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WWW.ESTRO.ORG/SCHOOL

Image-guided and adaptive radiotherapy

Marianne Aznar PhD,
Risgshopitalet, Copenhagen

Welcome !

- 133 participants from 21 countries
- 39 RTTs
- 48 MPs
- 41 MDs

Some concepts behind this course

- To cover both theoretical and practical aspects

- "you can only hit what you see": To understand the concept "target delineation – target localisation" at each particular step in the treatment chain

- To understand the functionality of the equipment (hardware AND software), and identify limitations of a particular method.

- To learn establishing an efficient image-guided work- flow through optimal integration of available technologies and understand the importance of **teamwork** and training.

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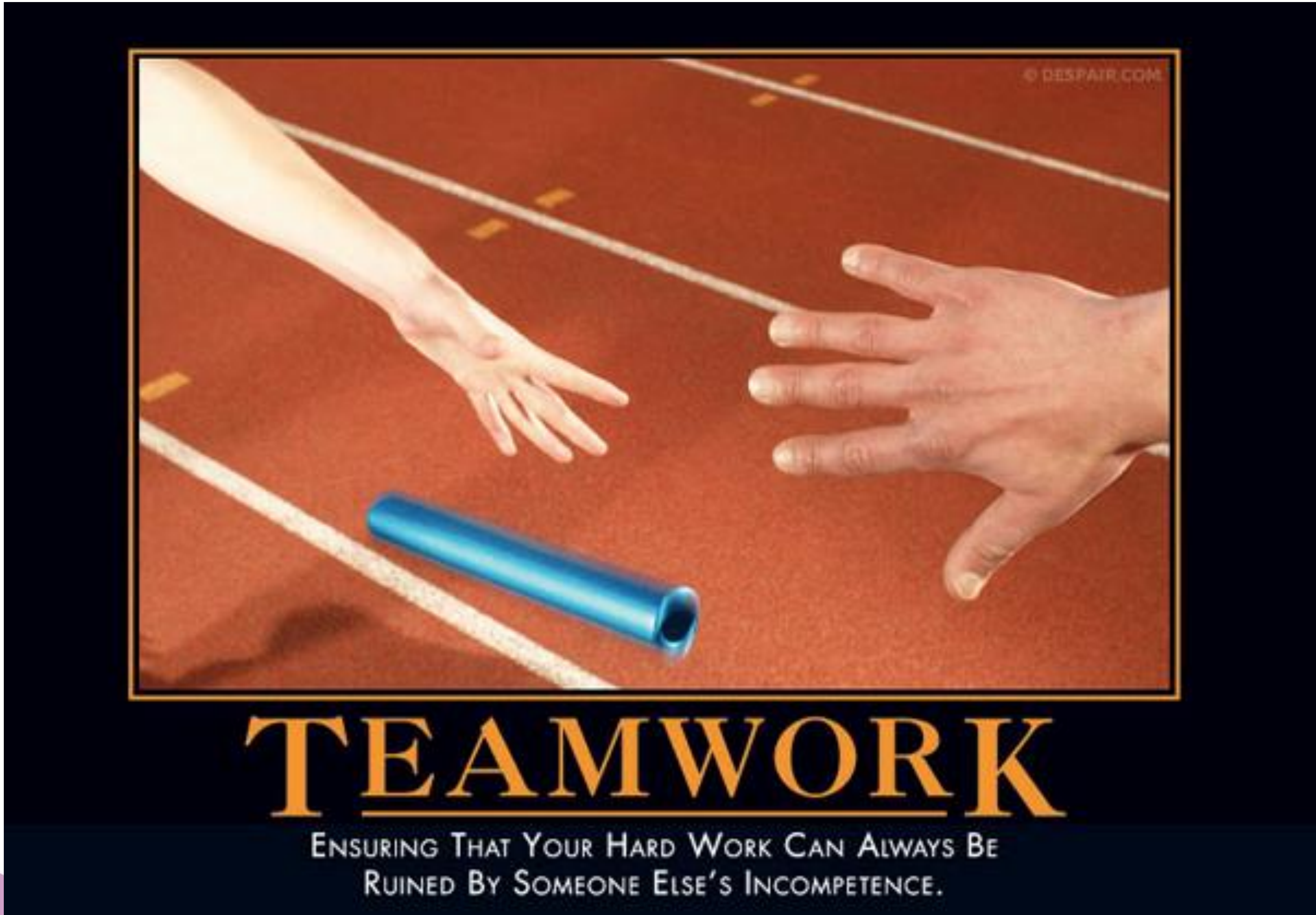
Multidisciplinarity: what does it mean ?



I’m an RTT… why do I need to hear about margins?

- Because margins have a big impact on the side effects the patient will experience
- Because to reduce margins, all working groups need to adress the uncertainties of <u>their</u> part of the process
- Because there is always a ”new project” ☺

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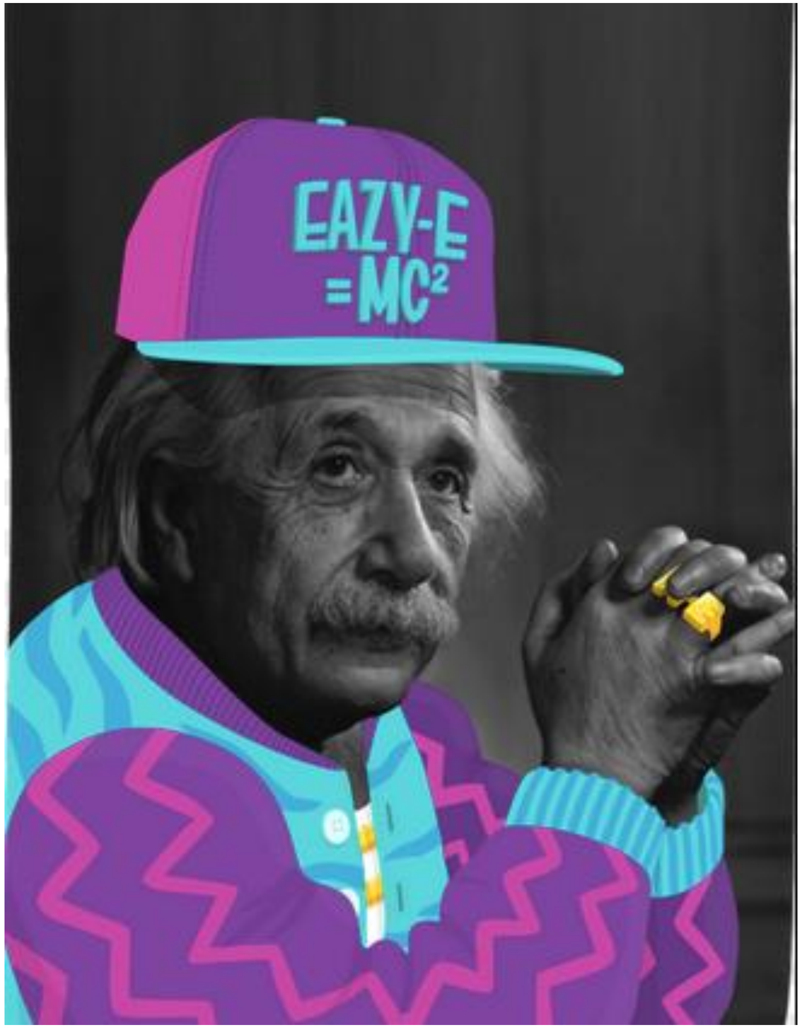
I'm a physicist… why do I need to hear about patient positioning?



- Because you can't design margins without knowing how the patient lies/moves
- Because even the fanciest imaging/adaptation software won't keep the distance between target and OAR constant…

I’m an MD… why do I have to hear about the technical details of imaging systems?

- Because you want the most efficient workflow (time, ressources, precision)

- Because a badly calibrated system, or a system used incorrectly, may introduce significant systematic errors in the treatment delivery

- Because you will have to review the images !

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The program…

- 4 days
- Increasing level of complexity
- Increasing levels of adaptation

- 2 split-up sessions

- Ask questions !
- We will ☺

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IGRT/ART: a physicist's point of view

Marianne Aznar
U of Manchester / The Christie
Rigshospitalet, Copenhagen, Denmark

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Outline

- A short history of IGRT technology
- Margins
- Adaptive Radiotherapy

A LITTLE TECHNOLOGICAL HISTORY ...

IGRT is not a new (or even "recent") idea

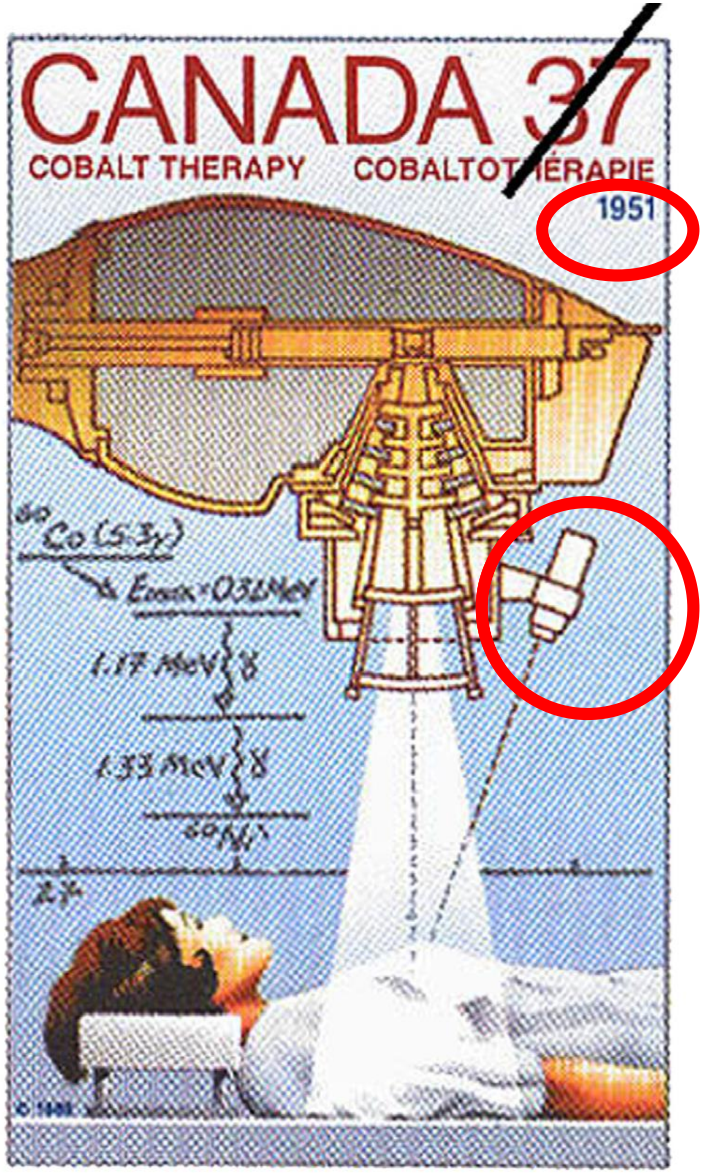

Fig. 1. Cobalt Therapy, 1951, issued 1988, 37 cents, 2003. Note the illustration of a positioning device mounted to the head of the machine that most likely refers to the X-ray systems reported in the literature by Johns, Cunningham and Holloway at that time [31,30]. (© Canada Post Corporation (1988). Reproduced with Permission).

Verellen et al RO 2008

The first "Cobalt Bomb"
London, Ontario

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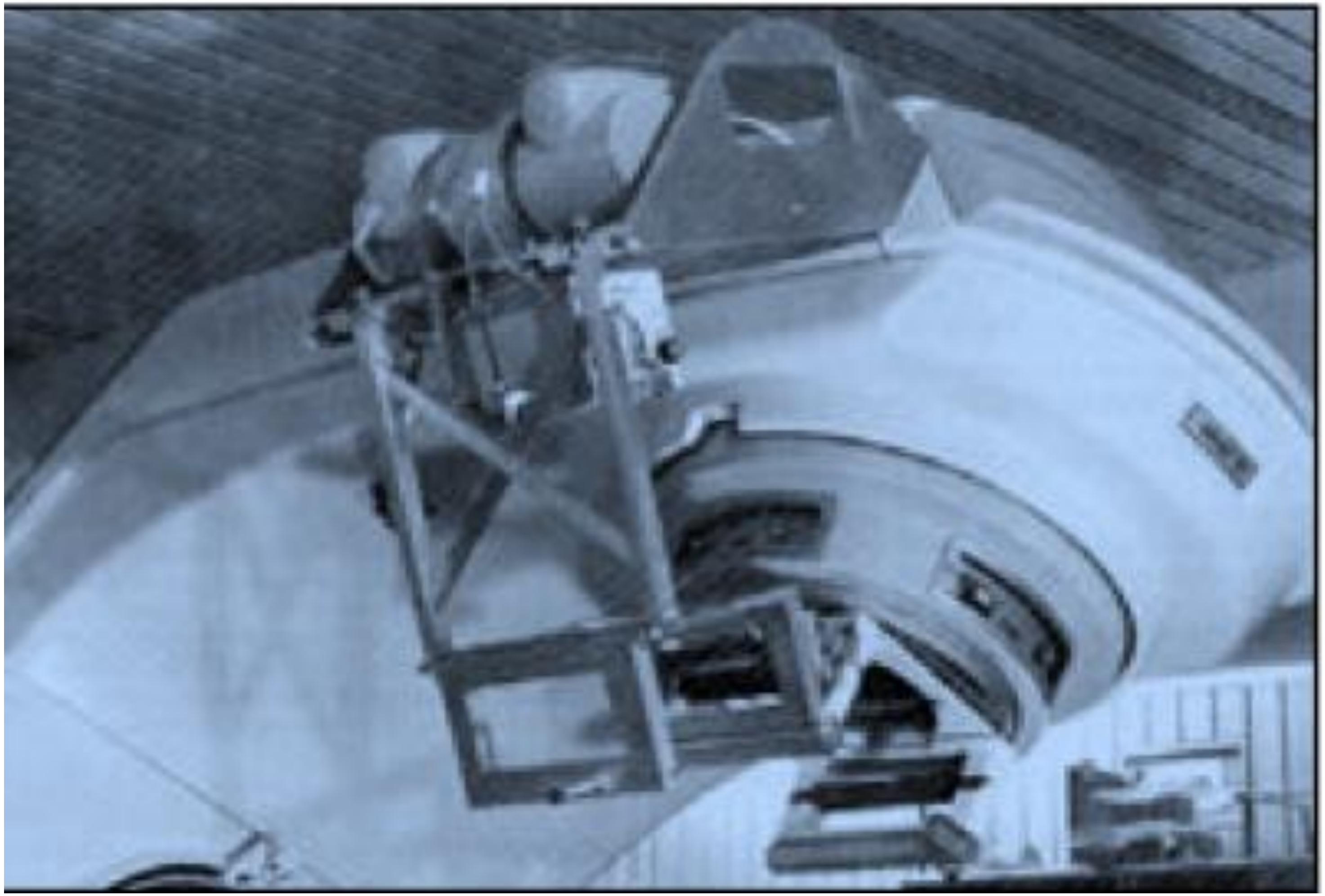
The idea didn't quite catch on for a few decades…



With a few exceptions: here, Biggs et al IJROBP 1985

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Why the lack of adoption ?

- Poor image quality (low film sensitivity, size of the Cobalt source)
- “Home made” systems in pioneer academic centers never reached other RT facilities

Conventional RT and simulation

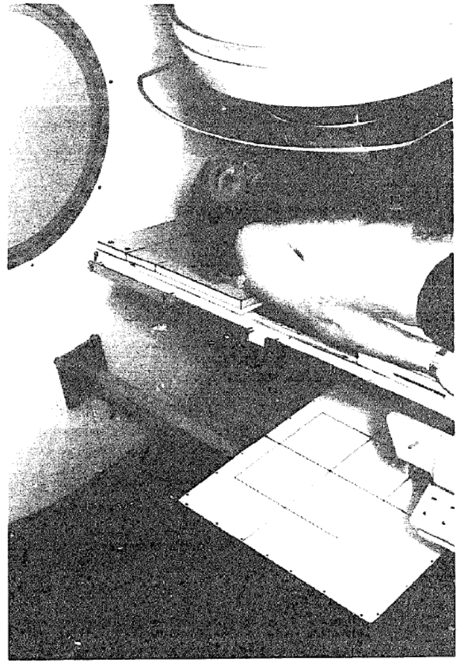
- At the end of previous century, patient set-up and the determination of treatment beams was mainly guided by using a **treatment simulator and drawing skin marks** on the patient's surface, consequently used to position the patient with respect to the treatment machine

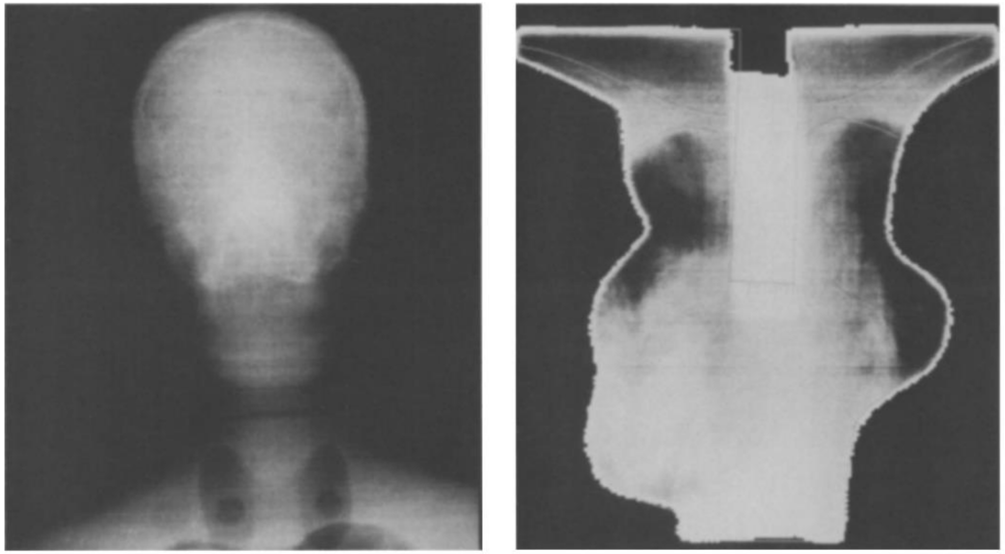
- only **35% of the radiotherapy centres were using a simulator** for target localization in the treatment planning process in 1983, and only 47% had access to this equipment in 1986

Chu *et al*, IJROBP 1989.

”simulator films” and ”portal films”

Van Herk et al,
RO 1988





Lam et al, BJR 1986

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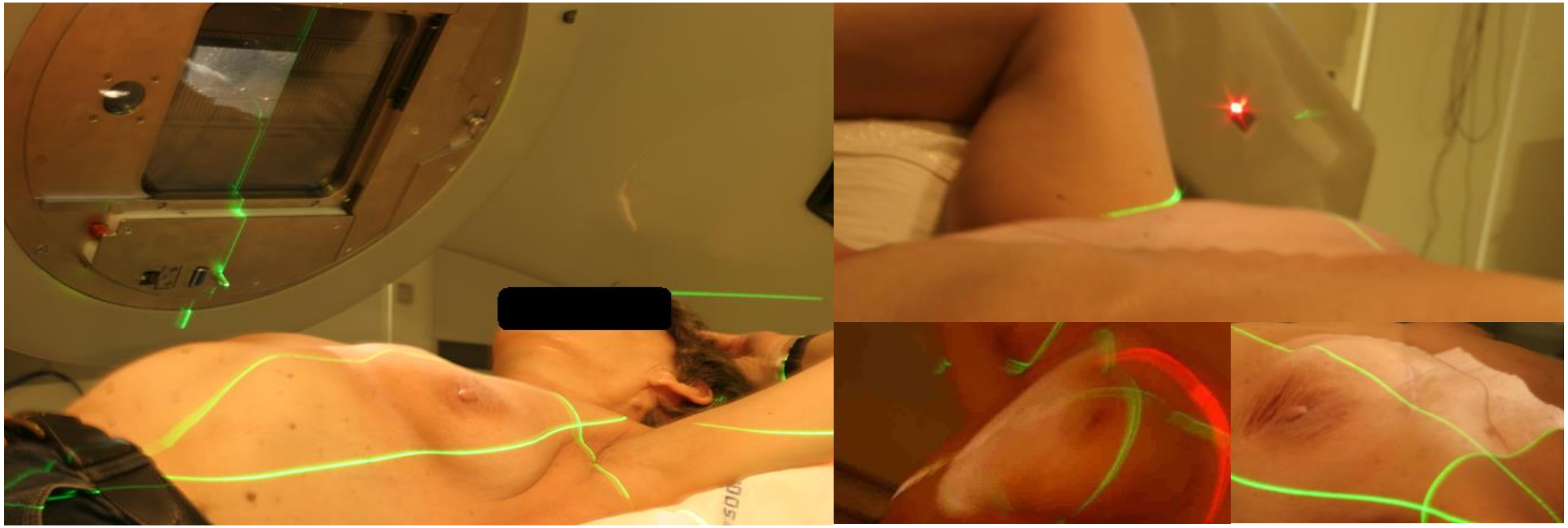
In practice:
One portal film on first treatment day
Then tatoo/light field check ?



- Avoided gross errors, but arguably didn’t improve accuracy much

With the exception of a few early studies:

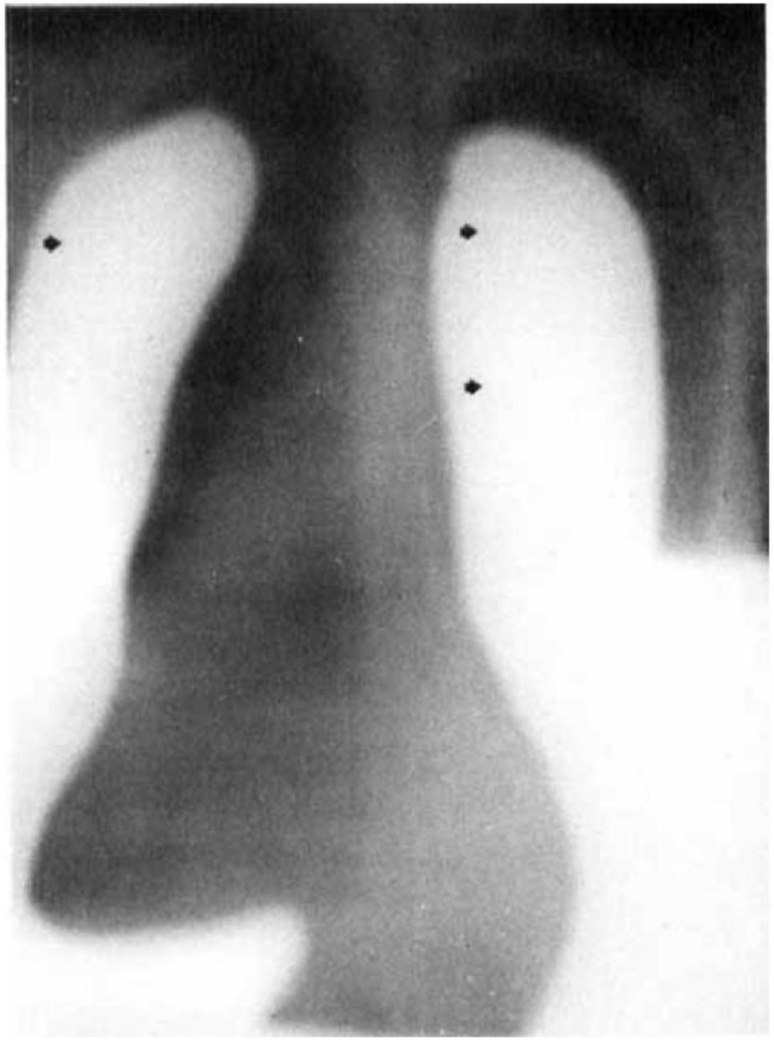


FIG. 4. Mediastinal localization error. Posterior pulmonary shield encroaches upon the soft tissues of the mediastinum.

- Marks et al 1976
- Daily films for Hodgkin Lymphoma patients
- Comfortable immobilization is a must (or 16% error incidence)
- Errors can be due to (1) movement of the patient and (2) movement of external land- marks in relation to internal anatomy.

- Stopped using films after the study !
- *"Perhaps, daily treatment films should be required in cases in which a precise treatment setup is necessary"*

Then came the EPIDs…
Significant time and workflow improvement !

1980ies: Introduction of “offline” approaches and subsequent margin recipes

1990ies: software tools necessary for quantitative image analysis

- Real “democratization” of IGRT

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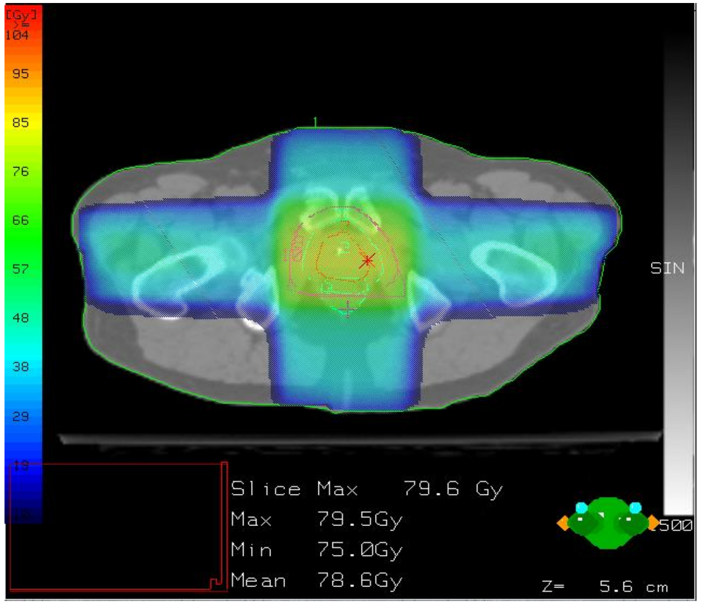
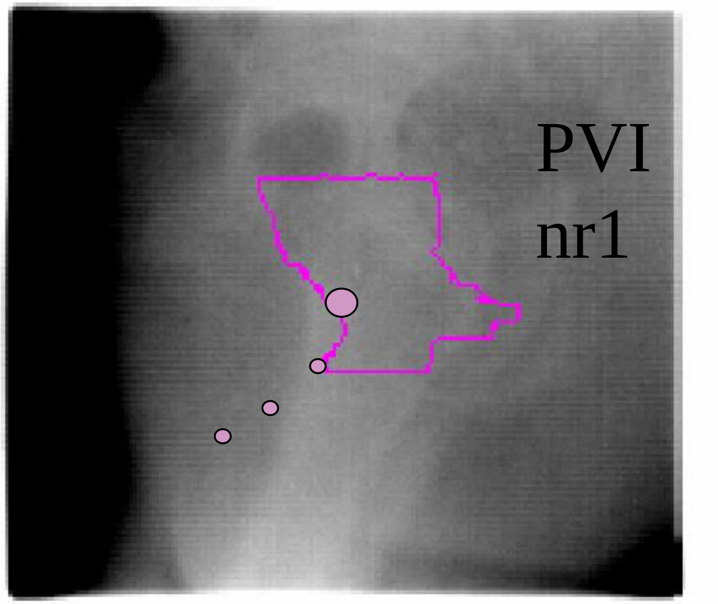
Still, it was hard (impossible!) to see the target

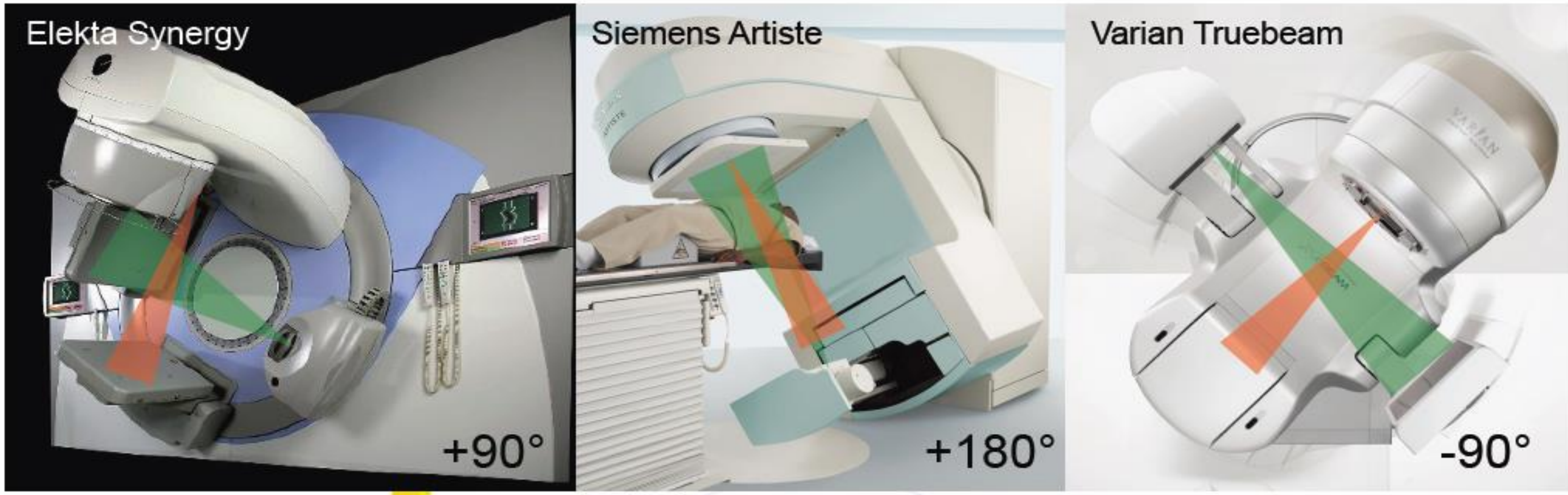
- I 2 fields with catheter; 2Gy x 3 (GTV1)
- II 4 fields 2 Gy x 2 (prostate w. small margin, PTV1a)
- III 4 fields 2 Gy x 8 (prostate w. margin, PTV1b)
- IV 4 fields 2 Gy x 25 (prostate + ves. semin. + margin)
  - Total dose to GTV1: 76 Gy

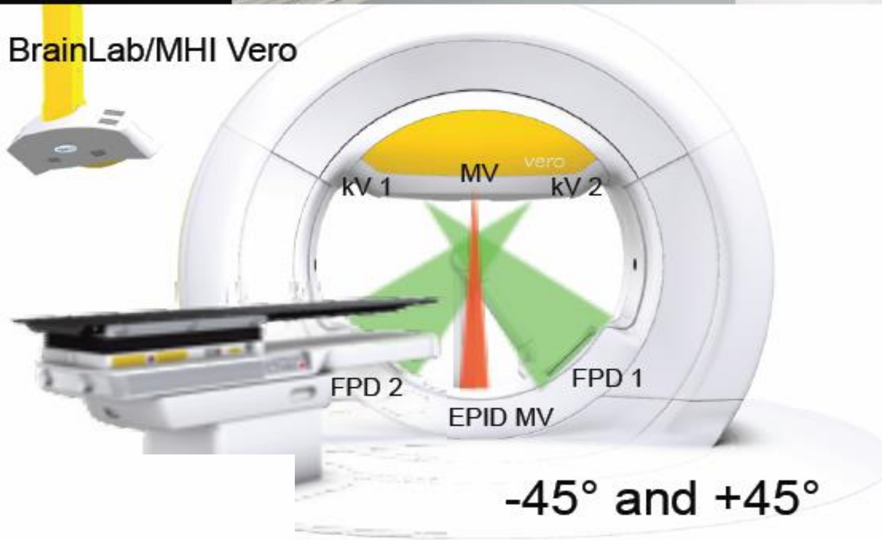


The ”Finsen frame”



IGRT CAPABILITIES TODAY


Elekta Synergy
+90°
Siemens Artiste
+180°
Varian Truebeam
-90°


BrainLab/MHI Vero
kV 1
MV
kV 2
FPD 2
EPID MV
FPD 1
-45° and +45°

kV imaging

Positioning the patient… vs positioning the tumour

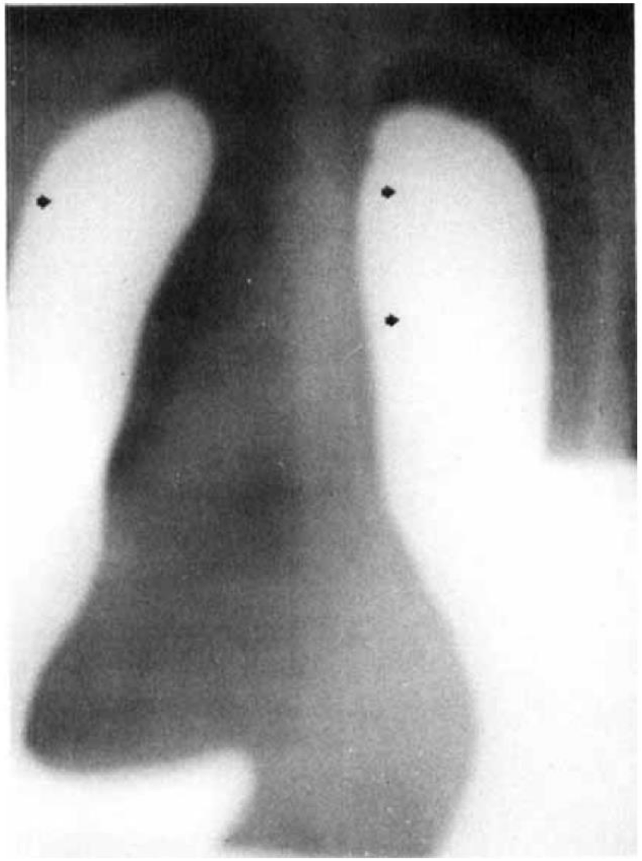
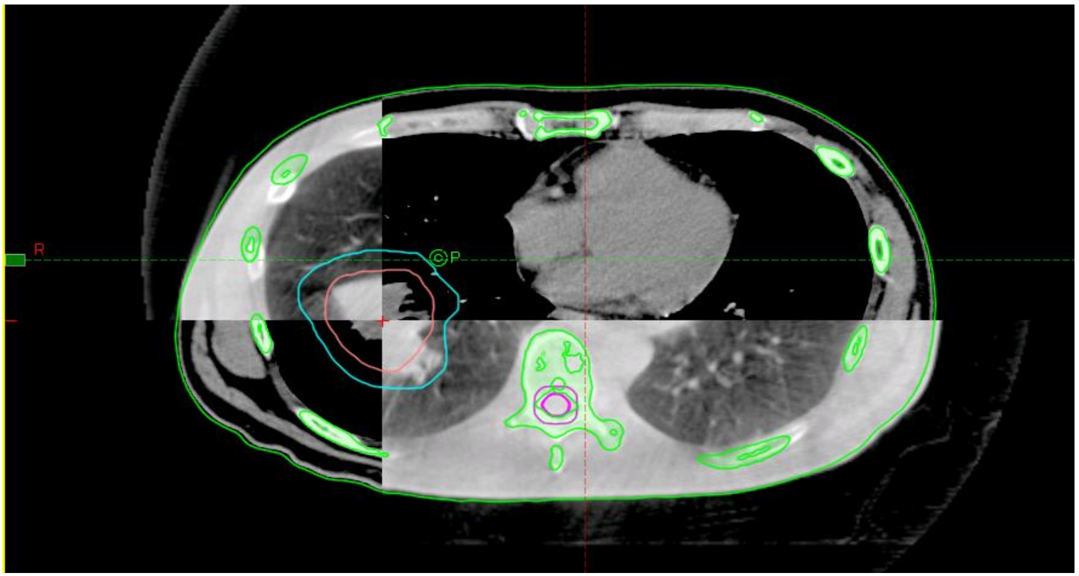


FIG. 4. Mediastinal localization error. Posterior pulmonary shield encroaches upon the soft tissues of the mediastinum.

CBCT



Availability of IGRT to day

- 50 centers in the UK
- 26 had kV IGRT capacity on 1 or more machine(s) but only 23 were using it
- Expected to increase to 43 within the coming years
- In contrast, **every center had IMRT capacity**

Mayles , Clin Onc 2010

Table 8
Reasons for lack of progress with image-guided radiotherapy. The reasons are listed in order of the number of centres indicating that the reason was relevant to them.

	An issue	Main reason	In top three
Lack of equipment capability	40	30	33
Lack of machine time	23	2	16
Radiographer availability	17	0	14
Lack of funding	17	3	11
Physicist availability	14	3	10
Time for training	8	0	4
Clinical oncologist availability	7	2	4
Dosimetrist availability	7	0	3
Concerns about dose	1	0	0
Number of respondents for this column	47	40	40

Availability of IGRT to day

ESTRO-HERO survey

Radiotherapy equipment and departments in the European countries: Final results from the ESTRO-HERO survey

CrossMark

Cai Grau [a,*], Noémie Defourny [b], Julian Malicki [c], Peter Dunscombe [d], Josep M. Borras [e], Mary Coffey [f], Ben Slotman [g], Marta Bogusz [h], Chiara Gasparotto [b], Yolande Lievens [i], on behalf of the HERO consortium [1]

[a] *Aarhus University Hospital, Denmark;* [b] *European Society for Radiotherapy and Oncology, Brussels, Belgium;* [c] *University of Medical Sciences, Greater Poland Cancer Center, Poznan, Poland;* [d] *University of Calgary, Canada;* [e] *University of Barcelona, Spain;* [f] *Trinity College Dublin, Ireland;* [g] *VU Medical Center, Amsterdam, The Netherlands;* [h] *Cancer Diagnosis and Treatment Center, Katowice, Poland;* [i] *Ghent University Hospital, Belgium*

R&O 2014

69% of MV machines equipped for IMRT
49% equipped for IGRT

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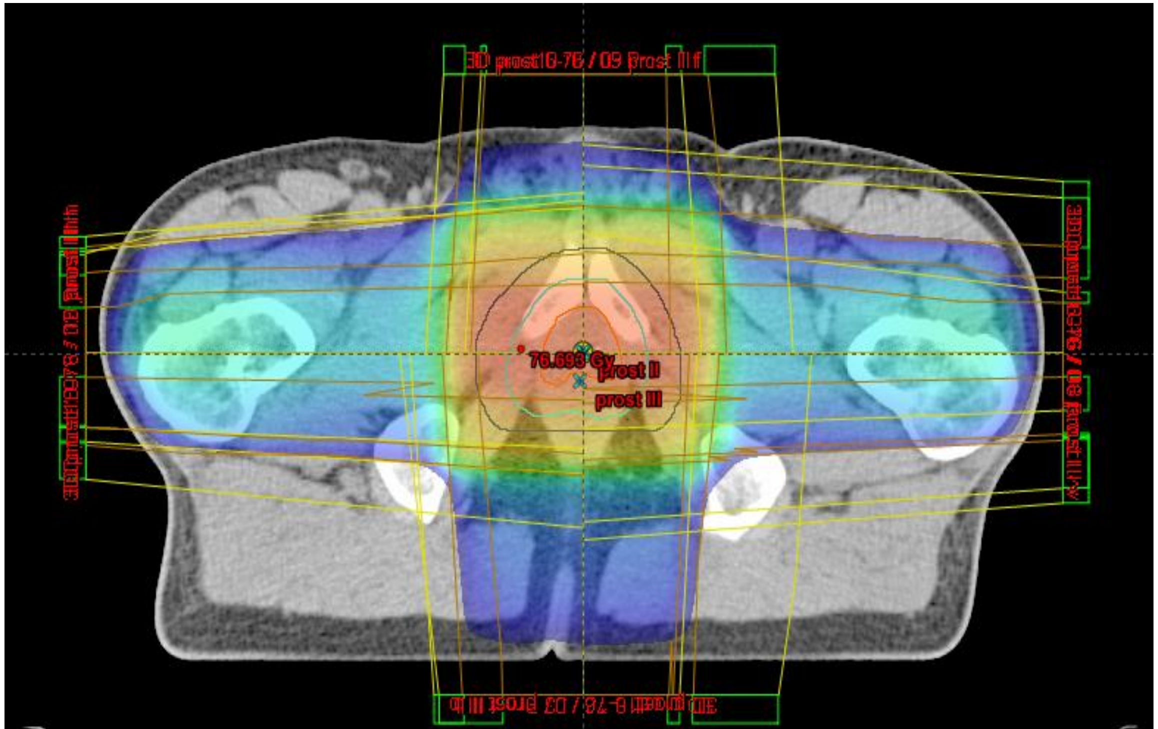
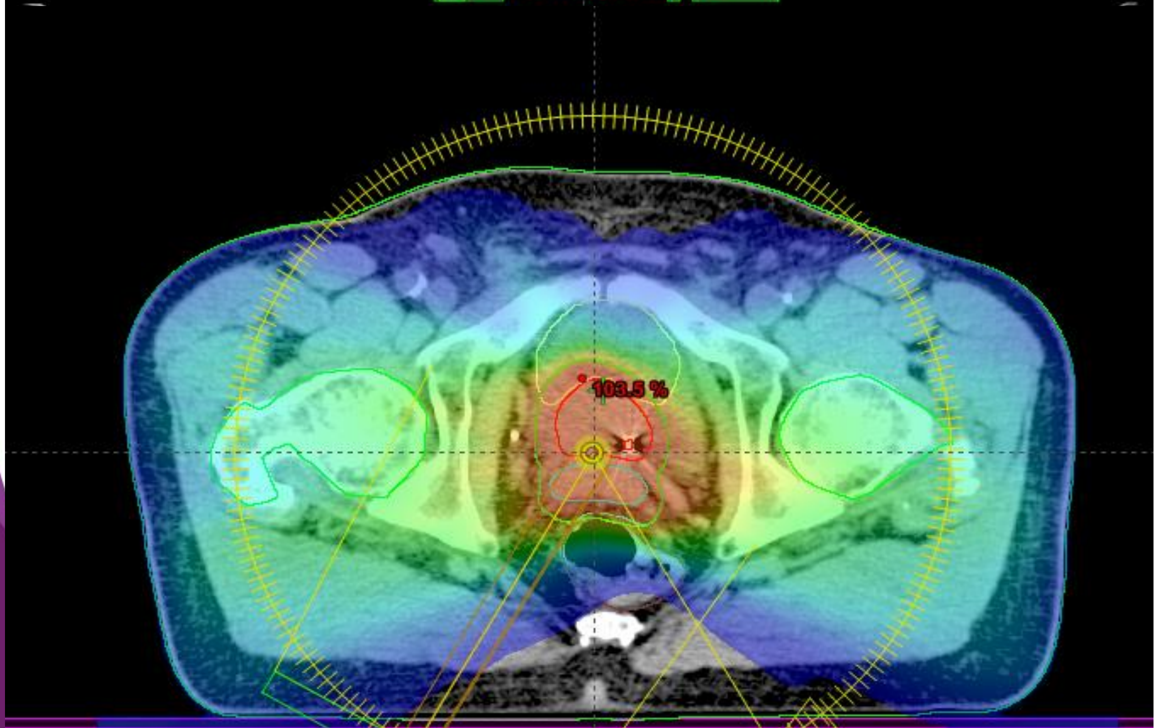


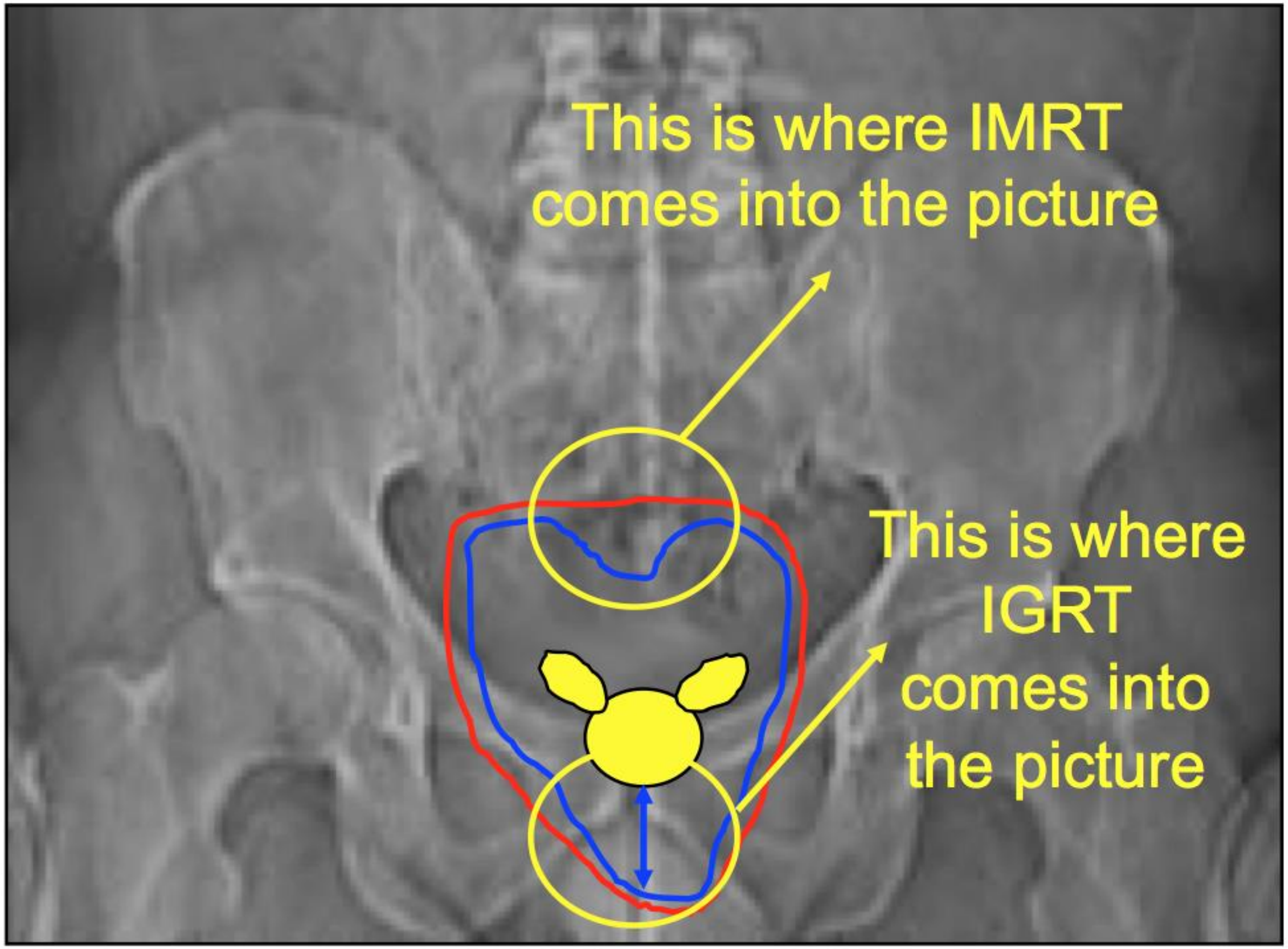
“conventional” therapy

- **Large fields**
- **The large amount of healthy tissue in the field prohibited the use of high doses**



- **More fields**
- **Smaller amount of healthy tissue in the field**
- **Opened the door to dose escalation**
- **Prostate cancer: 60 Gy to 80 Gy**

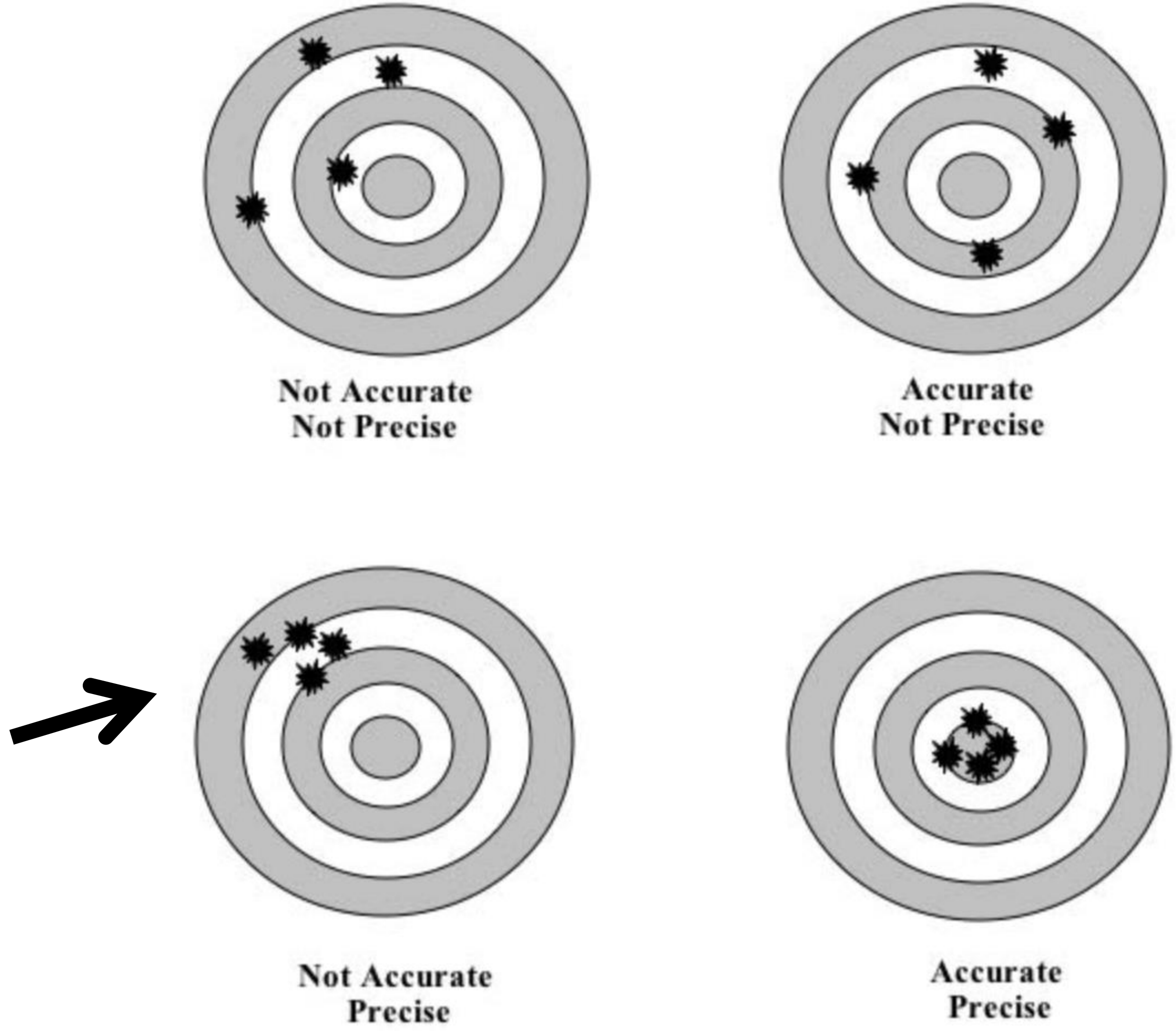
“Dose sculpting” vs “margin reduction”



Set up Margin
+
Internal Margin

Irradiated Volume

“we are at increased risk of missing very precisely” J. Rosenman



IMRT
without
IGRT
?

THE BENEFITS OF IGRT
AKA: THE JOY OF MARGINS !

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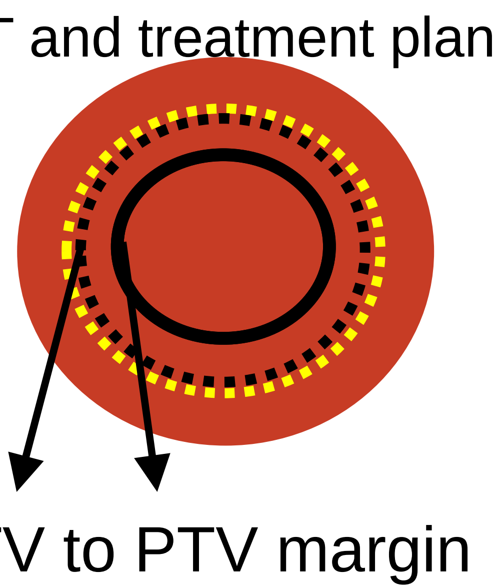
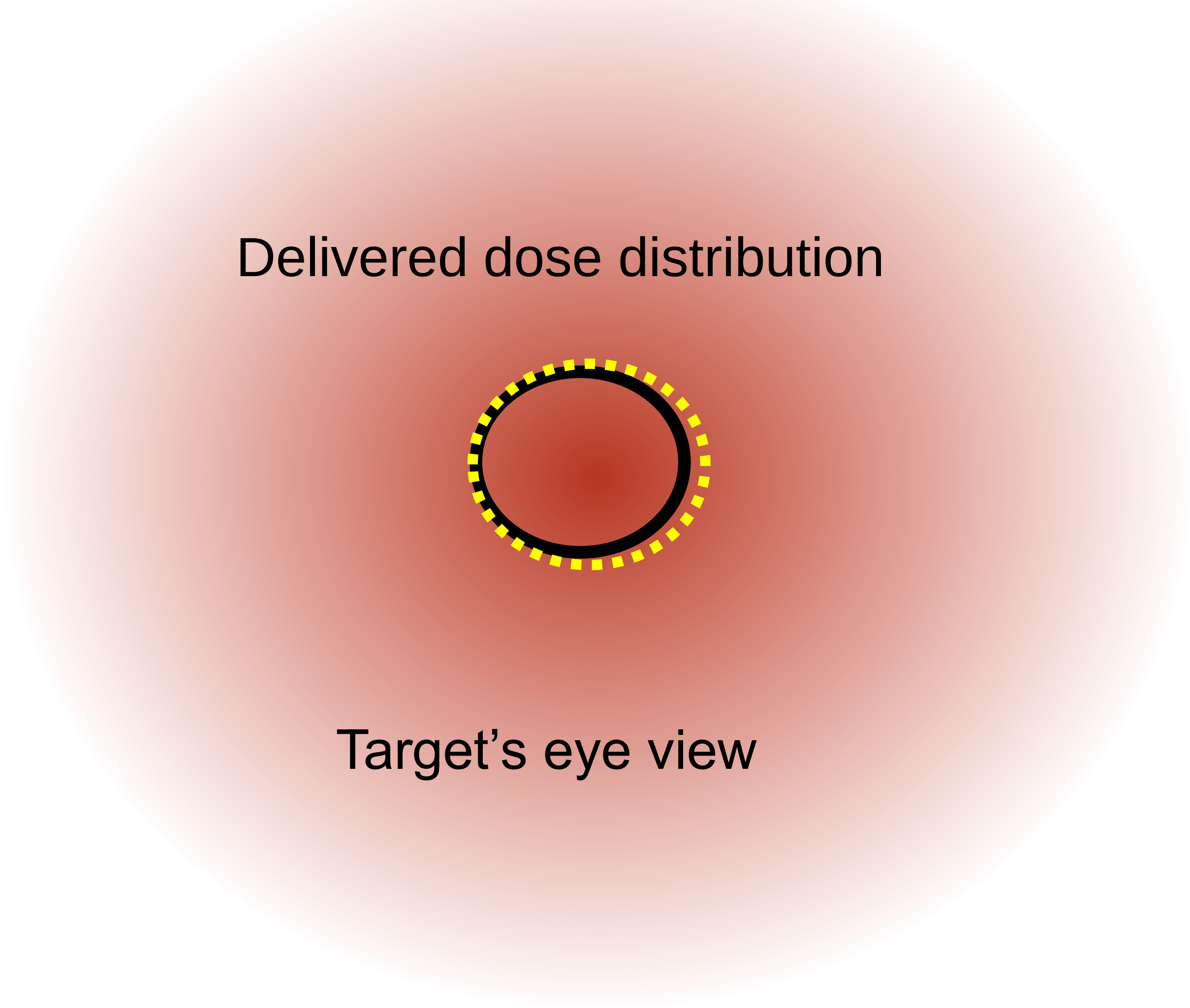




$$M = 2.5\ \Sigma_{tot} + 1.64\ (\sigma_{tot} - \sigma_p)$$

The myth of the “zero margin”

- Contouring uncertainties
- Algorithms (calculation, registration, etc…)
- Patient position
- Tumour position
- Intra fraction motion
- Changes in internal anatomy (weight loss, distance between targets, target and OARs)
- Etc…

Margins can not converge to zero

Margins should depend…

- On the patient group (immobilization, inter- , intra-fraction motion)
- On the type and frequency of images acquired during the treatment course

- Not on the referring physician!

CTV to PTV margins with respect to IGRT practice: a survey of RO in the US

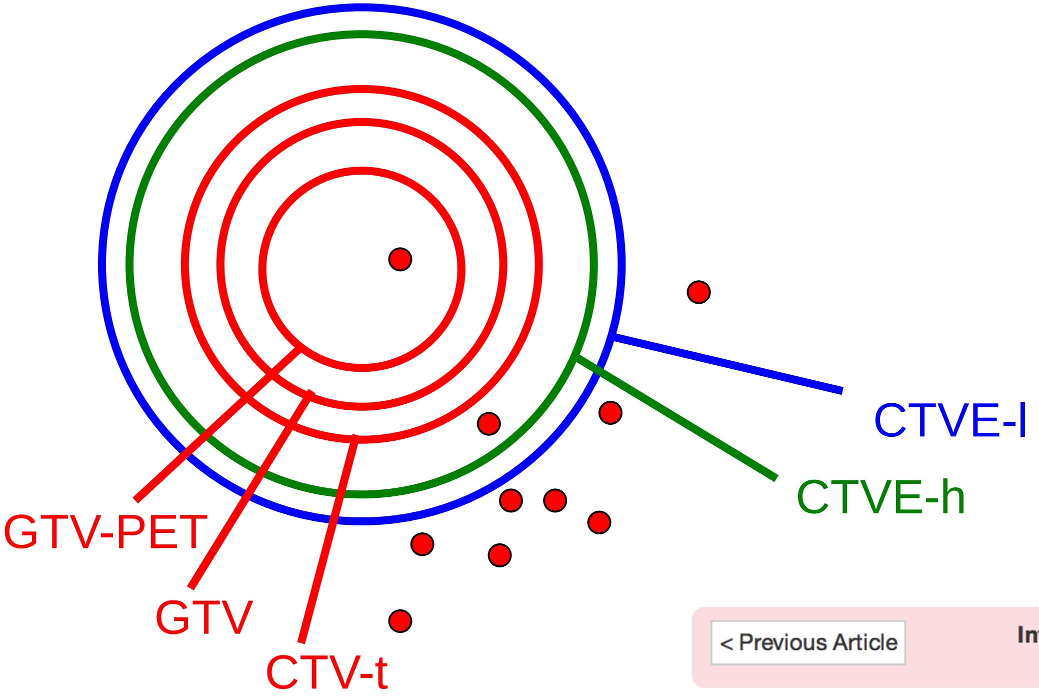
Treatment site	First few fractions	weekly	daily
Head and Neck	5 mm	4.9 mm	4.8 mm
Lung	6.4	6.6	6.2
Prostate IMRT	4.9	4.5	4.6

Nabavizadeh et al IJROBP 2015
(showing only data for CBCT)

Survey shows that margins are more dependent on the physician than on imaging type/frequency

It's not all about maths:
The proof is in the pudding

Margins too small:
- Marginal recurrences



< Previous Article
International Journal of Radiation Oncology • Biology • Physics
Volume 74, Issue 2, Pages 388–391, June 1, 2009
Next Article >

Conformal Arc Radiotherapy for Prostate Cancer: Increased Biochemical Failure in Patients With Distended Rectum on the Planning Computed Tomogram Despite Image Guidance by Implanted Markers

Benedikt Engels, M.D., Guy Soete, M.D., Ph.D., D. Verellen, Ph.D., Guy Storme, M.D., Ph.D.
Department of Radiotherapy, University Hospital Brussels, Brussels, Belgium

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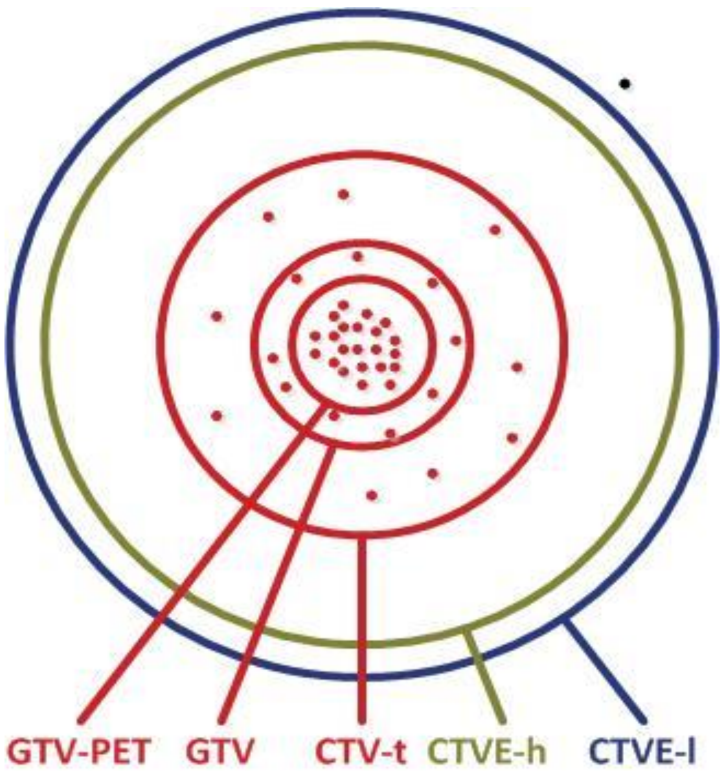
The proof is in the pudding:



Due et al R&O 2014

Margins too large ??

- No (few) marginal recurrence
- Might limit dose escalation and lead to in-field recurrence

Where it gets a little complicated…

- How many patients for how long?
- When RT is a consolidation treatment vs the only treatment modality
- When the risks to OARs exceeds the benefit of full target coverage

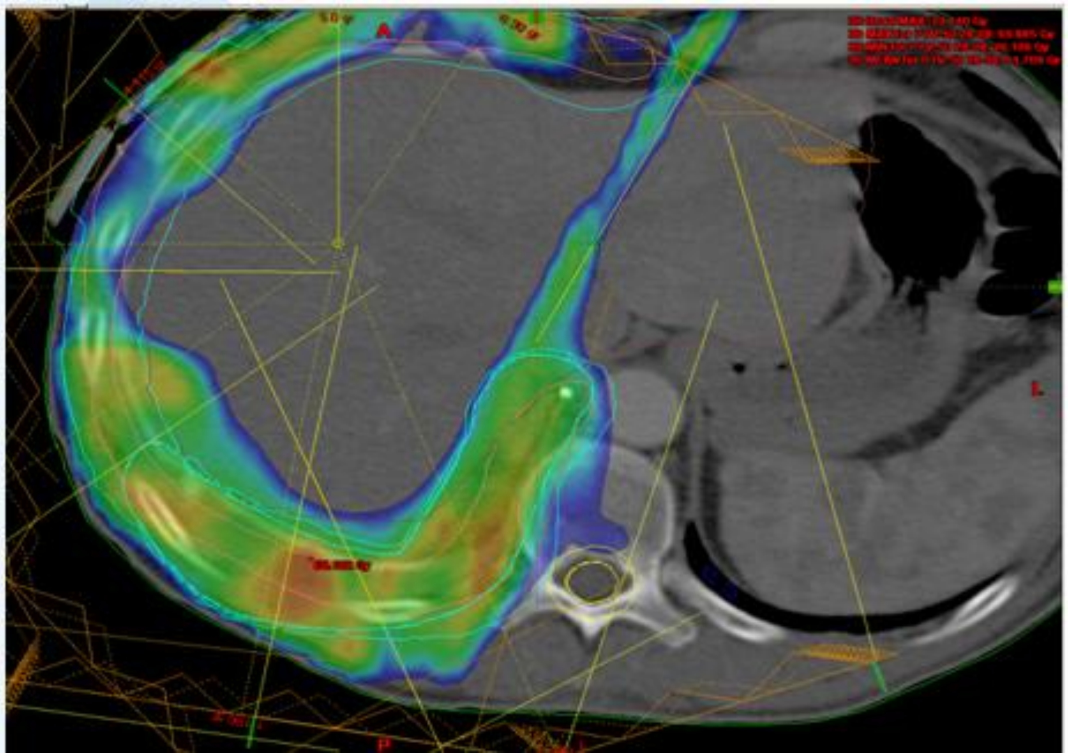
You need to know your uncertainties to make the best decision about risk/benefits balance

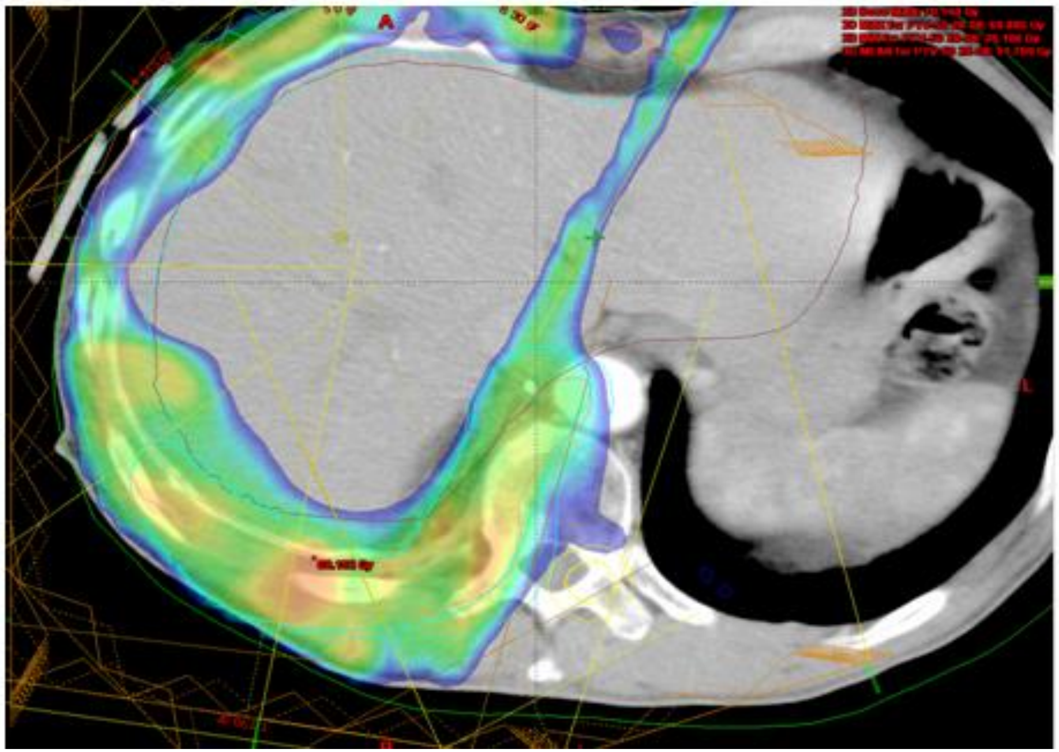
A new attempt at reducing margins

ADAPTIVE RADIOTHERAPY

Things we might not have seen without IGRT…

Mesothelioma patient. Weight loss = increased dose to spinal cord





Courtesy of Lotte S Fog, Rigshospitalet

What are we still missing ??

MR-guided RT

Two main challenges…

- **Identify patients who are likely to benefit**
- **Implement with a sustainable use of resources**

IGRT can be resource-intensive

- Acquire/commission the equipment
- Verify/calibrate on a regular basis
- Design imaging protocols for different patient groups (what kind of images, how often)

- Acquire the images + online verification
- Offline verification
- Multi-disciplinary review if recurring problems

- When applicable: calculation of average shift
- Continue the treatment as planned or adapt?

IGRT can be resource-intensive

How many images?

Who will look at them (and how often)?

Dose to the patient: adapt imaging protocols?

Tolerance levels: when to shift? When to adapt?

Conclusion (1)

- The technology has come a long way: we have many tools!
  - ➢ the challenge is to develop/introduce an IGRT approach adapted to the department's philosophy

- We need to be smart about how we use them (and this takes time!)
  - ➢ Where do you get the most "bang for your buck" in terms of resources, dose, etc..

Conclusion (2)

- IGRT is a requirement (and arguably more important than) IMRT, SIB, SBRT, CBRT, ART, RA, VMAT, …
- Adaptive RT is in this infancy: who, how, why?
- We need to keep pushing the manufacturers to include the tools that we are missing

With thanks to:

- Dirk Verellen
- Lotte Fog and Mirjana Josipovic

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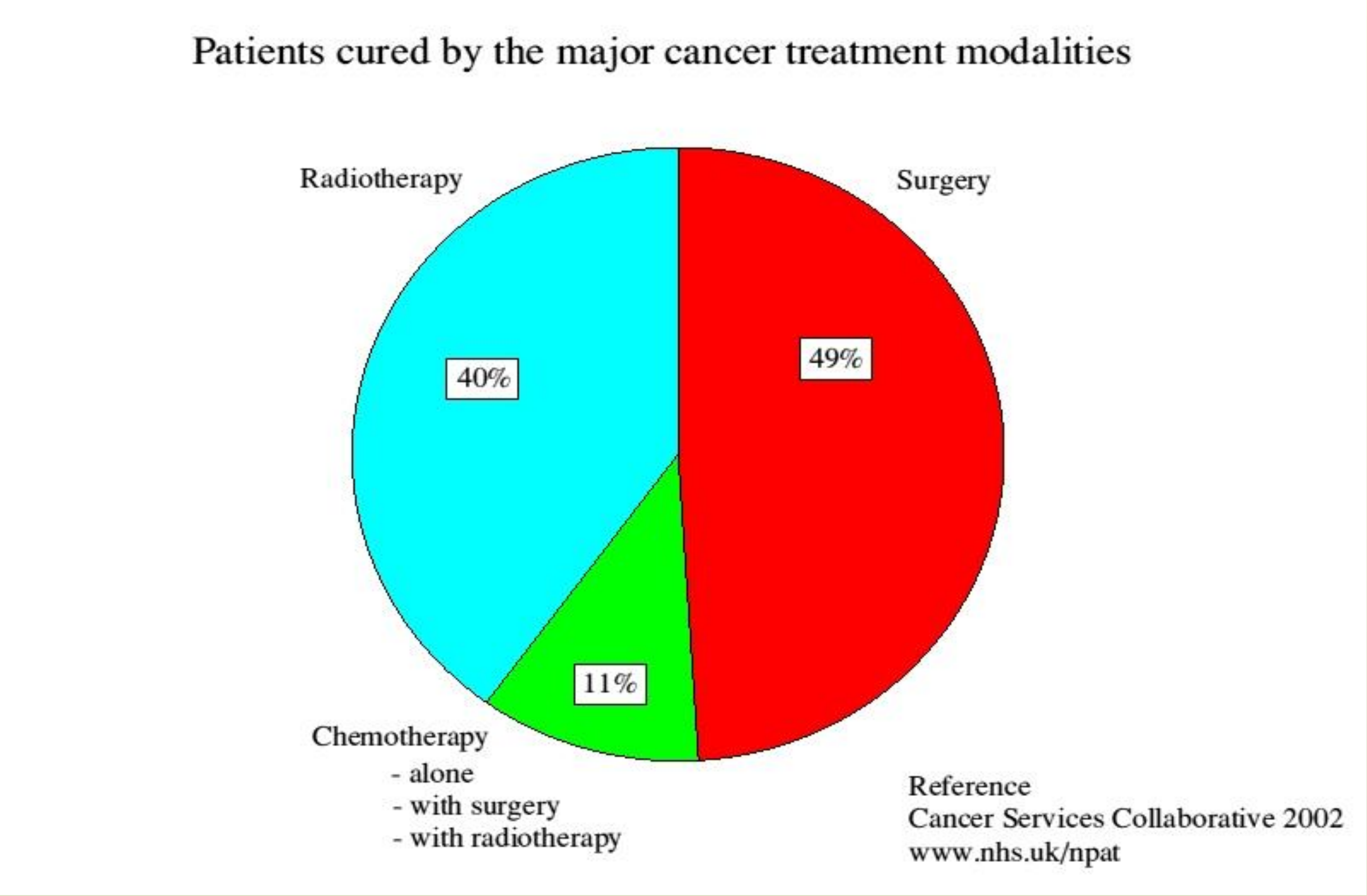
IGRT -
A Physician's Perspective

Coen Rasch

AMC, Amsterdam

Cancer Cure: Treatment Modality



Radiotherapy & Patient Outcomes

- Increase in XRT use
  - 32% (1992) to 47% (2003)
  - Curative intent ≈ 54%
  - XRT alone ≈ 20%
- Cost of XRT ≈ 6% of all cancer costs

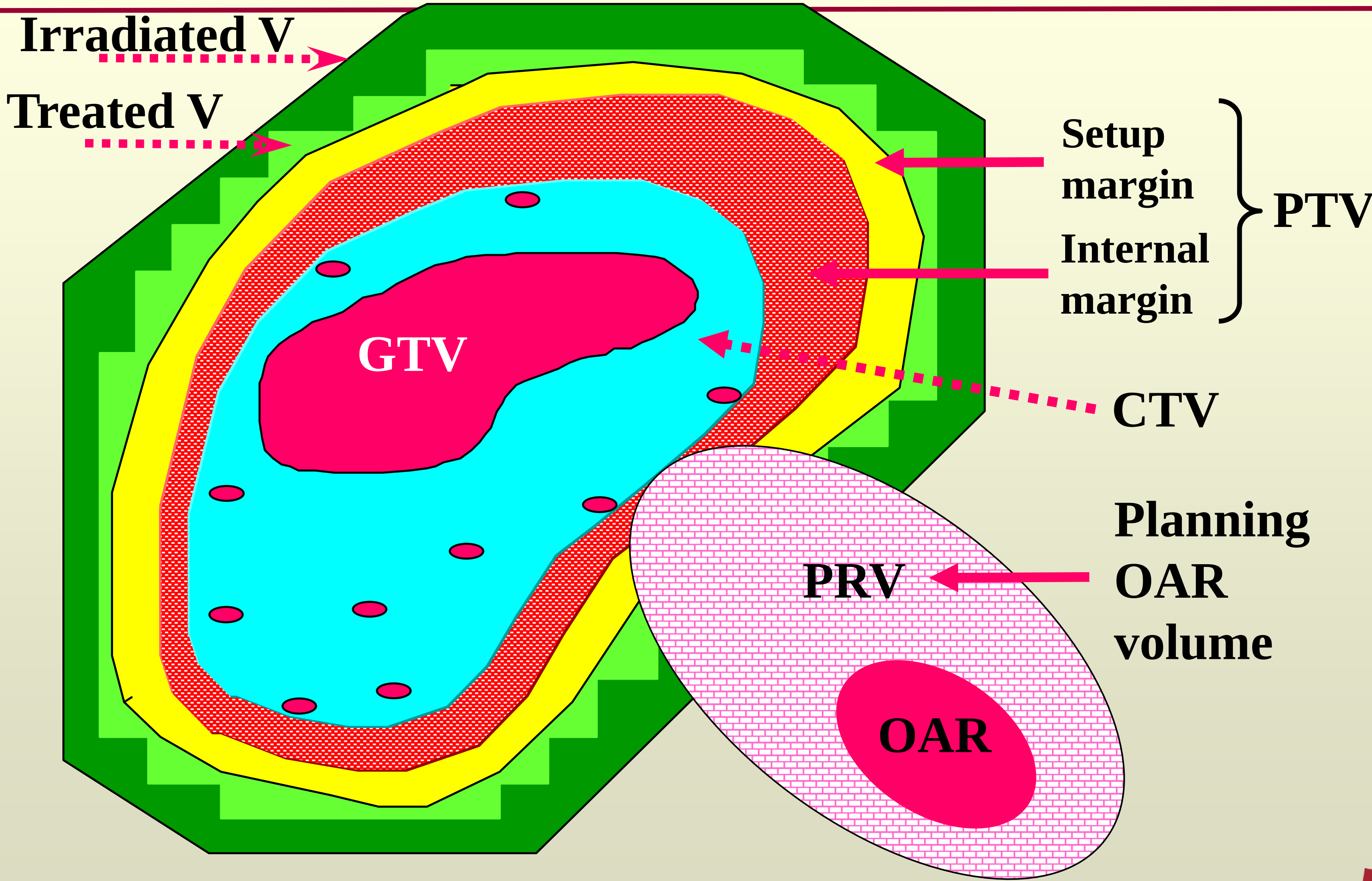
SBU II: Swedish Council on Technology Assessment in Health Care 2003

Definition of IGRT

- IGRT aims at reducing geometrical uncertainty by evaluating the patient geometry at treatment and either altering the patient position or adapting the treatment plan with respect to anatomical changes that occur during the radiotherapy treatment course.

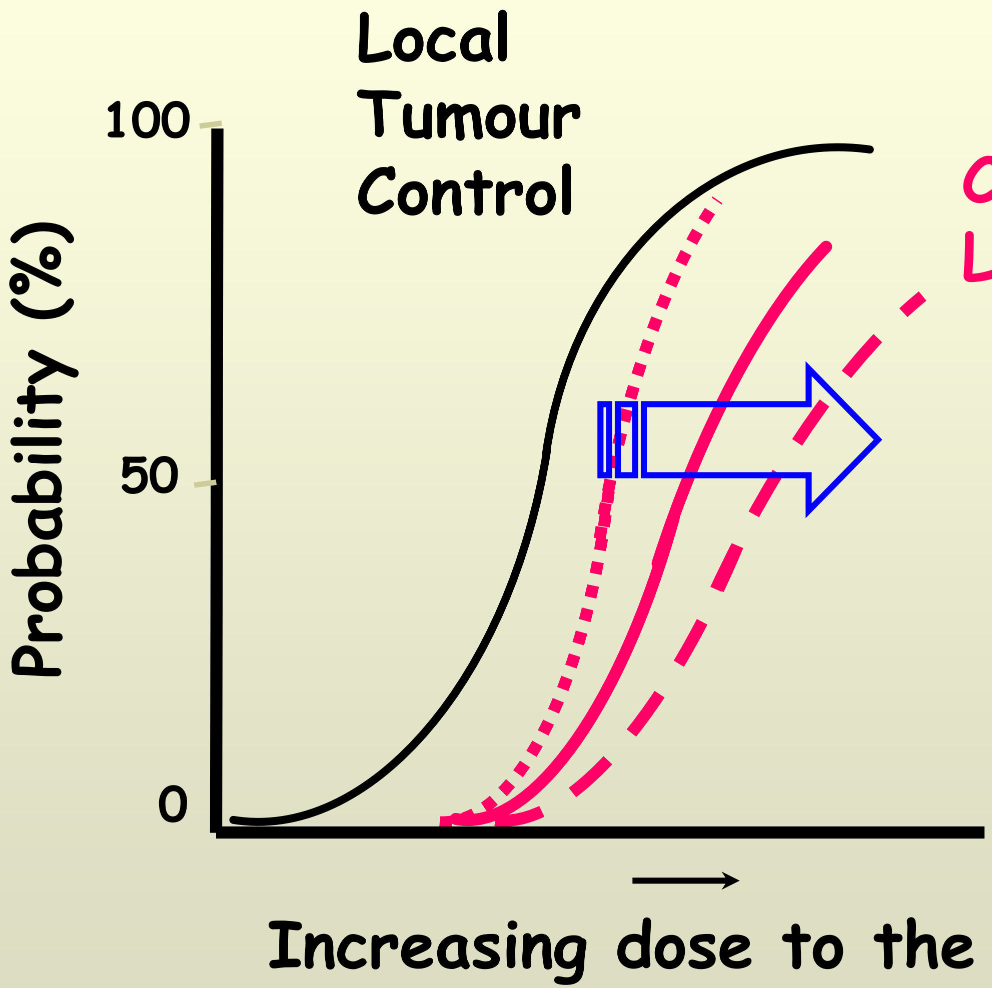
- Estro EIR report: Korreman et al 2010

ICRU 62 Planning Volumes



Khoo. Chap 53. Treatment of Cancer, Ed 5: Price, Sikora, Illidge 2008

Increase the Therapeutic Ratio



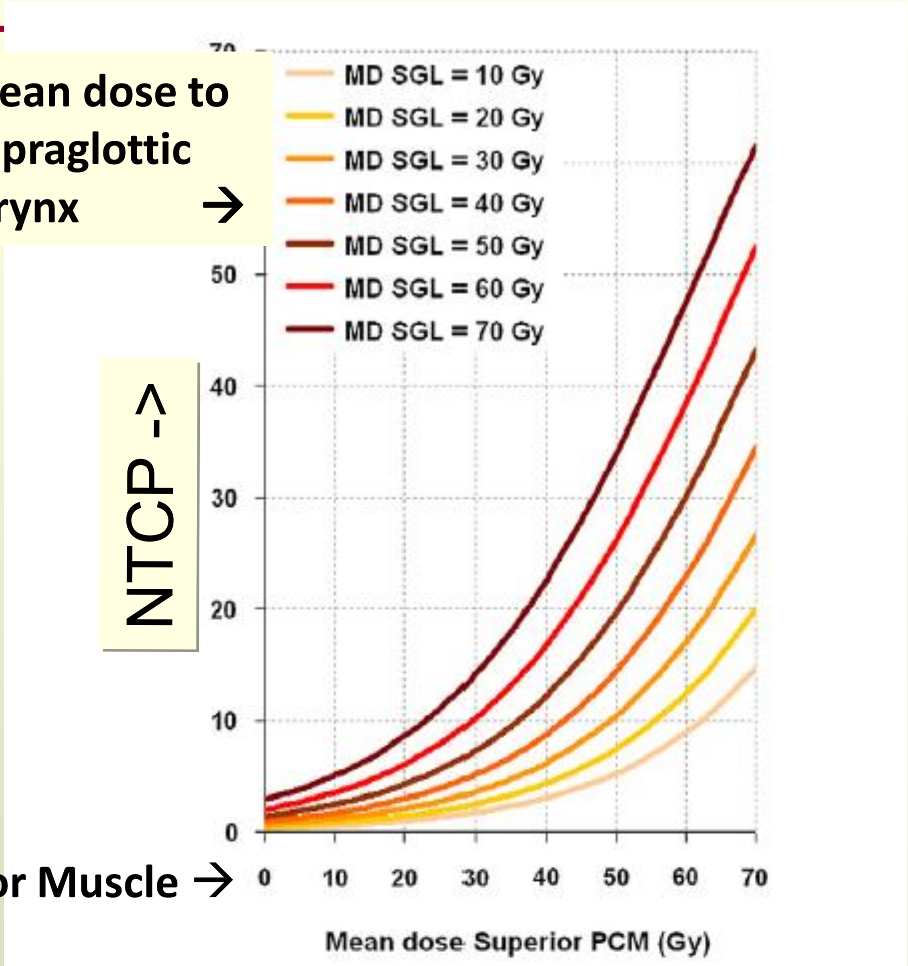
- TVD
- XRT Techniques
- Localise & Verify

Smaller margins matter

Size matters: NTCP modeling, of multiple factors

- Christianen et al
- Prospective analysis, 354 patients
- RTOG/EORTC and QoL HN35 questionnaire
- 6 months
- Head and Neck Cancer

Complication rate depends on dose to the whole functional chain



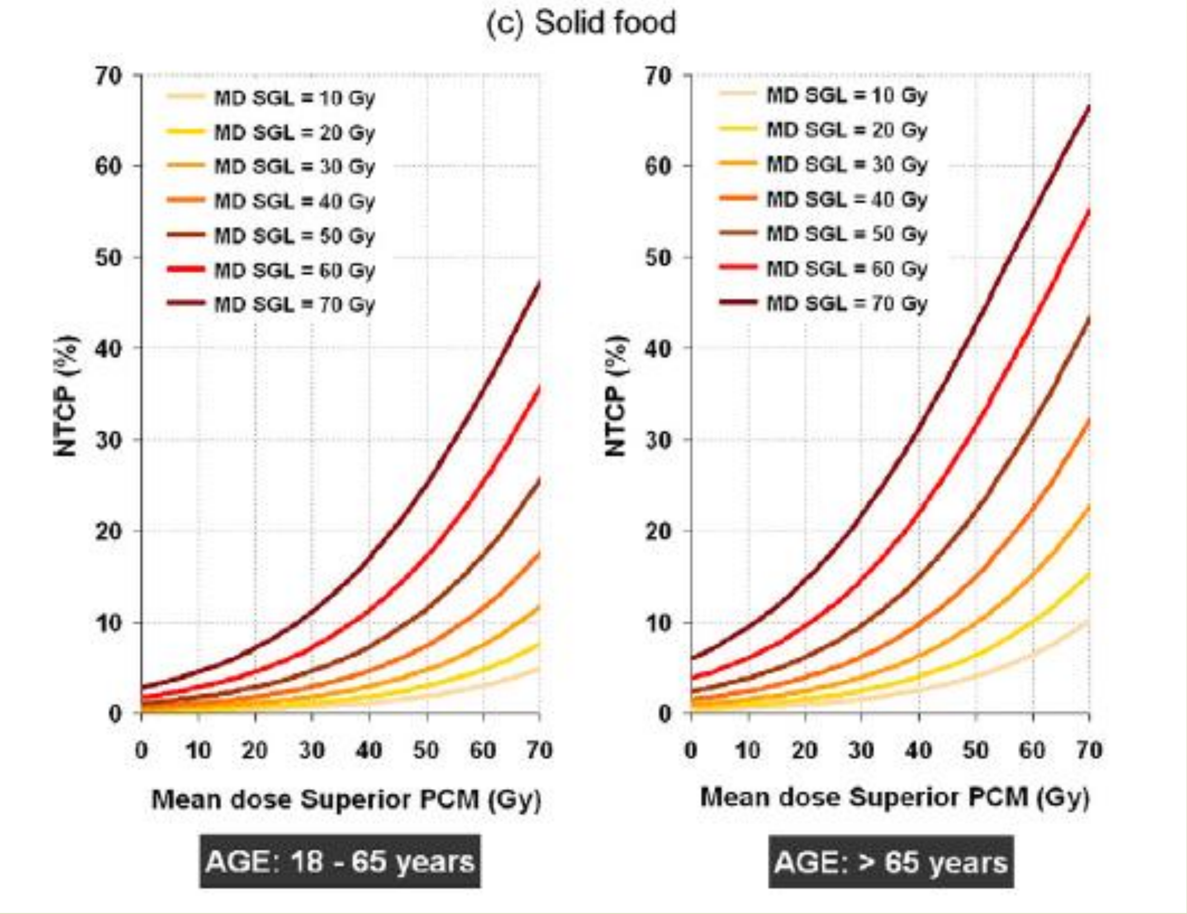
Christianen et al 2012

Mean dose to Pharyngeal Constrictor Muscle →

$$NCTP = (1 + e^{-S})^{-1}, \text{ in which}$$

$$S = -6.09 + (\text{mean dose PCM superior} \times 0.057) + (\text{mean dose supra-glottic larynx} \times 0.037).$$

Size and age matters

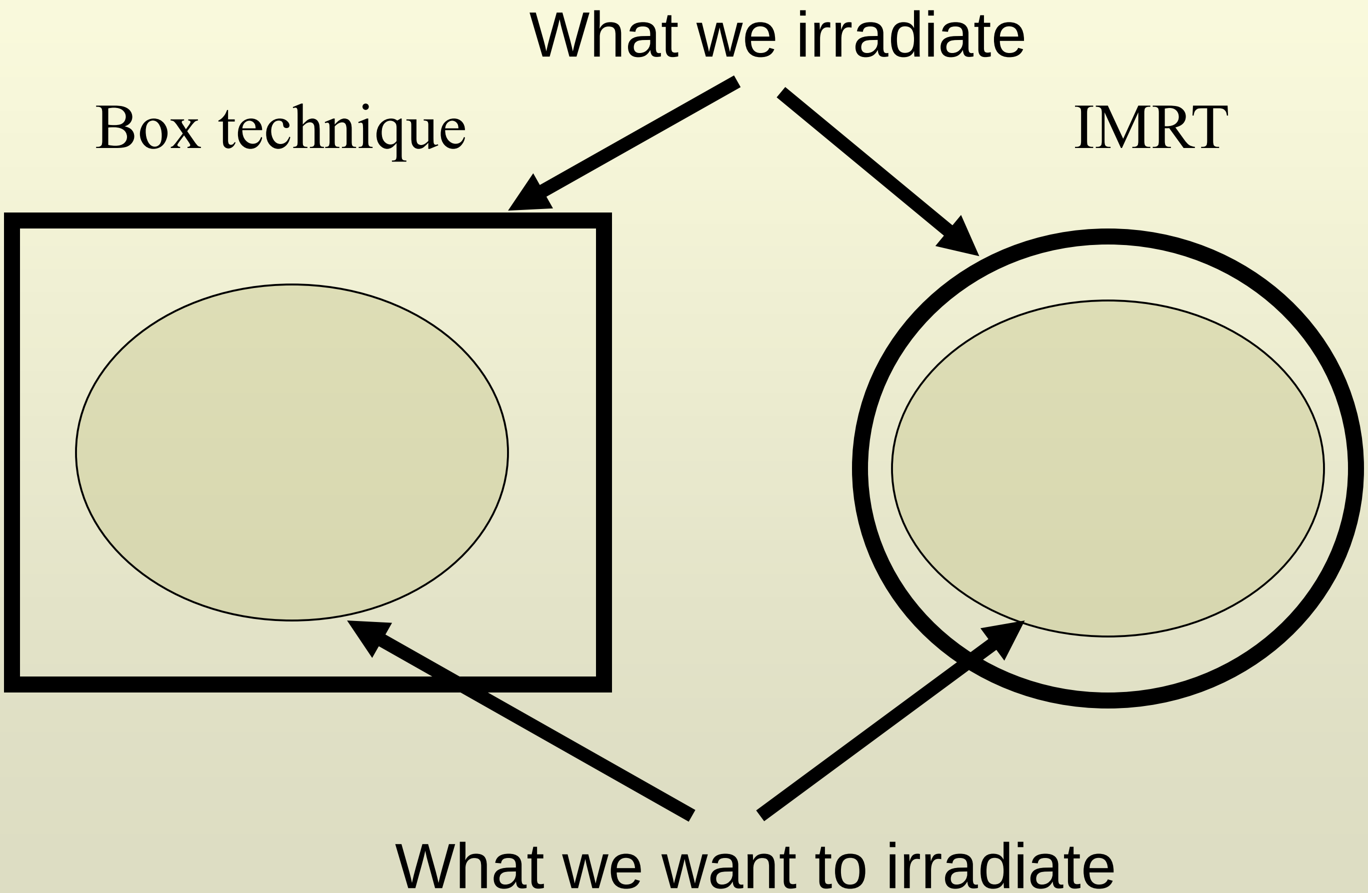


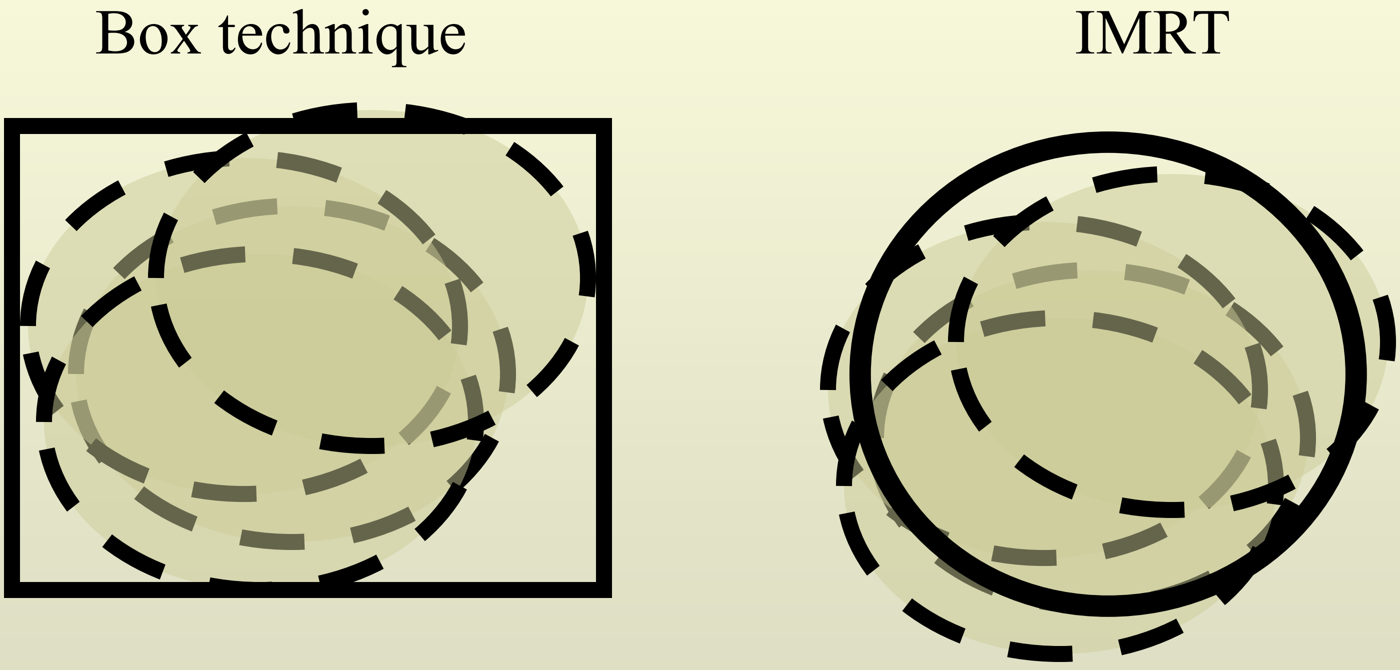
Christianen et al 2012

- So, There is clinical evidence, in this case packed in a model, that less irradiated volume means less damage.

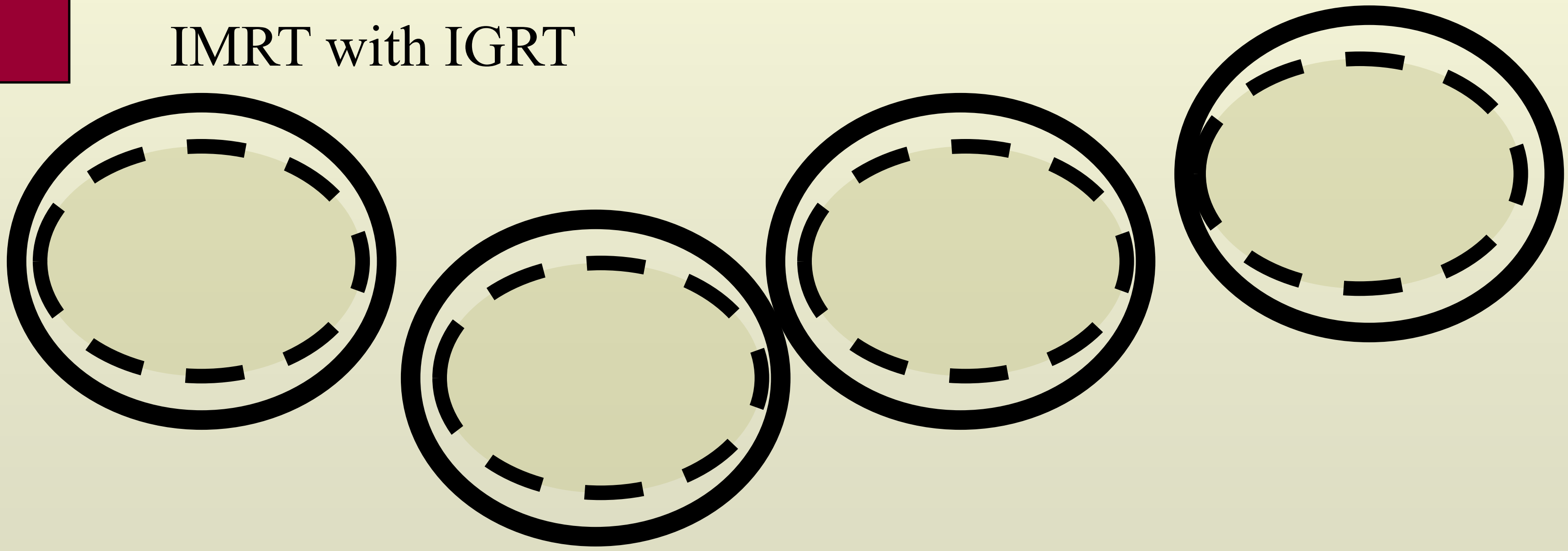
Less irradiated volume means effectively a tighter dose distribution

- IMRT aims at a tighter dose distribution
- Tighter dose distribution requires more knowledge on where the target is


What we irradiate
Box technique
IMRT
What we want to irradiate


Box technique
IMRT

IMRT with IGRT

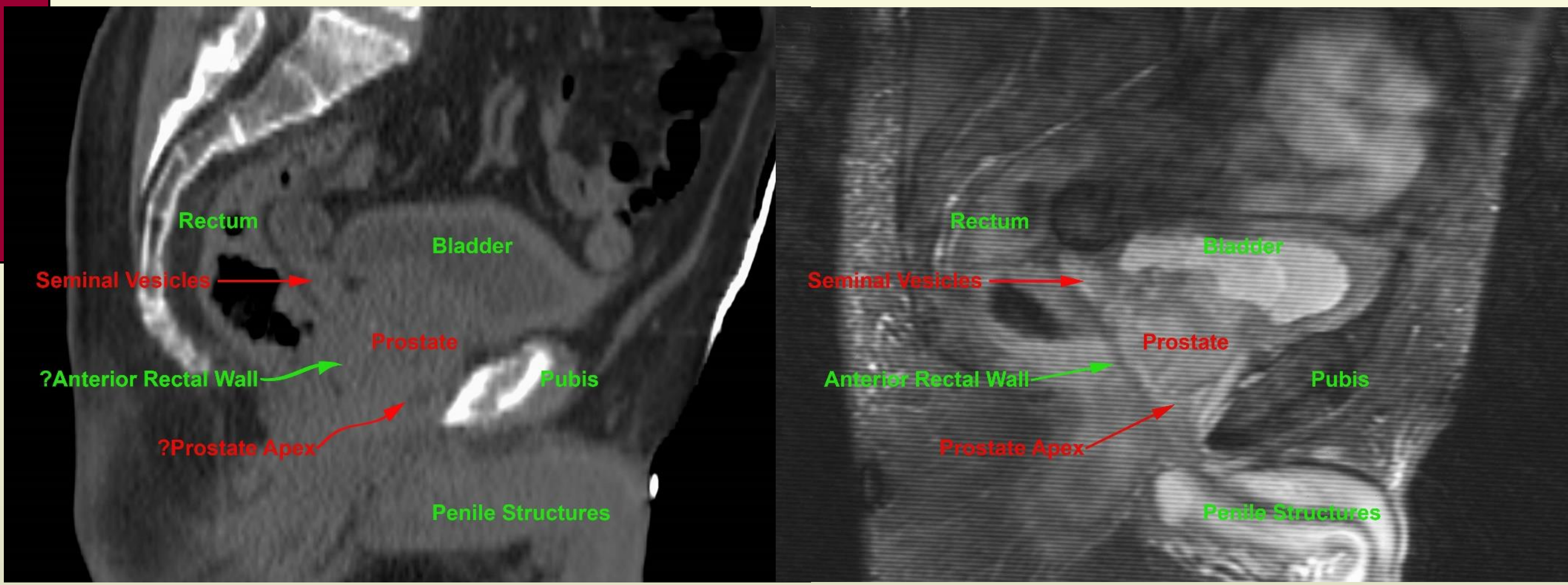


Defining GTV/CTV

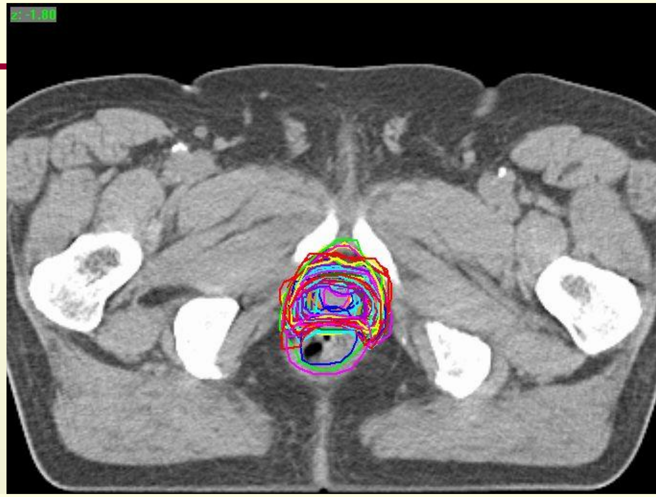
- A weak link getting more important also because of tighter dose distribution

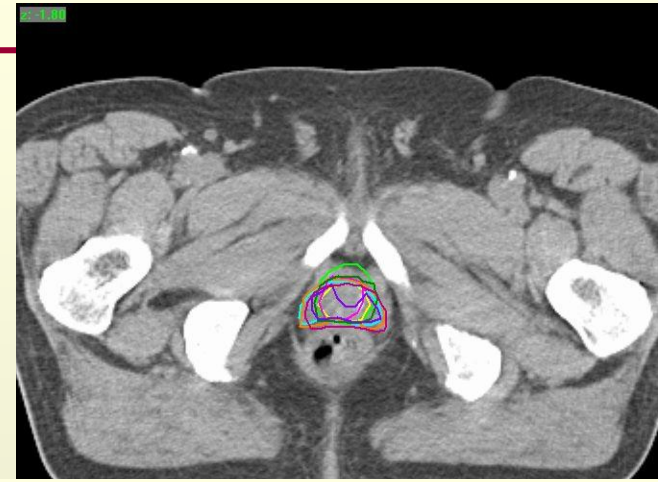
Prostate Cancer XRT: Imaging

Issues in Target Volume Determination

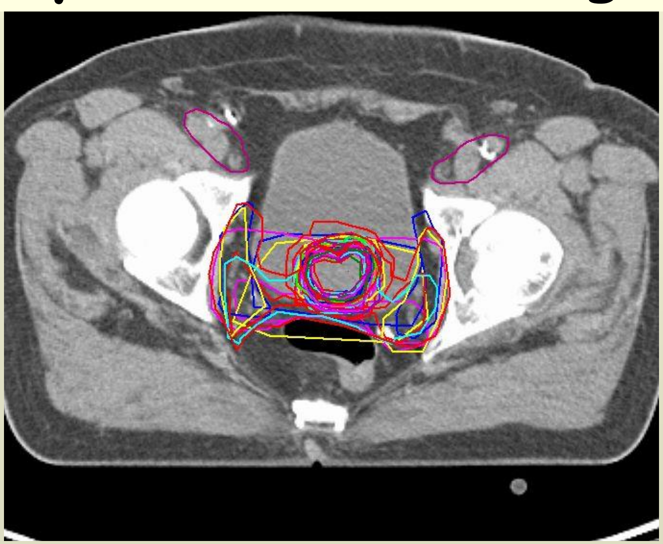


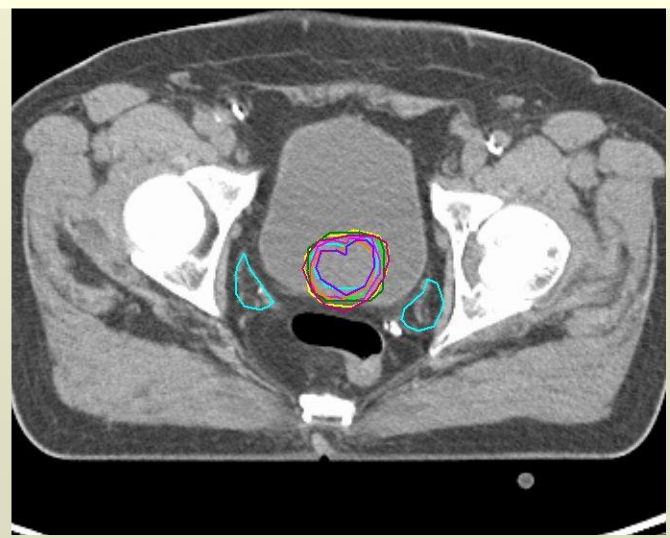
The Greatest Uncertainty: TVD





63y, PC, iPSA=15 ng/ml, Gleason 3+4, T2cN0M0

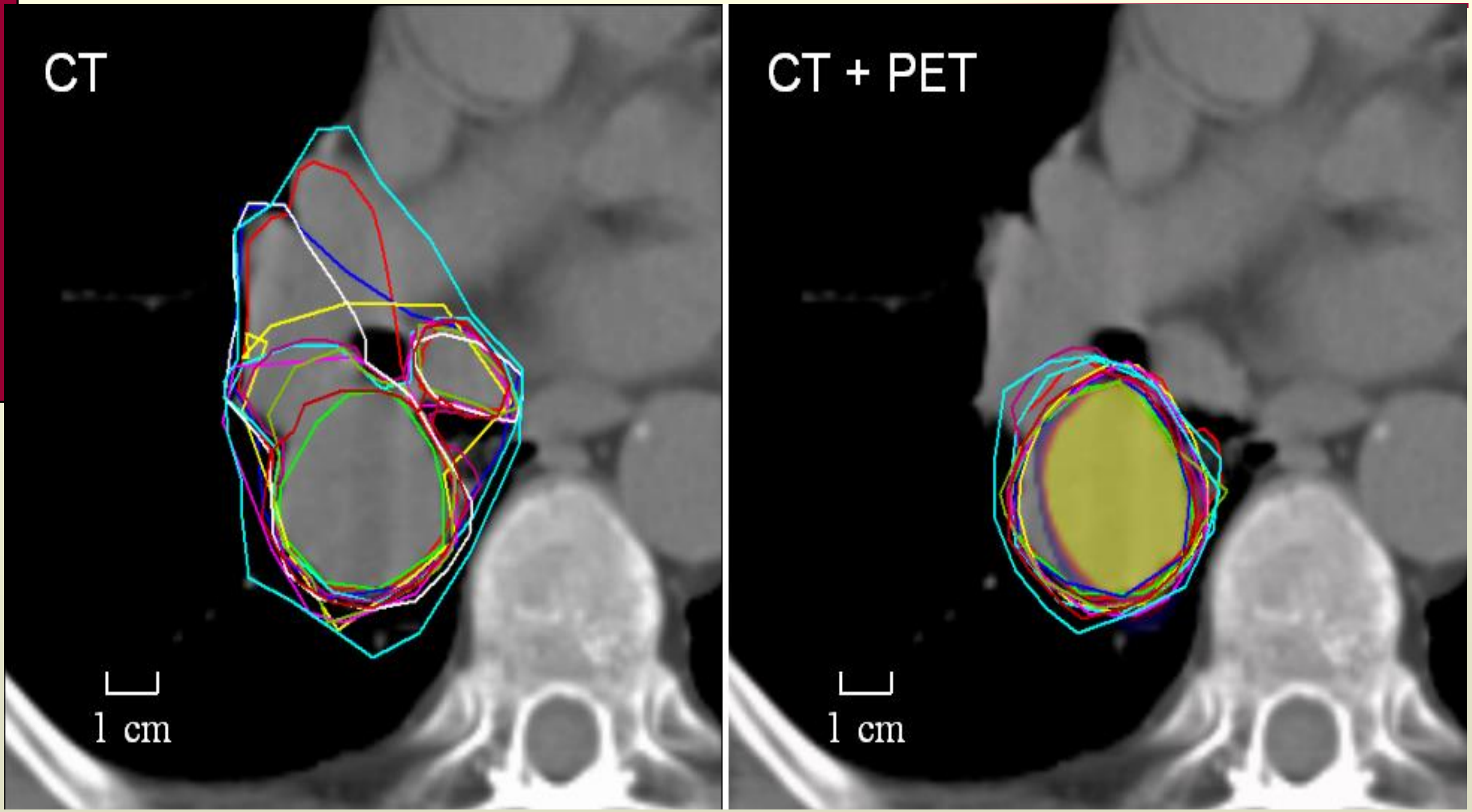




Students (N≈196): ESTRO TVD Course 2007: Turkey

Radiotherapy amc

Lung target delineation



Average SD: 10 mm

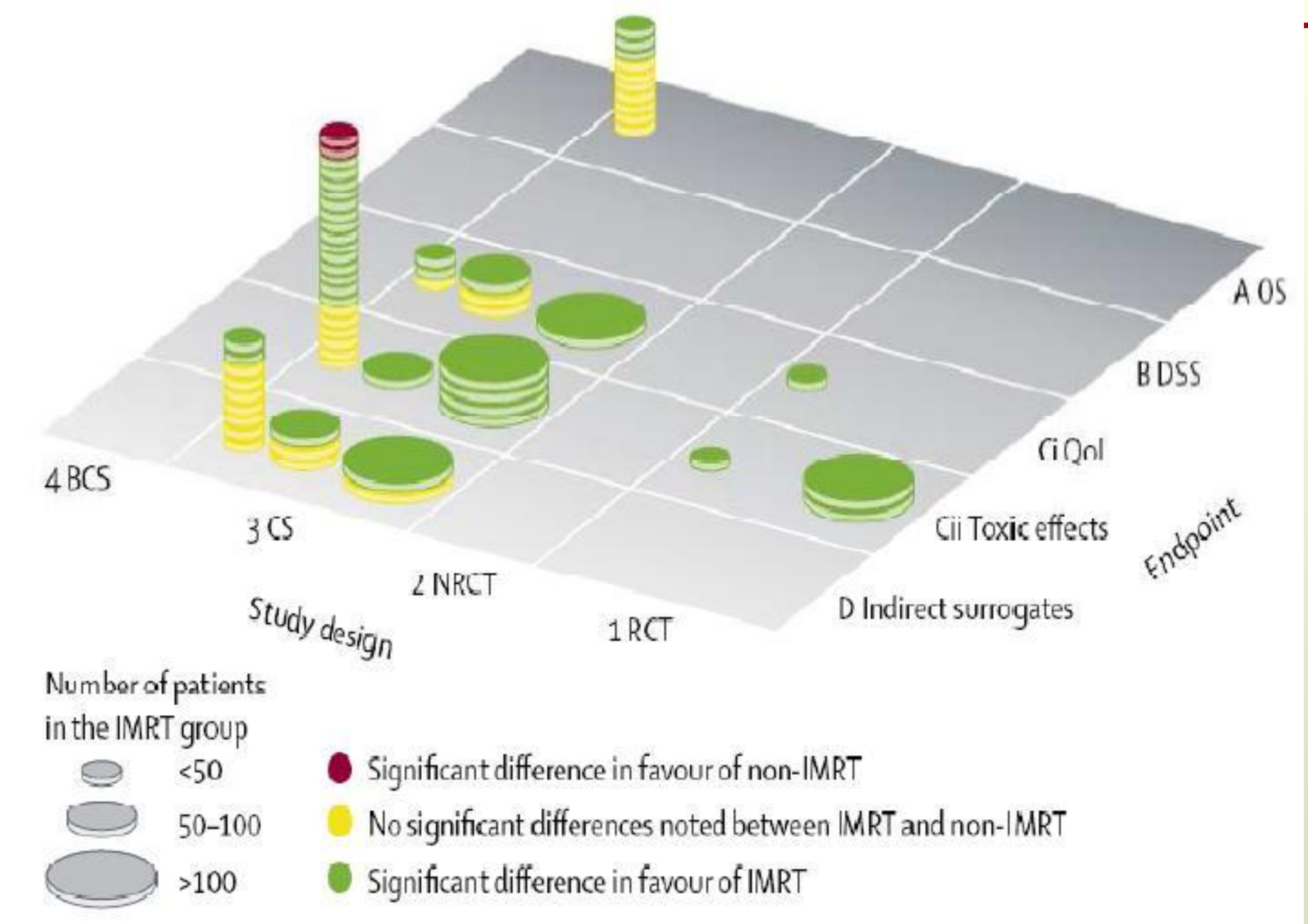
Average SD: 4 mm

Steenbakkers et al 2005

Clinical benefit

- What is the evidence of IMRT over conformal?

Is there Clinical Benefit of IMRT > CFRT?



C/most benefit in toxic effects or surrogates

Veldeman et al LO 2008

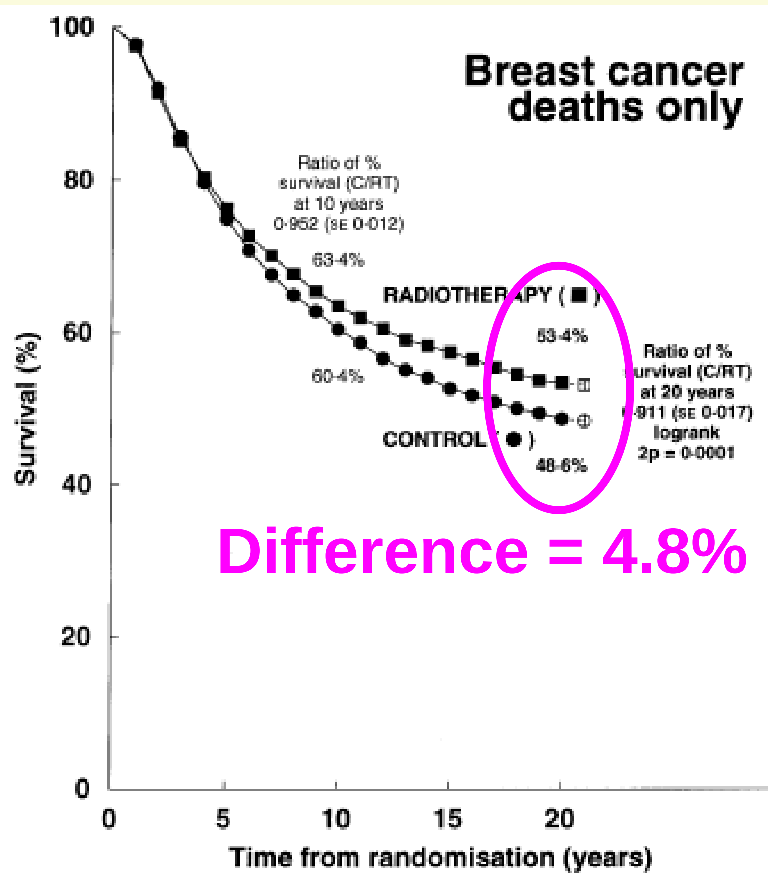
Breast Cancer solutions

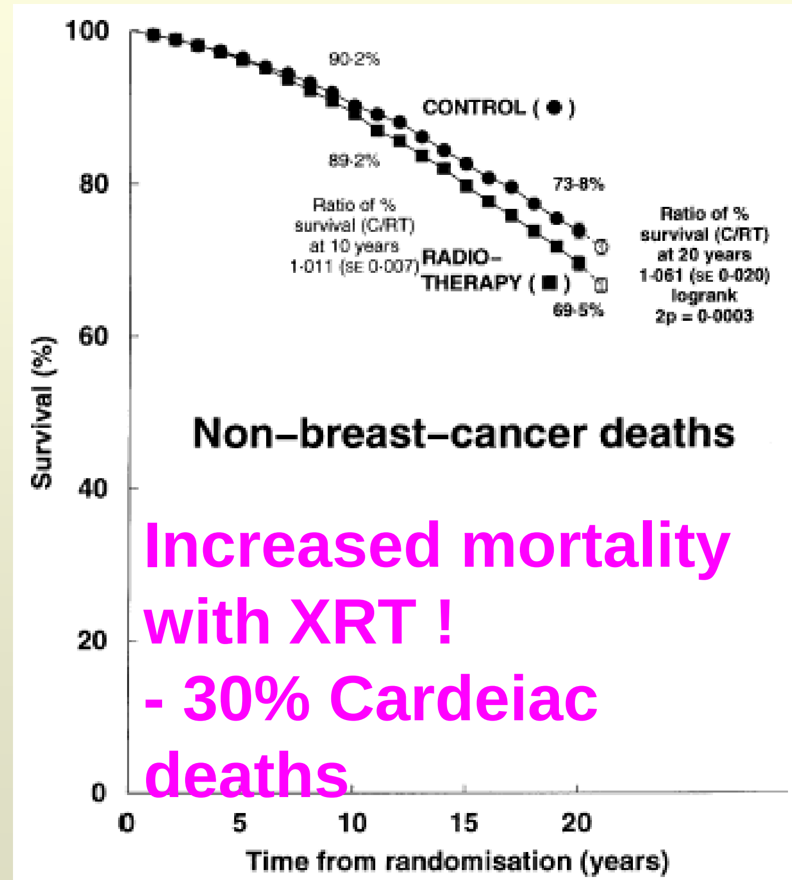
- Problem:
- Chest wall radiotherapy induces cure but at the cost of more heart diseases

Early Breast Cancer: S ± XRT meta-analysis

Total: 40 Prosp. Rand. Trials, N ≈ 20,000 (50% had N+ve disease),

XRT treating breast/chest wall, SCF, AX, IM regions





EBCT Collaborative Group. Lancet 2000

Solution: Breast XRT Reducing Cardiac Dose

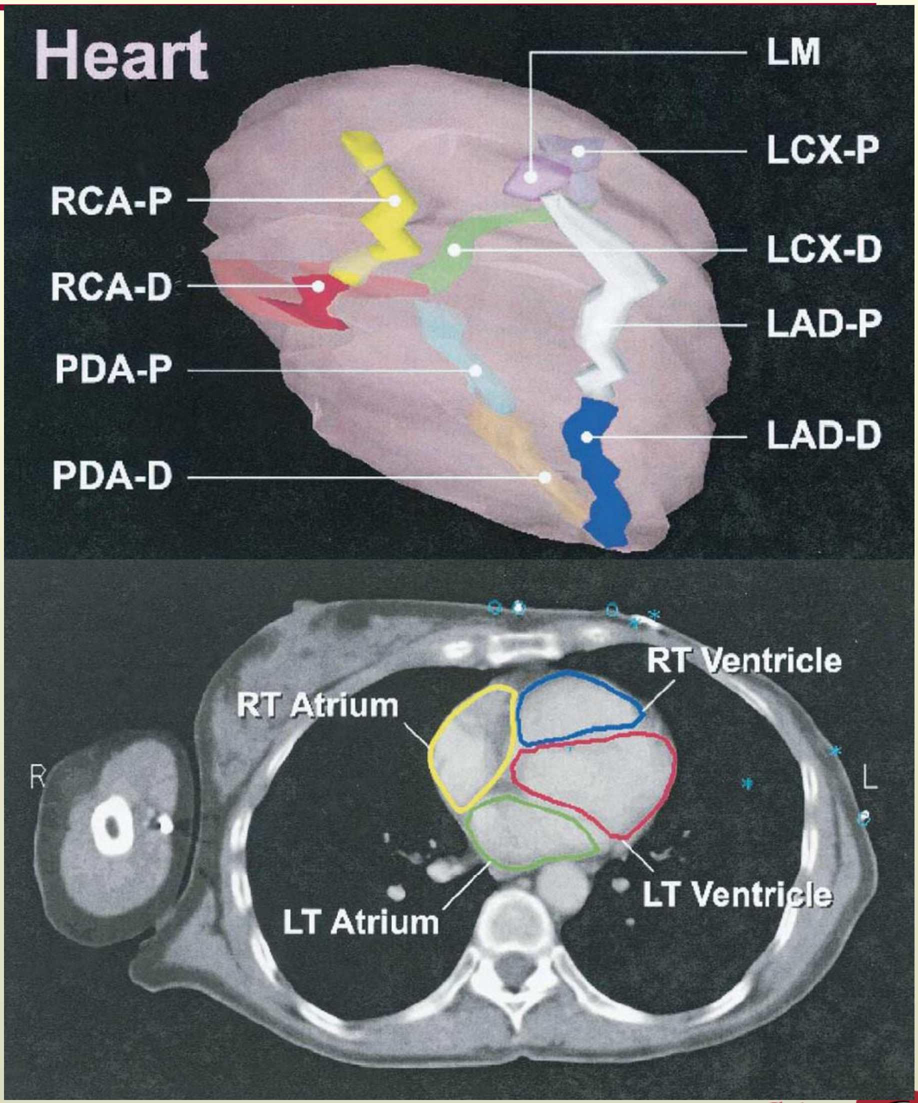
Methods:

1. Elevated Arm Position
2. Cardiac Shielding
3. CFRT / IMRT

4. Breath hold
    1. Deep Inspiration

5. ABC
    1. Gated /Gating

6. Real-time Tracking

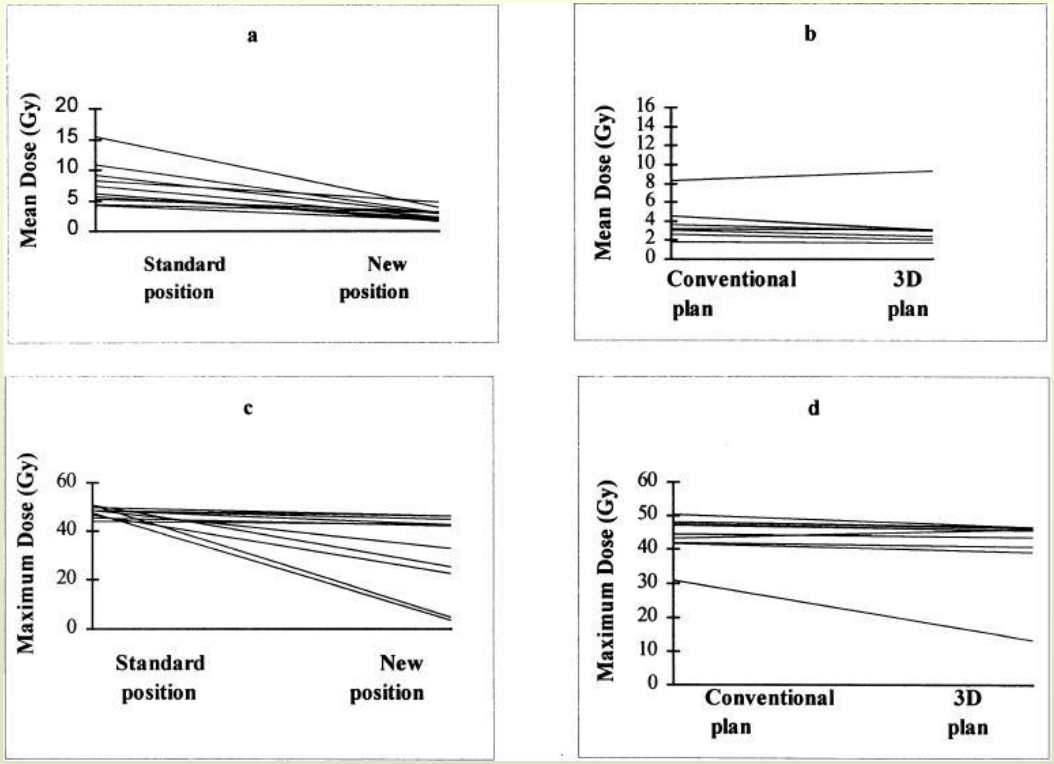


Krueger IJROBP 2004

Breast XRT: Reducing Cardiac Dose with Elevated arm position versus @90 degrees

Methods

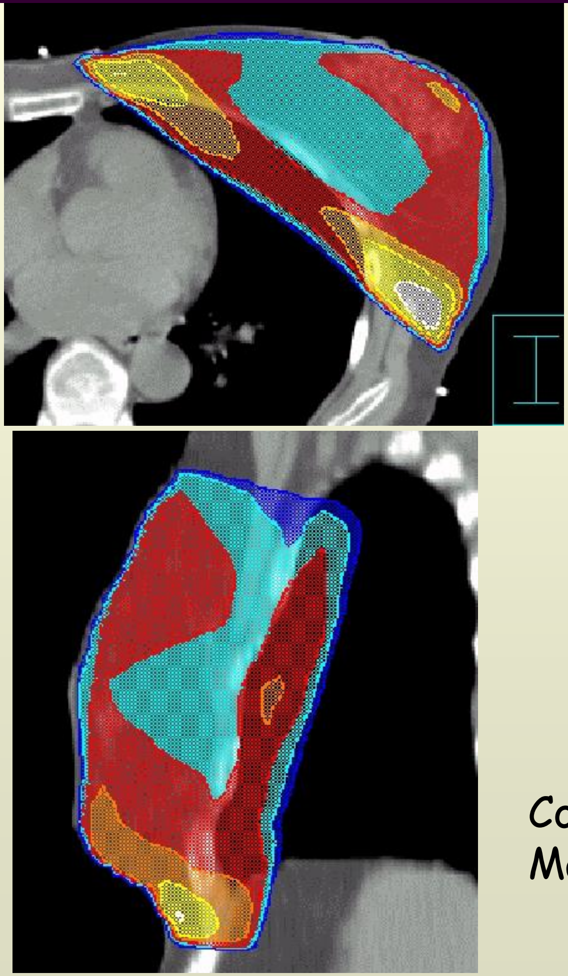
- Elevated Arm
  - Arm above head vs arm at 90º
  - Mean cardiac dose reduced by 60%

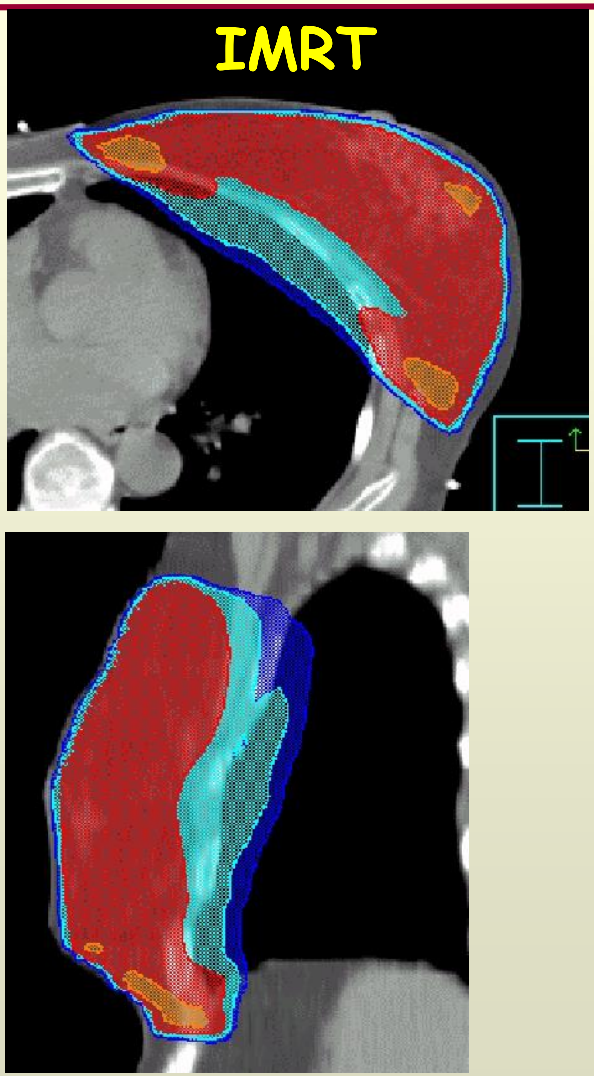


Canney et al BJR 1999

Breast: Reducing cardiac dose
Standard RT vs IMRT

Wedges (Lung Correction)



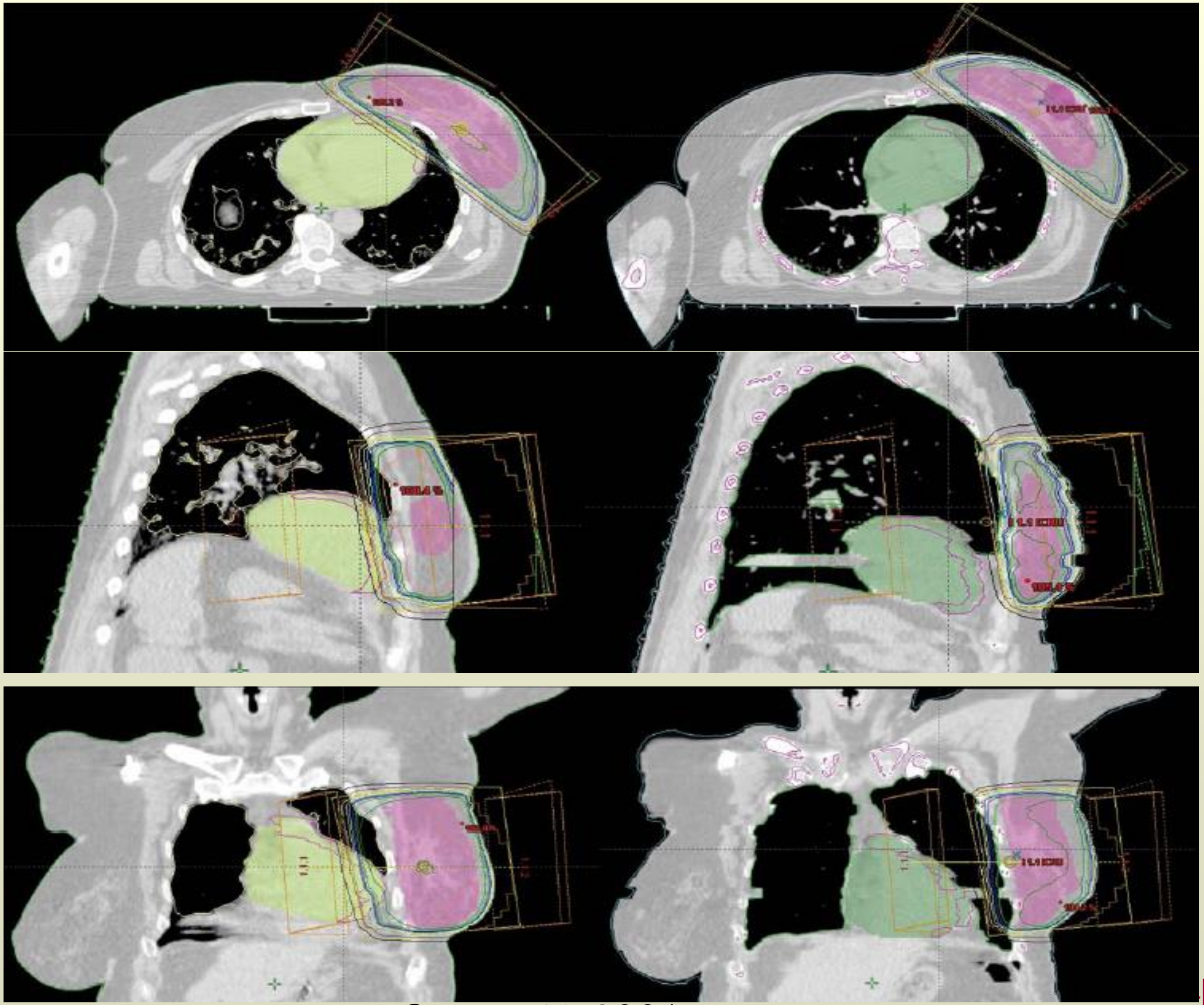


Courtesy: A Martinez

115%, 110%, 105%, 100%, 95%, 90%

Radiotherapy amc

Breast Reducing cardiac dose: normal breathing versus Breathhold



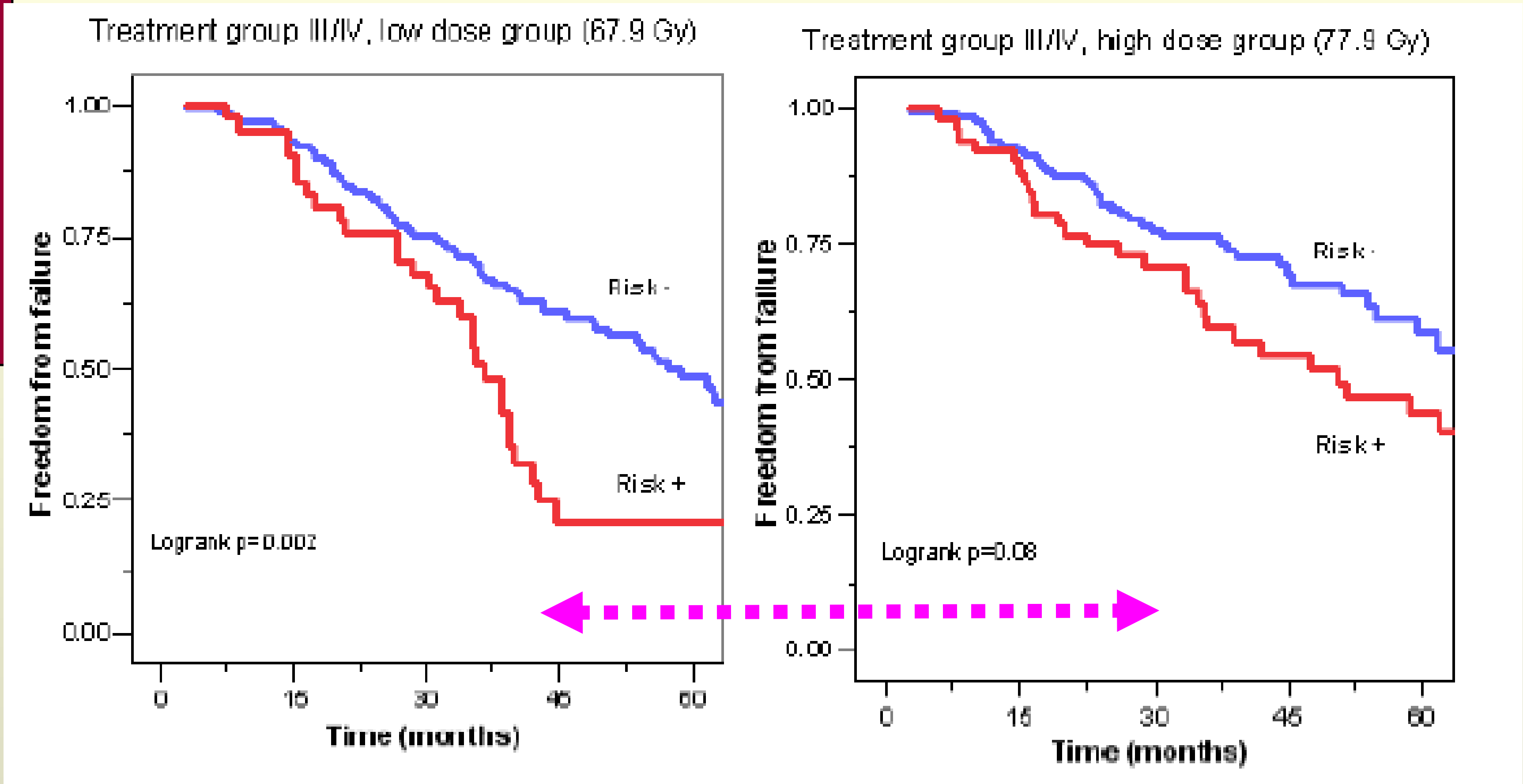
Beavis CO 2006

Prostate Cancer IMRT without IGRT

- Smaller margins are needed to reduce rectal toxicity and are at the same time dangerous because the posterior edge of the prostate is close to the rectum.
  - Initial full rectum gives rise to more recurrences

PC: Impact of Organ Displacement

(CKTO 96-10: N = 660 patients)



Risk+: initial full rectum, later diarrhoea

Heemsbergen et al, IJROBP 2006

Radiotherapy amc

Prostate Cancer IMRT with IGRT

- Smaller margins are needed to reduce rectal toxicity and are at the same time dangerous because the posterior edge of the prostate is close to the rectum.
  - More recurrences with zero margin and markers:

More biochemical prostate recurrences with zero margins and fiducials

- Engels, 2008
  - Prostate cancer
  - 213 patients with daily bony setup, 25 patients with daily marker setup.
  - Risk factors for recurrence:
    - Distended rectum at start
    - Daily marker setup

Head and Neck lessons from the IMRT era

Head and Neck lessons from the IMRT era

- 133 patients
- Stage I (1), II (6), III (26), IV (95)
- Contralateral neck negative but at high risk
- Bilateral irradiation 50 + 20-30 Gy
- FU 32 months

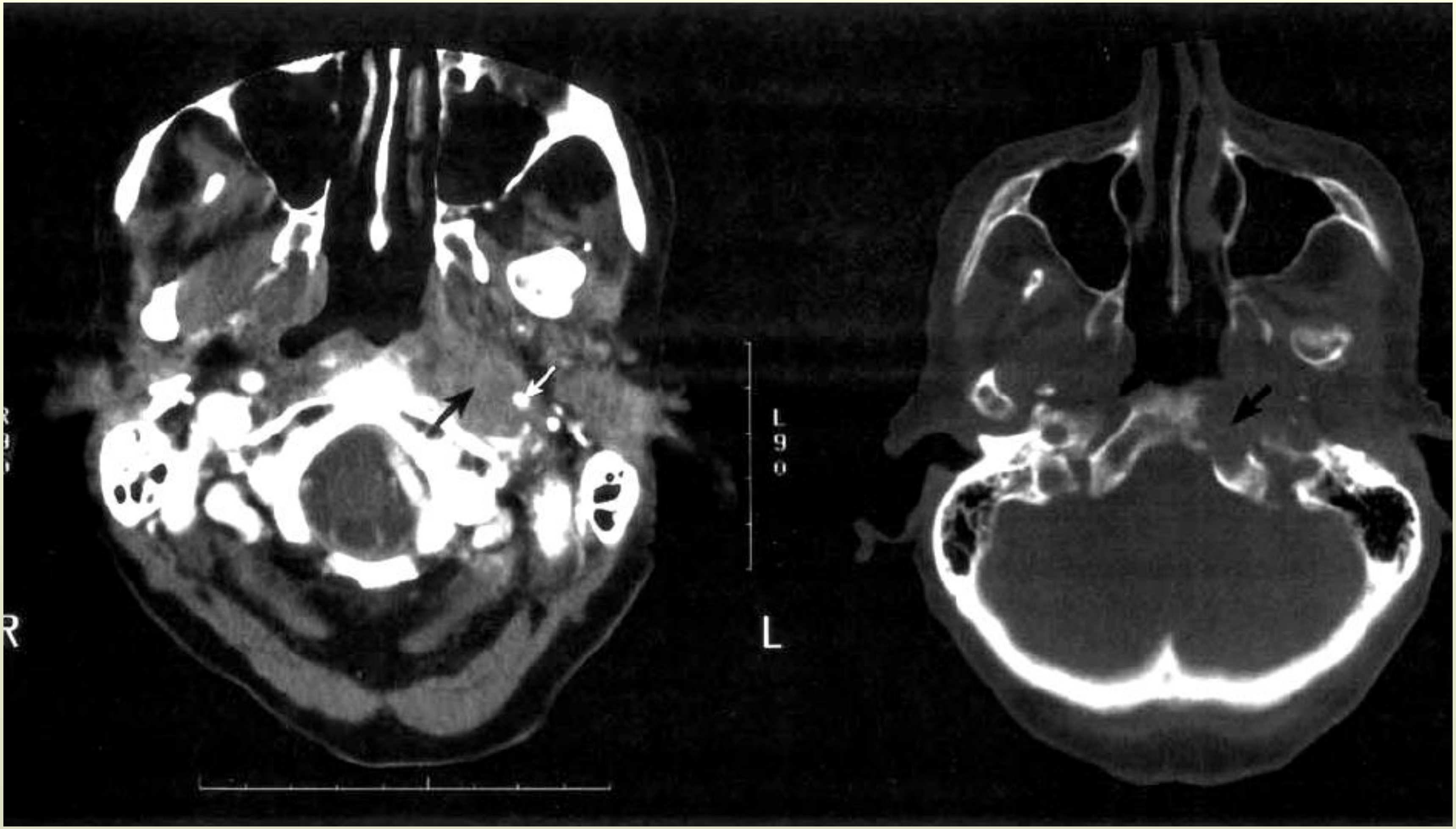
•Eisbruch et al IJROBP 2003

Head and Neck lessons from the IMRT era

- 21 (16 %) loco-regional recurrence
- 17 in field, 4 marginal
- No recurrences contralateral cranial to the SD nodes
- Three (marginal) Retropharyngeal node recurrences therefore target area extended to the level of C1 retropharyngeal
- 82% of cases contralateral dose to the parotid below 26 Gy

•Eisbruch et al IJROBP 2003

Head and Neck lessons from the IMRT era



•Eisbruch et al IJROBP 2003

Radiotherapy

Thoughts

- If IGRT is not level I proven better than IMRT should we be using it?

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  - Quality assurance?

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- If IGRT is not level I proven better than IMRT shoud we be using it?
  - Quality assurance?
  - If you can have better vision with glasses do you need to prove that you are a better driver in order to be allowed to use them?

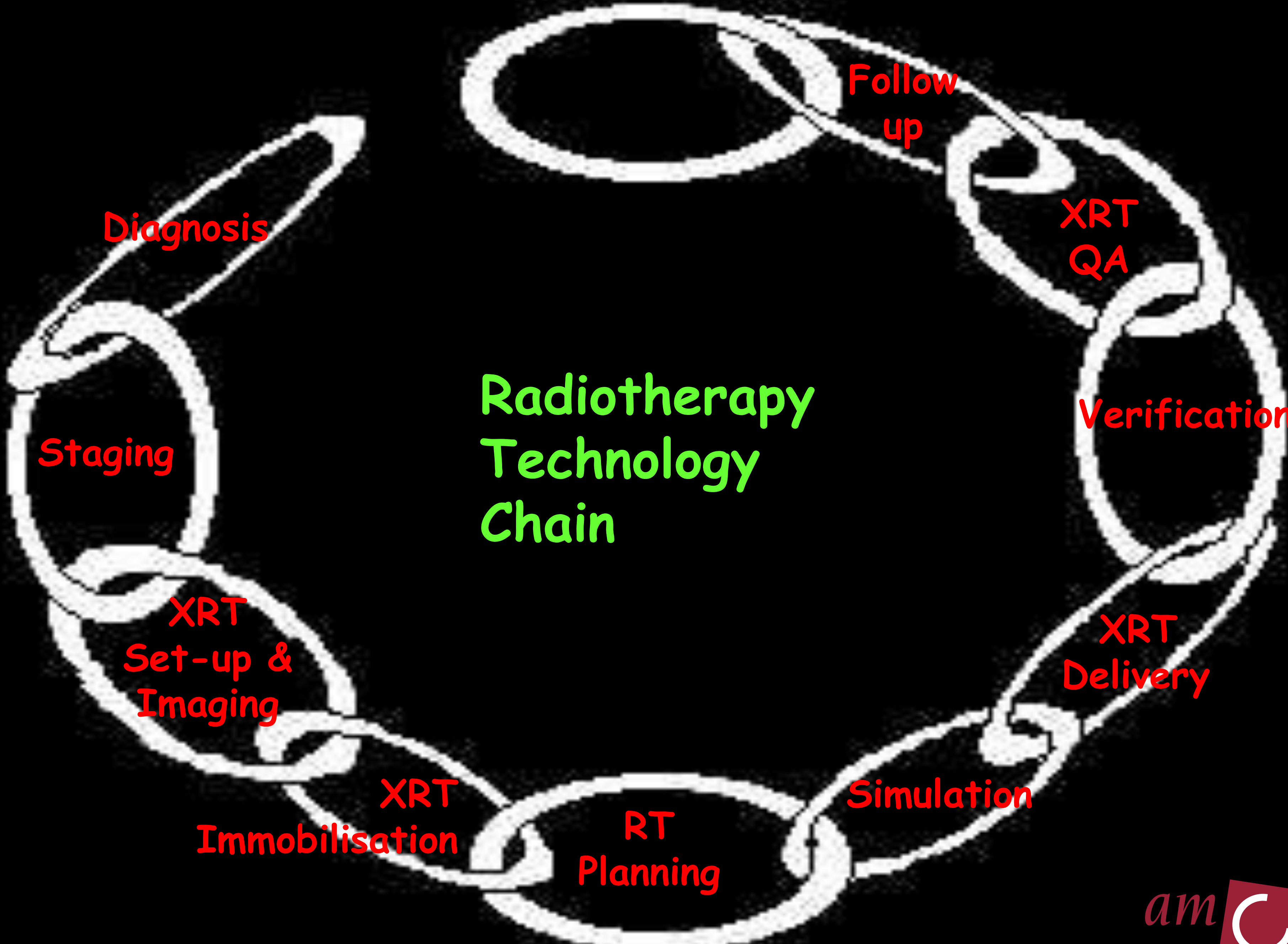
Thoughts

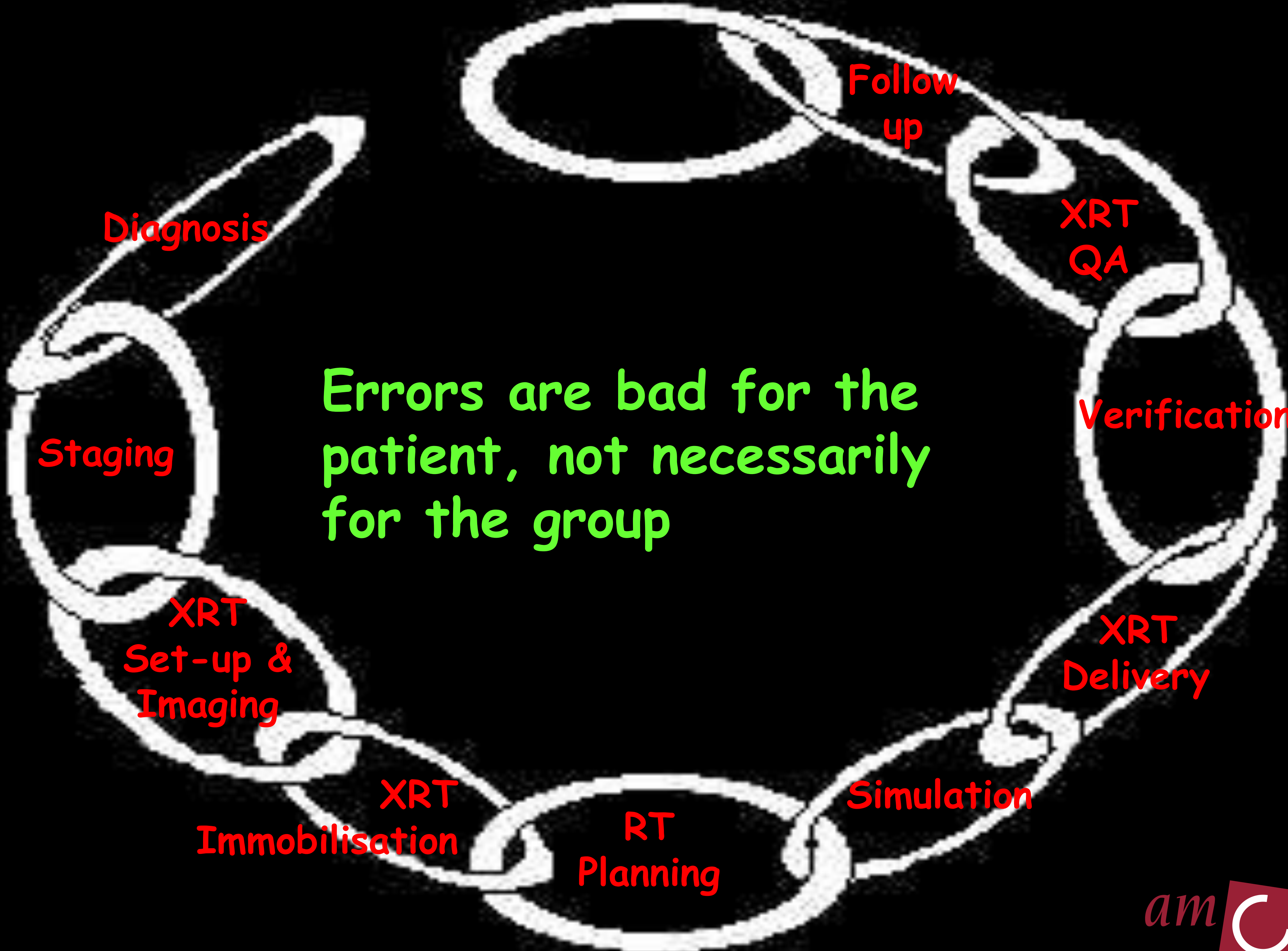
- If IGRT is not level I proven better than IMRT shoud we be using it?
  - Quality assurance?
  - If you can have better vision with glasses do you need to prove that you are a better driver?

  - Nevertheless: **reducing margins** will need clinical proof. Similar when from conformal to IMRT we will enter an era where marginal misses due to better technology comes on our doorstep. This is bad for the individual patient but can be good for the group provided you close the feedback loop.

Thank You

Radiotherapy Technology Chain





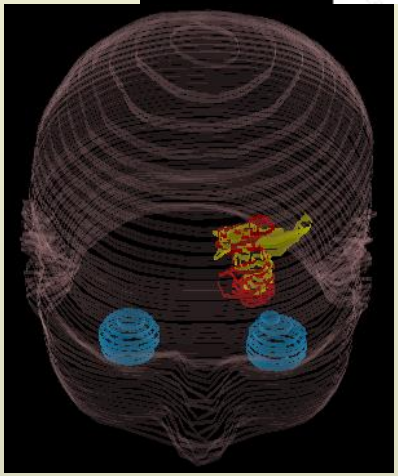
Errors are bad for the patient, not necessarily for the group

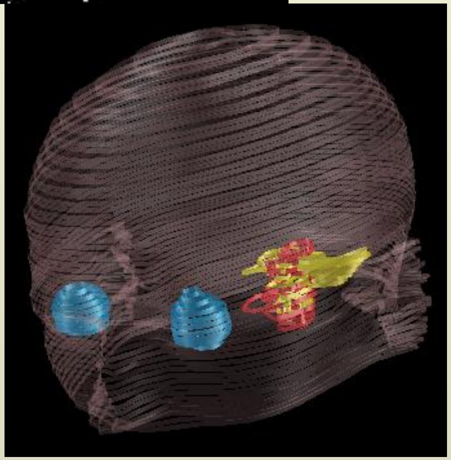
CT vs MRI comparison

Base of Skull Meningiomas

CT-defined CTV (red)

MRI-defined CTV (blue)





Red outlines = CT & Yellow outlines = MRI

Khoo et al IJROBP 2000

Treatment Uncertainties or Errors

- Therapy Uncertainties or Errors
  - Systematic (Σ)
  - Random (σ)
- For adequate coverage of the CTV
  - approximately 2.5 Σ + 0.7 σ
  - *van Herk et al IJROBP 2002*
- For adequate OARs margin
  - approximately 1.3 Σ + 0.5 σ
  - *McKenzie et al RO 2002*

Palliation in one-stop shop

- Single fraction / hypofractionation
- On-line strategy (CBCT) for spinal bone mets
- Time < 30 min (position, image, plan, treat)

- Adv: improved accuracy, convenience & ?outcome and/or QOL

Letourneau et al, IJROBP, 2007

IMRT & IGRT: My Logic

- IMRT
  - Dosimetric advantage
- IGRT
  - Enables us to address temporal spatial uncertainties in treatment delivery
  - 4D reliability and accuracy
  - Smaller margins
- IMRT + IGRT
  - Logical
- Any XRT + IGRT
  - Also logical and worthwhile
  - Need to rationalise potential benefit

IGRT: General Approach

- Determine what the ‘uncertainty’ is
  - Site and/or patient
- Define the ‘uncertainty’
  - Observe
  - Understand
  - Measure
- Modify the ‘uncertainty’
  - Reduce
  - Avoid or Eliminate
  - Account or Adapt

IGRT: 'Simple' Practice

- 'Gradual' changes in anatomy & shape
  - Changes over weeks eg weight loss in H&N patients
  - Adapt XRT plans
  - E.g. Adapt treatment to shrinking parotid gland/tumor
- 'Daily' changes eg organ filling or emptying
  - Eg bladder and rectum causing displacement or deformation, head and neck flexibility
  - Adjust treatment position ± adaptation
  - Use surrogates of target position or direct organ/target visualisation
- 'Fast' changes or rapid moving targets
  - Eg lung XRT with respiration
  - Prevent base line shift (gradual), Track or gate XRT or freeze the 'motion'

What drives progress?

Clinical rationale & gain

should 'drive'

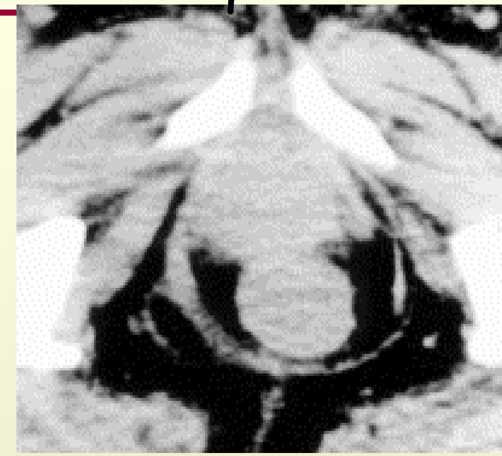
Technology

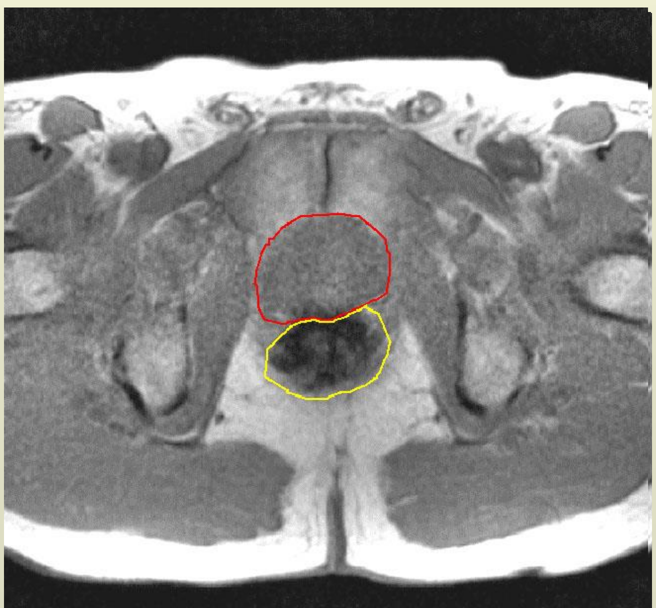
And not Technology 'driving' Rationale or Practice

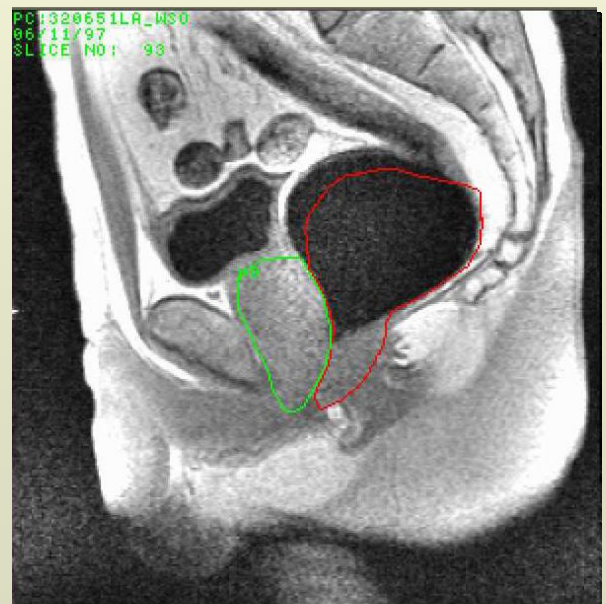
Prostate XRT: 4D Issues

Planning scan

Subsequent scan







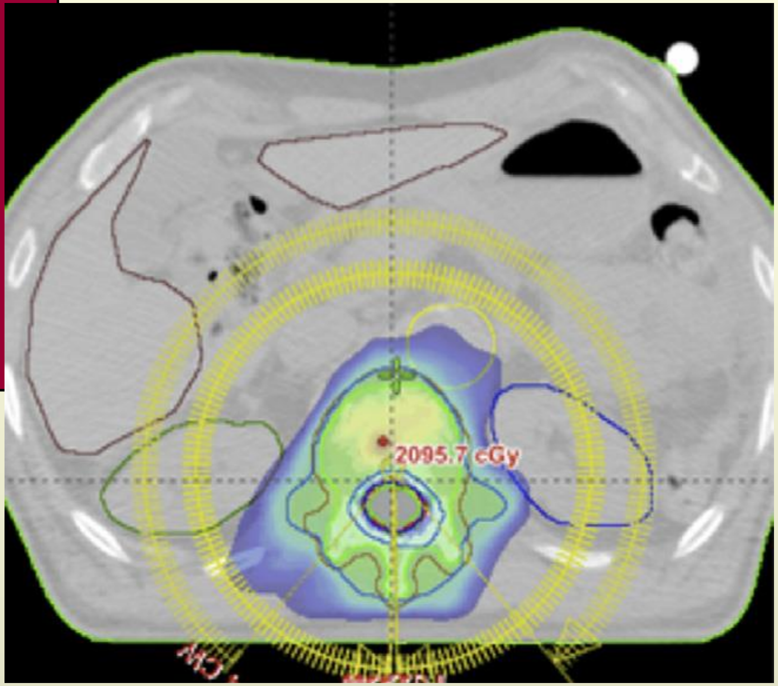
Radiotherapy amc

Khoo et al BJC 1998

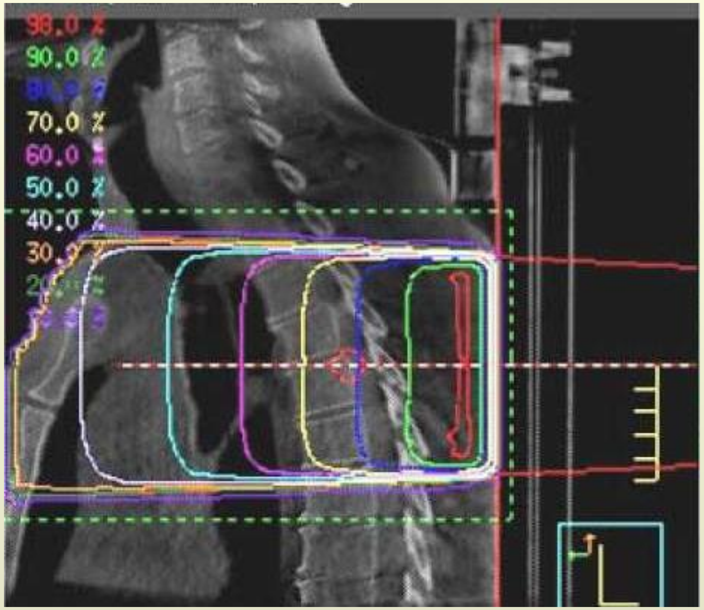
IGRT for palliation

- Over the top or not?

Stereotactic radiation for bone metastases?

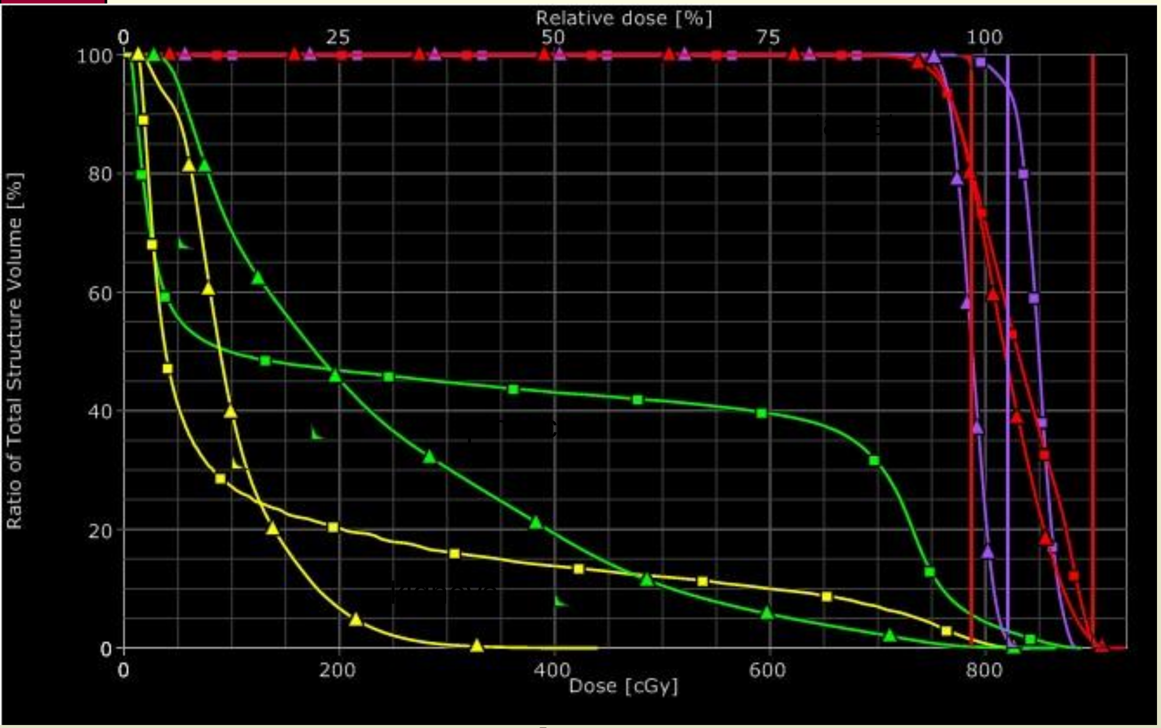


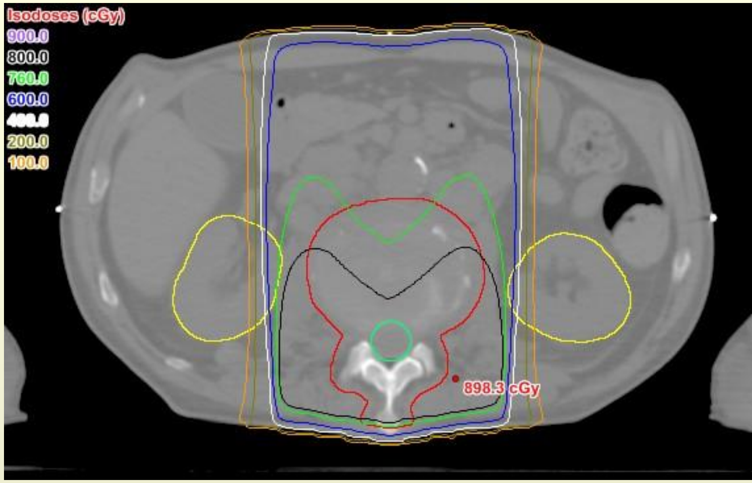
Stereotactic, two ARCs
Dahele 2011

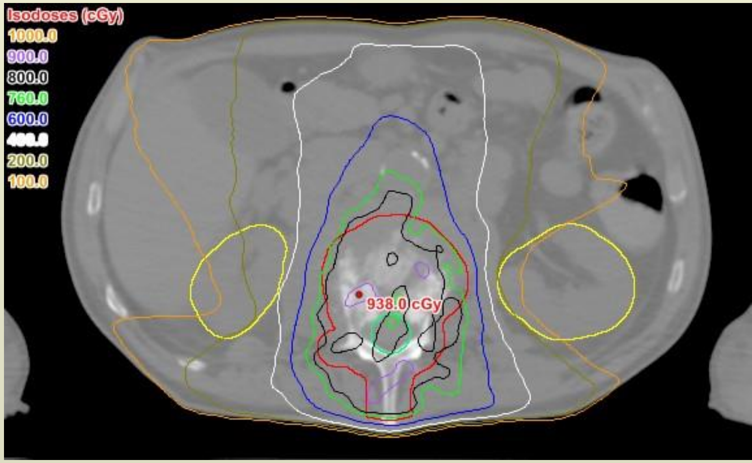


Single PA field
Letourneau 2007

3 Vertebrae, AP-PA versus 1 arc 8 Gy







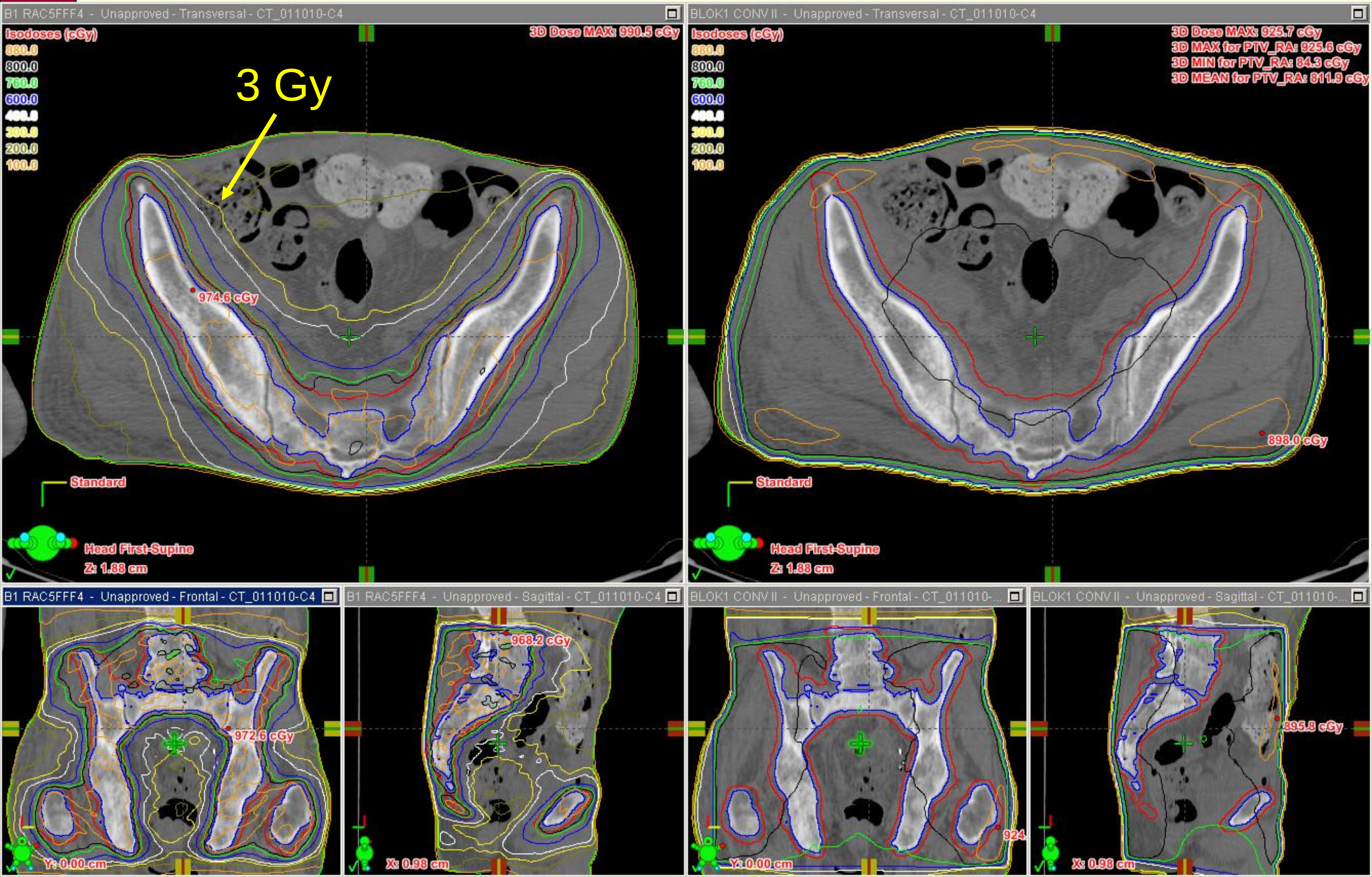
- Beam-on time:

  FFF: 1.24 min, FF: 2.34 min

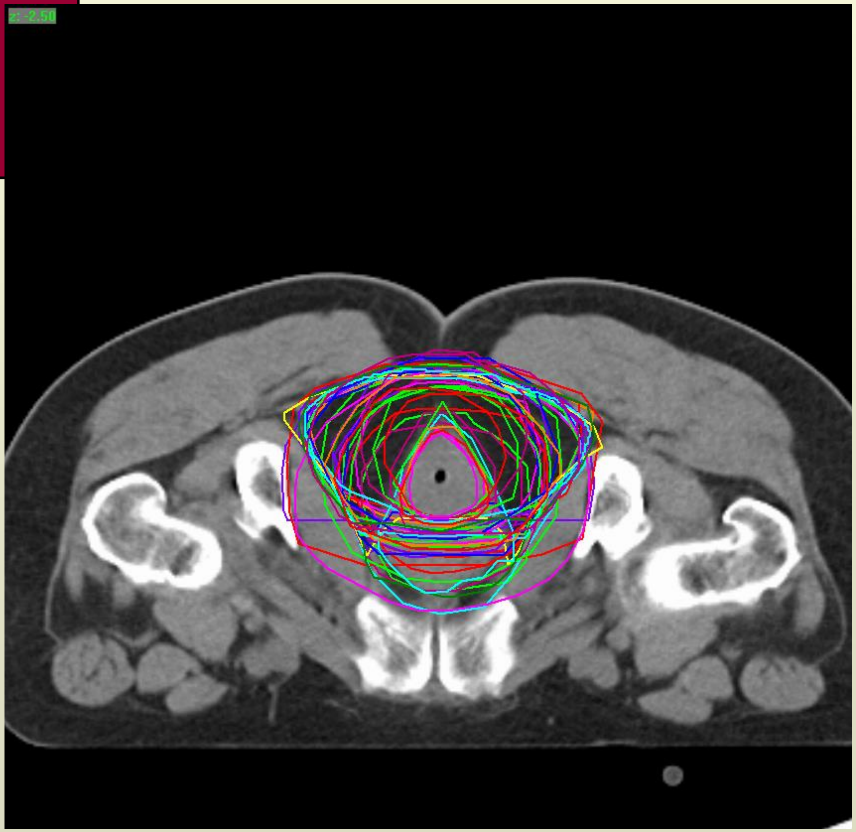
Courtesy W. Verbakel VuMC

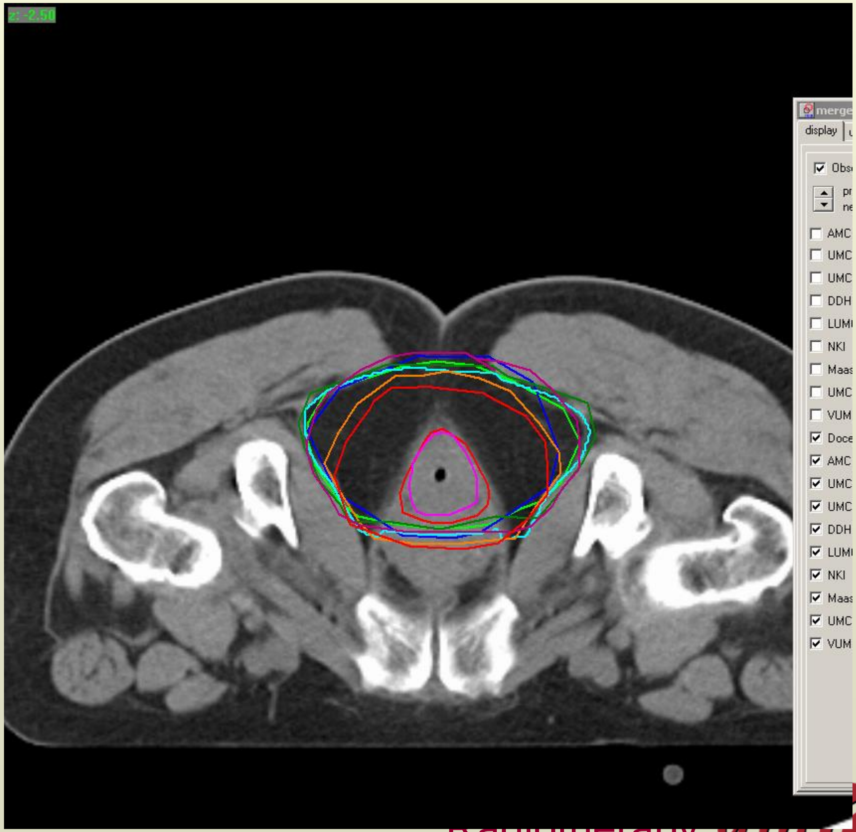
RArc versus conventional 8Gy

Courtesy W. Verbakel VuMC



Rectum Target delineation





Head and Neck lessons from the IMRT era

•Eisbruch et al IJROBP 2003

Radiotherapy

ESTRO School

RTT's Perspective on IGRT

Rianne de Jong *RTT,*
Academic Medical Centre
Amsterdam

Athene2017

m.a.j.dejong@amc.uva.nl

ESTRO School

Contents

- Introduction
- Starting IGRT
- Daily clinical routine
- Protocols – Shifting responsibilities
- Summary

Introduction

Netherlands/AMC:

- 4 + 2 linacs (Elekta) all equipped with portal imaging device
- All Cone-beam CT (Elekta)
- 3 RTT's per treatment machine
- 60 RTT's:
  - in-service or full time trained
  - 1 year of further education in department specific protocols and working instructions

Introduction

AMC: All registrations at Linac always by RTTs

IGRT infrastructure:

- 5 IGRT RTTs/ 4h per person per week
- 2 Research IGRT&ART RTTs/ 2 days per person

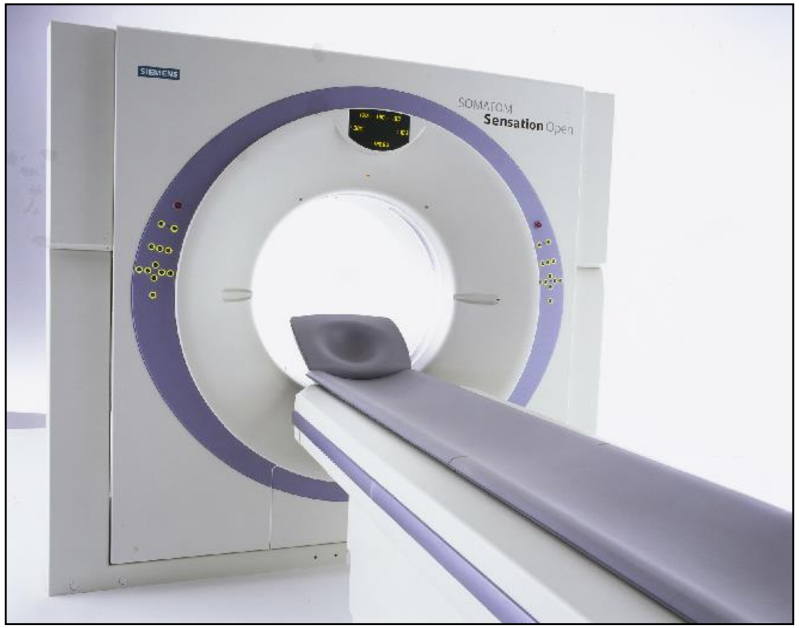
Introduction

Changes over the last years

Simulation:

from fluoroscopy to CT

2 D



3 D

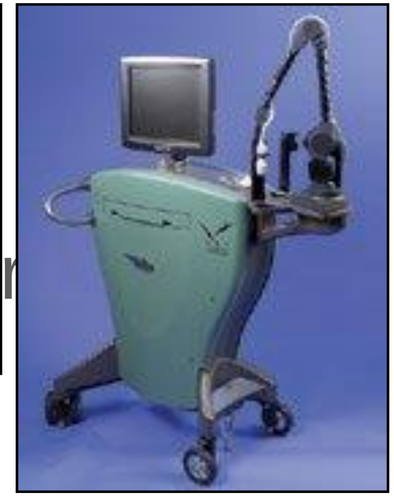
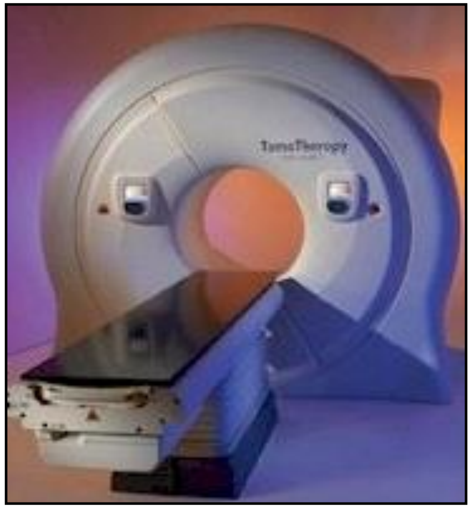
Introduction

Treatment machine:

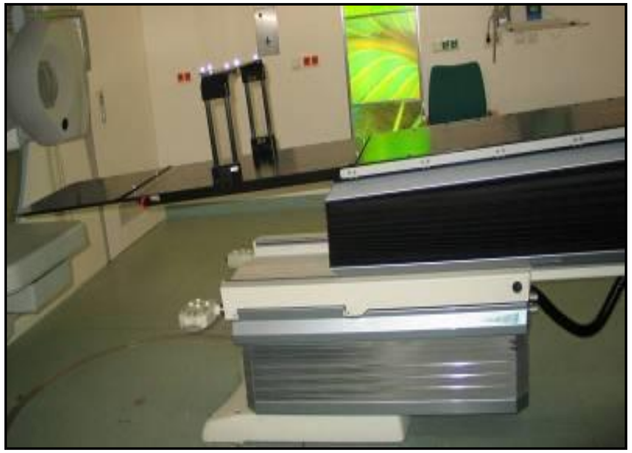
From patient set-up with skin marks to additional patient set-up verification

- Portal imaging (2D MV)
- Kilo voltage imaging (3D kV)

...using skin marks




TomoTherapy

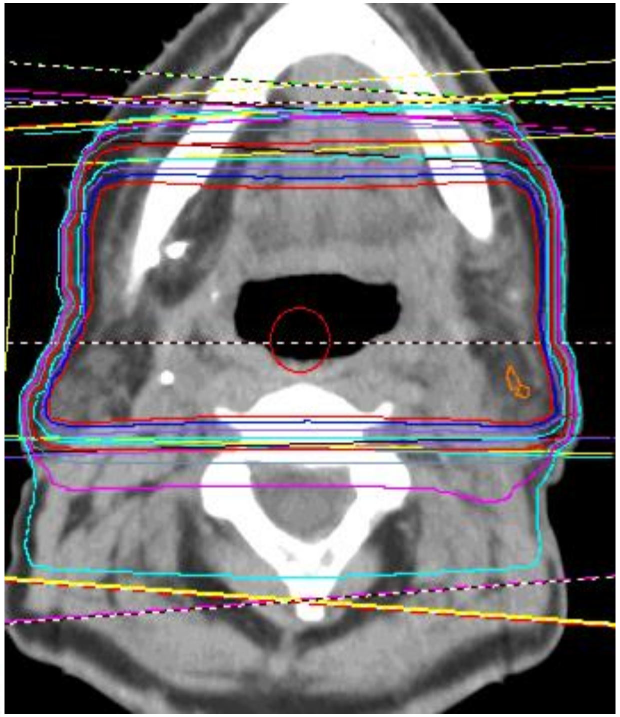
25

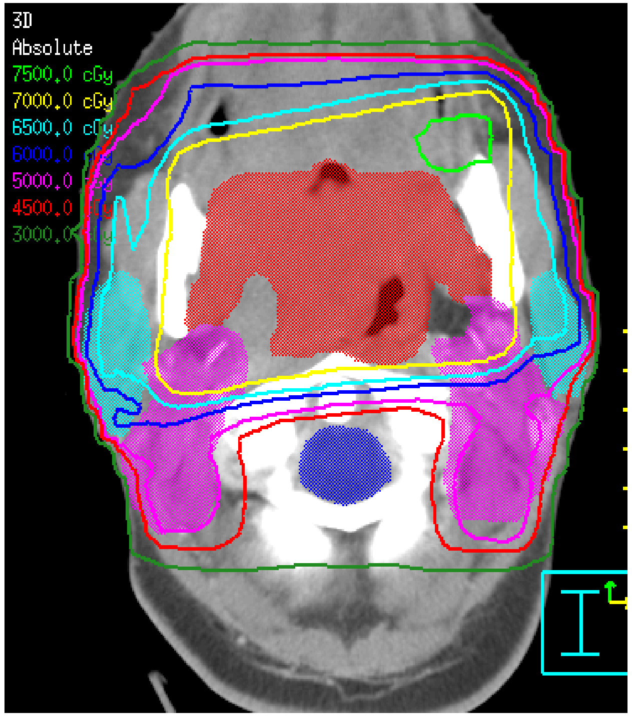


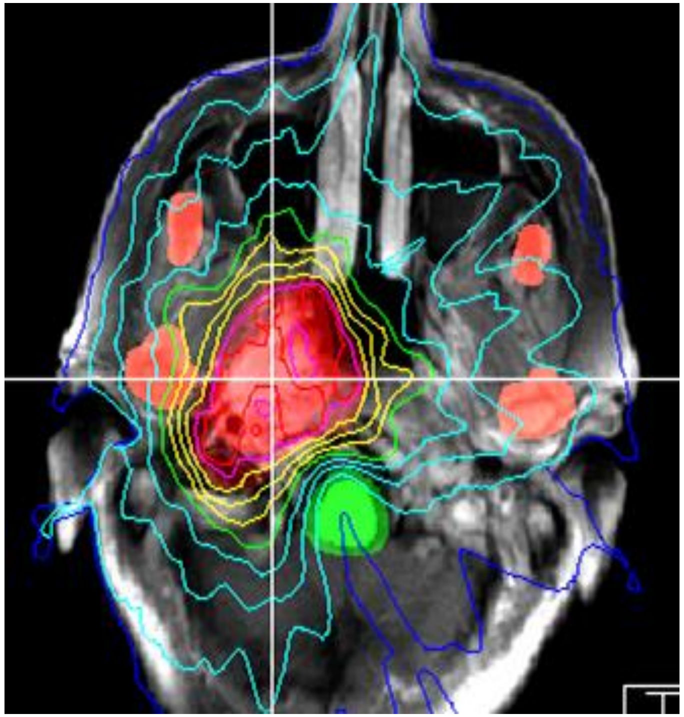

Introduction

Treatment planning:

from conventional to conformal to IMRT & arc therapy







Starting IGRT

Portal Imaging

AvL

In routine clinical use since 1987

RTT's responsibilities:

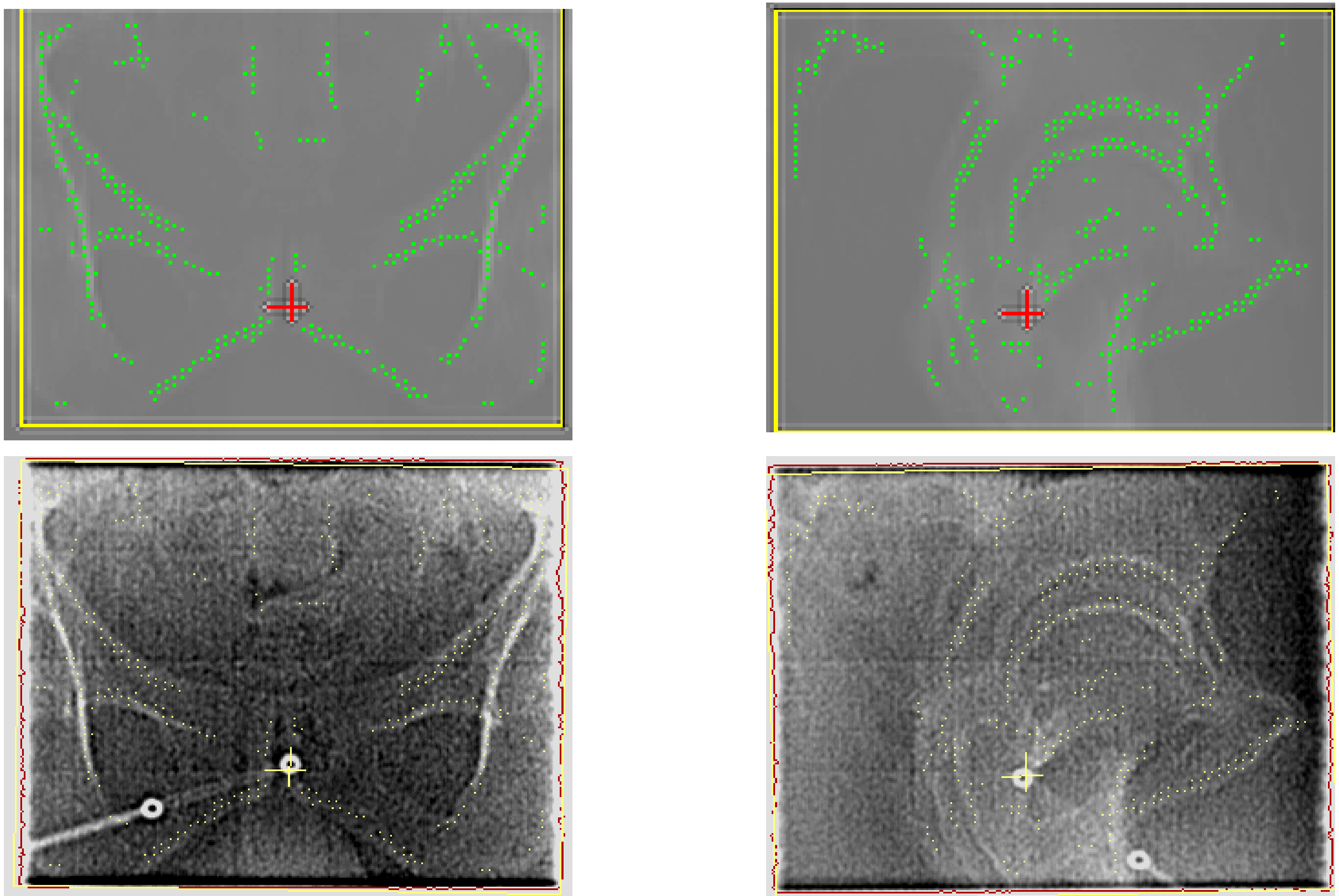
- Acquisition of portal images
- Registration of portal images
- Evaluation of portal images
- Execute decision rules off-line and on-line protocols

Portal Imaging

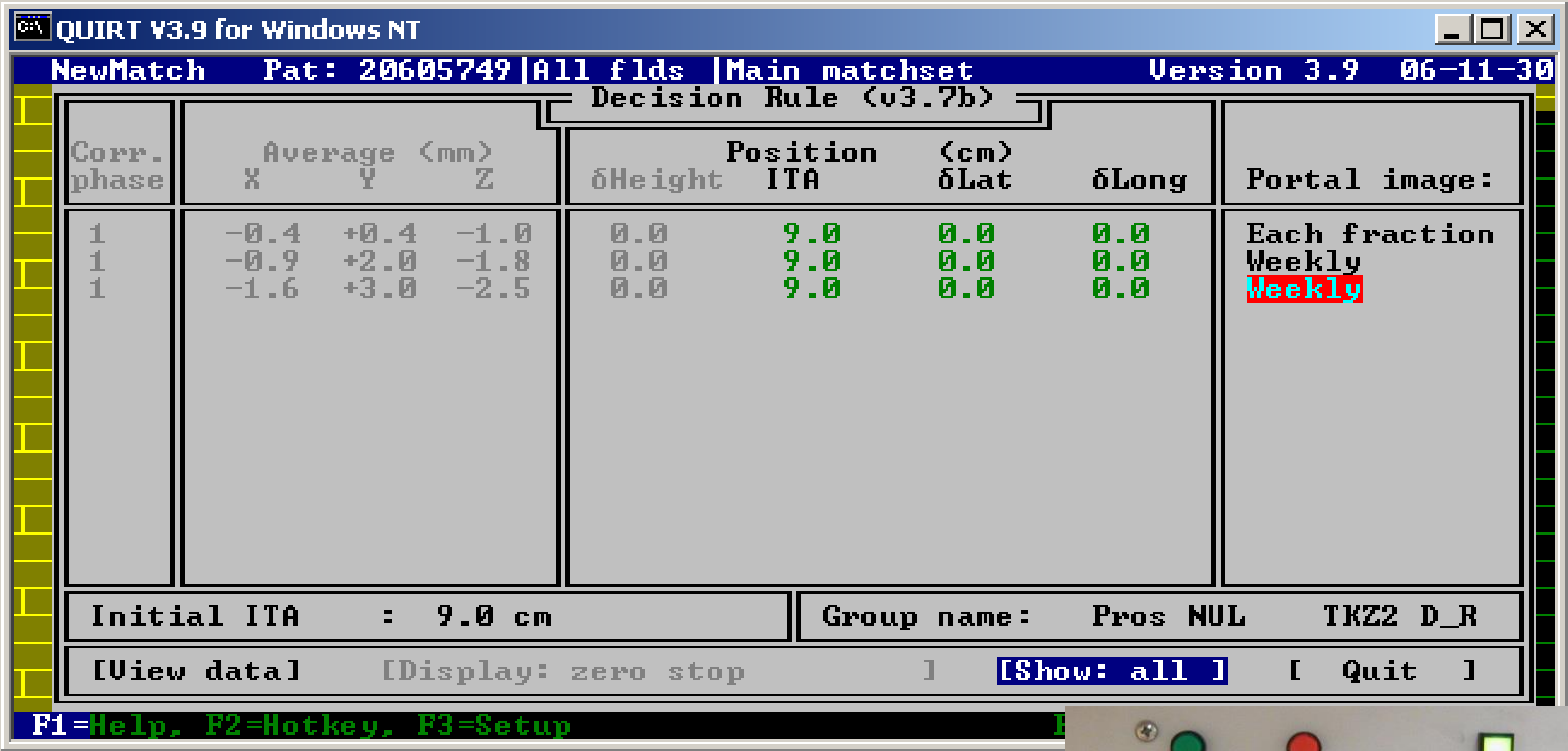
2 RTT's:

- Training and education
- Manuals and protocols
- Follow-up and quality assurance

Portal Imaging



Portal Imaging



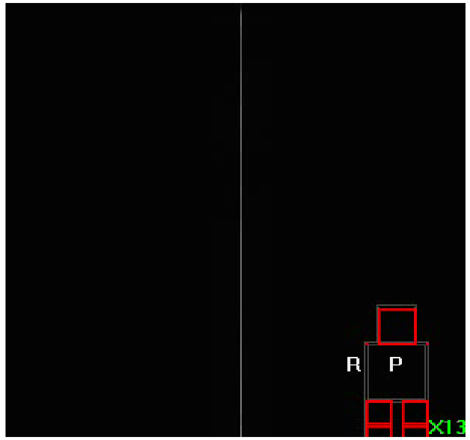
Implementing CBCT

June 2003:

- 4 RTT's
- 2 Physicists
- Patient program in the morning
- CBCT in the afternoon
- 8 months of validation

Implementing CBCT: validation of the system

3D match



Cross validation

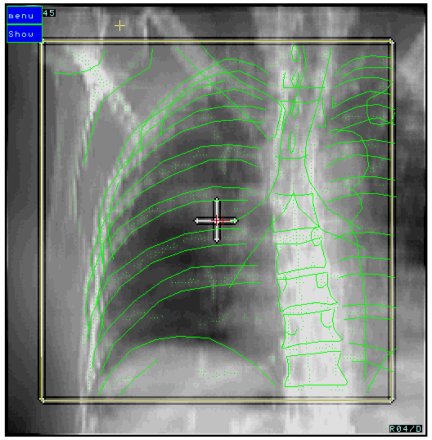
Planning CT

same ?

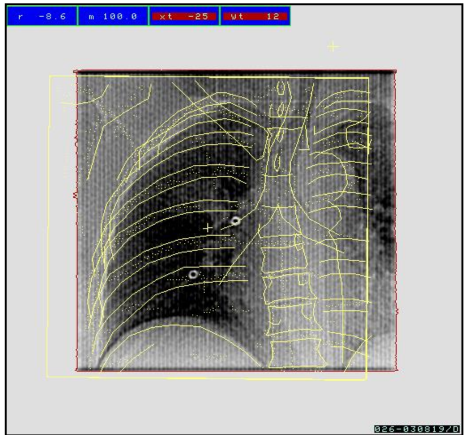
Cone beam CT

DRR +Template

MV image



2 x 2D match AP/LAT



ESTRO School

Implementing CBCT: role of RTT

- Understanding basic physics and technical aspects of new imaging modality
  - IQ: artefacts: influence on registration!
- Implementing in daily workflow
  - Protocols, manuals and working instructions
- Setting up training program for RTT's
- Involved in (international) meetings and research

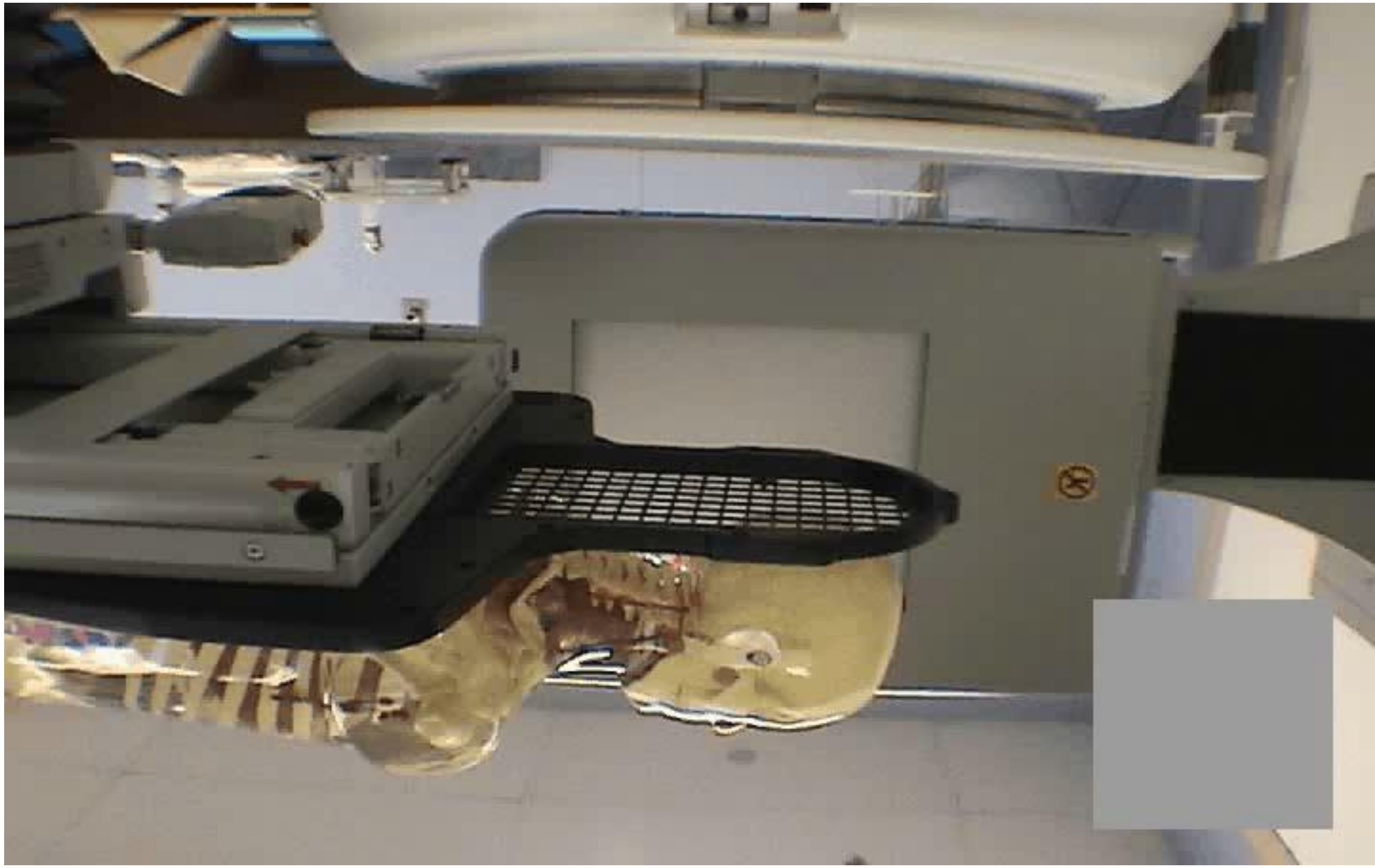
Starting clinical use of CBCT

RTT's responsibilities:

- Acquisition of CBCT
- Registration bony anatomy (CBCT)
- Evaluation registration (CBCT)
- Evaluation of treatment **! coverage and dosimetry**
- Execute decision rules off-line and on-line protocols

→ Same as portal imaging and a bit extra

Clinical daily routine



Courtesy to Doug Moseley (PMH) Jan-Jakob Sonke (AvL)

Princess Margaret Hospital

NKI-AVL

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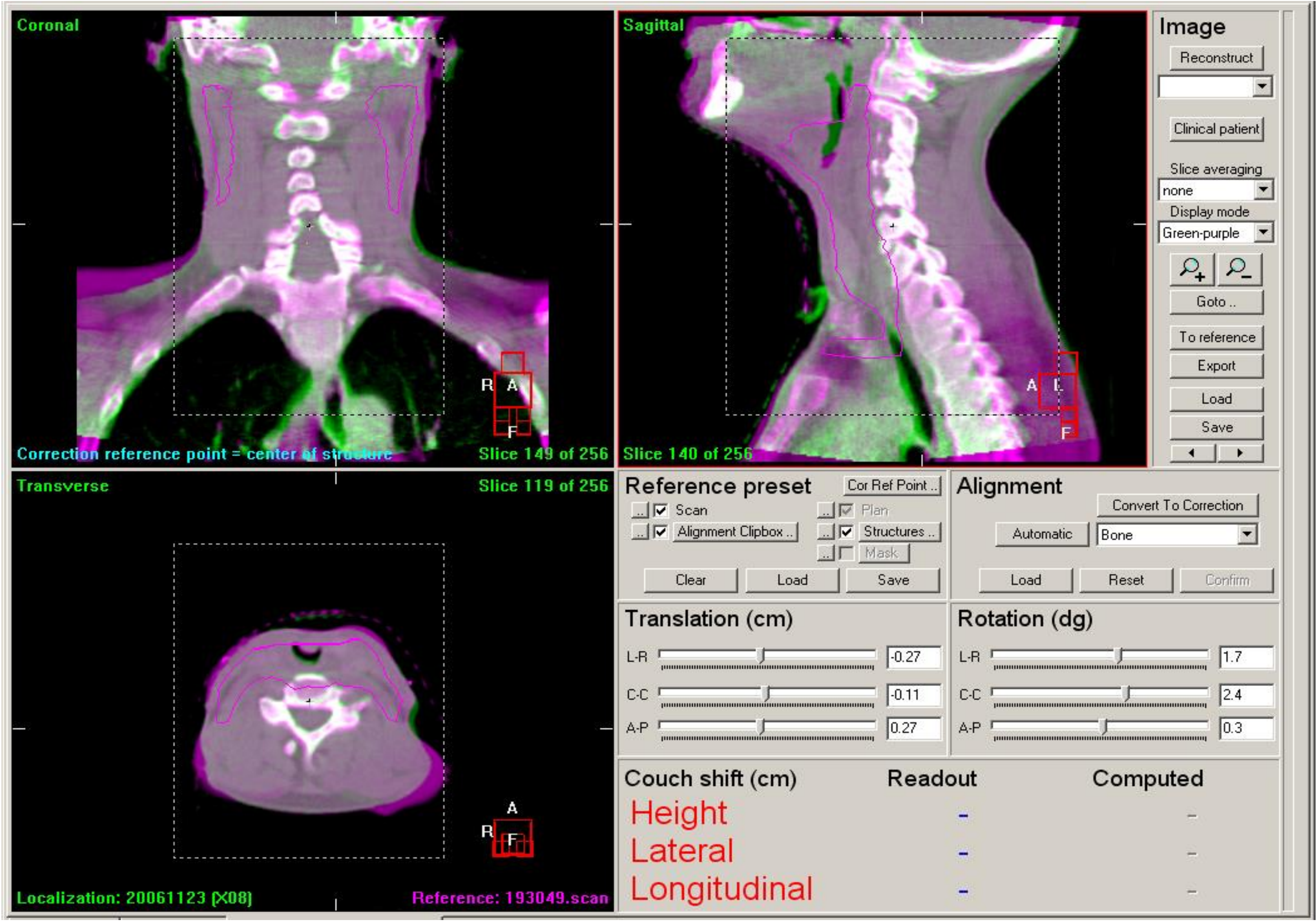
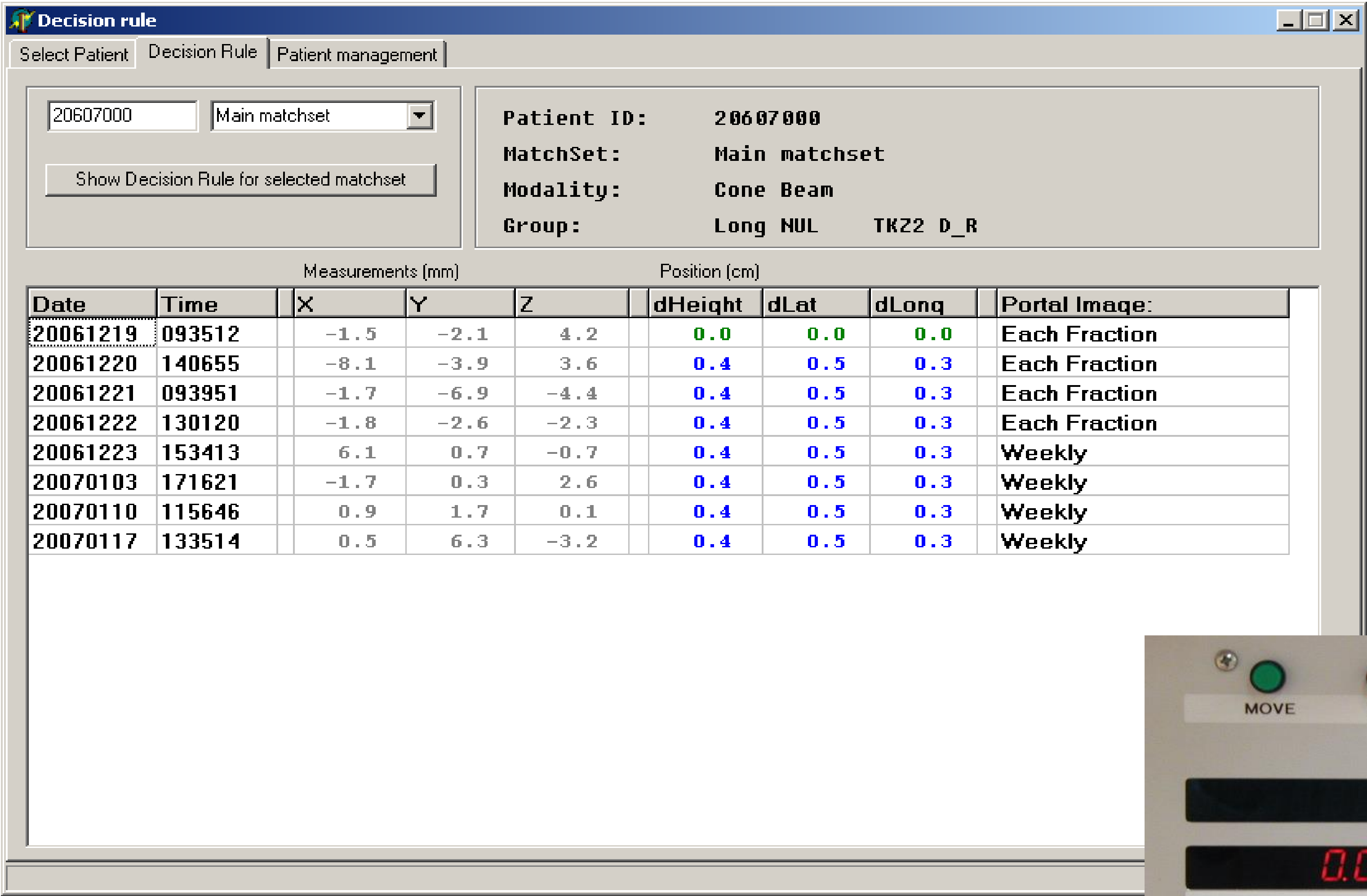
Clinical daily routine



Automatic registration CBCT scan

KV imaging



Date	Time	X	Y	Z	dHeight	dLat	dLong	Portal Image:
20061219	093512	-1.5	-2.1	4.2	0.0	0.0	0.0	Each Fraction
20061220	140655	-8.1	-3.9	3.6	0.4	0.5	0.3	Each Fraction
20061221	093951	-1.7	-6.9	-4.4	0.4	0.5	0.3	Each Fraction
20061222	130120	-1.8	-2.6	-2.3	0.4	0.5	0.3	Each Fraction
20061223	153413	6.1	0.7	-0.7	0.4	0.5	0.3	Weekly
20070103	171621	-1.7	0.3	2.6	0.4	0.5	0.3	Weekly
20070110	115646	0.9	1.7	0.1	0.4	0.5	0.3	Weekly
20070117	133514	0.5	6.3	-3.2	0.4	0.5	0.3	Weekly

Starting clinical use of CBCT

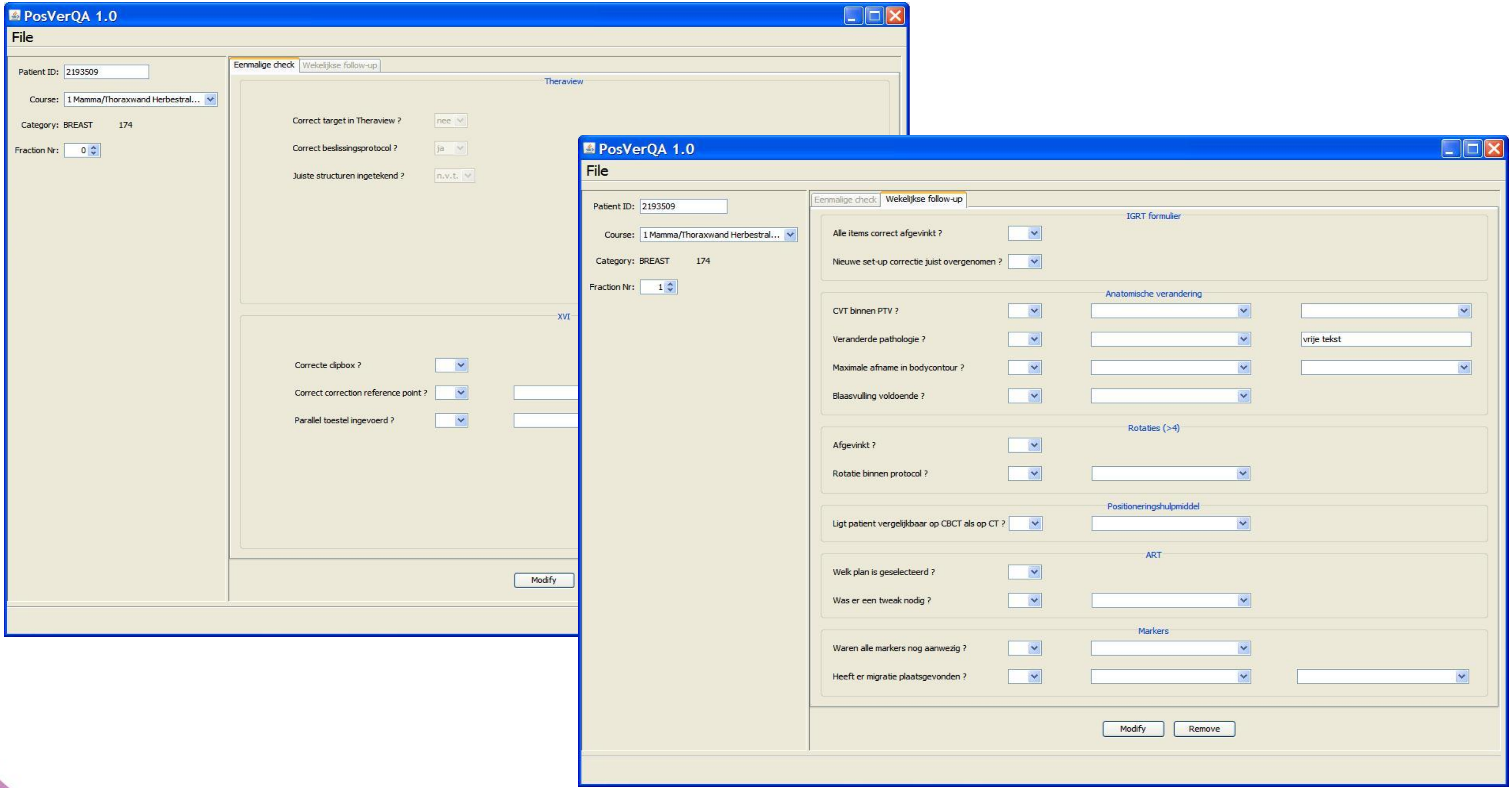
5 RTT's (4h per person per week):

- **Track, check patients** (QA)
- First contact of changes occur-trouble shooting
- Training and education
- Manuals and protocols

@AMC:

- *All linacs equipped with CBCT*
- *All protocols with CBCT*
- *~90% protocols online*

Track & check patients



Starting clinical use of CBCT

5 RTT's:

- Track, check patients
- **First contact of changes occur - trouble shooting**
- Training and education
- Manuals and protocols

Anatomical Changes

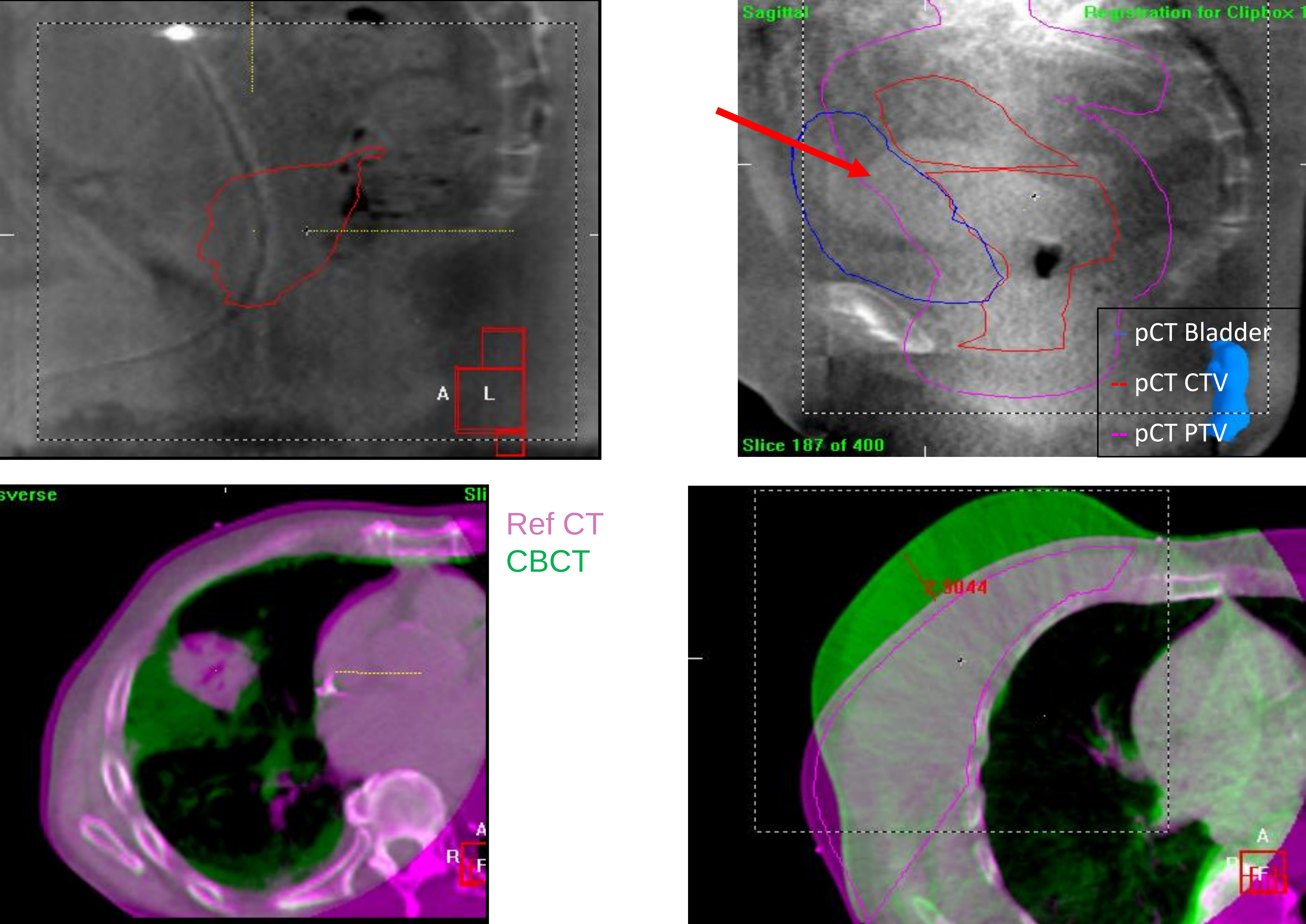
RTT should be trained in:

Recognizing patient changes/anatomical changes that have an influence on radiation treatment: Target coverage and/or dose distribution

&

RTT should have:

a management system for anatomical changes that flag the changes that may need intervention of some sort.


A
L
Sagittal
Slice 187 of 400
pCT Bladder
pCT CTV
pCT PTV
sverse
Ref CT
CBCT
R
A
F

Anatomical Changes

The important questions:

1: Is the target volume (CTV or GTV) within PTV?

2: Is the dose distribution compromised?

(green)	Level green, no action needed.
(yellow)	Level yellow, the radiation oncologist is notified by email, but no response is required to continue treatment.
(orange)	Level orange, the treating radiation oncologist (or back-up colleague) is informed by email and a response is required before the next fraction.
(red)	Level red changes, the radiation oncologist must be consulted immediately before the treatment fraction is allowed to be delivered.

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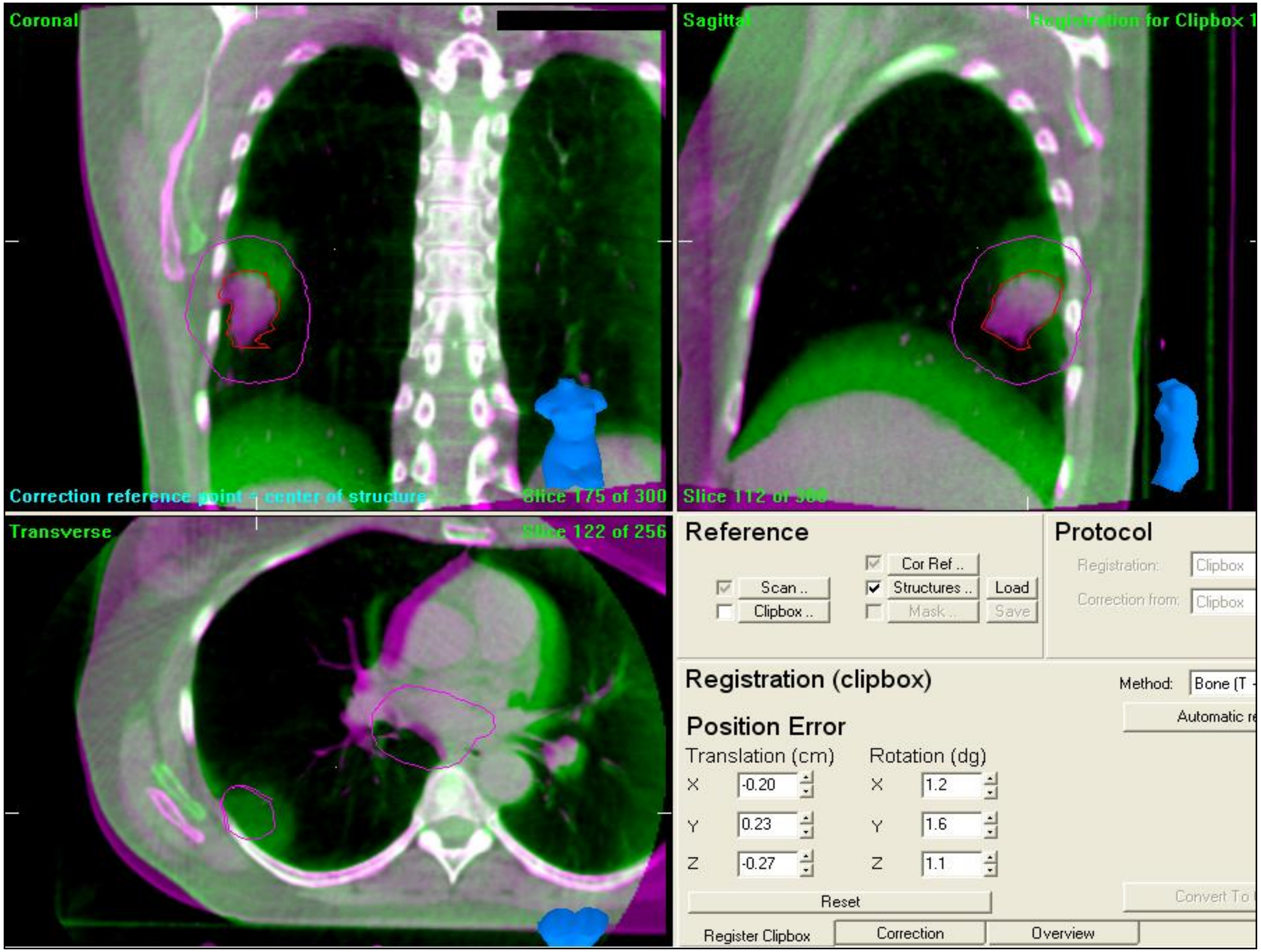
NEDERLANDS KANKER INSTITUUT

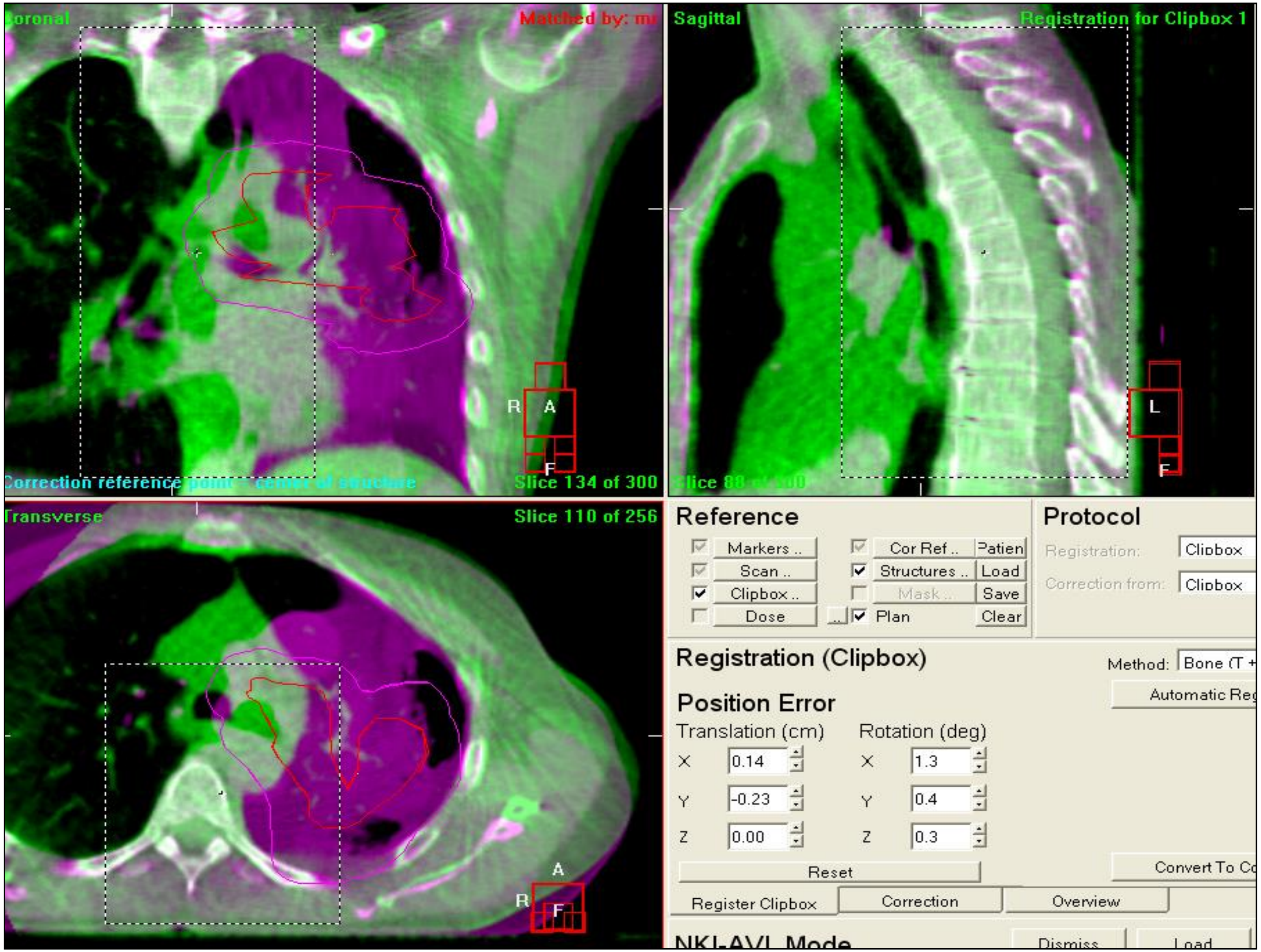
http://www.avl.nl/media/291805/xvi_engelse_protocols_16_7_2014
Kwint Radiother Oncol 2014

Level 1 Tumor shift



GTV is not within PTV

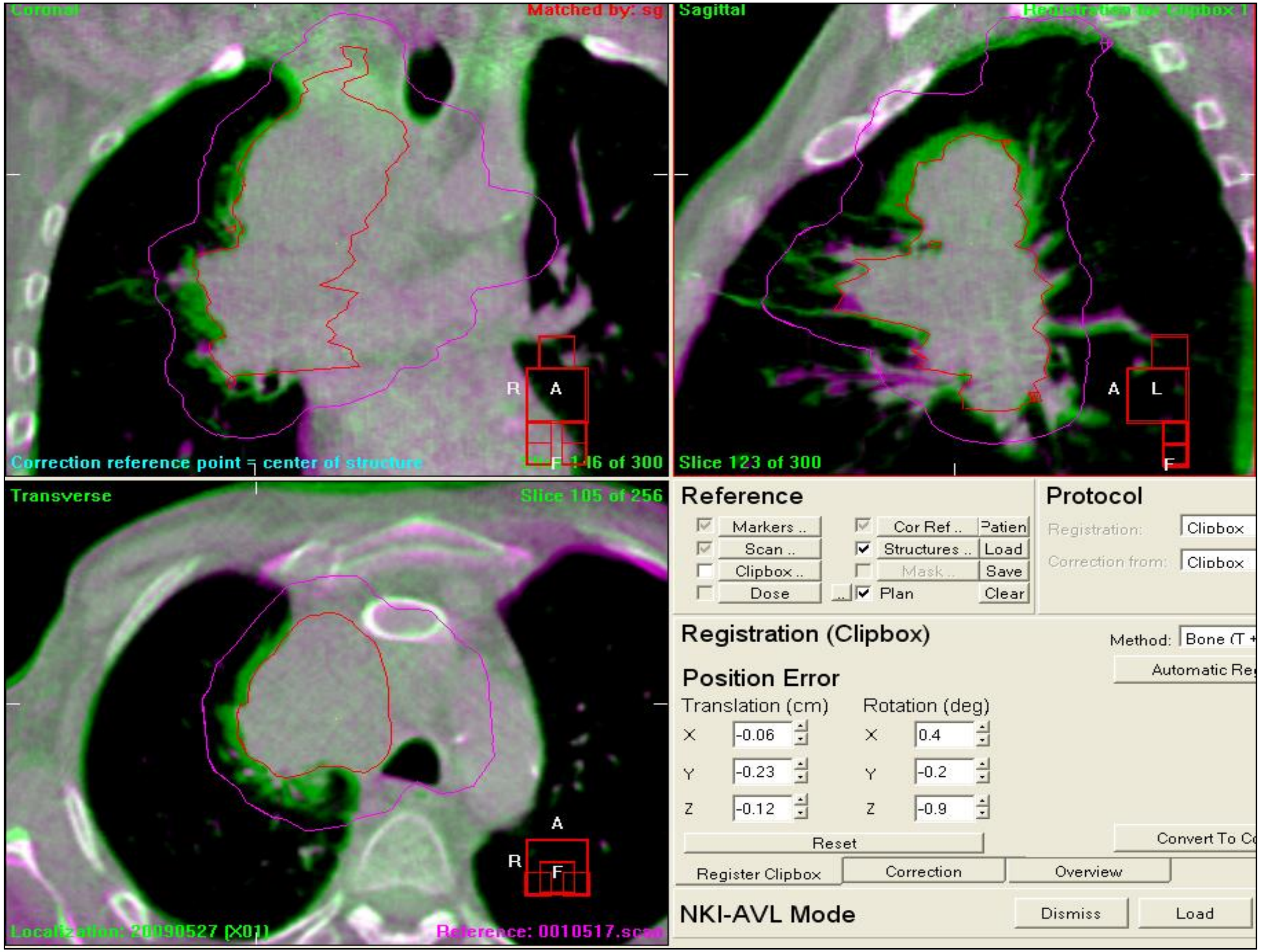
Level 1 Atelectasis resolved



GTV is not within PTV

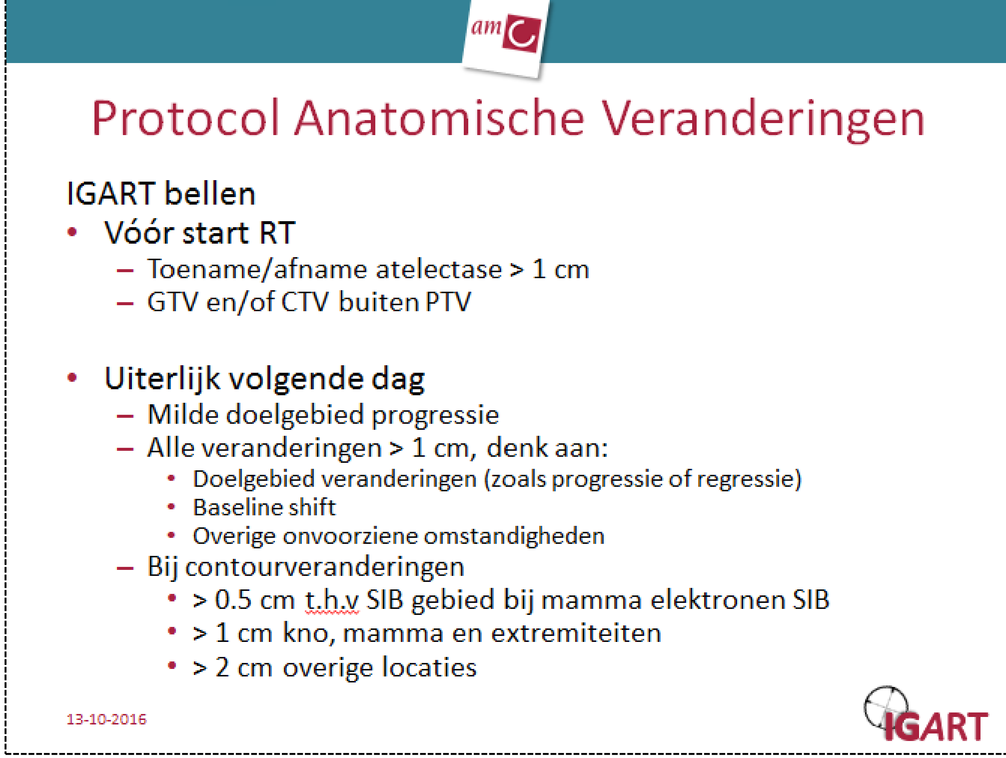
Dose distribution is compromised

Level 2 Tumour growth



GTV is within PTV

Anatomical Changes



Or keep it very simple:

Contact the IGRT-group when

- GTV is outside of PTV
- Anatomical changes > 1 cm

2x year: per site meeting with physicists, radiation oncologists and RTT to discuss images

Communication with physicians?

Clinical use of CBCT

5 RTT's:

- Track, check patients
- First contact of changes occur
- **Training and education**
- Manuals and protocols

Clinical use of CBCT

2 lectures (1h)

- Geometrical errors & correction strategies
- CBCT incl artefacts, image quality

2 Workshops (2h) in registration and image evaluation followed by a test

Clinical use of CBCT

5 RTT's:

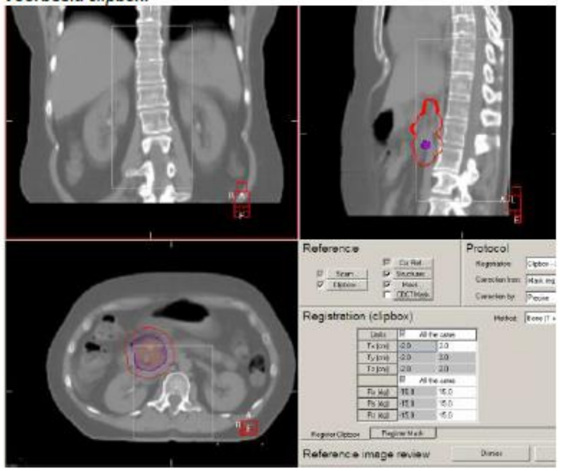
- Track, check patients
- First contact of changes occur
- Training and education
- **Manuals and protocols**

4.3 Pancreas

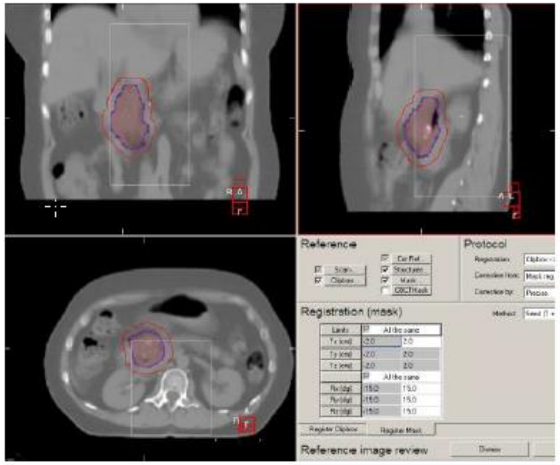
Invoer

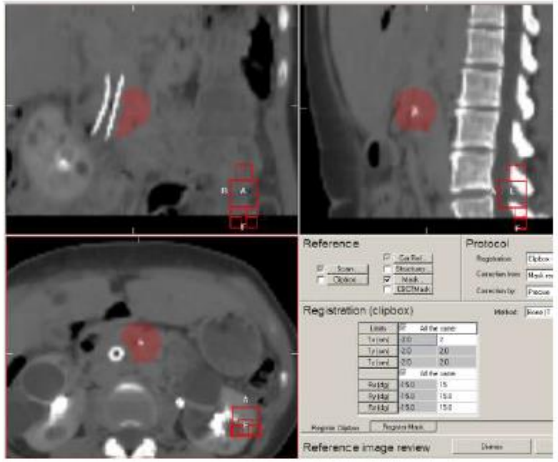
MATCH PARAMETERS		SCAN PARAMETERS	
Structures	GTV, ITV, PTV	**Preset selection**	A1 – A3
Correction ref point	PTV	**Rotatie**	-180° → 180°
Registration	Dual registration	**Gantry speed**	Normaal
Method	Clipbox : Bone (T + R) Mask : Seed/Greyvalue (T + R)	**Detectorstand**	M
Registr. Clipbox	1,0 cm, 4°	**Filter**	F1
Registr. Mask	0,1 cm, 4°	**Collimator**	M20

Voorbeeld clipbox:



- De clipbox omvat de wervels, gebruik in cranio-caudale richting het hele FOV.





Het masker wordt gemaakt van de structuur 'ITV' zonder marge. Zie uitleg voor het maken van het masker de IGART Handleiding op KWADRAET. Wanneer de patiënt ook een stent heeft dan via de optie 'empty' zelf een masker maken van alleen de markers.

Uitvoer

Wanneer er minder dan 3 markers geïmplanteerd zijn kan het algoritme moeite hebben met het definiëren van de rotaties. Voorbereiden als automatische match, maar in de praktijk zal dit een manual match worden waarbij de rotaties van de botmatch worden gebruikt.
Korte dikke stents zijn niet altijd betrouwbaar, is uit eigen onderzoek gebleken. Deze kunnen nog wel eens van vorm veranderen en/of 'uitzakken', *fig1*. Let daarom na de match ook altijd op omgevende structuren zoals de positie van de nieren en/of de leverrand.
Mocht de automatische stentmatch niet lukken dan kan er manual gematcht worden vanaf de botmatch. IGART zal deze manuele match uitvoeren en indien mogelijk overdragen aan het toestel met een werkinstructie, te vinden in het tabblad IGART in de navigator in Mosaiq. Indien de manuele match niet overdraagbaar is zal deze patiënt door IGART gematcht worden.

Fig1. Let op verschil in positie van stent tov markers, en vormverandering van de stent.

Stent week 1

stent week 4

Clinical use of CBCT

5 RTT's:

- Track, check patients
- First contact of changes occur
- Training and education
- Manuals and protocols

→ These RTT's also work in the clinic

Infrastructure IGRT in the Netherlands

Number of departments with (october2016):

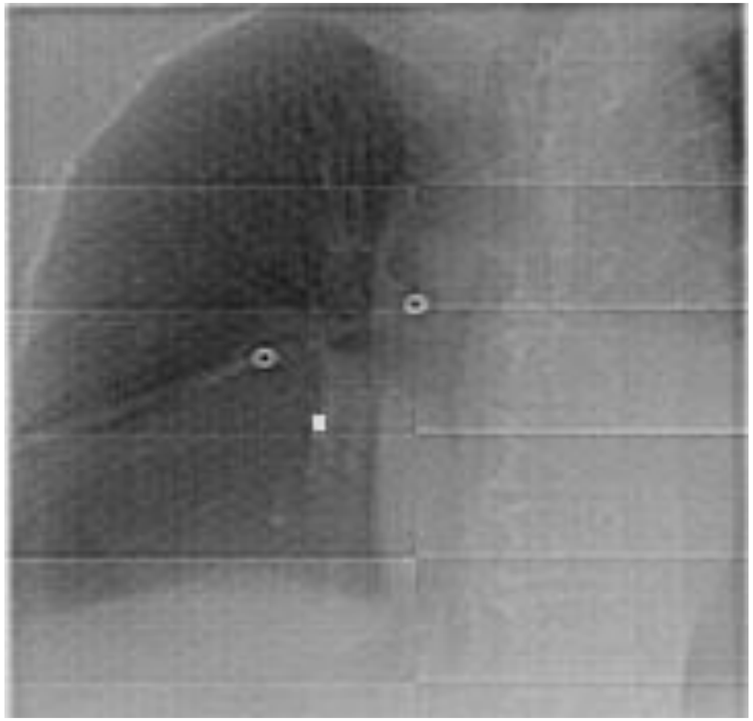
- Multi-disciplinairy steering groups: 13/17
- Daily dedicated RTT: 7/17
- RTT R&D (parttime): 6/17
    - As part of R&D groups

Daily Clinical Routine

Patient Support

Support patients and their relatives and friends:

During RT in RTT's working area for support and transparency



Portal image

CBCT image

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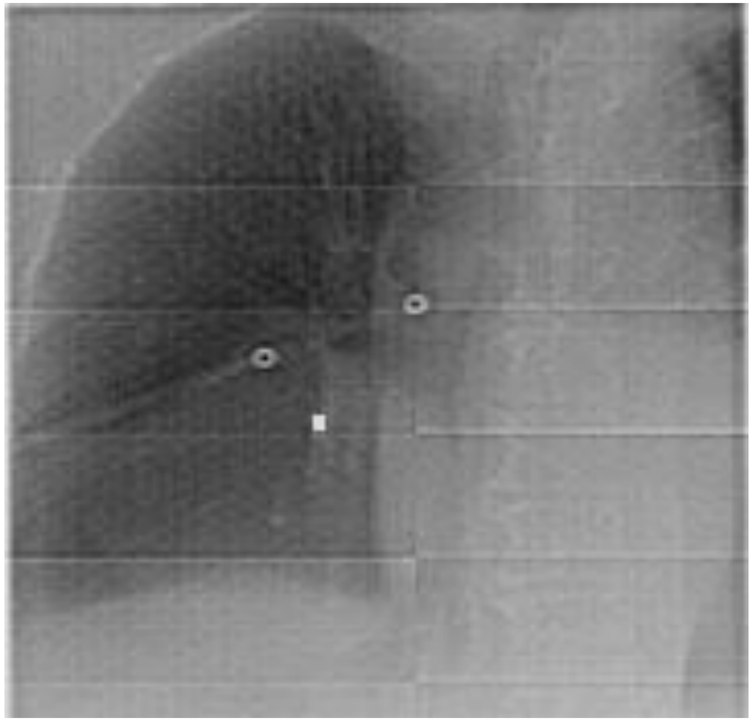
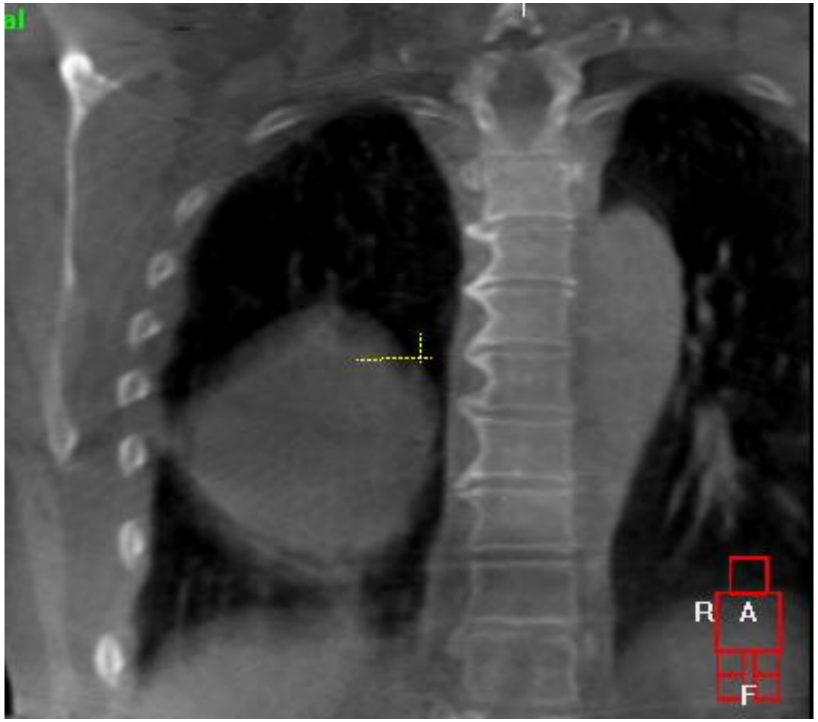


Portal image



CBCT image

Time Slots at the linac

Time-slot for patient treatment delivery

Learning curve:

1. **Add 5 minutes compared to portal imaging, same protocol.**
2. Approx. same time introduction IMRT, adding more time because of more gantry angles and segments
3. Development of new soft tissue IGRT protocols, nothing to compare with.
4. Using rotational treatment is reducing beam delivery time.

Time Slots at the linac

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Protocols

Methodical Registration Process

1 Visualize patient in full in color overlay

2 Use automatic registration(s)

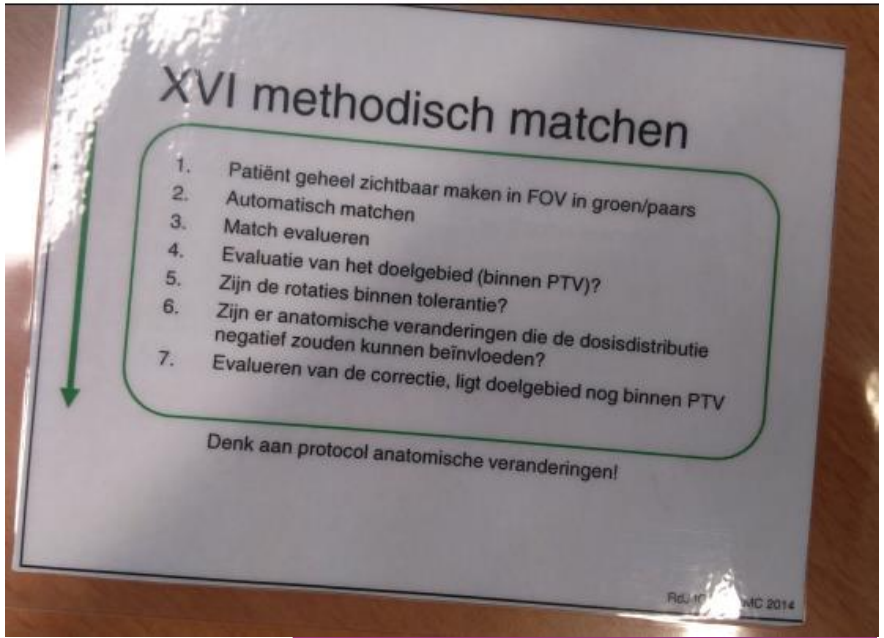
3 Evaluate automatic registration(s)

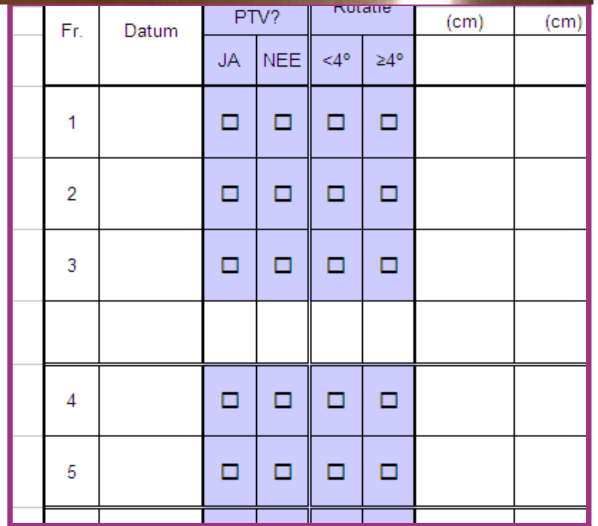
4 Evaluate Rotations

5 Evaluate Target coverage within PTV

6 Evaluate CB for anatomical changes that affect dose distribution

7 Evaluate Target Coverage of the correction after convert to correction





Fr.	Datum	PTV?		Rotatie		(cm)	(cm)
		JA	NEE	<4°	≥4°		
1		☐	☐	☐	☐		
2		☐	☐	☐	☐		
3		☐	☐	☐	☐		
4		☐	☐	☐	☐		
5		☐	☐	☐	☐		

Modern IGRT Protocols – shifting responsibilities?

Sterotactic Lung:	4D dual registration
Bladder ART:	Library of plans

IGRT 4D dual registration Lung

Hypo fractionated lung, 3x 18 Gy, On-line tumor match

Aligning the patient

First pre-treatment CBCT scan

Registration

Correction with automatic table shift

Second pre-treatment CBCT scan

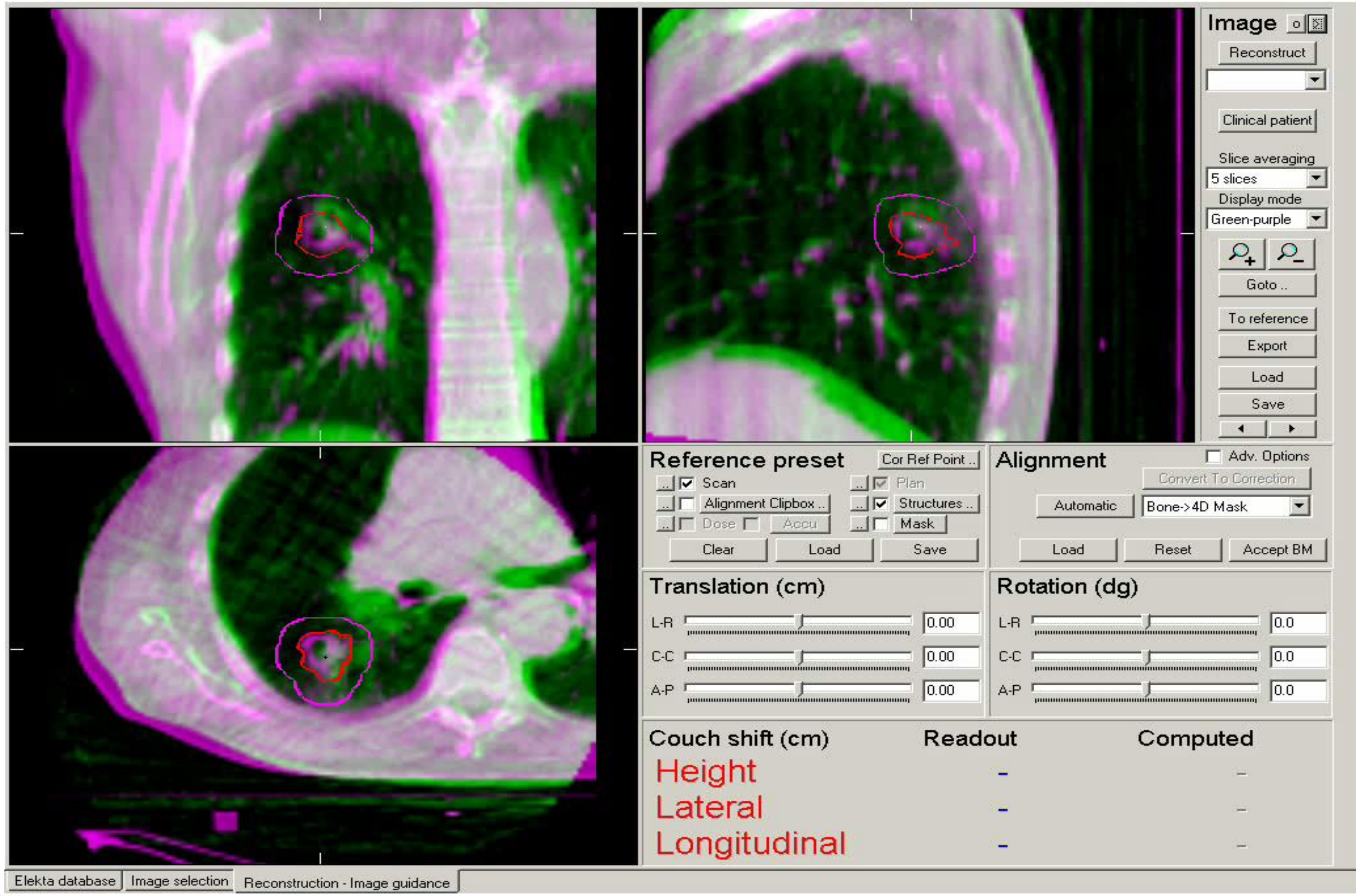
Evaluation CBCT scan

Beam delivery arc therapy

Post treatment CBCT scan

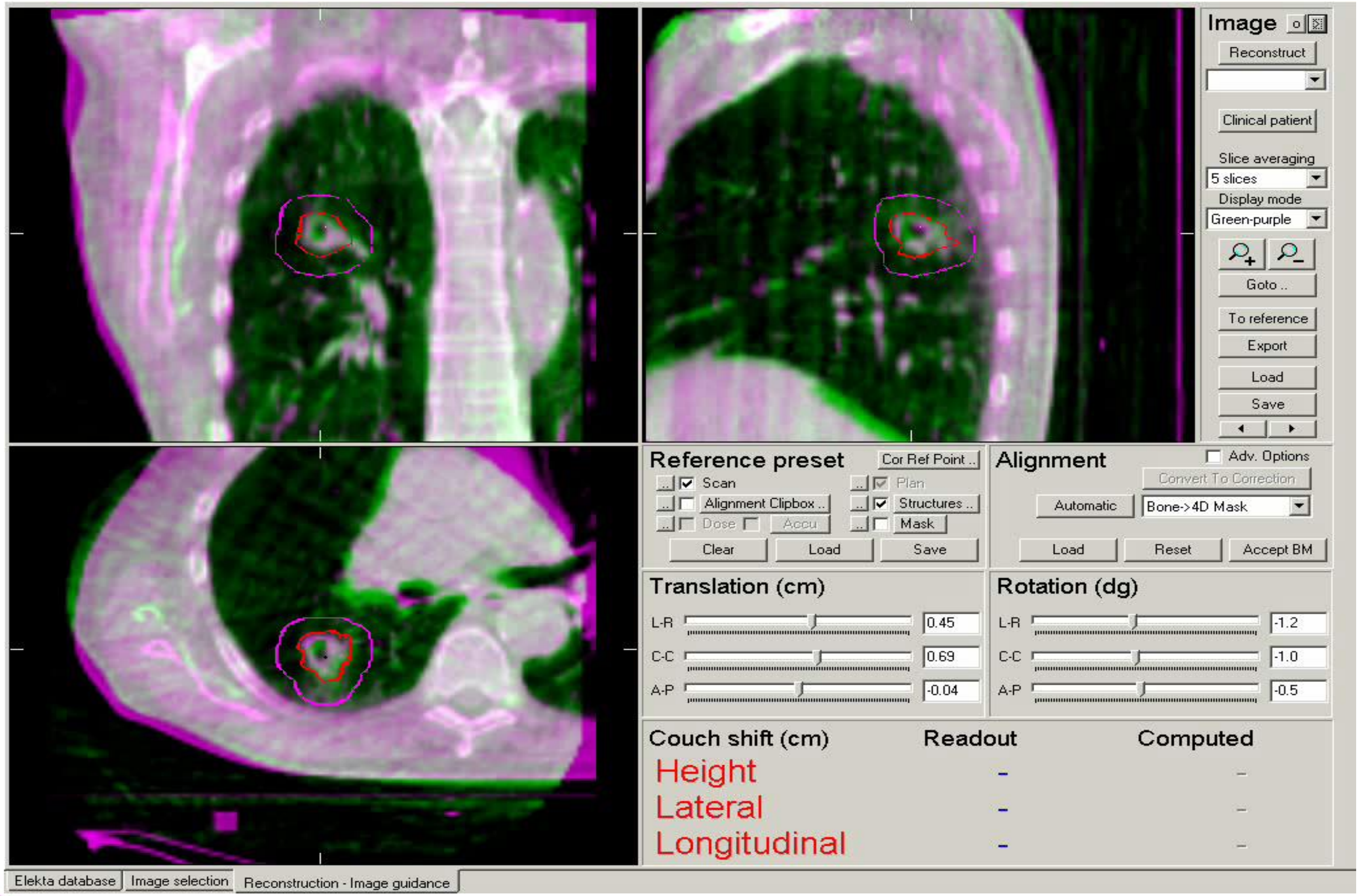
Timeslot of 30 minutes

IGRT 4D dual registration Lung



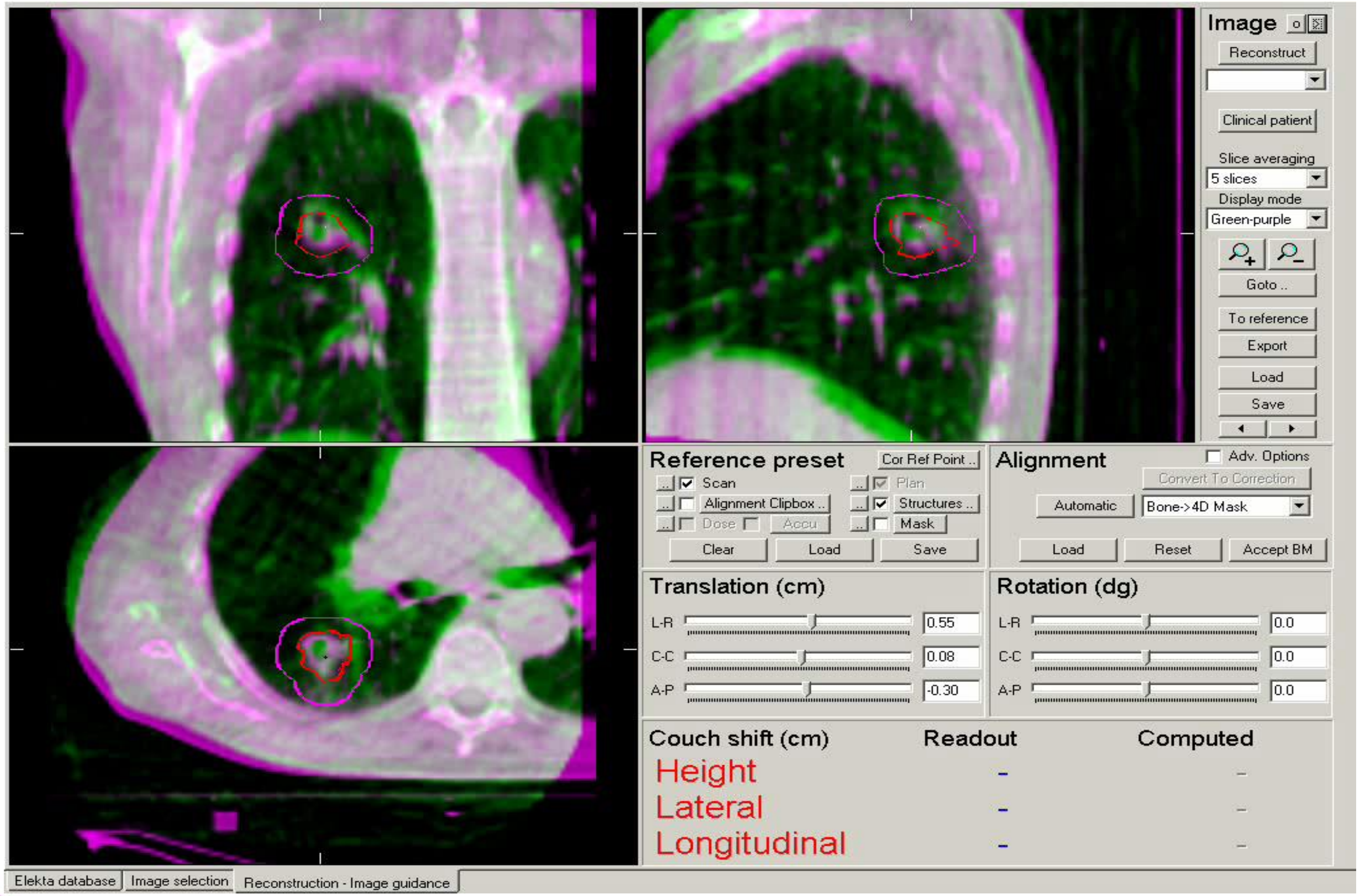
first scan

IGRT 4D dual registration Lung



matched on bone

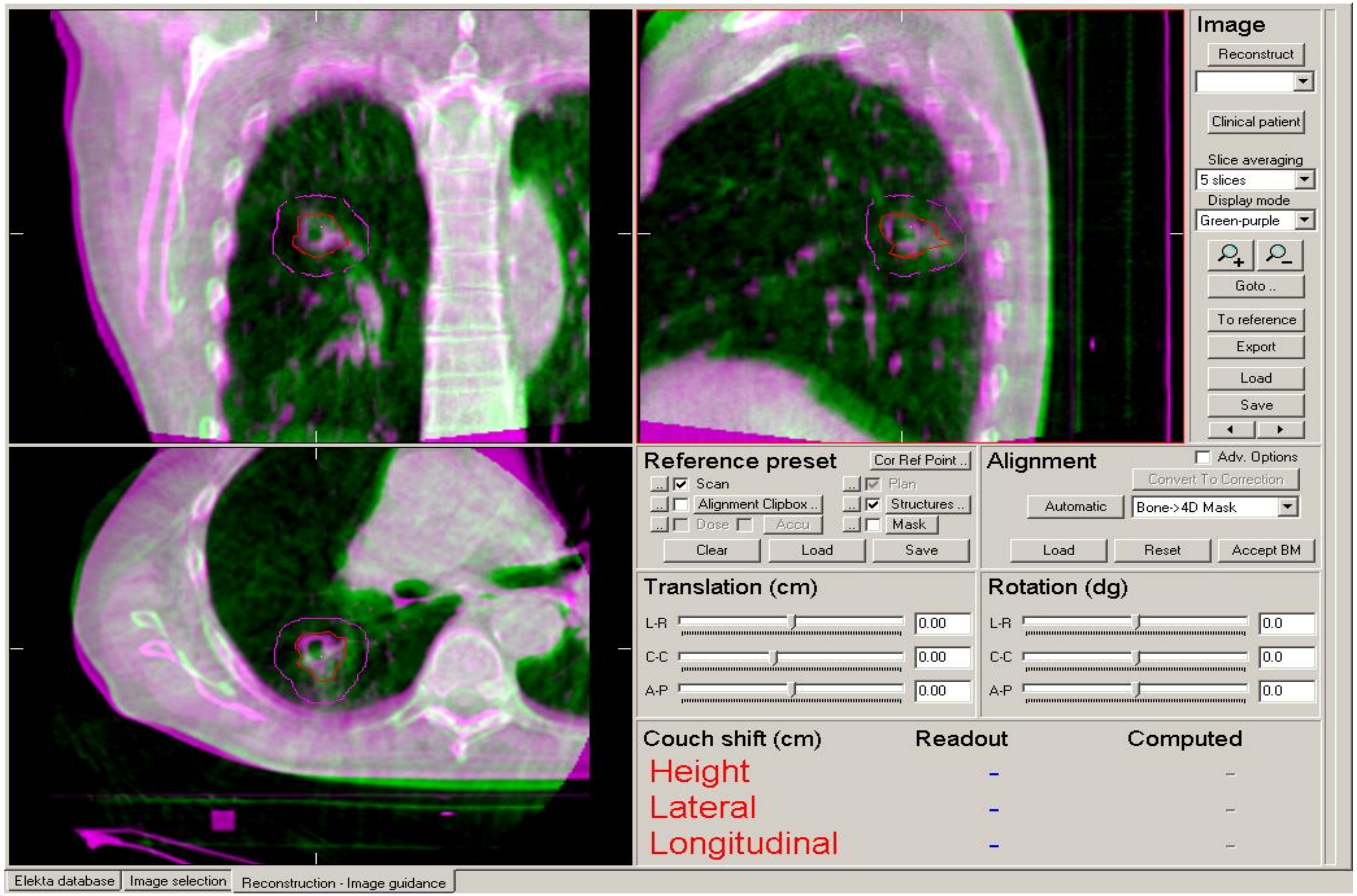
IGRT 4D dual registration Lung



matched on tumor

Critical structure avoidance

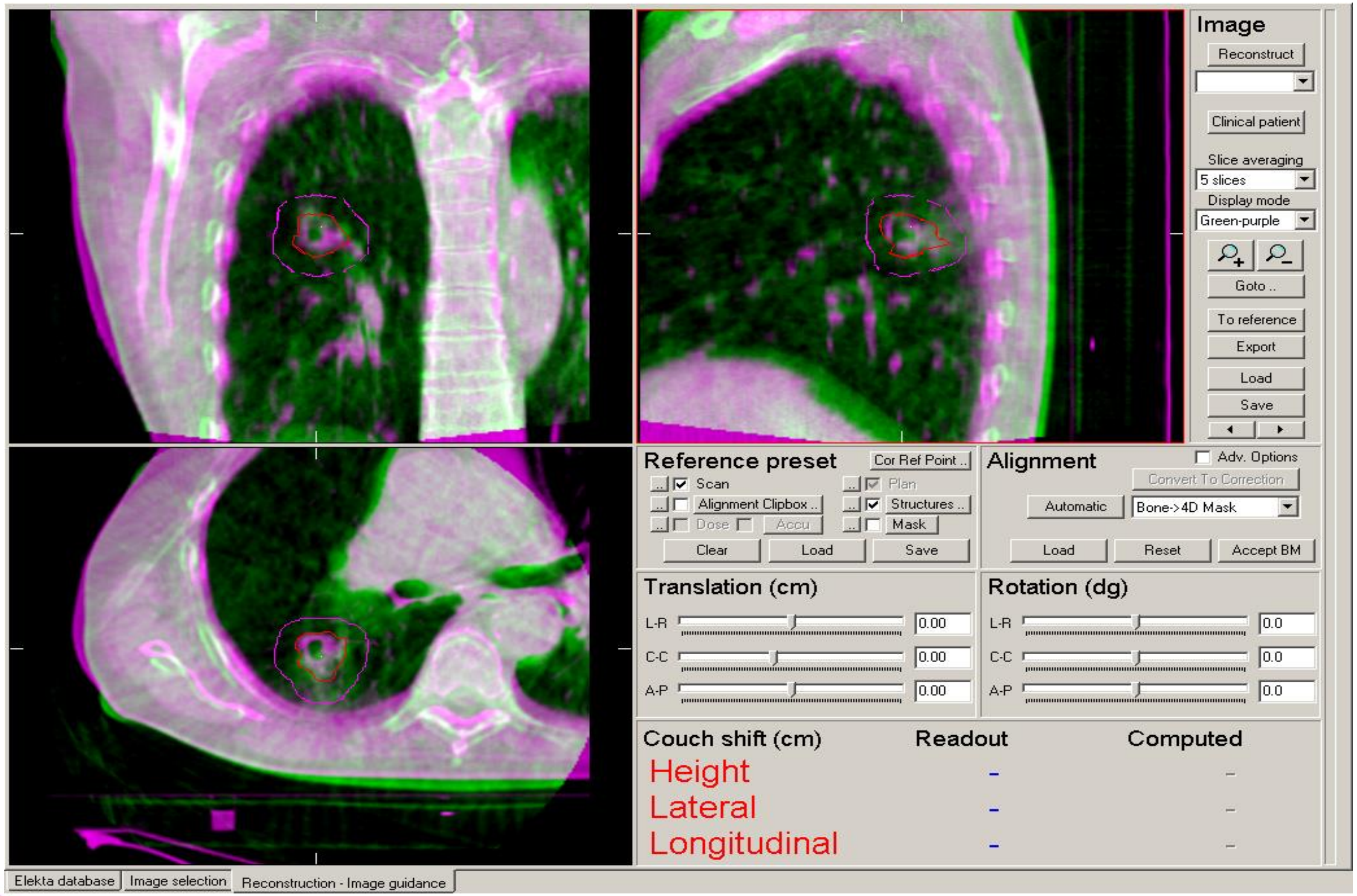
IGRT 4D dual registration Lung



prior to treatment

interfraction

IGRT 4D dual registration Lung



after treatment

Intra fraction

Stereotaxie - Long

Patiëntnummer:	
Patiëntnaam:	
Course:	2
Max. baselineshift R (cm):	0,5
Advies voor CB H1 bij FFF:	Geen FFF

Gegevens opslaan

Initialen laboranten:	lwr
Datum:	12 oktober 2016

NB1: BOTMATCH EN TUMORMATCH VOOR CO
NB2: TUMOR MATCHEN ZONDER ROTATIES (G
Indien tumorvector Tv kleiner of gelijk is aan 0,25 c

Moment	CBCT	Clipbox (T&R) (cm)			Mask (T) (cm)			Correctable (cm)			Baselineshift R (cm)	Tumorvector Tv (cm)
		X	Y	Z	X	Y	Z	X	Y	Z		
Vooraf	V1	-0,05	0,18	0,05	-0,03	0,26	0,05	-0,03	0,26	0,05	0,08	0,27
Vooraf	V2	-0,02	-0,05	-0,04	0,02	0,02	-0,01	0,02	0,02	-0,01	0,09	0,03
Vooraf	V3											
Vooraf	V4											
Vooraf	V5											
Halverwege	H1											
Halverwege	H2											
Halverwege	H3											
Halverwege	H4											
Halverwege	H5											
Eind	N1	-0,03	-0,04	-0,02	-0,05	0,04	-0,03	-0,05	0,04	-0,03	0,08	0,07

	X
H1tumor-Ref	
N1tumor-Ref	-0,07

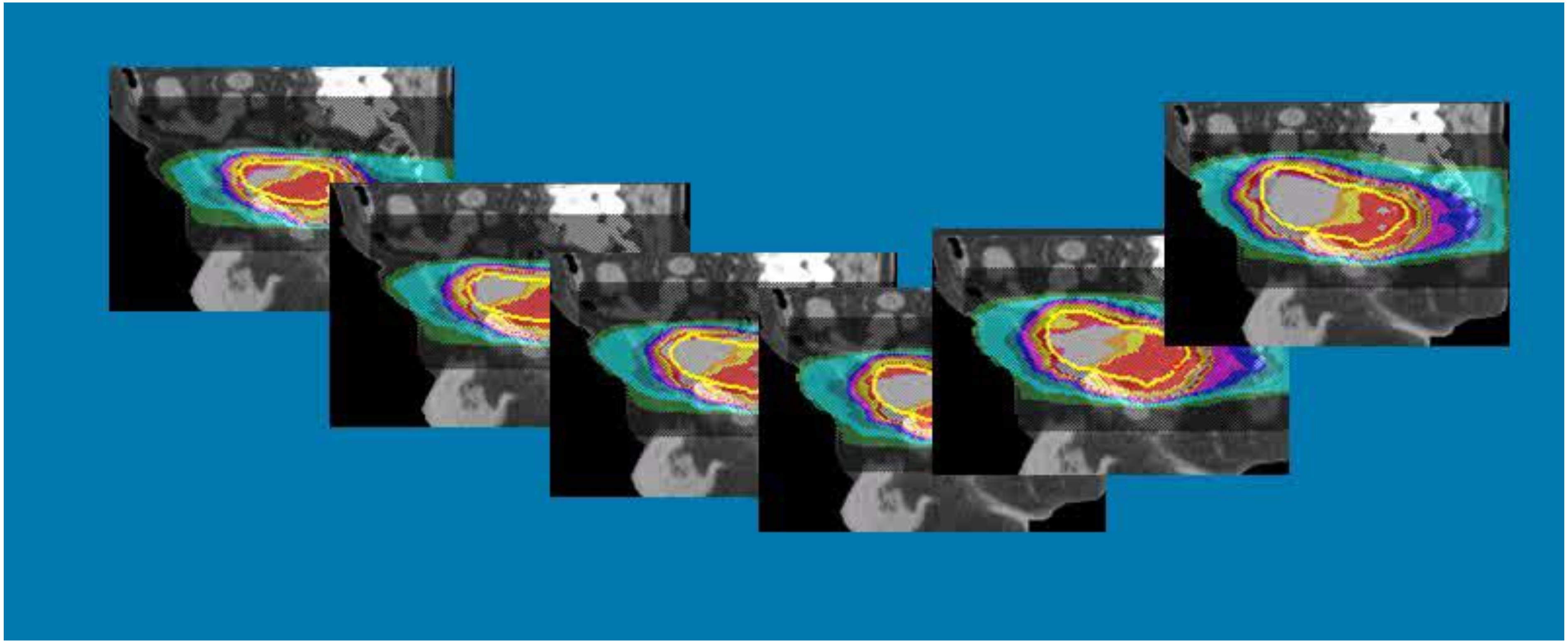
Overview — Current analysis data

	Tx (cm)	Ty (cm)	Tz (cm)	Rx (deg)	Ry (deg)	Rz (deg)
Clipbox	-0.24	0.23	-0.16	2.8	0.2	0.2
Mask	-0.18	-0.63	0.72	2.8	0.2	0.2
Correctable	-0.18	-0.58	0.72	0.0	0.0	0.0

Let op!
Rotaties moeten gelijk zijn!

ART: plan selection

Dealing with daily volume changes



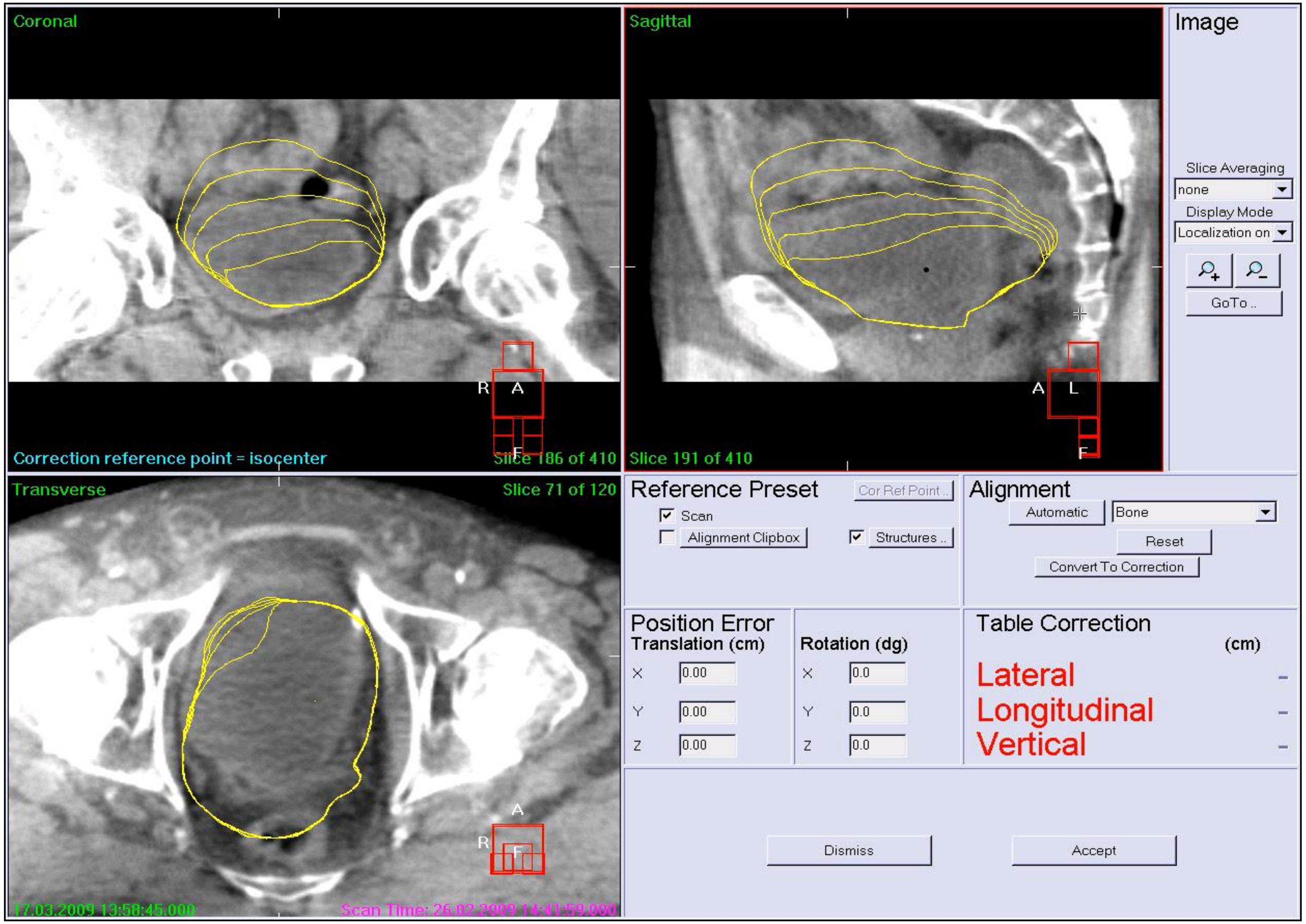
Courtesy Danny Schuring,
Catharina Ziekenhuis, Einhoven

Treatment Procedure

- Lipiodol demarcation of tumor by urologist
- Full & empty bladder CT scan
- Instructions to ensure full bladder
  - Good hydration prior to treatment
  - Empty bladder 1 hr before treatment
  - Drink 2 – 3 glasses
  - Continuous steering during treatment
- Cone-beam CT at start of treatment
- Selection of “plan of the day” based on bladder filling

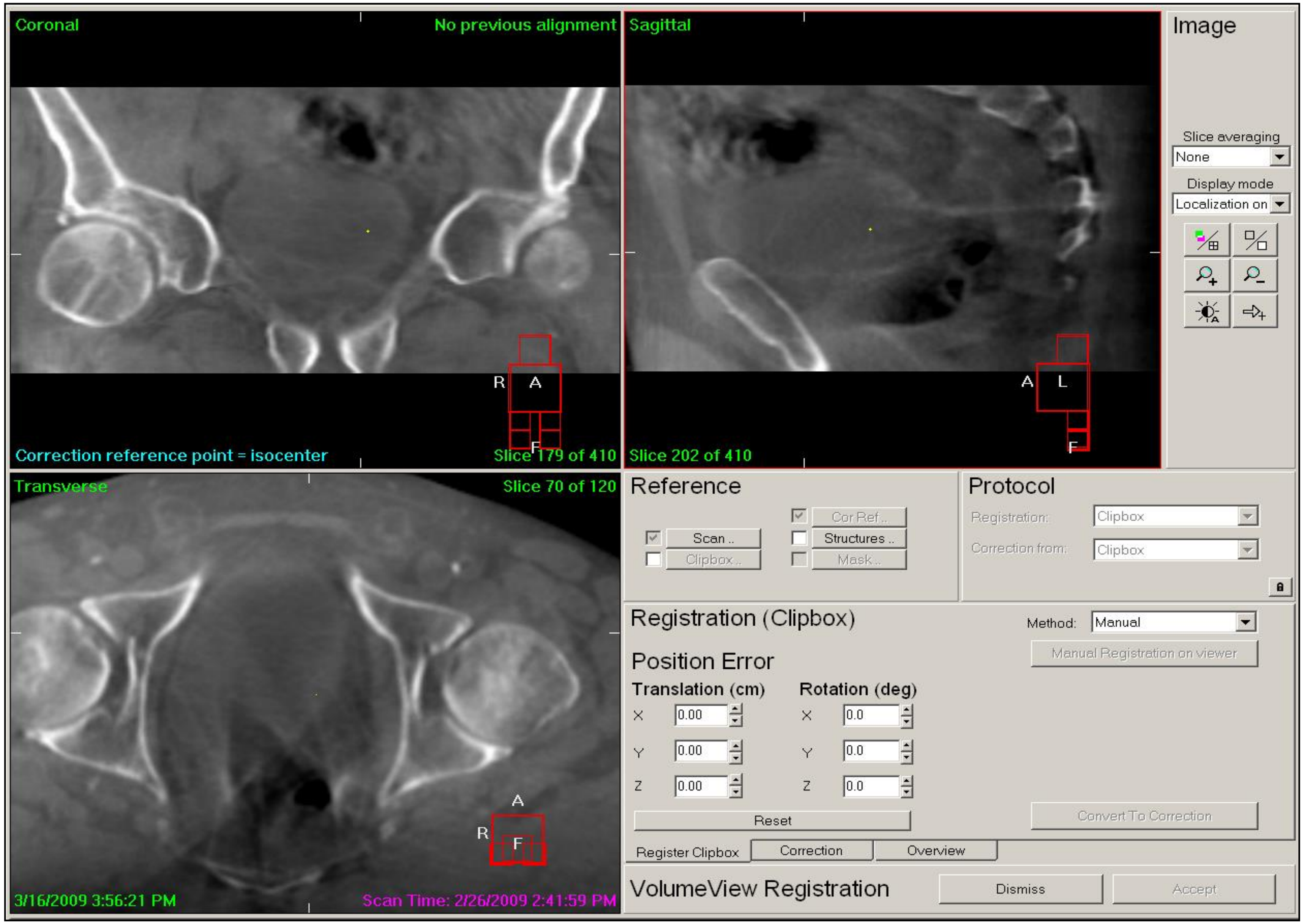
Courtesy Danny Schuring

Matching Procedure



Courtesy Danny Schuring

XVI quality



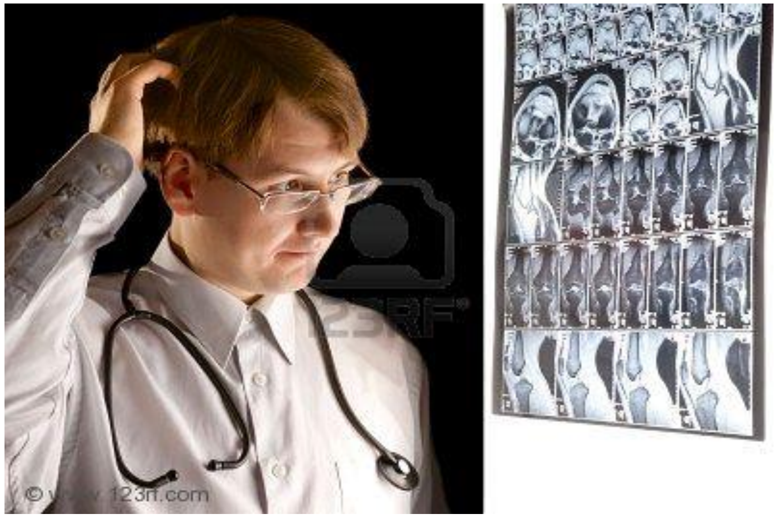
Courtesy Danny Schuring

Daily plan selection

- Daily plan selection at linac

  ⇓

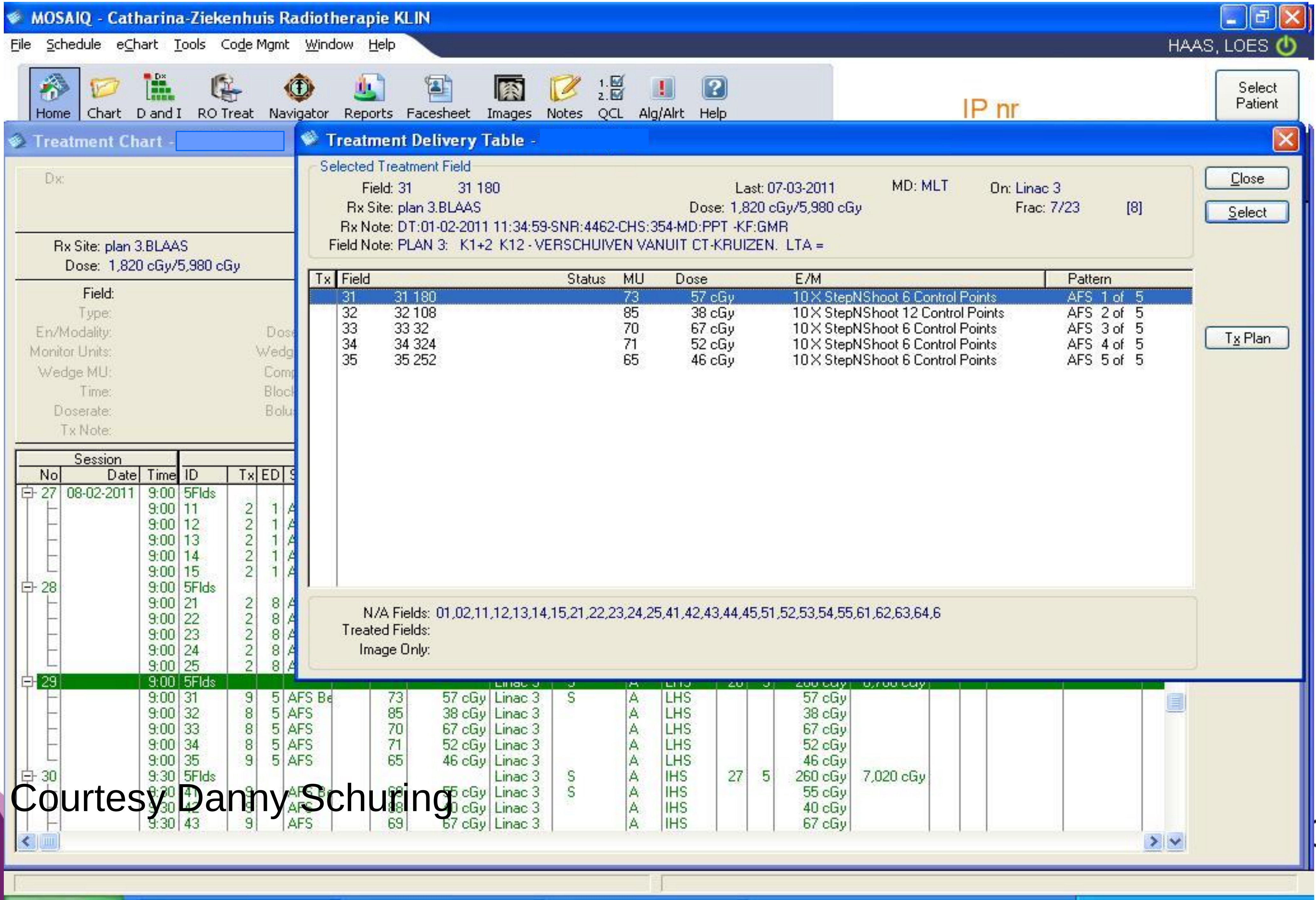
  Shift in responsibilities!



- Current practice: selection by physicist or specialized technologist

Courtesy Danny Schuring

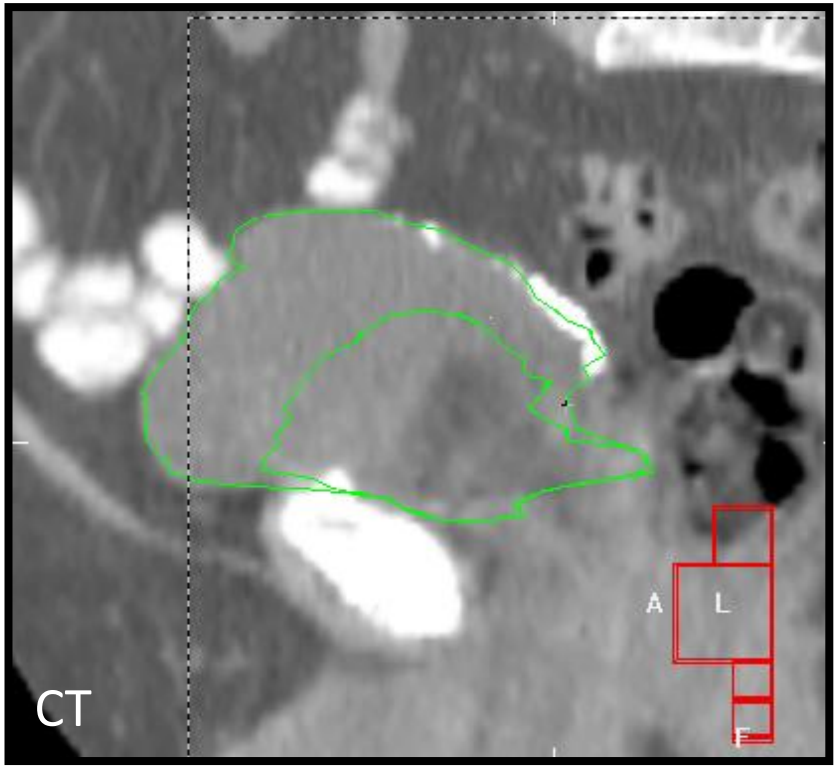
Plan selection in Mosaiq

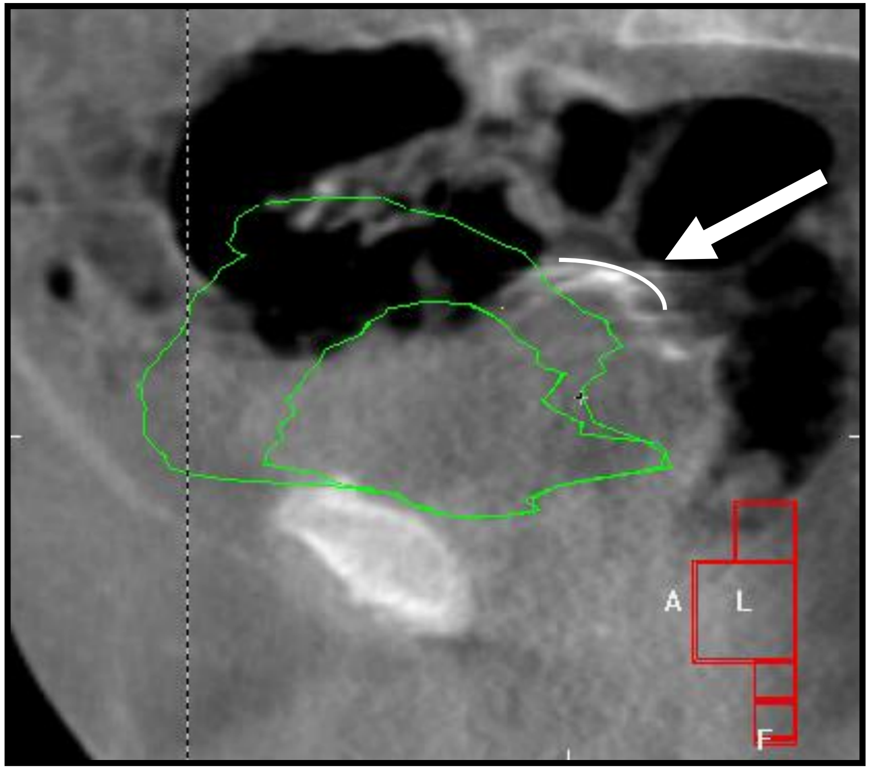


Courtesy Danny Schuring

3 van de 18 scans:

Groen: Bladder 0%, 100%





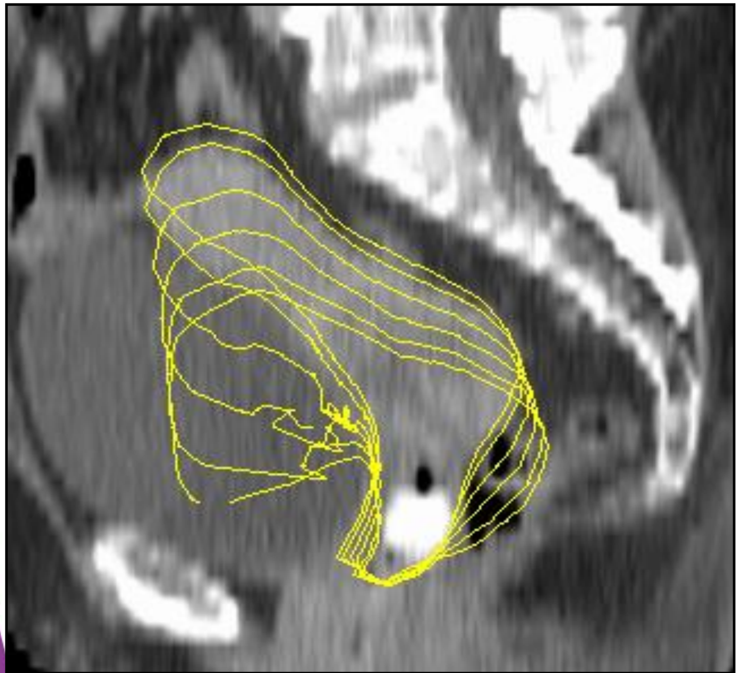
Implementation strategy for plan selection

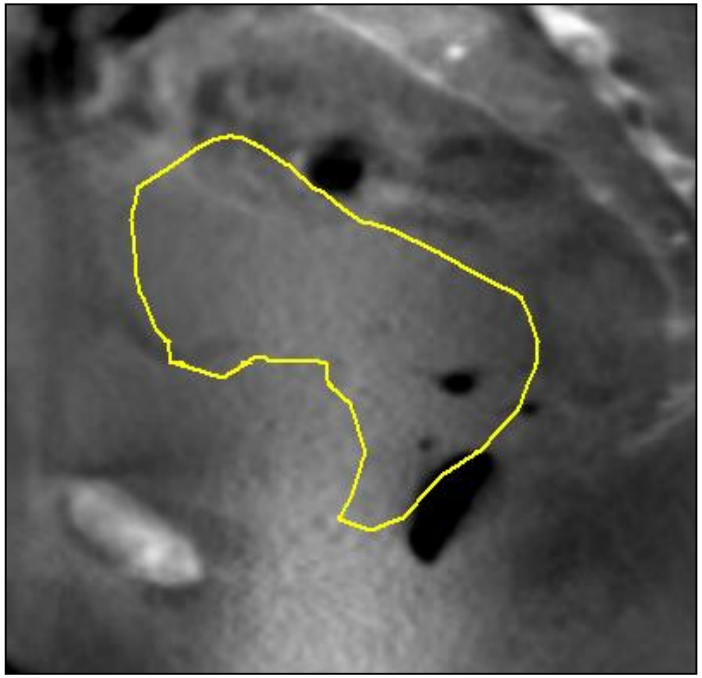
Design of the study

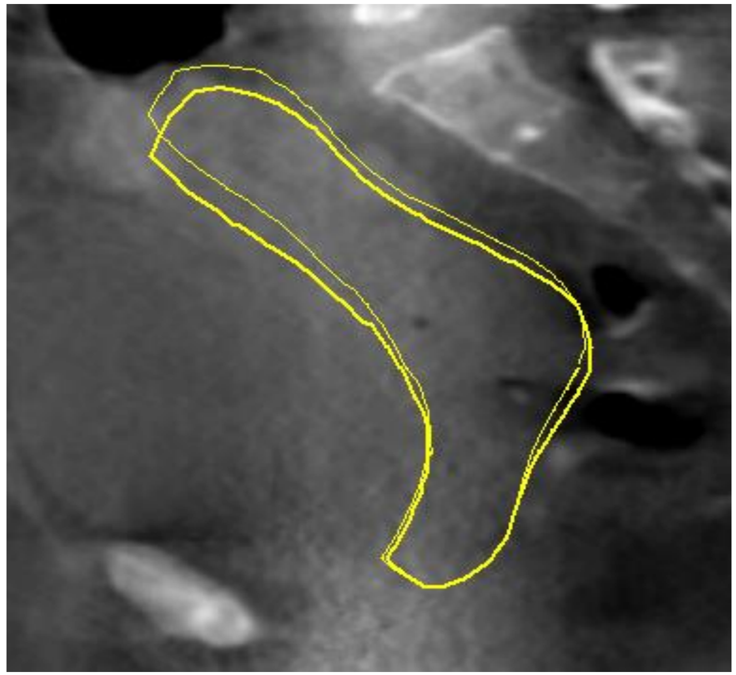
1. First measurement
2. Workshop
3. Second measurement

- 5 patients, 23 scans
- Per patient 6 structures
- 9 Observers:
  - 5 RTTs working treatment machine
  - 2 IGRT RTTs
  - 2 Research IGRT RTTs

Observer Study selection of plans for Cervix patients







Observer Study selection of plans for Cervix patients

First measurement **77.1%**, second **84.7%** agreement

Workshop very usefull:

Both RTT's and Radiation Oncologist gained trust that they all see the same things although there is not an 100% agreement.

⇨ There is more variation than just the variation captured with full & empty bladder CT scan! **rectum, small bowel, heamorrage, tumor shrinkage**

Treatment & Imaging Cervix Selection of Plans

Procedure imaging:

1. Registration of bony anatomy
2. Selection of plan in XVI with structure overlay
3. Check if markers (vagina) are within PTV.

- Big brother software checks correct plan: Do Mosaiq and XVI agree?
- Big brother software checks that not more than 1 plan is treated.

Nice!! But still not commercially available

Evaluation of Cervix Selection of Plans

1x a week by the imaging RTT's and/or physician

- Was the correct plan selected?
- Is the target volume moving as predicted in de pre-treatment full and empty bladder CT scans?
- Is the predicted movement still valid? (regression)

✓ *Only RTT's that participated in the workshop and observer study perform planselection in the clinic*

✓ Demo database for practice for new RTT's

De Jong et al. Radiother Oncol. 2016
Plan selection strategy for rectum cancer patients – inter observer study

Summary

IGRT is a multi disciplinary approach

IGRT has opened the field of RT for RTT’s:

1. RTT’s should be responsible for IGRT at the treatment machine
    - Registration & evaluation images
    - Training & education / Quality assurance
    - First assessment of anatomical / relevant changes
2. Research, development and implementation of IGRT

“patient preparation and positioning”:

Even with IGRT, setting up the patient remains **very** important!

Questions & Discussion

m.a.j.dejong@amc.uva.nl

ESTRO School

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Planar imaging: MV and kV

Marianne Aznar PhD,
Risgshopitalet, Copenhagen
U of Manchester/ The Christie

With thanks to: Dirk Verellen, Stine Korreman

Outline

EPIDs

Planar kV imaging systems

- Gantry-mounted
- Floor/ceiling mounted

Issues adressed:

Basic principles; pros and cons

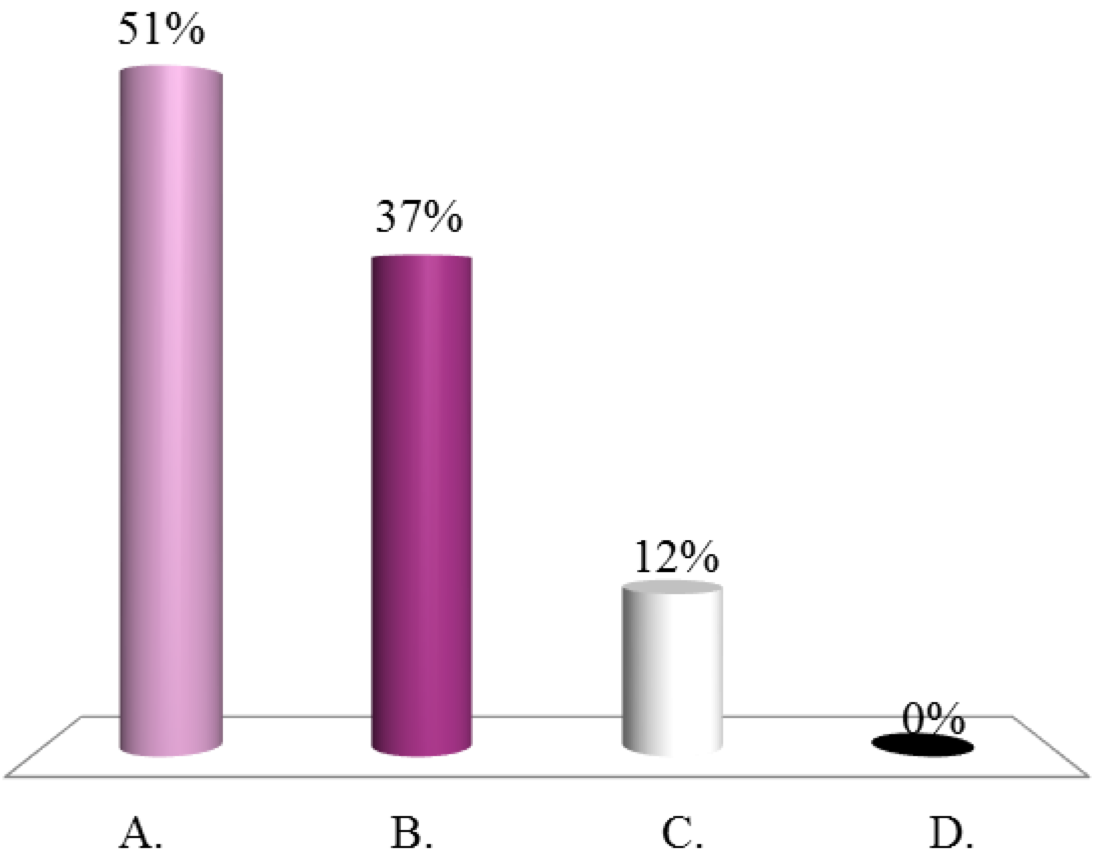
Alignment and calibration; QA issues

Intrafraction monitoring

Example of clinical strategy

MV vs kV capabilities: in your institution, do you have kV imaging capabilities:

A. On all treatment machines
B. On most treatment machines
C. On a few machines, but mostly MV
D. Only MV EPID on all treatment units



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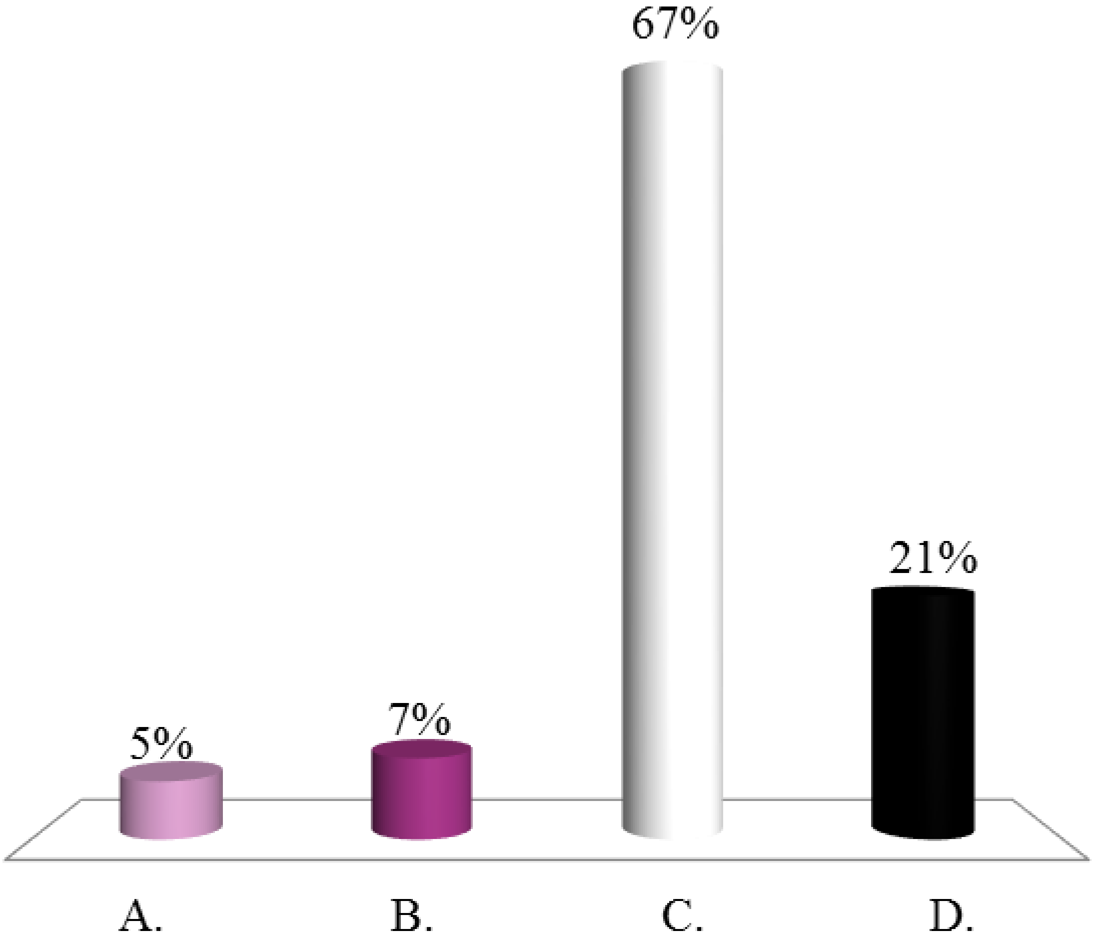
MV vs kV usage: which type of planar imaging do you use ?

A. Only MV planar
B. Mostly MV, occasionally planar kV
C. Mostly planar kV occasionally MV
D. We use only volumetric imaging



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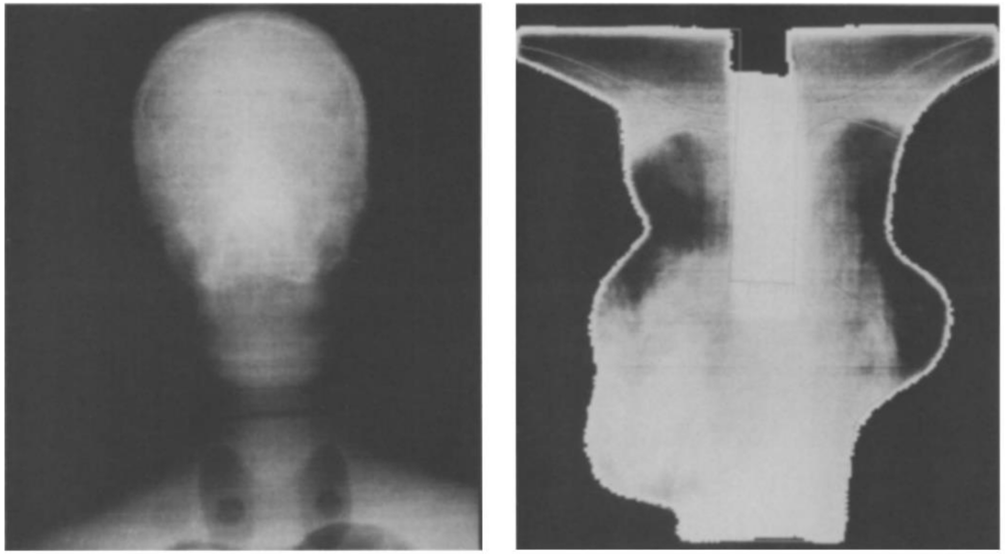
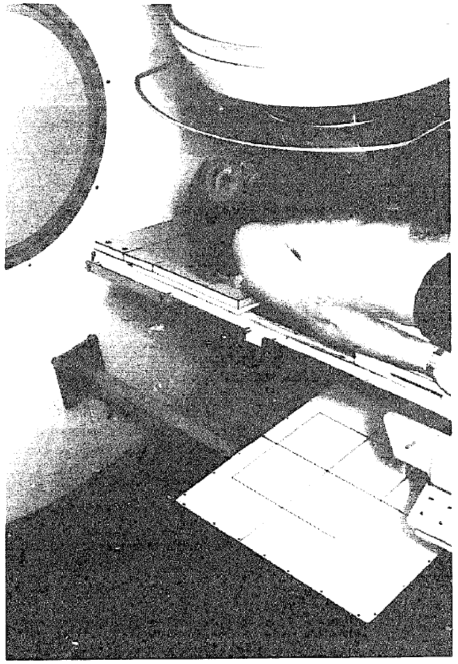
EPIDs: basic principles

Why EPIDs ?

Ca 25 years of experience



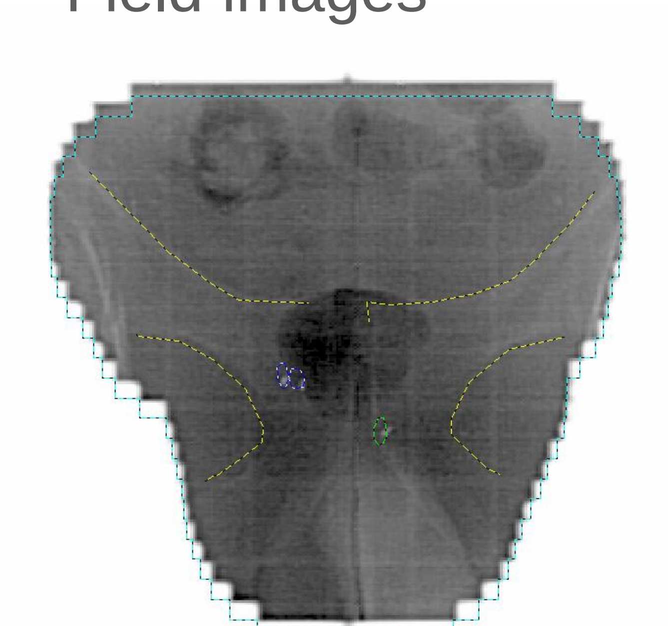
Lam et al, BJR 1986

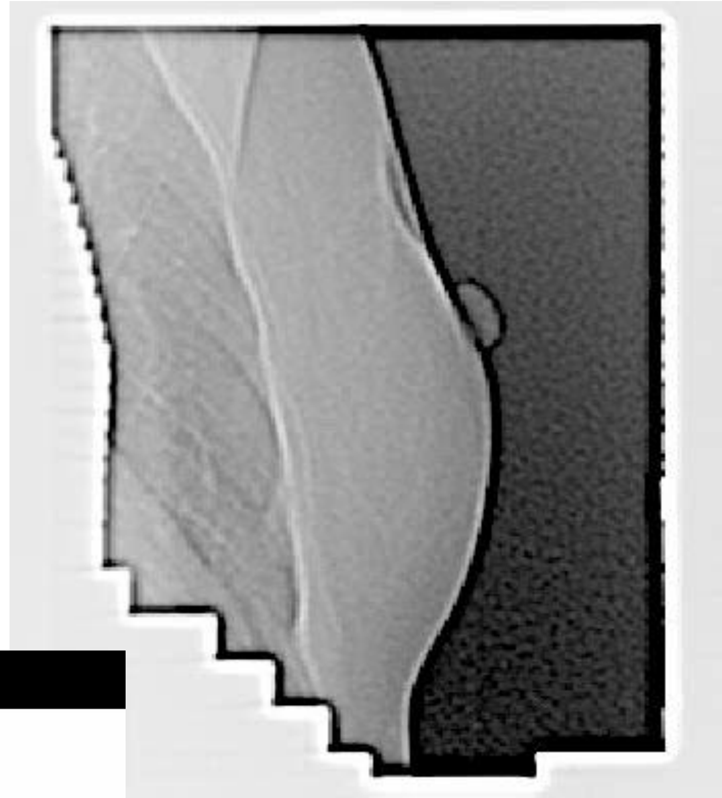


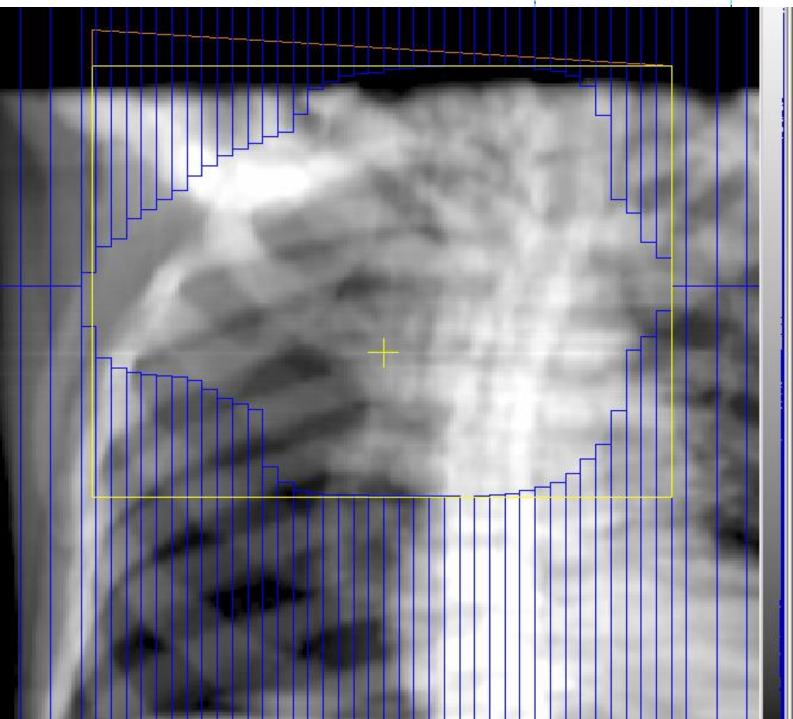
Van Herk et al,
RO 1988

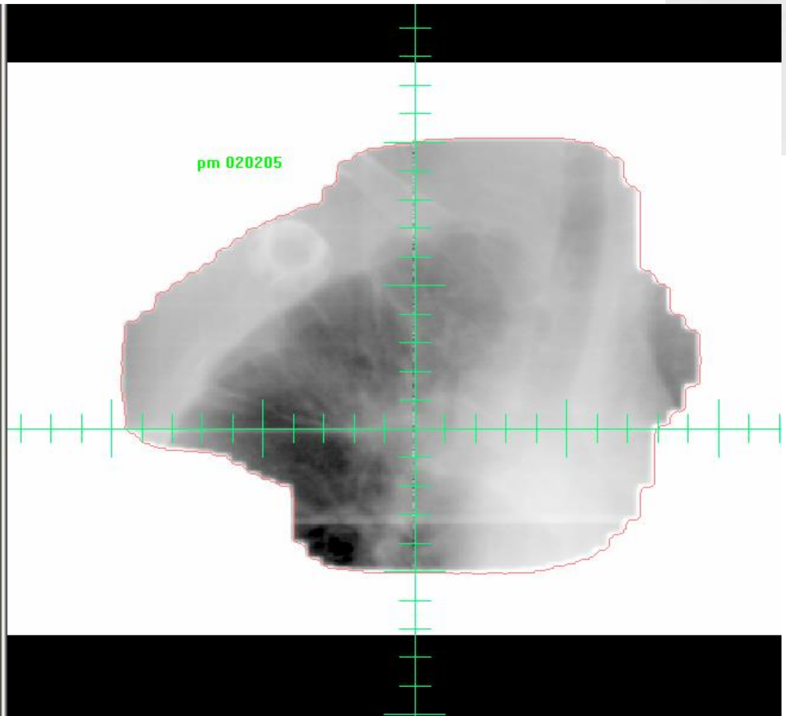
Why EPIDs?

Field images



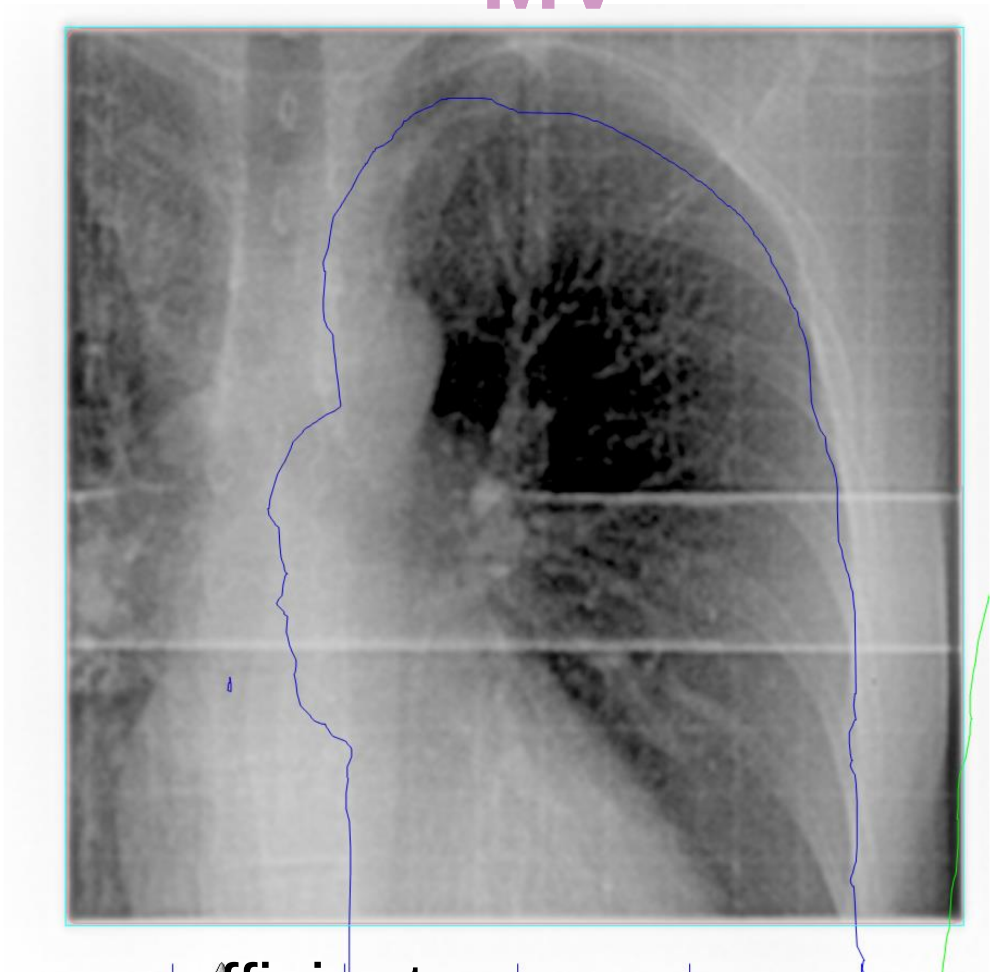






kV

MV



Mass energy absorption coefficient

$\sigma/\rho \sim Z^{3-\ 3.8}$

Photoelectric effect dominant

$\sigma/\rho \sim Z^{0}$

Compton effect dominant

ESTRO School

EPIDs: Pros and cons

Isocentric alignment: the imaging beam is the treatment beam (obs: gravity)

The imaging dose to the patient can be easily calculated in the TPS

Verifies the field outline with respect to the patient anatomy

Can use the EPID for transmission (in vivo) dosimetry

Monoscopic: needs several angles for 3D positioning information

Considerable dose for large FOV images outside the target volume (1 to 5 MU per image)

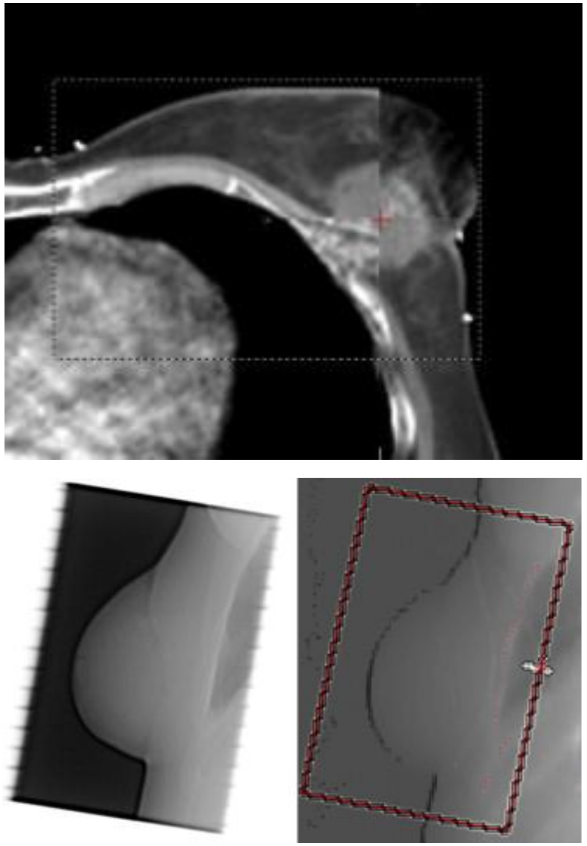
Low contrast (bony structures or markers)

EPIDs: example of clinical strategy

Limitation of MV imaging for set-up

kV CBCT

EPID



Topolnjak IJROBP 2010

- EPID field images (i.e. not orthgonal) underestimate <u>bony</u> set-up errors by 20% to 50%

- Difference probably insignificant for tangential whole breast irradiation

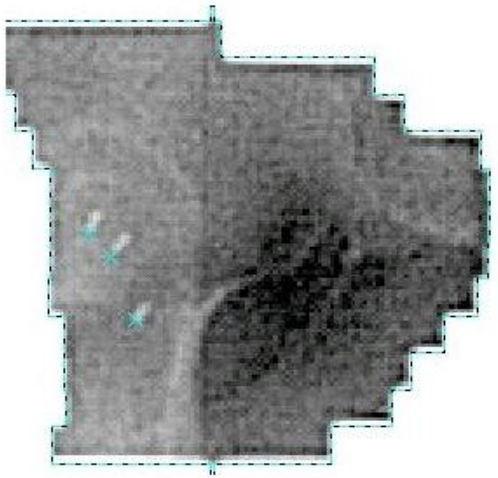
- Loco-regional treatment or more advanced techniques (SIB? IMRT?) could benefit from a more accurate set up.

EPIDs: intrafraction monitoring

Is it possible to do intrafraction monitoring with EPIDs ?

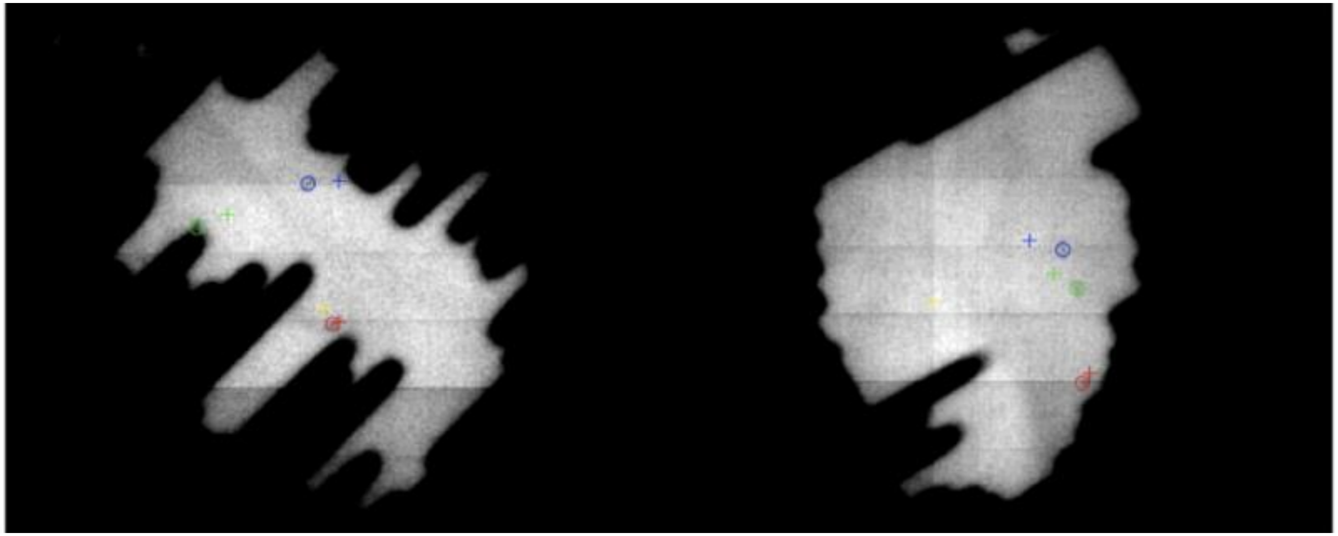
Tracking internal fiducials

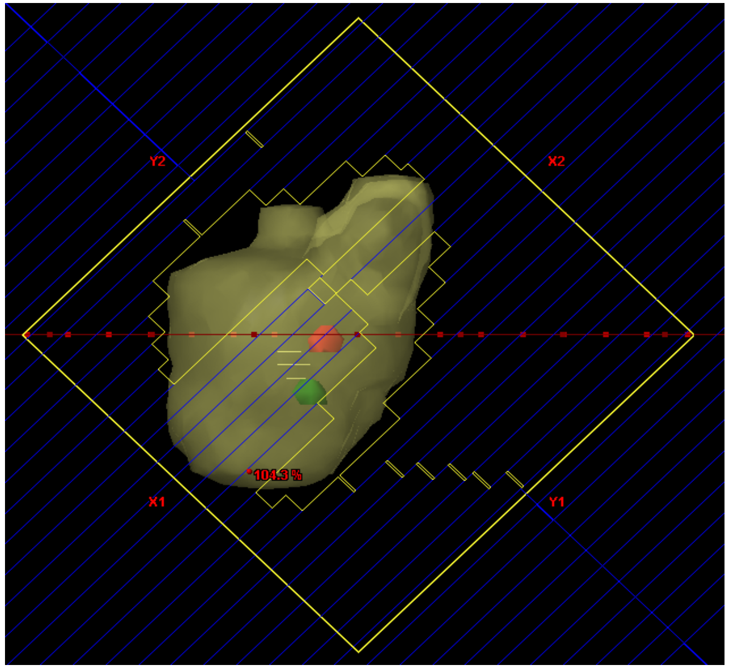
- Fiducials are visible with MV in Beams-Eye-View with EPID in cine mode
- Structures in the Beams-Eye-View can be used for image correlation analysis



- Advantage: least dose
- Pitfall: restricted to beam opening

Is it possible to do intrafraction monitoring with EPIDs ?



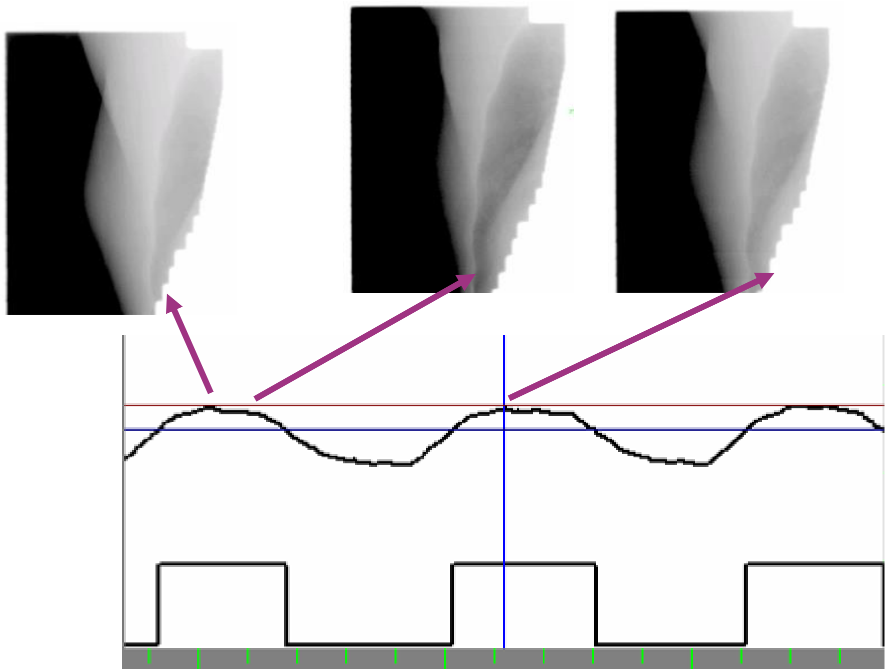


Azcona et al IJROBP 2013

Detectability of the markers: between 20 and 80%

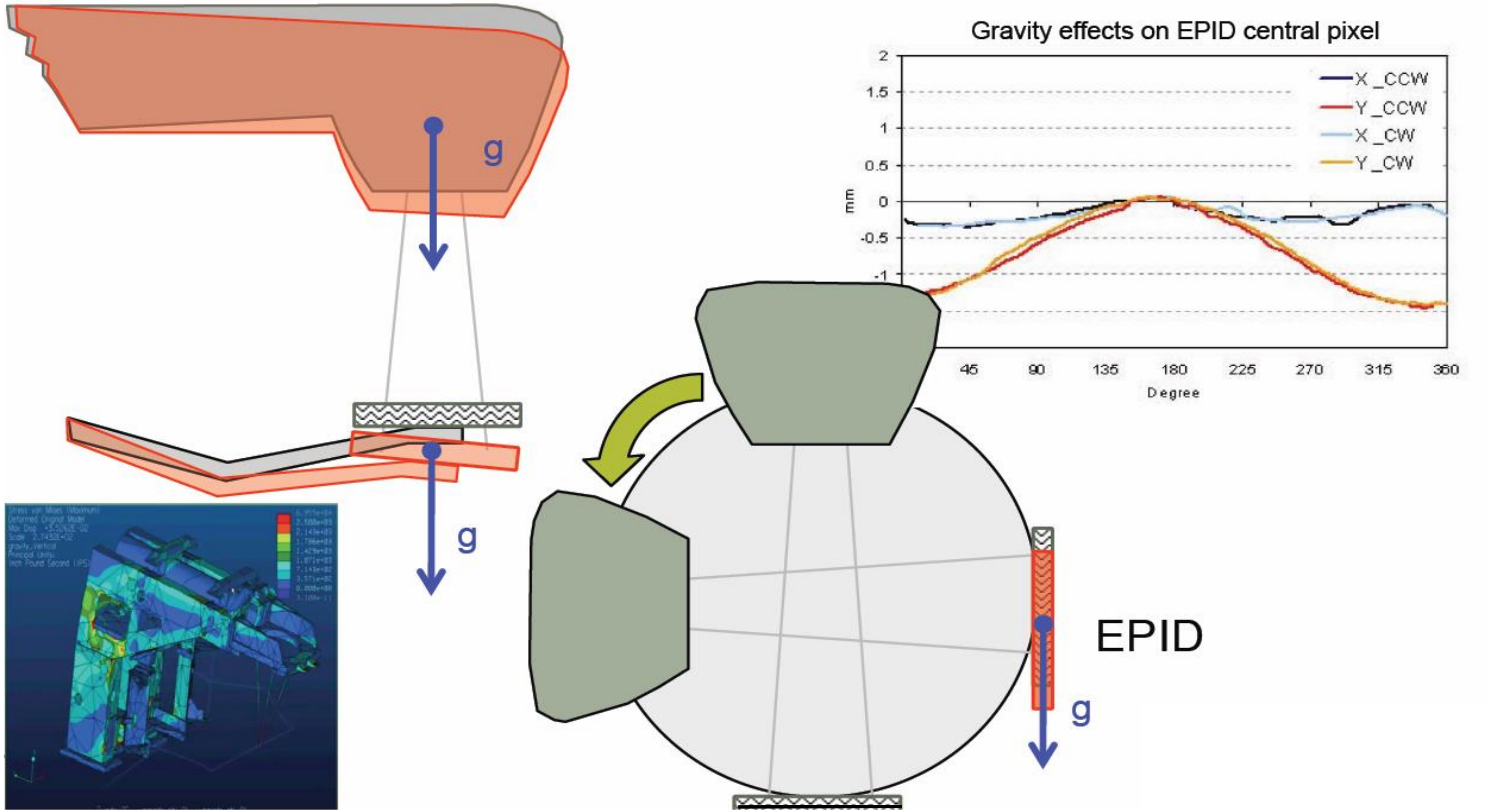
EPIDs at Rigshospitalet

- 12 linacs in total
- 1 without kV imaging (EPID-based set-up of palliative treatments; some breast patients)
- On other machines: ”beam’s eye view” checks (gating window with cine EPID)

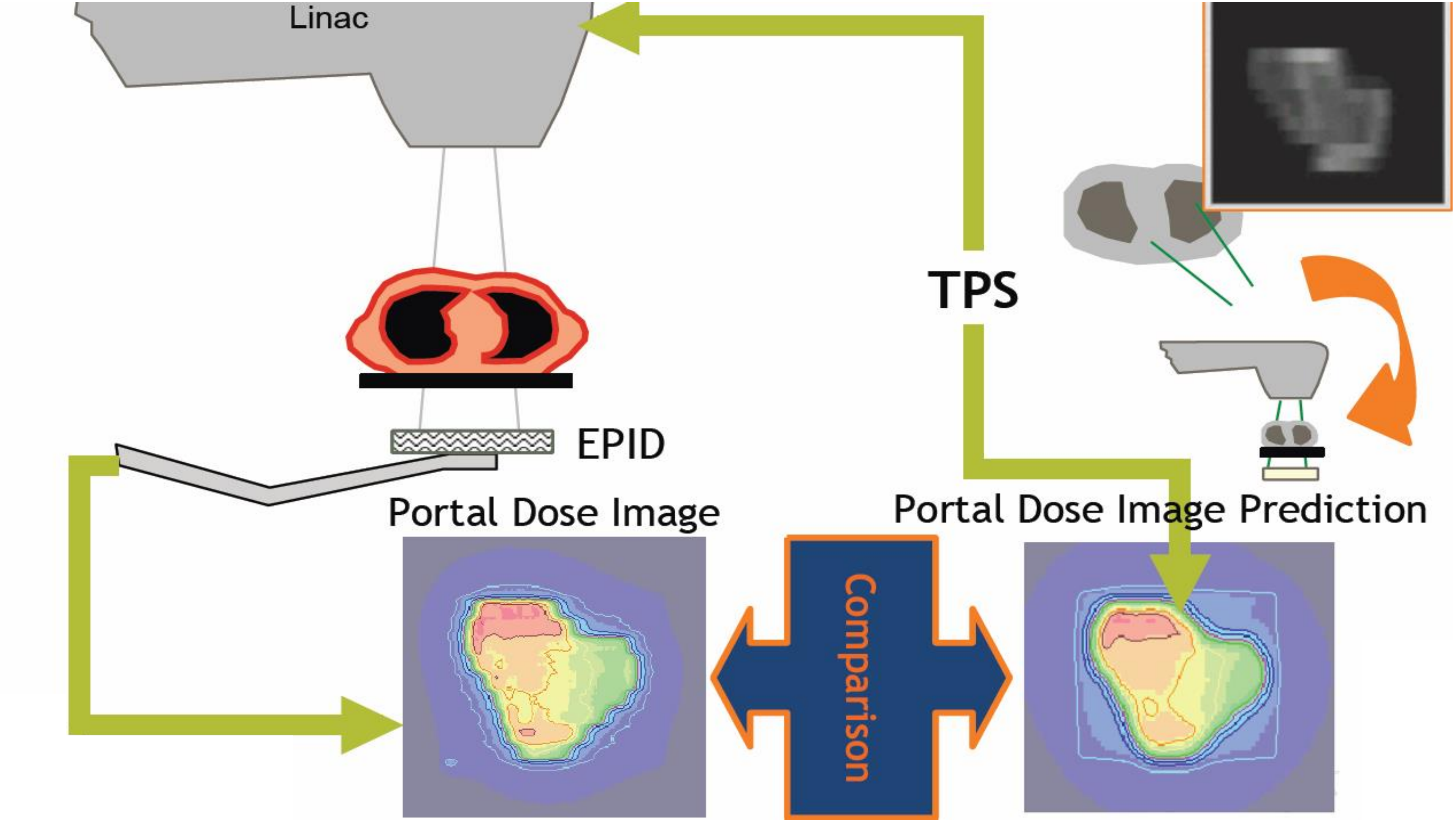


EPIDs: QA

QA /calibration for EPIDs



Non-imaging uses: portal dosimetry



•With/without phantom or patient
•commercial and non-commercial solutions

Non-imaging uses: portal/transit/"in vivo" dosimetry

Search results

Items: 1 to 20 of 129

<< First < Prev Page 1 of 7 Next > Last >>

1. Clinical Experience and Evaluation of Patient Treatment Verification With a **Transit** Dosimeter.
   Ricketts K, Navarro C, Lane K, Blowfield C, Cotten G, Tomala D, Lord C, Jones J, Adeyemi A.
   Int J Radiat Oncol Biol Phys. 2016 Aug 1;95(5):1513-9. doi: 10.1016/j.ijrobp.2016.03.021. Epub 2016 Mar 25.
   PMID: 27262359
   Similar articles

2. Implementation and evaluation of a **transit dosimetry** system for treatment verification.
   Ricketts K, Navarro C, Lane K, Moran M, Blowfield C, Kaur U, Cotten G, Tomala D, Lord C, Jones J, Adeyemi A.
   Phys Med. 2016 May;32(5):671-80. doi: 10.1016/j.ejmp.2016.04.010. Epub 2016 Apr 25.
   PMID: 27134042
   Similar articles

3. A comparison of electronic portal **dosimetry** verification methods for use in stereotactic radiotherapy.
   Millin AE, Windle RS, Lewis DG.
   Phys Med. 2016 Jan;32(1):188-96. doi: 10.1016/j.ejmp.2015.12.001. Epub 2015 Dec 31.
   PMID: 26748961
   Similar articles

4. Initial clinical experience with Epid-based in-vivo **dosimetry** for VMAT treatments of head-and-neck tumors.
   Cilla S, Meluccio D, Fidanzio A, Azario L, Ianiro A, Macchia G, Digesù C, Deodato F, Valentini V, Morganti AG, Piermattei A.
   Phys Med. 2016 Jan;32(1):52-8. doi: 10.1016/j.ejmp.2015.09.007. Epub 2015 Oct 26.
   PMID: 26511150
   Similar articles

- **Is MV portal imaging still relevant today?**

- Less and less...

- At least for set-up imaging purposes
- Unlikely that it will be the best solution for intrafraction monitoring
- **BUT** possibly increasing use for QA, transmission dosimetry, etc..

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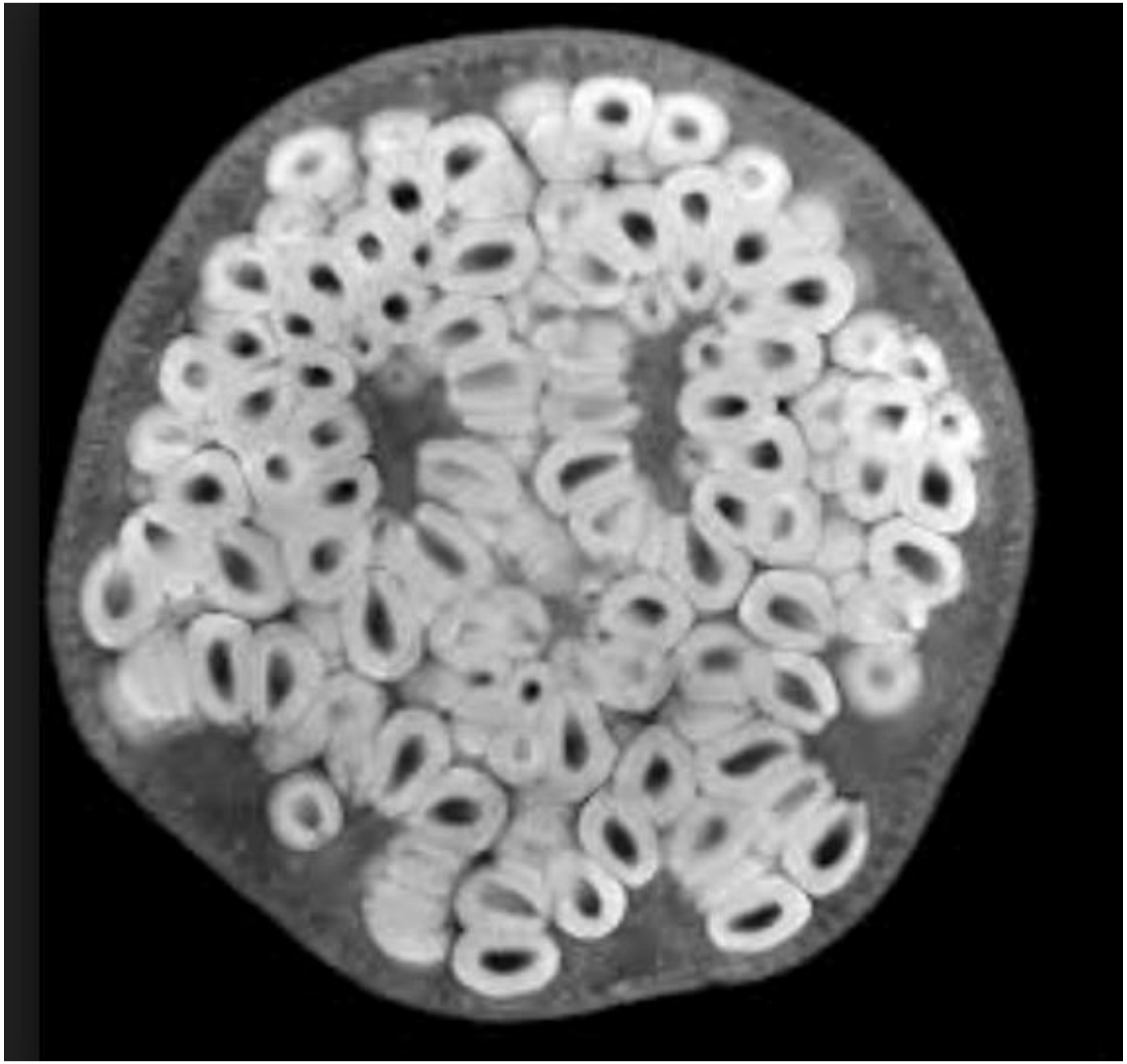
Fruit break !!



Why planar kV?

- Better contrast (vs EPID)
  - ➢But also other factors, resulting in a higher SNR
- Lower dose (vs EPID)
- Speed of acquisition (stereoscopic vs CBCT)
- Experience (transferrable from EPID)

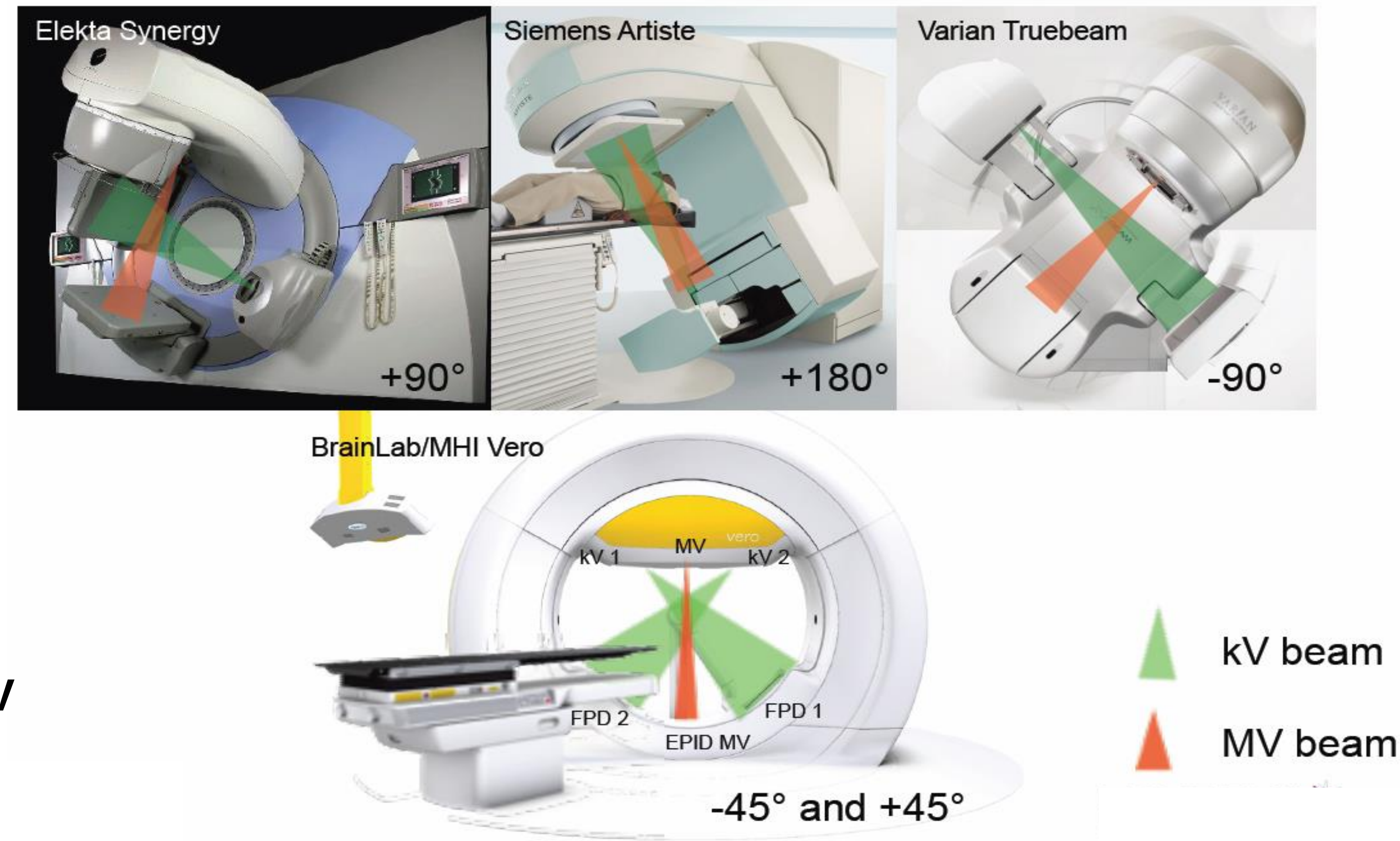
•Gantry-mounted vs floor/ceiling-mounted

Gantry-mounted kV: basic principles

Gantry-mounted systems

1x kV

2 x kV



On-Board Imager (Varian)

30 x 40 cm flat panel

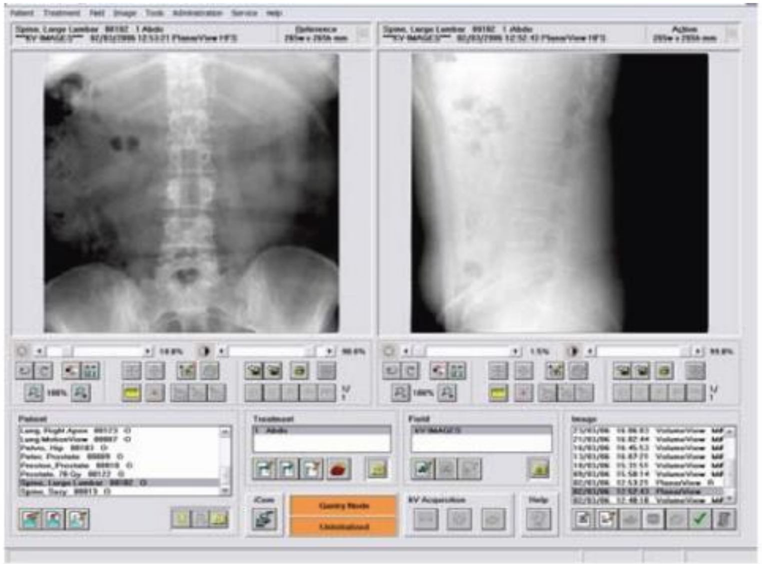
Pixel size 0.39 mm

15 frames/second rate

kV source 0.4 mm focal spot, 40-125 kVp

Robotic arms to position FPD and source

Synergy PlanarView (Elekta)



41 x 41 cm flat panel

Pixel size 0.4 mm

15 frames /sec rate

kV source 0.4 mm focal spot, 70-150 kVp

Manual positioning of FPD and source

Gantry-mounted kV: Pros and cons

Improved image quality

Low dose

Can acquire images at any angle

Possibility for volumetric imaging

Intrafraction monitoring?

Relatively poor soft tissue contrast (bone / marker match);

Monoscopic: needs several angles for 3D positioning information

Potential collision with different couch angles (and very lateral targets?)

Inexact coincidence of kV and MV isocentre

Intrafraction monitoring?

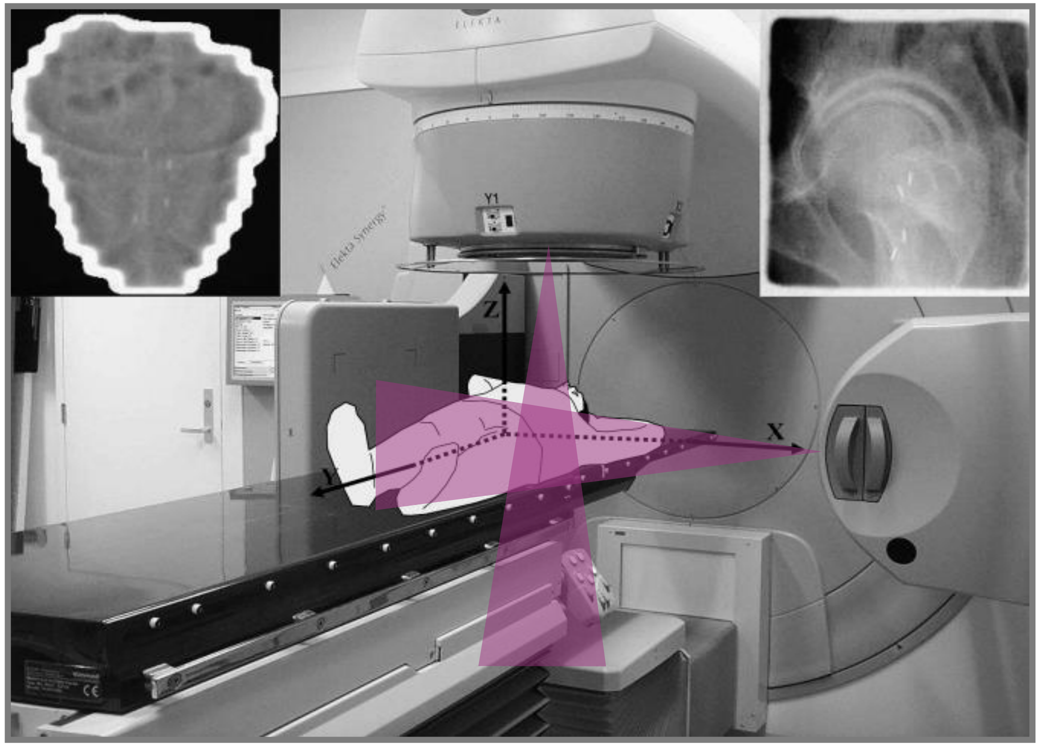
Gantry-mounted kV: intrafraction monitoring

Inter + Intrafraction management on Conventional LINAC

- Dual MV/kV imaging
- Quick extraction of markers
- Automated correction by couch

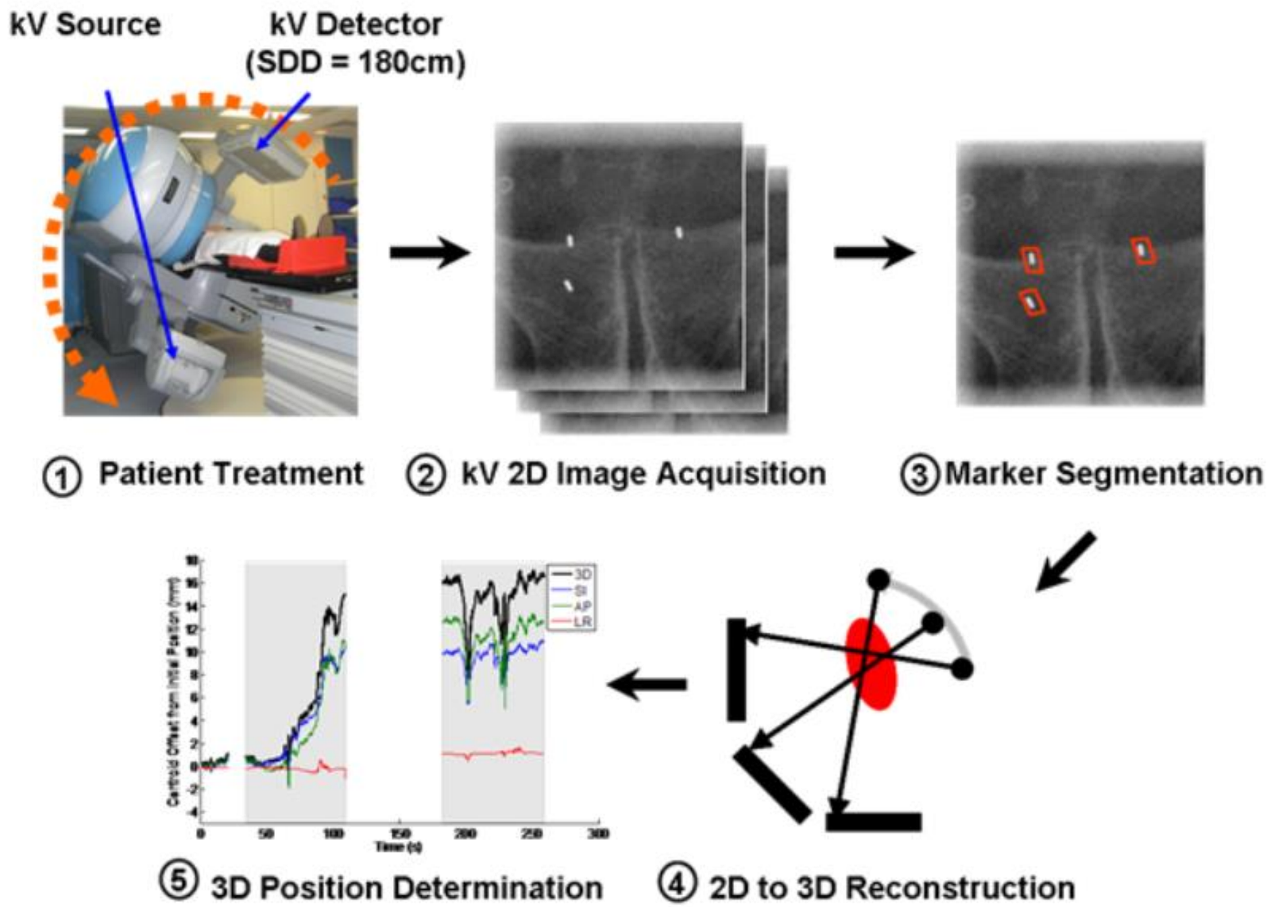
- Residual error < 1 mm in < 1 min added treatment time

- Also compensating intra-fraction motion



Mutanga TF et al. Stereographic targeting in prostate radiotherapy: speed and precision by daily automatic positioning corrections using kilovoltage/megavoltage image pairs. IJROBP 2008

Inter + Intrafraction management on Conventional LINAC



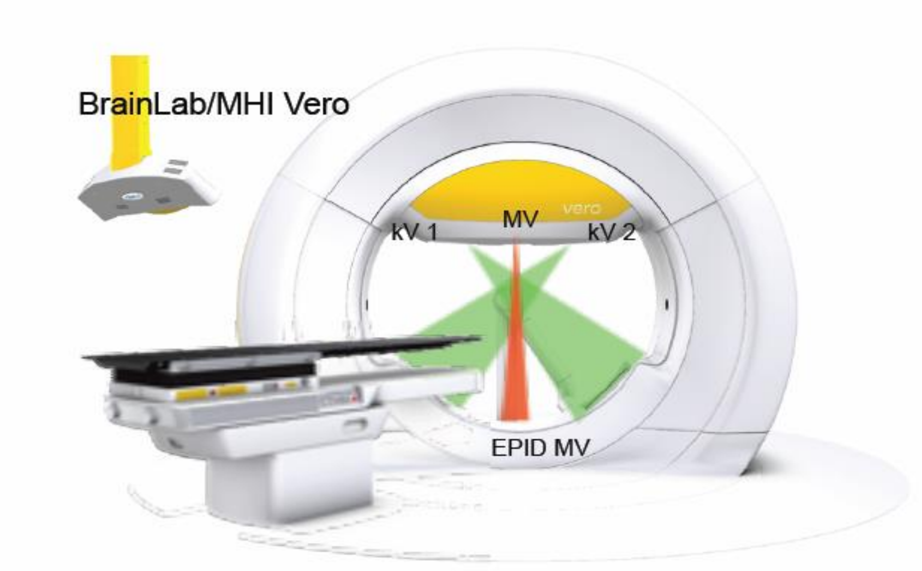
The clinical process workflow for Kilovoltage Intrafraction Monitoring gating.

Keall et al IJROBP 2015

Kilovoltage
Intrafraction
monitoring
gating

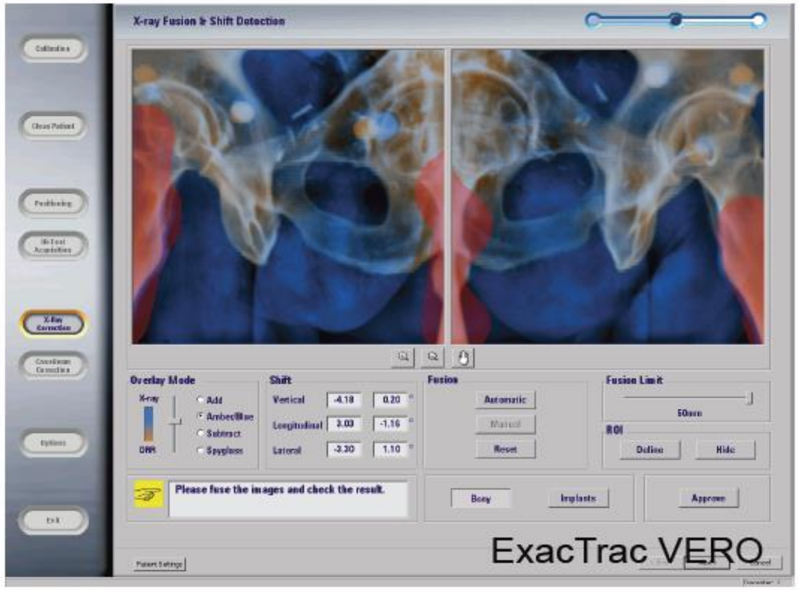
Software available at http://sydney.edu.au/medicine/radiation-physics/data/tumour-motion-prostate.php

”O-ring” gantry systems



Specifications
- 2 times 30x40cm flat panel aSi (PaxScan 4030CB)
- Pixel size 0.39mm, 1024x768 matrix
- 15 frames/sec rate
- kV source, 0.4mm focal spot, 40-125kVp
- kVs and FPB **fixed rigidly** to the O-ring gantry

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel



GANTRY (deg)	RING (deg)	Measured deviation X(mm)	Y(mm)
270	0	-0.2	0.0
0	0	0.0	0.2
90	0	0.2	0.0
180	0	0.2	0.2
180	20	0.0	0.2
90	20	0.2	0.2
0	20	0.0	0.2
270	20	-0.2	0.0
270	340	-0.2	0.0
0	340	0.0	0.2
90	340	0.2	0.0
180	340	0.2	0.0

MV-kV isocenter
Coincidence < 0.2mm

- Designed for intrafraction monitoring

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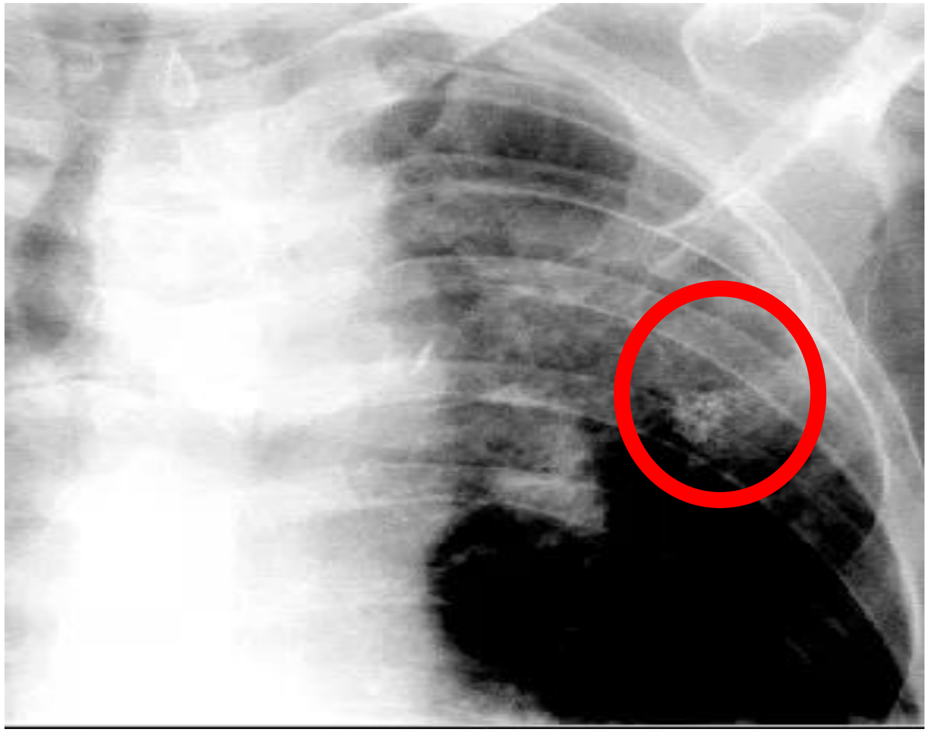
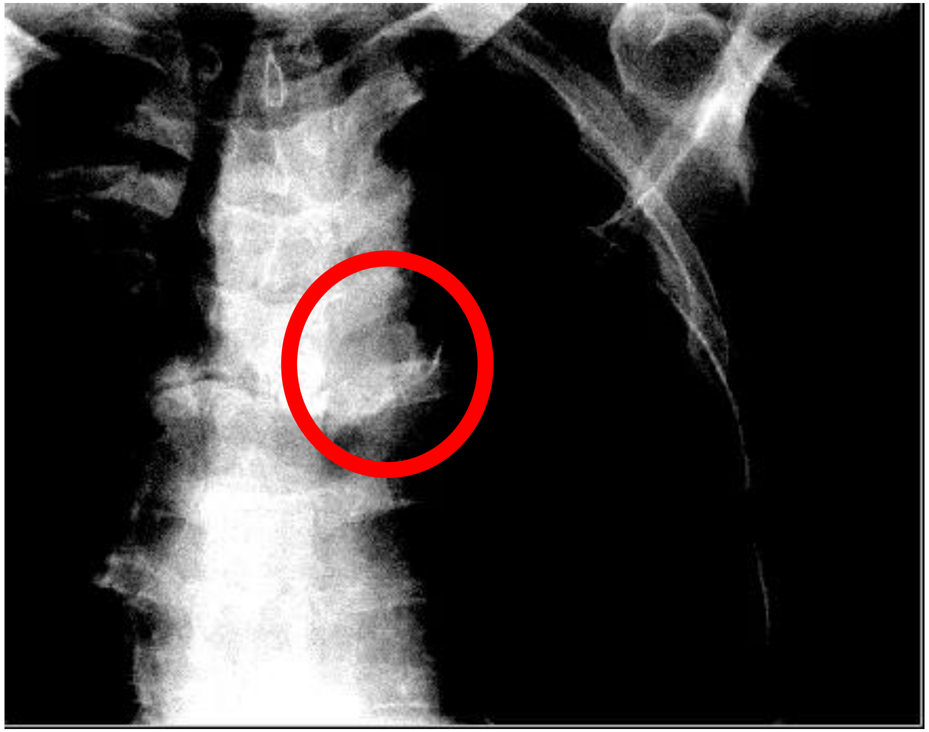
kV fluoroscopic imaging: pre- or during treatment

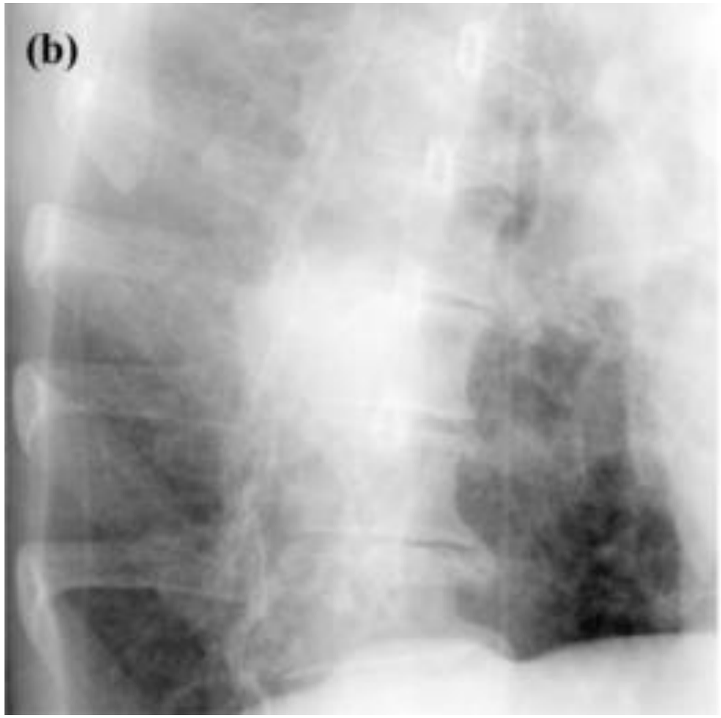
INHALE protocol for NSCLC

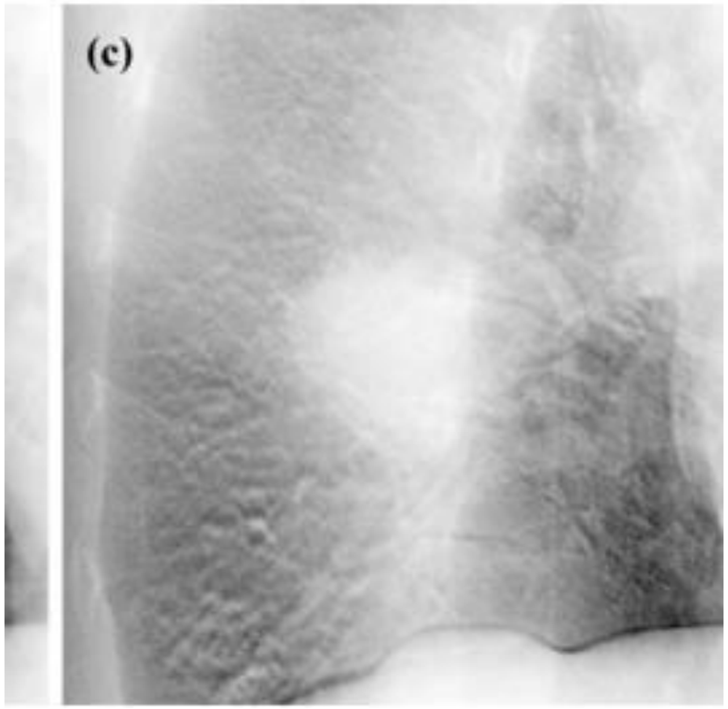




Courtesy: Jonas Scherman Ryghög and Nanovi

Dual energy planar kV imaging



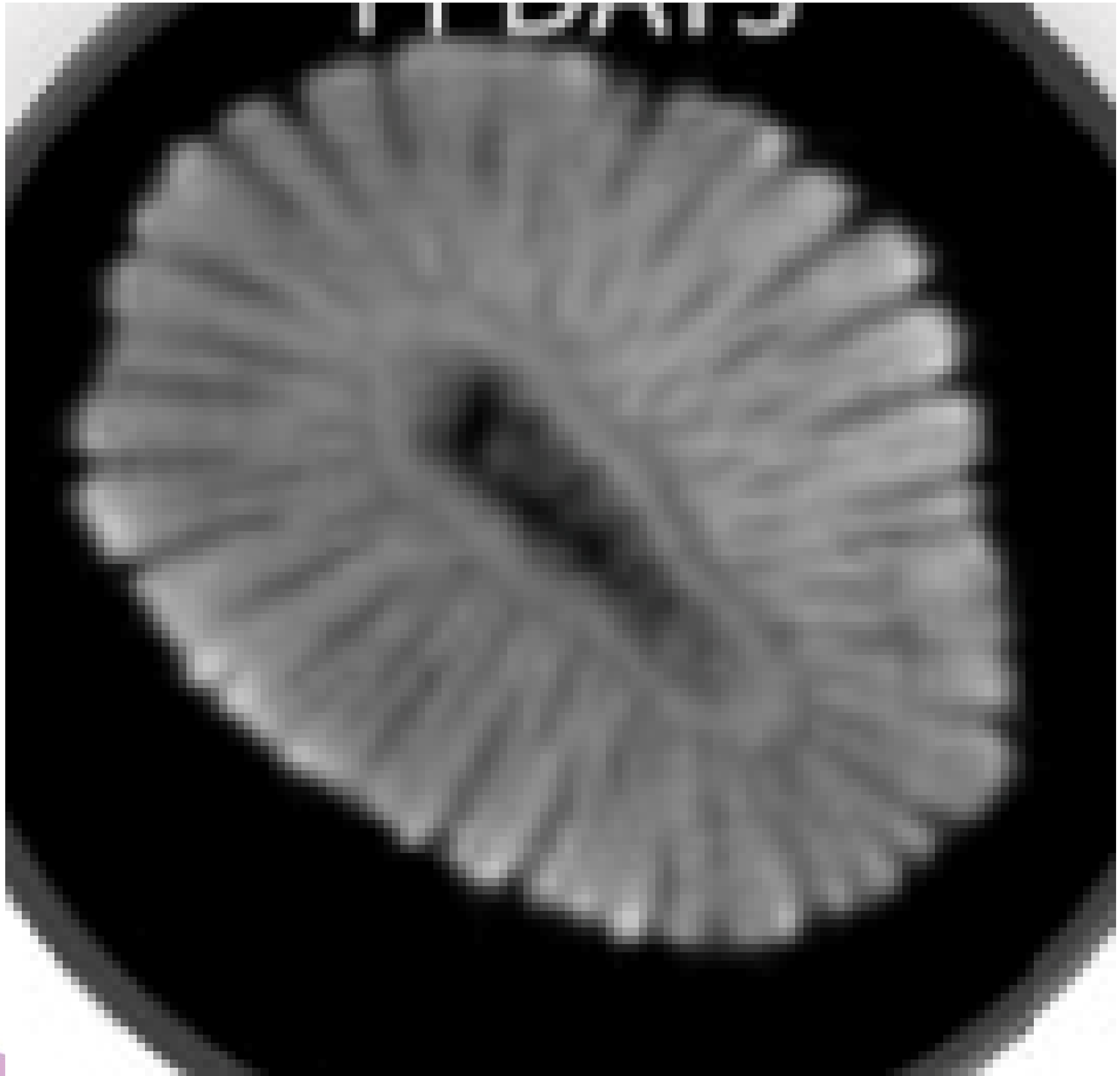


Standard 120 kVp

Soft issue DE image

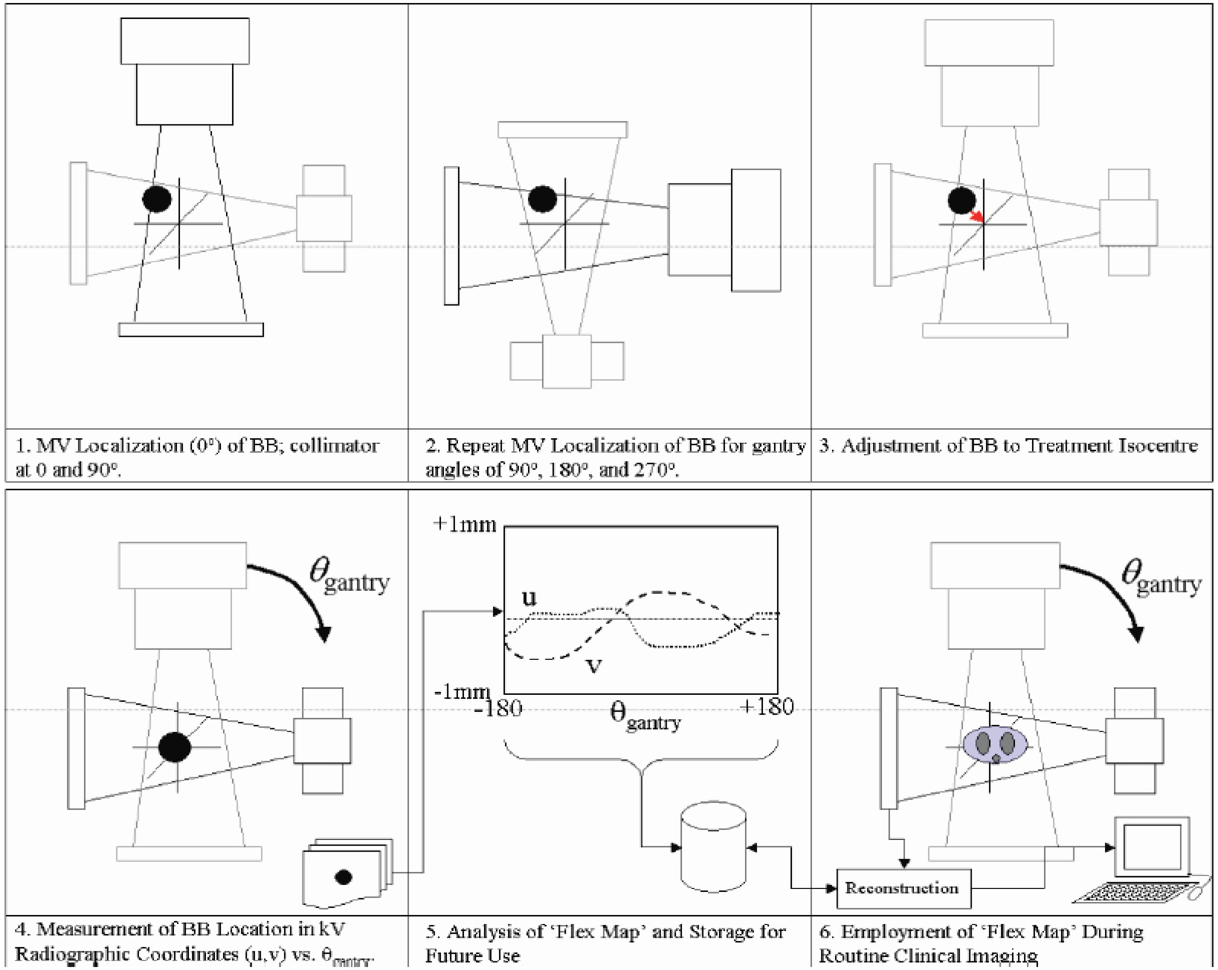
Sherertz et al IJROBP 2014

Fruit break !!



