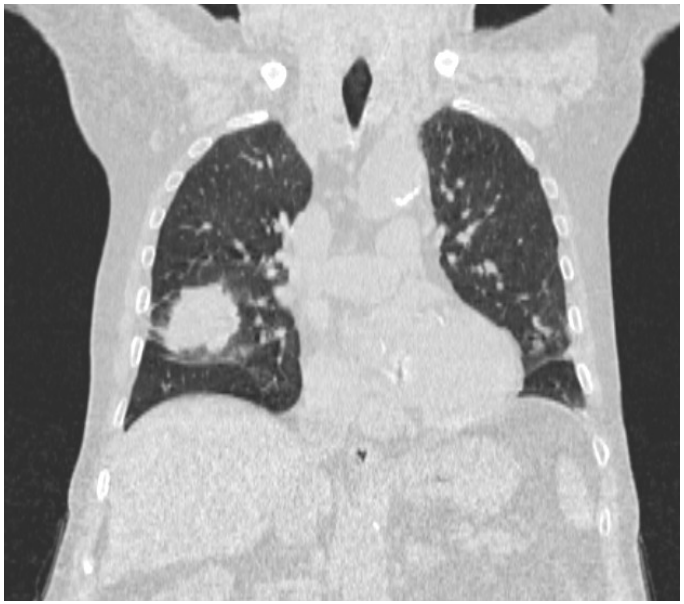


„Conventional“ slow CBCT

Guckenberger Acta Ocol 2006

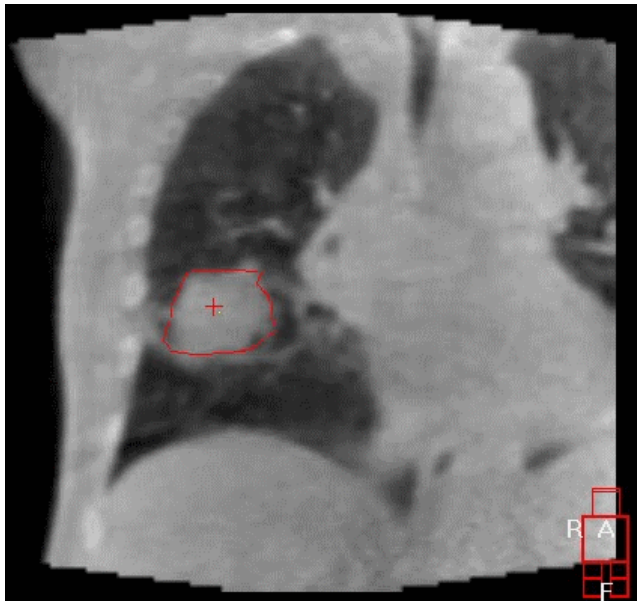
How to incorporate breathing motion into the IGRT work-flow ?

Treatment planning



XVI 4.5

Treatment delivery



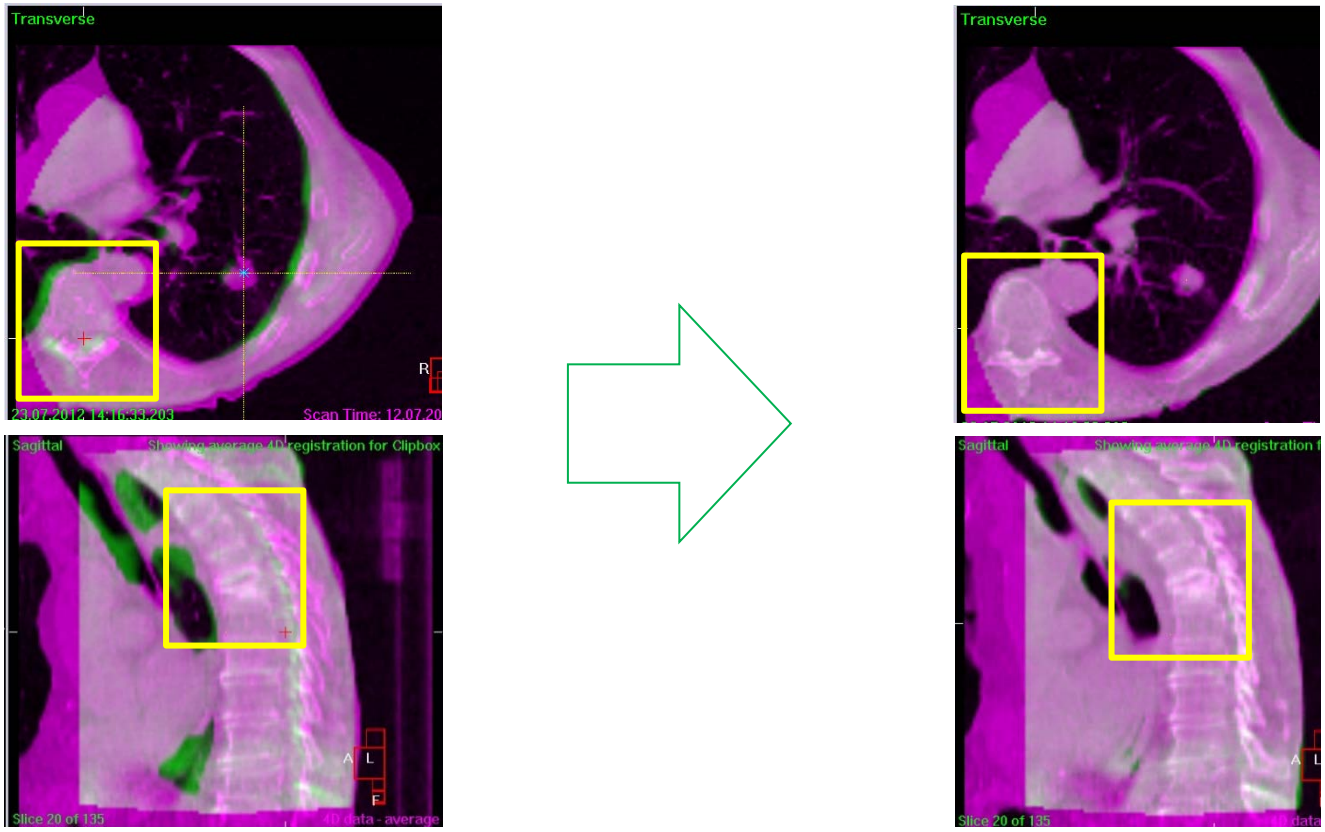
Respiration correlated CT

Respiration correlated CBCT

4D IGRT using CBCT technology

Image guidance: XVI 4.5

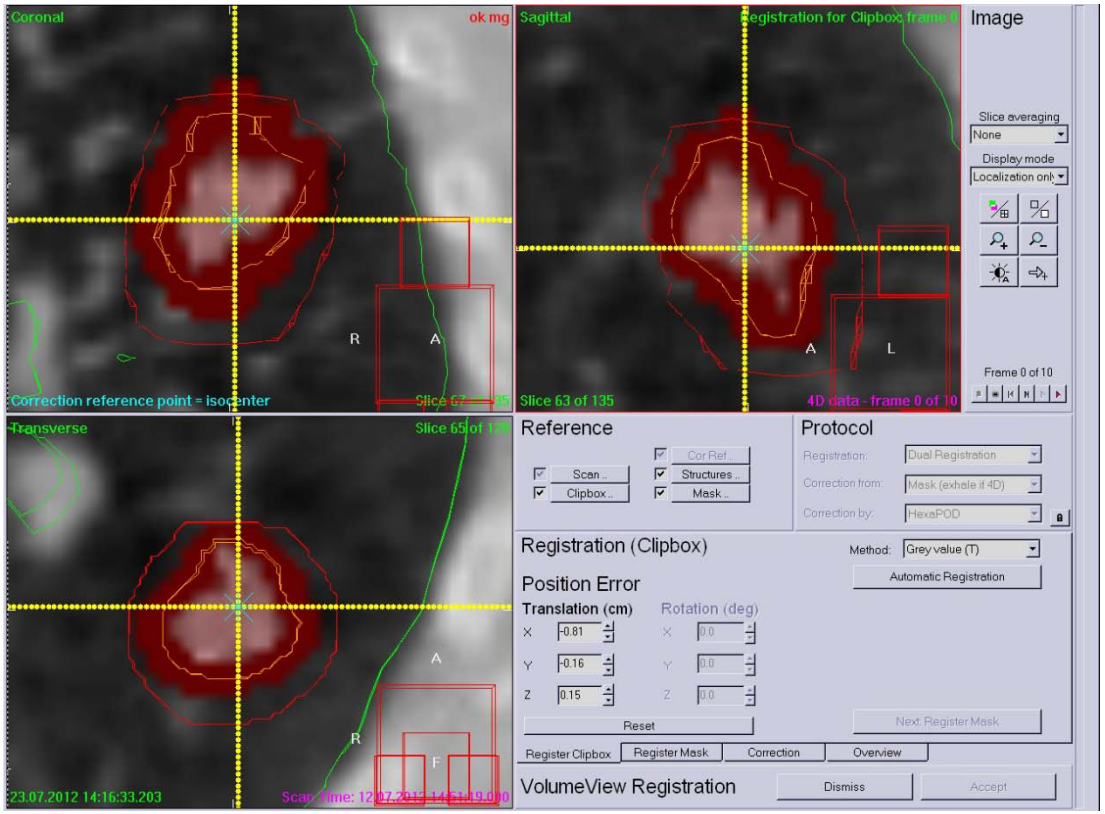
- Start with bone registration



4D IGRT using CBCT technology

Image guidance: XVI 4.5

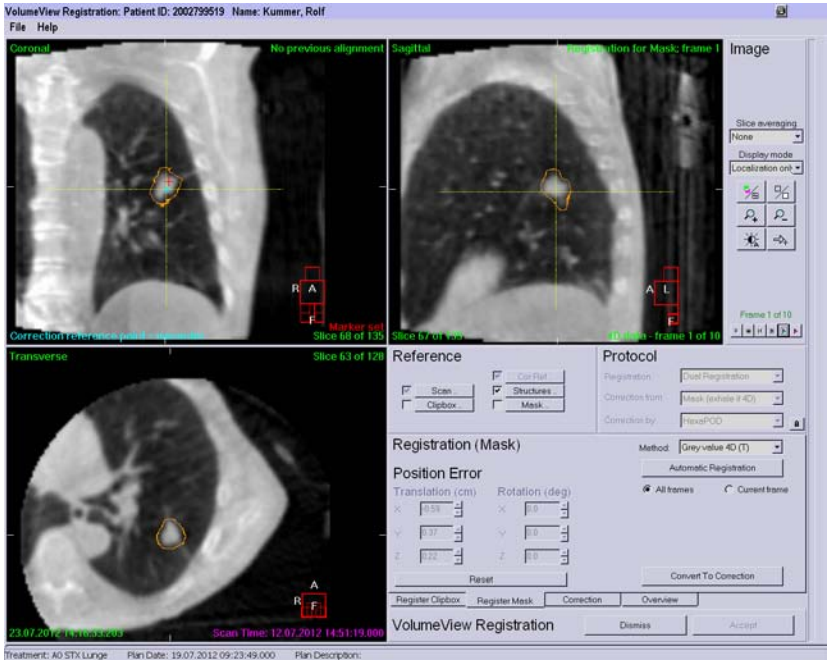
- "mask definition": CTV + 3mm excluding all bony structures



4D IGRT using CBCT technology

Image guidance: XVI 4.5

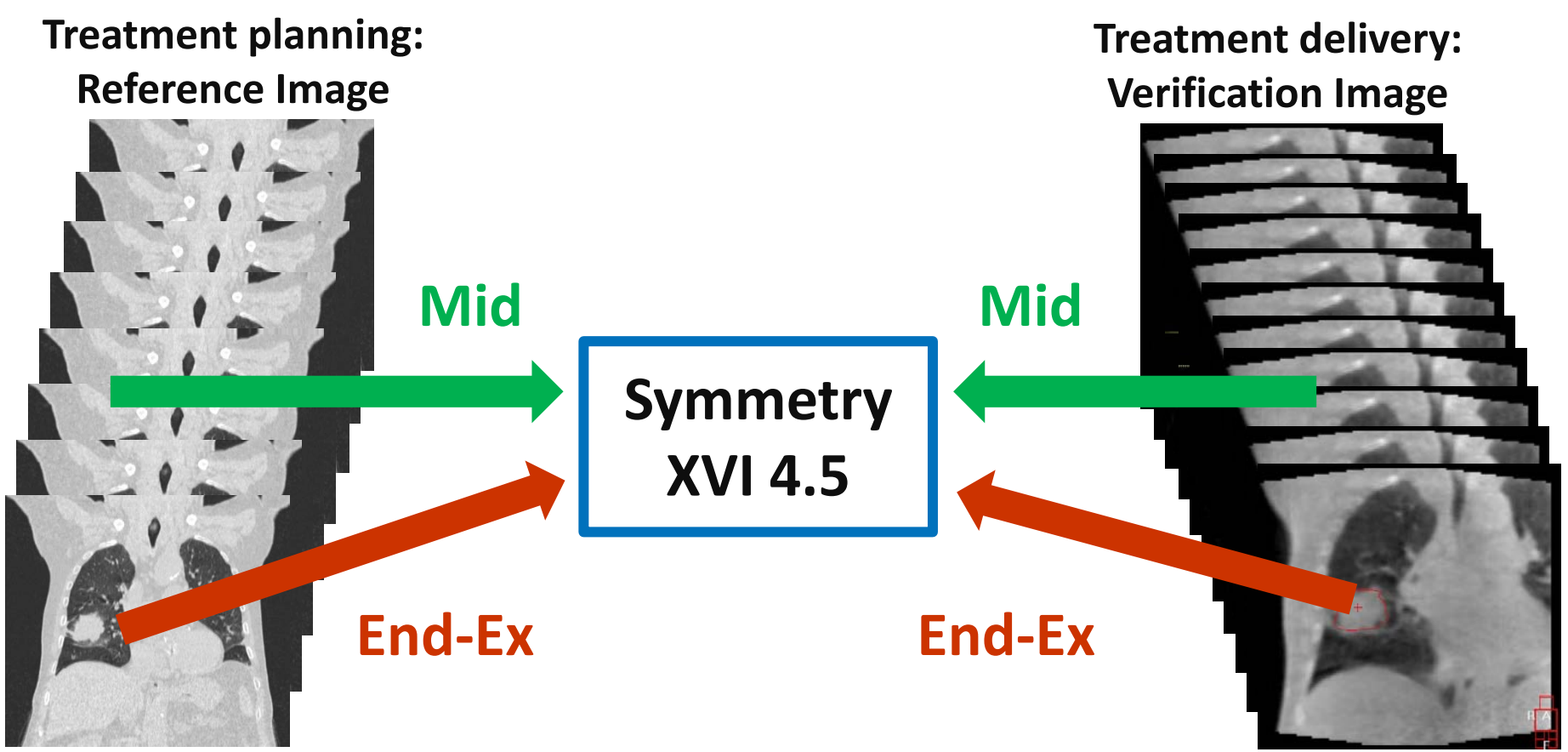
- 4D registration: finding the target in all 4D-CT phases



Target fixed in space

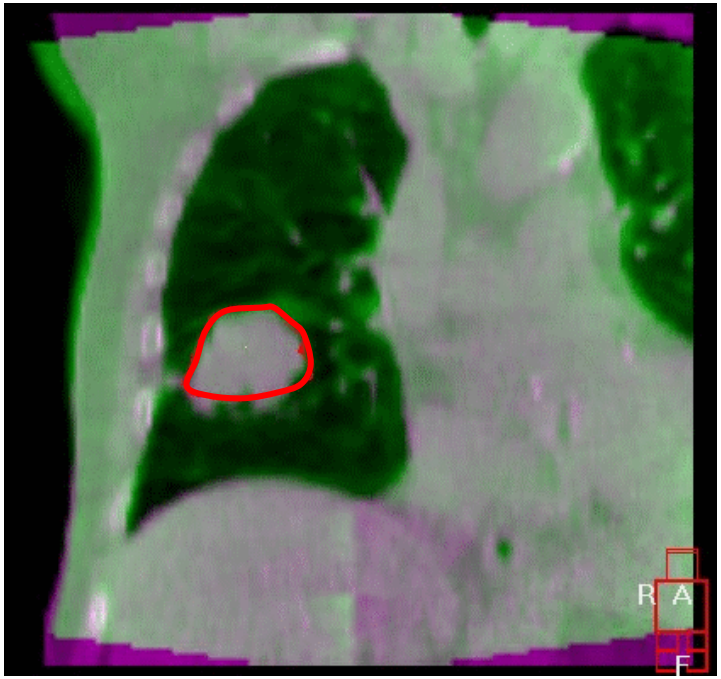
4D IGRT using CBCT technology

4D volumetric image guidance:



4D IGRT using CBCT technology

4D volumetric image guidance:



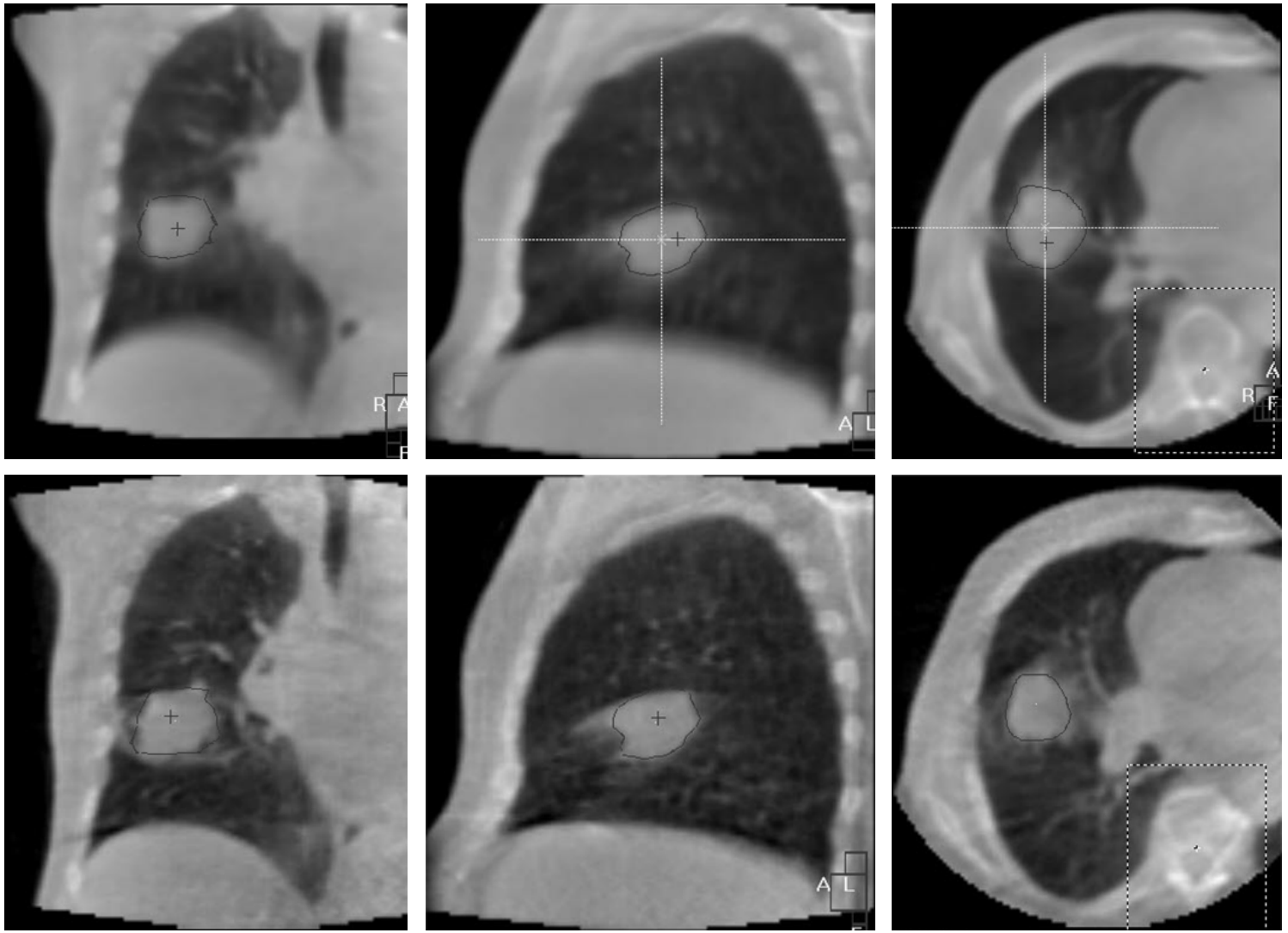
End-exhalation as reference: „tumor moves into the exhalation GTV contour and within the ITV contour“

Lung SBRT using Elekta technology

UniversityHospital Zurich

Conventional „slow“ CBCT

Respiration correlated CBCT



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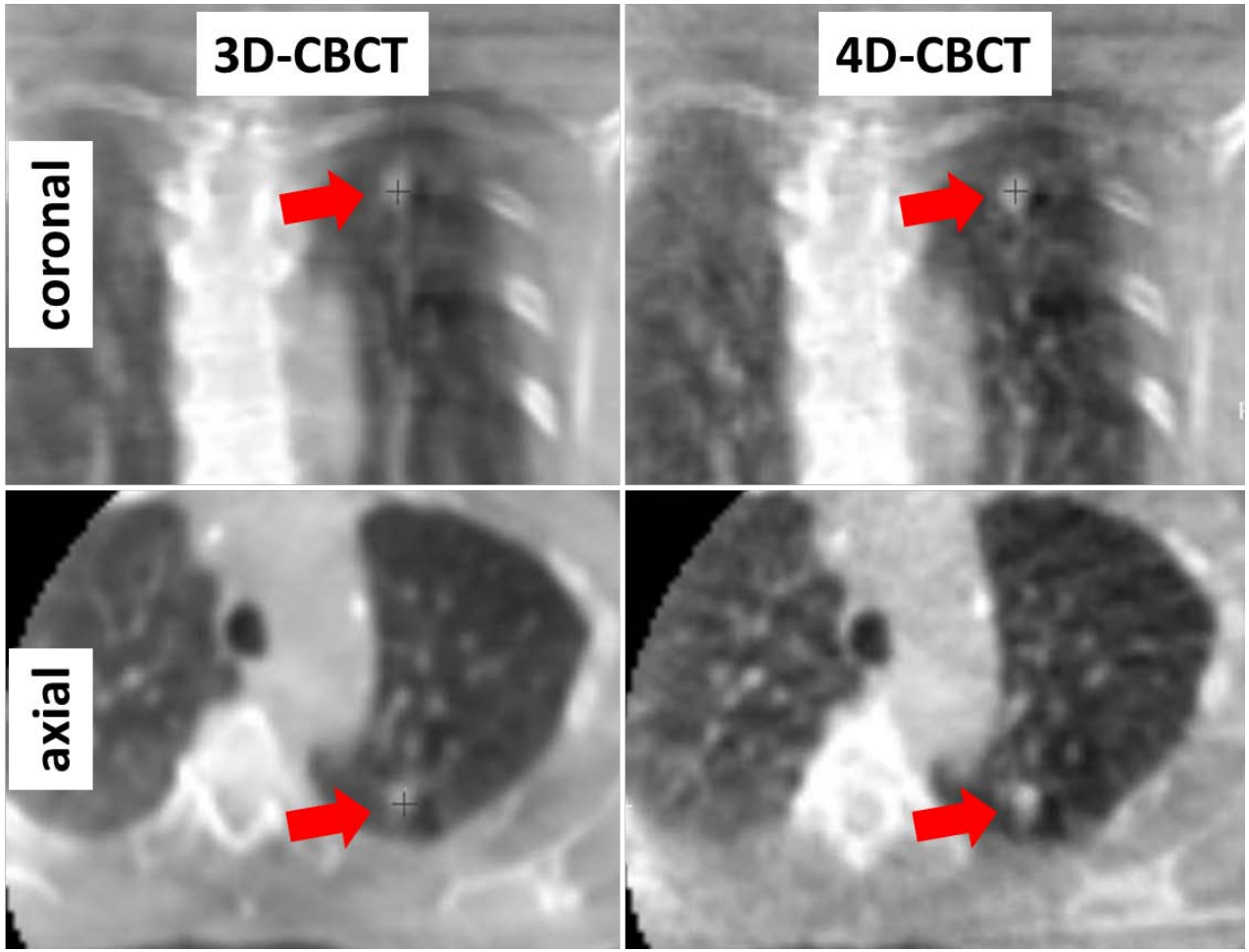
Where 4D CBCT improves accuracy



Small
Mobile
Tumors

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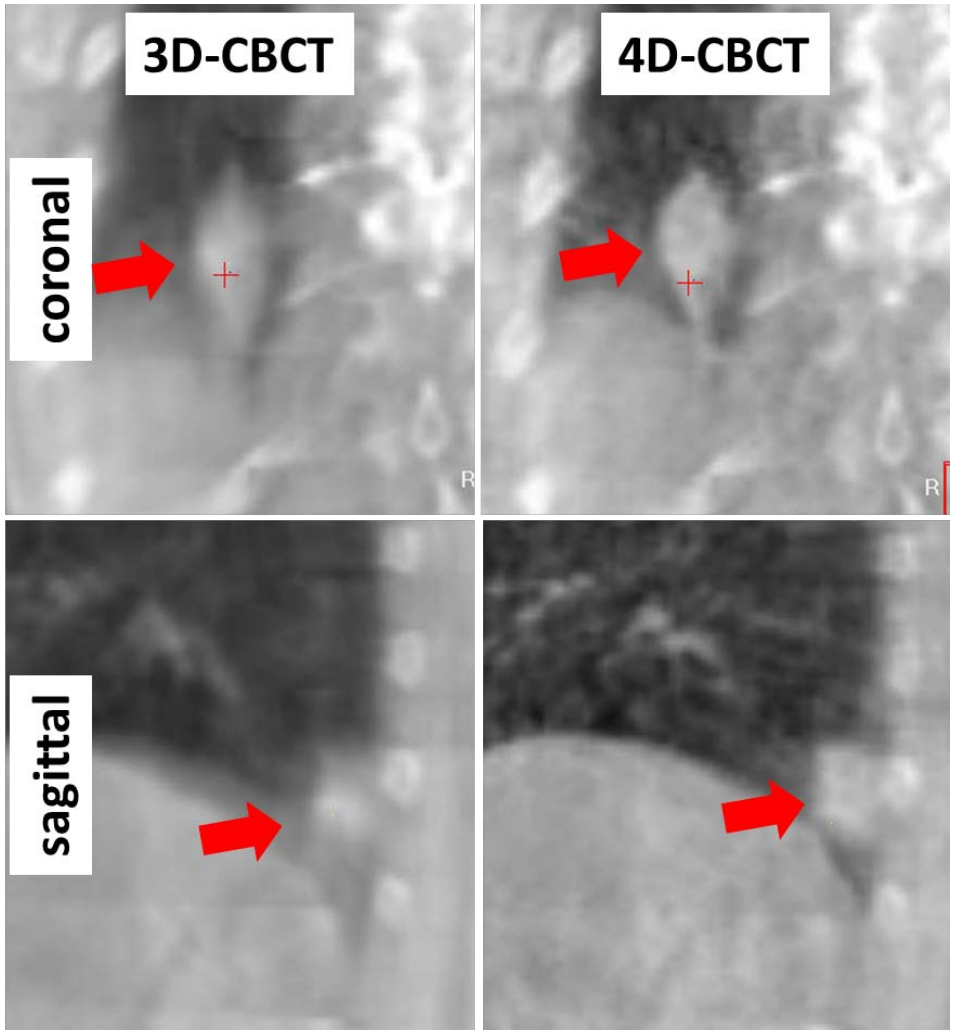
Where 4D CBCT improves accuracy



Mobile tumors located immediatly superior the diaphragm

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Where 4D CBCT improves accuracy

		Variability as standard deviation between observers	Variability as maximum range between observers
		SI [mm]	SI [mm]
IG-4D	All observers	0.6	1.8
IG-ITV	All observers	1.5	3.8

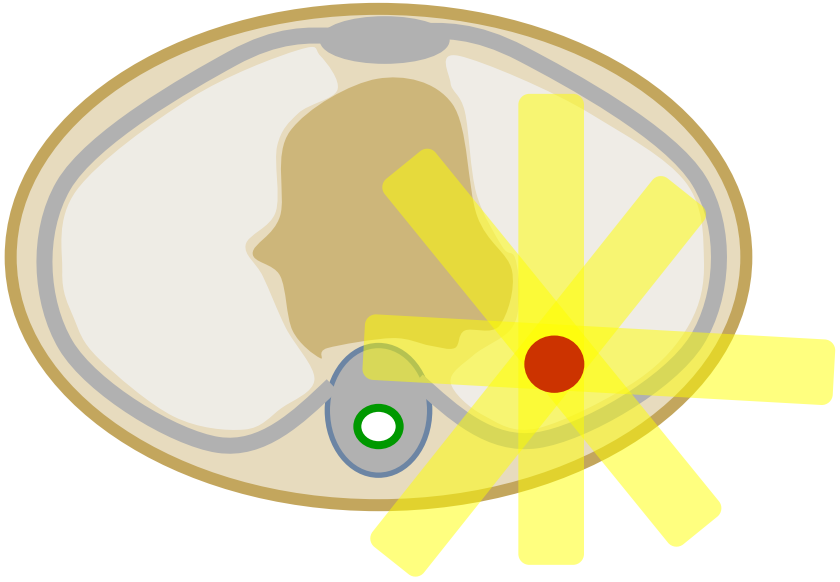
Sweeney RO 2012

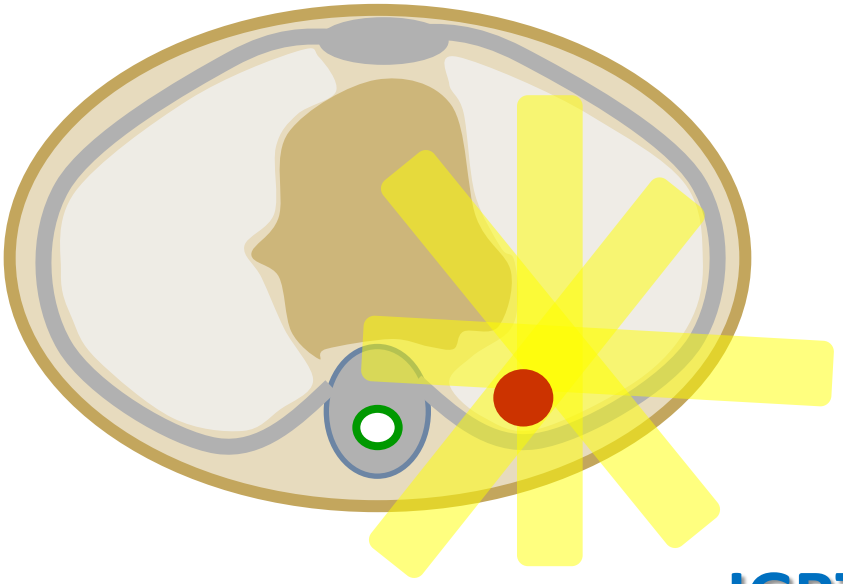
Reduced inter-observer variability using 4D-CBCT compared to 3D-CBCT

Pitfalls in IGRT

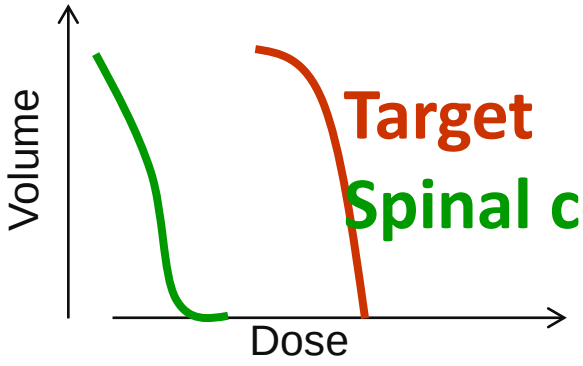
4D volumetric image guidance:

Treatment planning

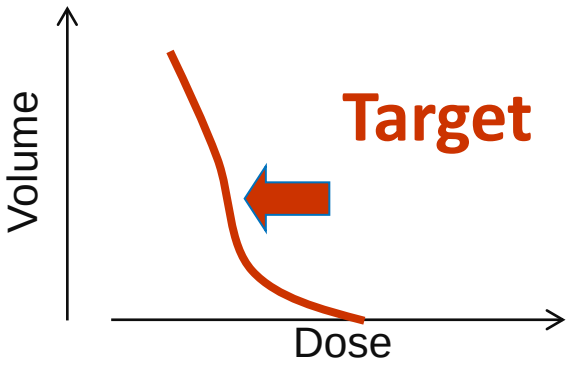




IGRT treatment



IGRT



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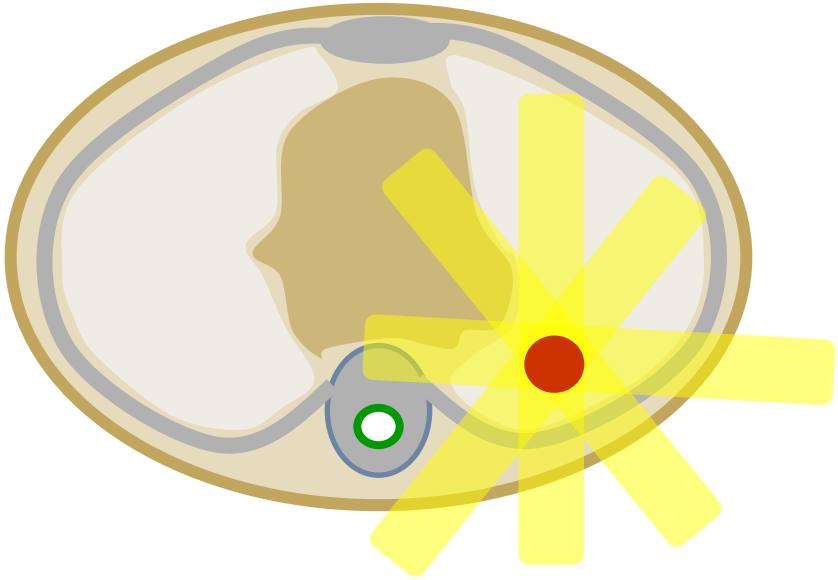
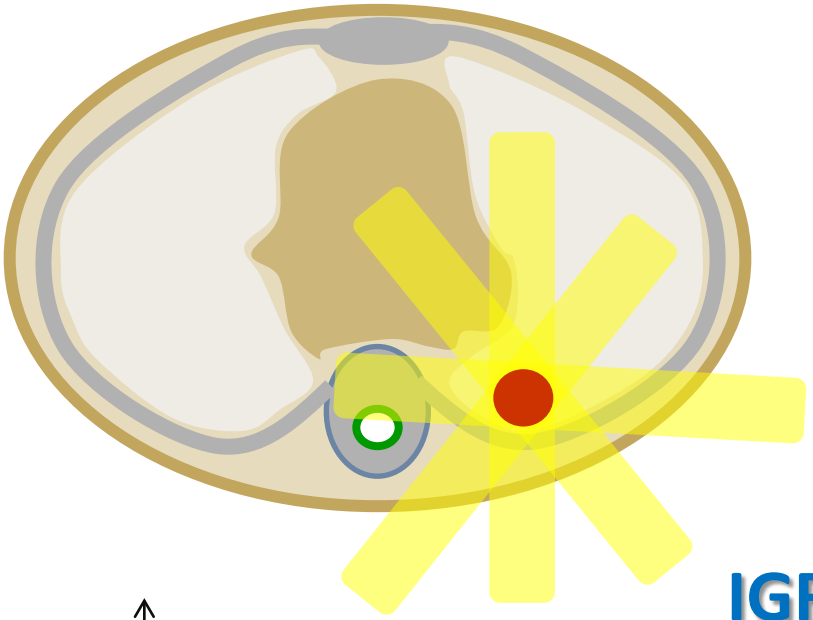
Pitfalls in IGRT

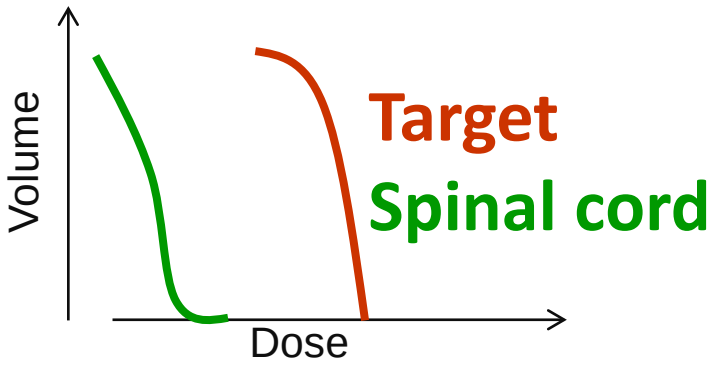
4D volumetric image guidance:

Treatment planning

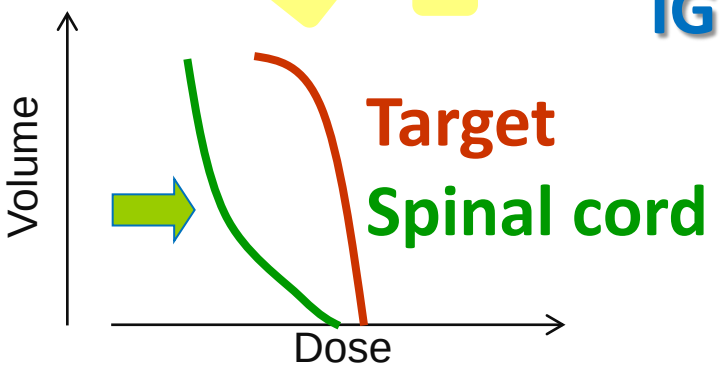


IGRT treatment





IGRT

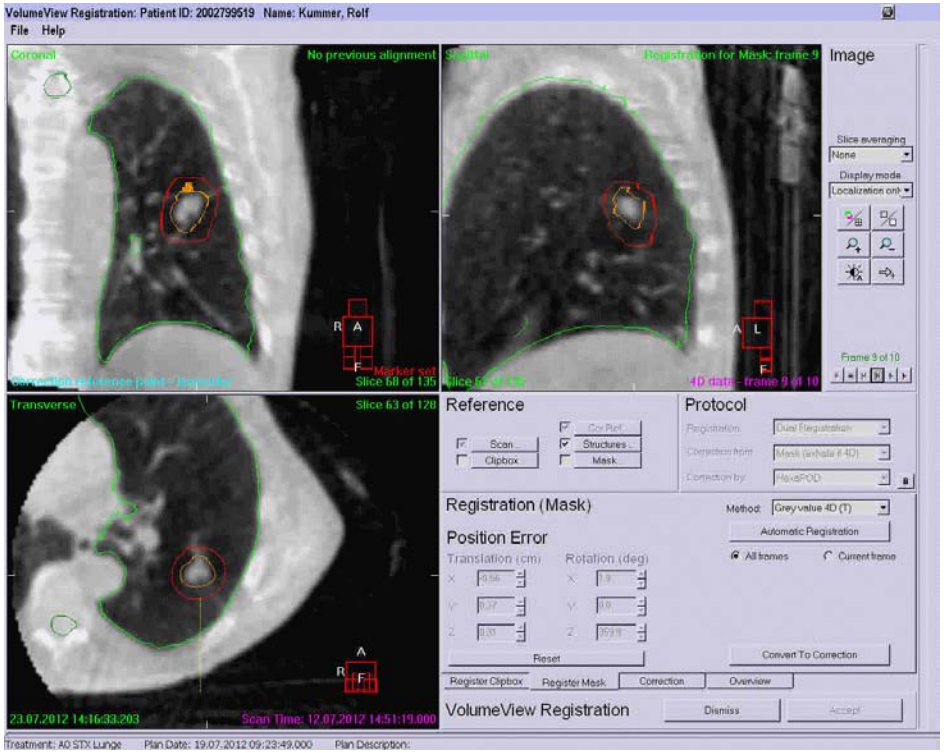


ESTRO

Pitfalls in IGRT

Image guidance: XVI 4.5

- Dual registration: target versus spinal cord (OAR)



Base-line shift:

Two choices:

- Precise set-up of target and error at OAR
- Precise set-up of OAR and error at target

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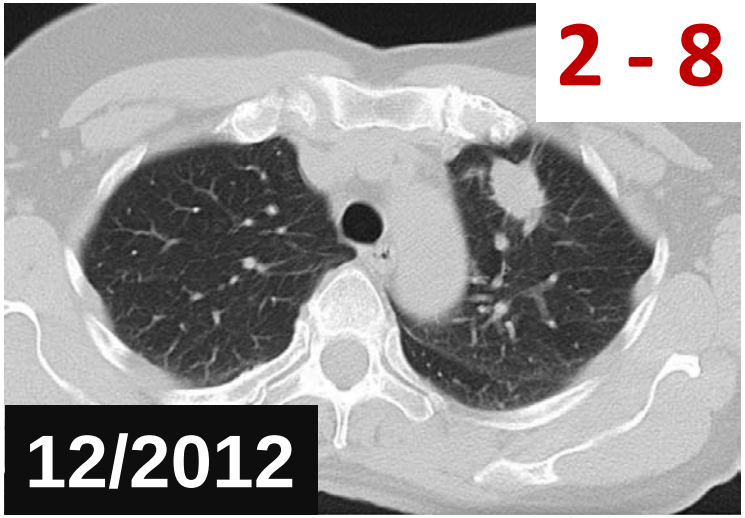
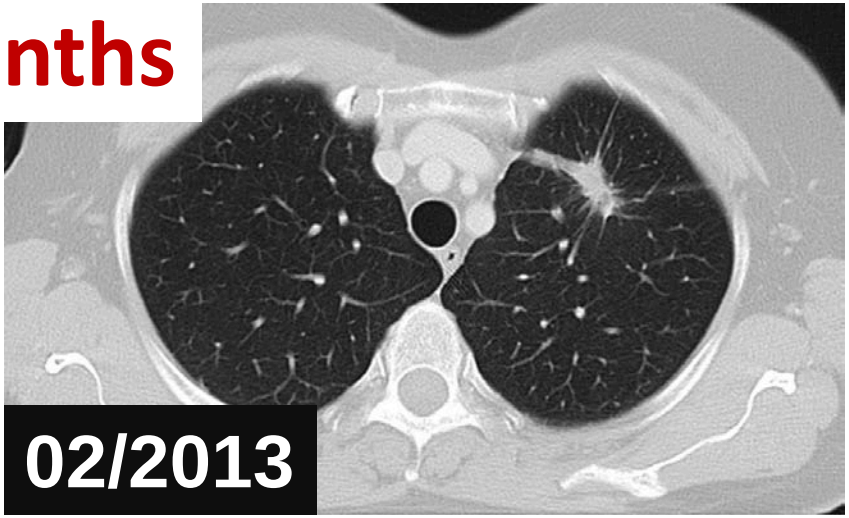
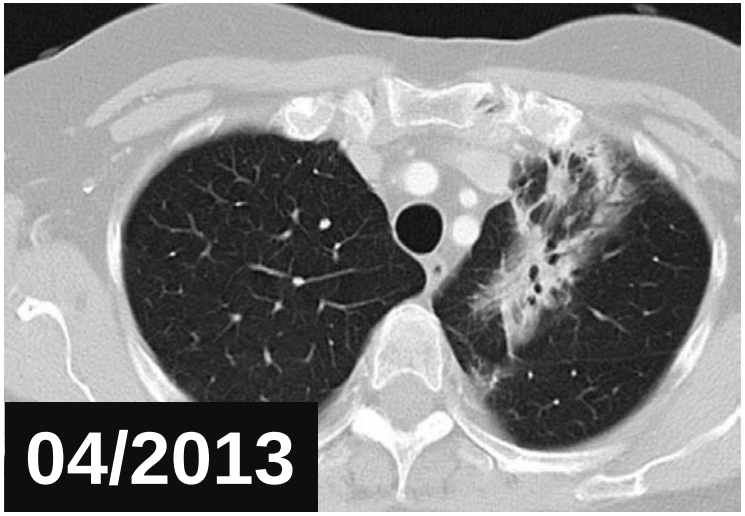
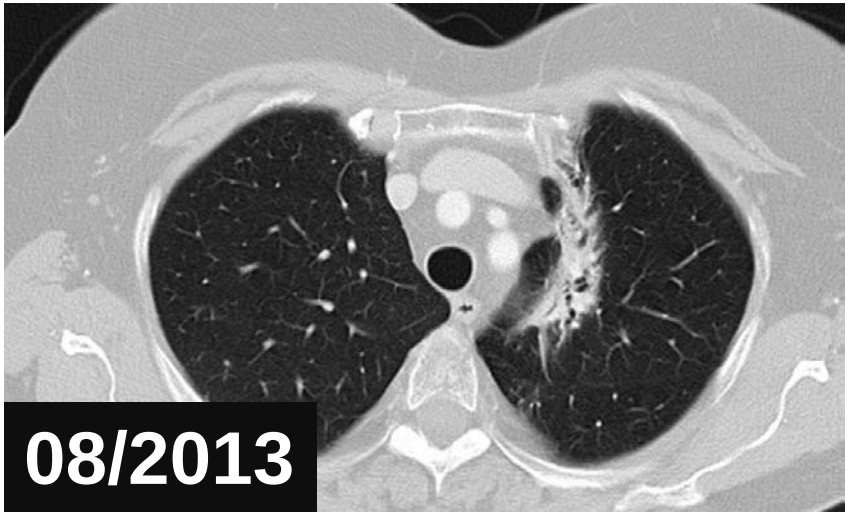
Follow-up: KI

2 - 8 Months









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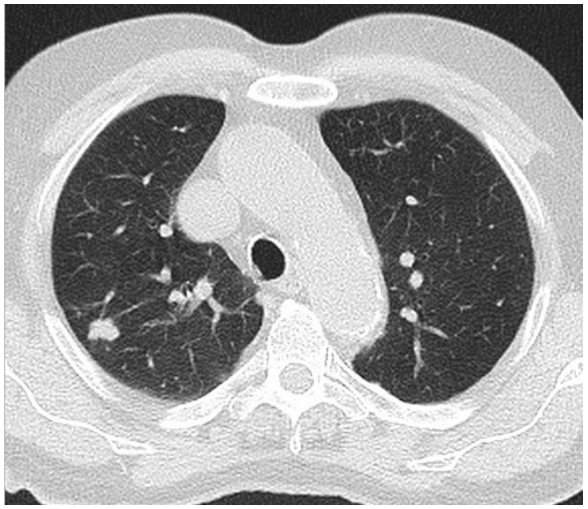
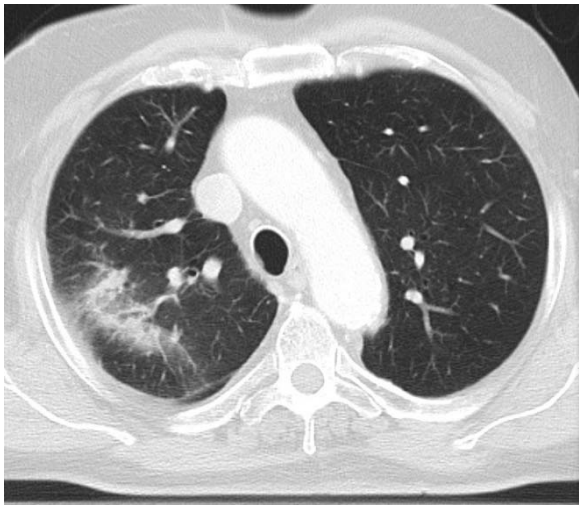
Follow-up: BB

2 - 6 Months

02/2013



05/2013



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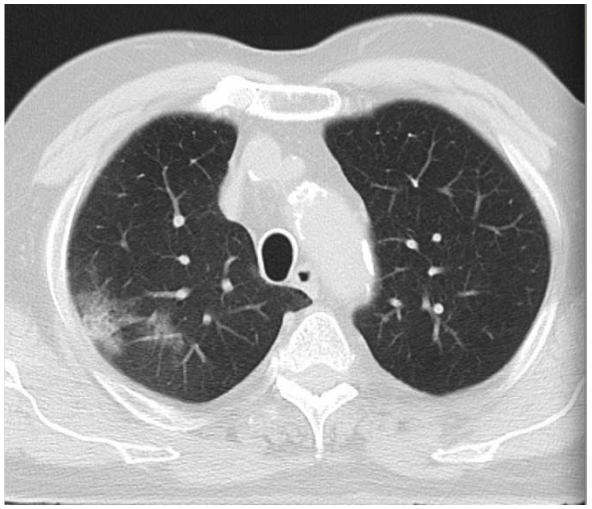

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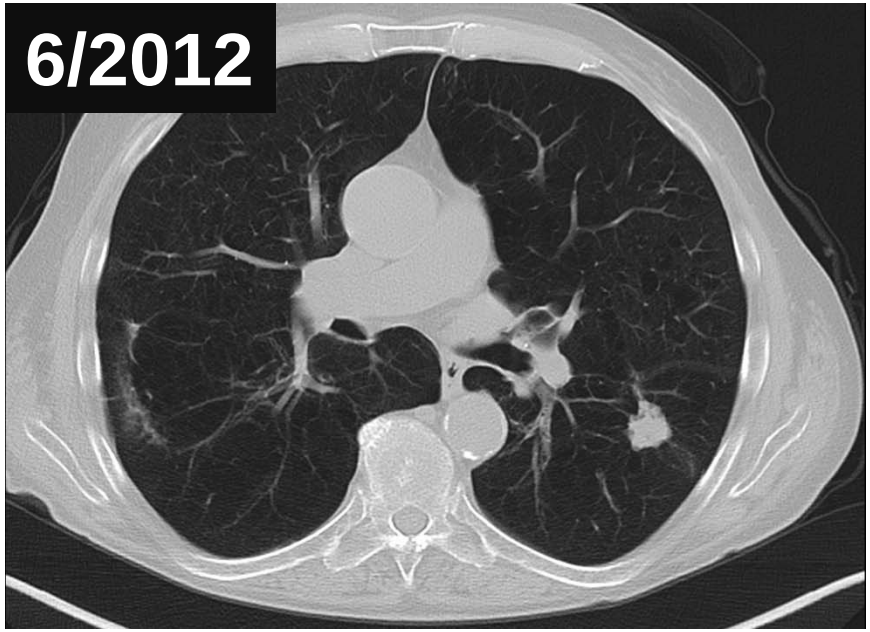
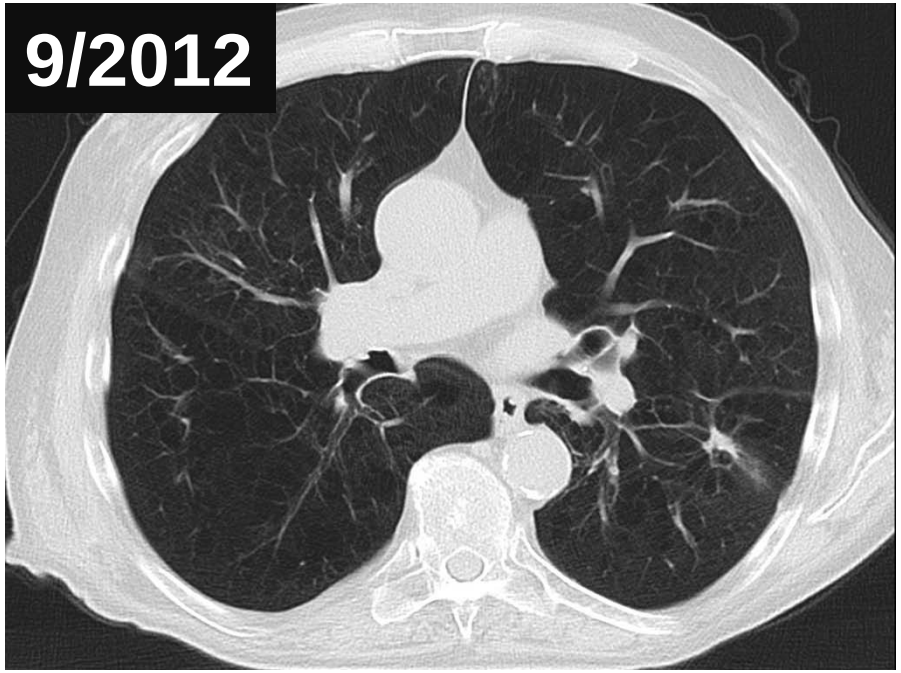
Follow-up: KR



3 Months



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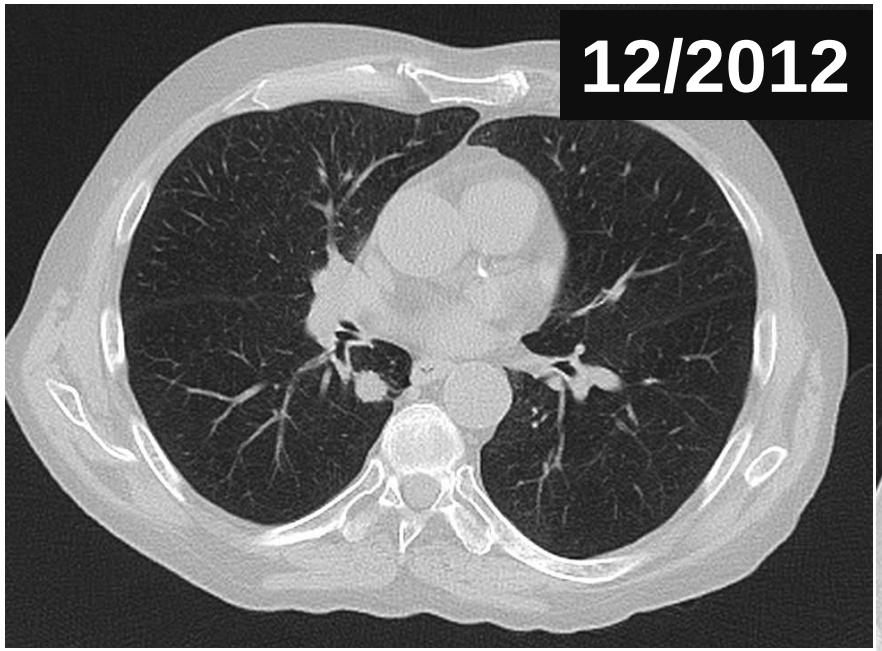
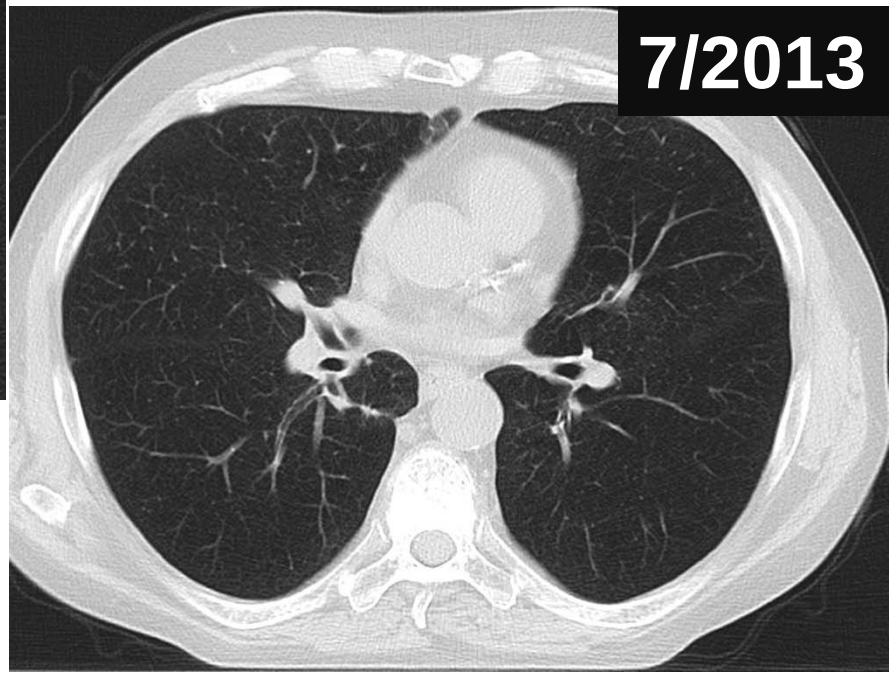
Follow-up: KK



7 Months



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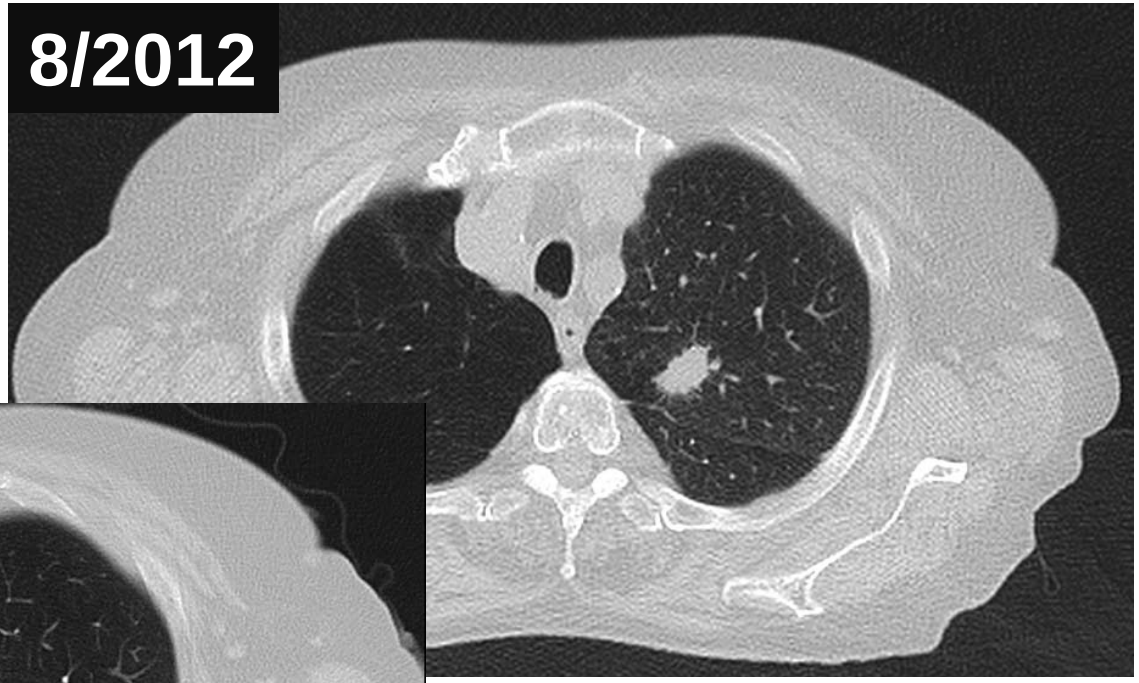
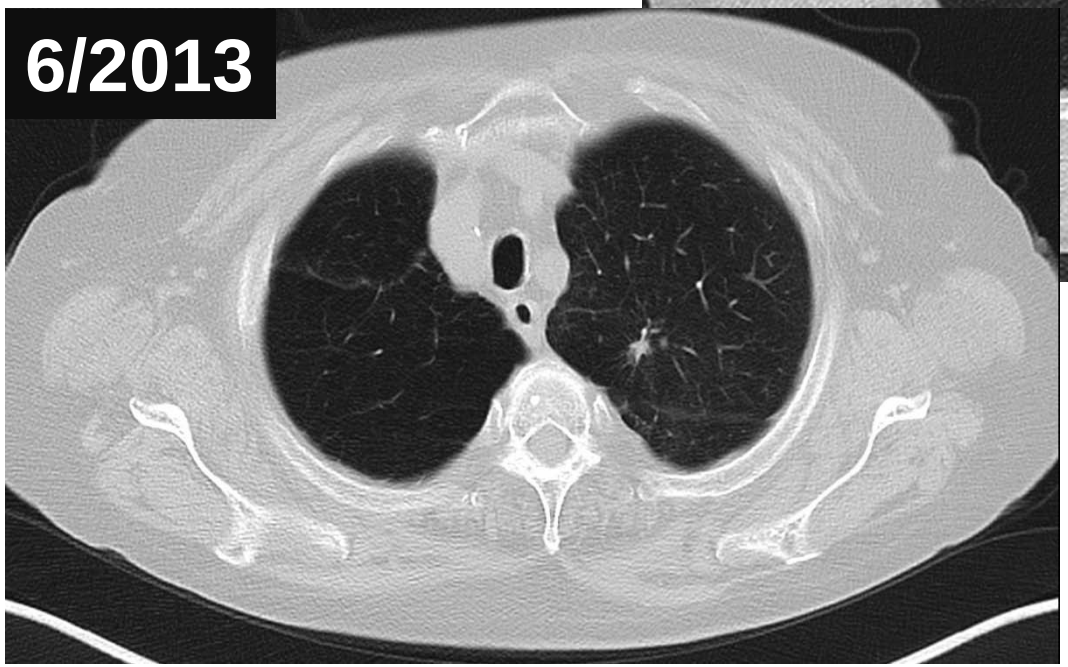
Follow-up: KrHe

10 Months





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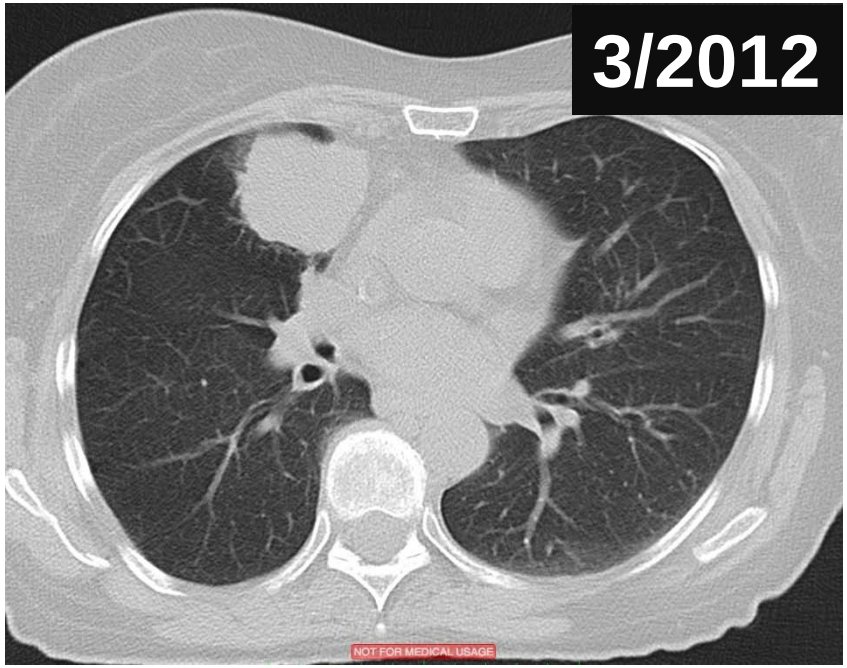
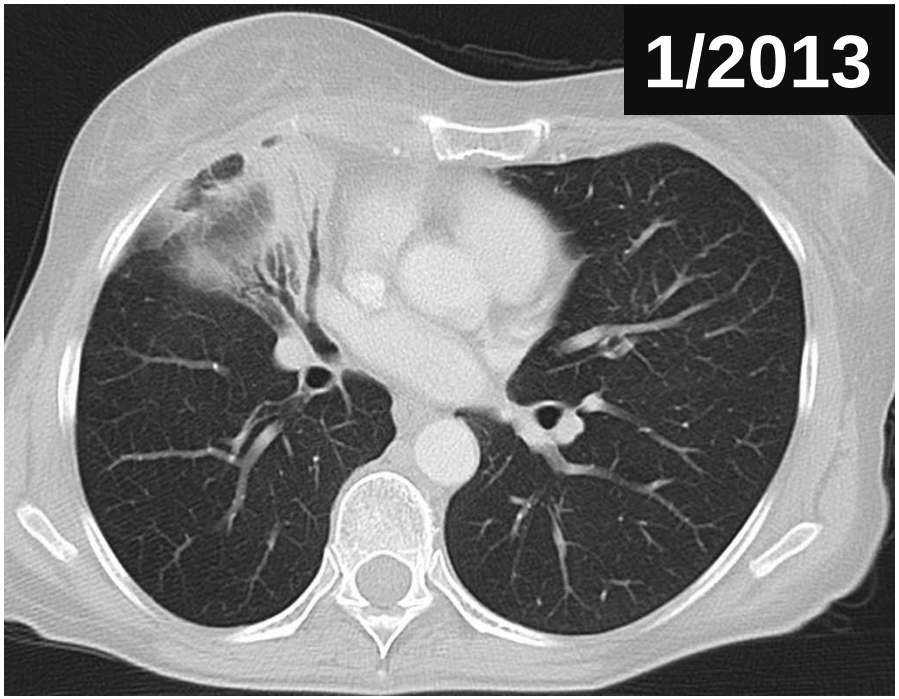
Follow-up: SJ



10 Months



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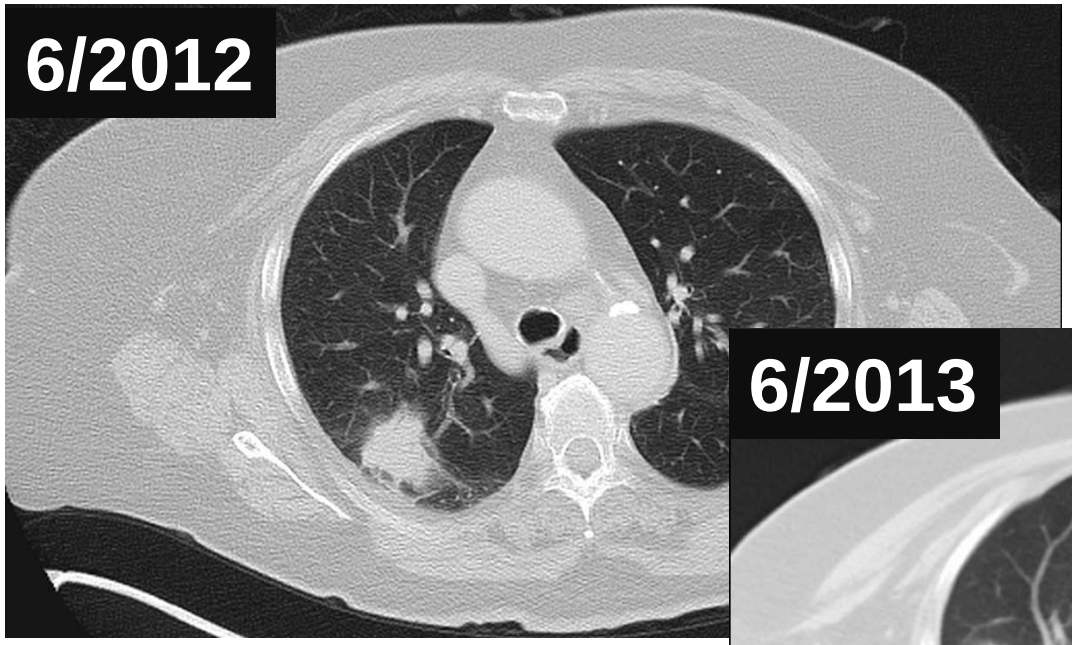
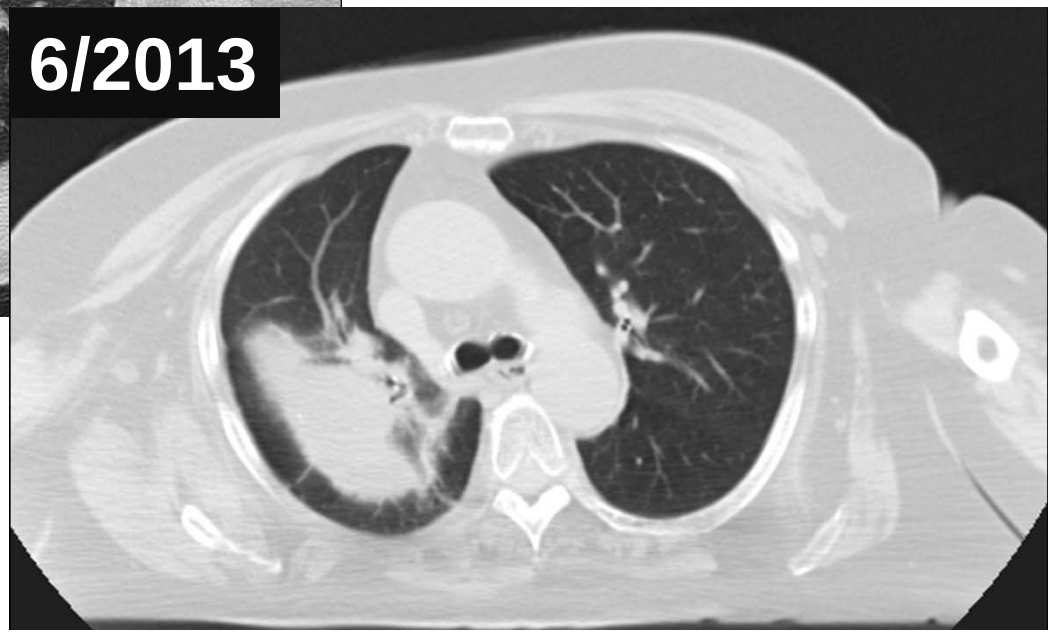
Follow-up: KeHe



12 Months



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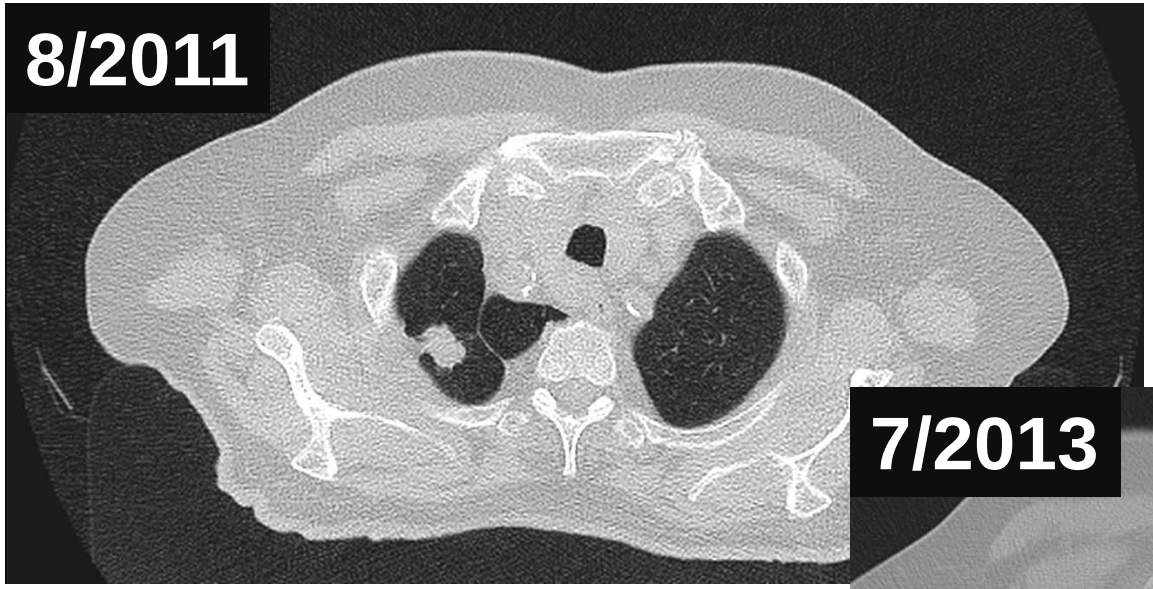
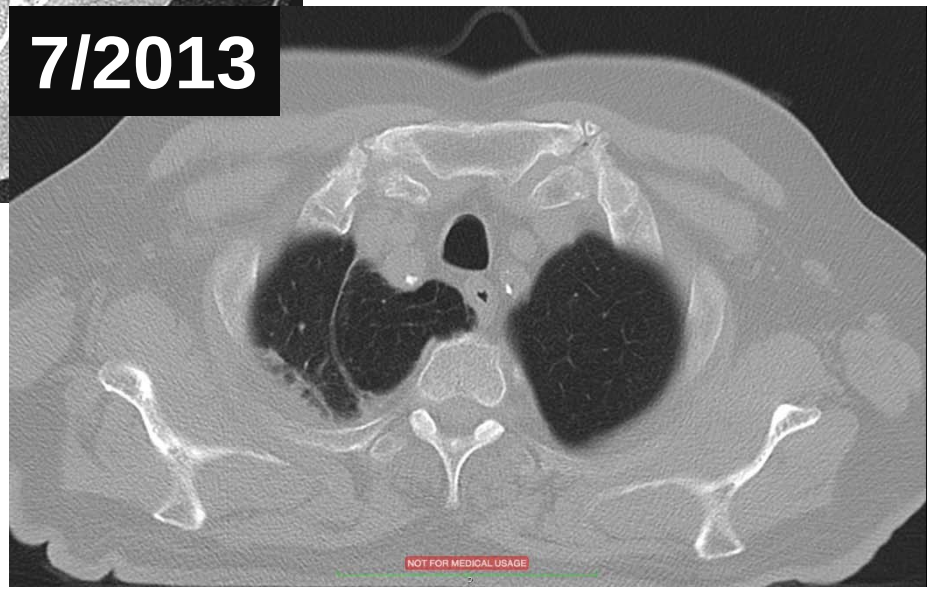
Follow-up: AW

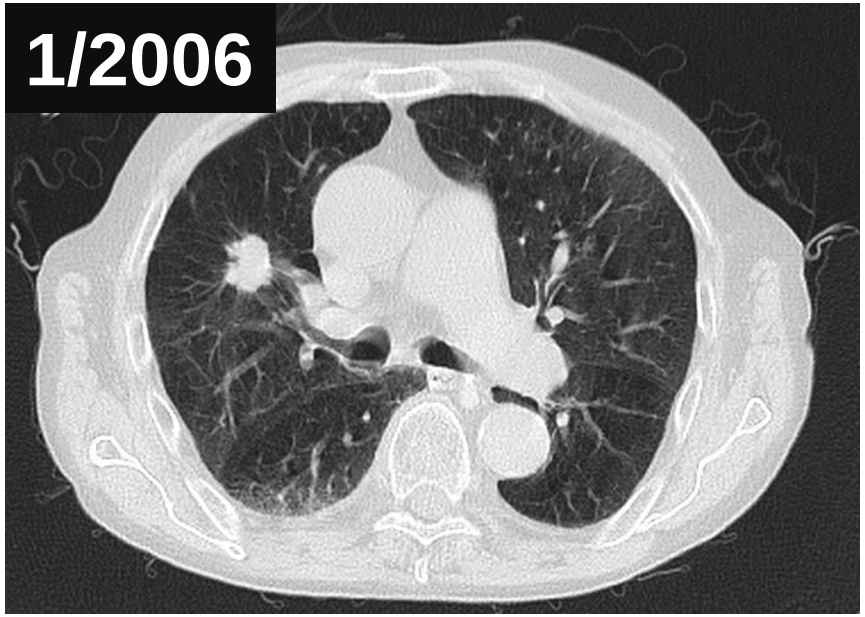


23 Months

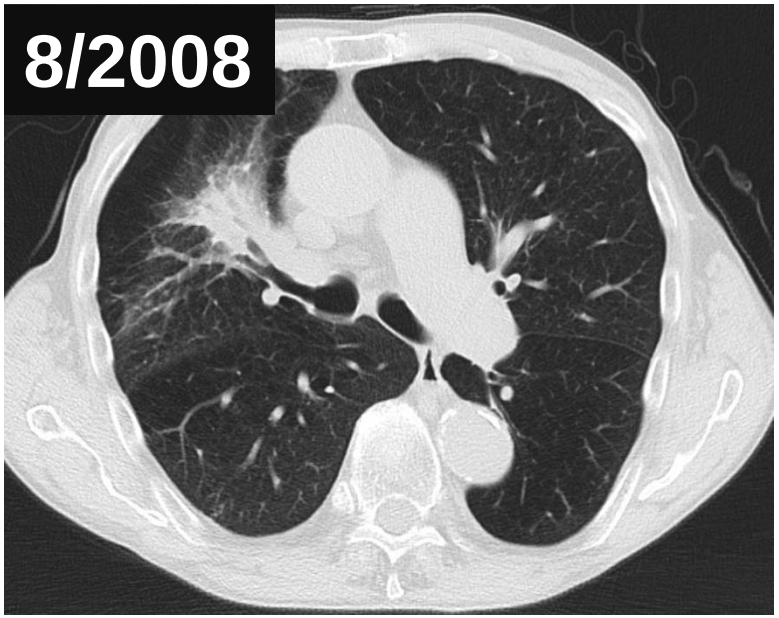


ESTRO

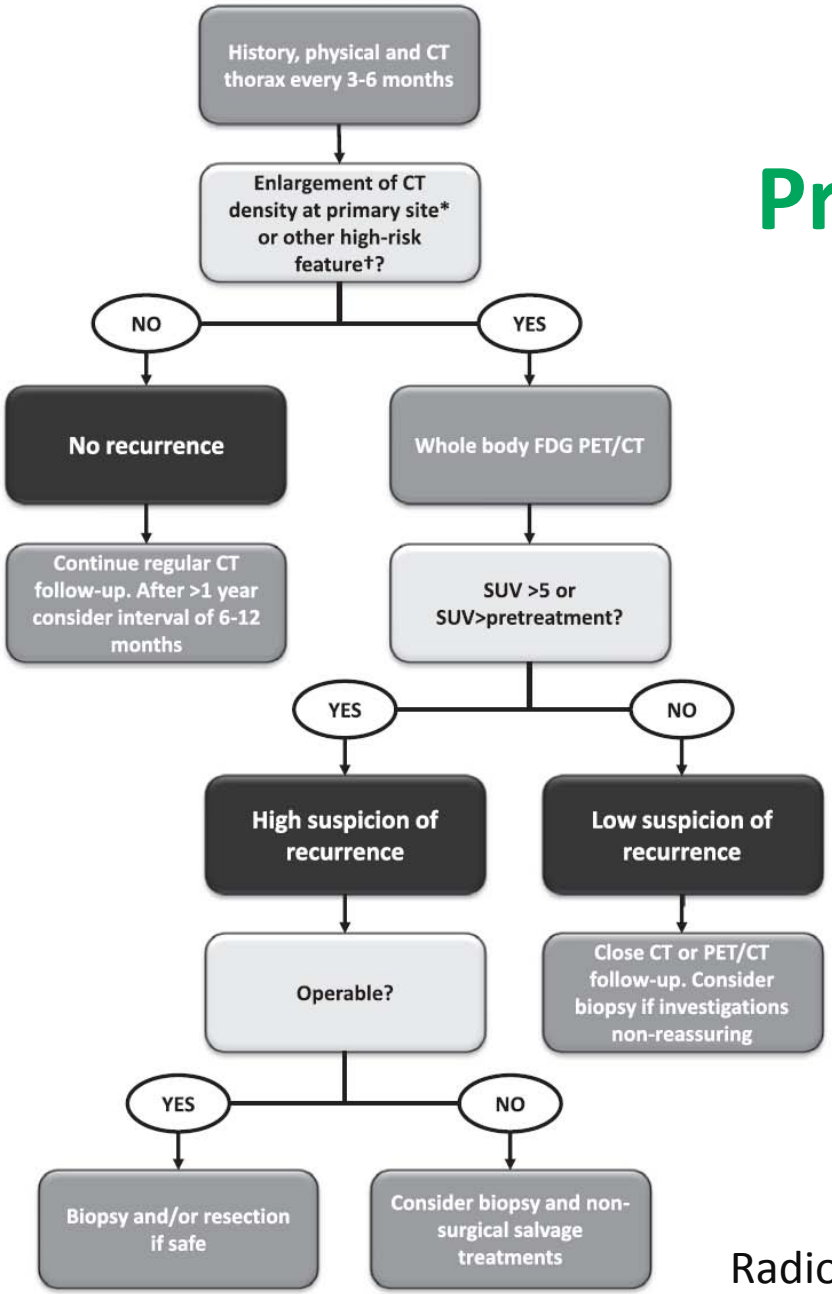
Follow-up: HJ



30 Months



Proposed FU after SBRT



High-risk features:

- sequential enlargement on repeat CT
- opacity enlargement after 12 months
- bulging margin
- disappearance of air bronchograms
- linear margin disappearance
- ipsilateral pleural effusion or lymph node enlargement.

Hung et al.
Radiother Oncol 2012

SBRT using Elekta equipment

CZE experience

Coen Hurkmans, Ph.D., clinical physicist

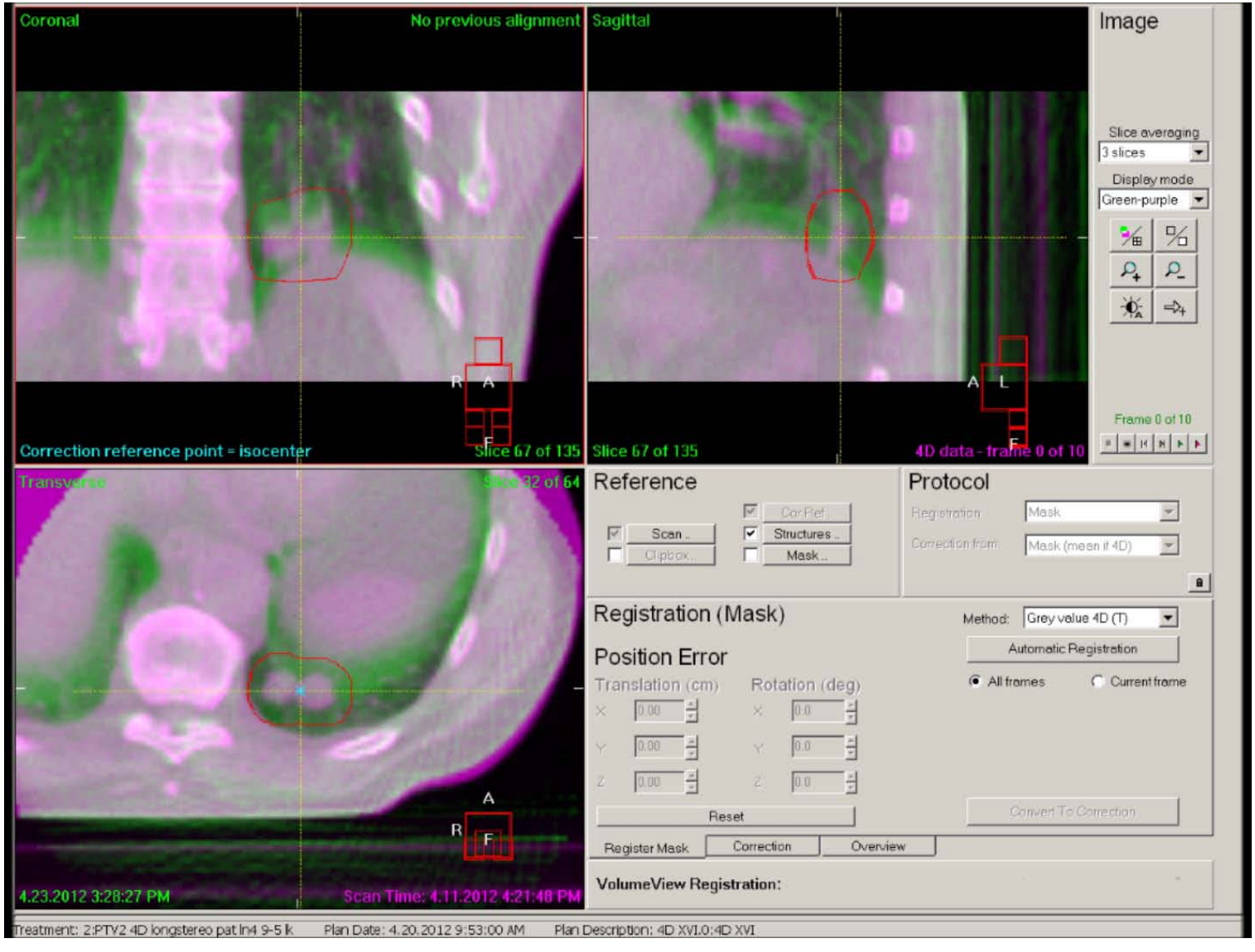
Catharina Hospital, The Netherlands

catharina hospital

Vmat CVDR option

- Improvement of gantry stability
- Possible improvement of dose accuracy
- Possibly less wear of gantry

4D-CBCT: Unmatched



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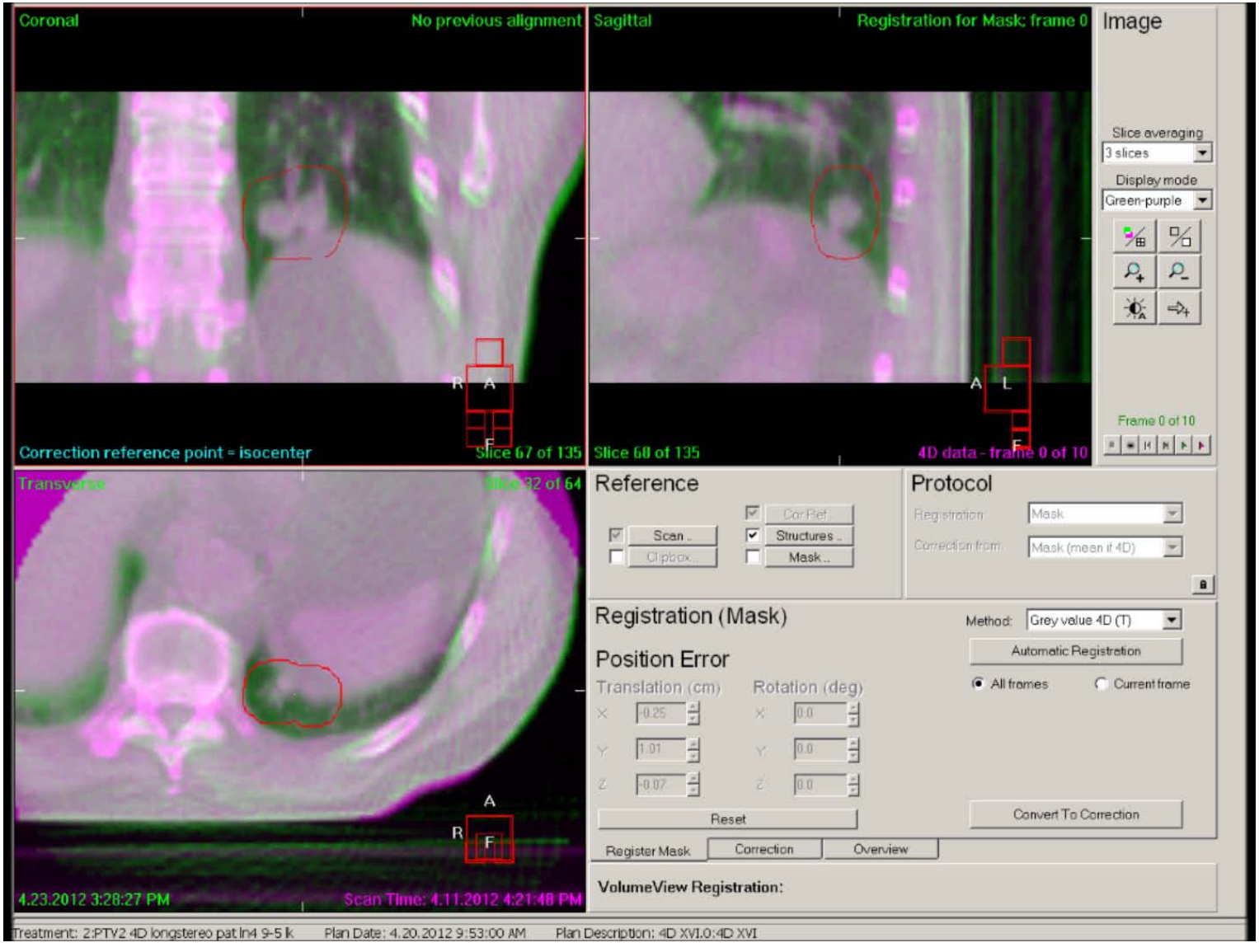
4D-CBCT: Matched



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4D-CBCT in-treatment (XVI 5)

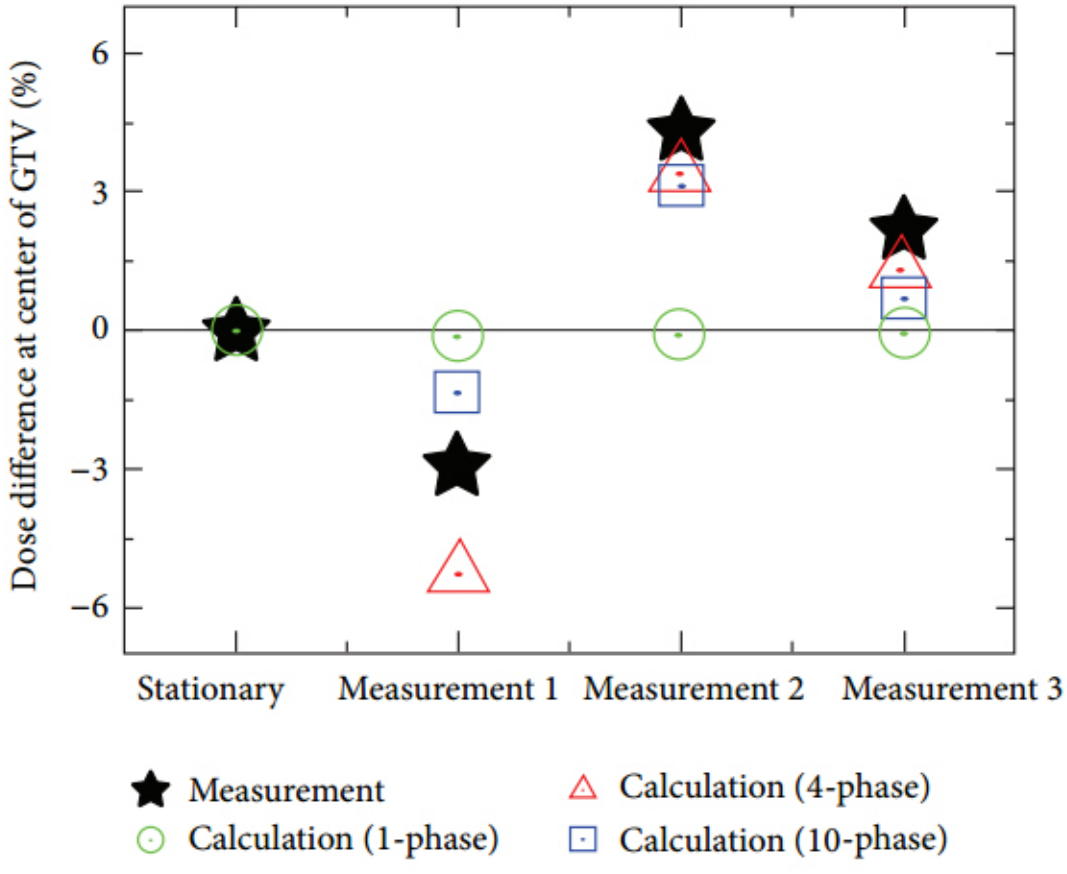

FIGURE 9: Relative dose difference at the center of target with and without motion using the QUASAR phantom. Here, the calculated dose was normalized at the measurement dose without motion ("Stationary" indicated in horizontal axis).

Yamashita BioMed Res Int 2014 article ID 136513

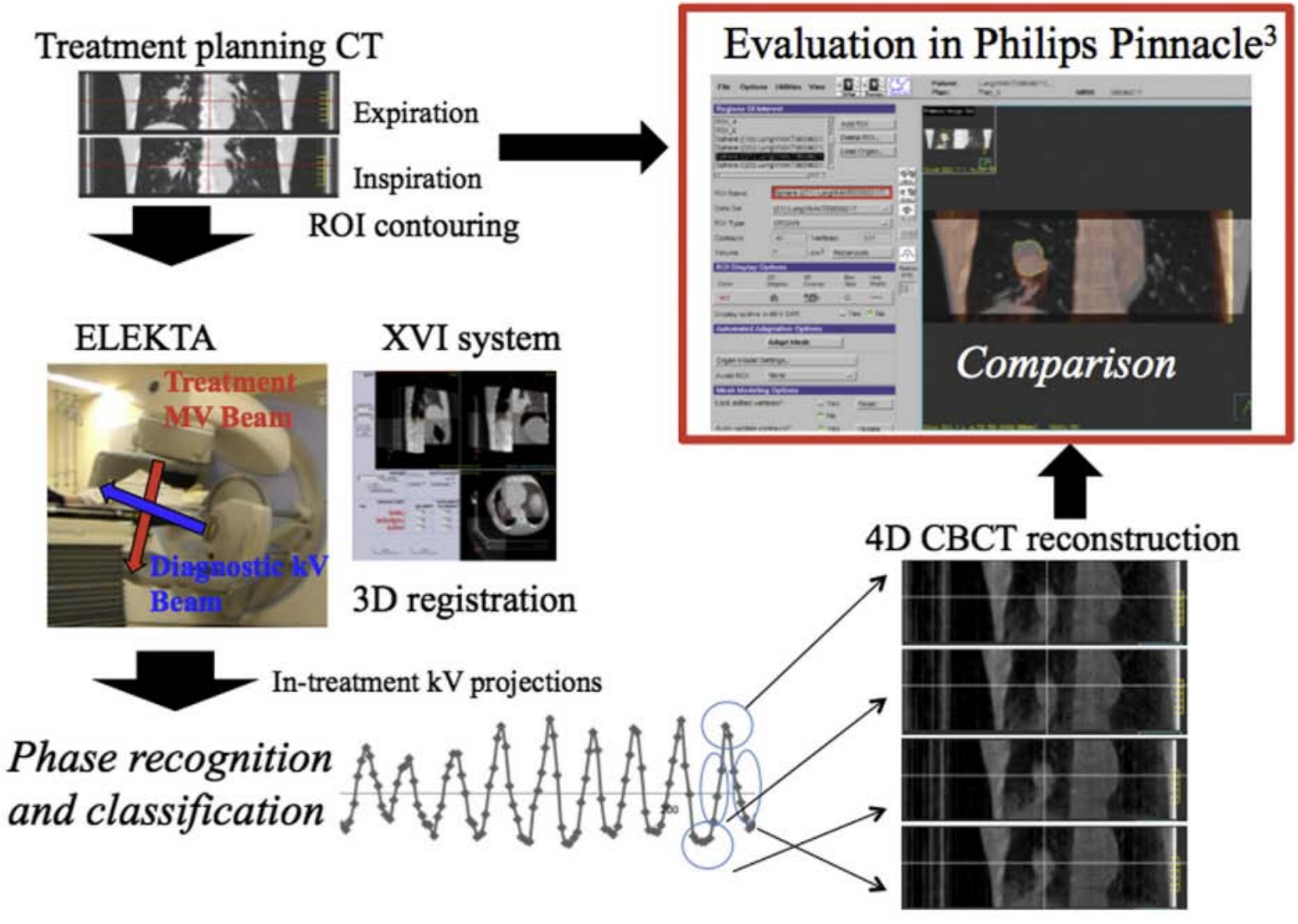

Fig. 2. Workflow of the verification of the PTV setting using in-treatment 4D CBCT.