Gantry-mounted kV: QA

kV, gantry-mounted: Isocenter calibration



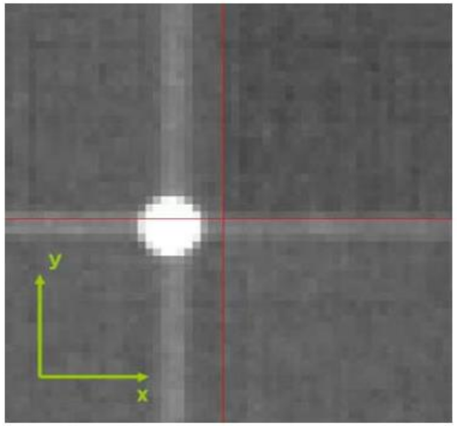
- ”gantry-mounted” does not guarantee the same isocenter as the treatment beam
- Geometric calibration to compensate for mechanical distortions (Flex Maps)
- good long-term stability

Bissonette JP, Princess Margaret Hospital, Canada

Disagreement between kV and MV isocenter at different gantry angles (cube isocenter phantom)

Table 3: Mean difference in position of the BB in kV images and MV images at different gantry orientations, n = 5.

Projection	Gantry/kVS orientation	Mean disagreement [mm] $\lvert\Delta x\rvert \pm 1\sigma$	$\lvert\Delta y\rvert \pm 1\sigma$
AP	0°	1.3 ± 0.1	1.5 ± 0.1
LR	90°	1.8 ± 0.1	1.3 ± 0.1
PA	180°	0.8 ± 0.1	1.5 ± 0.2
RL	270°	0.4 ± 0.1	1.6 ± 0.1



Milos Djordejvic ”evaluation of geometric accuracy and image quality of an OBI”, MSc thesis, Karolinska

X transverse
Y longitudinal

Gantry-mounted kV : example of clinical strategy

Gantry-mounted kV strategy at Rigshospitalet

11/12 linacs have OBI capabilities

OBI images are used:

- When bony anatomy is a good surrogate (breast + regional nodes; ~~mediastinal lymphoma~~)
- With ~~gated/ breath hold~~ treatments (left-sided breast)
- When dose is a concern (same + ~~pediatrics~~)
- ~~When the potential of CBCT hasn't been evaluated yet~~ (palliative)
- And…. As a back-up when problems with CBCT!

Floor/ceiling-mounted kV: basic principles

Ceiling/floor mounted kV

Exactrac, Brainlab

Specifications
•20cmx20cm flat-panel aSi imagers;
•spatial resolution 0.39 mm with 512x512 matrix
• max 150 kVp
•x-ray system + optical tracking system

CyberKnife
Accuray, Inc.

- 20cmx20cm or 40cmx40cm flat-panel aSi imagers;

- resolution 0.4 mm at 512x512 pixels

- 150 kVp X-ray sources Toshiba (separate power supplies)

- Designed for intrafraction monitoring:
    - Works integrated with tracking software for a number of tumour sites (includes an optical marker system for respiratory tumour tracking)

Main challenge: image interpretation !

Prostate: Planar oblique angle stereoscopic imaging with implanted markers

- This implies a certain reliance on the automatic fusion software
- Images should still be reviewed

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Floor/ceiling mounted kV: Pros and cons

Stereoscopic: very fast acquisition

Fixed system: high stability

Independent from MV source: intrafraction monitoring

Oblique images: interpretation?

Bone/marker match

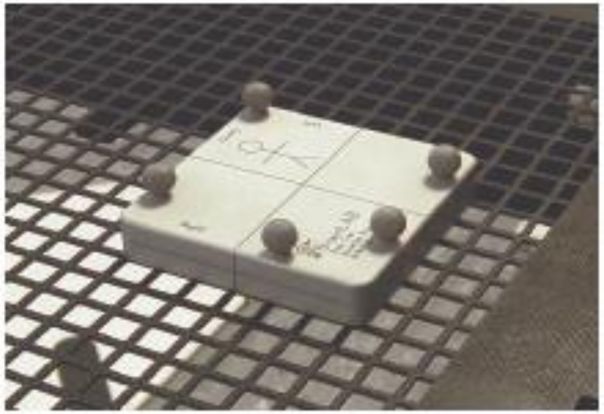
At some angles, the gantry can block the beam

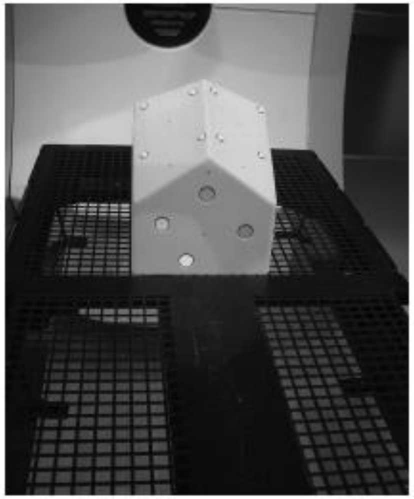
No CBCT possibility

Frequent calibrations necessary to check alignment of kV and MV isocentres

Floor/ceiling-mounted kV: QA

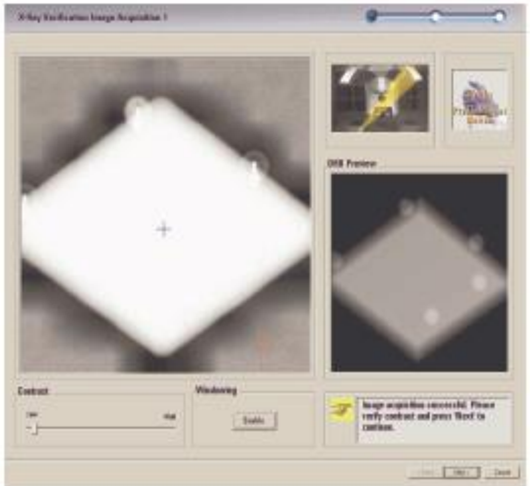
Example of alignment QA: ExacTrac

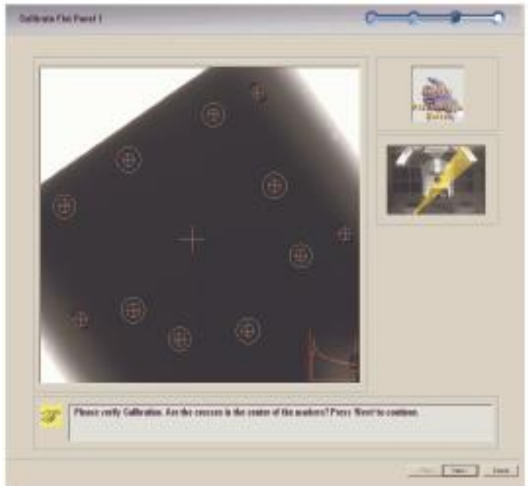




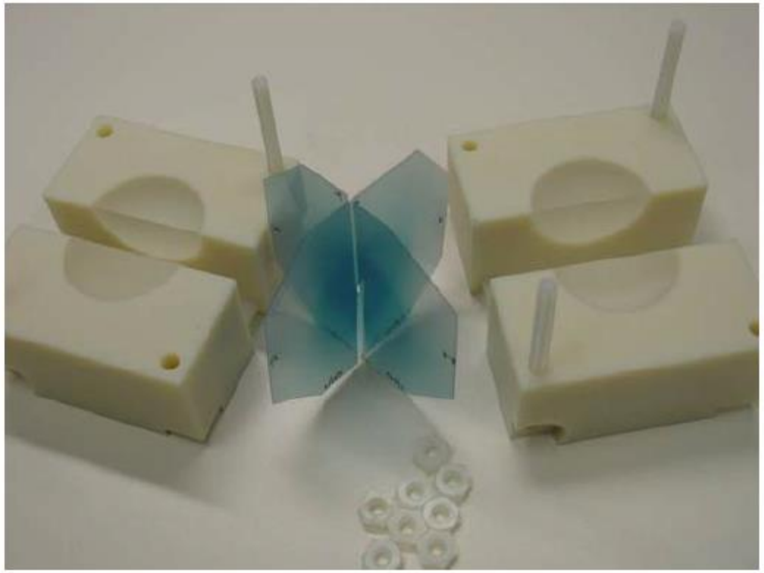
3 steps:

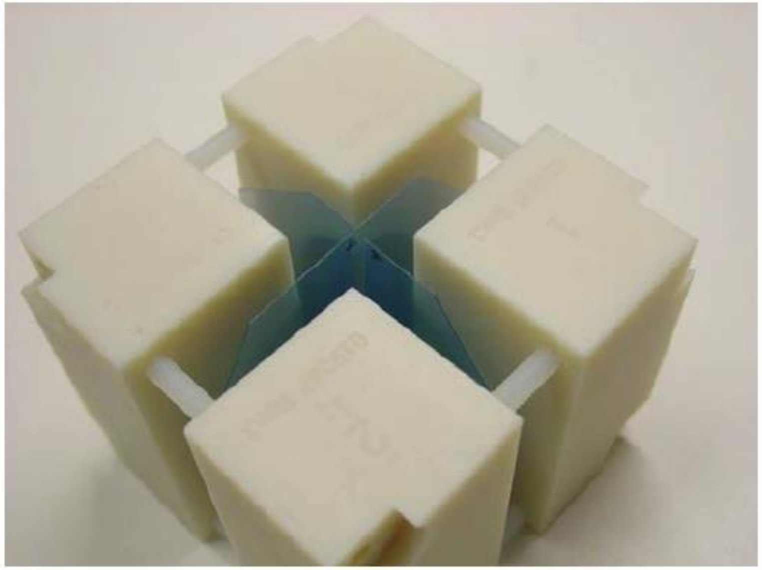
- Infrared isocenter to lasers
- Infrared to kV x-ray isocenter
- kV to MV isocenter





Cyberknife: ”end to end test”

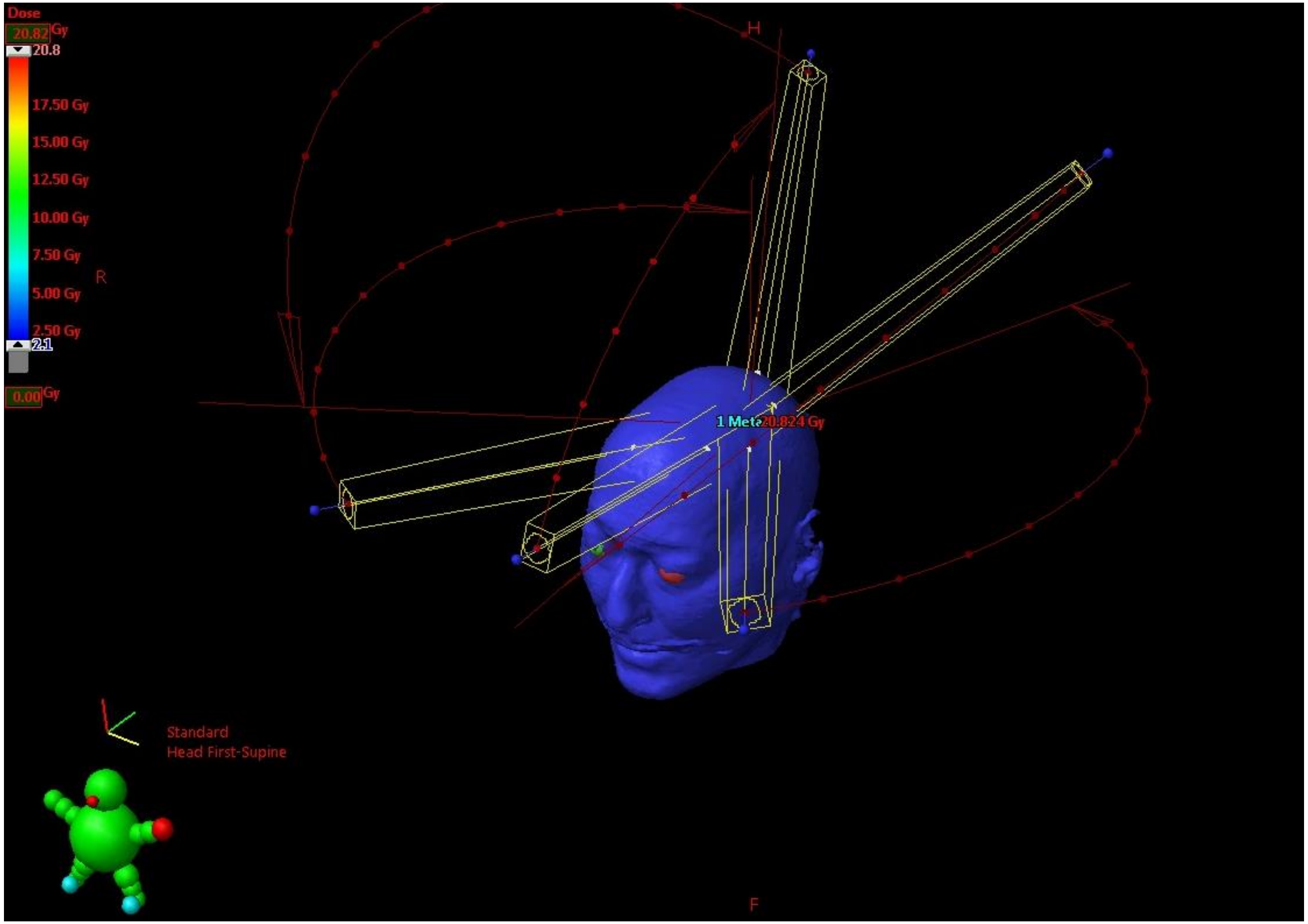




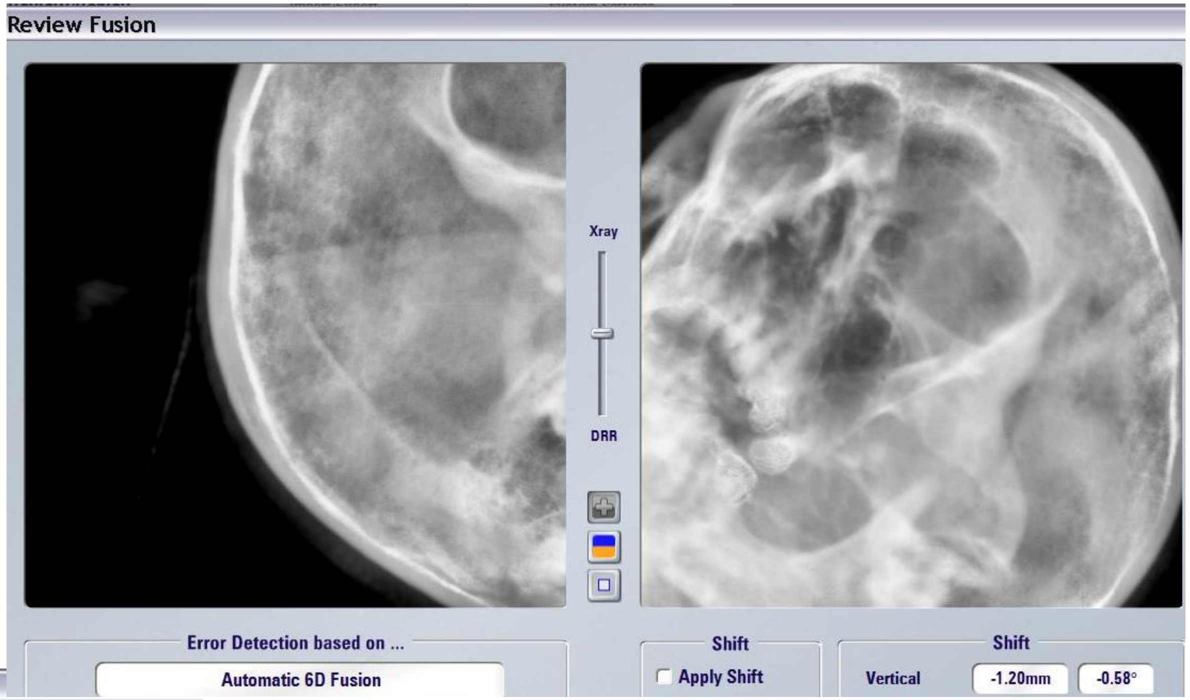
QA tool to check the alignment of robot coordinate system and image guidance system

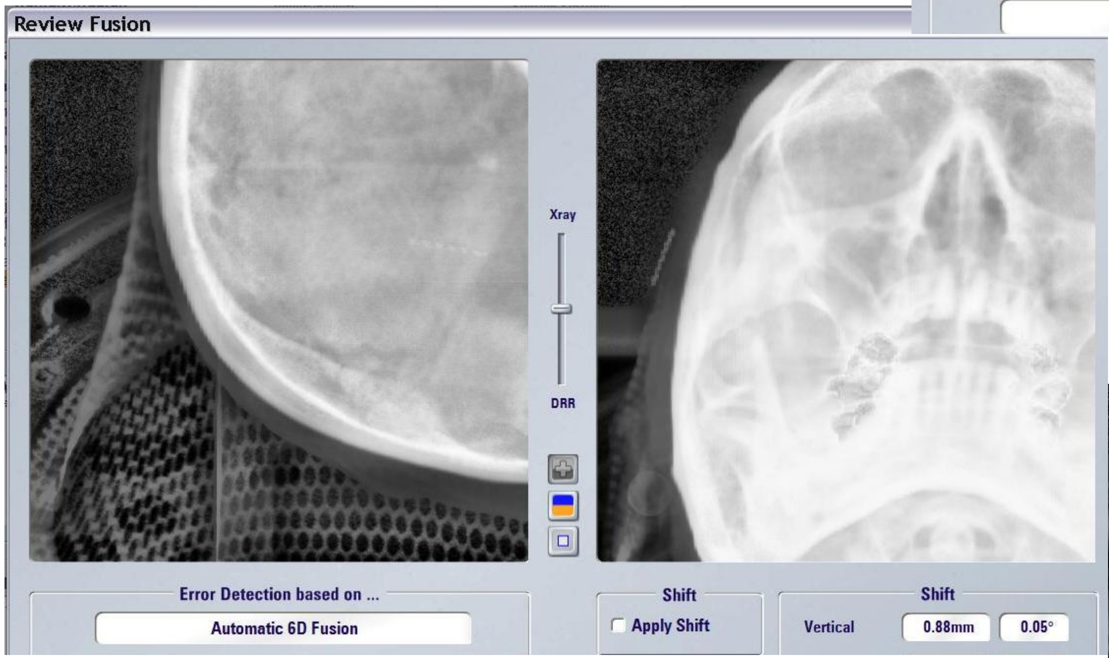
Floor/ceiling-mounted kV: example of clinical strategy

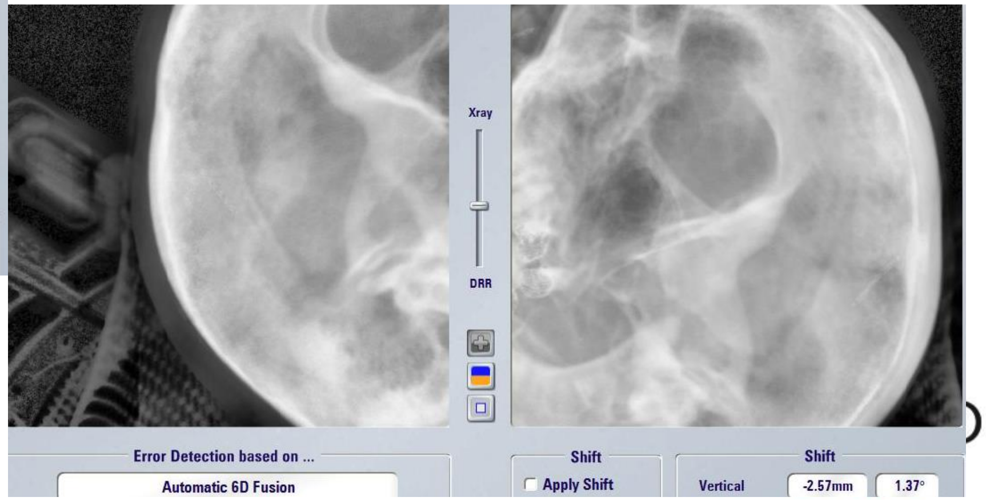
Intrafraction monitoring with stereoscopic kV: example of clinical application: Brain SRT



- 1 mm tolerance
- Image (and re-position) after every new couch angle
- Automatic fusion with visual review

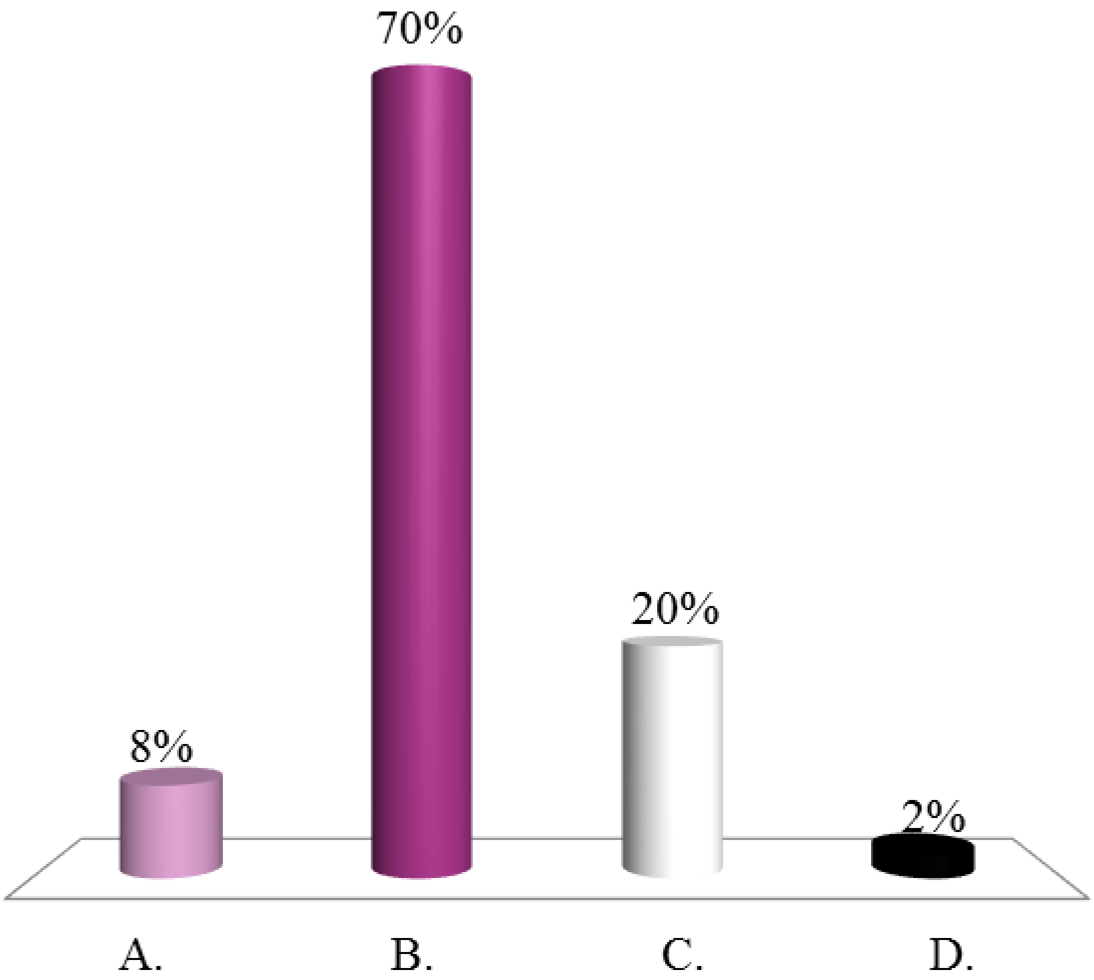






If you had unlimited resources (time/equipment), what do you think you would use?

A. Only CBCT
B. Mostly CBCT, but I still see some cases where planar imaging is preferrable
C. Mostly planar kV, CBCT only where a real benefit is demonstrated
D. I'm not sure, actually !



Conclusion

Planar imaging is widely available, and provides an excellent set-up/monitoring strategy when a match on markers or bony anatomy is possible/desired

It is an interesting option for intrafraction monitoring

It has clear advantage in terms of speed (especially stereoscopic systems) and, possibly, dose

Don't throw away your MV imager just yet: potential for "beam's eye view" and as a dosimetry tool

Trend towards increasing use of volumetric imaging

Take home message

- You can perform high quality treatments with planar imaging modalities (both kV and MV)

- Lower visibility (e.g. Lower soft tissue contrast) may mean you need to use larger margins

- Think of how your imaging modality fits into the larger picture:
  - Simple 3D treatments and planar MV
  - High modulation high precision treatments: needs more information (CBCT)

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WWW.ESTRO.ORG/SCHOOL

kV-cone beam CT/In-room kV-CT

MV CT

Uwe Oelfke

ICR/ RMH London
Joint Department of Physics
uwe.oelfke@icr.ac.uk

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Why volumetric radiologic imaging for IGRT?

- 3D definition of anatomy (volumetric imaging) in the treatment room
- CT with full FOV and adequate e^--density quantification for dose calculation
- CT images are widely accepted and familiar with radiation oncologists (delineation target and OAR)
- Single modality when compared with planning CT

Generic Features

kV vs MV

Fan Beam vs Cone Beam

Current status of RT delivery devices

C-Arm (Standard configuration):

- Multileaf collimators (2.5mm to 10mm leaf width)
- Multiple photon and electron energies
- Flattening filter free photon beams
- kV Cone Beam Computed Tomography
- Support non-coplanar treatments

Varian

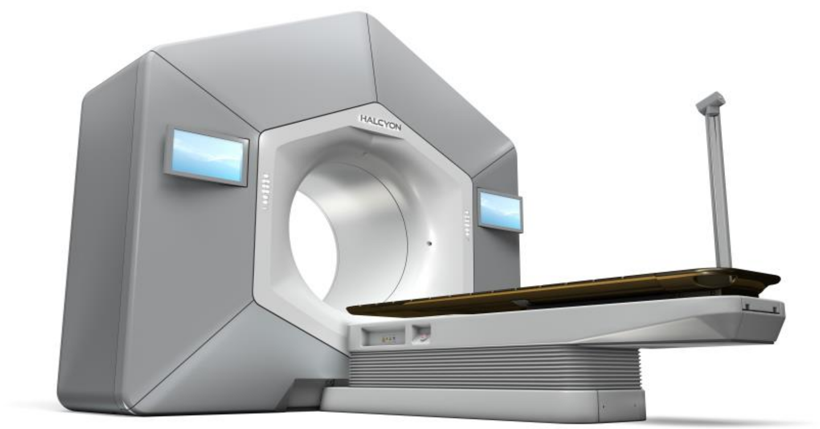
Elekta

Sources: Manufactures web site

Current status of RT delivery devices

Non C-arm systems:

- Single photon energy
- Flattening filter free photon beam



Halcyon (Varian)

Radixact (Accuray)

- Dual layer MLC (1cm leaf width)
- MV CBCT (kV upgrade announced)
- 28x28cm^2 field size

- Binary MLC (64 x 6.25mm)
- MV CBCT (kV upgrade announced)
- 40x5cm^2 max collimator opening
- 10 RPM gantry rotation

Sources: Manufactures web site

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Current status of RT delivery devices

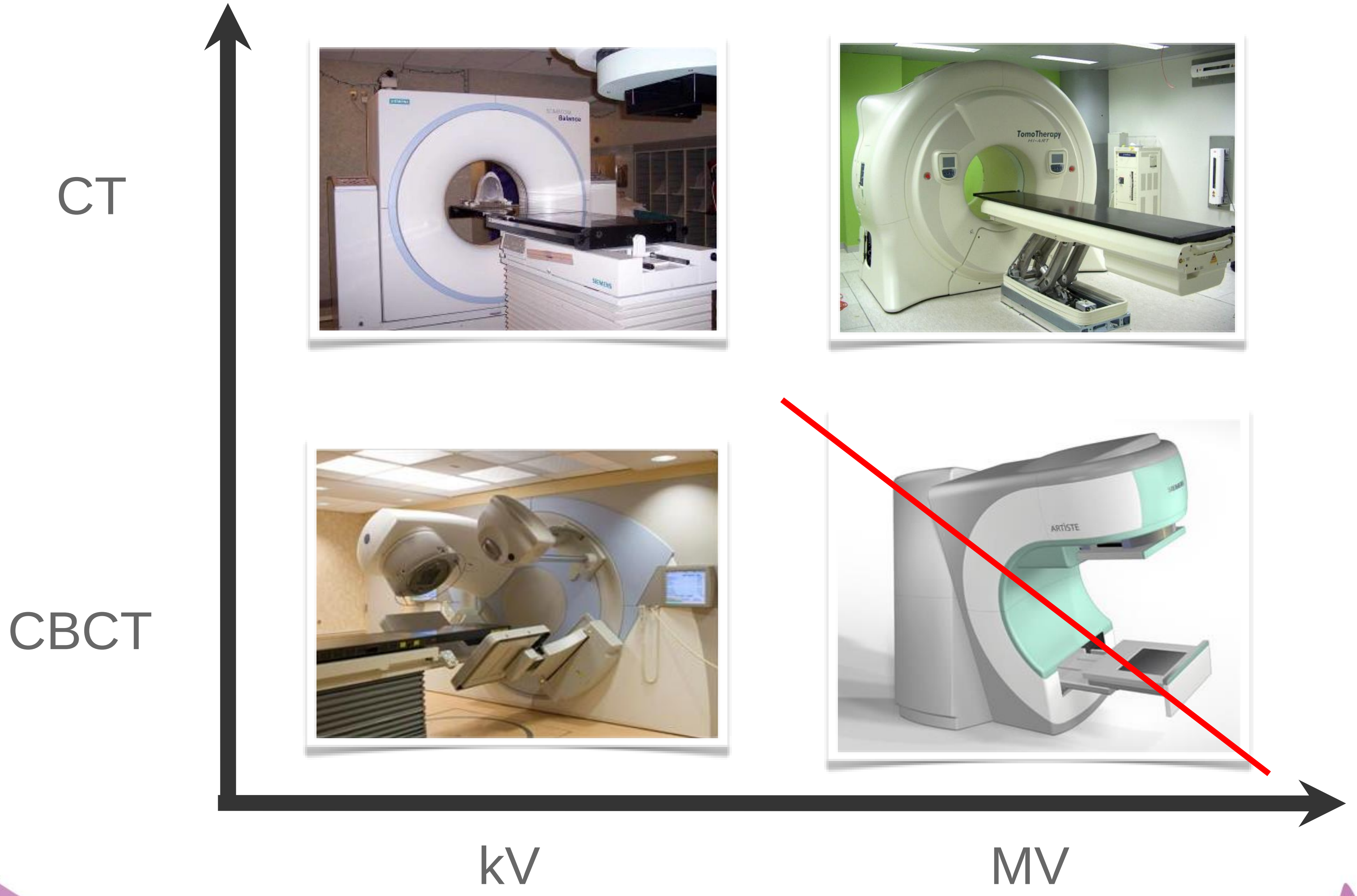
Cyberknife (Accuray) system

- Single photon energy
- Flattening filter free
- Fixed (circular) or variable (IRIS) collim
- MLC:
  - 11.5 x 10 cm^2
  - 3.85mm leaf width

- Stereoscopic kV imaging

Sources: Manufactures web site

Volumetric imaging systems for IGRT



kV vs MV - Contrast

Attenuation Process	Mass coeff. dependence		
Raleigh scattering	Z		
Photo-electric effect	Z^3	⇨	kV
Compton scattering	(only e^- density)	⇨	MV
Pair production	Z^2		

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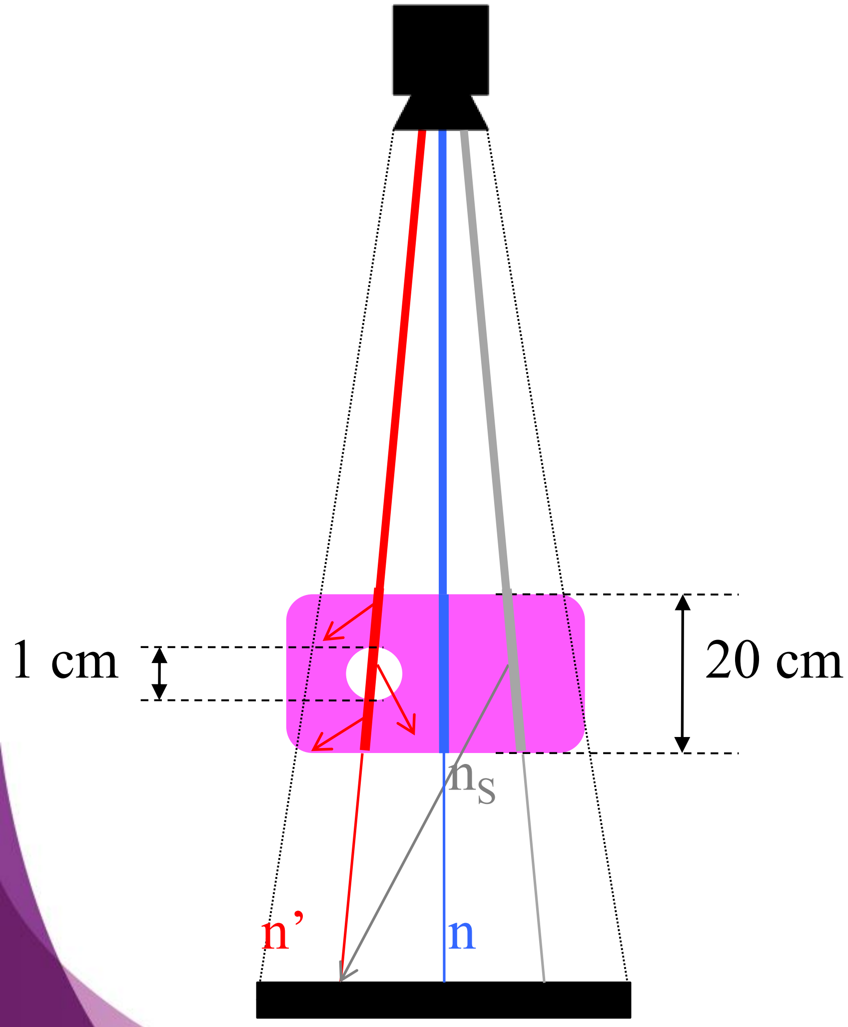
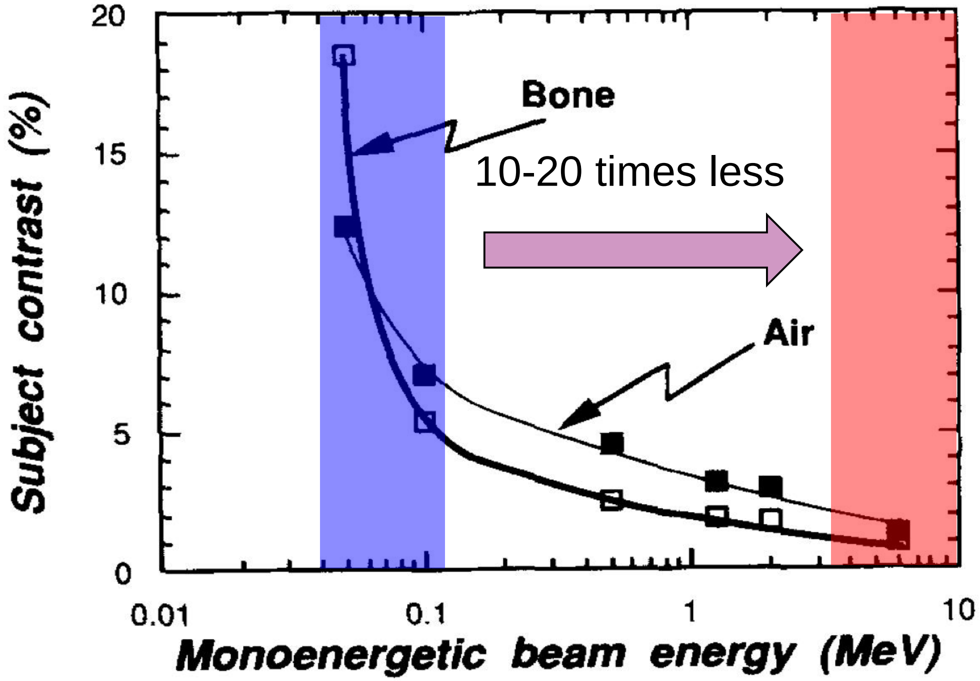
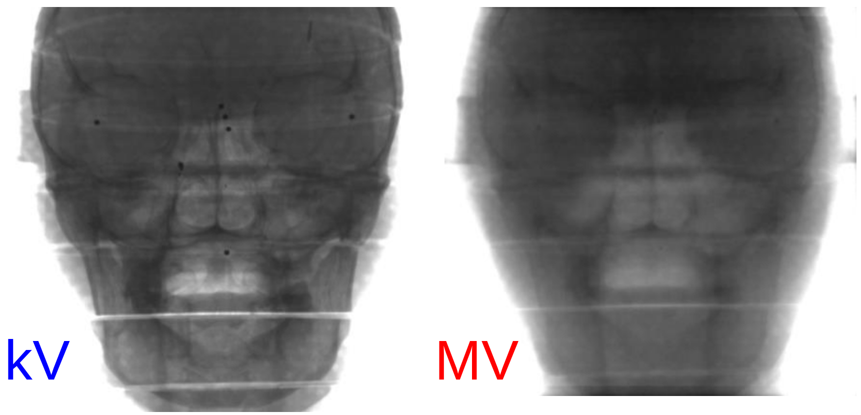
kV vs MV - Contrast

"Impact of imaging beam spectrum on image quality"





Energy	S
50 kV	18.5 %
1.25 MV	1.8 %
2.00 MV	1.4 %
6.00 MV	1.0 %

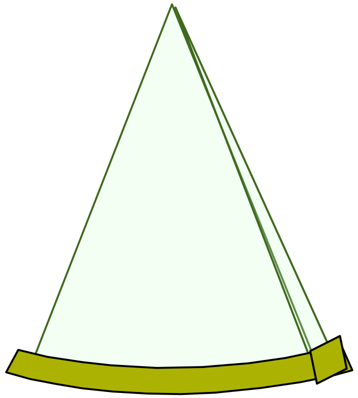


A. Boyer et al. Med. Phys 1992;19(1)

Volumetric IGRT systems: Fan Beam vs. Cone Beam

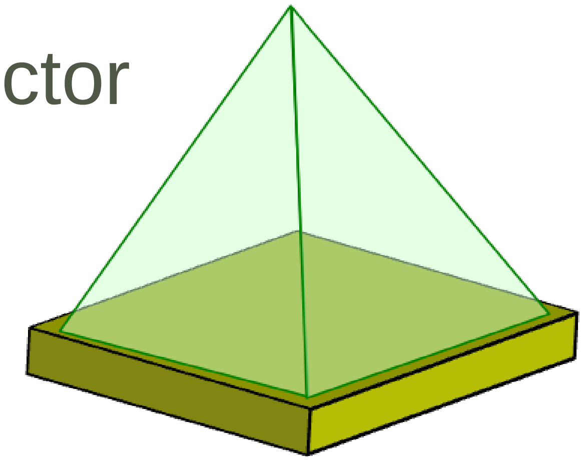
➔ Fan beam systems:

- Fan beam / linear detector array
- In room kV CT
- Helical Tomotherapy: MV CT



➔ Cone beam systems:

- Open beam / large area flat panel detector
- MV CBCT
- kV CBCT



Fan beam CT vs. Cone beam CT

(same radiation quality)

Advantages of FBCT:

- Efficient, ‘optimized’ detectors
  - ➢ Ionisation chambers, ultra-fast ceramics
  - ➢ Detectors are shielded against scattered radiation
- Reduced scatter (imaging a smaller volume per rotation)
- Faster gantry rotation

➡ FBCT Image quality > CBCT Image quality

X-ray based IGRT technologies

TABLE I. Commercially available CT-based IGRT systems.

Make and model		Elekta XVI	Varian On-Board Imager	Siemens Artiste	TomoTherapy	Siemens Primatom
Imaging configuration		kV-CBCT	kV-CBCT	MV-CBCT	MVCT	kVCT-on rails
Field of view		50 × 50 × 25.6	45 × 45 × 17	40 × 40 × 27.4	40 cm	50 cm
Correction method	Translation	Automatic couch motion	Automatic couch motion	Automatic couch motion	Automatic in 2 directions	Manual couch motion
	Rotation	Optional	None	None	Optional	Optional
Geometric accuracy		Submillimeter	Submillimeter	Submillimeter	Submillimeter	Submillimeter
Dose (cGy)		0.1–3.5	0.2–2.0	3–10	0.7–3.0	0.05–1
Image acquisition and reconstruction time		2 min	1.5 min	1.5 min	5 s per slice	3 s per sec

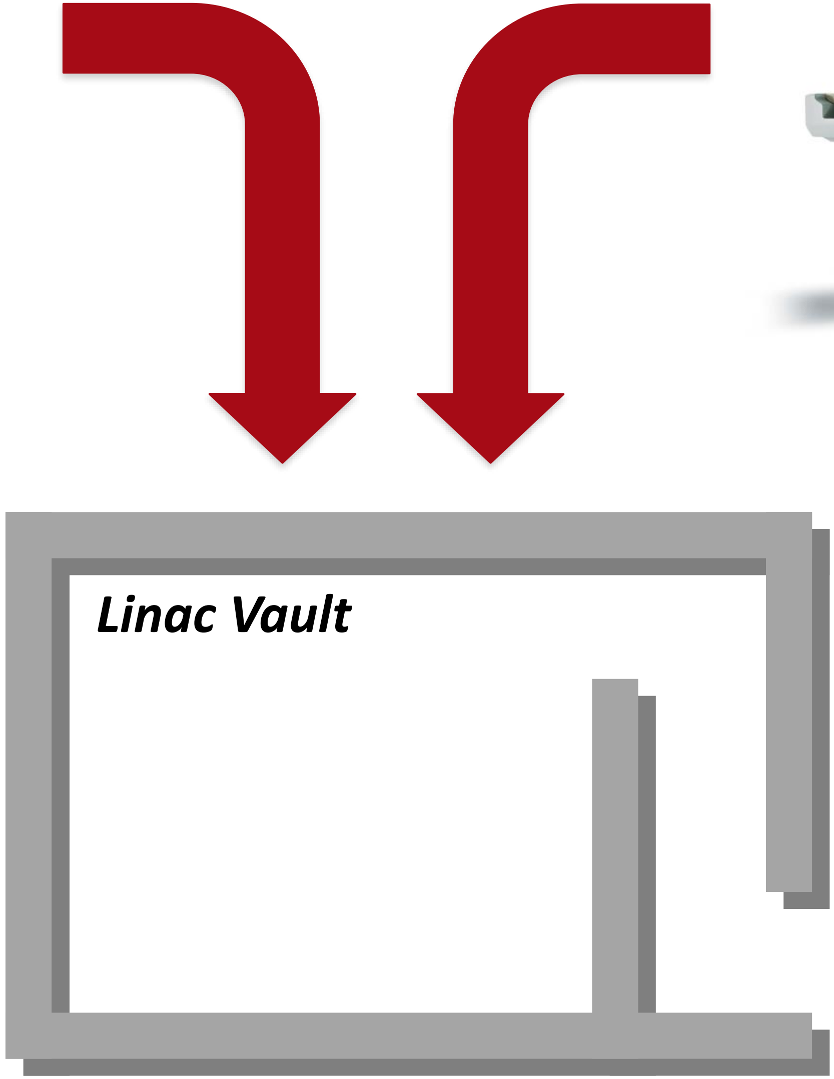
Bisonette et al. AAPM TG 179

Medical Physics, Vol. 39, No. 4, April 2012

Linac + CT (in the same room)= In-room CT IGRT?

RT Linac

Diagnostic CT scanner



In-room CT-on-rails setup

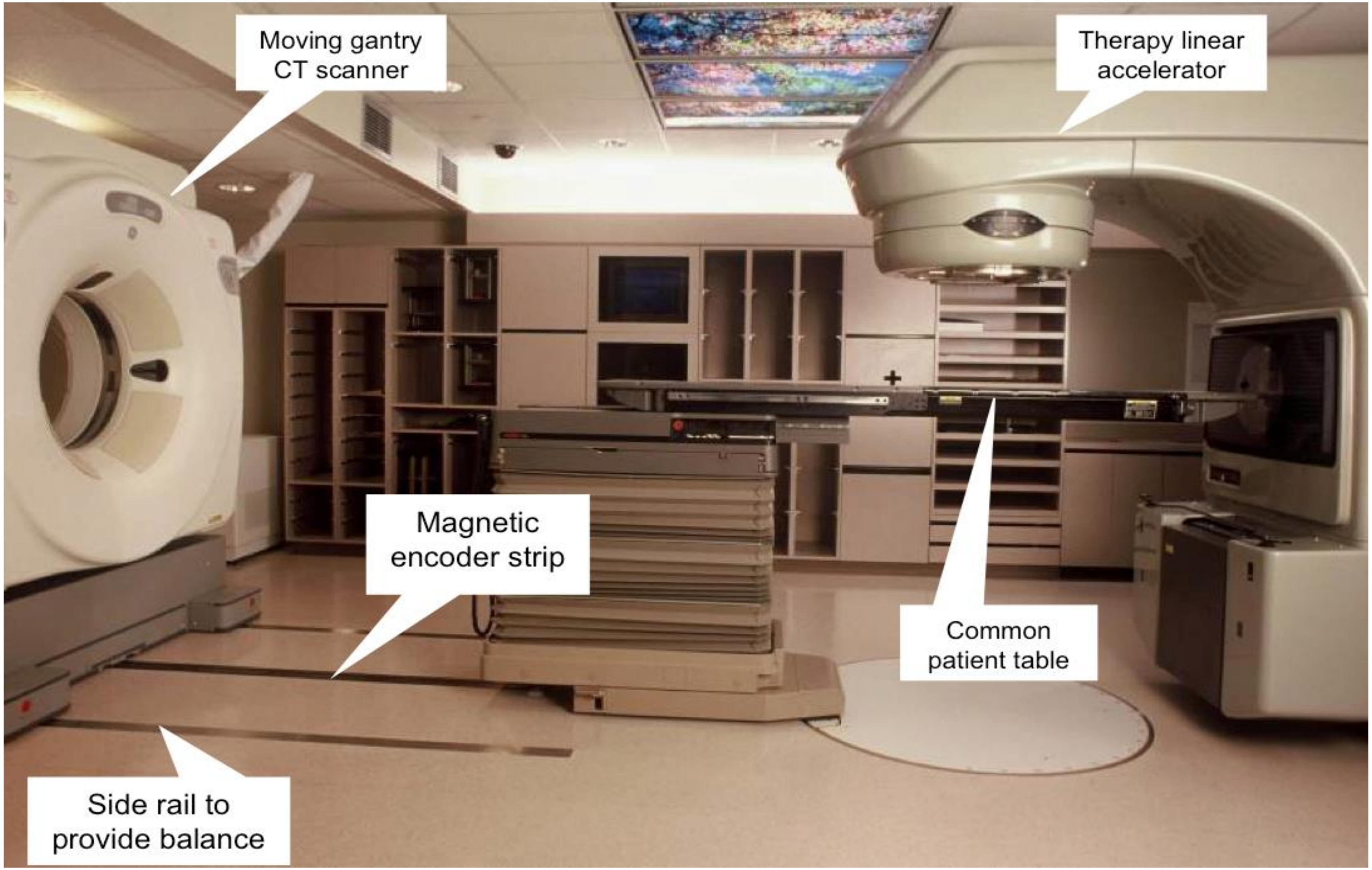
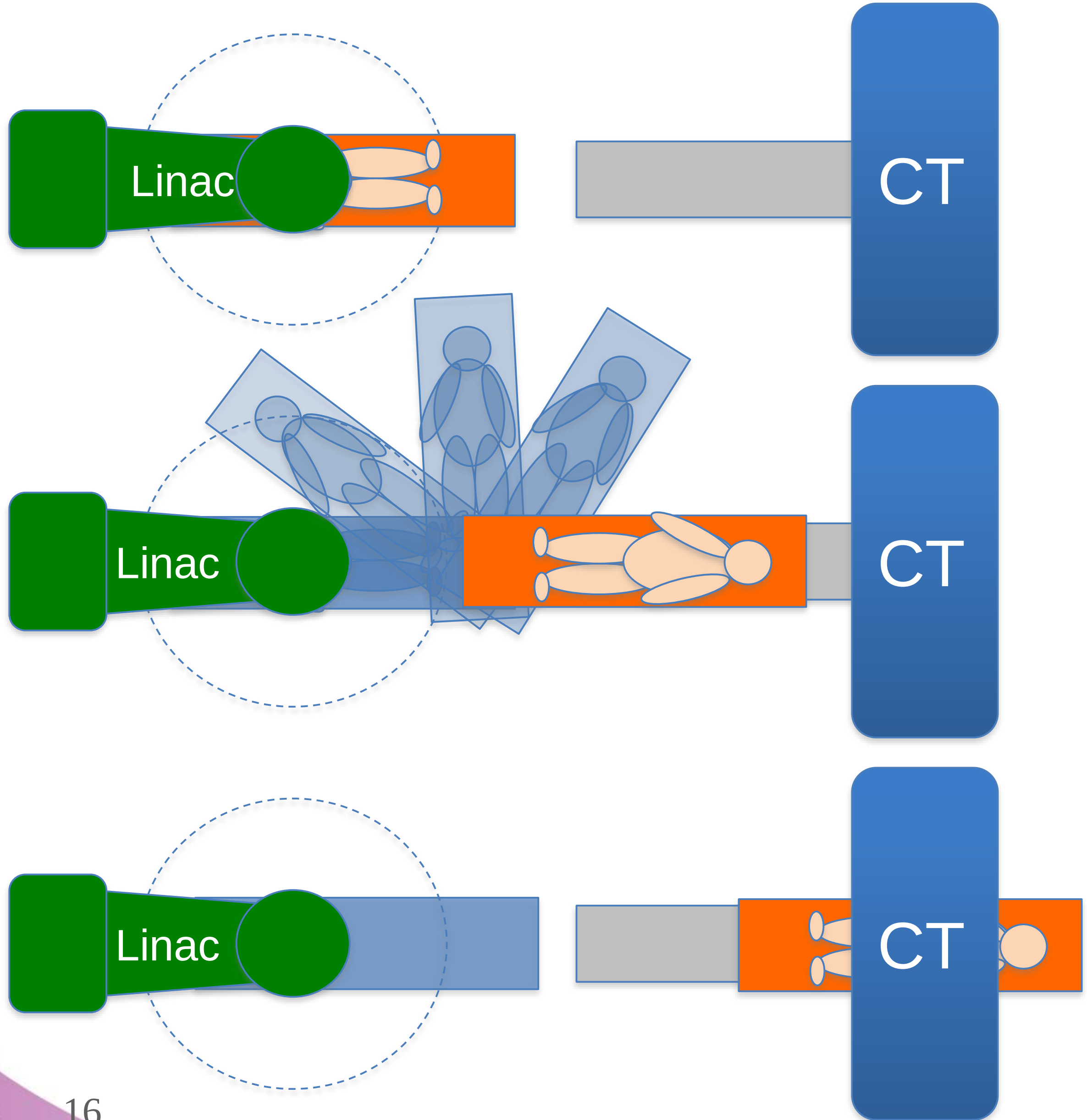


Figure 4. A CT-on-Rails system combining a GE Smart Gantry CT scanner and a Varian 2100EX linear accelerator was installed at the M.D. Anderson Cancer Center. After rotating the couch 180 degrees, a patient can receive a CT scan while in the immobilized treatment position just prior to the start of radiation treatment.

In-room CT setup



Initial setup on linac

↓

Transportation Patient to the CT

↓

CT image acquisition

→

Image fusion, Calculation shifts

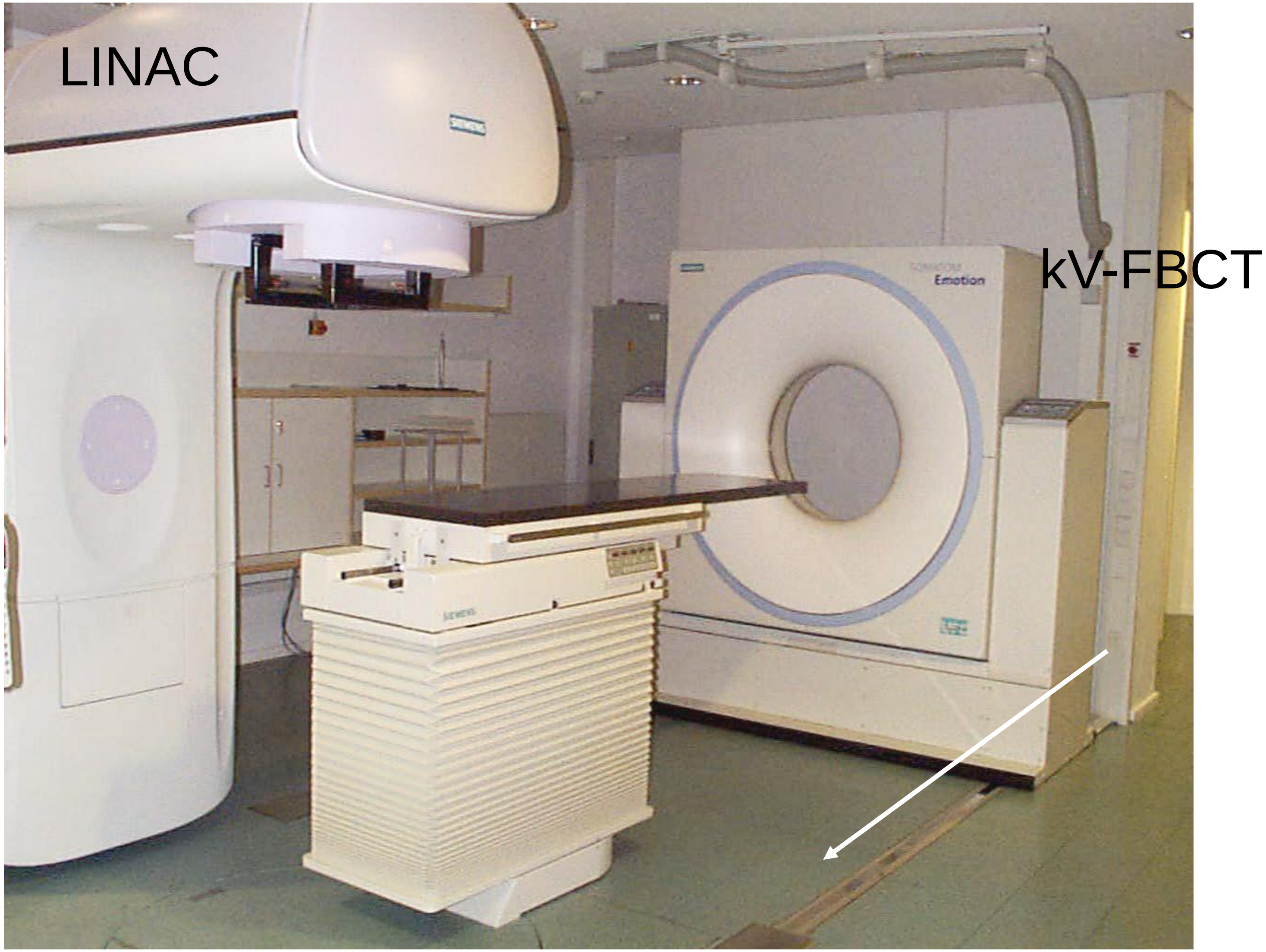
↑

Transportation Patient back to the linac

↑

Apply shift corrections, start treatment

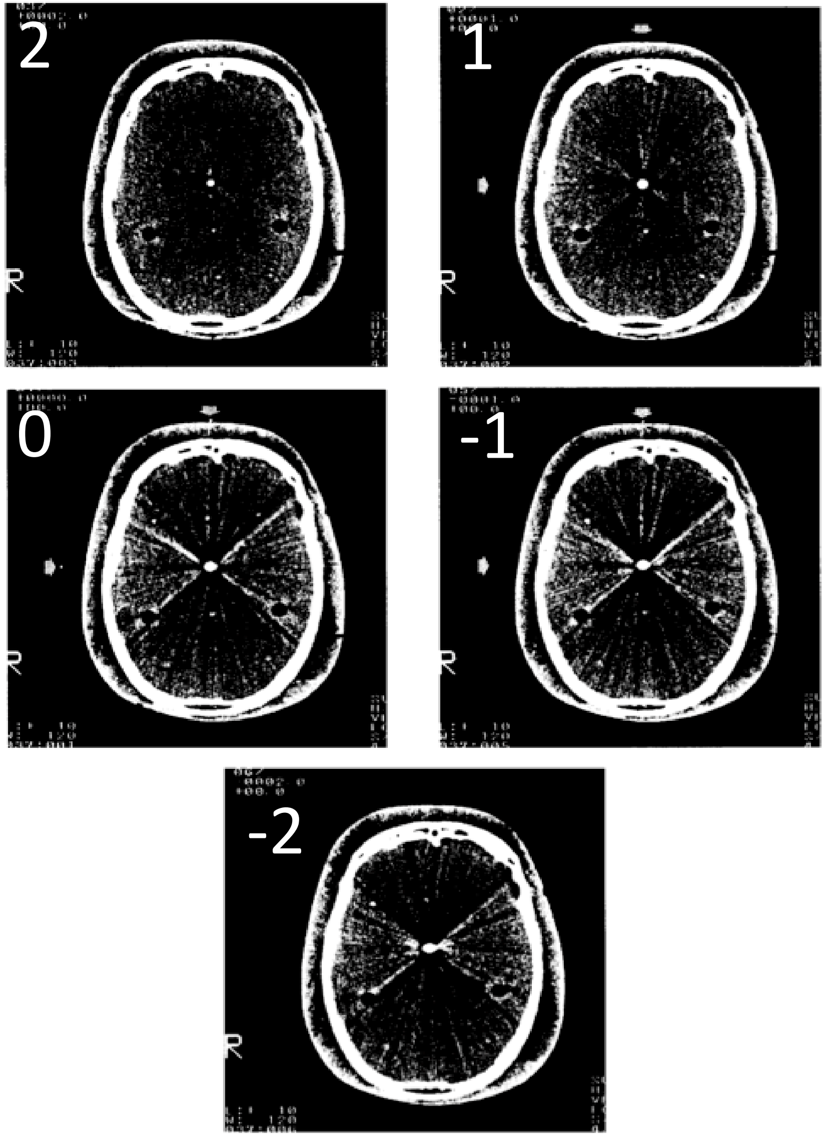
In-room kV-CT PRIMATOM



Patient positioning with CT-on rails

In-room CT setup

Common Linac-CT isocenter verification



Uematsu et al. 1996.

In-room CT

- Features
  - Diagnostic image quality (single-slice, multi-slice helical CT, 4D)
  - Short scanning times
  - Large FOV 50 -70 cm diameter
  - Isocenter calibration of the image has to be done
    - Stereotactic frame
    - Surface markers
  - Patient has to be moved

In-room CT

- ‚Diagnostic‘ image quality
  - ➢ Easy registration with planning CT, alignment of GTV
  - ➢ Reliable Hounsfield-units
    - ▪ Adaptive planning, re-planning

- Imaging doses
  - ➢ 2 – 10 mSv/Scan
  - ➢ well suited for adaptive planning, re-planning

In-room CT imaging dose

CT-guided treatments

– Multiple, repeated imaging

• 42 fractions for prostate treatments

– Low CT dose becomes a concern

Head & Neck

Scout:120kV,20mA

• HelicalScan

– 3mm thickness – 1.0 pitch

– 120kV, 110mA

Prostate

Scout:120kV,80mA

• HelicalScan

– 3mm thickness – 1.5 pitch

– 120kV, 200mA

One film = 6 - 8 MU

• Two orthogonal films each week,8 weeks of treatment, assuming no repeat films.

– 96-128MU~100cGy

• Typical prescription for prostate=7560cGy

• Typical prescription for head&neck=7000 cGy

~ 1.3% of prescription dose for prostate

~ 1.4% for prescription dose for head&neck

CT dose:

~2 cGy x 42 = ~84 cGy

Dong et al.

MV Based Imaging

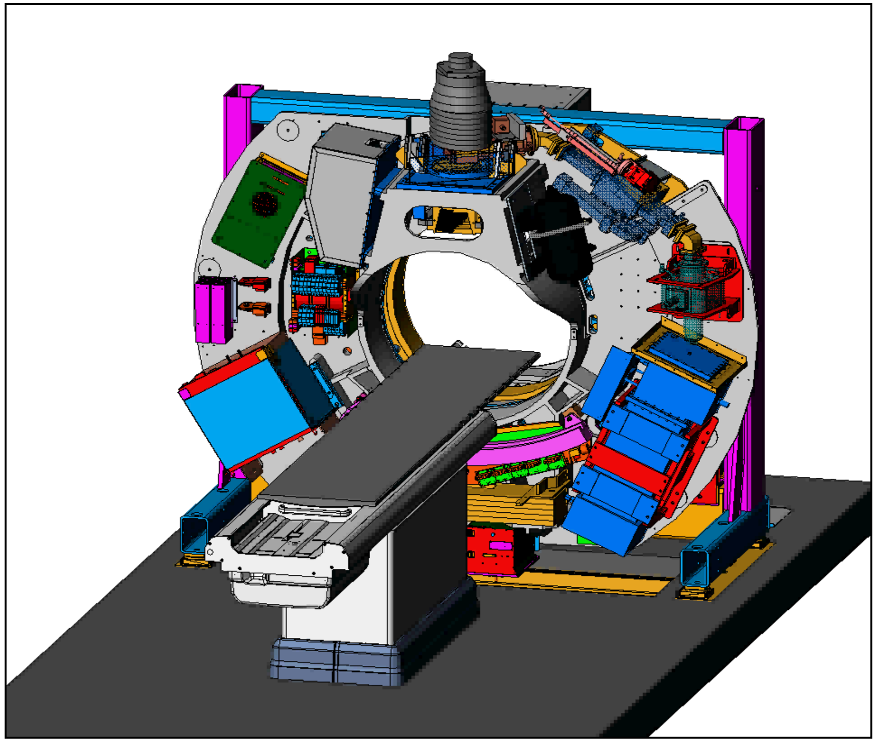
➔ General principles:

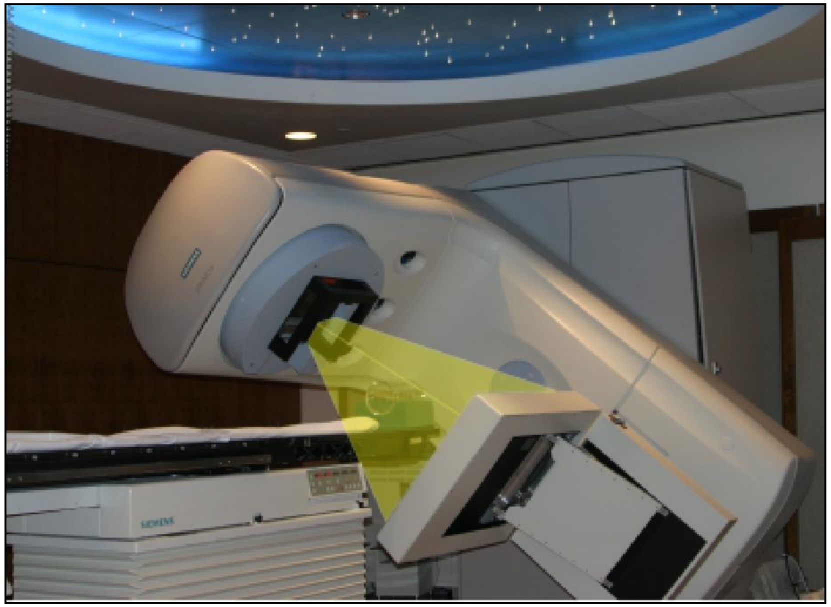
- Advantage: The actual treatment beam is used for imaging, therefore it provides direct geometric information concerning alignment of treatment beam and target
- Disadvantage: MV-based image quality will always be inferior to kV-based.

Advantages of MV tomography IGRT

- Actual treatment beam used for imaging
  - Direct geometric alignment
  - Beam has been modeled in TPS and concomitant IGRT dose can “easily” be incorporated into dose calculation.
- 3D volumetric imaging, no surrogates required.
- CT-CT registration, similar information
- Registration of dose distribution and anatomy possible
- No high-Z artifacts
- MV-CT usable for dose calculation and dose reconstruction

Same* beam used for imaging and treatment





- Alignment and calibration of system straightforward (identical beam axis, identical isocenter)
- Potential for dose reconstruction based on transmission measurements using CT-of-the-day

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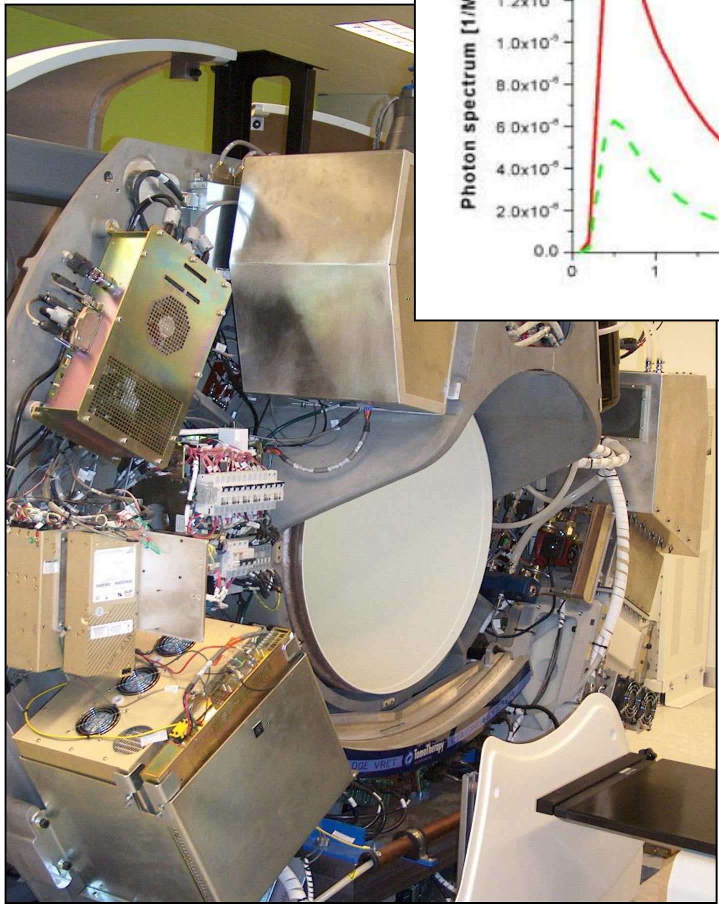
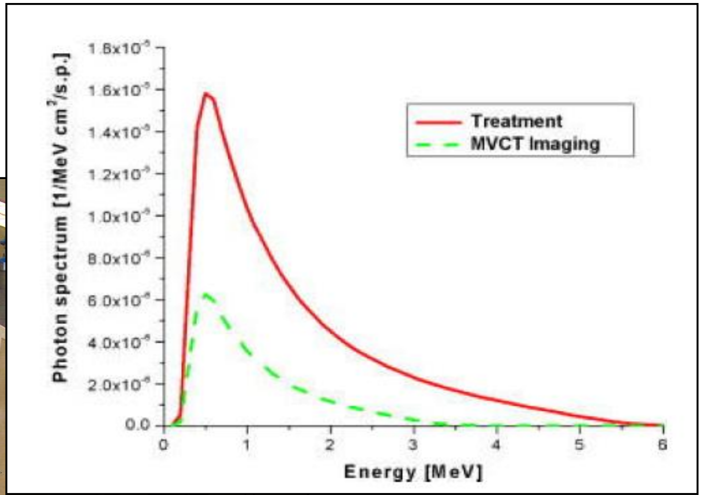
* … not really the same…

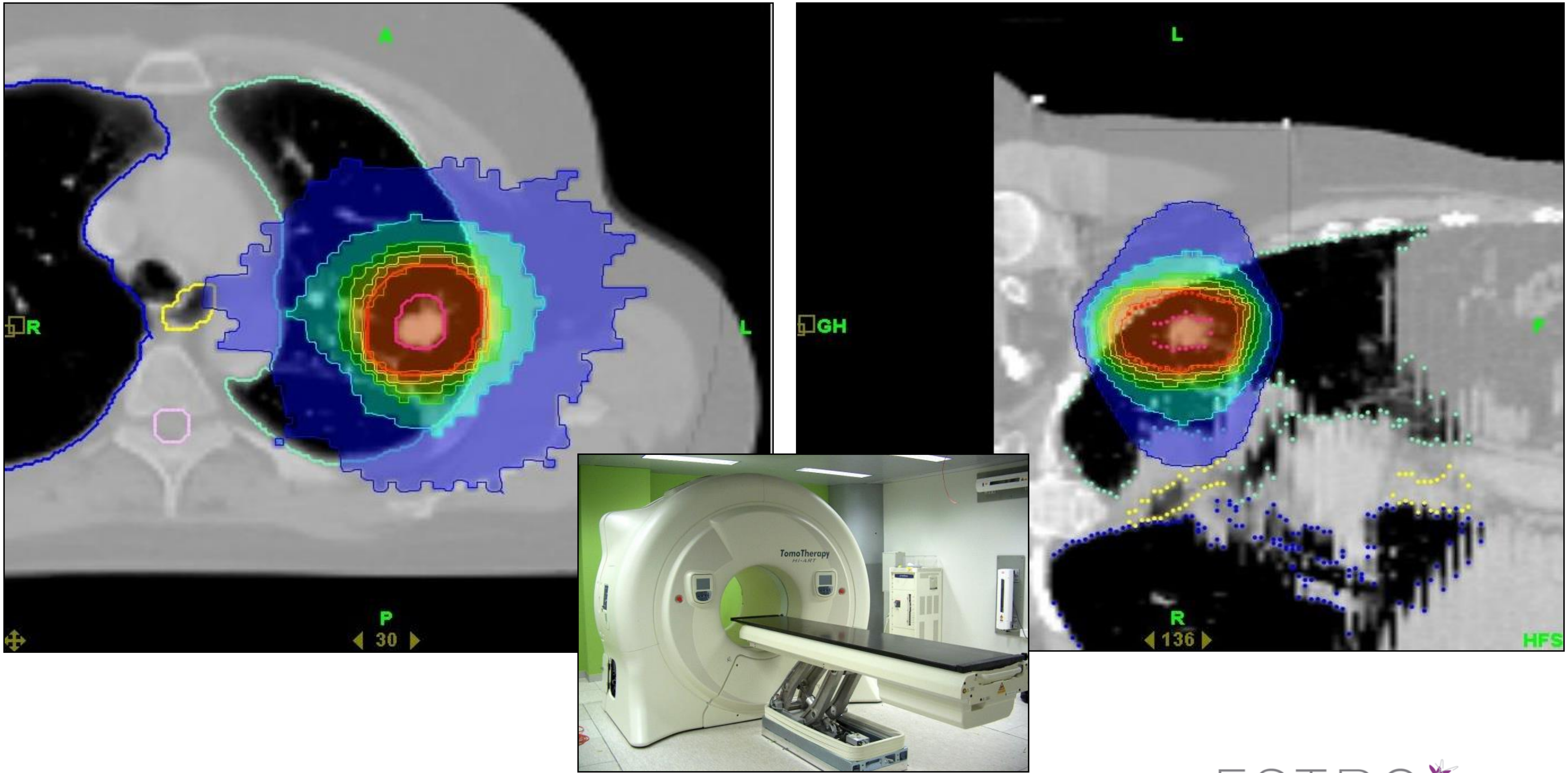
MV CT: Characteristics



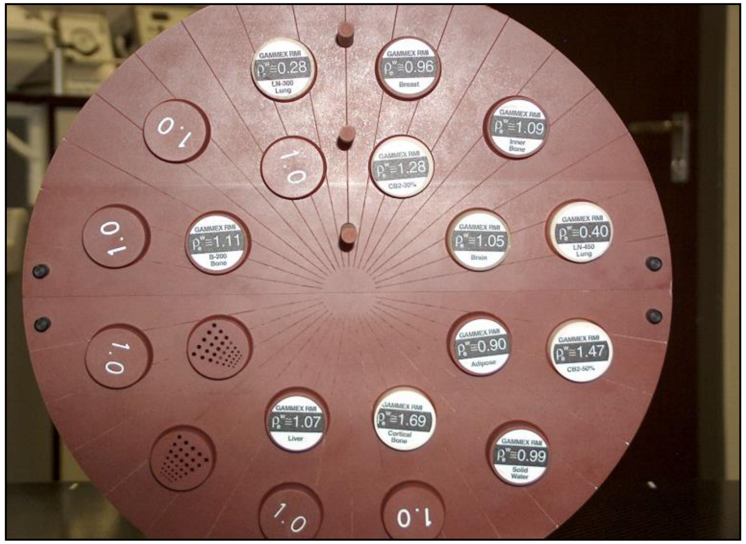


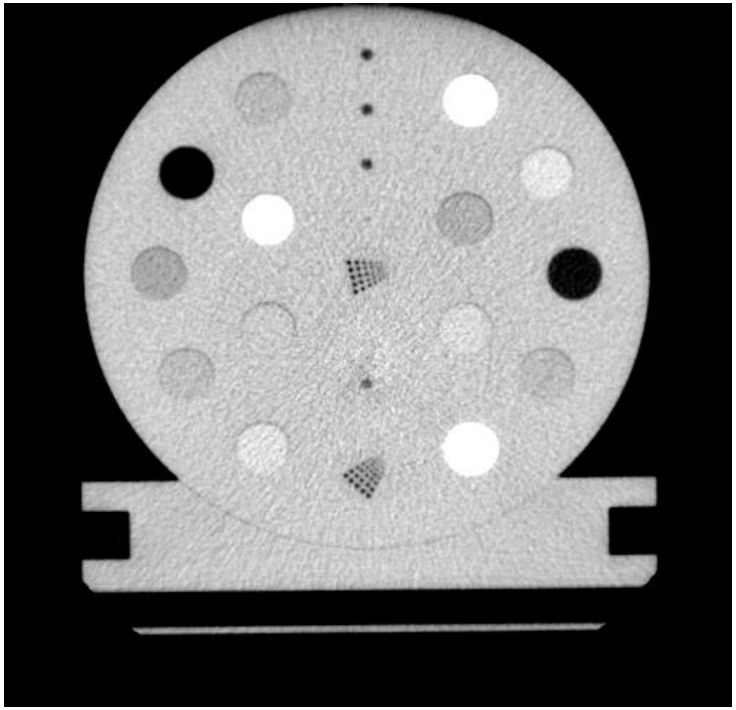
- ➔ Fan beam:
  - "de-tuned" treatment beam from 6MV to 3.5MV
- ➔ Lowered dose rate:
  - from 899 cGy/min to 11 cGy/min
- ➔ Xe-detectors (640 channels)

MVCT (dose based positioning)



MV CT: for dose calculation





- HU-to-electron density conversion can be used for dose calculation
- No high-Z artifacts (advantage for target delineation and dose calculation in presence of prosthesis)
- FOV: 400 mm diameter, but MV and kV set can be merged using the appropriate correlation tables

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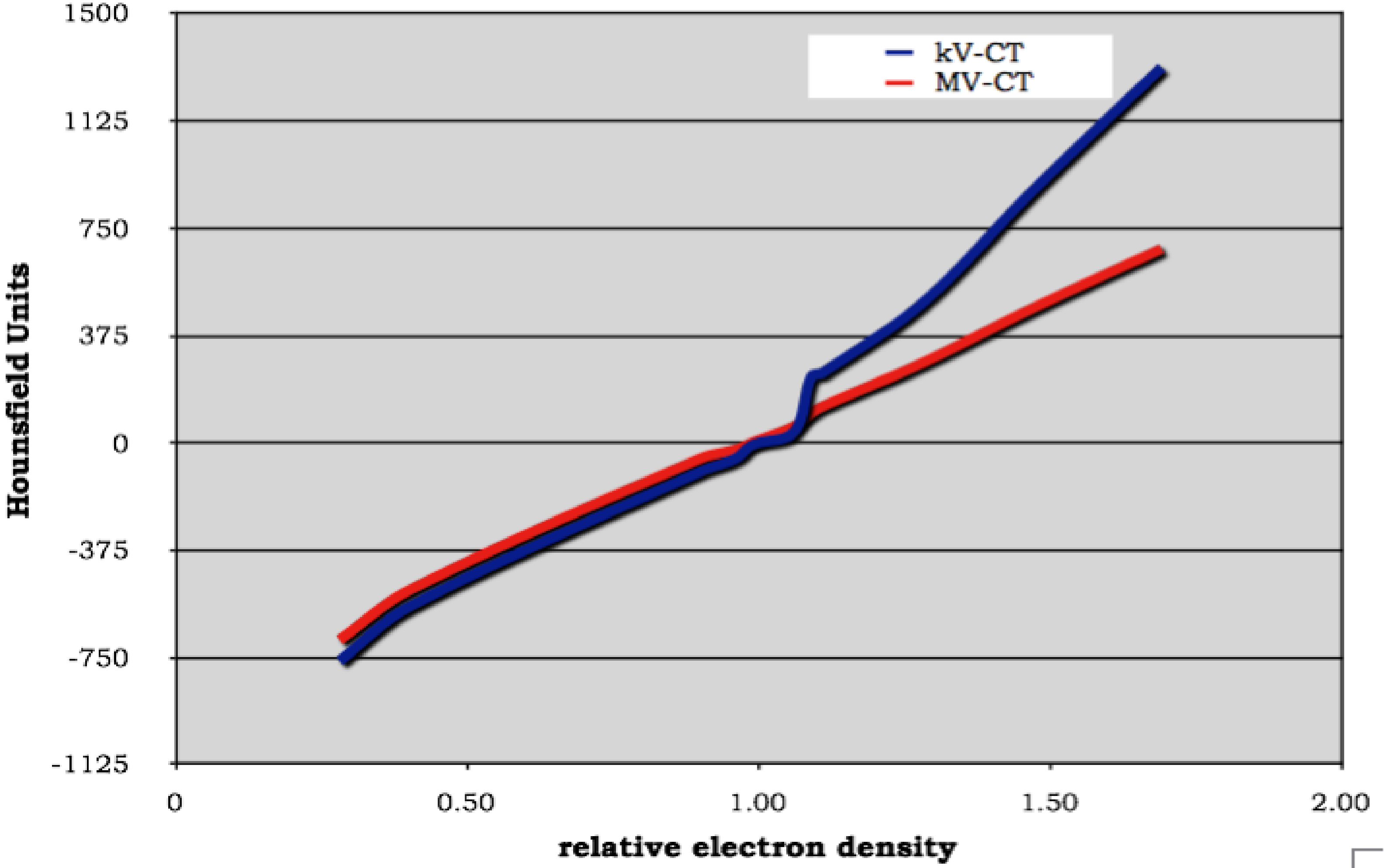
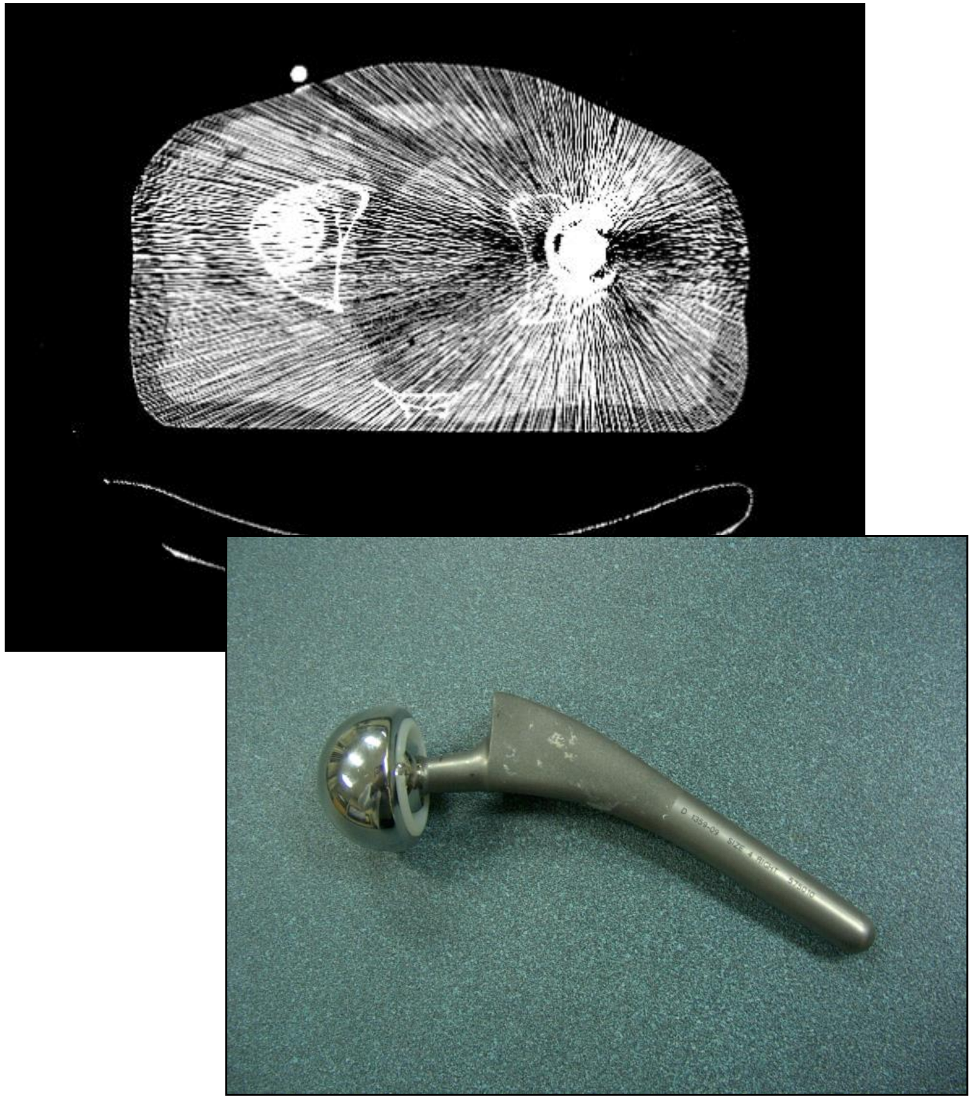
MV CT: for dose calculation

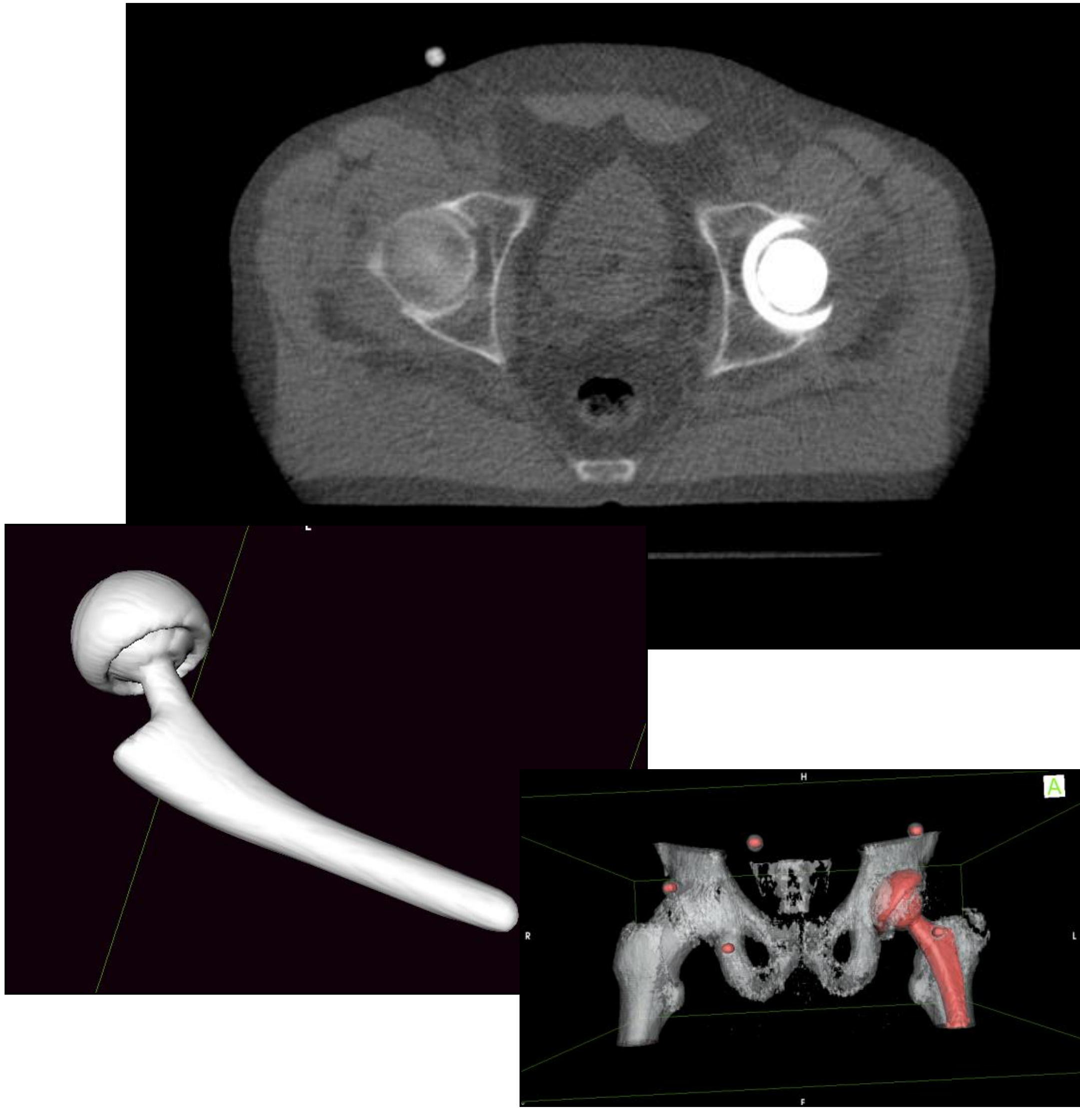


MV CT: for dose calculation

Hip prosthesis : kVCT



Hip prosthesis : MVCT



Conclusion: MVCT/MV CBCT

- Geometric accuracy:
  - MV CT: Mechanical rigidity of the system minimizes geometrical uncertainties.
  - MV CBCT: Geometrical uncertainties are quantified and included in projection matrices and filtered back projection algorithm.
- Image quality:
  - Always worse than planning CT
  - MV CT and CBCT mostly ready to be used for dose calculations
- Patient dose:
  - Depends on what you ask for.

Conclusion: MVCT/MV CBCT

- MV-CBCT and MV-CT present some interesting features for IGRT:
  - Same beam is used for imaging and treatment
  - Potential for dose reconstruction
  - Volumetric imaging

- Difficult to use for monitoring of intra-fraction organ motion

Linac-integrated Cone Beam CT

- kV-Cone Beam CT

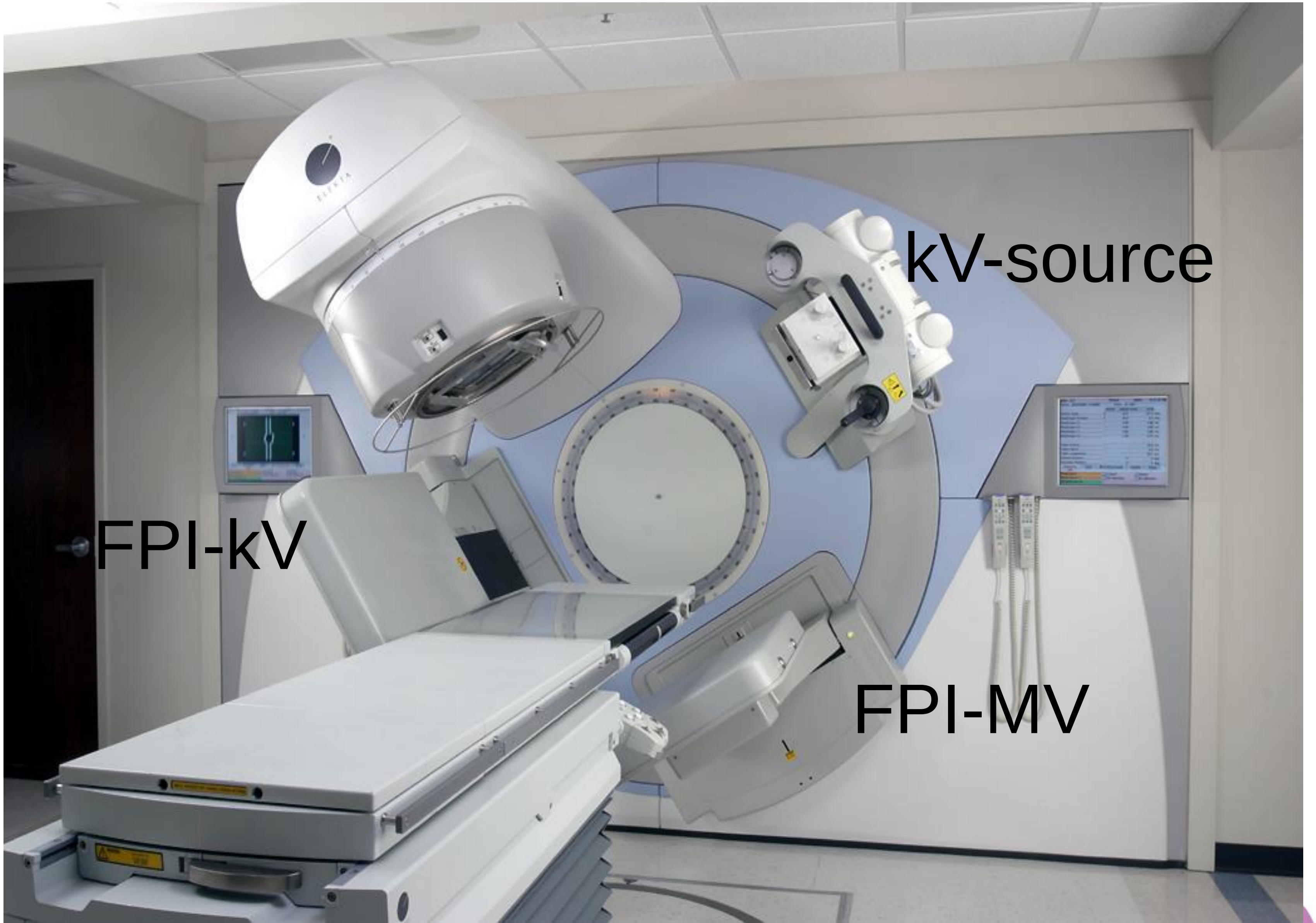
  - Linac integrated Hardware
    - kV-x-ray source
    - FPI Detector

  - Geometry
    - 90° angle between imaging- and treatment beam
    - 180° angle between imaging and treatment beam (only very few systems ....)

Prototype: Elekta Synergy

Courtesy of B. Groh

Elekta - Synergy



ELEKTA Aguility

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VARIAN TRUEBEAM

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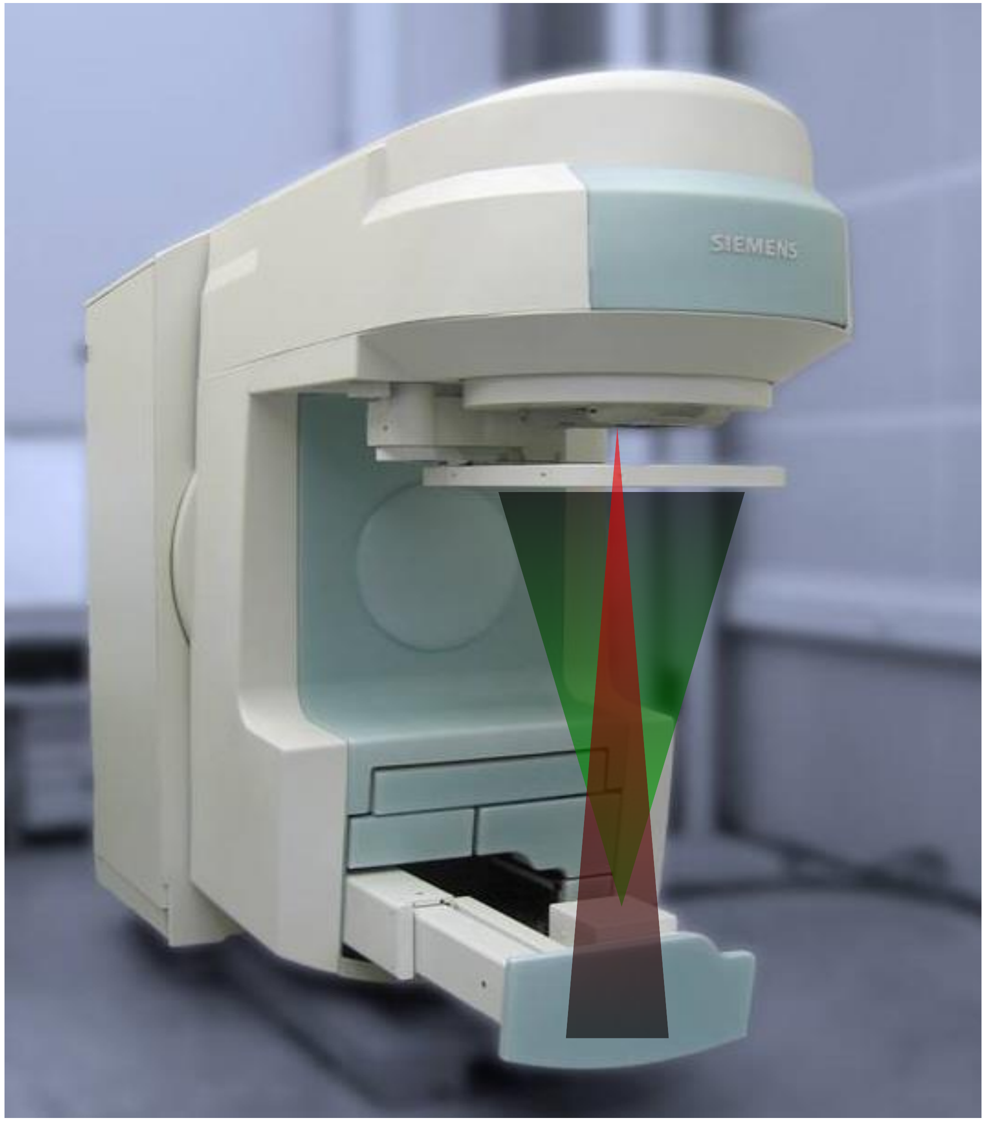
Artiste Linac



- External beam (photon) radiotherapy
- MLC with 160 leafs

- Prototype system
  - + kV inline imaging
  - + Gating
  - + kV CBCT

Scanning modes

- Short scan: 180° + (fan-beam angle) gantry rotation
  - 220 – 440 frames (e.g. head and neck)

- Full scan: 360° gantry rotation
  - 360 – 720 frames (e.g. prostate, extended FOV)

CBCT: limited FOV shifted detector

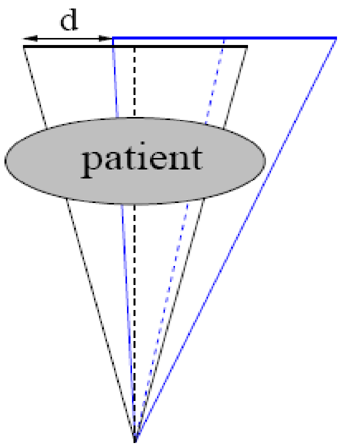
Original FOV: 27 cm

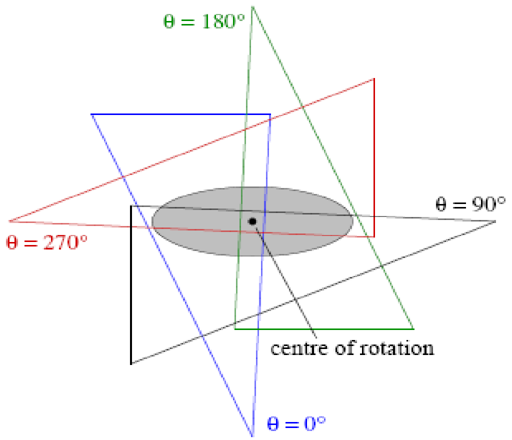
Shifted detect.: 48 cm

detector shift

Method: detector offset

- Approach to enlarge the FOV: lateral shift of the FPI

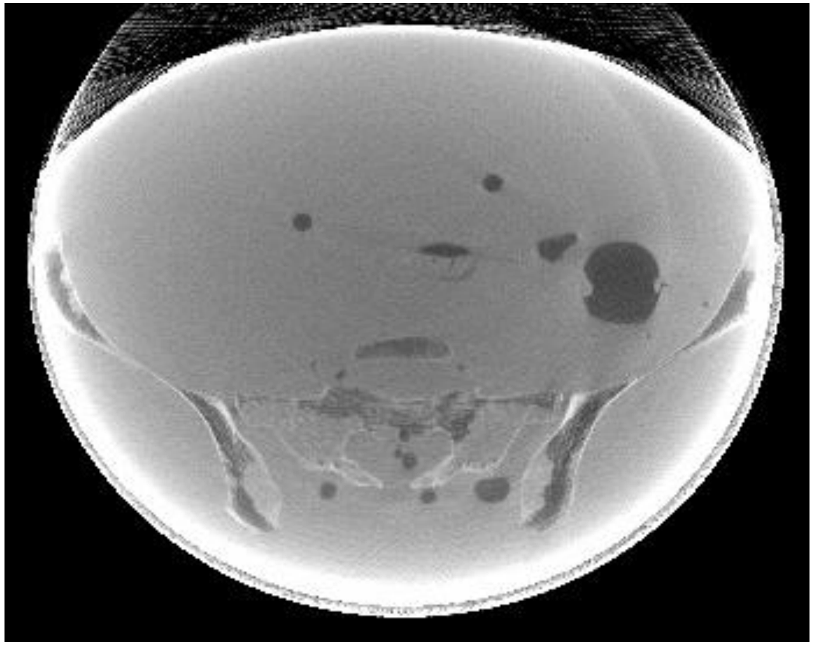




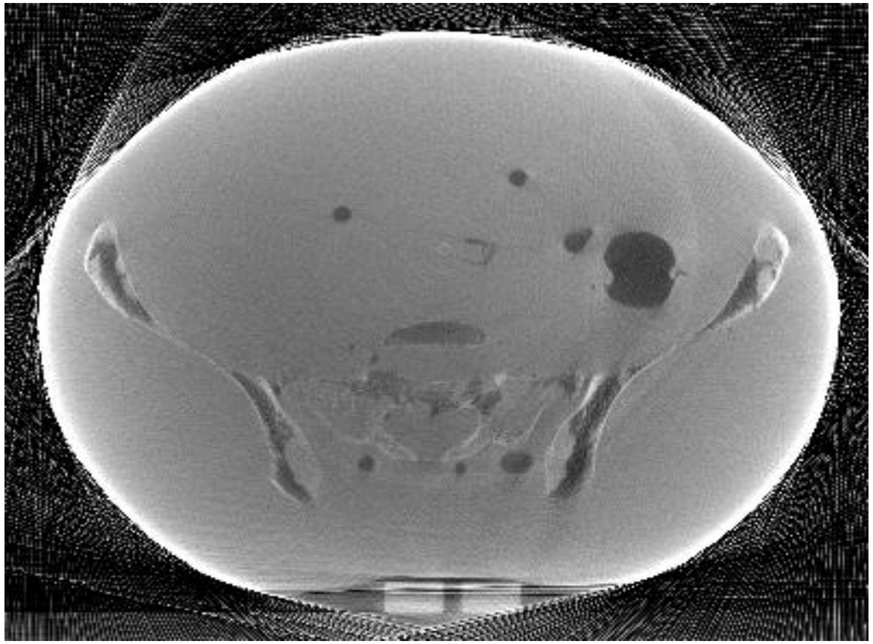
⇒ adaptation of the image reconstruction algorithm required:

Extended FOV

- FOV extension clearly visible
- Truncation artefacts reduced



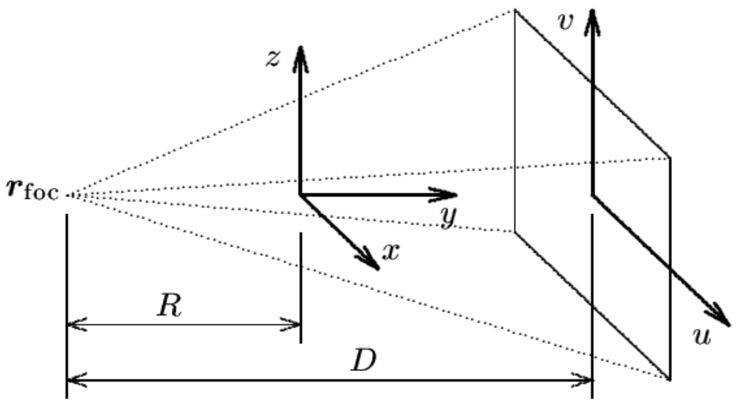
Centered detector



8 cm offset

Ideal imaging geometry

- Ideal projection geometry can be calculated given
  - ➢projection angle
  - ➢distances D (source-to-detector) and R (source-to-isocentre)



⇒ 3x4 projection matrix to map 2D detector (u,v) to (fixed) 3D patient (x,y,z) coordinate system

$$\lambda \begin{pmatrix} u_k \\ v_k \\ 1 \end{pmatrix} = \begin{pmatrix} p_{11} & p_{12} & p_{13} & p_{14} \\ p_{21} & p_{22} & p_{23} & p_{24} \\ p_{31} & p_{32} & p_{33} & p_{34} \end{pmatrix} \begin{pmatrix} x_k \\ y_k \\ z_k \\ 1 \end{pmatrix}$$

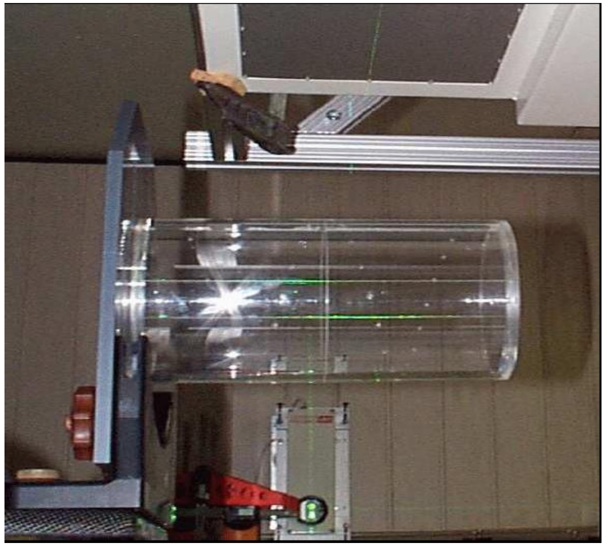
⇒ used for voxel-driven backprojection

Non-ideal projection geometry

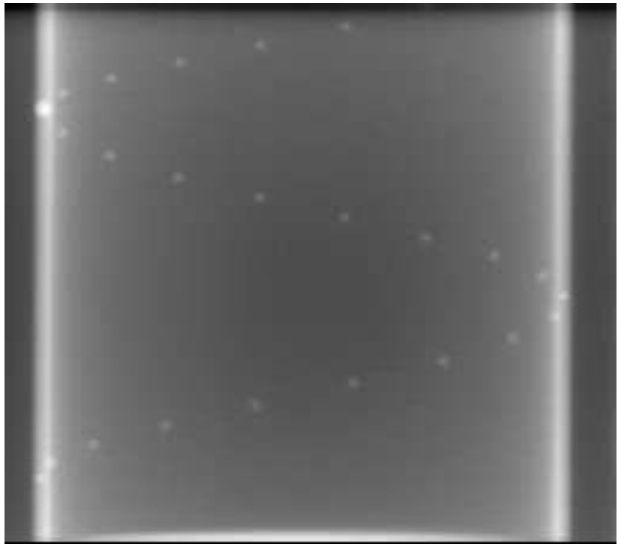
- Real world: projection geometry is non-ideal due to gravitational sag of the imaging hardware

  $\Rightarrow$ determine projection matrix experimentally:

calibration phantom



alignment at the isocentre

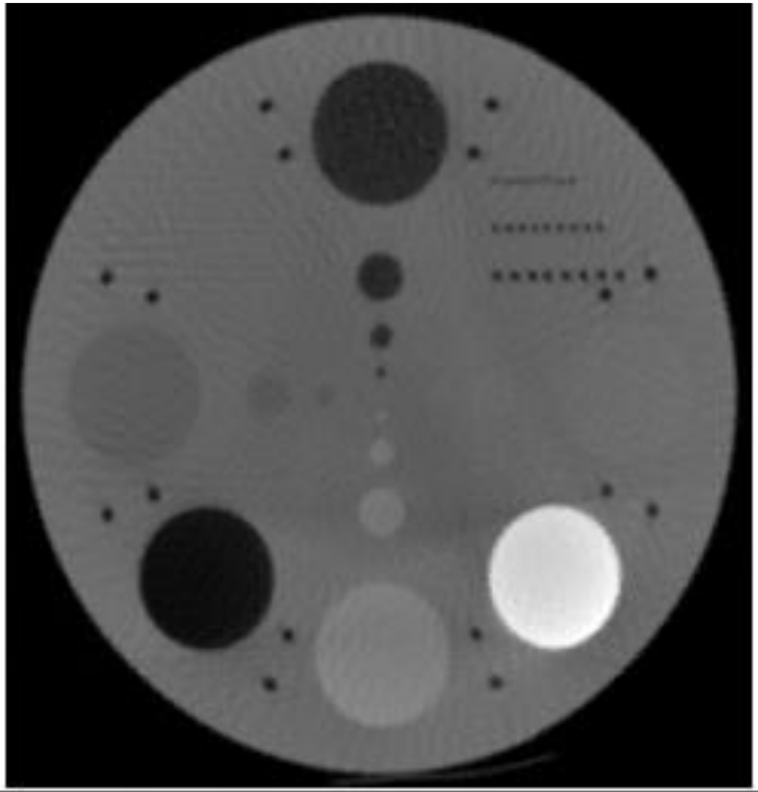


sample projection

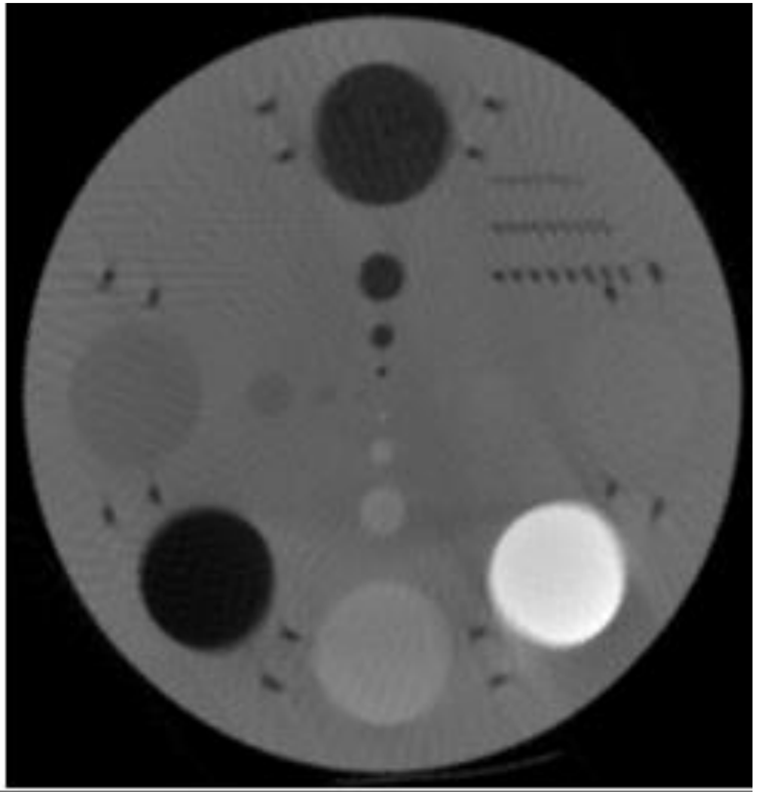
Geometrical calibration

Contrast/resolution phantom

calibrated



Not calibrated



QA Issues

Quality assurance for image-guided radiation therapy utilizing CT-based technologies: A report of the AAPM TG-179

Medical Physics, Vol. 39, No. 4, April 2012

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Initial application of a geometric QA tool for integrated MV and kV imaging systems on three image guided radiotherapy systems

W. Mao et al. 2335 Med. Phys. 38 (5), May 2011

TABLE I. Summary of nominal geometric parameters of imaging systems. SDD is the source-detector distance.

Linac	Energy	SDD (mm)	Detectors Pixel size (mm)	Detectors Dimensions
Trilogy	MV	1500	0.784	512 × 384
	kV	1500	0.392	1024 × 768
SynergyS	MV	1600	0.4	1024 × 1024
	kV	1536	0.8	512 × 512
Vero	MV	2212	0.4	1024 × 1024
	kV	1876	0.4	1024 × 1024

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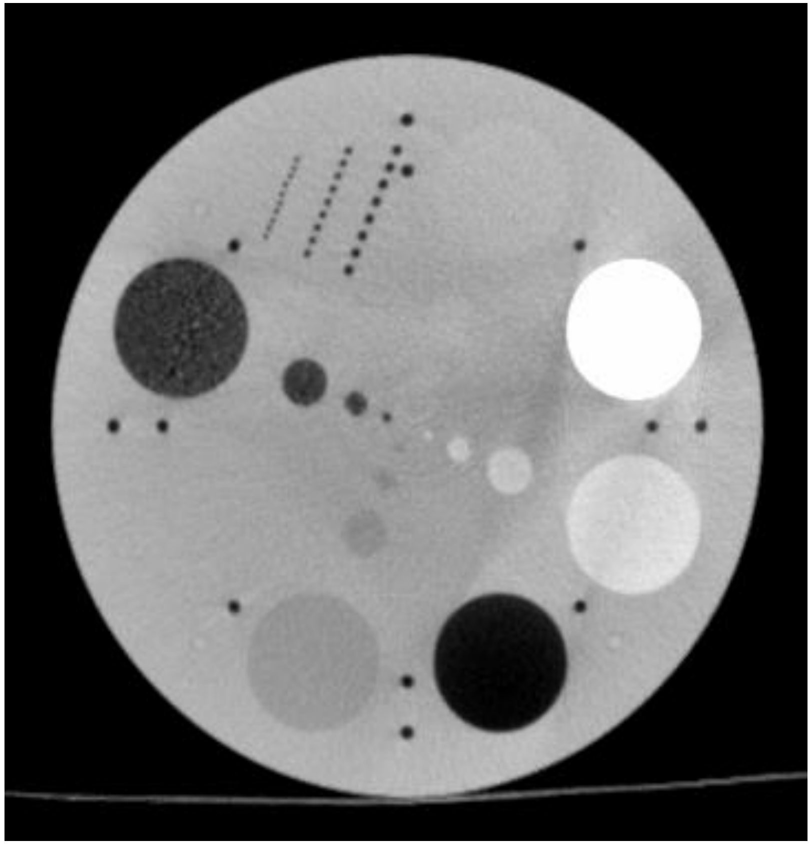
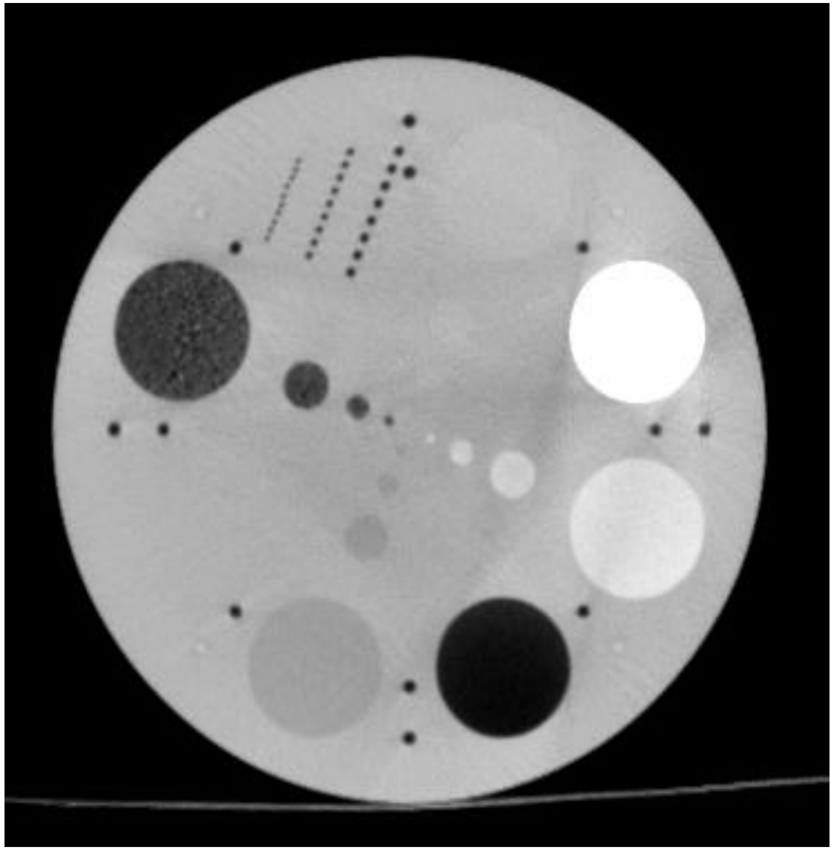
Image Quality and Imaging Dose

- Images: examples
- Images: artifacts
- Images: doses

kV-CBCT: Contrast phantom



1cGy

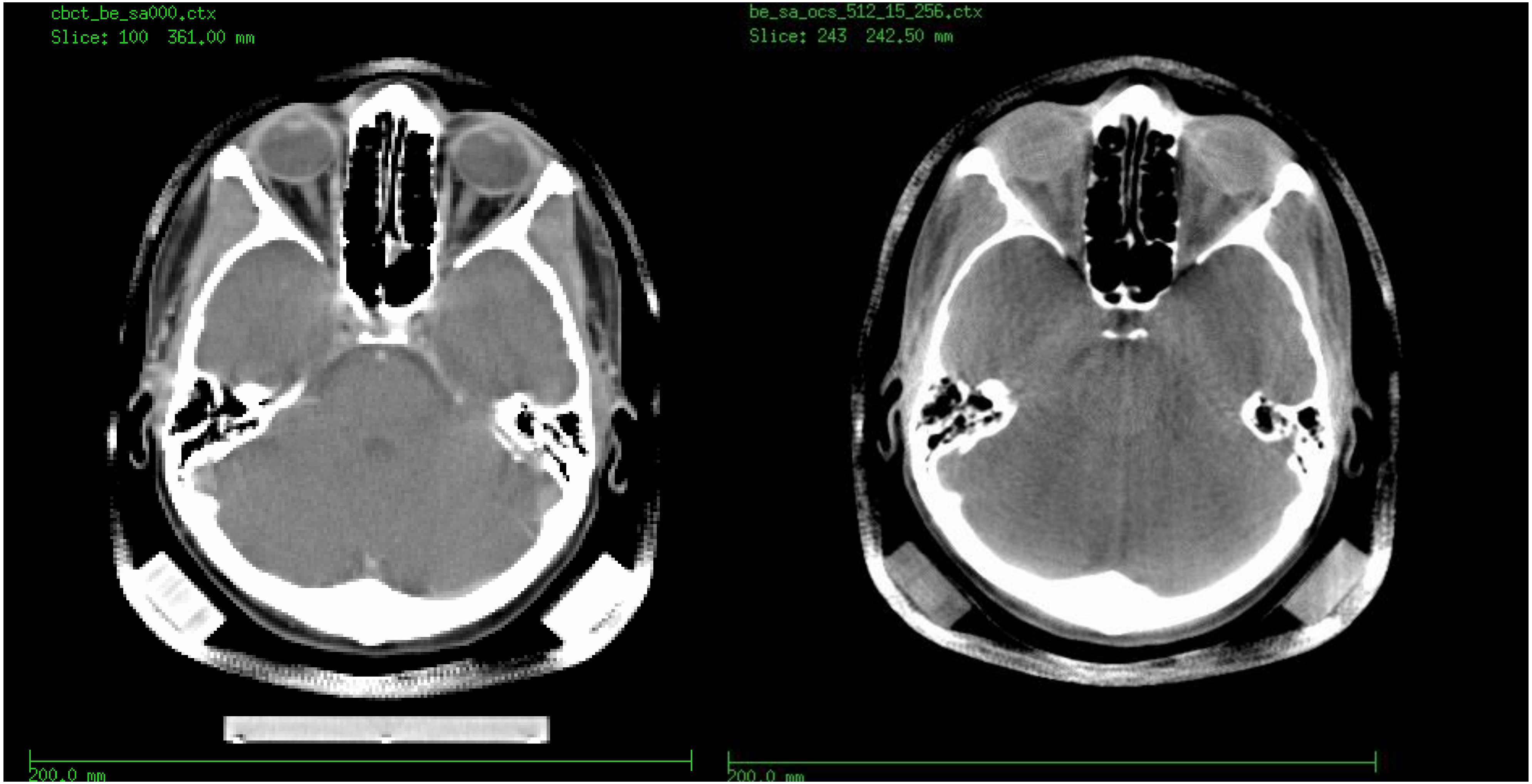


2cGy

440 projections over 220 degrees

Estimated dose at the isocenter

Cone beam CT @ LINAC

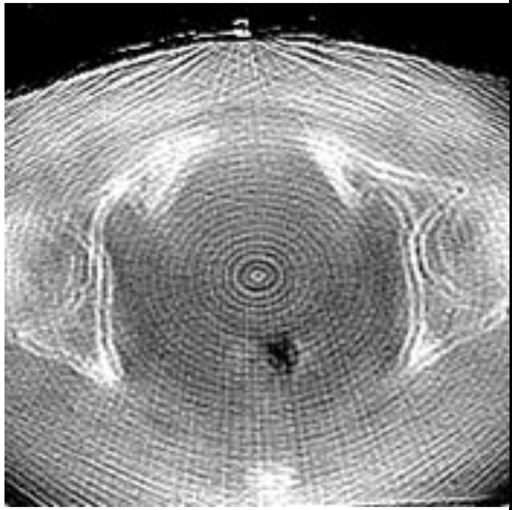


Planning CT

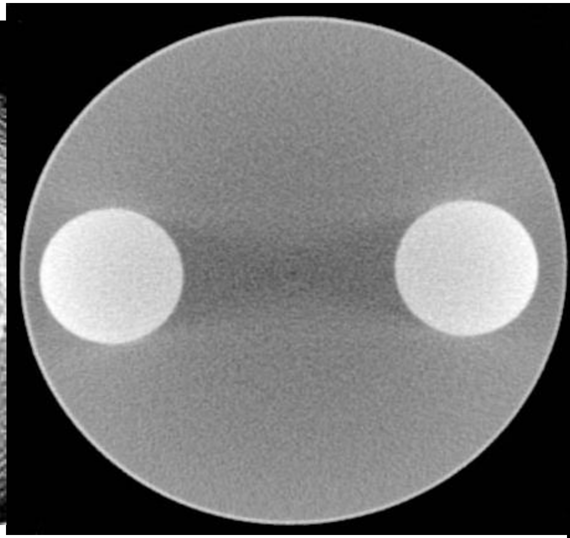
Cone beam CT @Linac

Image Artifacts

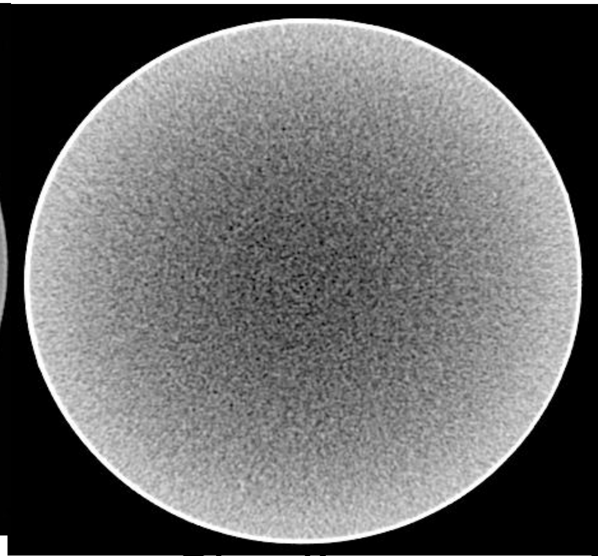
Courtesy of Jeffrey Siewerdsen



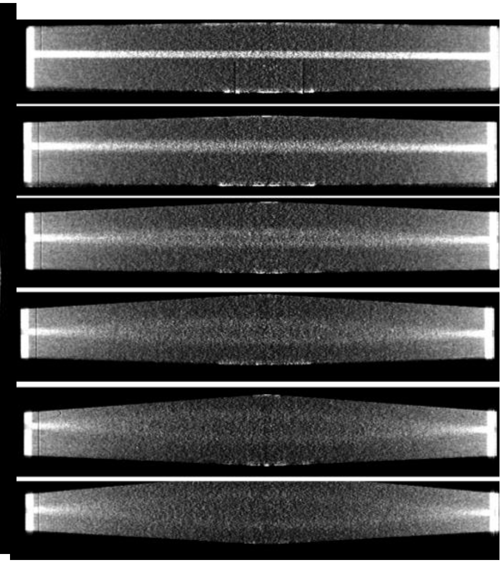
Rings & flex



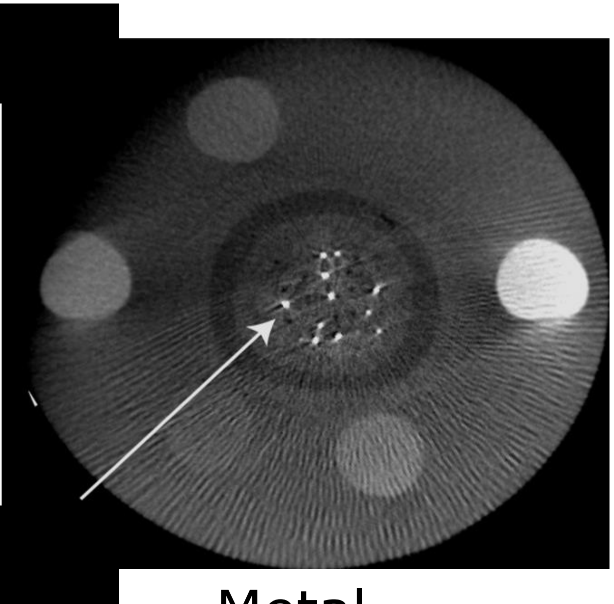
Streaks



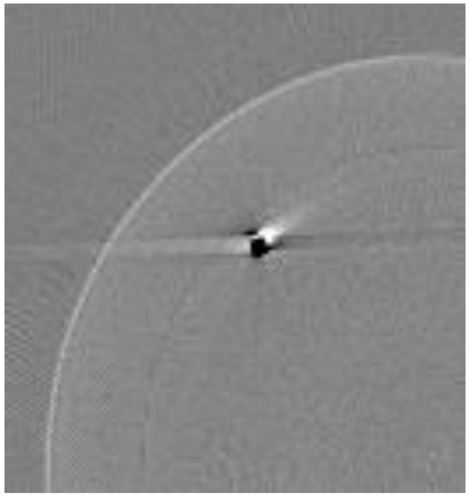
Shading



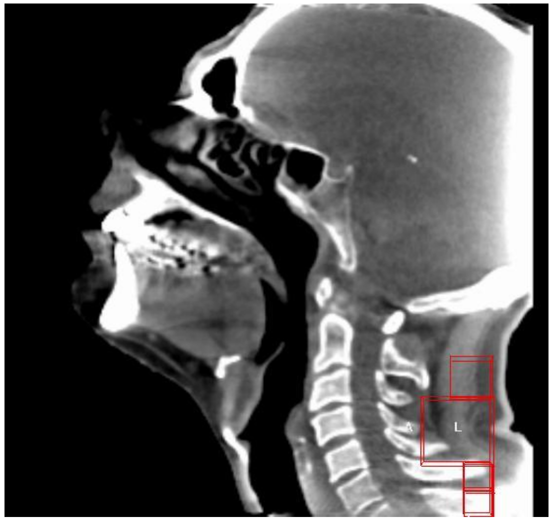
de Frise



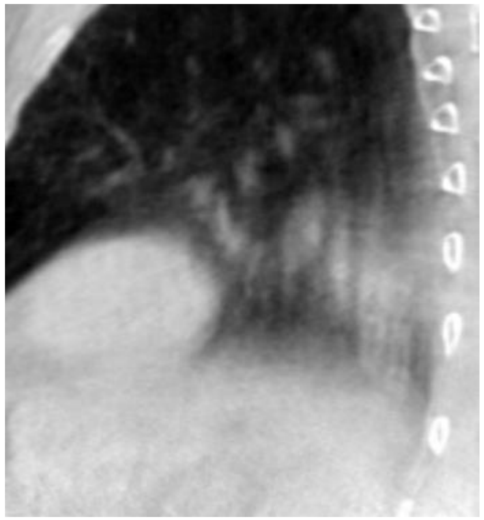
Metal



Lag

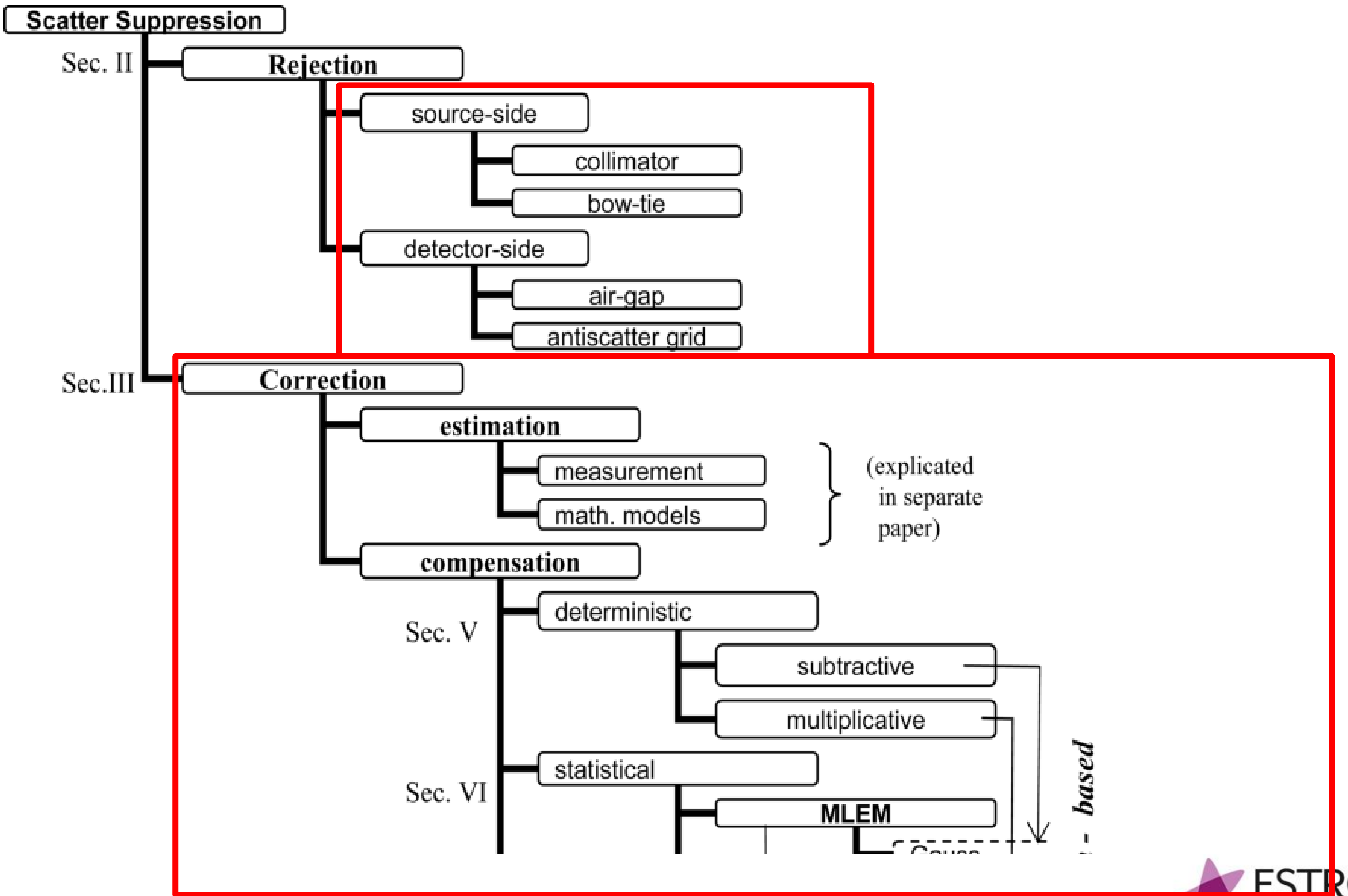


Truncation



Motion

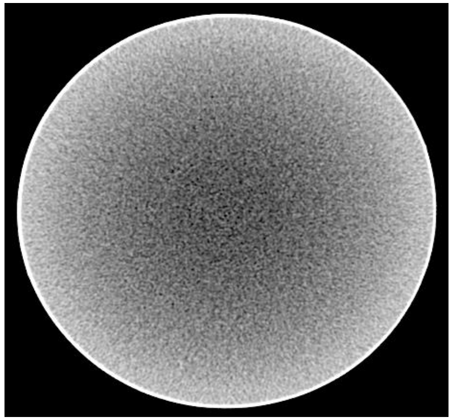
Scatter suppression for CBCT - CT



Ernst-Peter Rührnschopf[a)] and Klaus Klingenbeck
Siemens AG, Healthcare Sector, Imaging & Therapy Division, Forchheim, Germany

Medical Physics, Vol. 38, No. 7, July 2011

Scatter: Reduction/Correction



Water Phantom: Cupping Artifact

Scatter rejection

Hardware: Anti-scatter grid, Bow-tie filter

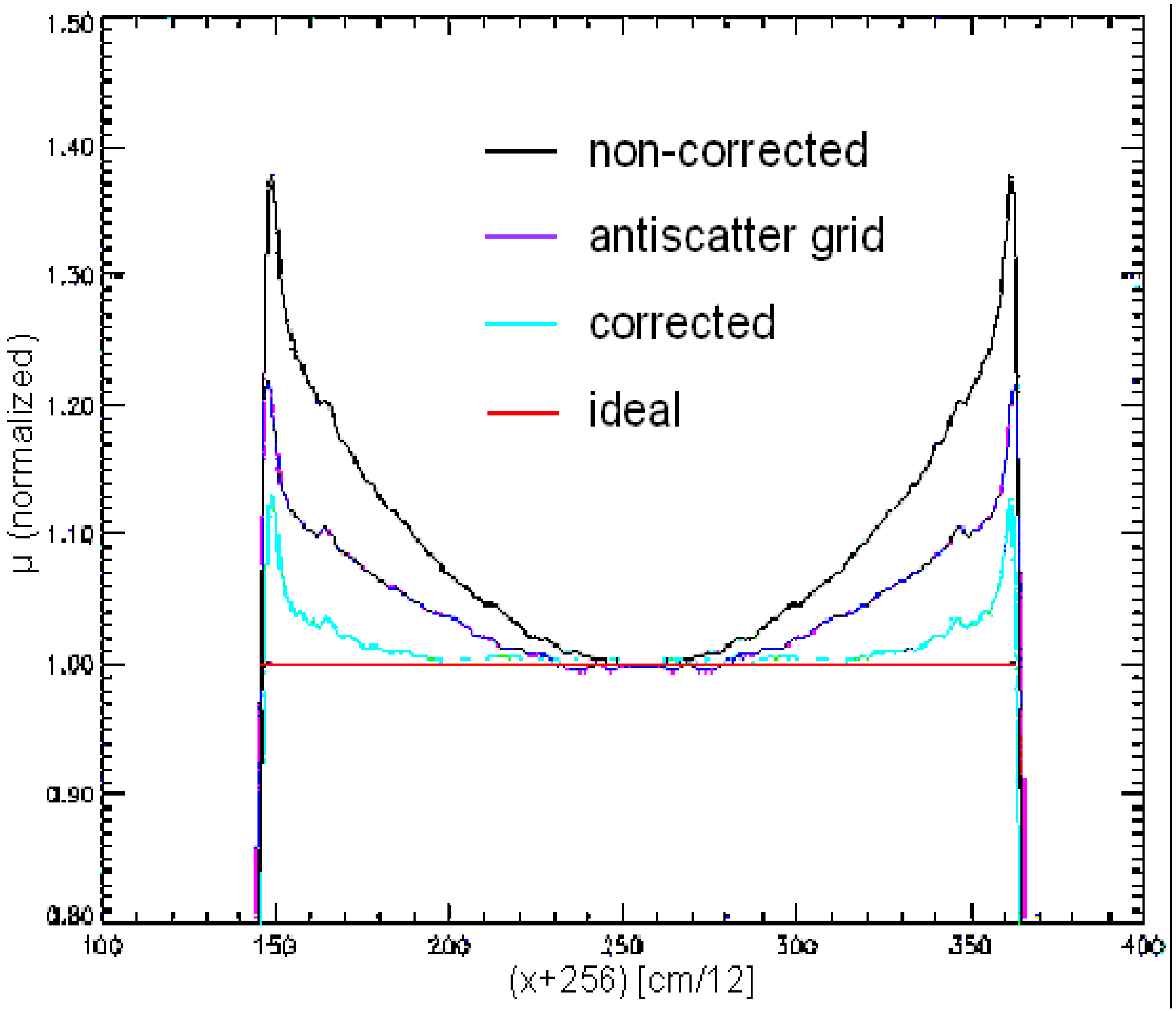
Scatter reduction

Software: Scatter correction algorithms

iterativ, heuristic …

closely related to Hounsfield calibration of CBCTs

Scatter – Cuping Artifact



Bow tie filters

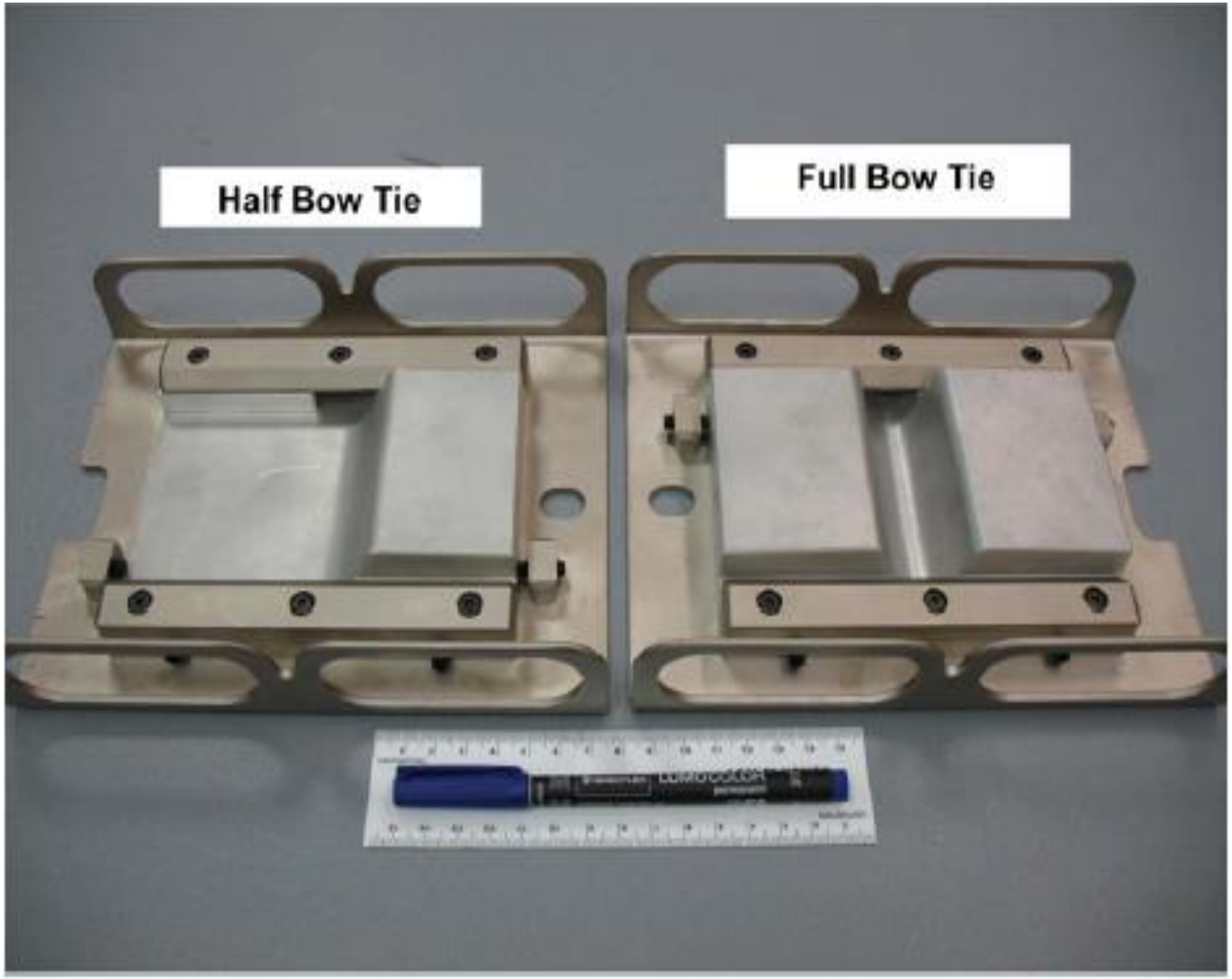
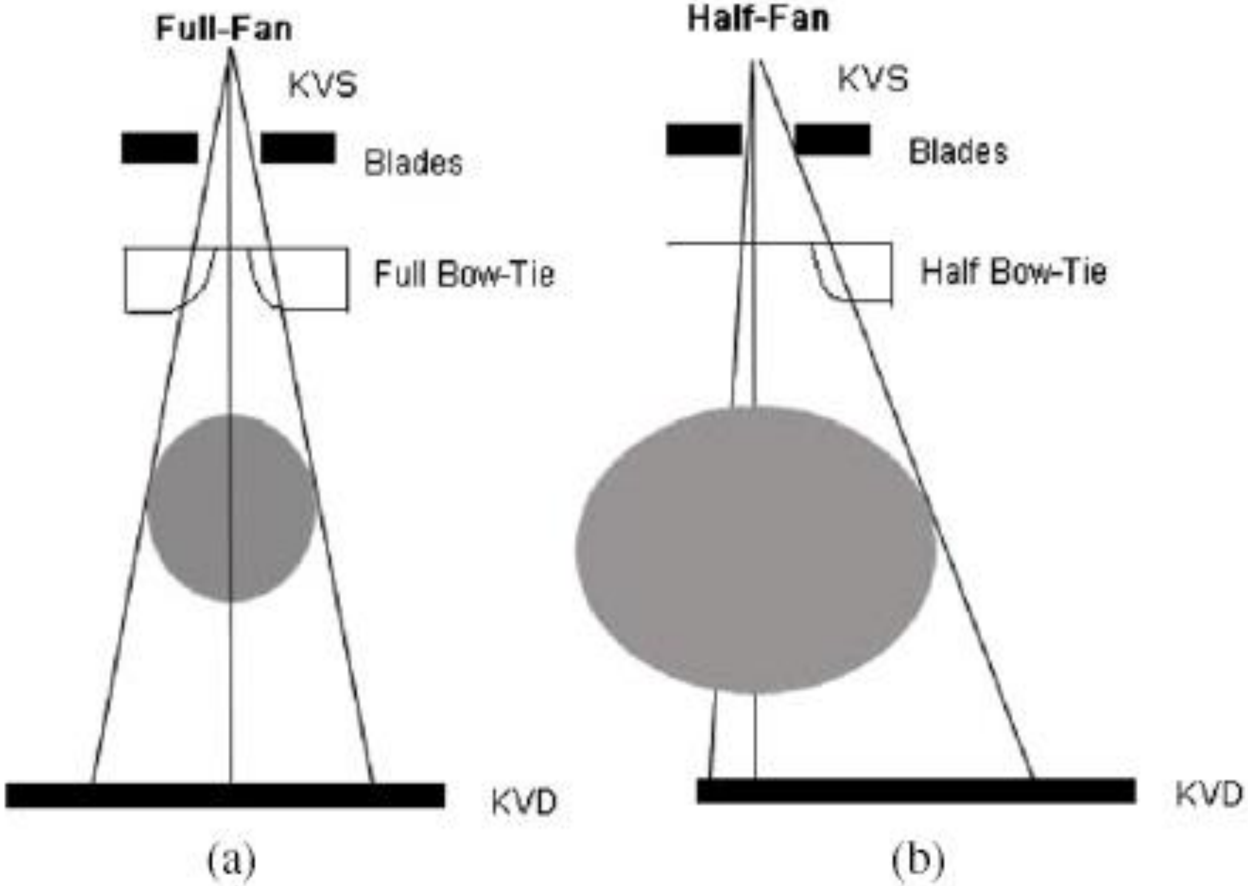


Figure 2. A photo showing the two types of bow tie filters: half bow tie (left) and full bow tie (right).

Ding et al. PMB 52 (2007), 1595 ff



Wen et al. Phys. Med. Biol. **52** (2007) 2267–2276

Imaging doses

<u>Range of measured/published doses</u>

- Head & Neck
  - ➢ 1 – 2 cGy (330 – 360 frames)

- Prostate
  - ➢ 4 – 7 cGy (640 – 720 frames)

Measured doses

DKFZ 30 cm diameter cylindrical water phantom

	dose calibration factors	
	peripheral [mGy/As]	central [mGy/As]
80 kV	**22**	**16**
120 kV	**70**	**52**

	Dose (central) (cGy)	Dose (periph.) (cGy)
DKFZ/SMS	1.7	2.3
Synergy*	1.6	2.3

*M. K. Islam, T. G. Purdie, B. D. Norrlinger, H. Alasti, D. J. Moseley, M. B. Sharpe, J. H. Siewerdsen, and D. A. Jaffray, "Patient dose from kilovoltage cone beam computed tomography imaging in radiation therapy", Med. Phys. 33(6), 1573-1582, 2006.

Imaging dose to patient anatomy

- MC simulation of imaging dose (VARIAN, OBI)
  - ➢ Full scan: 125 kVp, 80 mA, 25 ms
  - ➢ Low dose scan: 125 kVp, 40 mA, 10ms
- Anatomies:
  - ➢ Head & neck
  - ➢ Chest-lung
  - ➢ Pelvis

Ding et al.,Medical Physics, Vol. 35, No. 3,p 1135 ff, March 2008

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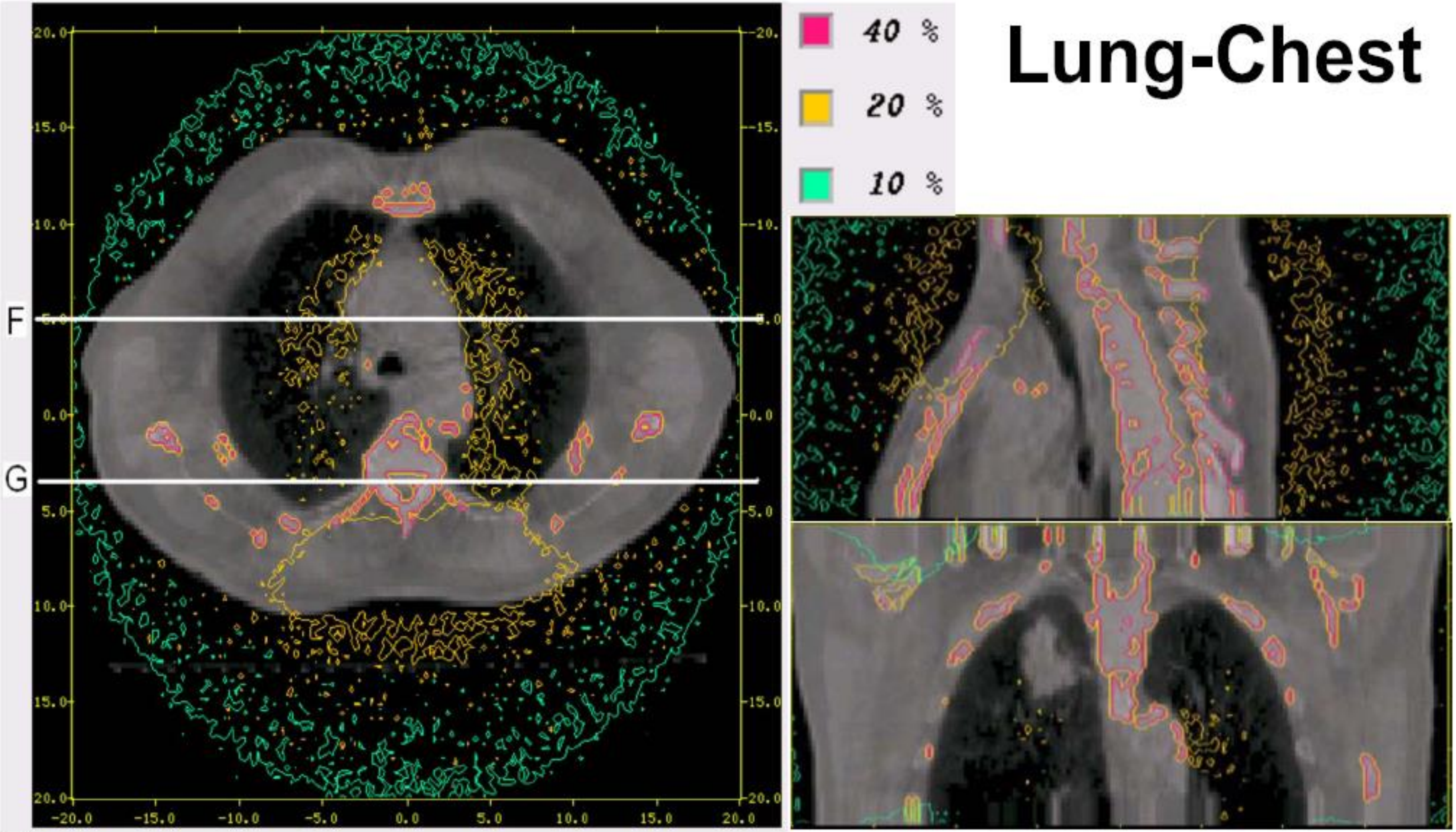
Lung-Chest



(a)

Ding et al.,Medical Physics, Vol. 35, No. 3,p 1135 ff, March 2008

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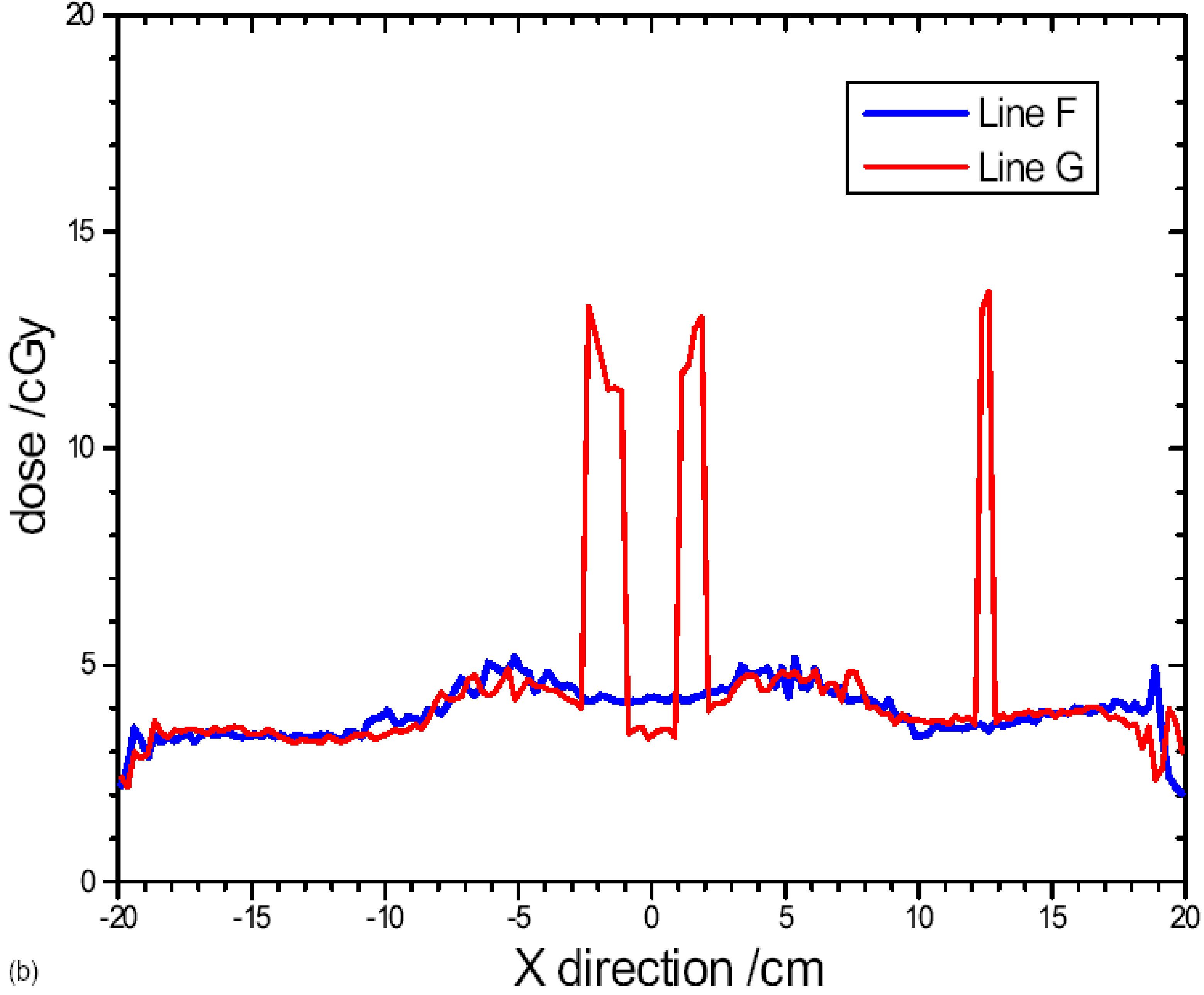

dose /cGy
X direction /cm
Line F
Line G
20
15
10
5
0
-20
-15
-10
-5
0
5
10
15
20

(b)

TABLE I. Monte Carlo calculated dose to different organs in a typical patient CBCT scan in clinical default half-fan mode settings.

Dose to organs (cGy)	Head and neck scan	Chest scan	Pelvis scan	Prostate scan
Skin	6–12	4–6	3–6	3–6
Soft tissue	4–7	4–6	3–8	4–7
Eye	8		⋯	⋯
Brain	4–5			⋯
Spinal cord	3–5	3–4	⋯	⋯
Lung	⋯	4–5	⋯	⋯
Prostate	⋯	⋯	⋯	4
Ovary	⋯	⋯	4	
Bone	23–27	10–15	8–22	8–20

Ding et al.,Medical Physics, Vol. 35, No. 3,p 1135 ff, March 2008

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Imaging dose kV-CBCT

- Dose depends on geometry patient thickness etc.
- Published measured doses cover a spectrum of ranges
- CBCT needs more dose for same image quality than diagnostic CT (noise from scatter)

Reference

The management of imaging dose during image-guided radiotherapy: Report of the AAPM Task Group 75

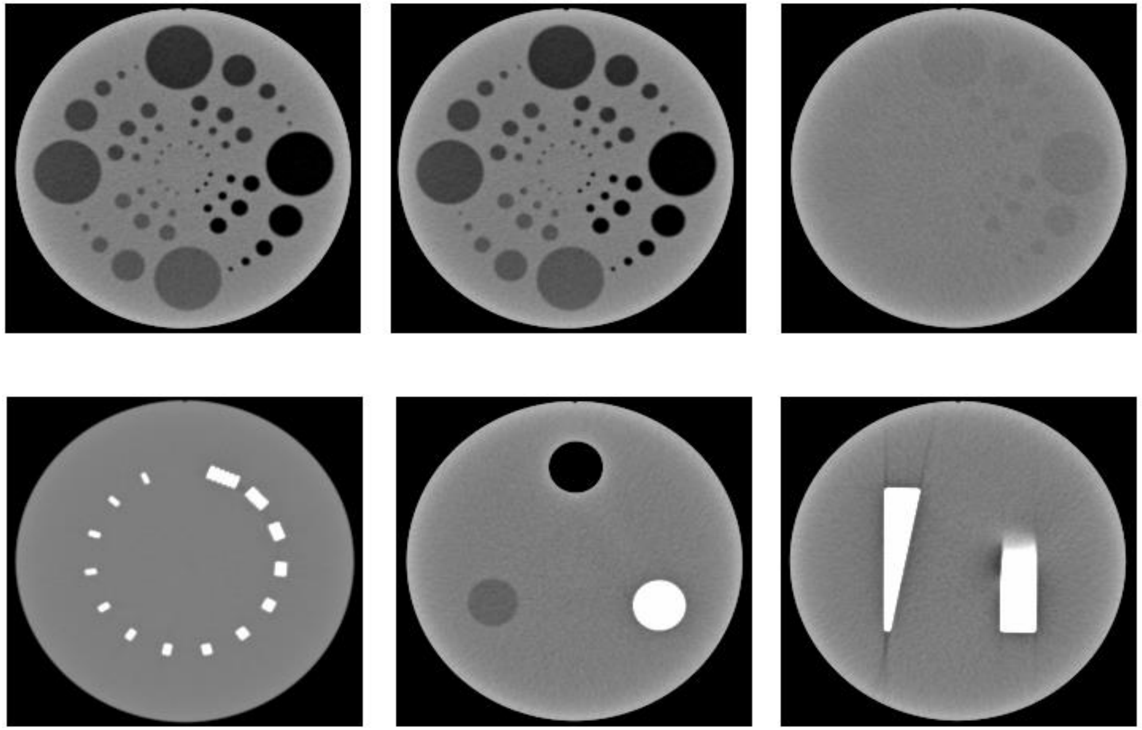
Med. Phys. 34 (10), October 2007 0094-2405/2007/34(10)/4041

In room 3D-imaging…MV/kV

- kV CBCT (cone beam, electron energy: 70 -140 keV,FPI)
- In room kV-CT (Spiral CT (fan), 60 -140 KeV, ion-chamber)
- MV – CBCT (Cone beam, 6 MeV,FPI)
- MV-CT (Fan beam, tomo, 3.5 MeV,FPI)
- IBL (‚inline kView‘, conebeam, 3.5 MeV, C-target,FPI)

Siemens Cone beam phantom

Contrast slices I,II,III,



spatial resolution slice, noise & scaling slice, MTF slice

The Siemens ConeBeam Phantom V2.5. From left to right: Contrast slice I (inserts have CT-numbers -200 HU, -120 HU, -90 HU, -60HU relative to the basic material, which has 35HU at 120 keV), Contrast slice II (-45 HU, -30 HU, -25 HU, -20 HU), Contrast slice III (-15 HU, -10 HU, -5 HU, -3 HU), Spatial resolution slice, Noise and scaling slice, MTF slice. (Images were acquired with the Siemens Primatom scanner.)

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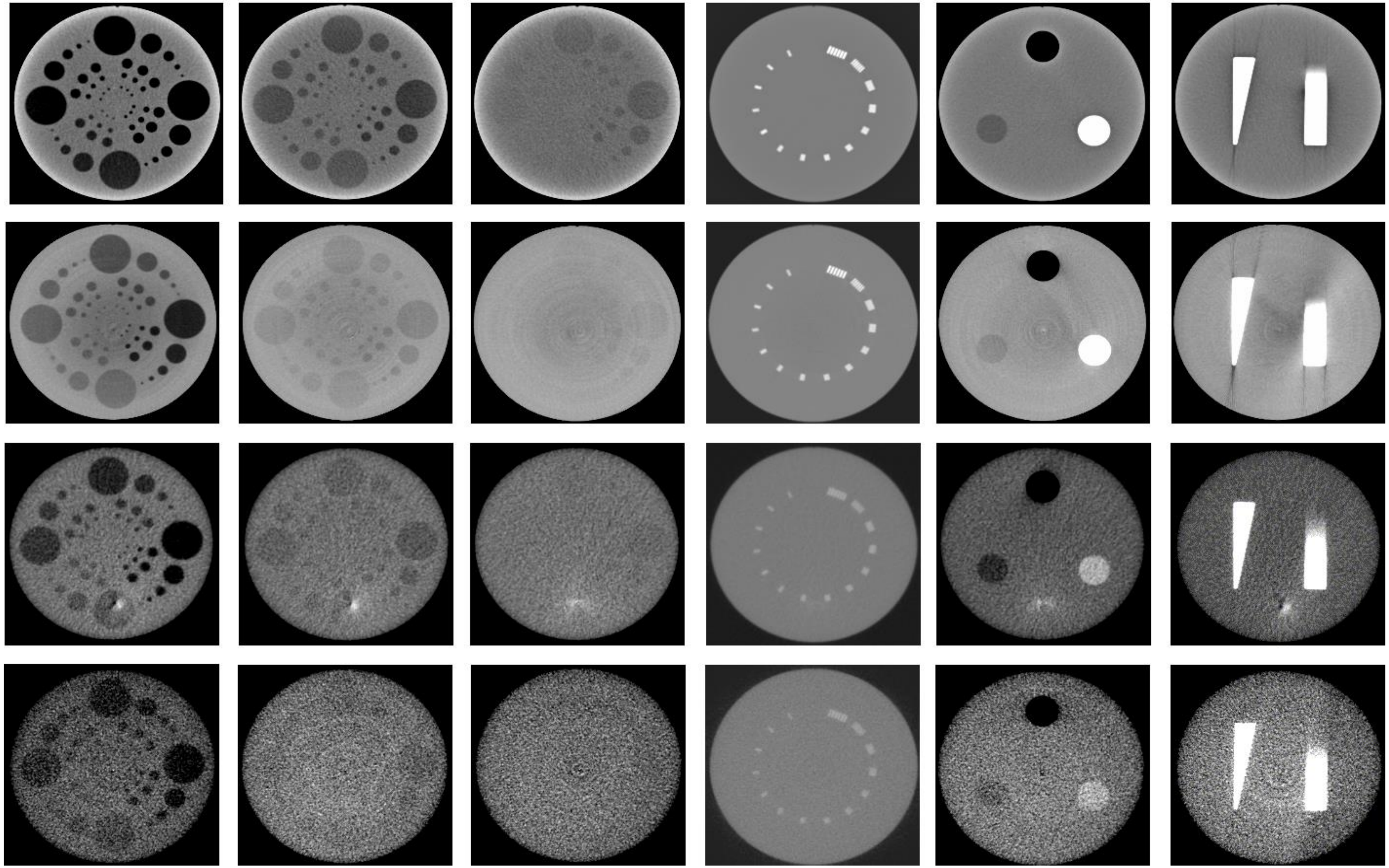
Example: Image quality and dose



Primatom
1.5cGy

kVCBCT
1.5cGy

MV CT
1.5cGy

MV- CBCT
8cGy

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Prostate Cancer: IGRT

Parag Parikh, BSE, MD

Associate Professor of Radiation Oncology & Biomedical Engineering

Washington University School of Medicine

St. Louis, Missouri, USA

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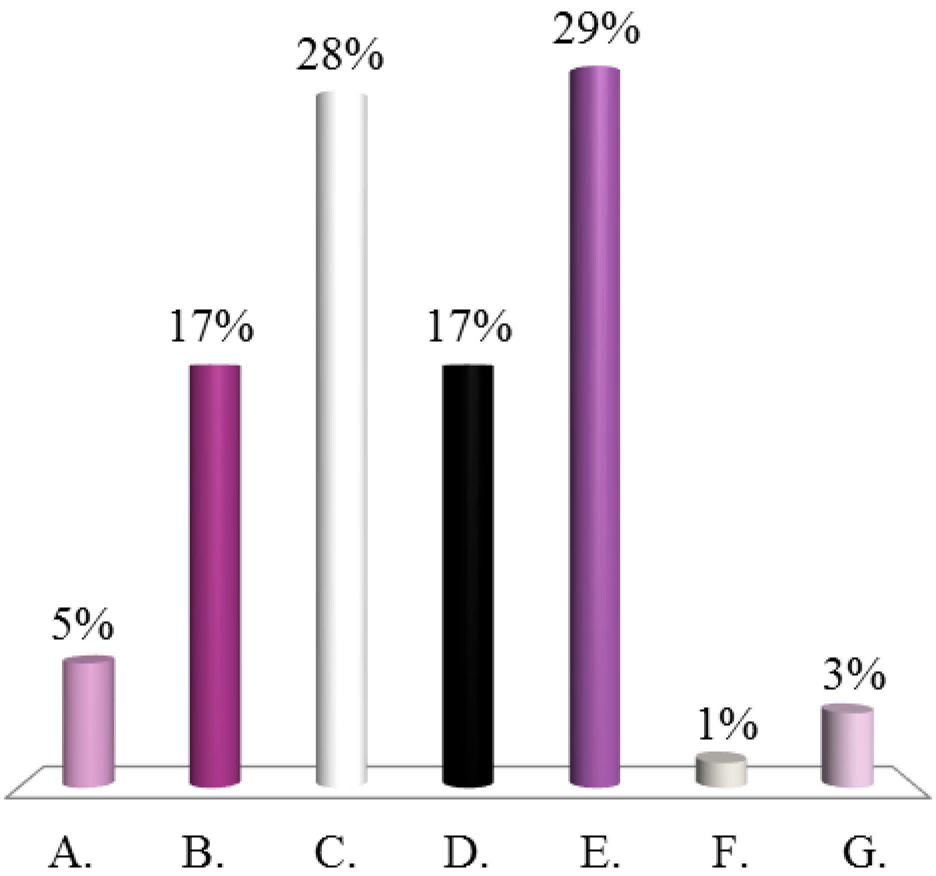
At our center we use the following for prostate cancer IGRT

A. Skin Marks
B. Bony anatomy
C. Fiducial markers – planar imaging
D. Fiducial markers – CBCT
E. CBCT w/o markers
F. Ultrasound, Electromagnetic Tracking, MRgRT
G. We don't treat prostate cancer



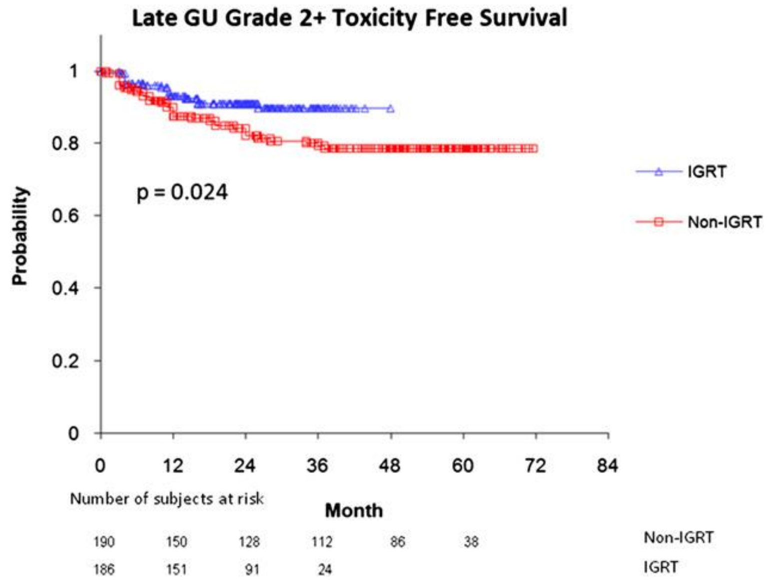
Agenda

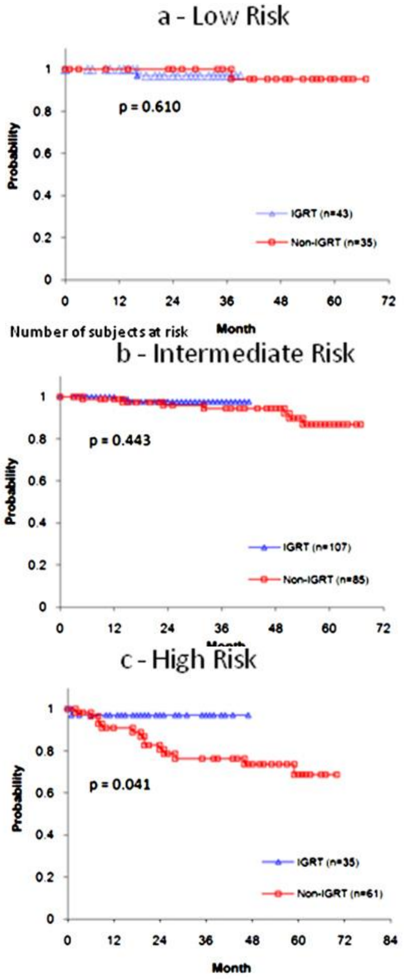
- Review of anatomy
- Review of recent clinical outcomes of radiation with respect to surgery and surveillance
- Comparison of toxicities between modalities
- Targets –subglandular, gland, seminal vesicle, lymph nodes
- Rectal displacement and/or separation (balloon and hydrogel)
- Techniques
    - Fiducial Marker – planar
    - Fiducial Marker – volumetric
    - Non-fiducial marker – volumetric

Why start with prostate cancer?

- Most common cancer in men
- Second leading cause of cancer death (behind lung cancer)
  - One in six men will develop prostate cancer in their lifetime
    - Incidence increases with age (1.8% between 40-59 yrs vs. 15% between 60-79)
    - In autopsy series, cancer seen in 30% (50 yr) and 80% (80 yr) old men
- Often one of the larger groups of patients in radiation oncology
  - Along with palliative patients, breast cancer patients and lung cancer
- Many, easy ways to improve practice with IGRT!

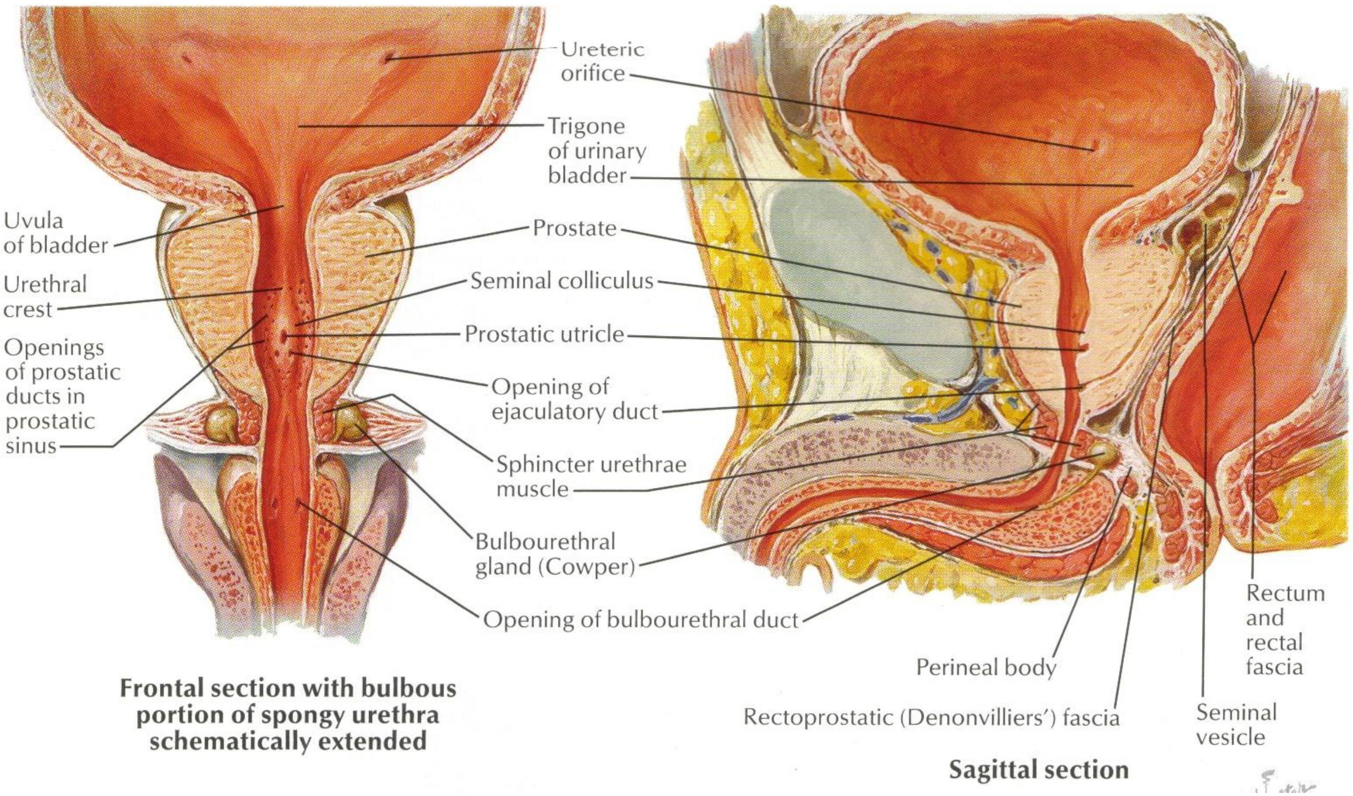
Prostate IGRT – single center outcomes

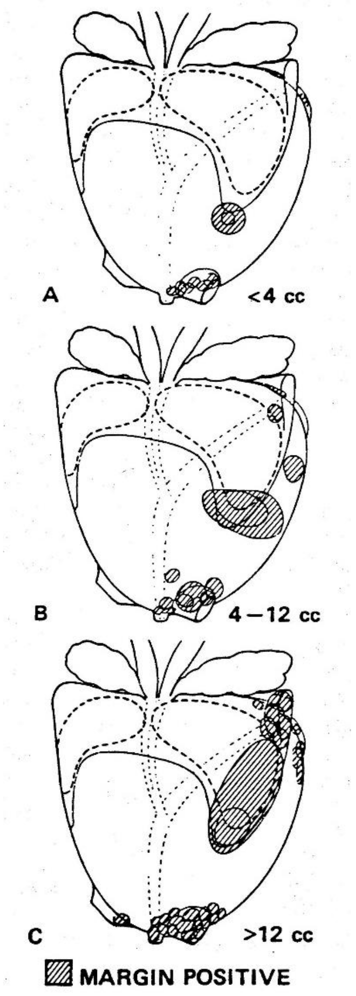




Zelefsky et al, IJROBP, 2012

Local anatomy





Lymphatic drainage

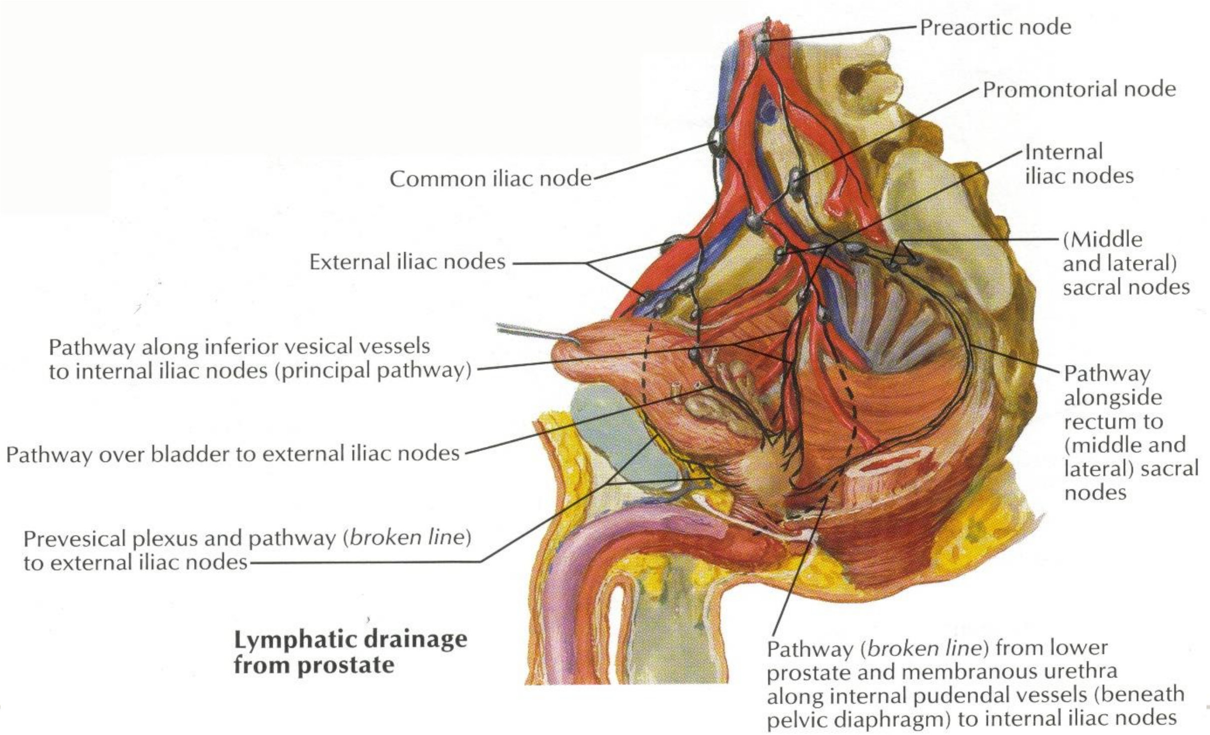
Prostate: lymphatics originate in extensive intraprostatic network; coalesces into periprostatic network and then out to four pedicles

1) External iliac pedicle – drains to external iliac nodes

2) Hypogastric (internal iliac) pedicle – drains to internal iliac nodes

3 and 4) Posterior and Inferior pedicles – drain to sacral, internal iliac, external iliac, and obturator nodes

Seminal Vesicle: lymphatics drain to internal and external iliac nodes



Optimizing management for localized prostate cancer

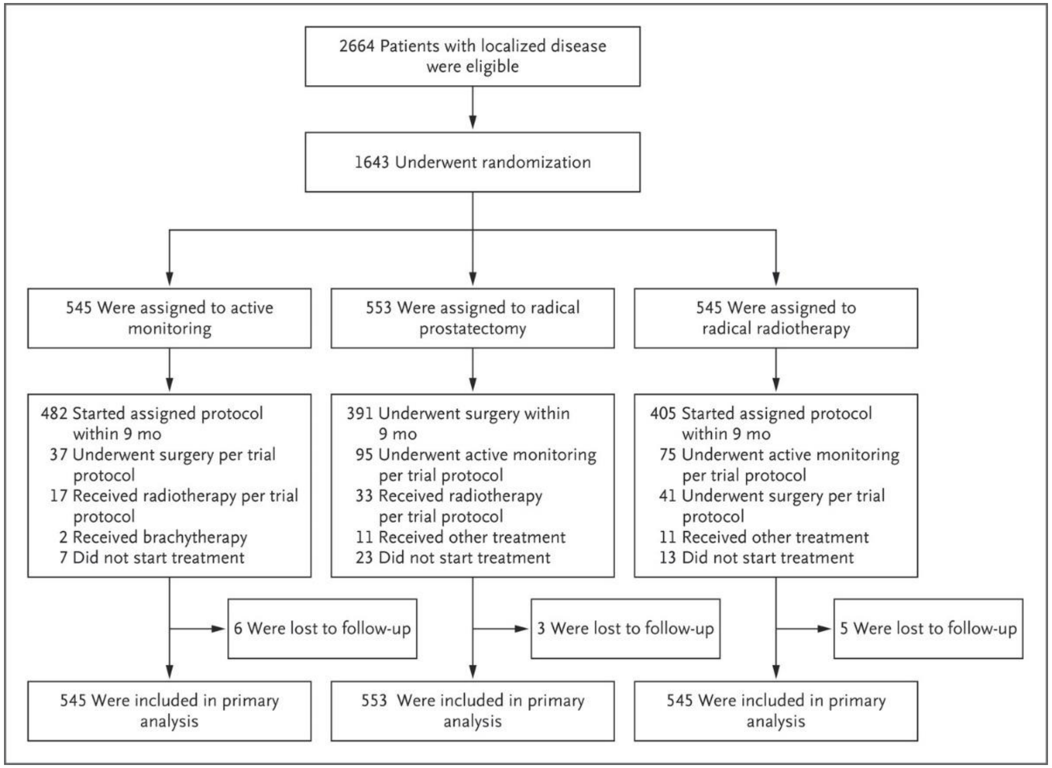
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

ESTRO School



Hamdy FC et al. N Engl J Med 2016;375:1415-1424.

The NEW ENGLAND JOURNAL of MEDICINE

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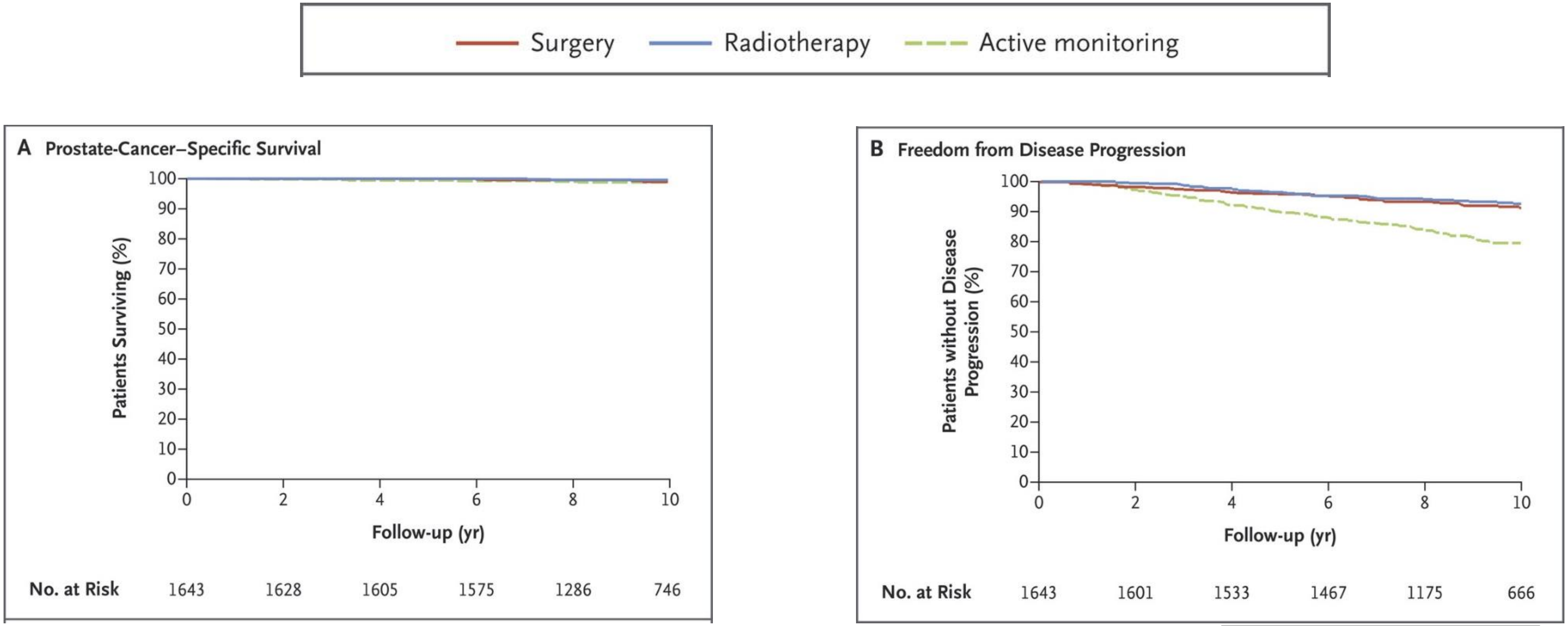

Hamdy FC et al. N Engl J Med 2016;375:1415-1424.

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Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48
Incidence of clinical progression‡				
Person-yr of follow-up free of clinical progression	4893	5174	5138	
No. of men with clinical progression	112	46	46	
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0–27.5)	8.9 (6.7–11.9)	9.0 (6.7–12.0)	<0.001
Incidence of metastatic disease				
Person-yr of follow-up free of metastatic disease	5268	5377	5286	
No. of men with metastatic disease	33	13	16	
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5–8.8)	2.4 (1.4–4.2)	3.0 (1.9–4.9)	0.004
All-cause mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to any cause	59	55	55	
All-cause deaths per 1000 person-yr (95% CI)	10.9 (8.5–14.1)	10.1 (7.8–13.2)	10.3 (7.9–13.4)	0.87

* P values were calculated with the use of a log-rank test of the null hypothesis of no difference in effectiveness across the three treatments. The planned adjusted analysis was not possible owing to the low number of events.

† Deaths due to prostate cancer were defined as deaths that were definitely or probably due to prostate cancer or its treatment, as determined by the independent cause-of-death evaluation committee.

‡ Disease progression was defined as death due to prostate cancer or its treatment; evidence of metastatic disease; long-term androgen-deprivation therapy; clinical T3 or T4 disease; and ureteric obstruction, rectal fistula, or the need for a permanent catheter when these are not considered to be a complication of treatment.

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2016 VOL. 375 NO. 15

Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh, J.M. Blazeby, T.J. Peters, P. Holding, S. Bonnington, T. Lennon, L. Bradshaw, D. Cooper, P. Herbert, J. Howson, A. Jones, N. Lyons, E. Salter, P. Thompson, S. Tidball, J. Blaikie, C. Gray, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, M. Davis, E.L. Turner, R.M. Martin, and D.E. Neal, for the ProtecT Study Group*

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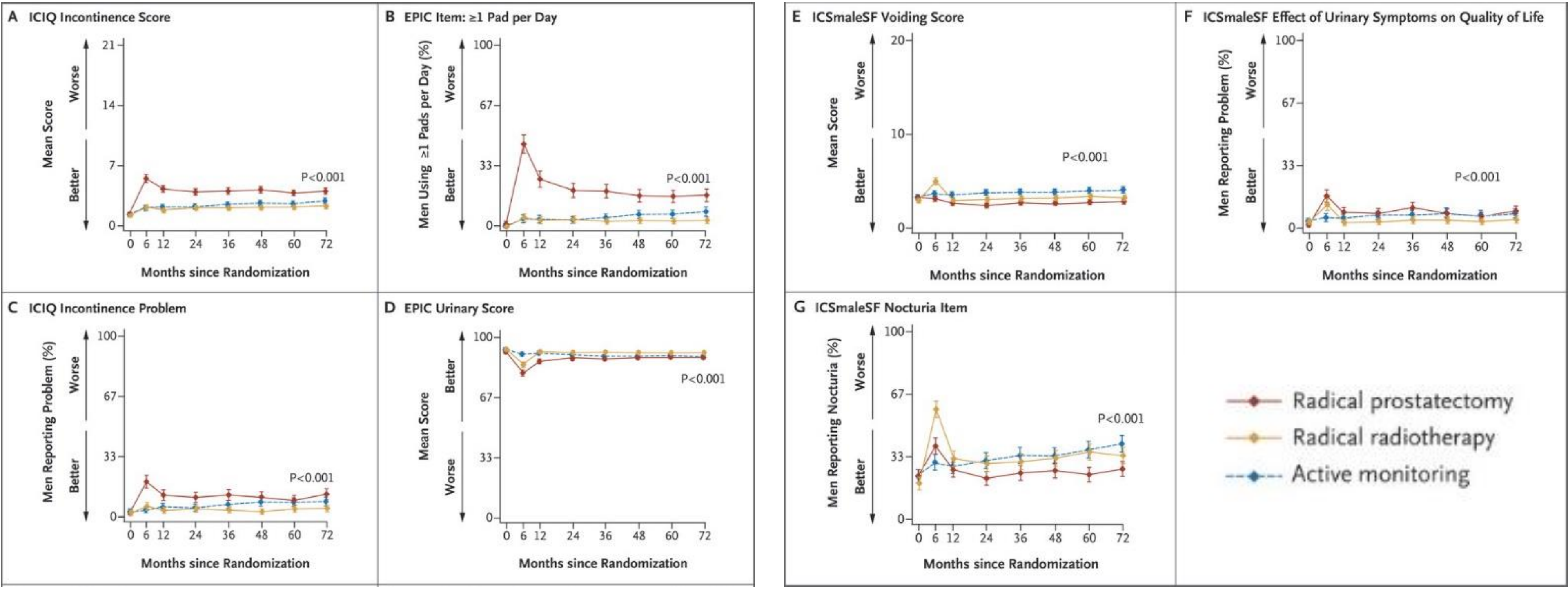
	Active monitoring (n=545)	Prostatectomy (n=553)	Radiotherapy (n=545)
Mean age in years at randomization (SD[1])	62 (5)	62 (5)	62 (5)
White ethnicity (%)	535 (99)	542 (99)	529 (98)
Married or living with partner (%)	457 (84)	458 (84)	460 (85)
Managerial / professional occupation (%)	229 (43)	229 (42)	226 (42)
Known family history prostate cancer (%)	43 (8)	32 (6)	44 (8)
Median PSA[2] in ng/ml (Inter-quartile range)	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
Gleason score			
6	421 (77)	422 (76)	423 (78)
7	111 (20)	120 (22)	108 (20)
8-10	13 (2)	10 (2)	14 (3)
Missing	0	1	0
Clinical stage			
T1c	410 (75)	410 (74)	429 (79)
T2	135 (25)	143 (26)	116 (21)

Symptom frequencies and generic quality of life were similar to those observed in populations screened for prostate cancer and control subjects without cancer

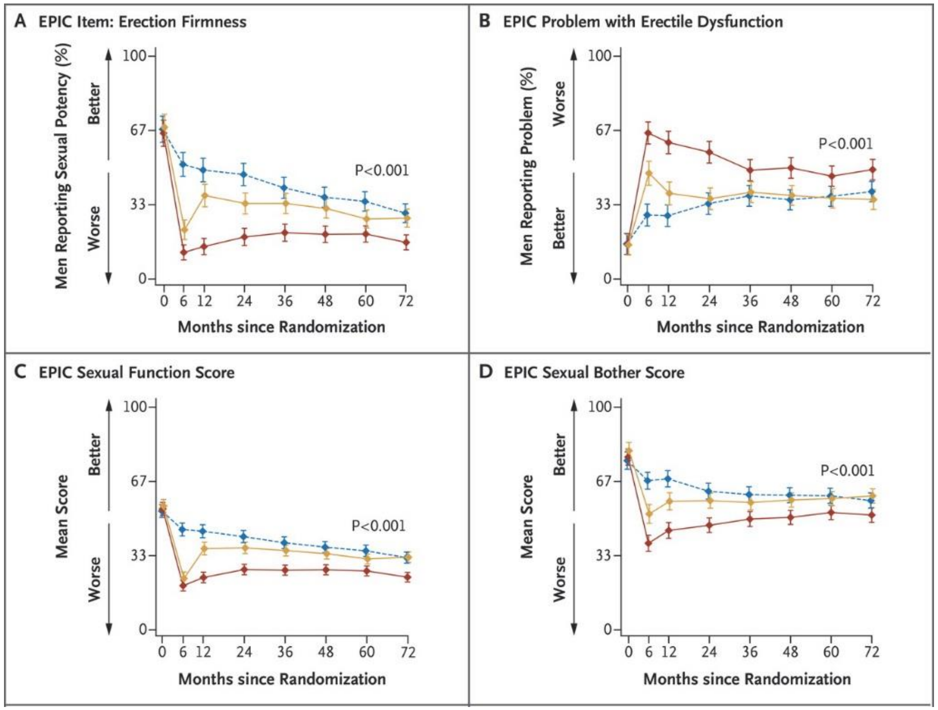
Outcomes for Urinary Function and Effect on Quality of Life.

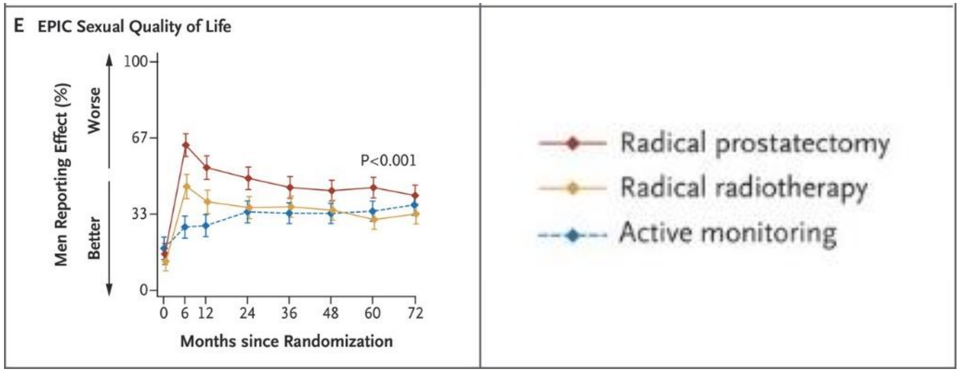


Donovan JL et al. N Engl J Med 2016;375:1425-1437.

The NEW ENGLAND JOURNAL of MEDICINE

Outcomes for Sexual Function and Effect on Quality of Life.

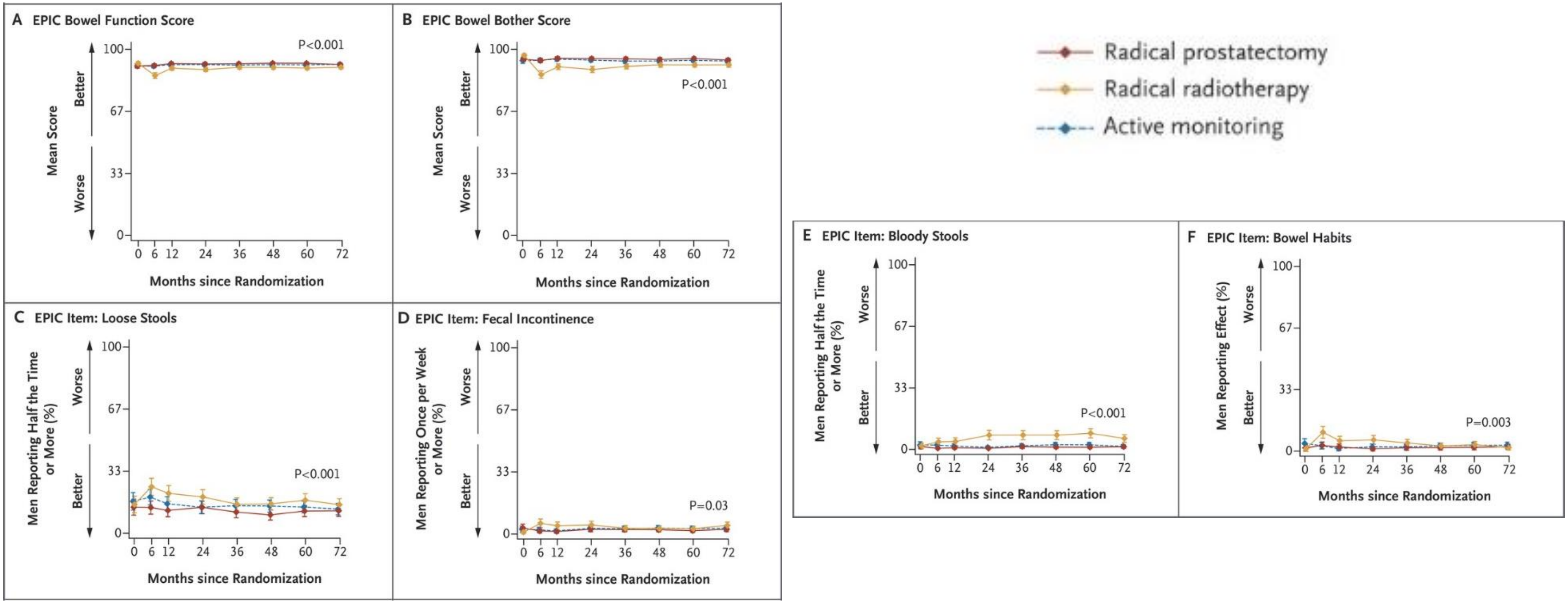




Donovan JL et al. N Engl J Med 2016;375:1425-1437.

The NEW ENGLAND JOURNAL of MEDICINE

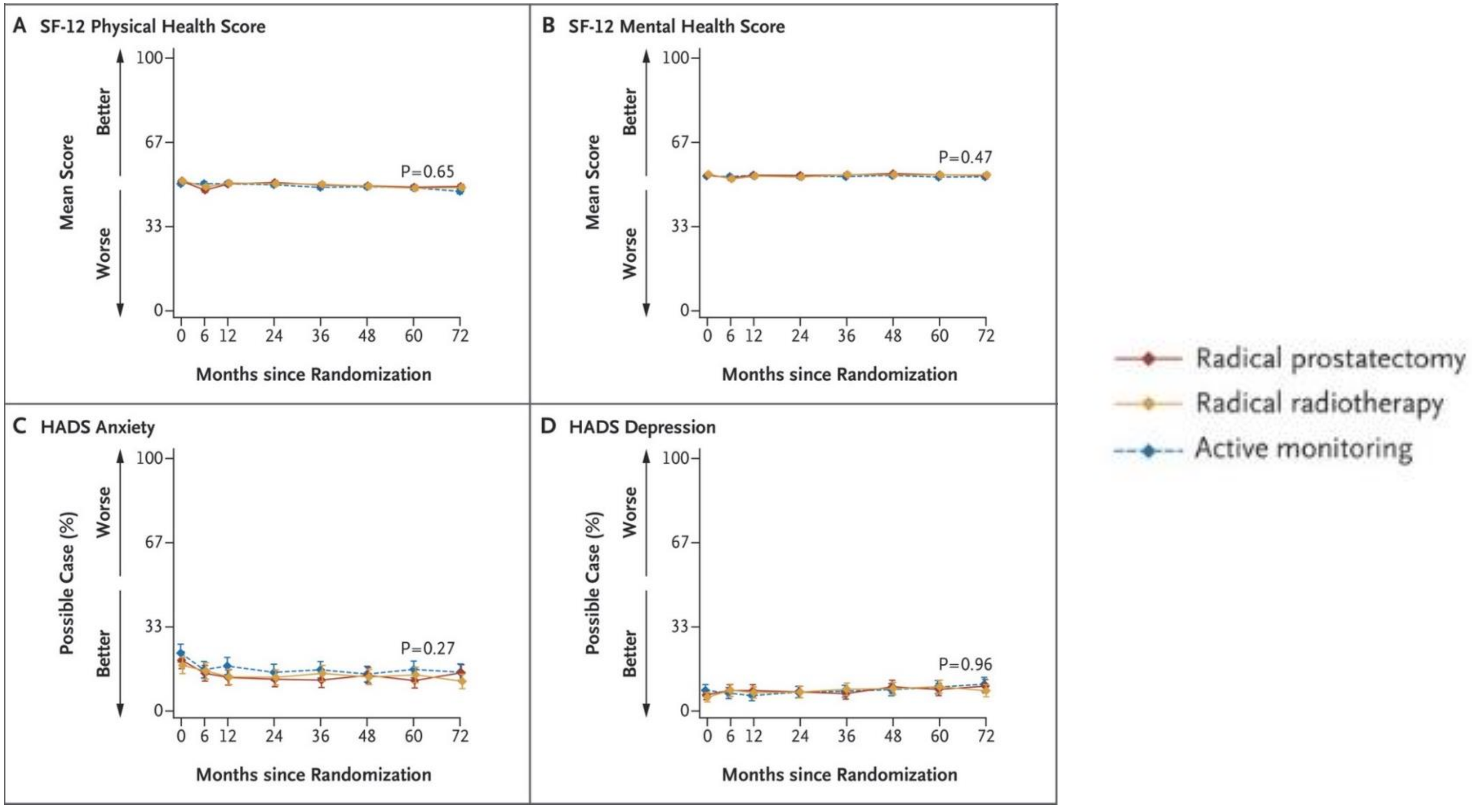
Outcomes for Bowel Function and Effect on Quality of Life.



Donovan JL et al. N Engl J Med 2016;375:1425-1437.

The NEW ENGLAND JOURNAL of MEDICINE

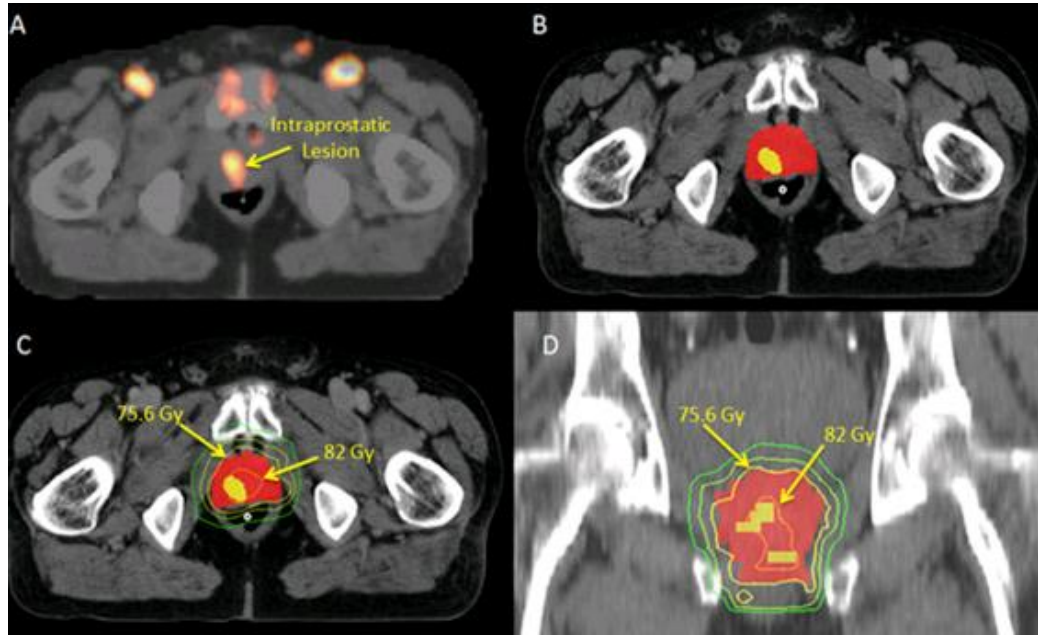
Outcomes for Health-Related Quality of Life.



Donovan JL et al. N Engl J Med 2016;375:1425-1437.

Subglandular

Courtesy of Jeff Michalski



Schild et al, IJROBP, 2017

- More and more popular with multiparametric MRI and hypofractionated regimens

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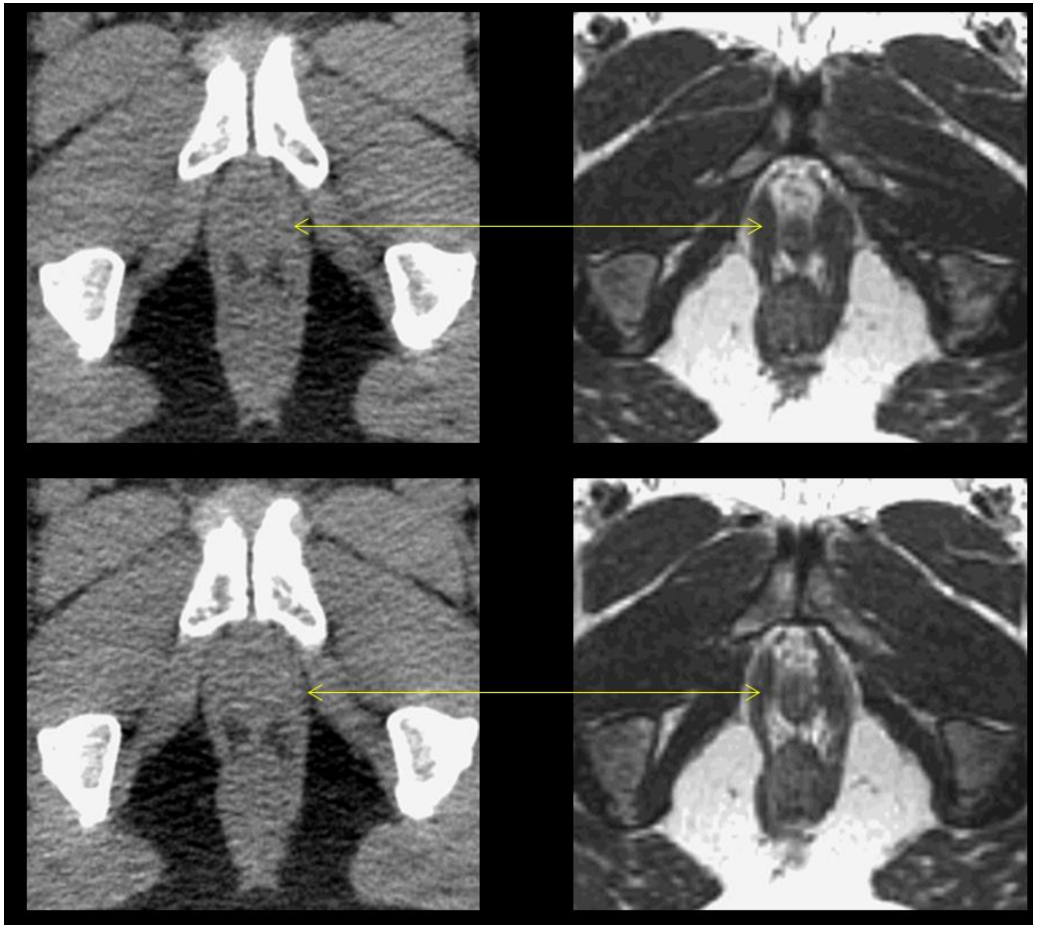
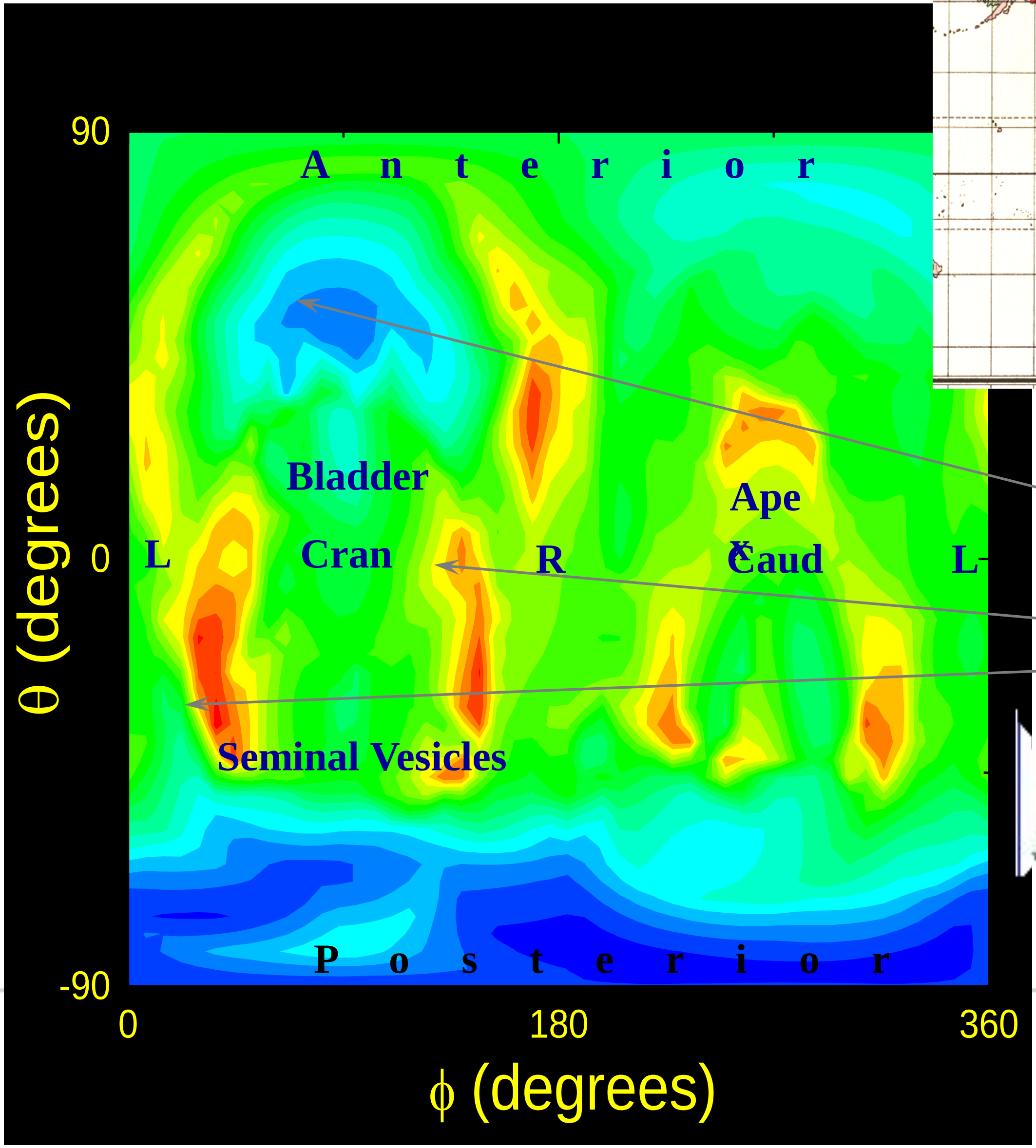
Whole gland

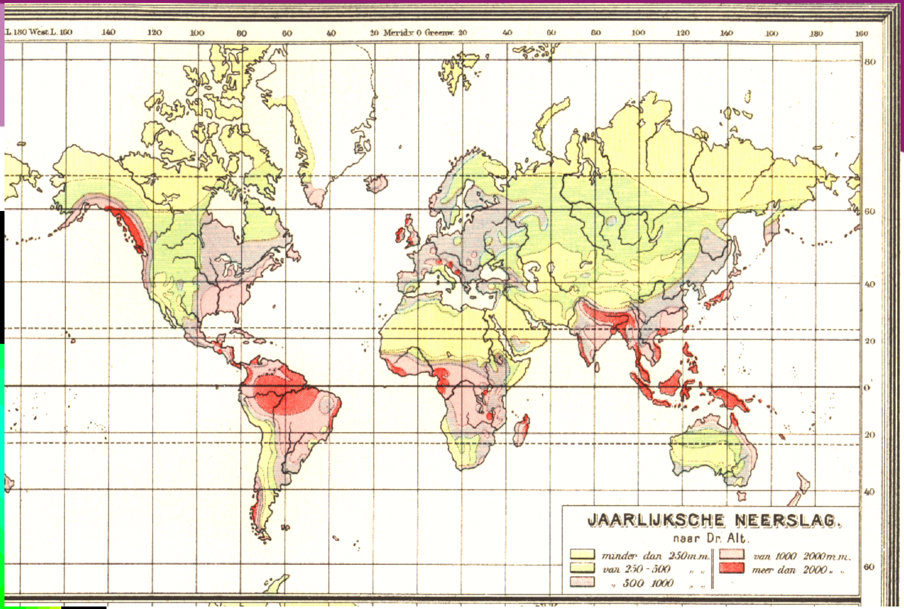
- Whole prostate (with proximal SV) remains most common target volume
- When possible, use simulation MRI as that this reduces prostate apex significantly (Debois, IJROBP, 1999)

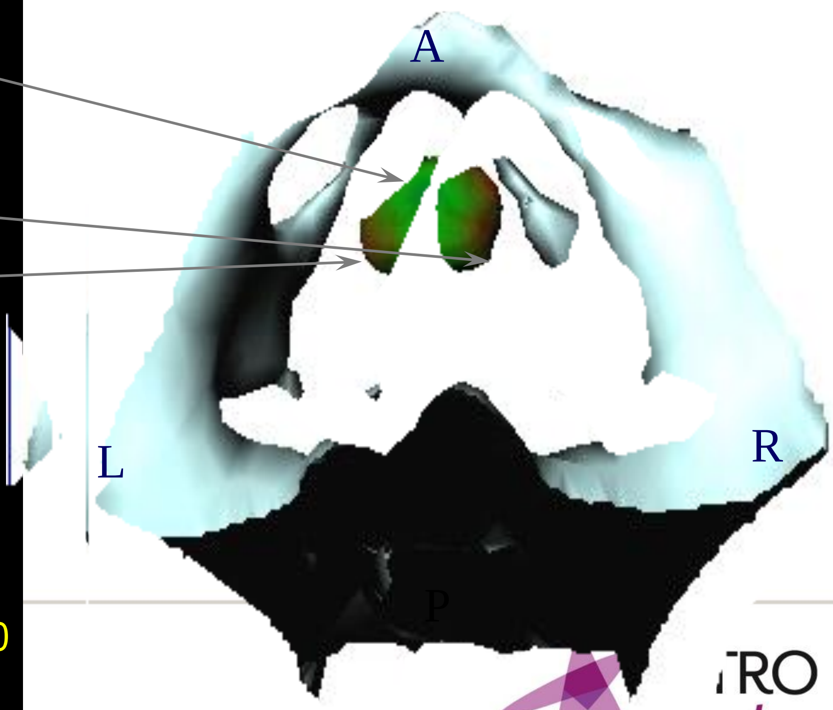


McLaughlin et al, prostatedoodle.com

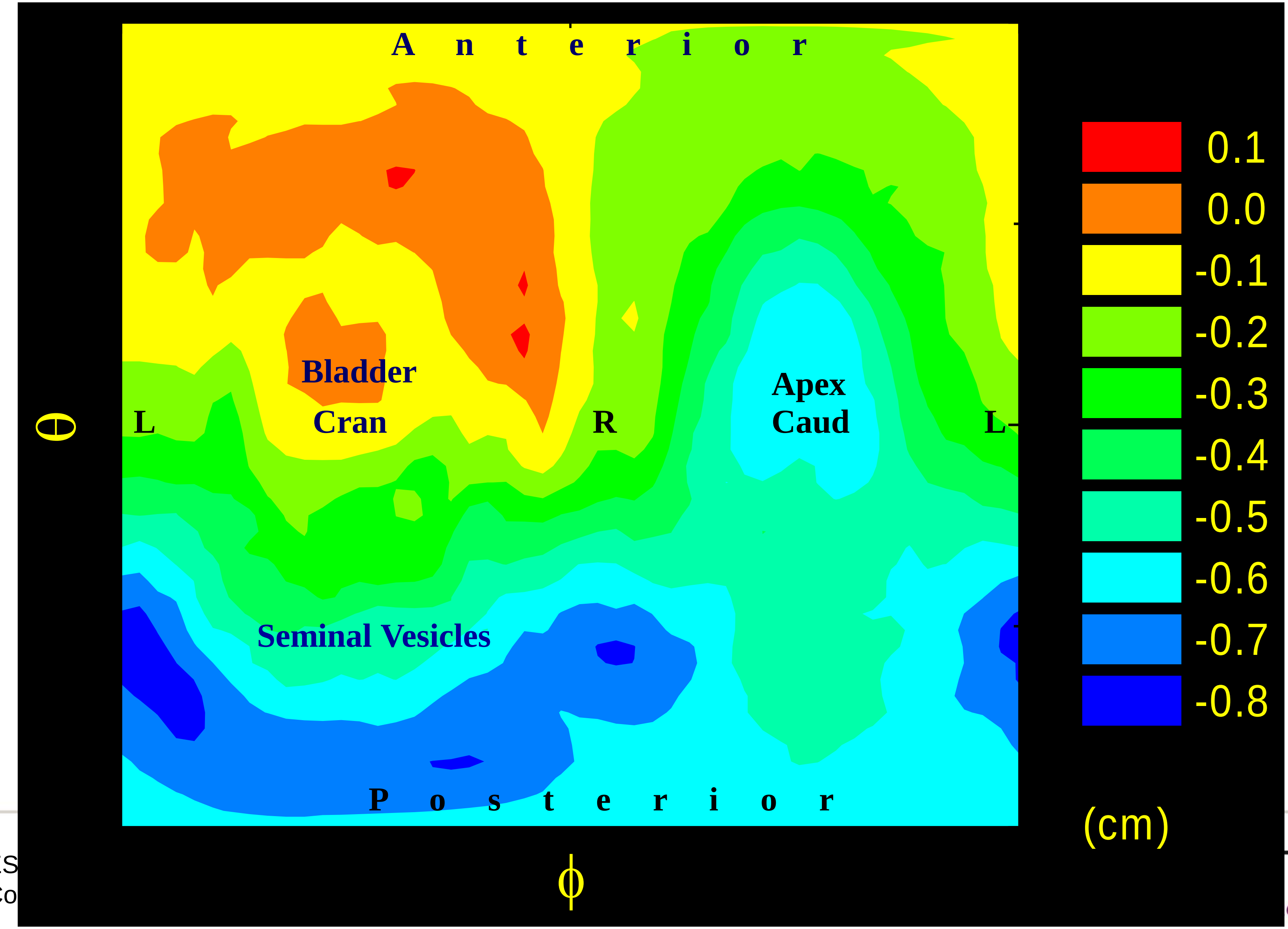
Distance maps



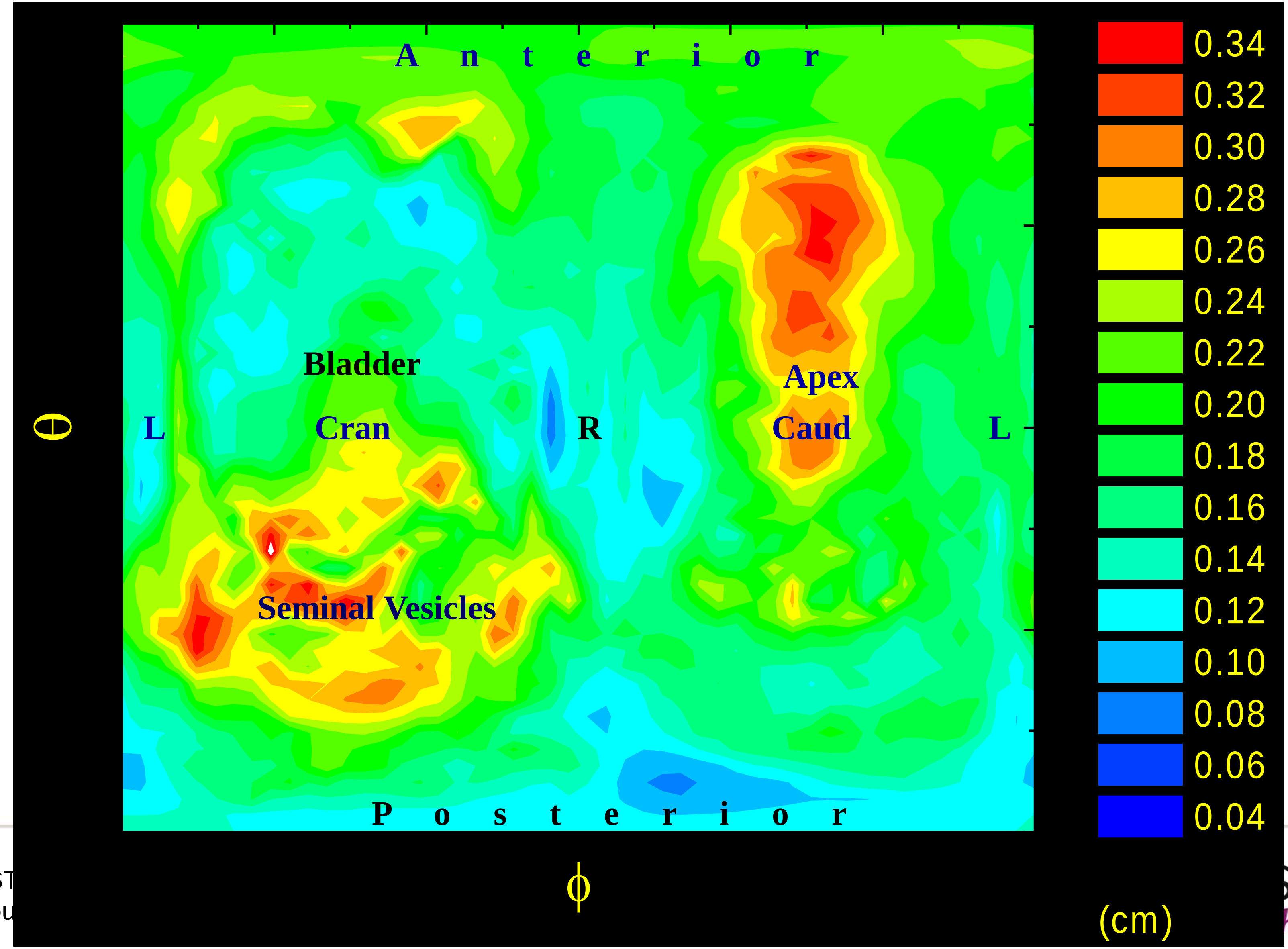




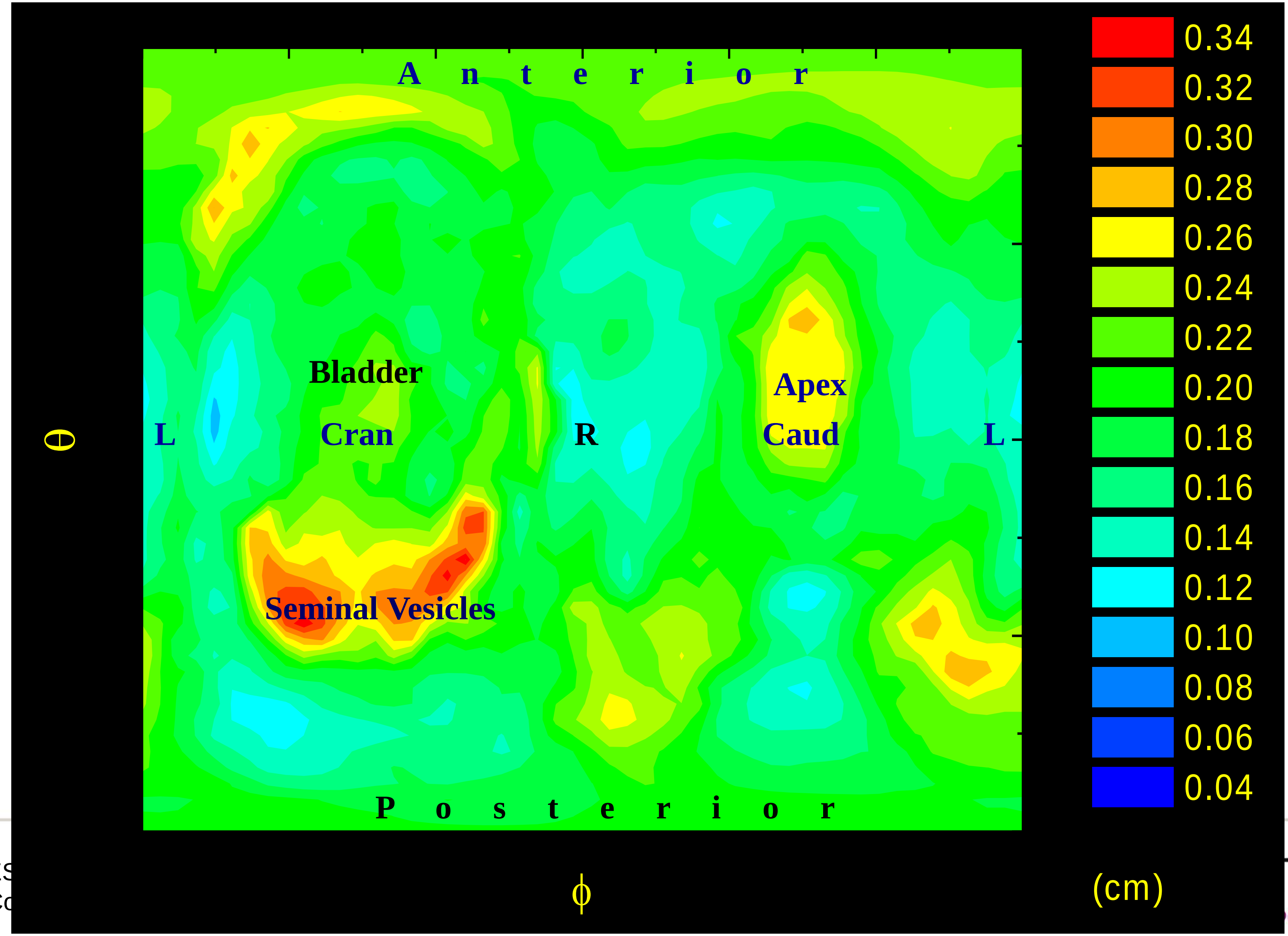
Systematic difference (axial MRI - CT)



Overall observer variation in CT (SD)



Overall observer variation in MRI (SD)



Impact on dose to the rectum and CT/MRI delineation of the prostate

Differences in target results in increased therapeutic ratio. This can be used in two ways:

Prostate dose 78 Gy (5 mm ctv-ptv margin)

EUD rectum 68 Gy is reduced to 62 Gy

If EUD 68 Gy is acceptable (5 mm margin)

Dose prostate 78 Gy is increased to 85 Gy

Impact of prostate target delineation variation on the clinic

Beware that MRI/CT difference can occur due to different rectal/bladder filling

Use a flat table top and same cushions

CT prostate 1,4 x MRI prostate

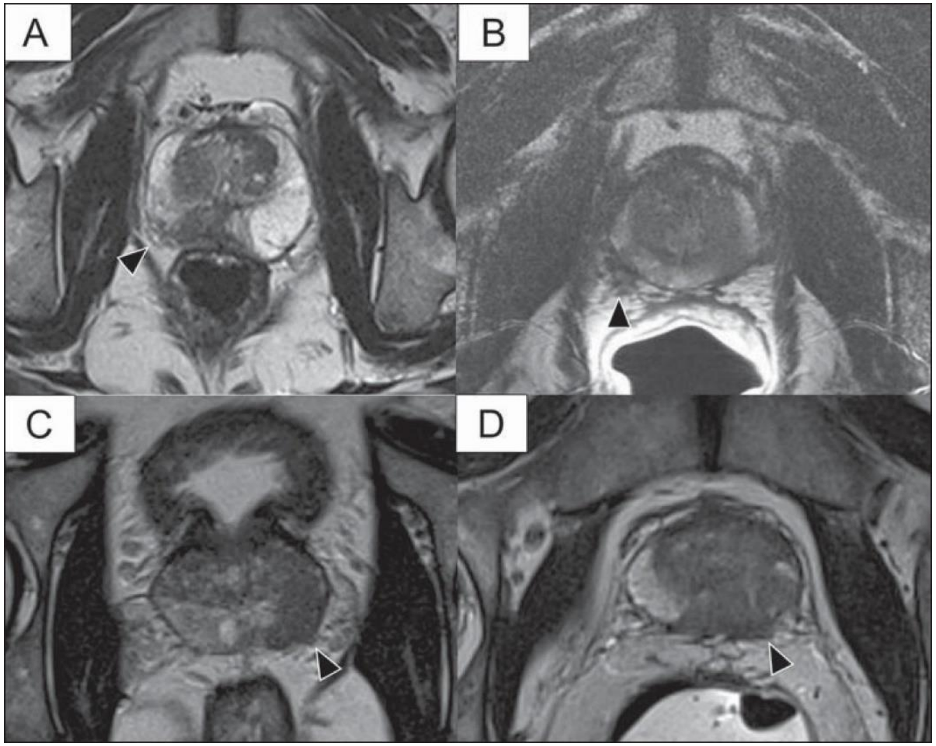
- Less dose to apex, base of seminal vesicles

Observer variation is smaller than impact of modality difference

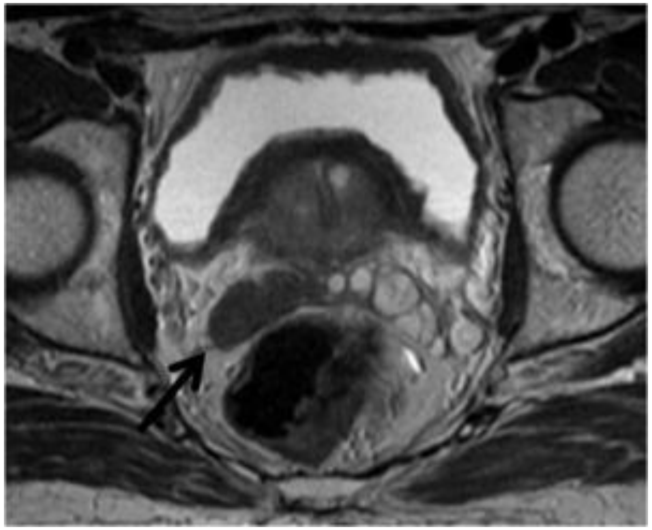
For **prostate only** MRI based delineation is superior to CT based delineation

RT according to delineation of the prostate on MRI decreases dose to the rectal wall

Seminal Vesicles/Extracapsular extension



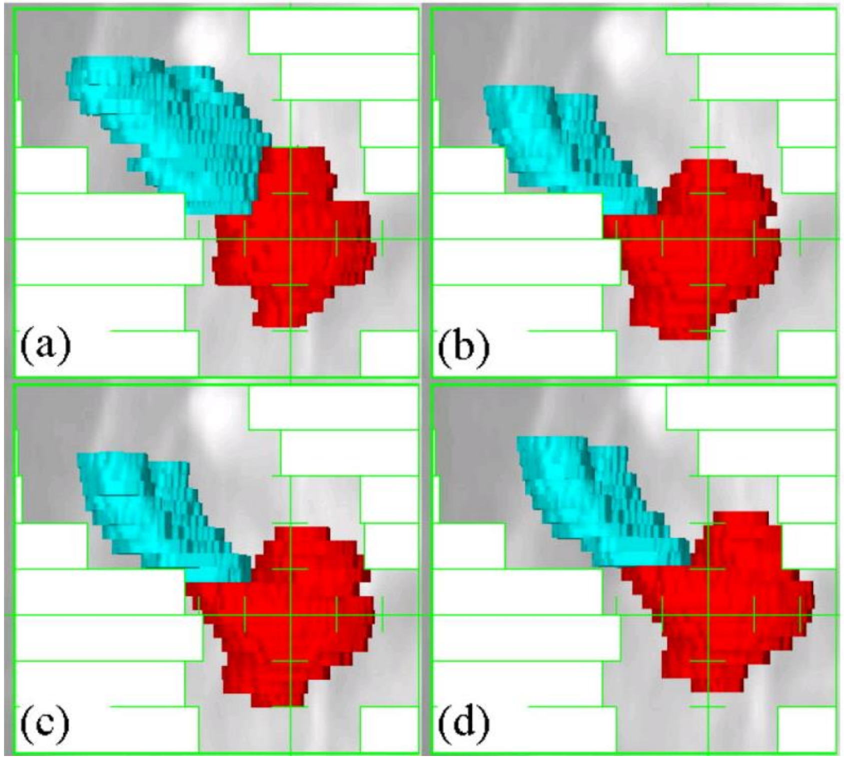
Extracapsular Extension

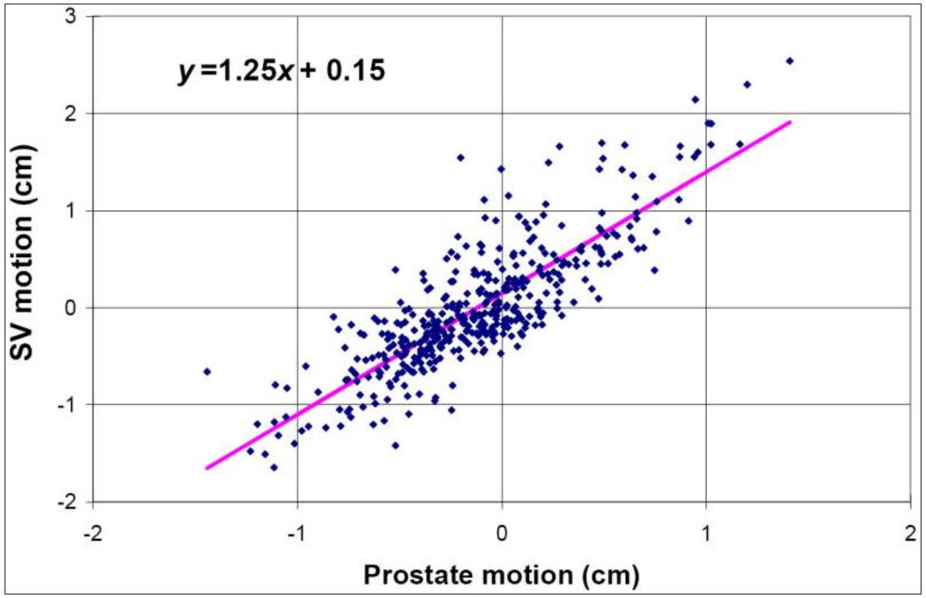


Seminal Vesicle Invasion

Courtesy of Jeff Michalski

Seminal Vesicle Motion





Liang et al, IJROBP, 2009

- Seminal vesicles move differently than the prostate
- The distal seminal vesicles are less correlated with prostate
- May need to use different margins to account for this

Pelvic Lymph Nodes

- High risk patients
- Treatment of Presacral LNs (subaortic only)
- 7mm around iliac vessels,carving out bowel, bladder and bone
- Commence contouring at distal common iliac vessels at L5/S1 interspace
- Stop external iliac contours at top of femoral heads (boney landmark for Ing. ligament)
- Stop contours of obturator LNs at top of symphsis pubis

Laswon et al, Prostate Pelvic Lymph Node Atlas
https://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx

Rectal Fixation

Used for over 15 years

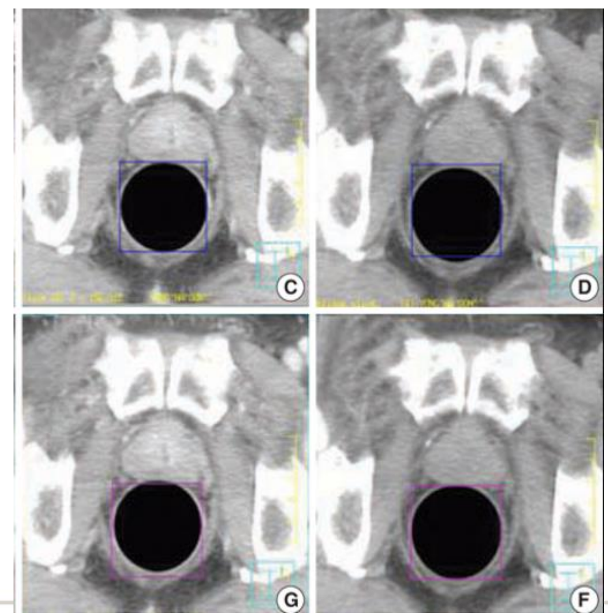
Allows fixation of prostate to reduce intrafraction prostate motion

Most (but not all studies) indicate reduction of rectal wall dosimetry

Can make volumetric imaging easier to interpret

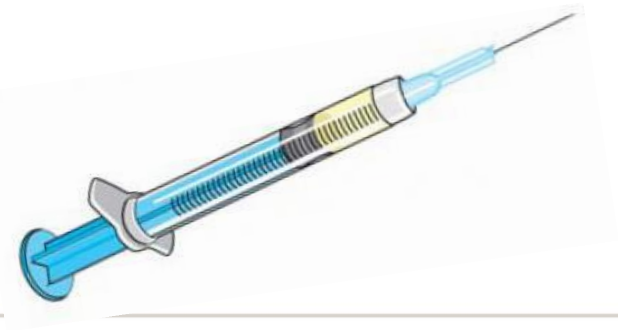
Many proton radiation centers use fixation to reduce risk of rectal toxicity with lateral beam arrangement

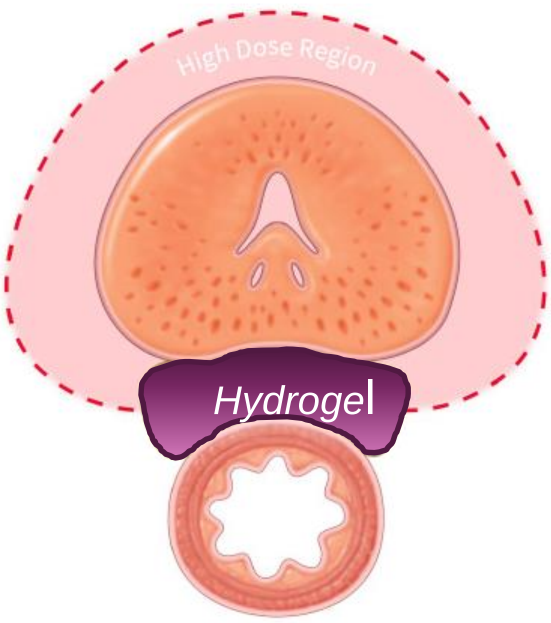
Requires department wide (MD, nursing, RTT, physics) training

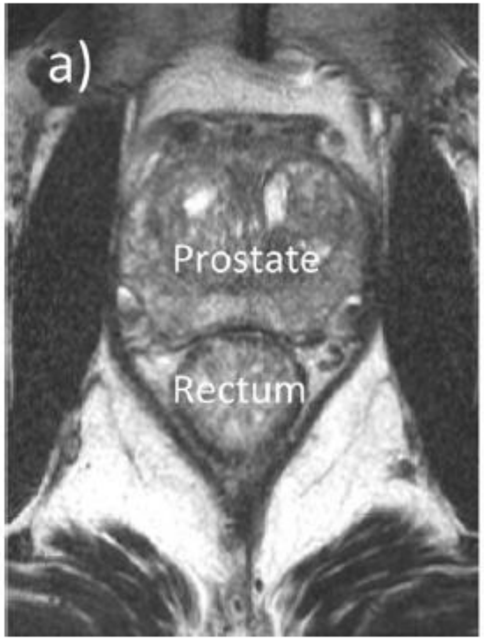


Cho, JKMS, 2009

Hydrogel





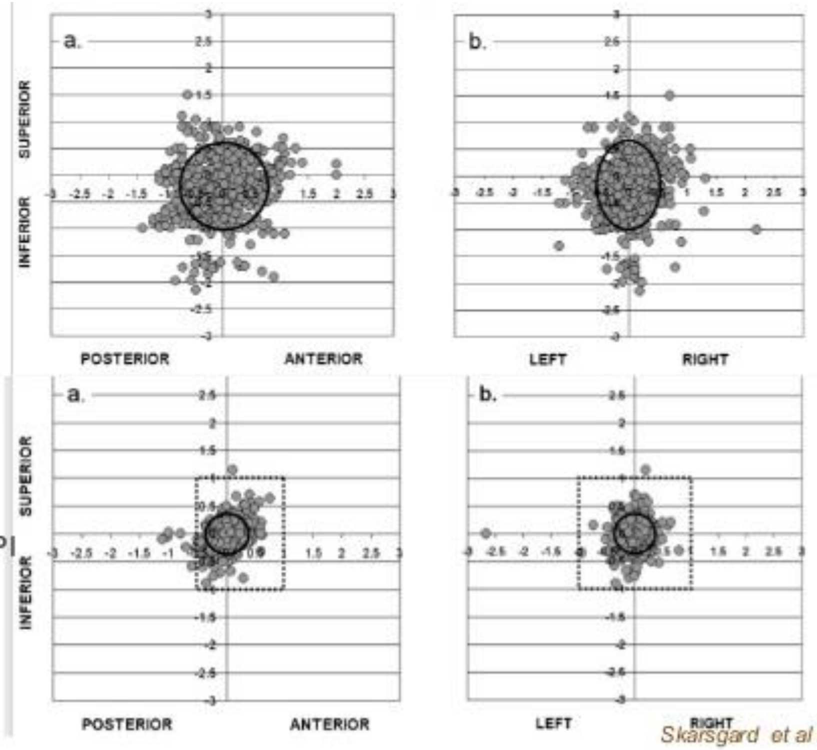


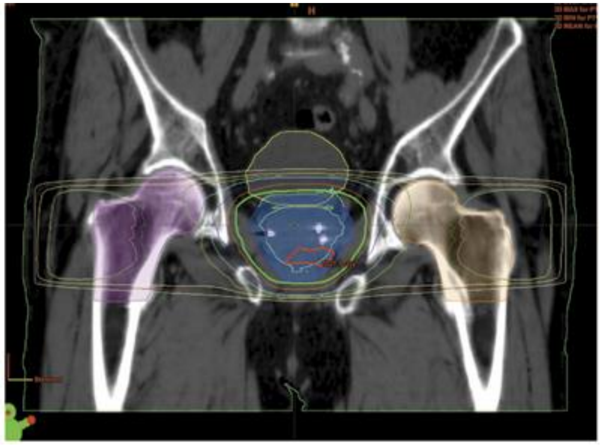
Mariados (2015) IJROBOP 92 (5): 971

Interfraction prostate motion

Isocentre placement accuracy with reference to skin markers

Isocentre placement accuracy post EPI and correction





Skarsgard et al Radiat Oncol 52 5 2010

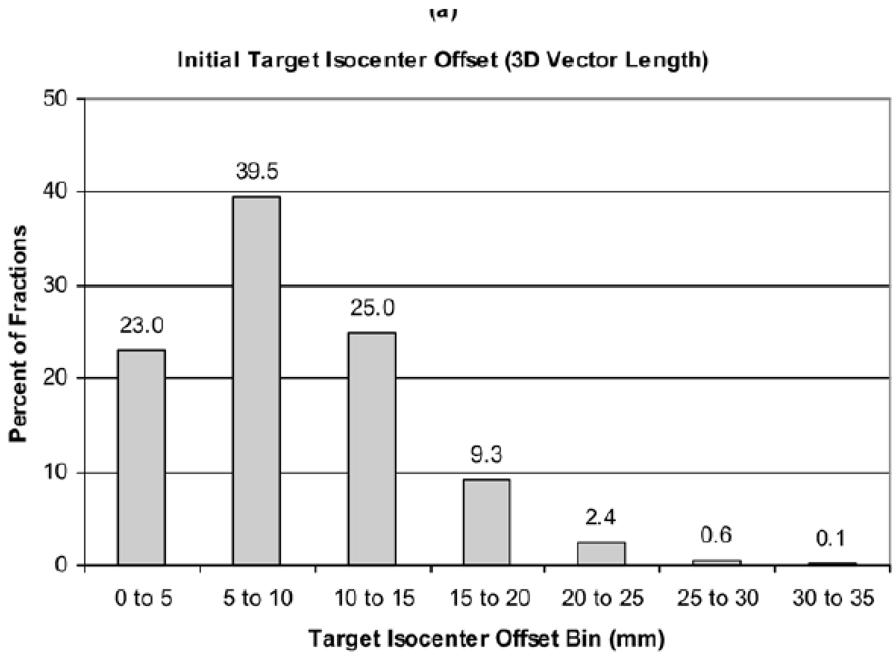
Intrafraction prostate motion

Kupelian, IJROBP, 2007

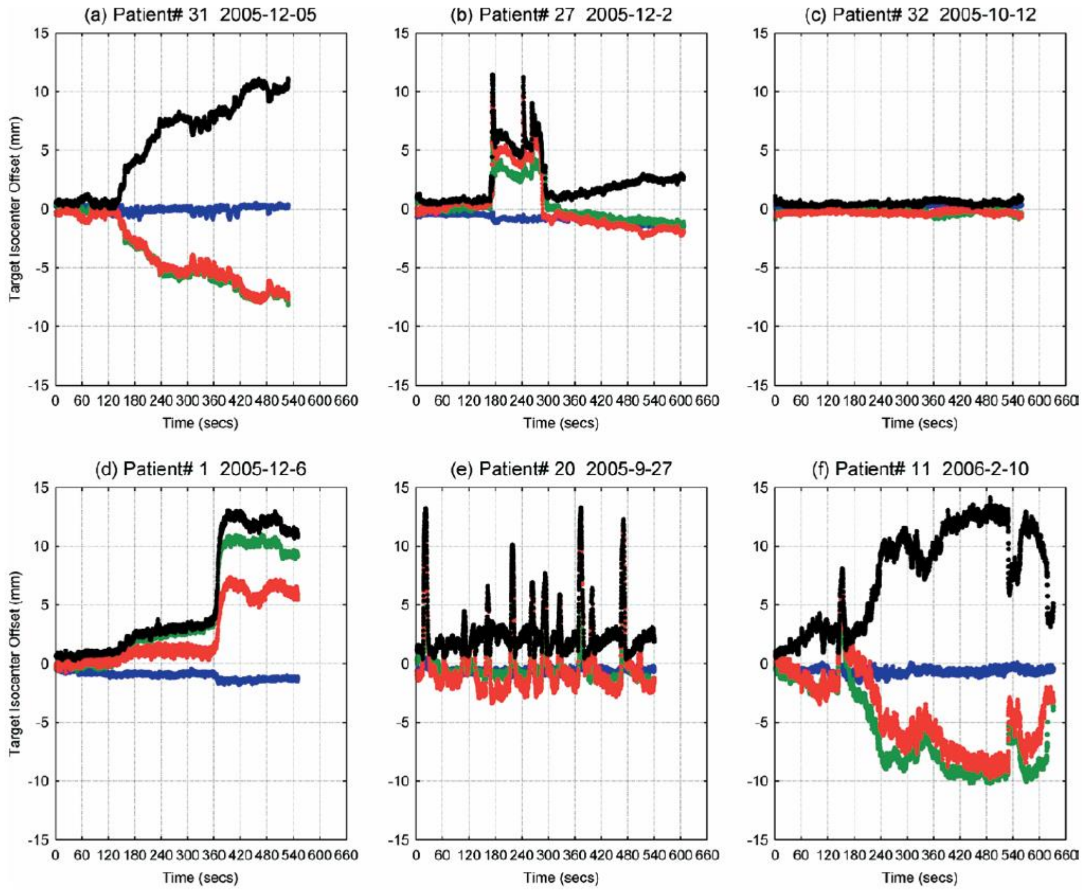
Multi-institutional study

35 / 41 patients were tracked

~1200 tracking sessions total



Intrafraction Motion Patterns



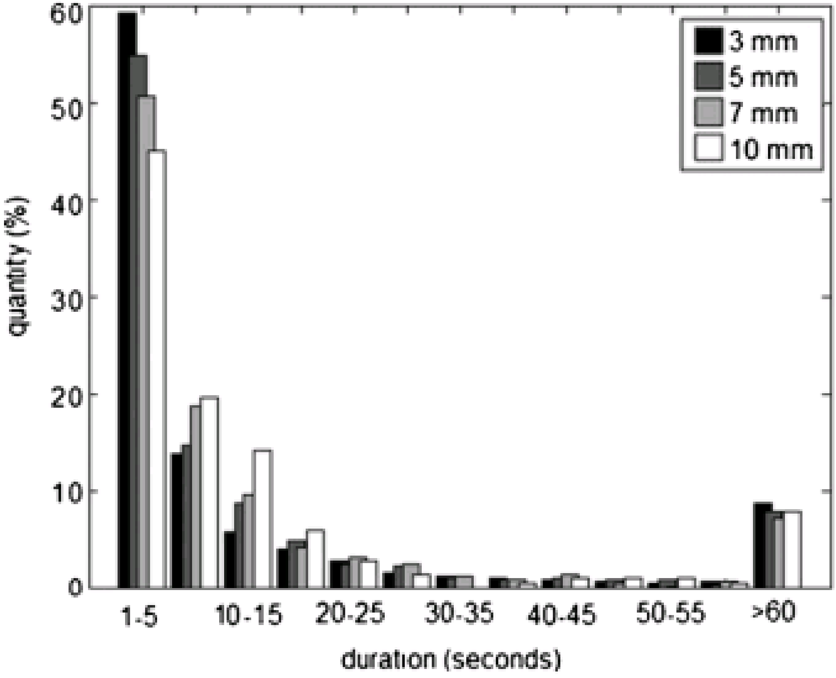
Intrafraction Prostate Motion Summary

Table 1. Characterization of the tracking data

No. fractions analyzed	Fractions with >3-mm excursion for >30 s cumulative		Fractions with >5-mm excursion for >30 s cumulative	
	#	%	#	%
1157	473	41	179	15

Looking at the electromagnetic tracking prostate trial

- No guidance on intervention for prostate motion
- Will be only trial that mostly **collected** data, not measured intervention
- Most of the intrafration motion was small
- Larger motion with larger time courses of treatment



Malinowski, PMB, 2008

Ideal Radiotherapy Fiducial Marker

Easy insertion

No radiation dose perturbation

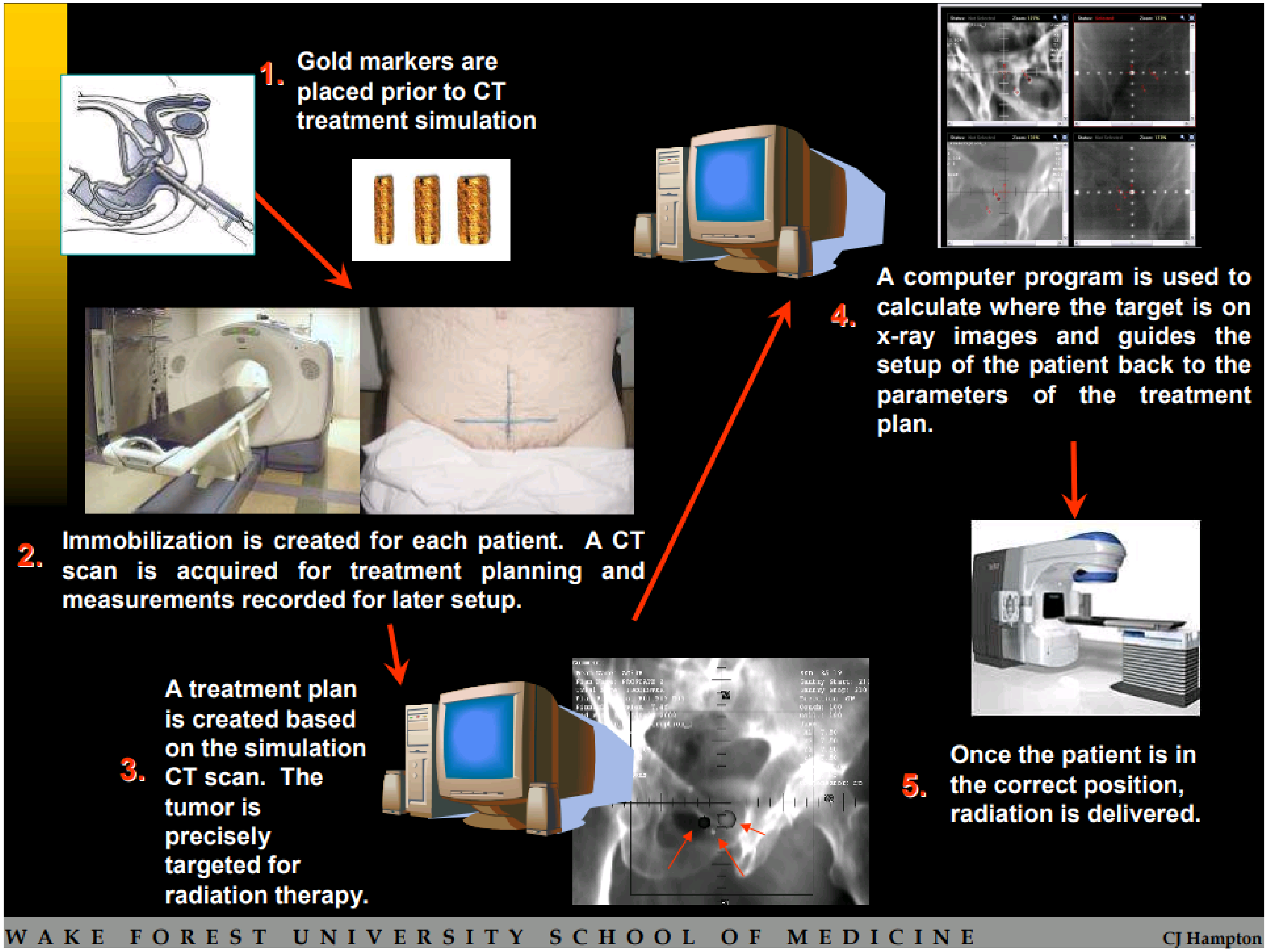
Visible on CT and MR

No artifact

Visible on both KV and MV X-ray images

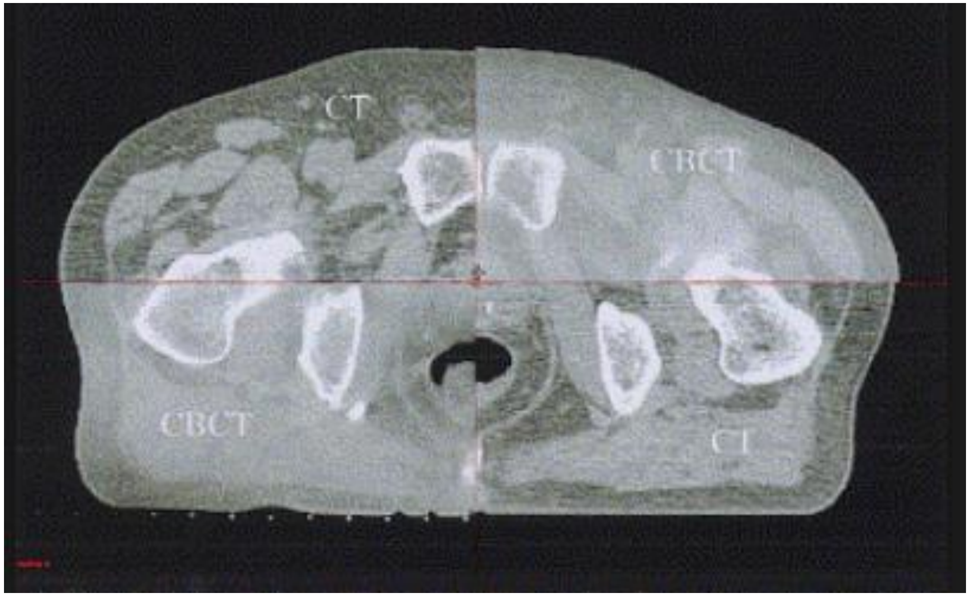
kV or MV imaging of fiducials

- Easiest to implement
- Use larger fiducials and oblique angles for MV imaging
- Smaller fiducials can be used for kV imaging



CBCT

- Can be used without fiducials
- Can use the prostate, or emphasis on prosate/rectal interface
- May require more training than fiducials
- Can find the ‘reason’ behind a large shift (ie change in rectal filling or bladder filling)



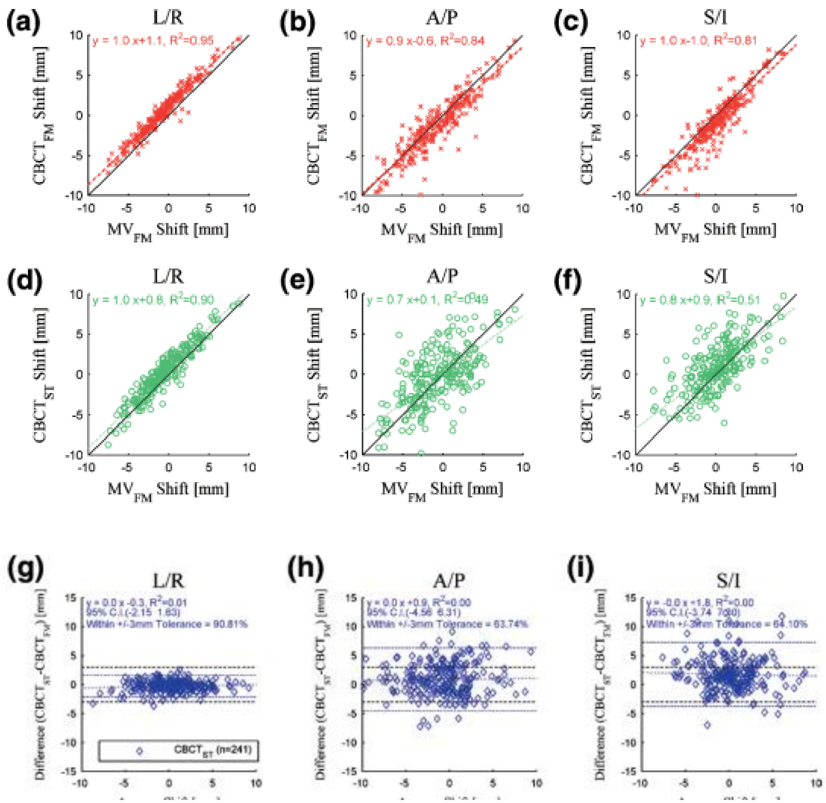
CBCT w/o markers vs Daily fiducial markers?

Probably no difference clinically

Compared portal imaging of fiducials with kVCBCT after ‘erasing fiducials’

Some difference, but below action level clinically

PMH went to CBCT only w/o fiducials over time



Mosely et al, IJROBP, 2007

Prostate IGRT analysis – American style

Prostate IGRT Comparison: Setup Accuracy

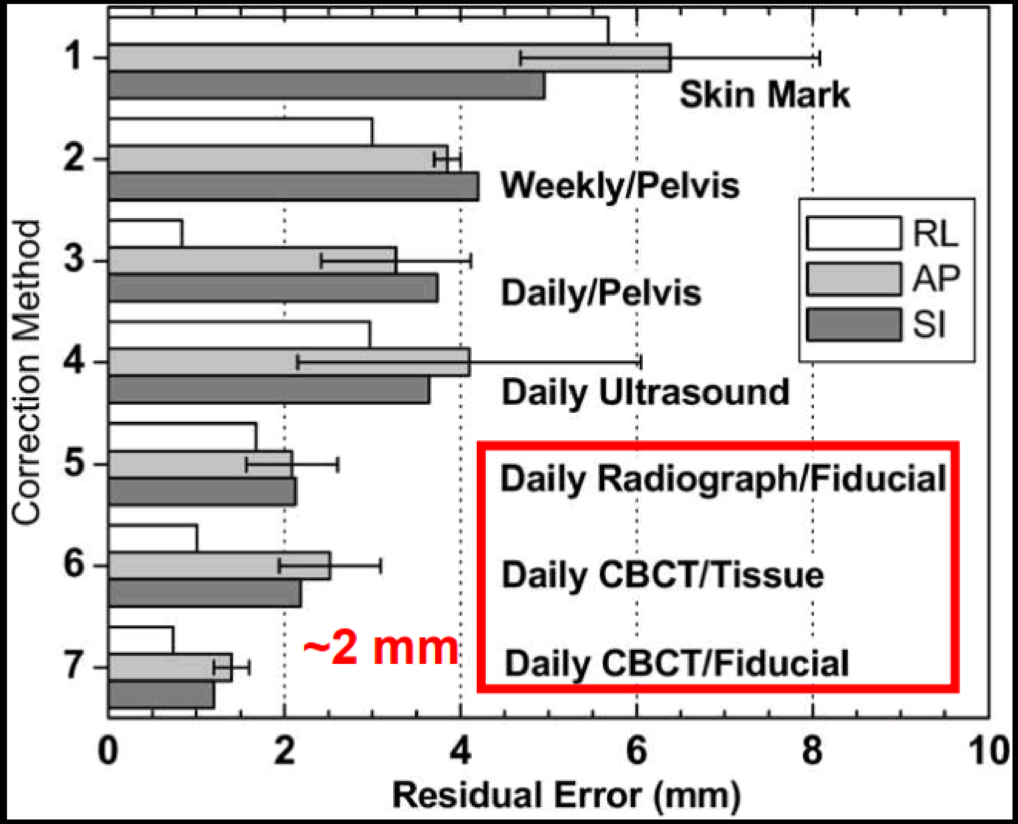


Figure 1
Comparison of residual errors for different image-guided correction techniques in prostate, in the left-right (LR), anteriorposterior, and superior-inferior directions.

GS Mageras et al, Seminars in Rad. Onc., 2007

What does our clinic do?

- Visicoil fiducials for most
- 5mm margins for prostate; 7mm for lymph nodes
- Daily kV imaging for markers
- Proton patients get rectal balloon and/of hydrogel with fiducials
- Non-fiducial patients either have MRgRT or CBCT guided RT

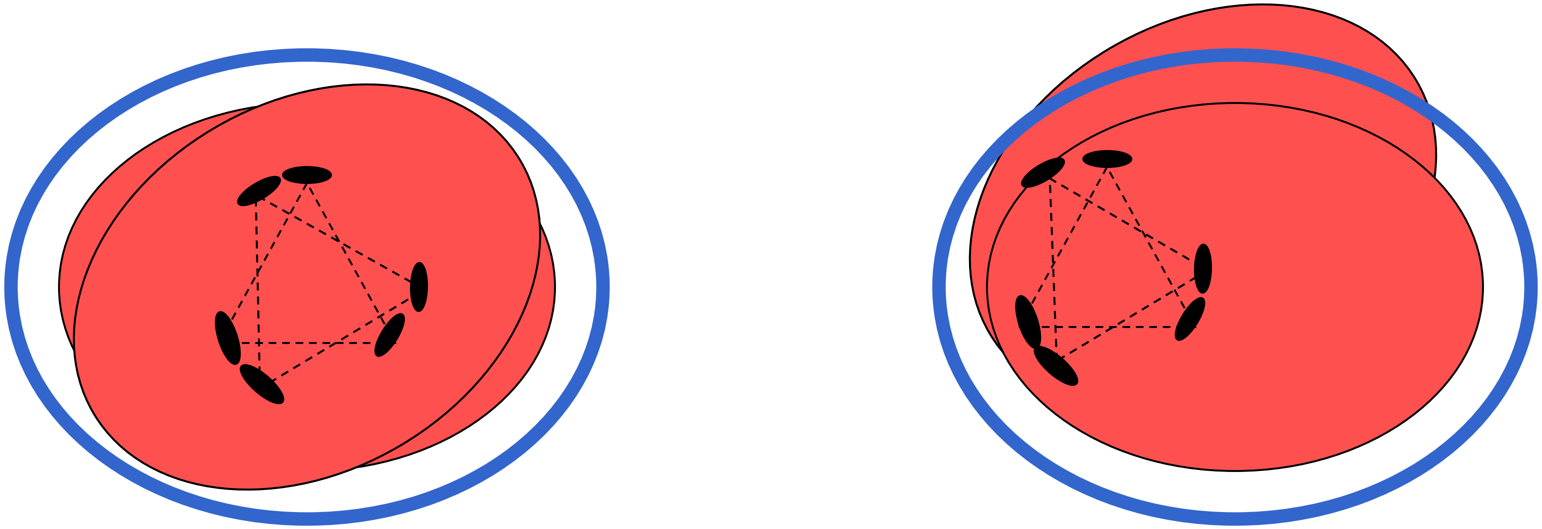
A last word - Rotation

Prostate motion didn't matter with traditional (1 cm) margins and low dose gradients

Now that prostate translational motion can be monitored and intervened upon, rotations have become more important

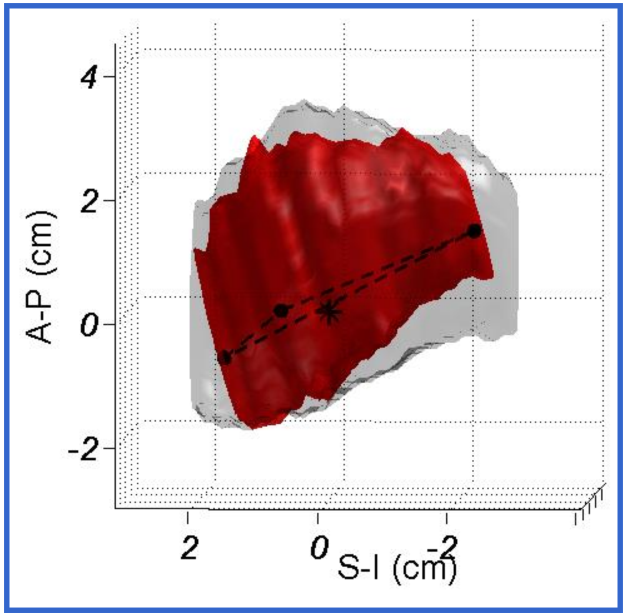
Theory
Rotation varies per implant

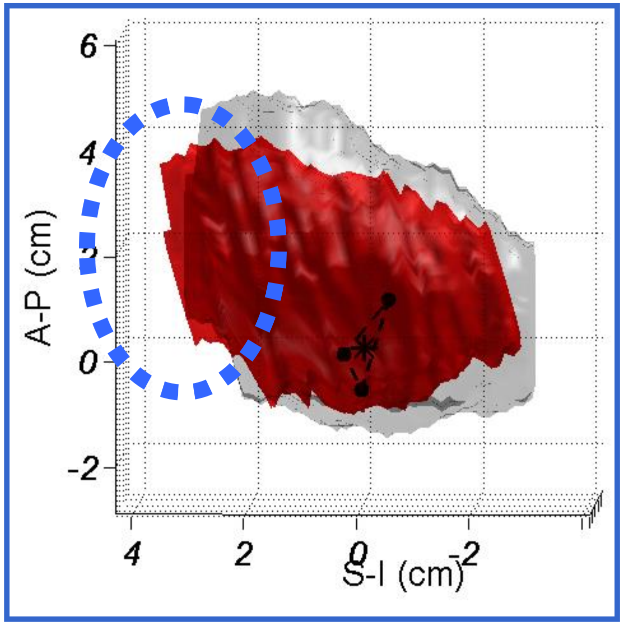
Rotational effects are dependent on the implant



Target
Rotation varies per target shape

Motion may effect coverage differently for different target shape





15 degree rotation for two different targets (3mm PTV)

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Cautionary Note

Localization Summary

Isocenter Localization	Lat(Left+)	Long(Sup+)	Vert(Ant+)
Shift from Initial Setup (cm):	0.46	0.32	-0.31
Confirmed Isocenter Offset (cm):	0.03	0.06	-0.03
Time:	03:07:20 PM		

Intertransponder Distances Planned Measured

	Limit	Measured
Geometric Residual (cm):	0.20	0.11
Rotation - Pitch (deg):	10.0	32.2
Rotation - Roll (deg):	10.0	7.0
Rotation - Yaw (deg):	10.0	0.9

Session Overrides:

Rotation compensation threshold exceeded at treatment time

Tracking Summary

Tracking Start Time:	03:07:35 PM
Total Tracking Time (hh:mm:ss):	0:08:50
Tracking Time while radiation detected:	0:01:58

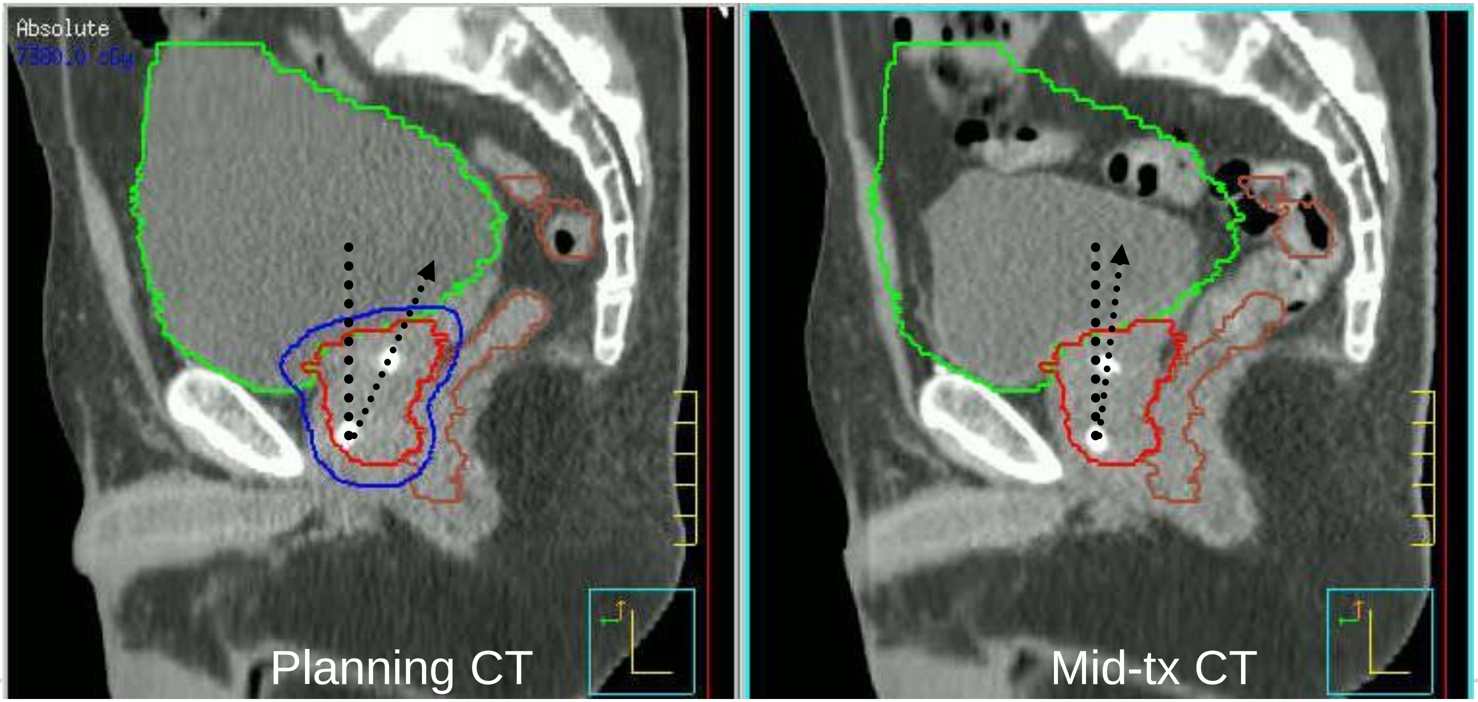
Summary of Target Excursions Outside of Tracking Limits

	Tracking	Total Tracking Time			Tracking while Radiation Detected		
Direction	Limit	Time	Percent	Max Excur	Time	Percent	Max Excur
Left	0.30 cm	0 sec	0%	0.05 cm	0 sec	0%	0.03 cm
Right	0.30 cm	0 sec	0%	0.09 cm	0 sec	0%	0.03 cm
Superior	0.30 cm	0 sec	0%	0.29 cm	0 sec	0%	0.25 cm
Inferior	0.30 cm	0 sec	0%	0.23 cm	0 sec	0%	-0.04 cm
Anterior	0.30 cm	6 sec	1%	0.39 cm	1 sec	1%	0.32 cm
Posterior	0.30 cm	0 sec	0%	0.19 cm	0 sec	0%	0.10 cm
Total		6 sec	1%		1 sec	1%	

Rescan of patient

Patient overfilled bladder at simulation CT (right) and so CT scan may not be representative of patient position for treatment

May see ‘systematic’ rotation during treatments



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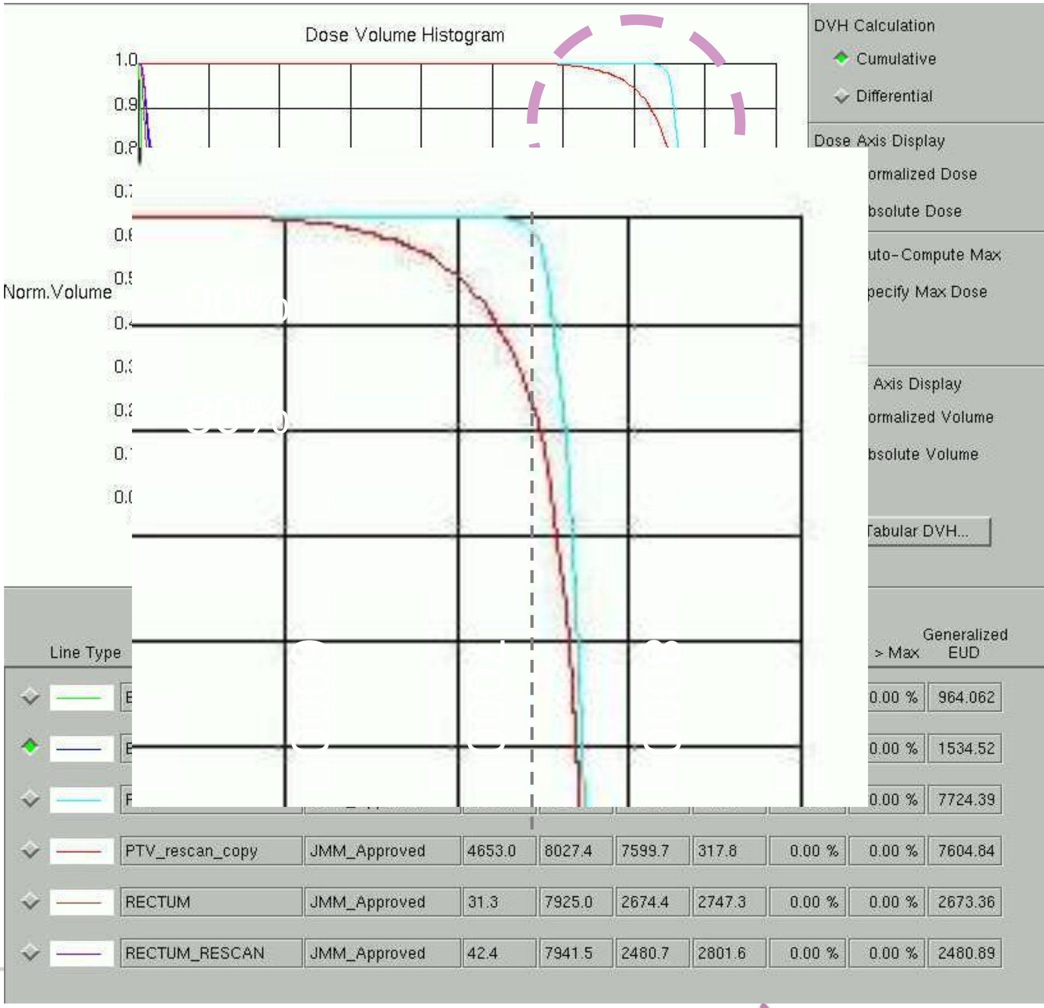
Dose Error

Patient may require re-scanning and plan evaluation with the prostate at a typical treatment position

New fiducial positions are acquired from new scan

Often can 'snap' original plan to new fiducial coordinates with good coverage

Uncommonly (5% of time), the patient needs a whole new plan



Summary

- Prostate cancer radiotherapy is extremely effective, but competes against surgery and surveillance for low grade disease
- The differentiating side effect for radiotherapy is related to the rectum
- IGRT will depend on
  - Target (subglandular, gland, seminal vesicles, pelvic lymph nodes)
  - Equipment/Technology
  - Interest/ability/resources for training
- Very straightforward to implement prostate IGRT – can be a 'team win' for department
- Don't forget about rotation!

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WWW.ESTRO.ORG/SCHOOL

Uncertainties and margins in image guided radiotherapy

Marcel van Herk

Institute of Cancer Sciences

Manchester University

The Christie NHS Trust

(Formerly at the Netherlands Cancer Institute)

MANCHESTER 1824

The University of Manchester

Manchester Cancer Research Centre

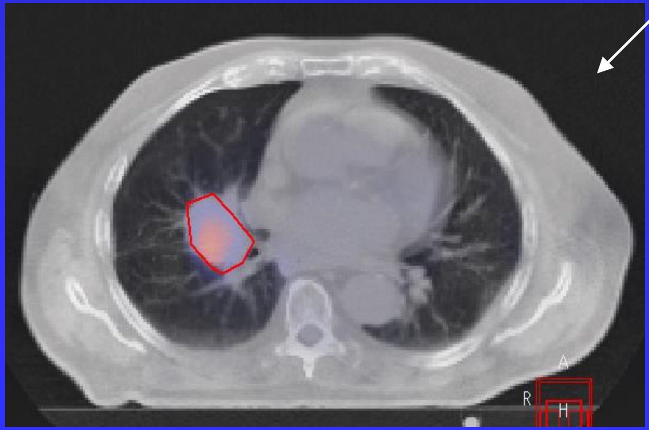
The Christie NHS

NHS Foundation Trust

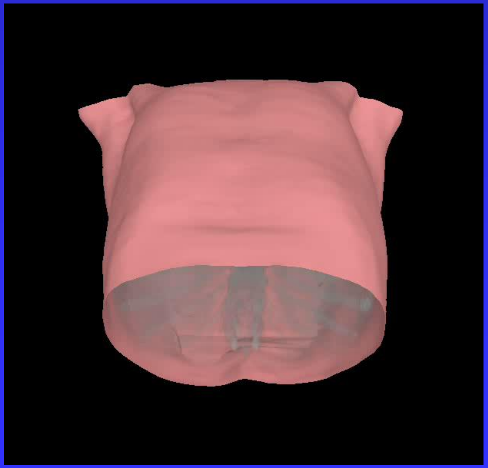
Classic radiotherapy procedure

Tattoo, align and scan patient

Align patient on machine on tattoos and treat (many days)

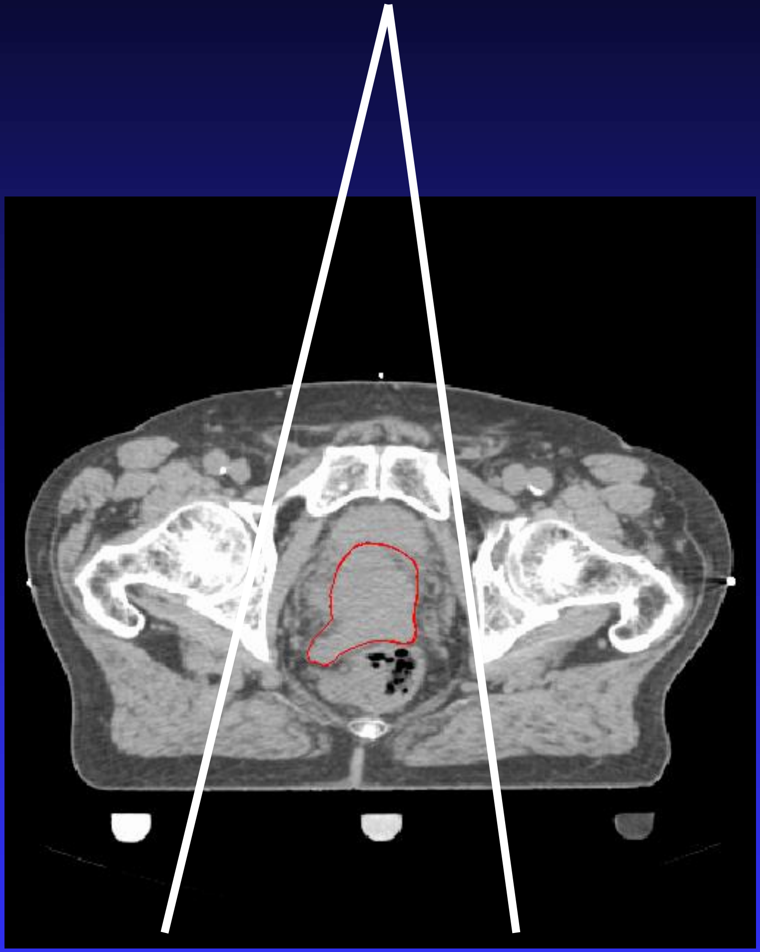


Draw target and plan treatment on RTP

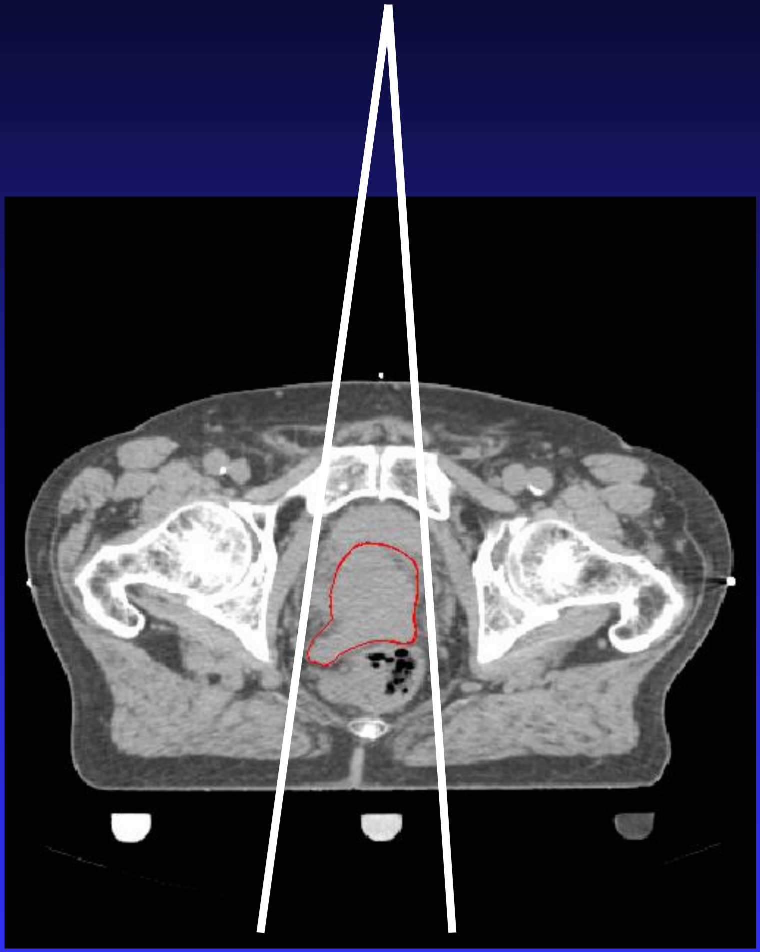


In principle this procedure should be accurate but …

Patients move !



1. Use large margins, irradiating too much healthy tissues



2. Use small margins, and risk missing the target

3. Or: use image guided radiotherapy

Nomenclature

- Gross error: mistakes, transcription errors, software faults:
  - must be caught by QA, not in this lecture

- Error: difference between planned measurand and its true value during treatment, however small

  - Uncertainty: unpredictable errors– quantified by standard deviations

  - Variation: predictable or periodic errors– quantified by amplitude or standard deviations

EPID dosimetry QA to catch gross errors: used for almost all patients at NKI

Reconstructed EPID dose (VMAT case)

EPID movie

-140° 140°

per frame

cumulative

Precision: within few %, enough to catch gross errors

Mans et al, 2010

Gross errors detected in NKI

TABLE I. Errors detected by means of EPID dosimetry from the clinical introduction to July 2009, grouped by (a) treatment site and (b) error type.

(a) Site	Clinical introduction	No. of patients	No. of errors
Prostate	02–2005	1018	2
Rectum	07–2006	602	4
Head-and-neck	06–2007	543	4
Breast	01–2008	1319	2
Lung	01–2008	454	2
Others	01–2008	401	3
	Total	**4337**	**17**

(b) Error type	No. of errors
Patient anatomy	7
Plan transfer	4
Suboptimally tuned TPS parameter	2
Accidental plan modification	2
Failed delivery	1
Dosimetrically undeliverable plan	1
Total	**17**

0.4% of treatments show a gross error (>10% dose)

9 out of 17 errors would not have been detected pre-treatment !!

Mans et al, 2010

What happens in the other 99.6% ?

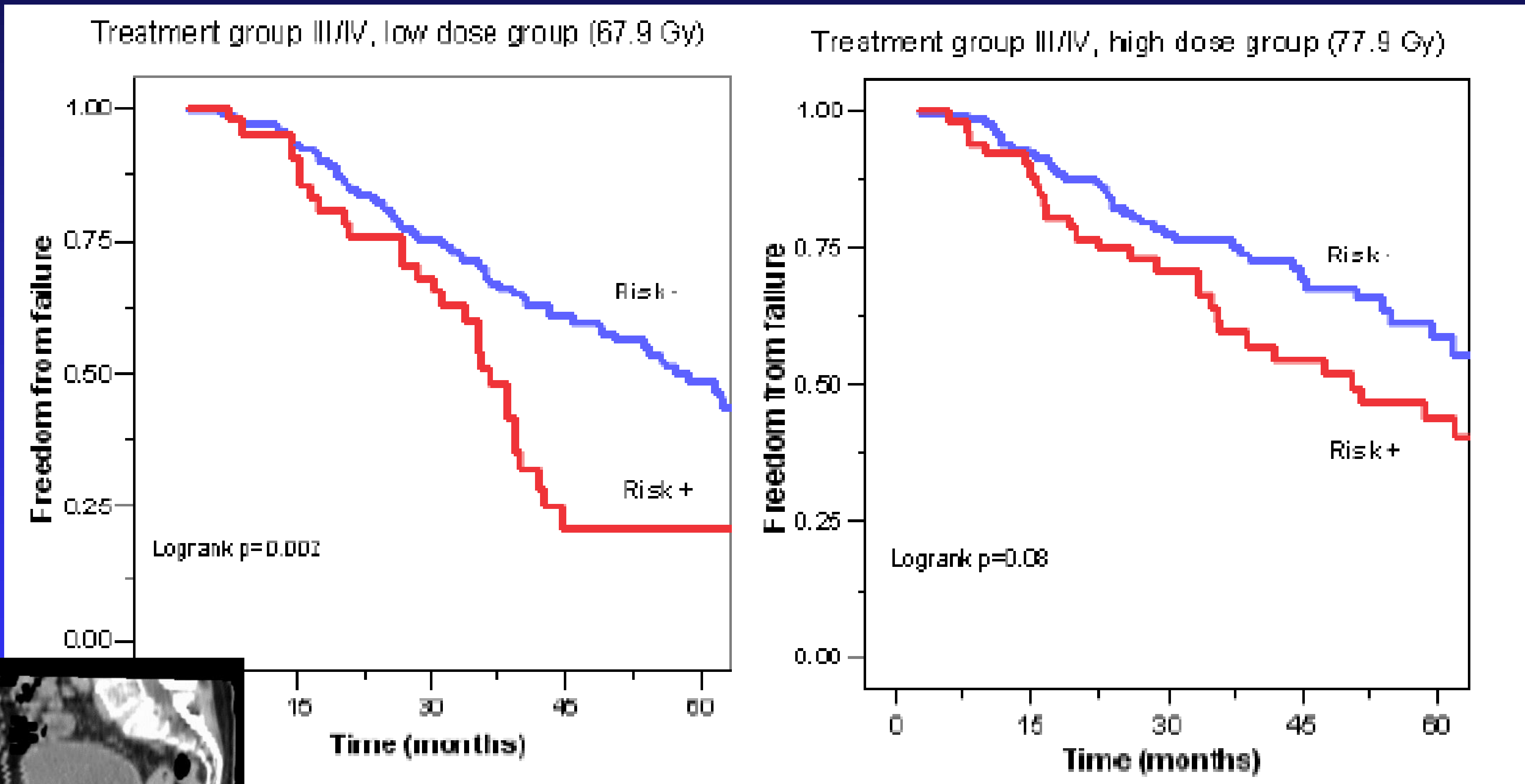
- There are many small unavoidable errors (mm size) in all steps of radiotherapy
  - In some cases many of these small errors point in the same direction
  - I.e., in some patients large (cm) errors occur(ed)

- This is not a fault, this is purely statistics

- What effect does this have on treatment?
  - We do not really know!

Motion counts? Prostate trial data (1996)

N=185 (42 risk+) N=168 (52 risk+)



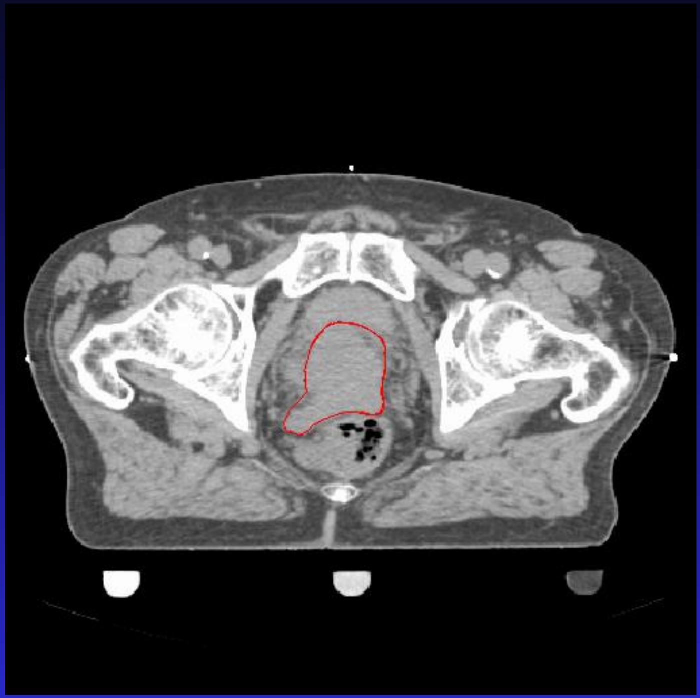
Risk+: initial full rectum, later diarrhea

Heemsbergen et al, IJROBP 2007

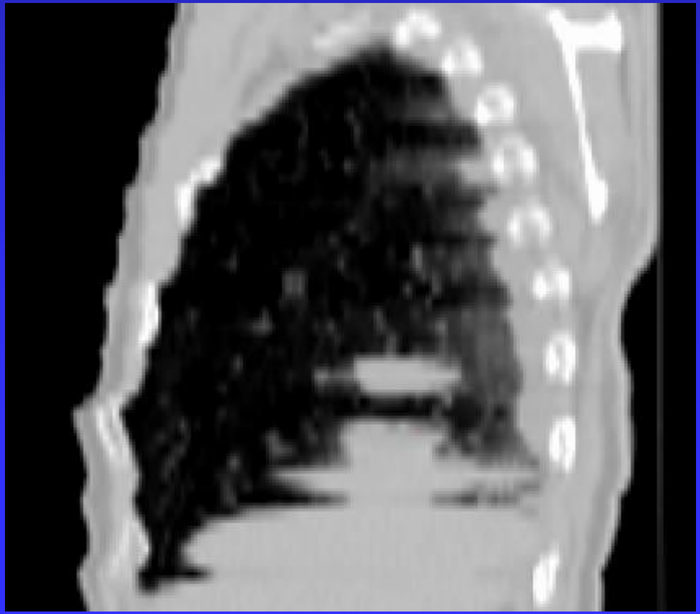
Did you do a good job planning the treatment?

Imaging errors

- CT scan is just a random snapshot of a changing patient
  - Organ motion and setup error are frozen in arbitrary position

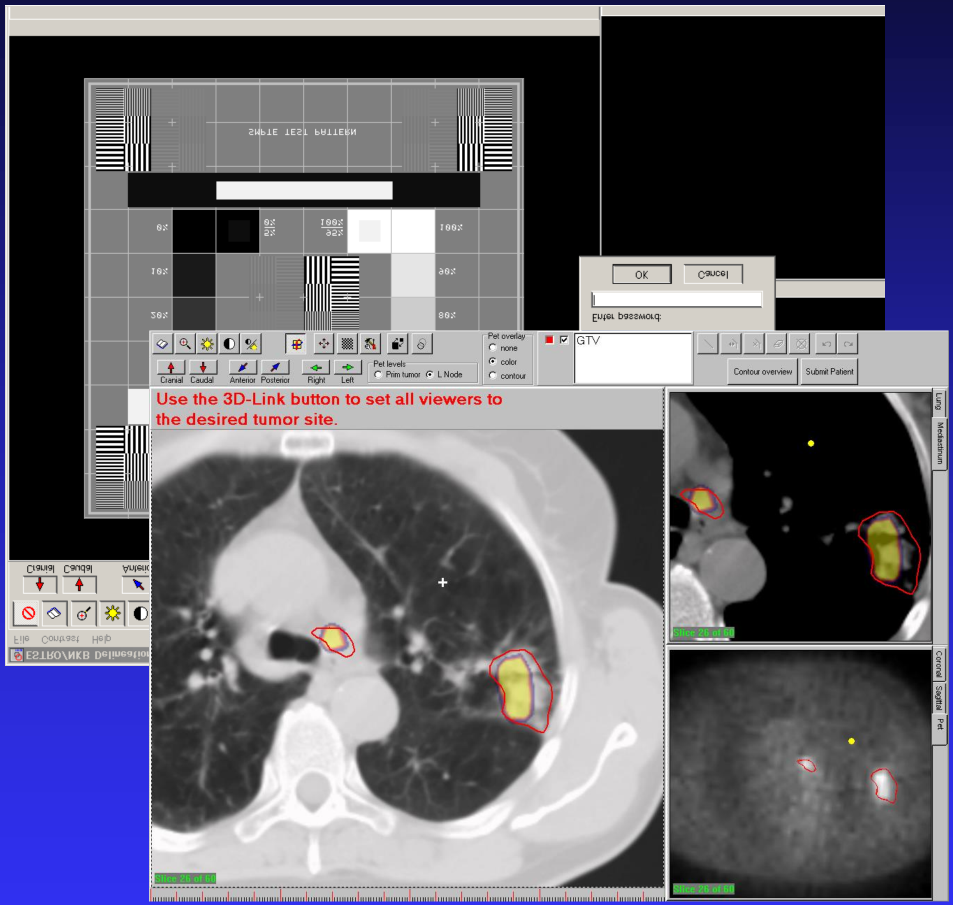


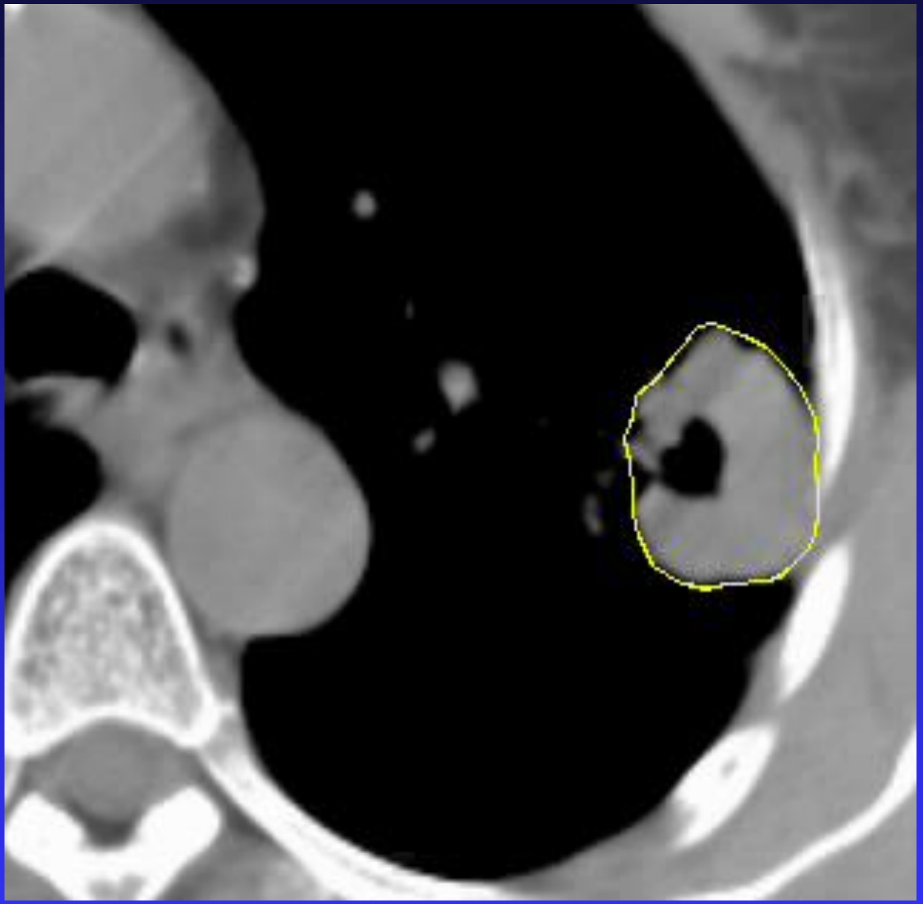
- Interference between motion and imaging distorts image contents



- The beams will be pointed to the target in this image → systematic error !

Main planning error: GTV/CTV delineation

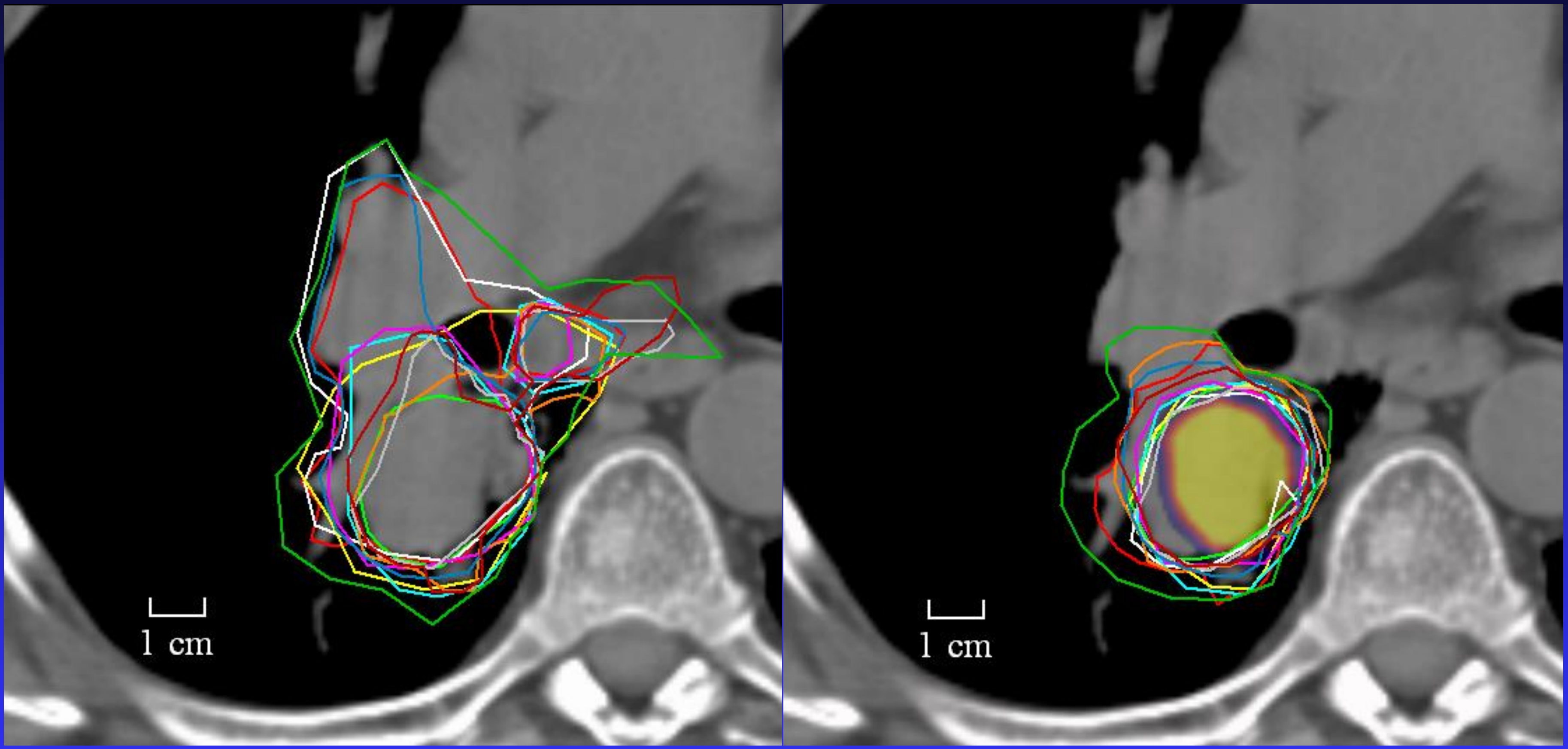




- 11 observers from 5 institutions, 22 patients
- newly developed delineation software (runs from CD)
- delineation on CT + (one year later) CT+PET

Steenbakkers et al, IJROBP 2005

Delineation variation: CT versus CT + PET

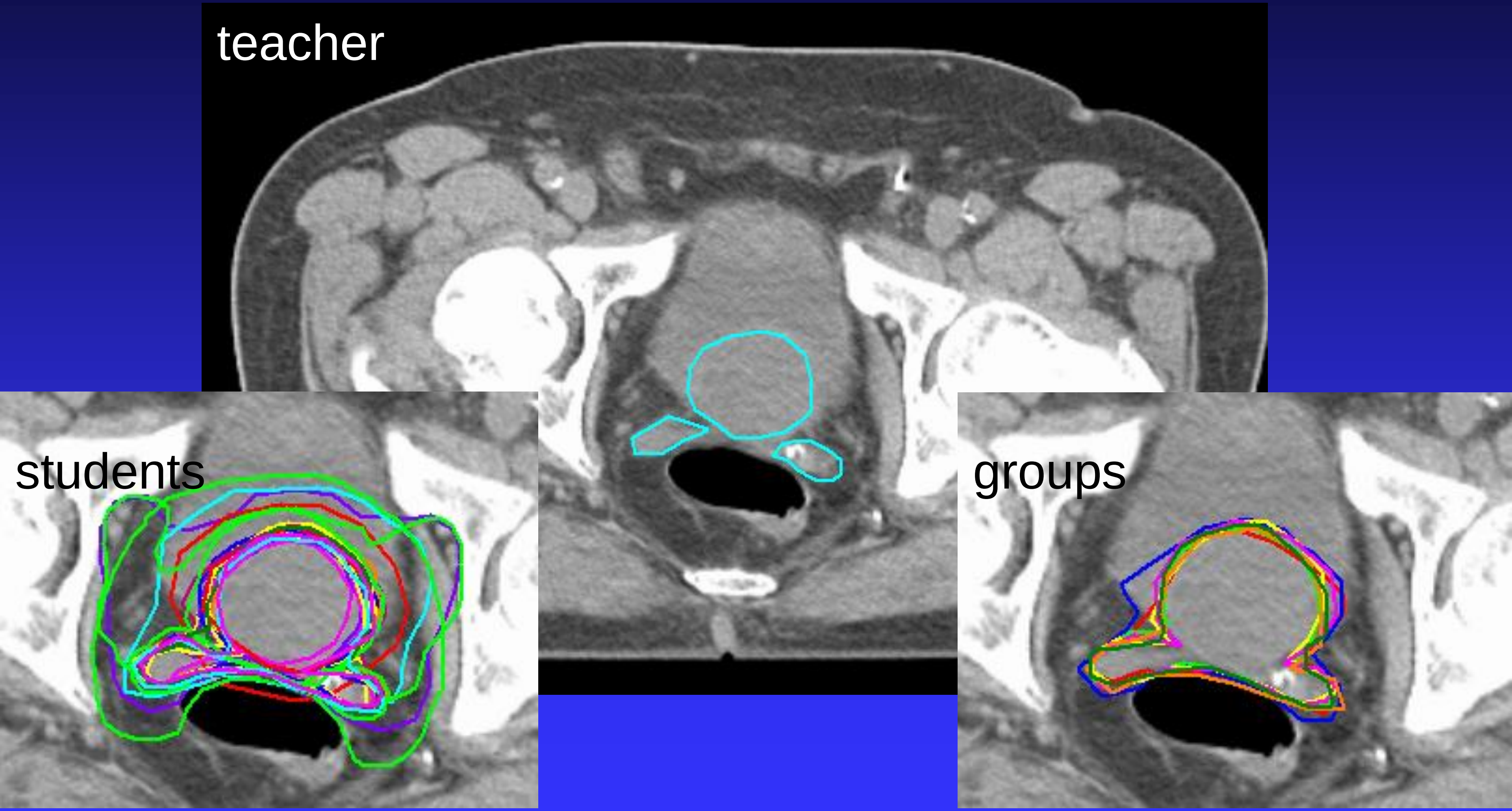


CT (T_2N_2) — SD 7.5 mm

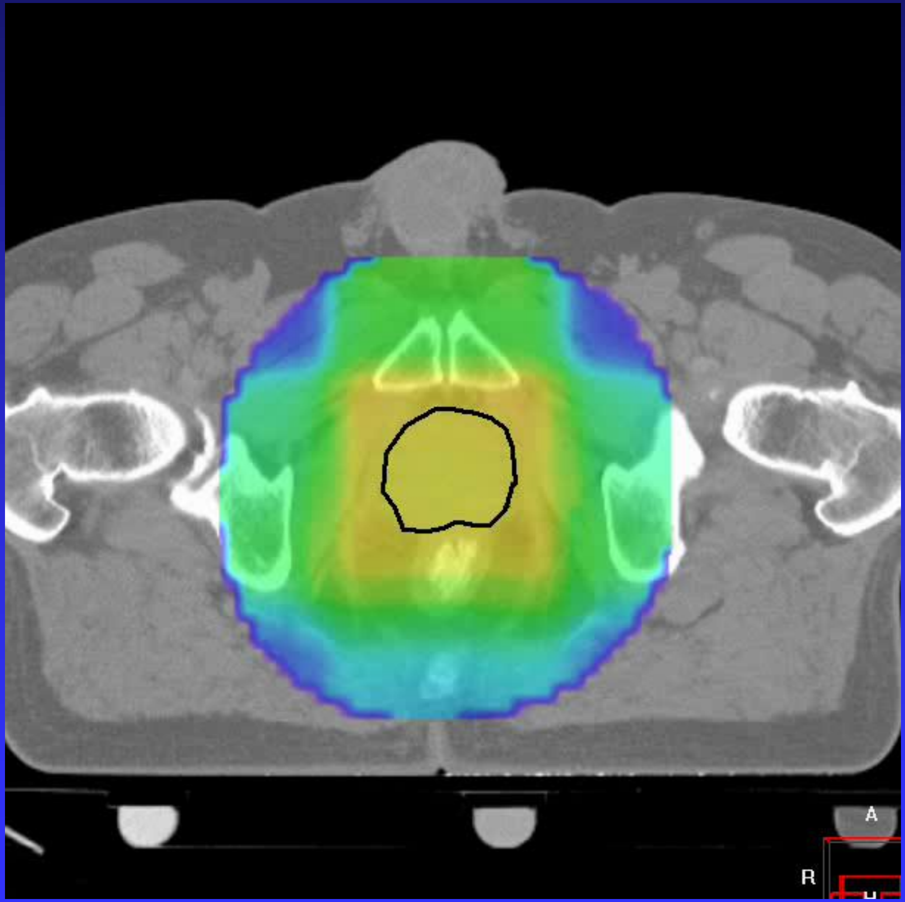
CT + PET (T_2N_1) — SD 3.5 mm

The beams will be pointed to the target the physician draws !

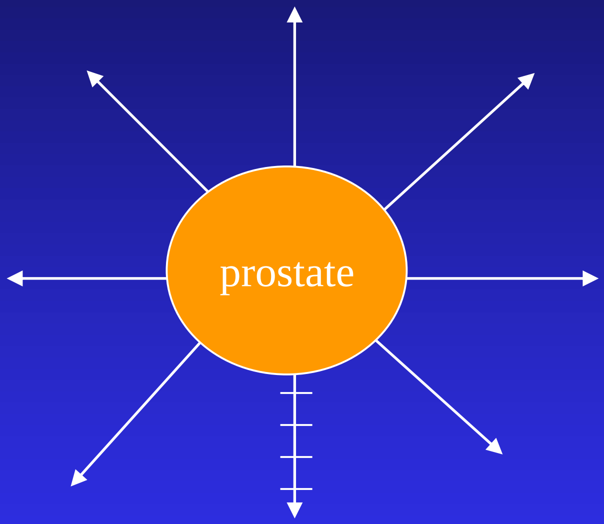
Effect of training



CTV: is dose outside the prostate related with outcome?
→ detect disease spread in historical data of high risk prostate cancer patients



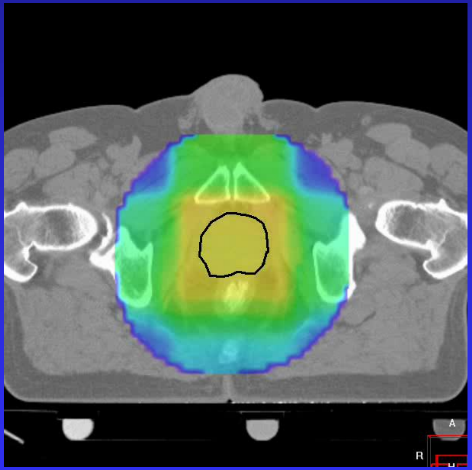
Mapping of planned dose cubes
to standard patient

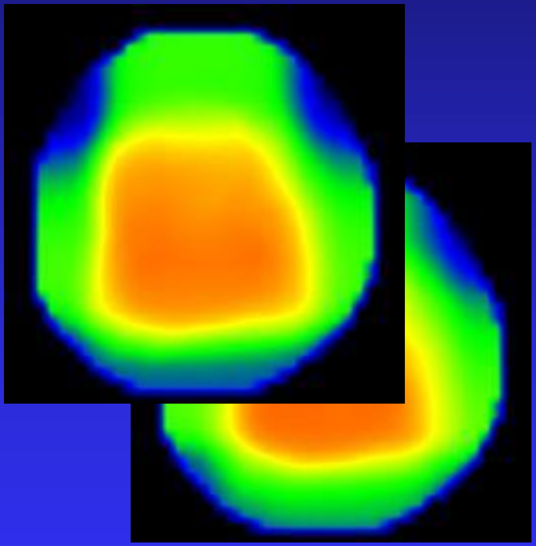


Dose differences due to:

- randomization
- anatomy
- technique

Question: where did we find the largest dose difference between failures and non-failures for high risk patients?

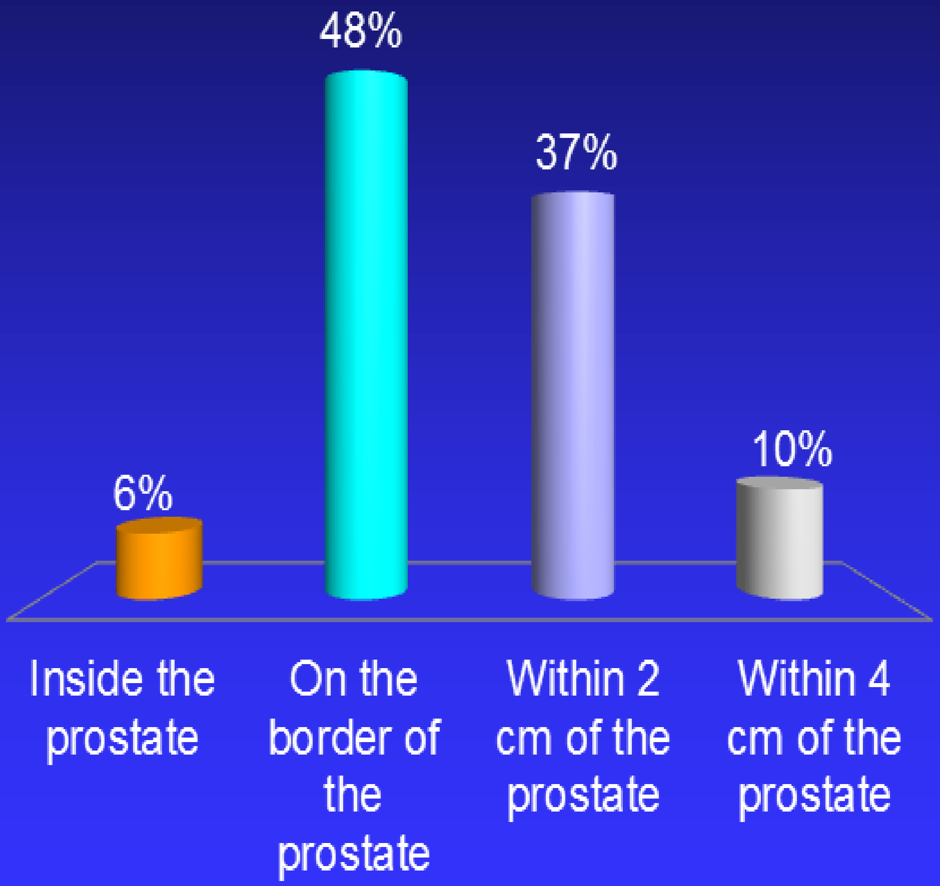




Controls/failures

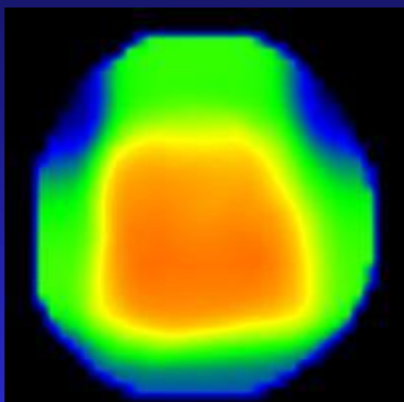
Where was the biggest dose difference?

A. Inside the prostate
B. On the border of the prostate
C. Within 2 cm of the prostate
D. Within 4 cm of the prostate



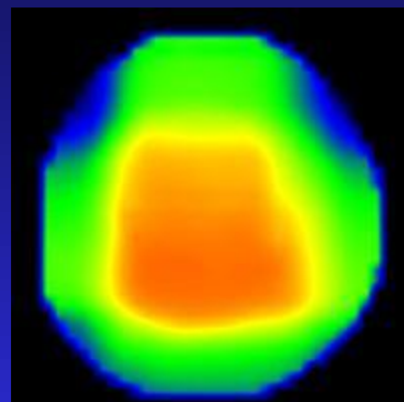
Estimate pattern of spread from response to incidental dose in clinical trial data (high risk prostate patients)

Average dose no failures –
average dose failures



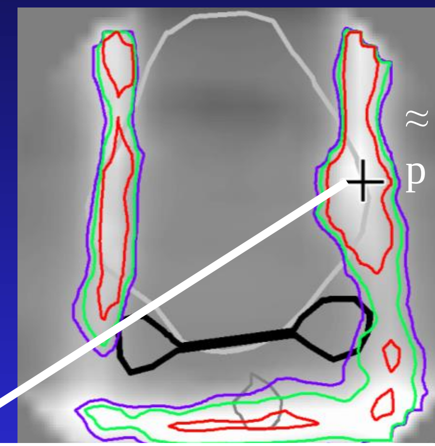
PSA controls

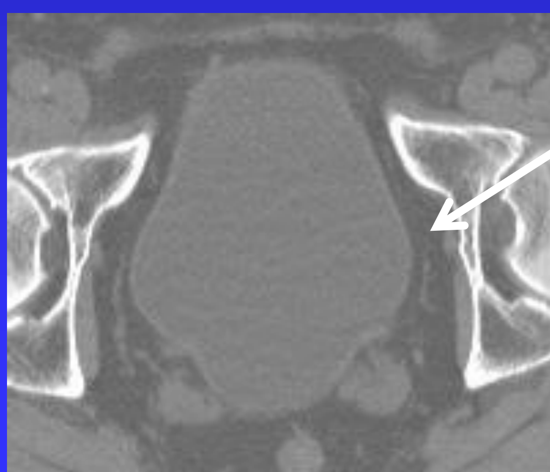
-

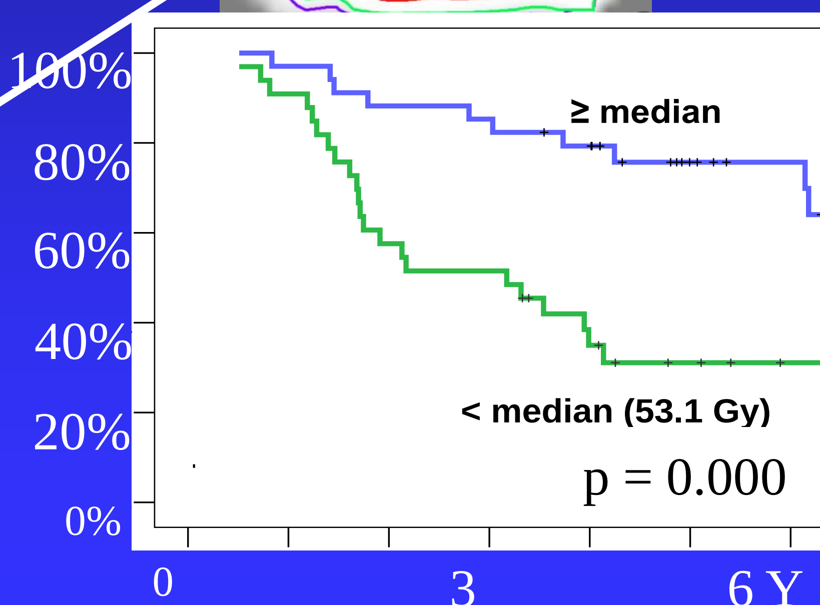


PSA failures

=







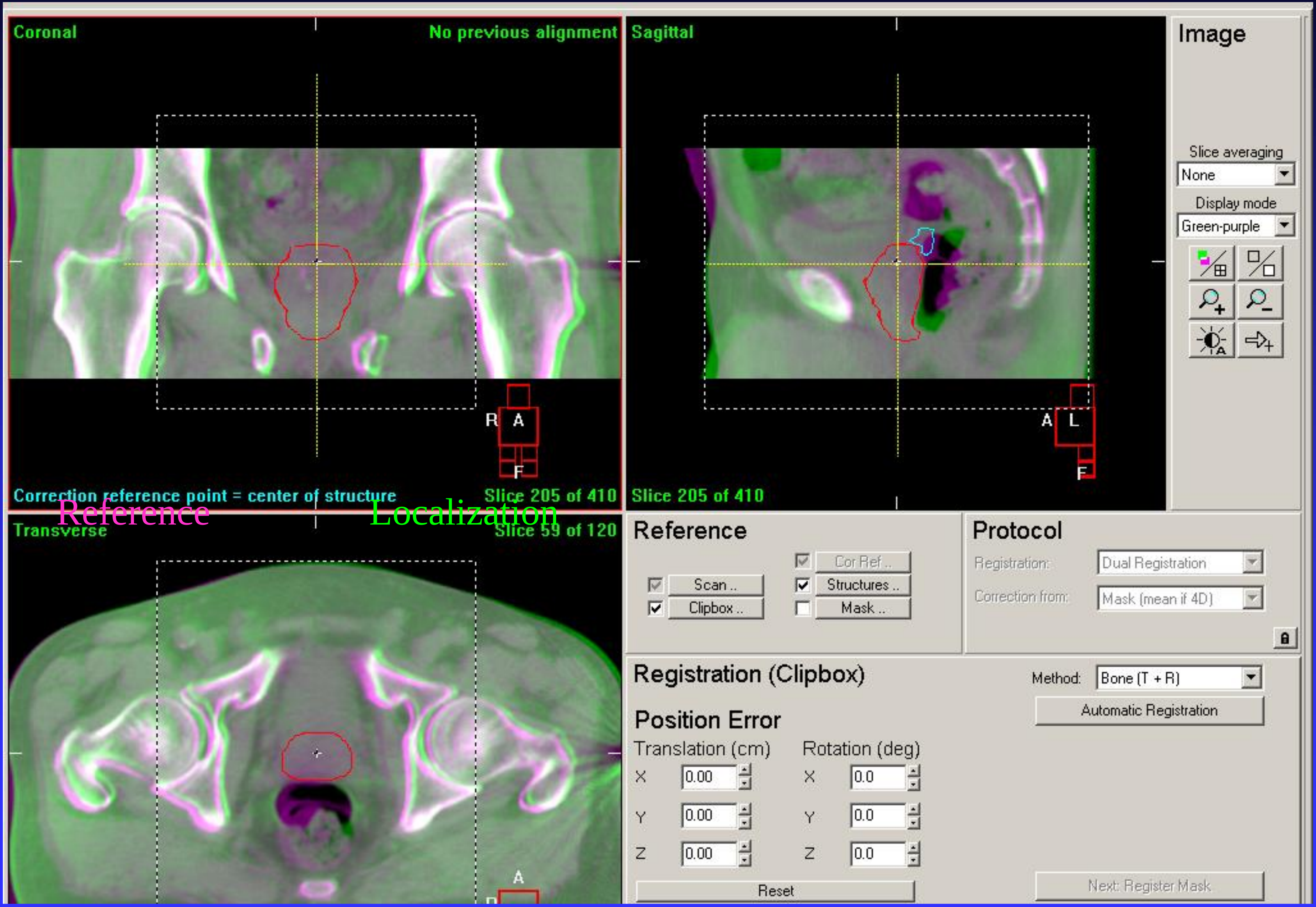
Witte et al, IJROBP2009; Chen et al, ICCR2010

Main errors in image guided RT

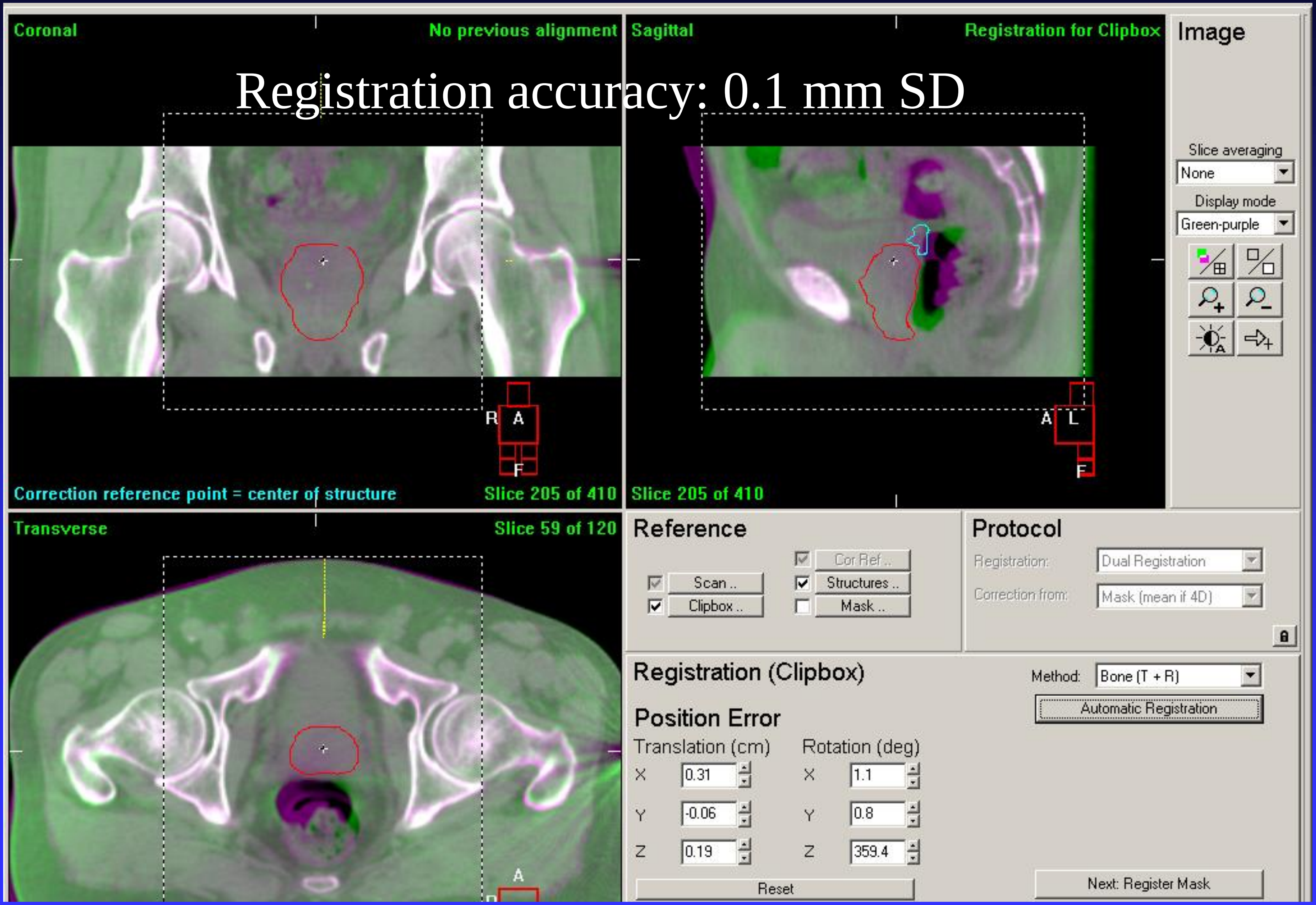
- Imaging (planning CT) and planning (delineation) errors
  - Systematic error not solved by image guidance
- Observer errors in image guidance
  - Random and systematic
- Short-term (intra-fraction) motion
  - Random and systematic
- Inadequacy of surrogate for tumor position
- Machine calibration

Are you an accurate observer ?

IGRT software: automatic bone localization



IGRT software: automatic bone localization



Does the tumor move after imaging ?

Short-term prostate motion (1 h)

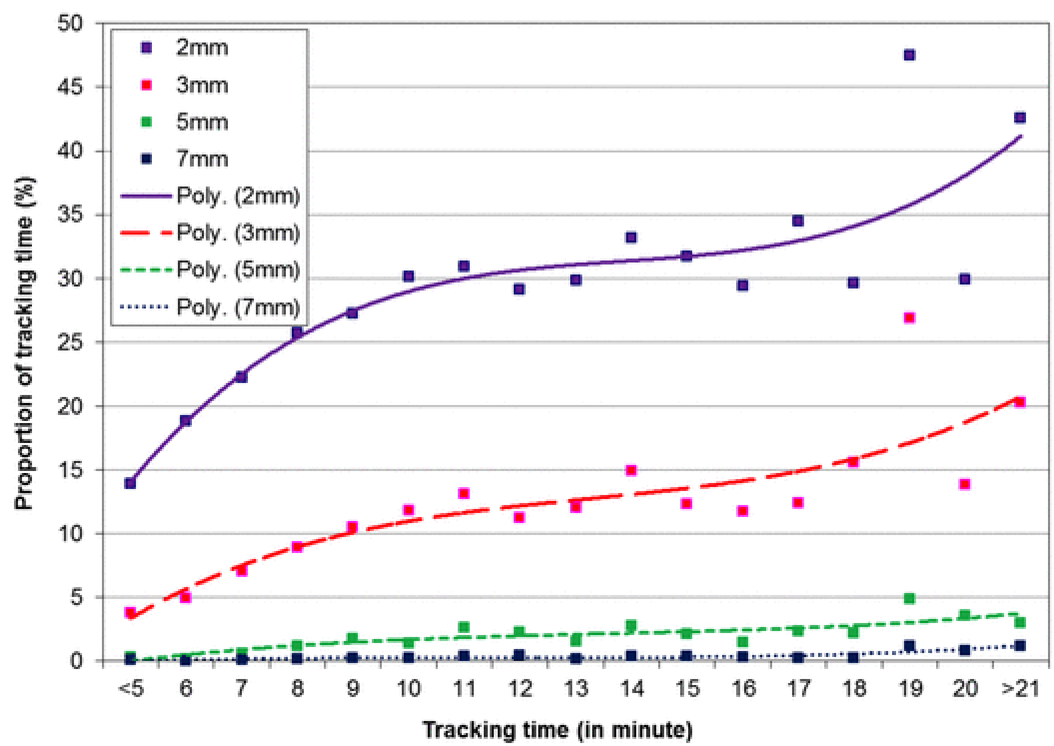
Data courtesy of Jaffray and Gilhezan, Beaumont

Intrafractional prostate motion during external beam radiotherapy monitored by a real-time target localization system

Xu Tong [1], Xiaoming Chen [2], Jinsheng Li [2], Qianqian Xu [1], Mu-han Lin [2], Lili Chen [2], Robert A. Price [2], Chang-Ming Ma [2,a]

Radiation Oncology Department,[1] Third-Affiliated Hospital of
China

Radiation Oncology Department,[2] Fox Chase Cancer Center,
Charlie.ma@fccc.edu



Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):609-18. Epub 2007 Nov 8.

Time dependence of intrafraction patient motion

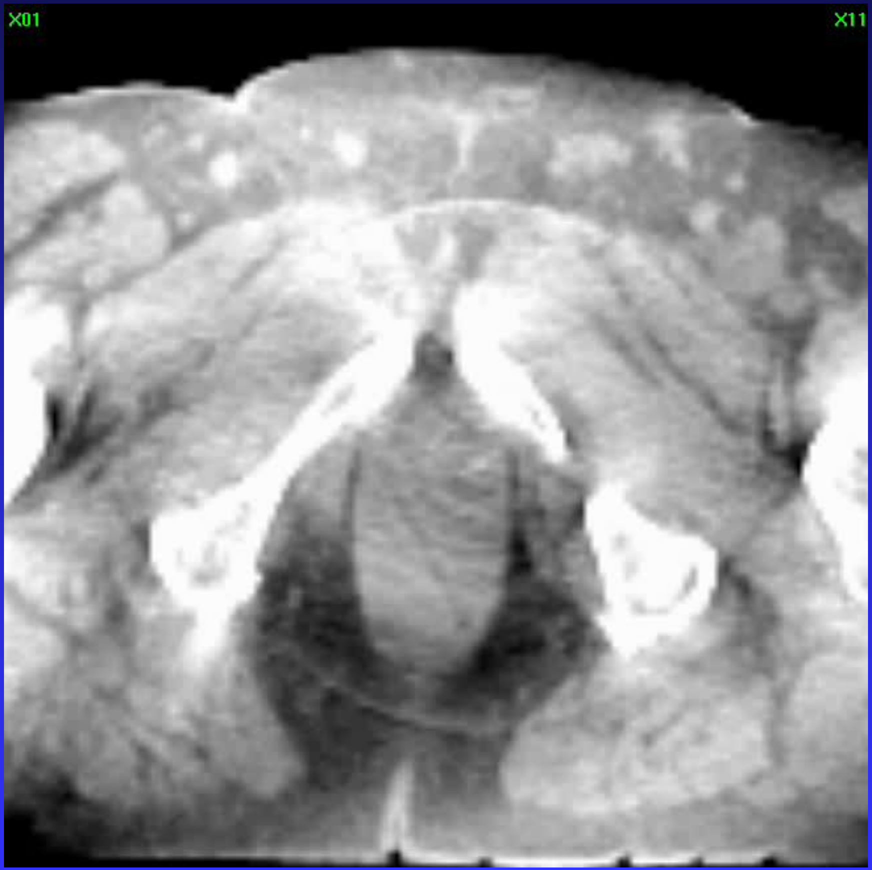
Hoogeman MS[1], Nuyttens JJ, Levendag PC, Heijmen BJ.

⊕ Author information

RESULTS: The SD of the systematic intrafraction displacements increased linearly over time for all three patient groups. For intracranial-, supine-, and prone-treated patients, the SD increased to 0.8, 1.2, and 2.2 mm, respectively, in a period of 15 min. random displacements for the prone-treated patients were significantly higher than for the other groups, namely 1.6 mm (1 SD) probably caused by respiratory motion.

Main problem for any prostate IGRT: moving gas

Projection images



cone-beam CT scan

Moving gas reduces image quality *and* introduces short term motion

Are you using a good surrogate for the tumor position?

Are markers perfect ?

Apex Base Sem. Vesicles

→ +/-1 cm margin required

Best: combine markers
with low dose CBCT ?

van der Wielen, IJROBP 2008
Smitsmans, IJROBP 2010

What should the margin be ?

Analysis of motion (random and systematic errors)

	patient 1	patient 2	patient 3	patient 4
fraction 1	0.5	0.0	0.2	0.7
fraction 2	0.6	-0.5	0.3	0.2
fraction 3	0.9	0.2	0.2	-0.4
fraction 4	1.3	-1.1	0.3	-0.1
mean	0.8	-0.4	0.3	0.1
sd	0.3	0.6	0.1	0.5

mean = M
SD = Σ
RMS = σ

Intra-fraction

0.0
0.3
0.4
0.1
0.3

Mean = 0.2

RMS of SD = σ_f

M = group systematic error (equipment)

Σ = standard deviation of the systematic (preparation) error

{ σ = standard deviation of the random (execution) error
σf = standard deviation of the intra-fraction motion

van Herk et al, Sem Rad Onc 2004

Definitions (sloppy)

- CTV: Clinical Target Volume
  The region that needs to be treated (visible plus suspected tumor)

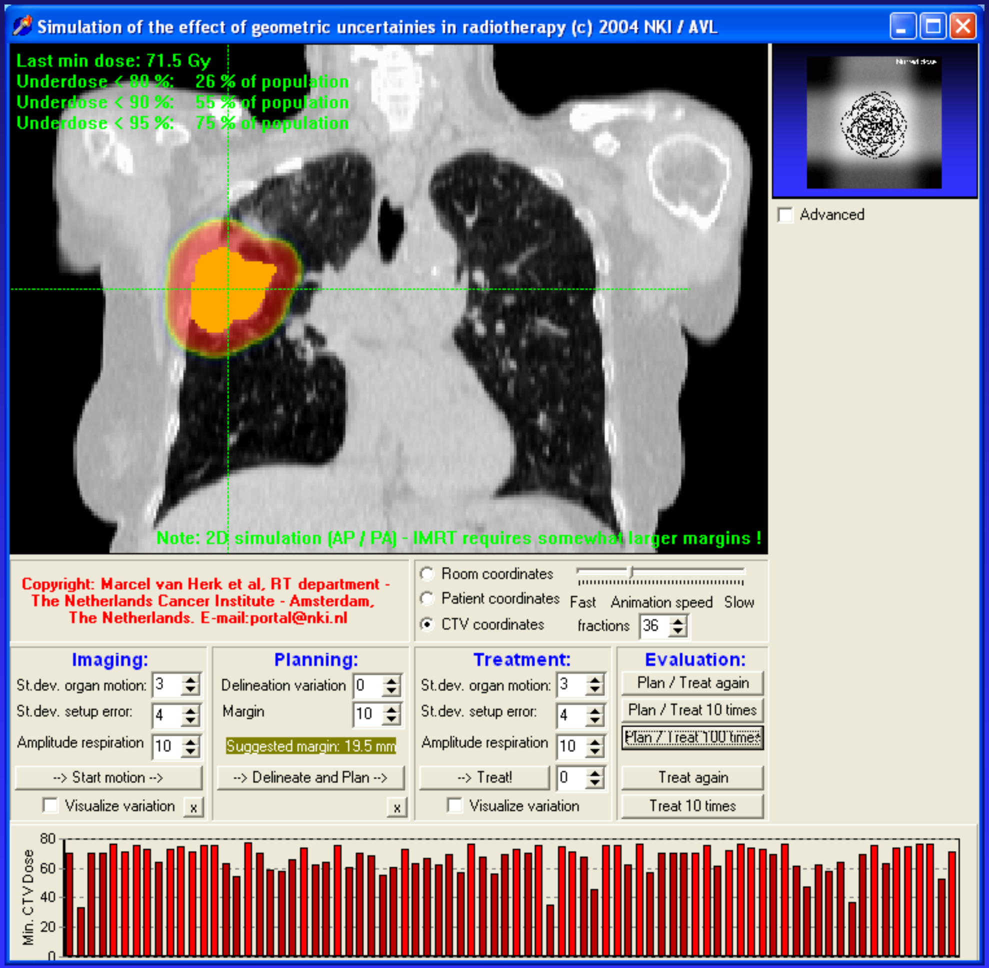
- PTV: Planning Target Volume
  The region that is given a high dose to allow for errors in the position of the CTV

- PTV margin: distance between CTV and PTV

- Don’t even think of using an ITV! (SD adds quadratically)

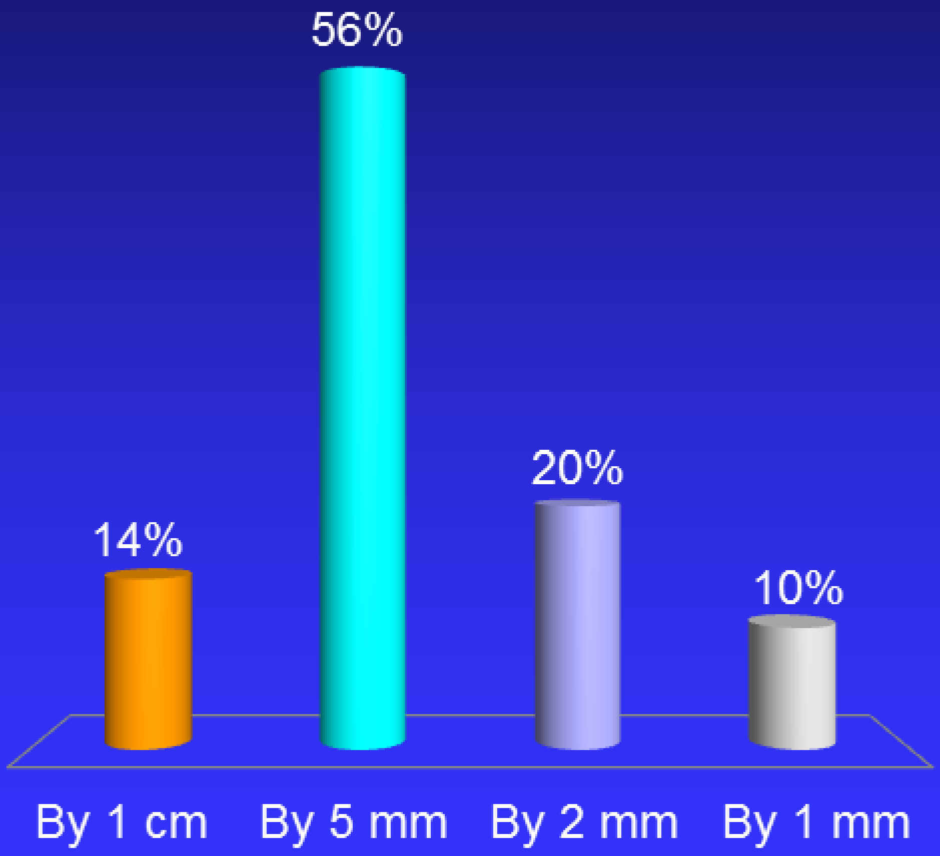
Demonstration – errors in RT

- Margin between CTV and PTV: 10 mm
- Errors:
  - Setup error:
    - 4 mm SD (x, y)
  - Organ motion:
    - 3 mm SD (x, y)
    - 10 mm respiration
  - Delineation error: optional



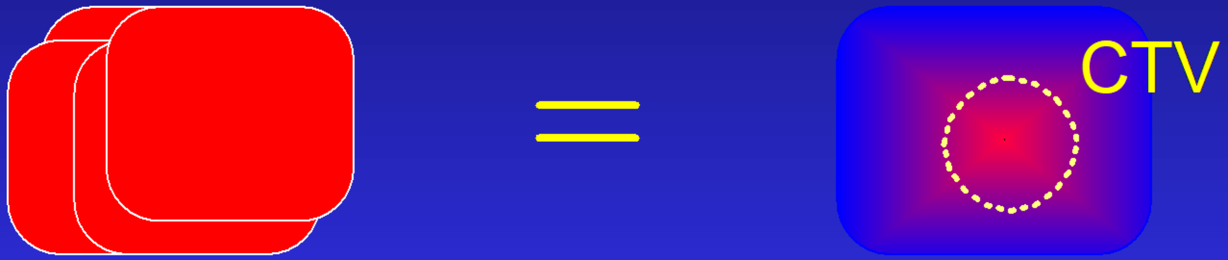
If we would gate the beam during treatment (eliminating respiratory movement) how much can the margin be reduced to keep 90% of patients treated correctly ?

A. By 1 cm
B. By 5 mm
C. By 2 mm
D. By 1 mm

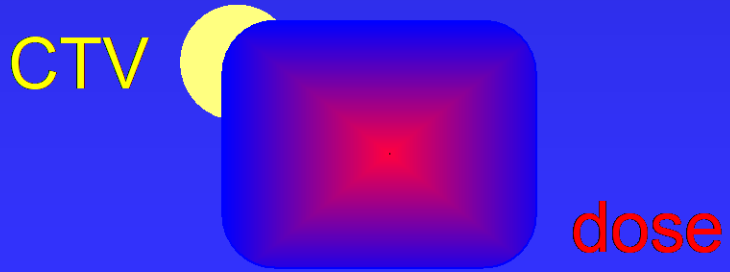


What is the effect of geometrical errors on the CTV dose ?

Treatment execution (random) errors blur the dose distribution



Preparation (systematic) errors shift the dose distribution

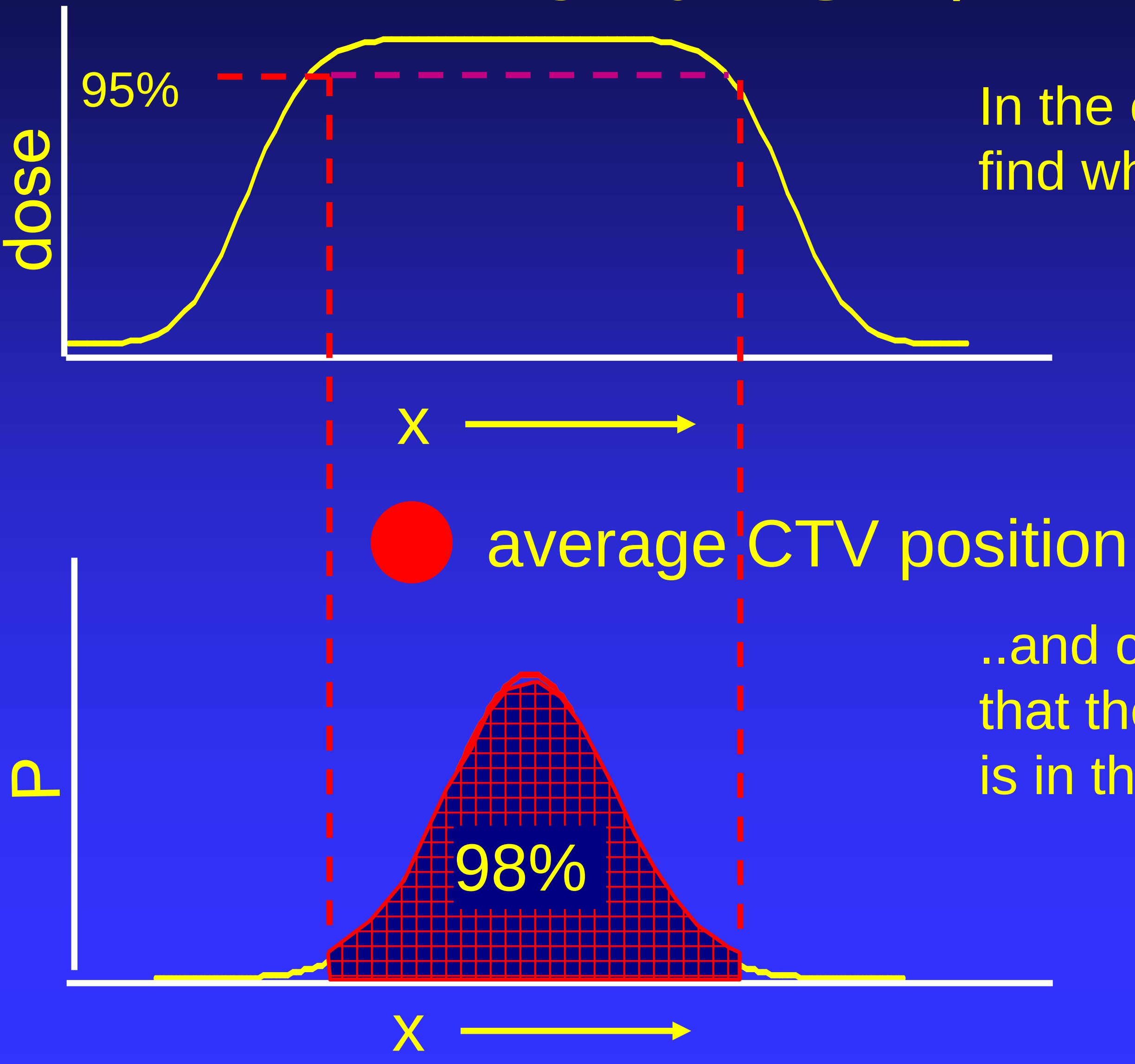


Analysis of CTV dose probability

- Blur planned dose distribution *with all execution (random) errors* to estimate the cumulative dose distribution

- For a given *dose* level:
  - Find region of space where the cumulative dose exceeds the given level
  - Compute *probability* that the CTV is in this region

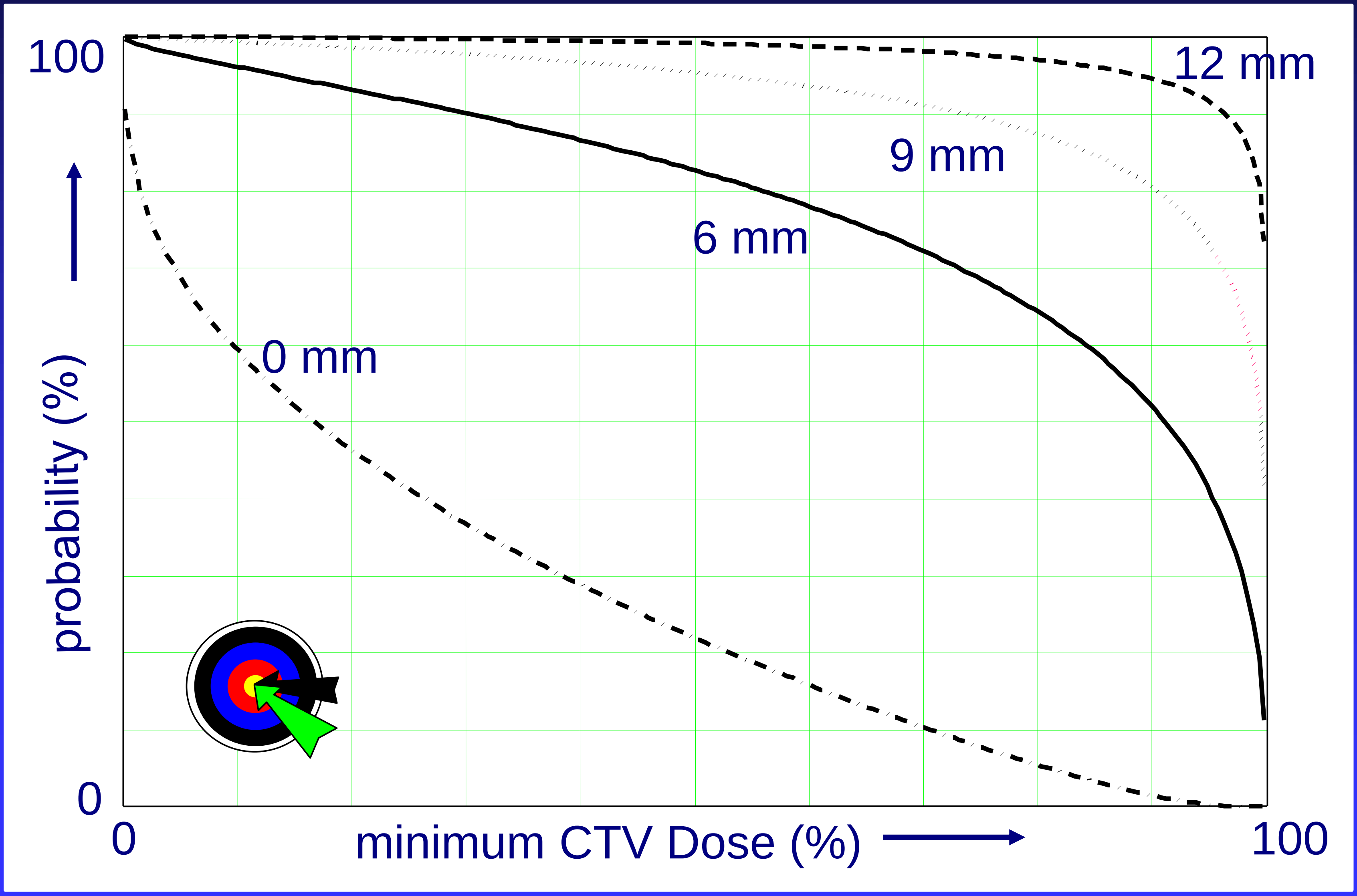
Computation of the dose probability for a small CTV in 1D



In the cumulative (blurred) dose, find where the dose > 95%

..and compute the probability that the average CTV position is in this area

What should the margin be ?



How to choose the PTV margin

- Express required CTV dose for a specified fraction of patients. For example: 90% of the patients must get a minimum CTV dose of 95% or more

- Add first margin so that 90% of the preparation (systematic) errors are covered

- Add margin for penumbra and execution (random) variation so that CTV + first margin lies within the 95% isodose

Simplified PTV margin recipe for dose - probability

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

PTV margin = 2.5 Σ + 0.7 σ

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

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

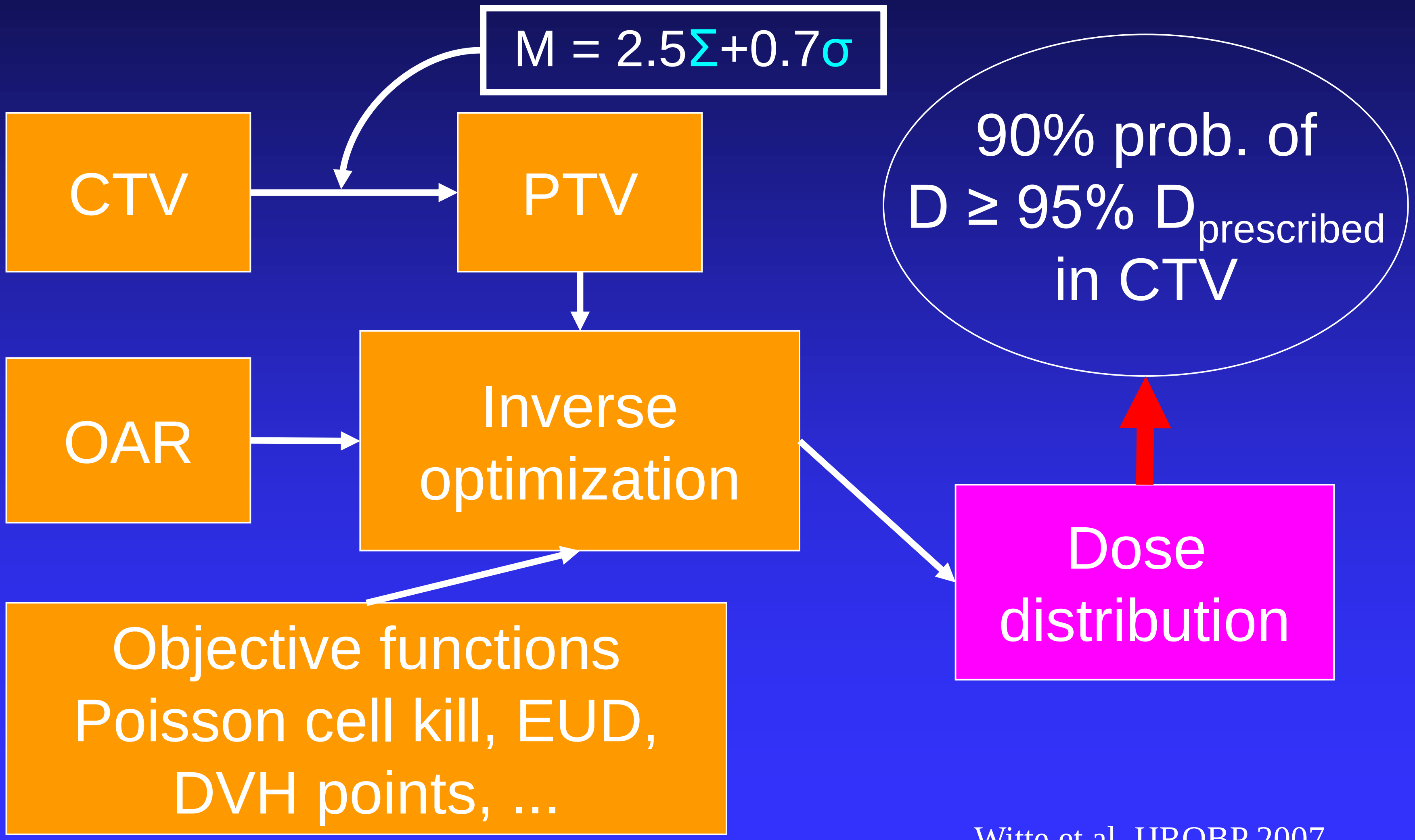
*For a big CTV with smooth shape, penumbra 5 mm

Prostate: 2.5 Σ + 0.7 σ

all in cm	**systematic errors**	squared	**random errors**	squared			
delineation	**0.25**	0.0625	**0**	0	Rasch et al, Sem. RO 2005		
organ motion	**0.3**	0.09	**0.3**	0.09	van Herk et al, IJROBP 1995		
setup error	**0.1**	0.01	**0.2**	0.04	Bel et al,IJROBP 1995		
intrafraction motion			**0.1**	0.01			
total error	**0.40**	0.16	**0.37**	0.14			
	times 2.5		**times 0.7**				
error margin	**1.01**		**0.26**				
total error margin		**1.27**					

Future developments

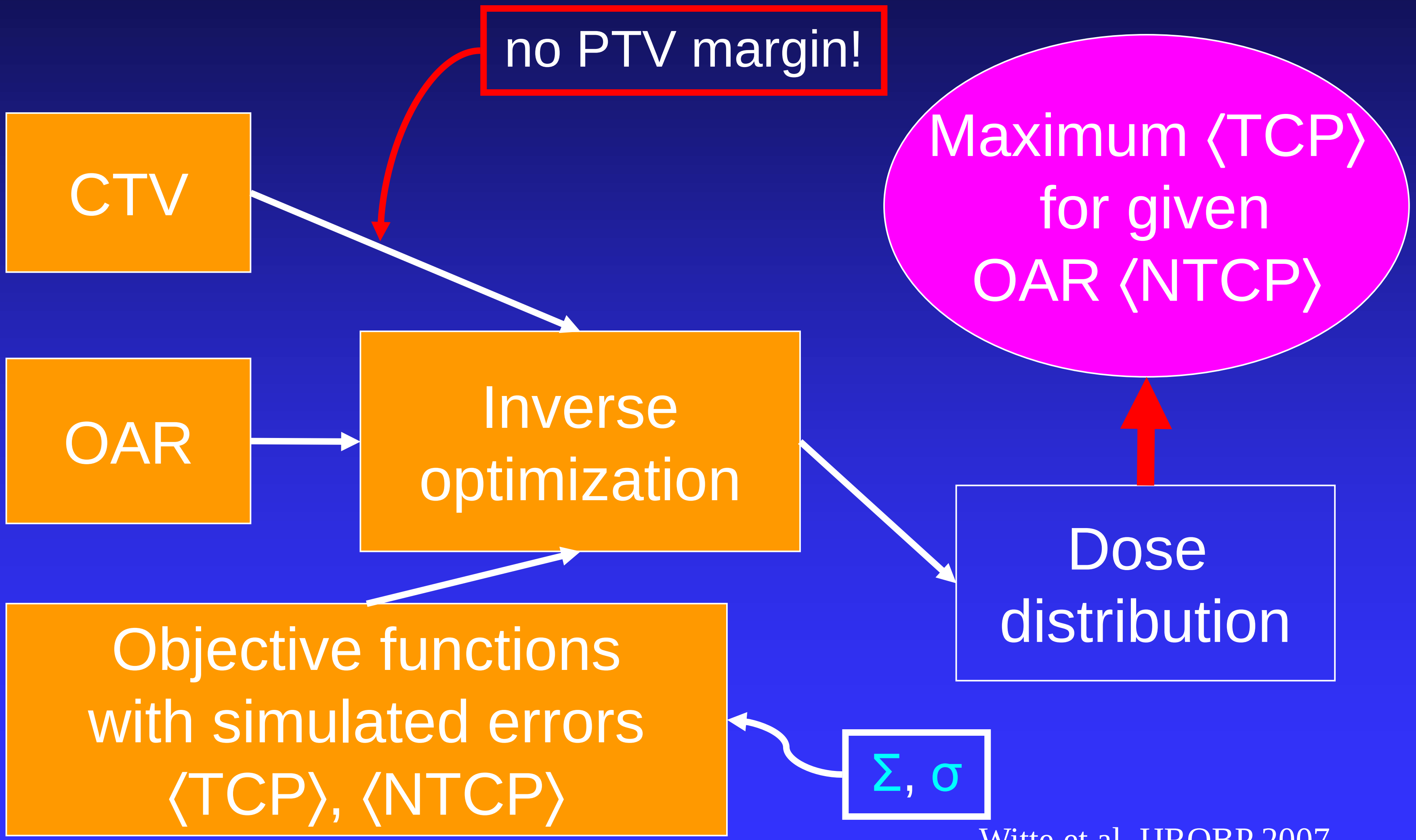
Uncertainty management: Conventional IMRT planning with margin



Witte et al, IJROBP 2007

Bohoslavsky et al IJROBP 2013

Uncertainty management: Probabilistic biological IMRT planning without margin



Witte et al, IJROBP 2007
Bohoslavsky et al, IJROBP 2013

Conclusions

- There are many error sources in radiotherapy, determine what they are in your department
- Focus on correcting remaining systematic errors
  - Do not forget the doctor's error – delineation, and CTV
- IGRT does not eliminate all errors; carefully consider the margins to be used
- IGRT introduces some new errors and makes old errors more important (where is the CTV?)
- Margin recipes assume that you know ALL ERRORS … USE AT YOUR OWN RISK

Correction Strategies and Adaptive Radiotherapy

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NKI-AVL
Het Nederlands Kanker Instituut
Antoni van Leeuwenhoek Ziekenhuis

ESTRO IGRT 2017

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- Marcel van Herk
- Robert Jeraj
- Di Yan
- Wouter Vogel
- Mike Sharpe
- Peter Remeijer

Outline

- Introduction
- Correction Protocols
- Advanced Correction Strategies
- Adaptive Radiotherapy


"LASER"

The radiotherapy chain

1 x	35 x
• CT room	• Treatment room
• Lasers	• Lasers
• Skin markers	• Skin markers
• Images	• Bone
• Bone	• Tumor
• Tumor	
• Delineation	• Beam
• Margin	• Accelerator
• Planned beam	• Treatment room

Patient →

Patient

Patient data

17 steps with a lot of room for errors

Portal imaging

1 x

35 x

Patient

Patient →

- CT room
- Lasers
- Skin markers
- Images
- Bone
- Tumor
- Delineation
- Margin
- Planned beam

- Treatment room
- Lasers
- Skin markers
- Bone
- Tumor

- Beam
- Accelerator
- Treatment room

Patient data

17 steps with a lot of room for errors

Image guided RT (on tumor)

1 x	35 x
Patient	

Patient →

- CT room
- Lasers
- Skin markers
- Images
- Bone
- Tumor
- Delineation
- Margin
- Planned beam

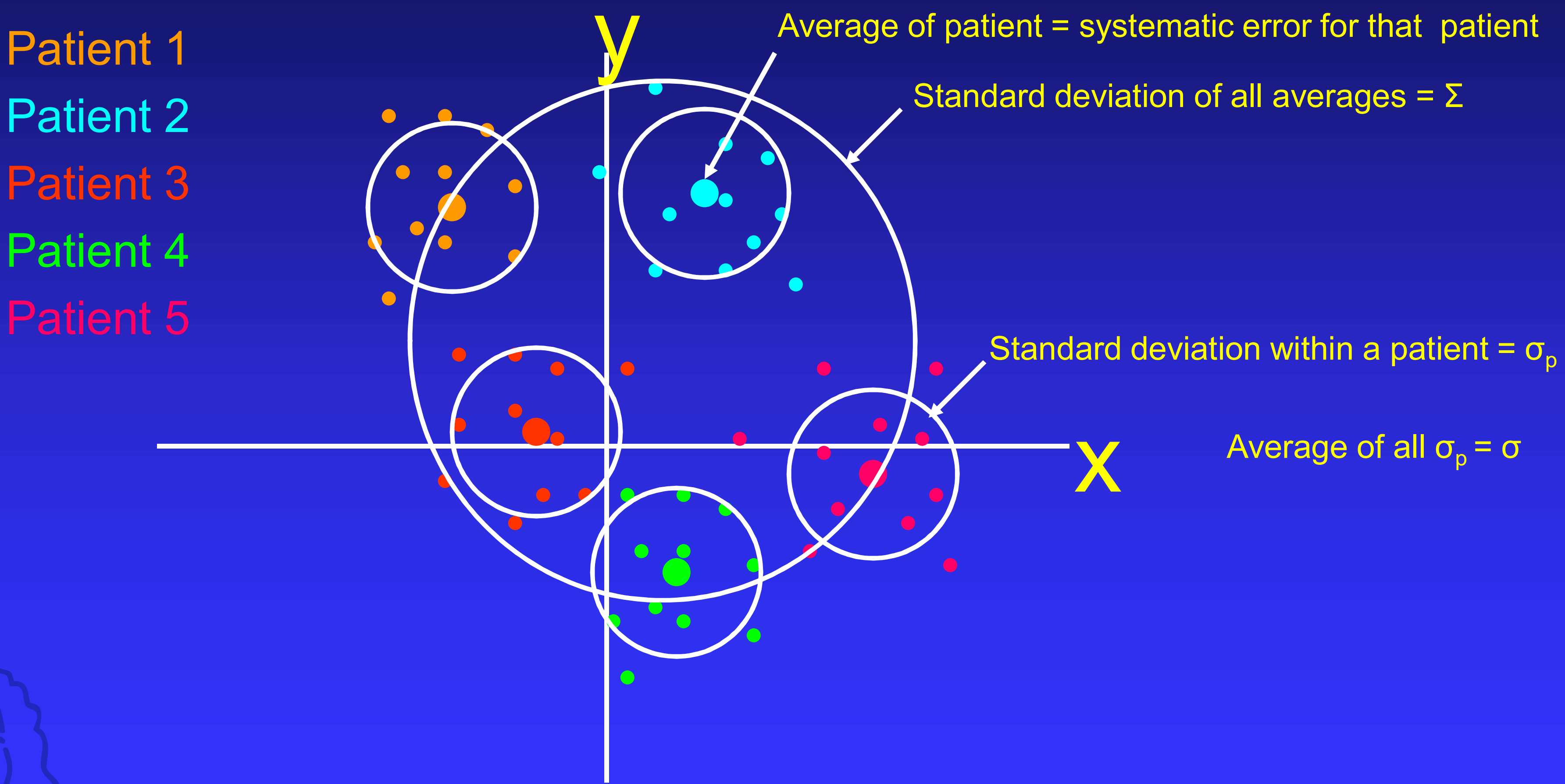
- Treatment room
- Lasers
- Skin markers
- Bone
- Tumor

- Beam
- Accelerator
- Treatment room

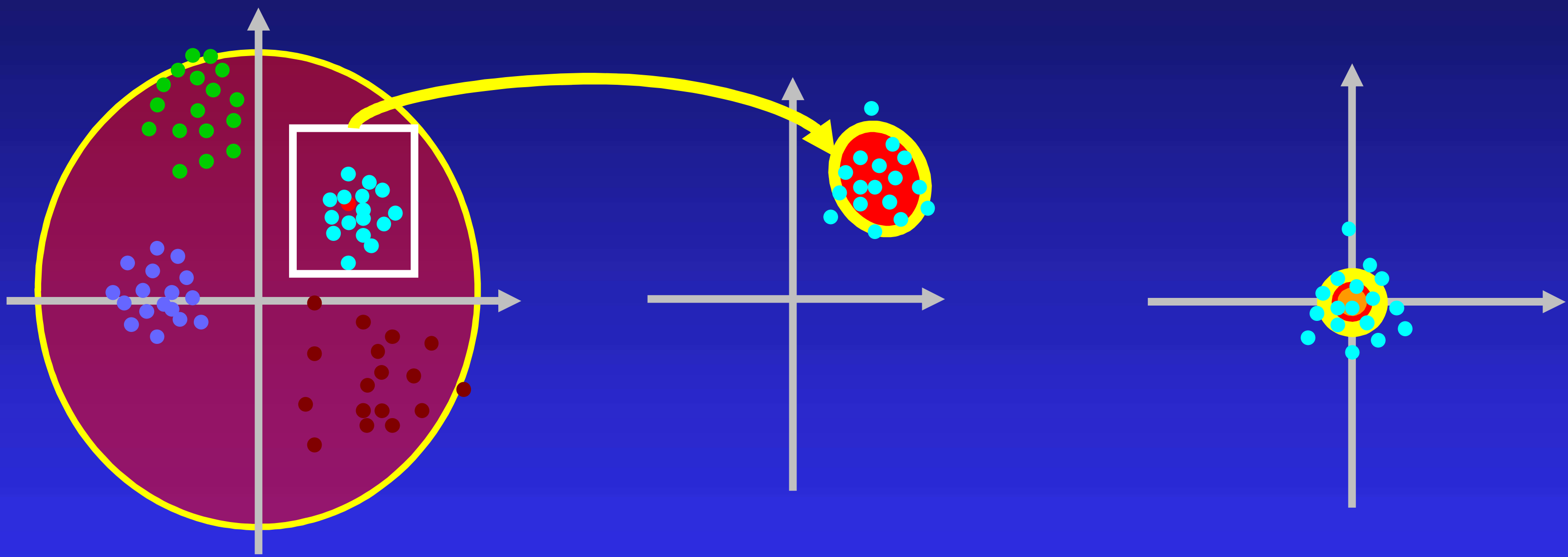
Patient data

17 steps with a lot of room for errors

Systematic and random errors



Variation Management vs Target Margin



No Corrections	*Off-line corrections*	*On-line correction*
Population only Large Margins	Data: k < N Considerable margin reduction	Data: N Further Margin reduction

Courtesy to Di Yan, WBH

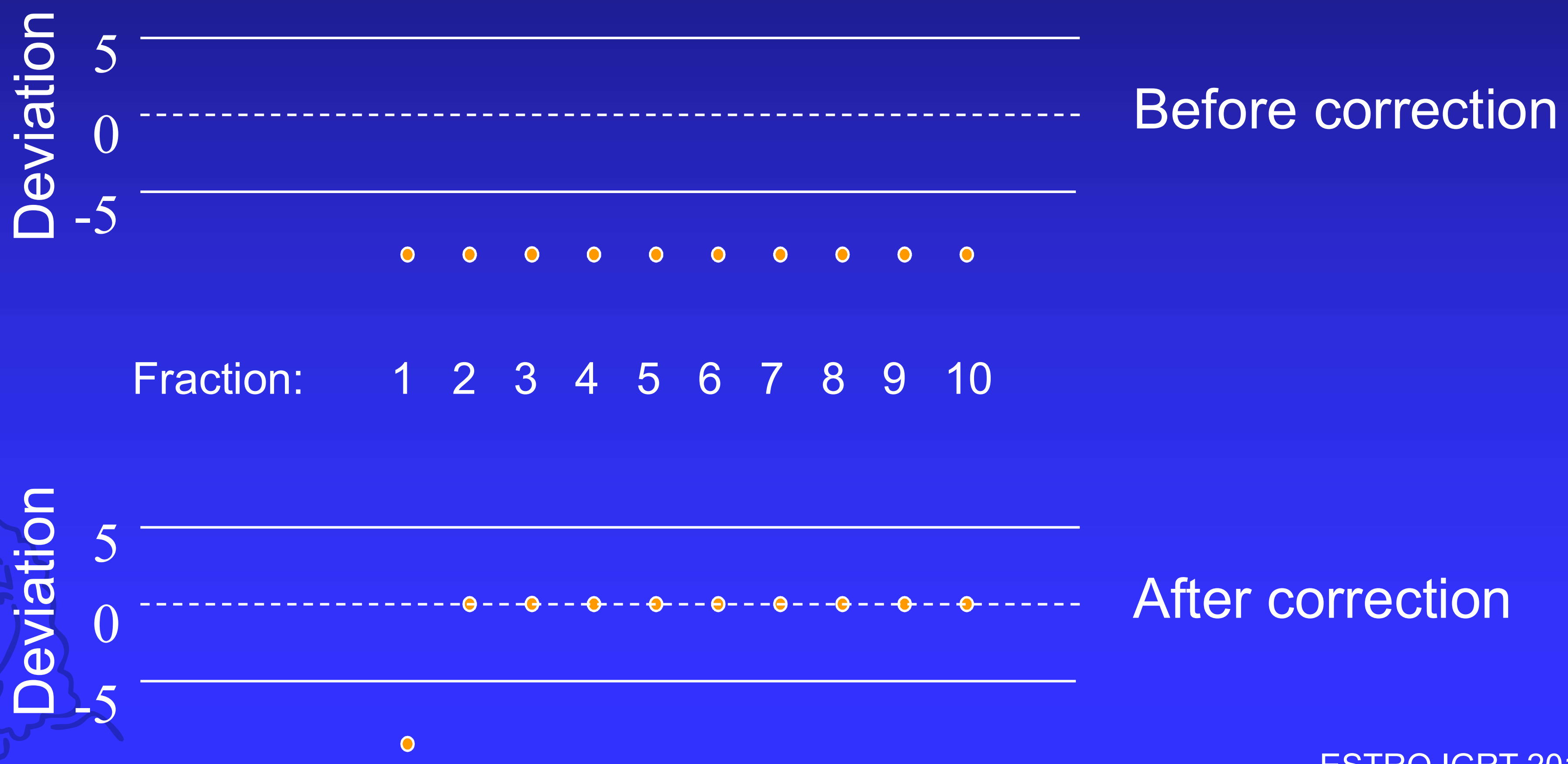
Correction Protocols

Correction protocols

- No corrections (monitoring)
  - Aimed at determining accuracy of clinical practice
- Ad-hoc corrections
  - Not recommended
- Off-line correction protocols
  - Aimed at correcting inter-treatment/systematic errors
  - SAL, NAL, etc
- On-line correction protocols
  - Aimed at correcting day to day variations

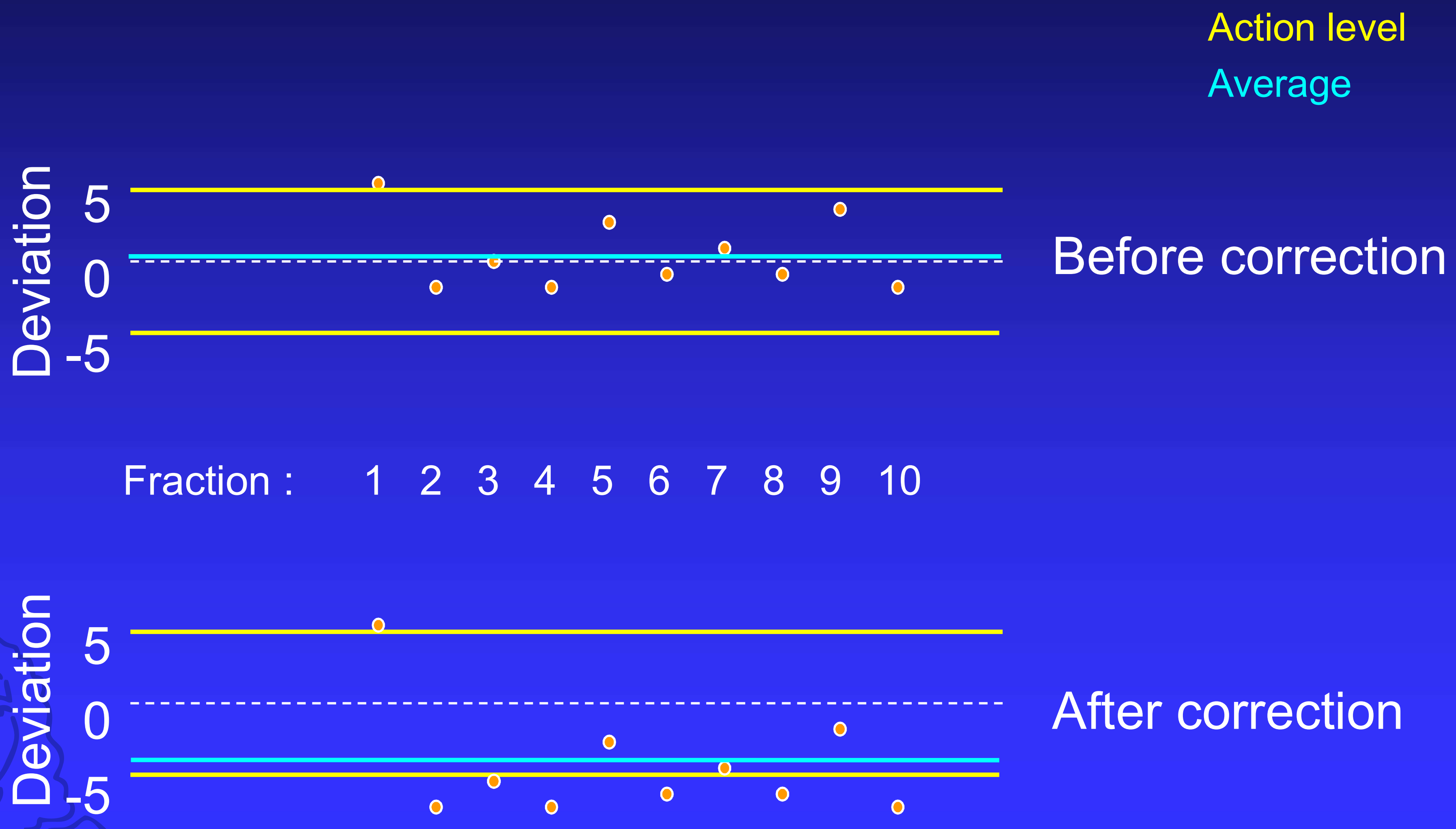
Ad-hoc correction protocol

- No day-to-day (random) variation

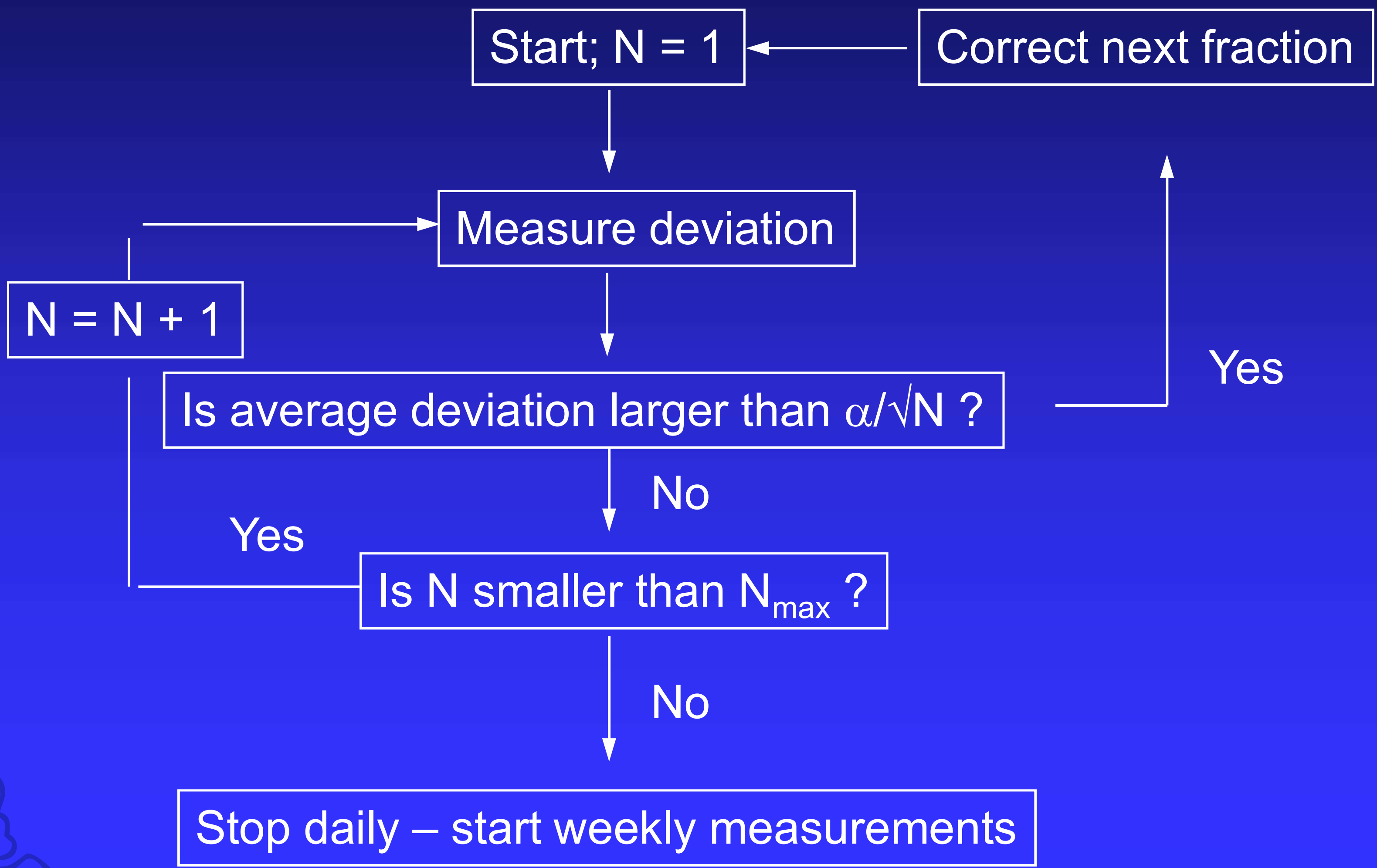


Ad-hoc correction protocol

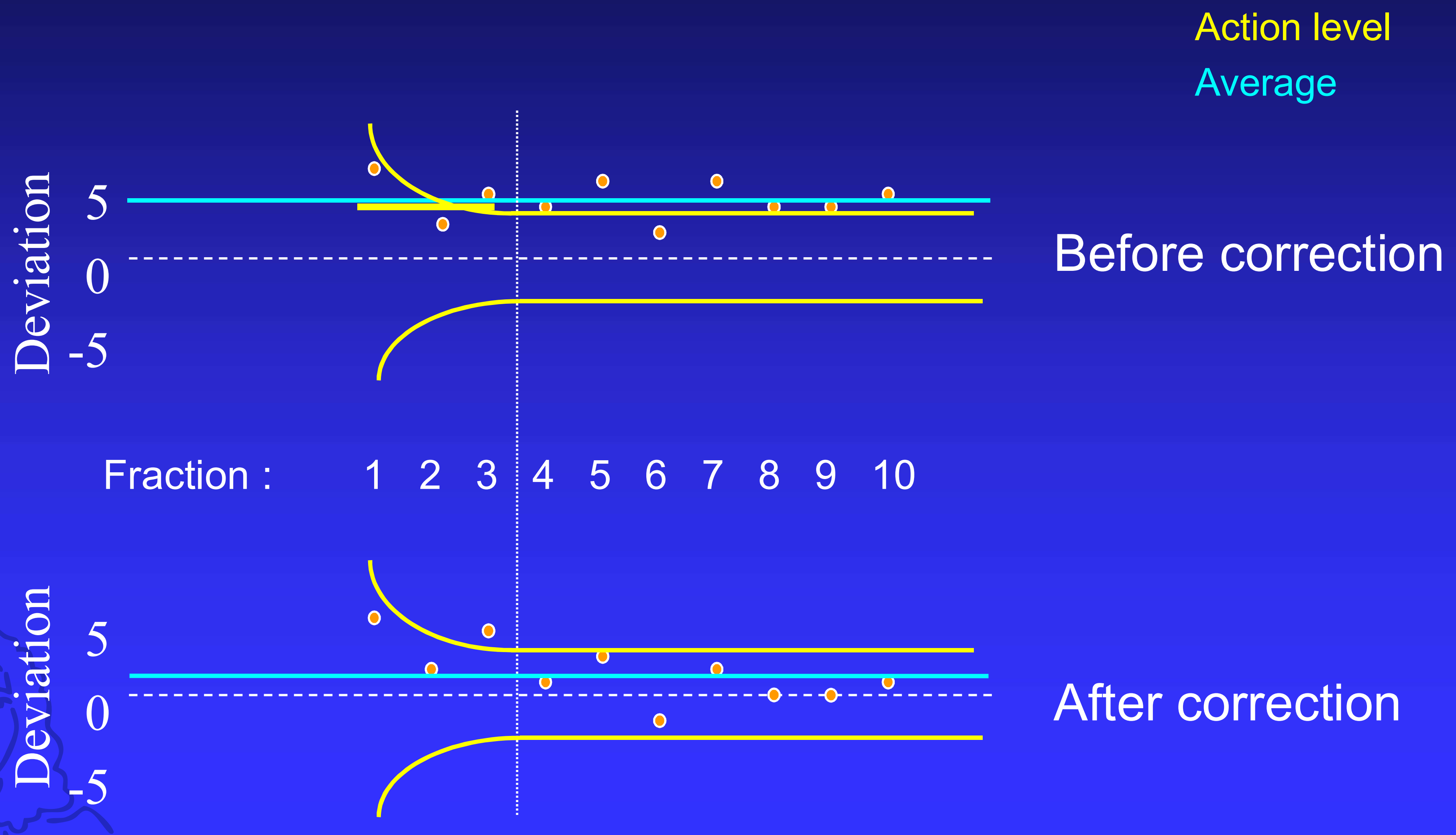
- Normal day-to-day variation



Shrinking action level protocol (SAL)



SAL protocol

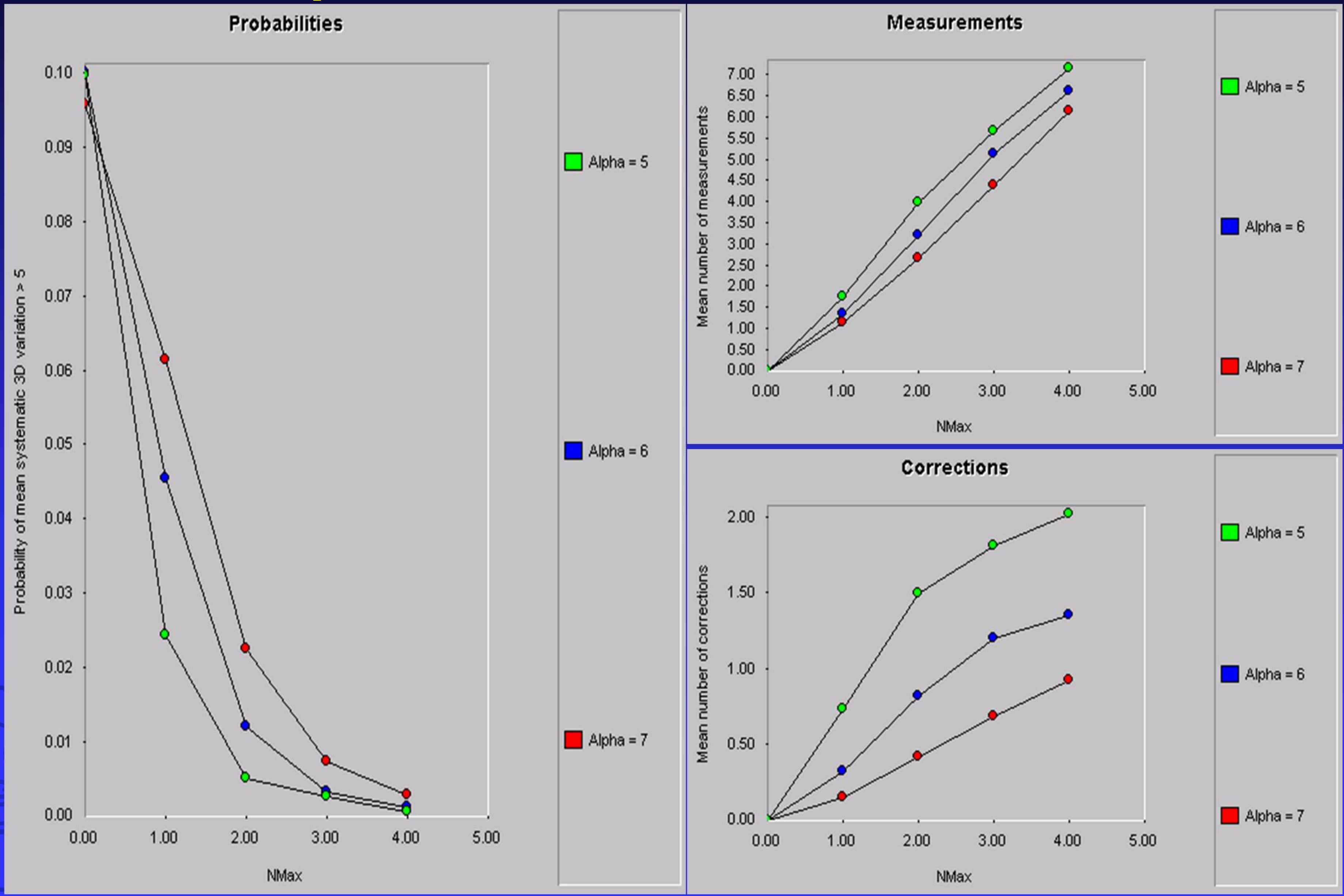


How to choose α and N_{max} ?

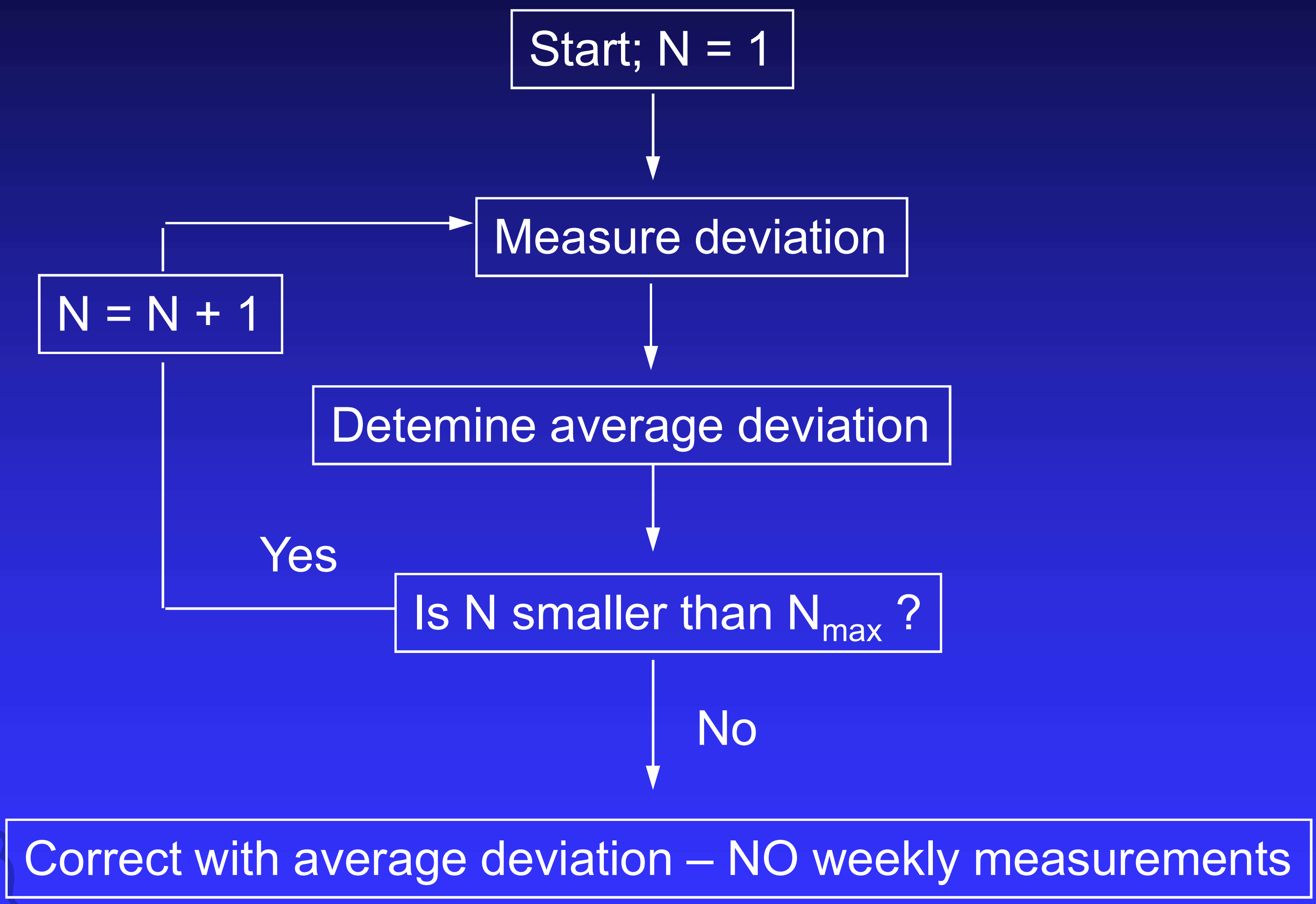
- Analytical computation not possible

$\Rightarrow$ Simulations: Apply Decision Rule on large number of ‘virtual’ patients

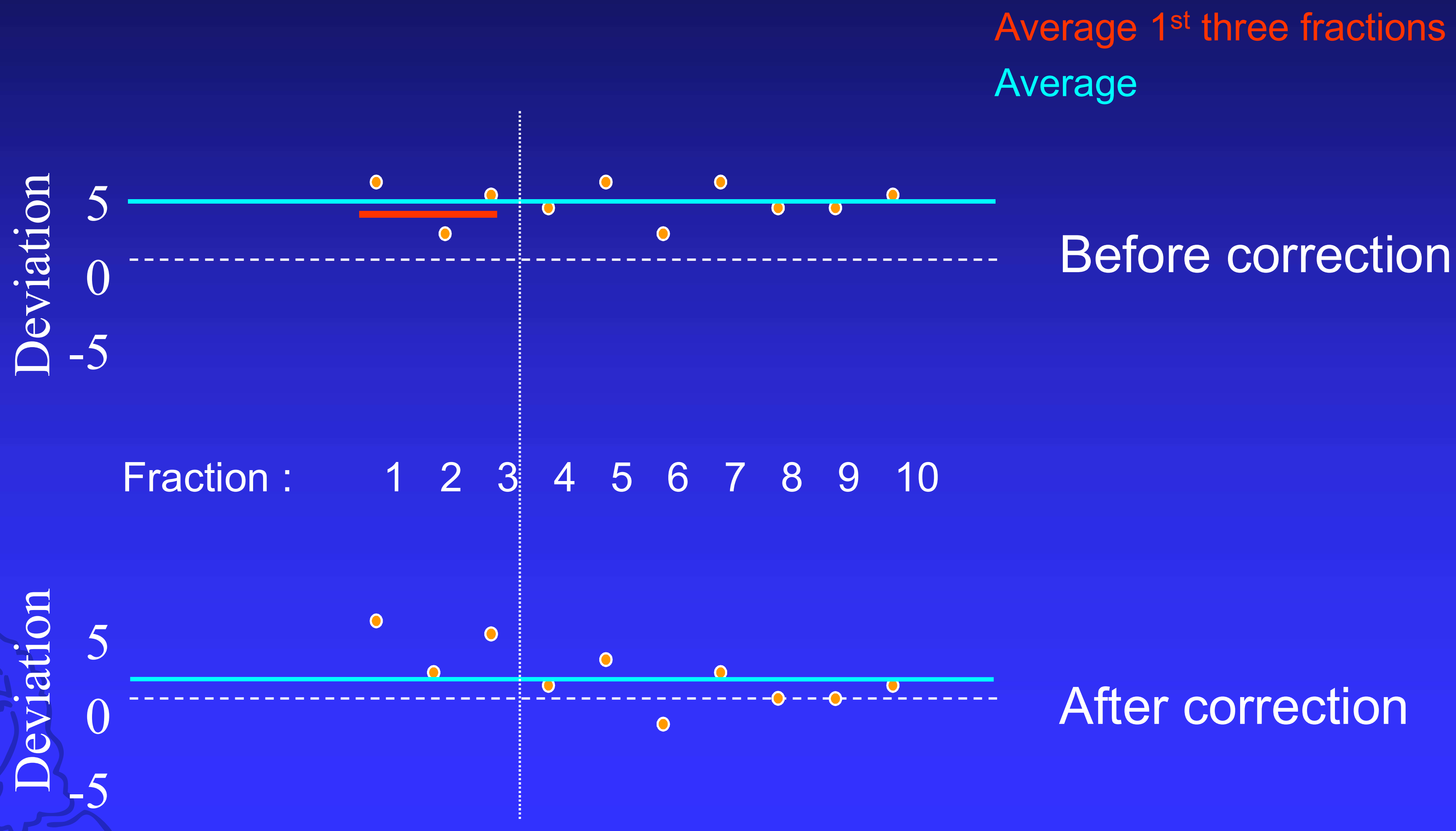
Example of simulation



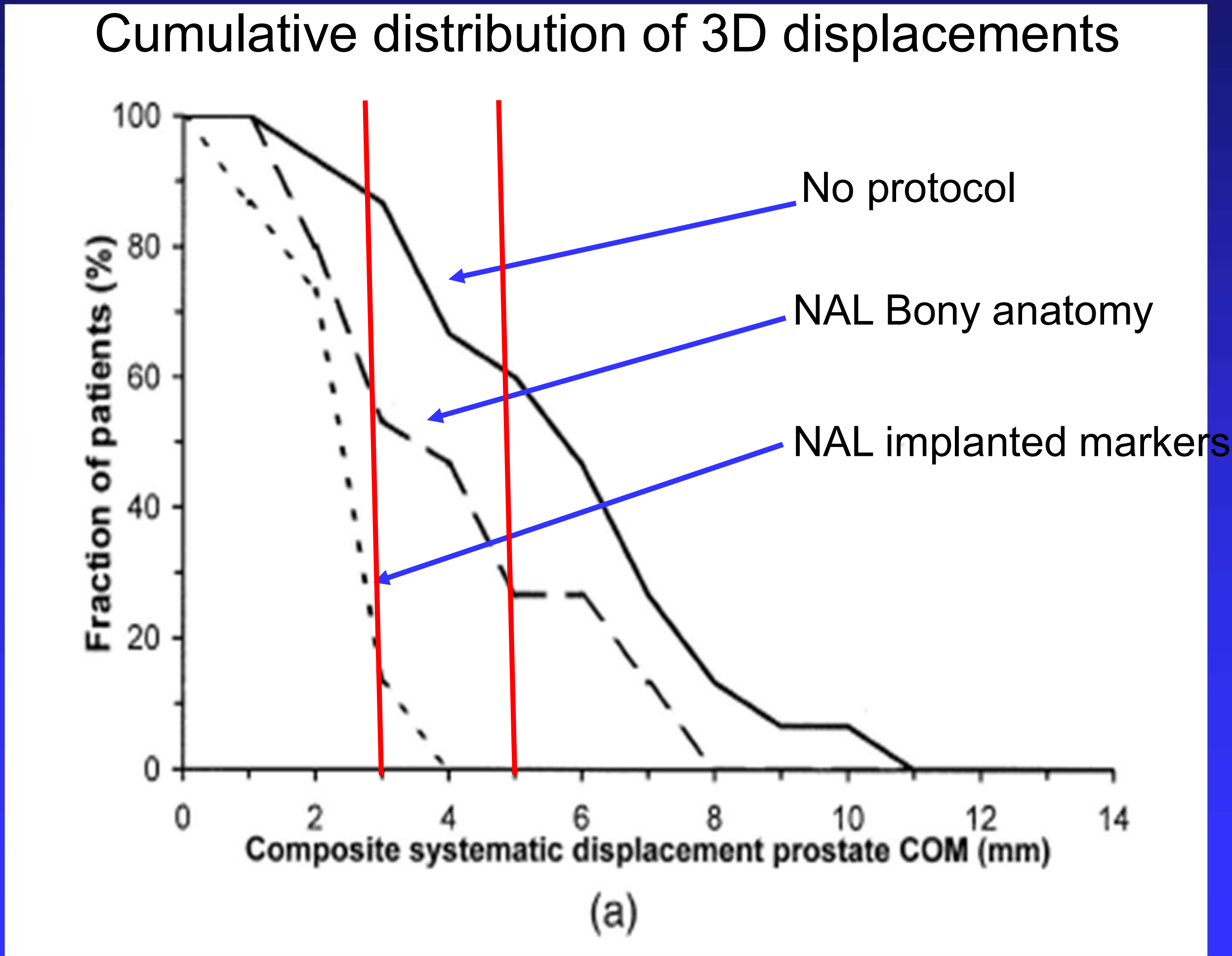
No action level protocol (NAL)



NAL protocol



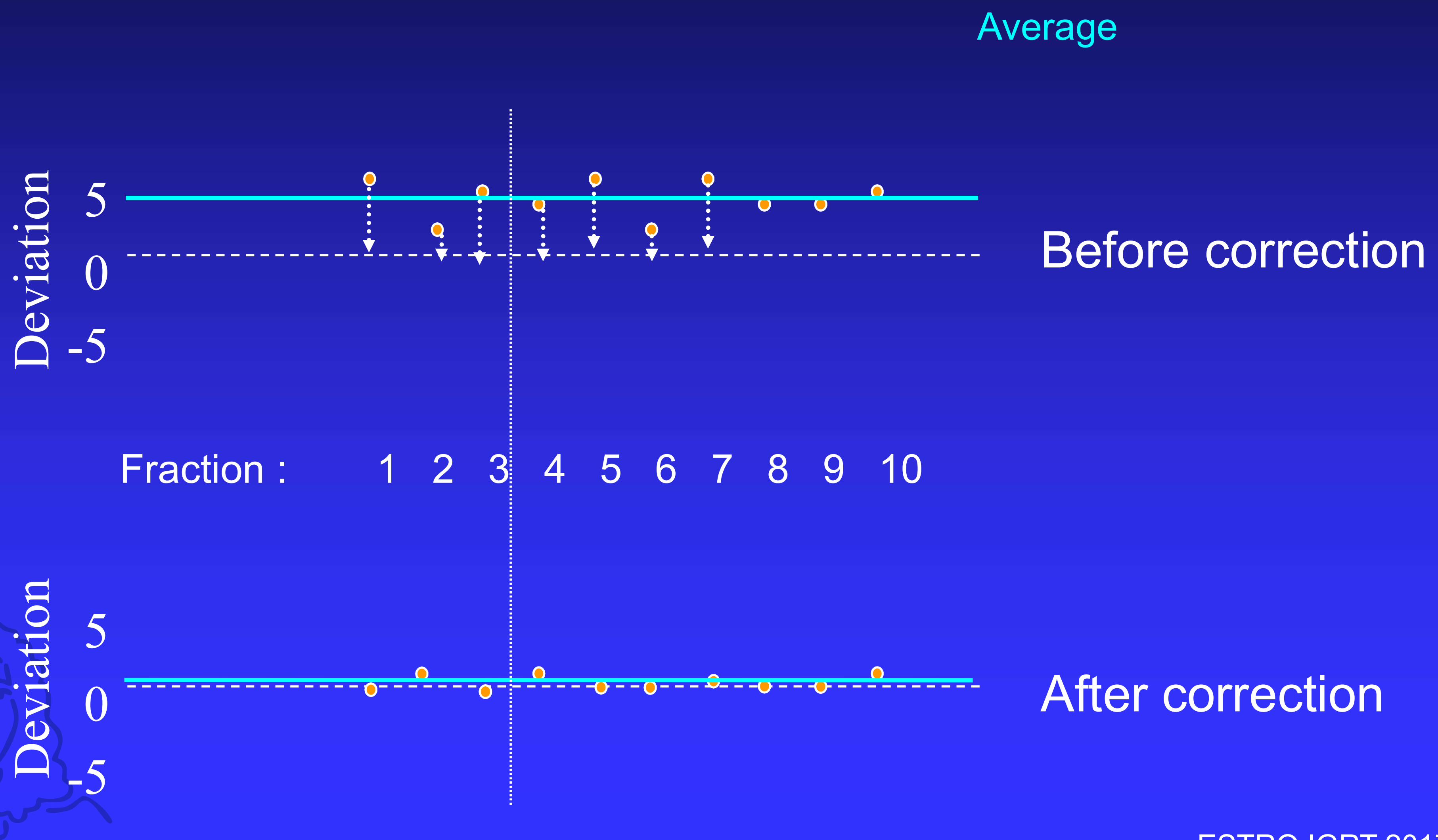
Benefit of the NAL protocol



*H.C. de Boer et al., Int J RO Biol Phys 2005, 61:969-983

Retrospective analysis of patient data

Online protocol



Margin Example

		No Correction
Setup	Σ	3 mm
	σ	3 mm
Organ	Σ	4 mm
	σ	4 mm
Breathing	A	15 mm
	a	15 mm
Margin		**23 mm**

Margin Example

		No Correction	Offline Bone
Setup	Σ	3 mm	0 mm
	σ	3 mm	3 mm
Organ	Σ	4 mm	4 mm
	σ	4 mm	4 mm
Breathing	A	15 mm	15 mm
	a	15 mm	15 mm
Margin		**23 mm**	**21 mm**

Margin Example

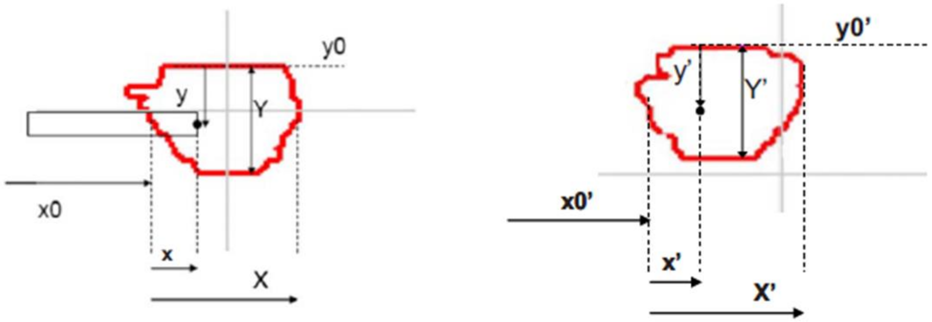
		No Correction	Offline Bone	Online Soft-tissue
Setup	Σ	3 mm	0 mm	0 mm
	σ	3 mm	3 mm	0 mm
Organ	Σ	4 mm	4 mm	1 mm
	σ	4 mm	4 mm	2 mm
Breathing	A	15 mm	15 mm	0 mm
	a	15 mm	15 mm	15 mm
Margin		**23 mm**	**21 mm**	**6 mm**

‘Small Errors’

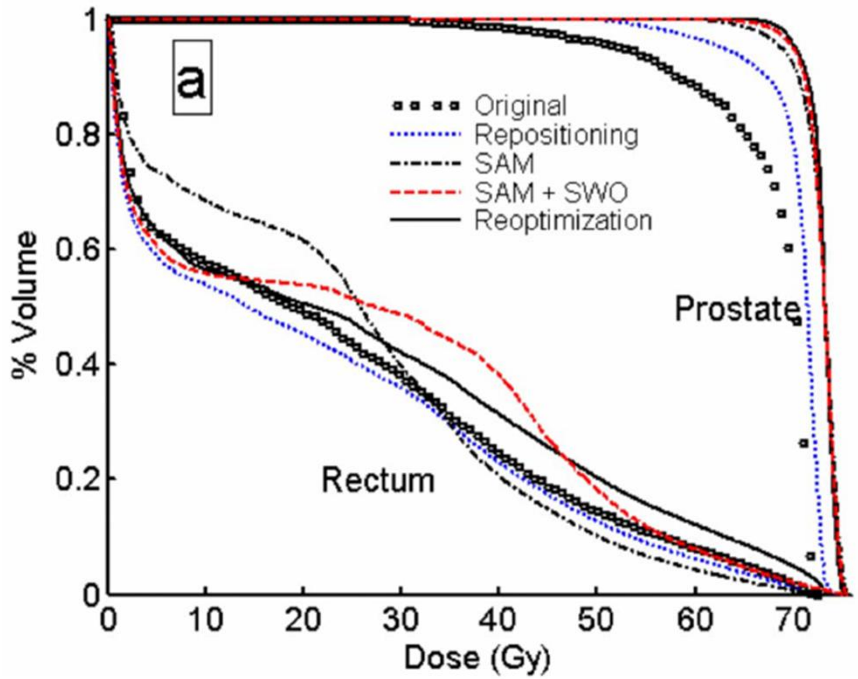
		No Correction	Offline Bone	Online Soft-tissue
Setup	Σ	3 mm	0 mm	0 mm
	σ	3 mm	3 mm	0 mm
Organ	Σ	4 mm	4 mm	1 mm
	σ	4 mm	4 mm	2 mm
Breathing	A	15 mm	15 mm	0 mm
	a	15 mm	15 mm	15 mm
Delineation	Σ	**2 mm**	**2 mm**	**2 mm**
Margin		**24 mm**	**22 mm**	**9 mm**

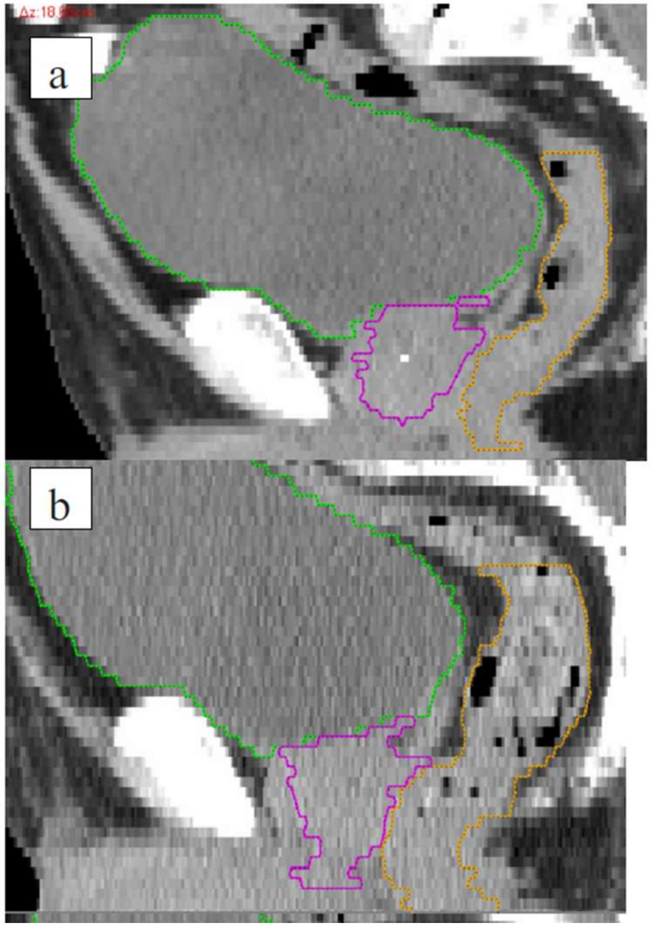
Advanced Correction Strategies

Segment Aperture Morphing



$$y' = \frac{Y'}{Y} y \quad , \quad x' = \frac{X'}{X} x$$

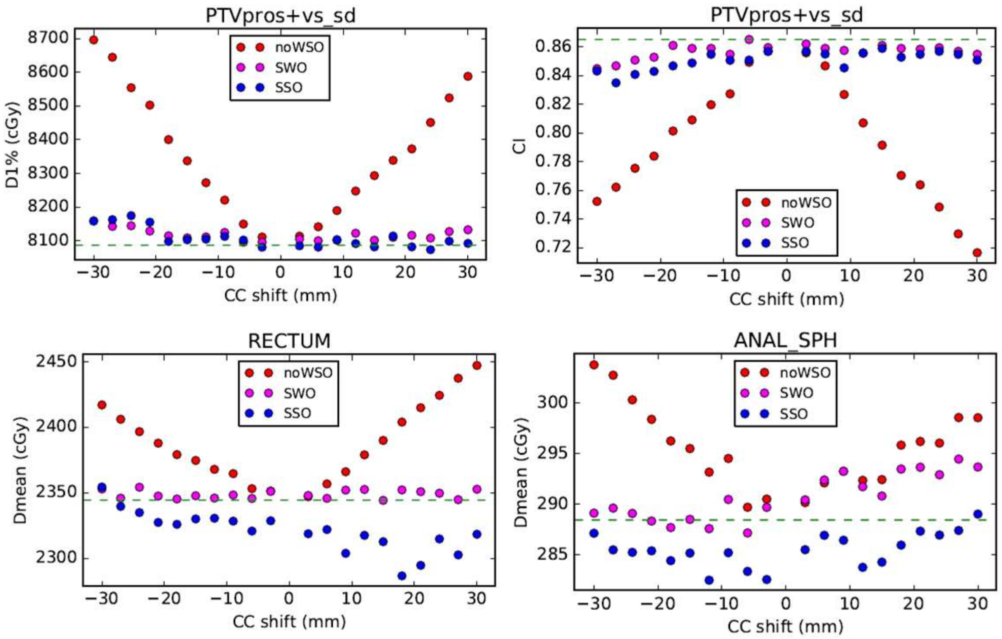


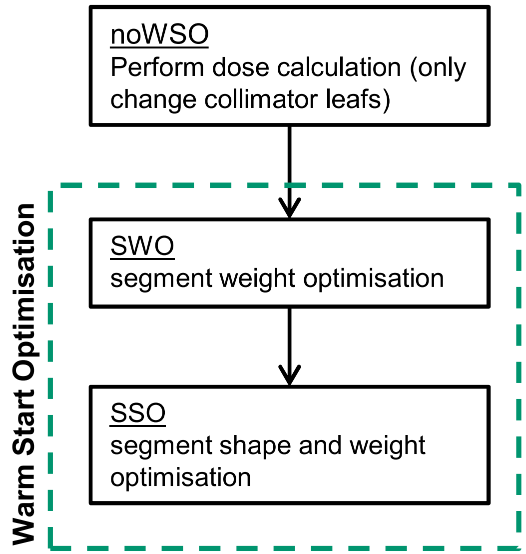


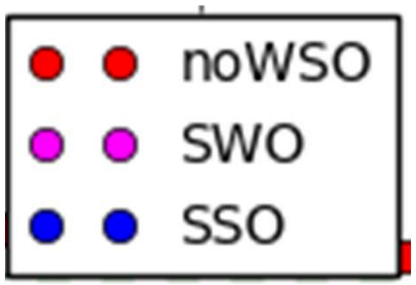
Ahunbay *et al. Med Phys, 2008*

Virtual Couch Shift

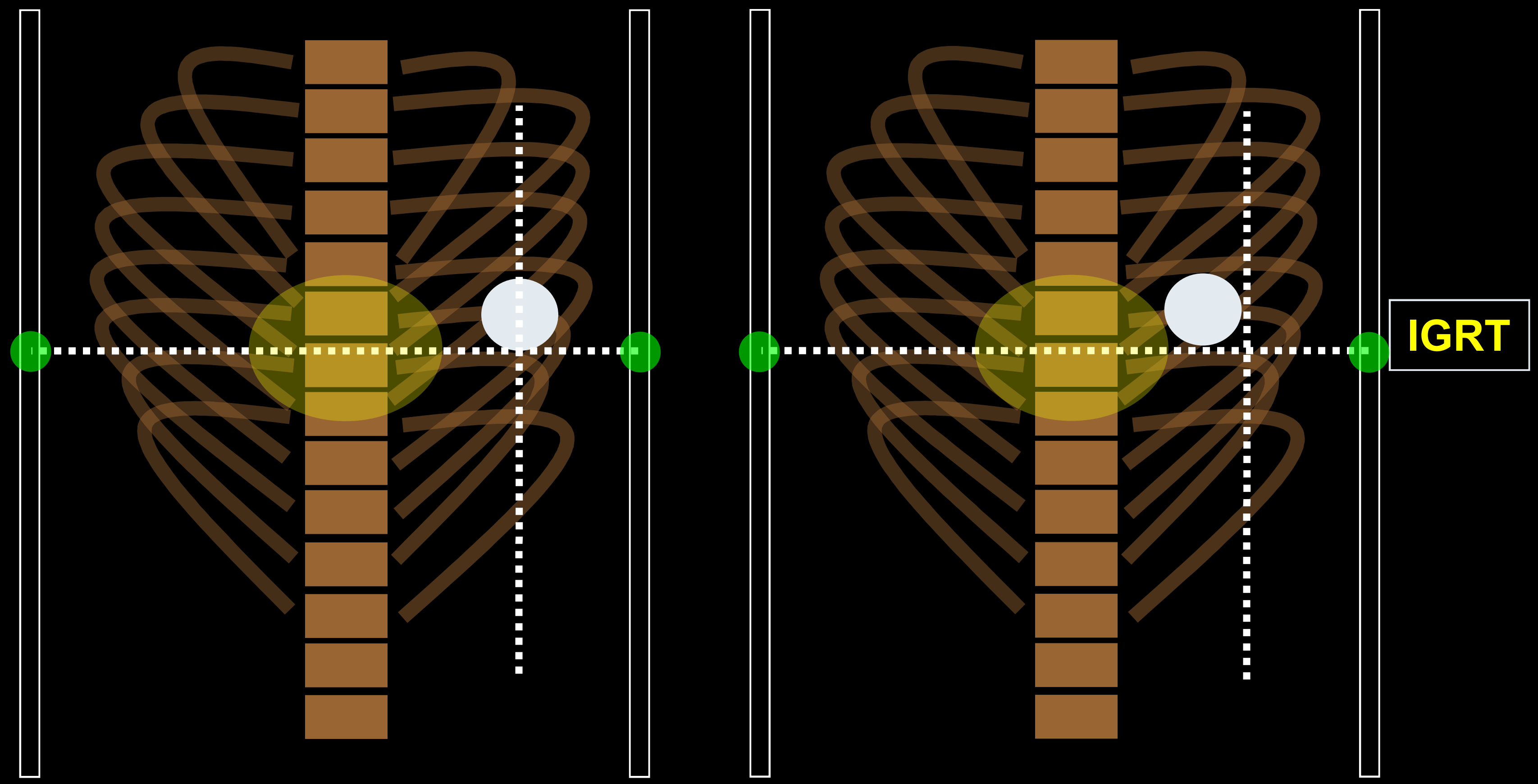
PROSTATE





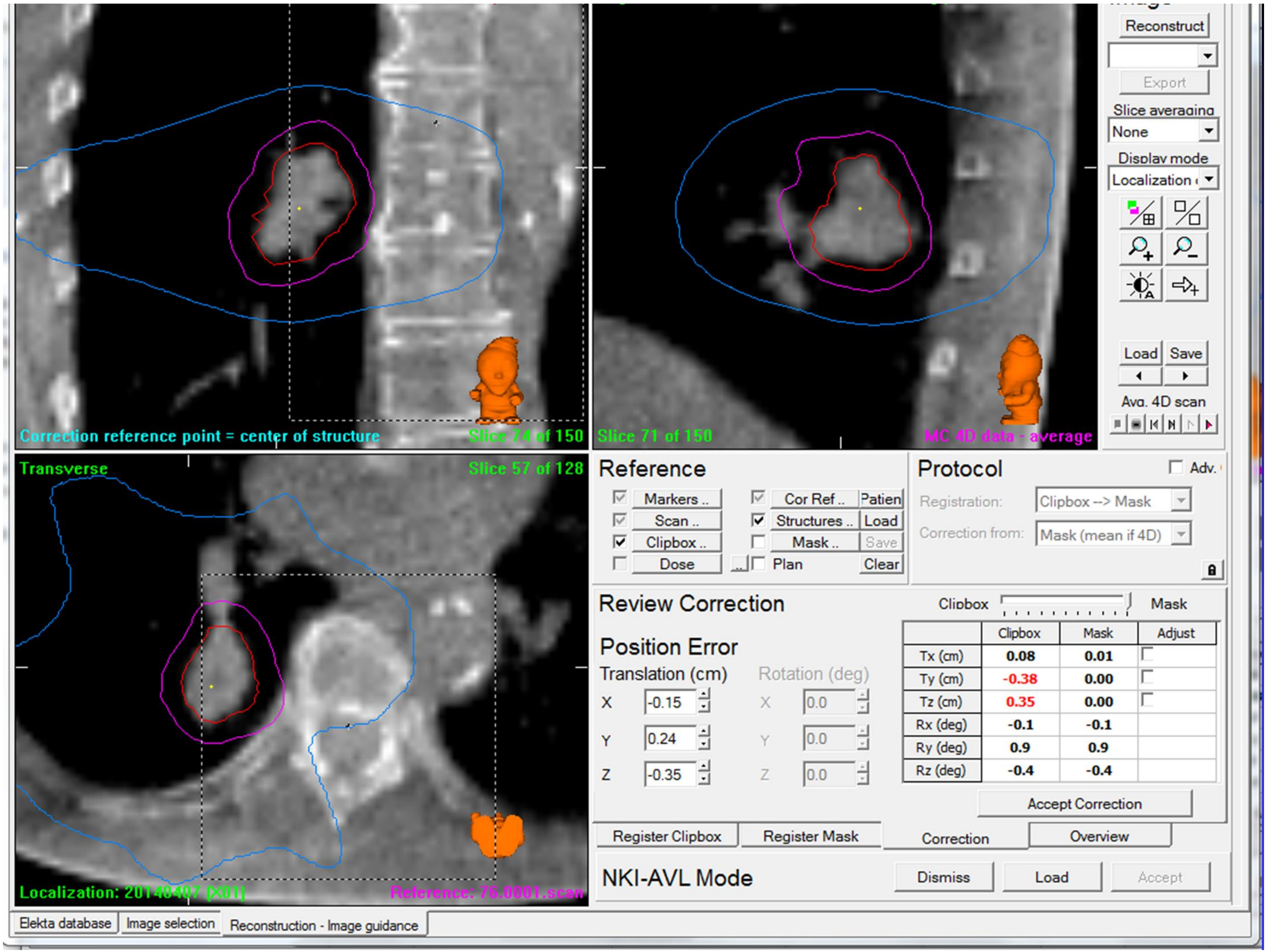


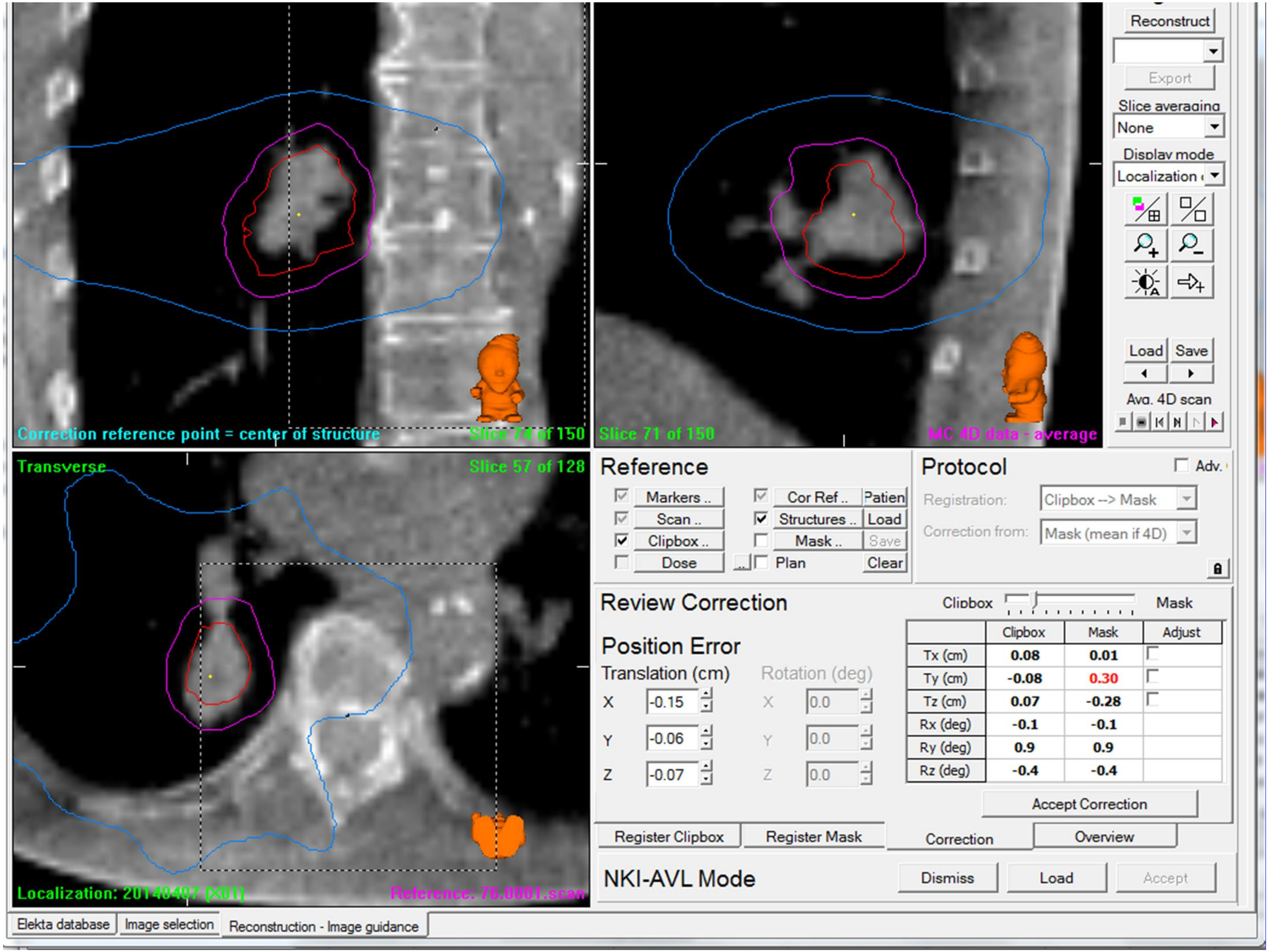
Internal target position variability – base line shift



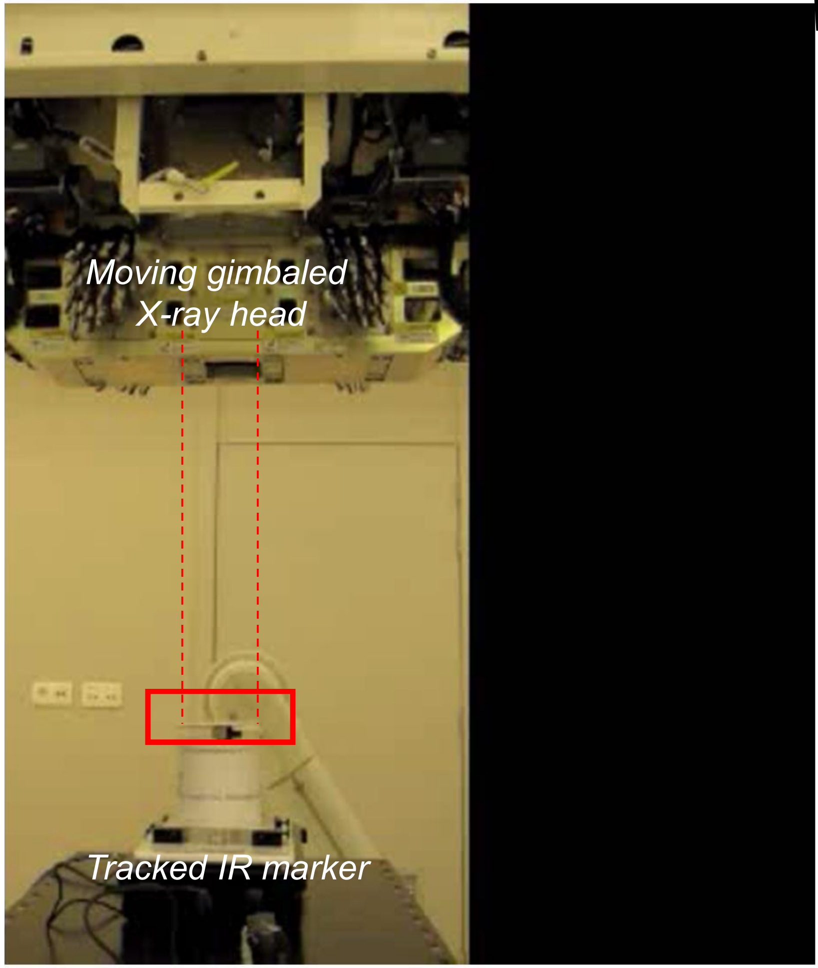
Planning:
Definition of stereotactic isocentre

Treatment:
Stereotactic positioning

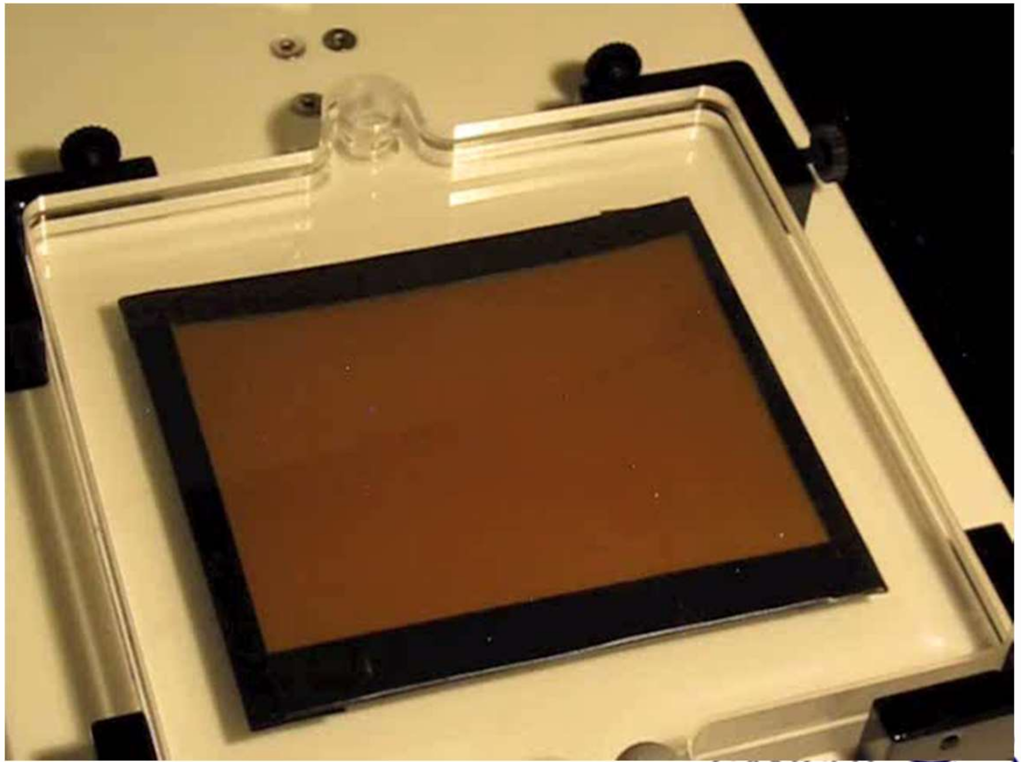

Reconstruct
Export
Slice averaging
None
Display mode
Localization
Load
Save
Avg. 4D scan
Correction reference point = center of structure
Slice 74 of 150
Slice 71 of 150
MC 4D data - average
Transverse
Slice 57 of 128
Reference
Markers ..
Scan ..
Clipbox ..
Dose
Cor Ref ..
Patien
Structures ..
Load
Mask ..
Save
Plan
Clear
Protocol
Adv.
Registration:
Clipbox --> Mask
Correction from:
Mask (mean if 4D)
Review Correction
Clipbox
Mask
Position Error
Translation (cm)
Rotation (deg)
X -0.15
Y 0.24
Z -0.35
X 0.0
Y 0.0
Z 0.0
Clipbox Mask Adjust
Tx (cm) 0.08 0.01
Ty (cm) -0.38 0.00
Tz (cm) 0.35 0.00
Rx (deg) -0.1 -0.1
Ry (deg) 0.9 0.9
Rz (deg) -0.4 -0.4
Accept Correction
Register Clipbox
Register Mask
Correction
Overview
NKI-AVL Mode
Dismiss
Load
Accept
Localization: 20140407 (X01)
Reference: 76.0001.scan
Elekta database
Image selection
Reconstruction - Image guidance


Reconstruct
Export
Slice averaging
None
Display mode
Localization
Load
Save
Avg. 4D scan
Correction reference point = center of structure
Slice 74 of 150
Slice 71 of 150
MC 4D data - average
Transverse
Slice 57 of 128
Reference
Markers ..
Scan ..
Clipbox ..
Dose
Cor Ref ..
Patien
Structures ..
Load
Mask ..
Save
Plan
Clear
Protocol
Adv.
Registration:
Clipbox --> Mask
Correction from:
Mask (mean if 4D)
Review Correction
Clipbox
Mask
Position Error
Translation (cm)
Rotation (deg)
X -0.15
Y -0.06
Z -0.07
X 0.0
Y 0.0
Z 0.0
Clipbox Mask Adjust
Tx (cm) 0.08 0.01
Ty (cm) -0.08 0.30
Tz (cm) 0.07 -0.28
Rx (deg) -0.1 -0.1
Ry (deg) 0.9 0.9
Rz (deg) -0.4 -0.4
Accept Correction
Register Clipbox
Register Mask
Correction
Overview
NKI-AVL Mode
Dismiss
Load
Accept
Elekta database
Image selection
Reconstruction - Image guidance

Tracking



Writing "UZB" with the 6 MV beam in a moving GafChromic film with gimbals pan/tilt movements

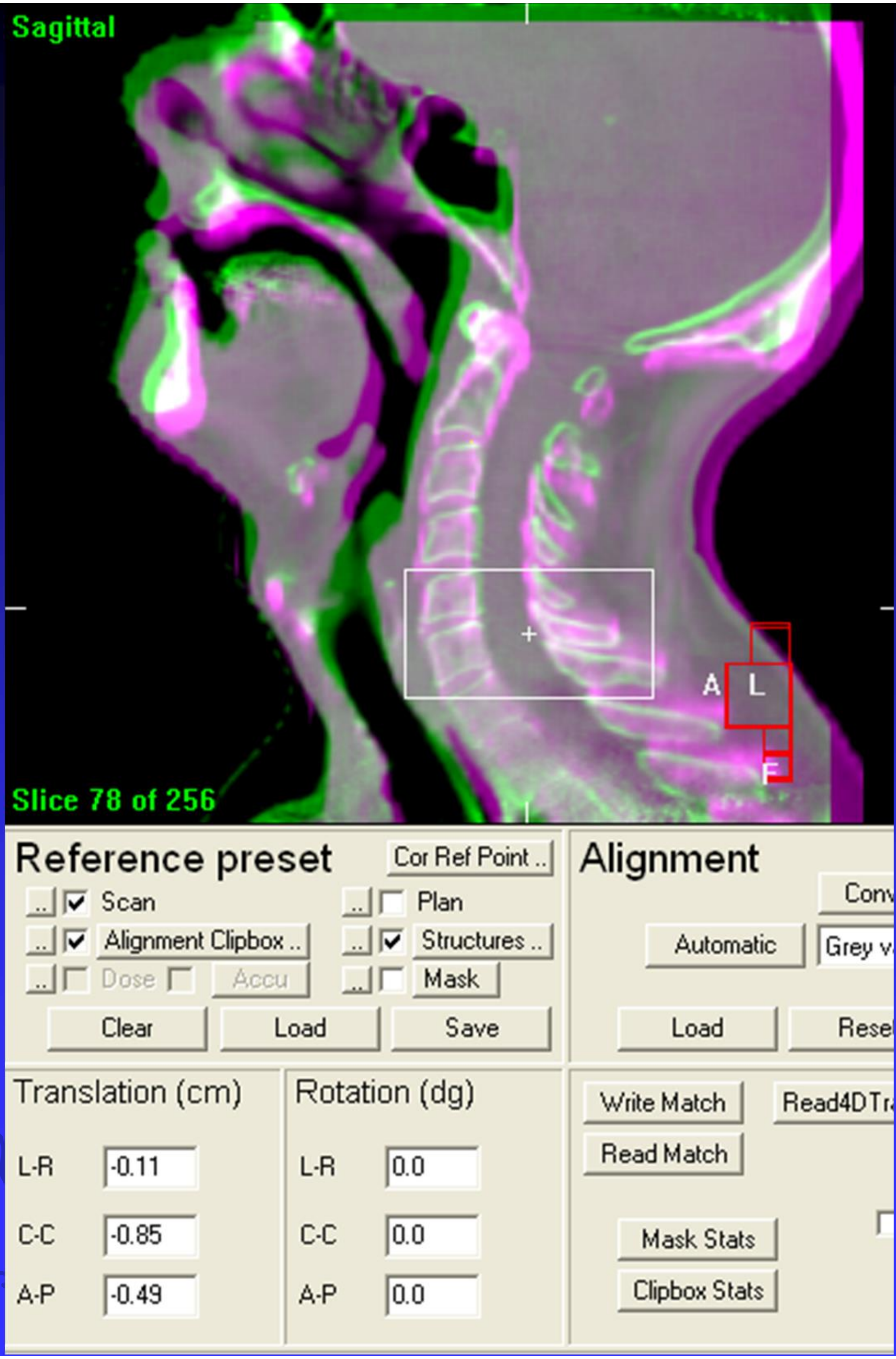


(3x FFW)

CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

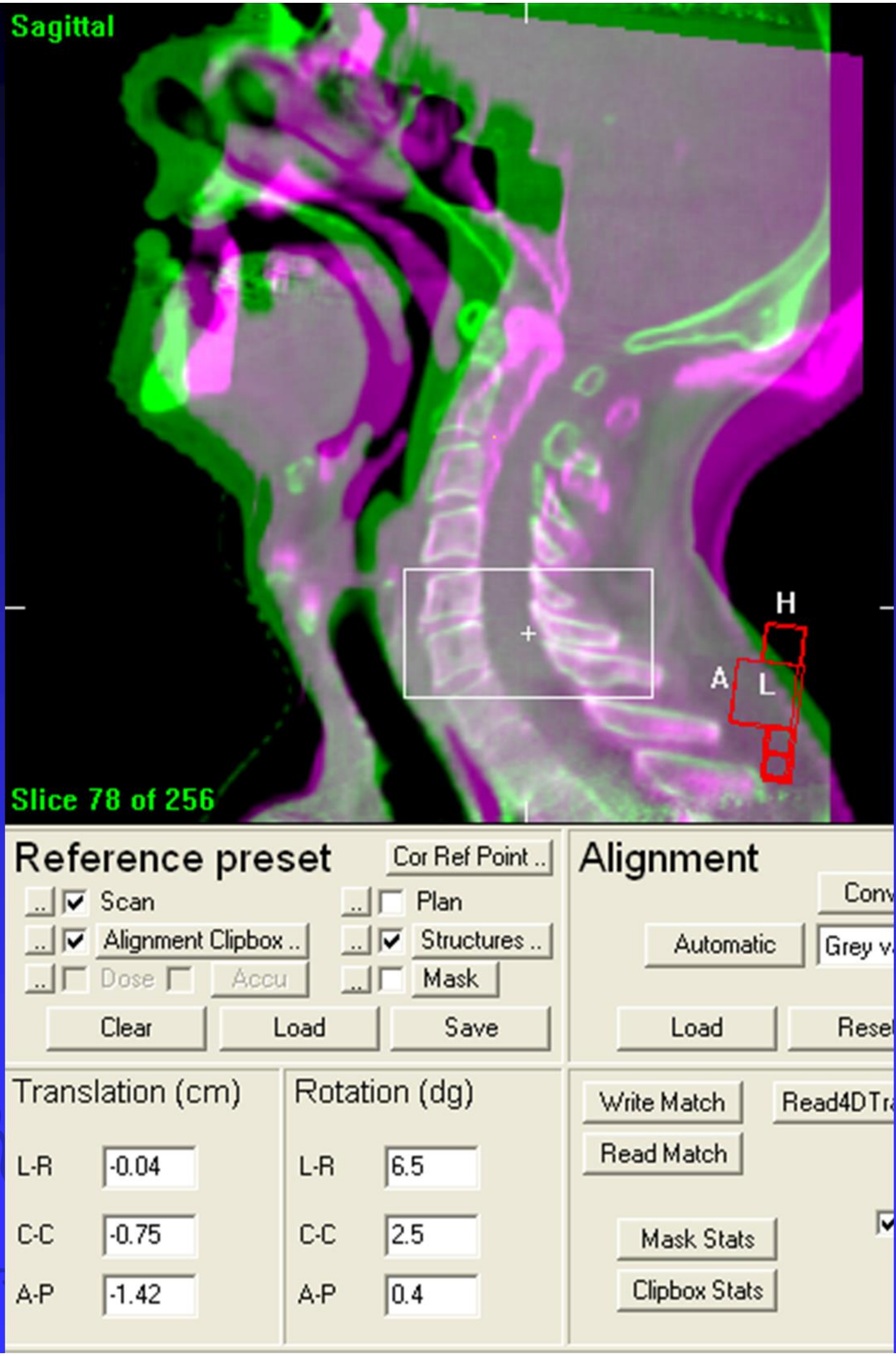
VERO system UZ Brussel, 2010

Courtesy of Tom Depuydt



Automatic matching on region of interest *without* rotations

reference
localization



Automatic matching on region of interest *with* rotations

reference
localization

Rotations (bone) measured with CBCT (°): SD (|max|)

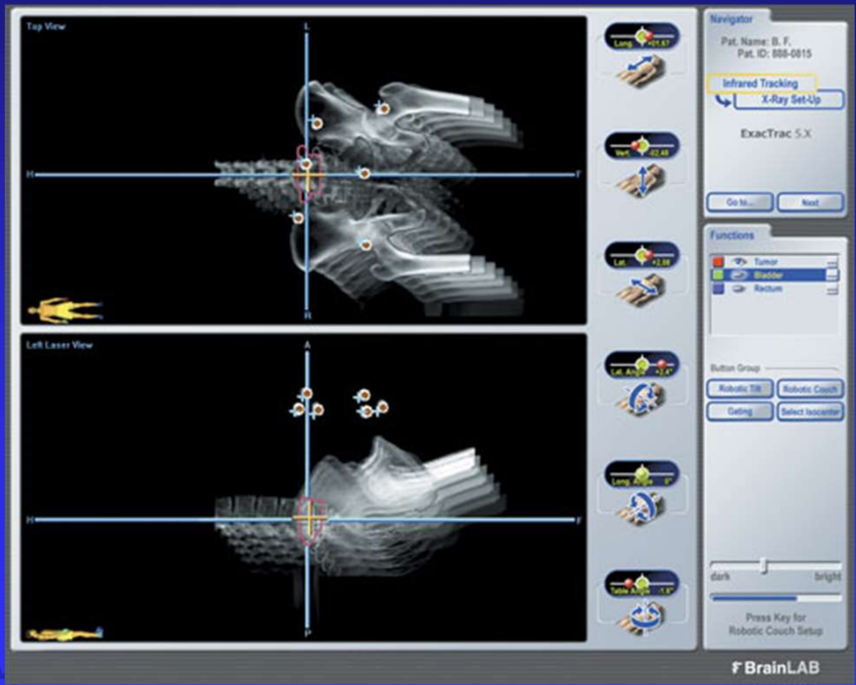
Head & neck (55 scans) [big clipbox]	LR	1.1 (2.6)
	CC	1.0 (3.3)
	AP	1.0 (3.2)
Pelvis (554 scans)	LR	1.6 (9.7)
	CC	0.8 (3.8)
	AP	0.5 (3.7)
Lung (274 scans)	LR	1.1 (5.3)
	CC	1.2 (3.6)
	AP	1.5 (4.7)

Tilt and roll couches

- Hornick DC, Litzenberg DW, Lam KL, Balter JM, Hetrick J, Ten Haken RK.
  - A tilt and roll device for automated correction of rotational setup errors. Med Phys. 1998 Sep;25(9):1739-40.
- Abandoned because of patient comfort:
  - More than 3 degrees rotation impossible
  - Is this a relevant angle to correct?

6 degrees of freedom couch

Stine Korreman



Literature

- Guckenberger et al. *Precision of image-guided radiotherapy (IGRT) in six degrees of freedom and limitations in clinical practice.* Strahlenther Onkol. 2007 Jun;183(6):307-13

  → Reported 0.6 mm compensating translation per degree rotation for non-immobilized patients

- Linthout et al. *Assessment of secondary patient motion induced by automated couch movement during on-line 6 dimensional repositioning in prostate cancer treatment.* Radiother Oncol. 2007 May;83(2):168-74.

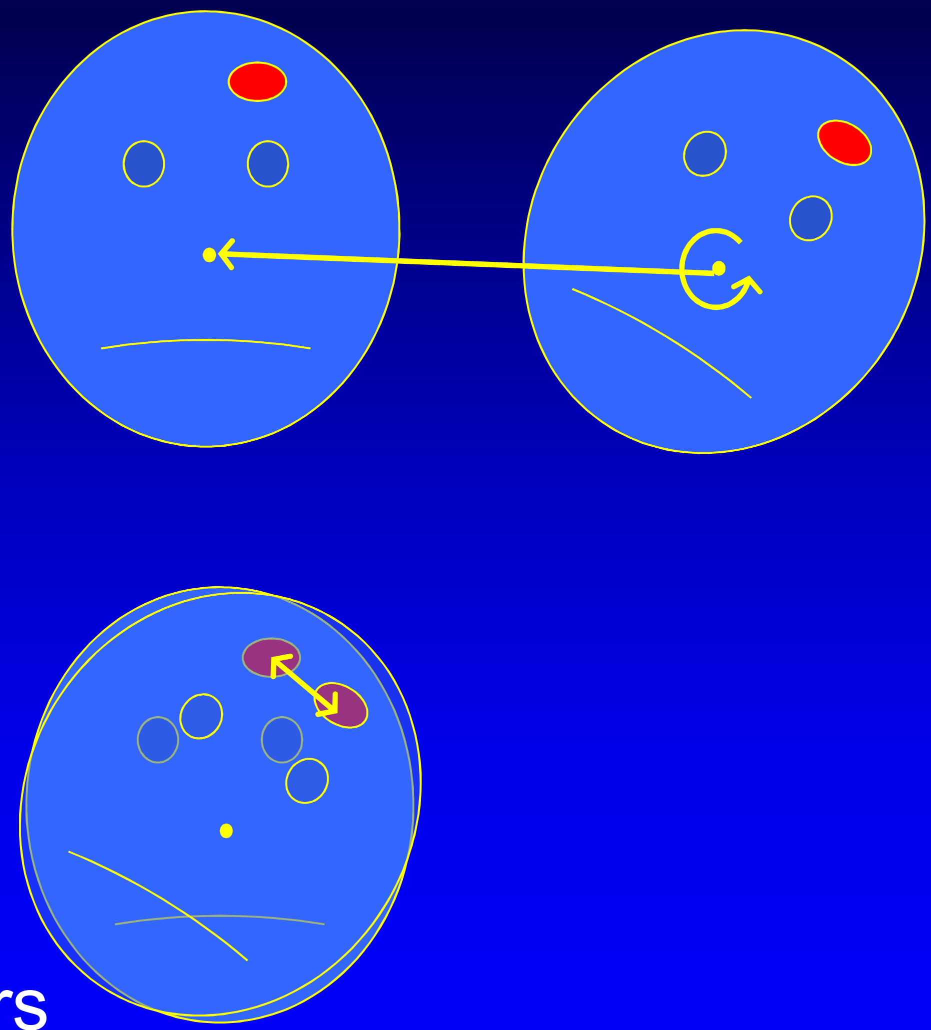
  → Reported negligible secondary motion, but did not correlate the motion to the amount of rotation

Smart ignoring of rotations

- Cone beam CT image guidance provides more detail about patient setup than currently can be corrected
- The solution is to make correction an optimization process: i.e., perform correction such that best CTV coverage is obtained
- For correcting rotations with just a couch shift, this is equivalent to optimizing one point: the correction reference point

Registration procedure

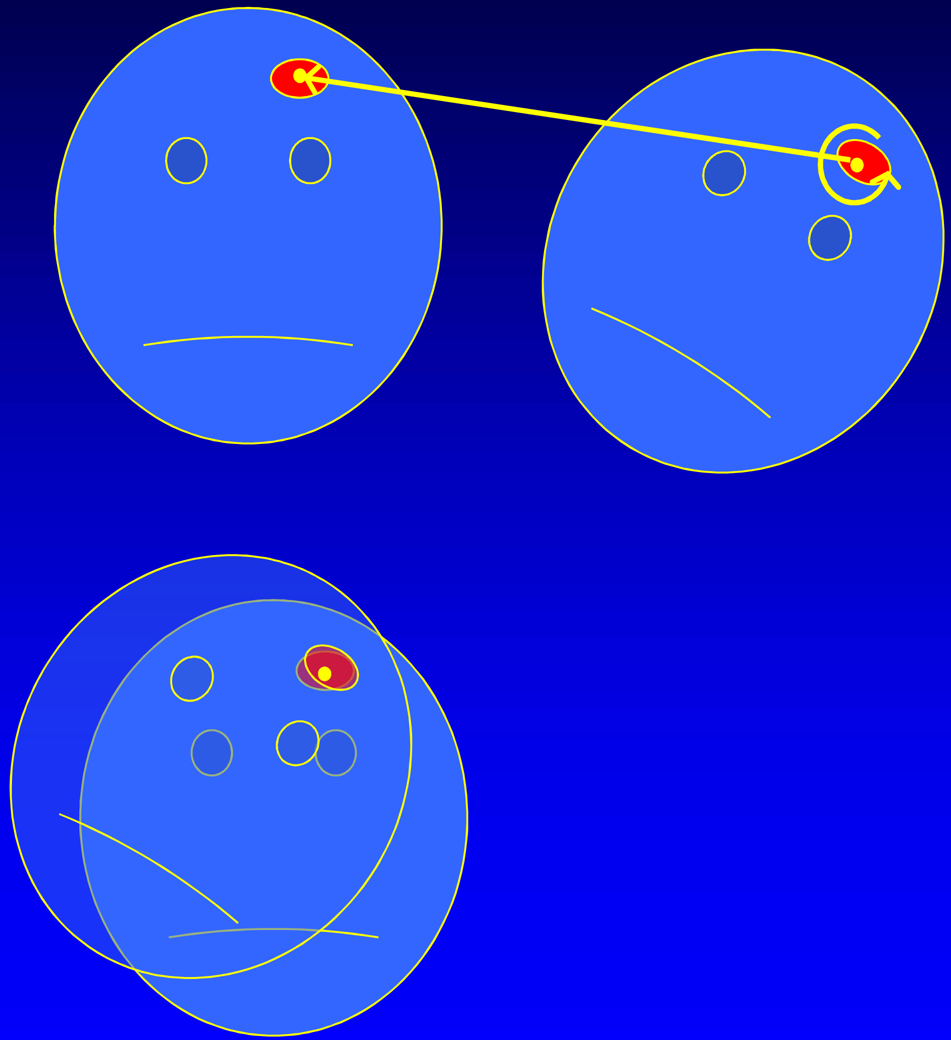
Registration
- Bony anatomy
- Translations and rotations
- Very accurate



Correction
- Only translations
- Potentially large errors

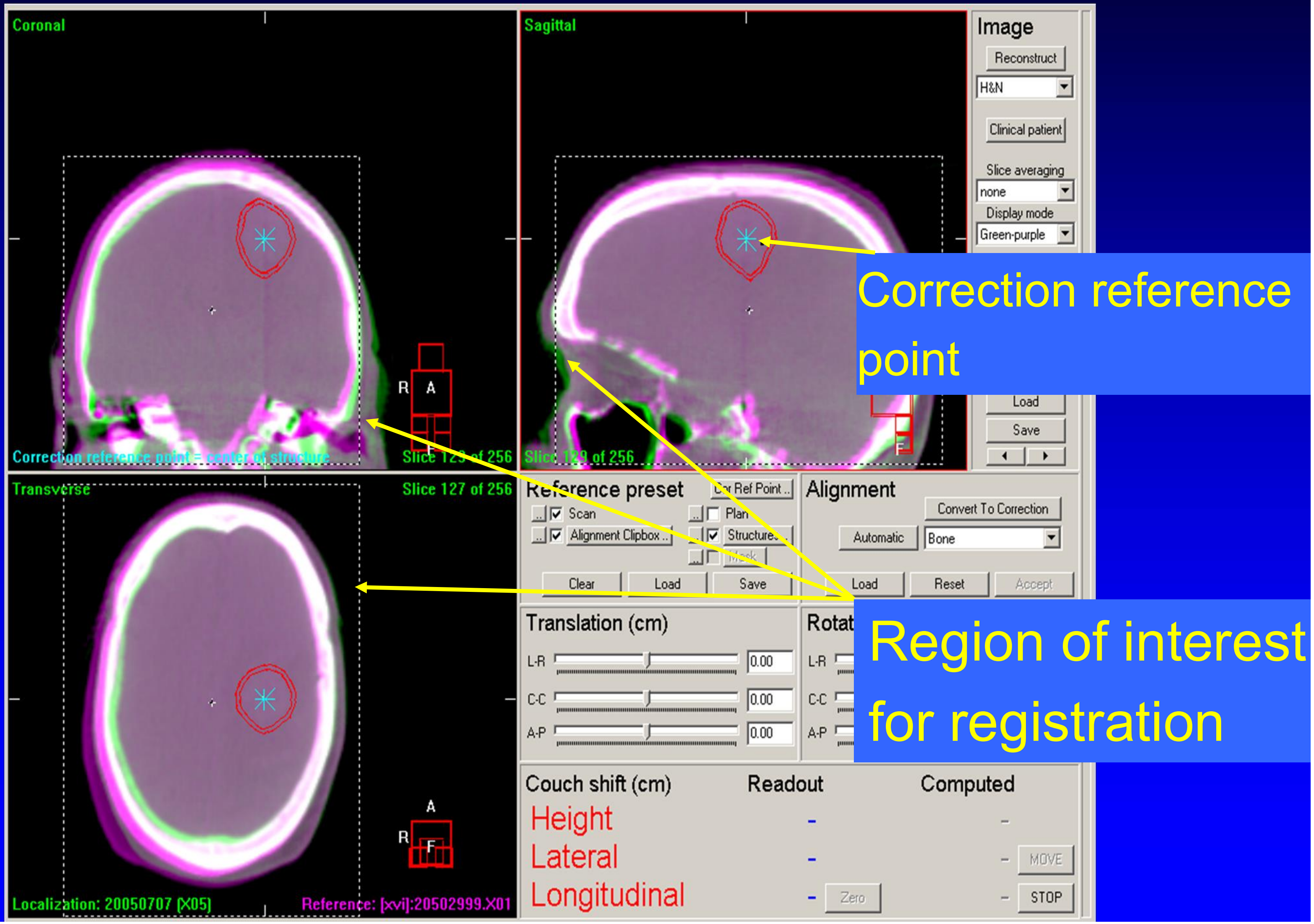
Registration procedure – Rotational errors

Registration
- Bony anatomy
- Redefine center of rotation (correction reference point)

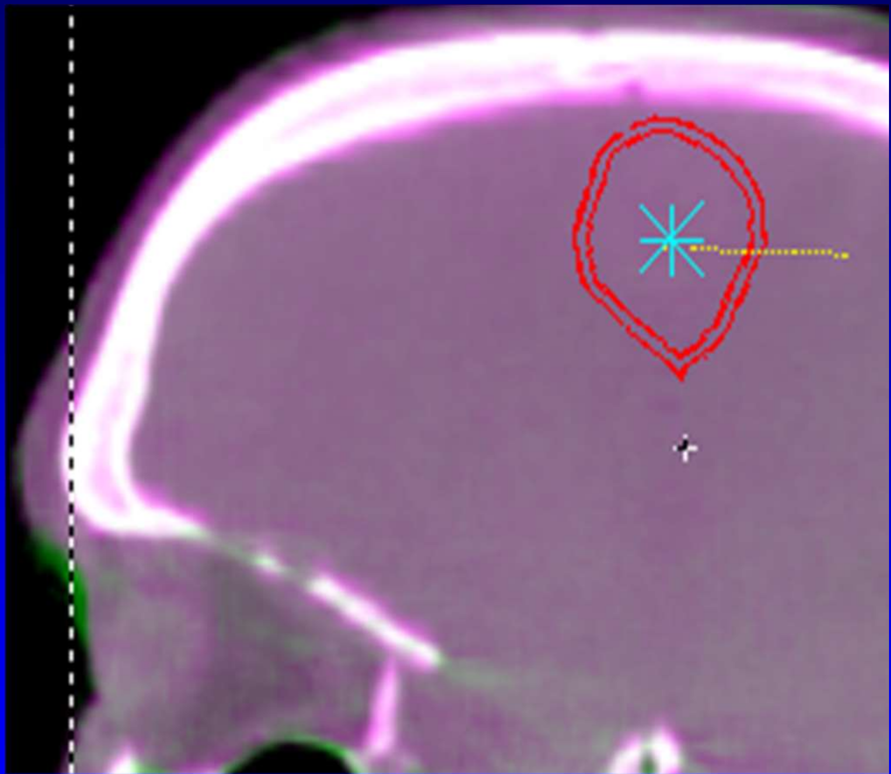


Correction
- Only translations
- Rotational errors are small close to rotation center

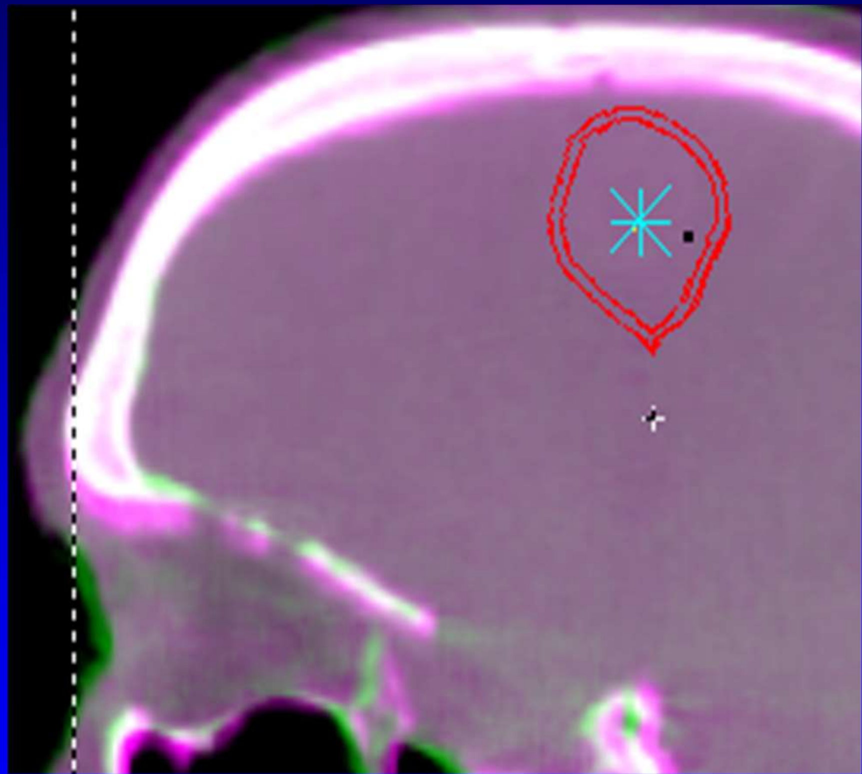
Registration procedure – not matched



Registration procedure – Rotational errors



6D Registration



3D Correction

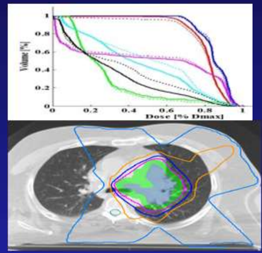
Difference between translation part of registration and correction (mm) - lung

	LR	CC	AP
Mean	0.1	0.0	0.1
SD	0.6	0.7	0.9
Range	-2.5 .. 2.0	-2.1 .. 3.4	-2.3 .. 5.9

The modern radiotherapy process

Pre-treatment Imaging

Treatment Planning



In Room Imaging

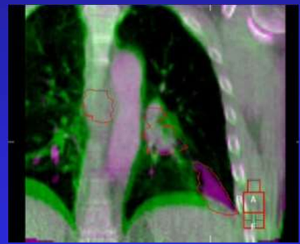
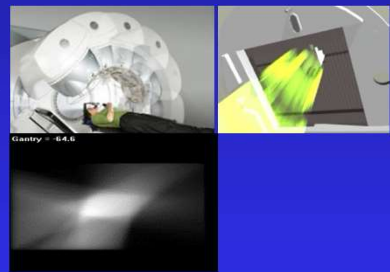


Image Registration & Correction

Treatment Delivery

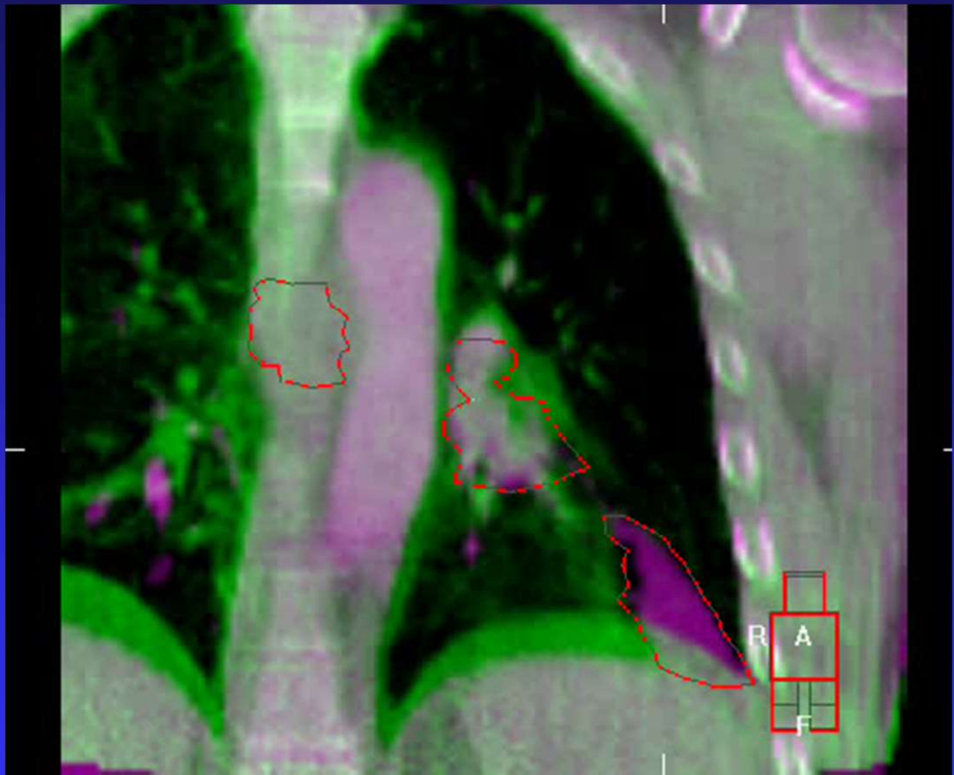


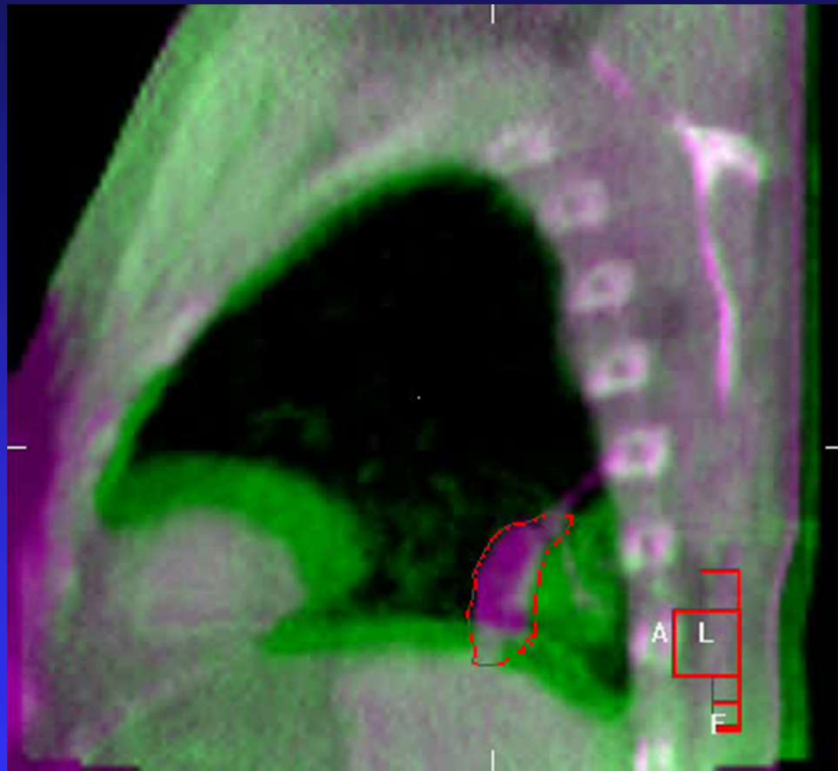
Dosimetry

Very high accuracy achieved

Are all problems now solved ?

Differential Motion





No couch correction can solve this problem

Adaptive Radiotherapy

The Start of Adaptive Radiotherapy

IJROBP 1997; 38: 197-206

● *Physics Contribution*

ADAPTIVE MODIFICATION OF TREATMENT PLANNING TO MINIMIZE THE DELETERIOUS EFFECTS OF TREATMENT SETUP ERRORS

Di Yan, D.Sc.,* John Wong, Ph.D.,* Frank Vicini, M.D.,* Jeff Michalski, M.D.[†]
Cheng Pan, Ph.D.,* Arthur Frazier, M.D.,* Eric Horwitz, M.D.*
and Alvaro Martinez, M.D., F.A.C.R.*

In this study, a new approach, called adaptive radiation therapy (ART), is introduced to minimize the deleterious effects of setup variation on each individual patient.

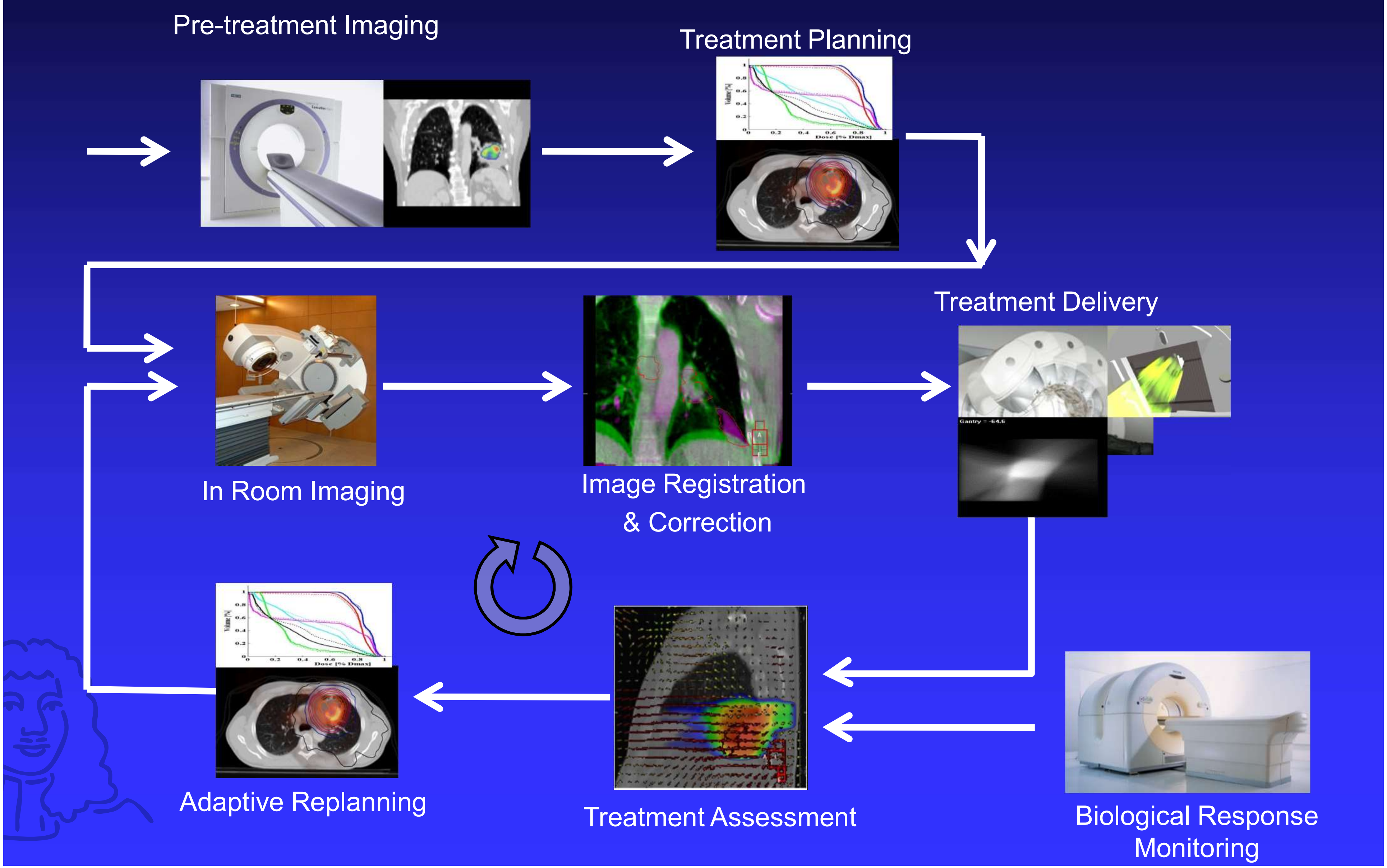
Adaptive Radiotherapy

Seminars in Radiation Oncology, 2005

The adaptive radiotherapy technique aims to customize each patient's treatment plan to patient-specific variation by evaluating and characterizing the systematic and random variations through image feedback and including them in adaptive planning.

Adaptive radiotherapy will become a new treatment standard.

The Adaptive Replanning Process



PTV Margins assure target coverage

- Most popular formulation is **2.5Σ + 0.7σ,** where:
  - Σ is the standard deviation of systematic uncertainty
  - σ is the standard deviation of random uncertainty

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

ART Strategies

Patient-specific PTV

- Constructed with repeated imaging.
- Based on the first few days of treatment.
- Adapt the plan once using MLC beam apertures to correct margins and systematic error.
- No on-line interventions.

Yan et al PMB 42 (1997) 123–132
D.Yan, D. Lockman et al, IJROBP 48, 289–302, 2000
Martinez, Yan et al IJROBP 50, 1226–1234, 2001
D. Brabbins et al, IJROBP 61. 400–408, 2005
Nuver et al IJROBP 67(5); 1559-67 (2007)

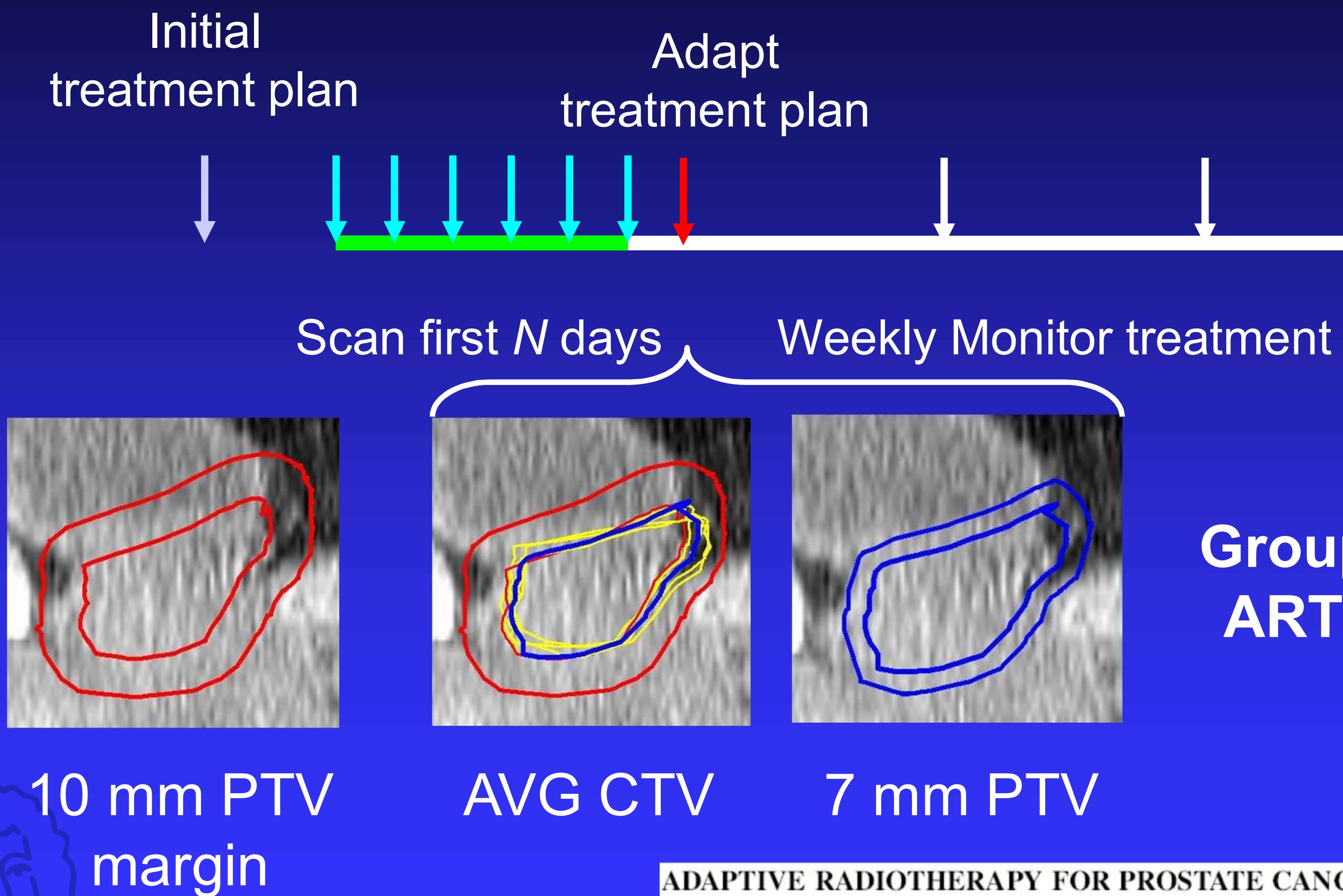
Hugo et al Radioth & Oncol 78 (2006) 326–331

Adapt Dose Distribution

- Imaging feedback to assess dose in moving and deforming organs.
- “4D” patient models.
  - Relate target/organ segmentations
  - Track deforming organs
  - Accumulate fraction doses
  - Evaluate dose delivered: to date, current fraction, anticipated “trajectory”.

J Löf et al, PMB 43 (1998) 1605–1628
Birkner M et al, Med Phys. 2003 30(10):2822-31
Rehbinder et al, Med Phys. 2004 31(12):3363-71

Adaptive Radiotherapy

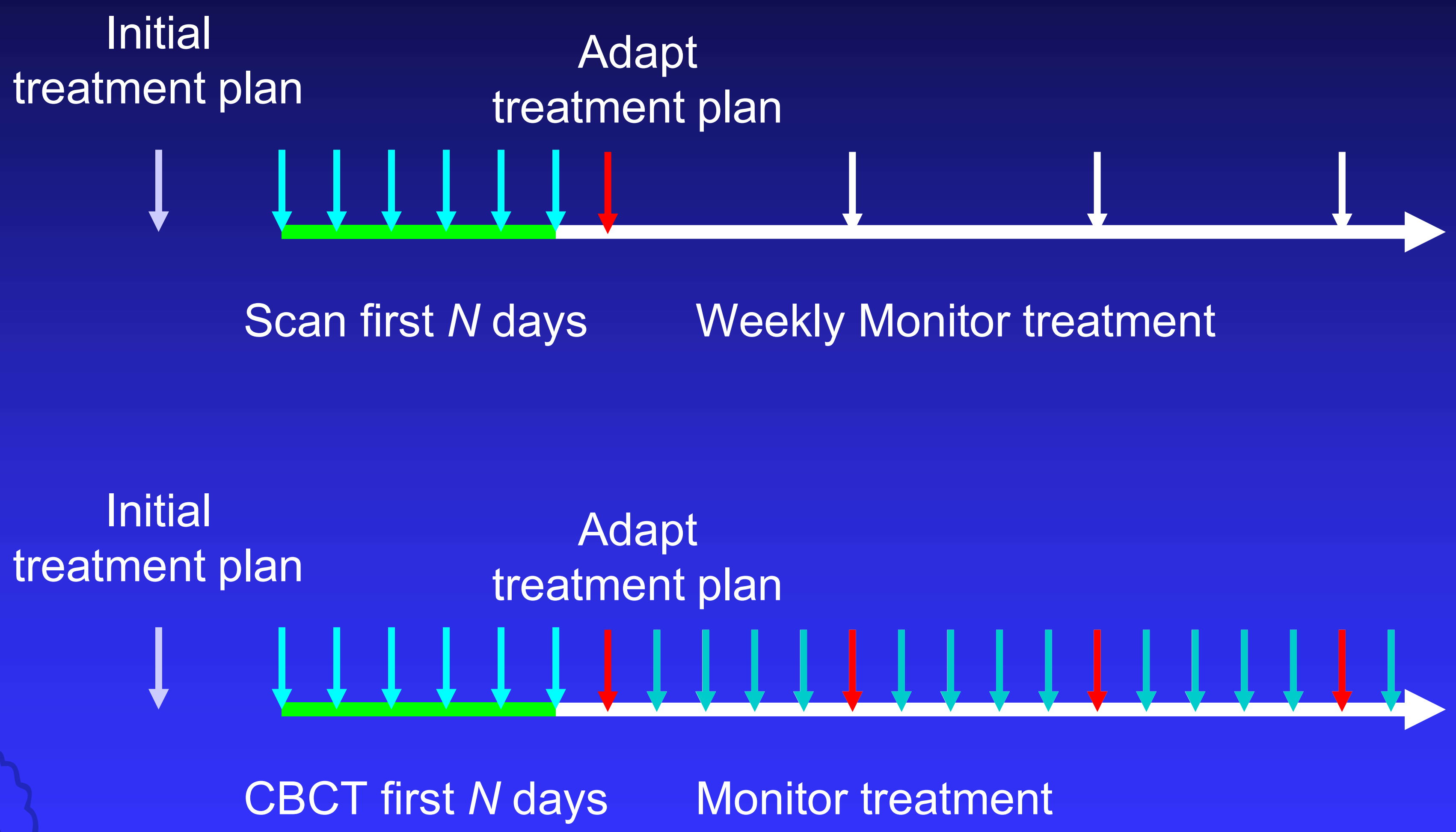


Group-specific ART strategy

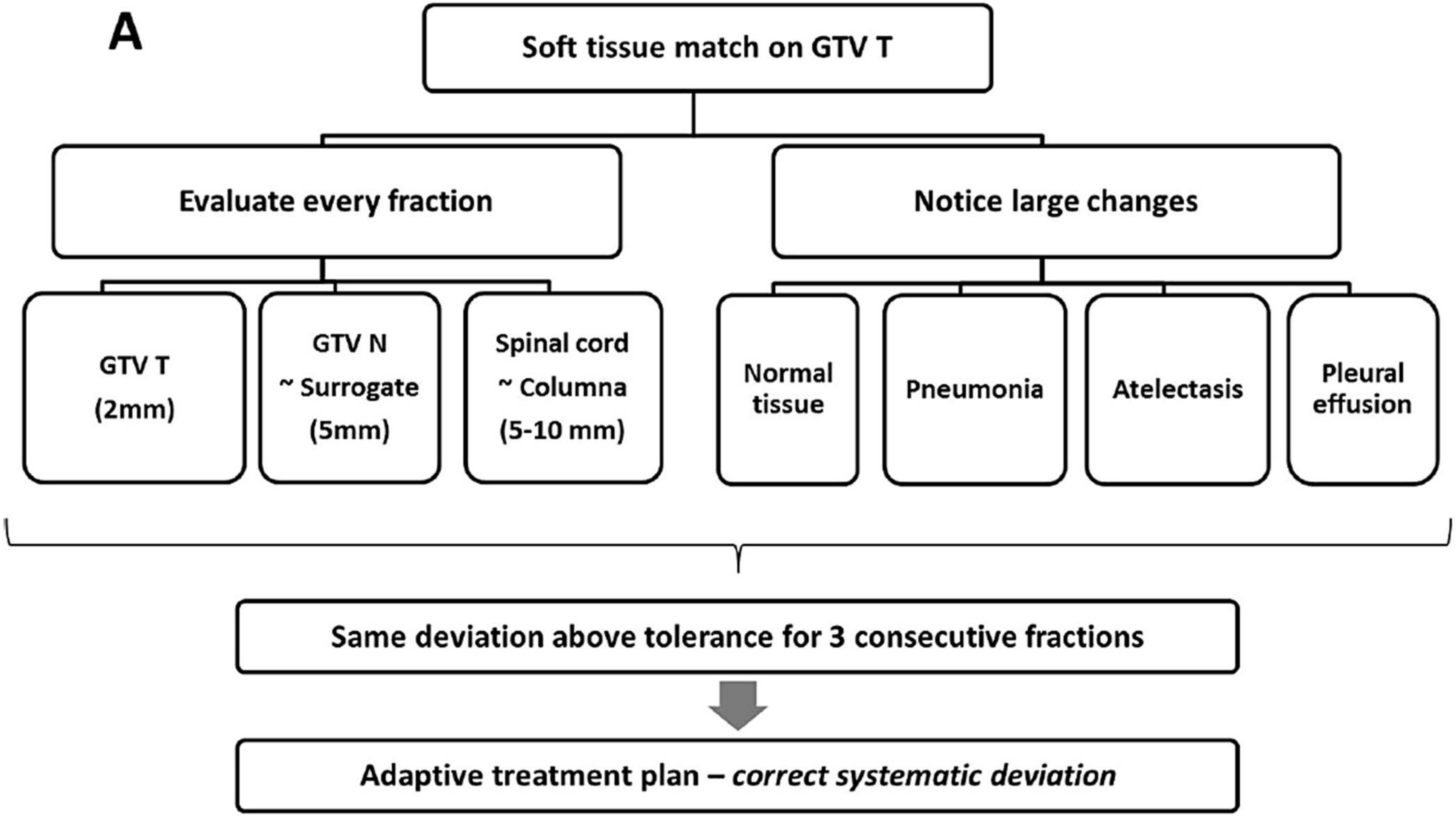
ADAPTIVE RADIOTHERAPY FOR PROSTATE CANCER USING KILOVOLTAGE CONE-BEAM COMPUTED TOMOGRAPHY: FIRST CLINICAL RESULTS

Jasper Nijkamp, M.Sc., Floris J. Pos, M.D., Ph.D., Tonnis T. Nuver, Ph.D., Rianne de Jong, R.T.T., Peter Remeijer, Ph.D., Jan-Jakob Sonke, Ph.D., and Joos V. Lebesque, M.D., Ph.D.

Adaptive Radiotherapy



ART Cohort study



Møller et al. Radiat. Oncol. 2016

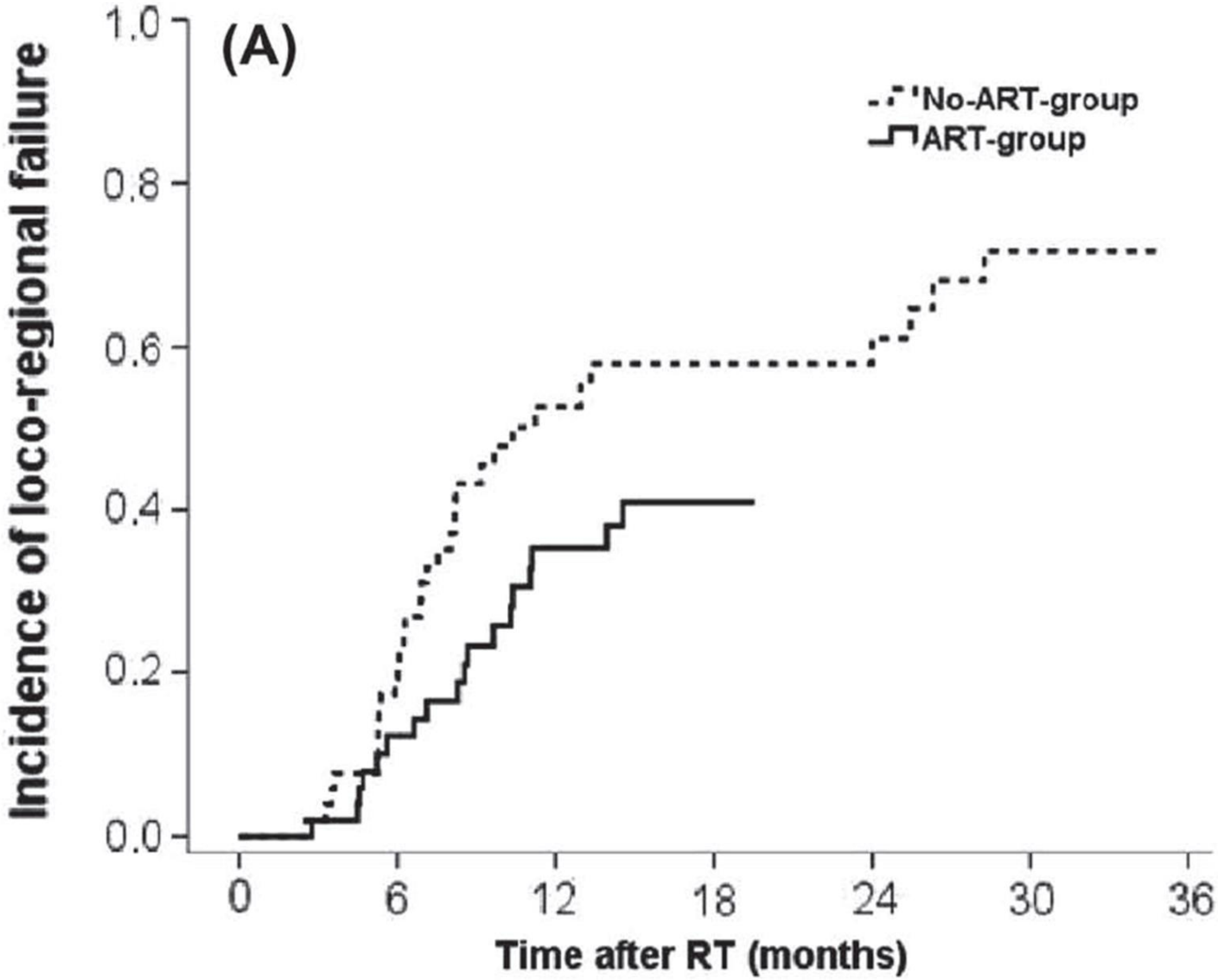
ART Cohort study

Table 2
Dosimetric parameters of the ART and pre-ART group.

Patients (*n*)	ART (*n* = 52)	Pre-ART (*n* = 52)	*p*-value (1 sided)
NSCLC/SCLC	38/14	38/14	
GTV size	98.3 cm^3	107.5 cm^3	0.39
PTV size	400 cm^3	599 cm^3	<0.001
Dose NSCLC	64.9 Gy	64.0 Gy	0.14
Dose SCLC	45.0 Gy	45.1 Gy	0.17
MLD	12.6 Gy	14.4 Gy	0.02
V20 – lung	22.6%	25.7%	0.03
V5 – lung	45.3%	49.6%	0.04
MHD	8.0 Gy	10.0 Gy	0.08
V20 Heart	13.1%	17.0%	0.10
V45 Esophagus	15.7%	20.6%	0.07

Møller et al. Radiat. Oncol. 2016

ART Cohort study



Tvilum et al. Acta. Oncol. 2015

Limitations

What can we detect ?

Tissue Dislocations

- Patient/Target Setup-Errors
- Interfractional organ motion
- Intrafraction organ motion

Tissue Deformations

- Posture change
- Interfractional organ deformations
- Tumor Shrinkage/Growth
- Tissue Swelling
- Weight-Loss/Gain of the Patient

What can we not detect?

- Remaining Uncertainties
  - Target Delineation Uncertainties
  - Microscopic disease
  - Uncertainty of the IGRT procedure

→ Appropriate Margins

Conclusions

- Systematic errors are most important for the margin
- Offline protocols can reduce the systematic errors effectively
- ART: Systematic improvement of treatment plan based on imaging information
- Development of clinical ART is one of the major tasks for future IGRT

Prostate

Helen McNair DCR(T), PhD

Lead research Radiographer

Royal Marsden NHS Foundation Trust and Institute of Cancer Research

UK

Rianne de Jong

IGRT Specialist radiographer

Academic Medical Centre,

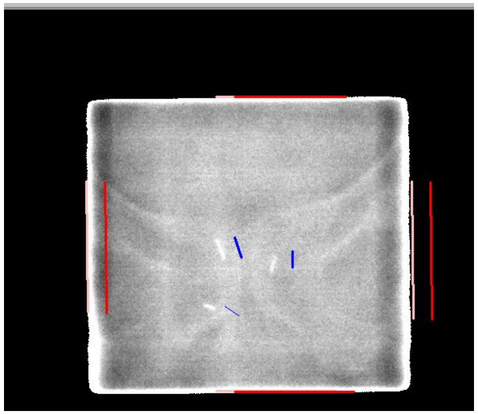
Amsterdam

The Institute of Cancer Research

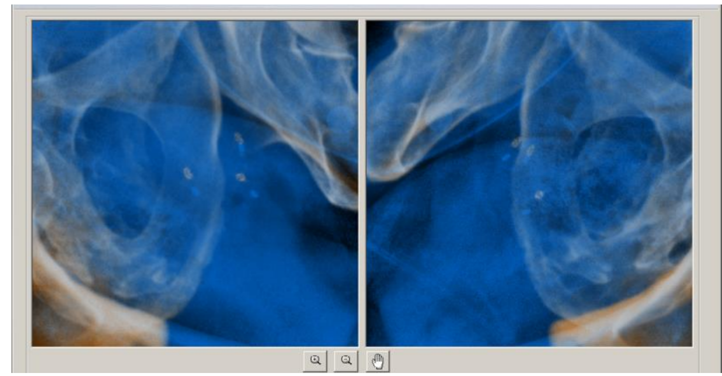
The ROYAL MARSDEN NHS Foundation Trust

ESTRO School

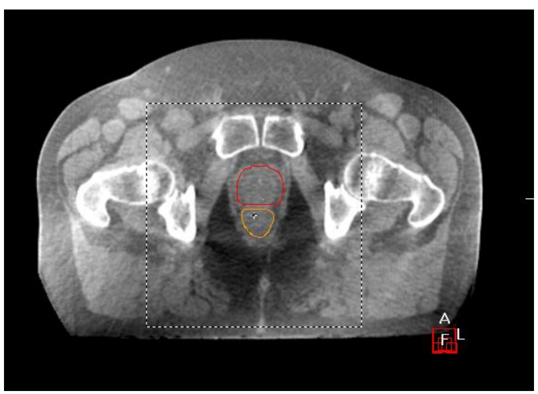
Methods of registration



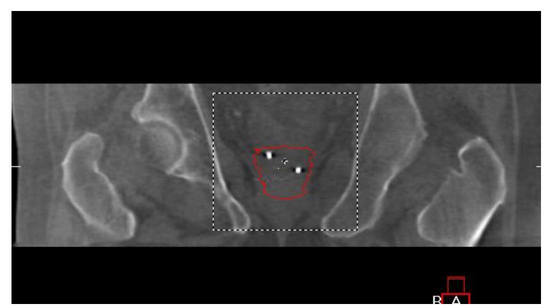
MV & markers



kV & markers



CBCT



CBCT & markers

Which method do you use?

MV imaging

MV imaging and markers

KV planar imaging

KV planar imaging and markers

3D soft tissue imaging

3D soft tissue imaging and markers

Which method would you prefer to use?

MV imaging

MV imaging and markers

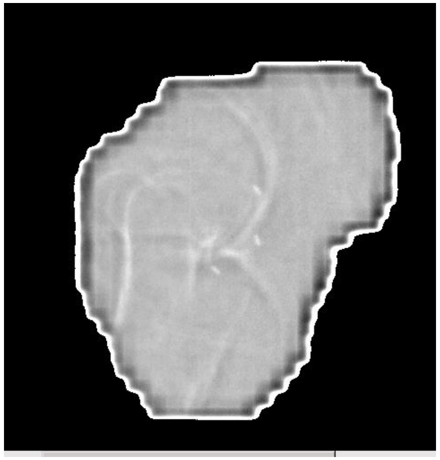
KV planar imaging

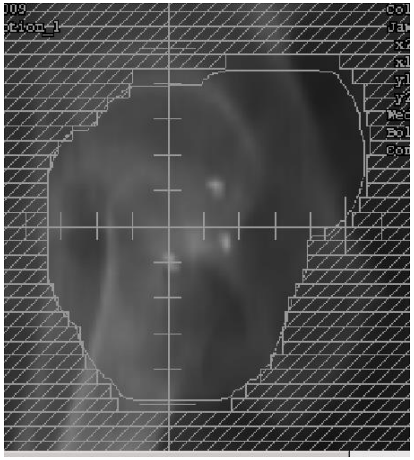
KV planar imaging and markers

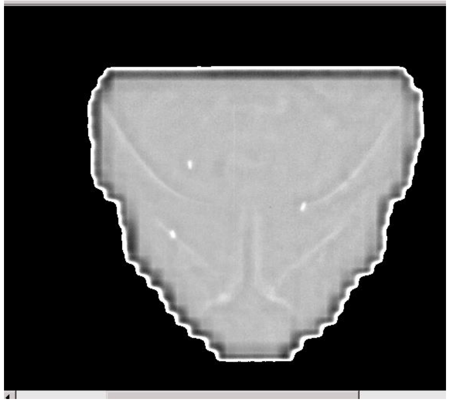
3D soft tissue imaging

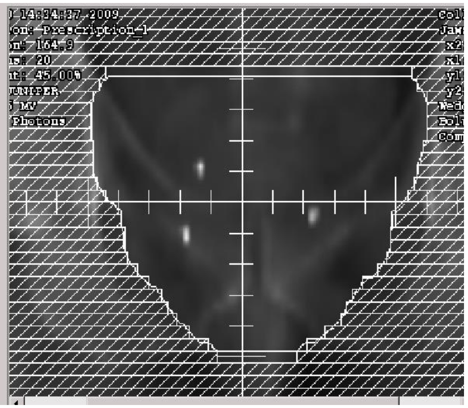
3D soft tissue imaging and markers

MV Marker registration

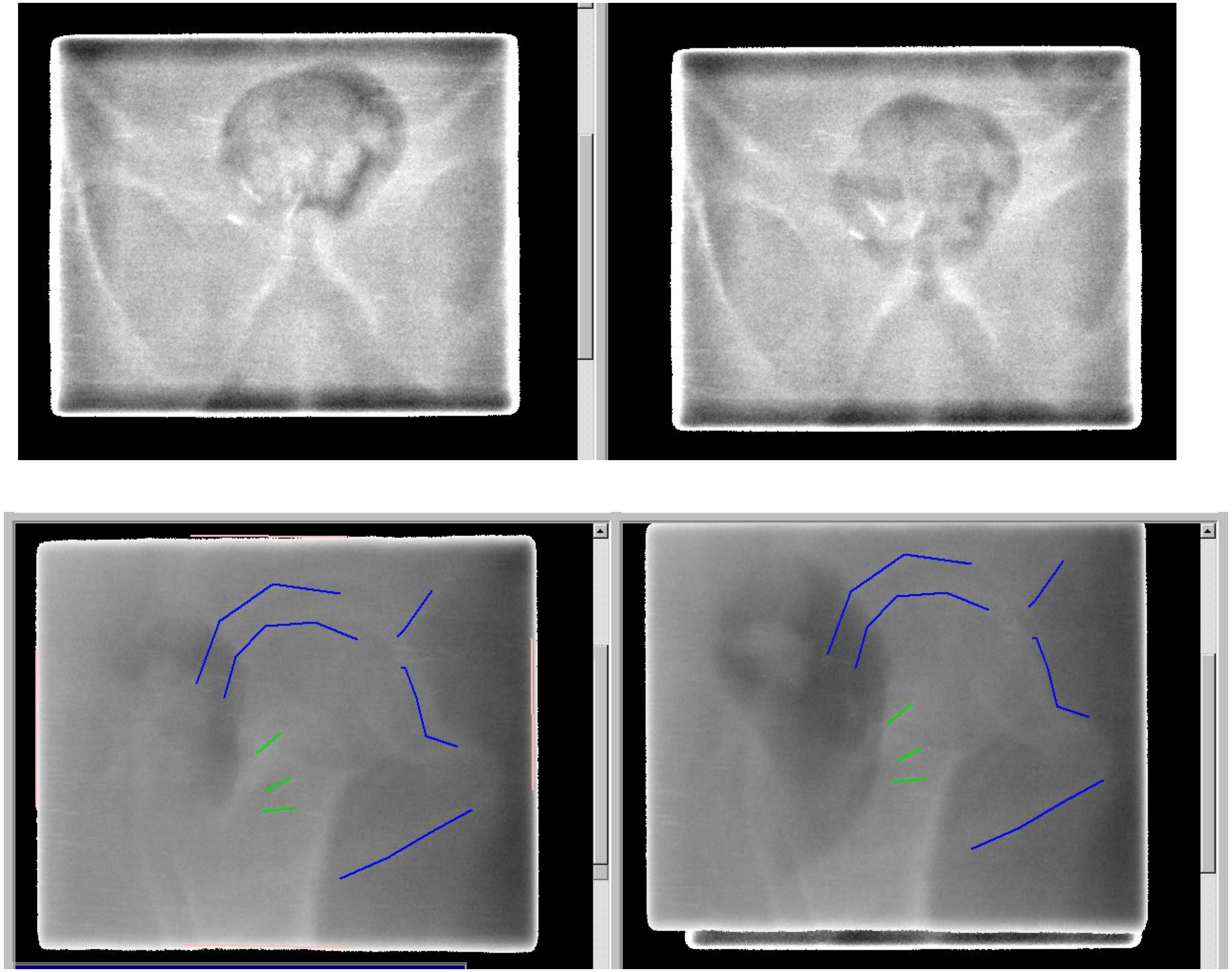




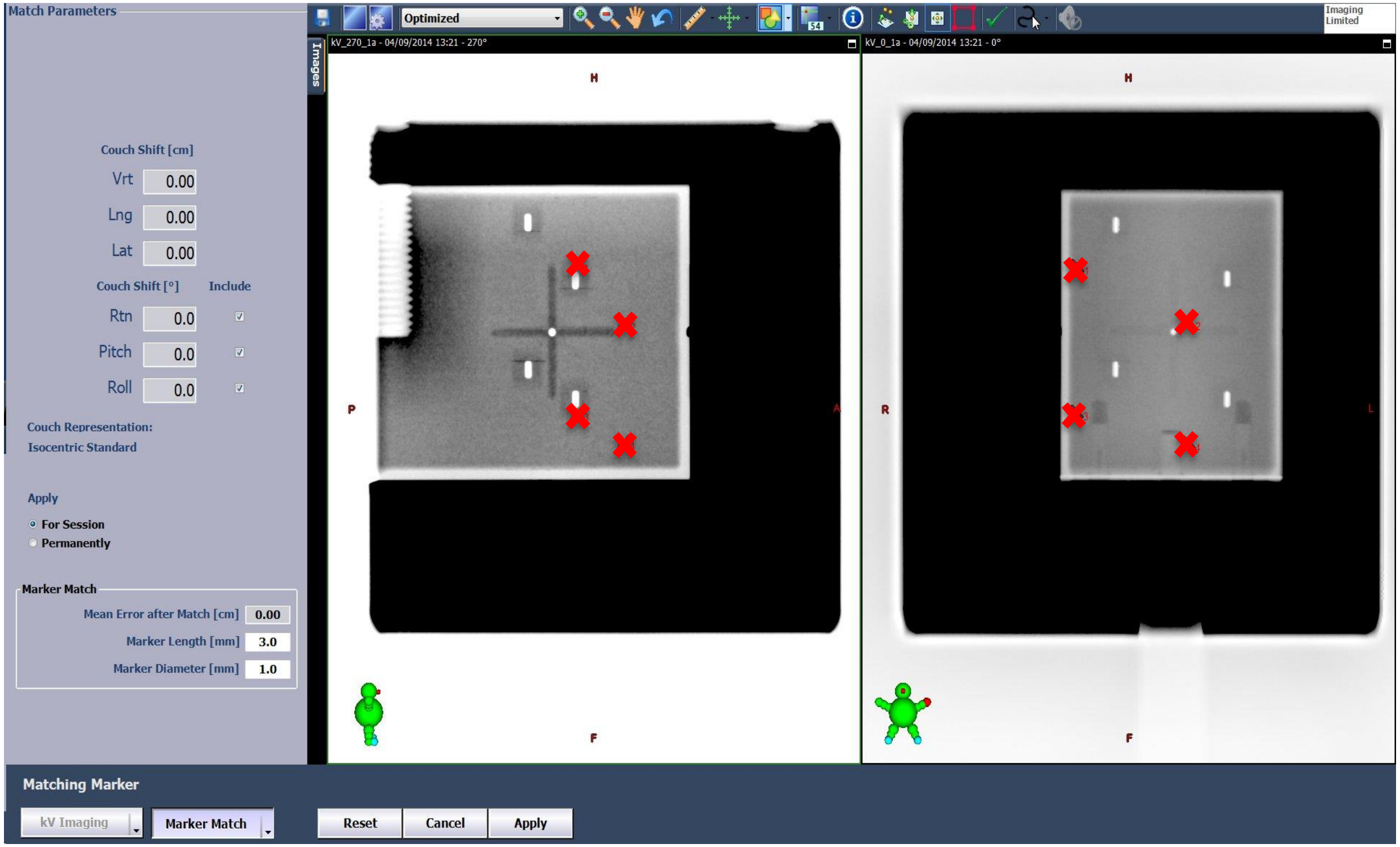




MV Marker registration

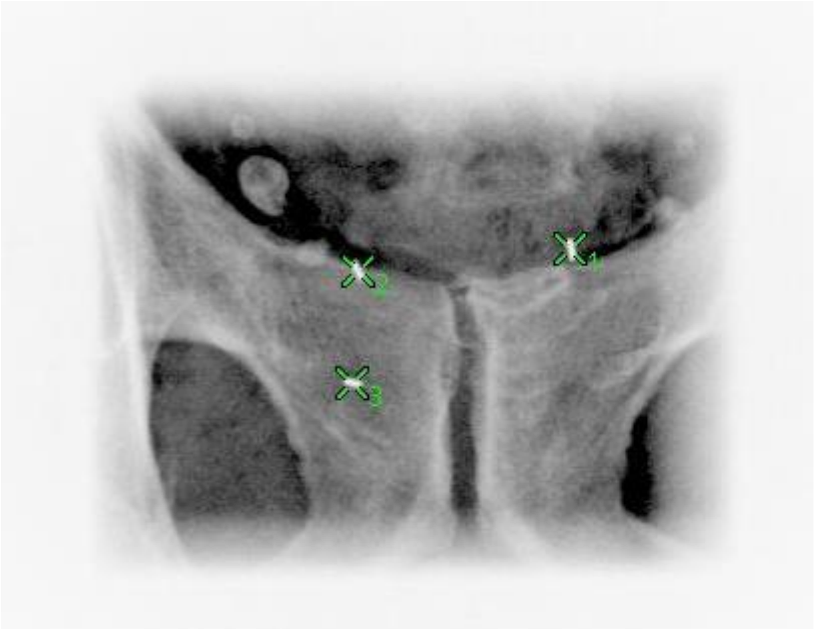


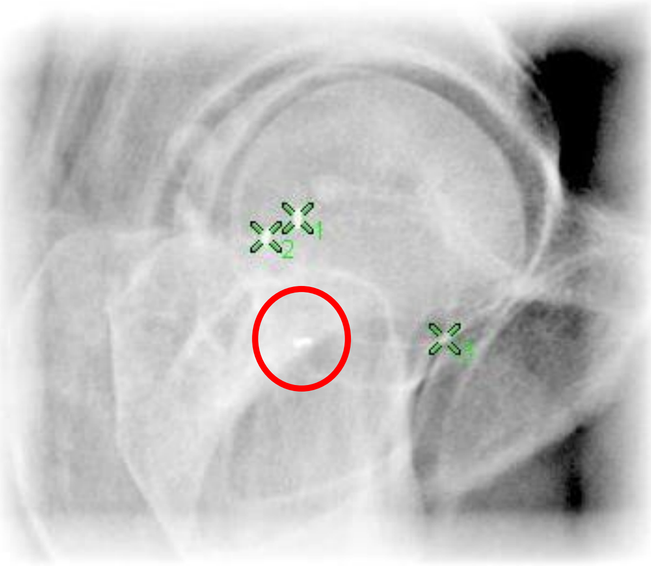
kV Marker registration –marker match



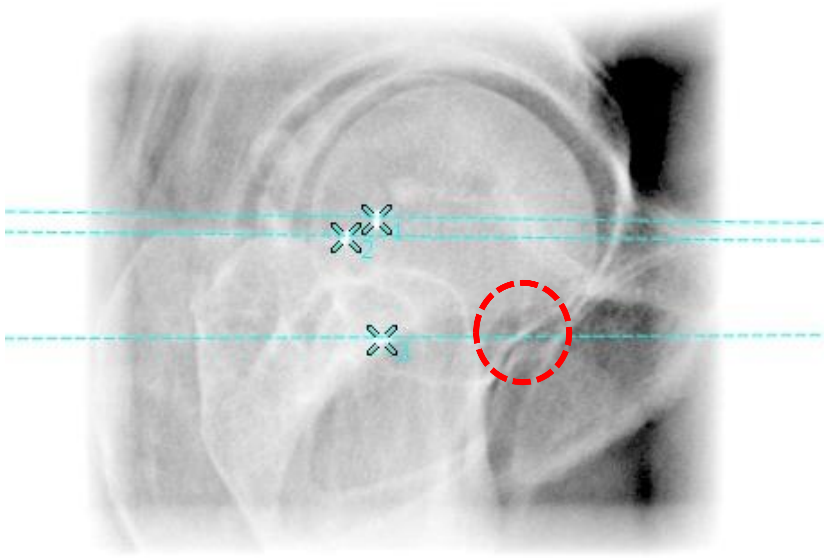
Eclipse – identify seeds from CT data set

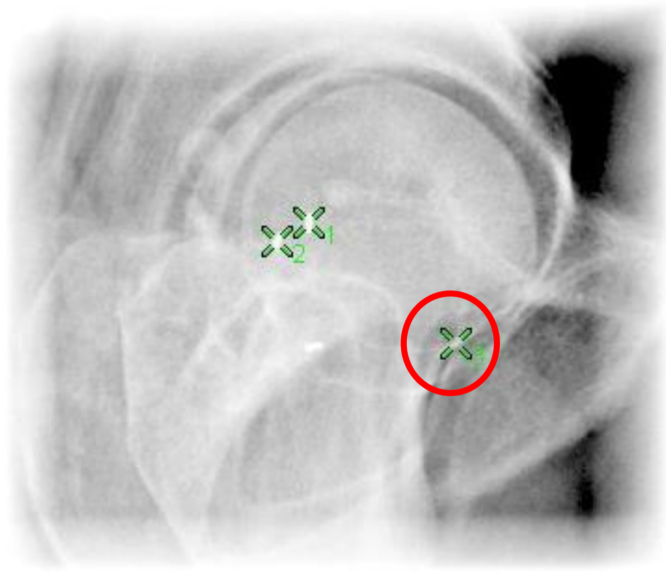
Automatic marker match





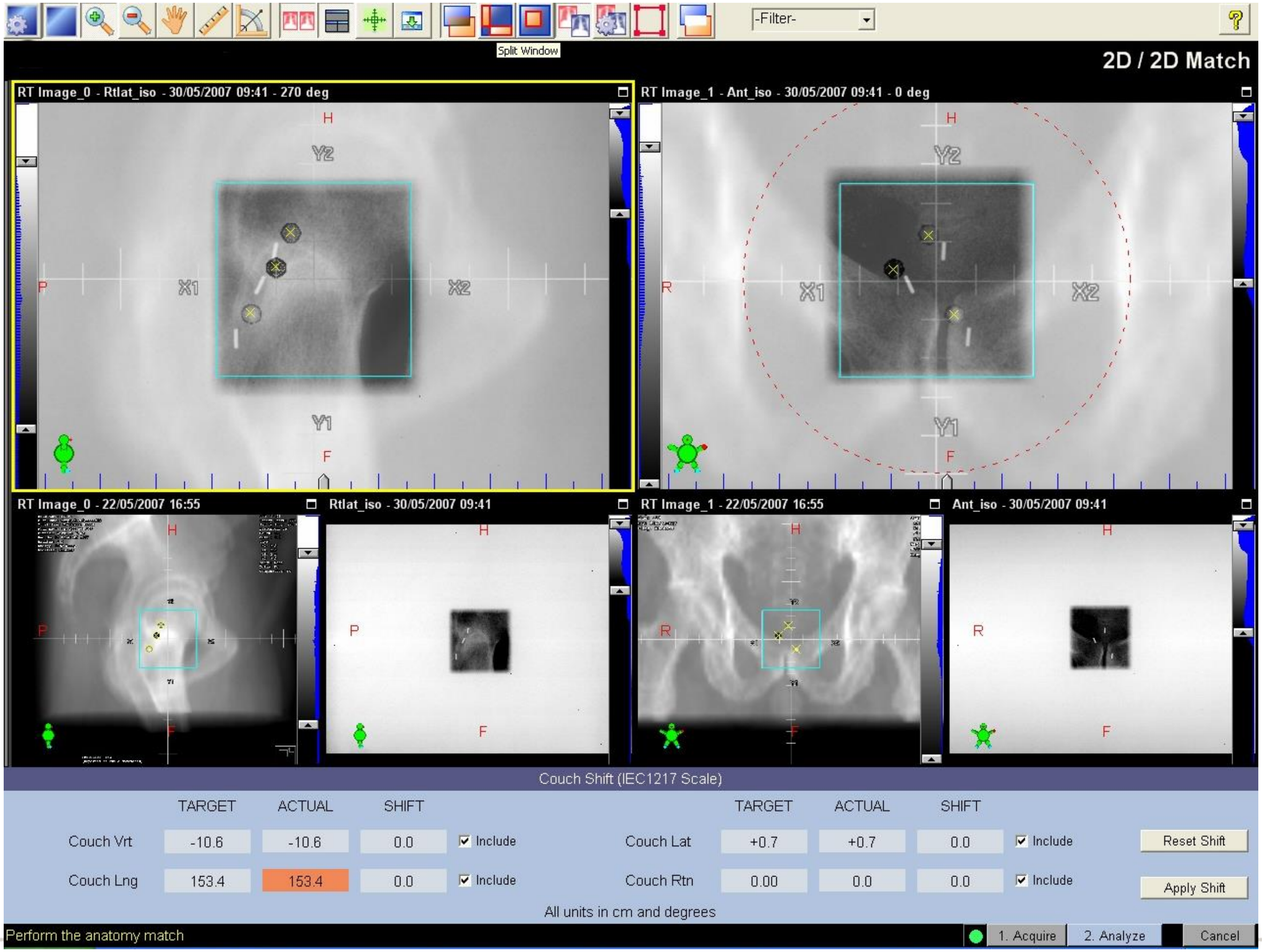
Automatic marker match





Manual adjustment of one seed

Marker registration – Image blend



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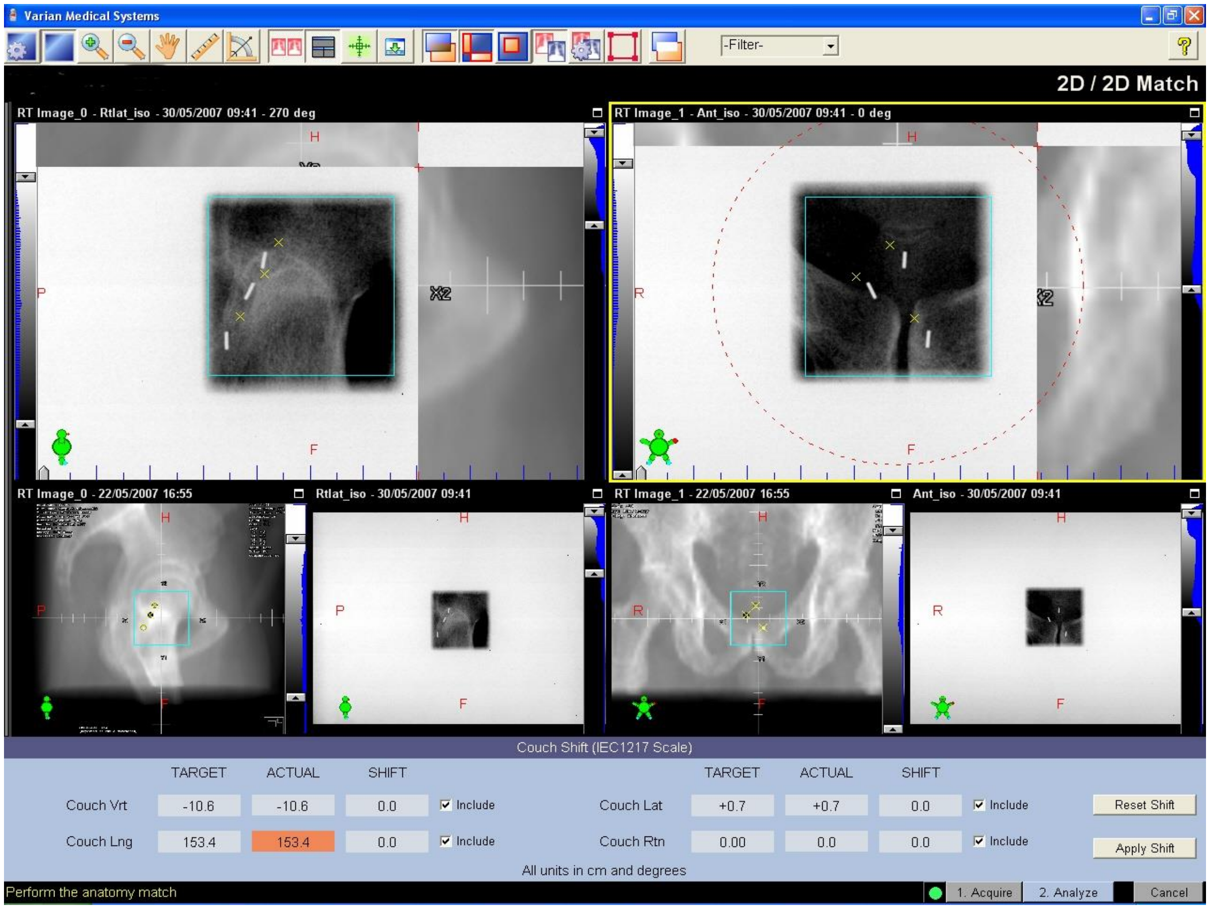
Marker registration – Image Analysis

Objective (template match)



observers	RL (%)	SI (%)	AP (%)
Off line (3) v on line (2)	100	99.1	99.3
Off line (3)	100	100	99.7

Deegan et al Journal of Medical Imaging and Radiation Oncology 2013

Marker registration – Apply couch corrections

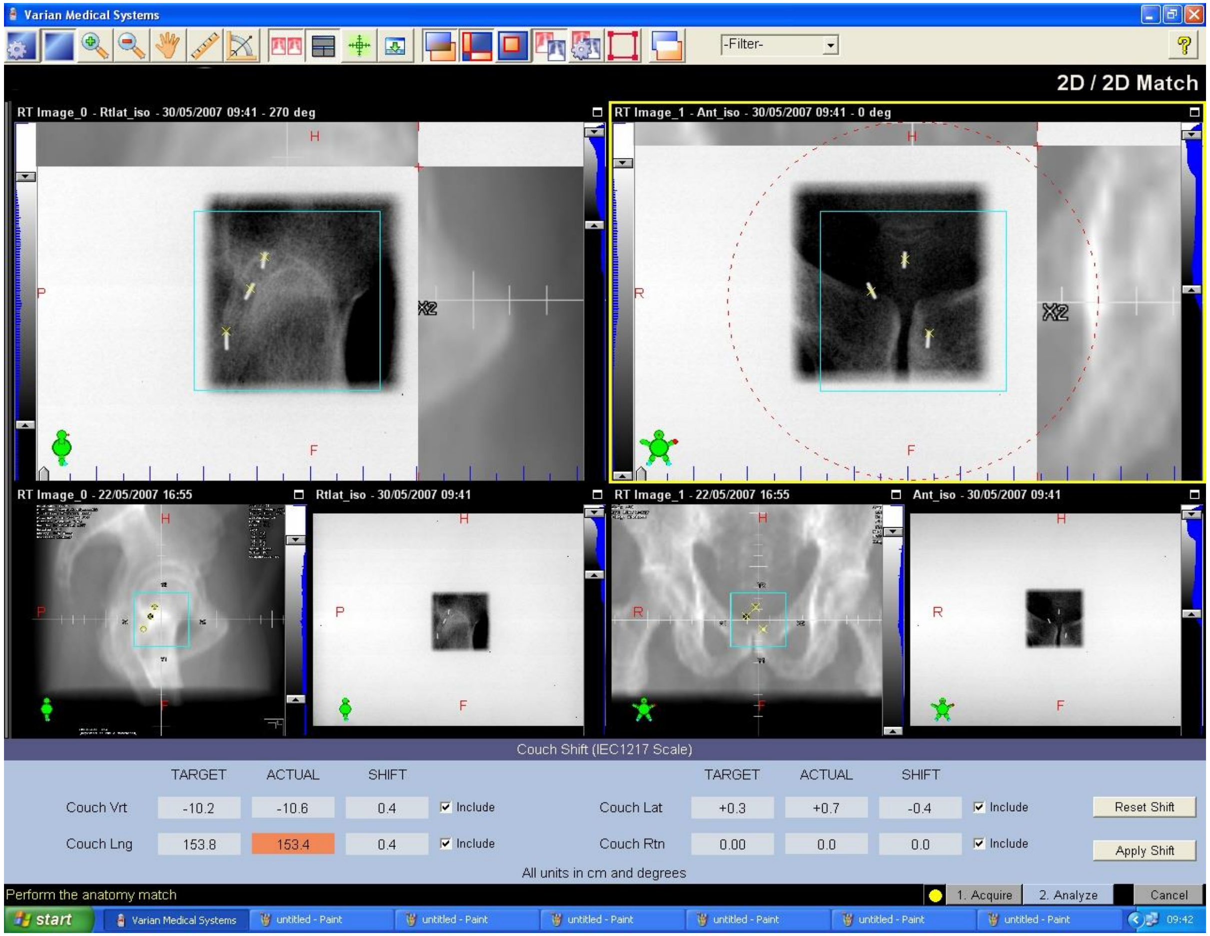
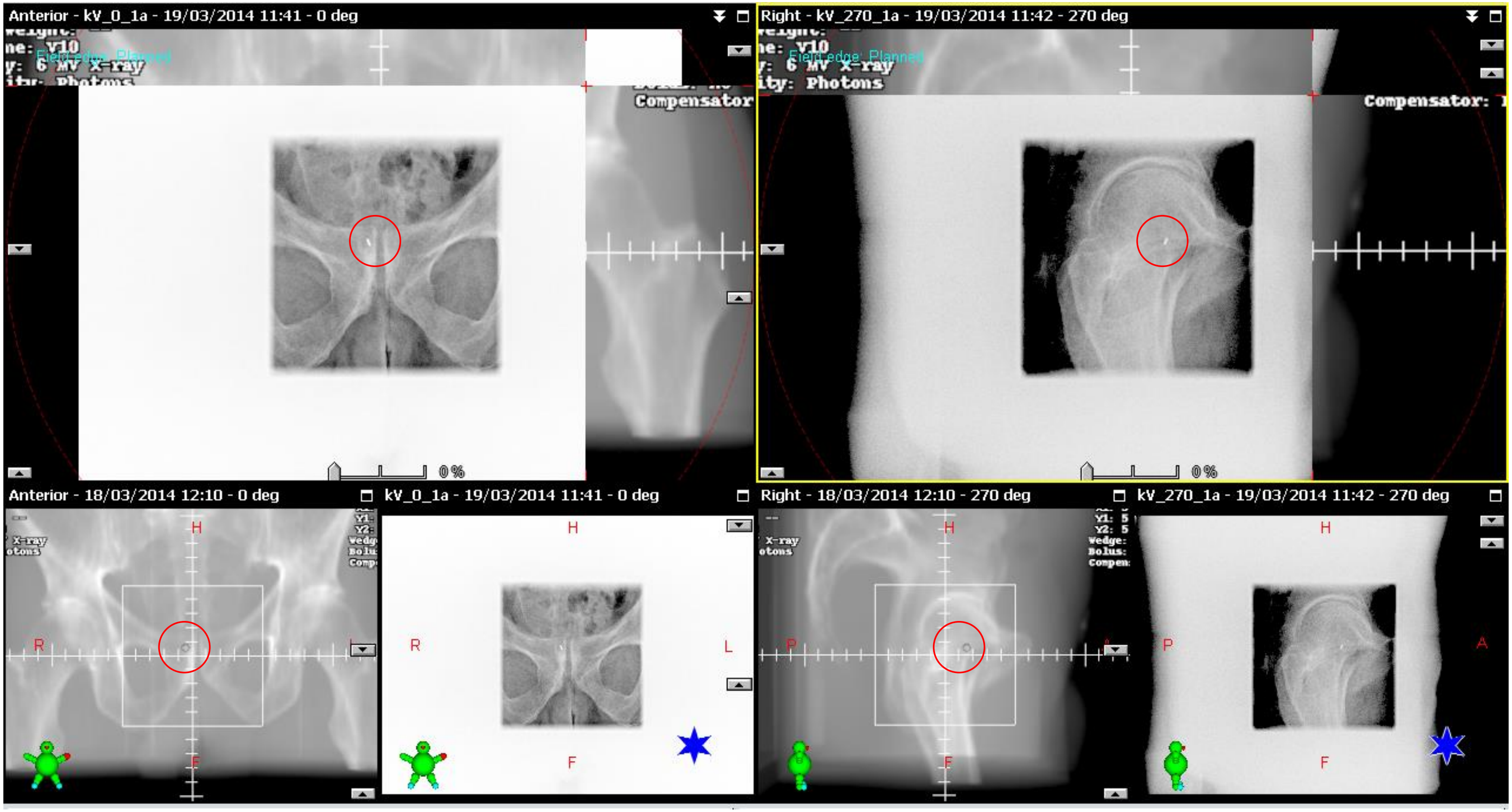


Image acquisition and analysis- 10 patients in-room timings (pre-VMAT)

Range 10.12 – 22.15 mins

Mean 14.36 mins, SD 1.95 mins

Registration issues –Lost seed(s)



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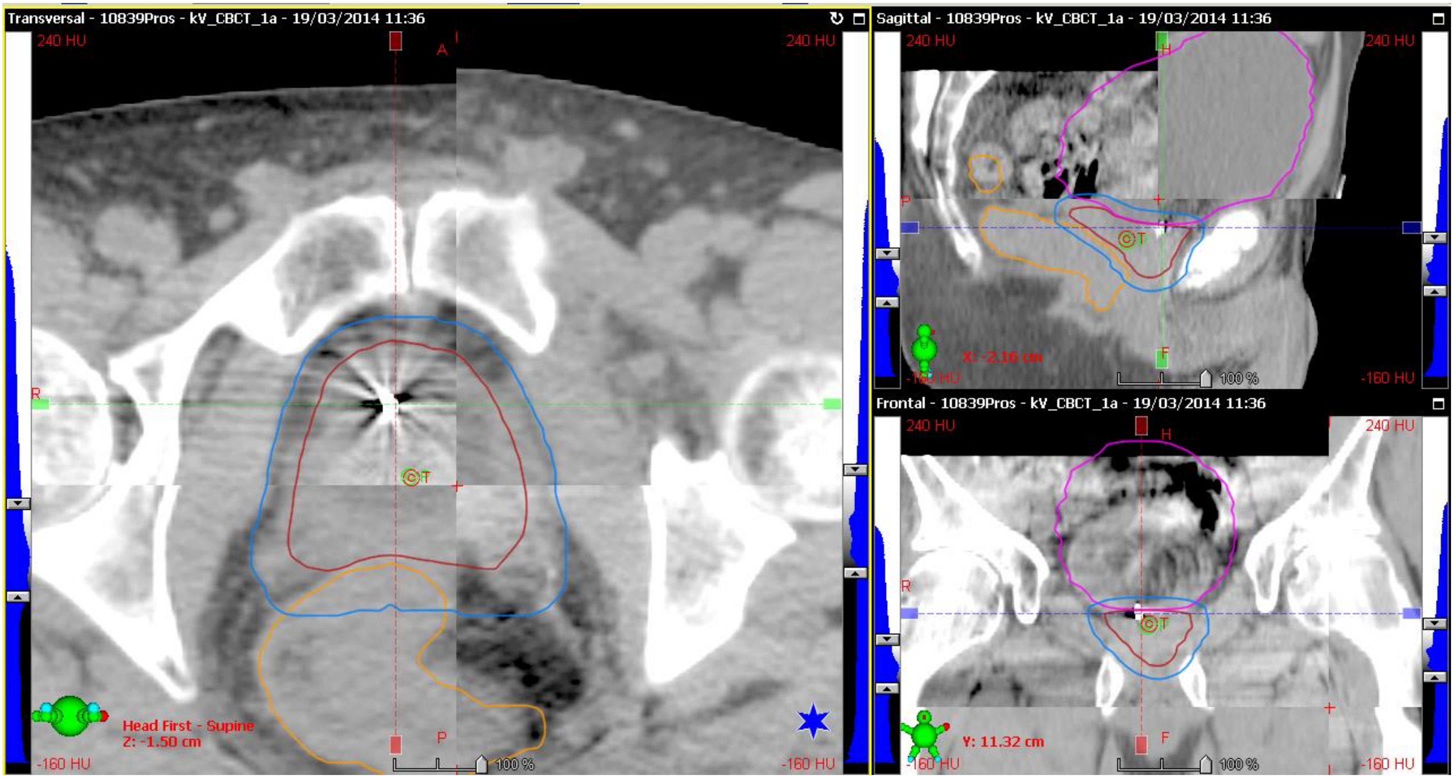
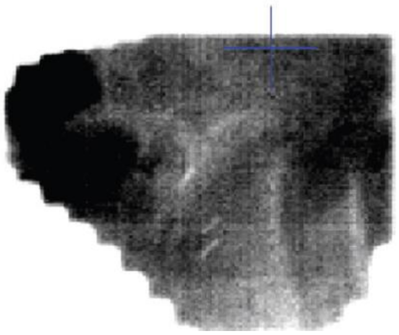
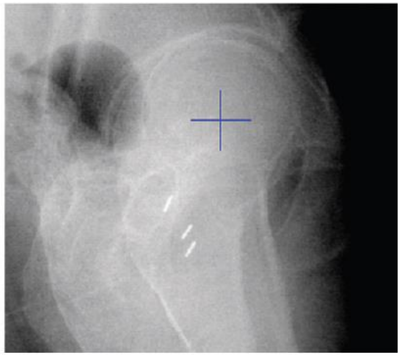
Registration issues –Lost seed(s)



Comparison of systems



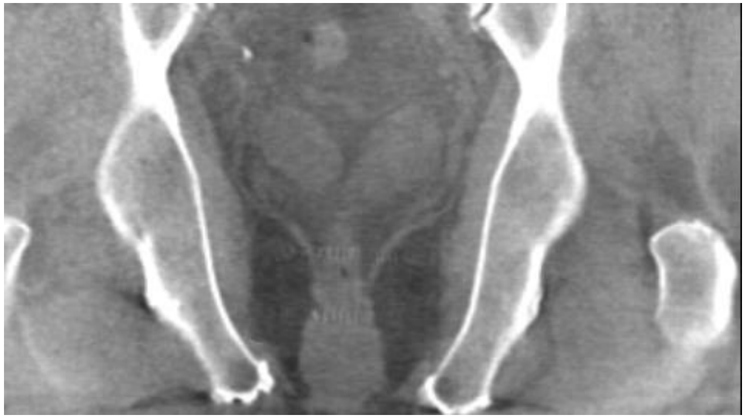


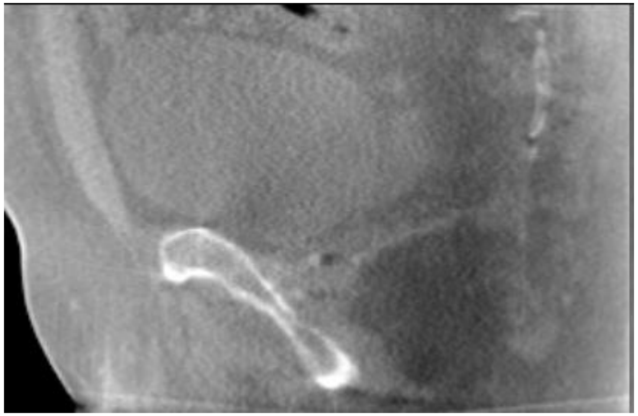
	Right Left (%)	Superior Inferior (%)	Anterior Posterior (%)
Proportion of displacements <3mm - KVI	62	56	45
Proportion of displacements <3mm - MVI	76	66	68
Proportion of displacements <5mm - KVI	88	79	74
Proportion of displacements <5mm - MVI	90	84	84

3 mm action level - 27% more shifts on KVI than on EPI; (p= 0.0001)

Gill, 2012 BJR

Soft tissue- image quality

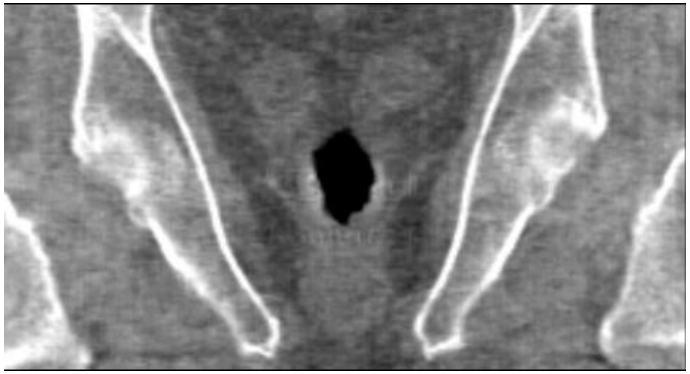


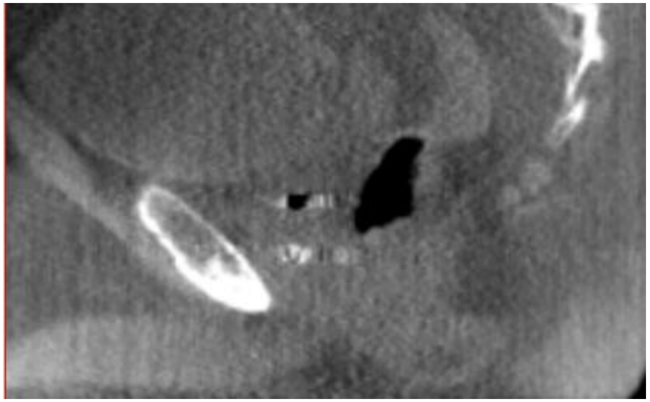


Elekta
64mA 40ms
700 frames - 3.5cGy
2min

100mA 40ms
410 frames - 3.5cGy
1 min

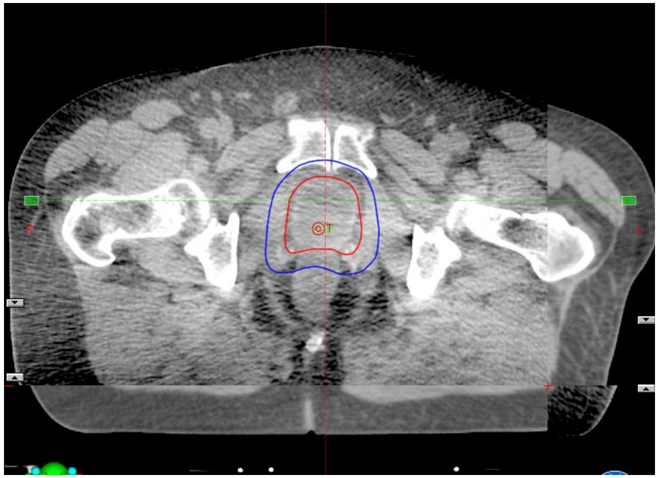
Soft tissue- image quality

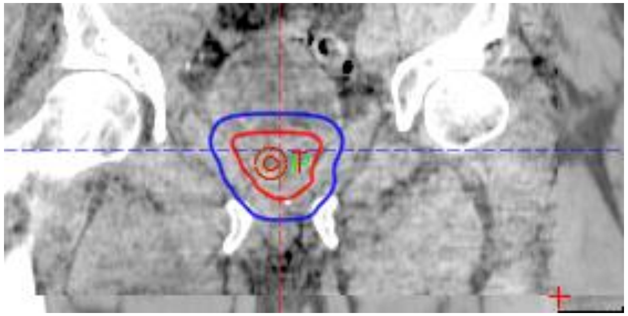




Elekta
S10 - 32mA 40ms
Fast scan (~180 frames) < 1.0 cGy

Soft tissue- image quality

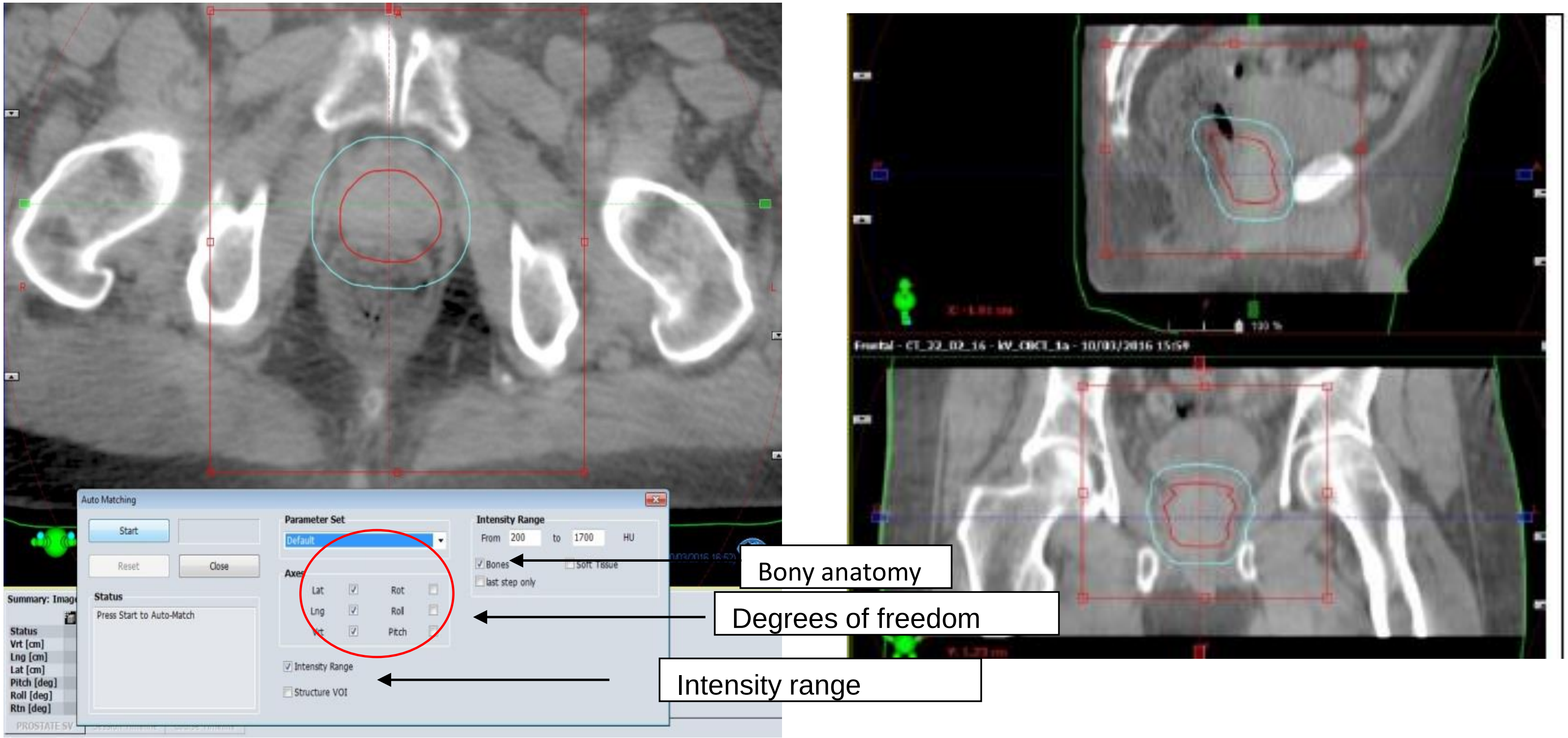




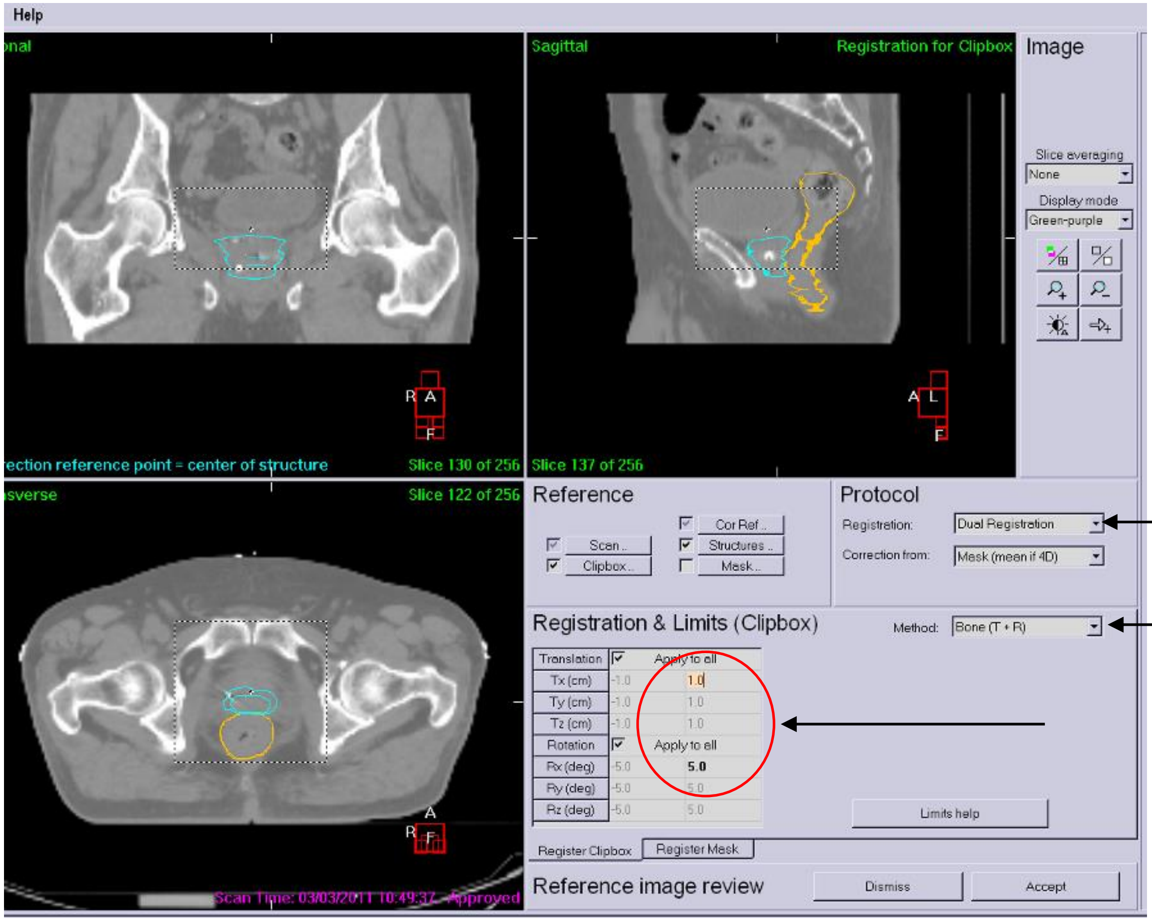
Large Pelvis 125kV 1314 mAs

True beam, 125kV 680 mAs

3D prostate registration- 1. Patient position



3D prostate registration- 1. Patient position

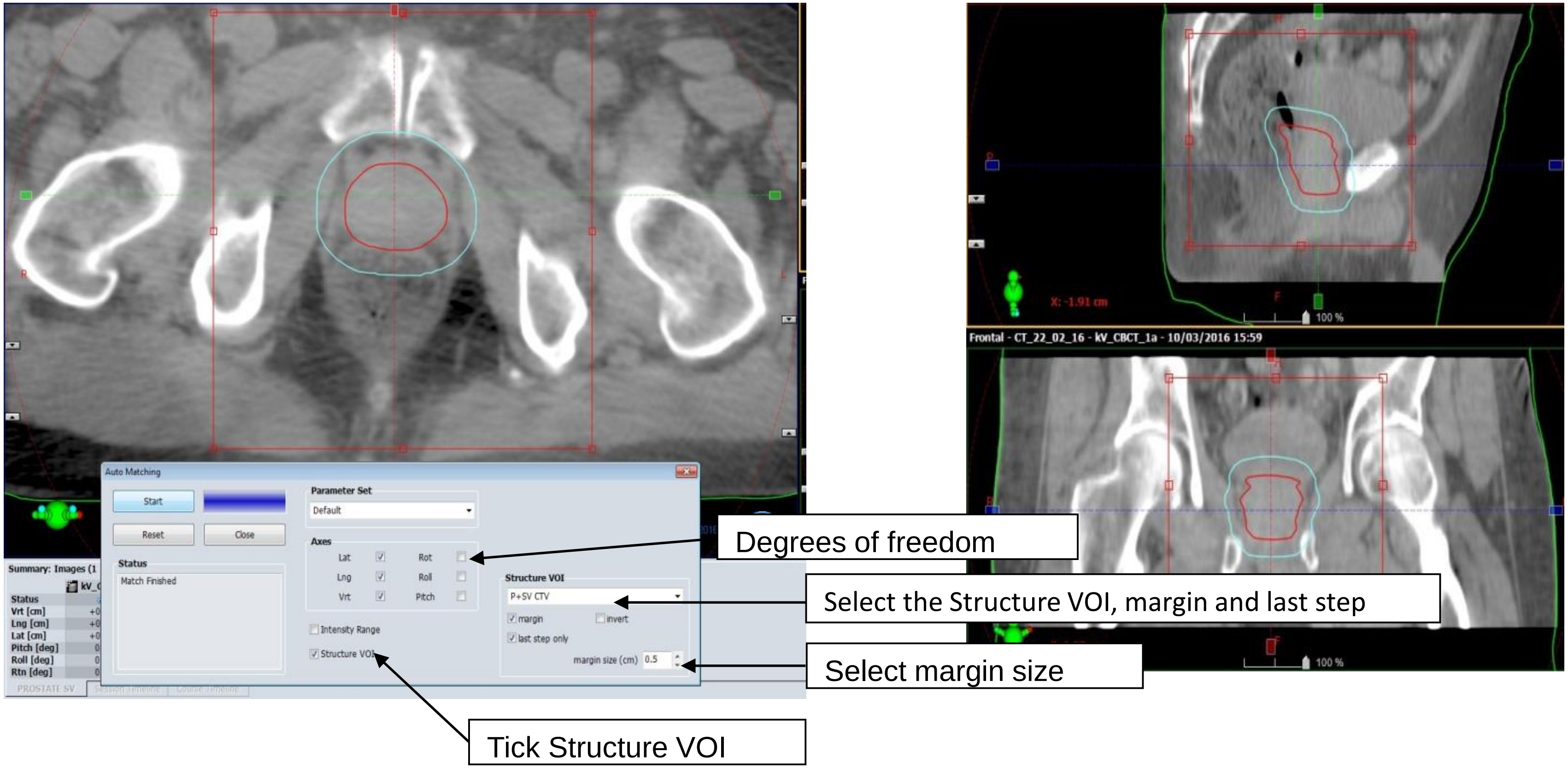


Dual registration

Bony anatomy

Limits set

3D prostate registration- 2. Prostate position



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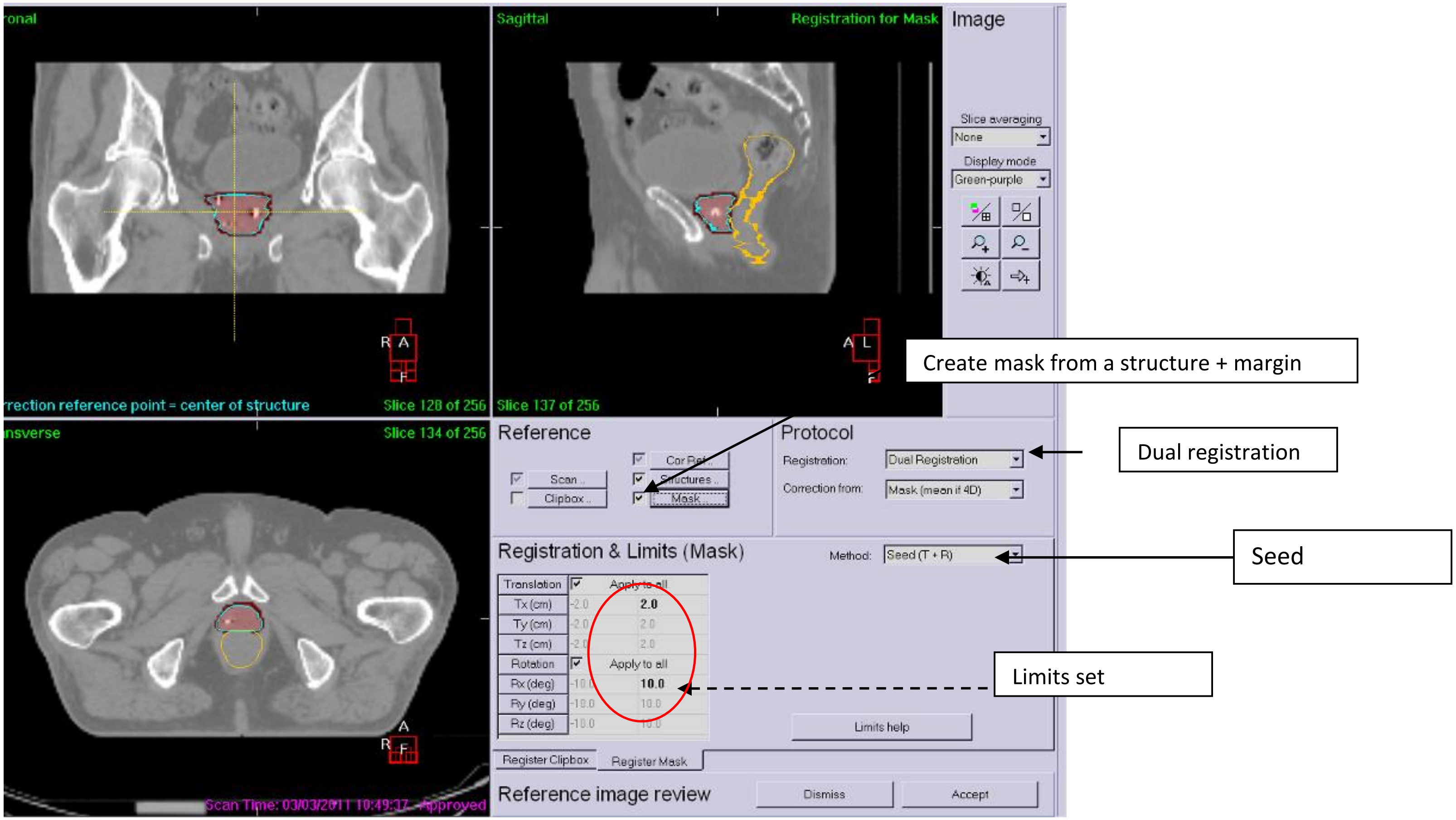
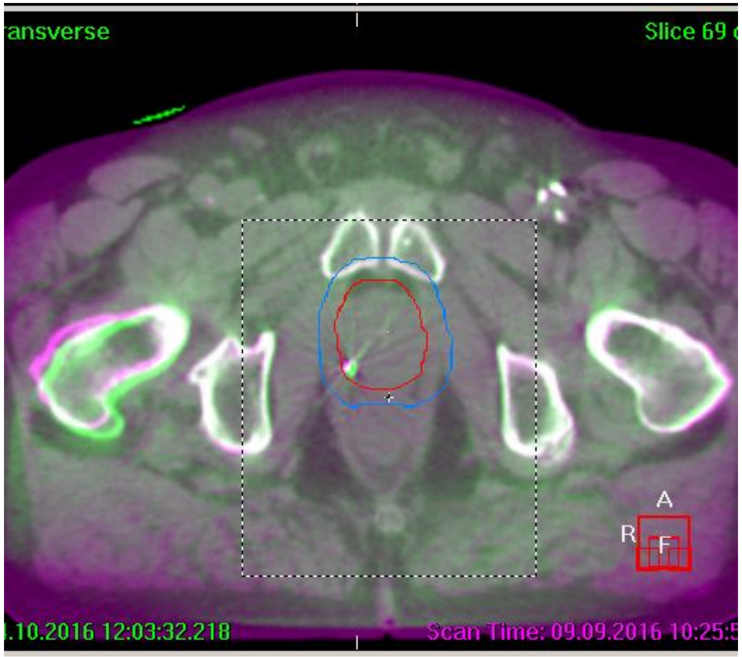
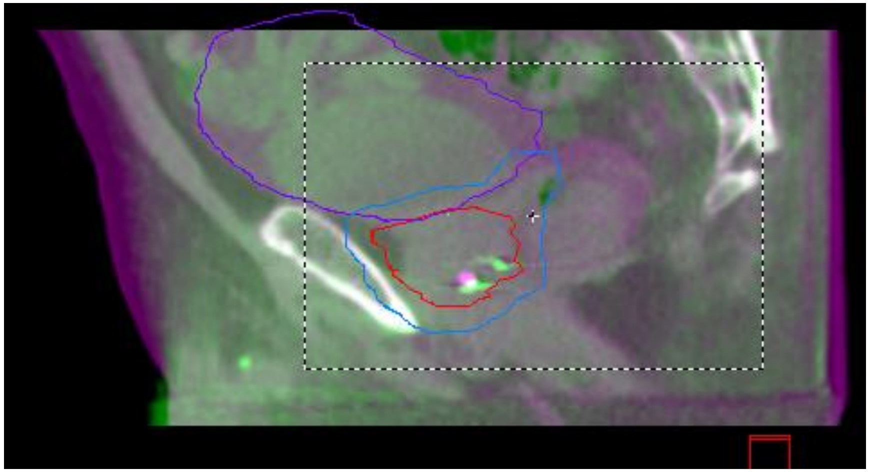
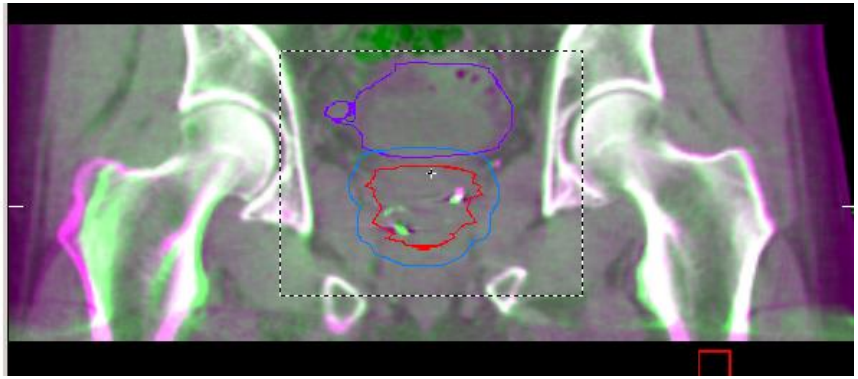
3D prostate registration- 2. Prostate position



3D prostate registration- 1.patient position







Bone registration

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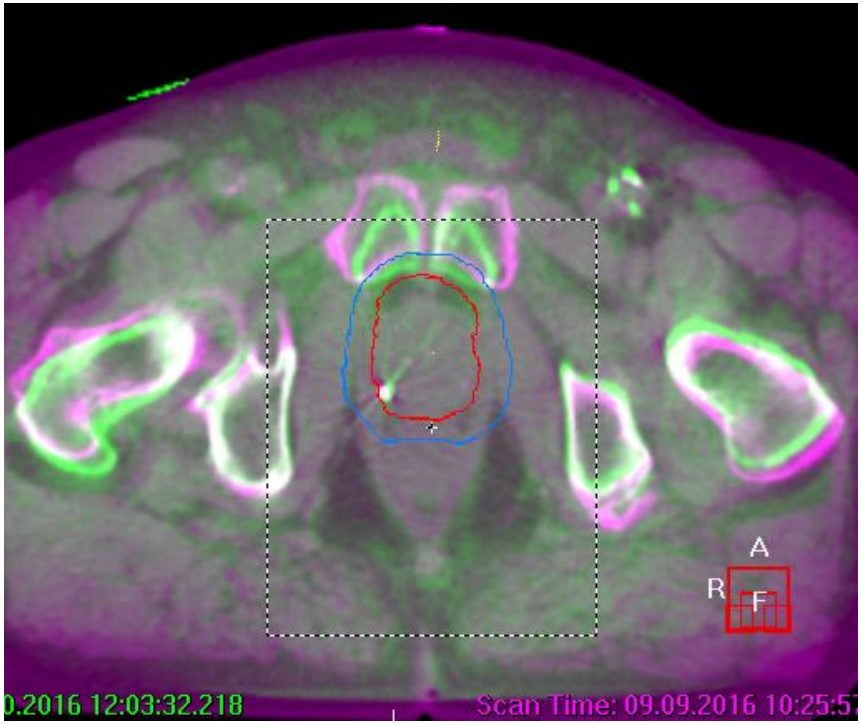
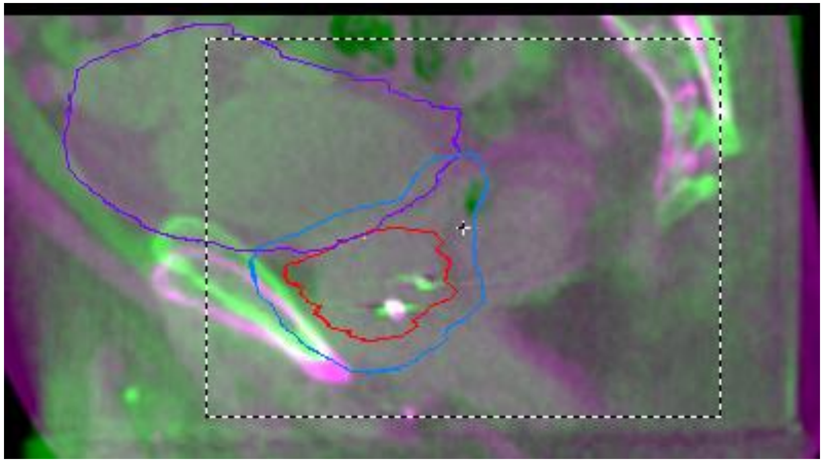
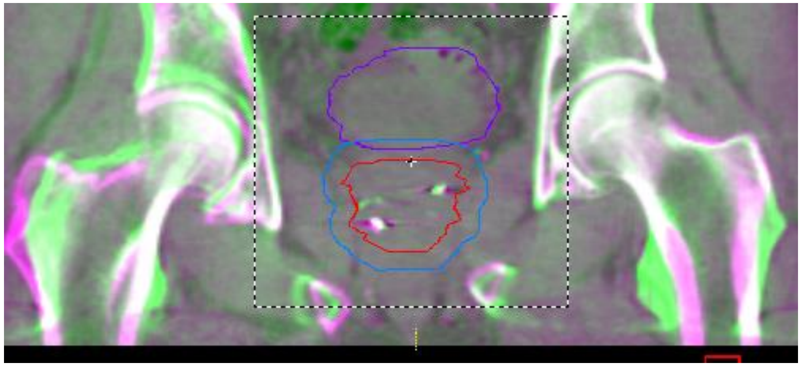
3D prostate registration- 2.prostate position

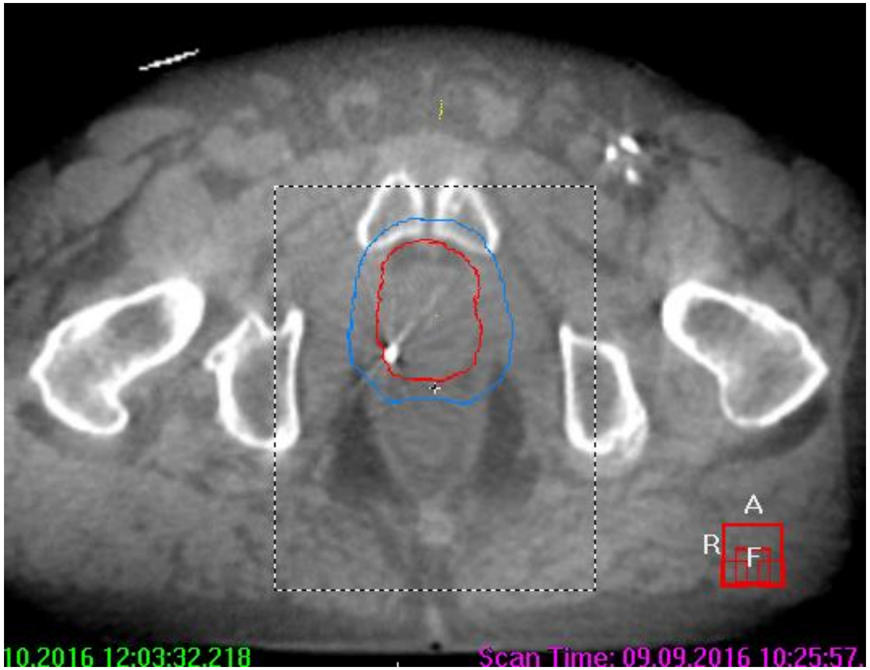


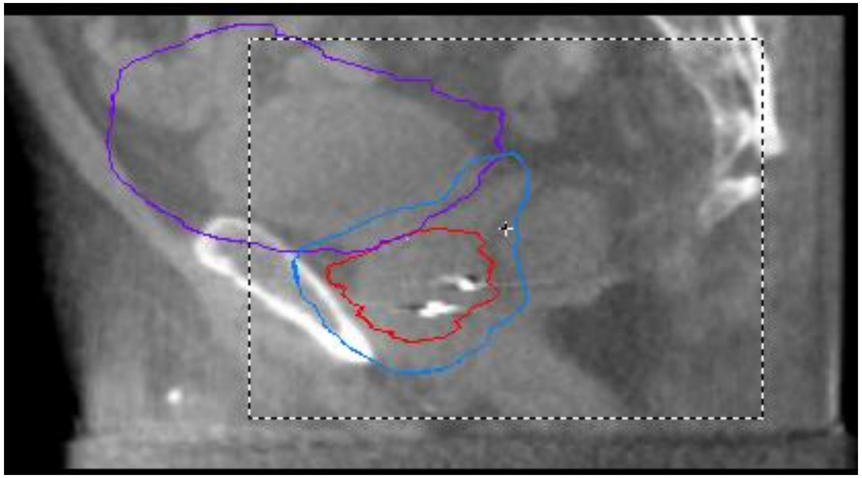


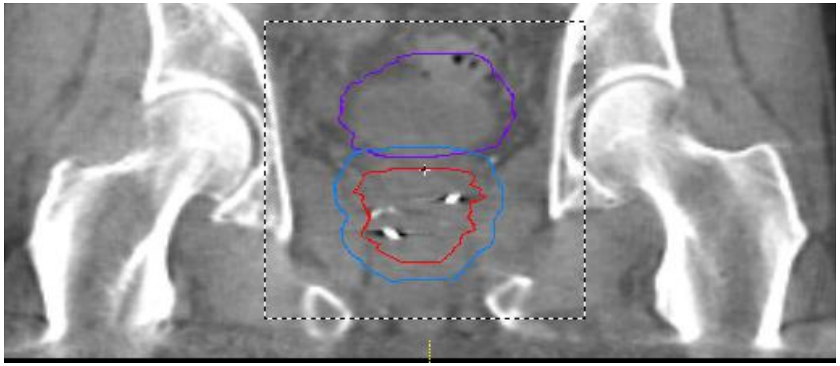


Prostate registration-6 degrees of freedom

3D prostate registration- 2.prostate position

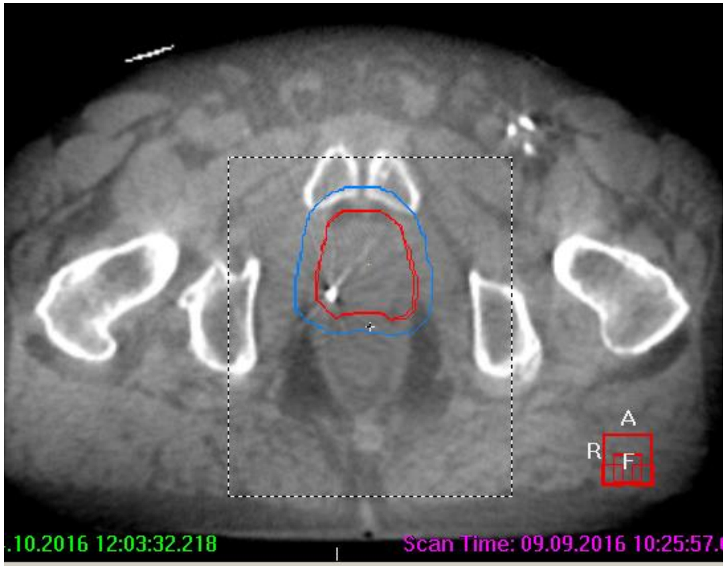


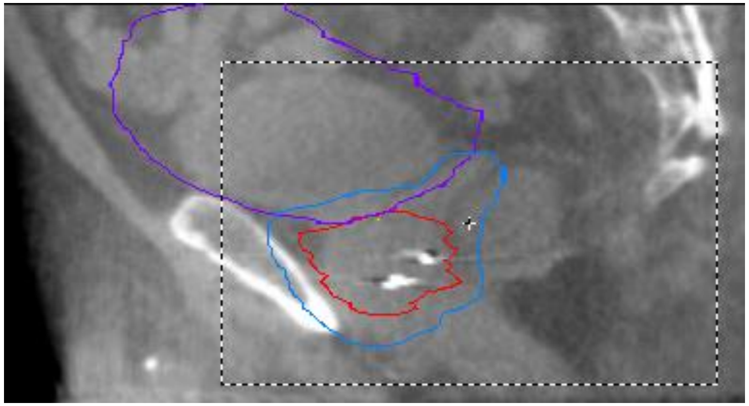


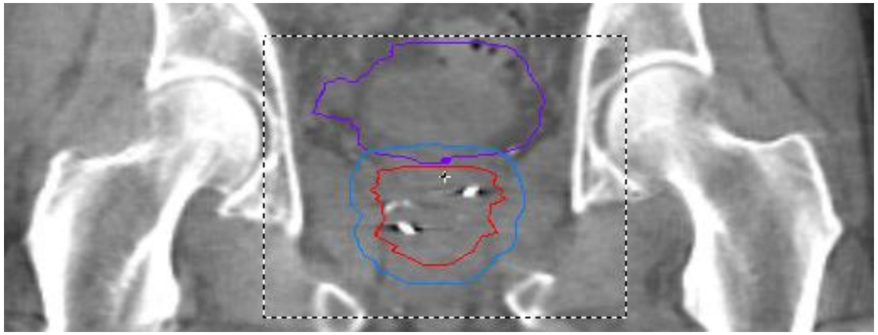


Prostate registration-6 degrees of freedom

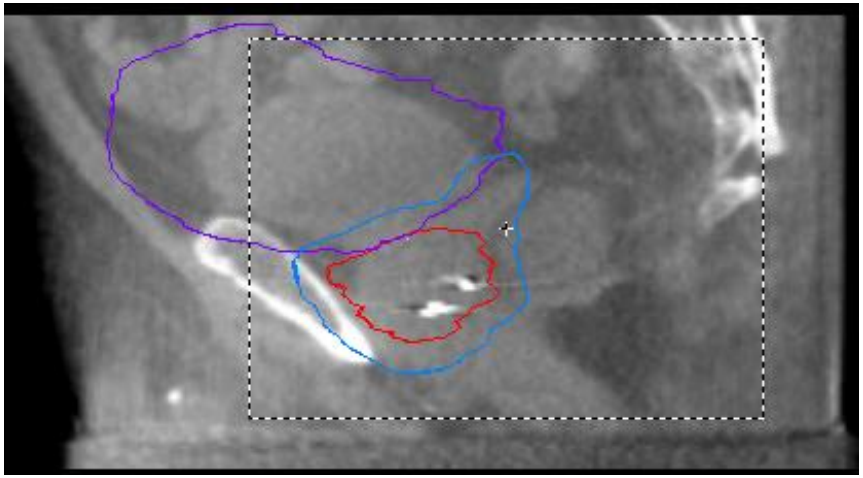
3D prostate registration- 2.prostate position



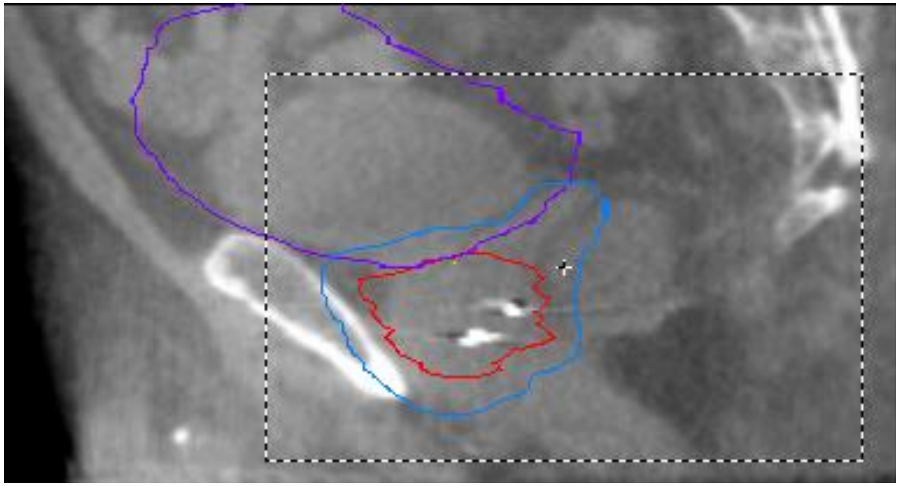




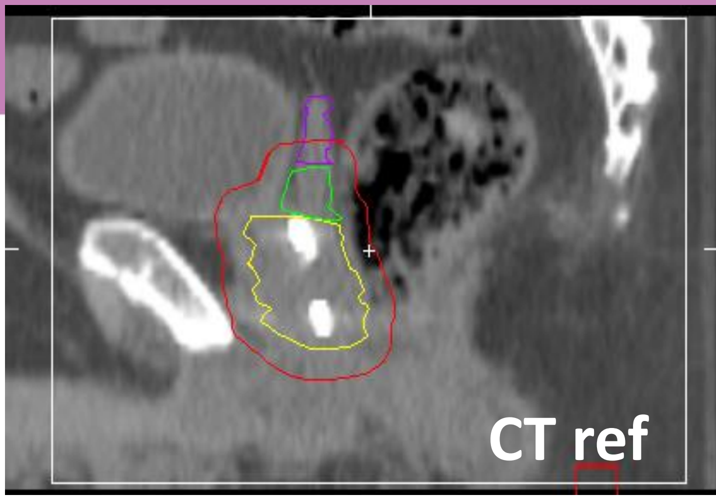
Prostate registration-3 degrees of freedom

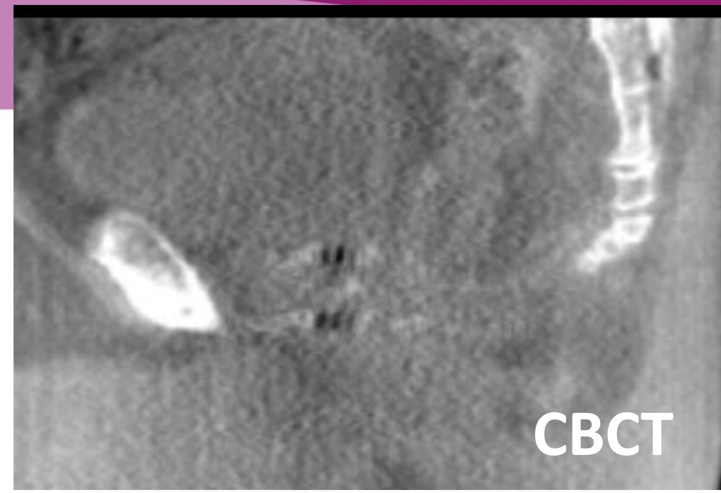


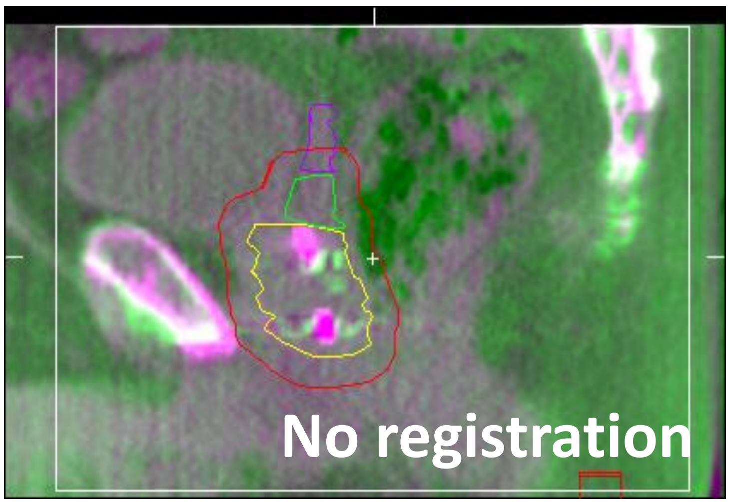
6 degrees



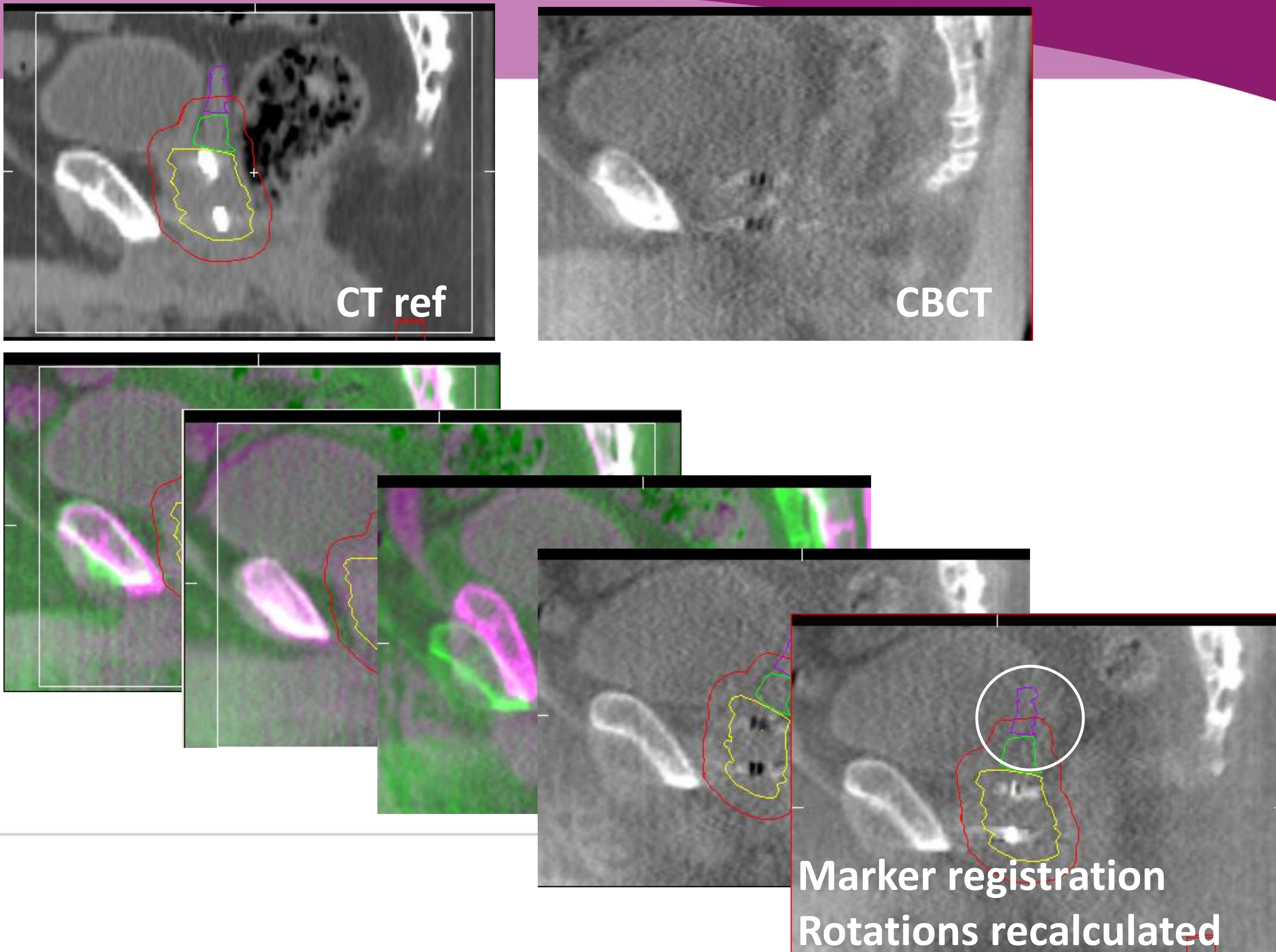
3 degrees

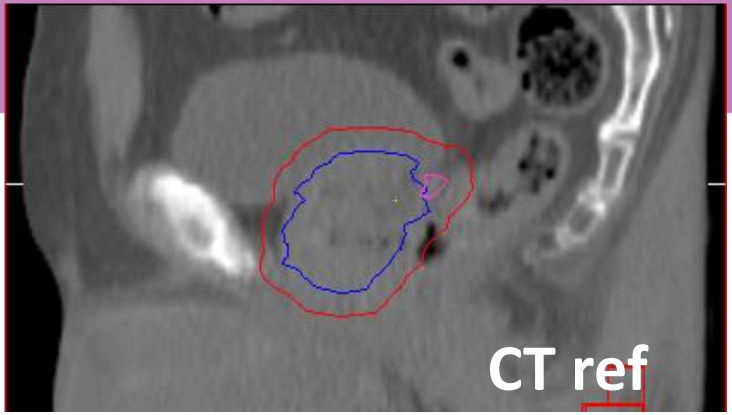


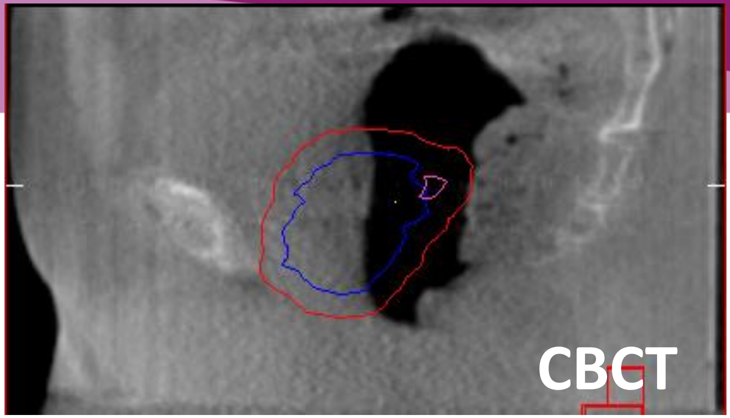


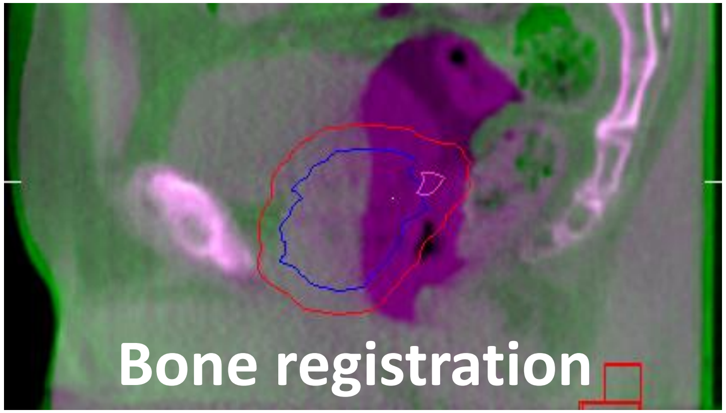


Full rectum on CT planning scan (CT ref)

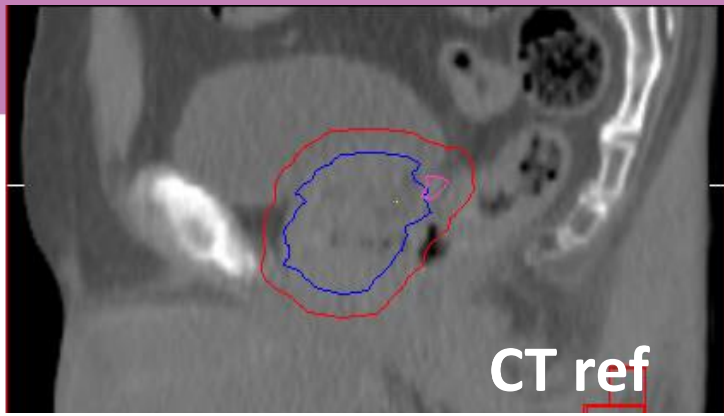

CT ref
CBCT
Marker registration
Rotations recalculated

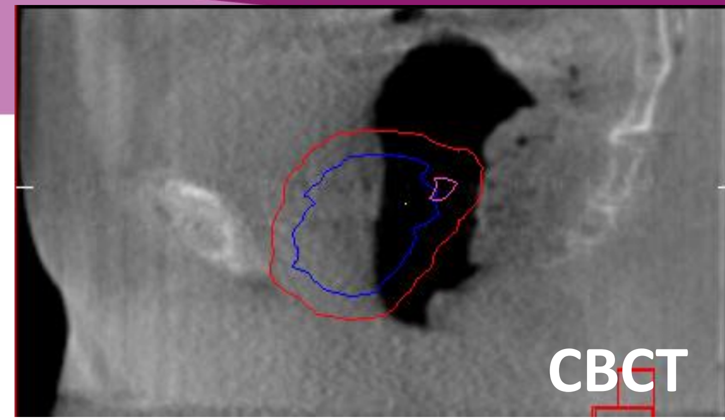


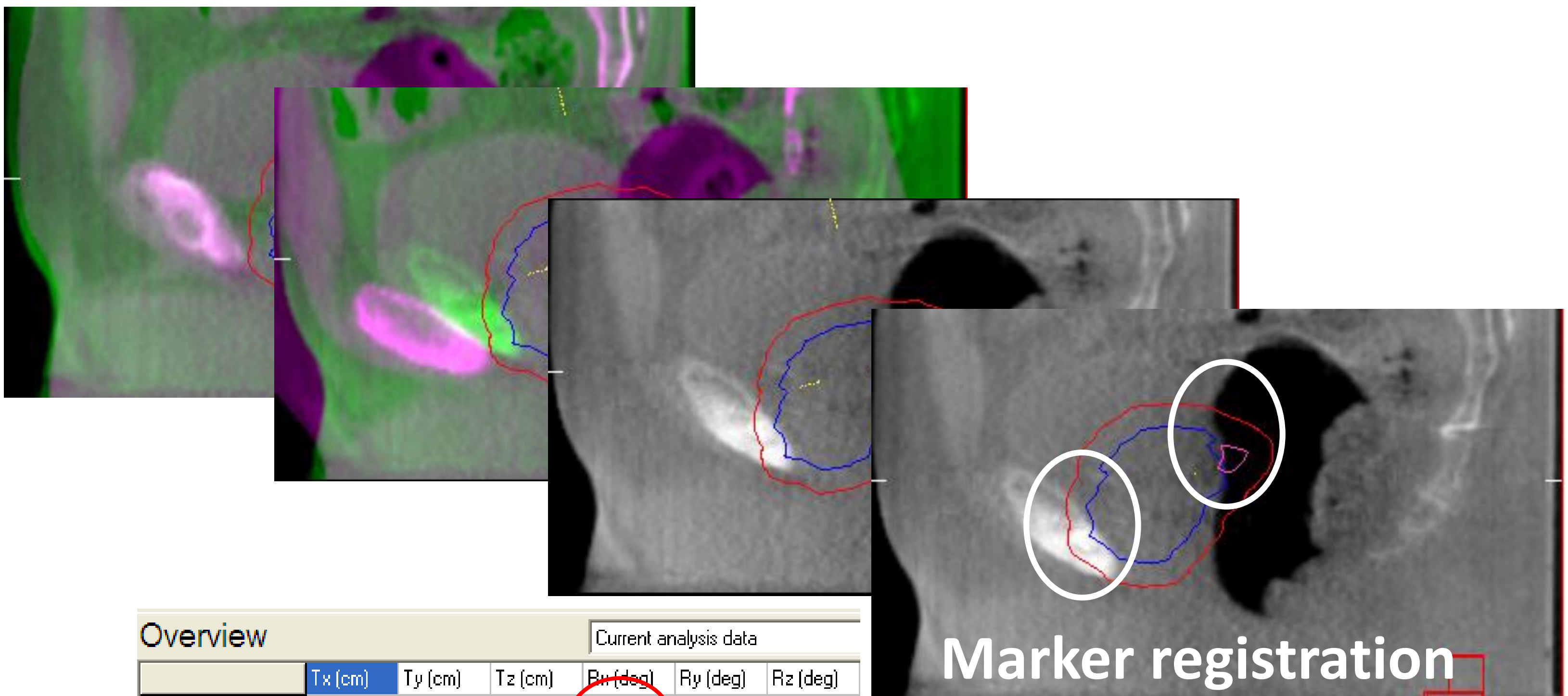




Empty rectum on CT planning scan (CT ref)







Marker registration rotations recalculated

Overview

Current analysis data

	Tx (cm)	Ty (cm)	Tz (cm)	Rx (deg)	Ry (deg)	Rz (deg)
Clipbox	0.34	0.30	-0.03	1.2	0.0	0.1
Mask	0.36	1.00	1.67	345.2	9.3	1.2
Correctable	0.34	1.03	1.67	0.0	0.0	0.0

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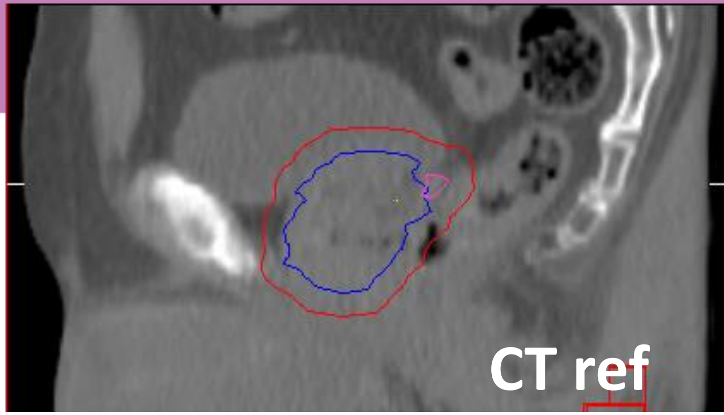

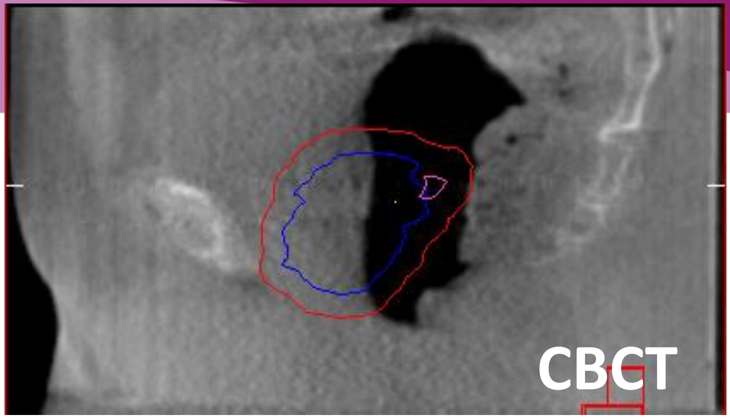

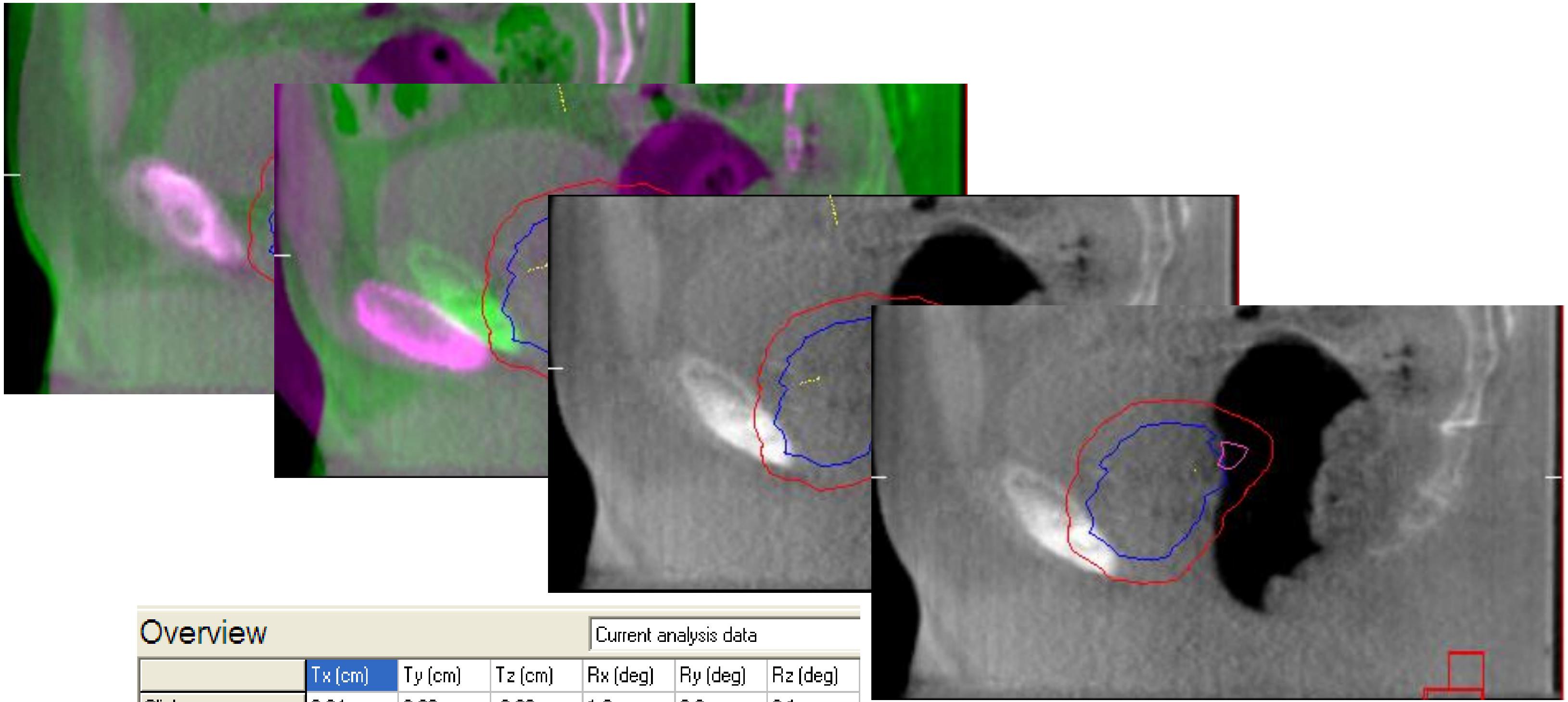

Overview

Current analysis data

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Mask	0.36	1.00	1.67	345.2	9.3	1.2
Correctable	0.34	1.03	1.67	0.0	0.0	0.0

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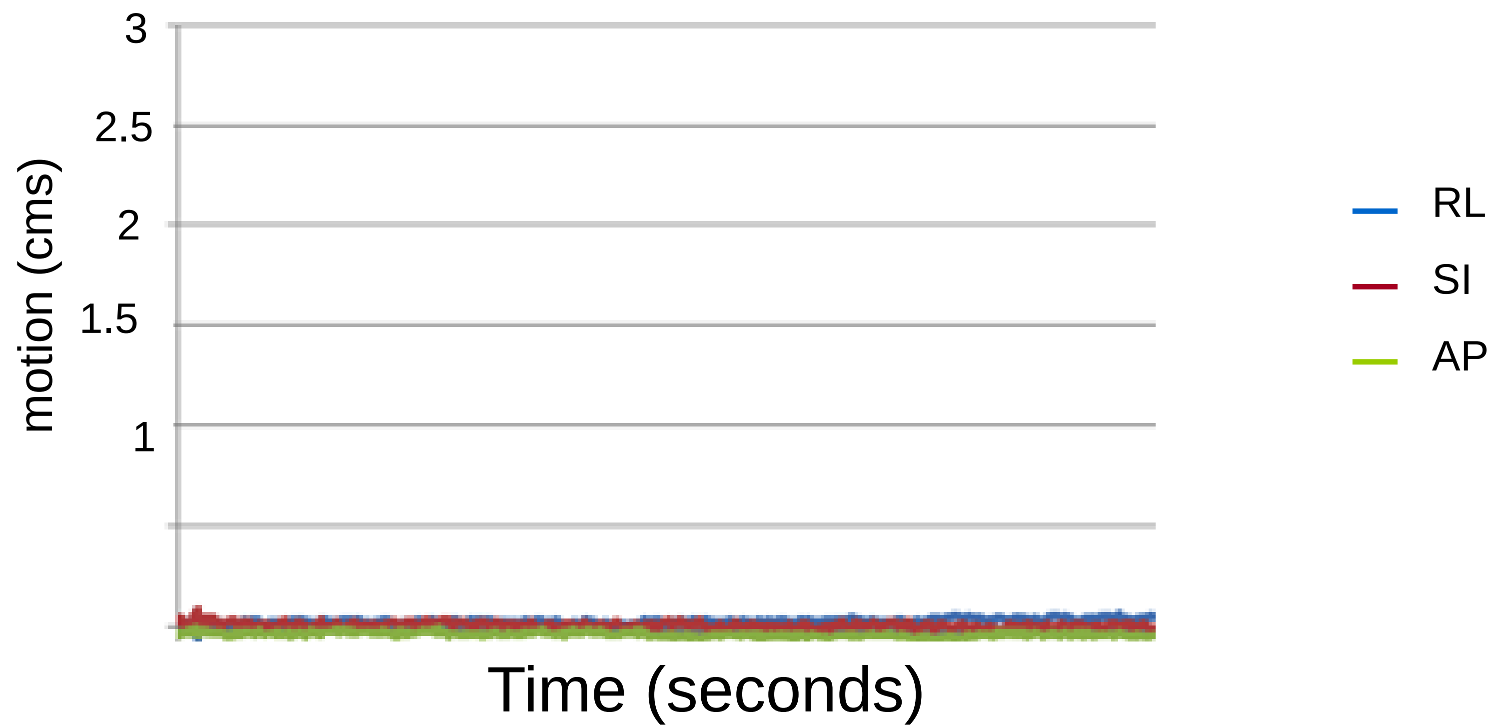
Pelvic floor muscle activation

"Ask patient to cough or to lift and squeeze inside as if they are trying to hold back urine"



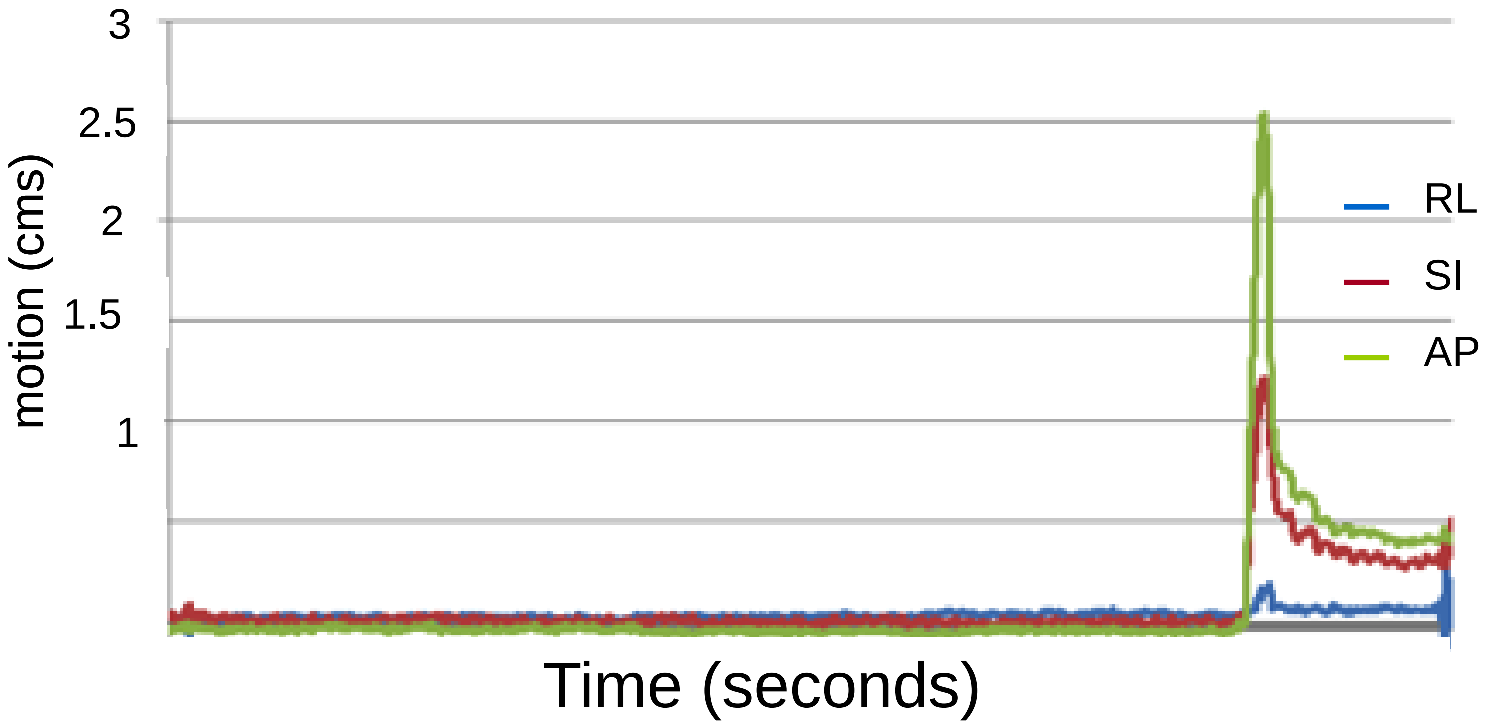
Calypso trace

Courtesy of Julia Murray , RMH & ICR

ESTRO School

Pelvic floor muscle activation

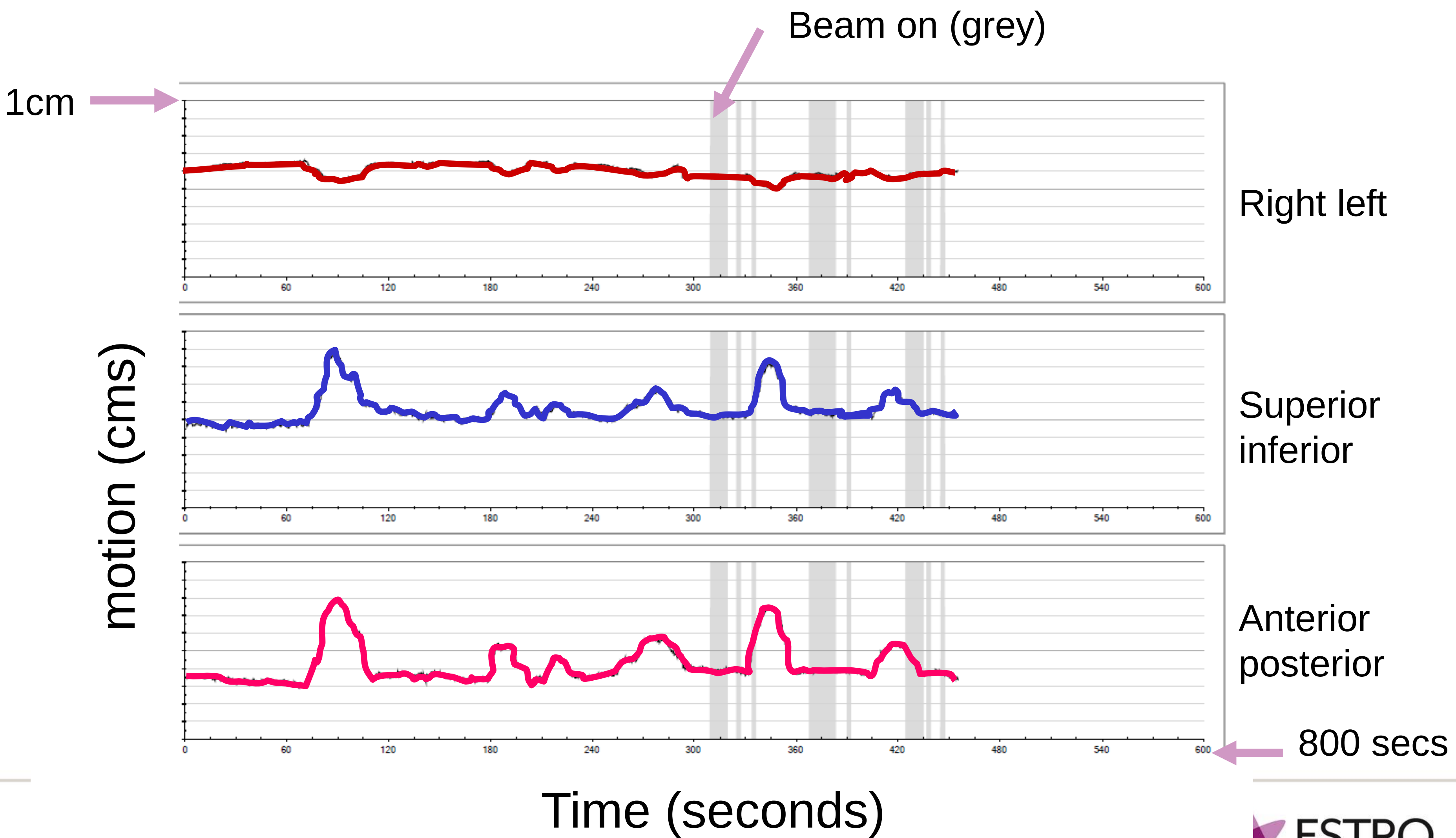
"Ask patient to cough or to lift and squeeze inside as if they are trying to hold back urine"



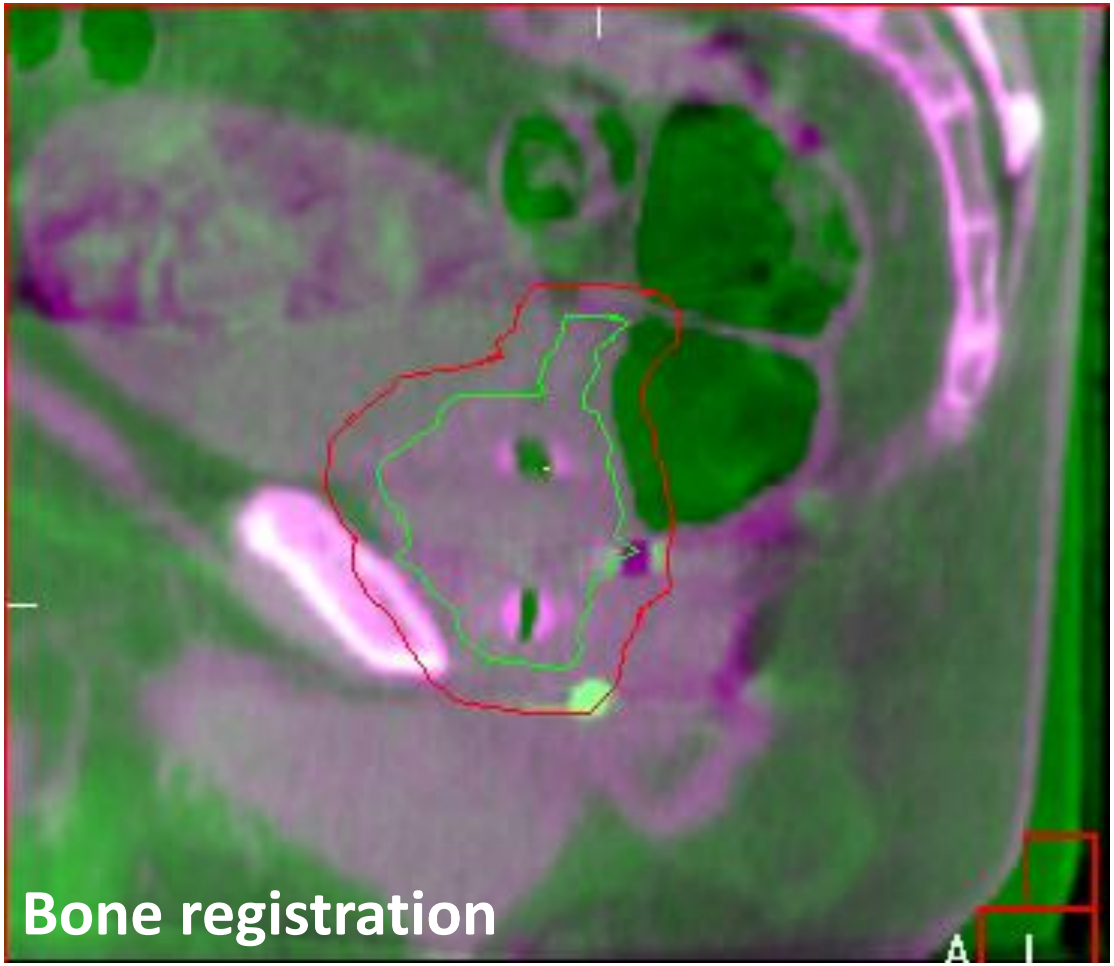
Calypso trace

Courtesy of Julia Murray , RMH & ICR

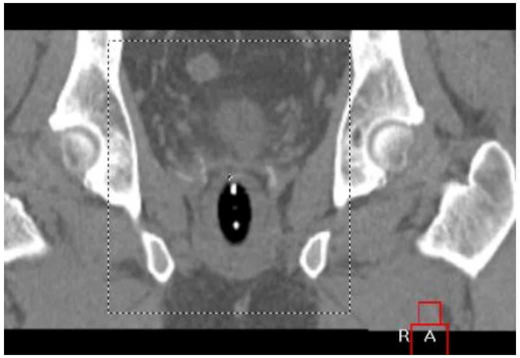
Pelvic floor muscle activation

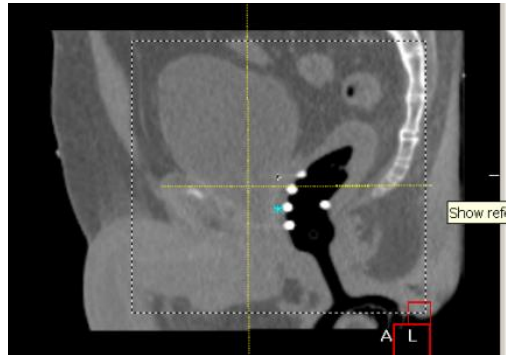


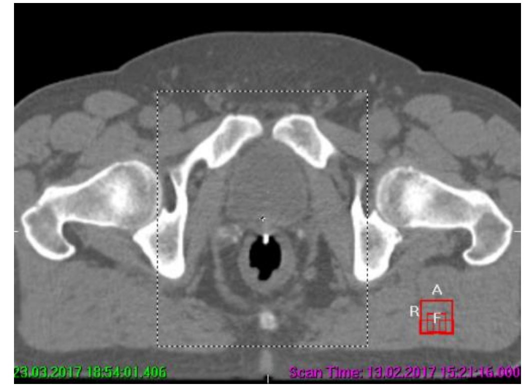
Muscular tension

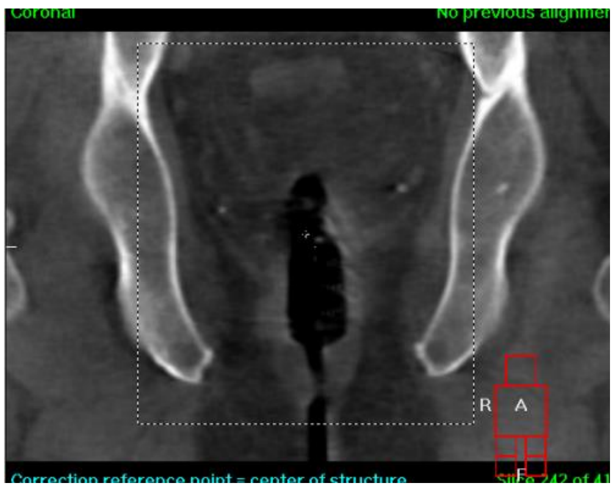


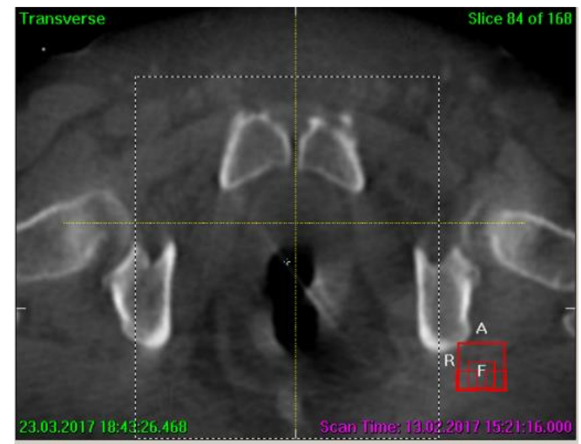
Muscle clenching











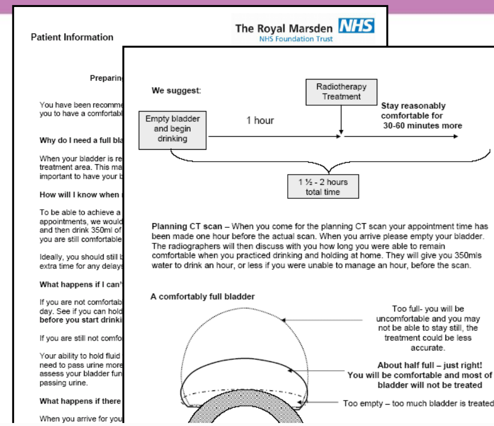
Full bladder

Bladder filling

Empty bladder

Empty

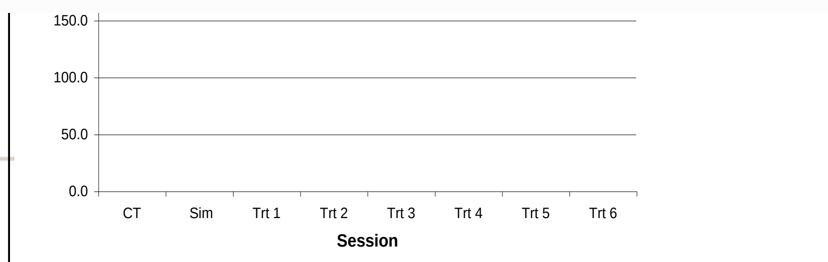
Drink 350 mls



Mike Ayliffe Bladder Filling for Marsden

Date	Location	Drain & Fill Time	Intake volume	Hold time	Delivery Volume	2nd delivery hold time & volume	3rd delivery hold time & volume
12/11/2003	RMH	9.50 am	350mls	1hr 20	"Busting"		
14/11/2003	Home	5.30 pm	350mls	2hr 10	200 mls		
15/11/2003	Home	4.30 pm	350mls	2hr 33	210mls		
16/11/2003	Home	5.15 pm	350mls	1hr 50	250mls		
17/11/2003	Home (breakfast)	7.00 am	900mls !				
"	Home	8.10 am	350mls	0hr 49	260mls		
"	Home (lunch)	1.40 pm	500mls !				
"	Home	3.15 pm	350mls	0hr 28	250mls	0hr 59 & 250mls	1hr 17 & 150mls
19/11/2003	Home (breakfast)	7.00 am	900mls				
"	Home	9.15 am	350mls	0hr 54	210mls	1hr 25	2hrs & 200mls

Also use rectal preparation



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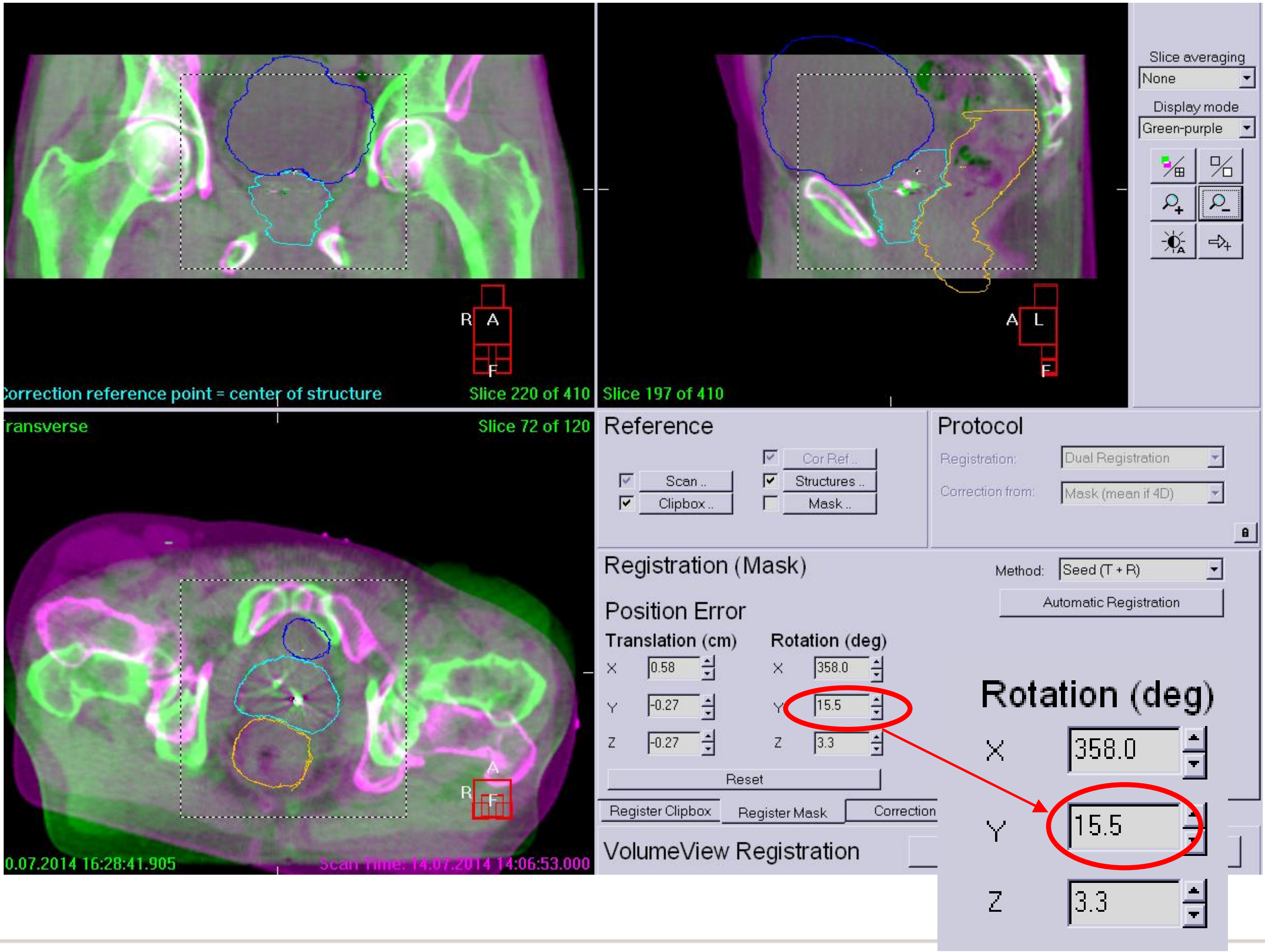
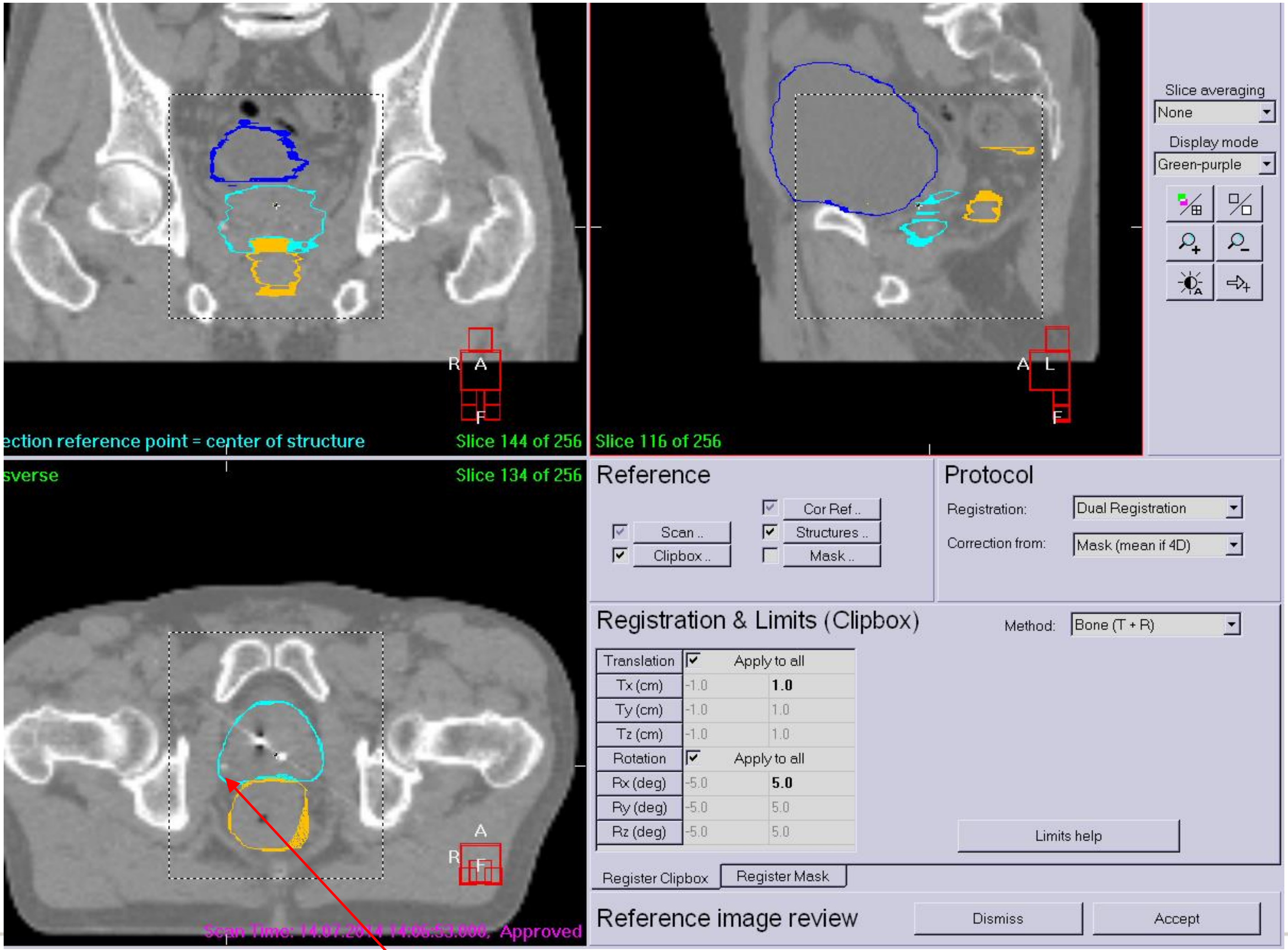
Rotations – check why?



ESTRO School

Rotations – check why?



Calcification in the reference image

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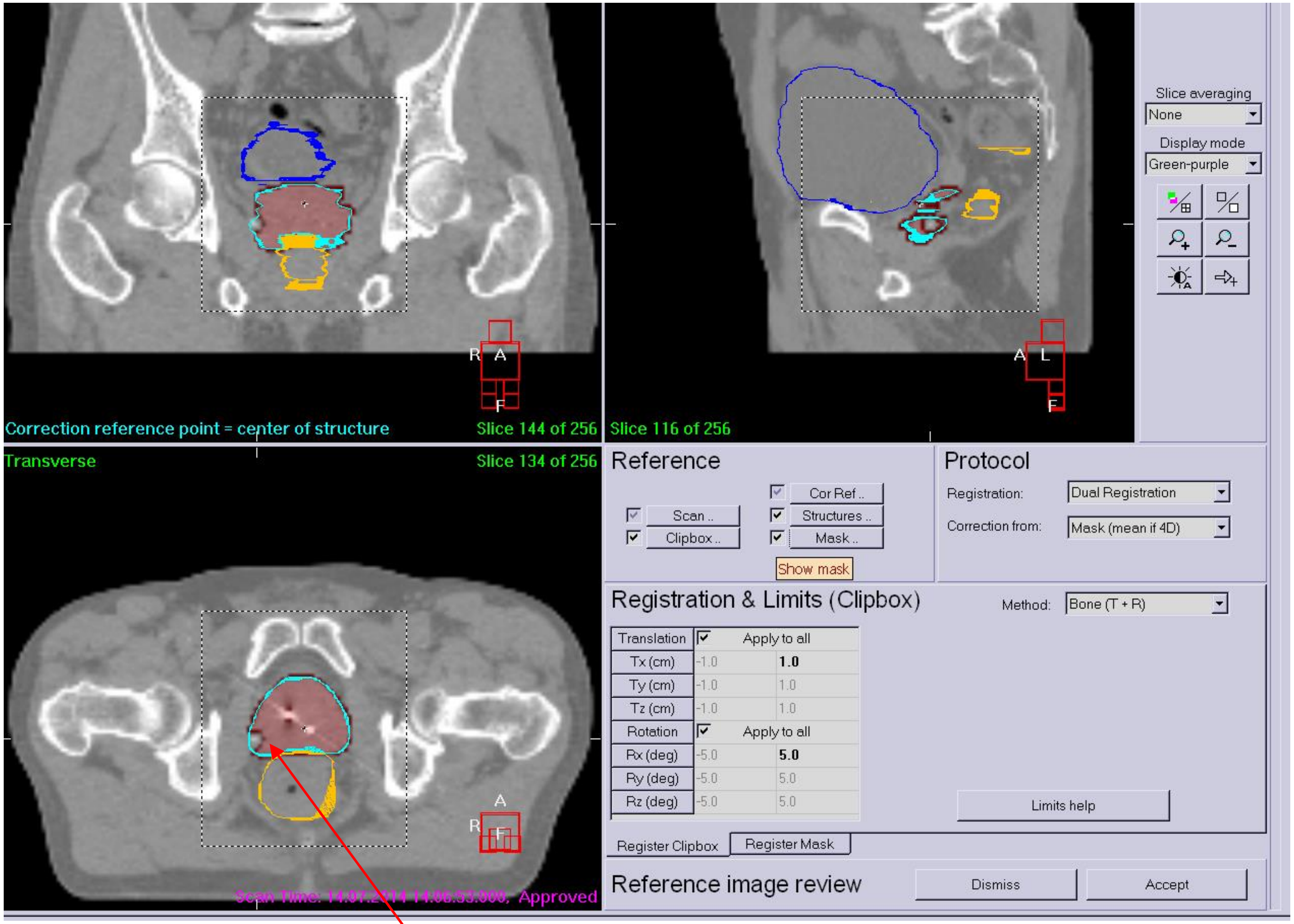
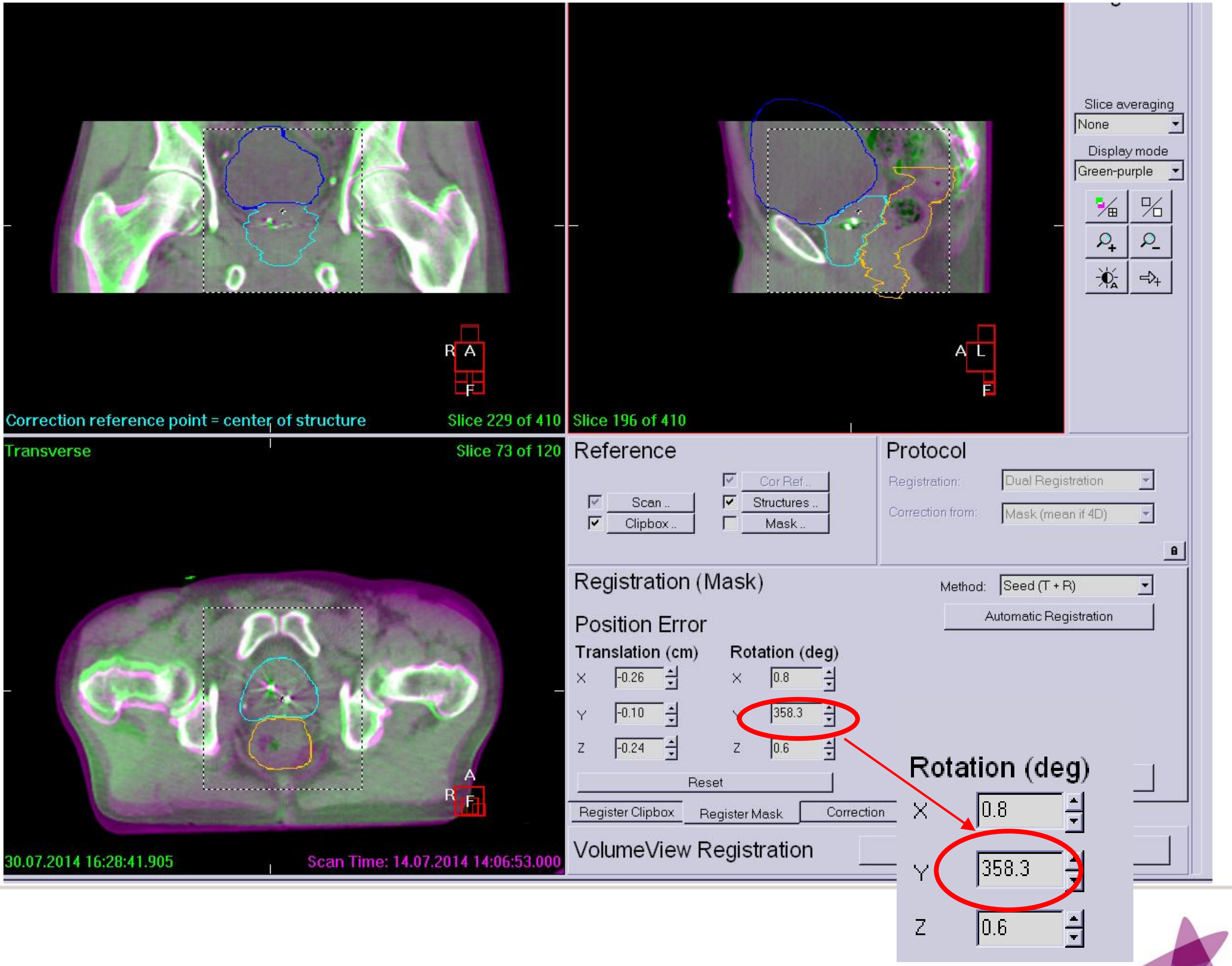
Rotations – check why?

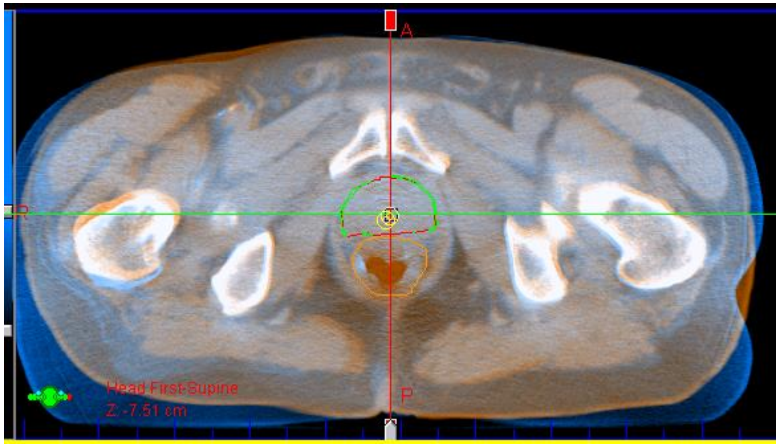


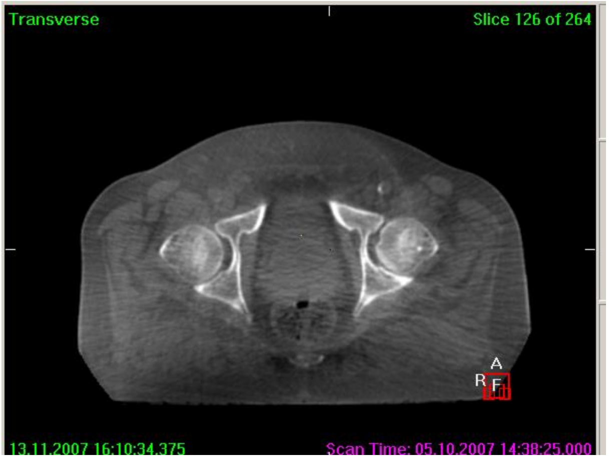
Erased

Rotations – check why?



Comparison of systems

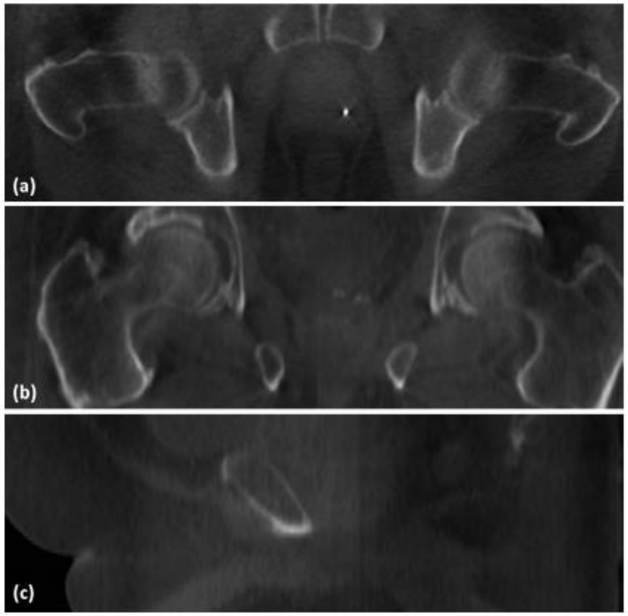




Modality	MV	CBCT Fiducial markers	CBCT Soft tissue
Largest source of uncertainty	Marker localisation	Intrafraction motion	Inter observer variability

Moseley 2007 IJROBP

Comparison of systems



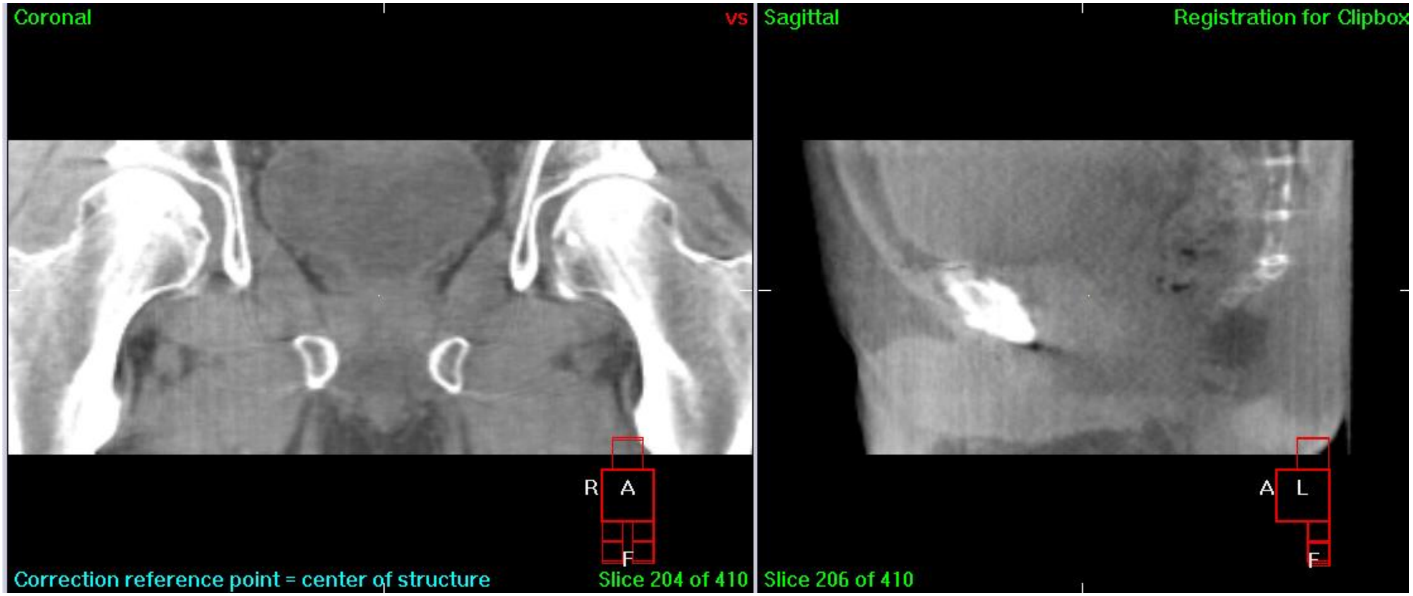
Seeds
0.9 × 3.0 mm, CIVCO

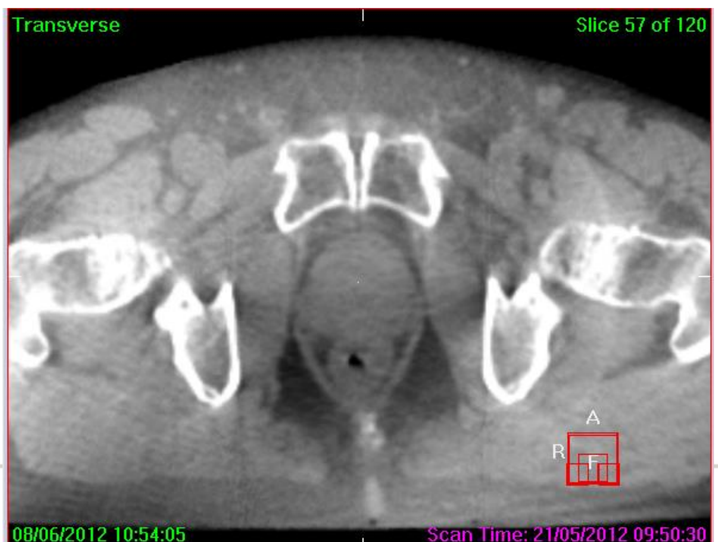
OBI
half fan
half bow-tie filter
360 degree gantry rotation
Reconstruction:512 × 512 resolution; 2mm slice thickness

95% Limits of agreement 3 observers	Right left (mm)	Superior Inferior (mm)	Anterior Posterior (mm)
CBCT fiducial markers	<2mm	<2mm	<2mm
CBCT soft tissue	<3mm	<3mm	<3mm
Average CBCT Fiducial markers compared CBCT Soft tissue	-1.6 to 2.5	-4.9 to 2.6	-4.7 to 1.9

Deegan 2014, Journal of Medical Imaging and Radiation Oncology

Soft tissue matching – no markers





Inter observer errors – evaluate

(CT definition = 5-6mm)*

Gain organ motion information

* Roach M, 1996; Kagawa K, 1997

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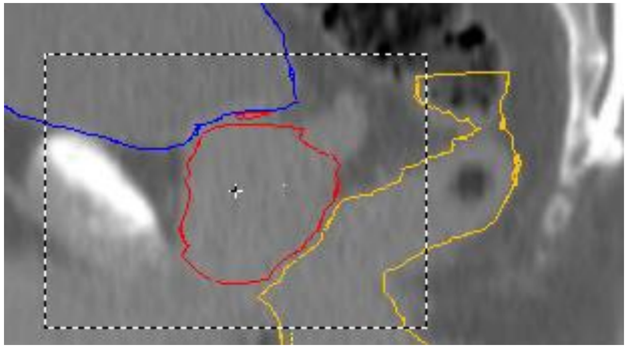
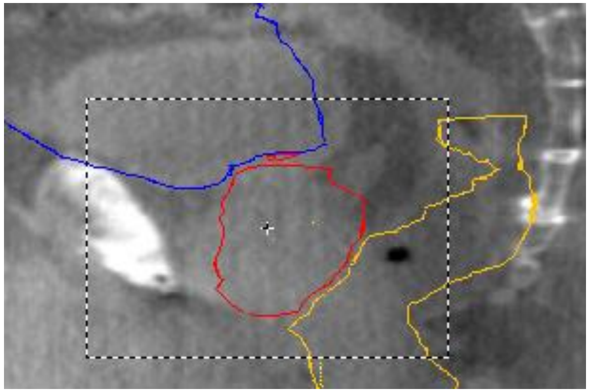
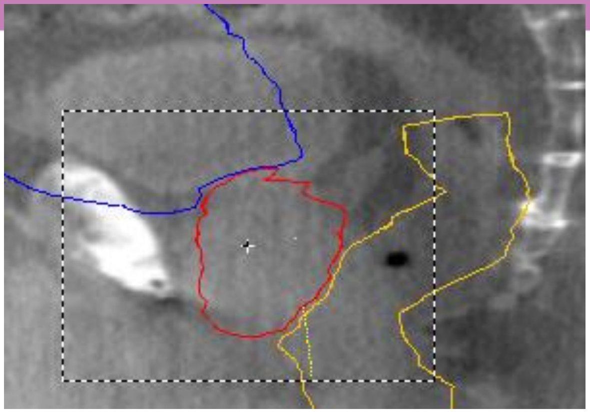
Difference between observers



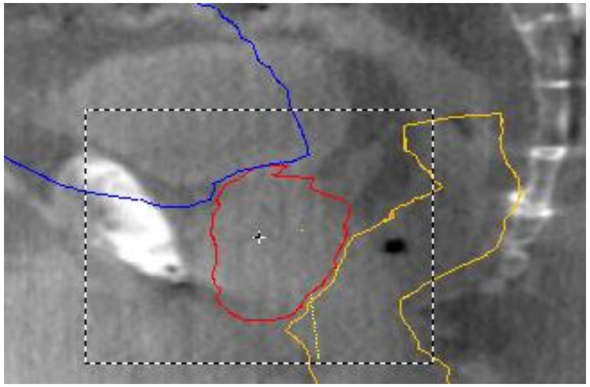
Reference



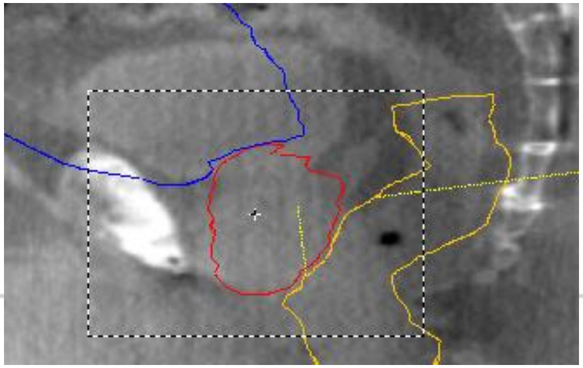
Automatic
SI= -0.43
AP=-0.78



OBS1
SI= -0.88
AP=-0.80



OBS2
SI= -0.98
AP= -0.89



OBS3
SI= -0.48
AP=-0.80

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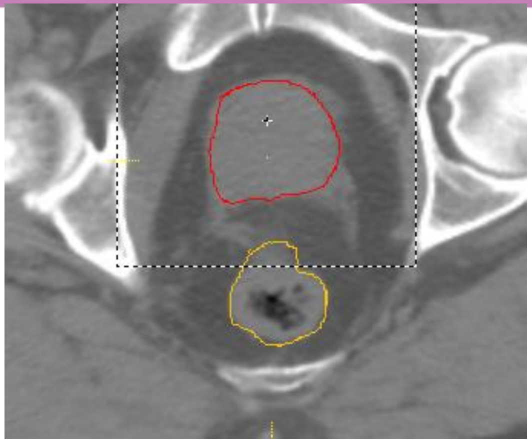
Difference between observers



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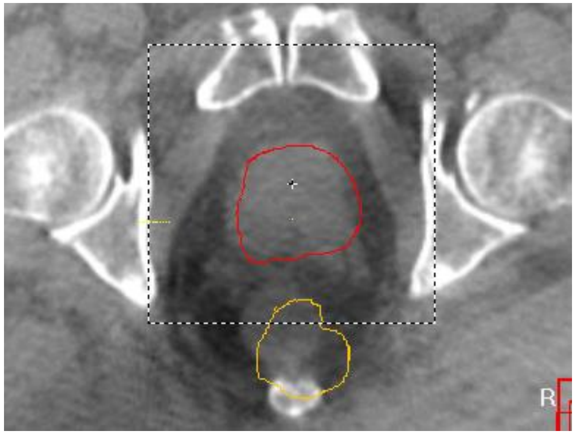

Automatic
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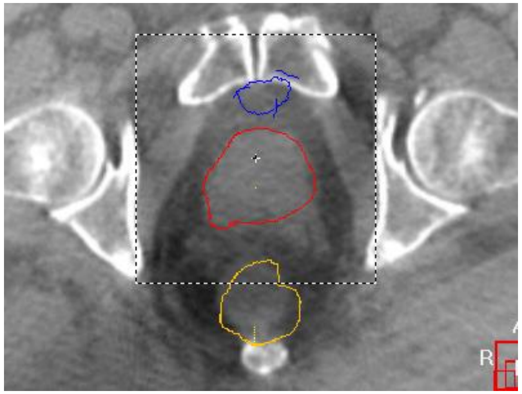
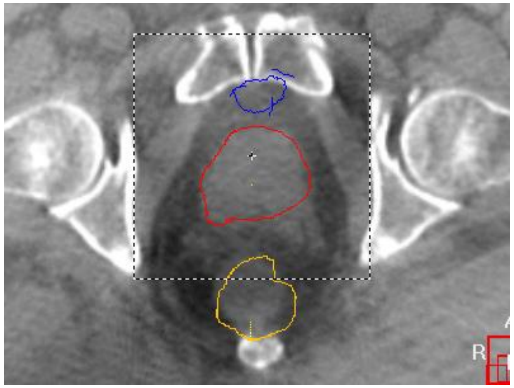
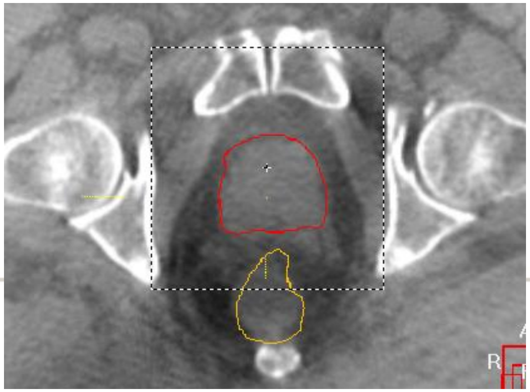
AP=-0.78



OBS1
RL=-0.54
AP=-0.80

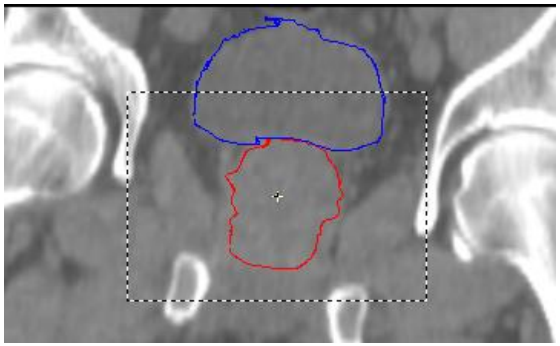


OBS2
RL=- 0.54
AP=-0.89

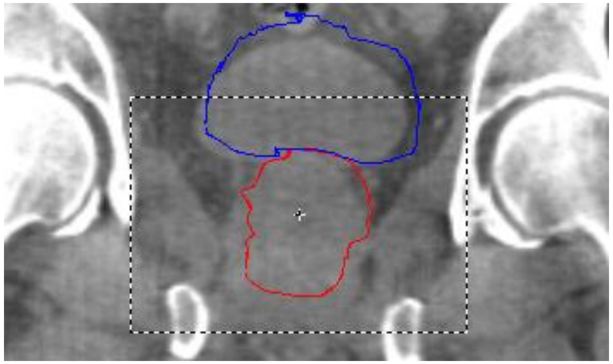


OBS3
RL=-0.64
AP=-0.80

Difference between observers



Reference



Automatic
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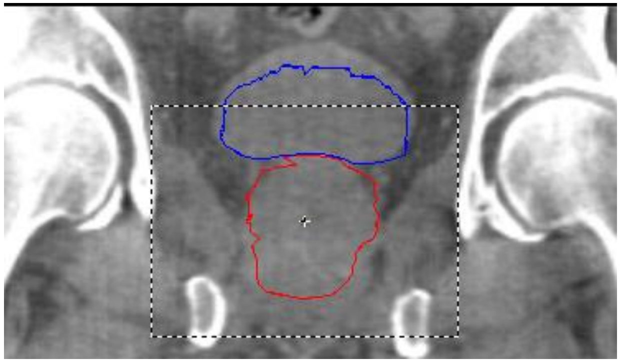
SI= -0.43



OBS1
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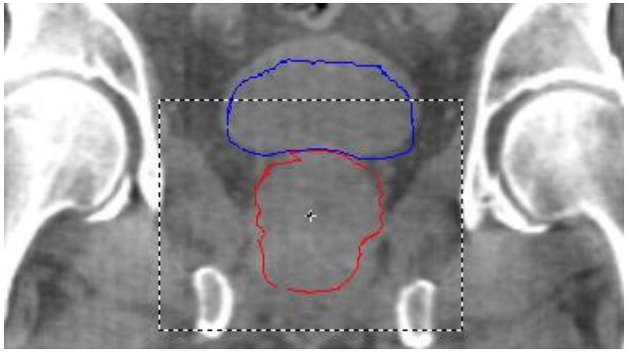
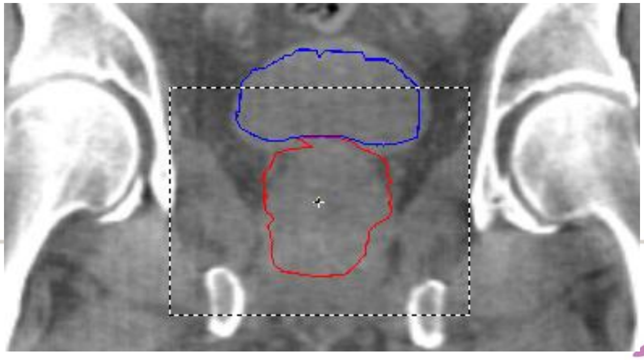
SI= -0.88



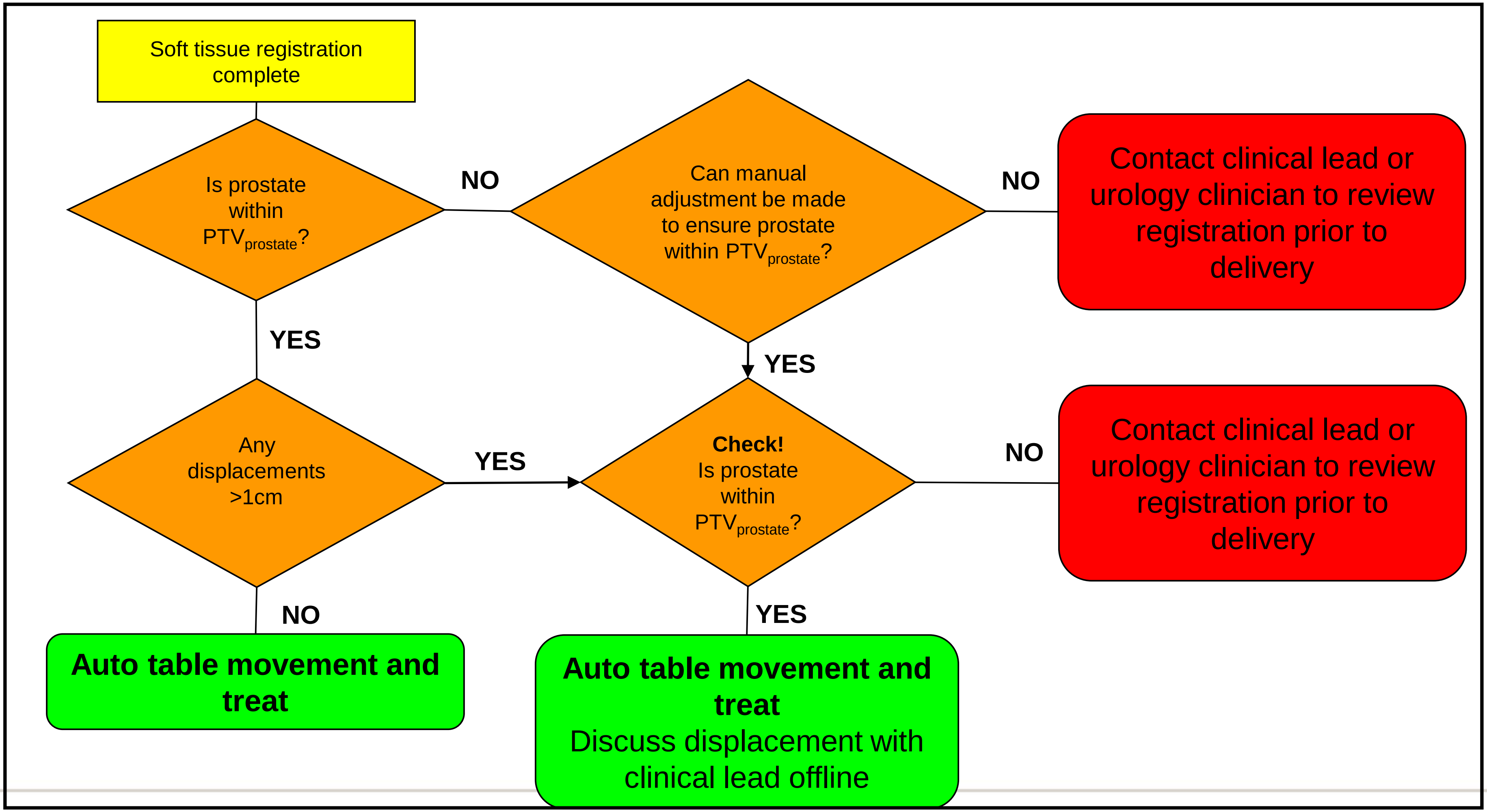
OBS2
RL = -0.54
SI= -0.98



OBS3
RL= -0.64
SI = -0.48

Online decision making soft tissue matching
Prostate +/- Seminal Vesicles only

NB All operators must have completed competency assessment (S-WB-019) to carry out prostate soft tissue matching. It may be necessary for the clinical lead or urology clinician to review imaging offline.



Courtesy of Steven Landeg, RMH

Offline decision making soft tissue matching Prostate +/- Seminal Vesicles only

NB All operators must have completed competency assessment (S-WB-019) to carry out prostate soft tissue matching. It may be necessary for clinical lead or urology clinician to review imaging offline.

Review rectum and bladder status

Is rectum ≥50% different from planning scan? (see example Figure 1)

- **YES** → Discuss with patient and check correct used of rectal preparation (as per J-CH-059). Record rectal status on S-RT-083-02.
- **NO** → Record ‘**Rectal status ‘good**’ on log S-RT-083-02

Is bladder under-filled?

- **YES** → Encourage hydration and record **‘under-filled bladder’** on XVI log S-RT-083-02.
- **NO** → Record ‘**Bladder status good**’ on XVI log S-RT-083-02

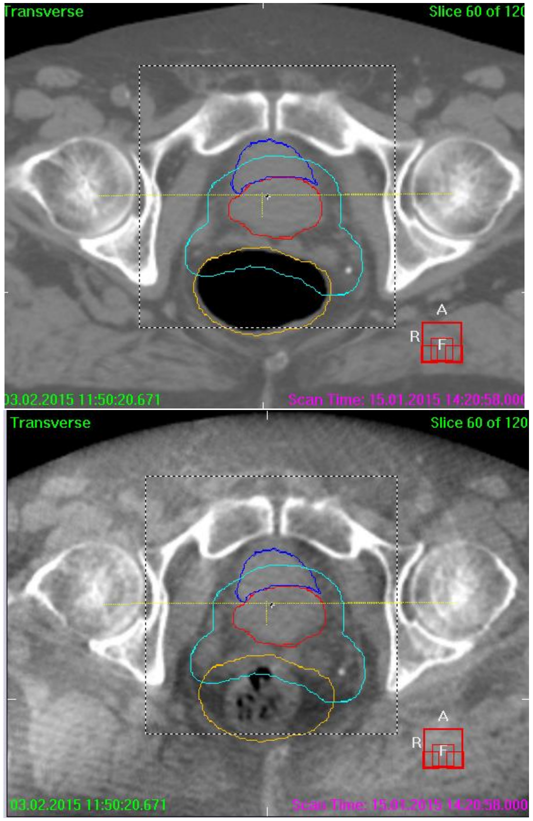


Figure 1: Planning scan (top) showing large gas filled rectum. CBCT (bottom) showing smaller, stool filled rectum on treatment (~50% smaller).

Courtesy of Steven Landeg, RMH

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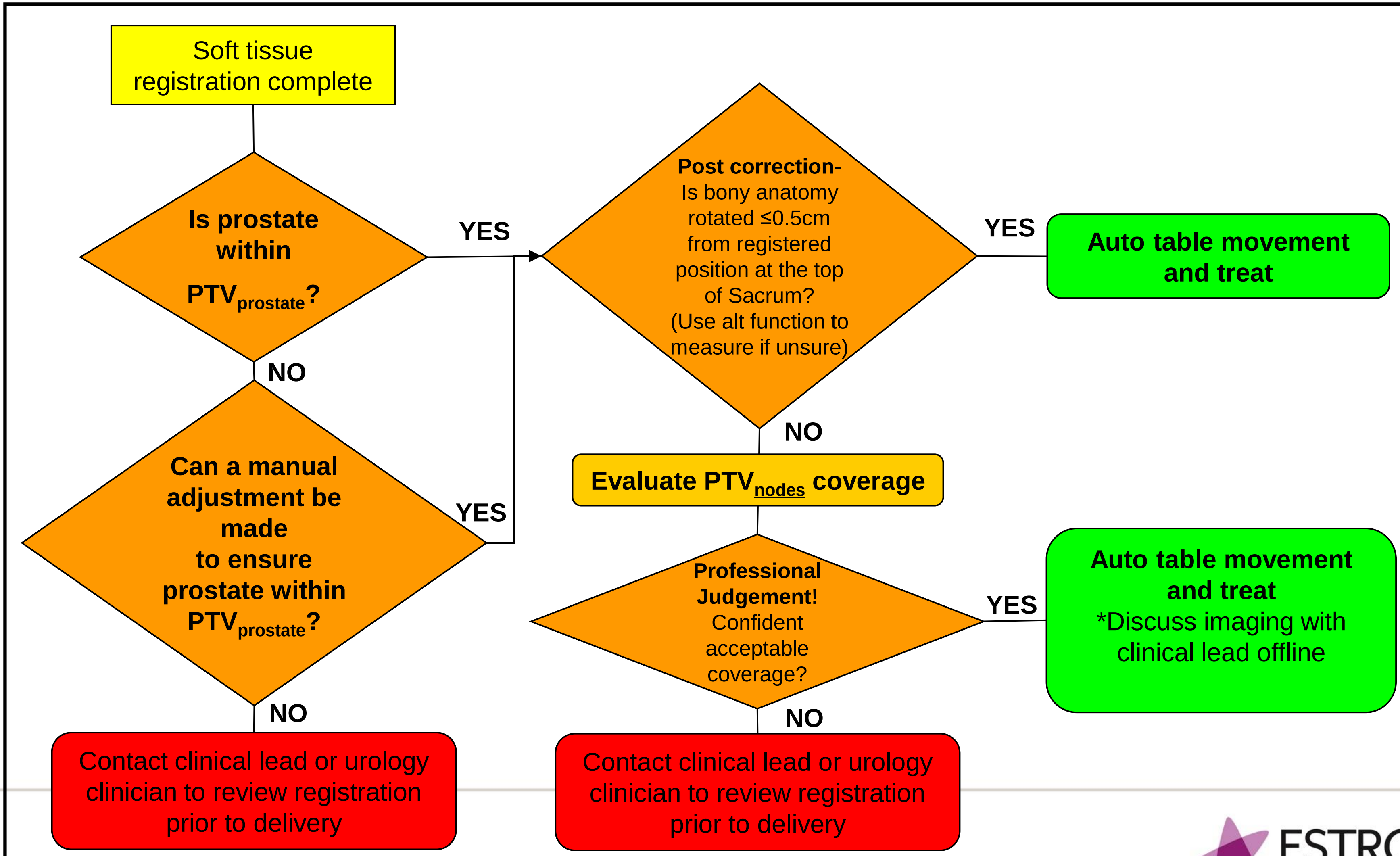
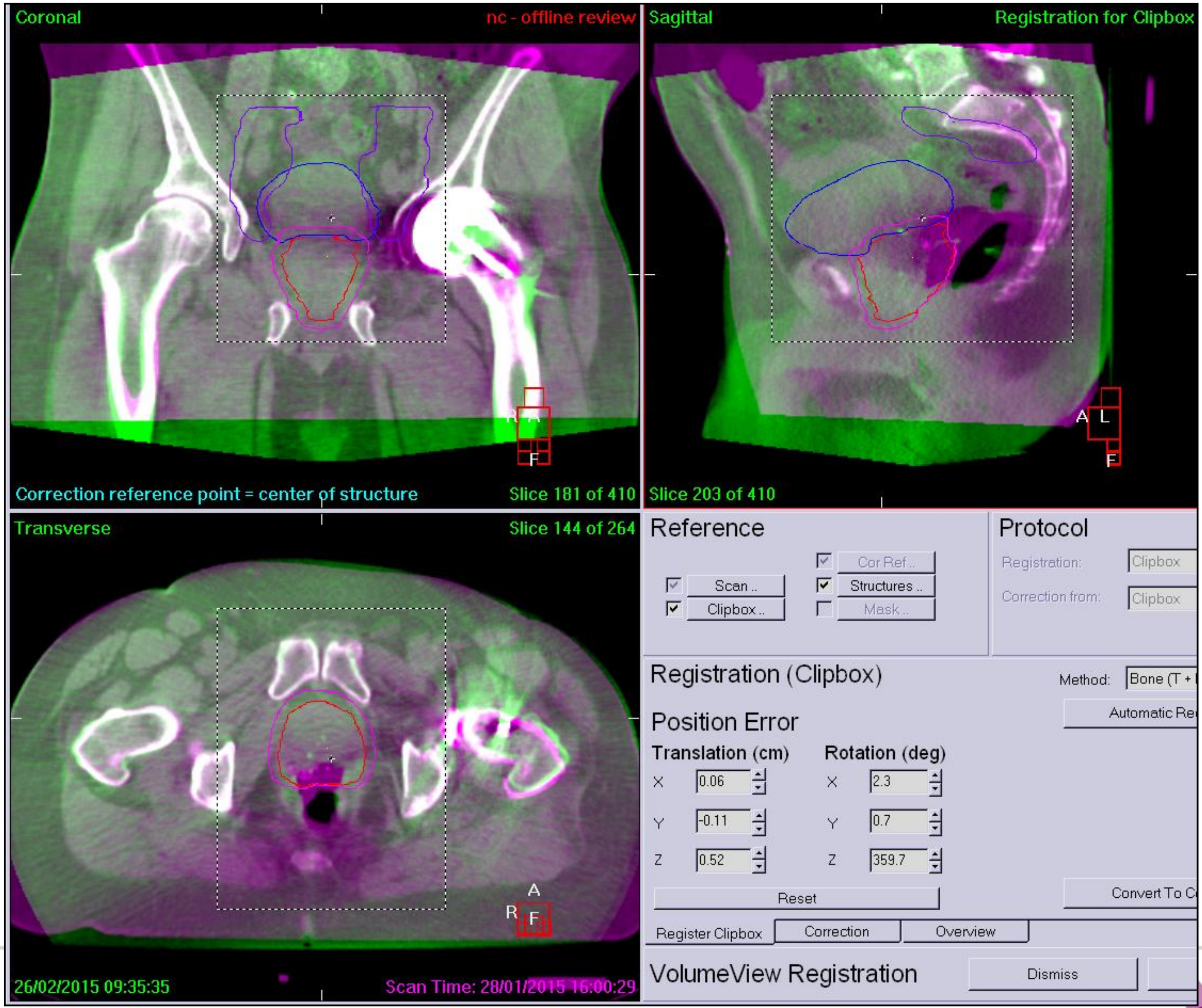
Online decision making for CBCT verification Prostate and nodes

NB All operators must have completed competency assessment (S-WB-019) to carry out prostate soft tissue matching. It may be necessary for the clinical lead or urology clinician to review imaging offline.



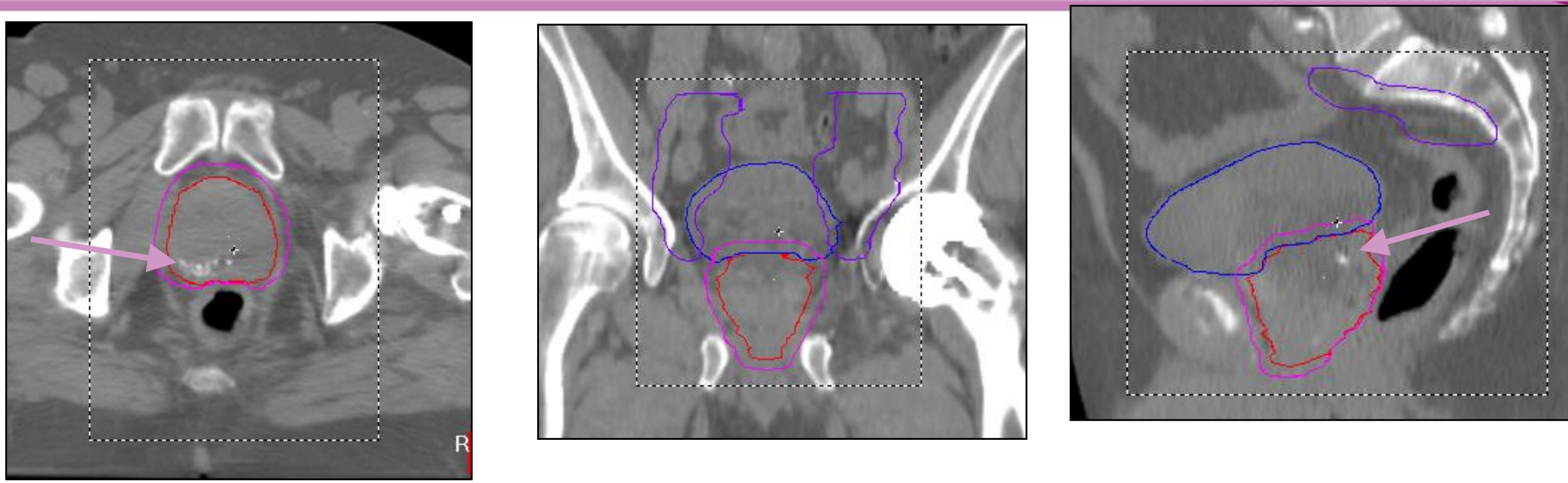
Courtesy of Steven Landeg, RMH

Prostate and nodes

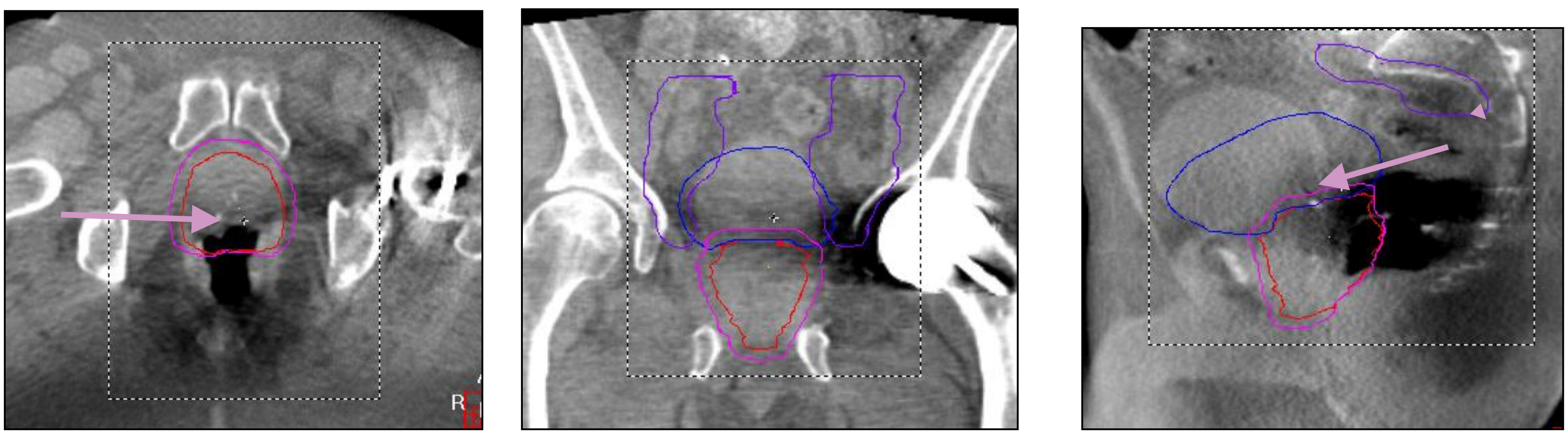


Images courtesy of Steven Landeg, RMH

Prostate and nodes



Reference Image



CBCT image

Images courtesy of Steven Landeg, RMH

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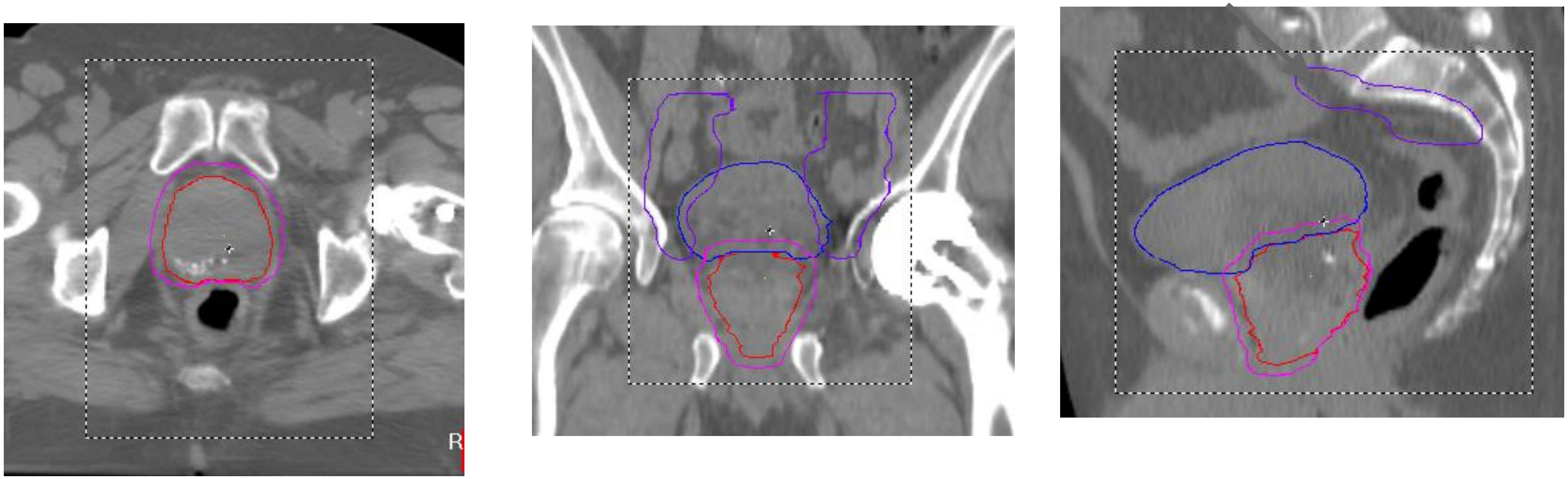
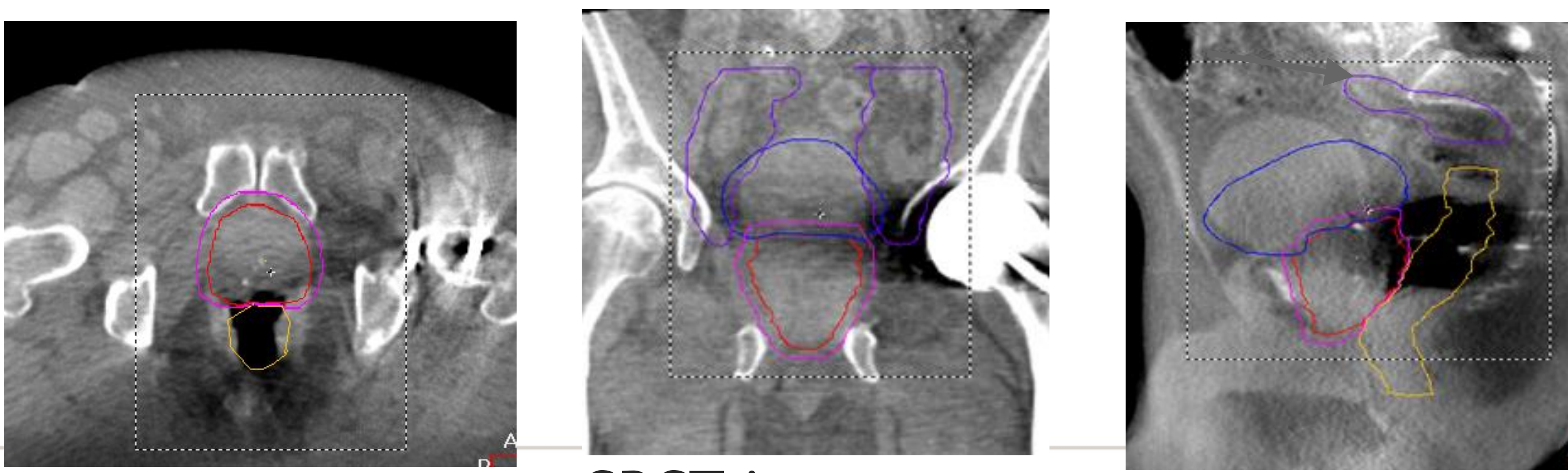
Prostate and nodes



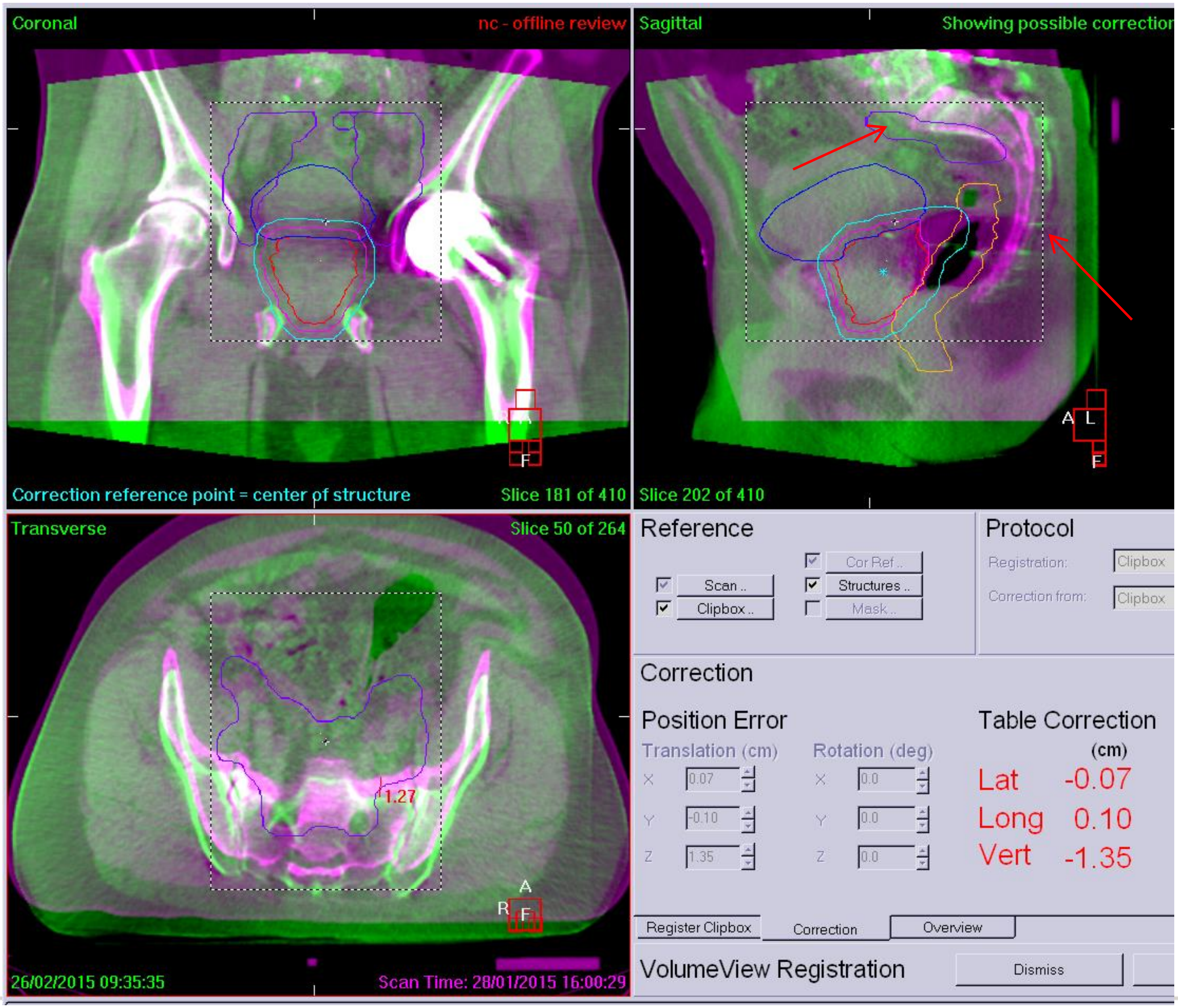
Reference Image



CBCT image

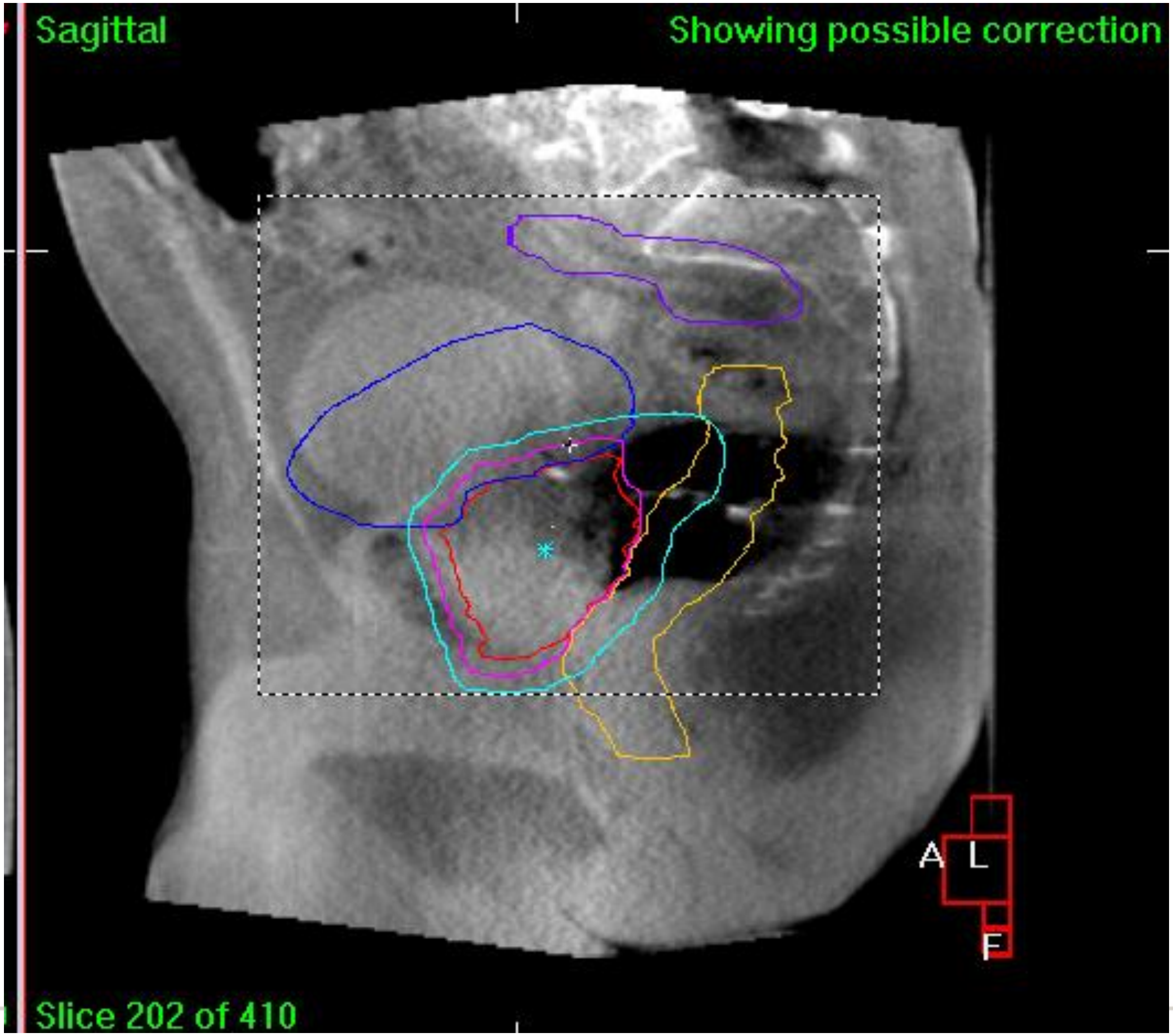
Images courtesy of Steven Landeg, RMH

Prostate and nodes



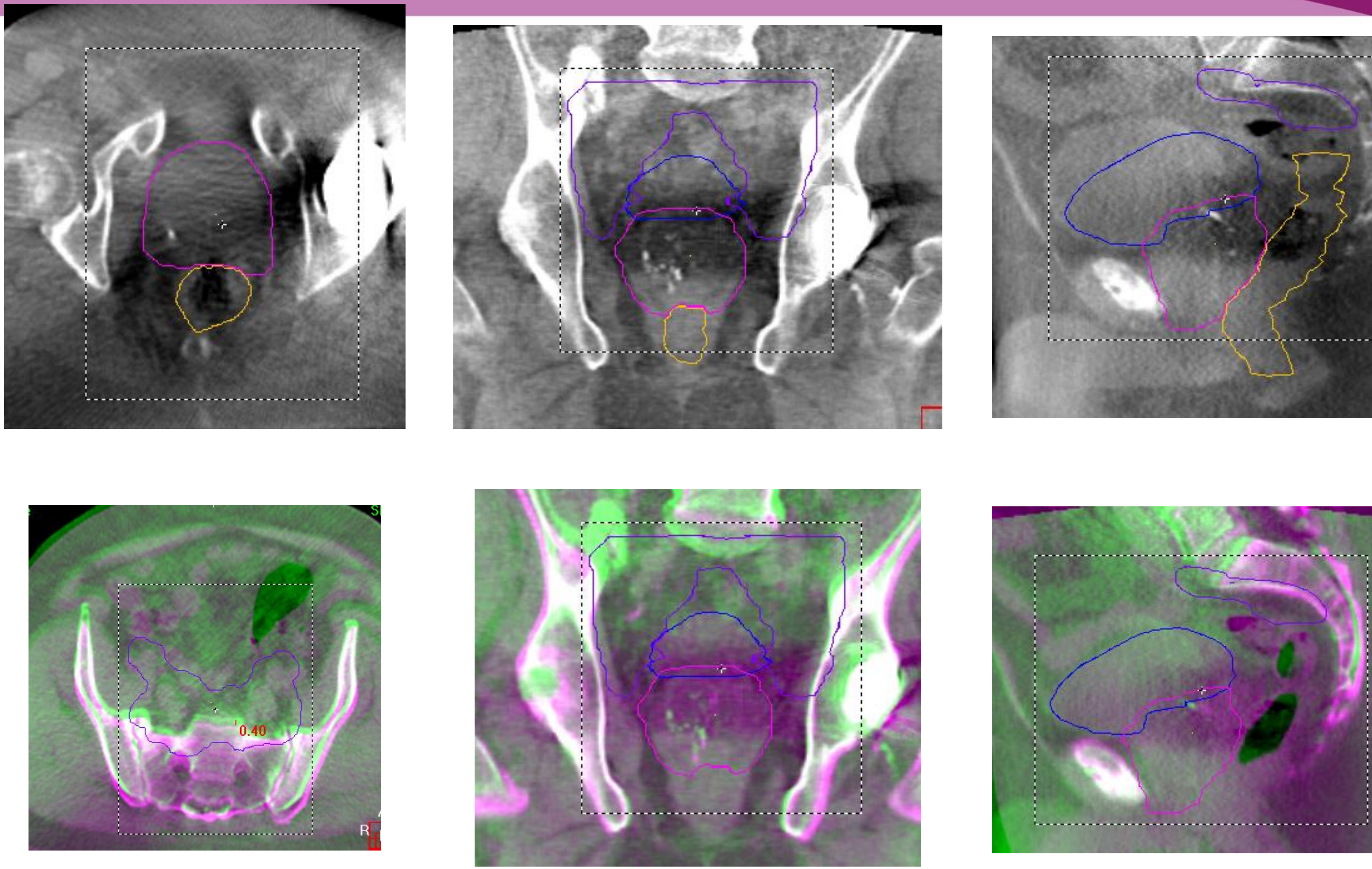
Images courtesy of Steven Landeg, RMH

Prostate and nodes



Images courtesy of Steven Landeg, RMH

The next day…



Images courtesy of Steven Landeg, RMH

Offline decision making for CBCT verification Prostate and nodes

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Review rectum and bladder status

Is rectum ≥50% different from planning scan?

YES → Discuss with patient and check correct used of rectal preparation (as per J-CH-059). Record rectal status on S-RT-083-02.

NO → Record **'Rectal status 'good'** on log S-RT-083-02

Is bladder over or under-filled?

YES →

Under-filled: Encourage hydration.

Over-filled: Discuss bladder preparation (J-CH-053-02) with patient. If consistently over-filled discuss with clinical team.

Record **'under** *or* **over-filled bladder'** on XVI log S-RT-083-02.

NO → Record **'Bladder status good'** on XVI log S-RT-083-02

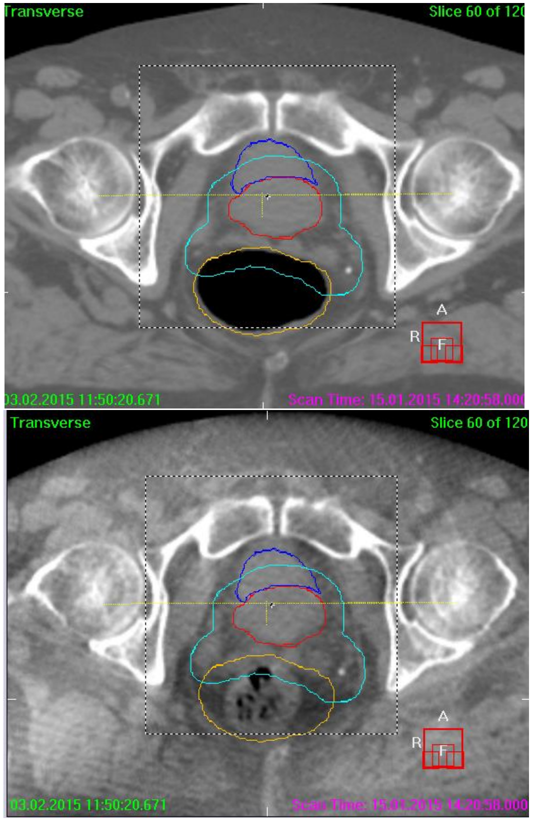

Figure 1: Planning scan (top) showing large gas filled rectum. CBCT (bottom) showing smaller, stool filled rectum on treatment (~50% smaller).

Courtesy of Steven Landeg, RMH

S-CH-364

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Summary

	Advantages	Disadvantages
Markers and MV	Image while treating	May not be visible No information regarding soft tissue anatomy
Markers and KV	Quick Objective	No information regarding soft tissue anatomy Not representative of deformation
3D (markers)	Soft tissue anatomical information Objective	Increase time Artefacts
3D (no markers)	Soft tissue anatomical information	Increase time Inter observer error

Summary

Know limitations

Work within limitations

Which method would you prefer to use?

MV imaging

MV imaging and markers

KV planar imaging

KV planar imaging and markers

3D soft tissue imaging

3D soft tissue imaging and markers

Acknowledgements

Rianne de Jong

Sophie Alexander

Angela Baker

Steven Landeg

ESTRO
School

WWW.ESTRO.ORG/SCHOOL

Non radiographic IGRT techniques for in-room target (and OAR) localisation

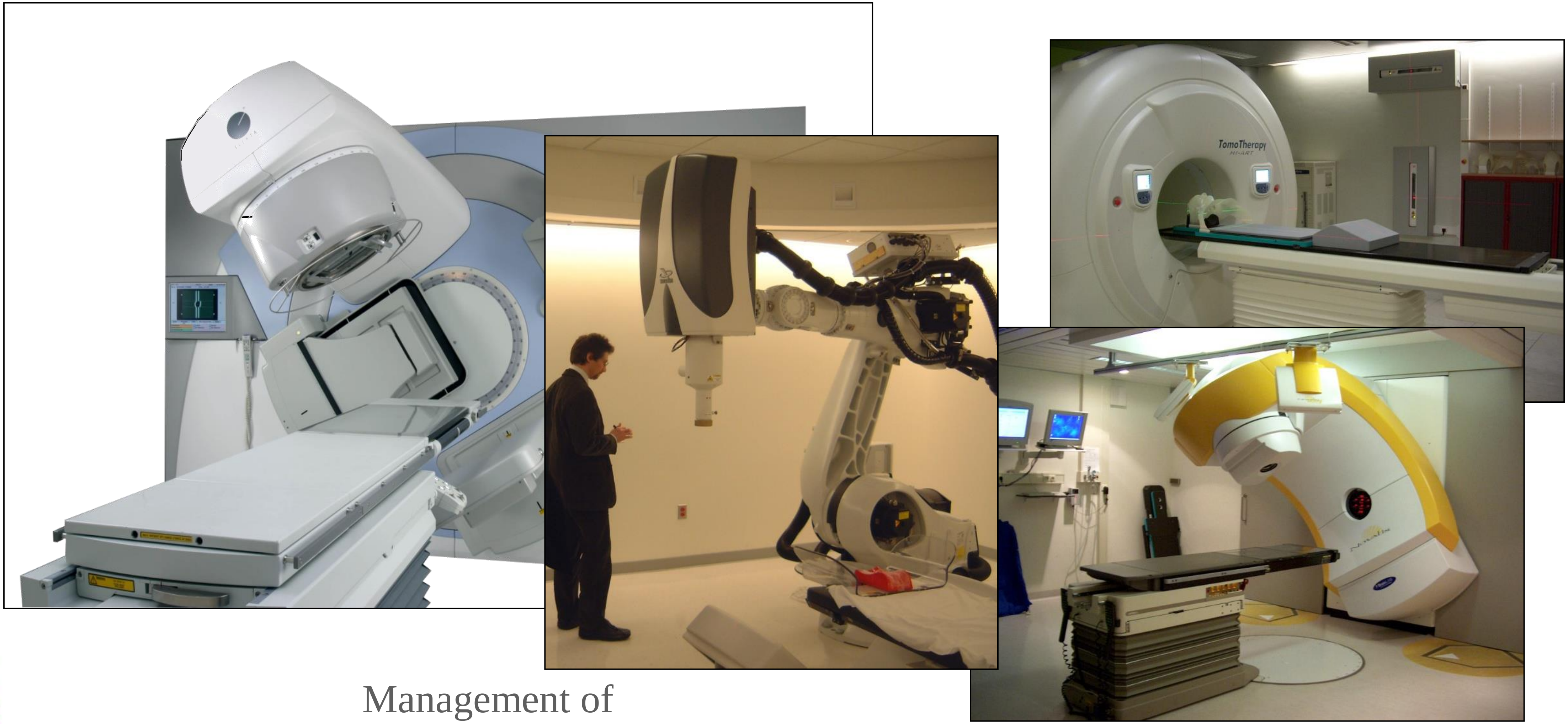
Uwe Oelfke

ICR/ RMH London
Joint Department of Physics
uwe.oelfke@icr.ac.uk

Outline

- Non-radiographic solutions
  - ➢ Surface based (optical scanners)
  - ➢ Ultrasound
  - ➢ RF transponders
  - ➢ In-room MRI

… image-guidance (IGRT)



Management of

- Inter-fraction geometric uncertainties
- Intra-fraction geometric uncertainties

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Real-time tracking - CyberKnife

Internal/external marker correlation

Model building

Courtesy of Accuray, Inc.

Models:

Linear

Elliptical

Polynomial

Model updated by use of online kV images

IGRT and Imaging dose…

	Dose / acquisition	Patient dose for a 78Gy treatment (2Gy fractions)
MV Electronic Portal Imaging Device	**~ 30 mSv** (3 MU, isocenter dose)*	2340 mSv
MV cone beam CT	**~ 20-90 mSv** (0.005 MU/°, isocenter dose)***	1950 mSv
Stereoscopic kV-imaging	**~ 0.51 mSv** (surface dose)*	40 mSv (400 mSv, gating)
kV cone beam CT	**~ 50 mSv** (surface dose)**	1950 mSv
MV CT (TomoTherapy)	**~ 20 mSv** (isocenter dose)*	780 mSv

* Dose measurements at UZ Brussel

** D. Jaffray 2006

*** J. Pouliot 2006

Patient dose due to IGRT

- Difficult to synthesize a complete picture of the patient's exposure:
  - Imaging modalities range from **planar portal images** to fluoroscopy to **CT-based solutions**.
  - Procedures can be as simple as acquiring **single set-up images** or as complex as assessment of **intra-fraction target tracking**.
  - Patient dose can be concentrated on the **skin** (planar kV x-ray imaging) or distributes throughout the anatomical **volume** of interest (CT-based)
  - High **image quality** versus **necessary information** has an impact on settings and dose

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Patient dose due to IGRT

- Should be managed case-by-case:

  - IGRT SRS for a 15 year old patient with AVM

    ≠

  - IGRT for a 70 year old patient with prostate ca

- The management of imaging dose during image-guided radiotherapy: Report of the AAPM Task Group 75 (Med Phys 2007; 34(10): 4041-4063

Non-radiografic IGRT

- Monitoring the patient surface
- Ultrasound
- RF-frequency
- MRI-in the treatment room

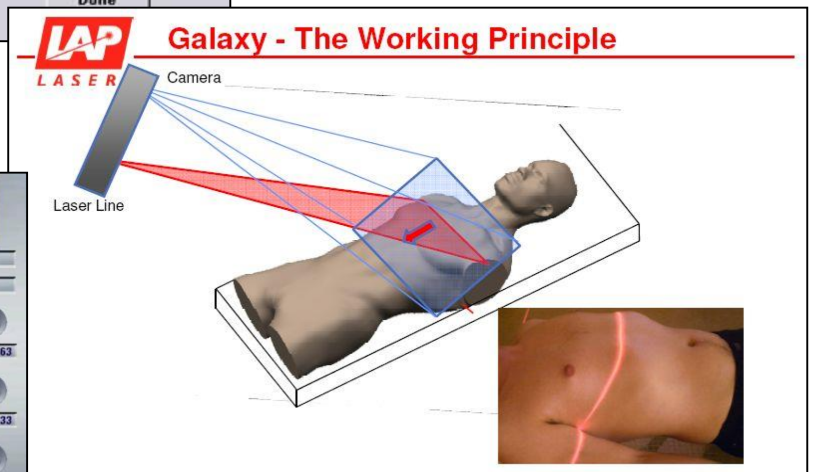
Objectives:

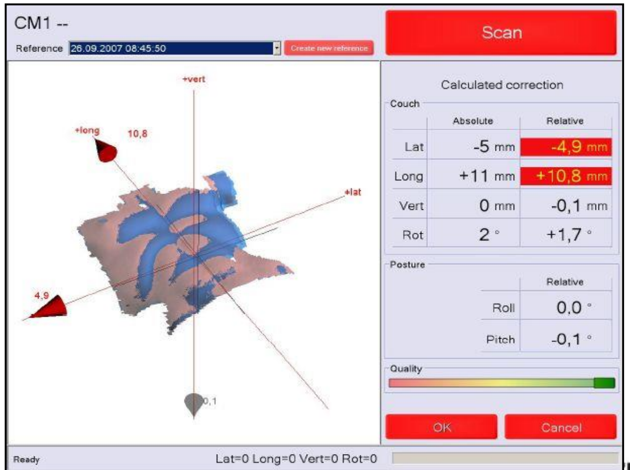
Automatic accurate target postioning

Real time monitoring of target movements

NO extra dose

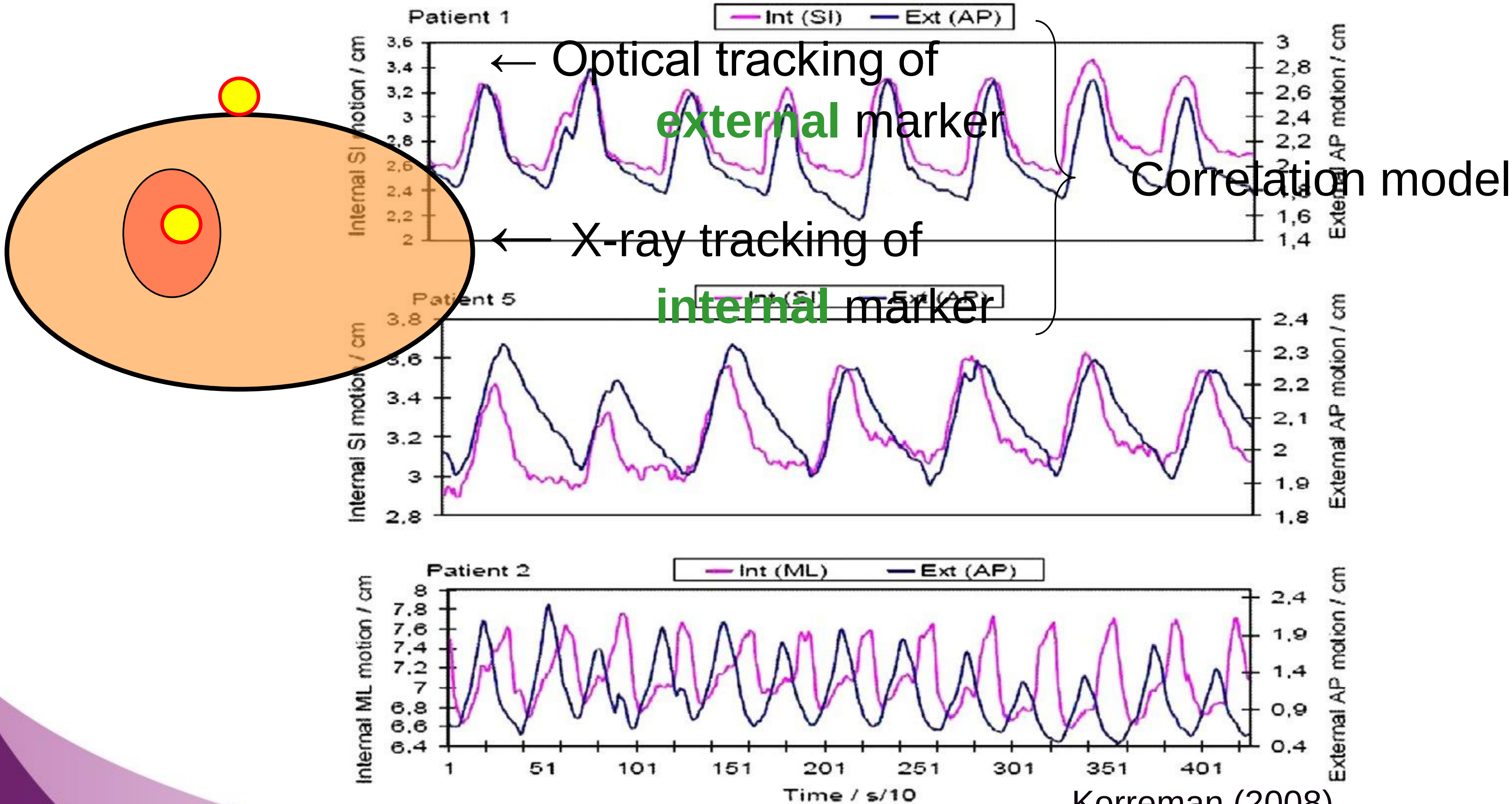
Patient surfaces..detection, monitoring





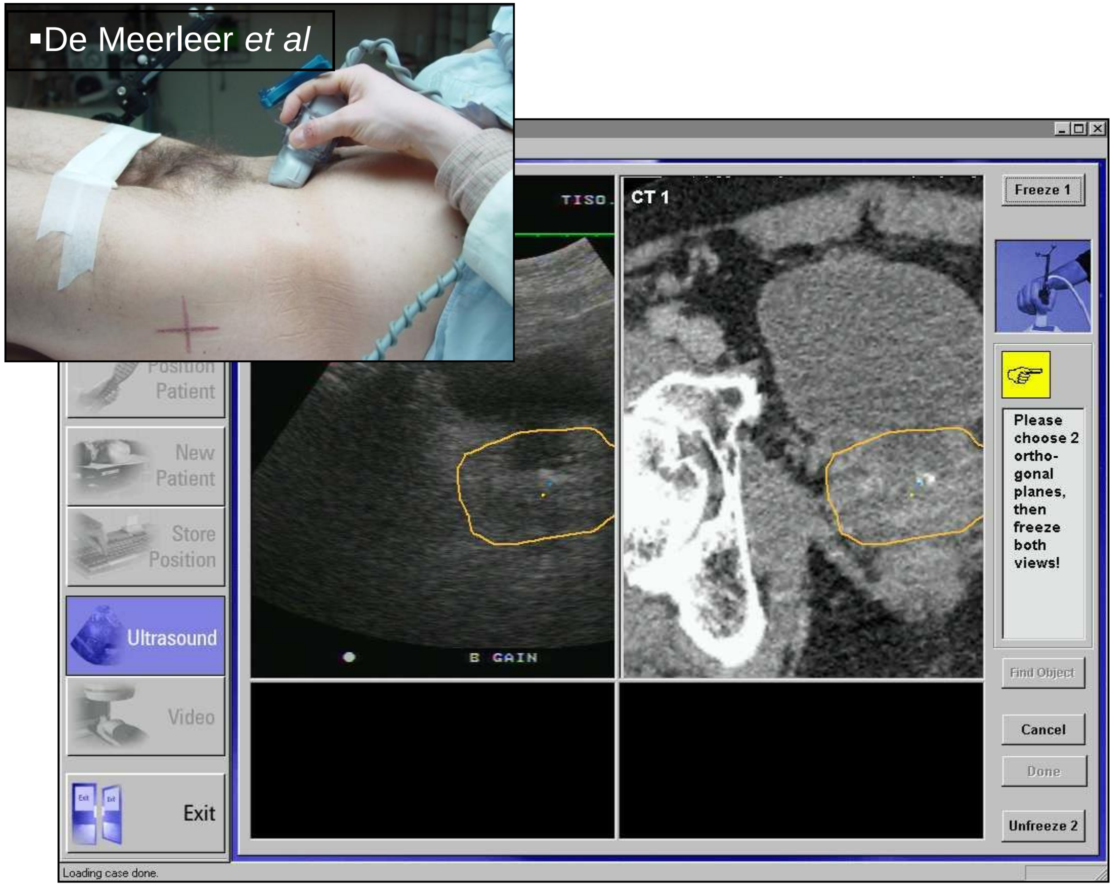
- Optically-guided or video-based systems
- Image-based and have potential to fully automate the positioning process
- High precision positioning of the skin NOT internal structures
- Increases efficiency but NOT efficacy

Limitations of surrogate technology



Korreman (2008)

Ultrasound



No surrogate required (soft tissue visualization)

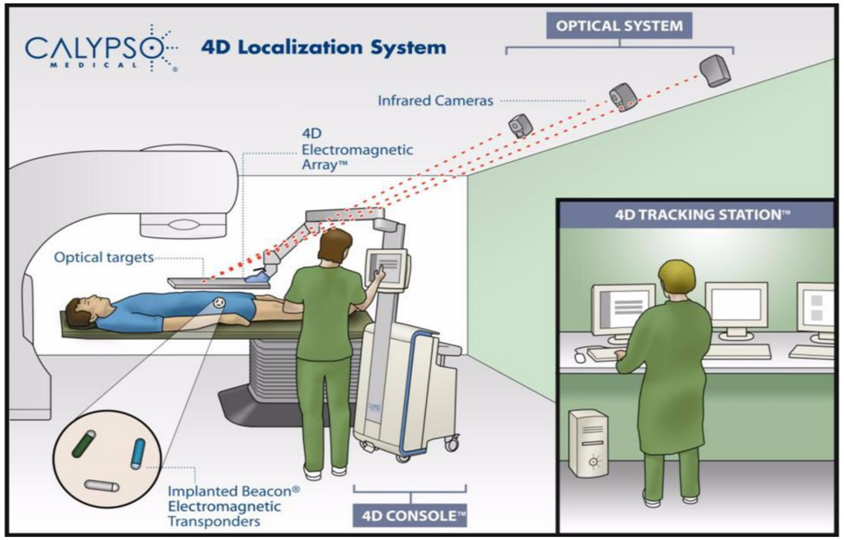
Marker vs US:

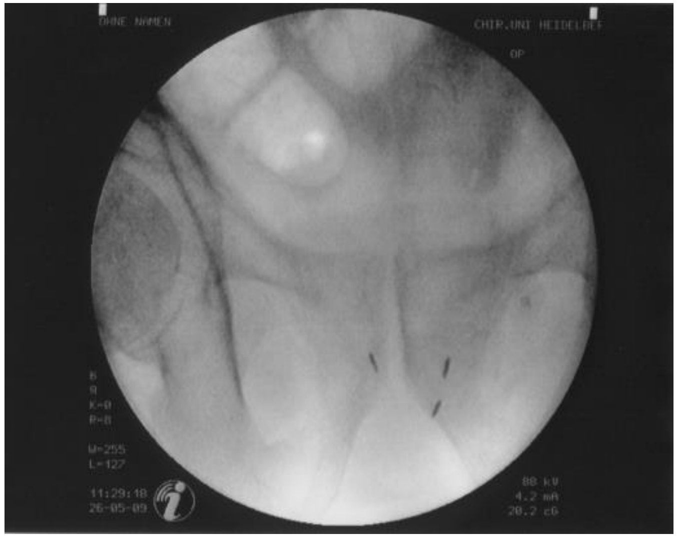
- Remaining random error same magnitude as with initial set-up
- CT-contour ≠ US-structure
- Important inter-user variability

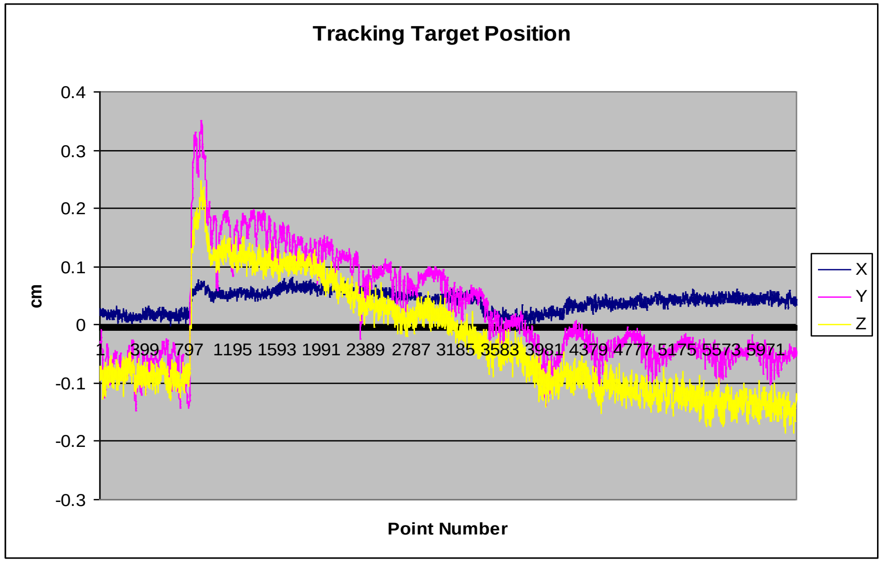
Van den Heuvel *et al*, Med.Phys. 2003; 30

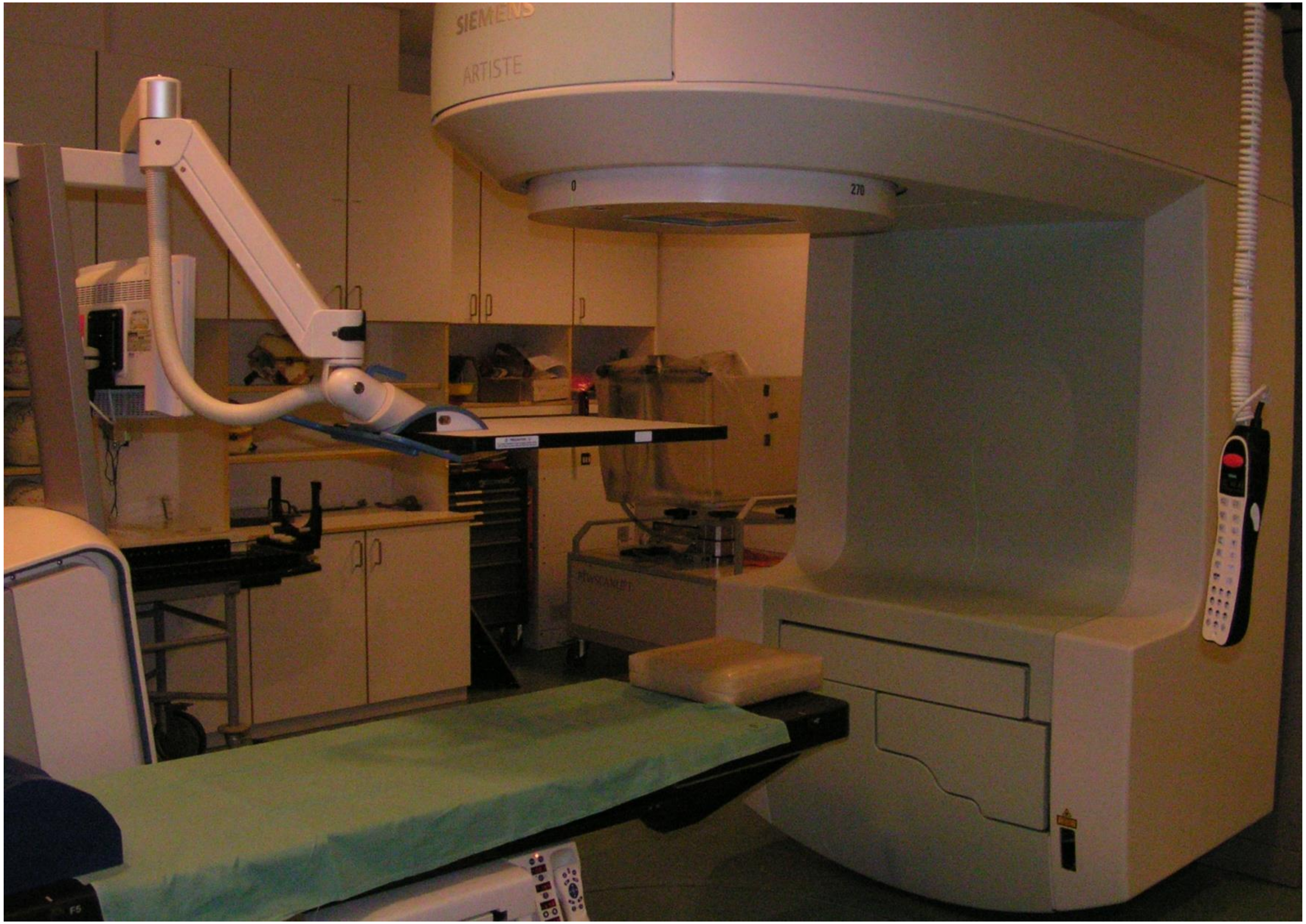
Langen *et al*, IJROBP 2003; 57

Internal Surrogat: Calypso System








SIEMENS
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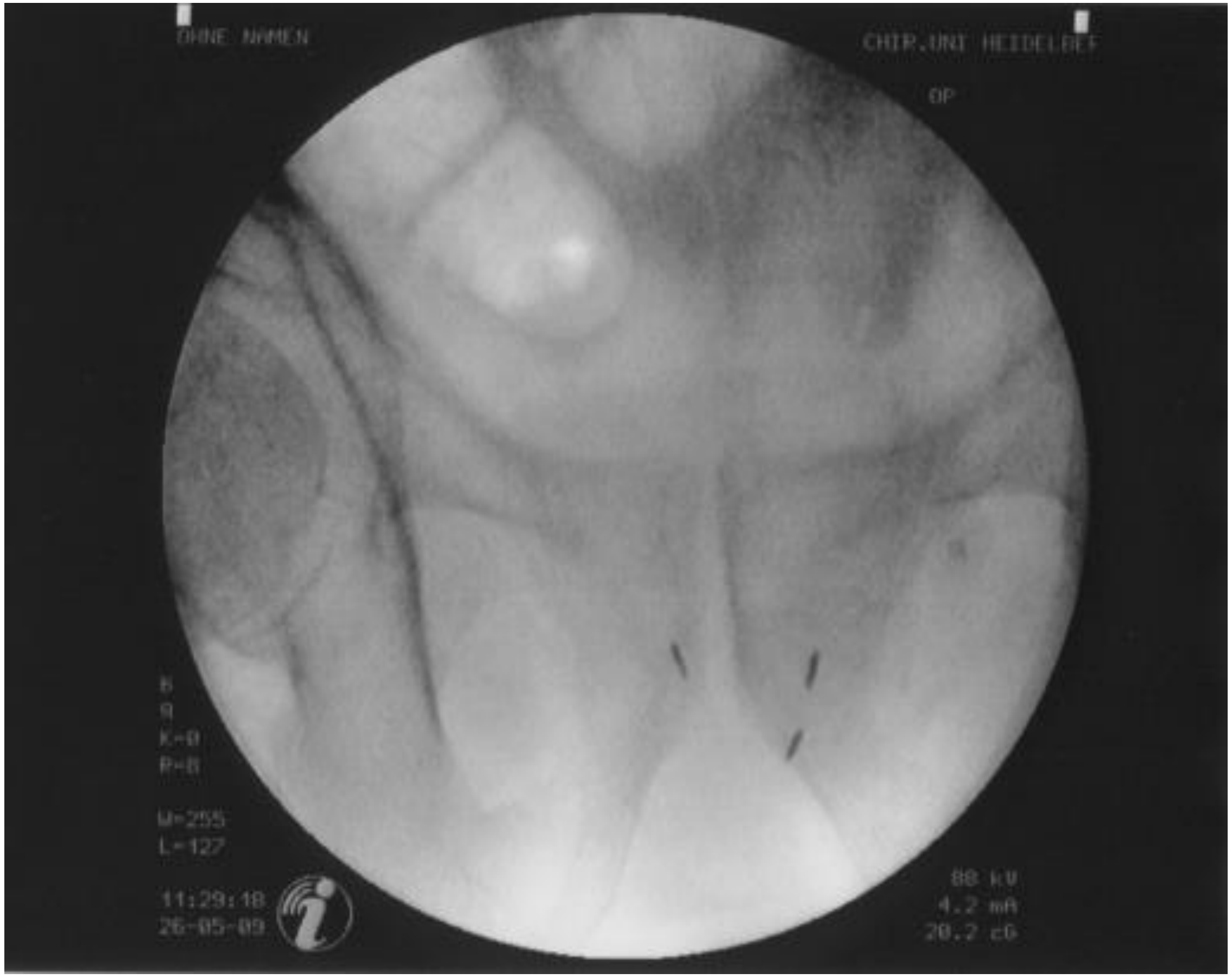
Clinical application of Calypso at DKFZ & Univ. Clinic HD



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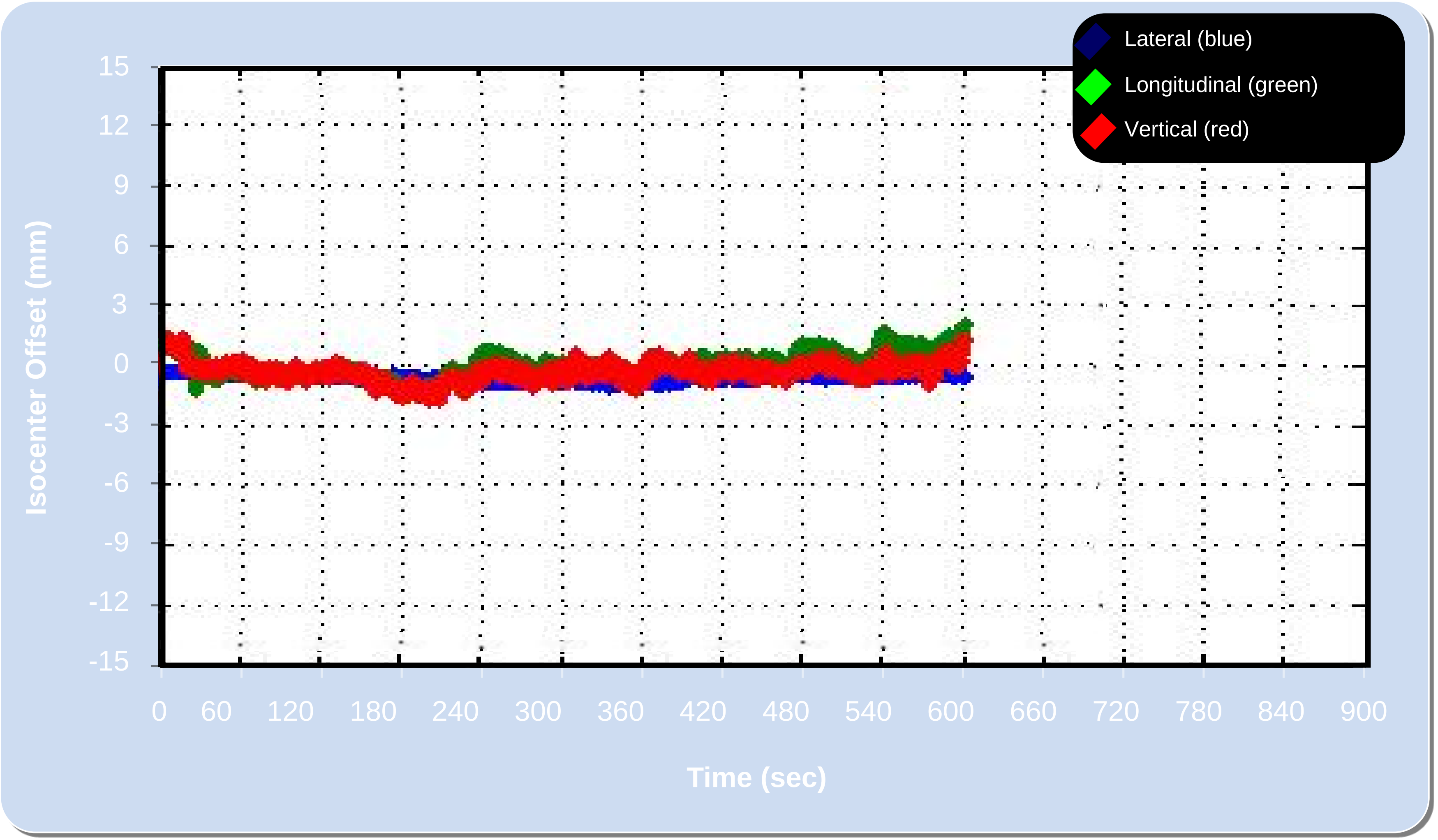
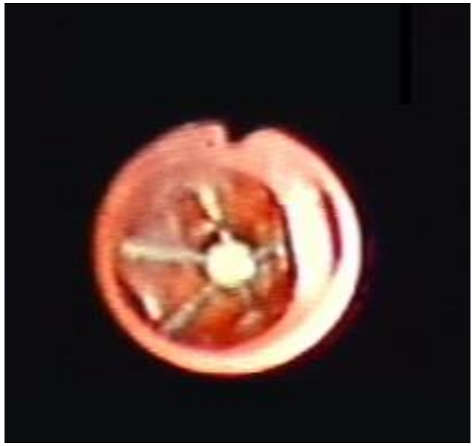
Same Patient, 39 Fractions



The Anchored Beacon Transponder

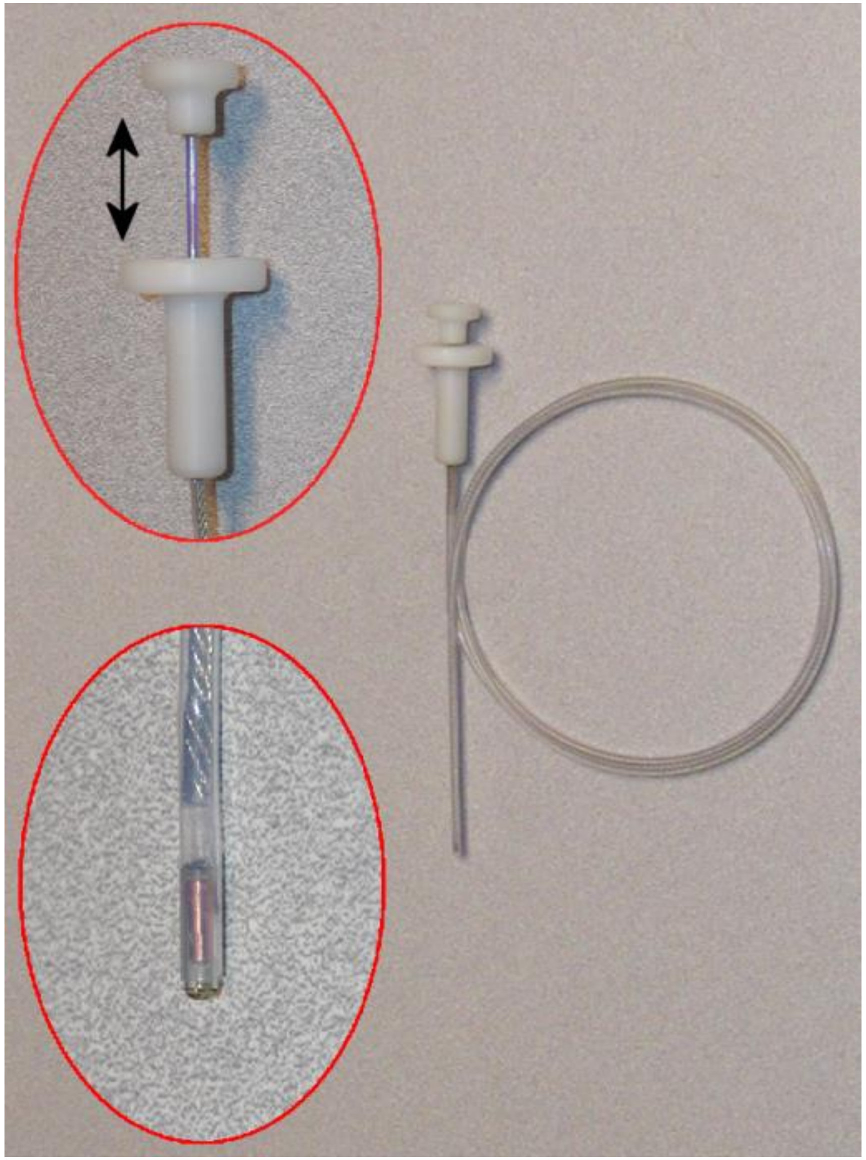
- Implanted in airways within or near the tumor
- Aimed at airways with diameter of approximately 2.5 mm or smaller
- Designed for bronchoscopic implantation



The anchored Beacon transponder is work in progress.