Yamashita BioMed Res Int 2014 article ID 136513

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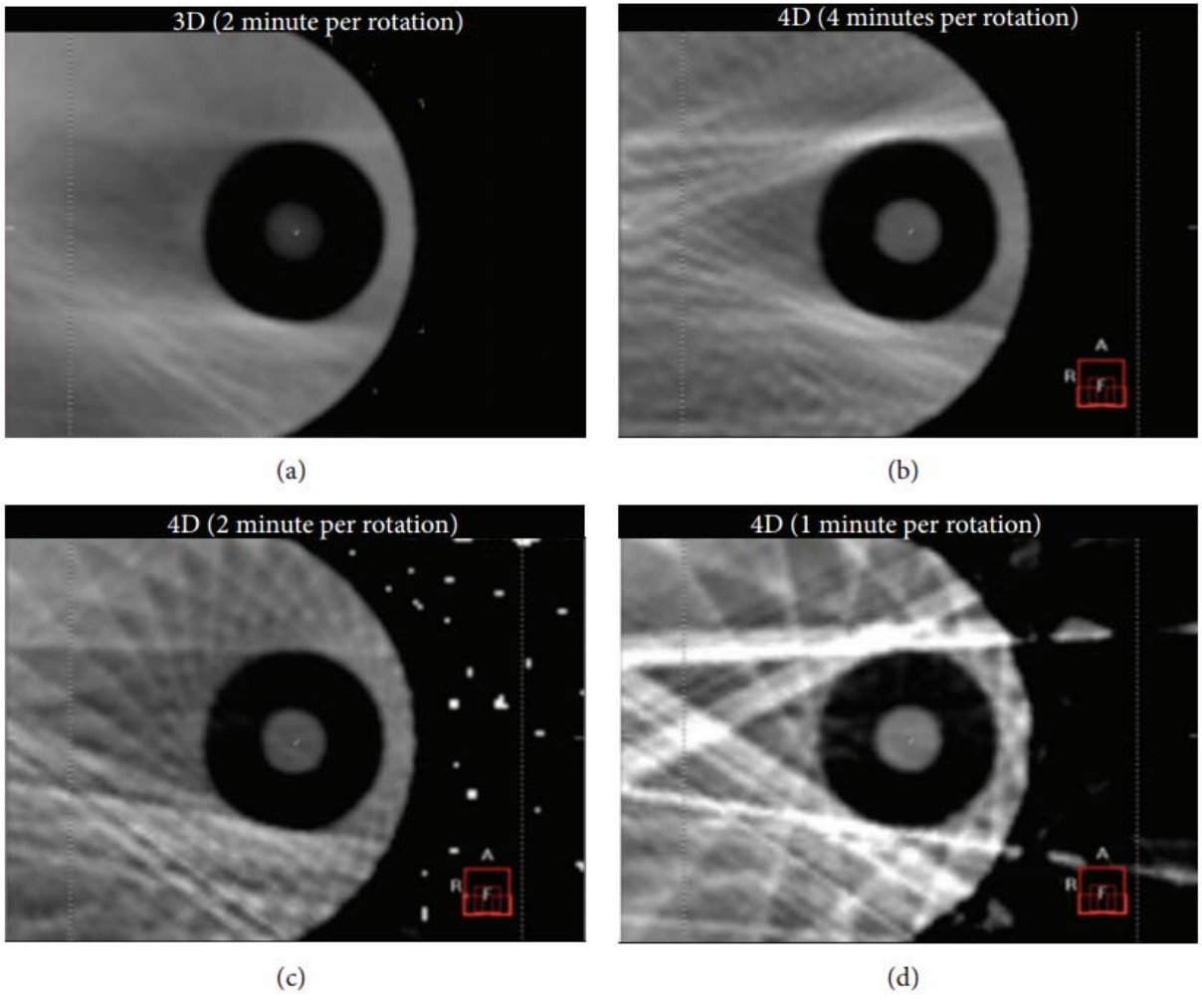

mages (axial view) for a moving phantom (QUASAR; Modus Medical Devices, Inc.): (a) 3D (2 minut
rotation), (c) 4D (2 minutes per rotation), and (d) 4D (1 minute per rotation) images.

Yamashita BioMed Res Int 2014 article ID 136513

The mA per frame and ms per frame are 20 mA/frame and

40ms/frame, which are used clinically in the University of

Tokyo Hospital (Figure 4). With those parameters, the CT

dose index (CTDI) volume is approximately 12 mGy for 4D

CBCT imaging with 4 minutes per rotation, measured with a

15 cm length CTDI phantom.

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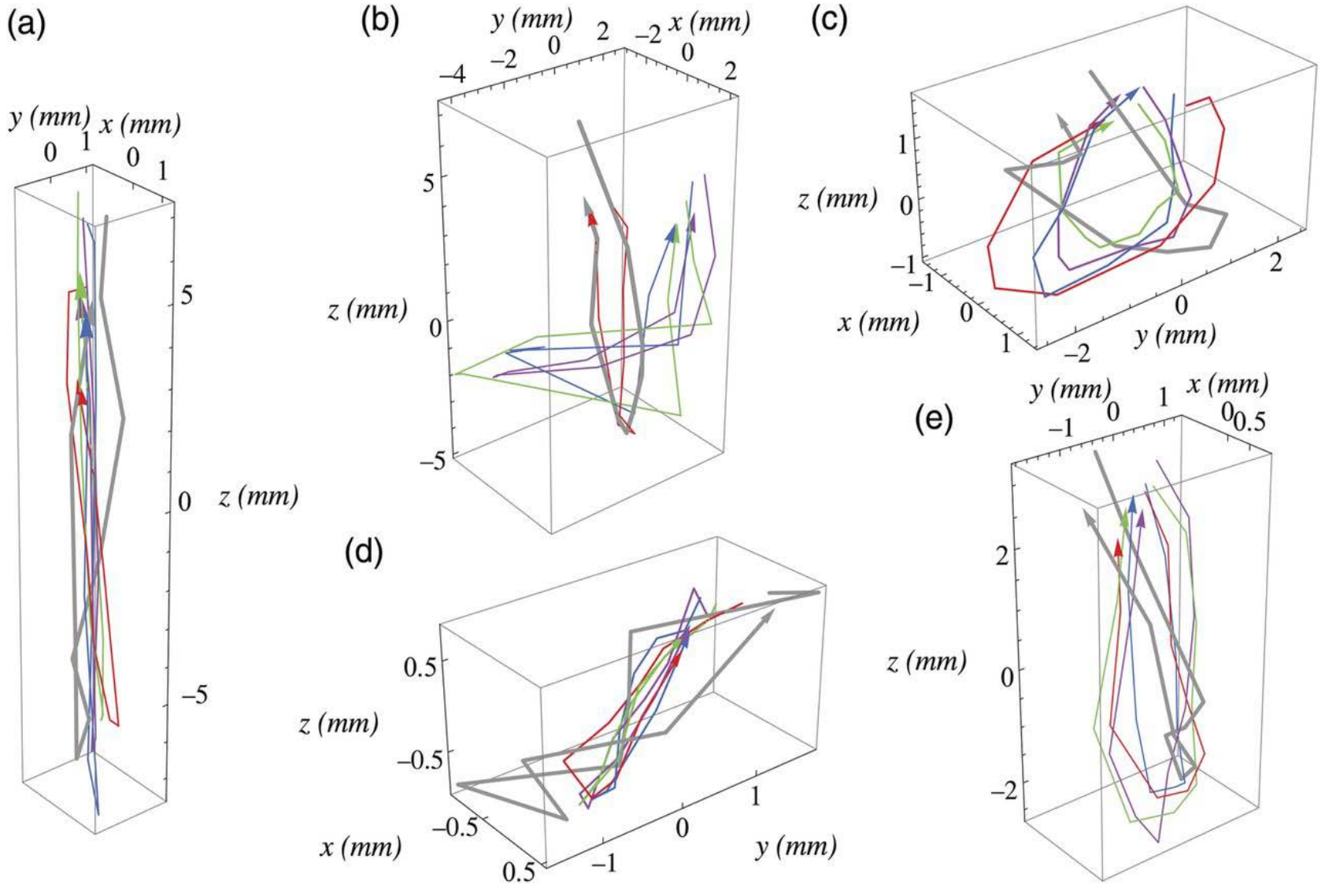
3D lung tumor trajectories during the planning time (in gray) and pre-treatment times in the four fractions (in red, green, blue and violet) for the five patients.



Nakagawa K et al. J Radiat Res 2014;jrr.rru055

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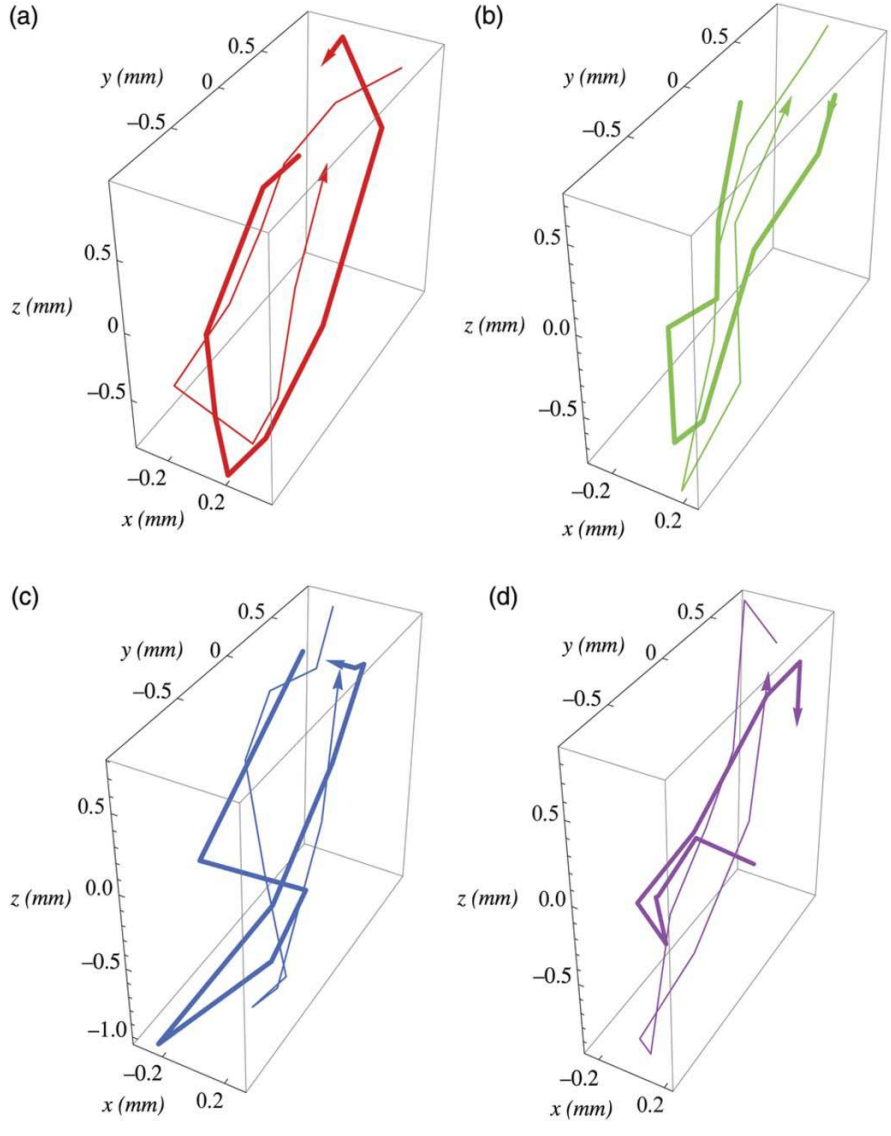
3D lung tumor trajectories obtained by pre-treatment 4D CBCT (thin line) and those obtained by in-treatment 4D CBCT (thick line), fraction by fraction, for a patient.



Nakagawa K et al. J Radiat Res 2014;jrr.rru055

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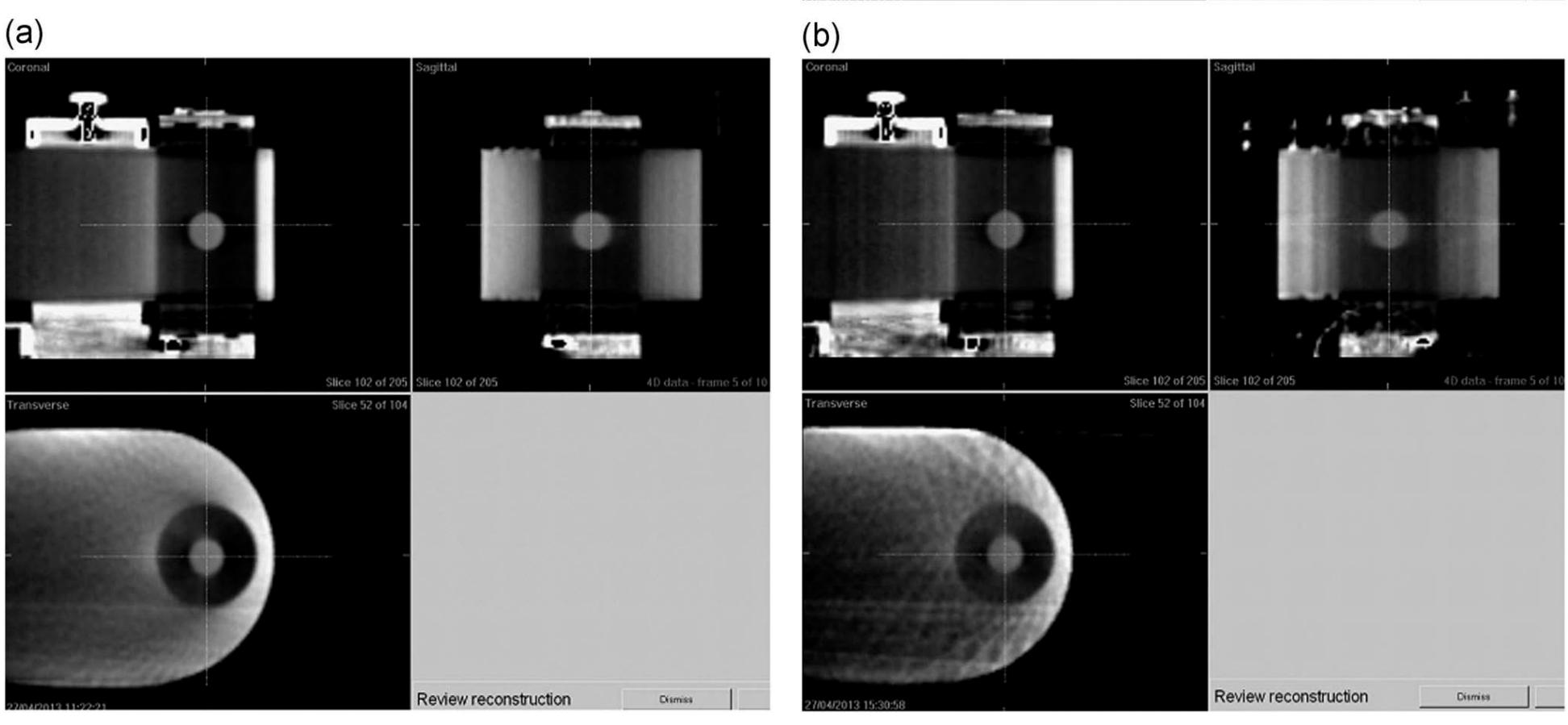
A comparison of inhalation-phase images of concurrent 4D CBCT during VMAT delivery with (a) FF and (b) FFF.



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

Nakagawa K et al. J Radiat Res 2014;55:200-202

ESTRO SBRT course sept 2013

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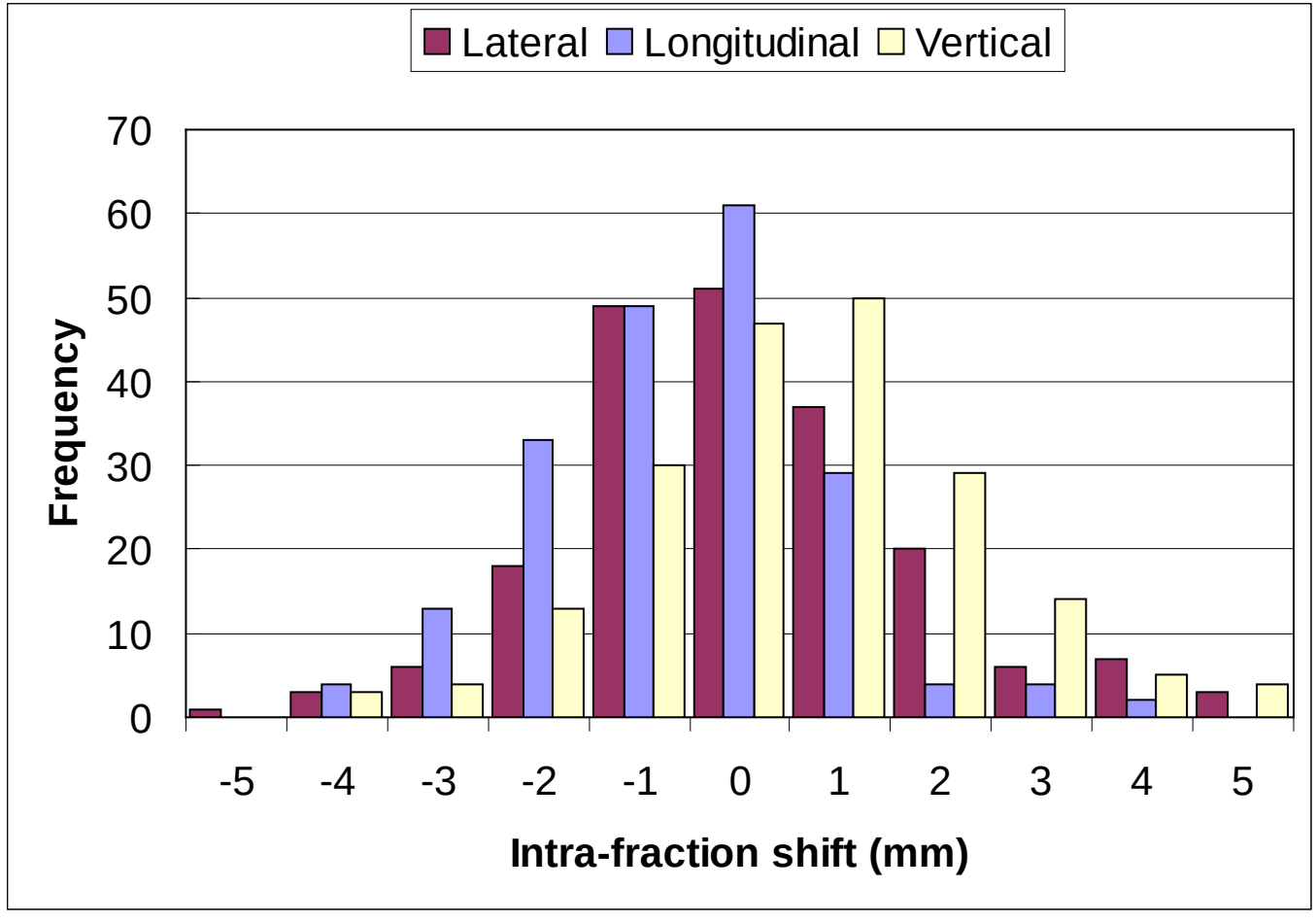
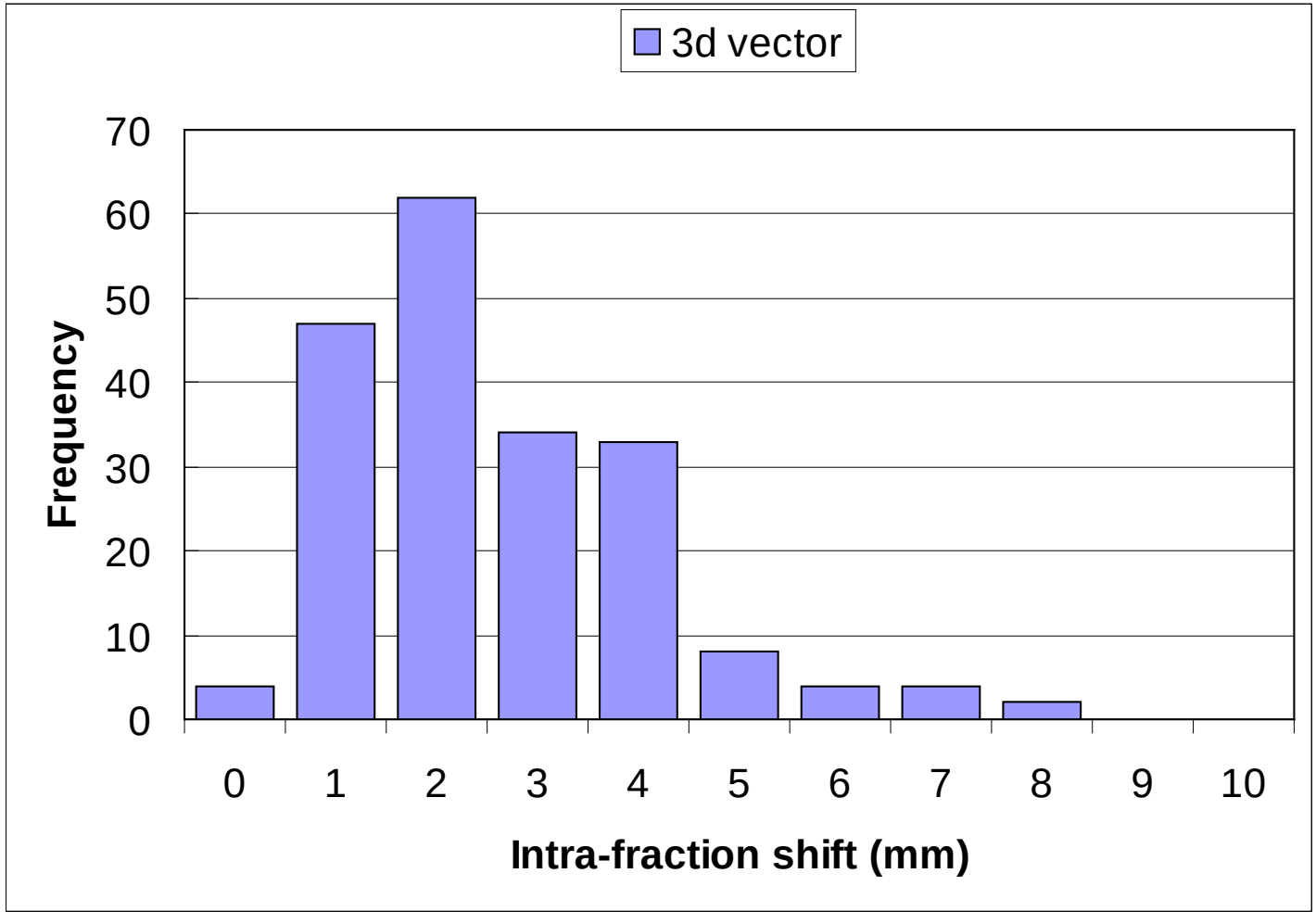
Journal of Radiation Research

Intra fraction stability CZE



Intra fraction stability CZE



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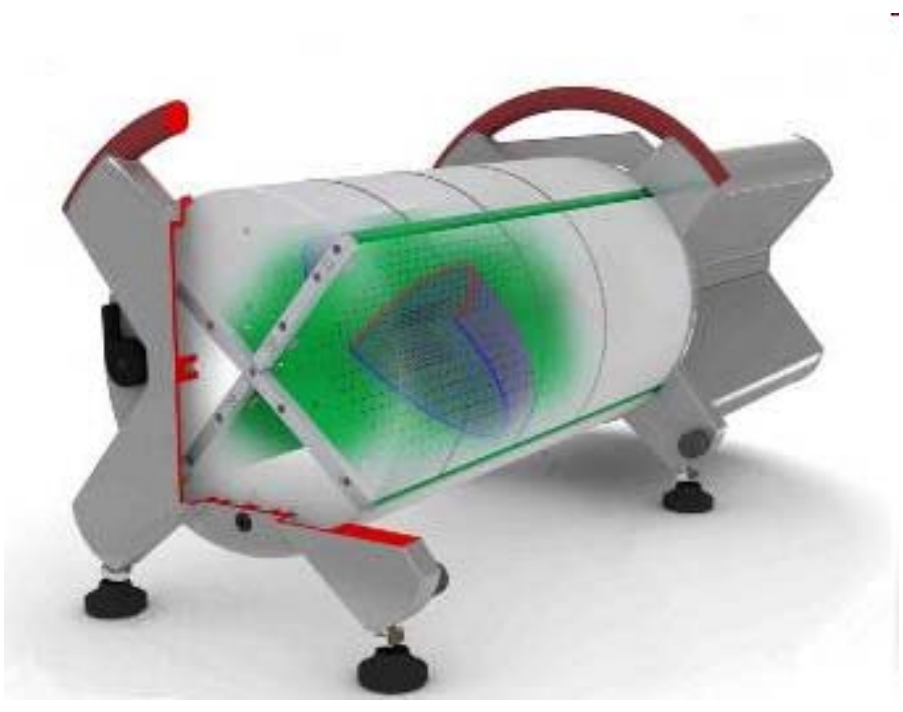
Patient specific dosimetry CZE

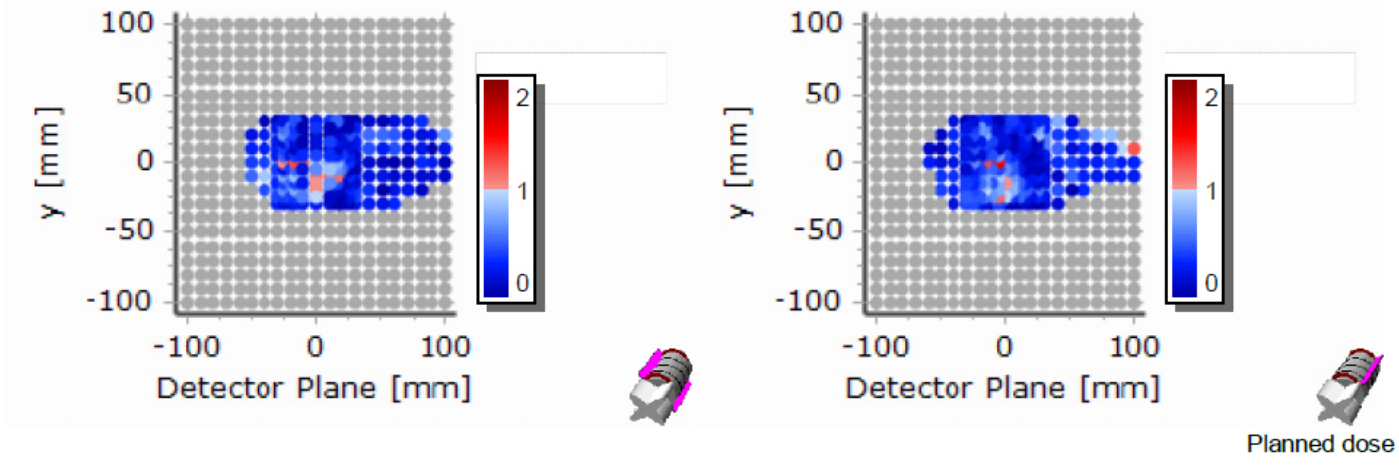


Gamma analysis

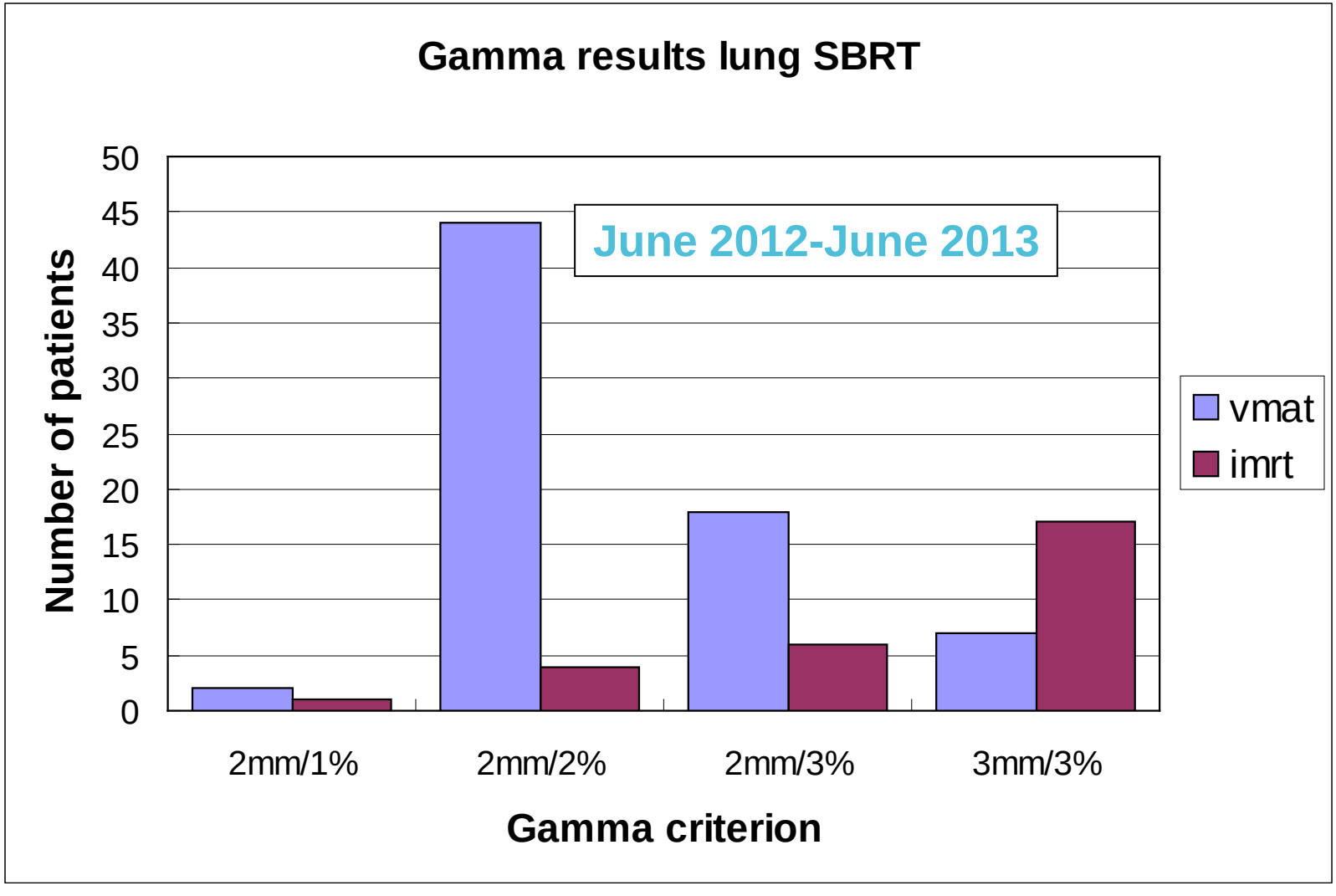
Parameter Definitions & Acceptance Criteria, Detectors

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

Gamma index, Fraction



Gamma results



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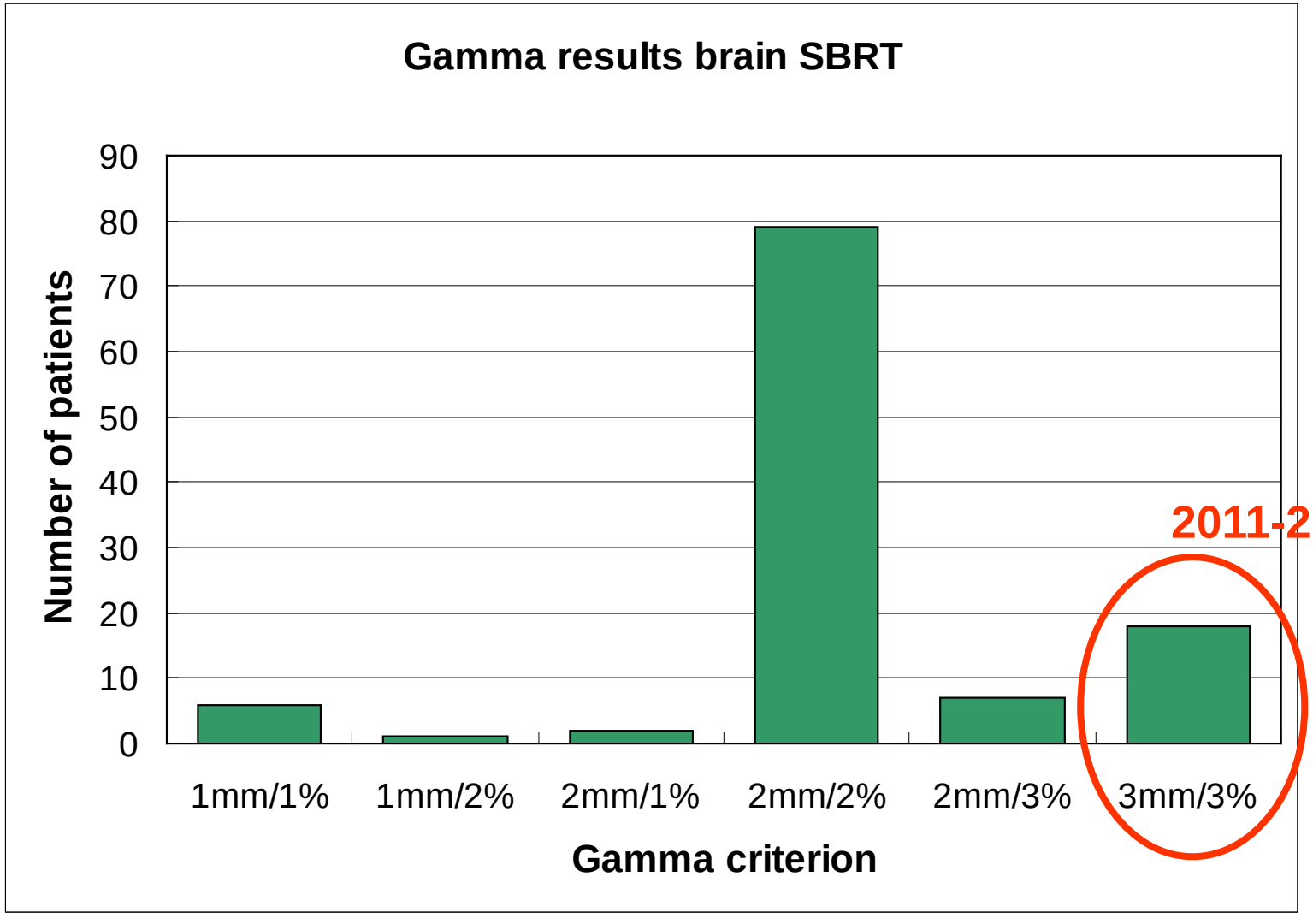
Gamma results brain VMAT



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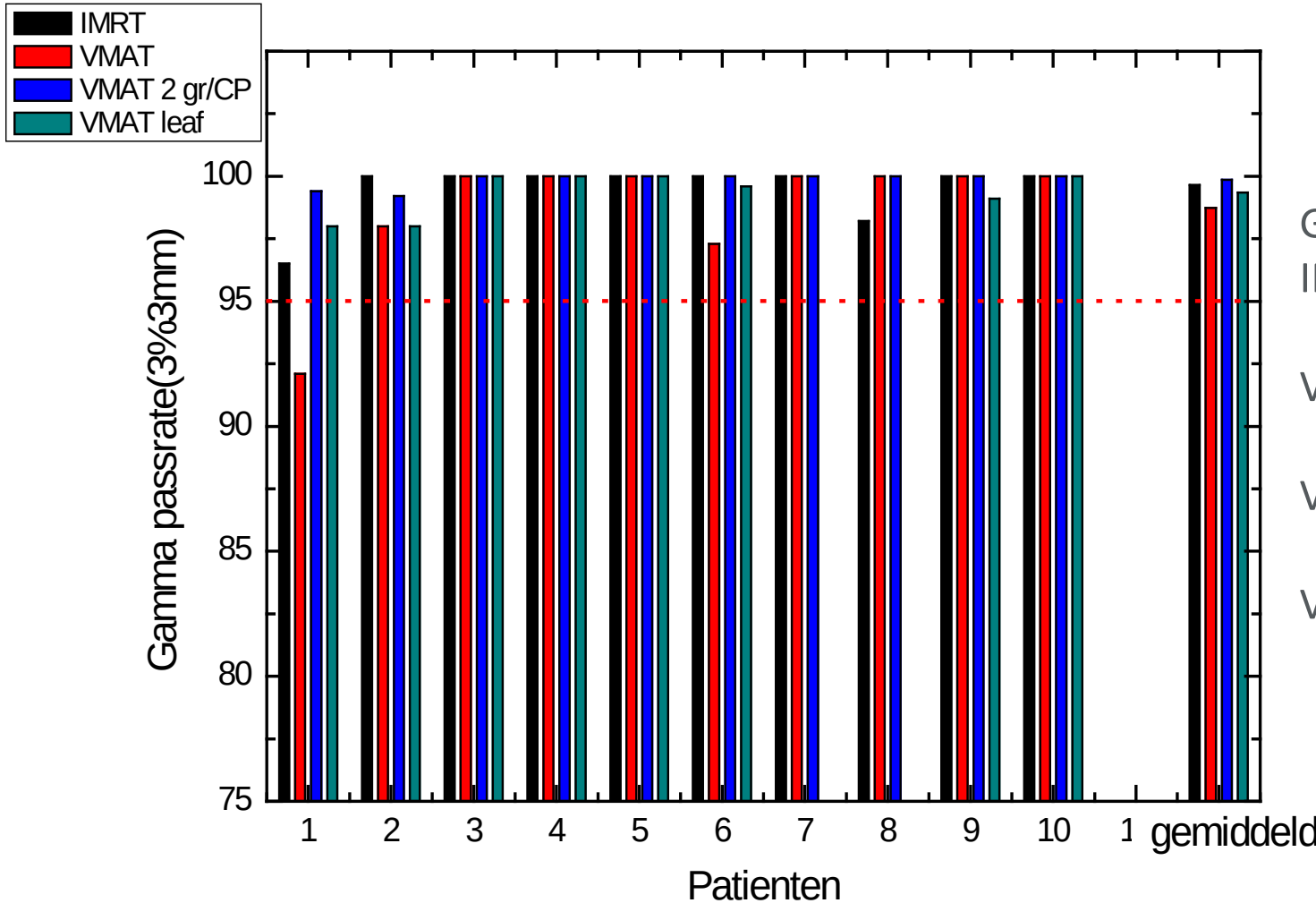
QA VMAT – 3% 3mm



Gemiddeld:

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

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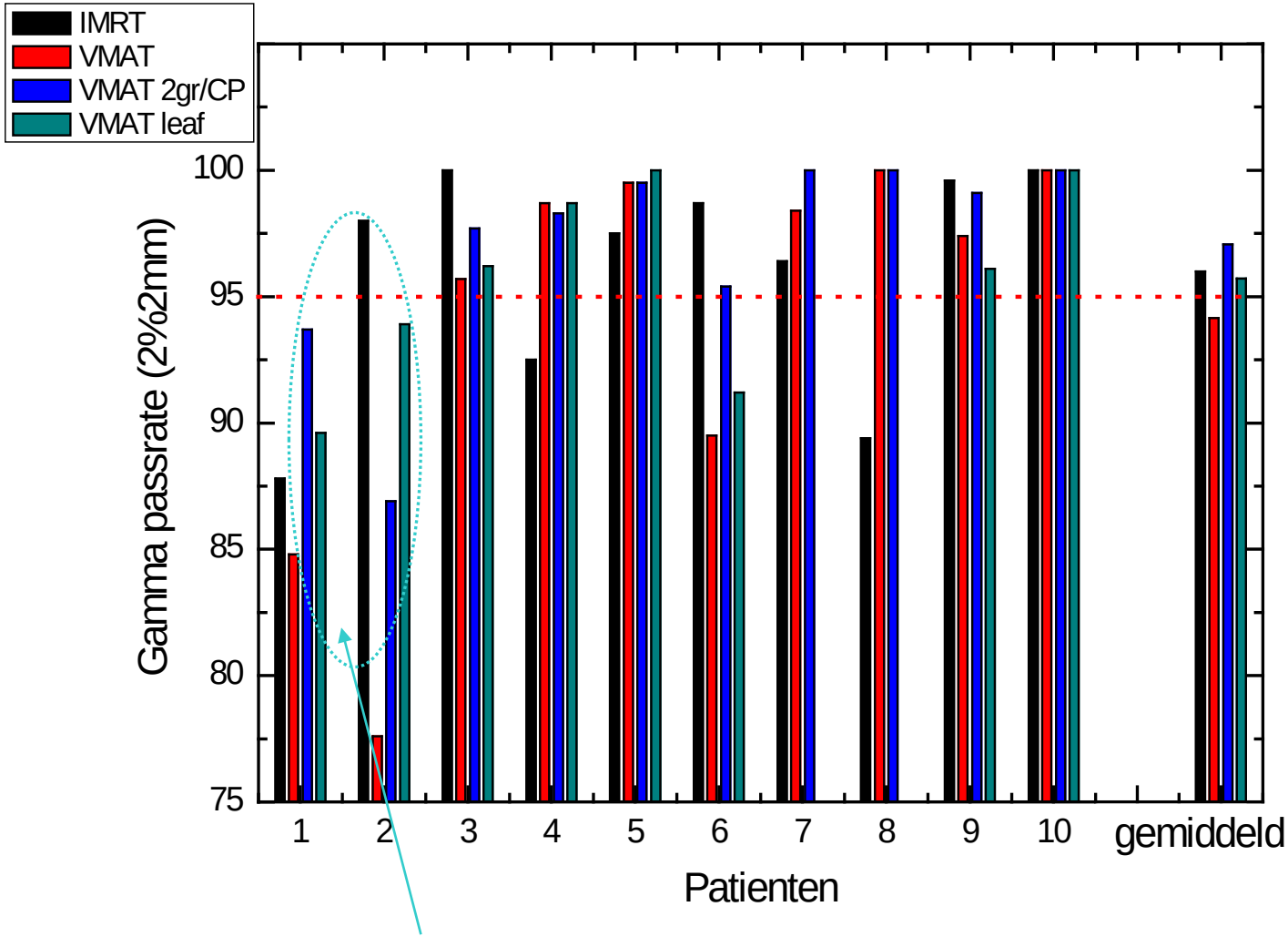
QA VMAT – 2% 2mm



- Gemiddeld:
- IMRT 95.99%
- VMAT 94.16%
- VMAT 2°/CP 97.06%
- VMAT leaf 95.71%

Met combinatie van 2°/CP en beperkte leaf beweging kom je boven 95%

ESTRO SBRT course sept 2013

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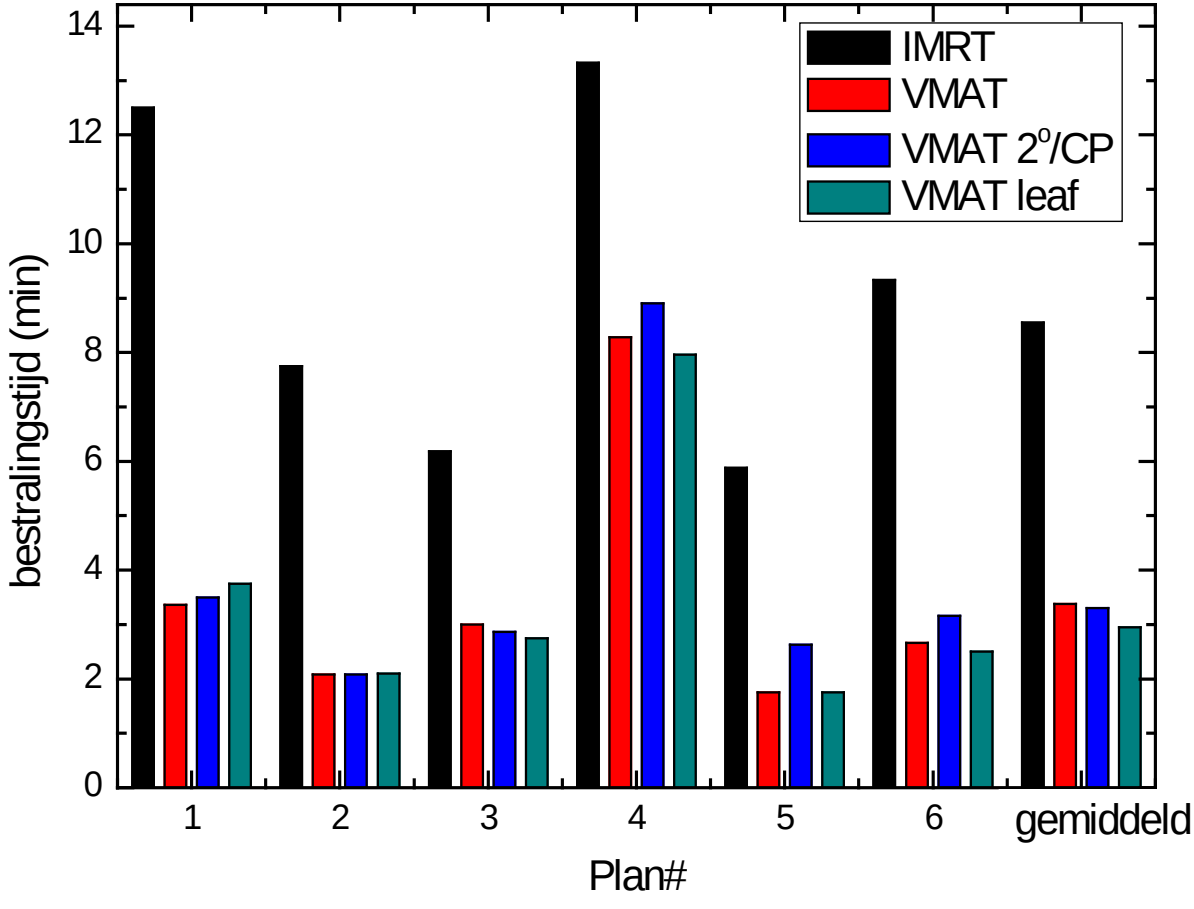
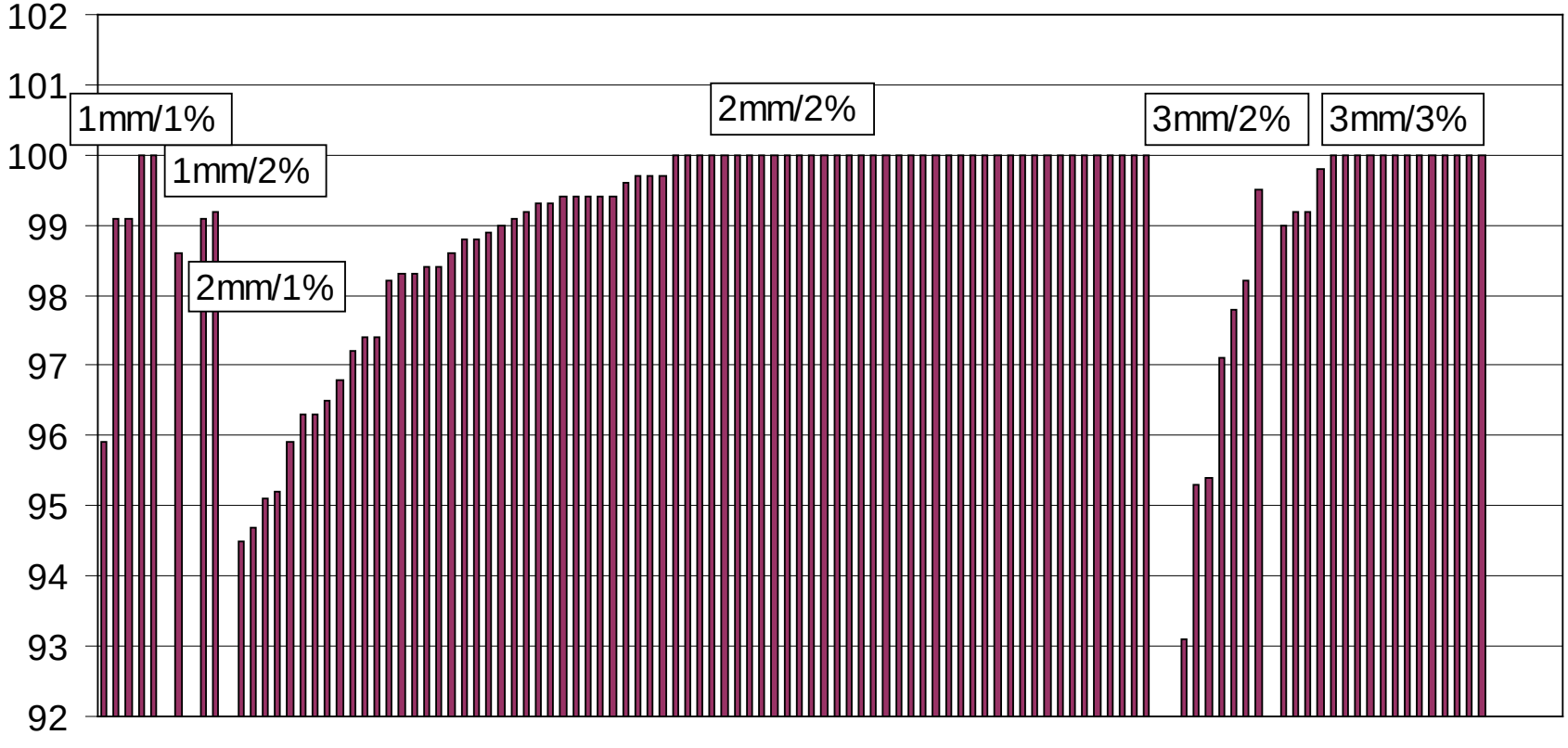
IMRT vs VMAT – irradiation time



- Average treatment time from 8’30” to 3’ (8 Gy/fraction)

Gamma results brain VMAT



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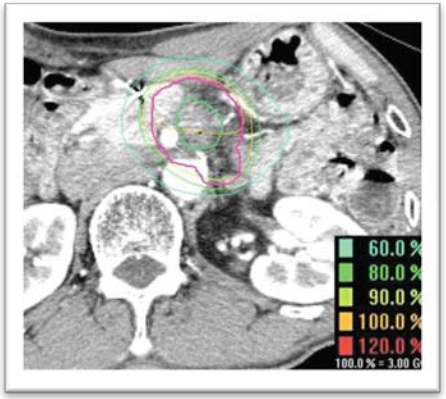
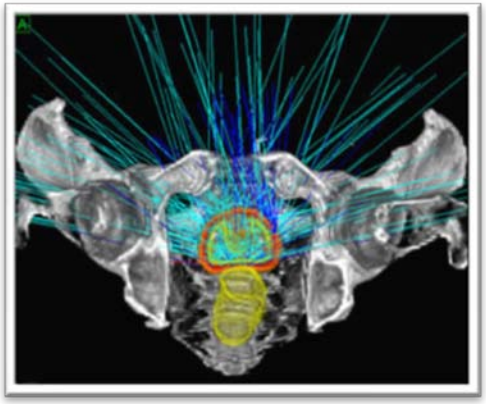
Emerging indications for SBRT





Matthias Guckenberger

UniversityHospital Zurich

1. **Pancreatic cancer**

2. **Prostate cancer**

Question 1

Which answer is NOT correct in pancreatic SBRT?

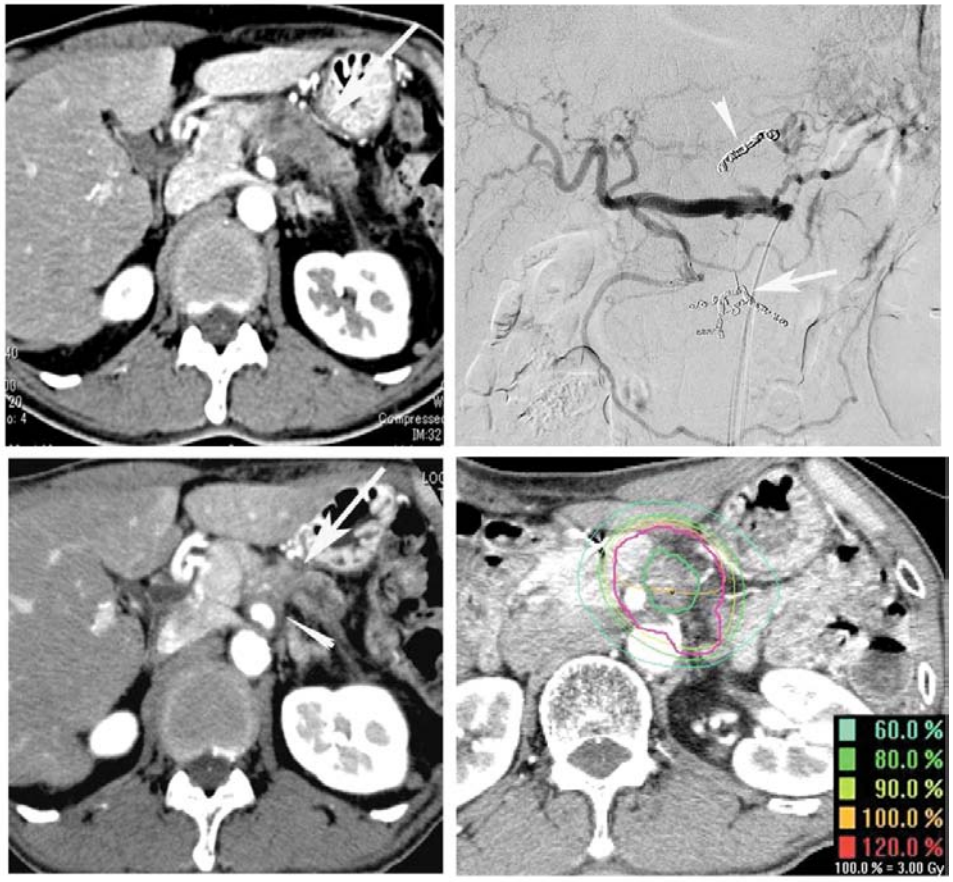
1. The duodenum is the dose limiting structure?
2. Single fraction radiosurgery is the preferred fractionation
3. Fractionated approaches using SFD <10Gy appear safe
4. OS is limited by systemic progression

Question 2

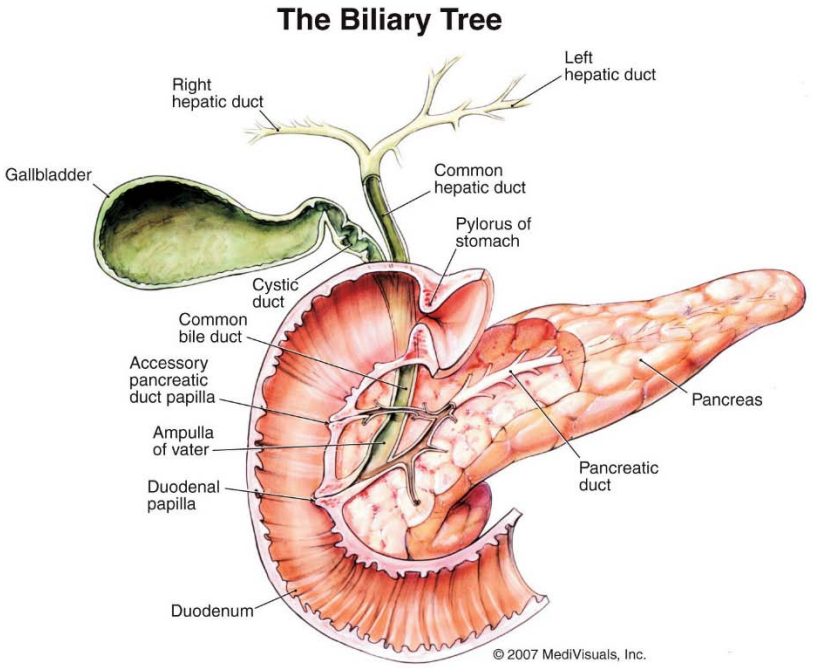
Which answer is NOT correct in prostate SBRT?

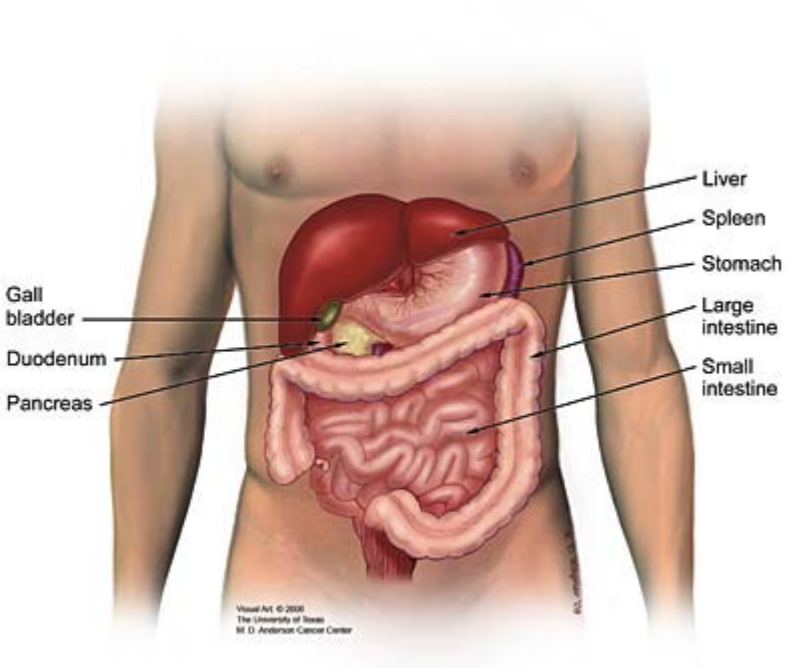
1. A low alpha/beta ratio is the rational for SBRT
2. 5 x 10Gy is the preferred fractionation based on prospective phase I / II trials
3. Long term follow-up is still lacking
4. Especially GU toxicity is an issue of concern
5. Very tight margins are achieved by daily IGRT and intra-fraction motion monitoring

Pancreatic cancer



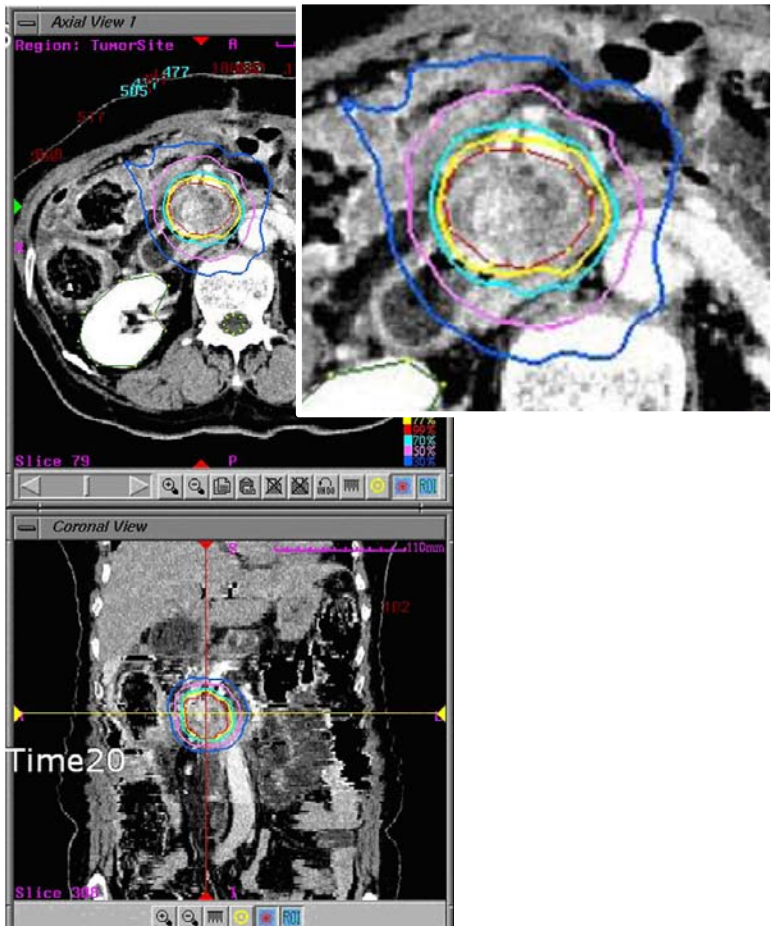
Pancreatic cancer





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

Pancreatic SBRT



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 PC

	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 PC

	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 overall survival – similar to systemic treatment only
- Interpretation of promising LC considering OS ?

SBRT for locally advanced PC

	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 gastrointestinal toxicity DESPITE short FU
- Difficult (impossible) sparing of duodenum

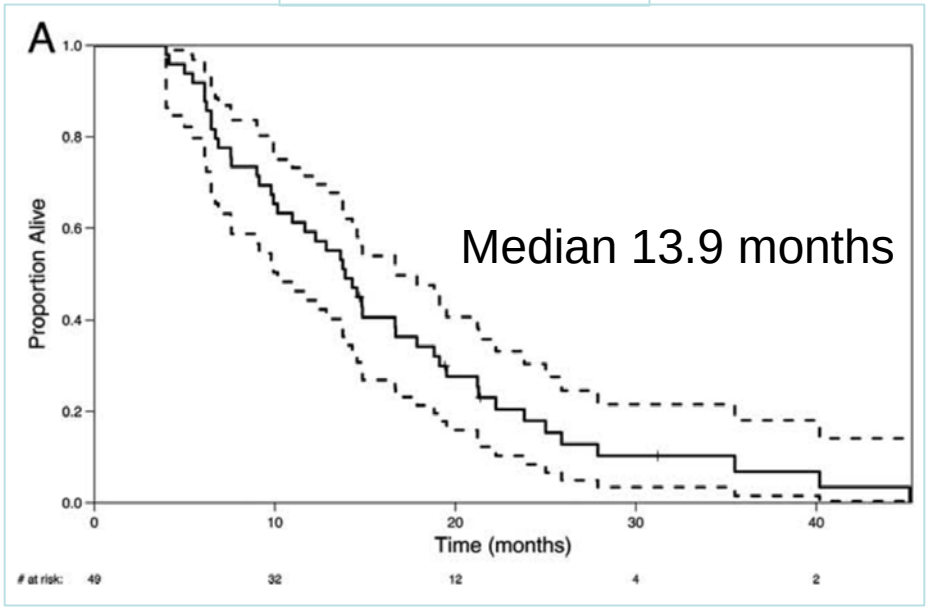
SBRT for locally advanced PC

Herman Cancer 2015

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

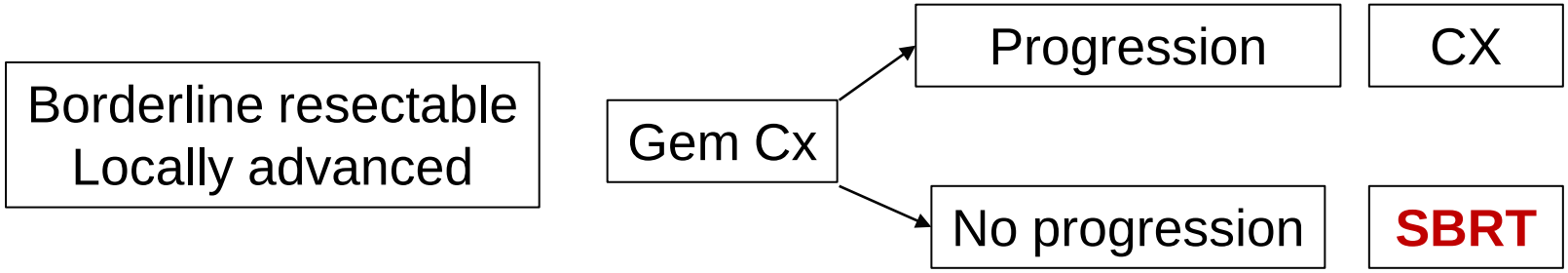
Acute GI Tox G >=2	Late GI Tox G >=2
2%	11%

Overall survival



➢ Fractionated SBRT with lower SFD well tolerated

SBRT to achieve resectability

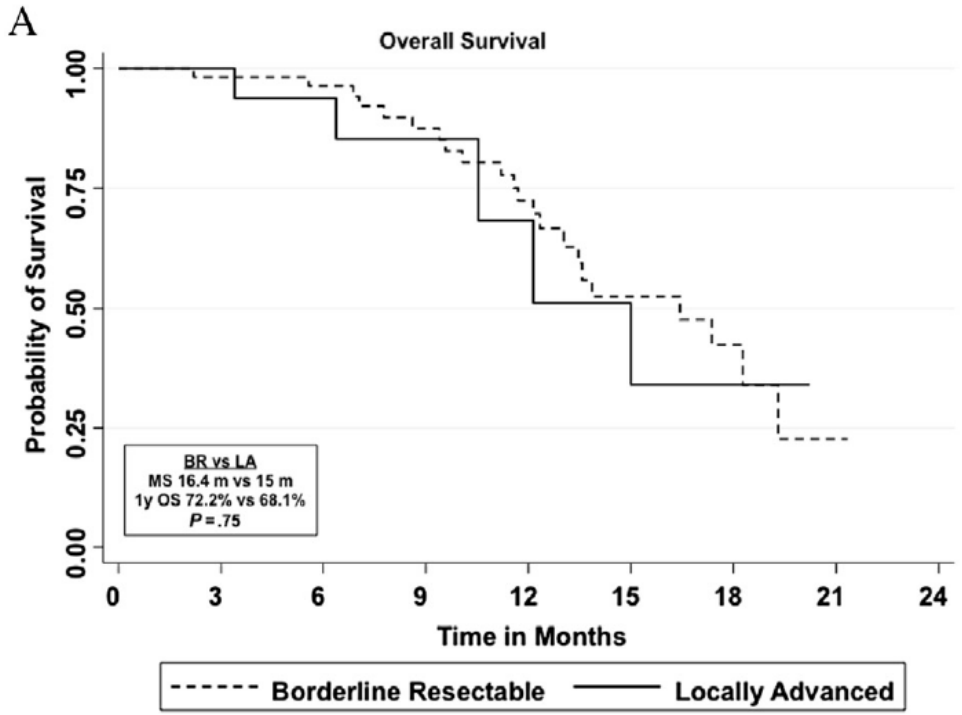


SBRT: 5 x 7Gy to vessle abutting region
5 x 5Gy to remaining tumor

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:

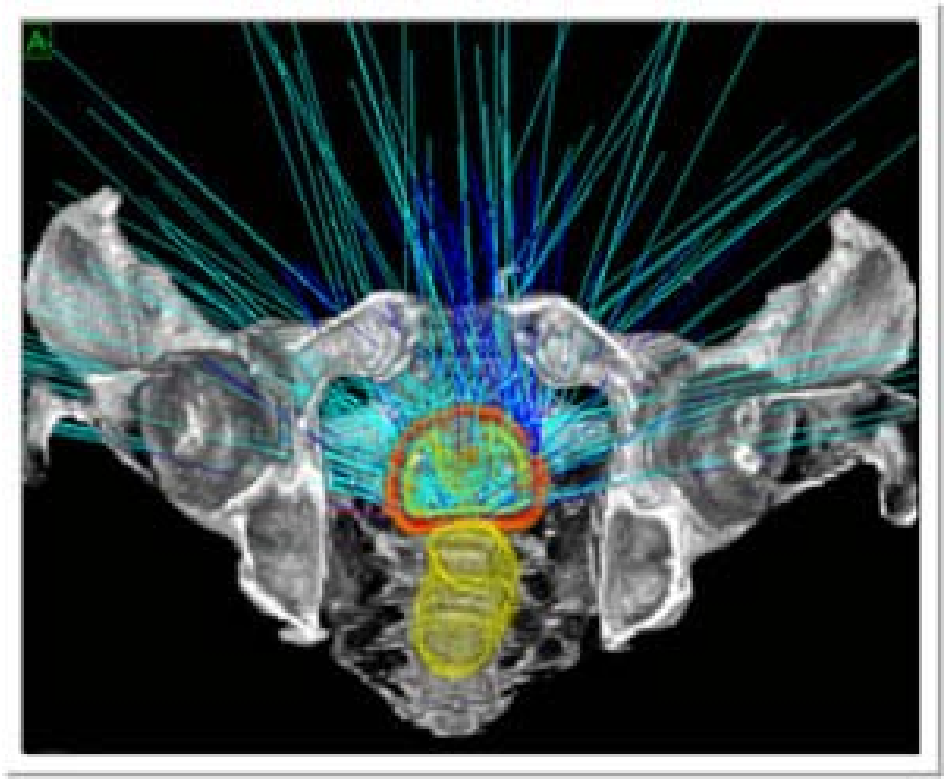
- Borderline resectable PC: 16.4 months
- Locally advanced pC: 15 months

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

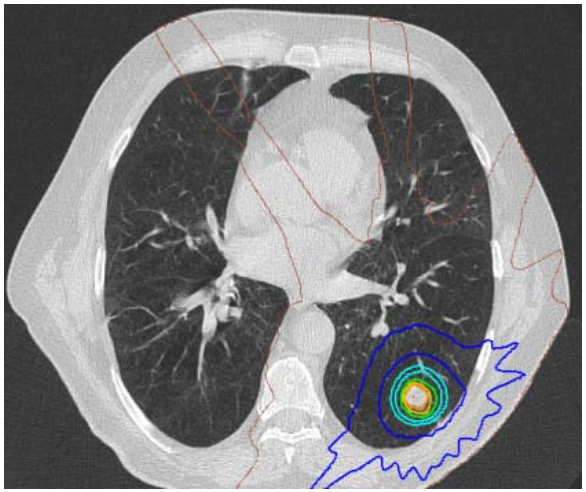
➢ **Should not be practiced outside of prospective trials**

SBRT for prostate cancer



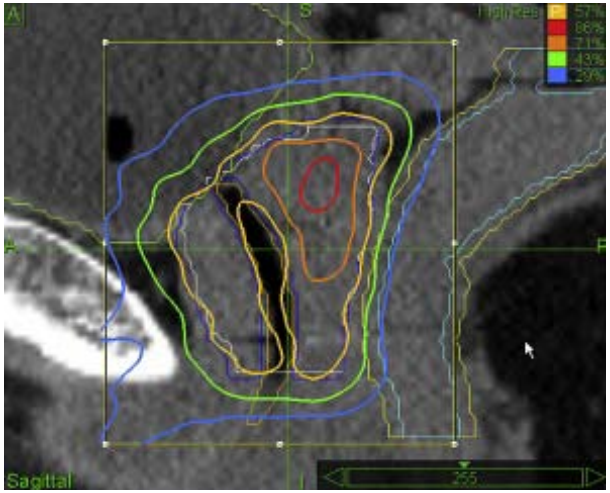
SBRT: basic considerations

SBRT for lung cancer



Small tumor surrounded by a large parallel organ

SBRT for prostate cancer



Urethra, anterior rectal wall, bladder, neurovascular bundle within the PTV

Clinical rational

α/β of prostate cancer

MIRALBELL IJROBP 2012

Author	Dose/fraction	Total dose	No. fractions	No. fractions/wk	OTT (wk)	Pelvic nodes RT	Technique
Kupelian	2 Gy	78 Gy	39	5	7.5	No	3d-CRT
	2.5 Gy	70 Gy	28	5	5.5	No	IMRT-BAT
Leborgne	2 Gy	76 Gy	38	5	7.5	No	3d-CRT
Logue	3.125 Gy	50 Gy	16	5	3	No	3d-CRT
Lukka	2 Gy	66 Gy	33	5	6.5	No	2d-CRT
	2.62 Gy	52.4 Gy	20	5	4	No	2d-CRT
Madsen et al (20)	6.7 Gy	33.5 Gy	5	5	1	No	SRT-IGRT
Miralbell	1.8–2 Gy	74–74.4 Gy	37–40	5	7.5–8	No/yes	3d-CRT
	4 Gy	56 Gy	14	2	6.5	No	SRT
Yeoh	2 Gy	64 Gy	32	5	6.5	No	2d-RT
	2.75 Gy	55 Gy	20	5	4	No	2d-RT

Pros: N= 5969

No brachytherapy studies included

Cons: Endpoint for α/β modelling: bRFS

Mix between 2D-RT, 3D-CRT, IMRT

α/β of prostate cancer

MIRALBELL IJROBP 2012

	α/β (95% CI) (Gy)
All patients	1.4 (0.9 – 2.2)

- Low α/β for all risk groups
- Small confidence intervals
- No influence of AHT

Clinical practice and evidence

Published data about SBRT for Prostate cancer

Study	Study type	# of patients	Median FU
McBride et a. 2012	Phase I	45	45 months
Madsen et al. 2007	Phase I / II	40	41 months
Boike et al. 2011	Phase I / II	45	12 – 30 months
King et al. 2012	Phase II	67	32 months
Jabbari et al. 2012	Retrospective	20	18 months
Katz et al. 2013	Retrospective	304	60 months

Few, early studies with small patient numbers and intermediate follow-up

Patient seletion for SBRT

Study	% low risk	% AHT
McBride et a. 2012	100%	0%
Madsen et al. 2007	100%	0%
Boike et al. 2011	40%	22%
King et al. 2012	100%	0%
Jabbari et al. 2012	45%	47%
Katz et al. 2013	69%	19%

- Low risk patients
- PTV does not cover potential extracapsular extension

Dose and fractionation

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“

Dose and fractionation

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

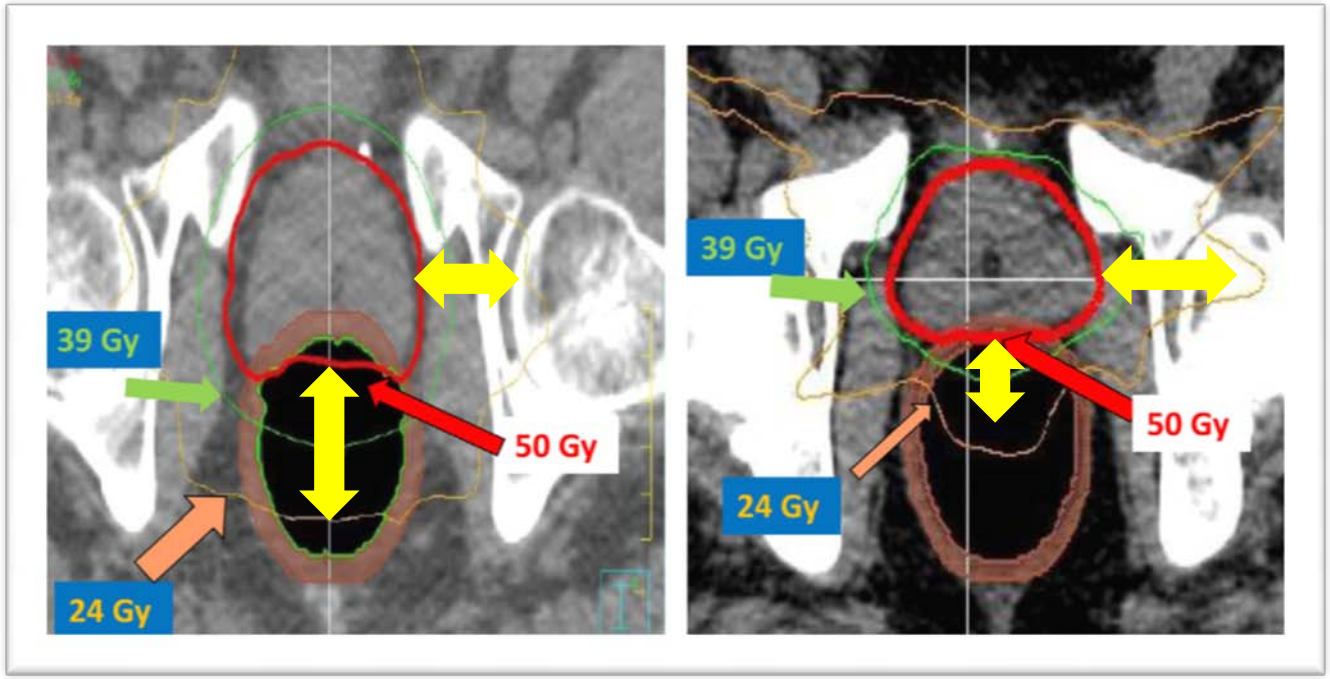
Table 2 Worst acute and delayed rectal toxicity in patients by radiation prescription dose level

	All patients (n=91)		45 Gy (n=15)		47.5 Gy (n=15)		50 Gy (n=61)	
Grade	Acute	Late	Acute	Late	Acute	Late	Acute	Late
0	39 (42.9)	38 (41.8)	9 (60.0)	10 (66.7)	7 (46.7)	8 (53.3)	23 (37.7)	20 (32.8)
1	33 (36.3)	27 (29.7)	6 (40.0)	4 (26.7)	4 (26.7)	2 (13.3)	23 (37.7)	21 (34.4)
2	17 (18.7)	21 (23.1)	0	1 (6.7)	4 (26.7)	5 (33.3)	13 (21.3)	15 (24.6)
3	1* (1.1)	3 (3.3)	0	0	0	0	1* (1.6)	3 (4.9)
4	1 (1.1)	2 (2.2)	0	0	0	0	1 (1.6)	2 (3.3)

6 / 61 patients with G3+ Toxicity
5 / 61 patients required colostomy

Dose and fractionation

Kim IJROBP 2014



Dose gradient:

distance 50Gy – 24Gy

Dose and fractionation

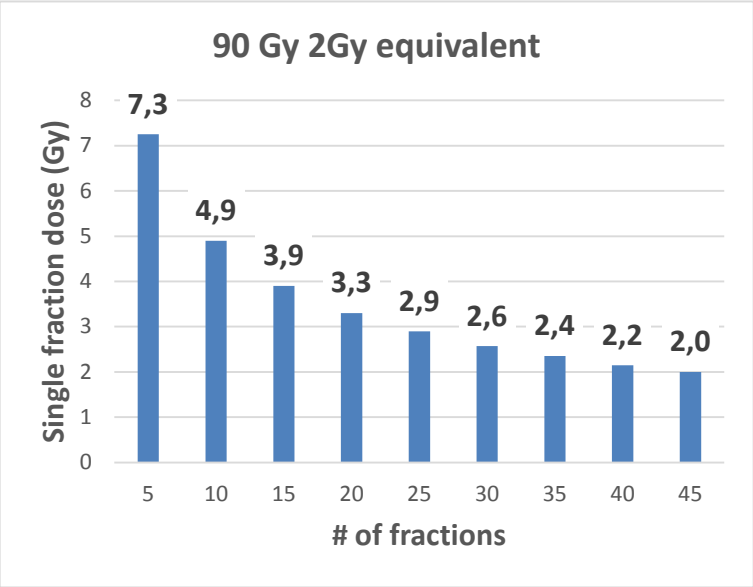
Most frequently used: 5 x 7.25Gy (EQD2 = 90Gy)

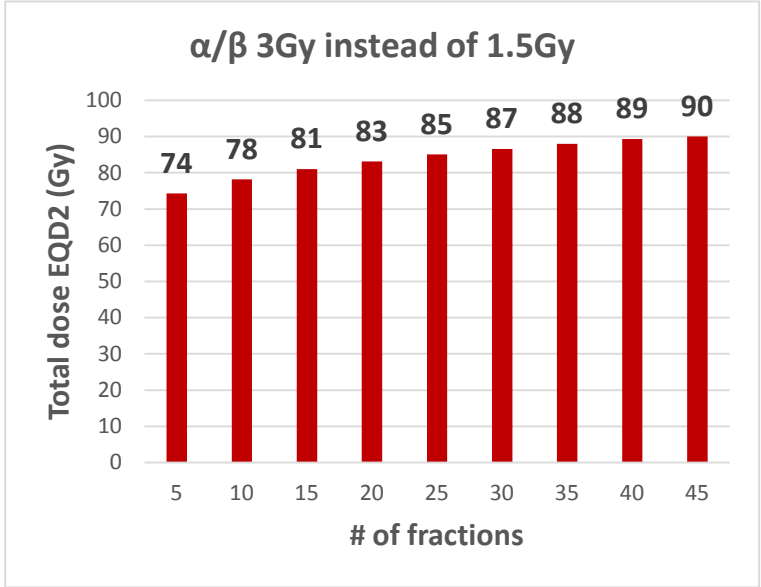
King 2009

Fractionation	5 x 7.25Gy every day	5 x 7.25Gy every other day
Patients	20	21
EPIC 4-5	38%	0%

- Current „standard“ 5 x 7.25Gy QID
- Evidence weak

The risk of biological „underdosage“ in hypofractionation





Hypofractionation based on
α/β = 1.5Gy

Error analysis based on
α/β = 3Gy

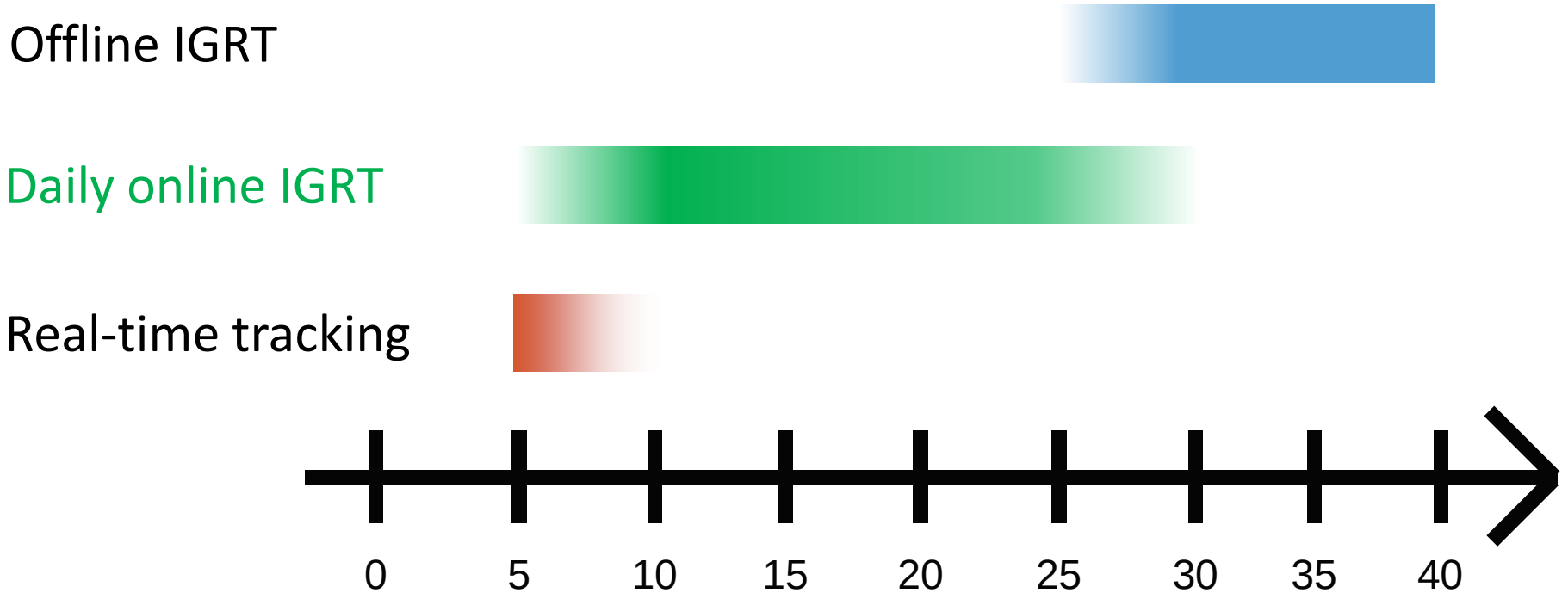
α/β lower than assumed especially critical in treatment with very high single fraction doses

Treatment delivery of prostate SBRT

Study	Technology	IGRT	IGRT
McBride et a. 2012	Cyberknife	Implanted markers	Real-time tracking
Madsen et al. 2007	Linac	Implanted markers	Daily IGRT
Boike et al. 2011	Linac	Implanted markers	Daily IGRT Rectal balloon
King et al. 2012	Cyberknife	Implanted markers	Real-time tracking
Jabbari et al. 2012	Cyberknife	Implanted markers	Real-time tracking
Katz et al. 2013	Cyberknife	Implanted markers	Real-time tracking

- Daily IGRT using implanted markers
- Intra-fraction motion management strategy

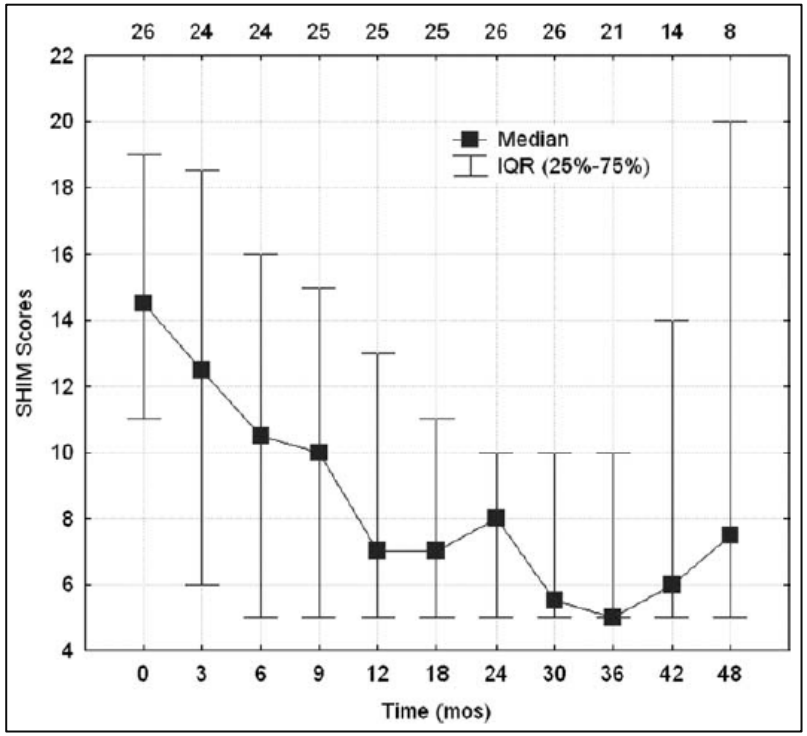
Requirements on accuracy of RT delivery



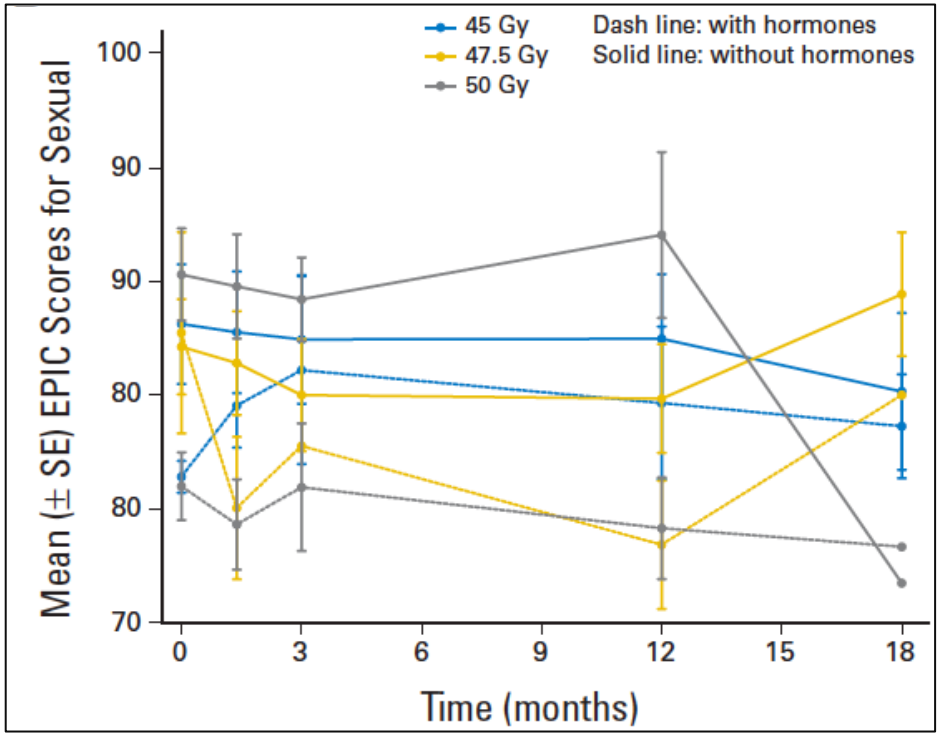
Toxicity

- Late toxicity = preliminary
- Relevant GU toxicity

Sexual function



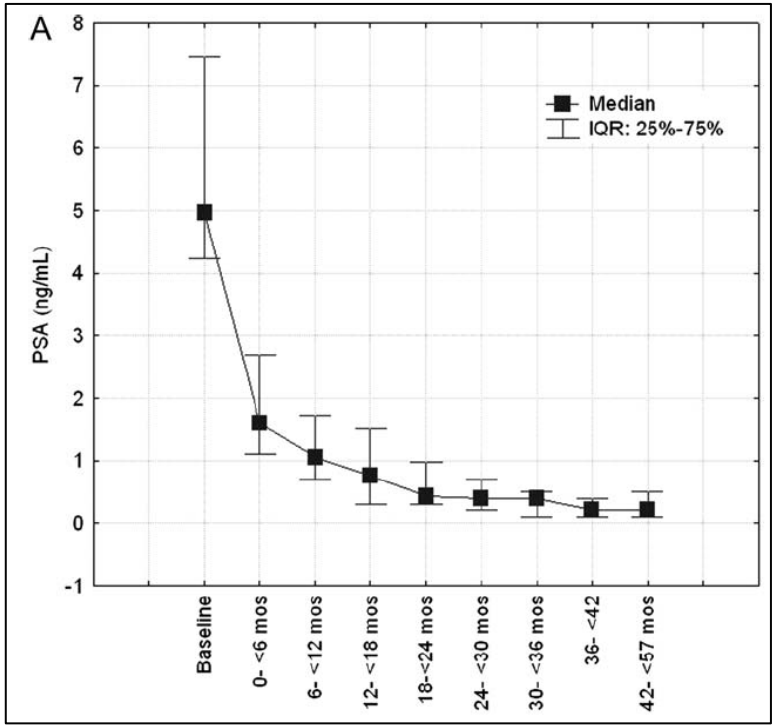
McBride Cancer 2012



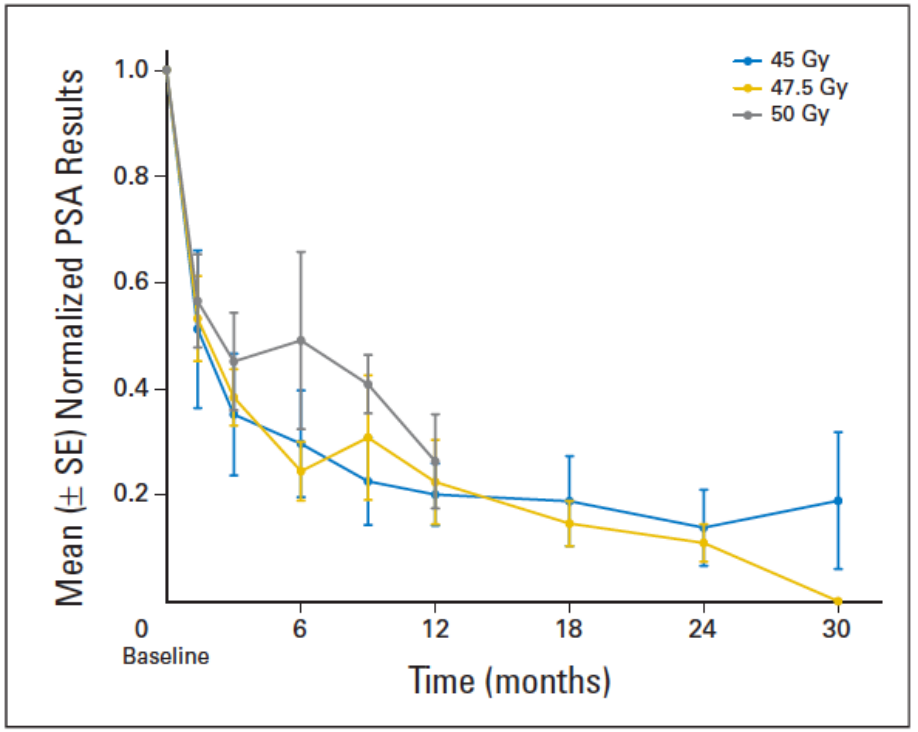
Boike JCO 2012

- Inconclusive

Biochemical response



McBride Cancer 2012

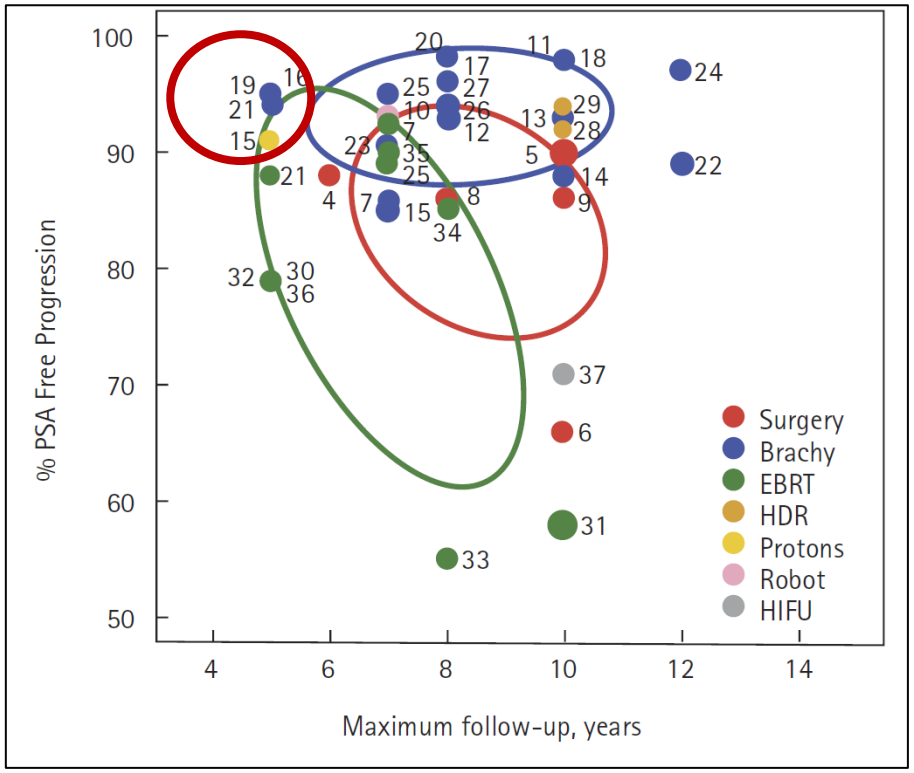


Boike JCO 2012

- Rapid PSA Response within 6 months

Biochemical control

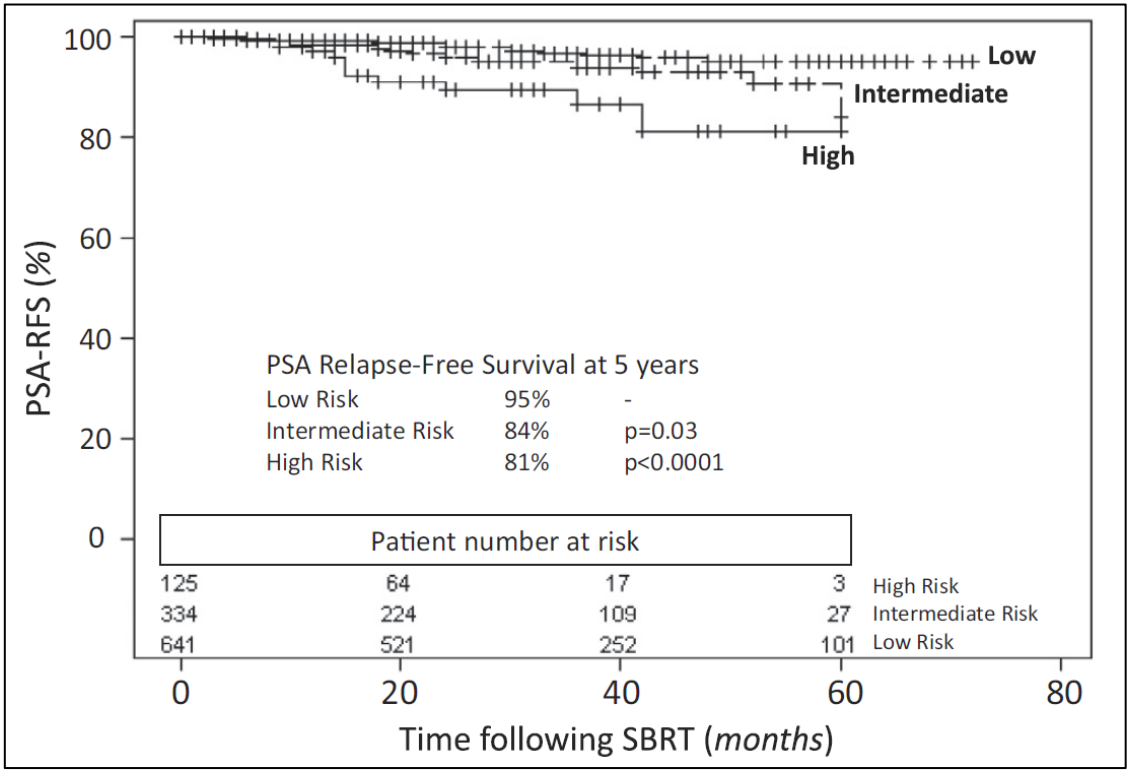
Study	Biochemical control
McBride et a. 2012	**98%** @ 3a
Madsen et al. 2007	**90%** @ 4a
Boike et al. 2011	**100%**
King et al. 2012	**100%**
Katz et al. 2013	**74 – 97%**@ 5a



Grimm 2012

Promising, but too early

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

Multi-center analysis: *King et al Radiat Oncol 2013*

	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%	$p = 0.83$

- No benefit of ADH
- No dose effect relationship

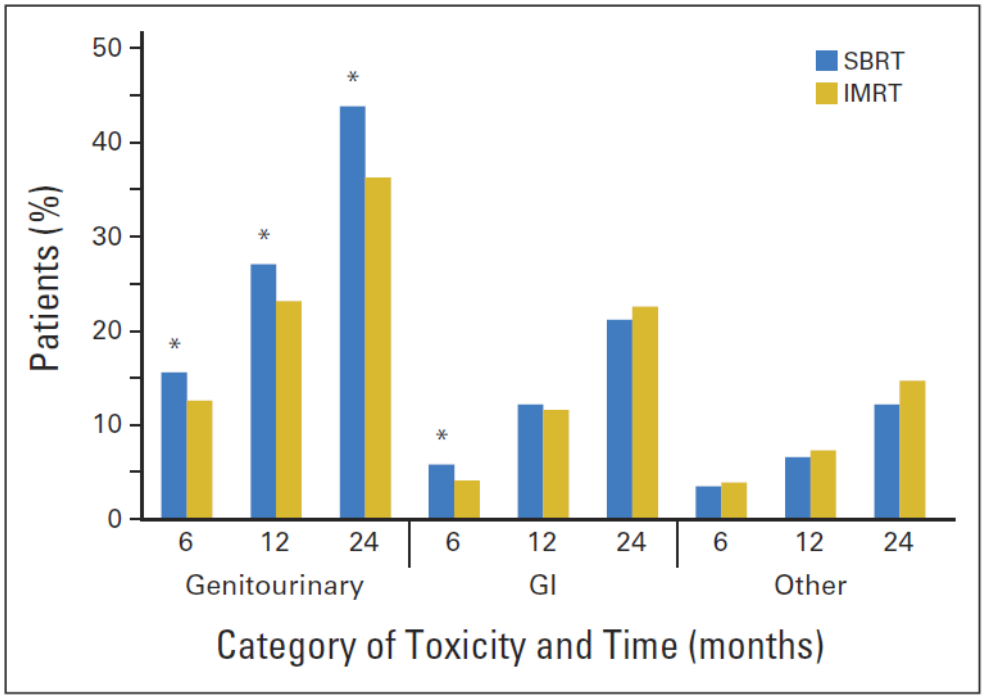
Population based analysis

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



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JCO 2014

Toxicity	Duration of Follow-Up					
	6 Months		12 Months		24 Months	
	OR*	*P*†	OR*	*P*†	OR*	*P*†
Diagnostic procedures to investigate incontinence or obstruction	**1.80**	**< .001**	**1.64**	**< .001**	**2.23**	**< .001**
Urethritis, urethral strictures, and bladder outlet obstruction	1.25	.14	**1.45**	**.002**	**1.78**	**< .001**
Therapeutic procedures to correct urinary incontinence	0.71	.22	1.00	1.00	1.33	.09
Other genitourinary toxicity	0.77	.45	1.14	.58	0.73	.23
Infections	1.01	.99	2.30	.11	2.42	.15
Erectile dysfunction	1.46	.03	1.15	.28	1.13	.35

- Significantly increased GU toxicity after SBRT vs IMRT
  - Strictures & obstruction

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 protocolls

SBRT :
EMERGING INDICATIONS ?

Pr. Eric F. LARTIGAU

Centre Oscar Lambret, Lille, France

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CyberKnife® Nord Ouest
www.ckno.fr

SBRT is a « standard » in many clinical situations

Centre Oscar Lambret

- **Today** : brain, lung, spine, retreatment
- **Tomorrow** : liver, prostate, partial breast …
- **After tomorrow** : most of ???

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Radiotherapy of prostate carcinoma

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The question is not anymore :
to treat or not to treat
but the question is :

What is the optimal therapeutic ratio ?

Cure versus morbidity

Precision, individualisation

Hypofractionation ???

Rational

- Extremely slow average growth kinetics: median Tpot of 42 days
- PSA doubling times: <12 months - >5y
- LI < 0.6%
- Alpha/beta : 1.5 to 5 Gy
- Such slow growth rate is typical for late-responding tissues

Brenner et al. Int J Radiat Oncol Biol, 43, 1095-1101, 1999

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78/80 Gy versus 70 Gy

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Randomized studies testing non IMRT dose escalation

LONG-TERM RESULTS OF THE M. D. ANDERSON RANDOMIZED DOSE-ESCALATION TRIAL FOR PROSTATE CANCER

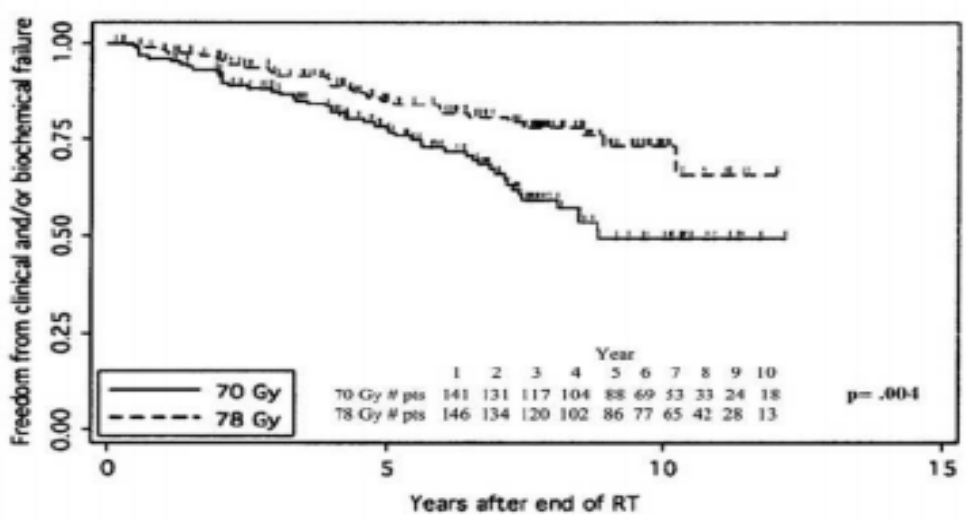
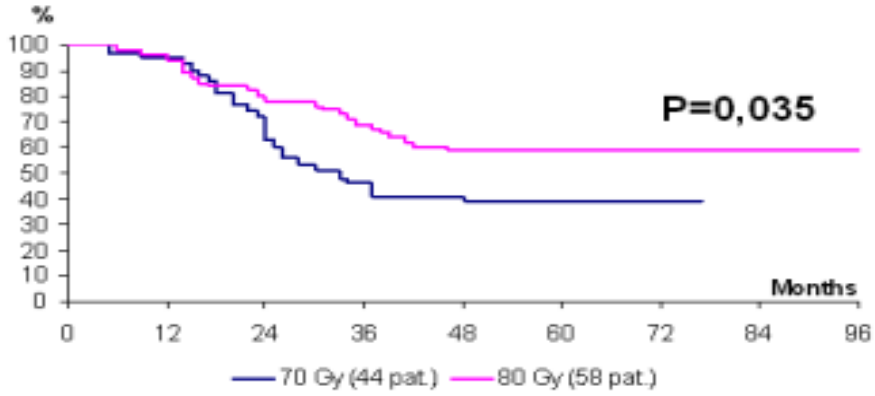


Fig. 1. Freedom from failure for all patients treated to 78 Gy versus 70 Gy.

GETUG 06

SURVIVAL WITHOUT CLINICAL OR BIOCHEMICAL RELAPSE, PSA > 15 - ASTRO



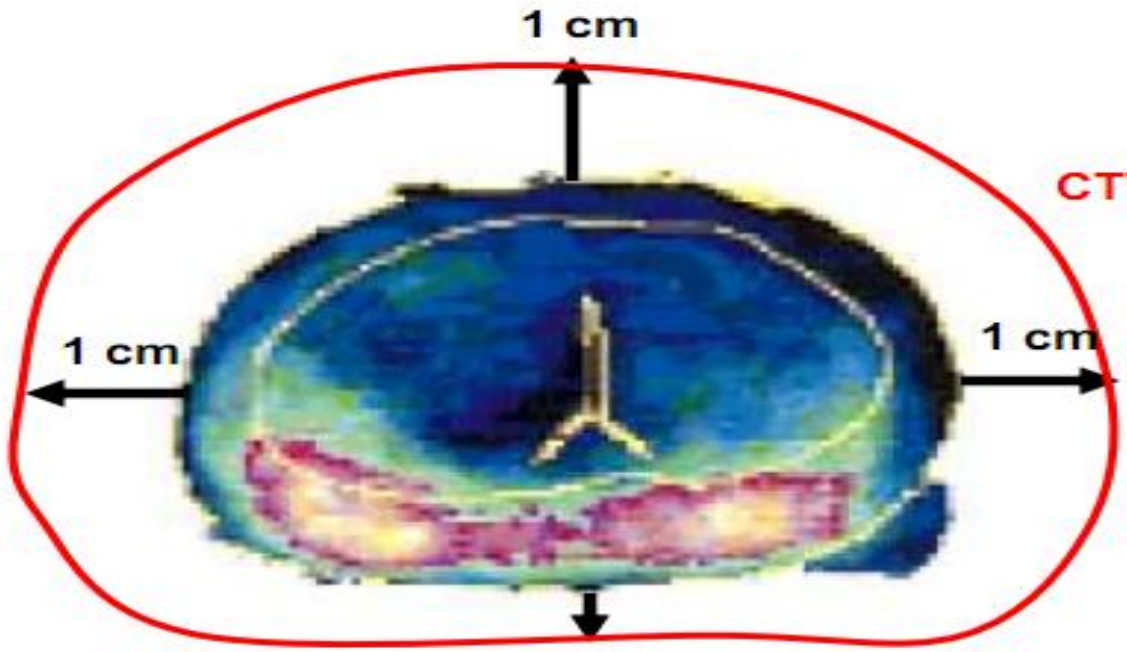
Clinical failures and PC deaths significantly reduced (50%) in the 78 Gy arm if PSA > 10 ng/ml

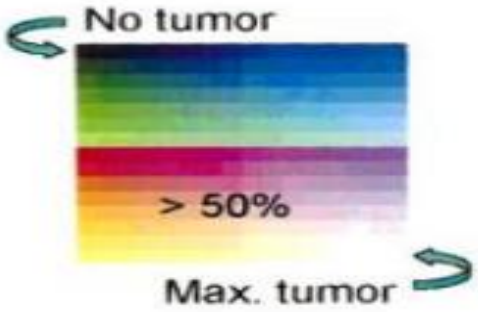
Kuban, ASTRO 2008

Beckendorf, ASTRO 2008

IMRT-IGRT

ANATOMIC VARIATIONS: clinical impact





Tumor distribution inside the prostate: mainly in the posterior peripheral zone

De Crevoisier IJROBP 2005

IMRT-IGRT

Rectal distension on the planning CT

↓

Posterior displacement of prostate during Tt

↓

Under-dosage of the peripheral tumor zone

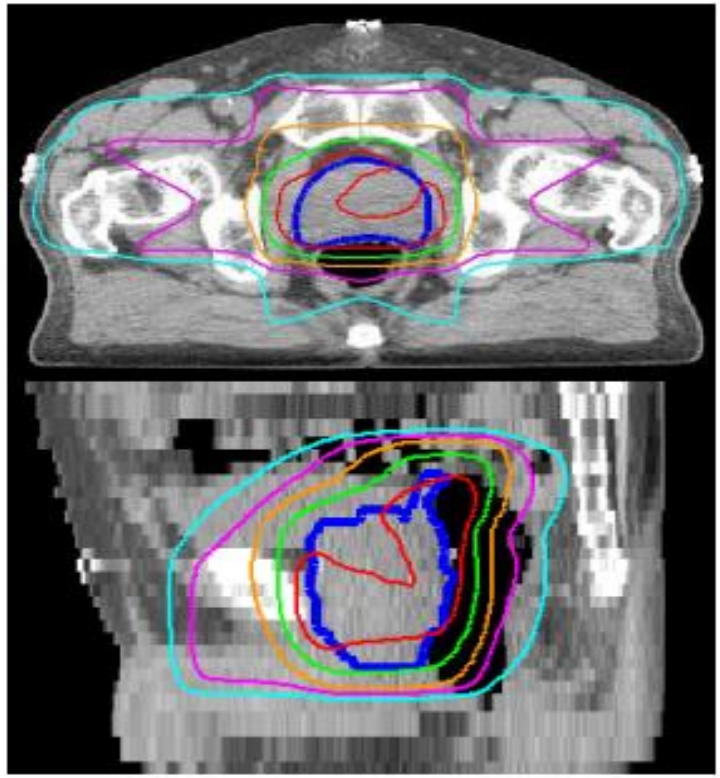
↓

↗ **Local recurrence**

Rectal distension =

absolute rectal volume / rectal length

= average rectal surface (cm²)



Isodose

De Crevoisier IJROBP 2005

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Margins are the issue !!!!

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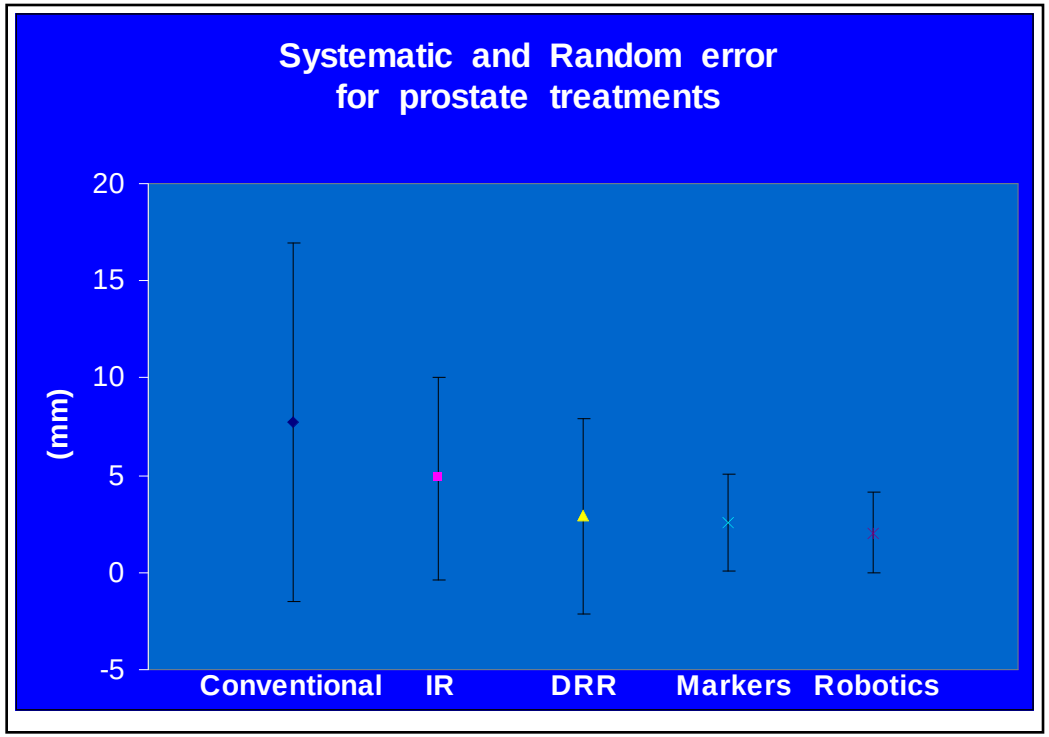

AZVUB, Bruxelles Stereoscopic kV

CTV + **10mm** except LR (**6mm**) : DRR registration on bony structures

CTV + 5mm except LR (3mm): implanted radio-opaque markers

Very careful on the margins !!!!!

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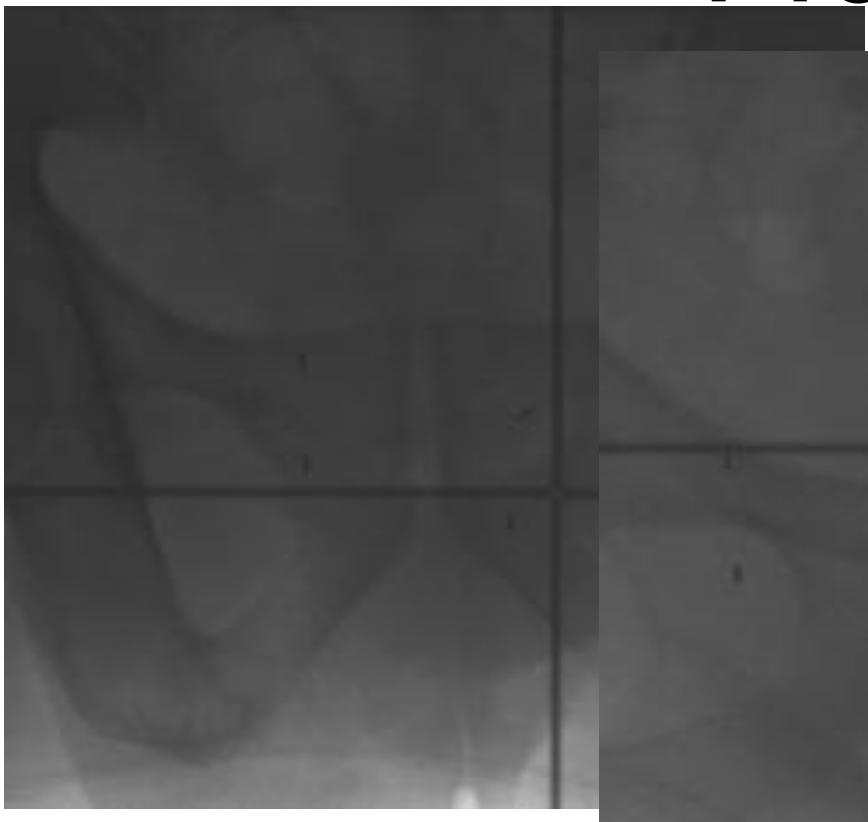
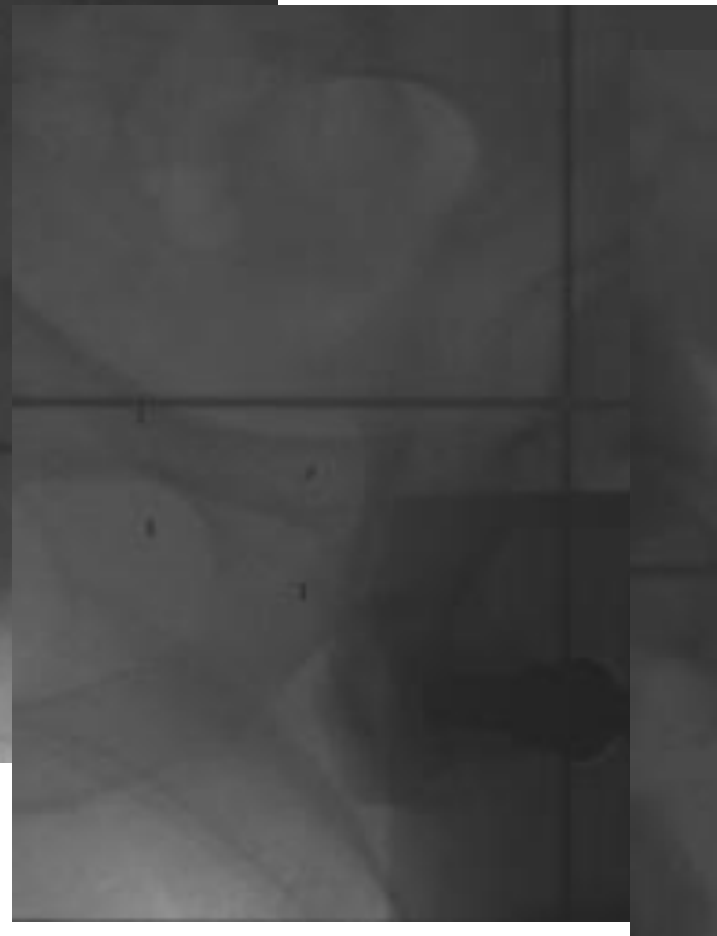
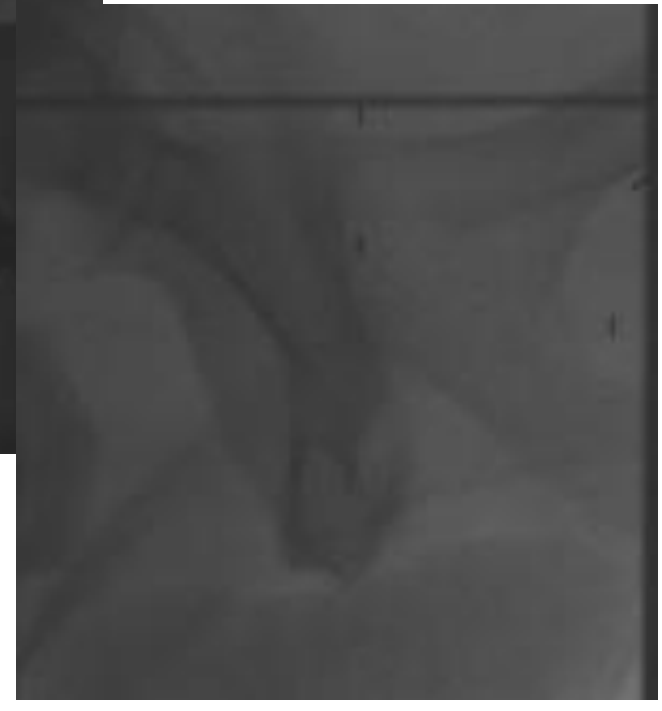
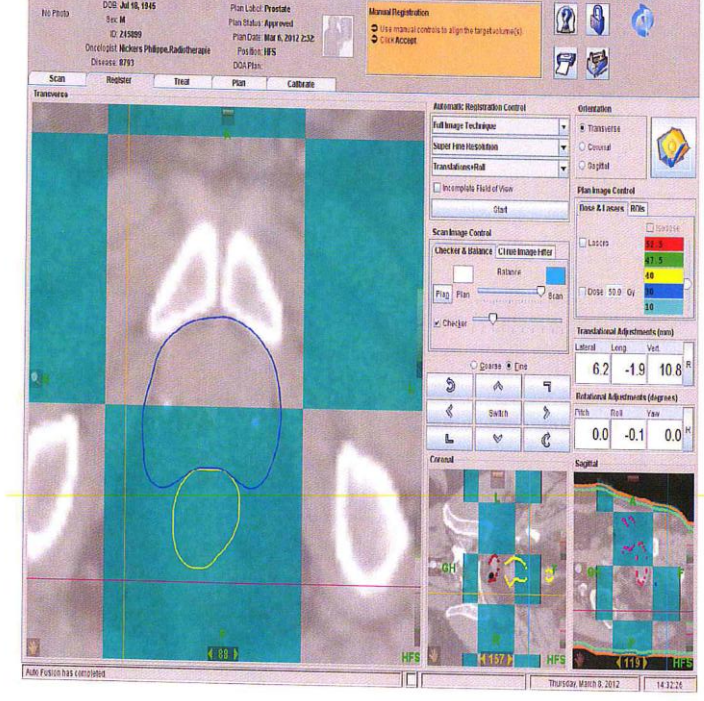
Fiducials









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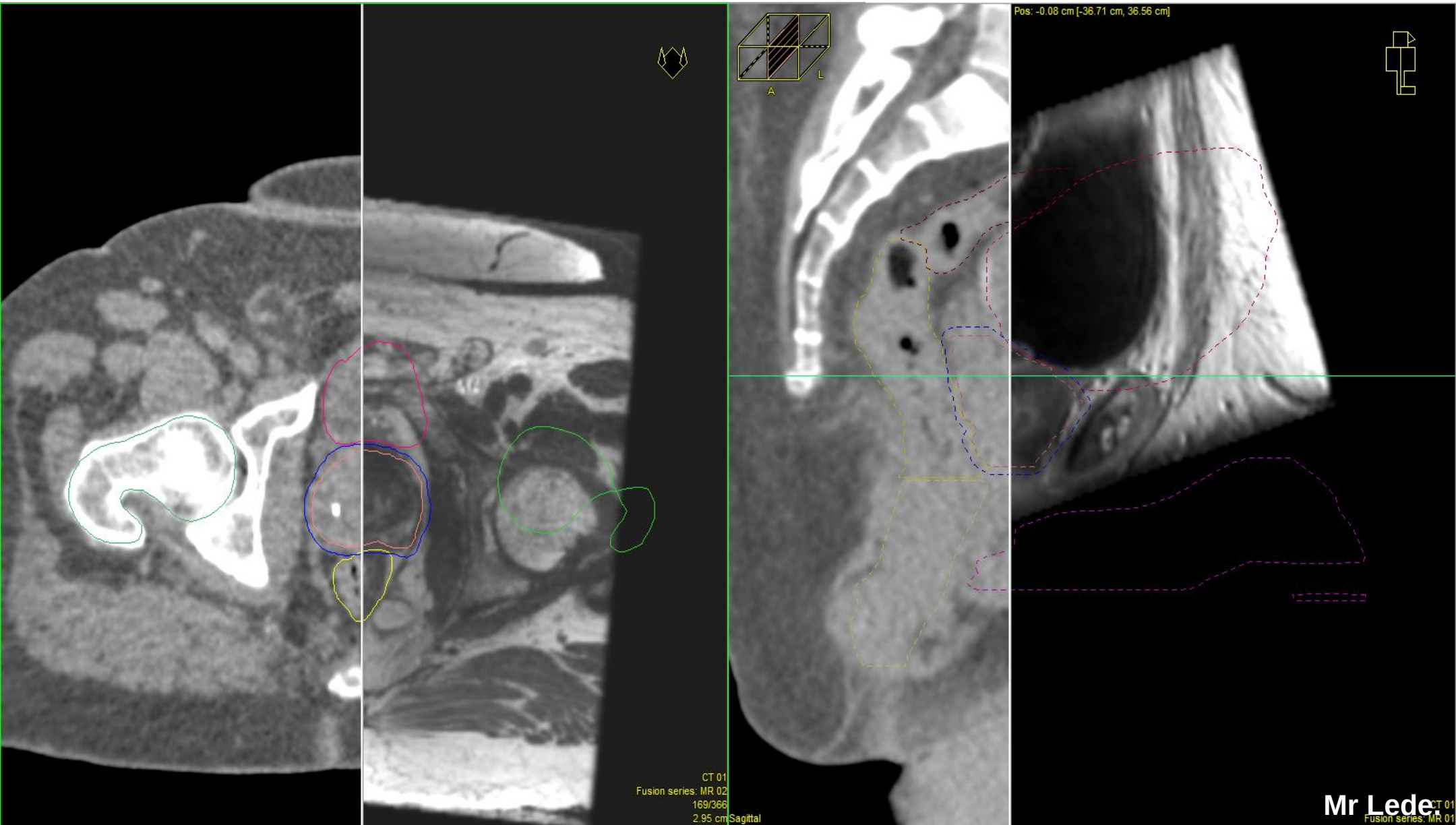
Exclusive SBRT/standard treatment

Centre Oscar Lambret



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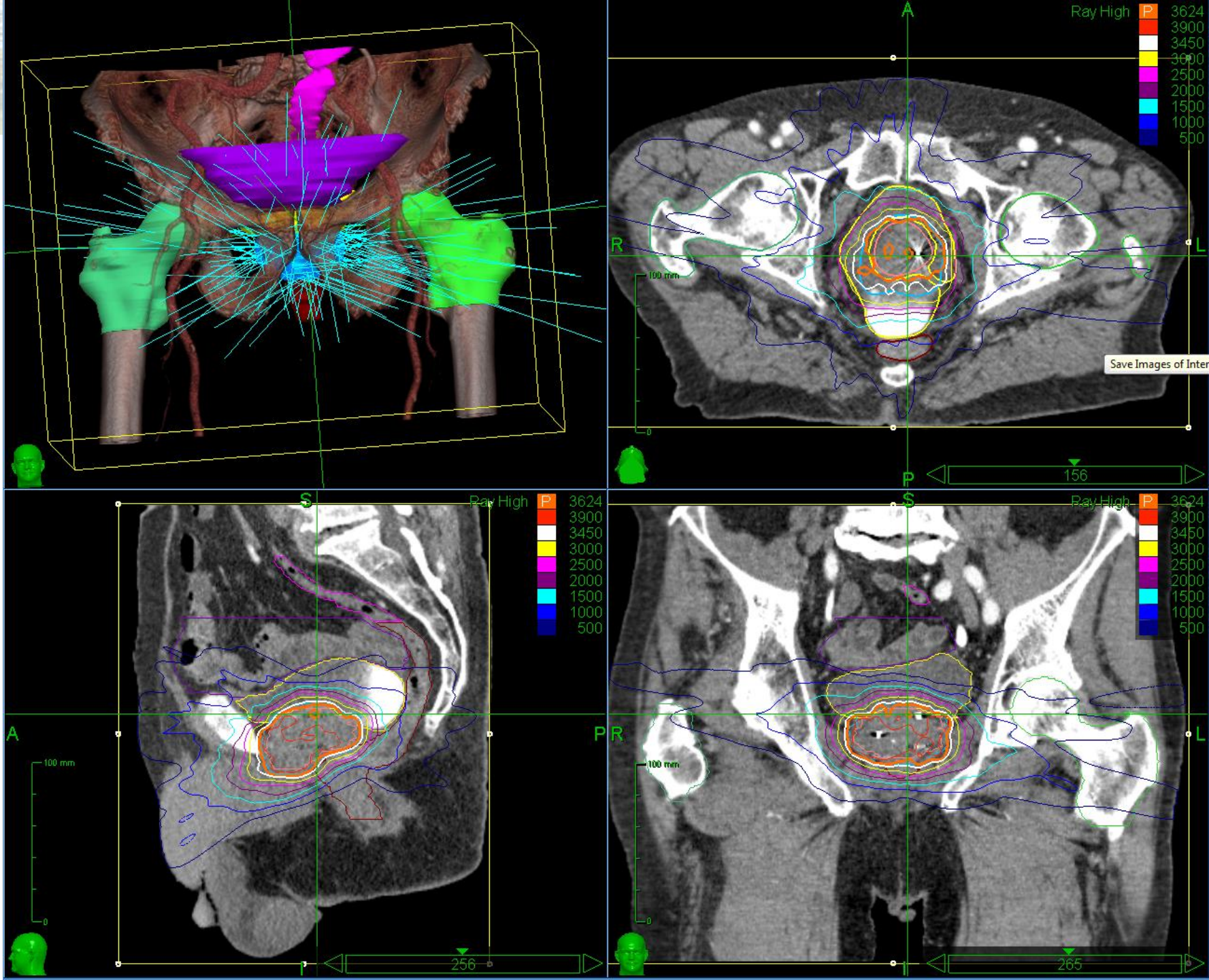

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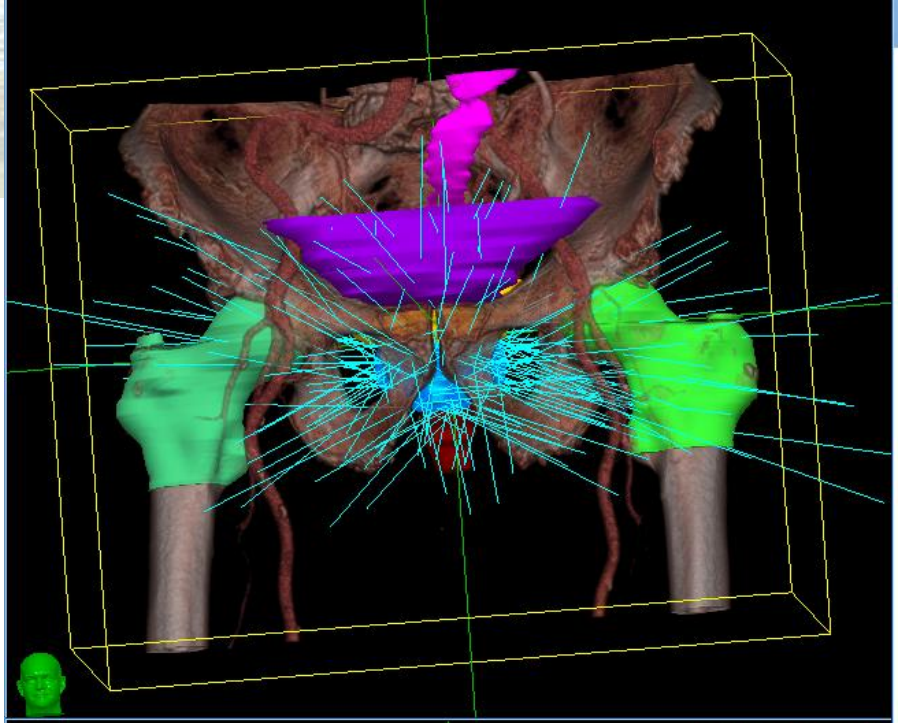
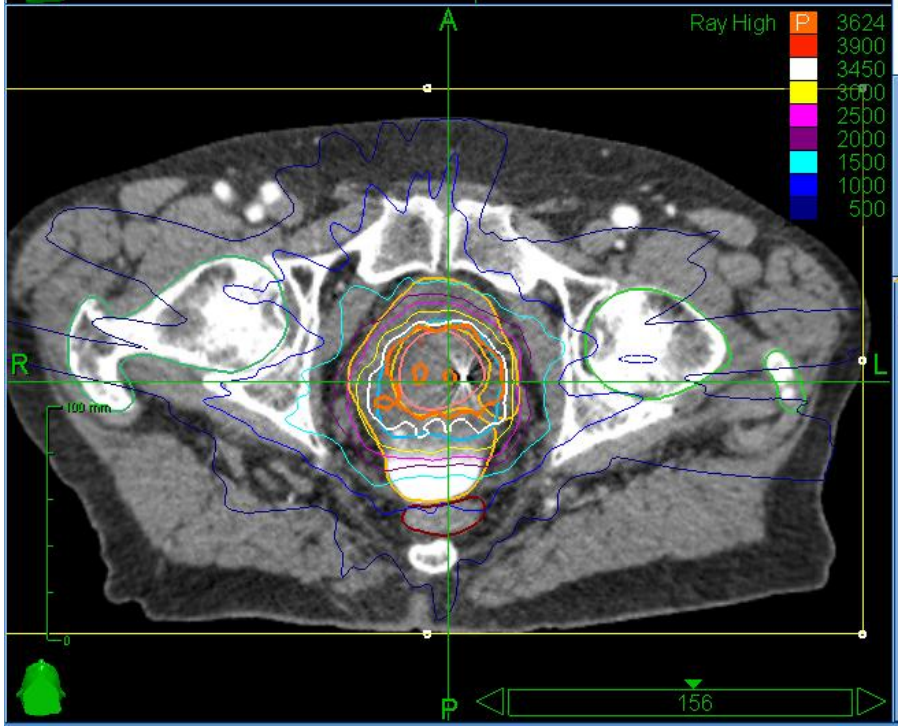
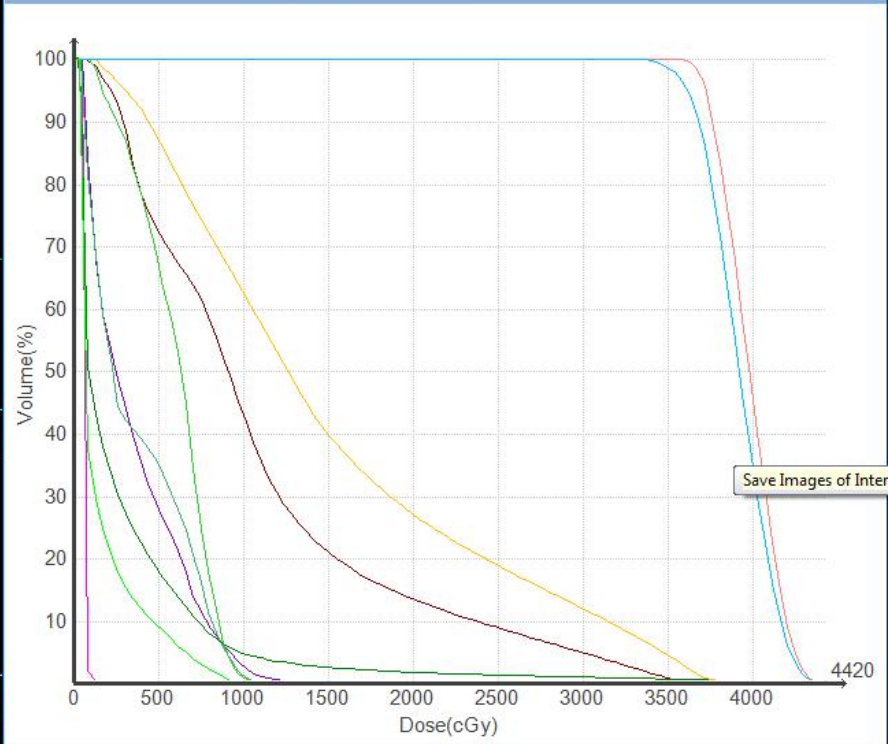




DVH Properties | Selected DVH: skin-rind



Nodes	49	Total MU	44618.99
Beams	181	Min MU	51.48
Max Dose (cGy)	4420.07	Max MU	644.21

Estimated Treatment Time Per Fraction (minutes) 40

Dose Statistics Table | Dx Vx Values | Plan Information

Name	Min (cGy)	Mean (cGy)	Max (cGy)	CI	nCI	HI	Coverage
skin-rind	32.99	158.74	1150.41	n/a	n/a	n/a	n/a
CTV	3492.97	3974.71	4420.07	1.63	1.64	1.22	99.43
PTV	3214.79	3914.09	4420.07	1.13	1.20	1.22	94.21
*Skin	30.86	291.69	4420.07	n/a	n/a	n/a	n/a
vessie	122.52	1506.04	4069.61	n/a	n/a	n/a	n/a
rectum	81.28	1082.87	3723.65	n/a	n/a	n/a	n/a
sigmoide	52.90	62.86	232.60	n/a	n/a	n/a	n/a
grele	55.30	352.07	1431.43	n/a	n/a	n/a	n/a
tete fem. d	45.85	368.02	1230.98	n/a	n/a	n/a	n/a

Patient Selection for Robotic Radiosurgery for Clinically Localized Prostate Cancer: Come One, Come All

Sean P. Collins, Simeng Suy, Eric Oermann, Siyan Lie, Xia Yu, Heather Hanscom, Joy Kim, Benjamin Sherer, Hyeon U. Park, Brian T. Collins, Kevin McGeagh, Nancy Dawson, John H. Lynch, and Anatoly Dritschilo

SBRT DATA

35Gy in 5f ≈ 85 Gy

Article	n	Médian f up	Dose (Gy)	Scheme	Psa free surv.
Madsen	40	41	33.5	6.5Gy*5	90% 4 years
Tang	30	12	35	7Gy*5	NP
Friedland	24	24	35	7Gy*5	NP
Bolzicco	45	20	35	7Gy*5	NP
Katz	300	30	35-36.25	7Gy*5 7.25Gy*5	4 recurences
Jabbari	20	18.3	38	9.5Gy*4	100%
Boike	15-15-15	30, 18, 12	45, 47.5, 50	5*9-9.5-10 Gy	100%

VOLUME 29 · NUMBER 15 · MAY 20 2011

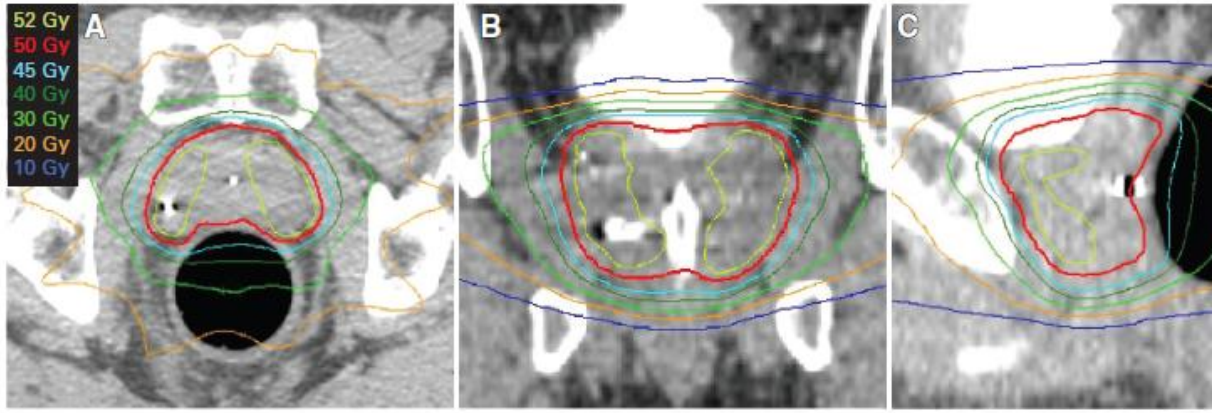
JOURNAL OF CLINICAL ONCOLOGY

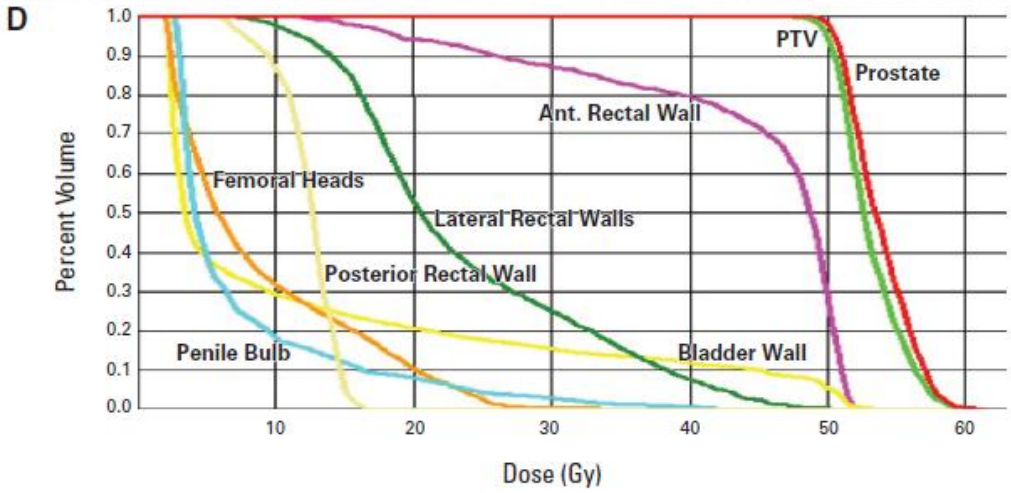
ORIGINAL REPORT

Centre Oscar Lambret

Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer

Thomas P. Boike, Yair Lotan, L. Chinsoo Cho, Jeffrey Brindle, Paul DeRose, Xian-Jin Xie, Jingsheng Yan, Ryan Foster, David Pistenmaa, Alida Perkins, Susan Cooley, and Robert Timmerman





SBRT for prostate can phase 1

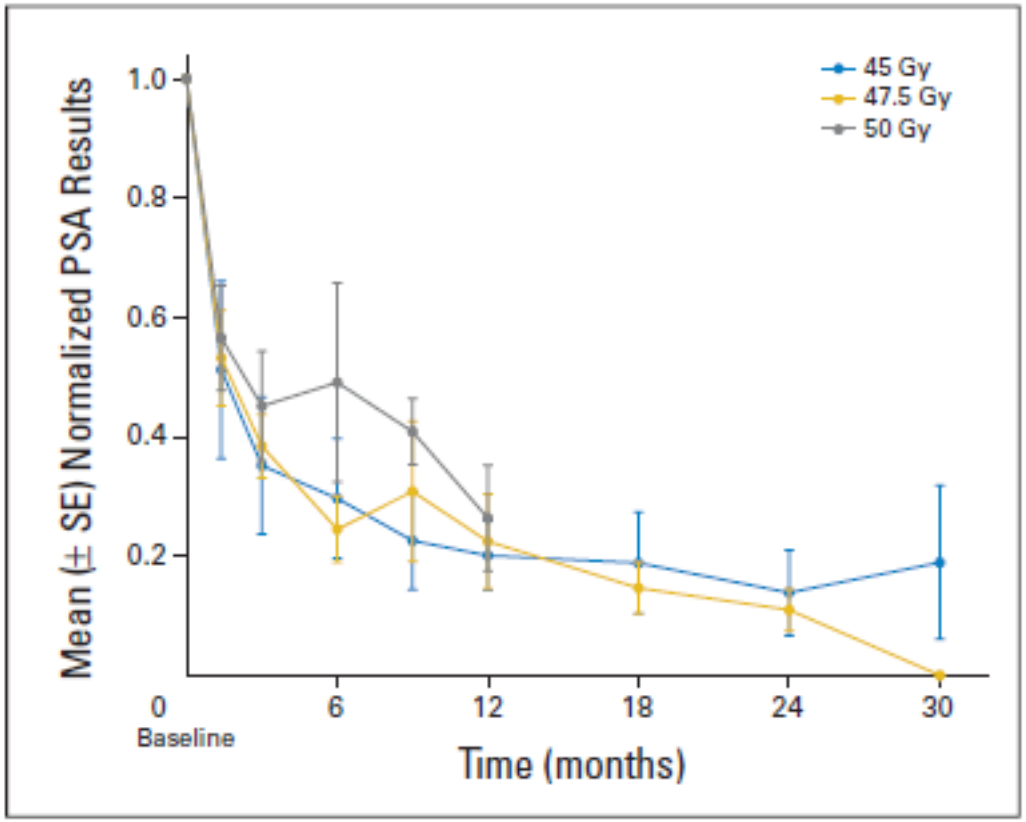


Fig 3. Mean prostate-specific antigen (PSA) with SEs. PSA was normalized using a given patient's baseline as the denominator.

Characteristic	45 Gy No.	45 Gy %	47.5 Gy No.	47.5 Gy %	50 Gy No.	50 Gy %	Total No.	Total %
No. of patients	15		15		15		45	
Age, years								
Median	67		67		67		67	
Range	55-82		58-76		53-78		53-82	
Prostate size, cm^3								
Median	31		38		30		31	
Range	19-60		17-52		17-55		17-60	
AUA score								
Median	4.5		4		7		5	
Range	0-15		0-13		2-12		0-15	
Hormones								
Yes	4	27	2	13	4	27	10	22
No	11	73	13	87	11	73	35	78
PSA								
Median	6.40		5.68		4.49		5.60	
Range	3.28-12.36		1.30-11.54		0.19-7.94		0.19-12.36	
T stage								
T1c	11	73	13	87	8	53	32	71
T2a	1	7	1	7	5	33	7	16
T2b	3	20	1	7	2	13	6	13
GS								
6 (3 + 3)	4	27	8	53	9	60	21	47
7 (3 + 4)	8	53	5	33	3	20	16	36
7 (4 + 3)	3	20	2	13	3	20	8	18
Treatment site								
A	14		8		10		32	
B	1		4		4		9	
C	0		3		1		4	
Low risk (GS ≤ 6, PSA < 10, ≤ T2a)	3	20	8	53	7	47	18	40
Intermediate risk (GS = 7 or PSA > 10 or T2b)	12	80	7	47	8	53	27	60

Boike *et al*., JCO, 2011

ESTRO school

Stereotactic Body Radiotherapy for Prostate Cancer: Updated Results from a Prospective Trial

CHRISTOPHER R. KING

Robotic Radiosurgery

LE Ponsky editor

Springer –Verlag 2012

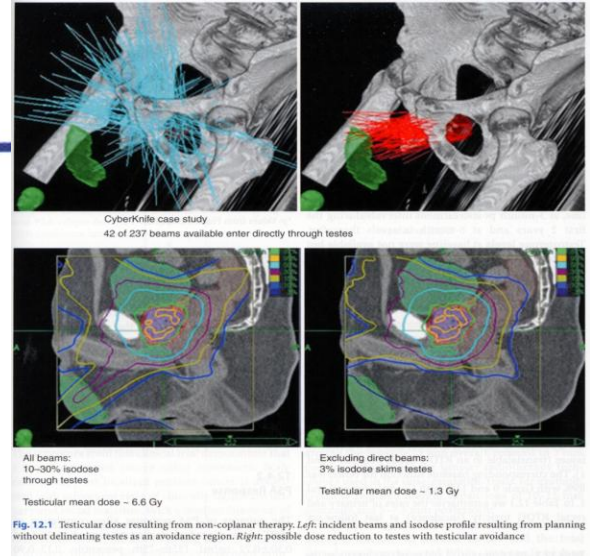


Fig. 12.1 Testicular dose resulting from non-coplanar therapy. *Left*: incident beams and isodose profile resulting from planning without delineating testes as an avoidance region. *Right*: possible dose reduction to testes with testicular avoidance

Table 12.1 Late urinary (GU) and rectal (GI) toxicity on the RTOG scale after prostate SBRT

RTOG grade	GU	GI
0	68% (39/57 pts)	84% (48/57 pts)
1	23% (13/57 pts)	14% (8/57 pts)
2	5% (3/57 pts)	2% (1/57 pts)
3	3.5% (2/57 pts)	0
4	0	0

RTOG Radiation Therapy Oncology Group, *GU* genitourinary, *GI* gastrointestinal

Stereotactic Body Radiotherapy for Prostate Cancer: Updated Results from a Prospective Trial

CHRISTOPHER R. KING

Robotic Radiosurgery

LE Ponsky editor

Springer –Verlag 2012

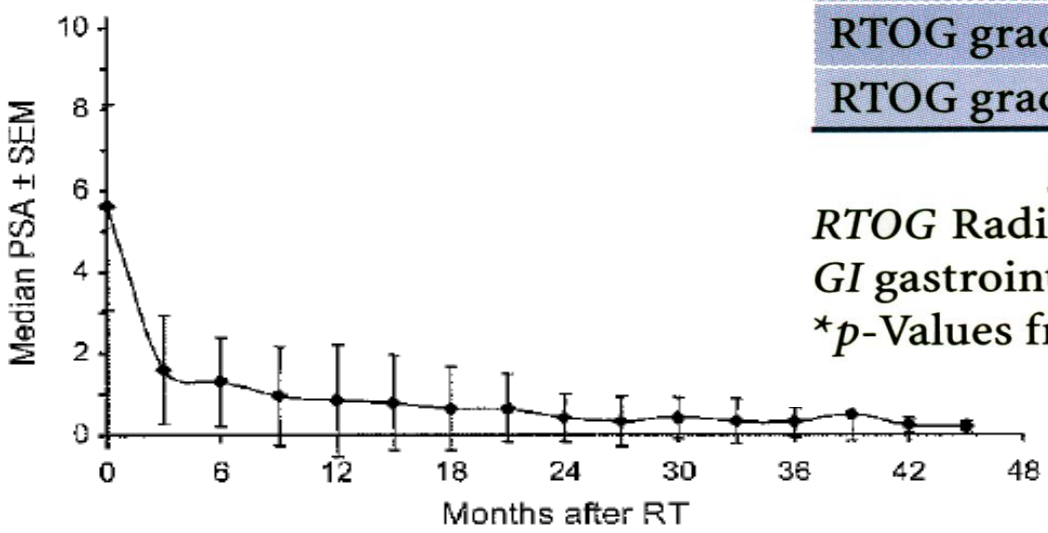
Centre Oscar Lambret

Table 12.2 Late urinary (GU) and late rectal (GI) RTOG toxicity compared between consecutive daily treatments (QD) vs. those delivered three times a week on alternating days (QOD)

	QD	QOD	*p*-Value*
GU toxicity			
RTOG grade 0	37% (6/16 pts)	80% (33/41 pts)	0.003
RTOG grade 1	50% (8/16 pts)	12% (5/41 pts)	0.004
RTOG grade 2	6% (1/16 pts)	5% (2/41 pts)	1
RTOG grade 3	6% (1/16 pts)	2% (1/41 pts)	0.48
GI toxicity			
RTOG grade 0	56% (9/16 pts)	95% (39/41 pts)	0.001
RTOG grade 1	37% (6/16 pts)	5% (2/41 pts)	0.0004
RTOG grade 2	6% (1/16 pts)	0% (0/41 pts)	0.28

RTOG Radiation Therapy Oncology Group, *GU* genitourinary, *GI* gastrointestinal

**p*-Values from Fisher's exact test



Virtual HDR® Prostate CyberKnife Radiosurgery: Intermediate–term Efficacy and Toxicity Evaluation

PSA Response:

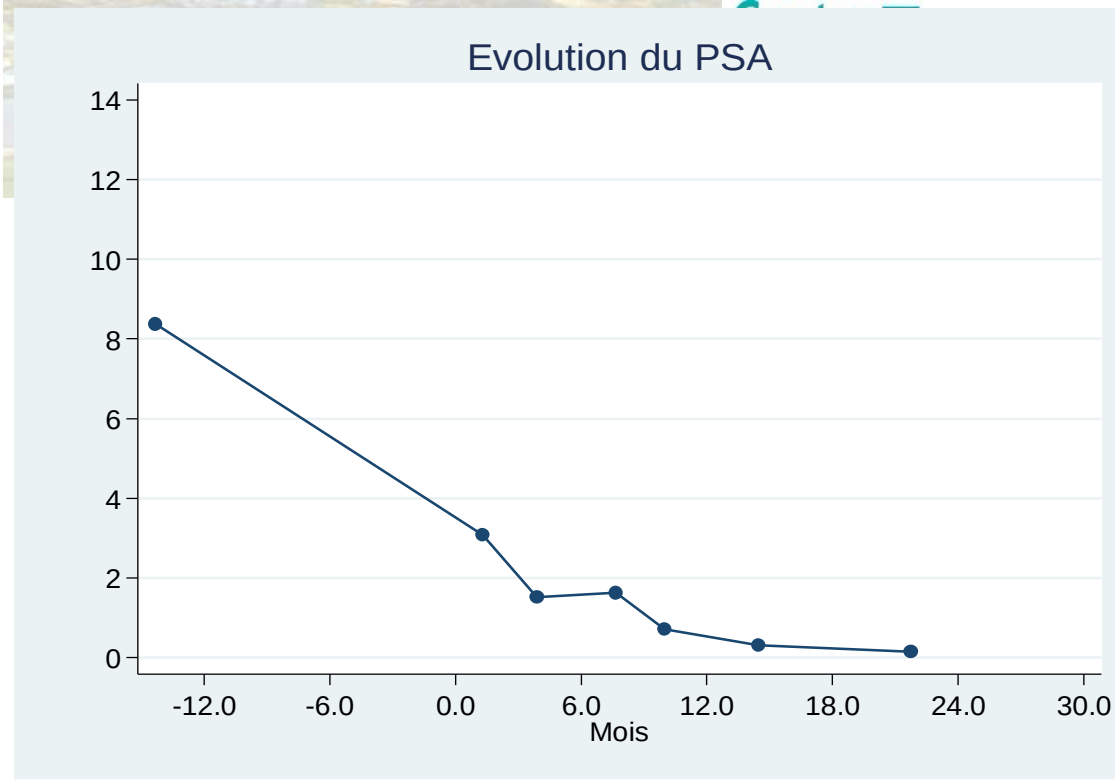
PSA nadir:	1-year	2-year	3-year
% of pts. ≤ 0.5 ng/ml	38%	59%	100%

PSA	1-year	2-year	3-year
Median (ng/ml)	0.8	0.36	0.1
Range (ng/ml)	(0 – 5.0)	(0 – 3.2)	(0 – 0.5)
(no. at risk)	(n = 40)	(n = 27)	(n =7)

CyberKnife Centers of San Diego
"Because Every Day Counts"

Lille

- 17 patients
- PSA : 7.8 ng/mL
- 4 fiducials
- 36.25Gy in 5 fractions 1on 2 days
- ≈ 160 beams / fractions
- 58 min / fraction (IC95 : 54-62)



Acute toxicity		
Urinary		
Grade 1	*6*	*29%*
Grade 2	*2*	*6%*
Rectal G2	1	6%

CKNO
CyberKnife® Nord Ouest
www.ckno.fr

Phase II CKNO-PRO

Centre Oscar Lambret

RT3D : 46 Gy en 23 x 2 Gy ⟷ **RTS : 18 Gy en 3 x 6 Gy**

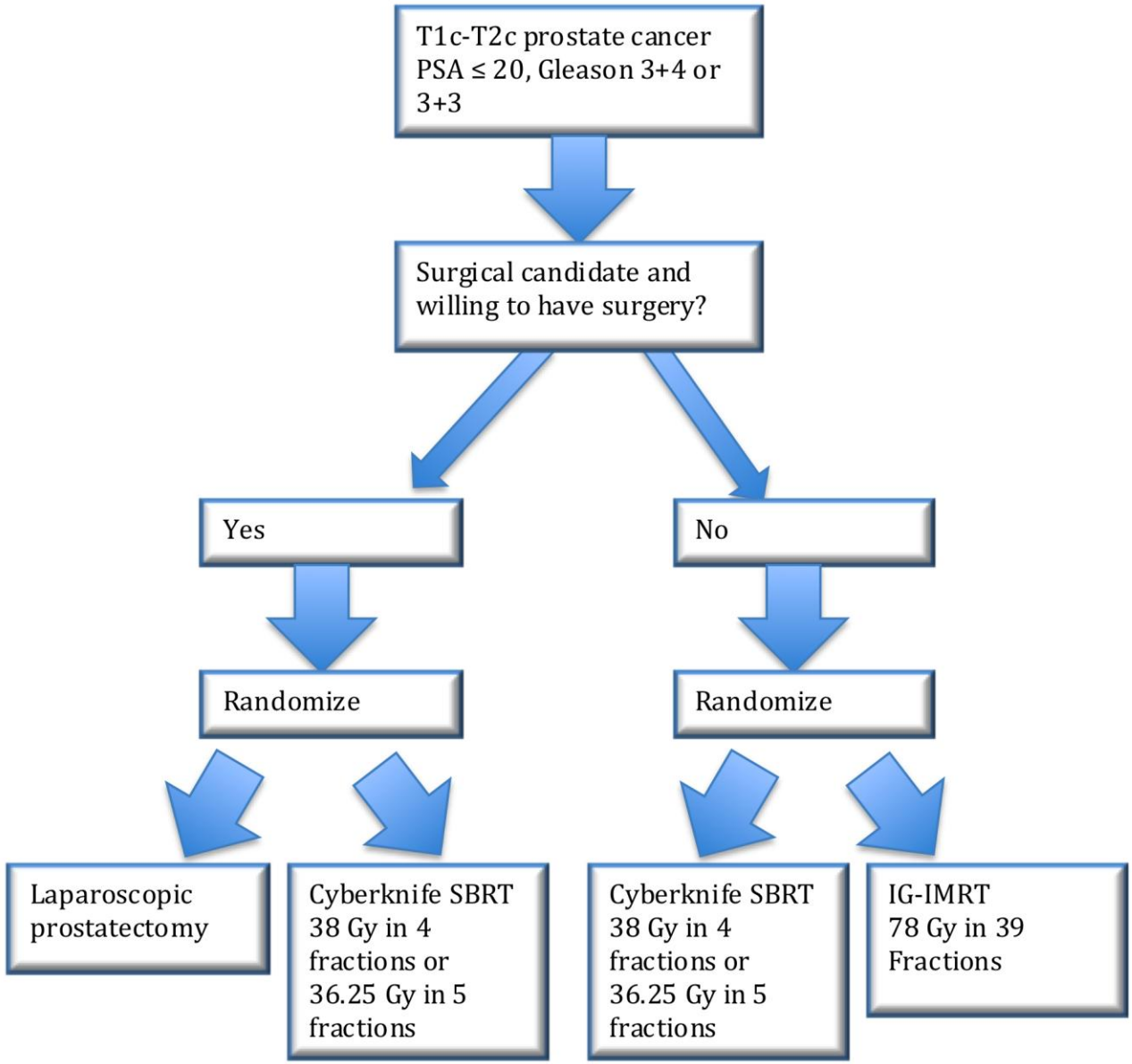
+/- IMRT

Gap : 10 days

CKNO
CyberKnife® Nord Ouest
www.ckno.fr

PACE Phase III R Study

Centre Oscar Lambret



RE IRRADIATION : 74 years

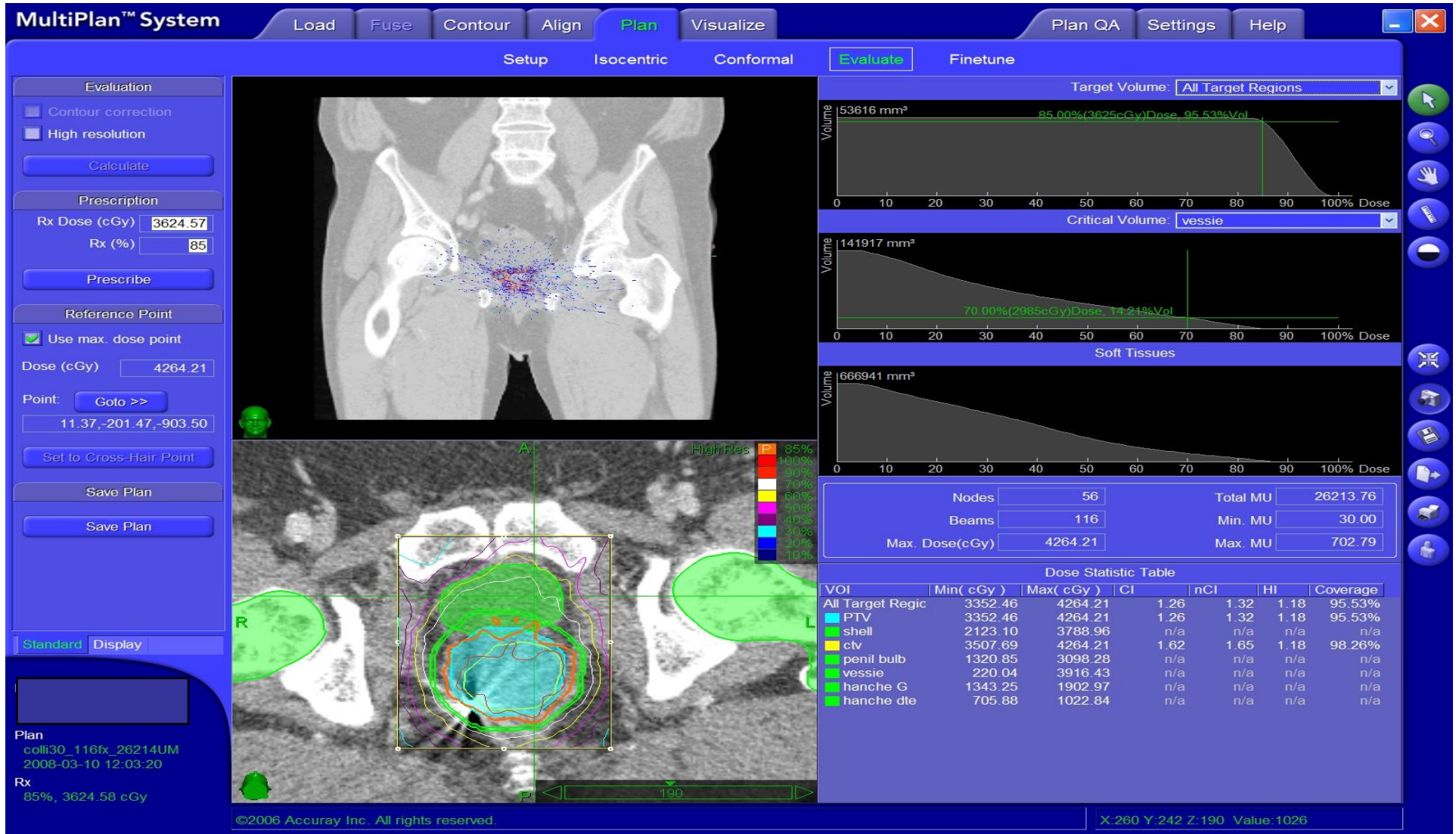
2000 : rectal adenocarcinoma + 5 X 5 Gy pre op, colectomy

2002 : PSA 4,79;

2008 : PSA 9,56 : Gleason 6

CyberKnife : 6 X 6 Gy march 2008

26/07/2009 : PSA 0,6 ng/ml



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SBRT-IGRT

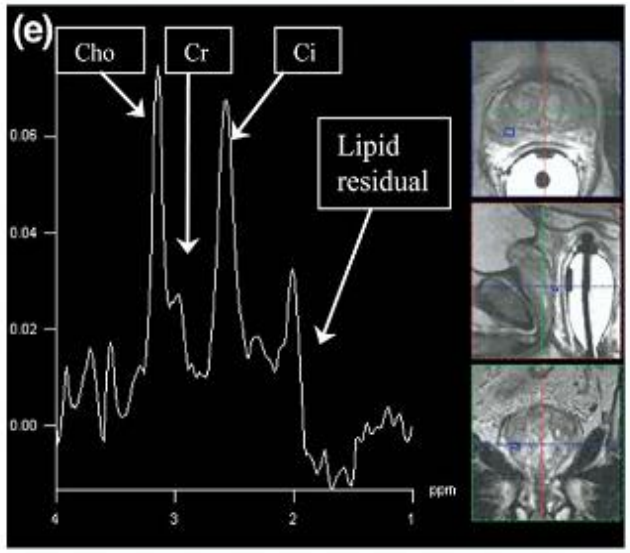
Centre Oscar Lambret

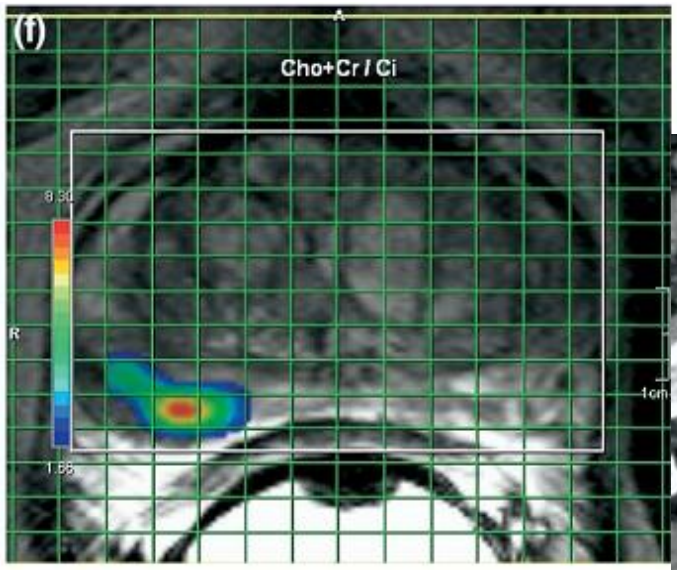
PHYSICS CONTRIBUTION

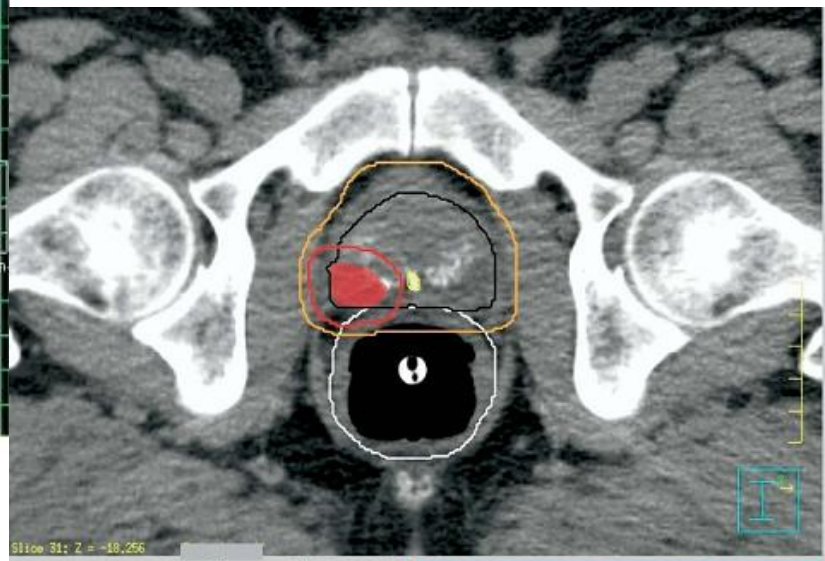
IMRT BOOST DOSE PLANNING ON DOMINANT INTRAPROSTATIC LESIONS: GOLD MARKER-BASED THREE-DIMENSIONAL FUSION OF CT WITH DYNAMIC CONTRAST-ENHANCED AND ^{1}H-SPECTROSCOPIC MRI

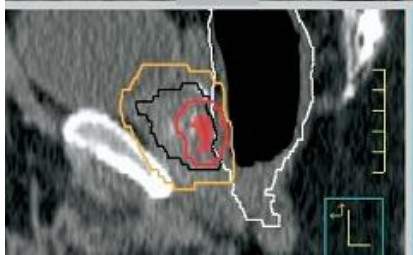
EMILE N. J. T. VAN LIN, M.D.,* JURGEN J. FÜTTERER, M.D., PH.D.,† STIJN W. T. P. J. HEIJMINK, M.D.,† LISETTE P. VAN DER VIGHT, B.SC.,* ASWIN L. HOFFMANN, M.SC.,* PETER VAN KOLLENBURG, B.SC.,* HENKJAN J. HUISMAN, PH.D.,† TOM W. J. SCHEENEN, PH.D.,† J. ALFRED WITJES, M.D., PH.D.,‡ JAN WILLEM LEER, M.D., PH.D.,* JELLE O. BARENTSZ, M.D., PH.D.,† AND ANDRIES G. VISSER, PH.D.*

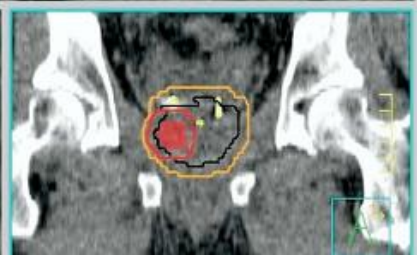
Departments of *Radiation Oncology, †Radiology, and ‡Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands











Futur : focal therapy ???

S.B.R.T. for Prostate Cancer !

- **YES (with preliminary results)**
- **EXCELLENT RESULTS**
- **LOW TOXICITY ?**

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Radioresistant tumours ?

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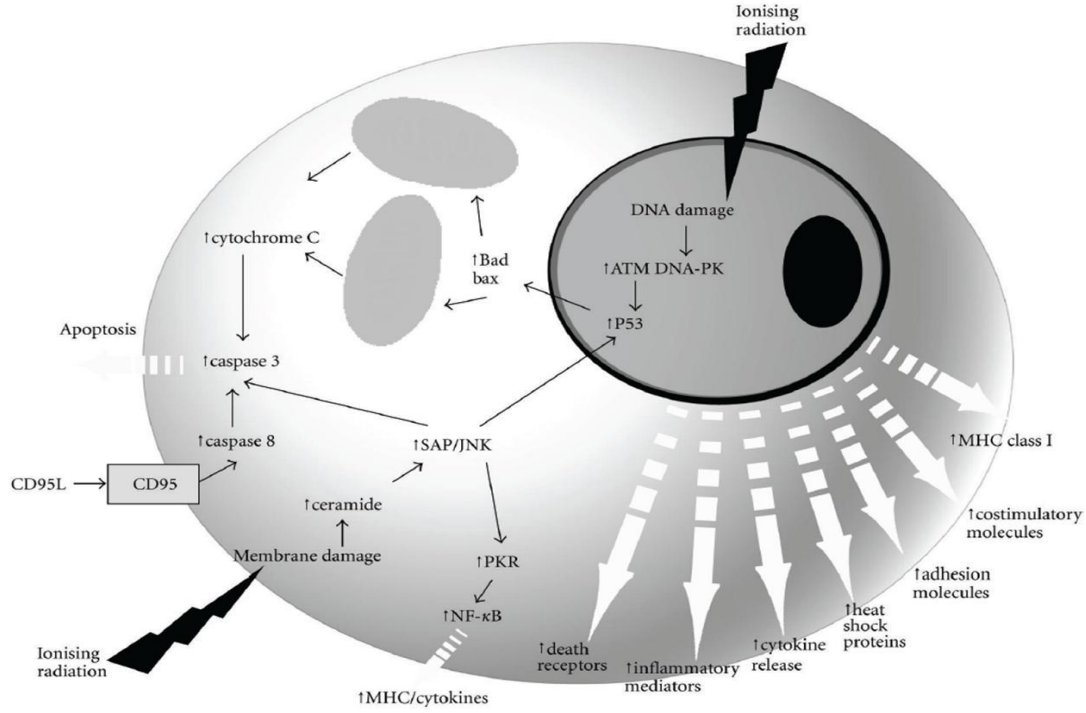
- Biology of High dose / fraction : **BED > 100 Gy**

- Melanoma
- Renal tumours
- Sarcomas
- …



Hindawi Publishing Corporation
Clinical and Developmental Immunology
Volume 2011, Article ID 439752, 7 pages
doi:10.1155/2011/439752

Review Article

The Confluence of Stereotactic Ablative Radiotherapy and Tumor Immunology

Steven Eric Finkelstein,[1] Robert Timmerman,[2] William H. McBride,[3] Dörthe Schaue,[3] Sarah E. Hoffe,[4] Constantine A. Mantz,[1] and George D. Wilson[5]

FIGURE 1: *Confluence of SABR and Immunotherapy.* Apoptosis can be initiated by SABR-induced DNA damage and upregulation of the p53 tumor suppressor gene. In addition, apoptosis can be triggered by SABR-induced damage to the cellular lipid membrane, which can induce ceramide formation and activate the SAPK/JNK signaling pathway. Thus, SAPK/JNK can upregulate PKR expression, which can induce MHC and cytokines via NF-κB. SABR can induce cellular expression of MHC Class I, adhesion molecules, costimulatory molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines, and death receptors.

BJUI
BJU INTERNATIONAL

Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma

Michael Staehler, Nicolas Haseke, Philipp Nuhn, Cordula Tüllmann, Alexander Karl, Michael Siebels, Christian G. Stief, Berndt Wowra* and Alexander Muacevic*

*Department of Urology, University of Munich, Klinikum Grosshadern, and *European CyberKnife Centre Munich, Max-Lebsche-Platz, Munich, Germany*

Accepted for publication 1 September 2010

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106 patients

spinal (*n*=55)

cerebral (*n*=51) metastatic lesions

E C O G: 0 or 1

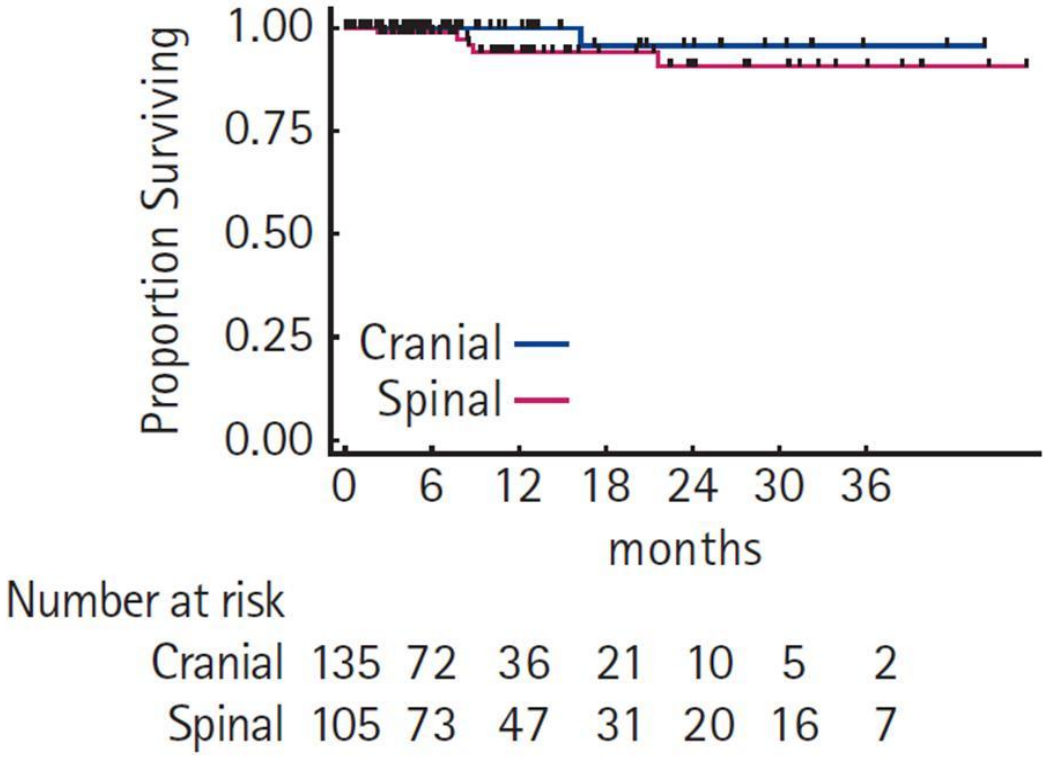
sorafenib or sunitinib

simultaneous SRS.

Primary : local control.

Secondary : toxicity and overall survival.

FIG. 1. Local tumour control of lesions treated with stereotactic radiosurgery by treatment arms; P < 0.5.



BJUI

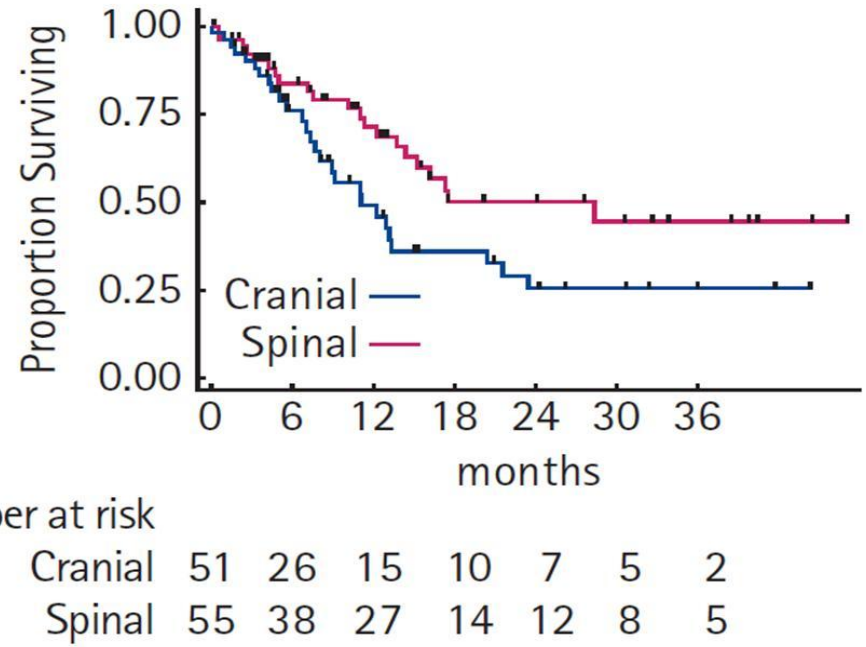
Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma

Michael Staehler, Nicolas Haseke, Philipp Nuhn, Cordula Tüllmann, Alexander Karl, Michael Siebels, Christian G. Stief, Berndt Wowra* and Alexander Muacevic*

*Department of Urology, University of Munich, Klinikum Grosshadern, and *European CyberKnife Centre Munich, Max-Lebsche-Platz, Munich, Germany*

Accepted for publication 1 September 2010

FIG. 2. Overall survival by treatment arms; P = 0.038 (log-rank).



Median follow up : 14.7 months

45 sunitinb , 61 sorafenib.

Two asymptomatic tumour haemorrhage

No skin toxicity, neurotoxicity or myelopathy

Local tumour control at 15 months : 98%

median pain score before SRS: 5 before and 0 after SRS.

Overall survival : 17.4 months spinal lesions

11.1 months cerebral lesions

(*P*=0.038).

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Posterior Fossa Renal Cell Metastasis*

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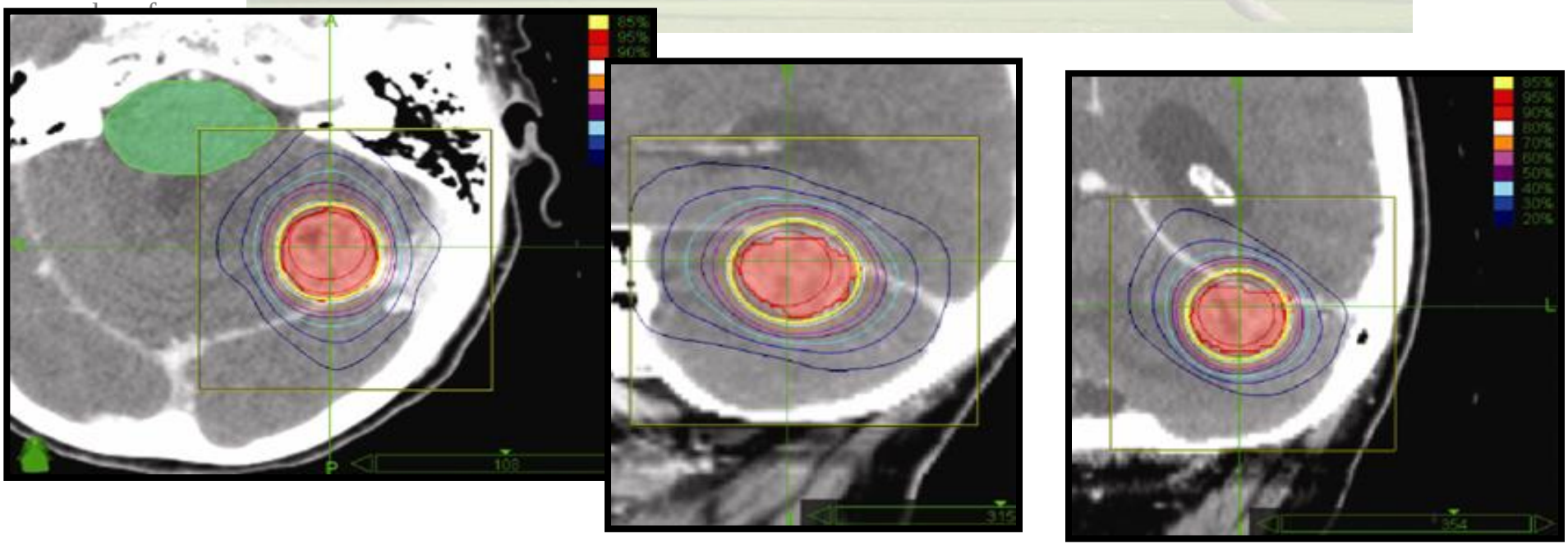
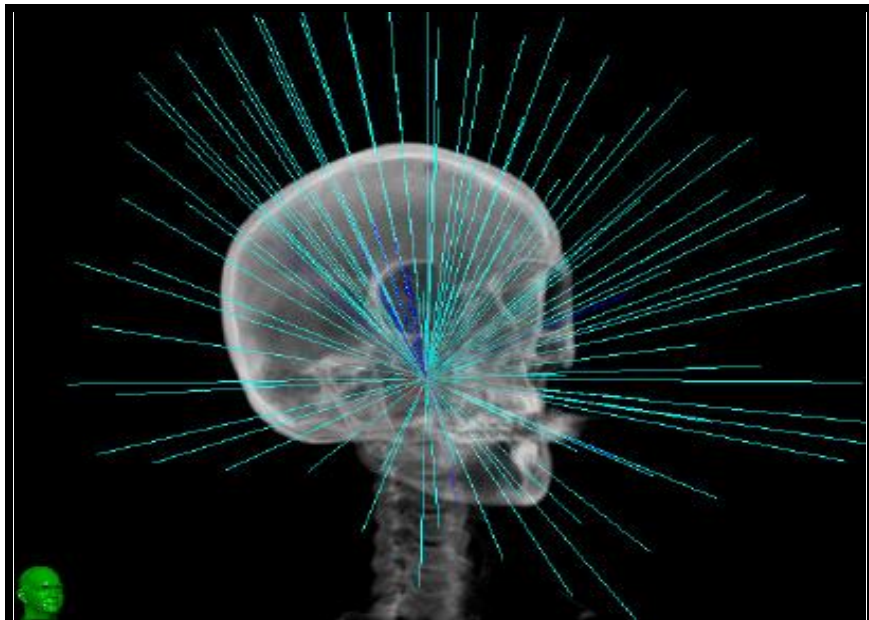


18 Gy X 1



*Case provided courtesy of NCH Regional Cancer Institute, Naples, Florida (USA)

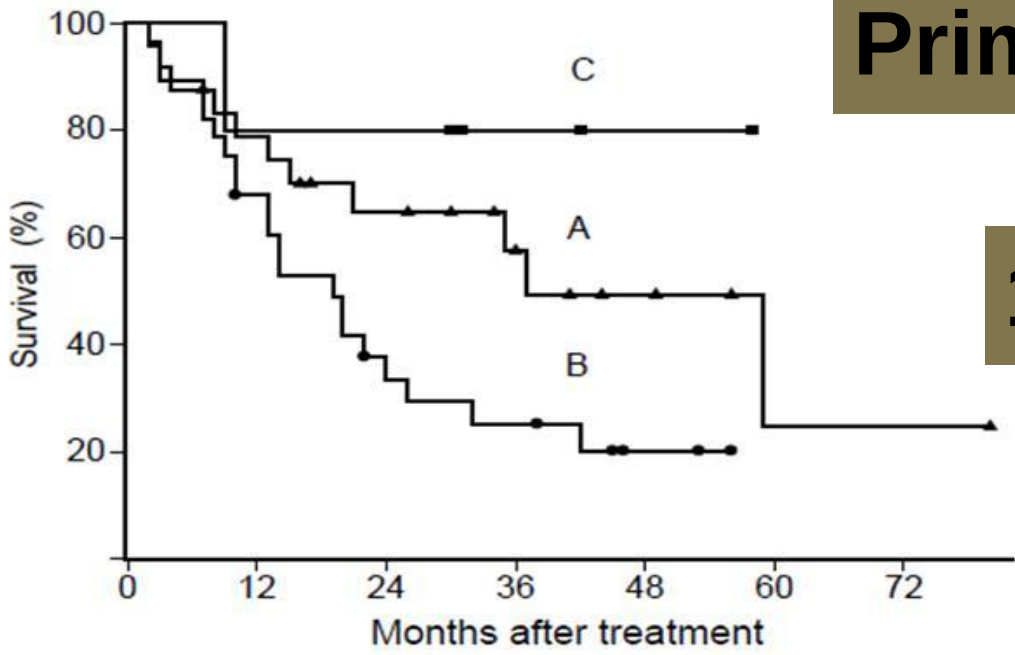
Radiotherapy and Oncology 77 (2005) 88-95
www.thegreenjournal.com

Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma

Peter J. Wersäll[a,*], Henric Blomgren[a], Ingmar Lax[b], Karl-Mikael Kälkner[a], Christina Linder[a], Göran Lundell[a], Bo Nilsson[a], Sten Nilsson[a], Ingemar Näslund[a], Pavel Pisa[c,d], Christer Svedman[a]

[a]Department of General Oncology, [b]Department of Radiotherapy, and [c]Department of General Oncology, Radiumhemmet, Karolinska Hospital, Stockholm, Sweden, [d]Cancer Center Karolinska, Karolinska Institute, Stockholm, Sweden

Primary



1-3

> 3

Fig. 2. Survival according to Kaplan-Meier of patients in Groups A, B, and C after a median follow-up time of 37 months. ($P=0.032$, $df=2$).