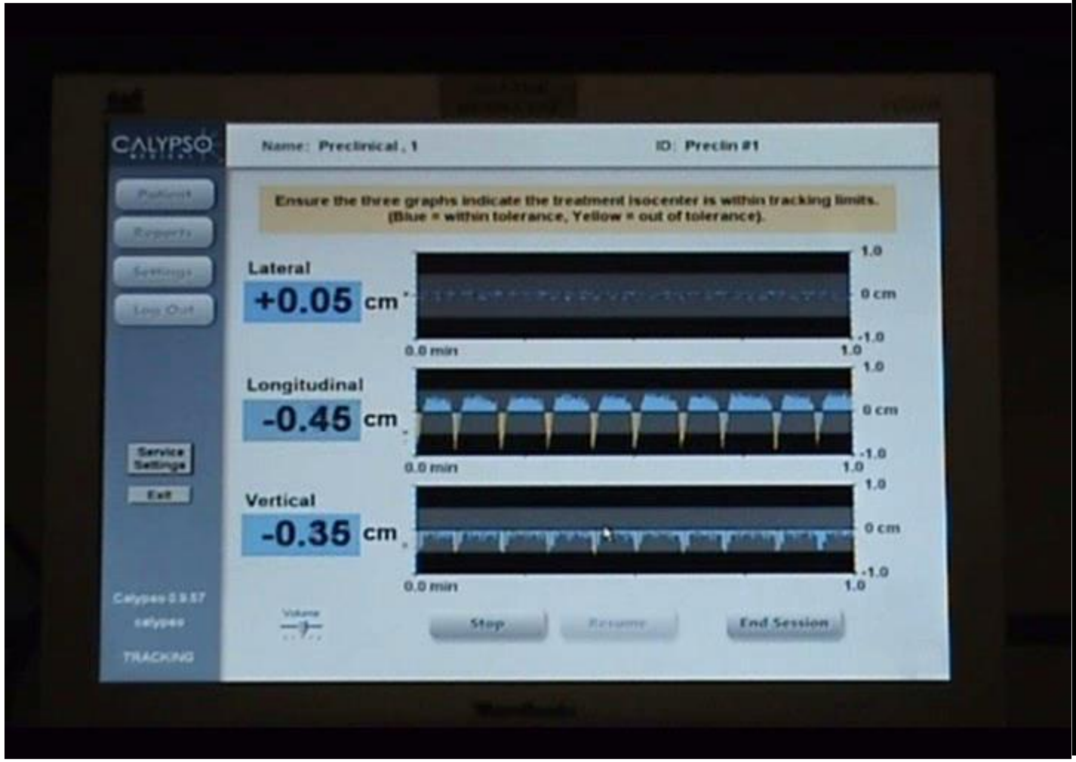
Implantation Procedure

- Custom, dedicated, pre-loaded delivery catheter
- Fluoroscopic guidance
- Optional superDimension® guidance

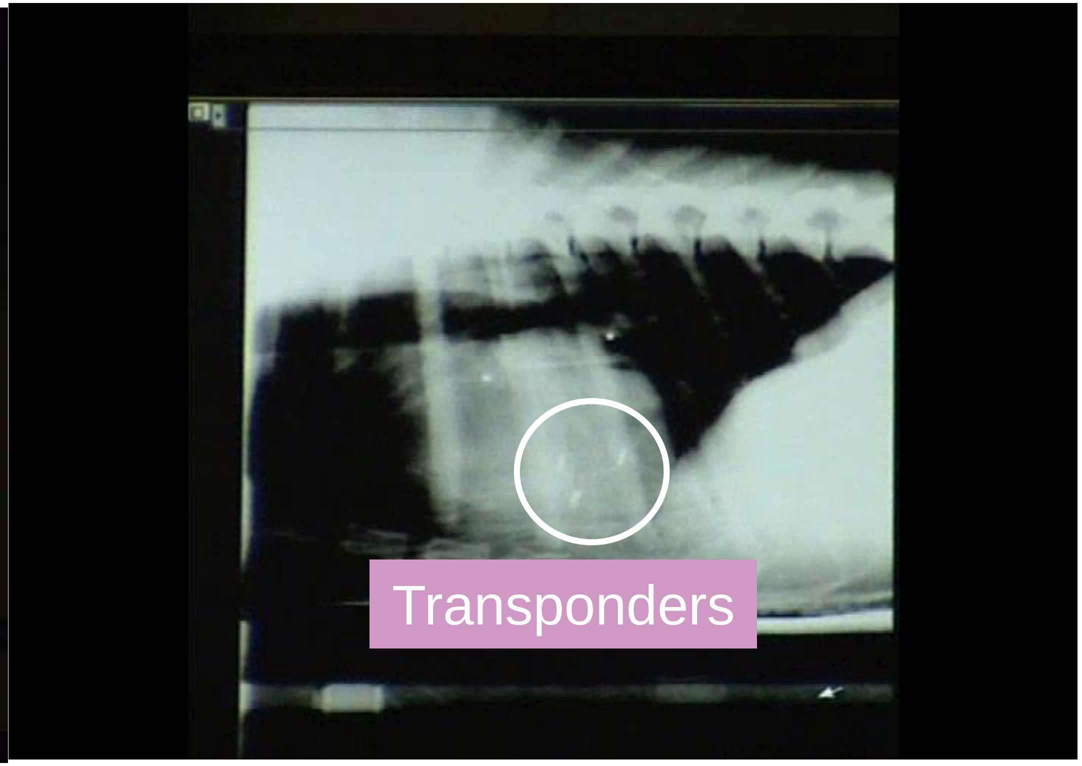


Preclinical In-vivo Lung Tracking

- Real-time, non-ionizing, objective lung tracking demonstration



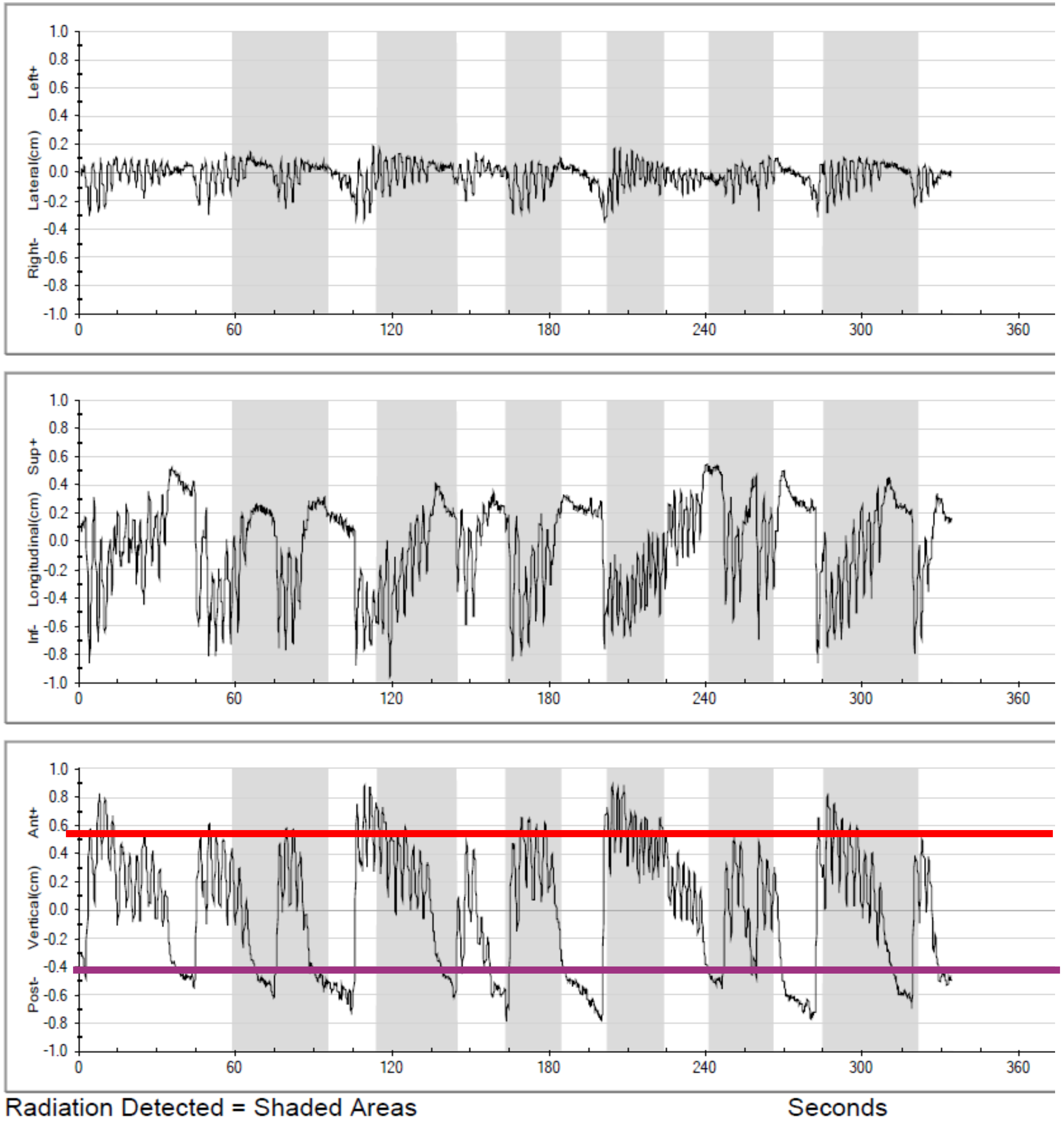
Calypso Tracking Station



Fluoroscopy View

Fraction 1

Baseline shift ?



Summary

- RF localization using implanted transponders is feasible
- This system has shown the potential to provide rapid positioning based on transponder location
- Intra-treatment monitoring is possible, and early studies show the potential value for detecting large transient shifts, as well as slower trends in position variation

Courtesy of J. Balter

In room MRI Guided RT

Reasons for MRIgRT

- MR imaging capabilities
  - No additional imaging dose
  - Improved soft-tissue contrast compared to CT
  - Functional imaging
    - Treatment response monitoring

- Adaptive RT
  - Daily treatment plan adaptation based on MR images
  - Real-time motion monitoring
  - MLC Tracking
  - Online dose reconstruction

CT – MRI Soft tissue contrast

kV CT image

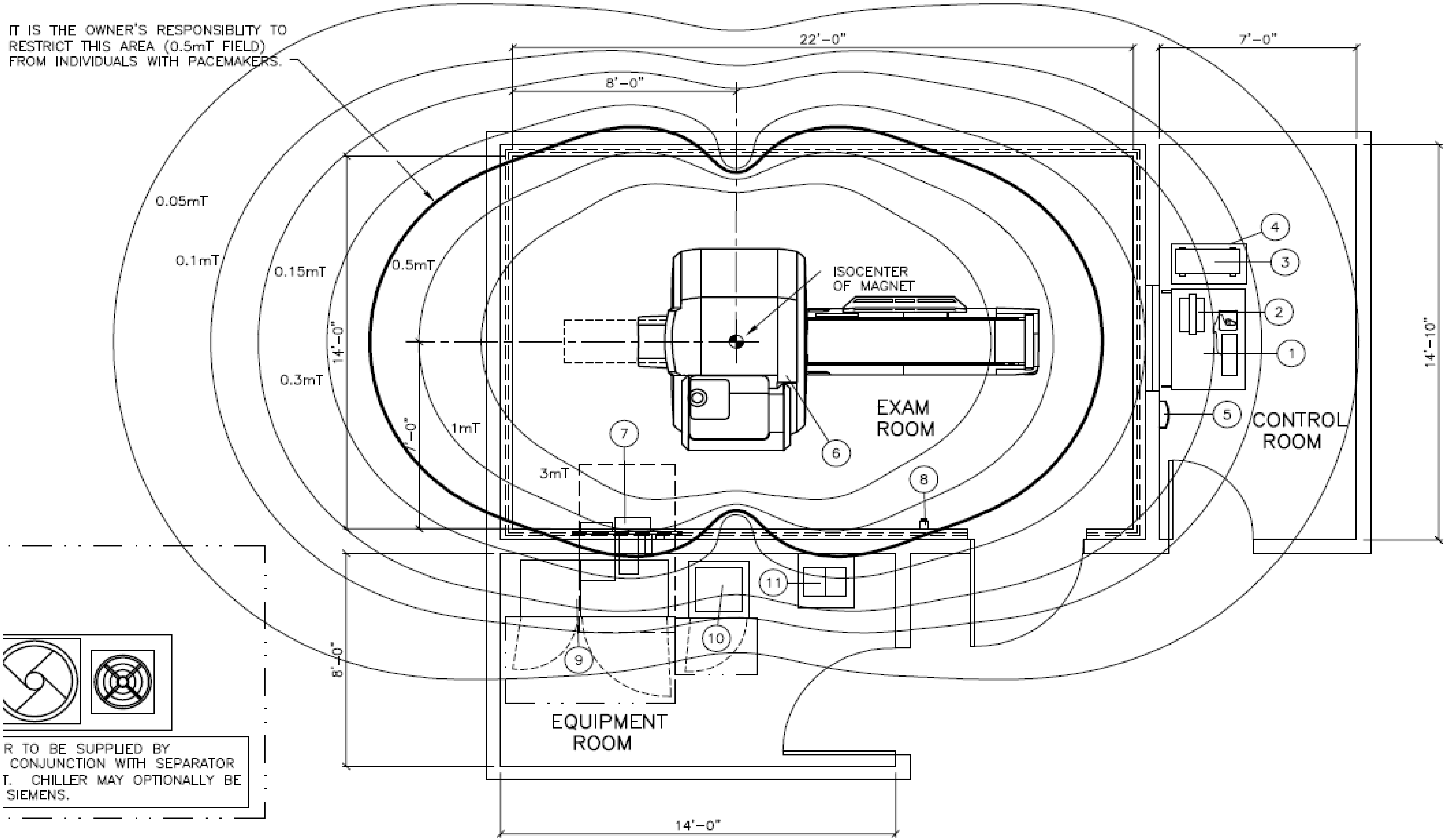
kV cone beam
CT image

MR image

Lack of Tissue Contrast
Radiation Dose to Acquire Image

Superb Tissue Contrast
Zero Radiation Dose

Technical Challenge: Magnetic field



From: Siemens Cutsheet 10023 Magnetom Aera 1.5T

Challenge: fringe fields of the MR scanner

MAGNETIC FRINGE FIELDS

MAGNETIC FIELDS MAY AFFECT THE FUNCTION OF DEVICES IN THE VICINITY OF THE MAGNET. THESE DEVICES MUST BE OUTSIDE CERTAIN MAGNETIC FIELDS. THE DISTANCES LISTED ARE FROM THE MAGNET ISOCENTER AND DO NOT CONSIDER ANY MAGNETIC ROOM SHIELDING.

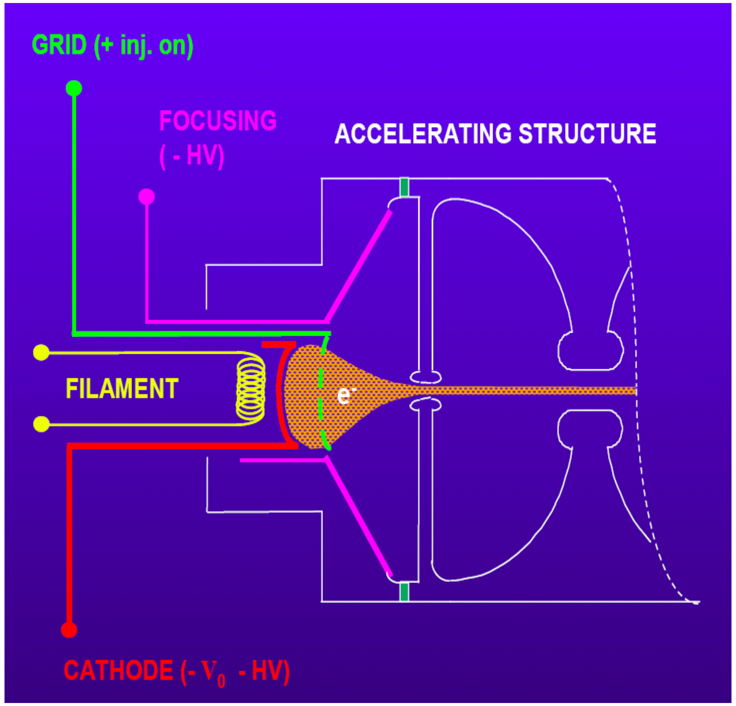
X/Y AND Z AXIS	DEVICES
6'–1" / 9'–2" 3.0mT	SMALL MOTORS, WATCHES, CAMERAS, CREDIT CARDS, MAGNETIC DATA CARRIERS (SHORT–TERM EXPOSURE)
7'–3" / 11'–6" 1.0mT	COMPUTERS, MAGNETIC DISK DRIVES, OSCILLOSCOPES, PROCESSORS
8'–3" / 13'–2" 0.5mT	CARDIAC PACEMAKERS, X–RAY TUBES, INSULIN PUMPS, B/W MONITORS, MAGNETIC DATA CARRIERS (LONG–TERM STORAGE)
9'–9" / 16'–1" 0.2mT	SIEMENS CT SCANNERS
10'–4" / 17'–1" 0.15mT	COLOR MONITORS, SIEMENS LINEAR ACCELERATORS
13'–1" / 22'–3" 0.05mT	X–RAY IMAGE INTENSIFIERS, GAMMA CAMERAS, PET/CYCLOTRON, ELECTRON MICROSCOPES, LINEAR ACCELERATORS

THE OWNER/USER IS TO VERIFY THE LOCATION OF THE 0.5mT FIELD AND ENSURE THAT IT IS MAINTAINED AS A RESTRICTED AREA.

From: Siemens Cutsheet 10023 Magnetom Aera1.5T

Challenge: Magnetic field impact on linac

- On beam generation



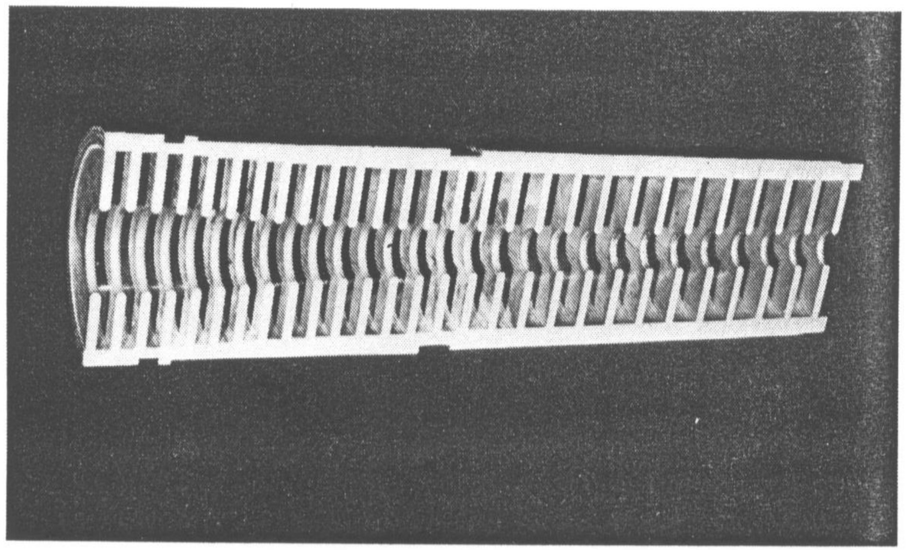


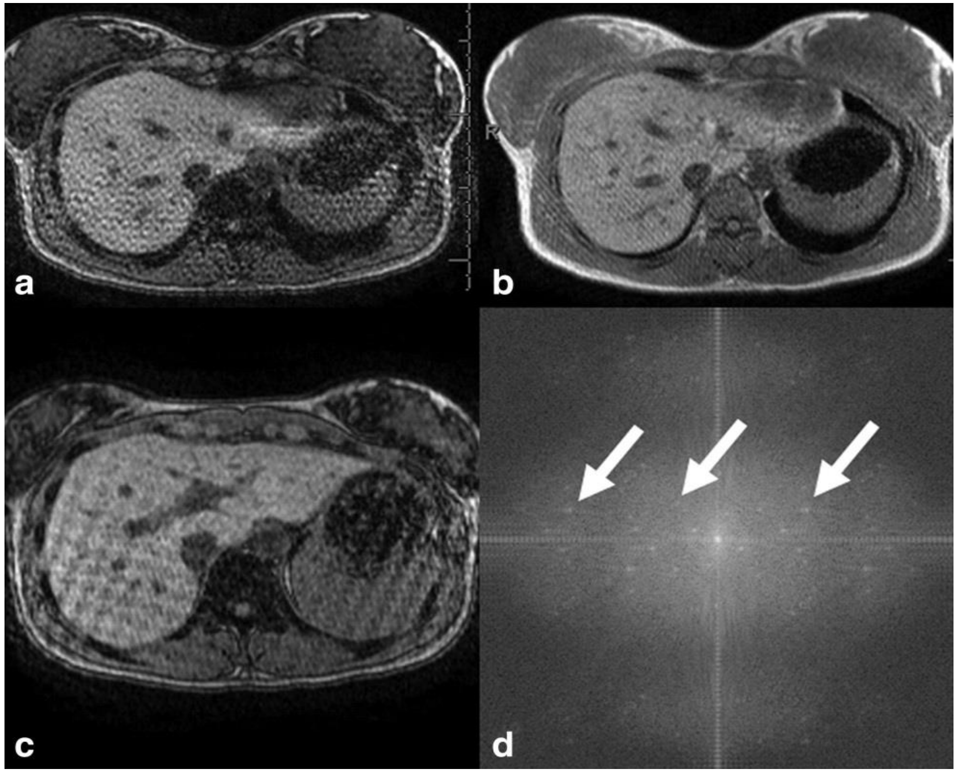
FIG. 2. Cutaway traveling wave accelerator structure; the buncher section is on the left and the uniform section is on the right.

- On electric motors (e.g. MLC)

Challenge: MR image acquisition affected by linac

- By radio frequency (RF) artefacts from beam generation

RF artefacts (not from a linac)



JMRI 38:268-287 (2013)

- By distortions due to
  - Magnetic objects close to the magnetic field
  - Eddy currents induced by moving (magnetic) objects (Gantry, MLC)

Treatment Devices: Current approaches

- Spatial separation of treatment and imaging device
- Use of an alternative radiation sources
- Optimize electron gun design / shielding to work in the fringe field
- Generate a low magnetic field zone at the location of the linear accelerator

4 Technical Approaches

MR on rails (IMRIS)

MR + rotating LINAC (Philips/Elekta, Utrecht))

Rotating MR/LINAC (Edmonton)

Cobalt sources/MR (ViewRay)
Linac/MR (ViewRay)

MR on rails

patient positioning

shielding of rooms

decoupling of MR and linac

no real time imaging at treatment

first installation PMH (2014)

Challenge: Image Quality - MRI on rails

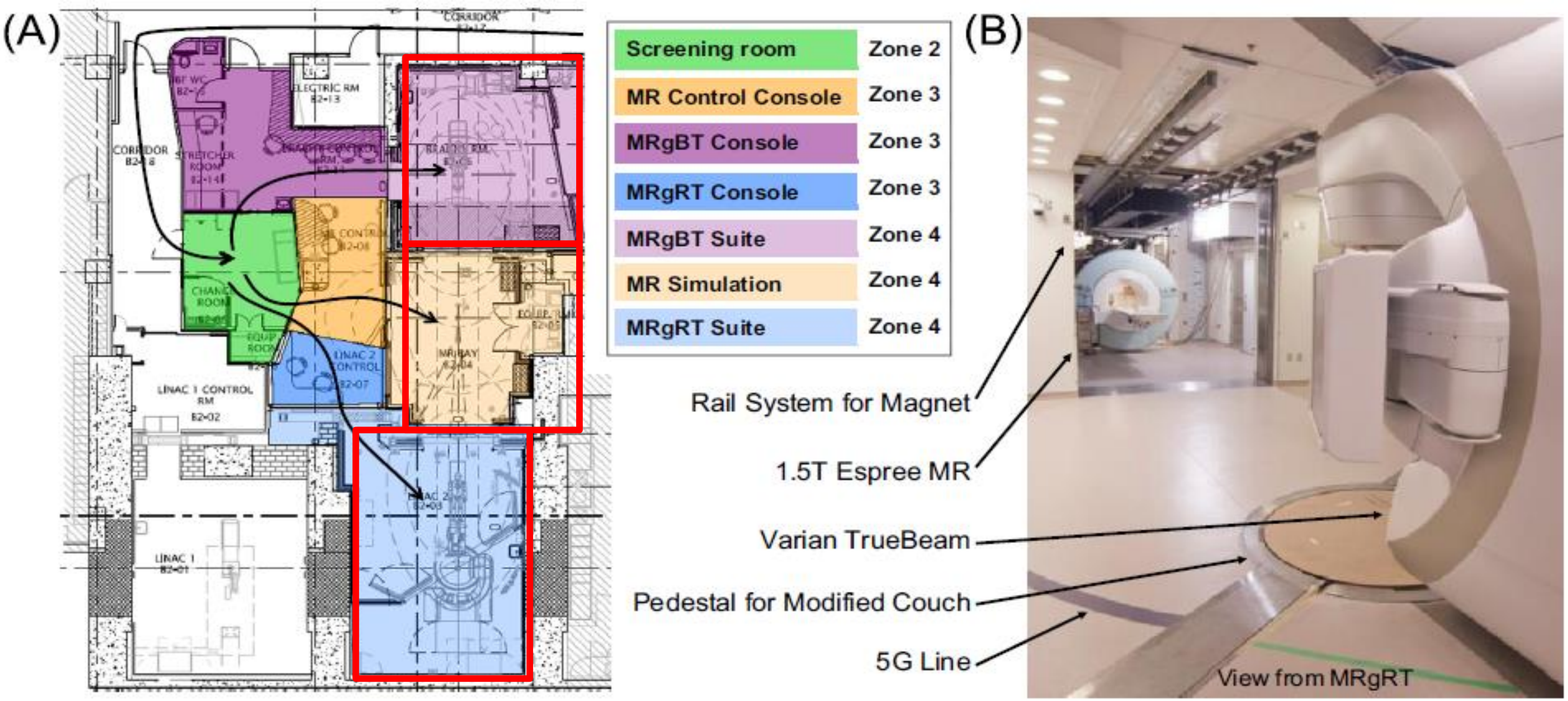


Figure (A) Floor plan and safety zones of the MR-guided RT facility at the Princess Margaret Cancer Centre showing brachytherapy, imaging, and external-beam RT suites. (B) Photograph of the accelerator and MR scanner in the facility. The magnet is advanced on the rail system into the MRgRT suite, and the patient is positioned via a modified treatment couch. At nearest approach, the magnet to linear accelerator isocenter distance is 3.1 m.

Jaffray et al. Seminars in Radiation Oncology
http://dx.doi.org/10.1016/j.semradonc.2014.02.012

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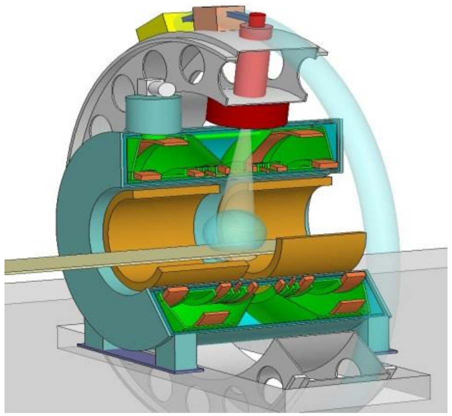
IGRT: Magnetic Resonance imaging

- Integrated devices

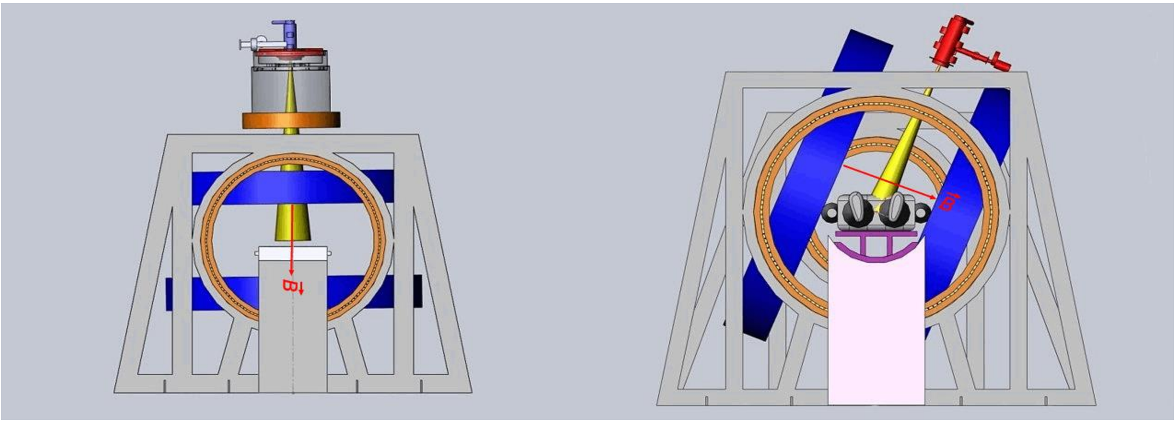


Utrect

Courtesy of Bas Raaymakers

Sydney (Paul Keall)

Renaissance Viewray



Alberta (B. Fallone)

Image sources: www.viewray.com http://www.inghaminstitute.org.au/Mri-linac.html http://www.mp.med.ualberta.ca/linac-mr/photo_gallery.html

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Treatment Device: ViewRay

MRIdian® from ViewRay:

- Low-field split coil 0.35 T MRI
- 50 cm field of view (70 cm bore)
- 3 Cobalt sources / MLCs
- Combined dose rate ≈ 6 Gy/min
- 180 MLC leaves (60 per head)
- 31.5 x 31.5 cm^2 treatment field

From: ViewRay web page

Mutic *et al.* Seminars in Radiation Oncology 24 196-199 2014

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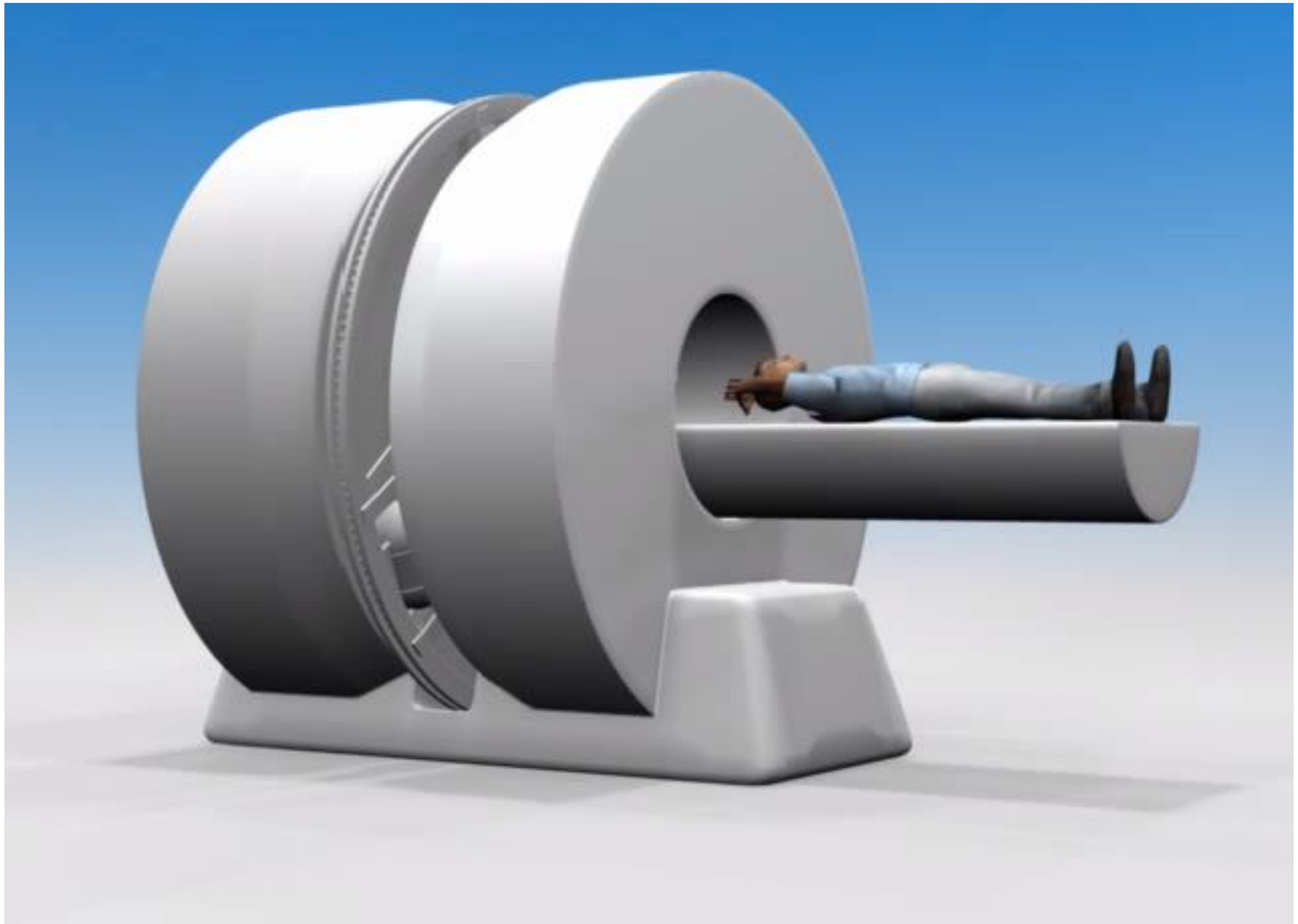
MRI + Cobalt RT - ViewRay



MRIdean System (ViewRay)

Treatment Device: ViewRay

Advantages compared to other approaches:

- Radiation source not affected by magnet
- Less impact on secondary electron trajectories due to low magnetic field

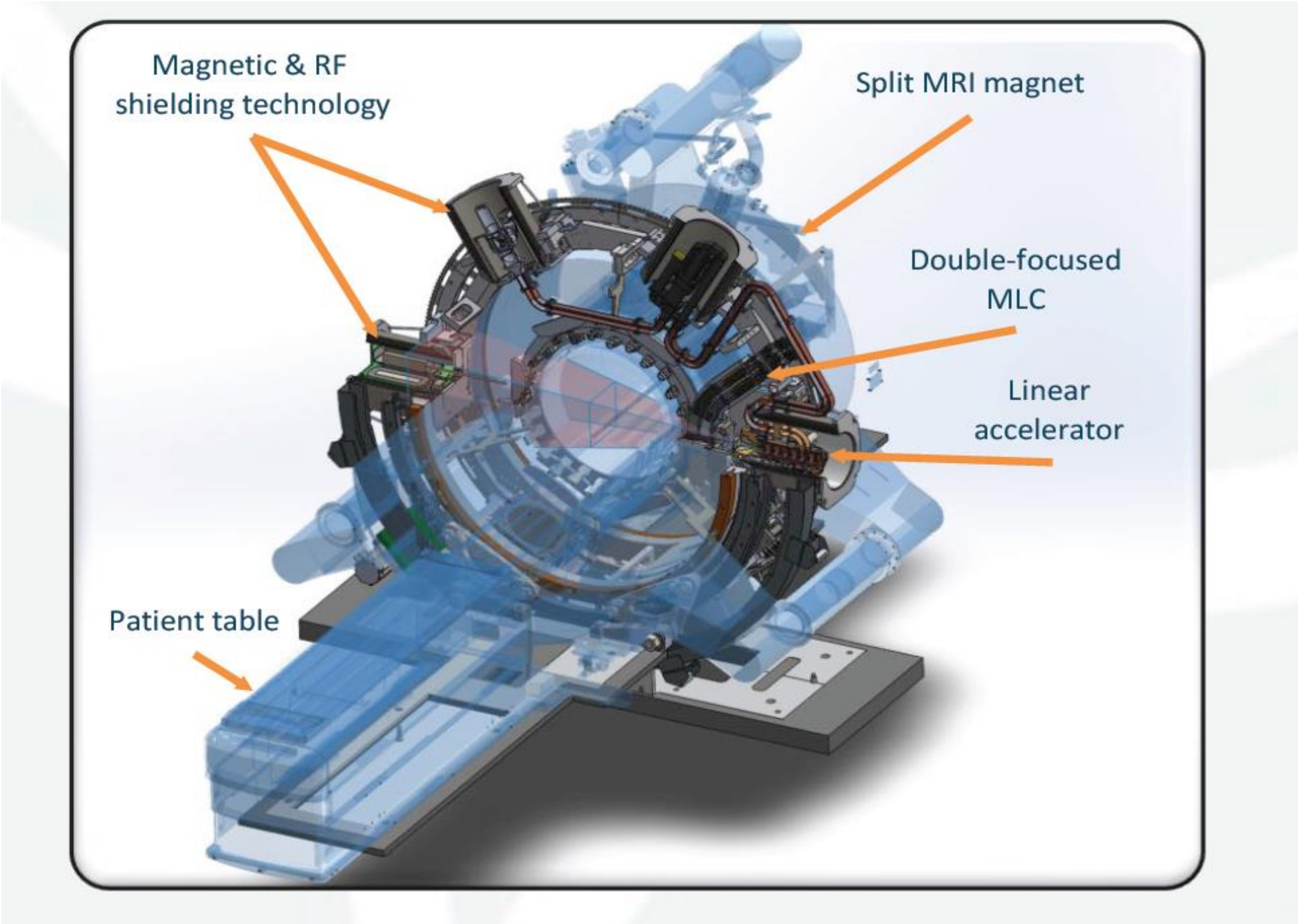
Disadvantages:

- Cobalt sources need to be replaced
- Low magnetic field, functional imaging capabilities probably limited

Current status:

- First patients treated in February 2014 at Washington University School of Medicine in St. Louis

Treatment Device: ViewRay MR Linac



From: Viewray Investor Presentation (September 2016) http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9NjQ2Njg0fENoaWxkSUQ9MzU0MDc5fFR5cGU9MQ==&t=1

Treatment Device: ViewRay MR Linac

MR Linac from ViewRay

- Low-field split coil 0.35 T MRI

- 50 cm field of view (70 cm bore)

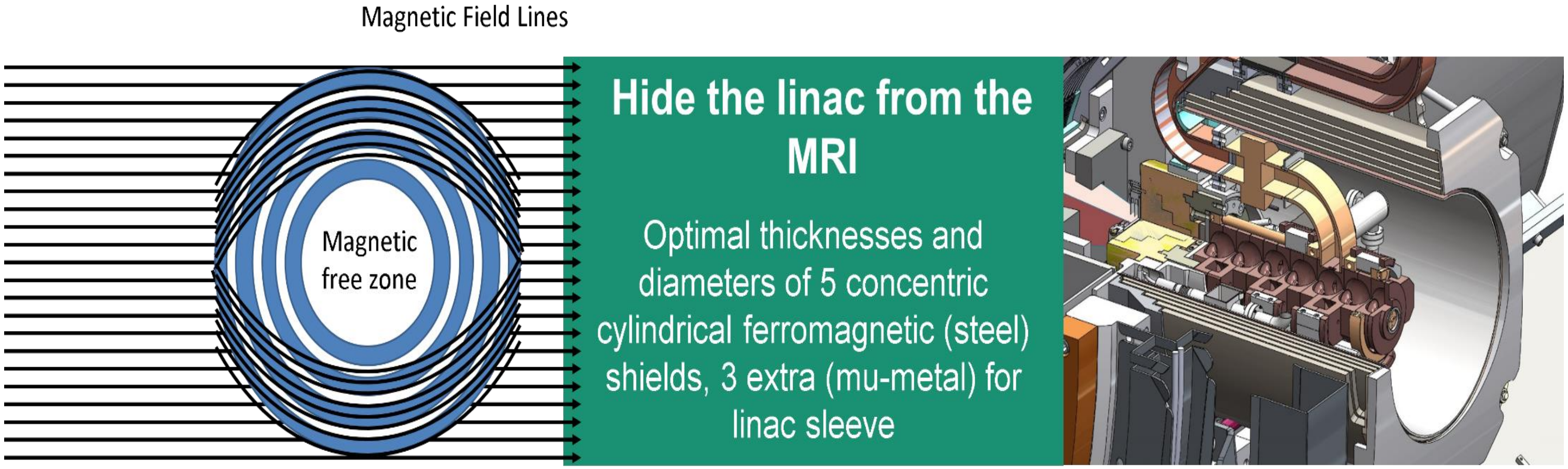
- 6 MV FFF linear accelerator (90 cm SAD)

- Double stacked MLC
  - 27.4x 24.1 cm^2 double focused MLC
  - Leaf width 8.3mm for each stack

- First patient treated at Henry Ford (Detroit) July 20th 2017

http://www.viewray.com/linac-system

Basic System Characteristics



- Strong magnetic fields would interfere with the operation of the linear accelerator if not properly shielded
- Can induce undesired Lorentz forces on moving charged particles (in the accelerator, magnetron, or in current carrying wires)
- Achieved by numerically solving Poisson's equation for the magnetic potential to optimize the shields.
- The magnetron, port circulator, and gun driver are able to operate in magnetic fields of < 100 Gauss
- The linear accelerator needs to have an electron path from the electron gun to near the target at less than <2 Gauss

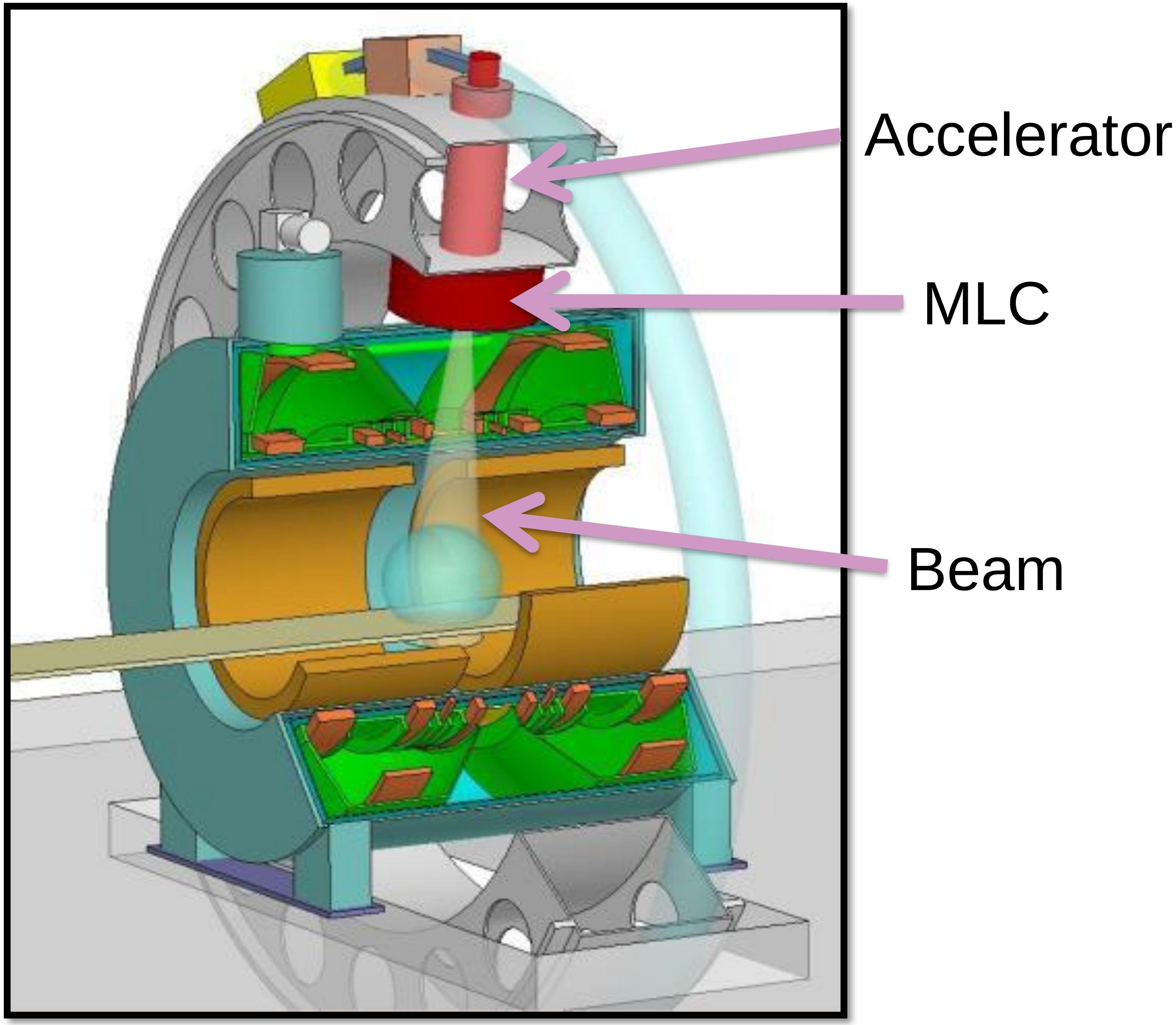
Slide content courtesy of Maria Bellon of ViewRay, Inc.

Basic System Characteristics

- Linacs produce radiofrequency emissions that can significantly degrade the quality of MRI images
- Shielding combines RF absorbing carbon fiber and RF reflecting copper materials for a robust shielding solution
- Surrounds the pulse transformer, magnetron, linear accelerator body, and gun driver components of the system

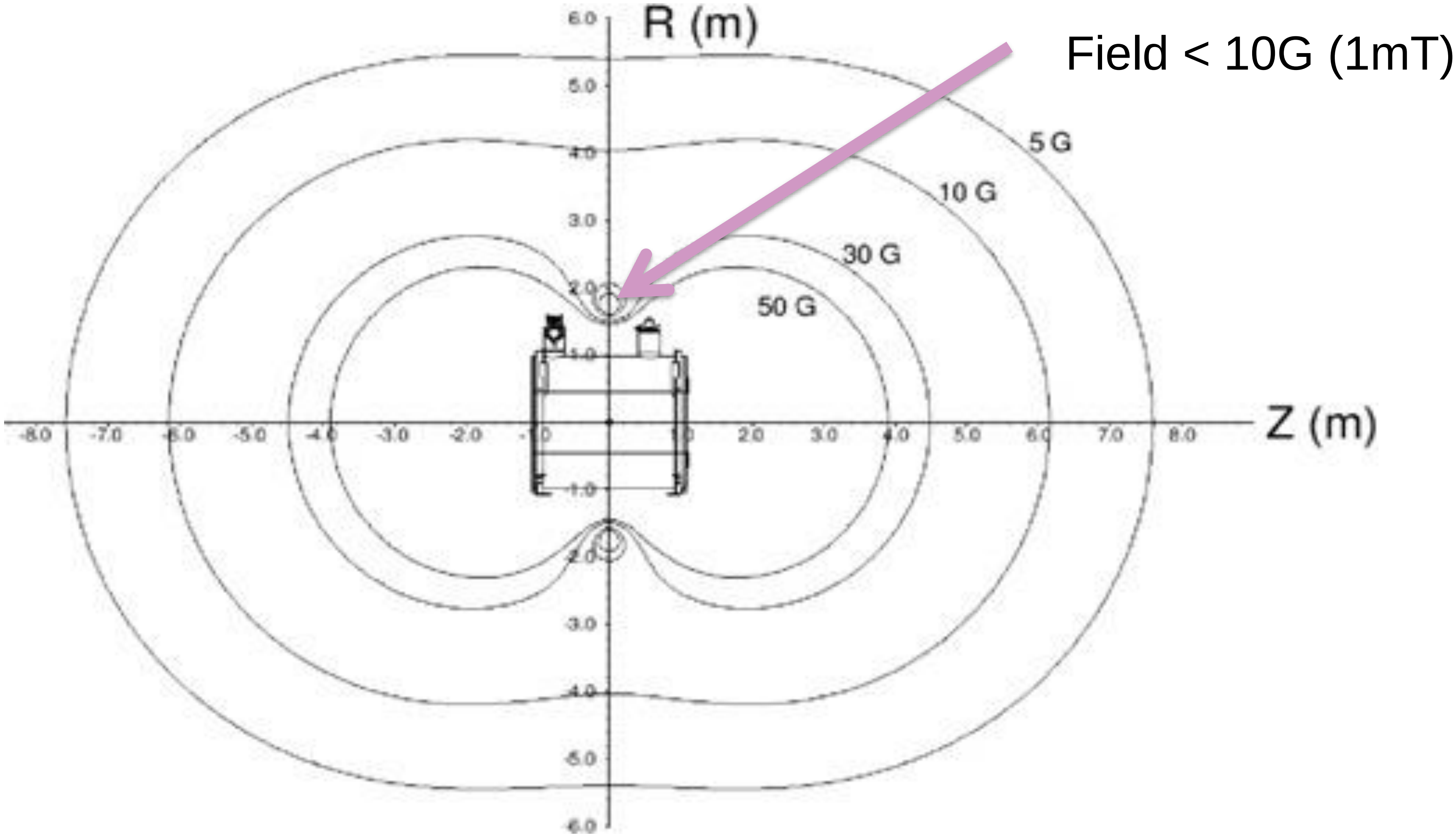
Slide content courtesy of Maria Bellon of ViewRay, Inc.

Treatment Device: Utrecht MR-Linac concept



Courtesy of Bas Raaymakers

Treatment Device: Utrecht MR-Linac concept



From Raaymakers *et al.* PMB 54:N229-N237 (2009)

MR Linac

Elekta Unity

Elekta Unity

7MV FFF Linac

1.5T MRI
70cm bore opening

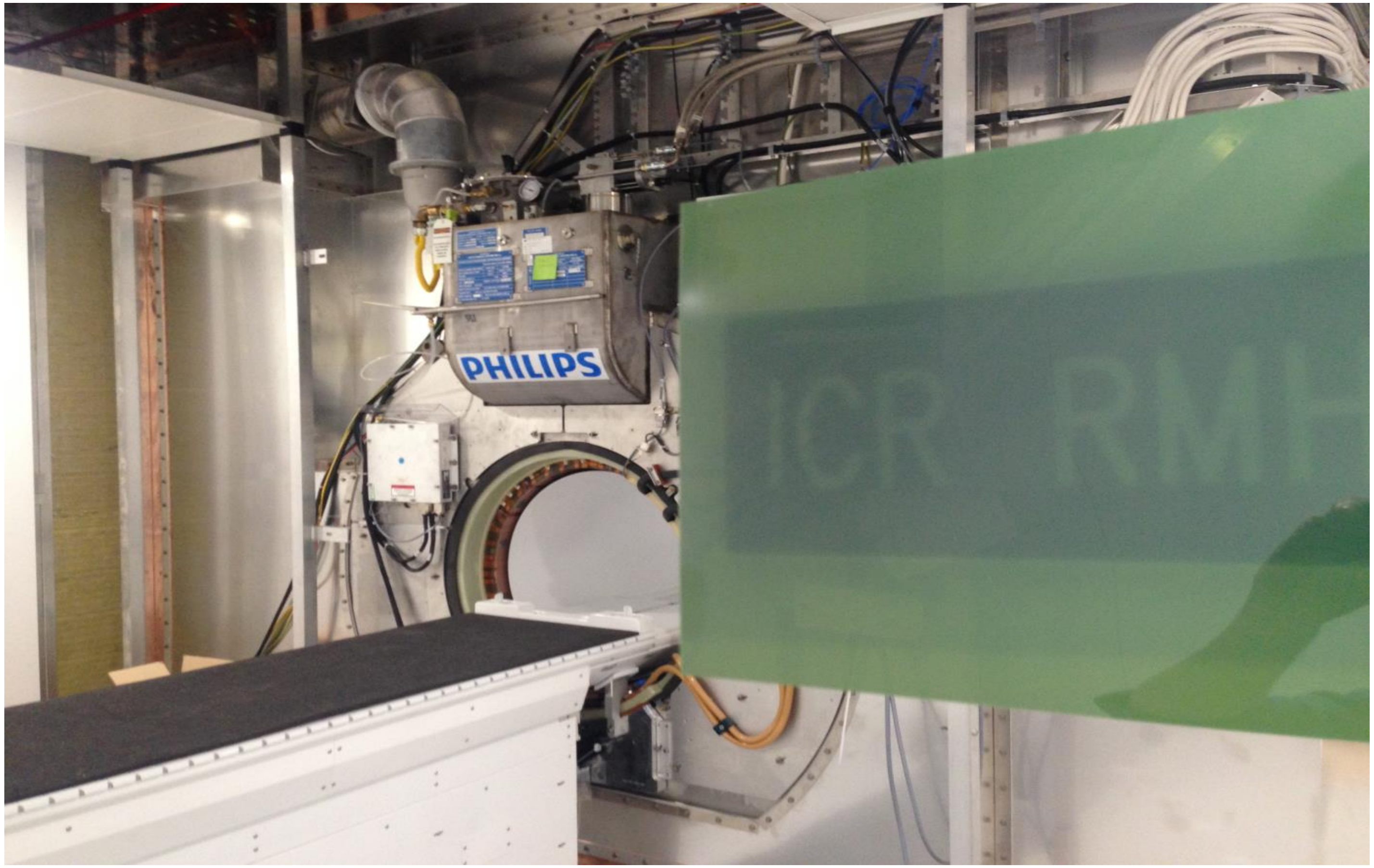
In-line linac
143.5cm SAD
57.4cm x 22cm field size
0.71cm leaf width @iso
On-board EPID

Monaco TPS


NEW
IDEAS DEVELOP
OUR REALITY

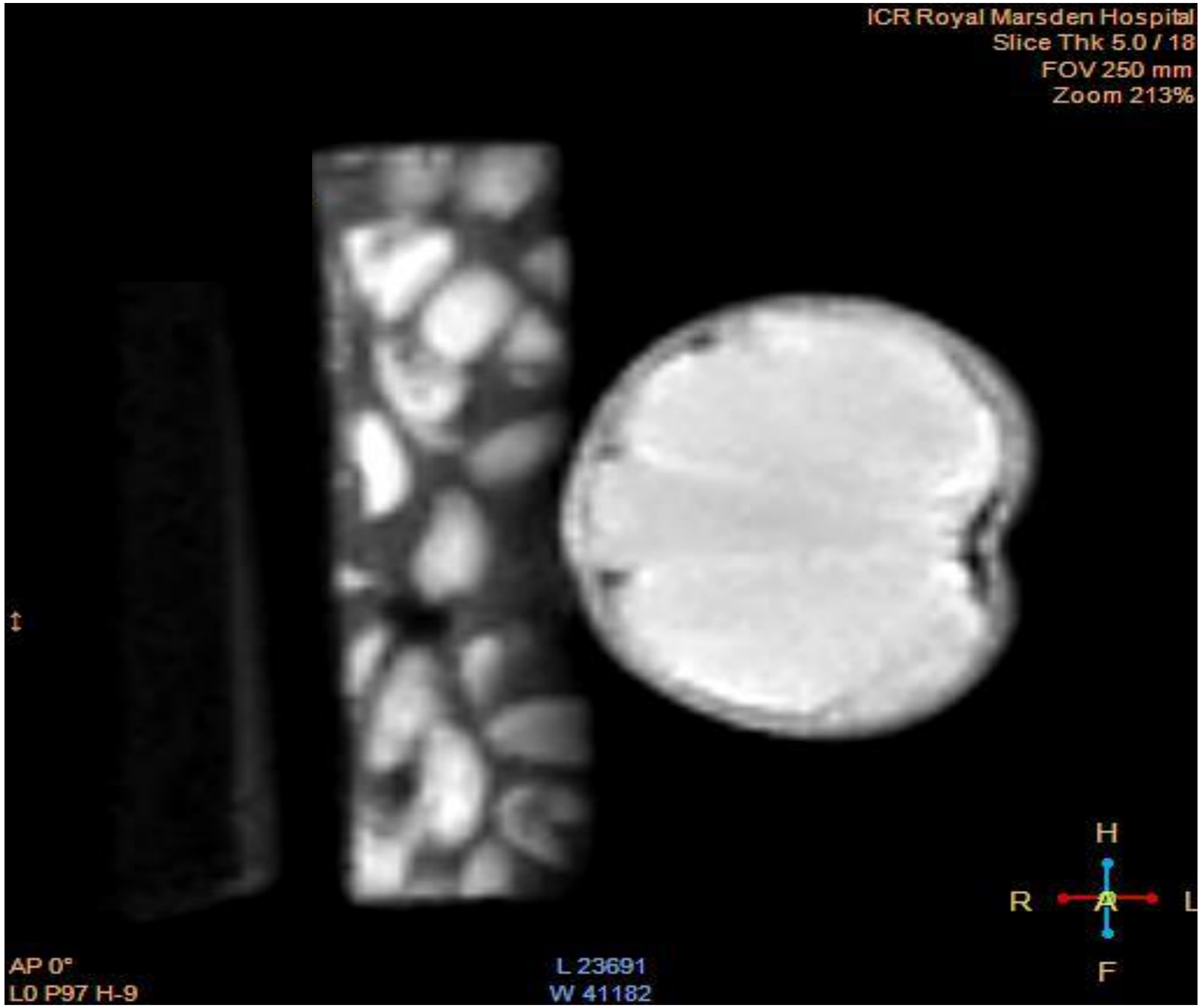
Elekta Unity @ ICR/RMH

MR Linac: First beam

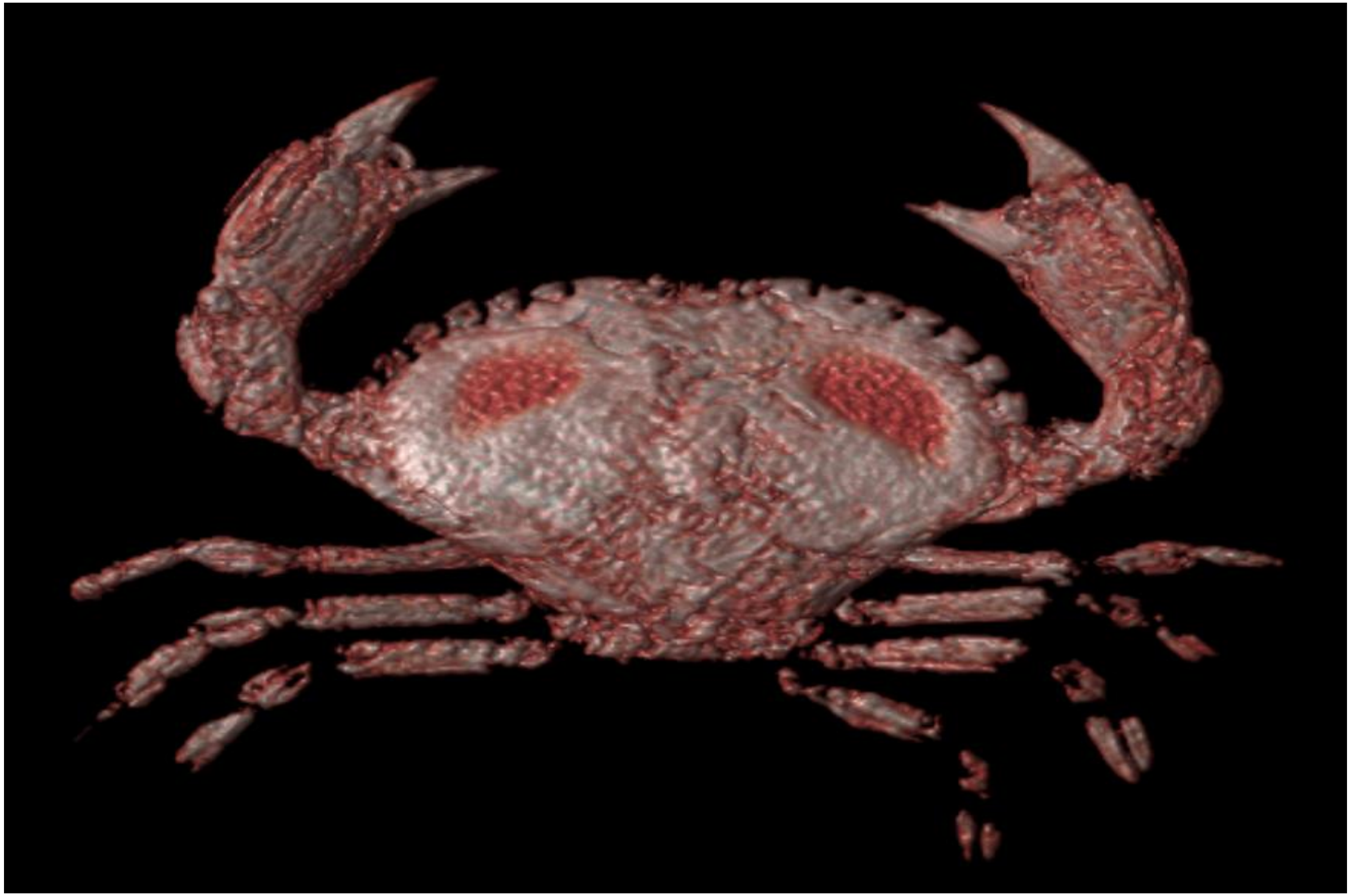


03/10/2016

MR Linac: First MR Image



MR First cancer image at RMH/ICR ….



Elekta Unity

University Medical Center
Utrecht

First patient treatment 20^{th} May 2017

From: http://medicalphysicsweb.org/cws/article/research/68865

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Treatment Device: Elekta Unity

Advantages compared to other approaches:

- High field MR scanner
- Large treatment field

Disadvantages:

- Radiation through the Cryostat

Current status:

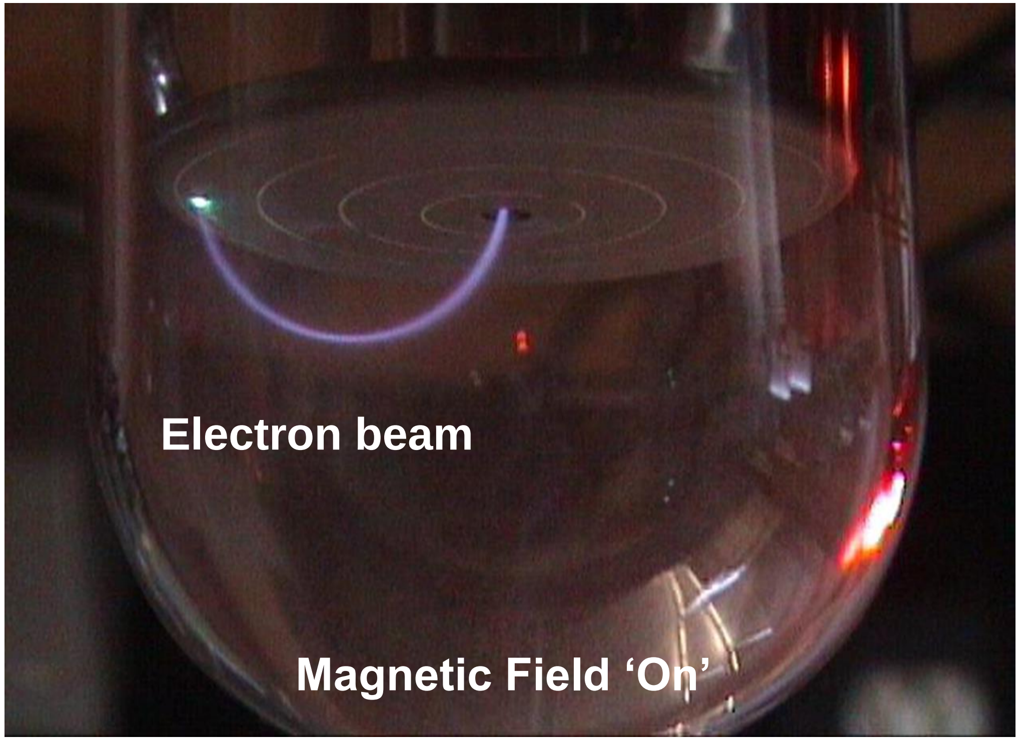
- 9 Unity systems installed
- First in man study completed at UMC Utrecht

Challenges

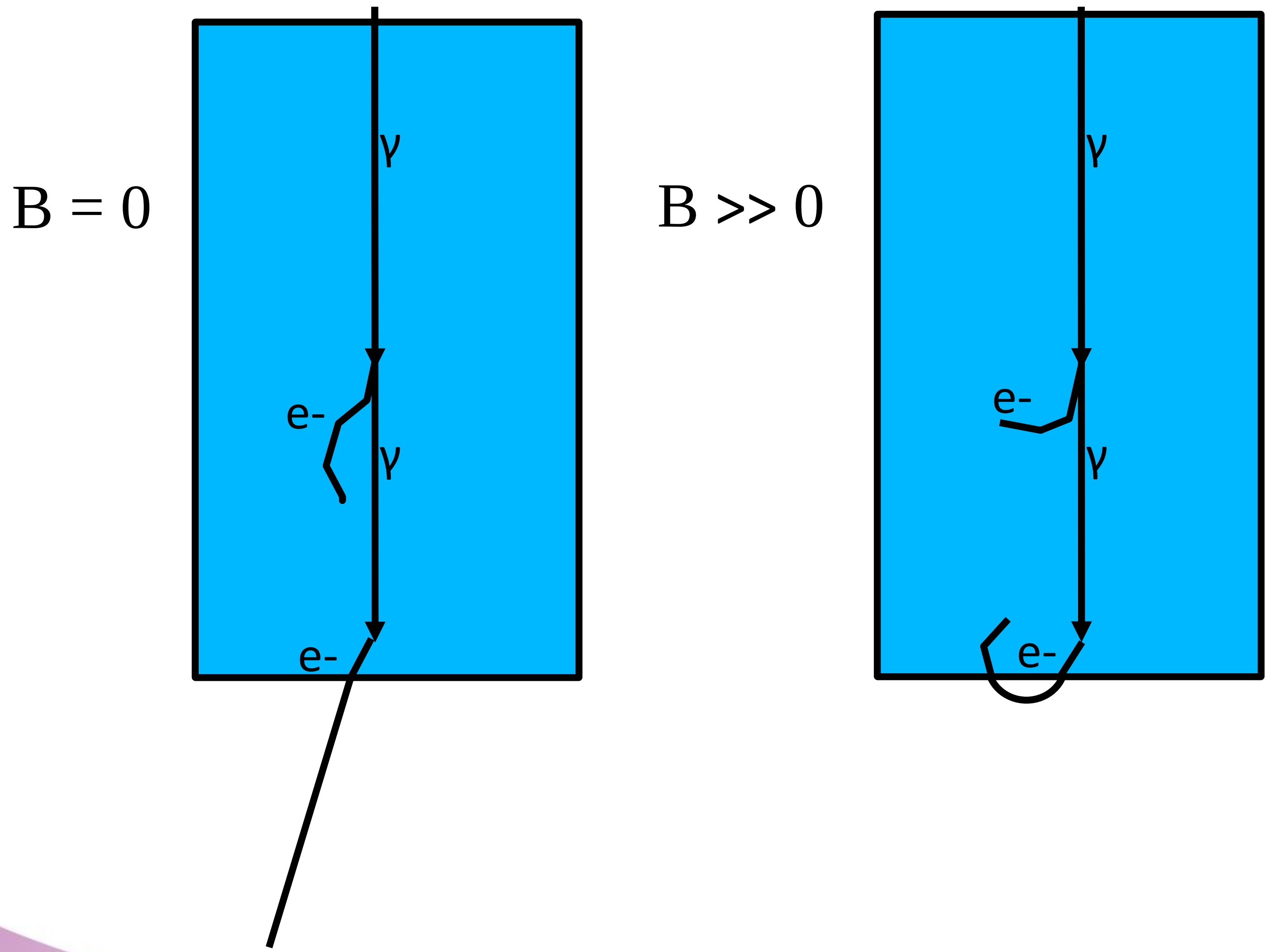
- Dosimetry
- Treatment planning

Development of Accurate and Reliable Dosimetry

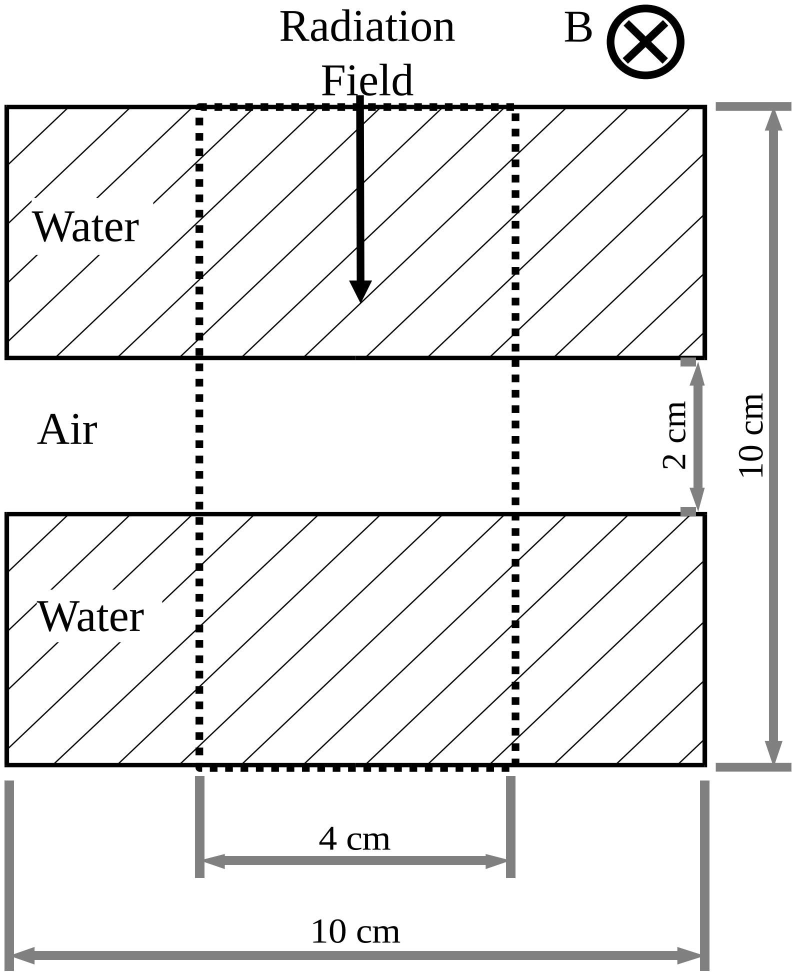
Electrons in a magnetic field

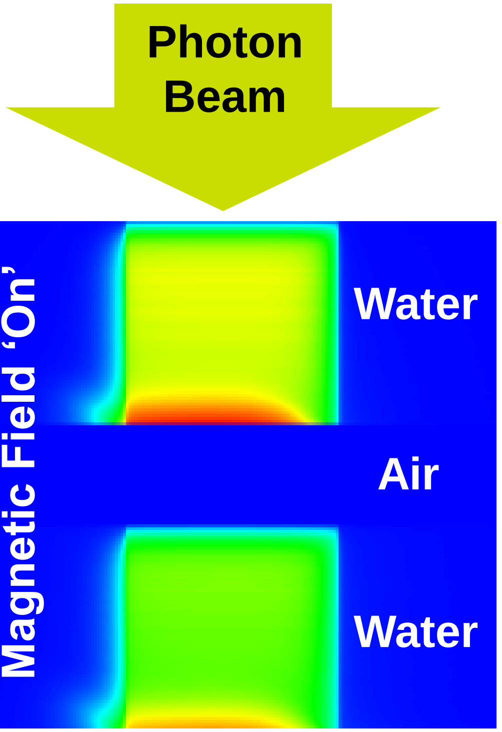


Electron return effect



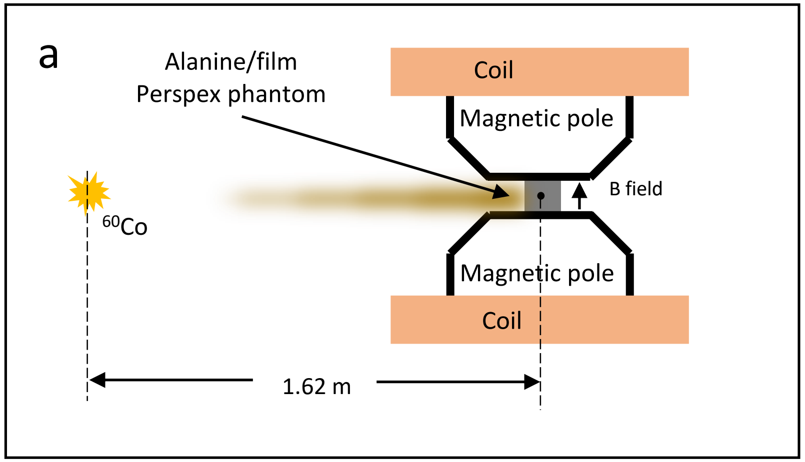
ERE at air gap

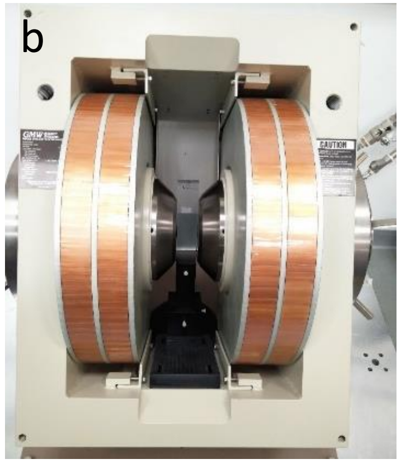


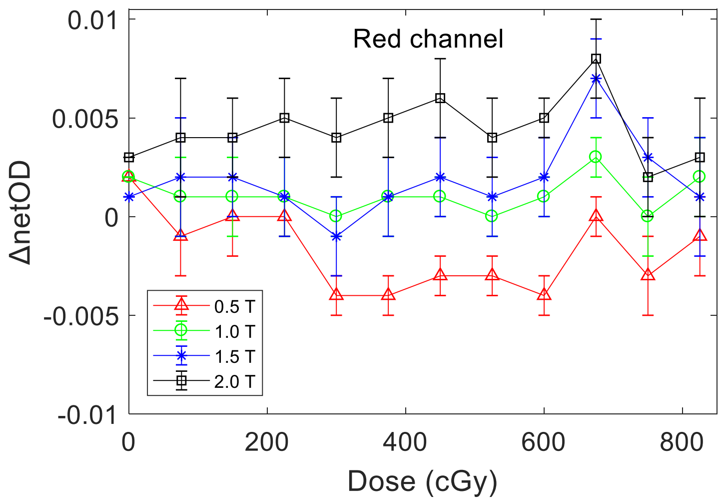


Impact of electron 'bending' on dosimetry

Dosimetry in a magnetic field: EBT3 films



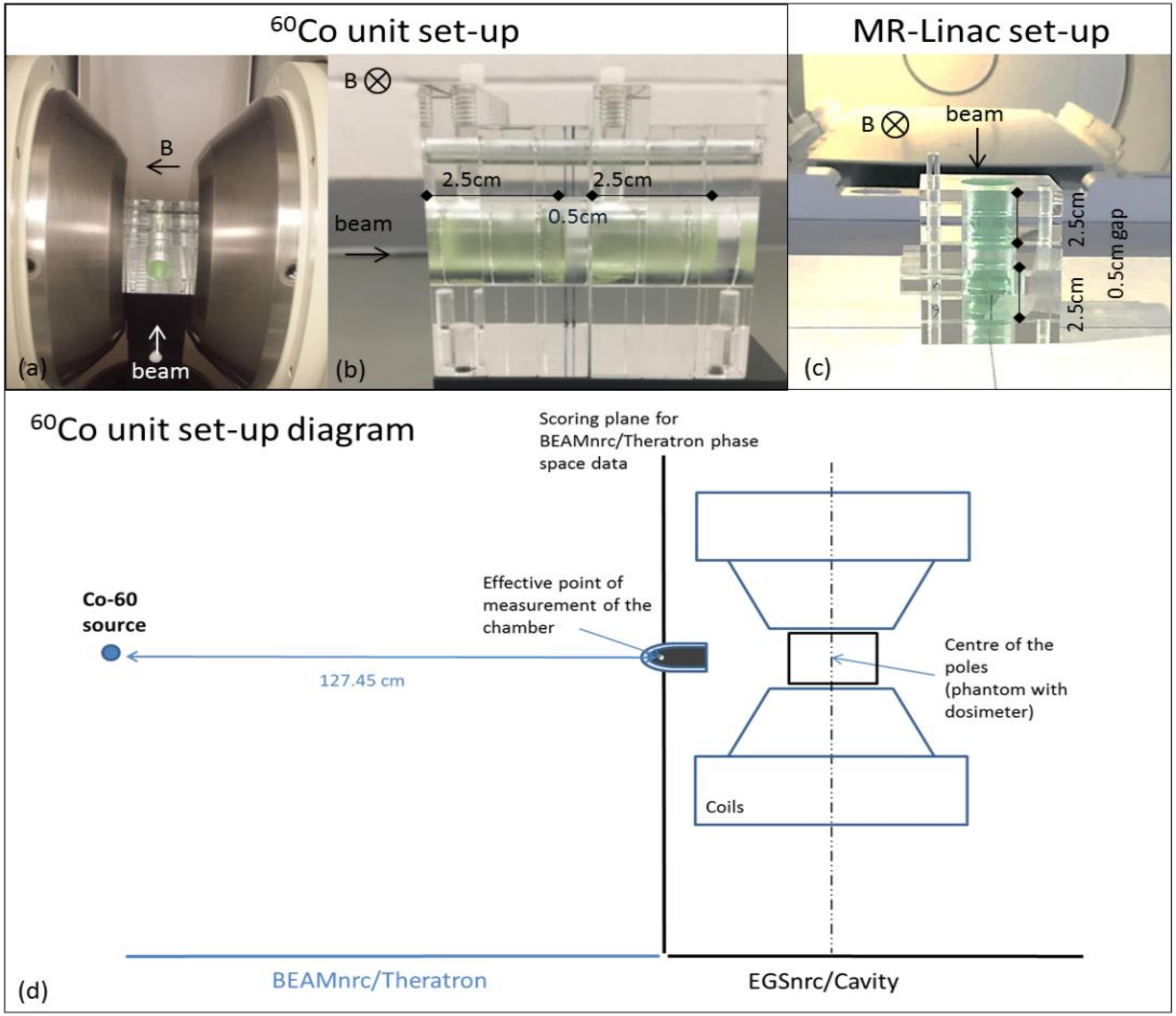




Ilias Billas[1,3], Hugo Bouchard[2], Uwe Oelfke[3] and Simon Duane[1]

[1]Metrology in Medical Physics, National Physical Laboratory, Teddington, UK
[2]Université de Montréal, Département de physique, Montréal, Canada.
[3]Joint Department of Physics, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK

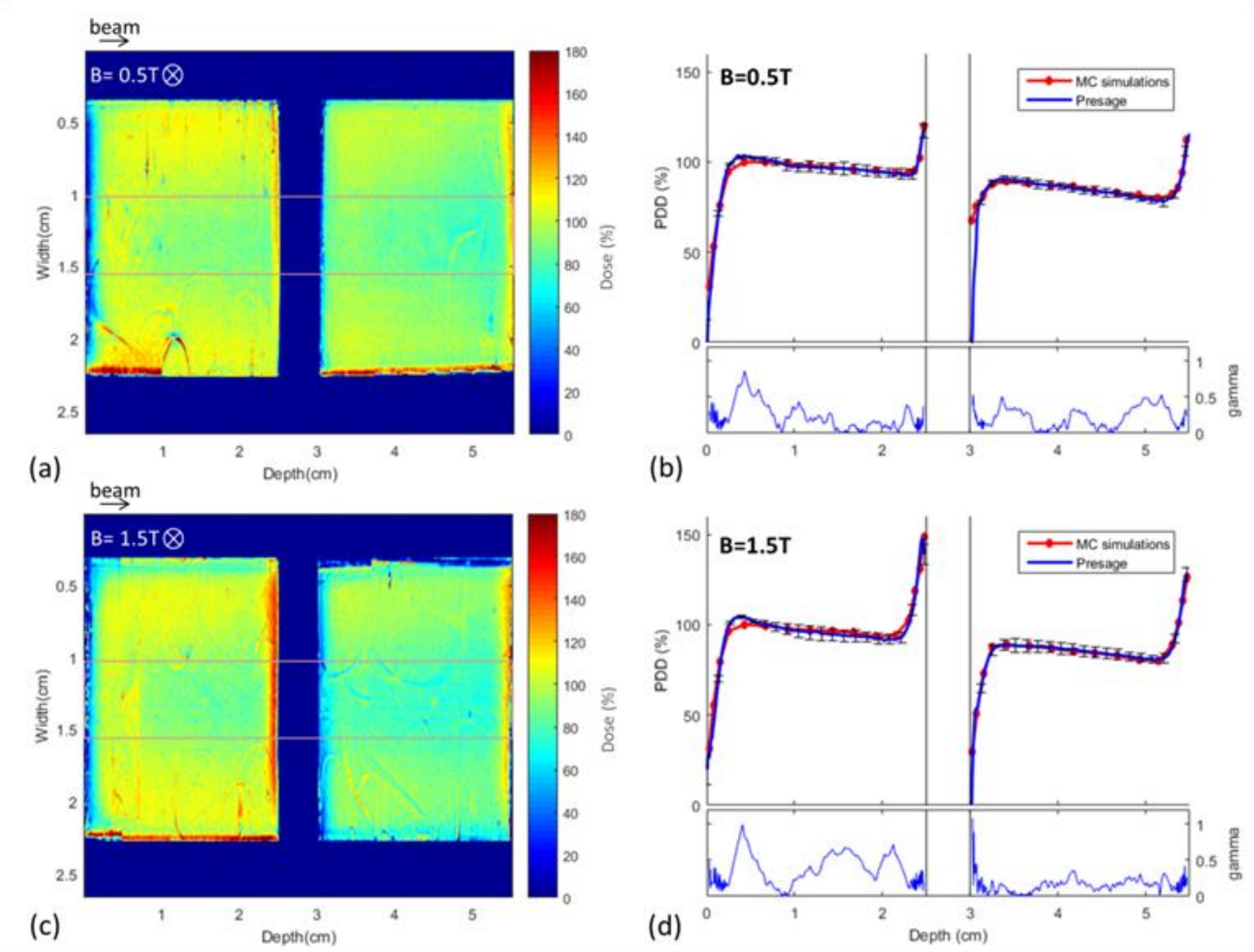
Dosimetry in a magnetic field: Presage Gels



Technical Note:Investigating the effect of magnetic field on dose distributions at dosimeter-air interfaces using PRESAGE® 3D dosimeter and Monte Carlo simulations

Filipa Costa[1], Simon Doran[2], Ian M Hanson[1], Simeon Nill[1], Ilias Billas[3], David Shipley[3], Simon Duane[3], John Adamovics[4] and Uwe Oelfke[1]

Dosimetry in a magnetic field: Presage Gels



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Challenges: Dosimetry in a magnetic field

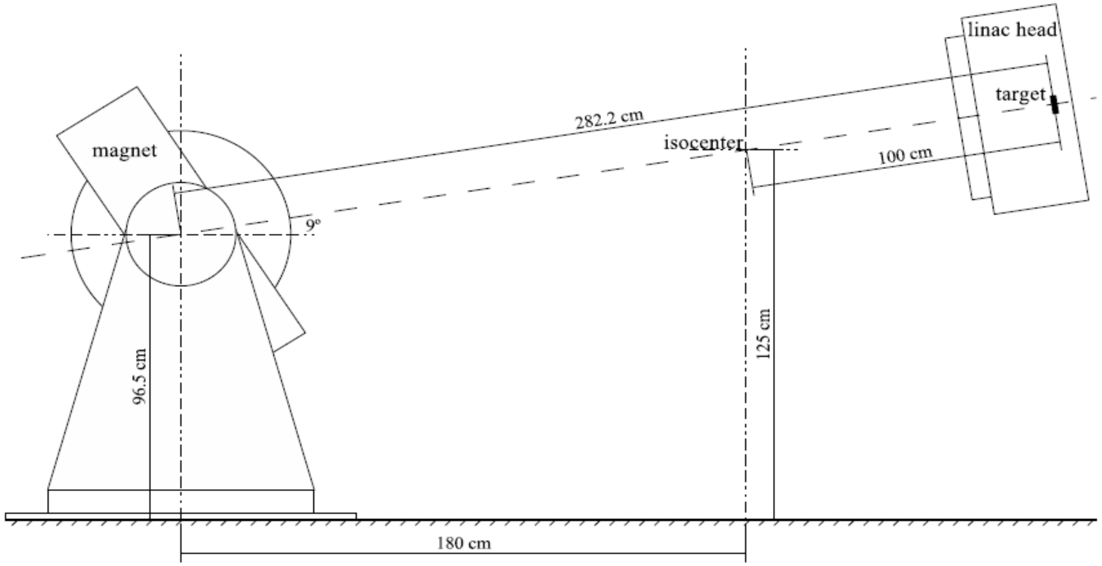


Figure 1. 1.25 T electro magnet positioned next to the Elekta SLi25 linear accelerator.

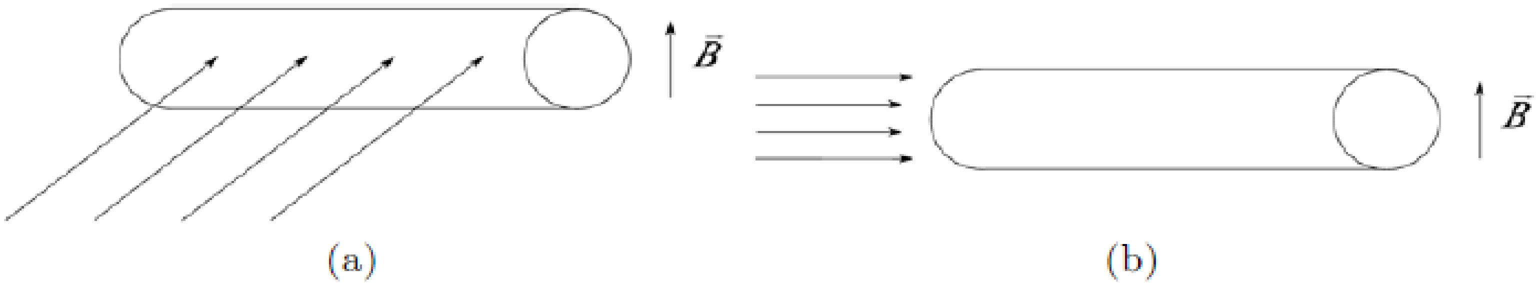
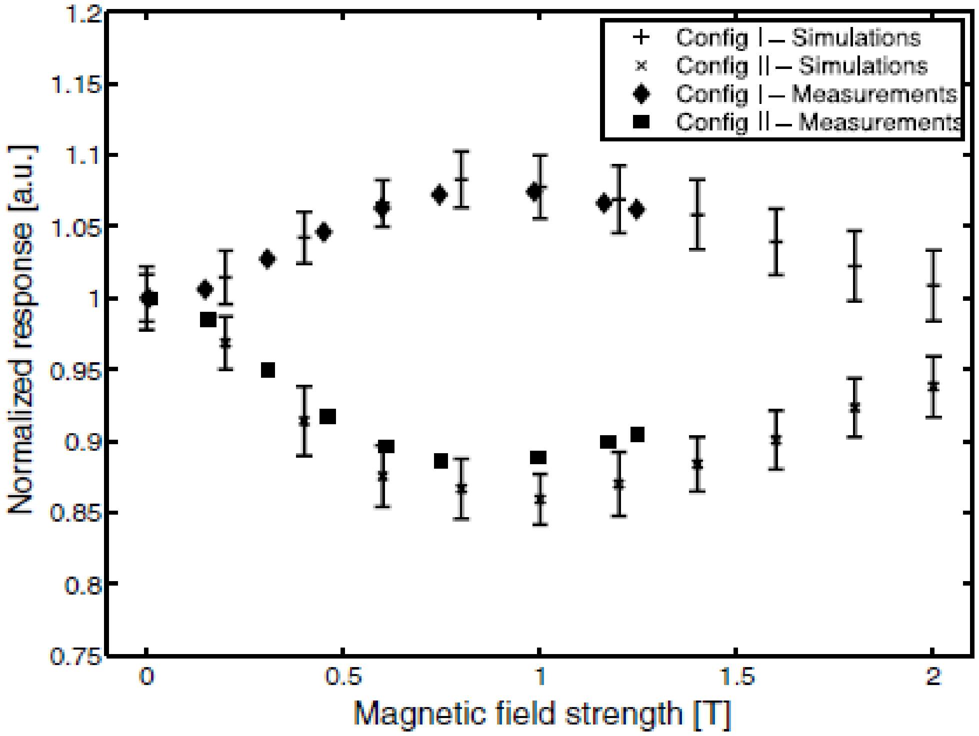


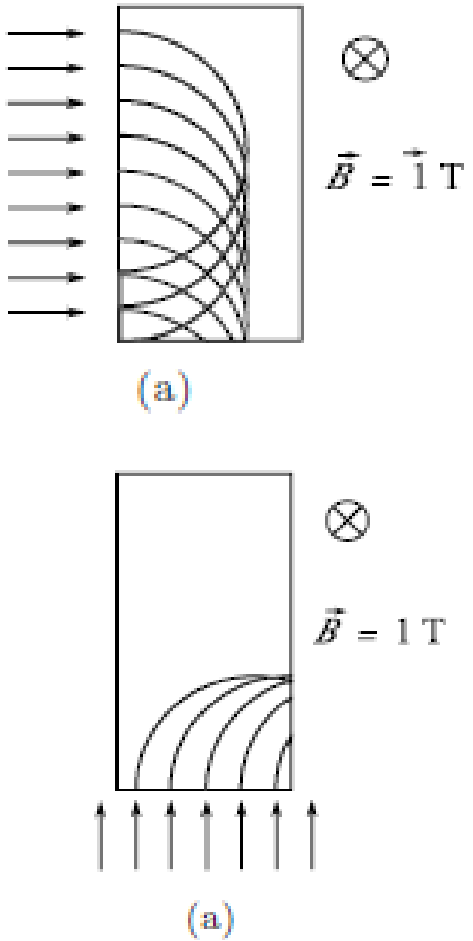
Figure 2. Schematic representation of the geometry set-up of the ionization chamber with respect to the external magnetic field and radiation beam. (a) Configuration I: $B \perp$ beam $\perp$ chamber and (b) configuration II: $B \perp$ beam $\parallel$ chamber.

From Meijsing *et al.* PMB 54:2993-3002 (2009)

Challenges: Dosimetry in a magnetic field



(b)



1MeV electron tracks

Chamber orientation has an impact on the reading

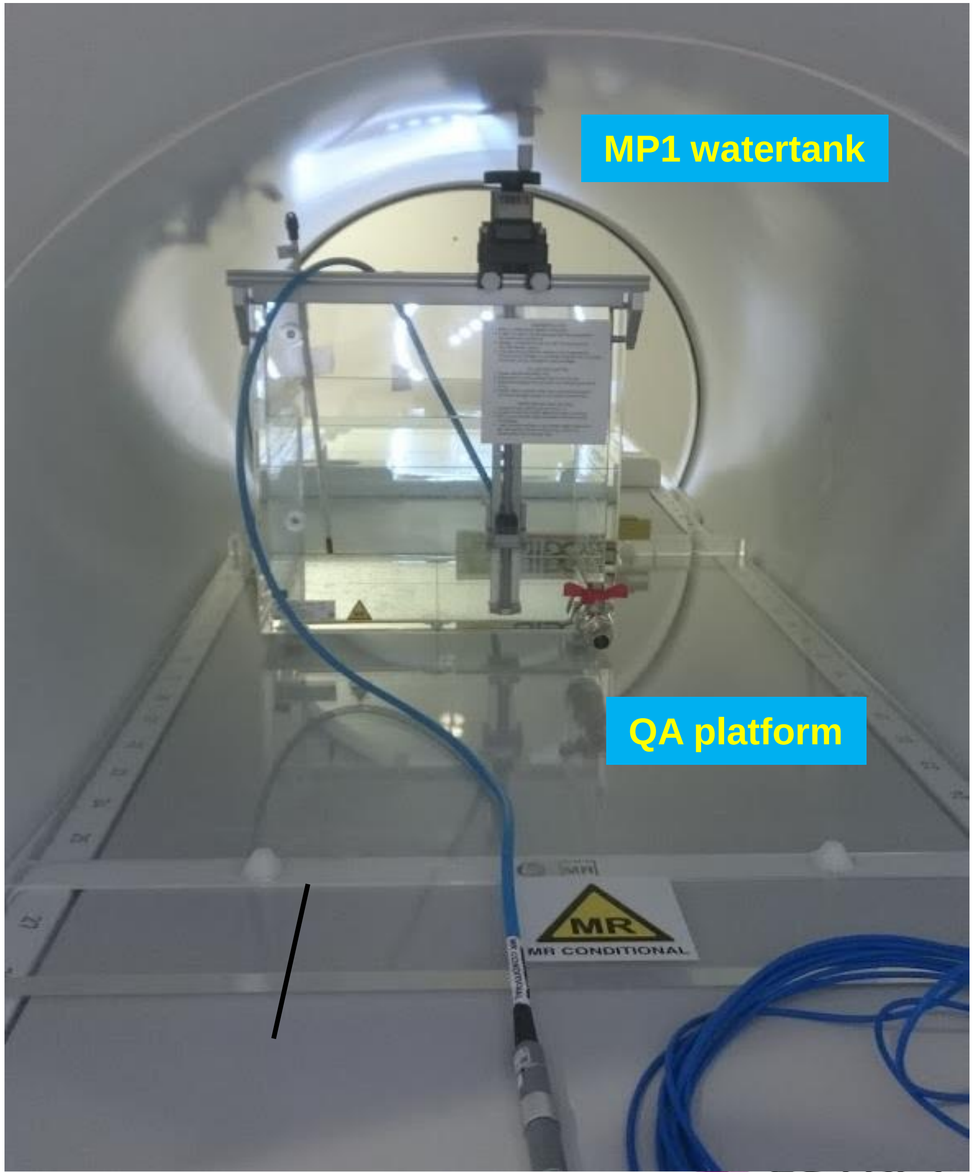
From Meijsing *et al.* PMB 54:2993-3002 (2009)

Reference Dosimetry

- Don't use solid water phantoms!!!
- Use chamber with known correction factor

$$D_{w,Q}^{B} = M_{Q}^{B}\, k_{Q}^{B}\, k_{Q,Q_0}\, N_{D,w,Q_0}$$

- Our reference conditions:
  - d = 10cm
  - Gantry 90 degree
  - SSD = 133.5cm
  - Water proof farmer chamber



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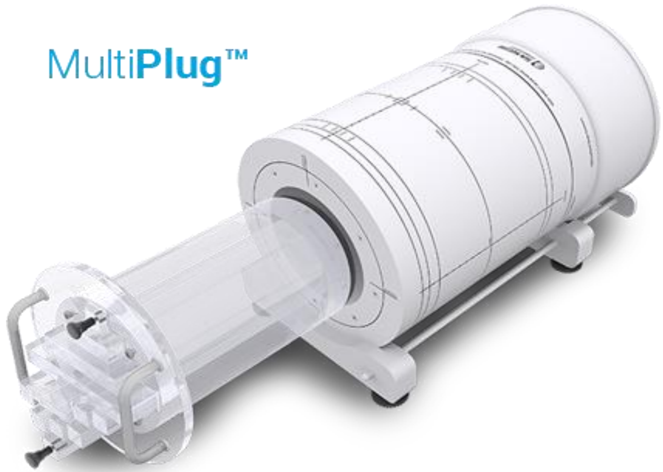
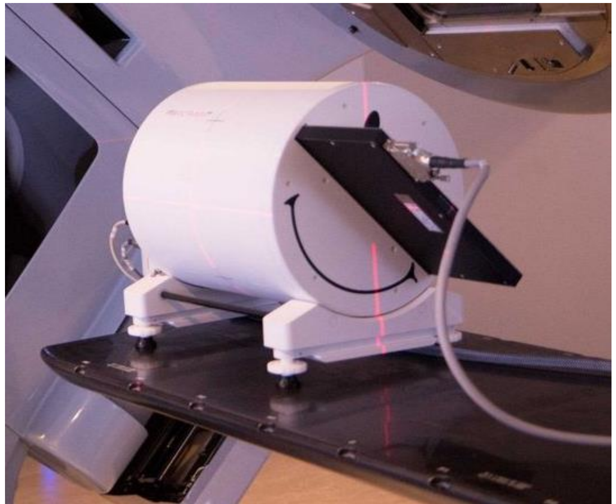
MR Compatible dosimetry devices

- Machine QA

sunnuclear.com
ptw.com

- Patient QA phantoms





Source: scandidos.com

sunnuclear.com

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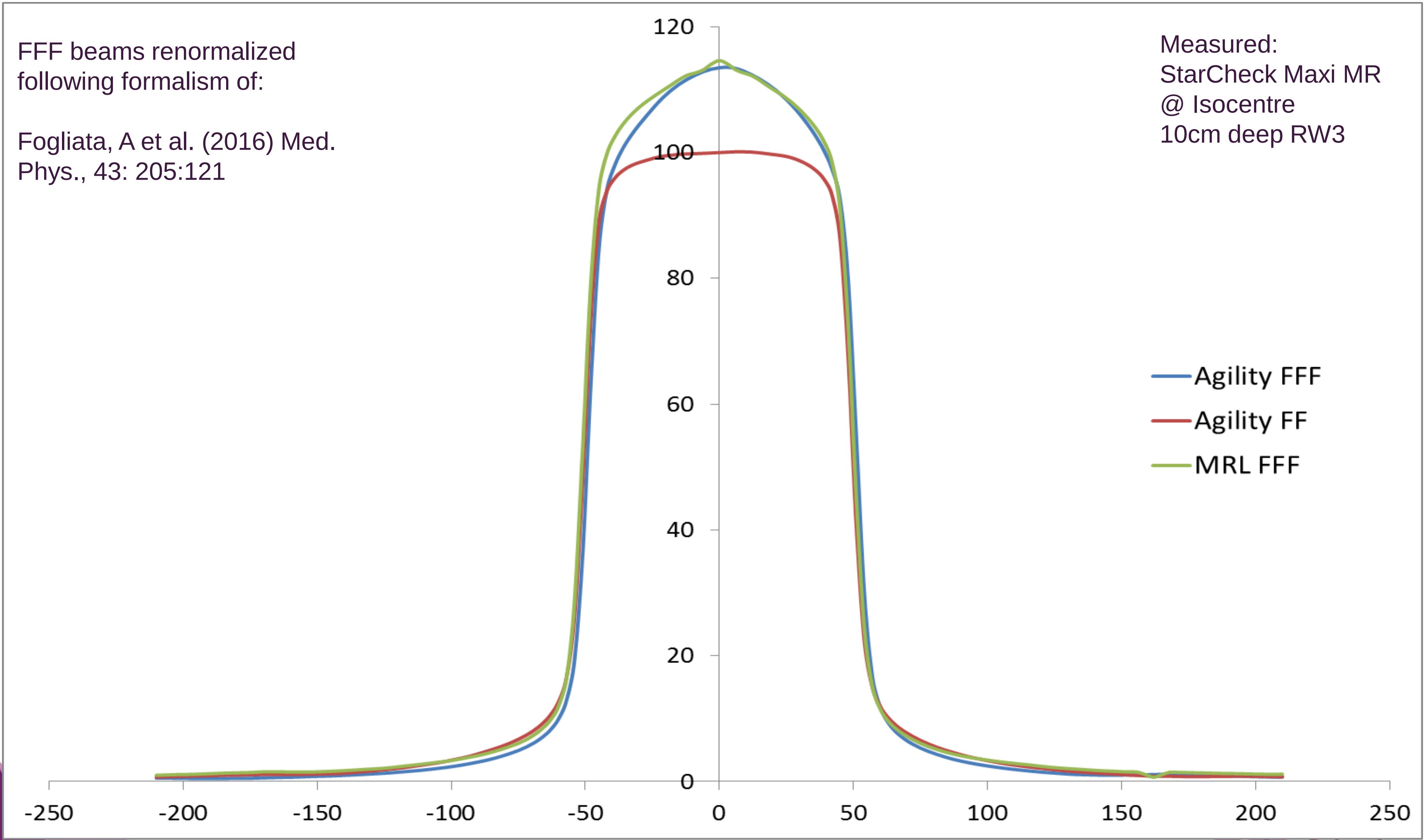
Elekta Unity: Profile – Left / Right



School

Elekta Unity: Penumbra in water (preliminary results)

FFF beams renormalized following formalism of:

Fogliata, A et al. (2016) Med. Phys., 43: 205:121

Measured:
StarCheck Maxi MR
@ Isocentre
10cm deep RW3

	L (mm)	R (mm)	S (mm)	I (mm)
Agility FF	8.7	8.6	9.2	9.0
Agility FFF	8.2	8.4	8.3	8.3
MRL FFF	***7.9***	***8.5***	***8.4***	***8.7***

Penumbra width defined as distance from D80 to D20

Challenges

- Dosimetry
- Treatment planning

Point spread kernels as a function of the magnetic field strength

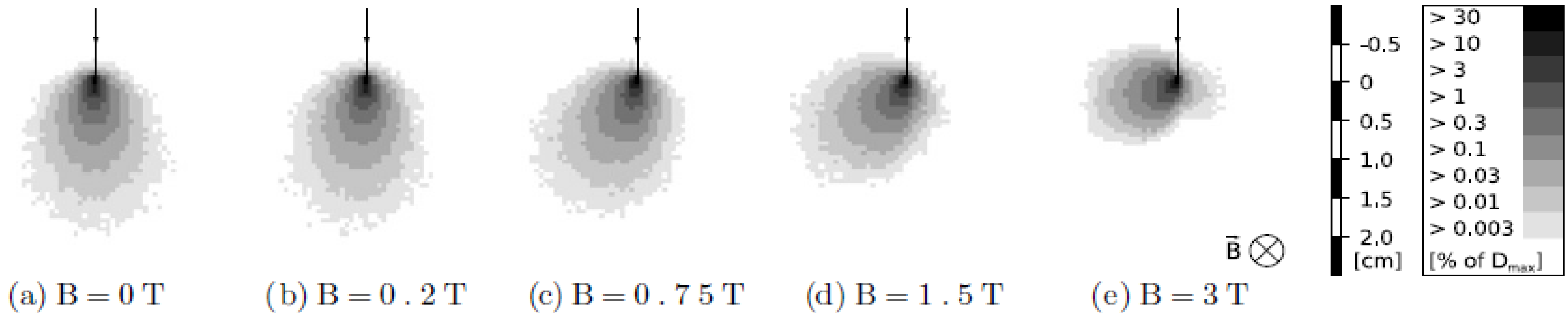


Figure 2. Monte Carlo calculated pointspread kernels for secondary electrons, depending on the magnetic field strength *B*. Logarithmic grey value scaling is used. Primary photons are simulated with a realistic 6 MV linear accelerator energy spectrum.

From Raaymakers *et al.* PMB 53:909-923(2008)

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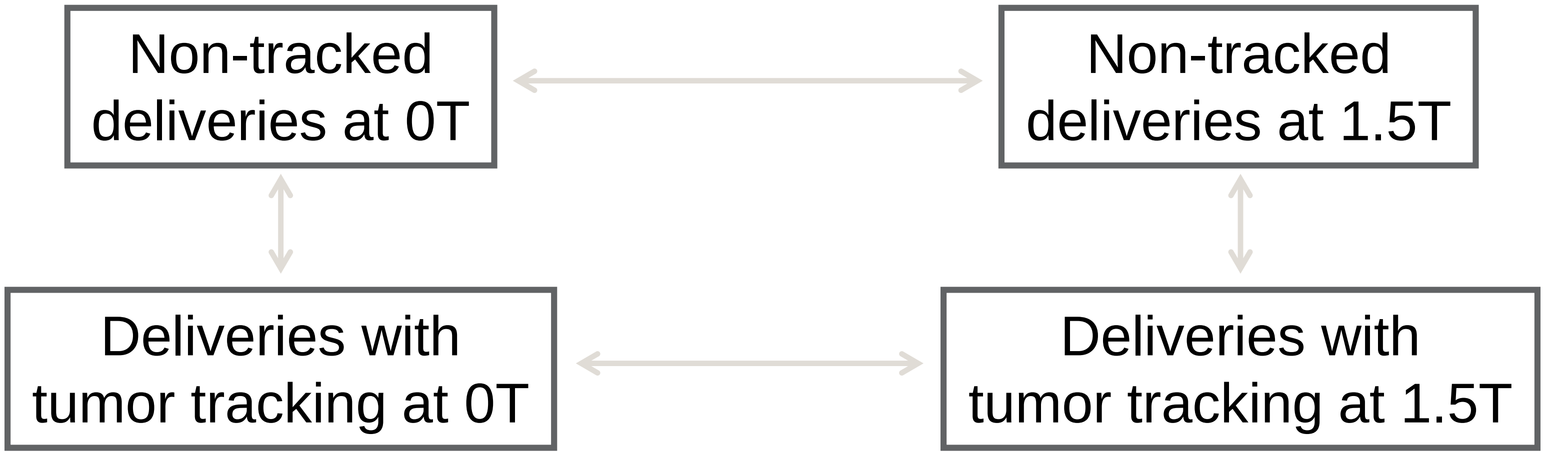
Treatment planning studies: Lung

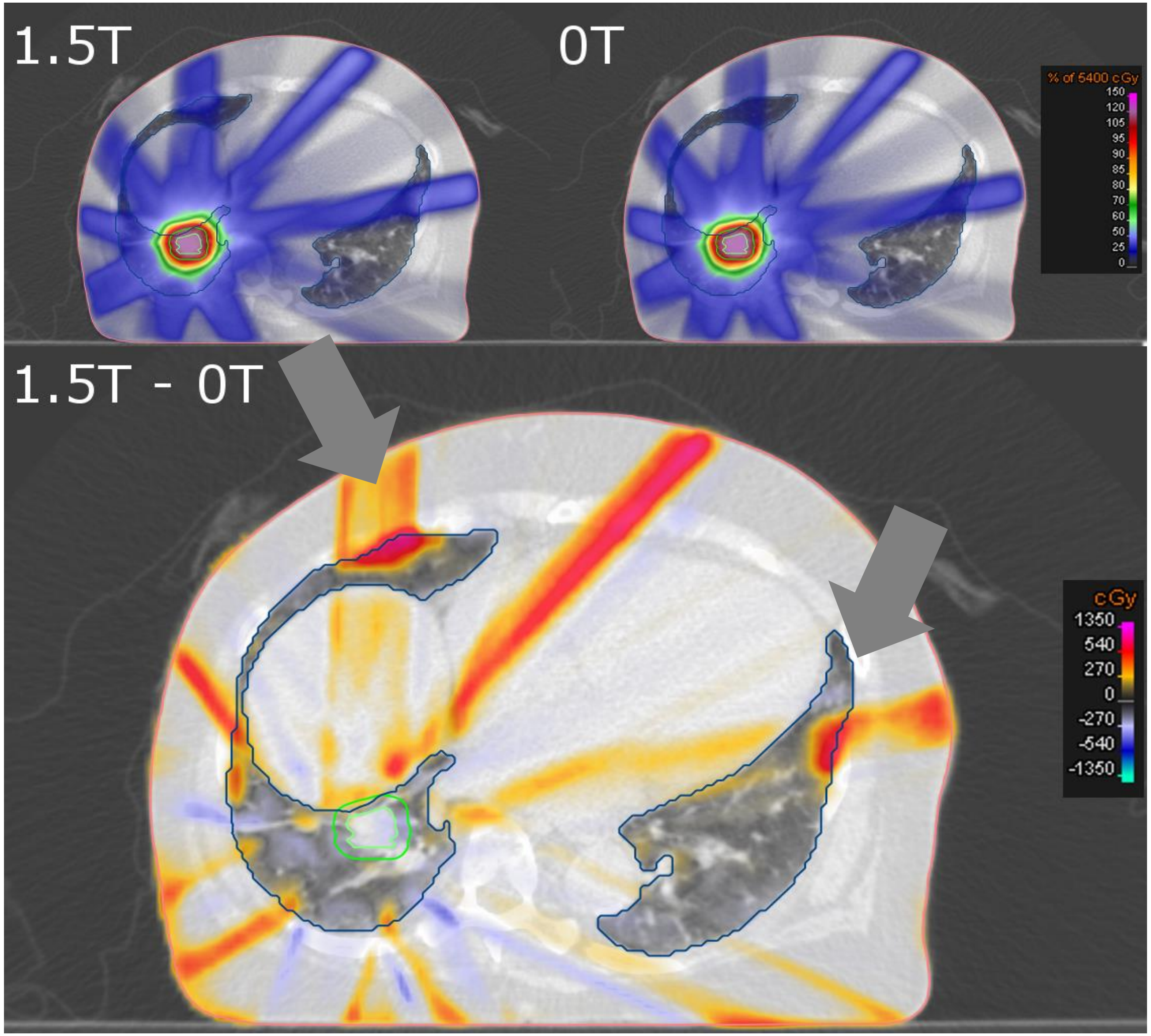
- Planning study using 4DCT scans of 9 stage I NSCLC patients
- Design of 4 SBRT treatment plans per patient:



- Simulation of dose delivery to all 10 4DCT phases
- Deformable dose accumulation
- Comparison of differences in several dose-volume metrics using paired t-test

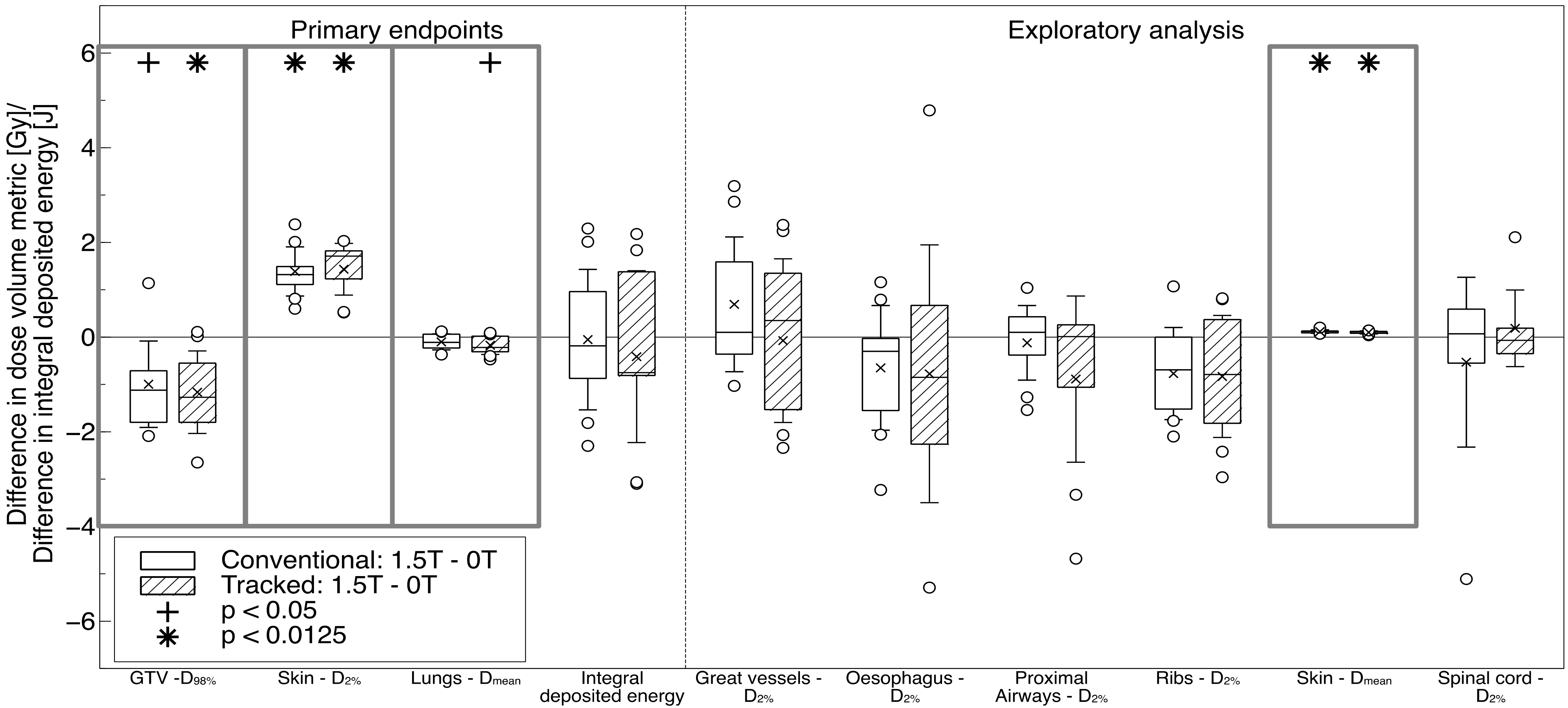
Treatment planning: NSCLC Stage 1

- 9 beam IMRT



From Menten *et al.* Radiother Oncol. 119:461-6 (2016).

Results: effect of 1.5T magnetic field



- Slight decrease in dose to the tumor
- Increase in dose at air-tissue interfaces
- All cases fulfilled RTOG 1021 planning constraints

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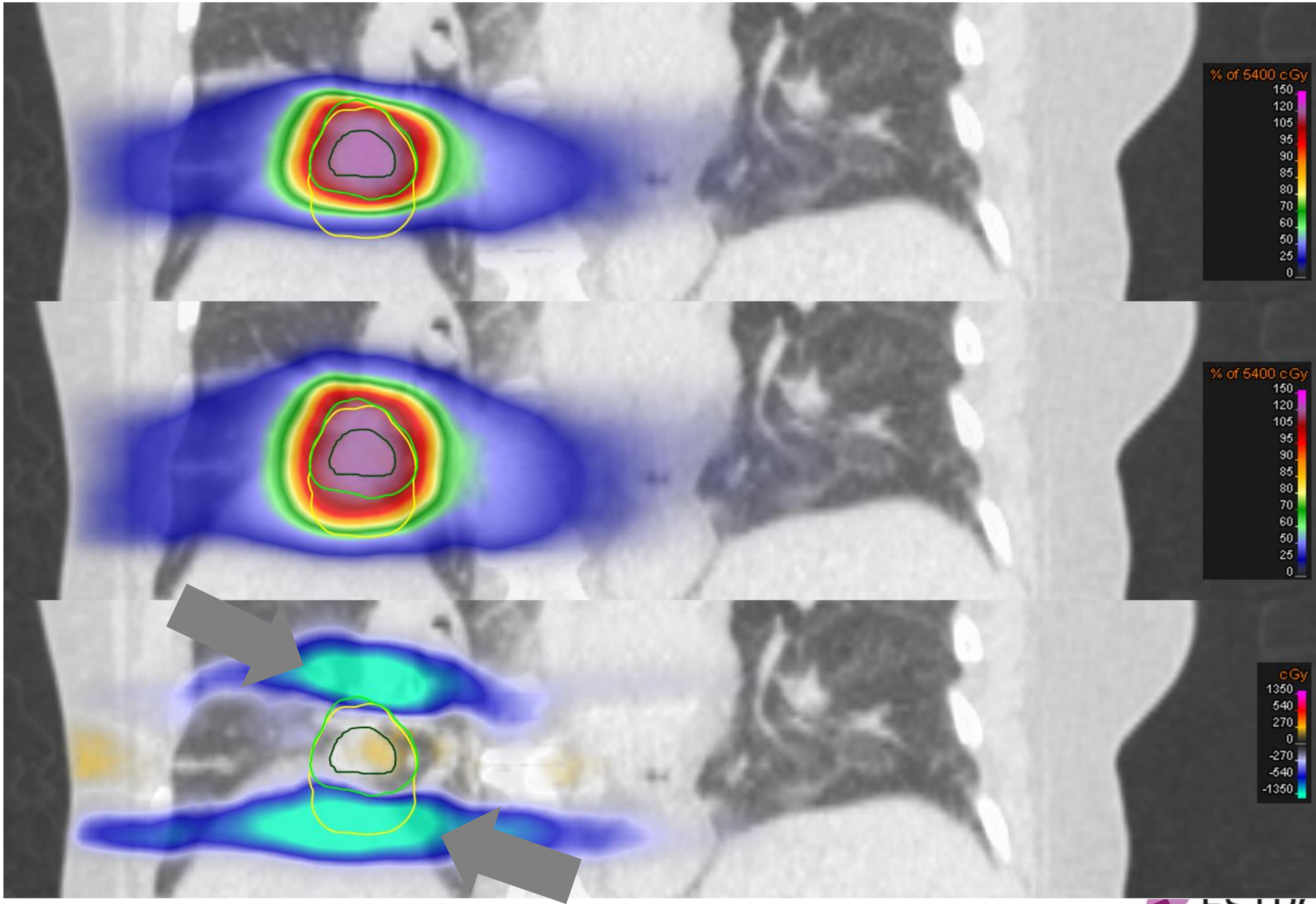
Results: effect of MLC tumor tracking

Tracked

Conventional

Tracked-Conventional



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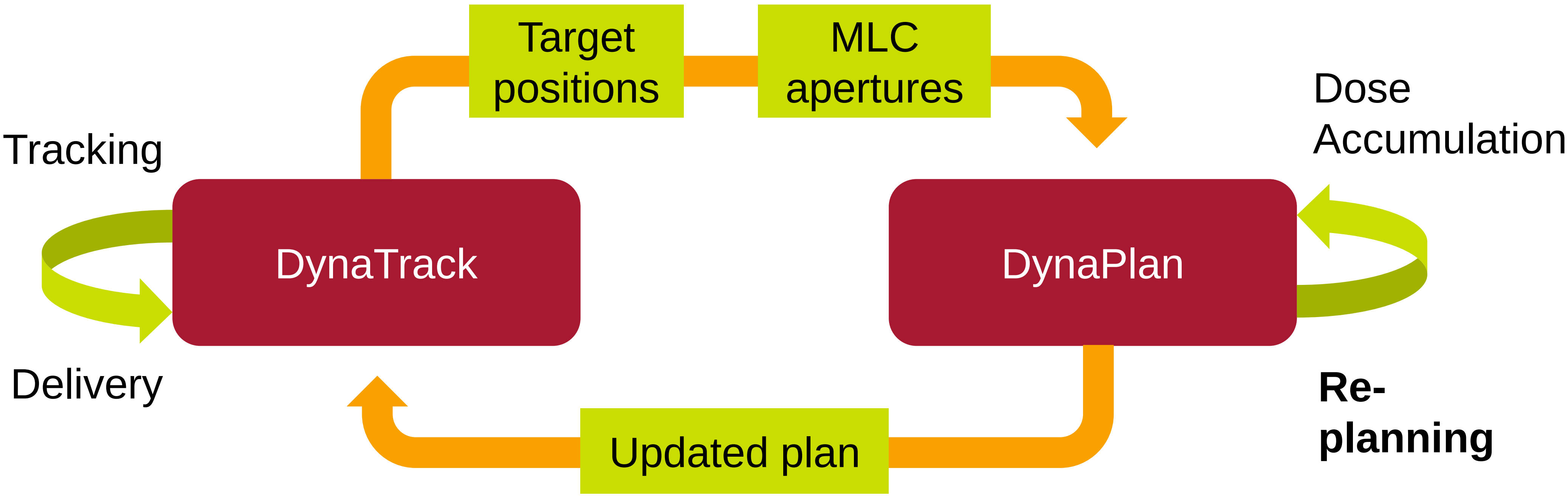
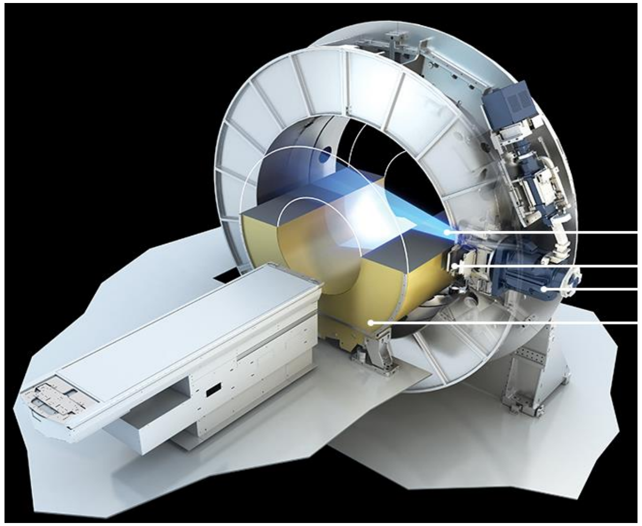
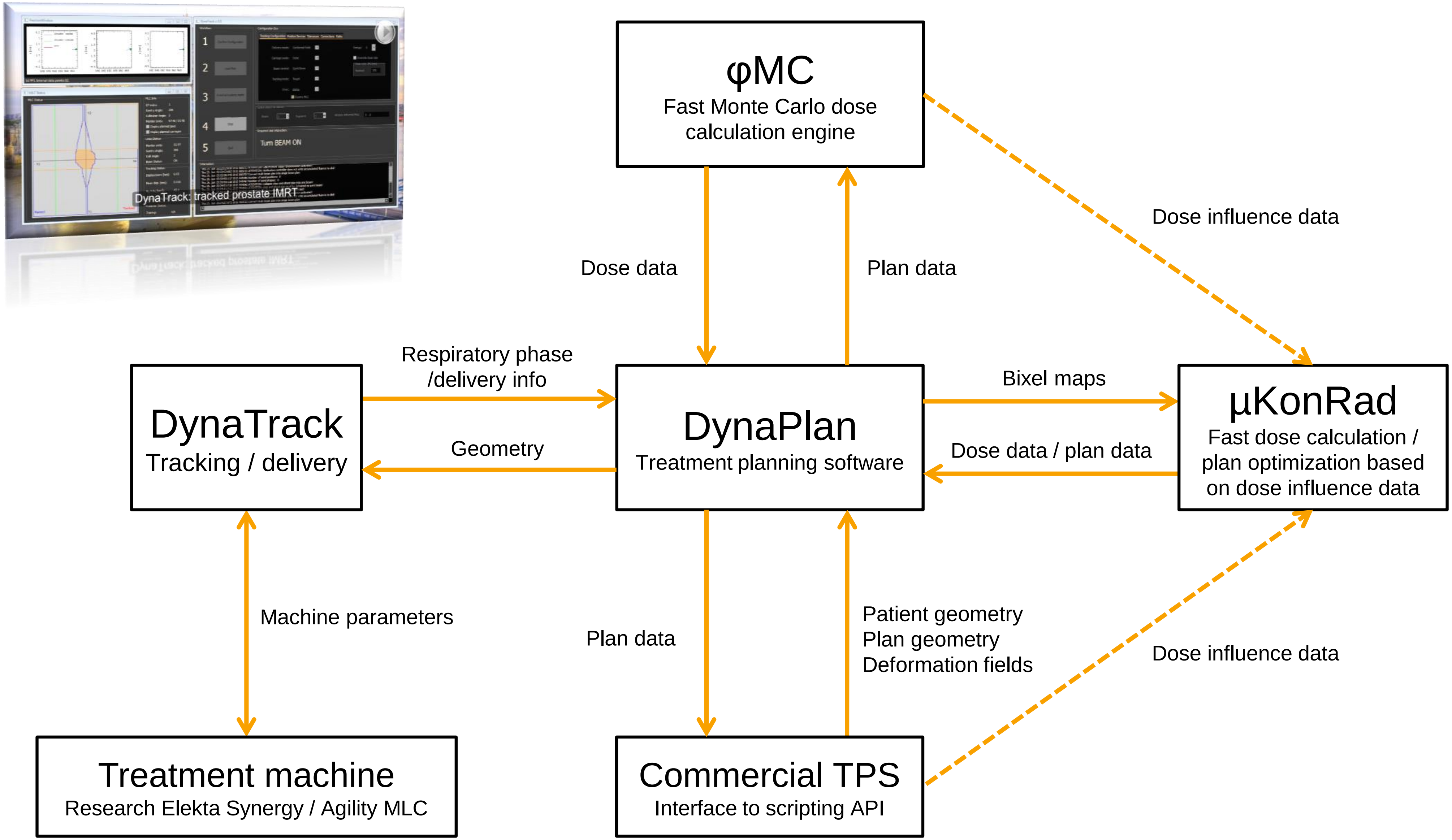
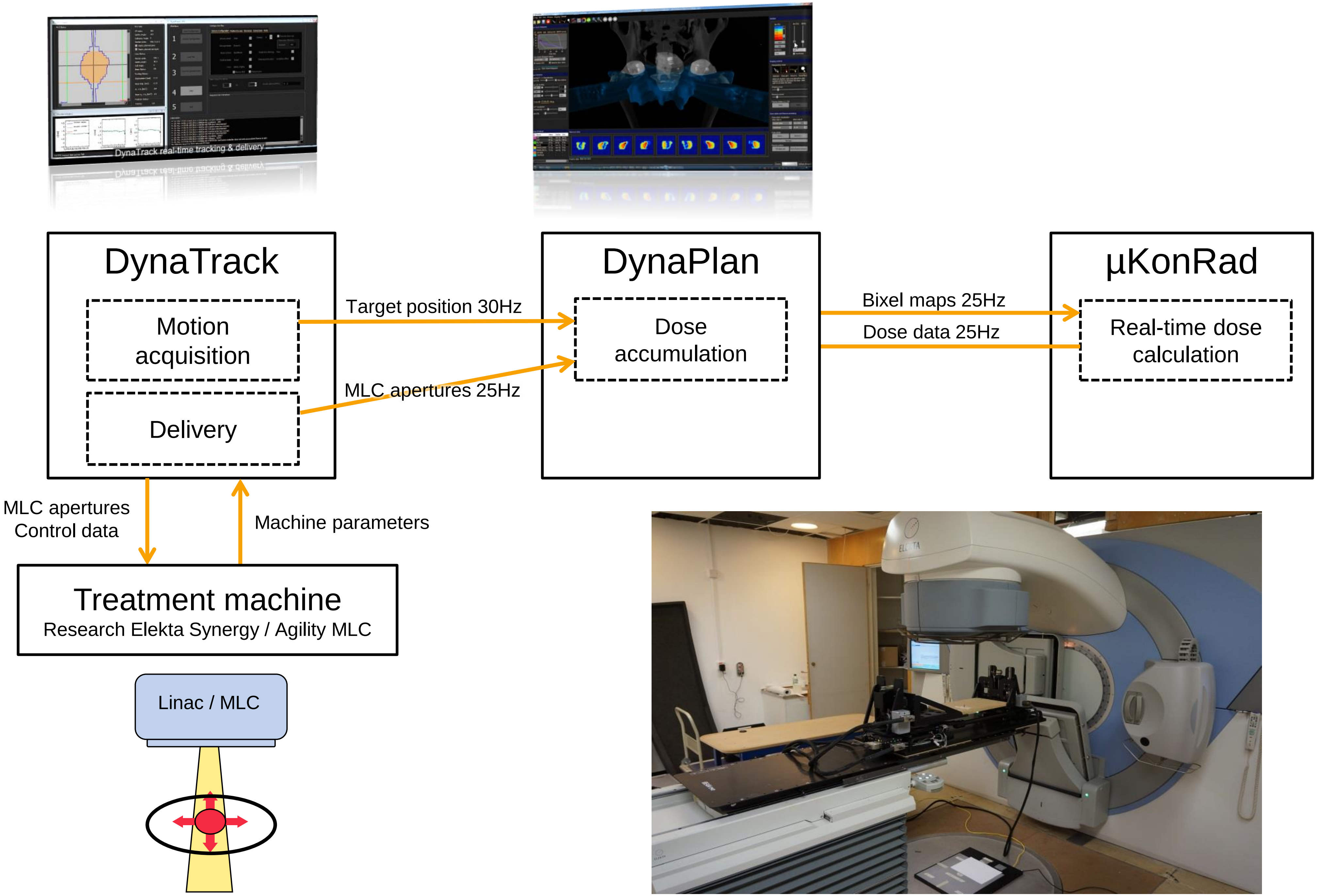
Online real time plan adaptation

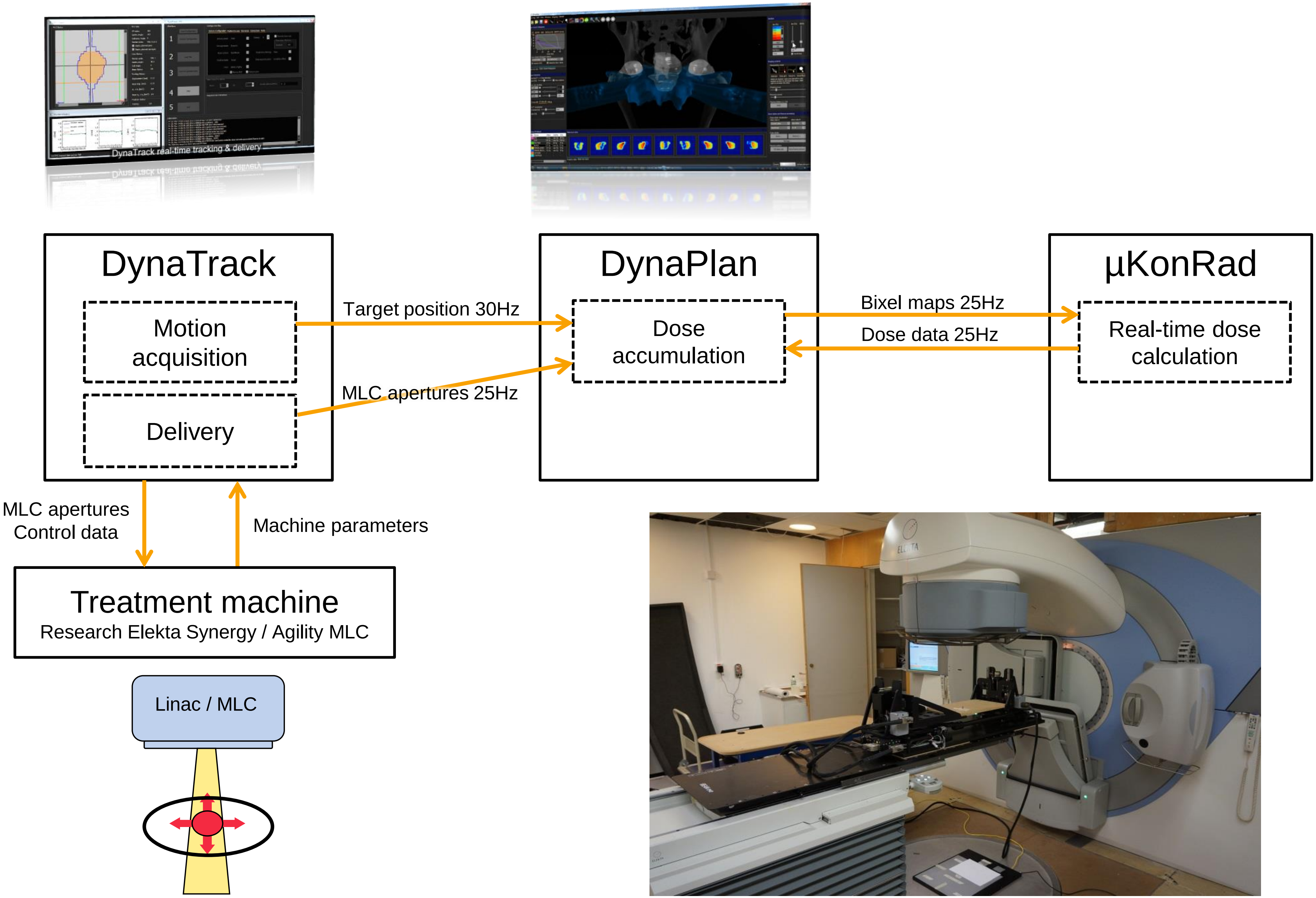




Research RT software platform at ICR




DynaTrack real-time tracking & delivery
DynaTrack
Motion acquisition
Delivery
Target position 30Hz
MLC apertures 25Hz
DynaPlan
Dose accumulation
Bixel maps 25Hz
Dose data 25Hz
µKonRad
Real-time dose calculation
MLC apertures
Control data
Machine parameters
Treatment machine
Research Elekta Synergy / Agility MLC
Linac / MLC


DynaTrack real-time tracking & delivery
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Target position 30Hz
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Dose accumulation
Bixel maps 25Hz
Dose data 25Hz
µKonRad
Real-time dose calculation
MLC apertures
Control data
Machine parameters
Treatment machine
Research Elekta Synergy / Agility MLC
Linac / MLC


DynaTrack + DynaPlan

Summary

- Multiple MR guided RT configuration are being investigated
- Commercial solutions already available
- Most technical challenges have been addressed
- Treatment planning studies have mostly shown that it is possible to mitigate/address the ERE effect
- MR Guided Radiation Therapy is currently a major topic in translational research

(Advanced) imaging in the 4th dimension

Jan-Jakob Sonke

NKI-AVL
Het Nederlands Kanker Instituut
Antoni van Leeuwenhoek Ziekenhuis

ESTRO IGRT 2017

Thanks to

- Stine Korreman
- Christoph Schneider
- Jochem Wolthaus
- Mathijs Kruis
- Tessa van Lindt
- Marcel van Herk
- Paul Keall
- Andrew Hope
- Bas Raaymakers

The time component of imaging

- Inter-fraction changes – from treatment planning to treatment delivery and between treatment fractions
- Irregular intra-fraction changes such as bowel movements and external positioning
- Regular intra-fraction changes such as respiration (and bladder filling)

Weeks

Days

Hours

Minutes

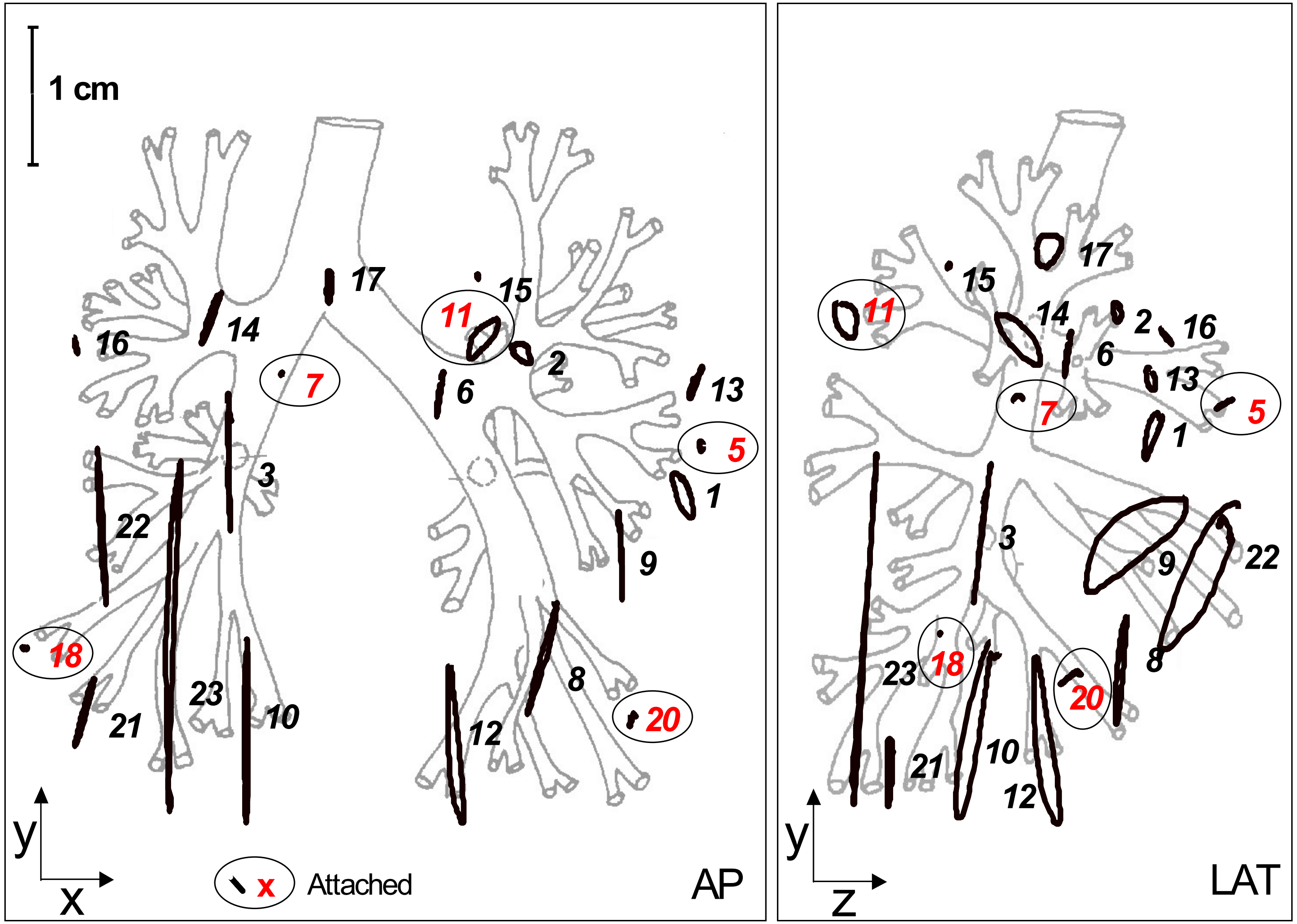
Seconds

The time component of imaging

- Regular intra-fraction changes such as respiration

Seconds

Respiration motion (not to scale)



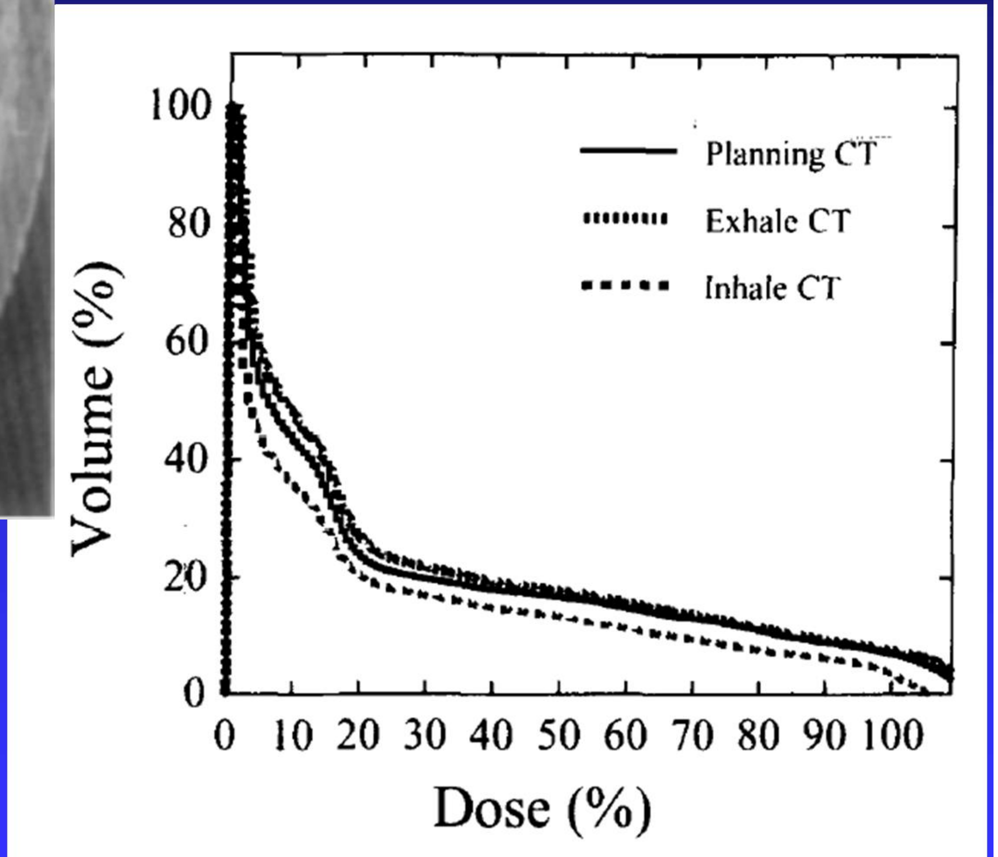
From Seppenwoolde et al., IJROBP 2002 53:822-834

Outline

- Effects of the time component on images
- 4D CT scanning
- 4D in treatment planning
- 4D PET scanning
- 4D MRI

Effect of Respiration

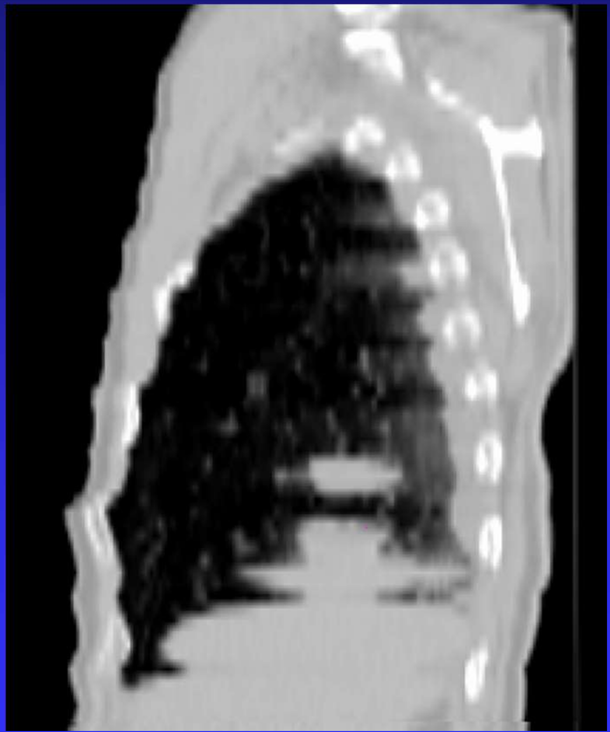
Effect of motion on CT and Dose



Balter et al. IJROBP 1996

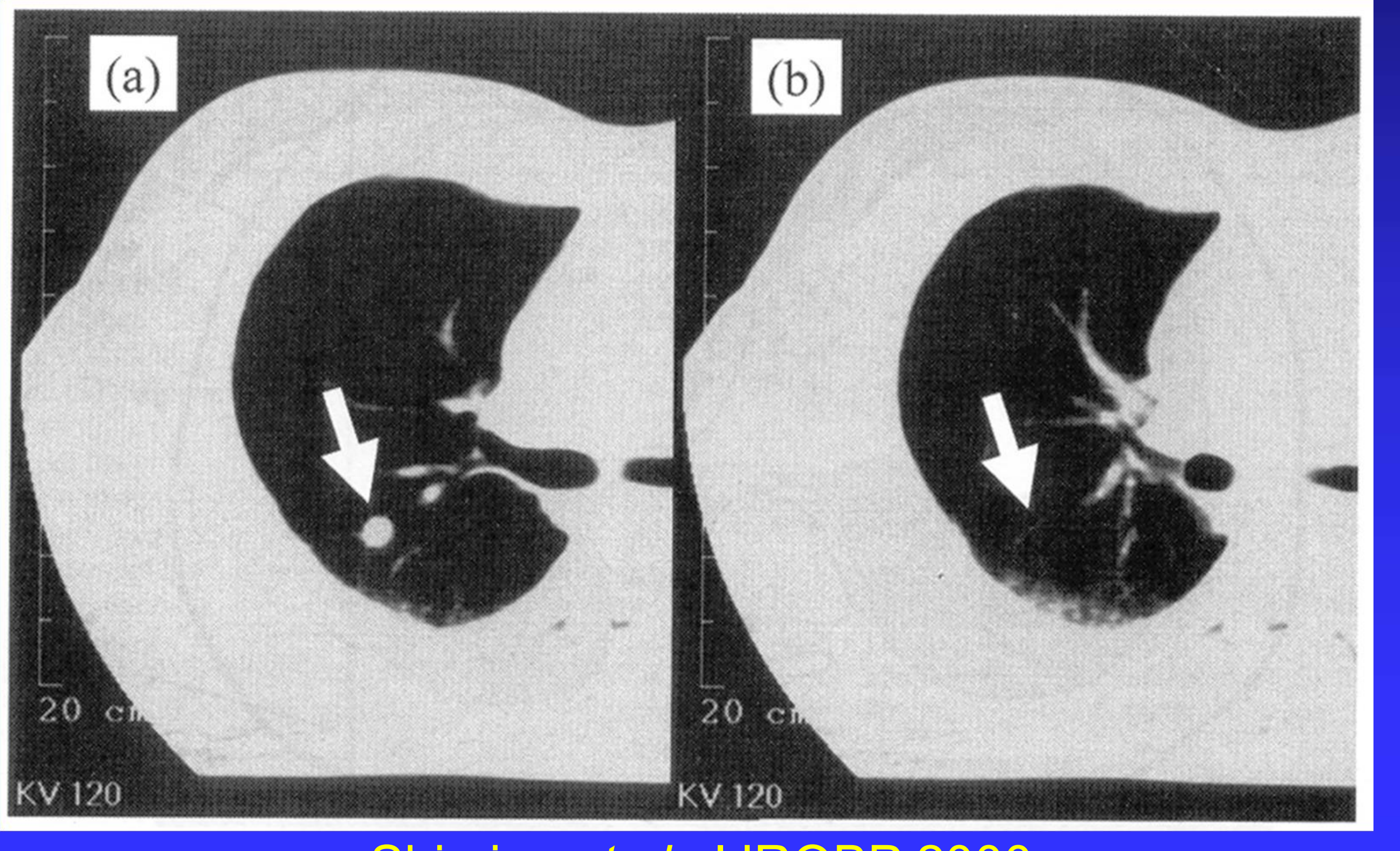
CT - effects of respiration

- Partial viewing and blurring



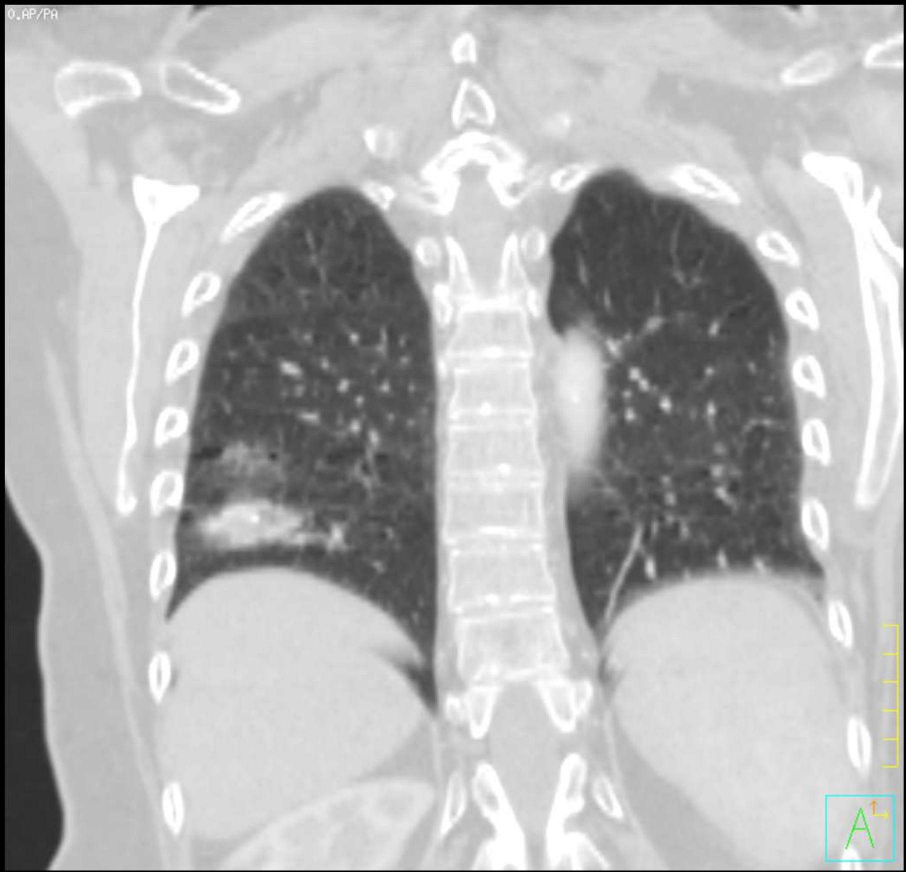

CT - effects of respiration

- Volume effects and disappearing structures

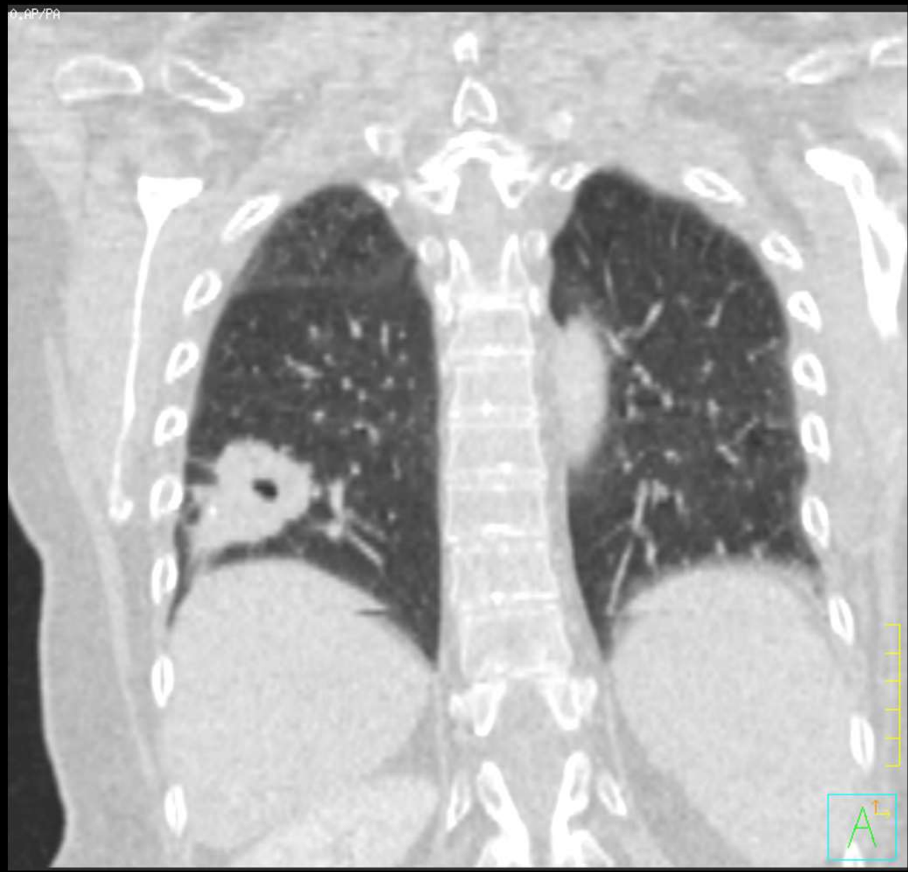


Shimizu *et.al.*, IJROBP 2000

Helical



Exhale

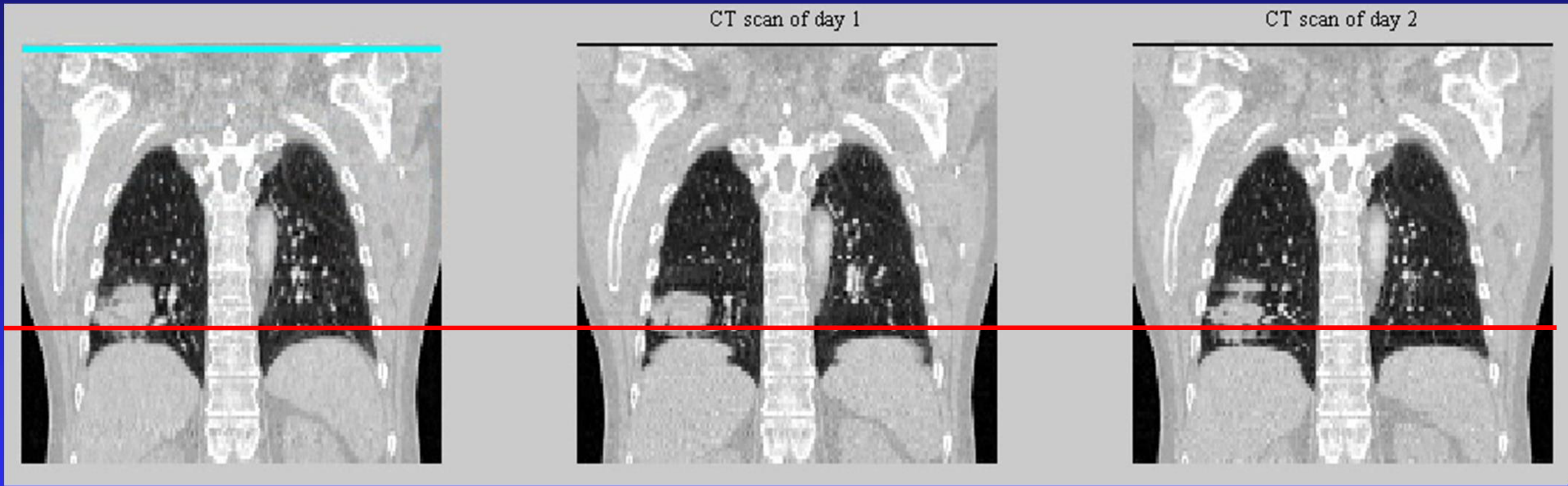


Andrew Hope

Radiation Oncology
UNIVERSITY OF TORONTO

Princess Margaret Hospital
University Health Network

The CT imaging problem



CT and time management

Approaches to CT time management

- Slow scanning
- Repeated fast scanning
- Gating/breath-hold (prospective respiratory correlation)
- Retrospective respiratory correlation (4D)

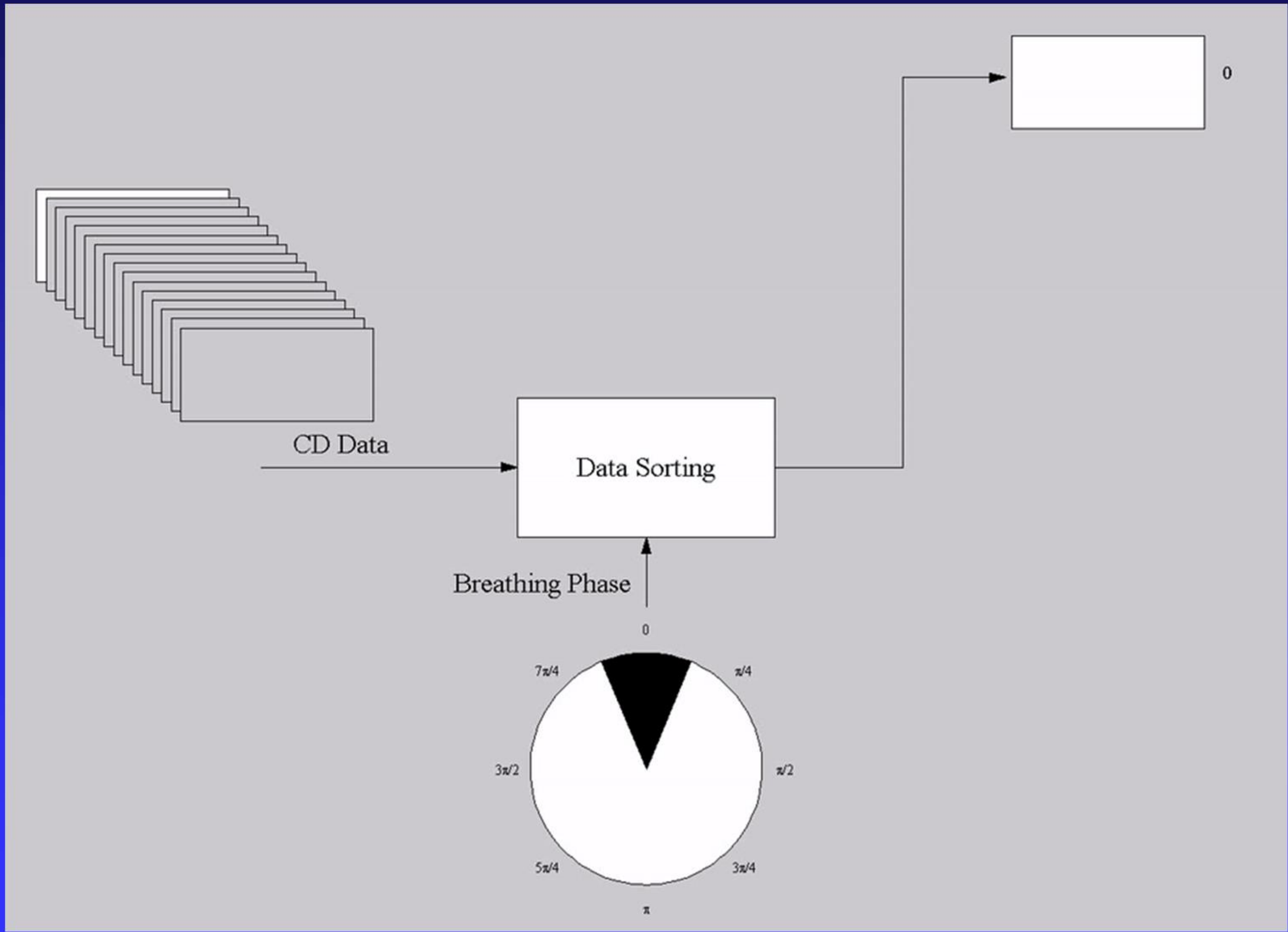
4D CT

Brief history of 4D CT

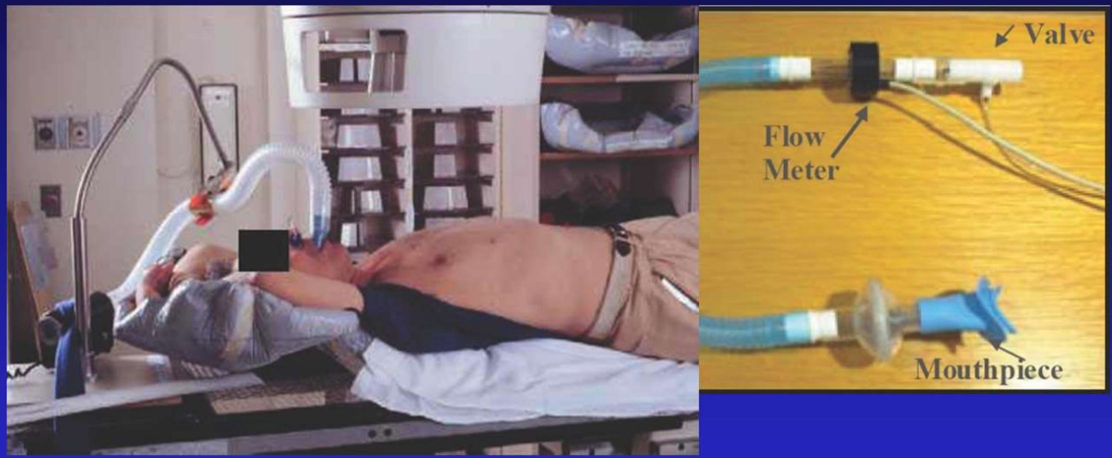
Development	Year	First author	Institution
Single slice helical	2003	Ford, Vedam	MSKCC, VCU
Multi-slice cine (commercial)	2003	Pan	GE/MGH/MSKCC
Cone beam (benchtop)	2003	Taguchi	Toshiba
Multi-slice cine	2003	Low	Wash U
Multislice helical	2004	Keall	VCU, MDACC
Multislice cine PET/CT	2004	Nehmeh	MSKCC
Cone beam (clinical)	2005	Sonke	NKI
Applications outside Rad Onc	…	Guerrero, Low, Keall	MDACC, Wash U, Stanford

* Courtesy of Paul Keall

Retrospective Sorting

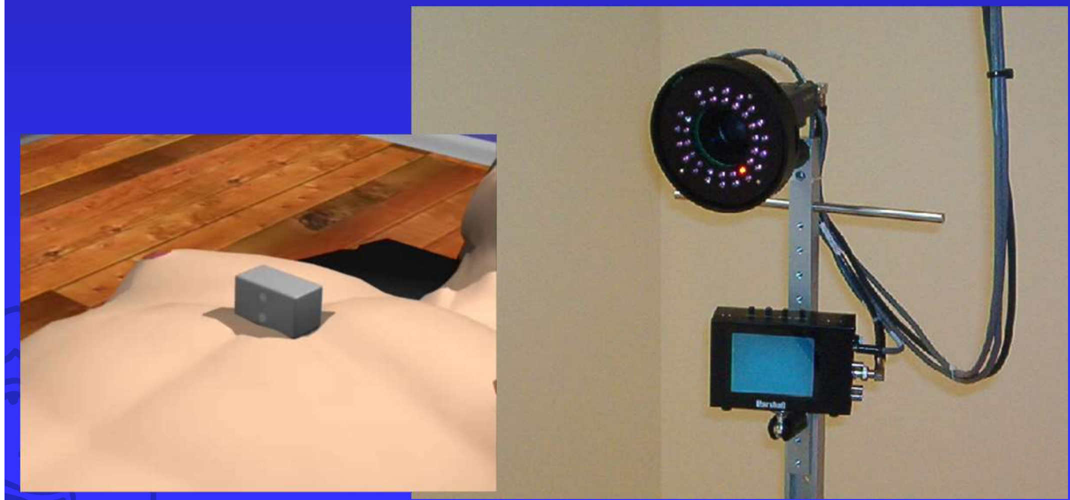


Recording respiration



Spiro meter

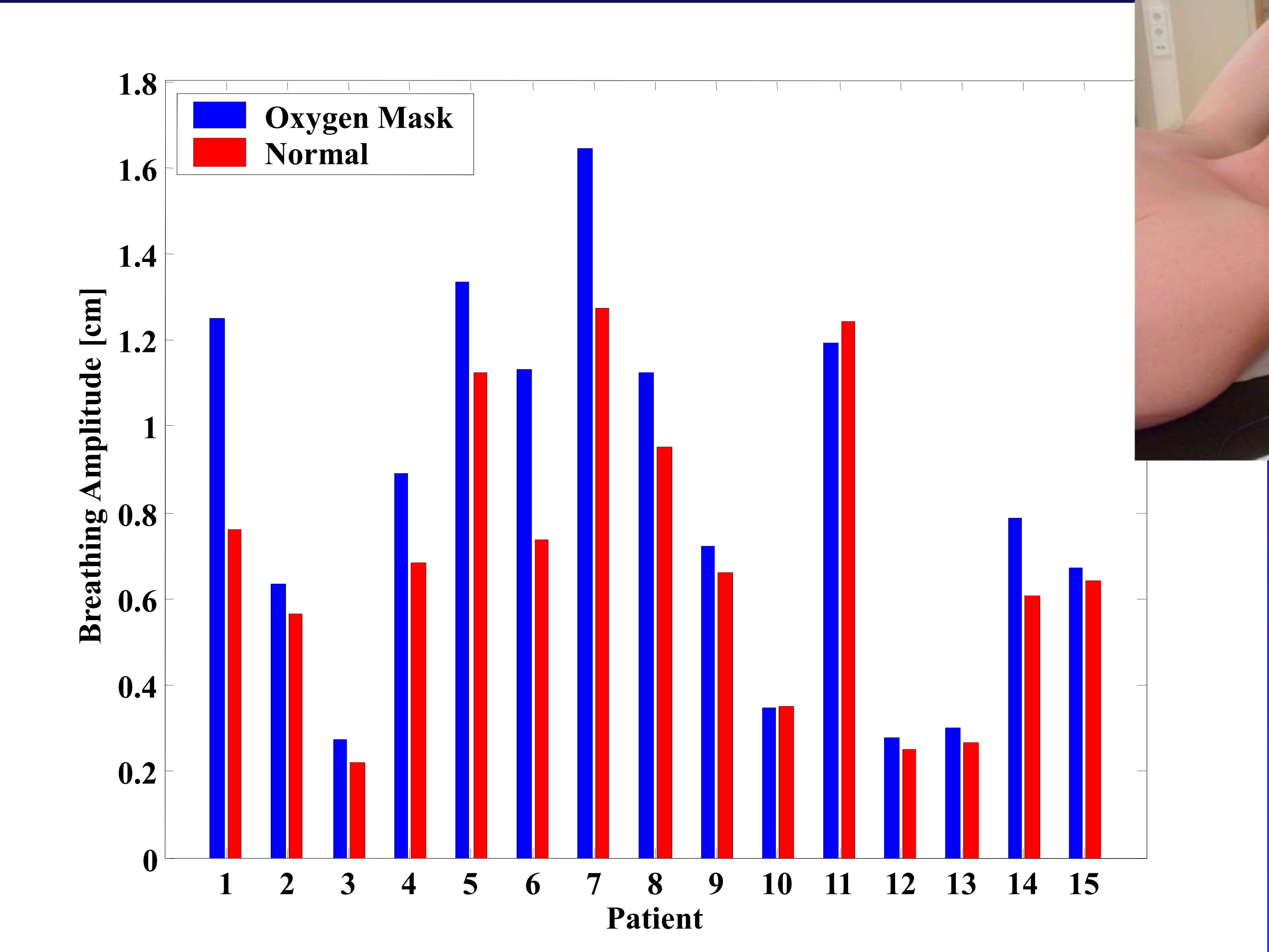
Anzai belt, Siemens

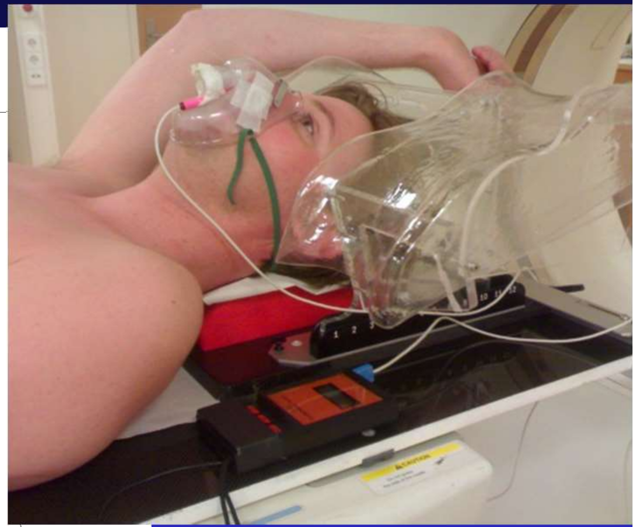


Varian RPM system

Stretch belt, Philips

Change in breathing amplitude



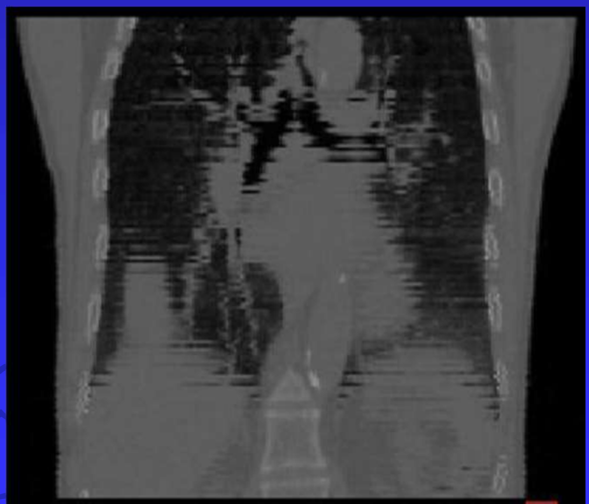


M = 21%, SD = 19%, p = 0.00076

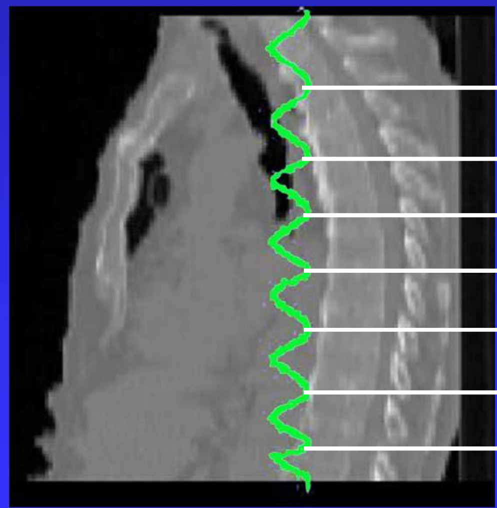
Sort slices

(1) Reconstructing many slices (2) Sorting CT slices

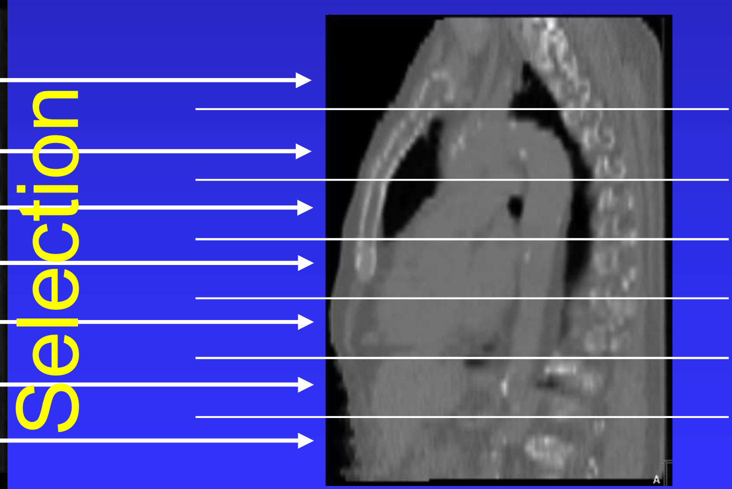
Raw CT



Raw CT with respiration signal



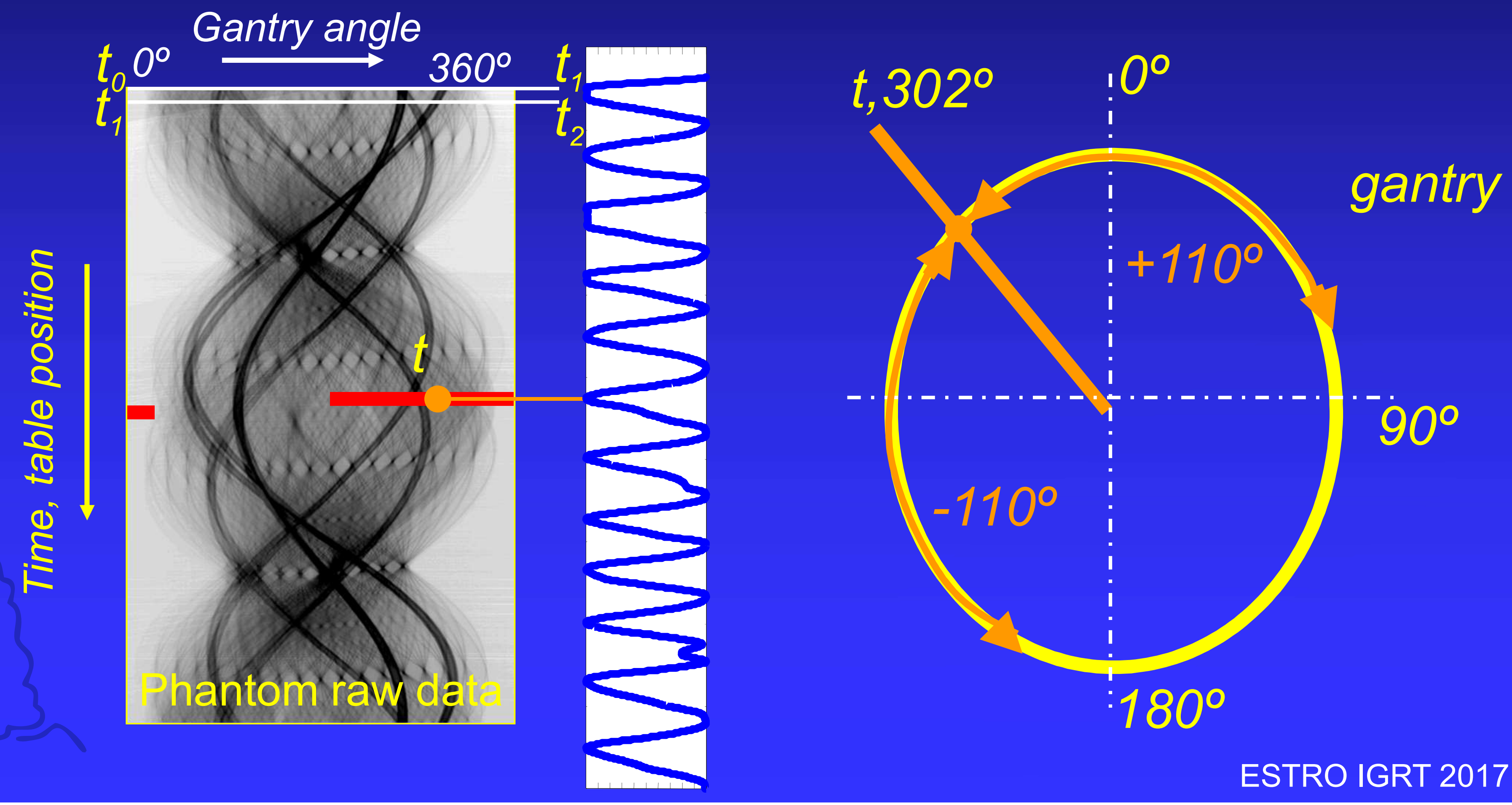
Selected slices gathered, yielding a single phase CT



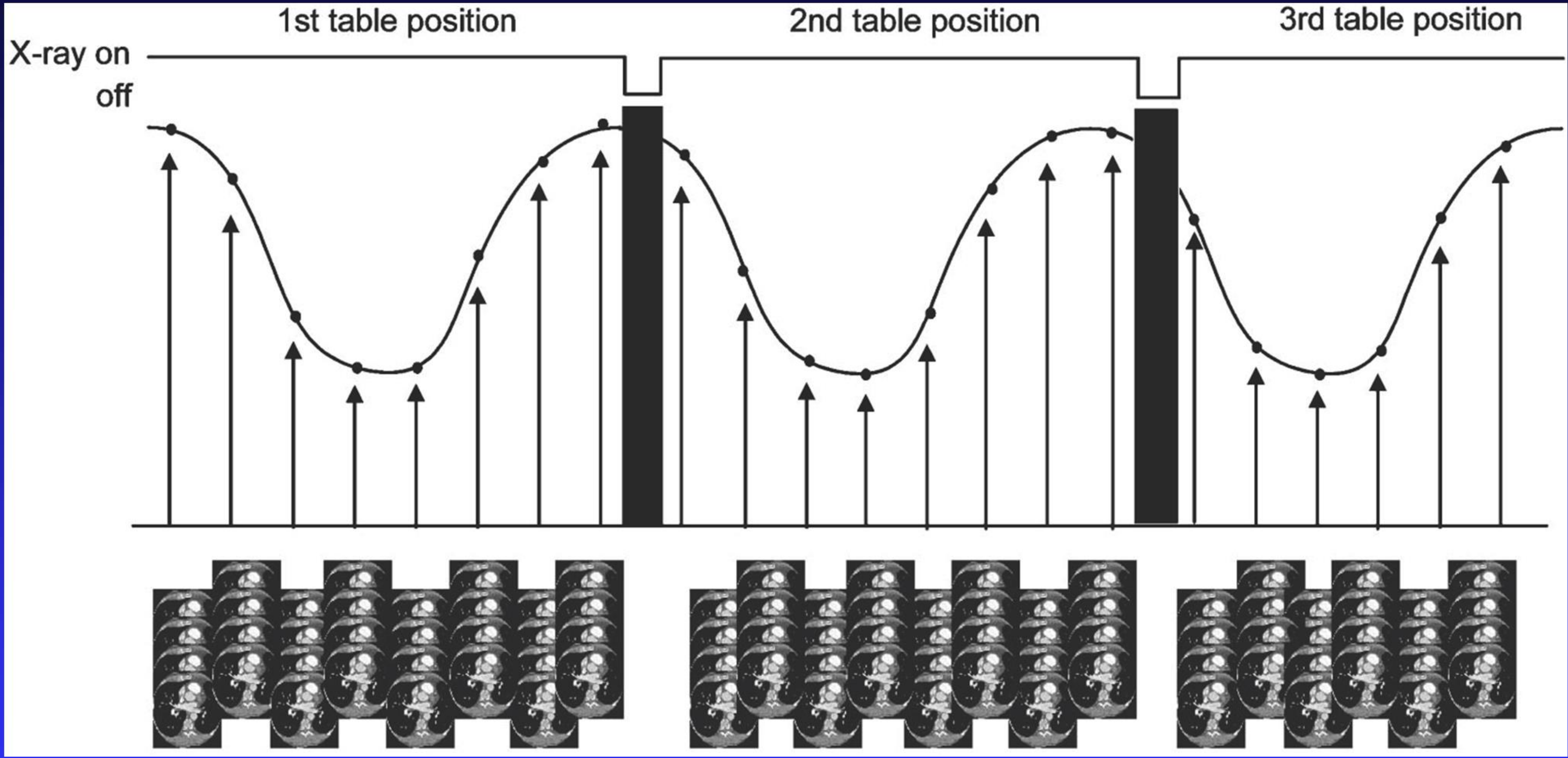
Sort sinogram

Selection by respiratory phase of raw CT sinogram data

→ (1) Sorting raw CT data. (2) Reconstructing slices



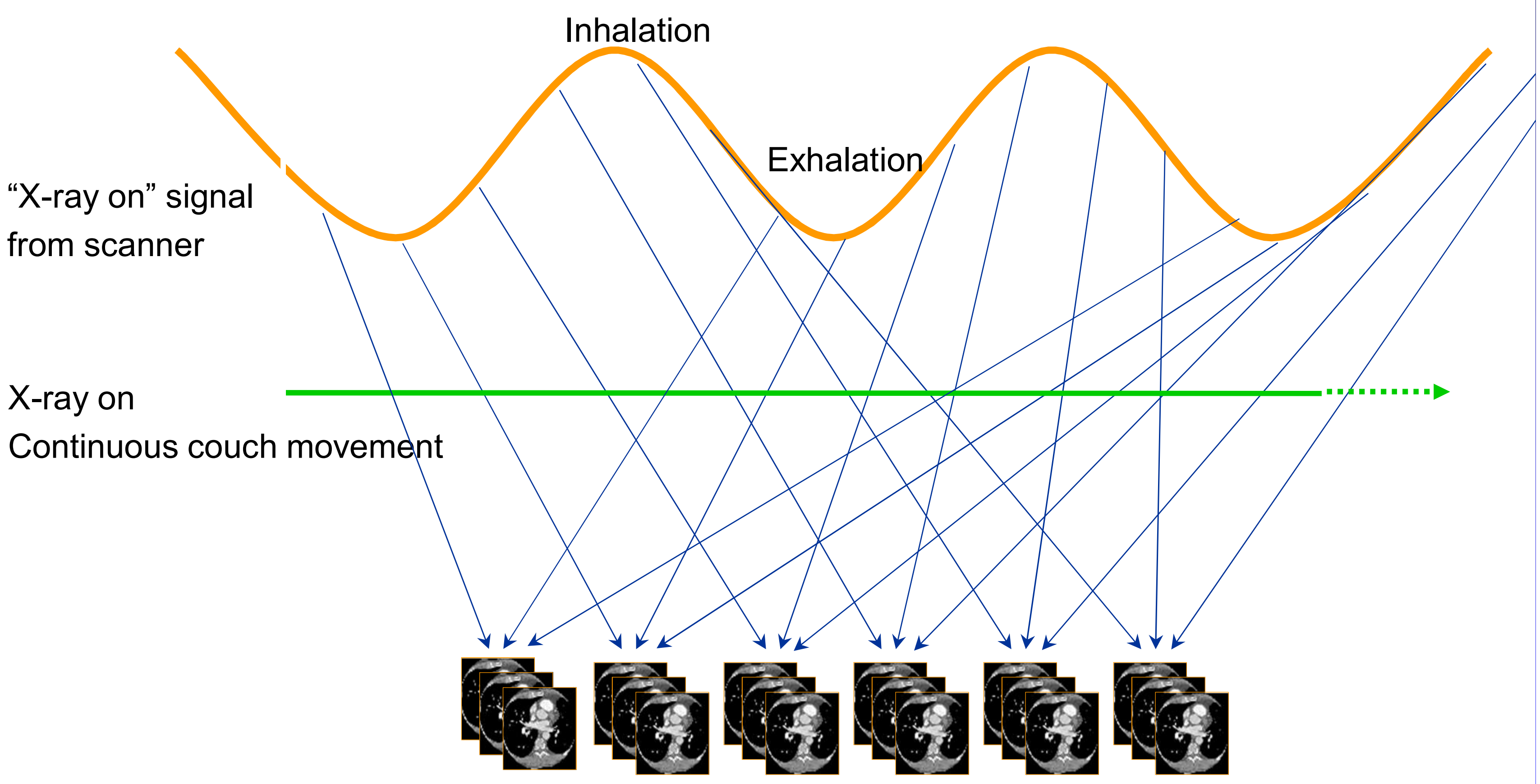
Acquisition – Ciné mode



Each step: continuous acquisition of slices for time interval (average CL + 1 Slice time)

* Tinsu Pan, Med.Phys. 31 (2), 2004
GE LightSpeed MS CT

Helical 4D CT



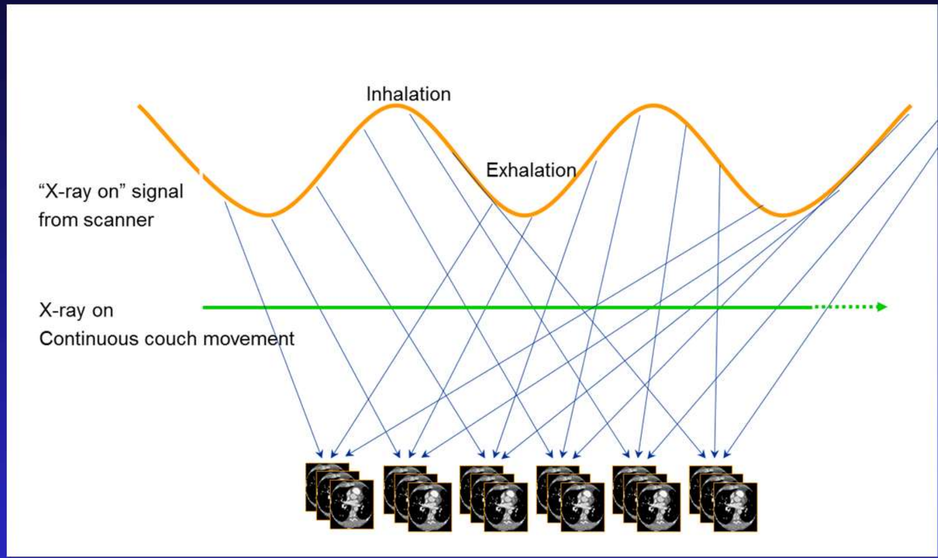
4D CT Example

Multi slice Siemens Sensation
(Sinogram sorting)

4DCT Non Idealities

Scanning protocols

$$CL_{Tube-rotation} = pitch \times CL_{Respiration}$$

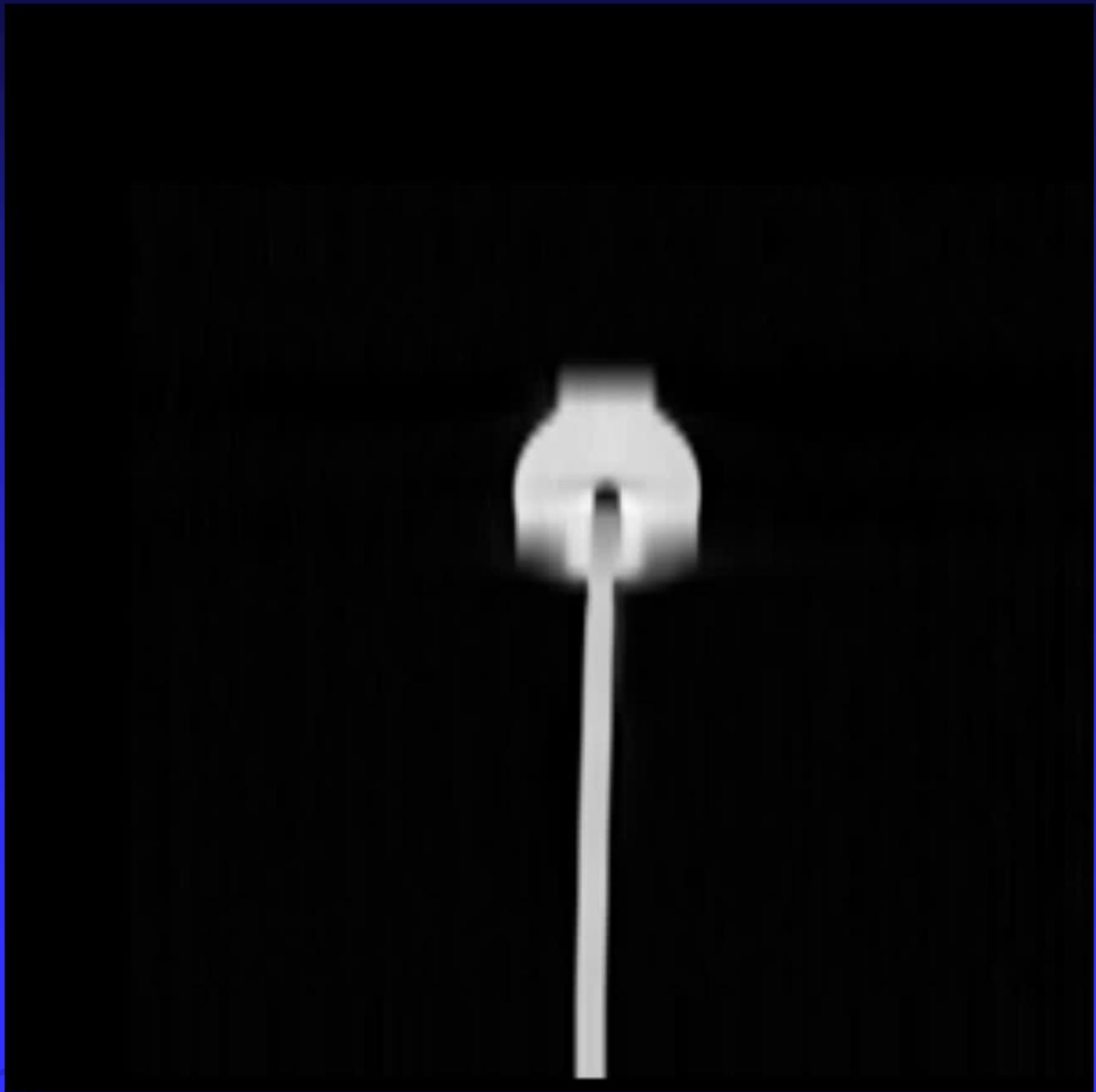


$$CL_{Respiration} \leq CL_{Tube\ Rotation} \setminus Pitch$$

Scanning protocol

- 0.5 sec (pitch 0.1, rot time 0.5 s => up to 5.0 sec cycles
- 1.0 sec (pitch 0.15, rot time 1.0 s => up to 6.7 sec cycles
- Slow (pitch 0.1, rot time 1.0 s => up to 10.0 sec cycles

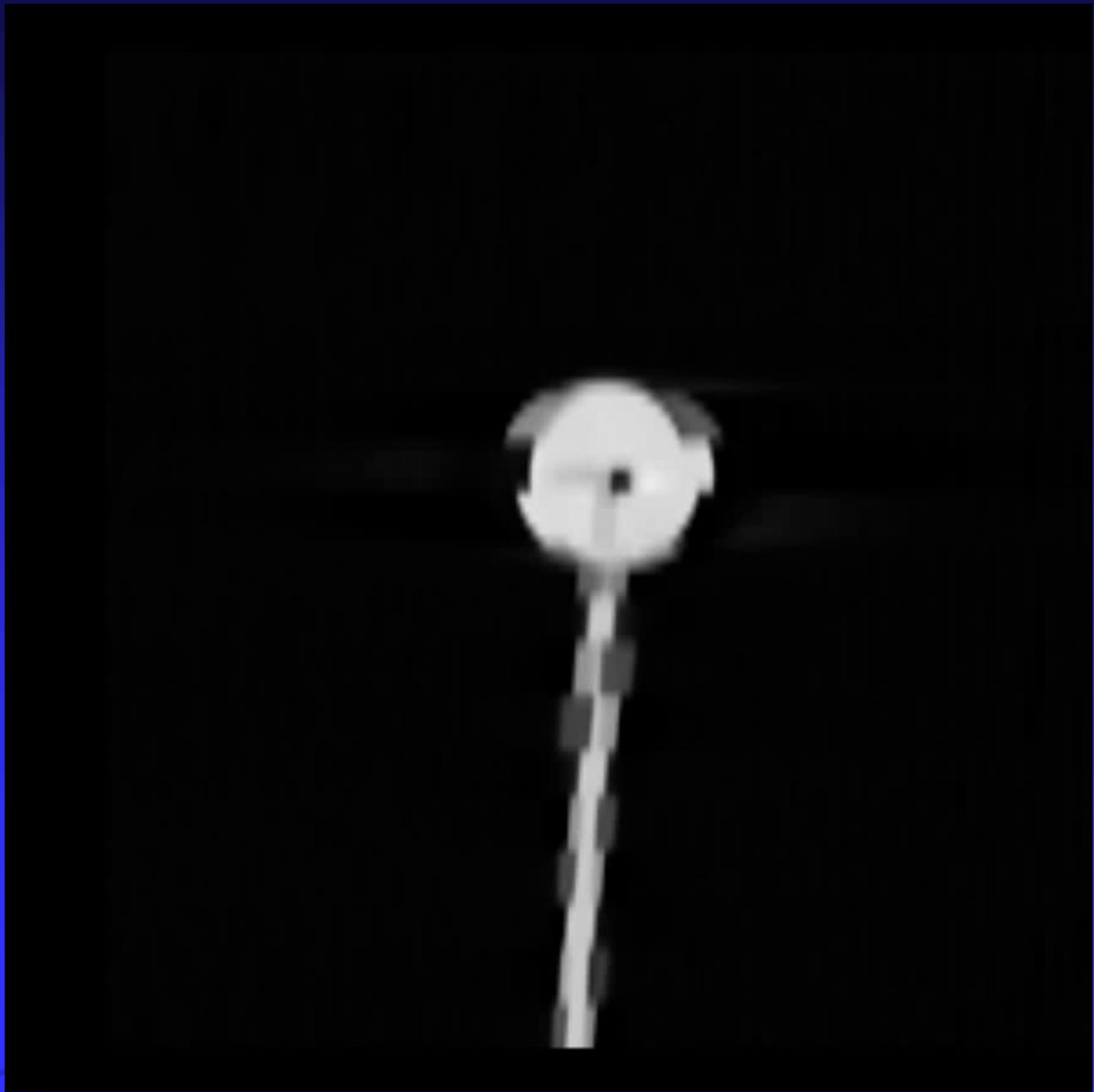
Scan too fast



Cycle = 8 s

Fast scanning protocol (5 s)

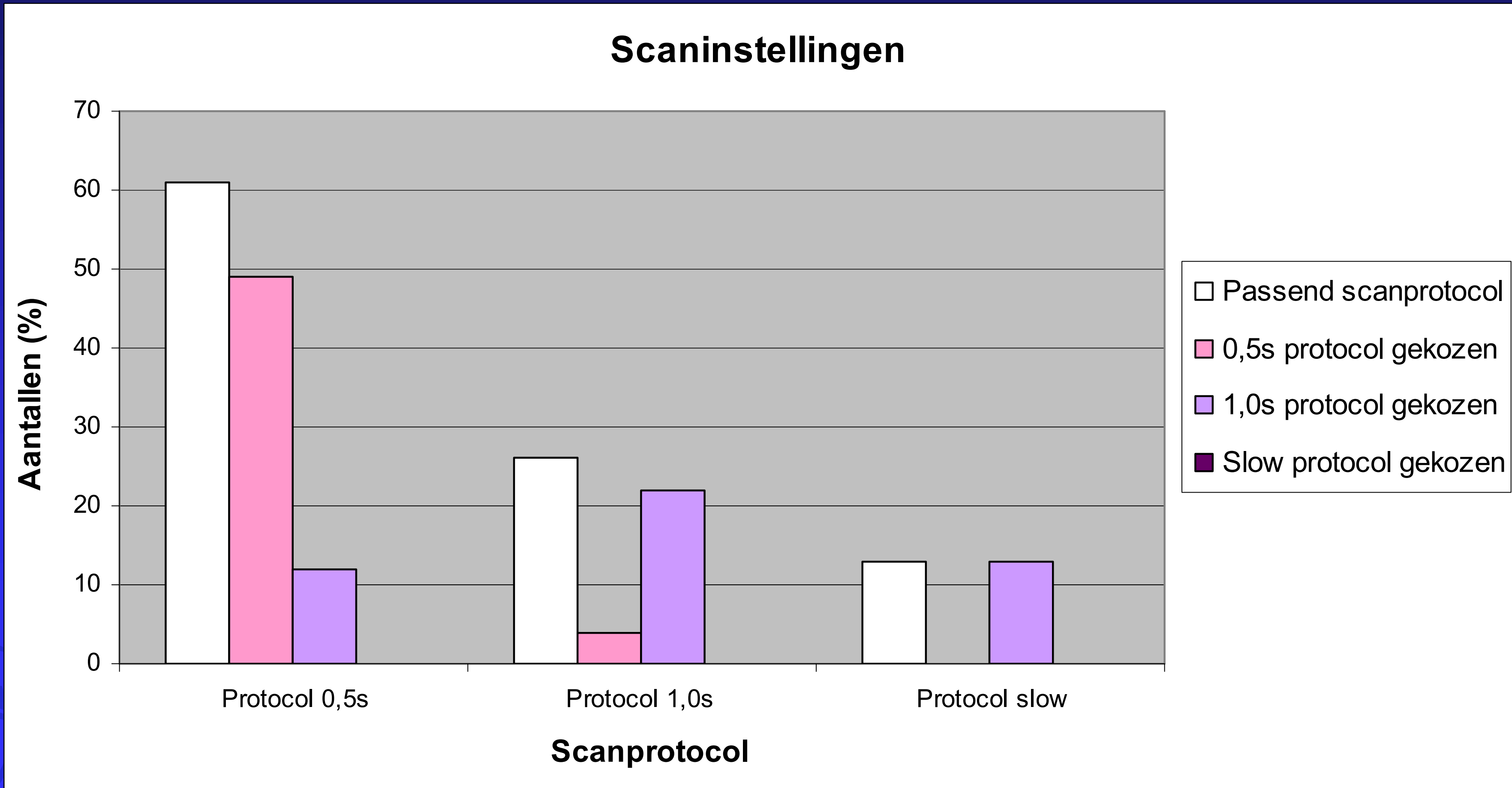
Scan too slow



Cycle = 3.5 s

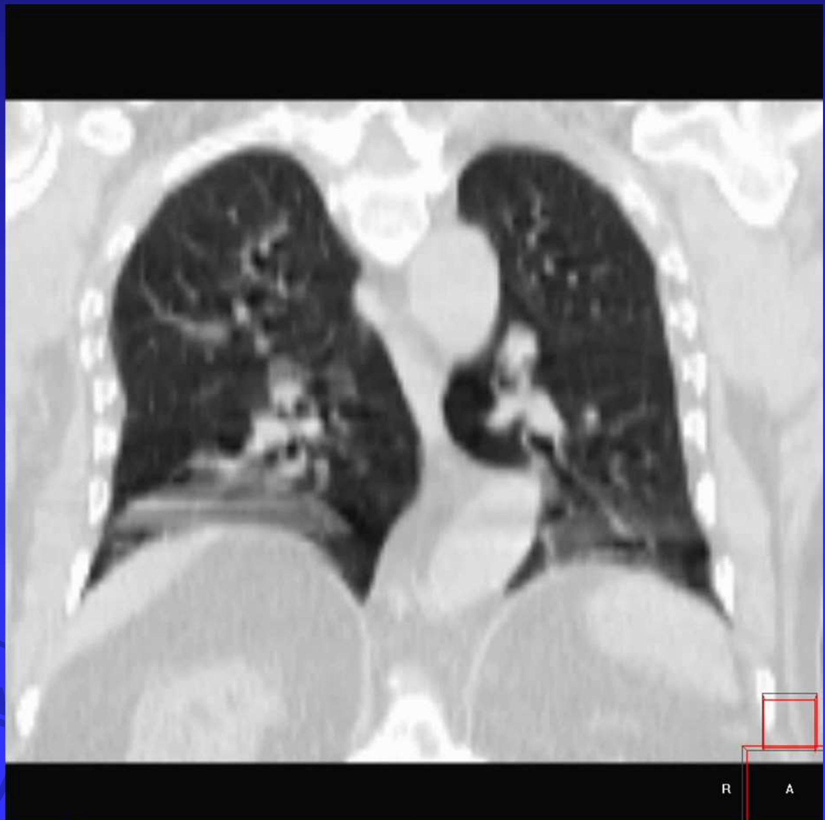
Slow scanning protocol (6.7 s)

Performance Evaluation

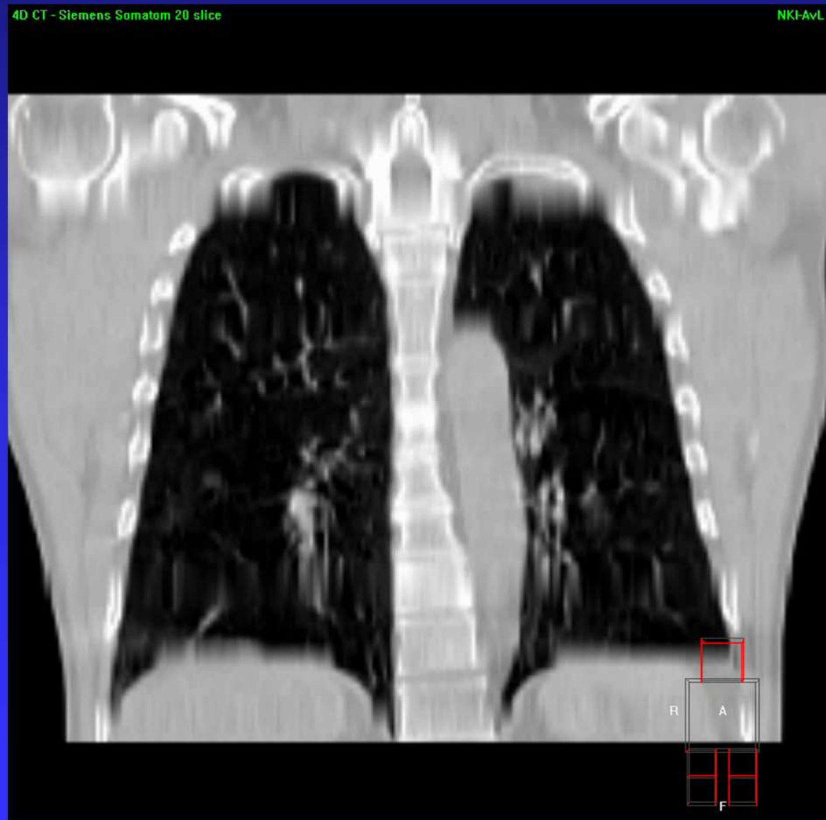


Scan speed vs. respiration cycle

Fast breathing + Slow scanner = blurring

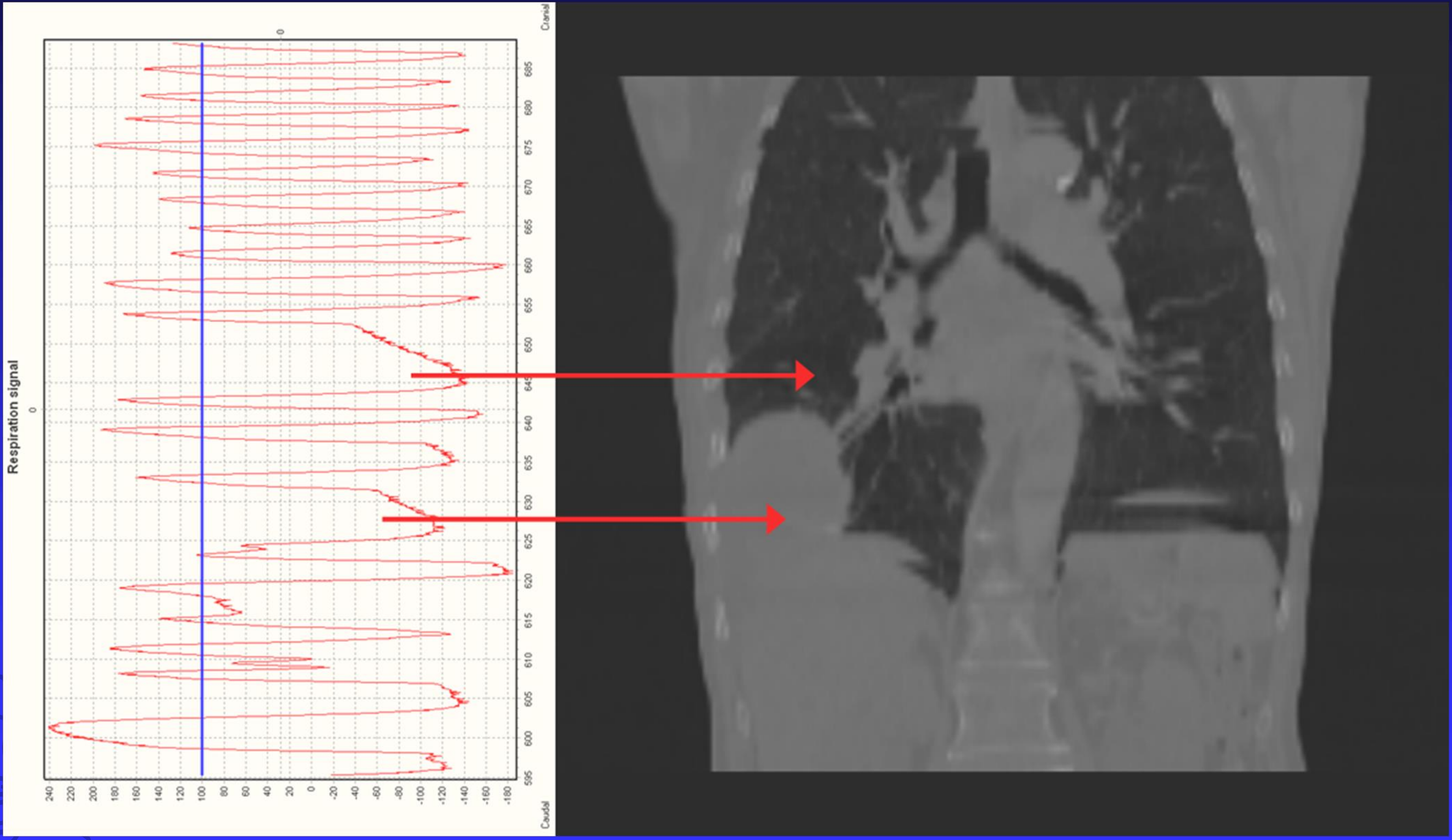


Slow breathing + Fast scanner = gaps

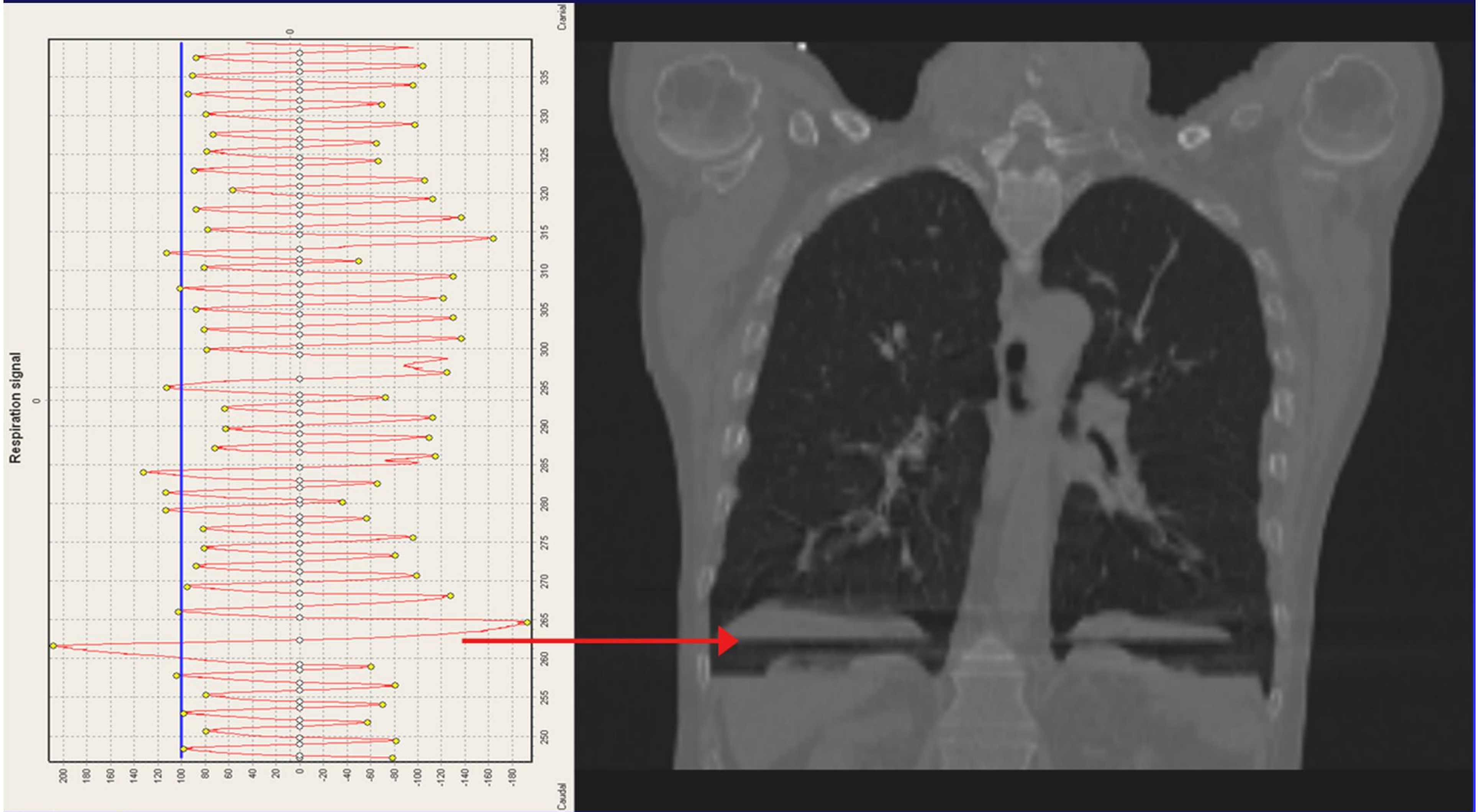


$$CL_{Tube-rotation} = pitch \times CL_{Respiration}$$

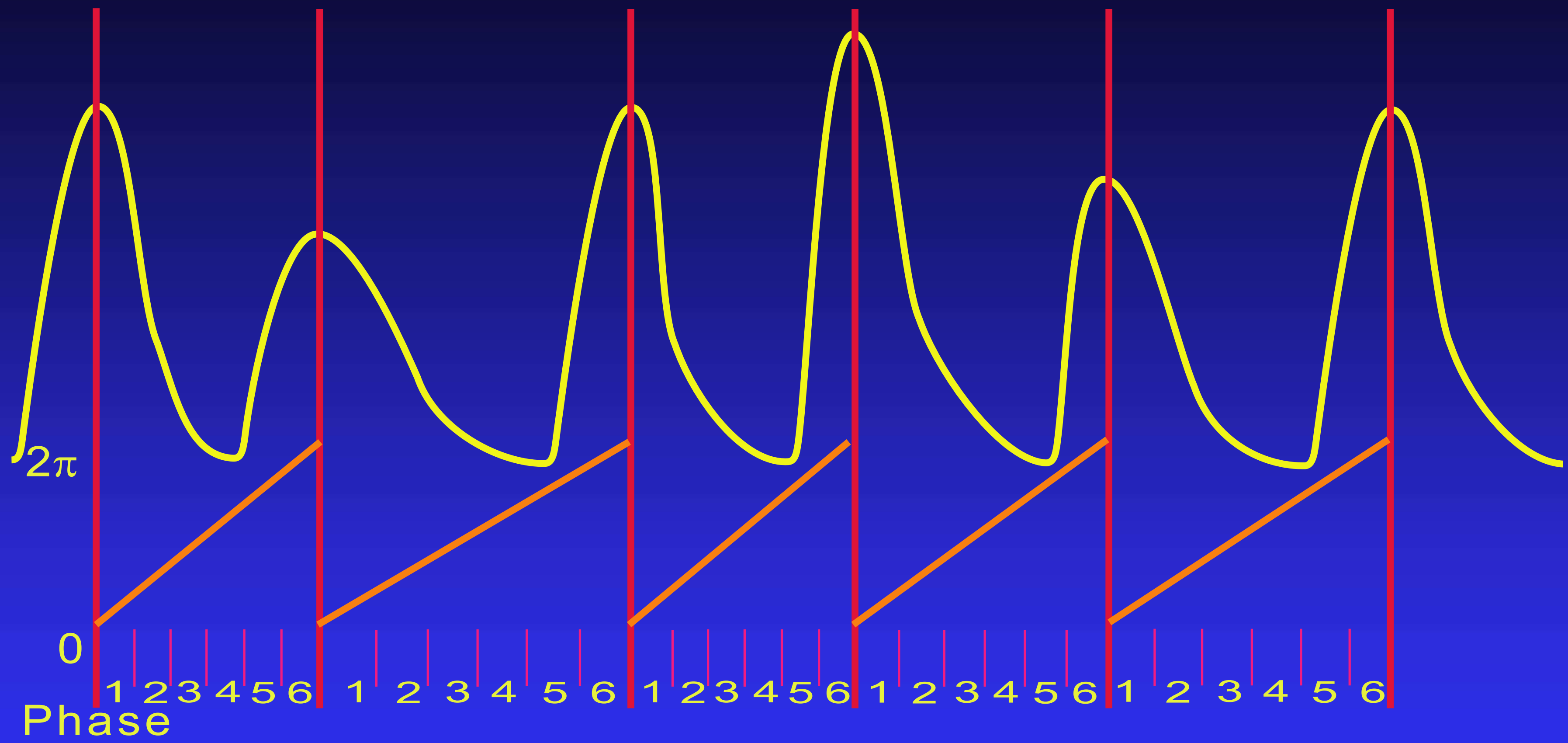
CT Artefacts



CT Artefacts

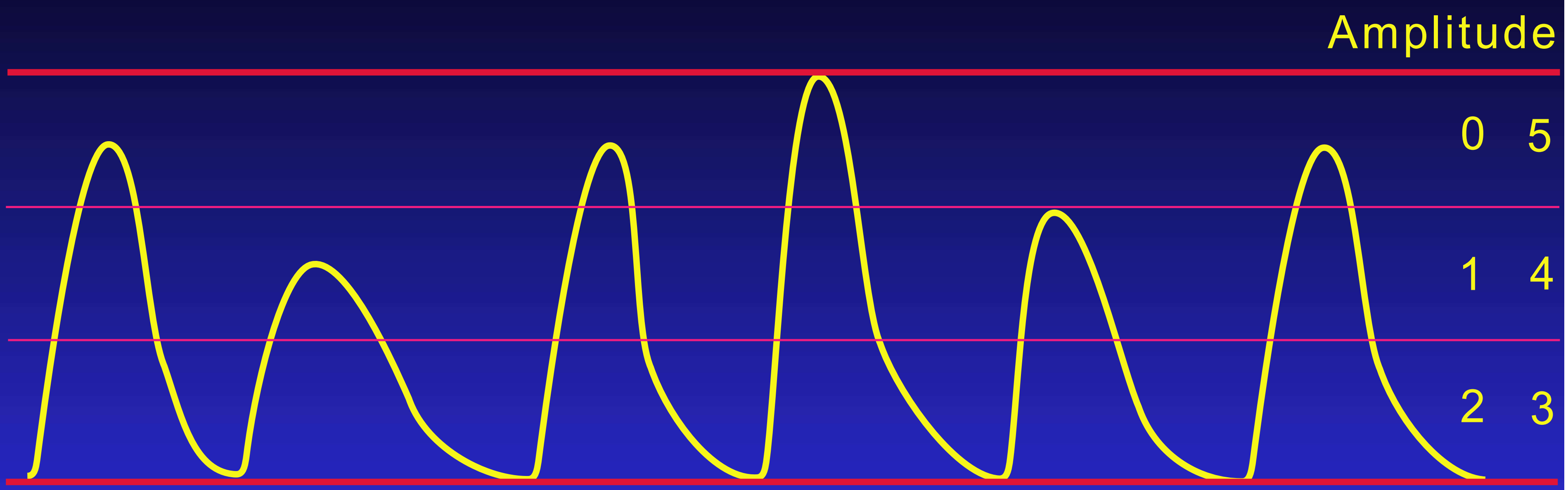


Phase vs. Amplitude sorting



- Data is linearly divided over the respiratory cycle
- More frames in exhale than inhale
- If amplitude is irregular → slices do not concatenate (blurring/distortions)

Phase vs. Amplitude sorting



- Data is sorted to the amplitude
- Same number of frames in exhale and inhale
- Gaps if no data is available
- Maximum inhale is less reproducible

Examples – Phase vs Amplitude

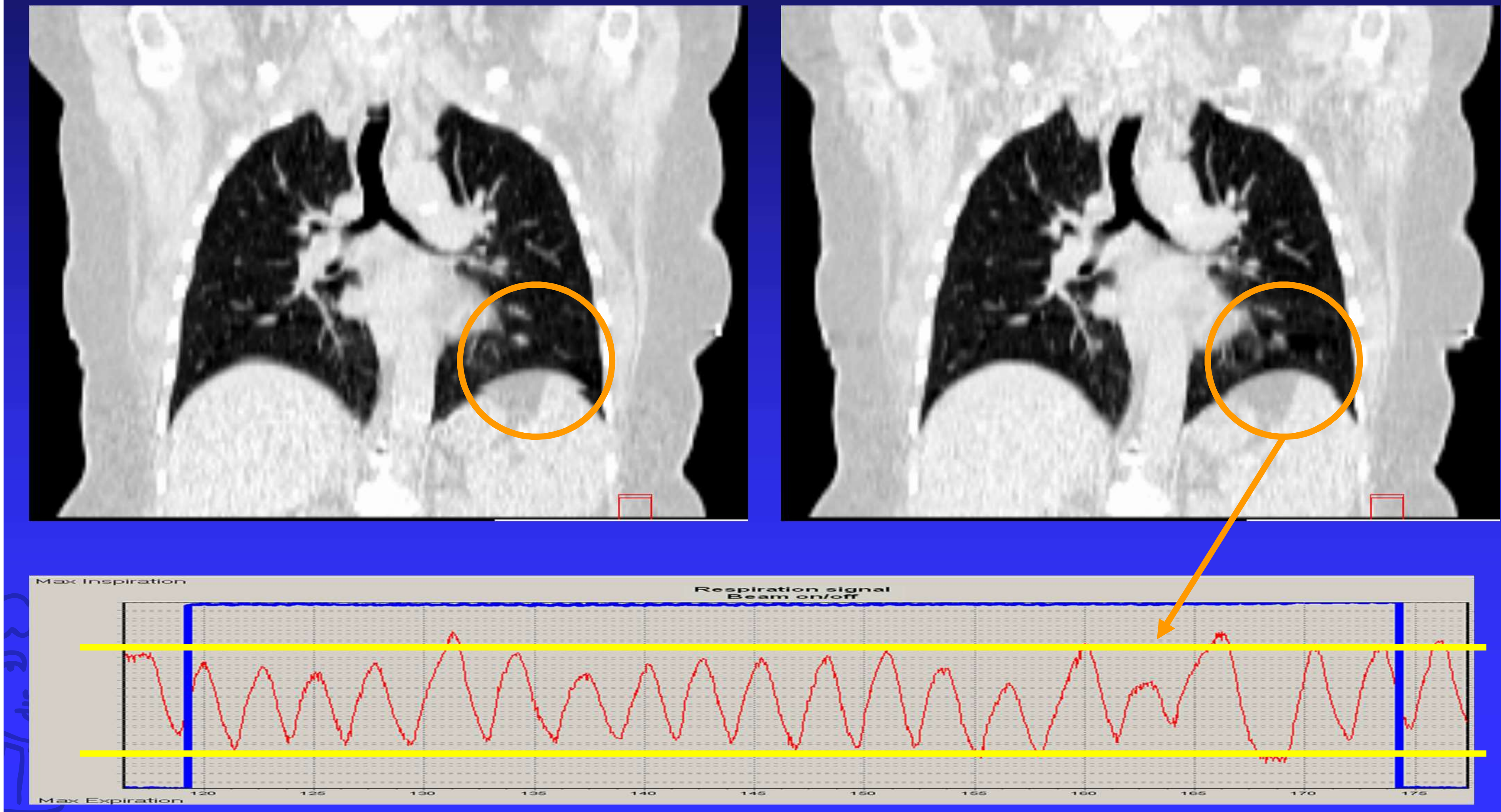
Phase wise

Amplitude wise

Examples – Phase vs Amplitude

Phase wise

Amplitude wise



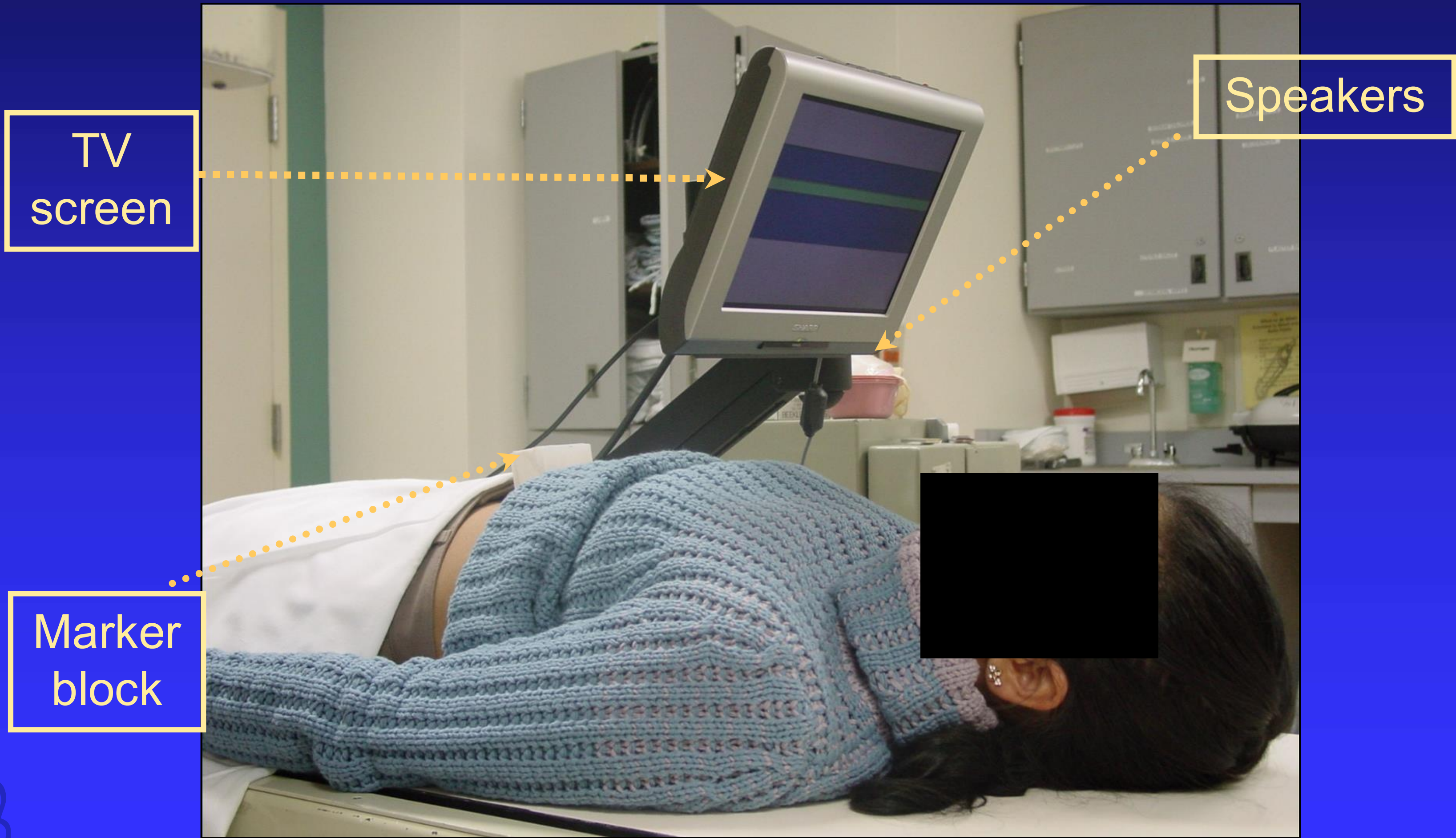
Current developments in 4D CT

- Audio-Visual feed-back to reduce motion
- Adaptive control
- Motion Compensation

Paul Keall

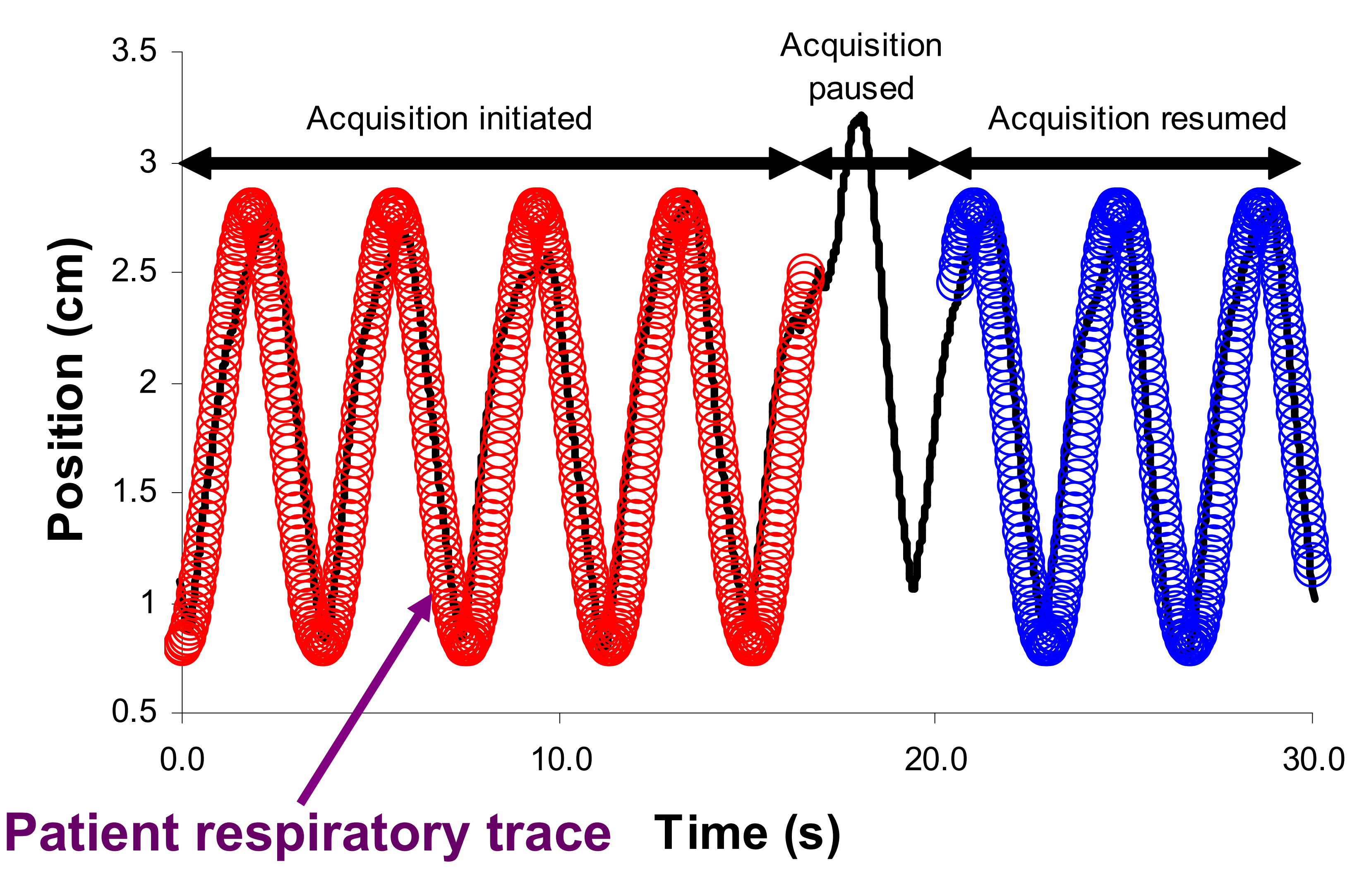
Audio-Visual Feed-back

Improve regularity of input signal



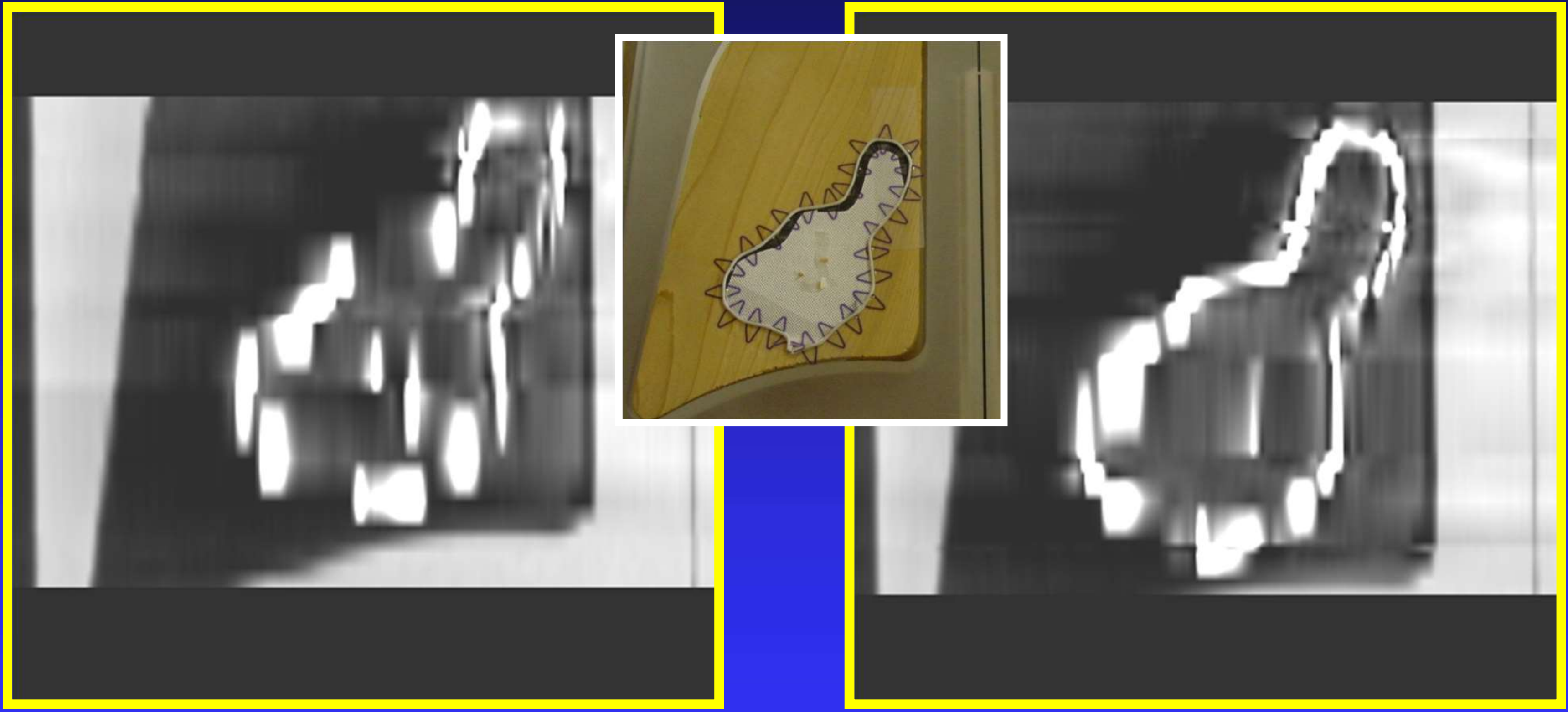
Adaptive control

Paul Keall



Adaptive control

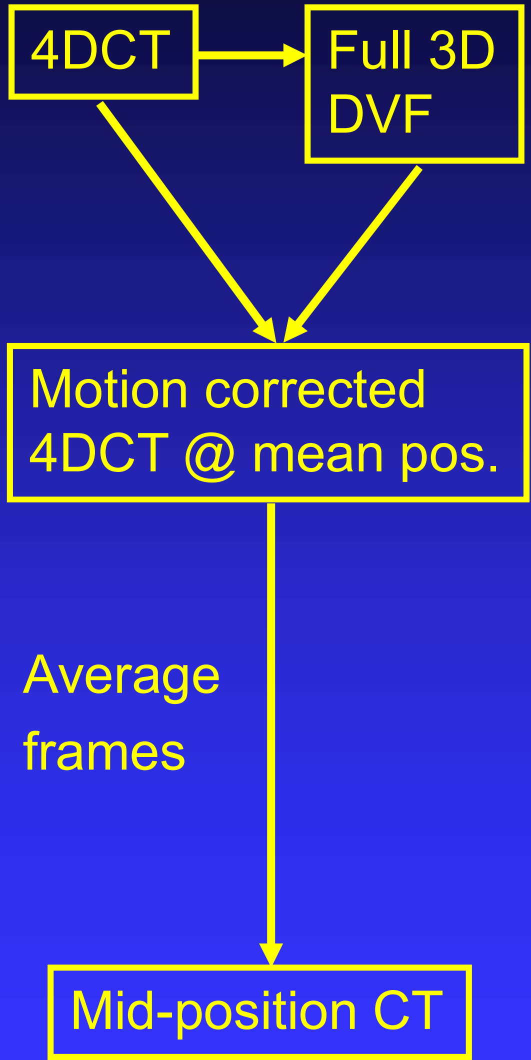
Paul Keall

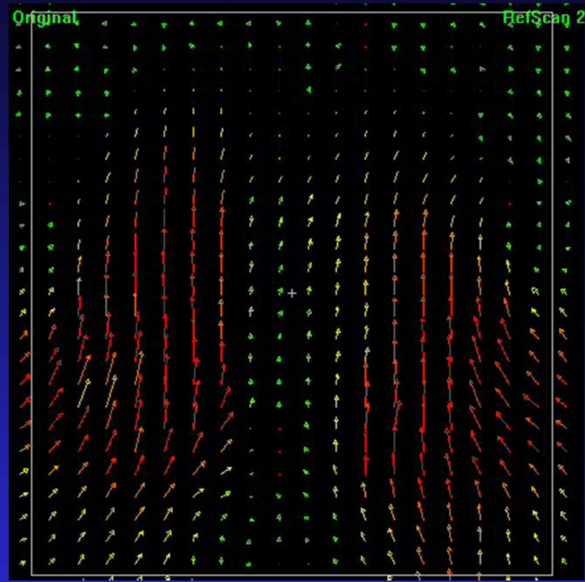


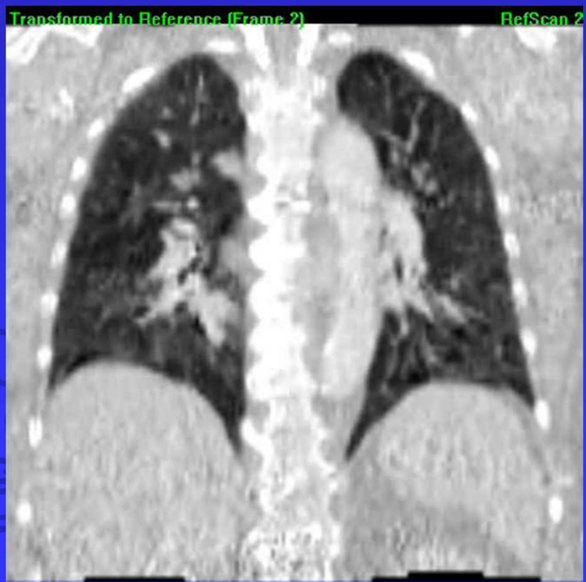
Conventional 4D CT

Adaptive 4D CT

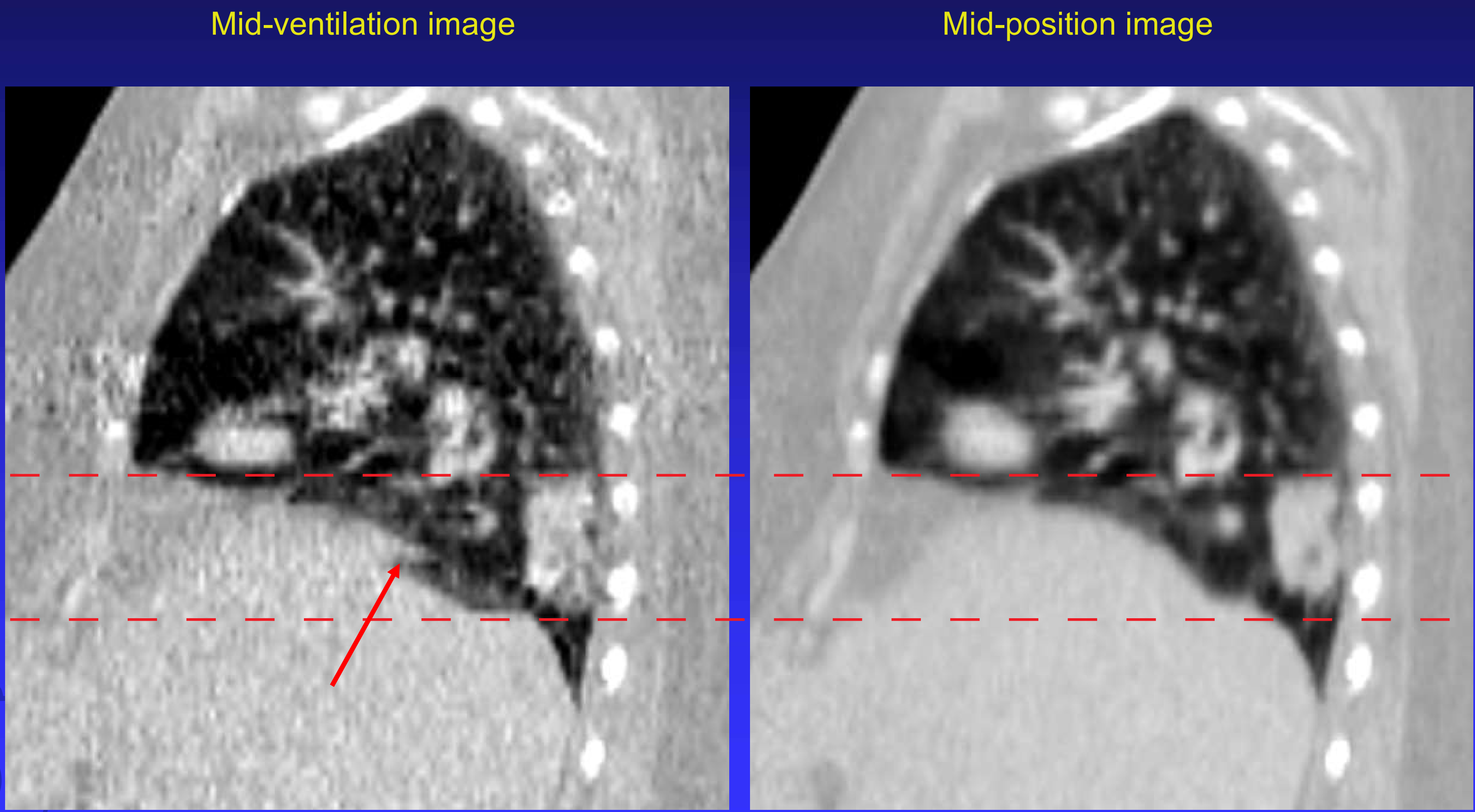
Image Enhancement







Mid-position CT: deform all anatomy to its mean position and average over all frames

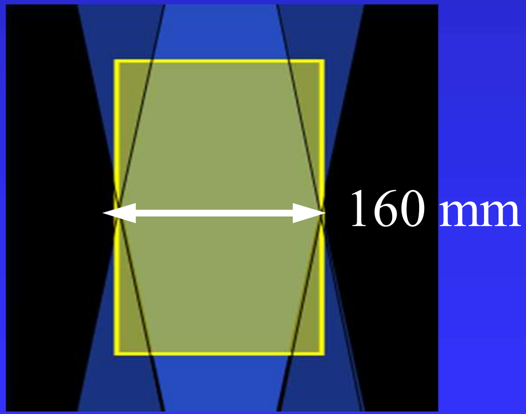


Reduces noise and artifacts

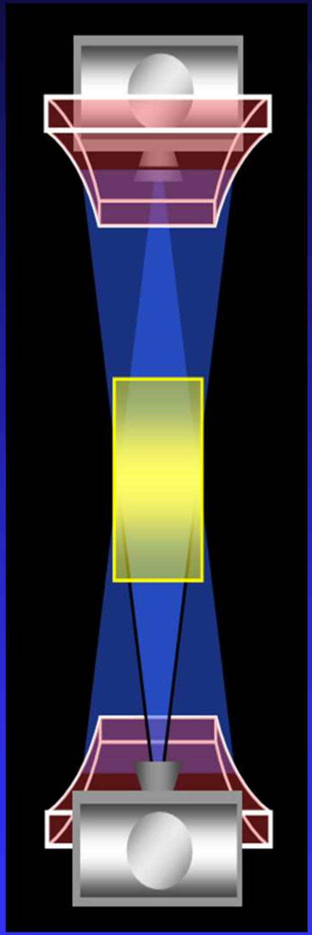
Wolthaus et al, Med Phys 2009

Background – Dynamic Volume

320-slice CT



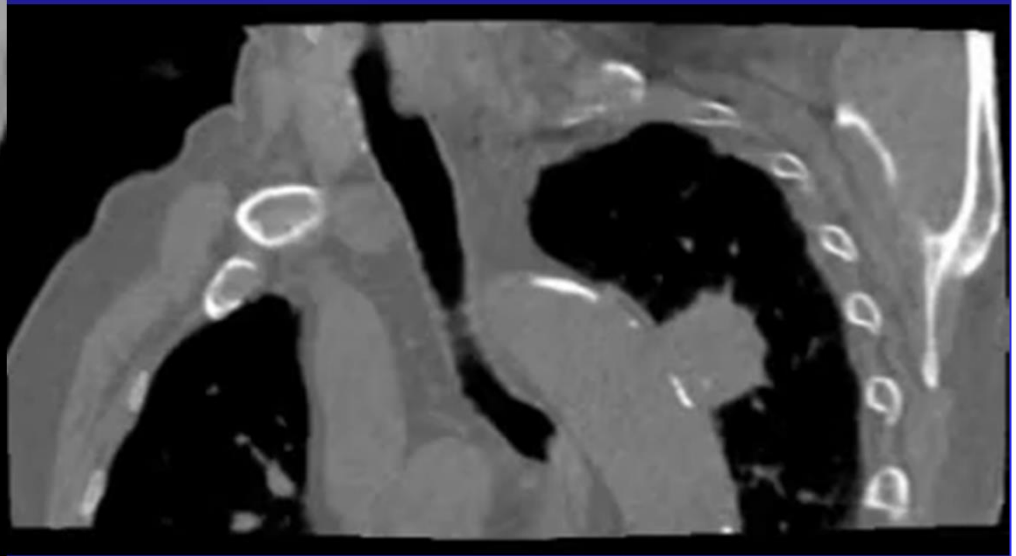
- Solid state detector
- 512 x 512 x 320
- 0.5 mm resolution
- 0.35 sec rotation
- Cone Angle 15.2°



Coolens *et al*. (2009), Implementation and Characterisation of a 320-slice CT scanner for radiotherapy simulation, Med. Phys., vol. 36 (11), pp. 5120-5127.

Respiratory Correlated 4DCT

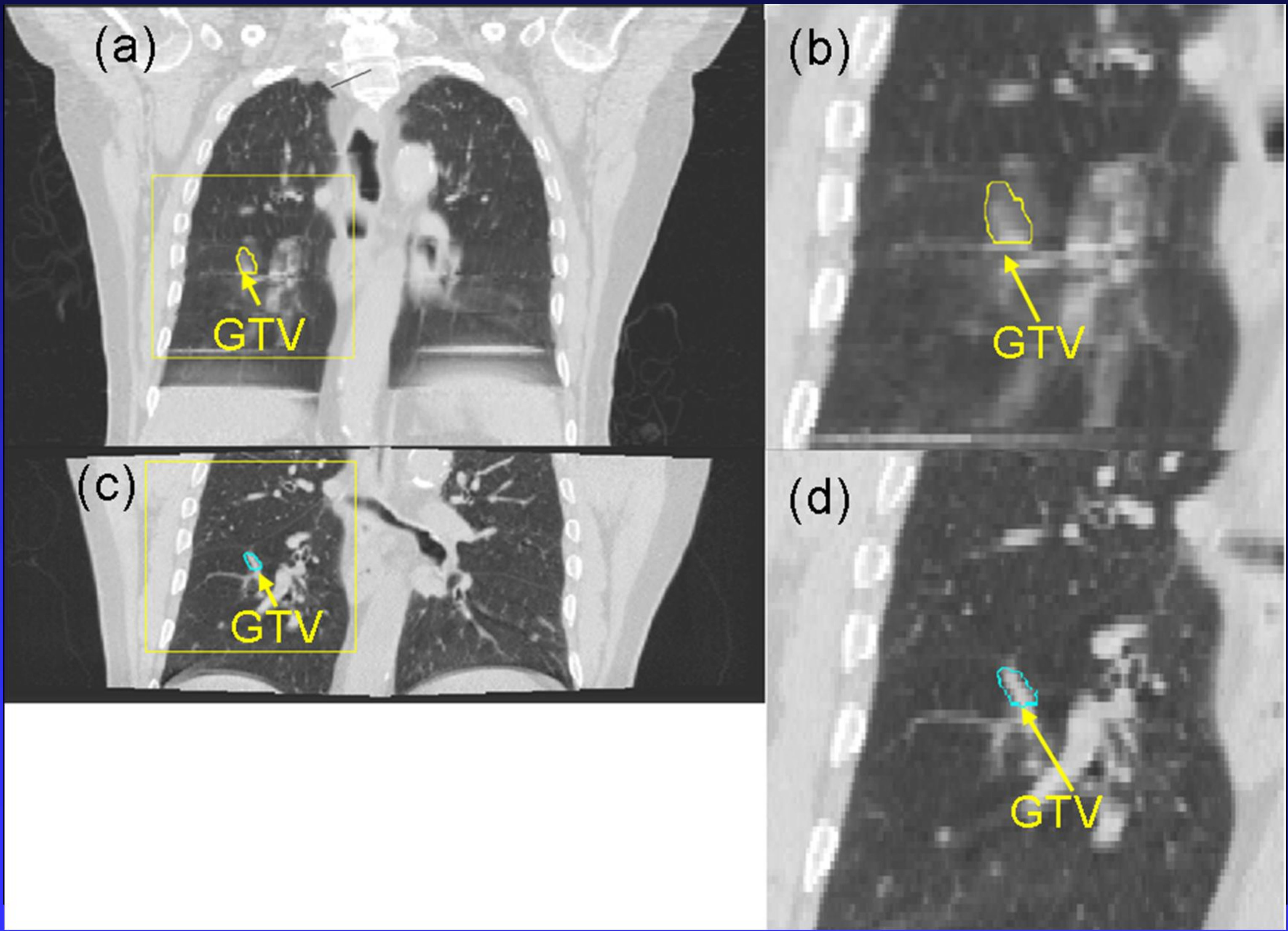
Volumetric 4DCT



Dr John Troupis, Co-director, Cardiac CT, Diagnostic Imaging, Southern Health

Courtesy of Catherine Coolens, PMH

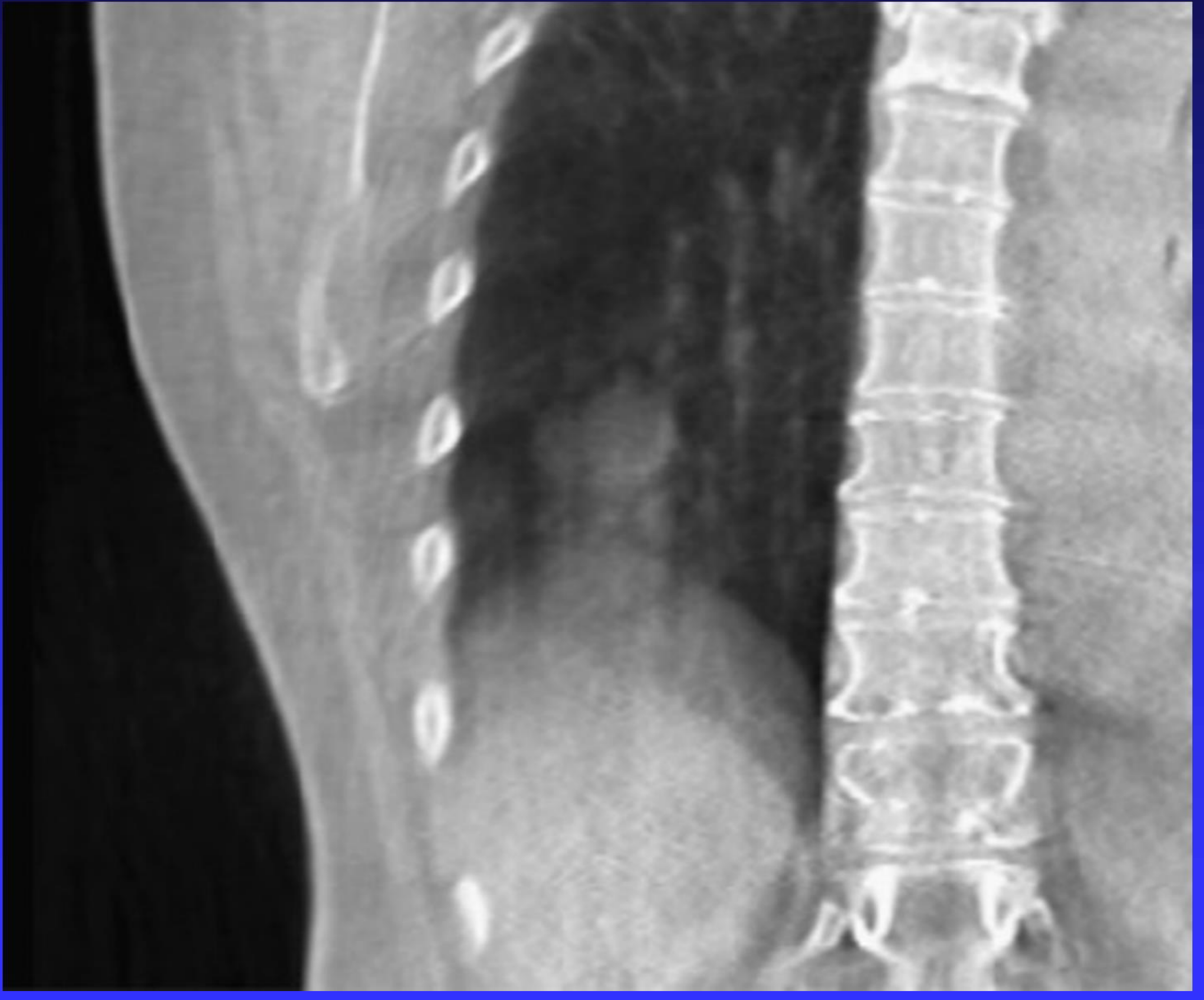
Results – Image Quality



4D Cone Beam CT

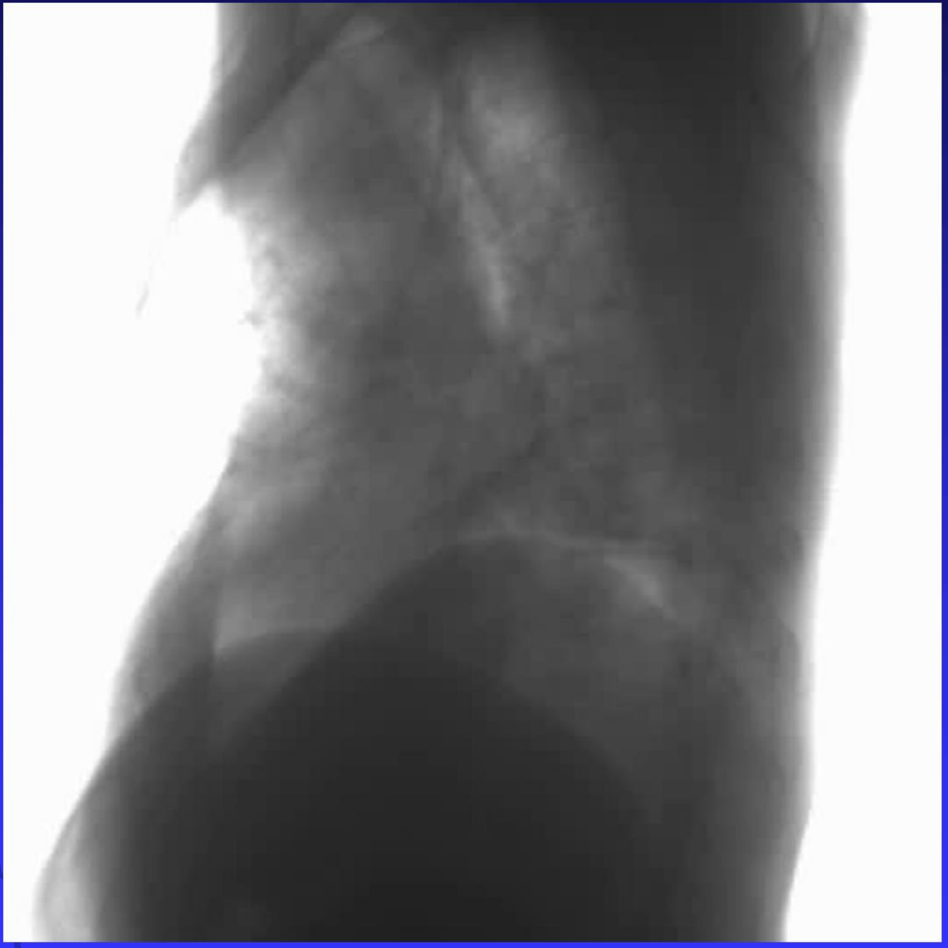
Cone Beam CT - effects of respiration

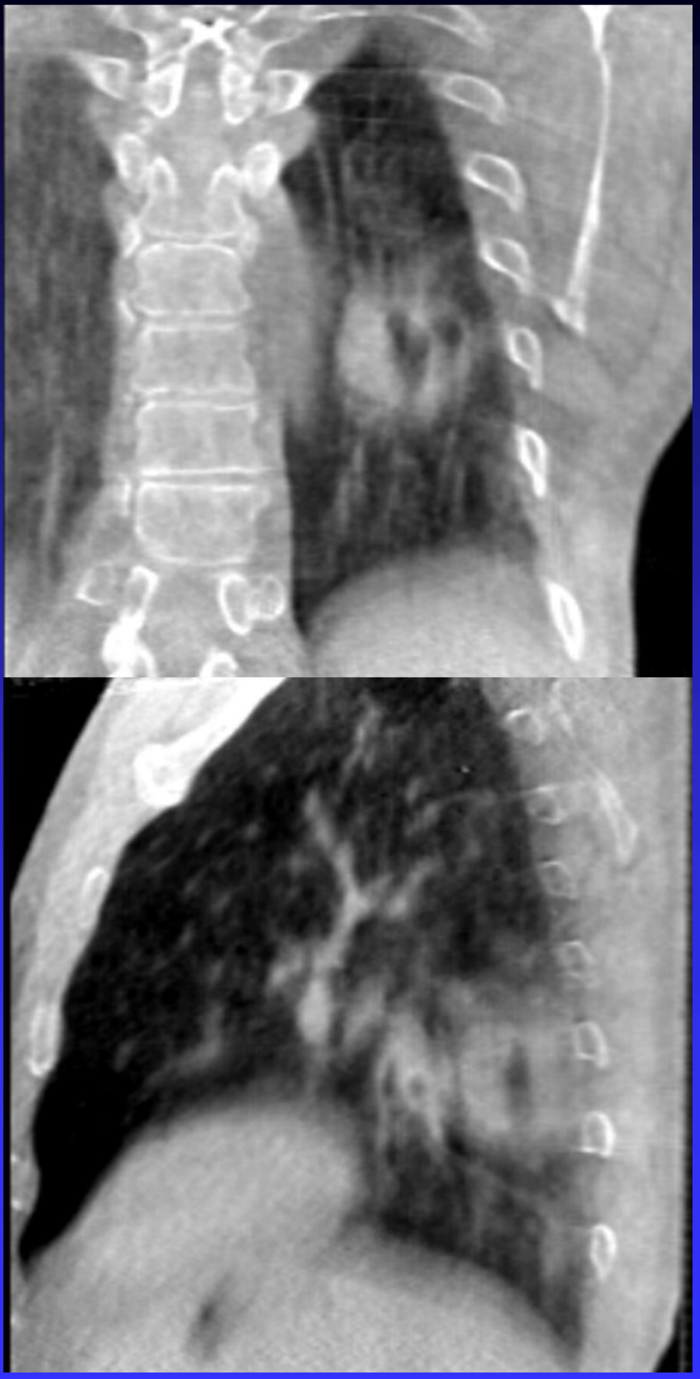
- Blurring and disappearing structures



Sonke *et.al.*, IJROBP 2008

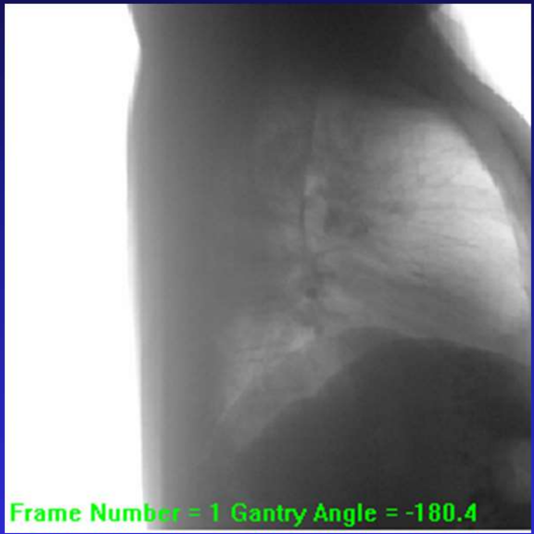
Breathing



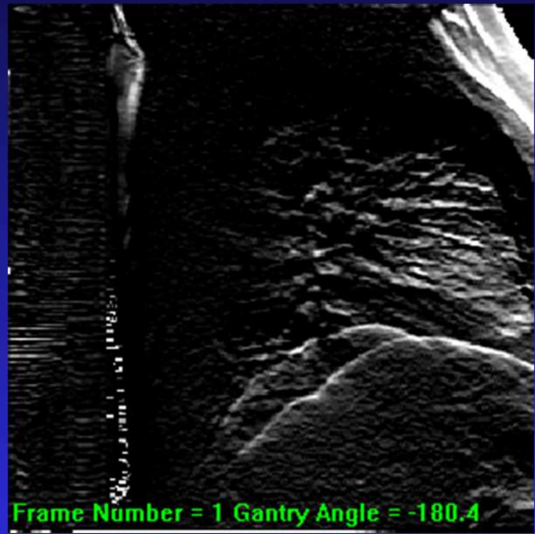


Sonke et al, Med Phys 2005

Respiratory Signal Extraction

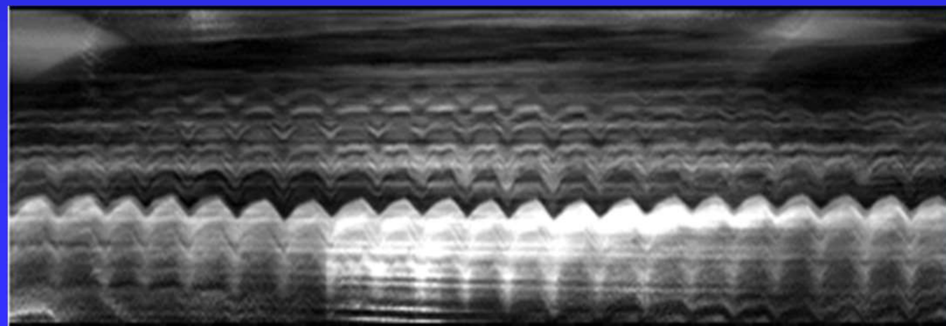


Vertical
derivative filter



Horizontal
projection

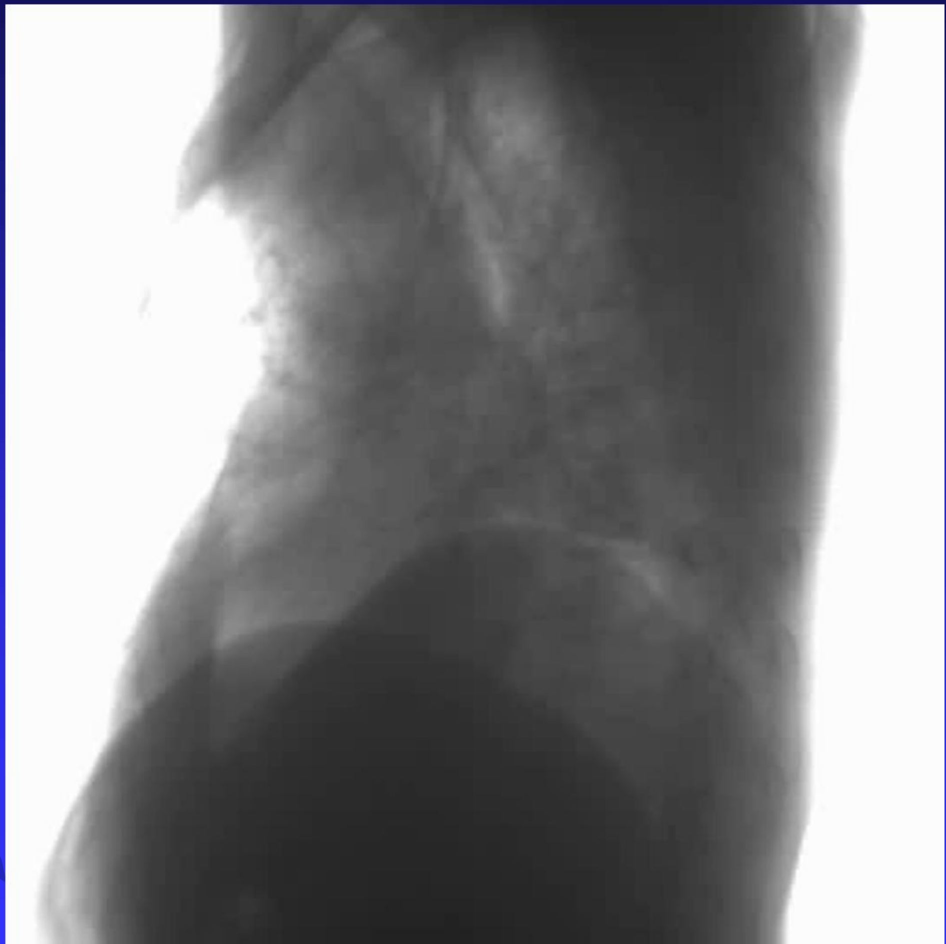
Temporal
concatenation

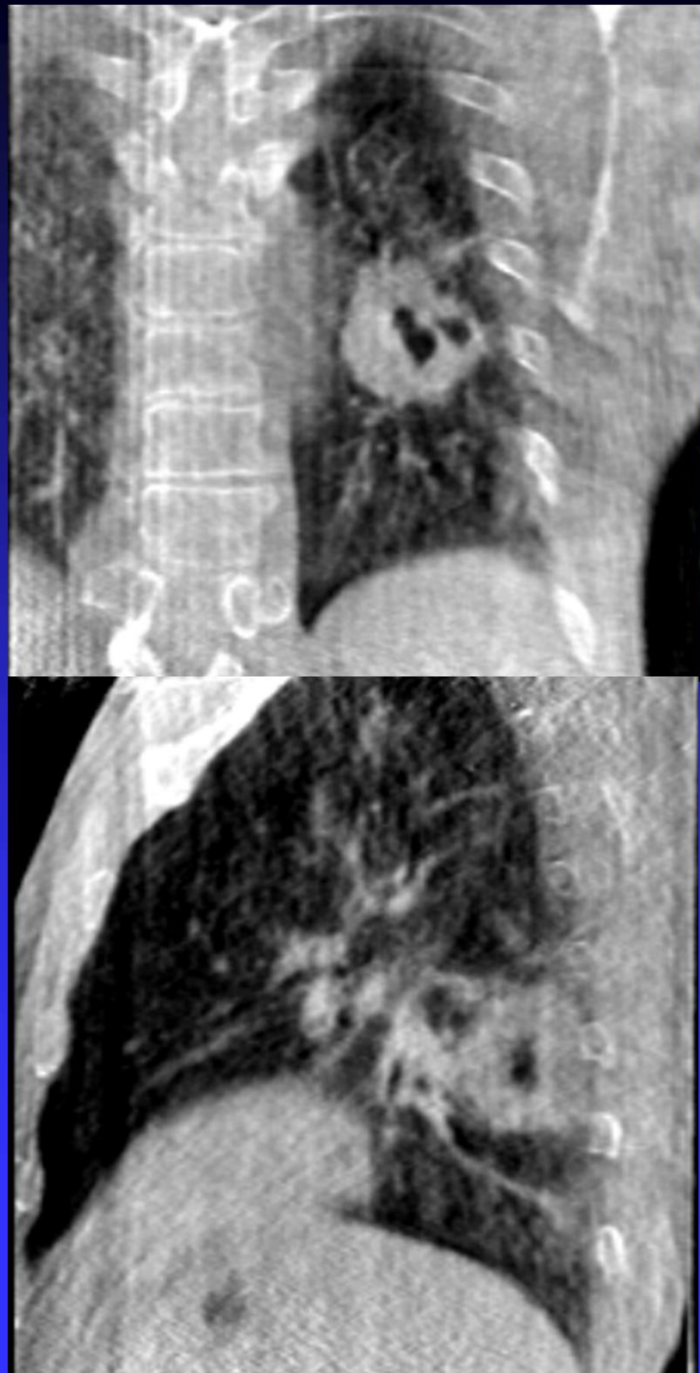


Amsterdam shroud (2D image)

Zijp et al., ICCR. 2004
van Herk et al., ICCR. 2007

RCCBCT

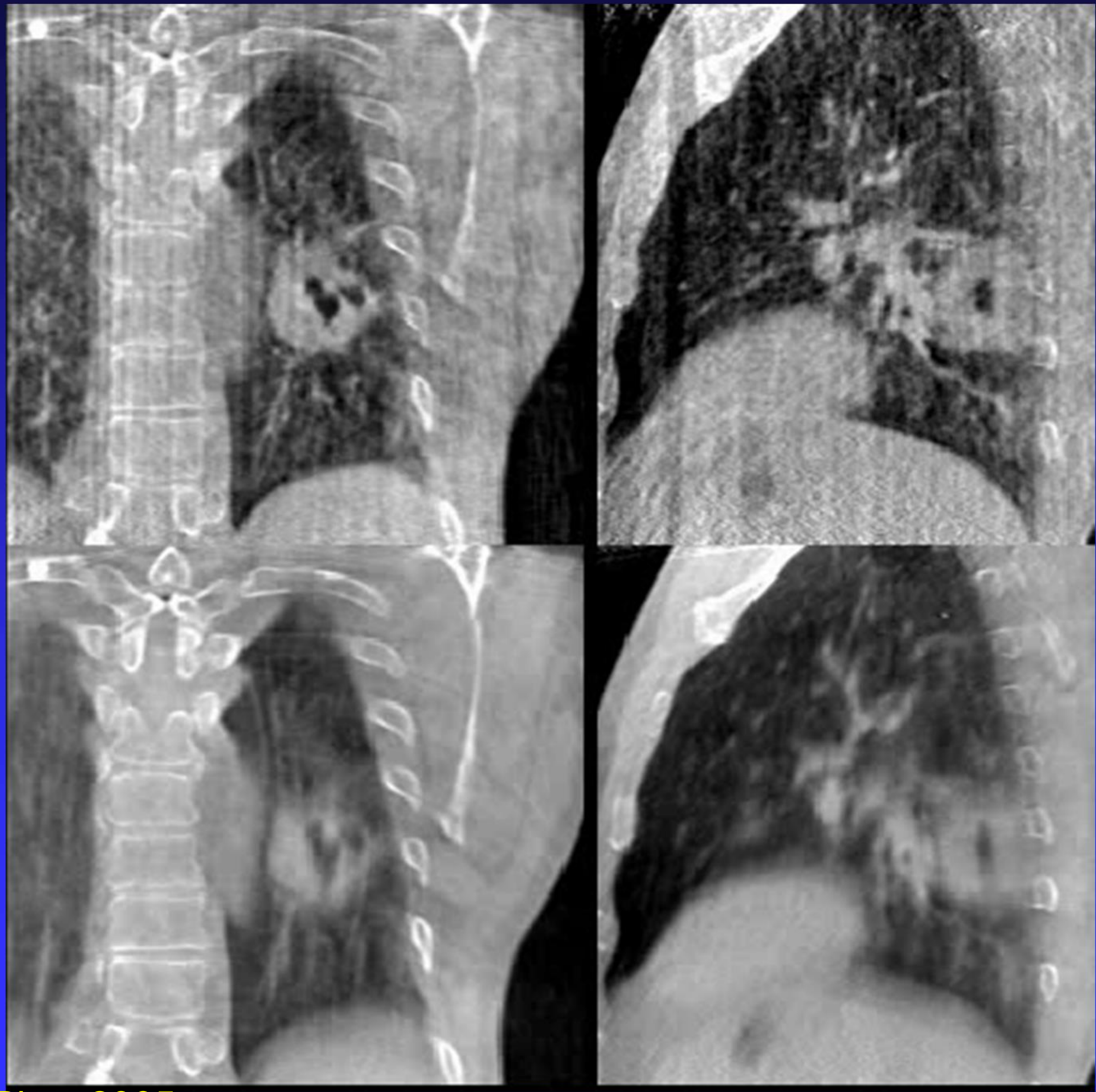




Sonke et al, Med Phys 2005

3D versus 4D CBCT

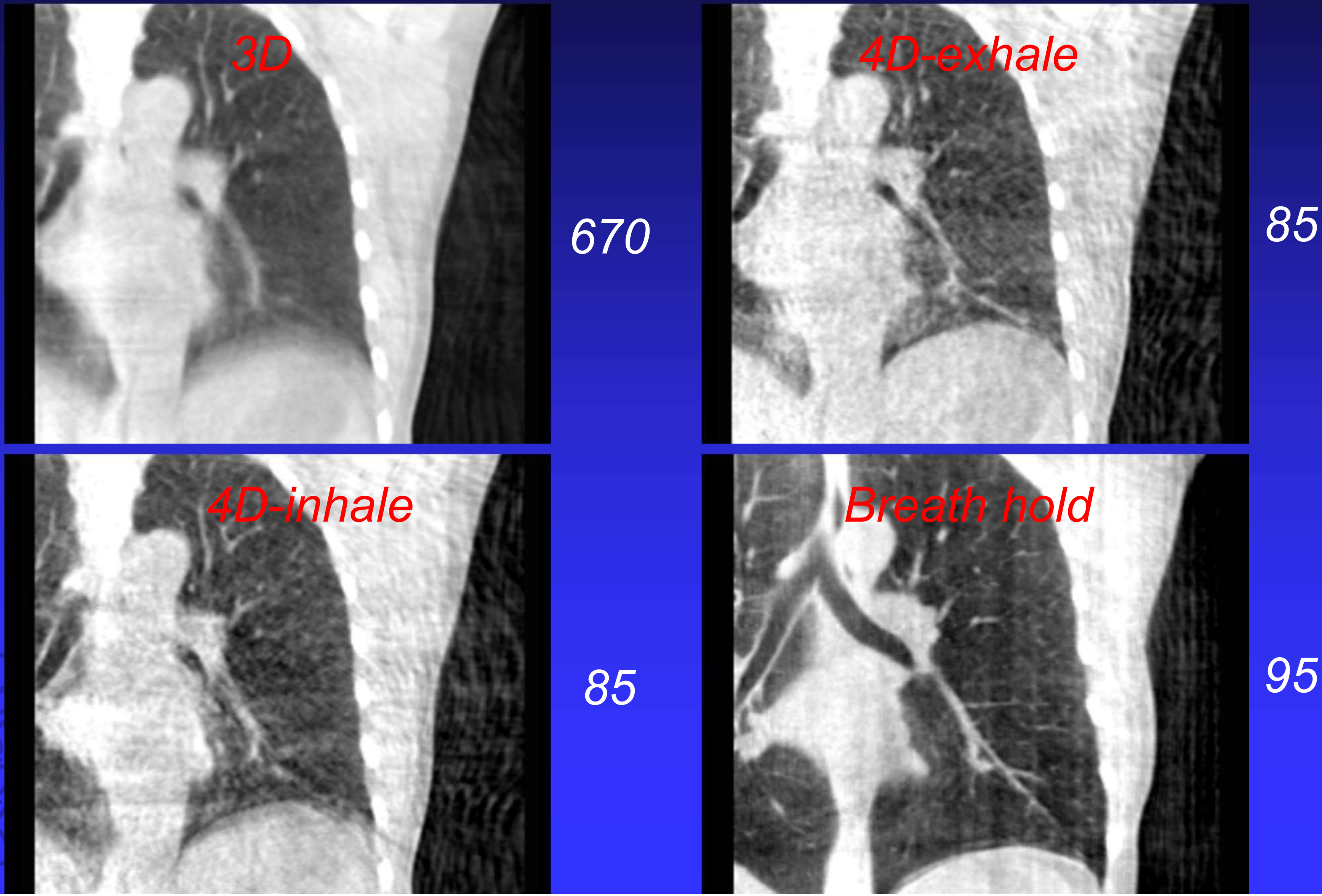
- 4D Data set
- 8 x 84 projections



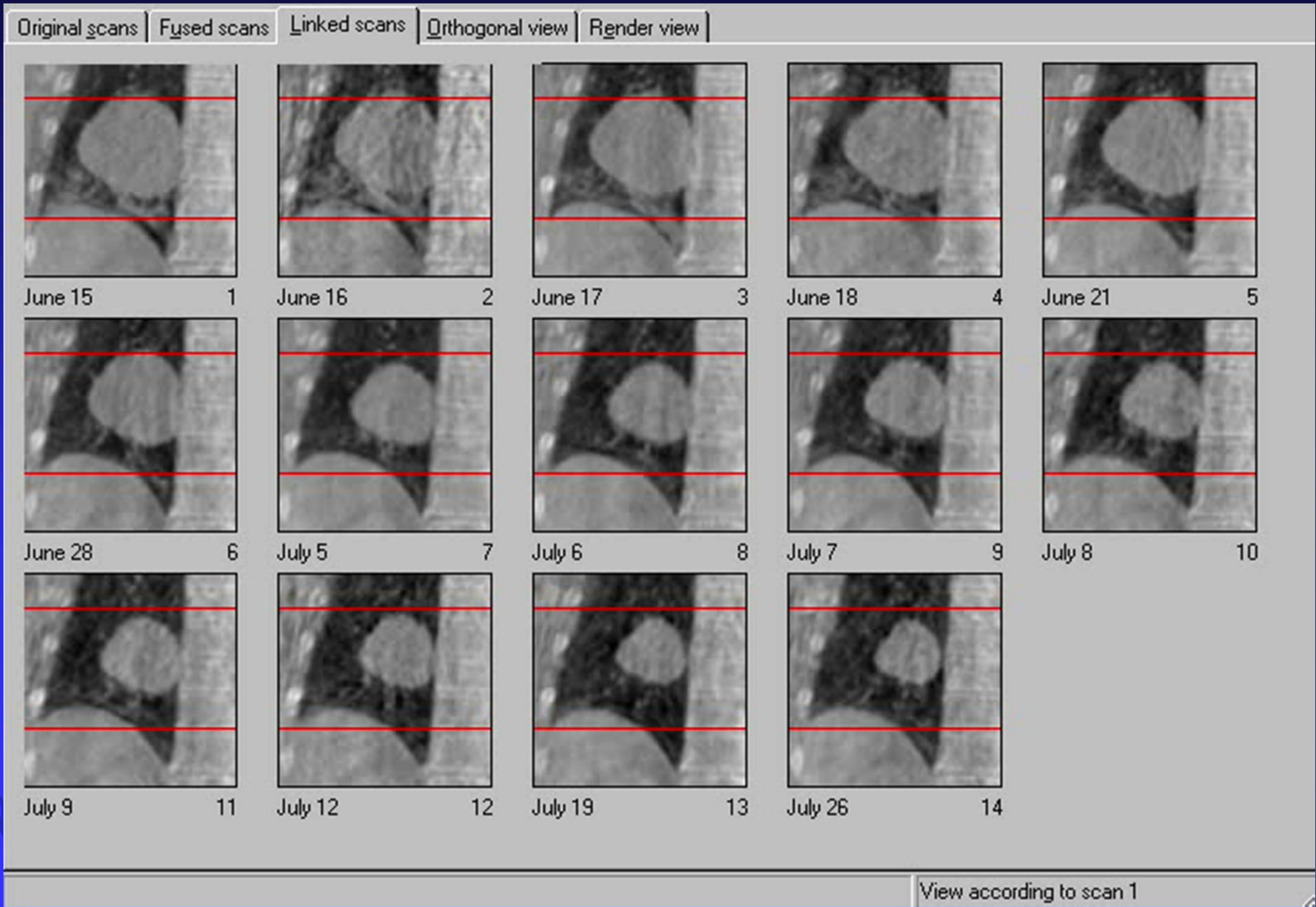
- 3D Data set
- 670 projections
- Same dose for 3D and 4D

Sonke et al, Med Phys 2005

Cone beam CT Image Quality



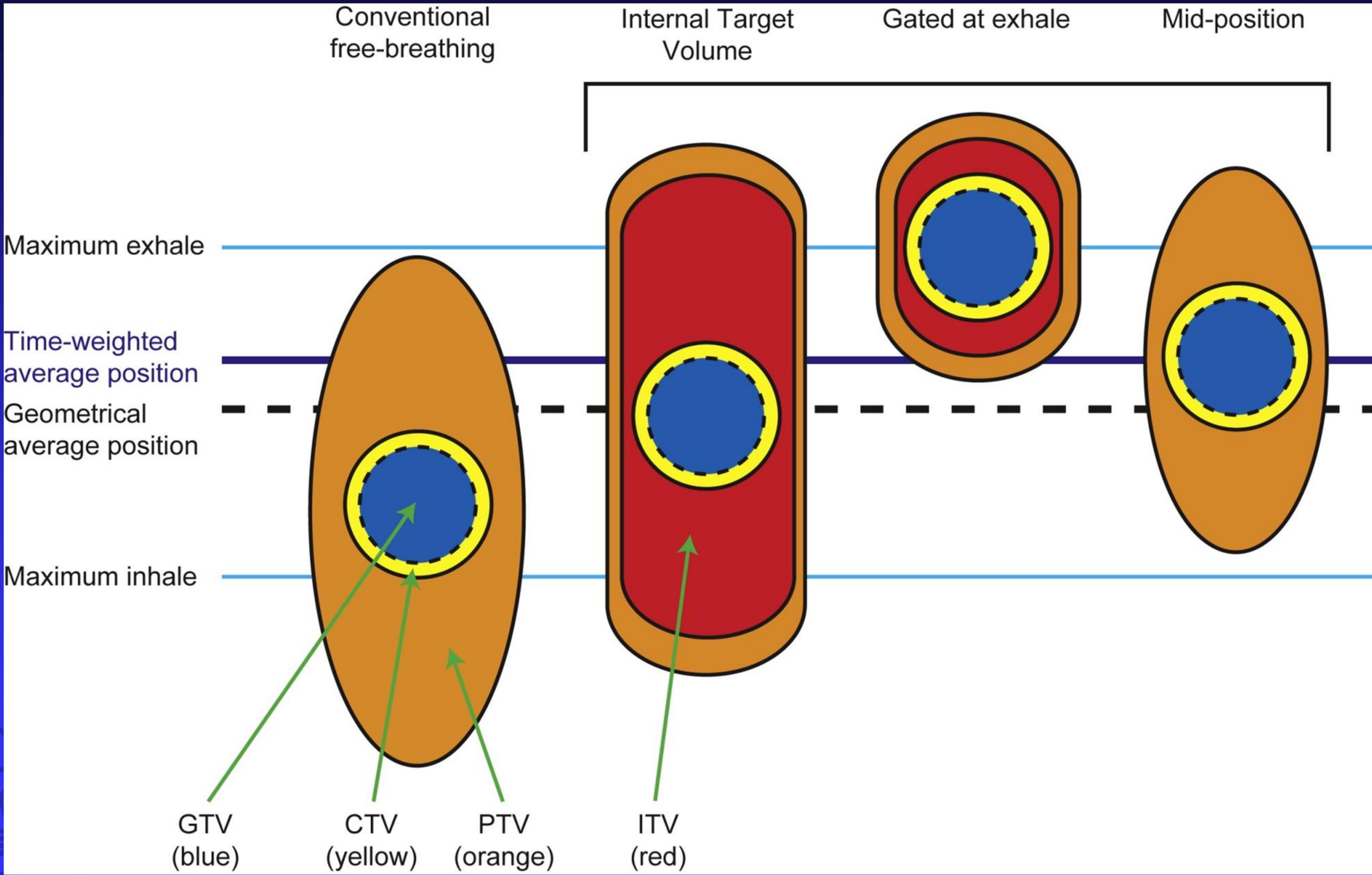
Repeat 4D cone beam CT



Shows respiration, tumor shrinkage and baseline position variation

4D in Treatment Planning

Impact on treatment Margins



Wolthaus et al. IJROBP 2008

Internal Target Volume

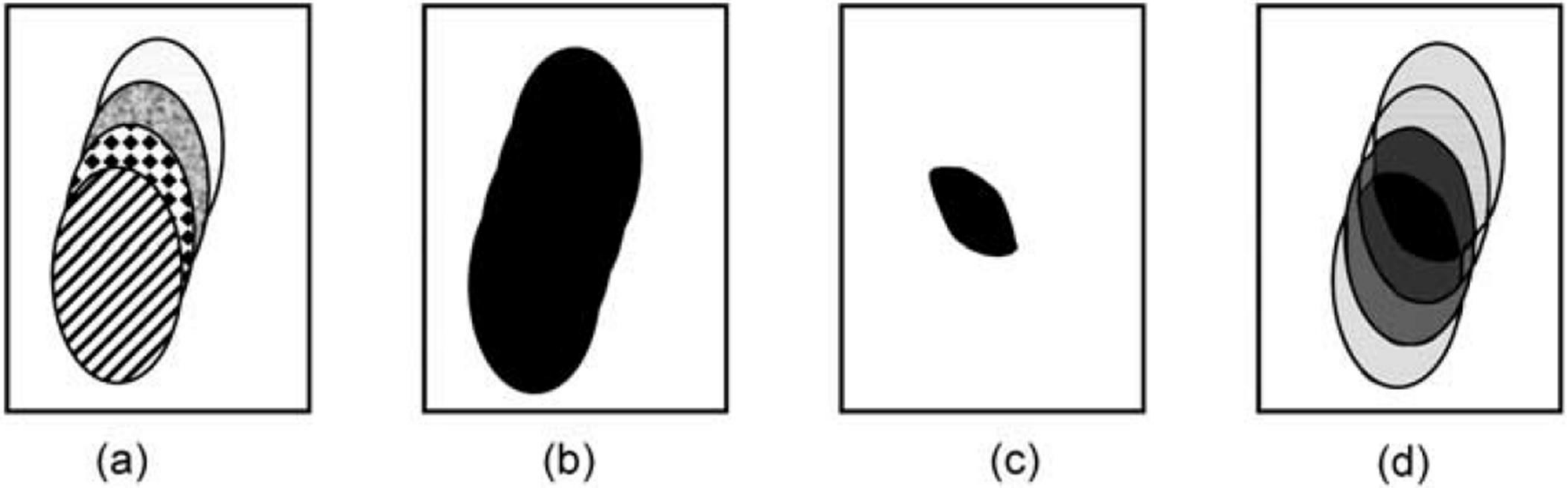
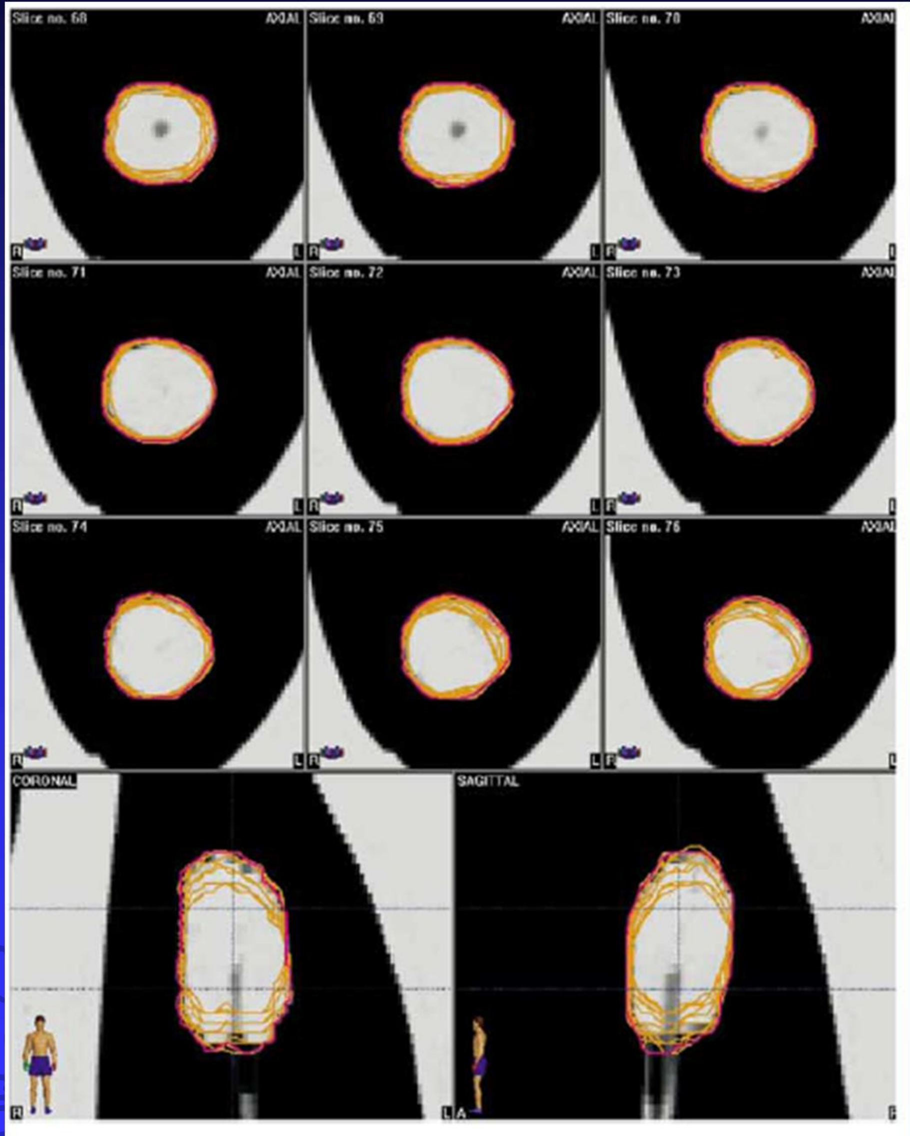


Fig. 1. Pixel-based intensity projection protocols from four-dimensional computed tomography (CT) data sets of a mobile tumor, illustrating (a) separate phases of the four-dimensional CT, (b) maximum intensity projection, (c) minimum intensity projection, and (d) mean intensity projection.

Underberg et al. IJROBP 2005

Internal Target Volume via MIP



Good correspondence between ITVs derived from 10 phases and MIPs:

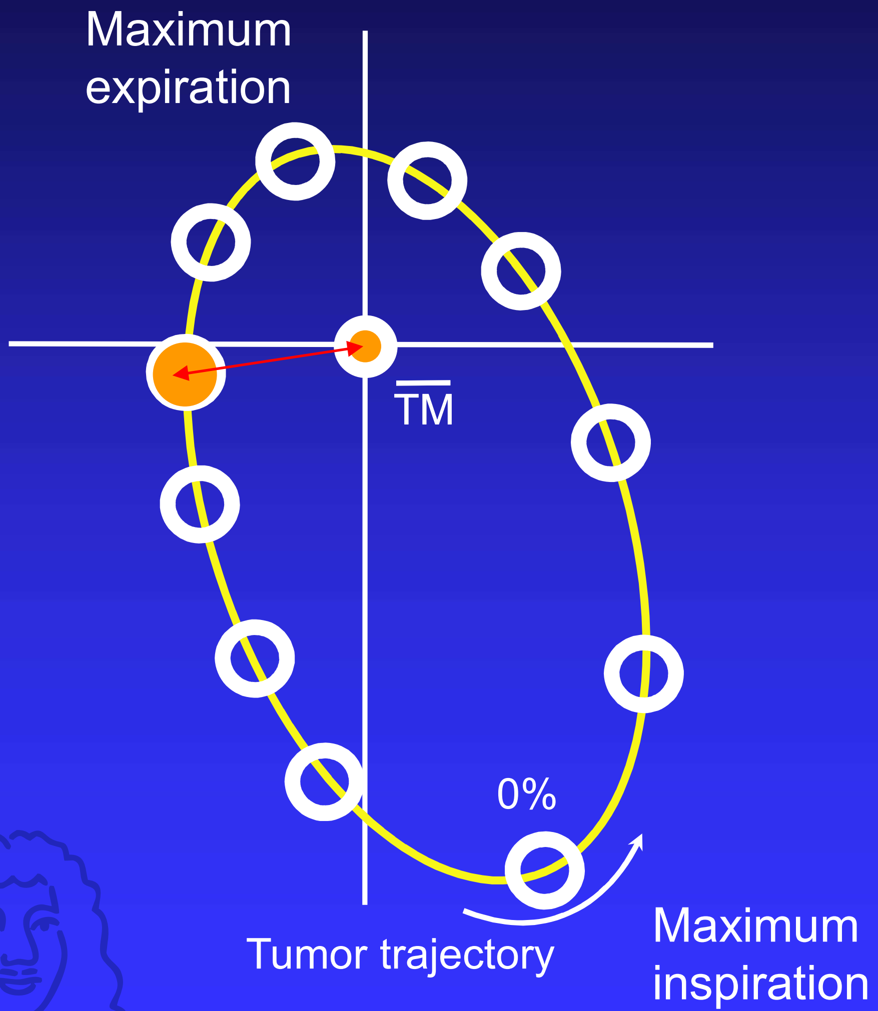
Volume ratios 1.07±0.05

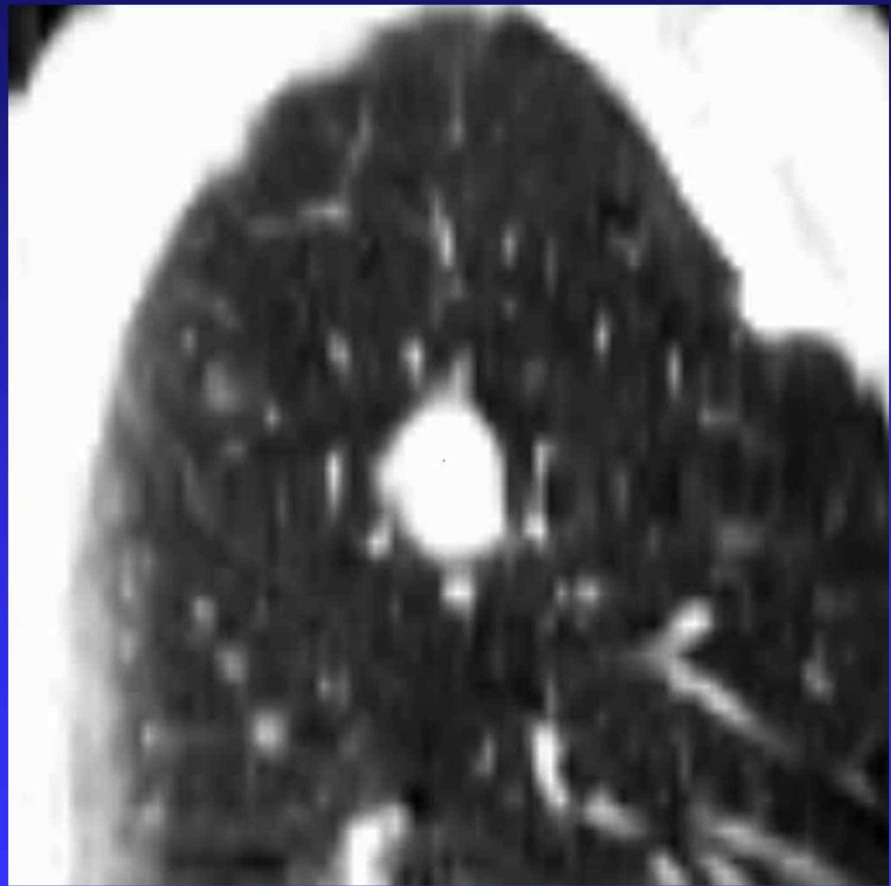
COM difference 0.4±0.2mm

Underberg et al. IJROBP 2005

Mid-ventilation

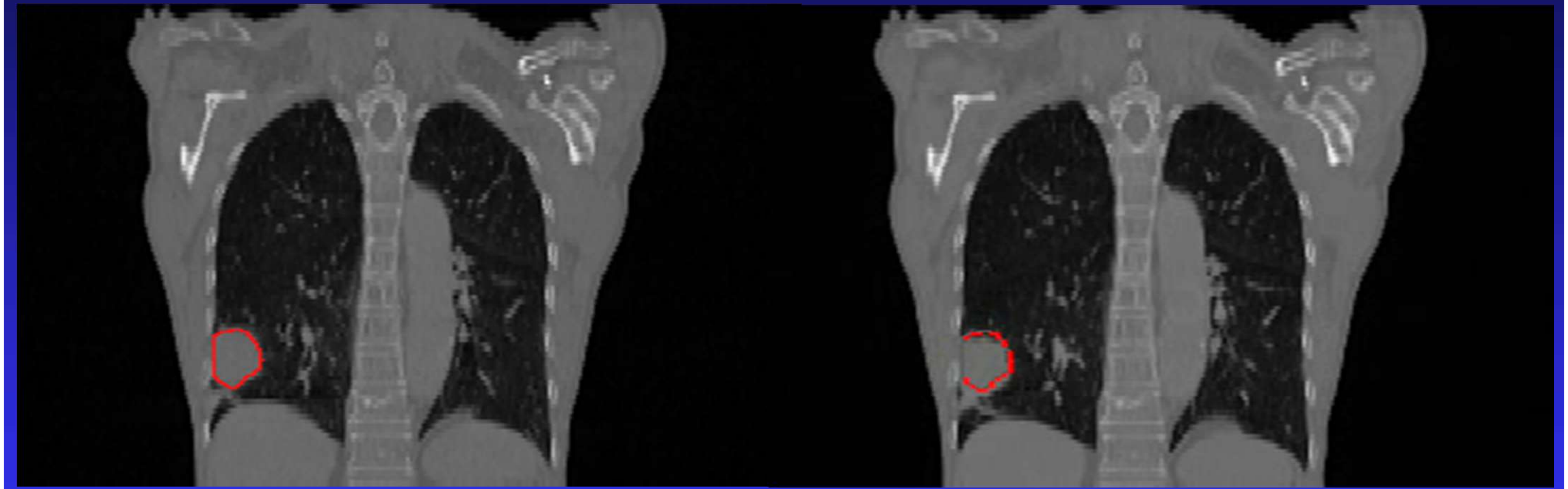
Selection of a single appropriate CT scan





Wolthaus et al, IJROBP 2006; Nijkamp et al ICCR 2007

Mid-ventilation is very simple (used clinically on hundreds of patients)



Mid-ventilation CT

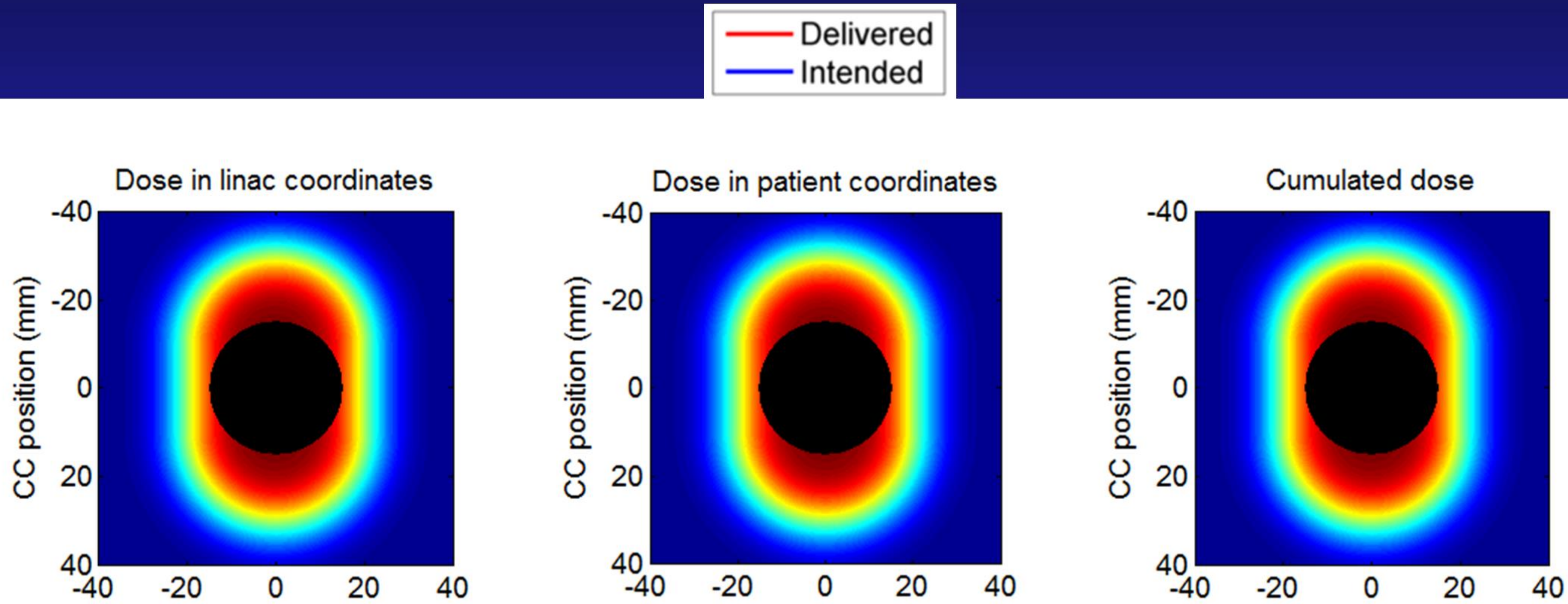
4D CT

Eliminates systematic error due to imaging (except hysteresis)
Geometrically and dosimetric very close to full 4D plan!

Wolthaus et al, IJROBP 2006; Nijkamp et al ICCR 2007

ITV illustration

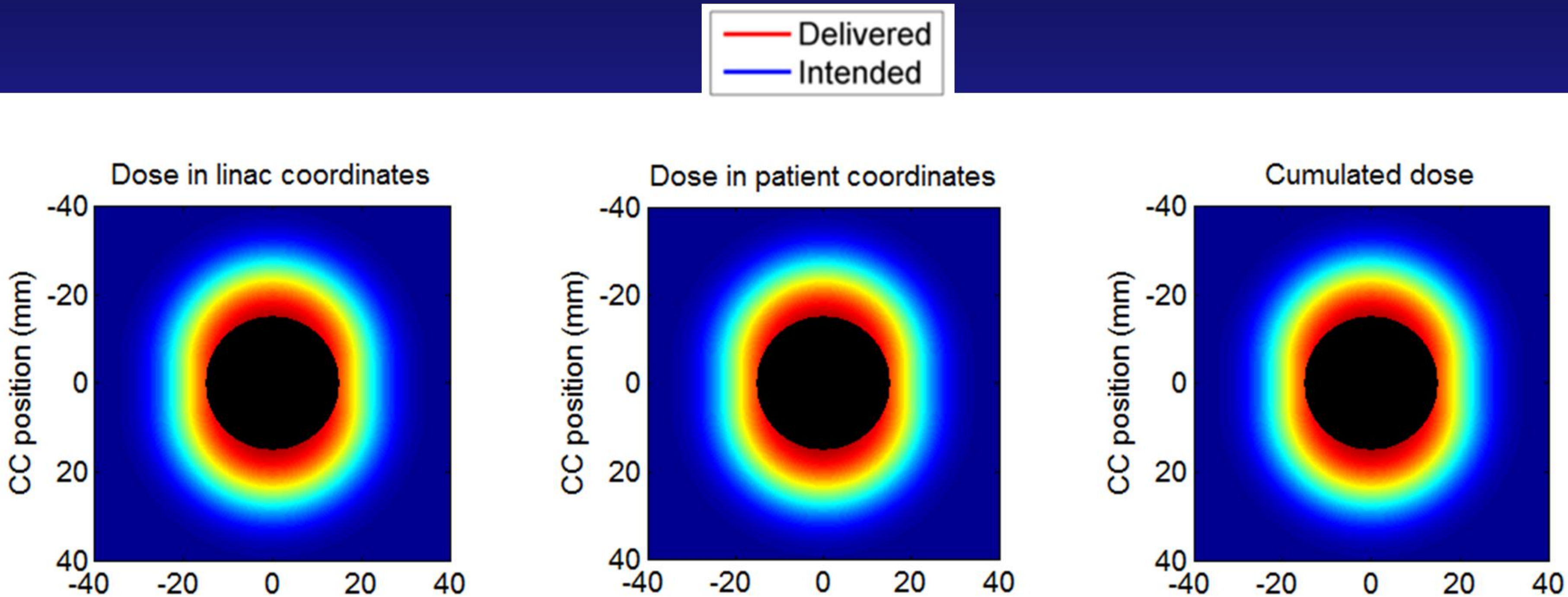
20 mm target with 20 mm CC motion



An ITV strategy uses a too large a margin

Mid-Position

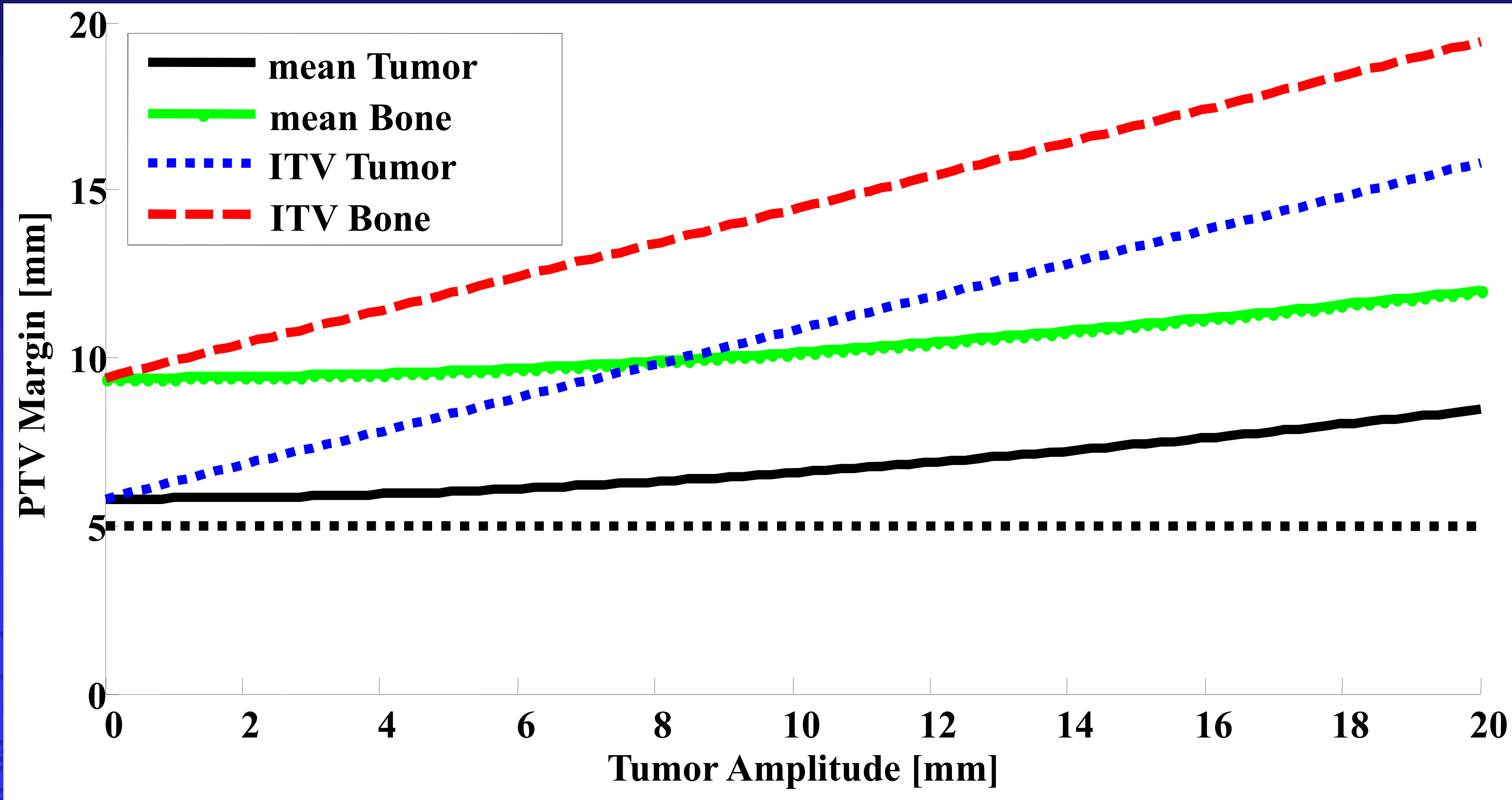
20 mm target with 20 mm CC motion



A MidP strategy allows an accurate delivery of the prescribed dose.

Margin for SBRT

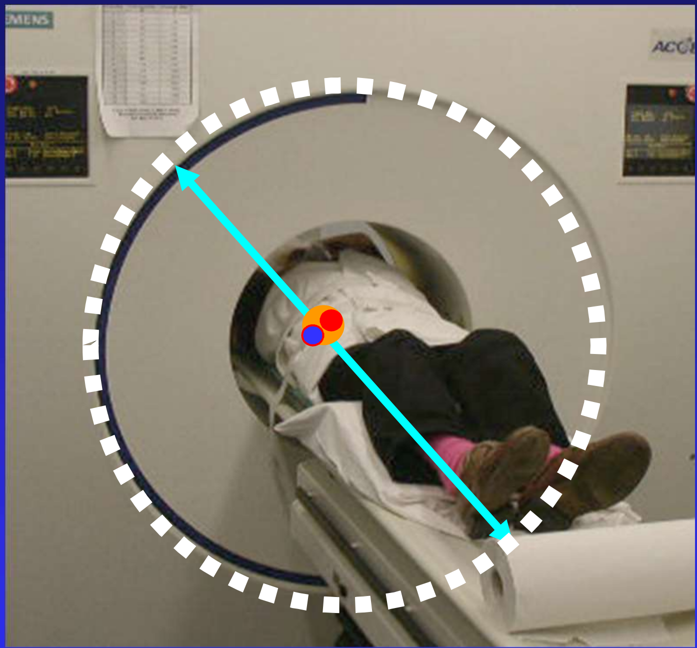
$$M = 2.5\Sigma + 0.84\sqrt{(\sigma_p^2 + \sigma^2)} - 0.84\sigma_p^2$$

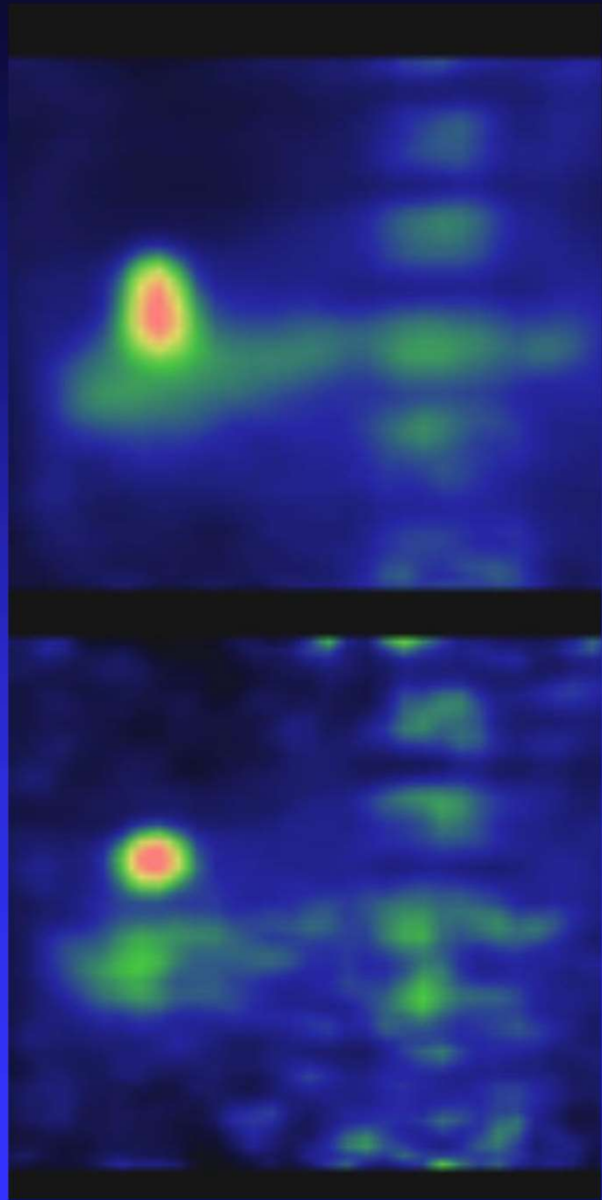


Sonke et al. IJROBP, 2009

4D PET

Motion Artifacts in PET

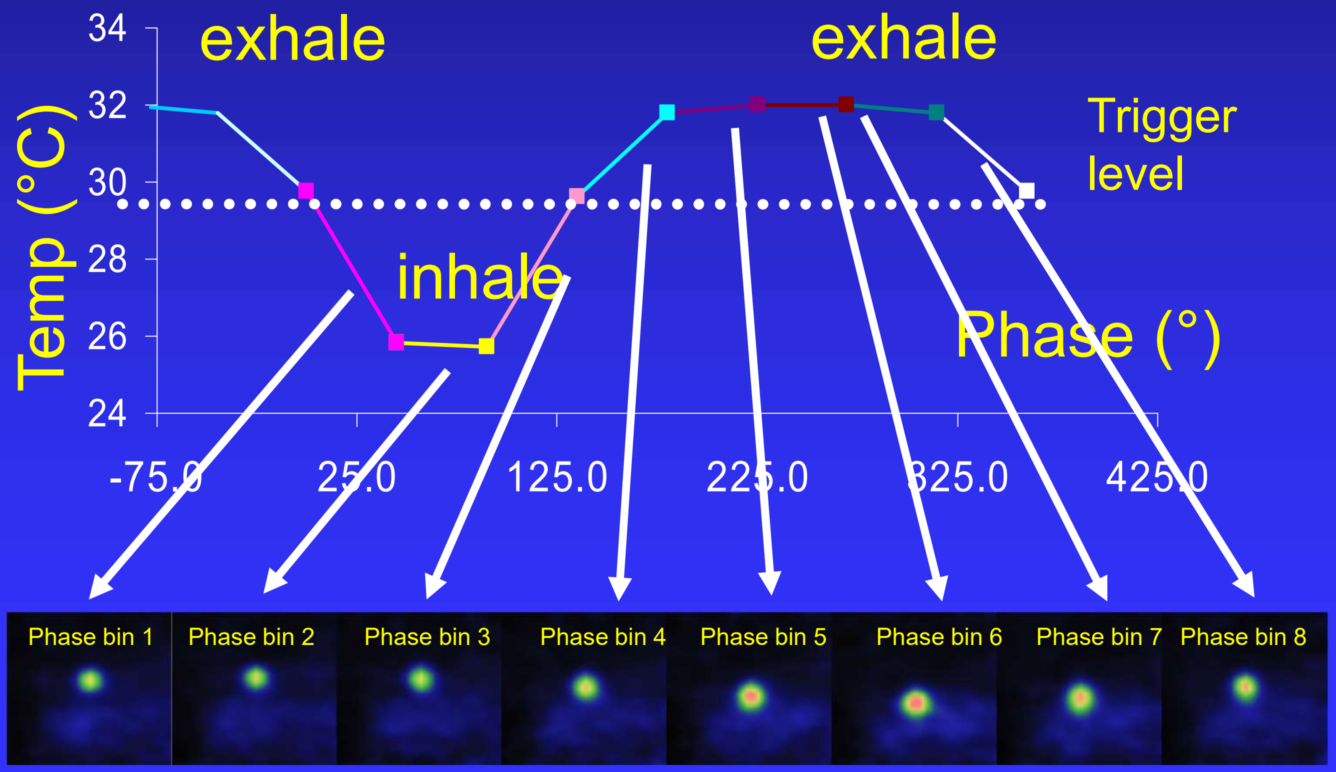




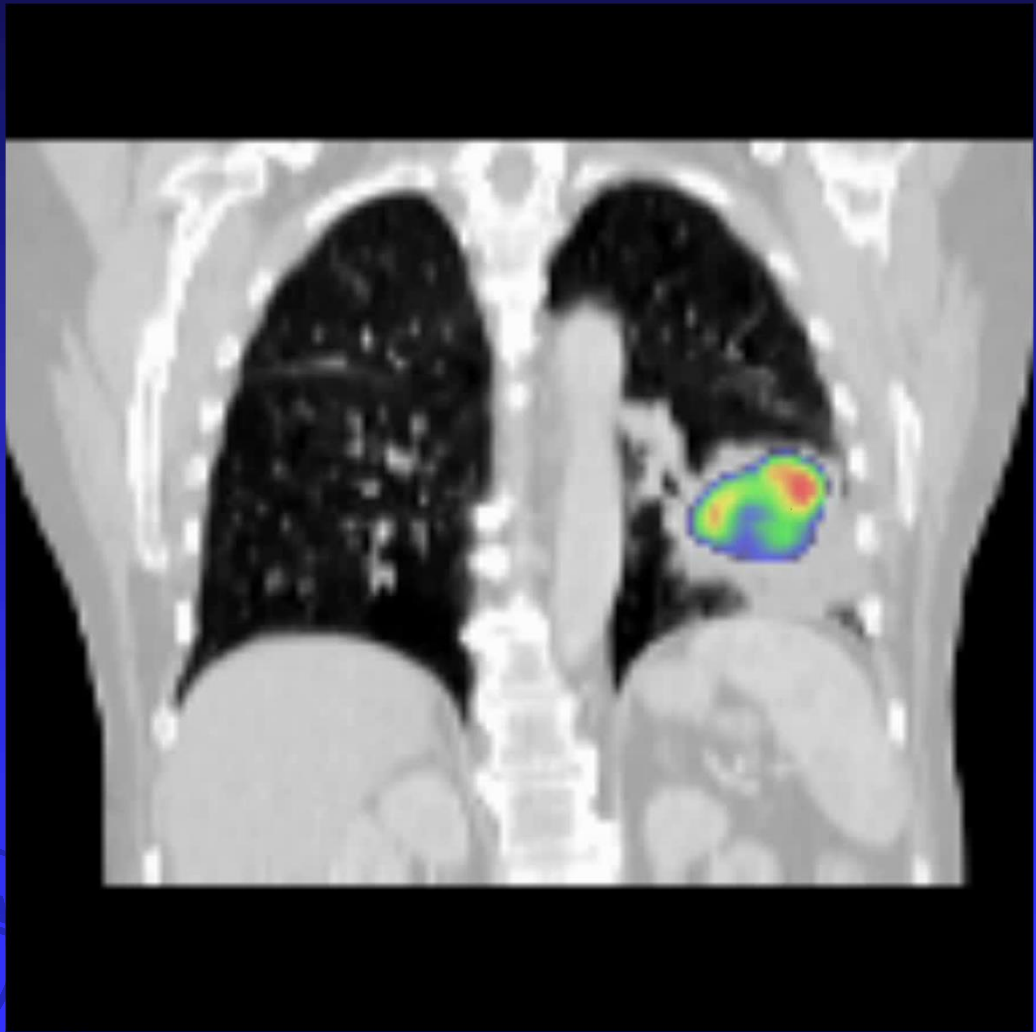
Tumor is enlarged due to blurring

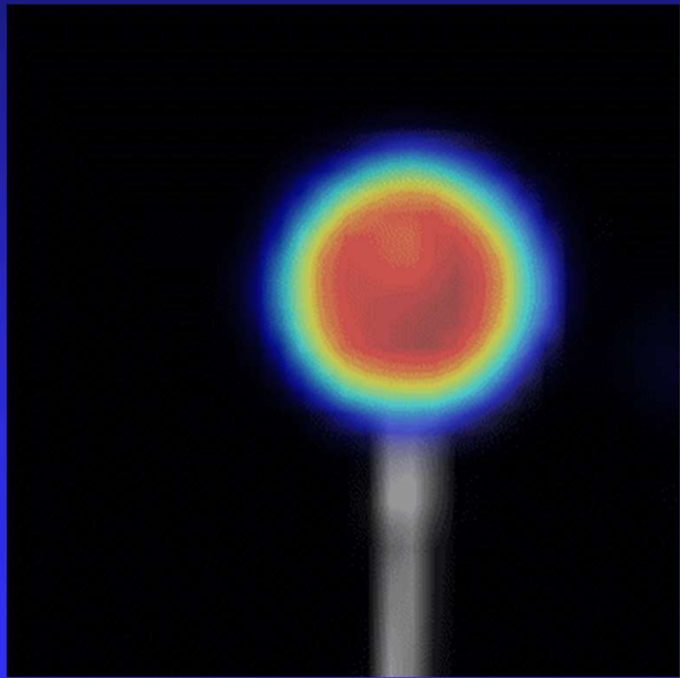
Respiration Correlated PET

- Continuous emission → division based on respiration phase
- Prospective gating:Respiratory trace triggers onset of binning for each breathing cycle
- Retrospective: Respiratory trace is used to bin counts from listmode



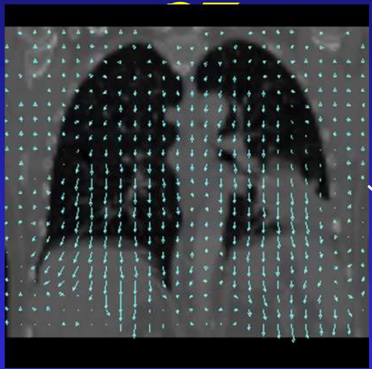
PET motion imaging





CT based Mid-Position PET

Motion detection in 4D



Deformation of 4D PET to CT MidP

Average of Respiration Phases

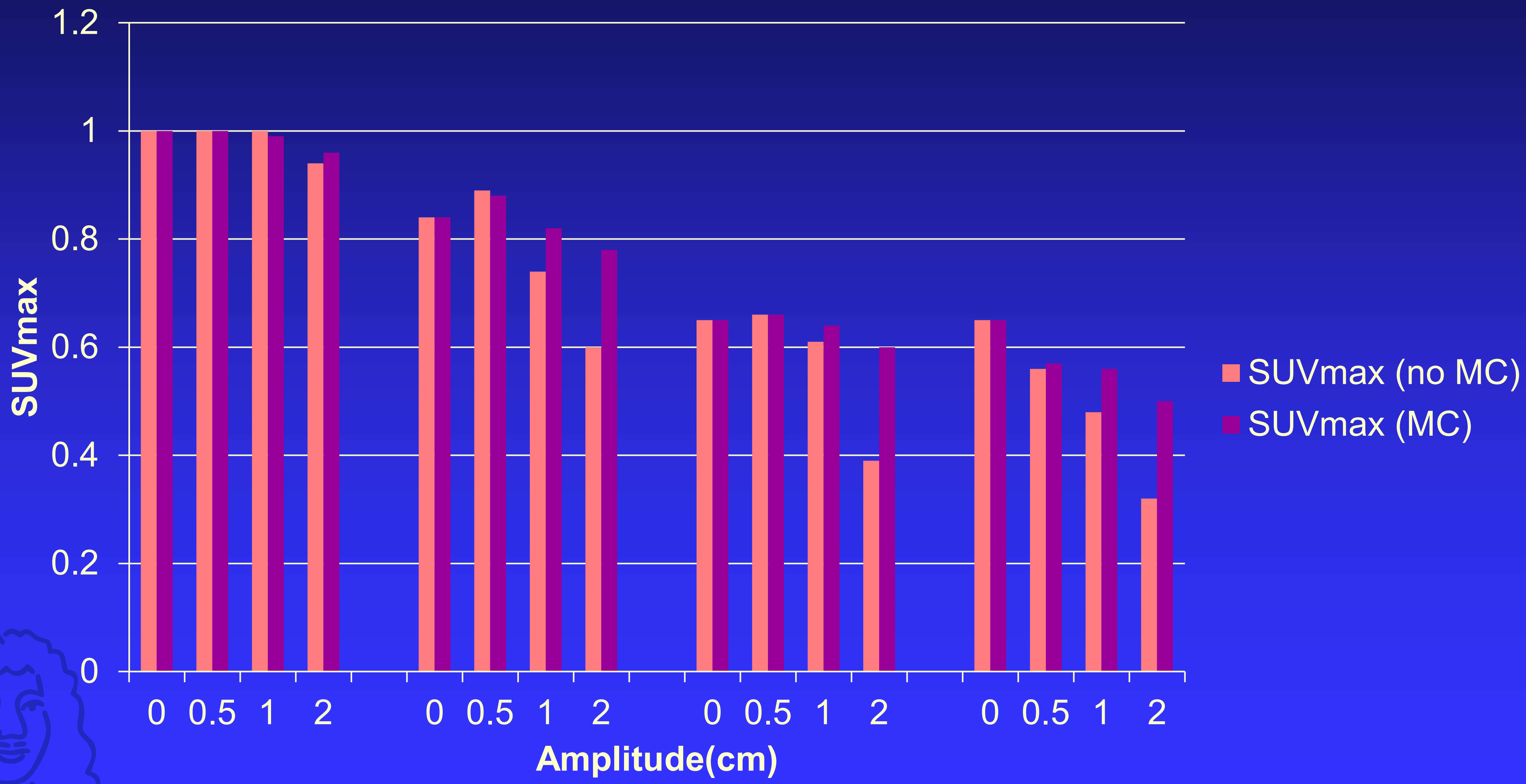
Wolthaus et al,
Medical Physics, 2008 (35)

Phantom Experiments

- Philips Gemini TF PET/CT
- Sinusoidal respiration phantom
- 4 radioactive spheres (diameters: 1.2cm, 1.5cm, 2.1cm, 3.4cm)
- 4 different amplitudes:

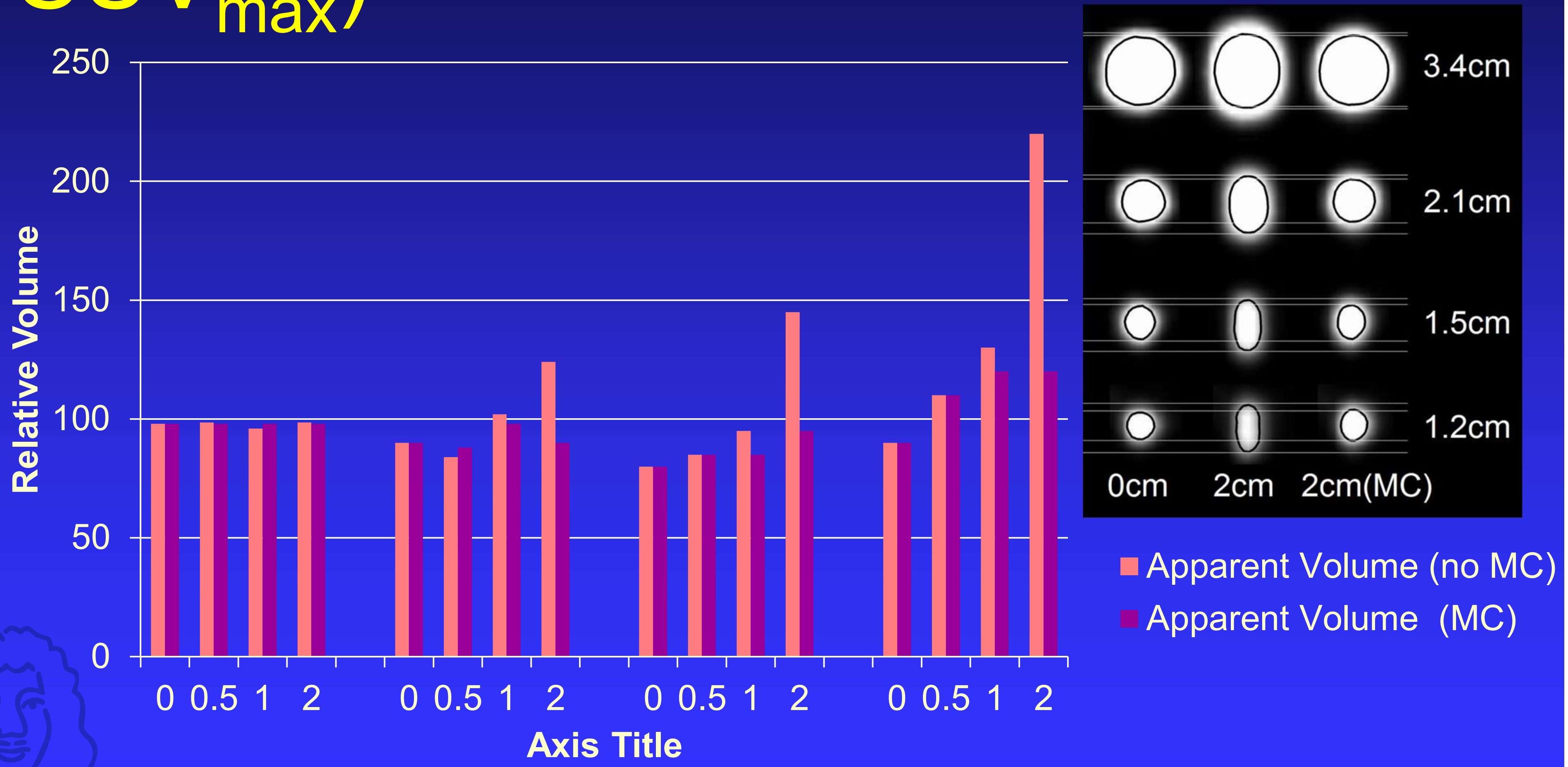
  (static, 0.5cm, 1cm, 2cm)

Maximum SUV in spheres



ESTRO IGRT 2017

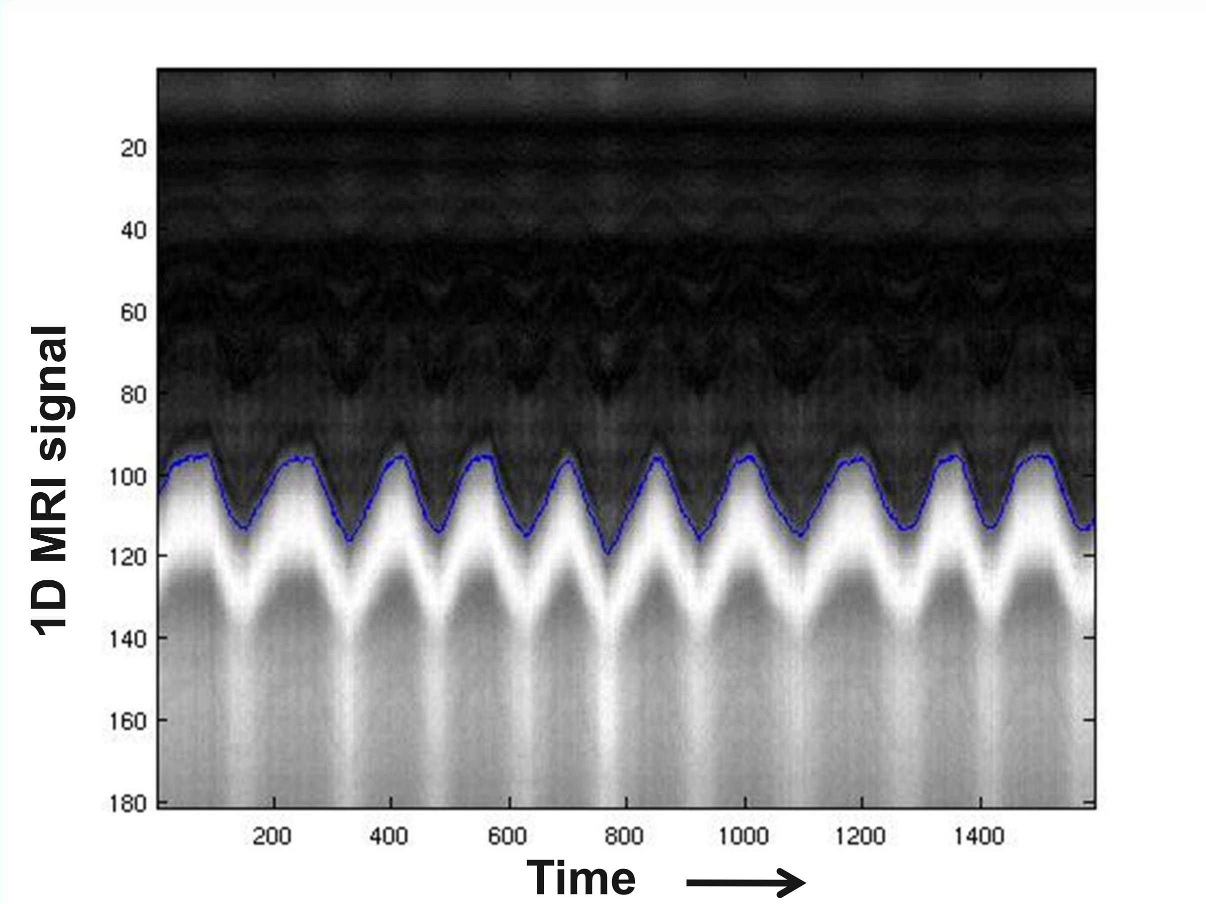
Apparent volume in spheres (based on threshold of 40% of SUV_{max})



4D MRI

1D MRI, Navigator echos (NE)
15 ms per acquisition

University Medical Center Utrecht

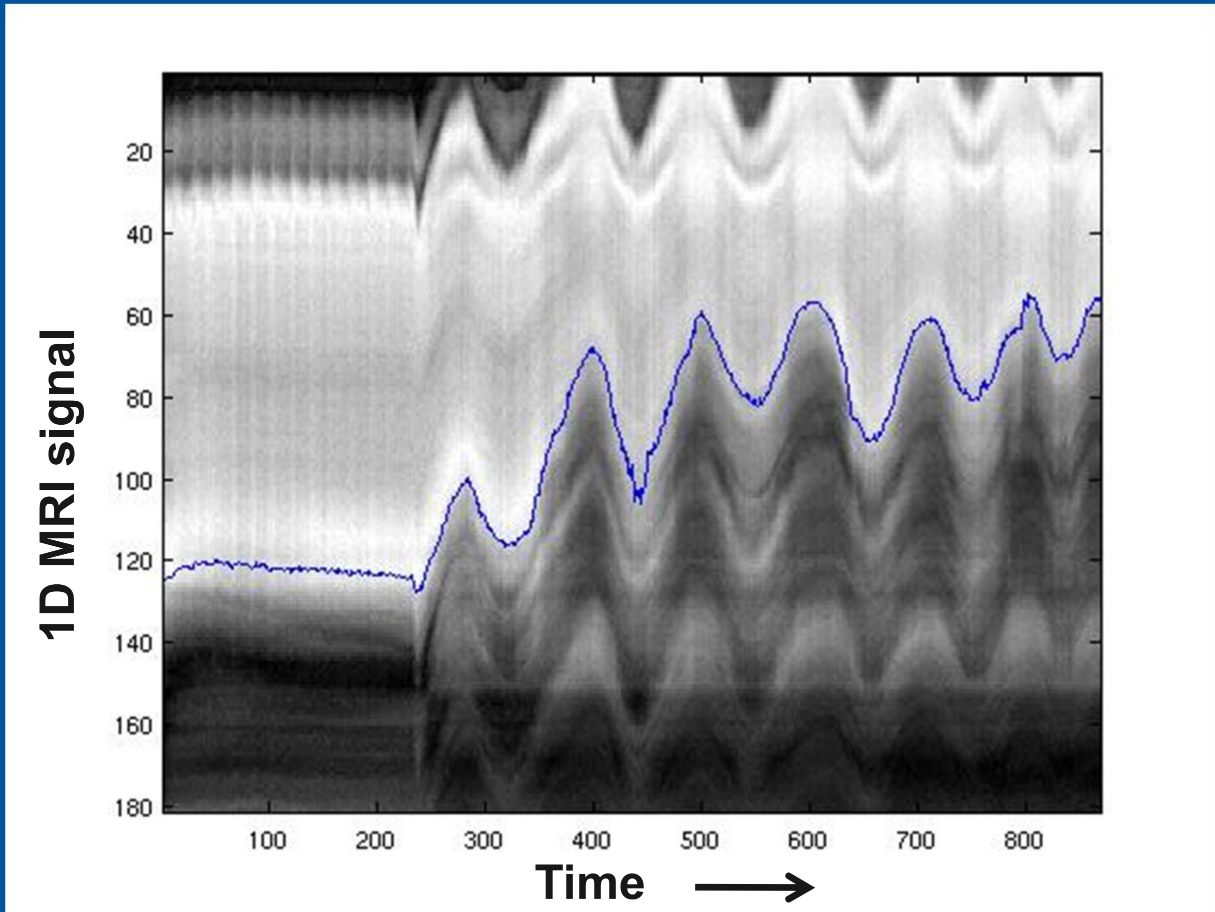


- In diagnostics used to track/gate respiration
- Imaging stack is moved according to NE signal
- Diaphragm monitored
- Can be positioned anywhere in any orientation

Monitoring breathing at superior side of liver

1D MRI navigators, monitoring breath hold stability and on-set of breathing

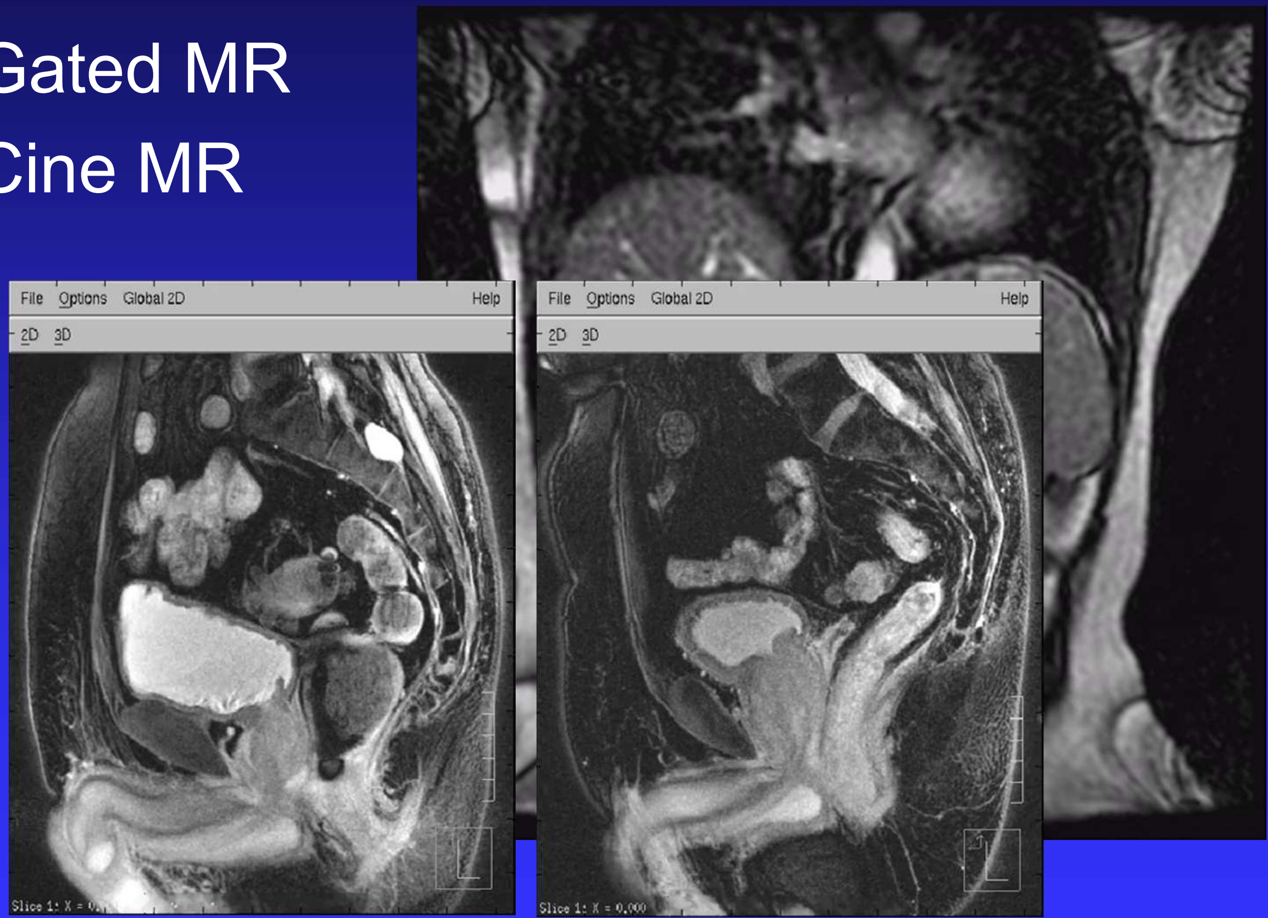
University Medical Center
Utrecht



Monitoring breath hold at inferior side of liver

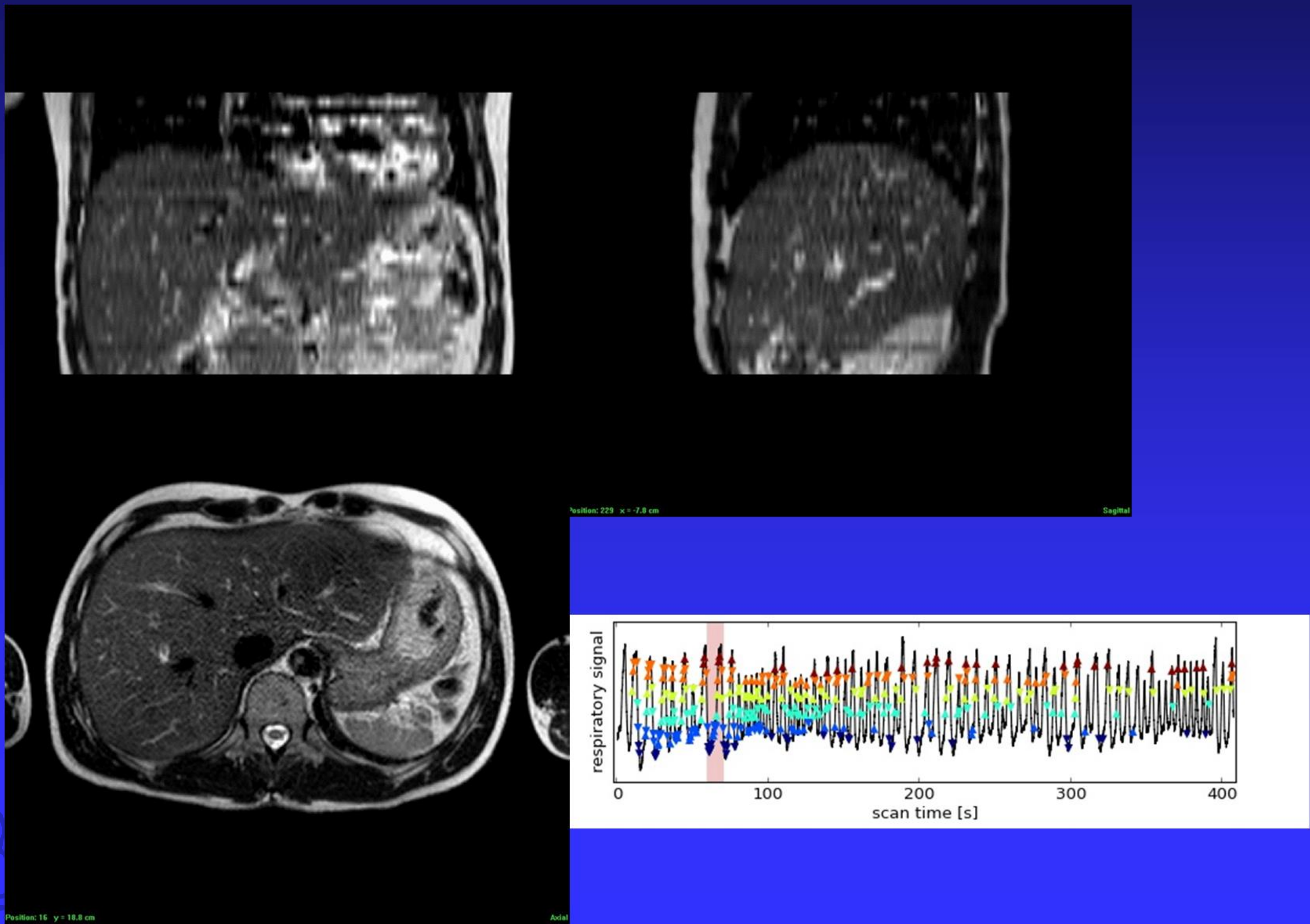
MRI and time management

- Gated MR
- Cine MR



- Mostly used for motion assessment

4D MRI



Summary

- Motion during imaging causes artifacts and distortions
- Effective ‘shutter time’ of the equipment determines type of artifacts
- Time resolved imaging through retrospective sorting reduces artifacts
- Irregular breathing remains a challenge

Rigshospitalet
Department of Oncology,
Section of Radiotherapy

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Technology: 4D-IGRT

Marianne Aznar

What is 4D?

- Usually respiration (not time)
  - Regular, predictable

- By extension: any intra-fraction motion

How much does it matter?

- Uncertainties from planning:
  - ➢ Catching the tumour in a ”un-representative position”
  - ➢ Under /over-estimating the tumour volume

- Uncertainties from delivery:
  - ➢ Mis-registration on a given day (wrong alignment between beam and average tumour position)
  - ➢ Interplay effect
  - ➢ Anatomical changes

Three approaches to motion management

- Removing motion
  - ➢ breath hold,
  - ➢ abdominal compression

- Assessing motion (”passive” strategies)
  - ➢ Adapt the treatment strategy **prior** to delivery

- Following motion (”active” strategies)
  - ➢ Adapt the treatment strategy **during** delivery

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SUPPRESSING/MINIMIZING THE DISPLACEMENT

Abdominal compression

Elekta Stereotactic Body Frame®

Can reduce the motion in CC direction

May introduce interfraction variations in tumour position (Mampuya Med Phys 2013)

IGRT is still necessary (AAPM TG 101)

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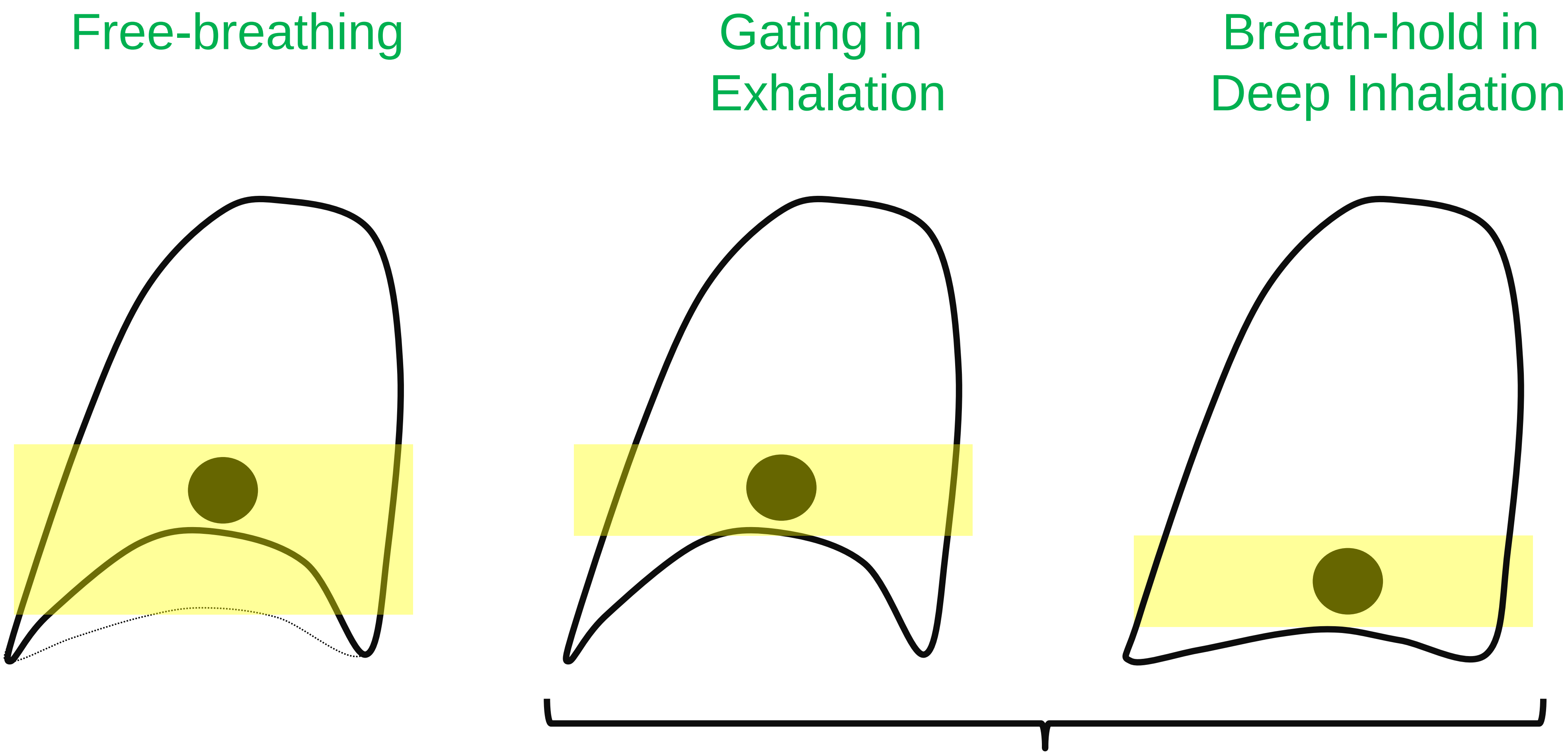
Gating / breath hold radiotherapy

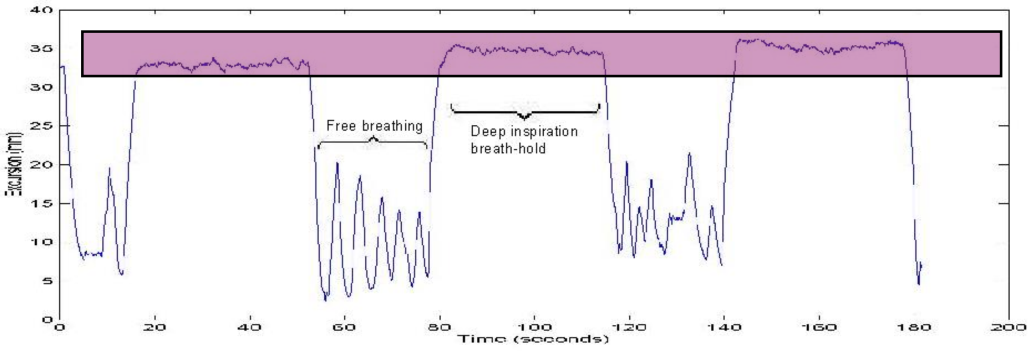


In Inspiration Breath-hold:

Lung is inflated and smaller lung volumes are irradiated

Deep inspiration gating / breath hold

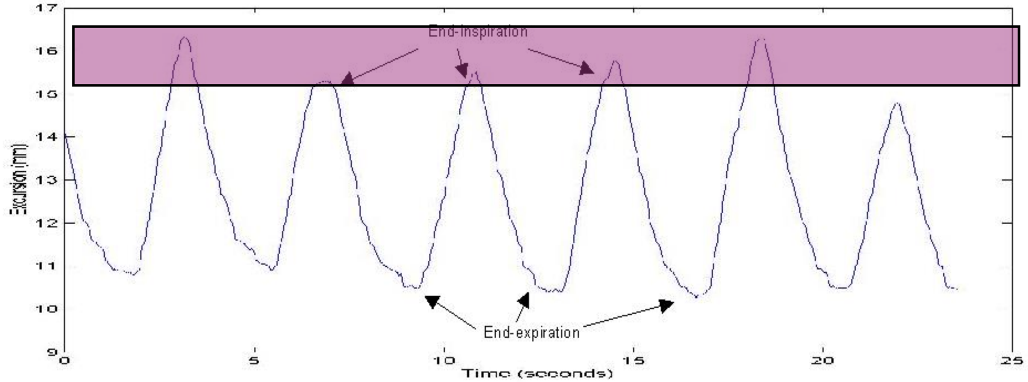
Breath hold (ca 20 sec)



Advantages:

- “natural” breath hold
- Separation between target and OAR
- Same dosimetric benefits

”hyperventilation”



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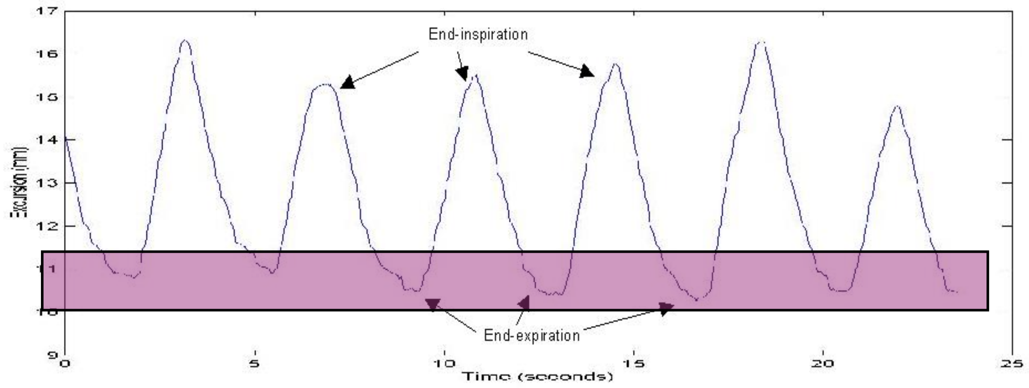
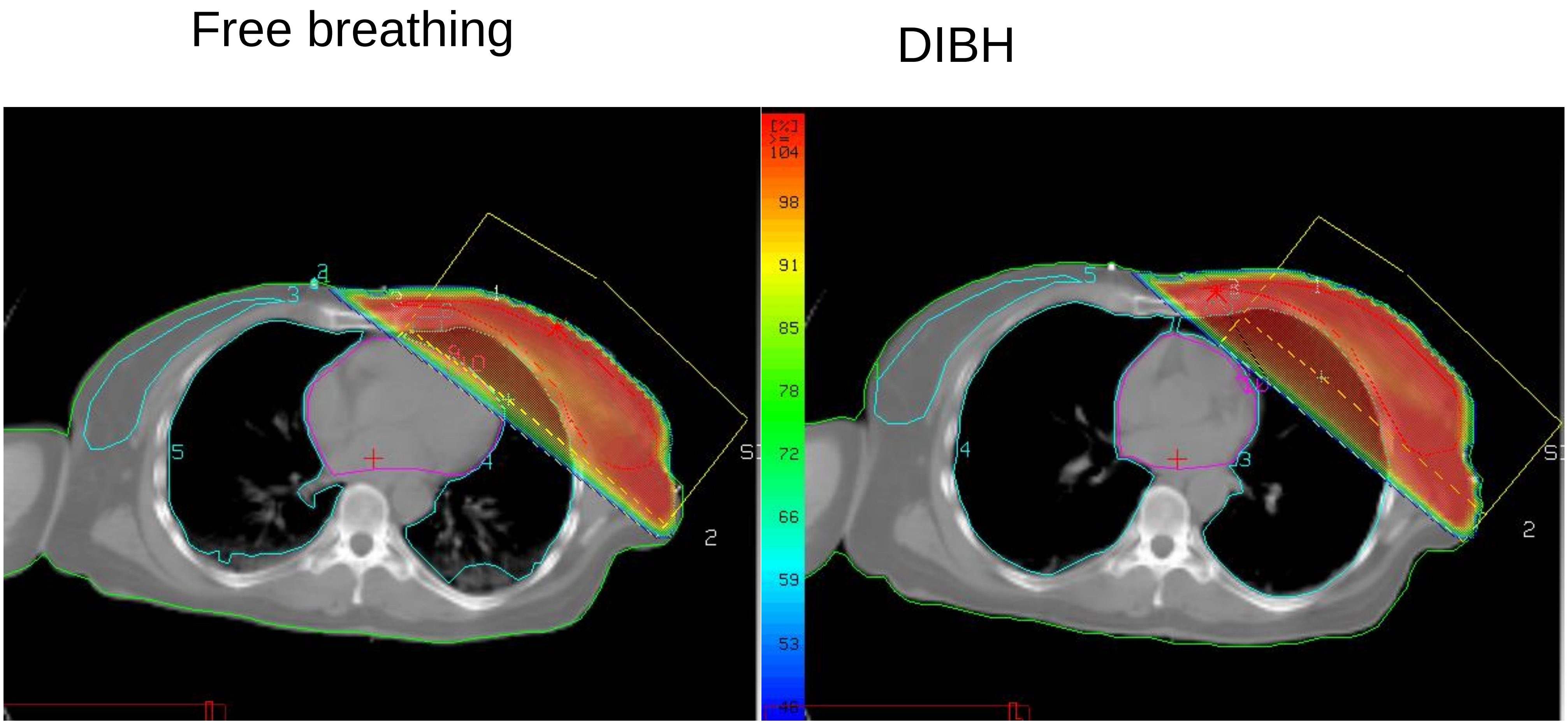
Expiration gating / breath hold



Advantages:

- Most “stable” position in the breathing cycle
- For gating: duty cycle possibly longer than at end inspiration

Lung inflation : Breast

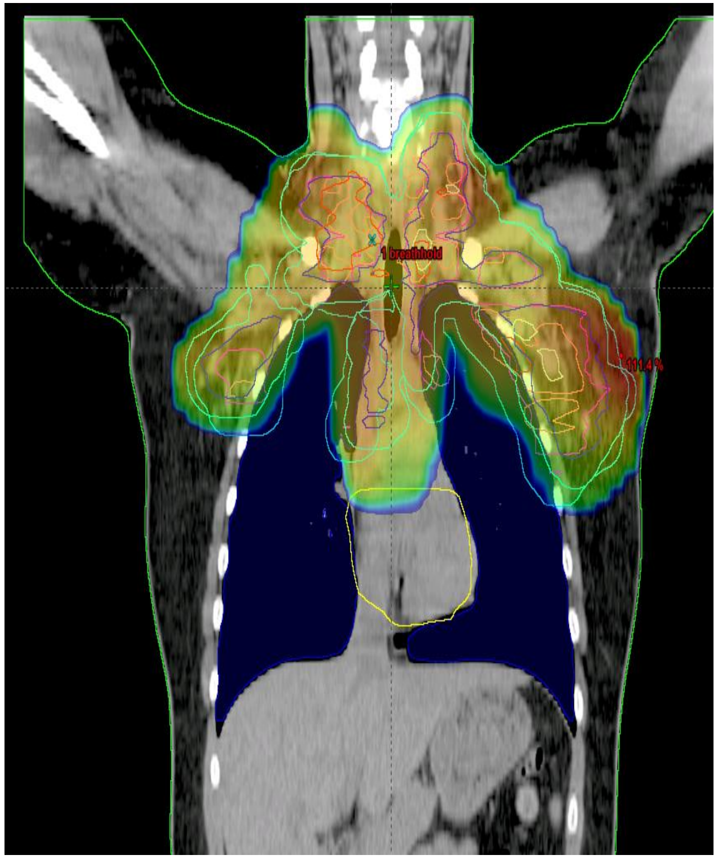


Courtesy of Stine Korreman

Lung inflation: Hodgkin lymphoma

Free breathing

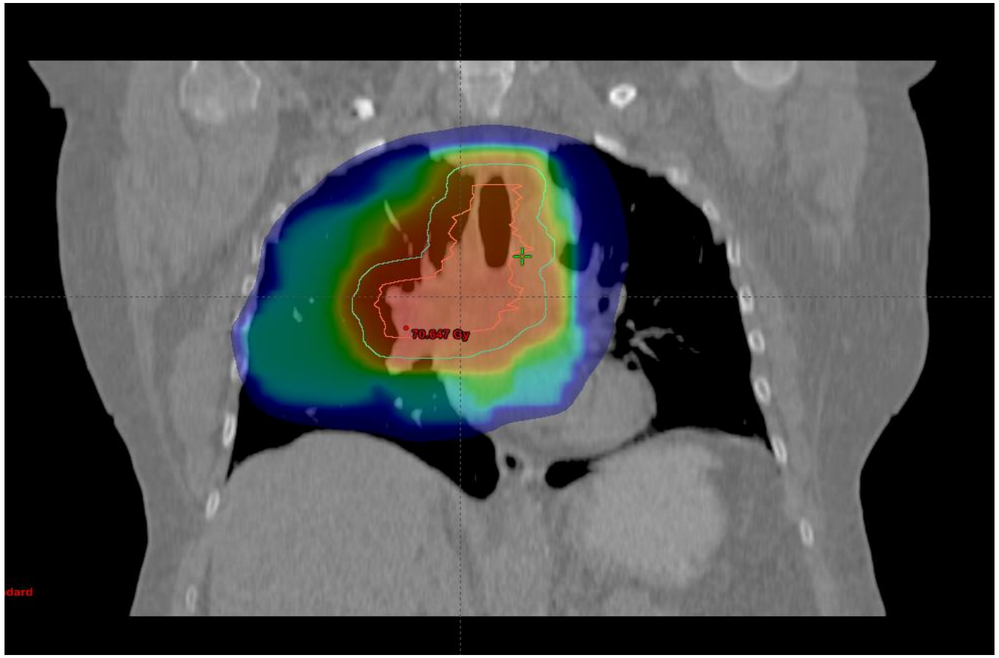
DIBH

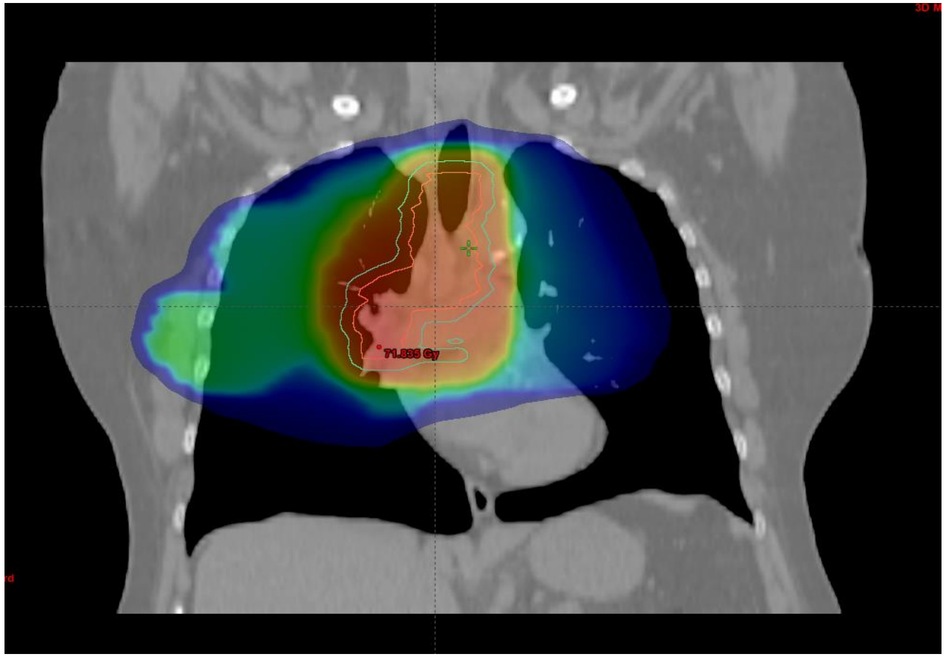


Lung inflation: lung cancer

Free breathing
(MLD 23.6Gy)

DIBH
(MLD 19.7 Gy)





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Most commonly used systems (non-exhaustive)

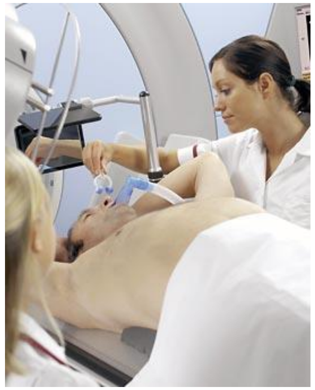
Based on an external signal (e.g. marker, surface)

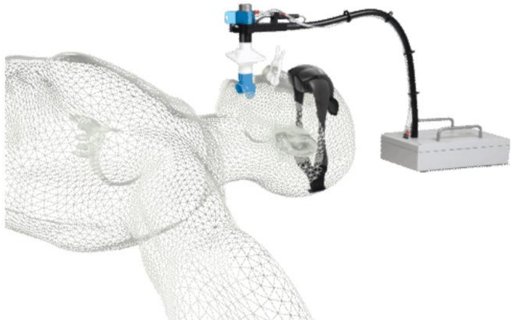
RPM/Gating

VisionRT

Based on expiratory volume

ABC





SpiroDynR'x

The simpler, the better?

Radiotherapy and Oncology 108 (2013) 242–247

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

The UK HeartSpare Study: Randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy

Frederick R. Bartlett [a,*], Ruth M. Colgan [b], Karen Carr [a], Ellen M. Donovan [b], Helen A. McNair [a], Imogen Locke [a], Philip M. Evans [b,c], Joanne S. Haviland [d], John R. Yarnold [a,e], Anna M. Kirby [a]

[a] Department of Academic Radiotherapy, Royal Marsden NHS Foundation Trust; [b] Joint Department of Physics, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton; [c] Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford; [d] Clinical Trials and Statistics Unit (ICR-CTSU); and [e] Division of Radiotherapy and Imaging, Institute of Cancer Research, Sutton, UK

Voluntary breath hold preferred over "forced"

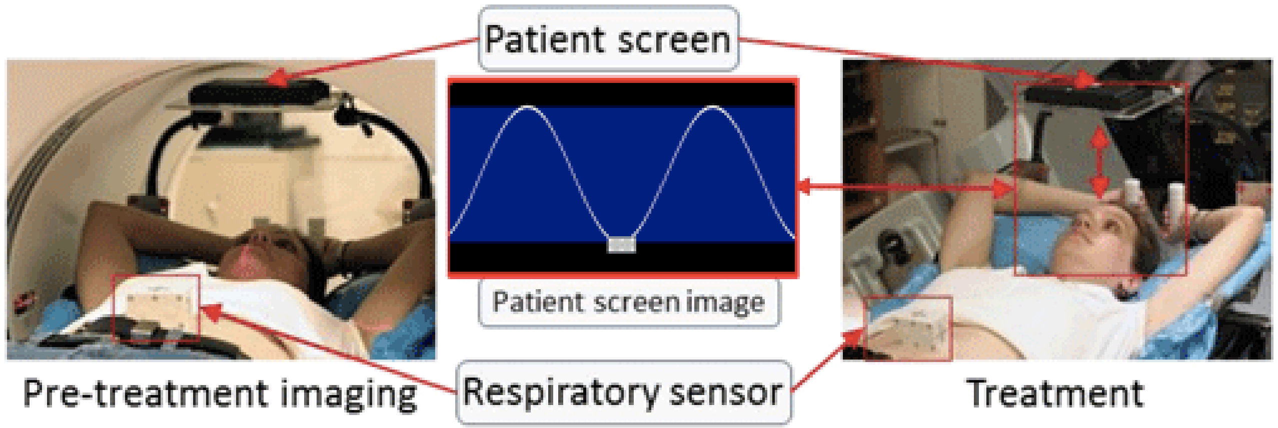


Figure 1. AV biofeedback system. Display screen and marker block on the abdomen shown. The visual display (centre) as seen by the subject (sans arrows) of the AV biofeedback system shows the guiding wave (white curve) and a marker position (marker block) in real time. The AV biofeedback system is compatible for both imaging (left) and treatment (right) environments.

Paul Keall
Sydney

School

Image guidance for deep inspiration: DIBH/gating monitoring

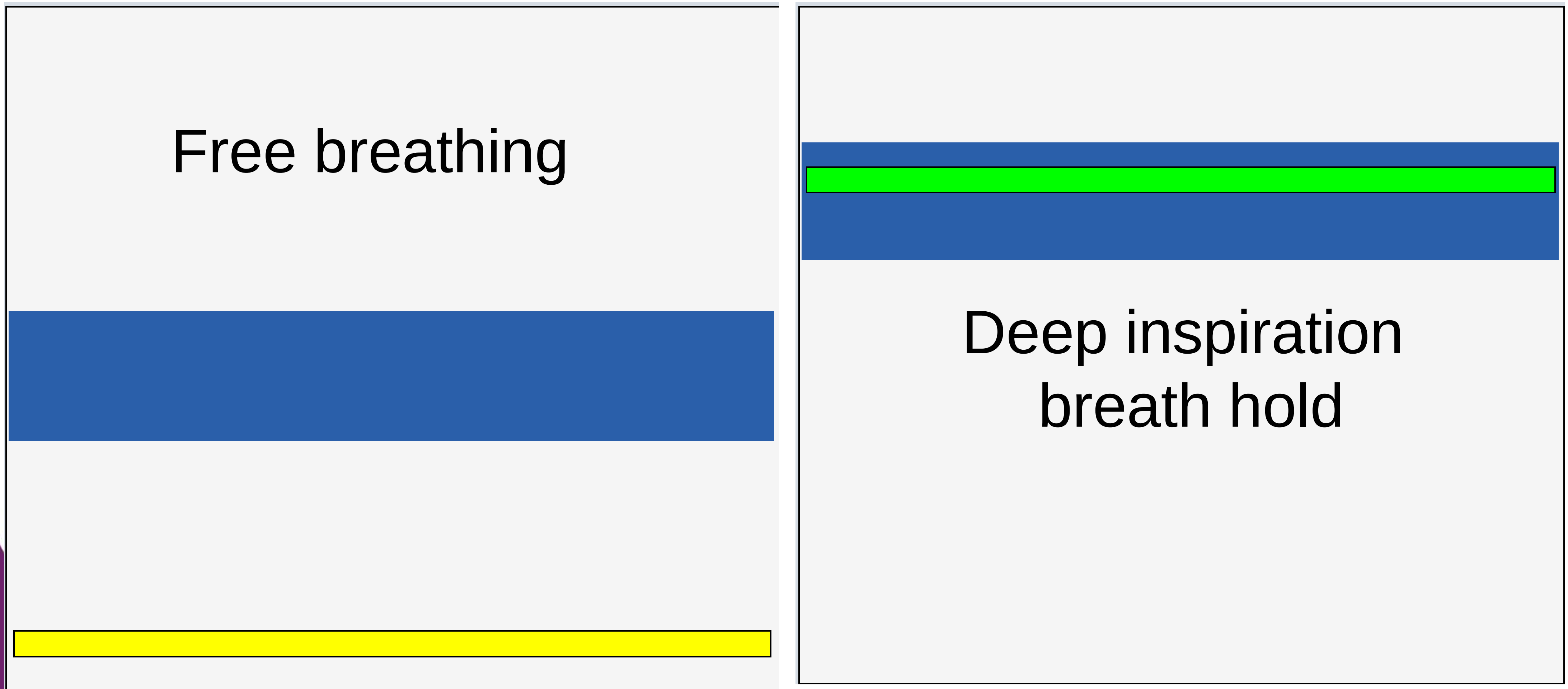
- Voluntary breath is hold is as efficient and more comfortable

Bartlett 2013

- The ”no equipment” solution:
  - ➢ short hyperventilation follwed by breath hold
  - ➢ Monitoring is visual (draw the light field on the patient, observed through control room monitors)
  - ➢ Video article: ***Bartlett et al J Vis Exp 2014***

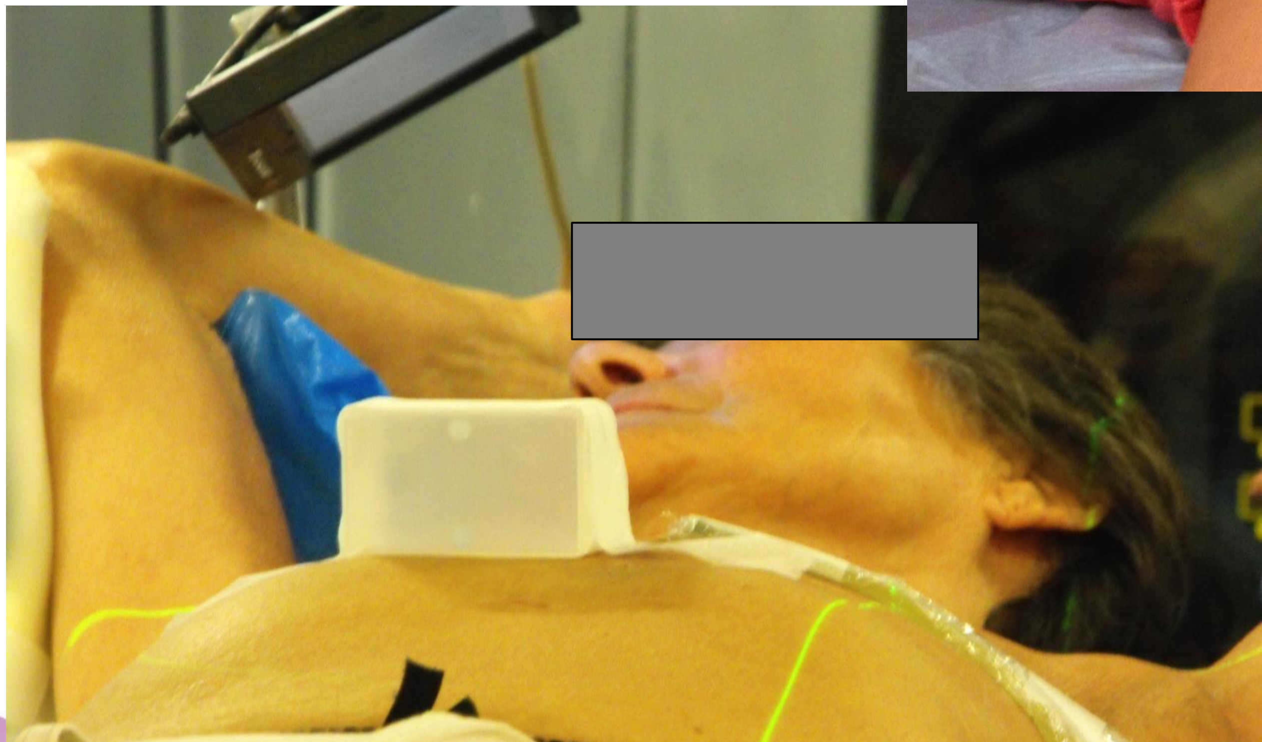
Audio/visual Coaching:

- Can improve performance / reproducibility
- Risk of having the patient “over-perform”
- Visual may be faster/more convenient



Visual guidance:

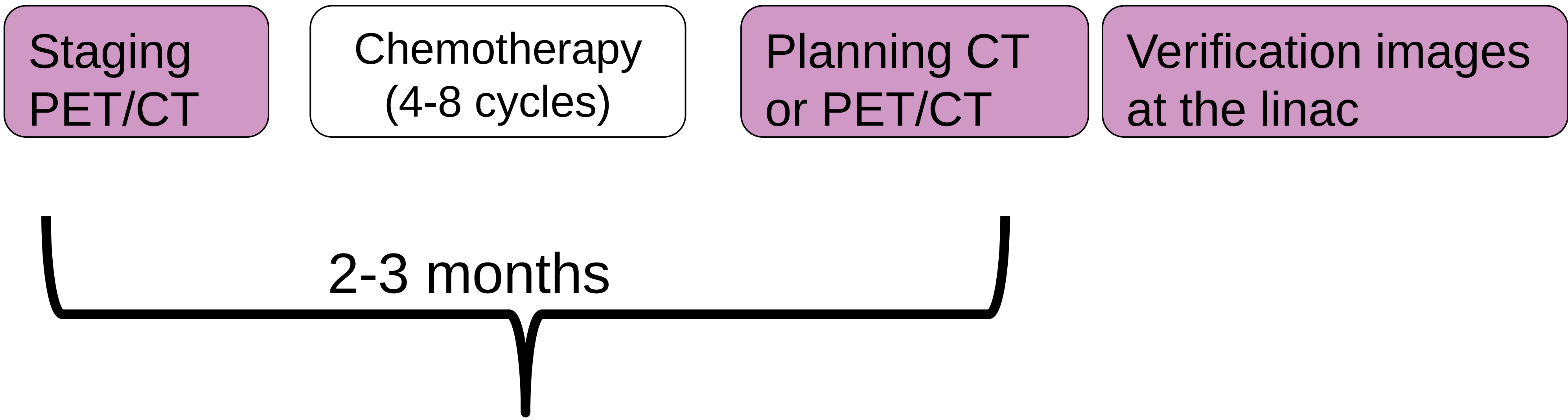
- Scanner
- linac



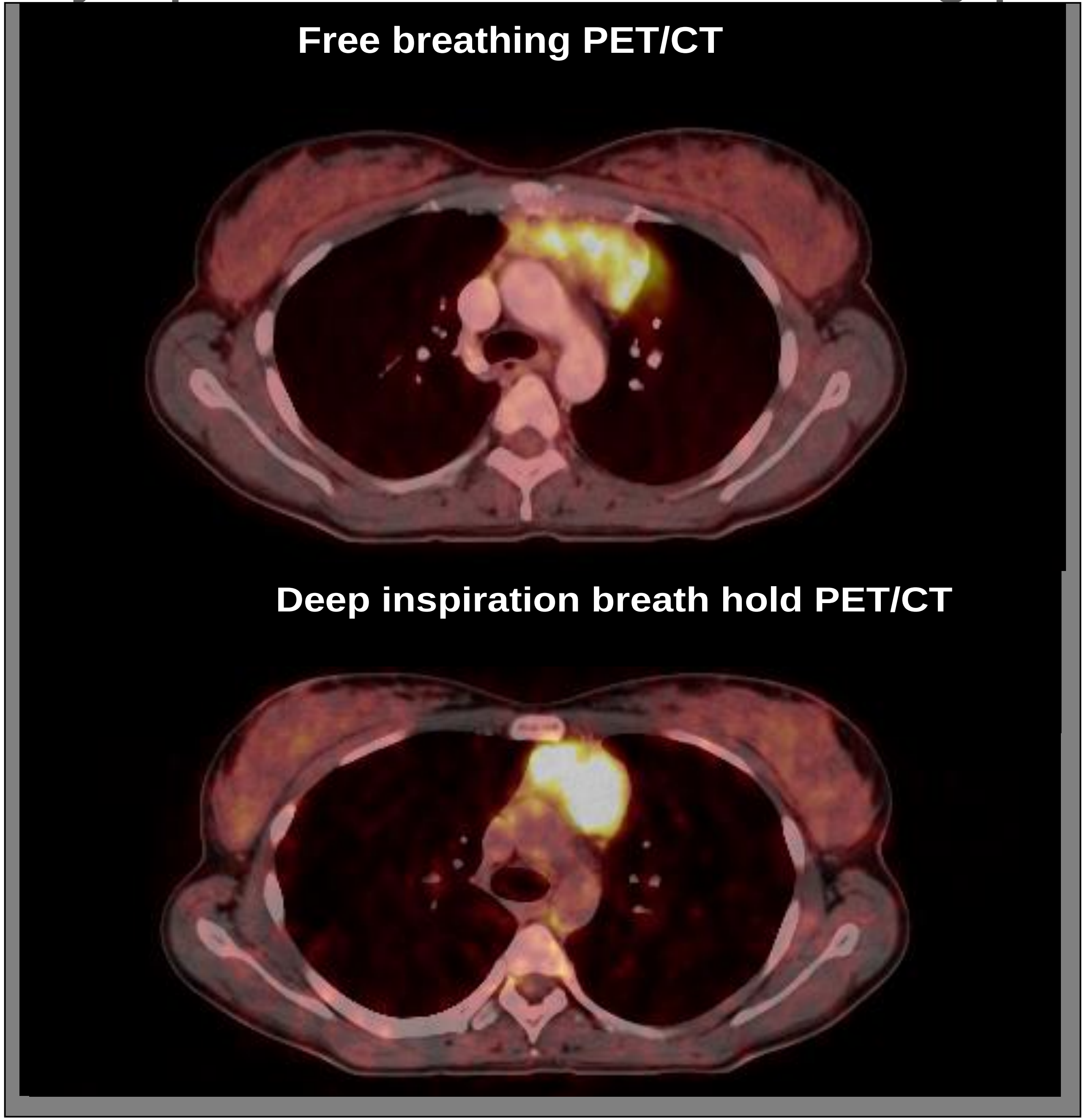
Methods

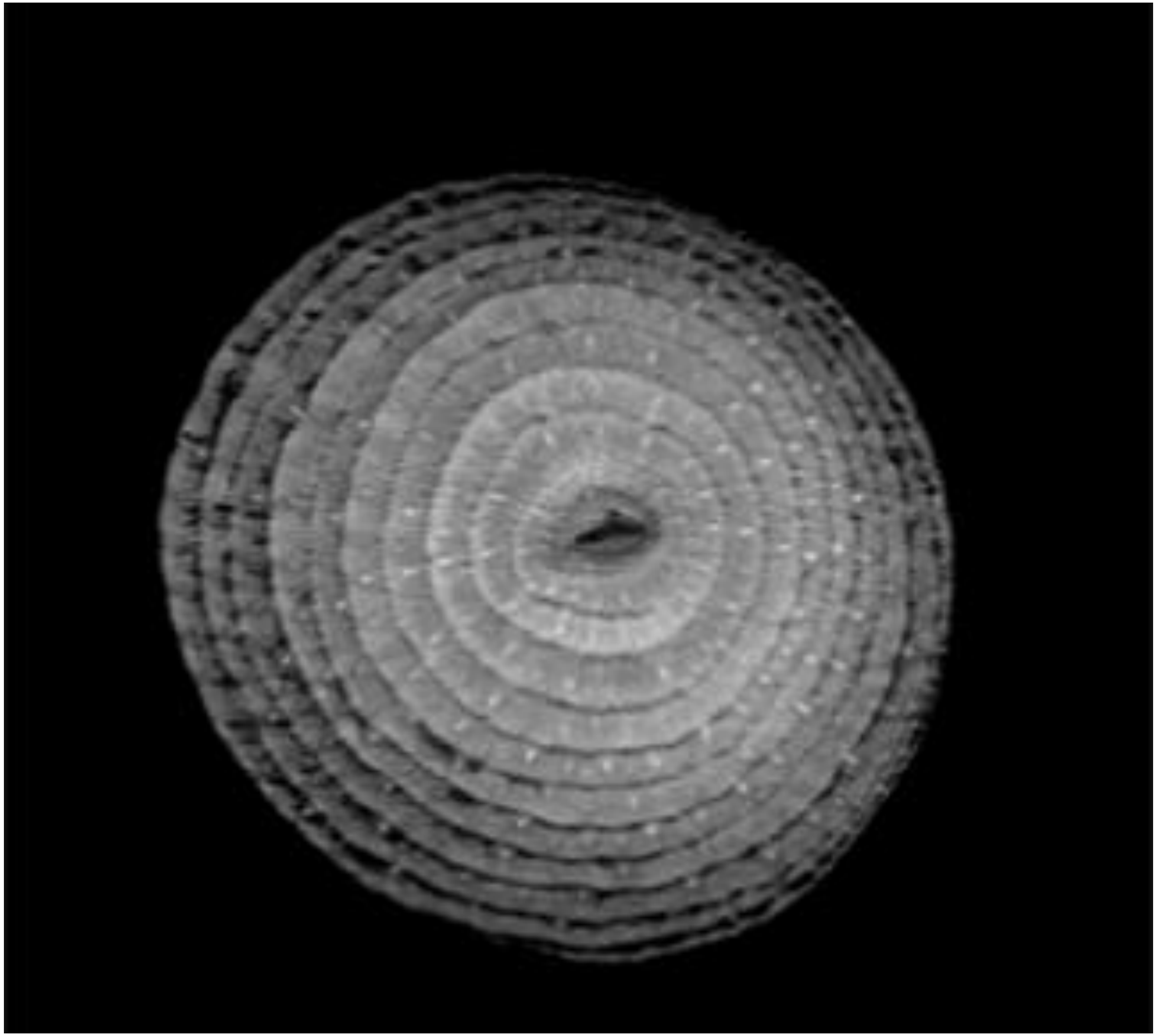
All images in DIBH throughout the treatment course

Example: Hodgkin Lymphoma



PET/CT in DIBH
mediastinal lymphoma and selected lung patients





How much can these methods facilitate margin reduction?

Dawson et al, IJROBP 2001

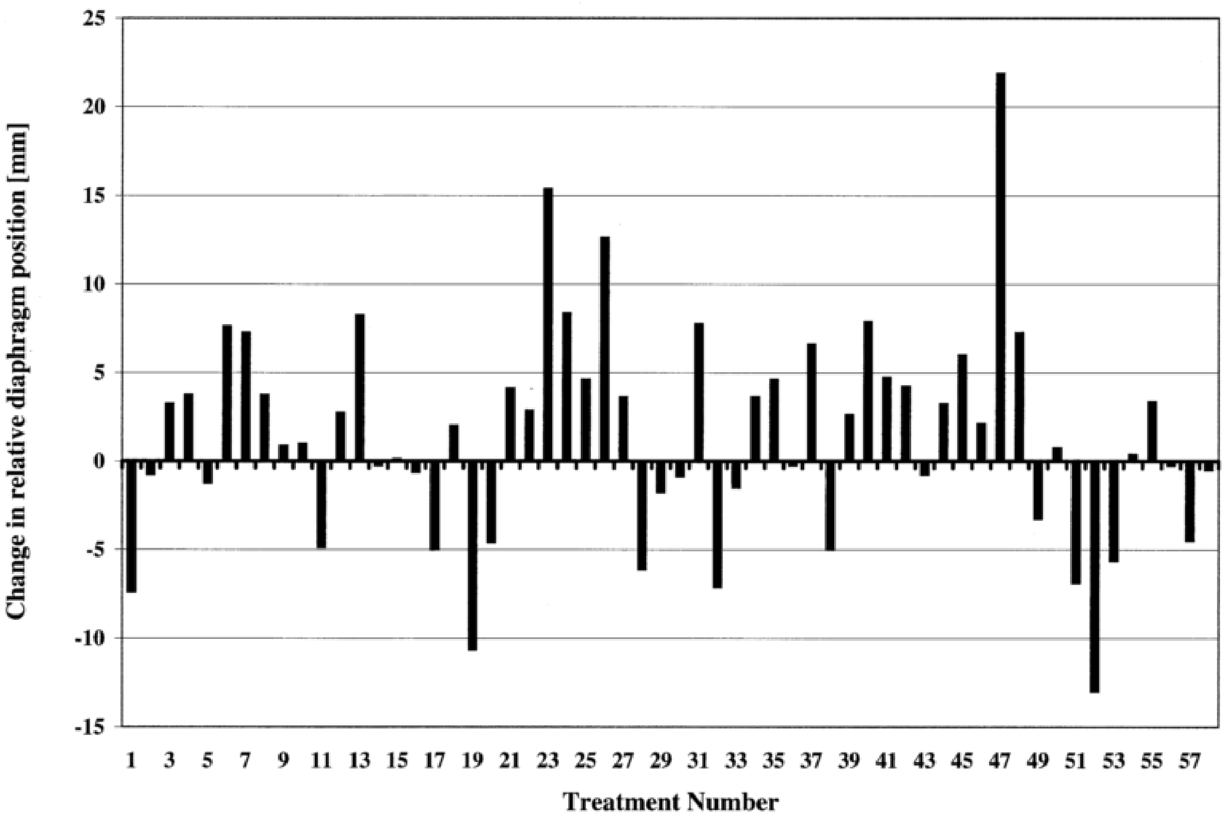


Fig. 6. An example of the interfraction variability of diaphragm-skeleton position for 1 patient (Patient 8) ove radiation course. Number of sequential treatments is displayed on *x* axis.

- Variation in position between the diaphragm and bony structures for the same inhale volume
- Up to 2 cm interfraction variation

Cheung et al, IJROBP 2003, 10 patients

field for a given breath hold. As such, we do not advocate reducing the daily PTV margin with the use of ABC breath hold for the treatment of peripheral lung tumors.

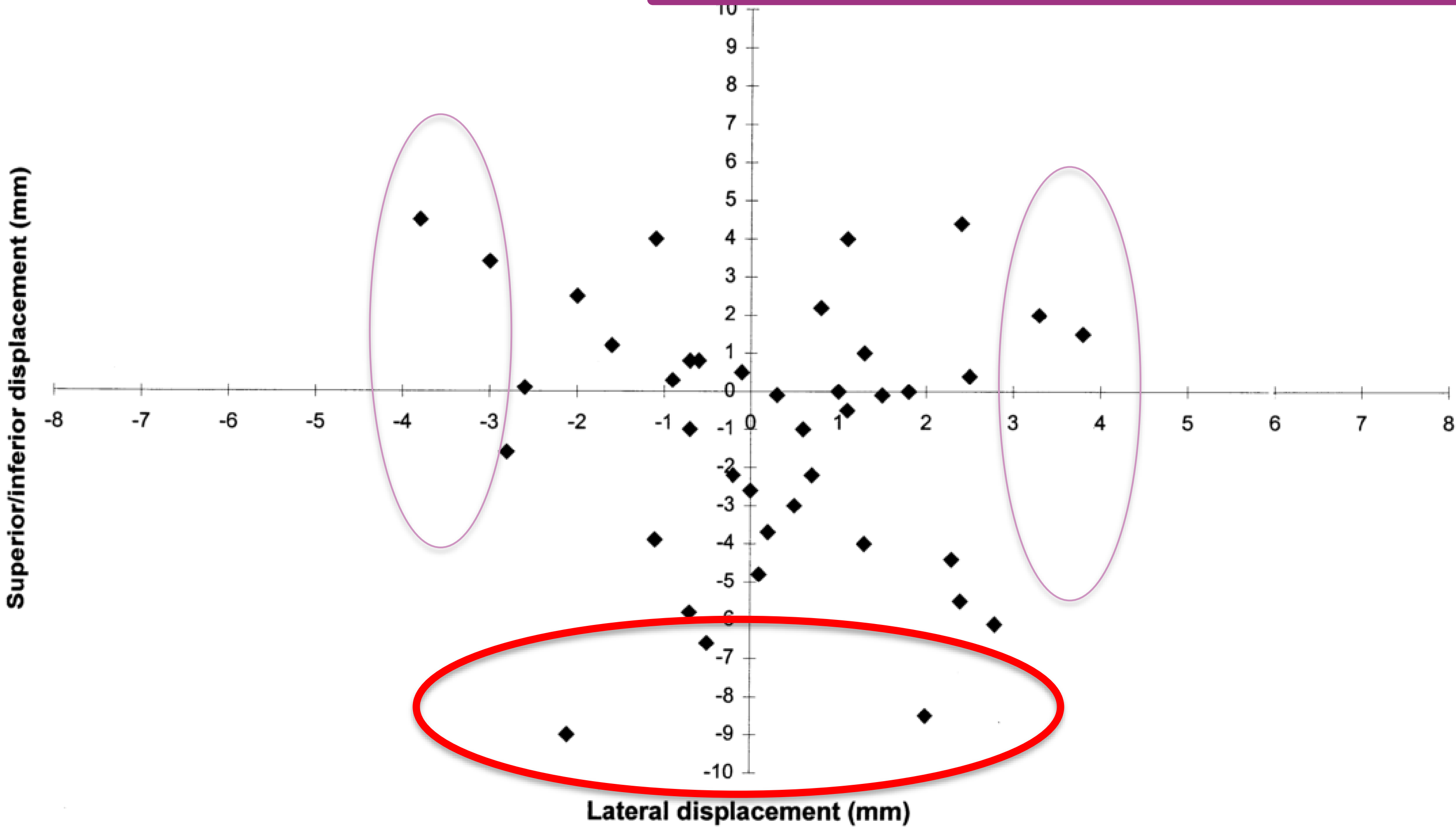


Fig. 1. Inter–breath hold displacements of daily GTV positions with ABC inspiration breath hold for all patients in the superior-inferior vs. lateral directions.

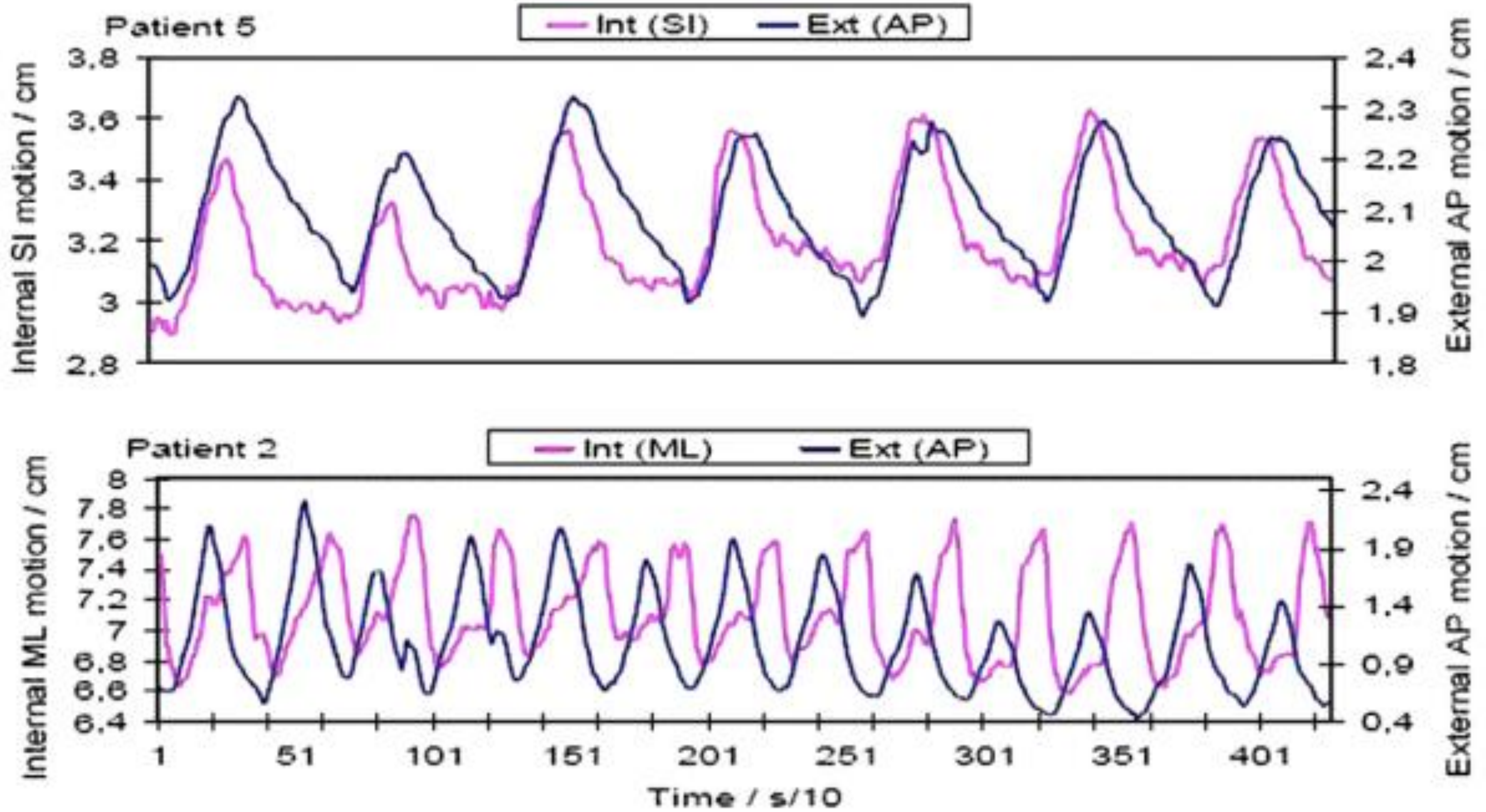


Fig. 2. Three examples of synchronously measured external optical marker and internal gold marker positions for three different patie
the Stanford protocol. The magenta curves are the internal marker positions and the blue curves are the external marker positions.

reminder

- Gating can not reduce margins without image verification of the tumour position

Korreman et al RO 2008

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Margin reduction?
Not necessarily !

- Hodgkin Lymphoma, considering daily CBCT and INRT (PET/CT in treatment position)

- Free breathing margins: 1cm all around

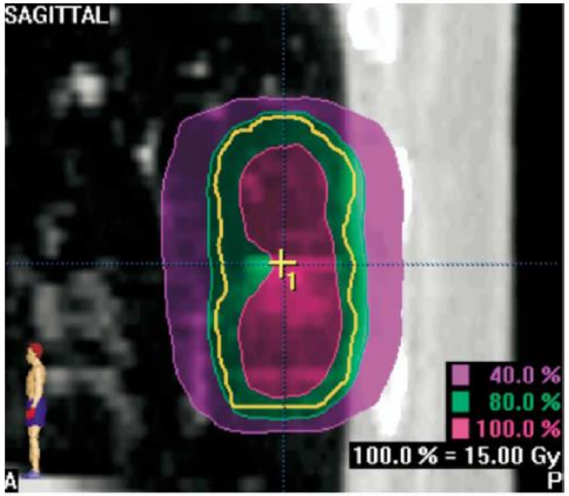
- DIBH margins
  - 3mm contouring uncertainty (systematic)
  - 2 mm breath hold uncertainty (random)
  - 3 mm image registration/ residual set up error (random)

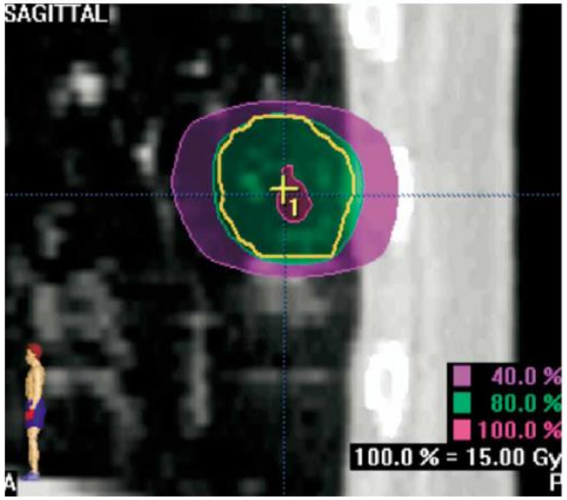
  - Margins = 1 cm !!!

Work in progress, courtesy of
Laura Rechner, Rigshospitalet

Gating and margin reduction

BENEFIT OF RESPIRATION-GATED STEREOTACTIC RADIOTHERAPY FOR STAGE I LUNG CANCER: AN ANALYSIS OF 4DCT DATASETS





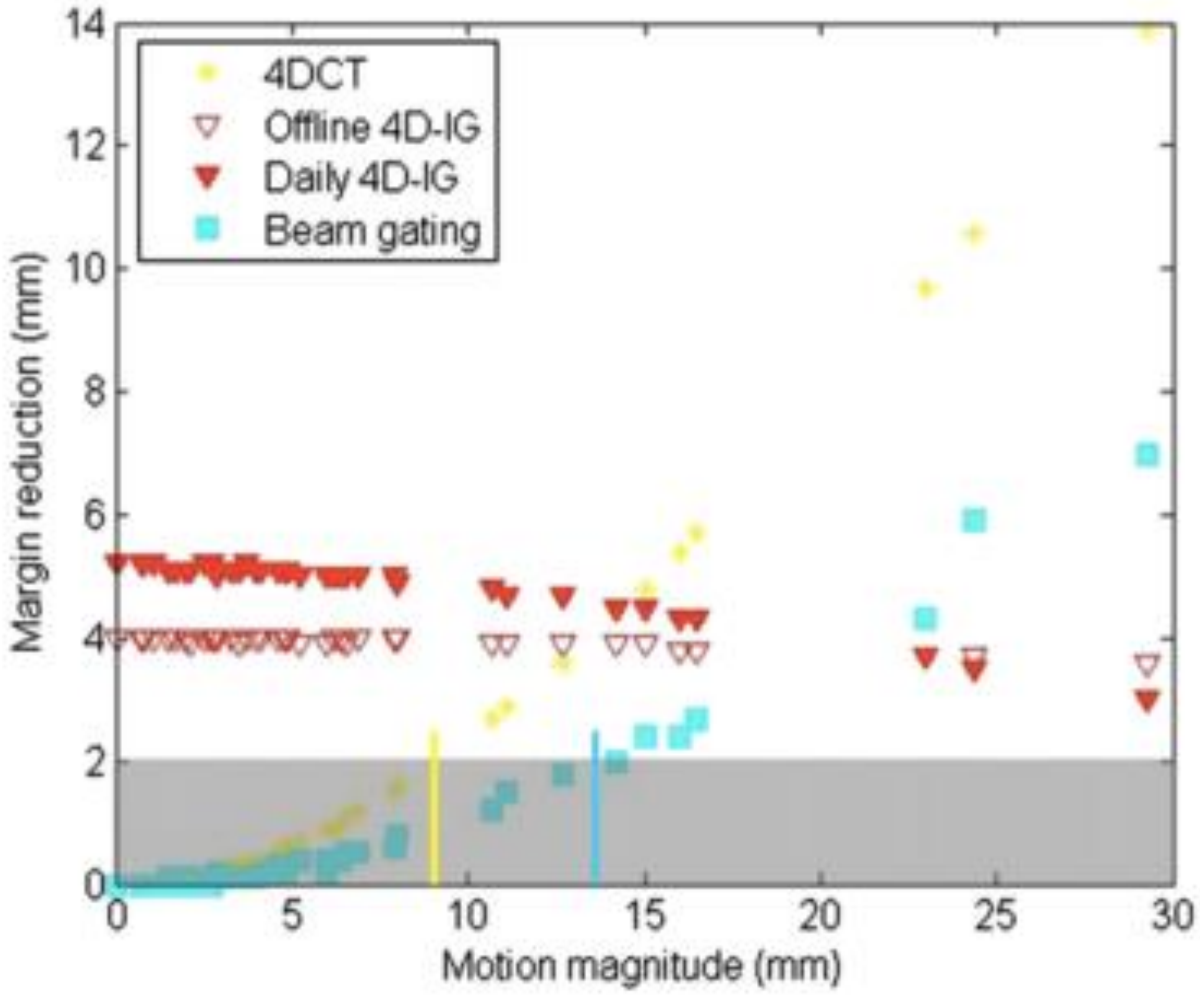
Reduction of motion amplitude
from 8.5mm to 1.4mm

Reduction of PTV volume by 45%

Duty cycle 30 %

Underberg IJROBP 2005

But.. This is a planning study !!!



Soft-tissue (or marker based) IGRT is the most efficient

(includes fluroscopy, 3D or 4D CBCT)

Korreman et al IJROBP2012

How much can these strategies reduce margins?

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Can there be a good surrogate for the position of a lung/liver tumour?

- No surrogate is so good that you can avoid IGRT

- Solution 1: use large margins (approx equal to free breathing)

  - Starkschall et al IJROBP 2011: ***treatment using methods designed to mitigate the effects of respiratory motion (breath hold or gating) with setup based on landmarks other than the actual tumour position requires margin of 0.7 to 0.8 cm***

Can there be a good external surrogate for the position of a lung/liver tumour?

- No surrogate is good enough
- Solution 1: use large margins (approx equal to free breathing)
- Solution 2: image the tumour position daily with respiration-correlated (4D) IGRT
  - 4D-CBCT for gated treatment
  - Breath hold CBCT
  - 2D + markers in the tumour

Take home message
Gating/breath hold delivery

- All external surrogates are suboptimal

- No *a priori* margin reduction from breath hold or gating

- Respiration-correlated IGRT is necessary to limit interfraction uncertainties

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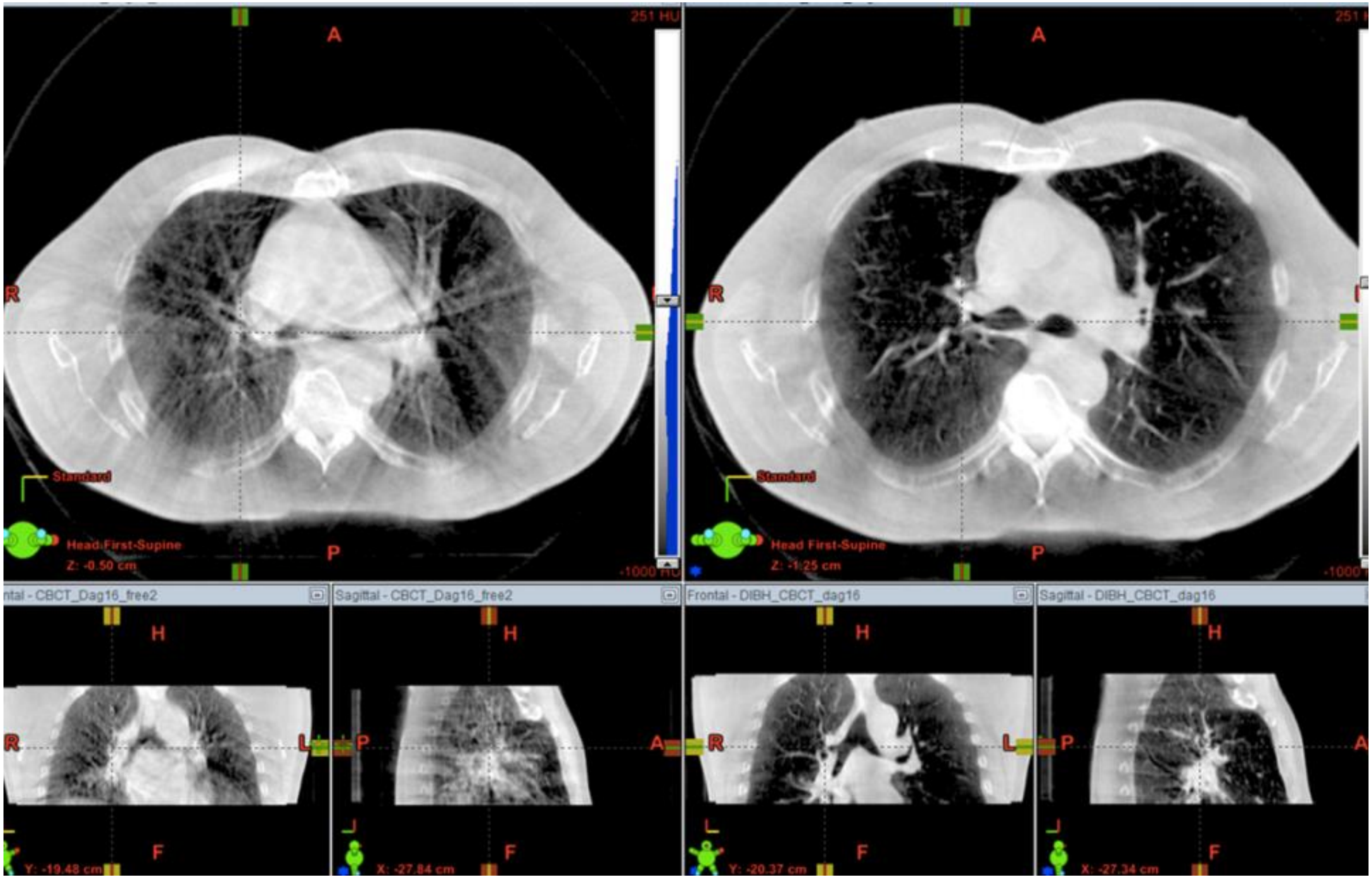
Is margin reduction really the only worthwhile goal of gating/DIBH ?

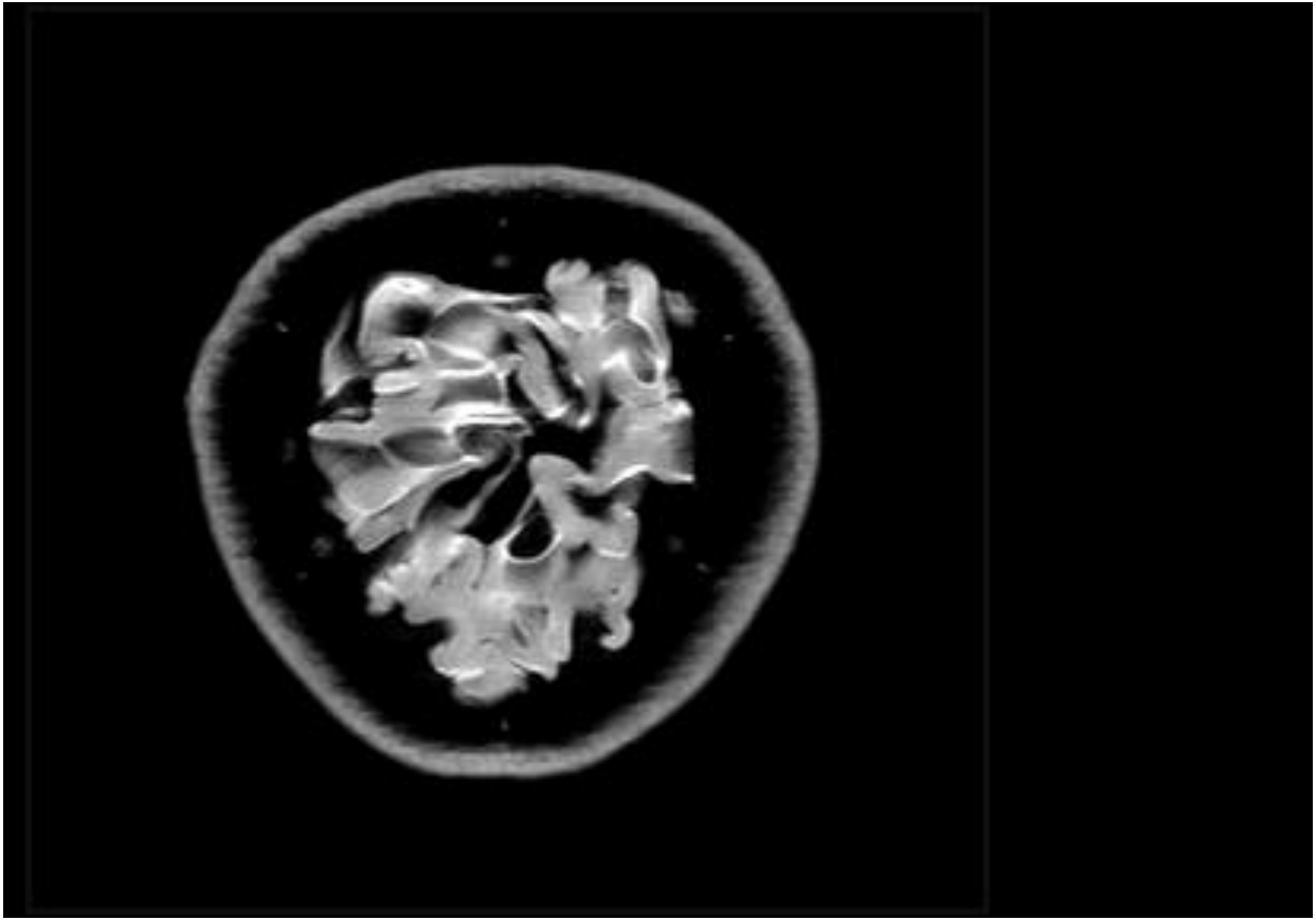
Target	Heart (mean dose)	Ipsilateral lung (mean dose)
Breast / CW	- 2.5 Gy	- 1 Gy
Breast/CW + axilla/SCF		-2 Gy
Breast/CW + axilla/SCF+ IMC	- 5 Gy	- 3 Gy

Sources: Taylor et al, IJROBP 2015
Aznar et al (in preparation)

Is margin reduction really the only worthwhile goal of gating/DIBH?

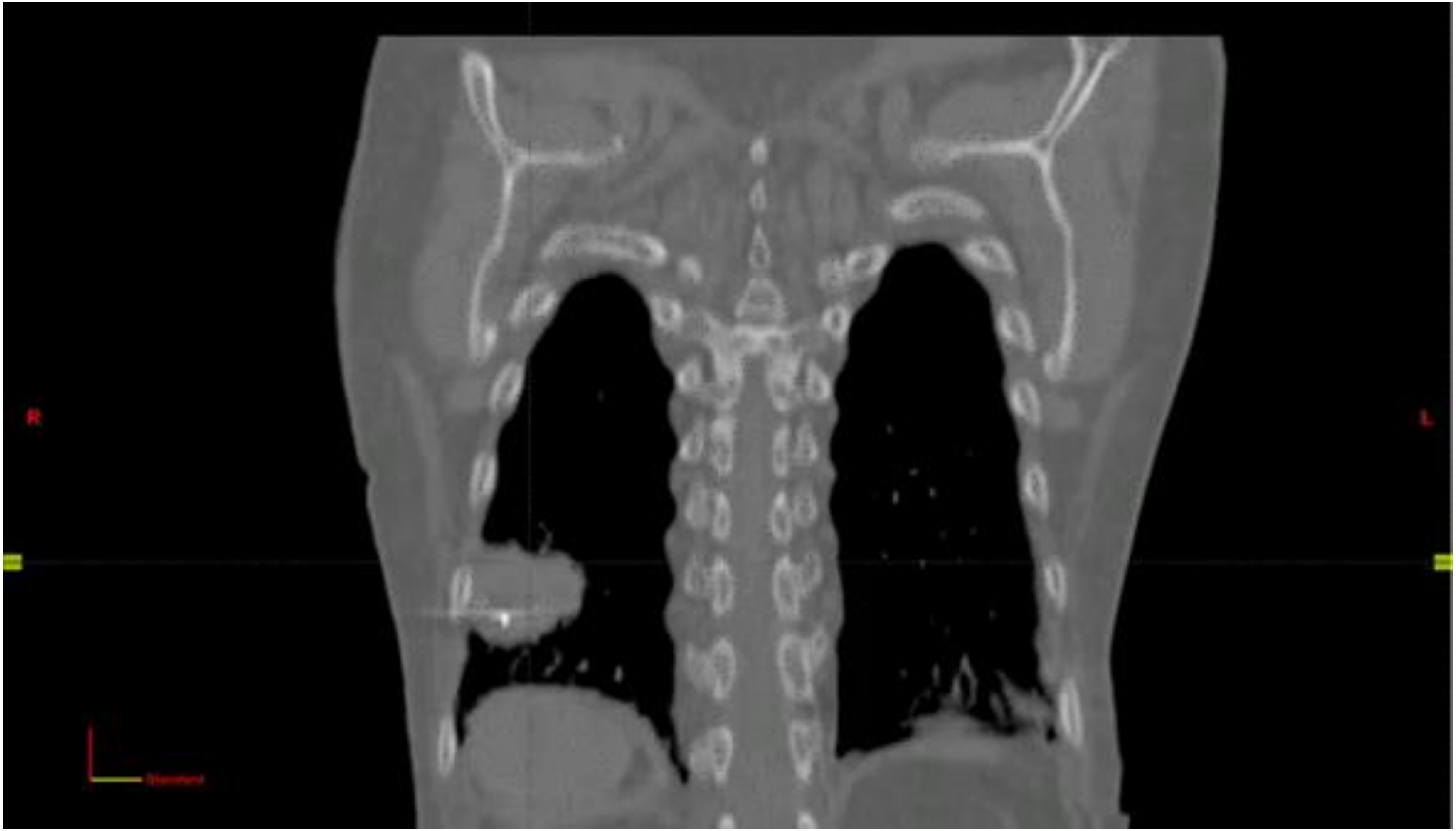


Josipovic et al BJR 2016



ASSESSING THE DISPLACEMENT OF THE TUMOUR

After the 4D CT acquisition…



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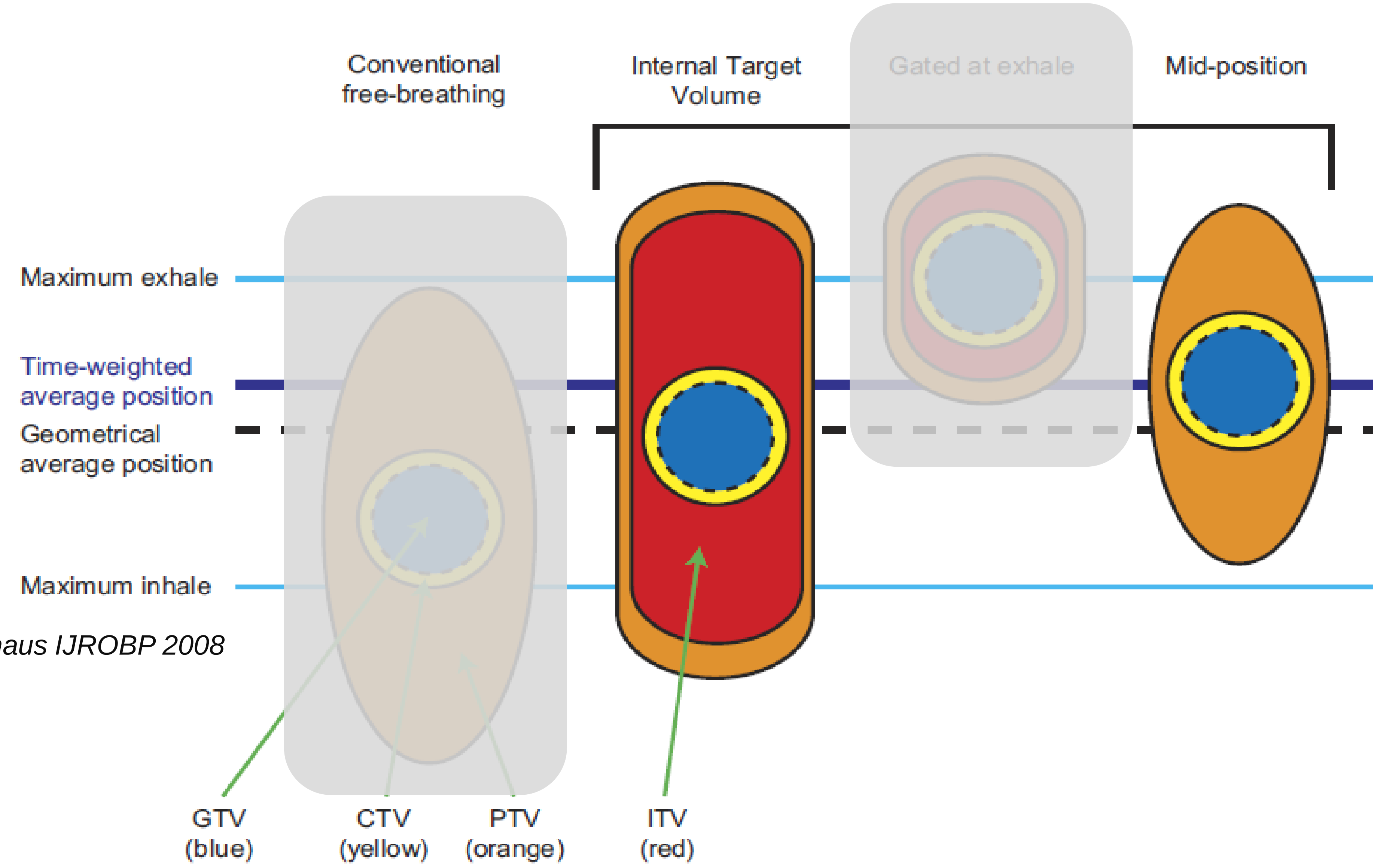
2 main strategies



Wolthaus IJROBP 2008

ITV	MidVentilation
• Straightforward (?)	• Counterintuitive (?)
• Physician time (contouring)	• Physicist time (choice of phase + margin calculation)
• Coverage is ensured	• Smaller lung volume irradiated
• Larger volumes of lung irradiated if large motion	
• Needs an elaborate 4D viewer?	• Requires special software?

Do not delay the introduction/routine use of 4D-CT because of this issue!

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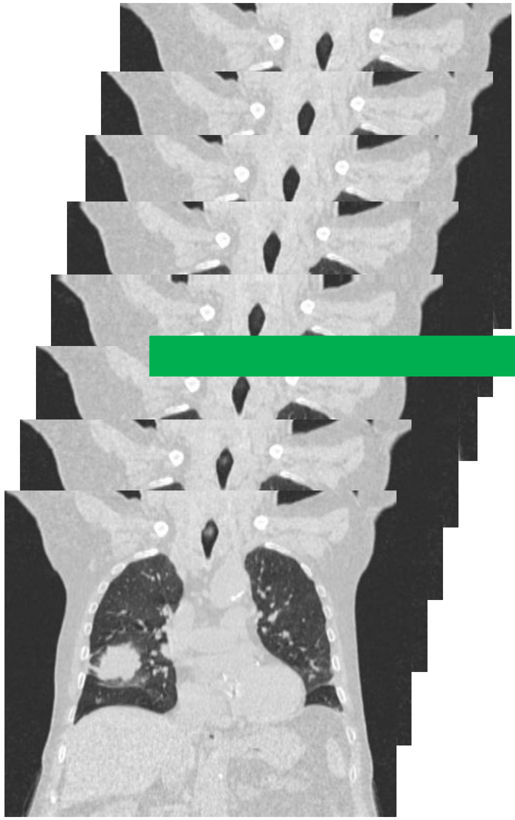
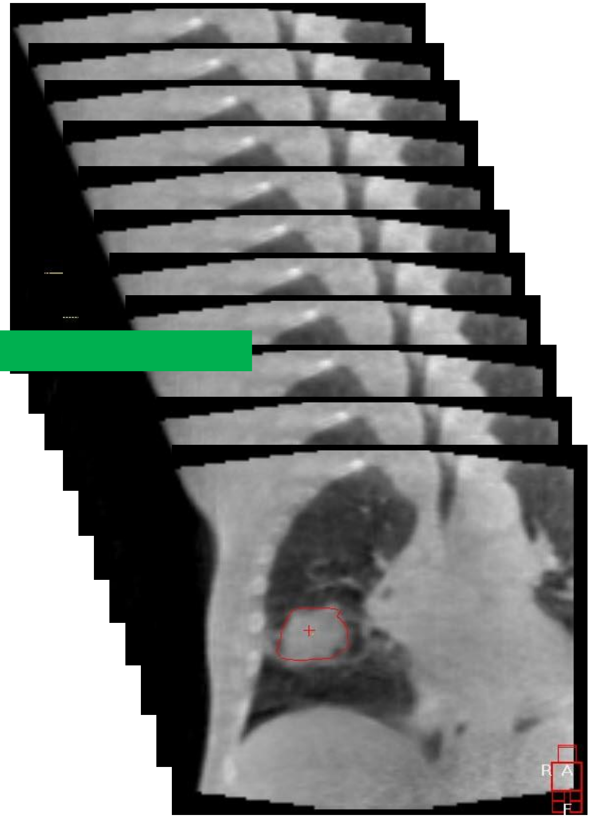
In-room image guidance

Treatment planning:
Reference Image

Treatment delivery:
Verification Image



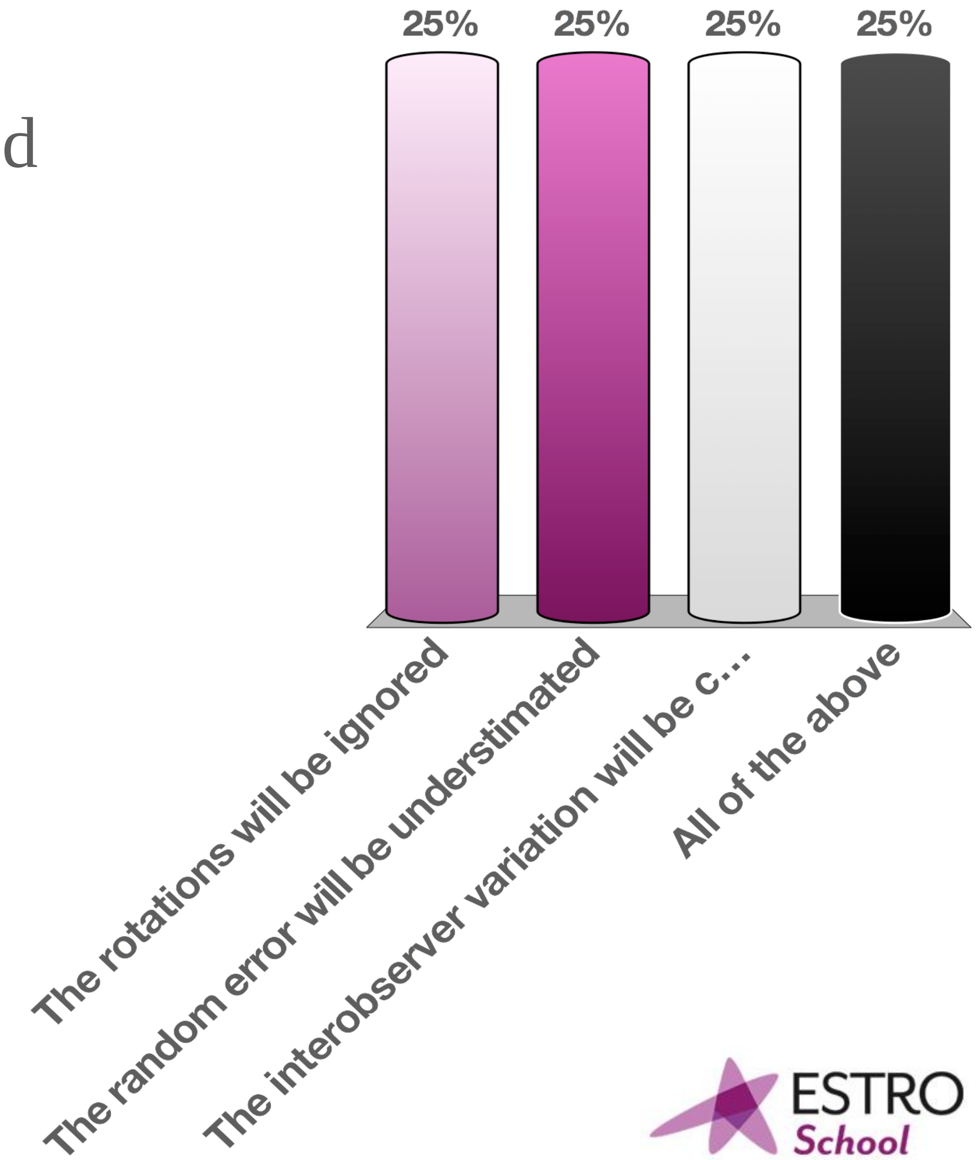
4D
IGRT



Delivery in free breathing and image verification :
3D CBCT will be blurry

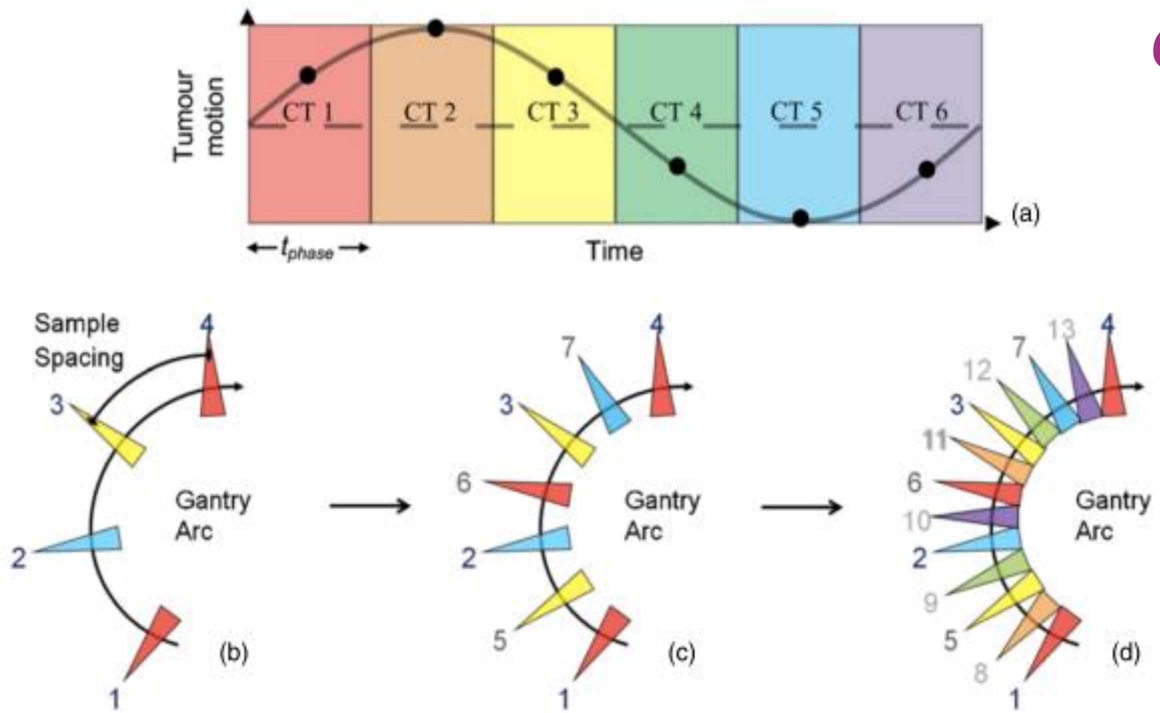
What is most likely to occur when manually registering a contour to a ”blurry” structure?

A. The rotations will be ignored
B. The random error will be understestimated
C. The interobserver variation will be considerable
D. All of the above



Integrating 4D CT information directly into treatment planning

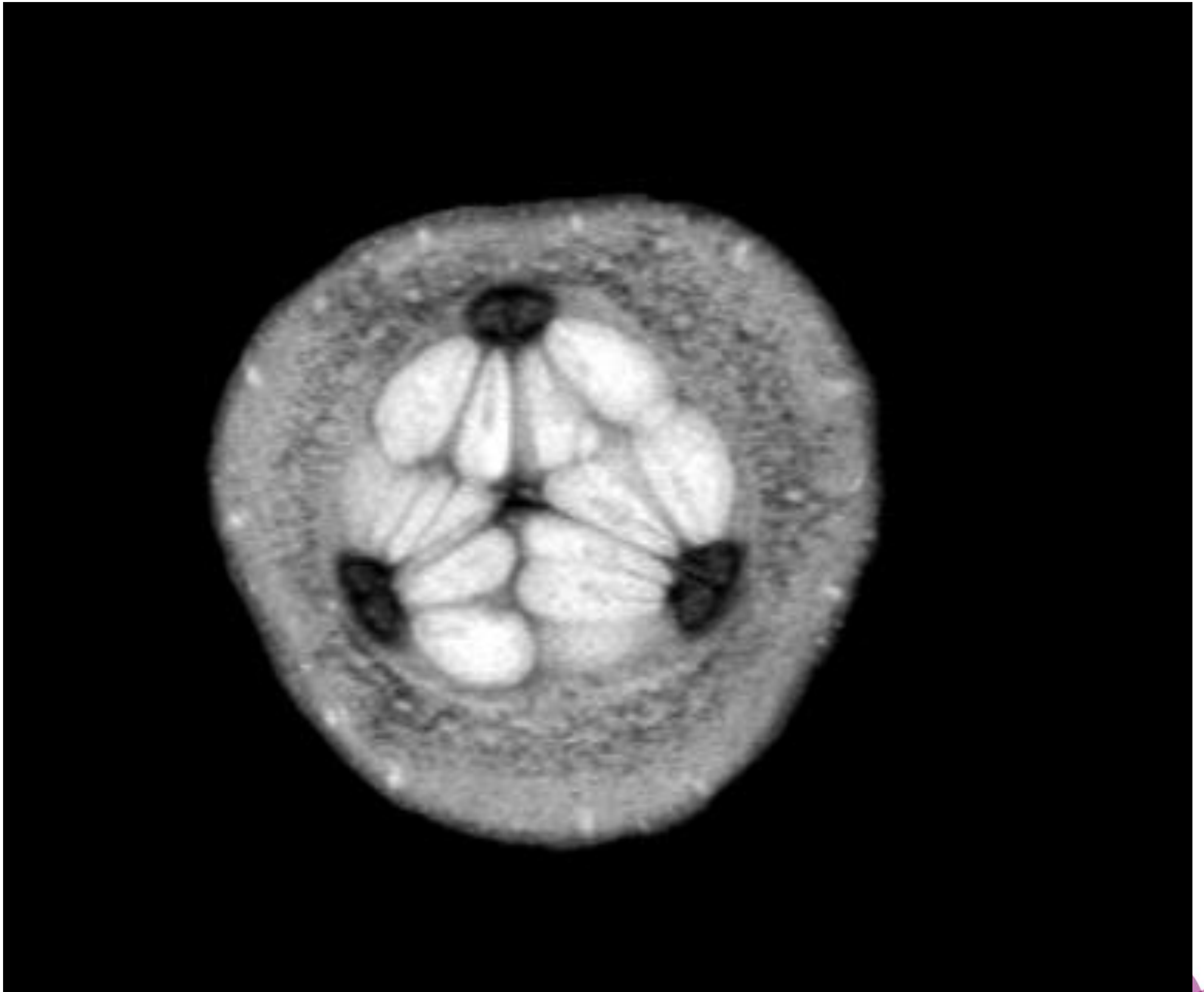
- Could make treatment faster (Ong et al 2010, 2012,Holt et al 2011, Brock et al 2012).
- Dosimetric results like gated VMAT, but with a time efficiency like 3D VMAT.



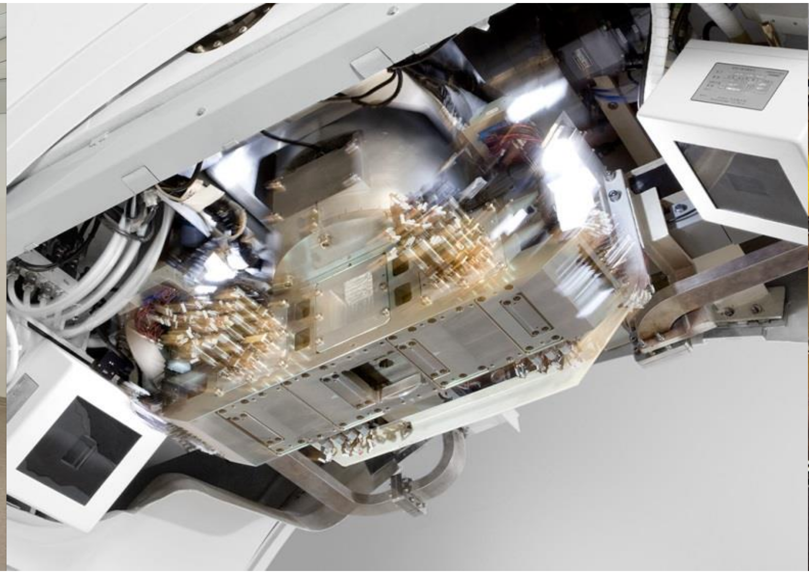
Chin at al PMB 2013

QA of treatment delivery for free-breathing treatment

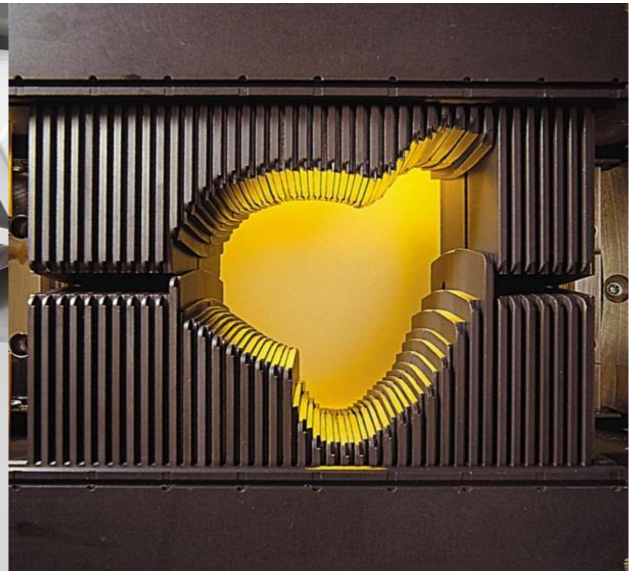
- How do you measure the dose actually received by the tumour?
- How do you control the consistency of the patient’s breathing pattern inter/intra-fraction ?
- Should one use respiration monitoring systems during treatment?



Robot arm and linear accelerator



Gimballed linear accelerator



Breathing MLCs

FOLLOWING MOTION

Courtesy of Dirk Verellen, free university Brussels
Mischa Hoogeman, Erasmus, Rotterdam

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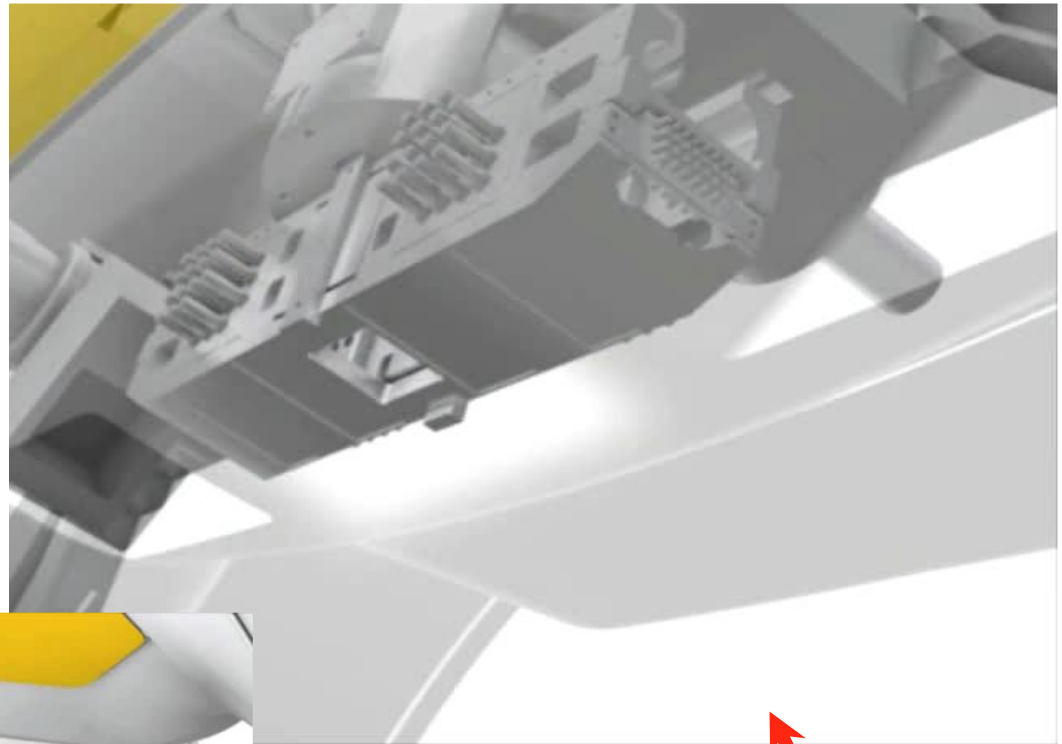
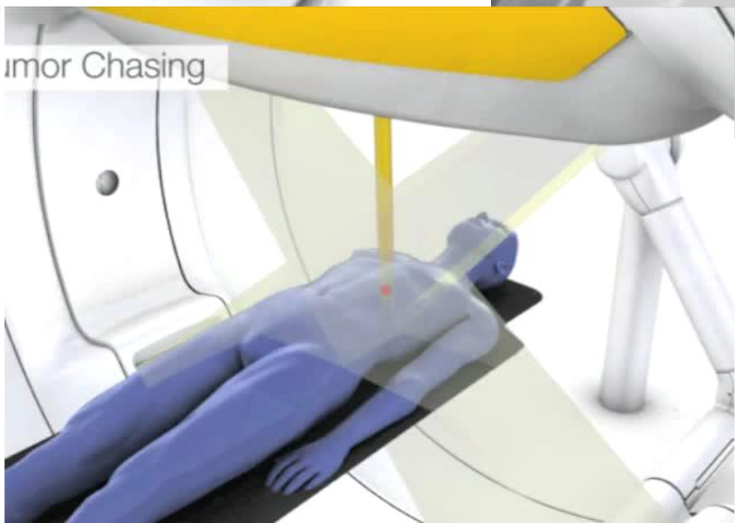
Cyberknife

X-ray Sources
Synchrony
Camera
Linear
Accelerator
Robotic
Arm
Robotic
Treatment Couch
Image Detectors

Tumor tracking: VERO





Courtesy of D. Verellen

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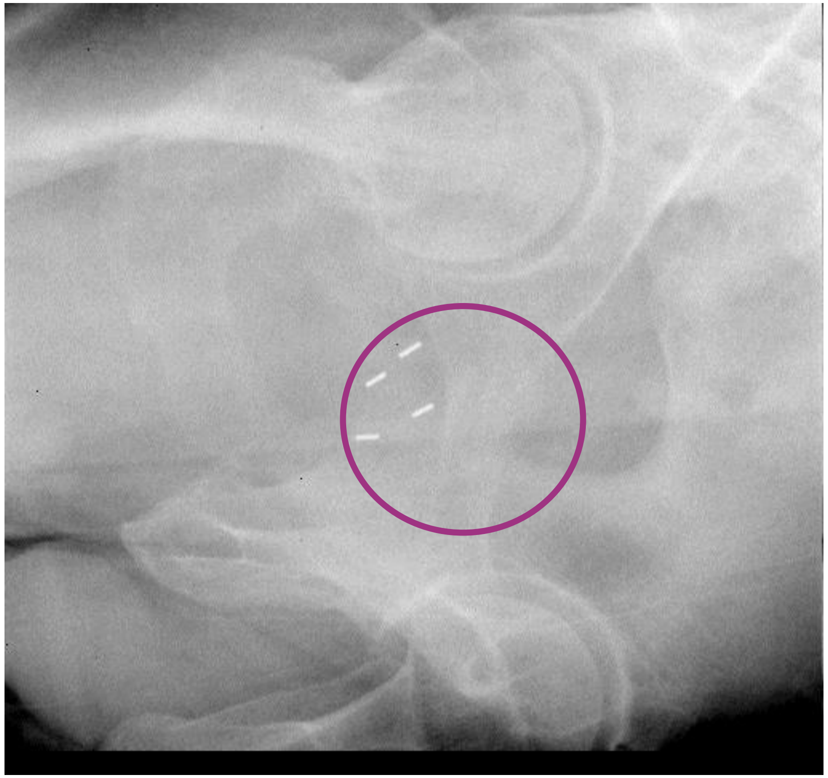
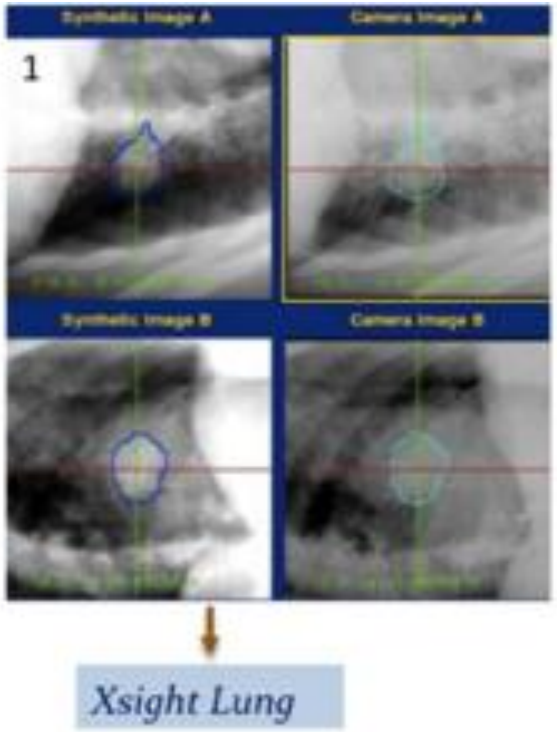
What can you track ?

- Markers



Bone: spine, skull,…

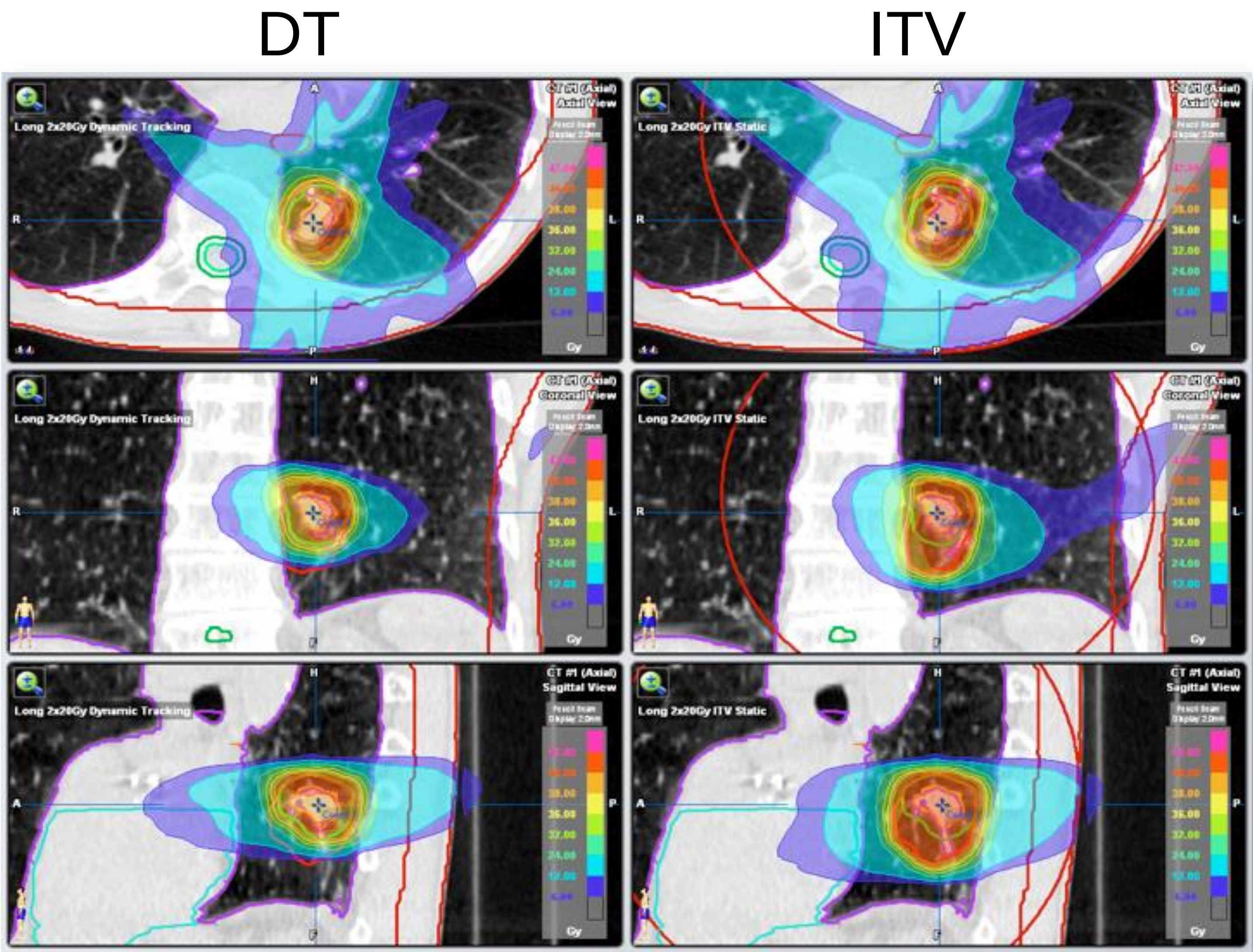
Soft tissue: 60% of tumour are visible



Bahig IJROBP 2013

PTV volume reduction

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



Dynamic tracking patients @ UZ Brussel (2012-2013)

D. Verellen

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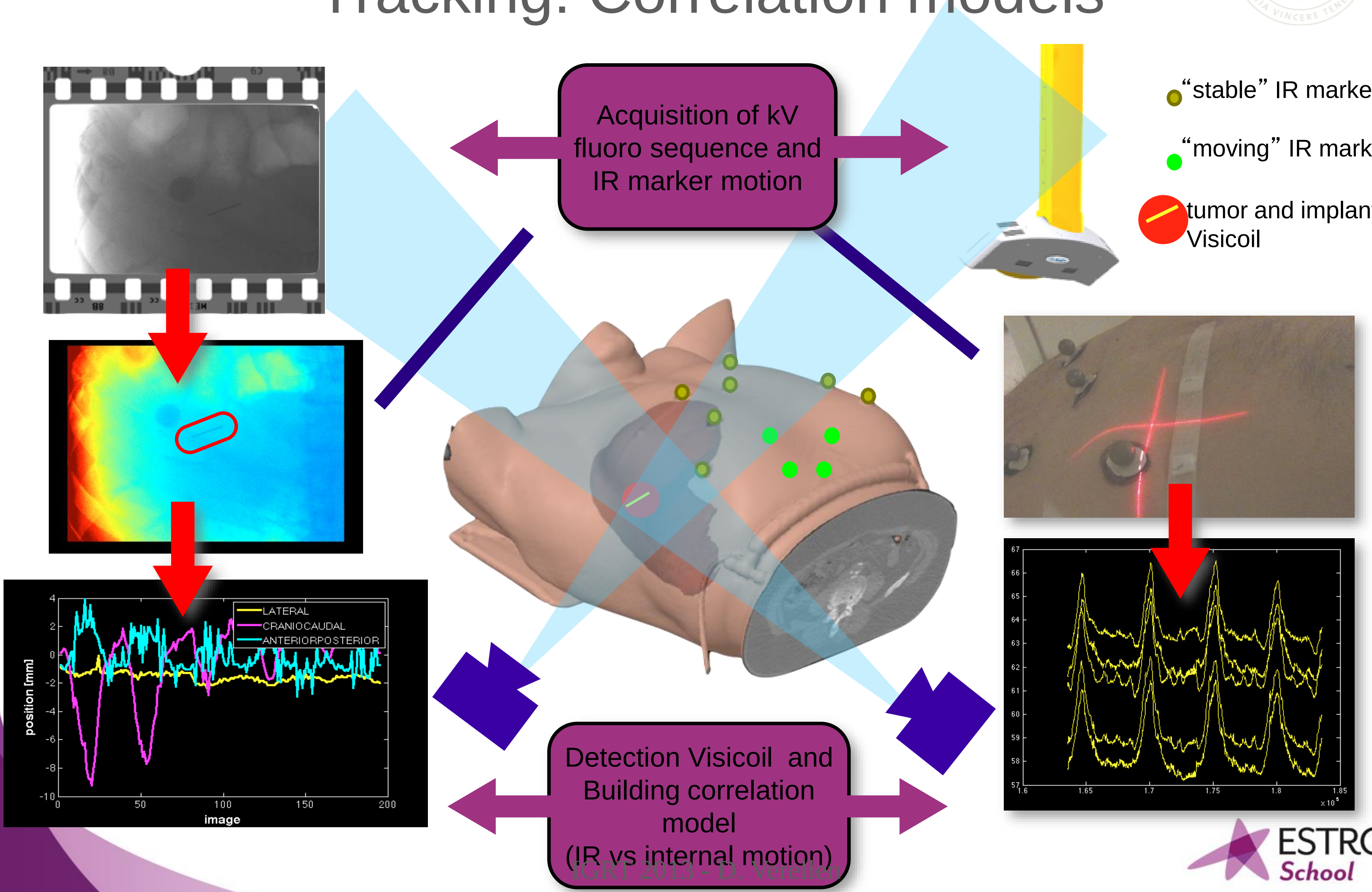
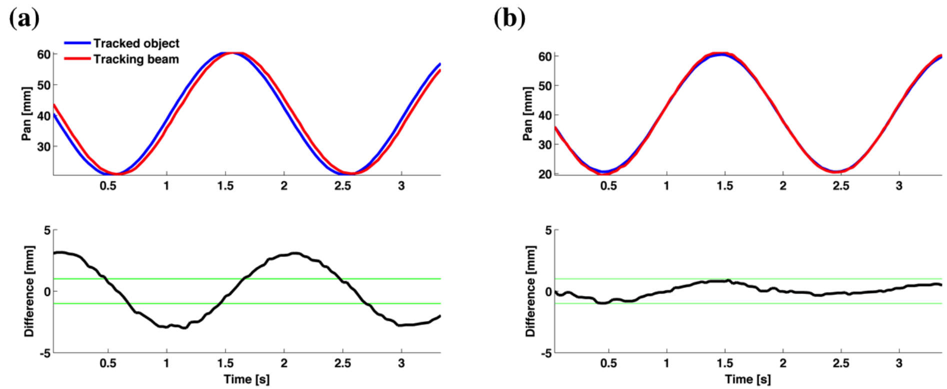
Tracking: Correlation models



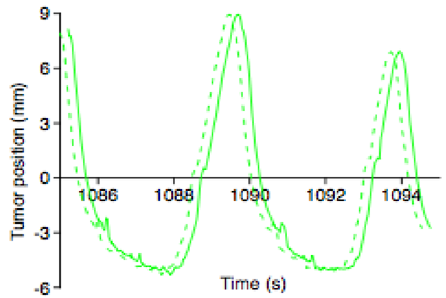
Tracking: system latency

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

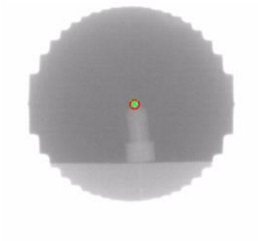


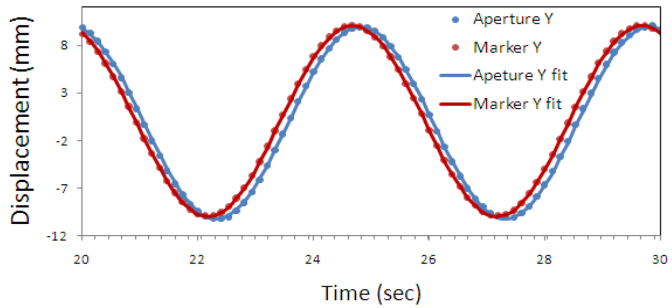
- Cyber Knife: System latency = 115 ms
  - ➢ Hoogeman *et al.*

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



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





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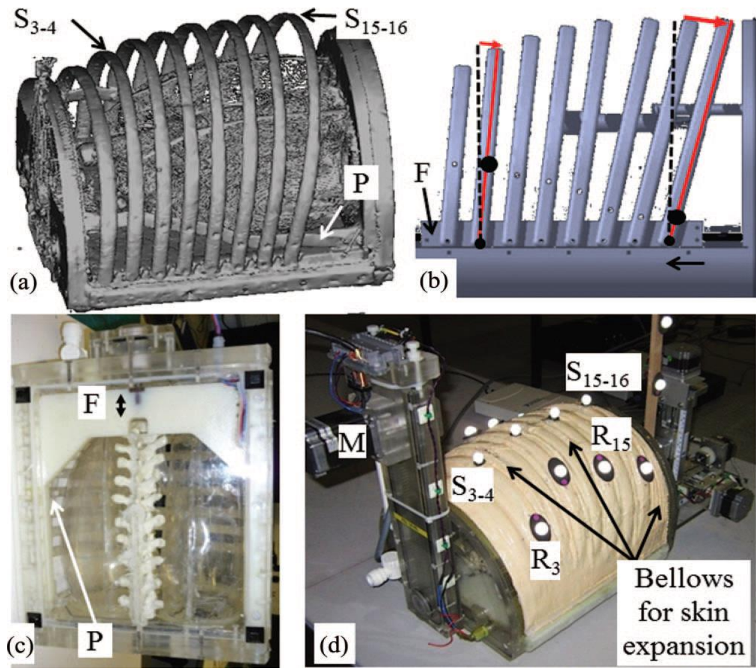
CIRS

QUASAR



QA of treatment delivery for tracking

Olivier MP 2014

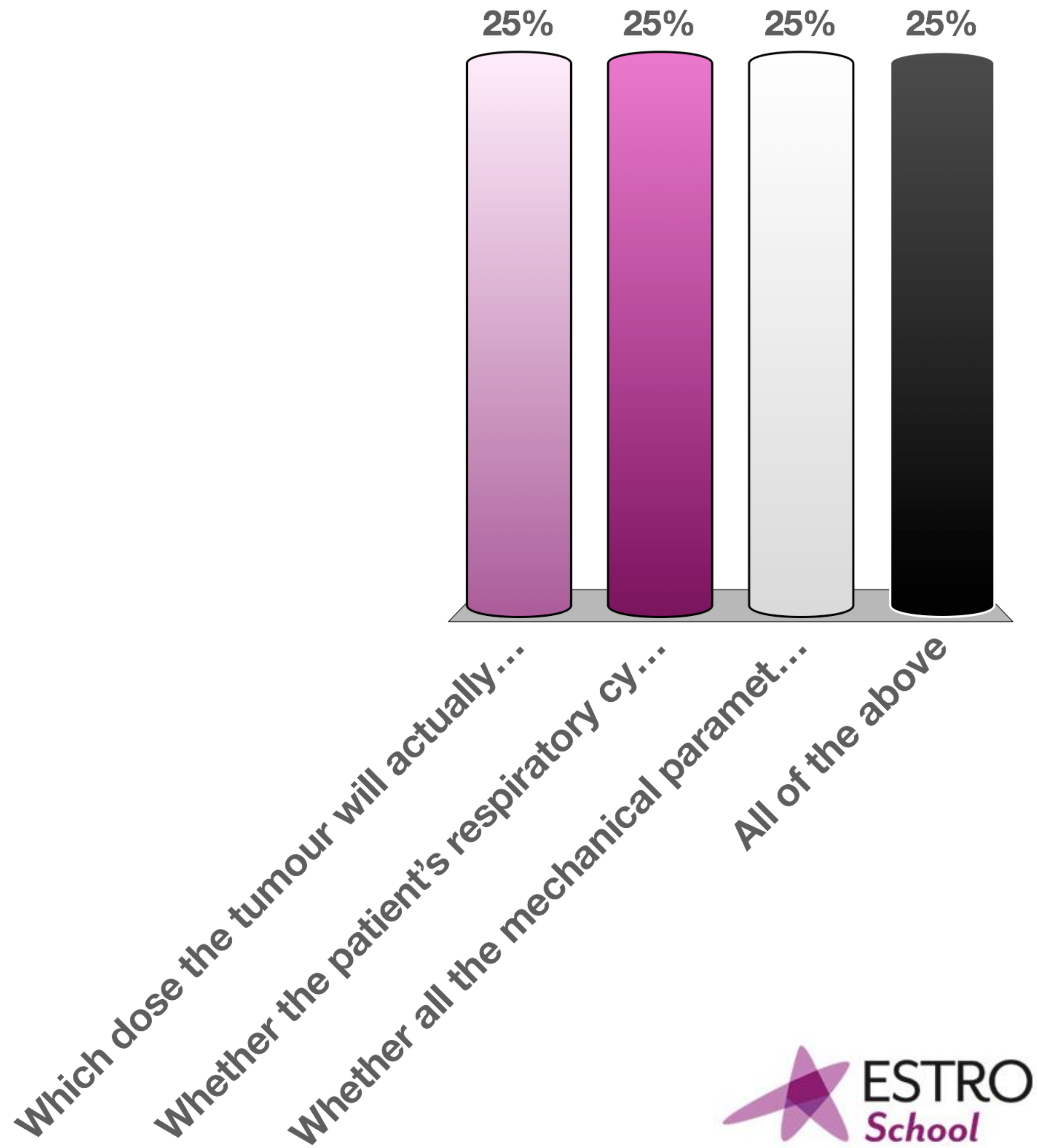
By using the patient's breathing trace (from an external surrogate) and a 4D phantom, are you checking…?

A. Which dose the tumour will actually receive over the whole treatment course

B. Whether the patient's breathing is similar to what you expected from your 4DCT

C. Whether all the technical parameters (alignment of the imaging system, etc…) are within constraints

D. All of the above



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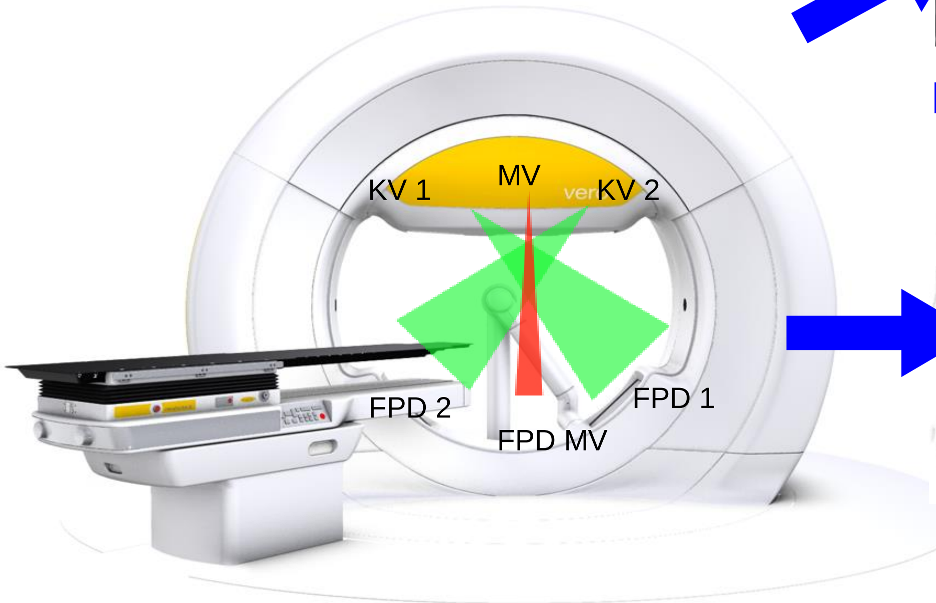
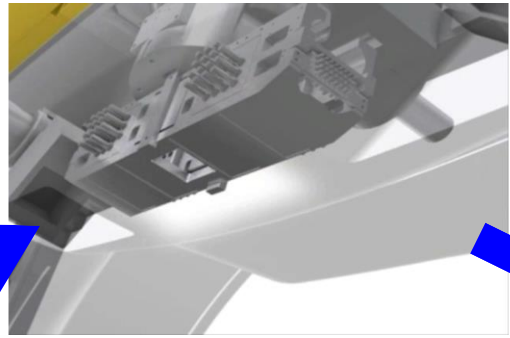
QA of treatment delivery for tracking

- “Real” 4D is not tested
- This is NOT individual patient QA
  - Irregular breathing?
  - Loss of surrogate/tumour relationship?
- You are still pretty much only checking the machine
- This will NOT give you any info on how the patient actually breathed during treatment
  - Unless you have thorough imaging
  - Log files of the beam/tumour position

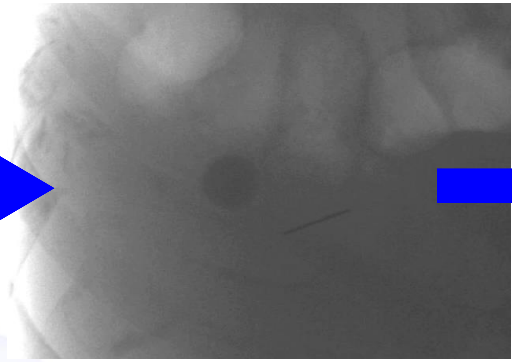
Tumour Tracking Verification



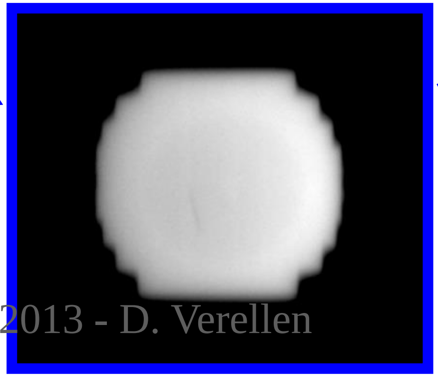
Gimbals position logging



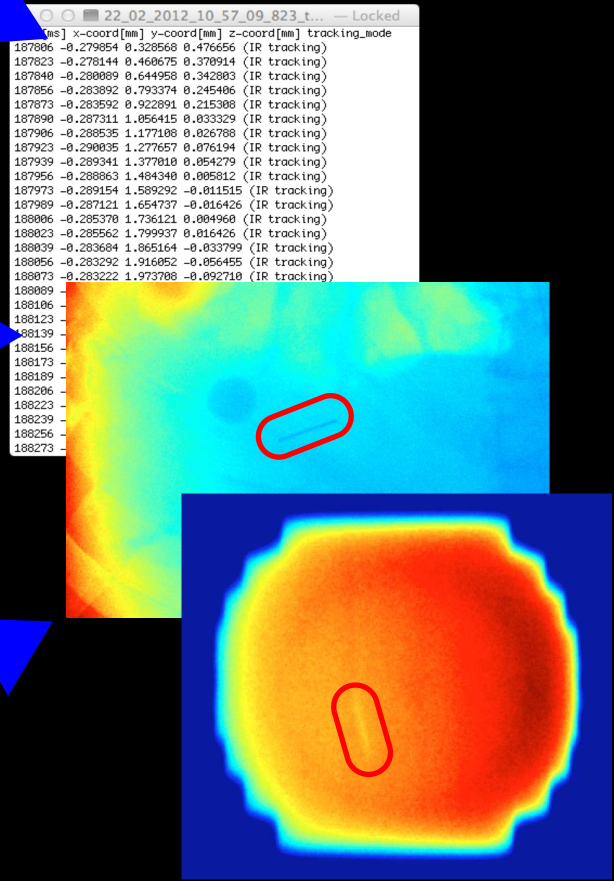
kV Monitoring Imaging



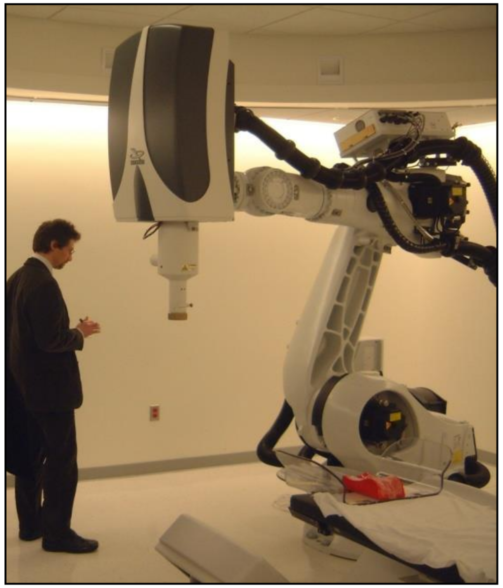
EPID MV Imaging



Per fraction QA through combination of different information sources

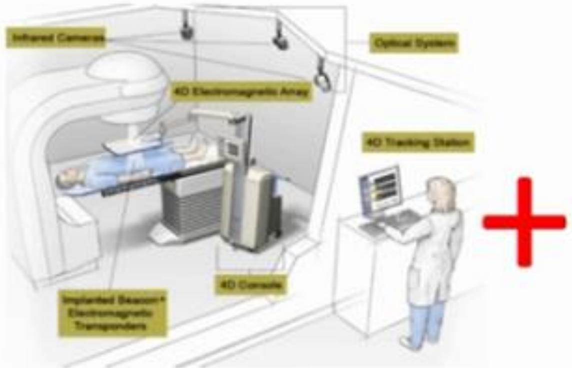


Tracking

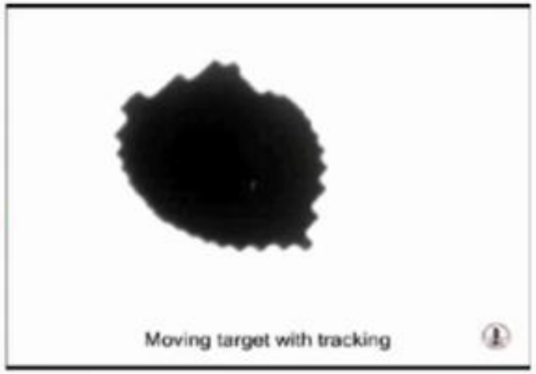


CALYPSO + MLC TRACKING

Booth et al ASTRO 2014



Varian Trilogy and Calypso research



University of Sydney MLC Tracking

Caveat: you can only track one target at a time

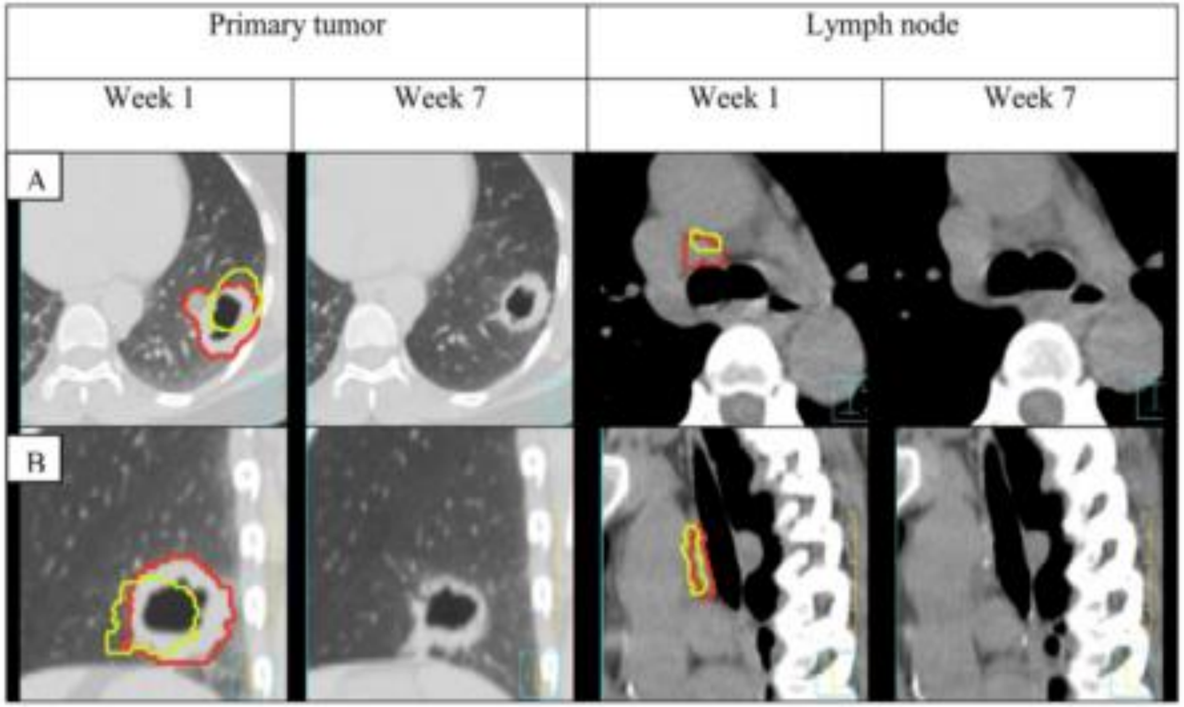


Figure 1.
Example of primary tumor and lymph node shrinkage and change in position between week 1 and 7 in patient 17. Week 1 contours are shown in red, week 7 in green. Week 7 contours are superimposed on week 1 images for better comparison.

So what if you have a peripheral and a mediastinal target ?

Weiss IJROBP 2012

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Conclusions

- Breath and gating should not be considering “margin reducing” strategies for most patients (though they may have other considerable advantages!!)

  - ➢ Don’t blindly trust your surrogates

- Smörgåsbord of technologies available, ranging from the simple to the highly elaborate

- Some room for improvement in terms of QA solution (during /after treatment)

THANK YOU FOR YOUR ATTENTION

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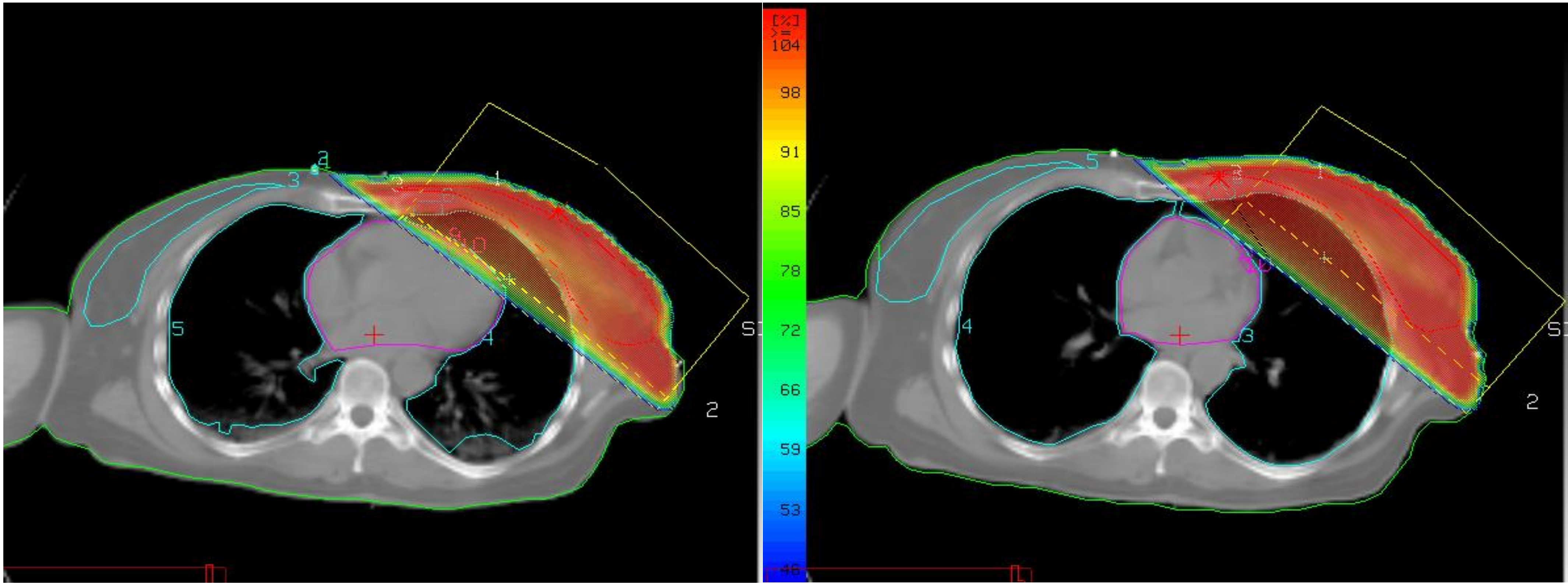
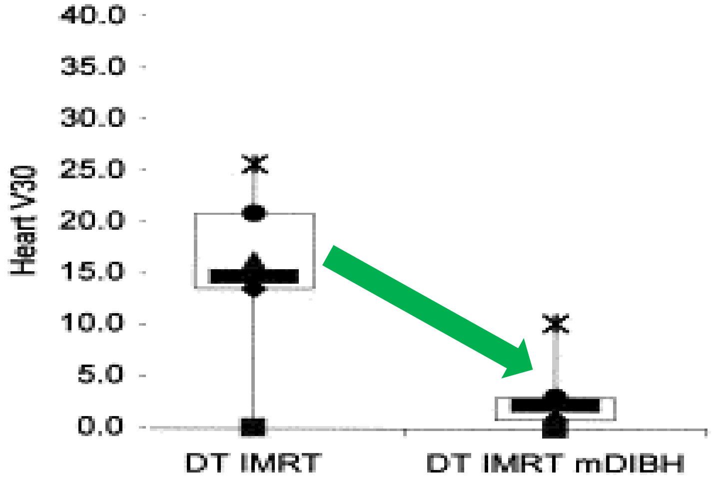
Techniques for reduction of cardiac toxicity

FB

DIBH

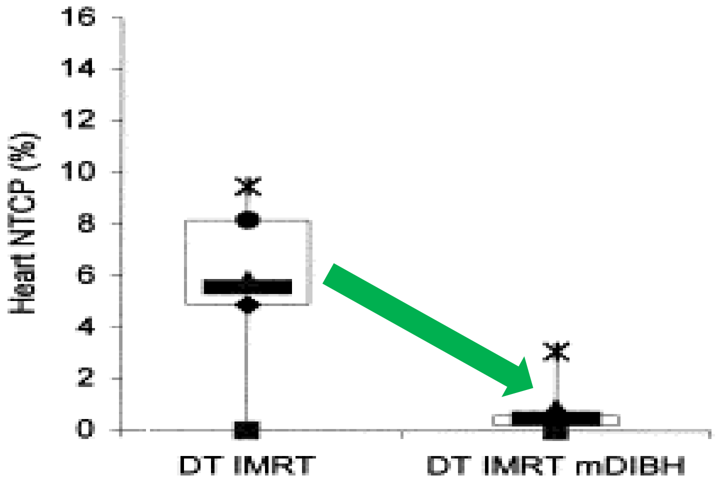


Techniques for reduction of cardiac toxicity



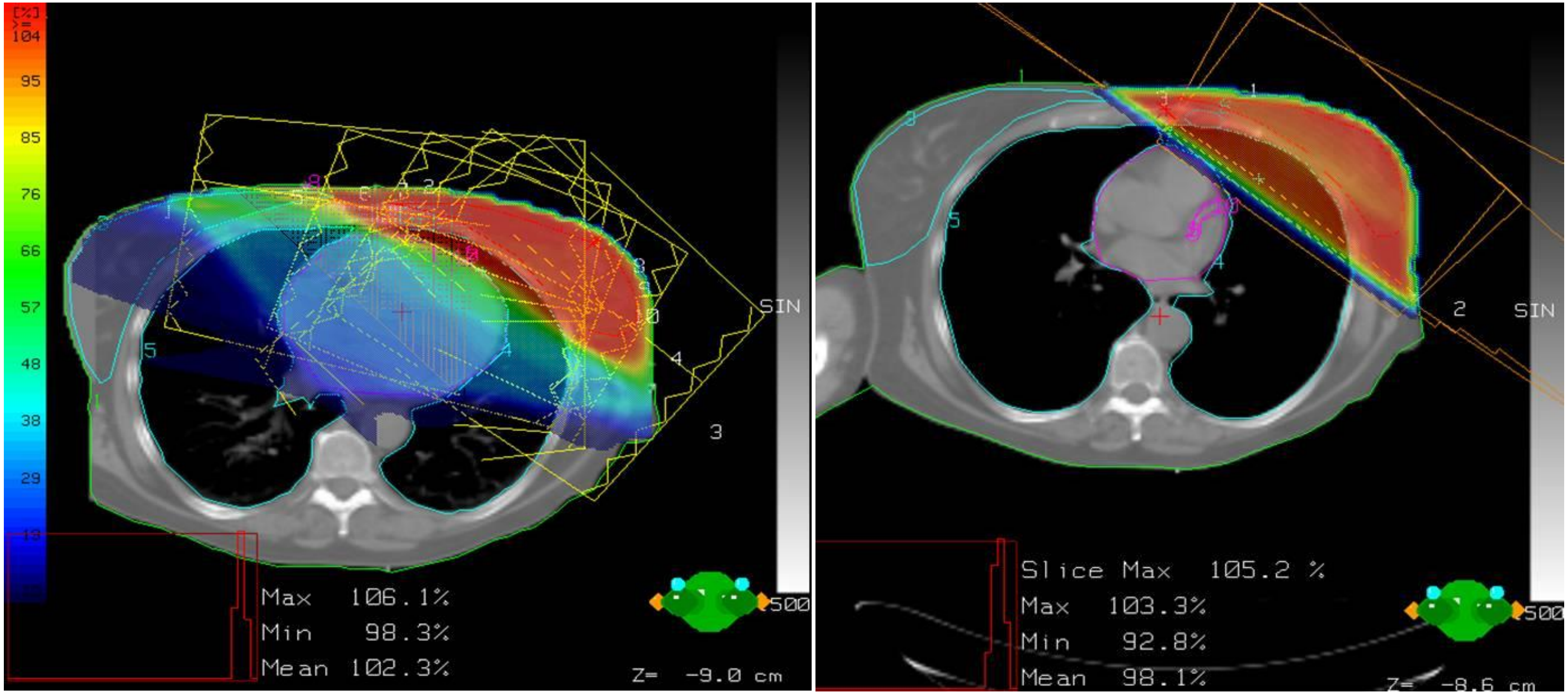
Remouchamps IJROBP 2003

Significant reduction of heart dose and heart NTCP in left sides breast cancer



Remouchamps IJROBP 2003

Techniques for reduction of cardiac toxicity
IMRT or inspiration gating?



Patients with unfavorable thoracic anatomy:

➢Improved sparing of the heart with IMRT at cost of increased dose to the normal tissue (e.g. contralateral breast)

➢Sparing of the heart can be more efficient with 3D_DIBH than with IMRT_FB.

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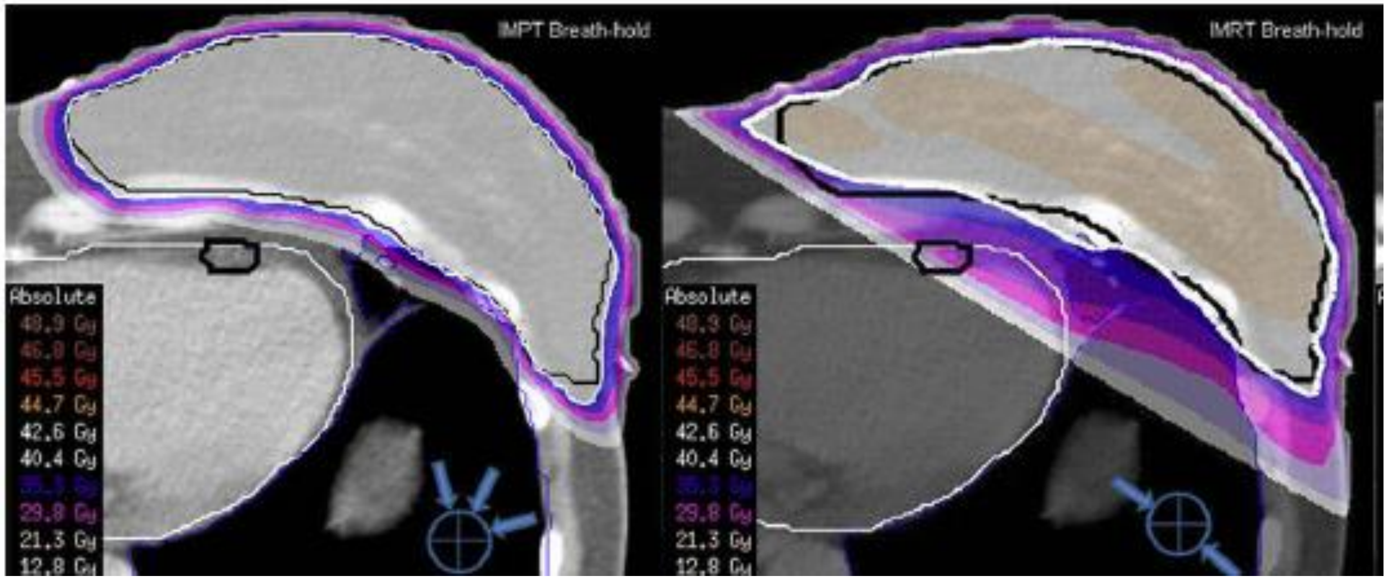
Don't get too fancy… at least until we have better evidence !

- ASTRO "choose wisely"
- (1) consider hypofractionation (>50 y, early stage)

- (5) don't routinely use ***(multi-field)*** IMRT to deliver whole-breast radiation therapy as part of breast conservation therapy.

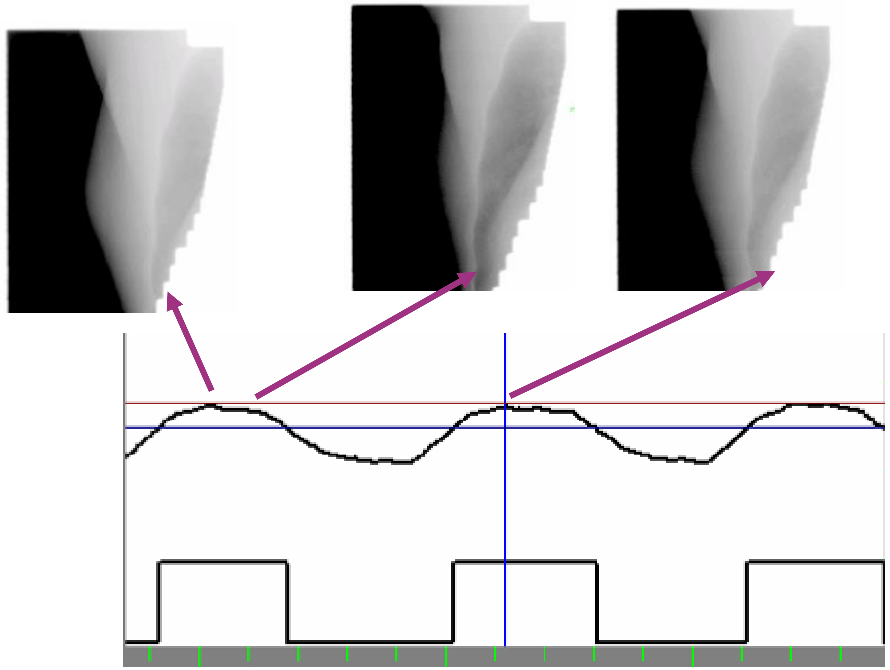
IMPT IMRT



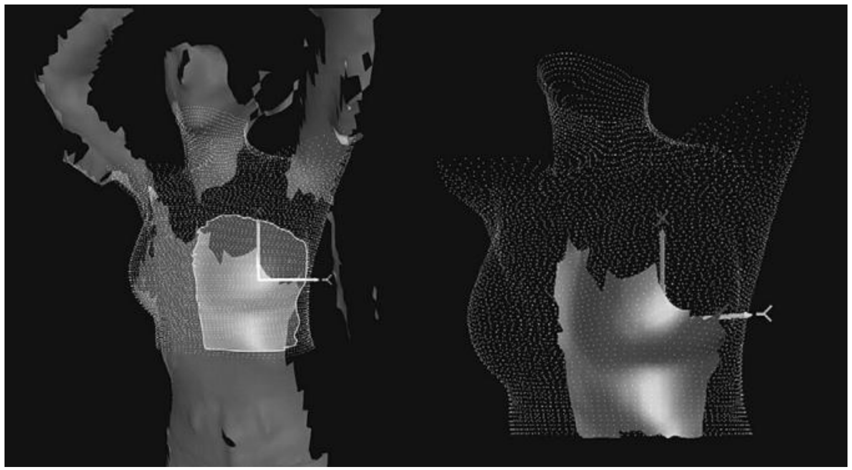
Mast BCRT 2014

Image guidance for deep inspiration: <u>DIBH/gating monitoring</u>

- Patient set up as for conventional treatment (i.e. planar or CBCT)



Residual motion can be verified by cine EPID



Align RT: potential for breath hold monitoring
Maintain use of CBCT for set-up

Alderliesten et al IJROBP 2012

Take home message: image-guidance for DIBH/gating monitoring

- Deep inspiration techniques are easy to implement and effective in reducing heart and lung dose

- They are vey well tolerated

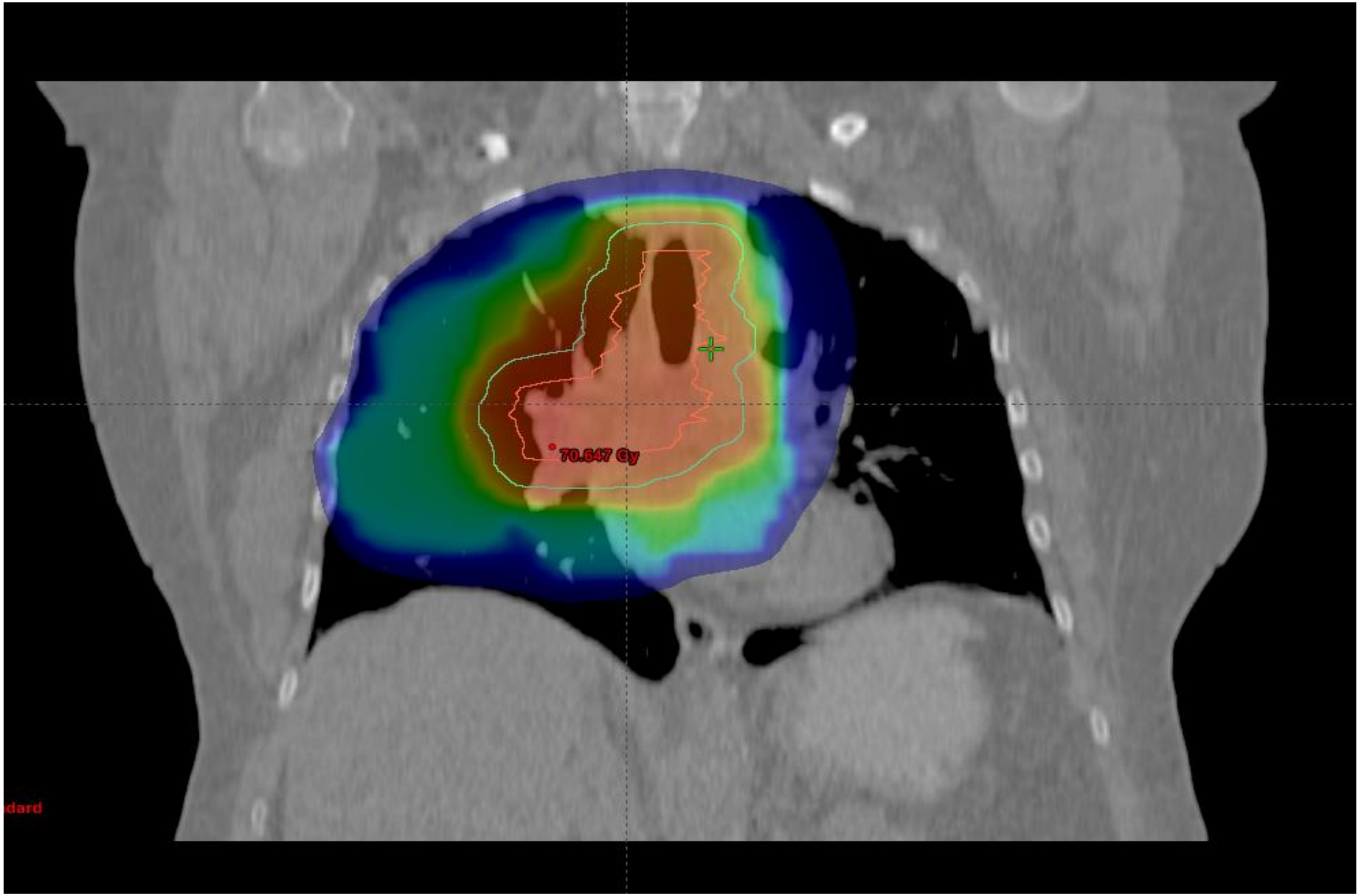
- Many technical solutions are available and they are all valid
  - ➢ choose what fits your workflow/resources best

- X-ray based imaging is still recommended in addition to ensure proper set-up

Take home message: image-guidance for breast cancer

- MV can be acceptable is you have a good surrogate (e.g. visible clips, not only ribs)
- The less robust your treatment technique, the more advanced the IGRT
- An offline strategy (NAL, eNAL, SAL, etc…) will go a long way towards reducing uncertainties
- Deep inspiration: just do it !

Lung Cancer

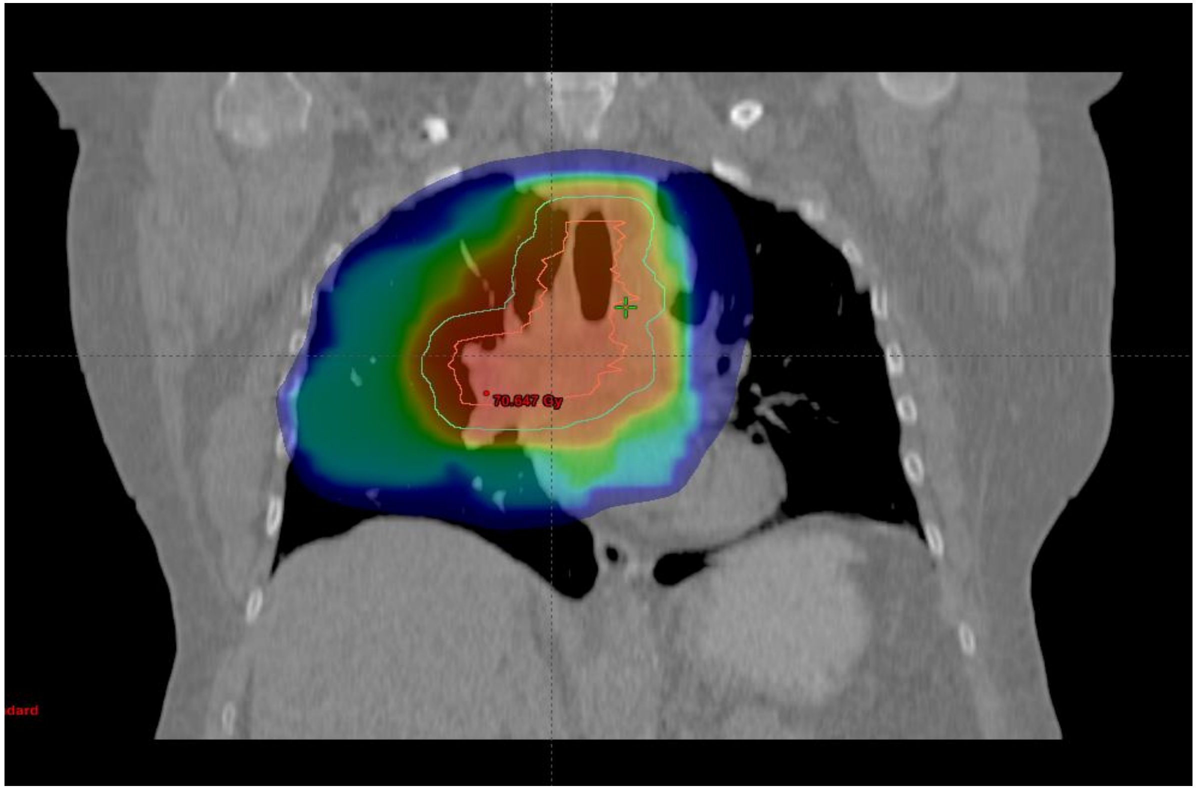


Pre-treatment image guidance

Gating /breath hold

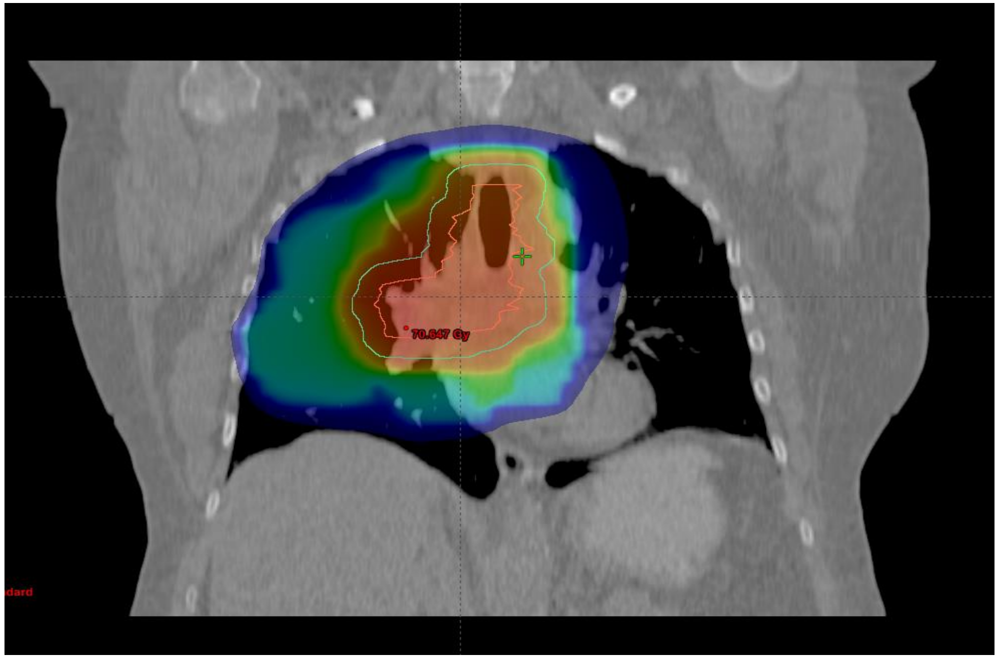
Breath hold radiotherapy

Challenge 2: how to deal with large tumours?

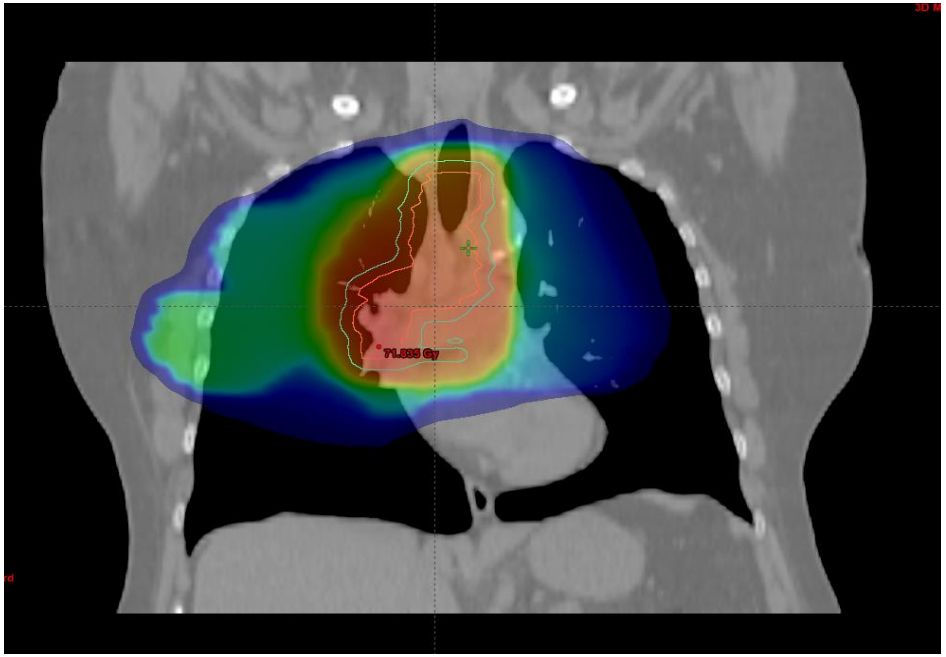


- 70-year old patient with poor pulmonary function
- Tumour motion < 5mm
- MLD unacceptable if a curative dose (66Gy) is delivered
- Gating won’t help (neither will tracking!)

Deep inspiration breath hold: not a motion-limiting strategy !!

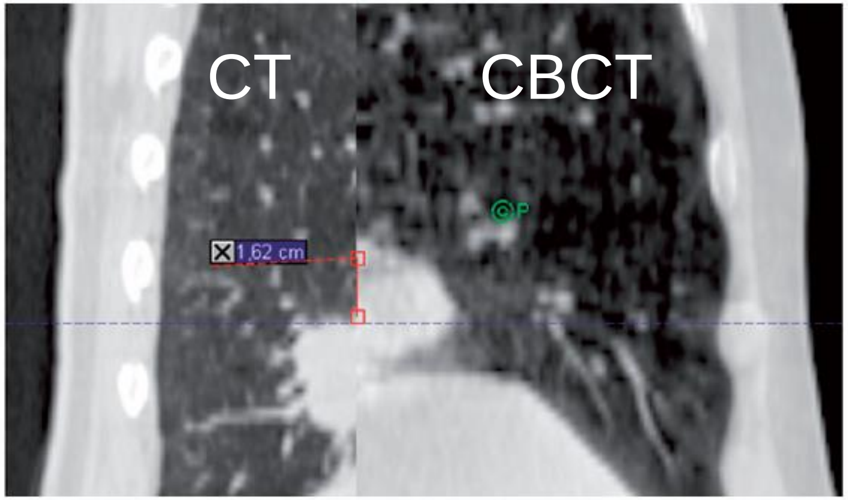


Free breathing
(MLD 23.6Gy)



Deep inspiration
(MLD 19.7 Gy)

Some caveats of breath hold (1)



Josipovic et al Acta Oncol 2014

2nd patient treated in DIBH

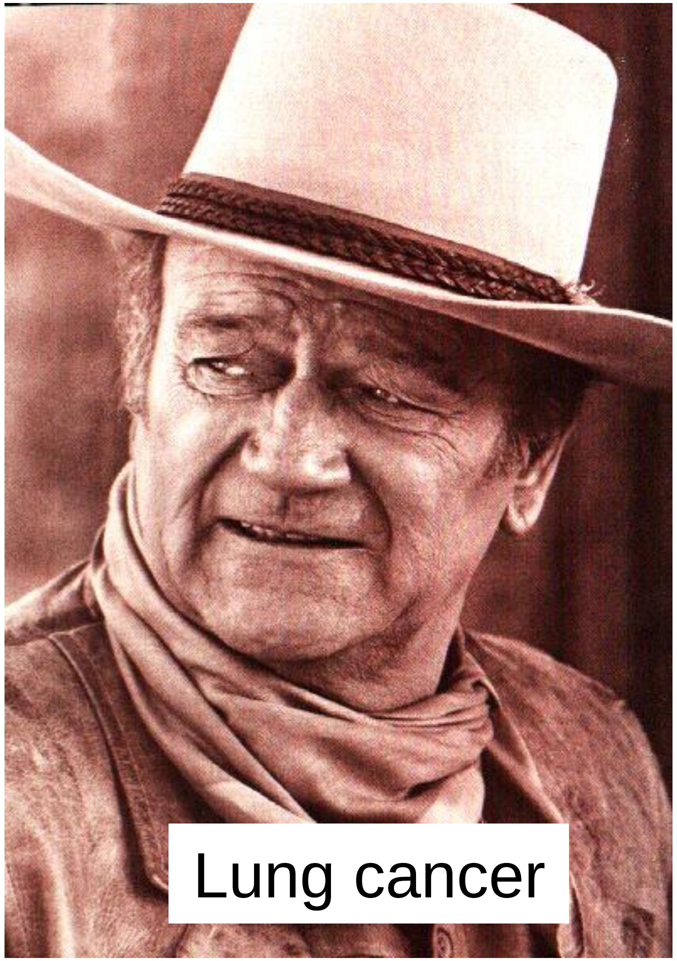
•peripheral target + mediastinal lymph nodes

•10th fraction: match on mediastinum, 1.6 cm shift CC direction for peripheral tumour

Don't (blindly) trust external surrogates: markers, spirometry, surface based etc…

Breath hold

Compliance ? Pulmonary function ?



Compliance

- All NSCLC patients perform a voluntary DIBH after 4DCT

- Pilot study (17 patients)
- Treated in free breathing
  - ➢ 3 time points: DIBH CT and CBCT

- 15 could perform DIBH until the end of their treatment course
  - ➢ 1 develop radiation pneumonitis
  - ➢ 1 wished to drop out of the study
  - ➢ All others had “reproducible” breath holds

Data submitted to Acta Oncol
Persson et al

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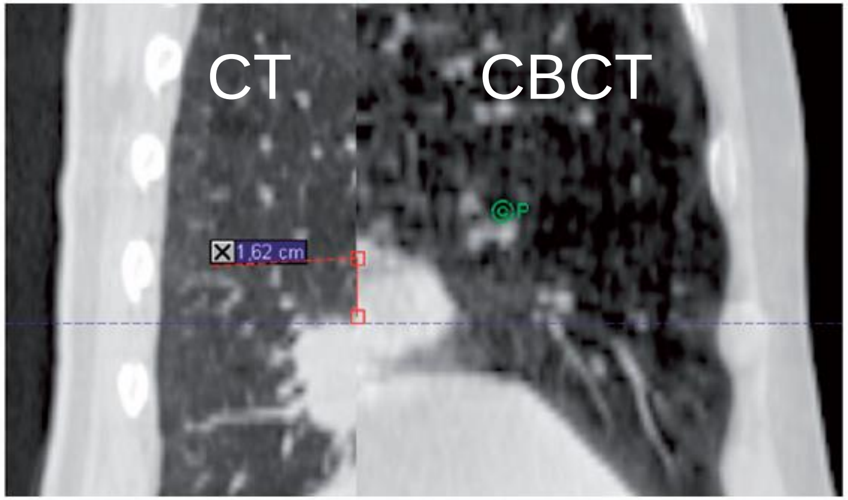
Some caveats of breath hold (1)



Josipovic et al Acta Oncol 2014

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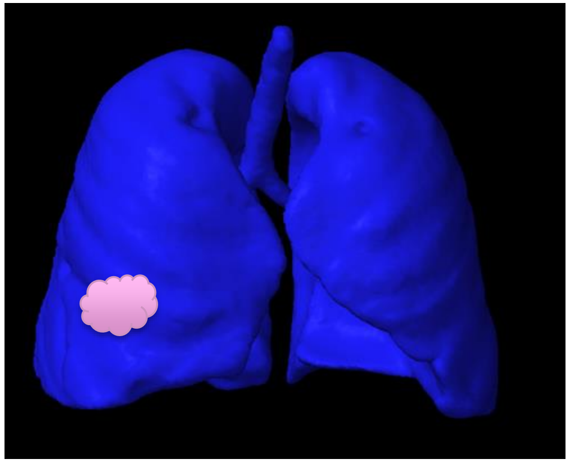
•10th fraction: match on mediastinum, 1.6 cm shift CC direction for peripheral tumour

Don’t (blindly) trust external surrogates: markers, spirometry, surface based etc…

INHALE
(phase 2 trial, target 80 patients)



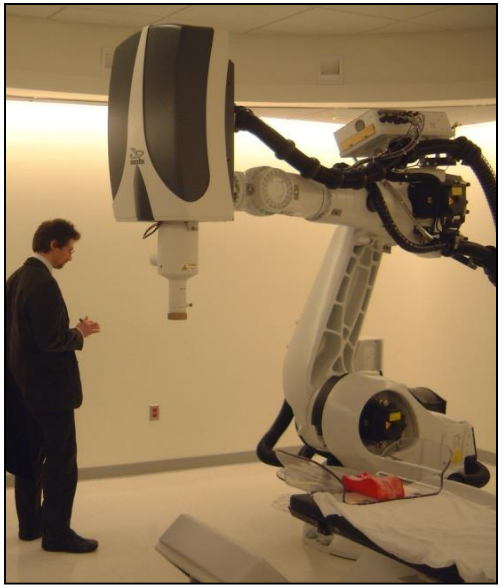
Registration on tumour
Verify OAR/bone

Registration on carina
Larger margins on peripheral tumour

LR

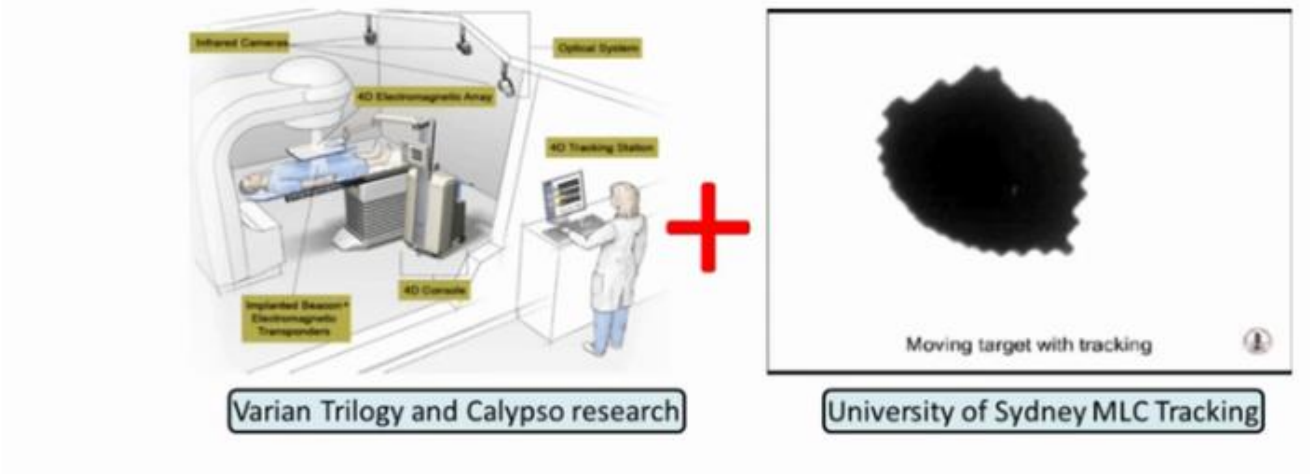
Josipovic et al R&O 2016

Tracking



CALYPSO + MLC TRACKING

Booth et al ASTRO 2014



Take-home messages for treatment verification in current clinical practice

- The most important is to see the tumour
  - ➢ in a representative position
- 2D imaging modalities (markers)
- 3D imaging modalities
  - \+ Volume imaging
  - \- No real-time imaging
- 4D imaging modalities
  - \+ fewer breathing motion artifacts
  - \- Actual benefit?

No single solution will be appropriate for every patient

Keep breathing ☺

Quiet free breathing **Breath hold**

Frameless IGRT and stereotactic radiotherapy

Andrew Hope, MD

Disclosures

Research support provided:

Elekta

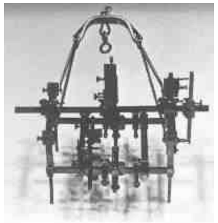
Philips

Thanks to Dr. M. Guckenberger

Stereotactic techniques are old

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



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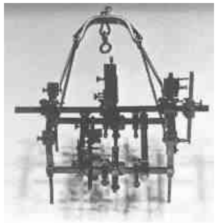
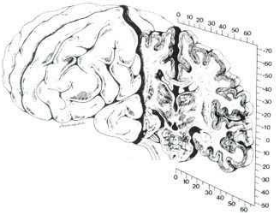




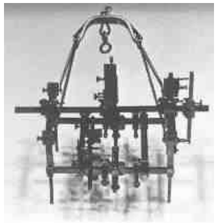
1908: Robert Henry Clarke and Victory Horsley

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

Problem: unsure relationship between bony landmarks and cerebral structures

- Targeting of subcortical structures only e.g. gasserian ganglion with foramen ovale as landmark
- Imaging e.g. ventriculography -> stereotactic atlas

Stereotactic techniques are old



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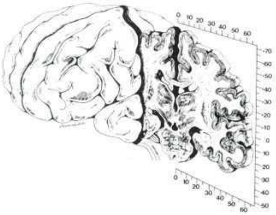

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Lars Leksell

1950s: Experiments with stereotactic proton therapy

1967: Gamma-knife radiosurgery using Co-60 for treatment of functional disorders

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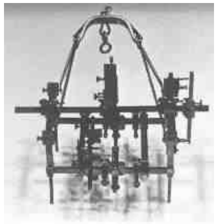
Stereotactic techniques are old



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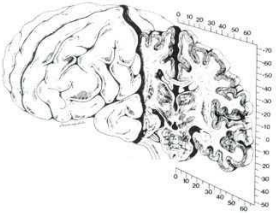

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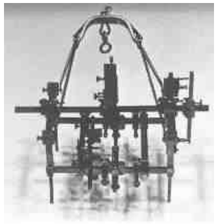
Lars Leksell

1950s: Experiments with stereotactic proton therapy

1967: Gamma-knife radiosurgery using Co-60 for treatment of functional disorders

Since 1980s: CT localization and linac based stereotactic radiotherapy

Stereotactic techniques are old



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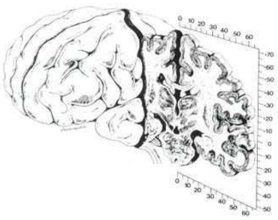
Stereotactic technique based on the reproducibility of the relationships between landmarks on the skull (external auditory canals, midline) and anatomical structures within the brain



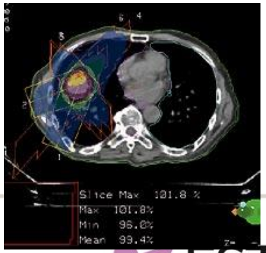
Problem: unsure relationship between bony landmarks and cerebral structures

- Targeting of subcortical structures only e.g. gasserian ganglion with foramen ovale as landmark
- Imaging e.g. ventriculography -> stereotactic atlas

Lars Leksell

1950s: Experiments with stereotactic proton therapy

1967: Gamma-knife radiosurgery using Co-60 for treatment of functional disorders



Since 1980s: CT localization and linac based stereotactic radiotherapy

Since 1994: (Lax & Blomgren): Stereotactic body radiotherapy

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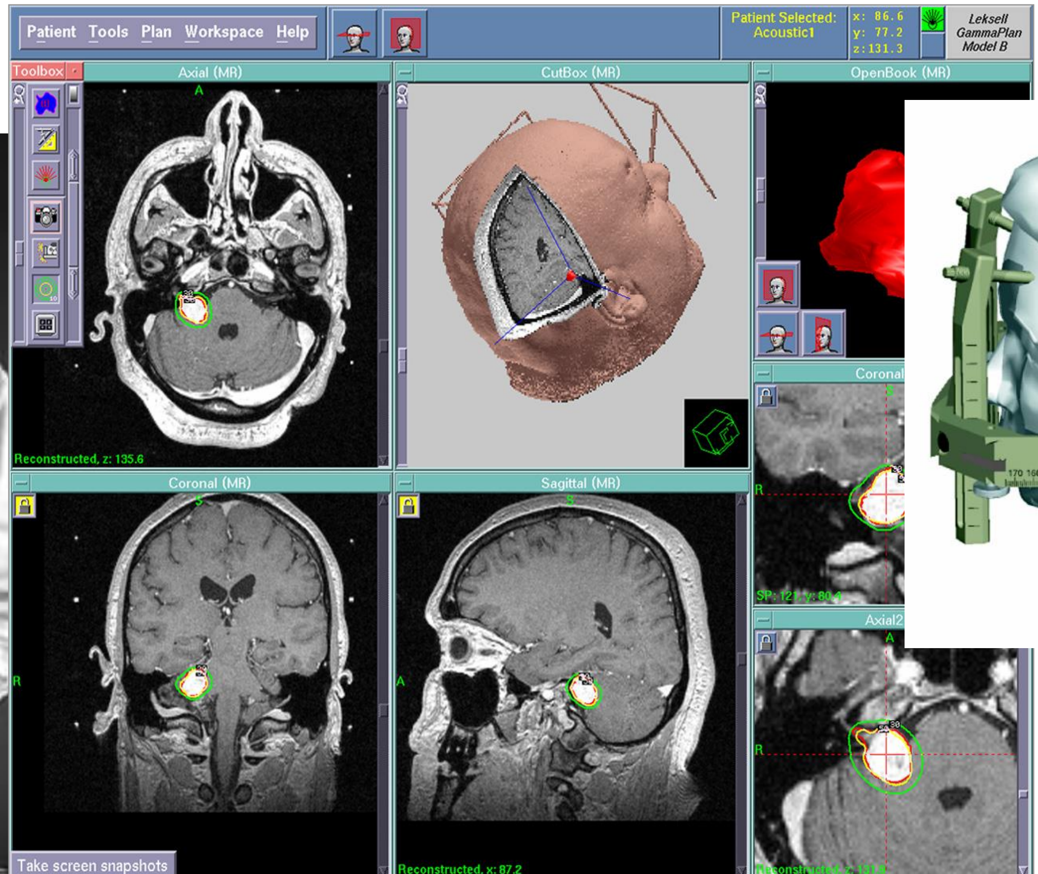
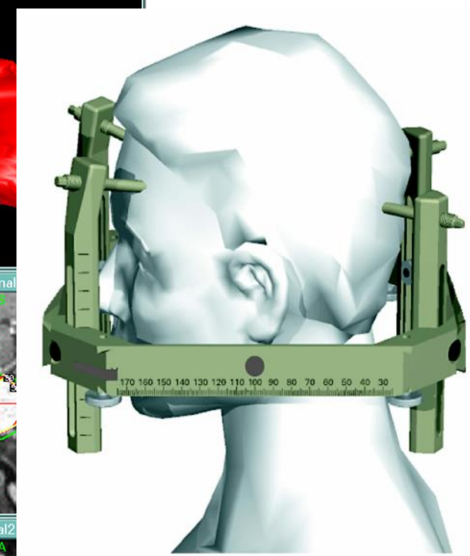
Intra-cranial stereotactic radiation

- :





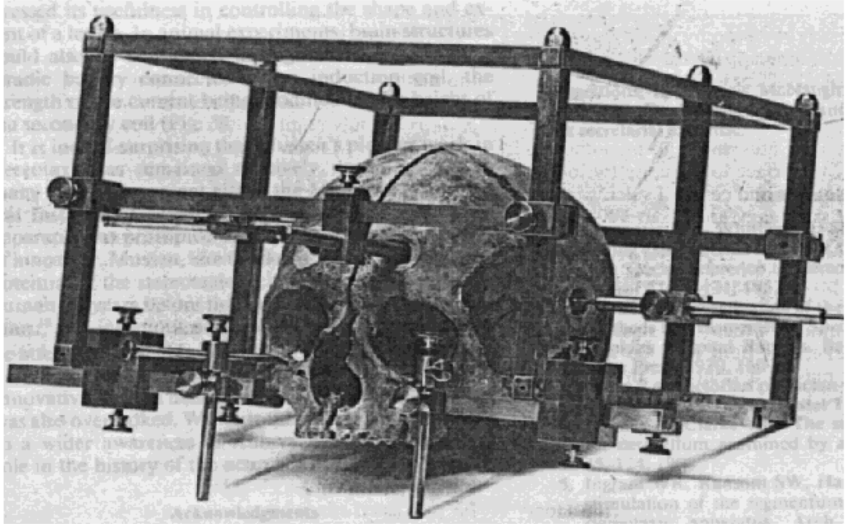
What is the ‘stereotactic’ frame?

Stereos (gr.): rigid, fixed

Taxis (gr.): ordering

Rigid relationship between an external system of coordinates and the internal anatomy of the brain (and the targets)

Invasive fixation of the stereotactic frame to the bony skull ensured sub-millimeter accuracy of surgery / radiotherapy



Nomenclature

Frame vs. Frameless

Invasive vs. Non-invasive

Nomenclature

Frame vs. Frameless

Are external coordinate systems used?

Invasive vs. Non-invasive

Nomenclature

Frame vs. Frameless

Are external coordinate systems used?

Invasive vs. Non-invasive

Is the patient fixed directly to the stereotactic system (screws, pins)?

Stereotactic: Invasive frame

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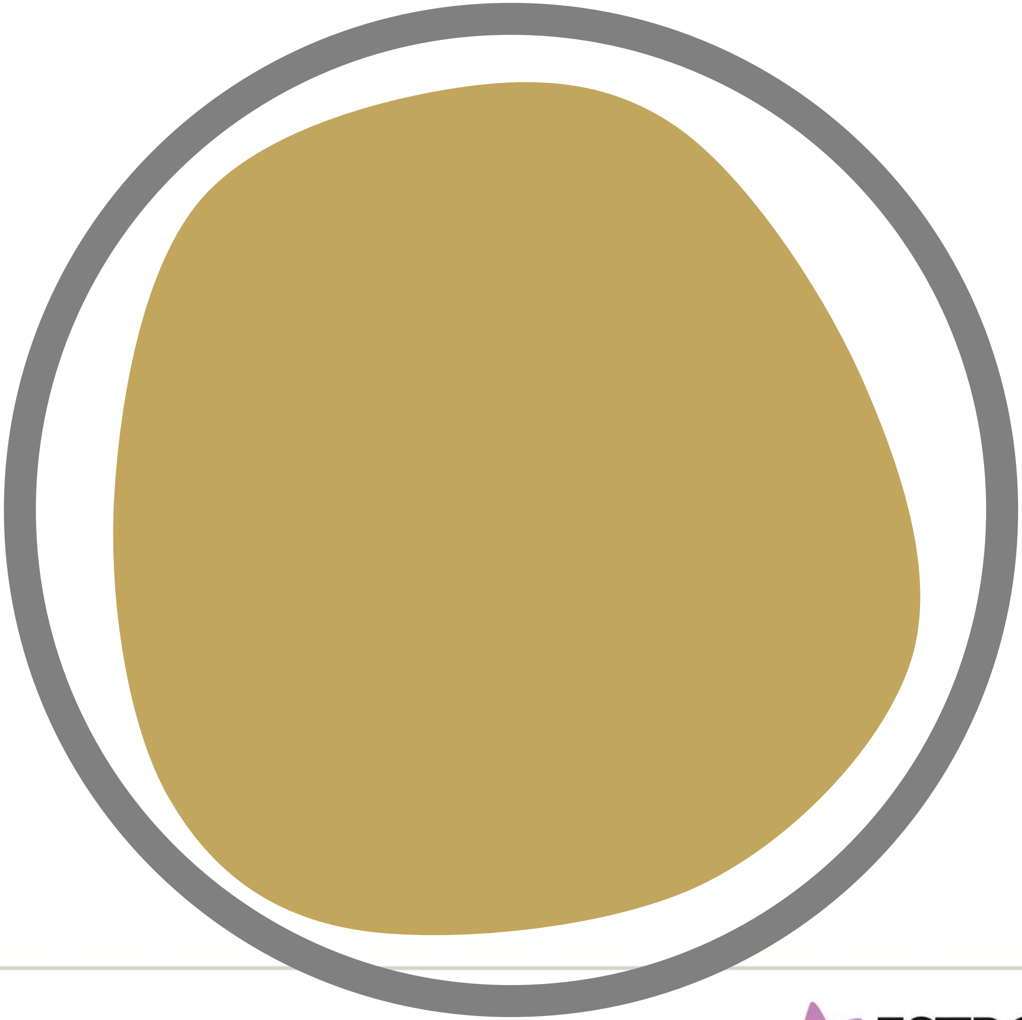
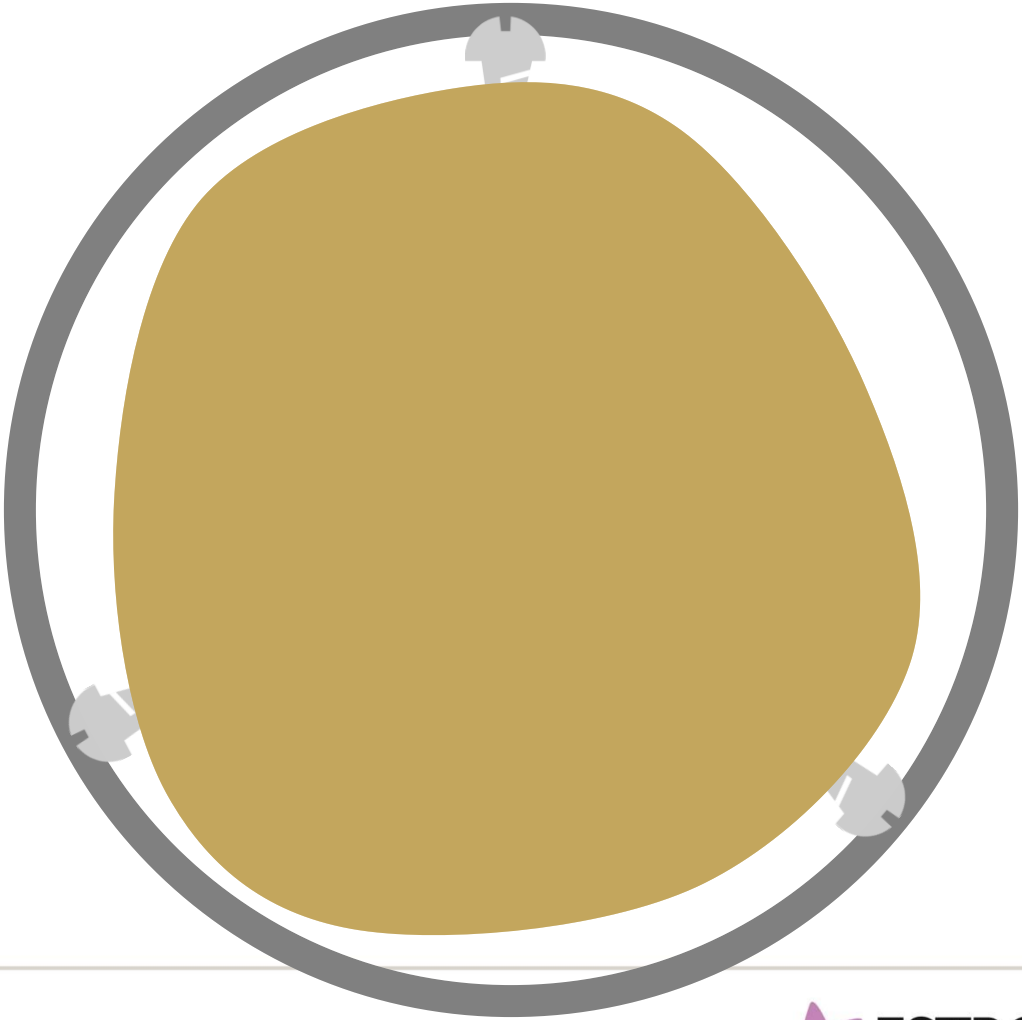
Stereotactic: Invasive frame

1. Invasive ring



Stereotactic: Invasive frame

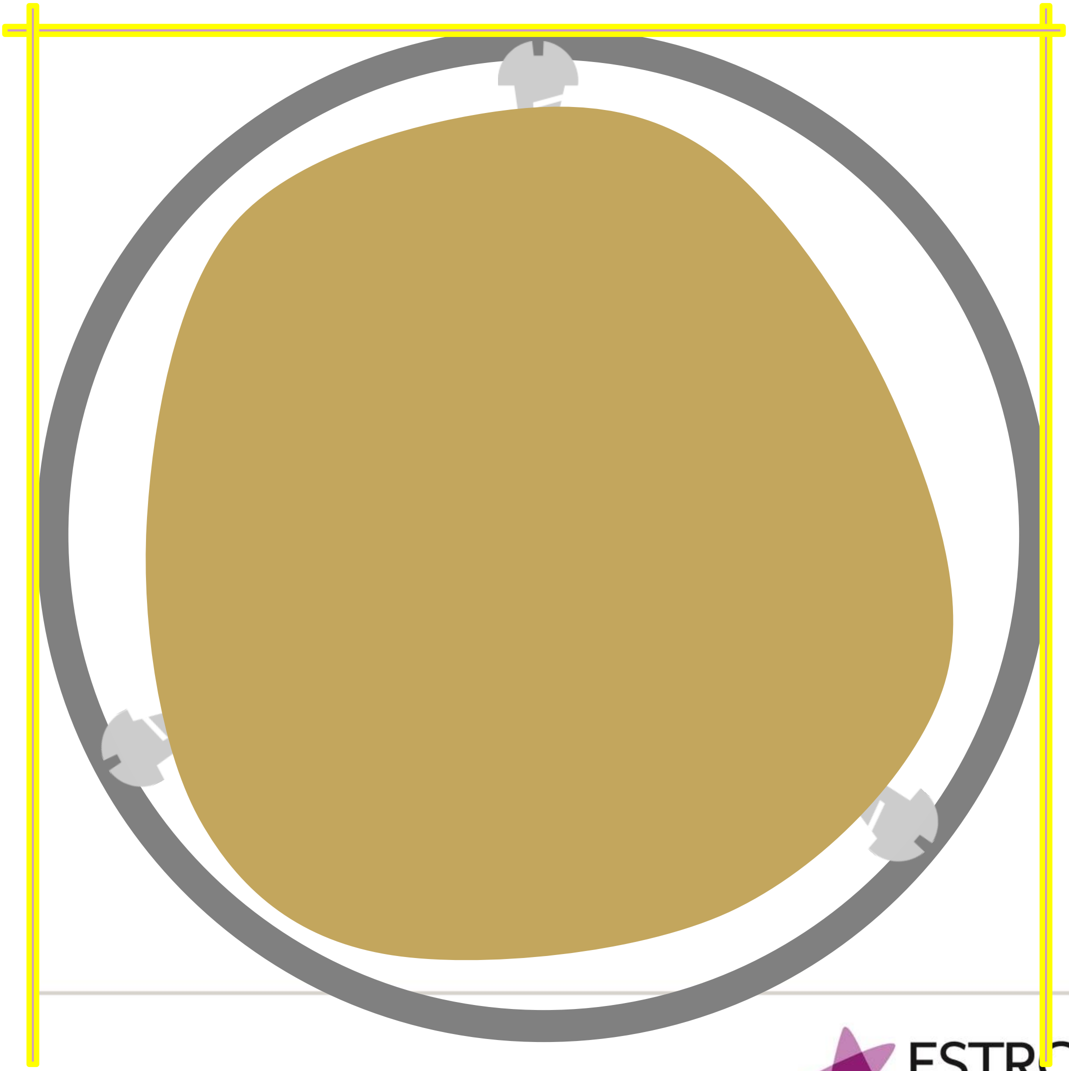
1. Invasive ring



Stereotactic: Invasive frame

1. Invasive ring

2. Localization system



Stereotactic: Invasive frame

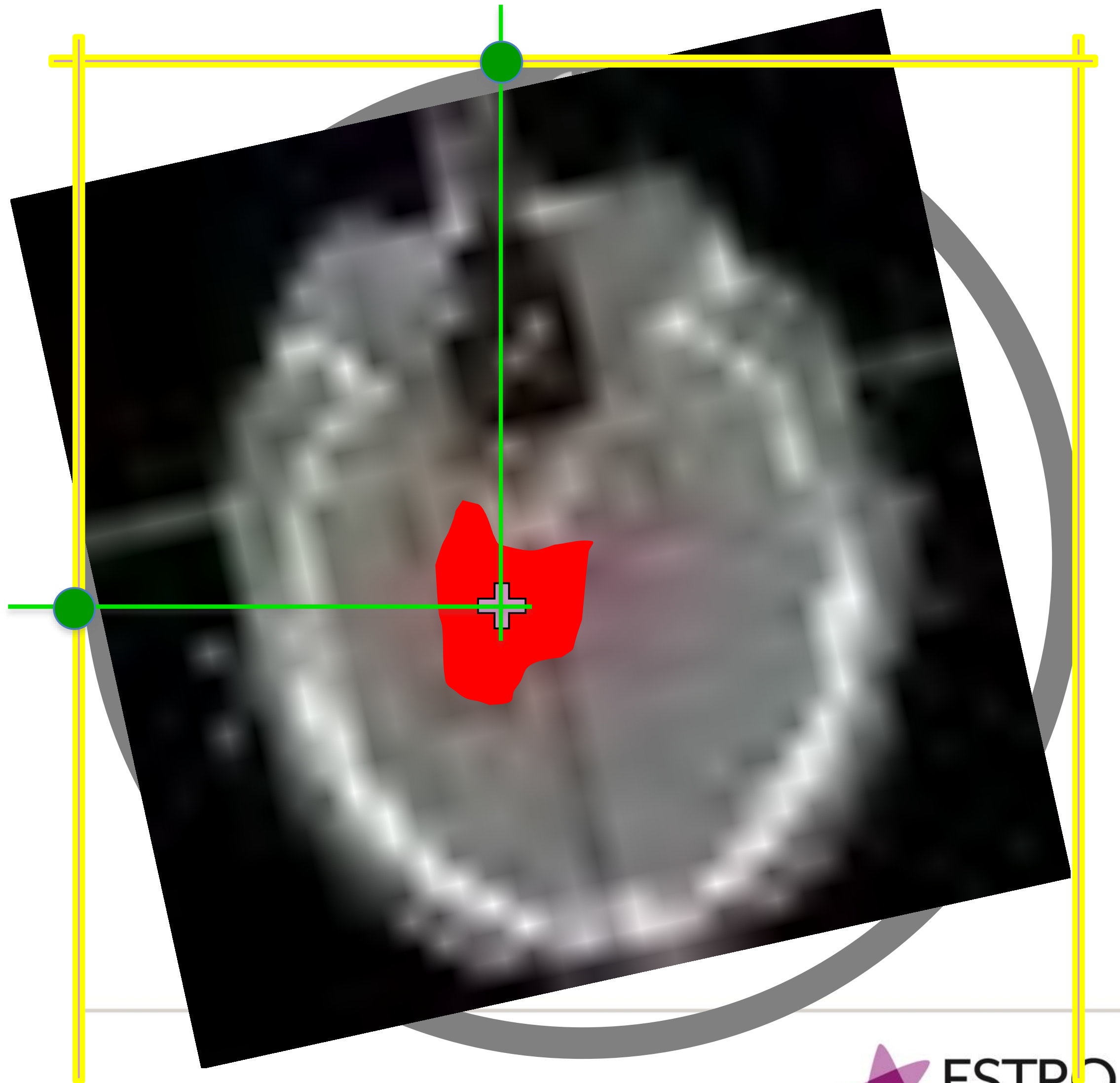
1. Invasive ring
2. Localization system
3. Imaging

Stereotactic: Invasive frame

1. Invasive ring
2. Localization system
3. Imaging
4. Target definition

Stereotactic: Invasive frame

1. Invasive ring
2. Localization system
3. Imaging
4. Target definition
5. Stereotactic isocenter position

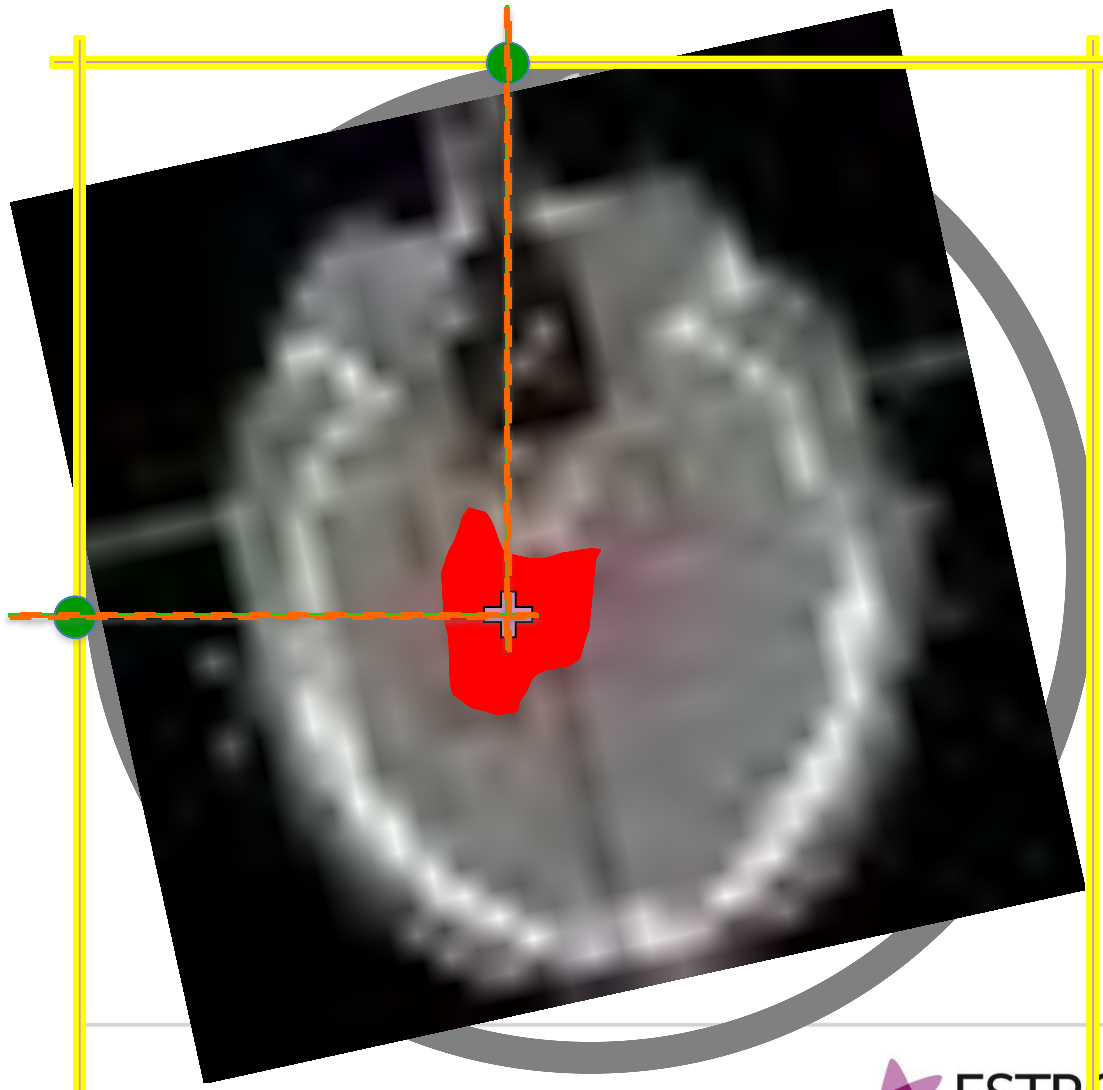


Stereotactic: Invasive frame

1. Invasive ring
2. Localization system
3. Imaging
4. Target definition
5. Stereotactic isocenter position
6. Stereotactic positioning

Stereotactic: Invasive frame

1. Invasive ring
2. Localization system
3. Imaging
4. Target definition
5. Stereotactic isocenter position
6. Stereotactic positioning
7. Treatment



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Intracranial stereotactic radiotherapy

<u>Stereotactic radiosurgery (SRS)</u>

Single fraction treatment

AVM, vestibular schwannoma, brain metastases, …

Usually invasive frame-based techniques

<u>Multiple fraction stereotactic radiotherapy</u>

Theoretical benefit of fractionation, if organs-at-risk with low α/β value are close to the target

For large target volumes

Usually practiced non-invasively (masks, bite-blocks,….)

patient comfort

risk of infection

Accuracy differs between invasive and non-invasive stereotactic systems!

Invasive frame-based stereotactic radiosurgery

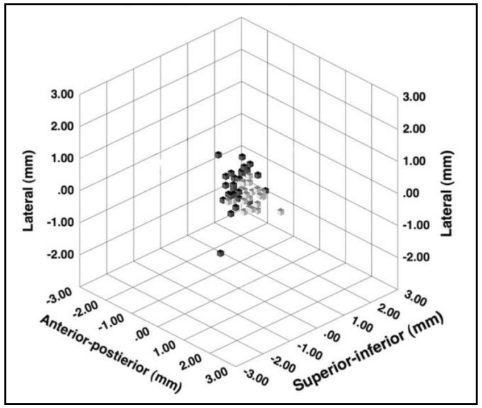
Novalis system:

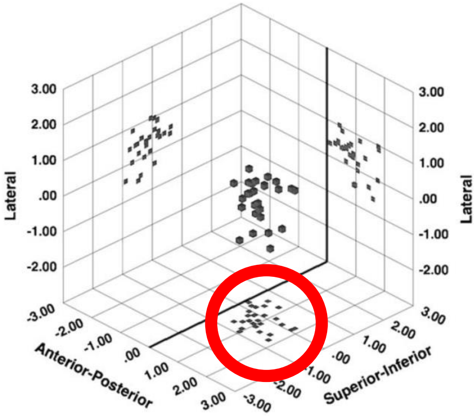
Phantom positioning:

frame-based vs. image-guided

Patient set-up:

frame-based vs. image-guided





Lamba et al., IJROBP 2009

Invasive frame-based stereotactic radiosurgery

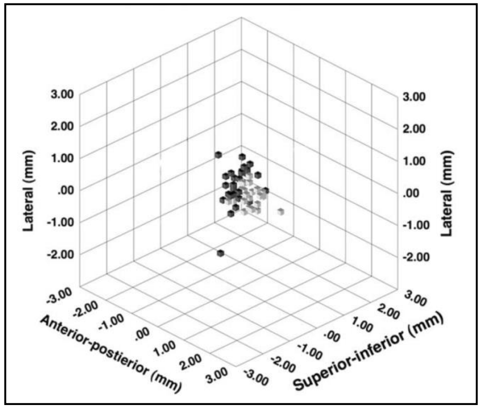
Novalis system:

Phantom positioning:

frame-based vs. image-guided

Patient set-up:

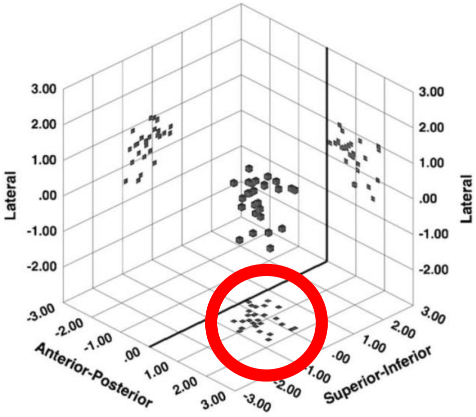
frame-based vs. image-guided



Why the difference?

Flex in the ring fixation system when attached to the couch

Torque due to placement of the localizer device on the ring



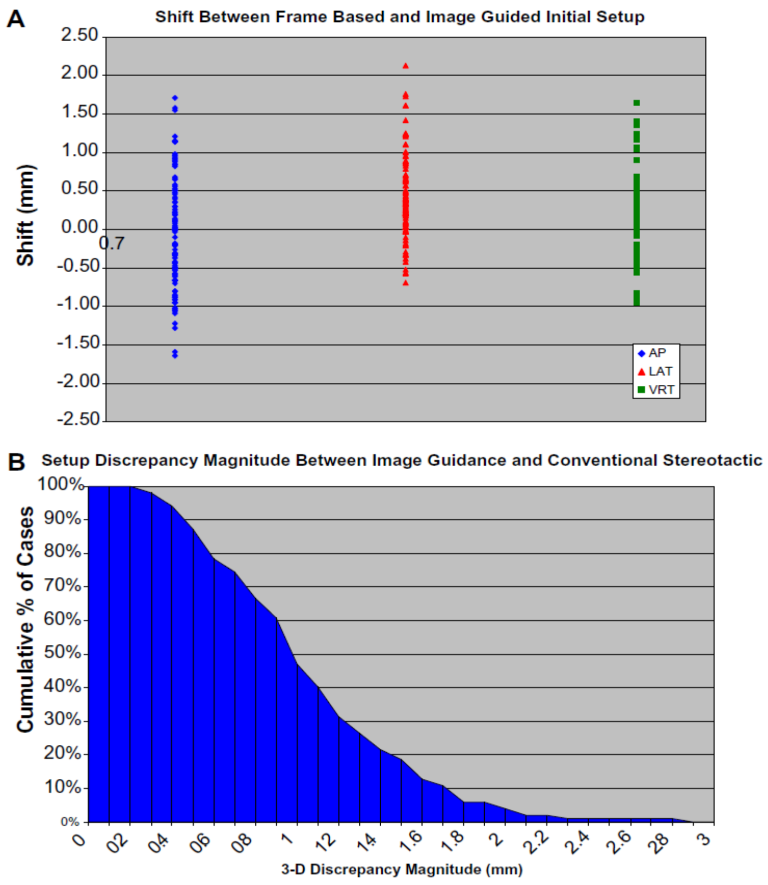
Lamba et al., IJROBP 2009

Accuracy of frame based SRS

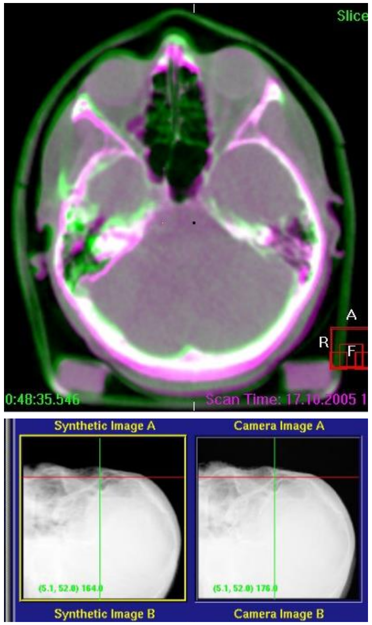
102 Patients treated with frame-based SRS

Passive verification of frame-based set-up with IGRT (CBCT)

Detected one patient with a 4.3mm frame “slip”



Moving from frame to frameless



Frameless stereotactic radiotherapy:

Replace the stereotactic external coordinate system with imaging-based patient positioning

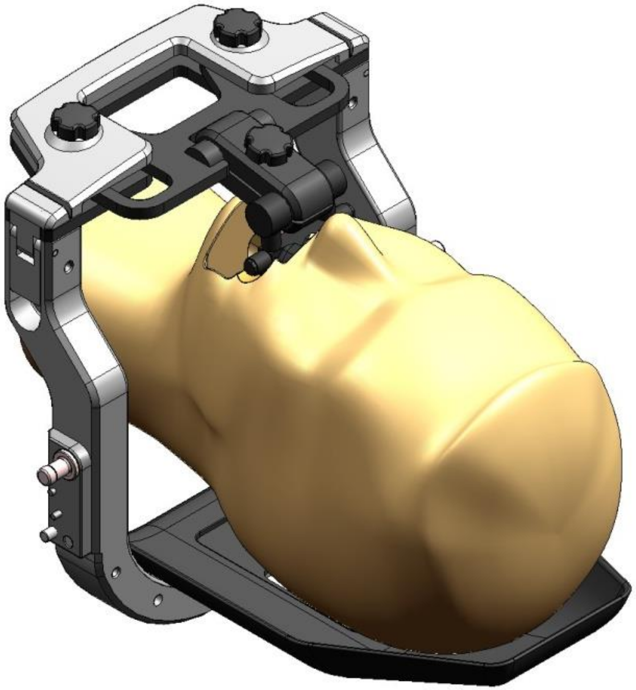
Requirements for frame-less image-guided radiosurgery

Accuracy to detect set-up errors

Accuracy to correct set-up errors

Ability to immobilize the patient in treatment position

Non-invasive Immobilization



Immobilization margin with Extend frame at Princess Margaret Hospital

1mm R-L and A-P
1.5 mm S-I

C. Chung, personal communication 2012

Fractionated non-invasive SRS

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**
Masi 2008	Thermoplastic mask & Bite block Bite-block	Cone-beam CT Cone-beam CT	**2.9mm ± 1.3mm** **3.2mm ± 1.5mm**

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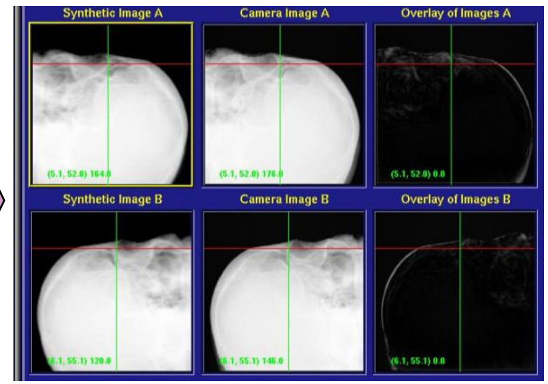
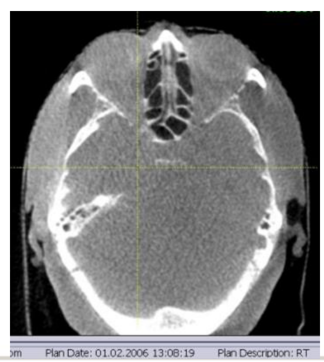
Frameless stereotactic RT: Bony landmarks?

2D



3D



Direct imaging of target

?

?

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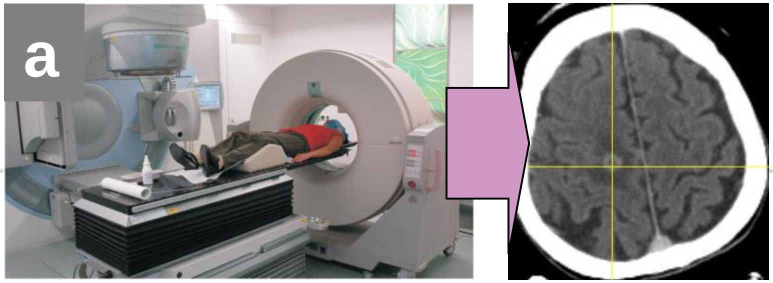
Reliability of bony anatomy

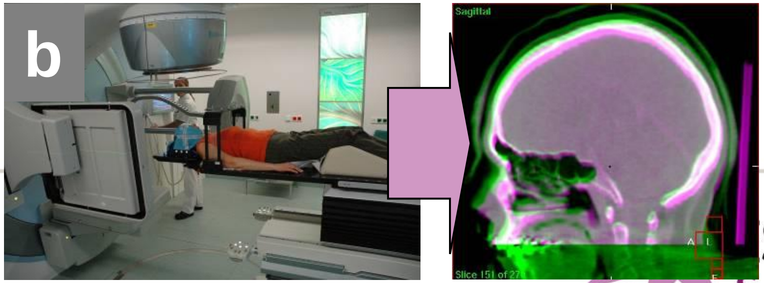
If visualization of the target is not possible, one has to use the bony skull as a surrogate for the actual intra-cranial target in IGRT

However, internal "motion" of intra-cerebral tumor could be caused by:
- Tumor progression
- Tumor shrinkage
- Changes of peritumoral edema

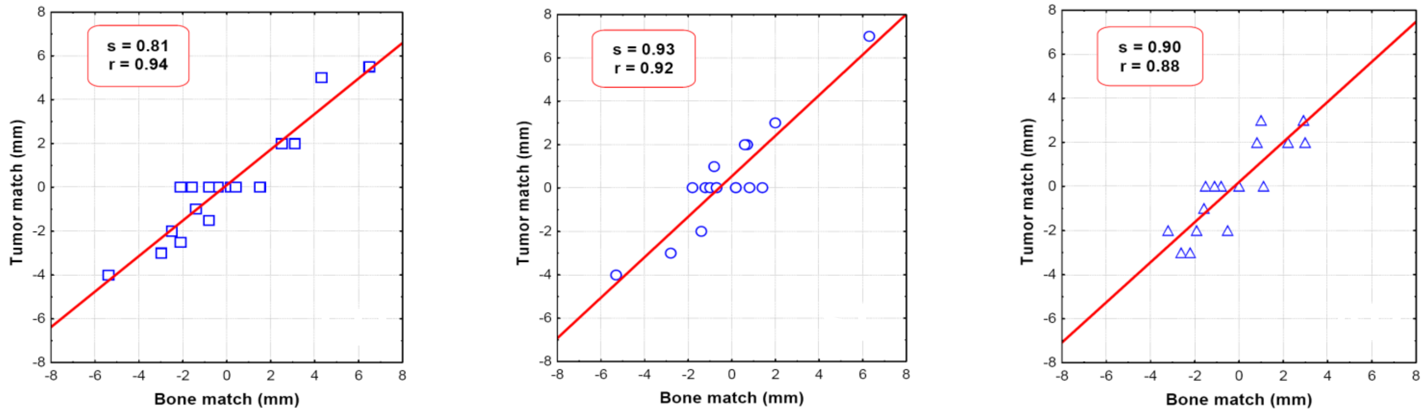
Set-up prior to treatment was verified based on the

a) position of the metastasis (soft tissue match): imaging using an in-room CT scanner after application of iv contrast
b) position of the bony anatomy (bone match): imaging using cone-beam CT





Reliability of bony anatomy



Correlation between soft-tissue registration and bone match

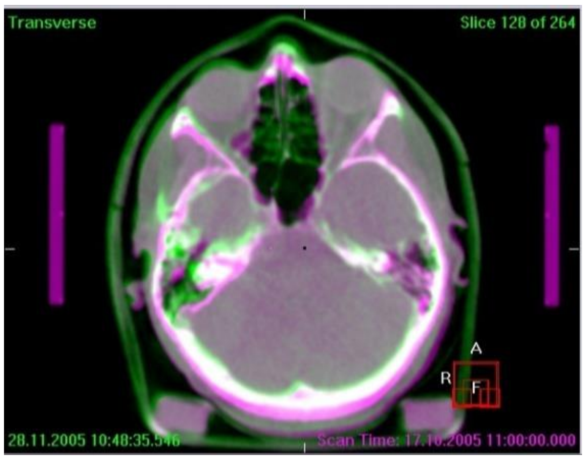
	Differences between bone and tumor match (mm)			
	LR	**SI**	**AP**	**3D**
Mean ± SD	-0.6 ± 1.0	0.0 ± 1.1	-0.2 ± 1.0	**1.7 ± 0.7**
Maximum	1.8	2.3	2	**2.8**

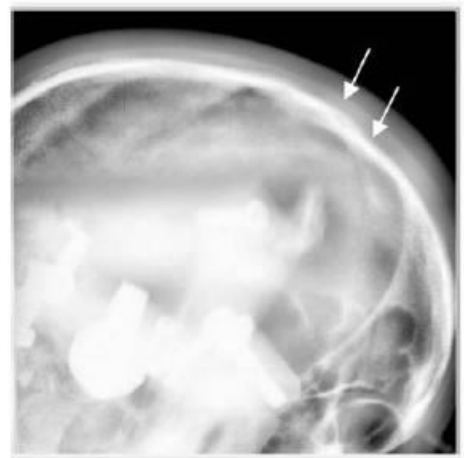
Stable tumor position relative to the skull for one week interval between planning and treatment

No influence of pre-treatment steroids (>48h prior)

Accuracy of imaging

Accuracy of IGRT to detect set-up errors





Cone-beam CT: Elekta Synergy S system

Meyer et IJROBP 2008

3D error always <0.5mm, "never observed a fusion error"

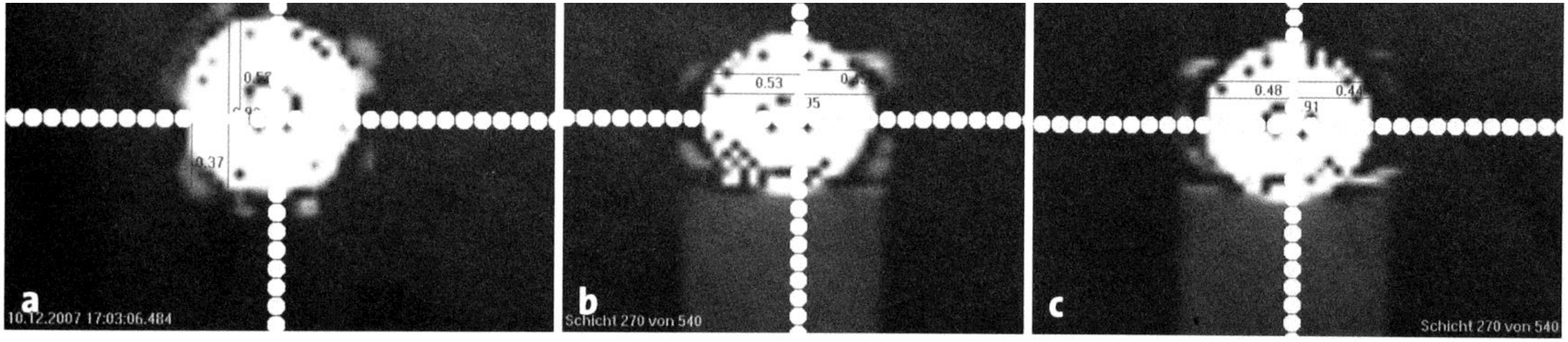
Orthogonal X-rays: Novalis Exactrak system

Ramakrishna Radiother Oncol 2010

Fusion errors in 3 / 102 patients: difference between DRR and X-ray

Alignment of imaging and treatment isocenter

Precise alignment of imaging and treatment isocenter is crucial in image-guided SRS



Ball bearing phantom:

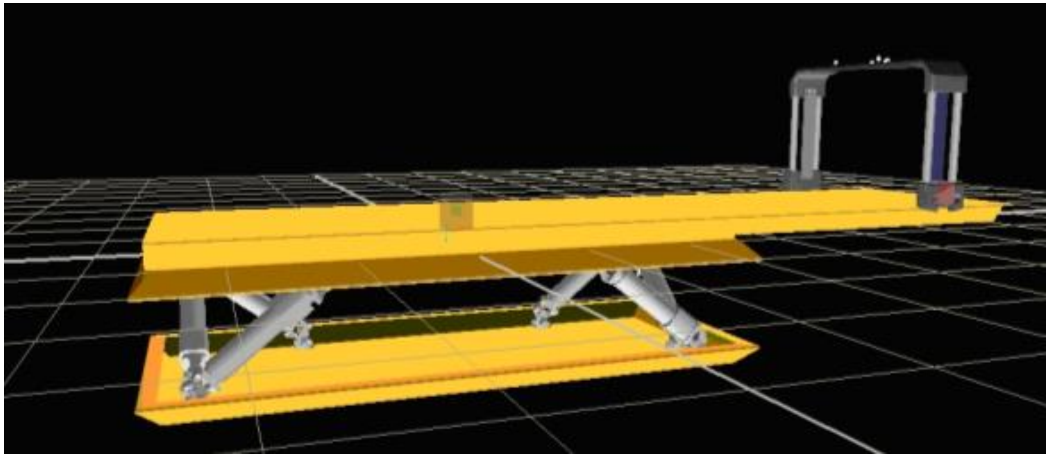
1. Phantom is positioned in the MV-treatment isocenter
2. Distance or phantom to imaging isocenter is measured

Accuracies of < 1mm are usually specified

- ➢ Alignment stable over time (Wiehle et al. 2009)
- ➢ Verification prior to each single fraction radiosurgery

Accuracy of correction

Accuracy of HexaPOD & XVI to correct set-up errors

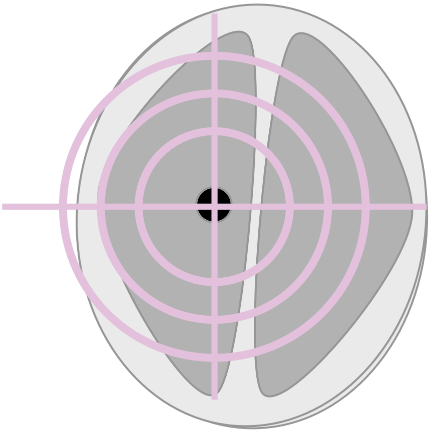


Meyer et al. IJROBP 2008

Residual errors after XVI and HexaPOD correction:
< 0.3mm <0.3˚

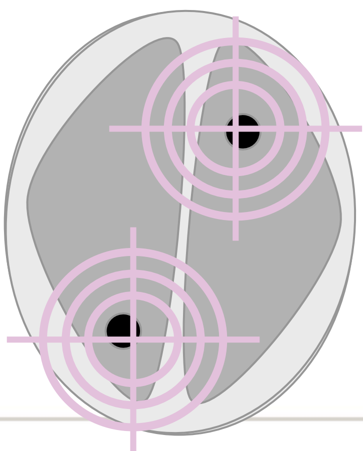
IGRT work-flow with CBCT imaging and robotic correction of set-up errors achieved sub-millimeter accuracy in phantom studies

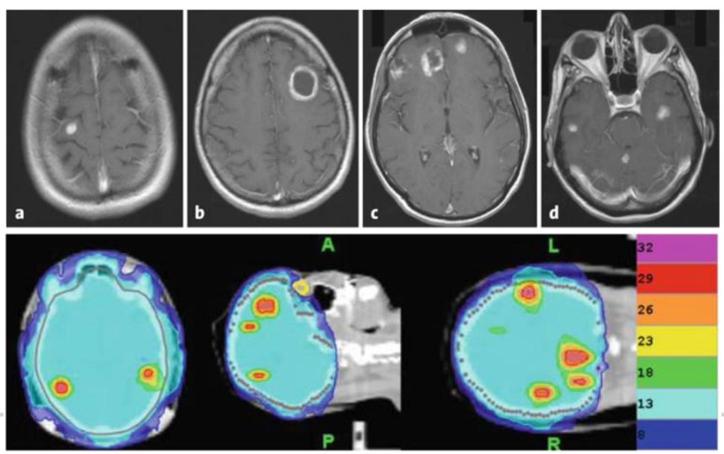
Correction of rotational errors



Rotations are probably not of highest priority for:

1. Single lesions
2. Small, spherical targets
3. Beams not immediately next to OARs





Simultanous SRS / Boost to multiple lesions

Sterzing et al. 2009

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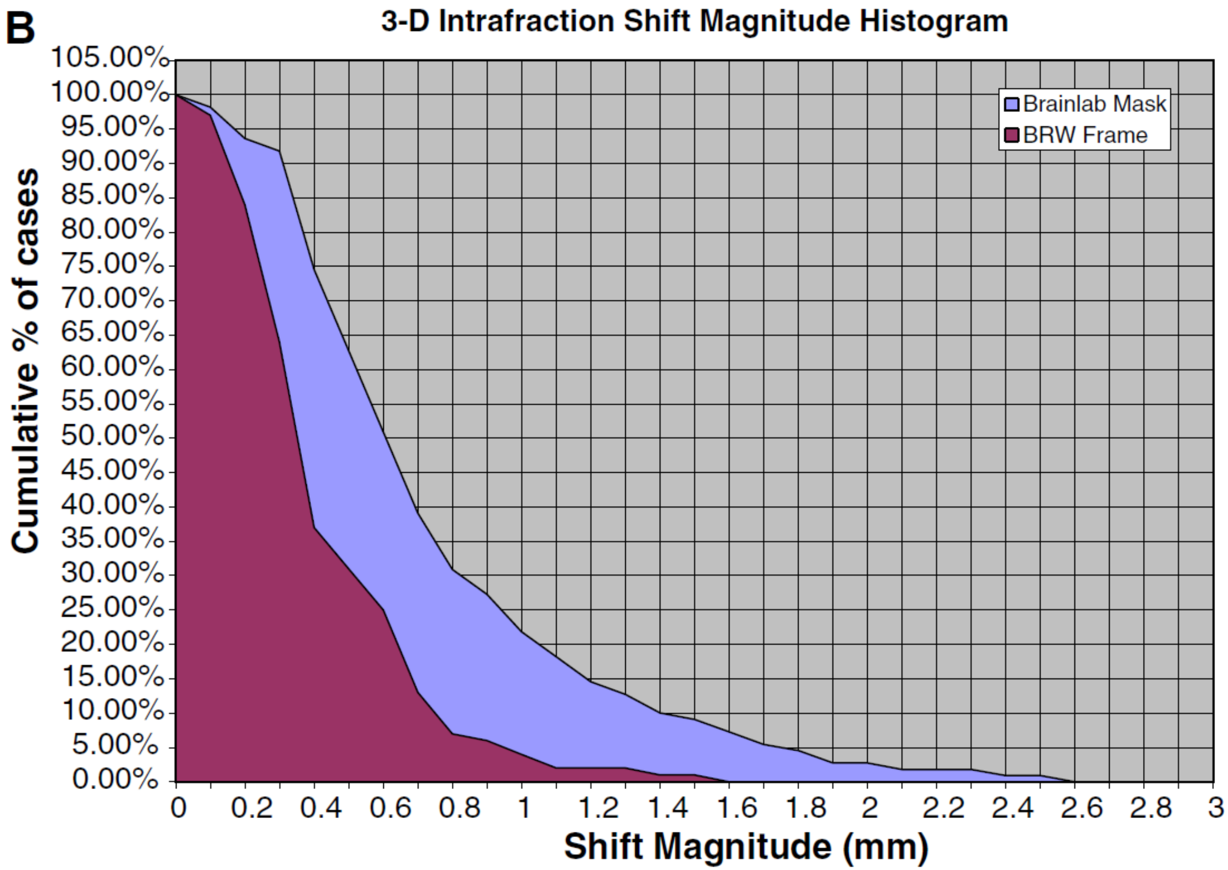
Intra-fractional stability

Intra-fractional uncertainties in frame-less IGRT

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	Scotch cast mask Thermoplastic masks	Cone-beam CT	**0.8mm ± 0.4mm** **0.8mm ± 0.5mm**

Intra-fractional uncertainties of ~ 1mm need to be considered in non-invasive frame-less IGRT

Intra-fractional stability

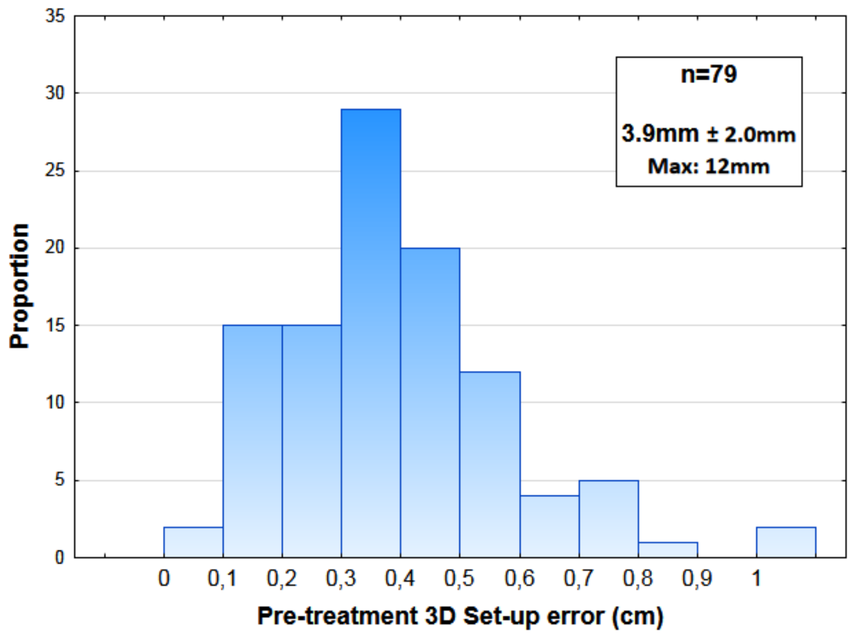


Frame based vs. frameless intrafraction motion

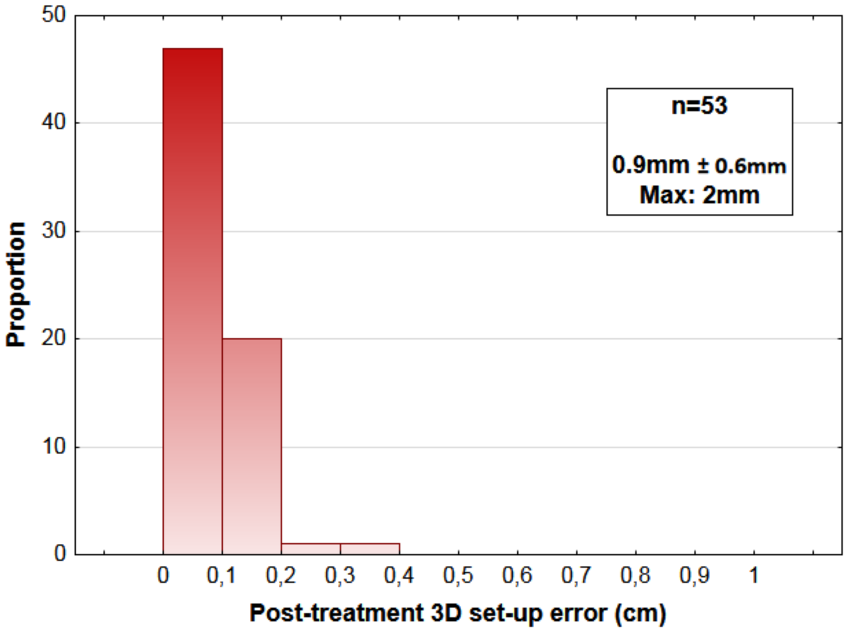
Ramakrishna Radiother Oncol 2010

Pre- and post treatment accuracy of frame-less SRS

Pre-treatment 3D errors

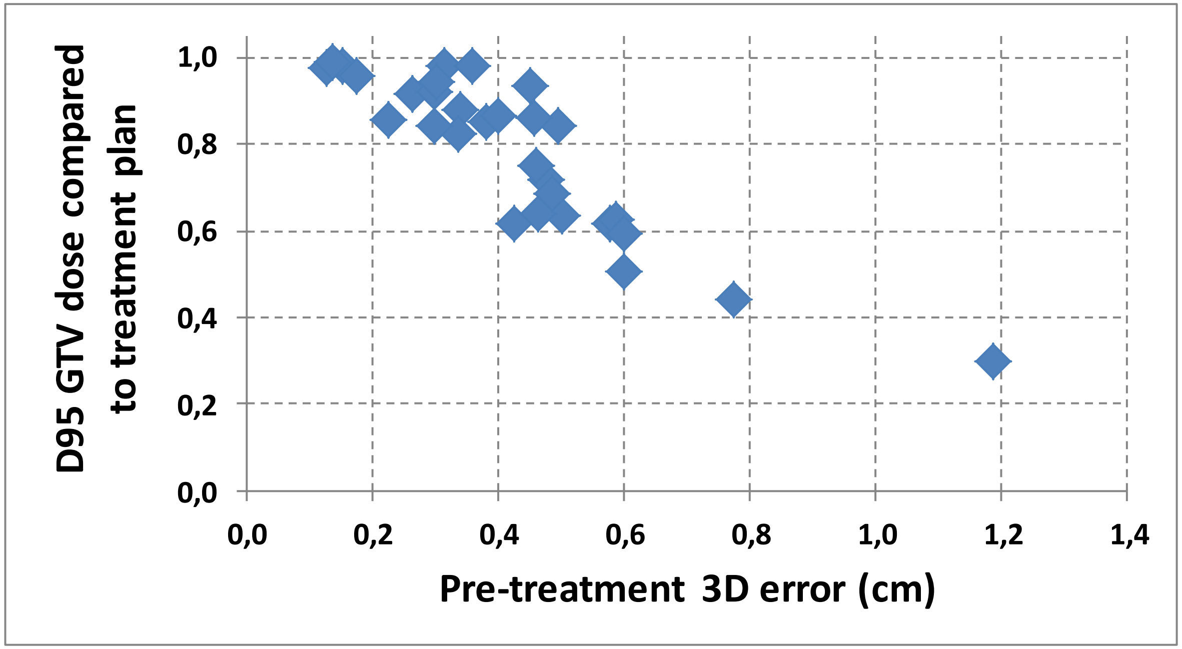


Post-treatment 3D errors



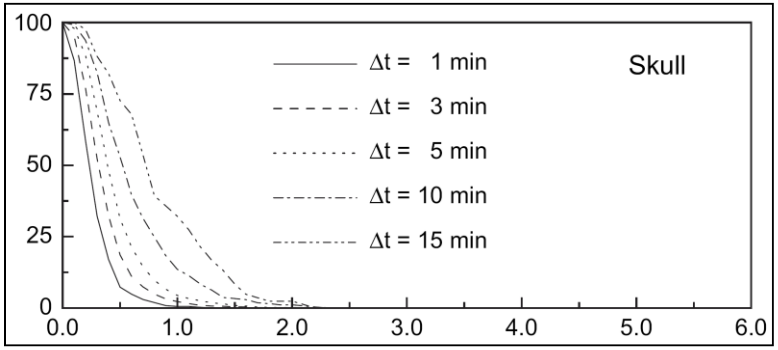
Excellent geometric accuracy with frame-less SRS

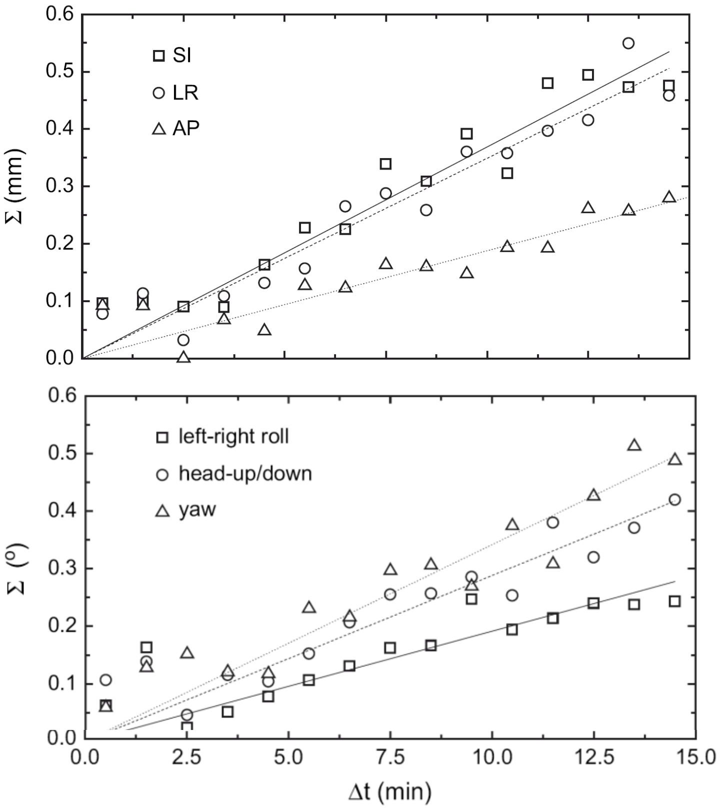
Dosimetric consequences of errors in frame-less SRS



D95 of GTV	Planned	Pre T & R	Pre R	Post T & R
Av ± StDev	100% ± 0	**78 ± 18%**	99 ± 2%	100 ± 4%

Movement during treatment?





Time dependence of intra-fractional patient motion:

Immobilization in conventional thermoplastic head masks

Keep total treatment time as short as possible !!!

Frame-based vs. Frameless stereotactic RT

Comparison of accuracy

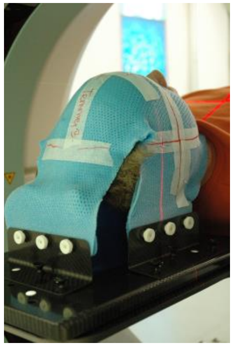
	Framebased FSRT	Framebased SRS	Frameless IGRT
Positioning error (3D)	3 – 3,5 mm	0,5 – 1,5 mm	< 1 mm
Intrafractional error (3D)	1 – 1,5 mm	< 1 mm	1 -1,5 mm
	Baumert 2005 *Boda-Heggemann 2006* *Guckenberger 2007*	*Maciunas 1994* *Lamba 2* *Ramakrishna 2010*	*Murphy 2003* *Boda-Heggemann 2006* *Guckenberger 2007* *Lamba 2009* *Ramakrishna 2010*

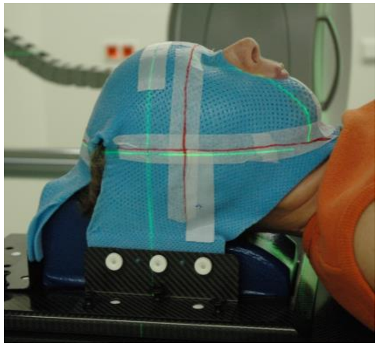
- Framebased FSRT: Precision is overestimated !
- Framebased SRS: Submillimeter precision ?
- Frameless IGRT: High precision with efficient work-flow

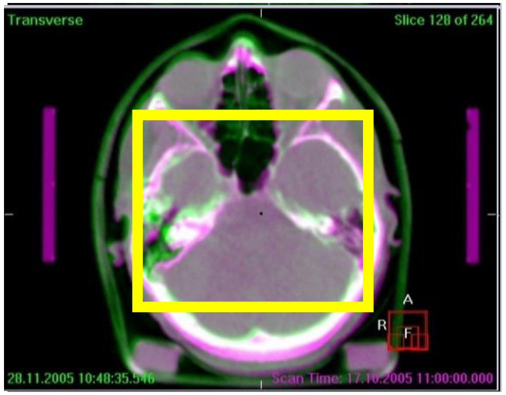
Intra-cranial stereotactic radiotherapy

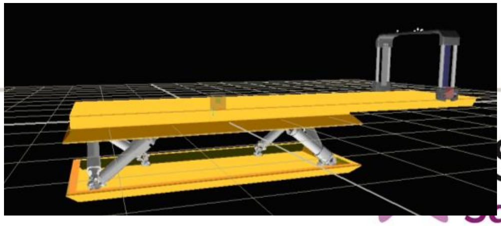
Work-flow of frame-less cranial SRT using CBCT imaging and robotic online correction of set-up errors

1. Double layer thermoplastic mask
2. Patient positioning based on drawings on the mask
3. Cone-beam CT imaging
4. Definition of region of interest for image registration
5. Registration planning CT vs verification CBCT
6. Automatic correction of errors in 6 DOF
7. Verification CBCT in SF treatment
8. Start of treatment

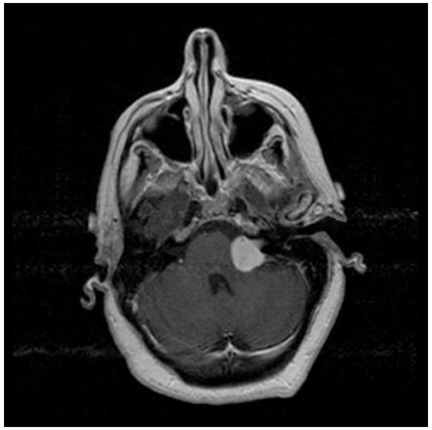








Intra-cranial stereotactic radiotherapy



Traditional frame-based SRS:
0mm margins
Minimum dose 13Gy
➢EXCELLENT local control & low Tox.
➢Delivered dose probably lower

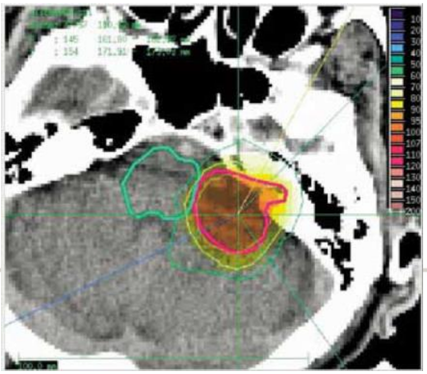


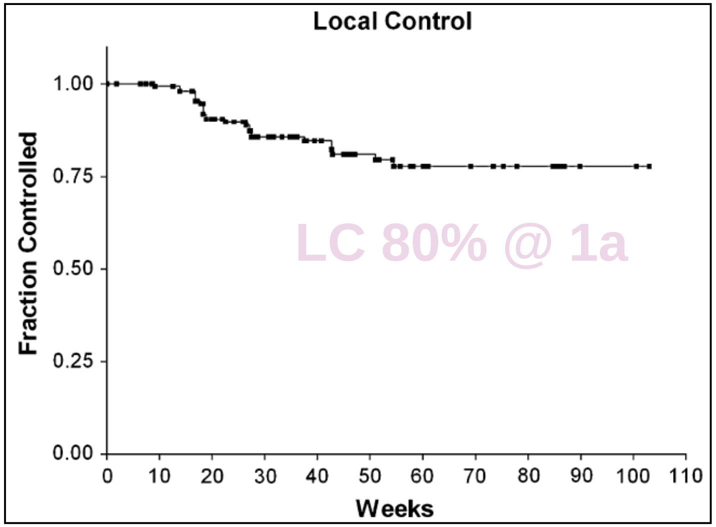
Image-guided SRS:
Uncertainties similar to frame-based SRS
➢Should we add margins?
➢Should we prescribe lower doses if margins are used?

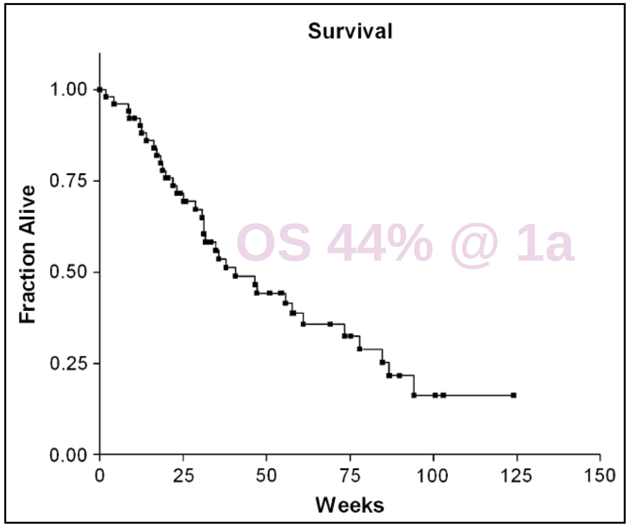
Intra-cranial stereotactic radiotherapy

Clinical outcome after frameless stereotactic radiosurgery

Breneman IJROBP 2009

- 2005 – 2006
- 53 patients with 158 metastases
- Frame-less radiosurgery with median dose 18Gy
- BrainLab Novalis system





➢ **Very similar to invasive frame-based SRS results**

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Conclusions: Intra-cranial

Why adopt non-invasive, frame-less IGRT for stereotactic techniques?

Frame-less fractionated cranial SRT

Improved accuracy

Efficient work-flow

Frame-less single fraction cranial SRS

Patient comfort, no risk of bleeding or infection

More time for multi-modality, complex treatment planning

No difference in accuracy ?

- Consistent work-flow with optimization of all steps of radiotherapy planning and delivery, strict QA and definition of standardized protocols to achieve maximum accuracy of treatment

SBRT has been used since 1990s.

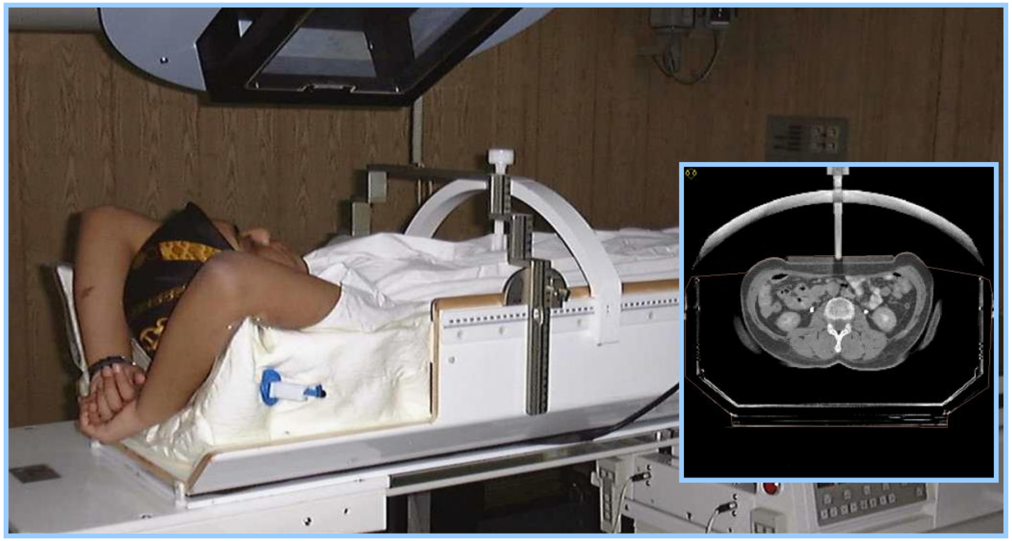
Six main “requirements” (as of 2005):

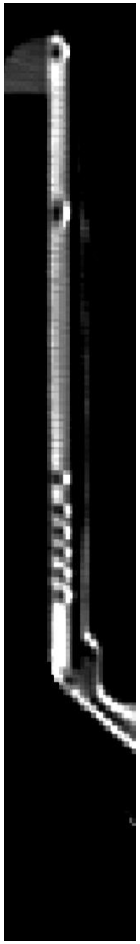
- Secure immobilization
- Accurate repositioning of the patient from planning to treatment
- Accounting for internal motion (breathing)
- Highly conformal dose distributions
- **Registration to stereotactic frame (?)**
- Few fractions, high doses

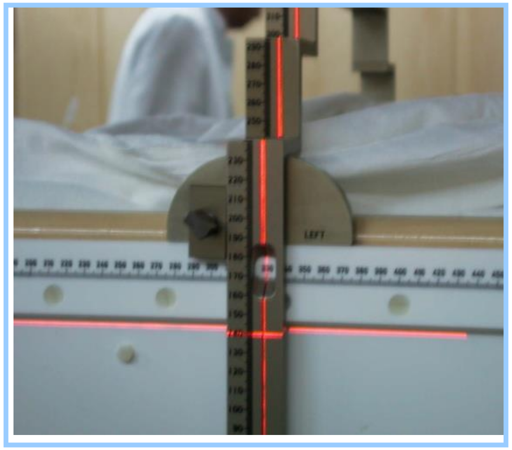
Stereotactic Bodyframe

Characteristics:

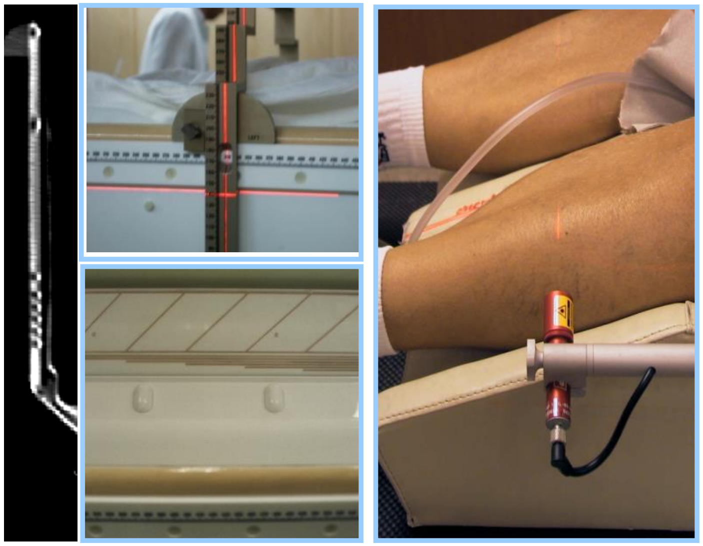
1. System of external stereotactic coordinates
2. Individualized vacuum cushion
3. Abdominal compression for reduction of breathing motion

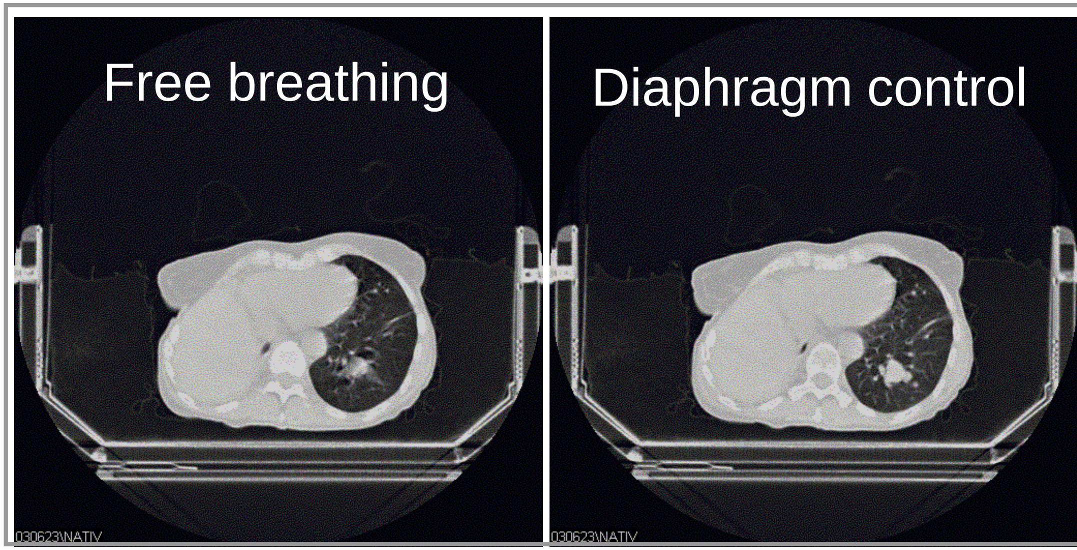






Pulmonary SBRT



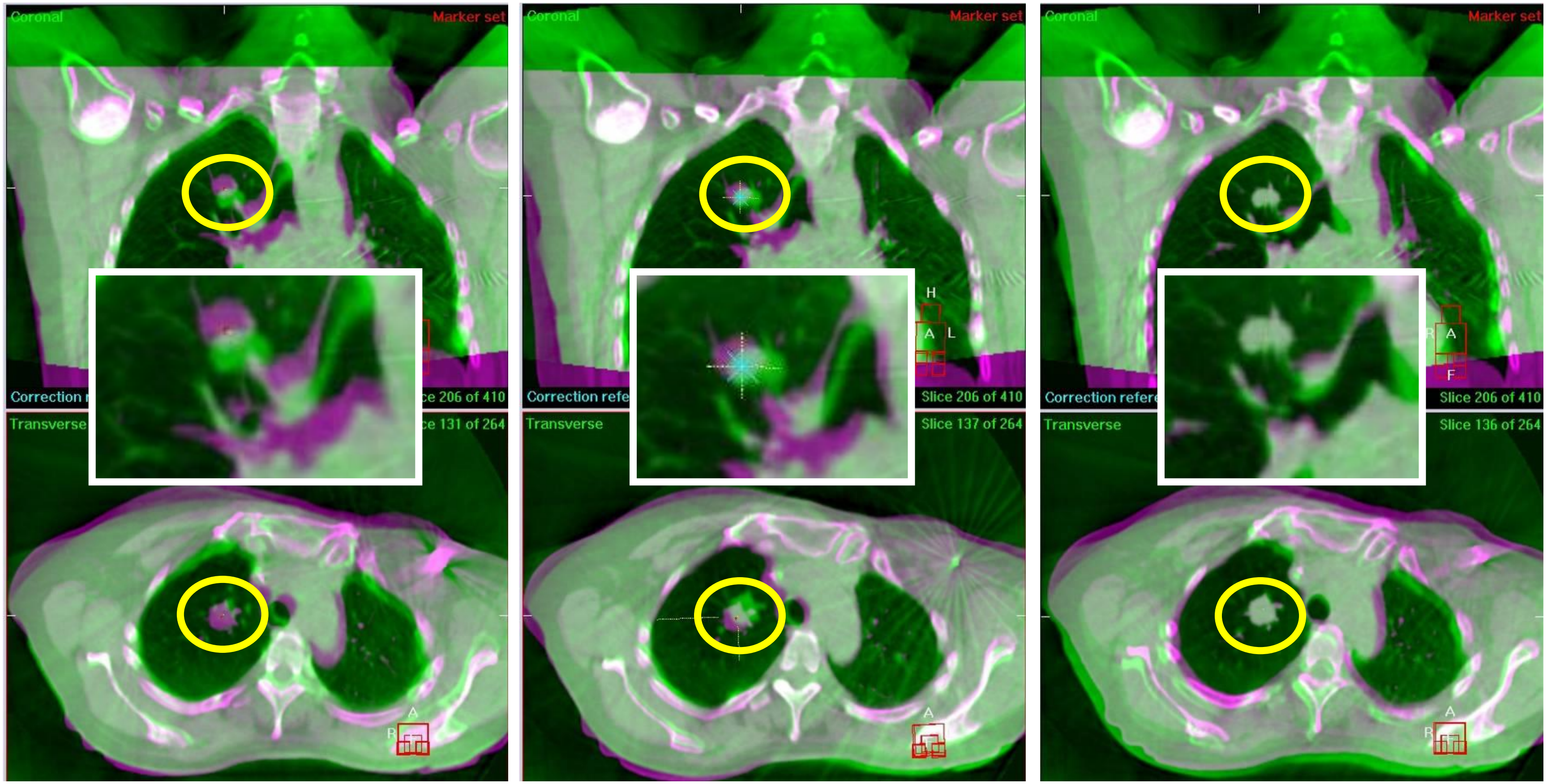


Basic assumptions of the stereotactic technique in the body region using the Stereotactic Bodyframe:

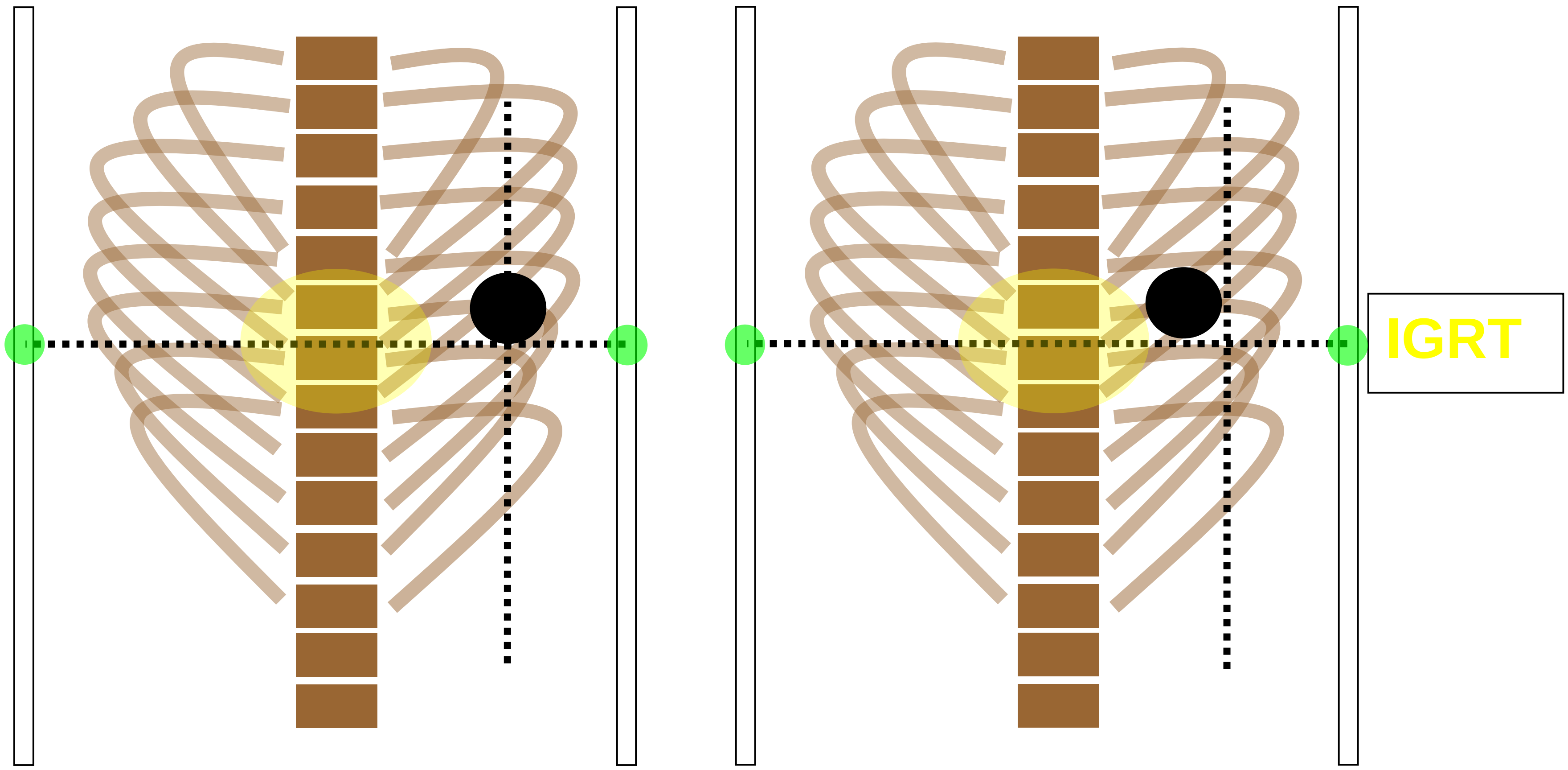
- **Reproducible positioning of the frame**
- **Reproducible positioning of the patient within the frame**
- **Reproducible positioning of the target within the patient**

Pulmonary SBRT

Patient positioning **Bone set-up** **Tumor set-up**



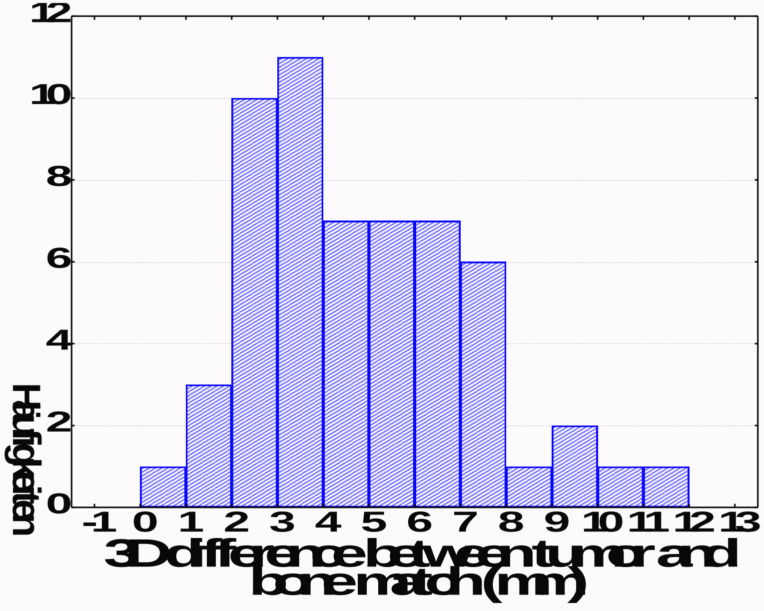
Internal target position variability – base line shift



Planning: **Treatment:**

Pulmonary SBRT

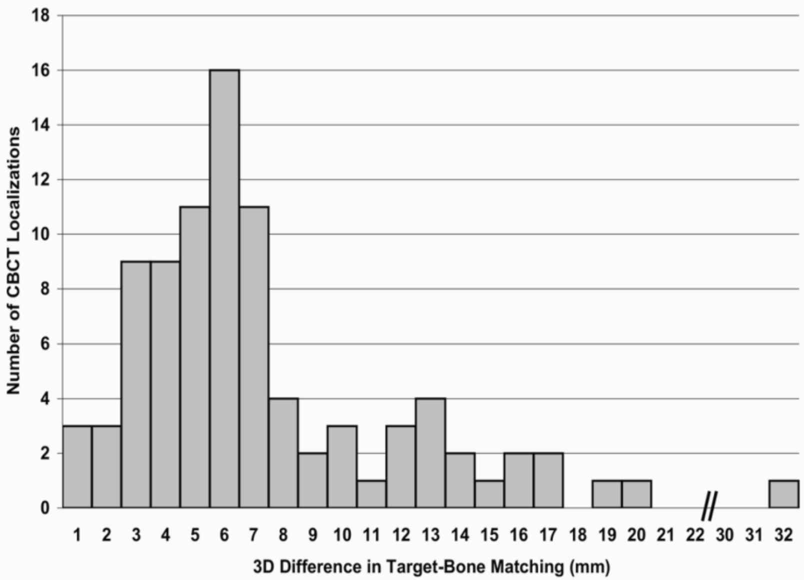
Magnitude of internal tumor position variability / base-line shifts in pulmonary SBRT



Mean: 5.3mm

90th percentile: 8mm

Guckenberger et al. 2006



Mean: 6.8mm

90th percentile: 13.9mm

Purdie et al., 2007

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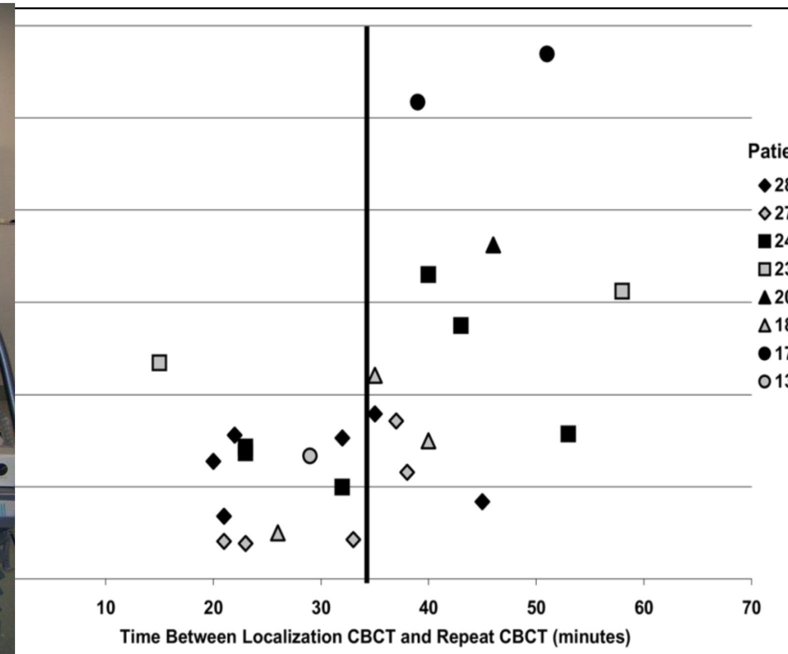
Pulmonary SBRT

Intra-fractional changes of the tumor position



2.8mm ± 1.6mm

Patient immobilization with vacuum cushion and double vacuum technique

Guckenberger Radiat Oncol 2006

Pulmonary SBRT

	Immobilization	LR (mm)	SI (mm)	AP (mm)
Σ	Yes	1.3	1.1	1.3
	No	1.2	1.2	1.8
σ	Yes	1.4	1.4	1.6
	No	1.3	1.5	1.8

Guckenberger 2007
Sonke 2009

Intra-fractional changes of the tumor position seen in CB-CT images after treatment

Assuming gross motion in 1% of the fractions:

➢Limited relevance in conventionally fractionation (blurring)

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Conclusions: SBRT

Why adopt frame-less IGRT stereotactic techniques for SBRT?

Frames in SBRT (without IGRT) are prone to geometric miss

IGRT (with or without immobilization) allows accurate, safe, reproducible setup

- Consistent work-flow with optimization of all steps of radiotherapy planning and delivery, strict QA and definition of standardized protocols to achieve maximum accuracy of treatment

Questions?

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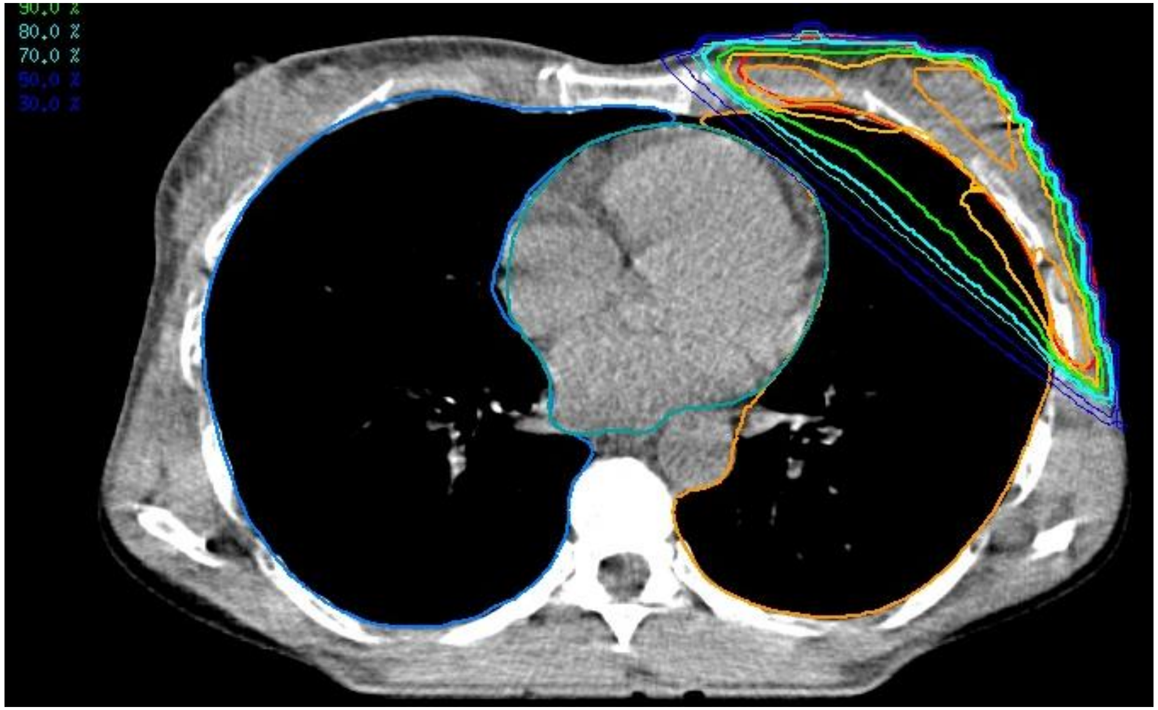
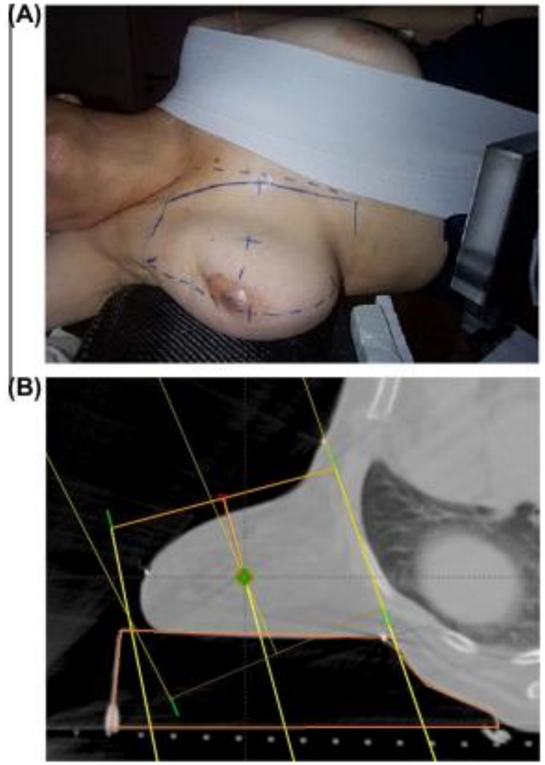
Image guidance

- Which modality?
- How often?
- whole breast vs partial/boost
- Image guidance for respiratory gating /inspiration breath hold



Imaging: Immobilisation techniques

Kirova et al RO 2014



Lymberis et al IJROBP 2012

WHOLE BREAST (+/- LN)

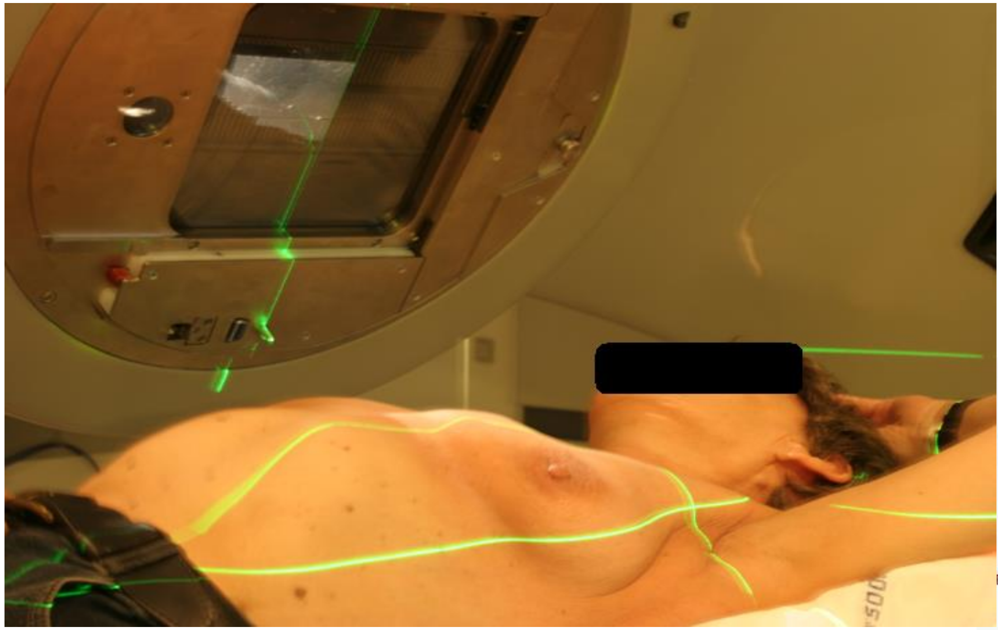
Universitätsklinikum Würzburg

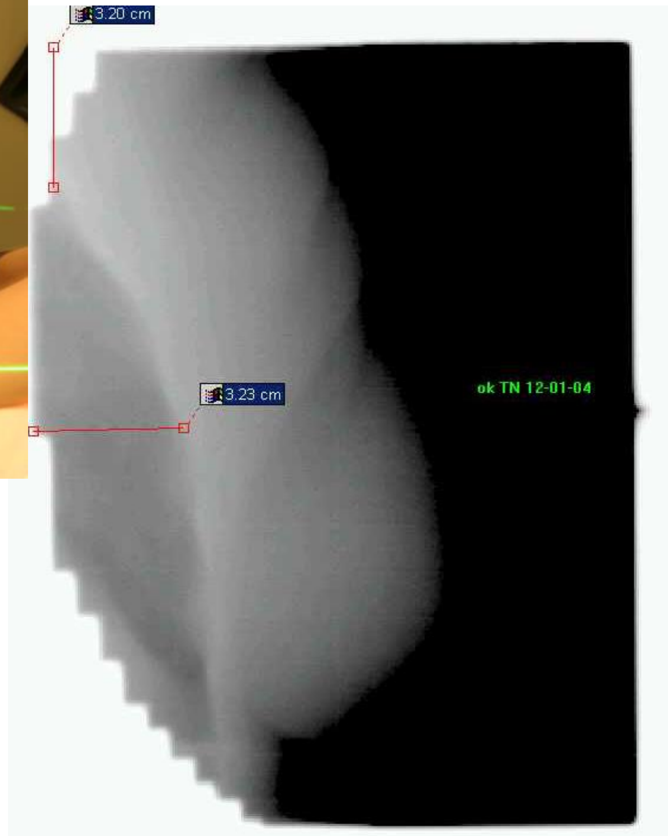
Rigshospitalet

ESTRO School

Image guidance

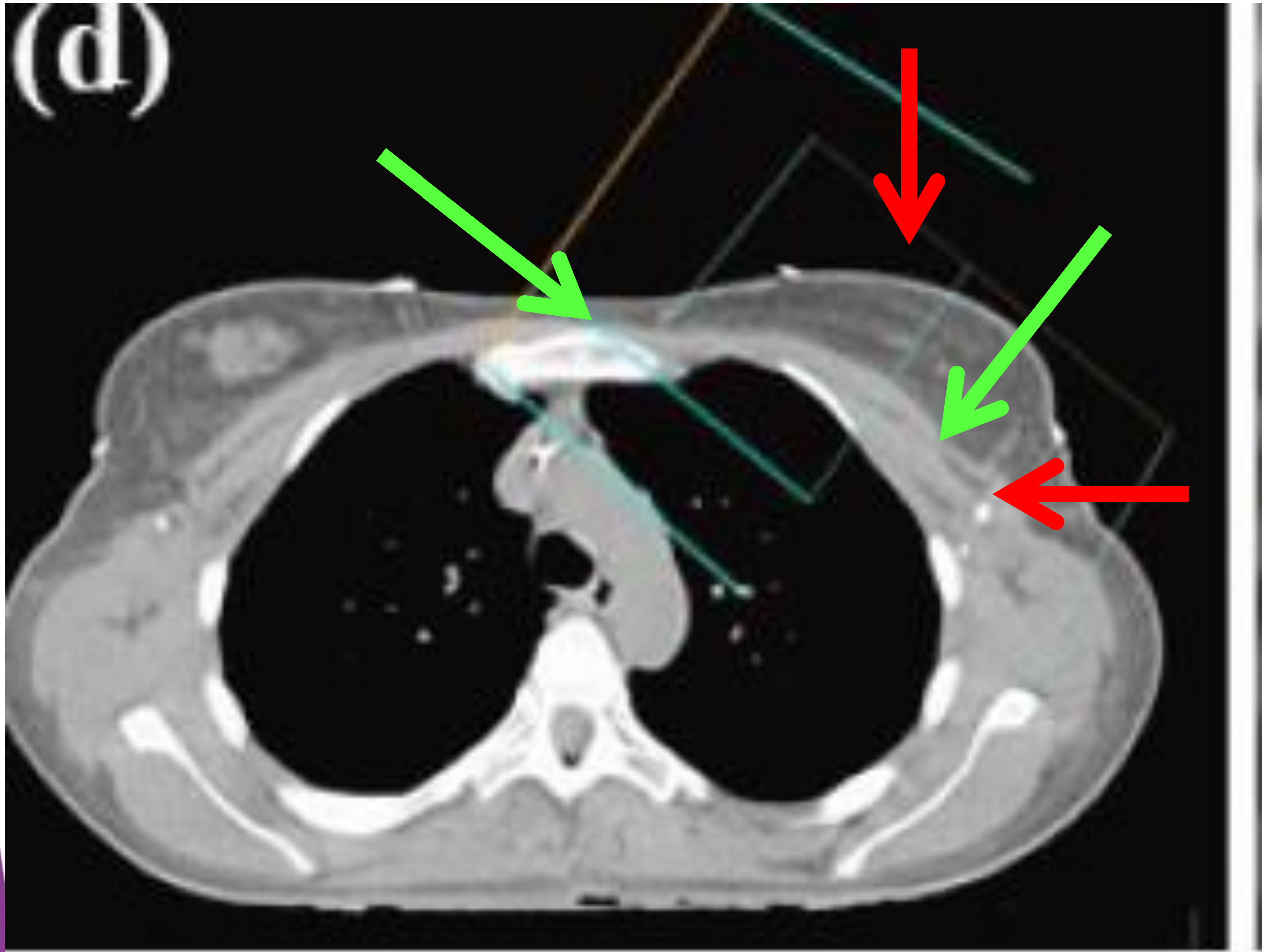
Field light / Beam's-eye-view (portal) images, MV





- Check the CLD
- long or vert ?
- Only one "direction"

Image-guidance for whole breast (+/- nodes)



Alternative 2D imaging strategy

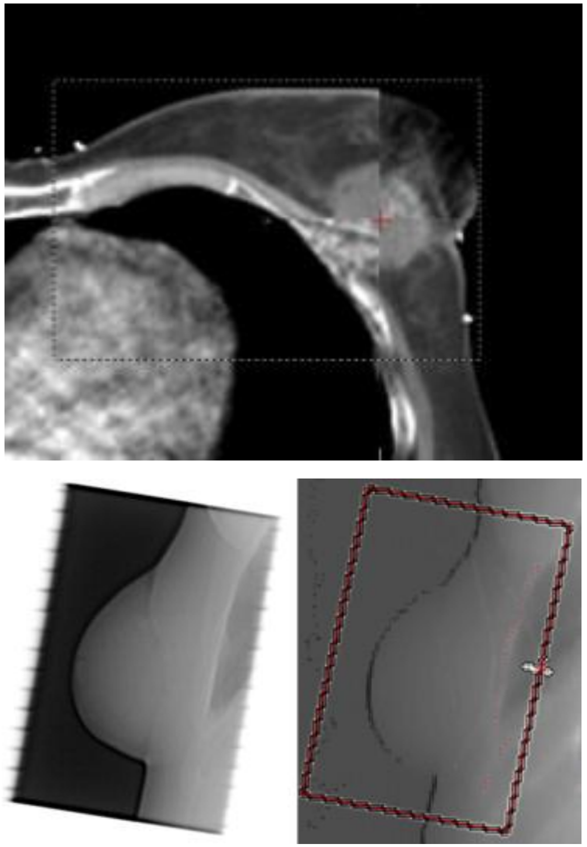
- AP-lat
- tangential +orthogonal
- kV-MV
- kV-kV

Petillion et al JACMP 2015 :
Tangential kV-kV (green) superior to AP-lat kV-MV (red)

Image-guidance for whole breast (+/- nodes)

kV CBCT

EPID



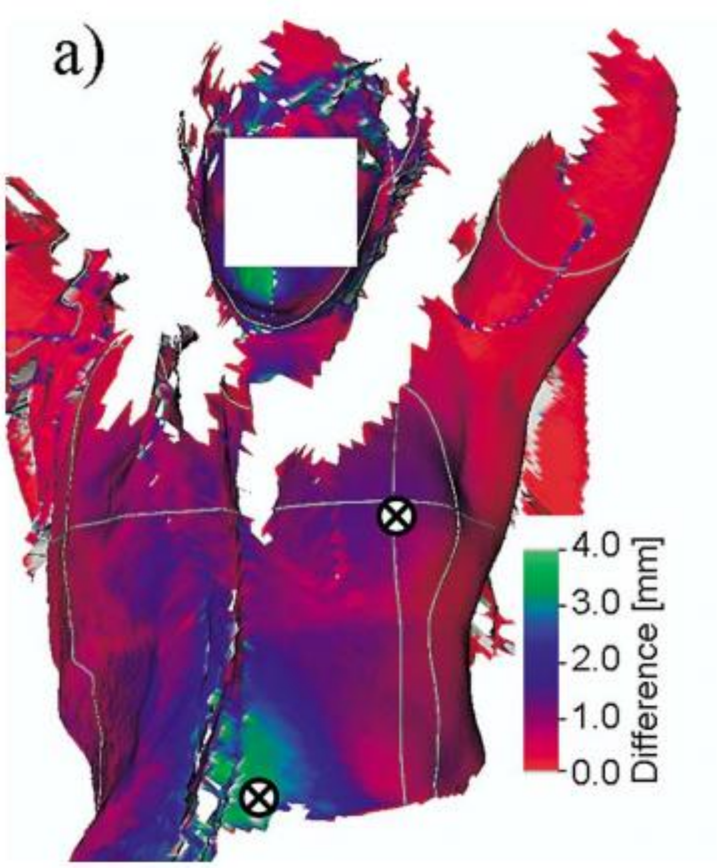
Topolnjak IJROBP 2010

- EPID field images (i.e. not orthgonal) underestimate bony set-up errors by 20% to 50%
- Difference probably insignificant for tangential whole breast irradiation
- Loco-regional treatment or more advanced techniques (SIB? IMRT?) could benefit from a more accurate set up.

Image-guidance for whole breast (+/- nodes)

- Target with “high deformability”
- Number of cameras ???

Bert et al (2 cameras)



- Difficult to distinguish between set-up error and anatomical changes (or breathing)

- Combination with x-ray IGRT still recommended (Betgen RO 2013)

How much accuracy do we actually gain ??

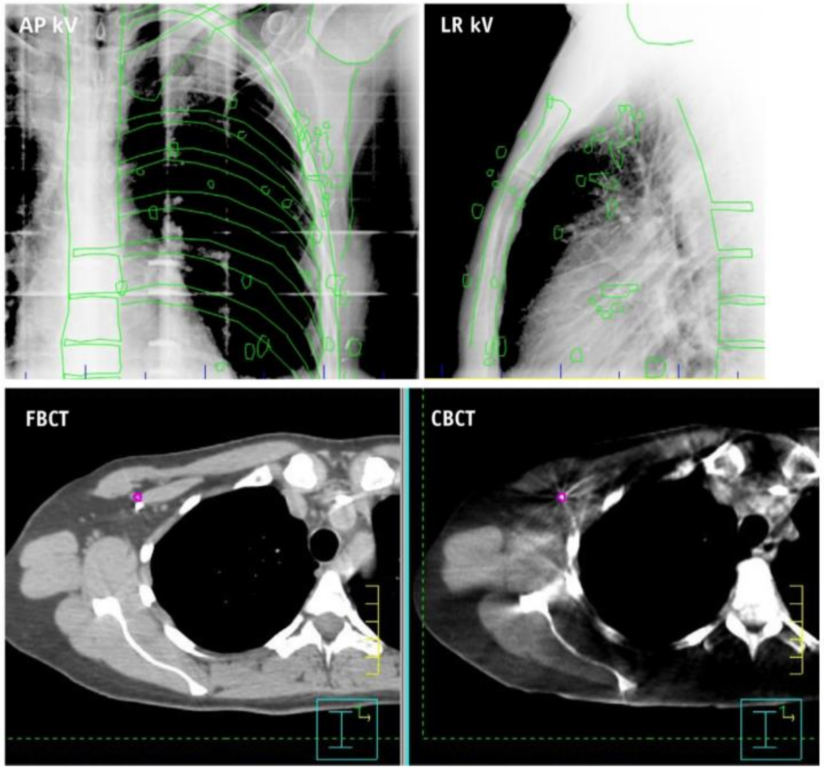
Comparing no images at all to one image on first day: no reduction of the systematic uncertainty

1SD	systematic [mm] lat	lng	vrt
1st fraction	3.7	3.3	3.4
tolerance of 5 mm			
no imaging	3.7	3.3	3.5
no tolerance			
with eNAL	1.5	1.6	1.6
3 mm tolerance			
with eNAL	1.1	1.0	1.0
2mm			

Unpublished data, courtesy of M Josipovic

Image-guidance for whole breast (+/- nodes)

- Highly conformal /complex techniques



Even with daily kV, the remaining set up error justifies a considerable margin (8mm SI)

(compared to CBCT, registered on clips)

Feng et al IJROBP 2014

Take home message:
IGRT for whole breast (+/- nodes)

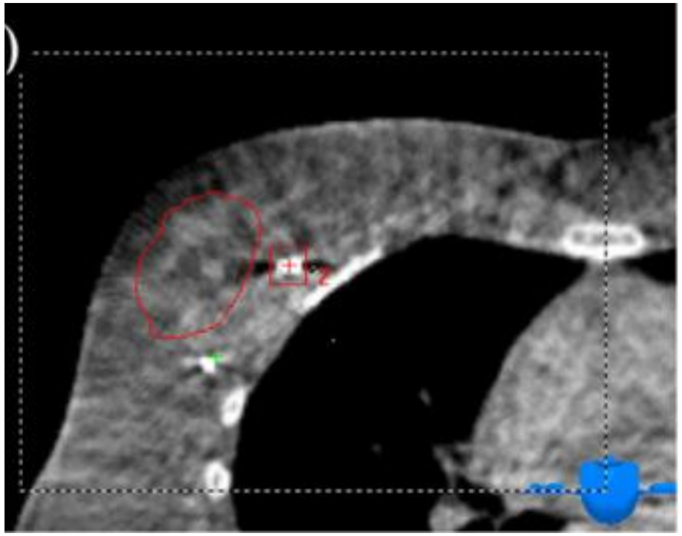
- Imaging only in the beam direction will underestimate the set up error

- No clear benefit of CBCT in terms of accuracy for "robust" techniques (3D tangents)
    - ➢but other considerations: workflow? SIB? IMRT?

- Surface image has interesting potential and properties (no dose) but shouldn't be the only modality for set-up (rotations, DIBH…)

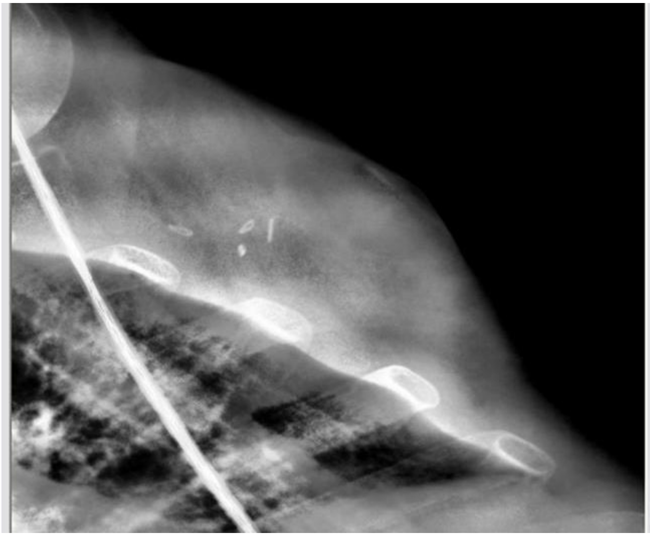
PARTIAL BREAST / BOOST

Image-guidance in partial breast irradiation: implanted markers

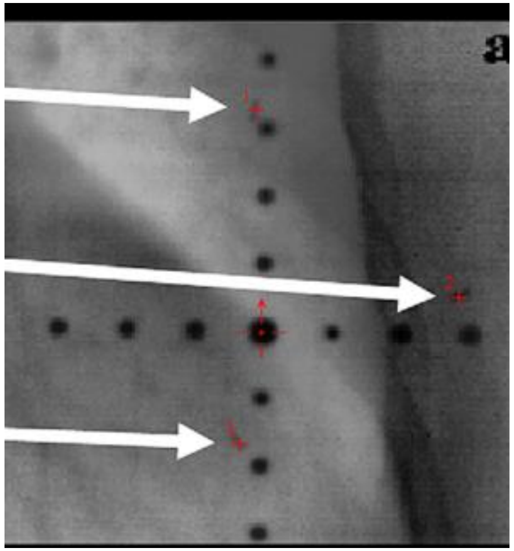


CBCT: match on soft tissue/clips

Topolnjak 2011



2D kV images: match on clips



MV images: match on clips

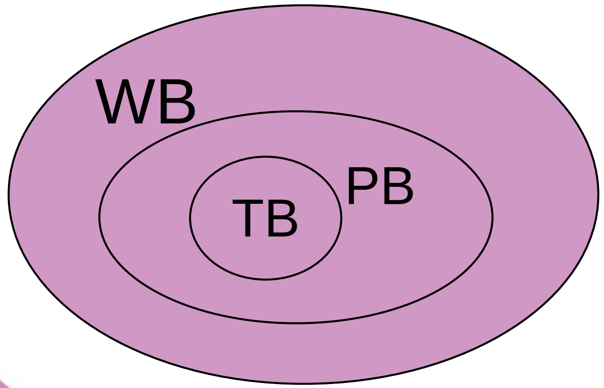
Leonard 2010

Partial breast /integrated boost

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

Emma J Harris,[1†] Mukesh Mukesh,[2†] Rajesh Jena,[2] Angela Baker,[3] Harry Bartelink,[4] Corrinne Brooks,[1] June Dean,[2] Ellen M Donovan,[1] Sandra Collette,[5] Sally Eagle,[6] John D Fenwick,[7] Peter H Graham,[8] Jo S Haviland,[9] Anna M Kirby,[10] Helen Mayles,[3] Robert A Mitchell,[1] Rosalind Perry,[11] Philip Poortmans,[12] Andrew Poynter,[13] Glyn Shentall,[14] Jenny Titley,[9] Alistair Thompson,[15] John R Yarnold,[10] Charlotte E Coles[2‡] and Philip M Evans[1,16*‡] on behalf of the IMPORT Trials Management Group

[1]Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK
[2]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]Department of Radiotherapy and Physics, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Statistics Department, EORTC Headquarters, Brussels, Belgium
[6]Department of Radiotherapy, Royal Marsden Hospital NHS Foundation Trust, London, UK
[7]Department of Oncology, University of Oxford, Oxford, UK
[8]Cancer Care Centre, St George Hospital, Kogarah, Sydney, NSW, Australia
[9]ICR-CTSU, Institute of Cancer Research, London, UK
[10]Breast Unit, Royal Marsden NHS Foundation Trust, London, UK
[11]Radiotherapy Department, Ipswich Hospitals NHS Trust, Ipswich, UK
[12]Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, the Netherlands
[13]Radiotherapy Department, Peterborough City Hospital, Peterborough, UK
[14]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[15]School of Medicine, University of Dundee, Dundee, UK
[16]Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK



Comparing bone registration to clips-based reg

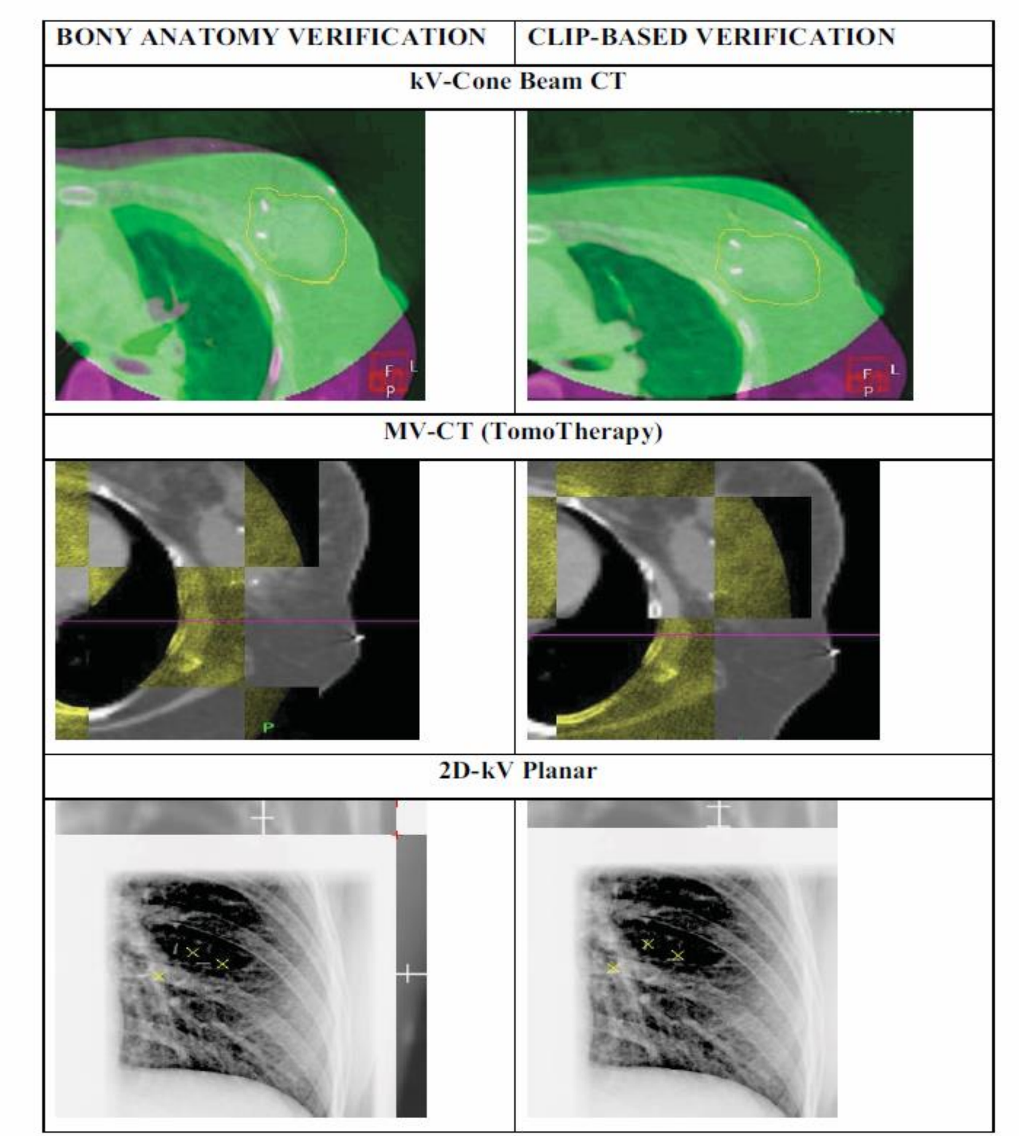


TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

	Delta error (S_{DIFF}), mean absolute delta [cm (range)]				Time, median [seconds (range)]	
Centre	LR	SI	AP	3D vector	T_{BA}	T_{clips}
All	0.20 (0–1.7)	0.26 (0–3.2)	0.21 (0–2.0)	0.32 (0–10.2)	73 (8–240)	66 (8–178)
A (kV-CBCT)	0.19 (0–0.7)	0.24 (0–3.2)	0.22 (0–1.7)	0.28 (0–10.2)	26 (8–51)	92 (11–177)
B (MV-CT)	0.14 (0–0.7)	0.12 (0–1.2)	0.18 (0–1.3)	0.17 (0–2.0)	102 (70–230)	110 (25–178)
C (2D-kVPI)	0.23 (0–1.7)	0.29 (0–2.4)	0.20 (0–2.0)	0.38 (0–6.29)	22 (20–76)	16 (8–52)
D (2D-kVPI)	0.21 (0–1.3)	0.32 (0–1.3)	0.21 (0–1.0)	0.35 (0–2.2)	79 (60–154)	28 (20–85)
E (2D-kVPI)	0.20 (0–1.5)	0.31 (0–1.4)	0.23 (0–1.0)	0.36 (0–3.3)	110 (28–240)	34 (16–120)

Difference between bone reg and clips reg: 2-3 mm

Reduction in PTV (tumourbed) from 8 to 5 mm with clips-based IGRT, daily or with eNAL

Modest dosimetric impact

TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

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Time varies per institution, even when using the same technique
2D kV scores both as fastest and slowest !
Inter and intra- observer error < 1.4mm for all modalities

Take home message:
Image-guidance for partial breast irradiation

Clips can be representative for

- the location of the tumor bed
- the location of the whole breast

Penninkhof Radiother Oncol 2009

Registering on clips is time-efficient and can allow for margin reduction of the tumour bed PTV

➢ Daily or eNAL

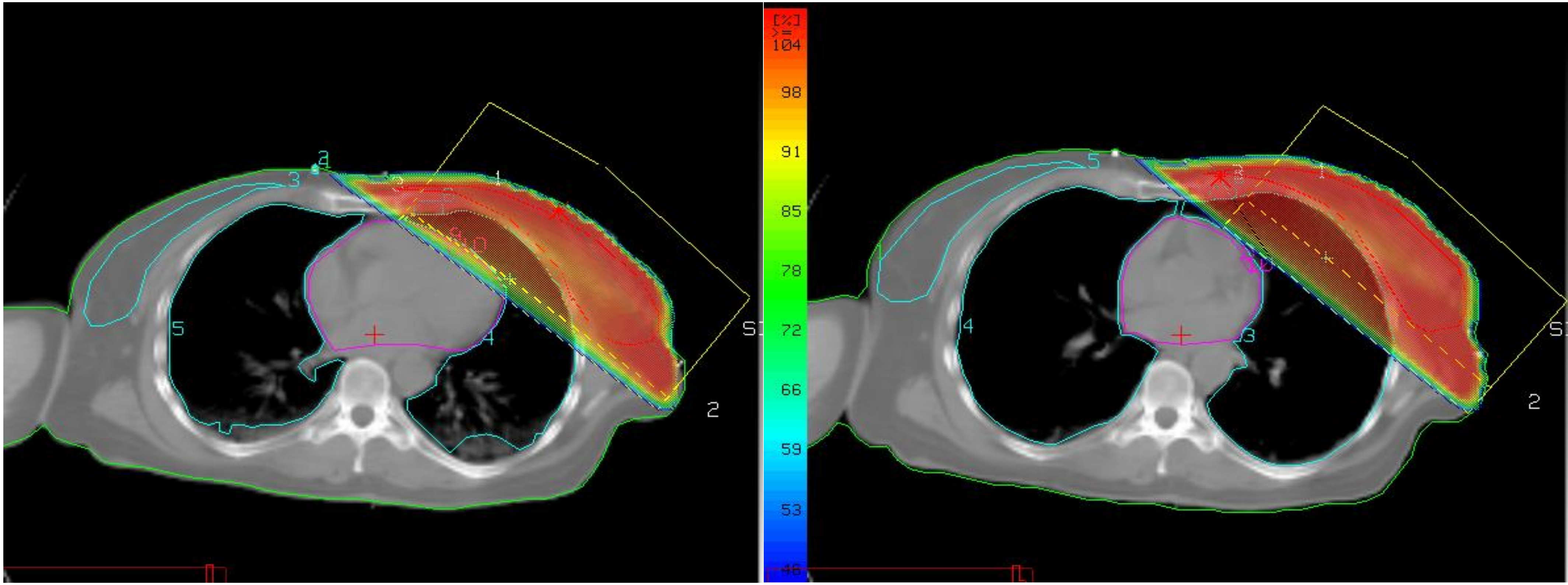
kV-CBCT, MV-CBCT, 2D kV are equivalent in terms of accuracy if registering on clips

➢ 2D MV as well, if clips are visible

GATING /BREATH HOLD

Techniques for reduction of cardiac toxicity

FB DIBH



Universitätsklinikum Würzburg

Rigshospitalet

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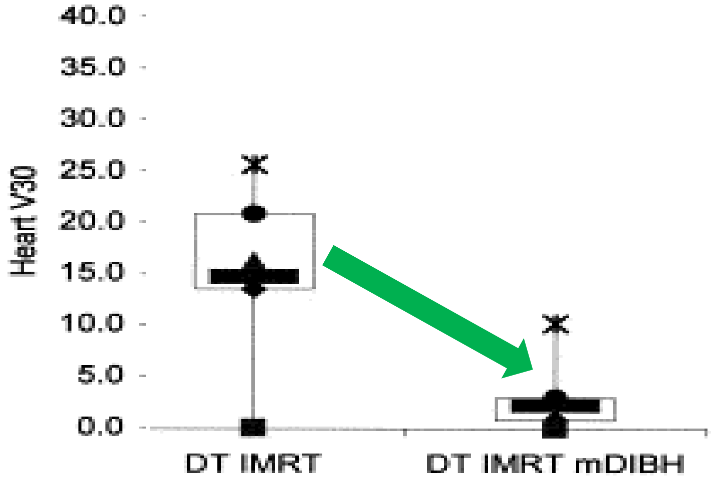
Techniques for reduction of cardiac toxicity

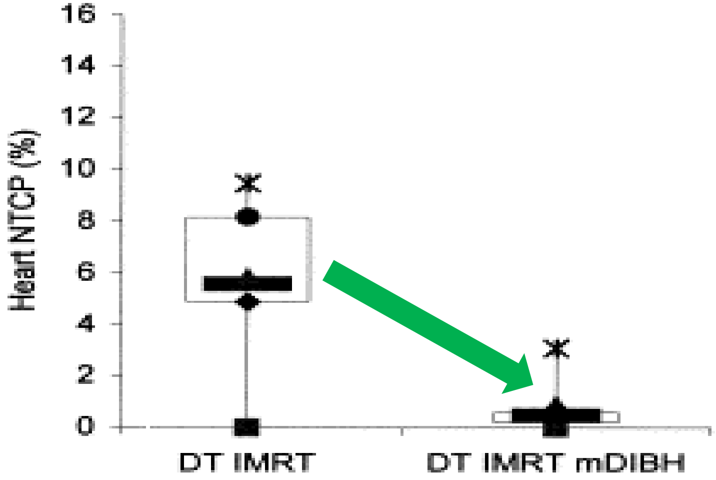
Heart V30



Remouchamps IJROBP 2003

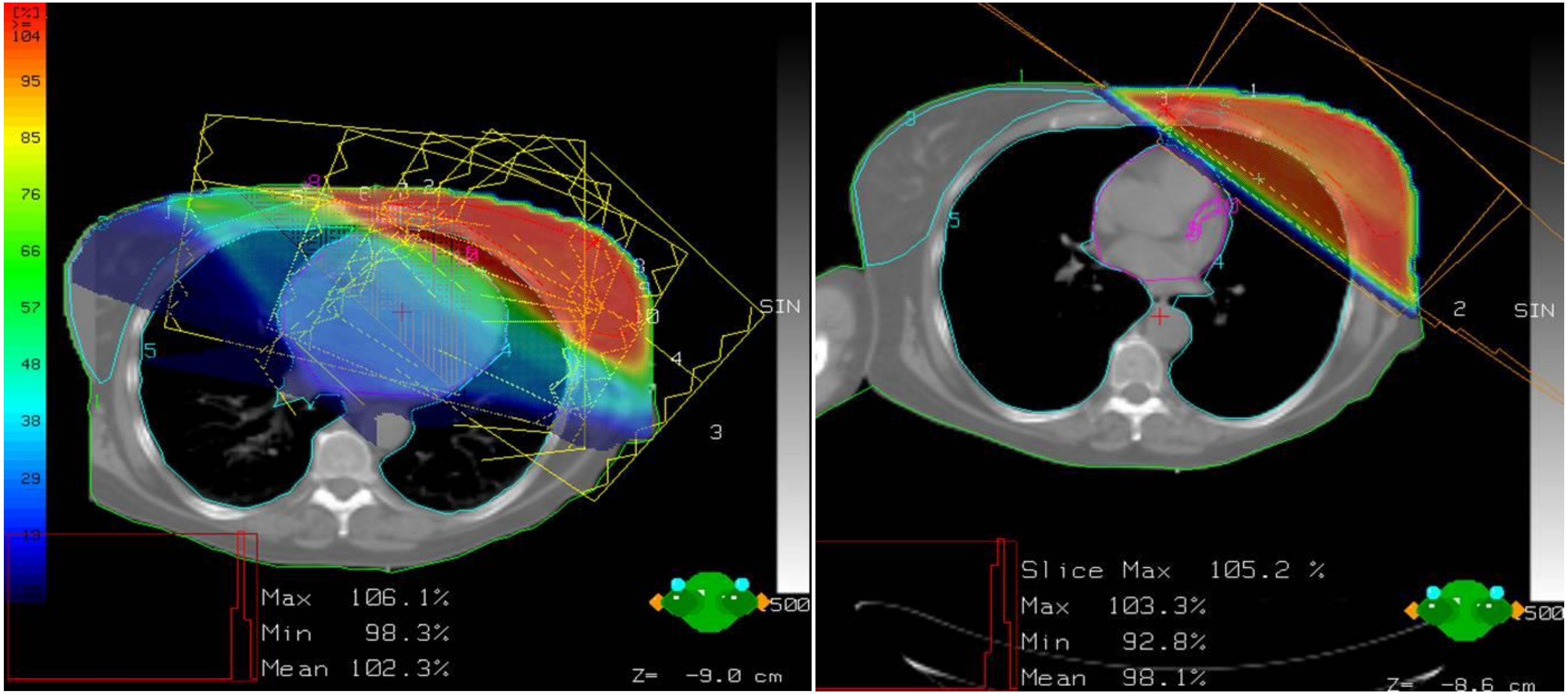
Significant reduction of heart dose and heart NTCP in left sides breast cancer

Heart NTCP



Remouchamps IJROBP 2003

Techniques for reduction of cardiac toxicity IMRT or inspiration gating?



Patients with unfavorable thoracic anatomy:

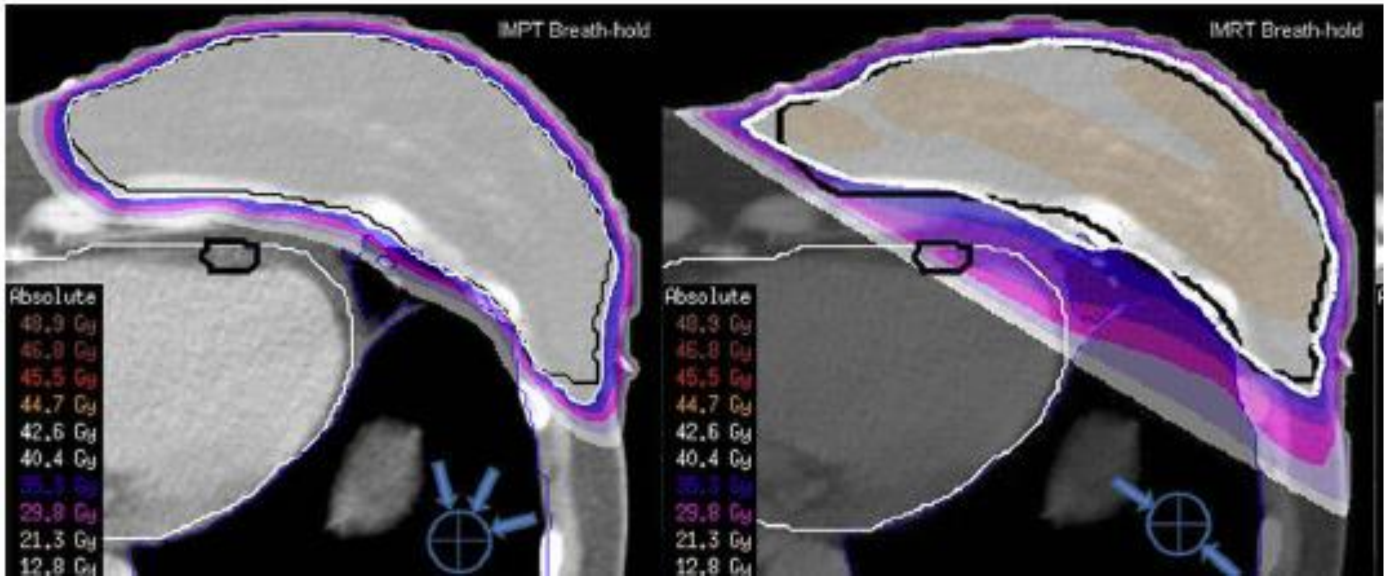
- Improved sparing of the heart with IMRT at cost of increased dose to the normal tissue (e.g. contralateral breast)
- Sparing of the heart can be more efficient with 3D_DIBH than with IMRT_FB.

Don't get too fancy… at least until we have better evidence !

- ASTRO "choose wisely"
- (1) consider hypofractionation (>50 y, early stage)

- (5) don't routinely use ***(multi-field)*** IMRT to deliver whole-breast radiation therapy as part of breast conservation therapy.

IMPT IMRT



Mast BCRT 2014

Image guidance for deep inspiration: DIBH/gating monitoring

- Voluntary breath is hold is as efficient and more comfortable

Bartlett 2013

- The ”no equipment” solution:
  - short hyperventilation follwed by breath hold
  - Monitoring is visual (draw the light field on the patient, observed through control room monitors)
  - Video article: ***Bartlett et al J Vis Exp 2014***

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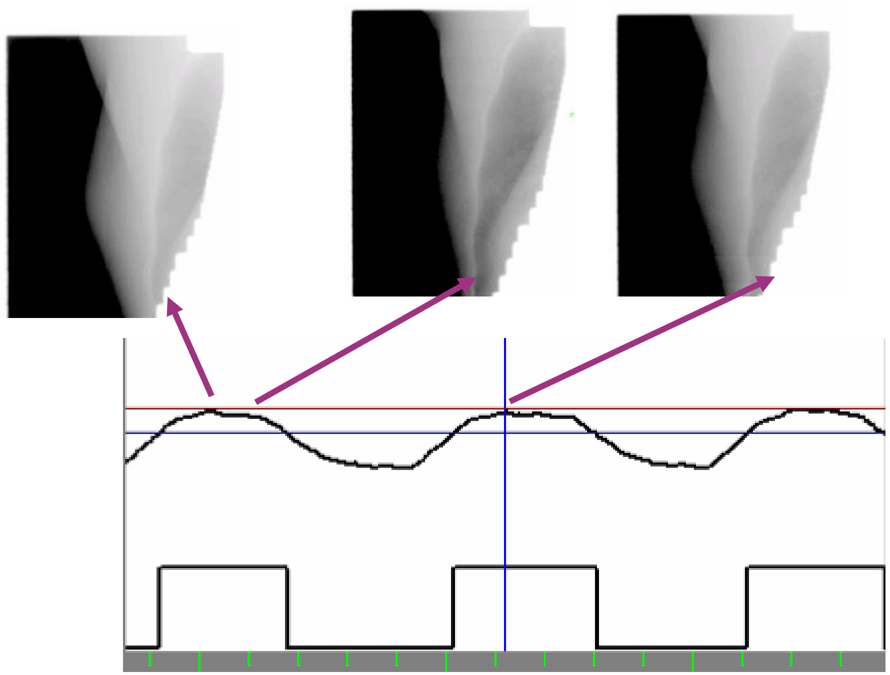
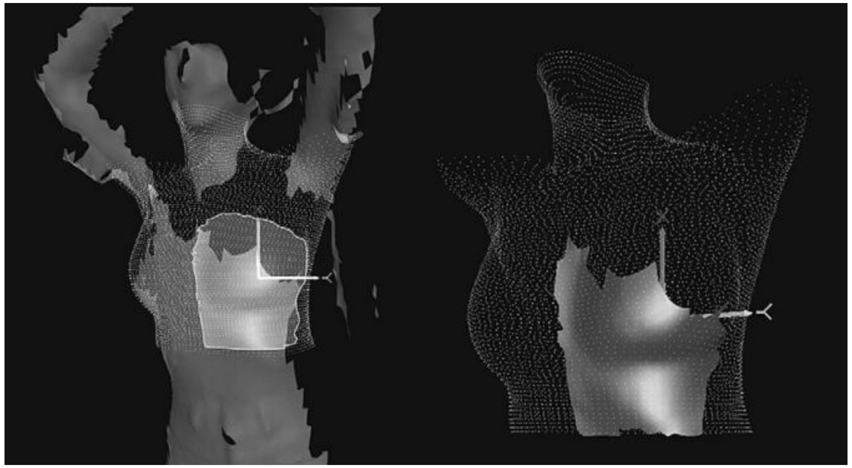
Image guidance for deep inspiration: DIBH/gating monitoring

- Patient set up as for conventional treatment (i.e. planar or CBCT)



Residual motion can be verified by cine EPID



Align RT: potential for breath hold monitoring
Maintain use of CBCT for set-up

Alderliesten et al IJROBP 2012

Take home message:
image-guidance for DIBH/gating monitoring

- Deep inspiration techniques are easy to implement and effective in reducing heart and lung dose

- They are vey well tolerated

- Many technical solutions are available and they are all valid
  - ➢ choose what fits your workflow/resources best

- X-ray based imaging is still recommended in addition to ensure proper set-up

Take home message: image-guidance for breast cancer

- MV is acceptable is you have a good surrogate (e.g. visible clips, not ribs)
- The less robust your treatment technique, the more advanced the IGRT
- An offline strategy (NAL, eNAL, SAL, etc…) will go a long way towards reducing uncertainties
- Deep inspiration: just do it !

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Alternative 2D imaging strategy

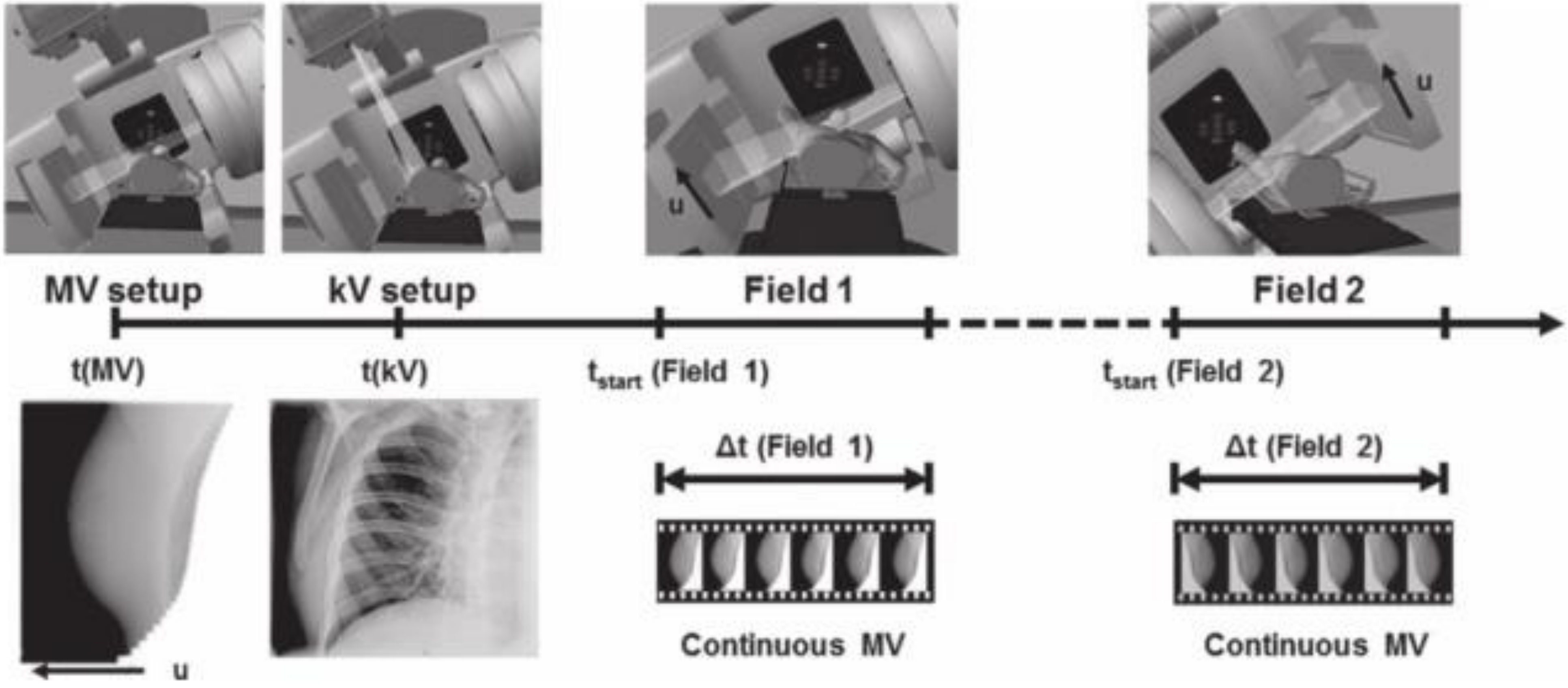


Figure 1. Daily setup procedure and imaging for a right-sided breast cancer patient. The MV and kV setup images were acquired at the same gantry angle (~60°).

Thomsen, Acta Oncol 2014

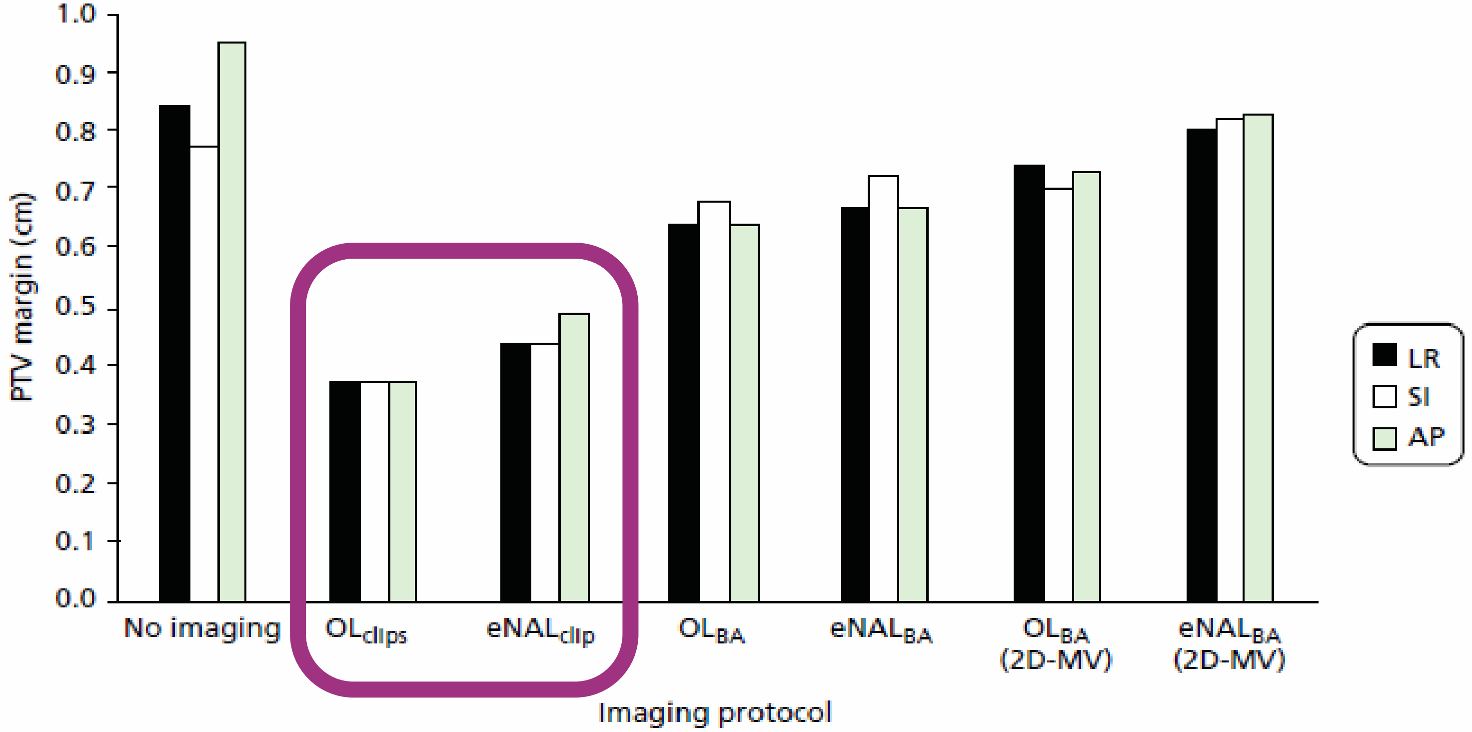


FIGURE 11 Tumour bed PTV margins required for the different imaging verification protocols considered in this study. Margins are given for the LR, SI and AP directions.

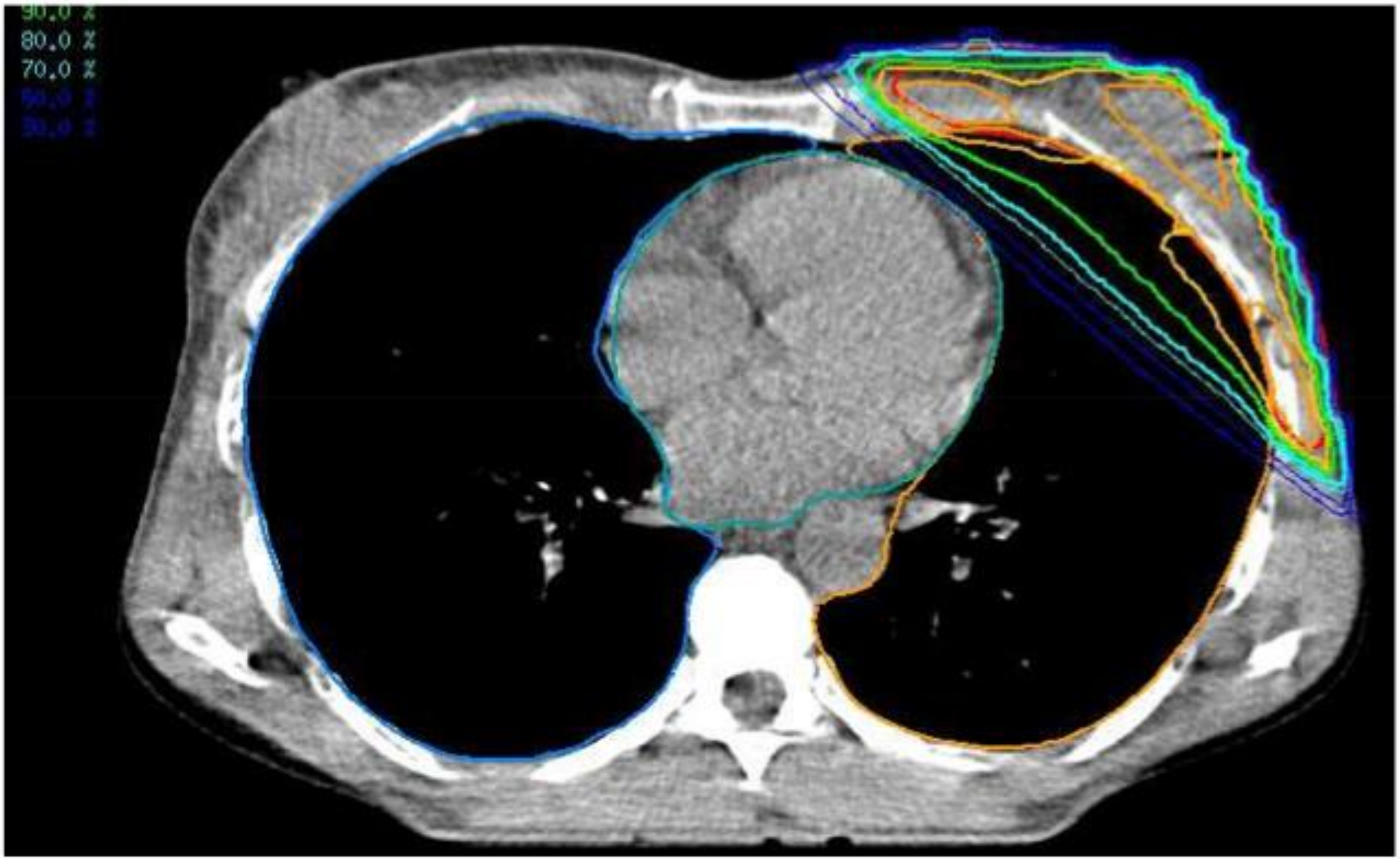
Image guided radiotherapy in breast and lung

Marianne Aznar

Andrew Hope

Thanks to Matthias Guckenberger!

Breast Cancer



Radiotherapy in breast cancer

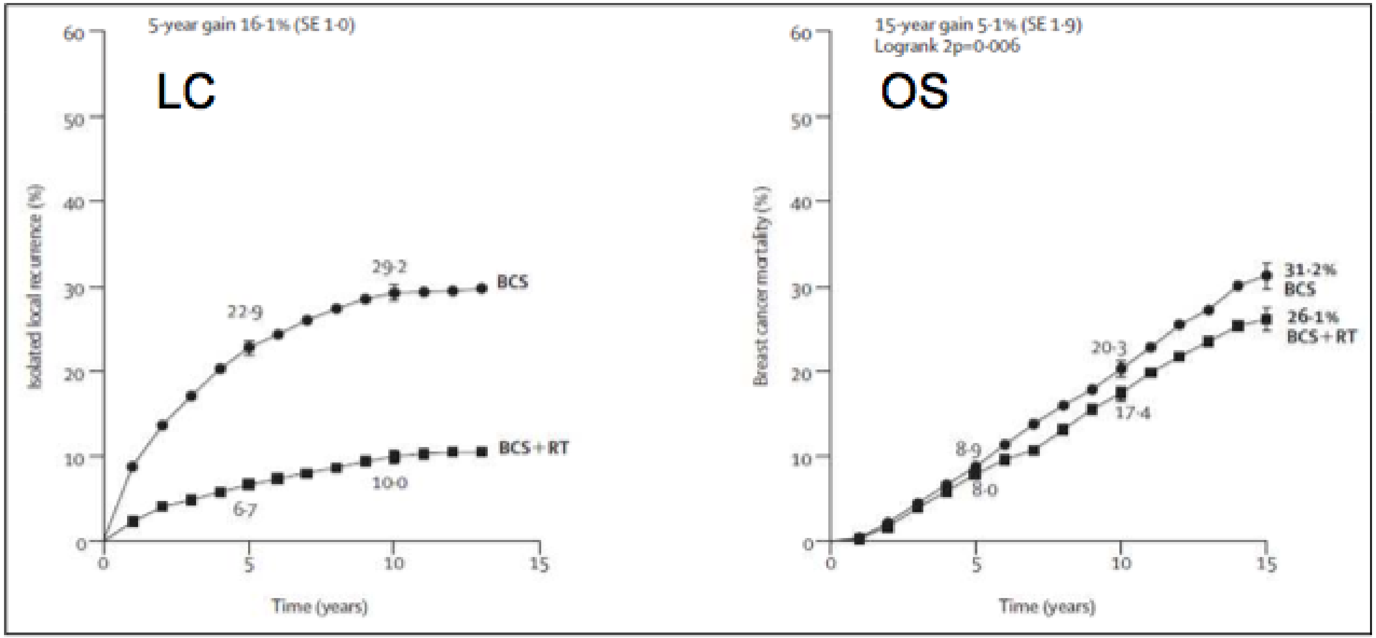
Irradiation increases overall survival after breast conserving surgery and mastectomy

EBCTCG Lancet 2005

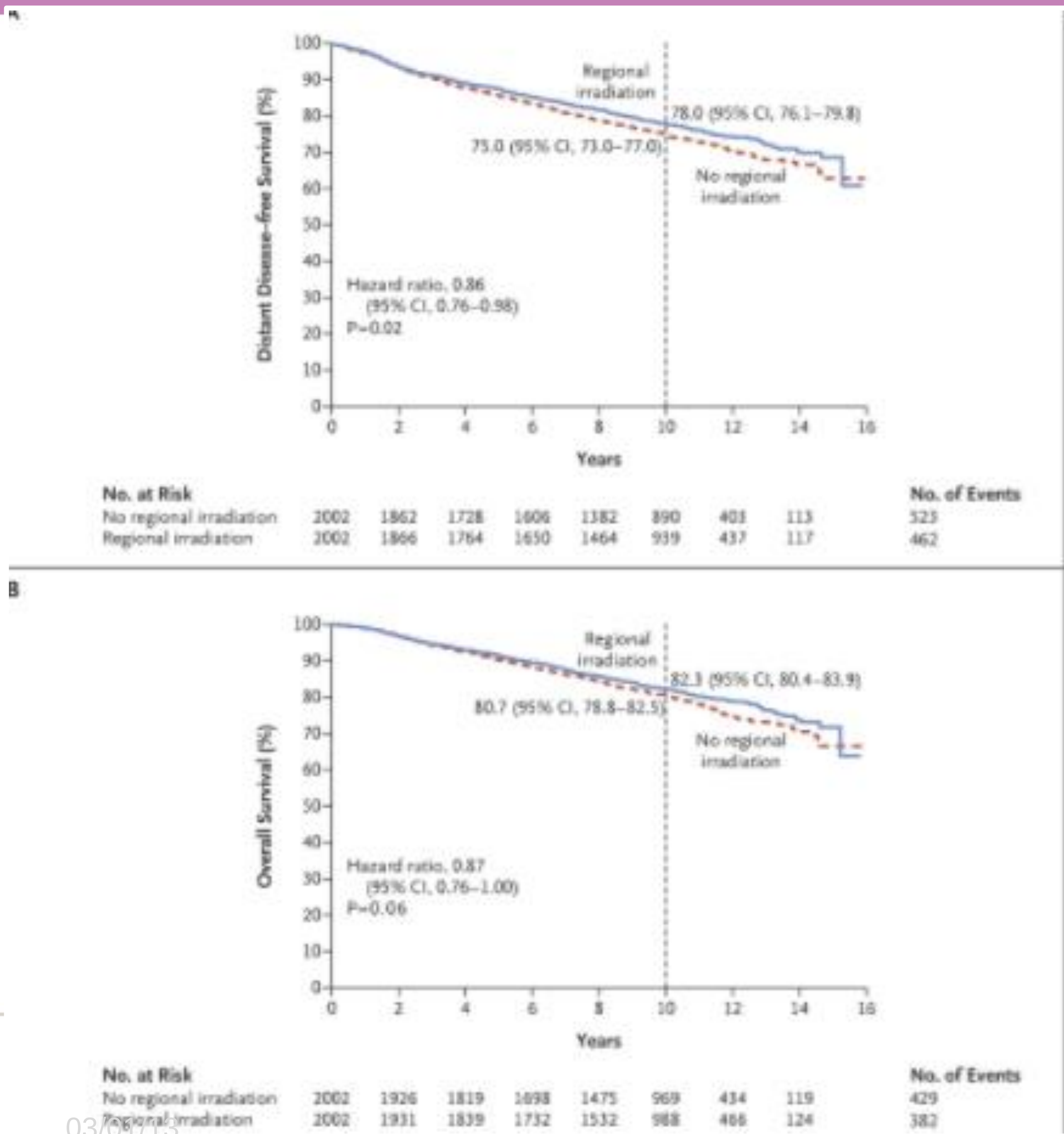
Excellent or good cosmesis achieved in 80% of the patients

Taylor 1995 IJROBP

Breast conserving surgery
pN0



Radiotherapy in breast cancer



Survival benefit of internal mammary chain irradiation

Radiotherapy in breast cancer: Heart Toxicity

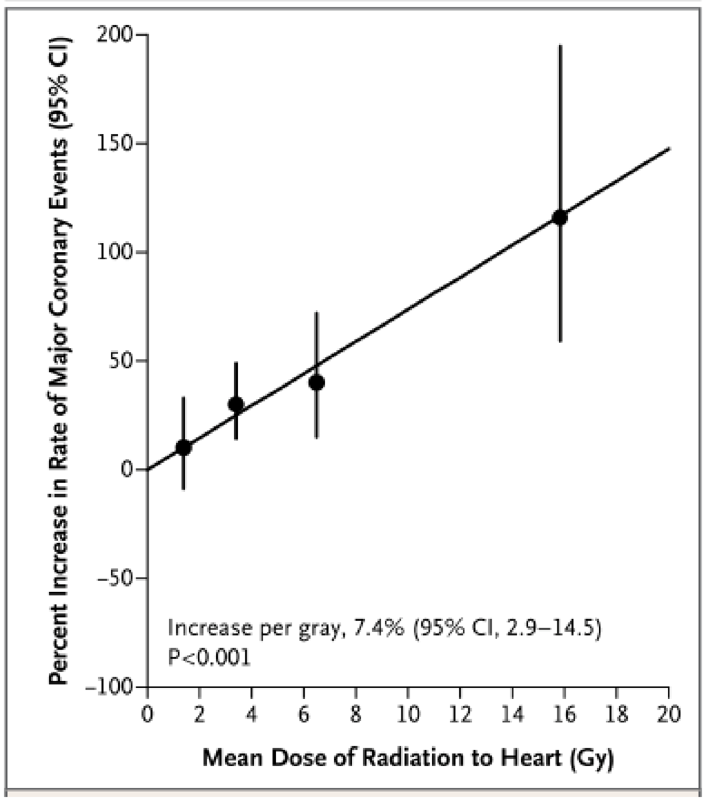
- Latency of 15-20 years
- Myocardial scintigraphy can detect perfusion changes as early as 6 mo

- Target structures:
  - Myocardium (e.g. left ventricle)
  - Vessels (e.g. left anterior descending coronary artery)

- Toxicity
  - Myocardial infarction
  - Angina
  - CHF
  - Valvular disorders
  - Electrical conductivity alterations

- Dose threshold??

Breast cancer data



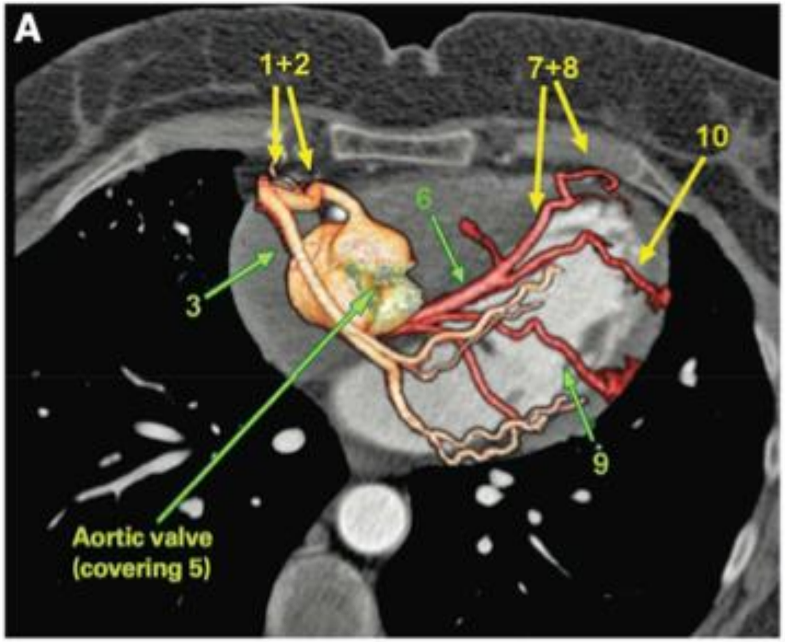
Darby et al NEJM 2013

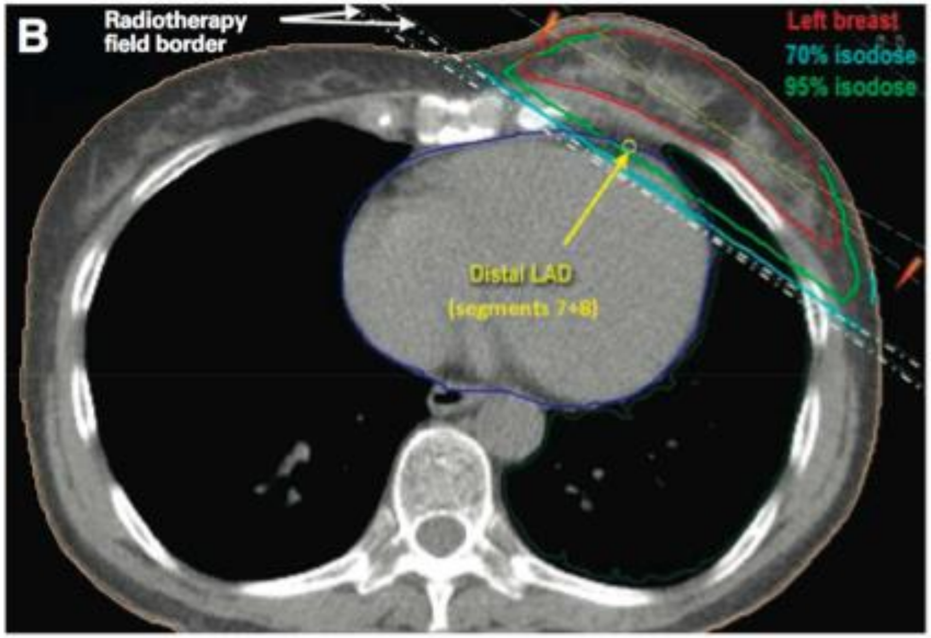
“major coronary event”

linear risk, no threshold

5y after RT

Radiotherapy in breast cancer: Heart Toxicity





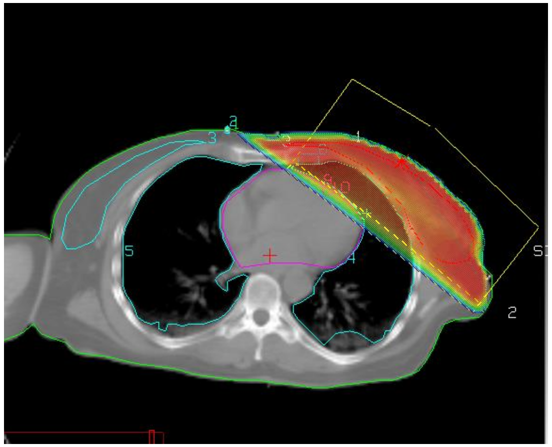
left **a**nterior **d**escending artery

Nillson JCO 2012

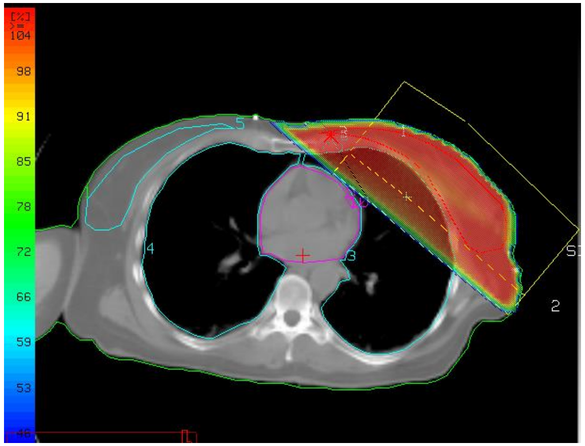
New trends in breast cancer RT

- More IMC irradiation: more interest in DIBH

FB



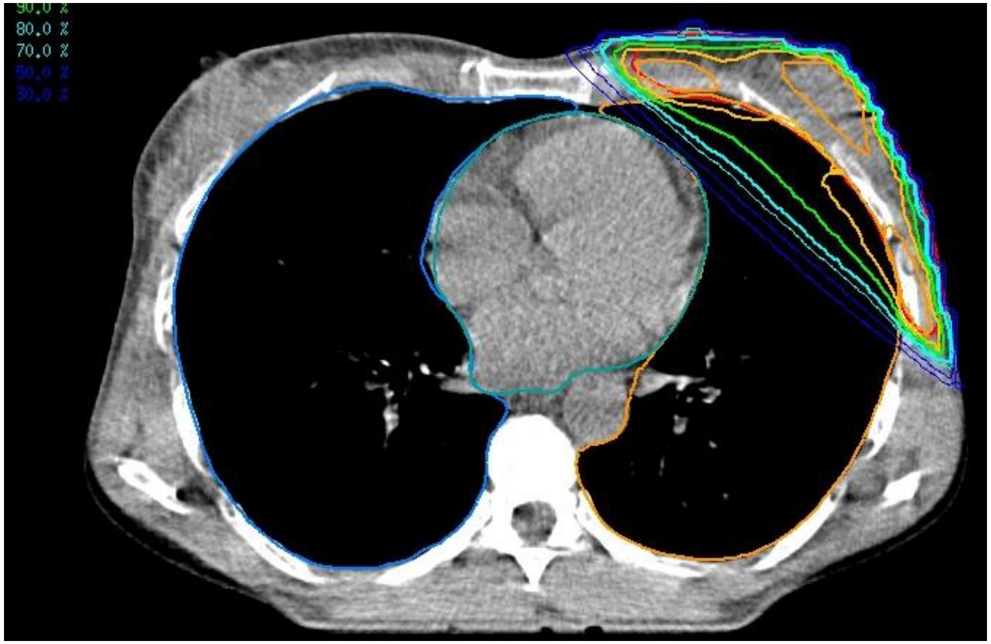
DIBH



- More complex, modulated techniques (e.g. integrated boost)

Image guidance

- Which modality?
- How often?
- whole breast vs partial/boost
- Image guidance for respiratory gating /inspiration breath hold



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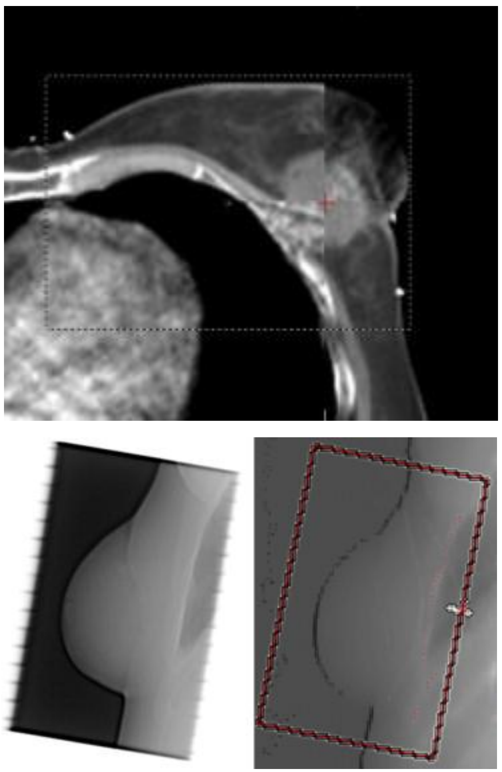
WHOLE BREAST (+/- LN)

Image-guidance for whole breast (+/- nodes)

kV CBCT

EPID

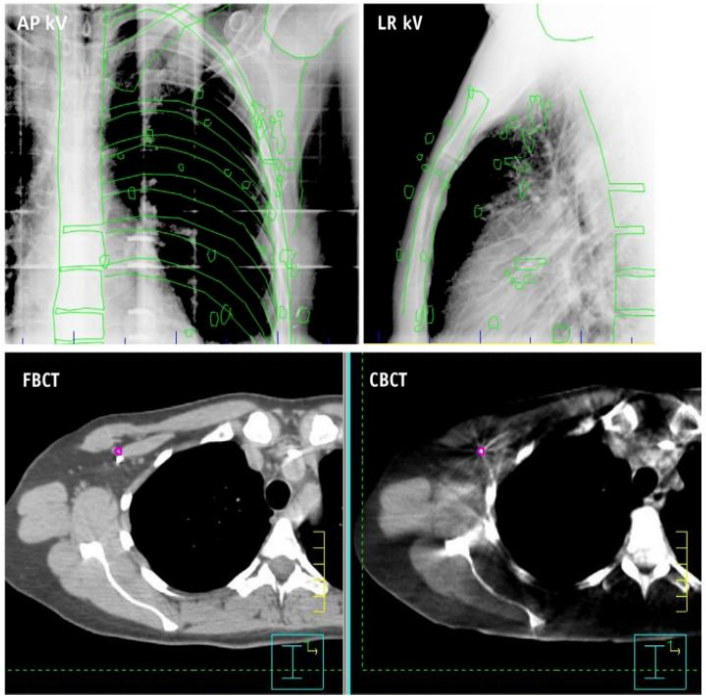


Topolnjak IJROBP 2010

- EPID field images (i.e. not orthgonal) underestimate bony set-up errors by 20% to 50%
- Difference probably insignificant for tangential whole breast irradiation
- Loco-regional treatment or more advanced techniques (SIB? IMRT?) could benefit from a more accurate set up.

Image-guidance for whole breast (+/- nodes)

- Highly conformal /complex techniques



Feng et al IJROBP 2014

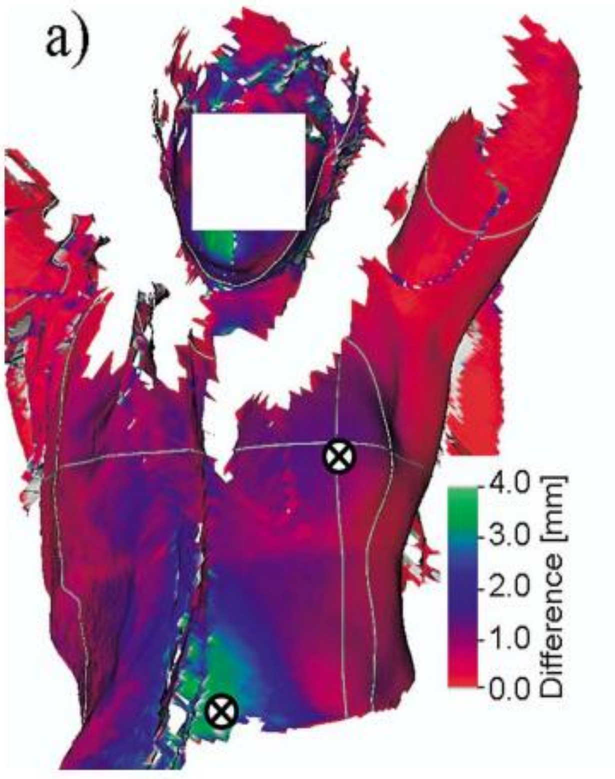
Even with daily kV, the remaining set up error justifies a considerable margin (8mm SI)

(compared to CBCT, registered on clips)

Image-guidance for whole breast (+/- nodes)

- Target with "high deformability"
- Number of cameras ???

Bert et al (2 cameras)

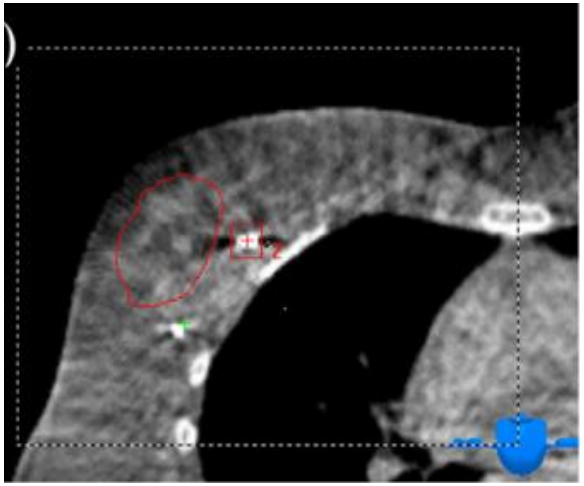


- Difficult to distinguish between set-up error and anatomical changes (or breathing)

- Combination with x-ray IGRT still recommended (Betgen RO 2013)

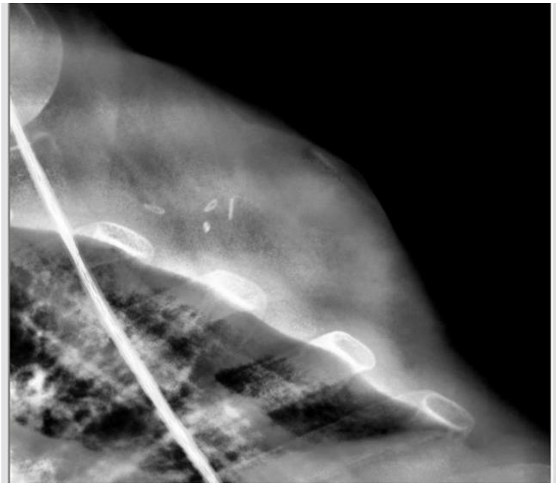
PARTIAL BREAST / BOOST

Image-guidance in partial breast irradiation: implanted markers

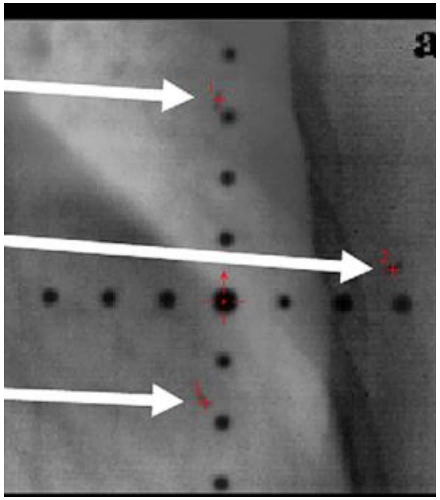


CBCT: match on soft tissue/clips

Topolnjak 2011



2D kV images: match on clips



MV images: match on clips

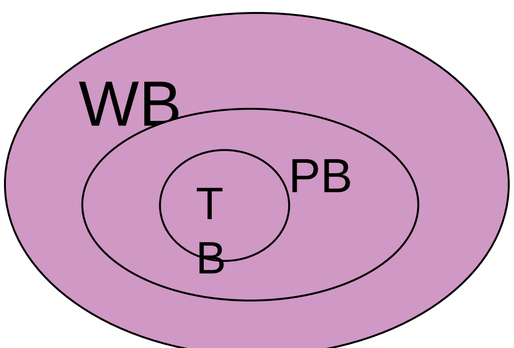
Leonard 2010

Partial breast /integrated boost

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

Emma J Harris,[1†] Mukesh Mukesh,[2†] Rajesh Jena,[2] Angela Baker,[3] Harry Bartelink,[4] Corrinne Brooks,[1] June Dean,[2] Ellen M Donovan,[1] Sandra Collette,[5] Sally Eagle,[6] John D Fenwick,[7] Peter H Graham,[8] Jo S Haviland,[9] Anna M Kirby,[10] Helen Mayles,[3] Robert A Mitchell,[1] Rosalind Perry,[11] Philip Poortmans,[12] Andrew Poynter,[13] Glyn Shentall,[14] Jenny Titley,[9] Alistair Thompson,[15] John R Yarnold,[10] Charlotte E Coles[2‡] and Philip M Evans[1,16*‡] on behalf of the IMPORT Trials Management Group

[1]Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK
[2]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]Department of Radiotherapy and Physics, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Statistics Department, EORTC Headquarters, Brussels, Belgium
[6]Department of Radiotherapy, Royal Marsden Hospital NHS Foundation Trust, London, UK
[7]Department of Oncology, University of Oxford, Oxford, UK
[8]Cancer Care Centre, St George Hospital, Kogarah, Sydney, NSW, Australia
[9]ICR-CTSU, Institute of Cancer Research, London, UK
[10]Breast Unit, Royal Marsden NHS Foundation Trust, London, UK
[11]Radiotherapy Department, Ipswich Hospitals NHS Trust, Ipswich, UK
[12]Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, the Netherlands
[13]Radiotherapy Department, Peterborough City Hospital, Peterborough, UK
[14]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[15]School of Medicine, University of Dundee, Dundee, UK
[16]Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK



Comparing bone registration to clips-based reg

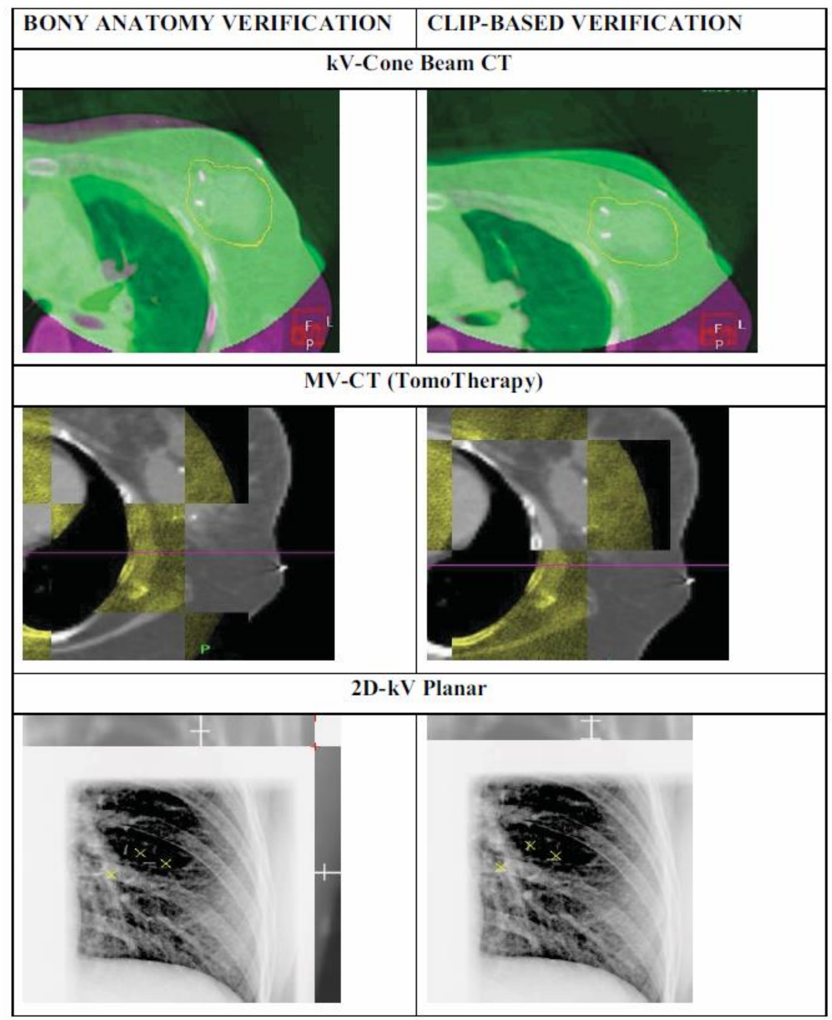


TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

	Delta error (S_{DIFF}), mean absolute delta [cm (range)]				Time, median [seconds (range)]	
Centre	LR	SI	AP	3D vector	T_{BA}	T_{clips}
All	0.20 (0–1.7)	0.26 (0–3.2)	0.21 (0–2.0)	0.32 (0–10.2)	73 (8–240)	66 (8–178)
A (kV-CBCT)	0.19 (0–0.7)	0.24 (0–3.2)	0.22 (0–1.7)	0.28 (0–10.2)	26 (8–51)	92 (11–177)
B (MV-CT)	0.14 (0–0.7)	0.12 (0–1.2)	0.18 (0–1.3)	0.17 (0–2.0)	102 (70–230)	110 (25–178)
C (2D-kVPI)	0.23 (0–1.7)	0.29 (0–2.4)	0.20 (0–2.0)	0.38 (0–6.29)	22 (20–76)	16 (8–52)
D (2D-kVPI)	0.21 (0–1.3)	0.32 (0–1.3)	0.21 (0–1.0)	0.35 (0–2.2)	79 (60–154)	28 (20–85)
E (2D-kVPI)	0.20 (0–1.5)	0.31 (0–1.4)	0.23 (0–1.0)	0.36 (0–3.3)	110 (28–240)	34 (16–120)

Difference between bone reg and clips reg: 2-3 mm

Reduction in PTV (tumourbed) from 8 to 5 mm with clips-based IGRT, daily or with eNAL

Modest dosimetric impact

TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

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Time varies per institution, even when using the same technique
2D kV scores both as fastest and slowest !
Inter and intra- observer error < 1.4mm for all modalities

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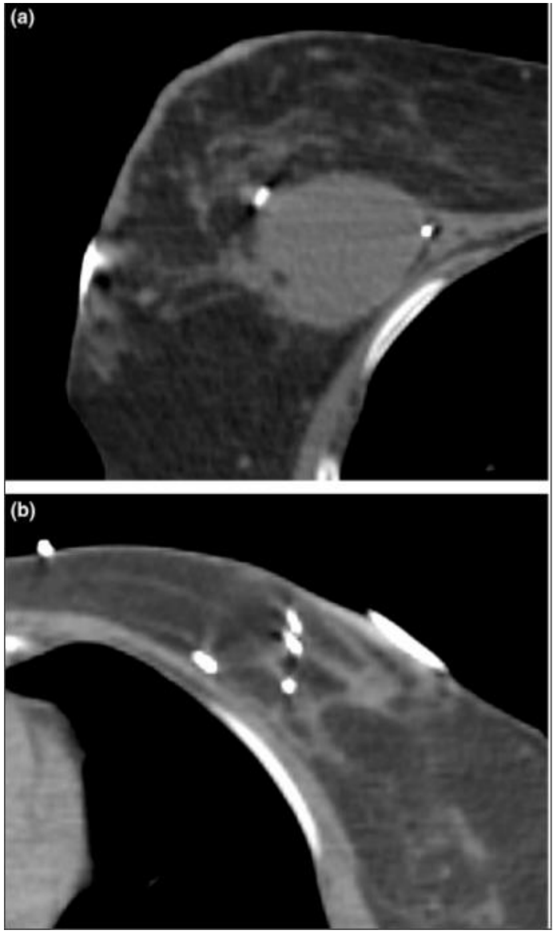
Note of caution using clips for registration

- seroma



Lewis et al J Med Rad Sci 2015

GATING /BREATH HOLD

Image guidance for deep inspiration: DIBH/gating monitoring

- Voluntary breath is hold is as efficient and more comfortable

Bartlett 2013

- The "no equipment" solution:
  - short hyperventilation follwed by breath hold
  - Monitoring is visual (draw the light field on the patient, observed through control room monitors)
  - Video article: ***Bartlett et al J Vis Exp 2014***

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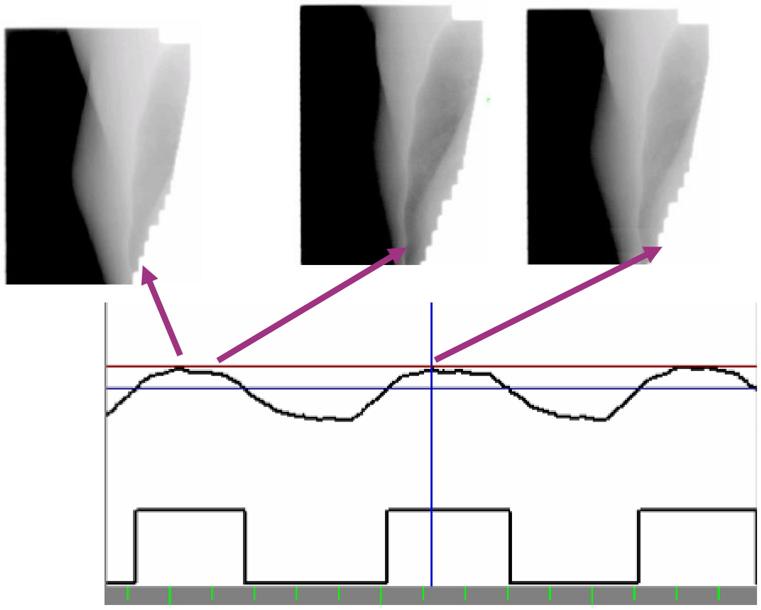
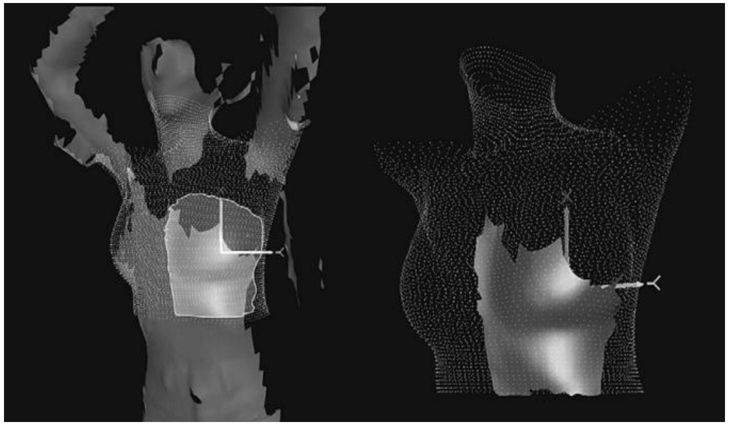
Image guidance for deep inspiration: DIBH/gating monitoring

- Patient set up as for conventional treatment (i.e. planar or CBCT)



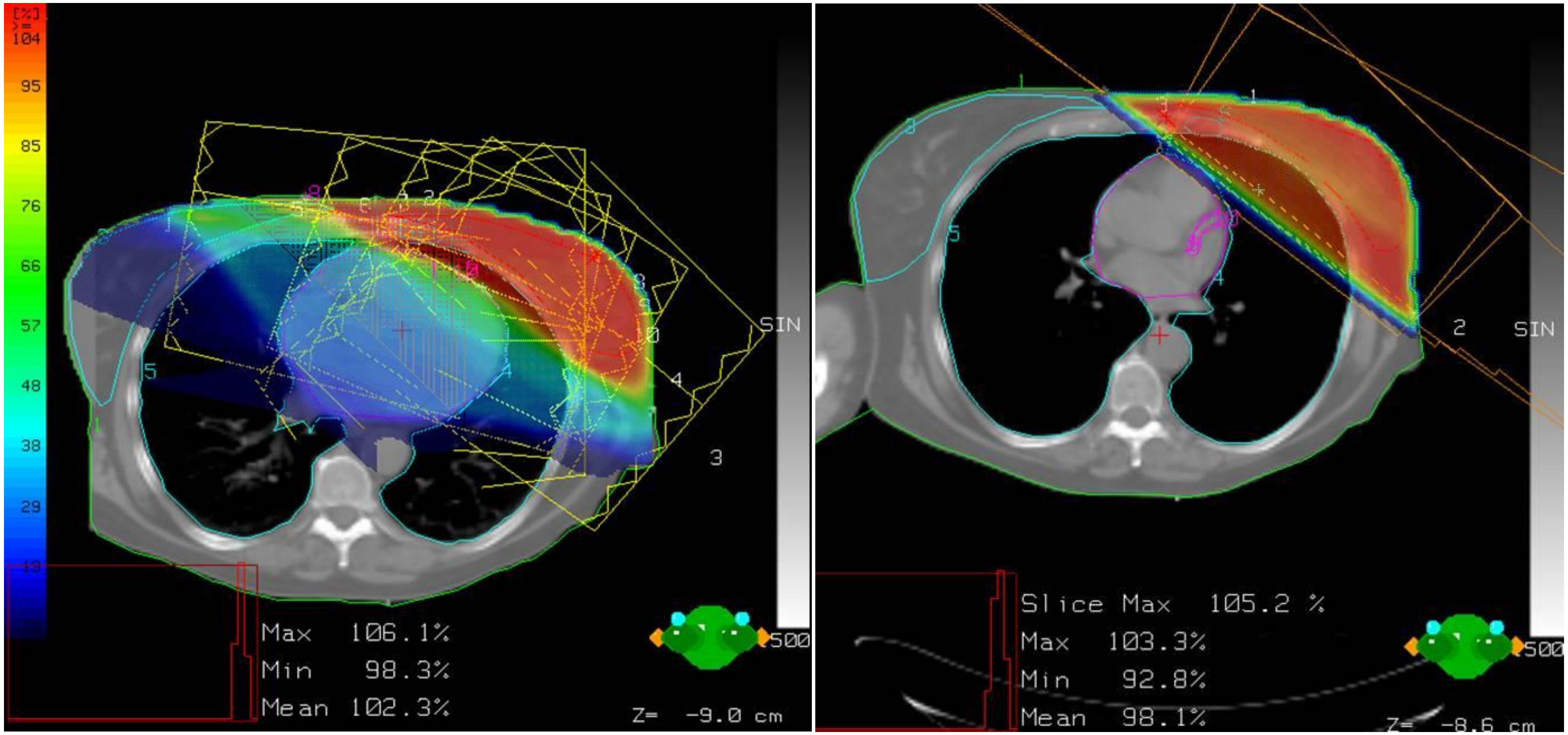
Residual motion can be verified by cine EPID



Align RT: potential for breath hold monitoring
Maintain use of CBCT for set-up

Alderliesten et al IJROBP 2012

Techniques for reduction of cardiac toxicity
IMRT or inspiration gating?



Patients with unfavorable thoracic anatomy:

➢Improved sparing of the heart with IMRT at cost of increased dose to the normal tissue (e.g. contralateral breast)

➢Sparing of the heart can be more efficient with 3D_DIBH than with IMRT_FB.

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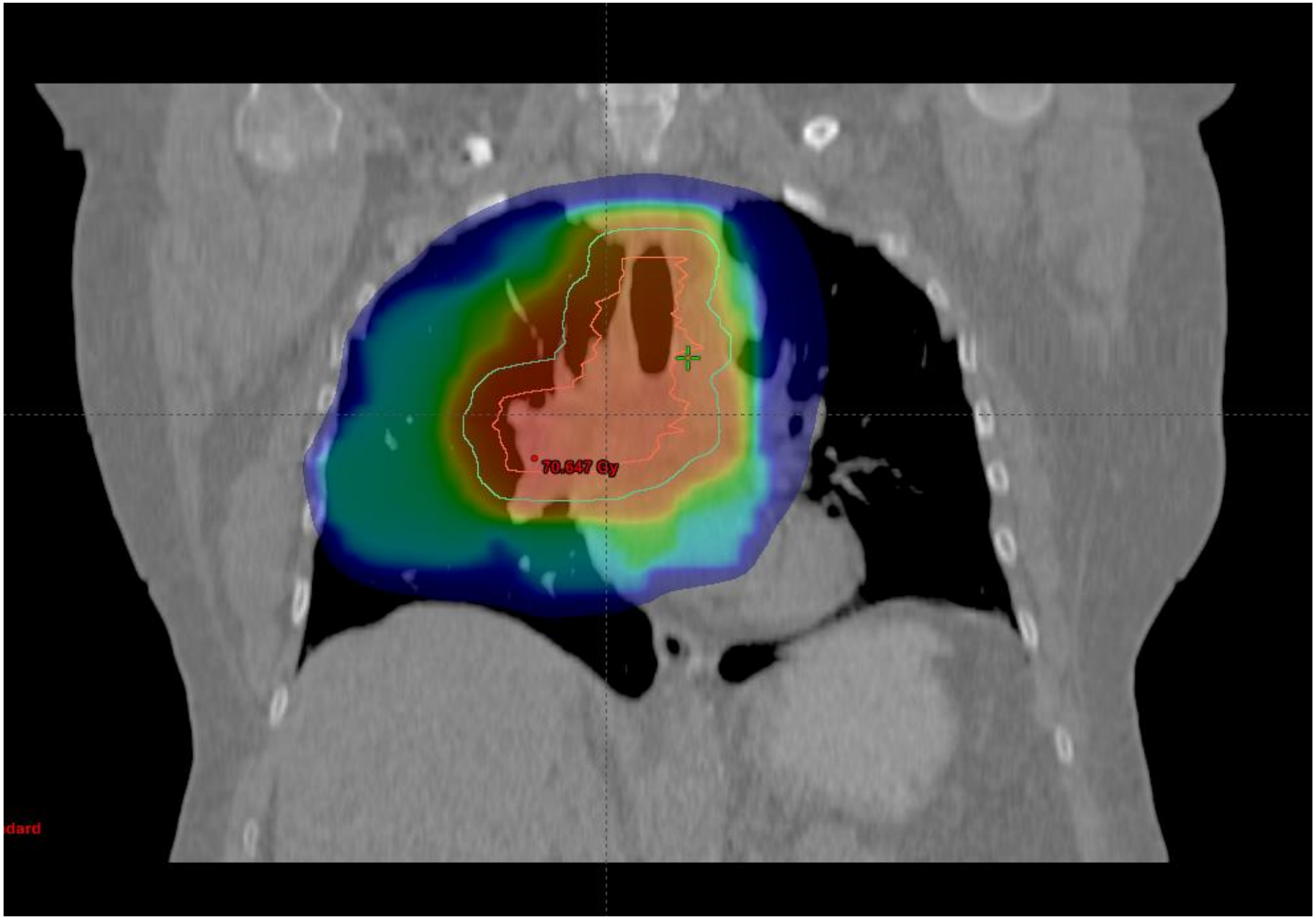
Take home message: image-guidance for breast cancer

- MV can be acceptable is you have a good surrogate (e.g. visible clips, not only ribs)

- The less robust your treatment technique, the more advanced the IGRT

- For robust treatments, an offline strategy (NAL, eNAL, SAL, etc…) will go a long way towards reducing uncertainties
- Surface image has interesting potential and properties (no dose) but shouldn't be the only modality for set-up (rotations, DIBH…)
- Deep inspiration: just do it !

Lung Cancer



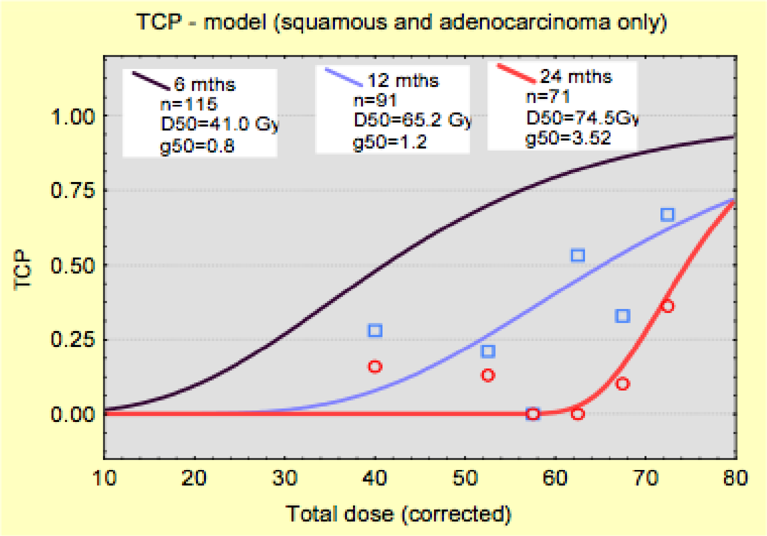
Dose escalation in lung NSCLC

High rates of local tumor recurrence with conventional irradiation doses (60-66Gy) and conventional RT techniques

- Early stage: >50% with RT only
- Advanced stage: >70% with RCHT

Sibley Cancer 1998

Le Chevalier J Natl Cancer Inst 1991



- Escalation of the irradiation dose increases local control and has the potential to increase overall survival

Willner IJROBP 2002
Kong IJROBP 2005

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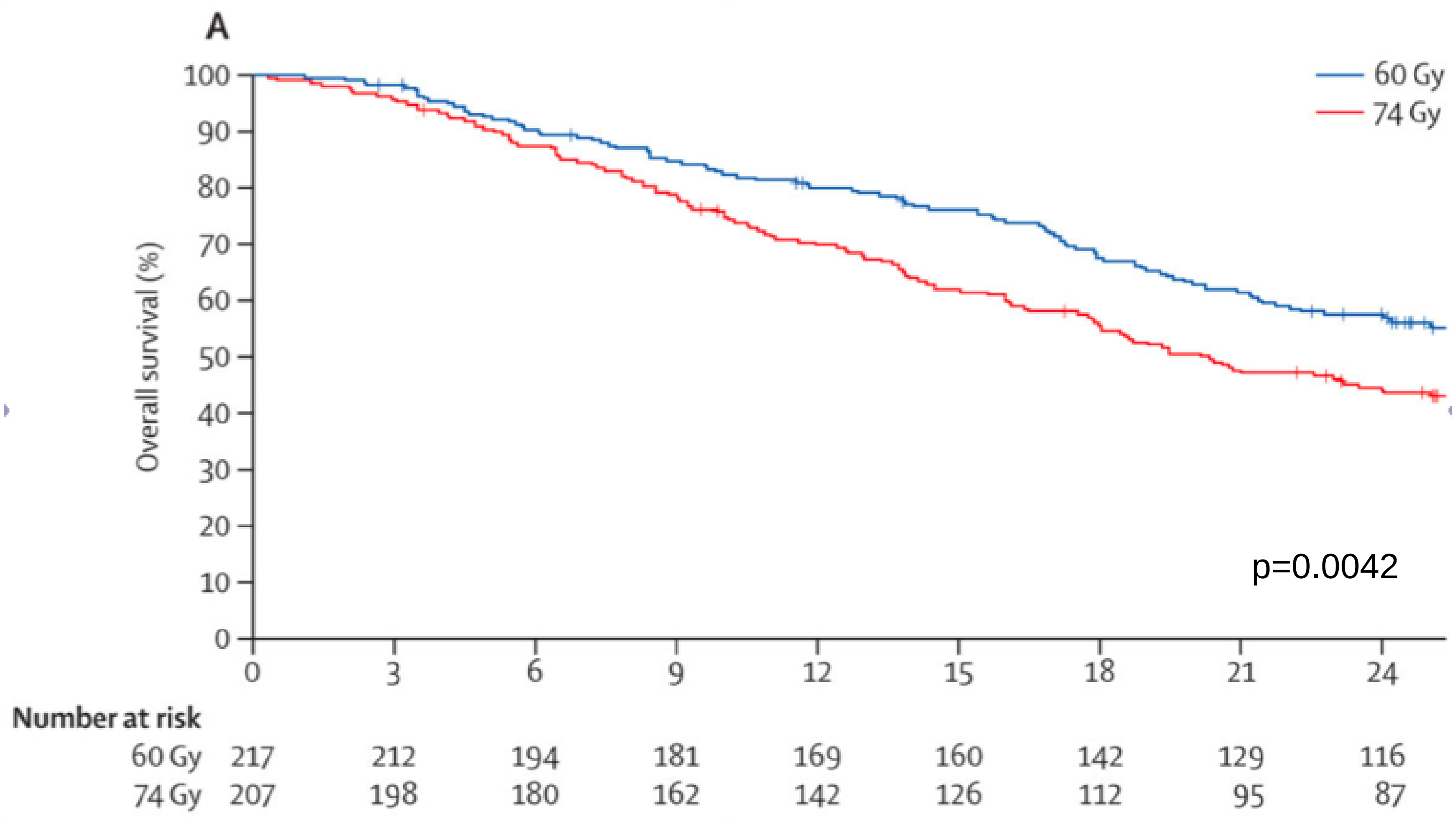
Is more dose better?

- RTOG 0617
  - Randomized controlled trial
  - Inoperable Stage III NSCLC
  - Concurrent radiation + chemotherapy
  - 2x2 randomization

60Gy	74Gy
RT + chemotherapy	RT + chemotherapy + cetuximab

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Overall survival (+/- Dose escalation)



Bradley et al., *Lancet Oncology* 2015

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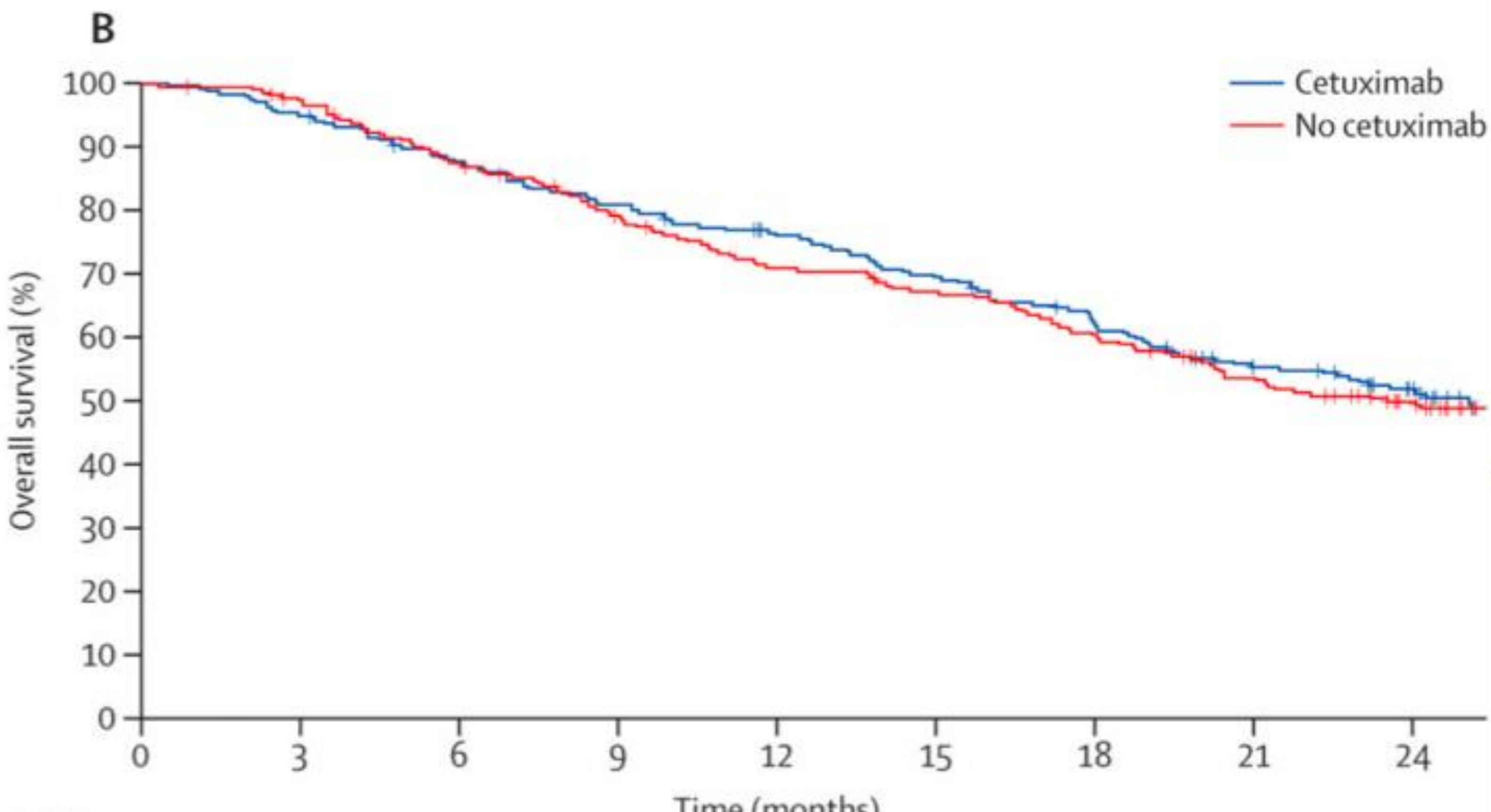
RTOG 0617 – Overall survival (+/- Cetuximab)



Number at risk									
Cetuximab	237	225	206	190	175	160	141	121	103
No cetuximab	228	219	196	174	155	146	131	113	96

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Overall survival modeling

Overall survival

Multivariate Cox Model Backwards Selection

Covariate	Comparison	HR (95% CI)	p-value
Radiation dose	60 Gy v 74 Gy	1.55 (1.07, 2.23)	0.020
Histology	Non-squam v Squam	1.37 (0.94, 1.98)	0.097
GTV (ITV if GTV unavailable)	Continuous	1.002 (1.000, 1.003)	0.034
Heart V5	Continuous	1.010 (1.004, 1.017)	0.002

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Outcomes

Toxicity and mortality

September 2011	Standard Dose: 60 Gy (n=192) Grade			High Dose: 74 Gy (n=183) Grade		
	3	4	5	3	4	5
Worst non-hematologic	79 (41.1%)	14 (7.3%)	4 (2.1%)	85 (46.4%)	17 (9.3%)	8 (4.4%)
Worst overall	84 (43.8%)	45 (23.4%)	4 (2.1%)	78 (42.6%)	52 (28.4%)	8 (4.4%)
Grade 5 Events	(n=4)			(n=8)		
As scored by institution No significant difference	2 Pulmonary 1 Thrombosis 1 Death NOS			2 Pulmonary 1 Thrombosis 1 Upper GI Hemorrhage 1 Pulmonary Hemorrhage 1 Pneumonia NOS 1 Esophageal 1 Death NOS		

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Dose escalation

Local failure rate at 18 months post-treatment:

60 Gy	**74 Gy**
25.1%	34.4%

Does this make sense?

Reasons?

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Dose escalation

Local failure rate at 18 months post-treatment:

60 Gy	**74 Gy**
25.1%	34.4%

Does this make sense?

Reasons?

Minimum margin was smaller in the high-dose group (mean 4·5 mm [2·9] in the standard-dose group *vs 3·9 mm [3·0] in the high-dose group; p=0·0047)*

Bradley et al., *Lancet Oncology* 2015

RTOG 0617

ARE THE RESULTS OF RTOG 0617 MYSTERIOUS?

JAMES D. COX, M.D.

Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

74Gy compared to 60Gy is **neither safe nor effective** for the patient population and using the technology of RTOG 0617

Bradley et al., *Lancet Oncology* 2015

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RTOG 0617

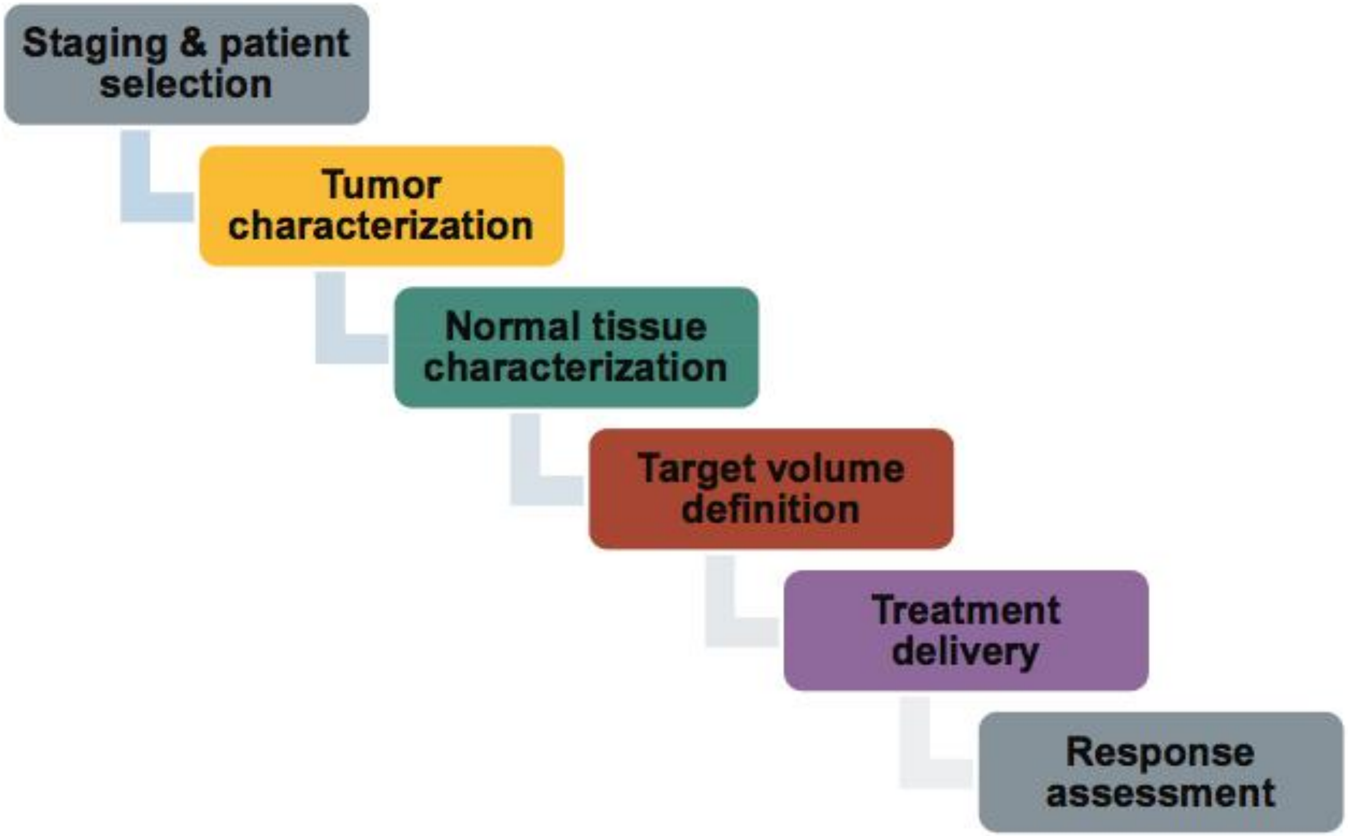
Interpretation of RTOG 0617

Technology	Study protocol
FDG-PET	encouraged, not mandatory
4D-CT	highly, encouraged not mandatory
IMRT	optional

74Gy feasible in the study patient population with the technology above?

- Violation OAR constraints?
- Smaller than necessary target safety margins?
- Experience in the centers?
- Necessary to „boost“ all macroscopic tumor?

Outline

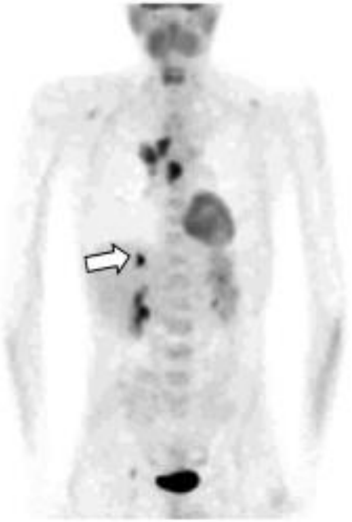


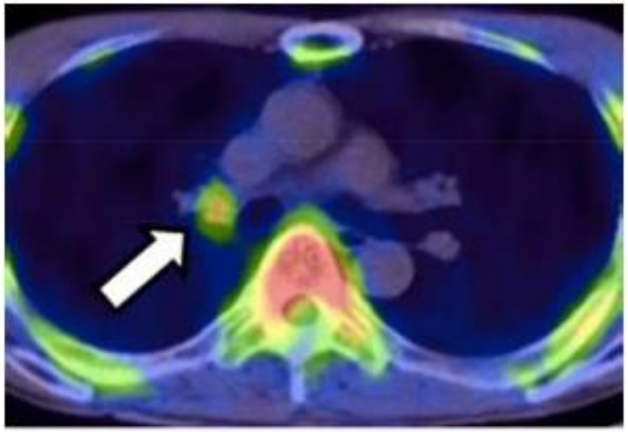
Staging & patient selection
Tumor characterization
Normal tissue characterization
Target volume definition
Treatment delivery
Response assessment

Staging and patient selection – FDG-PET

Staging of

Distant metastases | **Nodal metastases**





FDG-PET provides important information to select patients for high precision radiotherapy

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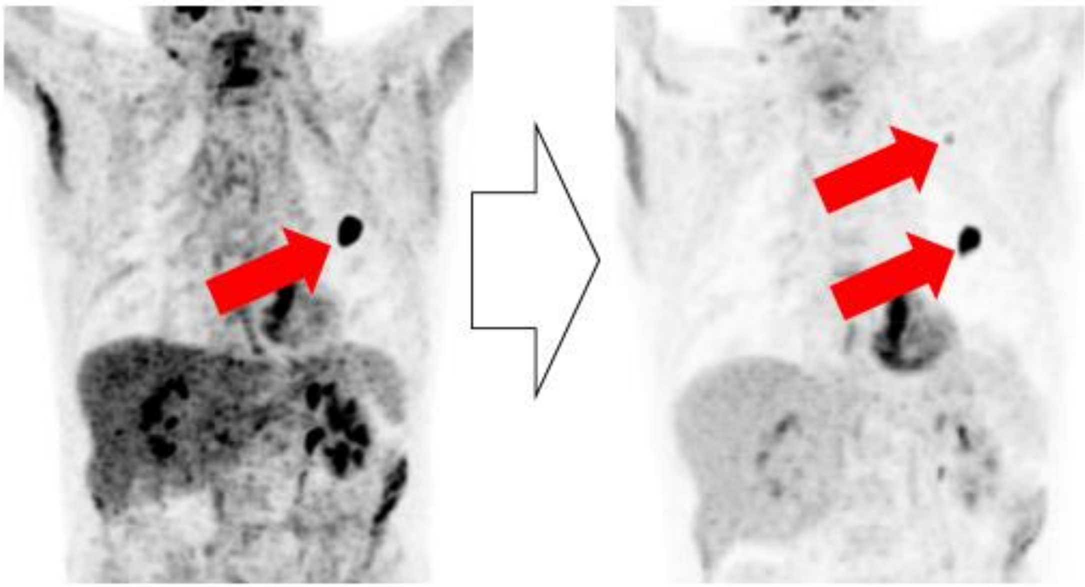
Staging and Patient Selection: Disease Progression



Median 23 days (max 176)

Progression to stage IV:

3 / 21 patients

Mac Manus Radiat Oncol 2013

6 weeks

Repeat Staging!
What time interval?