Table 8
Tumor response in relation to biological equivalent dose BED^2

Response	Prescribed dose BED^{2a} (Gy)	CTV			PTV		
		Min BED^2 dose (Gy)	Max BED^2 dose (Gy)	Mean BED^2 dose (Gy)	Min BED^2 dose (Gy)	Max BED^2 dose (Gy)	Mean BED^2 dose (Gy)
Tot. regression	57.9±16.9	91.8±36.7	117.9±33.8	109.9±32.8	43.4±20.9	119.5±36.4	98.2±30.6
Regression >50%	59.0±18.1	78.5±39.5	116.0±40.4	90. 8±33.5	32.5±18.5	122.5±43.4	90.8±33.5
Growthinhibition >50%<x<125%	62.2±16.7	74.7±42.7	117.2±38.9	105.5±35.8	31.1±18.9	118.7±36.3	91.7±31.5
Progression locally >125%	52.2±6.9	33.4±8.4	89.8±7.6	73.2±8.9	17.2±4.5	86.6	68.2±8.9
Non-evaluable[b]	62.5±20.4	72.2±29.6	111.8±39.0	102.4±34.1	33.6±14.9	119.5±47.8	92.3±30.8
Non-evaluable[c]	49.6±12.2	63.3±22.6	93.3±25.1	85.9±22.2	29.4±10.8	79.4±12.6	74.4±19.9

Group values were calculated as means±SD. Min, minimal; Max, maximum.

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Renal Radiosurgery: Initial Clinical Experience With Histological Evaluation

Lee E. Ponsky, MD, Arul Mahadevan, MD, Indebir S. Gill, MD, Toufik Djemil, PhD, and Andrew C. Novick, MD

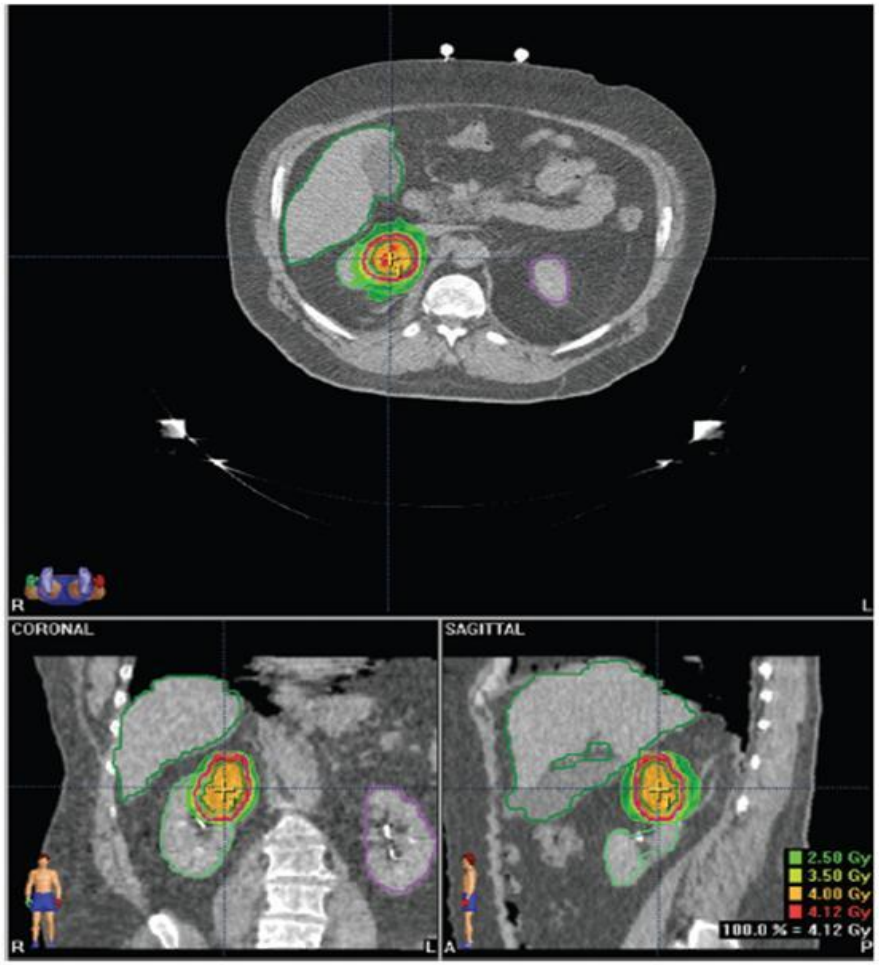


Figure 1. Radiosurgical treatment planning.

4 x 4 Gy

F UP : 1 year

No toxicity

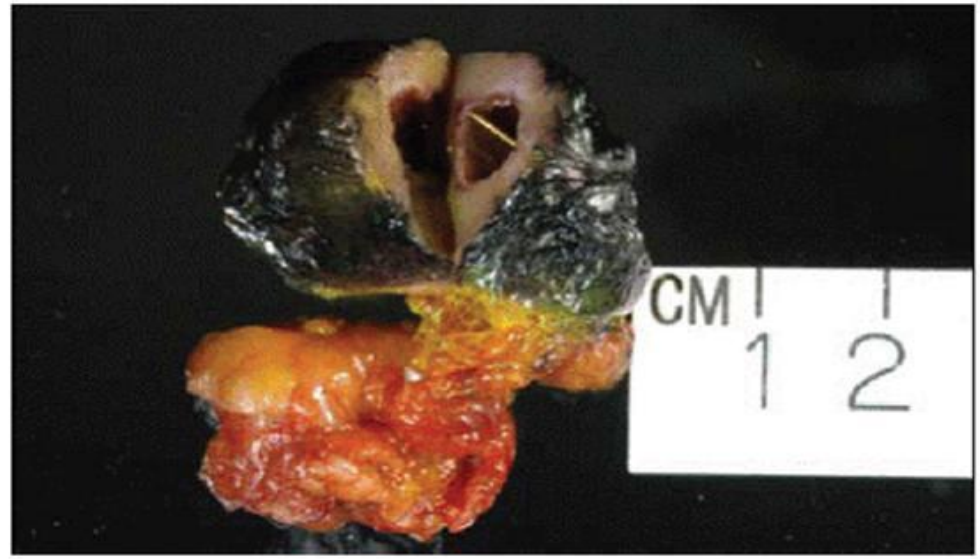
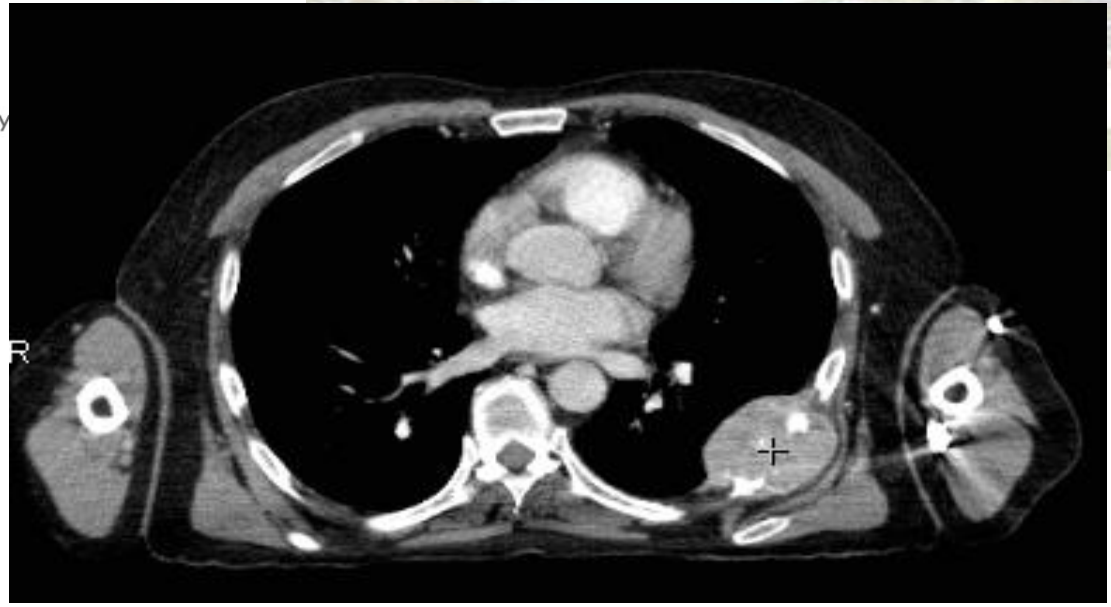
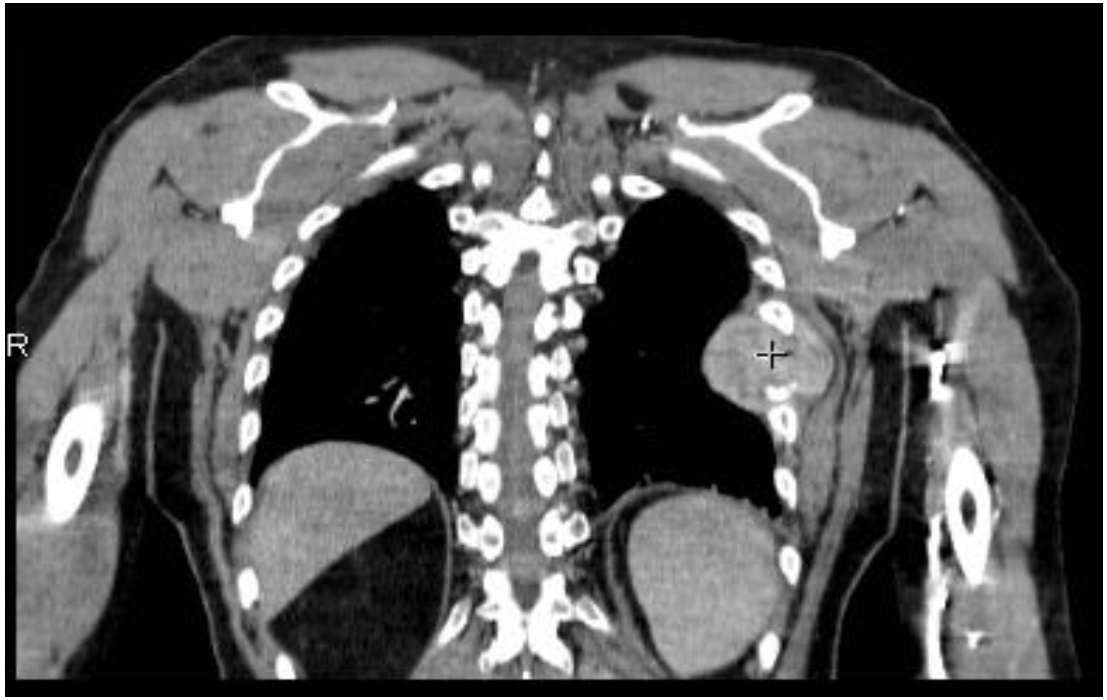


Figure 3. Gross specimen of patient 3. The fiducial marker is in the center of the tumor cavity, demonstrating no evidence of gross tumor.





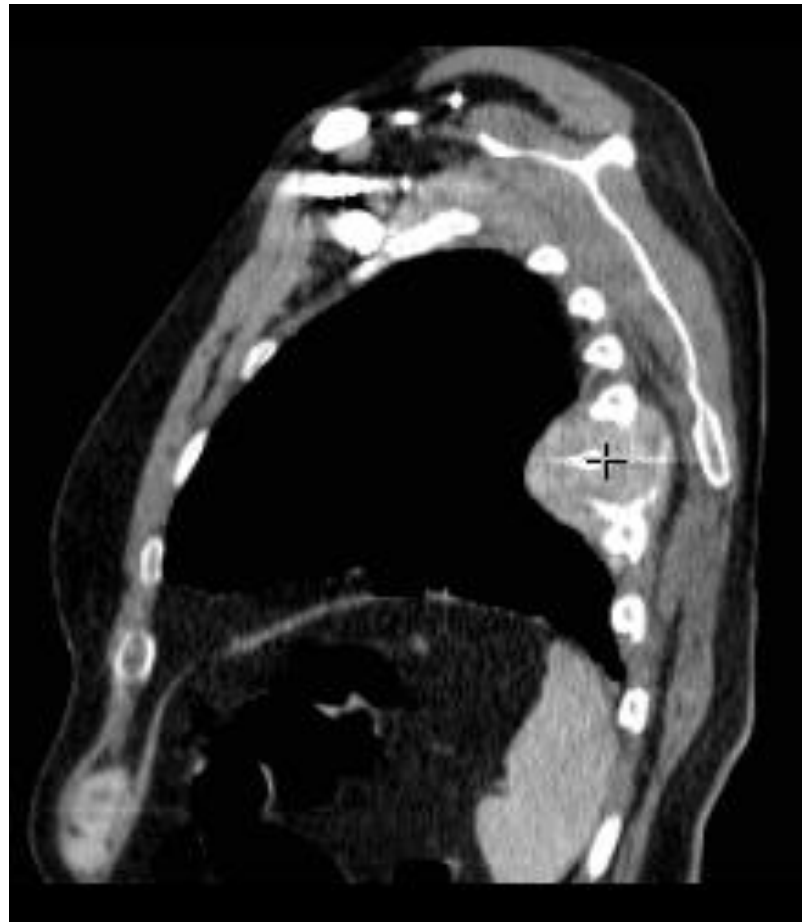
Man, 63

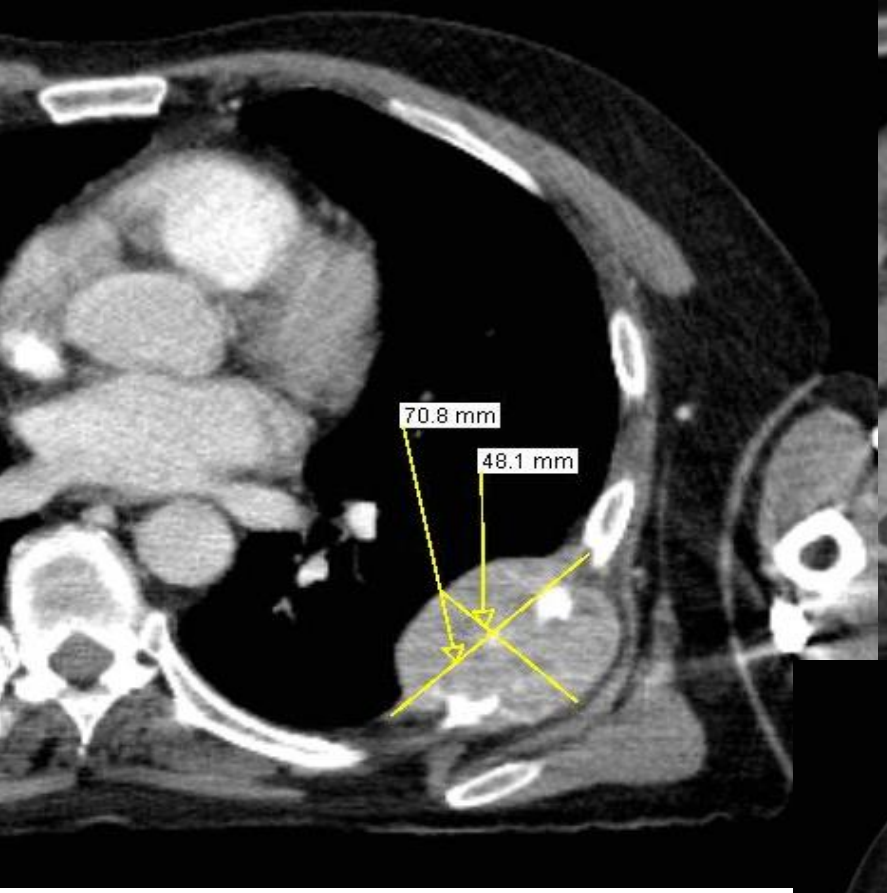
05/2007: RCC Führman II 8.5 cm

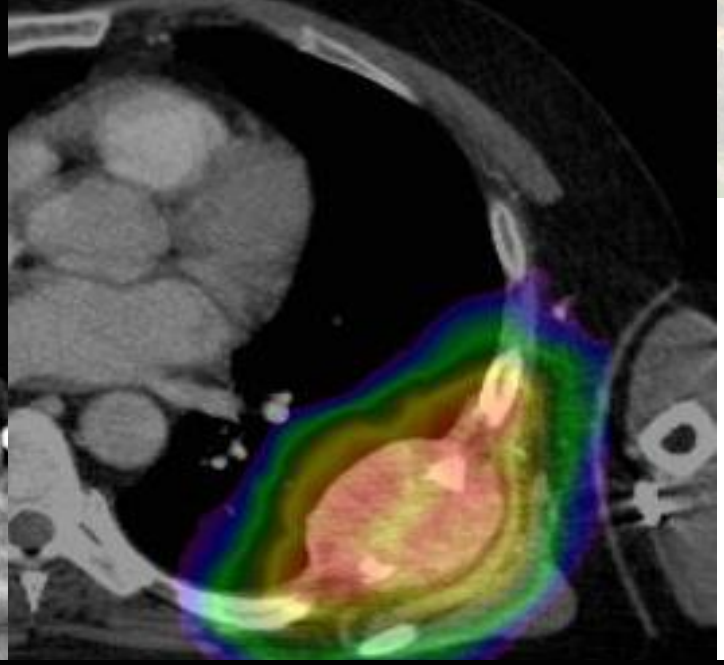
pT2 N0 MX

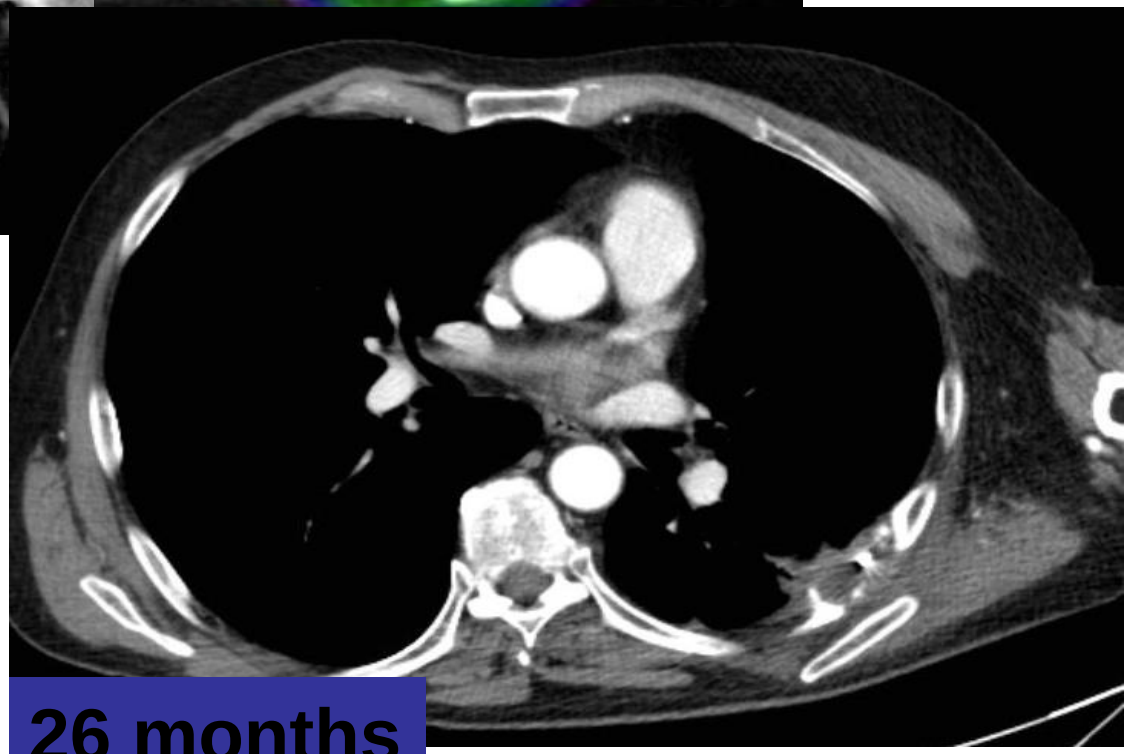
09/2007: 7 rib

SBRT 45 Gy (3 X 15 Gy)









26 months

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Melanoma

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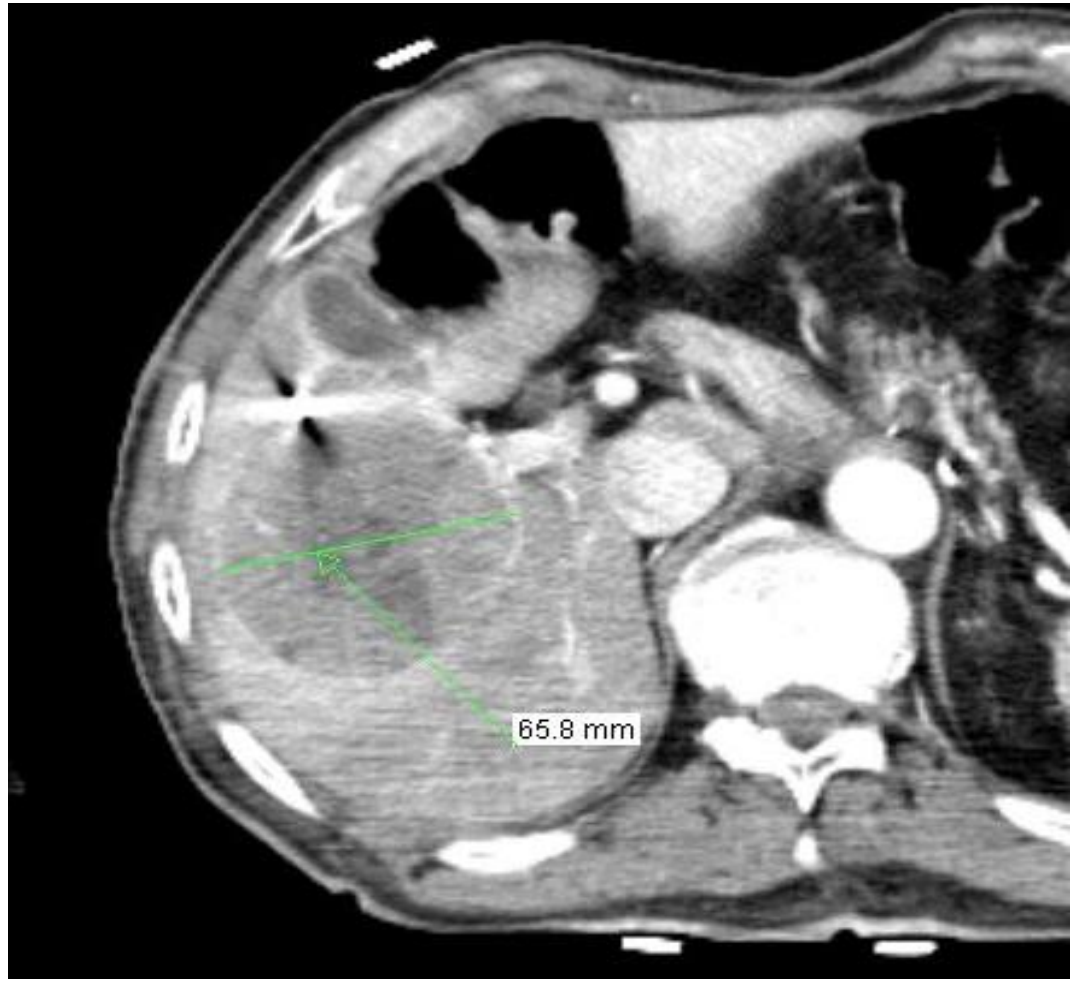
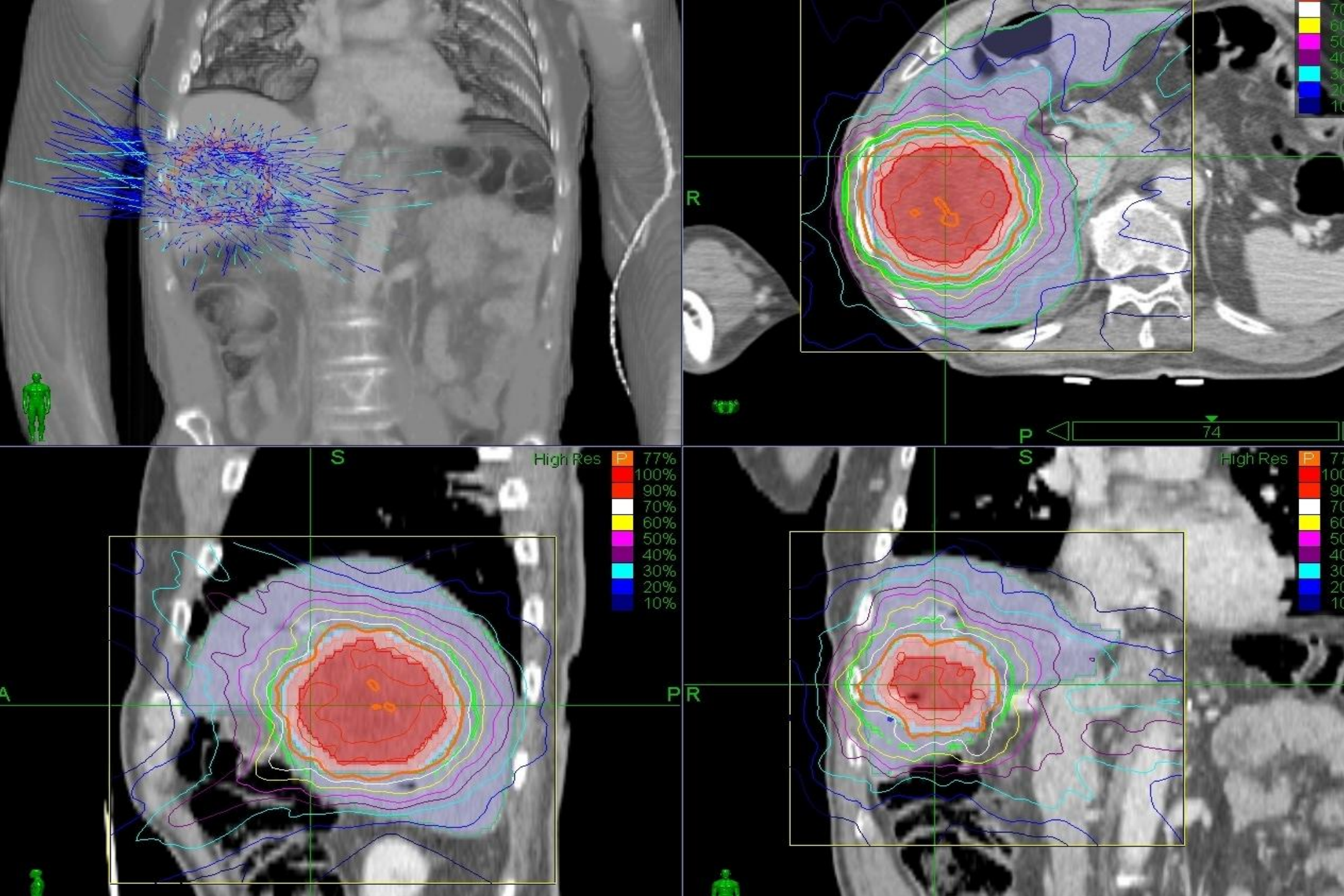
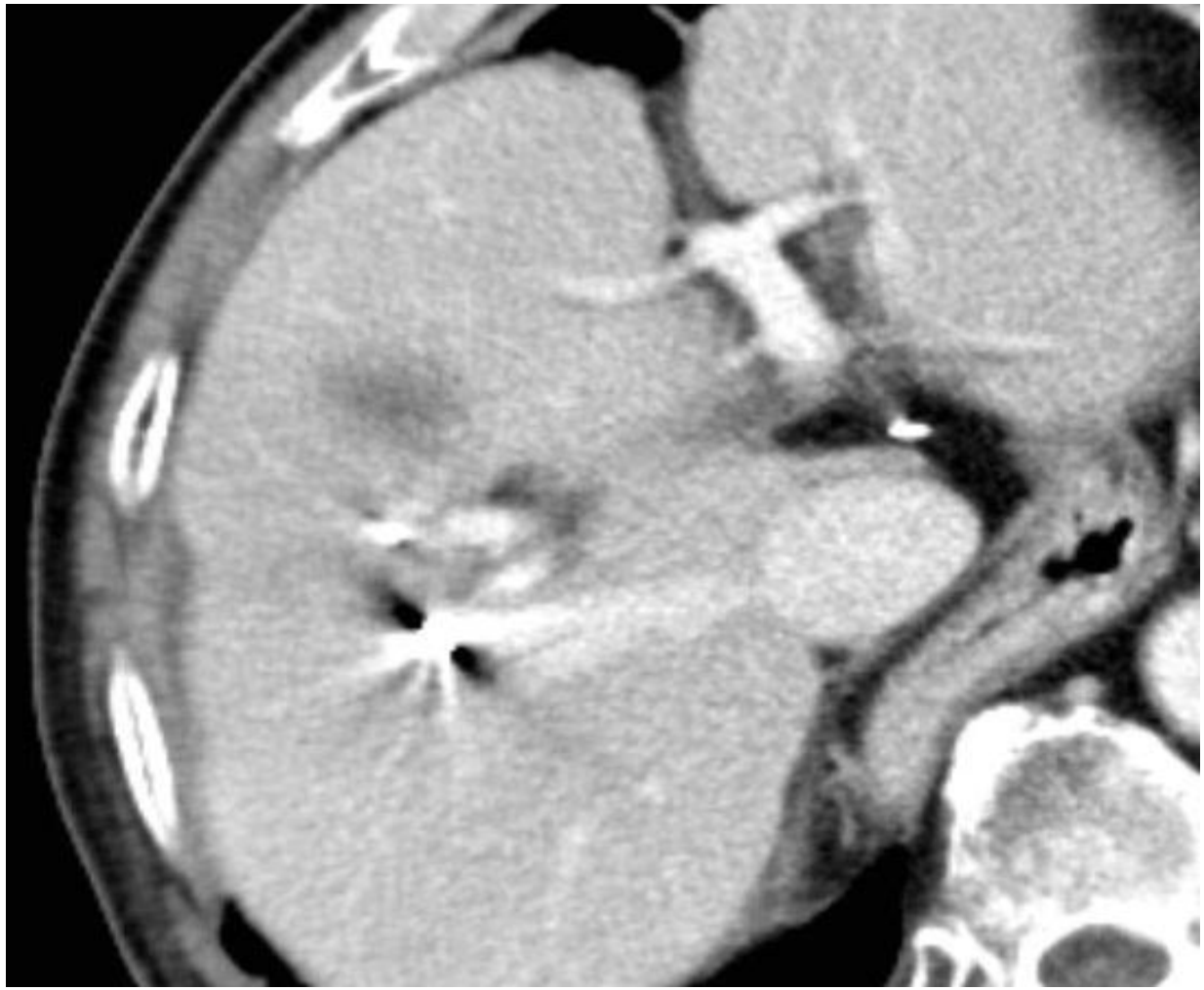
85 Y Old man

66 mm TEP+




R
P
74
S
High Res
P
77%
100%
90%
70%
60%
50%
40%
30%
20%
10%
A
P
S
High Res
R

- **51 months later**
- **No symptoms**



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CONCLUSION

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CURATIVE ???? Could be : dose effect

Do not wait for too long : volume effect

Need for studies !!!! 2 prospective : UK & Belgium

Role for combination : systemic + local ??

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X. MIRABEL,

B. PREVOST

Ph. NICKERS,

L. SCHIAPPACASSE

Th. LACORNERIE

F. CROP

SBRT for oligometastases

Alejandra Méndez Romero & Morten Høyer

Erasmus MC, University Centre, Rotterdam, The Netherlands
Department of Oncology, Aarhus University Hospital, Denmark

ESTRO School

SBRT for oligo-metastases

- Introduction of oligometastases (Morten)
- Clinical evidence (Alejandra)
  - Phase I/II trials
  - Retrospective cohort studies
- Selection of patients (Morten)

SBRT for metastases: *What is the aim?*

To cure of the patient? ***OS***

or

To prevent progression of the disease? ***PFS***

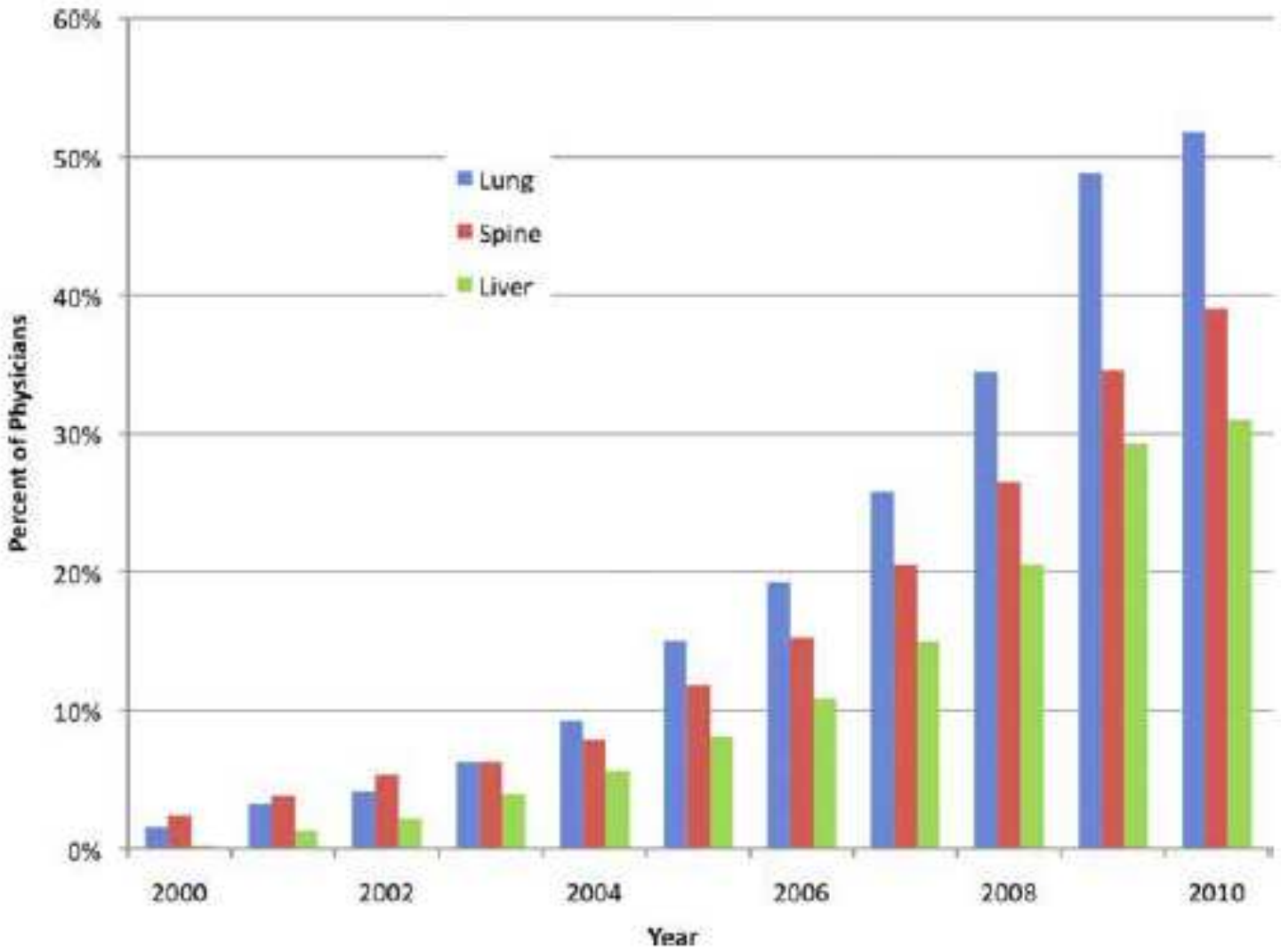
or

To ensure local control of the metastases? ***LC***

or

To prevent cancer related symptoms? ***Morb.***

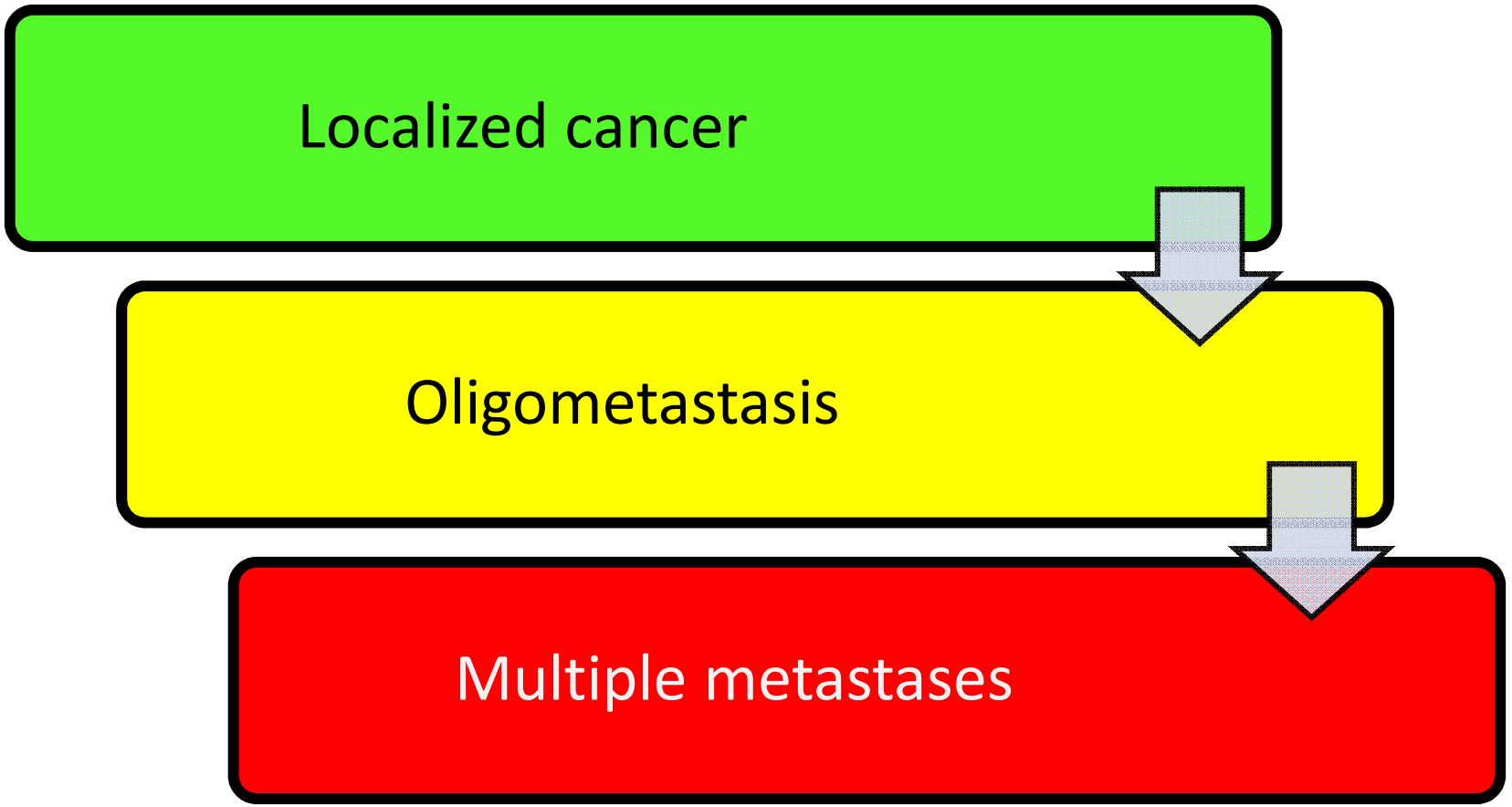
Survey: The use of SBRT in the US



Pan et al. Cancer 117: 4566-72; 2011

Rationale for SBRT of liver metastases

Rationale for ablation of metastases



Hellman &Weichselbaum JCO 1995

Nat Rev Clin Oncol 2014; 11: 549

OPINION

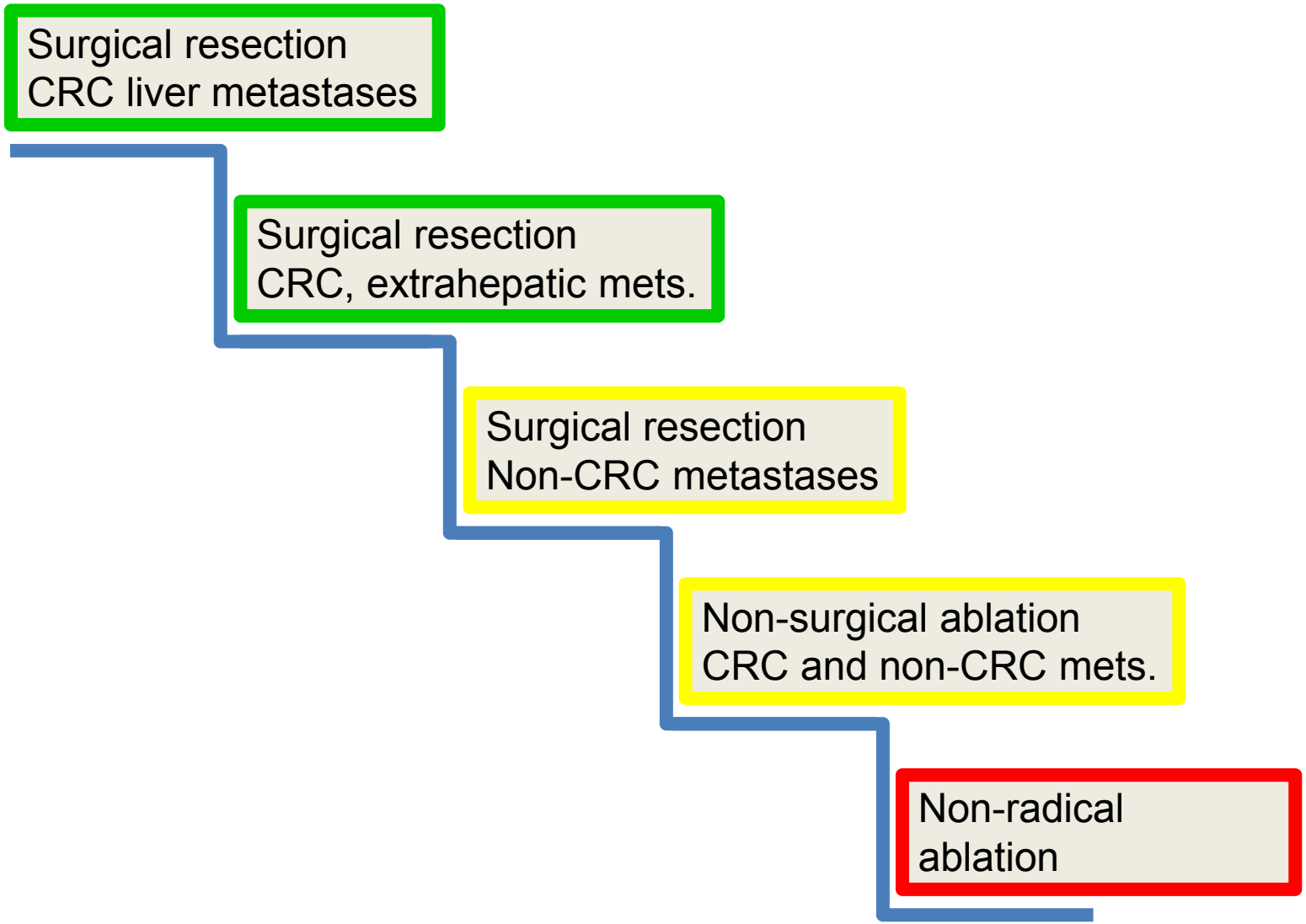
The oligometastatic state—separating truth from wishful thinking

David A. Palma, Joseph K. Salama, Simon S. Lo, Suresh Senan, Tom Treasure, Ramaswamy Govindan and Ralph Weichselbaum

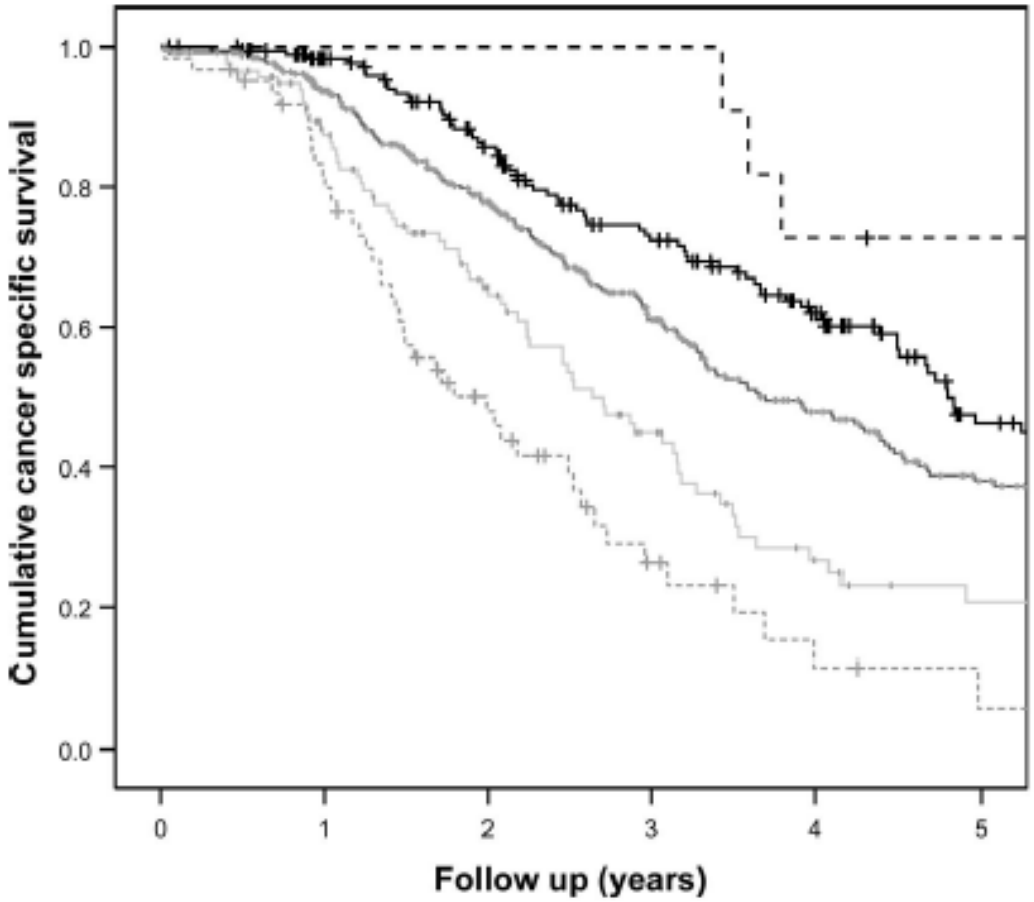
”We have a hammer, but ……?”

Clinical evidence

Surgery and ablation for oligo-metastases



Colorectal carcinoma liver metastases
Surgical resection



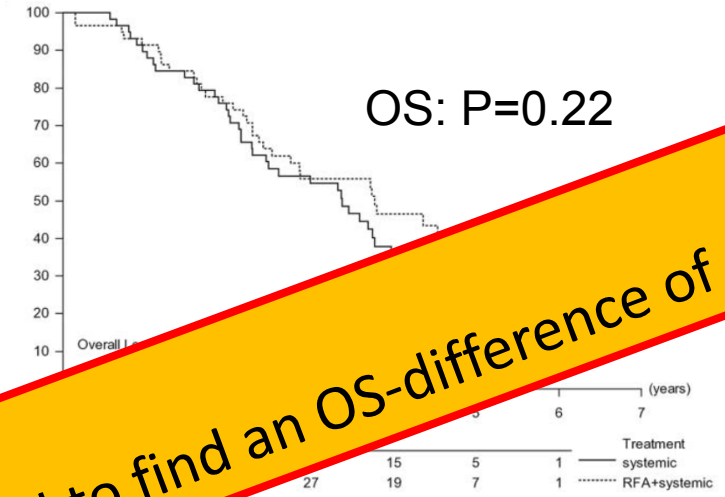
- Lymph node status (primary)
- Tumor differentiation (primary)
- CEA
- Number of metastases
- Diameter of largest metastasis
- Surgical resection margin
- Extrahepatic extension

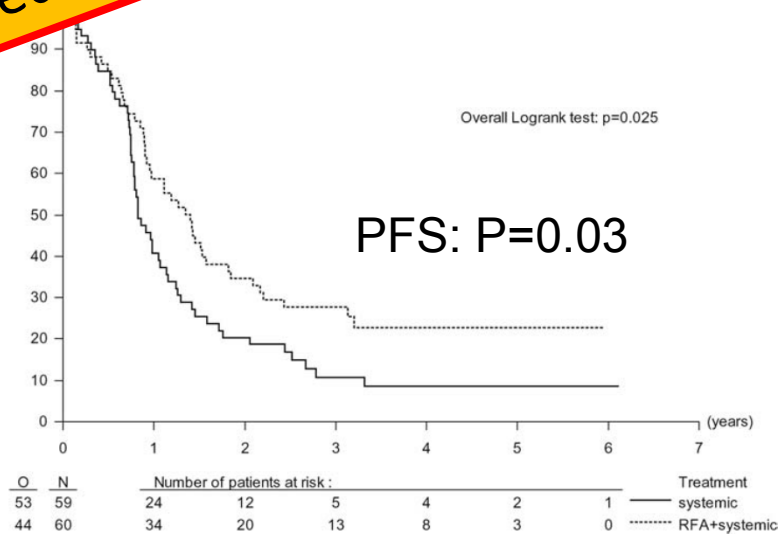
Rees et al. Ann Surg (2008) 247: 125; N=929 pts.

CLOCC - EORTC 40004

- Randomized phase III → phase II
- CT (FOLFOX + Avastin) + RFA vs. CT alone
- 2003-2007: 119 pts.; m
  4.4 yrs.
- Inclusi

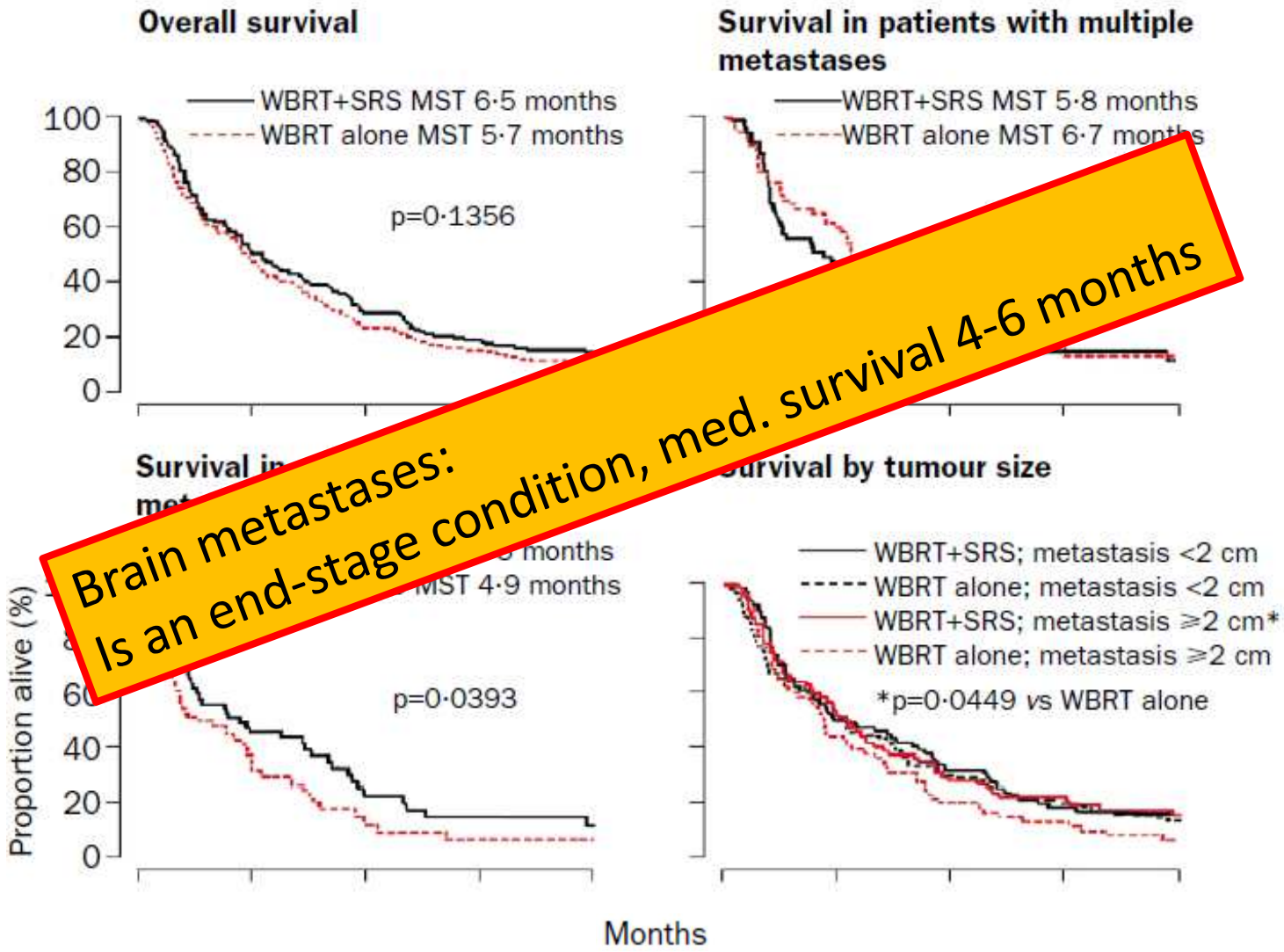
Power-calculation:
800 patients would have been needed to find an OS-difference of 10%





Ruers Ann Oncol 2012; 23:2619

Survival of patients with brain metastases



Brain metastases:
Is an end-stage condition, med. survival 4-6 months

Andrews et al Lancet 2004; 363: 1665

SBRT and systemic therapy

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

- *TOAD trial: early antiandrogen*
- *CHAARTED and STAMPEDE trials: early chemotherapy*

- *Combination with immune stimulating agents*

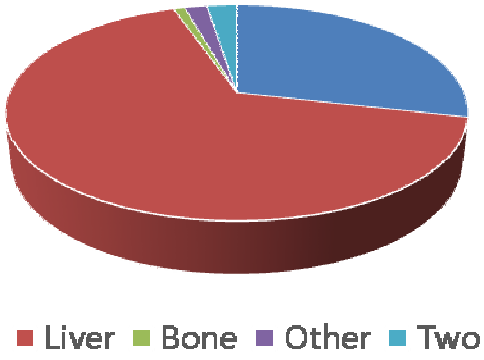
Let's look at the SBRT data.

How to select patients?

The Aarhus experience

Patient characteristics		
CRC/non-CRC	201 (63%)	120 (37%)
Dead/alive	214 (67%)	107 (33%)
Prior resection or RFA: yes/no	142 (44%)	179 (56%)
Prior systemic therapy yes/no	194 (60%)	127 (40%)
Median number of metastases	1 (range 1-6)	
Median size of largest metastasis	30 mm (5-88 mm)	

Metastatic organ

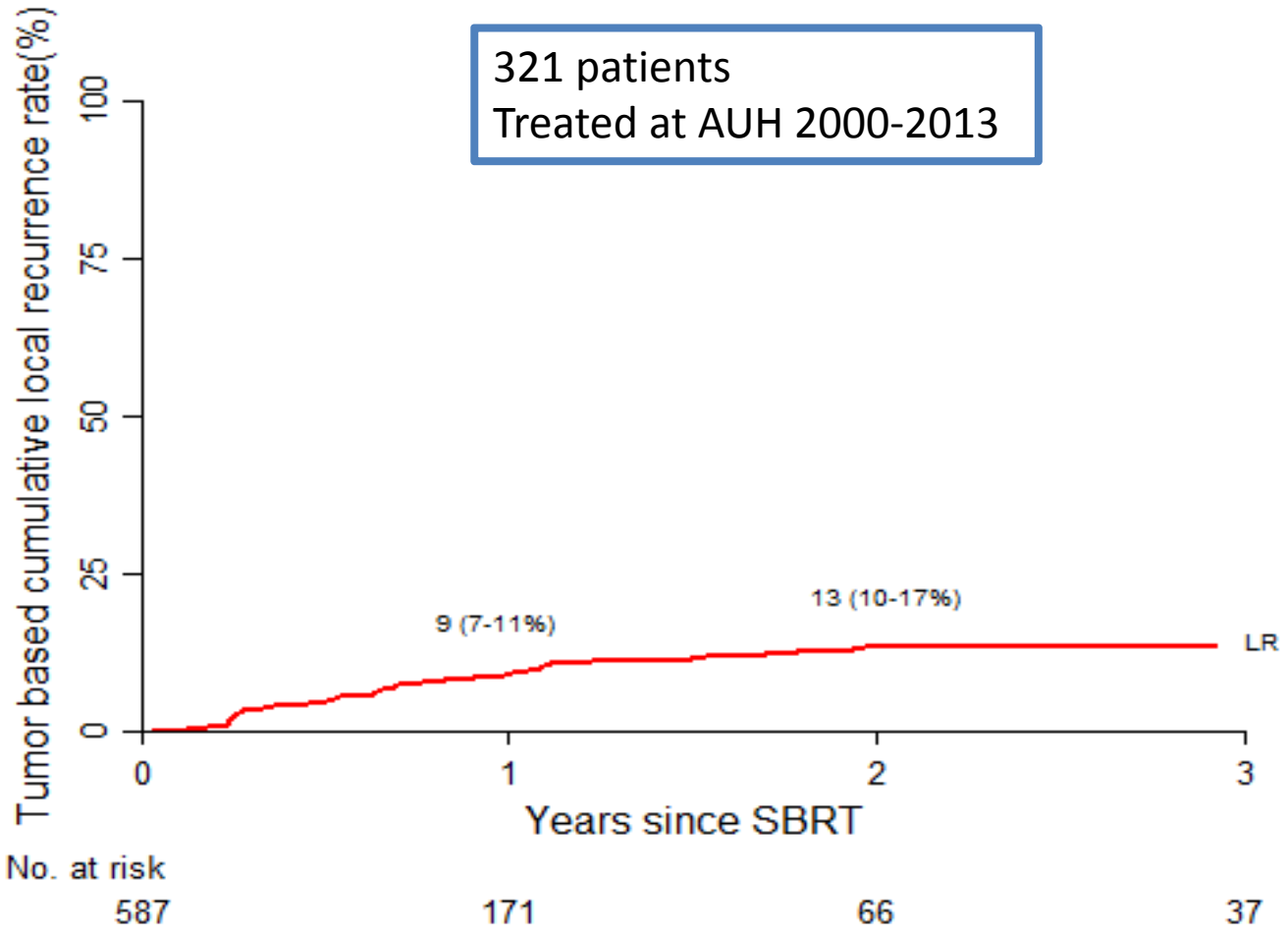


2000-2014:
N=321 pts.

Ineligible for surgery or RFA

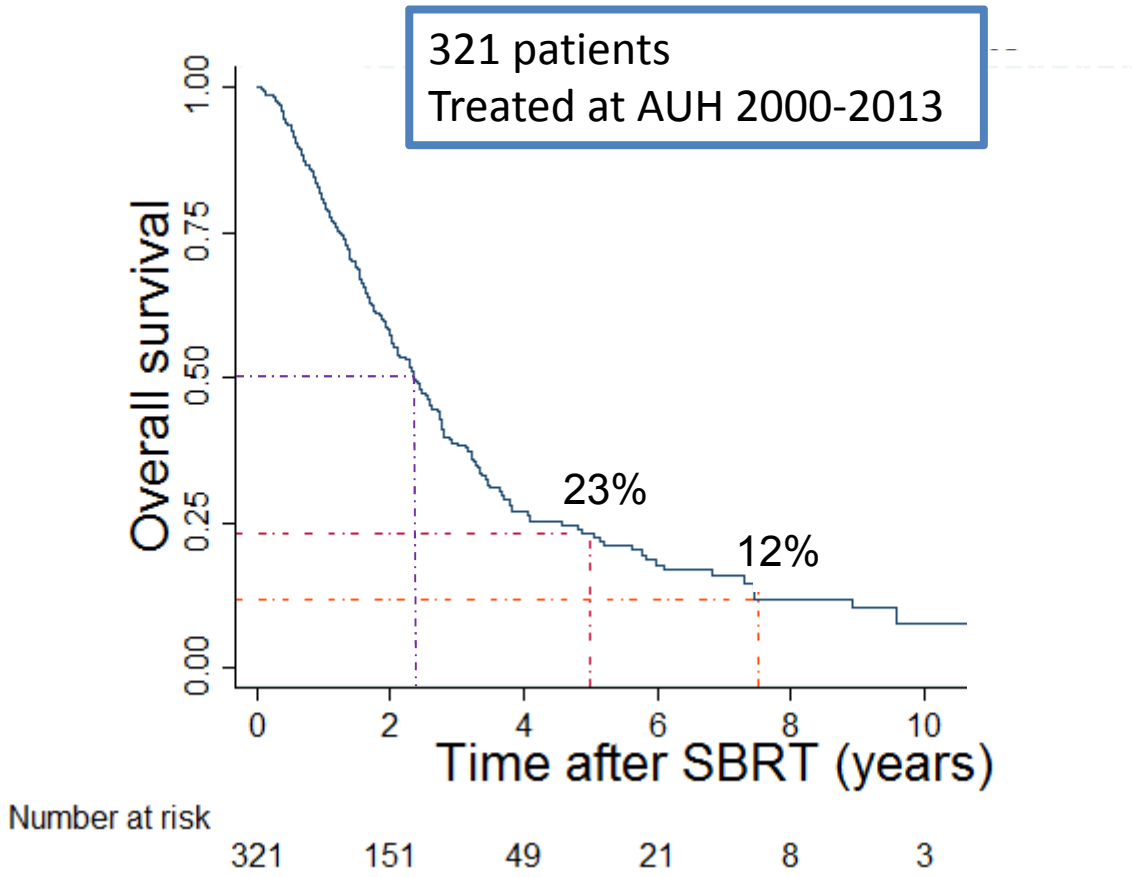
MM Fode et al. Radiother Oncol 2015; 114(2):155

Local control in SBRT for metastases



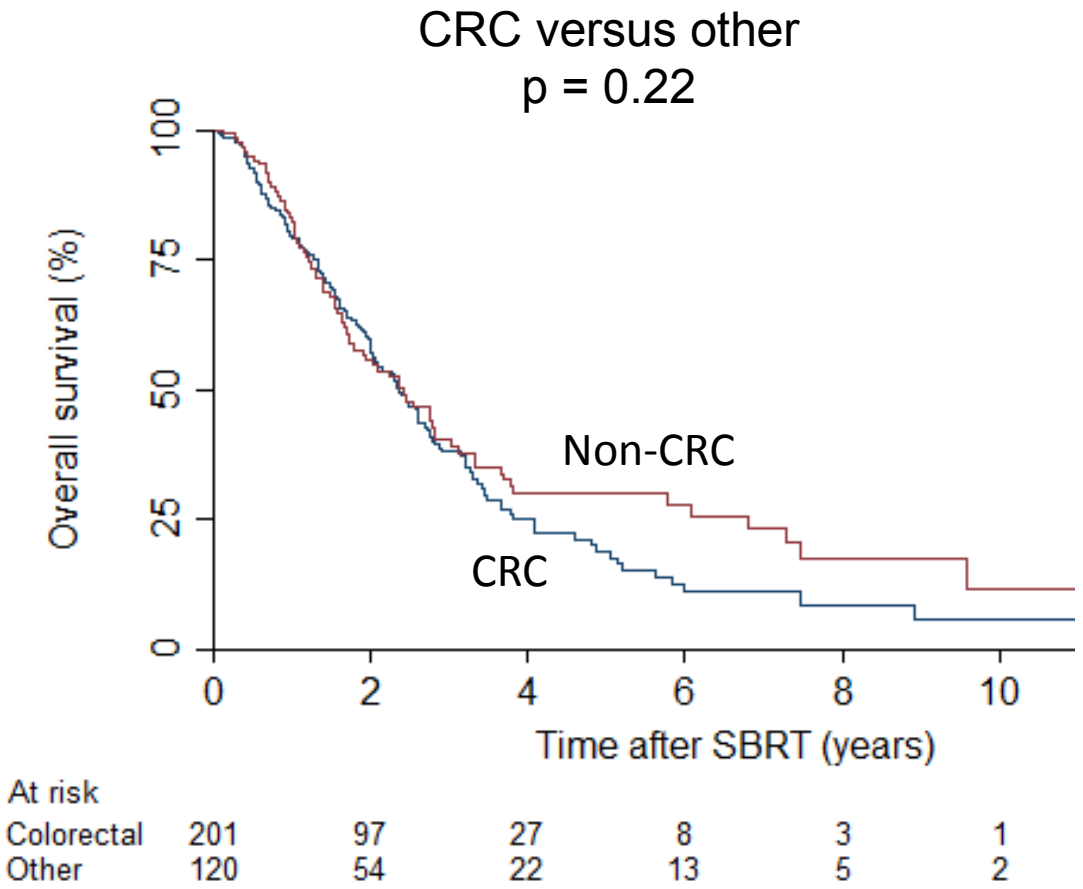
MM Fode et al. Radiother Oncol 2015; 114(2):155

Overall survival after SBRT for metastases



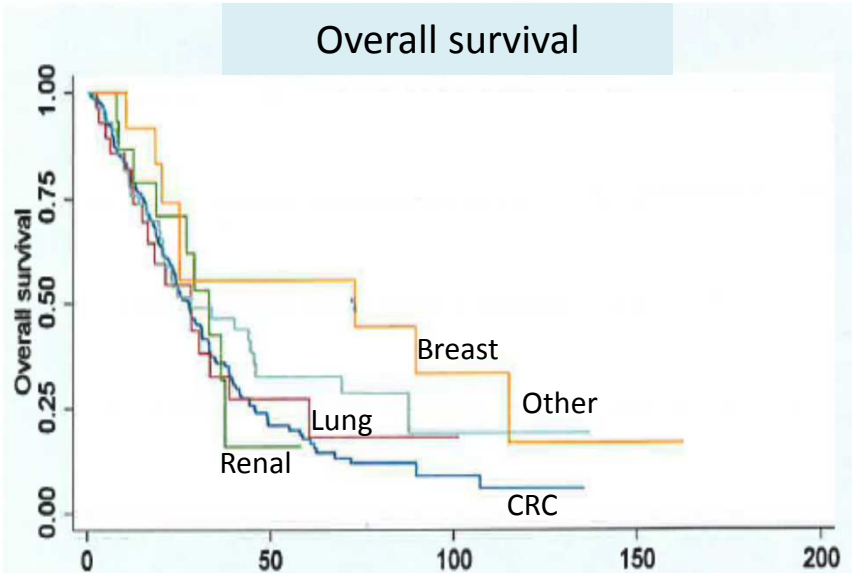
MM Fode et al. Radiother Oncol 2015; 114(2):155

Histological type



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

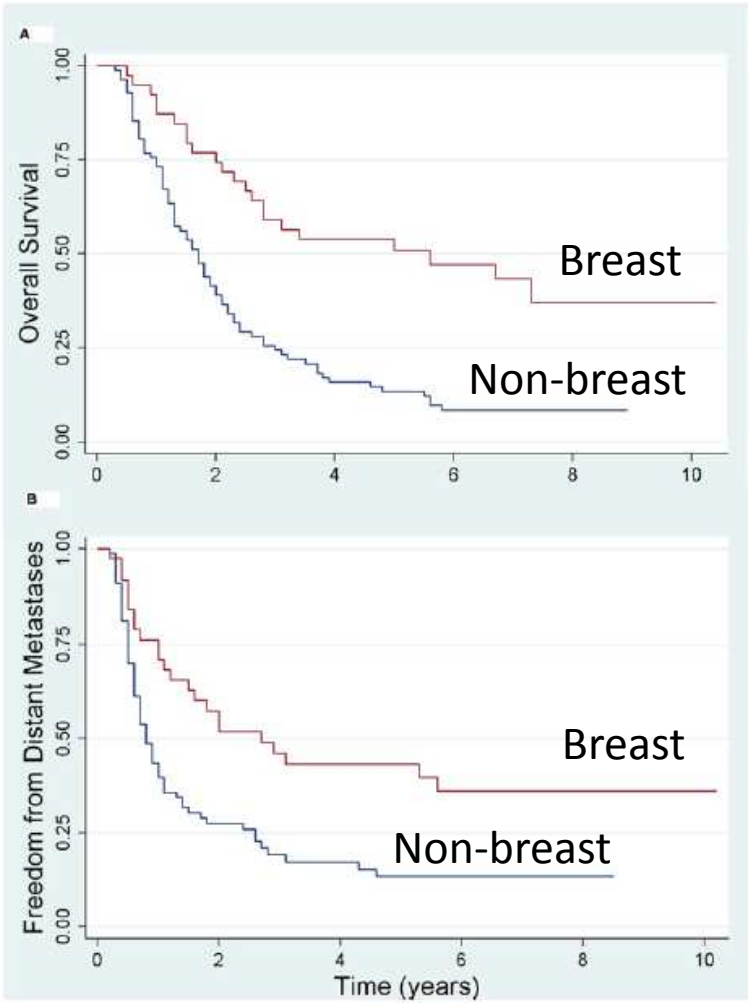
Survival by histological type



	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

Histological type (multiple metastasis site)

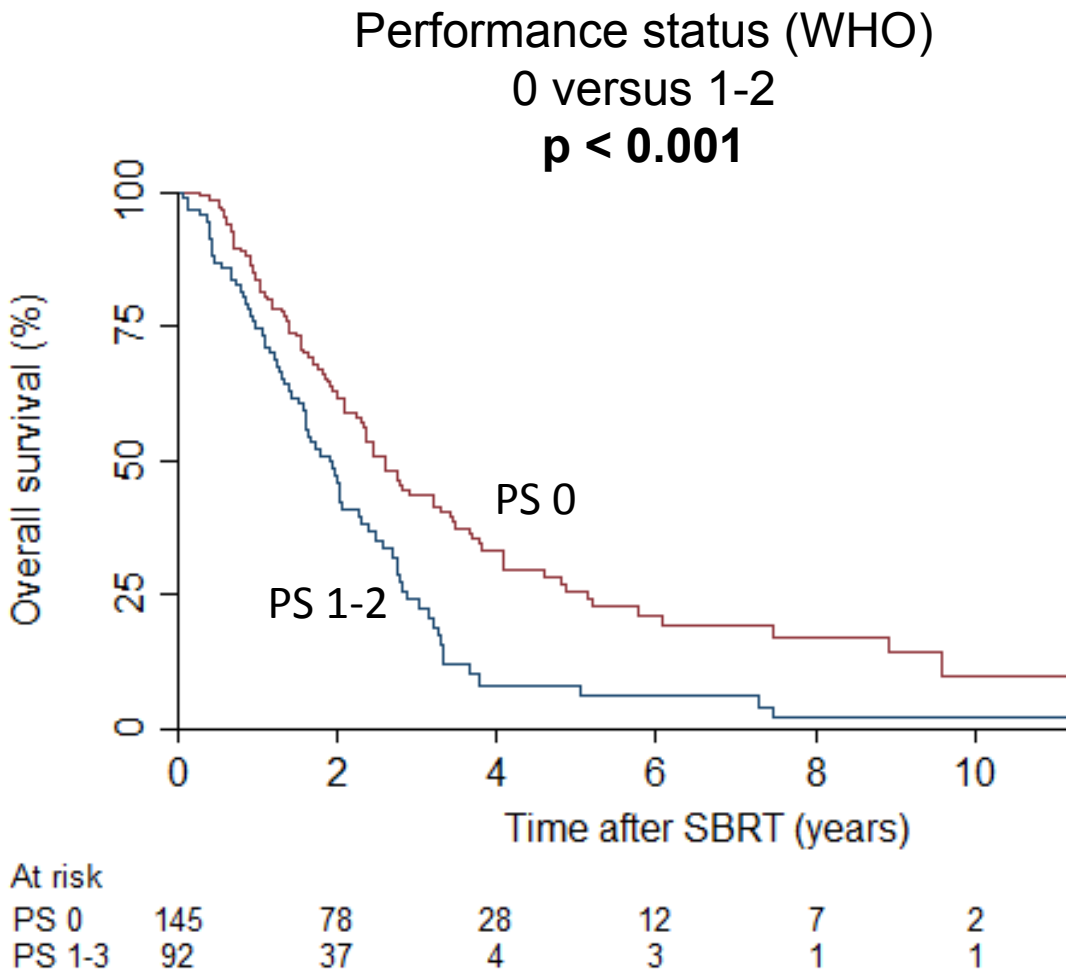


Primary cancer	
Breast	39 (32)
Colorectal	31 (26)
Lung, head/neck, esophagus	23 (19)‡
Other	28 (23)§
Initial sites involved with oligometastatic disease	
Lung	50 (41)
Thoracic lymph nodes‖	24 (20)
Liver	54 (45)
Pelvis/abdomen	6 (5)
Brain	5 (4)
Bone	15 (12)

Survival, time to distant progression and local control better for patients with *breast cancer* oligo-metastases

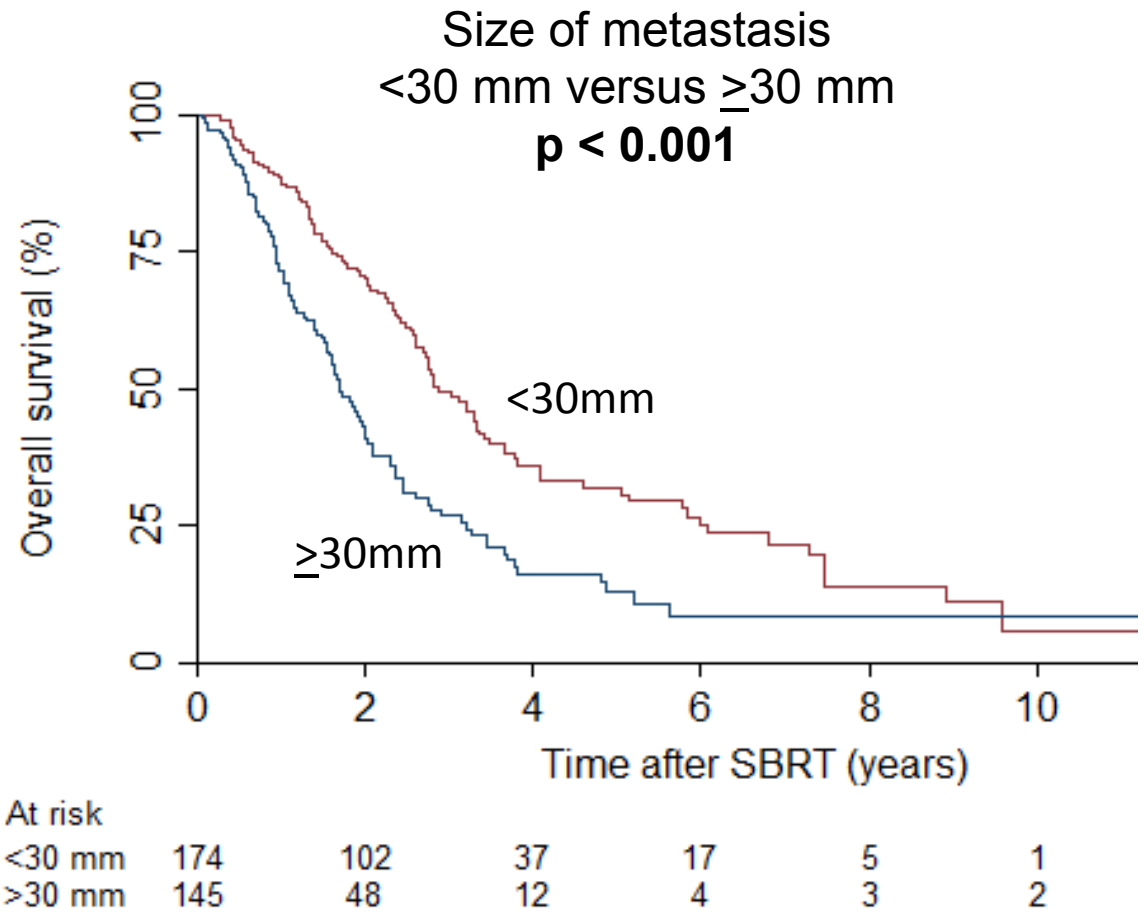
Milano et al. 83: 878-86; 2012

Performance status, age, gender & co-morbidity



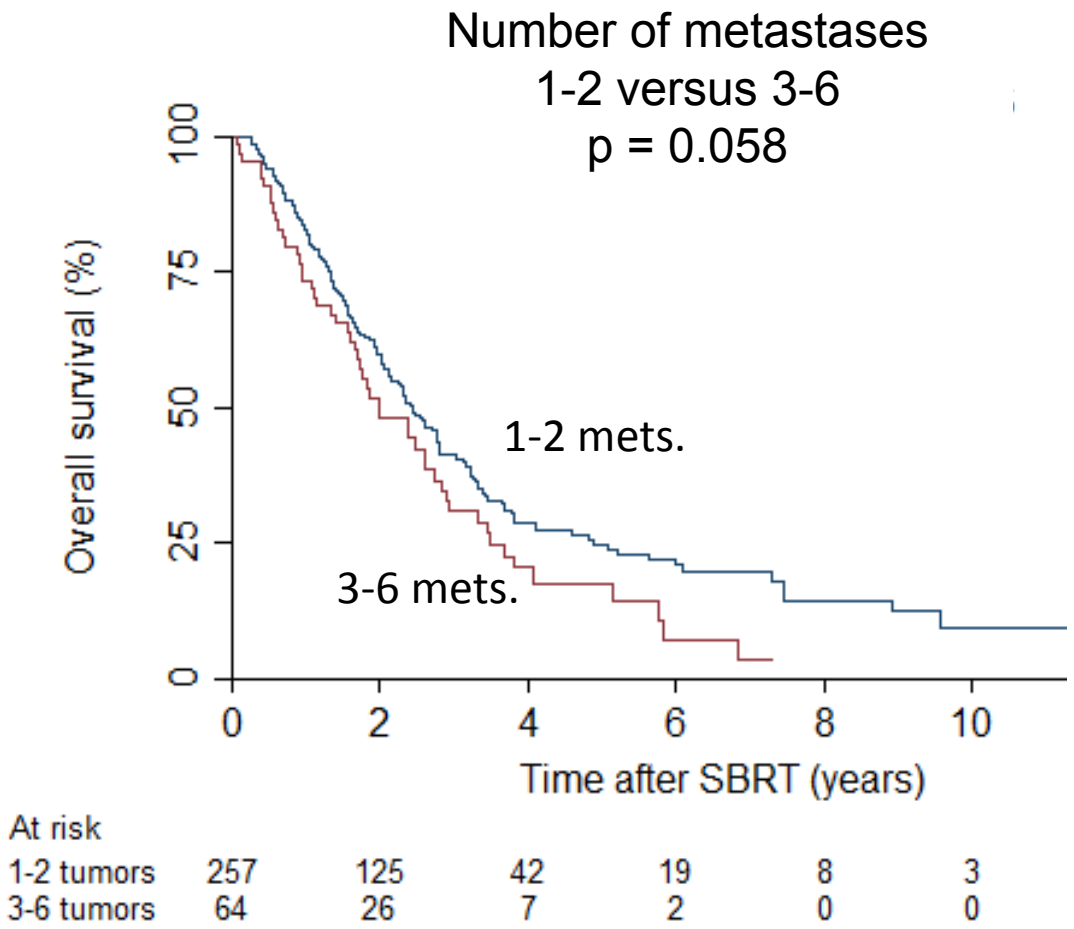
MM Fode et al. Radiother Oncol 2015; 114(2):155

Metastasis size



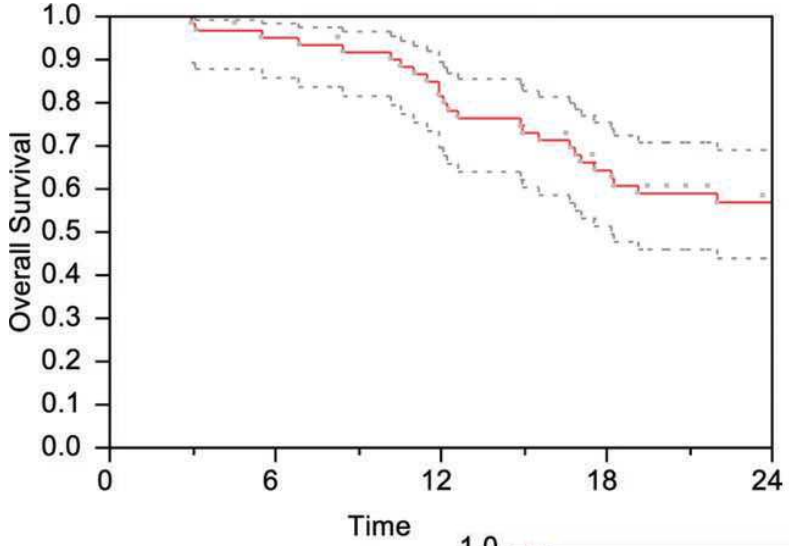
MM Fode et al. Radiother Oncol 2015; 114(2):155

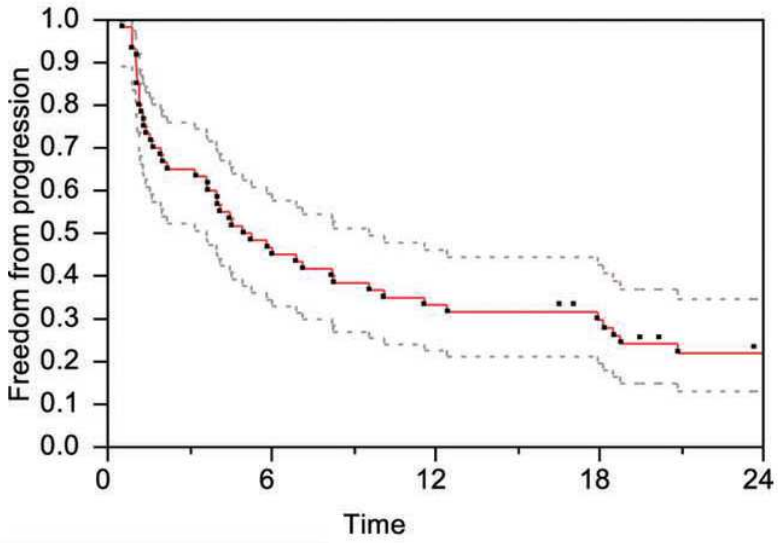
Number of metastases

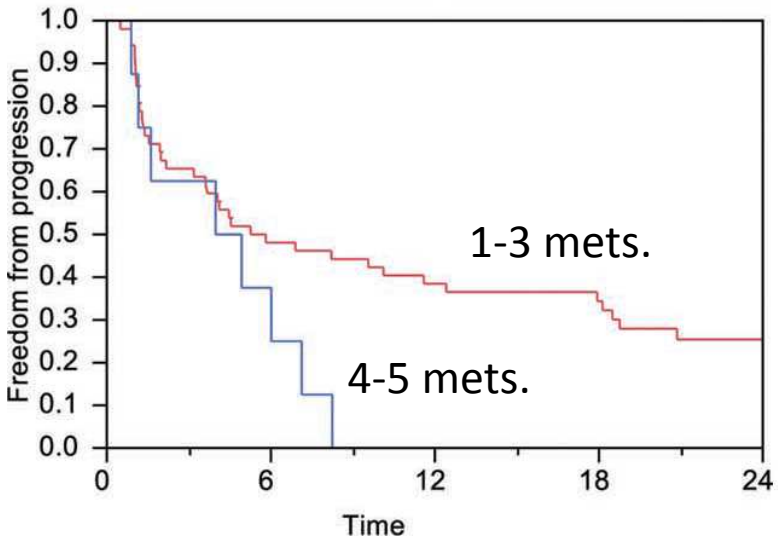


MM Fode et al. Radiother Oncol 2015; 114(2):155

Number of metastases

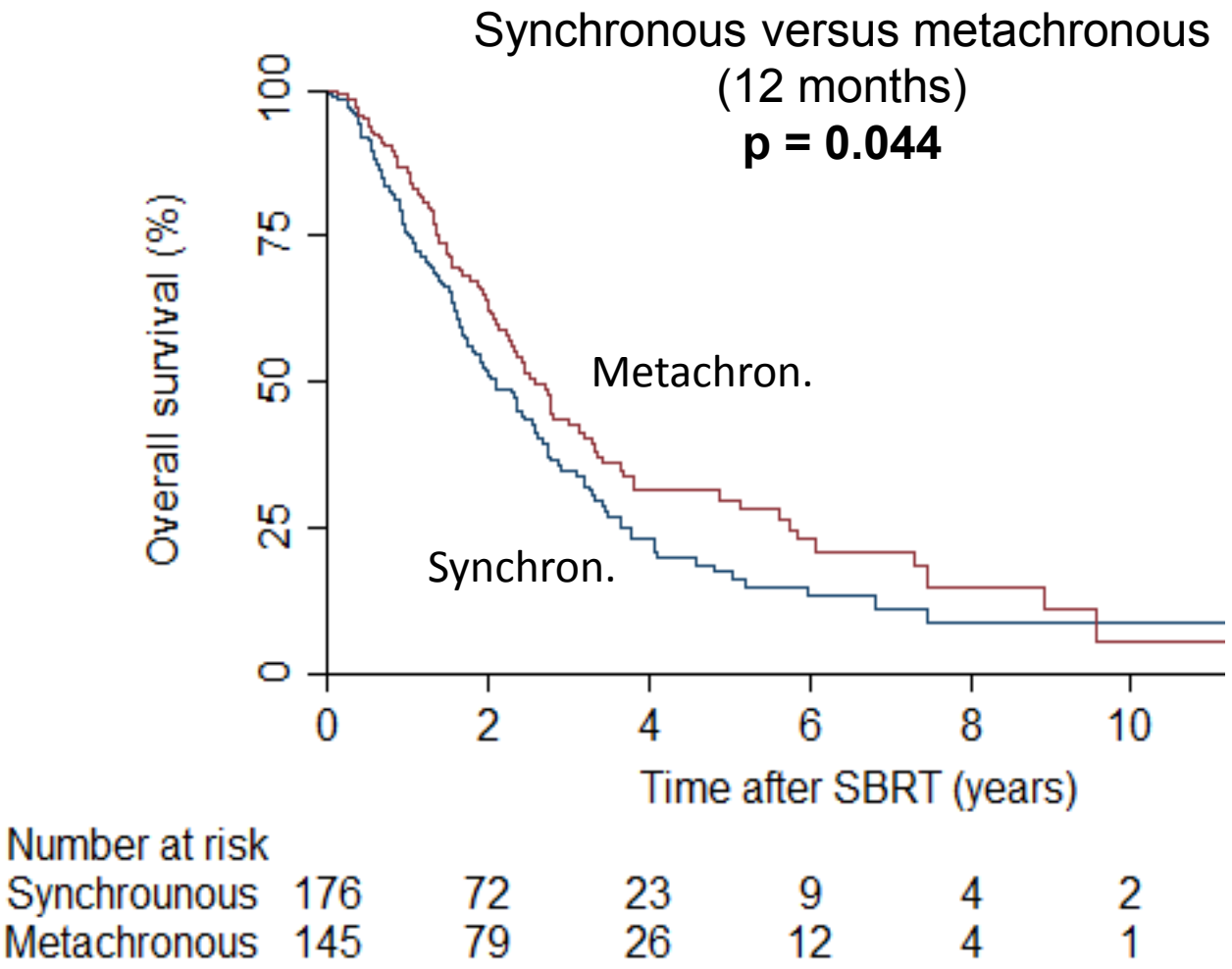






Salama et al. Cancer 2011; 118:2962

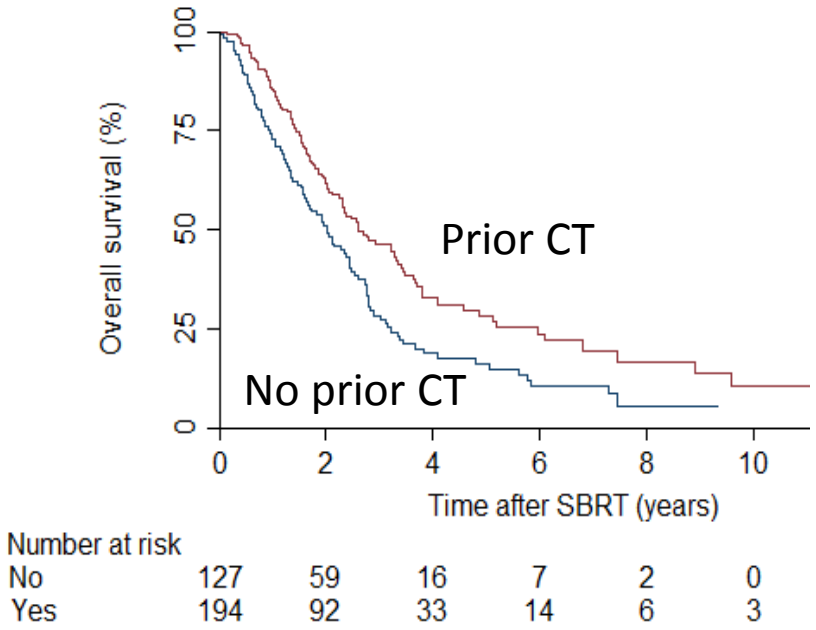
Timing of metastasis



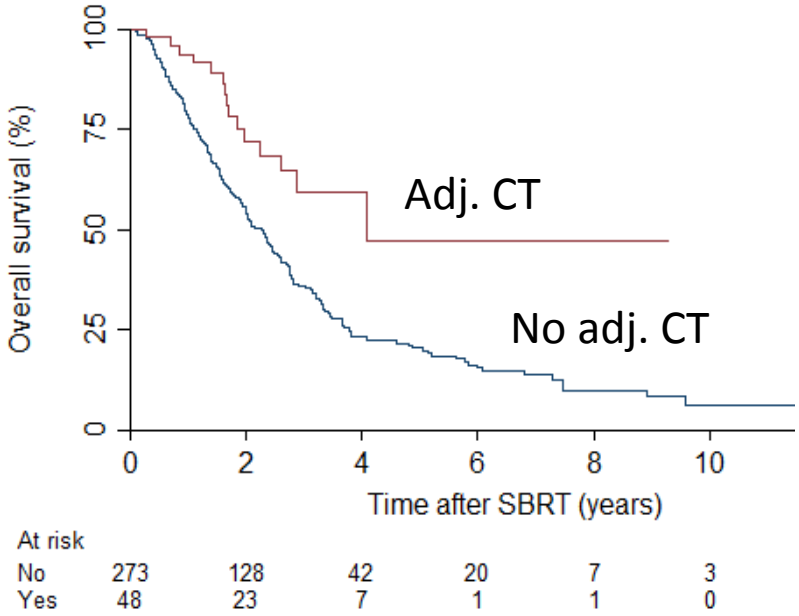
MM Fode et al. Radiother Oncol 2015; 114(2):155

Additional chemotherapy

Prior chemotherapy
HR: 0.65
95% CI: (0.49 – 0.85)
p = 0.002



Adjuvant chemotherapy
HR: 0.42
95% CI: (0.25 – 0.71)
p < 0.001



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

Multivariate analysis

Death from all causes

Variable	HR	95% CI	p-value
Performance status	2.06	1.35 – 3.13	< 0.01
Primary tumor type	0.96	0.67 – 1.37	0.83
Treatment site	0.91	0.61 – 1.34	0.63
Size of metastasis	1.90	1.45 – 2.51	< 0.001
Number of metastases	1.33	1.00 – 1.76	0.05
Synchronous vs. metachronous	1.40	1.05 – 1.86	0.02
Pre-SBRT chemotherapy	0.58	0.44 – 0.78	<0.01
Post-SBRT chemotherapy	0.54	0.29 – 0.98	0.042

CIRRO

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

Aarhus University Hospital

Multivariate analysis

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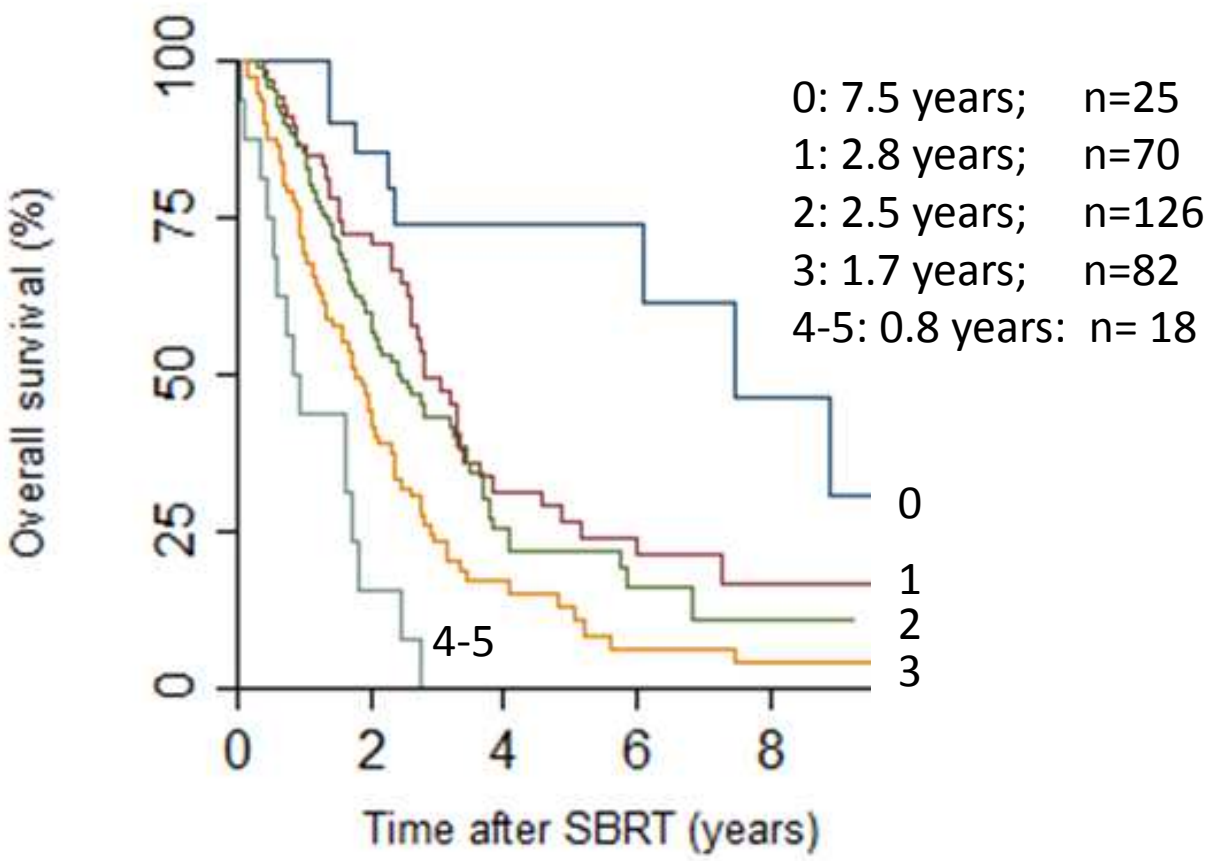
CIRRO

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

Aarhus University Hospital

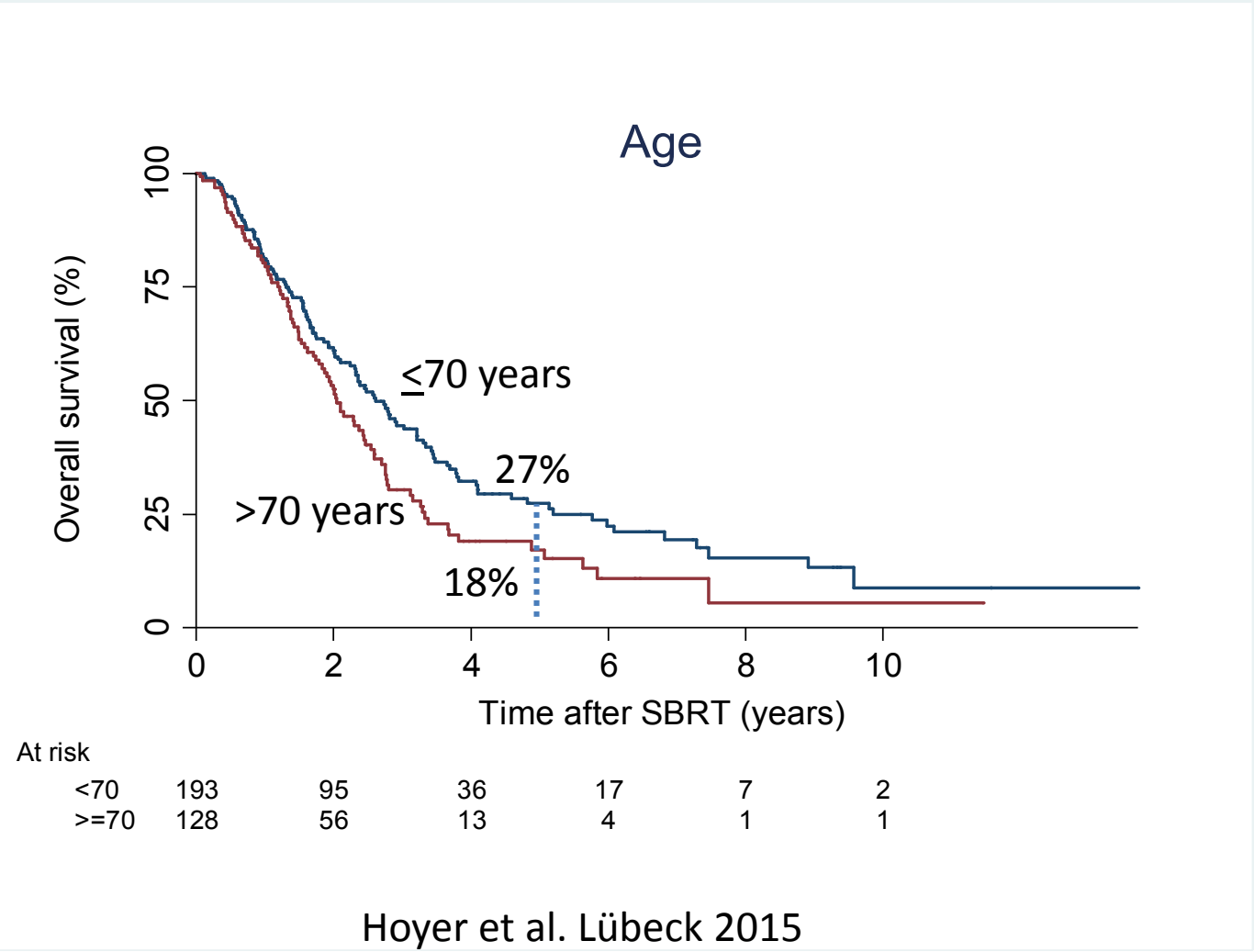
Overall survival

According to prognostic factors



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

Overall survival by age – all metastases



Hoyer et al. Lübeck 2015

CIRRO

AARHUS UNIVERSITY

Overall survival by age – all metastases

Multivariate analysis

	<70 years (n=192)			>70 years (n=127)		
Variable	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Performance status				1.81	1.05-3.12	0.03
Size of mets.	2.26	1.13 – 2.91	< 0.01	1.58	1.02-2.43	0.04
Number of mets.	1.98	1.31 – 2.97	0.001			
Pre-SBRT chemo	0.58	0.44 – 0.78	<0.01	1.66	1.05-2.62	0.03

Hoyer et al. Lübeck 2015

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Morbidity after liver SBRT

Morbidity

Acute and late

Acute morbidity	0	1	2	3	4	5
Deterioration of PS	296	22	2	-	-	1
Nausea	293	23	3	2	-	-
Pain	273	24	8	6	-	-
Gastritis	303	7	12	1	-	-
Skin	209	4	6	2	-	-
Liver function	294	23	4	-	-	1
Late morbidity						
Gastritis/ulcer/perforation	308	1	10	1	0	1
Rib fracture	311	-	10	-	-	-
Dyspnea	294	15	11	-	1	-
Skin reaction	308	4	7	2	-	-
Liver function	307	6	8	-	-	-

Fode et al. Radiother Oncol 2015 in press

Severe adverse events in SBRT for primary and metastatic liver tumors

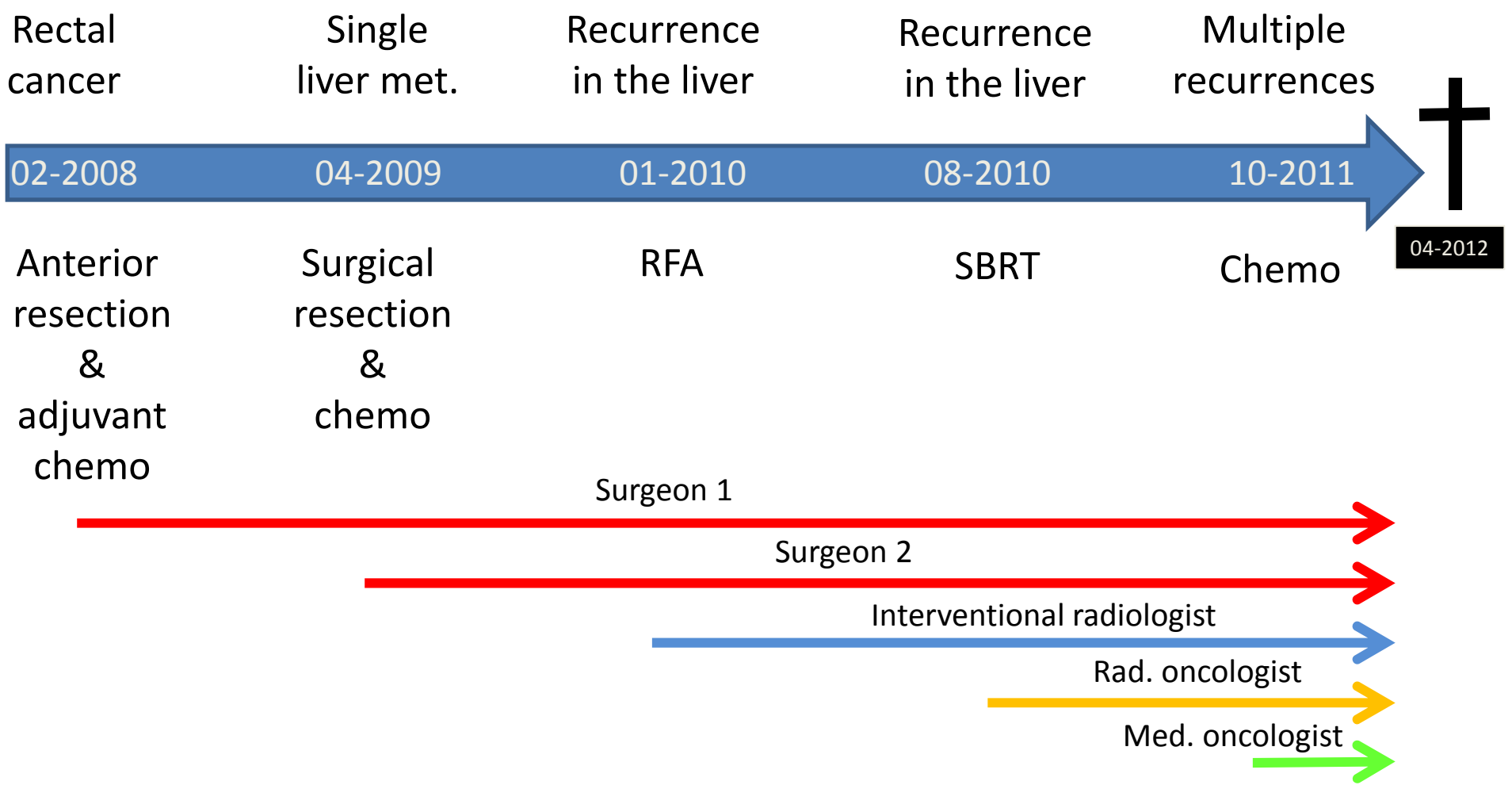
	No. pts.	Liver	Intestine/ stomach	Skin/soft tissue necr	
Herfarth	35				
M-Romero	25	1 grade 5 3 grade			
Fode	321 liver, lung, ot				1 grade 4
Rusthoven				1 grade 3	
		NO			
L		2 grade 3			
Am	27	1 no grade	1 no grade		2 no grade
Goodman	26	NO			
Rule	27	NO			

Mortality ~1%
Severe late adverse effects 2%

Surgical resection, RFA or SBRT?

Hunting metastases

Example: rectal cancer

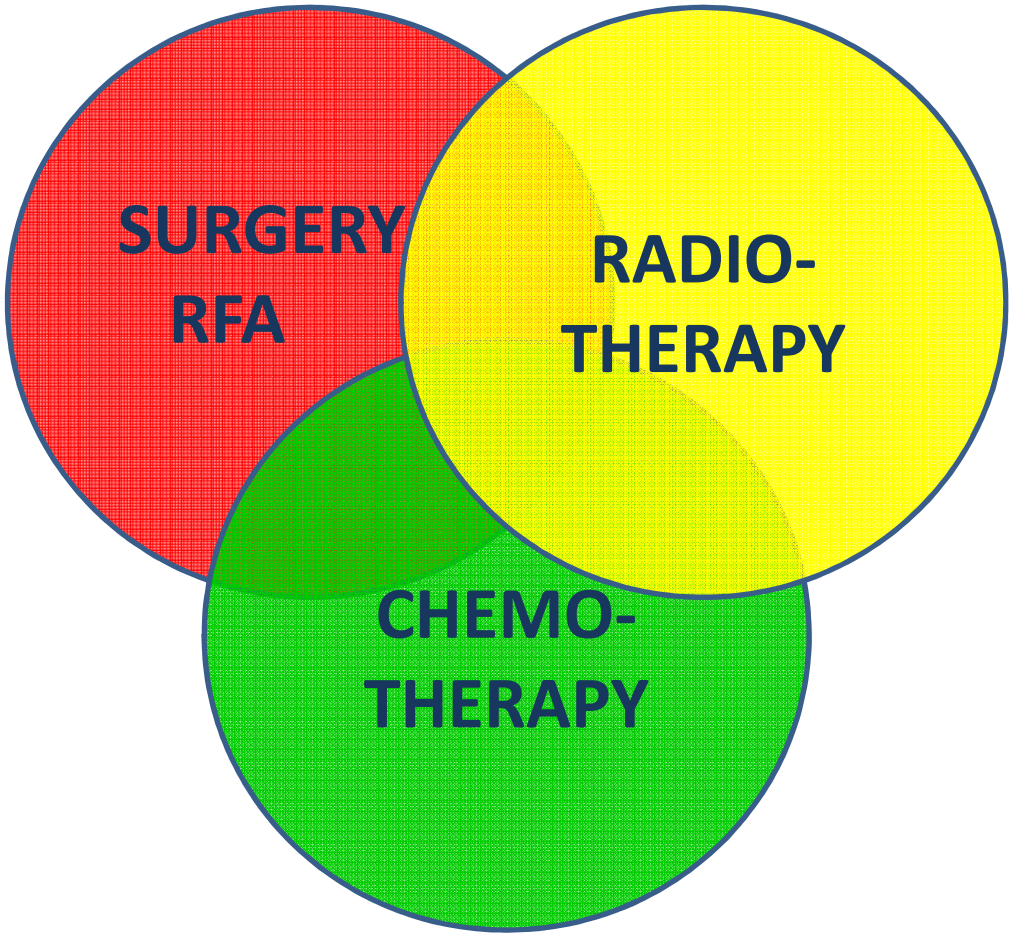


Outcomes after resection, RFA and SBRT of liver metastases

	Mortality	Severe complication	Local control	Survival
Resection Simmonds	2.8%	-	-	30% (5 yr)
RFA Wong	0-2%	6-9%	40-96% (crude)	14-55% (5 yr)
SBRT	0.5-1%	2%	74-92% (actuarial)	30-62% (2 yr)

Simmonds et al Br J Surgery 94: 982-99; 2006
Wong et al JCO 28:493-508 (ASCO 2009 syst. rev.)
Høyer et al IJROBP 83: 1047-57; 2012

Treatment of cancer in a Multidisciplinary Team



Conclusions – SBRT of oligometastases

Long-term survival may be achieved in patients with oligo-metastasis and favorable prognostic fac

- Good performance status/ accepta idity
- Small size of the metastas
- Number of metast
- Metachro asis
- P mic therapy

Experience based on highly selected patients

A is modetate

SBRT may be competable with other ablation methods

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Universitair Medisch Centrum Rotterdam

Cancer Institute

Physics in Implementing SBRT
QA of Imaging

Mischa Hoogeman

Contents

- **In-room Imaging**
  - Volumetric imaging
  - Planar imaging
- **Imaging for treatment planning**
  - 4D CT scanning
  - MRI
    - 3D geometrical correction
    - Tilted images and treatment planning systems

AAPM tg 179 QA for IGRT with CT

- CT on rails (not further assessed)
- On-board MRI (not further assessed)
- MV cone or fan beam CT (not further assessed)
- kV cone beam CT (Elekta and Varian LINACS)

- kV planar imaging (CyberKnife, Brainlab …)

Quality assurance for image-guided radiation therapy utilizing CT-based technologies: A report of the AAPM TG-179

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Task Group 179, Department of Radiation Physics, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada, M5G 2M9

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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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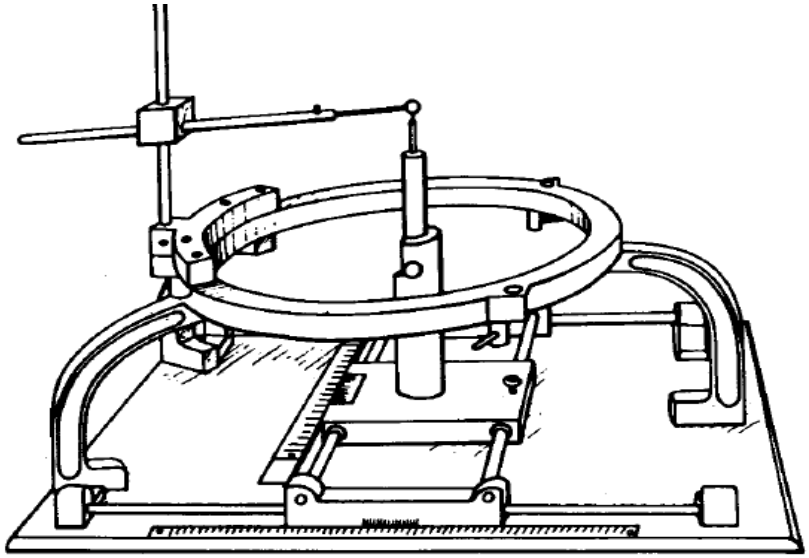
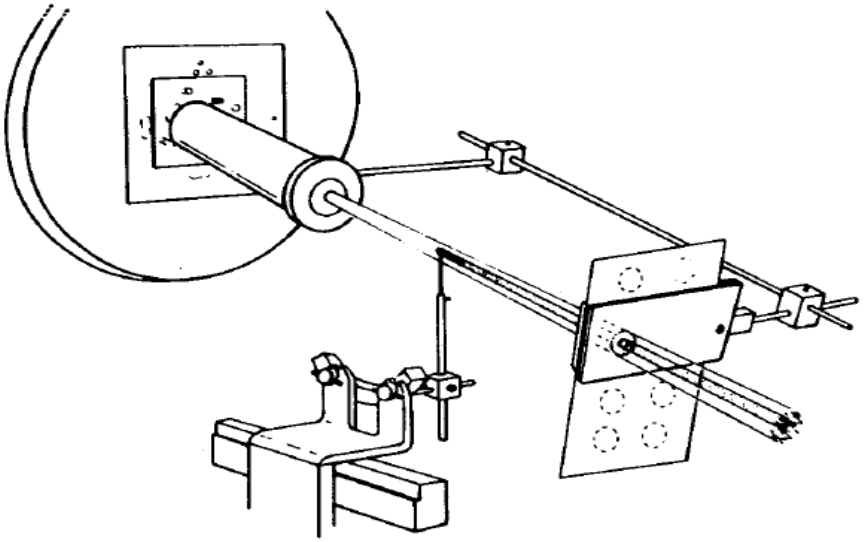
Lutz – Winston Test





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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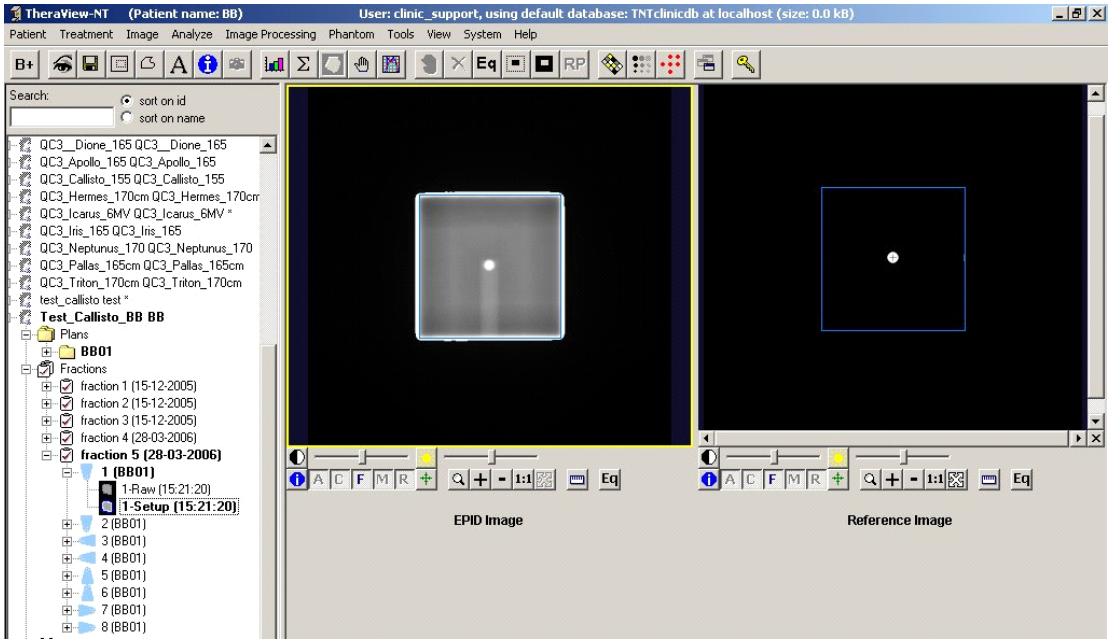
Imaging System and Radiation Isocenter Alignment

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



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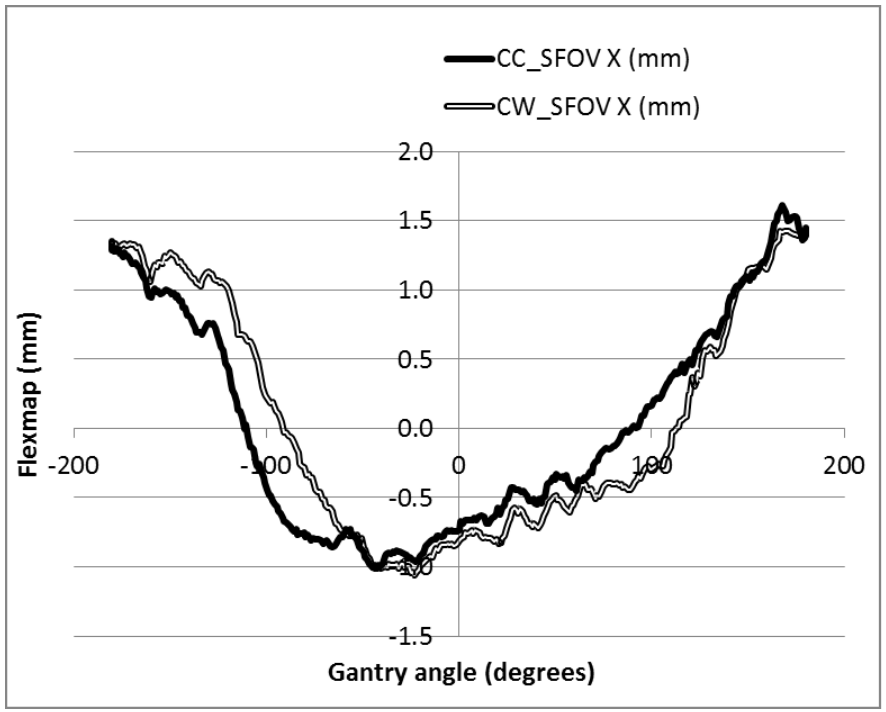
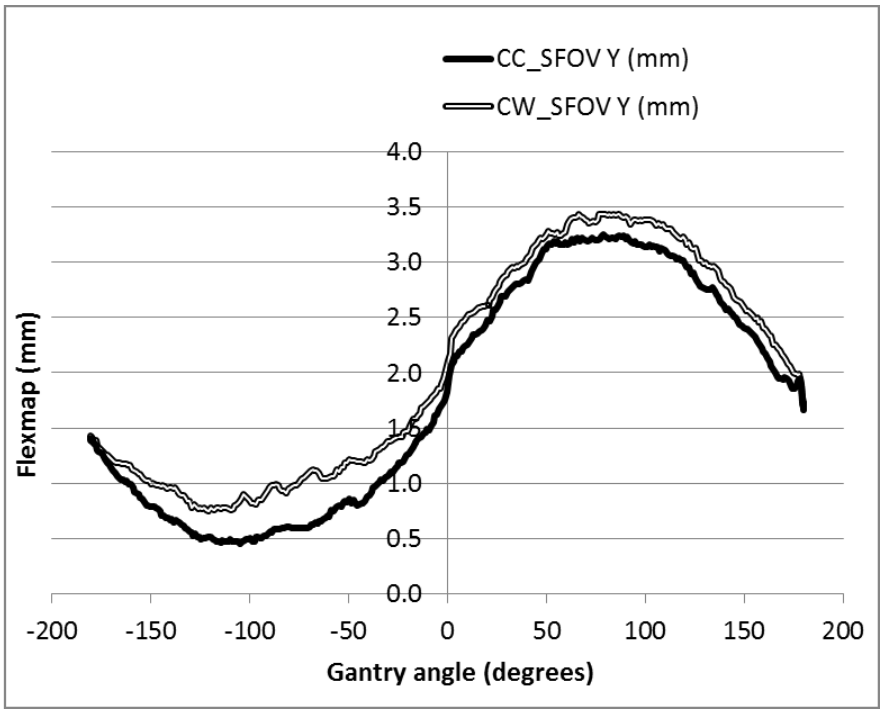
Example Flexmaps





- Varian system compensates flexes by moving the robotic arm

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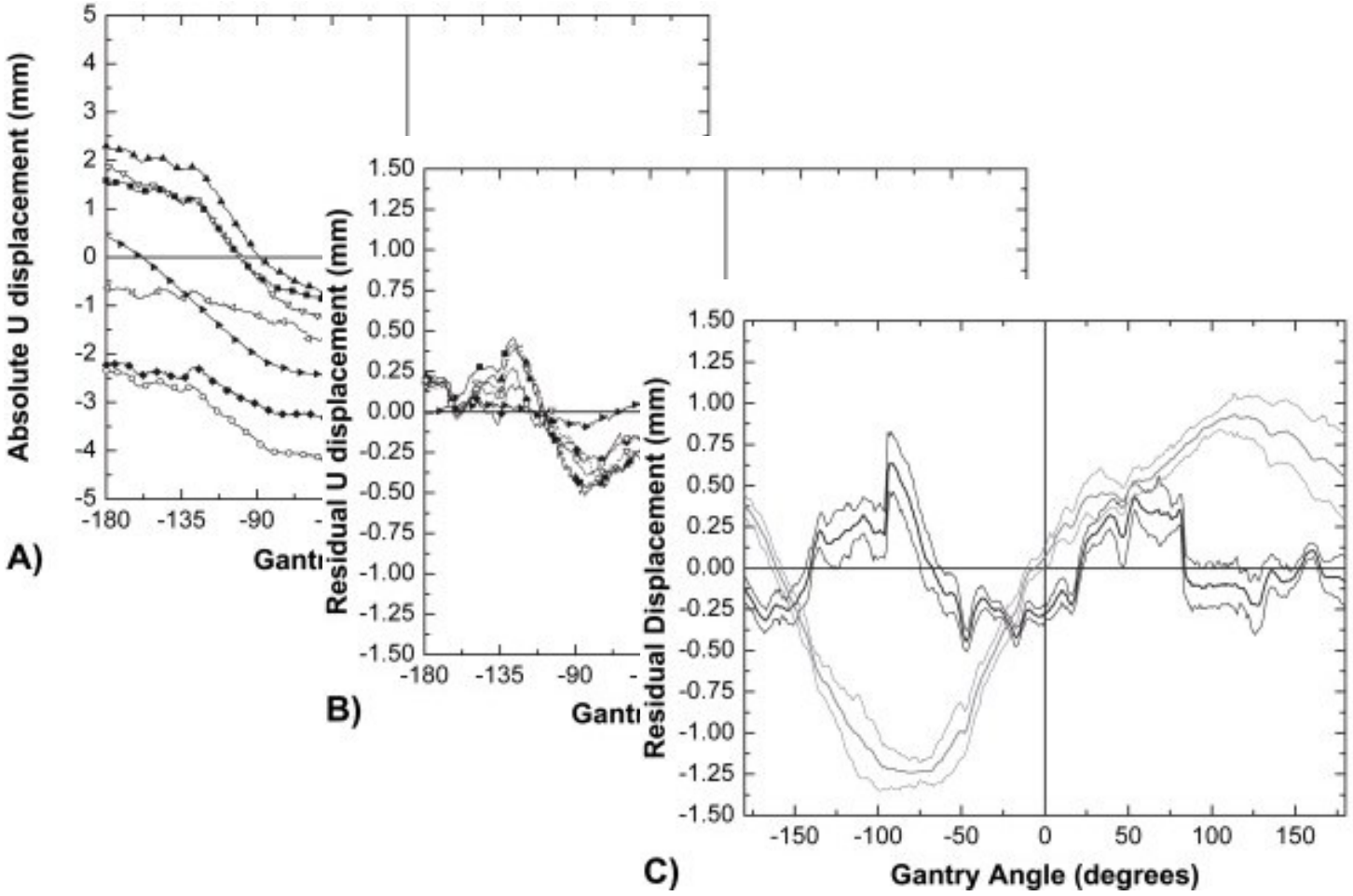
Stability of Flexmaps



[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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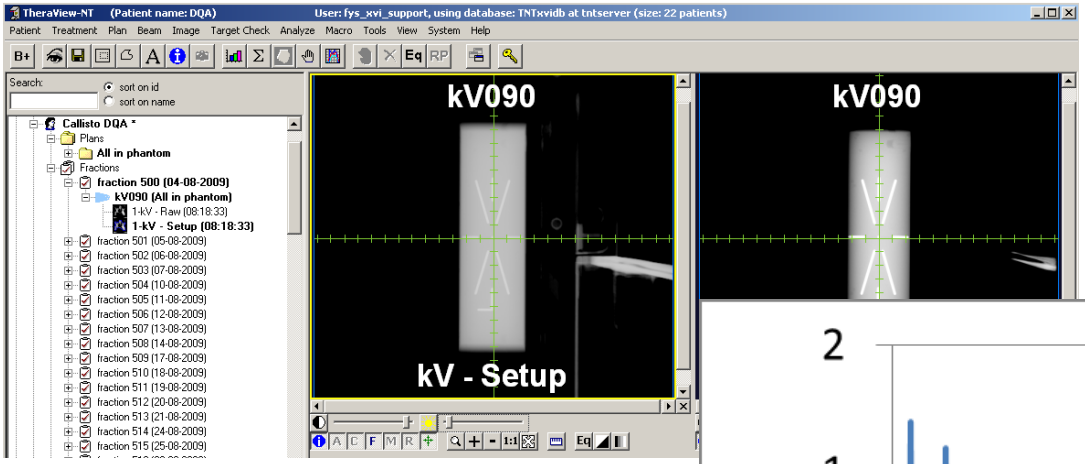
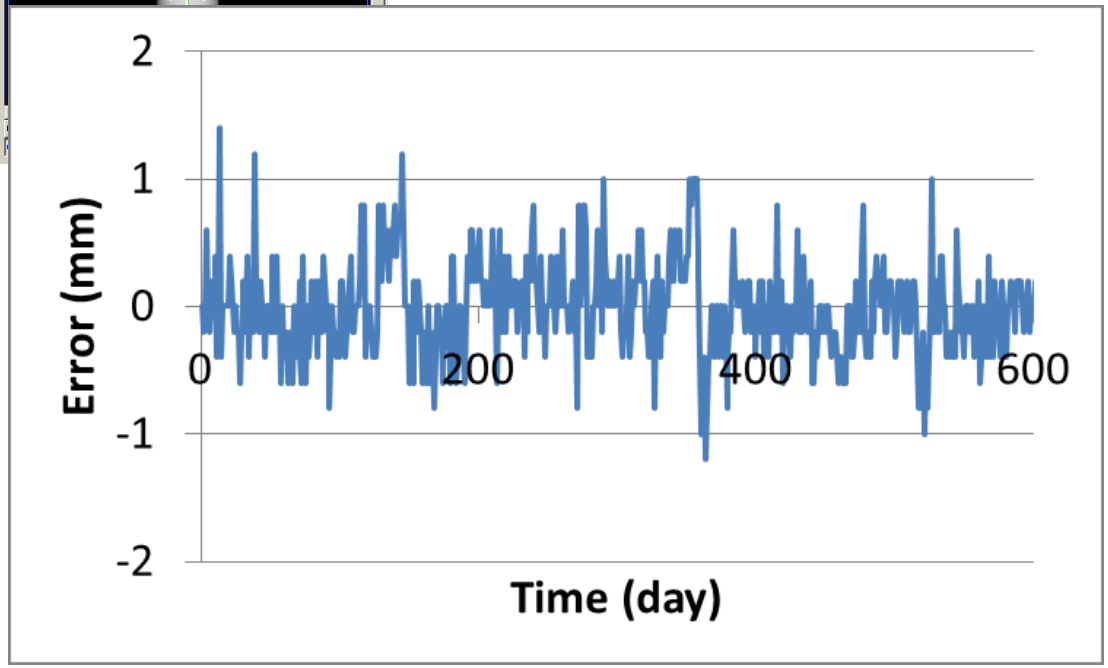
Daily QA Phantom





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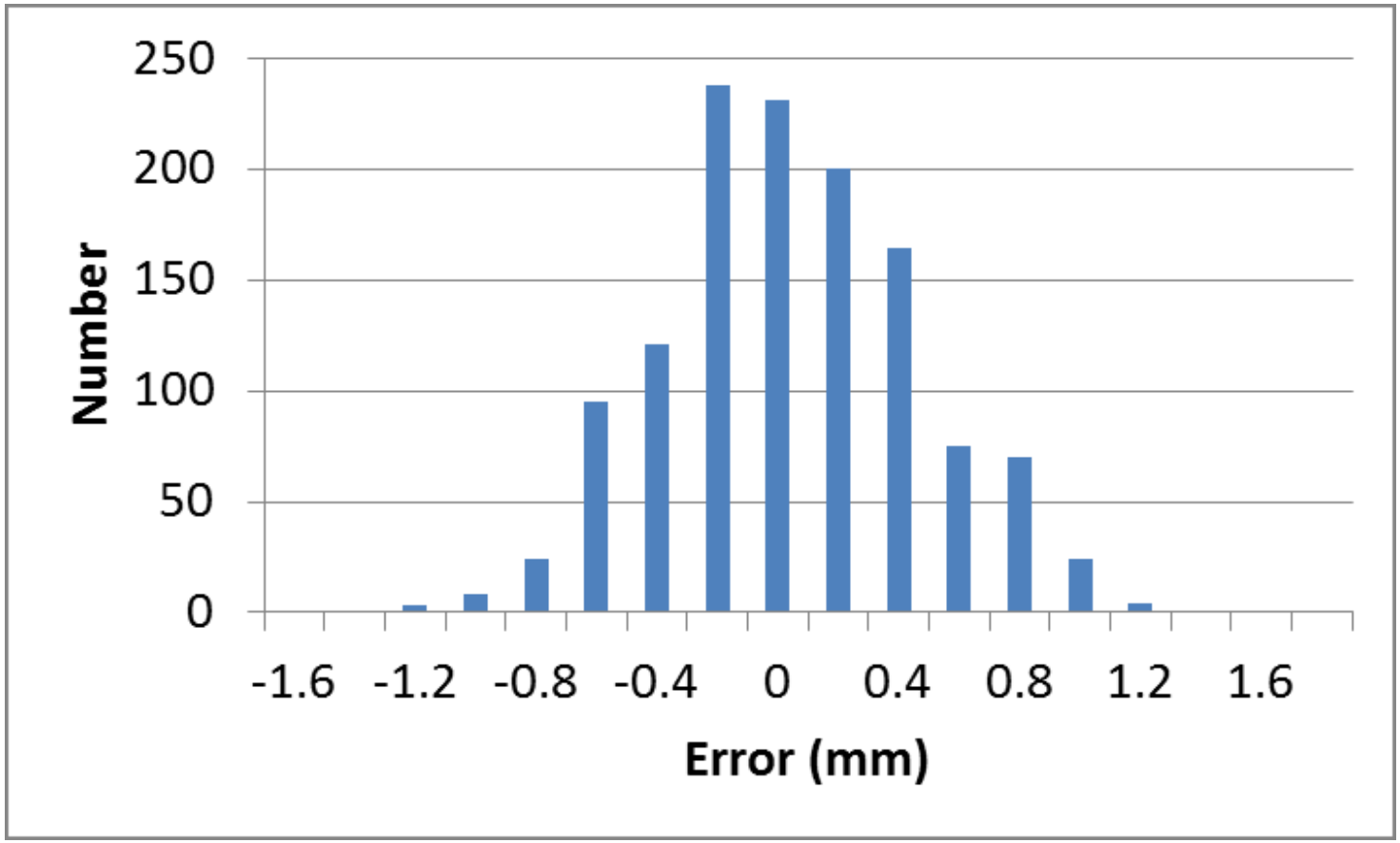
Imaging System - Radiation Isocenter Alignment Error



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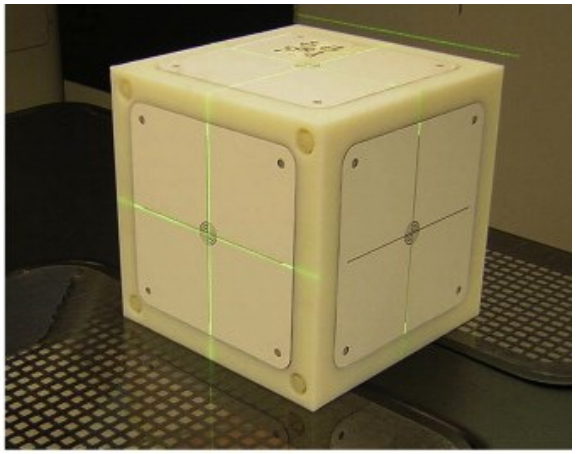
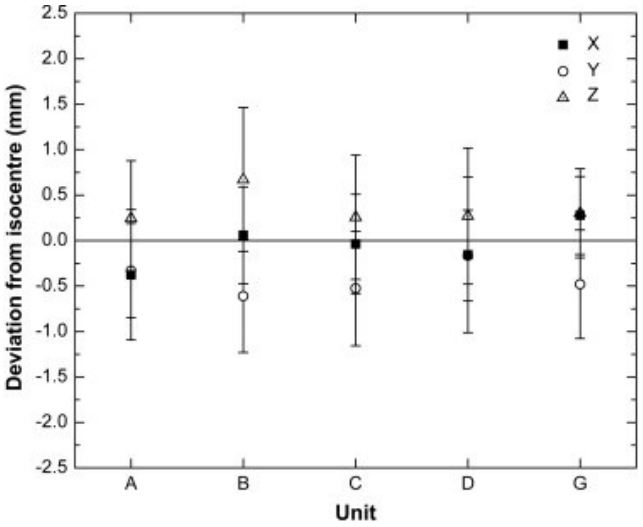
Imaging System and Radiation Isocenter Alignment





- 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 isocenter[1]

1J Bissonnette, D Moseley, E White, M Sharpe, T Purdie, D Jaffray, Quality Assurance for the Geometric Accuracy of Cone-Beam CT Guidance in Radiation Therapy. IJROBP, Volume 71, Issue 1, Supplement, 2008, S57–S61

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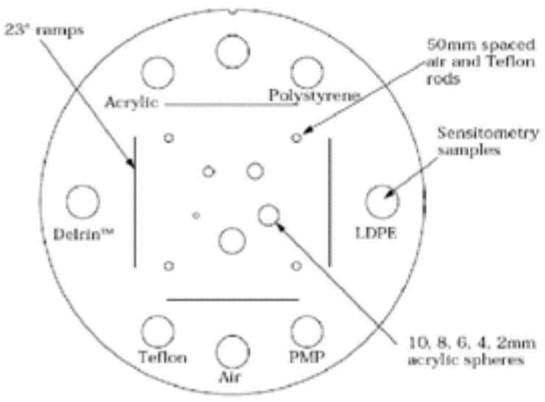
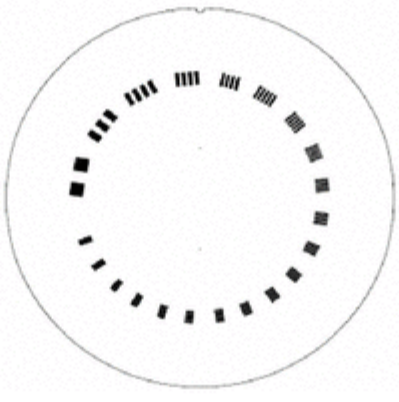
Accuracy of a Remotely Controlled Couch

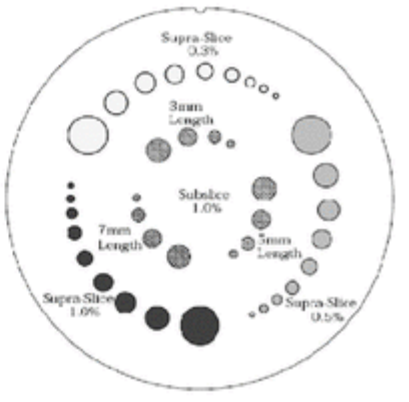
- Remotely controlled couches are available to correct translations or both translations and rotations
- Submillimeter couch position accuracy has been demonstrated (commissioning)
- For daily QA, incorporate couch test in imaging system - radiation isocenter test

Image Quality Assessed with Catphan Phantom

- Scale, distance, and orientation accuracy
- U
- H
  re
- L
- C
  stability







Kamath S, Song W, Chvetsov A, Ozawa S, Lu H, Samant S, Liu C, Li JG, Palta JR. An image quality comparison study between XVI and OBI CBCT systems. J Appl Clin Med Phys. 2011 Feb 4;12(2):3435.

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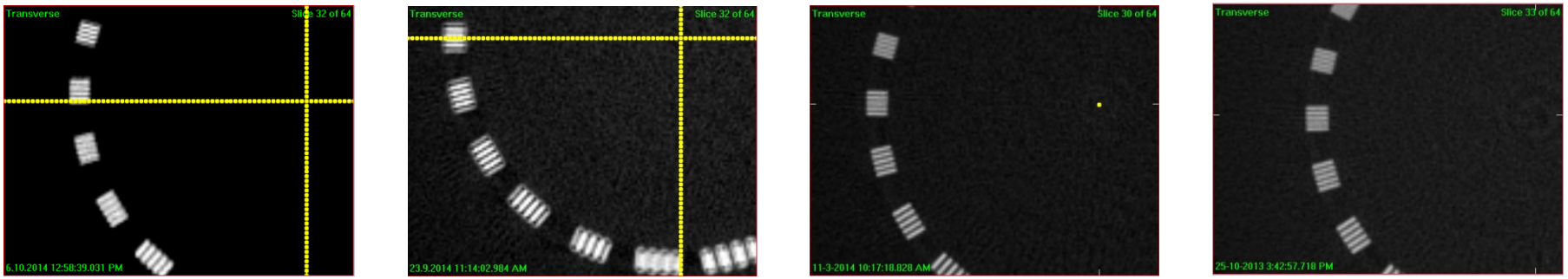
Image Quality Example



time

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Dose

[LarynxS20]
PresetDescription=Larynx S20 volume acquisition
Mode=Clinical
kV=100
NominalmAPerFrame=10
NominalmsPerFrame=10
kVCollimator=S20
kVFilter=F1
StartAngle=-105
StartAcqAngle=-100
StopAcqAngle=100
GantrySpeed=180
Direction=CW
Frames=361

Head and Neck

Filters: F0, S20
Registration: No
Start: 260 deg
Start: 100 deg
Direction: CW
Energie: 100 kV
Frames: 361
Nominal Scan Dose: 0.9 mGy
Total mAs: 36.1 mAs

		Dosis [cGy] (10 scans)	Dosis [cGy] (1 scan)
Hoofd	A (Plak 4) Rechter oor	0.6	0.06
	B (Top plak 0) Bovenkant hoofd	1.5	0.15
	C (Plak 4) Linker oor	2.8	0.28
	D (Plak 2) In de schedel	1.0	0.10
	E (Plak 2) Voorhoofd	1.6	0.16
	F (Plak 9) Schildklier	1.7	0.17
Lichaam	G (Plak 17) Sternum Borstbeen	0.1	0.01
	H (plak 17) Ribben zijkant borst	0.1	0.01

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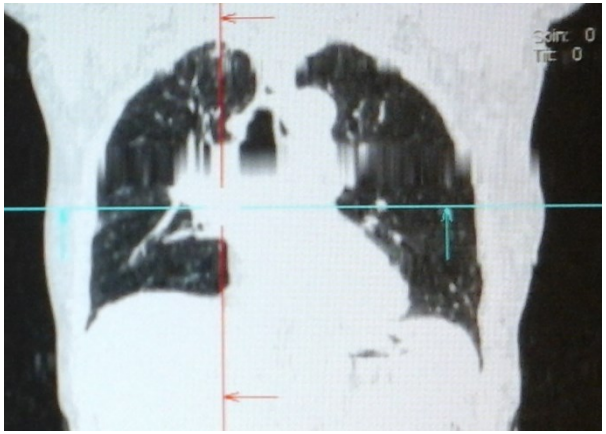
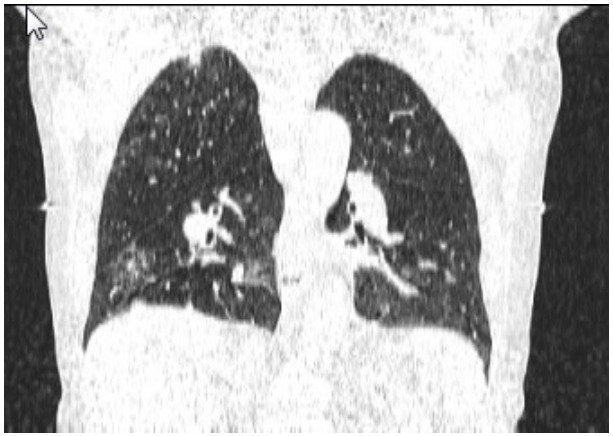
4D CT

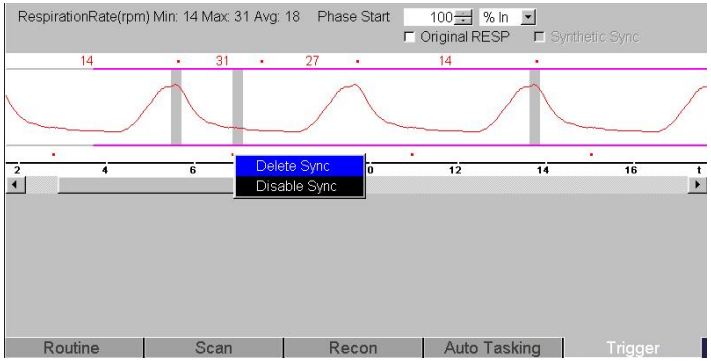
Checklist Reconstruction Improvement

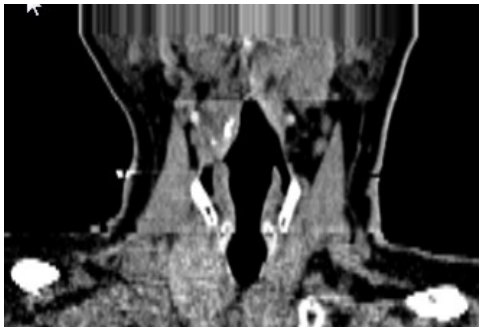
- Correct scan protocol (slow vs. normal breathing protocol)





- Correct placement of synchronization points





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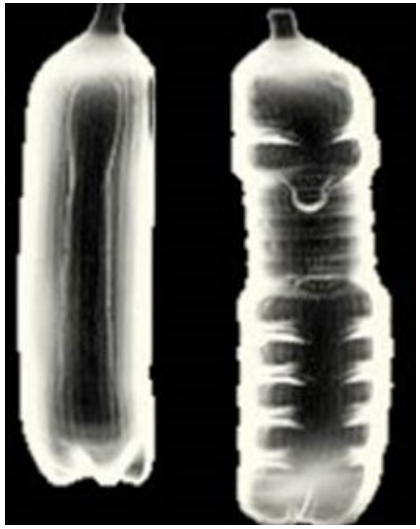
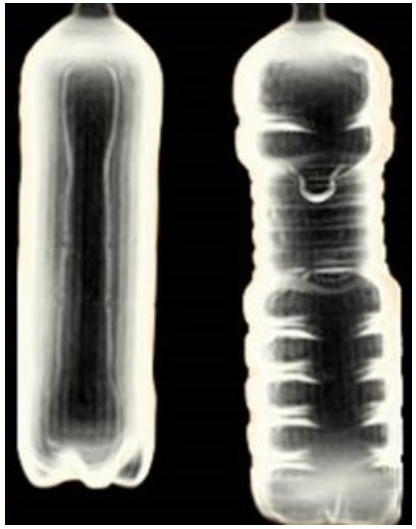
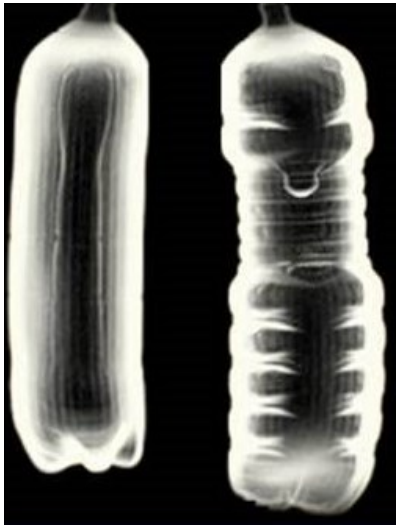
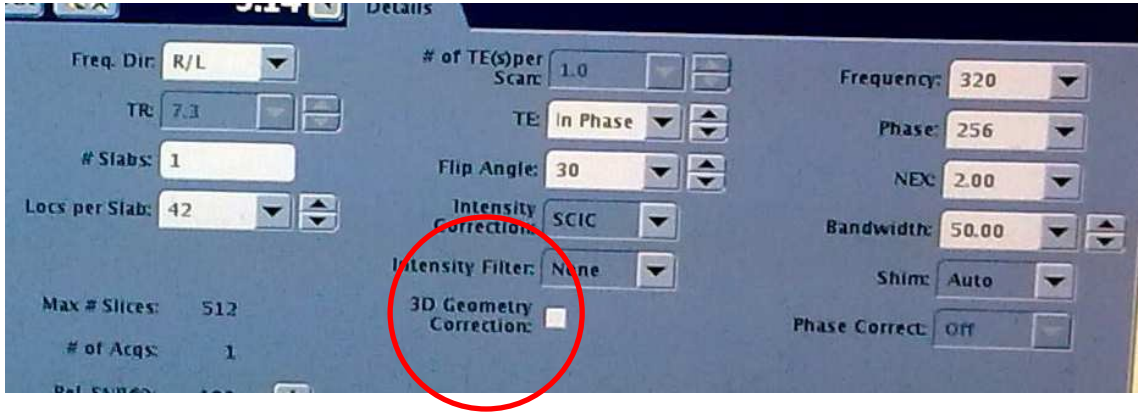
MRI

3D Geometrical Correction









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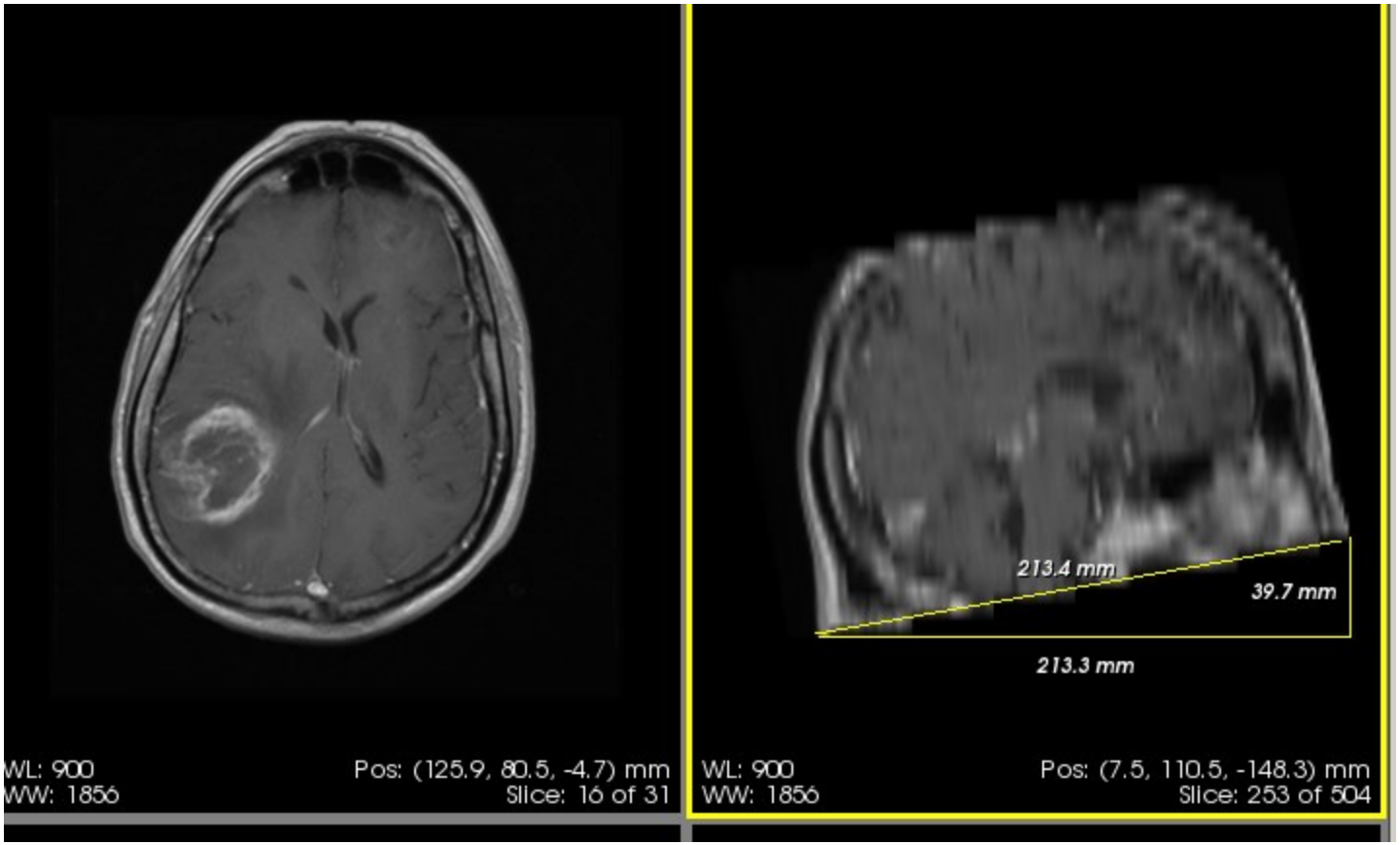
Observations

- The distance to the center of the magnet seems to be an important factor for geometric distortion in the CC direction. It is even more important than whether a T1w or T2w sequence is used
- The 3D geometrical correction seems to only work on the T1w scan. For this sequence the CC-error is reduced to a level below the slice spacing (4 mm)
- For the T2w scan the 3D algorithm does not seem to work: the CC-error can still be as large as 7 mm for points far away from the magnet center

Tilted MRIs



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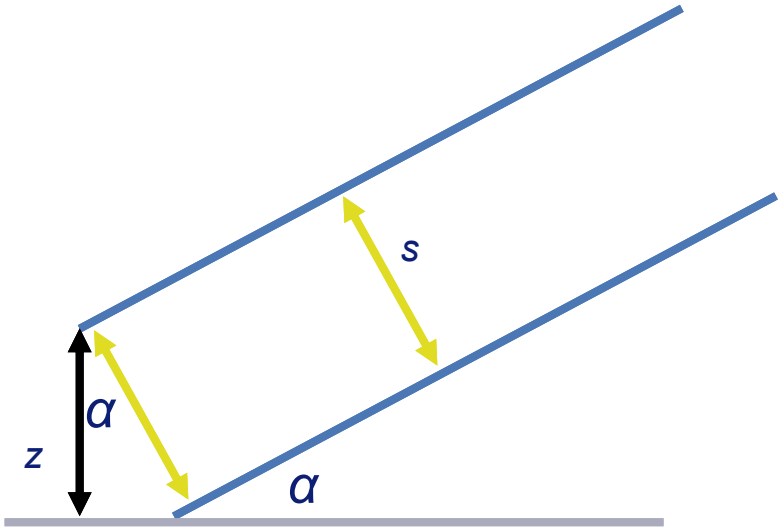
Tilted MRIs



- The slice distance is *s*. Some TPS look up the slice distance by comparing the z-position of adjacent slices. In this case *z*.
- If angle α > 0, *z* is not equal to *s*. E.g. for a tilt of 20^0 the difference is 6%. Pinnacle thus underestimates the length of the scan in the cranial caudal direction.

Q&A

QA OF PLANAR KV SYSTEMS

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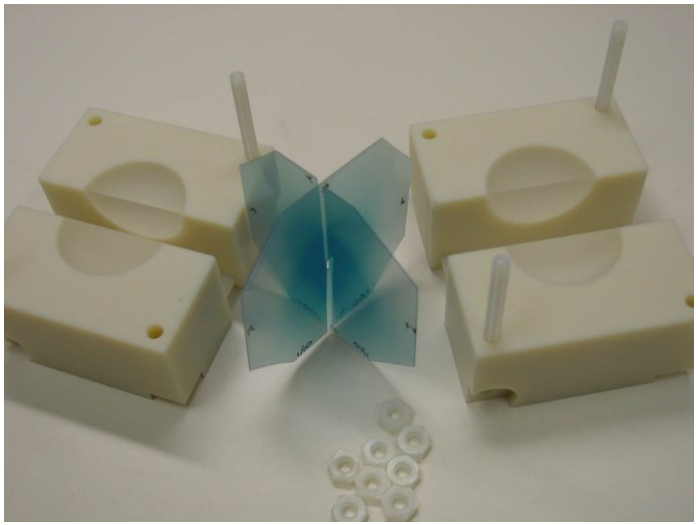
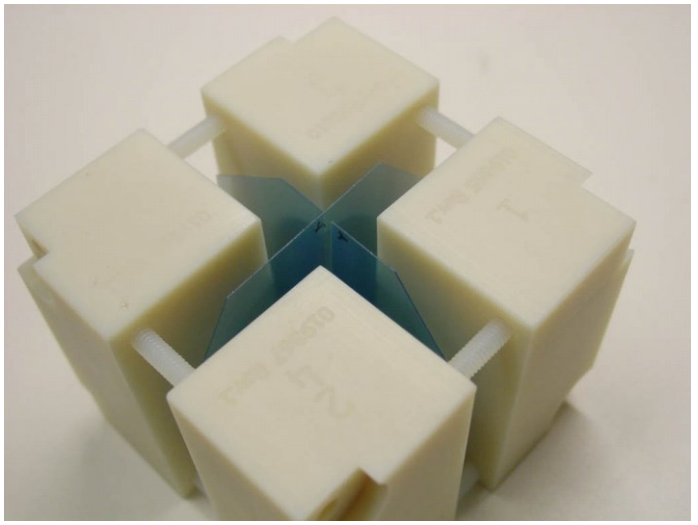
DeltaMan and End2End testing





- Final alignment of robot coordinate system and image guidance system
- QA tool to check the alignment of both systems

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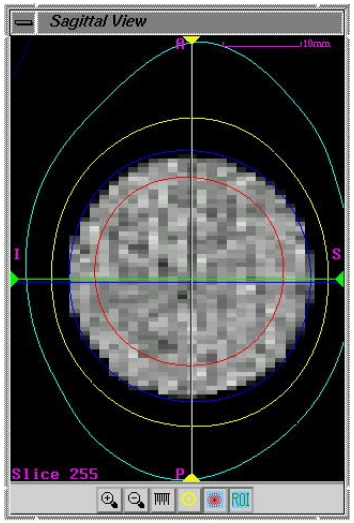
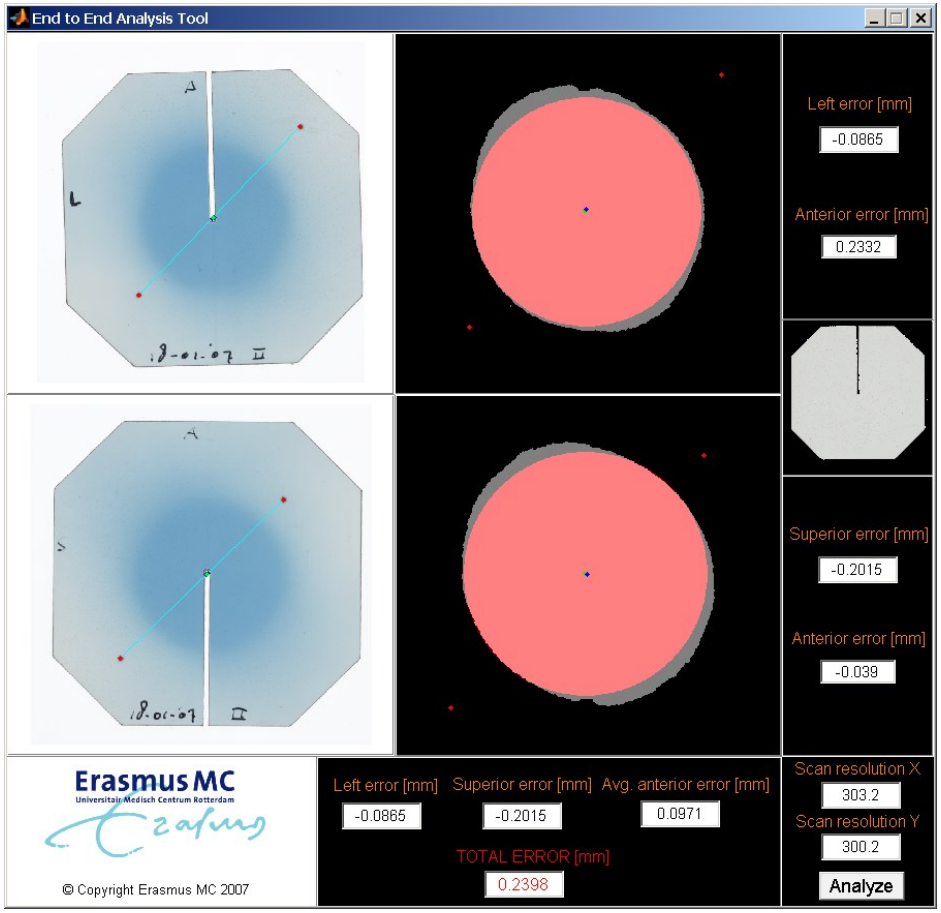
DeltaMan Analysis





Test out of imaging center

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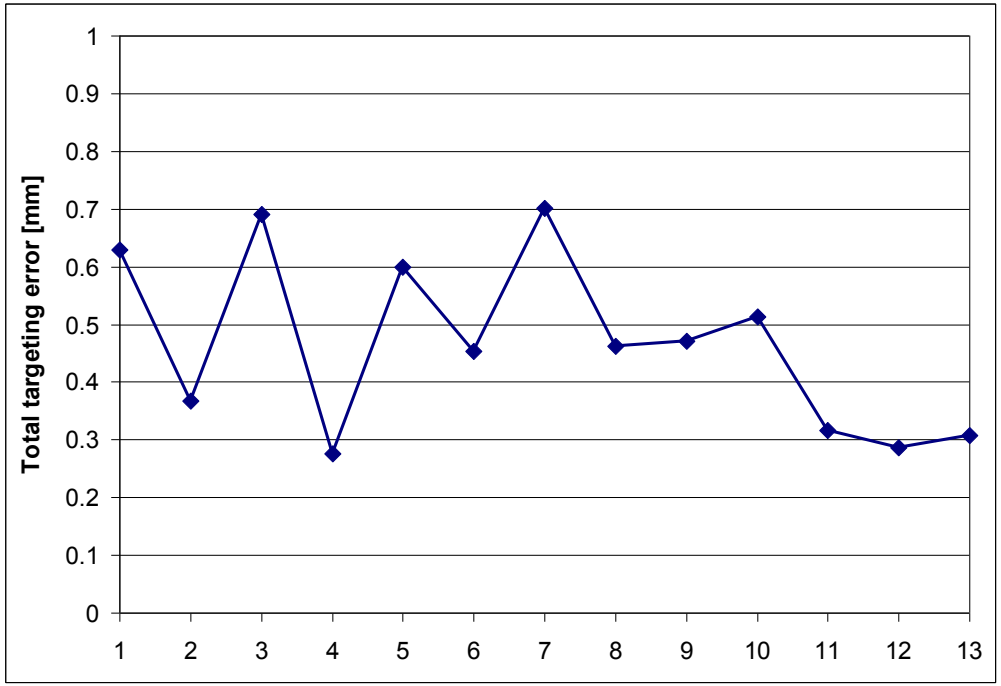
E2E Test Results

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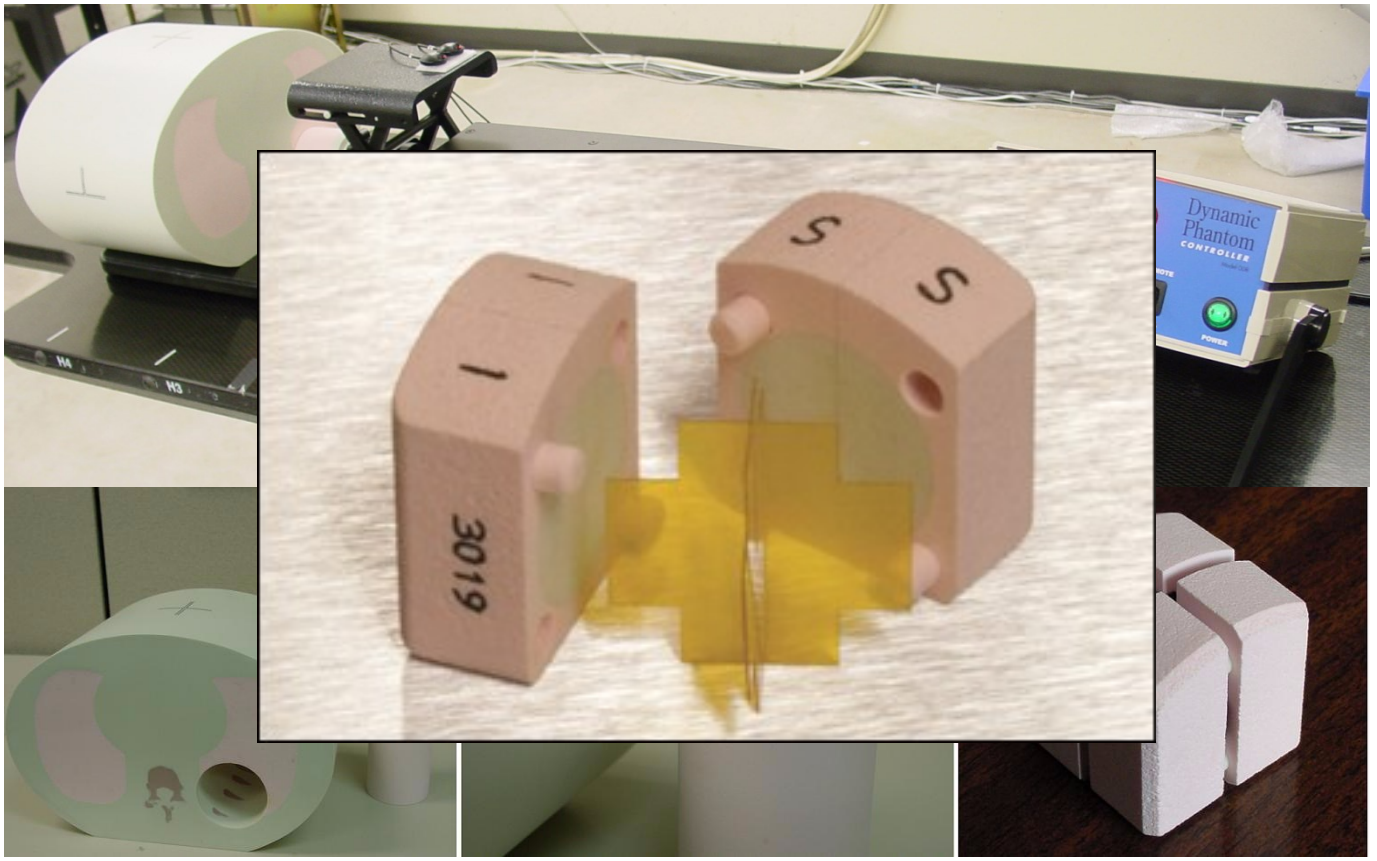
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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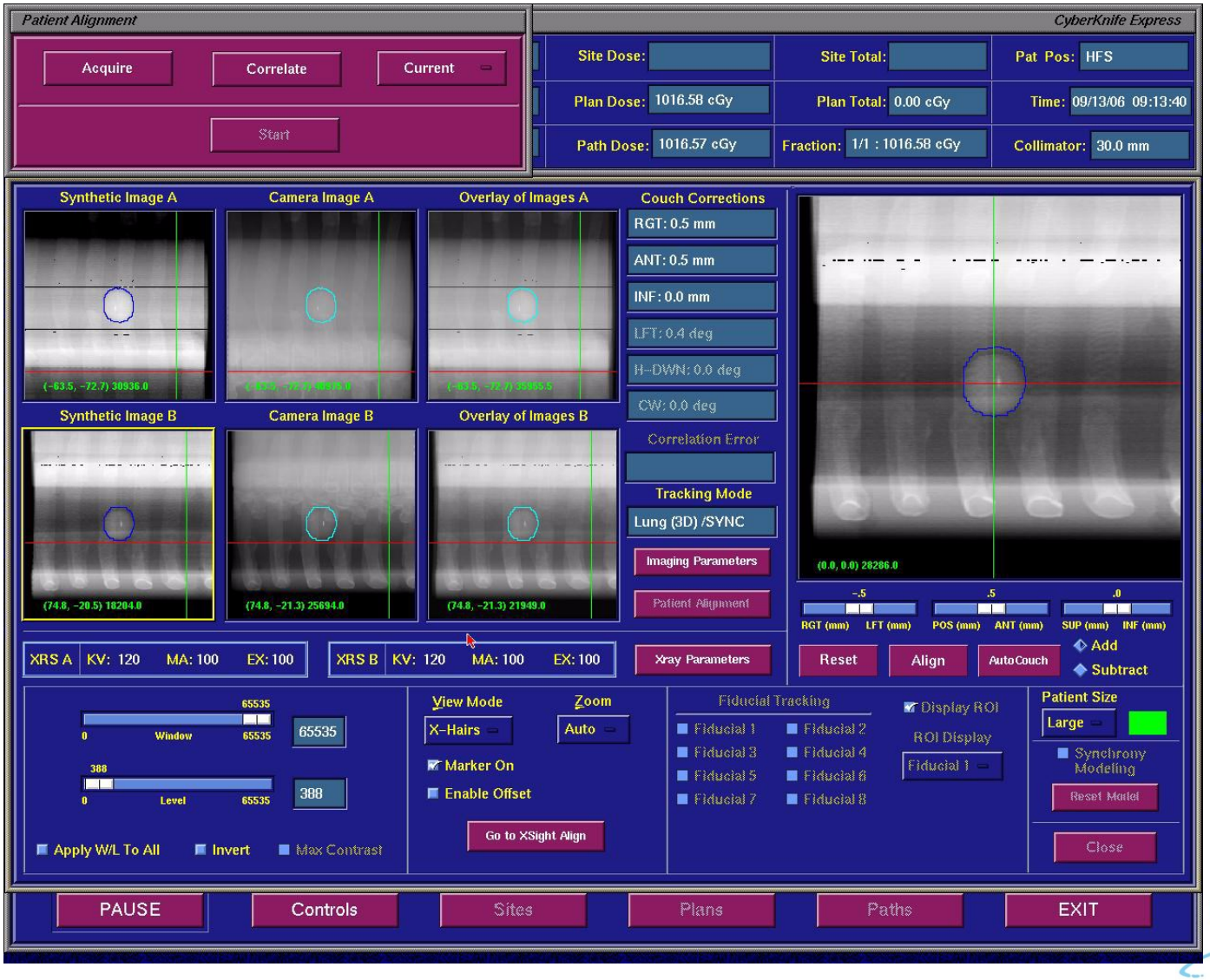
Treatment Delivery



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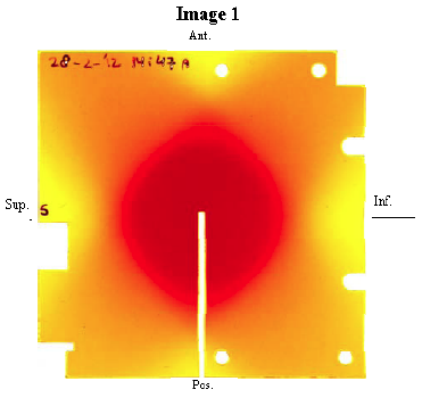
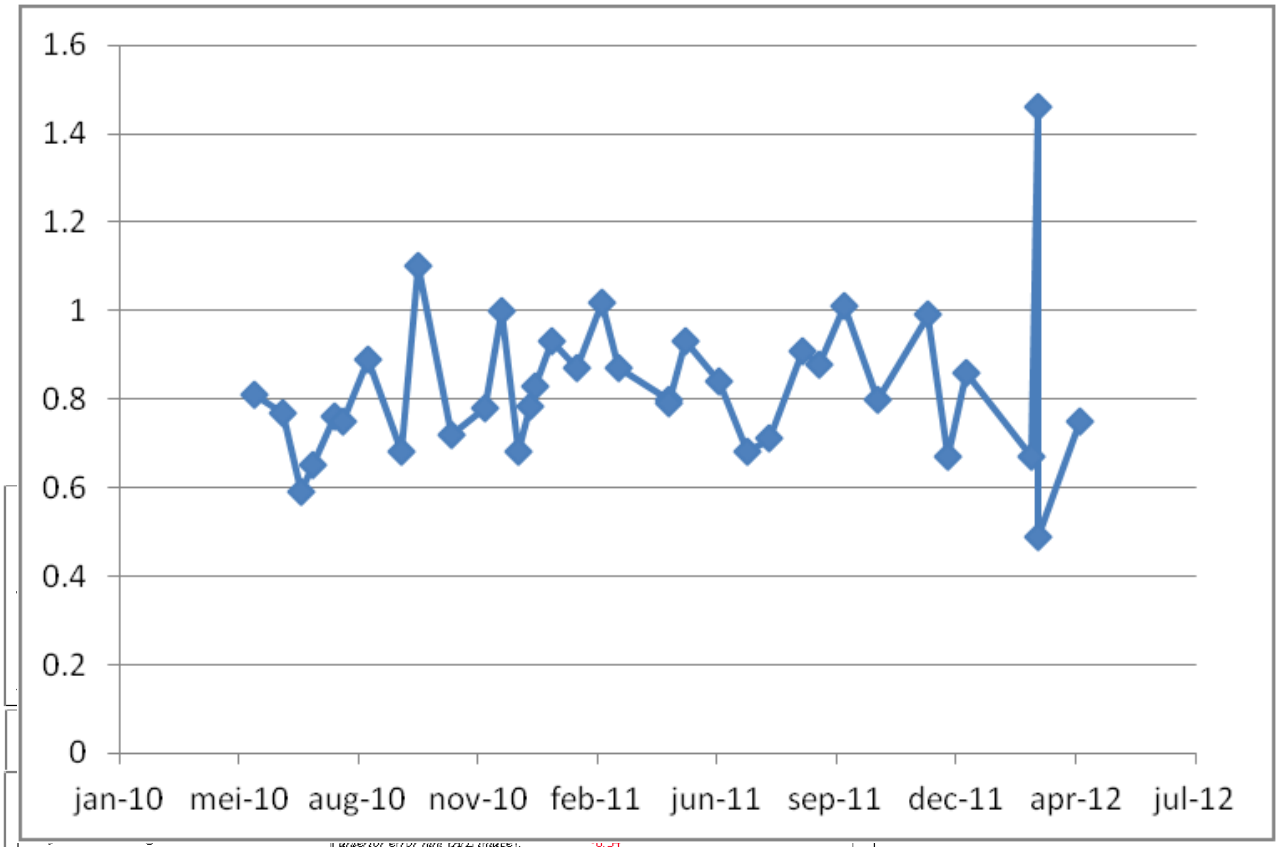
Analysis of Tracking Error





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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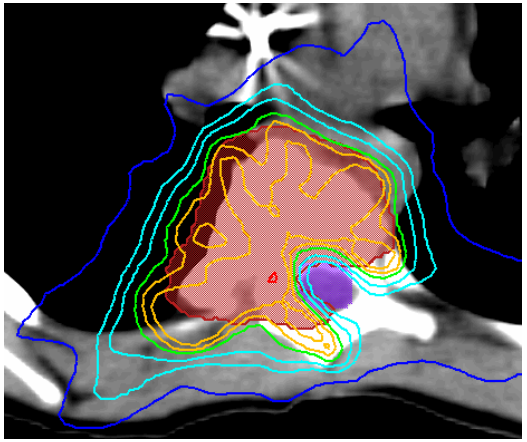
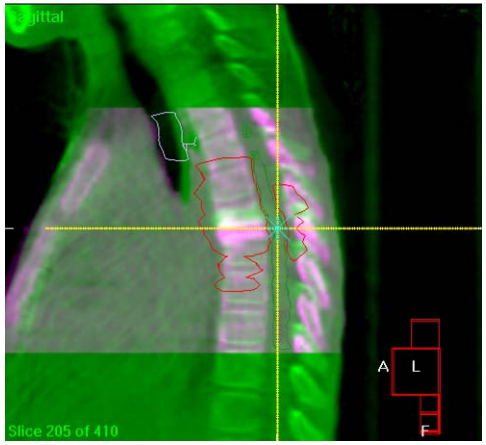
Stereotactic body radiotherapy for re-irradiation





Matthias Guckenberger

UniversityHospital Zurich

Questions

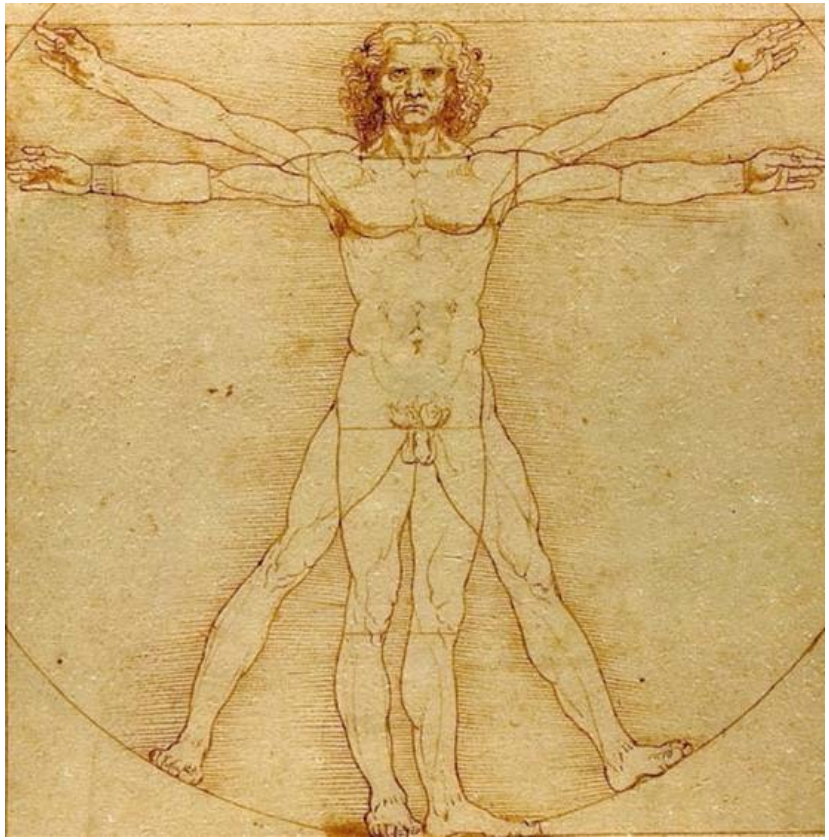
Which answer is **not** correct

1. Deformable image registration might help to minimize uncertianties due to different patient positionings
2. Most animal and clinical studies suggest substantial recovery of the spinal cord
3. Spinal cord tolerance needs to consider the interval between the 2 RT series and the total dose of the highest RT series
4. Re-irradiation of spinal metastases using SBRT is most frequently performed with single fraction radiosurgery

Overview

- Normal tissue tolerance of re-irradiation
- SBRT for re-irradiation of
  - Spinal metastases
  - Thoracic tumors

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 complications**

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.

Normal tissue tolerance

Repair of radiotherapy induced damage

Re-irradiation tolerance and recovery

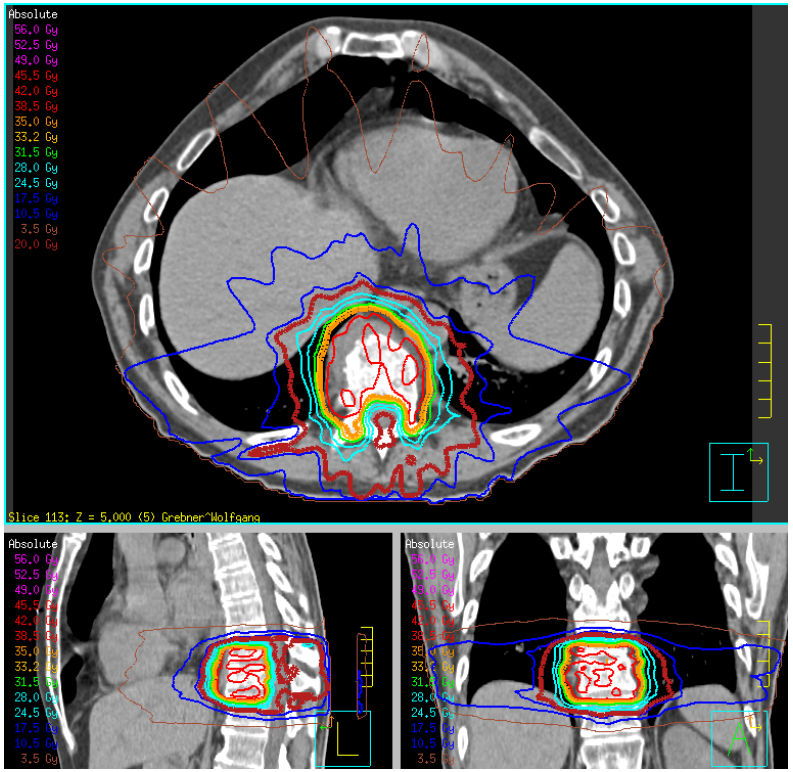
Skin & mucosa	Small intestine	Mesechymal	Bone
Full – partial	Partial	Partial	Partial

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



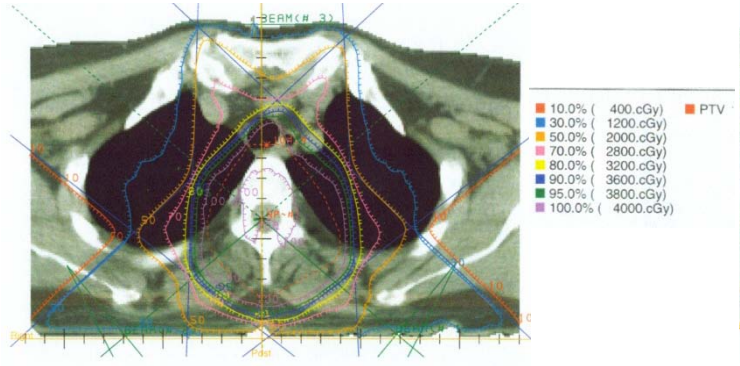
Case example: re-irradiation for verterbral metastasis

- 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

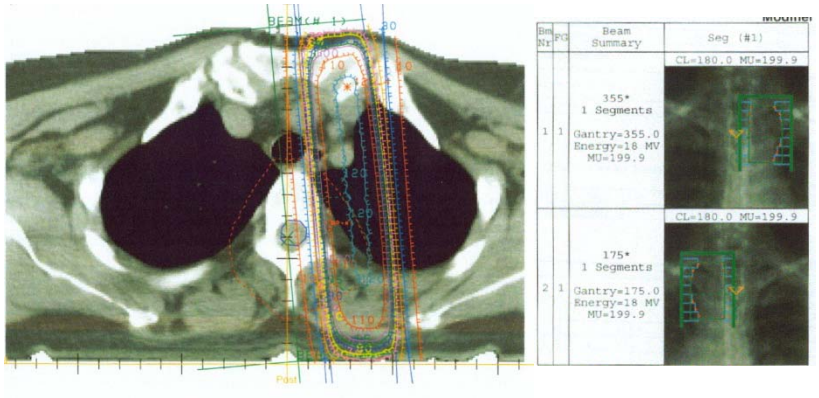
- Developed breast cancer in 2002 and bone metastases in 2007
- In 2008, a palliative radiotherapy of thoracic vertebras 2-4 was performed with a total dose of 40Gy
  - 20 Gy were delivered using posterior wedged fields
  - 20 Gy were delivered using AP/PA fields with sparing of the spinal cord

Case example: re-irradiation for verterbral metastasis

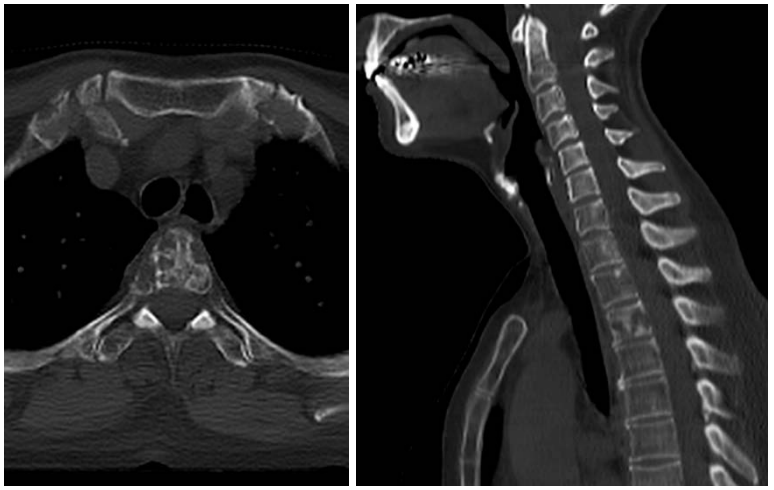
20 Gy wedged fields



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



Case example: re-irradiation for verterbral metastasis

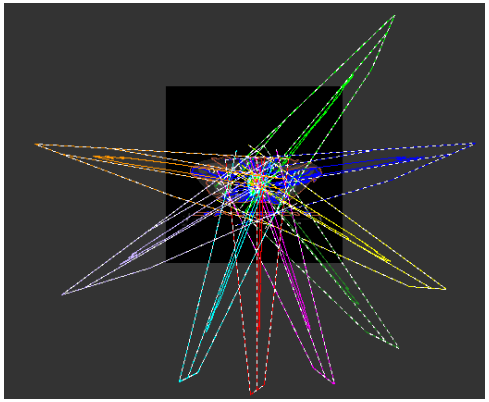
Assumption of spinal cord tolerance:

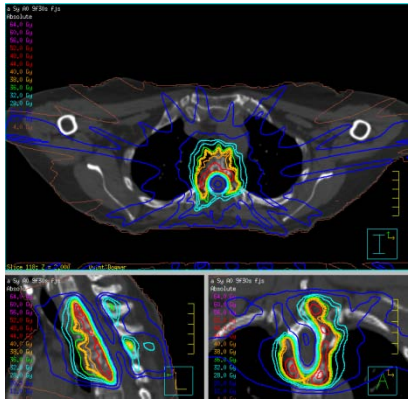
40Gy	-31 years
20 + 2 Gy	-2 years
62Gy	physical dose ->
30Gy	**residual „damage“**

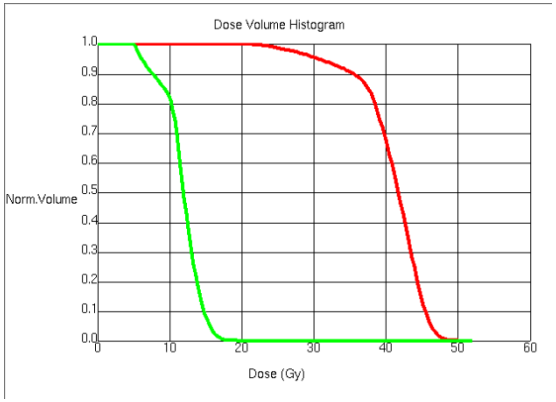
➢ **Maximum dose of 20Gy in 15 fractions**

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

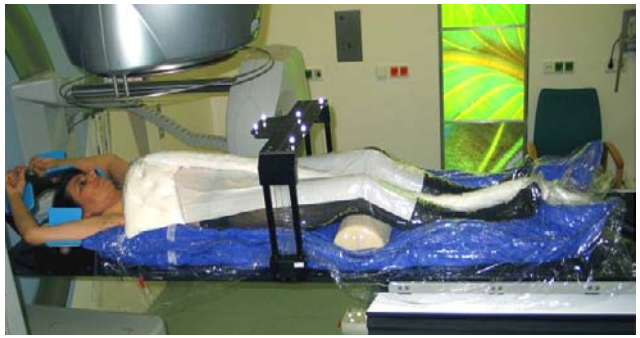
Case example: re-irradiation for verterbral metastasis

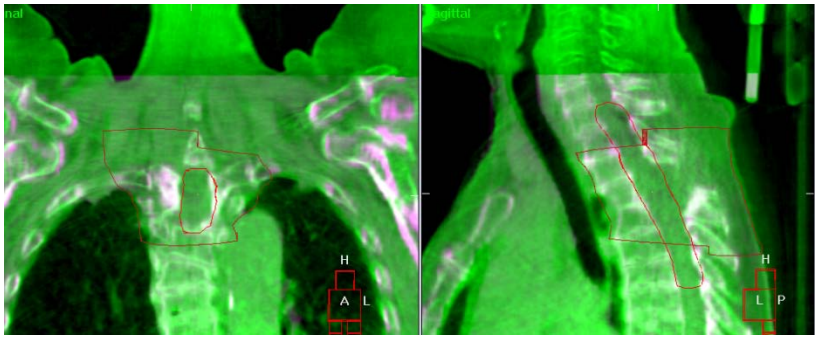






Target definition: only affected parts of the vertebrae included into TV
IMRT planning: 40Gy in 15 Fx with SC_{max} 20Gy





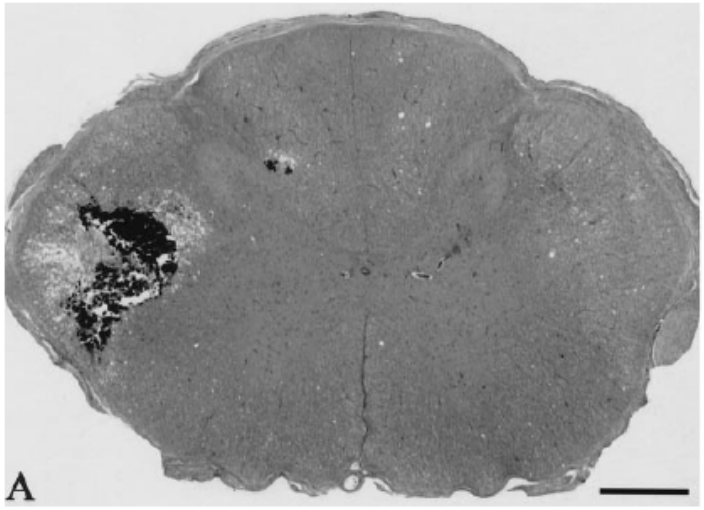
Immobilization: double vacuum BodyFIX
IGRT: daily using CBCT

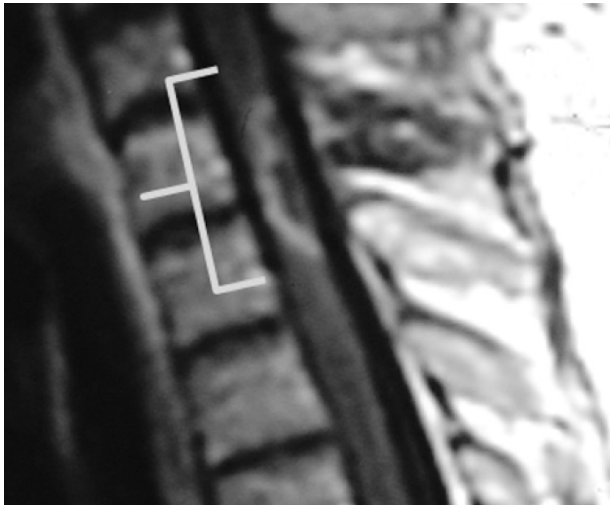
Clinical practice of SBRT for re-irradiation of spinal metastases

1. Spinal cord tolerance

2. Dose and fractionation

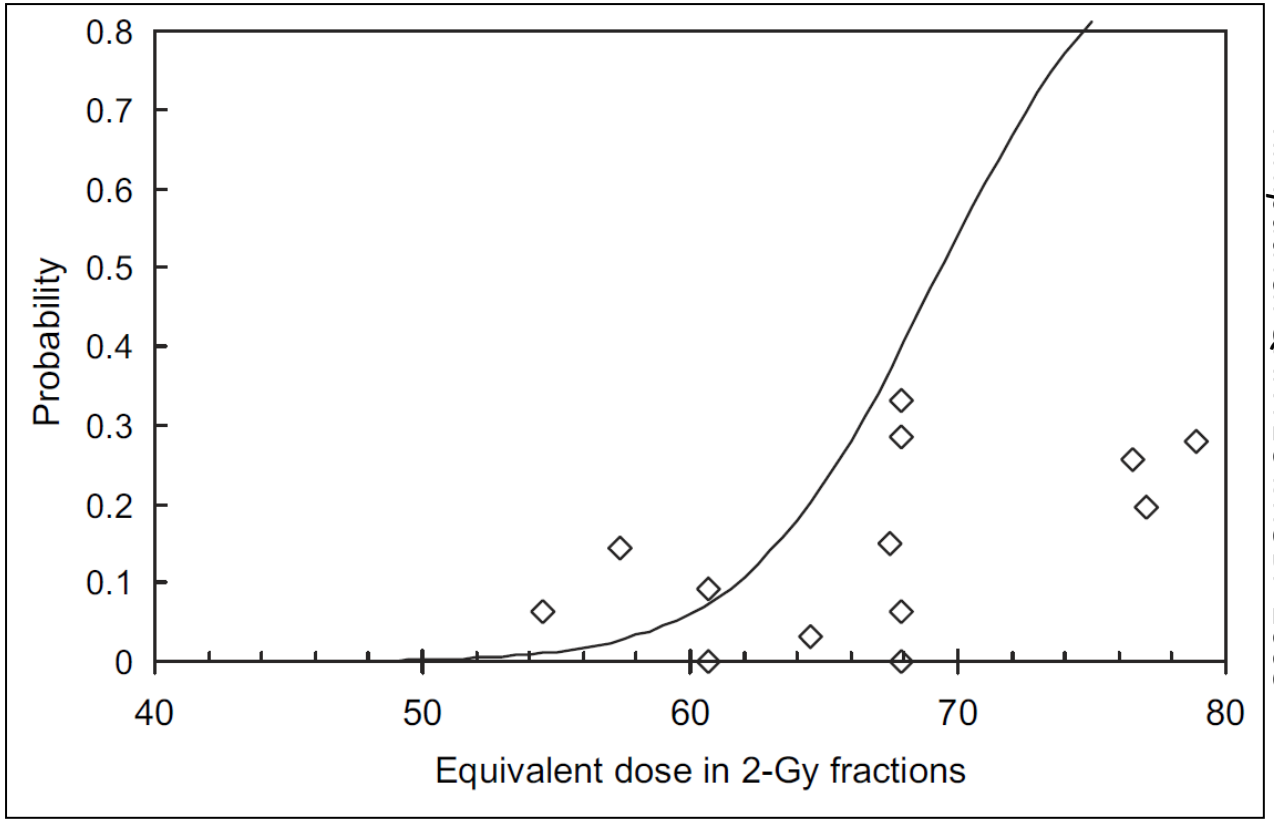
Radiation induced myelopathy





- 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 ~ 1-2Gy

Spinal cord tolerance – reirradiation: Animal studies

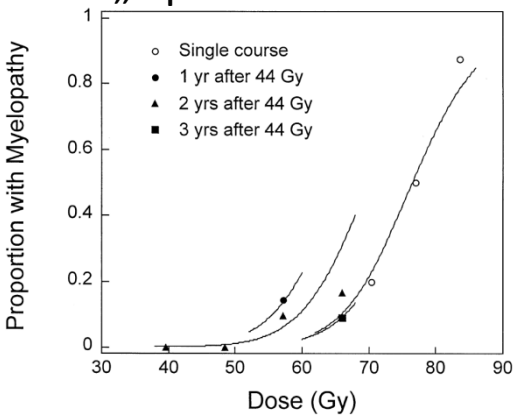
56 Rhesus monkeys, SFD 2.2Gy to 44Gy

Reirradiation

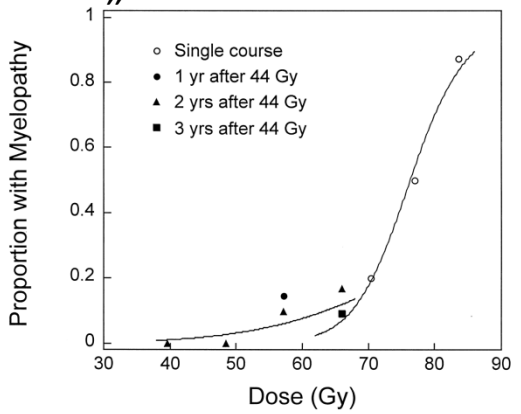
- 57.2Gy after 1 and 2 years
- 66Gy after 2 and 3 years

➢ **4 / 45 animals developed RMP**

„Optimistic“ model



„Pessimistic“ model



Ang IJROBP 2001

Optimistic model:

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

Conservative model:

➢ Recovery of 61%

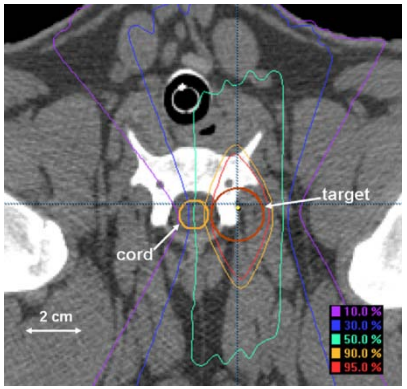
Spinal cord tolerance – reirradiation: Animal studies

26 minipigs, uniform 30Gy in 10 Fx

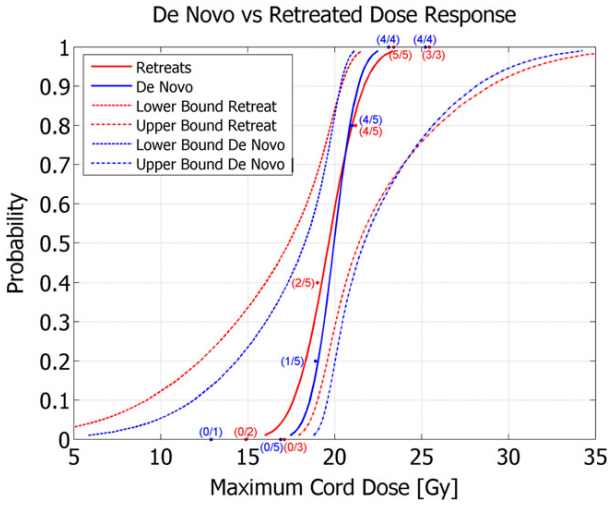
Reirradiation after 1 year:

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

➢ **ED_{50} of 19.7Gy**

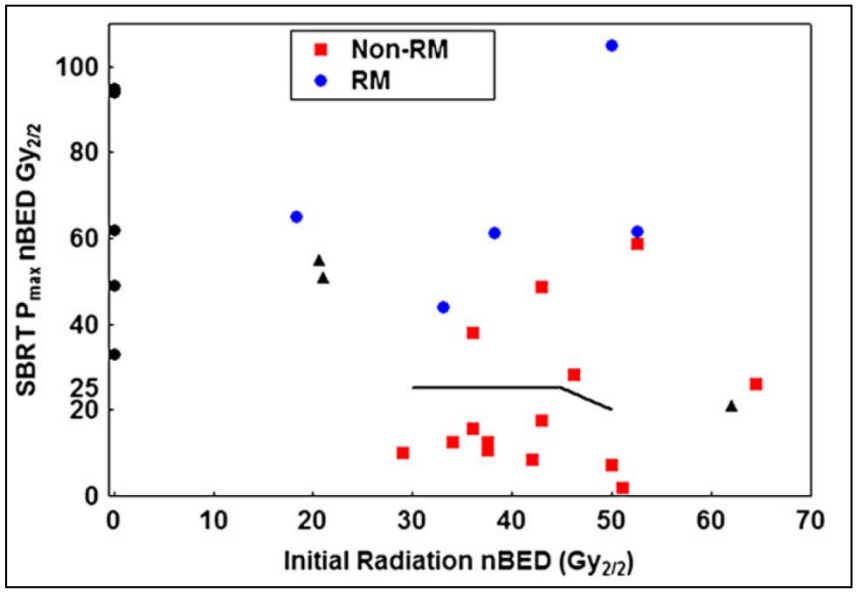


Medin IJROBP 2011



- ➢ Identical SRS tolerance as in the primary situation
- ➢ Full recovery of 30Gy in 10 Fx within 1 year

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



Sahgal IJROBP 2010:

Case-control study:

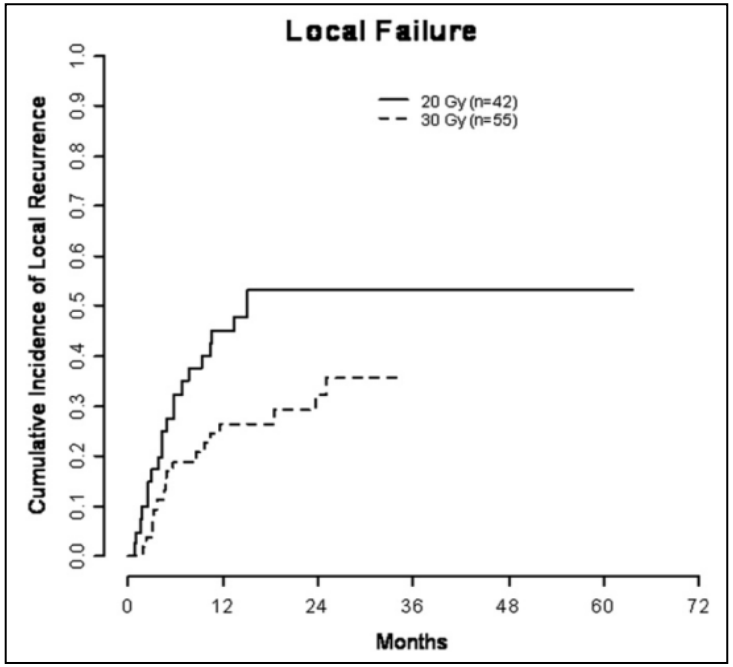
- 5 cases of RM after SBRT
- Thecal sack as OAR
- Maximum dose to thecal sack
- 2Gy equivalent with α/β=2Gy

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 fractions, 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%

SBRT for re-irradiation (part 2)

Eric F. LARTIGAU

Academic Radiotherapy Department

Centre Oscar Lambret, Lille, France

Salvage radiotherapy

Palliative versus Curative ?