Staging and Patient Selection: FDG-PET

Results of a prospective study: locally advanced NSCLC

CT staging | **PET-CT staging** | **Outcome**

- 76 patients
  - 50 radical RT possible → OS 78% @ 1a
  - 26 radical RT **not** possible → OS 16% @ 1a

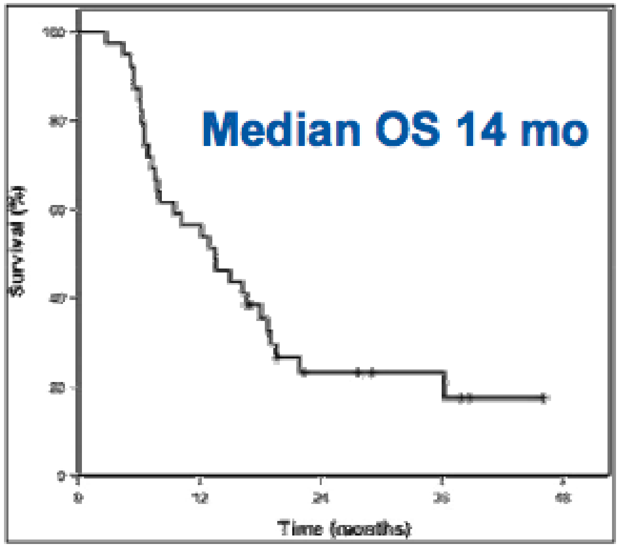
Mac Manus Radiat Oncol 2013

FDG-PET detected metastases in 12/76 patients
Treatment intent changed from curative to palliative

Staging and Patient Selection: Advanced disease

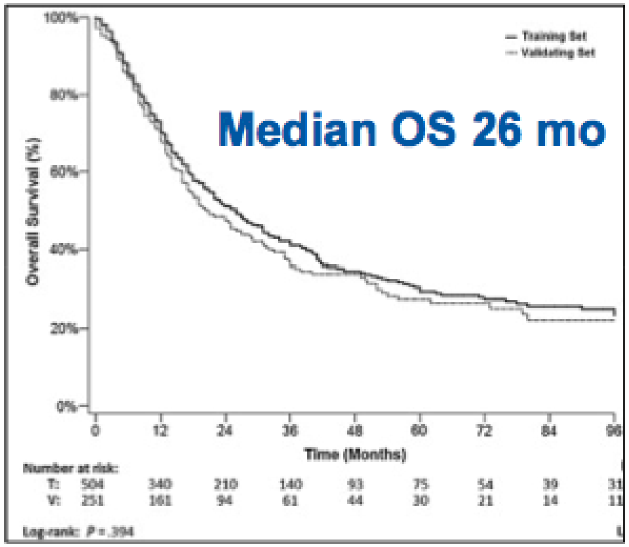
Radical treatment DESPITE stage IV disease

Prospective phase II trial: n=39



De Ruysscher JTO 2012

Multicenter analysis: n=757



Palma Clinical Lung Cancer 2014

Overall survival similar to Stage III NSCLC

Careful patient selection

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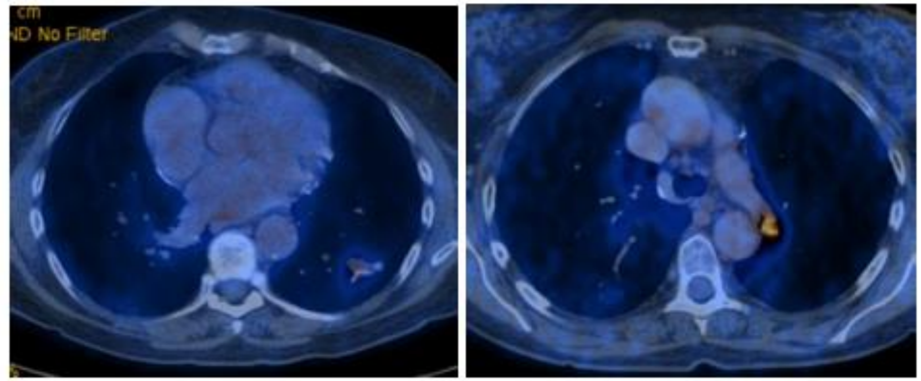
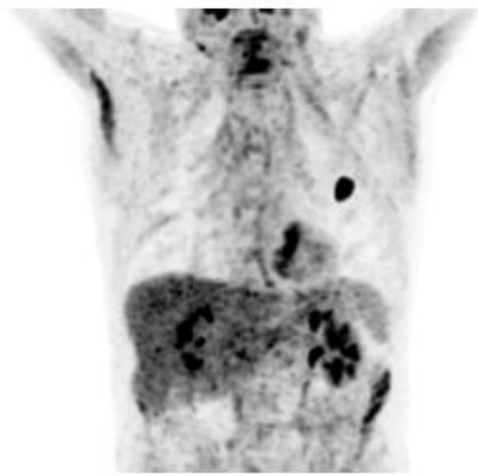
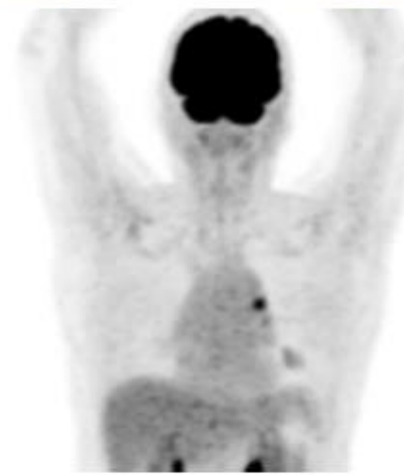
Nodal Staging in Stage I NSCLC



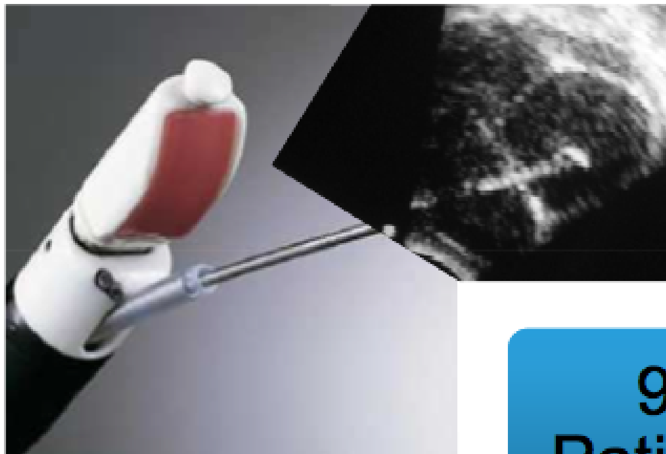




Nodal failure after local treatment with SBRT
Rates similar to surgical series (~10%)

Nodal Staging in Stage I NSCLC: EBUS

EBUS for staging of CT and FDG-PET N0 disease



- Systematic imaging of mediastinum and hilar regions (stations 2, 4, 7, 10, 11)
- Puncture of all visualized nodes with a size of 5 - 10mm

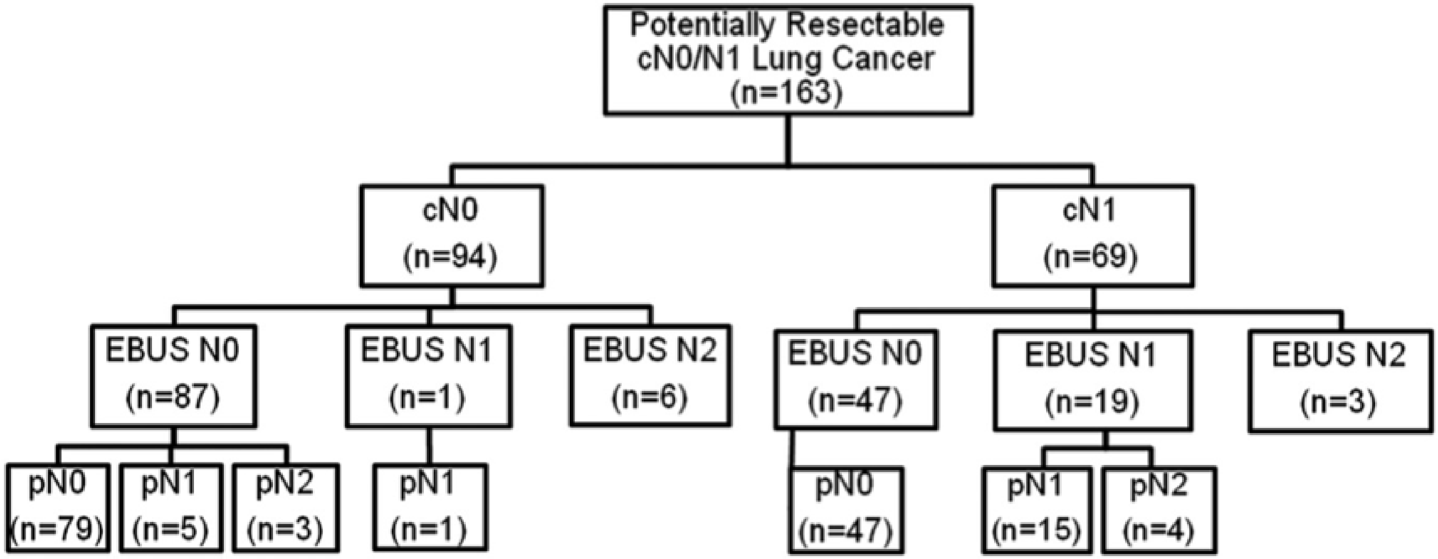
97 Patients → 156 LN biopsied → N+ 8 / 97 patients

Herth CHEST 2008

EBUS requires experienced providers, more common now
Pathologic “confirmation” of ultrasound imaging

Nodal Staging in Stage I NSCLC: EBUS

CT/PET negative patients planned for lobectomy



Differentiating N0 from N1
Sensitivity: 76%, Specificity: 100%
Accuracy: 96%, NPV: 96%

Yasufuku et al., *Ann Thorac Surg, 2013*

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Elective nodal irradiation in N+ disease

Study	# of patients	Isolated regional failure
Graham 1995	179	8%
Kong 2005	106	6%
Rosenzweig 2001	171	6.4%
Senan 2002	50	0
De Ruysscher 2005	44	2%
Belderbos 2006	67	3%
Rosenzweig 2007	524	6.1%

Randomized trial of ENI (60-64Gy) and IF (68-74Gy) N=200

Patients in the IF arm had significantly

- Increased local control and no increased regional failure
- Decreased rates of pneumonitis
- A trend to improved OS

Yuan American Journal of Clinical Oncology 2007

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Elective nodal irradiation in N+ disease

Practical considerations of selective nodal / involved field RT

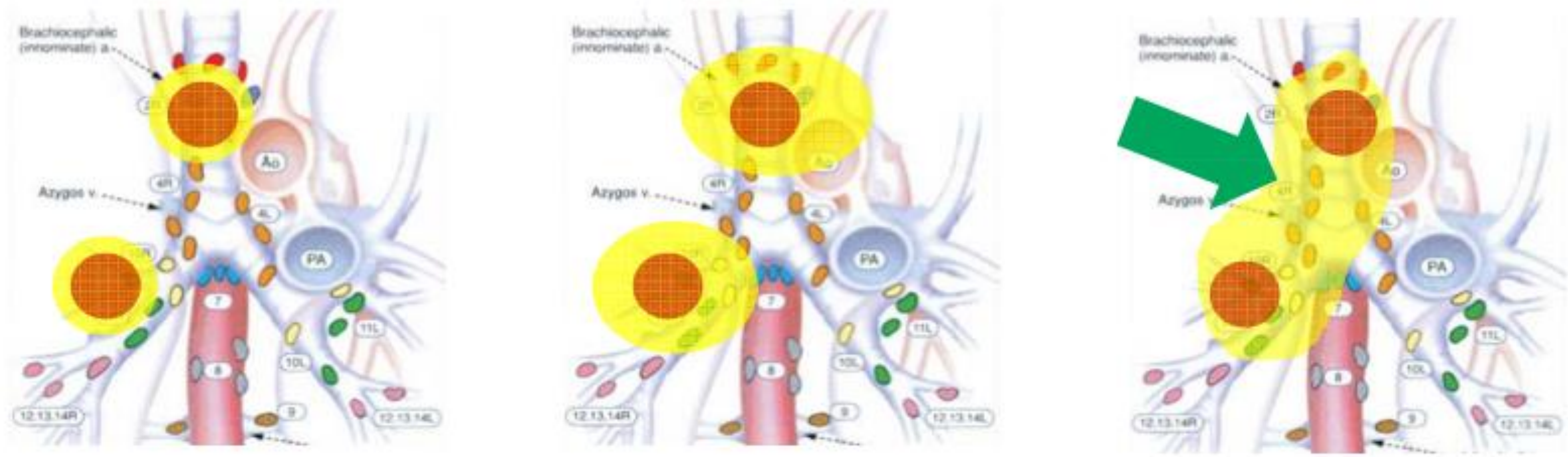
Study	CT criteria	FDG-PET
Graham 1995	≥ 1cm	-
Kong 2005	≥ 1cm	-
Rosenzweig 2001	≥ 1.5cm	-
Senan 2002	-	-
De Ruysscher 2005	1cm	„increased uptake“
Belderbos 2006	-	„increased uptake“
Rosenzweig 2007	≥ 1.5cm	„increased uptake“

- **No standard how to define an involved lymph node**

Nodal staging/treatment

Practical considerations of selective nodal / involved field RT

Involved node | Involved station | Involved station +



➢ **No standard how to define an involved lymph node**

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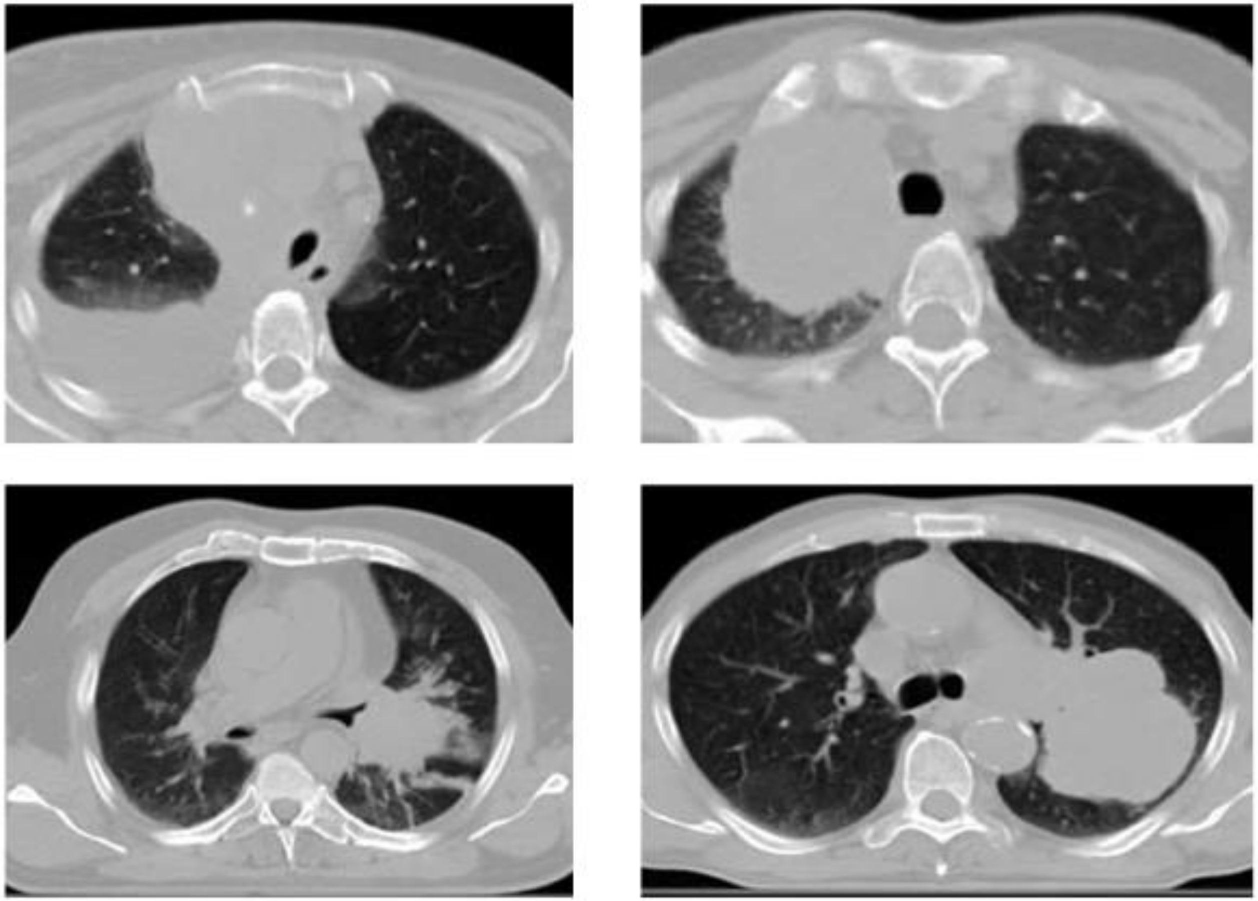
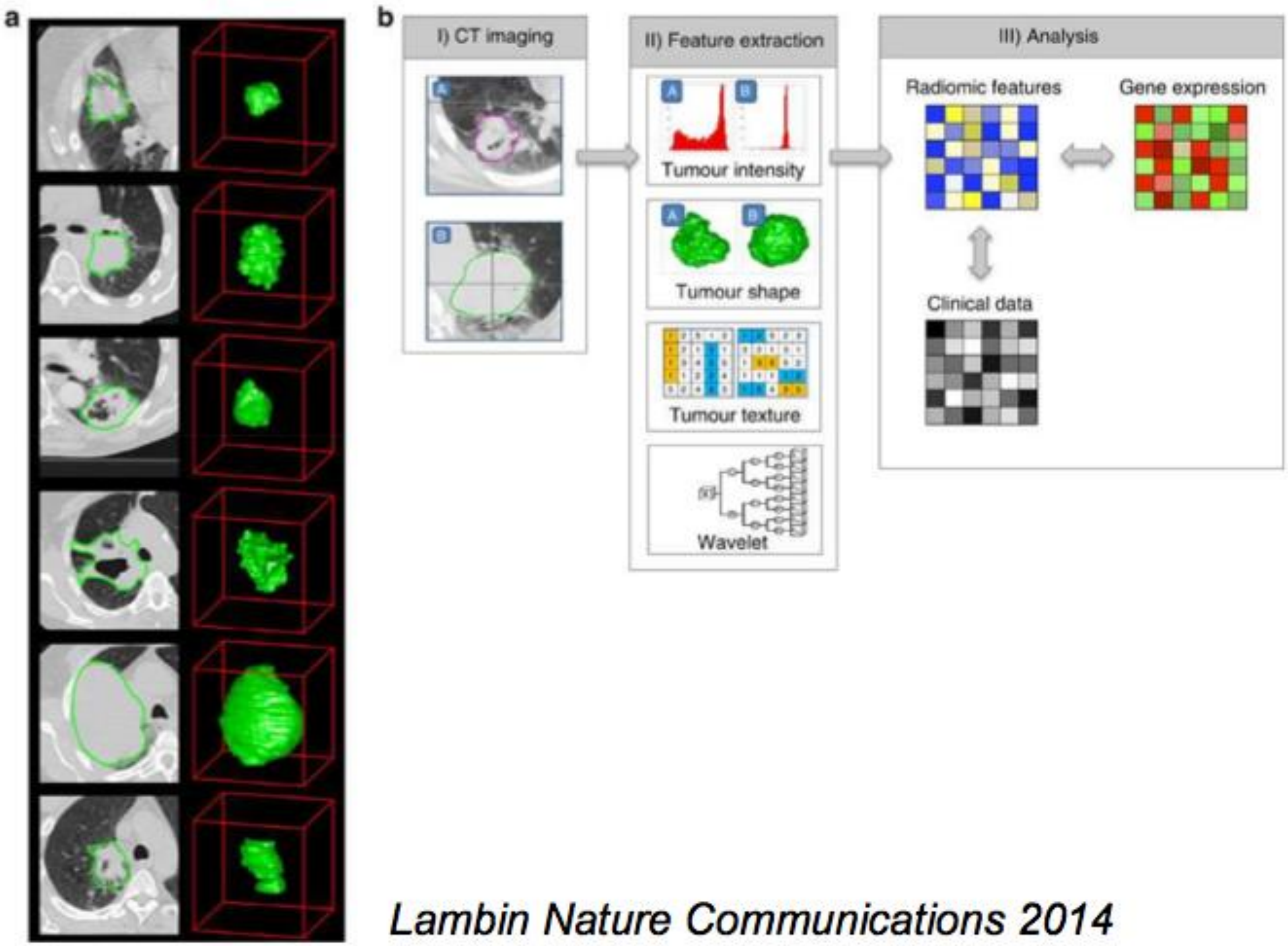
Tumor characterization: Radiomics



Different lung tumors look different!

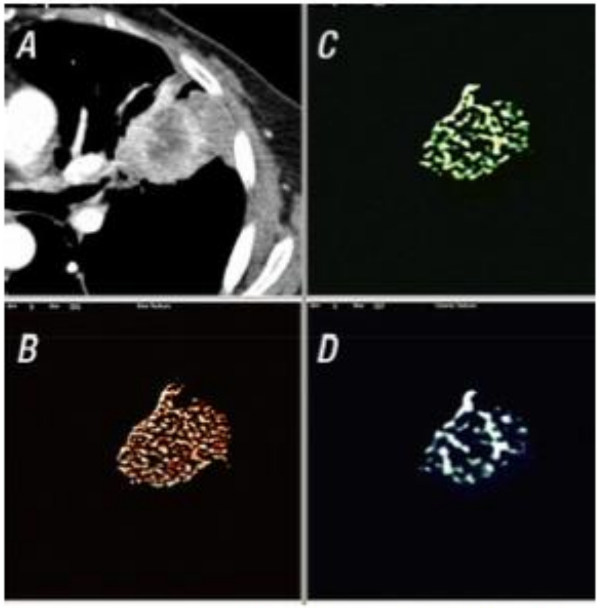
Tumor characterization: Radiomics



Lambin Nature Communications 2014

Tumor characterization: Radiomics

CT texture analysis



Ganeshan Radiology 2013

CT textures correlated with …

… histopathological tumor characterization:
- Tumor staining with pimonidazole
- Glut-1 expression

Ganeshan Radiology 2013

- Microscopic disease extension

Salguero Radiother Oncol 2013

- Loco-regional recurrence after SBRT

Salguero Radiother Oncol 2013
Mattonen Med Phys 2014

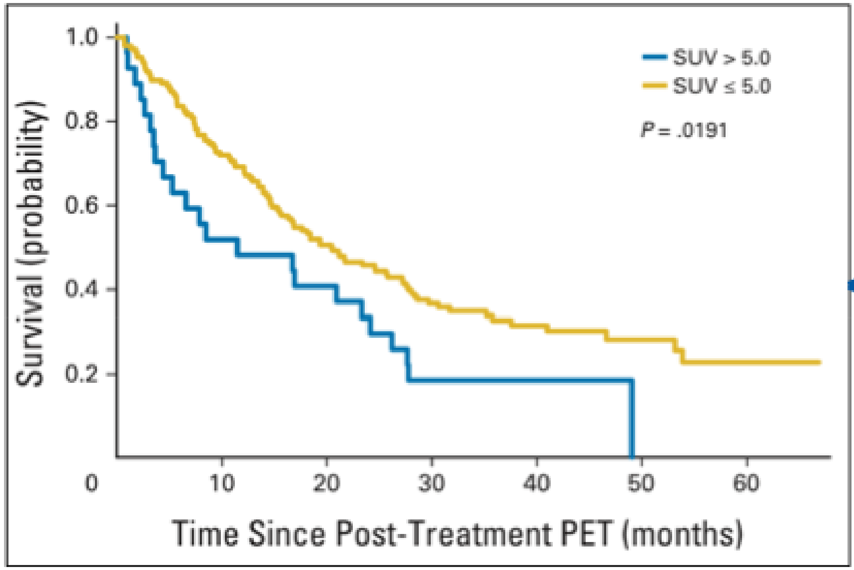
- Overall survival after RCHT

Fried IJROBP 2014

Most reports use 'standard' CT
Standardization and validation required

Tumor characterization: FDG-PET

Post-treatment FDG-PET



Machtay JCO 2013

Pre-treatment FDG-PET

Aerts Radiother Oncol 2009
Shusharina IJROBP 2014

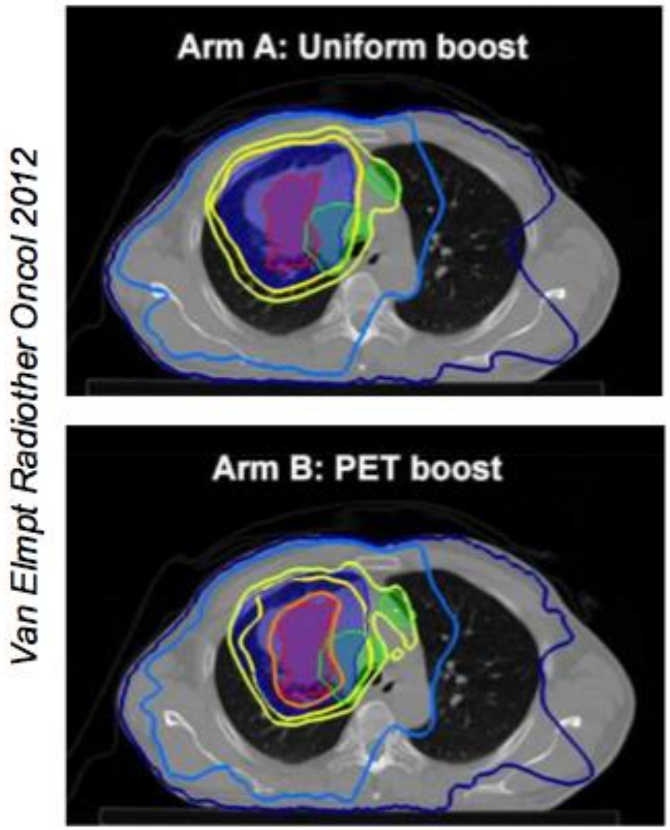
Mid-treatment FDG-PET

Kong JCO 2007

Residual FDG-PET activity associated with worse LC/OS

FDG-PET at early time-points (during treatment?) may be associated with outcomes

Tumor characterization: FDG-PET



Pre-treatment FDG-PET

Homogeneous boost	PET-Boost
79Gy	87Gy

Van Elmpt Radiother Oncol 2012

Mid-treatment FDG-PET

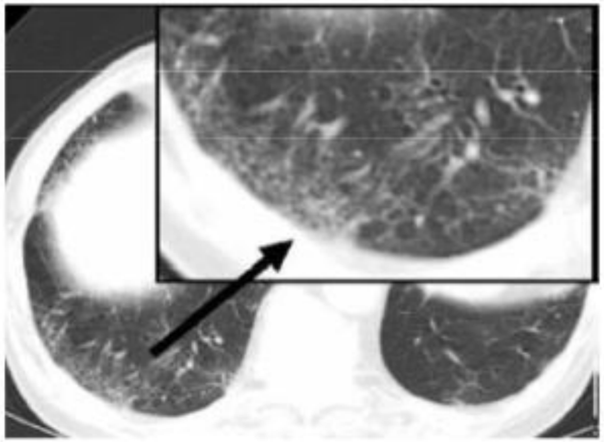
CT volume decrease	PET volume decrease
- 26%	- 44%

Feng IJROBP 2009

Boost limited to areas of high FDG-PET activity
Multiple on-going prospective studies

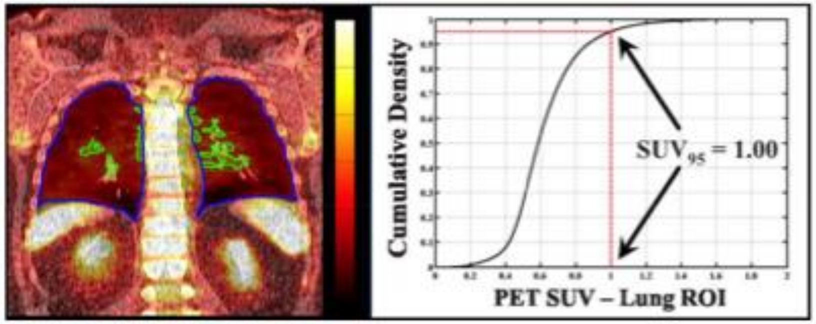
Normal Tissue Characterization

Interstitial pulmonary fibrosis



Increased risk (26% vs 3%) of RP
Sanuki J. Radiat. Res. 2012

Pulmonary FDG uptake



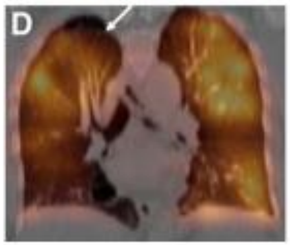
Increased risk in high FDG uptake lung volumes, especially when exposed to RT
Petet IJROBP 2012, Castillo Radiat Oncol 2014

Normal Tissue Characterization

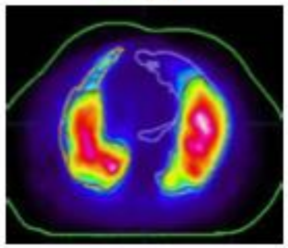
Regional lung function

Perfusion

SPECT

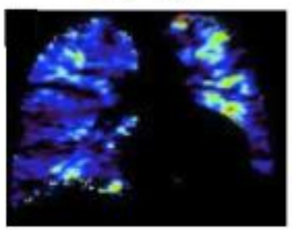


PET

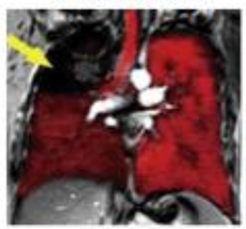


Ventilation

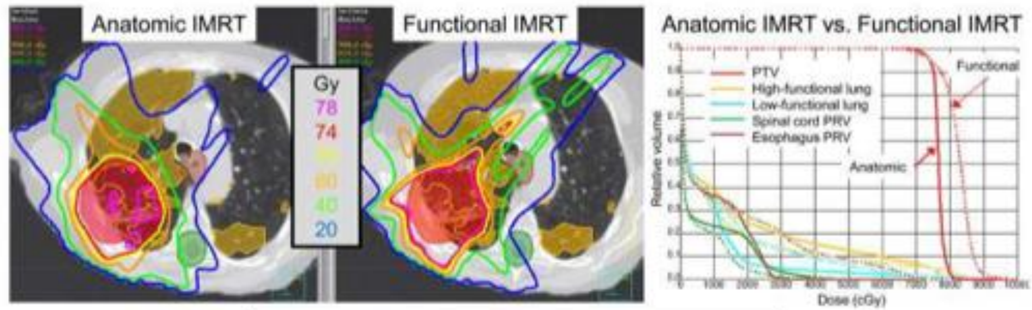
4D-CT



^{3}He MRI



Adaptive planning



STUDY PROTOCOL — Open Access

Functional lung avoidance for individualized radiotherapy (FLAIR): study protocol for a randomized, double-blind clinical trial

- Dose re-distribution from functional to non-functional lung tissue

McGuire IJROBP 2006; Shioyama IJROBO 2007; Yamamoto IJROBP 2010

Hard to implement as ‘bad’ lung tissue isn’t always in the same location day to day.

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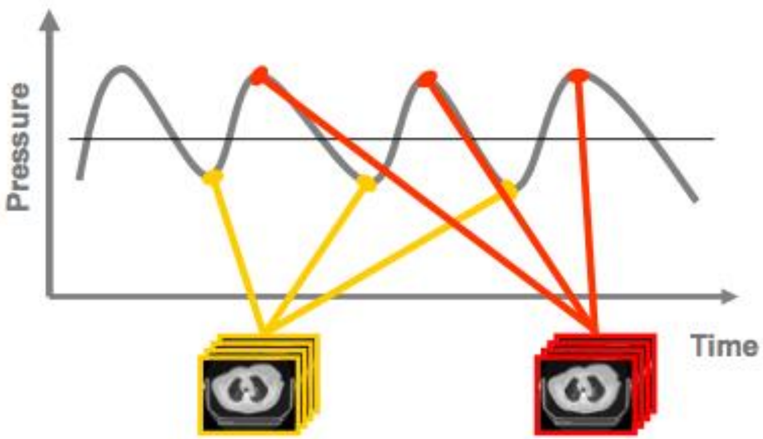
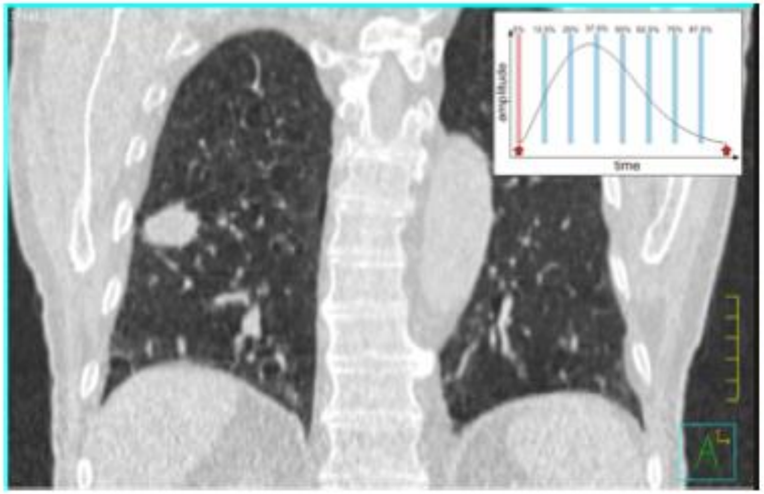
Target Volume Delineation – 4DCT

Respiration correlated 4D-CT





Patient specific motion analysis
Selection of appropriate motion management strategy

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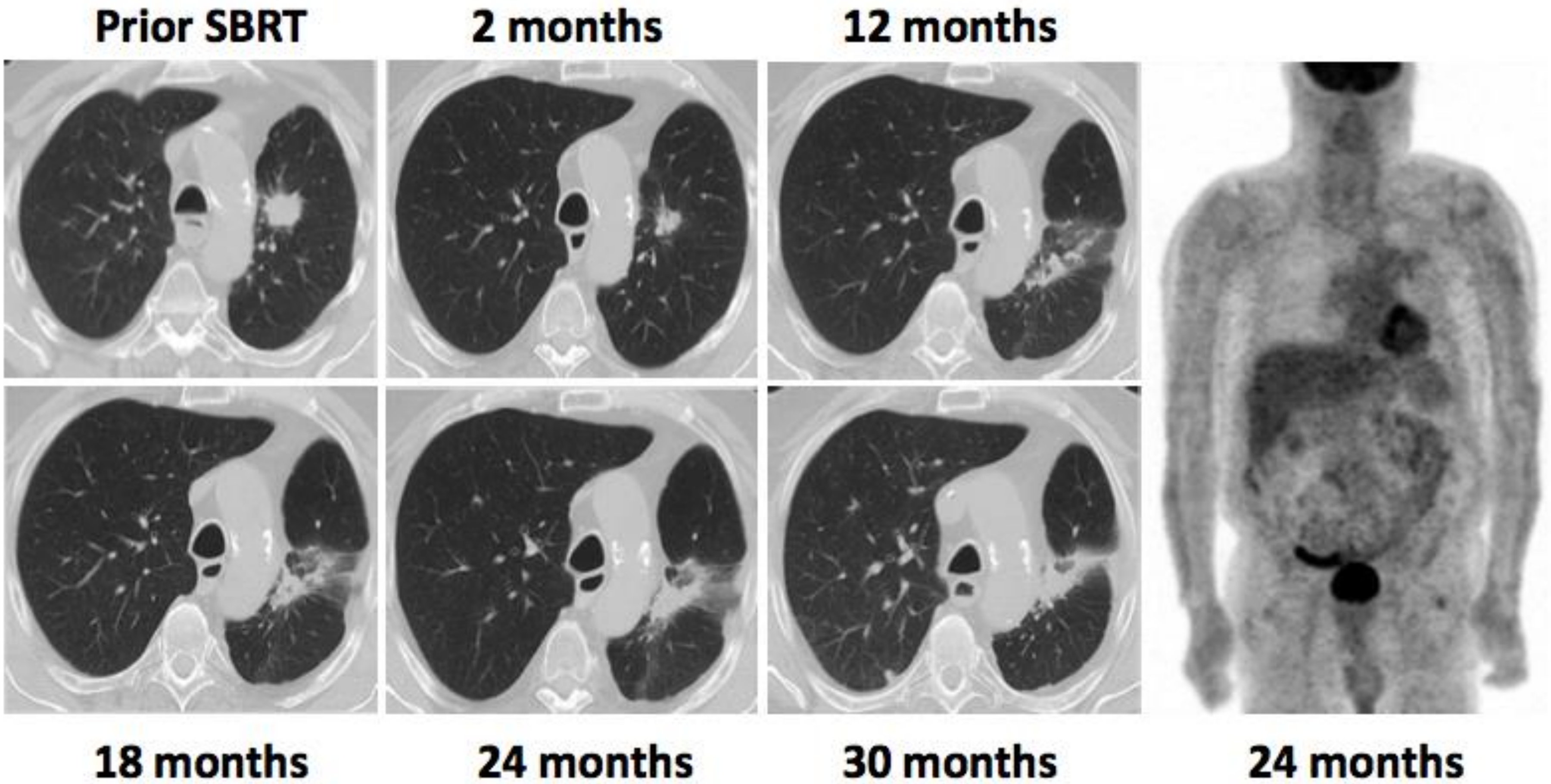
Follow-up imaging and response assessment



Normal tissue reaction vs. local failure?

Stereotactic Body radiation therapy (SBRT)

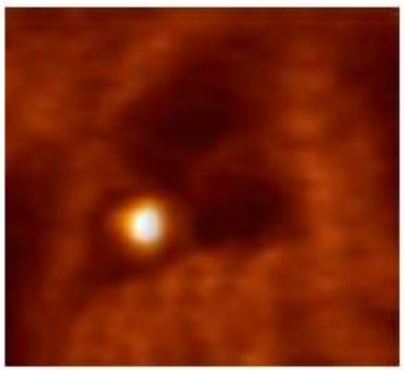
Combination of different high precision radiotherapy techniques

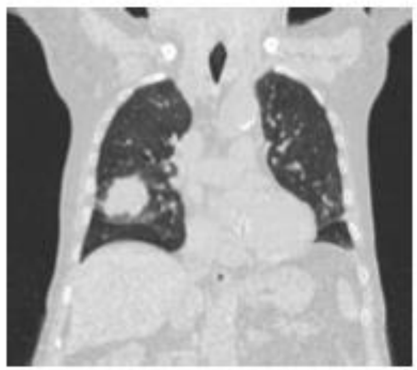
Staging LK Status

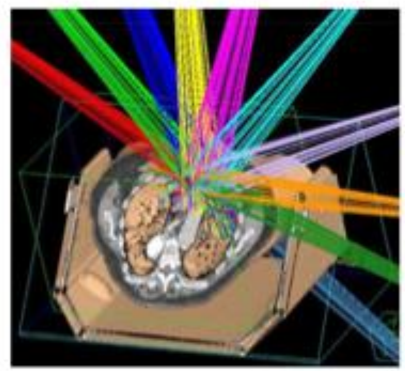
4D target volume definition

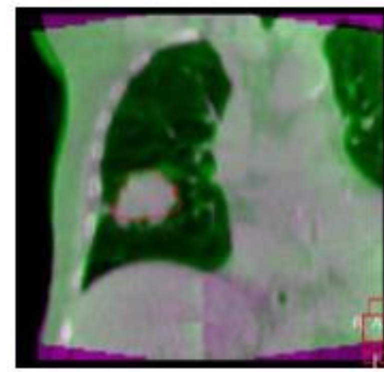
Highly conformal treatment planning

Image guided radiotherapy









Safe dose escalation to maximize local control

SBRT for early stage NSCLC

SBRT compared to conventionally fractionated RT

CF-RT

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

60%

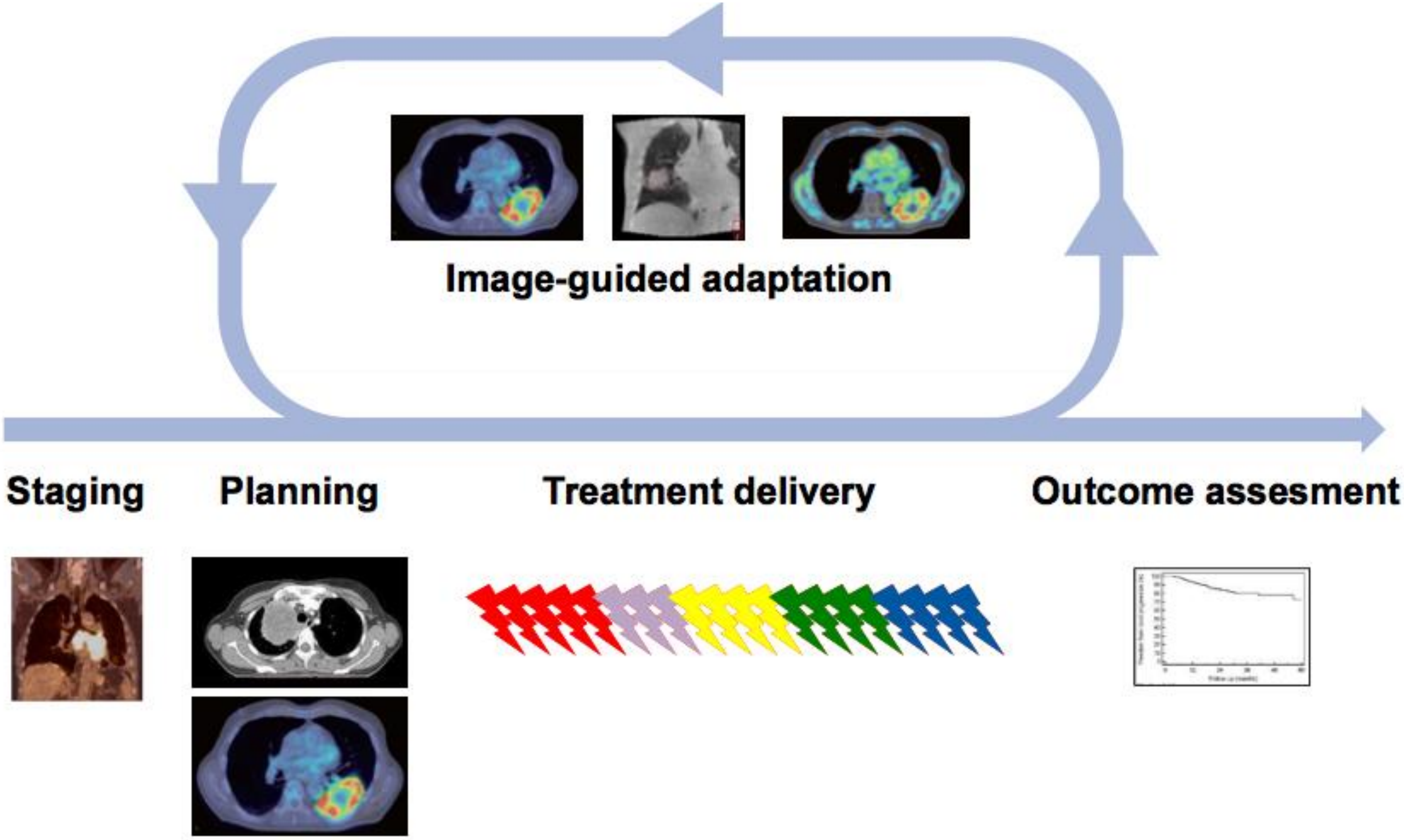
SBRT

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

90%

SBRT: Higher LC and higher OS

Imaging in the RT process for NSCLC



In-room image guidance: seeing the <u>tumour</u>

At Rigshospitalet

For all locally-advanced NSCLC patients

3D PET/CT with IV contrast

4D CT + short breath hold CT

- Contrast if central tumour

Visual review of the 4D CT (by a dosimetrist):

- if < 5mm peak-to-peak motion, plan on the PET/CT, where contouring is most reliable
- if > 5 mm peak-to-peak motion : MidVentilation

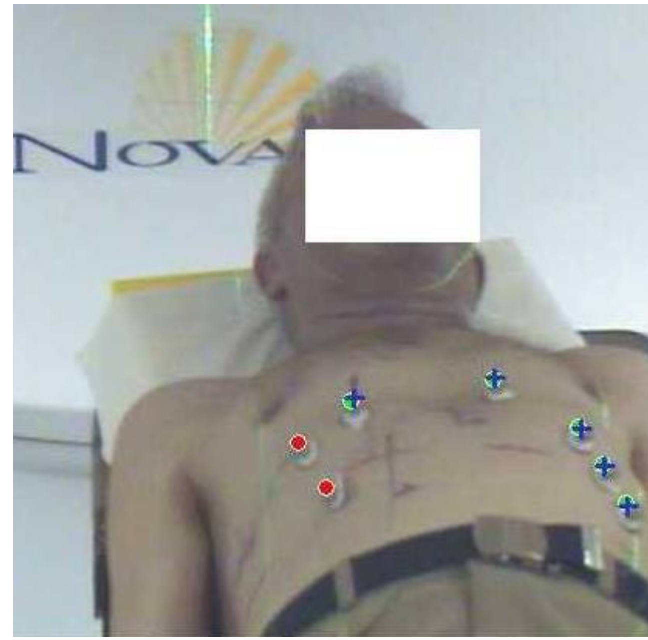
Occasional use of the ITV approach (e.g. if too many artifacts)

In-room image guidance

Modalities	Goals
➢ Field light ➢ EPID ➢ kV verification imaging ➢ In-room CT/CBCT	➢ **Inter-fraction imaging** ➢ Reproducibility of patient positioning ➢ Reproducibility of organ / target positioning ➢ Adaptive planning ➢ **Intra-fraction imaging** ➢ Catching intra-fraction baseline shifts

In-room image guidance

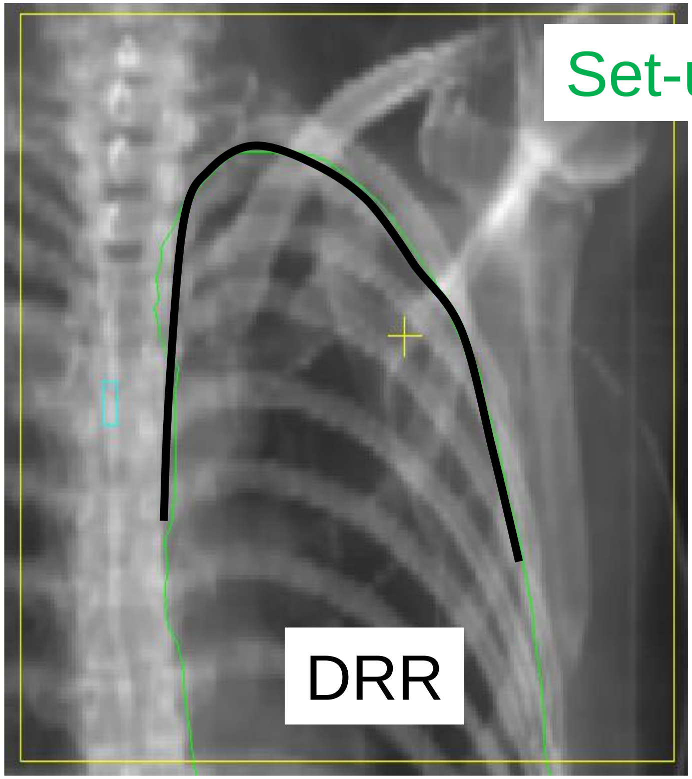
1. Field light / surface markers/surface matching

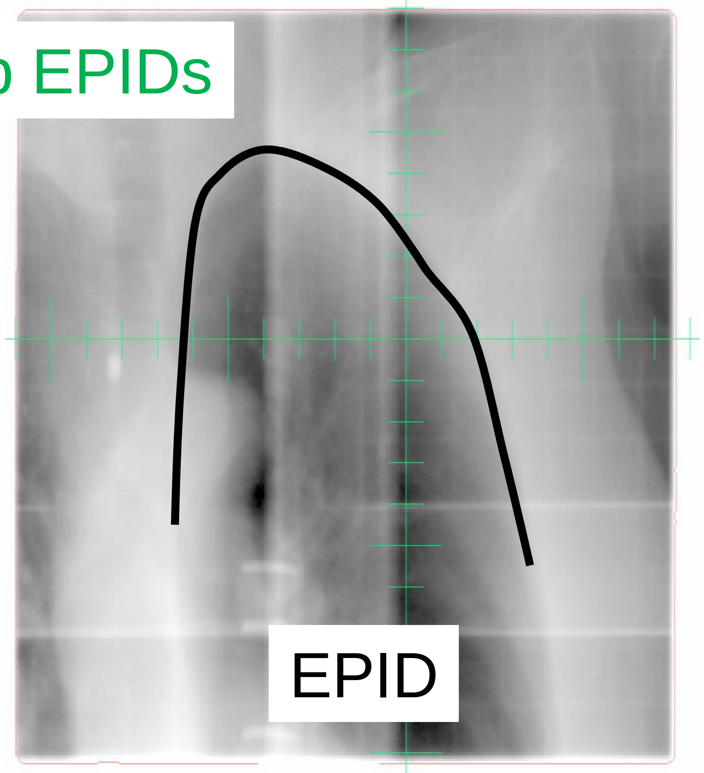


Verification that correct patient on the couch
Set-up verification of external target volumes (skin cancer…)

2. Electronic portal images (set up)

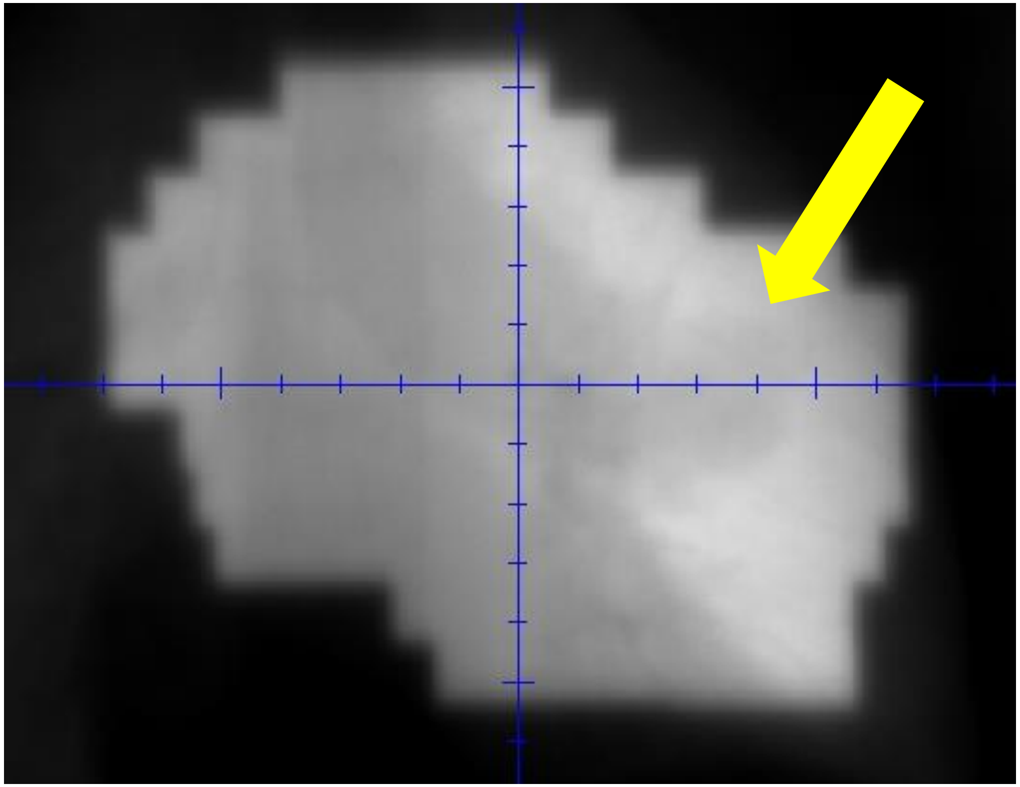
Set-up EPIDs





Pros: Large images with suitable anatomical landmark structures
Cons: Landmark structure might not be representative for target

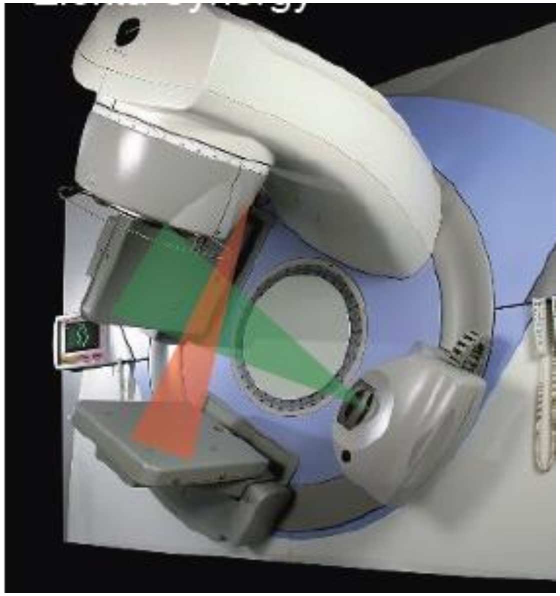
2. Electronic portal images (field or cine mode)



- "on flight" images
- NB: mostly if 3D- CRT planning

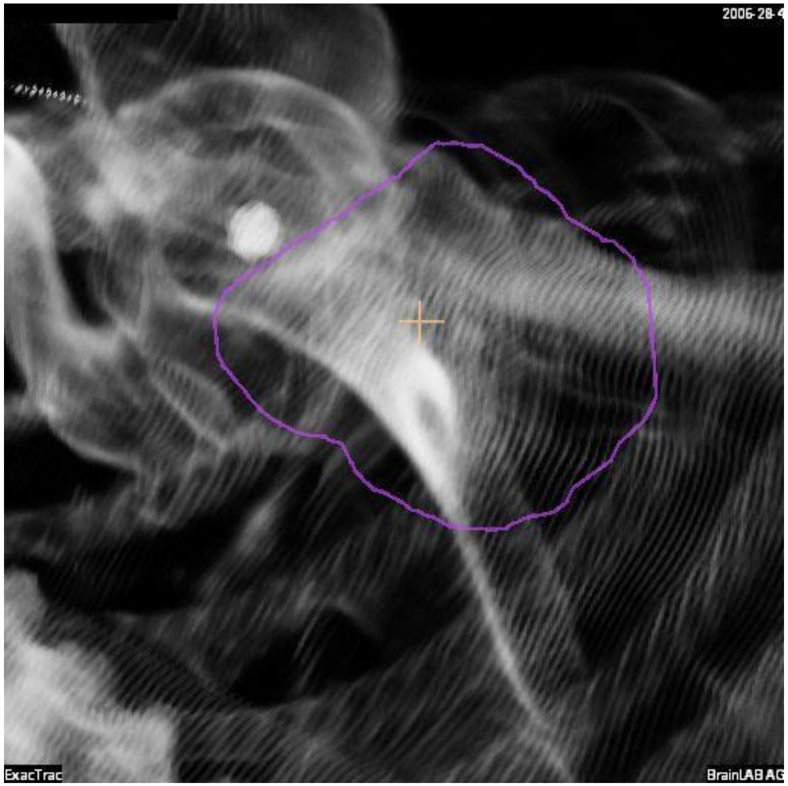
Pros:	No additional patient dose;
	Pulmonary tumor sometimes visible itself
Cons:	Difficult to interpret when only limited landmark structures in field

3. kV planar images



In-room image guidance

3. kV planar images



DRR image

kV image: better constrast than EPID... but still poor!

3. kV planar images

Markers required: poor soft-tissue contrast

•Surrogate, not the target itself

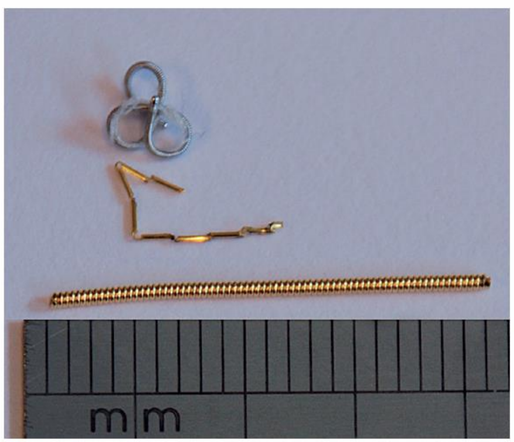


Figure 1. Photo showing the complex helical platinum marker (top), the Gold Anchor™ marker (middle) and the Visicoil™ gold marker (bottom).

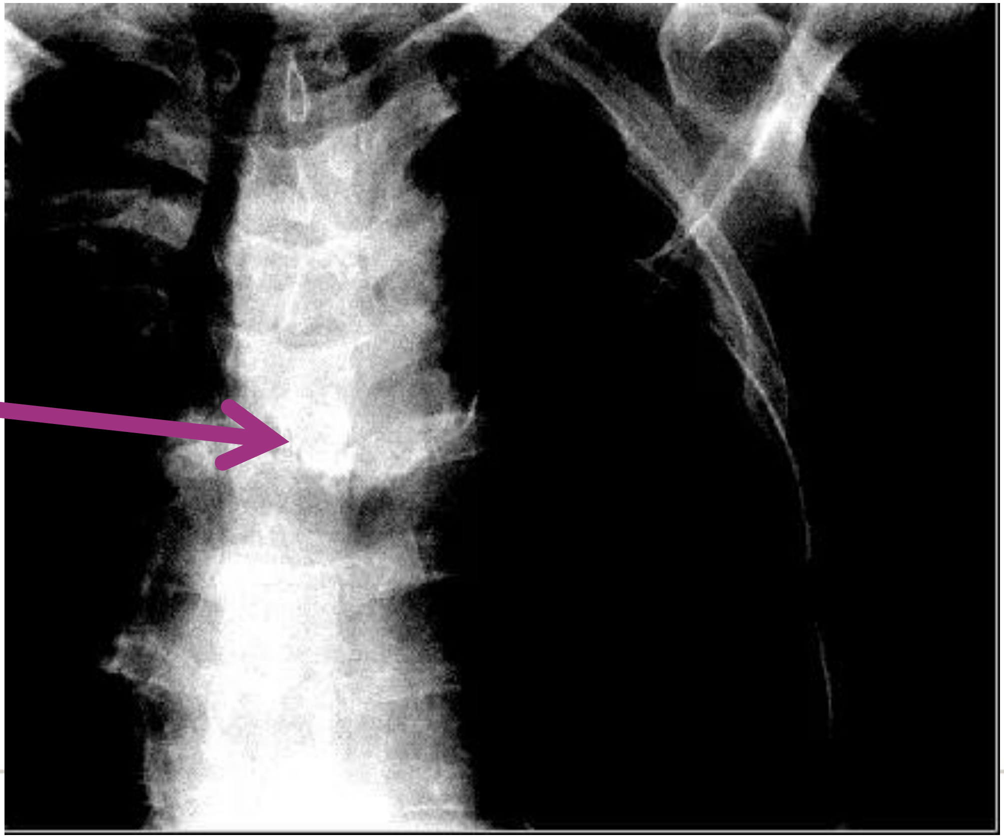
4 out of 15 patients developped pneumothorax (transthoracic implantation)

Persson et al Acta Oncol 2012

3. kV planar images

Markers required: poor soft-tissue contrast

•Surrogate, not the target itself



19 patients

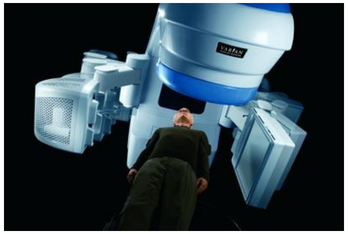
broncoscopic Bioxmark™

Can be implented in lymph nodes

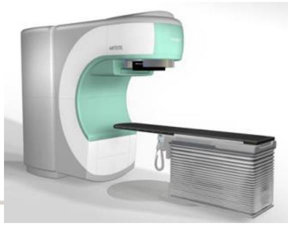
4. Volume imaging

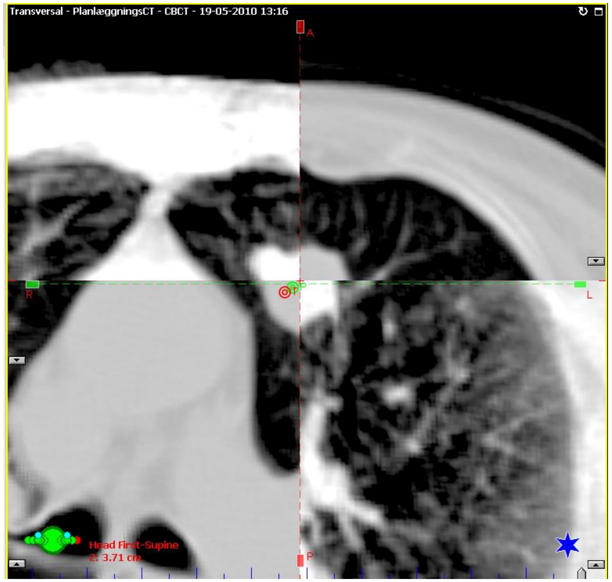
In-room CT

beam



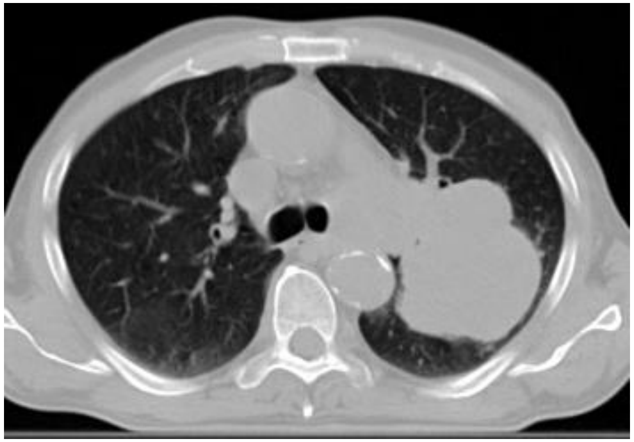
MV CT





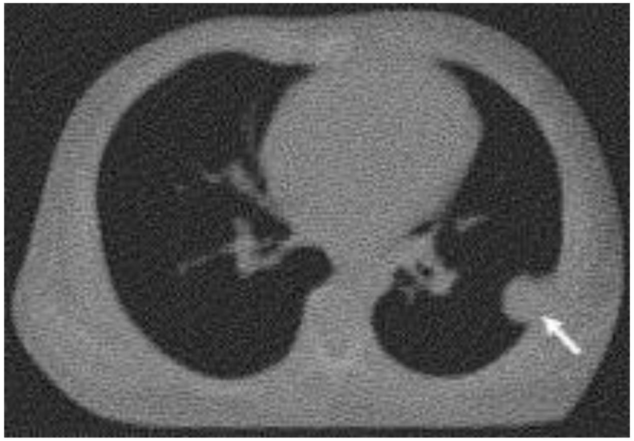
4. Volume imaging

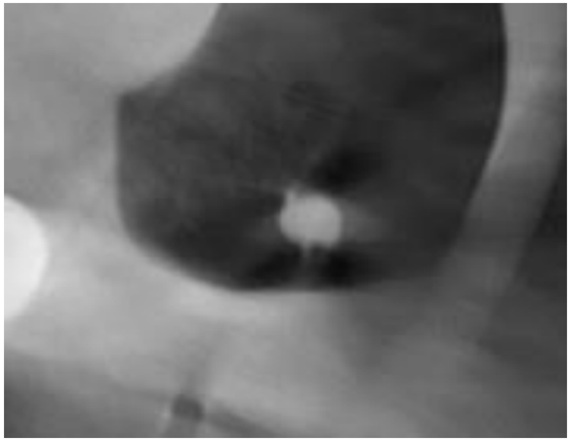
Helical



kV CBCT

MV CT





kV/MV CBCT

- Intra-pulmonary targets clearly visible in all imaging modalities
- IQ for mediastinum suitable only in kV helical CT

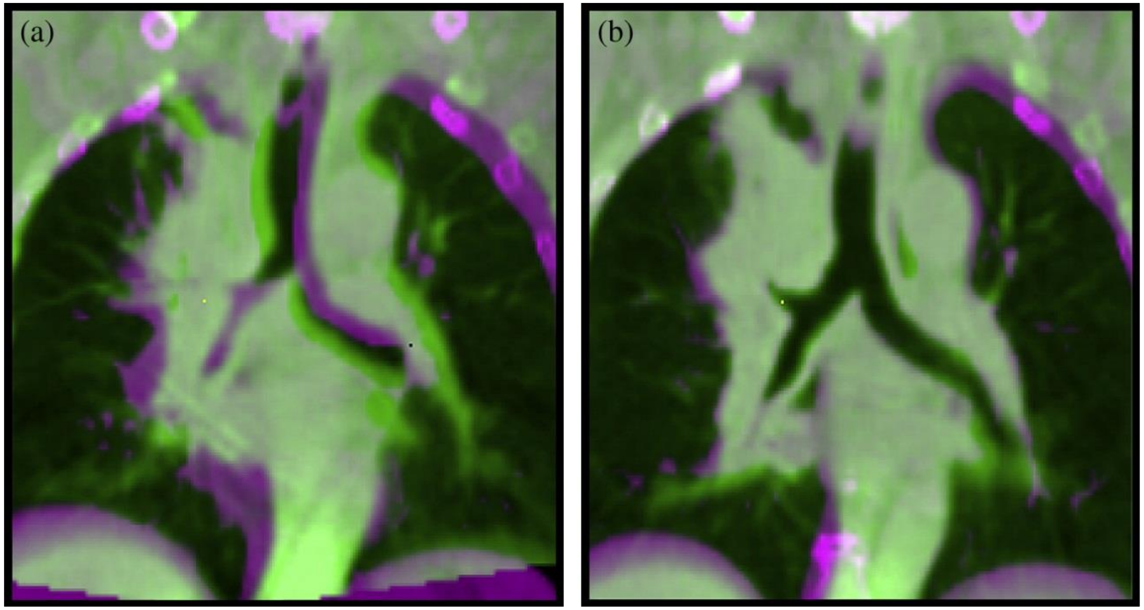
A side note: setting up according to landmarks

Spine vs Carina

Higgins et al (IJROBP 2009): feasible, better inter-observer agreement with match on the carina

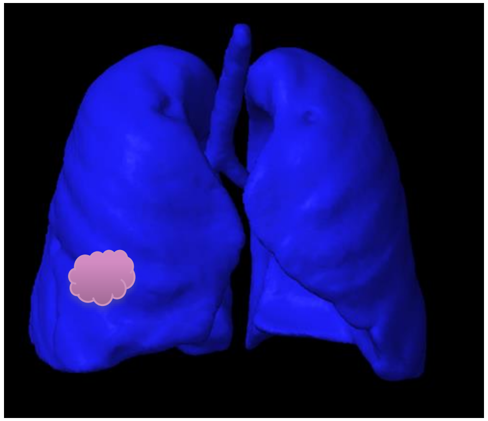
Lavoie et al (IJROBP 2012): especially node coverage is improved

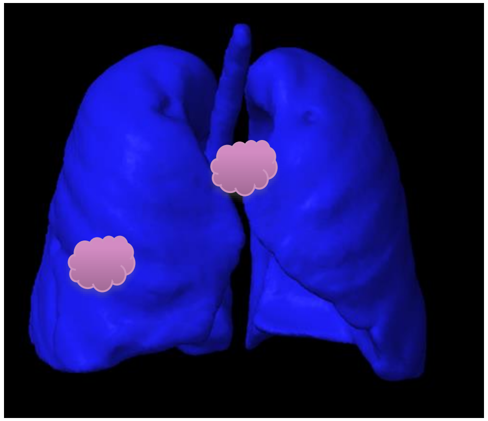
Schaake et al (IJROBP 2014): reduced LN margins if match on carina instead of bones



Spine match   Carina match

Registration strategy at Rigshospitalet





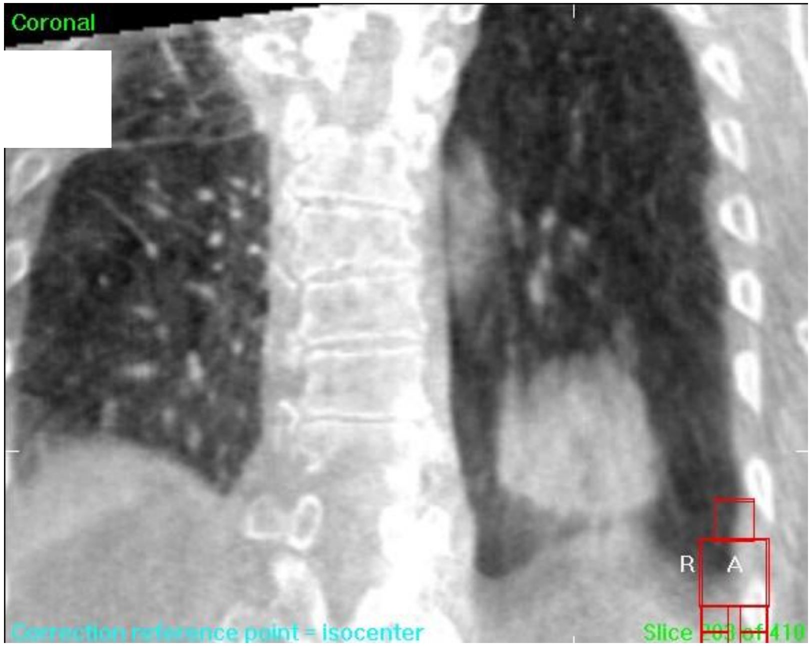
LR

Registration on tumour
Verify OAR/bone

Registration on carina
Larger margins on peripheral tumour

Josipovic et al R&O 2016

4. Volume imaging



Lower lobe tumor with large motion amplitude

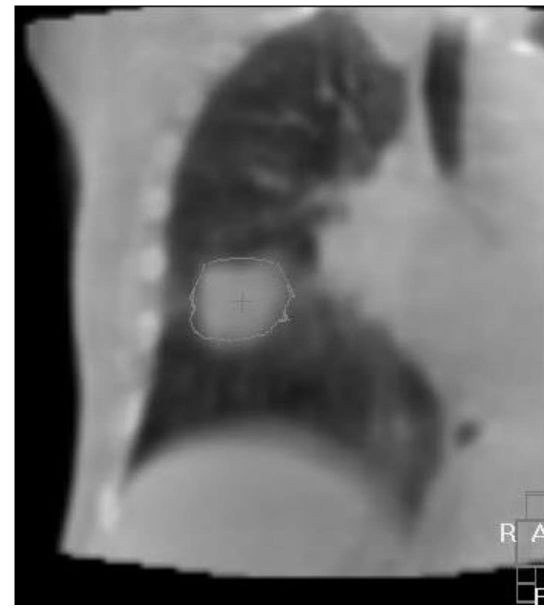
Blurred target because of long image acquisition time

Integration of 4th dimension into IGRT

Planning

Treatment

Manual contour registration



Respiration correlated CT

„Conventional“ slow CBCT

NB: what you see is a pseudo ITV/midventilation

Guckenberger Acta Ocol 2006

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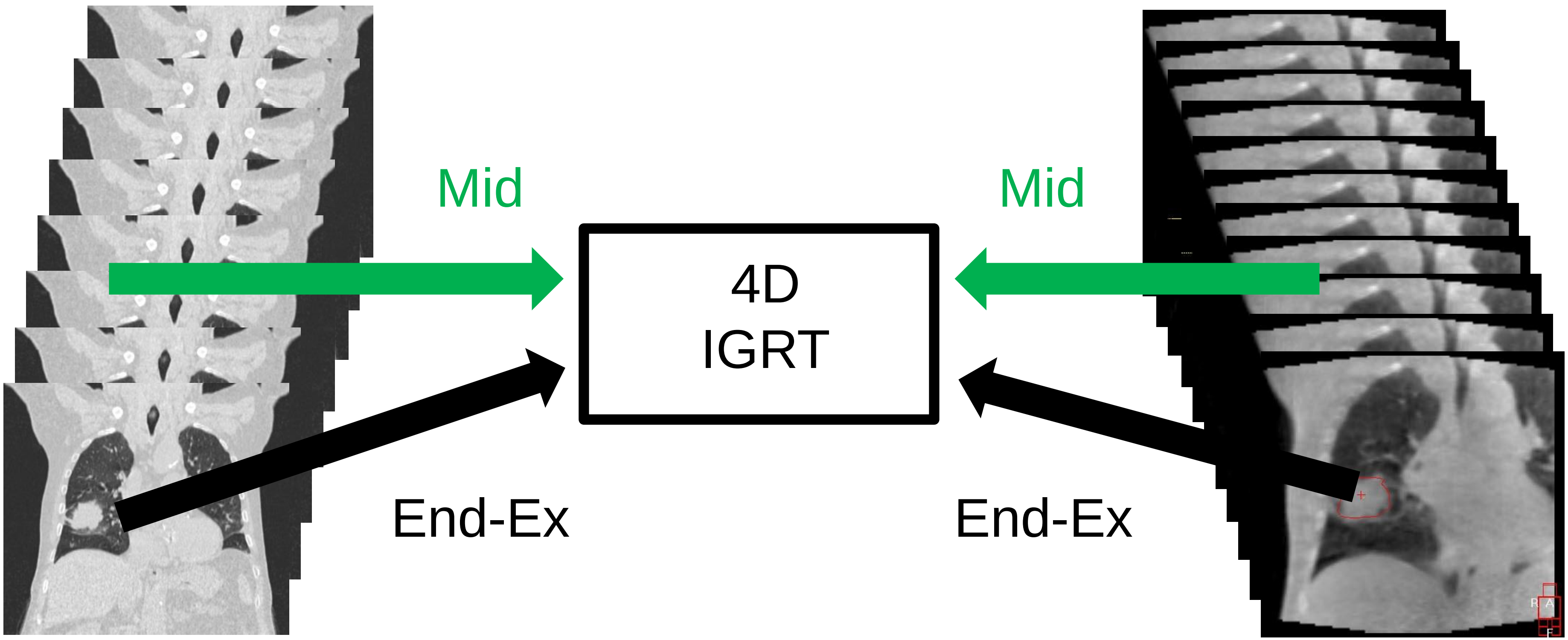
In-room image guidance for highly mobile tumours

Treatment planning:
Reference Image

Treatment delivery:
Verification Image



Possibility of matching a specific phase

Interobserver variability reduced (Sweeney at al RO 2012)

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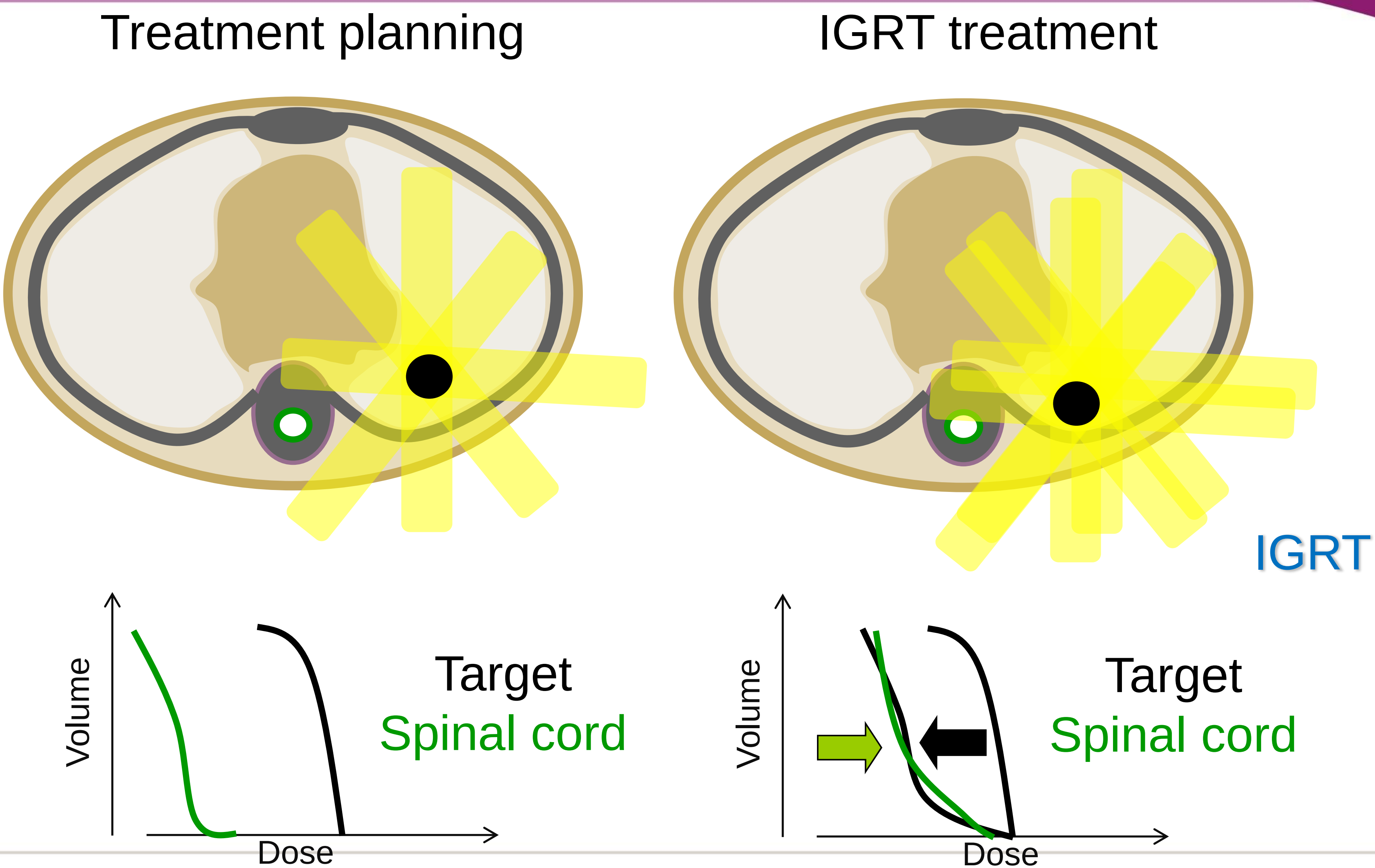
Alternatives

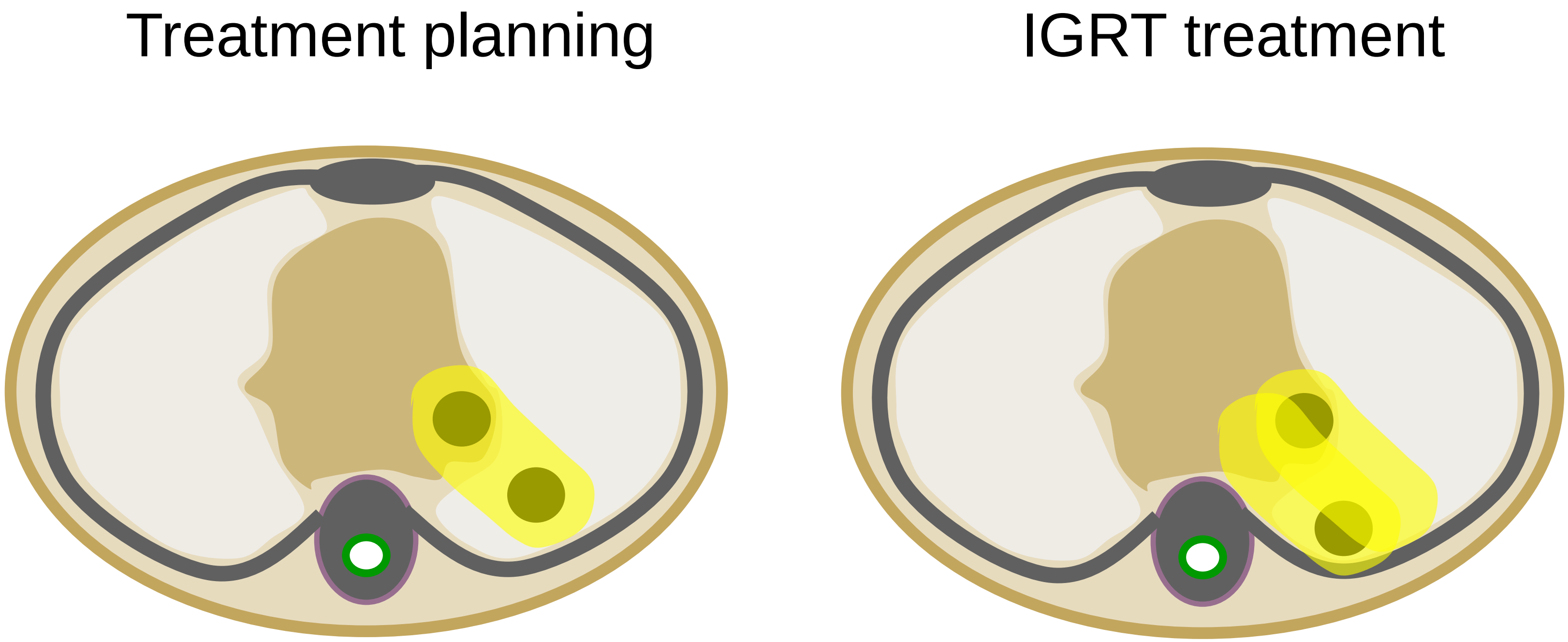
- **3D CBCT and larger margins (larger interobserver variation)**

- **If small, highly mobile tumours (e.g. SBRT):**
  - **Bony landmarks (large margins)**
  - **DIBH CBCT and treatment**
  - **Wait ???**

Challenge 1: baseline shifts



Challenge 1: baseline shifts



Shift of the primary relative to the nodal target

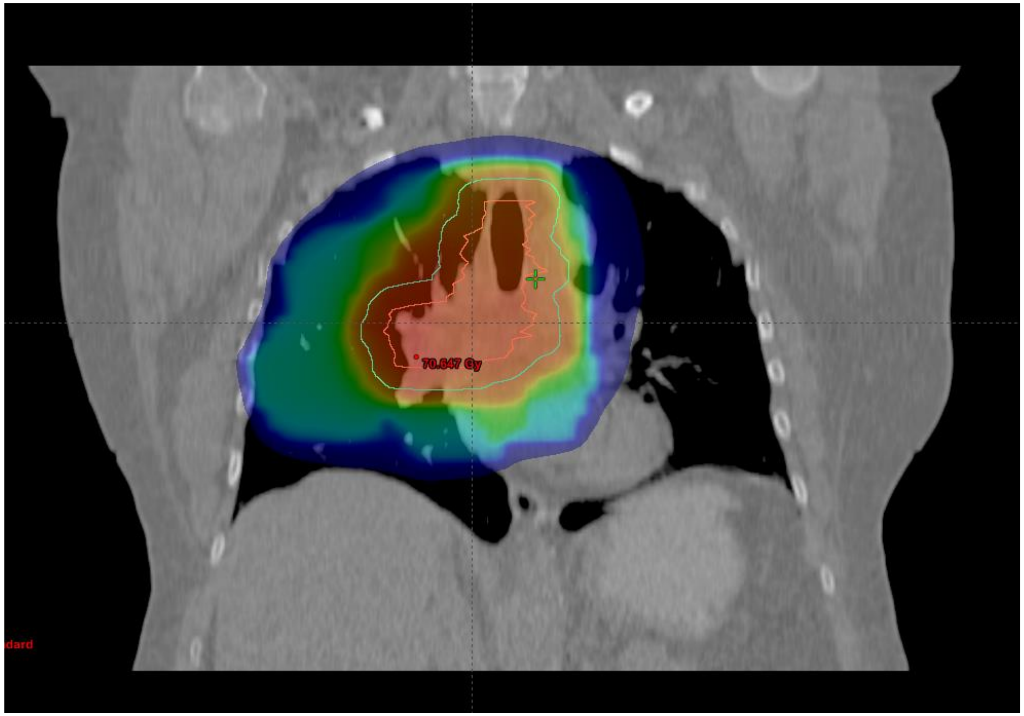
- Volume imaging is required for visualization of the these effects
- Shifting the patient does not solve the problem

JJ’s paper about differential motion

Challenge 1: baseline shifts, possible solutions

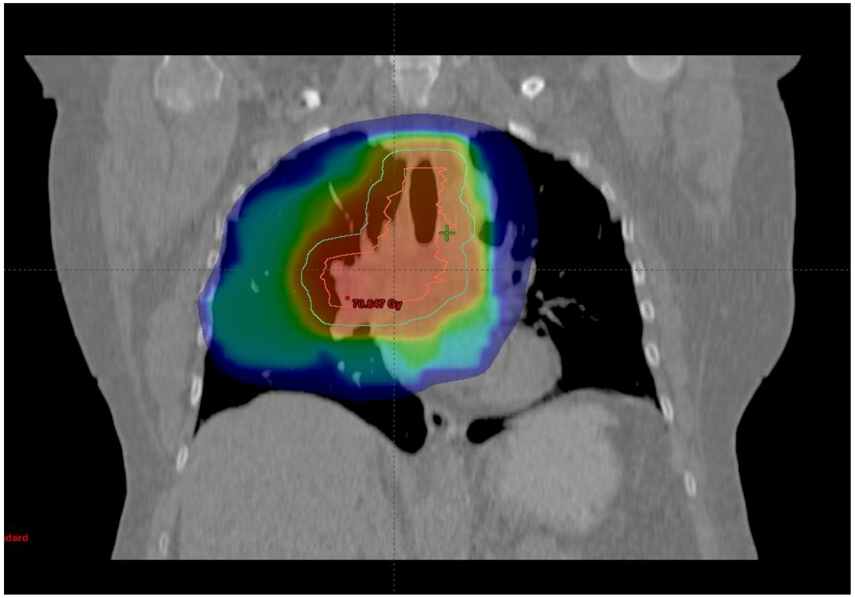
1. Volume image required to visualization
2. Quantification would require deformable image registration
   -> available but only offline
3. Online dosimetric evaluation would be required for a decision making process
   -> not available, yet
4. Compensation strategies:
   - Perform an average IGRT shift
   - Adapted PTV margins
   - Re-planning

Challenge 2: large tumours / small lung volume

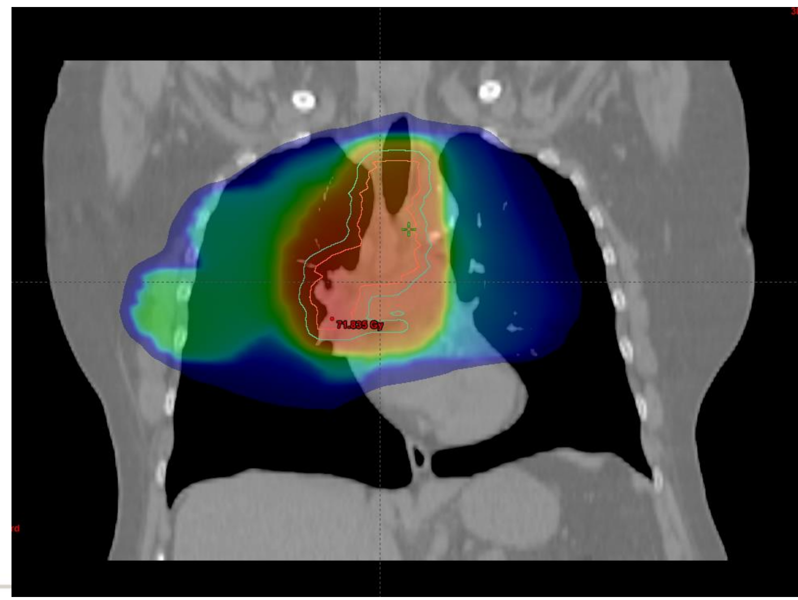


- 70-year old patient with poor pulmonary function
- Tumour motion < 5mm
- MLD unacceptable if a curative dose (66Gy) is delivered
- Gating won't help (neither will tracking!)

Challenge 2: large tumours / small lung volume



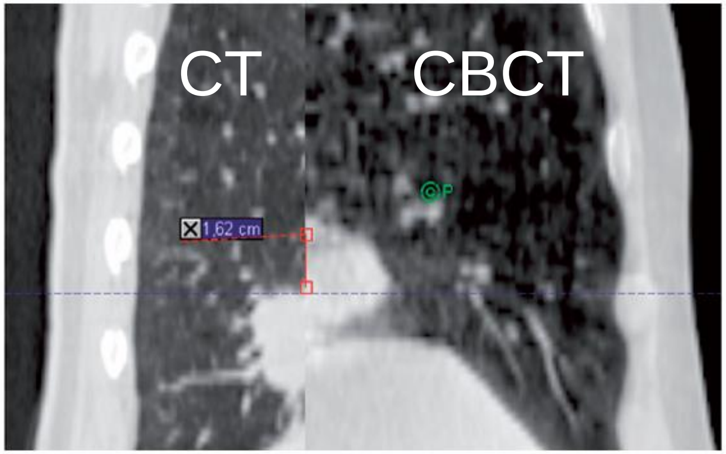
Free breathing
(MLD 23.6Gy)



Deep inspiration
(MLD 19.7 Gy)

As part of INHALE,
phase II protocol

Some caveats of breath hold



Josipovic et al Acta Oncol 2014

2nd patient treated in DIBH

•peripheral target + mediastinal lymph nodes

•10th fraction: match on mediastinum, 1.6 cm shift CC direction for peripheral tumour

Don’t (blindly) trust external surrogates:
markers, spirometry, surface based etc…
<u>Daily breath hold CBCT is mandatory</u>
<u>Intra fraction monitoring highly desirable</u>

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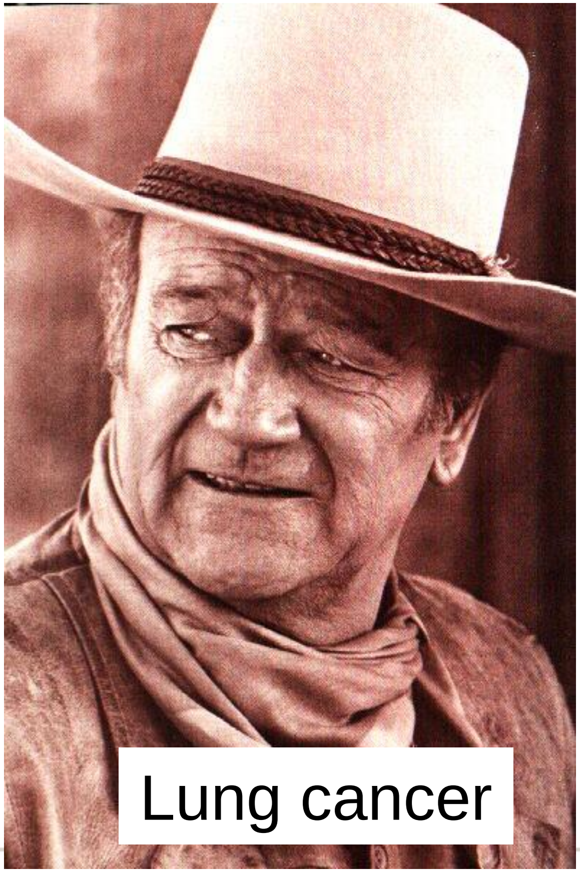
Compliance ? Pulmonary function ?



Take-home messages for treatment verification in current clinical practice

- The most important is to see the tumour
  - ➢ in a representative position
- 2D imaging modalities (markers)
- 3D imaging modalities
  - \+ Volume imaging
  - \- No real-time imaging
- 4D imaging modalities
  - \+ fewer breathing motion artifacts
  - \- Actual benefit?

No single solution will be appropriate for every patient

Keep breathing ☺

Quiet free breathing

Breath hold

Image guided radiotherapy in breast and lung

Marianne Aznar

Andrew Hope

Thanks to Matthias Guckenberger!

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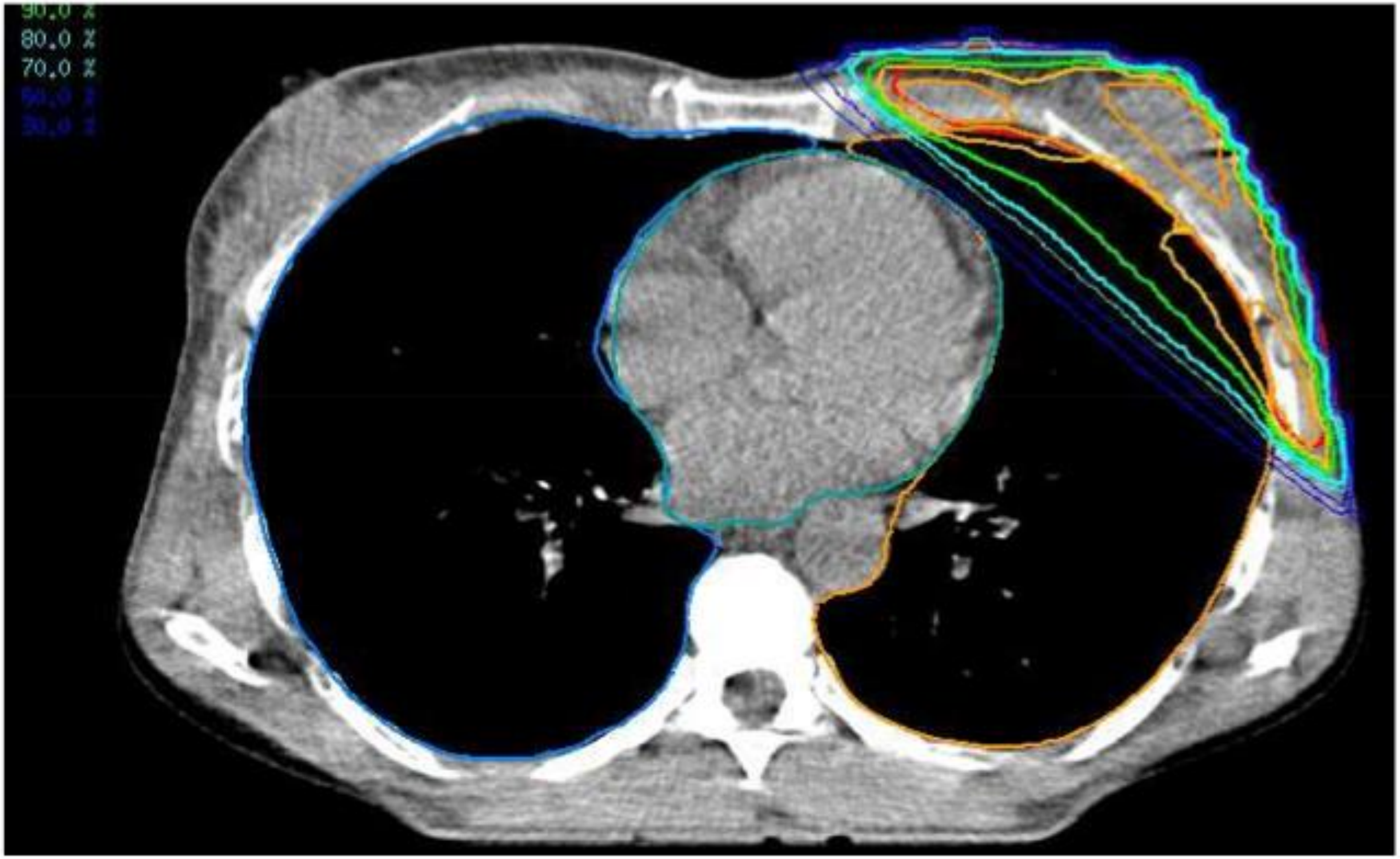
Breast Cancer



Radiotherapy in breast cancer

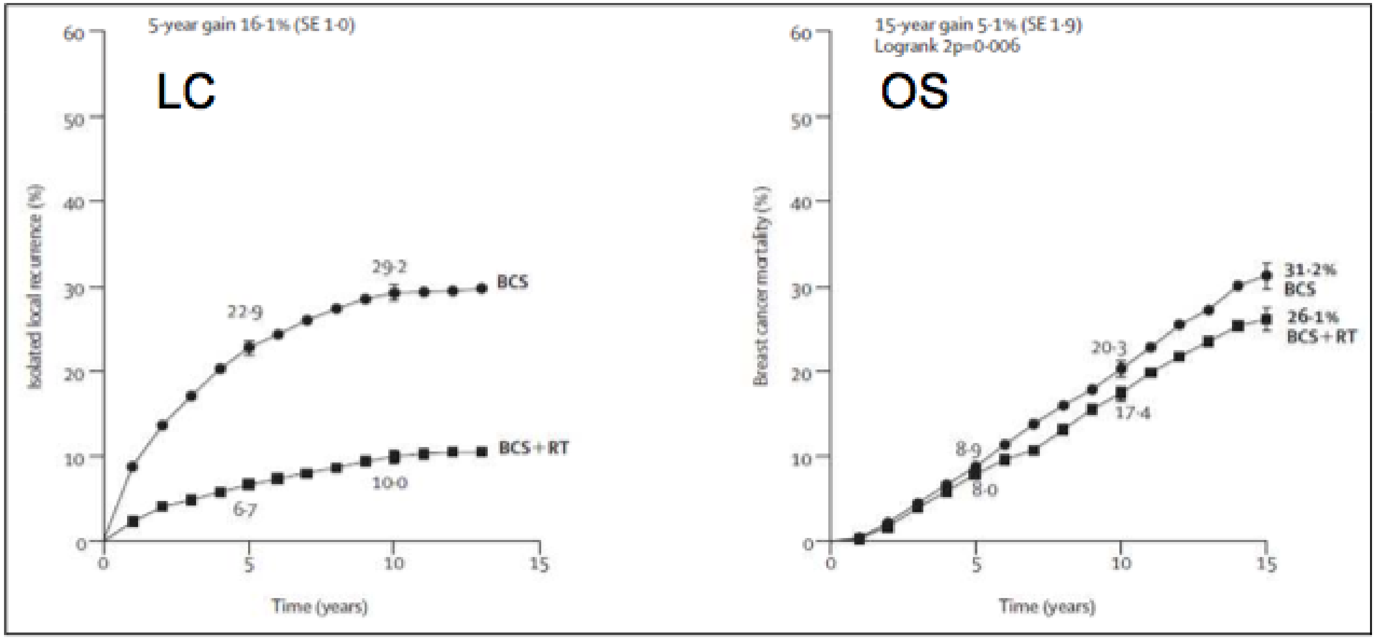
Irradiation increases overall survival after breast conserving surgery and mastectomy

EBCTCG Lancet 2005

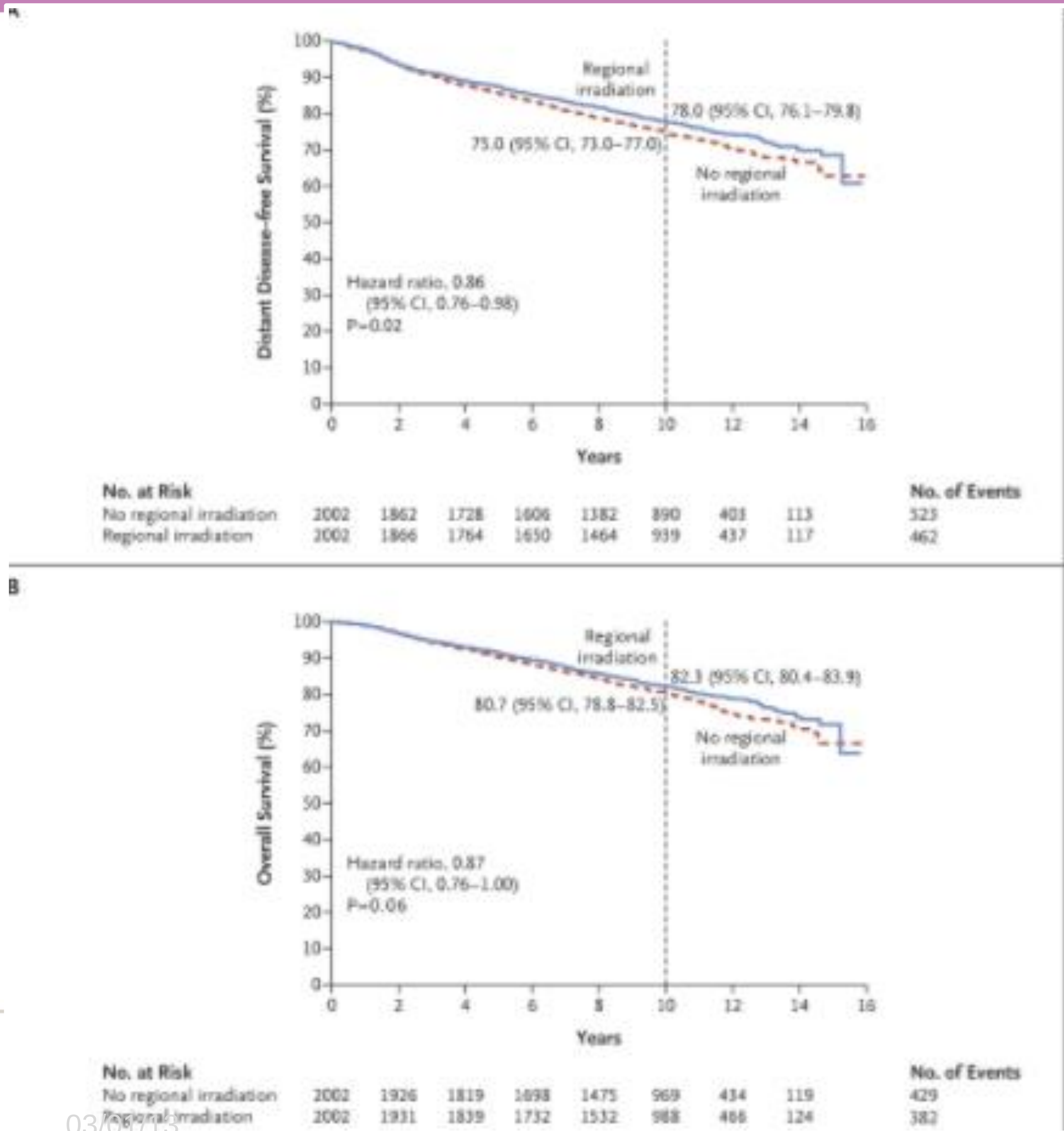
Excellent or good cosmesis achieved in 80% of the patients

Taylor 1995 IJROBP

Breast conserving surgery
pN0



Radiotherapy in breast cancer



Survival benefit of internal mammary chain irradiation

Radiotherapy in breast cancer: Heart Toxicity

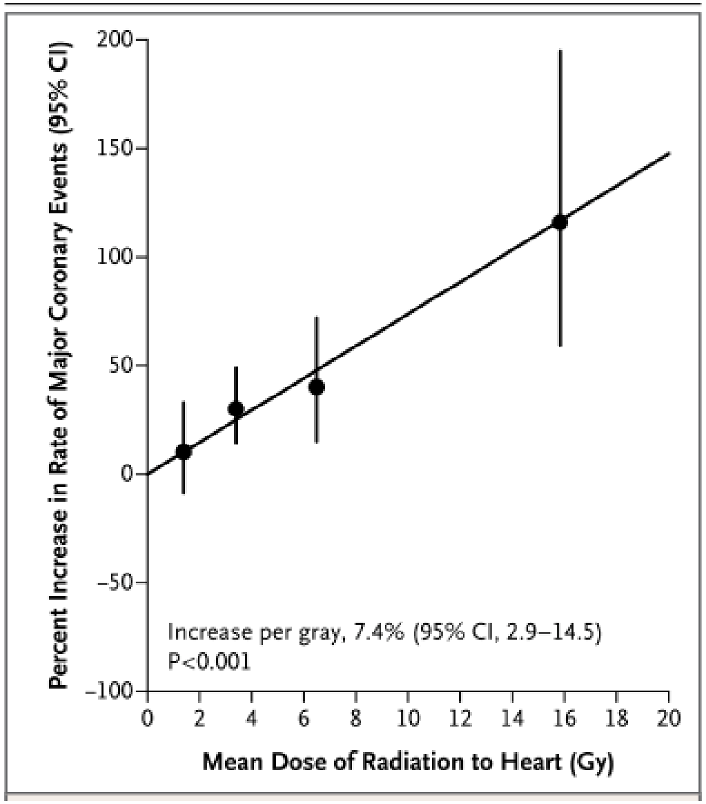
- Latency of 15-20 years
- Myocardial scintigraphy can detect perfusion changes as early as 6 mo

- Target structures:
  - Myocardium (e.g. left ventricle)
  - Vessels (e.g. left anterior descending coronary artery)

- Toxicity
  - Myocardial infarction
  - Angina
  - CHF
  - Valvular disorders
  - Electrical conductivity alterations

- Dose threshold??

Breast cancer data



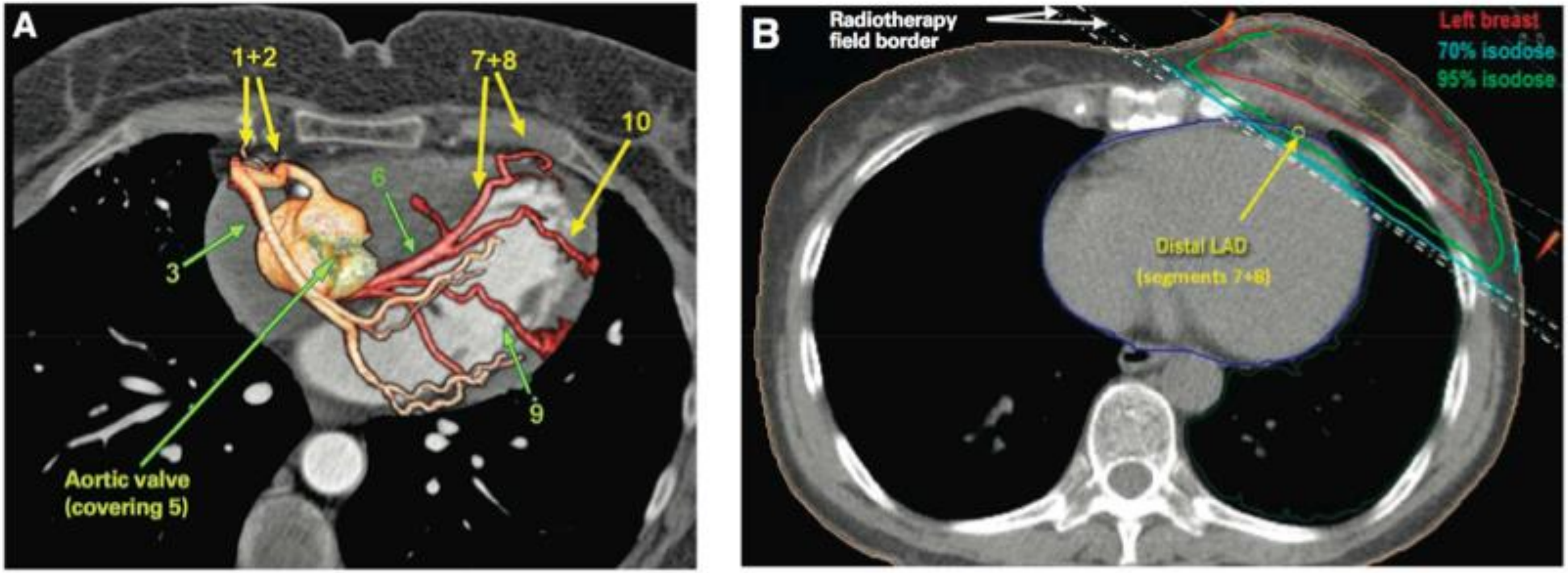
Darby et al NEJM 2013

"major coronary event"

linear risk, no threshold

5y after RT

Radiotherapy in breast cancer: Heart Toxicity



left **a**nterior **d**escending artery

Nillson JCO 2012

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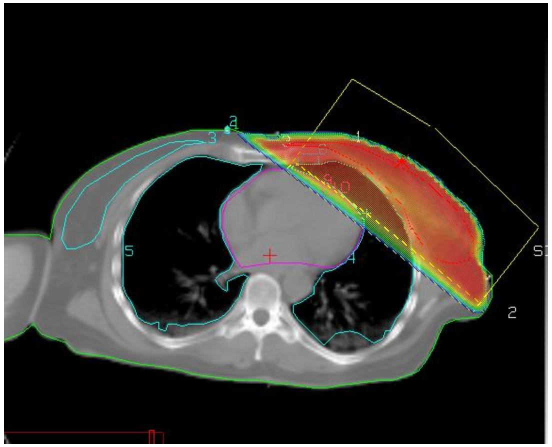
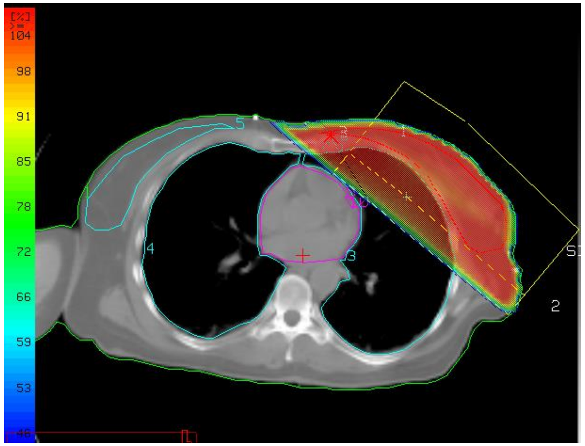
New trends in breast cancer RT

- More IMC irradiation: more interest in DIBH

FB



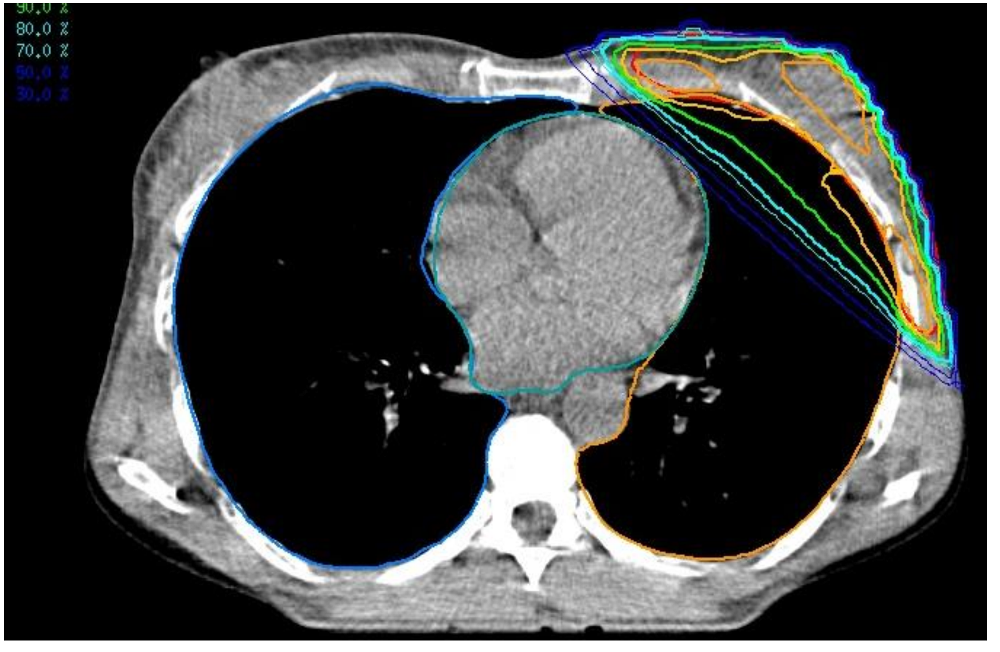
DIBH



- More complex, modulated techniques (e.g. integrated boost)

Image guidance

- Which modality?
- How often?
- whole breast vs partial/boost
- Image guidance for respiratory gating /inspiration breath hold



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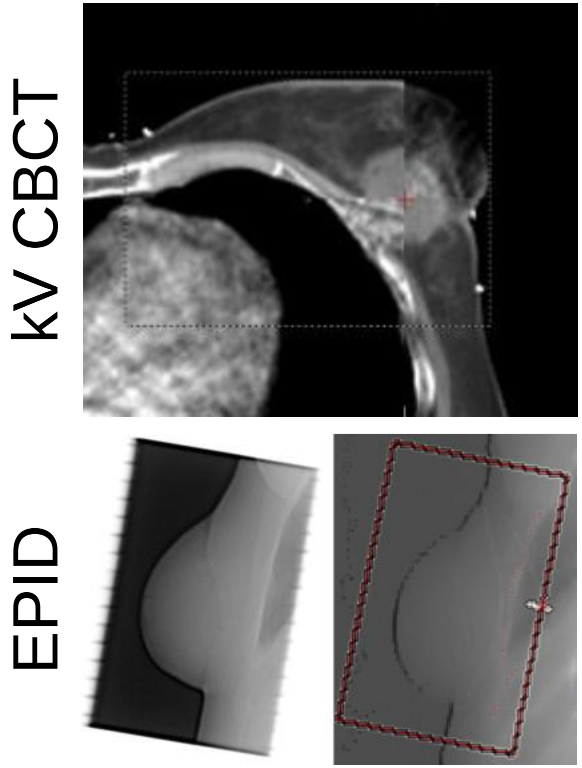
WHOLE BREAST (+/- LN)

Image-guidance for whole breast (+/- nodes)

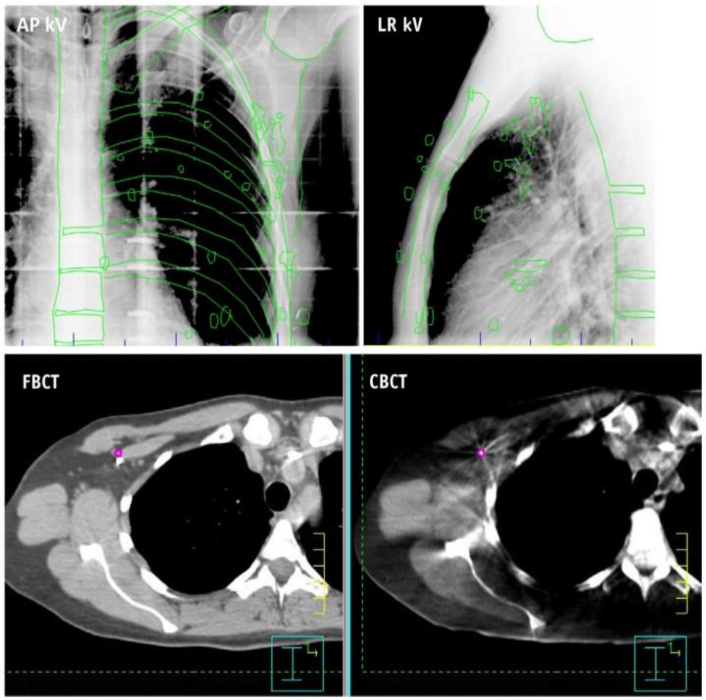


Topolnjak IJROBP 2010

- EPID field images (i.e. not orthgonal) underestimate bony set-up errors by 20% to 50%
- Difference probably insignificant for tangential whole breast irradiation
- Loco-regional treatment or more advanced techniques (SIB? IMRT?) could benefit from a more accurate set up.

Image-guidance for whole breast (+/- nodes)

- Highly conformal /complex techniques



Feng et al IJROBP 2014

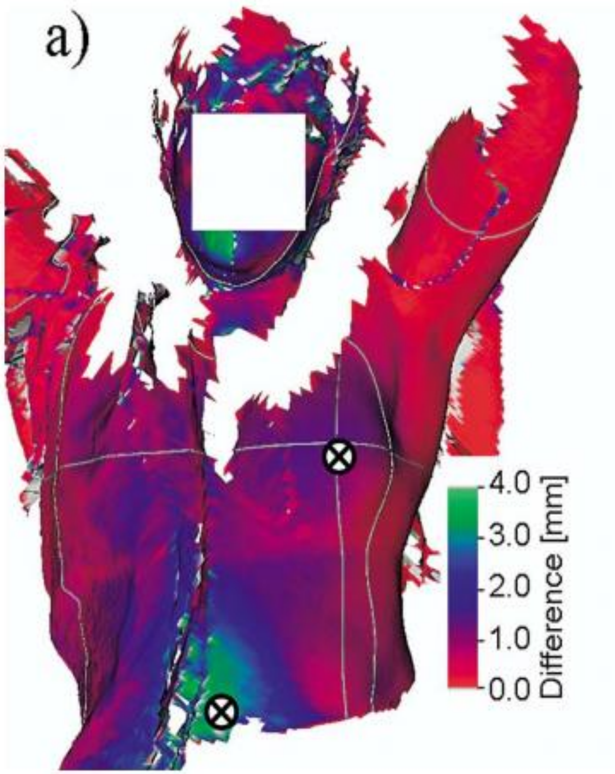
Even with daily kV, the remaining set up error justifies a considerable margin (8mm SI)

(compared to CBCT, registered on clips)

Image-guidance for whole breast (+/- nodes)

- Target with "high deformability"
- Number of cameras ???

Bert et al (2 cameras)

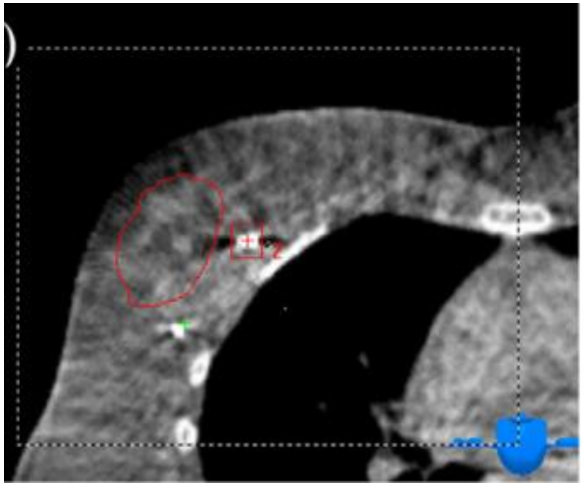


- Difficult to distinguish between set-up error and anatomical changes (or breathing)

- Combination with x-ray IGRT still recommended (Betgen RO 2013)

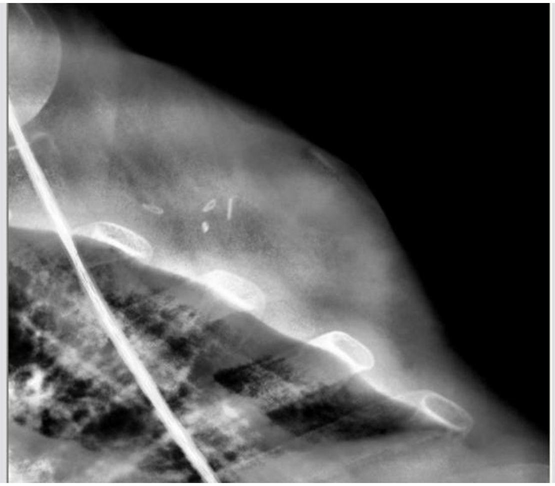
PARTIAL BREAST / BOOST

Image-guidance in partial breast irradiation: implanted markers

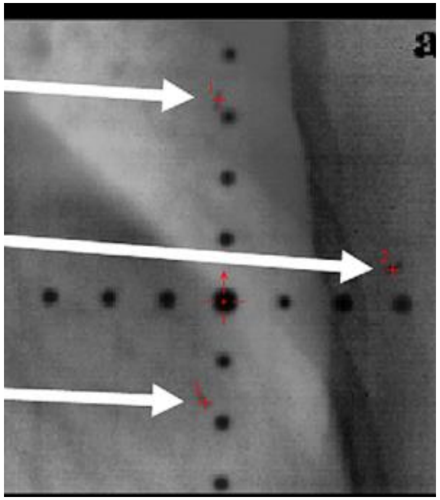


CBCT: match on soft tissue/clips

Topolnjak 2011



2D kV images: match on clips



MV images: match on clips

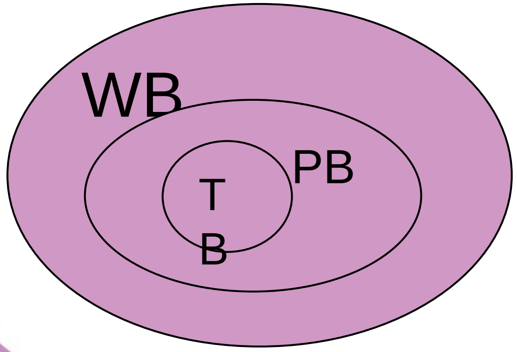
Leonard 2010

Partial breast /integrated boost

A multicentre observational study evaluating image-guided radiotherapy for more accurate partial-breast intensity-modulated radiotherapy: comparison with standard imaging technique

Emma J Harris,[1†] Mukesh Mukesh,[2†] Rajesh Jena,[2] Angela Baker,[3] Harry Bartelink,[4] Corrinne Brooks,[1] June Dean,[2] Ellen M Donovan,[1] Sandra Collette,[5] Sally Eagle,[6] John D Fenwick,[7] Peter H Graham,[8] Jo S Haviland,[9] Anna M Kirby,[10] Helen Mayles,[3] Robert A Mitchell,[1] Rosalind Perry,[11] Philip Poortmans,[12] Andrew Poynter,[13] Glyn Shentall,[14] Jenny Titley,[9] Alistair Thompson,[15] John R Yarnold,[10] Charlotte E Coles[2‡] and Philip M Evans[1,16*‡] on behalf of the IMPORT Trials Management Group

[1]Joint Department of Physics at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, London, UK
[2]Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[3]Department of Radiotherapy and Physics, The Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, UK
[4]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Statistics Department, EORTC Headquarters, Brussels, Belgium
[6]Department of Radiotherapy, Royal Marsden Hospital NHS Foundation Trust, London, UK
[7]Department of Oncology, University of Oxford, Oxford, UK
[8]Cancer Care Centre, St George Hospital, Kogarah, Sydney, NSW, Australia
[9]ICR-CTSU, Institute of Cancer Research, London, UK
[10]Breast Unit, Royal Marsden NHS Foundation Trust, London, UK
[11]Radiotherapy Department, Ipswich Hospitals NHS Trust, Ipswich, UK
[12]Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg, the Netherlands
[13]Radiotherapy Department, Peterborough City Hospital, Peterborough, UK
[14]Rosemere Cancer Centre, Lancashire Teaching Hospitals NHS Trust, Preston, UK
[15]School of Medicine, University of Dundee, Dundee, UK
[16]Centre for Vision, Speech and Signal Processing, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK



Comparing bone registration to clips-based reg

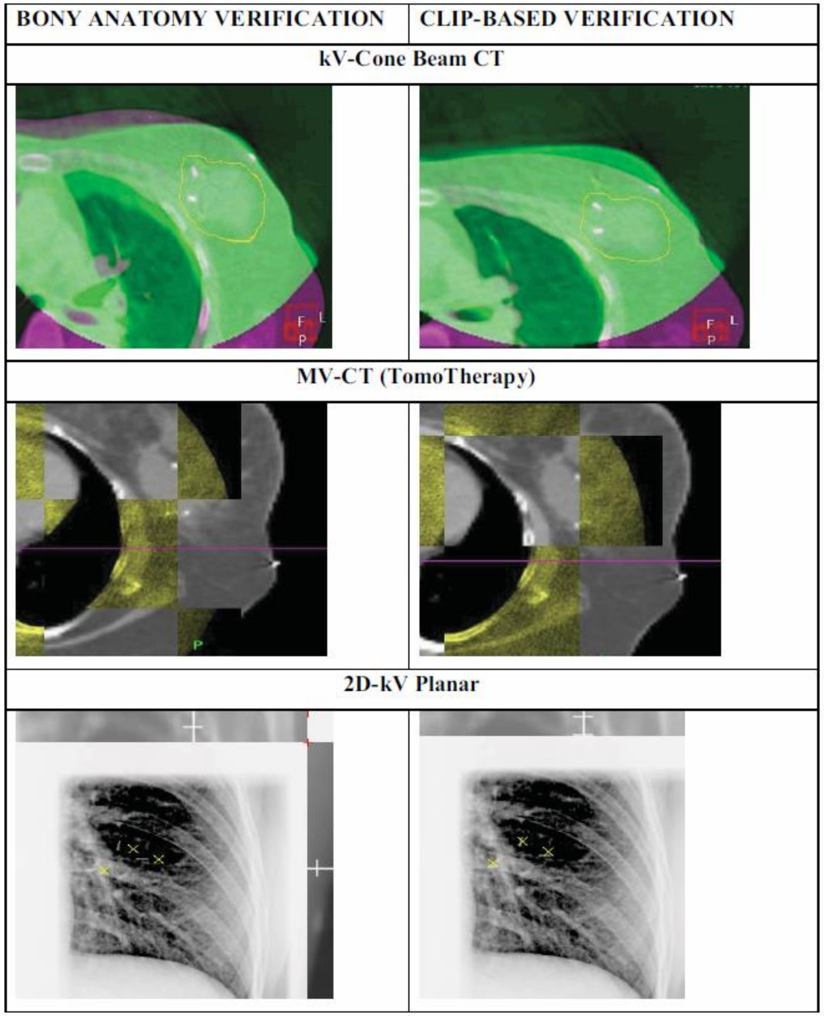


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TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

	Delta error (S_{DIFF}), mean absolute delta [cm (range)]				Time, median [seconds (range)]	
Centre	LR	SI	AP	3D vector	T_{BA}	T_{clips}
All	0.20 (0–1.7)	0.26 (0–3.2)	0.21 (0–2.0)	0.32 (0–10.2)	73 (8–240)	66 (8–178)
A (kV-CBCT)	0.19 (0–0.7)	0.24 (0–3.2)	0.22 (0–1.7)	0.28 (0–10.2)	26 (8–51)	92 (11–177)
B (MV-CT)	0.14 (0–0.7)	0.12 (0–1.2)	0.18 (0–1.3)	0.17 (0–2.0)	102 (70–230)	110 (25–178)
C (2D-kVPI)	0.23 (0–1.7)	0.29 (0–2.4)	0.20 (0–2.0)	0.38 (0–6.29)	22 (20–76)	16 (8–52)
D (2D-kVPI)	0.21 (0–1.3)	0.32 (0–1.3)	0.21 (0–1.0)	0.35 (0–2.2)	79 (60–154)	28 (20–85)
E (2D-kVPI)	0.20 (0–1.5)	0.31 (0–1.4)	0.23 (0–1.0)	0.36 (0–3.3)	110 (28–240)	34 (16–120)

Difference between bone reg and clips reg: 2-3 mm

Reduction in PTV (tumourbed) from 8 to 5 mm with clips-based IGRT, daily or with eNAL

Modest dosimetric impact

TABLE 8 Delta errors (difference between bony anatomy and clips, S_{DIFF}) in the LR, SI and AP directions and the magnitude of their 3D vector. Time required for image matching with both techniques has also been summarised

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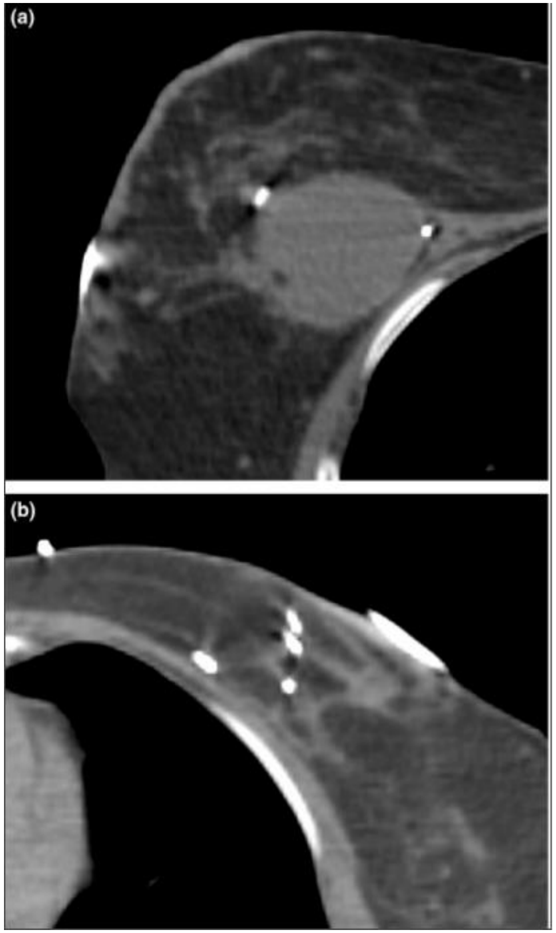
Time varies per institution, even when using the same technique
2D kV scores both as fastest and slowest !
Inter and intra- observer error < 1.4mm for all modalities

Note of caution using clips for registration

- seroma



Lewis et al J Med Rad Sci 2015

GATING /BREATH HOLD

Image guidance for deep inspiration: DIBH/gating monitoring

- Voluntary breath is hold is as efficient and more comfortable

Bartlett 2013

- The ”no equipment” solution:
  - ➢ short hyperventilation follwed by breath hold
  - ➢ Monitoring is visual (draw the light field on the patient, observed through control room monitors)
  - ➢ Video article: ***Bartlett et al J Vis Exp 2014***

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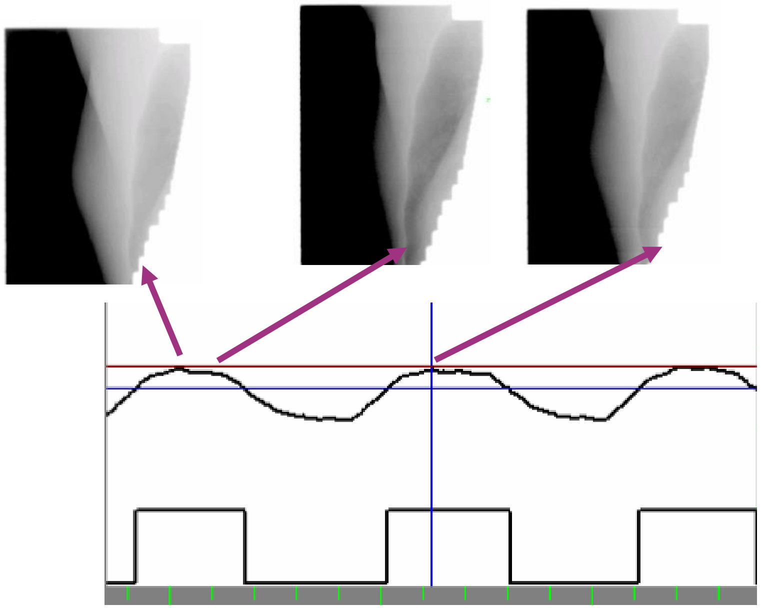
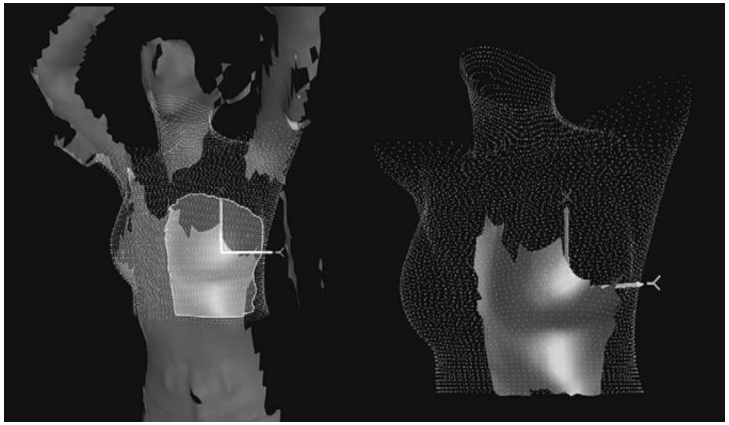
Image guidance for deep inspiration: DIBH/gating monitoring

- Patient set up as for conventional treatment (i.e. planar or CBCT)



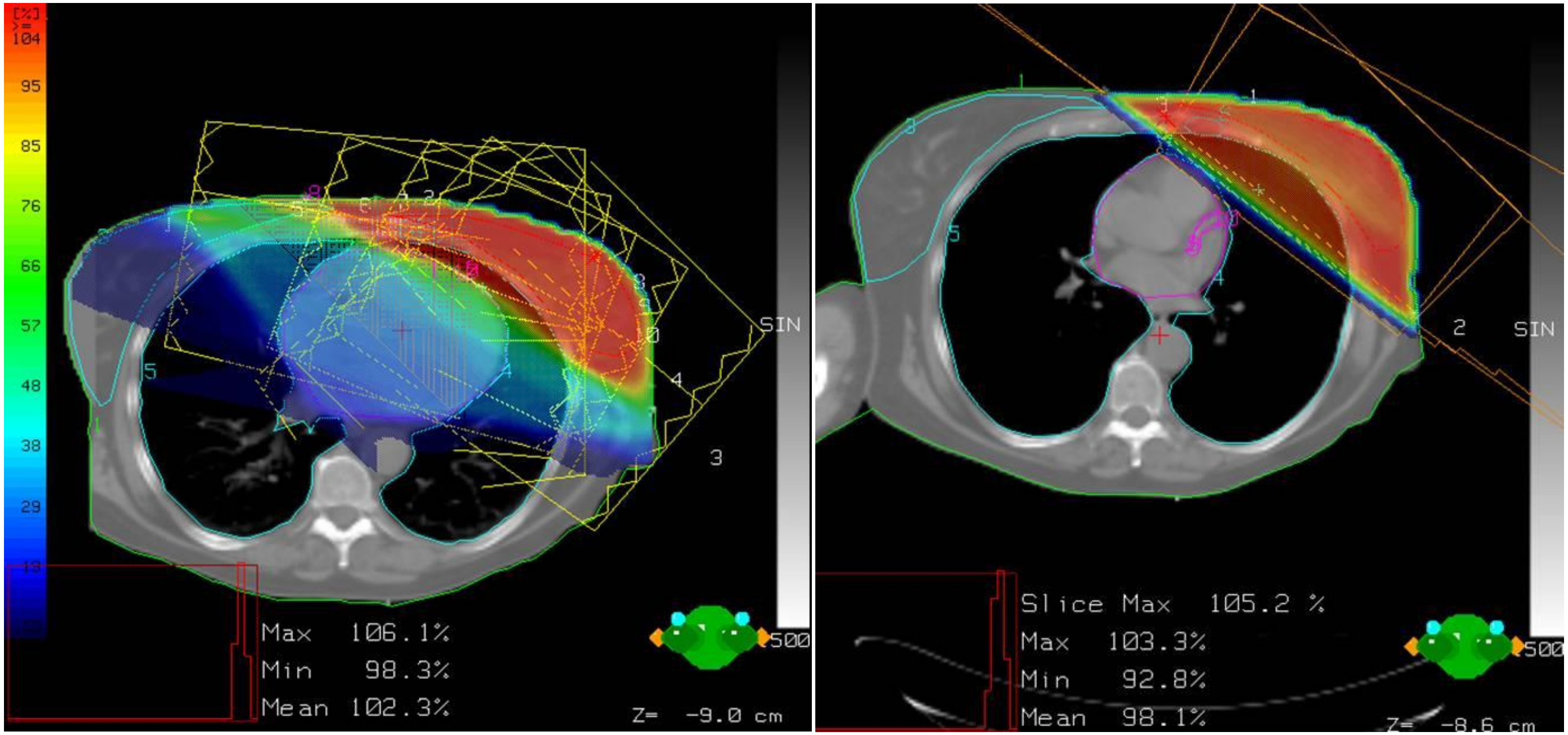
Residual motion can be verified by cine EPID



Align RT: potential for breath hold monitoring
Maintain use of CBCT for set-up

Alderliesten et al IJROBP 2012

Techniques for reduction of cardiac toxicity
IMRT or inspiration gating?



Patients with unfavorable thoracic anatomy:

➢Improved sparing of the heart with IMRT at cost of increased dose to the normal tissue (e.g. contralateral breast)

➢Sparing of the heart can be more efficient with 3D_DIBH than with IMRT_FB.

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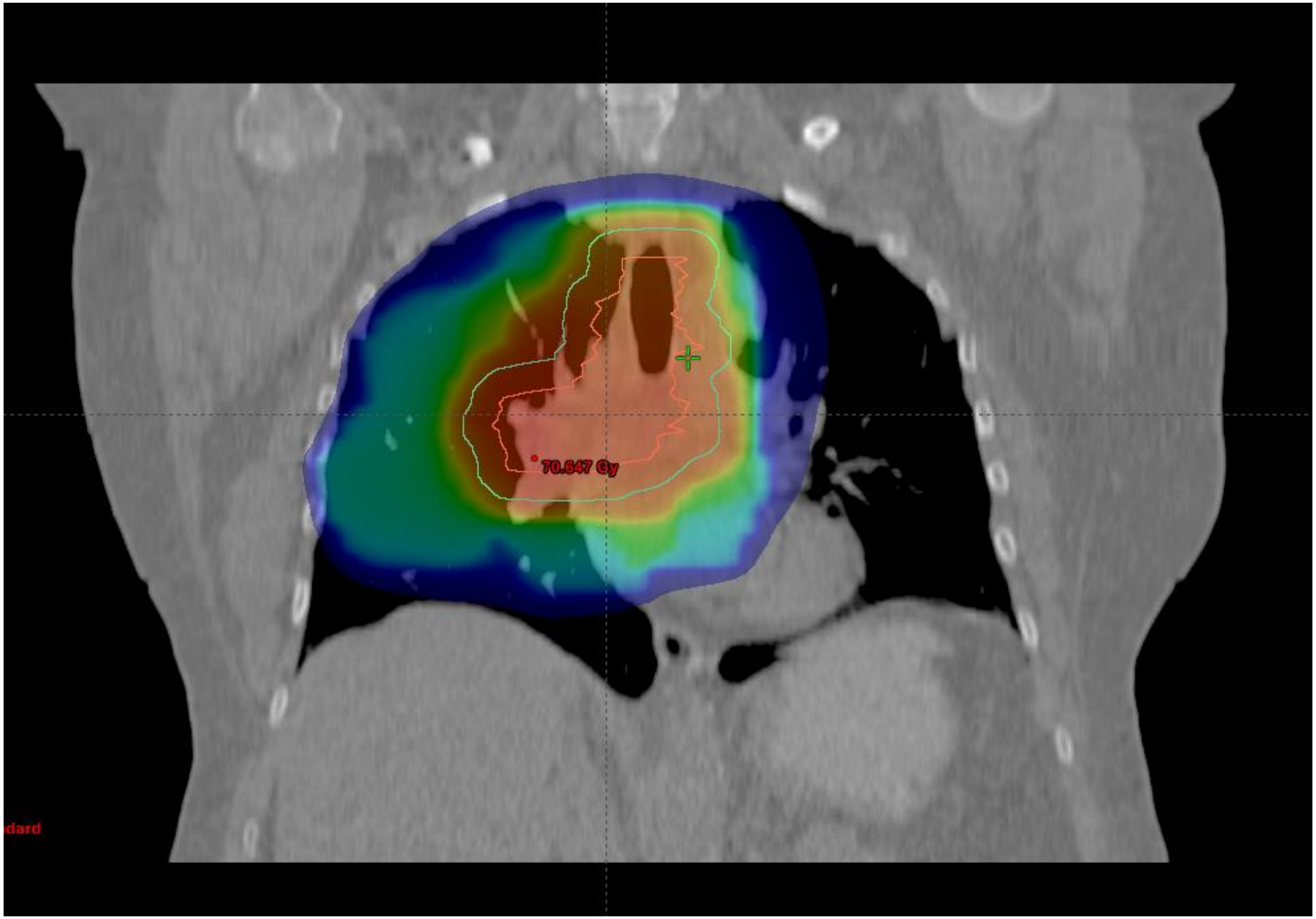
Take home message:
image-guidance for breast cancer

- MV can be acceptable is you have a good surrogate (e.g. visible clips, not only ribs)
- The less robust your treatment technique, the more advanced the IGRT
- For robust treatments, an offline strategy (NAL, eNAL, SAL, etc…) will go a long way towards reducing uncertainties
- Surface image has interesting potential and properties (no dose) but shouldn't be the only modality for set-up (rotations, DIBH…)
- Deep inspiration: just do it !

Lung Cancer



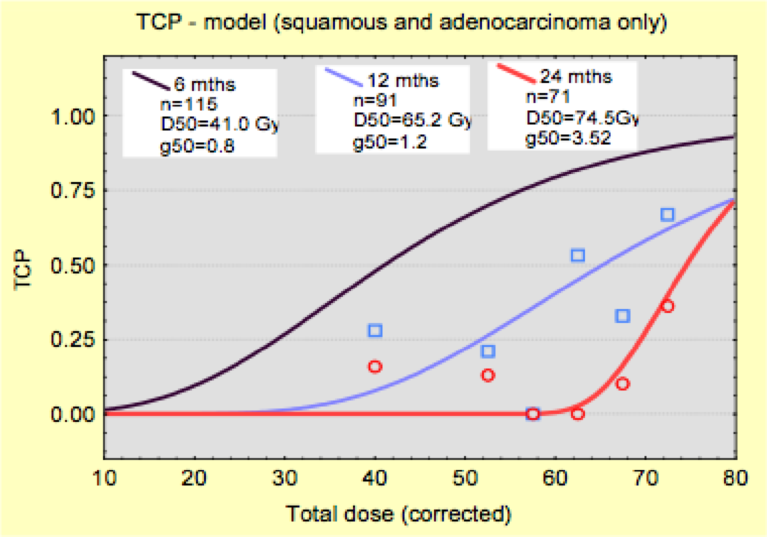
Dose escalation in lung NSCLC

High rates of local tumor recurrence with conventional irradiation doses (60-66Gy) and conventional RT techniques

- Early stage: >50% with RT only
- Advanced stage: >70% with RCHT

Sibley Cancer 1998

Le Chevalier J Natl Cancer Inst 1991



➢ Escalation of the irradiation dose increases local control and has the potential to increase overall survival

Willner IJROBP 2002
Kong IJROBP 2005

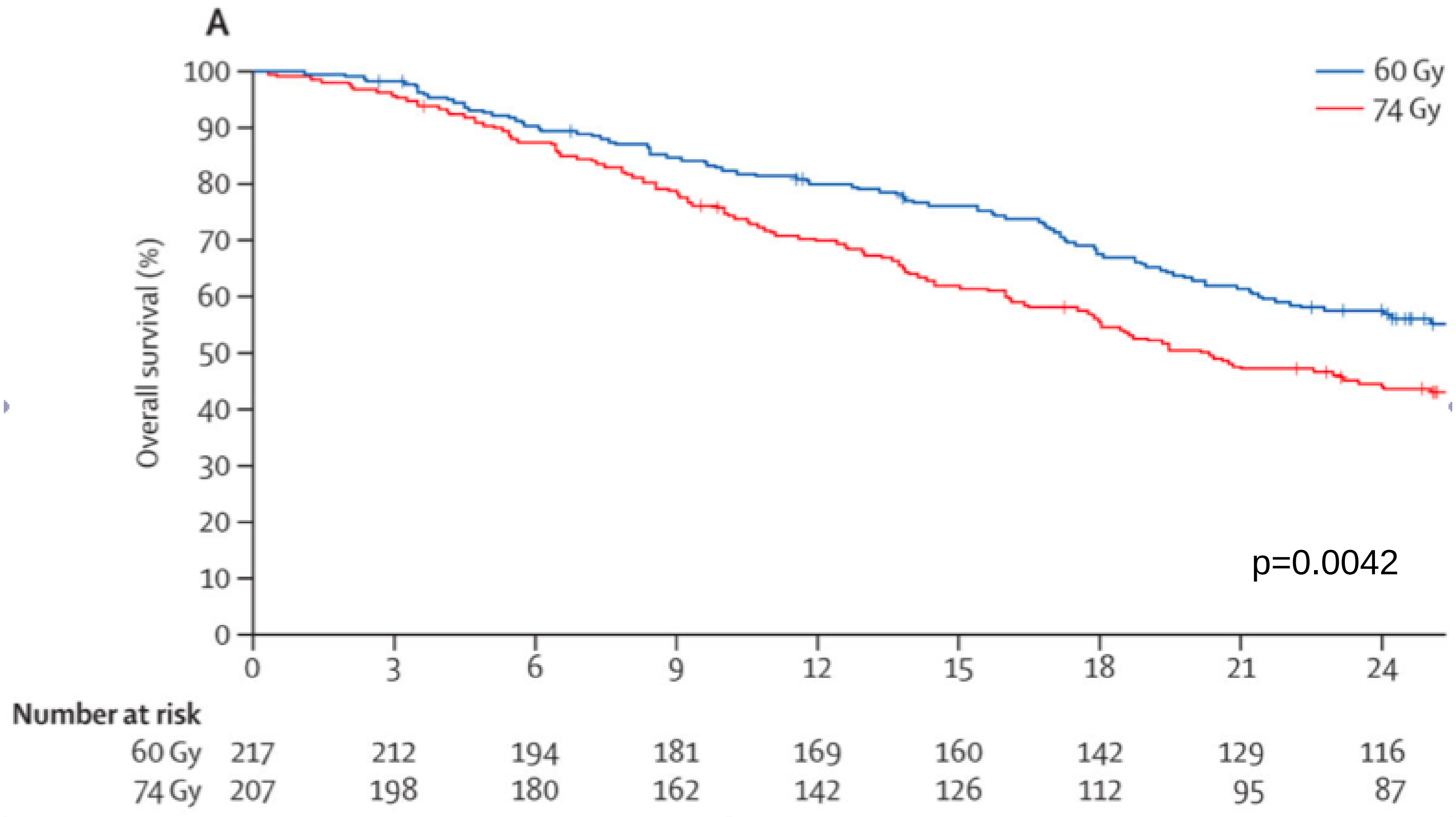
Is more dose better?

- RTOG 0617
  - Randomized controlled trial
  - Inoperable Stage III NSCLC
  - Concurrent radiation + chemotherapy
  - 2x2 randomization

60Gy	74Gy
RT + chemotherapy	RT + chemotherapy + cetuximab

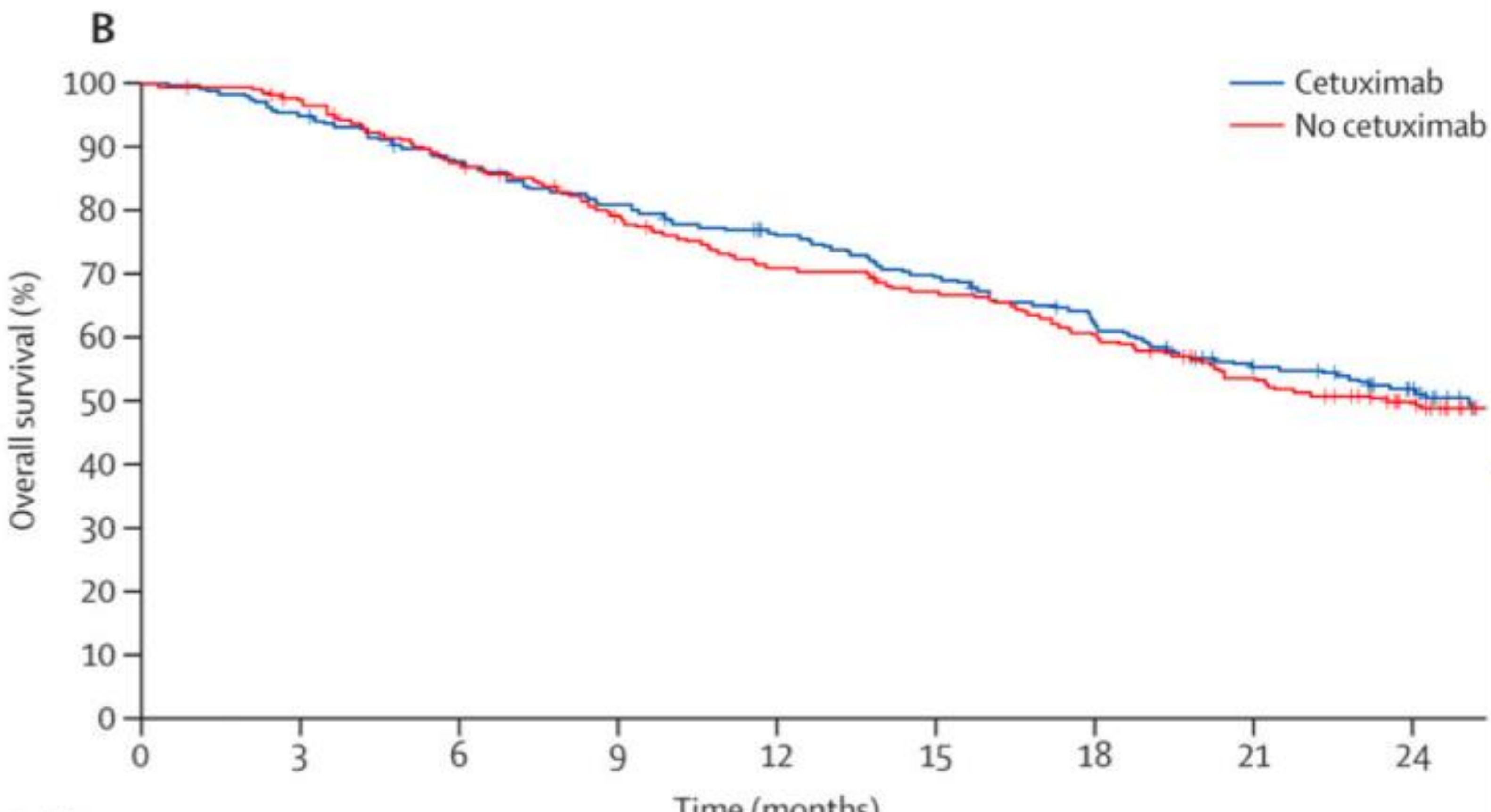
Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Overall survival (+/- Dose escalation)



Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Overall survival (+/- Cetuximab)



Number at risk									
Cetuximab	237	225	206	190	175	160	141	121	103
No cetuximab	228	219	196	174	155	146	131	113	96

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Overall survival modeling

Overall survival

Multivariate Cox Model Backwards Selection

Covariate	Comparison	HR (95% CI)	p-value
Radiation dose	60 Gy v 74 Gy	1.55 (1.07, 2.23)	0.020
Histology	Non-squam v Squam	1.37 (0.94, 1.98)	0.097
GTV (ITV if GTV unavailable)	Continuous	1.002 (1.000, 1.003)	0.034
Heart V5	Continuous	1.010 (1.004, 1.017)	0.002

Bradley et al., *Lancet Oncology* 2015

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RTOG 0617 – Outcomes

Toxicity and mortality

September 2011	Standard Dose: 60 Gy (n=192) Grade			High Dose: 74 Gy (n=183) Grade		
	3	4	5	3	4	5
Worst non-hematologic	79 (41.1%)	14 (7.3%)	4 (2.1%)	85 (46.4%)	17 (9.3%)	8 (4.4%)
Worst overall	84 (43.8%)	45 (23.4%)	4 (2.1%)	78 (42.6%)	52 (28.4%)	8 (4.4%)
Grade 5 Events	(n=4)			(n=8)		
As scored by institution No significant difference	2 Pulmonary 1 Thrombosis 1 Death NOS			2 Pulmonary 1 Thrombosis 1 Upper GI Hemorrhage 1 Pulmonary Hemorrhage 1 Pneumonia NOS 1 Esophageal 1 Death NOS		

Bradley et al., *Lancet Oncology* 2015

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RTOG 0617 – Dose escalation

Local failure rate at 18 months post-treatment:

60 Gy	74 Gy
25.1%	34.4%

Does this make sense?

Reasons?

Bradley et al., *Lancet Oncology* 2015

RTOG 0617 – Dose escalation

Local failure rate at 18 months post-treatment:

60 Gy	74 Gy
25.1%	34.4%

Does this make sense?

Reasons?

Minimum margin was smaller in the high-dose group (mean 4·5 mm [2·9] in the standard-dose group *vs 3·9 mm [3·0] in the high-dose group; p=0·0047)*

Bradley et al., *Lancet Oncology* 2015

RTOG 0617

ARE THE RESULTS OF RTOG 0617 MYSTERIOUS?

JAMES D. COX, M.D.

Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX

74Gy compared to 60Gy is **neither safe nor effective** for the patient population and using the technology of RTOG 0617

Bradley et al., *Lancet Oncology* 2015

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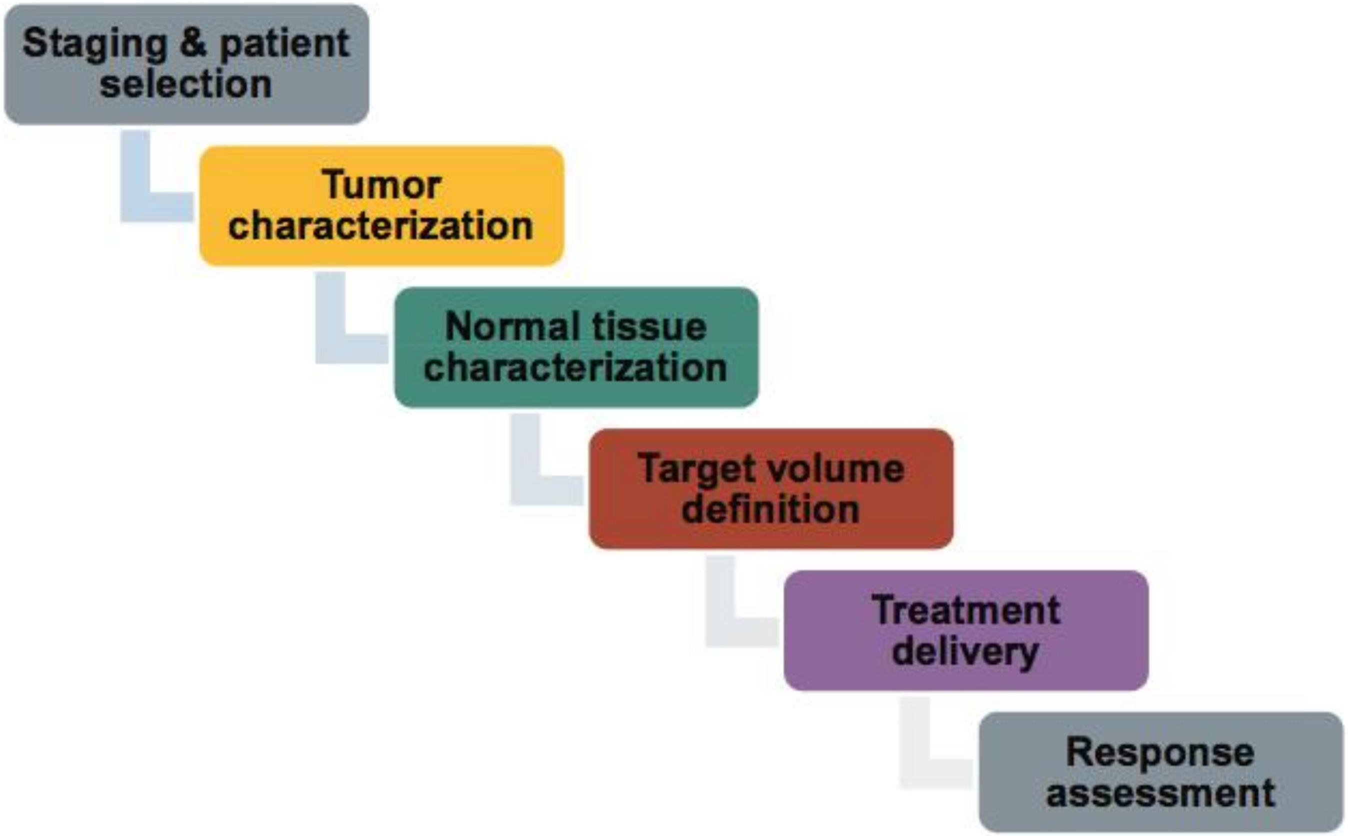
Interpretation of RTOG 0617

Technology	Study protocol
FDG-PET	encouraged, not mandatory
4D-CT	highly, encouraged not mandatory
IMRT	optional

74Gy feasible in the study patient population with the technology above?

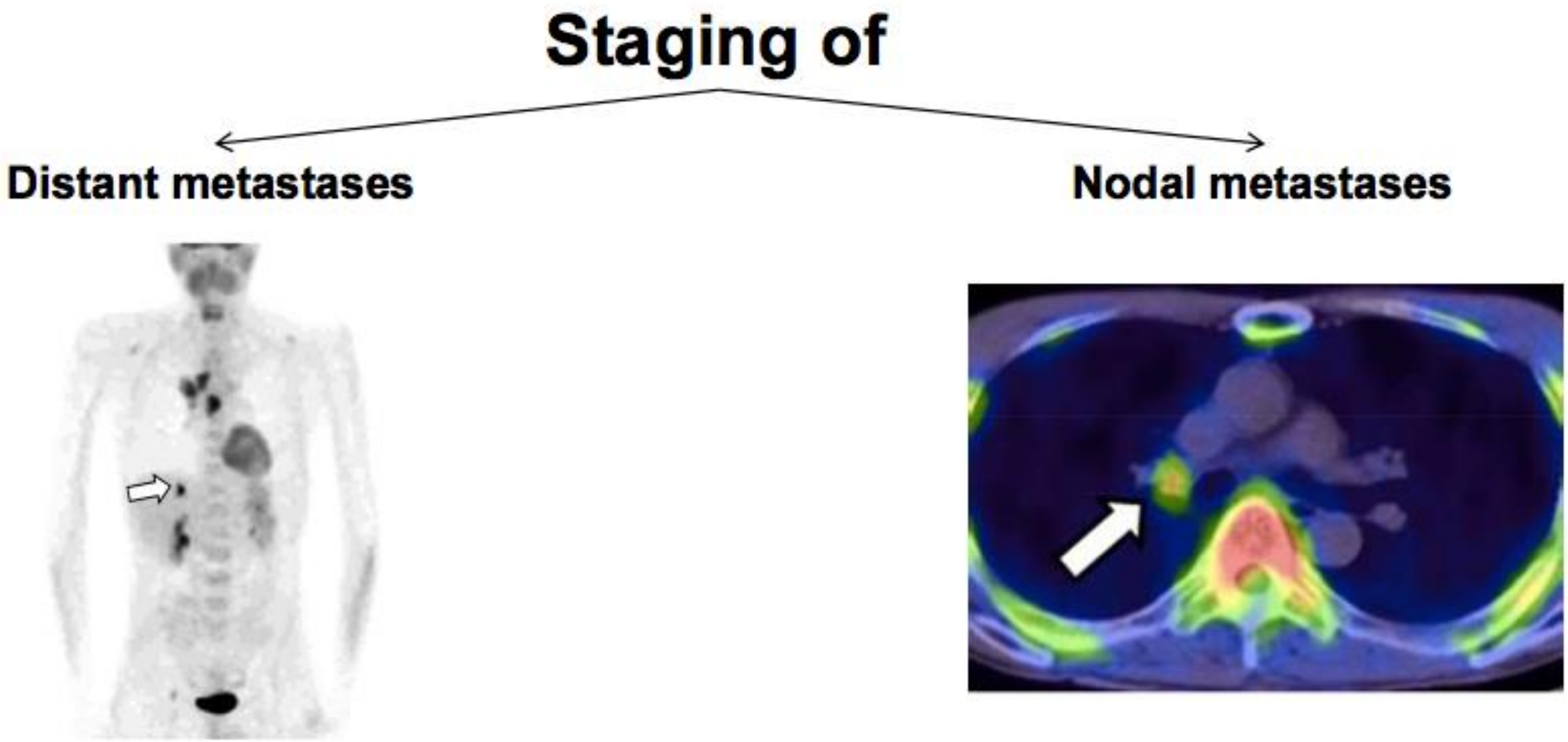
- Violation OAR constraints?
- Smaller than necessary target safety margins?
- Experience in the centers?
- Necessary to „boost“ all macroscopic tumor?

Outline



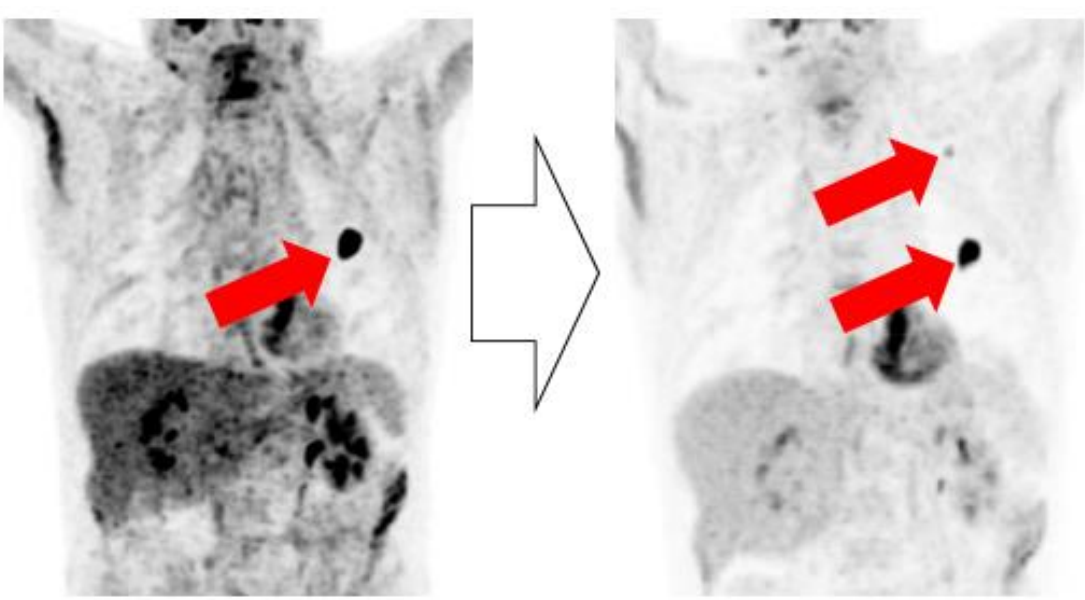
Staging & patient selection
Tumor characterization
Normal tissue characterization
Target volume definition
Treatment delivery
Response assessment

Staging and patient selection – FDG-PET



FDG-PET provides important information to select patients for high precision radiotherapy

Staging and Patient Selection: Disease Progression



Median 23 days (max 176)

Progression to stage IV:

3 / 21 patients

Mac Manus Radiat Oncol 2013

6 weeks

Repeat Staging!
What time interval?

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Staging and Patient Selection: FDG-PET

Results of a prospective study: locally advanced NSCLC

CT staging **PET-CT staging** **Outcome**

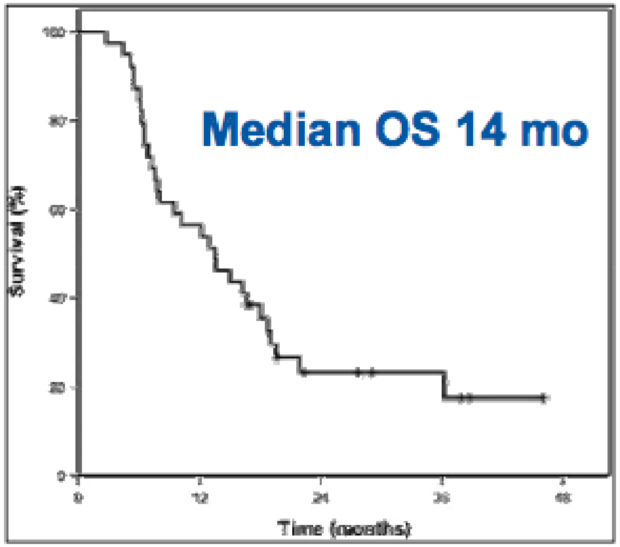
Mac Manus Radiat Oncol 2013

FDG-PET detected metastases in 12/76 patients
Treatment intent changed from curative to palliative

Staging and Patient Selection: Advanced disease

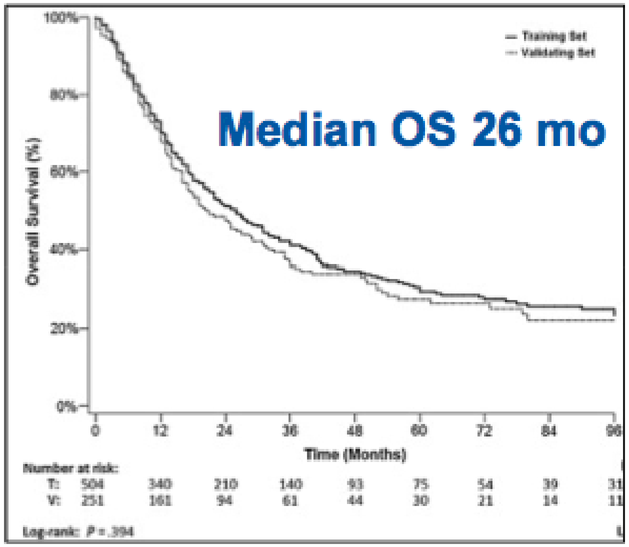
Radical treatment DESPITE stage IV disease

Prospective phase II trial: n=39



De Ruysscher JTO 2012

Multicenter analysis: n=757

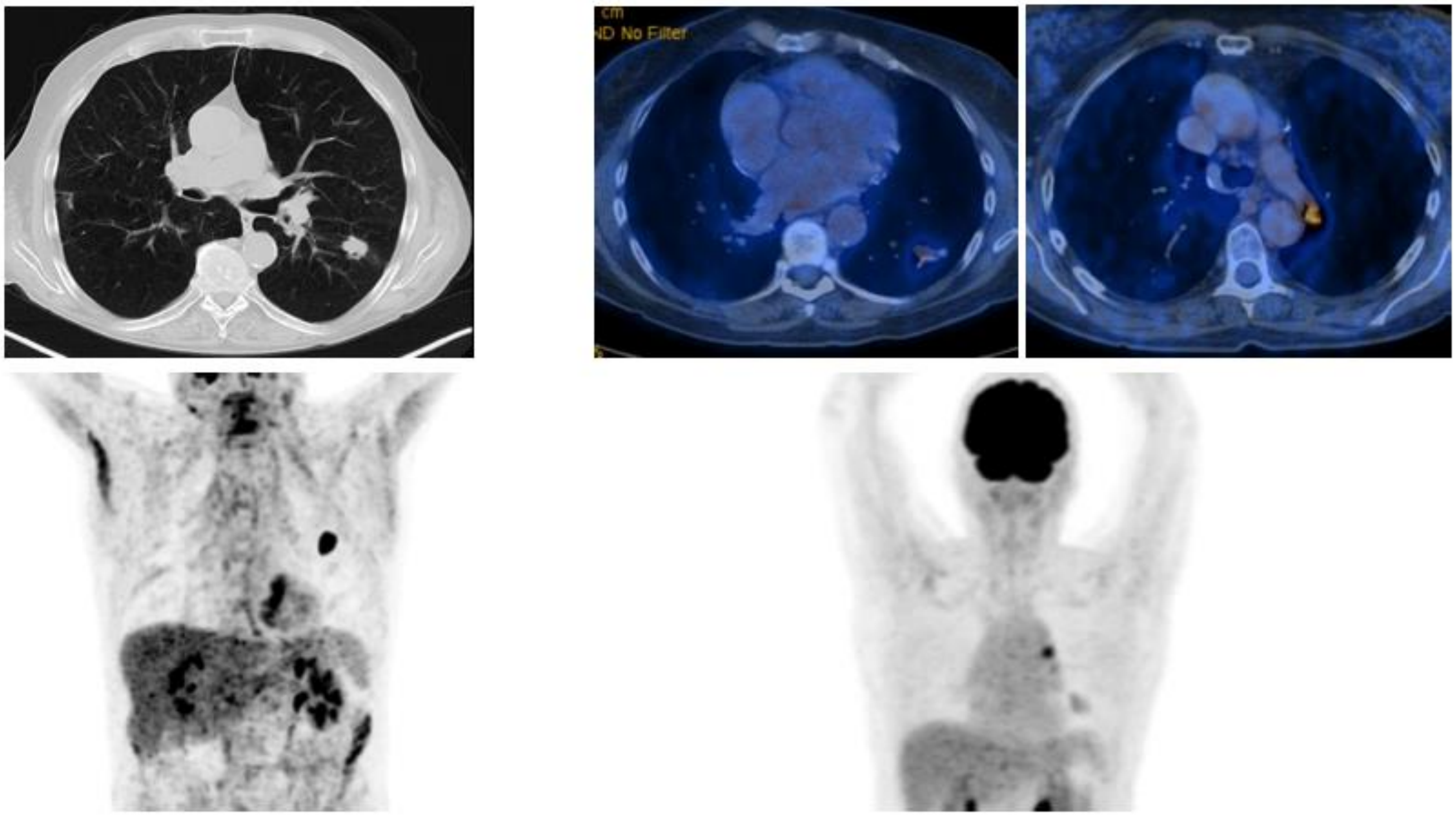


Palma Clinical Lung Cancer 2014

Overall survival similar to Stage III NSCLC

Careful patient selection

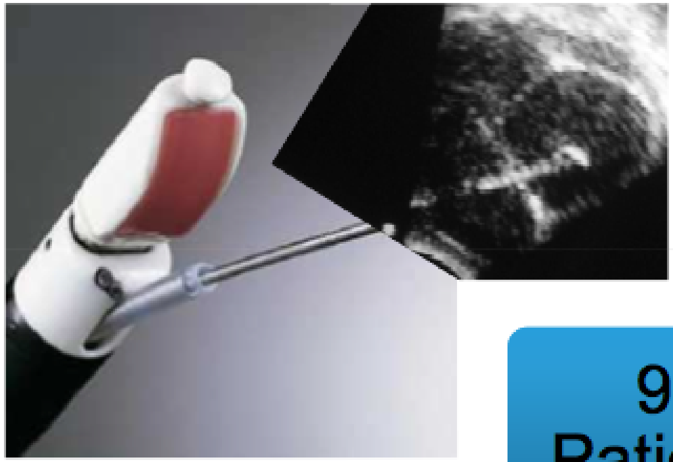
Nodal Staging in Stage I NSCLC



Nodal failure after local treatment with SBRT
Rates similar to surgical series (~10%)

Nodal Staging in Stage I NSCLC: EBUS

EBUS for staging of CT and FDG-PET N0 disease



- Systematic imaging of mediastinum and hilar regions (stations 2, 4, 7, 10, 11)
- Puncture of all visualized nodes with a size of 5 - 10mm

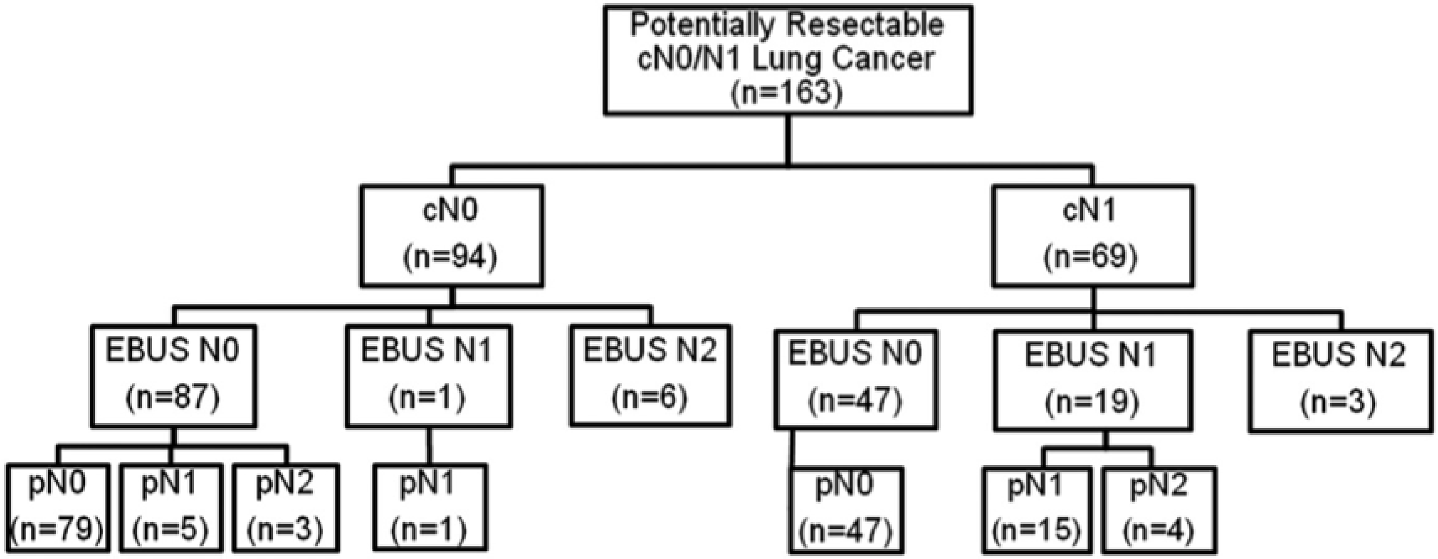
97 Patients → 156 LN biopsied → N+ 8 / 97 patients

Herth CHEST 2008

EBUS requires experienced providers, more common now
Pathologic “confirmation” of ultrasound imaging

Nodal Staging in Stage I NSCLC: EBUS

CT/PET negative patients planned for lobectomy



Differentiating N0 from N1
Sensitivity: 76%, Specificity: 100%
Accuracy: 96%, NPV: 96%

Yasufuku et al., *Ann Thorac Surg, 2013*

Elective nodal irradiation in N+ disease

Study	# of patients	Isolated regional failure
Graham 1995	179	8%
Kong 2005	106	6%
Rosenzweig 2001	171	6.4%
Senan 2002	50	0
De Ruysscher 2005	44	2%
Belderbos 2006	67	3%
Rosenzweig 2007	524	6.1%

Randomized trial of ENI (60-64Gy) and IF (68-74Gy) N=200

Patients in the IF arm had significantly

- Increased local control and no increased regional failure
- Decreased rates of pneumonitis
- A trend to improved OS

Yuan American Journal of Clinical Oncology 2007

Elective nodal irradiation in N+ disease

Practical considerations of selective nodal / involved field RT

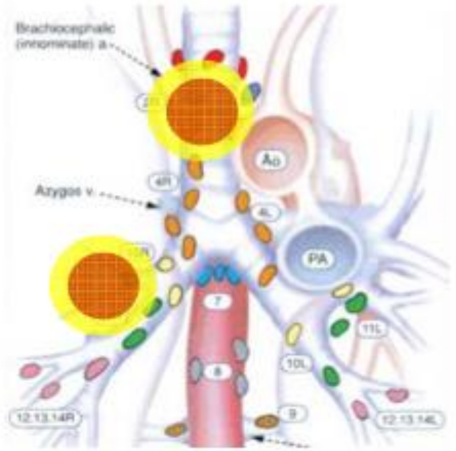
Study	CT criteria	FDG-PET
Graham 1995	≥ 1cm	-
Kong 2005	≥ 1cm	-
Rosenzweig 2001	≥ 1.5cm	-
Senan 2002	-	-
De Ruysscher 2005	1cm	„increased uptake“
Belderbos 2006	-	„increased uptake“
Rosenzweig 2007	≥ 1.5cm	„increased uptake“

➢ **No standard how to define an involved lymph node**

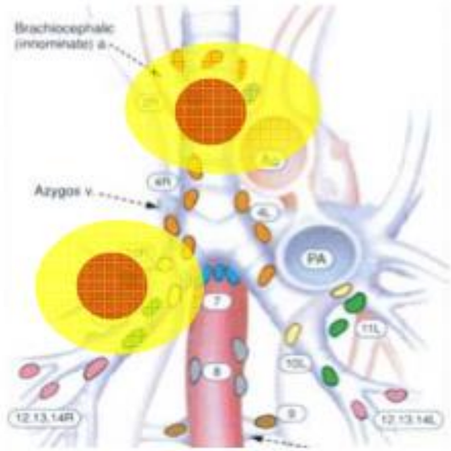
Nodal staging/treatment

Practical considerations of selective nodal / involved field RT

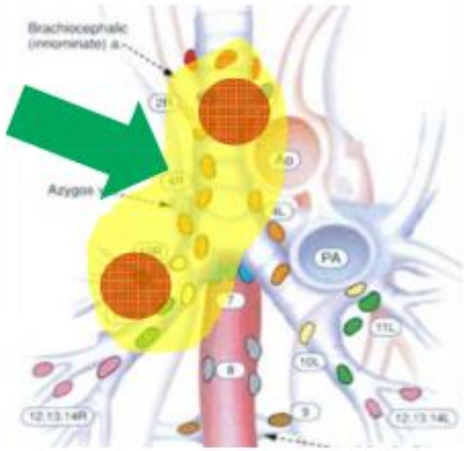
Involved node



Involved station

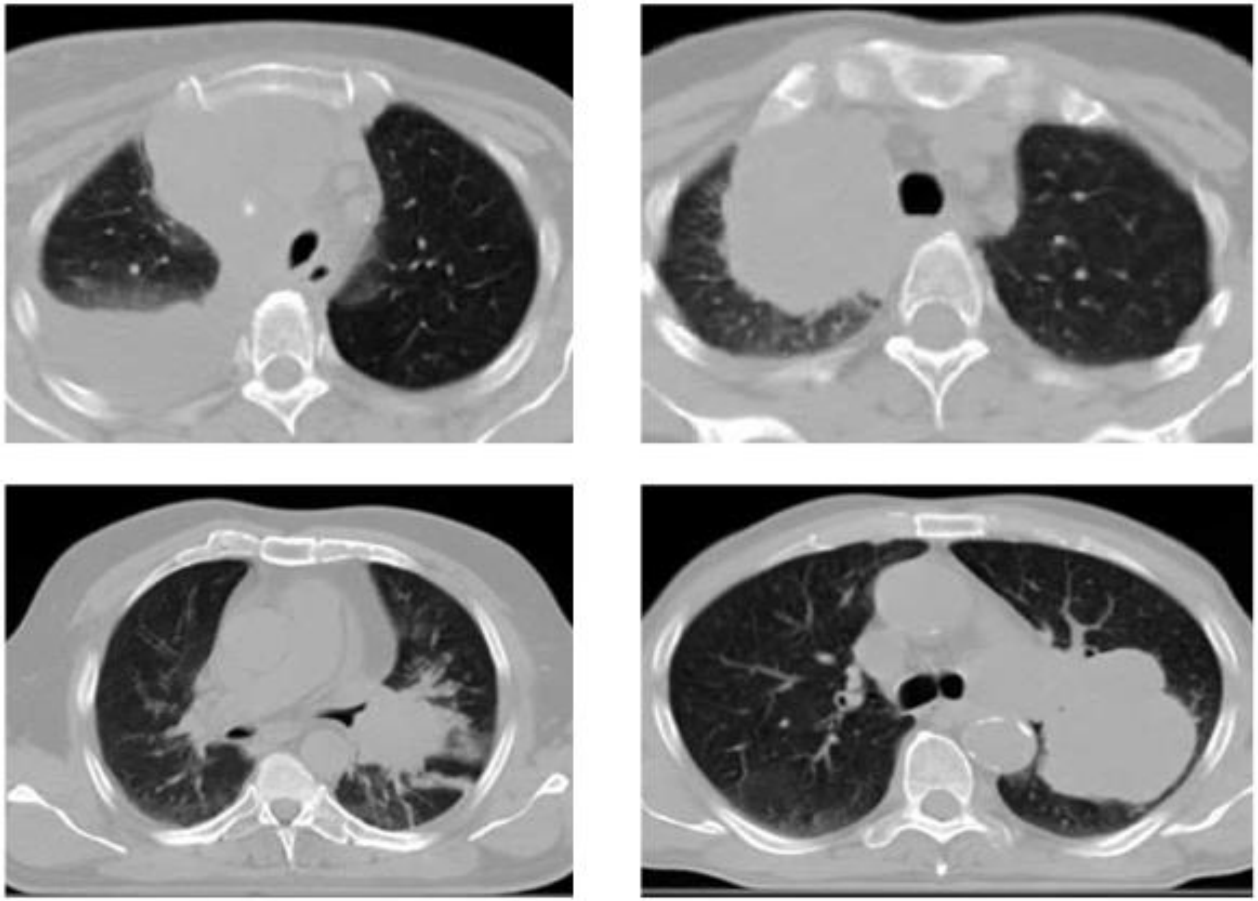


Involved station +



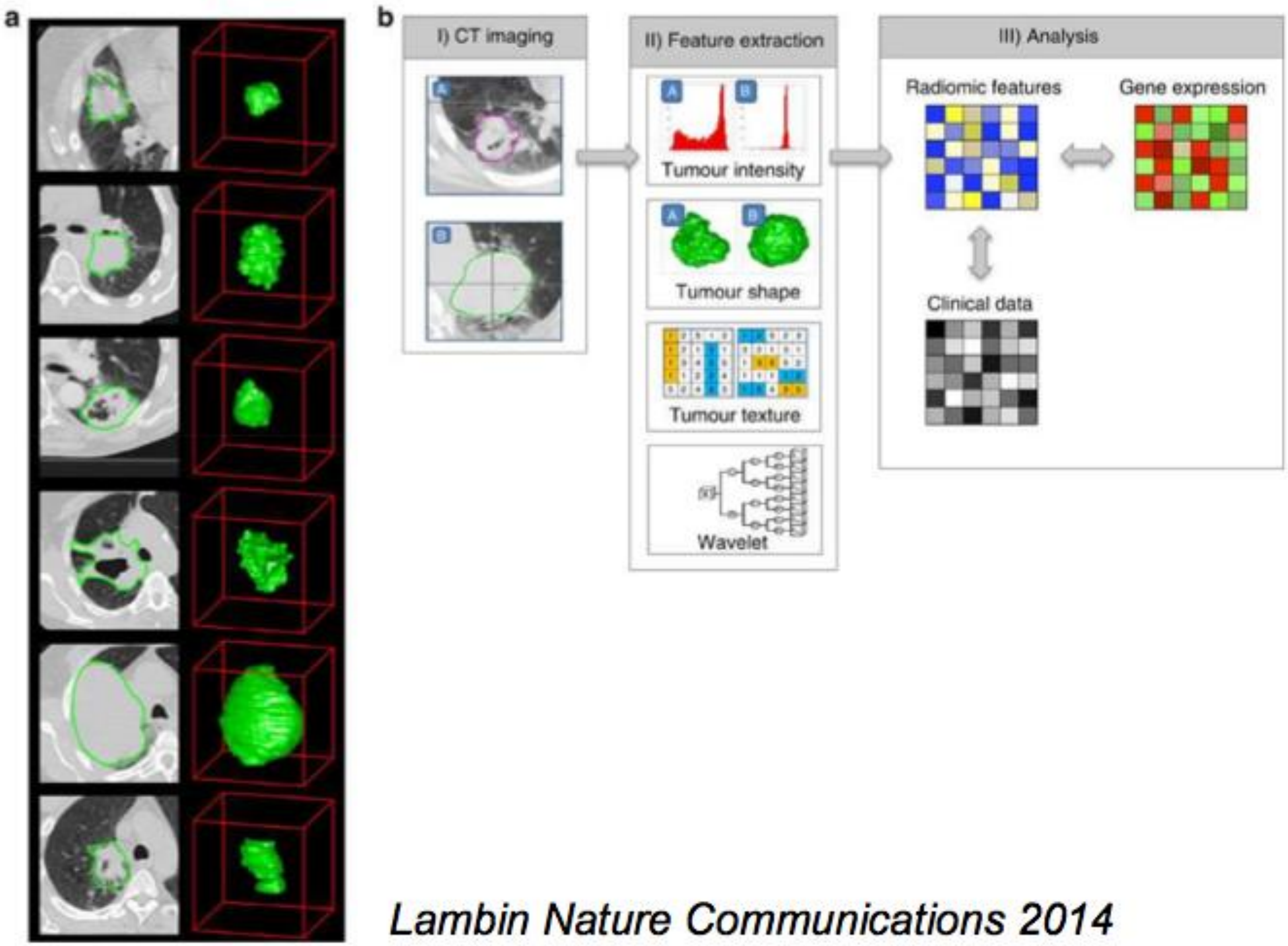
➢ **No standard how to define an involved lymph node**

Tumor characterization: Radiomics



Different lung tumors look different!

Tumor characterization: Radiomics



Lambin Nature Communications 2014

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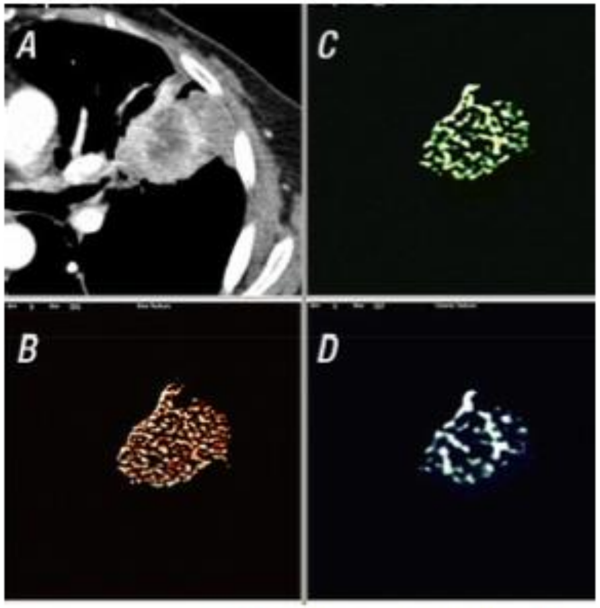
Tumor characterization: Radiomics

CT texture analysis



Ganeshan Radiology 2013

CT textures correlated with …

… histopathological tumor characterization:

- Tumor staining with pimonidazole
- Glut-1 expression

Ganeshan Radiology 2013

- Microscopic disease extension

Salguero Radiother Oncol 2013

- Loco-regional recurrence after SBRT

Salguero Radiother Oncol 2013
Mattonen Med Phys 2014

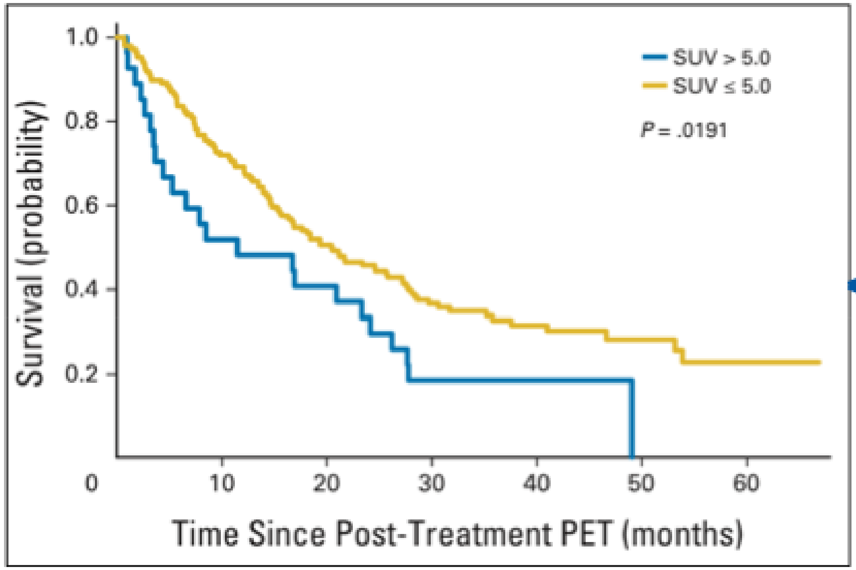
- Overall survival after RCHT

Fried IJROBP 2014

Most reports use ‘standard’ CT
Standardization and validation required

Tumor characterization: FDG-PET

Post-treatment FDG-PET



Machtay JCO 2013

Pre-treatment FDG-PET

Aerts Radiother Oncol 2009
Shusharina IJROBP 2014

Mid-treatment FDG-PET

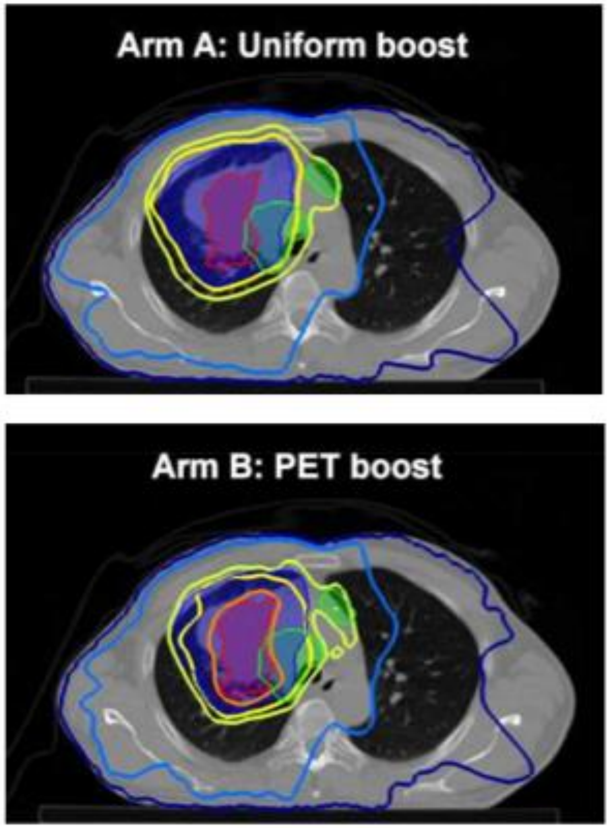
Kong JCO 2007

Residual FDG-PET activity associated with worse LC/OS

FDG-PET at early time-points (during treatment?) may be associated with outcomes

Tumor characterization: FDG-PET

Van Elmpt Radiother Oncol 2012



Pre-treatment FDG-PET

Homogeneous boost	PET-Boost
79Gy	87Gy

Van Elmpt Radiother Oncol 2012

Mid-treatment FDG-PET

CT volume decrease	PET volume decrease
- 26%	- 44%

Feng IJROBP 2009

Boost limited to areas of high FDG-PET activity
Multiple on-going prospective studies

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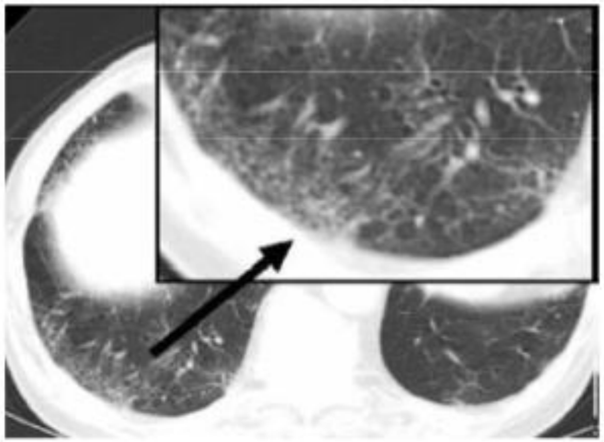
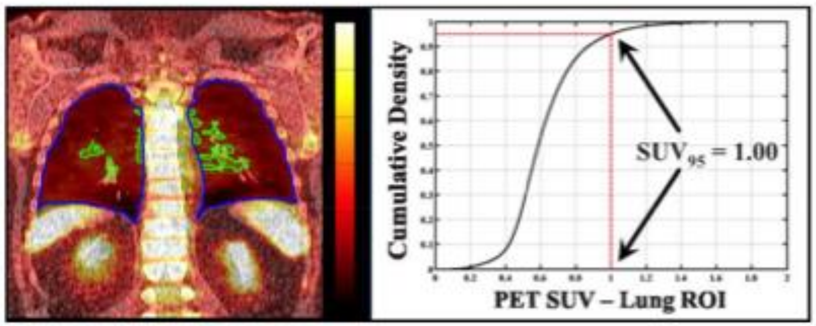
Normal Tissue Characterization

Interstitial pulmonary fibrosis



Increased risk (26% vs 3%) of RP
Sanuki J. Radiat. Res. 2012

Pulmonary FDG uptake



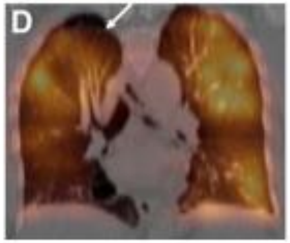
Increased risk in high FDG uptake lung volumes, especially when exposed to RT
Petet IJROBP 2012, Castillo Radiat Oncol 2014

Normal Tissue Characterization

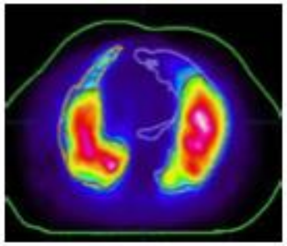
Regional lung function

Perfusion

SPECT

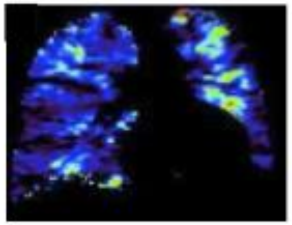


PET

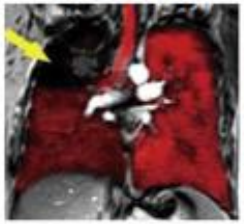


Ventilation

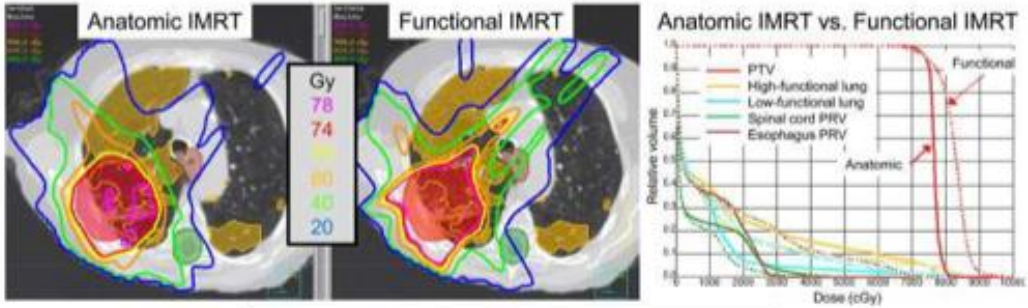
4D-CT



^{3}He MRI



Adaptive planning



STUDY PROTOCOL Open Access

Functional lung avoidance for individualized radiotherapy (FLAIR): study protocol for a randomized, double-blind clinical trial

- Dose re-distribution from functional to non-functional lung tissue

McGuire IJROBP 2006; Shioyama IJROBO 2007; Yamamoto IJROBP 2010

Hard to implement as 'bad' lung tissue isn't always in the same location day to day.

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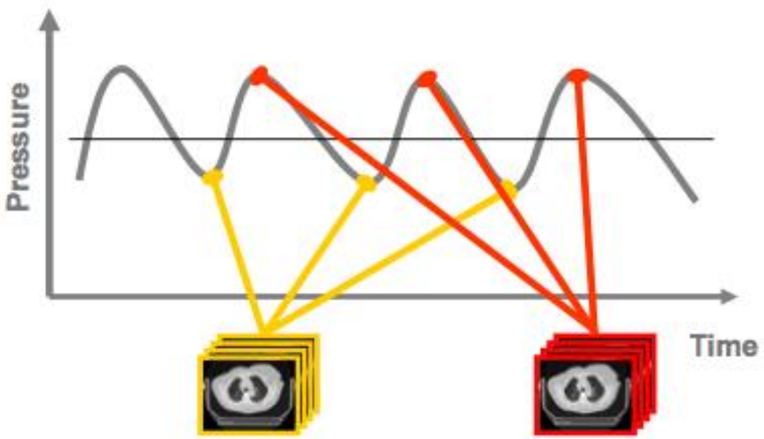
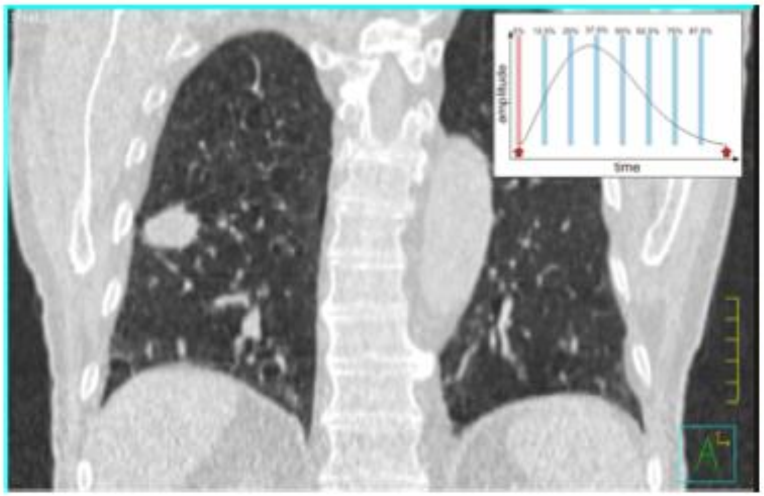
Target Volume Delineation – 4DCT

Respiration correlated 4D-CT

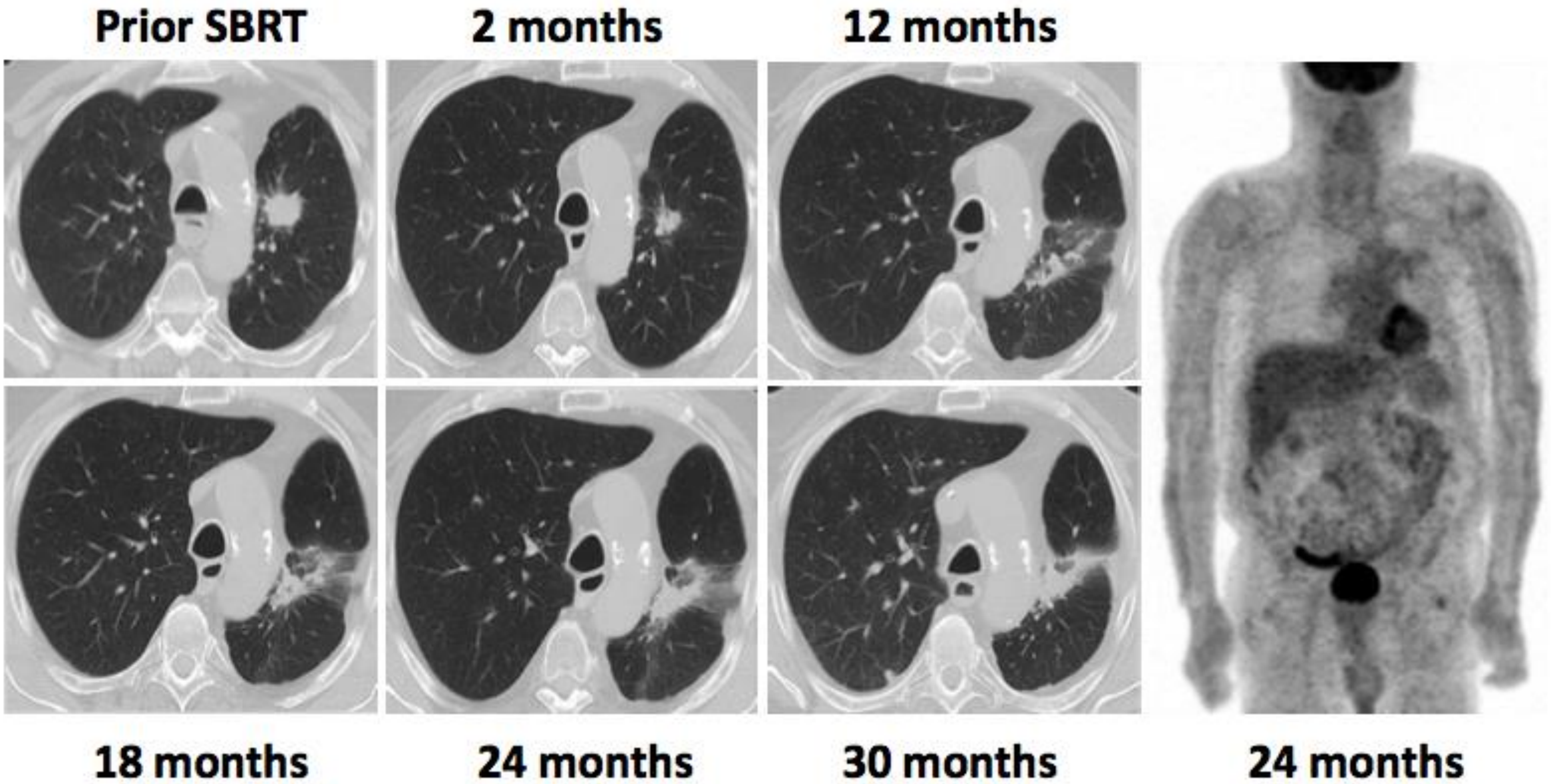




Patient specific motion analysis

Selection of appropriate motion management strategy

Follow-up imaging and response assessment

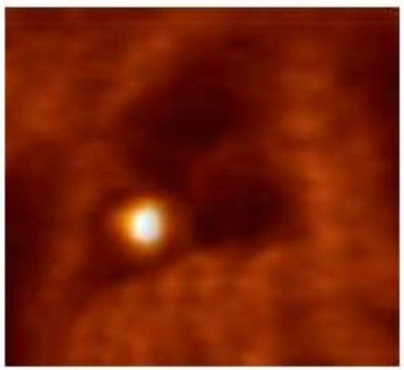


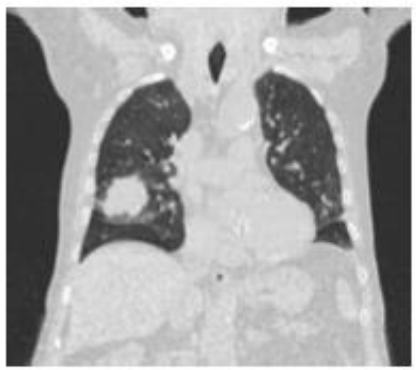
Normal tissue reaction vs. local failure?

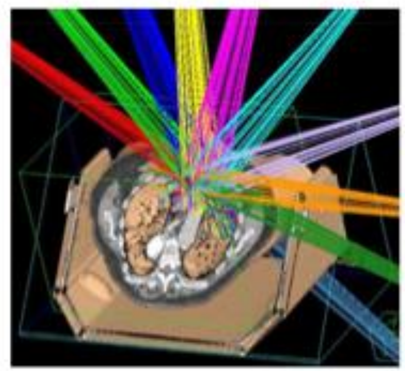
Stereotactic Body radiation therapy (SBRT)

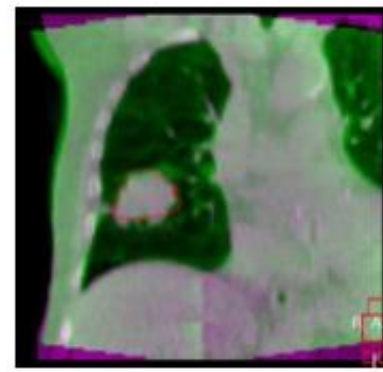
Combination of different high precision radiotherapy techniques

Staging LK Status	4D target volume definition	Highly conformal treatment planning	Image guided radiotherapy









Safe dose escalation to maximize local control

SBRT for early stage NSCLC

SBRT compared to conventionally fractionated RT

CF-RT

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

60%

SBRT

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

90%

SBRT: Higher LC and higher OS

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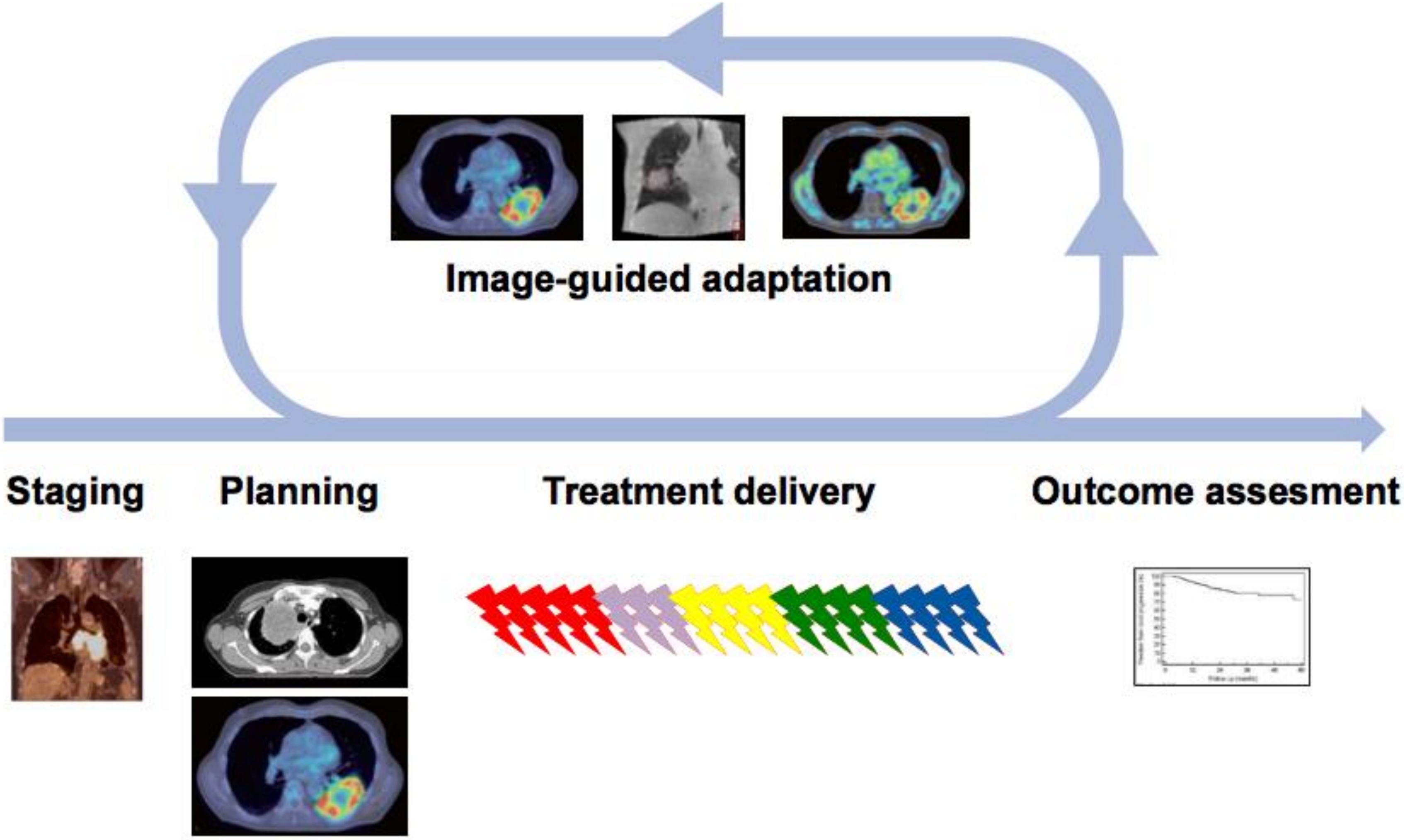
Imaging in the RT process for NSCLC



In-room image guidance: seeing the tumour

At Rigshospitalet

For all locally-advanced NSCLC patients

3D PET/CT with IV contrast

4D CT + short breath hold CT

Contrast if central tumour

Visual review of the 4D CT (by a dosimetrist):

if < 5mm peak-to-peak motion, plan on the PET/CT, where contouring is most reliable

if > 5 mm peak-to-peak motion : MidVentilation

Occasional use of the ITV approach (e.g. if too many artifacts)

In-room image guidance

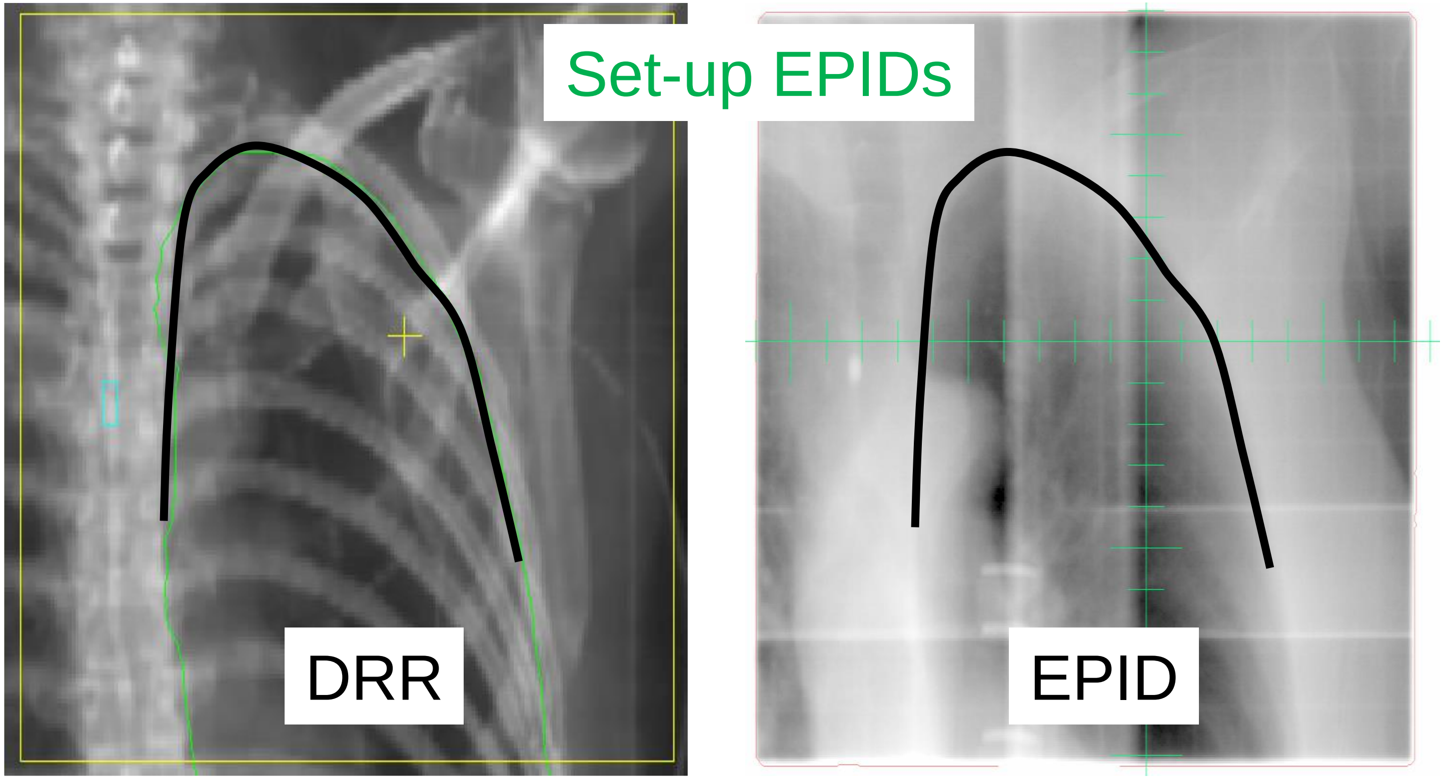
Modalities	Goals
➢ Field light ➢ EPID ➢ kV verification imaging ➢ In-room CT/CBCT	➢ **Inter-fraction imaging** ➢ Reproducibility of patient positioning ➢ Reproducibility of organ / target positioning ➢ Adaptive planning ➢ **Intra-fraction imaging** ➢ Catching intra-fraction baseline shifts

In-room image guidance

1. Field light / surface markers/surface matching

Verification that correct patient on the couch
Set-up verification of external target volumes (skin cancer…)

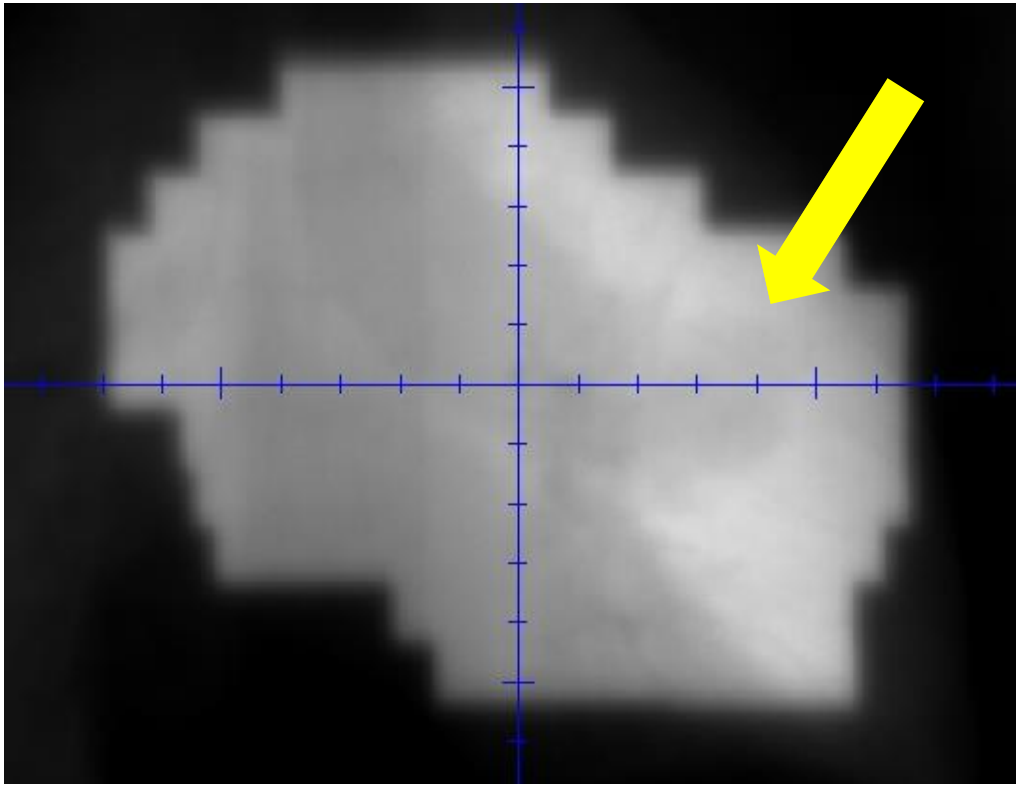
2. Electronic portal images (set up)



Pros: Large images with suitable anatomical landmark structures
Cons: Landmark structure might not be representative for target

In-room image guidance

2. Electronic portal images (field or cine mode)



- ”on flight” images
- NB: mostly if 3D- CRT planning

Pros:	No additional patient dose;
	Pulmonary tumor sometimes visible itself
Cons:	Difficult to interpret when only limited landmark structures in field

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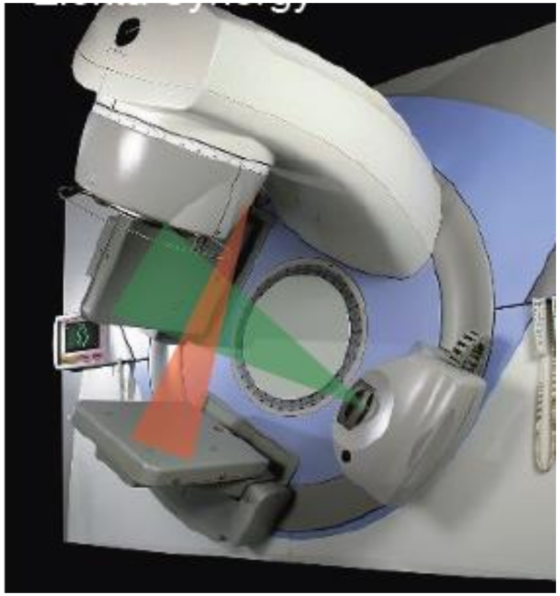
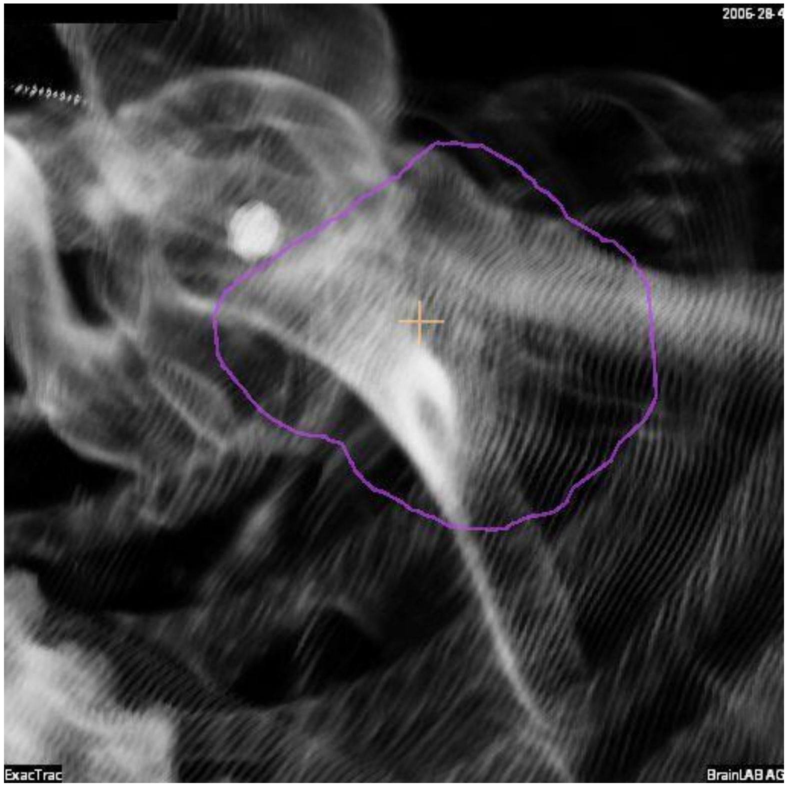
In-room image guidance

3. kV planar images



In-room image guidance

3. kV planar images



DRR image

kV image: better constrast than EPID… but still poor!

In-room image guidance

3. kV planar images

Markers required: poor soft-tissue contrast

•Surrogate, not the target itself

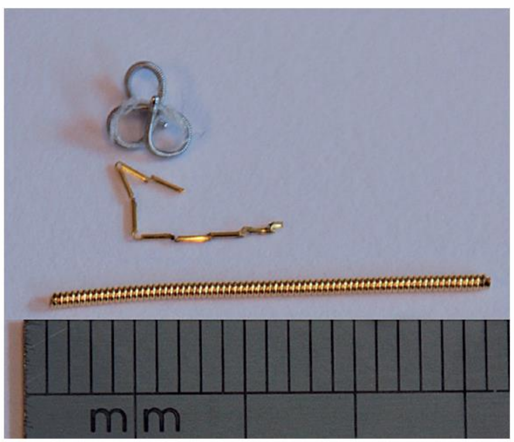


Figure 1. Photo showing the complex helical platinum marker (top), the Gold Anchor™ marker (middle) and the Visicoil™ gold marker (bottom).

4 out of 15 patients developped pneumothorax (transthoracic implantation)

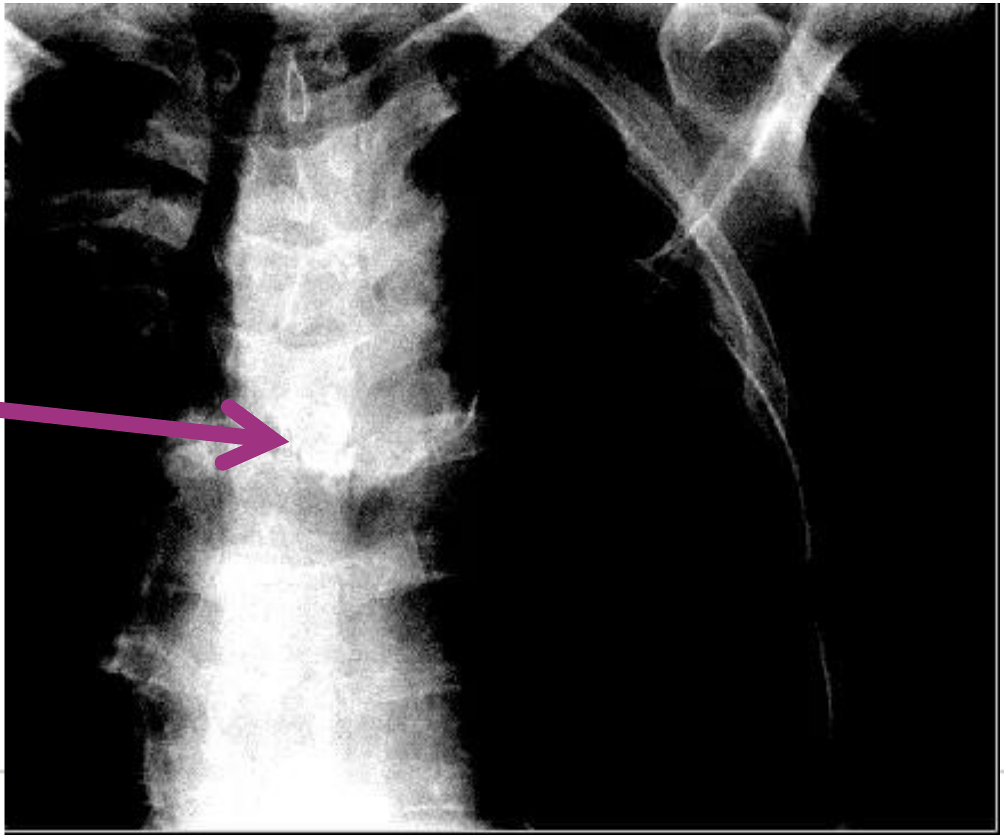
Persson et al Acta Oncol 2012

In-room image guidance

3. kV planar images

Markers required: poor soft-tissue contrast

•Surrogate, not the target itself



19 patients

broncoscopic Bioxmark^{TM}

Can be implented in lymph nodes

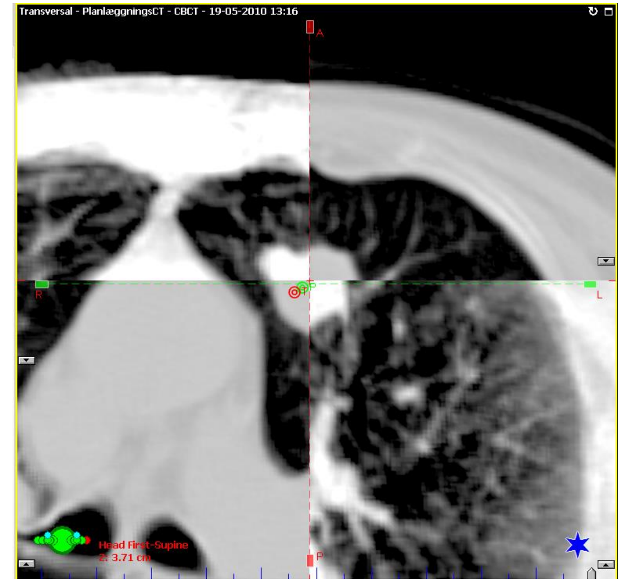
In-room image guidance

4. Volume imaging

In-room CT

beam

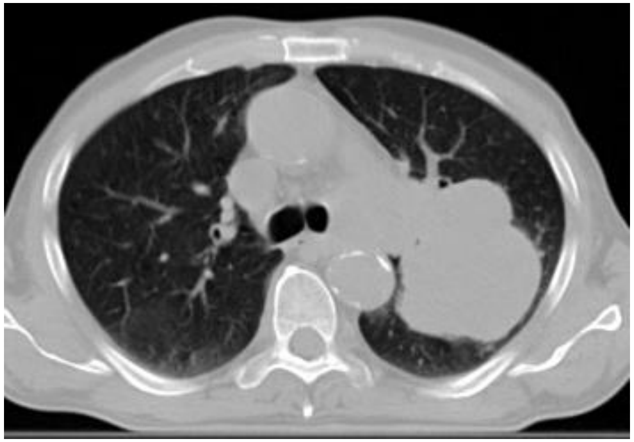
MV CT



In-room image guidance

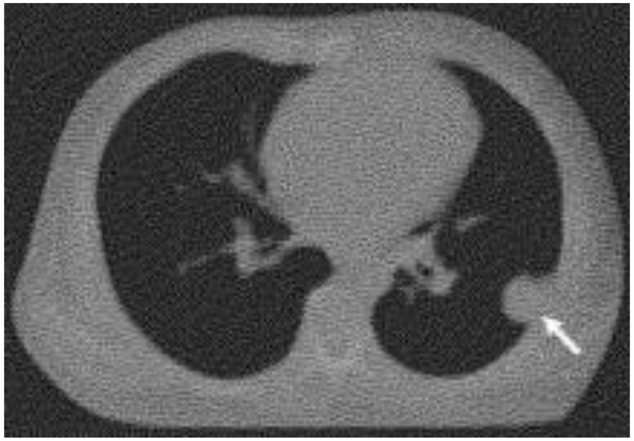
4. Volume imaging

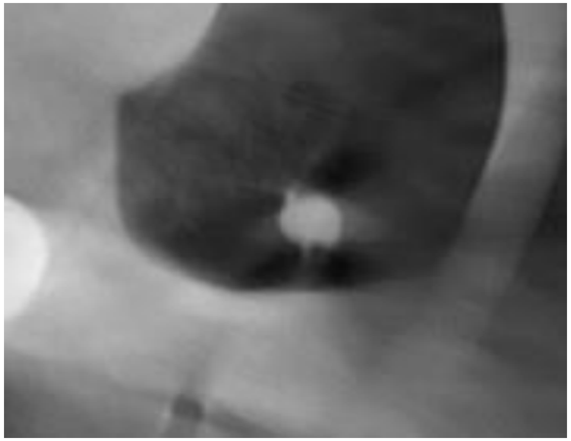
Helical



kV CBCT

MV CT





kV/MV CBCT

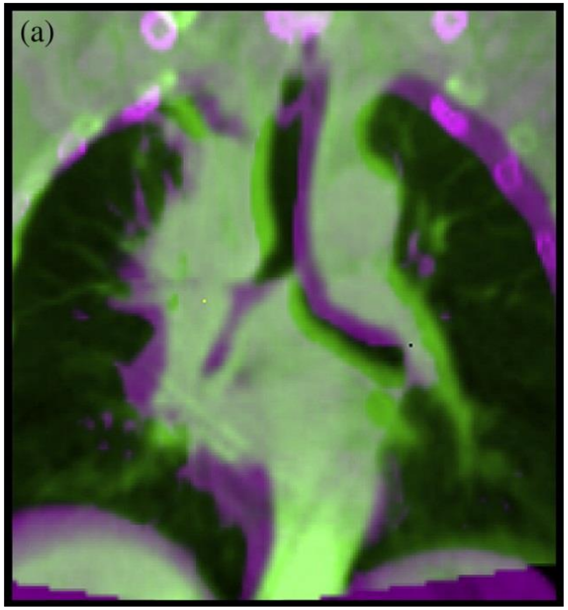
- Intra-pulmonary targets clearly visible in all imaging modalities
- IQ for mediastinum suitable only in kV helical CT

A side note: setting up according to landmarks

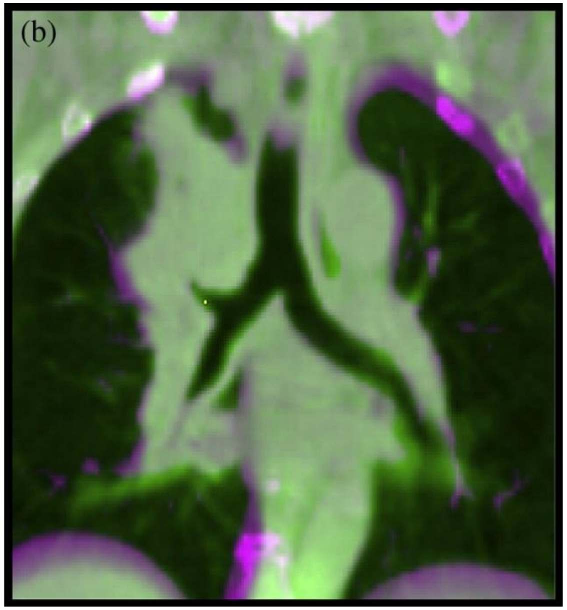
Spine vs Carina

Higgins et al (IJROBP 2009): feasible, better inter-observer agreement with match on the carina

Lavoie et al (IJROBP 2012): especially node coverage is improved



Spine match



Carina match

Benefit from carina match

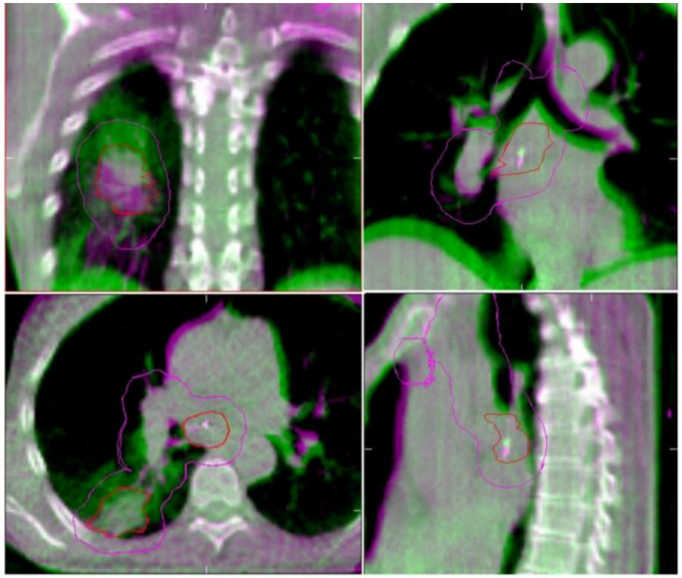
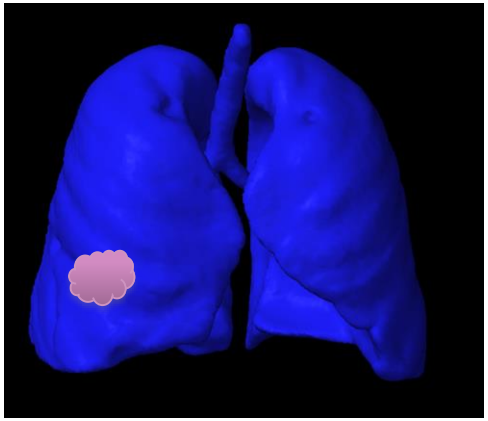


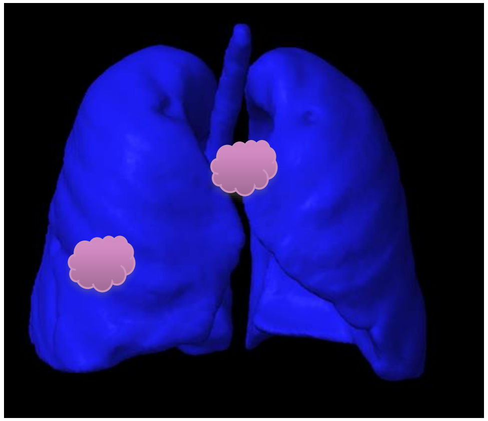
Fig. 1. Color fusion of a midposition planning computed tomography scan (purple) and single phase of a 4-dimensional cone beam computed tomography scan (green) illustrating a baseline shift of both lymph node (green purple marker displacement visible in coronal and sagittal view, top and bottom right) and primary tumor (large green purple tumor displacement visible in coronal view, top left).

- PTV margins reduced 27% (from bony to carina match)
- Baseline variations observed both for tumour and lymph nodes (marker)

Schaake 2014 IJROBP

Registration strategy at Rigshospitalet





LR

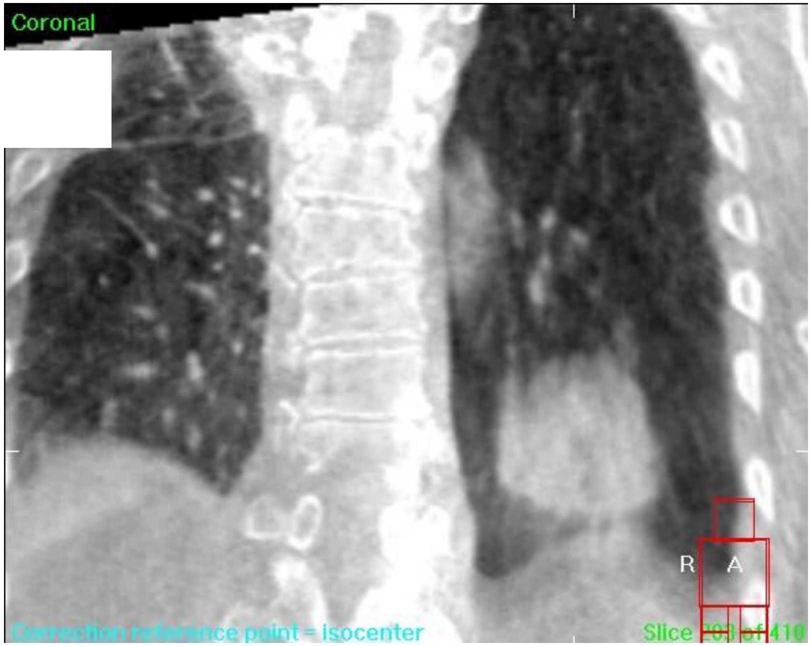
Registration on tumour
Verify OAR/bone

Registration on carina
Larger margins on peripheral tumour

Josipovic et al R&O 2016

4. Volume imaging

Lower lobe tumor
with large motion amplitude



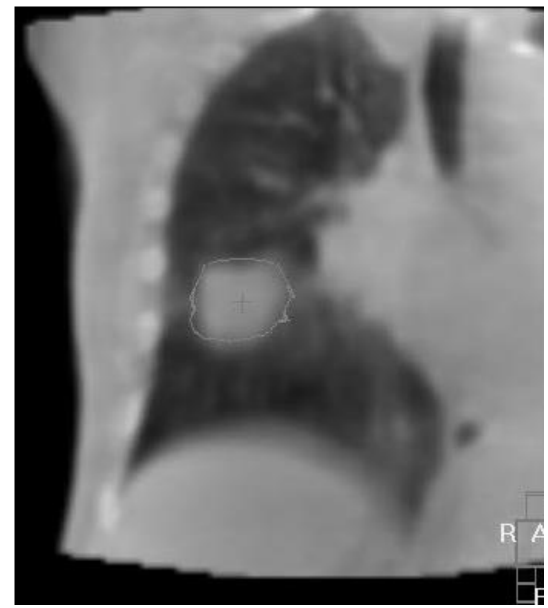
Blurred target because of
long image acquisition time

Integration of 4th dimension into IGRT

Planning

Treatment

Manual contour registration



Respiration correlated CT

„Conventional“ slow CBCT

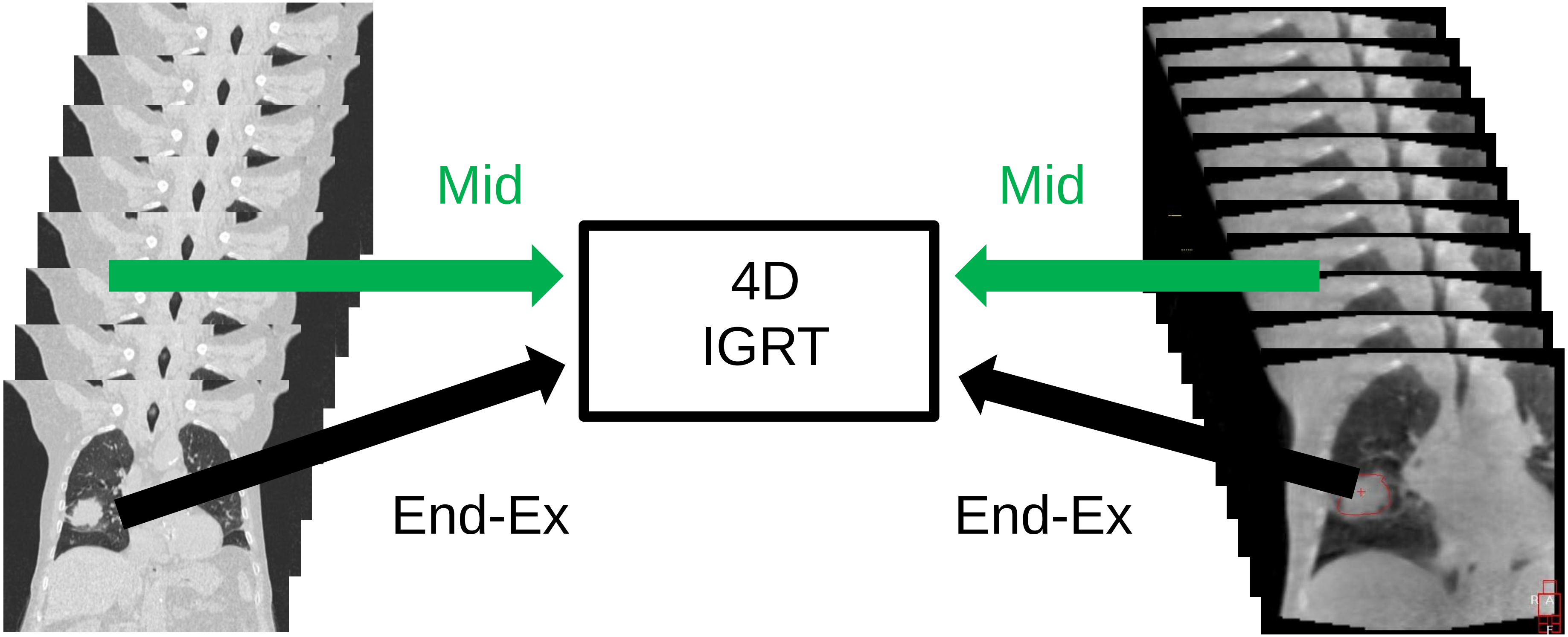
NB: what you see is a pseudo ITV/midventilation

Guckenberger Acta Ocol 2006

In-room image guidance for highly mobile tumours

Treatment planning:
Reference Image

Treatment delivery:
Verification Image



Possibility of matching a specific phase

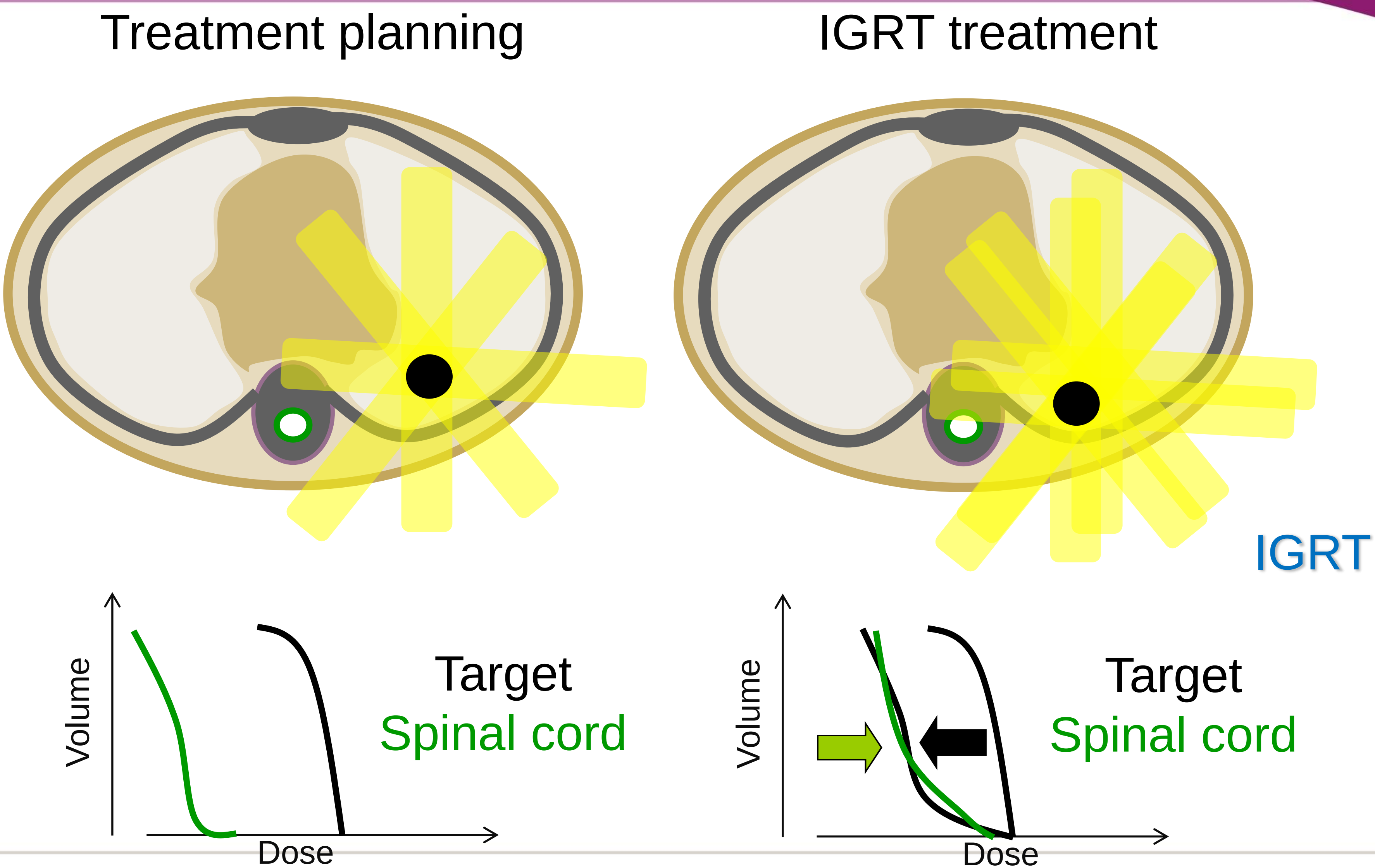
Interobserver variability reduced (Sweeney at al RO 2012)

Alternatives

- 3D CBCT and larger margins (larger interobserver variation)

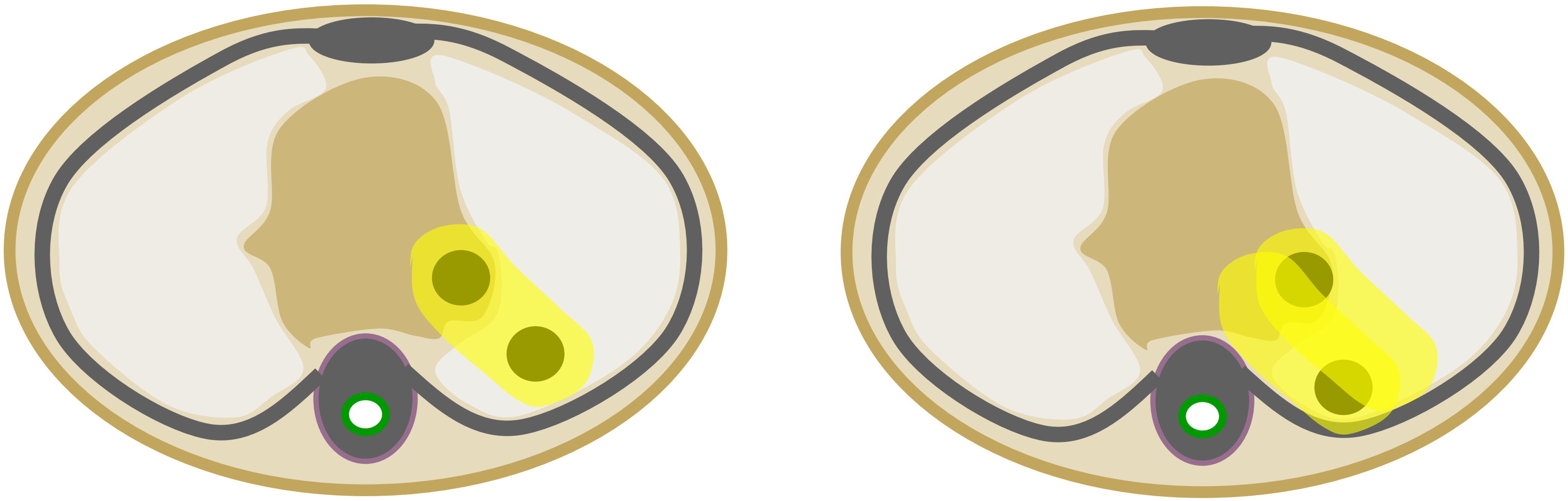
- If small, highly mobile tumours (e.g. SBRT):
  - Bony landmarks (large margins)
  - DIBH CBCT and treatment
  - Wait ???

Challenge 1: baseline shifts



Challenge 1: baseline shifts

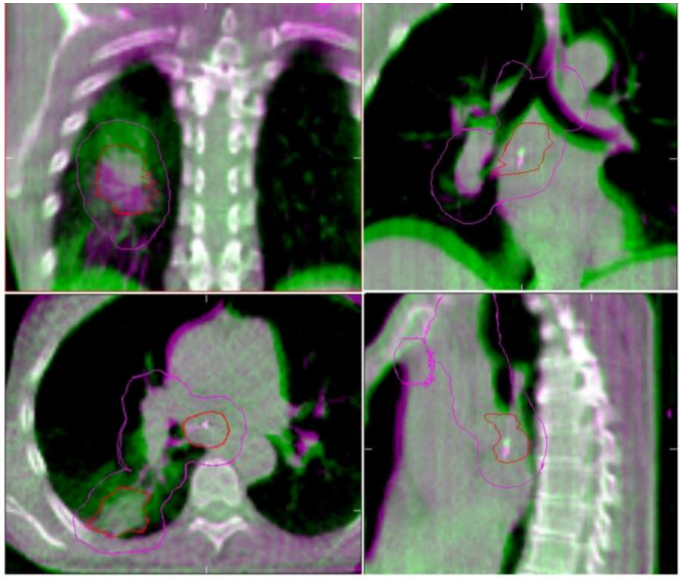
Treatment planning | IGRT treatment



Shift of the primary relative to the nodal target

- Volume imaging is required for visualization of the these effects
- Shifting the patient does not solve the problem

Differential motion lymph nodes / target



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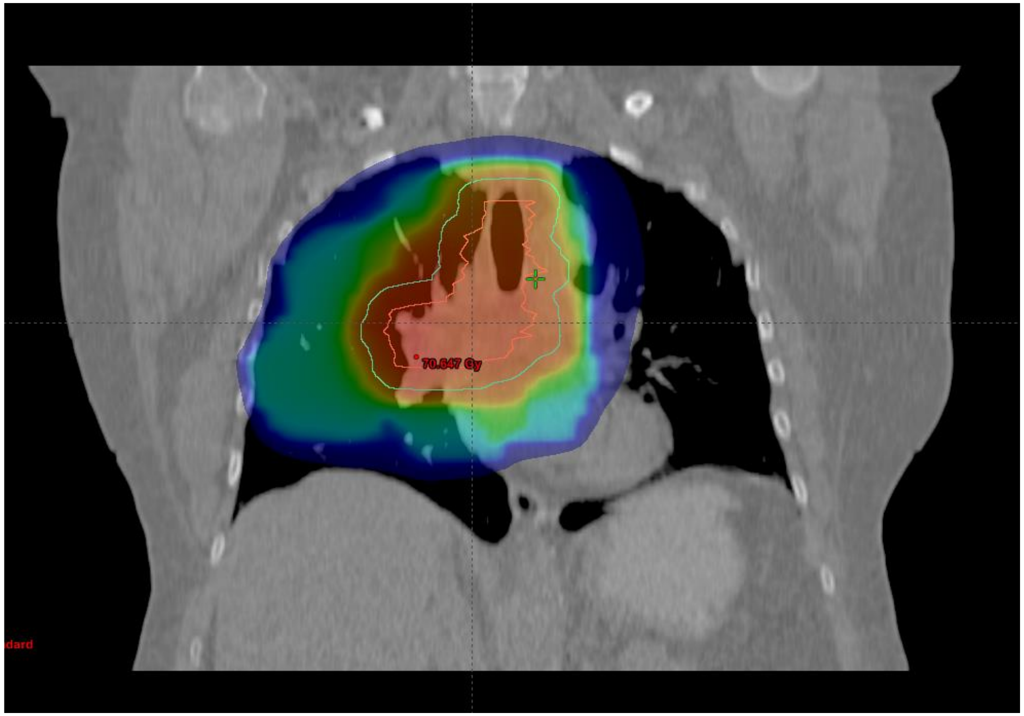
- PTV margins reduced 27% (from bony to carina match)
- Baseline variations observed both for tumour and lymph nodes (marker)

Schaake 2014 R&O

Challenge 1: baseline shifts, possible solutions

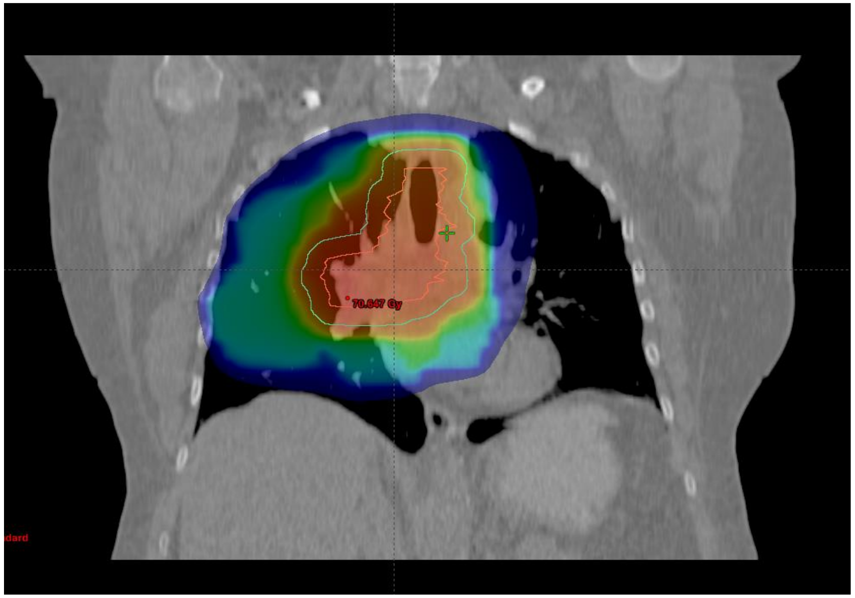
1. Volume image required to visualization
2. Quantification would require deformable image registration
   -> available but only offline
3. Online dosimetric evaluation would be required for a decision making process
   -> not available, yet
4. Compensation strategies:
   - Perform an average IGRT shift
   - Adapted PTV margins
   - Re-planning

Challenge 2: large tumours / small lung volume

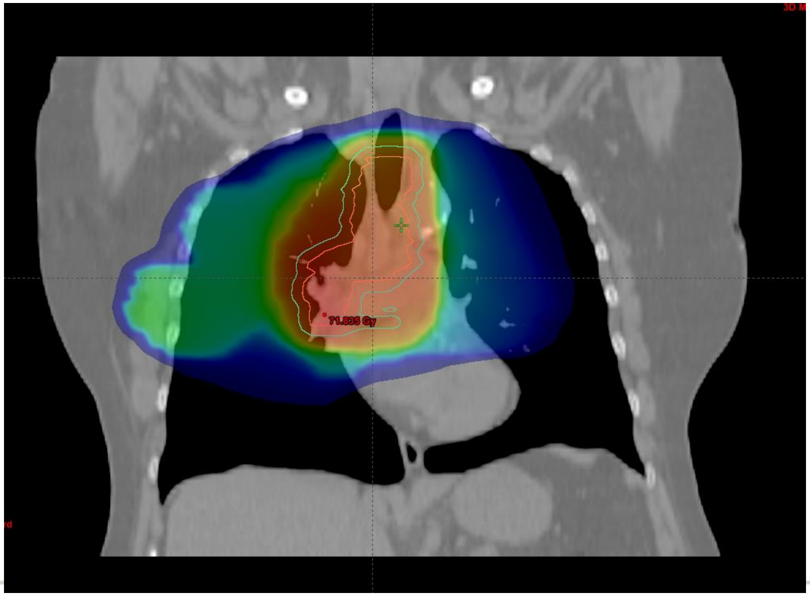


- 70-year old patient with poor pulmonary function
- Tumour motion < 5mm
- MLD unacceptable if a curative dose (66Gy) is delivered
- Gating won't help (neither will tracking!)

Challenge 2: large tumours / small lung volume



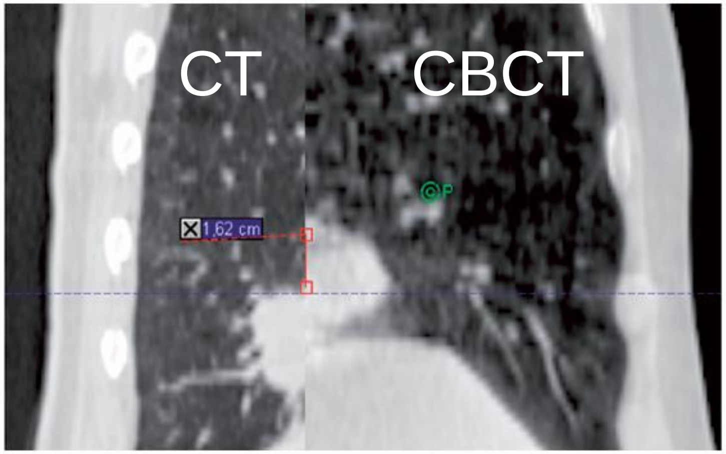
Free breathing
(MLD 23.6Gy)



Deep inspiration
(MLD 19.7 Gy)

As part of INHALE,
phase II protocol

Some caveats of breath hold



Josipovic et al Acta Oncol 2014

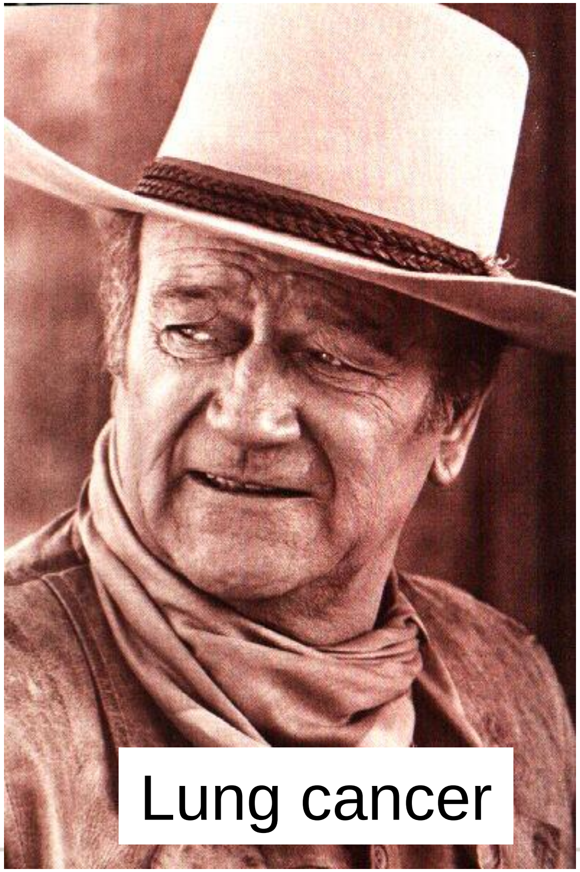
2nd patient treated in DIBH

•peripheral target + mediastinal lymph nodes

•10th fraction: match on mediastinum, 1.6 cm shift CC direction for peripheral tumour

Don’t (blindly) trust external surrogates:
markers, spirometry, surface based etc…
<u>Daily breath hold CBCT is mandatory</u>
<u>Intra fraction monitoring highly desirable</u>

Compliance ? Pulmonary function ?



Take-home messages for treatment verification in current clinical practice

- The most important is to see the tumour
  - ➢ in a representative position
- 2D imaging modalities (markers)
- 3D imaging modalities
  - \+ Volume imaging
  - \- No real-time imaging
- 4D imaging modalities
  - \+ fewer breathing motion artifacts
  - \- Actual benefit?

No single solution will be appropriate for every patient

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Keep breathing ☺

Quiet free breathing

Breath hold

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WWW.ESTRO.ORG/SCHOOL

Image Registration Issues for Breast

Athens 2017

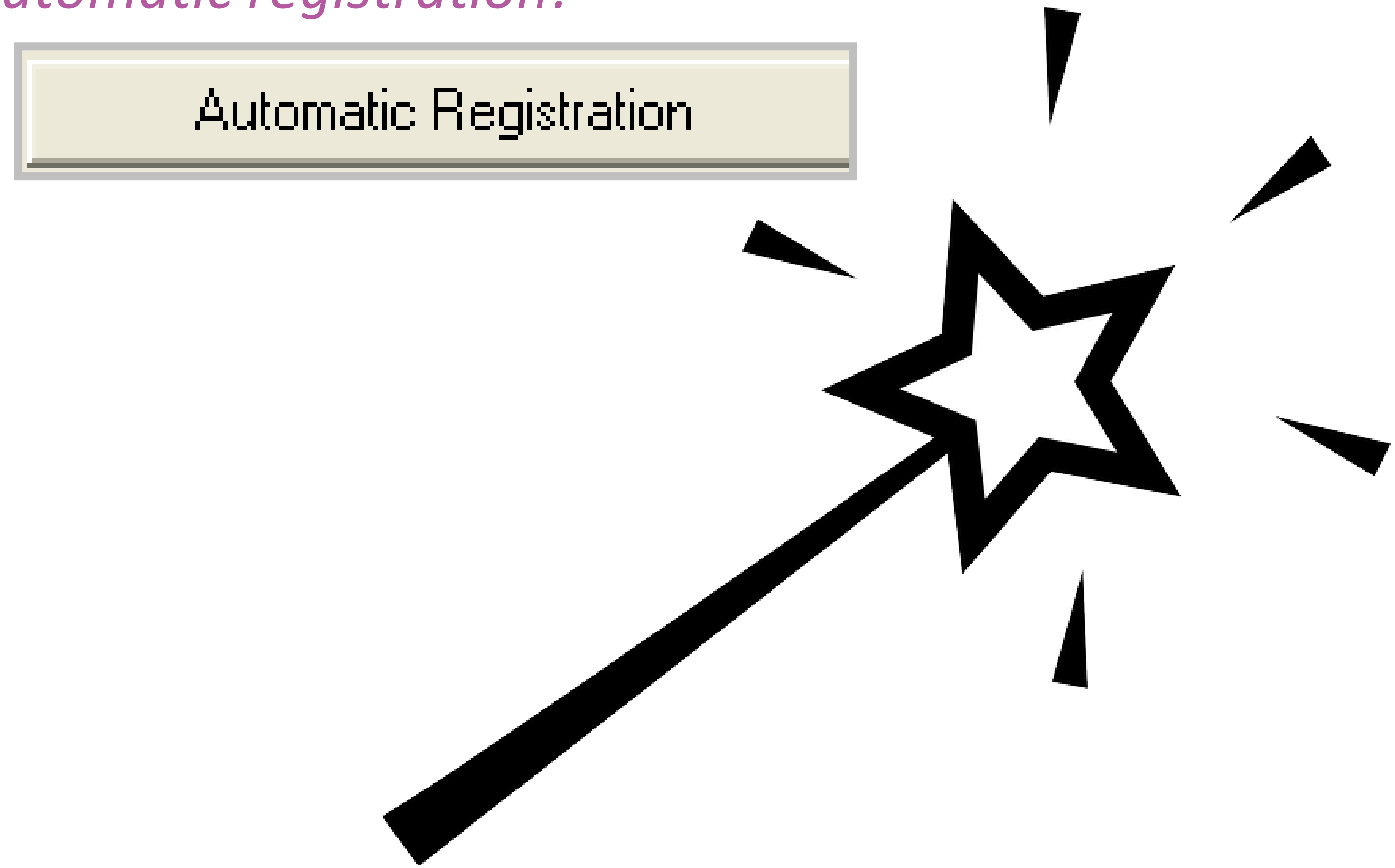
Helen McNair
Rms.nhs, London

Rianne de Jong
Academic Medical Centre, Amsterdam

CBCT Registration

- Bony anatomy registration (ribs & sternum / thoracic wall)
- Surface registration
- Marker registration

Big fan of automatic registration!

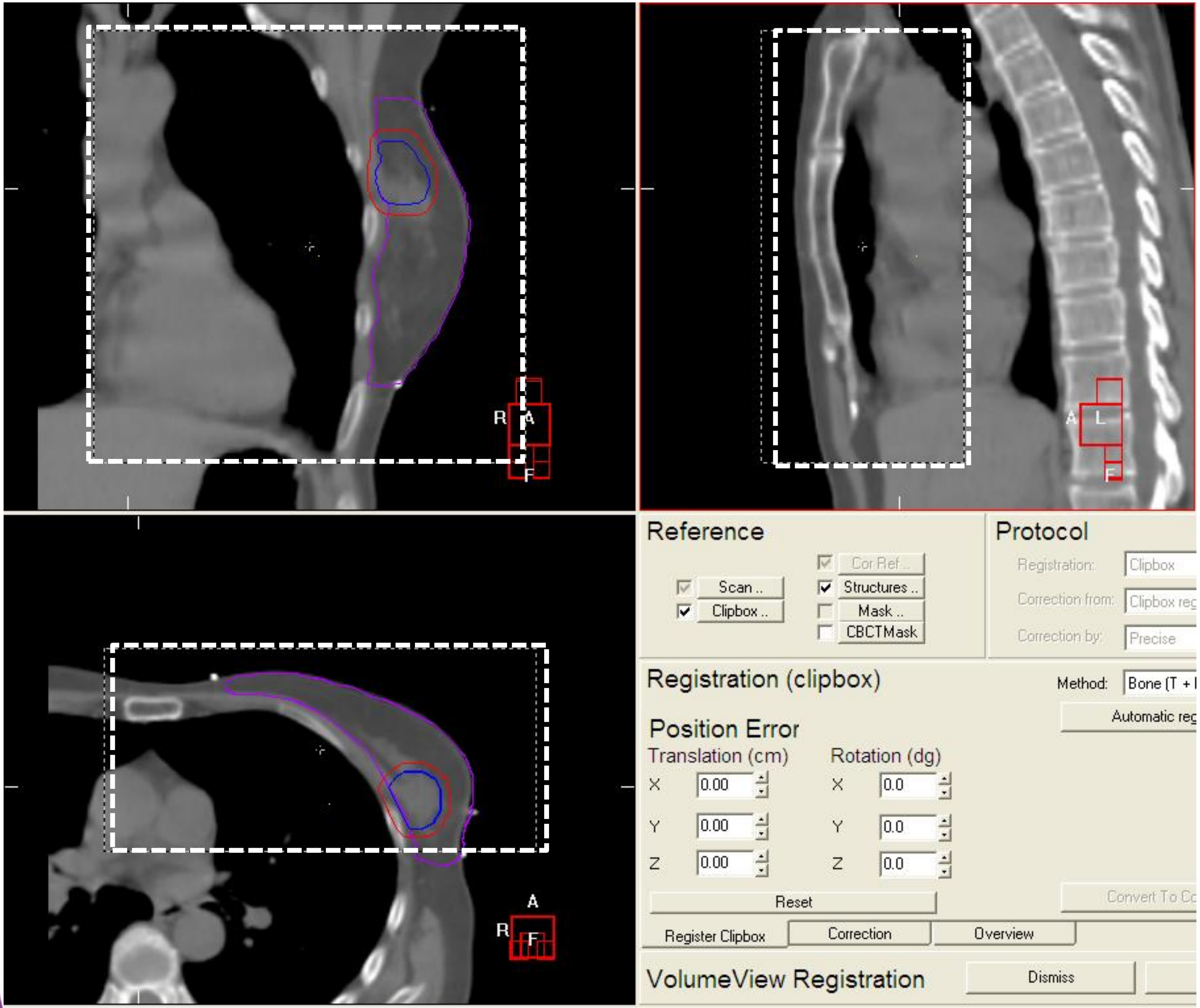


CBCT Registration

- Bony anatomy registration (ribs & sternum / thoracic wall)
- Surface registration
- Marker registration

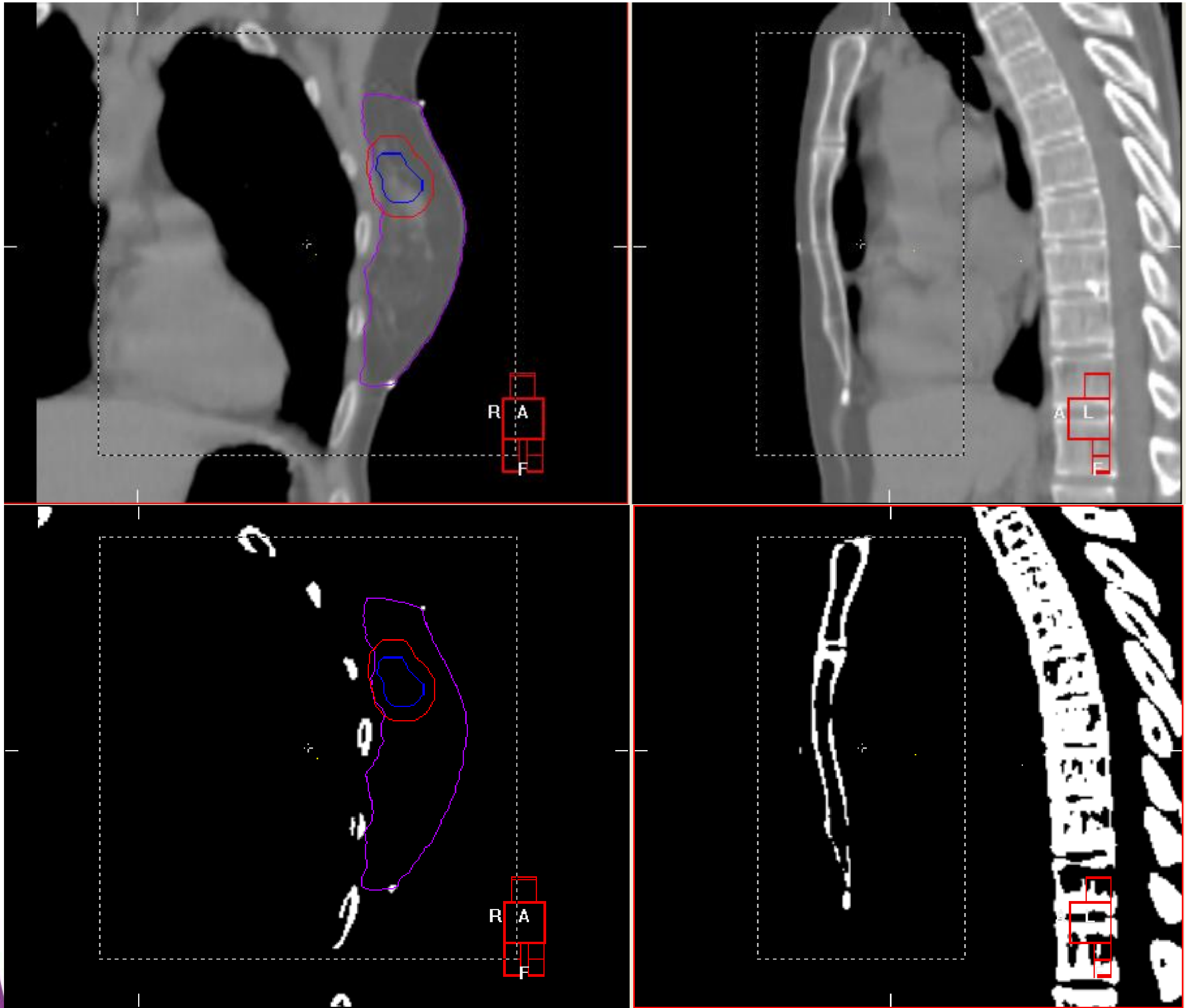
Big fan of automatic registration!

- Definition of the region of interest (clipbox)
- Choice of algorithm (Elekta)
- Choice of windowing HU (Varian)



Bony anatomy that is a good surrogate: ribs

What are you registering with this ROI?



Chamfer registration

Segmentation of range of HU
- bones -

Registration on ribs

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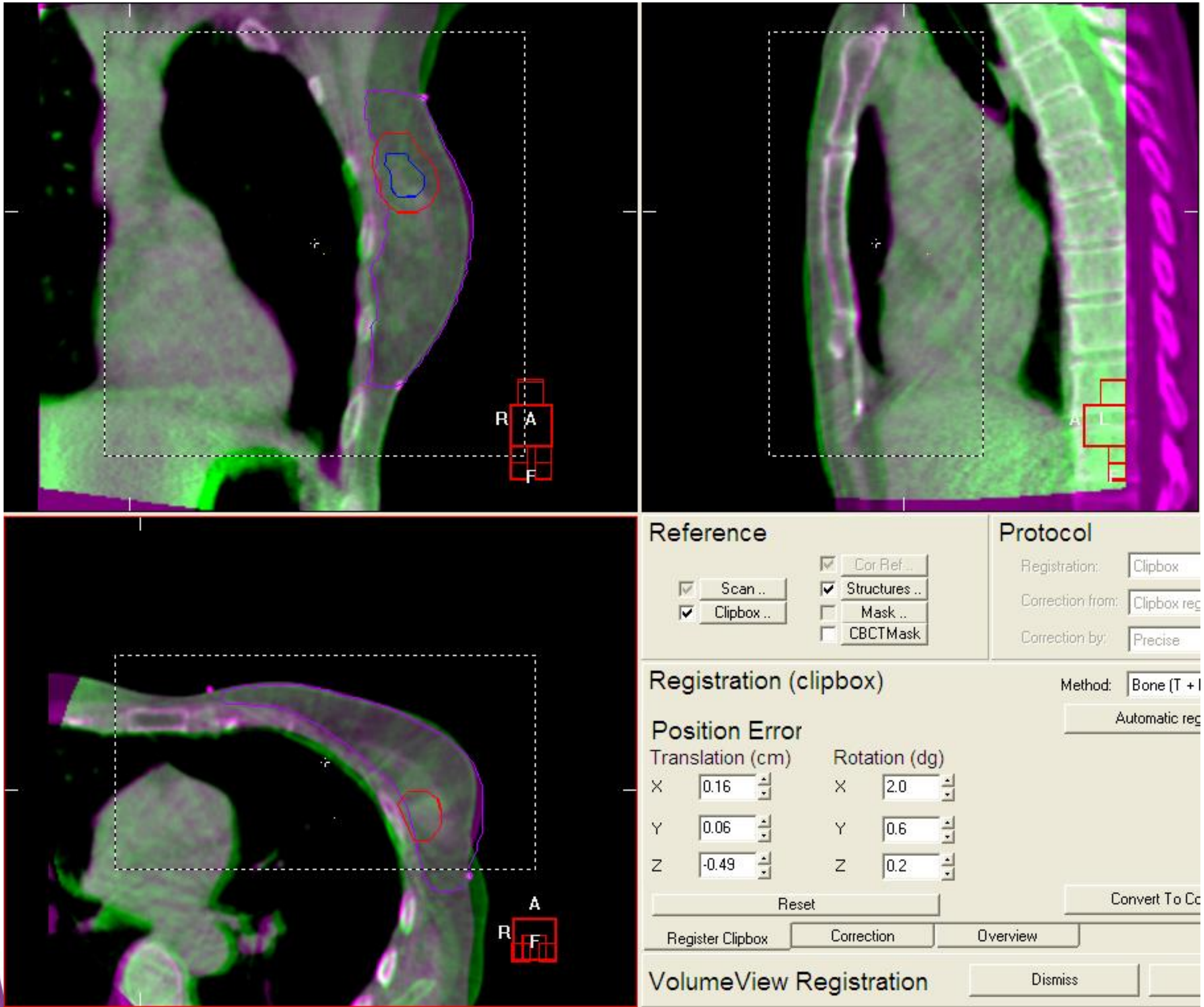


CT ref

CBCT

Bony anatomy that is a good surrogate: ribs

What are you registering with this ROI?

Bone algorithm (chamfer match)

Registration on ribs

Registration on ribs

So, did the algorithm work perfectly?

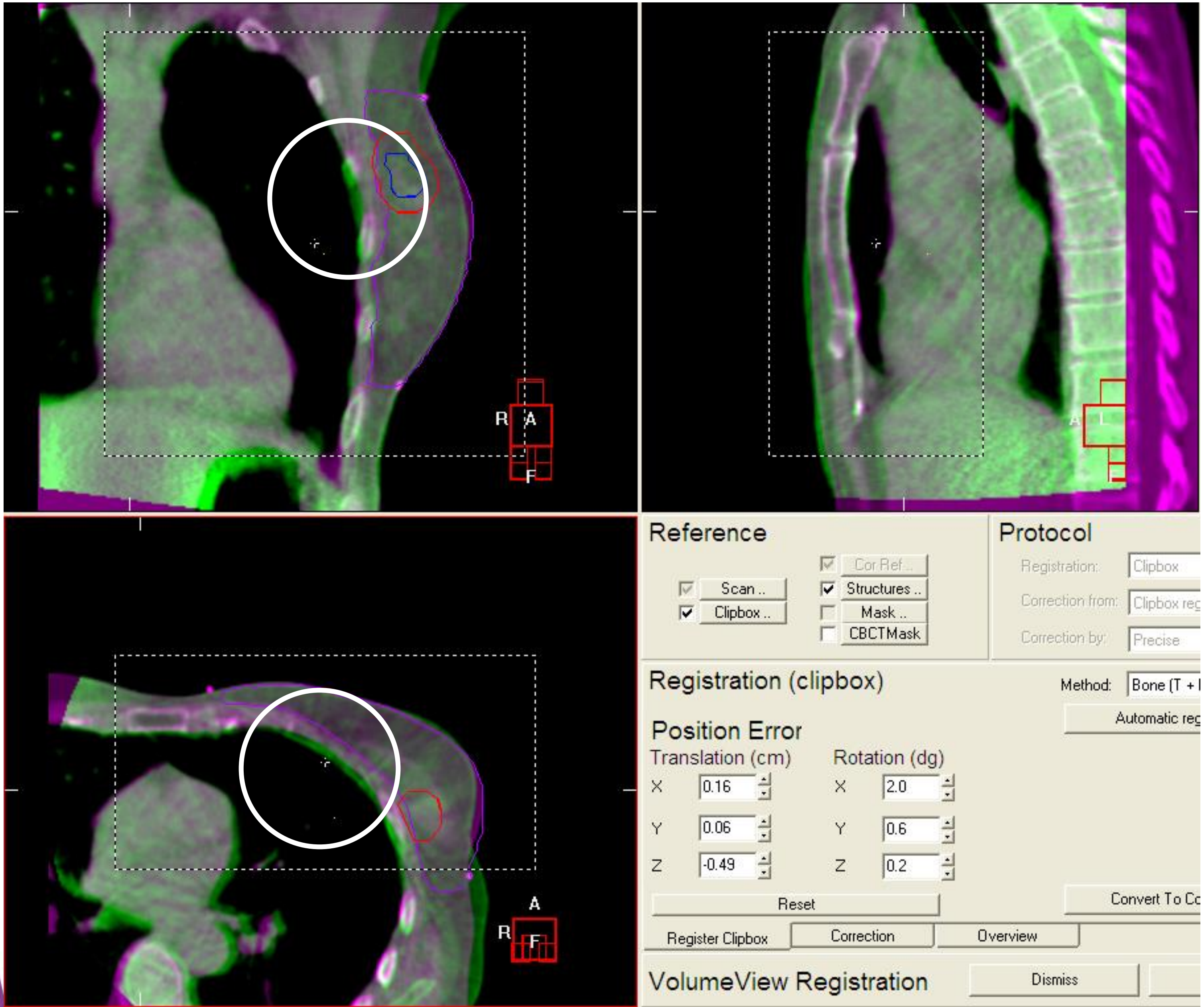
CT ref

CBCT

Bony anatomy that is a good surrogate: ribs

What are you registering with this ROI?

Bone algorithm (chamfer match)



CT ref

CBCT

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Registration on ribs

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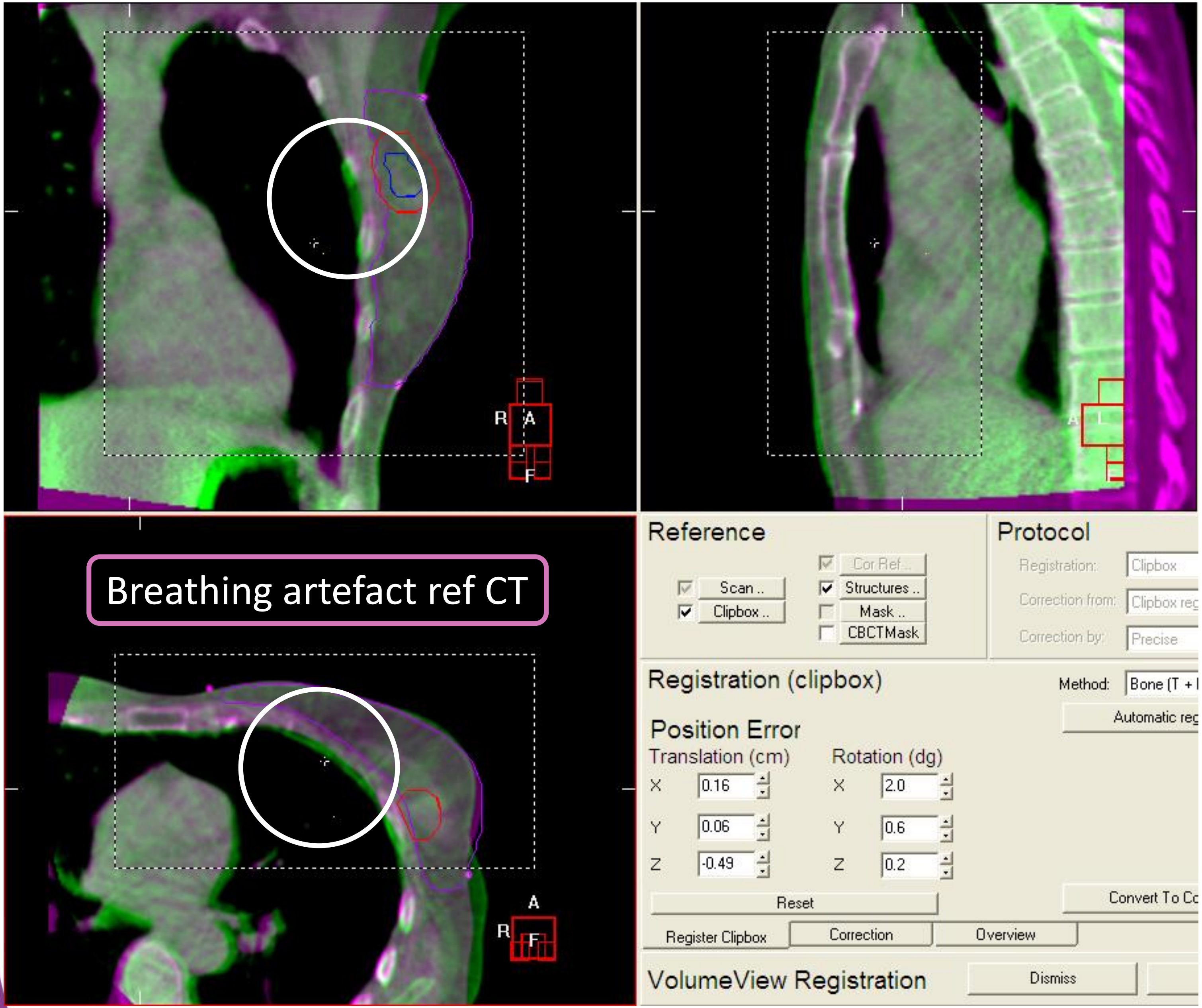

CT ref

CBCT

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Registration on ribs

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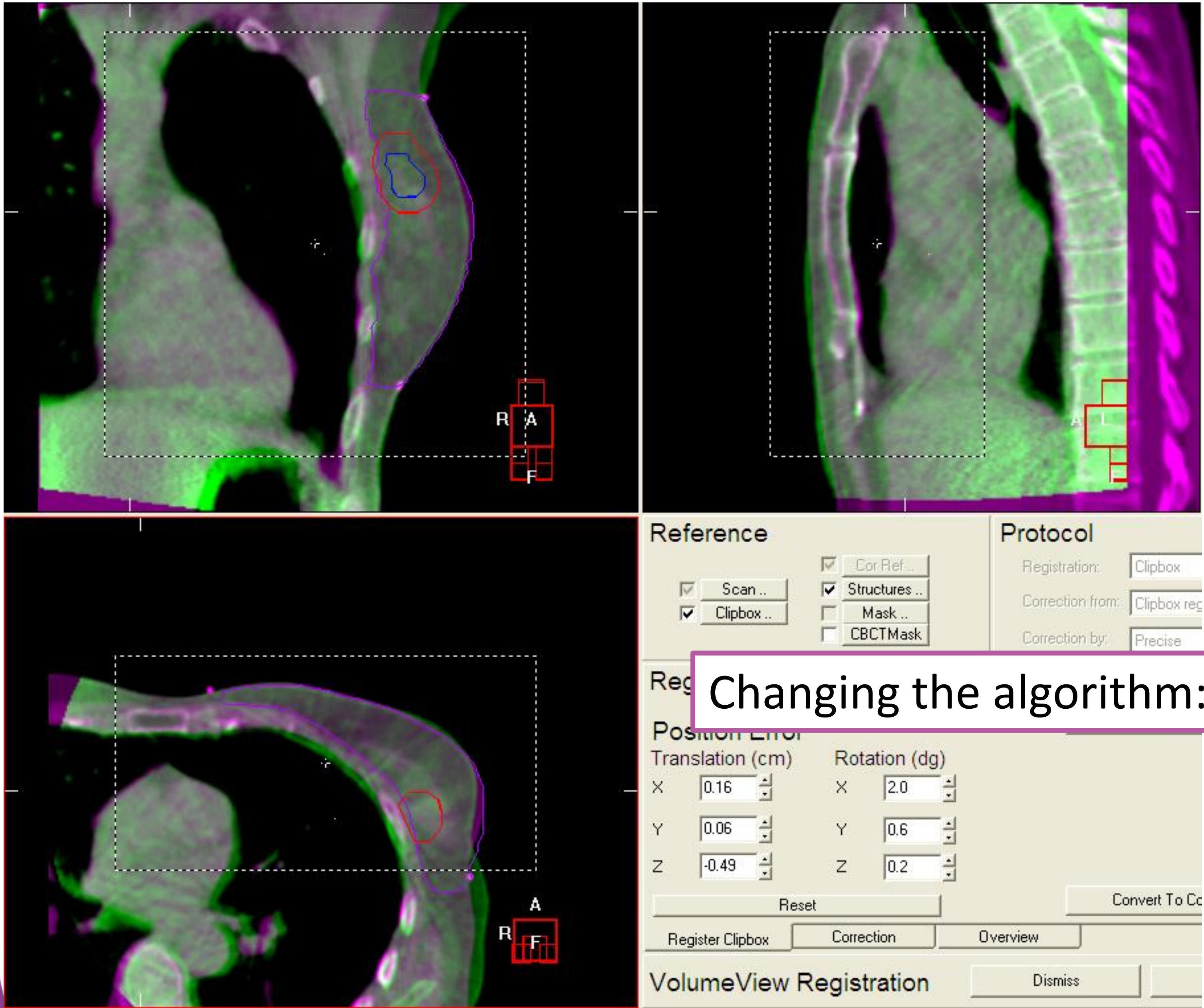


Changing the algorithm:

CT ref

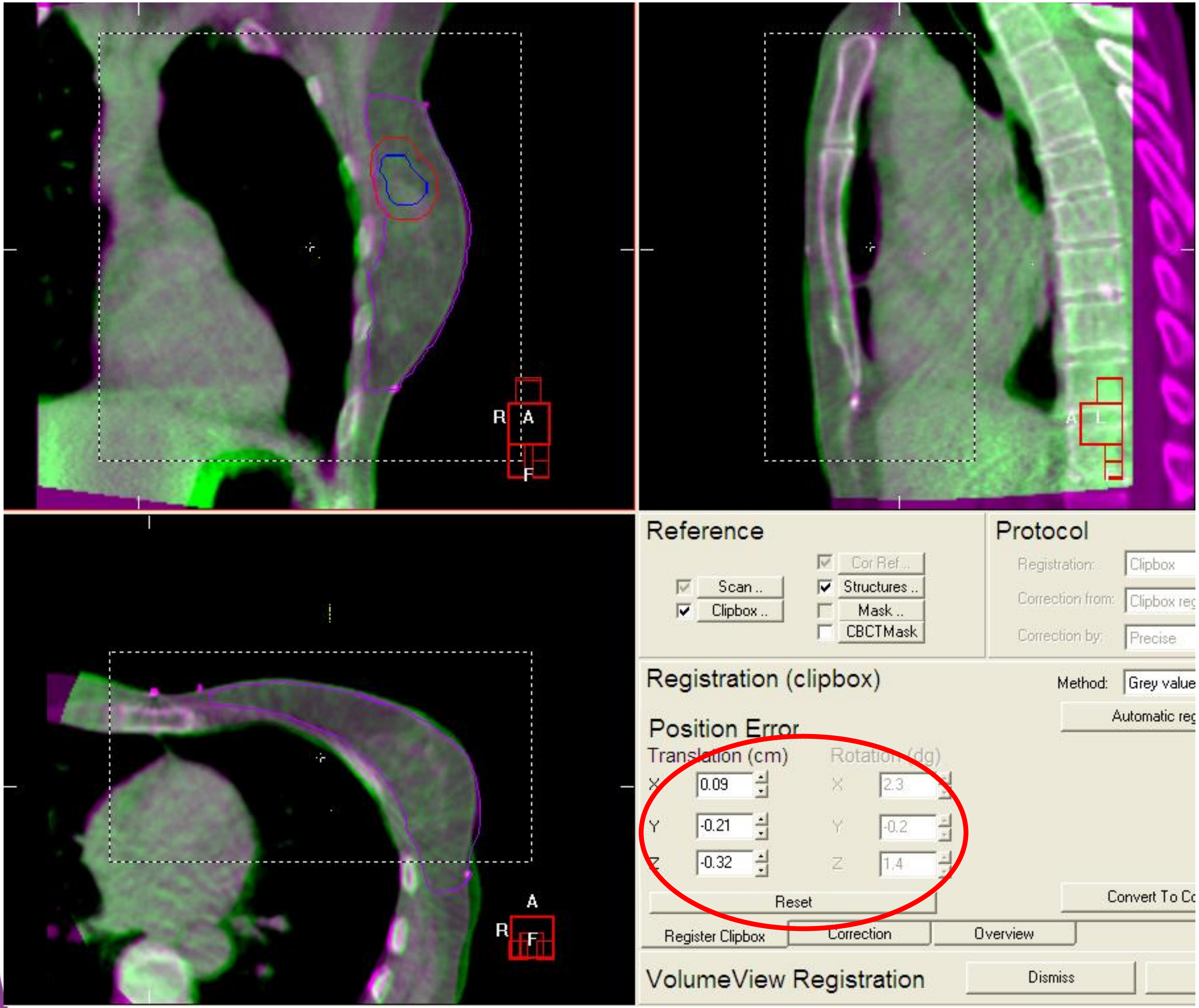
CBCT

Bony anatomy that is a good surrogate: ribs

What are you registering with this ROI?

Grey value algorithm

Registration on ribs



CT ref

CBCT

Bony anatomy that is a good surrogate: ribs

What are you registering with this ROI?

Grey value algorithm

Registration on ~~ribs~~ surface!

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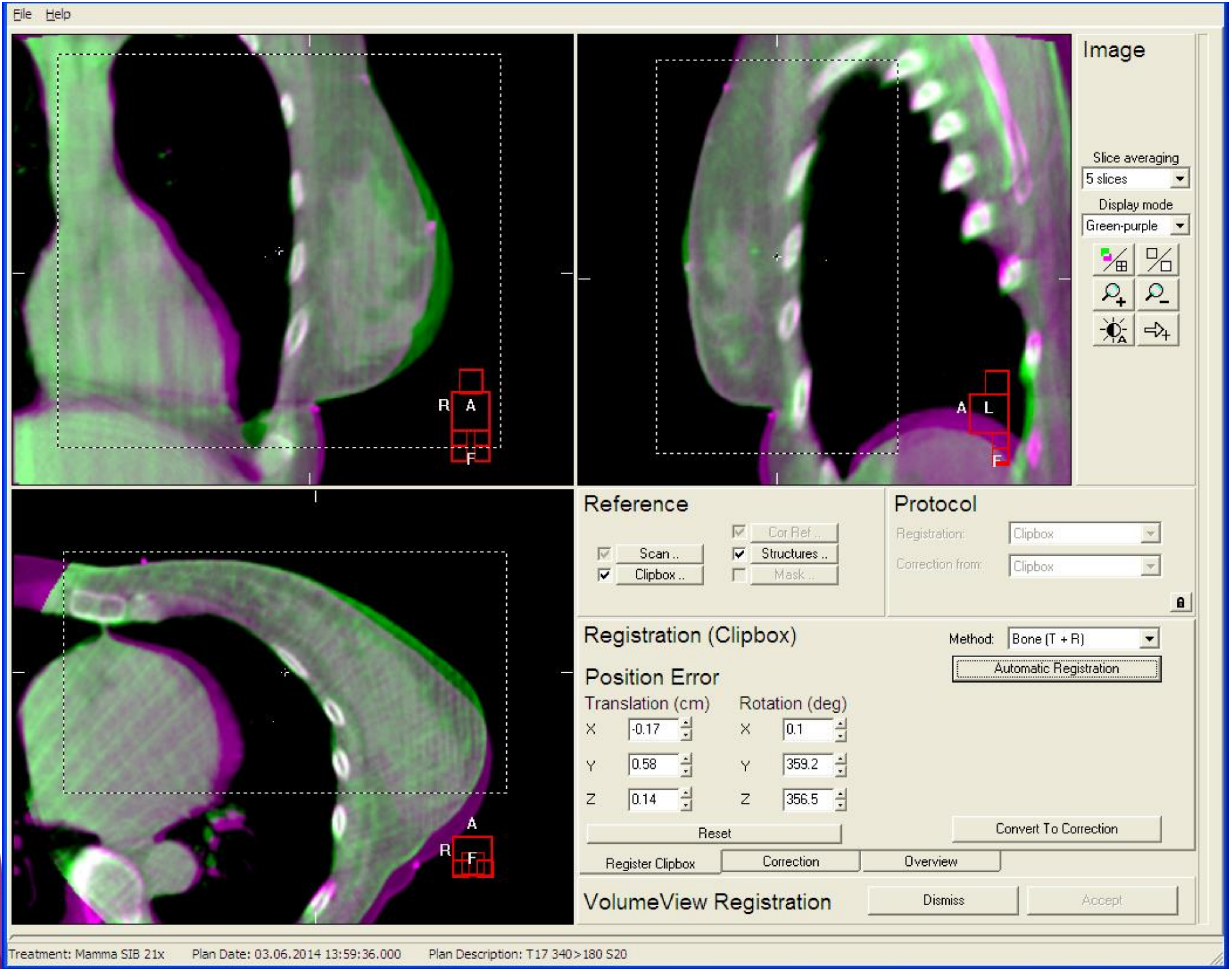


CT ref
CBCT

Ribs using:

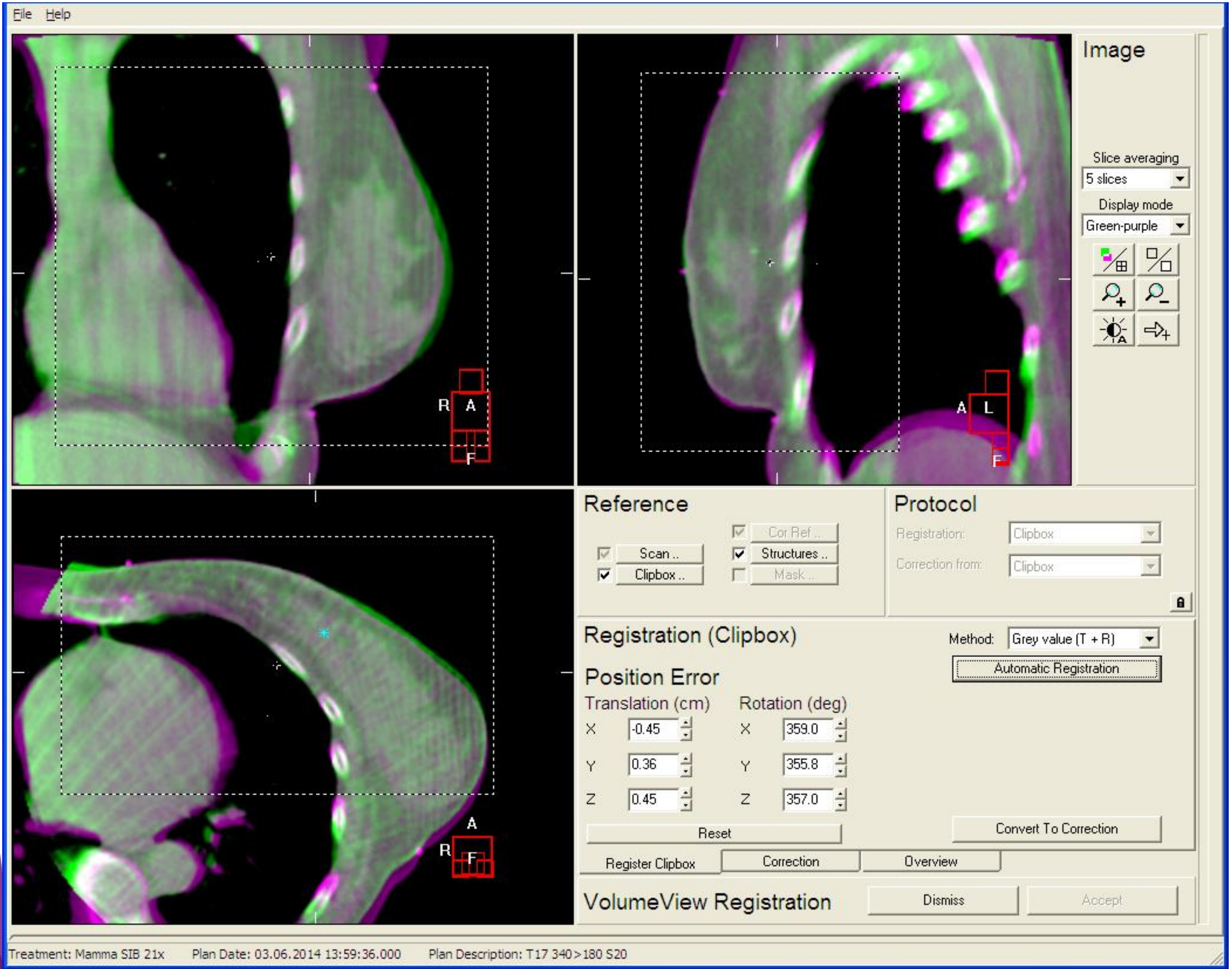
Clipbox
&
Bone algorithm
(chamfer match)

Same example , different patient

Registration on …

ESTRO School

Registration on …



CT ref

CBCT

Surface using:

Clipbox

&

Grey Value algorithm

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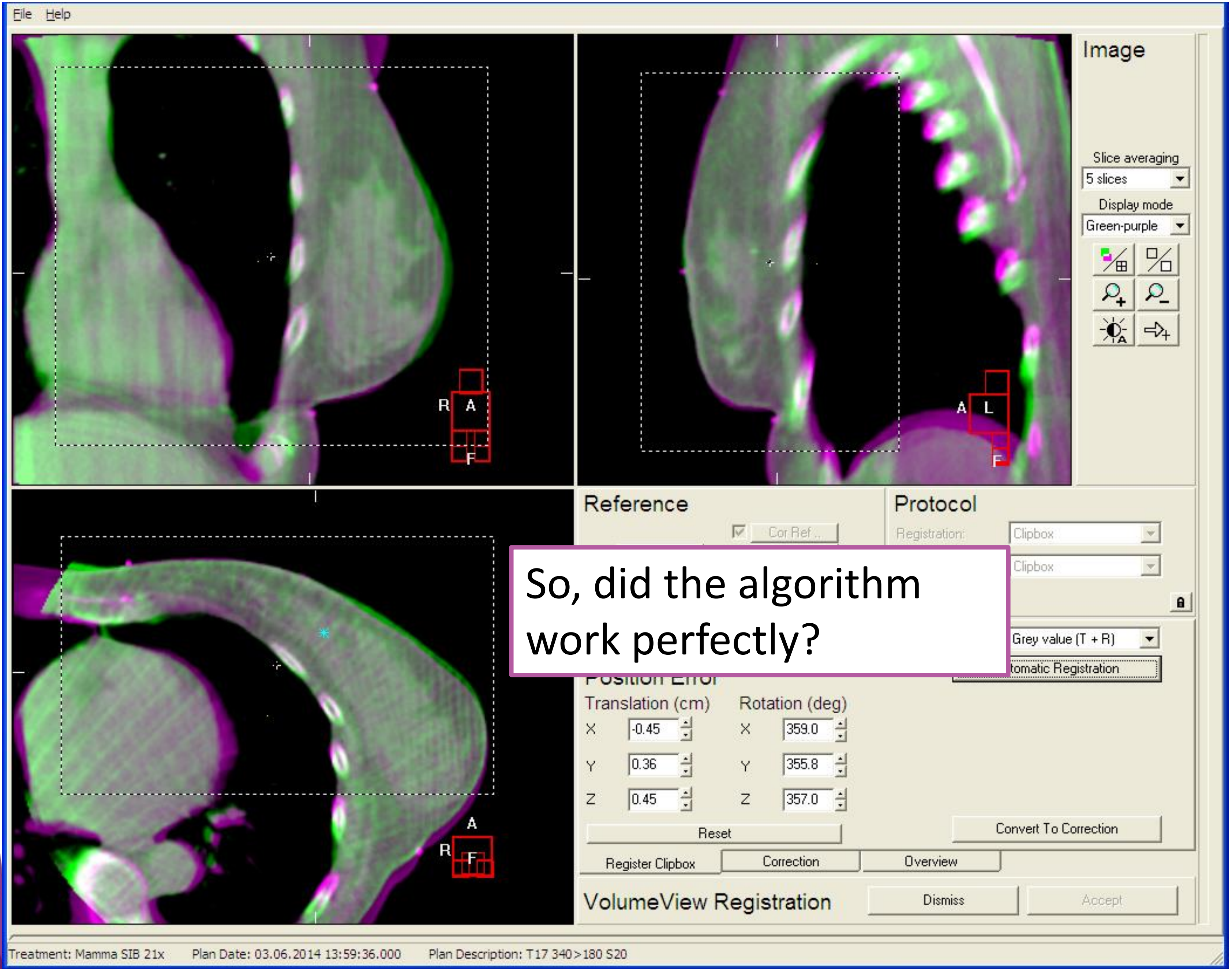


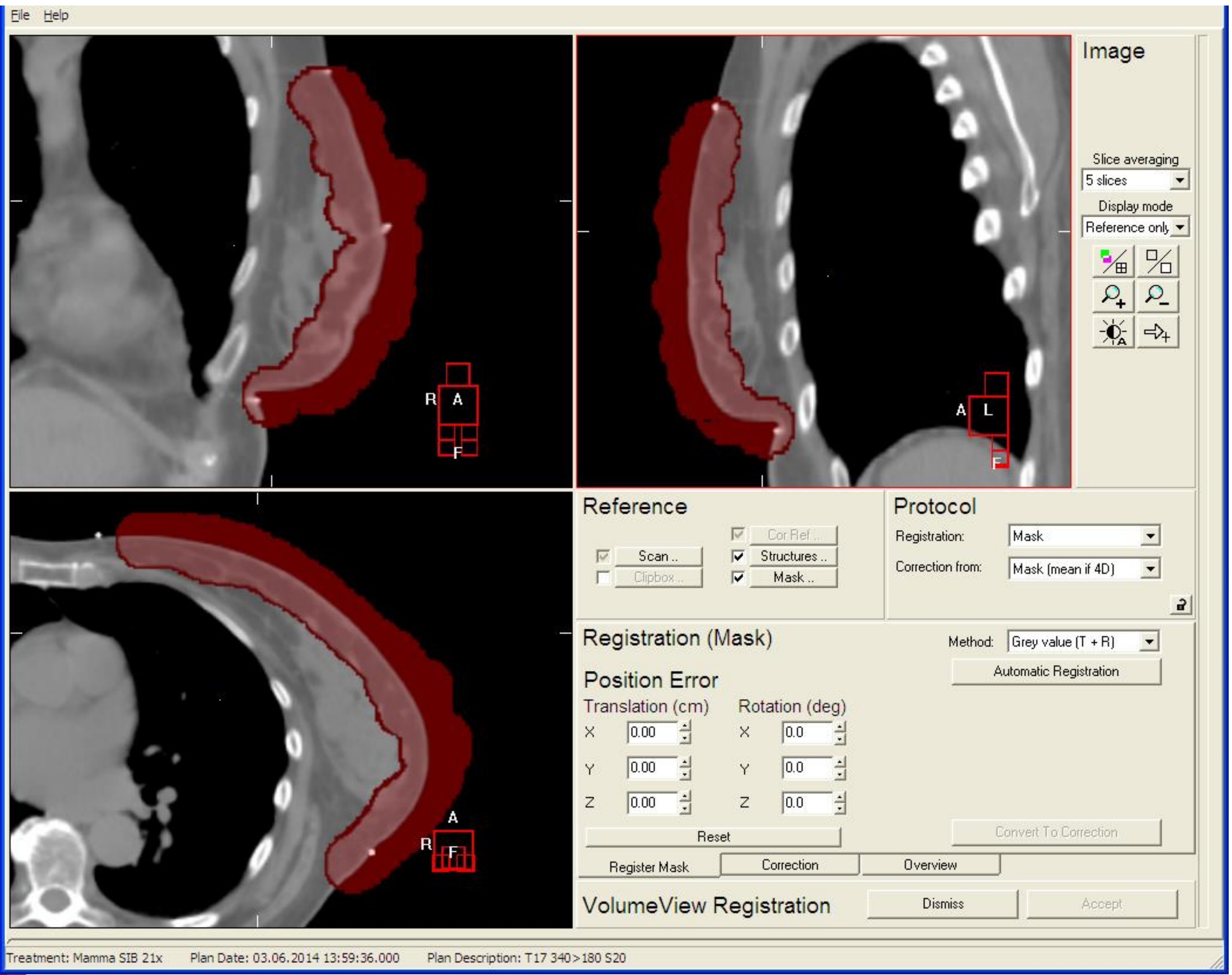
CT ref
CBCT

Surface using:

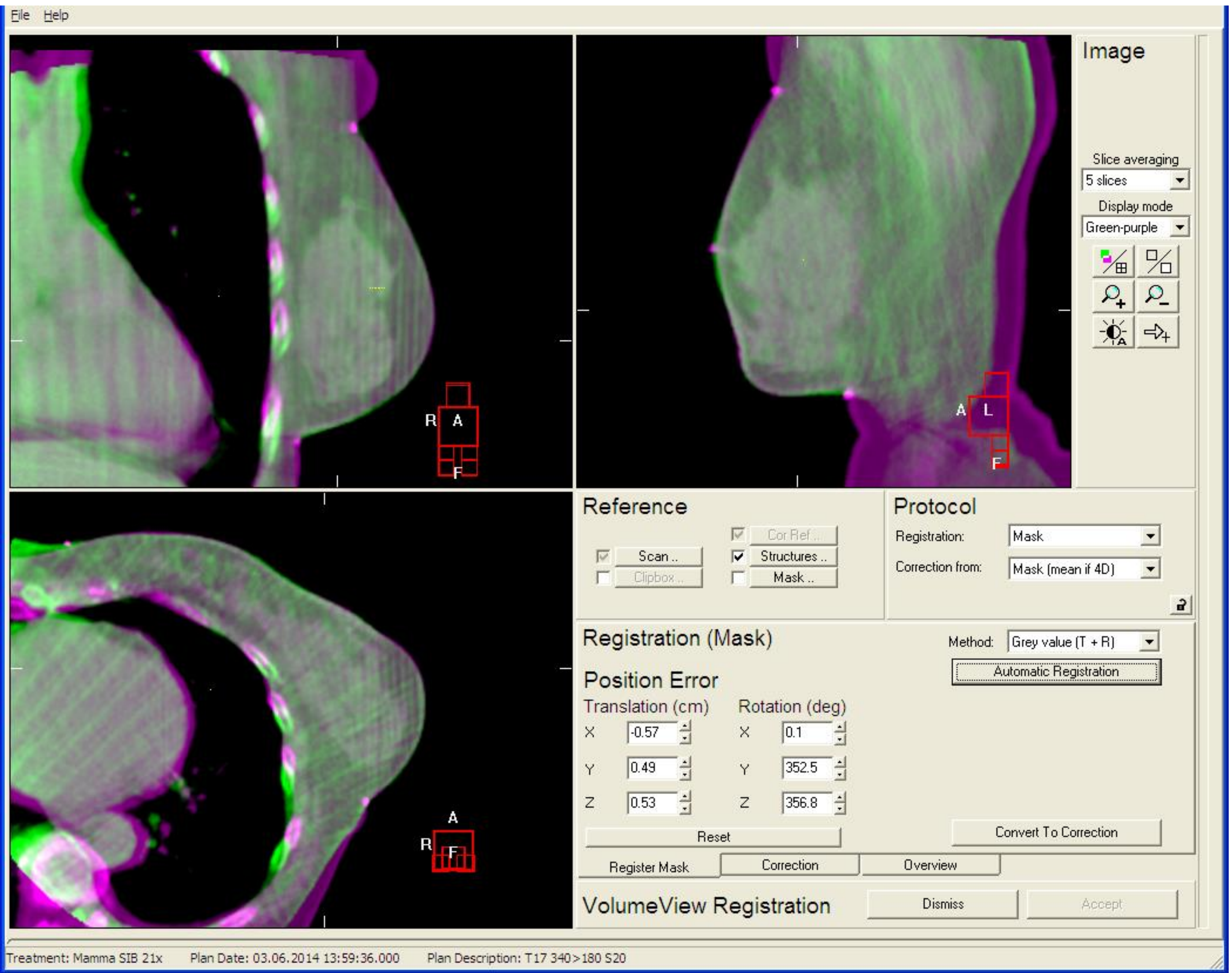
Clipbox
&
Grey Value
algorithm

Registration on …

ESTRO School



Registration on …



CT ref

CBCT

Surface using:

SROI

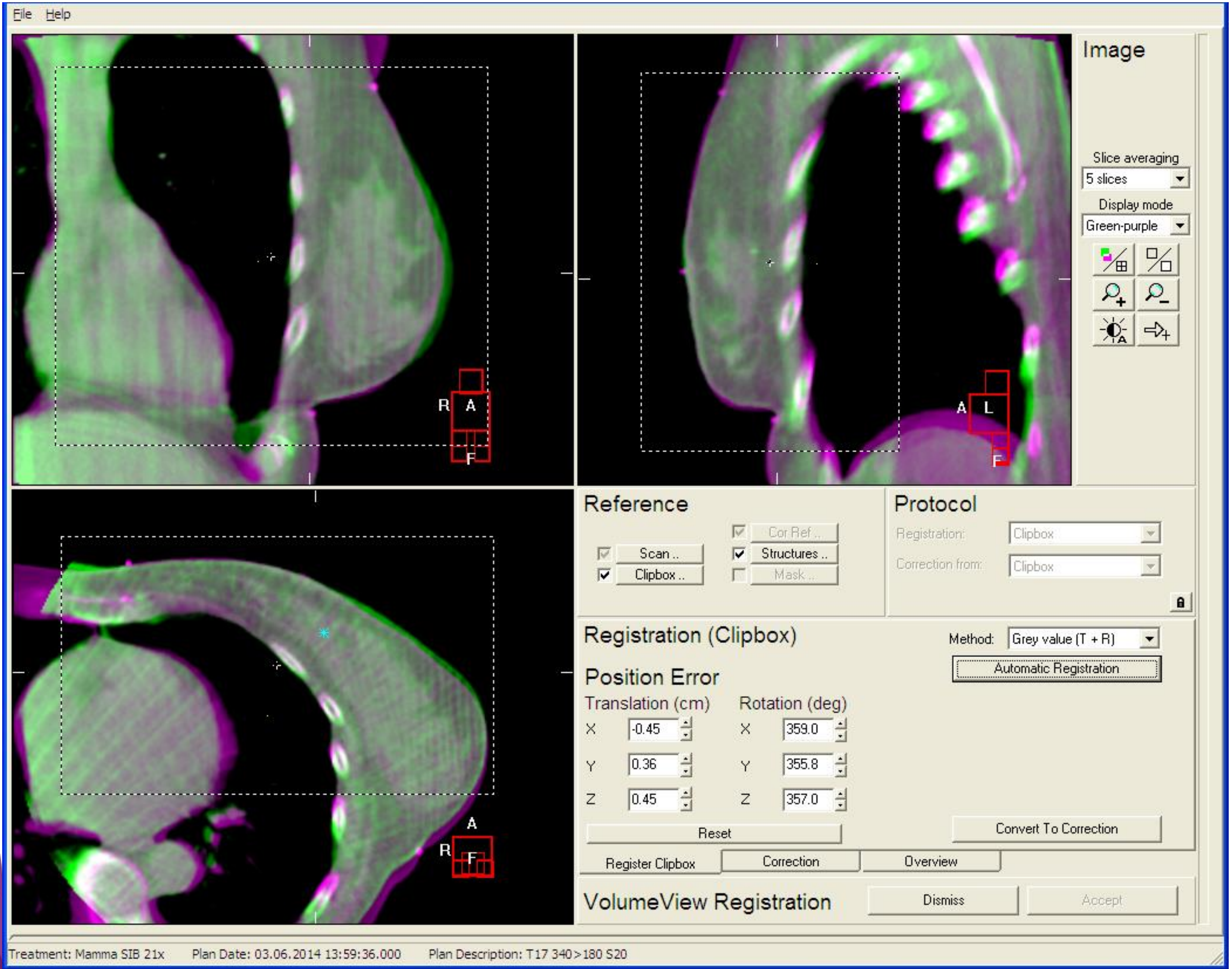
&

Grey Value

algorithm

Registration on …

ESTRO School



CT ref

CBCT

Surface using:

Clipbox

&

Grey Value

algorithm

Registration on …

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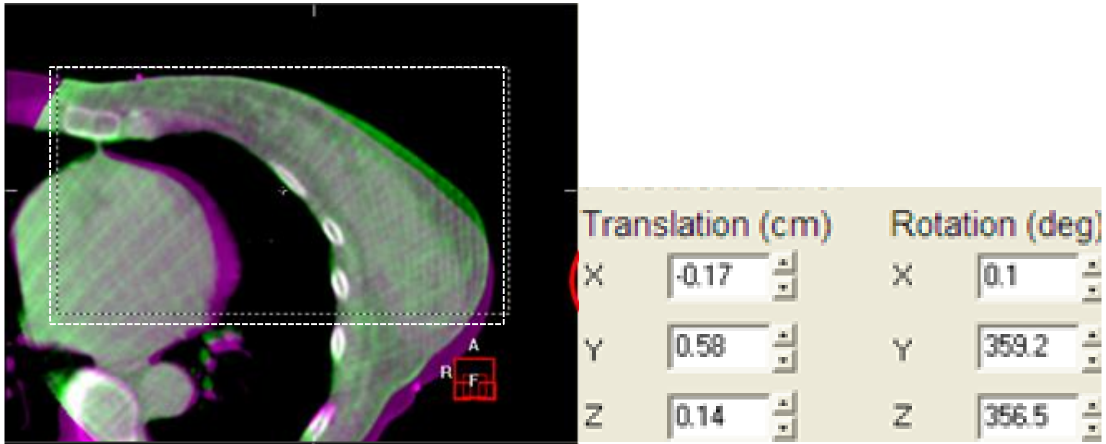
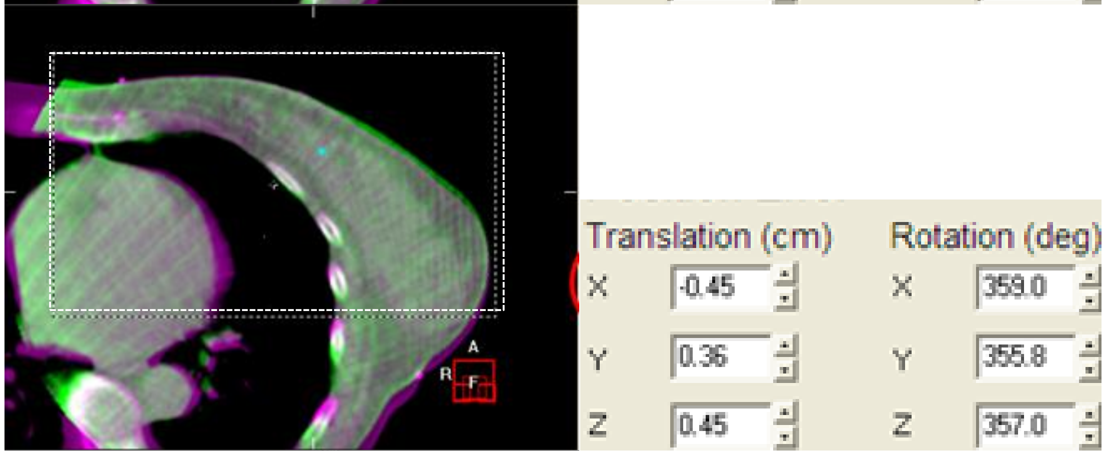
CT ref
CBCT

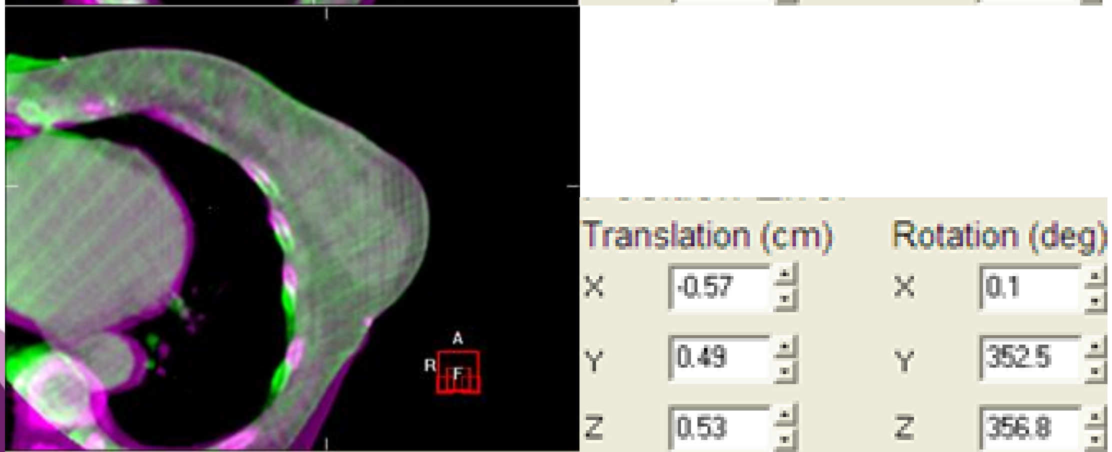
Registration on …



Ribs using clipbox and bone



´Surface´ using clipbox and grey value



Surface using shaped ROI and grey value

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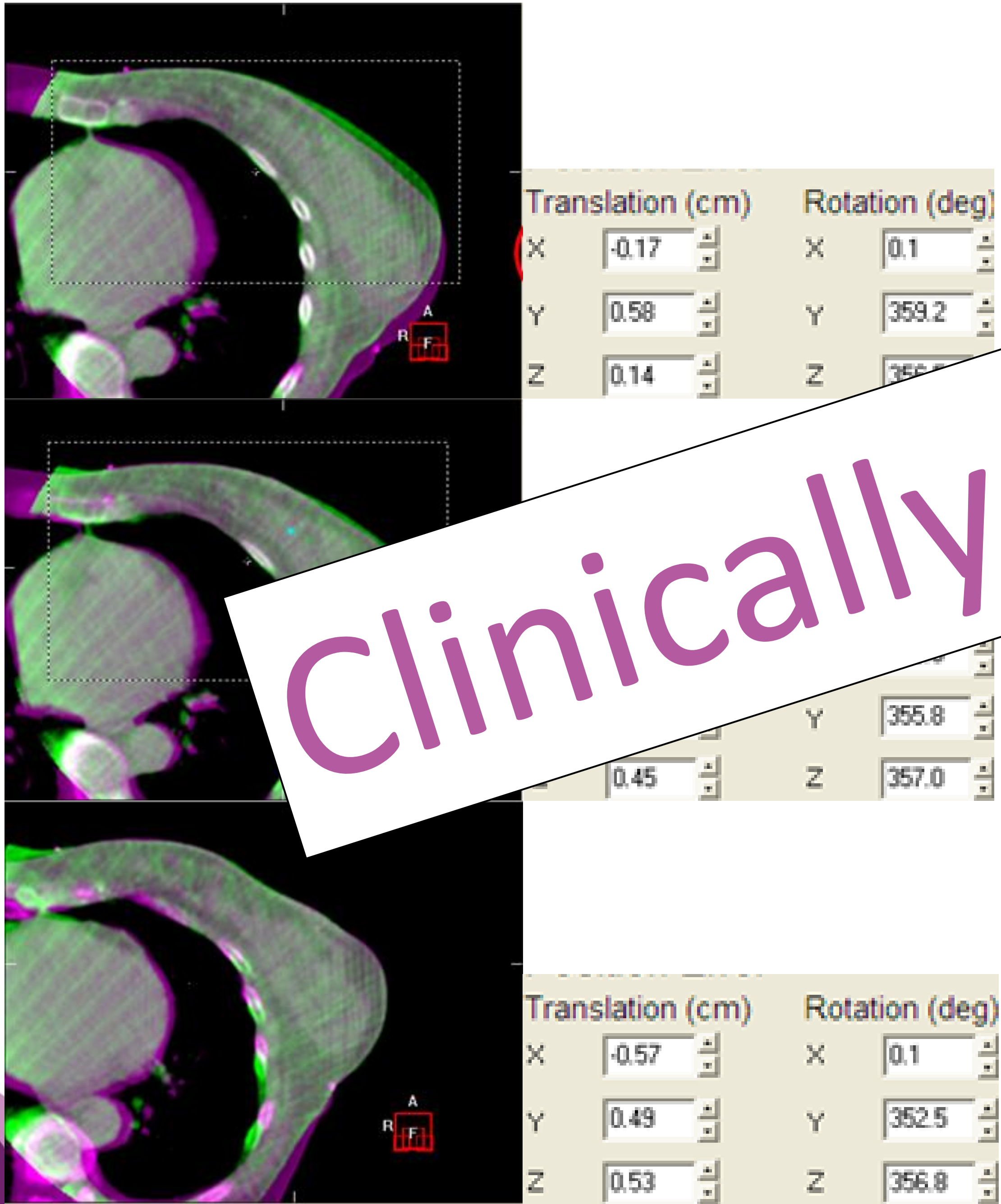
CT ref
CBCT

Registration on …



Ribs using cli…

Clinically relevant?

Surface using clipbox and grey value

Surface using shaped ROI and grey value

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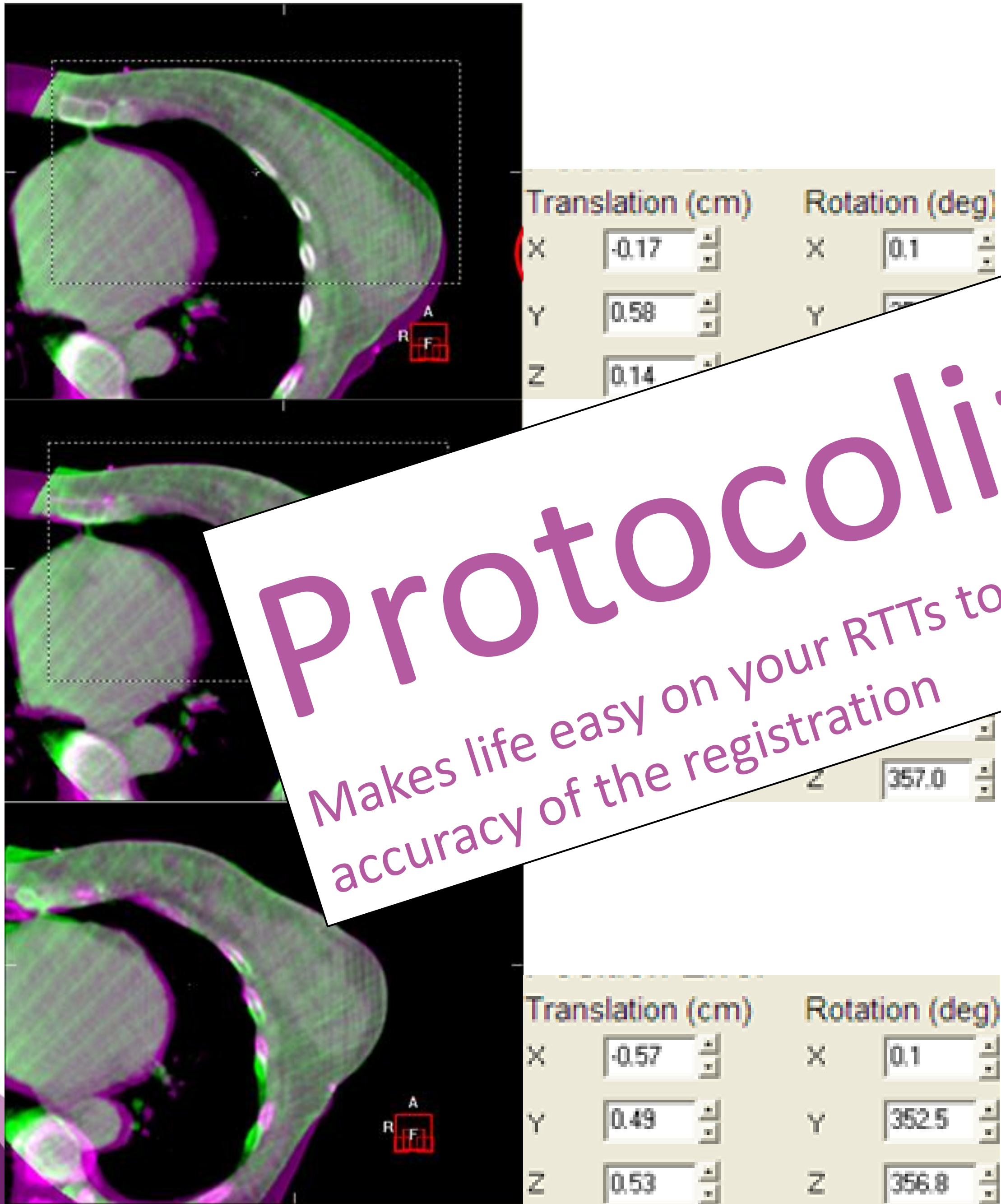
CT ref

CBCT

Registration on …



Ri… box and bone

…rface using clipbox and grey value

Surface using shaped ROI and grey value

Protocolize!!

Makes life easy on your RTTs to visually inspect accuracy of the registration

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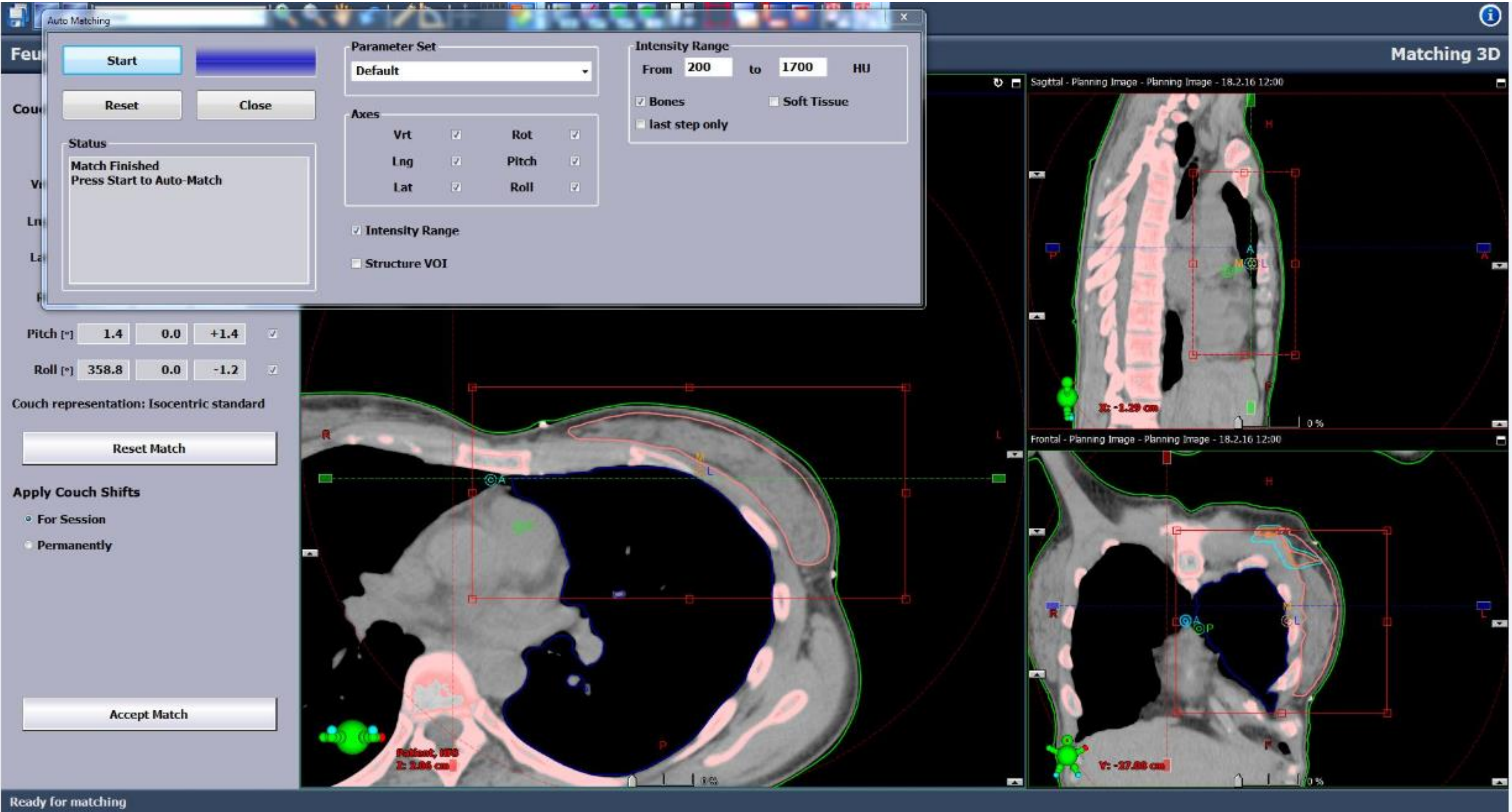
Registration thoracic wall



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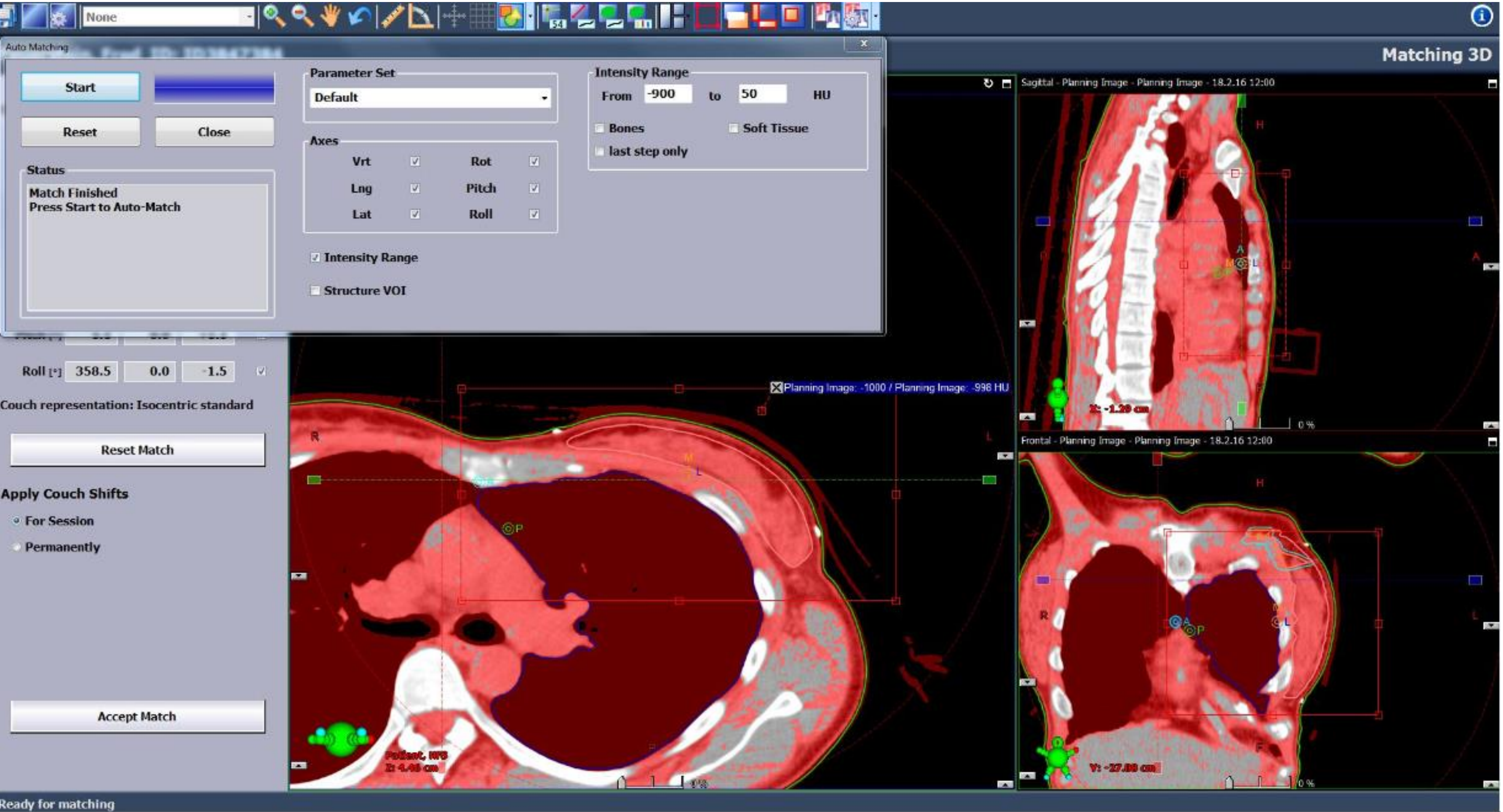
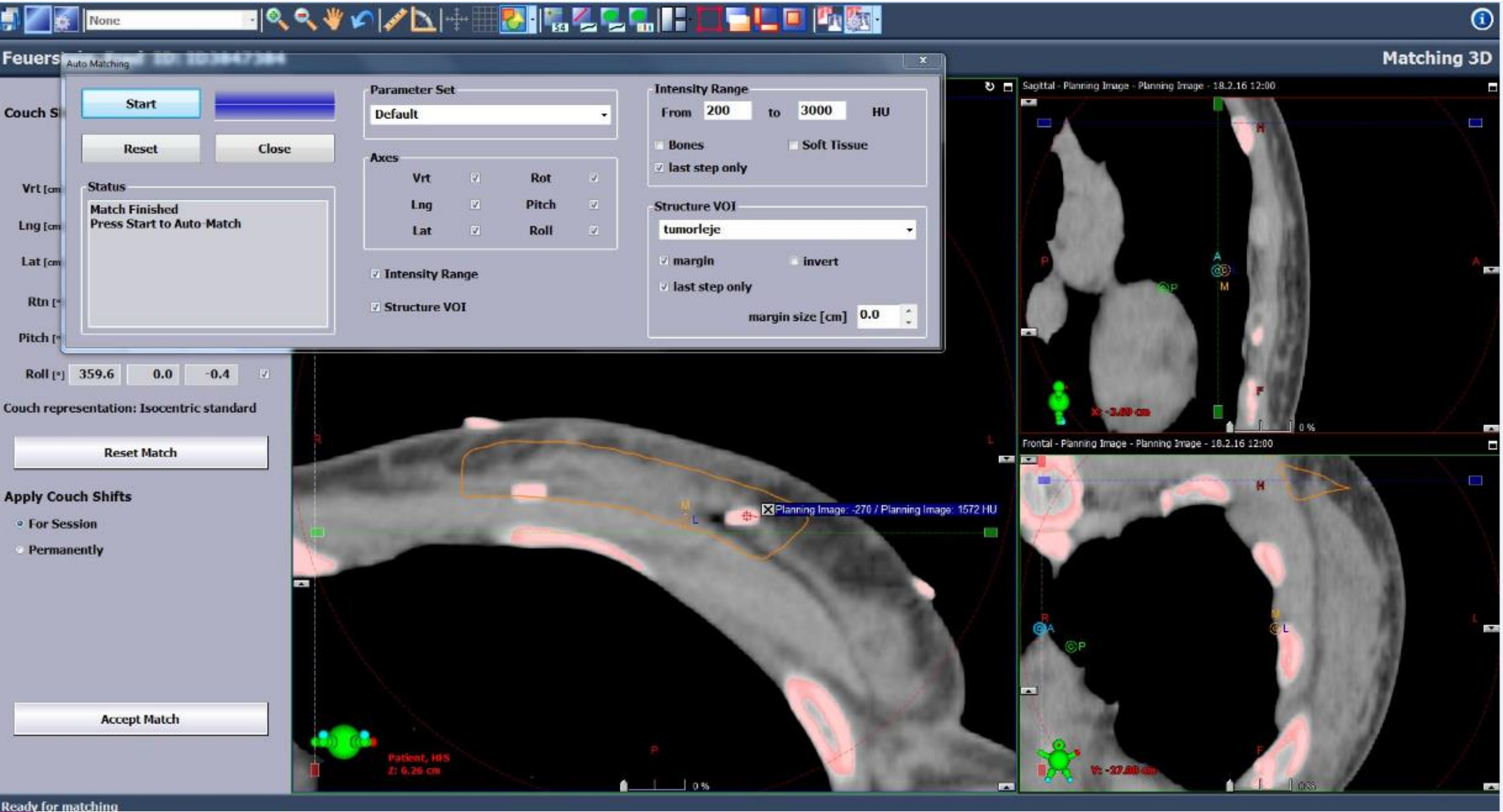
Registration surface



Registration markers



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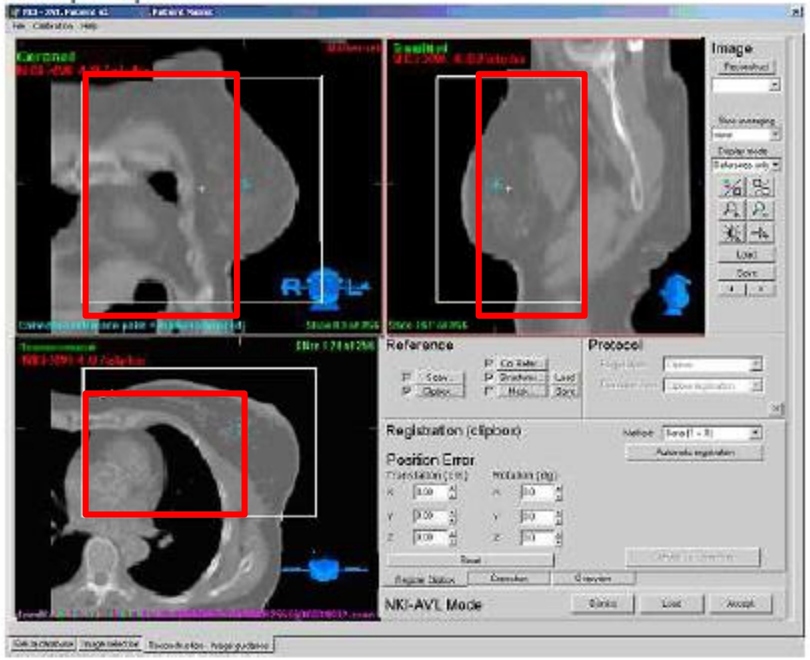
Breast

MATCH PARAMETERS		SCAN PARAMETERS	
Structures	TV_IMRT	**Preset selection**	Breast left/right
Correction ref point	TV_IMRT	Gantry rotation	Breast right: -180° → 25° Breast left: 330° → 180°
Registration	Clipbox	Gantry speed	0.5 rpm
Method	Bone (T + R)	Detector position	S
Restriction Rotation	5°	Filter	F1
Restriction Translation	[illegible]	Collimation	S20

Example clipbox:

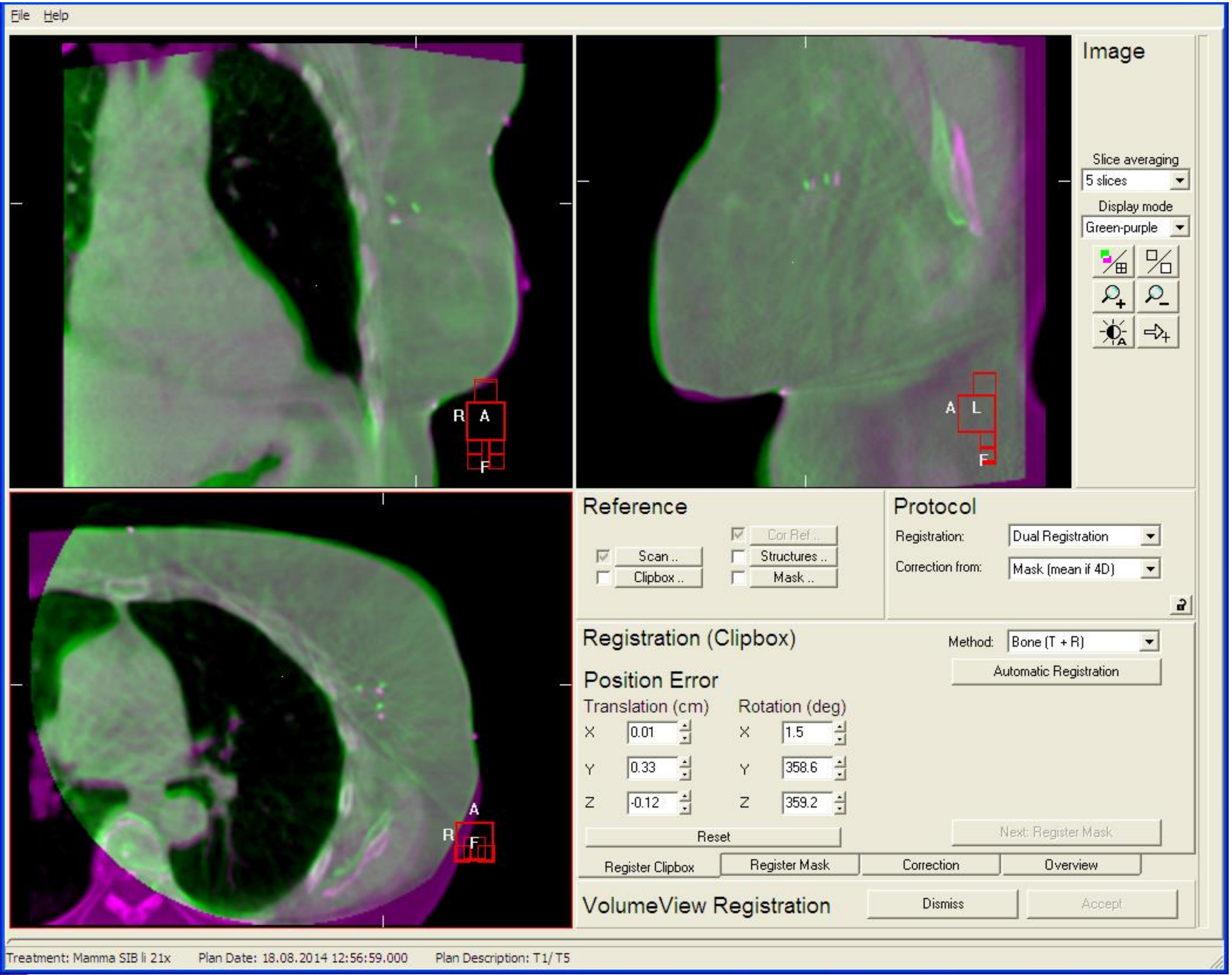


For setting the clipbox:

- Include as much breast tissue as possible in the clipbox and also include part of the sternum.
- Do not include (any) vertebrae.

Breast including integrated boost: the correction ref point is placed in de PTV of the boost area. If the boost area is placed asymmetrically within the breast tissue, consider placing the correction reference point on the edge of the boost area more towards the centre of the breast PTV. This can be done by placing a marker in this position and putting the correction reference point on the marker.

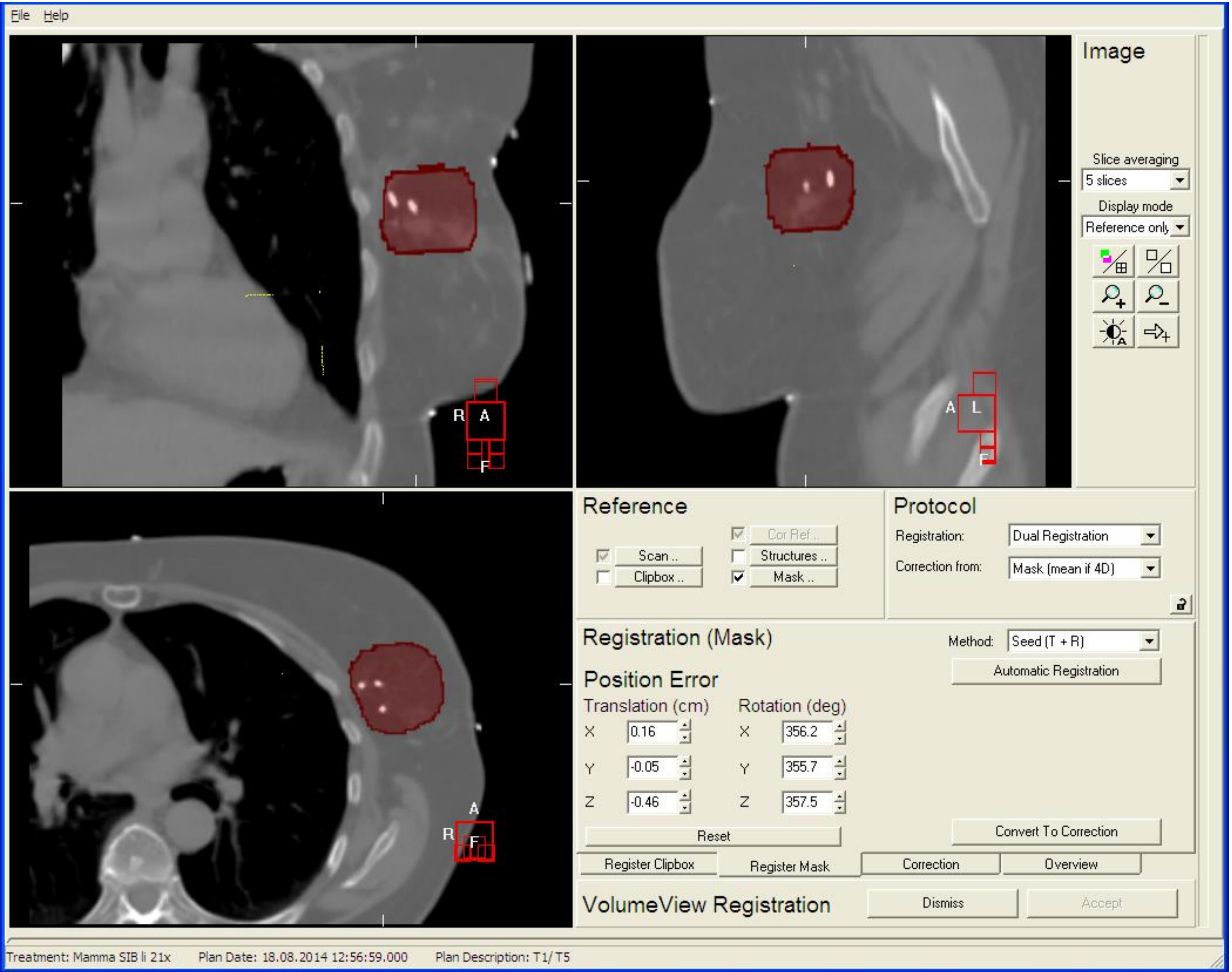
Upgrade 5.04
Clipbox small to encompass bones only



CT ref

CBCT

How to register these markers?



Markers
HU's
Seed algrorithm

Marker registration with shaped ROI

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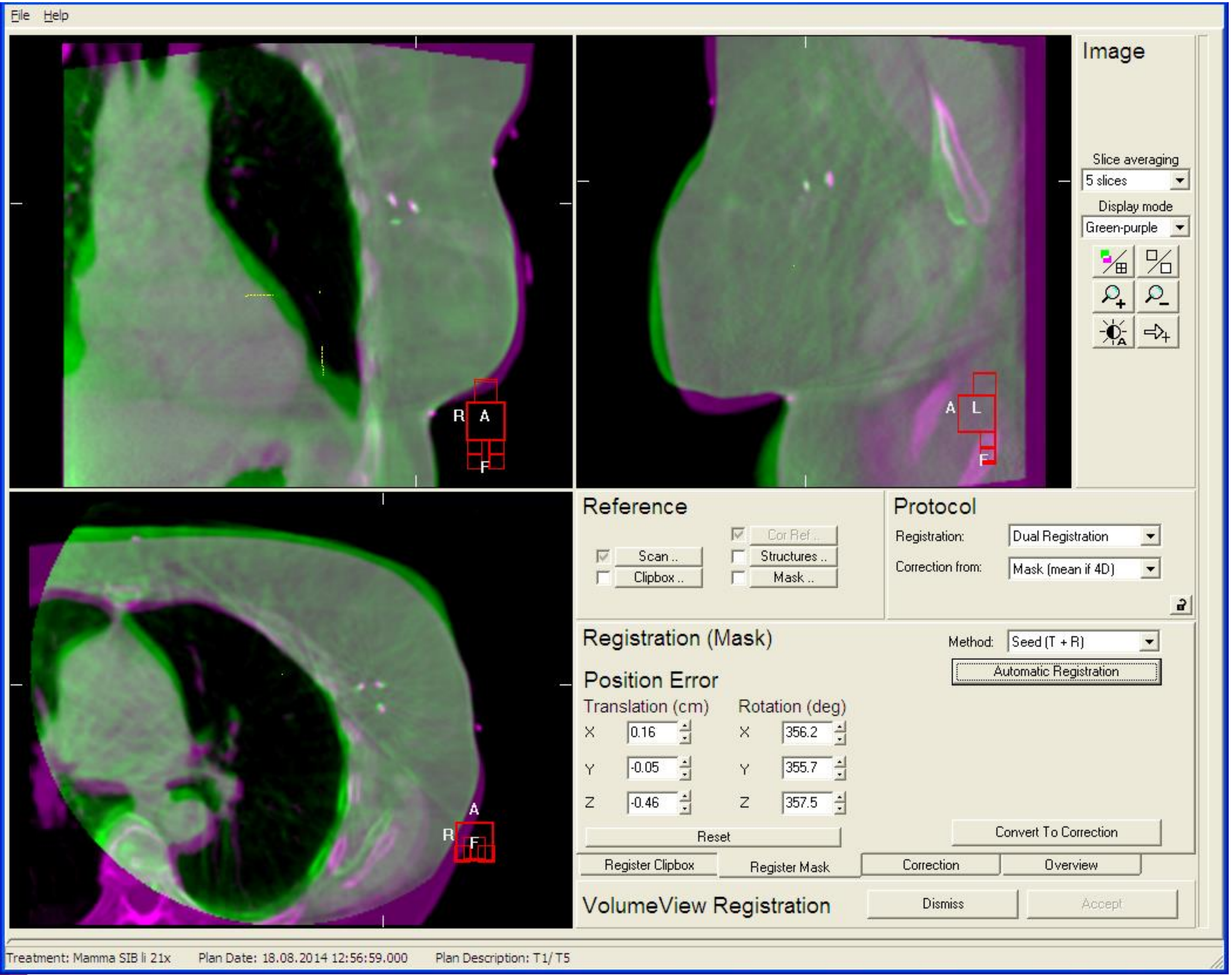


CT ref

CBCT

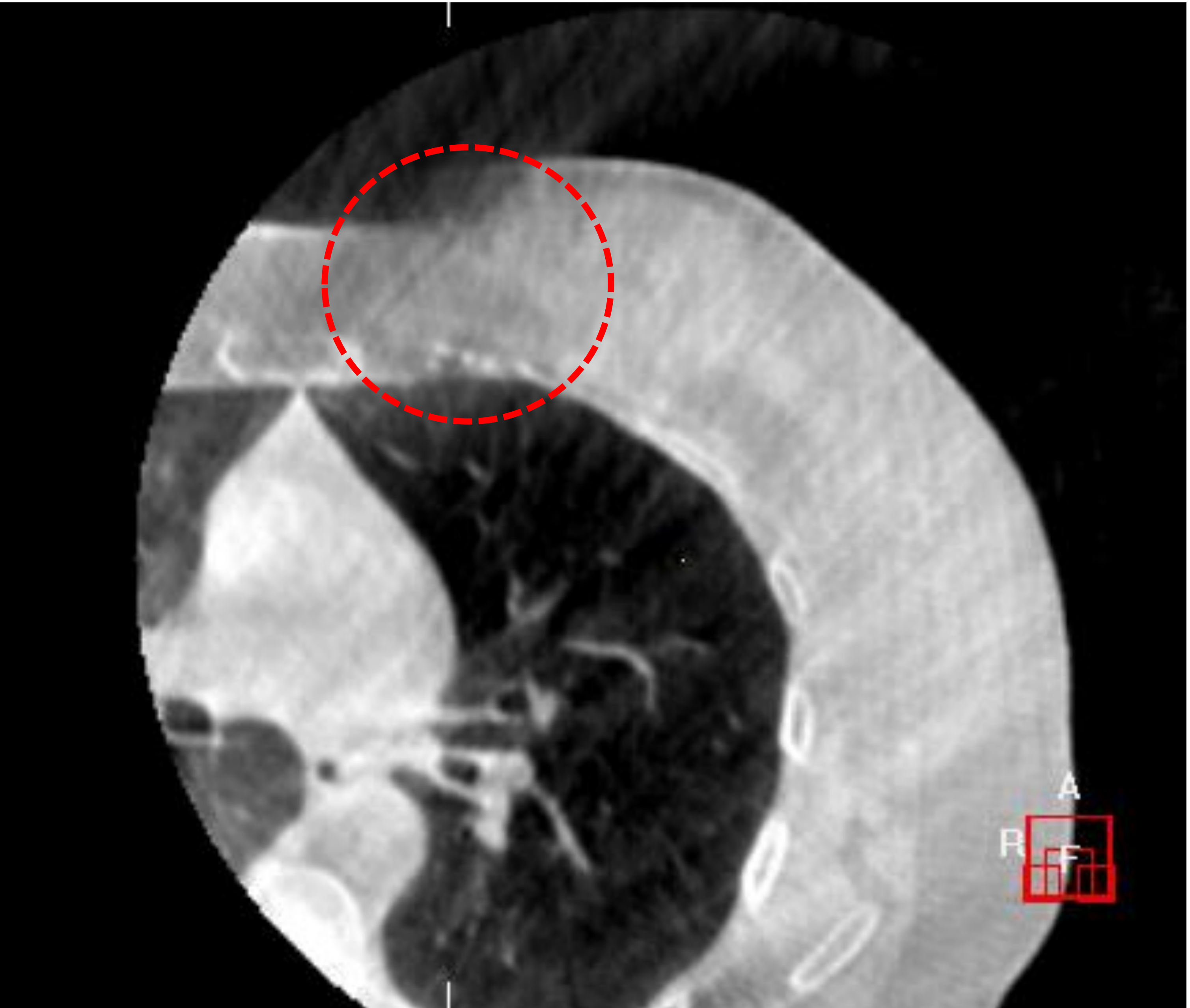
Markers

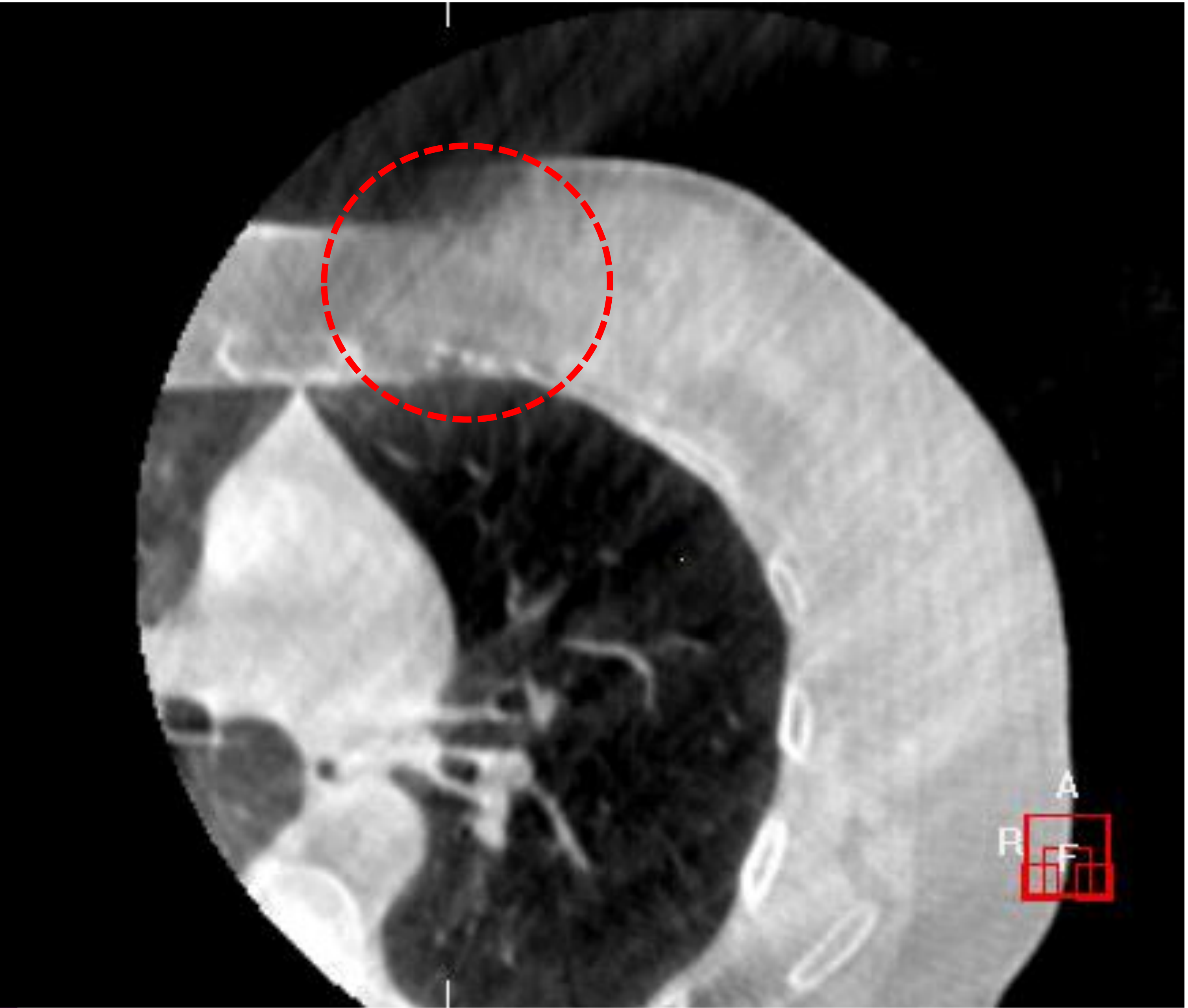
HU's

Seed algrorithm

Marker registration with shaped ROI

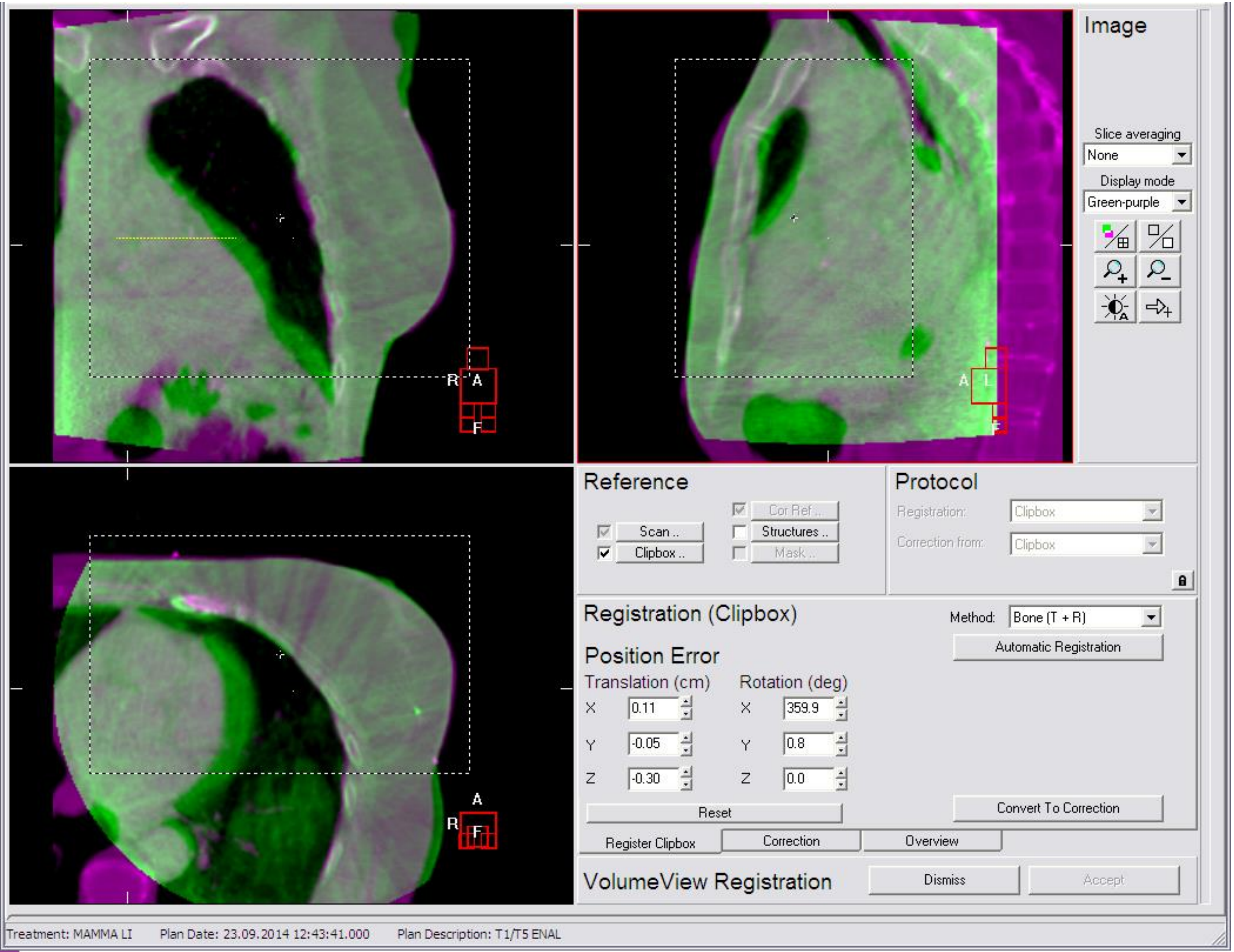
ESTRO School


A
R
F

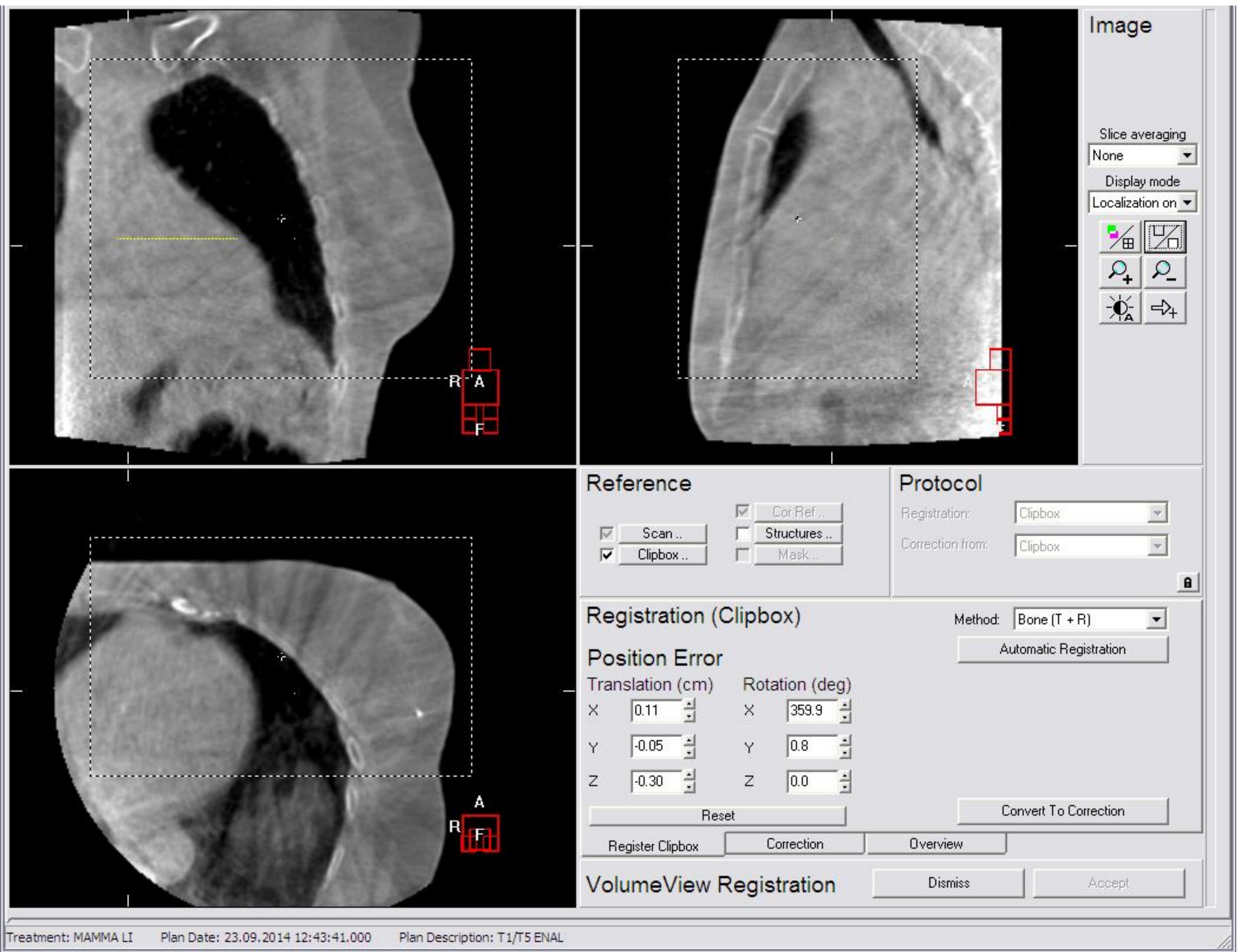


Change in breathing pattern during acquisition

Breathing artefact CBCT



Good bony anatomy registration?