Head & Neck: A model ?

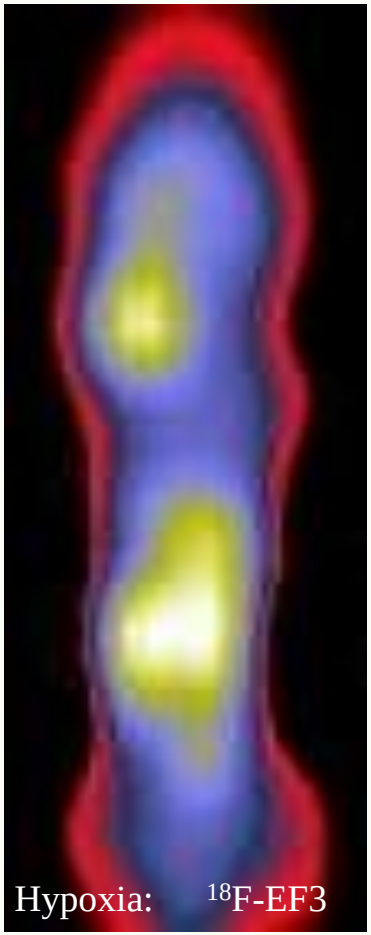
Recurrence and second (3rd…) primary : 30 - 60% patients

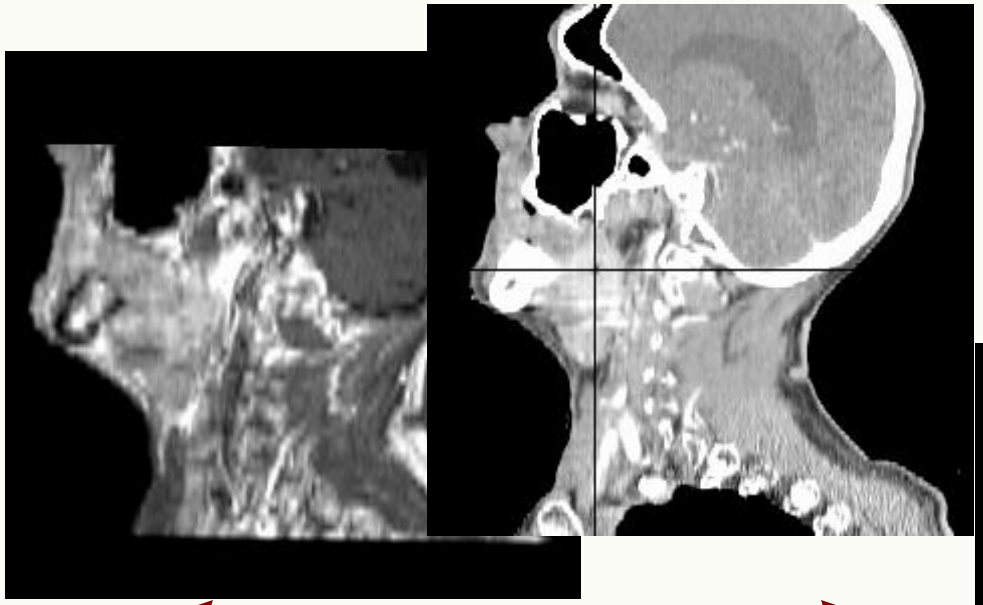
Mostly irradiated area (80%)

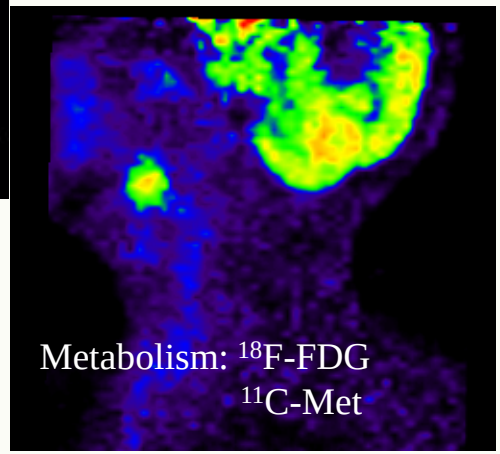
Complex strategy

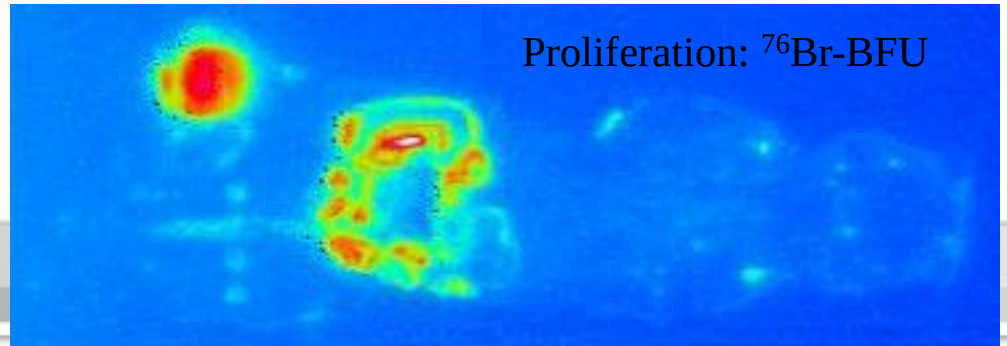
Cure ???

Recurrences : the target ?









Recurrences : the strategy

SALVAGE SURGERY

Reference treatment

In < 25% recurrences

Local control : 30-50%

Temam et al. Head&Neck 2005

BRACHYTHERAPY

Alternative to surgery

< 10 %

Local control : 40-60%

OS at 5years : 15-30%

Peiffert et al. IJROBP 1994

Recurrences : if operable

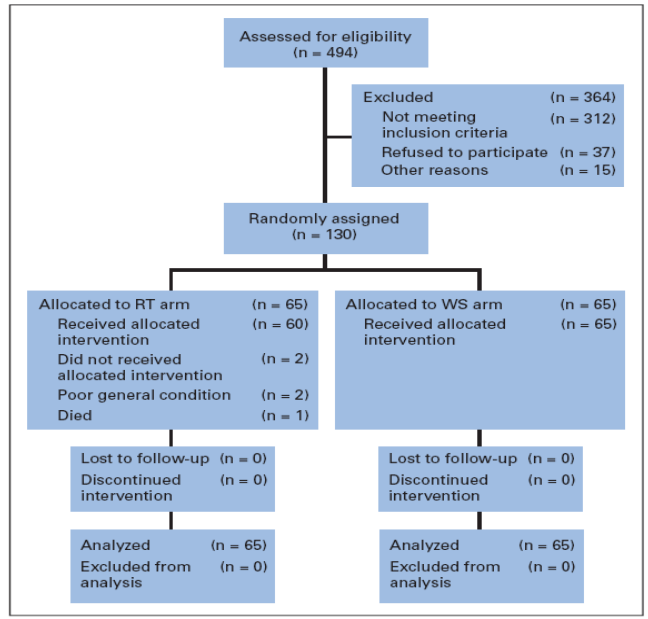


Fig 1. CONSORT diagram. RT, full-dose reirradiation combined with chemotherapy; WS, "wait and see" approach.

Concomittant post op RT-CT

GETTEC-GORTEC 99-01 phase III

130 patients (on 494 screened)

<u>SALVAGE SURGERY :</u> 39% N+, 29% + margins, 55% E+, neural….

<u>RANDOMISATION</u> : Follow up vs RT-CT (60Gy/11w 3D + CT type Vokes)

Toxicity :

Acute : 30% Gr 3-4

At 2 years : 39% versus 10% Gr 3-4

5 toxic death (8%)

impact on LRC & DFS

No impact on OS

Janot et al. JCO 2008

Recurrences : if operable

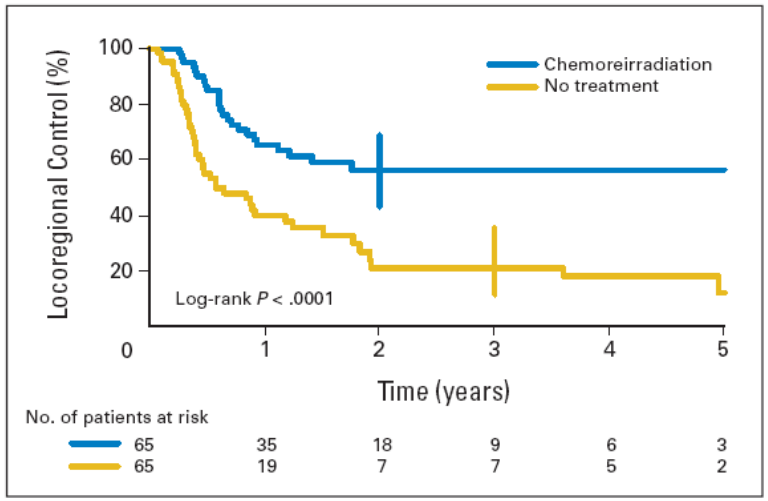


Fig 2. Locoregional control. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

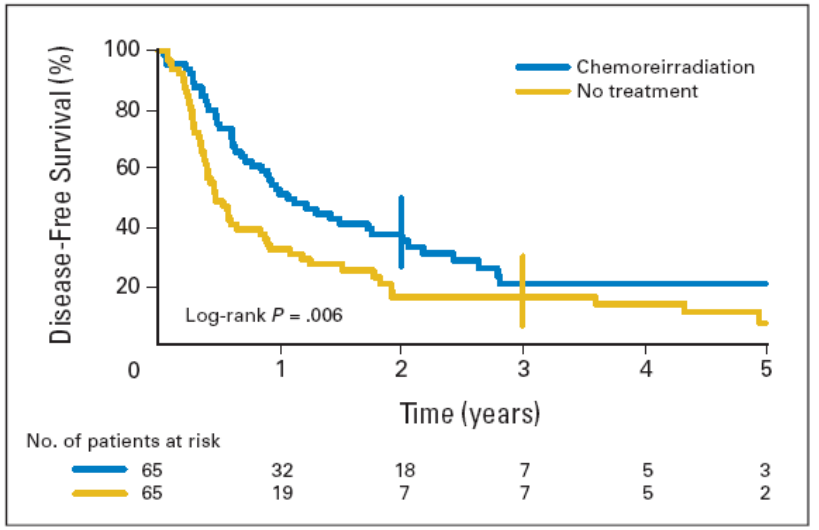


Fig 3. Disease-free survival. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

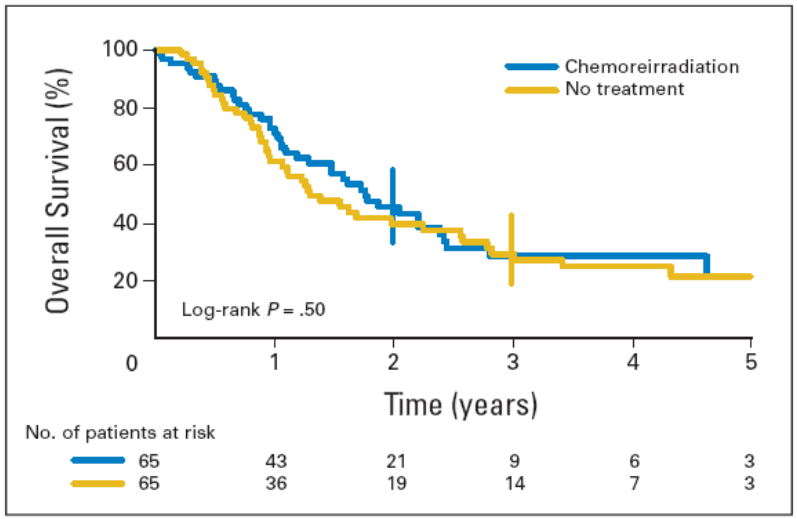


Fig 4. Overall survival. Large tick marks represent the 95% CI of the point estimates. Chemoirradiation, reirradiation plus concomitant chemotherapy.

Causes of deaths

	RT-Chem	W and S
Loco-regional recurrence	**21**	**34**
LR rec + 2nd primary	0	2
Second primary	4	1
Isolated metastasis	6	3
Toxicity	**5 ***	**0**
Intercurrent disease	2	3
Unknown	2	2
TOTAL	**40**	**45**

*** 3 acute toxicity (< 6 months) : 2 fatal infections and one cataclysmic hemorrageae**

2 toxicity : one extensive mucosal necrosis (13 months) + one laryngeal oedema (16 months)

No toxic deaths after 2 years

Recurrences : not operable !!!

Chemotherapy/targeted therapies

- Response rate 10-35%
- Median survival 5-9 months
- CDDP,
- Targeted therapy (EGFr, VEGF…)

Soulieres *et al JCO 2004*

Vermorken *et al. 2008*

Reirradiation +/- CT ???

- New drugs
- New irradiation techniques ?
  - 3D
  - IMRT
  - STEREOTAXIE

	n	Treatment	Toxicity	Median OS	LRC/OS 2 ans
De Crevoisier 1998	169	66 Gy / OHurea-5FU 60 Gy/ CDDP-5FU-myto	13% acute 12% late 3% bleeding	10 m	11% / 21%
Kramer 2005	38	60 Gy / CDDP-paclitaxel	16% acute 29% late	12,4 m	37% / 35%
Salama 2006	66	66-74 Gy / 3 agents de CT	13% late 5% bleeeding	11 m	36% / 11%
Lee 2007	69	60 Gy 70% IMRT 70% CT conco	4% neuro	15 m	19% / 12%
Langer 2007	99	60 Gy / CDDP-paclitaxel	28% acutes, 9% DC	12,1 m	19% / 26%
Spencer 2008	81	60 Gy / OHurea-5FU	23% acutes	8,2 m	NR / 16%
Sulman 2009	54	66 Gy 100% IMRT 66% CT conco	32%acute	25,2 m	58% / 54%

Recurrences : stereotactic RT

NO COMBINED TT

	n	Doses	BED Gy	CT	toxicity	CLR 2 year	OS 2 year
Voynov et al 2006	22	4x5Gy 6x5Gy	28-48	no	4,5% Gr 3 no Gr 4	26%	22%
Roh et al 2009	35	3x10Gy 3x13Gy 5x5Gy 5x8Gy	80-130 40-90	no	30% Gr 3 3 ORN 2 necrosis 2 trismus	52%	30%

Protocol CyberKnife

46 patients (32 H / 14F) june 2007 to december 2008

Median Age : 58 years (24-80)

Eligibility

Recurrence or second primary

Lesion ≤ 6 cm non operable

OMS ≤ 2

Int J Radiation Oncol Biol Phys, Vol. 84, No. 1, pp. 203-209, 2012.

CKNO
CyberKnife® Nord Ouest

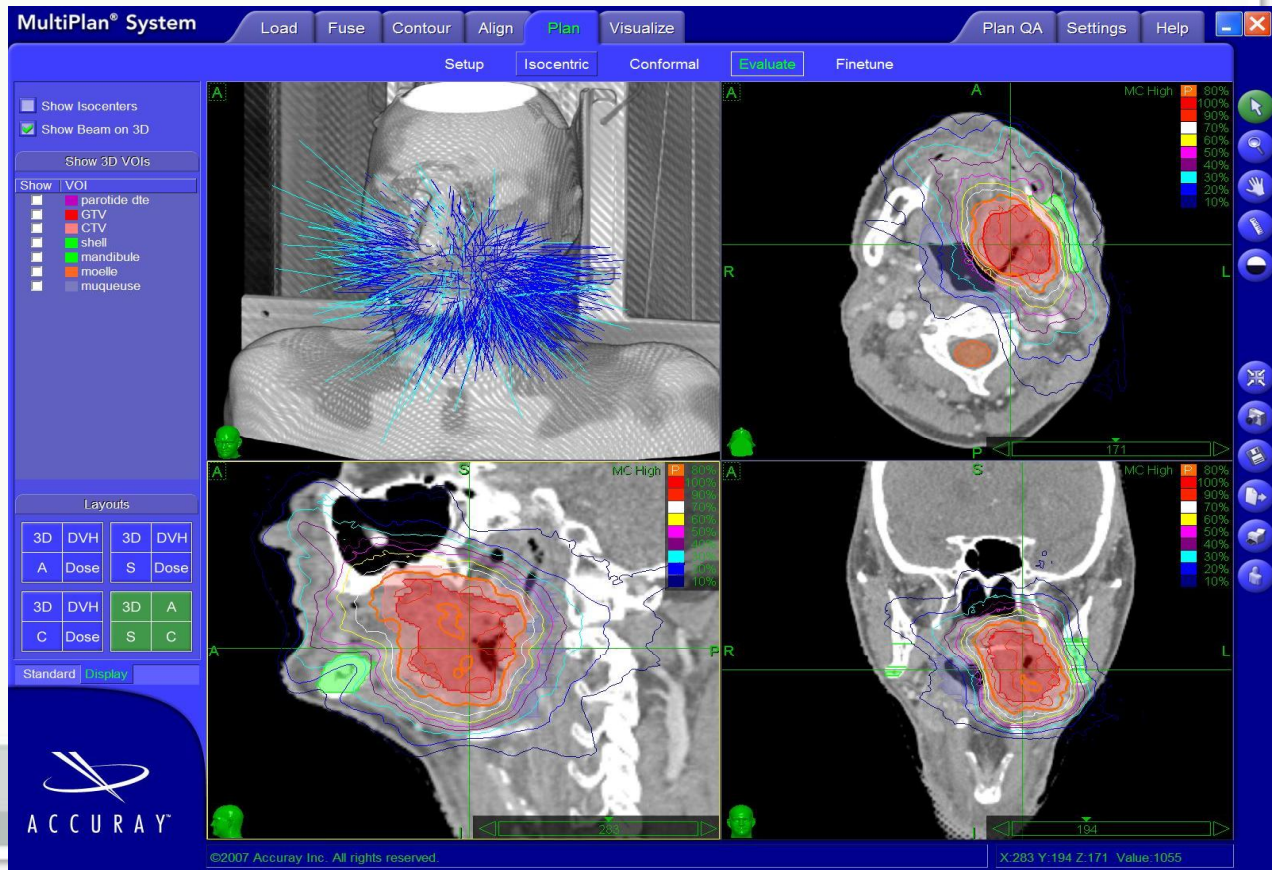
CKNO RERT protocol

36 Gy in 6 fractions / 12 days

Isodose 80% : 95% of PTV

Cetuximab (400 +250 mg/m² x 4) for SCC

Volume GTV cm^3	Median **15**
Volume PTV cm^3	Median **43,5**
Beams	Median **156** (103-225)
Duration	Median **48 min** (28-100)



MultiPlan™ System

Load | Fuse | Contour | Align | Plan | Visualize | Plan QA | Settings | Help

Setup | Isocentric | Conformal | Evaluate | Finetune

Evaluation

- Contour correction
- High resolution

Calculate

Prescription

Rx Dose (cGy) 3659.66

Rx (%) 72

Prescribe

Reference Point

- Use max. dose point

Dose (cGy) 5000.00

Point: Goto >>

15.47,-229.28,213.60

Set to Cross-Hair Point

Save Plan

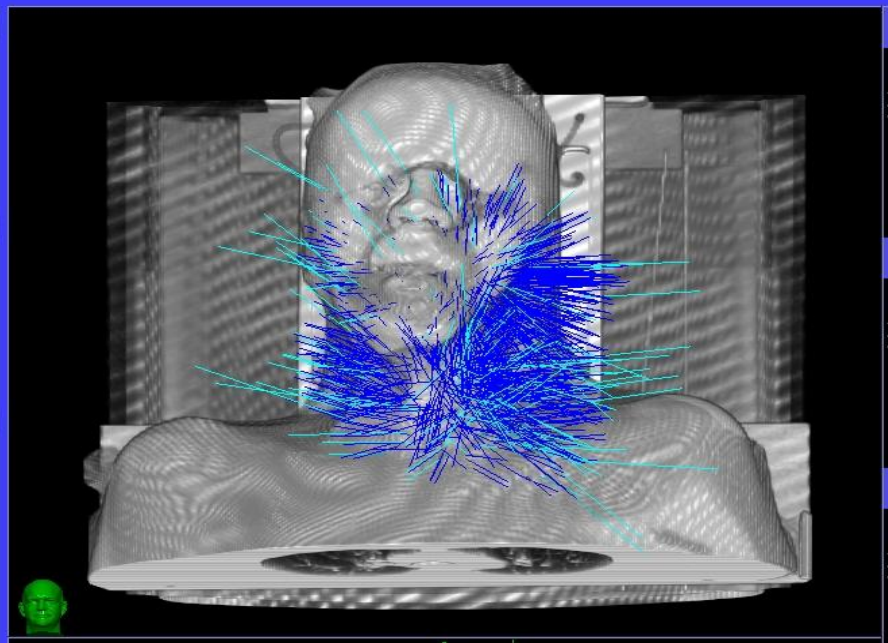
Save Plan

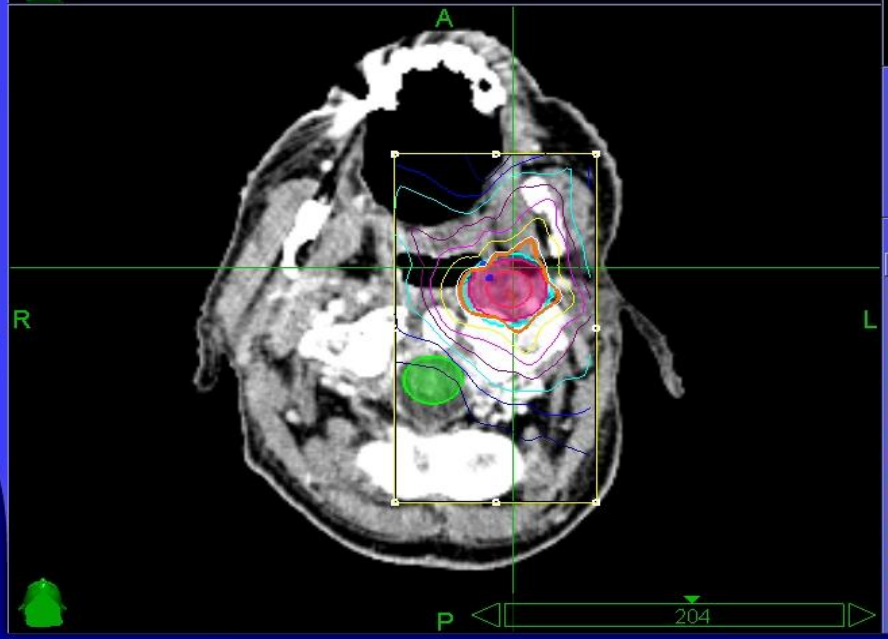
Standard | Display

Patient

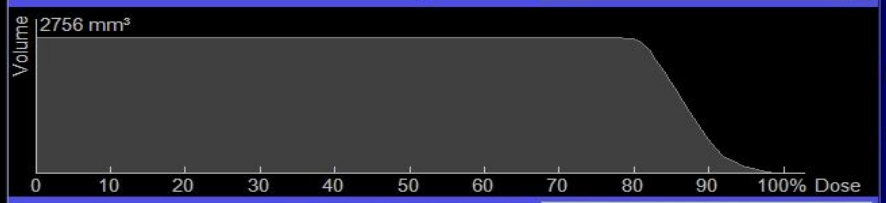
Rx

72%, 3659.66 cGy

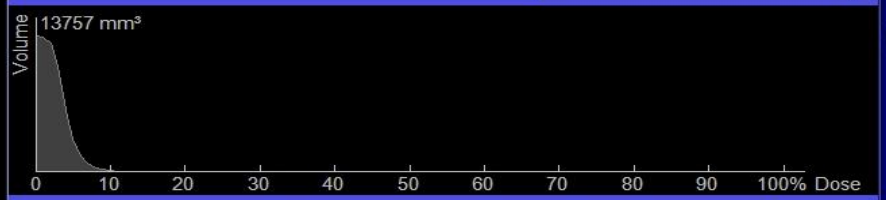




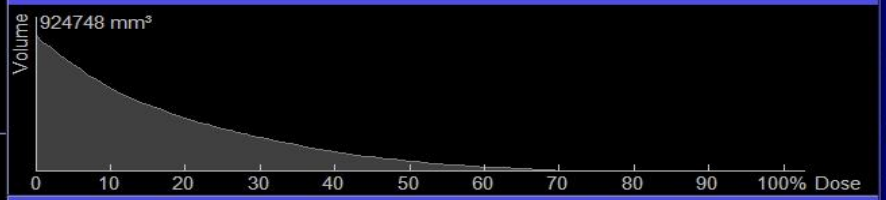
Target Volume: GTV1



Critical Volume: moelle



Soft Tissues



Nodes	47	Total MU	40667.80
Beams	132	Min. MU	31.13
Max. Dose(cGy)	5000.00	Max. MU	1089.42

Dose Statistic Table

VOI	Min(cGy)	Max(cGy)	CI	nCI	HI	Coverage
All Target Regic	2054.07	5000.00	1.08	1.45	1.39	74.17%
CTV1	3354.08	5000.00	5.08	5.15	1.39	98.57%
PTV1	3060.09	5000.00	3.82	4.15	1.39	92.23%
GTV1	3911.50	5000.00	20.33	20.33	1.39	100.00%
shell 1	2008.44	3740.75	n/a	n/a	n/a	n/a
CTV2	2407.36	4426.49	1.68	2.08	1.39	80.68%
PTV2	2054.07	4426.49	1.50	2.18	1.39	68.88%
GTV 2	3242.31	4426.49	3.90	3.93	1.39	99.28%
spine	5.43	4408.05	n/a	n/a	n/a	n/a
shell 2	1022.01	3521.52	n/a	n/a	n/a	n/a
tronc	198.01	1110.45	n/a	n/a	n/a	n/a
moelle	31.13	743.54	n/a	n/a	n/a	n/a
oeil g	0.00	0.00	n/a	n/a	n/a	n/a
oeil dt	0.00	0.00	n/a	n/a	n/a	n/a
larynx	10.44	4020.02	n/a	n/a	n/a	n/a

X:274 Y:180 Z:204 Value:899

Acute toxicity

Mucousitis	Global Pop.	CK+Erbitux	CK alone
Gr 1	38% (17/45)	46,5%(13/28)	23,5%(4/17)
Gr 2	22% (10/45)	25% (7/28)	17,5%(3/17)
Gr 3	4,5% (2/45)	7% (2/28)	0% (0/17)
None	35,5% (16/45)	21,5% (6/28)	59%(10/17)
NE	1	1	0

Late toxicity

Mucosal necrosis	4	> 6 months

CK Group

Mucosal necrosis	5	> 6 months
Osteonecrosis	1	18 months

CK + Erbitux Group

Tumour response

Response	CK	CK+Erbitux	Total
RC	1	8	9
RP	6	5	11
SD	4	6	10
PD	1	0	1
NE (F Up)	*5*	*10*	*15*
	n=17	n=29	n=46

64,5%

95%

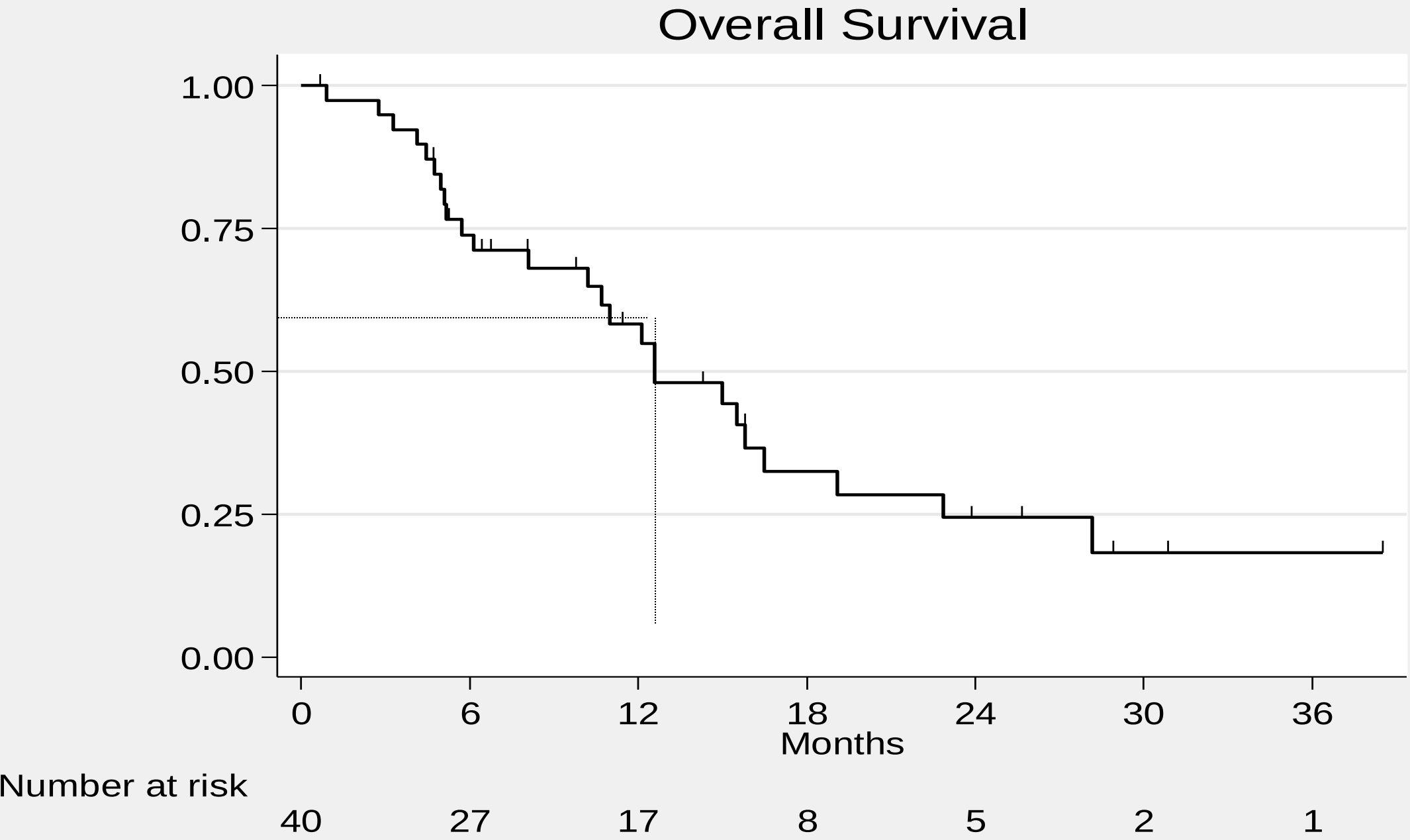
F. Up. > 6 months

Tumour response (2)

On 31 patients

Tumor size	CR	PR	SD
< 30 mm	8	3	6
> 30 mm	1	8	4
PTV Volume			
< 43,5 cm^3	7	3	5
> 43,5 cm^3	1	7	5

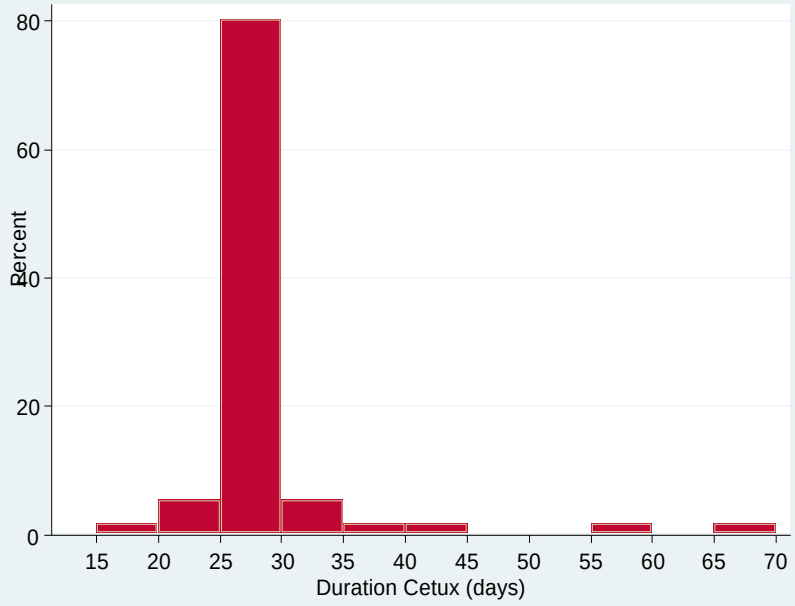
Int J Radiat Oncol Biol Phys. 2012 Sep 1;84(1):203-9.

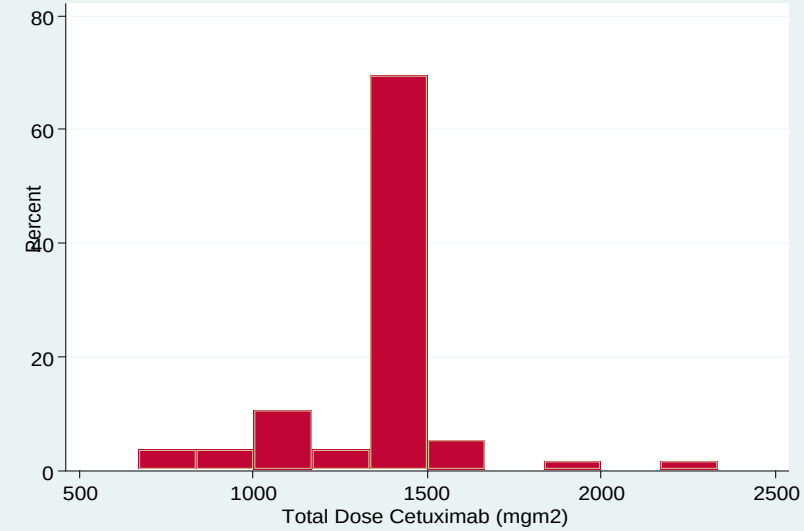


Multicentric phase II
Lille, Nancy & Nice

Patients	N = 56
Sex n (%)	
M	43 (75.4)
F	14 (24.6)
Age,	60 (42 – 80)

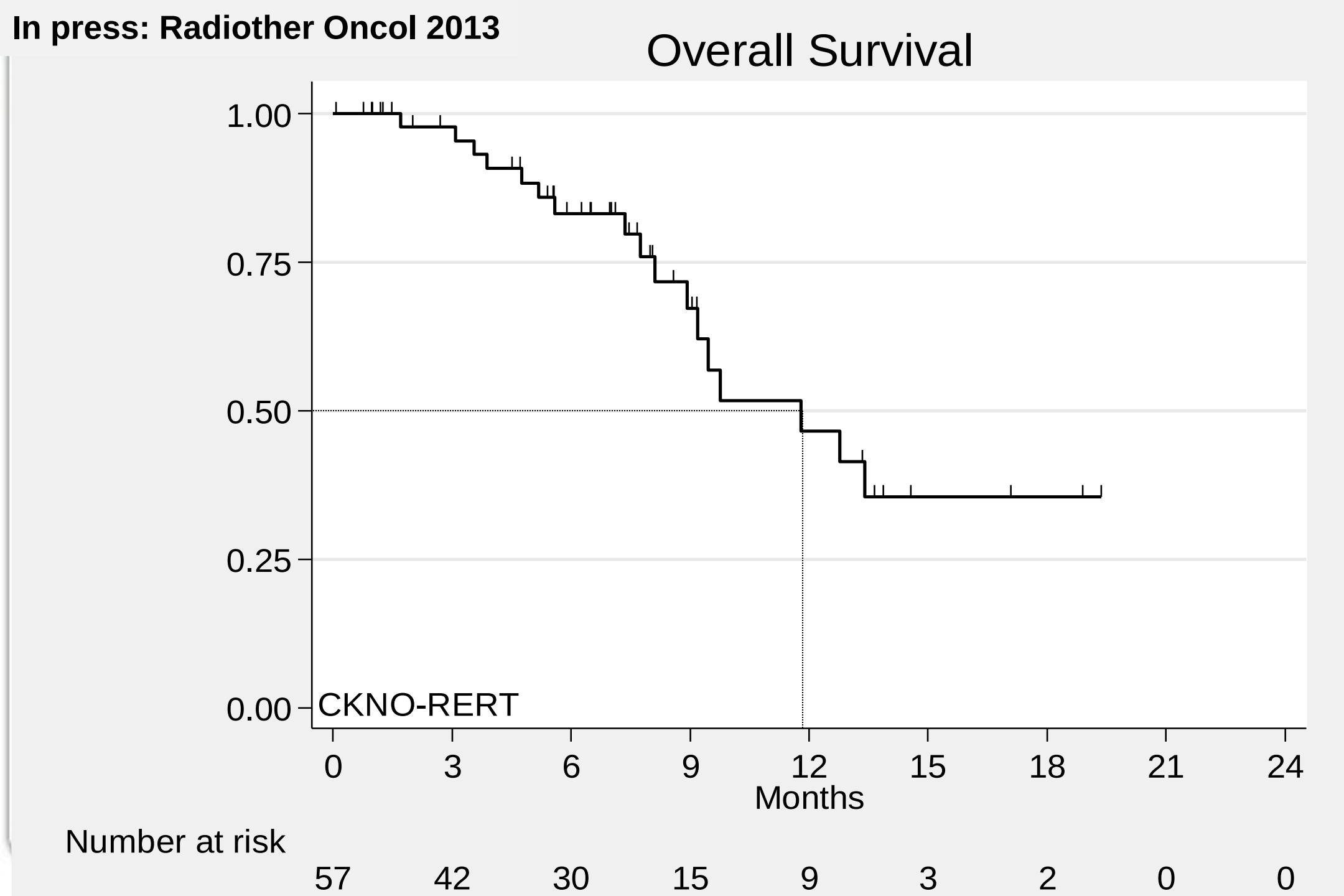
Dose and duration	N=56
Duration (days) Median (range)	28 (15-70)
Total dose cycle 1 (mg/m²) Median (range)	400 (307-426)





77 % response at 3 months

In press: Radiother Oncol 2013



Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e263–e268, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.02.054

CLINICAL INVESTIGATION **Head and Neck**

A RETROSPECTIVE COMPARISON OF ROBOTIC STEREOTACTIC BODY RADIOTHERAPY AND THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR THE REIRRADIATION OF LOCALLY RECURRENT NASOPHARYNGEAL CARCINOMA

GOKHAN OZYIGIT, M.D., MUSTAFA CENGIZ, M.D., GOZDE YAZICI, M.D., FERAH YILDIZ, M.D., MURAT GURKAYNAK, M.D., FARUK ZORLU, M.D., DEMET YILDIZ, M.S., SEFIK HOSAL, M.D., IBRAHIM GULLU, M.D., AND FADIL AKYOL, M.D.

Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey

Table 2. Treatment characteristics of 24 patients receiving stereotactic body radiotherapy

	Median	Range
Maximum dose within PTV (Gy)	39	36–50
Prescription isodose	77.5%	63%–85%
Number of beams	246	153–369
Conformity index	1.58	1.19–2.3
Homogeneity index	1.29	1.18–1.59
Collimator size	20 mm	12.5–40.0 mm
Tumor volume	63.4 cc	26.3–170.4 cc

Abbreviation: PTV = planning target volume.

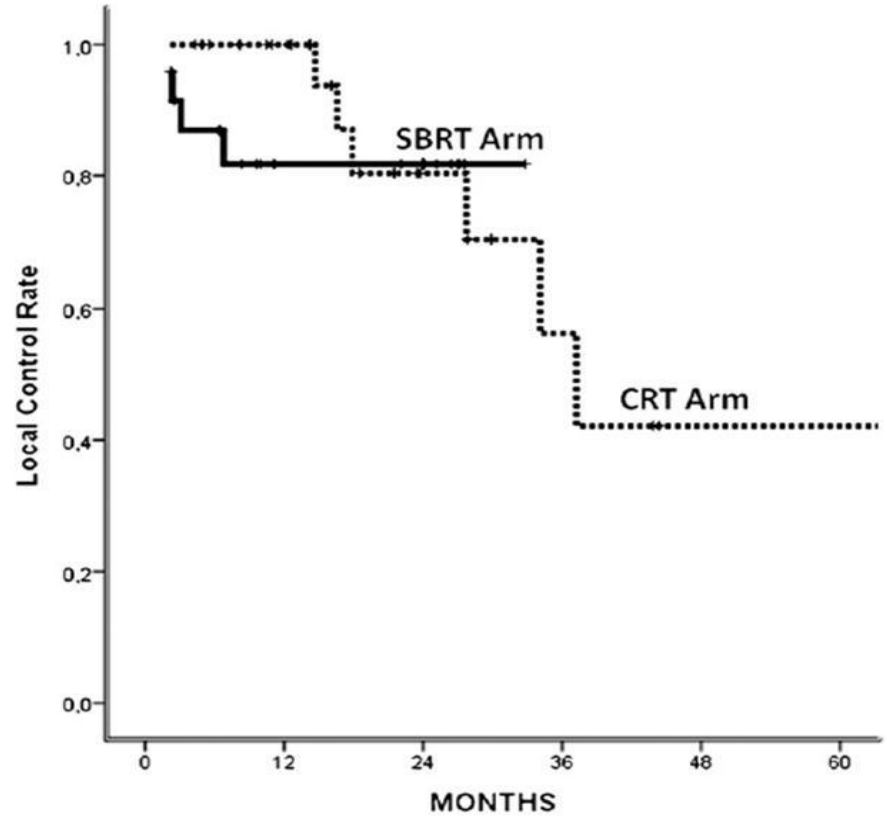


Fig. 1. Kaplan-Meier curves for the actuarial local control rates of the stereotactic body radiotherapy (SBRT) and three-dimensional conformal radiotherapy (CRT) arms.

WILEY ONLINE LIBRARY Head & Neck
Early View, Article first published online: 11 NOV 2011
Abstract | Full Article (HTML) | References | Cited By

ORIGINAL ARTICLE

STEREOTACTIC BODY RADIATION THERAPY FOR LOCALLY RECURRENT, PREVIOUSLY IRRADIATED NONSQUAMOUS CELL CANCERS OF THE HEAD AND NECK

John A. Vargo, MD,[1,2] Rodney E. Wegner, MD,[1] Dwight E. Heron, MD,[1,3]
Robert L. Ferris, MD, PhD,[1,3] Jean-Claude M. Rwigema, MD,[1] Annette Quinn, RN, MSN,[1]
Patricia Gigliotti, CRNP,[1] James Ohr, MD,[4] Greg J. Kubicek, MD,[1] Steven Burton, MD[1]

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Published online Month 00, 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21889

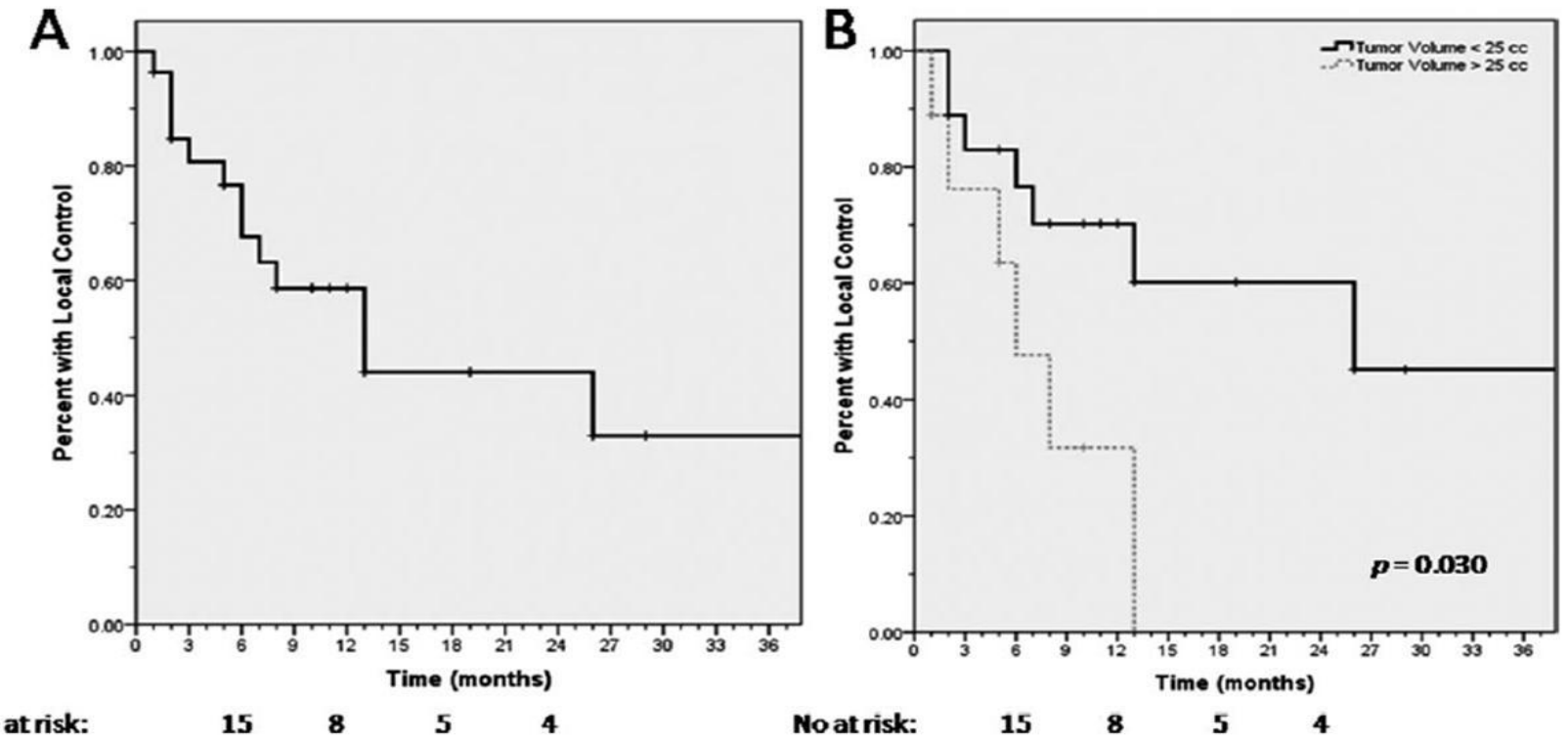

FIGURE 2. Kaplan–Meier plots of local control. (**A**) Actuarial local control for all patients following SBRT reirradiation. (**B**) Impact of tumor volume on local control, where tumors were stratified by planning target volumes using 25 mL as a cutoff (log rank, $p = .030$).

Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 5, pp. 1493–1500, 2009

0360-3016/09/$–see front matter
doi:10.1016/j.ijrobp.2008.12.075

CLINICAL INVESTIGATION Head and Neck

STEREOTACTIC BODY RADIOTHERAPY FOR RECURRENT SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: RESULTS OF A PHASE I DOSE-ESCALATION TRIAL

Dwight E. Heron, M.D., F.A.C.R.O.,* Robert L. Ferris, M.D., Ph.D.,† Michalis Karamouzis, M.D.,‡ Regiane S. Andrade, M.D.,* Erin L. Deeb, B.S.,§ Steven Burton, M.D.,* William E. Gooding, M.S.,|| Barton F. Branstetter, M.D.,†¶ James M. Mountz, M.D., Ph.D.,§ Jonas T. Johnson, M.D.,† Athanassios Argiris, M.D.,† Jennifer R. Grandis, M.D.,† and Stephen Y. Lai, M.D., Ph.D.†

Departments of *Radiation Oncology, †Otolaryngology, ‡Radiology, §Biostatistics, and ¶Biomedical Informatics, and ||Division of Medical Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA

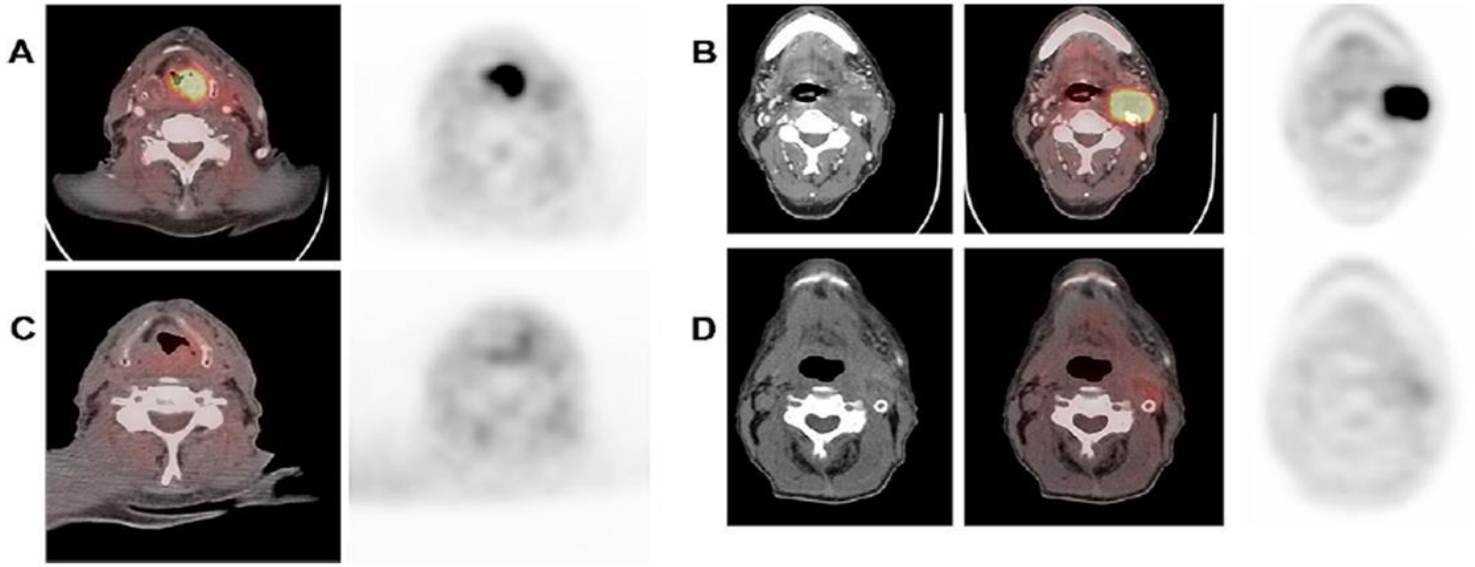

Fig. 1. Positron emission tomography–computed tomography (PET-CT) scans of recurrent squamous cell carcinoma of the head and neck: primary (A, C) and cervical (B, D) metastatic disease before (A, B) and after (C, D) stereotactic body radiotherapy.

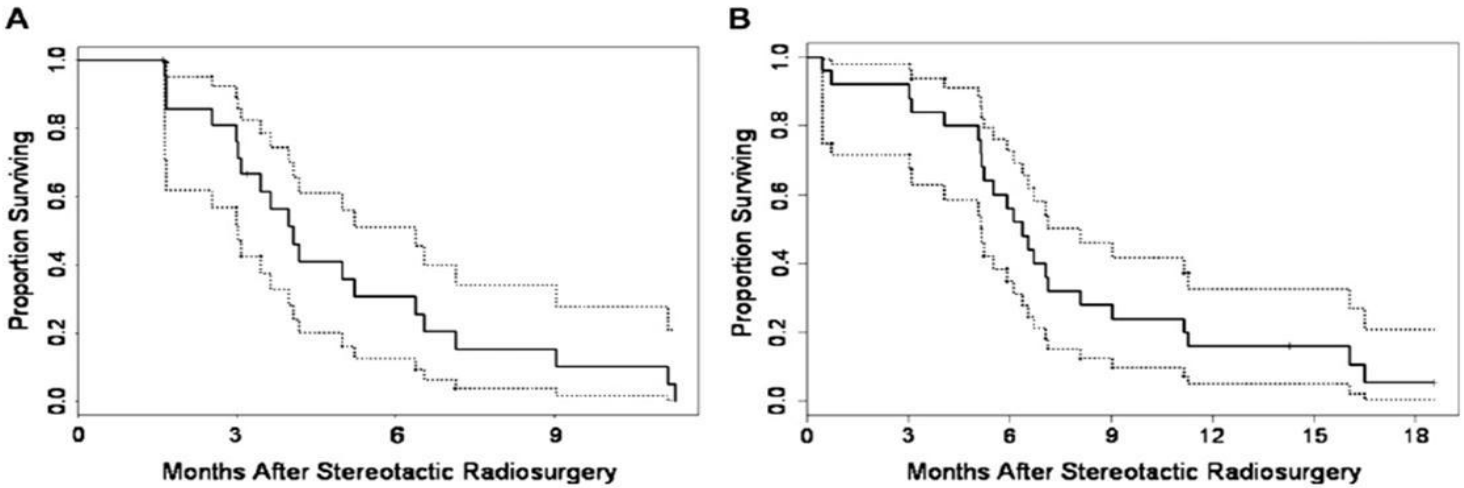

Fig. 2. Progression-free and overall survival. (A) Kaplan-Meier curve depicts progression-free survival for 23 patients completing stereotactic body radiotherapy with known disease status. The dashed lines represent the 95% confidence intervals. (B) Kaplan-Meier curve depicts overall survival for 25 patients completing stereotactic body radiotherapy. The dashed lines represent 95% confidence intervals. Tick marks represent censoring times/events.

Dewas et al. Radiation Oncology 2011, 6:77
http://www.ro-journal.com/content/6/1/77

RADIATION ONCOLOGY

RESEARCH Open Access

Robotic image-guided reirradiation of lateral pelvic recurrences: preliminary results

Sylvain Dewas[1], Jean Emmanuel Bibault[1], Xavier Mirabel[1,2], Philippe Nickers[1,3], Bernard Castelain[1,3], Thomas Lacornerie[1], Hajer Jarraya[4] and Eric Lartigau[1*]

Table 1 Characteristics of patients treated with CyberKnife for pelvic re-irradiation.

	Number (%)	Mean (range)	Comments
Patients	16		
Sex (M/F)	6 (37%)/10 (63%)		
Age*	55	(34 - 70 y.o.)	
Primary disease			
Anal canal	6 (38%)		
Cervix	4 (25%)		
Uterus	1 (6%)		
Rectum	4 (25%)		
Bladder	1 (6%)		
Primary treatment			
Surgery	9 (56%)		
Chemotherapy	13 (81%)		9 concomitant; 4 adjuvant
Radiotherapy	14 (87%)		
Dose*		45 Gy (20-75 Gy)	
Eq D2*			
Early side effects (α/β = 3 Gy)		45 Gy (33-58 Gy)	
Late side effects (α/β = 10 Gy)		72 Gy (53-96 Gy)	
Treatment of the recurrence			
Surgery	6 (38%)		
Chemotherapy	8 (50%)		
Radiotherapy	3 (19%)		
Dose*		53.7 Gy (36-66 Gy)	
Eq D2*			
Early side effects (α/β = 3 Gy)		65 Gy (45-66 Gy)	
Late side effects (α/β = 10 Gy)		106 Gy (72-110 Gy)	

* Median value

Dewas et al. Radiation Oncology 2011, 6:77
http://www.ro-journal.com/content/6/1/77

RADIATION ONCOLOGY

RESEARCH Open Access

Robotic image-guided reirradiation of lateral pelvic recurrences: preliminary results

Sylvain Dewas[1], Jean Emmanuel Bibault[1], Xavier Mirabel[1,2], Philippe Nickers[1,3], Bernard Castelain[1,3], Thomas Lacornerie[1], Hajer Jarraya[4] and Eric Lartigau[1*]

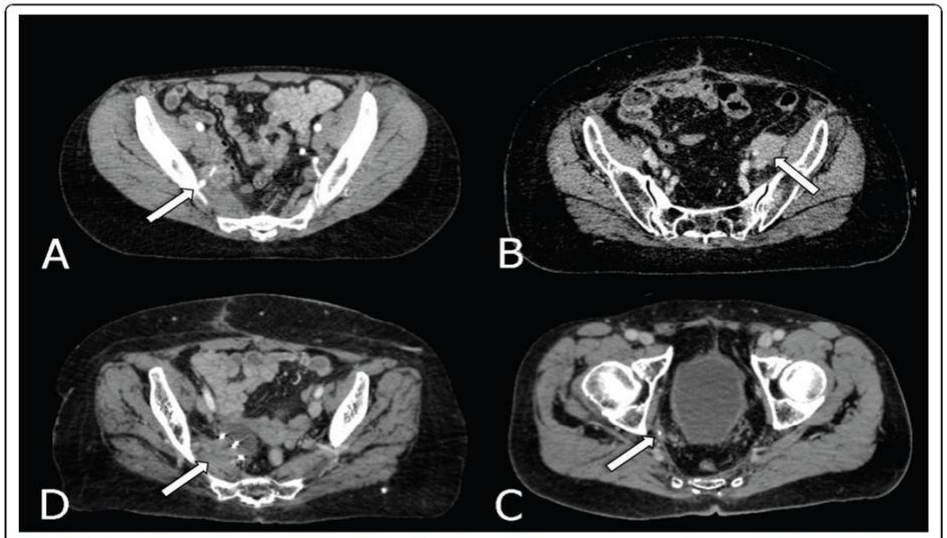

Figure 1 Examples of pelvic recurrence in previously irradiated areas: (A) Rectal cancer recurrence near the right iliac vessels (B) Cervix cancer recurrence near the left iliac vessels (C) Right pelvic anal canal recurrence (D) Rectal cancer recurrence previously (3 surgical clips visible).

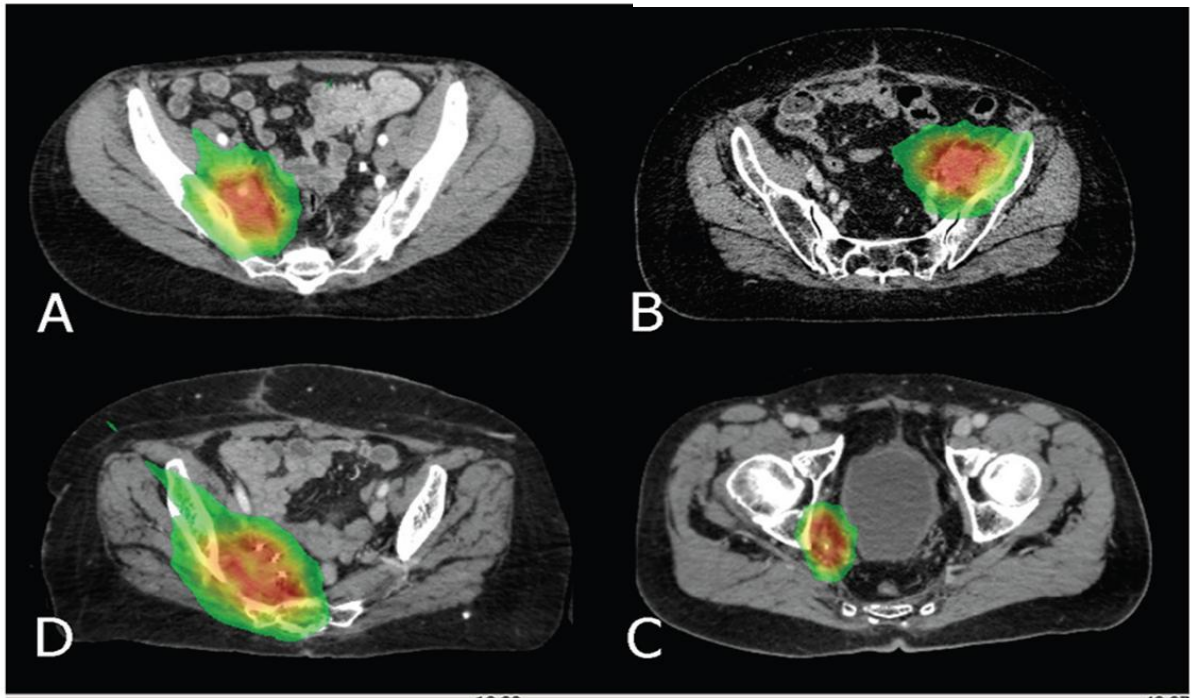

Figure 2 Dosimetry for pelvic stereotactic radiotherapy by CyberKnife for each patients presented in figure 1. Prescription to the 80% isodose line covering 95% of the PTV.

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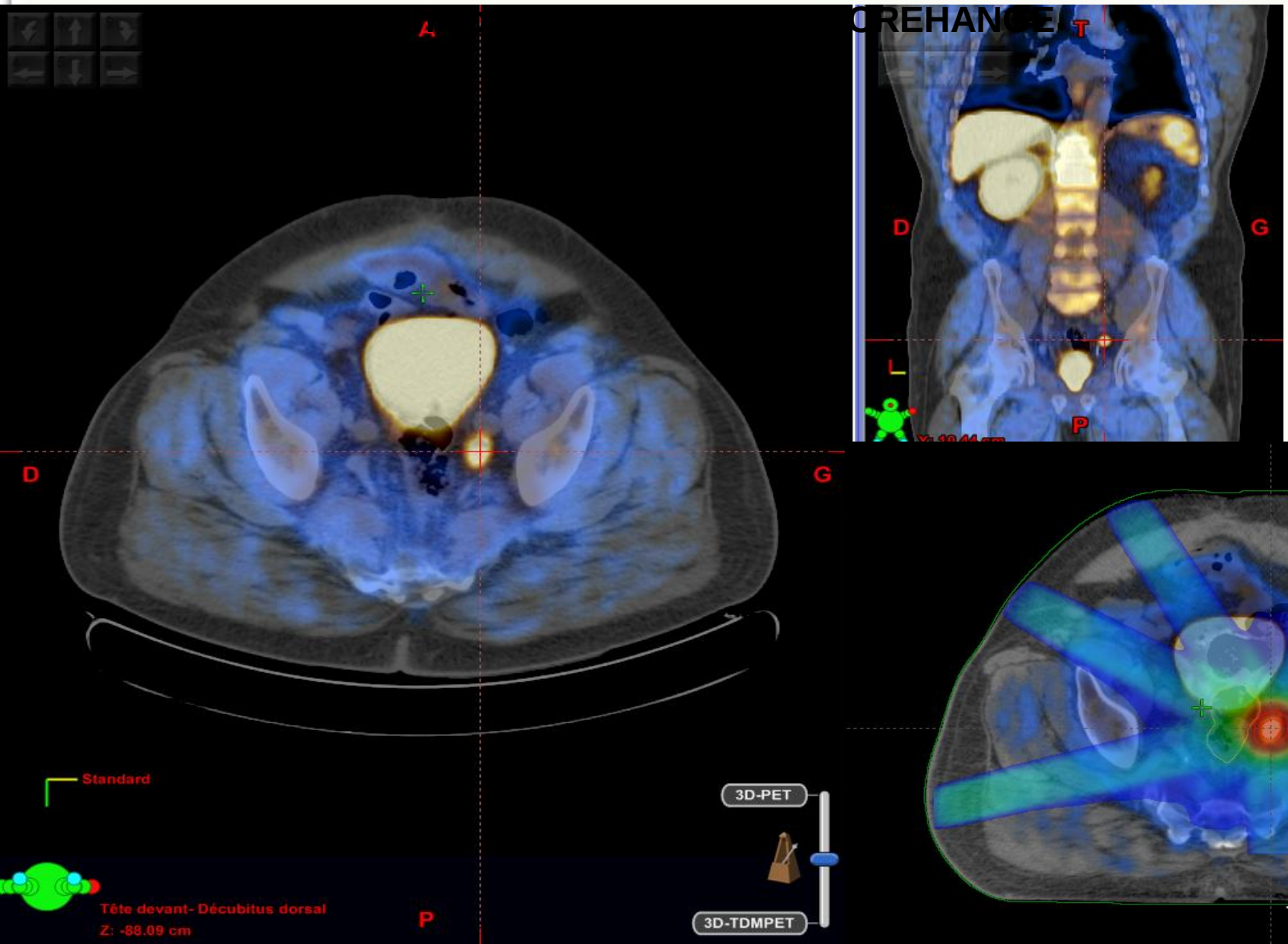
PHRC 2007: ICHOROPRO :

FLUOROMETHYLCHOLINE-(18F) in prostate cancer

CGFL
CENTRE GEORGES
FRANÇOIS LECLERC



Strahlenther Onkol 2008;184:36–40
DOI 10.1007/s00066-008-1783-9

Original Article

Three-Dimensional Conformal or Stereotactic Reirradiation of Recurrent, Metastatic or New Primary Tumors

Analysis of 108 Patients

Barbara A. Jereczek-Fossa[1,2], Anna Kowalczyk[1,3], Alberto D'Onofrio[4], Gianpiero Catalano[1], Cristina Garibaldi[5], Genoveva Boboc[1], Viviana Vitolo[1], Maria Cristina Leonardi[1], Raffaella Cambria[5], Roberto Orecchia[1,2]

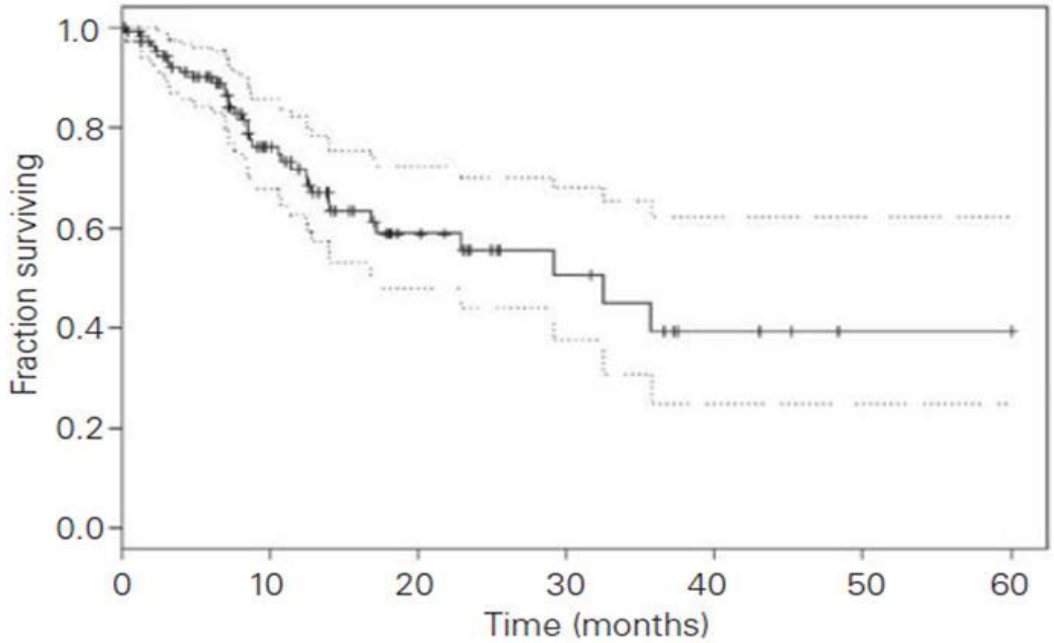


Figure 1. Overall survival curve calculated from the start of reirradiation (in months).

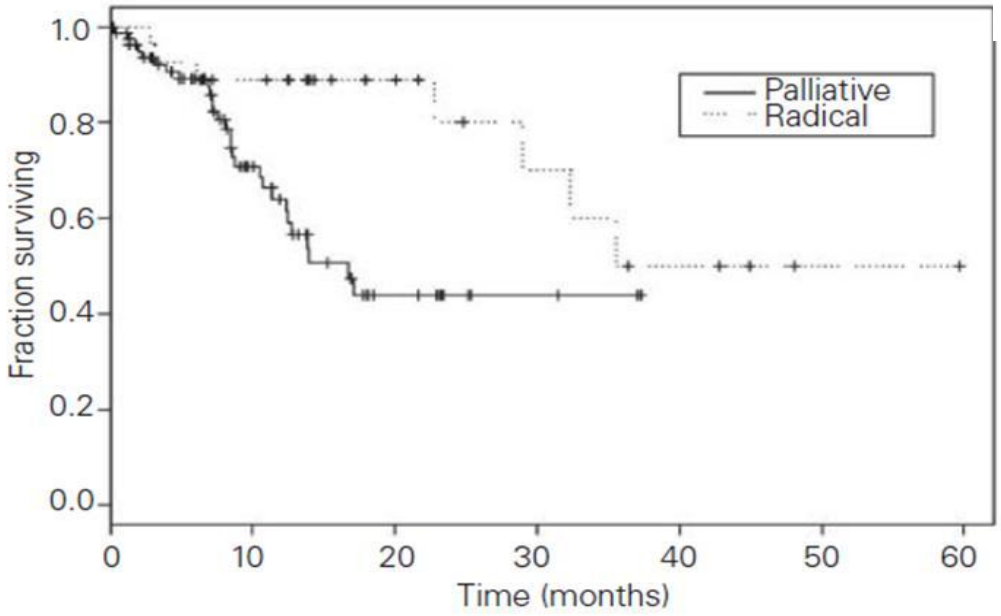
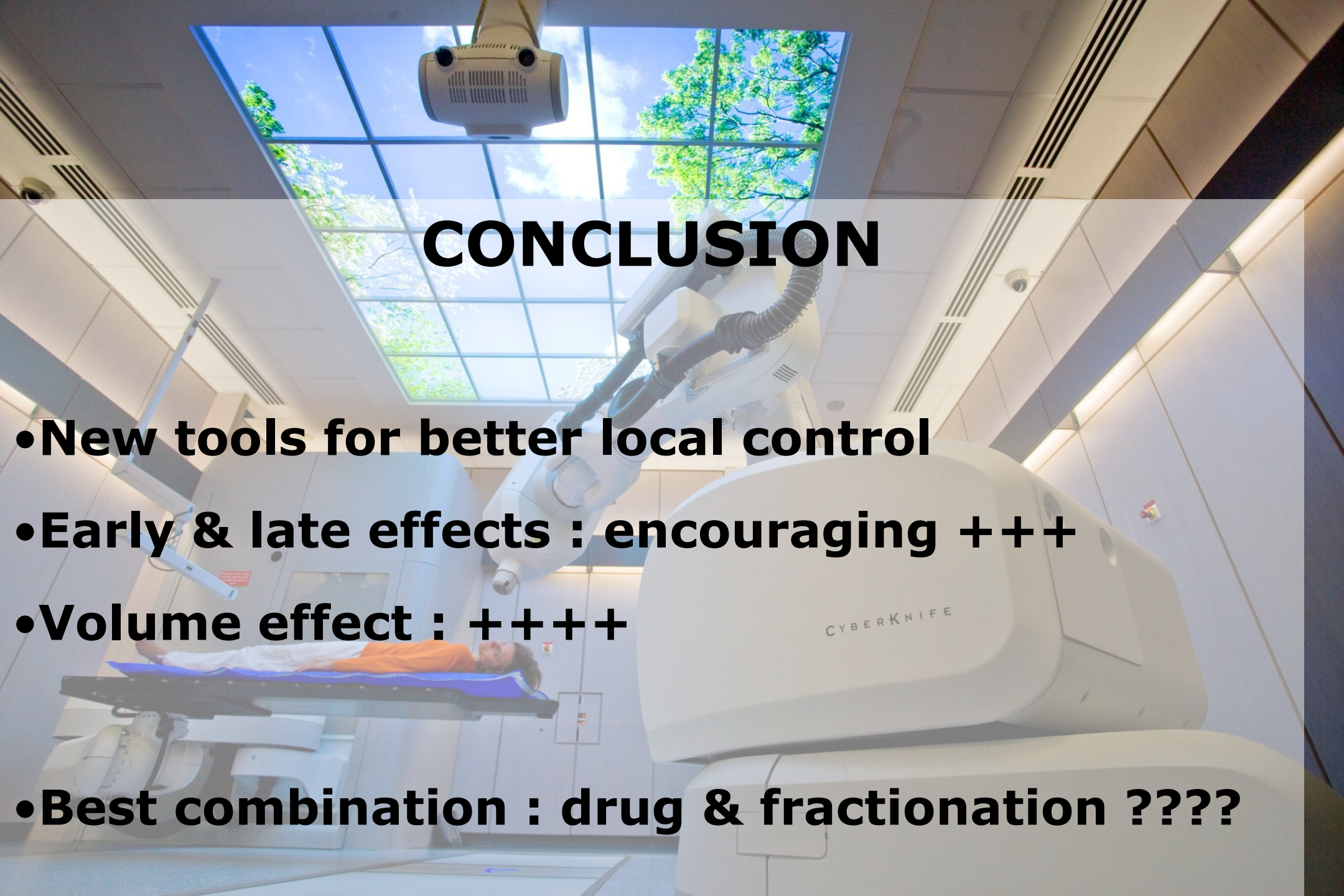


Figure 2. Overall survival curves with regard to the intent of reirradiation, calculated from the start of reirradiation (in months).



CONCLUSION

- New tools for better local control
- Early & late effects : encouraging +++
- Volume effect : ++++

- Best combination : drug & fractionation ????