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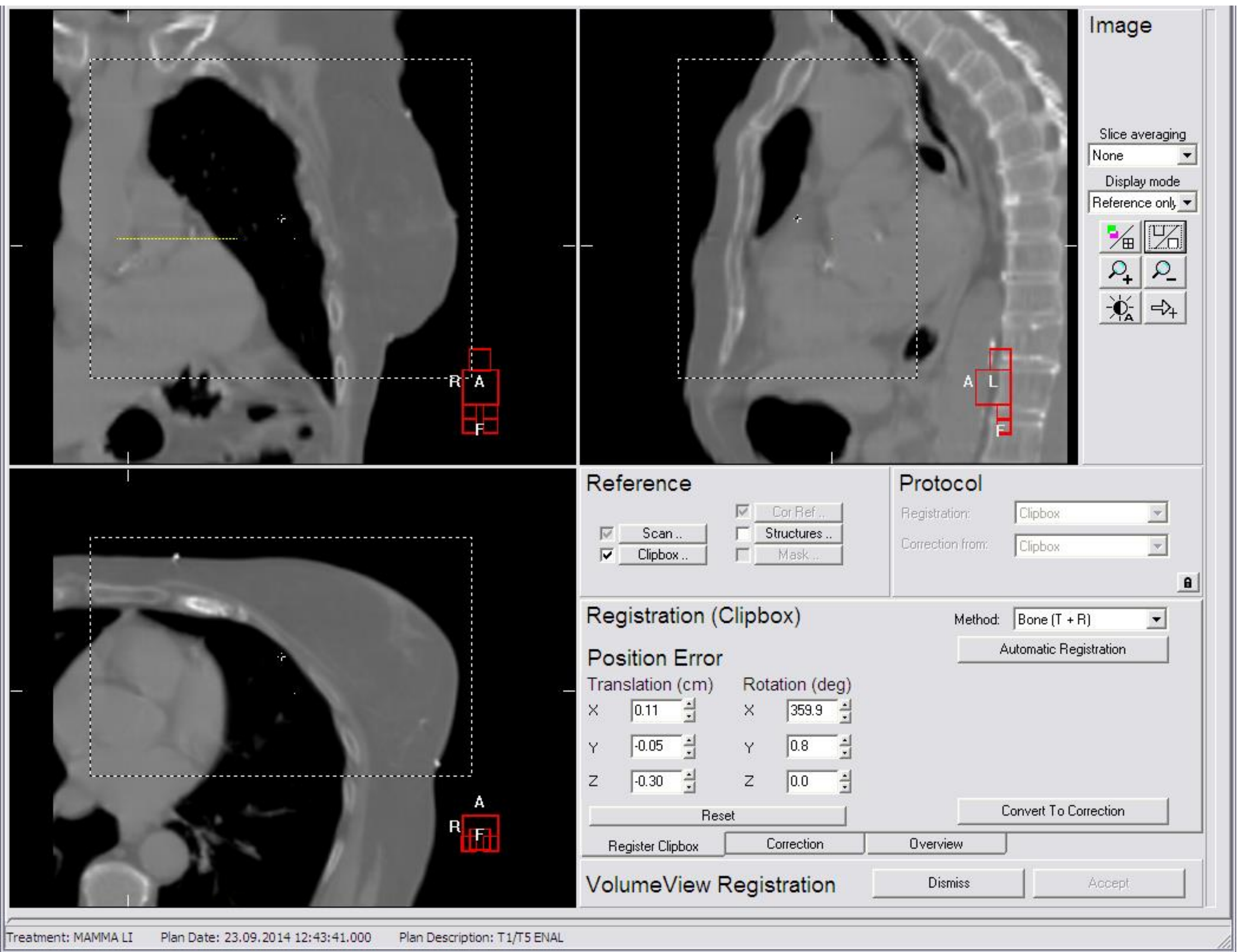
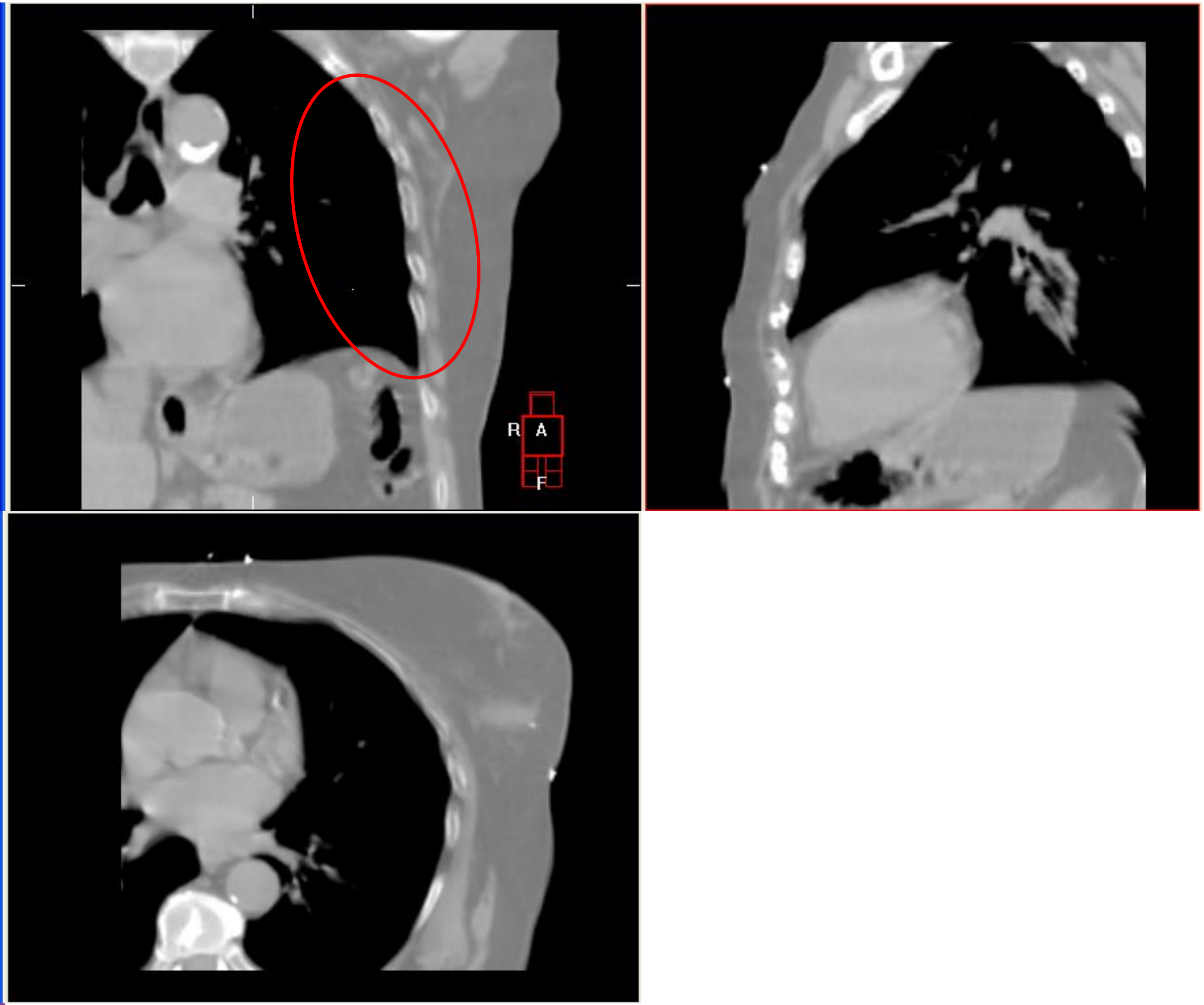
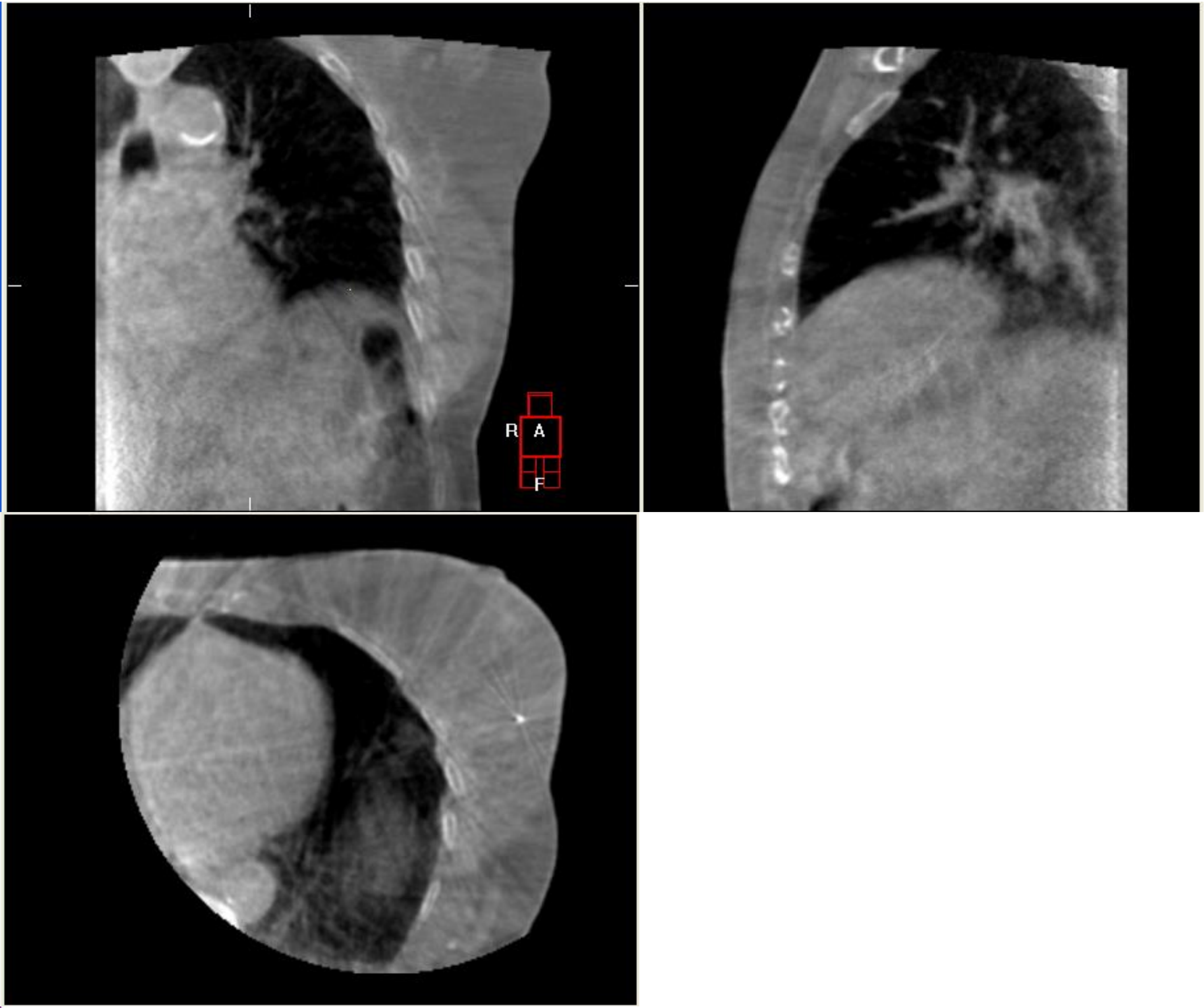


Breathing artefact CT ref!



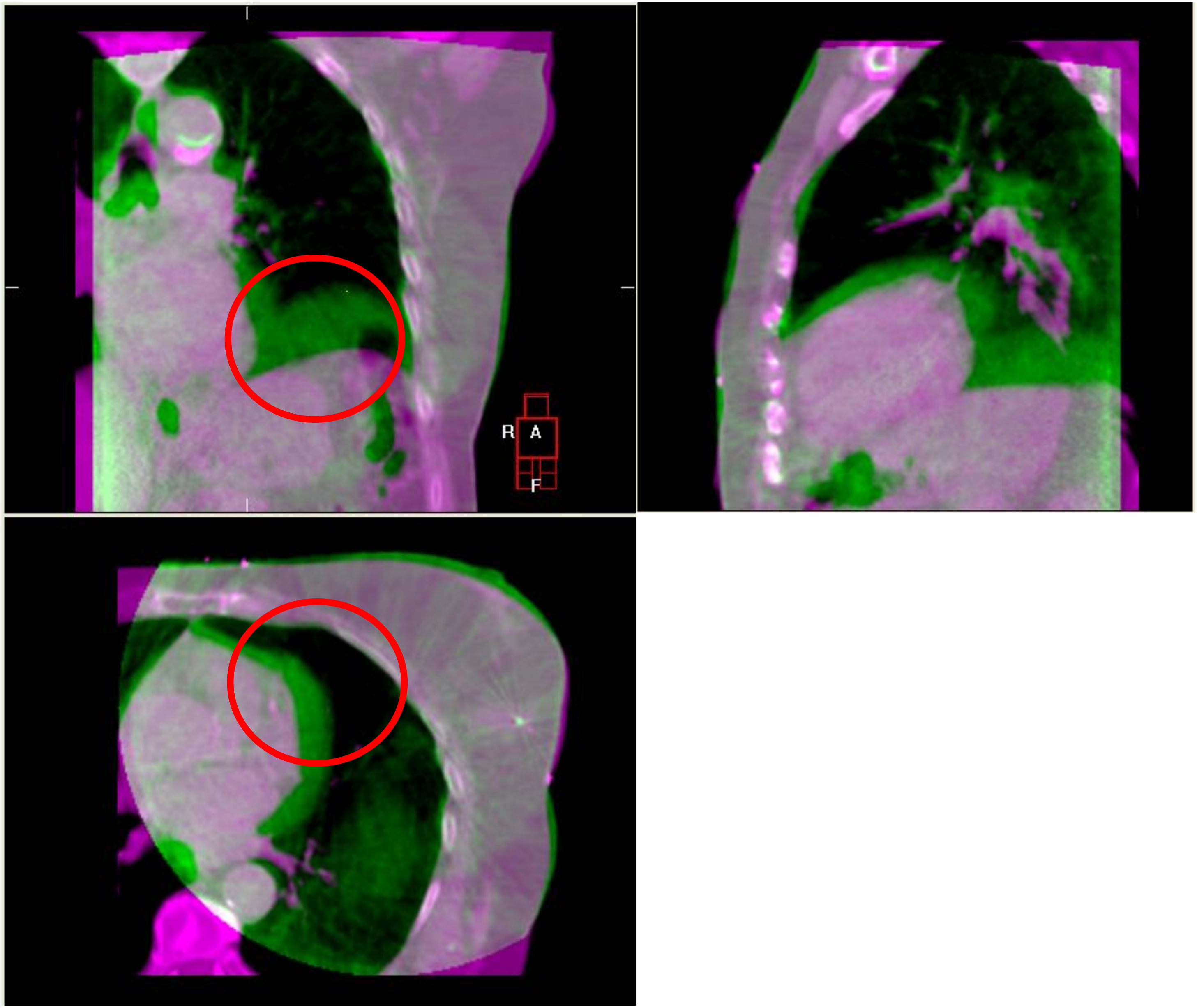
Free breathing CT ref scan …

Quality of Ct ref?



CBCT scan

Quality of Ct ref?



CT ref
CBCT

Registration on ribs

Average breathing position changed
- baseline shift –

Heart moves into treatment fields: BreathHold?

Quality of Ct ref & anatomy change!

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Traffic Light System

"decision support system to guide the RTT in prioritizing anatomy changes"

Level green, no action needed.

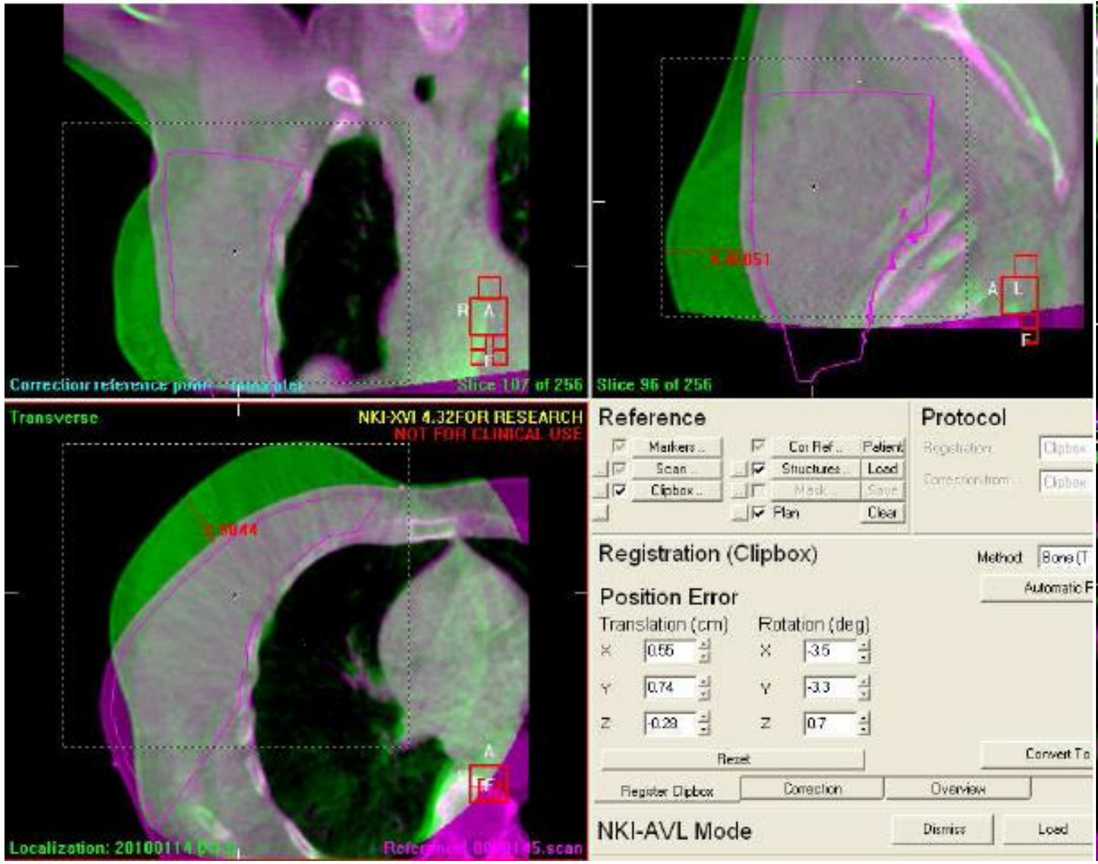
Level yellow, the radiation oncologist is notified by email, but no response is required to continue treatment.

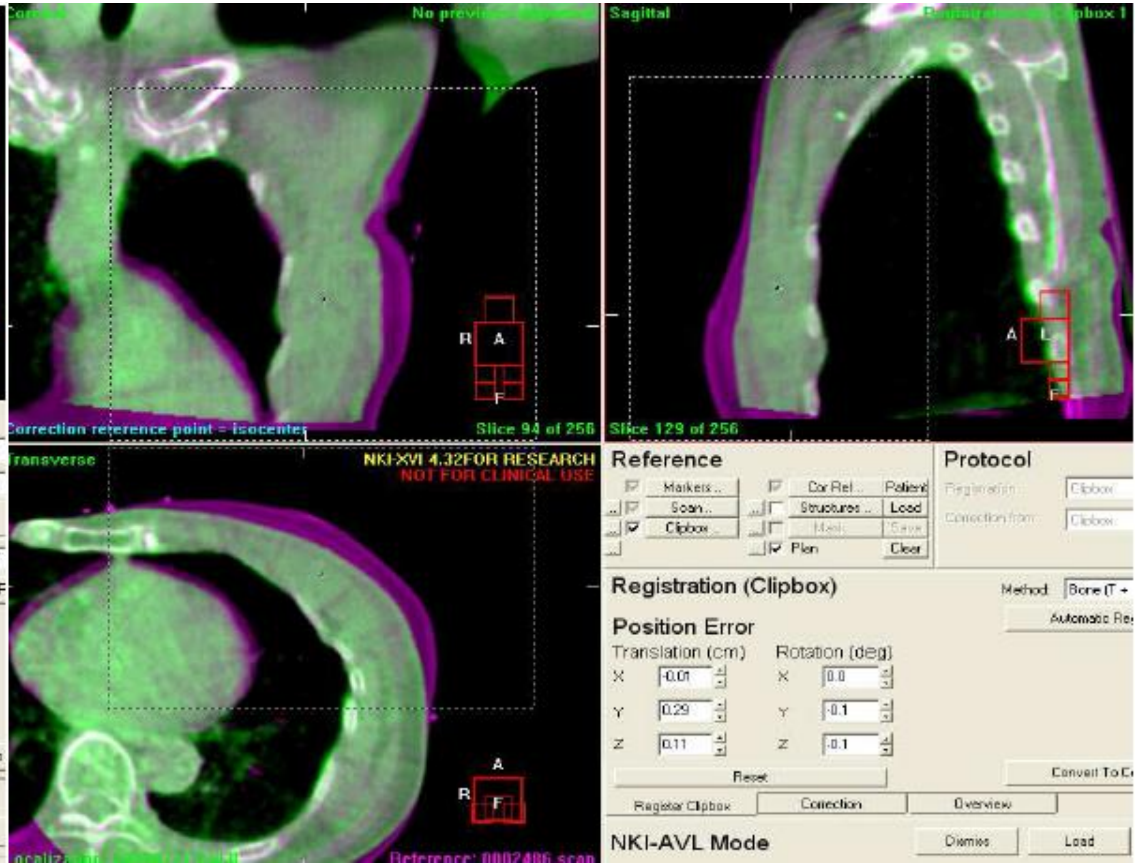
Level orange, the treating radiation oncologist (or back-up colleague) is informed by email and a response is required before the next fraction.

Level red changes, the radiation oncologist must be consulted immediately before the treatment fraction is allowed to be delivered.

http://www.avl.nl/media/291805/xvi_engelse_protocols_16_7_2014.pdf

Traffic Light System





Shift/increase contour

decrease contour

Contour change is < 2 cm.

Contour change is ≥ 2cm.

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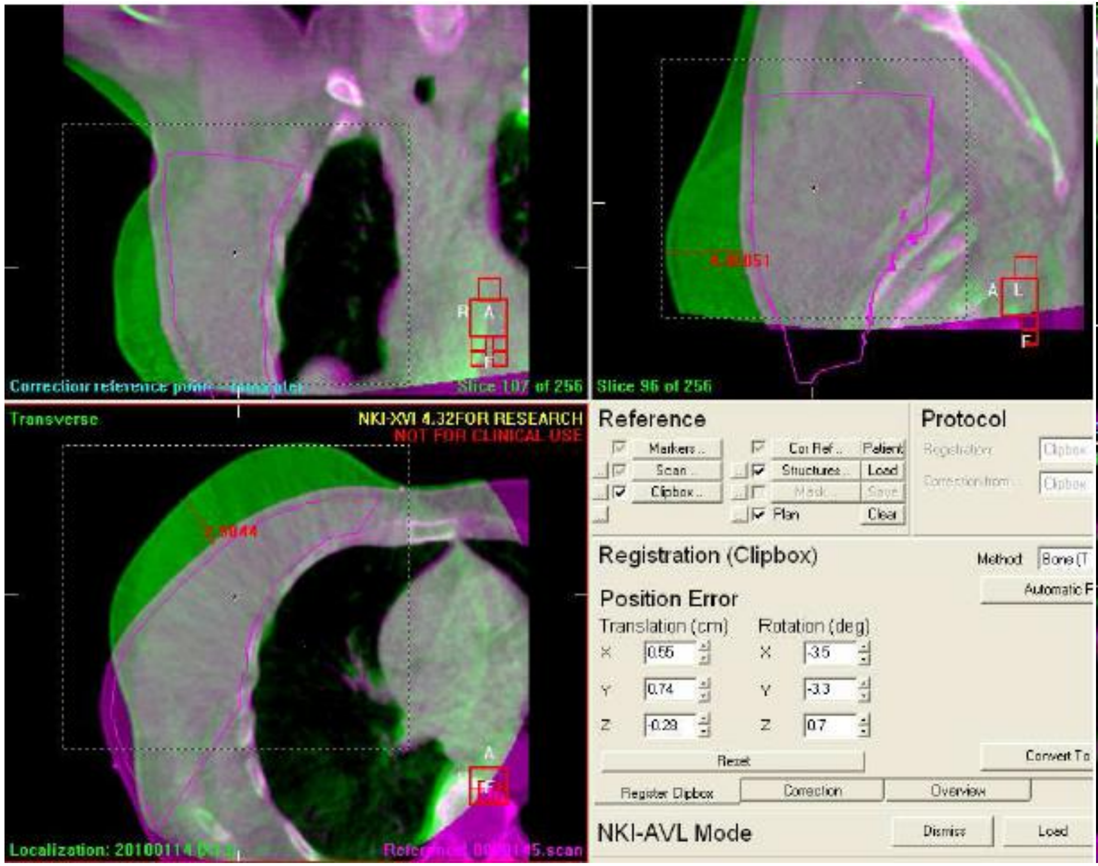
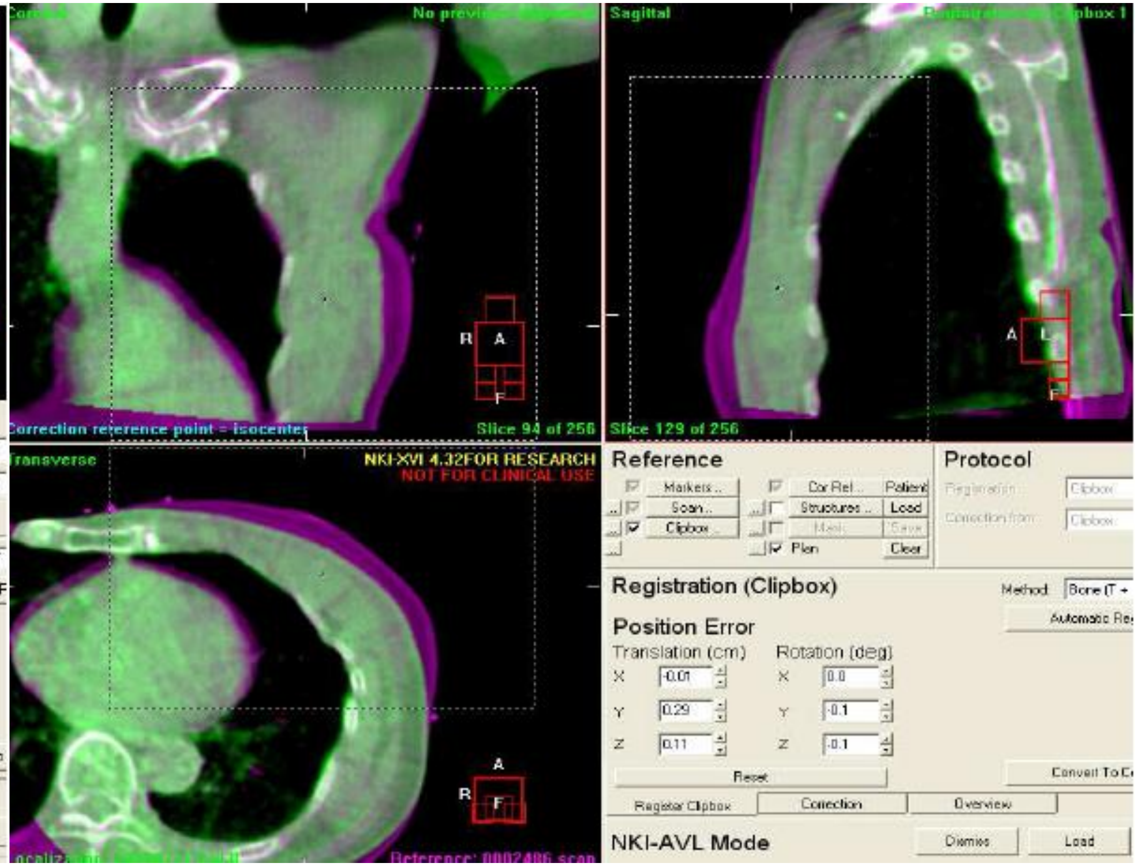
NEDERLANDS KANKER INSTITUUT

Traffic Light System





Shift/increase contour

decrease contour

Treatment planning techique

Contour change is < 2 cm.

Contour change is ≥ 2cm.

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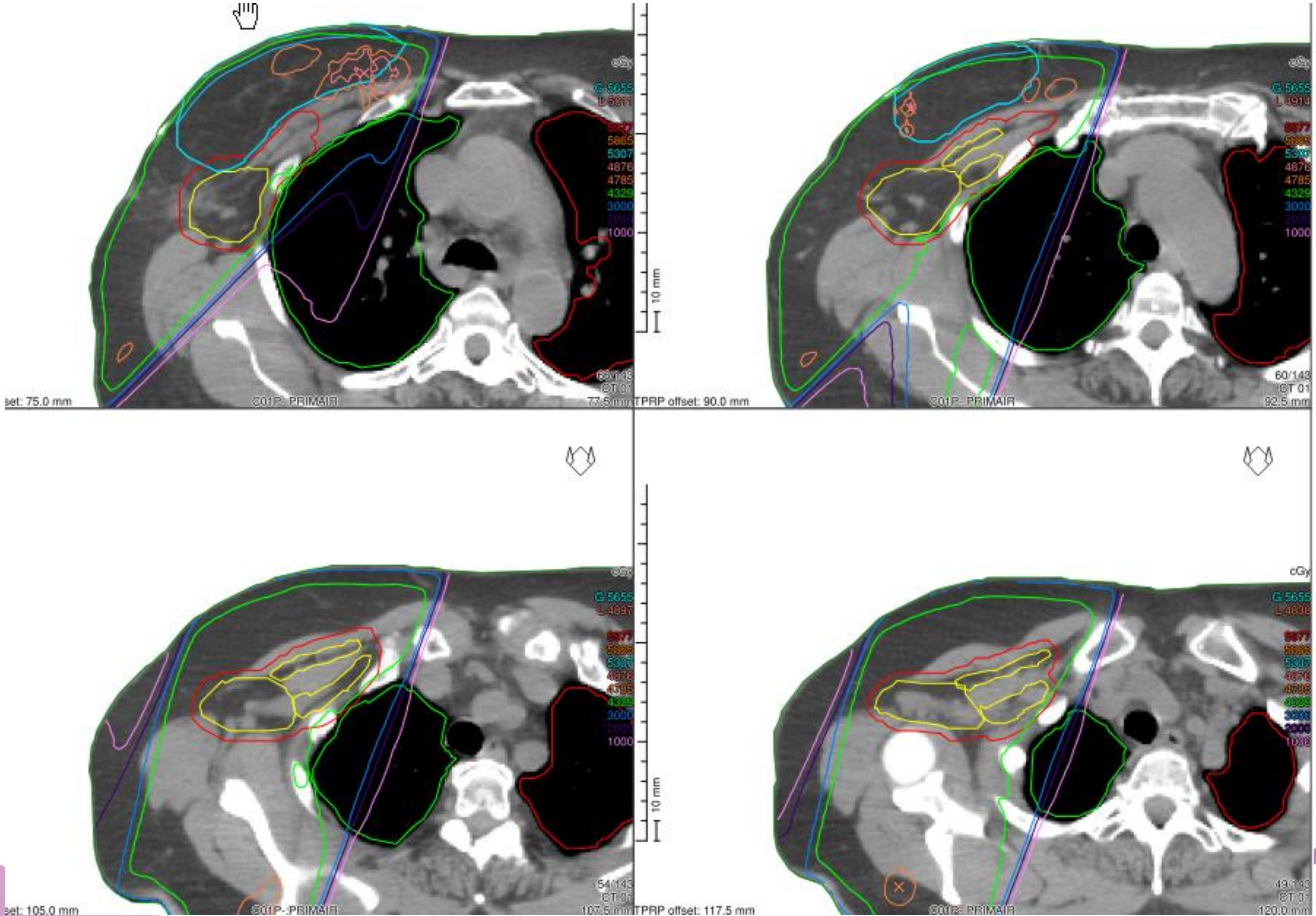
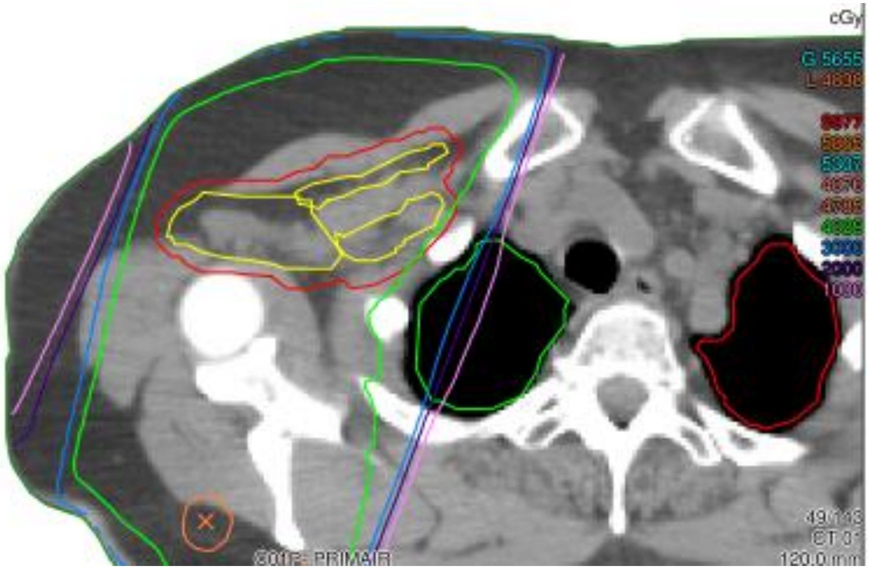
NEDERLANDS KANKER INSTITUUT

Design of breast boards:

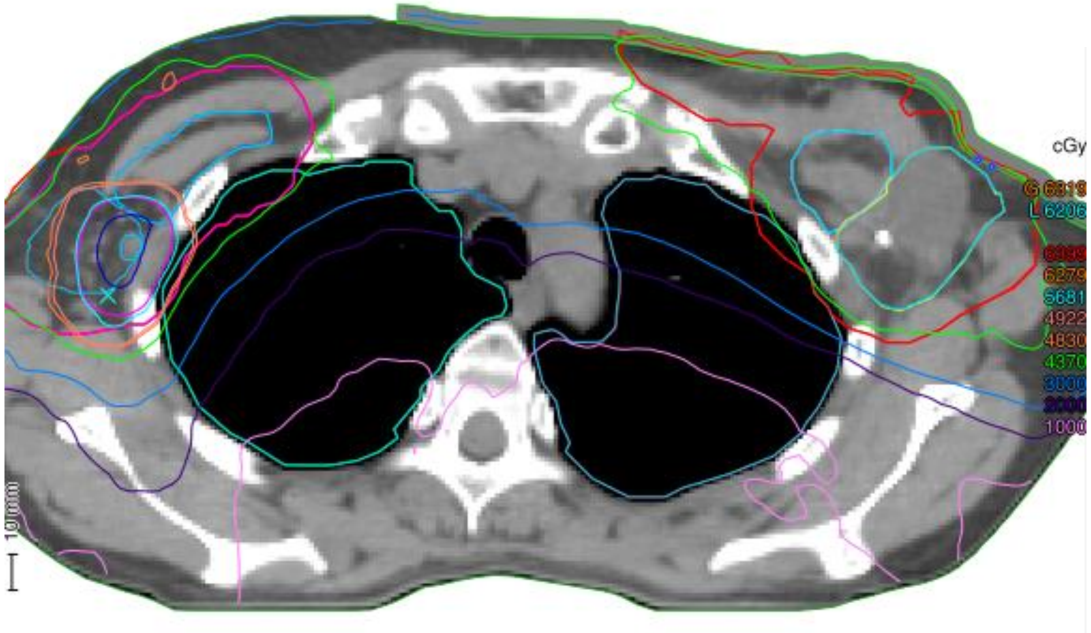
Breast and axillary nodes:
From conformal



Breast and axillary nodes:
From conformal to IMRT/VMAT to reduce dose to shoulder joint



Conformal (AP/PA)



VMAT / IMRT

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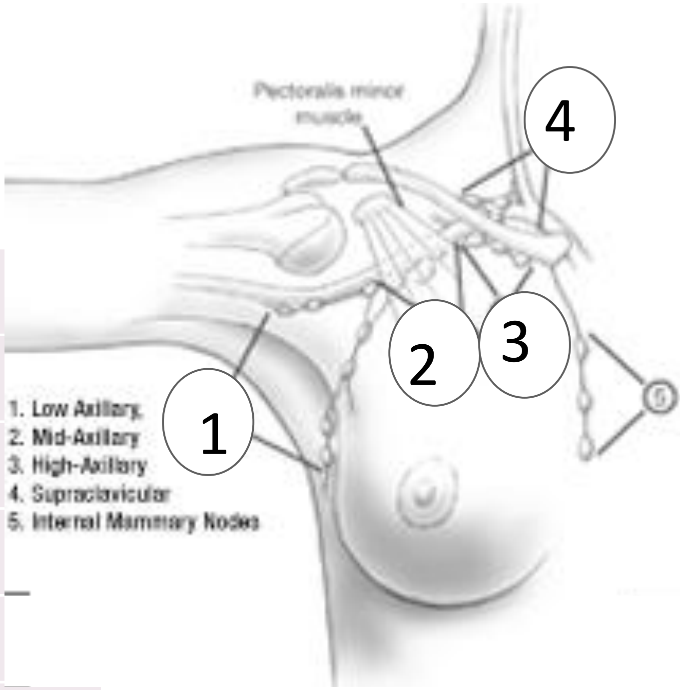
Margin calculation level 1-4

Residual error (mm) nodes after registration of thoracic wall
(incl 2mm delineation variation)

	LR mm(X)	CC mm (Y)	AP mm (Z)
Level 1	7.5	10.7	14.8
Level 2	8.0	7.7	7.8
Level 3	6.7	6.1	6.5
Level 4	6.1	7.1	6.3



Courtesy Karin Goudschaal, AMC

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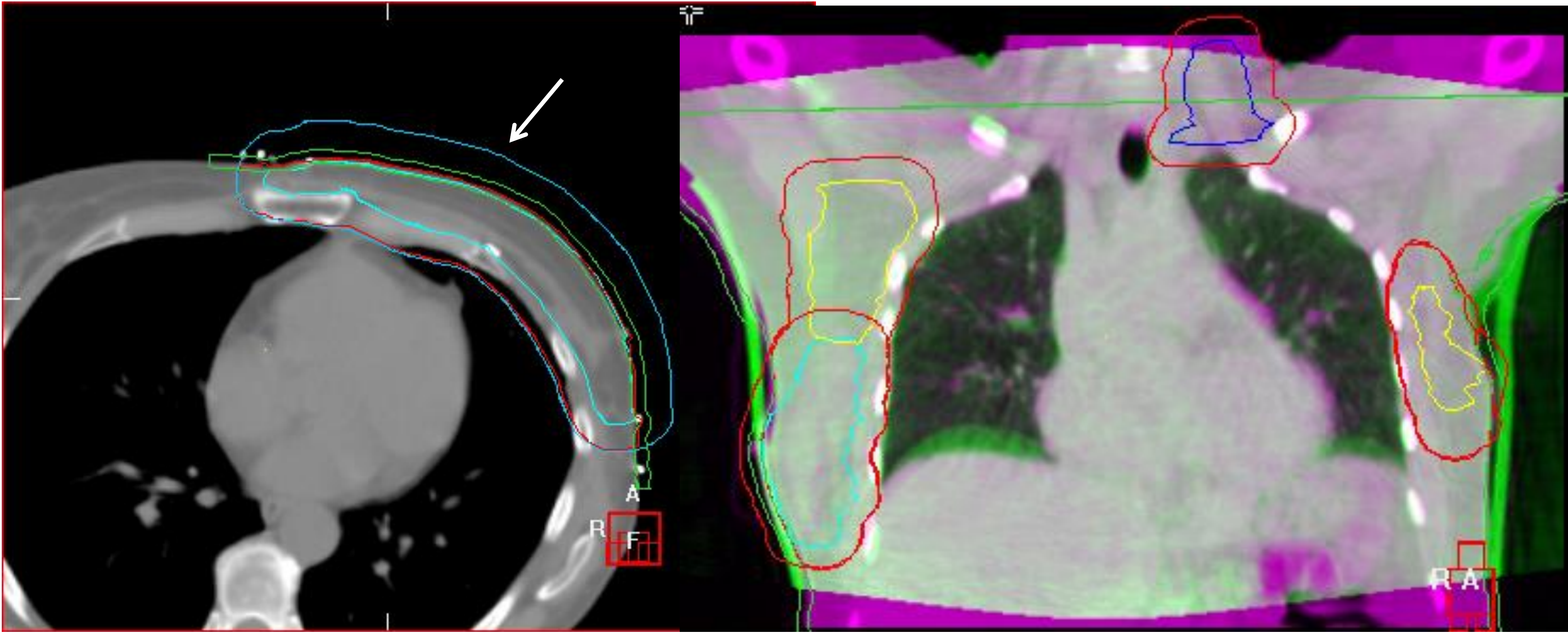

- New structure for anatomical change: PTV + 10mm into air (blue)
- CTV inside PTV
- !! Position of the arm: blocking treatment

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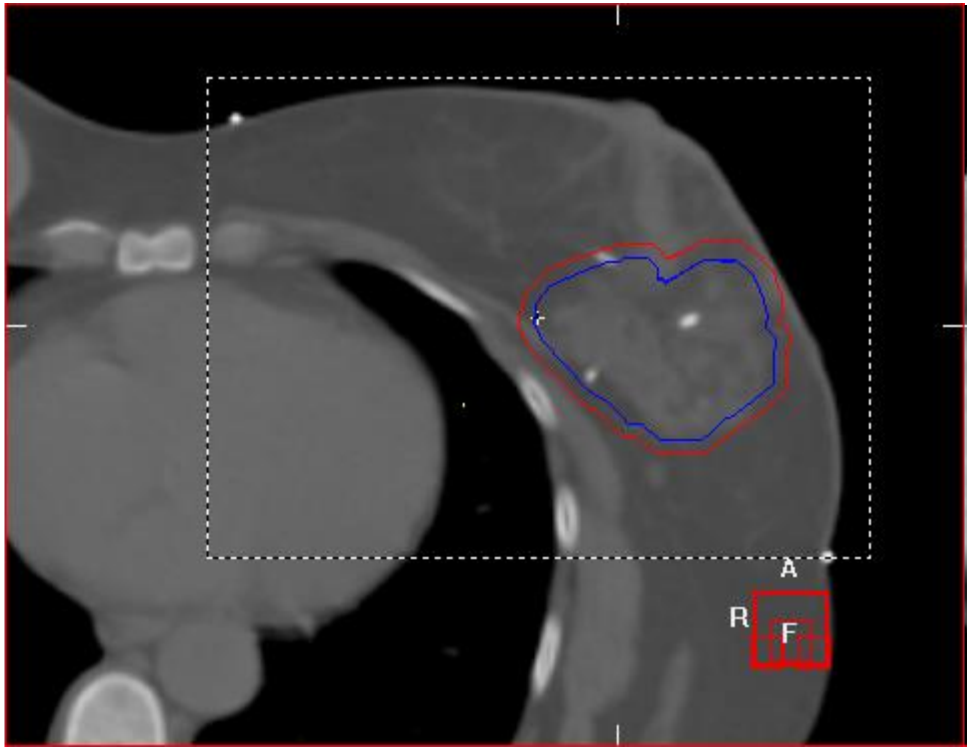
My take home message, *but up for discussion!*

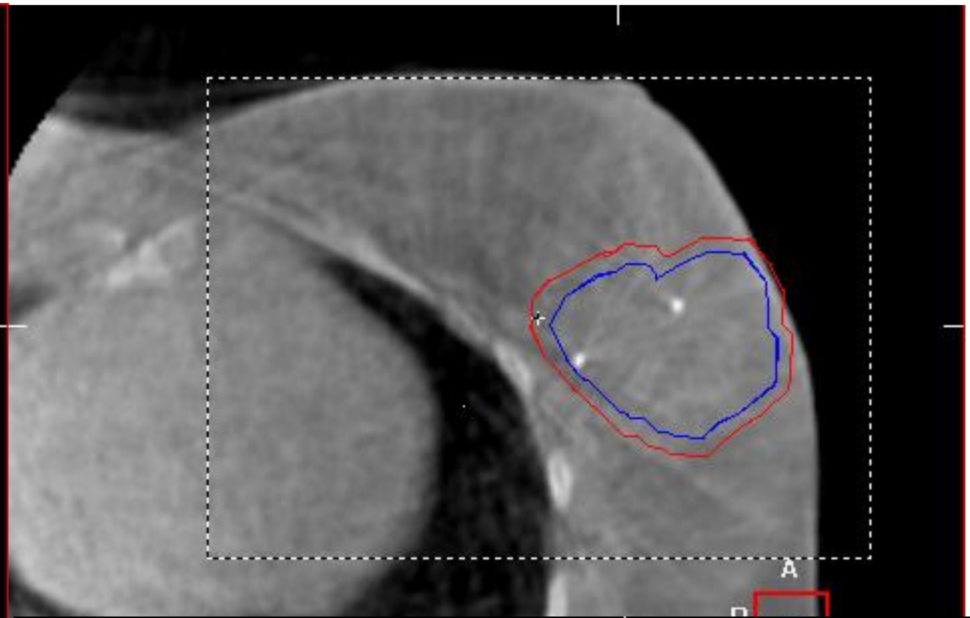
- ✓ Let the (expensive) software work for you! Train your RTTs to be very critical

  … Majority can be registered automatically!

- ✓ Protocolize

Marker check @AMC





After registration on the ribs

Adaptive RT

Coen Rasch

- No disclosures

A reminder:

- GTV
  - Imaging, Clinical investigation
- CTV
  - Statistics, Experience
- PTV / ITV
  - Possible positions of the CTV
- Treated Volume / irradiated Volume
  - Collateral damage

- IGRT
- ART
- IMRT

What is adaptive RT

- Adaptive radiotherapy (ART) is an approach to correct for variations in geometry of tumor and bystander anatomy with repeated (imaging-based (?)) modification of treatment delivery

- Schwartz et al Curr Oncol Rep 2012

How does adaptive RT translate

- (4D) adaptive RT is RT with time weighted adaptation
  - I.e.
    - Measuring and correcting for day to day variation
    - Adaptation of RT based upon (anatomical, functional, biological) changes during RT either expected (weight loss, shrinkage) or unexpected like atelectasis

    - Basics: it is per patient, not per group

Ask yourself:

- Do I want adaptation for:
- 1) Day to day, random changes
  - Bladder, cervix
- 2) Expected changes
  - Head and Neck
- 3) Random occurring systematic changes?
  - (base line shift, suddenly changed anatomy in e.g. Lung)

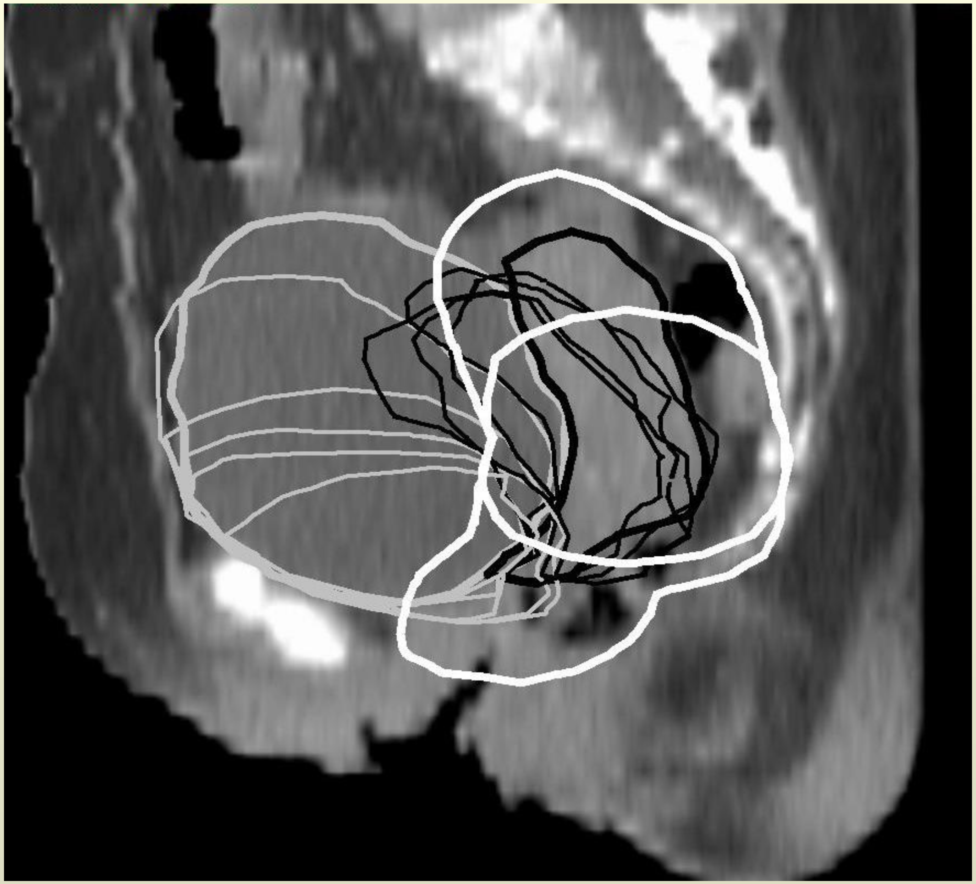
1: Day to day, random changes

- Cervix
- Bladder

Cervix cancer, classical approach

- Uterus motion: large and depending on bladder filling
- Cervix motion: smaller and depending on rectal filling
- Margin proposals:
  - Taylor: 15, 15 and 7 mm
  - Chan et al:
    - (90% of the fractions within the PTV)
      - 40 mm at fundus (top of uterus)
      - 15 mm at cervix
    - 90% for <u>intrafraction</u> (30 minutes) only:
      - 10 and 5 mm

Example of target outside PTV "mover"



CT and CBCT week 1-5

Grey: Bladder

Black: CTV combined

White:
- PTVuterus (CT)
- PTVcervix (CT)

Courtesy Peter de Ruyter and Monique Bloemers

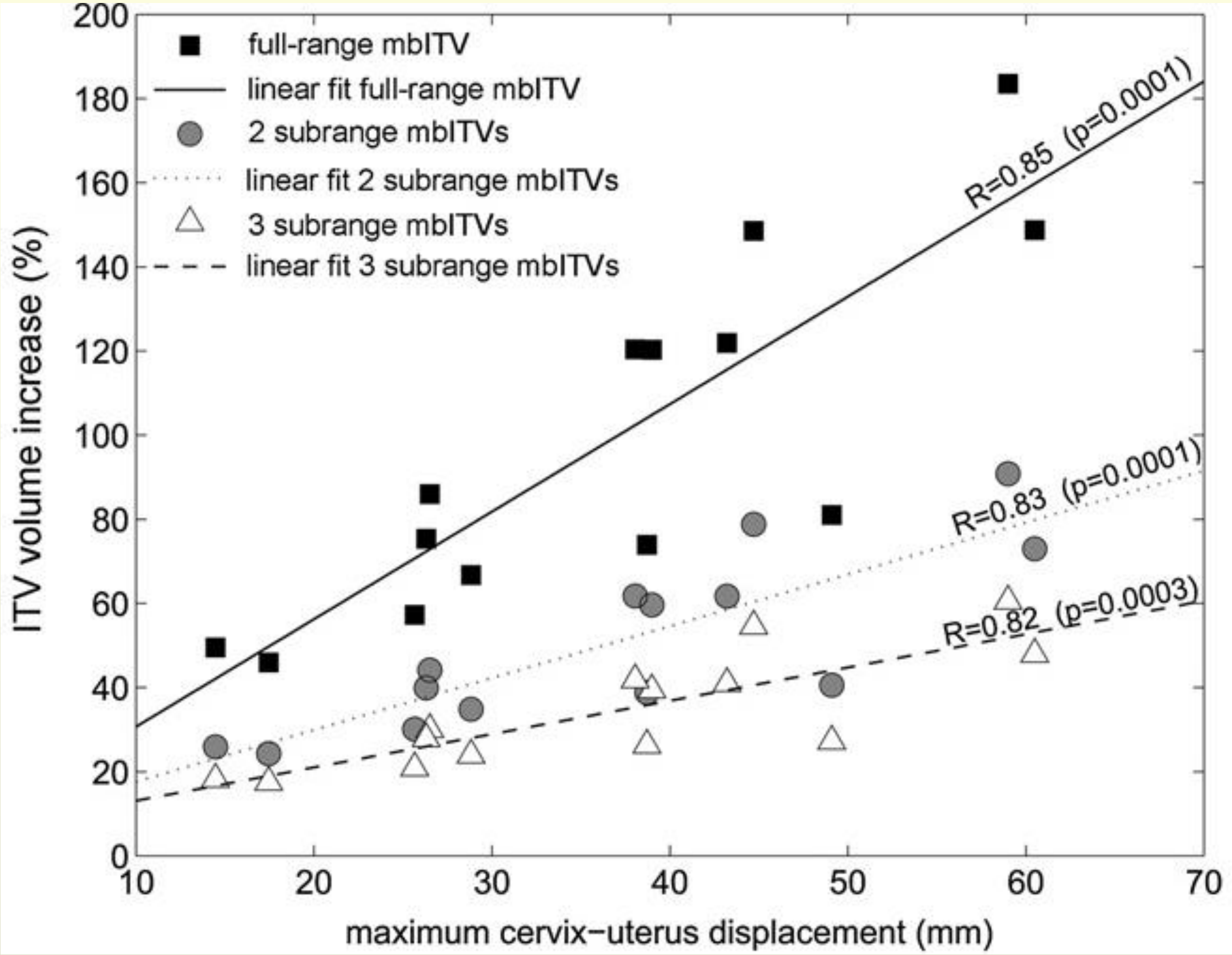
Example of target inside PTV
"non-mover"

CT and CBCT week 1-5

Grey:	Bladder
Black:	CTV combined
White:	- PTVuterus (CT)
	- PTVcervix (CT)

Courtesy Peter de Ruyter and Monique Bloemers

Cervix plan of the day made easy



1 PTV

2 PTV's

3 PTV's

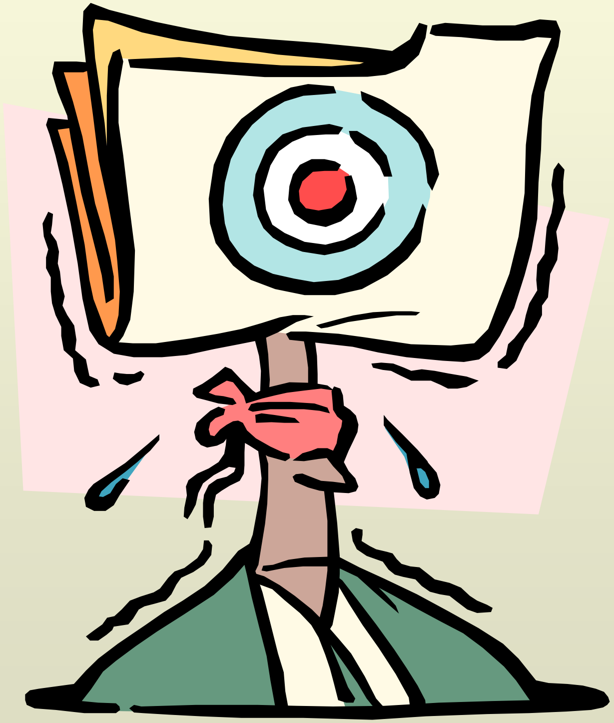
•Bondar et al IJROBP 2011

Radiotherapy amc

Still the most determining aspect of IGRT!

Cervix: back to the basics:

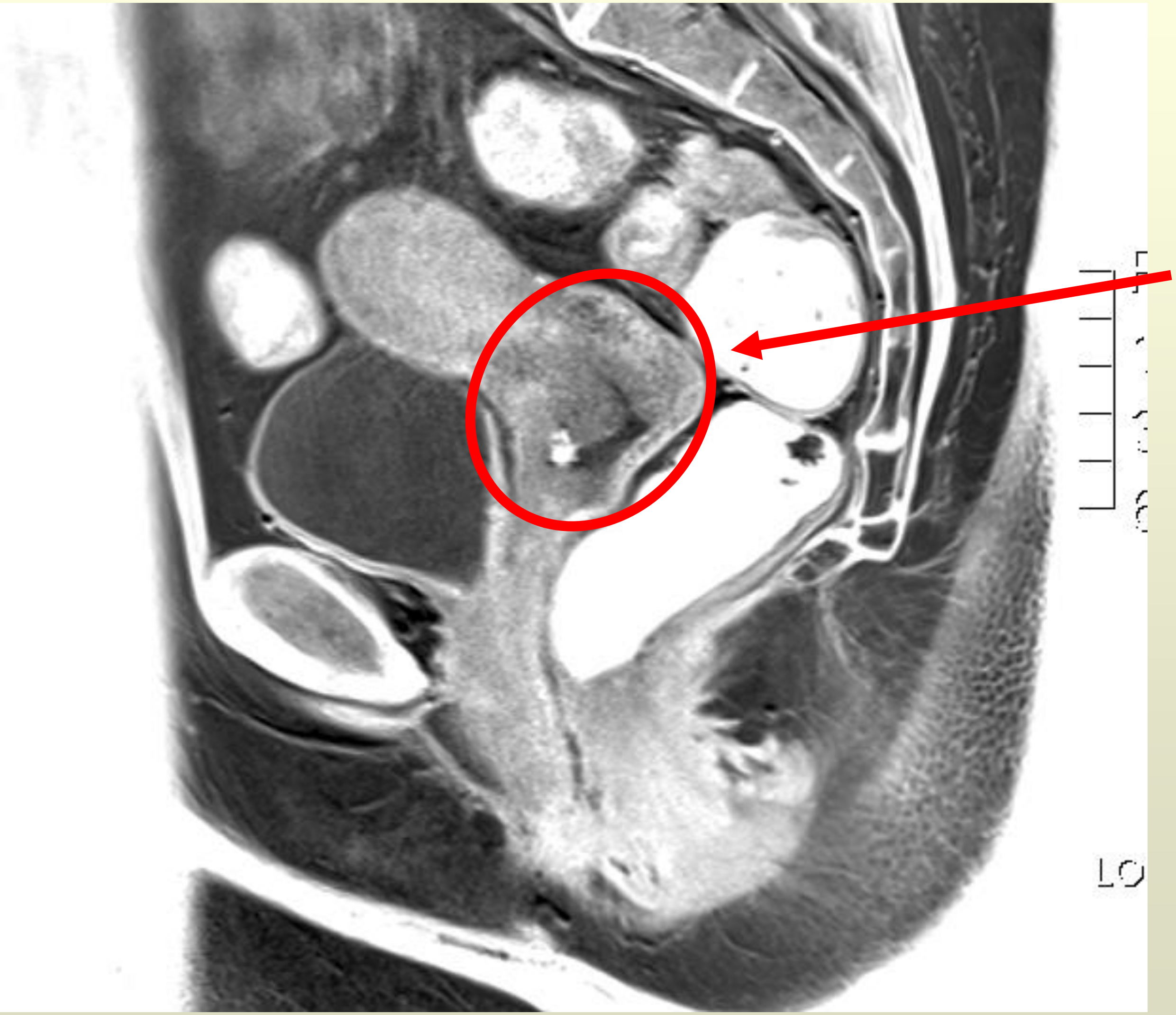
The Target



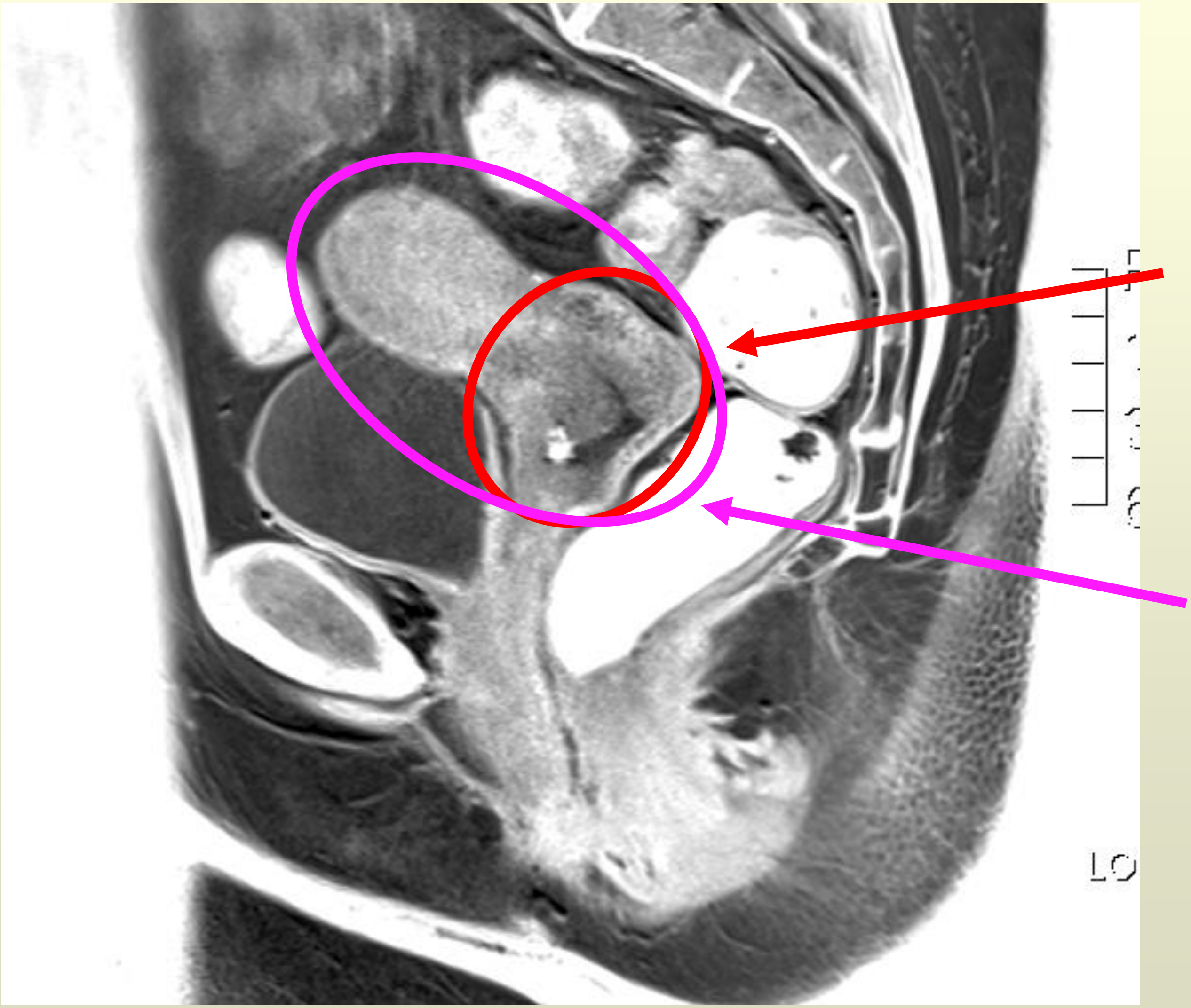
Cervix Target

Radiotherapy

Cervix Target



Cervix Target



Here it is

Why do all the effort in irradiating all this?

2: Art for expected changes

- Head and neck cancer

Adaptive RT for head and neck tumors

- Should we redesign our treatment plan along the way?
  - Adaptive RadioTherapy (ART) for expected changes

Changes over treatment time

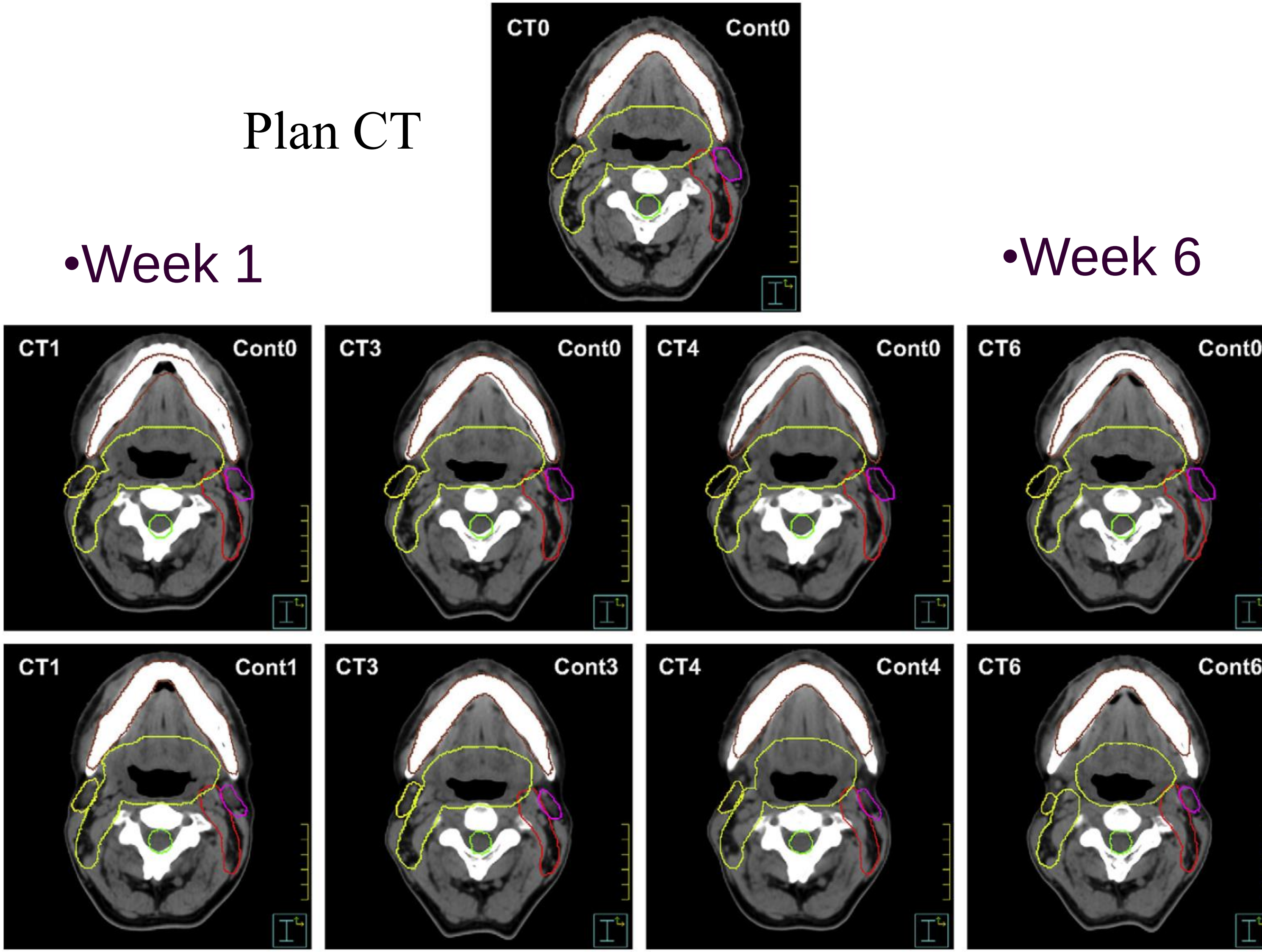
Plan CT

•Week 1

•Week 6

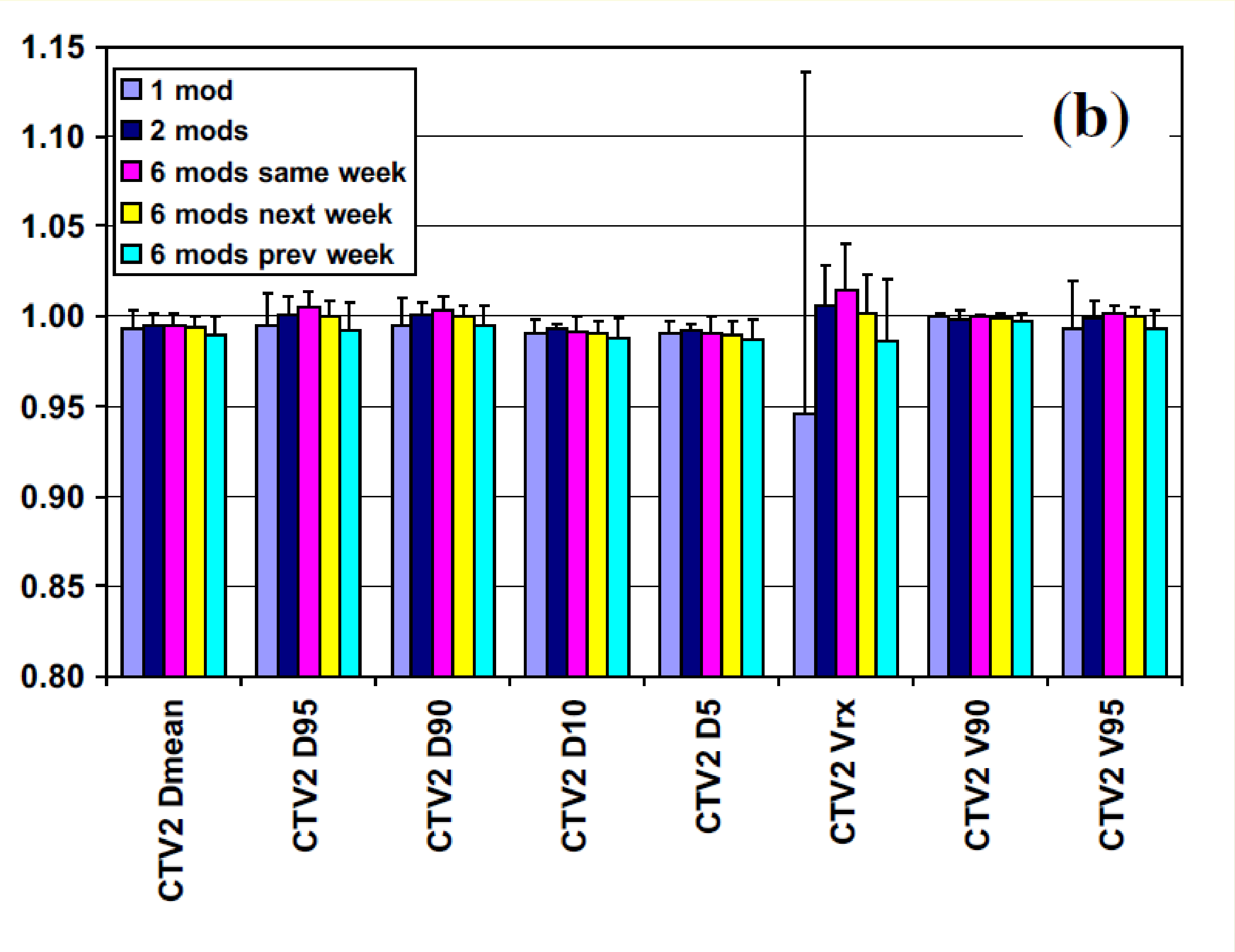
Unchanged contours on repeat scans

Deformed contours on repeat scans



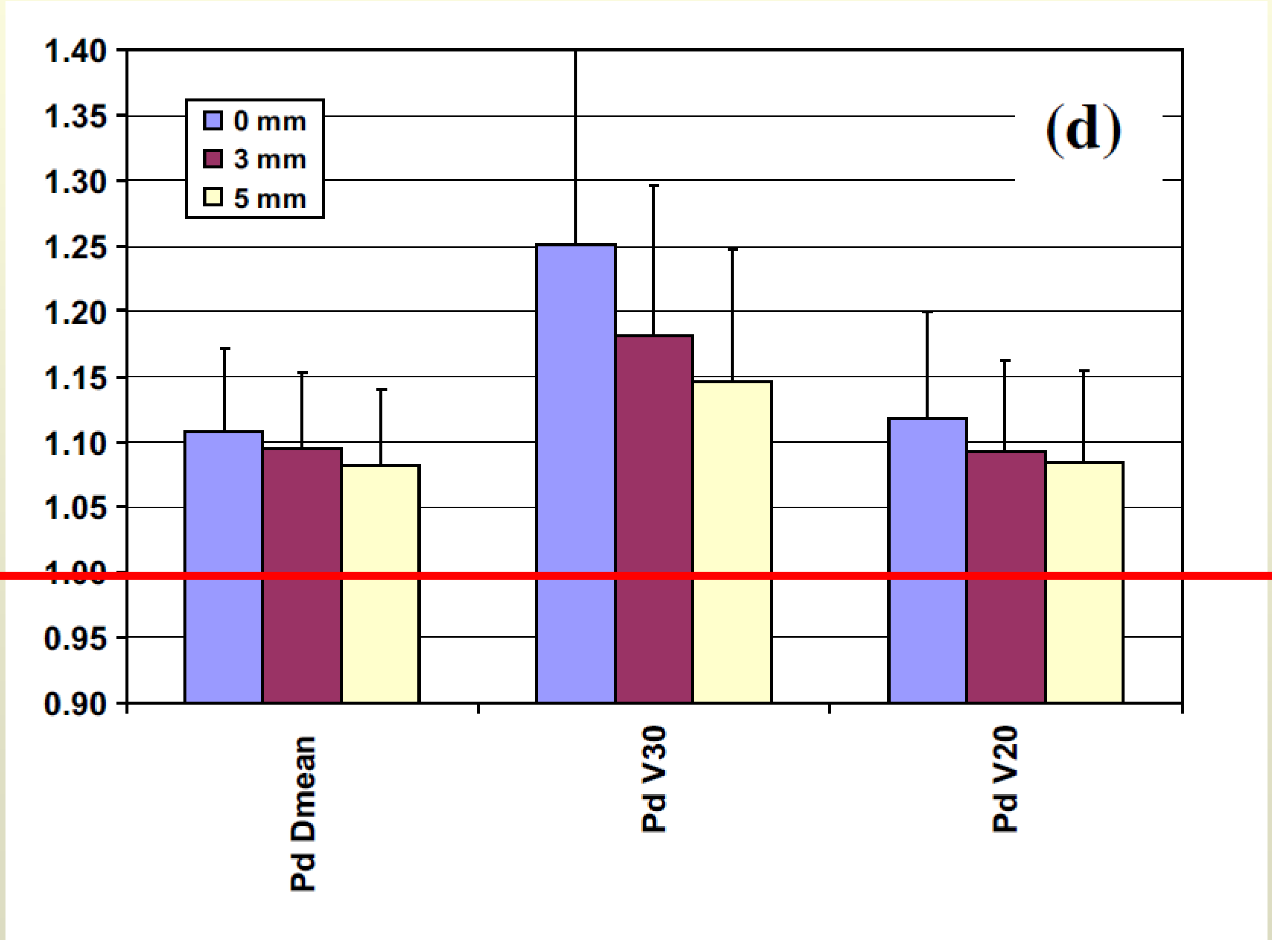
Wu et al 2009 IJROBP

Target dose with replanning remains good



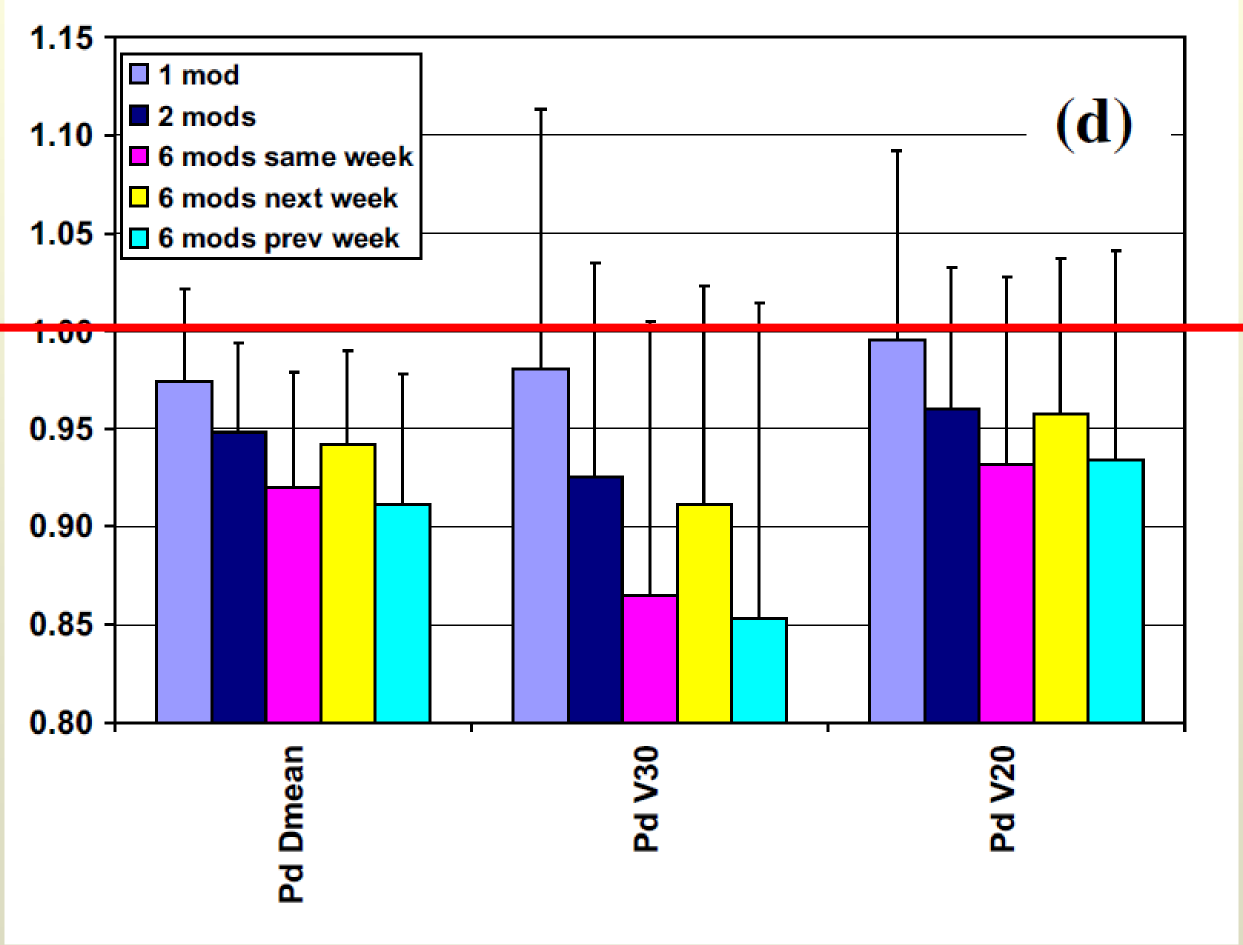
Wu et al 2009 IJROBP

Relative dose to the Parotid without replanning is around 10% higher



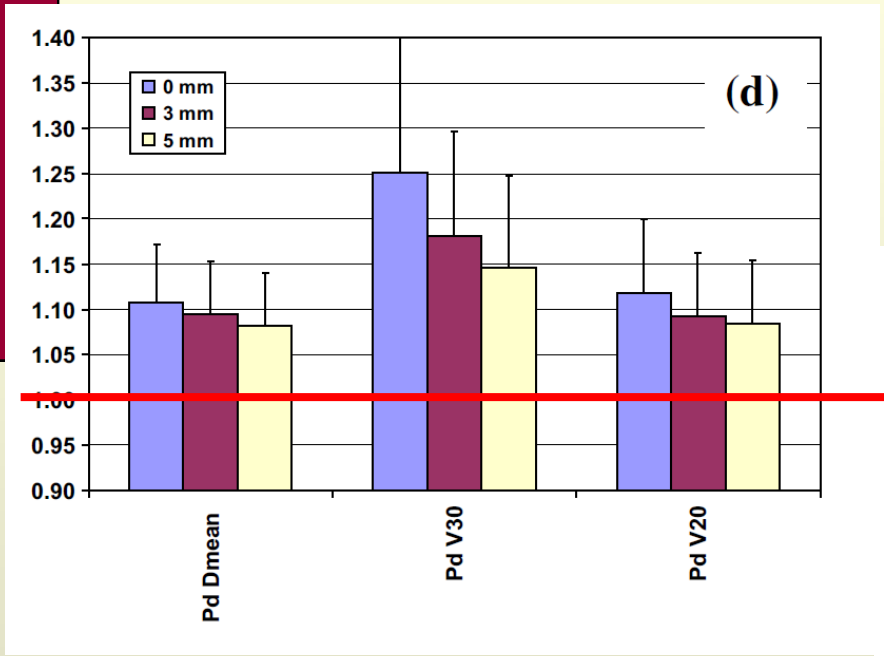
Wu et al 2009 IJROBP

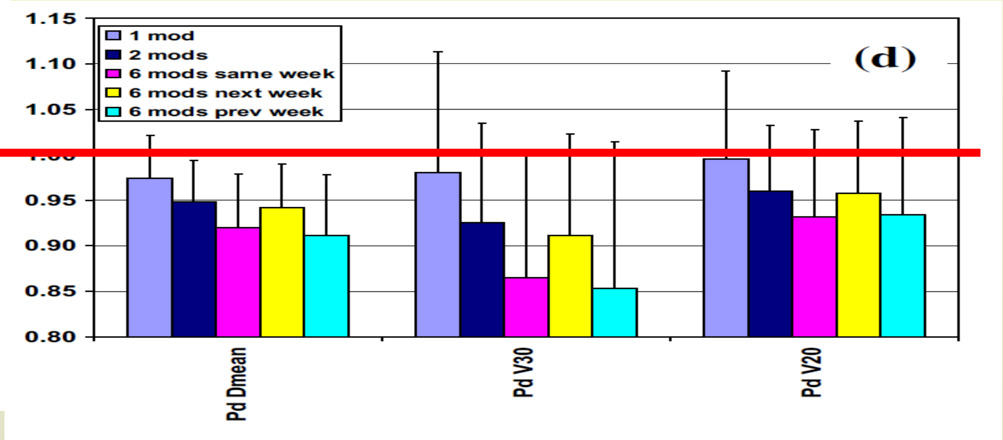
Parotid dose and replanning improves with around 5%



Wu et al 2009 IJROBP

Largest gain with replanning y/n





Wu et al 2009 IJROBP

Warning….

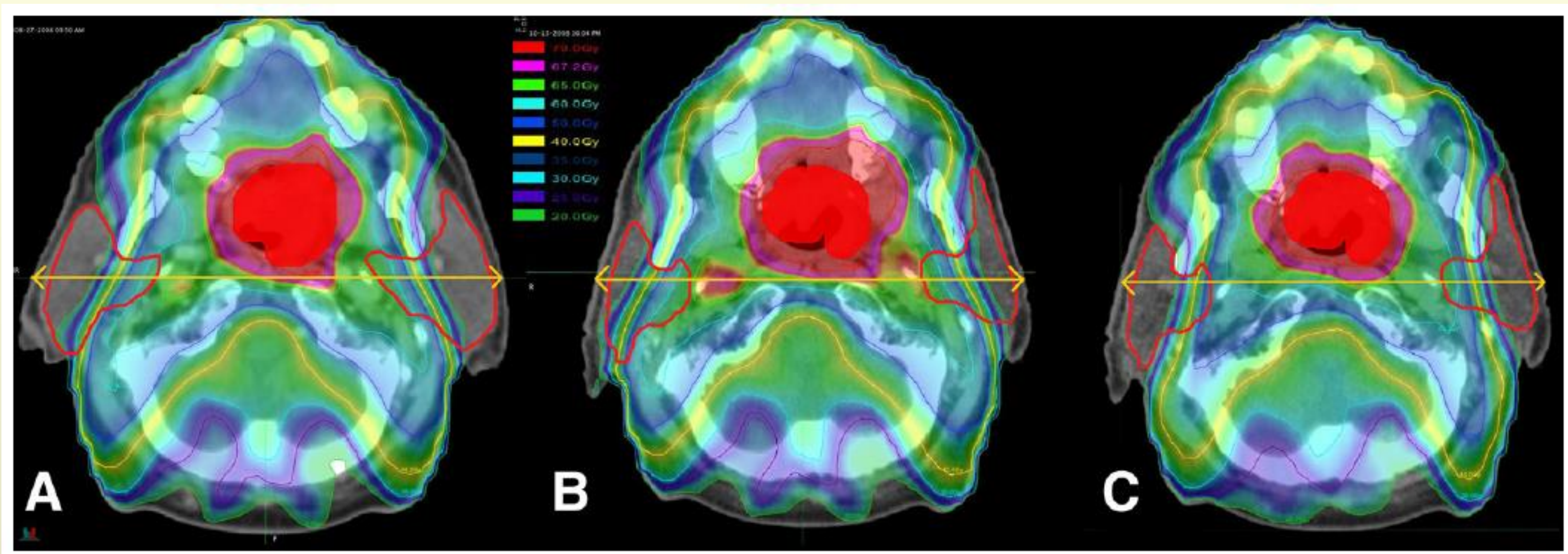
- Supposedly a large portion of the observed effect is because of shrinking of the target
- The publications/trials were not designed for equivalent or superior outcome (you would need a lot of patients and a long FU)
- Nevertheless: adapting for obvious changes like air etc. is safe, for non-obvious boundaries like tongue it might be safe.

Adaptive RT in Head and Neck

- 15 patients with advanced HN cancer
- 70 Gy 7 weeks
- Weekly repeat CT

Castelli 2015

Planning | No adaptation | With adaptation



This is what you **think** you get

This is what you **get**

This is what you **can make of it**

Castelli 2015

Adaptive RT in Head and Neck

- 15 patients with advanced HN cancer
- 70 Gy 7 weeks
- Weekly repeat CT
- Results:
  - 4 Gy more mean dose to the parotid than planned without adaptation
  - 5 Gy less mean dose to the parotid gland with weekly replanning compared to no adaptation

Castelli 2015

Summary: ART for head and neck

- Careful when adapting for tumor shrinkage
- You can overcome the deleterious effect of parotid gland shrinkage on parotid dose
- One adaptation dose most of the tric
- You do not need deformable registration:
  - if the individual plans are safe the summation is also safe

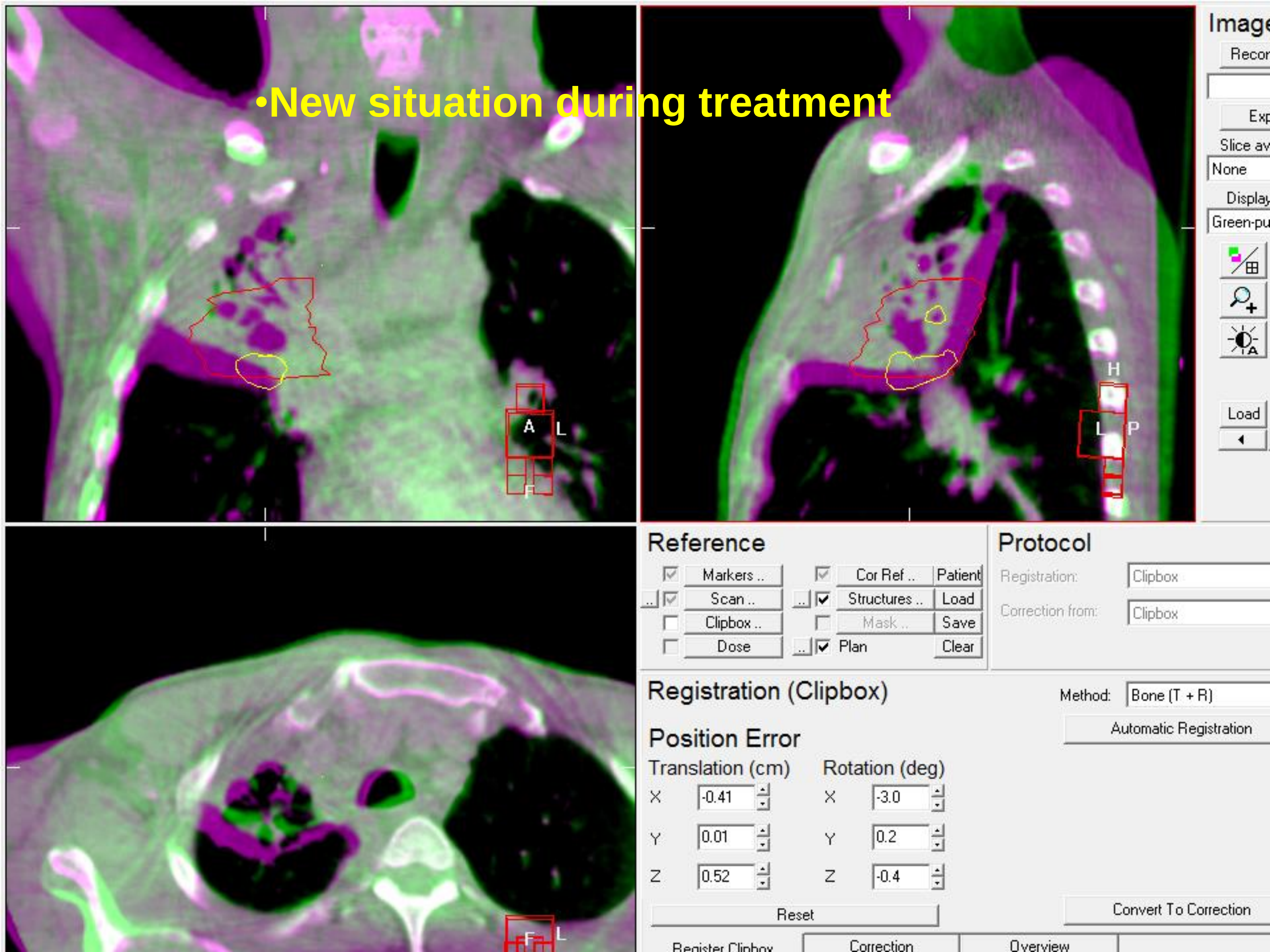
3: Art for (Un) expected changes

- Lung cancer, tumor regression (?), atelectasis (either appearing or dissolving)
- Cervix, void of hematocolpos (Uterus with blood)

ART for (un-)expected changes

- Lung cancer and atelectasis
  - Rianne demonstrated the traffic light warning system (i.e. guidelines on what to do with an image finding at the treatment machine)

•New situation during treatment



Management system anatomical changes

"decision support system to guide the RTT in prioritizing anatomy changes"

- Level green, no action needed.
- Level yellow, the radiation oncologist is notified by email, but no response is required to continue treatment.
- Level orange, the treating radiation oncologist (or back-up colleague) is informed by email and a response is required before the next fraction.
- Level red changes, the radiation oncologist must be consulted immediately before the treatment fraction is allowed to be delivered.

ART for un-expected changes

- So, it is used for **safety or quality control** not for improved dose distribution perse

Adaptive RT for lung cancer

- What if you would want to adapt to the shrinking tumor?
  - Is it predictable?
  - Is replanning advisable?

Tumor reduction during RT

- Zwienen et al 2008
  - 114 patients
  - 1 pt with progression
  - 40% of patients noticable regression
  - 8% >25% regression in third week
  - When Atelectasis present at beginning:
    - Atelectasis changed in 29% (23% smaller, 6% larger)

Tumor reduction during RT

	No. Patients	Modality	Regression Rate (%/d)	Observations
Erridge 2003 Edinburgh–NKI/AvL	25	EPID	−0.9	Microscopic extensions mentioned
Kupelian 2005 M.D. Anderson	10	In room MV-CT	−1.2	Increased dose to PTV and lungs
Siker 2006 Wisconsin	25	MVCT	−2.4	Mixed group, radical, palliative and stereotactic RT
Bosmans 2008 Maastro	23	FDG-PET/CT	−0.39	Lymph node regression only
McDermott 2006 NKI/AvL	1	EPID	−1.5	Increased dose to PTV and lungs
Underberg 2006 VUMC	40	4D-CT and conventional CT	−1.4	Volume. increase 1st and 2nd wk
Britton 2007 M.D. Anderson	8	In room KV-CT	−1.3	Volume increase 1st and 2nd wk
Woodford 2007 Ontario	17	In room MV-CT	−0.79	
Fox 2009 Johns Hopkins	22	MVCT	−1.2	Regression greater (−1.4%) in first 3 wk
Feng 2009 Michigan	14	Mid-RT FDG-PET/CT	−1.4	Planning study
Van Zwienen 2008 NKI/AvL	114	In room kV-CBCT	−0.6	Frequent anatomical changes occurred

C/ 1vol%/day

Sonke et al 2010

Radiotherapy amc

ART for lung: mid-treatment adaptation

Adaptive radiotherapy in lung cancer: dosimetric benefits and clinical outcome

T KATARIA, MD, DNB, D GUPTA, MD, S S BISHT, MD, N KARTHIKEYAN, MSc, S GOYAL, MD, DNB, L PUSHPAN, DNB, A ABHISHEK, MD, HB GOVARDHAN, MD, DNB, V KUMAR, MD, K SHARMA, MD, DNB, S JAIN, MD, T BASU, MD and A SRIVASTAVA, MD, DNB

15 patients stage III lung cancer
Replanning after 44 of 66 Gy with new target delineation
Clinical trial

ART for lung: mid-treatment adaptation

Delineated structure	Pre-treatment median (range)	Mid-treatment median (range)	Median reduction (%) (range)	*p*-value
GTV primary (cm³)	313 (45.0–829.0)	113 (30.0–691.0)	34.00 (13.8–73.0)	0.02
GTV nodal (cm³)	33 (9.4–141.0)	8 (4.5–20.0)	49.00 (6.0–53.0)	0.14
PTV (cm³)	773 (169.0–1826.0)	565 (130.0–1272.0)	34.70 (32.0–76.0)	0.00

GTV, gross tumour volume; PTV, planning target volume.

Significant decrease of +/- 30% in tumor and target volume

ART for lung: mid-treatment adaptation

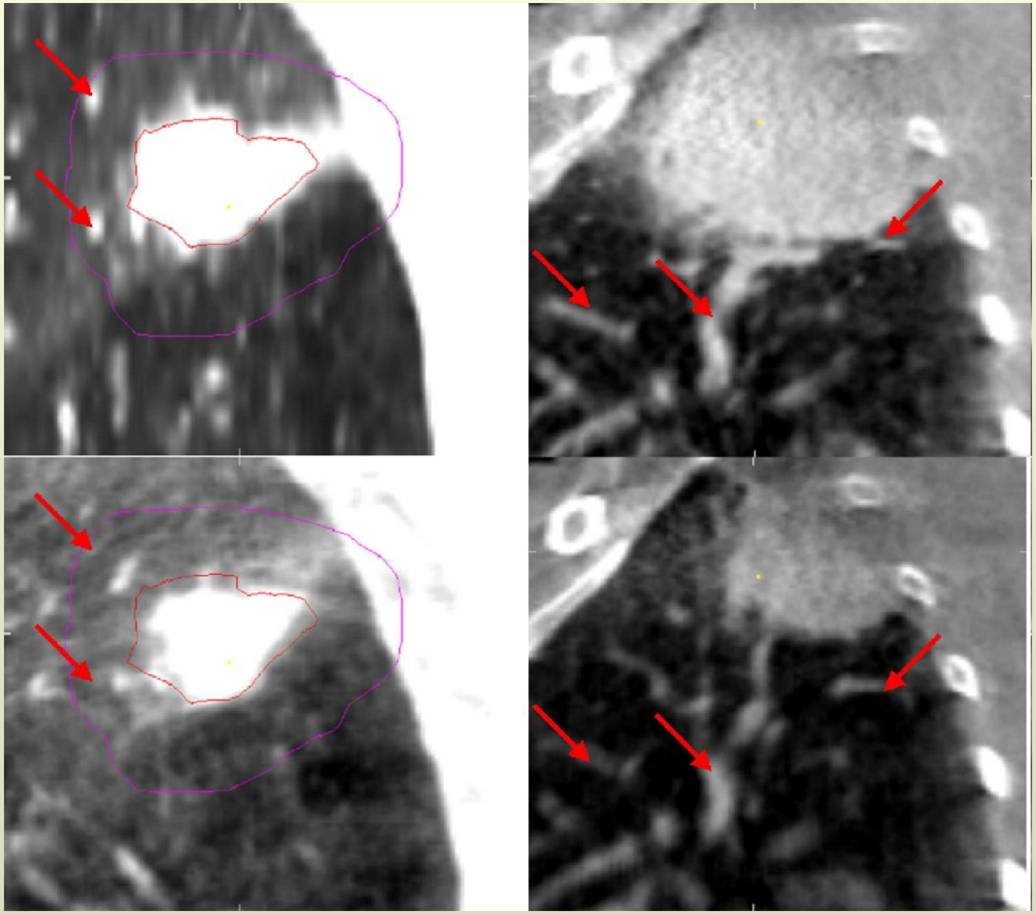
Dose parameters	Pre-treatment mean ± SD (range)	Mid-treatment mean ± SD (range)	Mean reduction (%)	p-value
Ipsilateral lung without PTV				
$V20$ (cm^3)	238.51 ± 149.25 (98–471)	114.05 ± 116.63 (60–317)	52.18	0.01
$V5$ (cm^3)	510.65 ± 145.30 (285–912)	399.49 ± 105.13 (233–612)	21.76	0.05
Mean (cGy)	784.39 ± 302.05 (392–1182)	596.65 ± 297.33 (345–943)	23.93	0.00
Contralateral lung				
$V20$ (cm^3)	21.80 ± 12.58 (0–30)	1.24 ± 3.00 (0–9)	42.85	0.15
$V5$ (cm^3)	351.66 ± 222.65 (112–803)	297.22 ± 200.67 (52.6–646)	15.48	0.31
Mean (cGy)	402.49 ± 167.06 (192–697)	284.00 ± 121.79 (78–546)	29.43	0.01
Heart				
$V20$ (cm^3)	16.86 ± 29.16 (0–85)	3.12 ± 0.23 (0–4)	81.47	0.13
$V10$ (cm^3)	97.57 ± 65.56 (0–184)	42.32 ± 32.90 (0–97)	56.62	0.00
$V5$ (cm^3)	169.98 ± 97.94 (0–276)	115.88 ± 56.46 (0–234)	31.82	0.04
Mean (cGy)	531.53 ± 447.03 (31–1477)	344.38 ± 241.26 (12–736)	35.21	0.02
Oesophagus				
Mean (cGy)	1020.00 ± 351.00 (616–1245)	709.00 ± 370.00 (464–1139)	19.03	0.17
Spine				
$D2$ (cGy)	1130.47 ± 160.03 (221–1701)	706.18 ± 151.78 (152–1311)	37.53	0.00
D_{max} (cGy)	1215.02 ± 184.84 (336–1989)	771.09 ± 178.69 (259–1817)	36.53	0.00

What does a smaller image of the tumor mean?

Shrinkage Dissolvement

Start

Half way



Note: Arrows point at vessels

Sonke et al 2010

ART for lung: mid-treatment adaptati

Adaptive radiotherapy in lu … etric benefits and clinical outcome

T KATARIA, MD, DNB, D GUPTA, MD, … MSc, S GOYAL, MD, DNB, L PUSHPAN, DNB,
A ABHISHEK, MD, HB GOVARDH … ARMA, MD, DNB, S JAIN, MD, T BASU, MD and
A SRIVASTAVA, MD, DNB

My opinion:

DON't DO THIS OUTSIDE a CLINICAL TRIAL

15 pa … ung cancer

R … 44 of 66 Gy

Do you need deformable registration if you want to do adaptive radiotherapy?

- **No**: if all individual plans are safe AND with adequate coverage, the summation will be safe and appropriate for the target as well
- **Yes**: if you want to know the actual dose to the OAR's

In summary:

- Ask yourself what kind of adaptation you want
- Act accordingly
- Careful when adapting on a smaller projection of the tumor:
  - Would you have accepted an upfront underdosage to the microscopic part of the original CTV?

Question

- Is there clinical evidence for the usefullness of adaptive RT?
  - Yes and no
  - Yes:
    - Less irradiation reduces toxicity in earlier efforts in shrinking the irradiated volume (plan of the day, expected changes)
    - Adaptation is a QA instrument (plan of the day, unexpected changes)
  - No:
    - No randomized trials performed, therefore no information on safety available
    - Replanning on tumor regression is not advised unless obvious borders

Special thanks to:

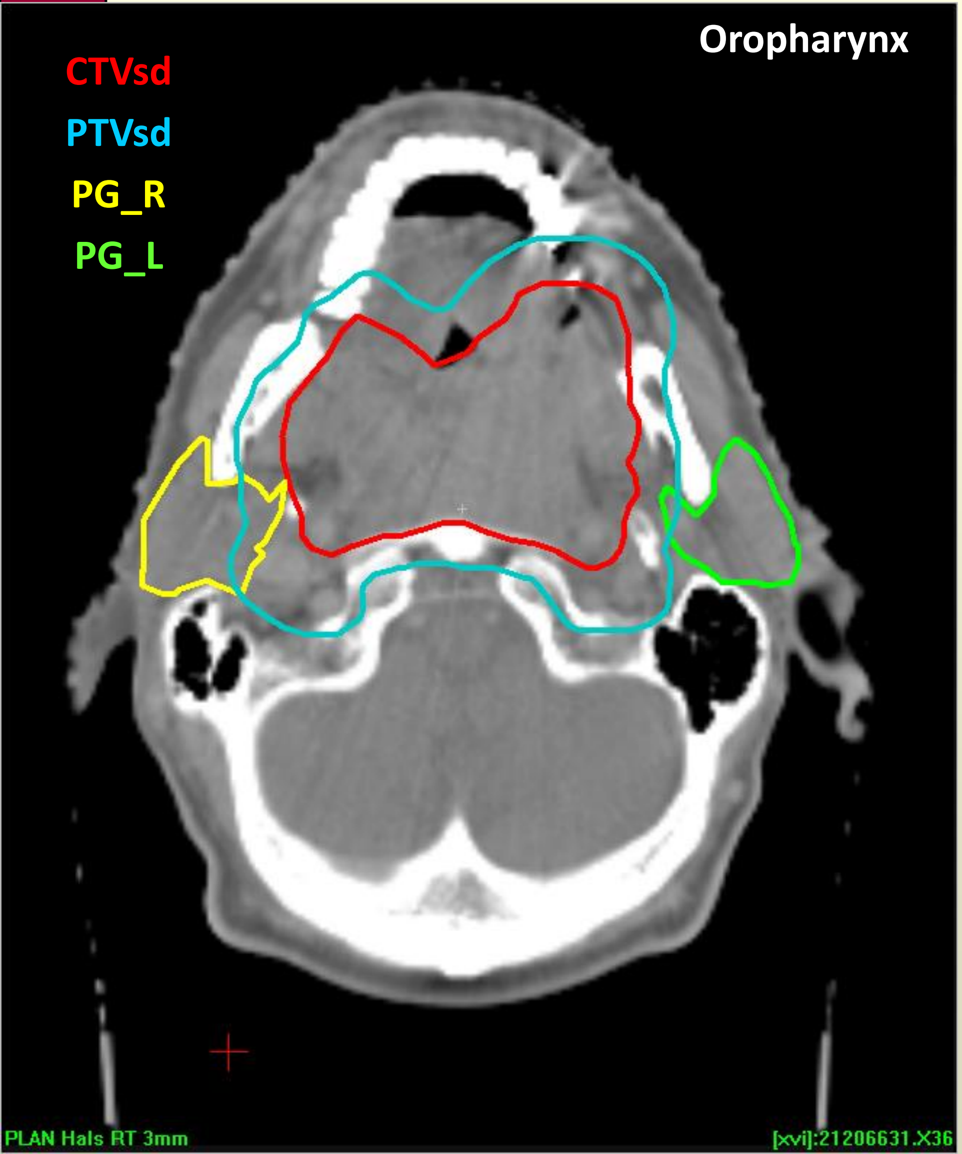
- Marcel van Herk
- Jan-Jakob Sonke
- Peter Remeijer
- Danny Minkema
- Rianne de Jong
- Suzanne van Beek
- Jasper Nijkamp
- Anja Betgen
- Monique Smitmans
- Harry Bartelink
- Olga Vrieze
- Frank Hoebers

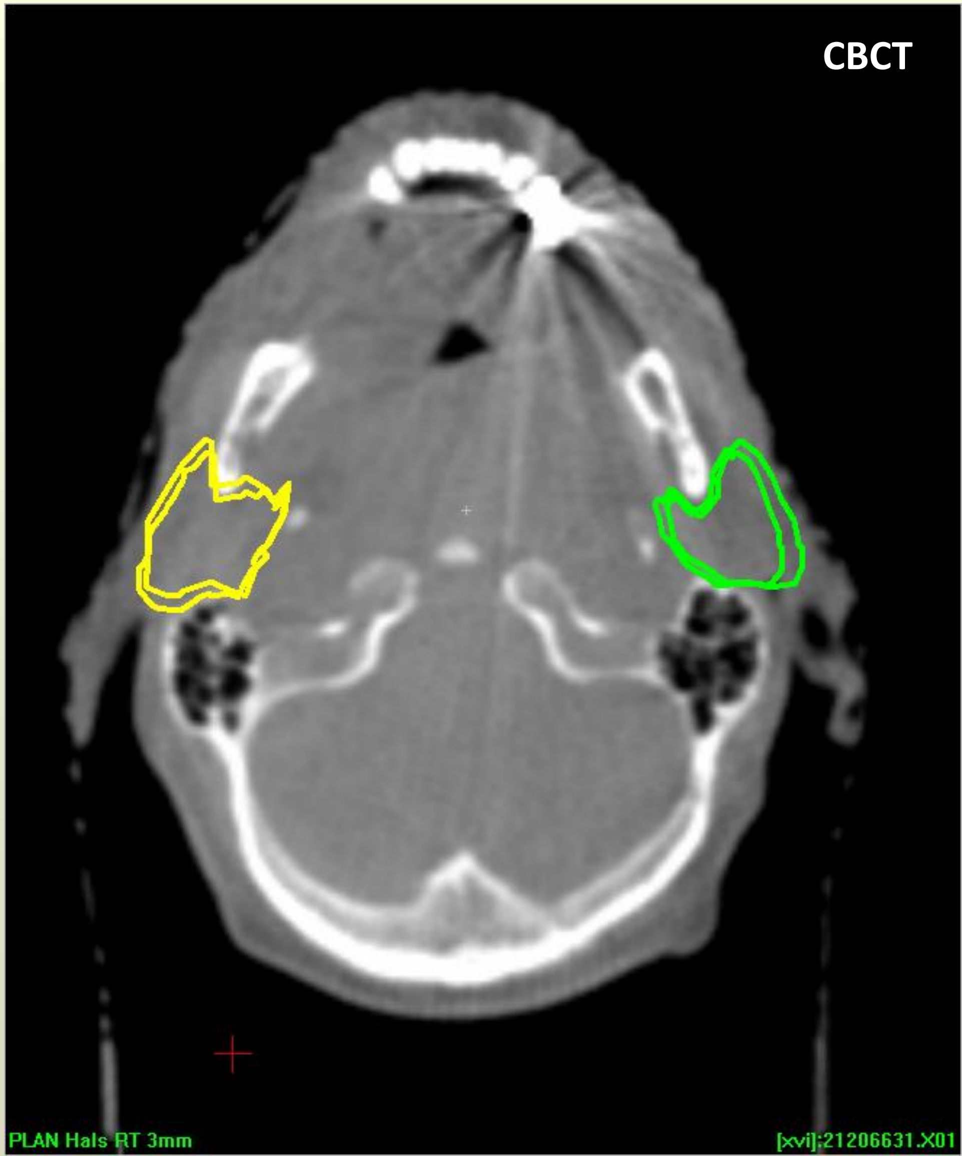
- Josien de Bois
- Lambert Zijp
- Joop Duppen
- Simon van Kranen
- Joos Lebesque
- Caro Koning
- Peter de Boer
- Maarten Hulshof
- Monique Bloemers
- Michiel van den Brekel
- Fons Balm
- Ludy Smeele
- Dept. RT AMC en AvL
- And many Others………

Clinical trial on dose redistribution with adaptation

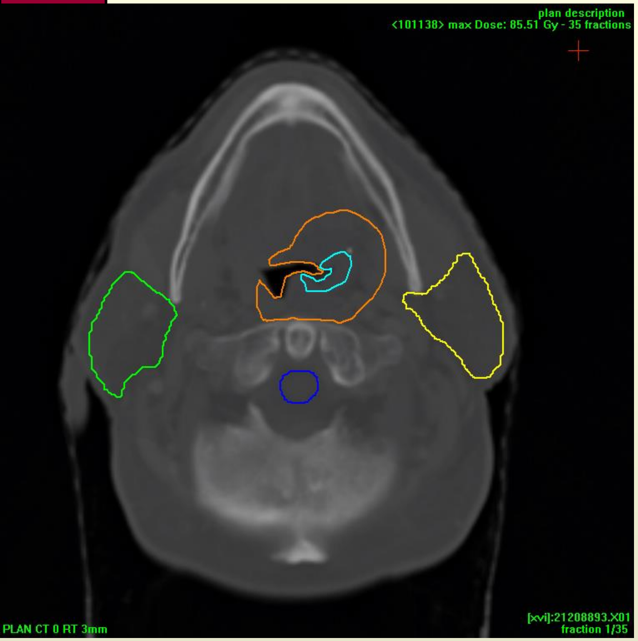
- Advanced head and neck cancer
- 70 (ICRU)vs 84 Gy focussed on FDG with 66 Gy at the edge of the tumor
- Two adaptations in 6 weeks
- Ongoing trial

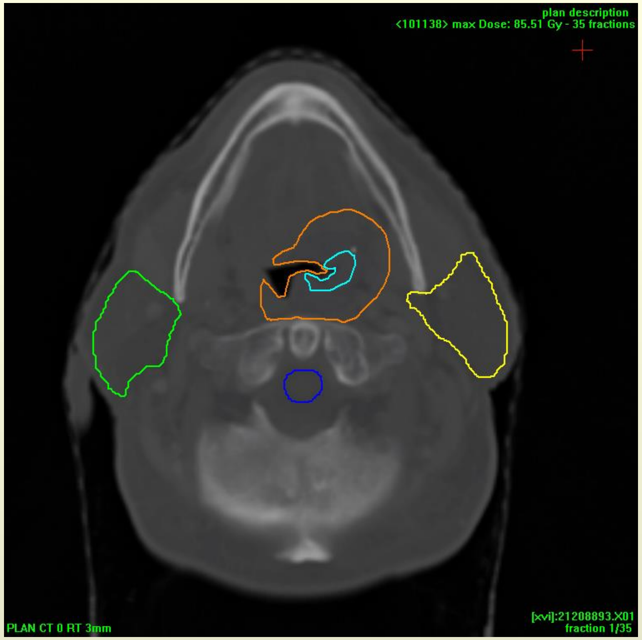
Contour Propagation

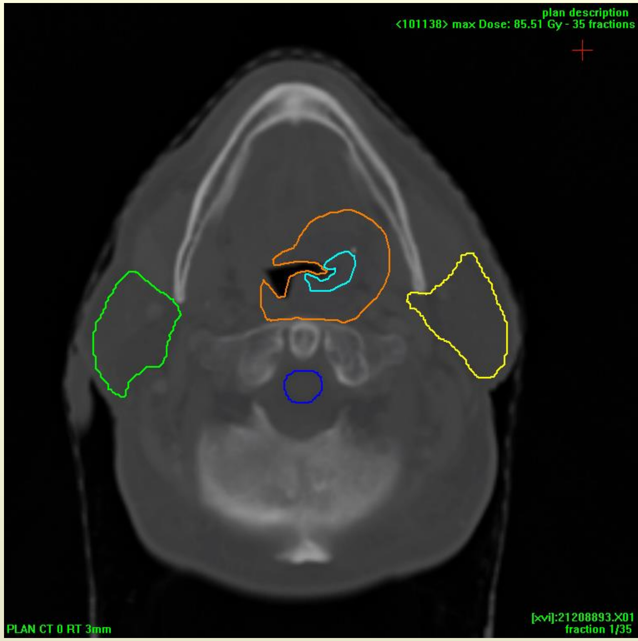




Dose accumulation during treatment





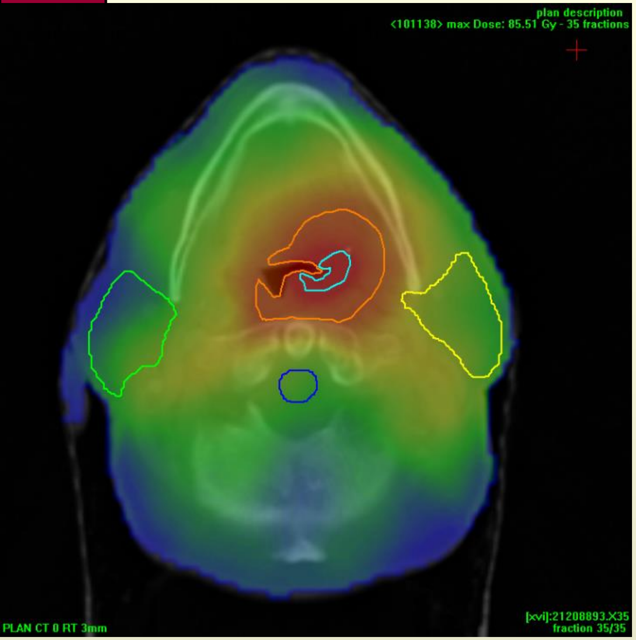


Initial plan

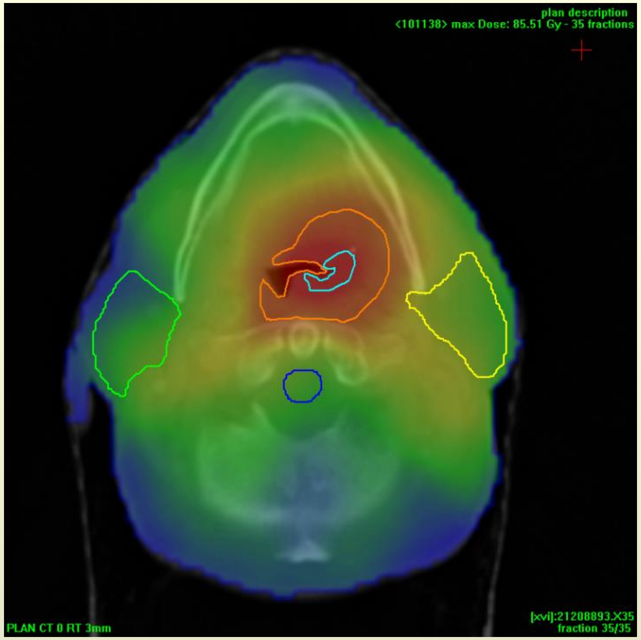
Without ART

With ART

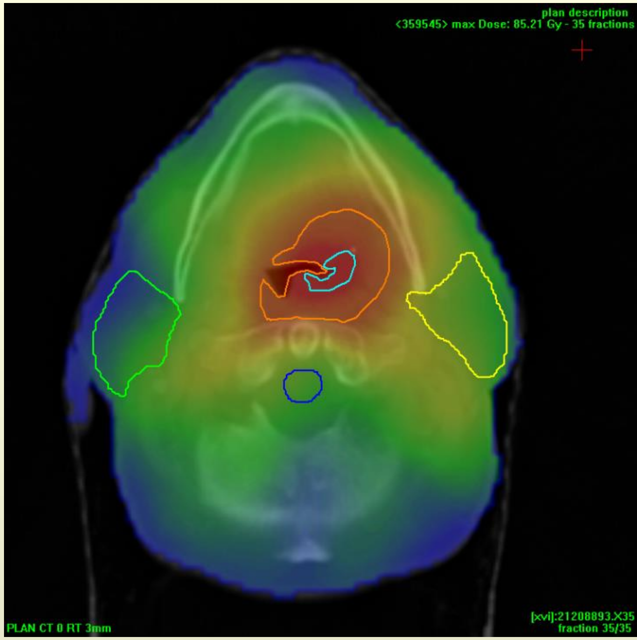
Dose accumulation during treatment



Initial plan



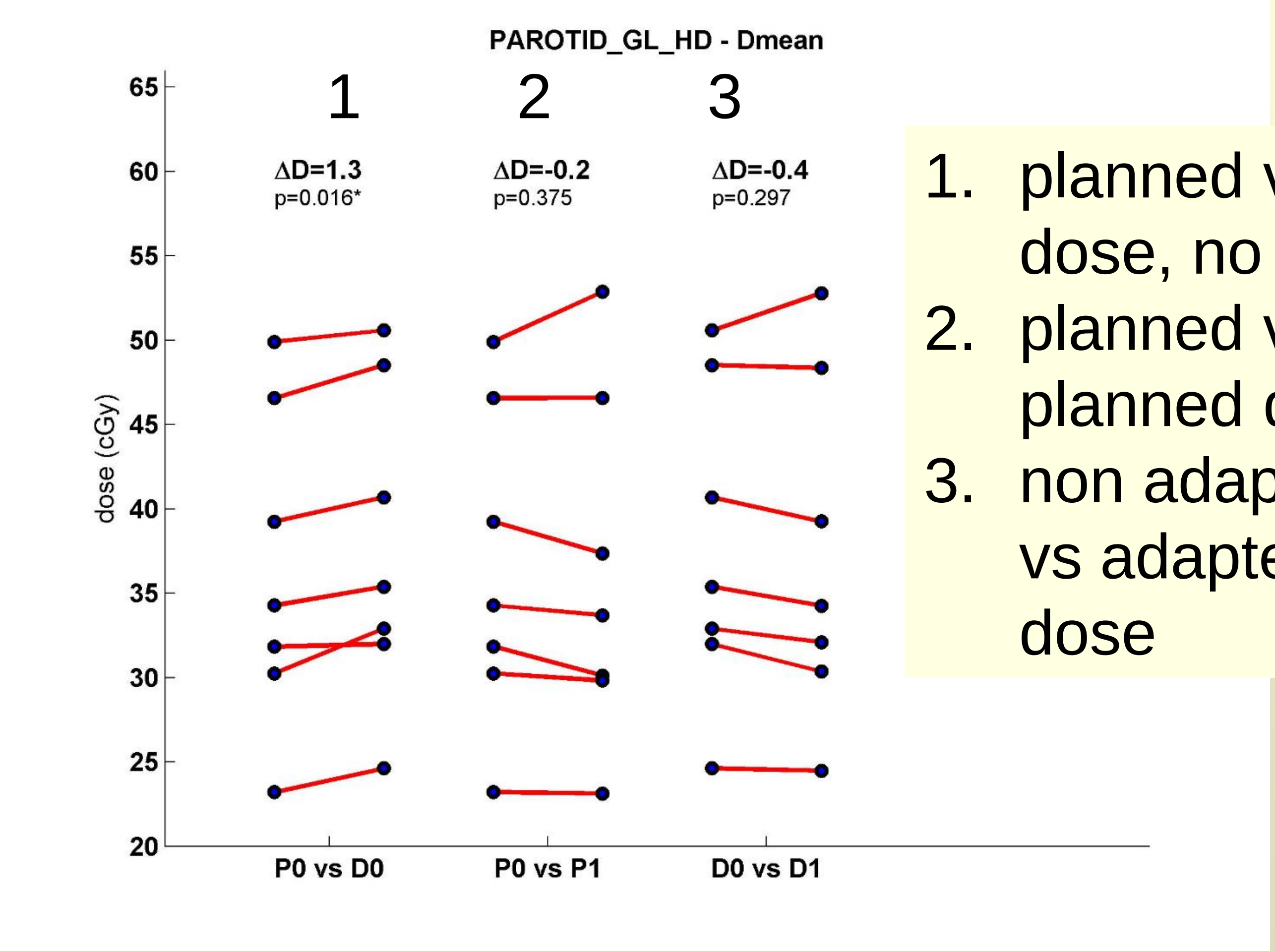
Without ART



With ART

Impact of Adaptation ARTFORCE Trial

7 patients: Mean Dose difference – parotid gland



1. planned vs delivered dose, no adaptation
2. planned vs adapted planned dose
3. non adapted delivered vs adapted delivered dose

Plan selection approach

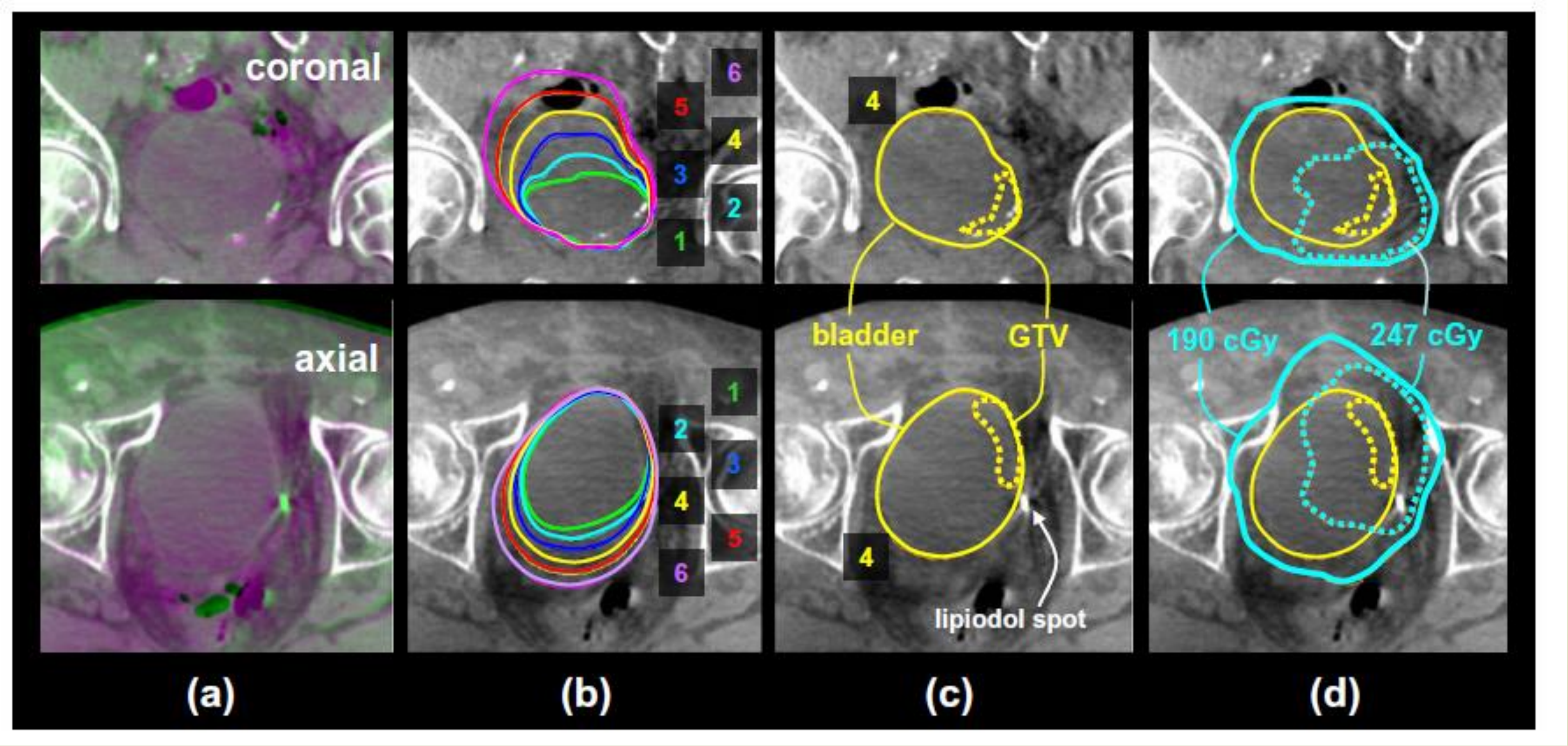
- Bladder cancer
  - G. Meijer et al R&O 2012

ART for bladder

- Lipiodol (or equivalent) injection around the tumor by the urologist
- Treatment planning CT scan with empty and full bladder
- Interpolation of 6 (?) positions of the bladder/tumor
- Generate 6 (?) treatment plans for several bladder volumes
- CBCT scan:
  - Identify bladder volume and select appropriate plan
  - Match on lipiodol
  - Verify bladder is covered by (drawn) isodose line
  - Treat

•Meijer et al R&O 2012

ART for bladder: selection of plan



measure choose check dose summation

- Meijer et al R&O 2012

ART for bladder made easy

- What if you don’t have the interpolation software?

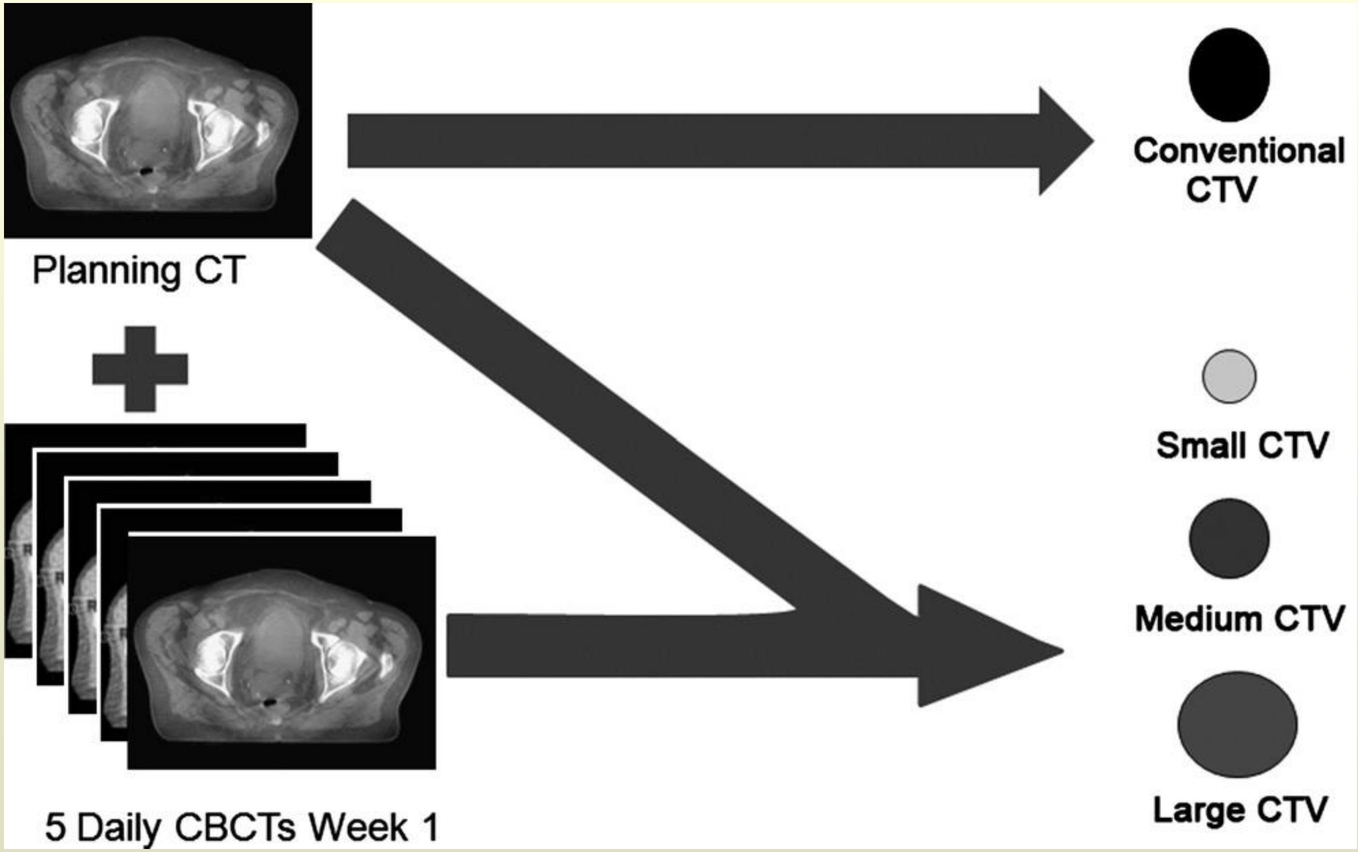
ART for bladder made easy

- 27 patients T2-4 N0M0
- 32 fractions
- Conventional plan with large margins on CT scan
- Scan first five fractions on CBCT
- Calculate
  - Small (around smallest bladder volume)
  - Large (around all the volumes)
  - Medium: manually in between
- Add 0.5 cm and plan

•Foroudi et al 2011

Voila!

ART for bladder made easy



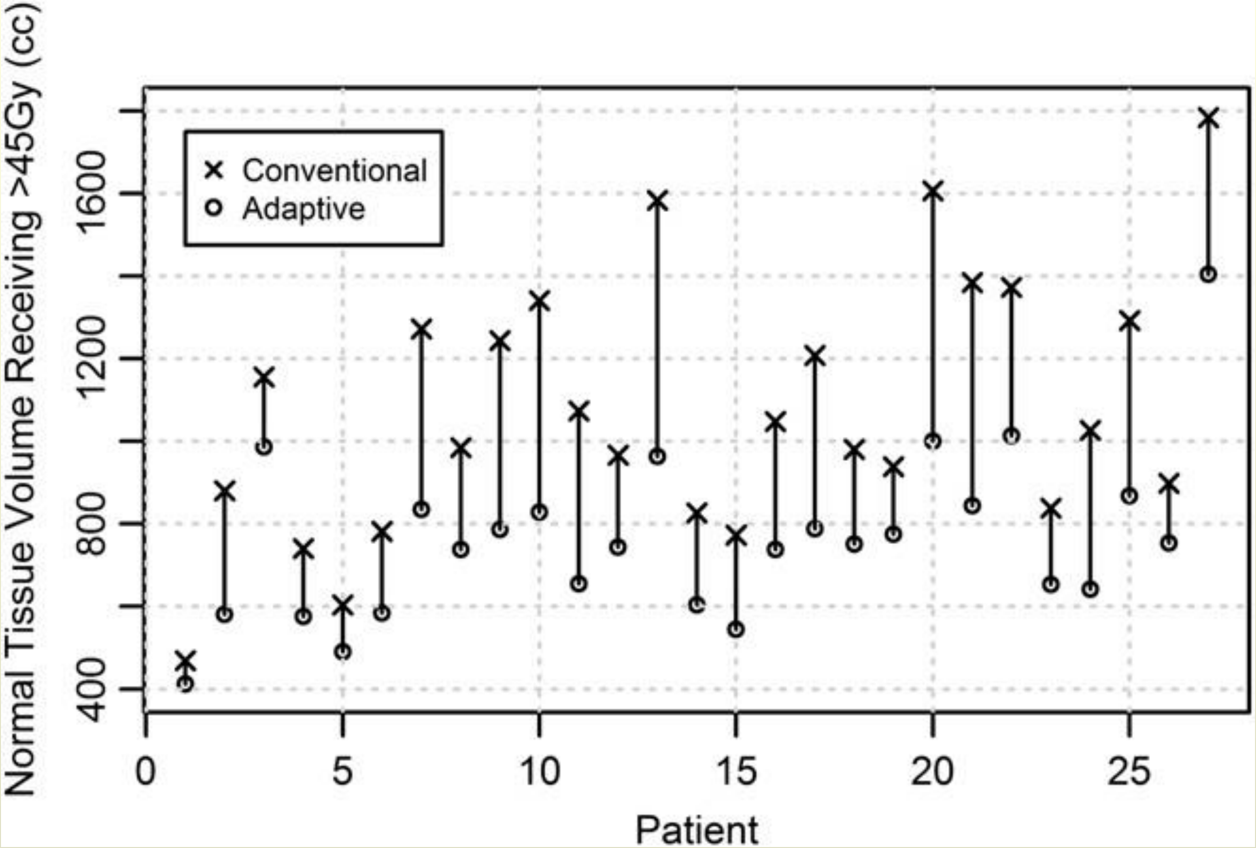
- Foroudi et al 2011

ART for bladder made easy

- Bladder volume decreased with fraction number
- Less underdosage (2.5→4.8% of the fractions)
  - small CTV: 9.8%,
  - medium CTV: 49.2%,
  - large: CTV: 39.5%,
  - conventional: 1.5% of the fractions was used

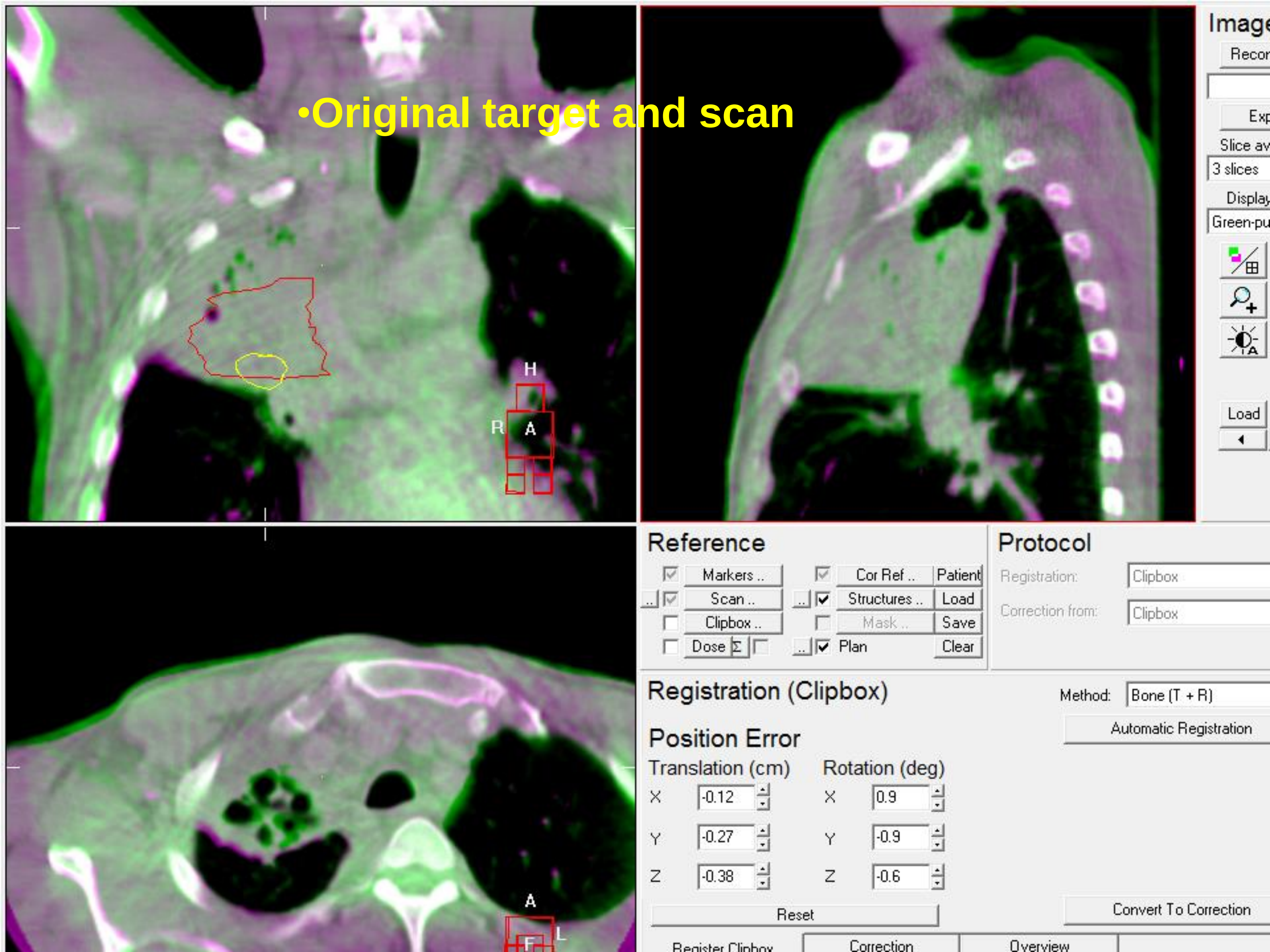
•Foroudi et al 2011

ART for bladder made easy

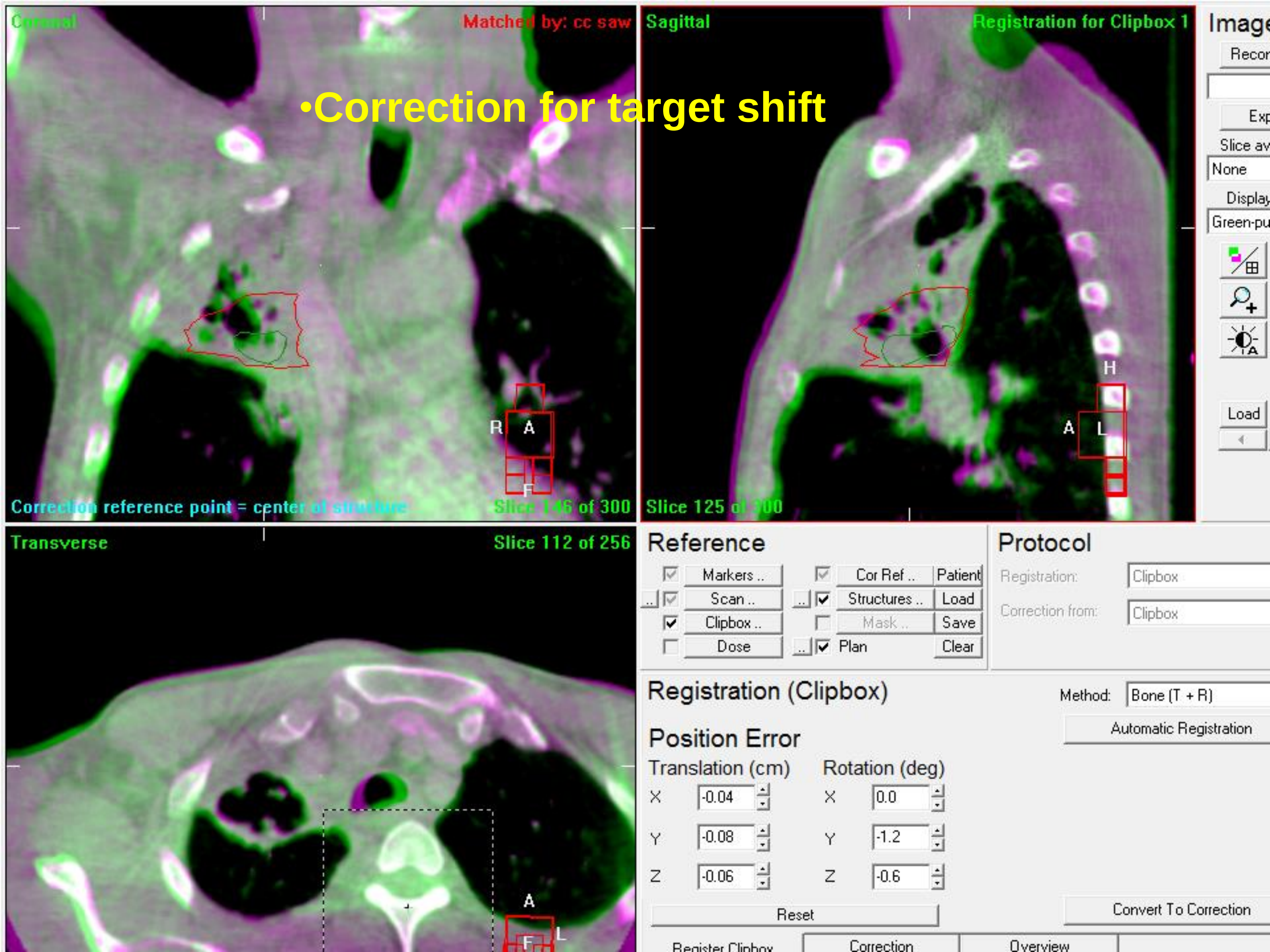


•Foroudi et al 2011

•Original target and scan



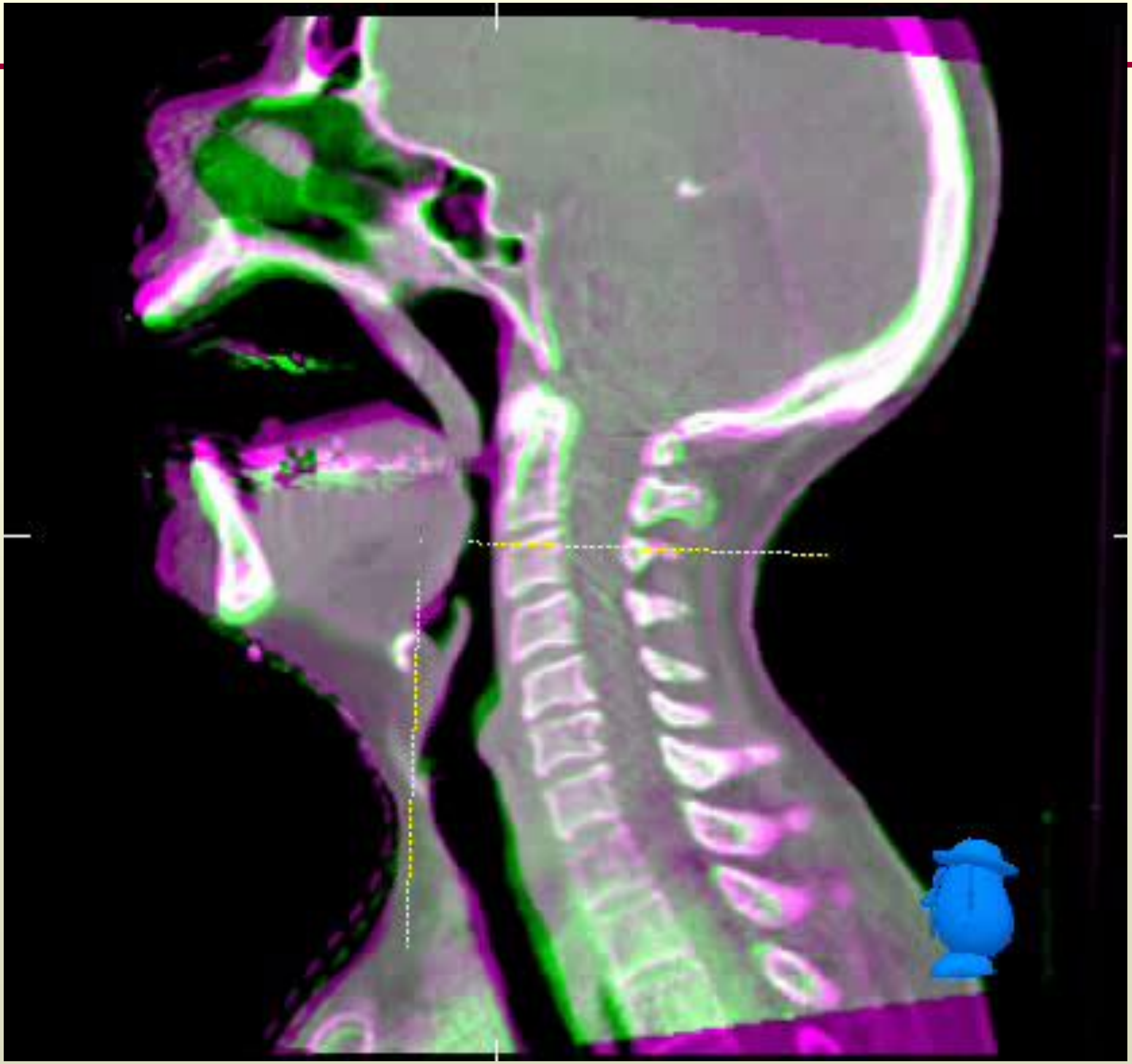
• Correction for target shift



Anatomy and posture changes in H&N

Radiotherapy amc

Full deformable registration



Cubic B-splines, Mutual Information

Cervix cancer, classical approach, NO ART

- Larger margin to account for motion
- 33 patients, 2 T2 MRI images

Table 2
Magnitude of displacement of Points U, C and V in the anterior–posterior (AP), superior–inferior (SI) and lateral (Lat) directions

		Uterus (Point U)			Cervix (Point C)			Vagina (Point V)	
		AP	SI	Lat	AP	SI	Lat	AP	Lat
Magnitude of displacement (mm)	Median	5.0	5.0	0.0	3.0	3.0	0.0	1.0	0.0
	Mean	7.0	7.1	0.8	4.1	2.7	0.3	2.6	0.3
	SD	9.0	6.8	1.3	4.4	2.8	0.8	3.0	1.0
	Range	0–48	0–32	0–5	0–19	0–12	0–3	0–10	0–5

•Taylor et al R&O 2008

Cervix plan of the day made easy

Cervix

- Uterus moves (sometimes)
- If you don’t want plan selection:
  - Population based margins tailored around cervix and uterus
  - Daily CBCT imaging with online verification of target within the PTV
    - i.e.: Stop when outside the PTV
    - Urinate or wait (the patient... ☺) and treat again

Cervix plan of the day in one slide

- Make scans with full bladder and with empty bladder
- Co-register both CTs
- Generate 3-5 CTV positions
- Generate 3-5 PTV's and treatment plans
- Generate "old-fashioned all-in" backup plan for comfort choice at treatment machine
- Perform CBCT, register on bones, choose plan manually based upon bladder filling (or Uterus if you can reliably see it) and treat
- No deformable registration needed

Warning….

- Supposedly a large portion of the observed effect is because of shrinking of the target!

Patient change over time

Patient change over time

ART for un-expected changes

- Kwint et al. 2014
  - In 128 patients (72%), 210 anatomical changes were observed with a maximum level of red (12%), orange (36%) and yellow (24%).
  - Types of observed changes were,
    - tumor regression (35%)
    - tumor baseline shift (27%)
    - changes in atelectasis (19%)
    - tumor progression (10%)
    - pleural effusion (6%)
    - and infiltrative changes (3%)
  - Plan adaptation in case of safety issues (under or overdosage)

Adaptive Rectal Cancer Radiation – with a pelvic overview

Parag Parikh, BSE, MD

ESTRO School

Table 1. Results from the PubMed searches and paper selection.

Site	Pubmed search hits	Pubmed hits after title and abstract screening	Pubmed hits after full paper screening (clinical/simulation)
Prostate	341	177	33 (8/25)
Gynecological	200	72	22 (14/8)
Bladder	162	100	17 (10/7)
Ano-rectal	194	114	2 (1/1)
Total	897	463	74 (33/41)

Thornqvist, Acta Oncologica, 2016

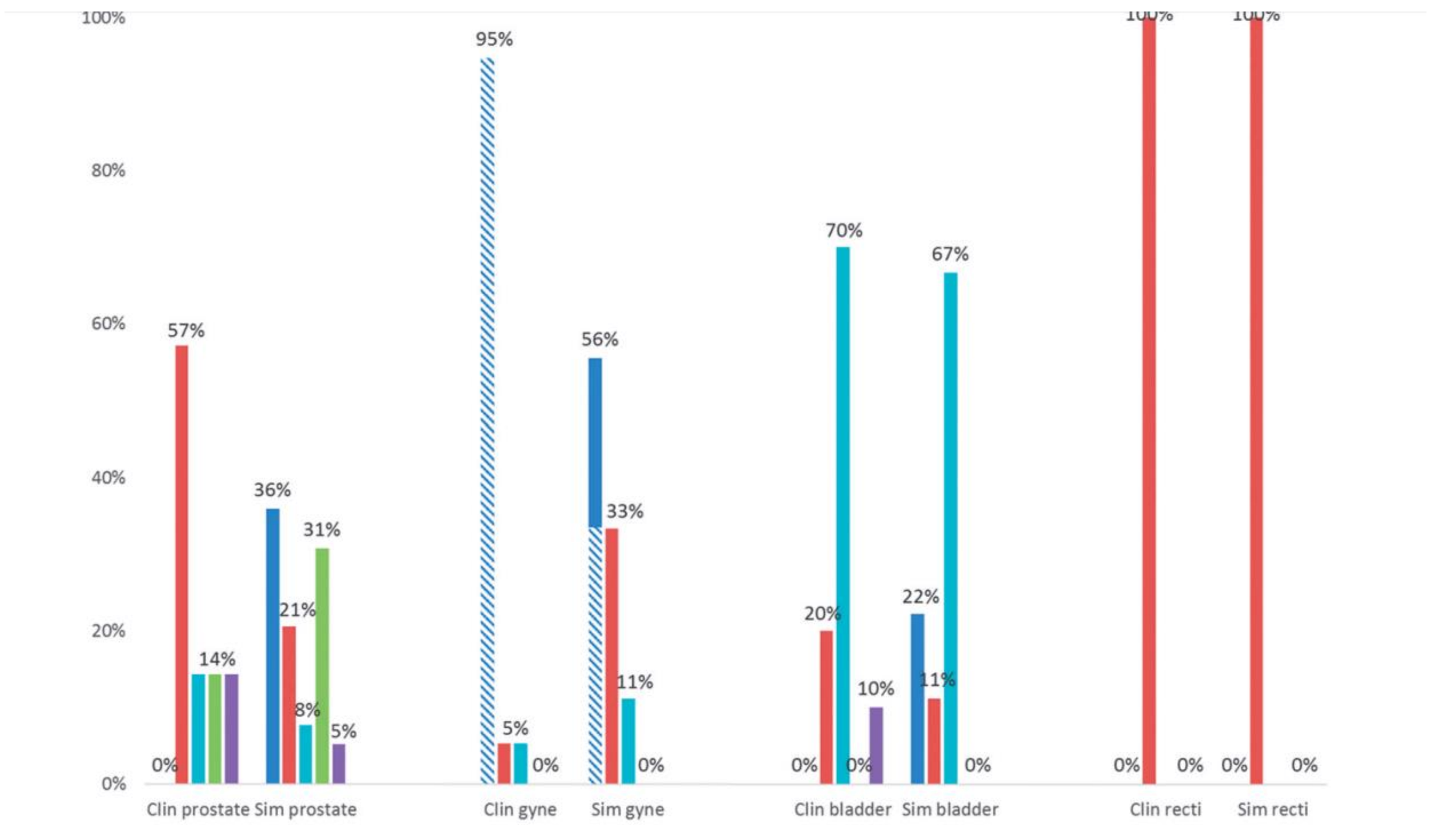


Figure 3. Different categories of the implemented and the simulated ART workflows: online re-planning (blue), offline re-planning (red), online plan selection (turquoise), online MLC/field alteration (green), offline MLC/field alteration (violet). The workflows are plotted as percentage of the total number of either implementation or simulation workflows. Studies concerning brachytherapy additionally marked with striped pattern. clin: clinical; sim: simulation; gyne: gynecological.

Thornqvist, Acta Oncologica, 2016

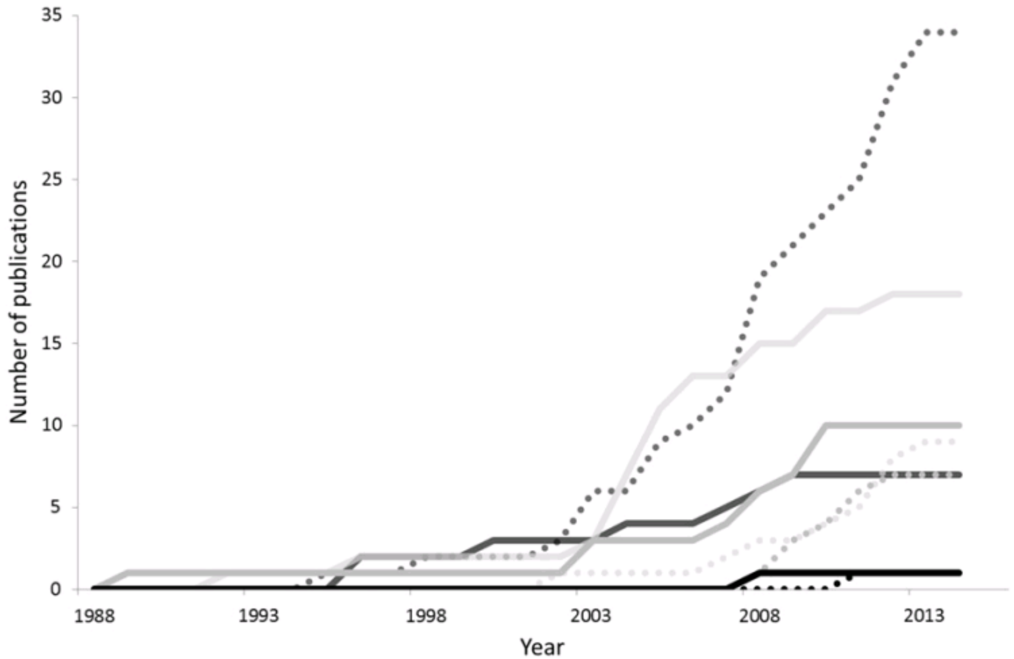


Figure 1. Accumulation of clinical implementation and simulation studies for prostate (dark gray), gynecological (light gray), bladder (gray) and ano-rectal (black) cancer. Date of enrollment of the first patient were denoted for the clinical implementations (solid lines) and date of acceptance for publication of the simulation studies (dotted lines).

Thornqvist, Acta Oncologica, 2016

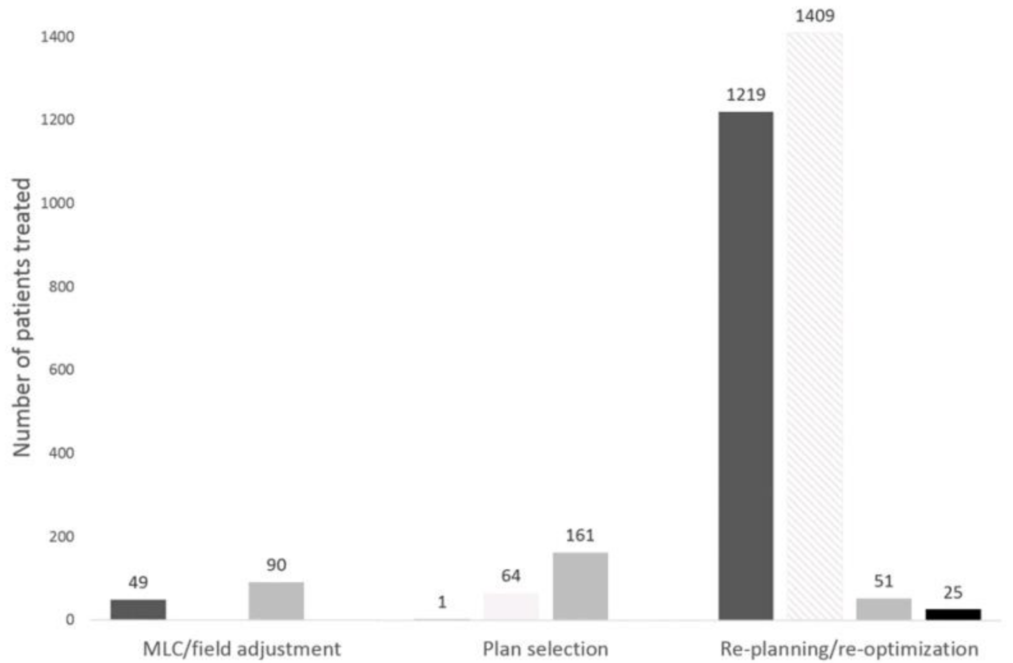


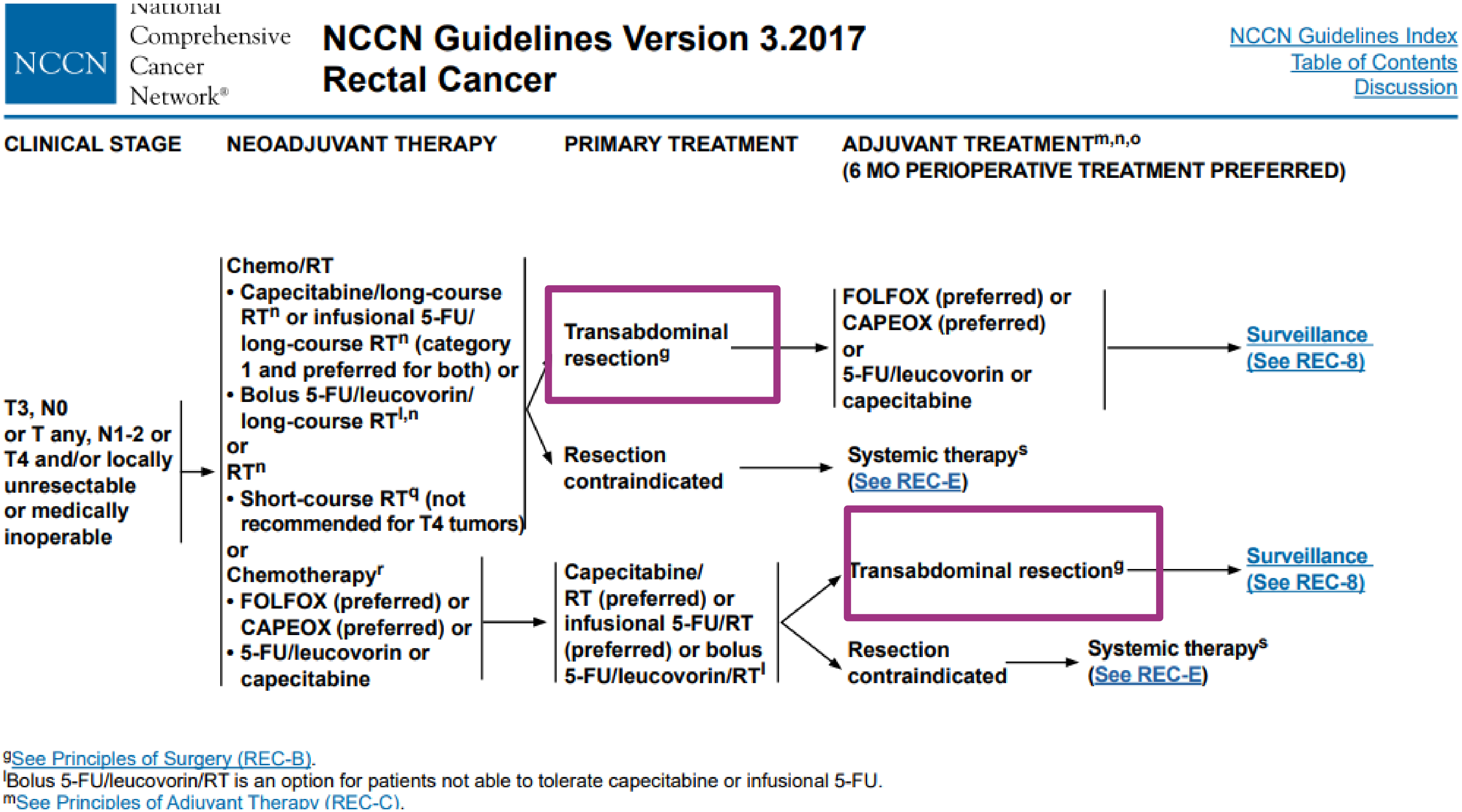
Figure 2. The number of prostate (dark gray), gynecological (light gray), bladder (gray) and ano-rectal (black) patients treated with the different categories of ART workflows. Patients treated with brachytherapy additionally marked with striped pattern.

Thornqvist, Acta Oncologica, 2016

Rectal Agenda

- Review of different clinical rectal cancer goals with radiation
- Review of recent clinical outcomes of radiation
- Clinical implementation of adaptive radiation (courtesy of AMC / R De Jong)

NCCN Rectal Cancer Guidelines



National Comprehensive Cancer Network® NCCN

NCCN Guidelines Version 3.2017 Rectal Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGE — T3, N0 or T any, N1-2 or T4 and/or locally unresectable or medically inoperable

NEOADJUVANT THERAPY

Chemo/RT
- Capecitabine/long-course RT[n] or infusional 5-FU/long-course RT[n] (category 1 and preferred for both) or
- Bolus 5-FU/leucovorin/long-course RT[l,n]

or

RT[n]
- Short-course RT[q] (not recommended for T4 tumors)

→ **PRIMARY TREATMENT**: Transabdominal resection[g] → **ADJUVANT TREATMENT[m,n,o] (6 MO PERIOPERATIVE TREATMENT PREFERRED)**: FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine → Surveillance (See REC-8)

→ Resection contraindicated → Systemic therapy[s] (See REC-E)

or

Chemotherapy[r]
- FOLFOX (preferred) or CAPEOX (preferred) or
- 5-FU/leucovorin or capecitabine

→ Capecitabine/RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT[l]

→ Transabdominal resection[g] → Surveillance (See REC-8)

→ Resection contraindicated → Systemic therapy[s] (See REC-E)

[g]See Principles of Surgery (REC-B).
[l]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[m]See Principles of Adjuvant Therapy (REC-C).

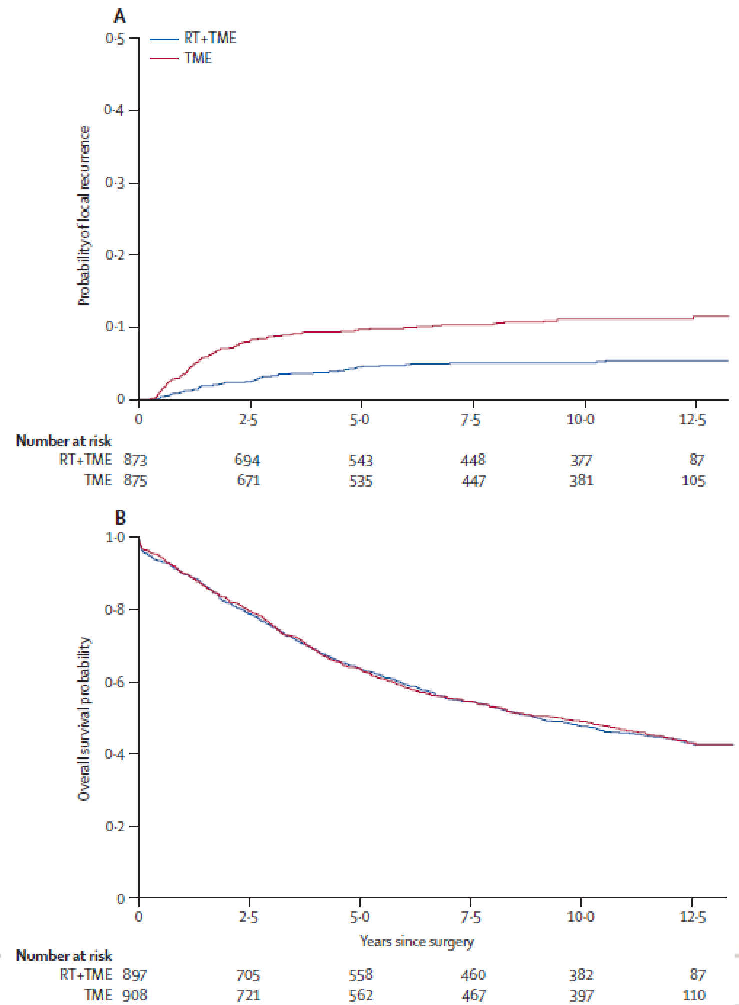
Dutch Trial
van Gijn et al, Lancet Oncol 2011

1861 patients with resectable rectal cancer randomized:

- **TME alone vs 25 Gy / 5 fx preop**
  - **If surgery alone, postop RT required for SM ≤ 1mm**

- **10 year LR 11 vs 5% favoring preop RT**

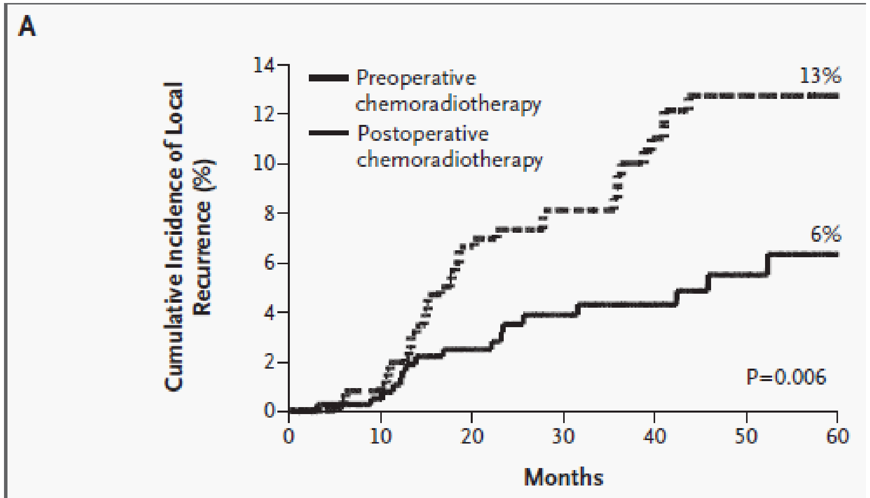
- **No difference in OS**



Neoadjuvant vs Adjuvant ChemoRT

Sauer et al JCO 2012

- **823 pts T3-4 or N+ randomized to pre-op vs post op chemoRT**
  - **Pre-op RT 50.4 Gy/1.8 Gy fx, concurrent 5FU**



No. at Risk	0	10	20	30	40	50	60
Preoperative chemoradiotherapy	397	368	312	250	190	133	97
Postoperative chemoradiotherapy	384	351	299	240	184	135	85

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

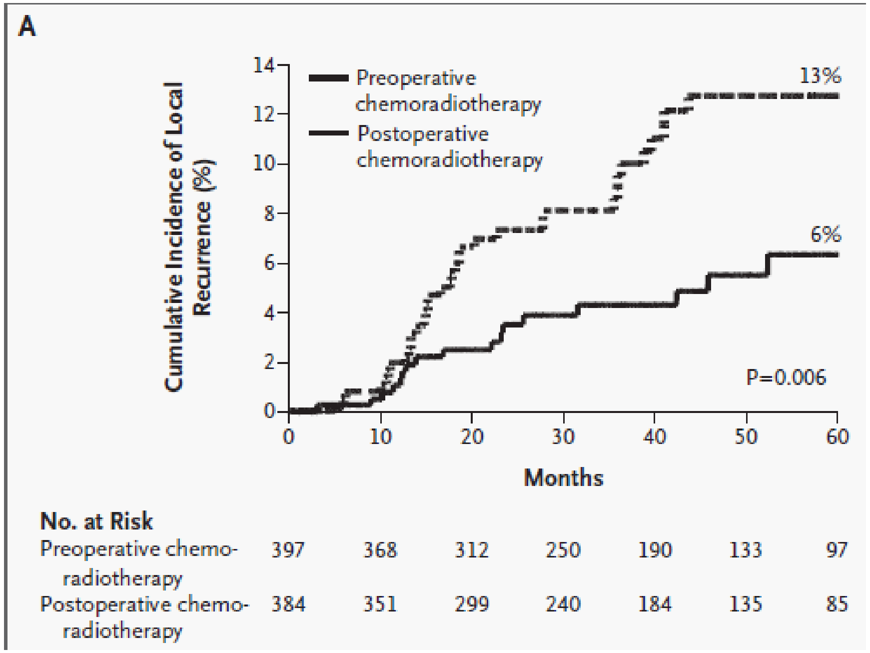
Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

Neoadjuvant vs Adjuvant ChemoRT

Sauer et al JCO 2012

Improved local control for neoadjuvant chemoRT, fewer acute and late toxicities

Increased rate of sphincter-preserving surgery (LAR) for neoadjuvant chemoRT?



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Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

Target Volumes

GTV: Tumor + involved nodes

rectal exam, rigid proctoscopy, MRI, CT and/or PET

CTV : Elective lymph nodes +/- ischiorectal fossa for low tumors

Whole mesorectum

Standard: perirectal nodes, internal iliac, superior rectal artery

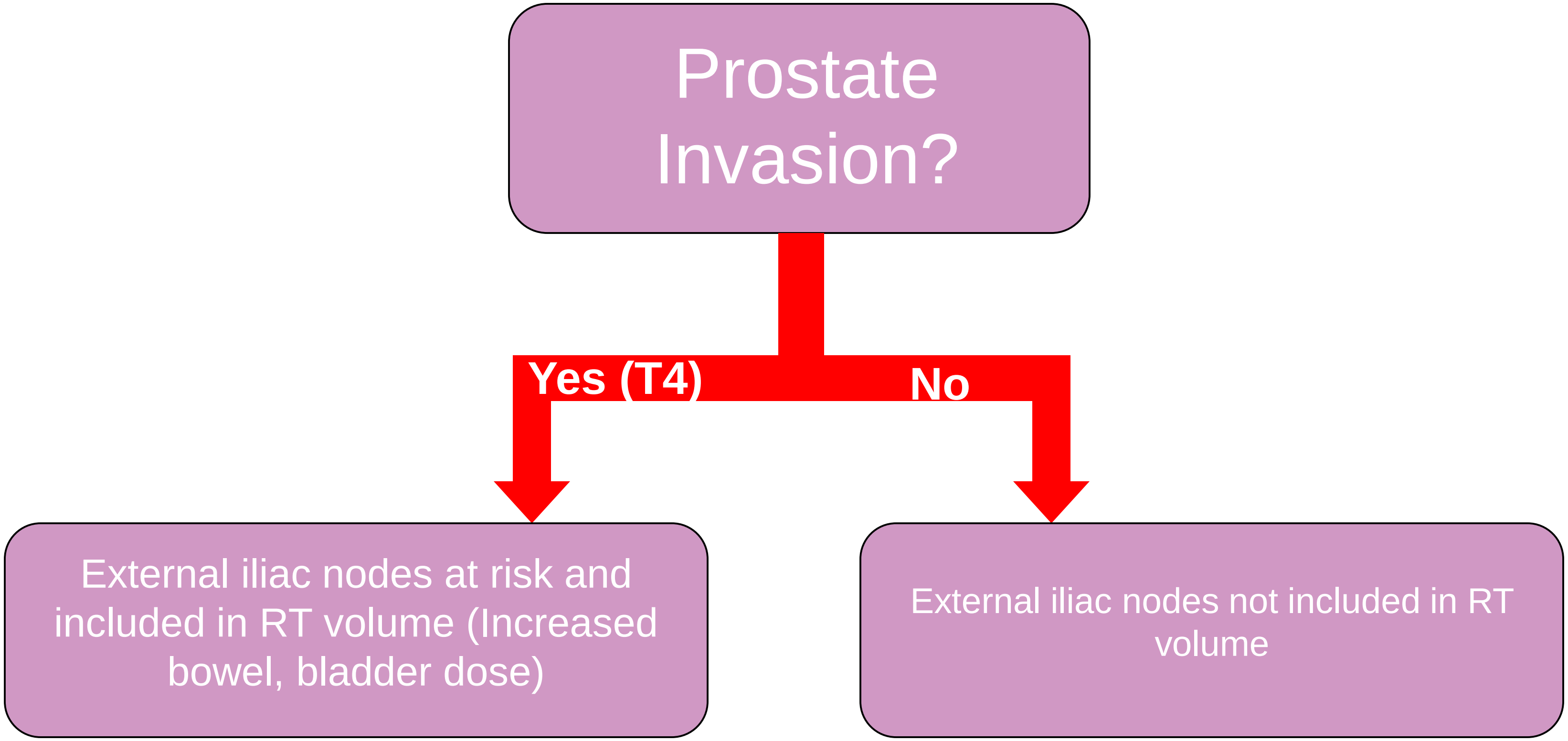
T4 – anterior structures = + external iliac

T4 or gross anal canal = +inguinal ln and external iliac LN

Myerson, Kachnic 2009

MR Impacts RT Volume

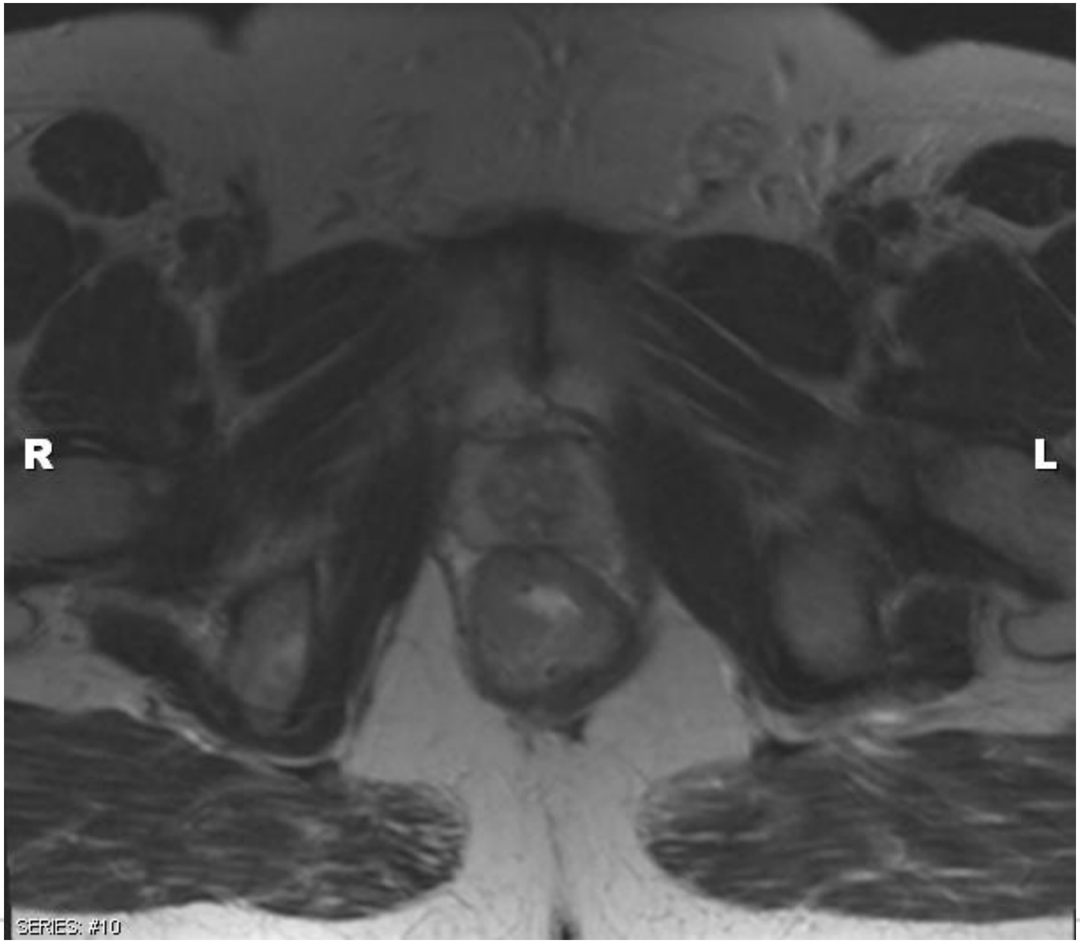
Case Example



MR Impacts RT Volume

Case Example

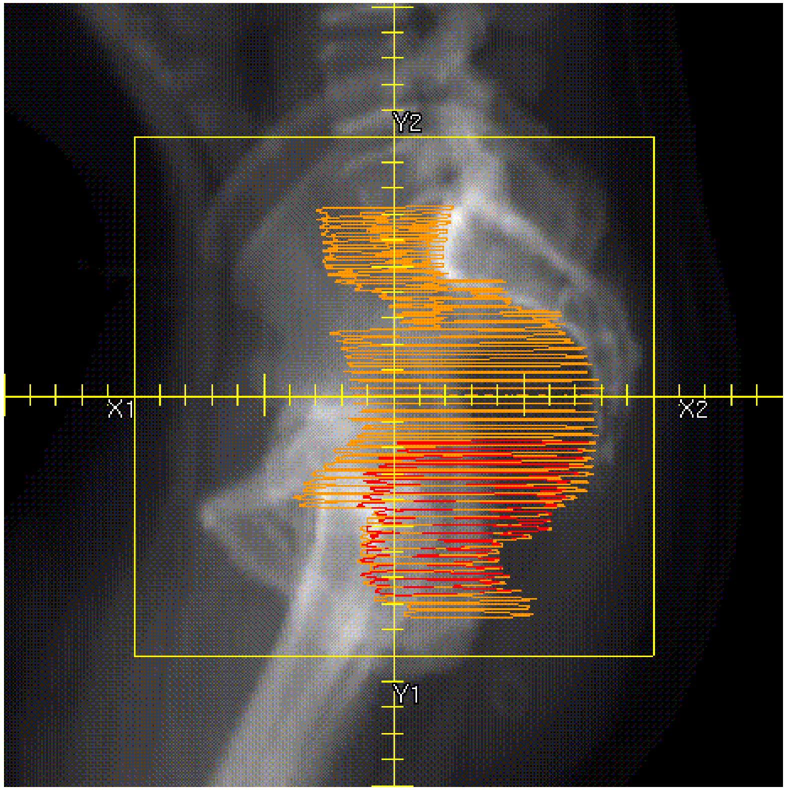
MRI obtained, tumor noted to abut, not invade prostate

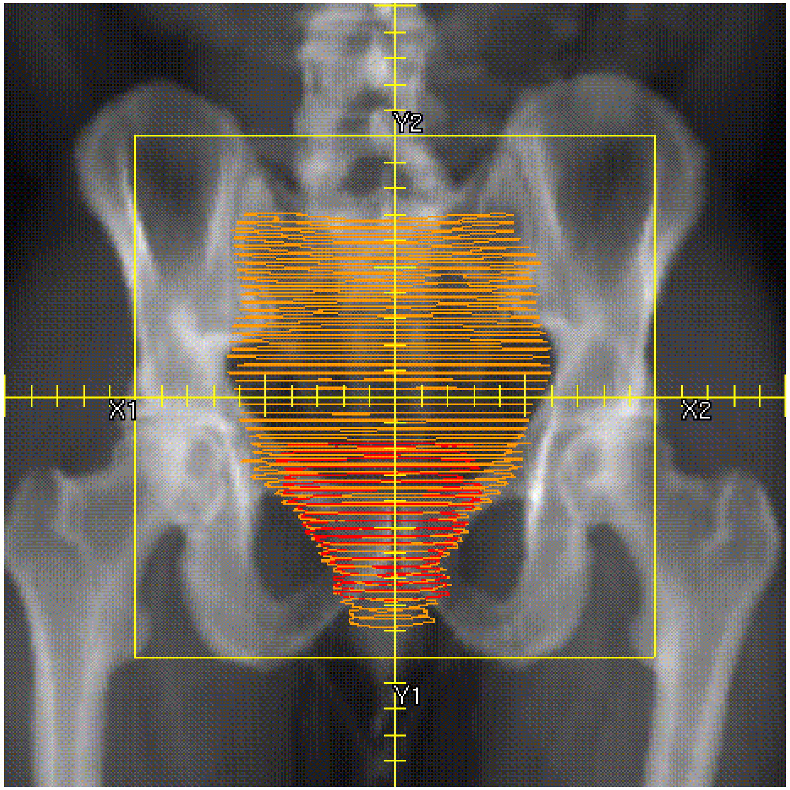


MR Impacts RT Volume

Case Example

- 41 yo M cT4N1 (prostate invasion by ERUS) rectal adenocarcinoma, seen in consultation for preop chemoRT.





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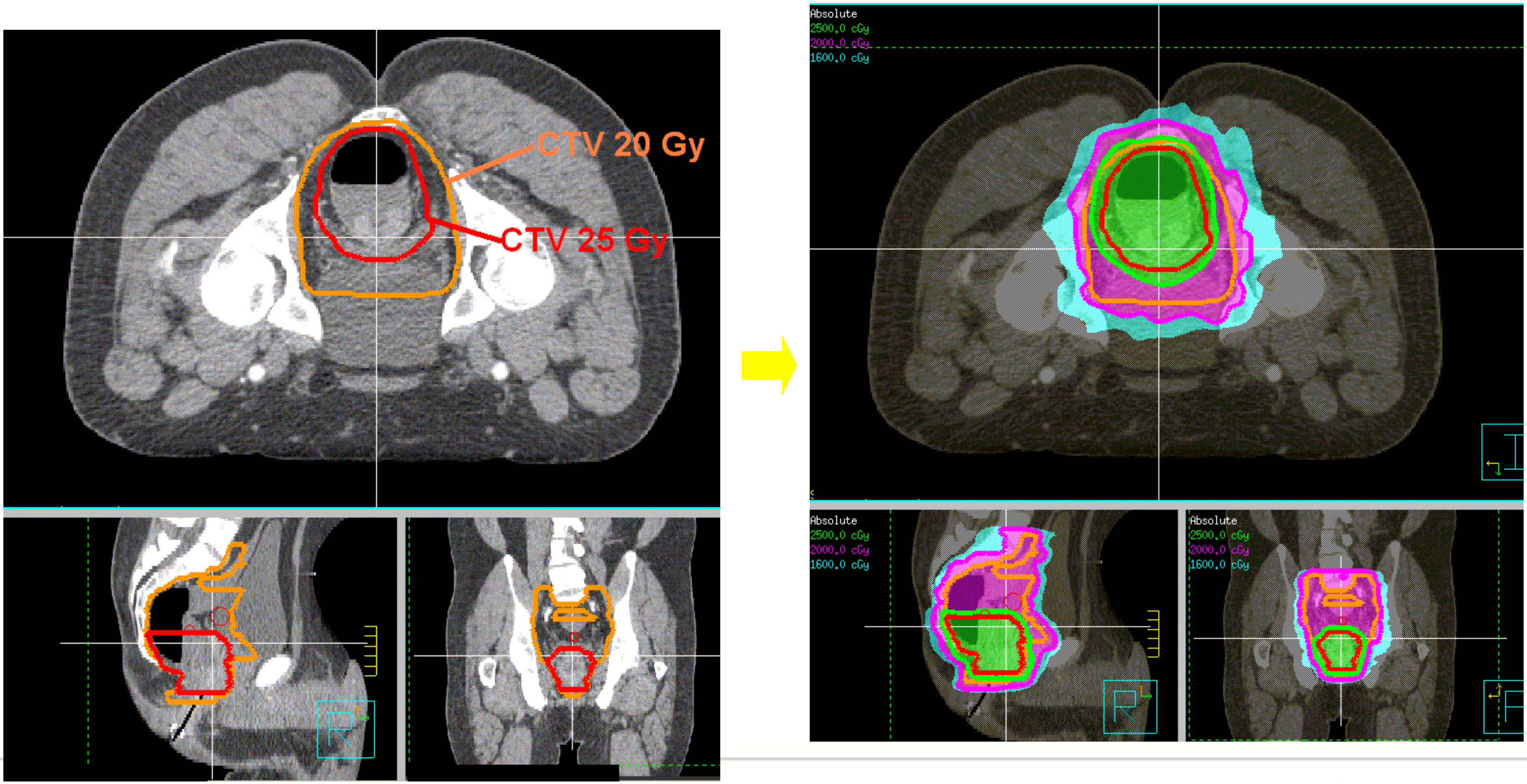

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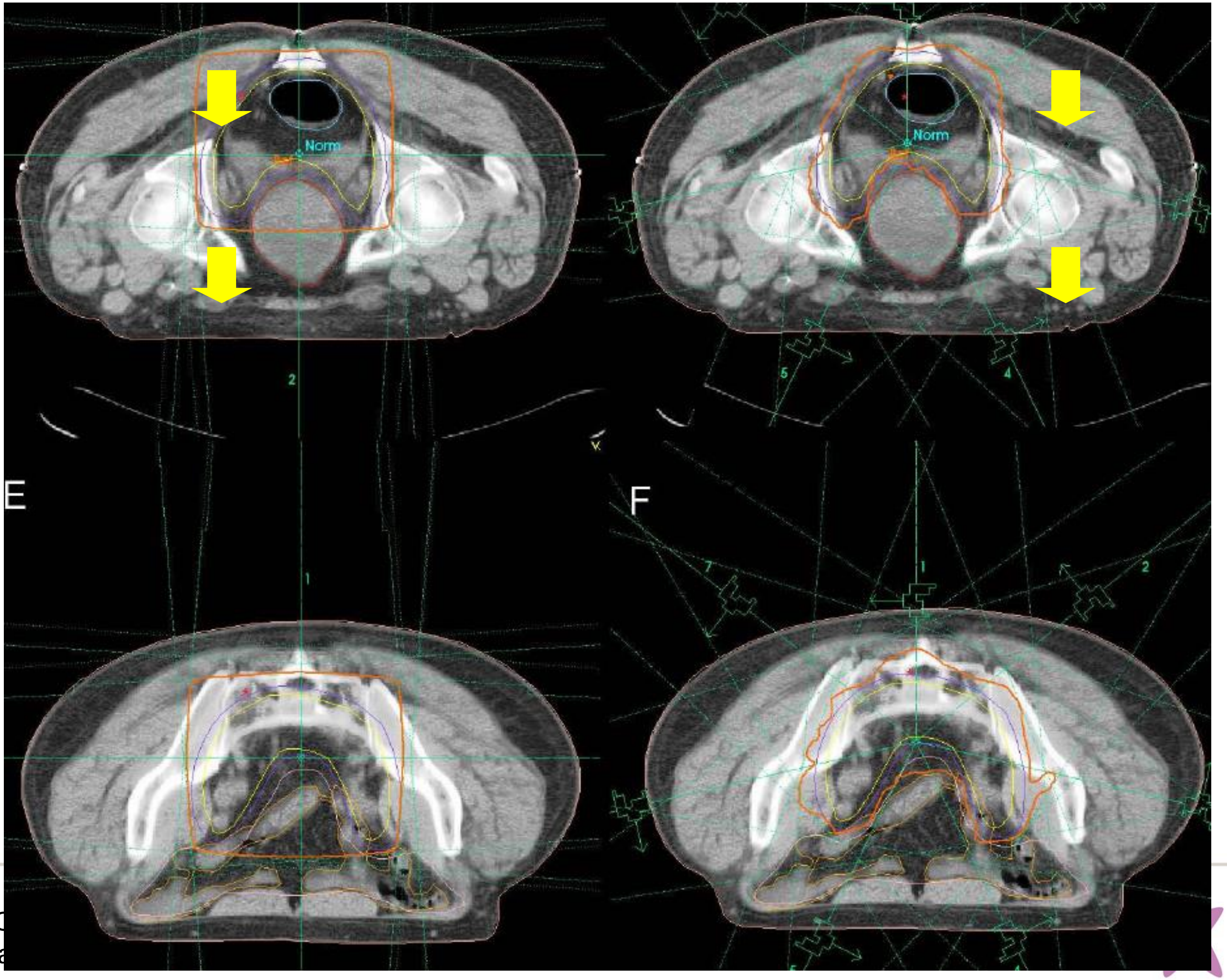
3D Conformal   IMRT



SCRT much cheaper!

Table A1. Radiotherapy Costs

Description	CPT Code	Global Cost	SCRT Quantity	CRT Quantity
Consult level 5	99205	$169.55	1	1
Simulation				
Complex simulation	77290	$493.09	1	1
Complex treatment device	77334	$445.05	3	3
Treatment Planning				
Treatment planning, complex	77263	$164.91	1	1
CT planning for treatment planning	77014 (TC)	$70.37	1	1
Special treatment procedure	77470	$153.30	1	1
Physics plan				
Basic dose calculation	77300	$61.84	1	1
Weekly physics	77336	$73.83	1	6
3D planning	77295	$477.04	1	1
Treatment/management				
Treatment mannagement	77427	$185.26	1	6
Treatment delivery, 3D	77414	$246.07	5	28
Sim CT/CT Prof	77014	$70.37	5*	6
Port films	77417	$10.32	1	6
X-ray image guidance	77421	$52.53	0	22
Total Cost			**$4,105.16**	**$12,379.31**

Based on CPT 2015 for Metropolitan St. Louis, MO region

*Daily CBCT during treatment

SCRT + Chemo Trial

Rationale:

- SCRT with delayed surgery can induce similar tumor response/downstaging to CRT
- Adding 'stronger' chemo to chemoradiation doesn't help (negative trials with incorporation of oxaliplatin)
- Move standard multi-drug chemotherapy from adjuvant to neoadjuvant setting
    - Treat micro-metastatic disease earlier
    - Compliance
    - Downstaging effect

SCRT + Chemo Trial

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Gastrointestinal Cancer

Five Fractions of Radiation Therapy Followed by 4 Cycles of FOLFOX Chemotherapy as Preoperative Treatment for Rectal Cancer

Robert J. Myerson, MD, PhD,* Benjamin Tan, MD,† Steven Hunt, MD,‡ Jeffrey Olsen, MD,* Elisa Birnbaum, MD,‡ James Fleshman, MD,‡ Feng Gao, MD,§ Lannis Hall, MD, MPH,* Ira Kodner, MD,‡ A. Craig Lockhart, MD, MHS,† Matthew Mutch, MD,‡ Michael Naughton, MD,† Joel Picus, MD,† Caron Rigden, MD,† Bashar Safar, MBBS, MRCS,‡ Steven Sorscher, MD,† Rama Suresh, MD,† Andrea Wang-Gillam, MD, PhD,† and Parag Parikh, MD*

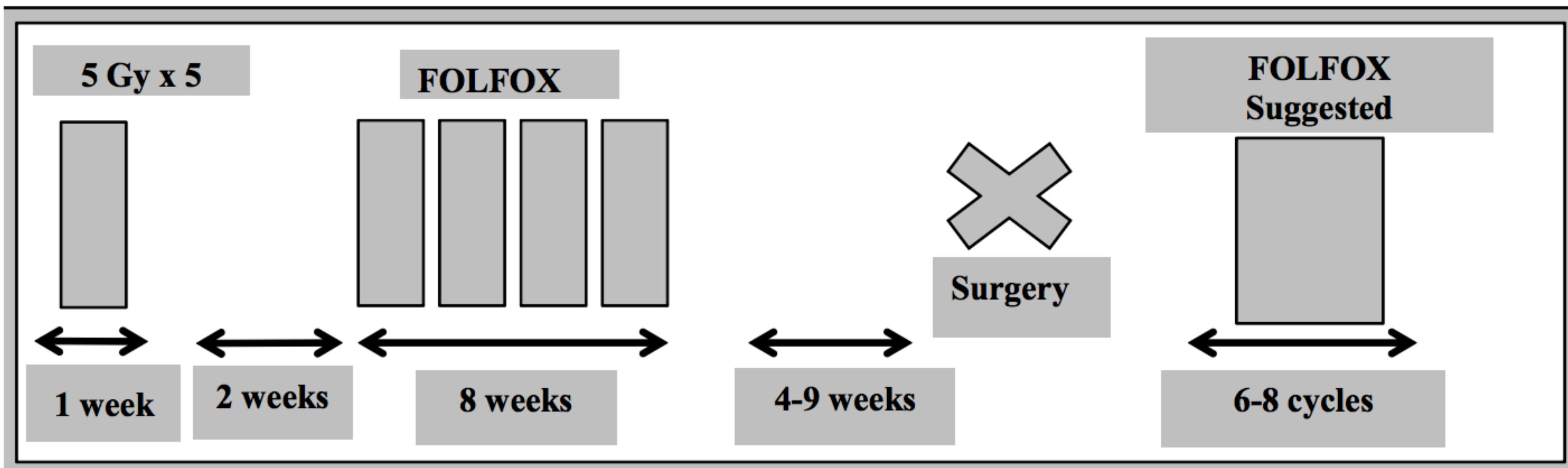
***Department of Radiation Oncology, †Division of Medical Oncology, ‡Section of Colorectal Surgery, and §Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri**

SCRT + Chemo Trial

Single arm, phase II trial (2009-2012)

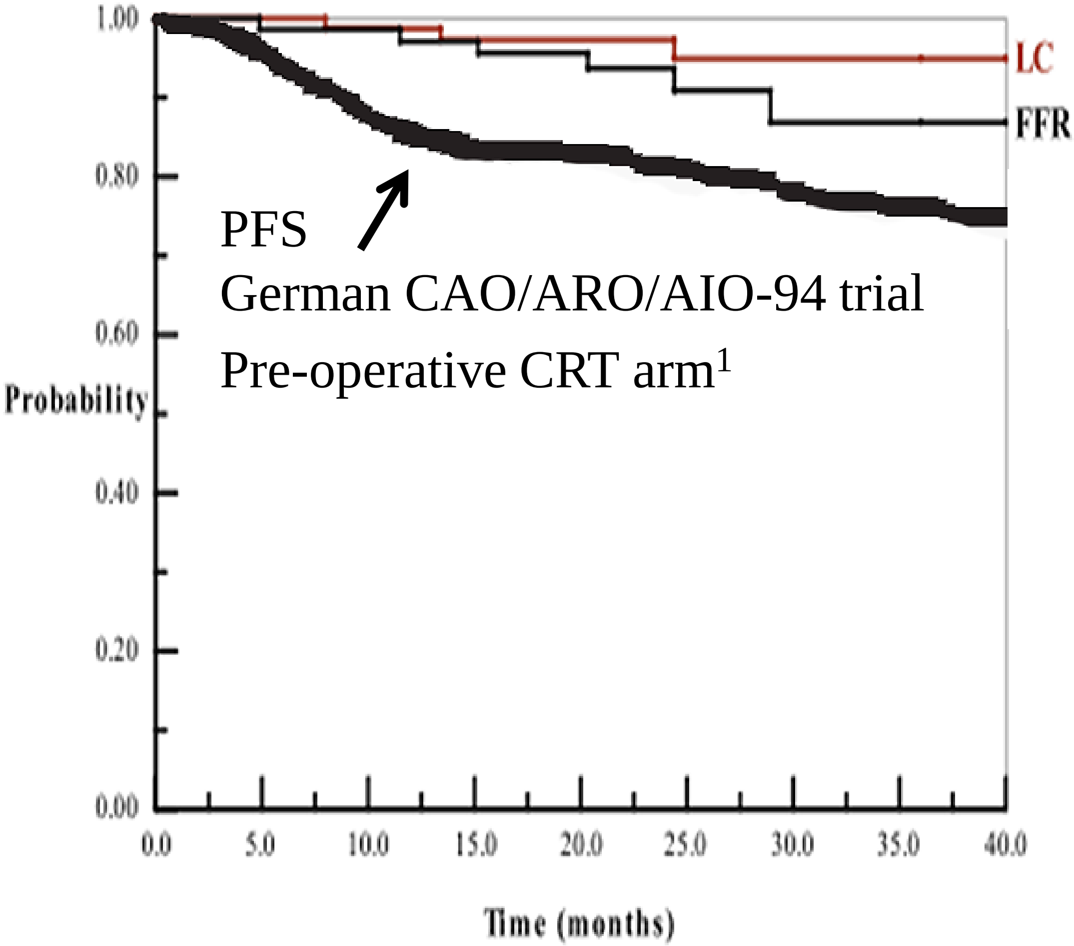
76 patients with cT3-4 and/or N+ (9 patients had cM1)

Regimen: Short course RT (5 x 5) + 4 cycles FOLFOX → delayed surgery +/- adjuvant chemo



Abbreviations: FOLFOX, folinic acid/leucovorin + 5-fluorouracil + oxaliplatin. For further details see Myerson et al (9)

Disease Status



PFS
German CAO/ARO/AIO-94 trial
Pre-operative CRT arm[1]

Local Control
- 1 year: 99%
- 2 year: 97%

)FS among cM0 patients
- 1 year: 97%
- 2 year: 94%

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SCRT + Chemo Trial

Toxicity

- Pre-operative: G3 GI 9%, G3 Heme 14%, G4 Heme 13%
- Late toxicity: 21 ≥ G3 events, 13 RT-related

75% had sphincter-preserving surgeries

4% R1 resections

25% ypCR

Conclusion: Well-tolerated with good treatment response, but need longer follow-up to assess disease outcomes

SCRT + Chemo vs. CRT: Randomized Data

original articles

Annals of Oncology

Annals of Oncology 27: 834–842, 2016
doi:10.1093/annonc/mdw062
Published online 15 February 2016

Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study

K. Bujko[1*], L. Wyrwicz[2], A. Rutkowski[2], M. Malinowska[3], L. Pietrzak[1], J. Kryński[2], W. Michalski[4], J. Olędzki[5], J. Kuśnierz[6], L. Zając[2], M. Bednarczyk[2], M. Szczepkowski[7,8], W. Tarnowski[9], E. Kosakowska[2], J. Zwoliński[2], M. Winiarek[2], K. Wiśniowska[1], M. Partycki[1], K. Bęczkowska[1], W. Polkowski[10], R. Styliński[11], R. Wierzbicki[12], P. Bury[13], M. Jankiewicz[10,14], K. Paprota[14], M. Lewicka[10], B. Ciseł[10], M. Skórzewska[10], J. Mielko[10], M. Bębenek[15], A. Maciejczyk[16], B. Kapturkiewicz[15], A. Dybko[17], Ł. Hajac[17], A. Wojnar[18], T. Leśniak[19], J. Zygulska[20], D. Jantner[19], E. Chudyba[20], W. Zegarski[21], M. Las-Jankowska[21], M. Jankowski[21], L. Kołodziejski[22], A. Radkowski[23], U. Żelazowska-Omiotek[23], B. Czeremszyńska[24], L. Kępka[24], J. Kolb-Sielecki[24], Z. Toczko[25], Z. Fedorowicz[25], A. Dziki[26], A. Danek[1], G. Nawrocki[27], R. Sopyło[27], W. Markiewicz[28], P. Kędzierawski[29] & J. Wydmański[30] for the Polish Colorectal Study Group

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SCRT + Chemo vs. CRT: Randomized Data

Polish, randomized phase III trial (2008-2014)

515 patients with fixed cT3 or cT4

Two Arms:

- SCRT (5 × 5 Gy) and 3 cycles of FOLFOX4 with delayed surgery
- CRT with 5-FU, LV, and oxaliplatin

Adjuvant chemotherapy not mandated, 39% received in both

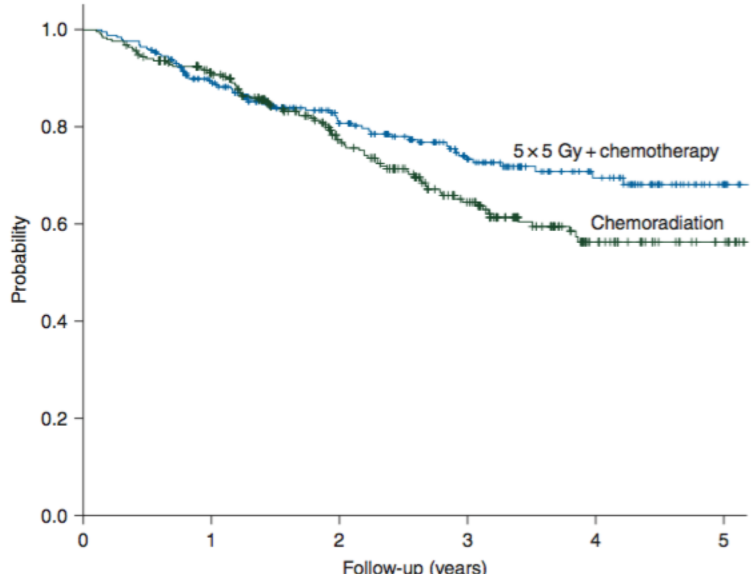
Primary endpoint: R0 resection rate

Similar compliance and tolerability for each arm

R0 resection rates 77% vs. 71% (NS) and pCR 16% versus 12% (NS)

Lower acute toxicity with SCRT, similar post-op and late complications

SCRT vs. CRT: Randomized Data

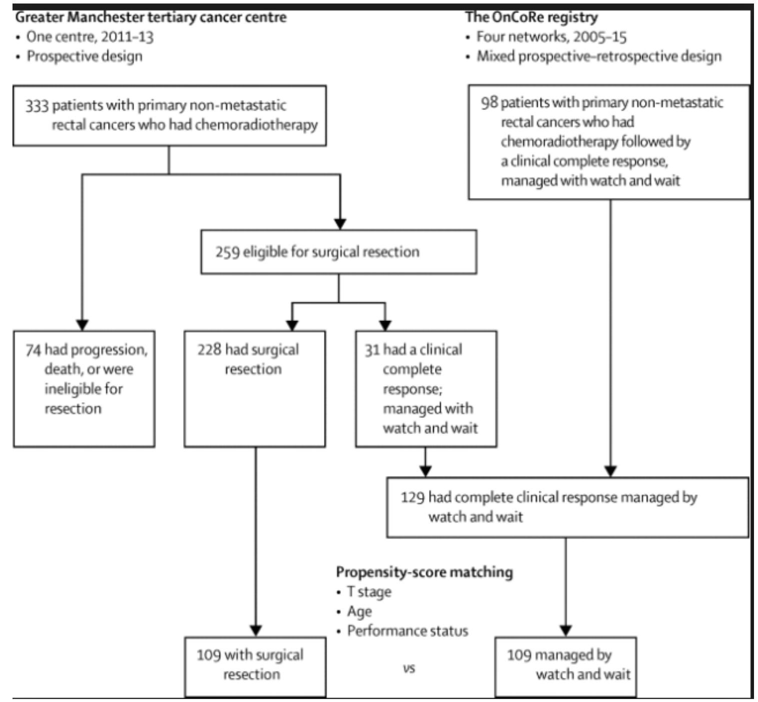


Number at risk	0	1	2	3	4	5
5 × 5 Gy + chemotherapy	261	218	154	103	56	21
Chemoradiation	254	217	148	93	46	23

Figure 2. Overall survival.

Radiation as part of organ preservation

- More and more interest in non-operative management
- Uses conventional doses of radiation and chemotherapy; and deferring surgery for patients with a complete clinical response
- Also leading to custom external beam and/or brachytherapy boosts for tumors
- This is where adaptive radiation may increase cure/toxicity

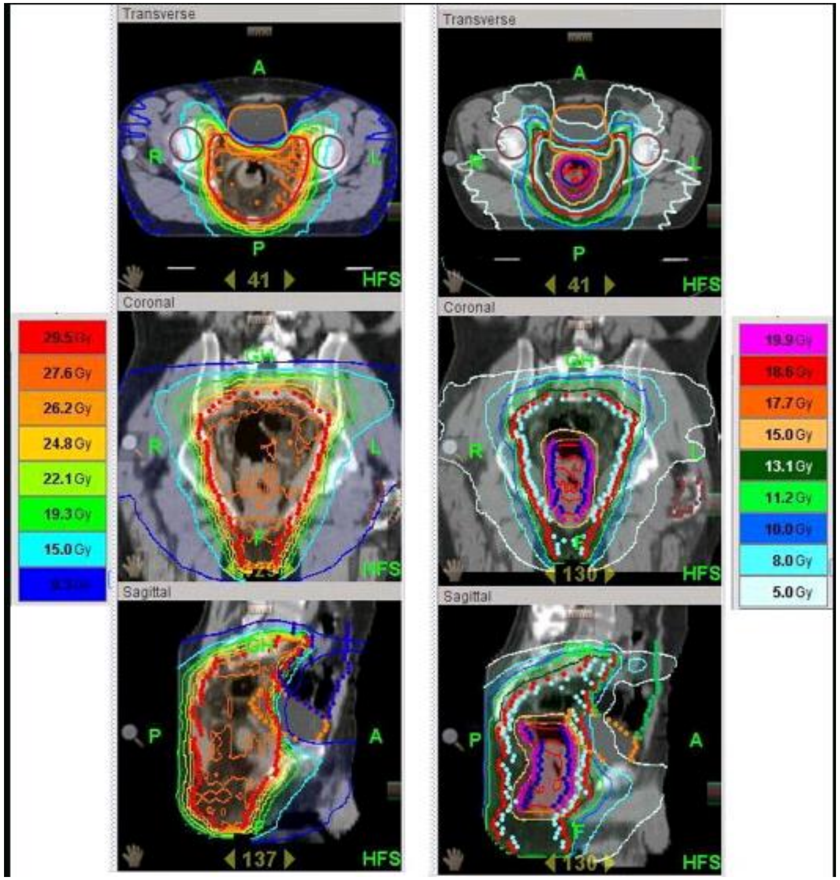


Renehan, Lancet Oncology, 2016

Van der Valk Van de Velde, 2017

Clinical Outcomes from adaptive rectal cancer RT?

- Not well developed
- Only 1 study from 2016 and prior (Passoni, IJROBP, 2013)
- Used a resimulation with CT and MRI to plan a concomitant boost at end
- Elective 41.4 Gy / 18 fractions
- Boost 45.6 Gy / 18 fractions (go from 2.3 Gy / fx to 3 Gy / fx for last six fractions)



Adaptive rectal cancer - outcomes

Table 1 Characteristics of patients

N	25
Sex (male/female)	15/10
Age (y), median (range)	59 (37-77)
PS 0 vs 1-2	15/9
T2N0	1*
T3N0	3
T3N1	9
T3N2	6
T4N0	3
T4N2	2
Anastomotic relapse	1
Distance from anus ≤ 6 cm	14
C-C length (cm), median (range)†	5 (1.2-11)
Site of T4 disease	
Anal canal structures	4
Vagina and cervix	1

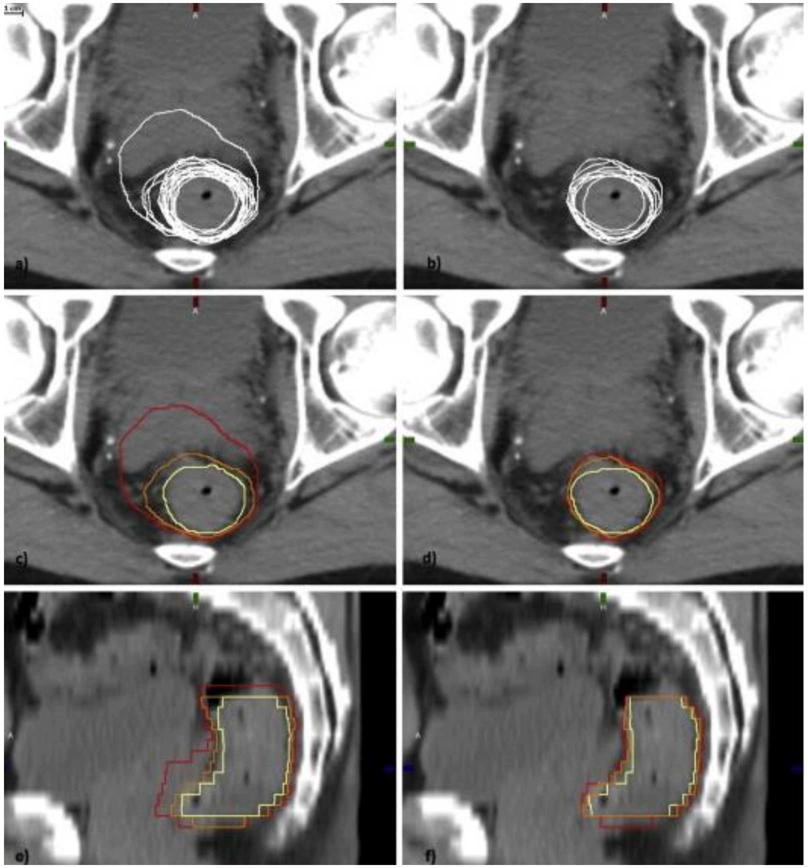
Abbreviation: PS = Eastern Cooperative Oncology Group Performance Status.
Values are number unless otherwise noted.
* A 37-year-old man with lesion in inferior third of rectum.
† Median cranium-caudal length of tumor.

Table 3 Surgical procedures and results

Resected	23/25*
Median end RT—surgery timing (wk)	11 (9-19)
Type of surgery	
Anterior resection	18
Anterior resection + hysterectomy	1
Intersphynteric resection	1
Abdominal—perineal resection	3
R0/R1 resections†	22/1
Evaluable patients for TRG	23/23
TRG 0	1 (4)
TRG 2	1 (4)
TRG 3	14 (61)
TRG 4 (pCR)	7 (30)
Residual vital cells in TRG3	
1%	3 (13)
2-5%	5 (22)
10%	4 (17)
20%	1 (4)
"Residual microfoci"	1 (4)

Abbreviations: RT = radiation therapy; pCR = pathologic complete response; TRG = tumor regression grade.
Values are number (percentage) or median (range).
* Two patients in clinical complete response refused surgery and were free of progression at 17.2 and 28.5 months, respectively.
† Circumferential margin.

Measuring daily motion of rectum



Rasso, Physica Medica, 2015

Introduction – Plan of the Day

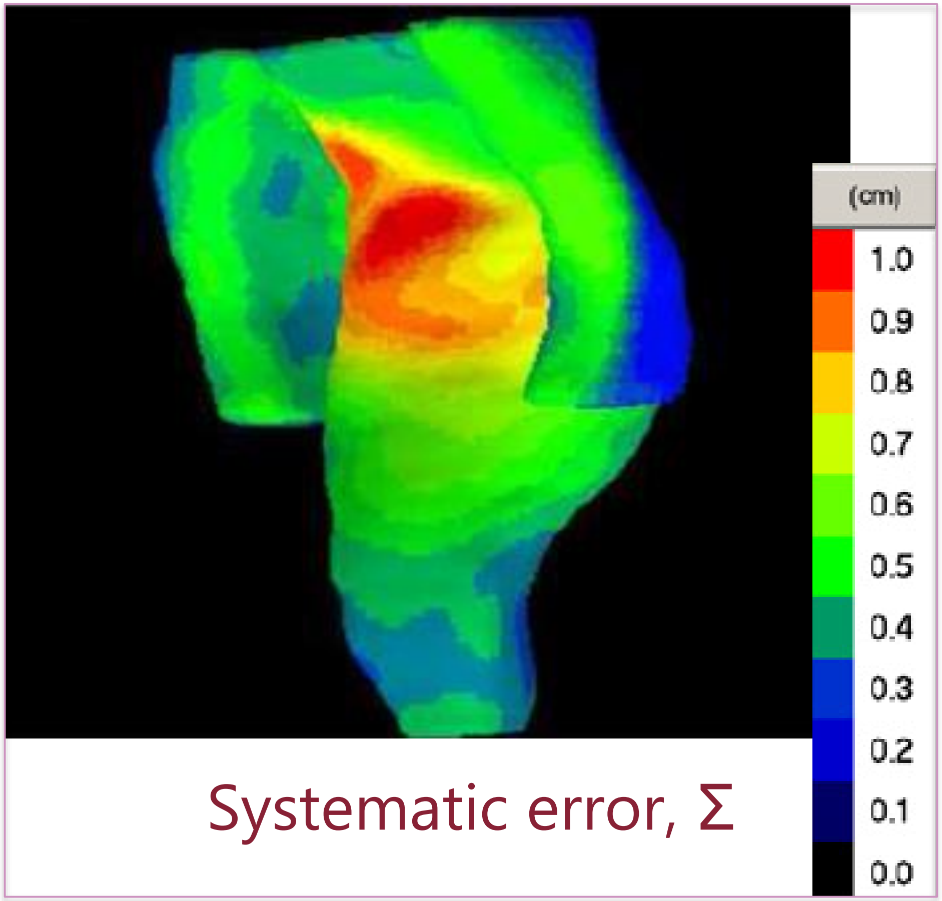
Largest uncertainty:

Upper-anterior side

No correlation with bladder but <u>rectum filling!</u>

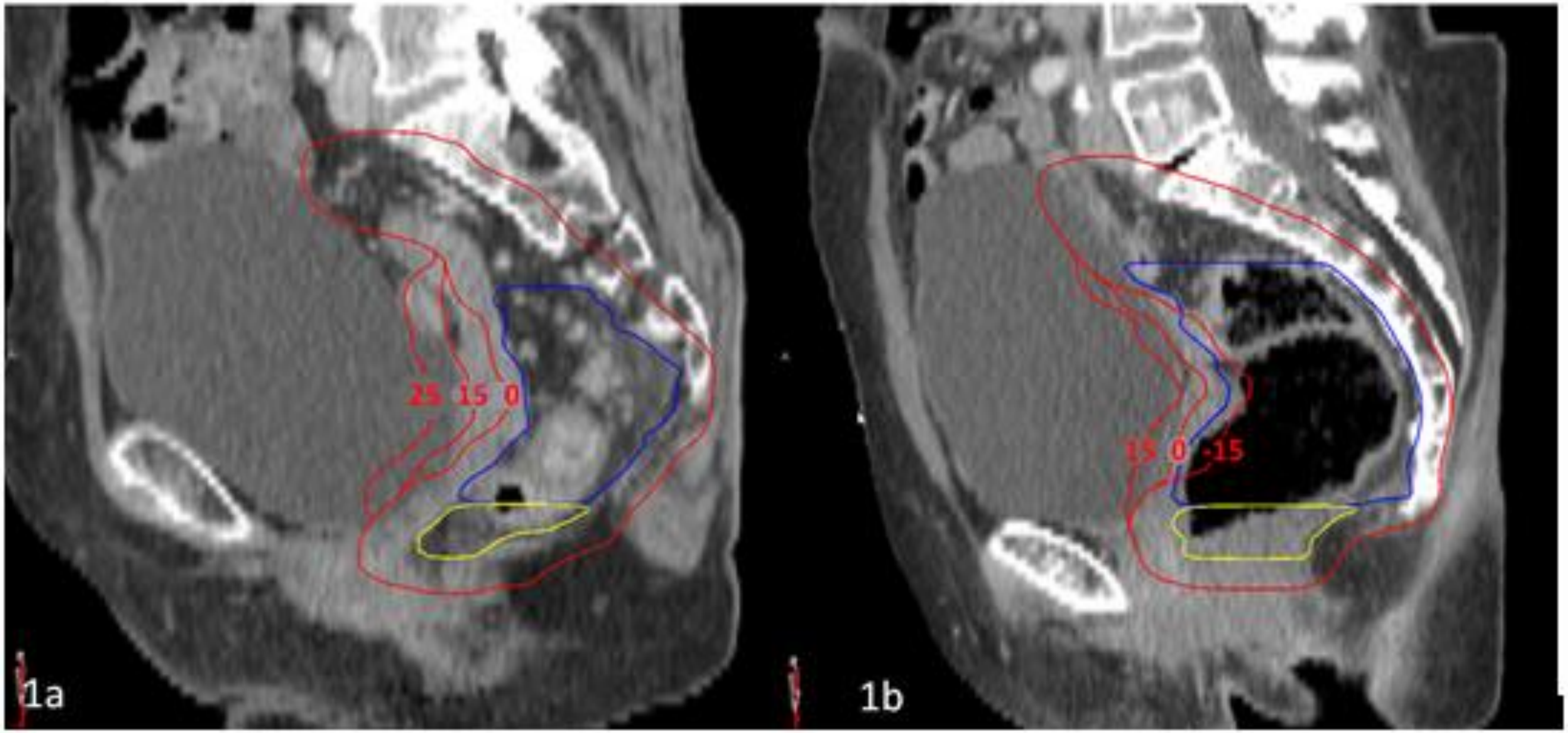
Choice & Number margins:

- Encompass largest uncertainty
- Feasible workload for treatment planning
- Complexity of selection at Linac



Systematic error, Σ

Slides courtesy of R de Jong



PTV Margins Upper Mesorectum

1 Planning CT scan with full bladder

A. Empty rectum on planning CT: *25 mm, 15 mm, 0 mm* anterior margins

B. Full rectum on planning CT: *15 mm, 0 mm, -15 mm* anterior margins

Introduction

- 2 sets of 3 margins
- Long (25x2Gy) and short (5x5Gy) treatment
- VMAT
- Daily CBCT
- 1/w post treatment CBCT: intra fraction motion
- 1/w retrospective review: all plan selections

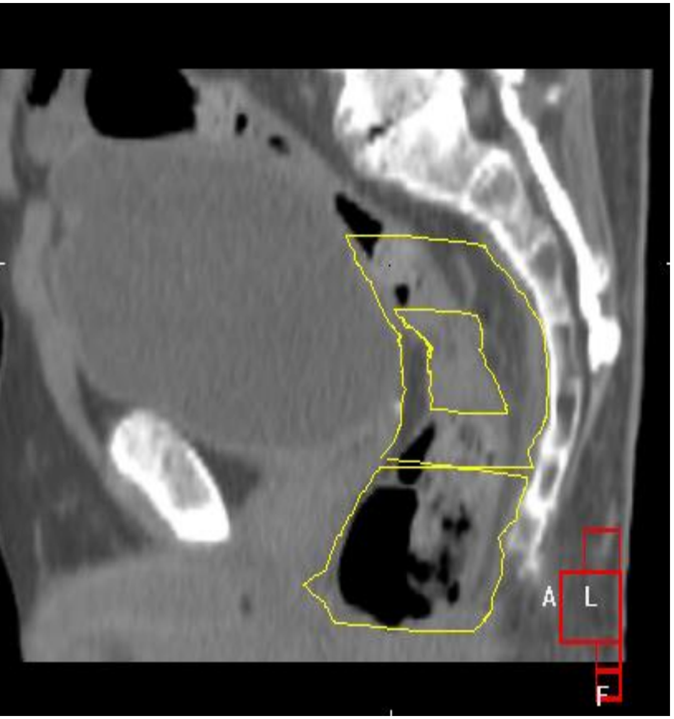
  consistency imaging- and management system

Introduction

Plan selection at the treatment machine:

First week: *1 trained* RTT and 1 physicist, 1 physician*

Second week: *2 RTTs (1 trained)*



Target volume
on Planning CT

Introduction

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First week: *1 trained* RTT and 1 physicist, 1 physician*

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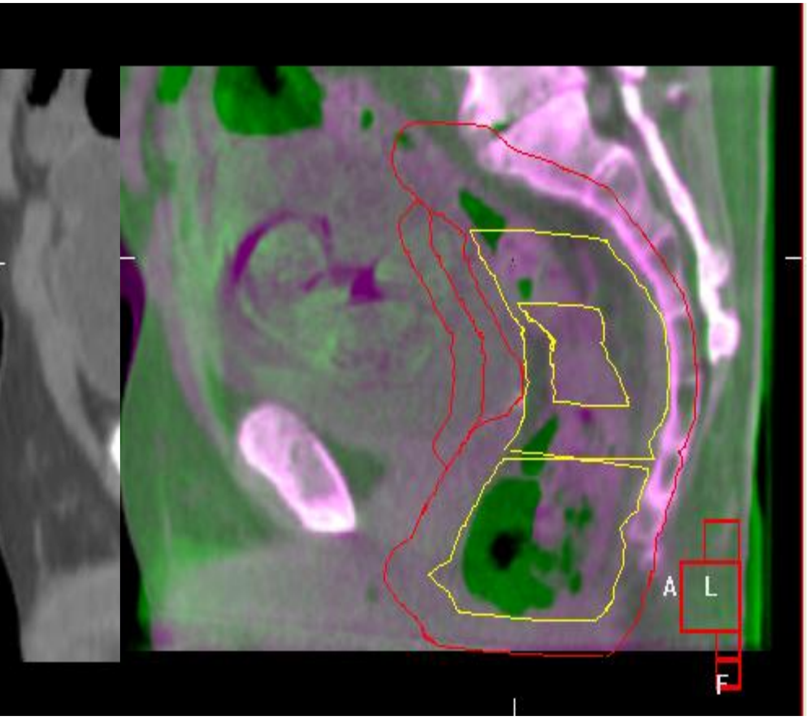


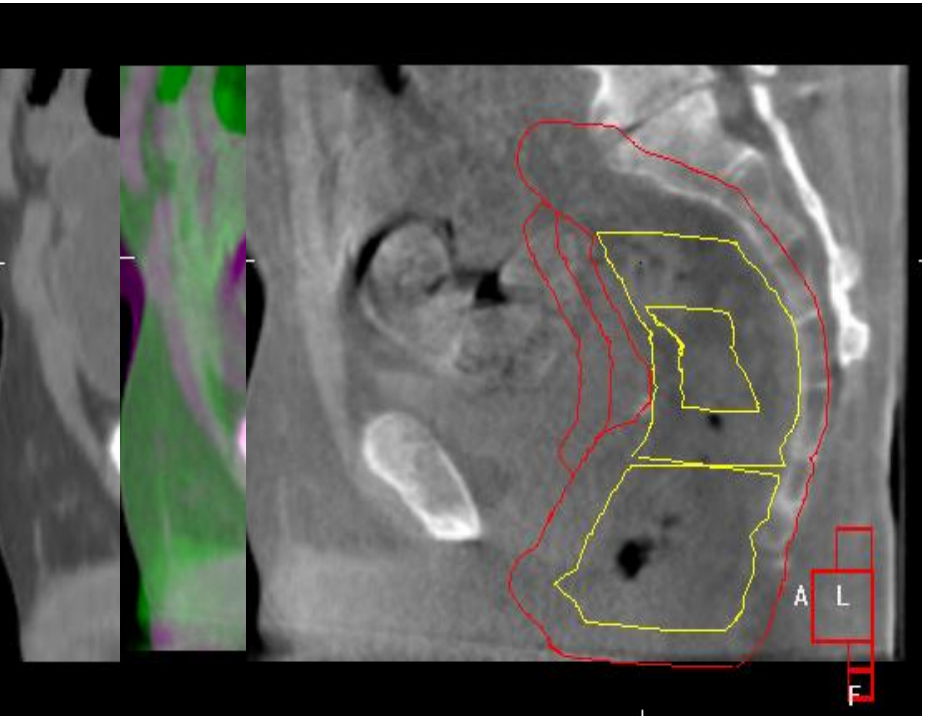
Bone match
Overlay CT/CBCT

Introduction

Plan selection at the treatment machine:

First week: *1 trained* RTT and 1 physicist, 1 physician*

Second week: *2 RTTs (1 trained)*



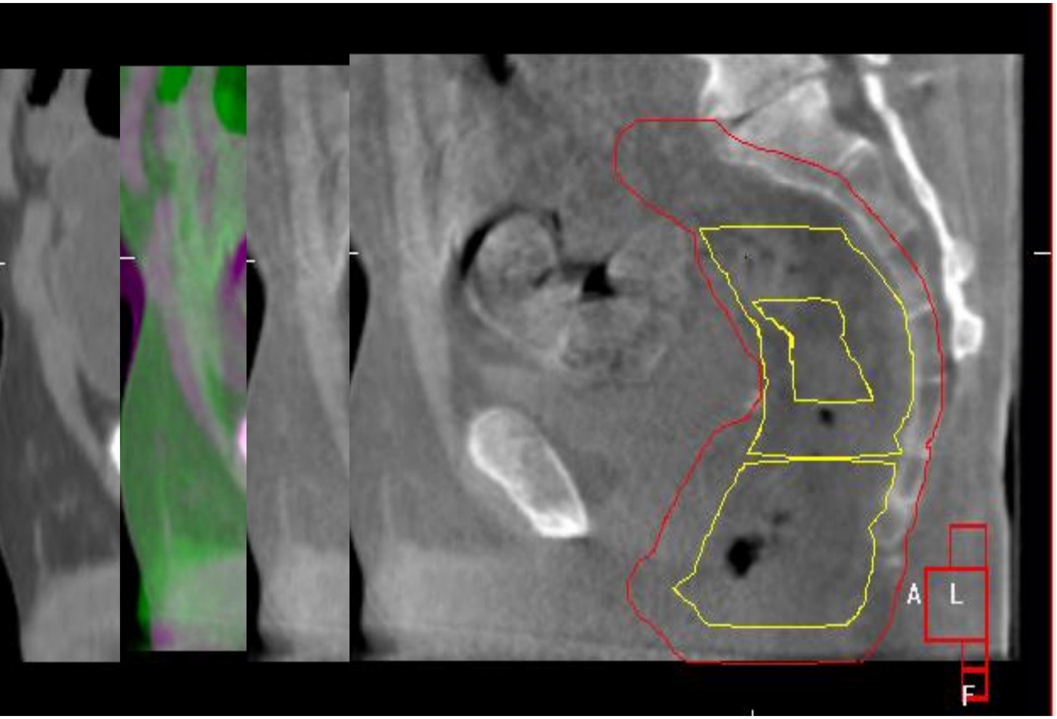
Target volume & margins on CBCT

Introduction

Plan selection at the treatment machine:

First week: *1 trained* RTT and 1 physicist, 1 physician*

Second week: *2 RTTs (1 trained)*



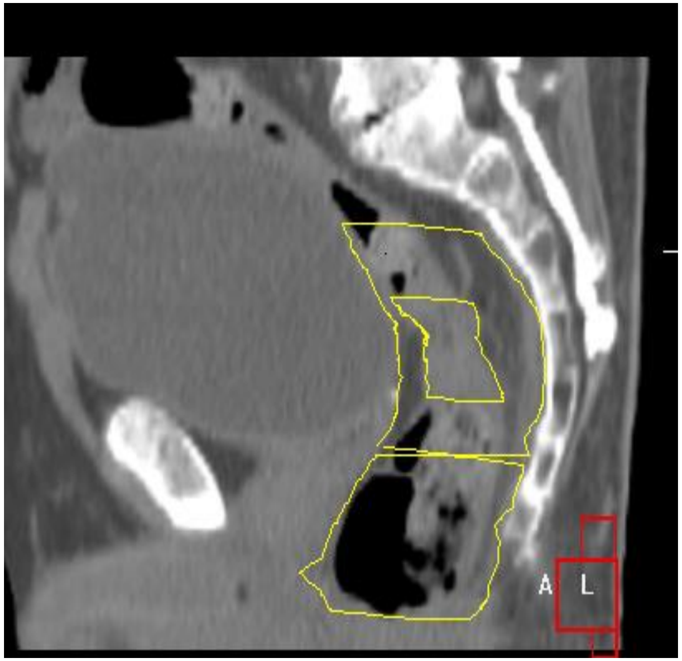
Selected margin
On CBCT

Introduction

Plan selection at the treatment machine:

First week: *1 trained* RTT and 1 physicist, 1 physician*

Second week: *2 RTTs (1 trained)*



Aim of study

Evaluate plan selection strategy for rectum with respect to available plans, selected plans, consistency and safety.

Methods & Materials

March 2016 – May 2017

70 patients treated with plan selection

*Evaluation of the **first 20** (consecutive) patients*

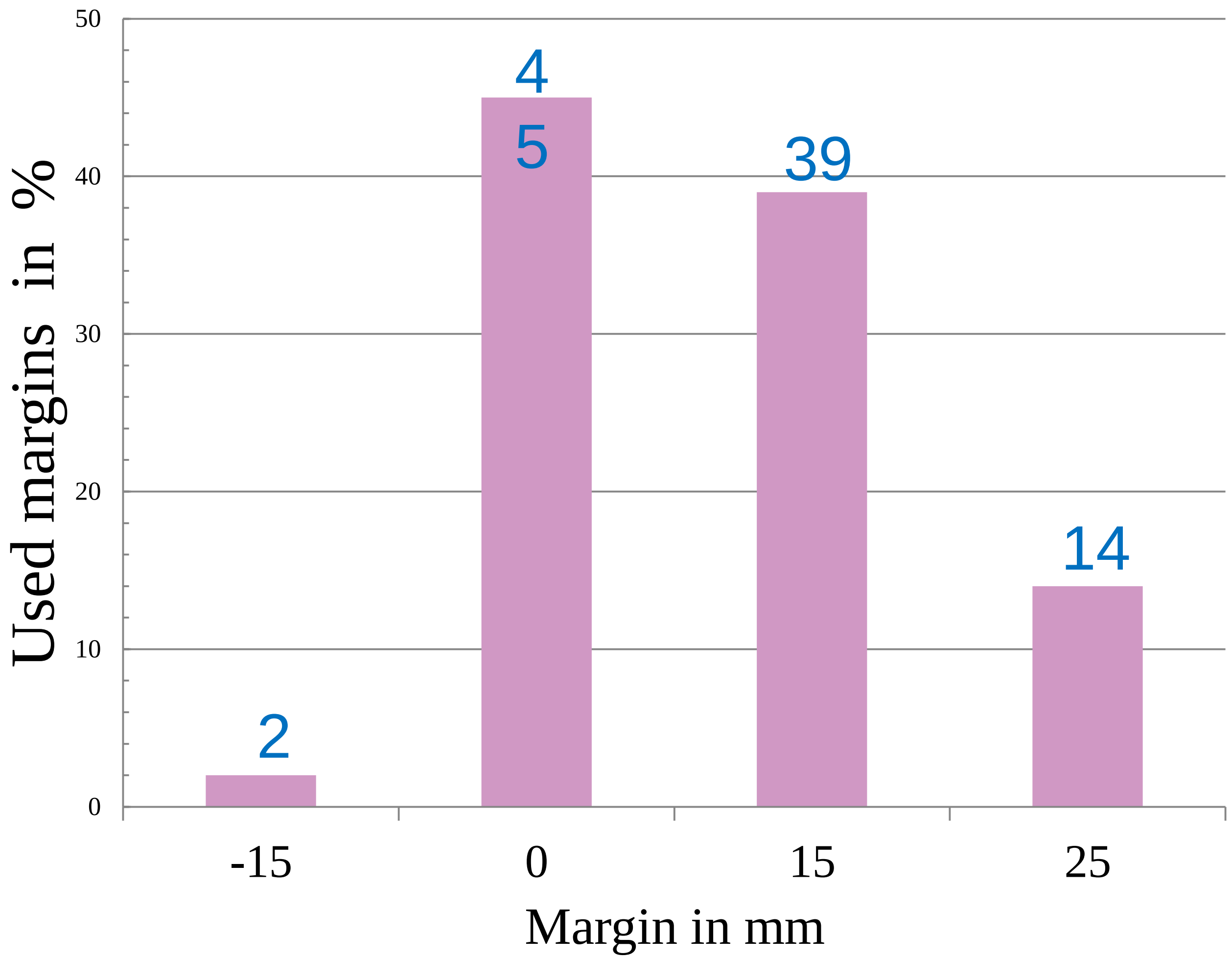
10x short treatment scheme (5x5Gy)

10x long treatment scheme (25x2Gy)

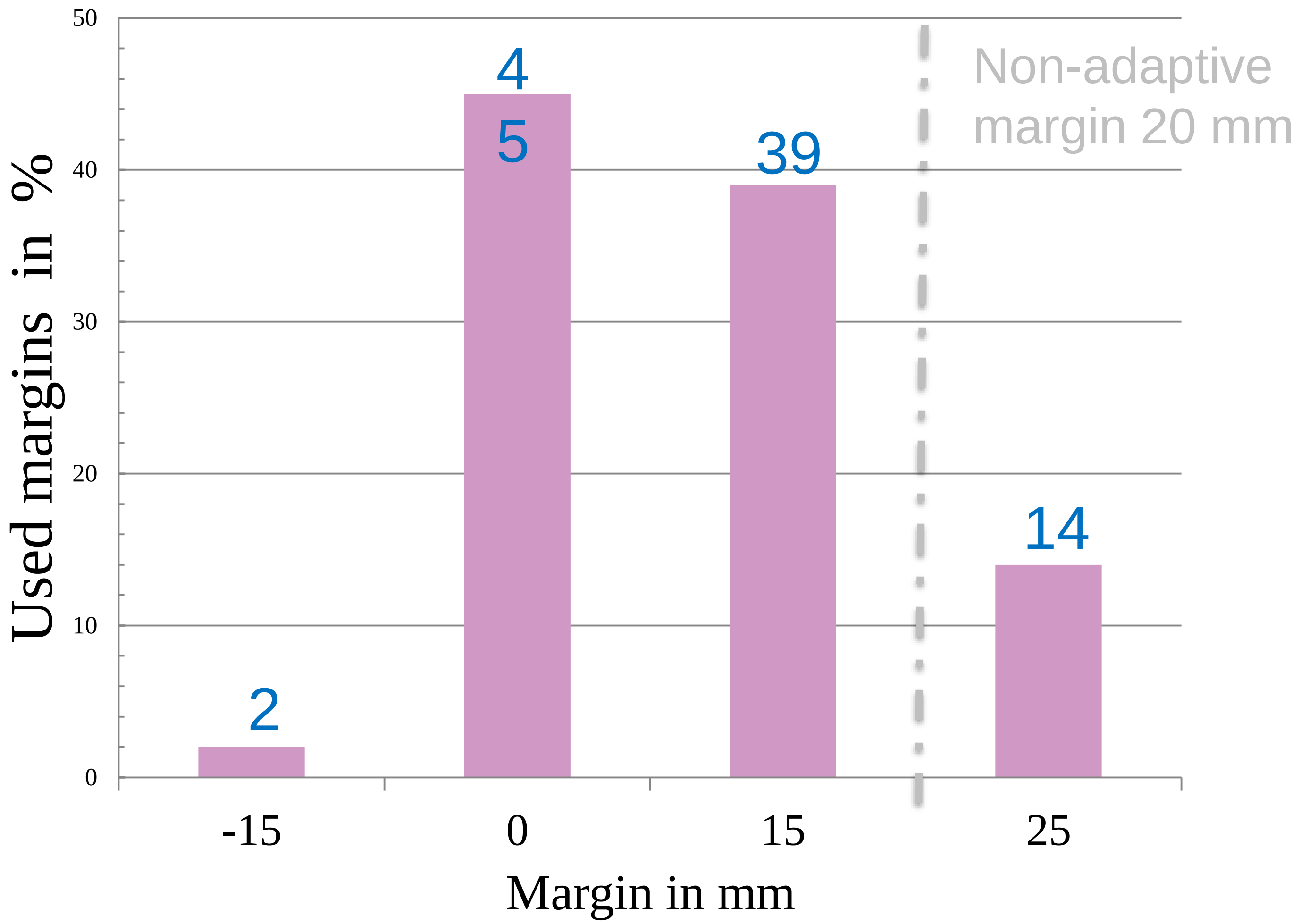
Margins sets used:

Full rectum	(+15 / 0 / -15mm)	30%	
Empty rectum	(+25/ +15 / 0 mm)	65%	
Full rectum	(+15 / 0 mm)	5%	(insufficient TP time)

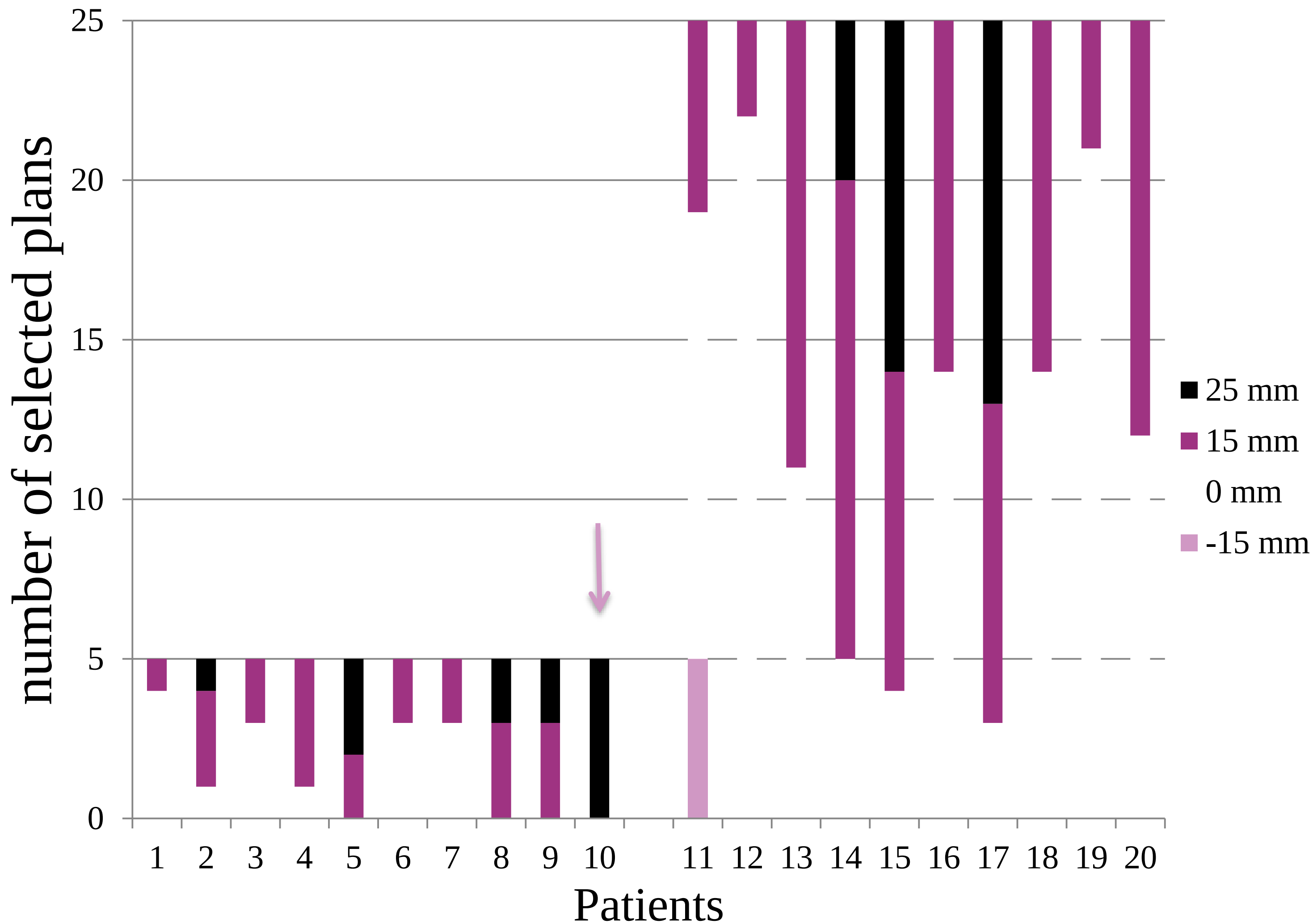
Results: Distribution of total selected plans



Results: Distribution of total selected plans



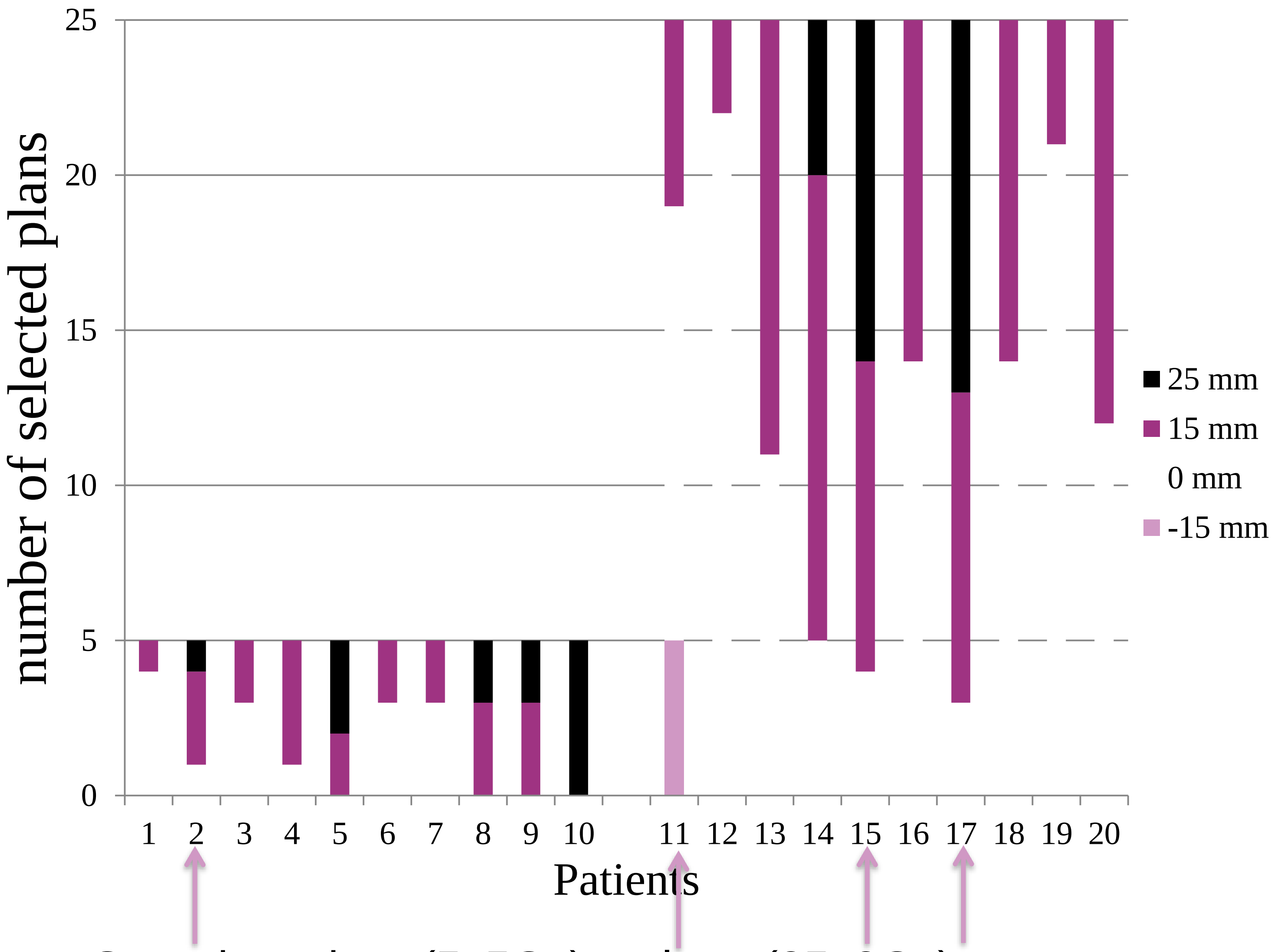
Results: Distribution of plans per patient



Sorted on short (5x5Gy) en long (25x2Gy) treatment scheme

Slides courtesy of R de Jong

Results: Distribution of plans per patient



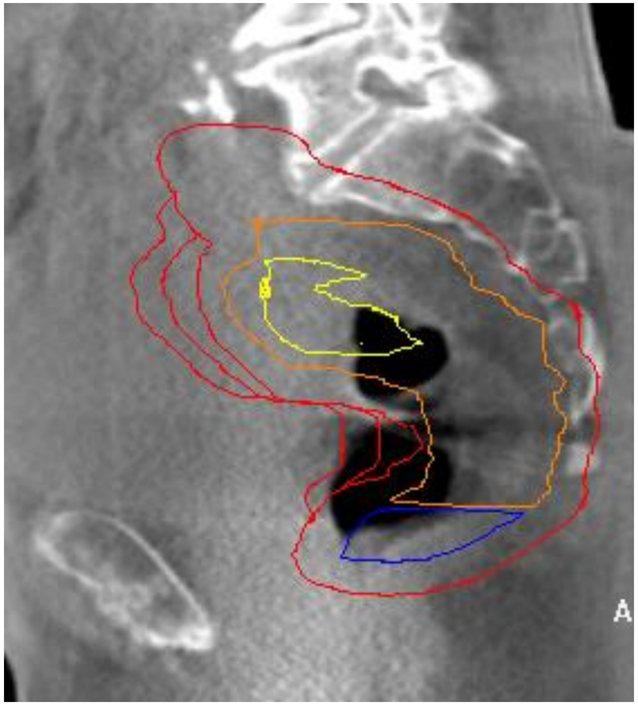
Sorted on short (5x5Gy) en long (25x2Gy) treatment scheme

Slides courtesy of R de Jong

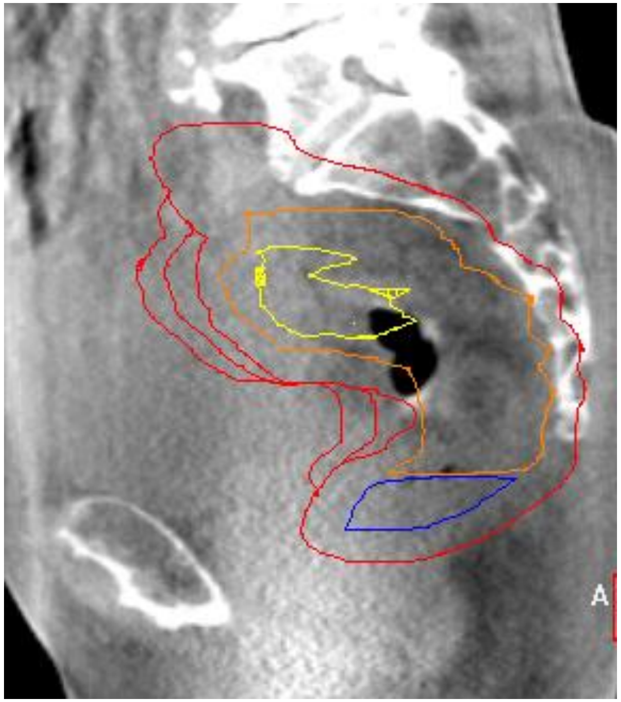
Results: Evaluation of plan selection

Delayed treatment: 7 x (5 x in 1 patient)

→ To obtain a more favorable anatomy in case of a very full rectum, usually caused by gas pockets



CBCT 1,
fraction 3



CBCT 2,
fraction 3

Slides courtesy of R de Jong

Results: Evaluation of plan selection

Delayed treatment: 7 x (5 x in 1 patient)

→ To obtain a more favorable anatomy in case of a very full rectum, usually caused by gas pockets

Post-treatment CBCT 1pw:

→ 1 fraction the selected plan was no longer suitable due to a moving gas pocket

Slides courtesy of R de Jong

Results: Evaluation of plan selection

Delayed treatment: 7 x (5 x in 1 patient)

→ To obtain a more favorable anatomy in case of a very full rectum, usually caused by gas pockets

Post-treatment CBCT 1pw:

→ 1 fraction the selected plan was no longer suitable due to a moving gas pocket

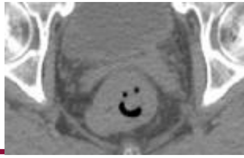
The weekly review:

→ Smaller margin could have been selected in 20% of fractions, and a larger margin in 2% of fractions

→ No inconsistencies between the imaging system and radiotherapy management system!

Slides courtesy of R de Jong

Conclusion



Plan selection for rectum cancer with variable margins for upper mesorectum for first 20 patients:

Both sets of margins used

Majority of patients needed multiple margins

Limited influence of intra fraction motion

Good consistency in weekly review

No errors between imaging and management system

Limited delay remains due to anatomy on CBCT

- Successfully and safely implemented! -

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Adaptive Bladder RT

Strategies and their potential impact

- Adaptive Bladder Protocols at RMH – Plan of the day concept
  (Robert Huddart, Shaista Haifeez et al.)

- Adaptive Bladder RT: The Aarhus approach –
  From plan selection to re-optimization
  (Anne Vestergaart et al.)

Adaptive Bladder Protocols at RMH

Plan of the Day Concept

Acknowledgements: Dr Robert Huddart, Shaista Hafeez

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Dr K Warren-Osseni
Mr AP Warrington
Dr M Partridge
Dr J Bedford
Dr V Khoo
Prof D Dearnaley
Prof A Horwich
Ms C Doolan

THE ROYAL MARSDEN

ICR The Institute of Cancer Research

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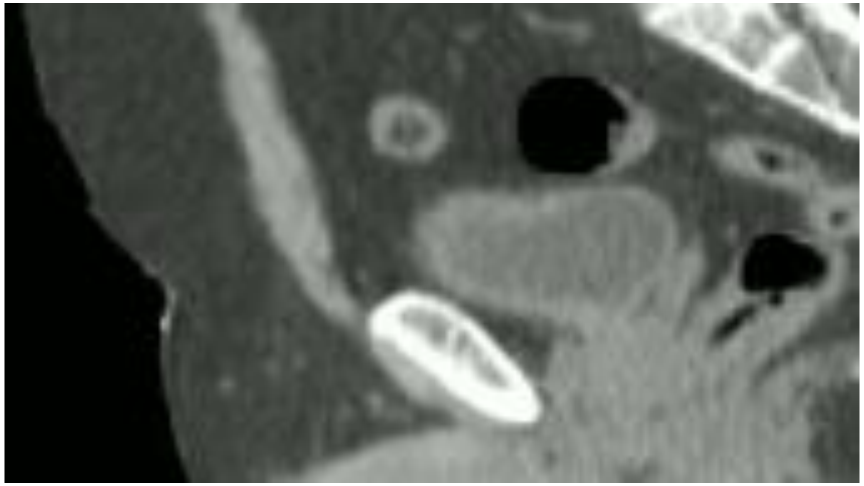
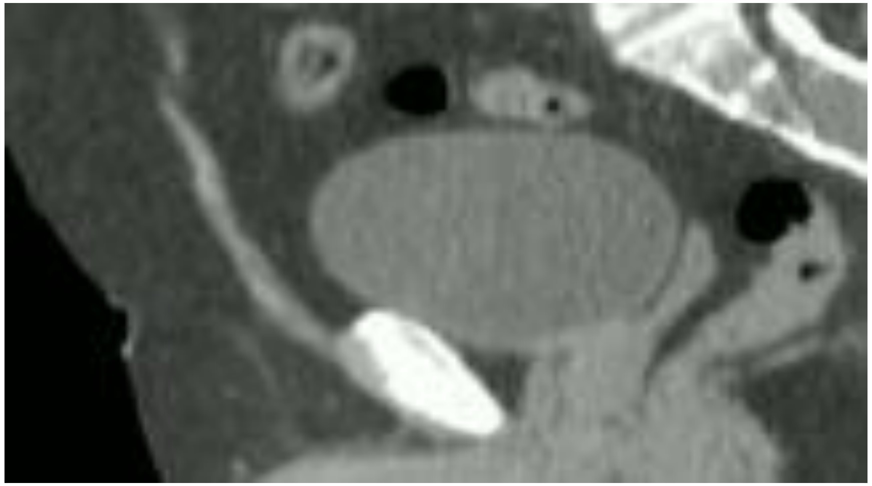
Adaptive bladder radiotherapy in clinical practice

THE ROYAL MARSDEN

Bladder radiotherapy challenges

- Highly deformable organ
- Mobile organ within the pelvis



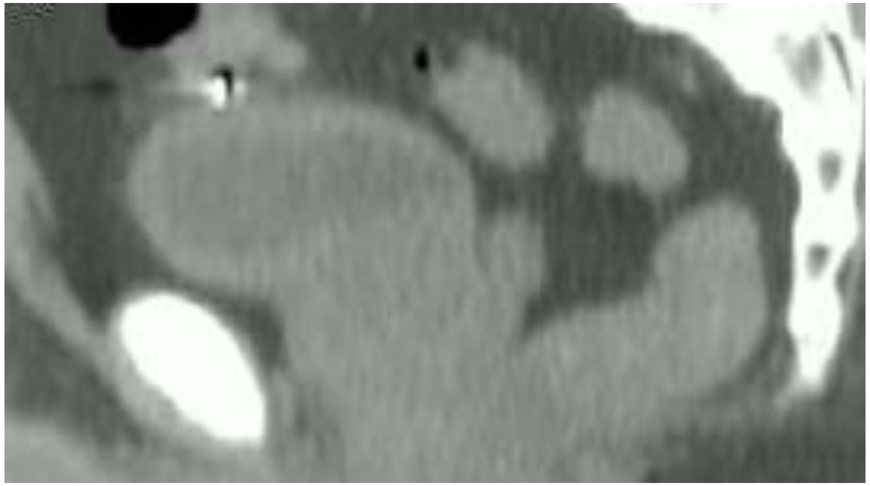


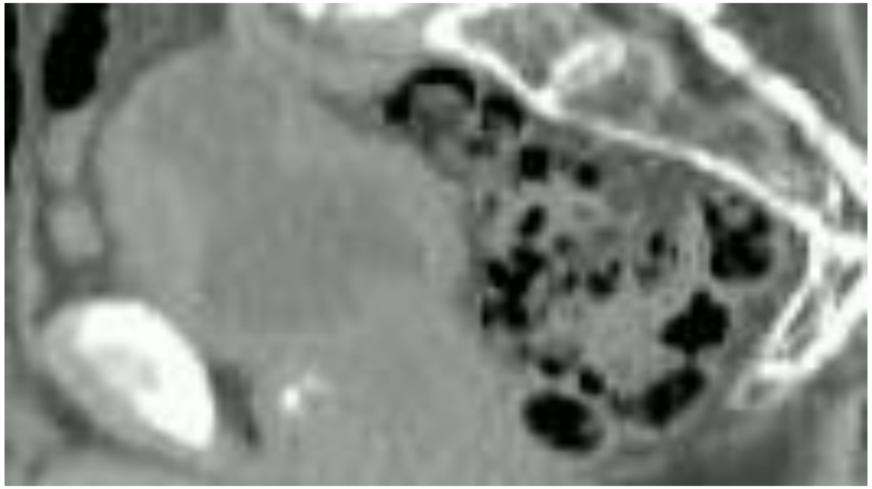
Presumed empty bladder on two different occasions

Bladder radiotherapy challenges

Highly deformable organ

Mobile organ within the pelvis





Influence of rectal filling

How big a problem is it?

- For a bladder tumour at dome
- Systematic errors ∑
  - translation 10 mm
  - Rotation/shape 3mm
- Random errors σ
  - Translation 10mm
  - Rotation/shape 3mm
- According to ‘margin recipe’
- [Van Herk equation 2.5 ∑ + 0.7 σ] = 4cm margin

Meijer NKI ESTRO 2010

ESTRO School

Established need for radiotherapy image guidance and adaptation

Retrospective analysis of 27 patients having daily CBCT

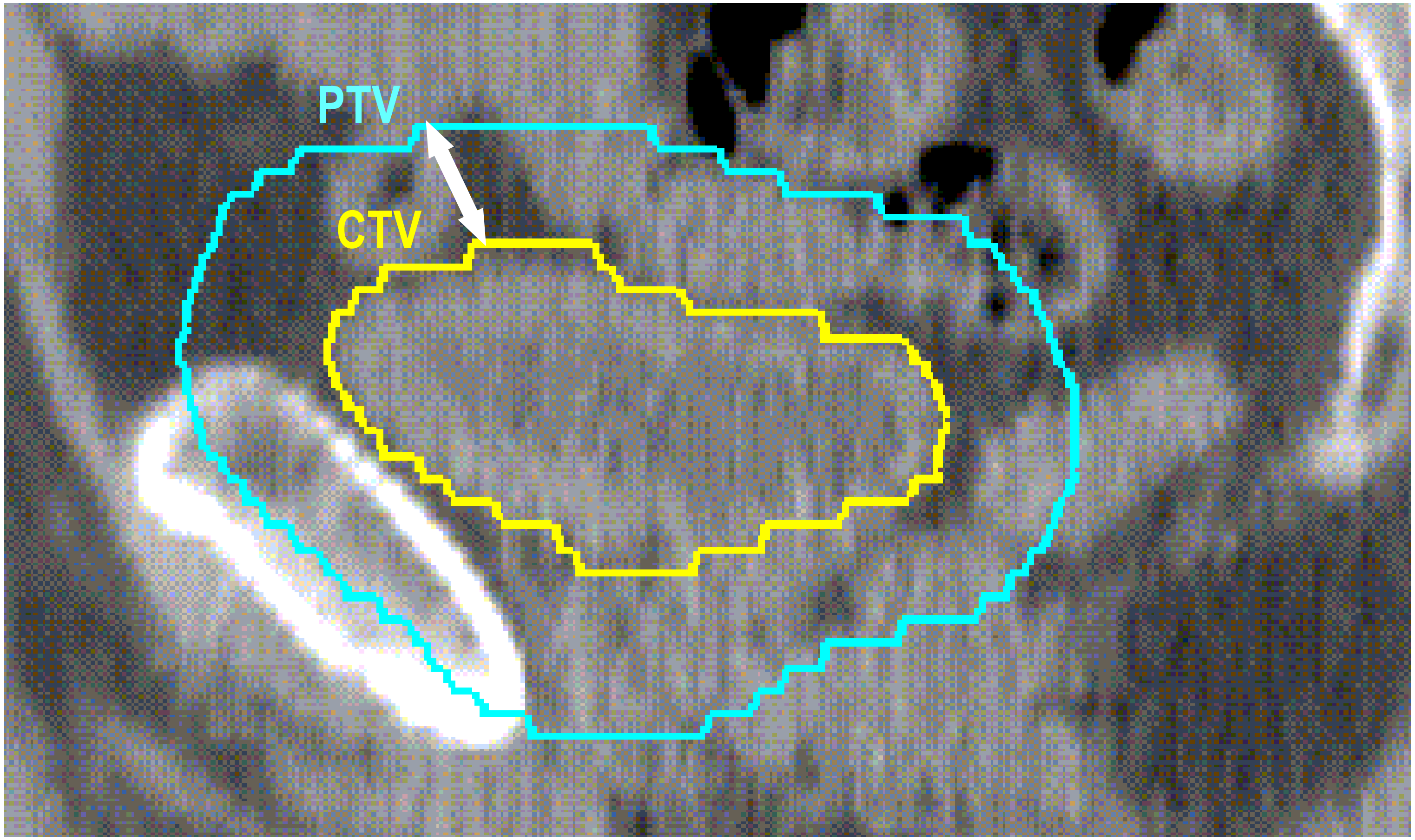
To determine CTV to PTV margin required to achieve coverage of bladder when using skin, bone or soft tissue matching

% of patients where expanded CTV covered 95% of wall displacements

	CTV+0.5	CTV+1.0	CTV+1.5	CTV+2.0	CTV+2.5
Skin	0	19	56	93	96
Bone	0	41	63	89	96
Soft tissue	52	89	96	100	100

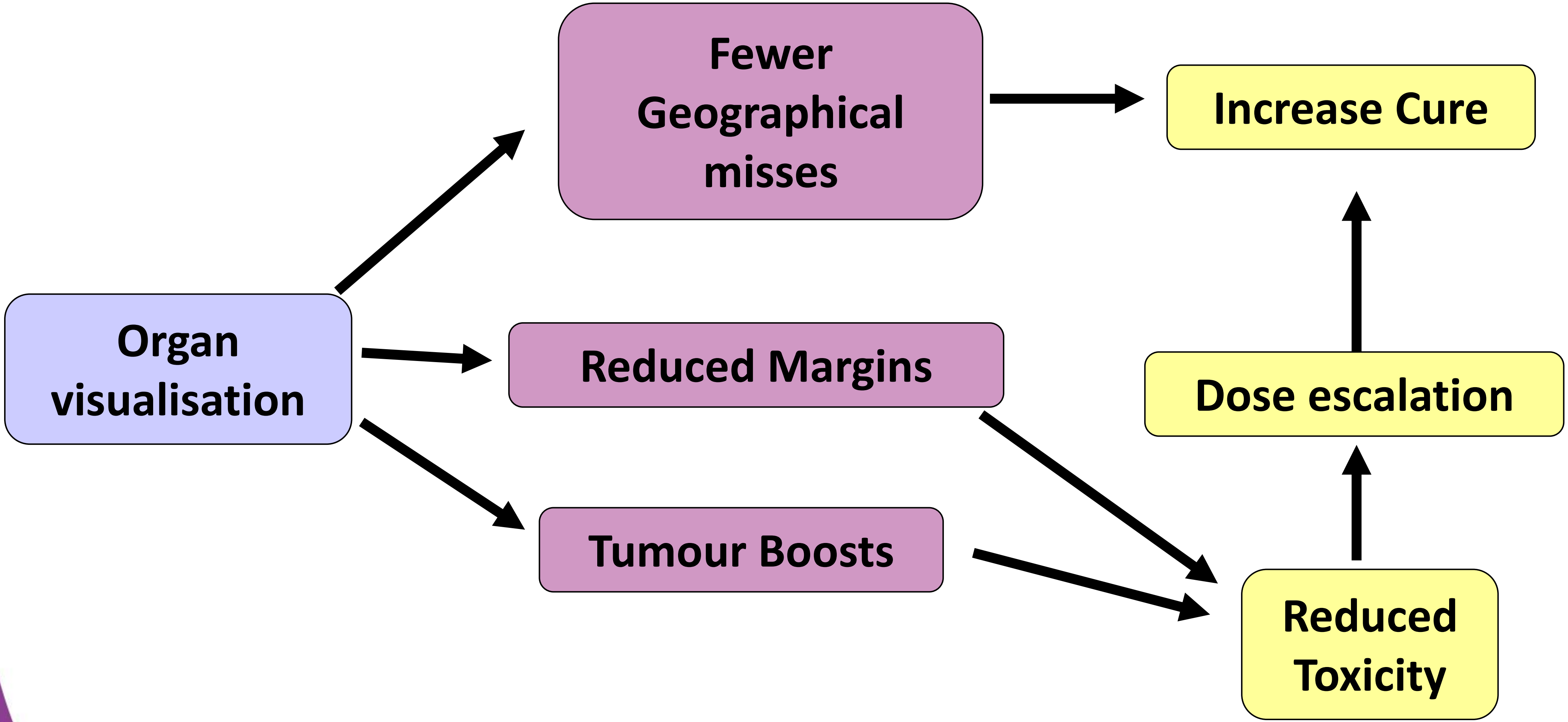
Foroudi et al. Bladder cancer radiotherapy margins: a comparison of daily alignment using skin, bone or soft tissue 2012 Clin Oncol 24 673-681

Conventional population margin



Isotropic margin (1.5–2 cm)

Possible benefits of Image Guided RT:



Potential IGRT solutions

- Ultrasound -Volume limitation
- [Mangar et al 2008 Mcbain et al 2009]

- Fiducial markers
  - Gold seeds [Mangar et al 2006]
  - Lipiodal [Pos et al 2009]

- Cone beam CT etc

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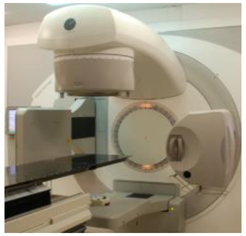
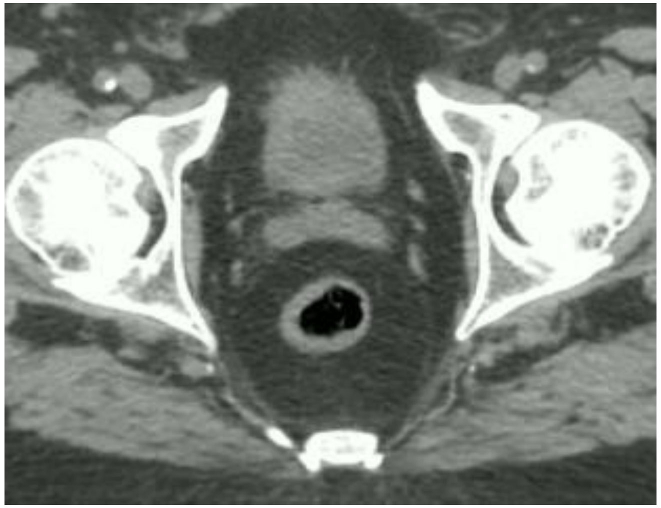
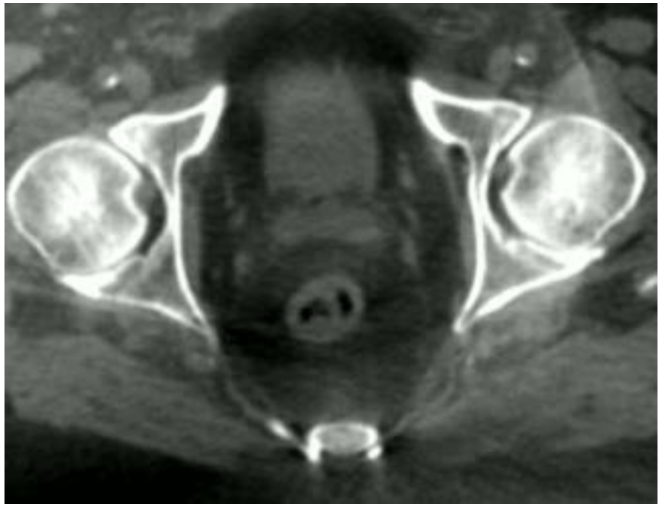


Cone beam CT image quality

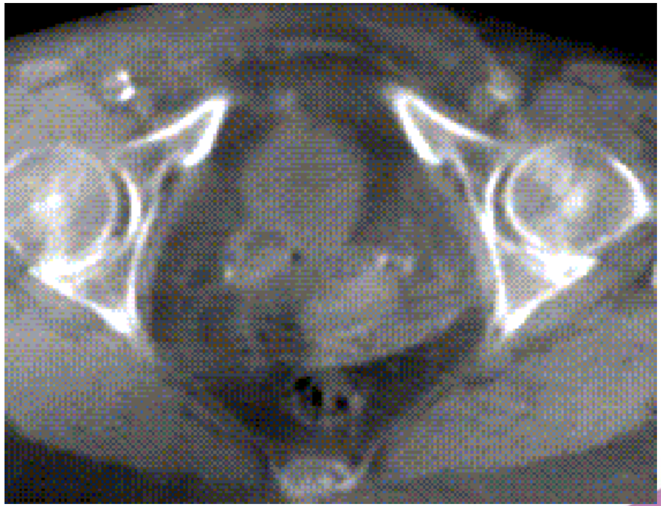
A





Planning CT **Cone beam CT**

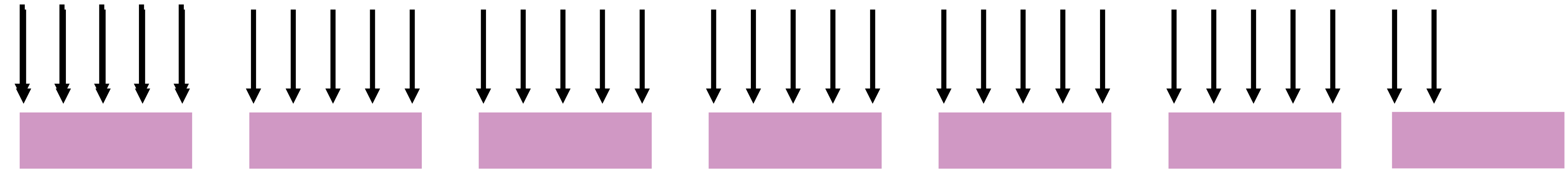
B



How can we use this information to change (adapt) treatment?

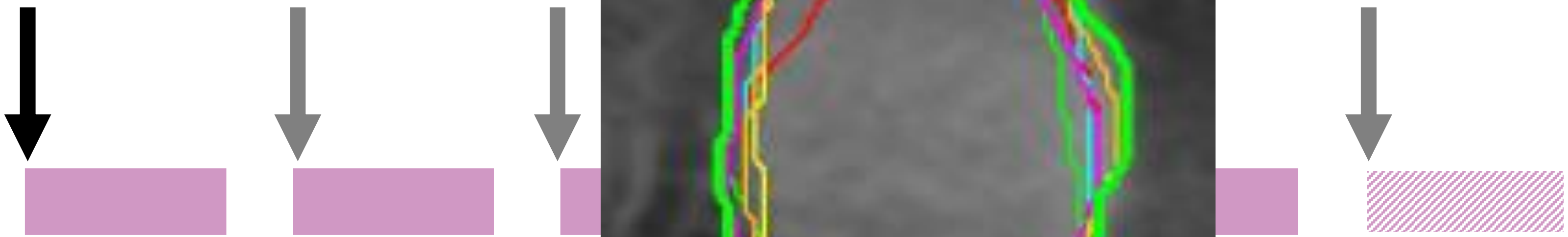
Bladder radiotherapy schedule

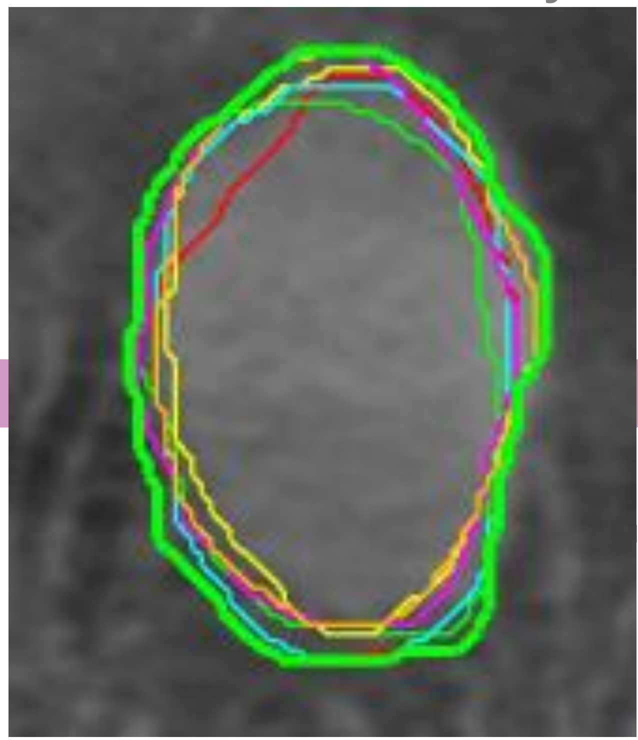
Conventional



64Gy 2Gy/# daily over 6.5 weeks

Hypofractionated

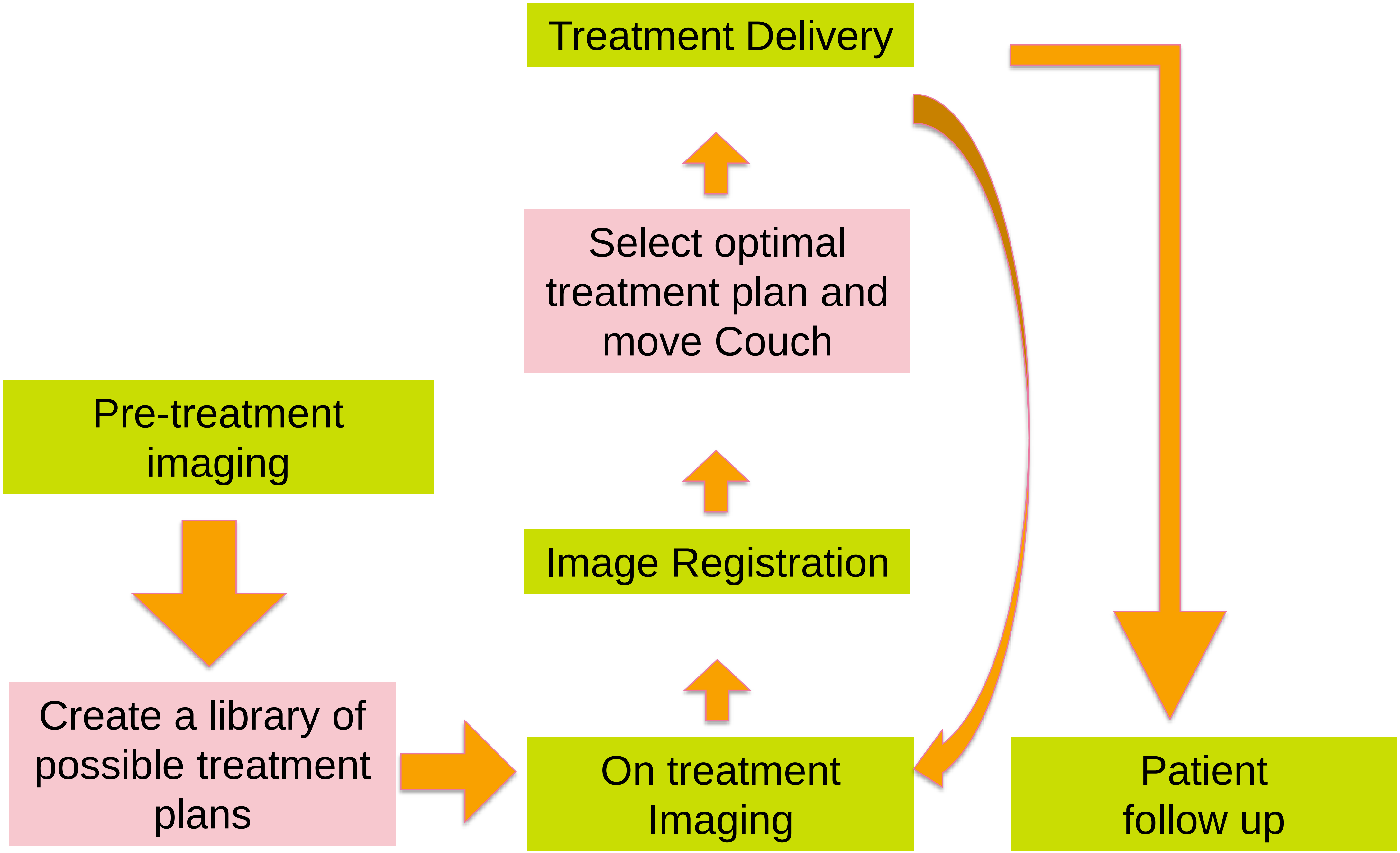




y/# weekly over 5-6 weeks

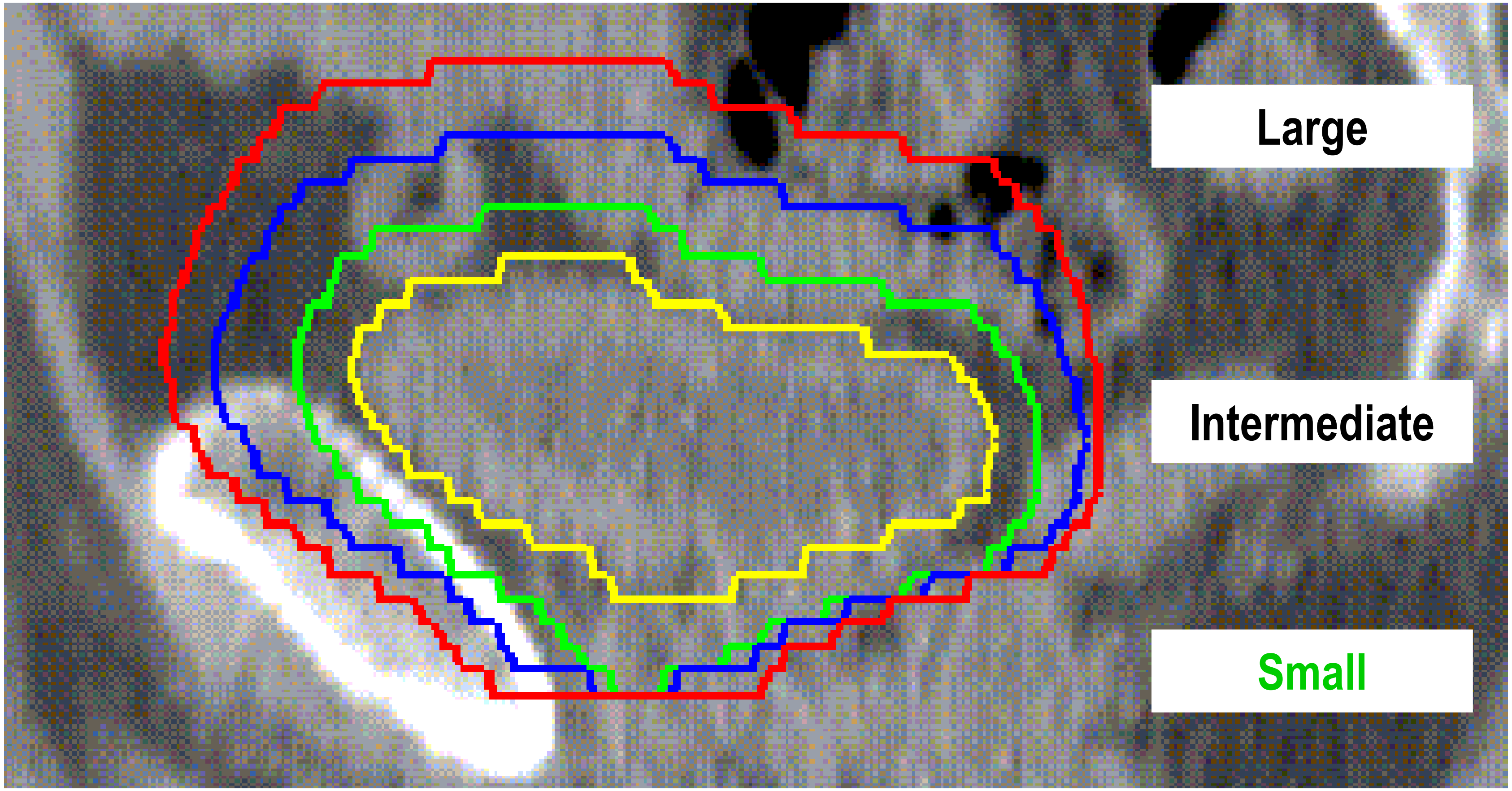
Jose et al Clin Oncol 1999

Plan of the day ART workflow



APPLY study

Adaptive-predictive organ localisation

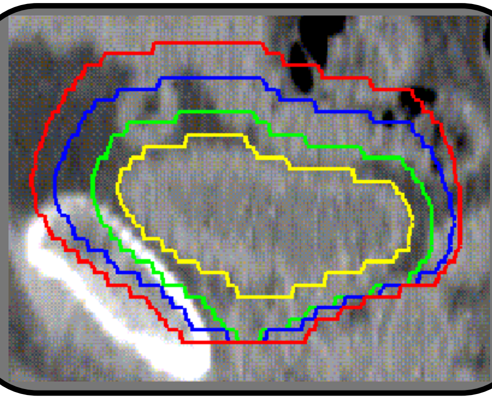


Large or small volume 78% fractions

Lalondrelle et al IJORBP 2010

Treatment planning

Planning
CT0 and CT30
post-void



Individualised
library of plans

Planning target volume margins

CTV → PTV (cm)	Small PTV	Intermediate PTV	Large PTV Based on CT30	Large PTV Based on CT0
Anterior	0.5	1.5	1.5	2.0
Posterior	0.5	1.0	1.0	1.2
Lateral	0.5	0.5	0.5	0.75
Superior	0.5	1.5	1.5	2.5
Inferior	0.5	0.5	0.5	0.75

ESTRO School

Planning target volume margins

CTV → PTV (cm)	Small PTV	Intermediate PTV	Large PTV Based on CT30	Large PTV Based on CT0
Anterior	0.5	1.5	1.5	2.0
Posterior	0.5	1.0	1.0	1.2
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Superior	0.5	1.5	1.5	2.5
Inferior	0.5	0.5	0.5	0.75

ESTRO School

Planning target volume margins

CTV → PTV (cm)	Small PTV	Intermediate PTV	Large PTV	
			Based on CT30	Based on CT0
Anterior	0.5	1.5	1.5	2.0
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Planning target volume margins

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Superior	0.5	1.5	1.5	2.5
Inferior	0.5	0.5	0.5	0.75

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Clinical example: Bladder

Plan library

PTV small

PTV medium

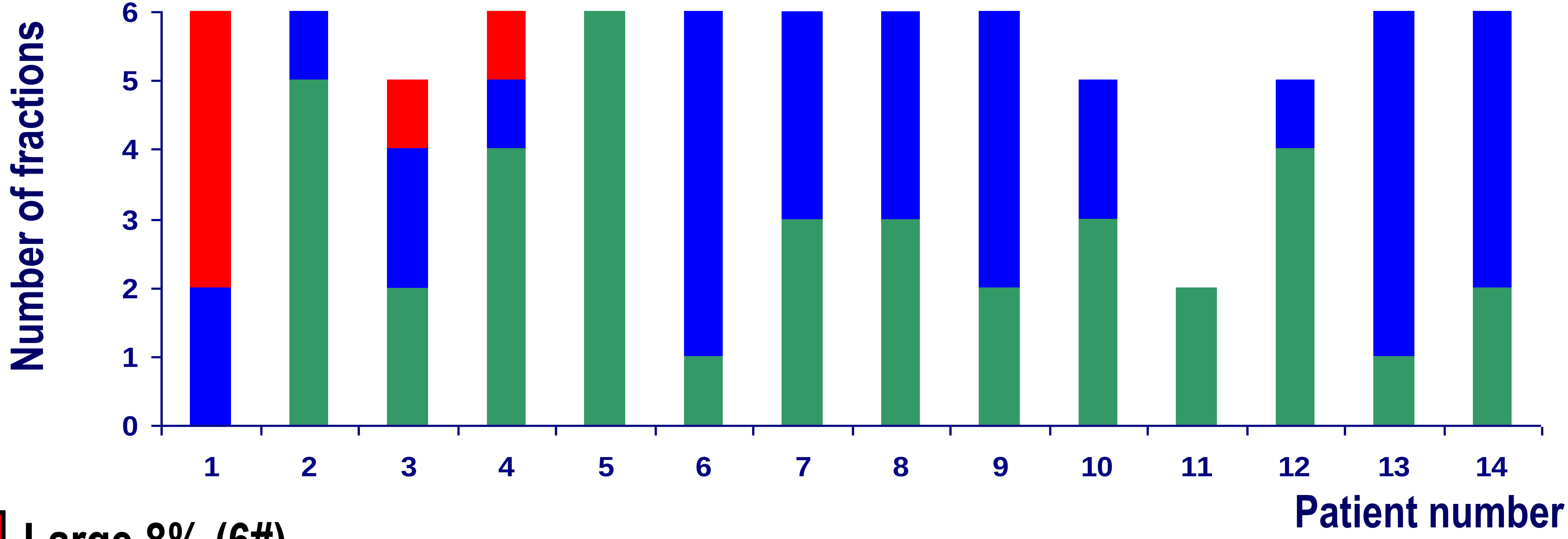
PTV large

Courtesy of Shaista Hafeez

ESTRO School

On-line volume

Large or small volume selected 57% (44/77#)

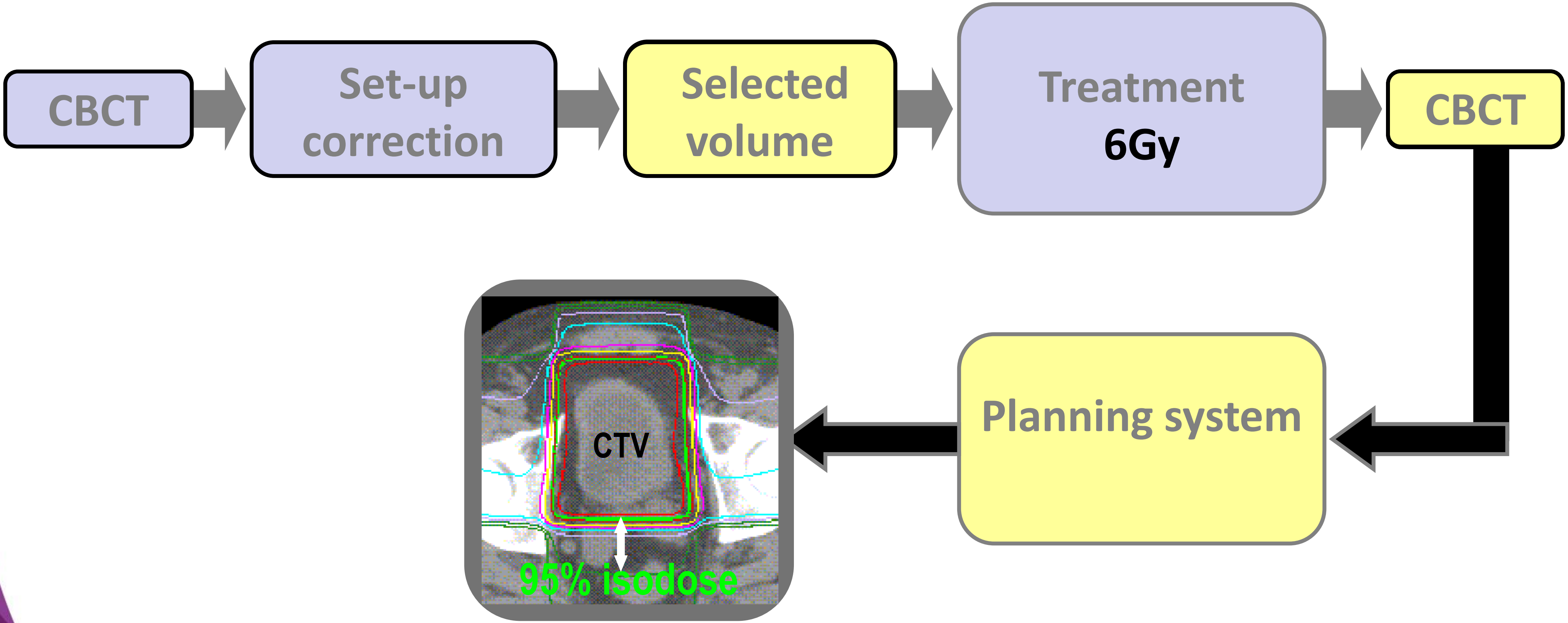


Large 8% (6#)

Intermediate 43% (33#)

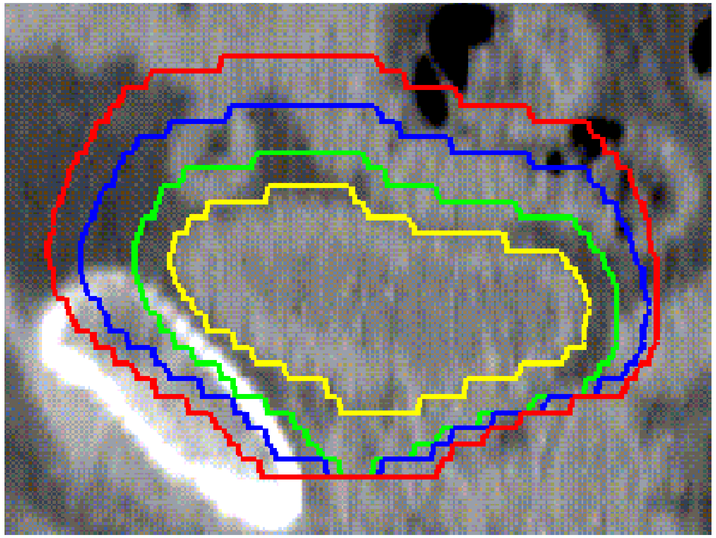
Small 49% (38#)

Target coverage

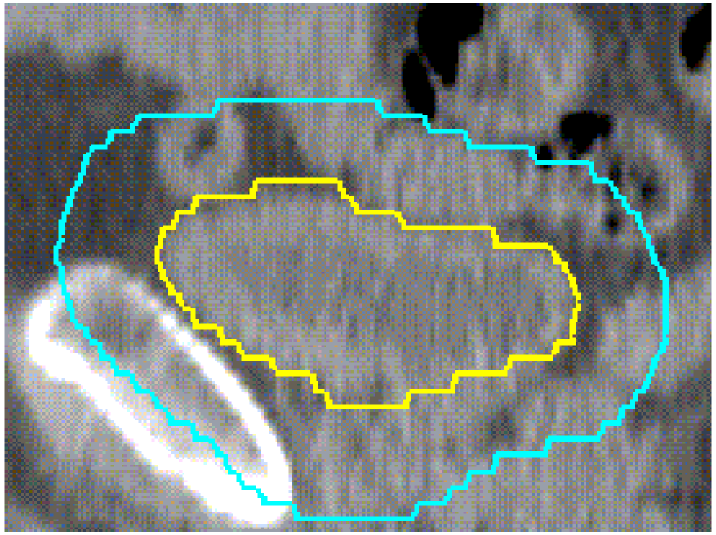


Planning target volume comparison

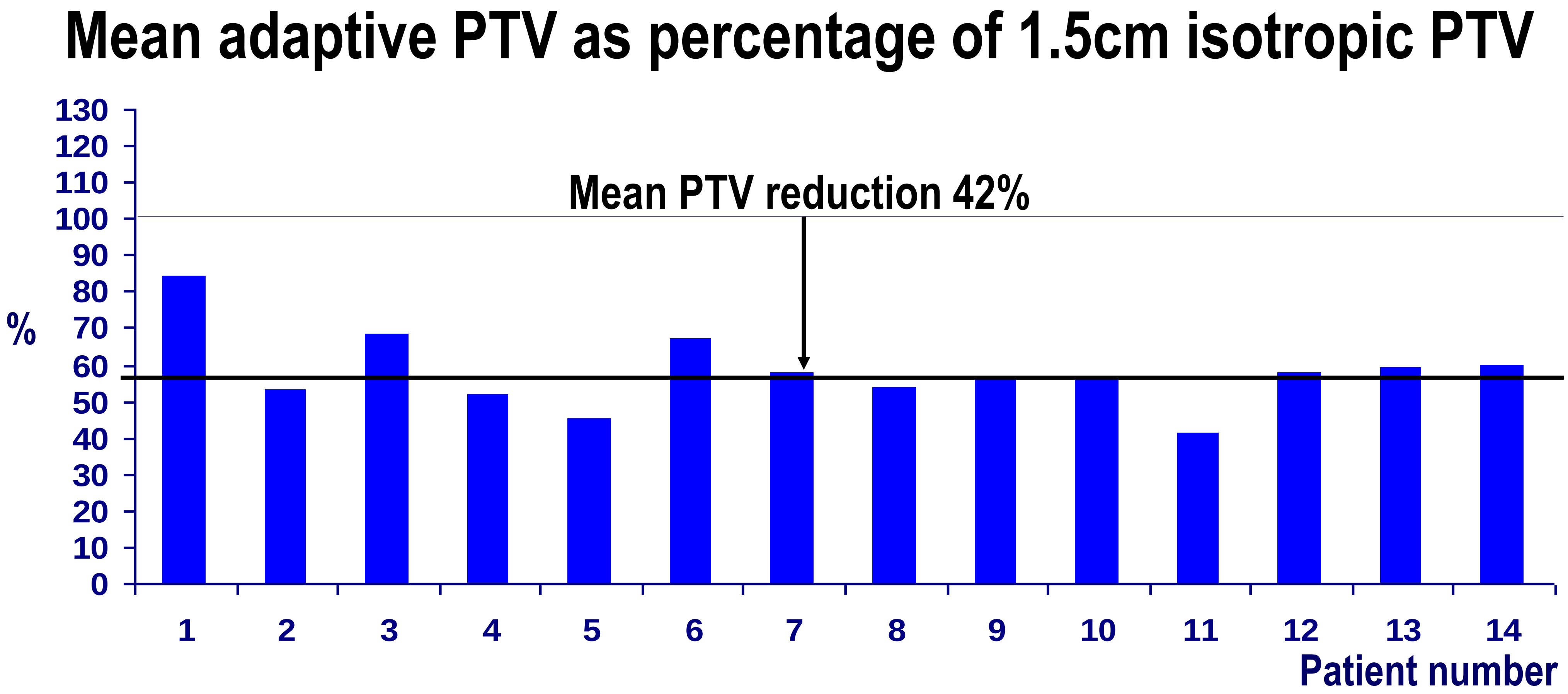
Mean adaptive PTV



1.5cm isotropic PTV

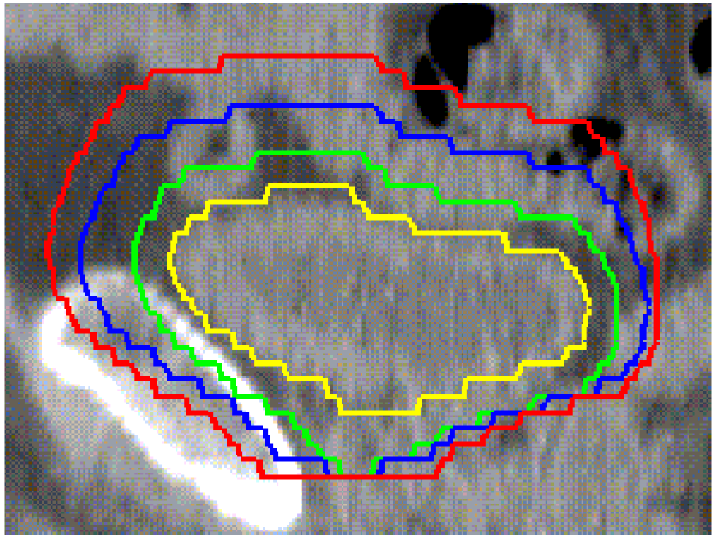


Planning target volume comparison

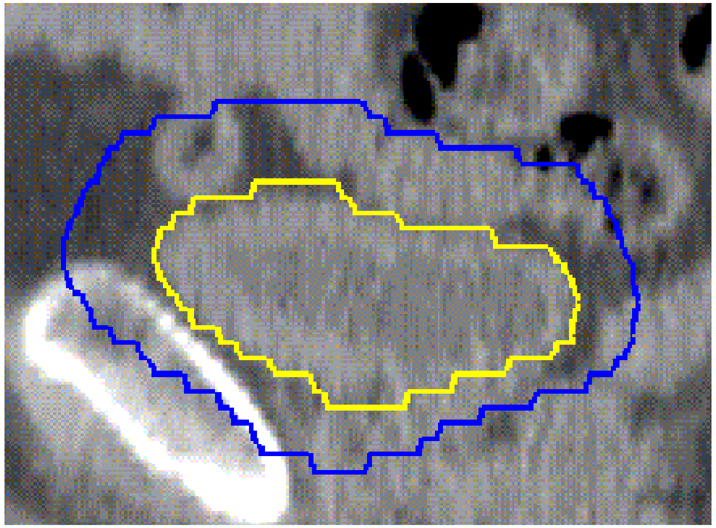


Planning target volume comparison

Mean adaptive PTV



Intermediate PTV



HYBRID study

Hypofractionated **B**ladder **R**adiotherapy with or without **I**mage guided a**D**aptive planning

- A multicentre randomised phase II study (36Gy in 6f)

RANDOMISE

1:1

Group 1:
Standard planning (control)

Planning CT scan post void. Clinical target volume (CTV): whole bladder plus any area of extravesical spread.

One 3D conformal plan will be generated with 1.5cm expansion margin.

Pre-treatment Cone Beam CT will be used to verify CTV coverage.

Group 2:
Adaptive planning (experimental)

Planning CT scan post void. CTV: whole bladder plus any area of extravesical spread.

Three 3D conformal plans will be generated:
1. Small; 2. Medium; 3. Large

Pre-treatment Cone Beam CT will be used to select appropriate plan, this will be confirmed by a second trained observer.

CANCER RESEARCH UK

Chief Investigator Prof Robert Huddart

ESTRO School

RAIDER

A **R**andomised phase II trial of **A**daptive **I**mage guided standard or **D**ose **E**scalated tumour boost **R**adiotherapy in the treatment of transitional cell carcinoma of the bladder

240 patients with pT2-T4a N0 M0 urothelial bladder carcinoma fulfilling eligibility criteria

RANDOMISATION
1:1:2

Group 1:
Standard planning and delivery RT (control)

64GY32f cohort n=30
55Gy/20 f cohort n=30

Group 2:
Adaptive image guided Tumour focused RT (SART)

64GY32f cohort n=30
55Gy/20 f cohort n=30

Group 3:
Adaptive image guided Dose escalated Tumour boost RT (DART)

70Gy/32f cohort n=60
60Gy/20 f cohort n=60

Joint protocol UK NCRI and TROG

PRIMARY ENDPOINT
Stage I: Proportion of patients meeting radiotherapy dose constraints to bladder, bowel & rectum in DART groups.
Stage II: Proportion of patients experiencing any ≥G3 Common Terminology Criteria for Adverse Events (CTCAE) v.4 late toxicity (6-18 months post radiotherapy).

Chief Investigator Prof Robert Huddart

Normal tissue sparing in an adaptive radiotherapy trial for urinary bladder cancer

Anne Vestergaard, Ludvig P Muren, Henriette Lindberg, Kirsten L Jakobsen, Jørgen B Petersen, Ulrik V Elstrøm, Morten Høyer

Department of Medical Physics and Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
Department of Oncology, Copenhagen University Hospital, Herlev, Denmark

Aim of the study

- To quantify the normal tissue sparing achieved with daily plan selection based ART compared to non-adaptive RT

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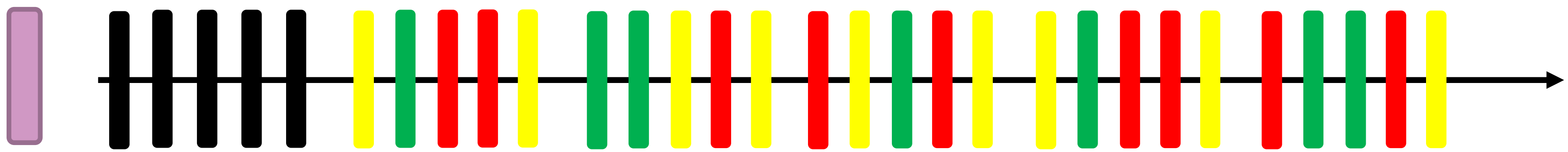
REGION H Herlev Hospital
Aarhus University Hospital

Introduction to plan selection in bladder cancer

Planning of plan selection treatment

Plan CT and 4 CBCTs → Delineation of bladders → **Library of dose plans** → **Treatment evaluation**

Delivery of plan selection



First week of treatment
Non-adaptive RT

Fraction 6 to 30 delivered using plan selection

Large
Medium
Small

Pre-treatment imaging

Phase II trial initiated November 2012 at Aarhus University Hospital and are now including at Copenhagen University Hospital, Herlev and at Odense University Hospital as well

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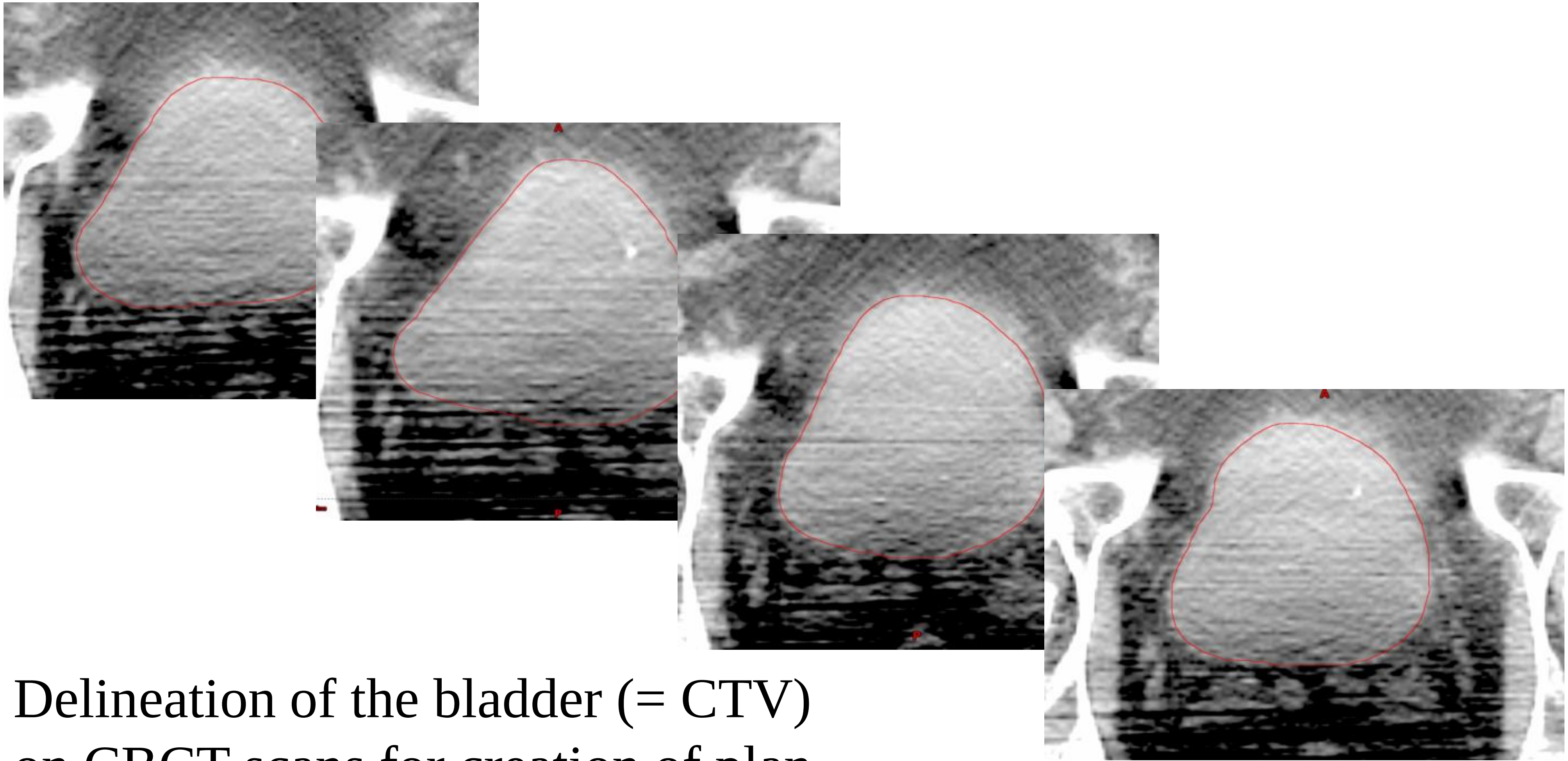
M&M: Delineation on first four CBCTs



Delineation of the bladder (= CTV) on CBCT scans for creation of plan selection volumes

Wright et al.: Phys Med Biol 2009

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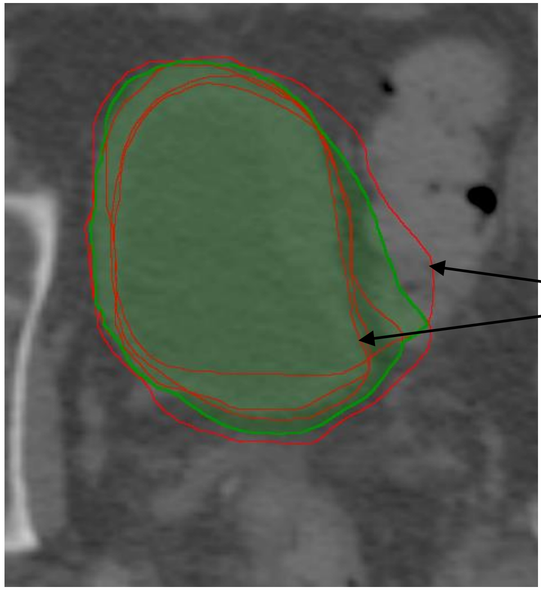
Aarhus University Hospital

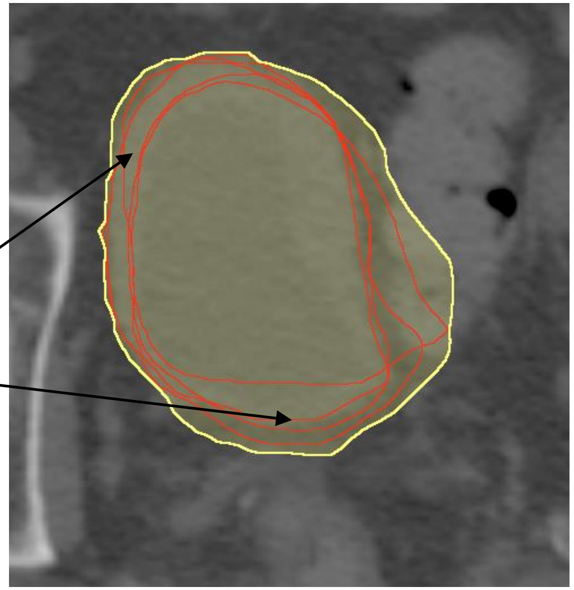
M&M: Generating plan selection volumes

Small: The volume contained in at least two out of five CTVs

Medium: Union of same five CTVs



Individual CTVs in red



Large: Standard non-adaptive margins

Wright et al, Phys Med Biol 2009; Vestergaard et al, Acta Oncol 2010

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M&M: PTVs and organs at risk

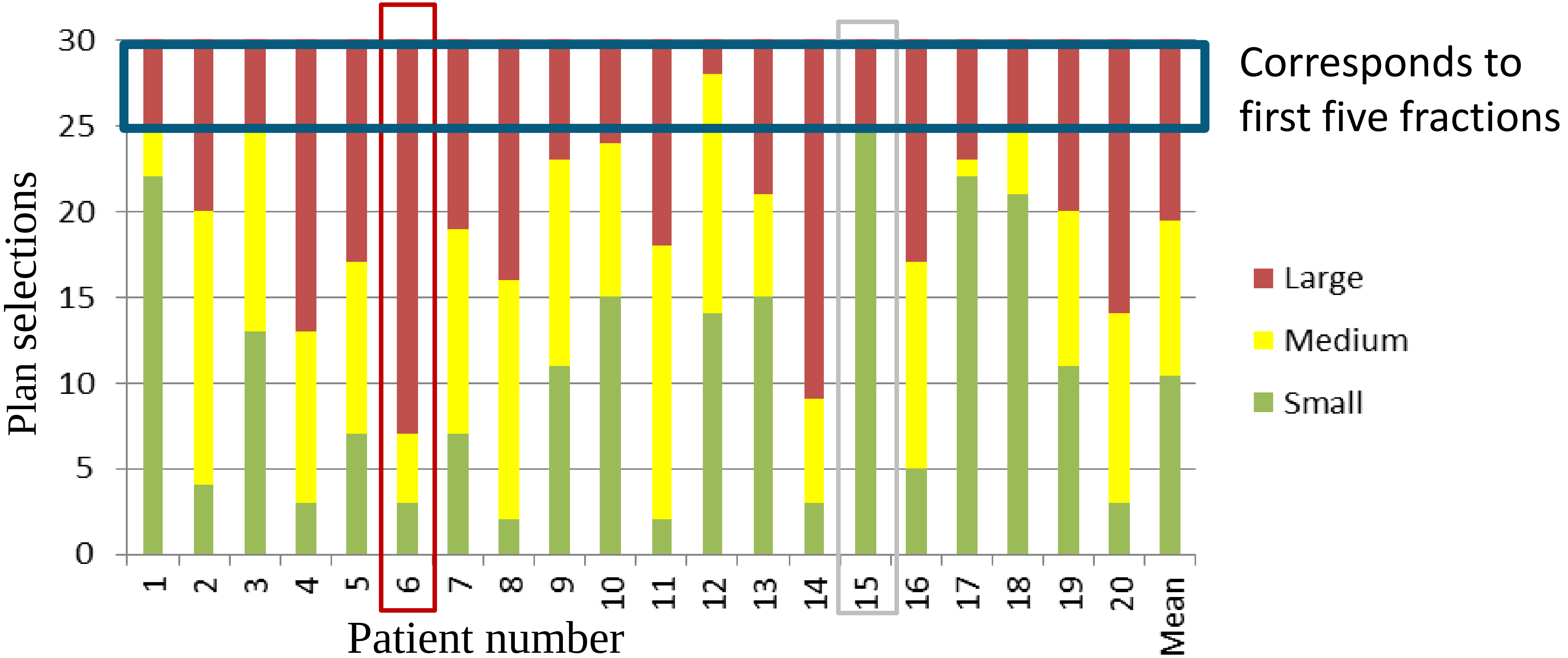
- A 3 mm isotropic margin was added to the plan selection volumes to account for uncertainties
- Planning target volumes (PTVs) were generated from plan selection volumes adding 5mm isotropic margin
- Bowel cavity: Superior border L5, inferior last slice with bowel segment
- Rectum including rectal wall and content from the recto-sigmoid transition or sacro-ili[illegible] the anal canal

DVH analysis based on plan CT geometries

M&M: Plan selection

- Plan selection was performed online
  - Online match on bony anatomy (equivalent to treatment position)
  - The smallest plan covering the bladder as identified on pre-treatment CBCT was selected
  - Plan selection frequencies were assessed

Results: Plan selection frequencies



Median [range] volume ratio of course-averaged PTV_{ART} /PTV_{nonART}: 0.70 [0.46;0.89]

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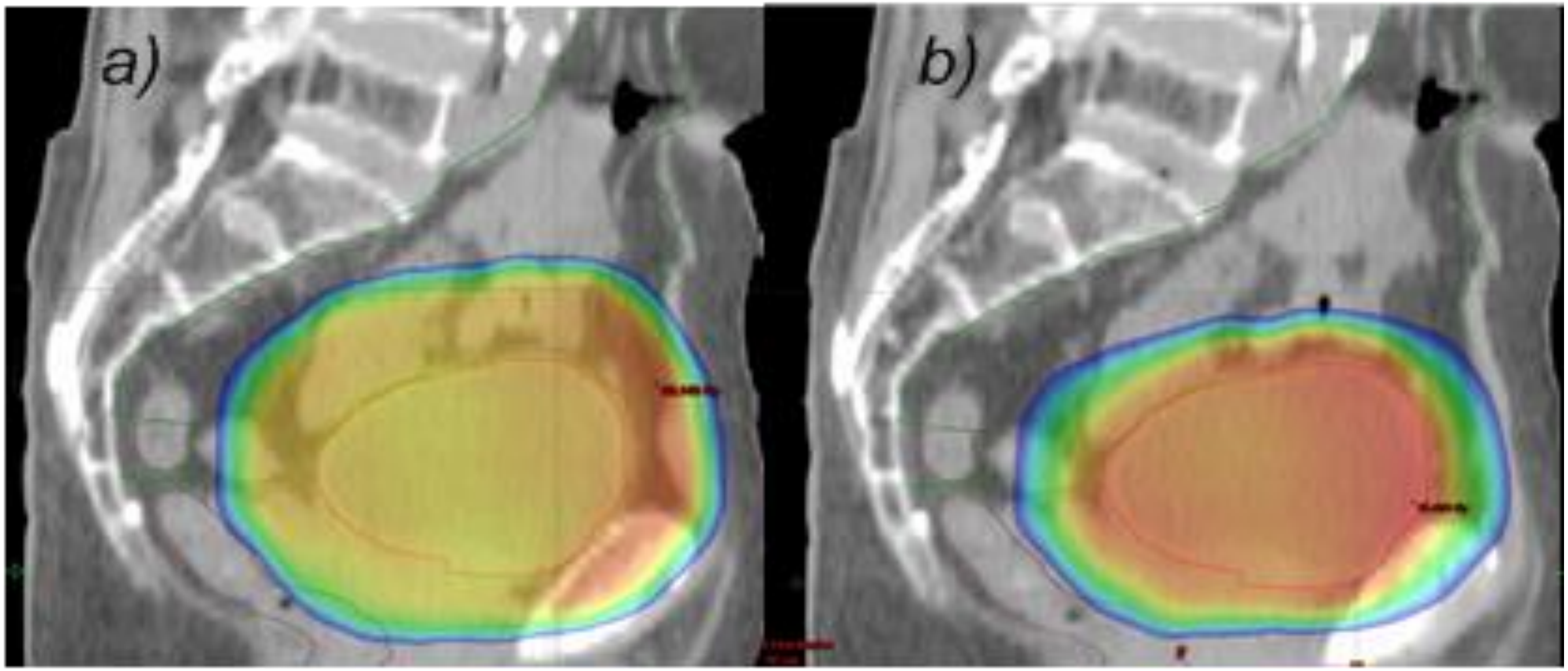
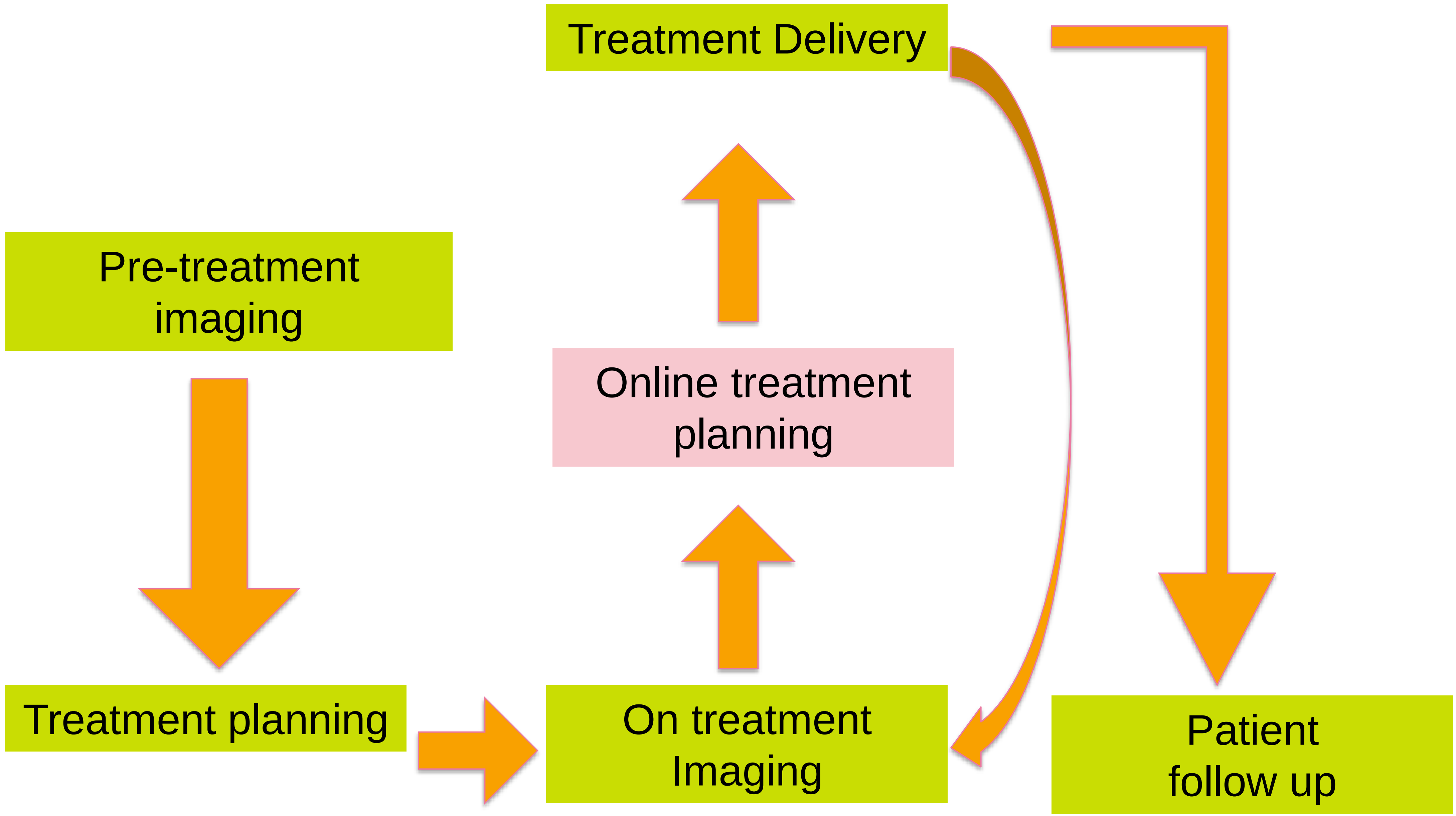
Dose distributions for ART vs. non-ART

Non-ART ART



Colour scale (blue to red): 45-60 Gy

Online ART Replanning workflow



A dose accumulation study of adaptive plan selection vs. re-optimisation in bladder radiotherapy

Anne Vestergaard, Jimmi Søndergaard, Ludvig P. Muren, Ulrik V. Elstrøm, Morten Høyer and Jørgen Petersen

Department of Medical Physics and Department of Oncology
Aarhus University Hospital, Aarhus, Denmark

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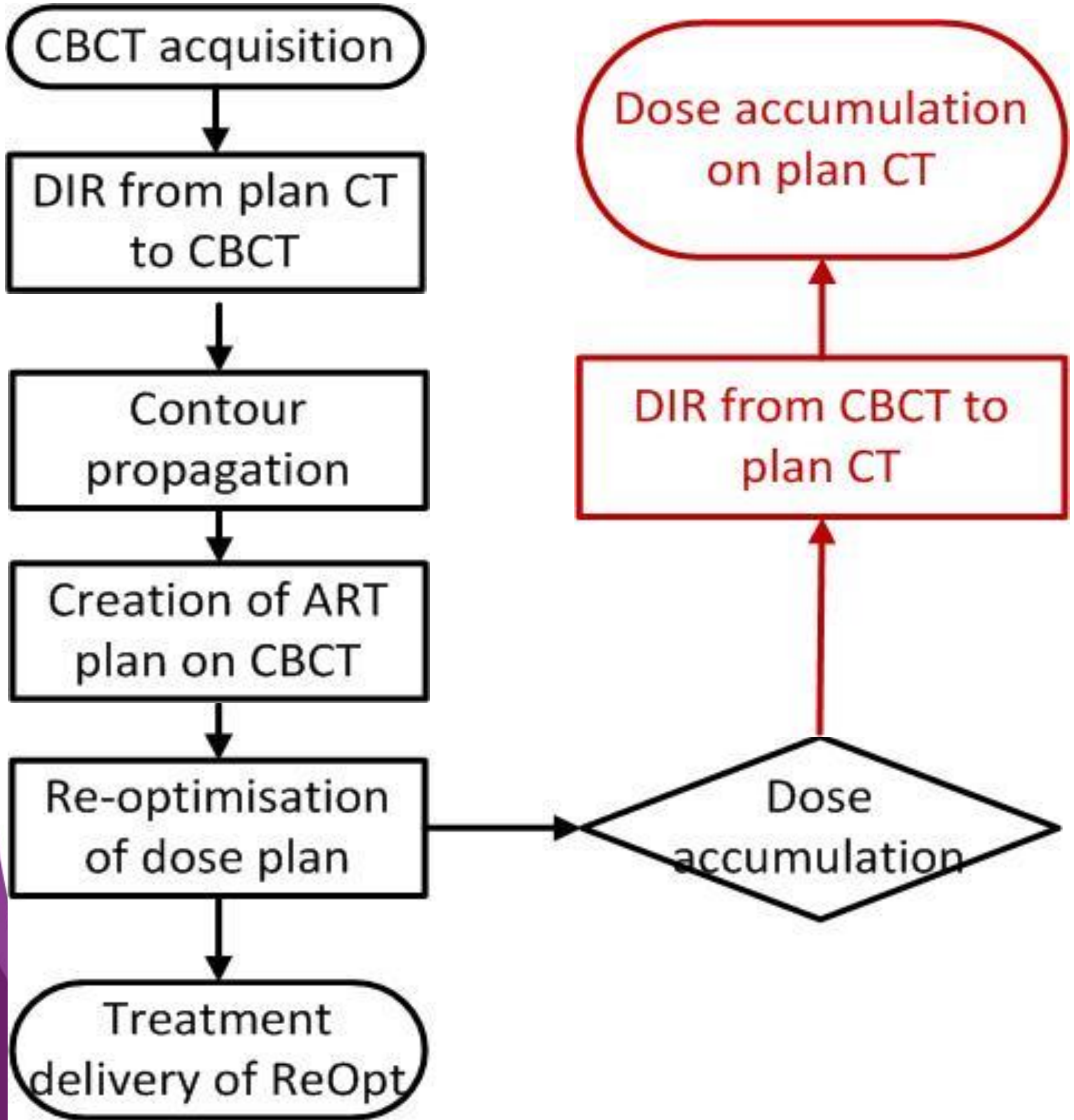
Methods: Re-optimisation



- Re-optimisation strategy compared to non-ART as well as plan selection ART for 7 patients

- For both the clinical and the re-optimisation strategy, dose accumulation was performed in DART™ (Dynamic Adaptive RT, Varian Medical Systems)

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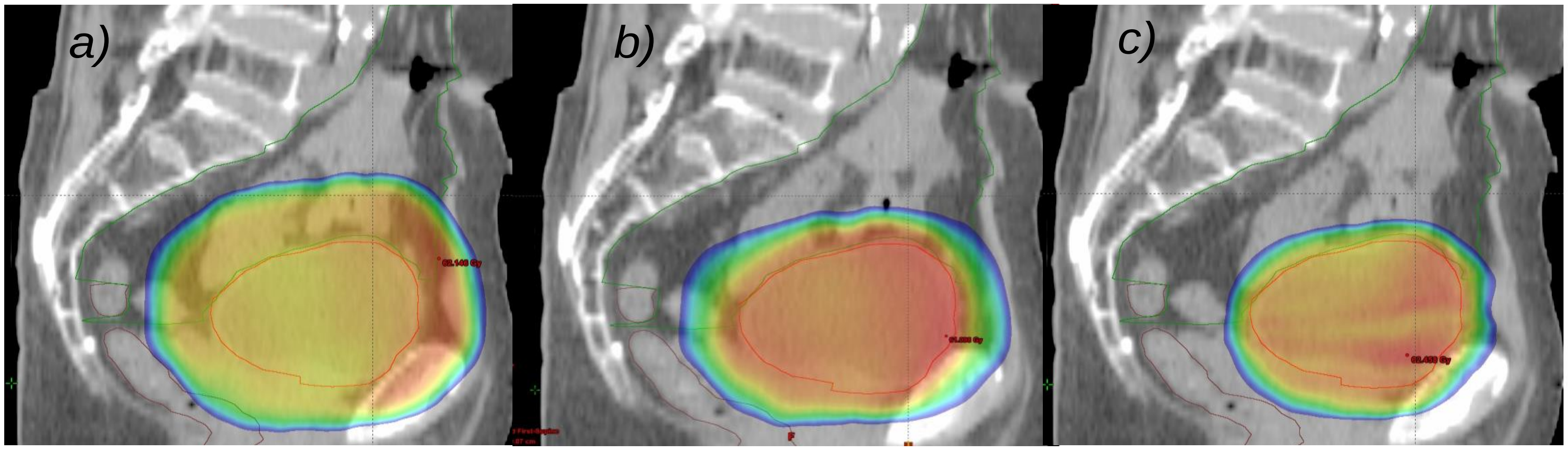
Results: Plan selection vs. Re-opt

- Overall a considerable reduction in the volume receiving high doses was seen for both plan selection and re-opt strategies – resulting in reduction of dose to bowel and rectum

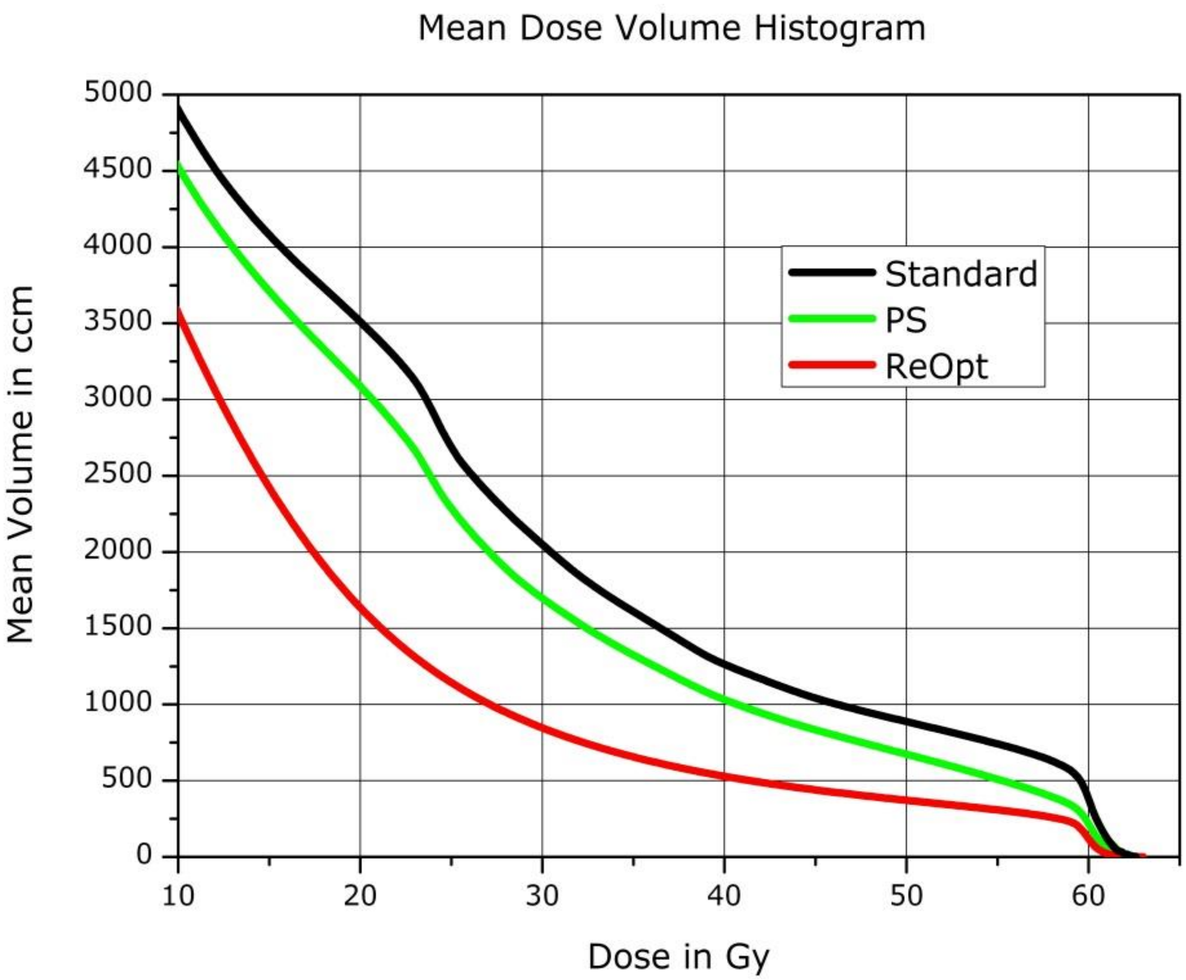
Non-adaptive RT | Daily plan selection | Daily re-opt



Outer blue contour 45Gy – red 60Gy

Results: Average DVHs

- Outcome assessed using the ‘overall’ normal tissue
- Mean reduction of the volume receiving ≥ 45 Gy
  - PS: 20% (range 0-39%)
  - Re-opt: 58% (range 48-66%)
- Mean reduction of the high dose volume (≥57 Gy)
  - PS: 34% (range 0-52%)
  - Re-opt: 59% (range 50-67%)



Vestergaard et al, Radiother Oncol 2013

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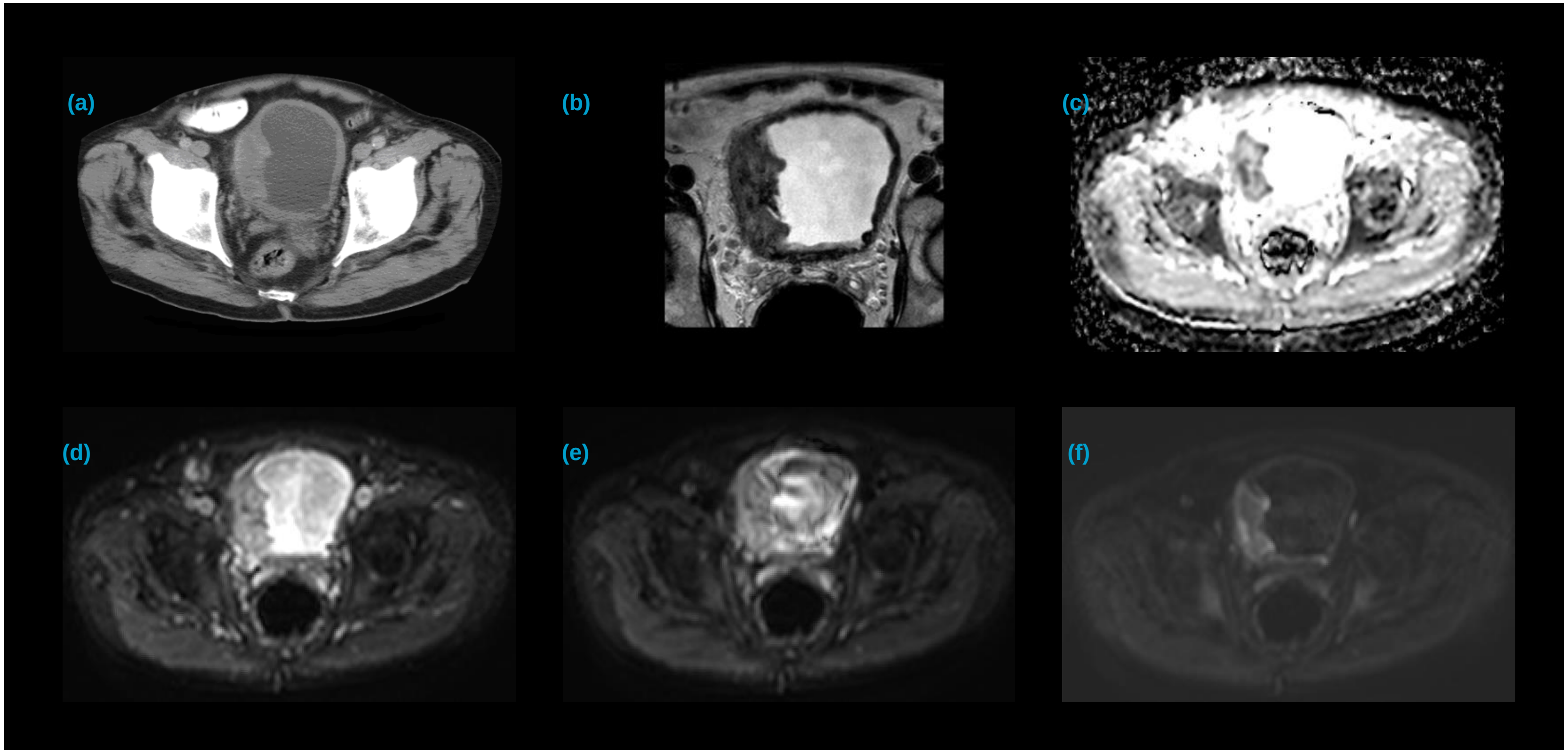
Future: MRI informed real-time planning

- 3D gradient echo T1-weighted mDixon sequence scan time: 40 s; (Philips Ingenia 1.5T)
- MRI at t = 0, 2, 4, 6, 8, and 10 minutes
- Bladder CTV, bowel loops and rectum were delineated on MRI_0 and MRI_10
- Dose plans calculated on MRI_0
- Target coverage assessed on MRI_10

- Reduction in PTV course average (median 304 cc compared to plan selection)
- Improved bowel loop sparing (V25)
- V95 <98% in 2 patients (intra-fraction shifts)

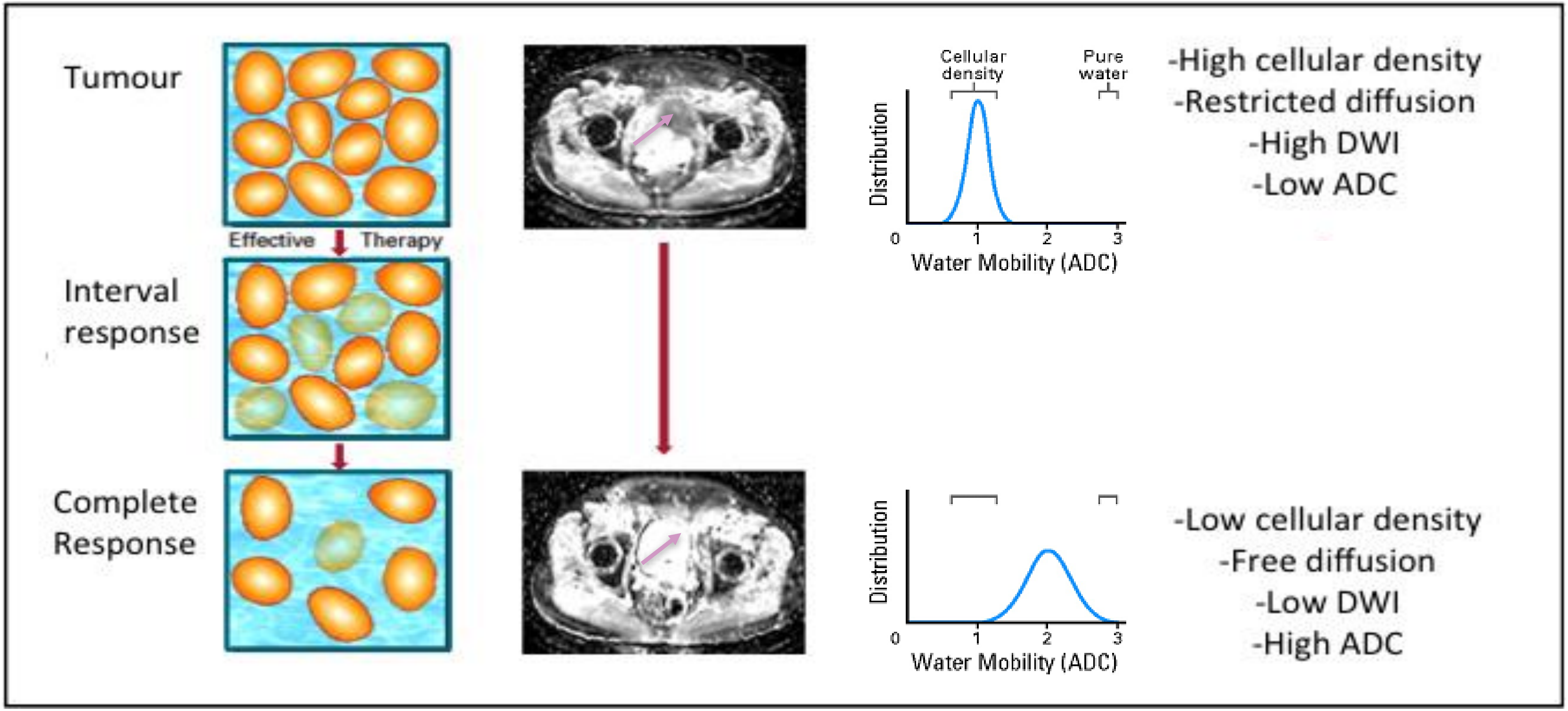
Vestergaard A, Hafeez S, Muren LP, Nill S, Hoyer M, Hansen VN, Gronborg C, Pedersen EM, Petersen JB, Huddart R et al. The potential of MRI-guided online adaptive re-optimisation in radiotherapy of urinary bladder cancer. Radiother Oncol 2016, 118(1):154-159.



Example of images generated. 76 year old male with known T3 N0 M0 bladder cancer (right bladder wall)

(a) contrast enhanced CT scan, (b) axial T2 weighted image performed on a 1.5T MRI unit showing hypo intense lesion, (c) corresponding ADC map, (d) axial DW MRI at b-value=0, (e) axial DW MRI at b-value=100, (f) axial DW MRI at b-value=750

DW-MRI as a bladder imaging biomarker



A schematic of the change in cellularity and increased molecular water mobility measured as an apparent diffusion coefficient (ADC), ADC map of the bladder and histogram as a tumour responds to treatment (top to bottom).

Hafeez S, Huddart R: Advances in bladder cancer imaging. BMC Med 2013, 11:104.

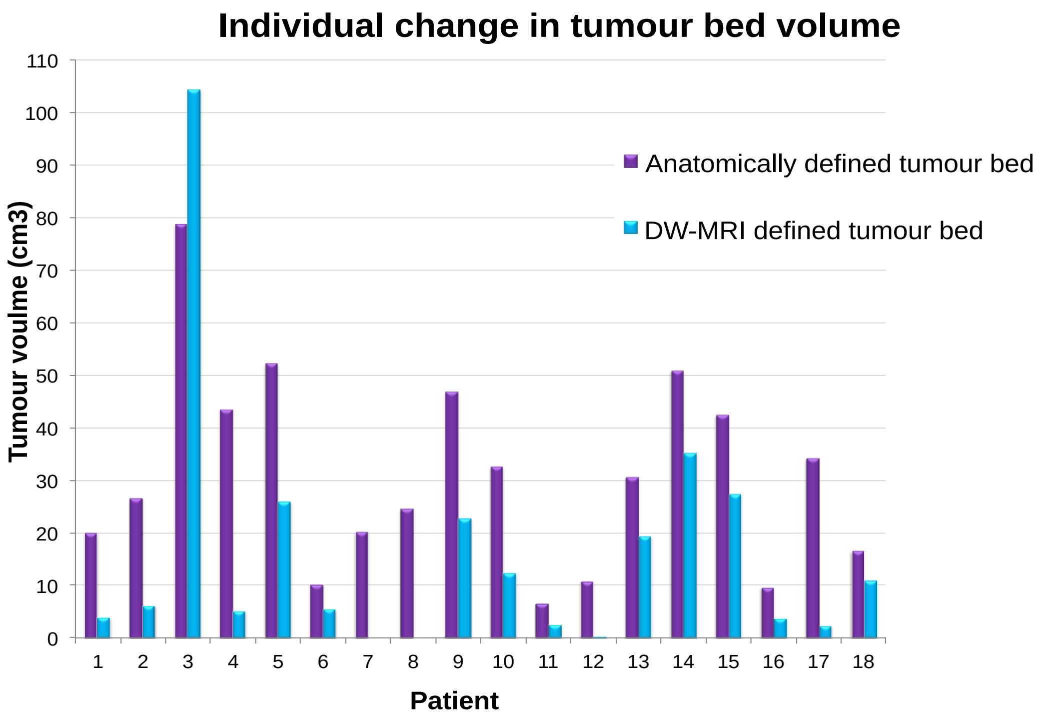
DW-MRI to inform tumour boost

Mean conventional GTV was 31.0 cm^3 (range 6.7-78.7cm^3).

Mean DW-MRI GTV was 16.1cm^3 (range 0-35.3cm^3).

There was significant reduction in GTV using DW-MRI (p=0.002).

Acquiring DW-MRI for radiotherapy planning may complement target volume delineation and inform non-uniform dose delivery to biological sub-volumes for bladder radiotherapy dose escalation trials.



Hafeez et al., Characterisation of tumour boost with diffusion weighted MRI (DW-MRI) to inform biological target volume for radical radiotherapy in muscle invasive bladder cancer (MIBC) NCRI 2015.