ESTRO School

SABR versus non-SABR practice : the RTTs role

Angela Baker
Lead Research and Development RTT
The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
Honorary Research Assistant, The University of Liverpool

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Overview

- The RTTs role in SABR practice
  - Pre-SABR programme
  - IGRT considerations
  - Motion management
  - Per-SABR programme
  - Data collection /audit
  - (New technologies)

Image courtesy of Helen McNair, RMH

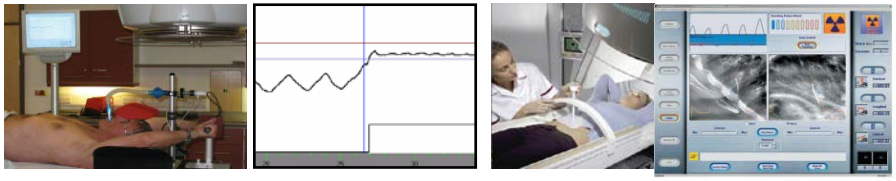
Patient selection / immobilisation

Data collection and audit

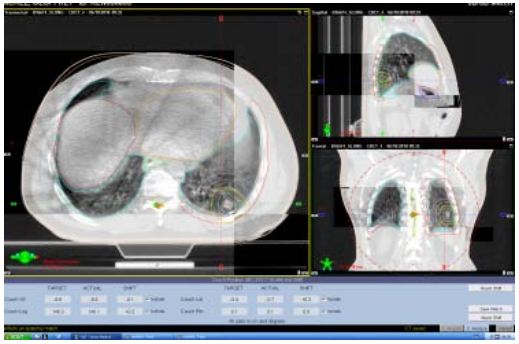
Pre-Treatment/Simulation/ Planning

SABR - “the RTT’s role”

Treatment delivery/ IGRT decision making



Motion Management



IGRT protocol development

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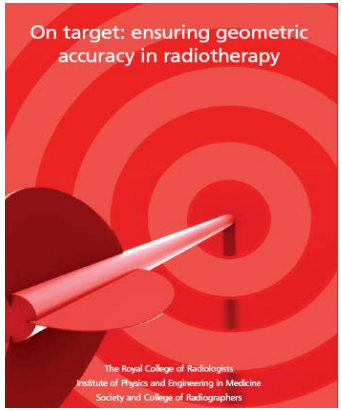
Pre-SABR programme

- Consider immobilisation for each SABR site
- Audit set-up uncertainties for system used for non-SABR patients
- Calculate systematic and random uncertainties
- Assess if appropriate for SABR by comparing with suggested SABR margin
- Adapt as necessary e.g. chin strap, vac bag



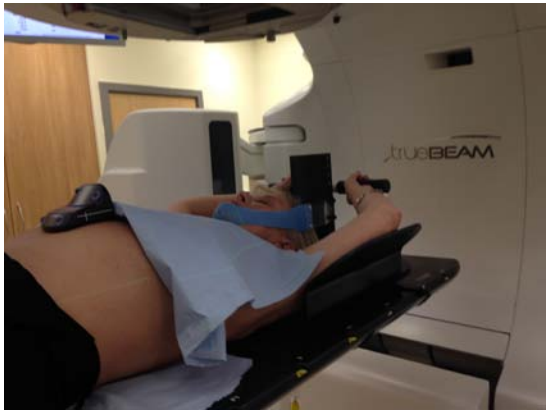
Population (cm)	vert syst	vert rnd	long syst	long rnd	lat syst	lat rnd
	0.094044	0.14978	0.202467	0.406479	0.152902	0.269381

Margins (mm)	Vert	Long	Lat
	3.4	7.9	5.7

Standard lung immobilisation 35 patients

Standard lung = 9mm PTV margin

SABR lung = 5mm PTV margin



IGRT Considerations (1)

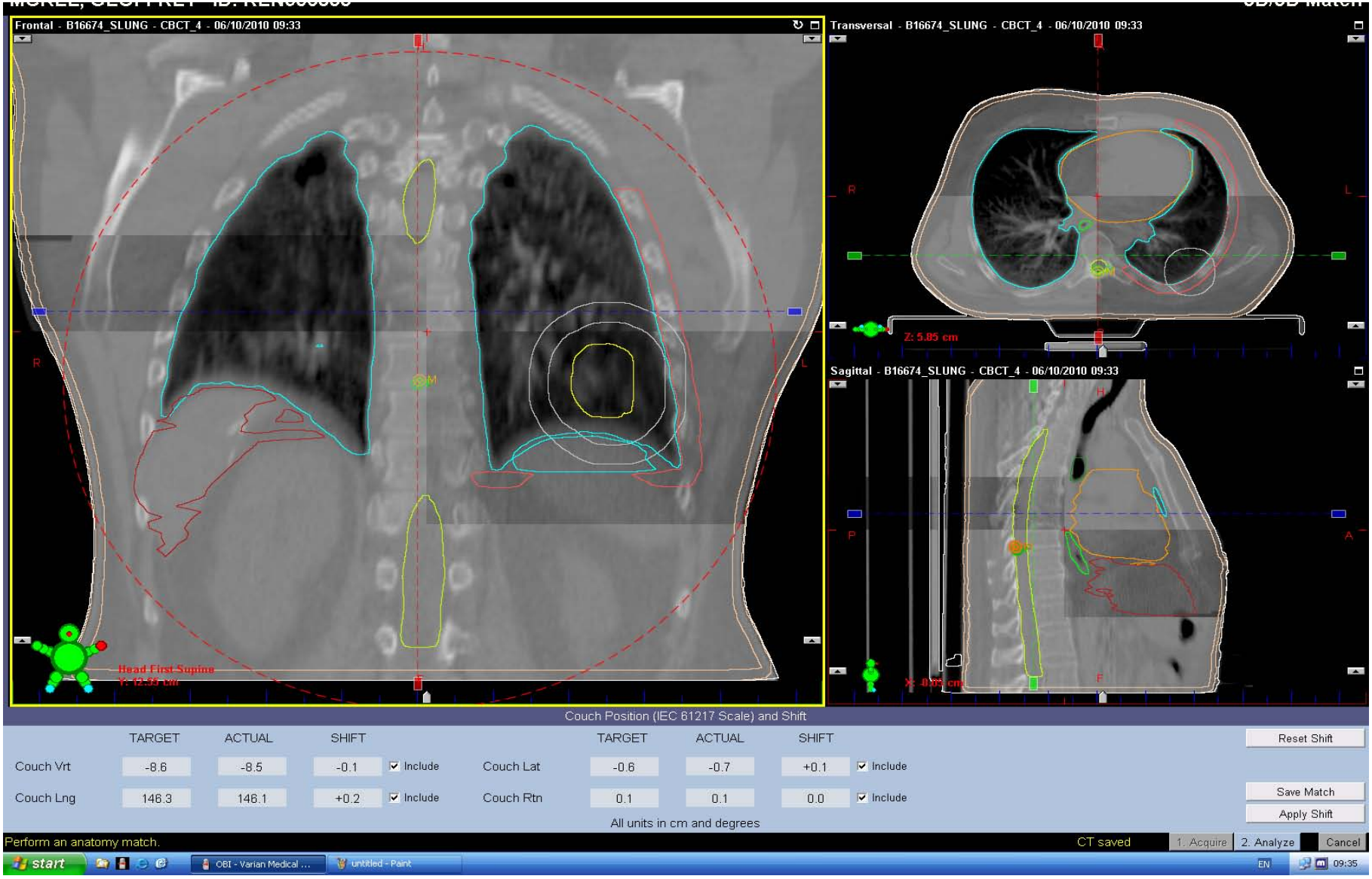
- Roles and responsibilities
- IGRT protocol development – example for lung
- Frequency of imaging – treatment time, immobilisation
- Day 0 for familiarisation, decision of registration process
- Mid treatment CBCT?
- Post treatment CBCT?
- Image quality – new CBCT modes
- Decision making flow charts
- Evaluation of registration methods
- RTTs play a key role within MPT

CBCT Bone Match – Step 1

manual match /bone windows

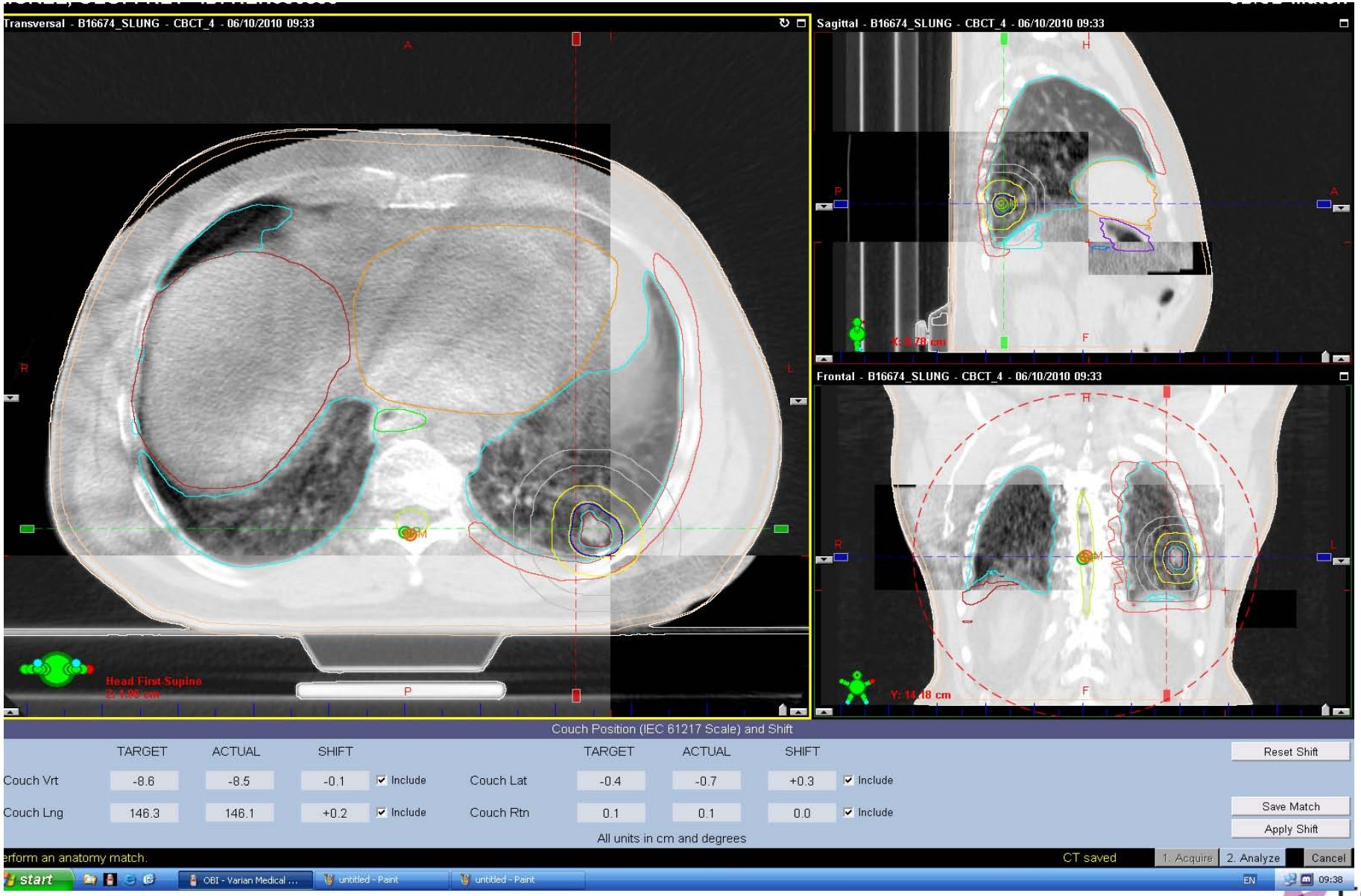
CBCT Bone Match – Step 1

manual match /bone windows



CBCT PTV Match – Step 2

manual match, lung windows



CBCT PTV Match – Step 3

auto match,PTV,1cm margin / lung windows

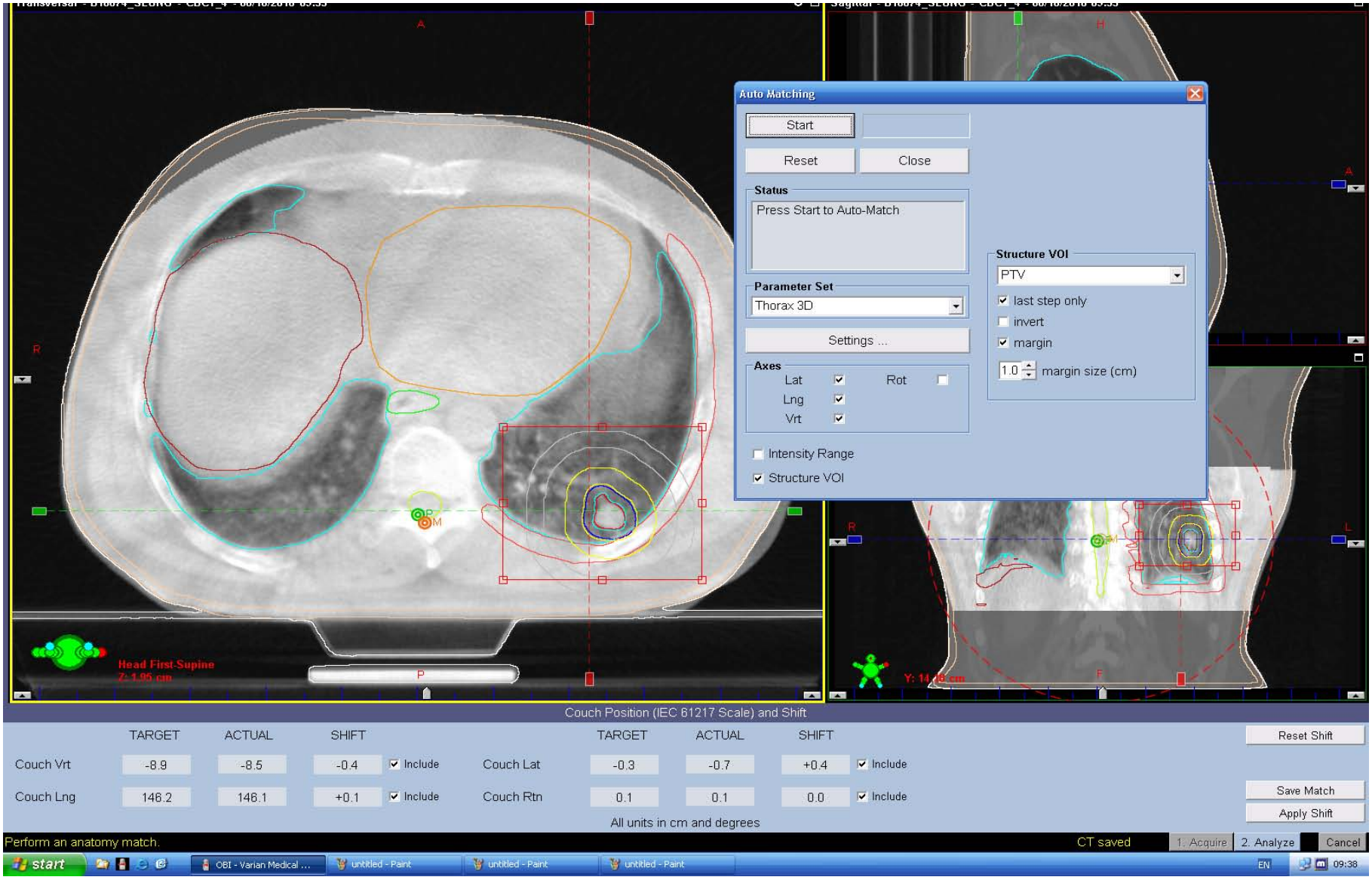
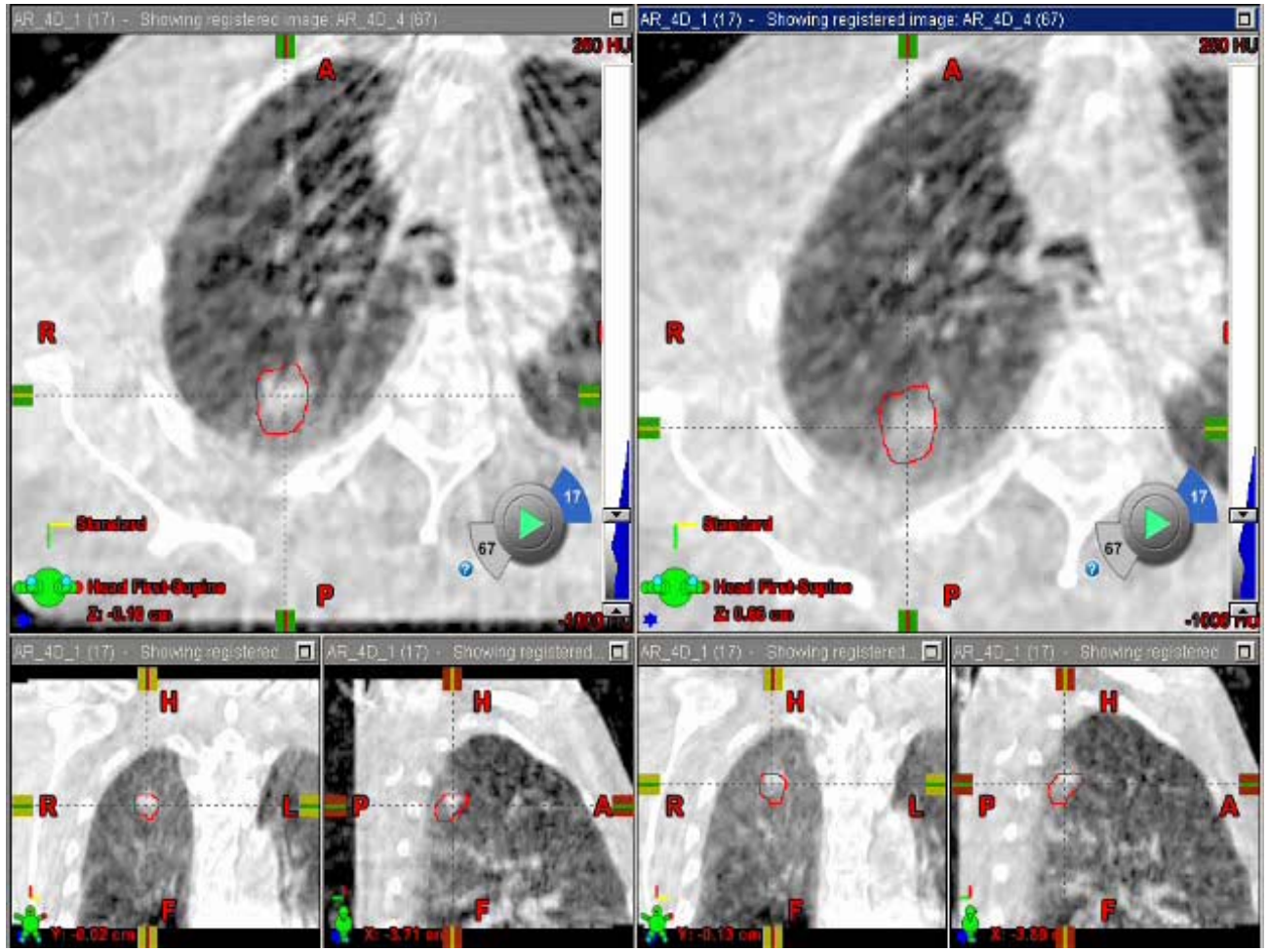


Image Quality : optimising imaging protocols

MPT role : clinicians, radiographers, physicists



Standard: 125kVp, 40mA, 20ms

LD: 125kVp, 20mA, 20ms

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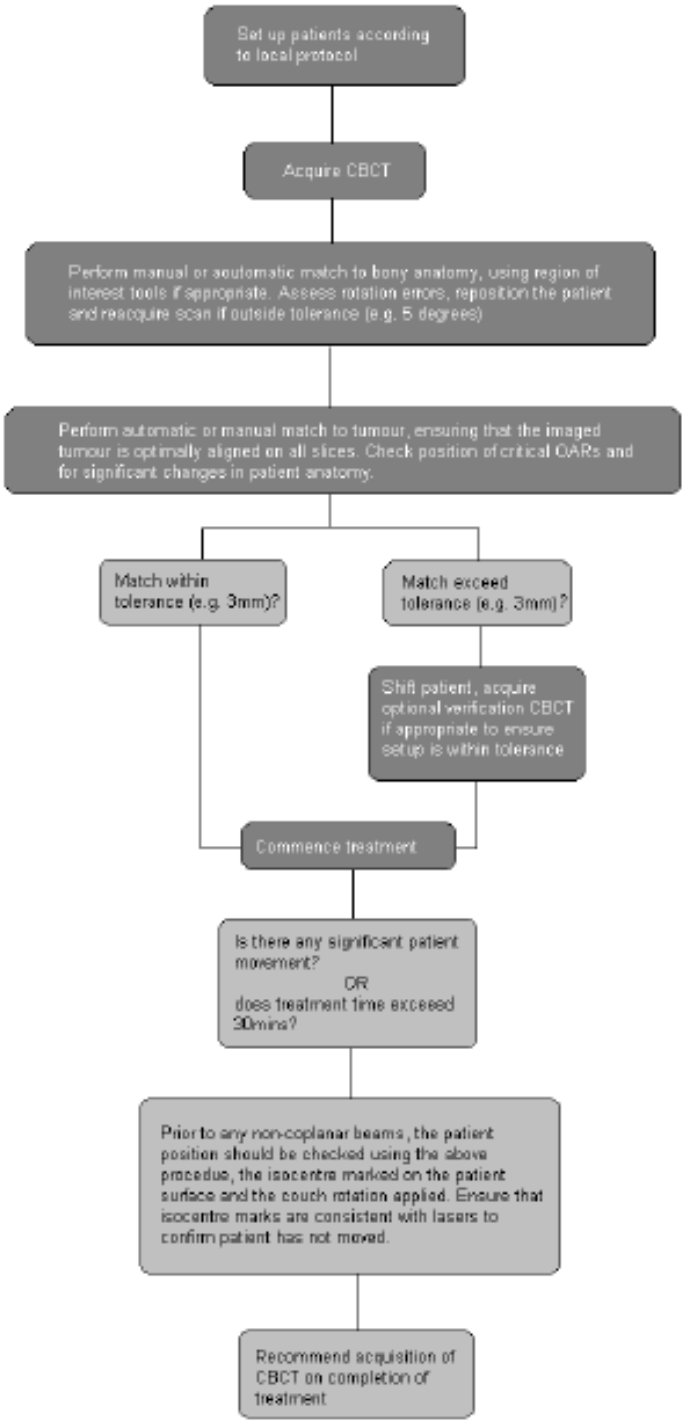
IGRT workflow using volumetric imaging



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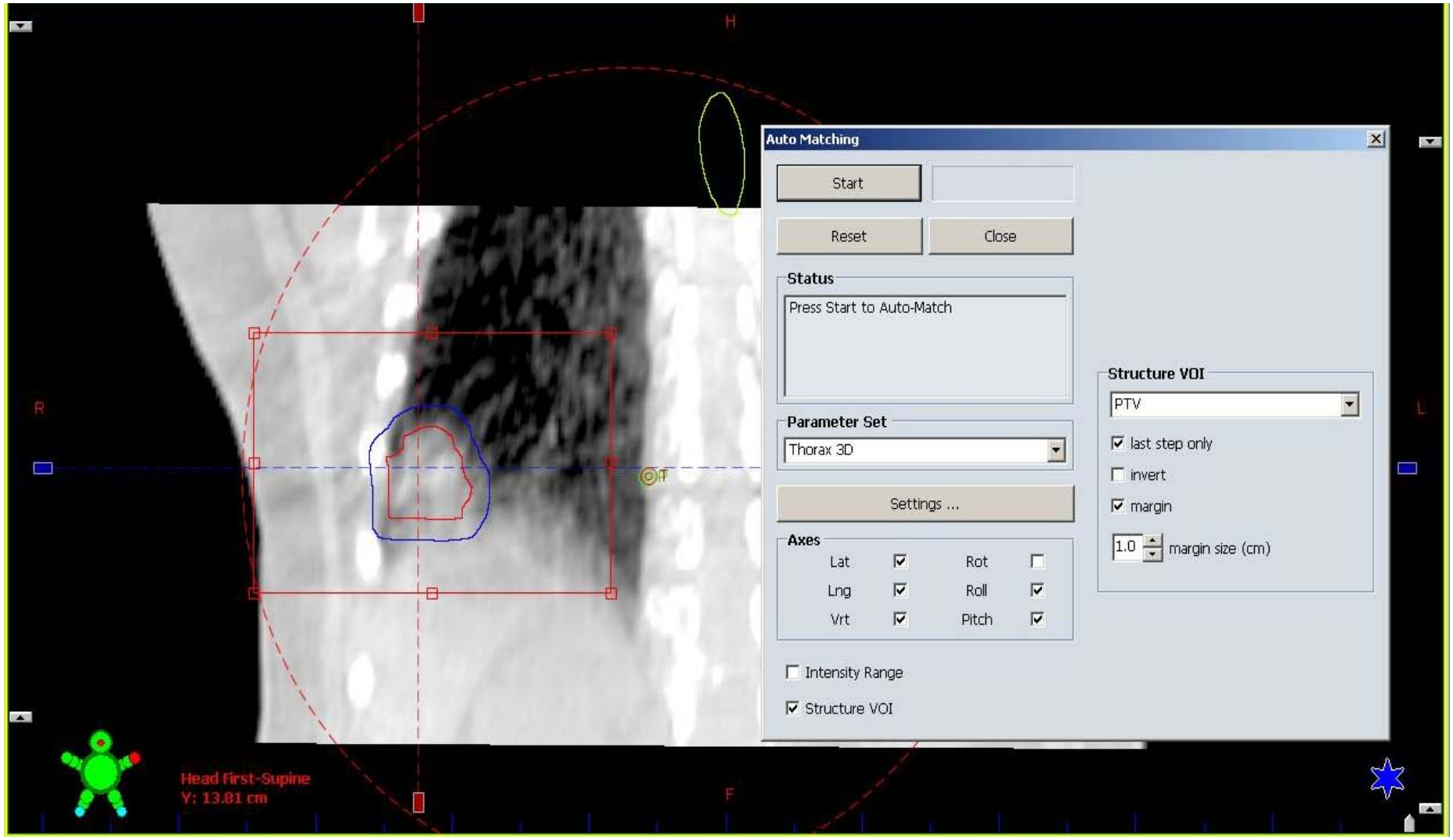
Use of automatic registration options

Problems if close to diaphragm : use with caution and careful checking



IGRT Considerations (2)

- RTT led process : advanced IGRT competency
- Training and competency assessment

Example from RMH:

A 4 stage training programme was implemented including:

- Training session for RTT on good practice for SABR verification
- Competency based testing of matching 20 offline CBCT lung SABR verifications.
- To be assessed as competent a 90% concordance with clinicians verification was required. An acceptable match was translocation $\leq$ 2mm and rotation $\leq$ 2° compared to the clinicians. To audit, a clinician retrospectively verified 20 patients lung SABR CBCT images matched by RTT.

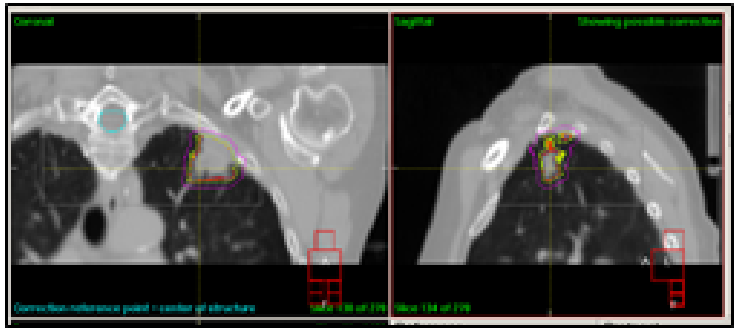
Audit of Advanced Competency for Radiographer led lung Stereotactic Ablative Body Radiotherapy (SABR) verification. David Frost et al. Royal Marsden NHS Foundation Trust.

IGRT Considerations (2)

- **Spot the difference?**

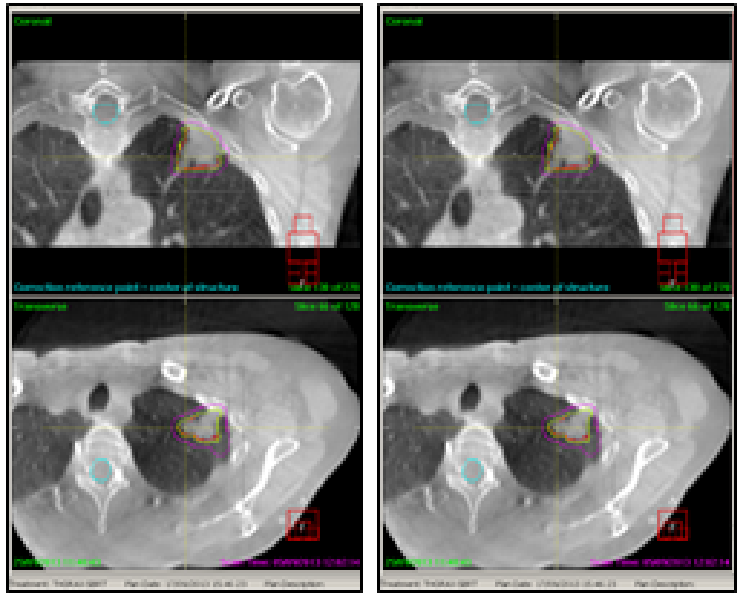
Which image did the Radiographer verify?
Localisation Image A or B

Reference Image

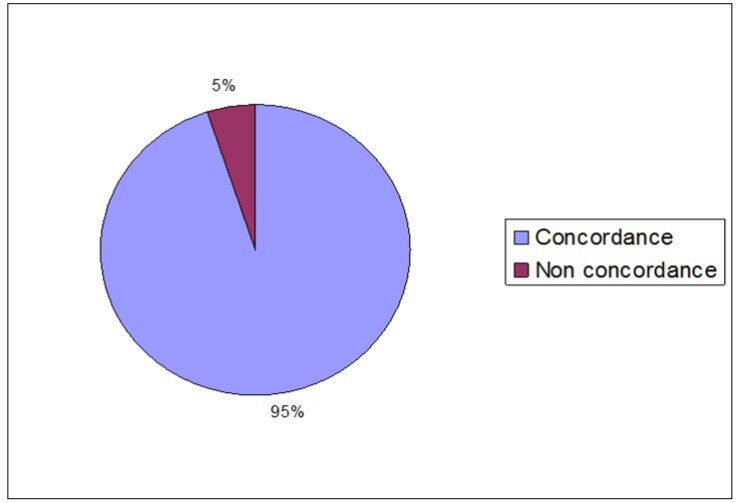


Localisation Image

A **B**



Answer= A
There was 100% concordance of the match

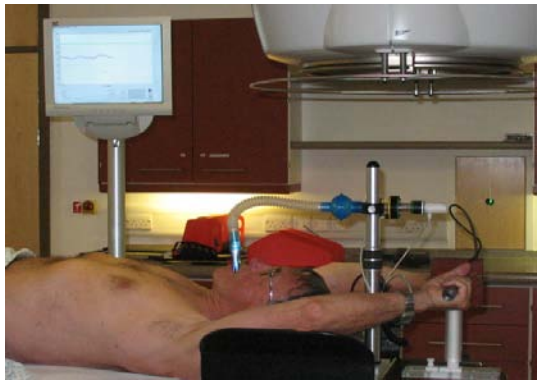


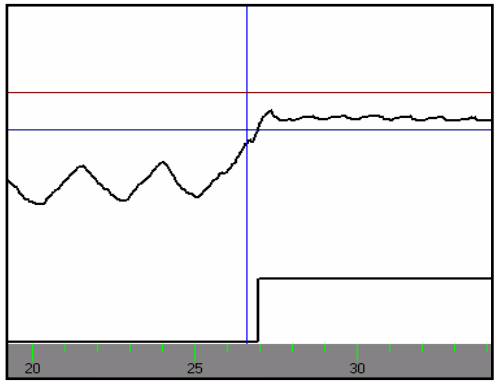
Of the 20 matches 35% (7) required manual adjustment to achieve an optimal verification. There was 1 non concordance which was 2.5mm in the A/P direction.

Audit of Advanced Competency for Radiographer led lung Stereotactic Ablative Body Radiotherapy (SABR) verification. David Frost et al. Royal Marsden NHS Foundation Trust.

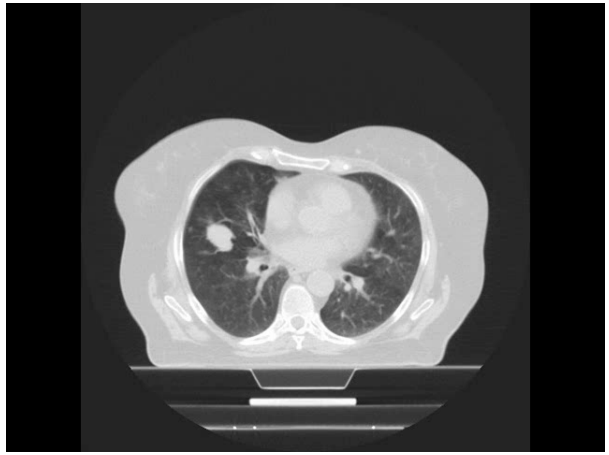
Motion management (1)

Stop / reduce tumour movement





Allow for motion in margins



Treat in only part of respiratory cycle

The management of respiratory motion in radiation oncology report of AAPM Task Group 76[a)]

 0094-2405/2006/33(10)/3874/27/$23.00

Motion management (2)

- A strategy for motion management is essential in SABR for anatomical indications effected by breathing motion (e.g. lung, liver, adrenal gland, lymph node)
- RTTs role in decision making for use of these techniques
- Dependant on departmental availability of kit (CK tracking, DIBH, ABC, gating etc.)
- Pre-treatment role
- Role in coaching / training patient
- Additional considerations when these techniques are used e.g. longer on treatment couch

Per-SABR process

- Audit set-up uncertainties after initial patients
- Then ongoing to verify that there hasn't been any unknown changes in process

26 PTS	Pre-treatment CBCT			Post-treatment CBCT		
Set-up error	VERT	LONG	LAT	VERT	LONG	LAT
M	-0.8	-0.3	0.1	0.7	0.1	0.1
SD	1.8	2.6	2.5	1.3	1.2	1.2
$\sum_{setup}$	1.9	3.6	3	0.8	0.7	0.8
σ_{setup}	2.3	3.2	2.7	1.5	1.3	1.5

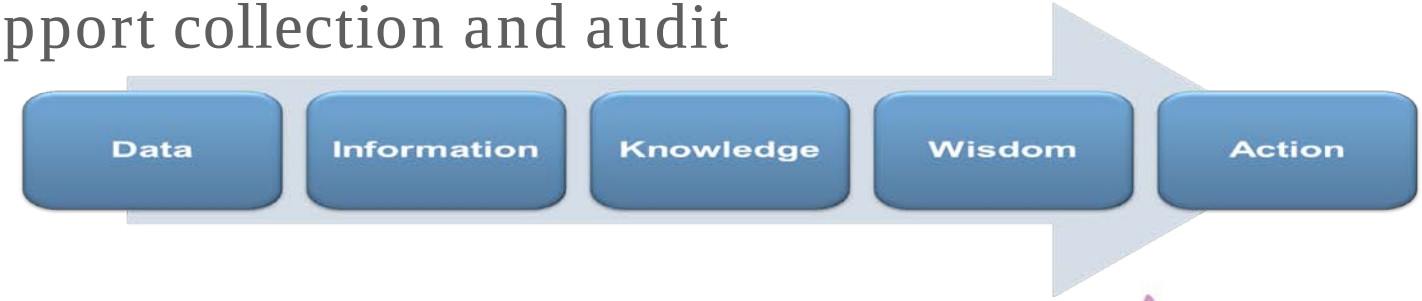
- The post-treatment systematic and random set-up uncertainties show the residual displacement error together with intrafraction motion
- Gives confidence in immobilisation/treatment accuracy
- Margin calculation (Van Herk formula) – RL 3.1 mm, SI 2.4 mm, AP 3.3 mm

Data Collection / Audit

- Especially important when introducing SABR for a new anatomical site outside a clinical trial
- Quality of life : EQ5D
- Toxicity data
- Visual Pain Analogue
- Image analysis data

- Data input/analysis

- Resources to support collection and audit



Summary

- RTTs involved in same aspects for both SABR and non-SABR practice.
- SABR uses advanced IGRT techniques which RTTS can perform following appropriate training and competency assessment.
- Provide continuity throughout patient process.
- SABR offers RTTs the scope for role extension.
- Increasing numbers of anatomical indications for SABR delivery (e.g. oligomets, HCC, re-irradiation) utilise same principles as lung SABR.
- Empowering and motivating to be involved in a multi-professional SABR programme.

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- Margin formula

Van Herk et al IJROBP **47** 1121-1135 2000

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http://webarchive.nationalarchives.gov.uk/20130513211237/http://ncat.nhs.uk/sites/default/files/work-docs/National%20Radiotherapy%20Implementation%20Group%20Report%20IGRTAugust%202012l.pdf

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- Hudson, J (2015) Are Therapeutic Radiographers able to achieve clinically acceptable verification for Stereotactic lung radiotherapy treatment (SBRT) . Journal of Radiotherapy in Practice Volume 14 / Issue 01 / March 2015, pp 10-17
- AAPM SABR, AAPM IGRT, ASTRO guidelines

Potters L., Gaspar L.E., Kavanagh B., Galvin J.M., Hartford A.C., Hevezi J.M., Kupelian P.A., Mohiden N., Samuels M.A., Timmerman R., Tripuraneni P., Vlachaki M.T., Xing L., and Rosenthal S.A. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for image-guided radiation therapy (IGRT). *Int. J. Radiat. Oncol. Biol. Phys.* 76, 319-325. 2010

Acknowledgements

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- Ruth Clements : SABR Lung Lead RTT, The Clatterbridge Cancer Centre
- Lisa Hallam: Imaging Specialist RTT, The Clatterbridge Cancer Centre

MEDICAL UNIVERSITY OF VIENNA

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SBRT versus non-SBRT practice

What are the competencies and responsibilities of the multidisciplinary team from the view of a clinician

„Doctors Job"

Interdisciplinary Tumorboard ❖

Treatment planning and delivery ❖

Reproducible high precision positioning

4D –Imaging With „ motion management" ❖

Target delineation and physical Treatment planning ❖

Daily Image guidance (IGRT) ❖

Follow up

Workflow for SBRT

Workflow for conventional RT

Interdisciplinary Tumorboard

Treatment planning and performance

Reproducible positioning

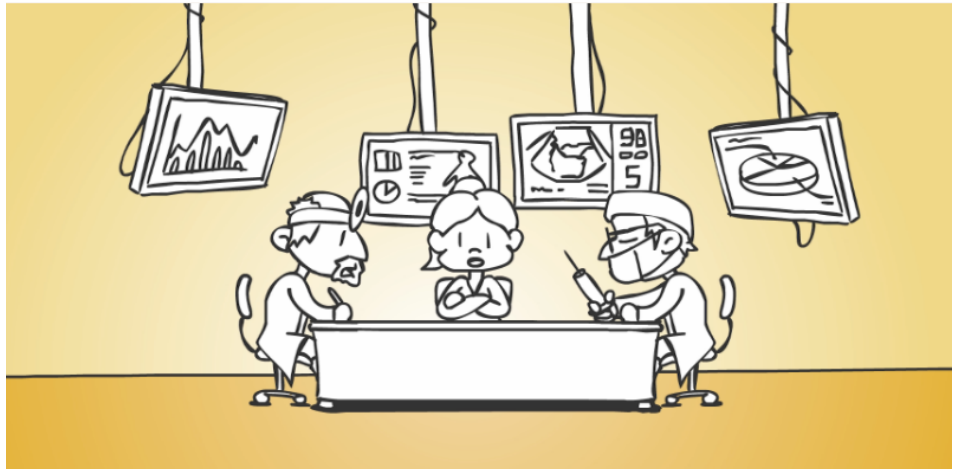
3D or 4D Treatment planning

Imaging according to an indiv. Department program

Follow up

SBRT what is different

Tumorboard Decision



Patient Selection:

- ✧ Currative but medically inoperable patients

  Currative patients refusing surgical resection

- ✧ Patients with limited disease:

  small localized tumor

  oligometastasis

  re-irradiations

More critical selection of the patients compared to conventional fractionated Radiotherapy

SBRT what is different

Doctor's decision

Patient selection

- ✧ Patients suitable for high dose (longer treatment time)
- ✧ Tumor location in relation to OAR

based on expert knowledge

based on national/ international guidelines

(RTOG ; DEGRO.....)

based on Scores (ECOG, Charlston Co-morbidity Score.....)

?

SBRT what is different

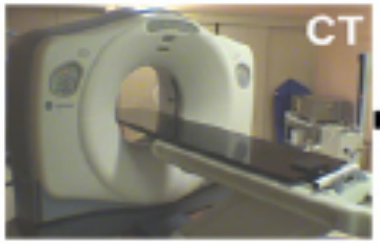
Increasing/ limited List of Indications

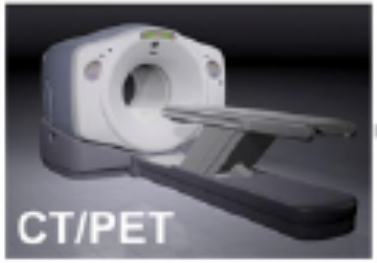
Indications :

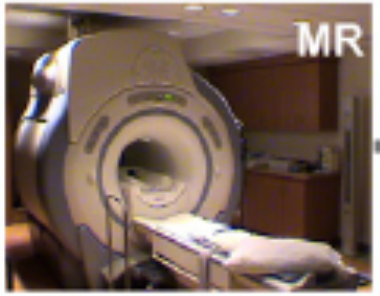
Lung tumors (stage I)/ Lung metastasis
Liver tumors / Liver metastasis
Small kidney tumors
Spinal cord tumors
Early stage Prostate cancer
Pancreatic tumors
Oligometastasis
Bone metastasis
Reirradiations
.....

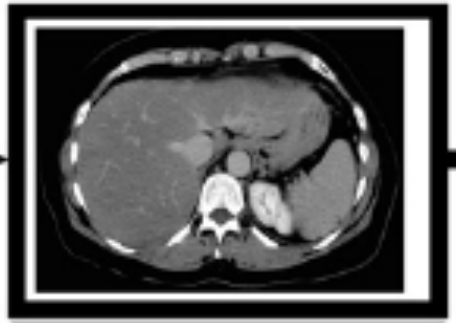
Indications based : On evidence based literature
On scientific questions instudies

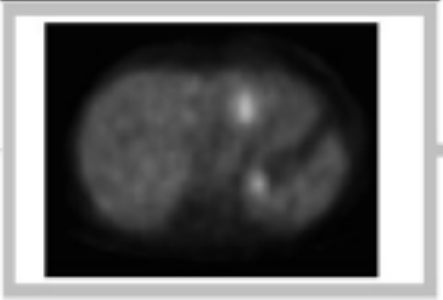
Treatment Planning
Selection of the Images and Image fusion

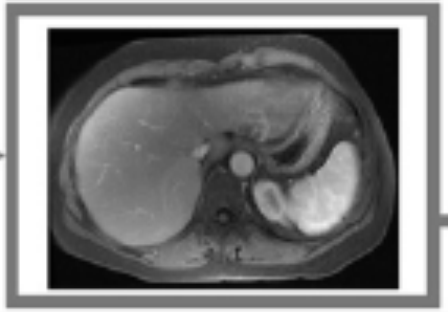


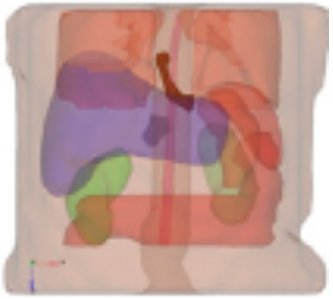








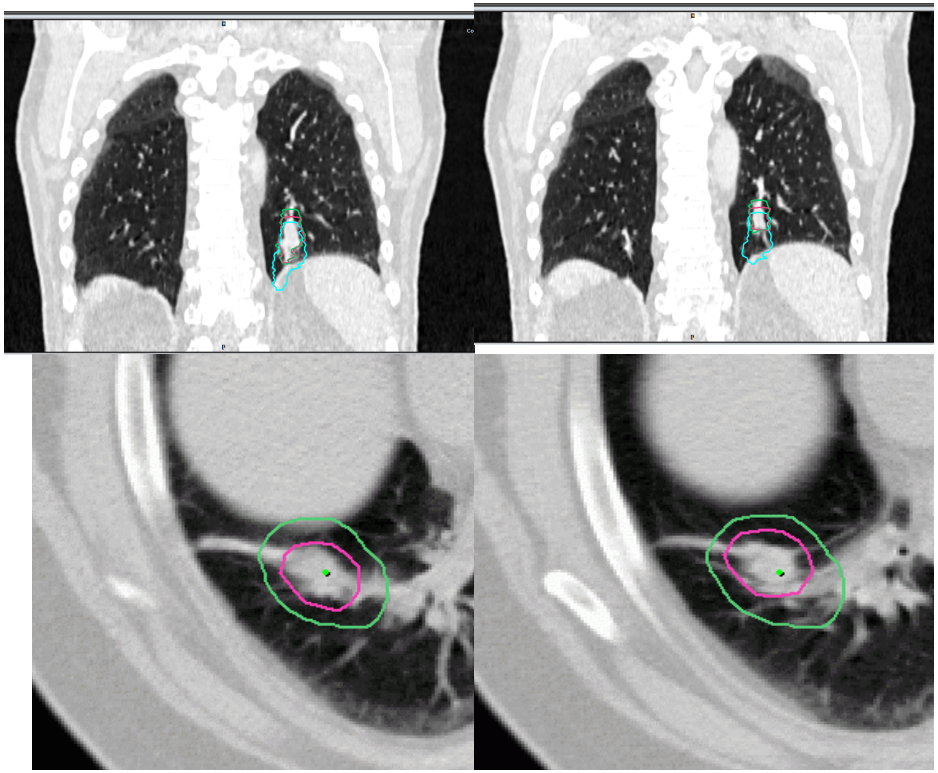




- Arrange the Imaging
- Select the right Images
- Control of the image fusion

Treatment planning
Responsibilities of the doctor

Target delineation



CTV in different inhalation phases → ITV → PTV

CTV in the mid inhalation phase → PTV

(taking into account the individual tumor motion, gating, tracking and patient movement)

Treatment planning
Responsibilities of the doctor

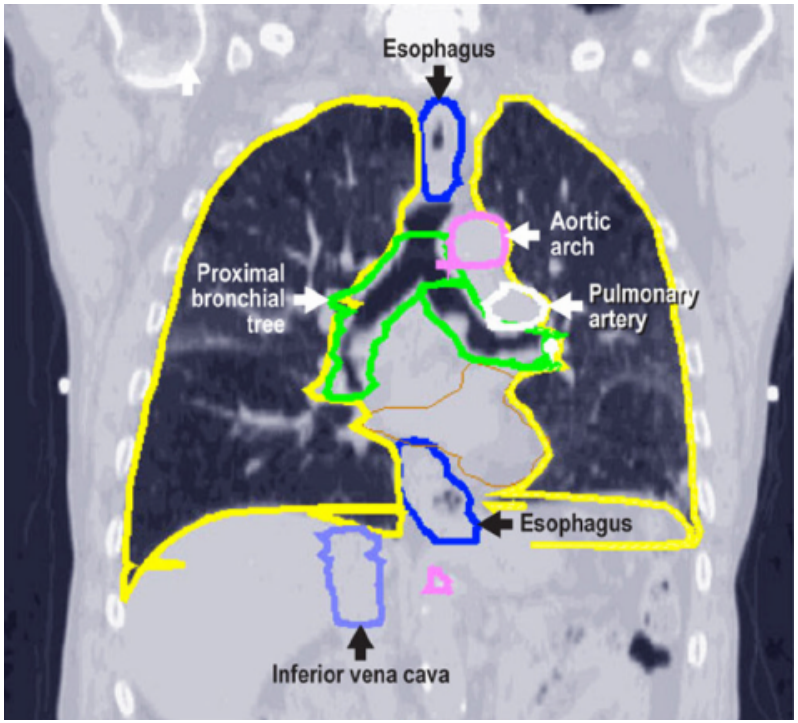
OAR-Delineation according to the position of the tumor:

Lungs, Oesophagus

Spinal Cord, Heard

Stomach, Kidneys

Pancreas, Bowl, Bladder

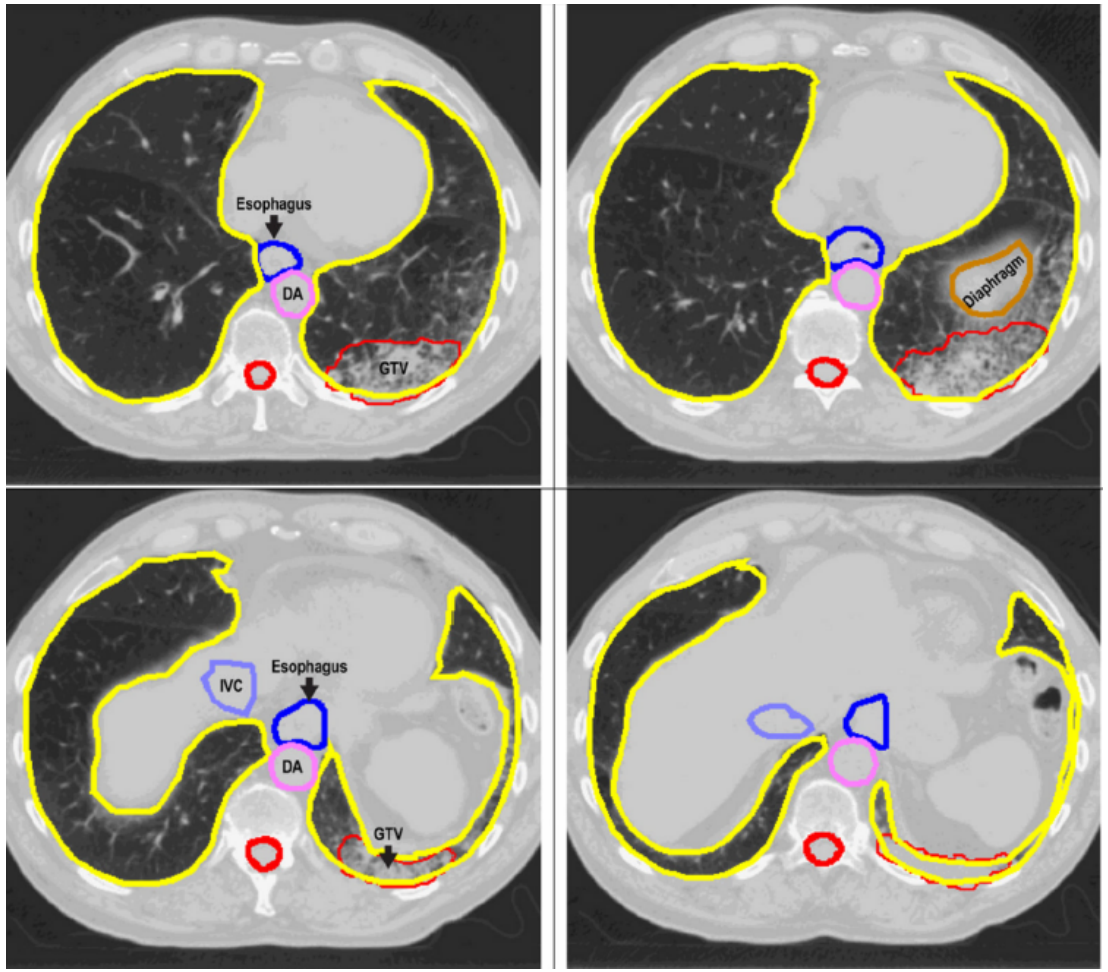


- ✧ Movement of the OAR
- ✧ Dose constrains of the OAR, maximal dose /fraction/volume

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

Feng-Ming (Spring) Kong, M.D.,

Target definition of the OAR have to be done individually according to the movement of the organ.

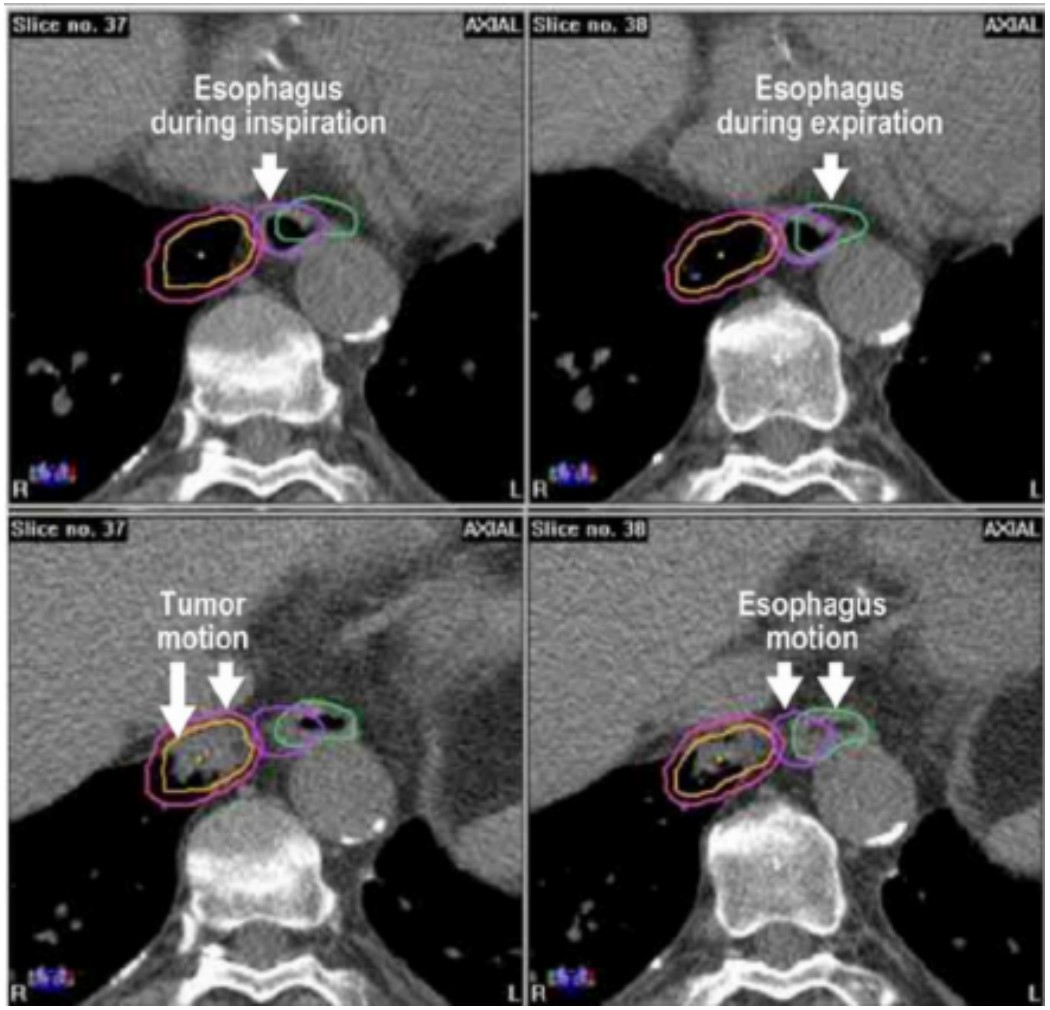


Int J Radiat Oncol Biol Phys. 2011 December 1; 81(5): 1442–1457.

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

Feng-Ming (Spring) Kong, M.D.,

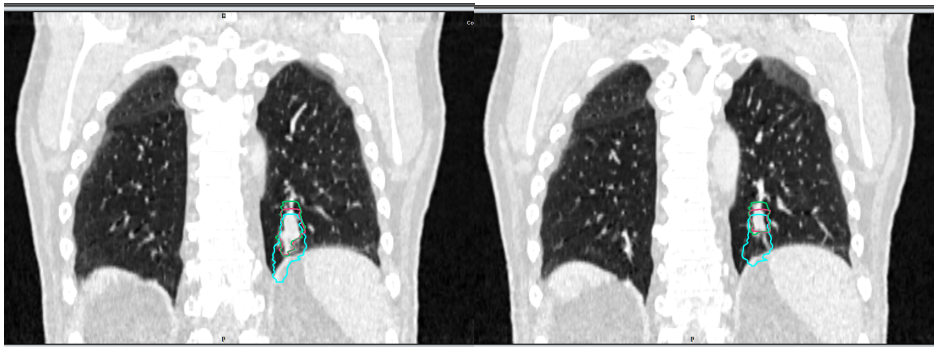
Cheque the motion of the Organs and the tumor.



Int J Radiat Oncol Biol Phys. 2011 December 1; 81(5): 1442–1457.

Treatment planning
Responsibilities of the doctor

Dose prescription



- Prescription of the dose defined on isodose line.
  Specification of the isodose (60, 65%, 80%)

- Prescription of the dose per fraction and number of fractions.

Dose constraints

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

Feng-Ming (Spring) Kong, M.D.,

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

Int J Radiat Oncol Biol Phys. 2011 December 1; 81(5): 1442–1457.

Accreditation and quality assurance for Radiation Therapy Oncology Group: Multicenter clinical trials using Stereotactic Body Radiation Therapy in lung cancer

ROBERT TIMMERMAN[1], JAMES GALVIN[2], JEFF MICHALSKI[3], WILLIAM STRAUBE[3], GEOFFREY IBBOTT[4], ELIZABETH MARTIN[5], RAMZI ABDULRAHMAN[1], SUZANNE SWANN[5], JACK FOWLER[6] & HAK CHOY[1]

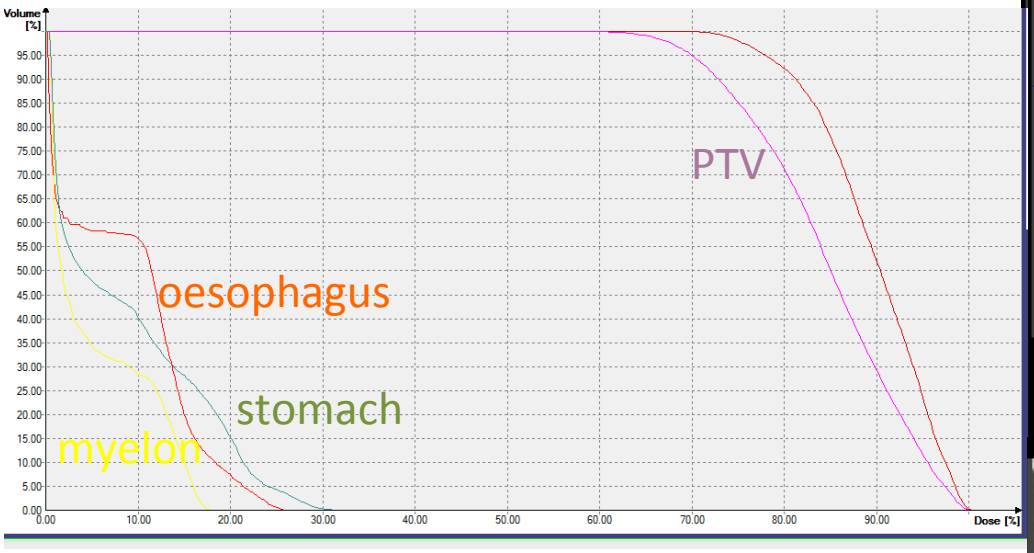
Table II. Normal Tissue Constraints for RTOG 0618

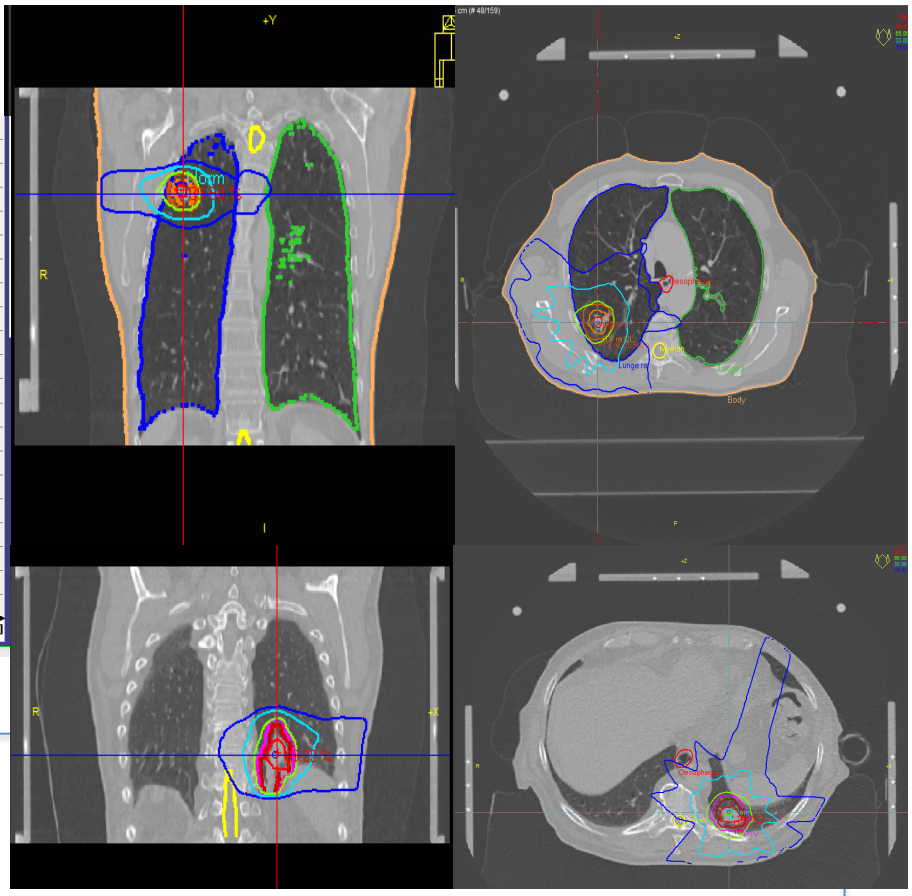
Organ	Volume	Dose (cGy)
Spinal Cord	Any point	18 Gy (6 Gy per fraction)
Esophagus	Any point	27 Gy (9 Gy per fraction)
Ipsilateral Brachial Plexus	Any point	24 Gy (8 Gy per fraction)
Heart/Pericardium	Any point	30 Gy (10 Gy per fraction)
Trachea and Ipsilateral Bronchus	Any point	30 Gy (10 Gy per fraction)
Whole Lung (Right & Left)	(See table in Section 6.4.2)	(See table in Section 6.4.2)
Skin	Any point	24 Gy (8 Gy per fraction)

Acta Oncologica, 2006; 45: 779–786

Treatment planning
Responsibilities of the doctor

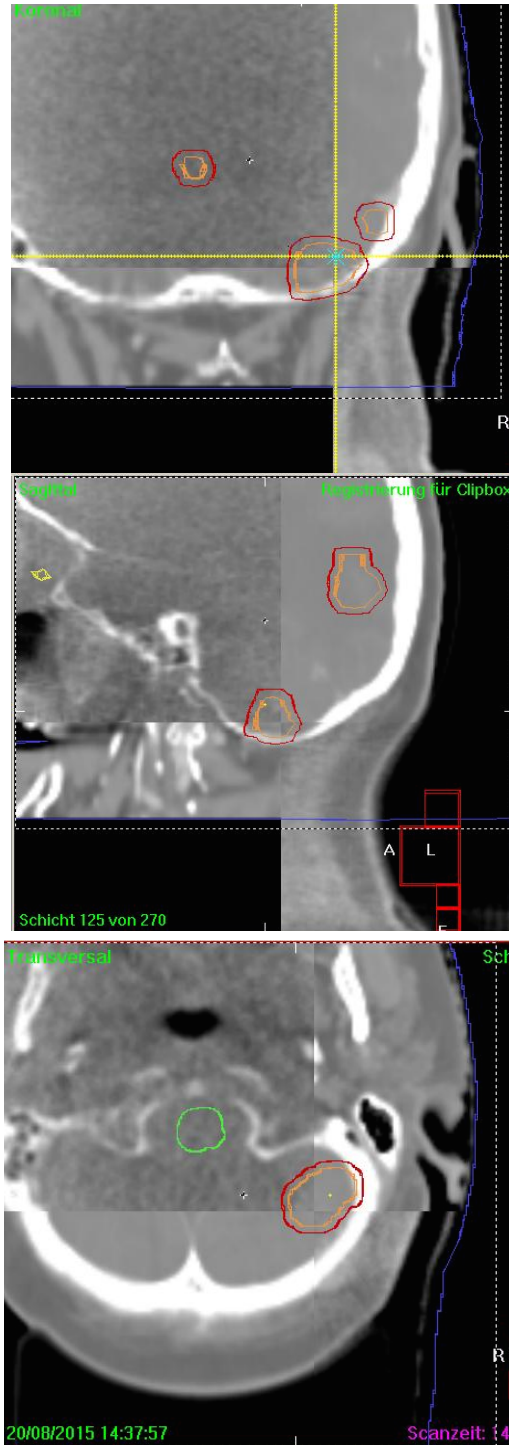
Target coverage





- ✧ Analysis of the treatment plan : dose at the PTV, Tumor , OARs
- ✧ Convert the applied dose into conventional fractionated dose schedule
- ✧ Accept the plan

Treatment delivery Responsibilities of the MD at the LINAC



- Attending and directing the radiosurgical treatment delivery
- Ensuring that patient positioning on the treatment unit is appropriate
- Control of the Conebeam CT
- Give the permission to start the treatment

Follow-up

Following the patient and participating in the monitoring of disease control, survival and complications

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.††

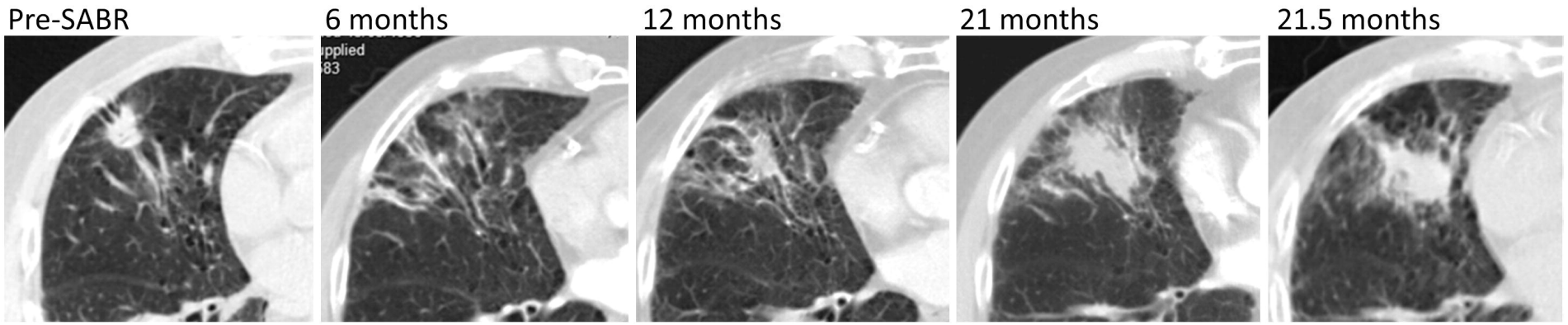
Follow-up

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

B. Recurrence



Checklist for SBRT/ conventional RT

		MD		Physicist	RTT
	Indications	+	+		
PLANNING	Positioning of the pt at CT/ MRI, Organ movement	+			+
	Tumor Target delineation (GTV/CTV)	+	+		
	Target delineation OARs	(+)	+		+
	Treatment planning			+	+
	Constrains of OARs	+	(+)		
	Plan control and acceptance	+	+	+	
	Acquisition of data and control	+	(+)	+	+

Checklist for SBRT/ conventional RT

PERFORMANCE

	MD		Physicist	RTT
Presence at first Treatment	+	+	+	+
Positioning of the patient	(+)	+		+
Positioning control of the Tumor	+	+	+	+
Breathing /movement control	+			+
Presence at following Treatments	+		(+)	+
Positioning control of the Tumor	+		(+)	+
Documentation/Data analysis	+			+
Follow-up	+			

Establishing clear protocols (Cheque list) for your own institution is necessary for the safe delivery of SBRT.

Starting a SRT Program for Brain and Body: Clinicians perspective

- Karin Dieckmann
- Matthias Guckenberger

Motivation for SRS / SBRT

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

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

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

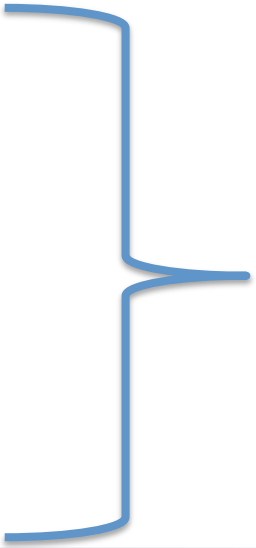
- **READ THE LITERATURE**

- 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

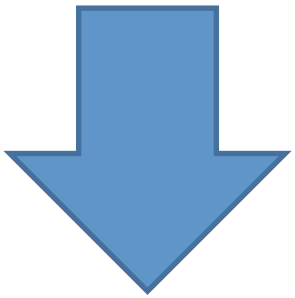
Staffing-Building a SRT Team

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



Good logistic

- LINAC
- Tomotherapy

Much more than one patient per day

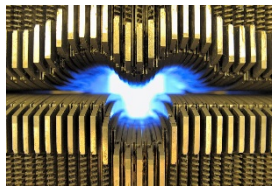
Stereotactic Unit

- Dedicated LINAC
- CyberKnife
- GammaKnife

Collection of Pro and Cons

Device	Non-Dedicated LINAC	Dedicated LINAC	Cyberknife	Gammaknife
Pro	Flexibility IMRT, Dyn. Arc Frameless Body and brain Other treatment options	Flexibility IMRT, Dyn. Arc Frameless Body and brain	Frameless Body and brain	High precision (Frameless) Short process of planning and treatment
Cons	Long treatment time Additional equipment Interfaces	Longer treatment time Additional equipment depending on device	Longer treatment time	Frame-based dedicated to brain; skull base Upper neck

Equipment demands



Linac

≤ 5 mm leafs
circular collimators

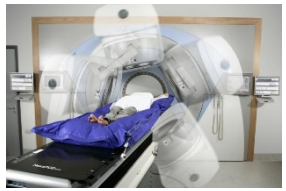
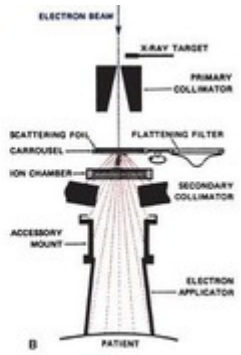


Image guidance

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

Equipment demands

„Don´t miss the target with high precision!“

Planning system

Commissioning for small fields

Tissue heterogeneity for lung

End to End test

Quality assurance at a LINAC and TPS for SRT

- Treatment Isocenter (e.g. Winston Lutz)
- Imaging Isocenter Control every day
- Image Quality for IGRT every 6 months
- Dry run of treatment
- Field check
- Independent dose calculation check

Workflow
Written SOPs

Written **SOPs** covering

- implementation and
- practice of the total SRS work-flow
  - Patient selection
  - Consent
  - Imaging
  - Target volume definition
  - Treatment planning
  - QA
  - Treatment delivery
  - Follow-up

Workflow: Logistics

- SRT based on decisions of the tumour board
- Free access to CT and MRI: every day, twice a week.....
- Mask / CT / MRI: performed at the same day
- Tools for Imaging and Image handling
- Planning: Interval between planning data acquisition and treatment delivery after 2-3 days
- Treatment delivery:

  Inpatient

  Outpatient

Contract with Insurances
Number / Size/ Location of metastasis
Status of the patient
Distance to the hospital

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,.....)

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: clinicians perspective

Professor Suresh Senan
VU University Medical Center


Developing your SABR program

- An oncology center is incomplete without facilities for SABR

- Be aware of current **guidelines*** and discuss them with your colleagues and administrators (* broad consensus in your speciality)

- Obtain support of your tumor board, and use it for patient selection purposes

Starting your SBRT program

- Motivation of others in your tumor board, department or hospital - not everyone can be persuaded with scientific data alone.
- Minimise unsubstantiated comments ('*SBRT is a breakthough for pancreas carcinoma*')
- Recognize positive effect on retaining skilled personnel
- Consider equipment available or planned acquisitions (workflow or 'latest' technology)

Starting your SABR program

- Do you have sufficient facilities? For example, MRI slots for vertebral lesions, interventional radiologists
- Focus first on established indications with little competition (e.g. stage I NSCLC, re-irradiation of vertebral tumors)

Dahele M

I. J. Radiation Oncology ● Biology ● Physics Volume 81, Number 2, 2011

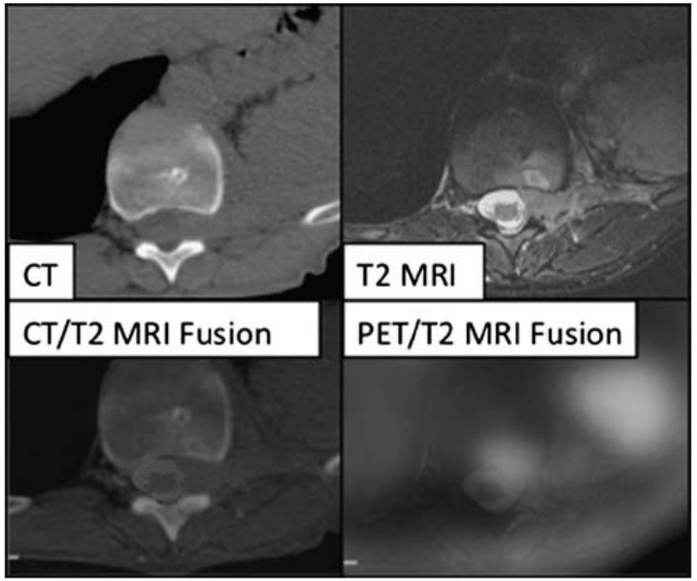
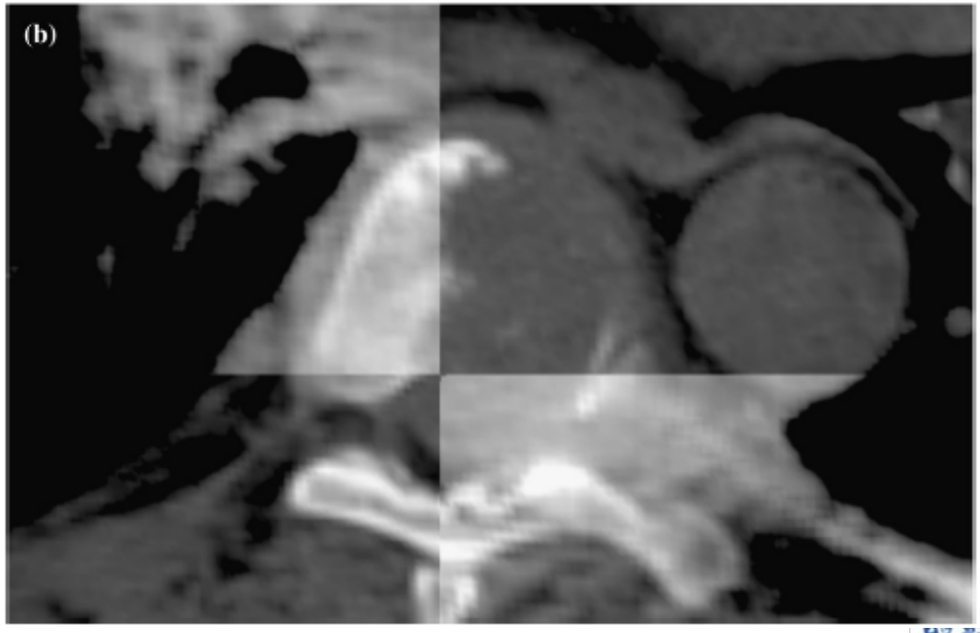


Fig. 3. Use of T_2-weighted MRI to show contents of spinal canal is illustrated, and the impact of CT-MRI fusion is demonstrated. The images show tumor within the spinal canal,which displaces the thecal sac. Although detected on CT, the latter structure is more easily appreciated on T_2-weighted MRI and CT and/or T_2-weighted MRI fusion. The presence of metabolically active tumor is seen on the fused PET and MRI images.



Starting your SABR program

- Mono-disciplinary meetings (e.g. clinicans treating oligometastases) to limit public disagreements

- Develop written protocols with input from physicists and technologists, standardize contouring of critical organs etc.

Opinion makers to influence (2003)

VUmc

Surgeons

Lung physicians

Insurance companies

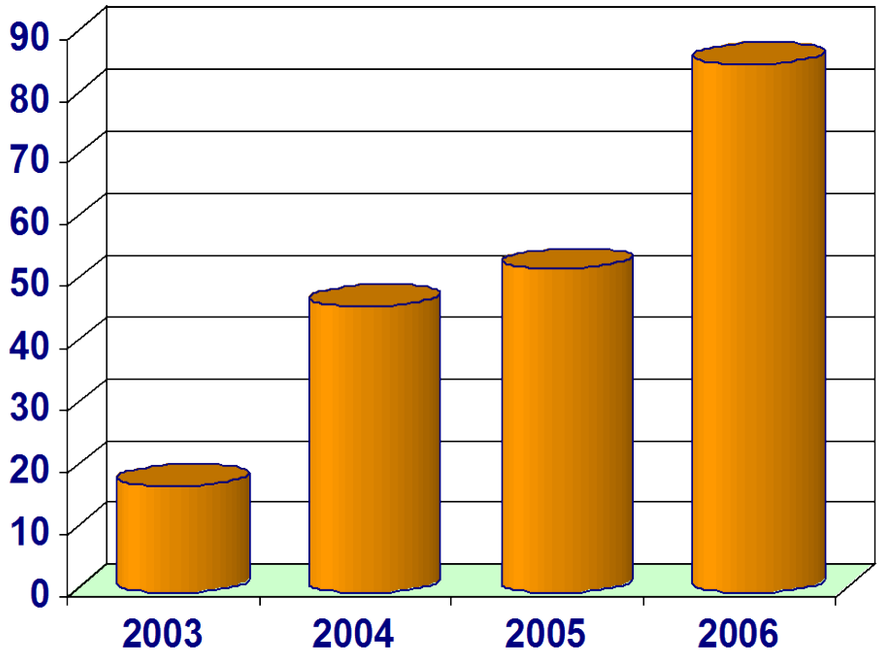
Radiation oncologists

Medical oncologists

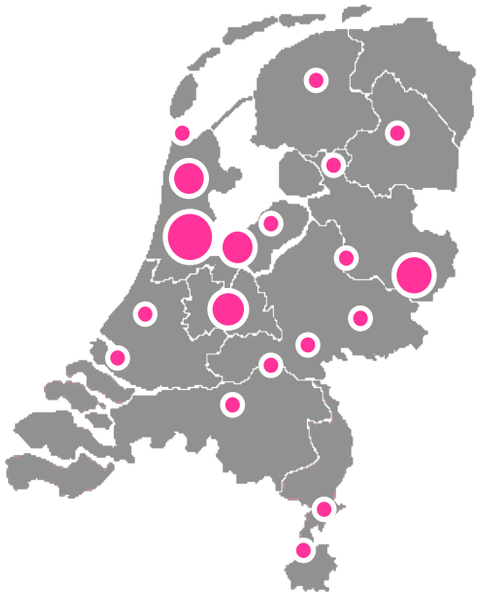
Health regulators

Identify gatekeepers for disease

- Teaching course for Dutch pulmonologists (*showing 4DCT movie loops*)
- Mail following CT scans to pulmonologists
- ‘Generic guidelines’ - ROSEL techniques

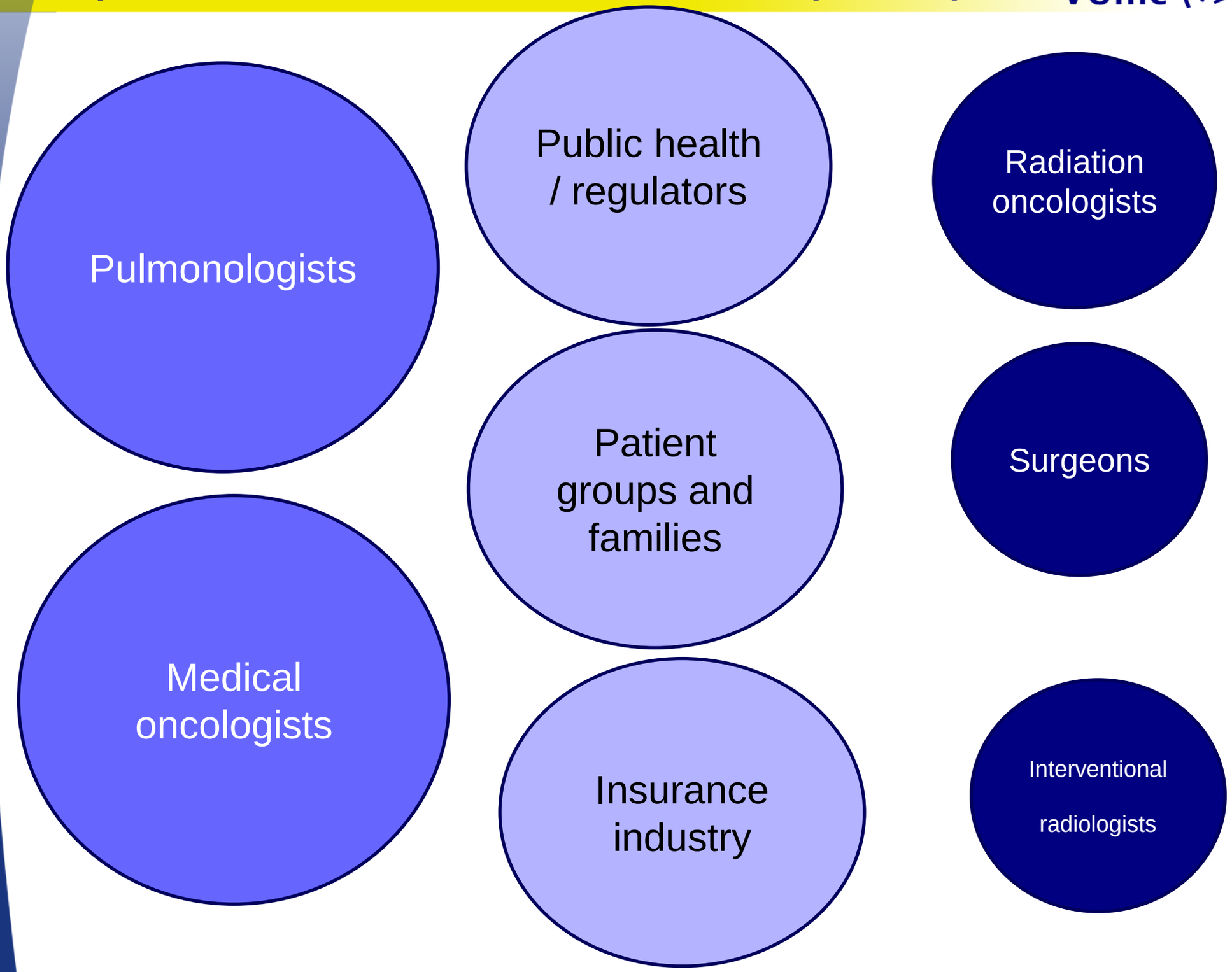


Source of referrals



Referrals to VUMC for stage I NSCLC

Opinion makers to influence (2015)



Doctors preferences: Binary choice experiment

Are surgery and SABR comparable treatment options in stage I NSCLC?

Of 126 Dutch thoracic oncologists, 55% agreed

- 49.3% of pulmonologists,
- 17.6% of thoracic surgeons
- 83.3% of radiation oncologists

Hopmans W, Radioth Oncol 2015

Patient's right to know

VUmc

The Oncologist® 2014

European Perspectives

A Catalyst for Change: The European Cancer Patient's Bill of Rights

Mark Lawler,[a] Thierry Le Chevalier,[b] Martin J. Murphy, Jr.,[c] Ian Banks,[d] Pierfranco Conte,[e] Francesco De Lorenzo,[f,g] Françoise Meunier,[h] H.M. Pinedo,[i] Peter Selby,[j] Jean-Pierre Armand,[k] Mariano Barbacid,[l] Michèle Barzach,[m] Jonas Bergh,[n] Gerlind Bode,[o] David A. Cameron,[p] Filippo de Braud,[q] Aimery de Gramont,[r] Volker Diehl,[s] Sarper Diler,[t] Sema Erdem,[u] John M. Fitzpatrick,[v,w] Jan Geissler,[x,y] Donal Hollywood,[z,†] Liselotte Højgaard,[aa,bb] Denis Horgan,[cc] Jacek Jassem,[dd] Peter W. Johnson,[ee,ff] Peter Kapitein,[gg] Joan Kelly,[v,hh] Sandra Kloezen,[ii] Carlo La Vecchia,[jj] Bob Löwenberg,[kk] Kathy Oliver,[ll] Richard Sullivan,[mm] Josep Tabernero,[nn] Cornelis J. Van de Velde,[oo] Nils Wilking,[pp] Roger Wilson,[qq] Christoph Zielinski,[rr] Harald zur Hausen,[ss] Patrick G. Johnston[a,tt]

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News

Doctors should not cherry pick what information to give patients, court rules

BMJ 2015 ; 350 doi: http://dx.doi.org/10.1136/bmj.h1414 (Published 13 March 2015)
Cite this as: *BMJ* 2015;350:h1414

Article Related content Metrics Responses

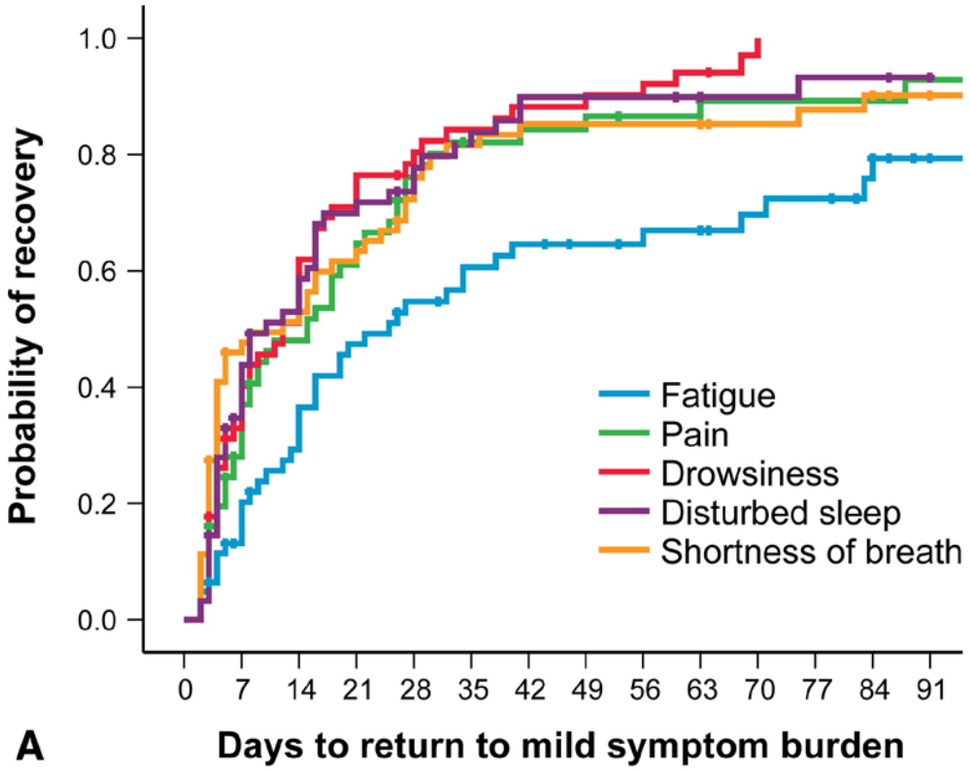
Clare Dyer

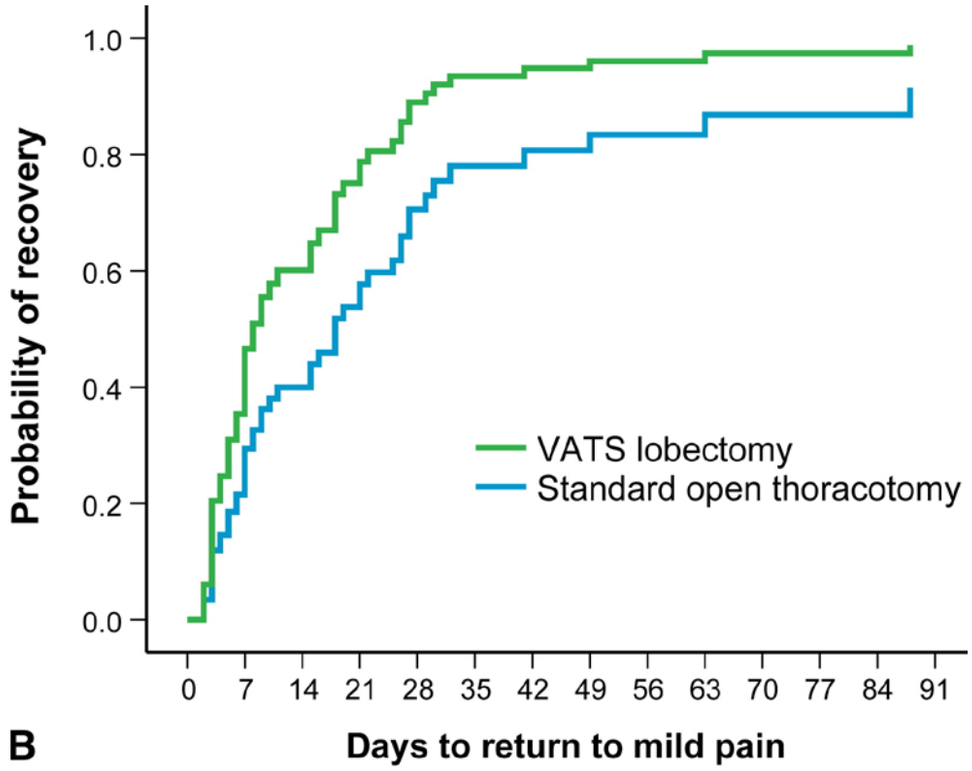
Author affiliations

Patient-reported symptom recovery post-surgery

VUmc

Measures using MD Anderson Symptom Inventory





Fagundes CP, JTCVS 2015

Starting your SABR program

- True improvements arising from local treatments are uncommon, and healthcare costs are important (cost-benefit ratio)
- Avoid over-promising and under-delivering (e.g. proton therapy …)
- Developments in competing ablative therapies (RFA, Nanoknife® Irreversible Electroporation)

Medscape Medical News > Oncology

Nanoknife Ablation Doubles Survival in Pancreatic Cancer

Alexander M. Castellino, PhD

September 01, 2015

It can be a hard toil, but an oncology center is incomplete without facilities for SABR

ESTRO School

Starting an SBRT program: Physics perspective

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

Outline

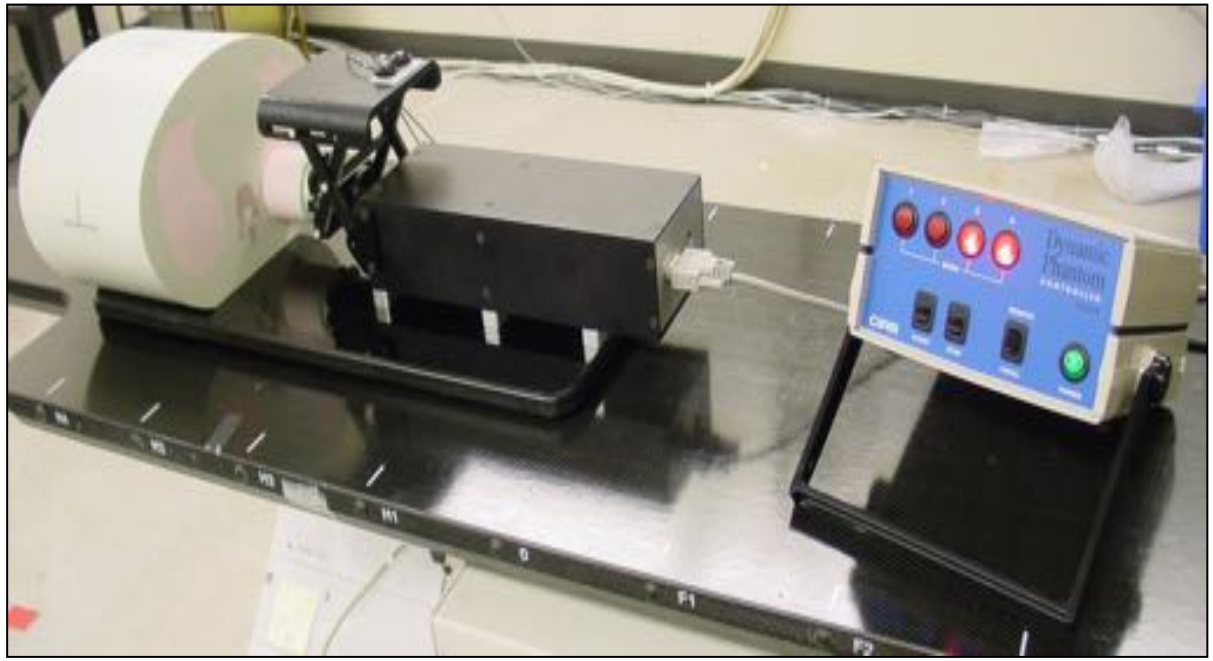
- Commissioning
  - New game, new tools?
  - Some examples
- Become comfortable with workflow
  - eg perform dry run
- Pre-treatment QA
  - Some examples
- Verification during treatment
  - eg tracking errors / variations in anatomy
- FMEA (It's not plug and play)
- Follow-up

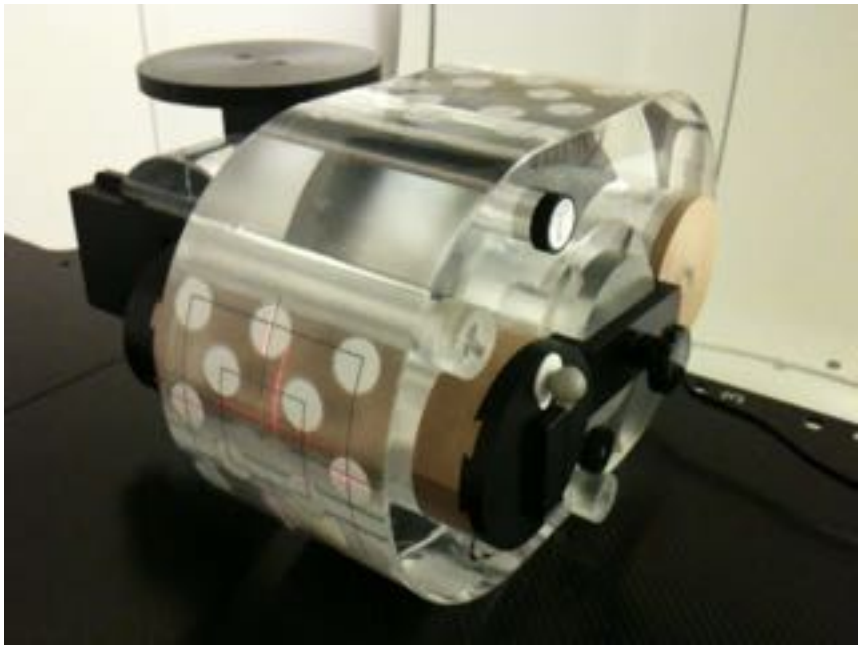
Commissioning

- Usually, this is the only time physicists can perform EXTENSIVE testing, make time.
- Don't forget QA of the QA material
  - eg mechanical performance of phantoms, leakage/noise chambers, performance film dosimetry and analysis, …
- New game, new tools?
  - Specific requirements for dosimetry
    - eg heterogeneity correction
    - eg non-standard and small field dosimetry
    - eg interplay effects (VMAT?)
  - Specific requirements for image-guidance system
    - eg coincidence of imaging isocentre and treatment isocentre
    - eg timing gating trigger, tracking accuracy
  - Specific requirements for QA tools (4D?)
- End2End testing
- External audits

Phantoms

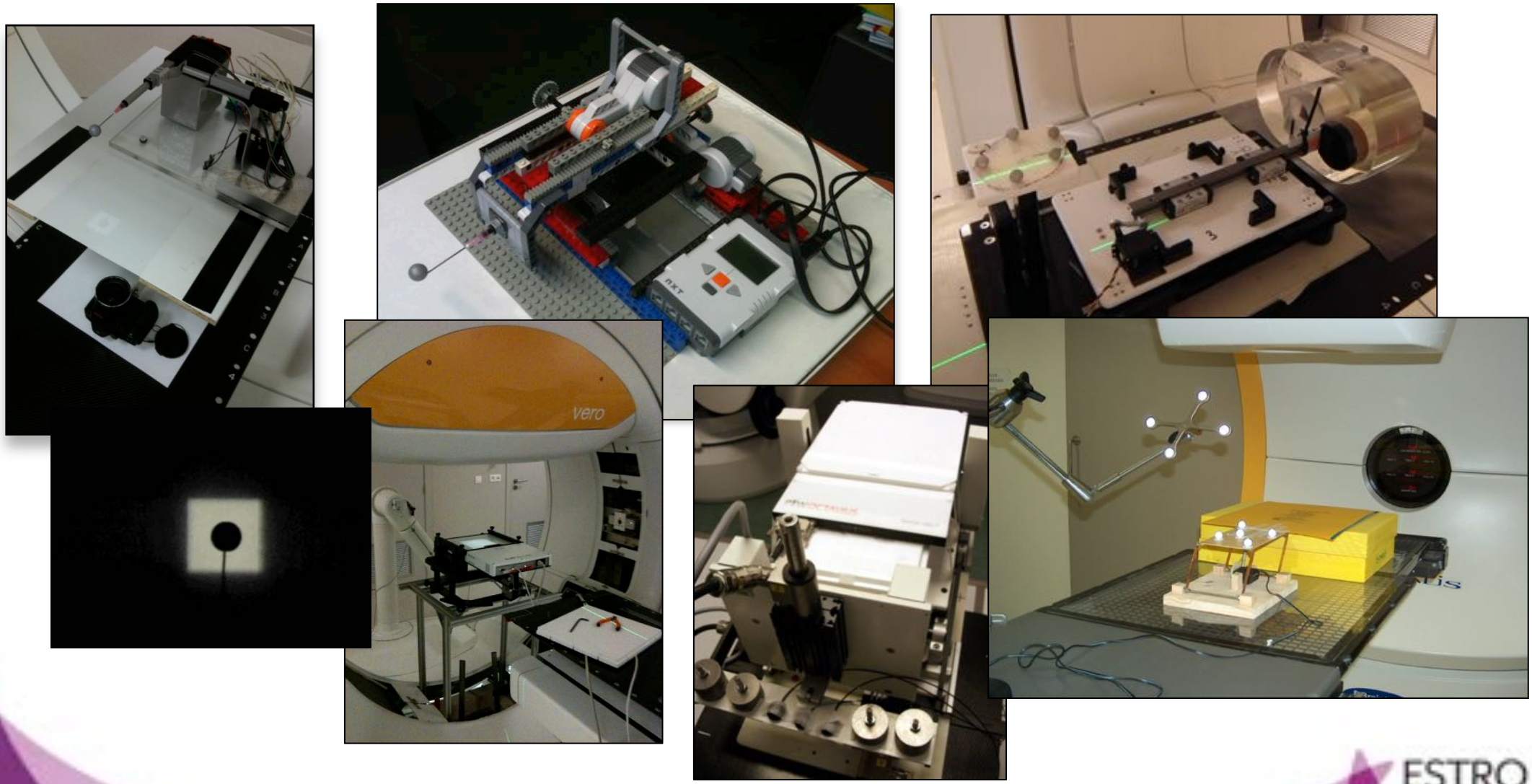
- Commercial solutions



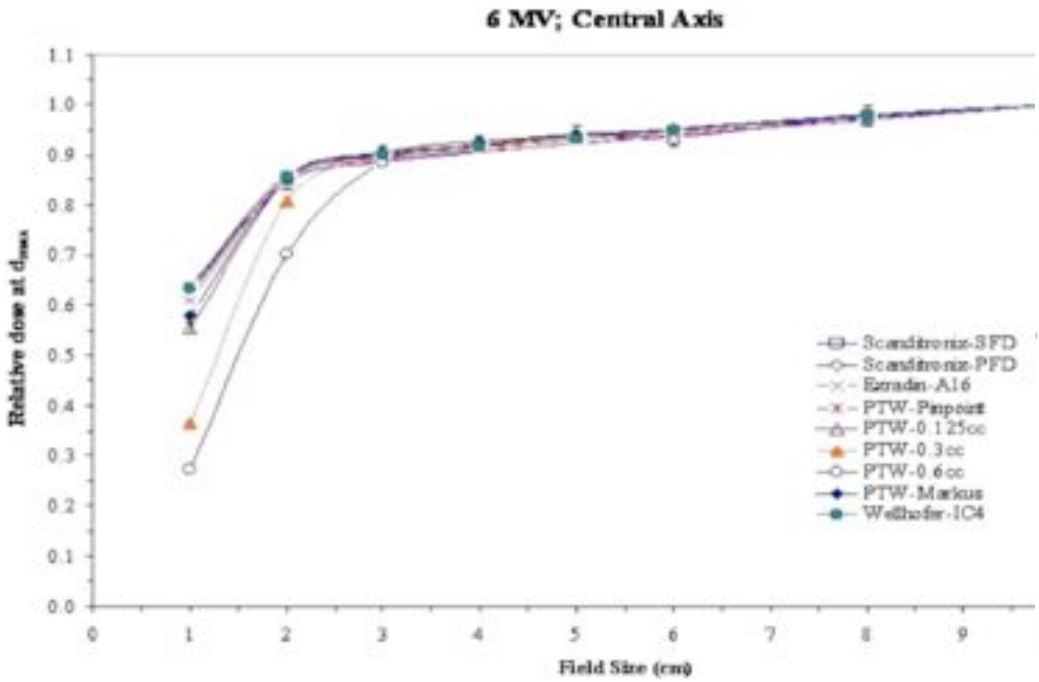


Phantoms

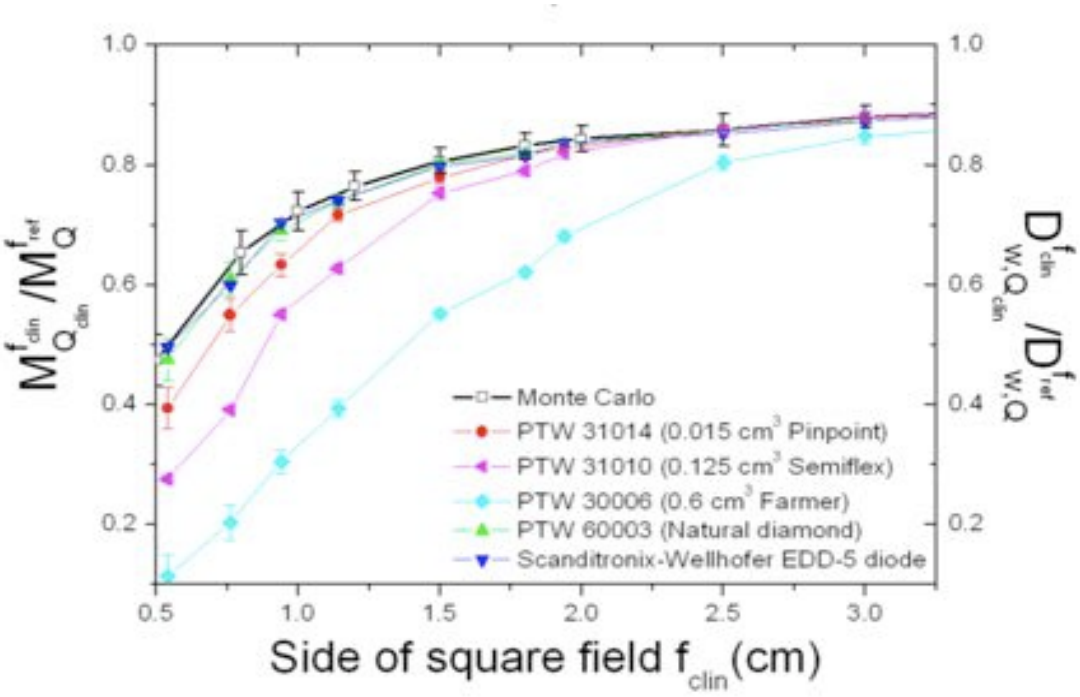
- Commercial solutions … sometimes require improvisation



Detectors

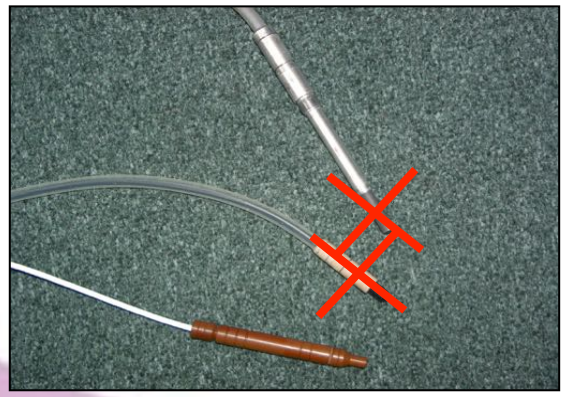


Das IJ, *et al.*, Med Phys, 2008



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

In this case … size does matter!!!



Toulouse: 2006-2007

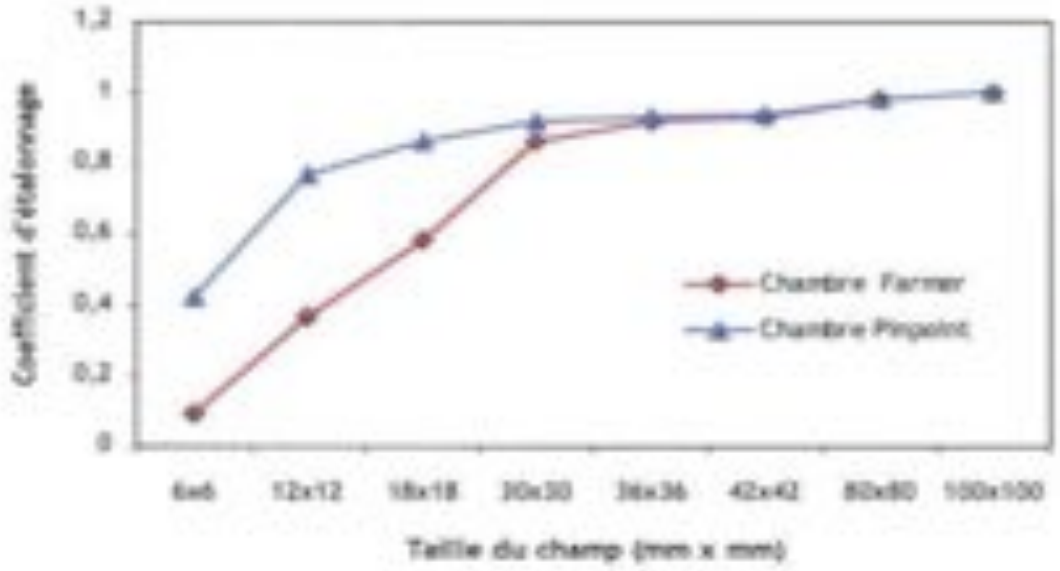
L'ACCIDENT DE RADIOCHIRURGIE STEREOTAXIQUE AU CENTRE HOSPITALIER UNIVERSITAIRE DE TOULOUSE

Rapport d'expertise N°2

Evaluation dosimétrique et clinique
Analyse de risque

Les surdosages sont liés à une erreur initiale d'étalonnage de l'accélérateur Novalis en avril 2006 causée par l'utilisation d'un détecteur inapproprié, dont le volume sensible était trop grand devant les dimensions des faisceaux à étalonner. La procédure de Brainlab WOI 10-26, § 6.3.4 spécifie que les mesures de coefficients d'étalonnage[1] doivent être réalisées à l'aide d'une chambre d'ionisation de volume maximal 0,03 cm^3. Malgré ces spécifications, ces mesures ont été effectuées, en avril 2006, à l'aide d'une chambre d'ionisation « Farmer », de volume sensible 0,65 cm^3 (cylindre de longueur 23,1 mm et de diamètre 6,2 mm), 20 fois plus élevé que celui de la chambre recommandée.

145 patients affected



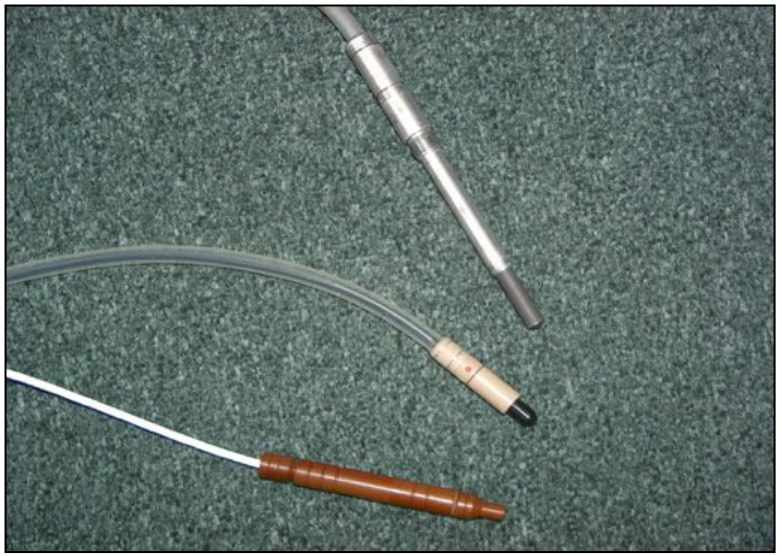
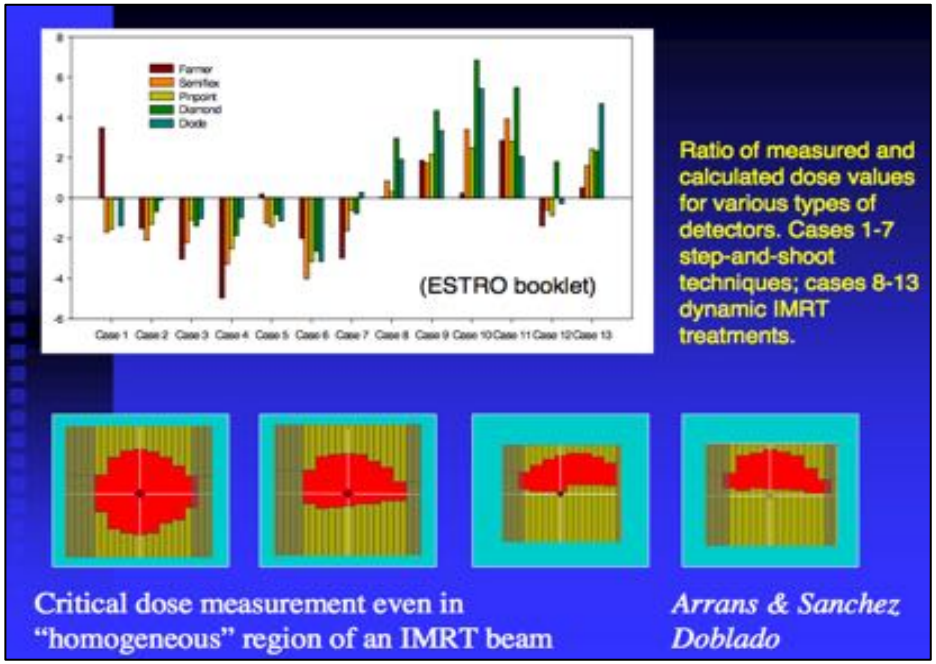


Figure 4 : *Coefficients d'étalonnage mesurés avec les chambres Farmer et Pinpoint pour différentes tailles de champ.*

ESTRO School

Non-standard & small field dosimetry



- 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

Heterogeneity correction

- The problem is that with the evolution of more accurate or different dose calculations, the reported doses using one system are not always comparable to doses obtained with another (e.g. lung treatment).
- Type A and B … modeling and verification is important

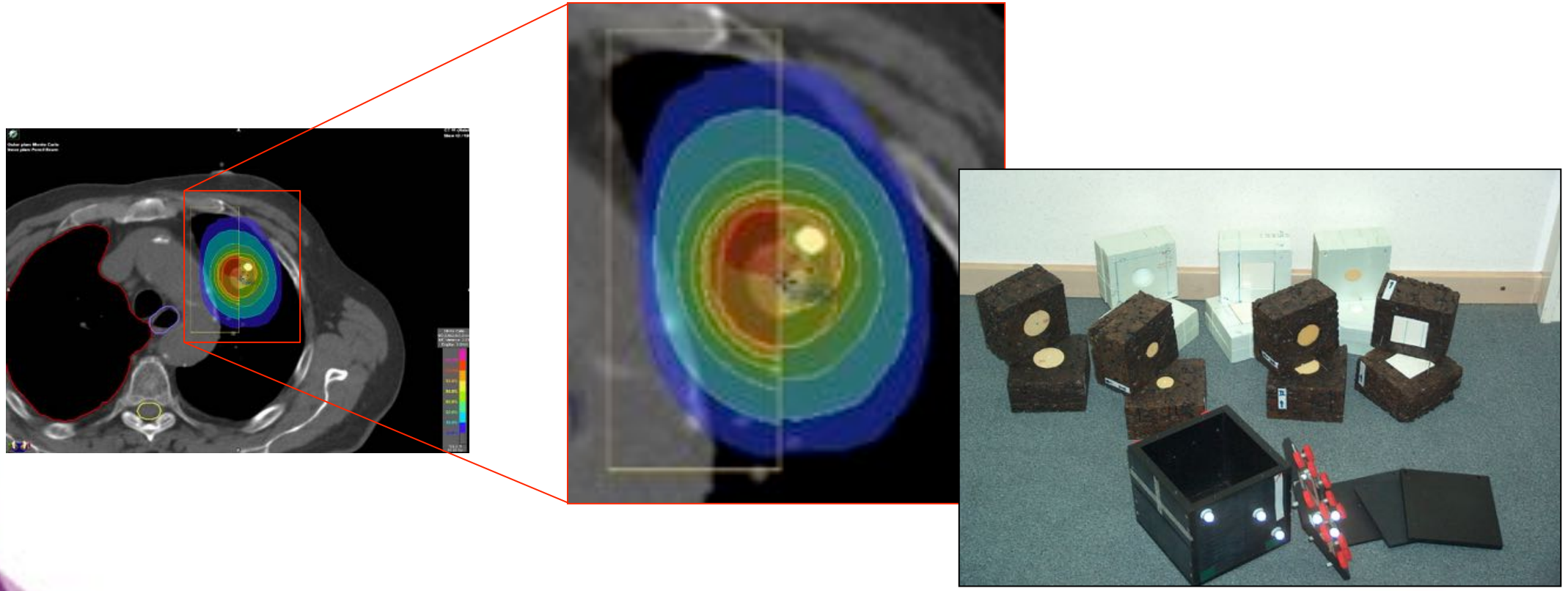
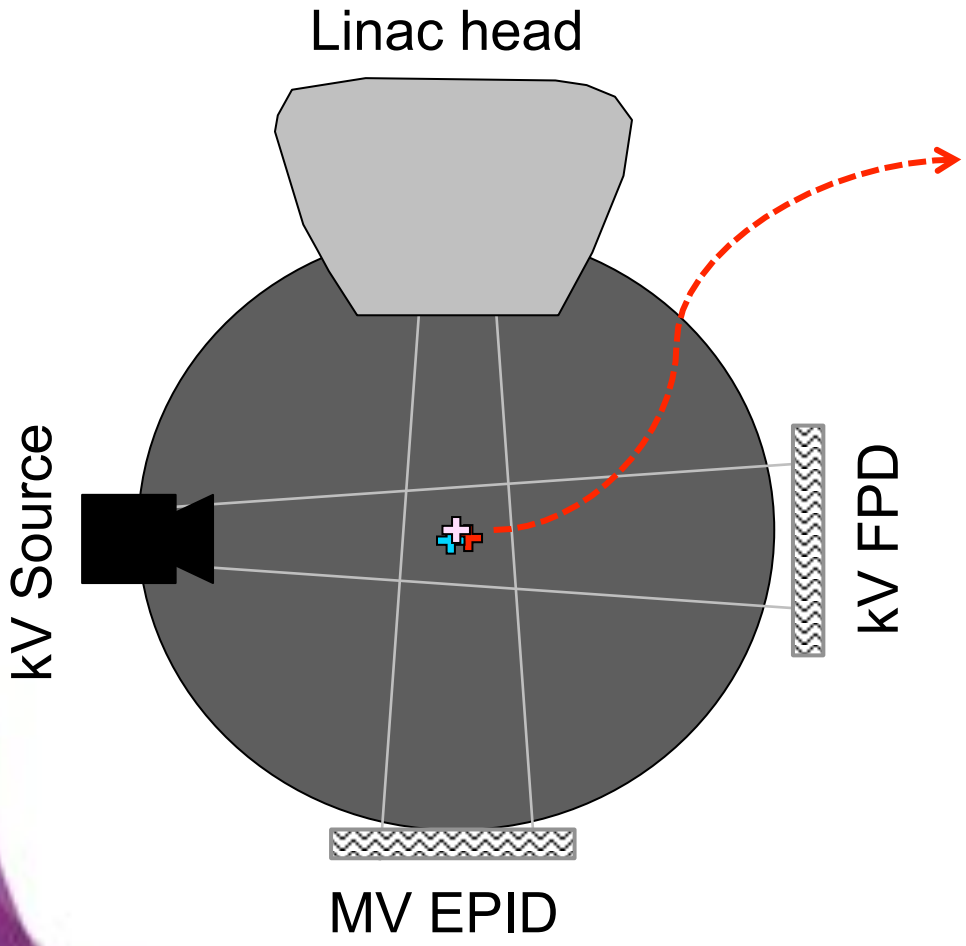
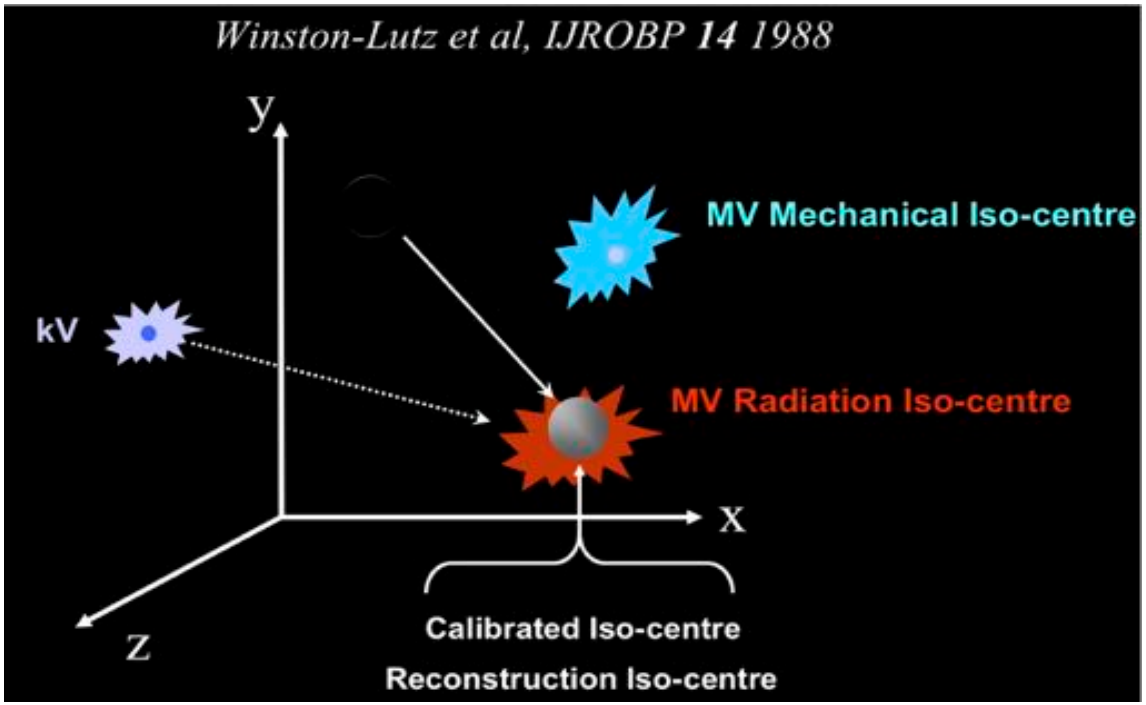


Image-guidance

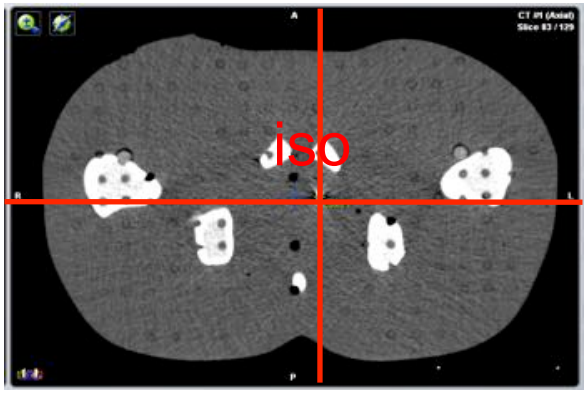
"Even if a kV system is mounted on the same gantry the kV isocentre does not coincide exactly with the MV isocentre "



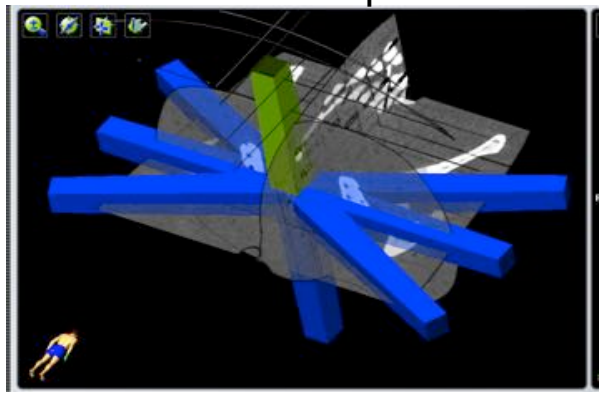


Hidden Target Test

2mm BB in isocenter

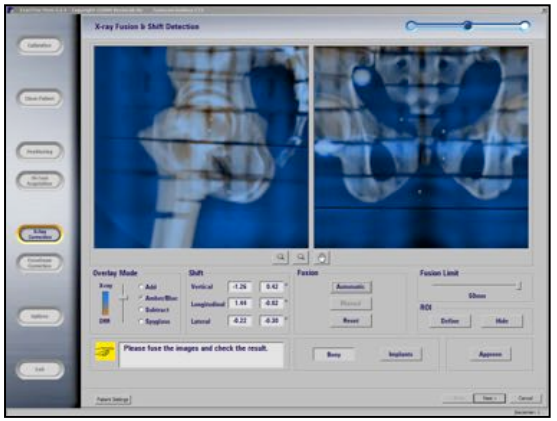


Plan 30x30mm open fields

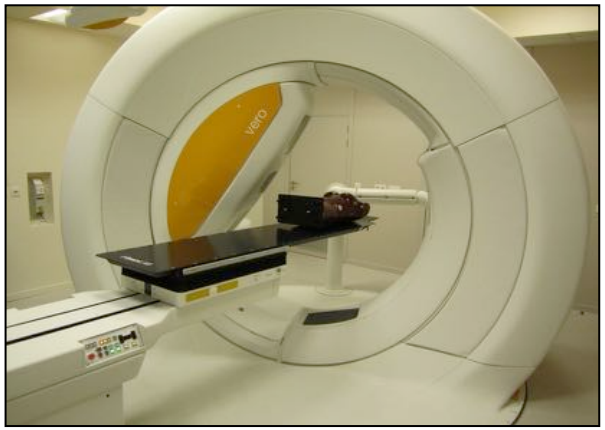


Phantom positioning

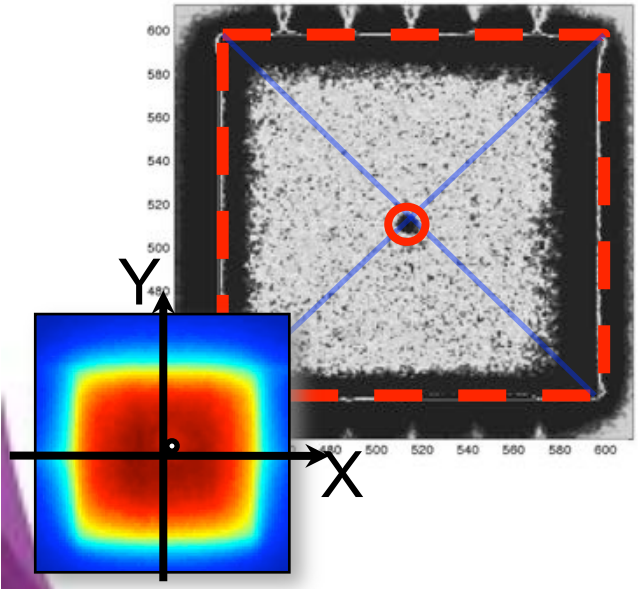
kV planar, kV CBCT imaging



Treatment plan delivery



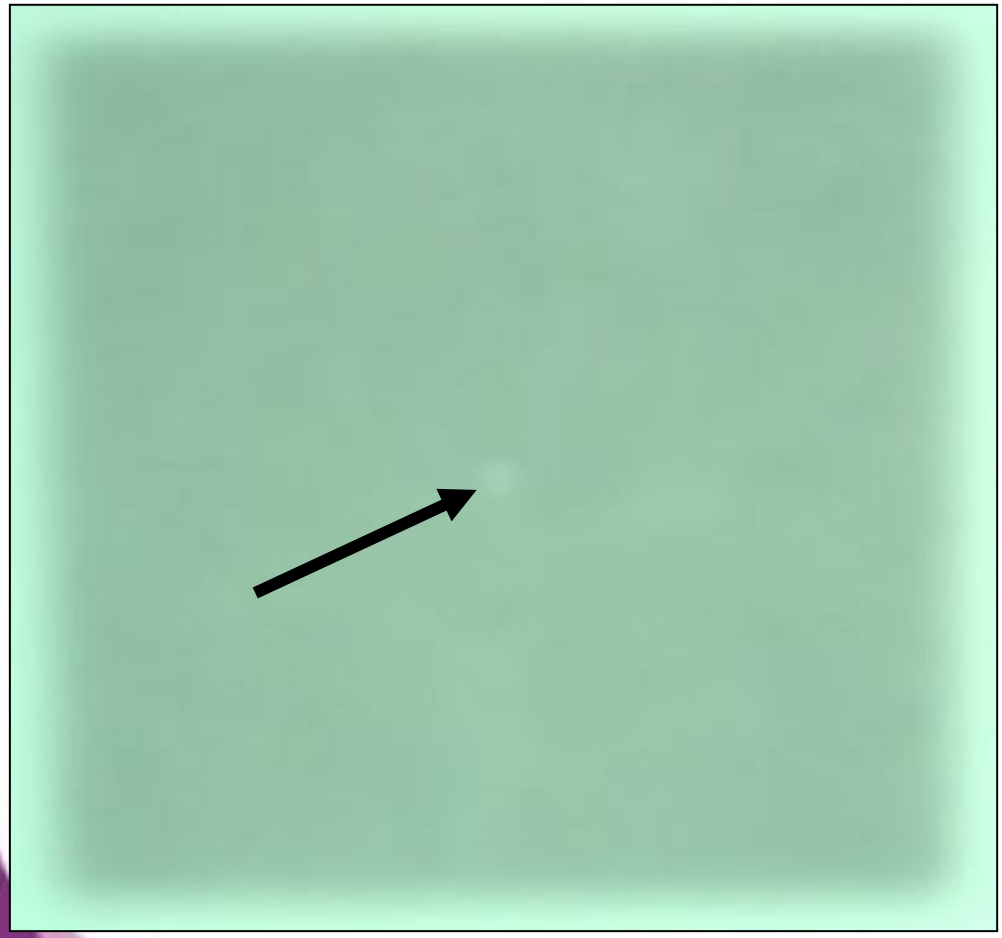
EPID Image analysis



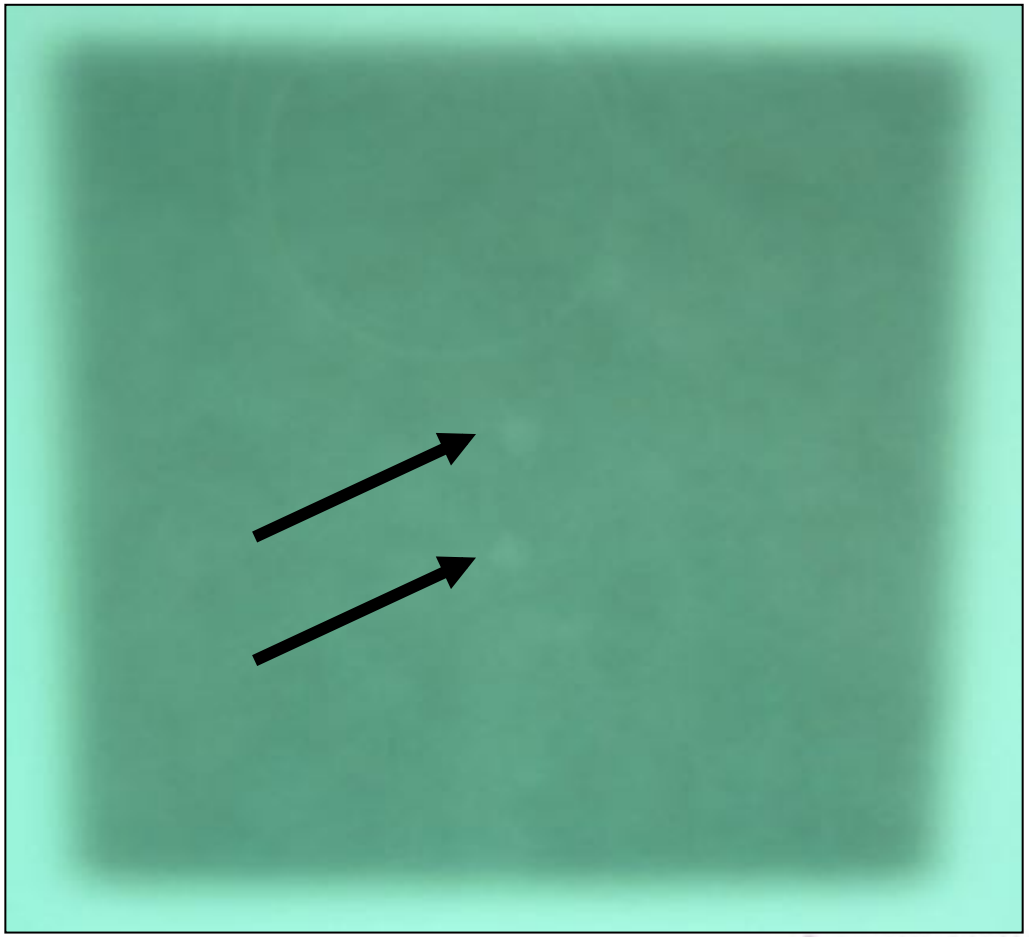
QA of trigger synchronization

- Synchronization of marker detection and linac triggering

Static BB



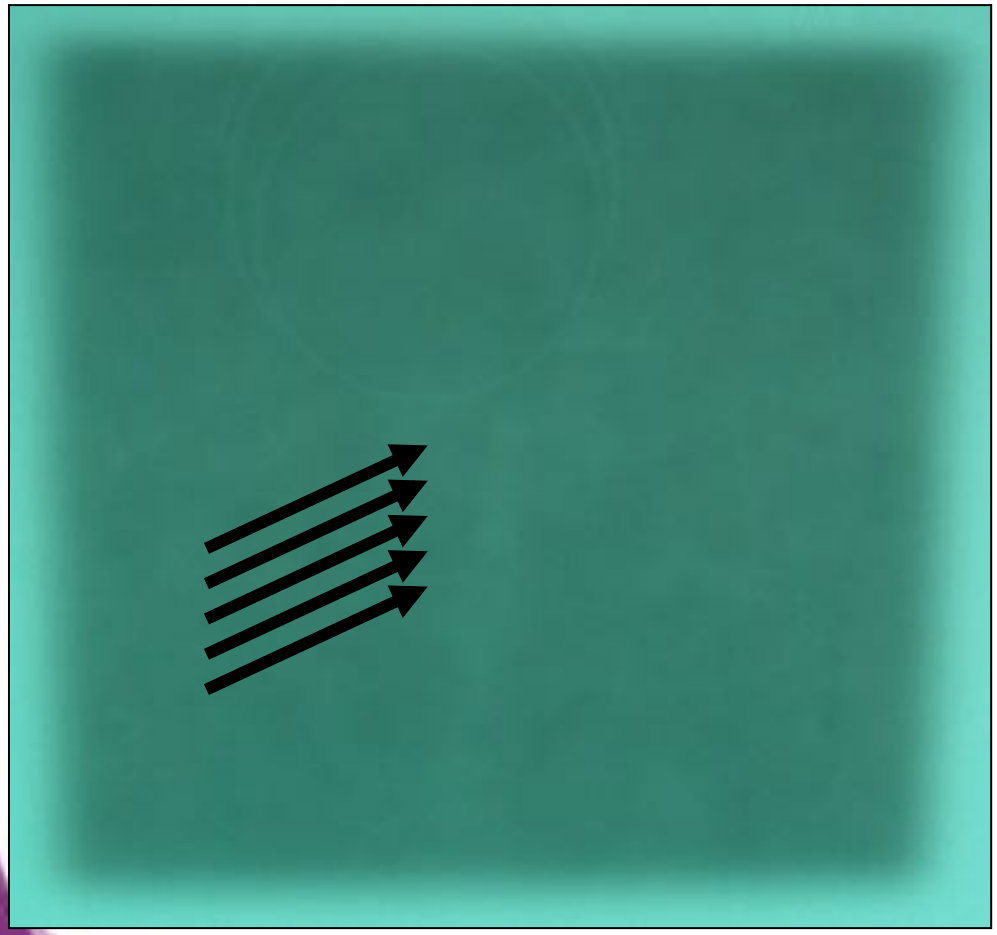
Extreme positions (1 cm)



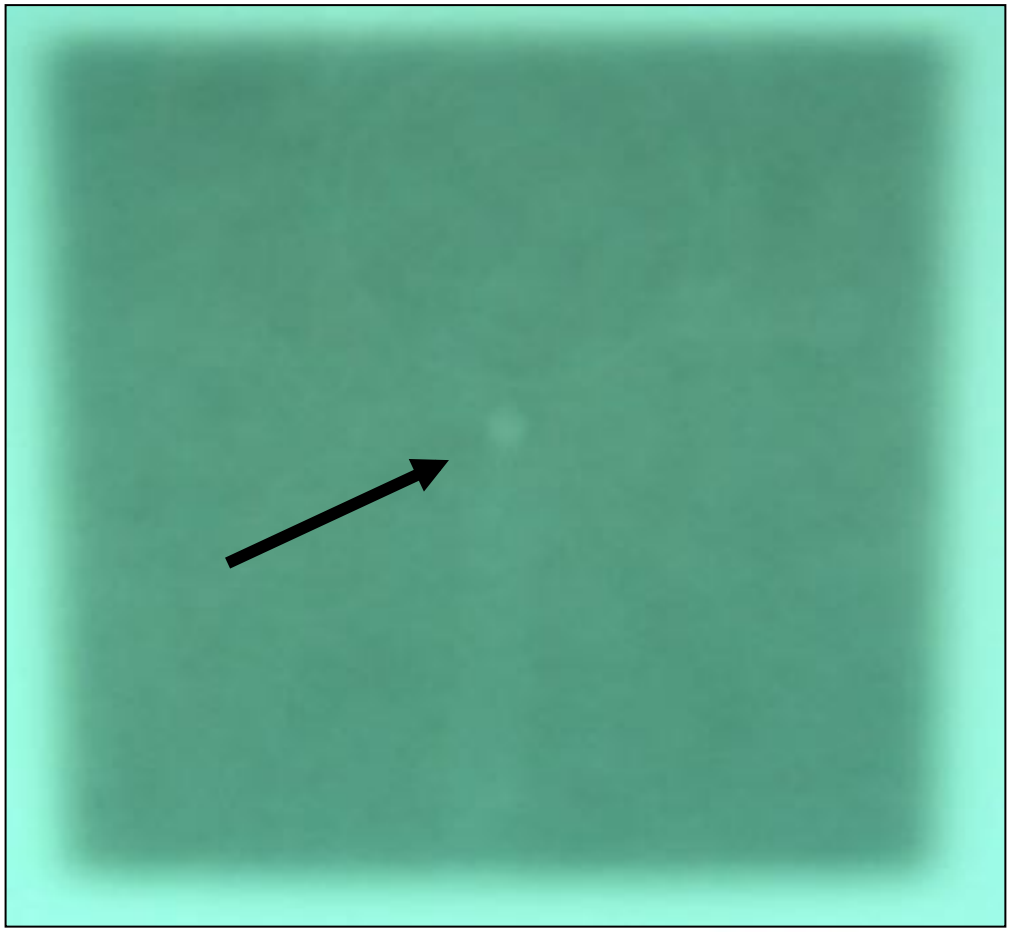
QA of trigger synchronization

- Synchronization of marker detection and linac triggering

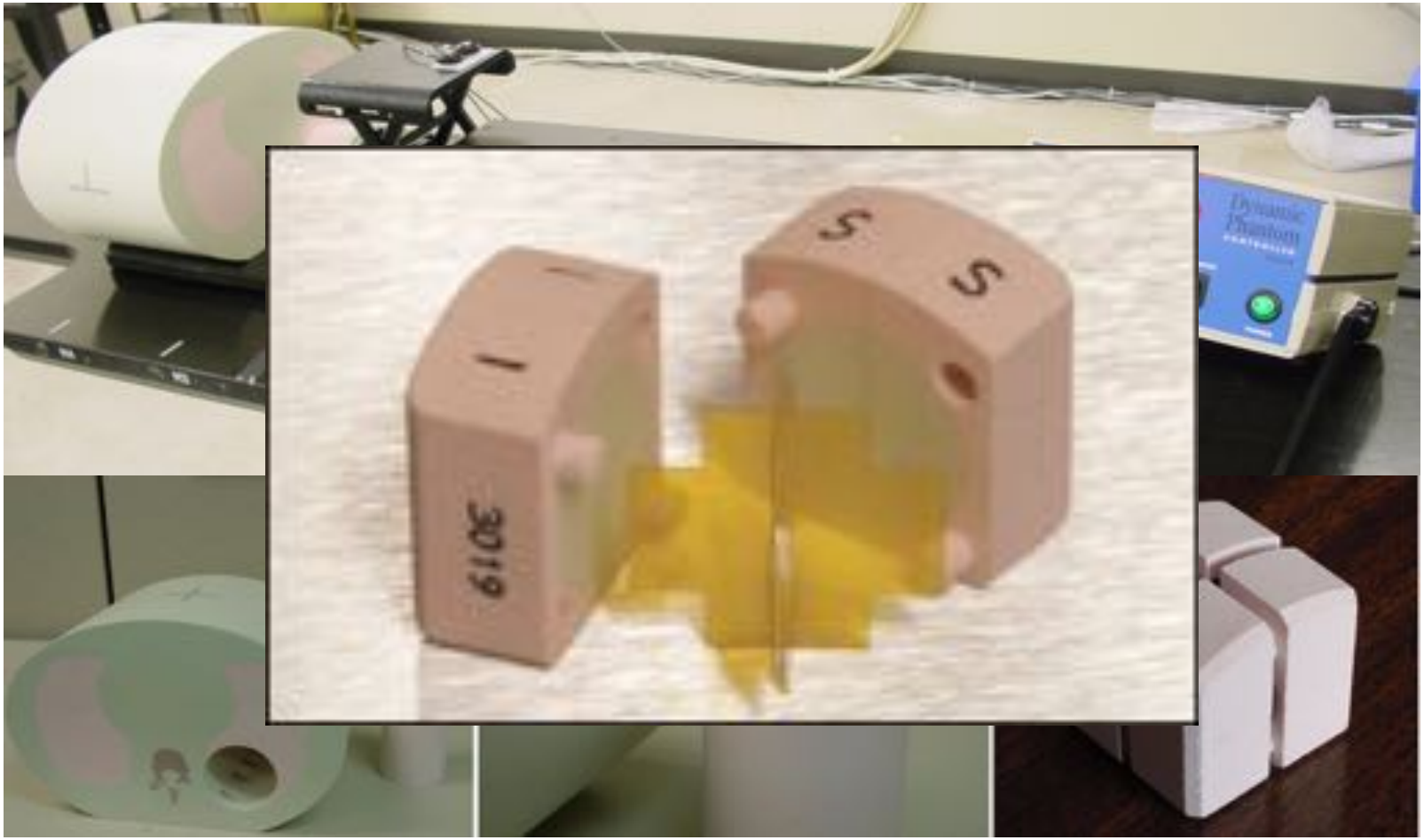
Moving BB



Gated BB

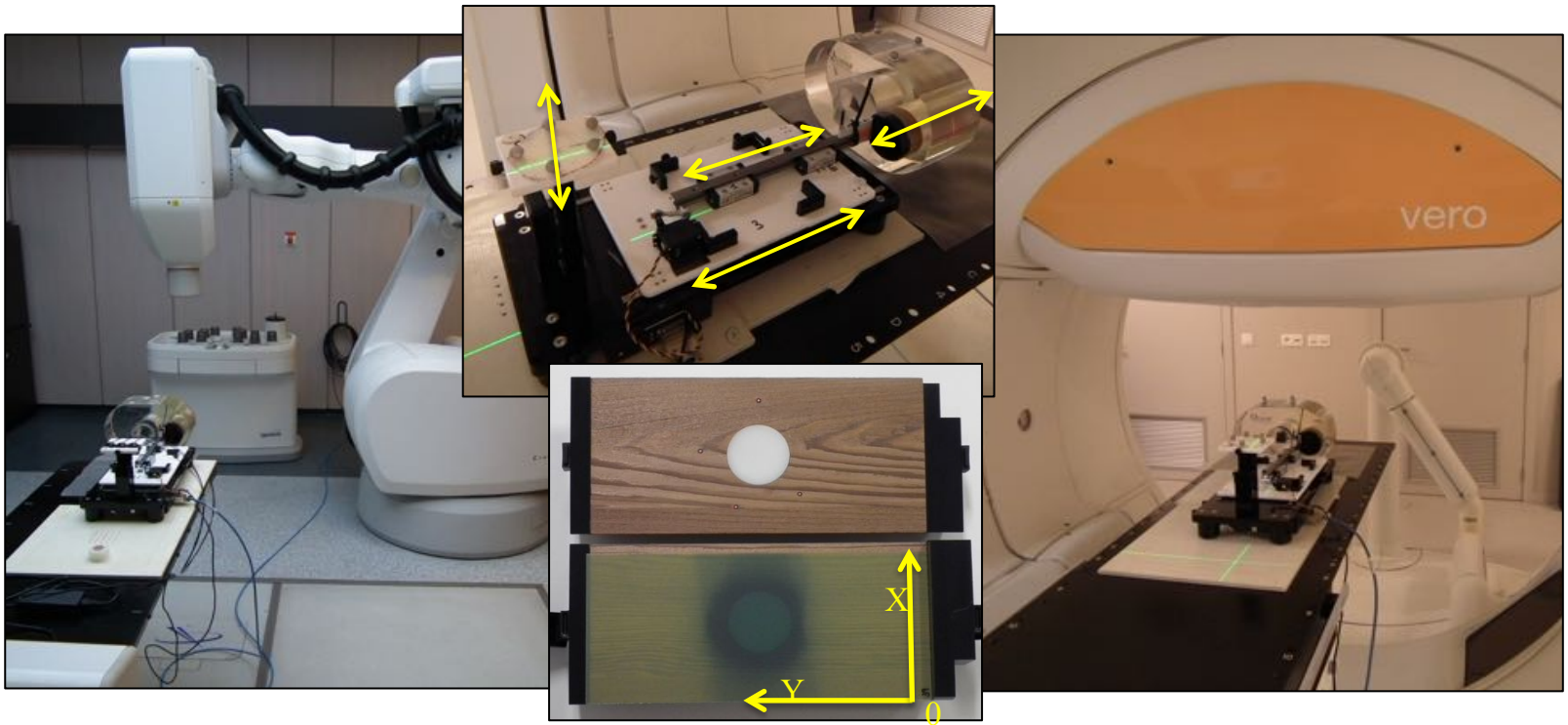


E2E Tests: Direct Target Localization



External audits

- 1D moving phantom reproducing identical patient motion patterns
- Delivered dose measured with gafchromic film

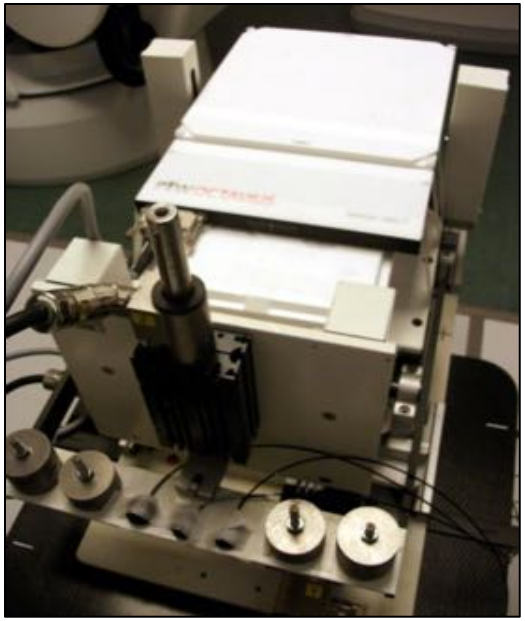


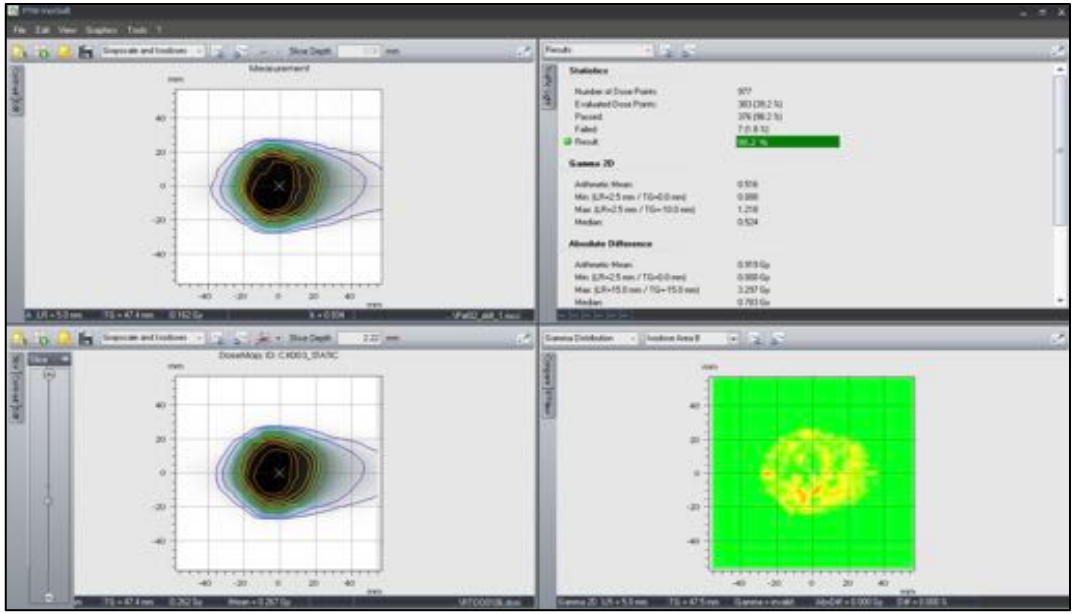
Accuray CyberKnife system
Centre Oscar Lambret, Lille, France

BrainLab/MHI Vero system
UZ Brussel, VUB

External audits

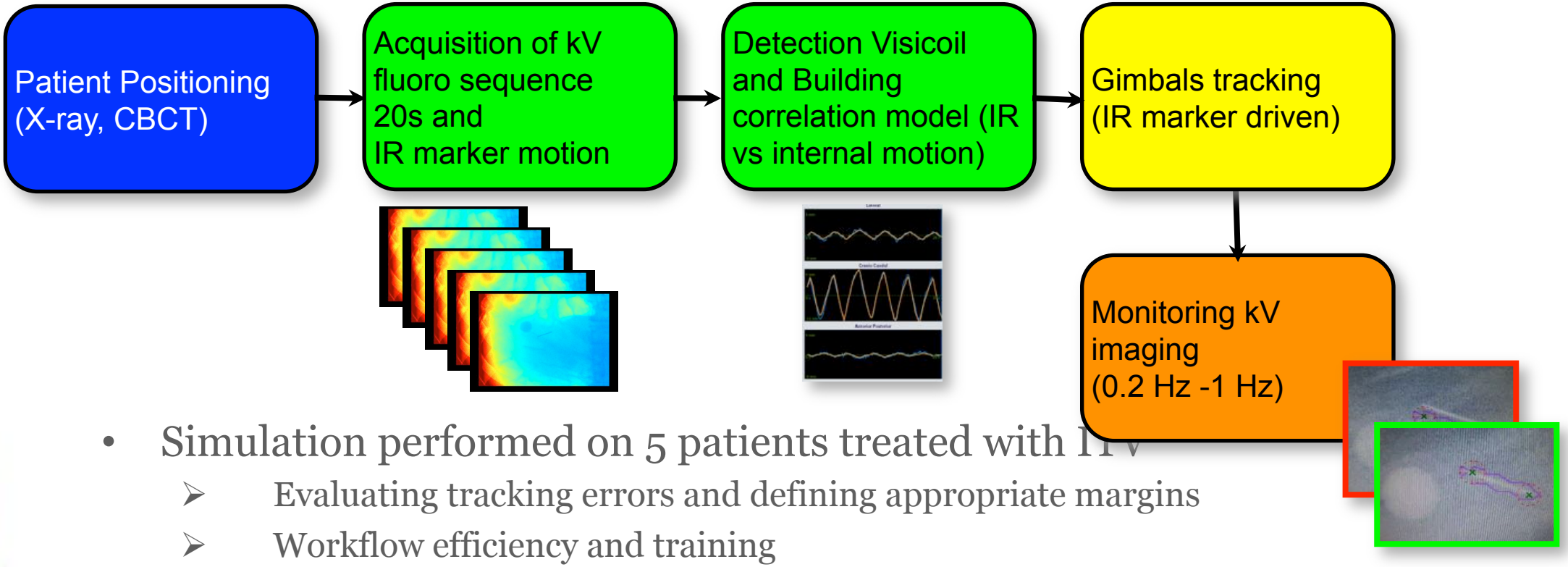
- Vero (UZ Brussel) – CK (Universitätsklinikum Schleswig-Holstein, Kiel)
- PTW 1000SRS, 4D motion platform, 3D patient trajectories (0.5–2.0cm)





Workflow

- "Dry run": Preliminary study to optimize the workflow in a clinical situation and assess tracking accuracy.



- Simulation performed on 5 patients treated with ITV
  - Evaluating tracking errors and defining appropriate margins
  - Workflow efficiency and training
  - Optimizing imaging dose

SBRT Affects the Whole Treatment Chain

- **CT imaging**
  - Slice spacing (for DRR generation), contrast, Field of View (non-coplanar, …)
  - 4D-CT: respiration signal, phase-based/amplitude-based, …
  - Immobilization techniques
- **Secondary image sets**
  - Investigate and discuss MRI Sequences to be used
  - Assess registration methods and registration accuracy
- **Margins**
  - Calculate / estimate required margins and discuss these with the team (radiation oncologist, Physicist, RTT). Discuss the incentive of the treatment.
  - Use your own data!!
  - For differential motion between tumor and organ at risk consider margins around organs at risk
- **Treatment planning**
  - Dose prescription, normalization, reporting (prescription iso-dose 50% - 80%; normalization)
  - Constraints for organs at risk for hypofractionated schedules
  - Plan acceptance: eg hotspots far away from target, skin dose

Workflow & responsibilities

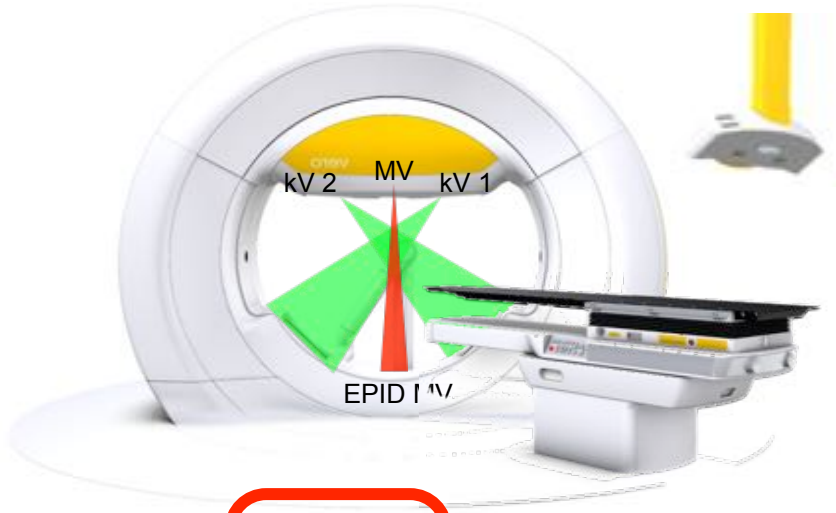
Routine QA

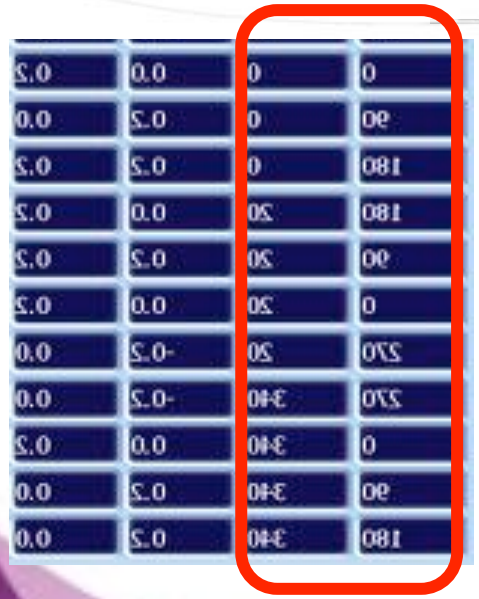
- eg daily checks – AAPM TG 142

TABLE I. Daily.

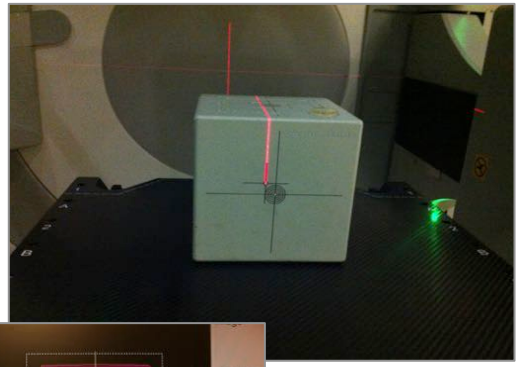
Procedure	Machine-type tolerance		
	Non-IMRT	IMRT	SRS/SBRT
Dosimetry			
X-ray output constancy (all energies)		3%	
Electron output constancy (weekly, except for machines with unique e-monitoring requiring daily)			
Mechanical			
Laser localization	2 mm	1.5 mm	1 mm
Distance indicator (ODI) @ iso	2 mm	2 mm	2 mm
Collimator size indicator	2 mm	2 mm	1 mm
Safety			
Door interlock (beam off)		Functional	
Door closing safety		Functional	
Audiovisual monitor(s)		Functional	
Stereotactic interlocks (lockout)	NA	NA	Functional
Radiation area monitor (if used)		Functional	
Beam on indicator		Functional	

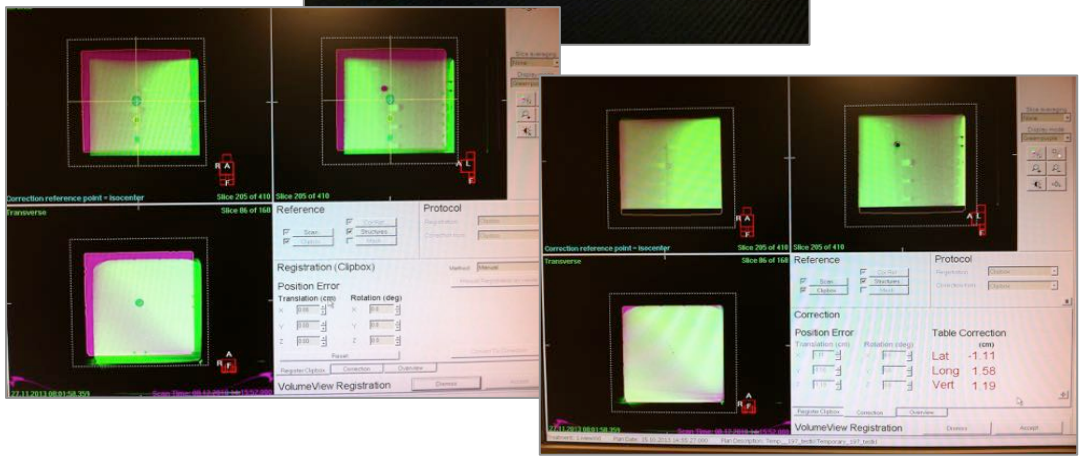
Imaging and Radiation Isocentre Alignment

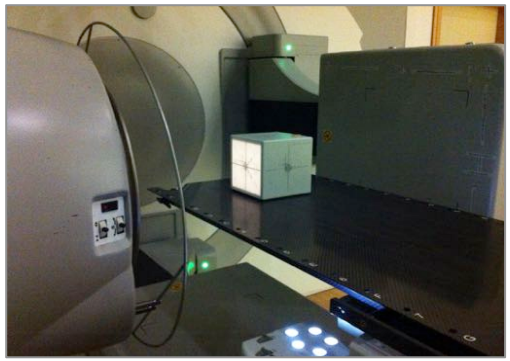




MV-kV isocentre Coincidence < 0.2mm

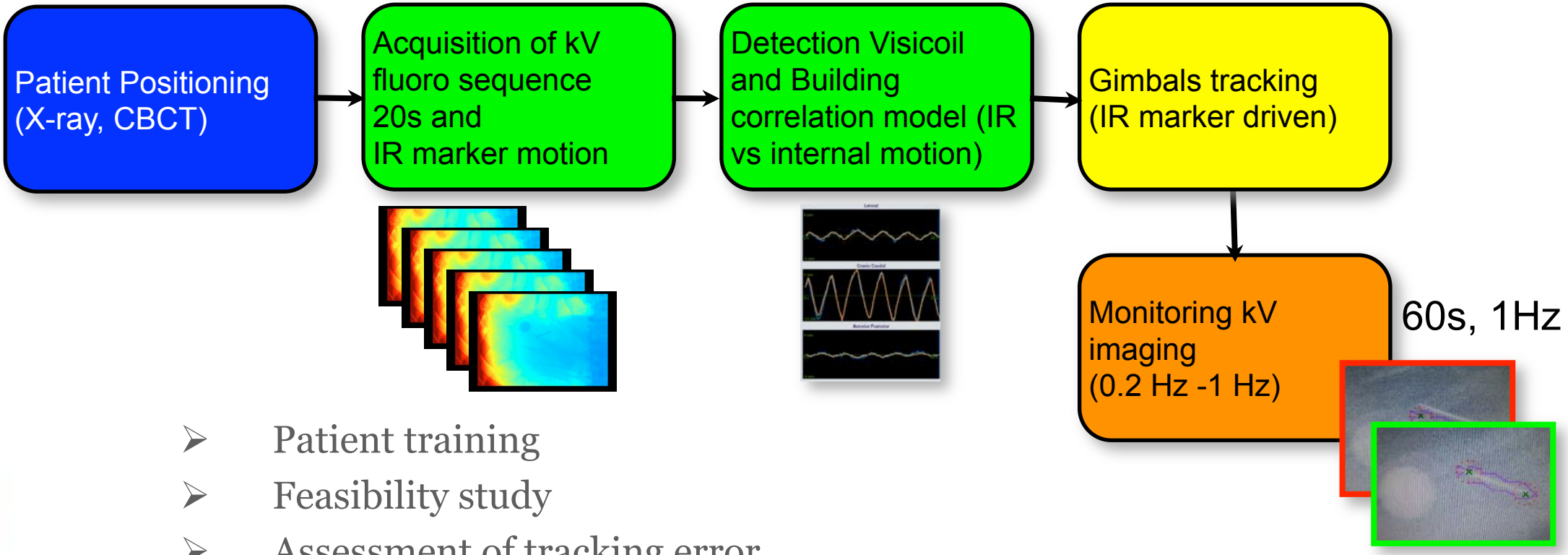






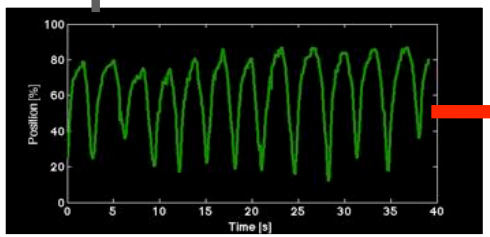
Patient specific pre-treatment QA

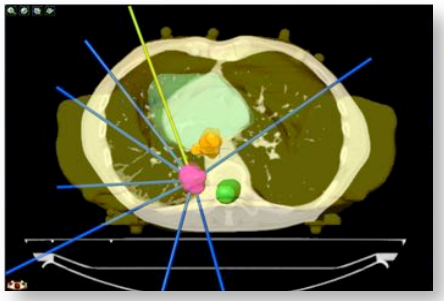
- Dry run or simulation on the treatment machine

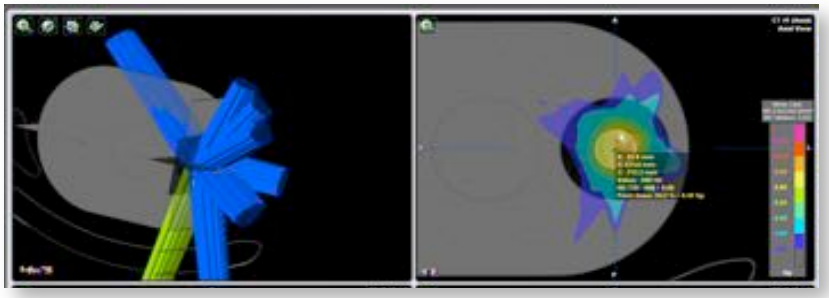


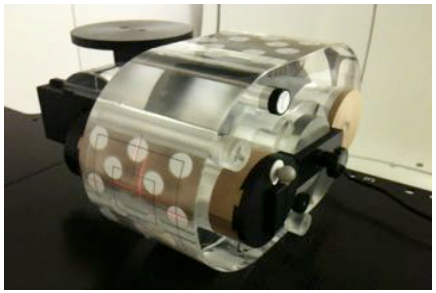
- Patient training
- Feasibility study
- Assessment of tracking error
- Acquiring patient specific respiration signal for QA

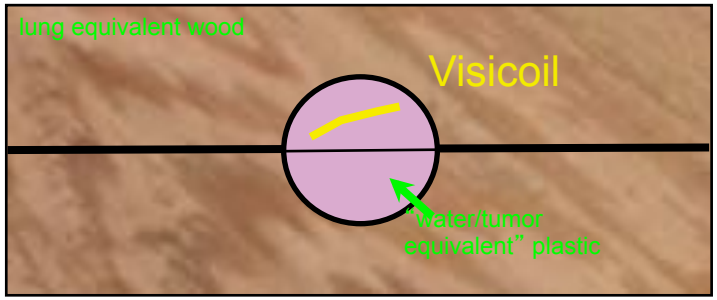
Patient specific pre-treatment QA



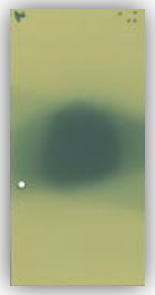


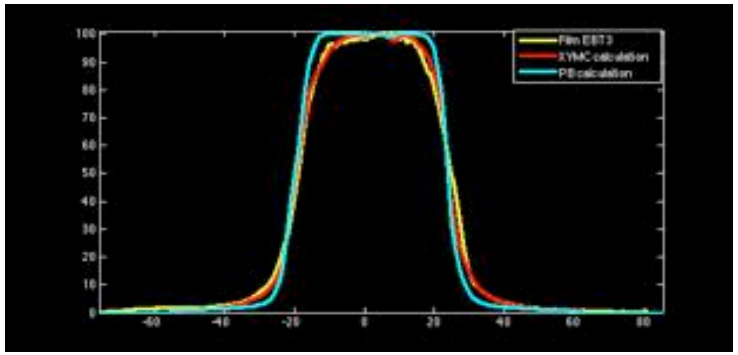


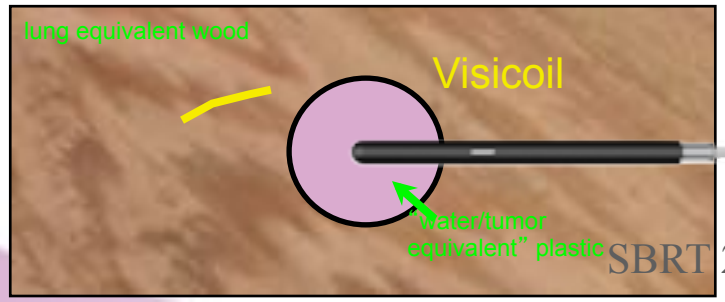




EBT3 film



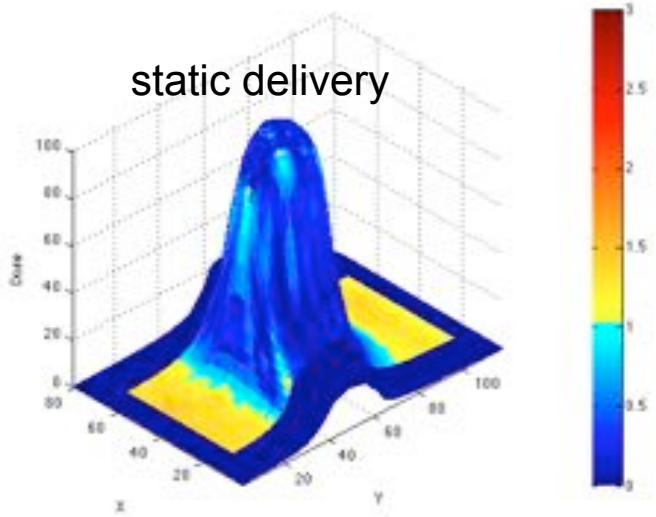


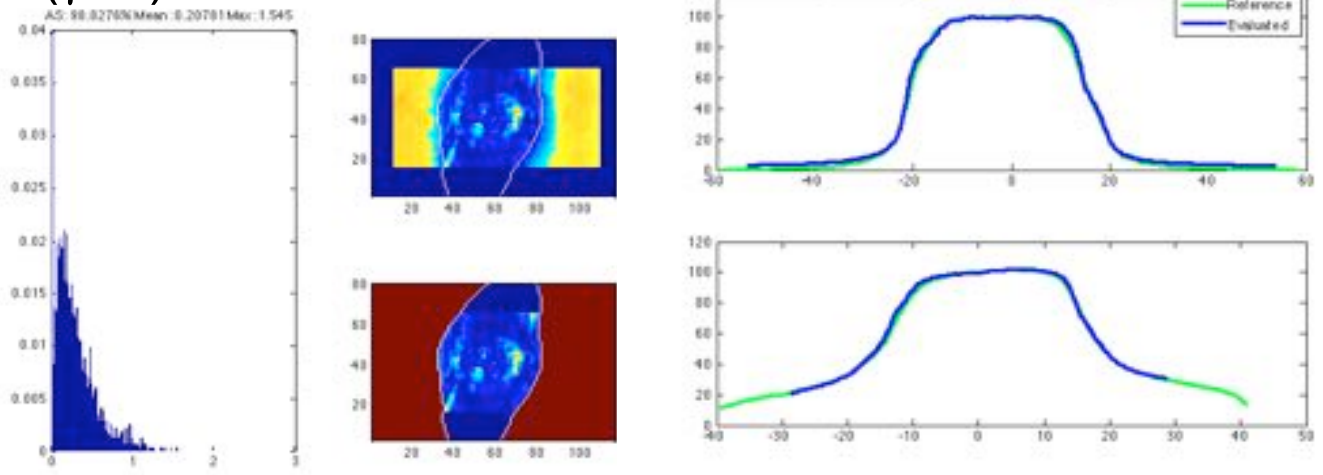


Absolute dose

Patient specific pre-treatment QA

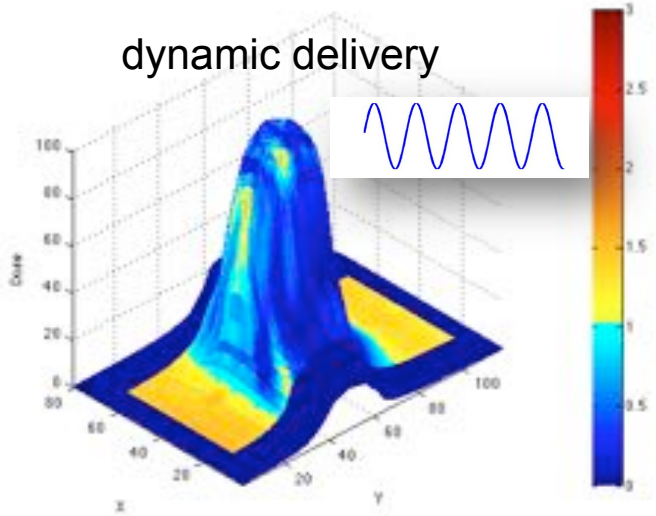
static delivery

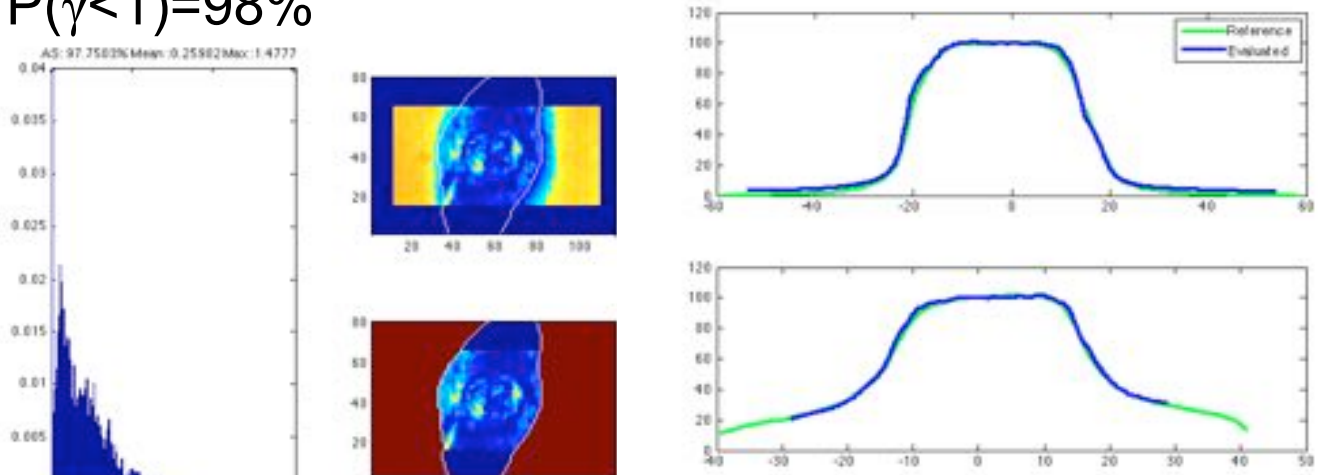




P(γ<1)=99%

dynamic delivery





P(γ<1)=98%

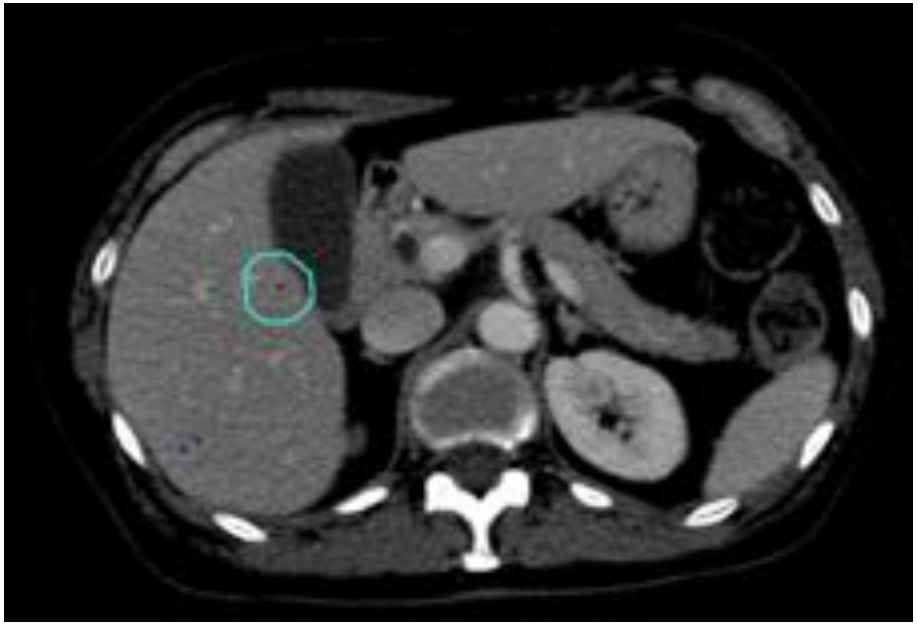
gamma 2%, 2mm (normalized in iso, 2% of isocenter dose)

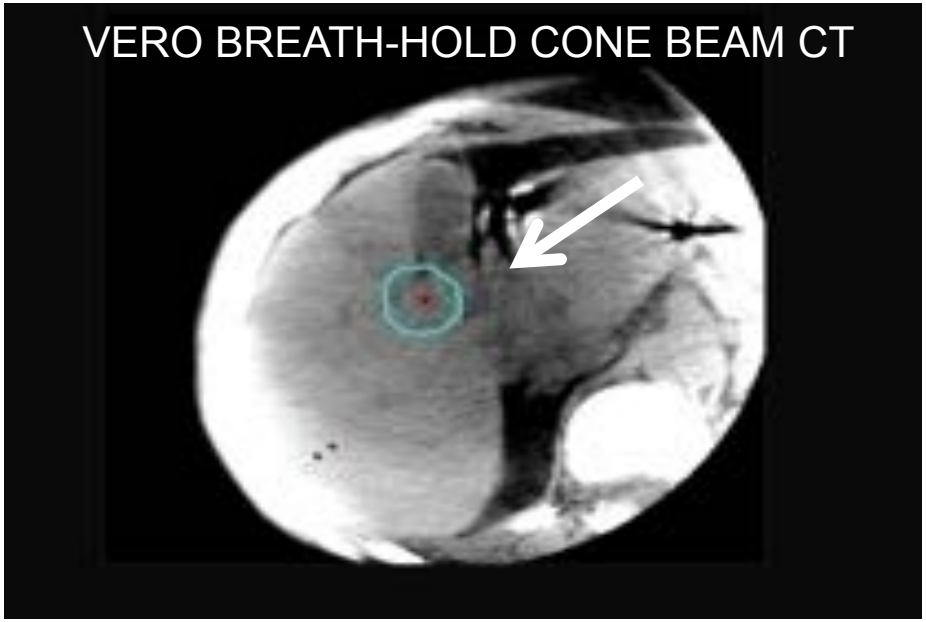
During Treatment Delivery

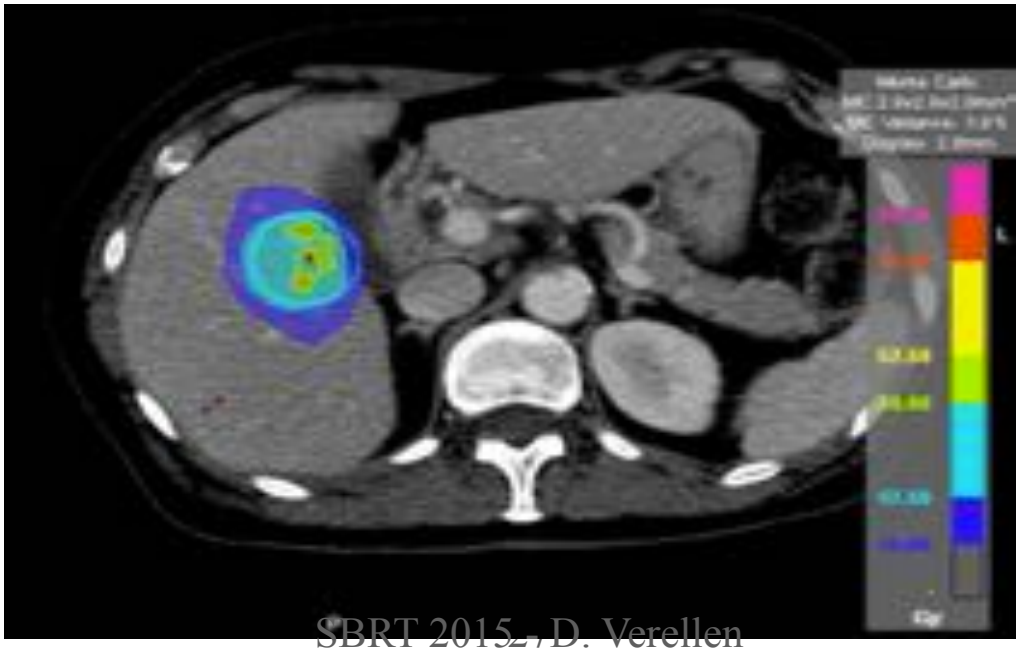
- **Well-trained staff is required**
  - Recognize failures in targeting
    - Understands metrics displayed by the system
    - Understands consequences of adjusting an imaging parameter
    - Visual verification (independent)
  - Failures in the correlation model in case of real-time tracking
  - Understand registration algorithm and correction methods
  - Correct handling of system interruptions

- **Attendance of medical physicist and radiation oncologist**
  - Medical physicist present during first patient treatments?
  - Radiation oncologist on site? Present every fraction?
  - Clear written protocols and/or decision trees (SOP!)!

Inter-fractional organ-at-risk motion





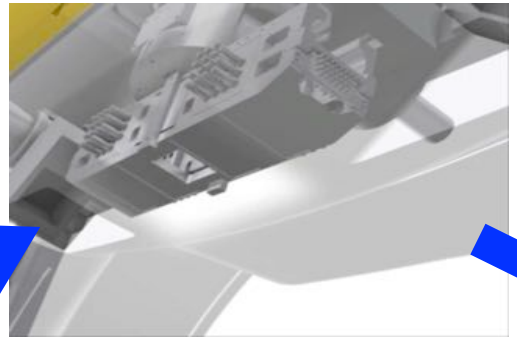


During Treatment Delivery

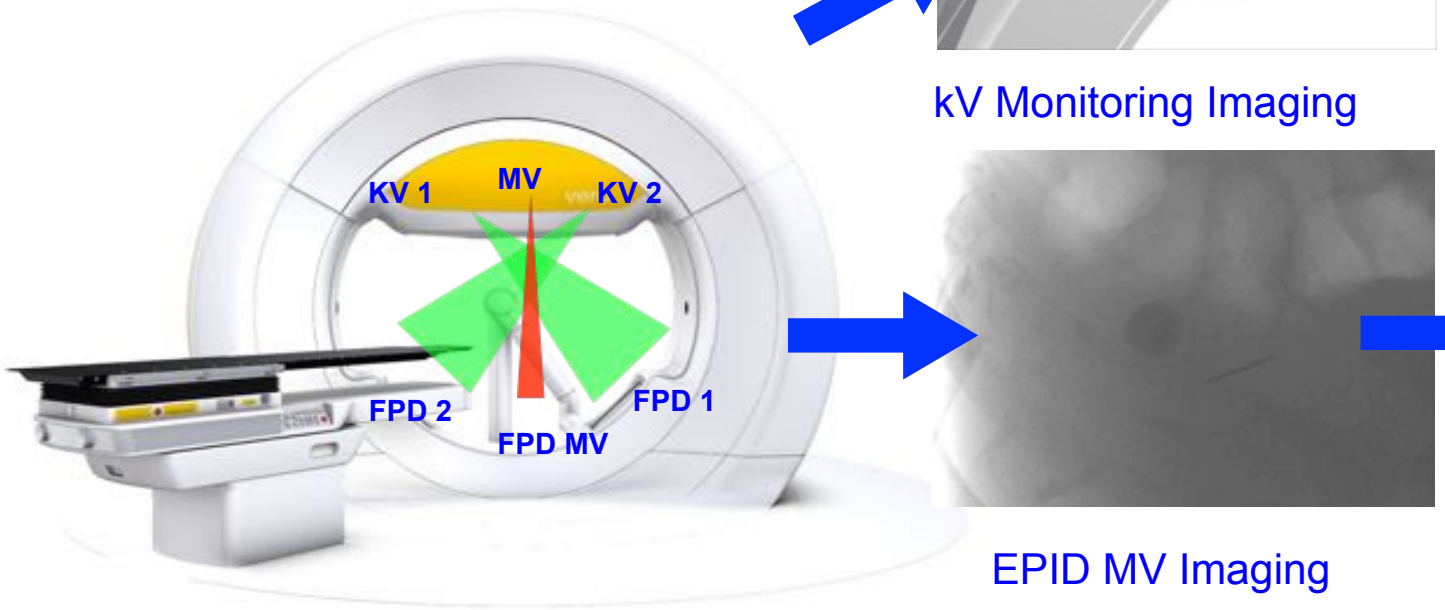
- **Treatments with tight safety margins**
  - No lock on the target => no treatment
    - Tumor cannot be localized (Xsight Lung Tracking)
    - Marker distances changed (Marker Tracking)

Tumour Tracking Verification

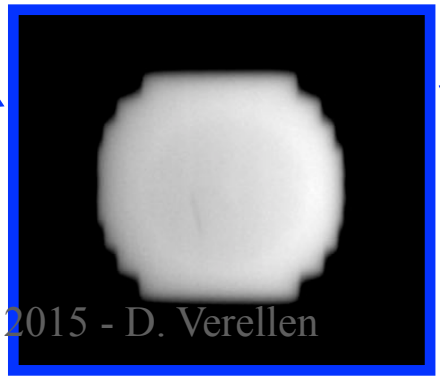
Gimbals position logging



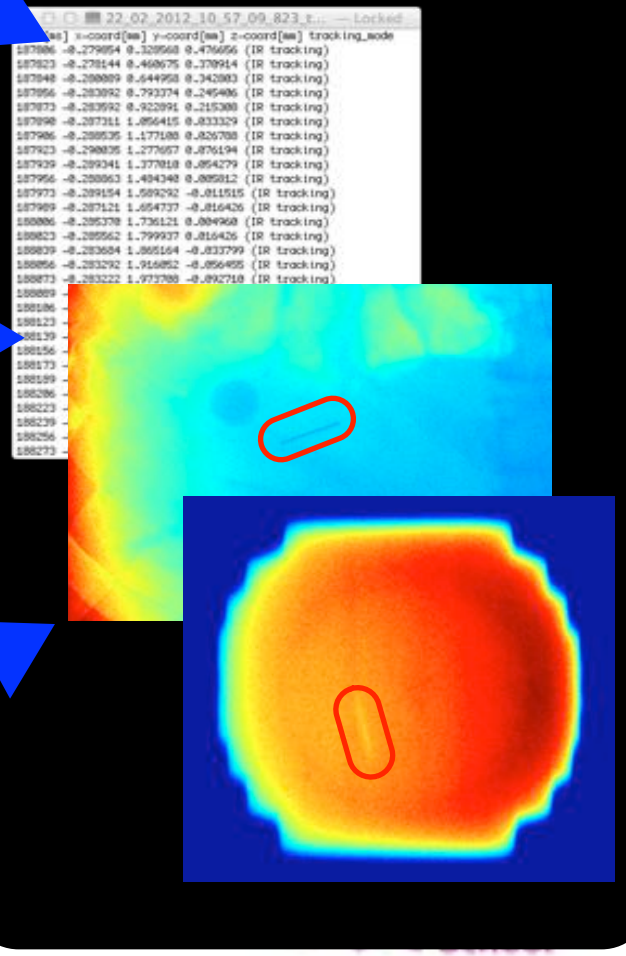
kV Monitoring Imaging



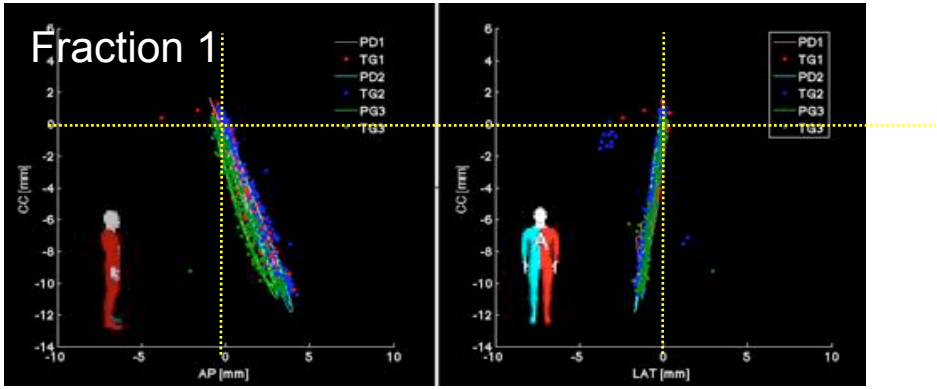
EPID MV Imaging

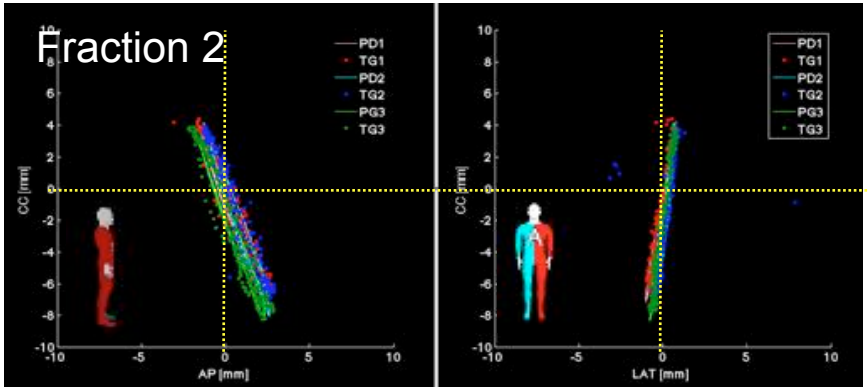


Per fraction QA through combination of different information sources



Tumour Tracking Verification





Fraction 1

	1+2+3 [mm]	4+5+6 [mm]	7+8 [mm]	total (1-8) [mm]
Mean tracking error	1.43	1.84	1.50	1.58
E90% tracking error	2.62	2.60	3.32	2.82
Pan Error	0.59 +/- 0.84	0.59 +/- 0.84	0.89 +/- 2.08	0.66 +/- 1.26
Tilt Error	1.21 +/- 1.60	1.56 +/- 1.95	1.08 +/- 1.76	1.29 +/- 1.80

Fraction 2

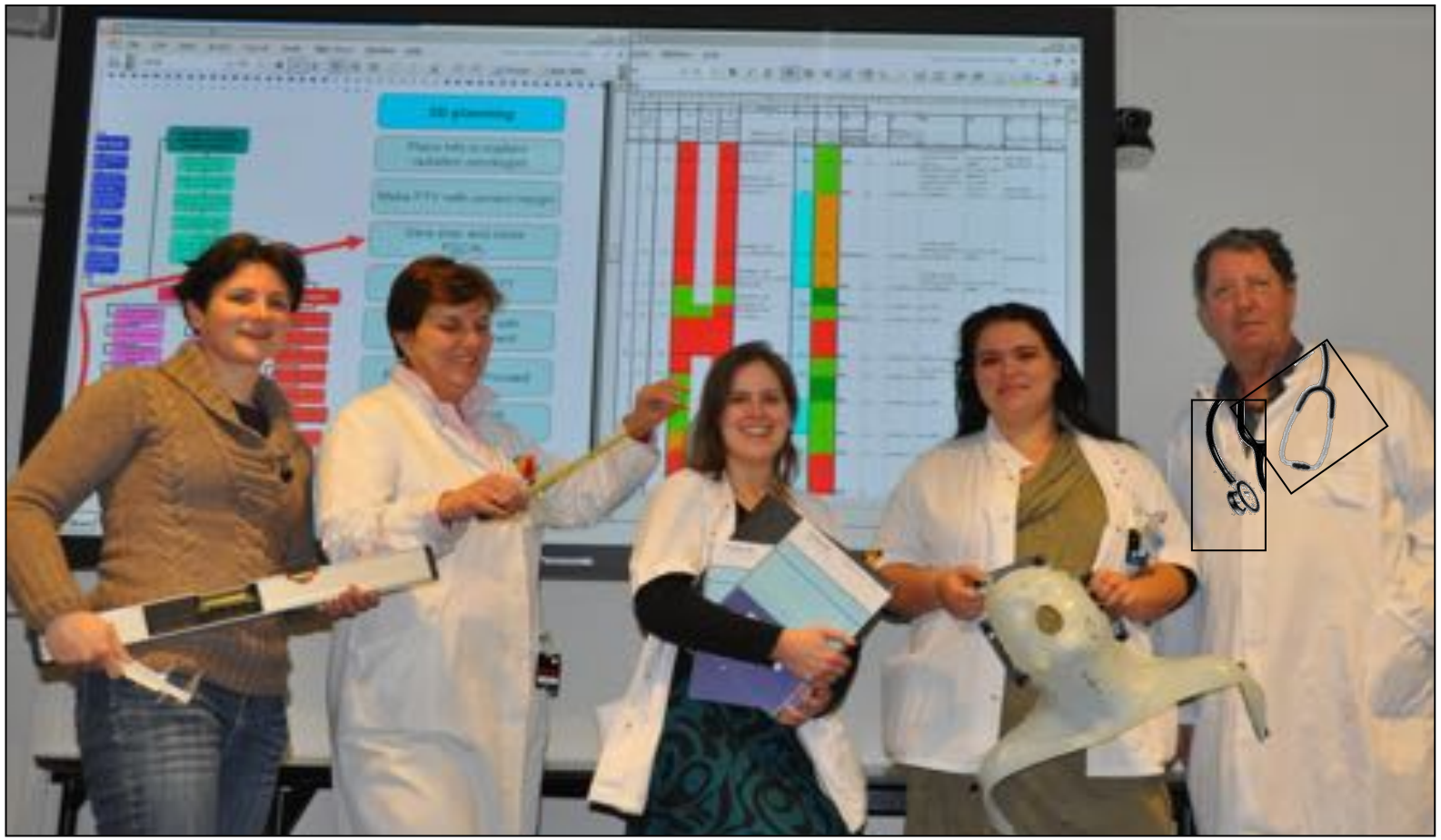
	1+2+3 [mm]	4+5+6 [mm]	7+8 [mm]	total (1-8) [mm]
Mean tracking error	2.10 +/- 1.4 (2SD)	0.98 +/- 0.9	1.52 +/- 1.2	1.61 +/- 1.54
E90% tracking error	2.99	1.51	2.39	2.76
Pan Error	0.58 +/- 0.92 (2SD)	0.54 +/- 0.65	0.50 +/- 0.70	0.55 +/- 0.79
Tilt Error	1.95 +/- 1.48 (2SD)	0.43 +/- 1.53	1.34 +/- 1.45	1.33 +/- 1.96

Average $E_{90\%}$= 2.63 mm, Mean Tracking error = 1.57mm

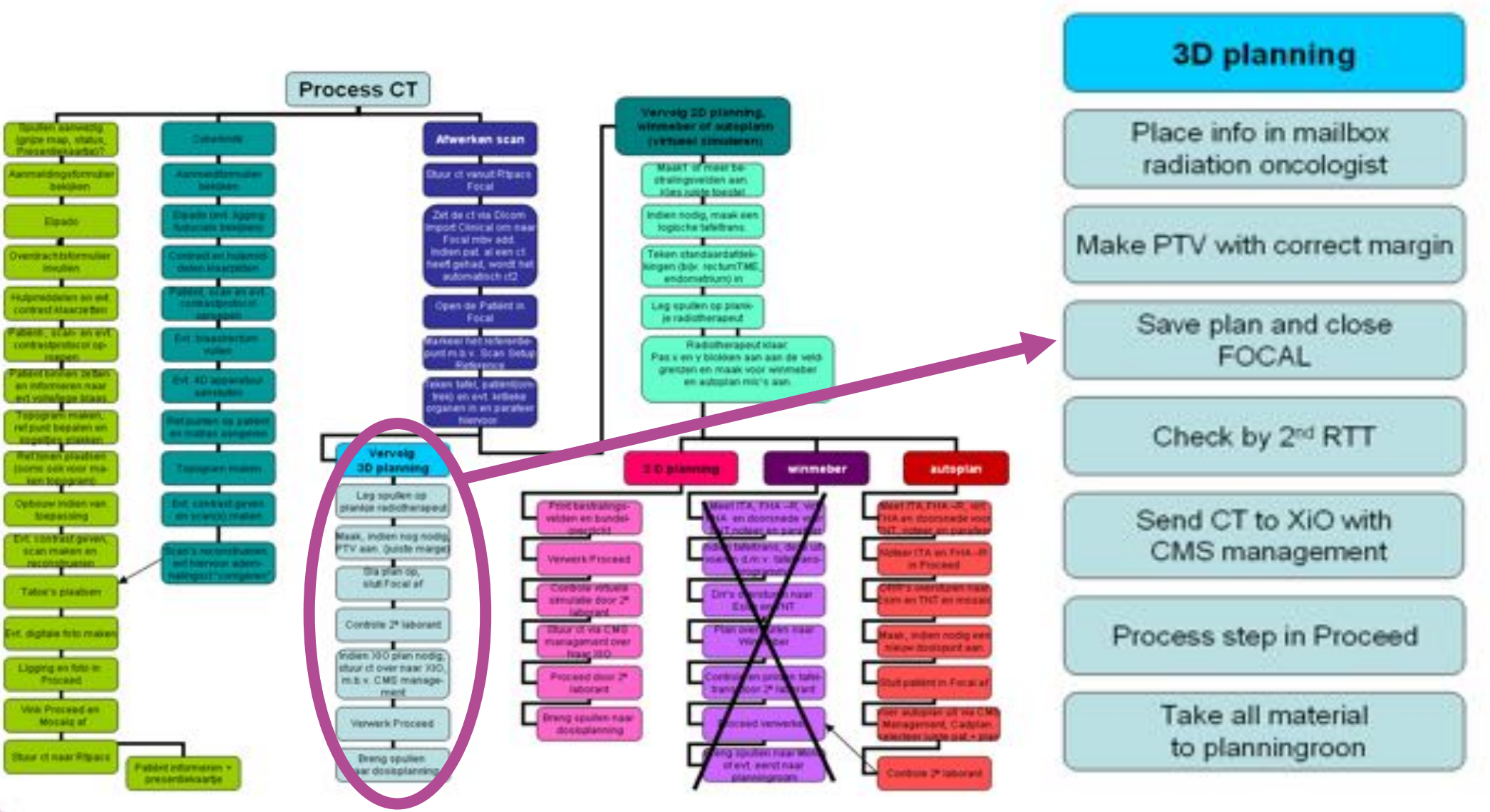
Total treatment time for a 20 Gy fraction ≈ 40 min

Perform Risk Analysis

- A **multidisciplinary team** has to be assembled including experts and an advisor



Graphically Describe the Process



Analyze the separate steps

- Identify failure modes in process
- 3 factors associated with each mode:
  - **Probability**:
    - Likelihood of occurrence
    - Event happening to 1% of patients (score 1), all (score 10)
  - **Detectability**:
    - How likely are we to catch the event?
    - Easy catch (score 1), almost impossible to detect (score 10)
  - **Severity**:
    - What is the consequence if it reaches the patient?
    - Causes discomfort or inconvenience (score 1), dose difference > 20%, injury or death (score 10).
- Calculate Risk Probability Number (RPN)

HFMEATM Hazard Scoring Matrix

Probability	Severity			
	Catastrophic	Major	Moderate	Minor
Frequent	16	12	8	4
Occasional	12	9	6	3
Uncommon	8	6	4	2
Remote	4	3	2	1

Take home message

- There is not one superior technology, it's all about how you use it!
- Don't take unnecessary risks, start slowly
  - Conservative margins
  - Lung and liver metastasis
  - **From ITV concept to gating to tracking … and back**
- Carefully evaluate the pitfalls and uncertainties of your approach, and adapt the QA process accordingly: **FMEA**!
- Build in proper verification tools
- Build up your own clinical experience
- When initiating new techniques (eg gating or tracking), have a back up plan
- Participate in external audits!