Conclusions bladder ART

- Adaptive RT for bladder gives considerable normal tissue sparing, that likely translates into reduced GI morbidity

- Bladder filling is a concern, but its impact is limited with short fraction delivery times (VMAT)

- Daily adaptive re-optimization might give an additional advantage but is not yet clinically feasible

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QA of deformable image registration and contour propagation

Marcel van Herk

on behalf of the imaging group

Institute of Cancer Sciences,
University of Manchester / The Christie

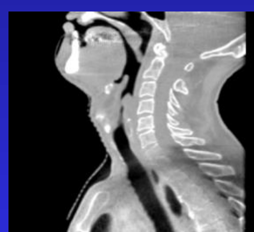
Includes slides from:

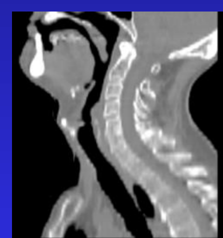
Netherlands Cancer Institute

Academic Medical Center

Terminology

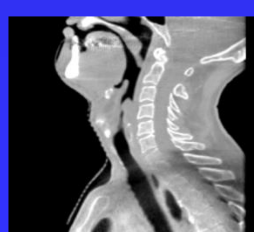
- Image registration:
  - The process of finding the transformation that aligns two images

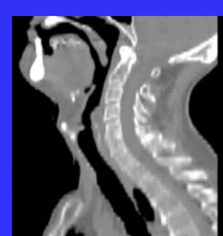




1	0	0	Tx
0	1	0	Ty
0	0	1	Tz
0	0	0	1

- Image fusion:
  - Displaying a combination of aligned images





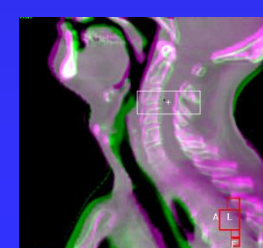


Image registration

- Find translation….deformation to align two 2D..4D data sets (2 .. 1000000 degrees of freedom)

- Allows combination of scans on a point by point basis

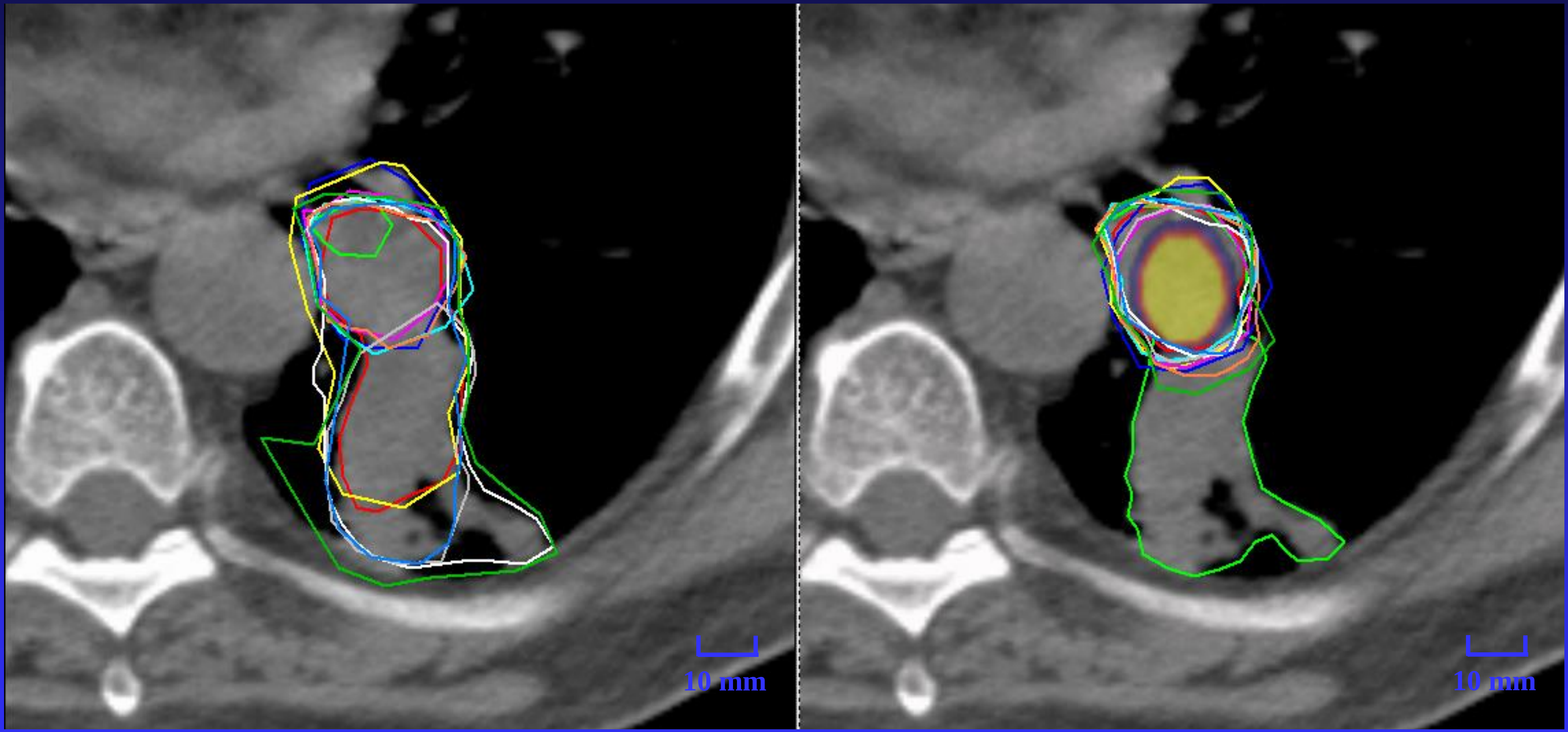
- Applications:
  - Complementary data
  - Motion tracking and compensation (imaging)
  - Image guidance
  - Adaptive radiotherapy
  - Response monitoring
  - Dose accumulation
  - Data mining

easy

↓

difficult

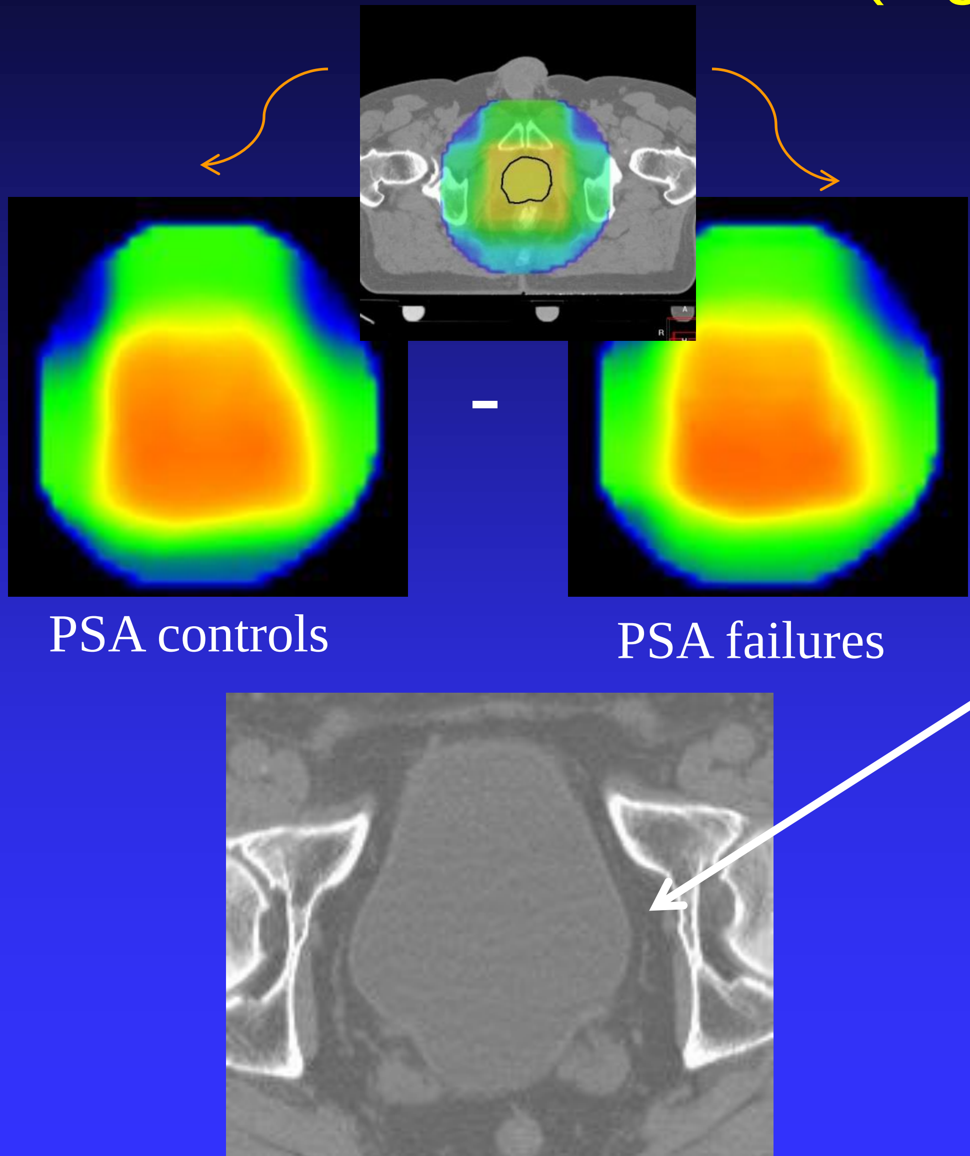
Delineation: CT versus CT + PET reduce observer variations

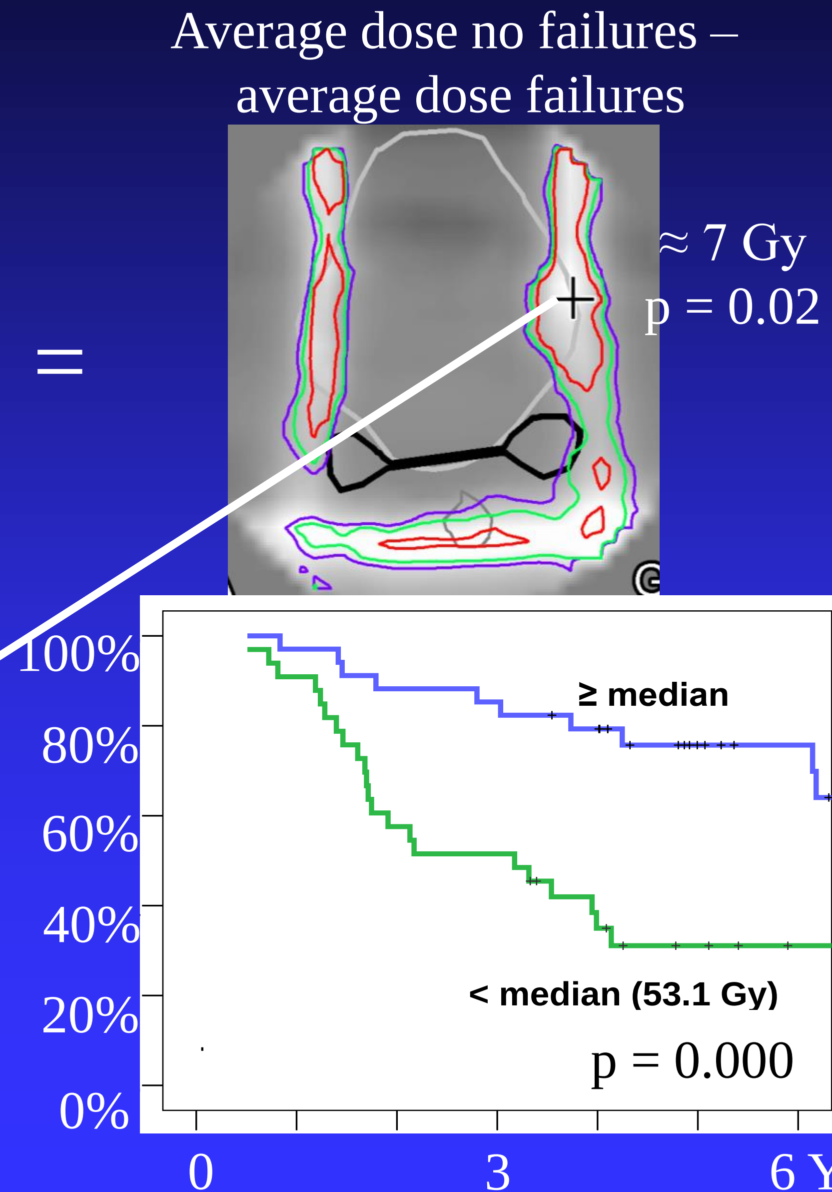


CT CT + PET

11 observers from 5 institutions delineated
22 patients (stage I to IIIB)

Estimate pattern of spread from response to incidental dose in clinical trial data (high risk prostate patients)





Witte et al, IJROBP2009; Chen et al, ICCR2010

Types of transformation

Rigid:

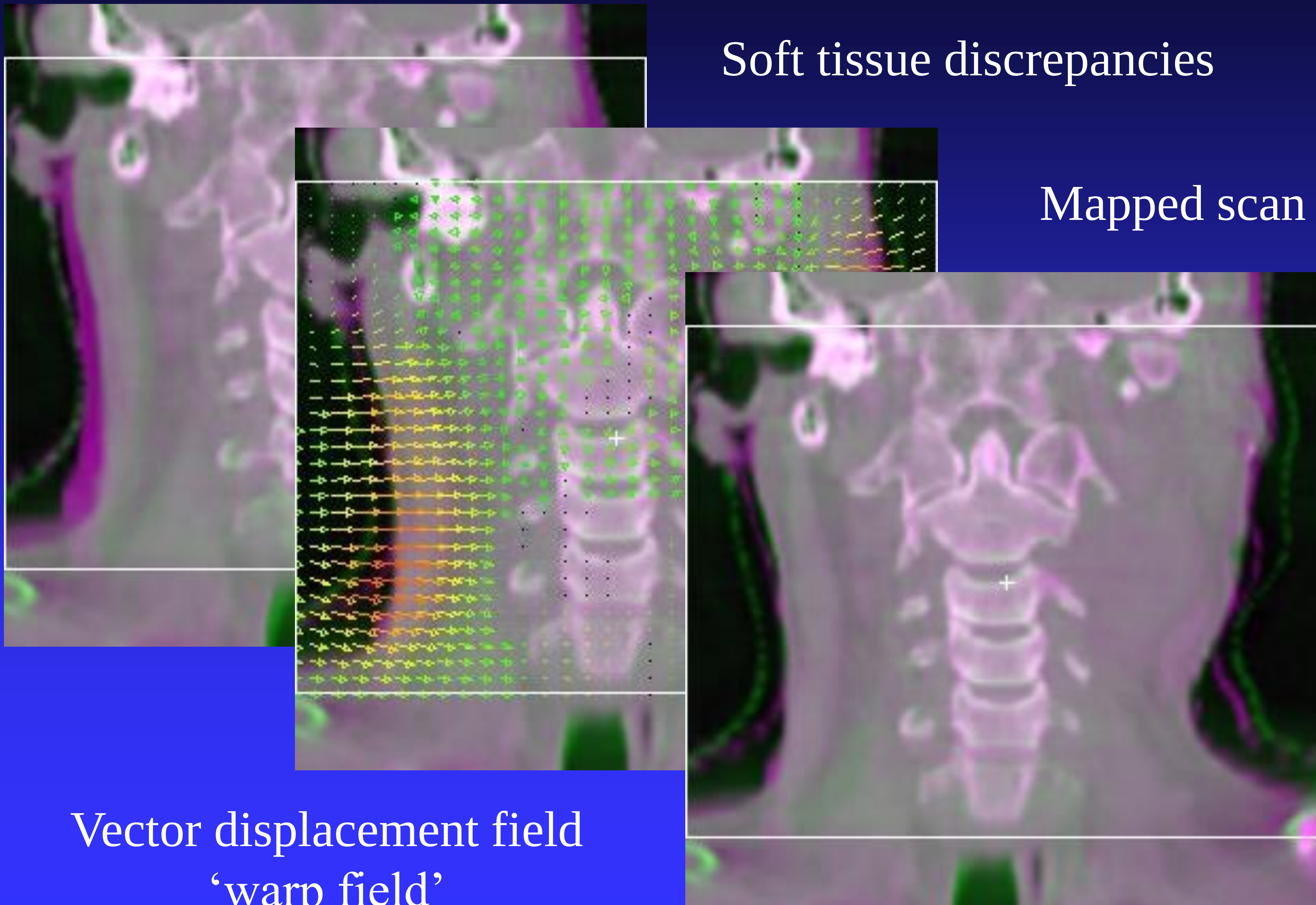
- Translation → for round objects (single seed)
- Translation + Rotation

Deformable:

- Deformation based on control points

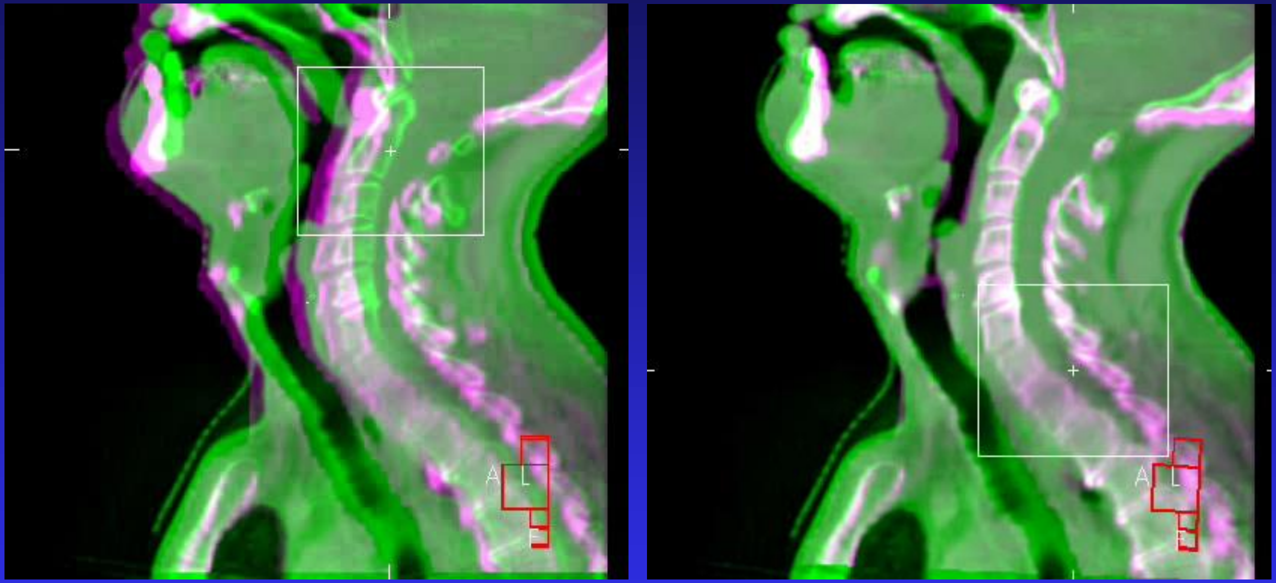
Rigid registration for deformed patients only works well if you limit the region of interest

Deformation vector fields



Rigid registration is still the standard. Which region of interest ?

reference localization reference localization



Tumor in top of neck

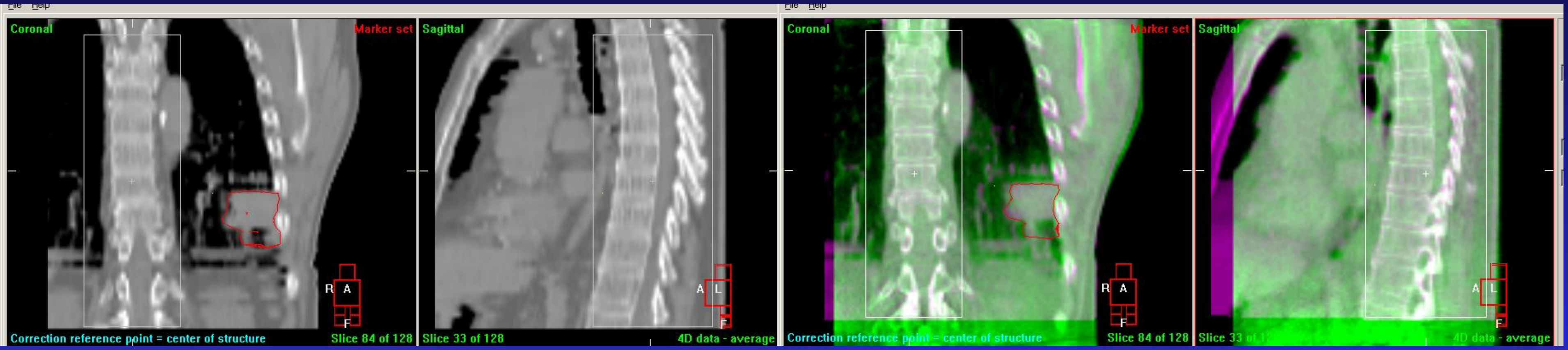
Required table shift:
(-3.2, -1.5, -0.6) mm

Tumor in lower part of neck

Required table shift:
(+1.5, -3.2, -6.1) mm

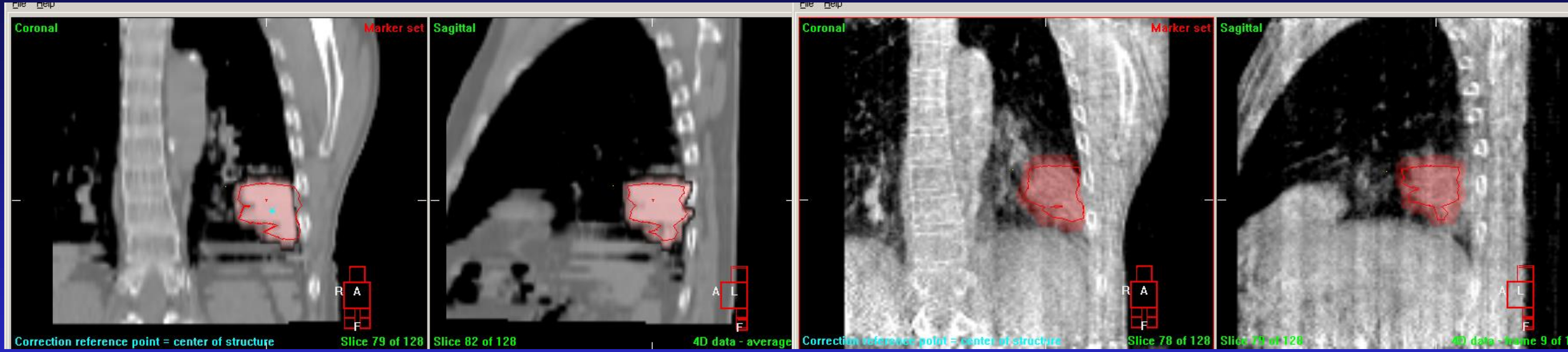
Sub-mm accuracy can be achieved for bony anatomy

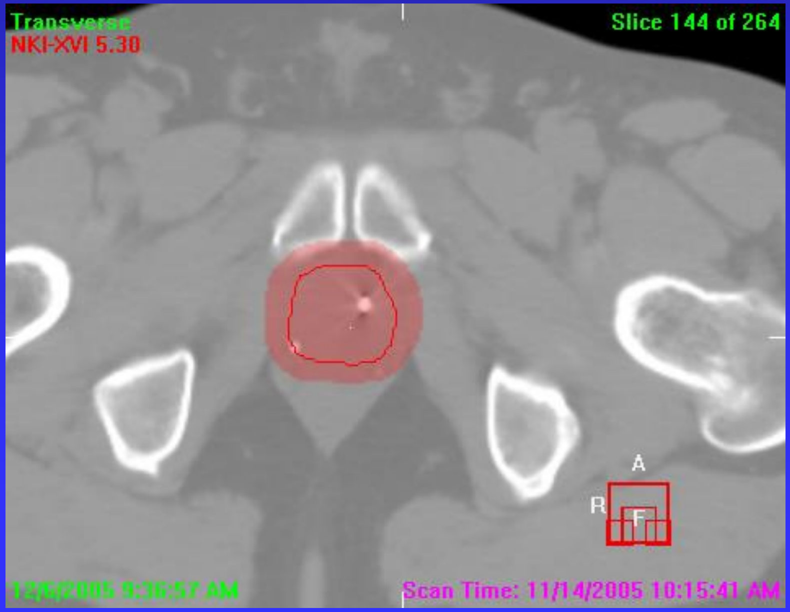
2. Region of interest: rectangular



Easily defined: well suited for ‘easy’ registration (e.g., bone)
Pitfall: contrast may look like bone and cause problems

2. Region of interest: shaped





Define by expanding delineation:
well suited for local registration (e.g., tumor)

Pitffall: tumor region of interest
contains bone with different movement

Need tools to edit

Wolthaus et al 2005, Smitsmans et al 2004/2005

5. Similarity measures (cost function)

Based on segmentation: distance/area

Used for contour or bone matching

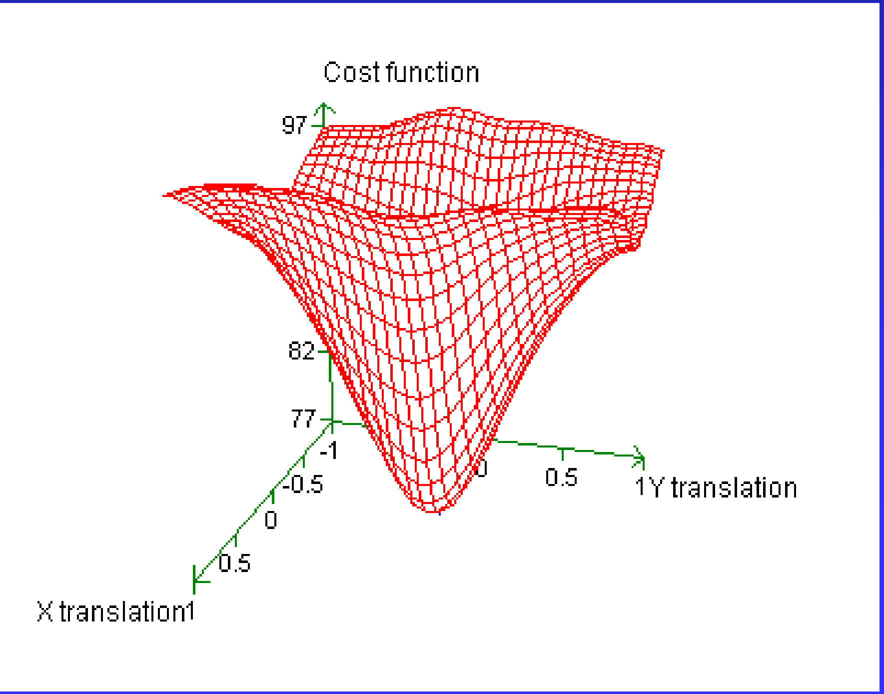
Based on pixel gray values:

Mean absolute difference

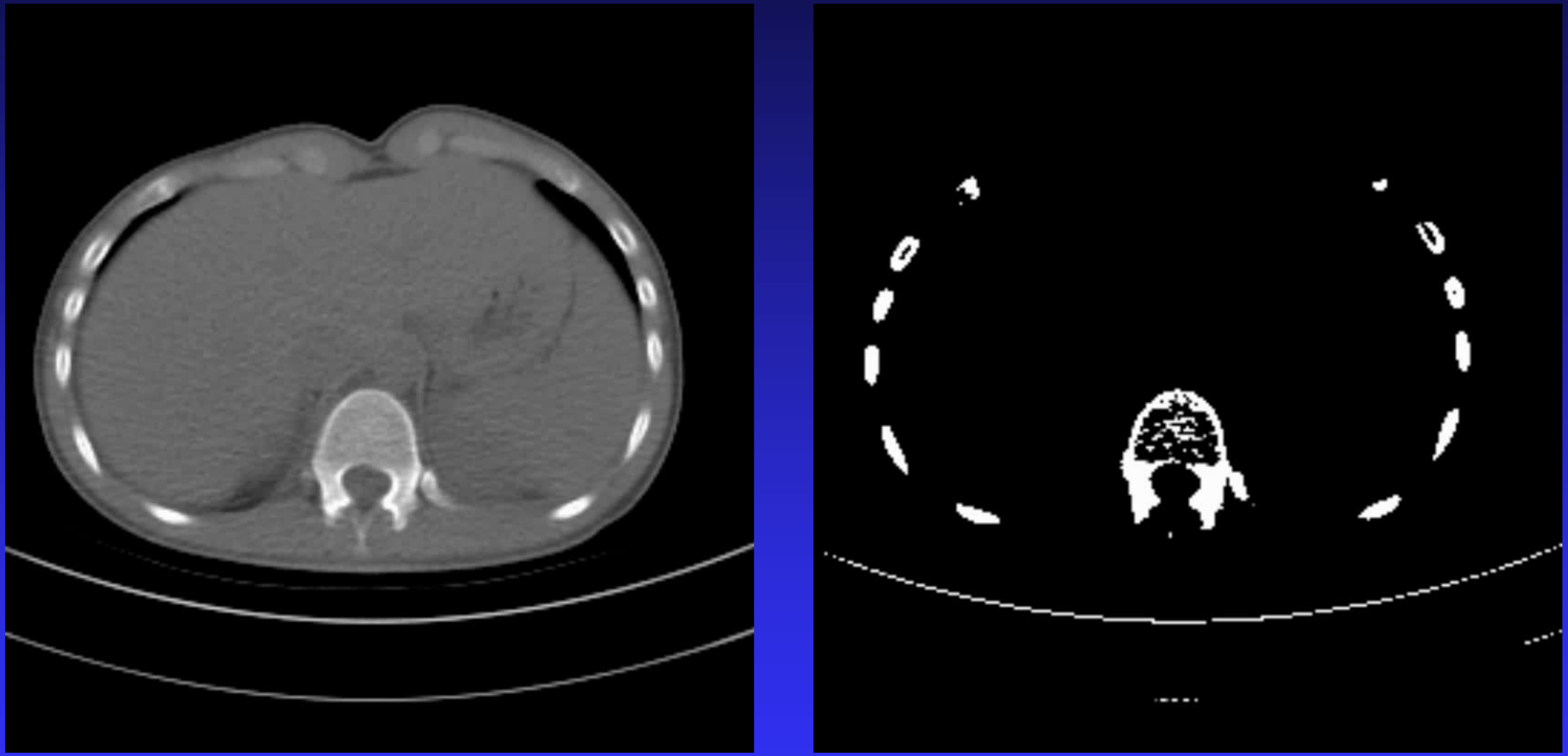
Correlation

Mutual information

Pitfall: noise causes local minima

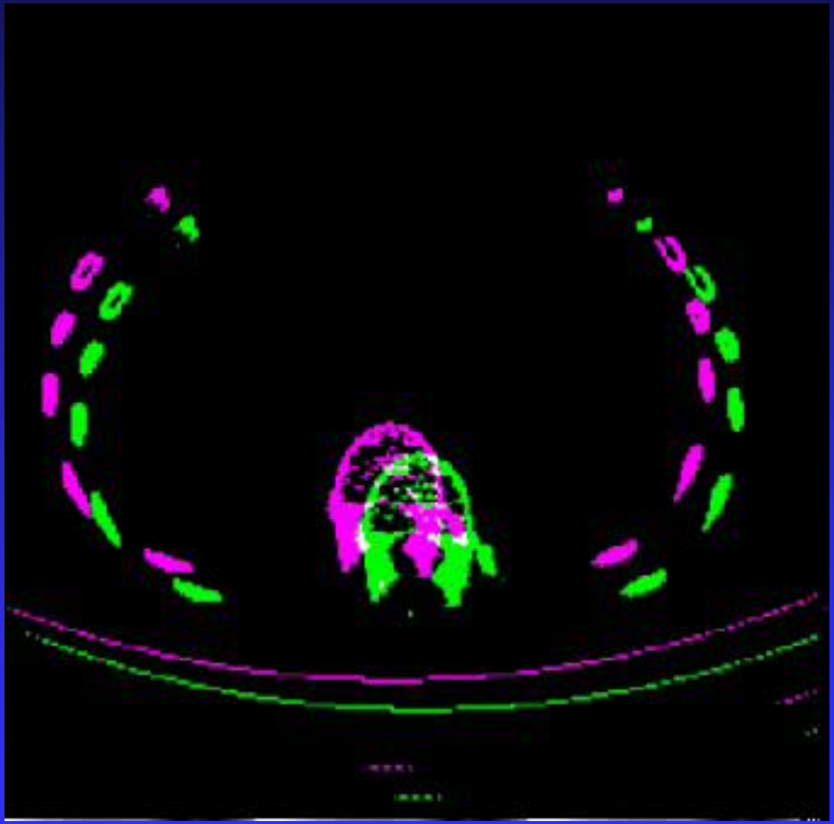


Chamfer matching (bone algorithm) segmentation

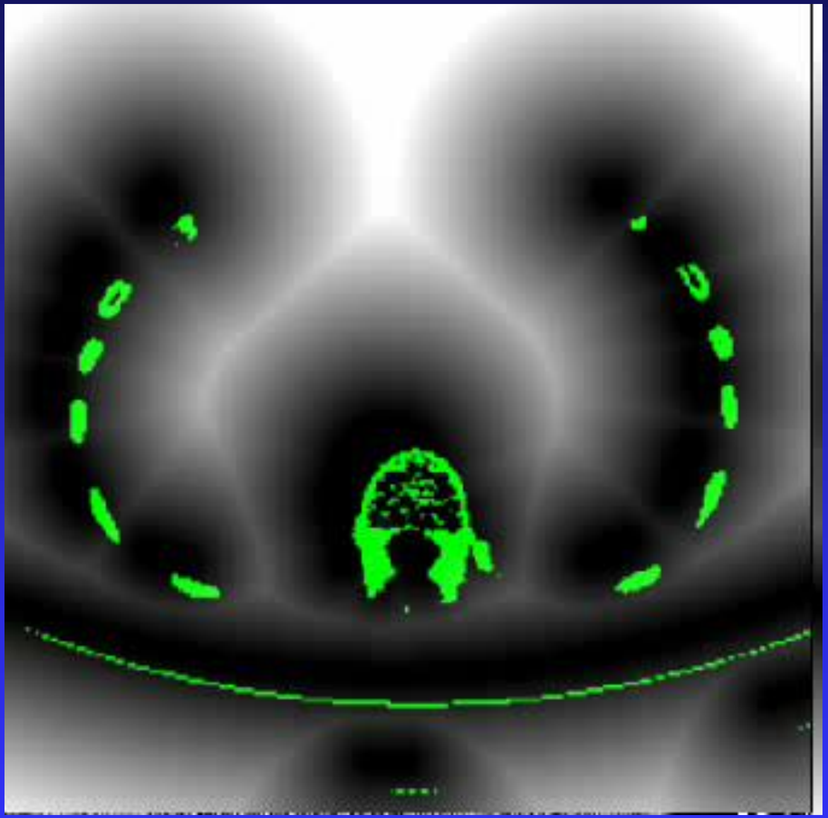


Segment all voxels above a certain intensity

Chamfer matching
minimize (mean absolute) distance



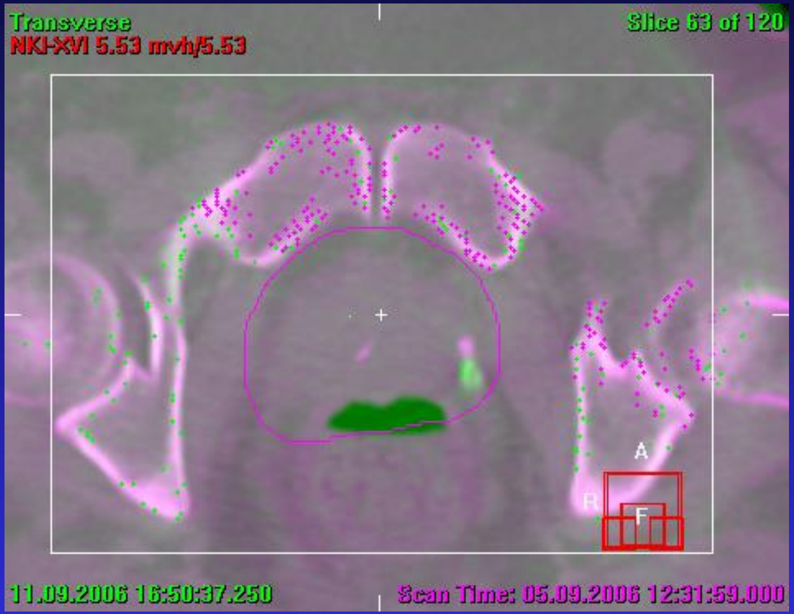
Very fast (1 s): well suited for bony anatomy alignment



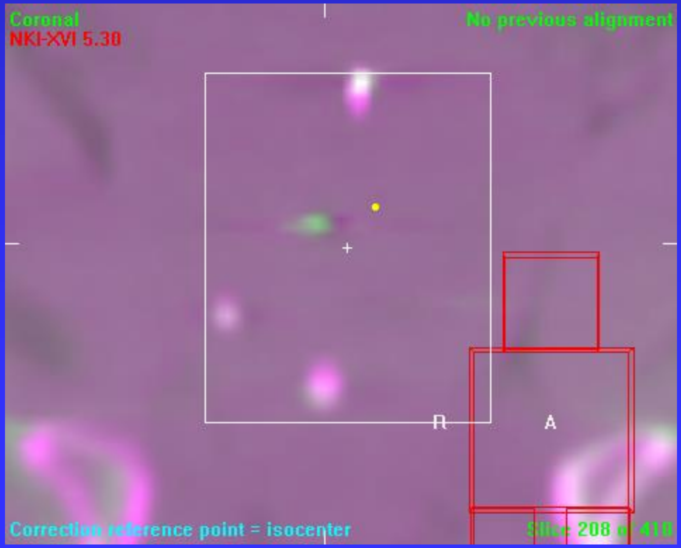
Minimize the sum of all distances for the floating images in the corresponding distance transform

Bone vs seed matching (Elekta algorithm)

- Bone matching:
  - Throw away small objects
  - Minimize mean distance
  - → Get majority right, ignore outliers

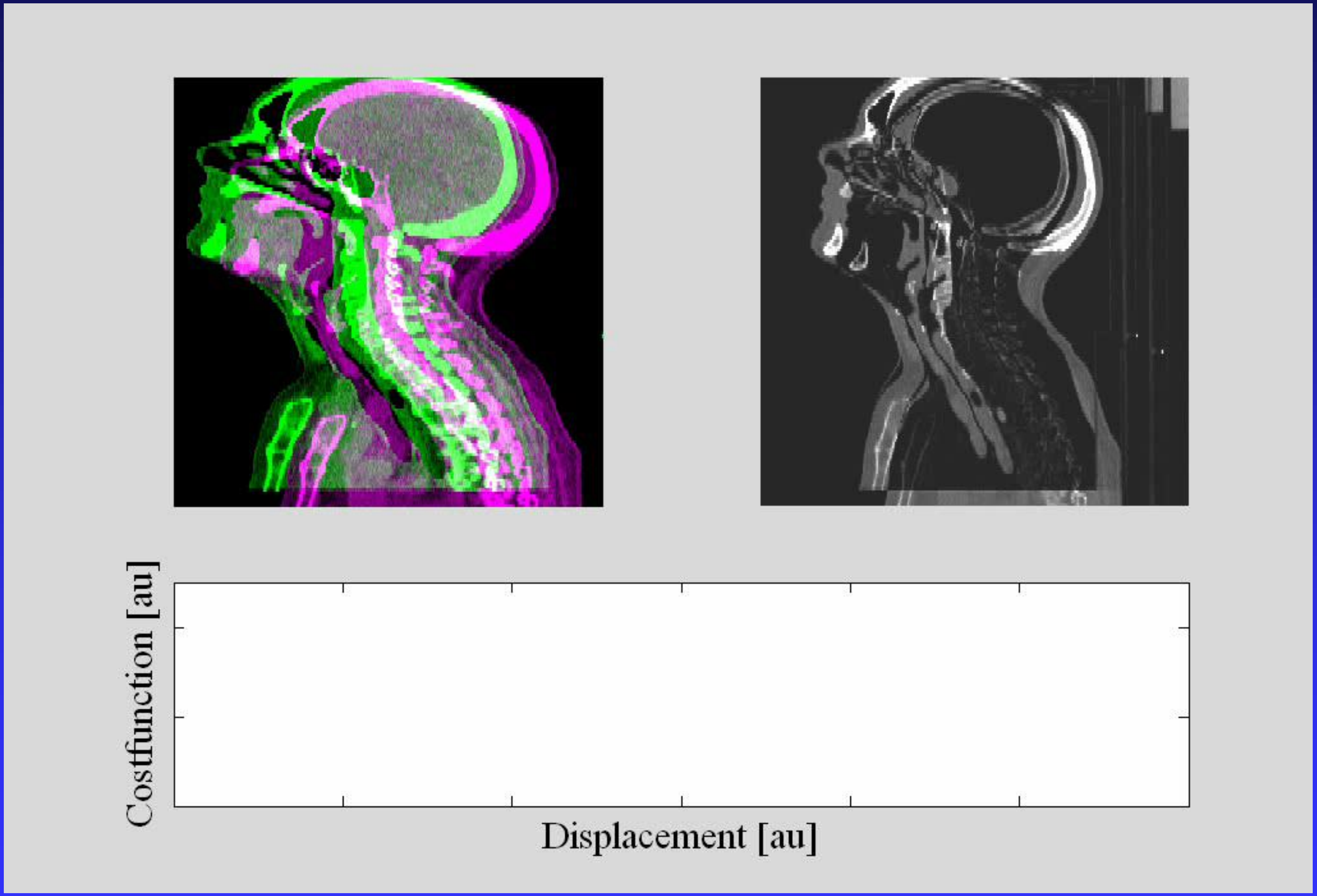


- Seed matching
  - Keep small objects
  - Minimize RMS distance
  - → Spread error sensitive for outliers



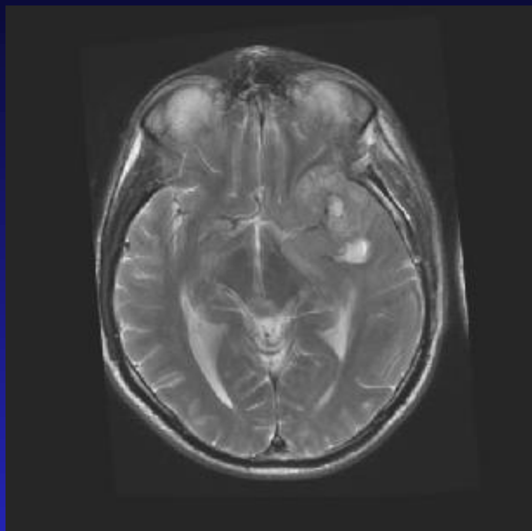
Grey Value / Intensity matching

Uses all pixel values in ROI: e.g., sum of squared differences

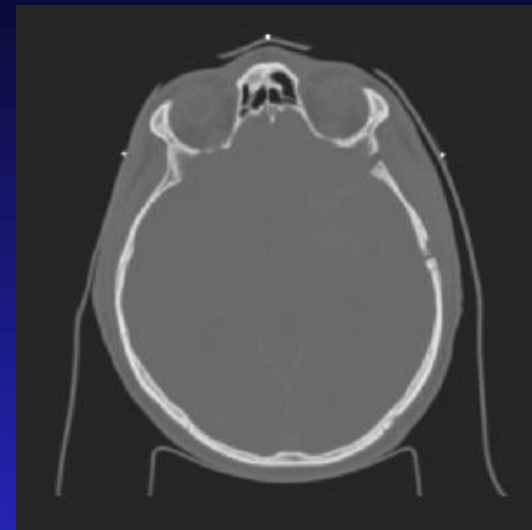


Somewhat slower to process all voxels: depends on the size of the ROI

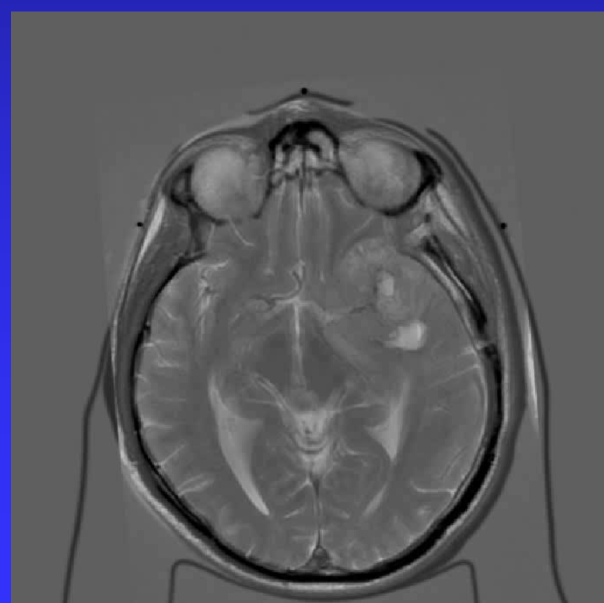
Cost function depends on images



$H(I_{MRI})$



$H(I_{CT})$

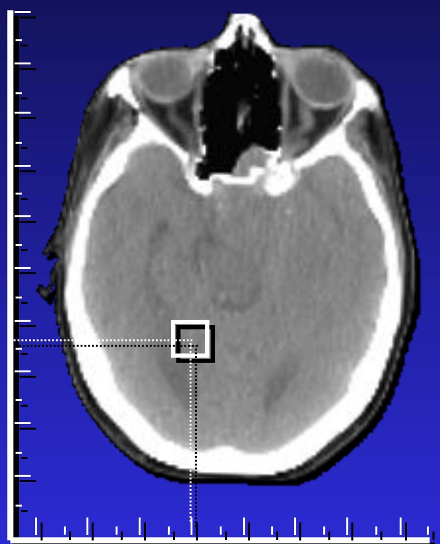


$H(I_{MRI\text{-}CT})$

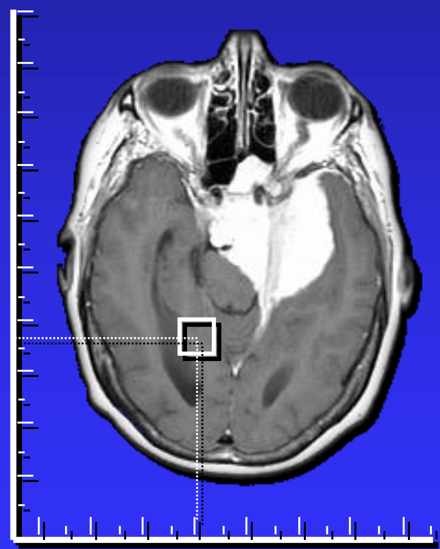
Marc Kessler / UM

Mutual Information

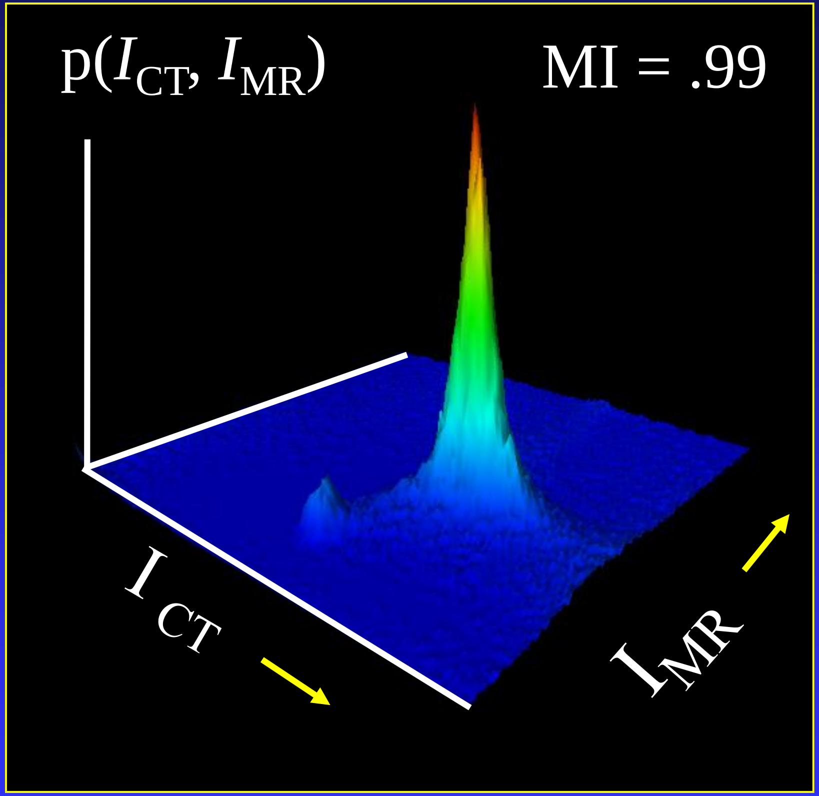
Aligned!



reformatted CT



original MR

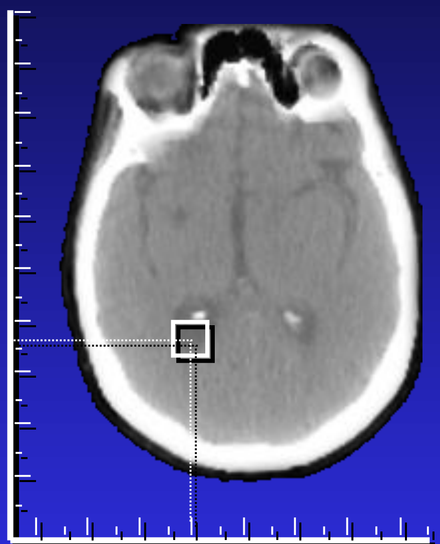


2D joint intensity histogram

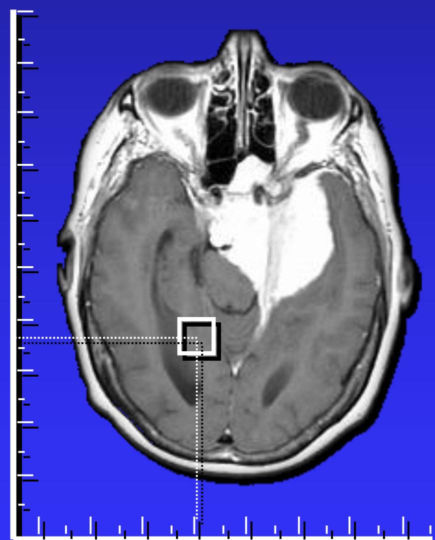
Marc Kessler / UM

Mutual Information

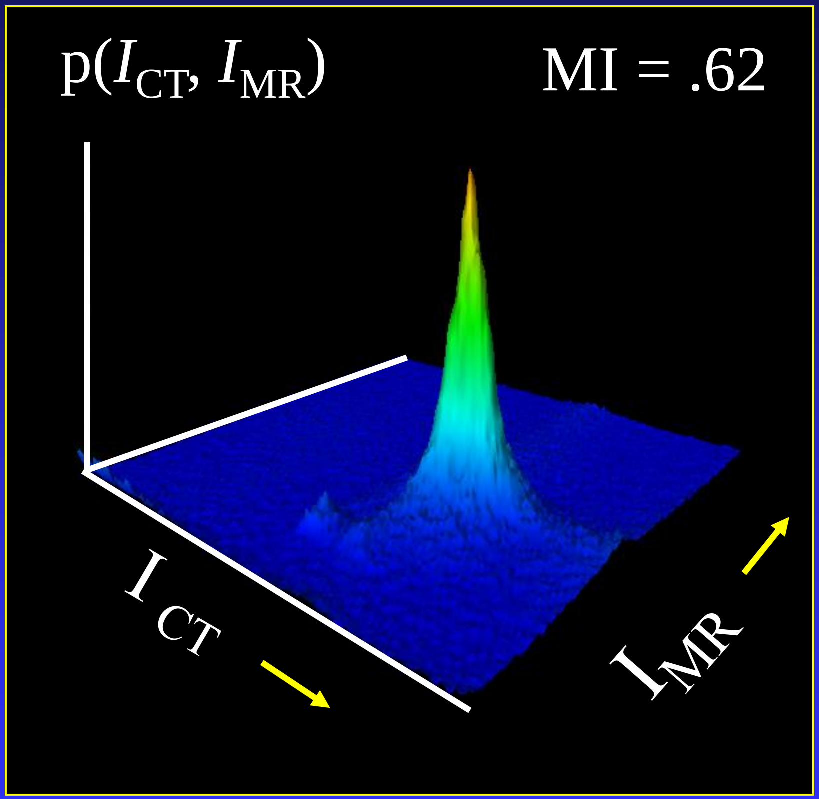
Not so Aligned!



reformatted CT



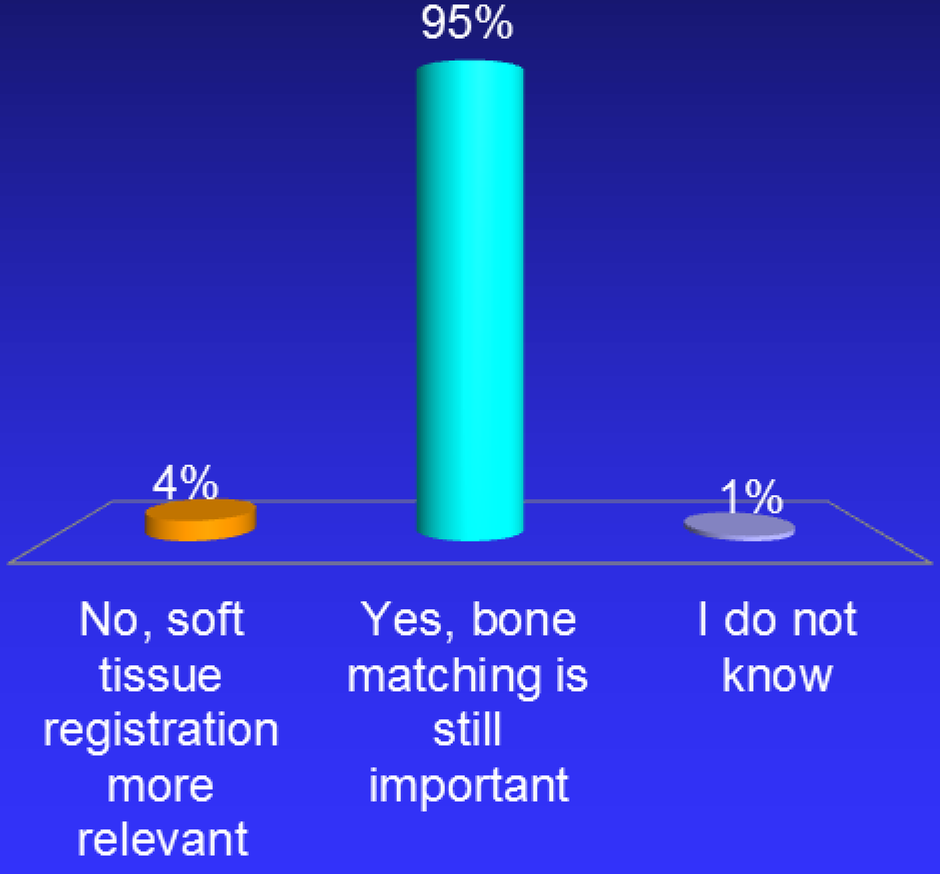
original MR



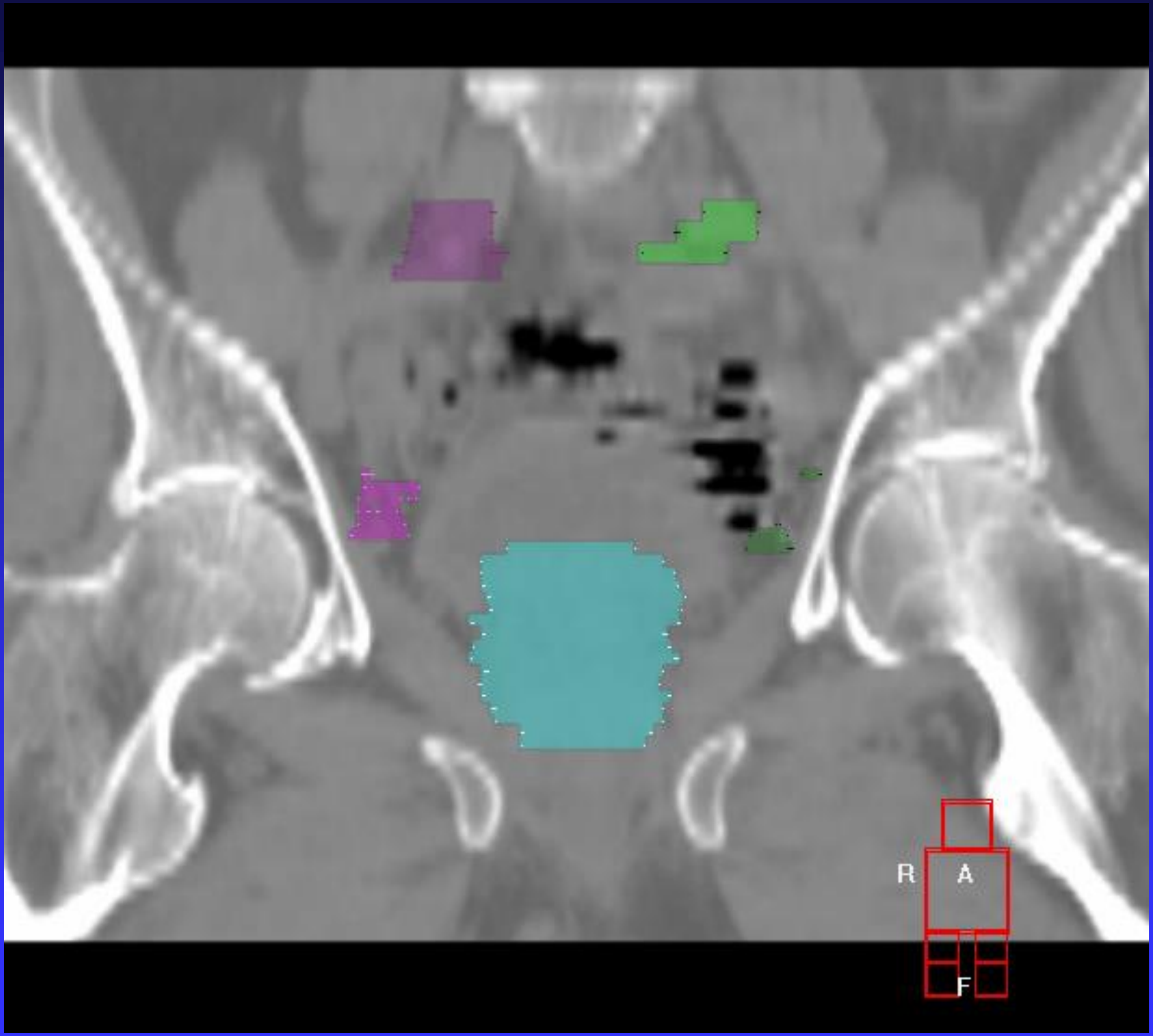
2D joint intensity histogram

Computers are so fast that soft tissue registration is no longer slower – is there still and application for bone matching?

A. No, soft tissue registration more relevant
B. Yes, bone matching is still important
C. I do not know

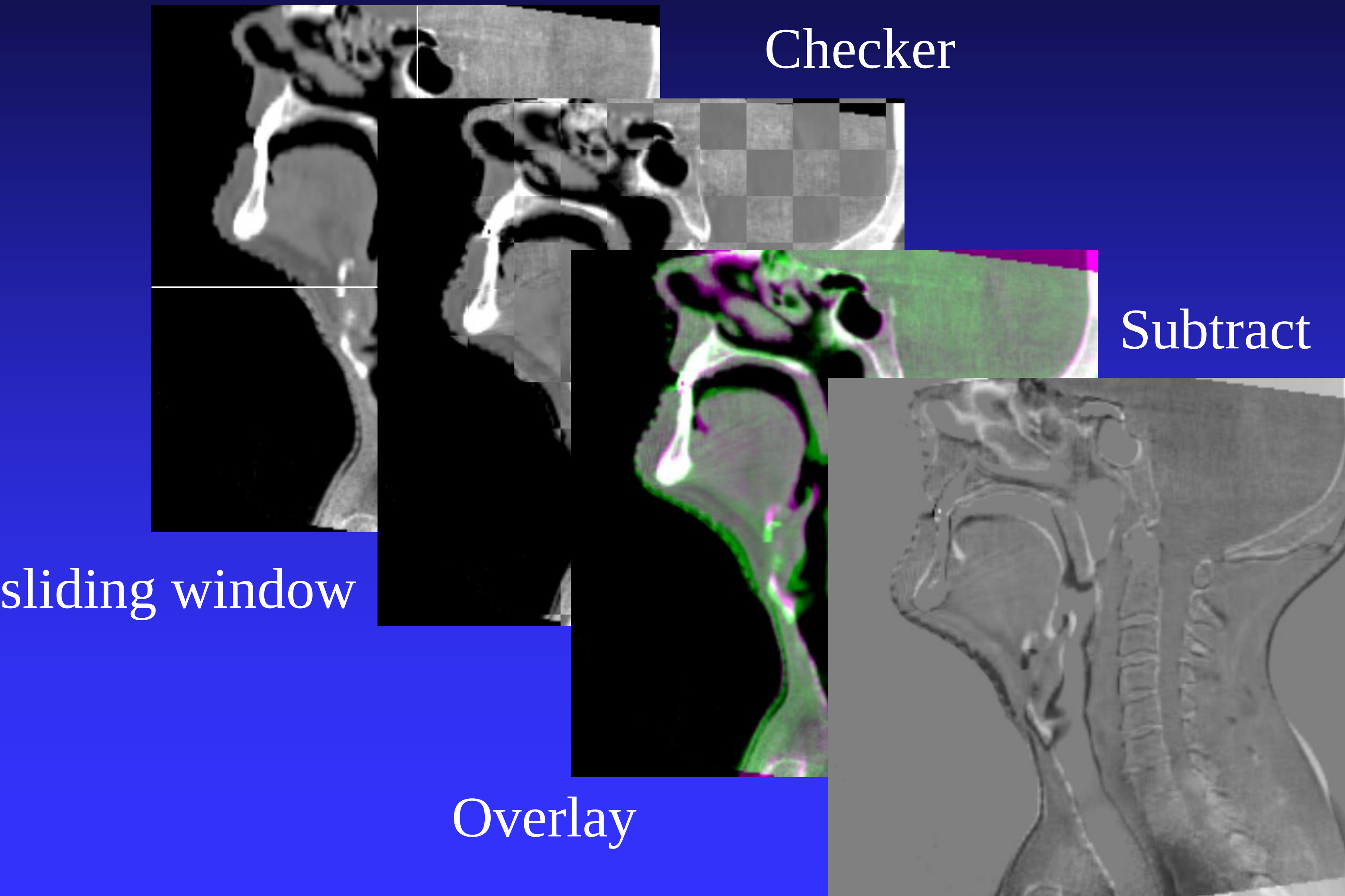


Bone is a valid surrogate for LN

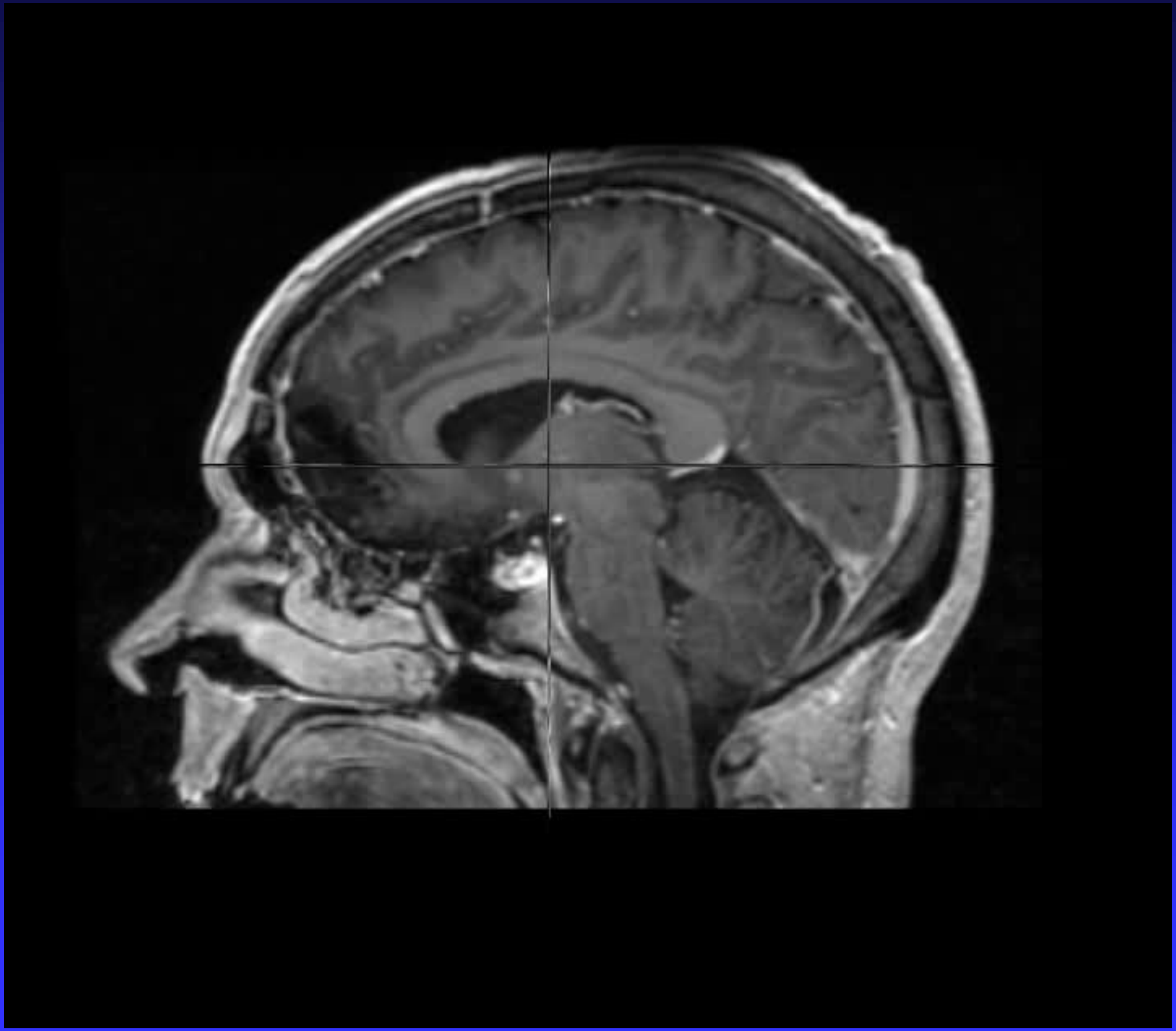


Registration is poorly defined when there are large deformations

Visual verification

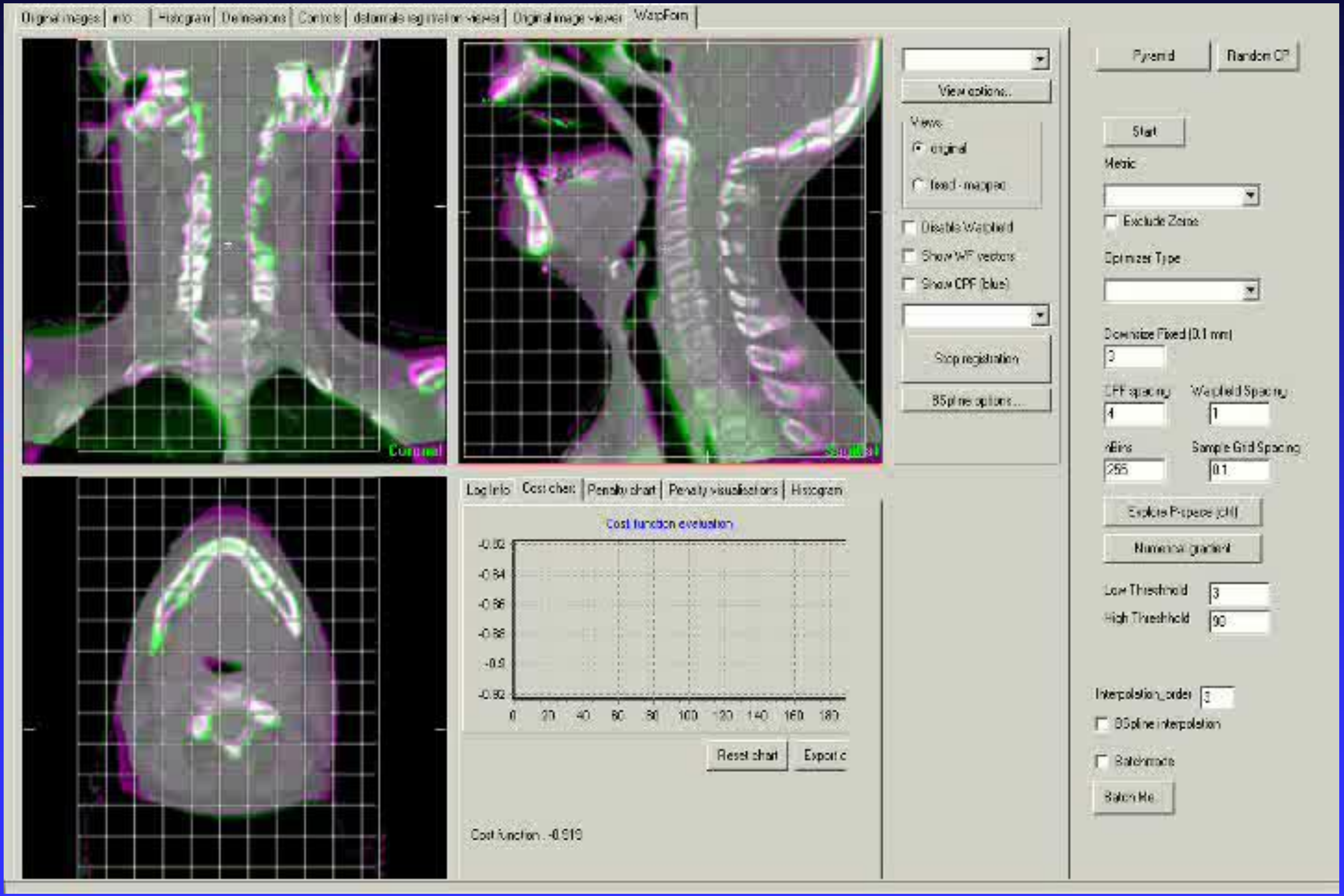


The power of 4D animation



Simon van Kranen/ NKI

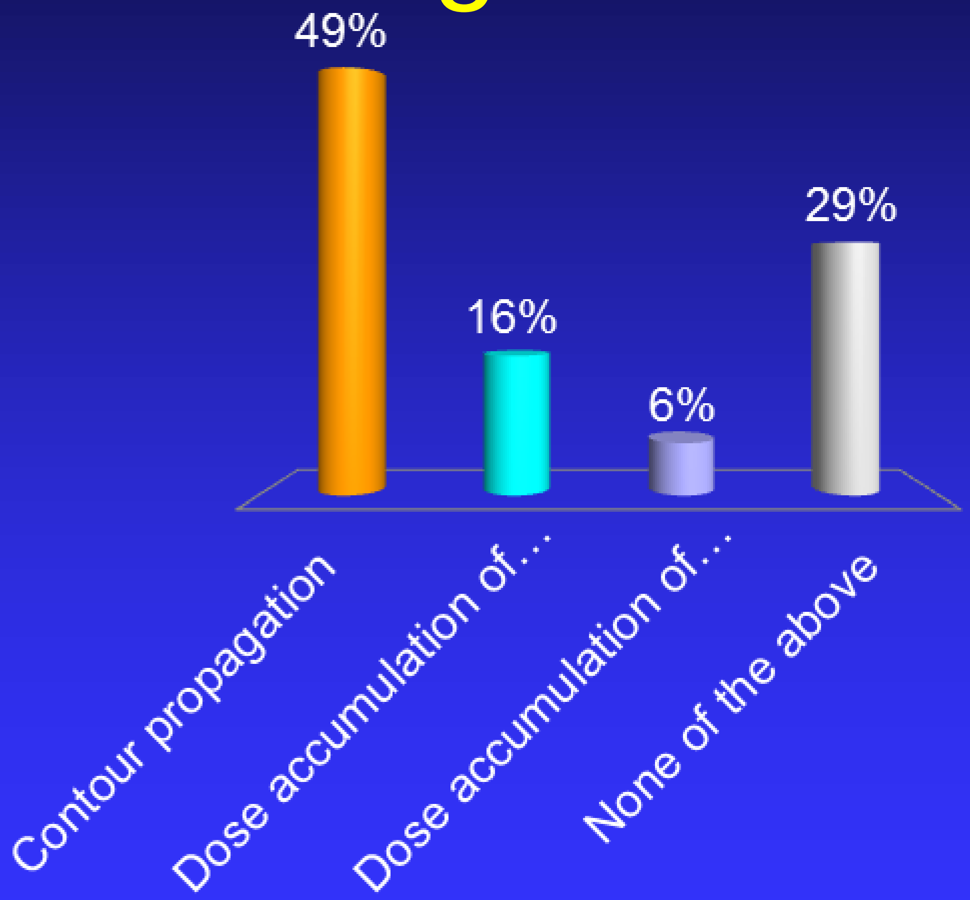
Deformable Registration Movie



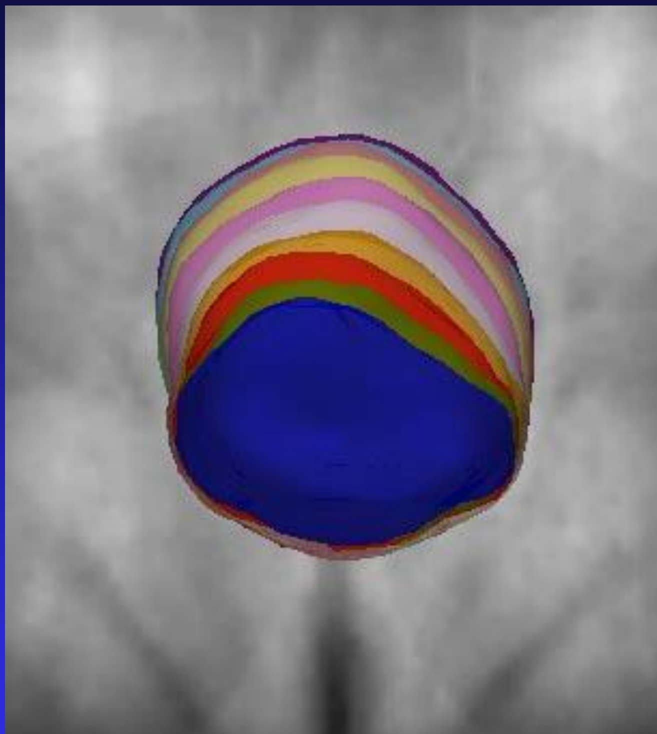
Deformable image registration is considered a cornerstone of 4D and adaptive RT

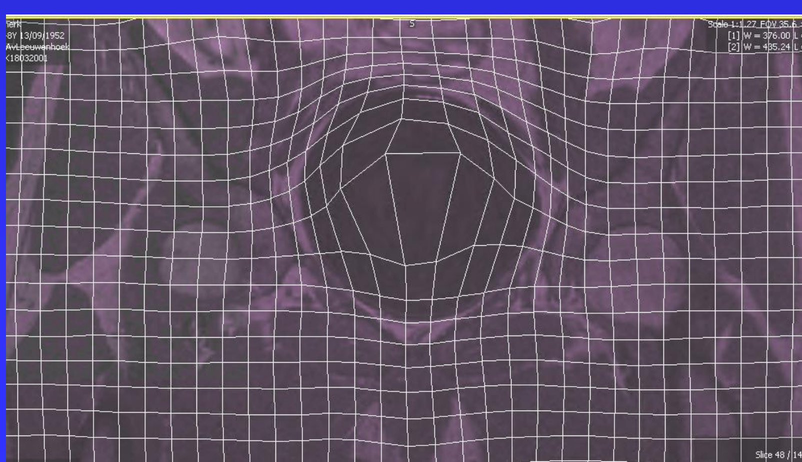
What applications of deformable registration are safe in a clinical setting?...

A. Contour propagation
B. Dose accumulation of OAR
C. Dose accumulation of shrinking tumors
D. None of the above



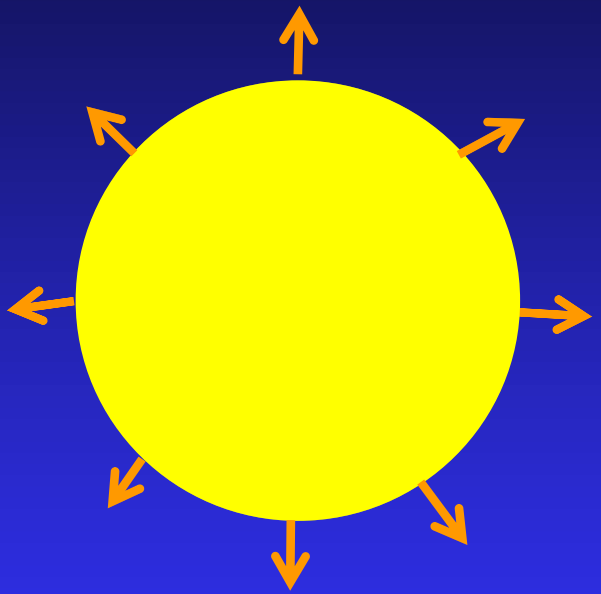
Easy deformable registration of the bladder?

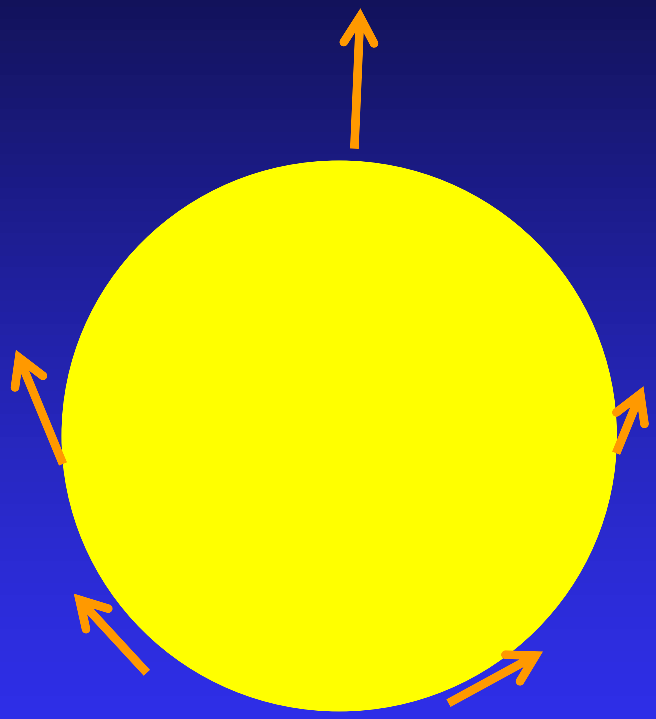


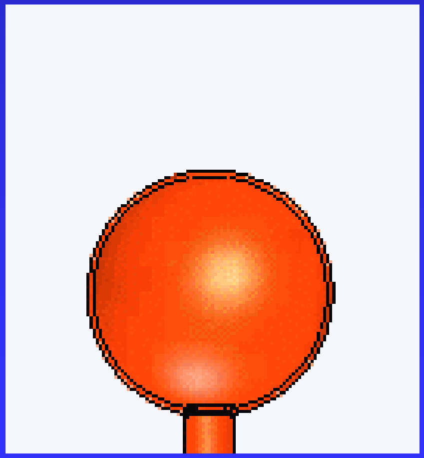


Very high contrast but does software 'understand' the anatomy ?

The bladder is a balloon in a box with stuff – it expands isotropic constrained by the organs around it







You get the contours right, but not the tissue cells → danger for dose accumulation

Landmark validation of contour-based bladder registration

Control over structure-specific flexibility improves anatomical accuracy for point-based deformable registration in bladder cancer radiotherapy

S. Wognum, L. Bondar, A. G. Zolnay, X. Chai, M. C. C. M. Hulshof, M. S. Hoogeman, and A. Bel

Citation: Medical Physics **40**, 021702 (2013); doi: 10.1118/1.4773040

View onl

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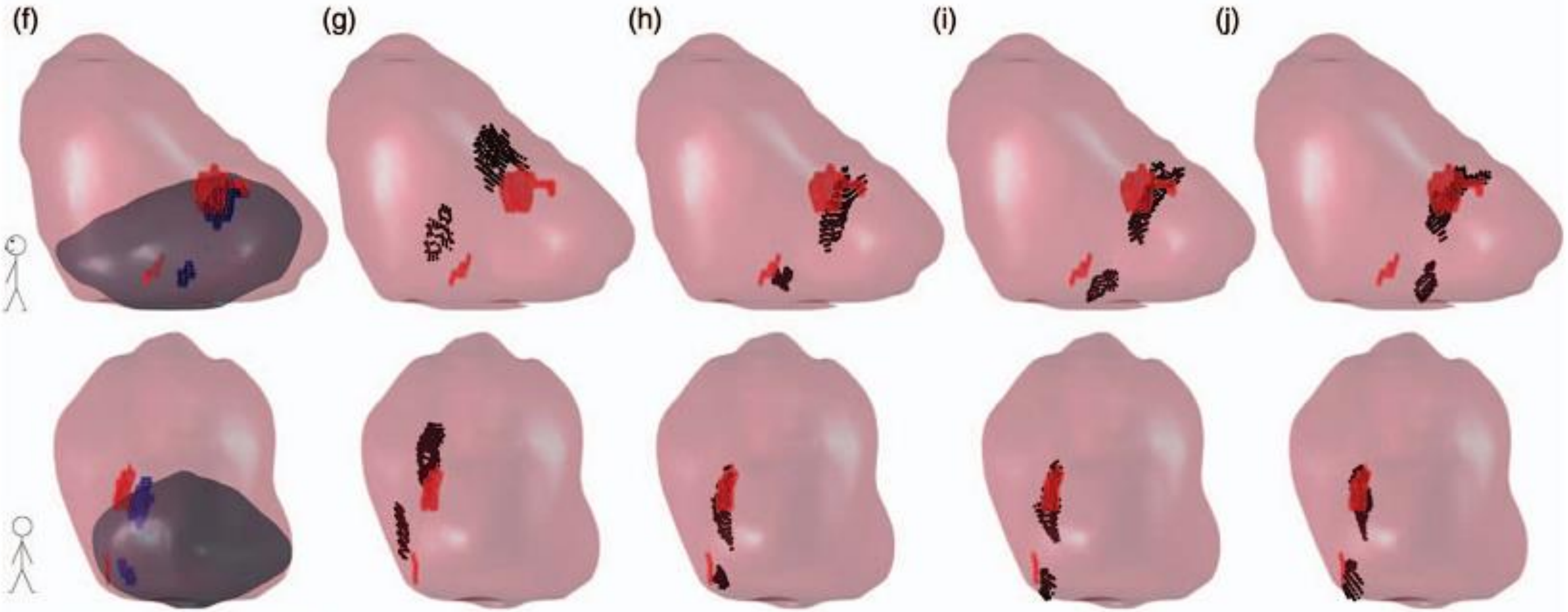
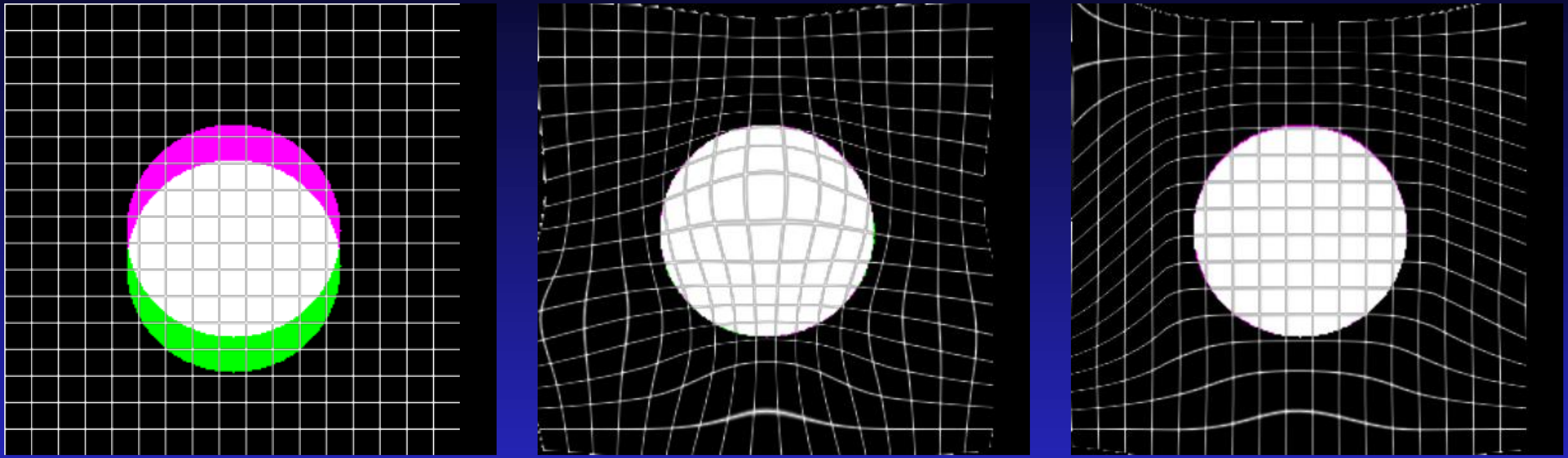


RDE lipiodol (mm)

1	5.9	6.4	3.6	3.1	2.2
2	11.8	8.9	4.0	8.6	14.1

Deformable registration classes

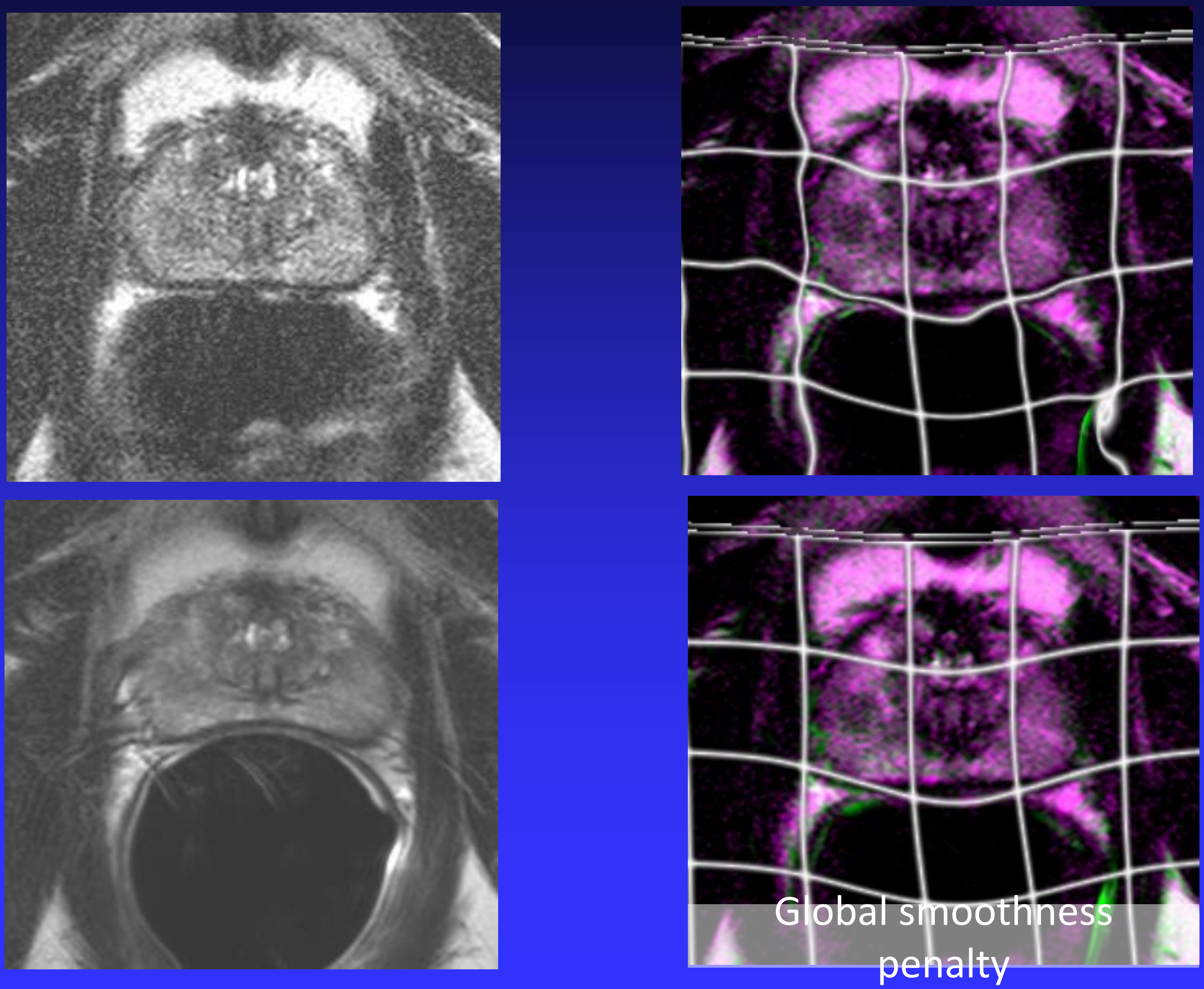


Different DVF provide same visual registration result

- Descriptive: it must look good
  - e.g. contour propagation
- Quantitative: it must be an anatomically correct, also inside homogeneous organ
  - e.g. dose accumulation

You can morph anything to anything but do you add information?

Prostate MRI w/wo Endo Rectal Coil

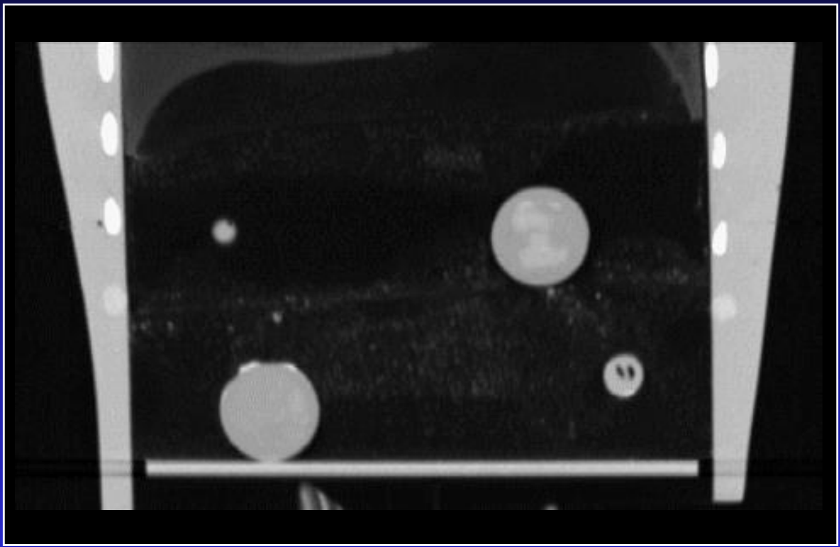


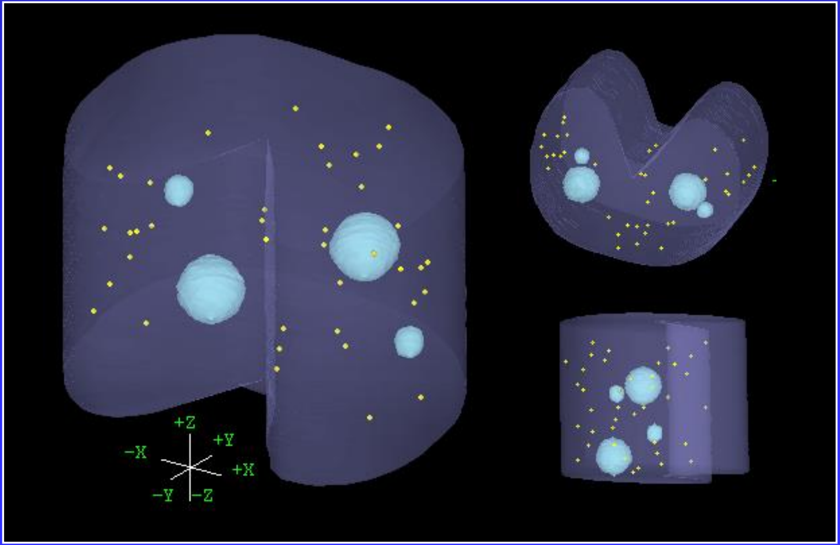
Validation

QA methods

- The algorithm works technically
  - Use phantom or simulated data
- The program works in general
  - Best: use patients with implanted markers (data scarce)
  - Second: compare with human observers
- The program works for this patient
  - Visual verification
  - Consistency, plausibility

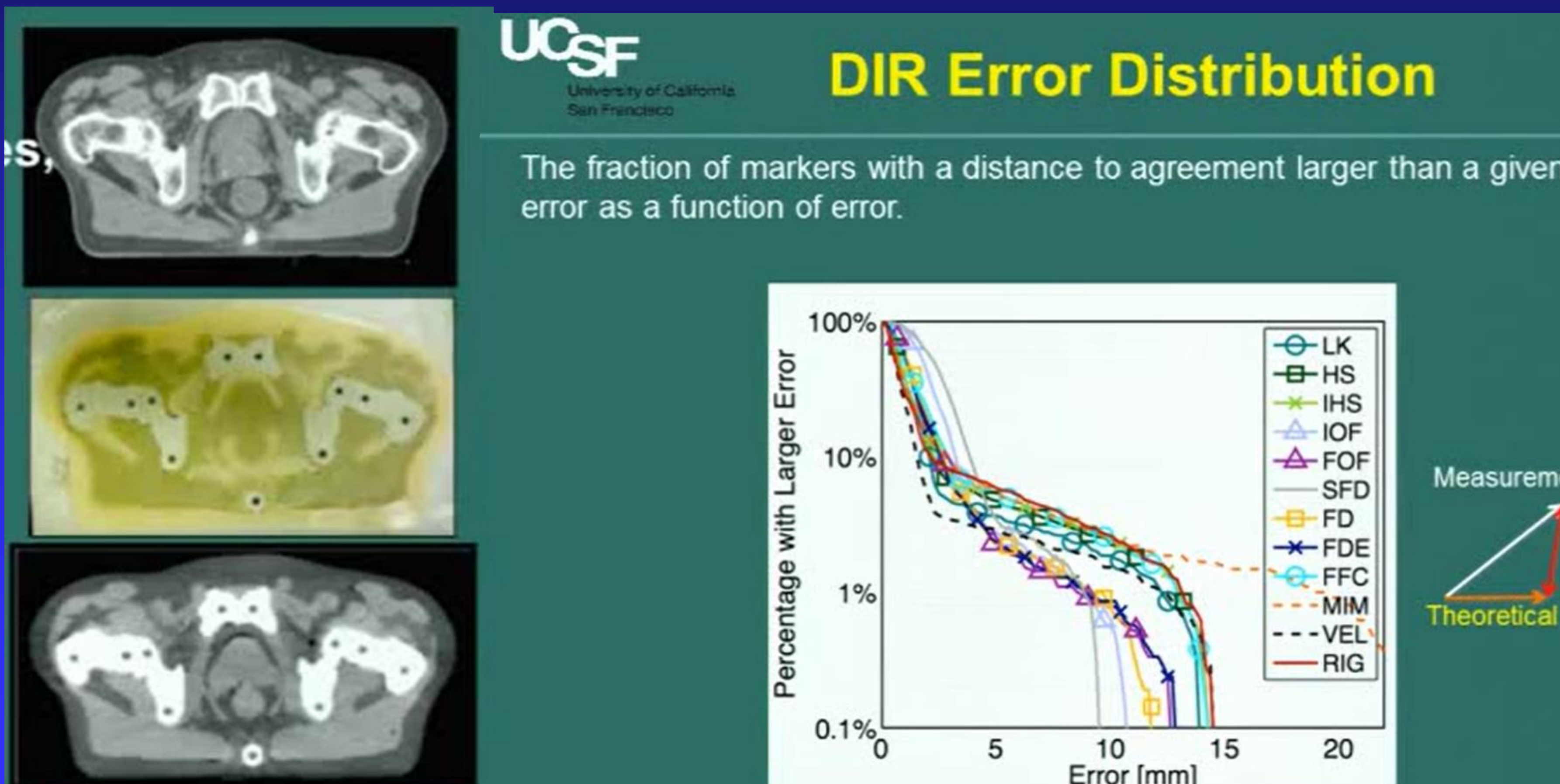
4D Phantoms





		RL[a] (cm)	AP[b] (cm)	SI[c] (cm)	3-D distance (cm)
Affine	Average	−0.01	0.00	0.05	0.38
	Stdev[d]	0.04	0.04	0.44	0.22
	Max[e]	−0.12	−0.13	0.90	0.90
B-splines	Average	−0.02	−0.01	0.05	0.18
	Stdev[d]	0.08	0.06	0.22	0.16
	Max[e]	−0.42	0.19	0.67	0.81
Thin-plate splines	Average	−0.07	−0.15	−0.14	0.37
	Stdev[d]	0.12	0.19	0.28	0.19
	Max[e]	−0.56	−0.58	−0.74	0.75

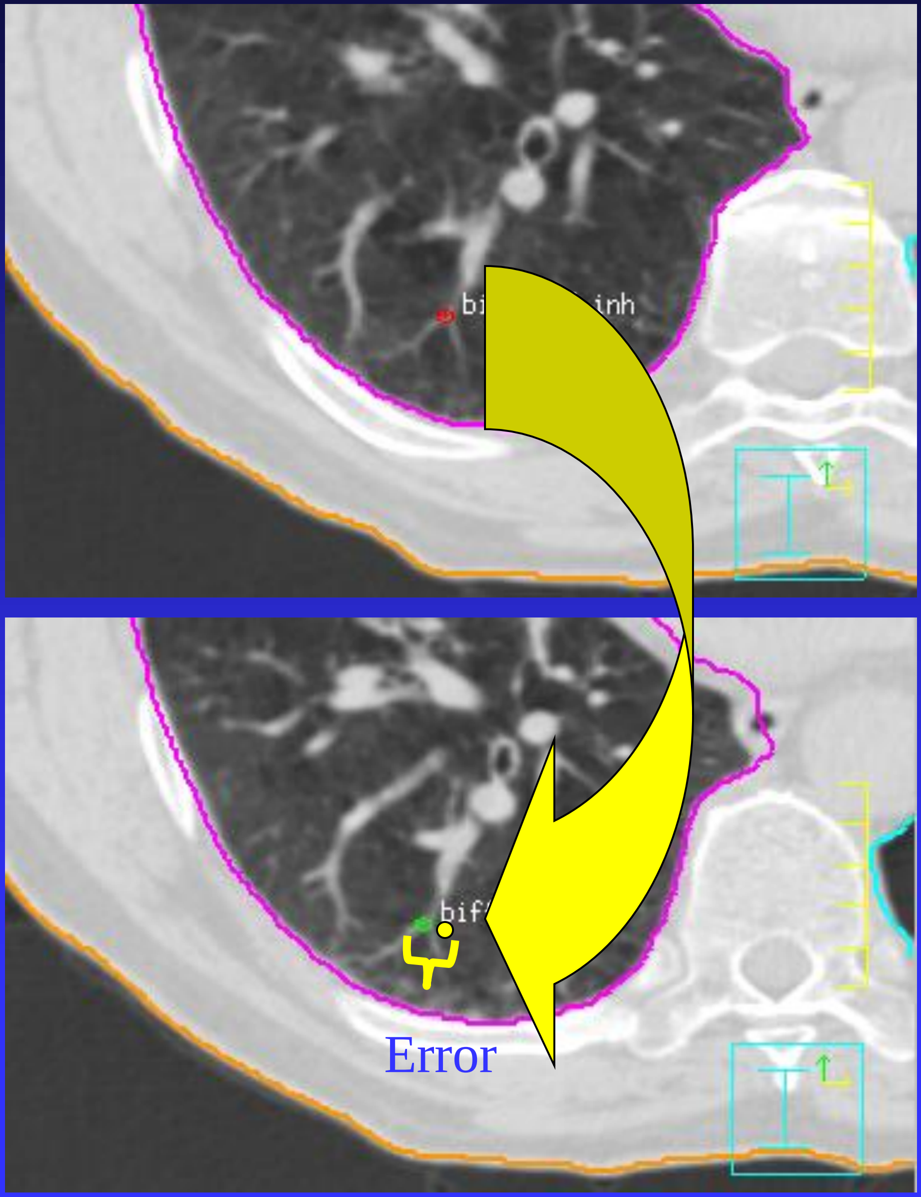
Registration of anatomically realistic phantom in pelvis



J Pouliot, UCSF

Kristy Brock / PMH

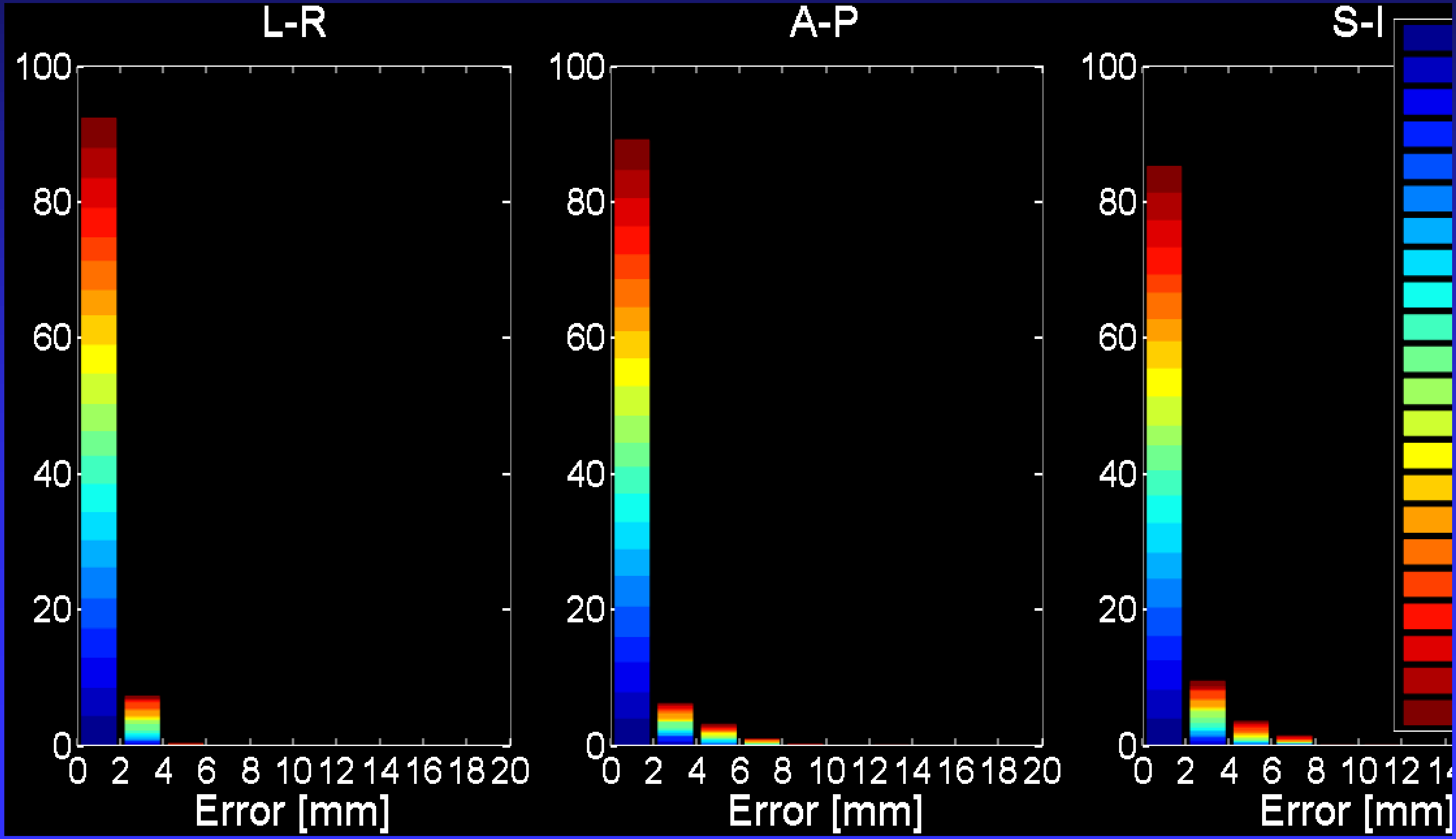
Natural Fiducials



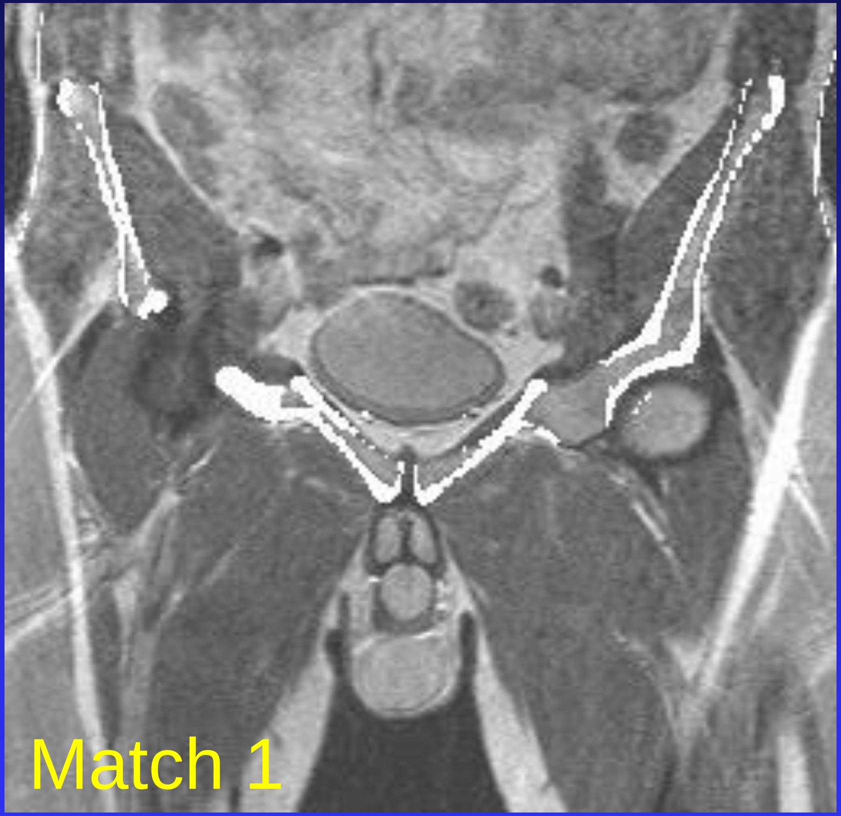
Kristy Brock / PMH

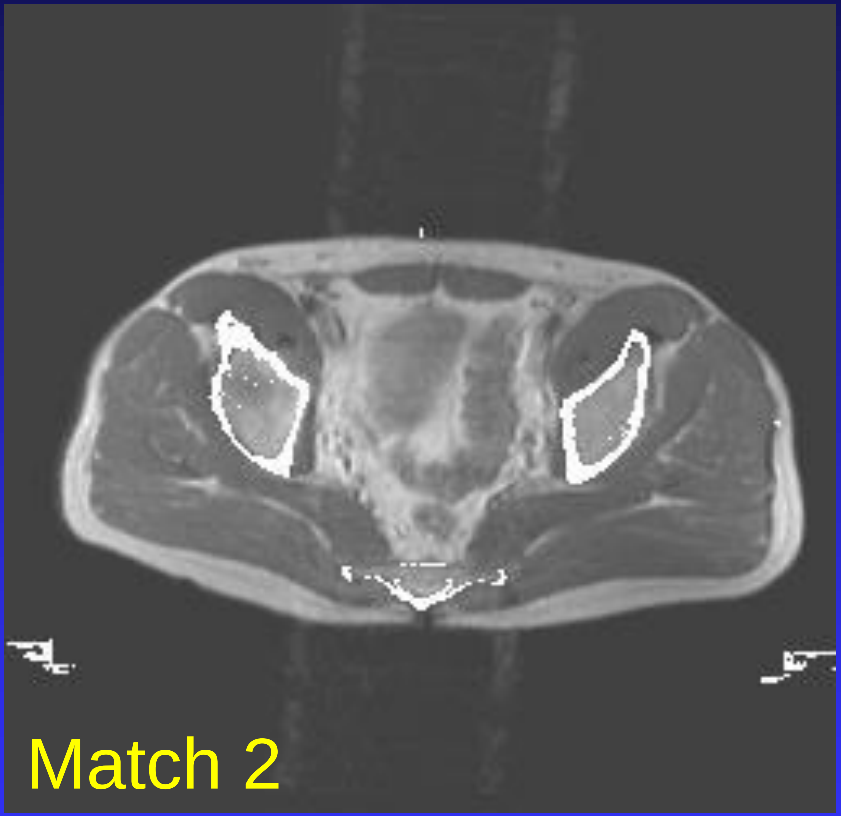
Results: Lung 4D CT (22)

% Bifurcation Points



Consistency check as QA tool

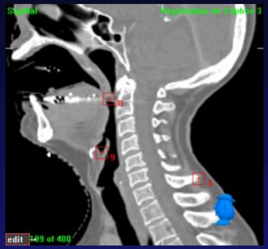




Deviation	Δ x (L-R)	Δ y (A-P)	Δ z (C-C)	Δ rx (L-R)	Δ ry (A-P)	Δ rz (C-C)
between match 1 and 2	-0.5 mm	2.0 mm	-1.6 mm	-0.9 dg	-0.8 dg	-0.7 dg

Van Herk et al, 1998

Analysis of variance



O_1  O_2  O_3 

Analysis of variance

Accuracy of the observers O_1, O_2, O_3

O_1 : First human observer

O_2 : Second human observer

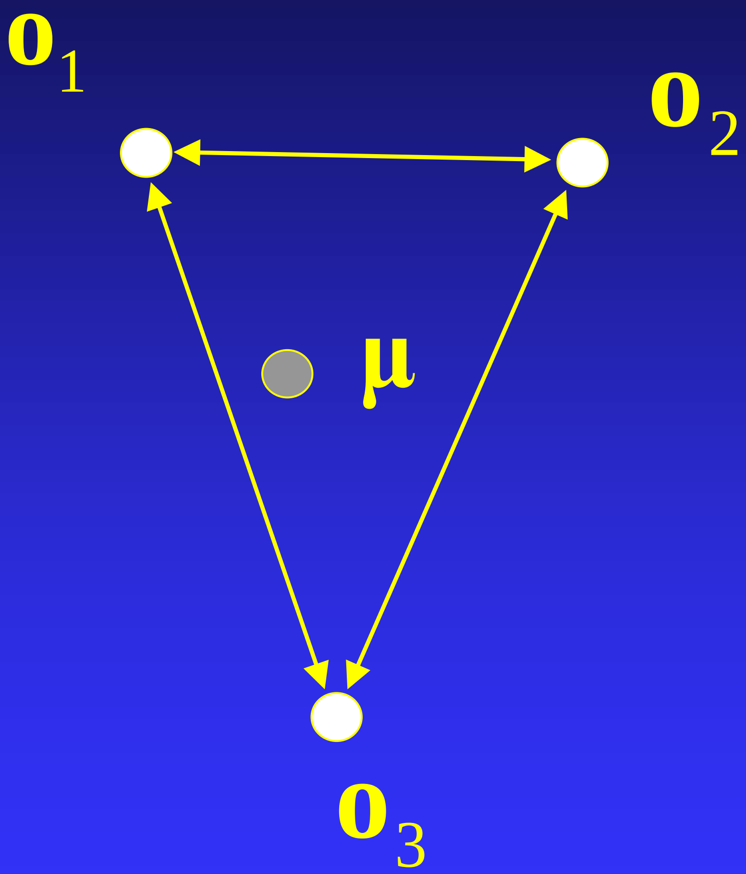
O_3 : Registration method

Analysis of variance

$$\sigma_1^2 = (\sigma_{2-1}^2 + \sigma_{3-1}^2 - \sigma^2_{3-2})/2$$

$$\sigma_2^2 = (\sigma_{3-2}^2 + \sigma_{2-1}^2 - \sigma^2_{3-1})/2$$

$$\sigma_3^2 = (\sigma_{3-1}^2 + \sigma_{3-2}^2 - \sigma^2_{2-1})/2$$

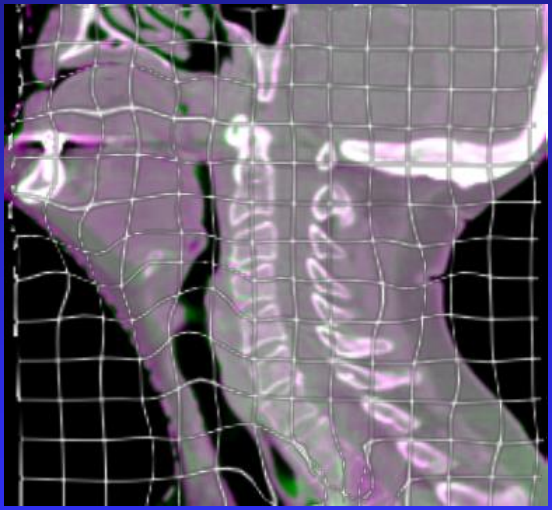


Analysis of variance

- Landmark validation
- 7 patients, 7 - 8 fractions
- 23 landmarks per CBCT, two human observers
- B-spline deformable registration for landmark propagation
- Use of ANOVA method to correct for observer variation

Results

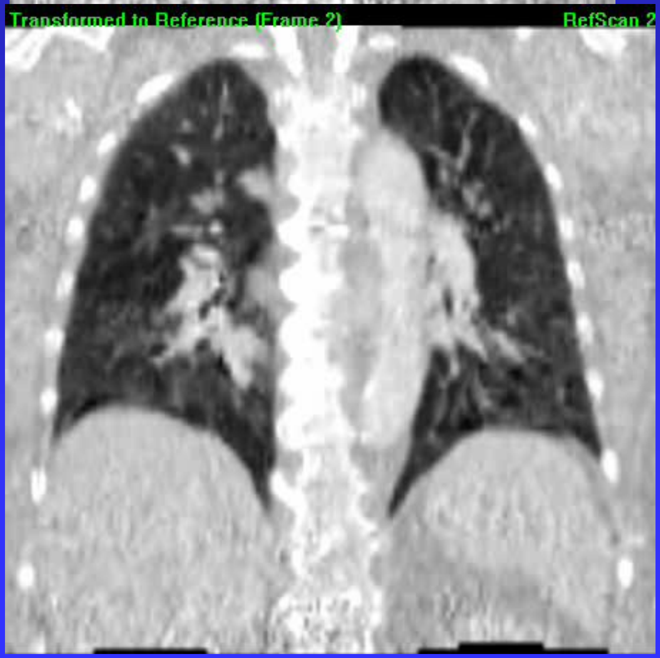
Method	Accuracy (1SD mm)		
	SD_{LR}	SD_{CC}	SD_{AP}
Rigid registration	**1.8**	**2.0**	**1.7**
B-spline *No penalties*	**1.4**	**1.5**	**1.1**
B-spline + *penalties*	**0.9**	**1.0**	**0.9**



Mencarelli et al, Med Phys 2012

Applications

Image Enhancement

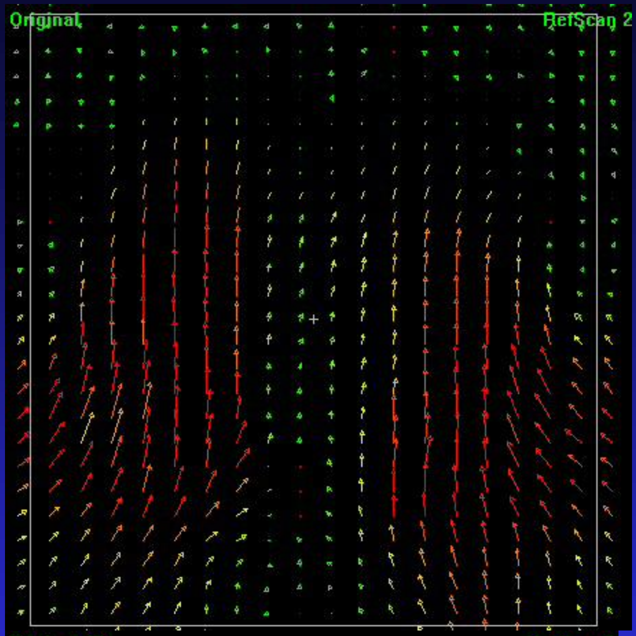


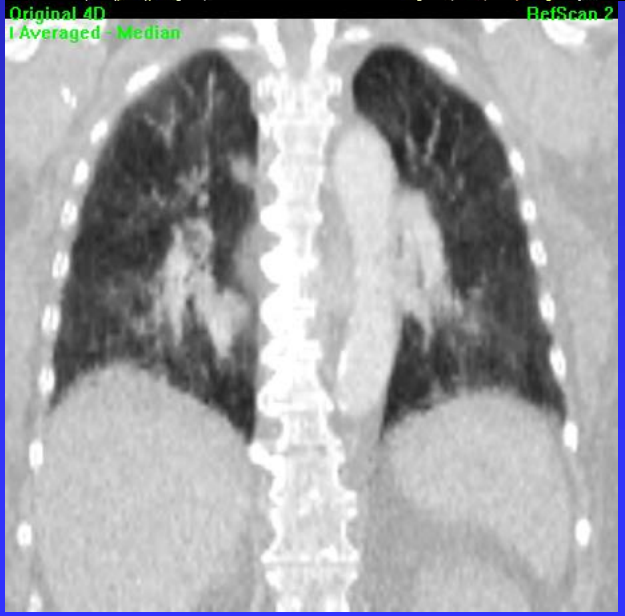
4DCT → Full 3D DVF

Motion corrected 4DCT @ mean pos.

Average frames

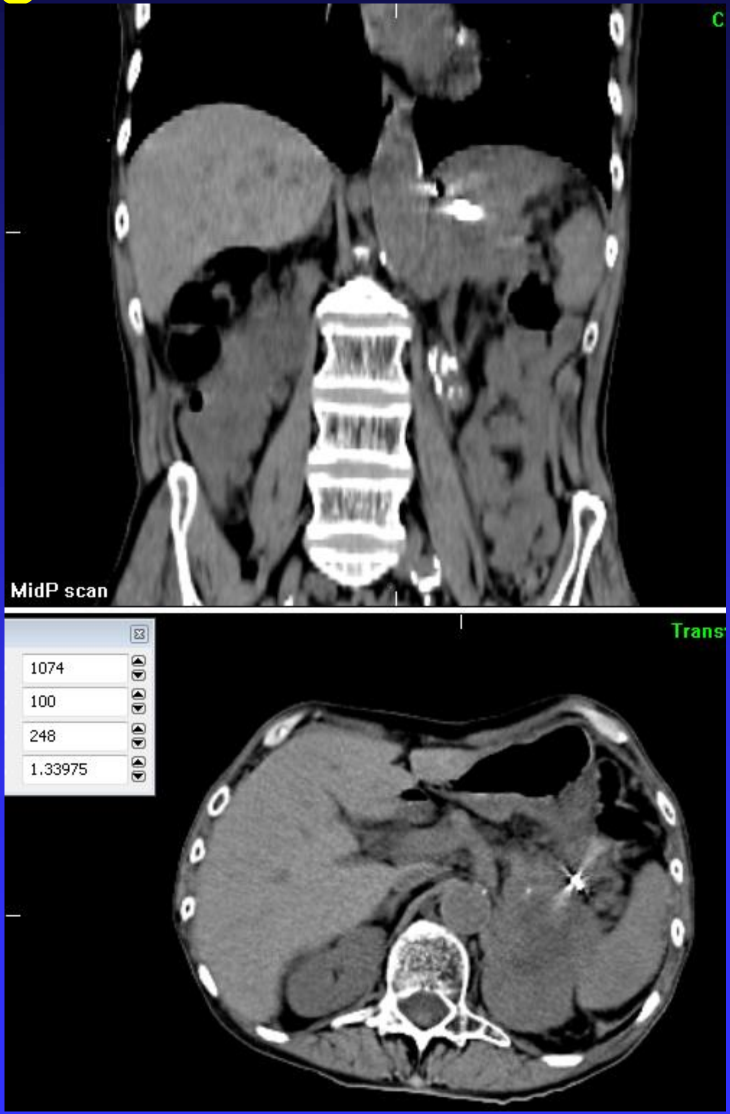
Mid-position CT





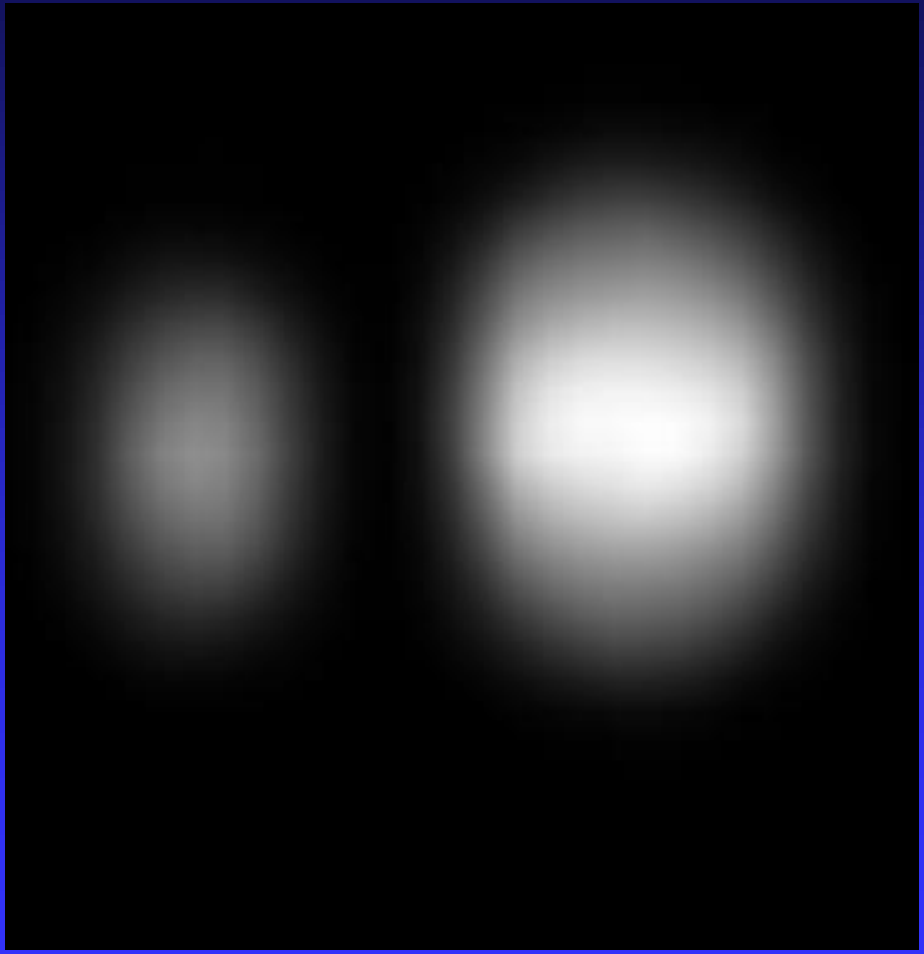
Mid-ventilation method versus mid-position reconstruction (motion compensated 4DCT) using deformable registration

Mid-ventilation (one bin)

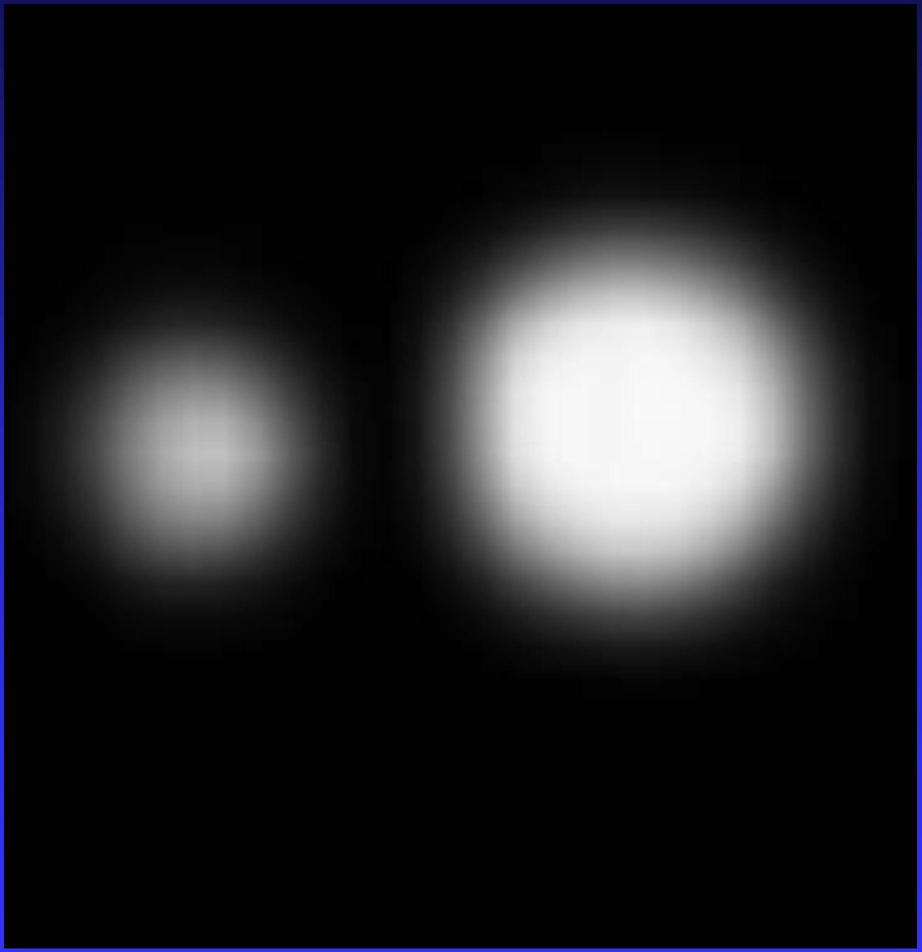


Median of all bins deformed pixel by pixel to mid-position

PET-CT motion compensation

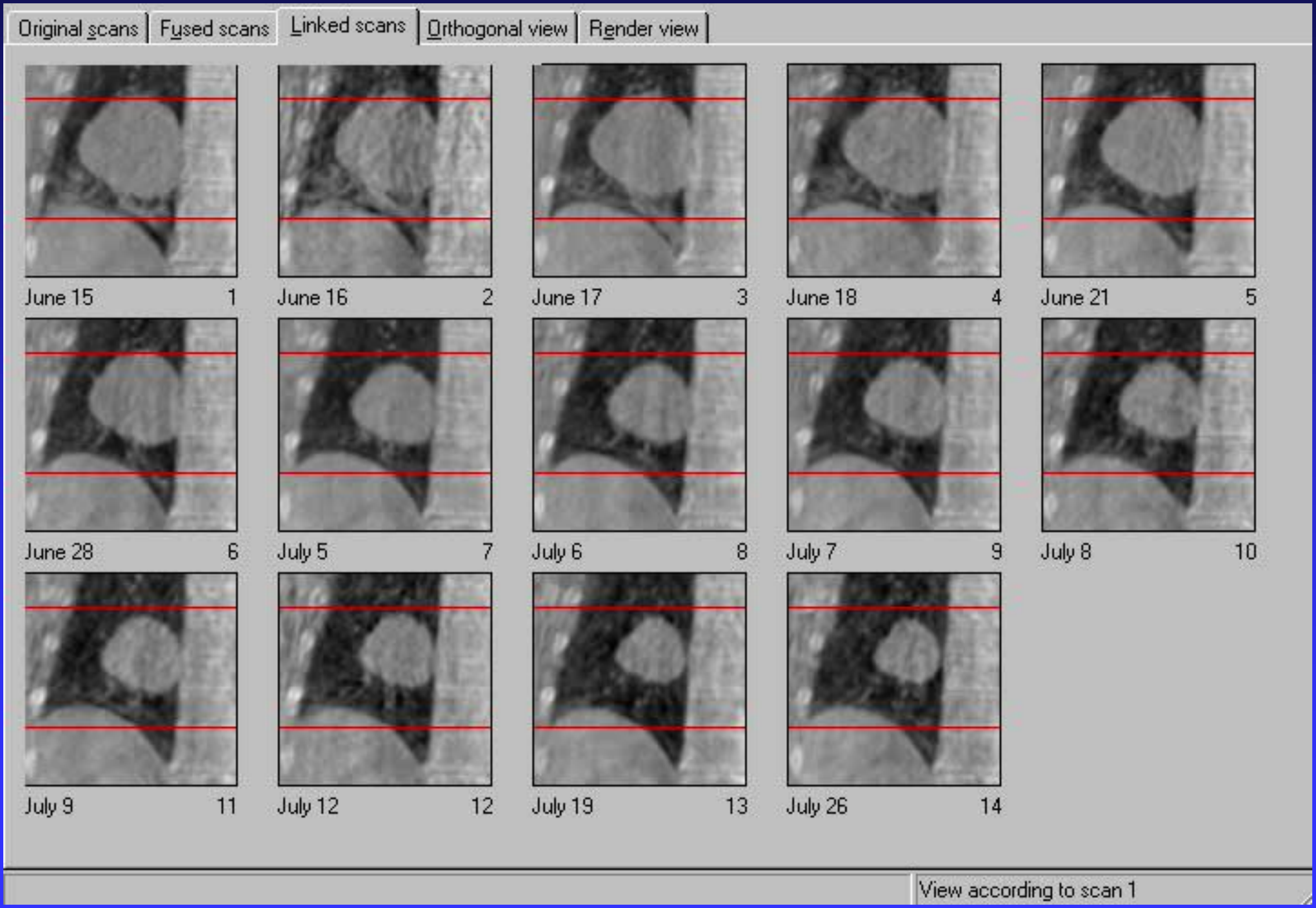


2.5 cm motion

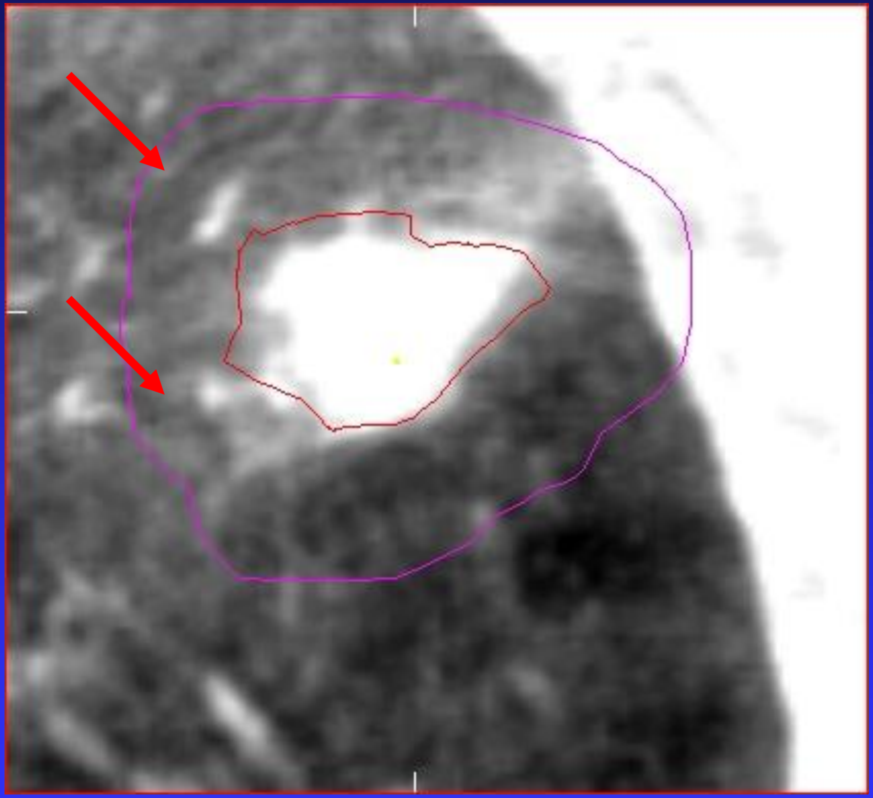


Compensated

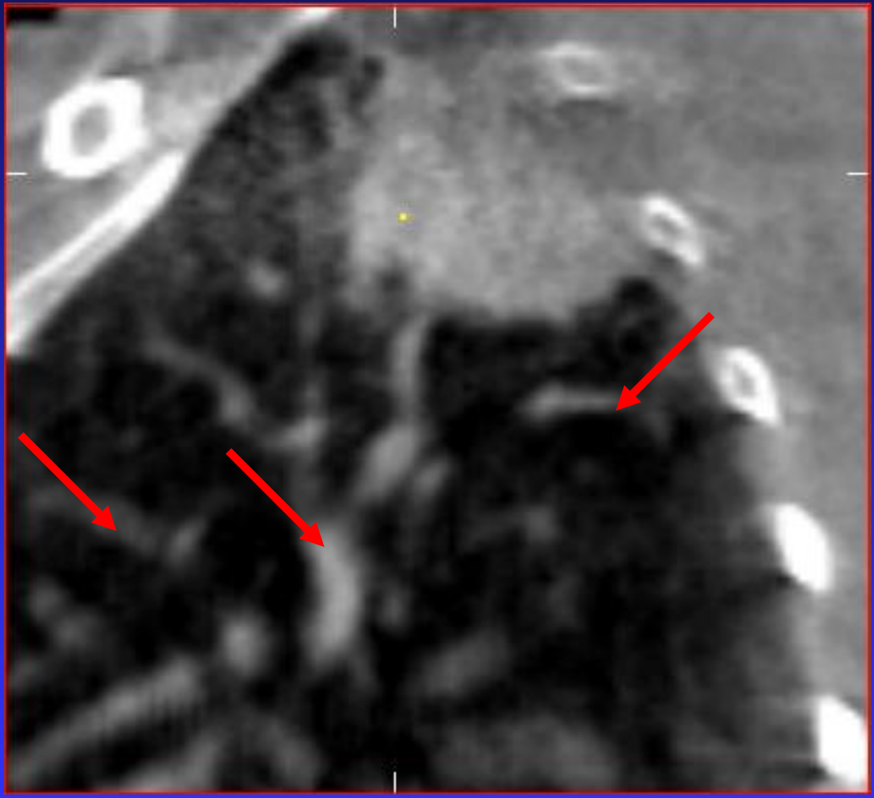
Repetitive 4D CT: treatment response



Modes of Tumor Regression

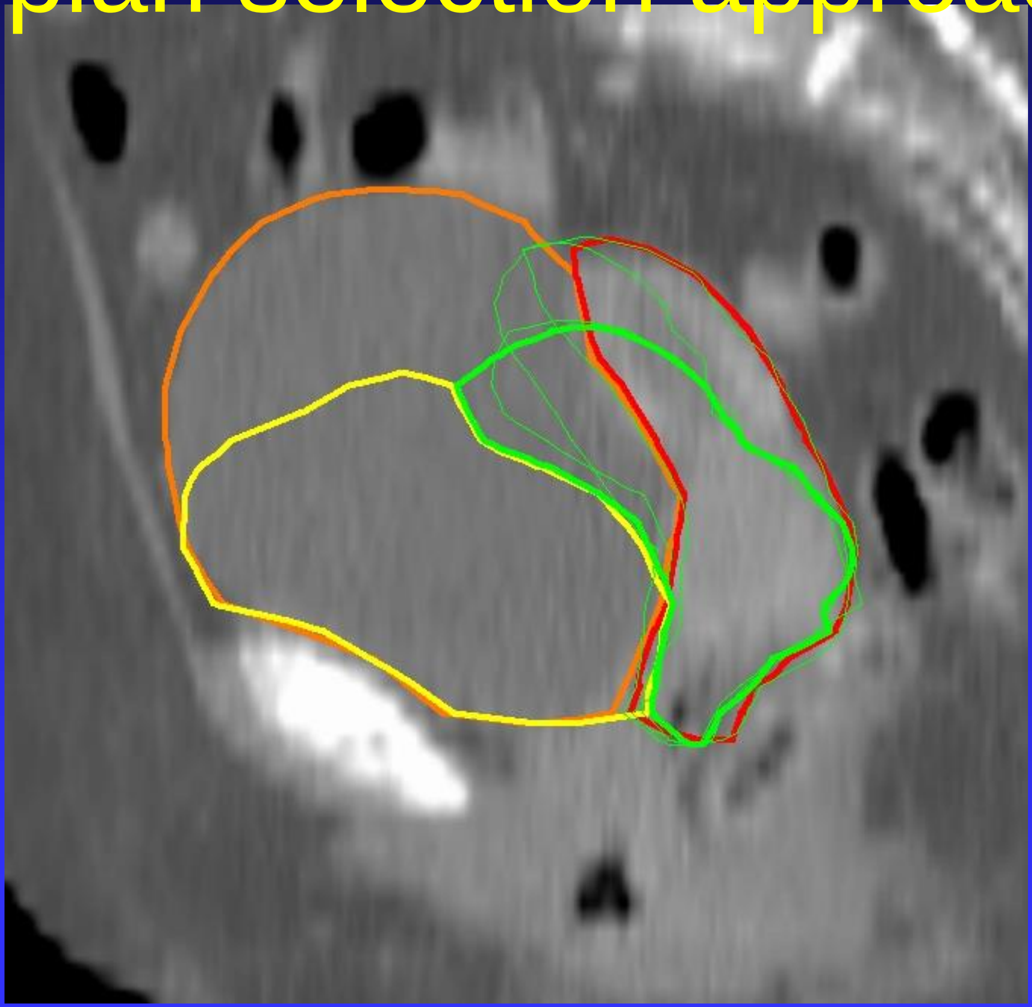


'elastic'

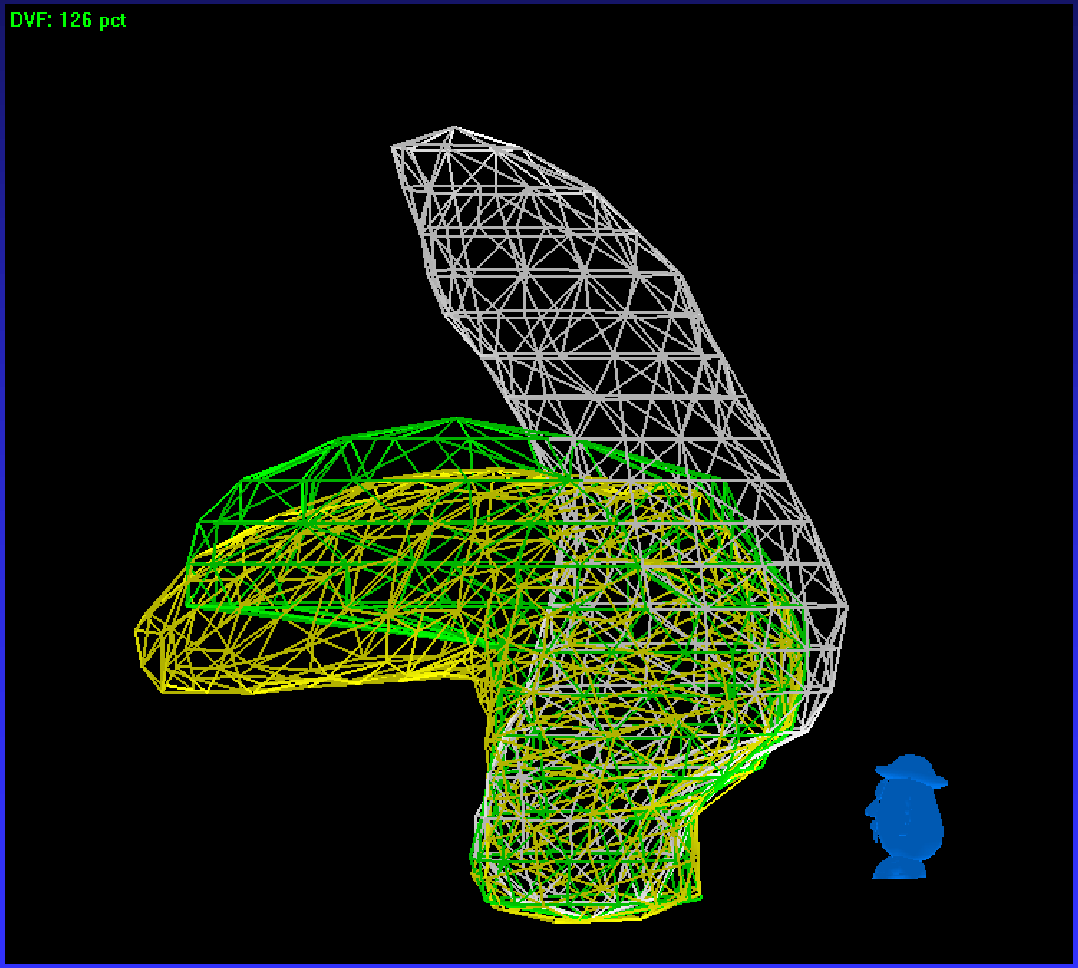


'erosion'

Generate intermediate contours for plan selection approaches



Interpolation of cervix motion



Data mining in lung, local dose correlated to survival?

Alive @ 12 months

Dead @ 12 months

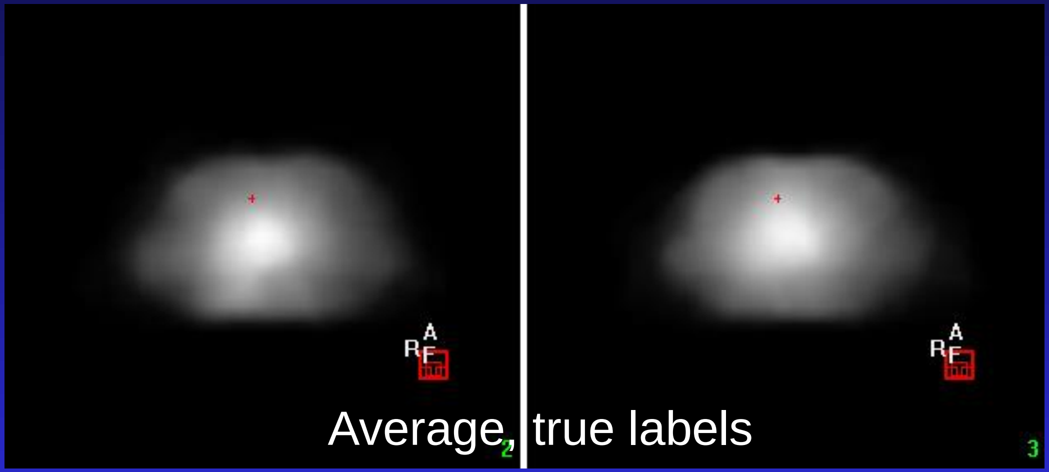
Registered CT

Average

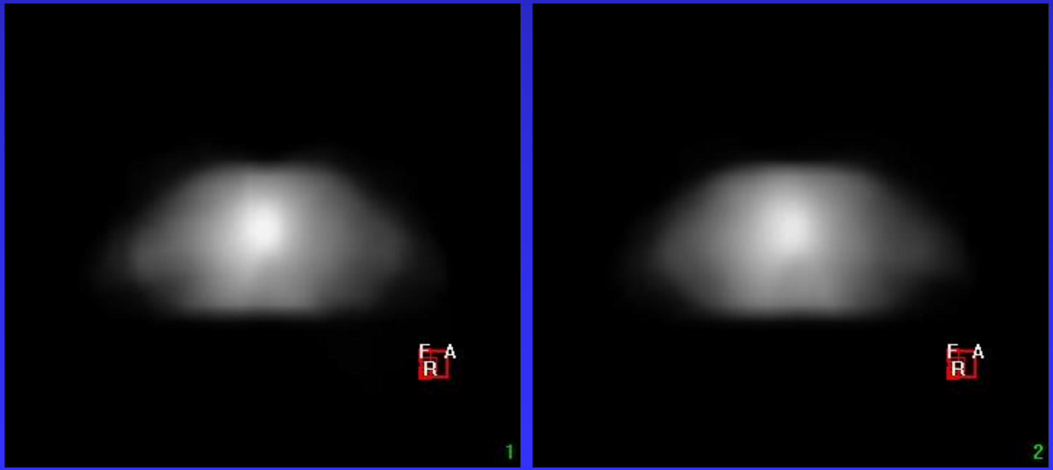
Difference

Permutation testing (minutes)

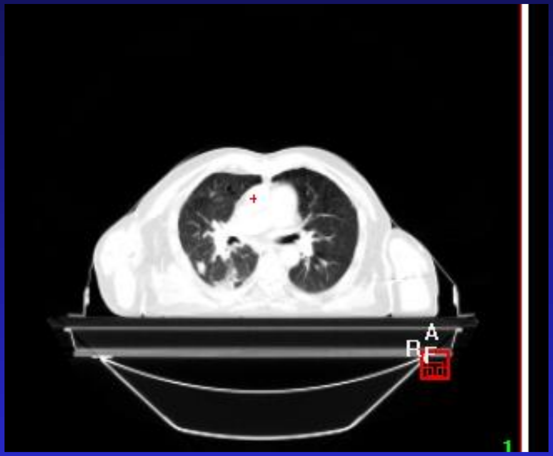
Alive Dead

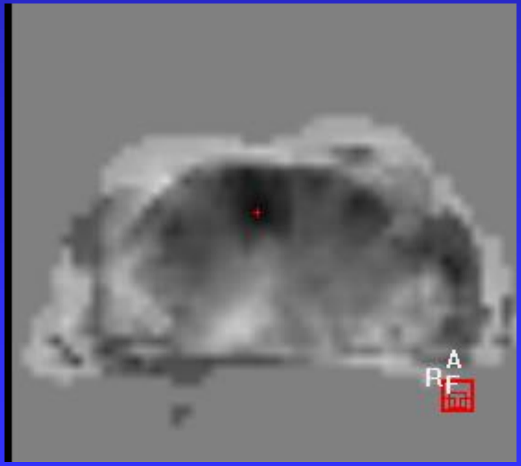


Average, true labels



Average, random labels



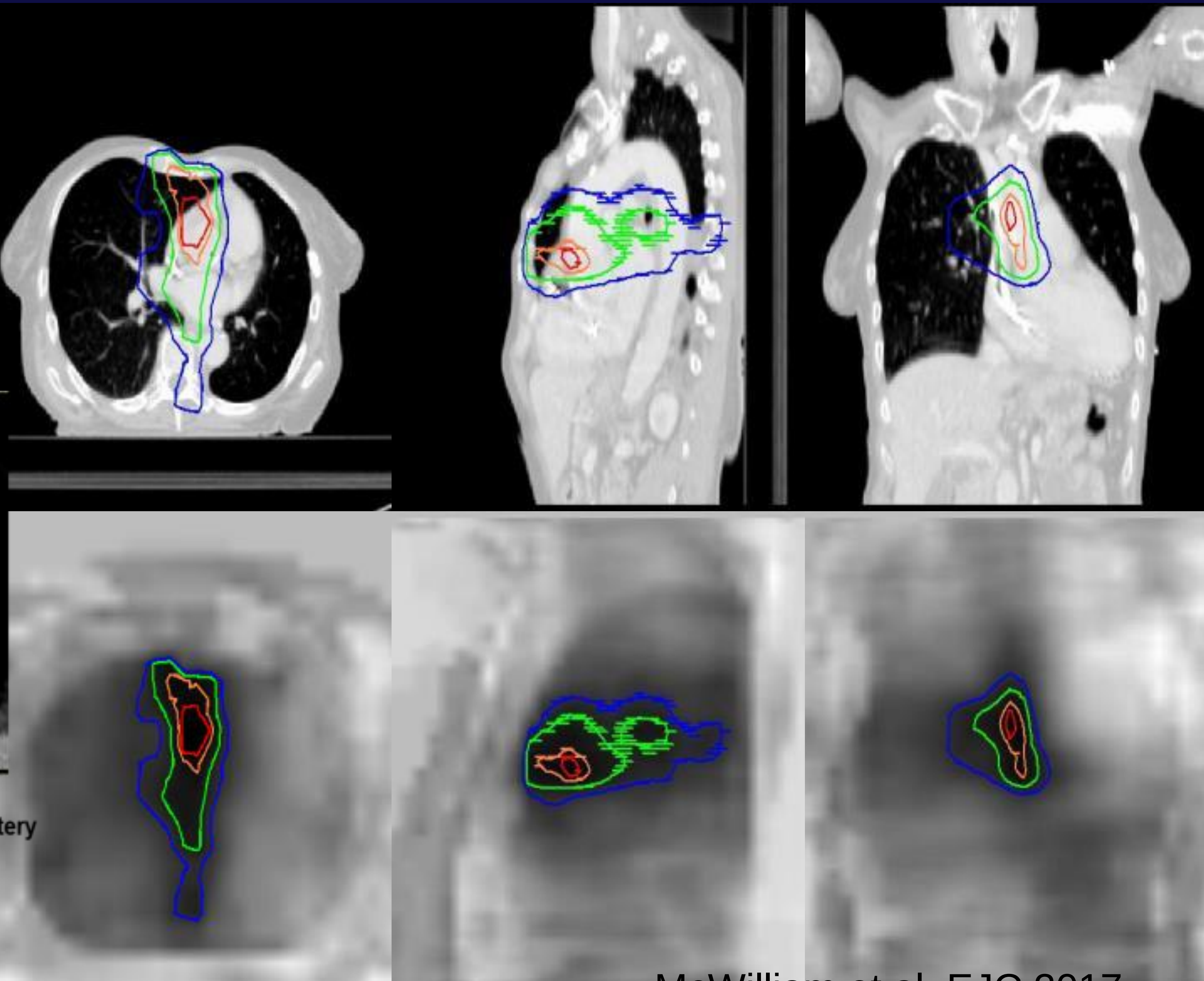


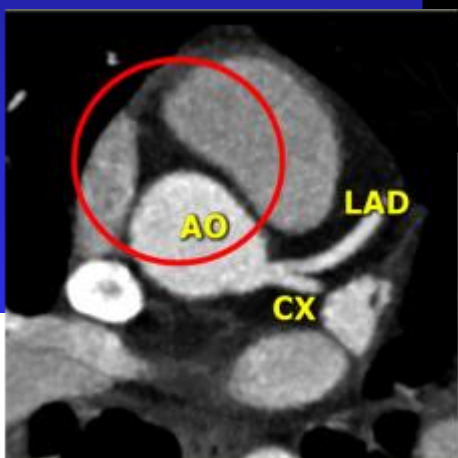
Chen, Witte, van Herk 2013
McWilliam, ASTRO 2016

Significance– dose difference @ 12 months

t - statistics

- ---- -5.7
- ---- -5.5
- ---- -5.0
- ---- -4.5



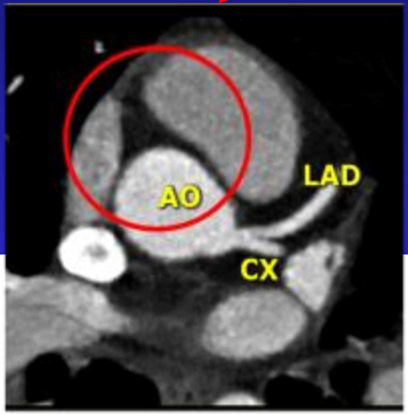


AO = Aorta
LAD = Left-Anterior Descending artery
CX = Circumflex artery

McWilliam et al, EJC 2017

MANCHESTER 1824
The University of Manchester

Analysis



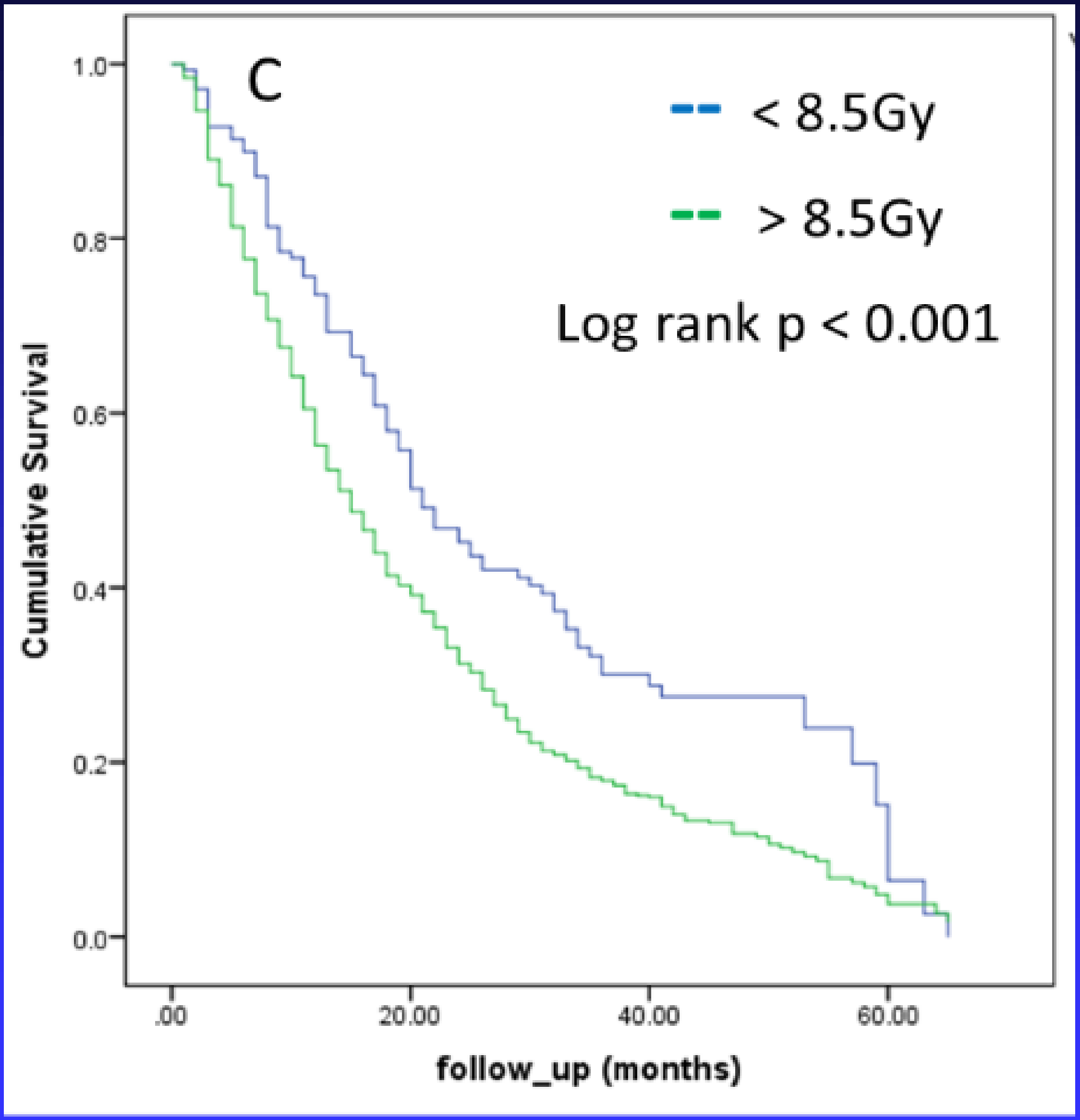
AO = Aorta
LAD = Left-Anterior Descending artery
CX = Circumflex artery

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Dose to defined region (> 16.3 Gy)	1.51 (1.01 – 2.27)	0.04	1.21 (1.02 – 1.44)	0.029
Tumour size (> median)	2.27 (1.55 – 3.32)	<0.001	1.67 (1.43 – 1.95)	<0.001
Age	1.03 (1.01 – 1.05)	0.005	1.02 (1.01 – 1.02)	0.045
Gender (female vs. male)	1.68 (1.19 – 2.36)	0.003	-	-
Induction Chemotherapy (yes vs. no)	0.97 (0.62 – 1.52)	0.88	-	-
T-Stage		0.03	-	-
T1	1.45 (0.92 – 2.29)	0.11		
T2	2.19 (1.24 – 3.87)	0.007		
T3	2.31 (1.19 – 4.50)	0.014		
N-stage		0.003		<0.001
N0	0.66 (0.41 – 1.06)	0.085	0.90 (0.72 – 1.14)	
N1	1.76 (1.08 – 2.85)	0.022	1.45 (1.20 – 1.75)	
N2	1.86 (0.85 – 4.07)	0.12	1.64 (1.21 – 2.22)	

MANCHESTER
1824
The University of Manchester

Cox-regression survival analysis

- Controlling for:
  Age + tumour size
- Split on first quartile dose to region
  - 8.5 Gy
- Hazard ratio between curves
  - ~1.2



McWilliam et al, EJC 2017

MANCHESTER 1824 The University of Manchester

Summary

- Deformable image registration plays an important role in target definition, advanced treatment planning and image guidance

- Validation of registration accuracy is essential for each clinical problem

- Visual verification remains essential as automatic algorithms are never perfect

- Work towards faster and more robust deformable images registration continues

- In most clinics, rigid registration is still a cornerstone, e.g. for tumor contour propagation

Summary 2

- Image registration does not know about biology and biomechanics
  - Sliding tissue
  - Tumor growth and regression
  - Weight loss
- This is OK to make pretty pictures and propagate HU and OAR contours
- This is not OK for dose accumulation
- Data mining studies hold promise to learn about toxicity
- In strongly believe DIR is not a solved problem!

Library of plans

Helen McNair DCR(T), PhD

Lead research Radiographer

Royal Marsden NHS Foundation Trust and Institute of Cancer Research

UK

Rianne de Jong

IGRT Specialist radiographer

Academic Medical Centre,

Amsterdam

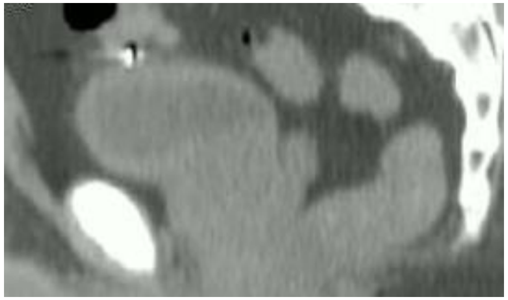
ICR The Institute of Cancer Research

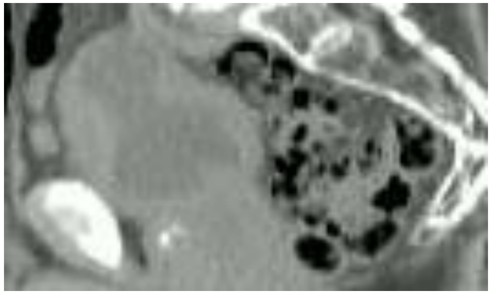
The ROYAL MARSDEN NHS Foundation Trust

amc

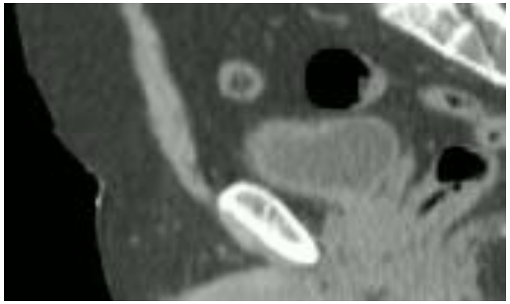
ESTRO School

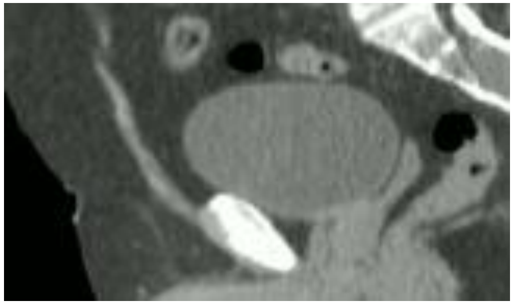
Tumour sites





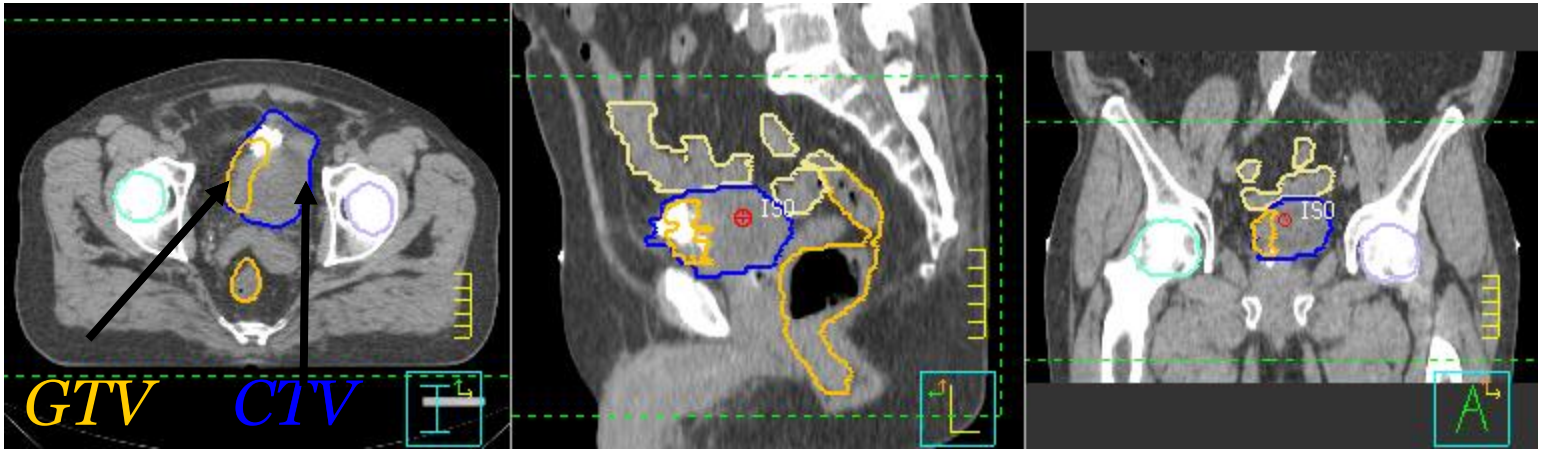
Rectal changes





Bladder changes

Plan of the day



No significant difference outlining on CT compared to CBCT

Faroudi Med Imaging Radiat Oncol 2009

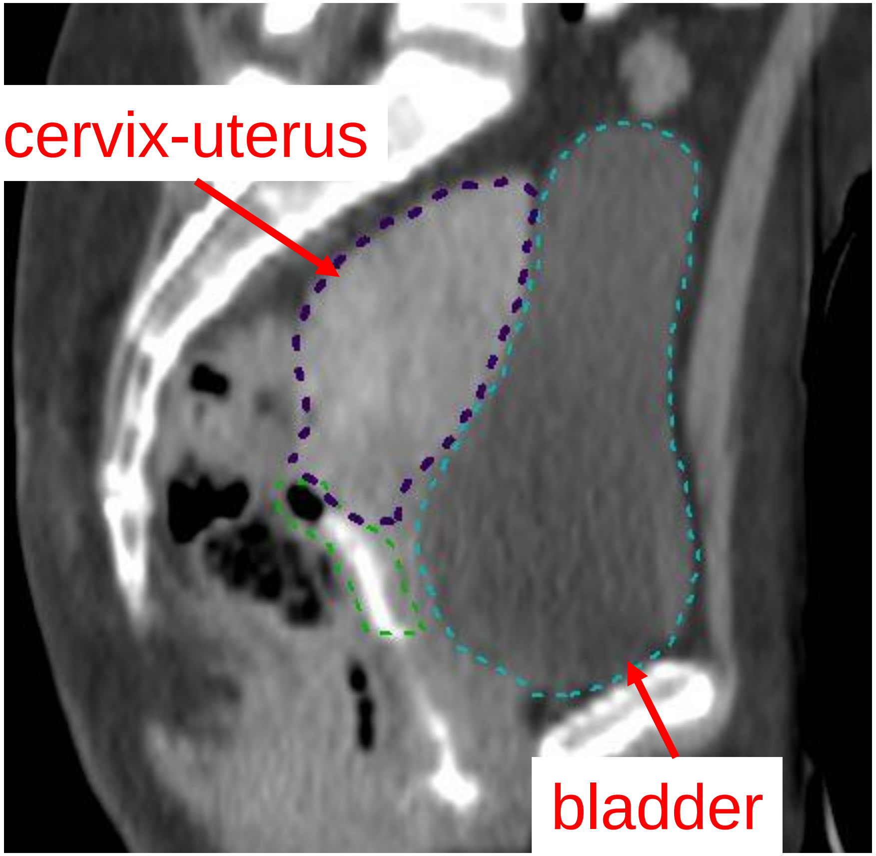
Nishioka et al Radiat Oncol 2013

Lütgendorf-Caucig J Eur Society for Therapeutic Rad Oncol 2011

Weis Int J Radiat Oncol Biol Phys 2010

Tumour sites

Planning CT



Conebeam CT

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Issues

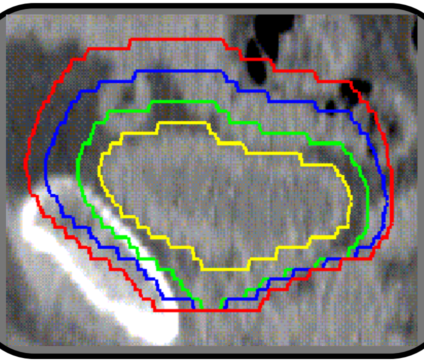
Pre treatment → Representative reference Image

Treatment → Inconsistent plan selection

Treatment → Too full bladder | Too empty bladder

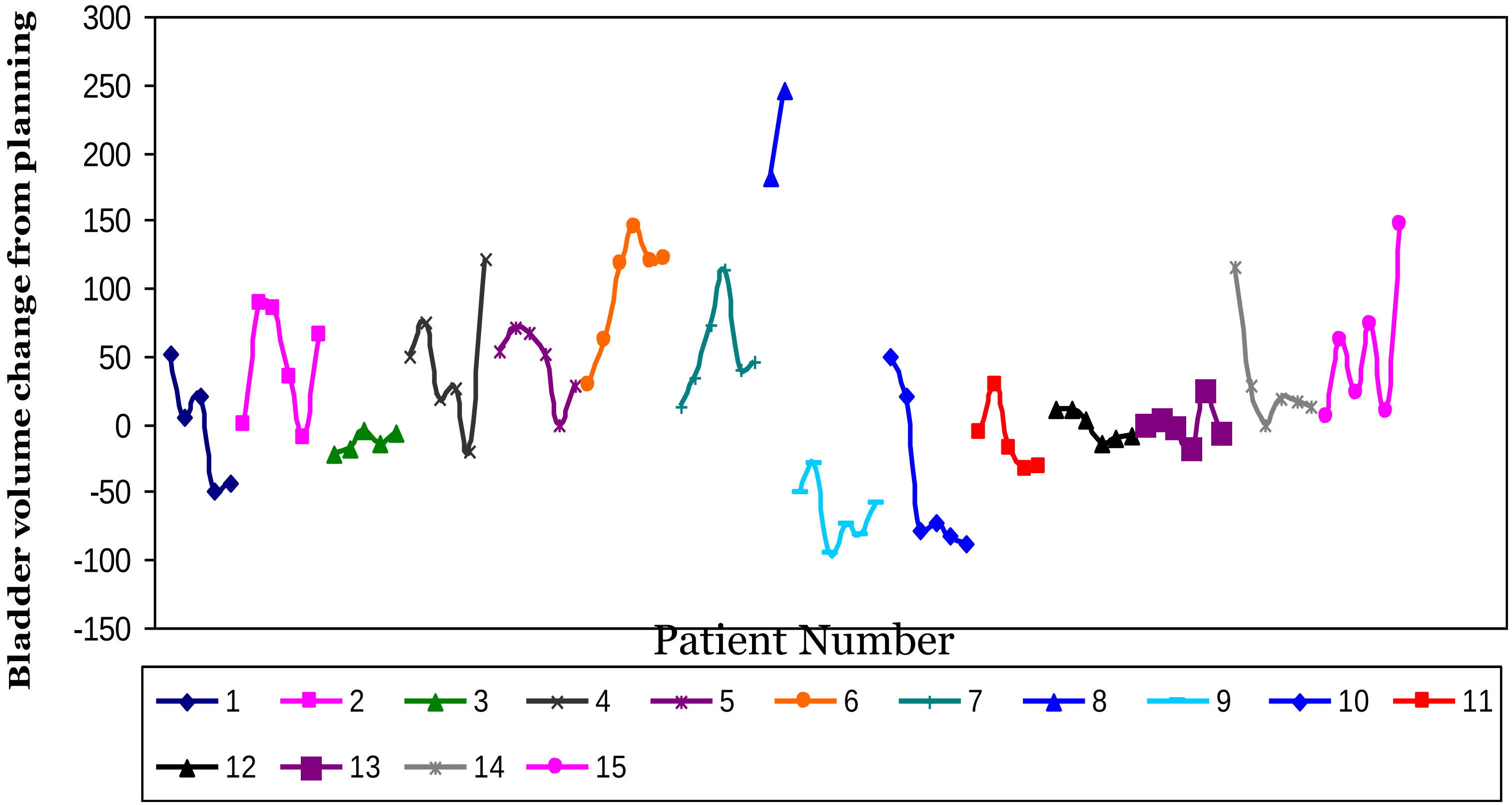
Treatment planning

Planning
CT0 and CT30
post-void



Individualised library of plans

Interfraction volume variation



No predictive factors

Lalondrelle , IJROBP, 2011

Pre treatment Imaging

Bladder Status	Empty	Partially full
Patient preparation	Empty bladder immediately prior to scan	Empty bladder prior to scan and drink 350mls
First CT Scan (CT1)	CT0	
Second CT Scan (CT2)	NA	CT0
Third CT scan (CT3)	NA	CT30

Empty bladder

Margins respective of filling

CTV → PTV (cm)	Small PTV	Intermediate PTV	Large PTV	
			If difference CTV1 and CTV3 is > 50 cc: Based on CT30	If difference CTV1 and CTV3 is < 50 cc: CT0
Anterior	0.5	1.5	1.5	2.0
Posterior	0.5	1.0	1.0	1.2
Lateral	0.5	0.5	0.5	0.75
Superior	0.5	1.5	1.5	2.5
Inferior	0.5	0.5	0.5	0.75

Empty bladder

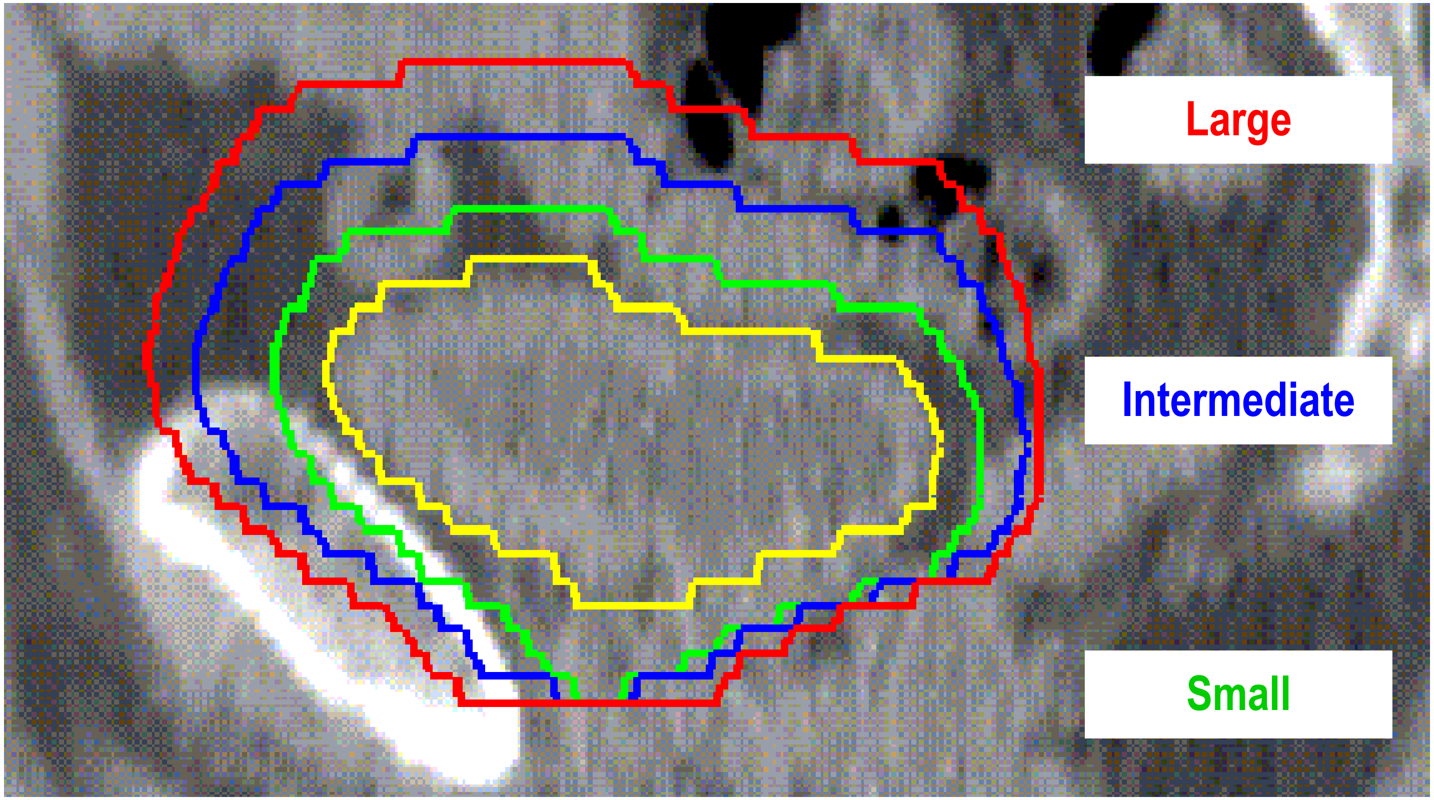
Margins

CTV → PTV (cm)	Small PTV	Intermediate PTV	Large PTV
Anterior	0.5	1.5	2.0
Posterior	0.5	1.0	1.2
Lateral	0.5	0.5	0.8
Superior	0.5	1.5	2.5
Inferior	0.5	0.5	0.8

Full bladder

		CTV to PTV expansion (cm)					GTV to PTV2 expansion (cm)				
	PTV	Lat	Ant	Post	Sup	Inf	Lat	Ant	Post	Sup	Inf
Group 1 **Standard Plan**	Standard	0.8	1.5	1.2	1.5	0.8					
Group 2 and **Group 3** **Adaptive plan**	Small	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Medium	0.5	1.5	1.0	1.5	0.5	0.5	1.5	1.0	1.5	0.5
	Large **based on CT30 if CTV60-CTV30<50cm^3**	0.8	2.0	1.2	2.5	0.8	0.8	2.0	1.2	2.5	0.8
	Large **Based on CT60 if CTV60-CT30=>50cm^3**	0.5	1.5	1.0	1.5	0.5	0.5	1.5	1.0	1.5	0.5

Adaptive-predictive organ localisation



51% of fractions in 10 out of 15 patients required adaptive

73% fractions delivered correctly using adaptive

Remaining 27% improved coverage

Lalondrelle , IJROBP, 2011

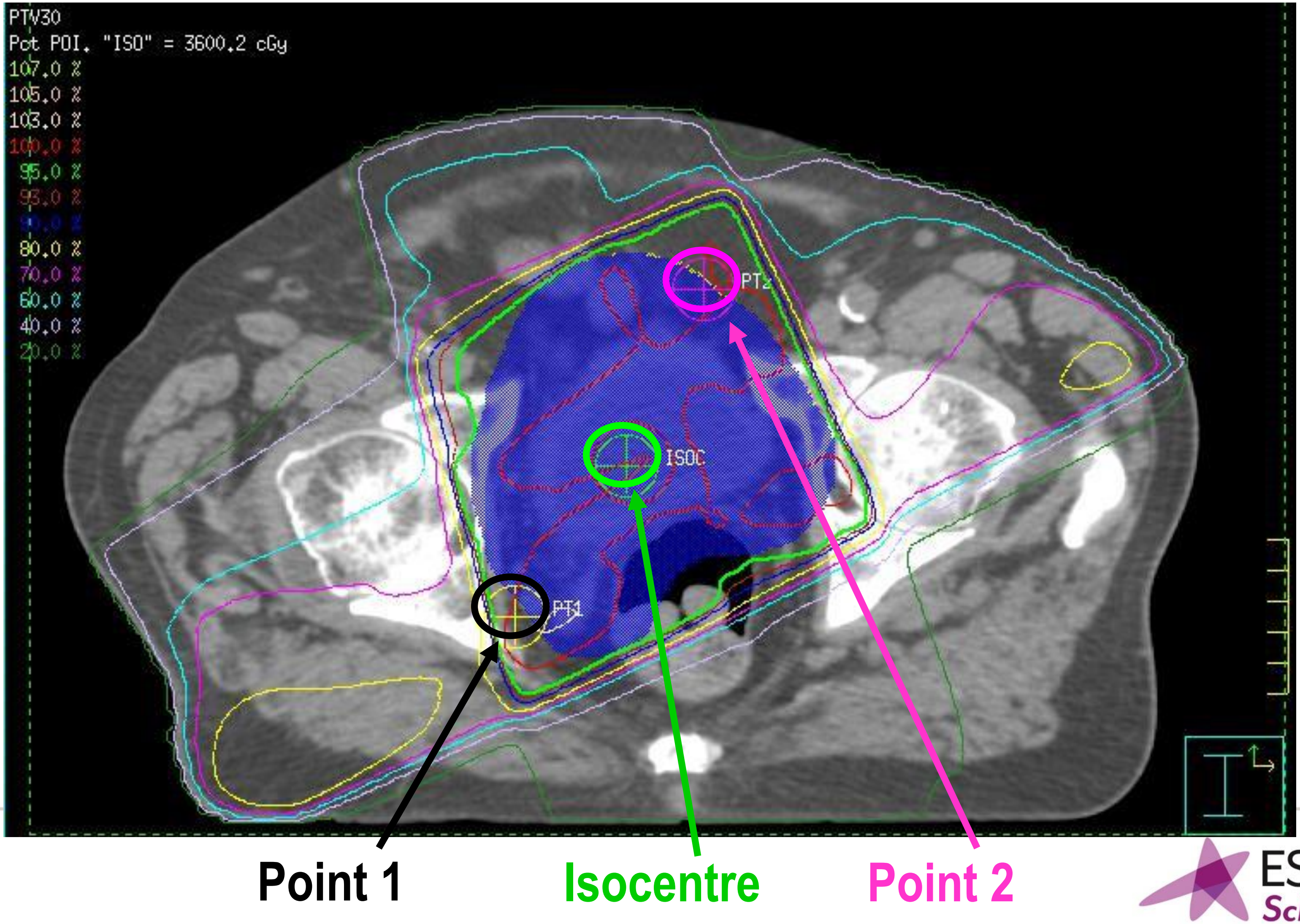
Plan of the day

PTV small

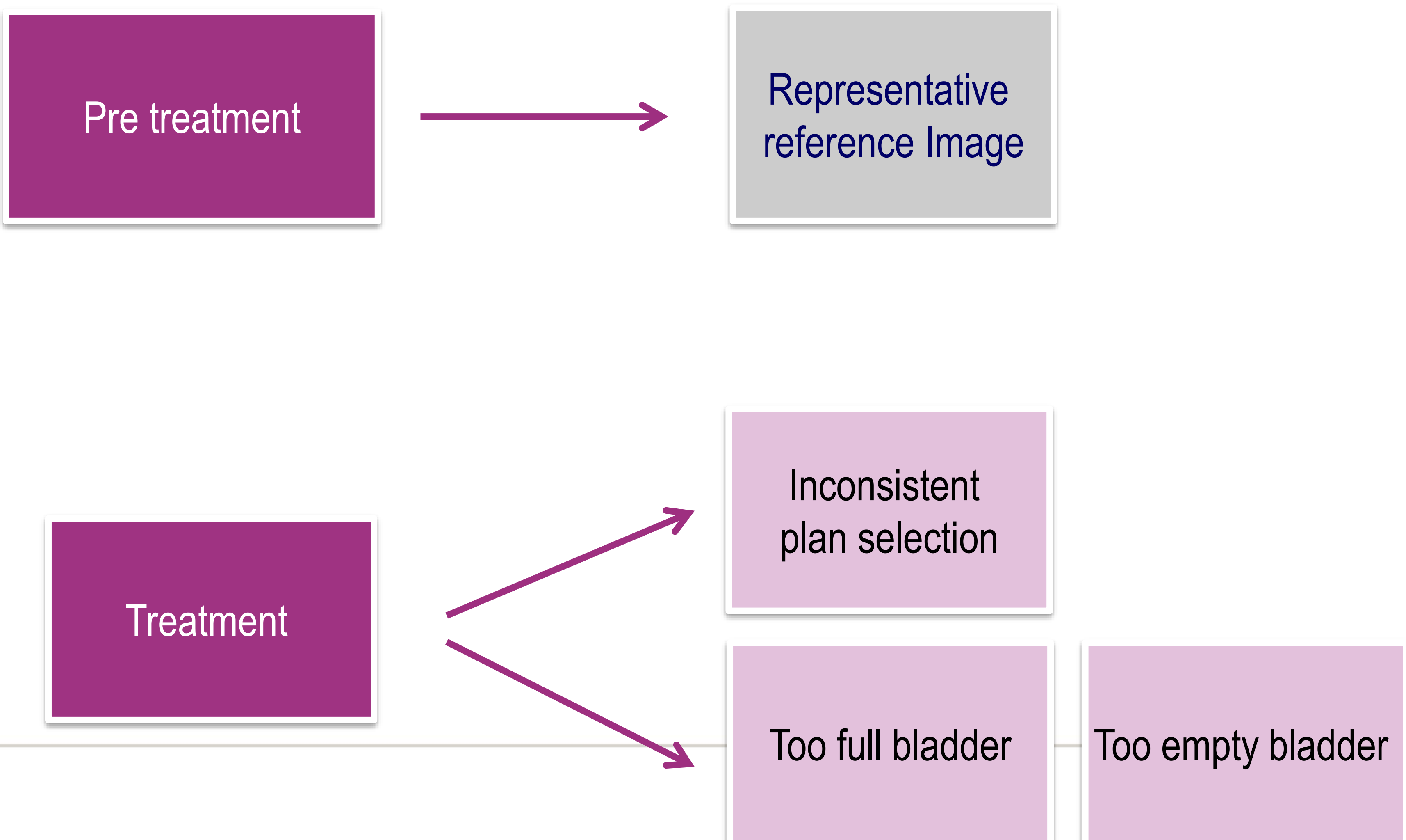
PTV medium

PTV large

Treatment delivery-plan of day



Issues

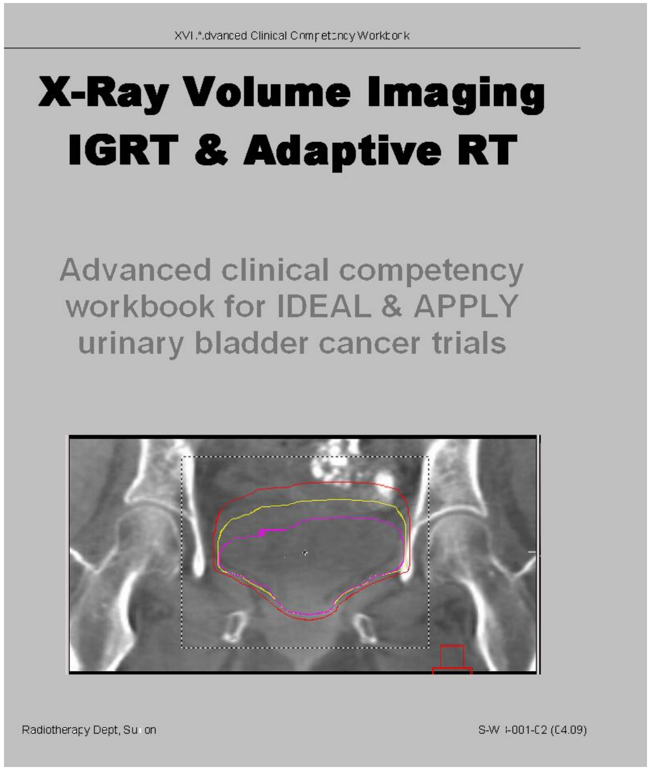

Pre treatment
Representative reference Image
Treatment
Inconsistent plan selection
Too full bladder
Too empty bladder

Training

Anatomy teaching provided by University & clinicians

Normal/abnormal pelvic pathology

Complete competency workbook



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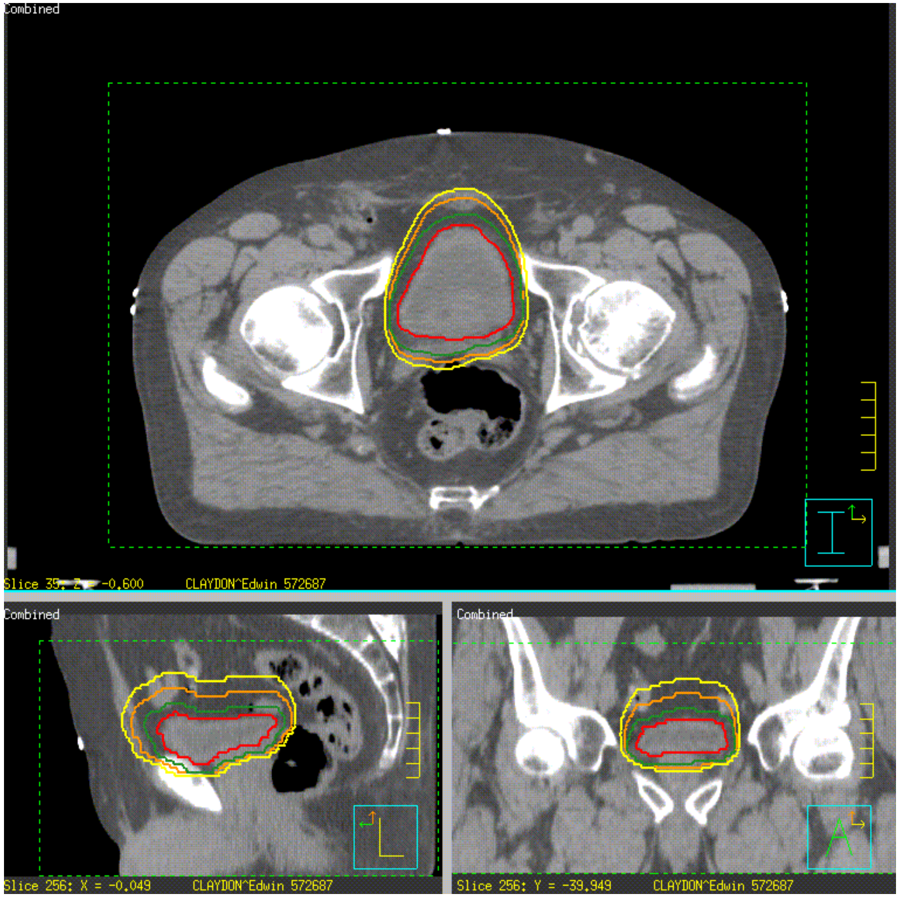
Training-Bladder



12 radiographers

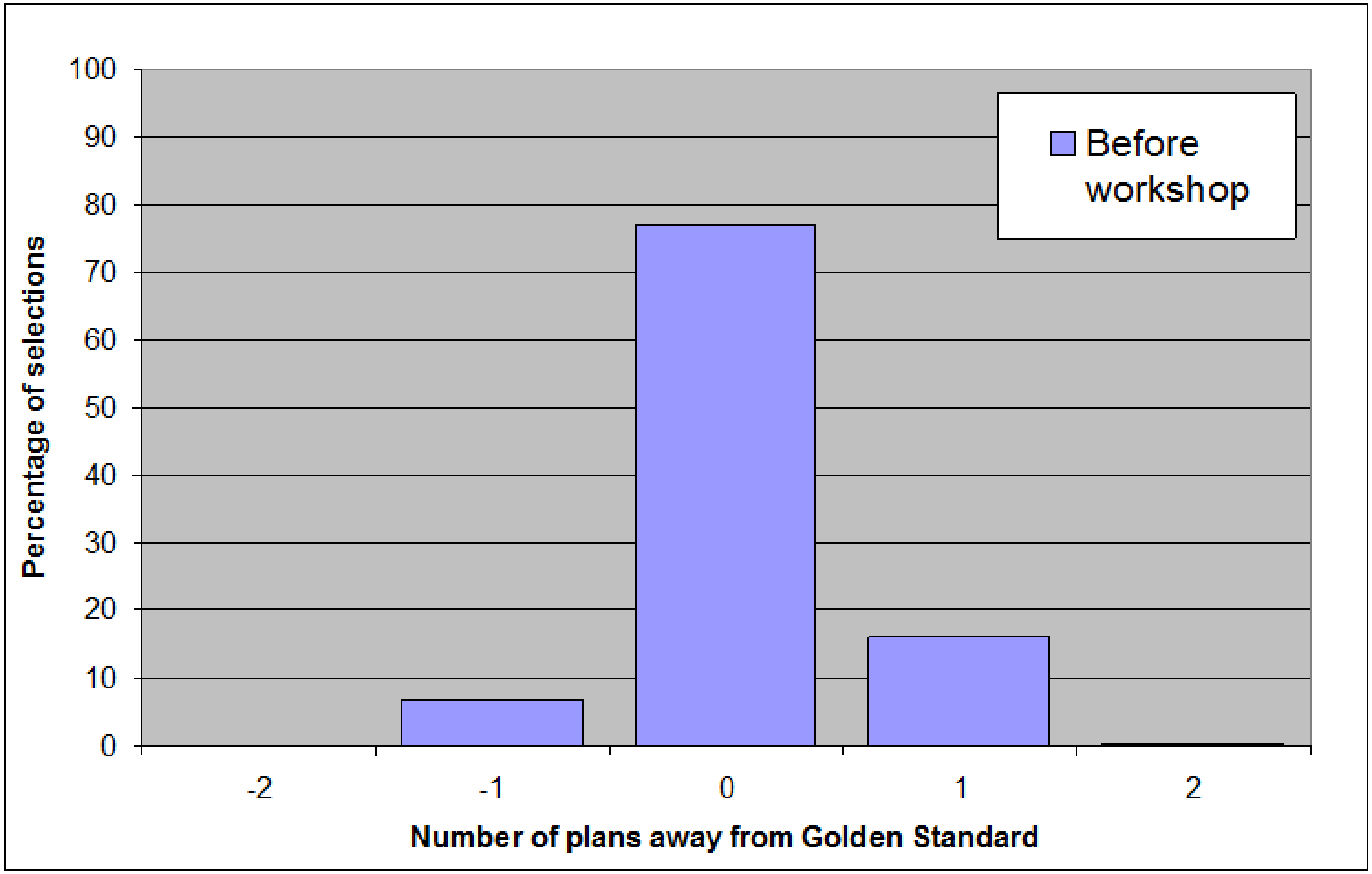
2 clinicians

Mean concordance 76%

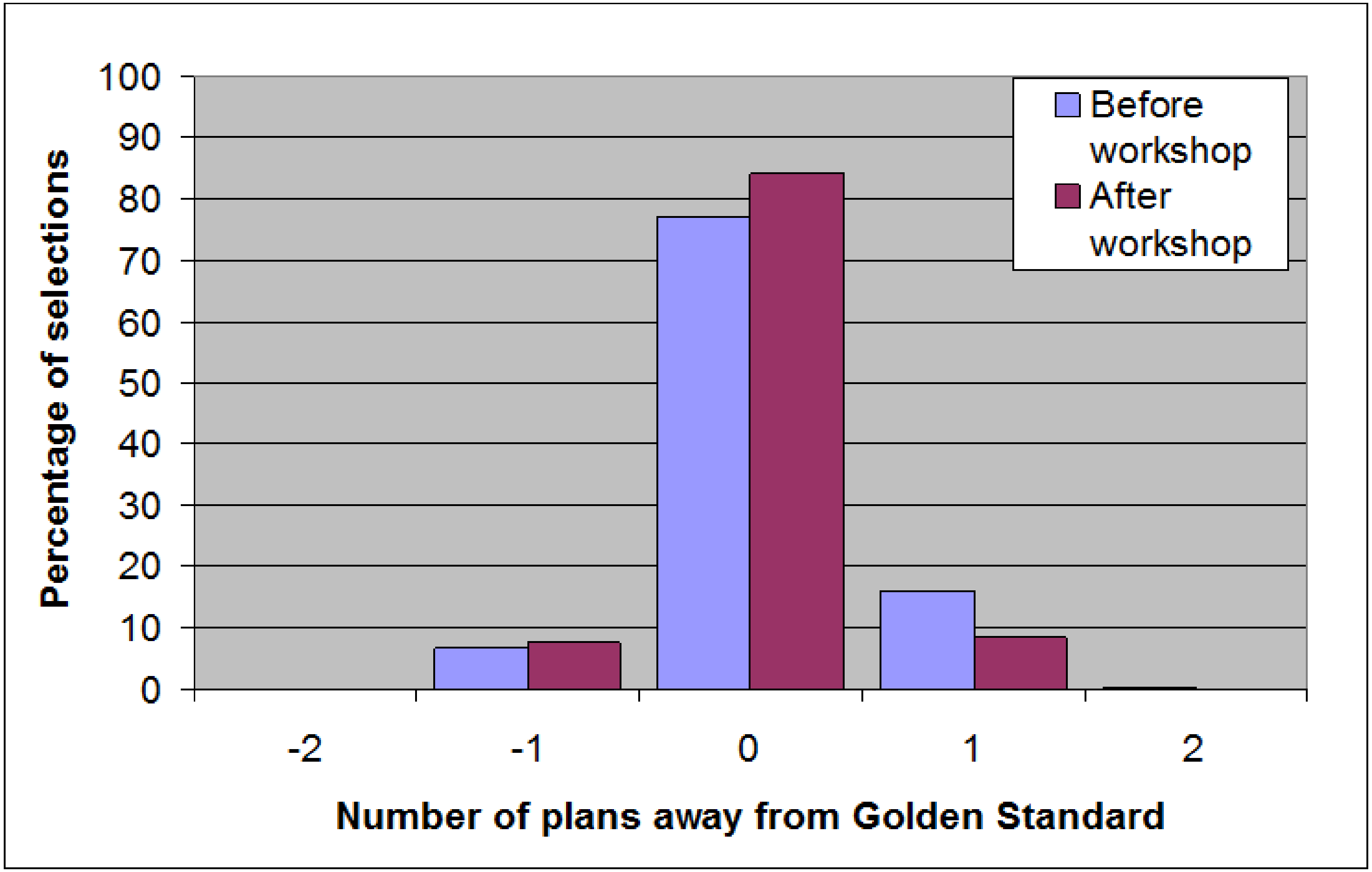
Matching/ set up: 2 min 28s

Plan selection: 1 min 24s

Training- cervix

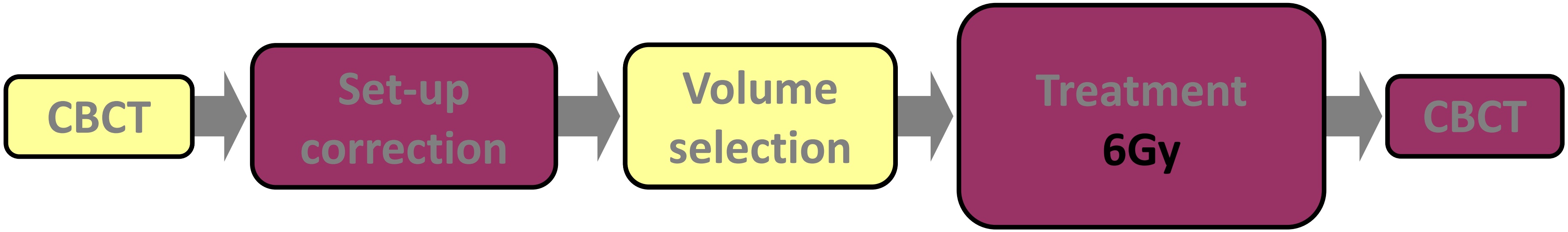


Training-cervix



Volume selection

On-line by 2 trained observers

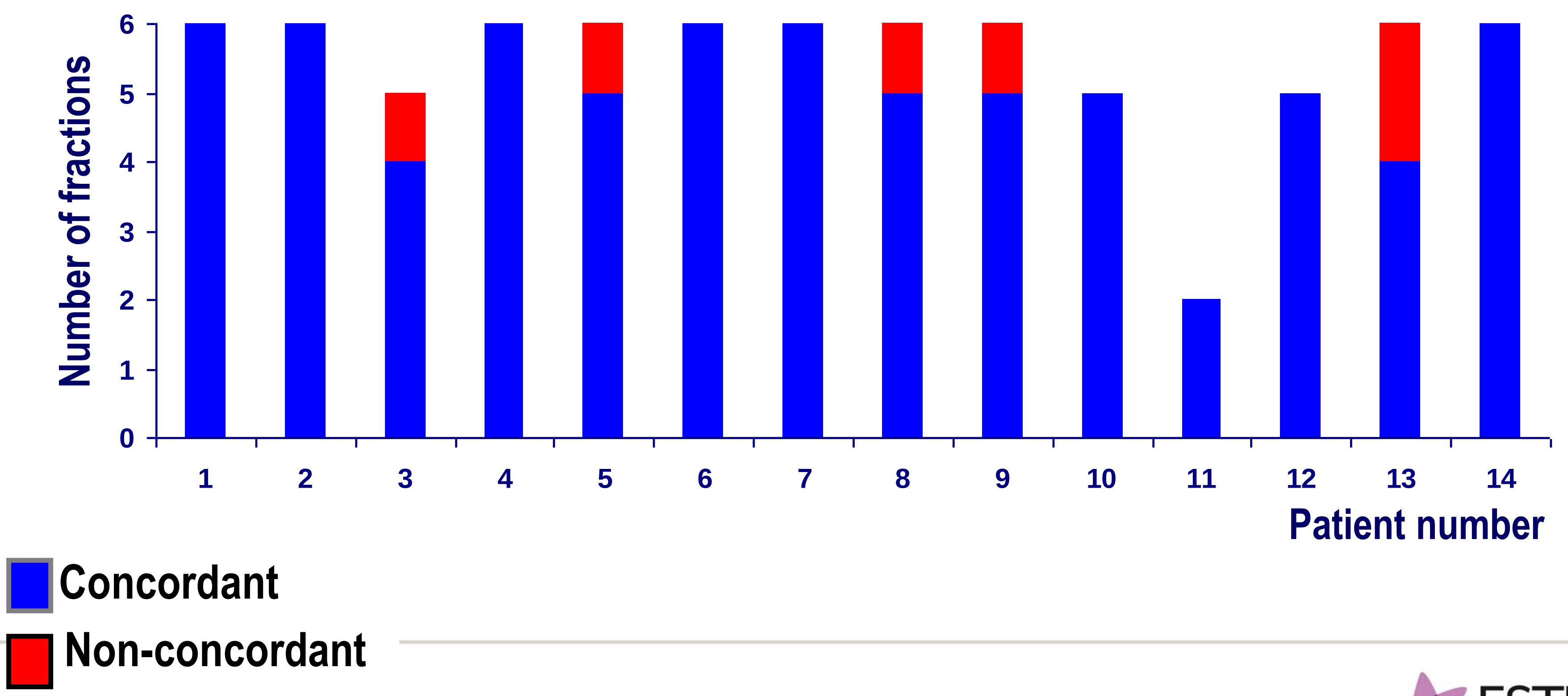


Off-line by independent blinded observer

Courtesy of Fiona McDonald

Volume selection

Concordance rate 92% **(71/77#)**



Courtesy of Fiona McDonald

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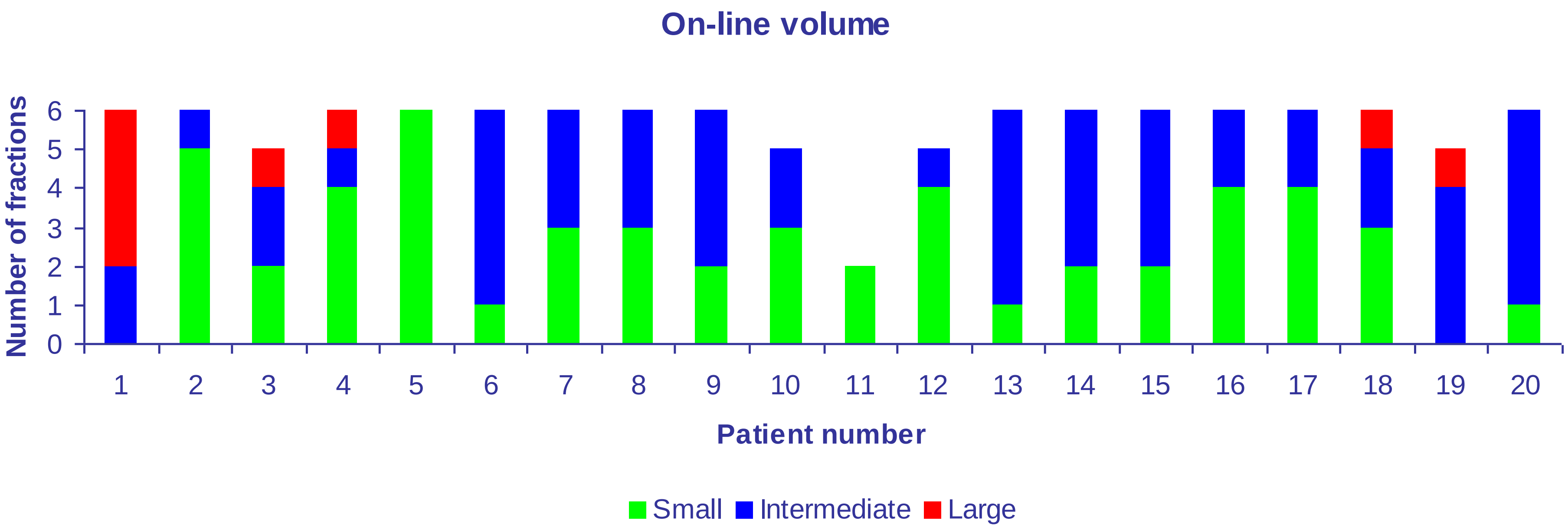
On-line volume



139 RT fractions assessed

- 68 (49%) small, 63 (45%) medium and 8 (6%) large selected
- 3 (12%) same plan throughout the course
- Manual isocentre shift in 15 fractions (10%)
- 1 fraction CTV considered too large for the large plan

National Trial

HYBRID

62 patients with **pT2-T4a N0 M0** bladder carcinoma unsuitable for standard daily radiotherapy

↓

Due to receive six 6Gy fractions of radiotherapy delivered weekly (total dose: 36Gy over 6 weeks)

↓

RANDOMISE

1:1

↓

Group 1:
STANDARD PLANNING
(CONTROL)

Group 2:
ADAPTIVE PLANNING
(EXPERIMENTAL)

↓

Follow up

- Weekly on treatment
- 4 weeks after last treatment
- **3 months after last treatment**
- 6, 12 and 24 months

ICR The Institute of Cancer Research

in partnership with

CANCER RESEARCH UK

Endpoints

HYBRID

Primary endpoint

•Acute non-genitourinary grade 3 or greater toxicity (up to 3 months following treatment completion)

Secondary endpoints

•Local disease control rate at 3 months
•Control rate of presenting symptoms
•Patient reported outcomes
•Late toxicity
•Time to local disease progression
•Overall survival
•Proportion of fractions benefiting from adaptive planning
•Appropriate identification and correction of fractions requiring adaptive planning

in partnership with

CANCER RESEARCH UK

ICR The Institute of Cancer Research

RTTQA IGRT Credentialing programme

Evidence of in-house IGRT training programme (bladder)

HYBRID specific training programme

IGRT independent review cases: this acts as competency assessment

Verification of electronic data transfer: CBCT and registration objects

IGRT site visit: during first patient's treatment. Review process/decision making

RTT QA for plan selection

Remote access to Elekta/Varian databases

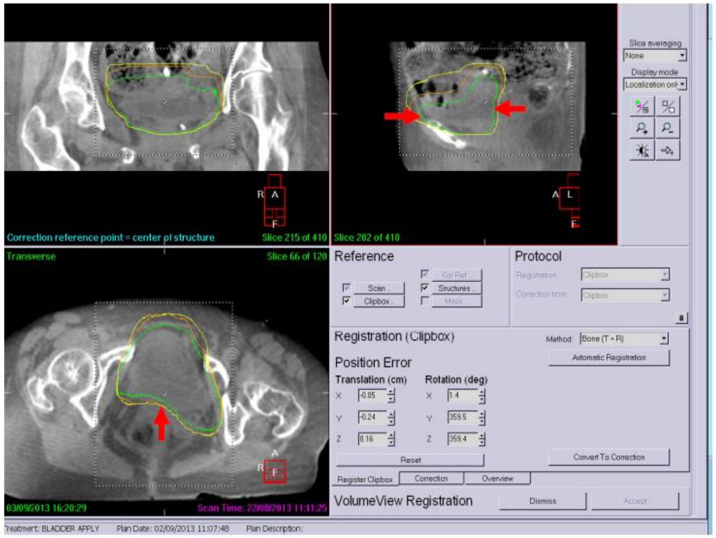
5 patients, 6 CBCT each

Patient 1: step by step process of how plan selected

Patient 2-3: practice with answers provided

Patient 4-5:test cases

Figure 1: Axial, sagittal and coronal view of PTVsmall (green), PTVmedium (orange) and PTV large (yellow) with arrows highlighting where the bladder is close to the boundary of PTVsmall.



- Remove PTV small as it does not incorporate the bladder volume and a margin of 3mm in the anterior-posterior dimension (Figure2).

51 Staff assessed, 9 centres

Maintenance of competency

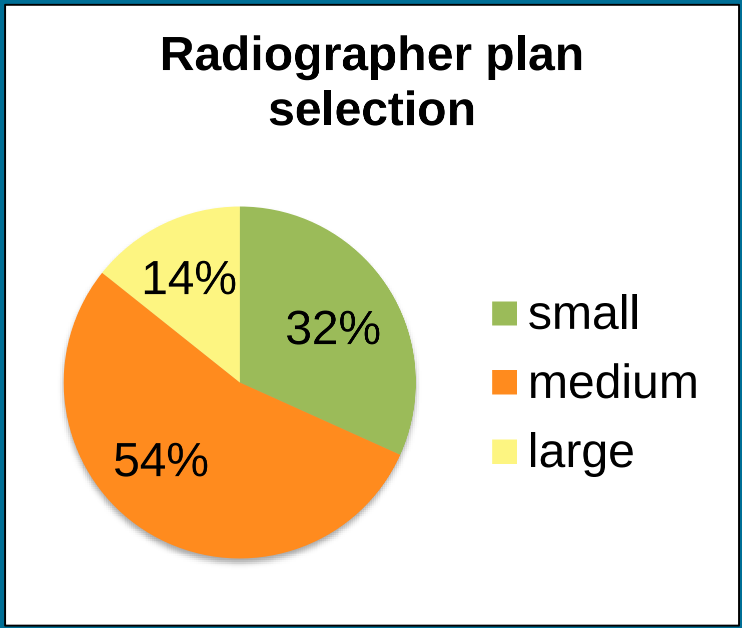
Advanced competency assessment record of practise in adaptive bladder radiotherapy for bladder cancer

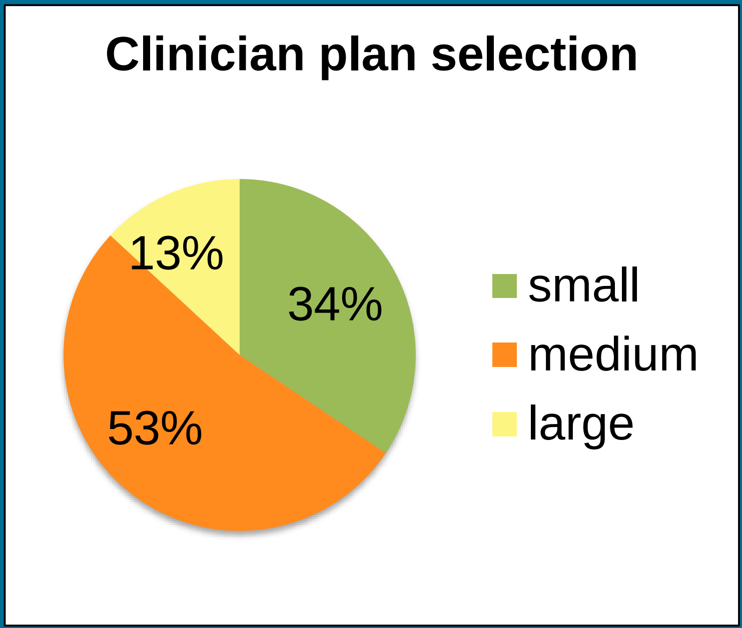
A maximum of 2 scans per patient, should be recorded as part of the competency assessment.

Date	Relevant Experience	Outcome / Reflection
	Patient ID: PTV selected: Agreement with comparative match*: Y / N	
	Patient ID: PTV selected: Agreement with comparative match*: Y / N	

Maintenance of competency

16 radiographers trained
Audit 3 years after

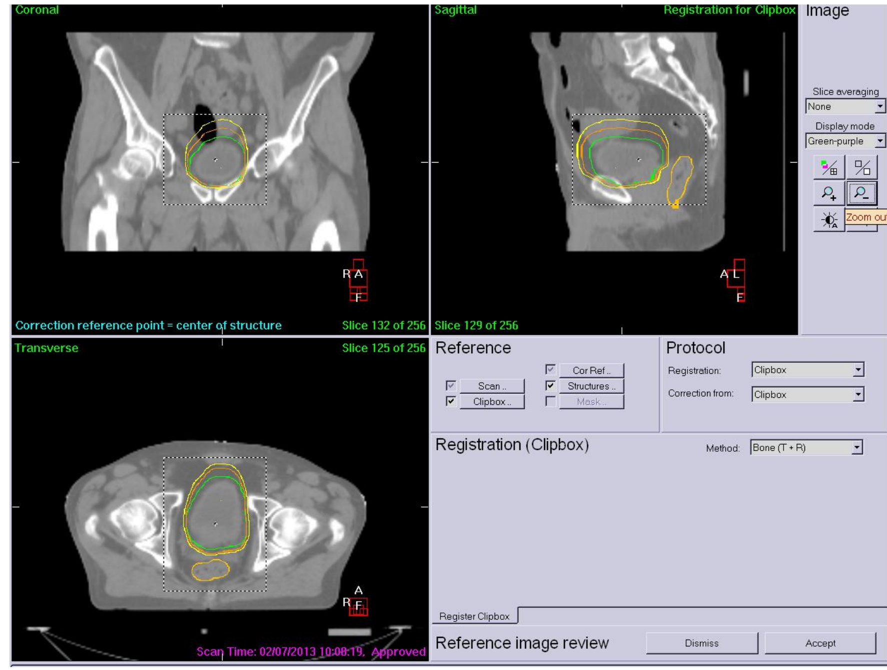




125 CBCTs (63 pre; 62 post radiotherapy) were evaluated
Concordance of plan selection was 92% (58/63)

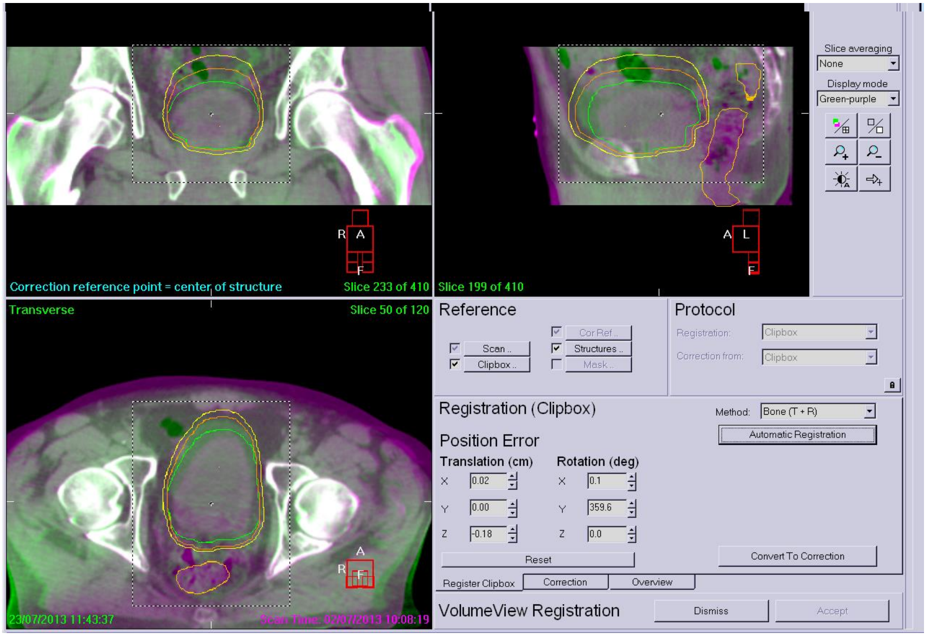
Registration-guidelines

Assess reference image



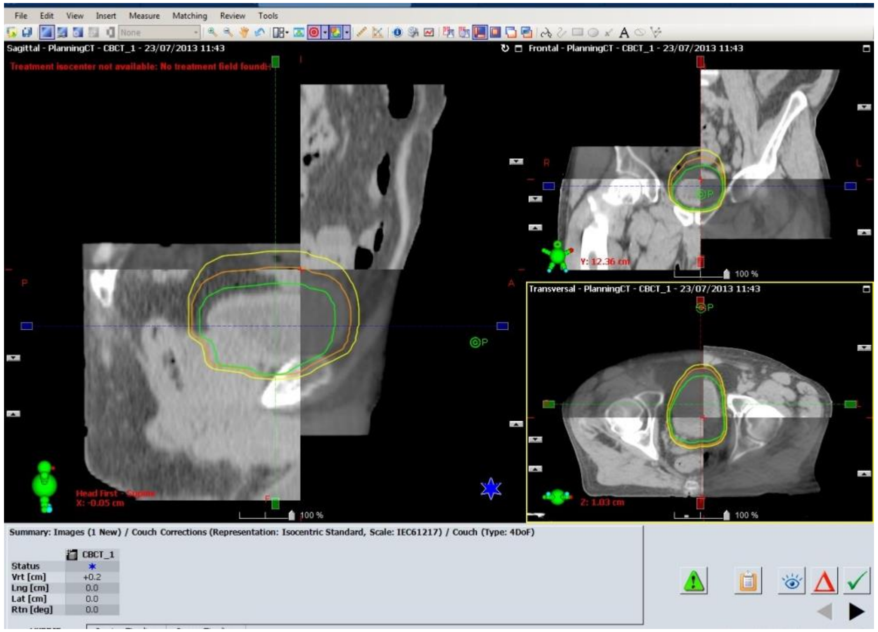
Registration-standard process

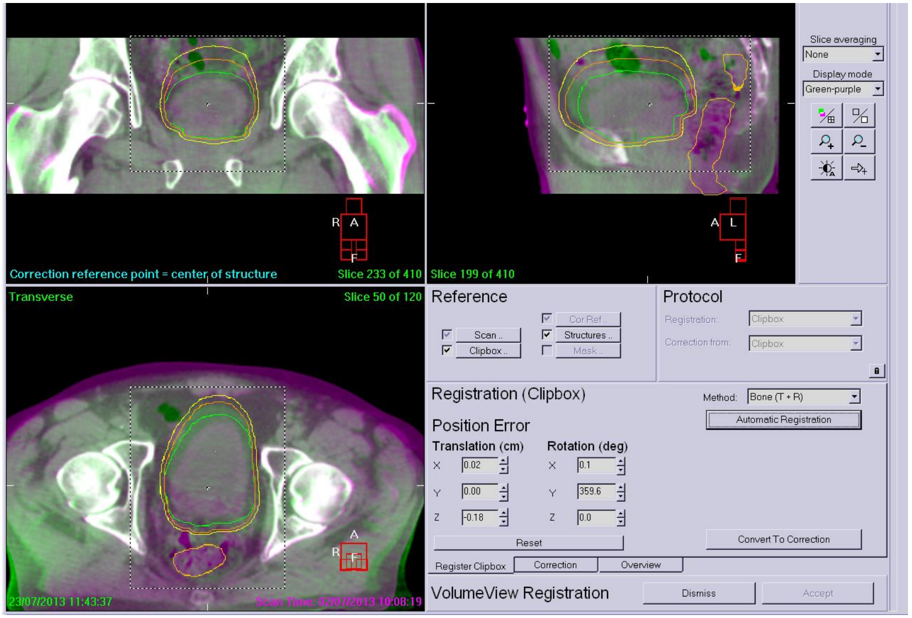
Contrast and Bone registration



Registration-guidelines

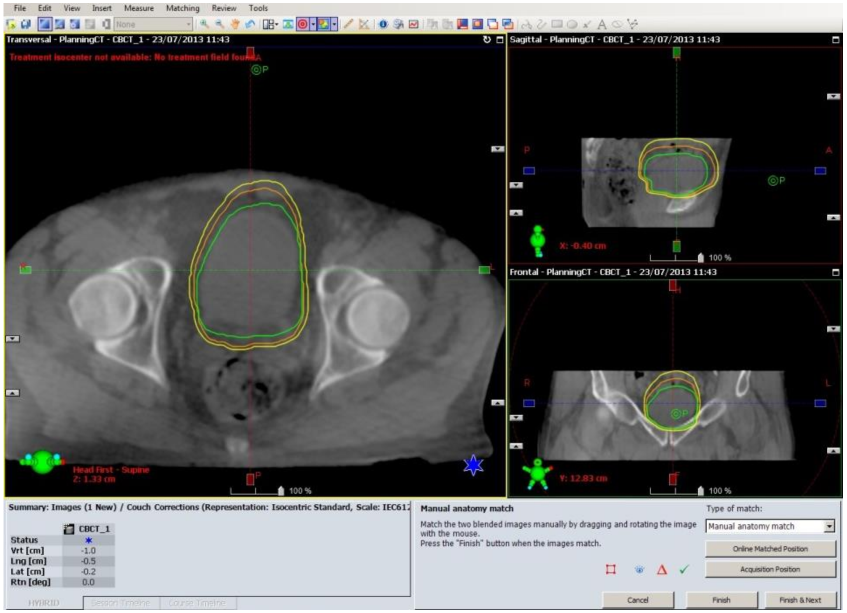
Check match

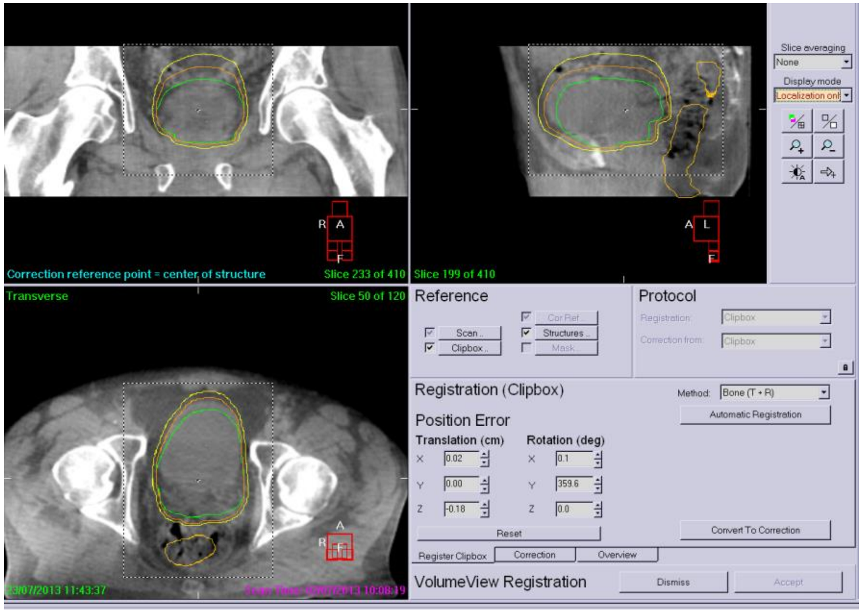




Registration-guidelines

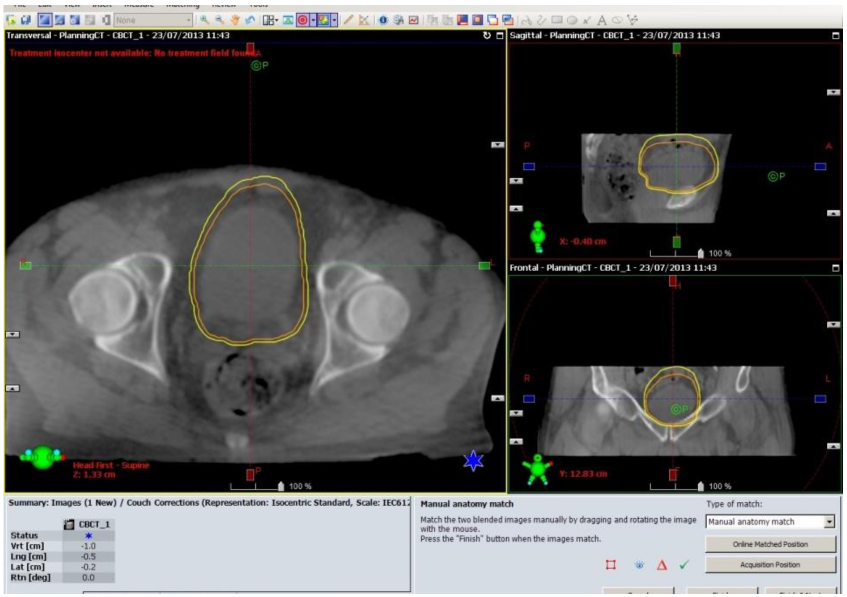
Quick gross assessment

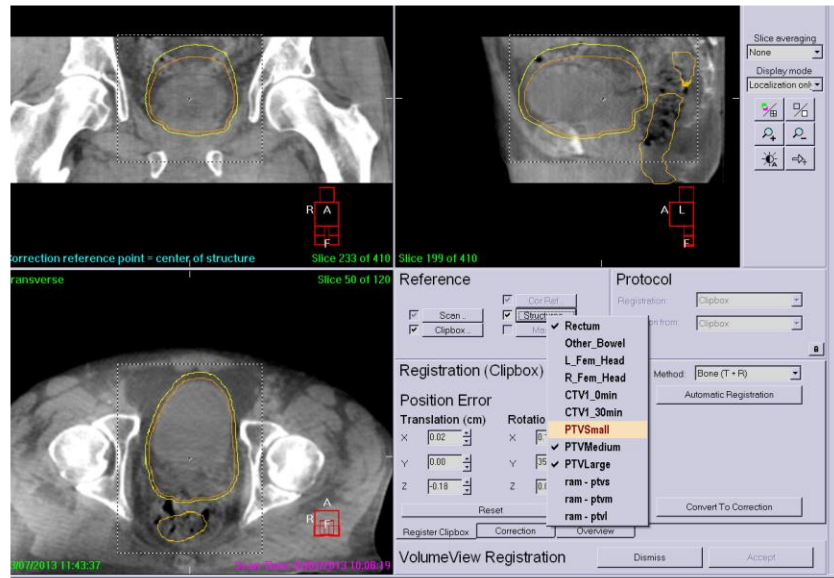




Registration-guidelines

Assess next plans

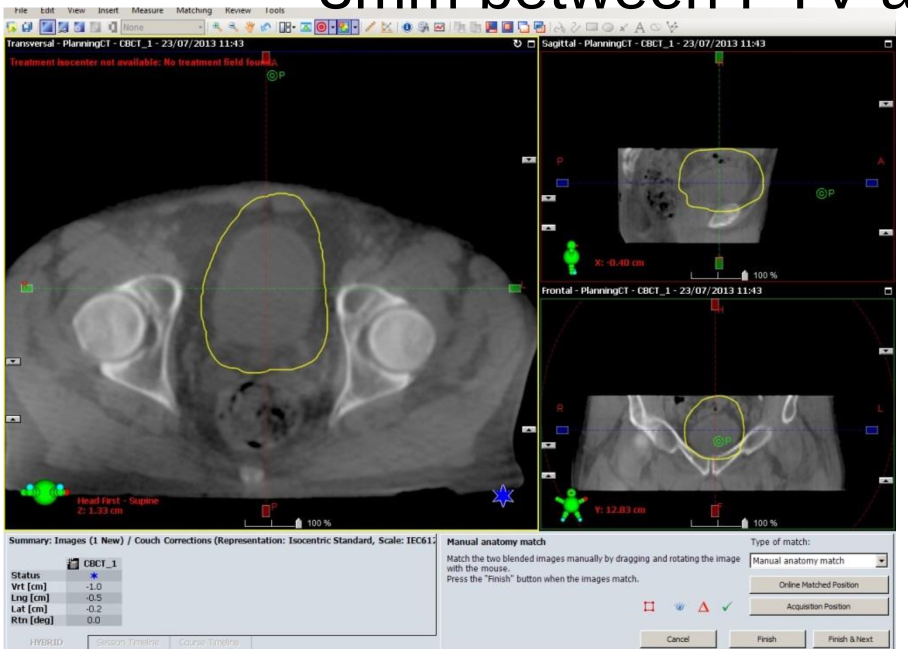


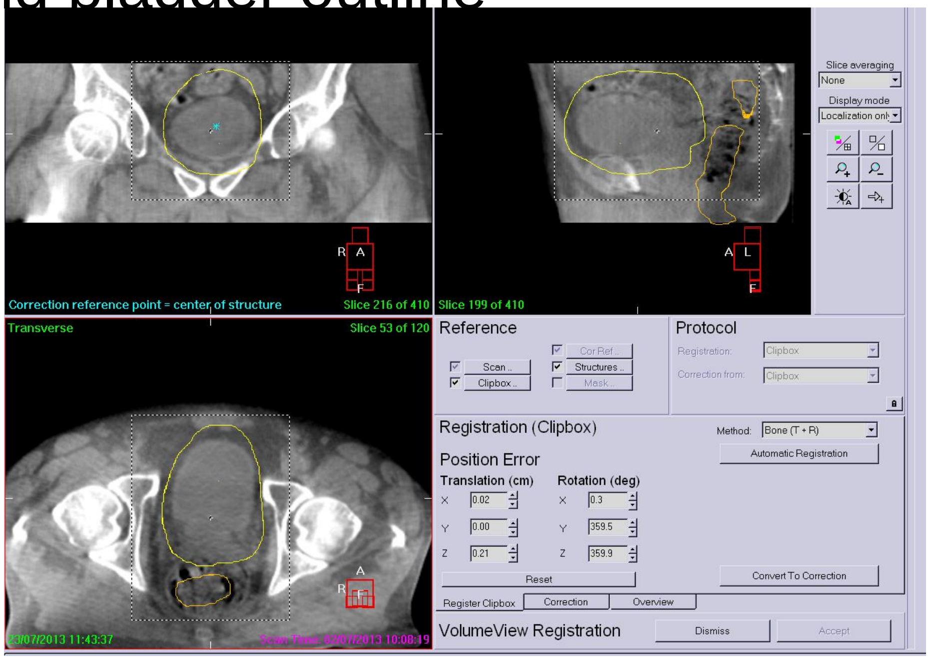


Registration-guidelines

Manual adjustment

3mm between PTV and bladder outline





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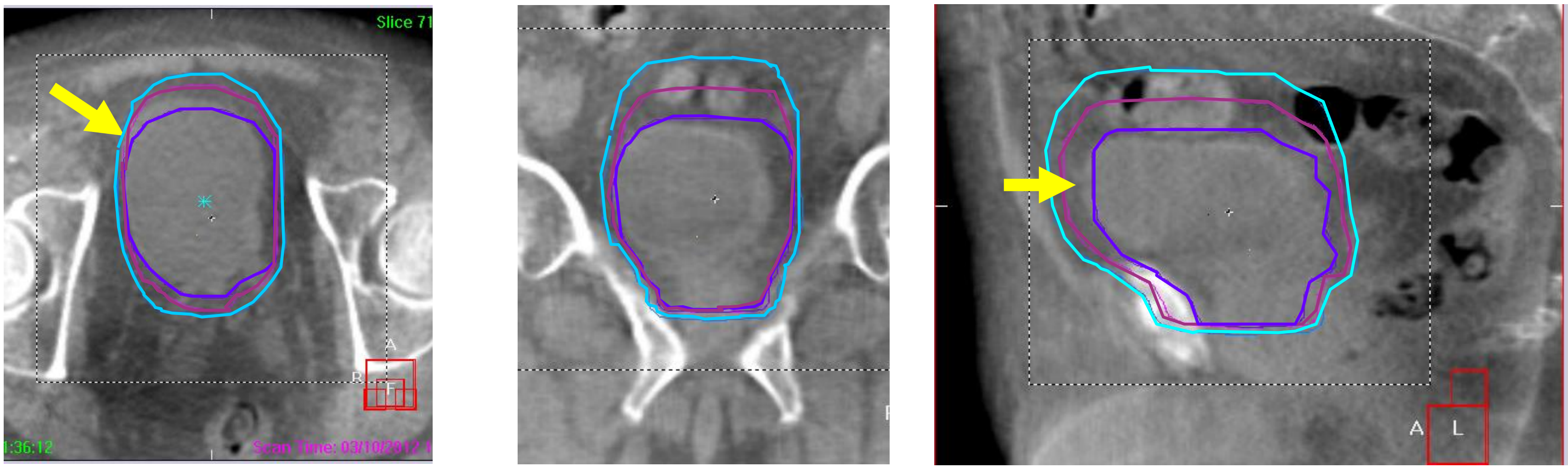
Case 1

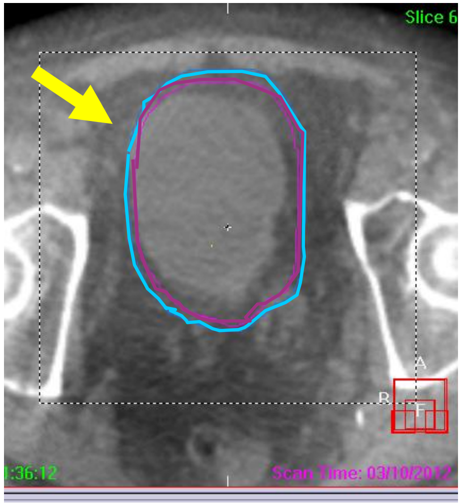
Gross assessment

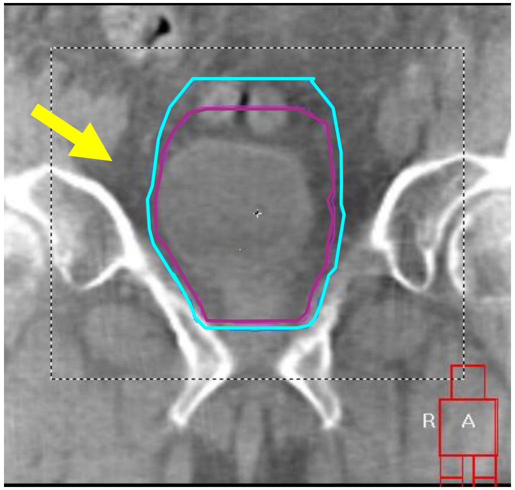


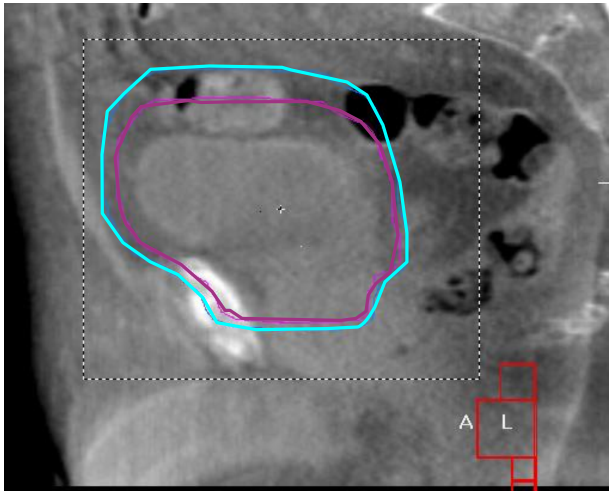
Small too small

Case 1

View all images/slices

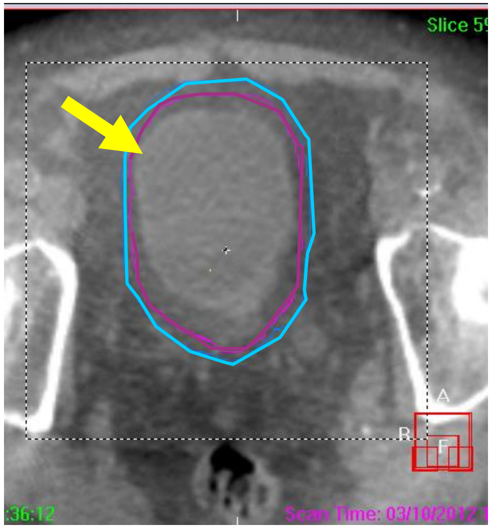


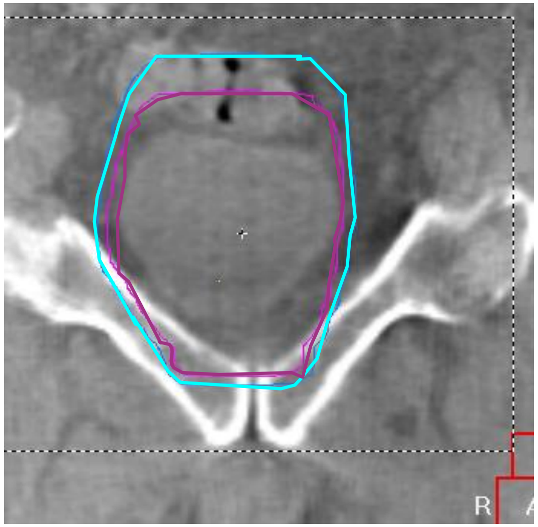


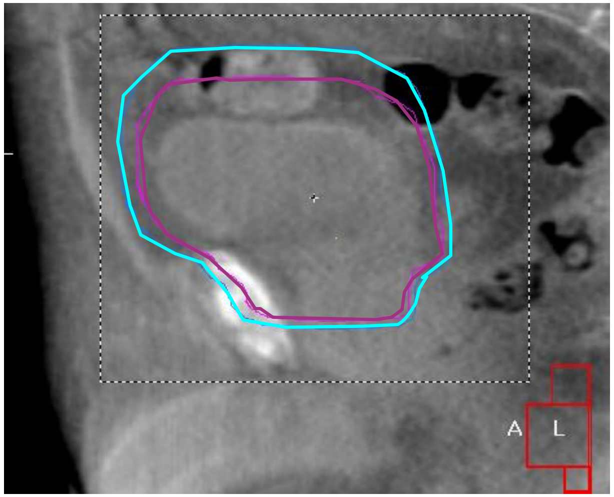


Needs right left shift

Shift Right-left

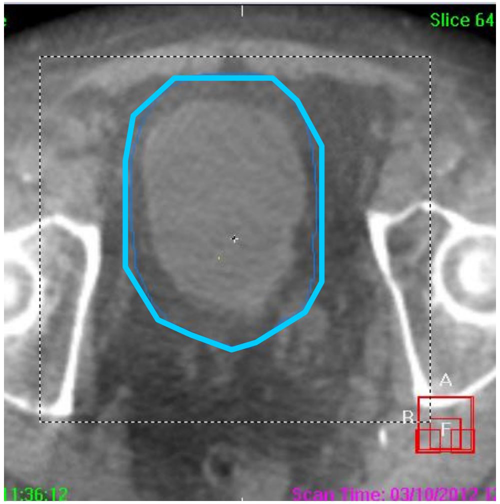


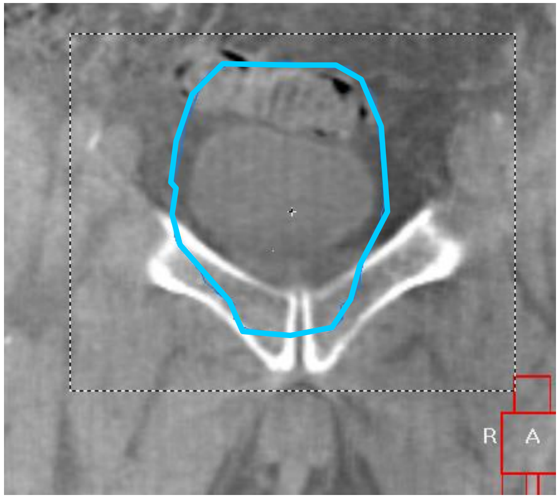


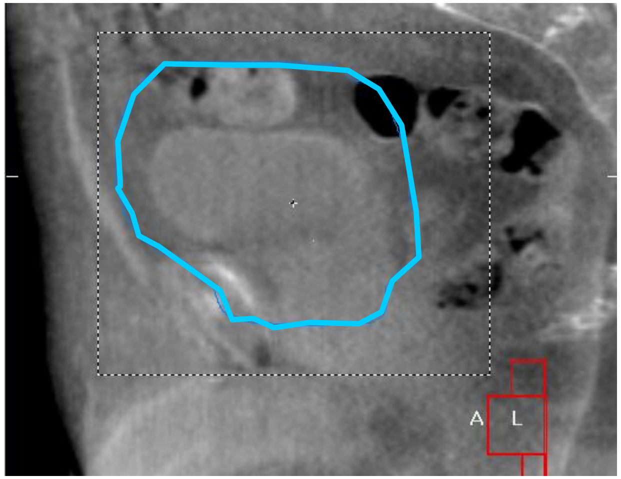


Medium still too tight

Case 1

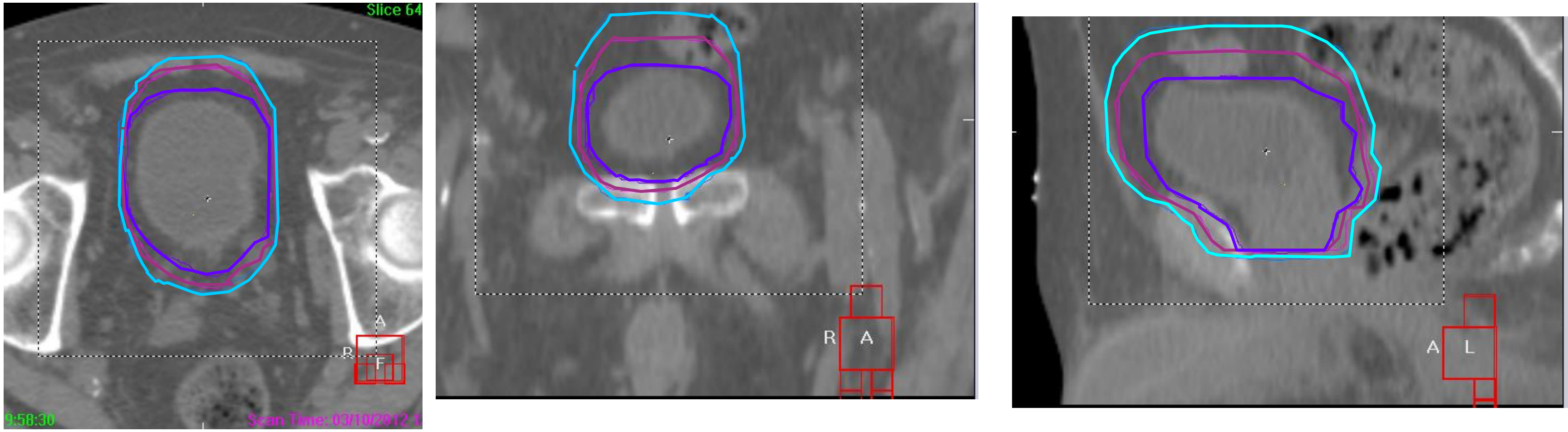






Select large

Case 2
1. Small; 2.Medium; 3.Large; 4.Shift; 5.None



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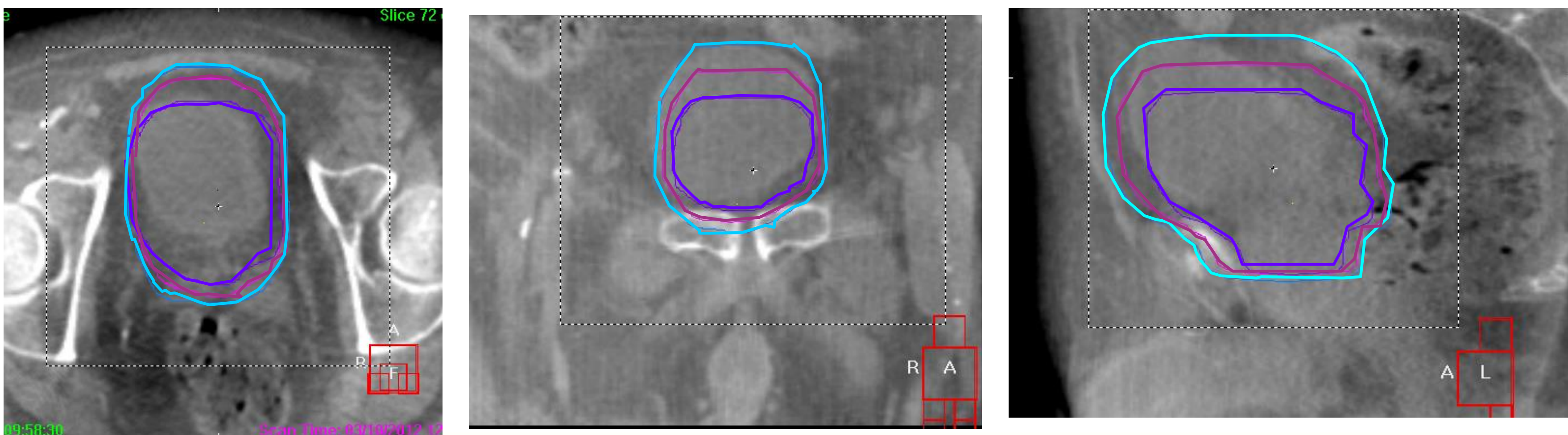

Treatment image

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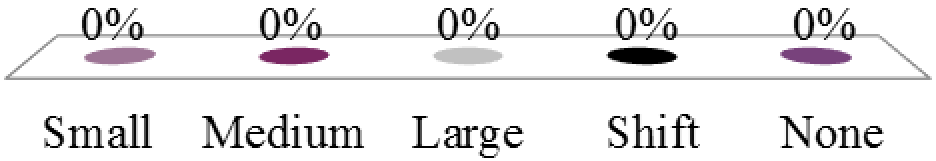
Which choice is best

1. Small
2. Medium
3. Large
4. Shift
5. None



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Registration issues

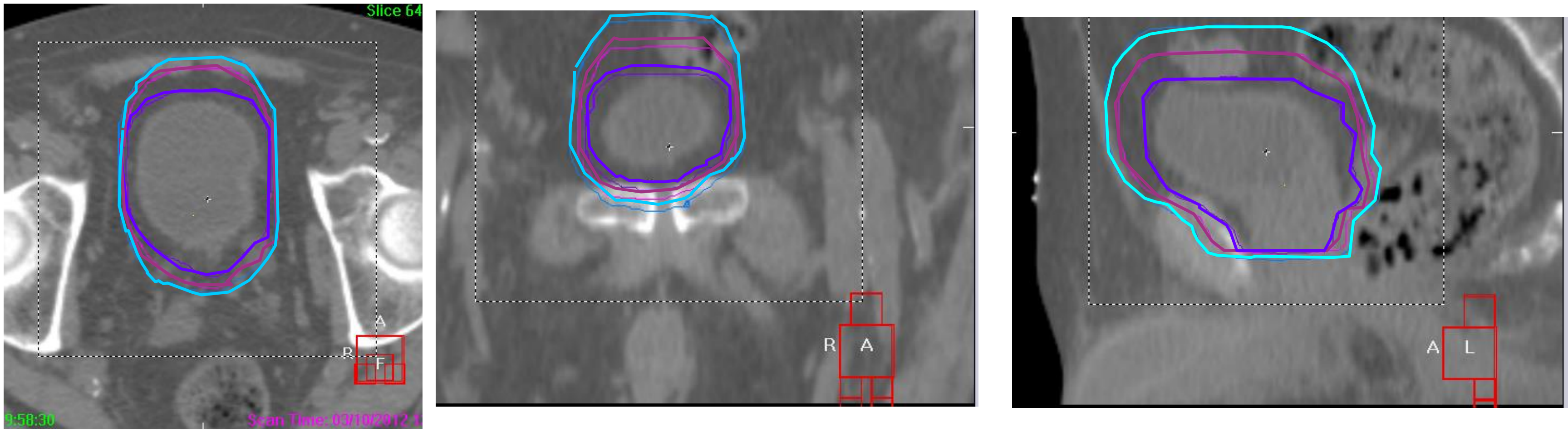
Consistent PTV selection between observers

No PTV is suitable- too large

No PTV is suitable – too small

Case 2

Too large- empty bladder



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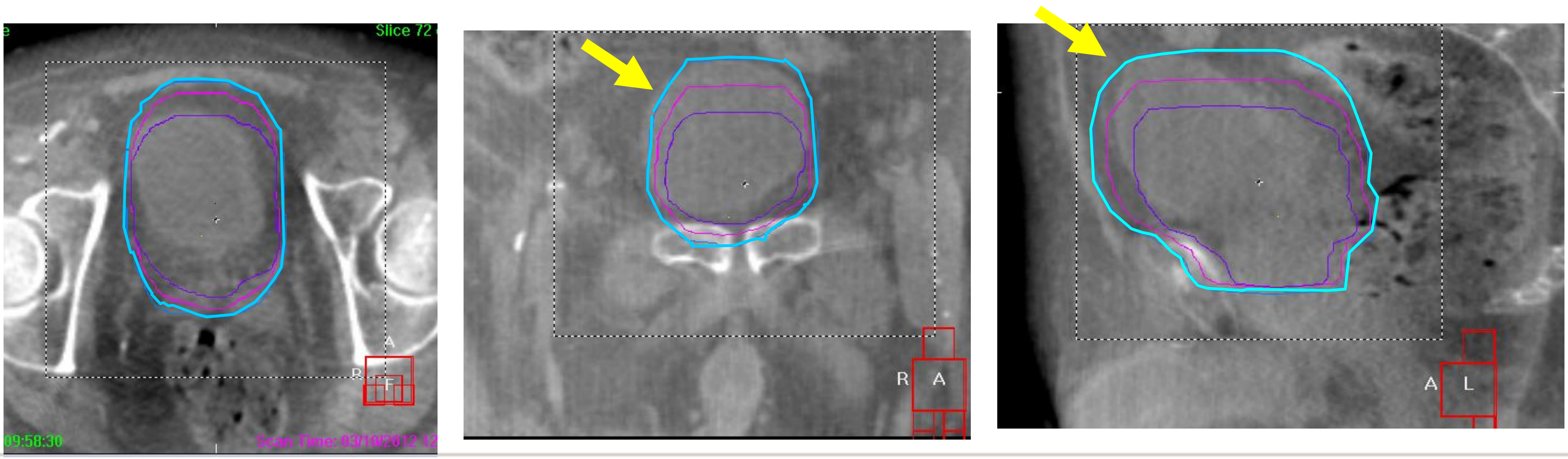

Treatment image

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Significant shape change

Bladder too big

No plan provides appropriate coverage

Shape change due to bladder overfilled

Shape change due to rectal filling (flatus/faeces)

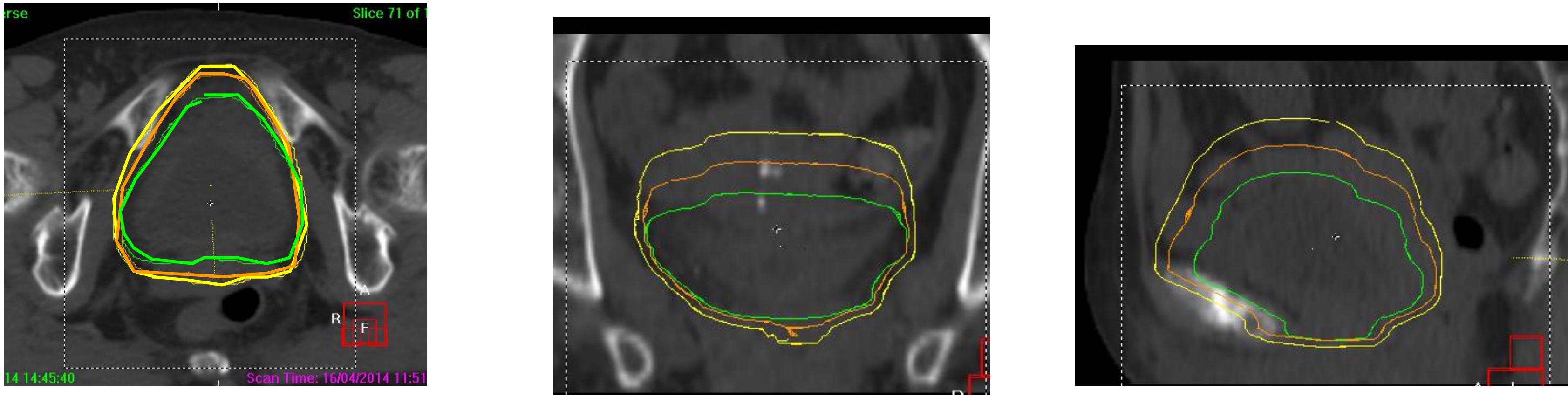
Remove patient from couch, void bladder, repeat drinking protocol but review

i) volume of fluid drank and or

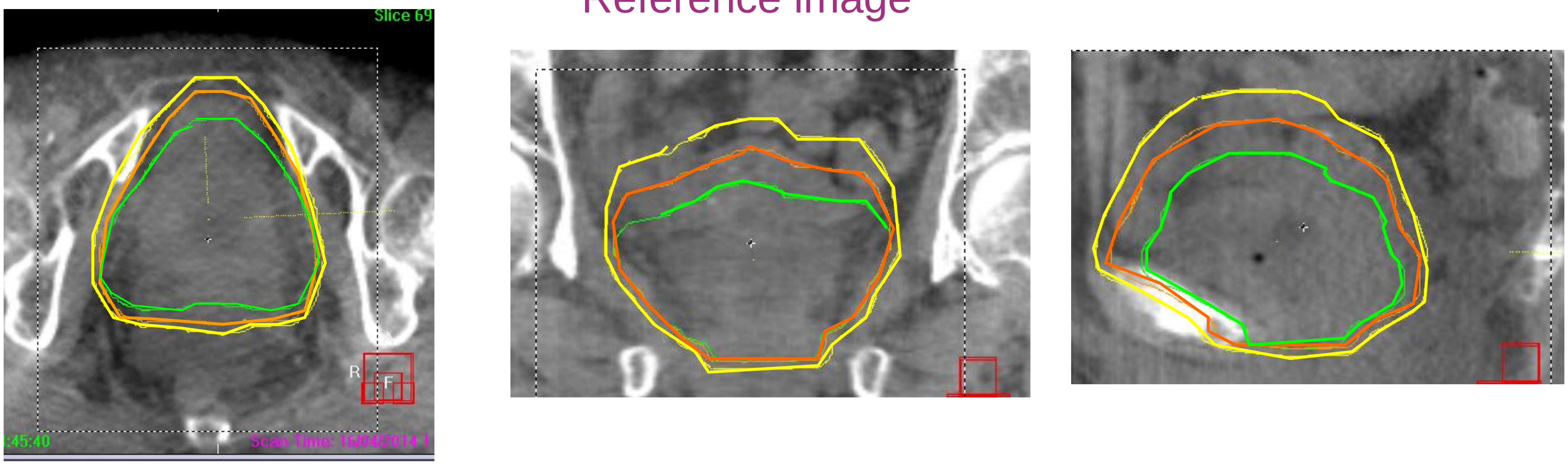
ii) reducing time to image acquisition (<30mins),

iii) ensure appropriate clinical assessment is made and that patient is not developing toxicity necessitating intervention and preventing from appropriate voiding

Which choice is the best
1. Small; 2.Medium; 3.Large; 4.Shift; 5.None



Reference image

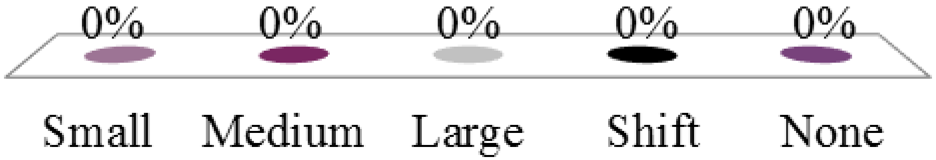


Treatment image

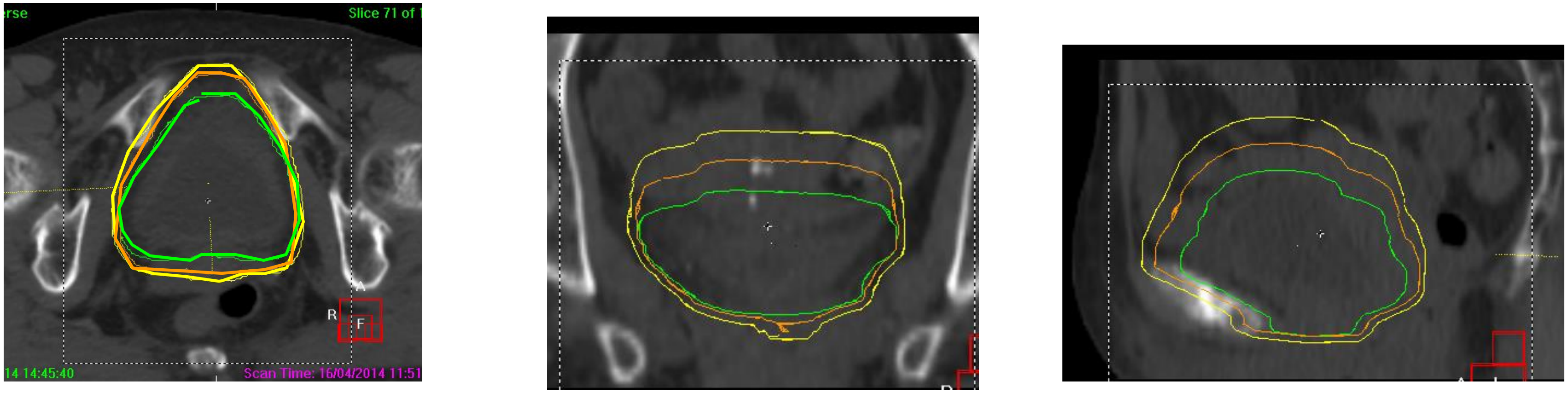
ESTRO School

Which choice is the best

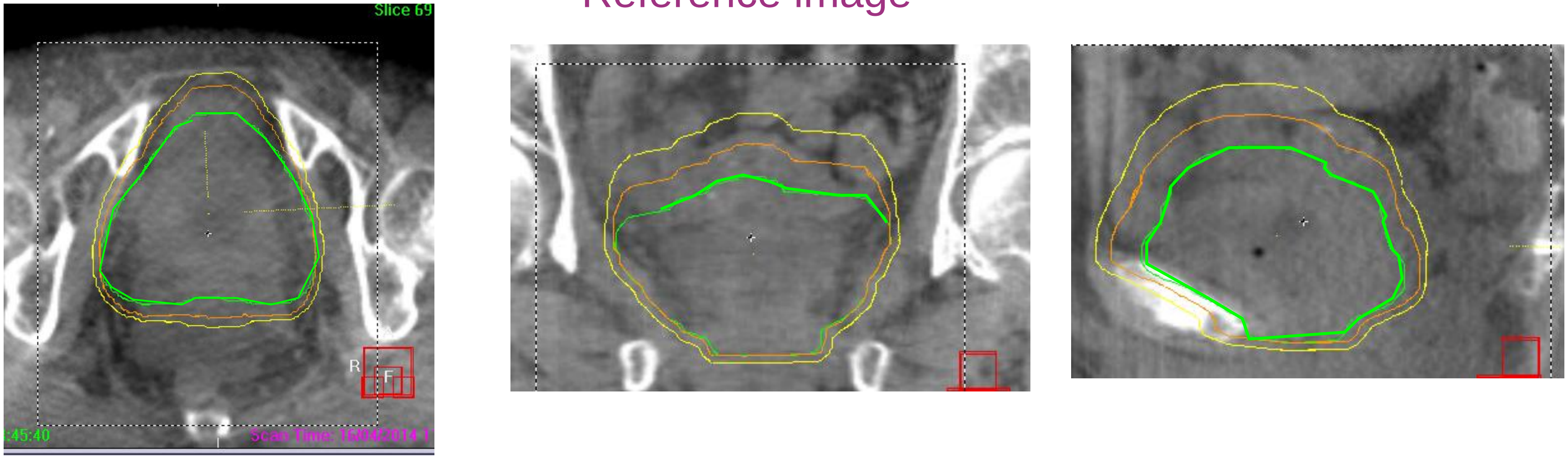
1. Small
2. Medium
3. Large
4. Shift
5. None



Case 3-Small



Reference image



Treatment image

Registration issues

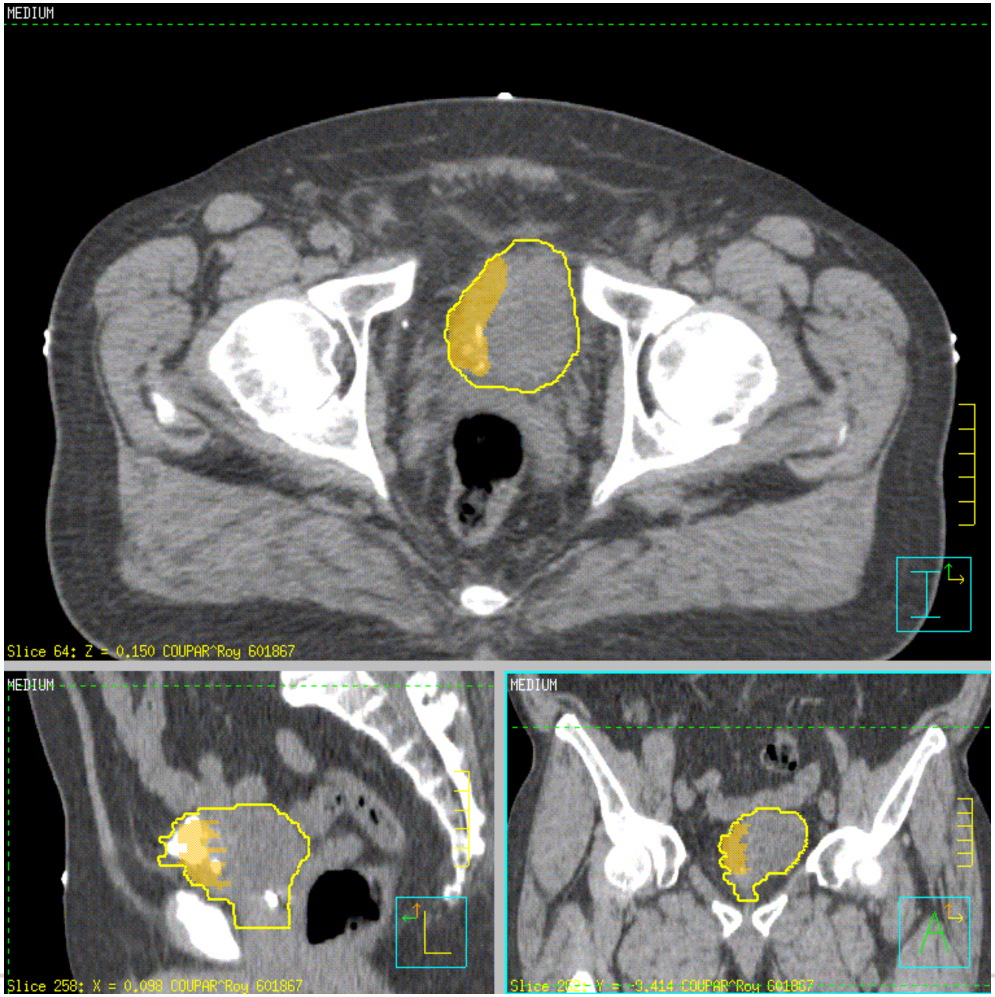
Consistent PTV selection between observers

No PTV is suitable- too large

Small

Replan of systematically smaller ?

Plan of the day – Full bladder

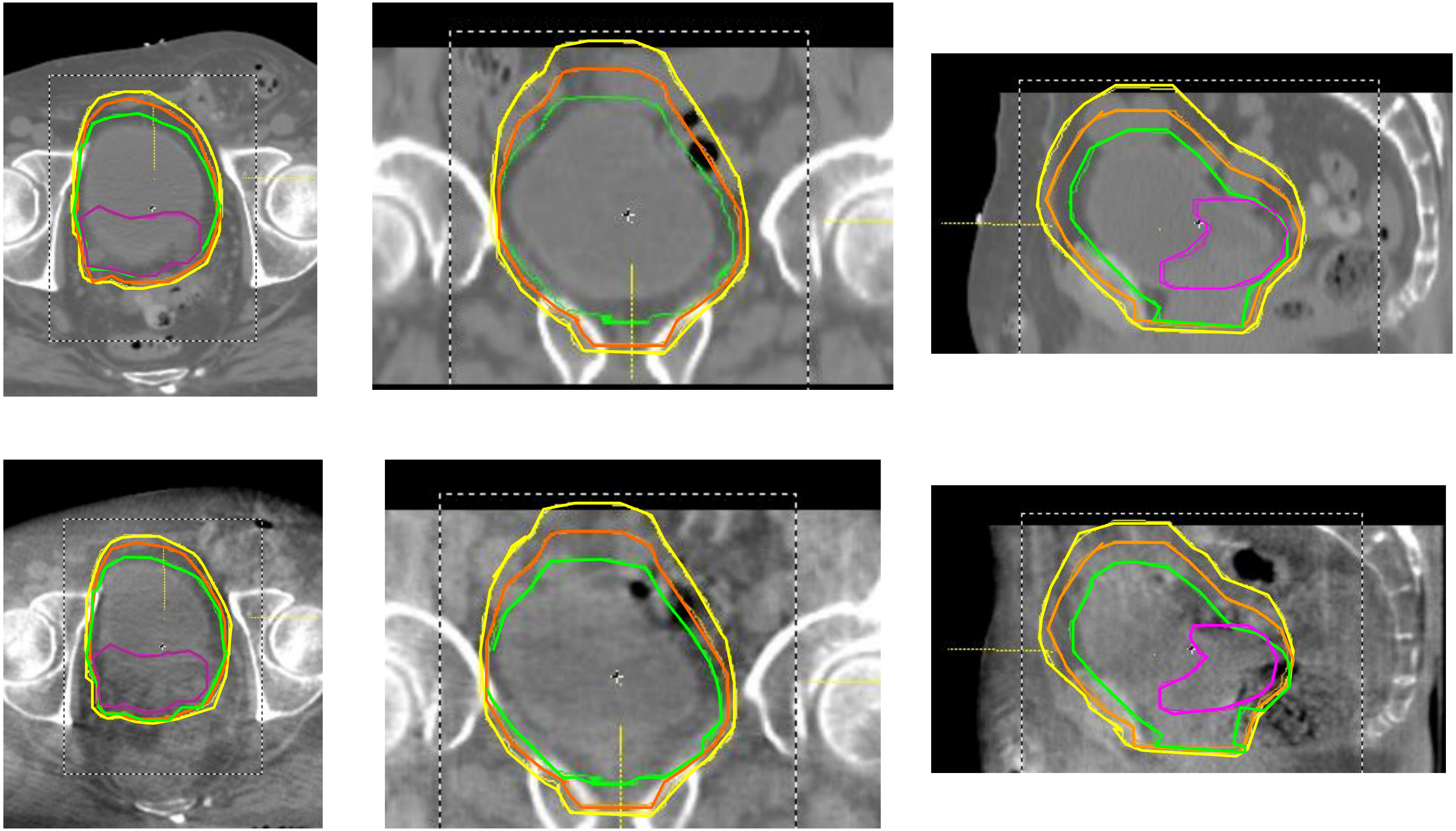


Partially' full bladder

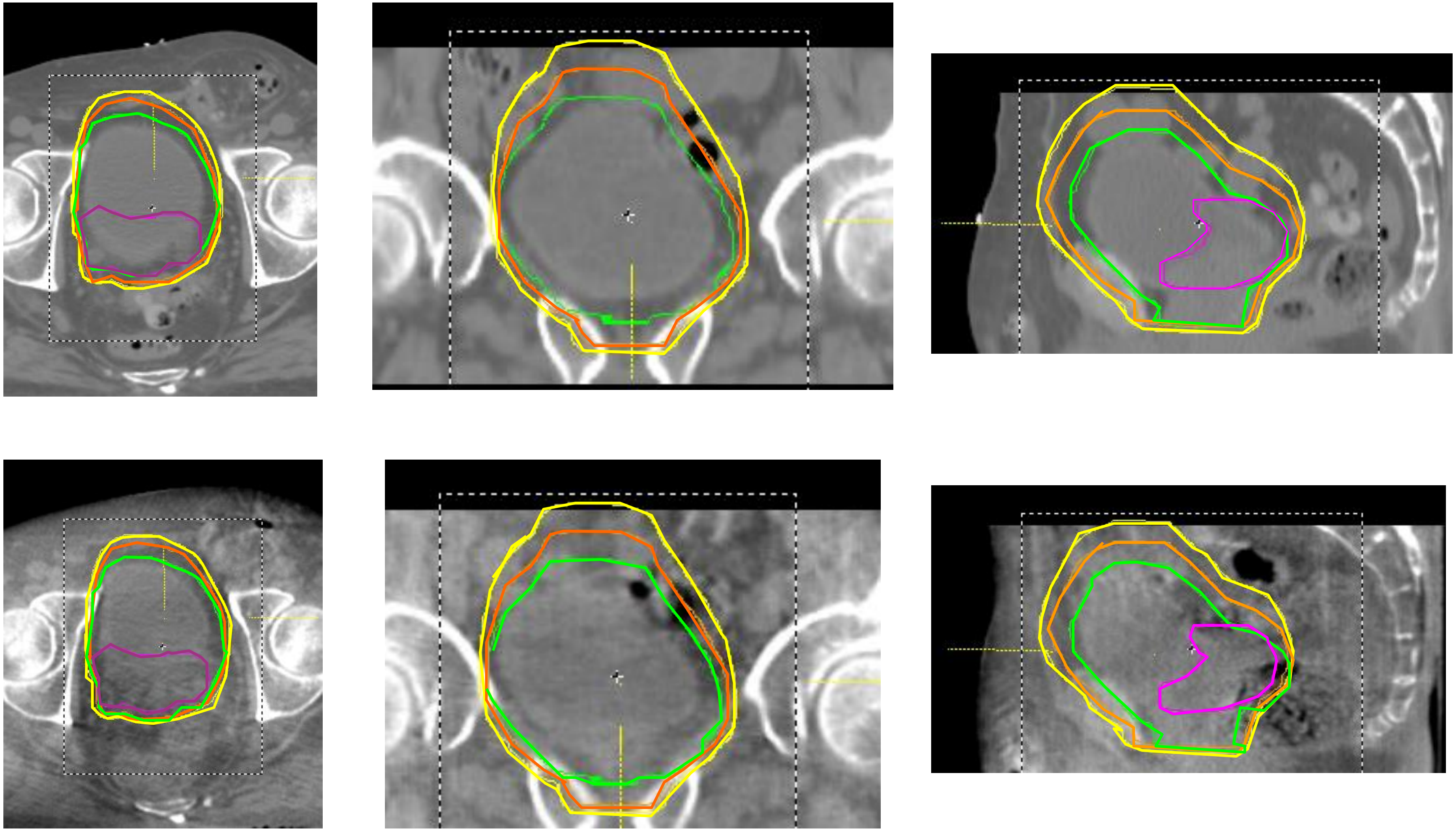
30 and 60 min scans after emptying + 350mls of fluid

Concomitant boost

Plan of the day – Full bladder



Which outline is not good?
1. Small; 2.Medium; 3.Large;



Which outline is not good?

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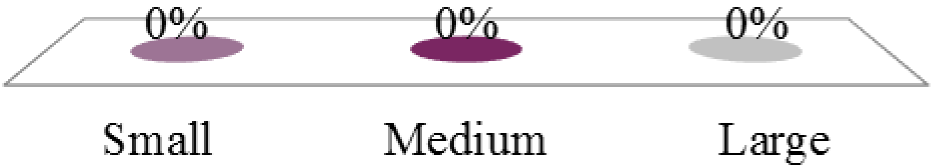
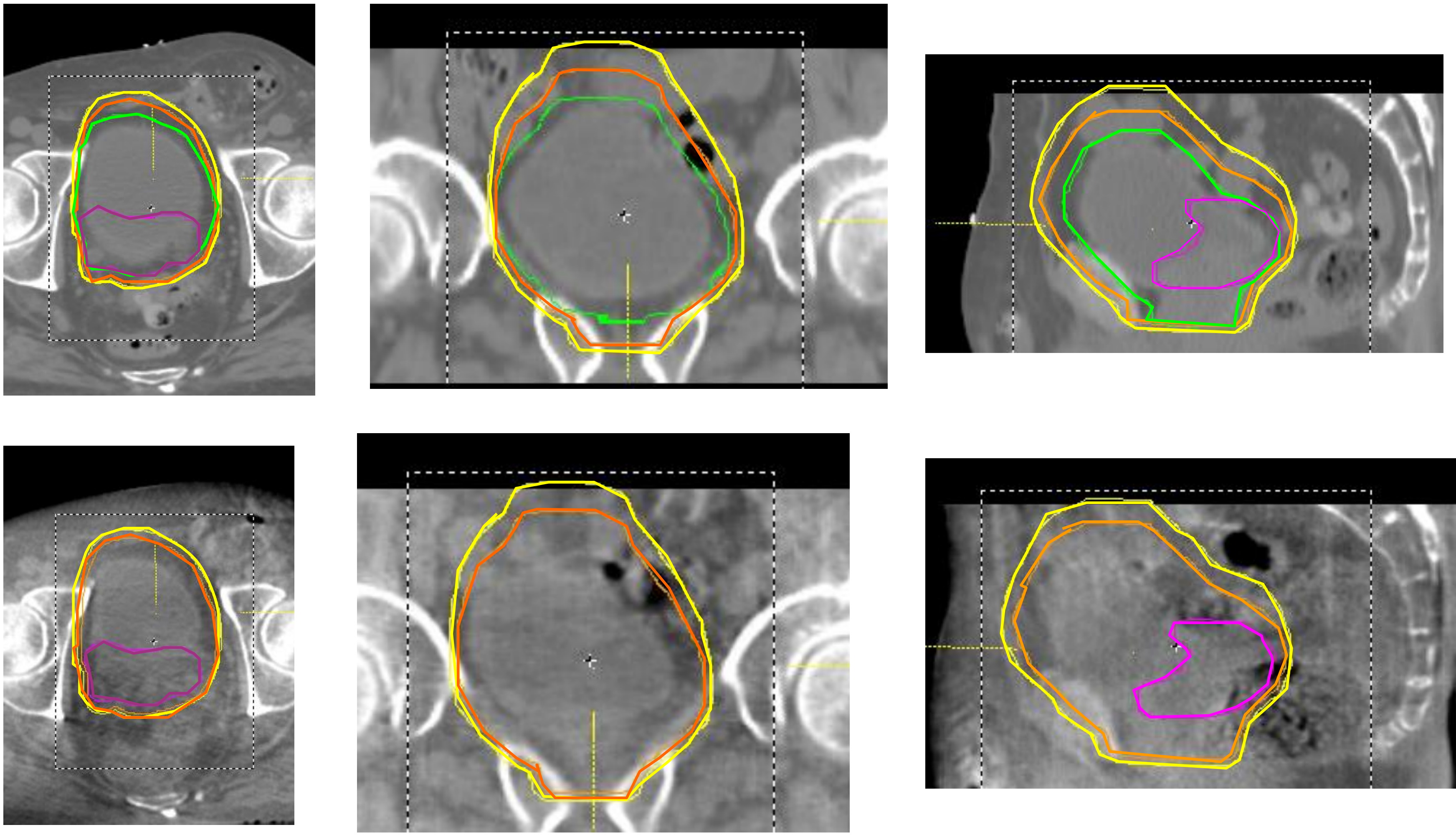
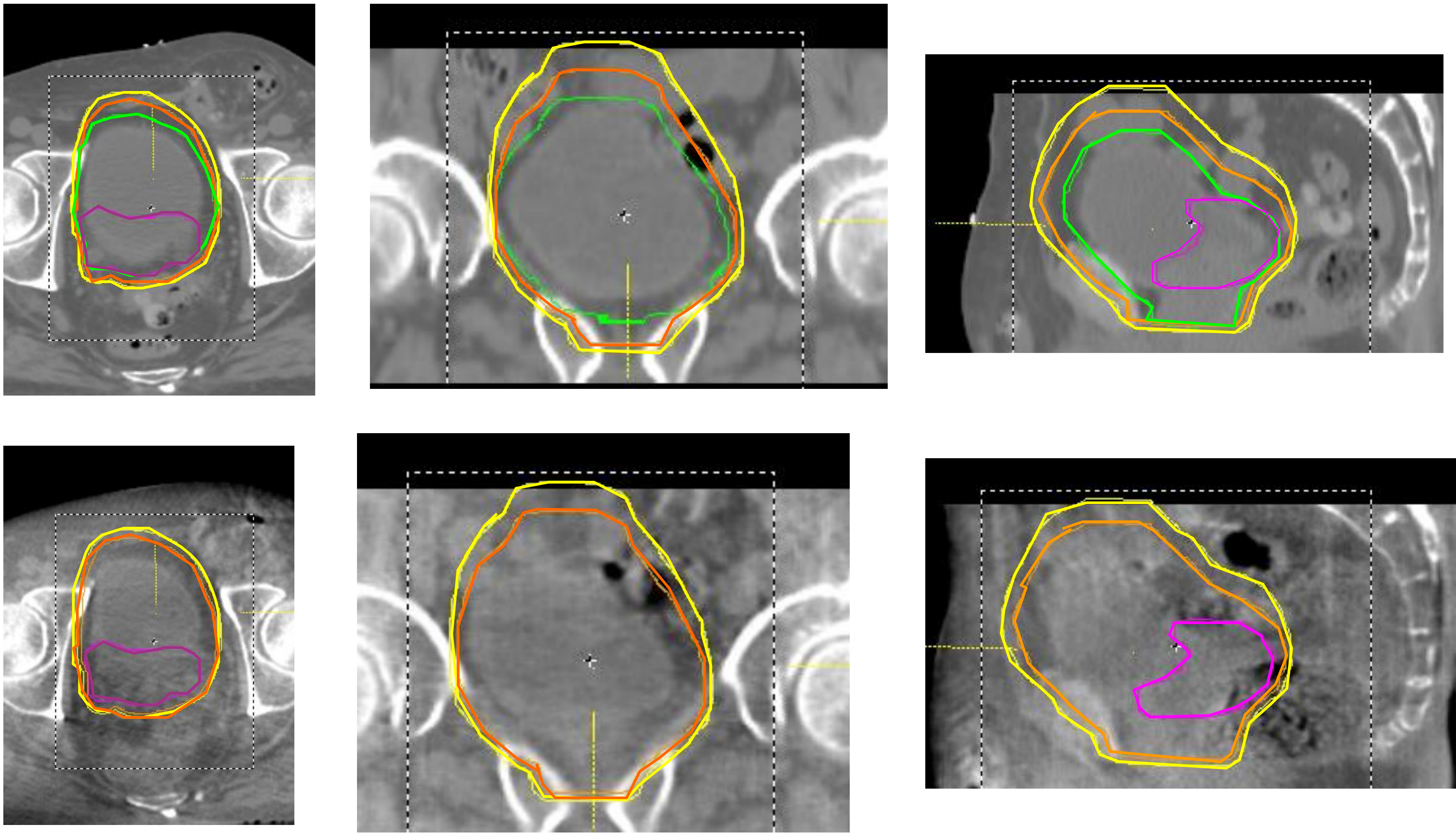
2. Medium
3. Large



Reject small

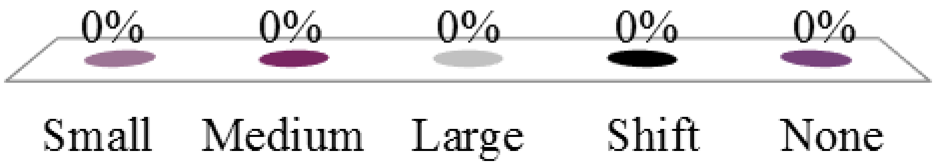


Which choice is the best
1. Small; 2.Medium; 3.Large; 4.Shift; 5.None

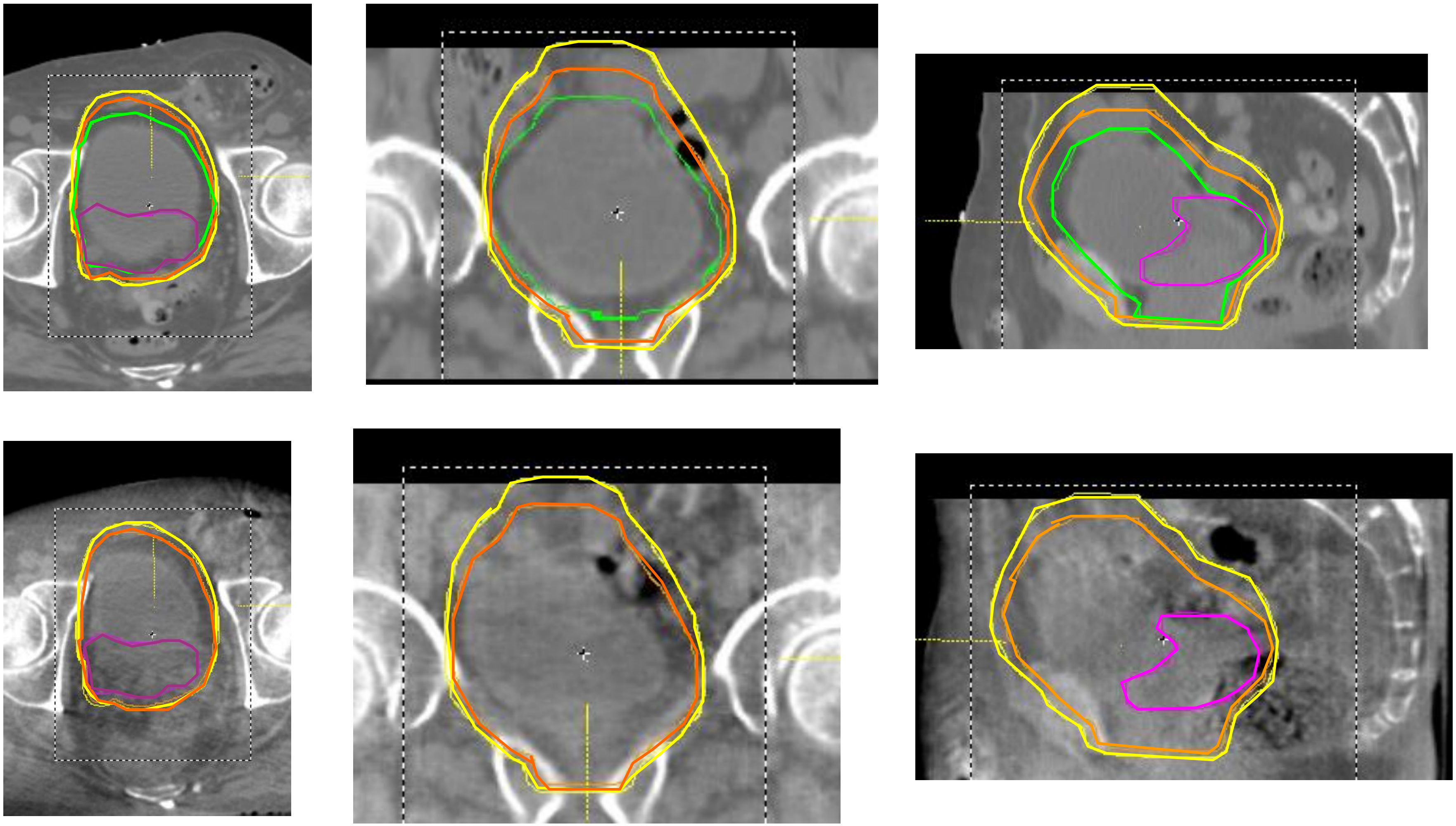


Which choice is the best

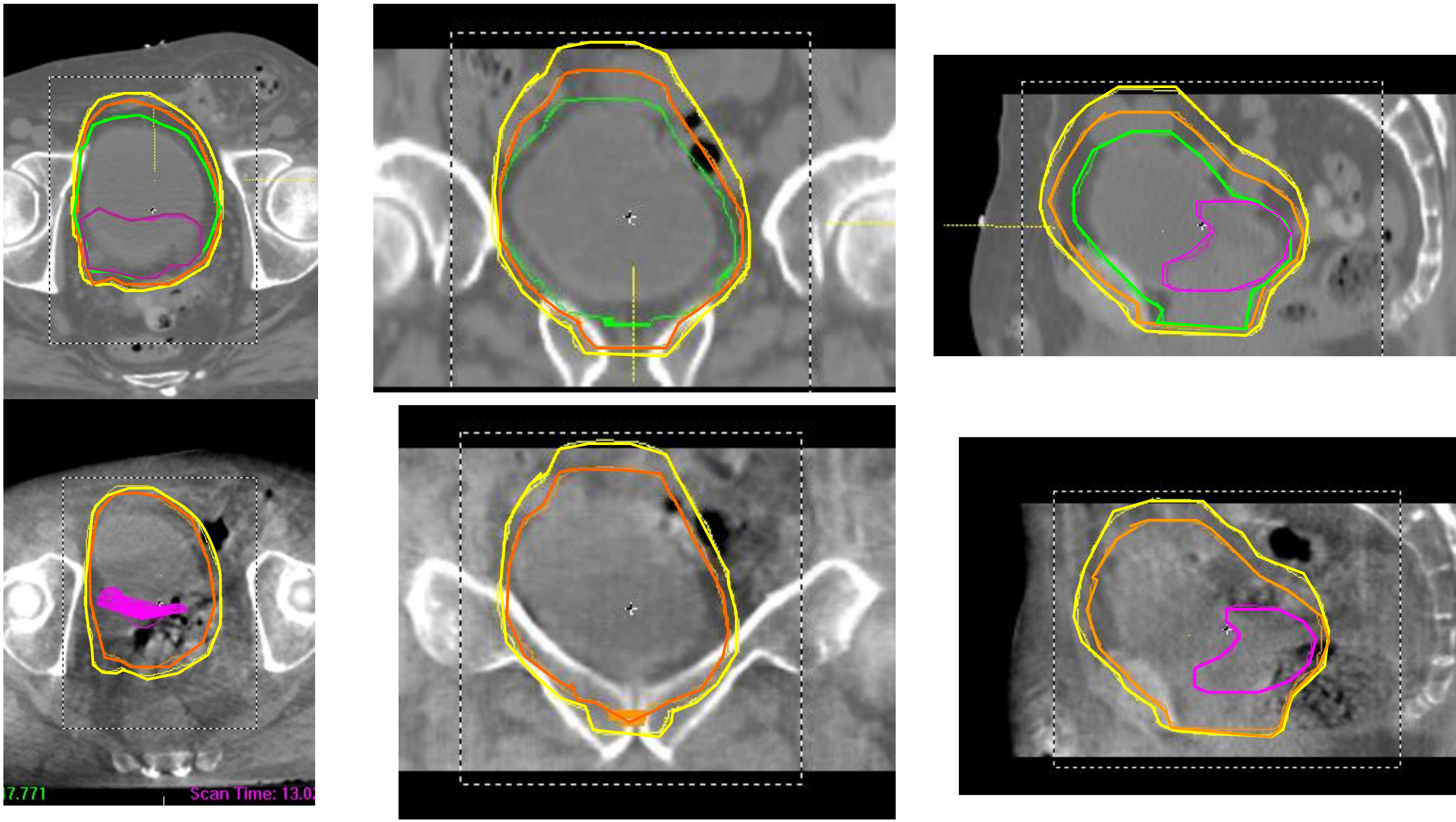
1. Small
2. Medium
3. Large
4. Shift
5. None



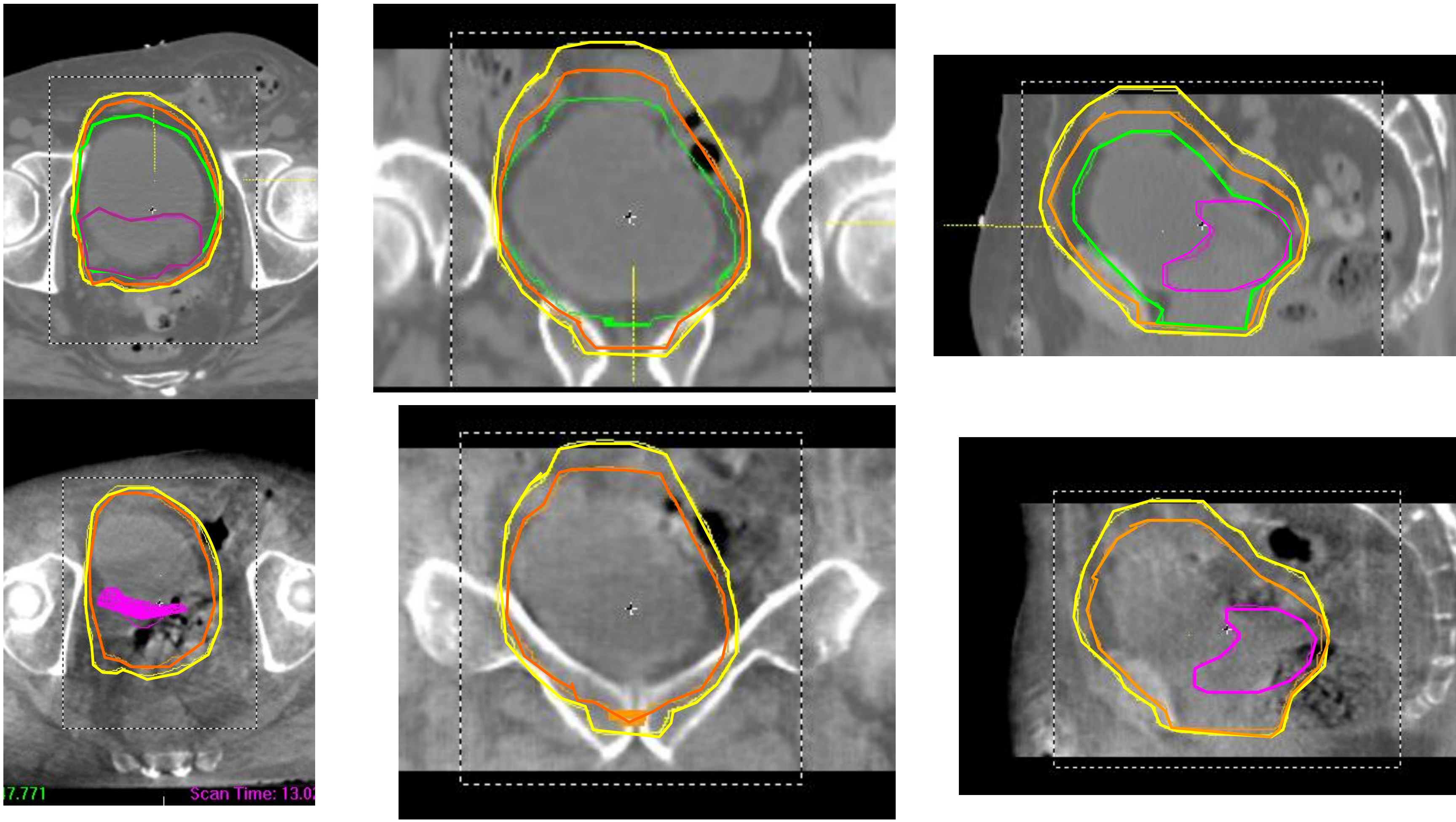
Shift



Check



Which choice is the best
1. Small; 2.Medium; 3.Large; 4.Shift; 5.None



Which choice is the best

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3. Large
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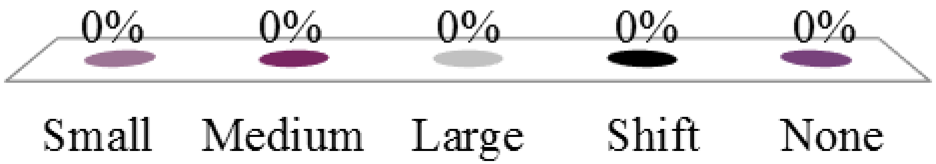
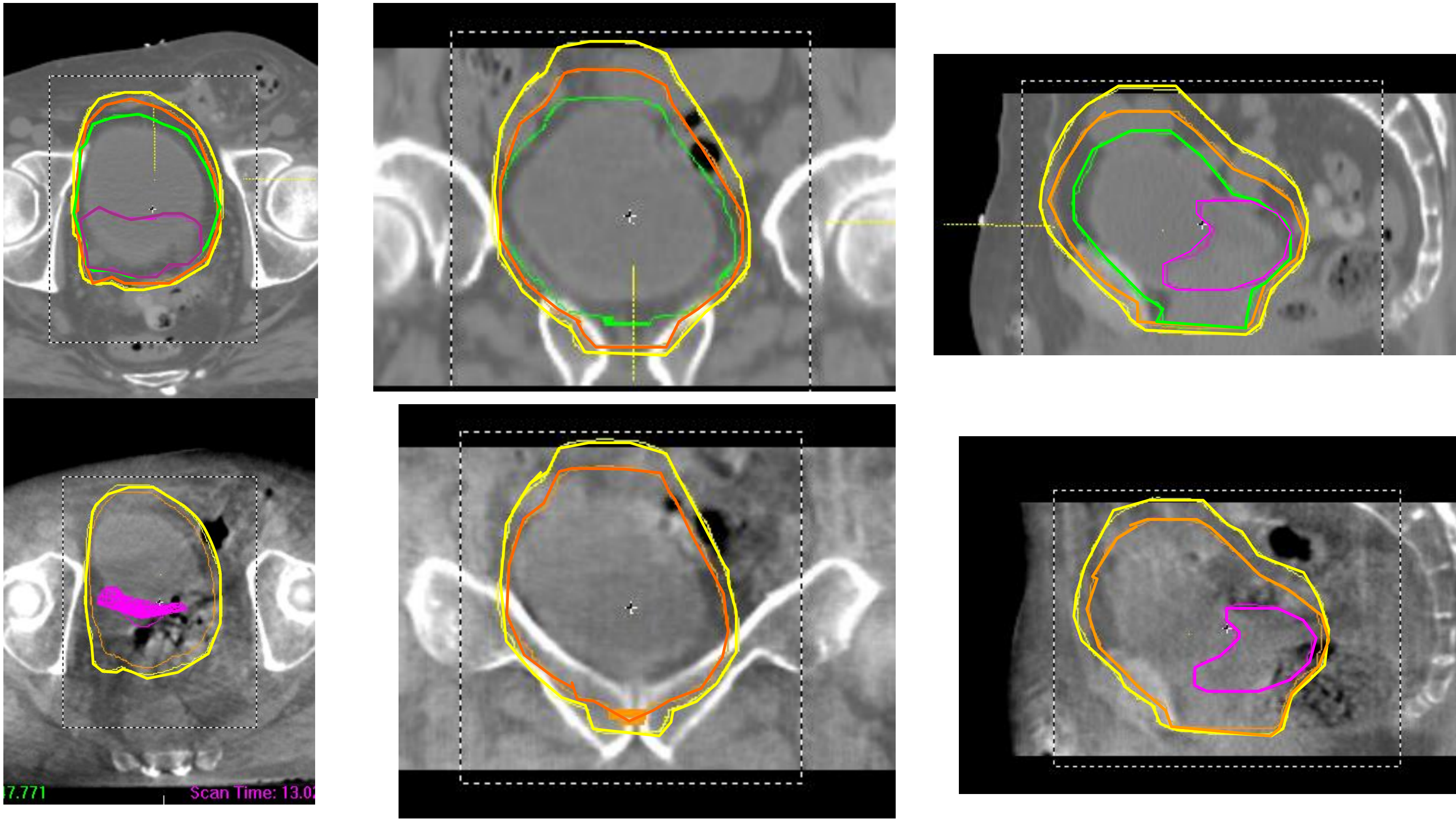
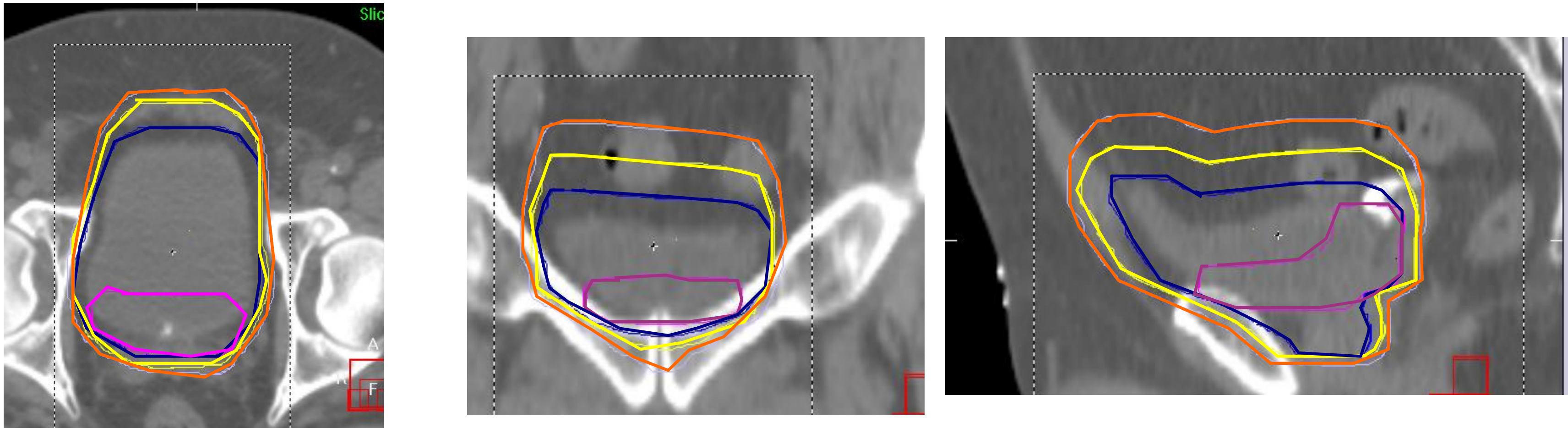
5. None



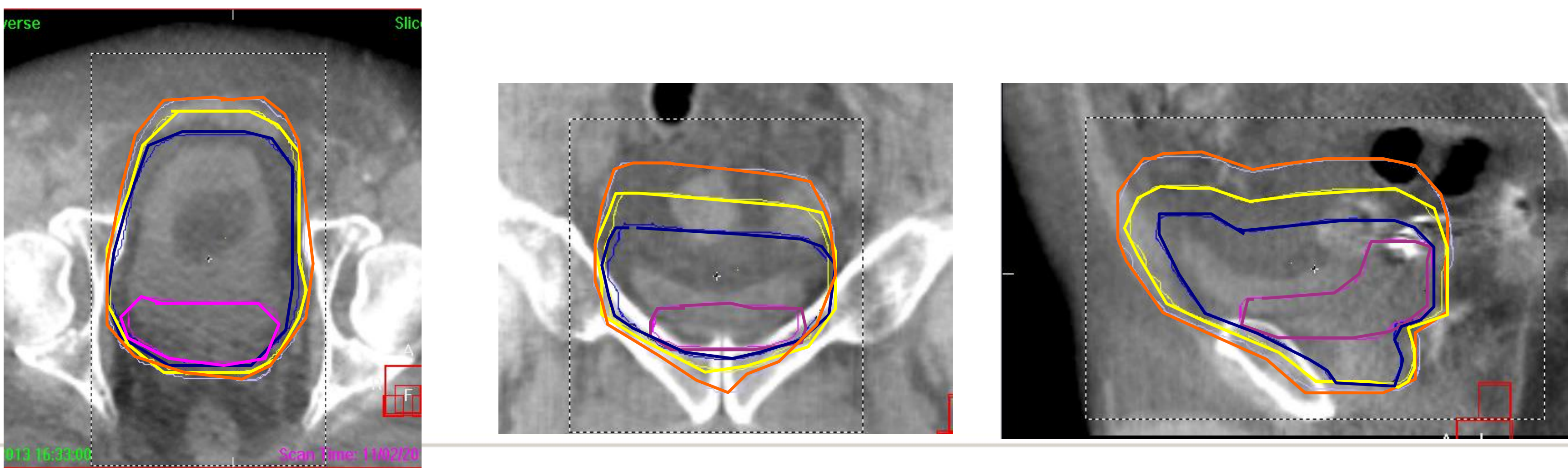
Plan of the day



Case 5

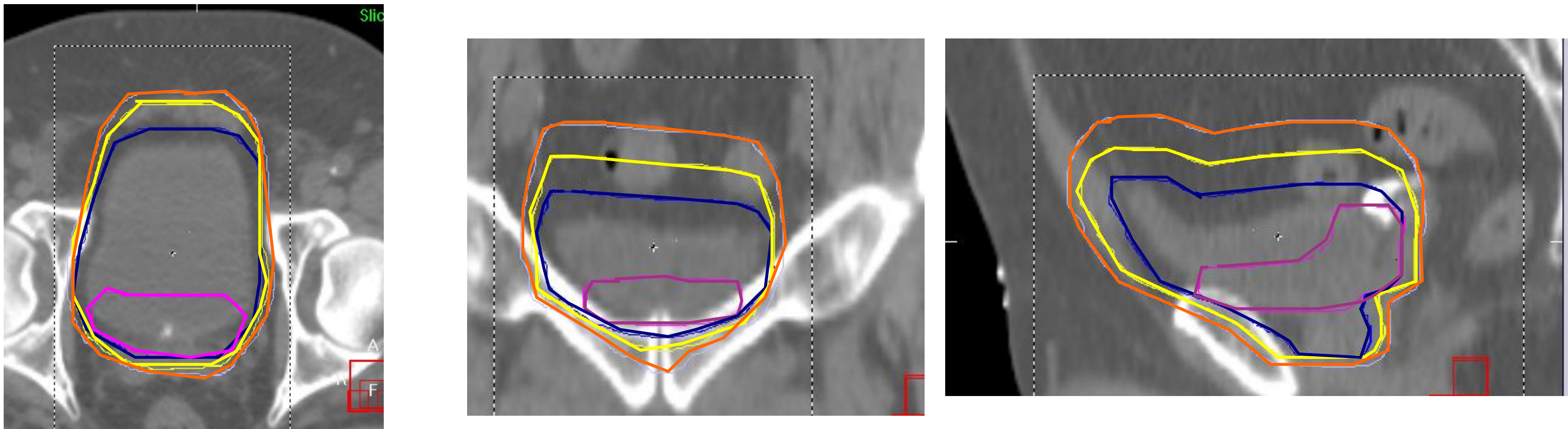


Reference image

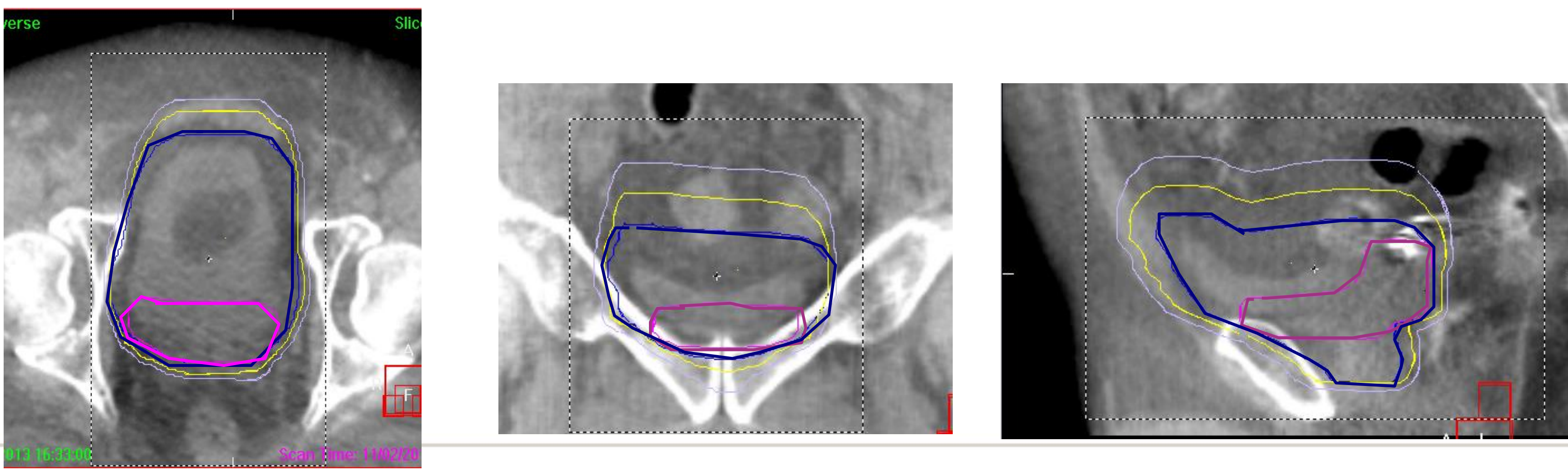


Treatment image

Which choice is the best
1. Small; 2.Medium; 3.Large; 4.Shift; 5.None



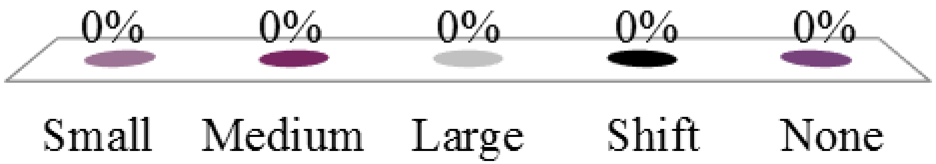
Reference image



Treatment image

Which choice is the best

1. Small
2. Medium
3. Large
4. Shift
5. None



Significant shape change

Bladder too small

↓

Small plan provides appropriate coverage of bladder but normal tissue sparing from high dose region compromised

↓

Appropriate to consider treatment with small plan

↓

Requires clinical review prior to next fraction.
Assessment :-
i) general hydration status
ii) development of urinary toxicity requiring intervention (preventing from appropriate holding)
iii) increasing time to image acquisition>30mins and, or
iv) increasing volume of fluids in drinking protocol

ESTRO School

Registration issues

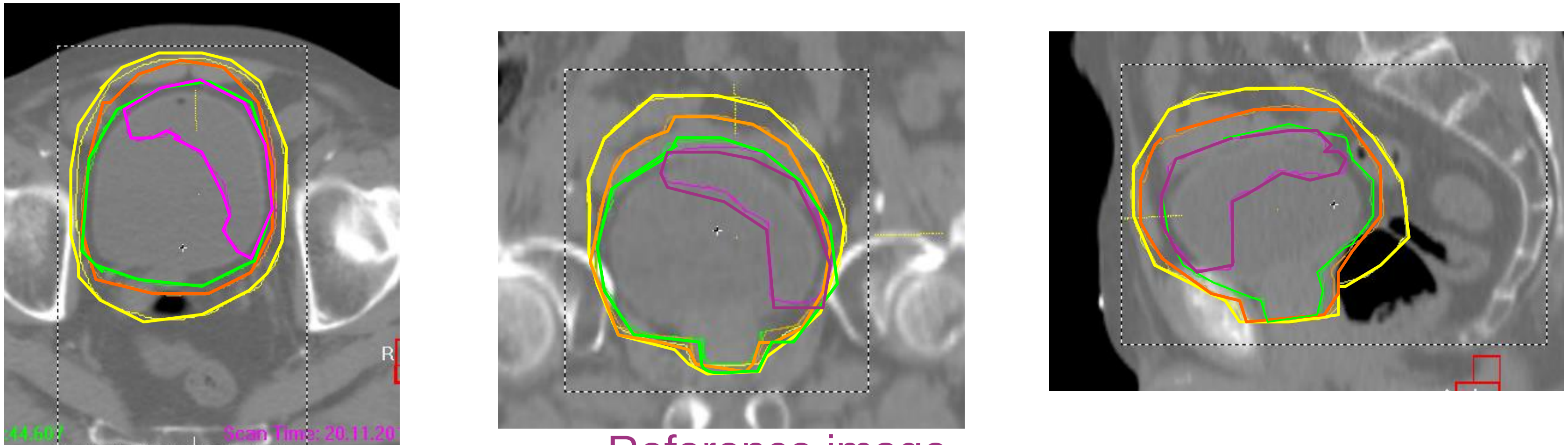
Consistent PTV selection between observers

No PTV is suitable- too large

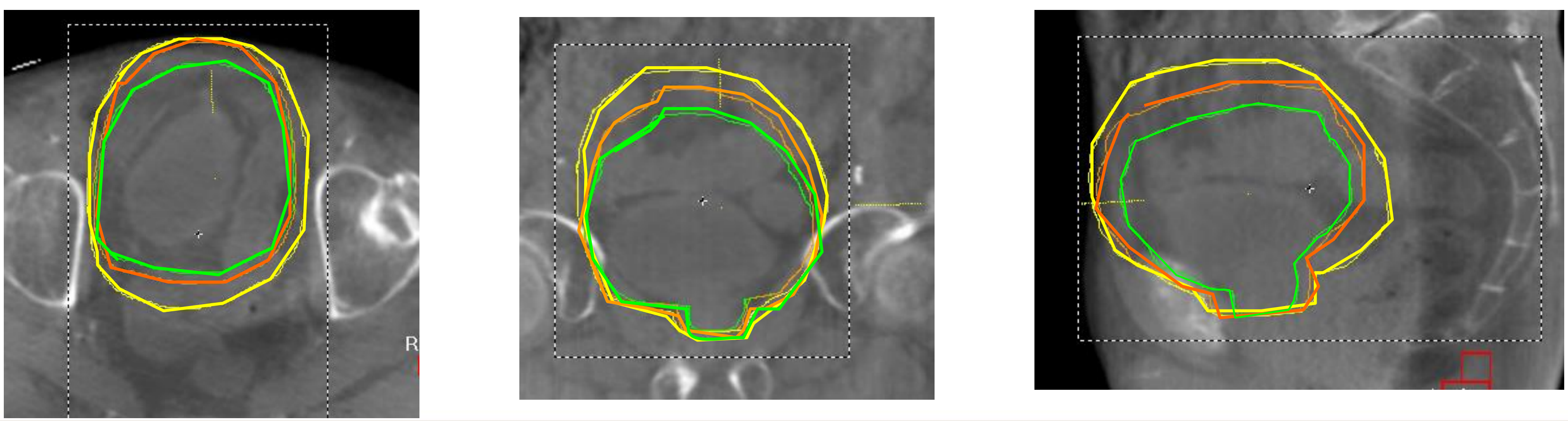
No PTV is suitable – too small

Replan of systematically smaller ??

Case 6



Reference image



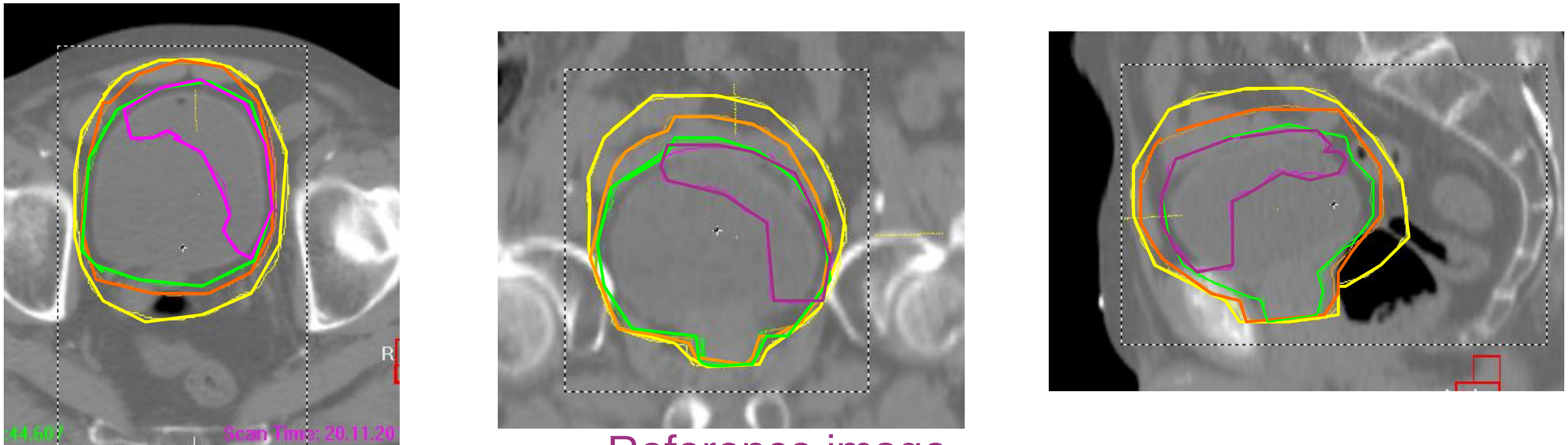
Treatment image

ESTRO School

Which choice is the best

1. Treat
2. Shift and treat
3. Ask patient to get off bed and drink more
4. Adjust drinking protocol for tomorrow

Which choice is the best



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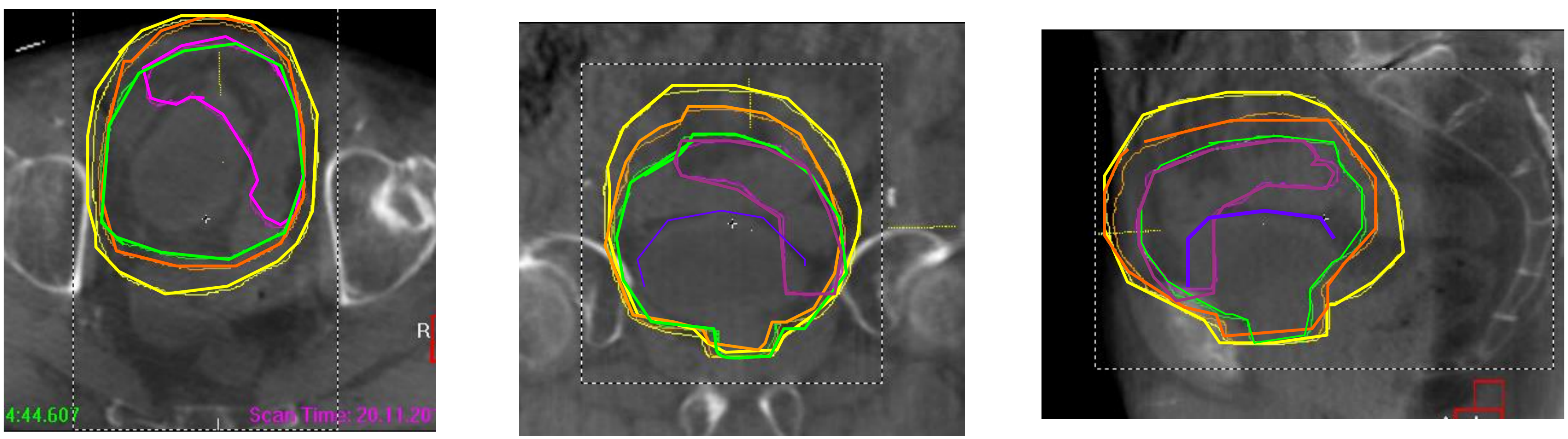
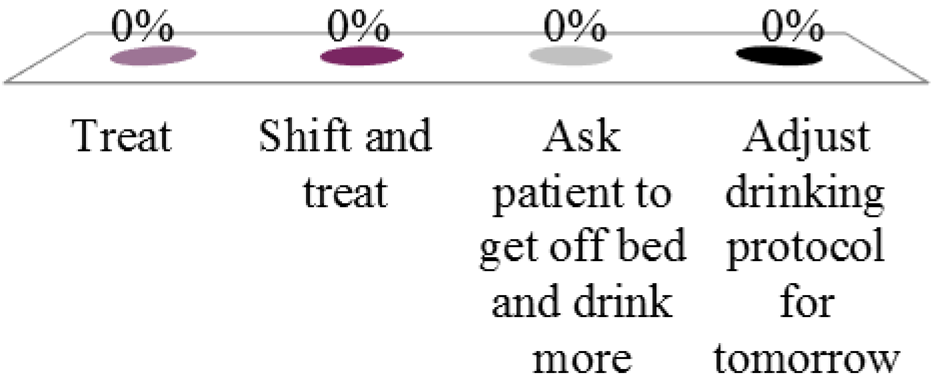


Treatment image

Which choice is the best

1. Treat
2. Shift and treat
3. Ask patient to get off bed and drink more
4. Adjust drinking protocol for tomorrow



ESTRO School

Significant shape change

Bladder too small

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↓

Appropriate to consider treatment with small plan

↓

Requires clinical review prior to next fraction.
Assessment :-
i) general hydration status
ii) development of urinary toxicity requiring intervention (preventing from appropriate holding)
iii) increasing time to image acquisition>30mins and, or
iv) increasing volume of fluids in drinking protocol

Significant shape change

Bladder too small

↓

Small plan provides appropriate coverage of bladder but normal tissue sparing from high dose region compromised

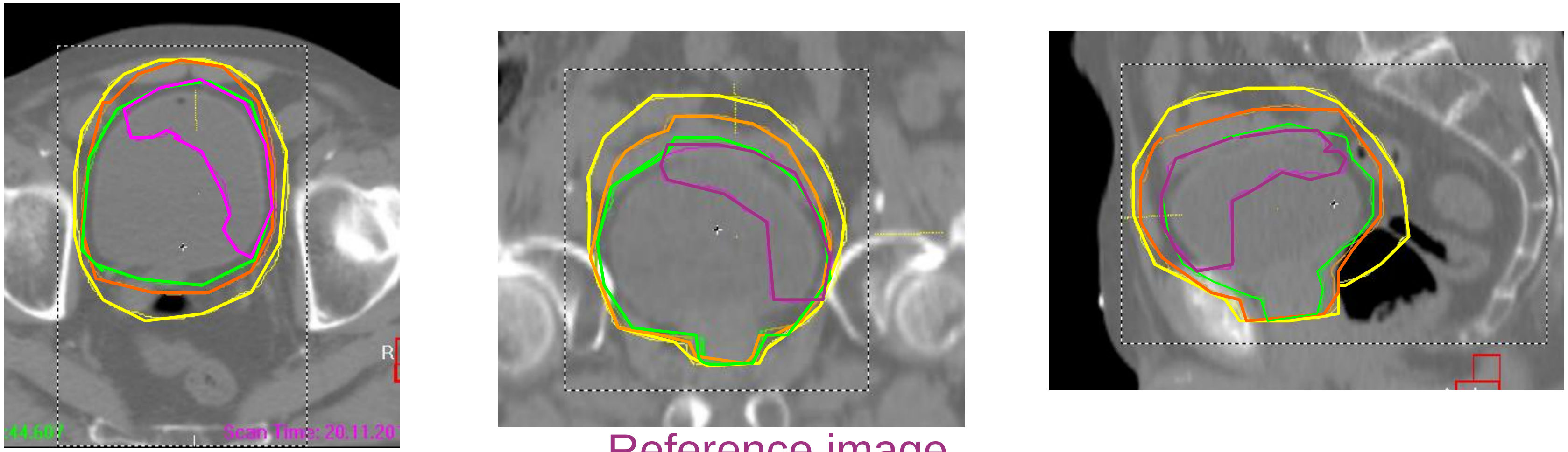
↓

Appropriate to consider treatment with small plan

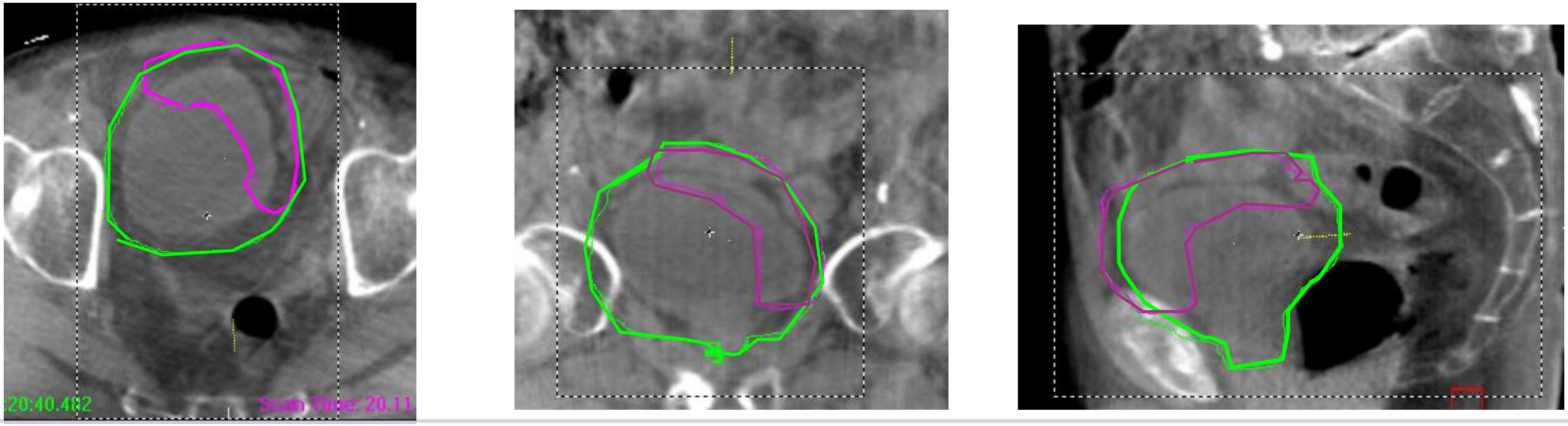
↓

Requires clinical review prior to next fraction.
Assessment :-
i) general hydration status
ii) development of urinary toxicity requiring intervention (preventing from appropriate holding)
iii) increasing time to image acquisition>30mins and, or
iv) increasing volume of fluids in drinking protocol

Case 6 – extra drinking-40mins + more water

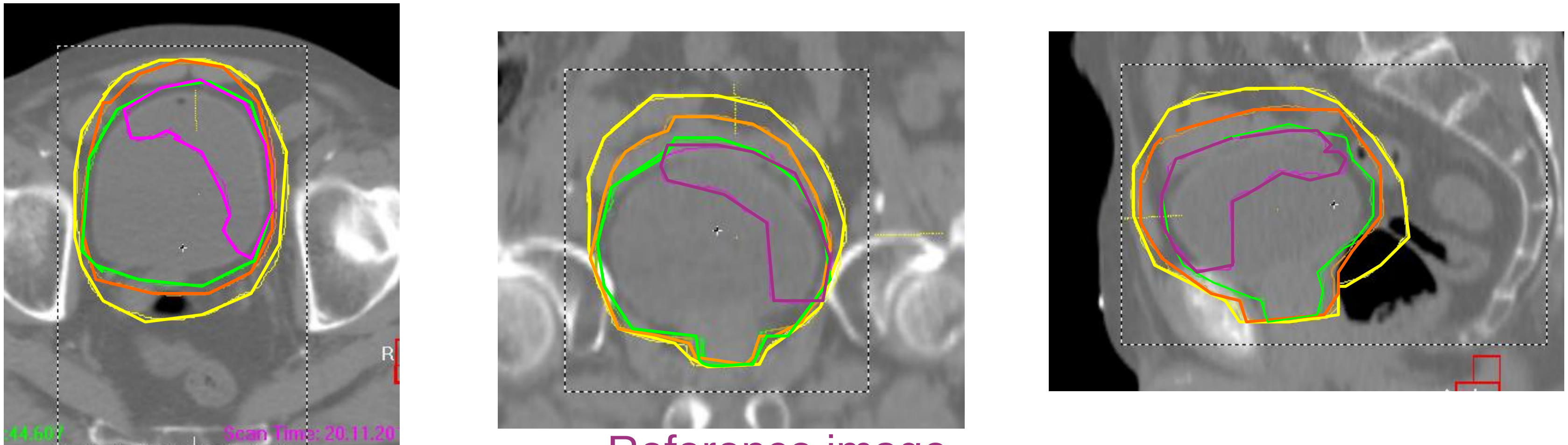


Reference image

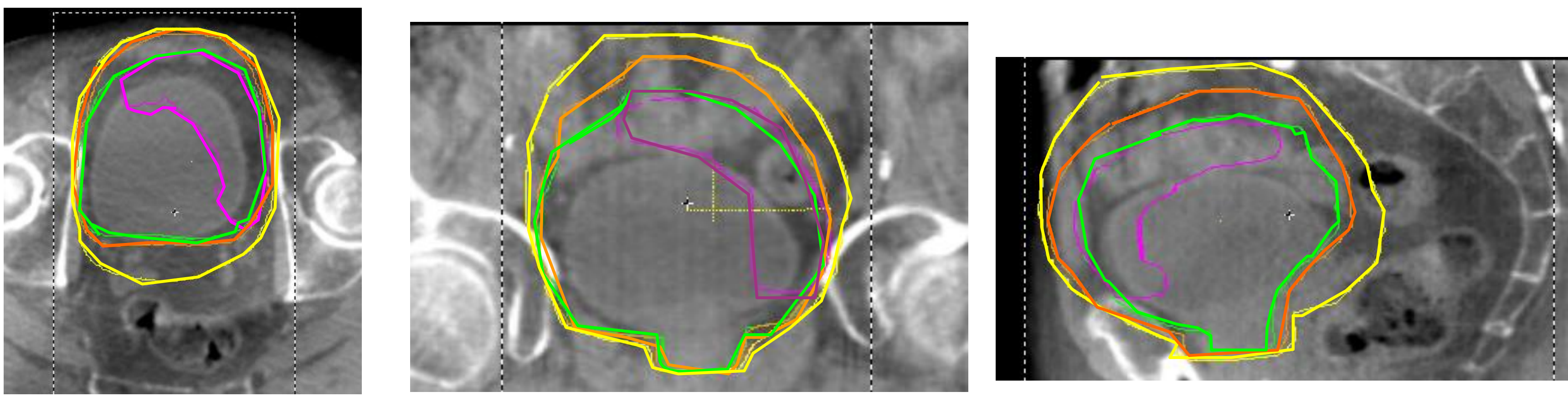


Treatment image

Case 6 (Day 2)- bony match

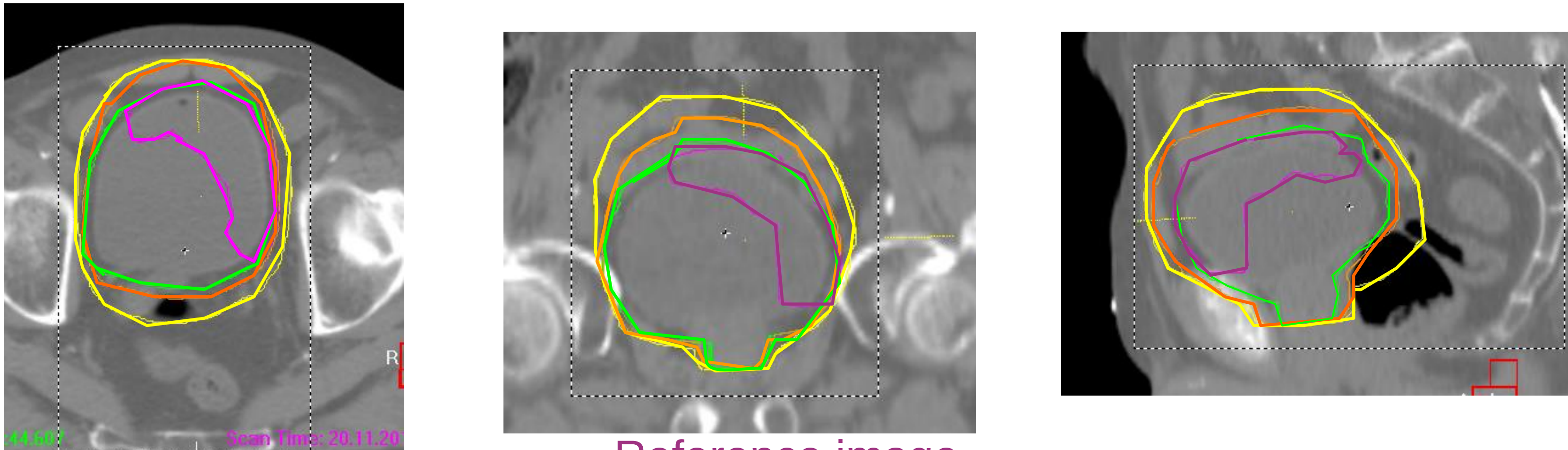


Reference image



Treatment image

Case 6 - soft tissue adjustment



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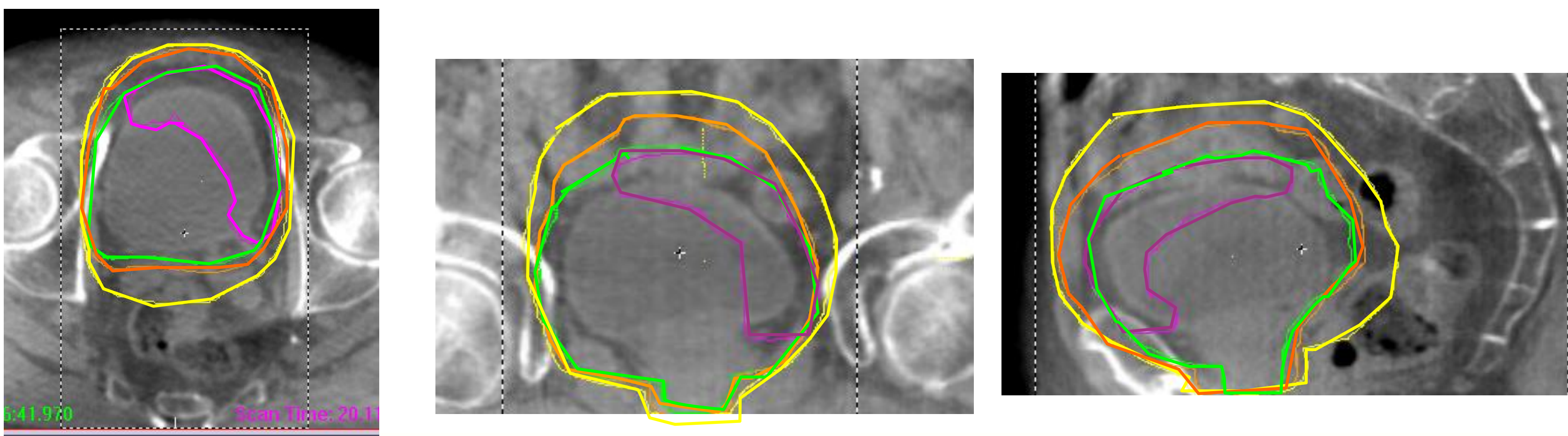
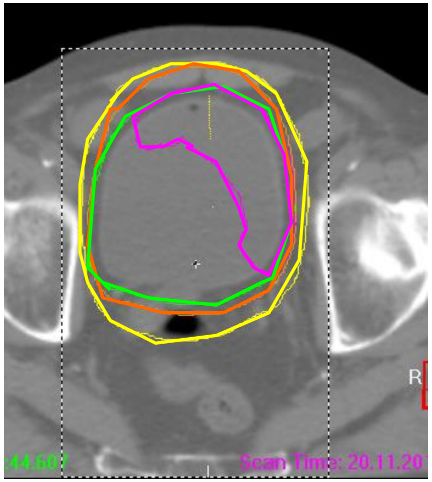
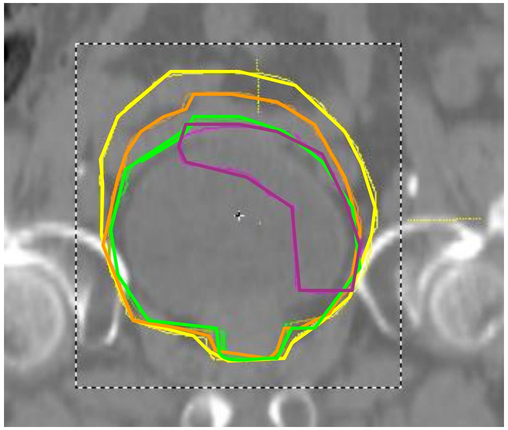


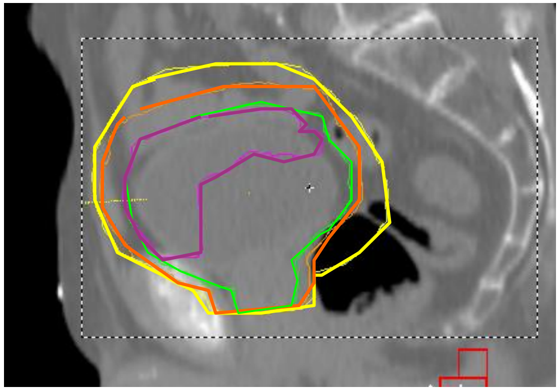
Treatment image

ESTRO School

Check coverage







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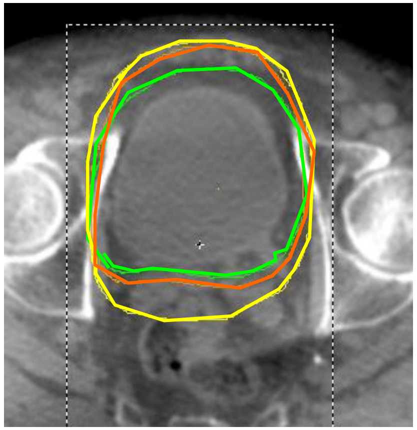
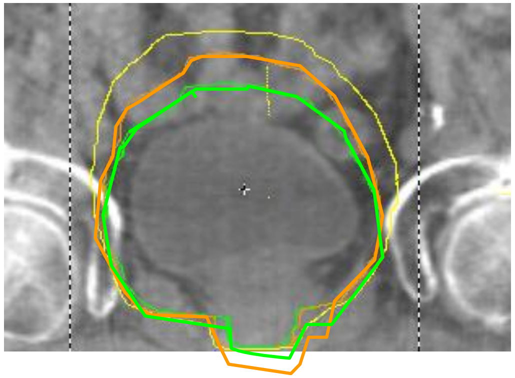
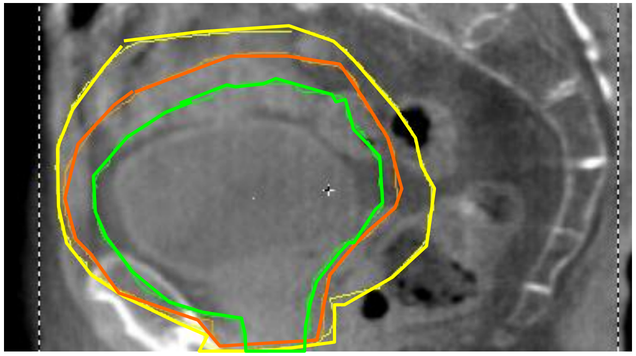
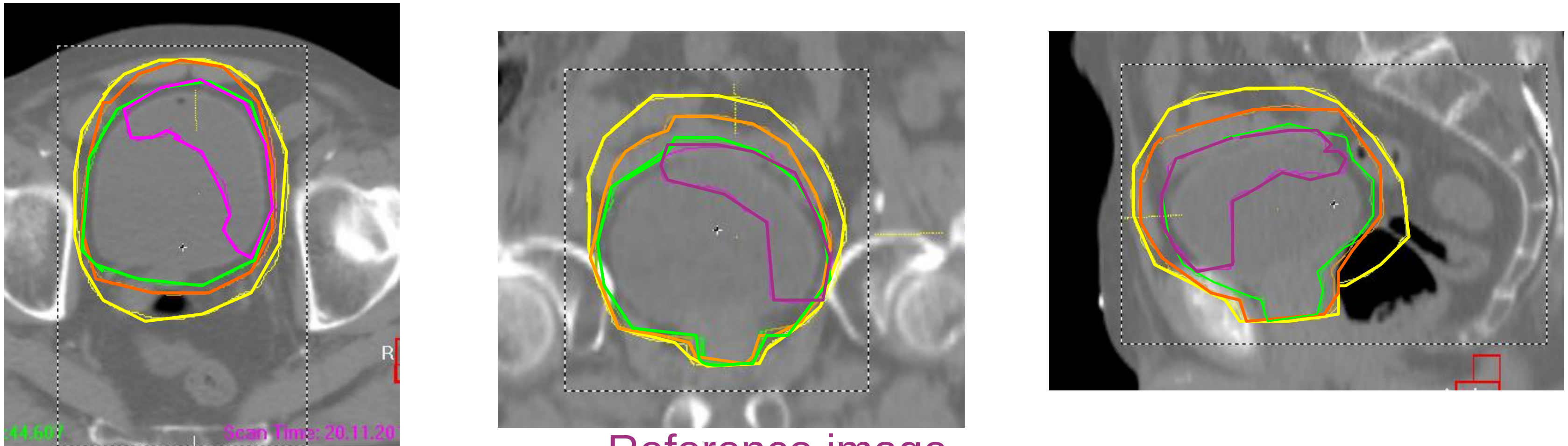






Treatment image

Check coverage



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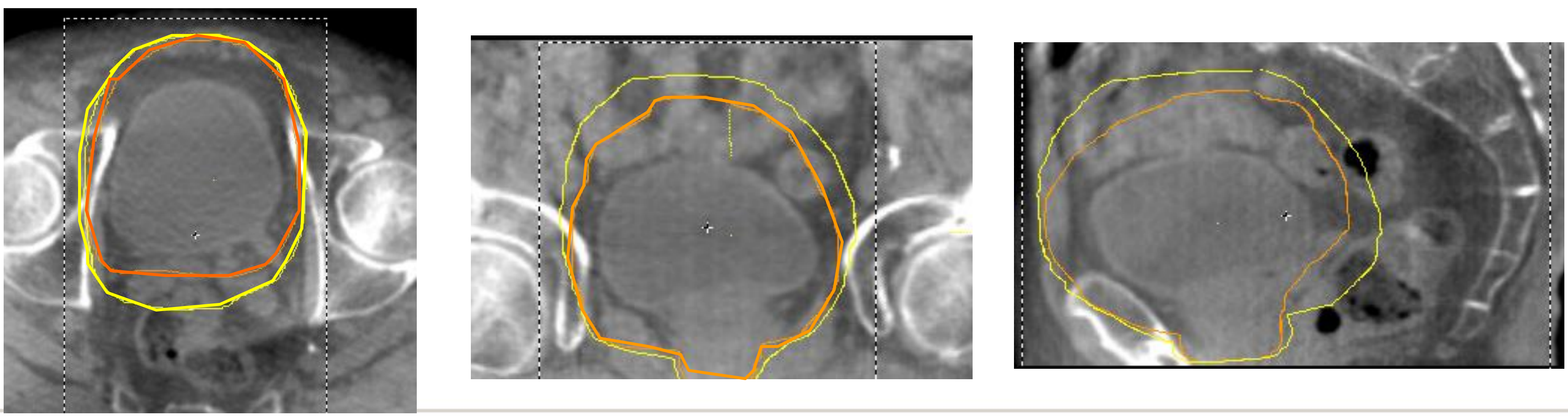
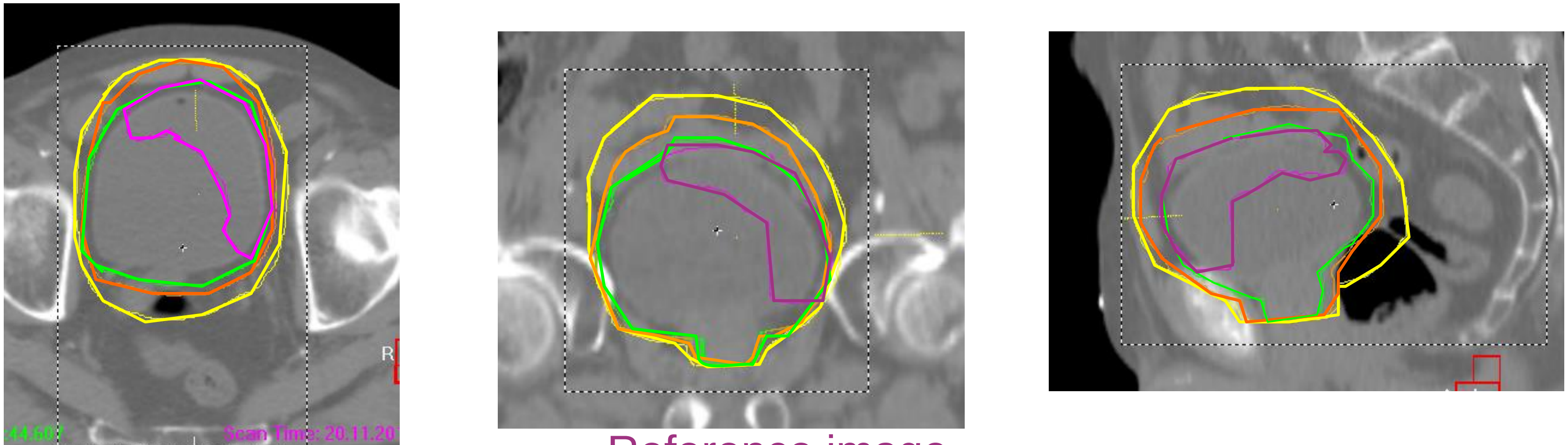


Treatment image

ESTRO School

Check boost



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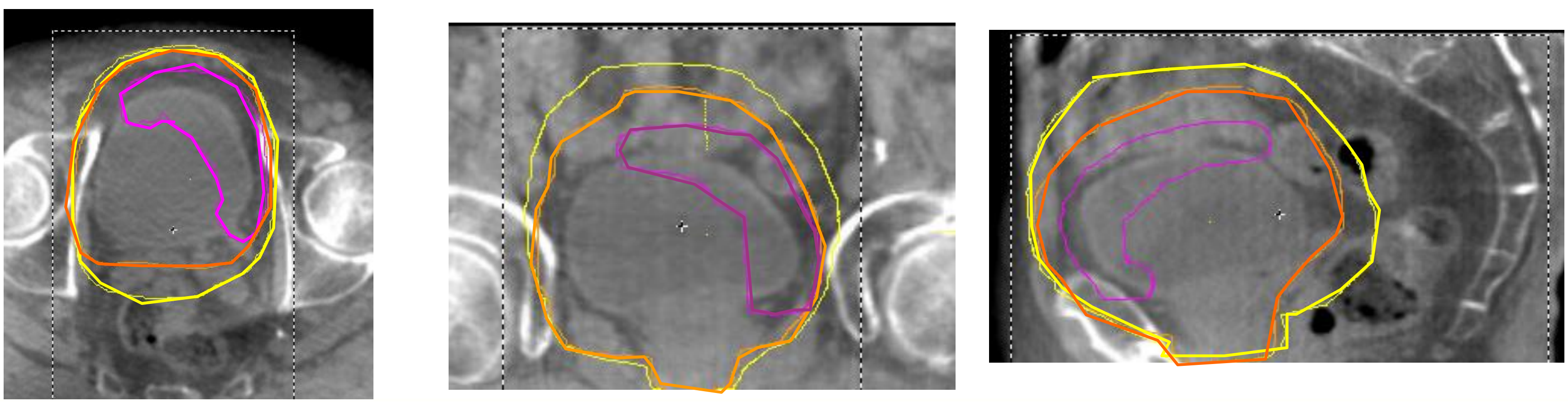
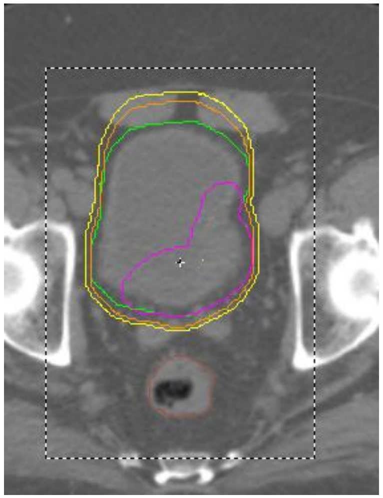
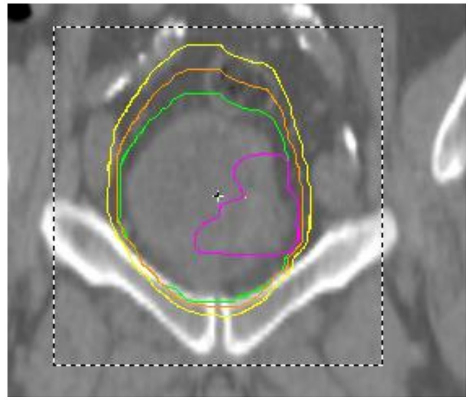
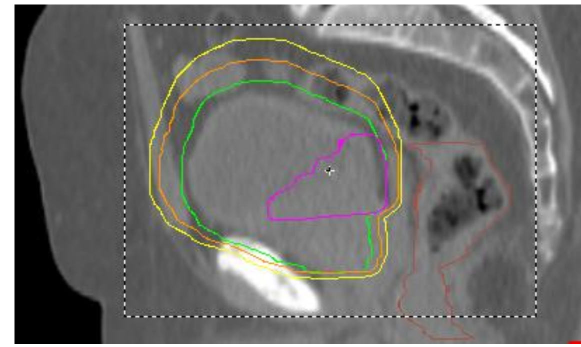


Treatment image

Case 7 - gas







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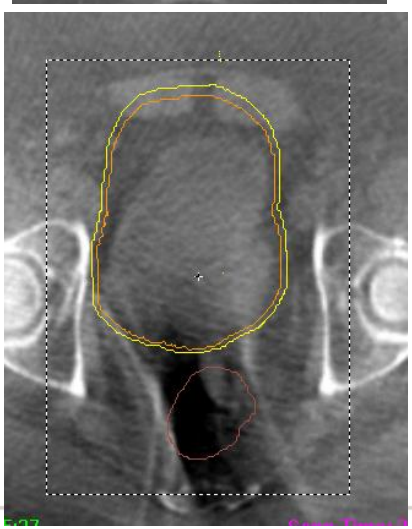
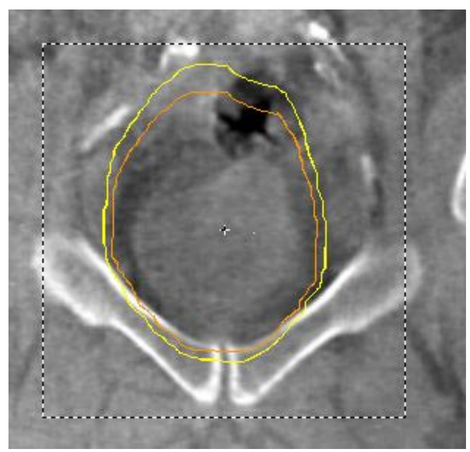
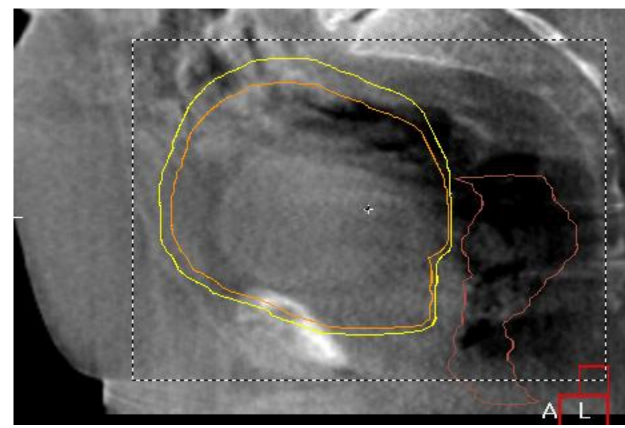
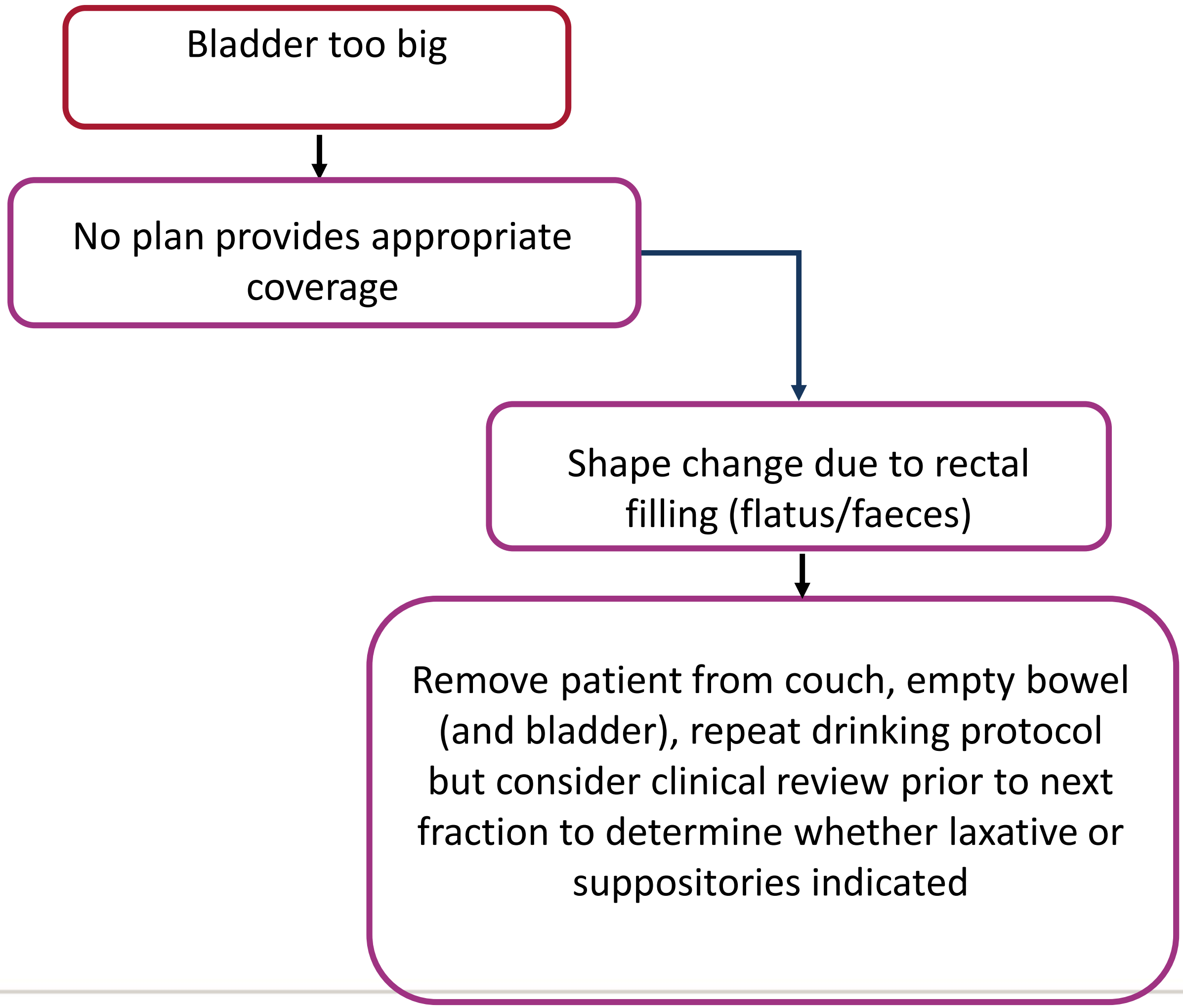






Treatment image

Significant shape change



HYBRID and RAIDER- assessment

HYBRID RAIDER

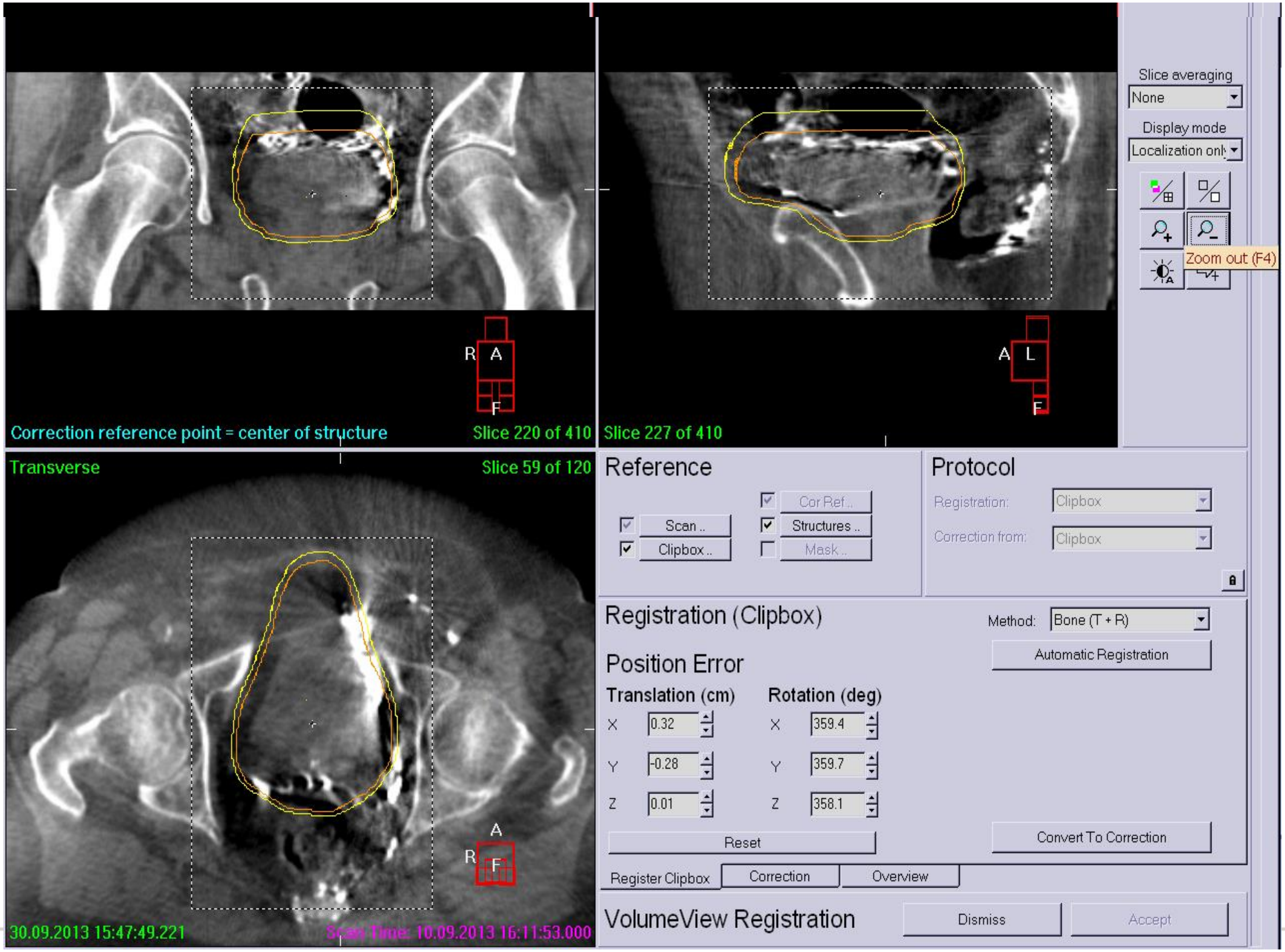
244 individuals (HYBRID=73, RAIDER=171)

24 recruiting centres.

86% of individuals achieved the score required for the QA approval on their first attempt

Courtesy of Emma Parsons
RTTQA

Case 9- boost and contrast?



ESTRO School

More Registration issues

Tolerance for movement   for example >1cm

Re plan if systematically smaller

Bladder and nodes

Training for selection

Guidelines for selection

Acknowledgements

Robert Huddart

Shaista Hafeez

Susan Lalondrelle

Fiona McDonald

Helen Taylor

RTTQA team

The Netherlands Cancer Institute

Antoni van Leeuwenhoek Huis

IGRT for stereotactic RT using cone beam CT

Marcel van Herk, Peter Remeijer, Anja Betgen,
Danny Minkema, Luc Dewit, Jan-Jakob Sonke, and Coen Rasch

Introduction

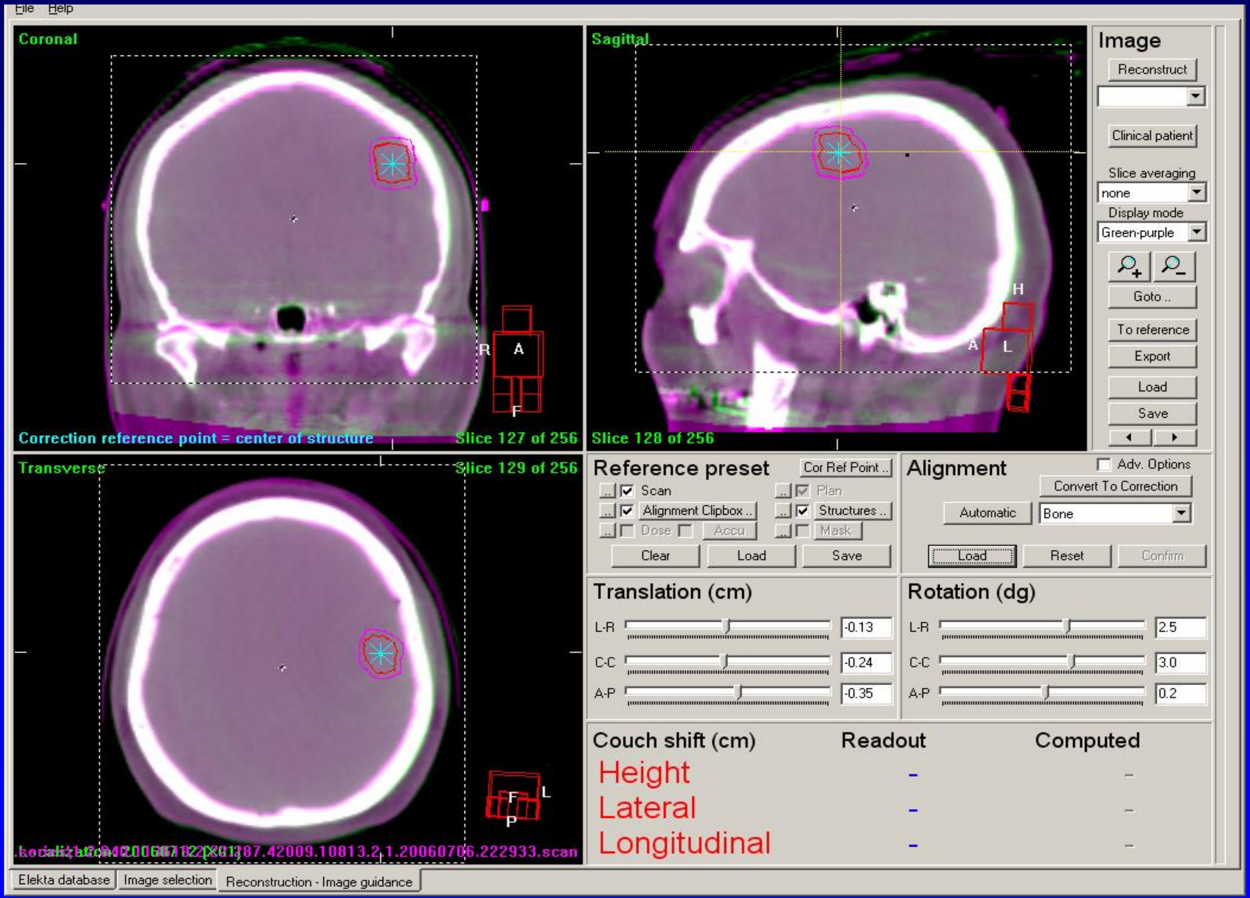
- High precision stereotactic treatments of the brain often involves the use of invasive frames
- Short term stability of mask fixation may be sufficient
- Accurate registration to reference data will be necessary

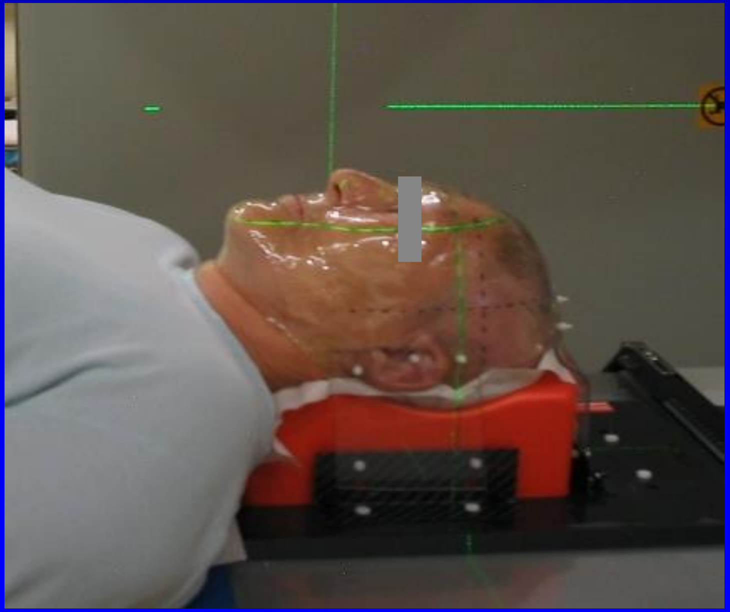
Aim:

Determine precision of online setup corrections for brain patients using cone-beam CT

With IGRT, this is no longer needed to precisely irradiate a brain tumor

We can use this instead: focus on patient stability, but let computer position the patient with better than one mm precision



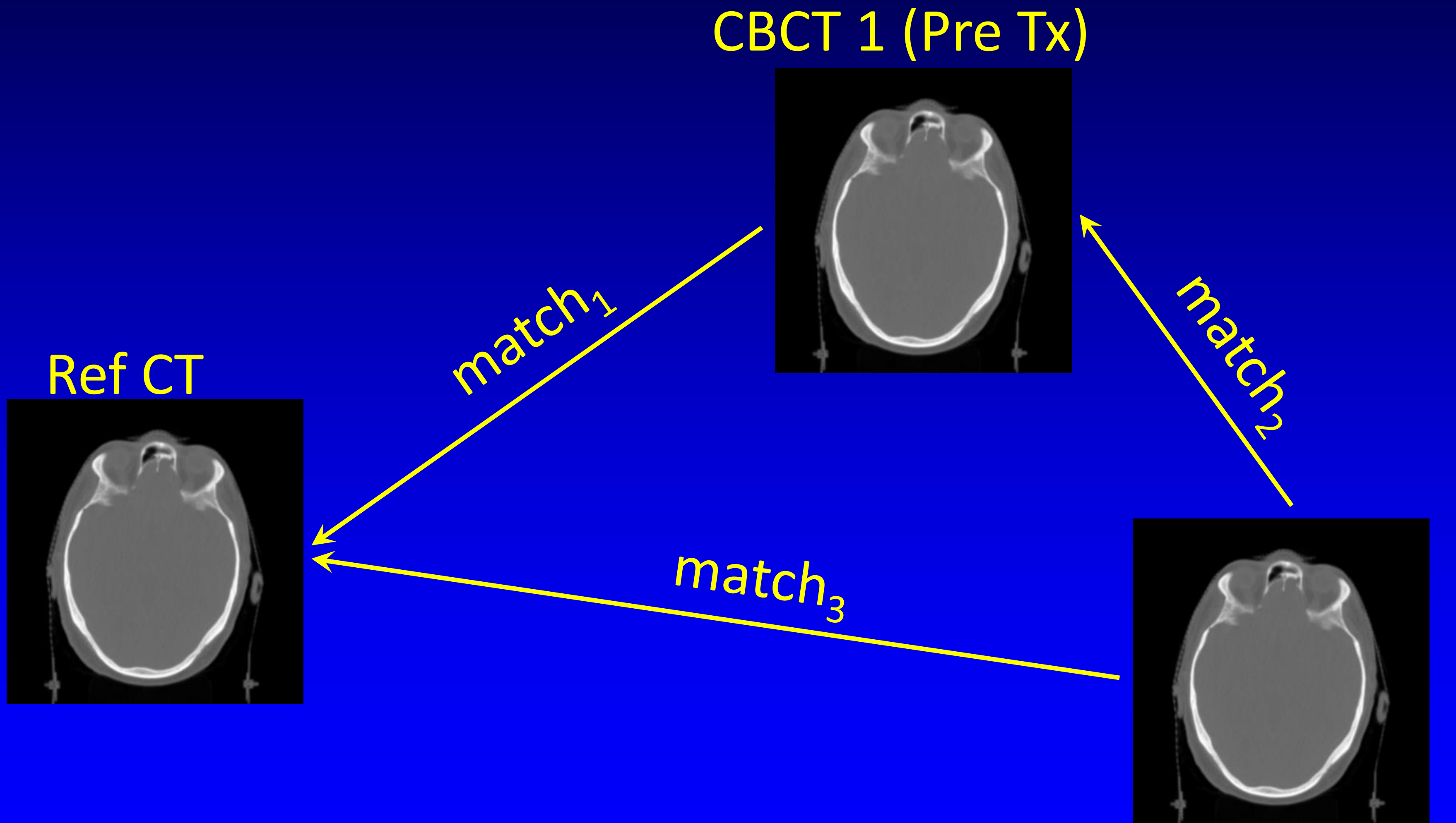


v Beek et al, R&O 2011

- Accuracy registration: 0.1 mm SD
- Accuracy table: 0.2 mm SD {x, y, z}
- Intra-fraction motion: 0.3 mm SD

Demo brainstem IGRT

Registration accuracy – Full circle method

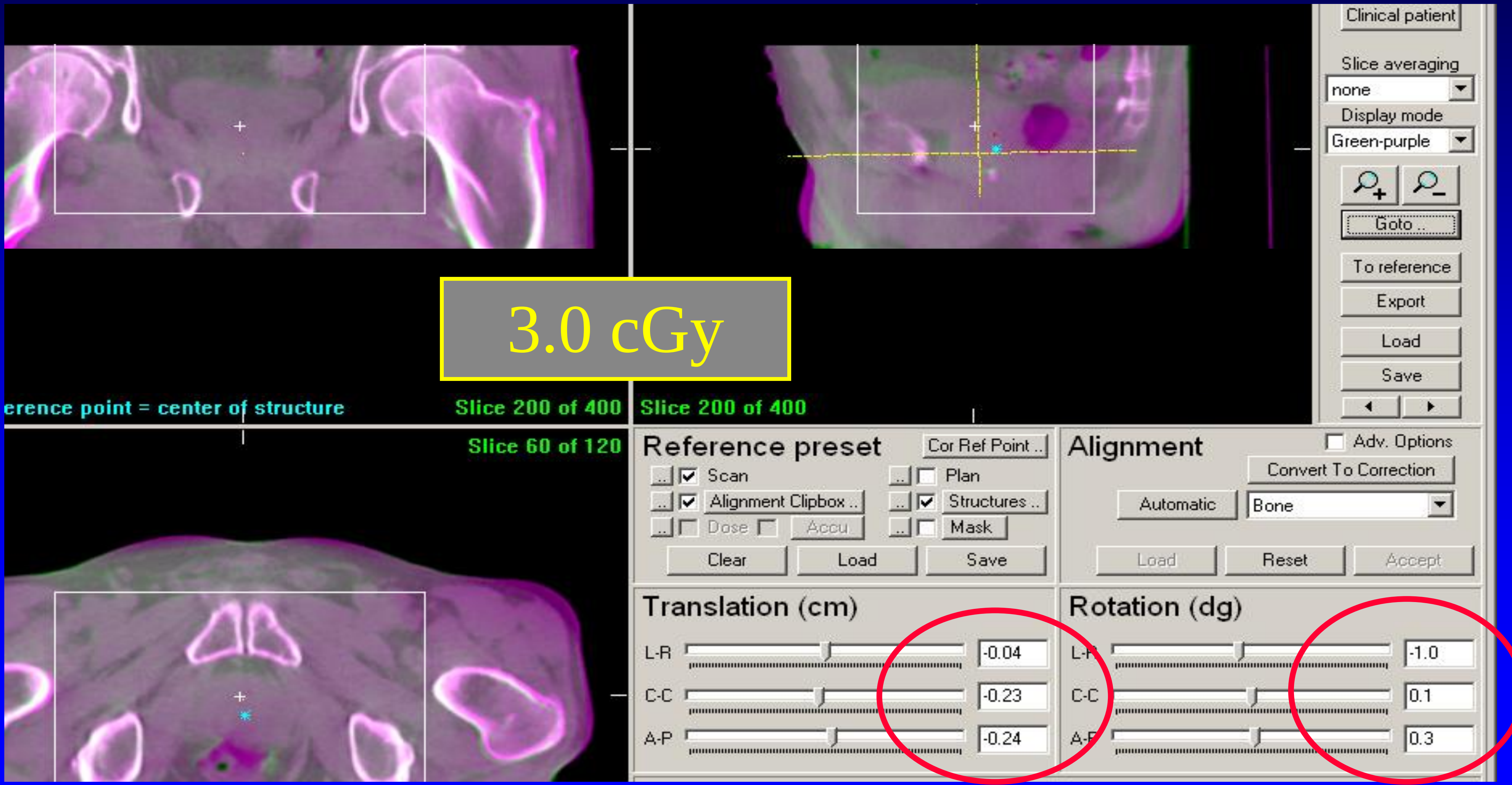


If no errors: $match_1 + match_2 - match_3 = 0$

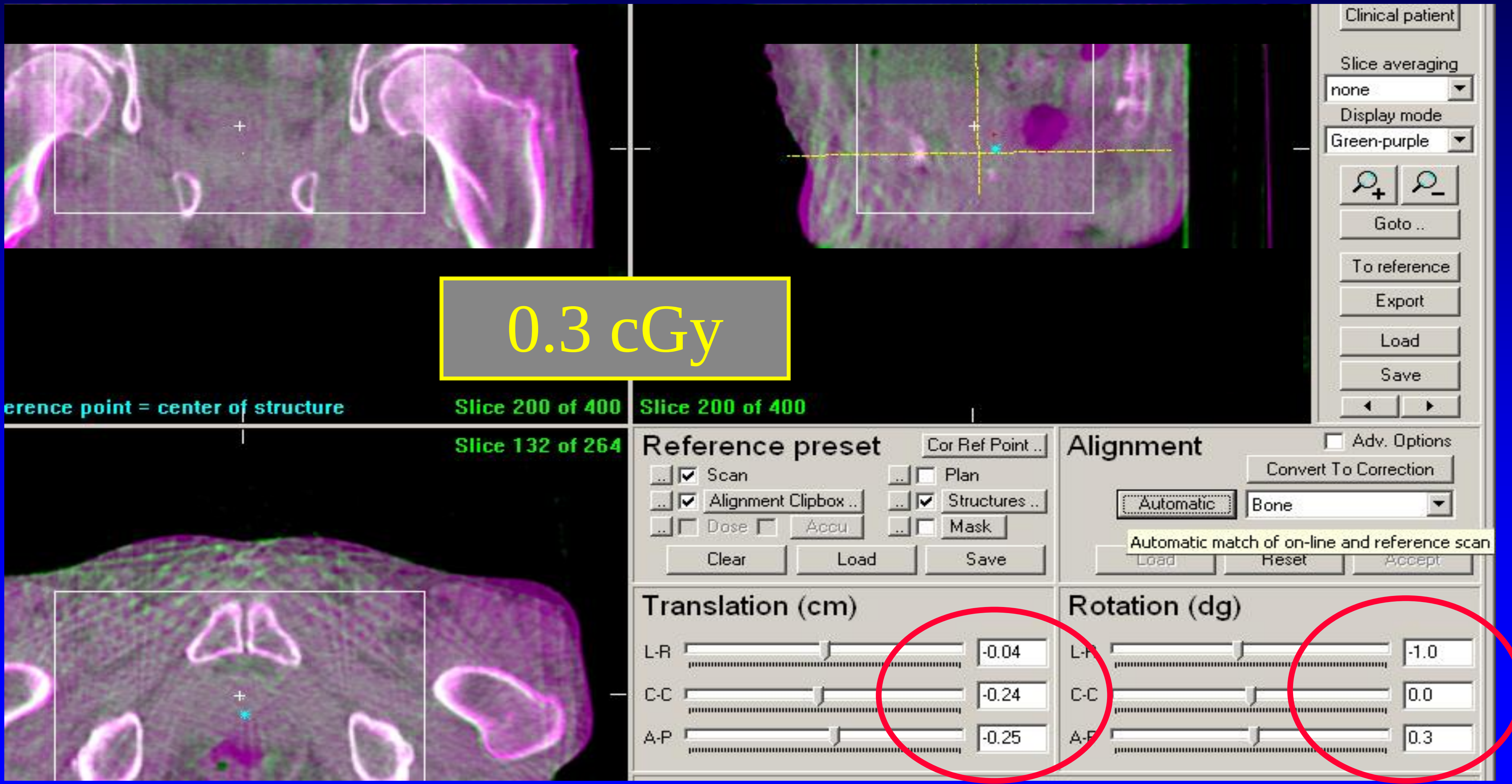
Results – Registration accuracy: bone matching for skull

Left-right (mm)		Cranial-caudal (mm)		Ant-post (mm)	
Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
0.0	0.2	-0.2	0.2	-0.1	0.3

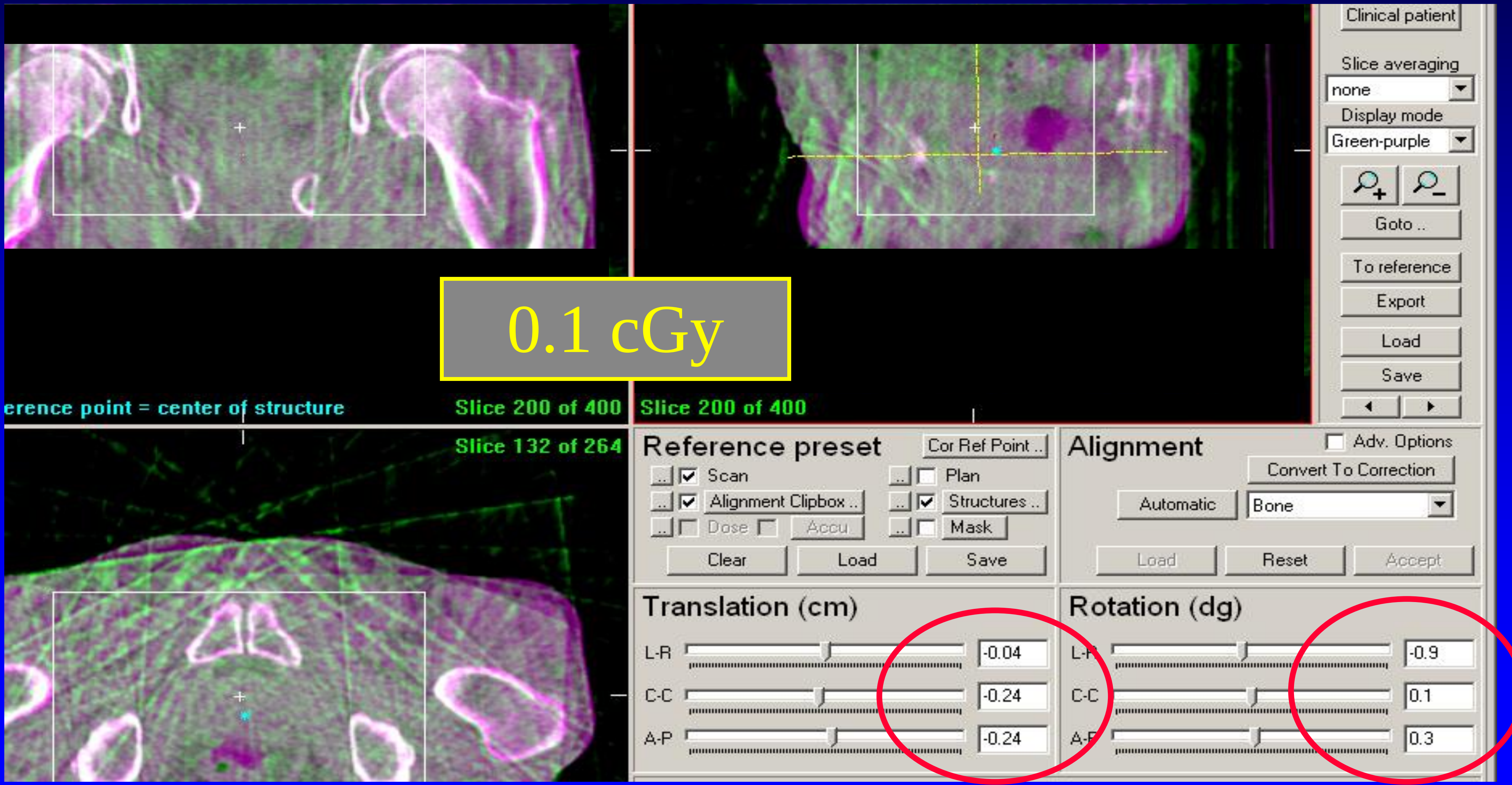
Dose required to localize bone with CBCT



Dose required to localize bone with CBCT



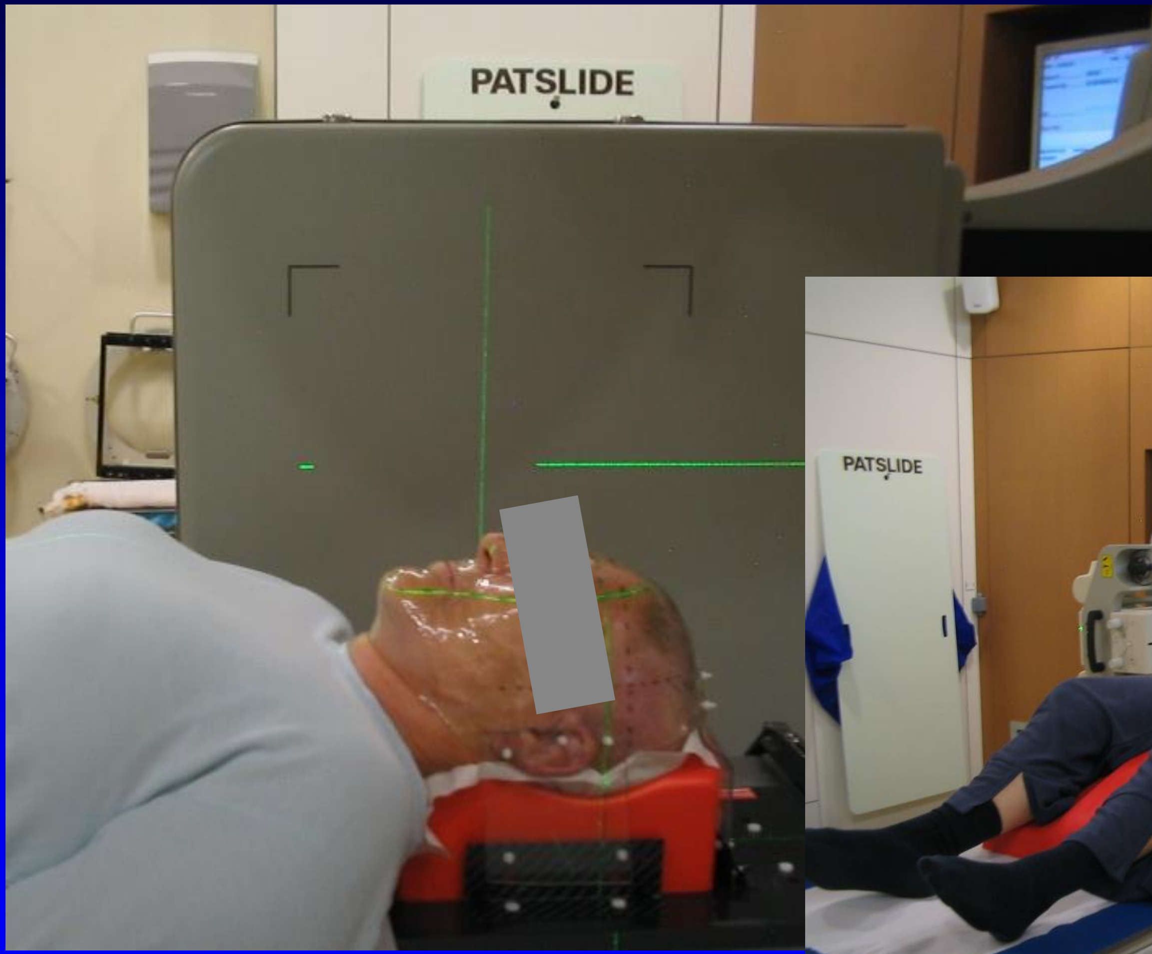
Dose required to localize bone with CBCT



Patient study: setup accuracy

- 10 patients
  - Posicast mask fixation
  - Single fraction boost of 15-20 Gy
  - Minimum field size 3 cm
  - Regular MLC (5 mm leaves)

Methods - Patient set-up



Procedure

Scan

↓

Match and convert to correction

↓

Correct all errors

↓

Pre-treatment scan (to check patient position)

↓

Treat & Scan

↓

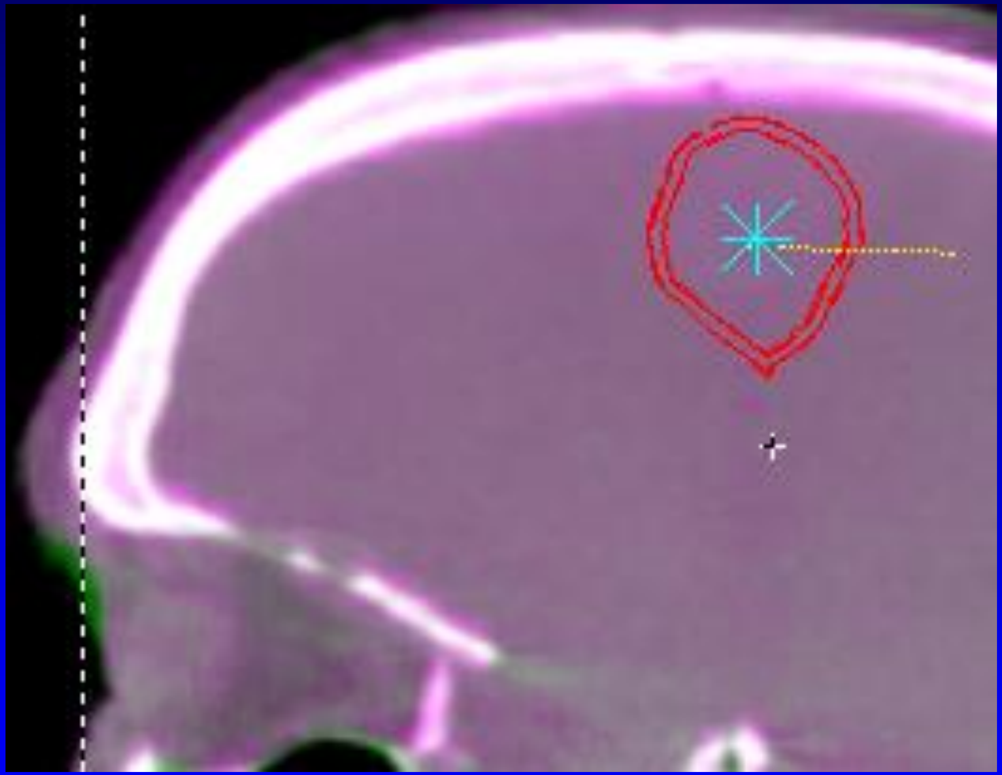
(Post-treatment scan to check patient position)

- Use of 1 minute scans, 1 cGy dose per scan

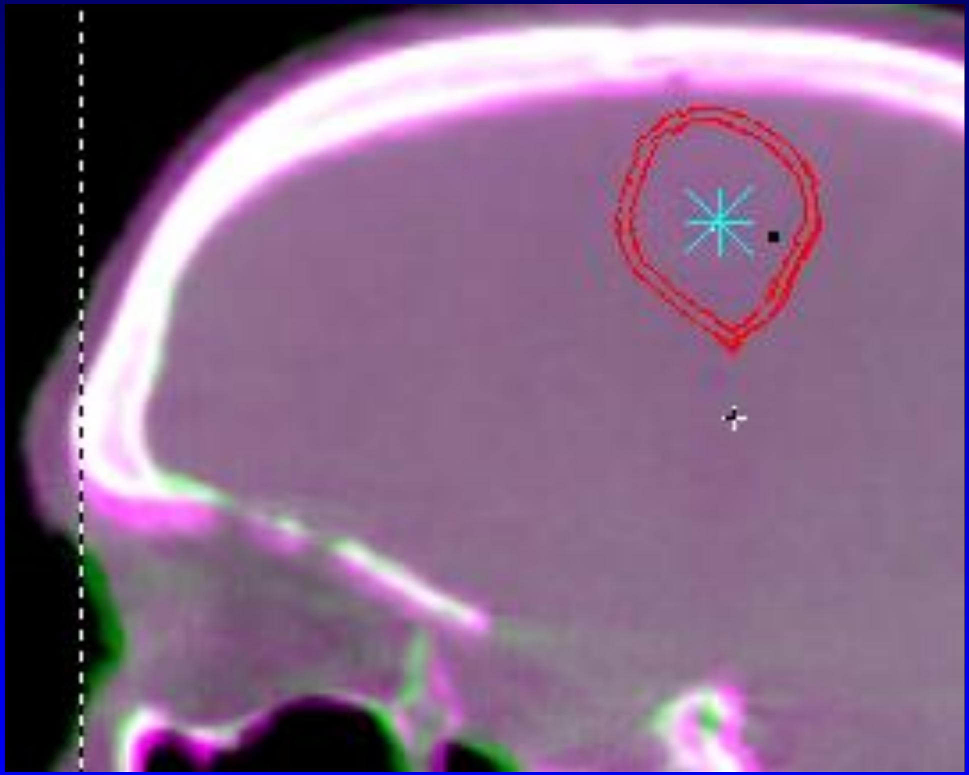
Online Correction Protocol at NKI (brain metastasis 1 x 18 Gy)

• scan patient with CBCT	1 min
• image analysis + visual verification	2 minutes
• correct errors	0.5 min
• rescan for verification	1 min
• treat & image during treatment (2 arcs)	2-5 min
• rescan after treatment	1 min
	+4.5 min

Registration procedure – Rotational errors

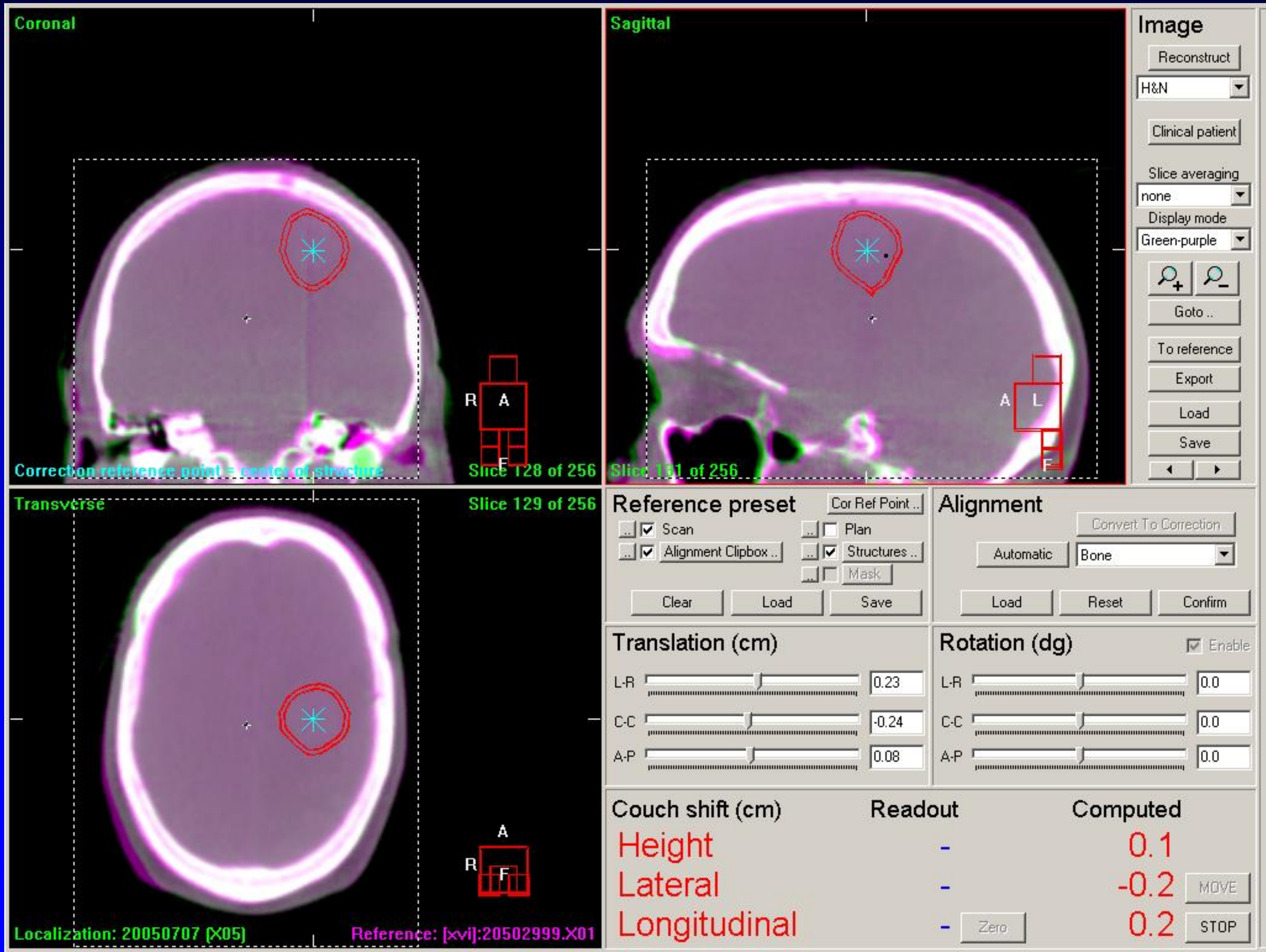


Match including rotations

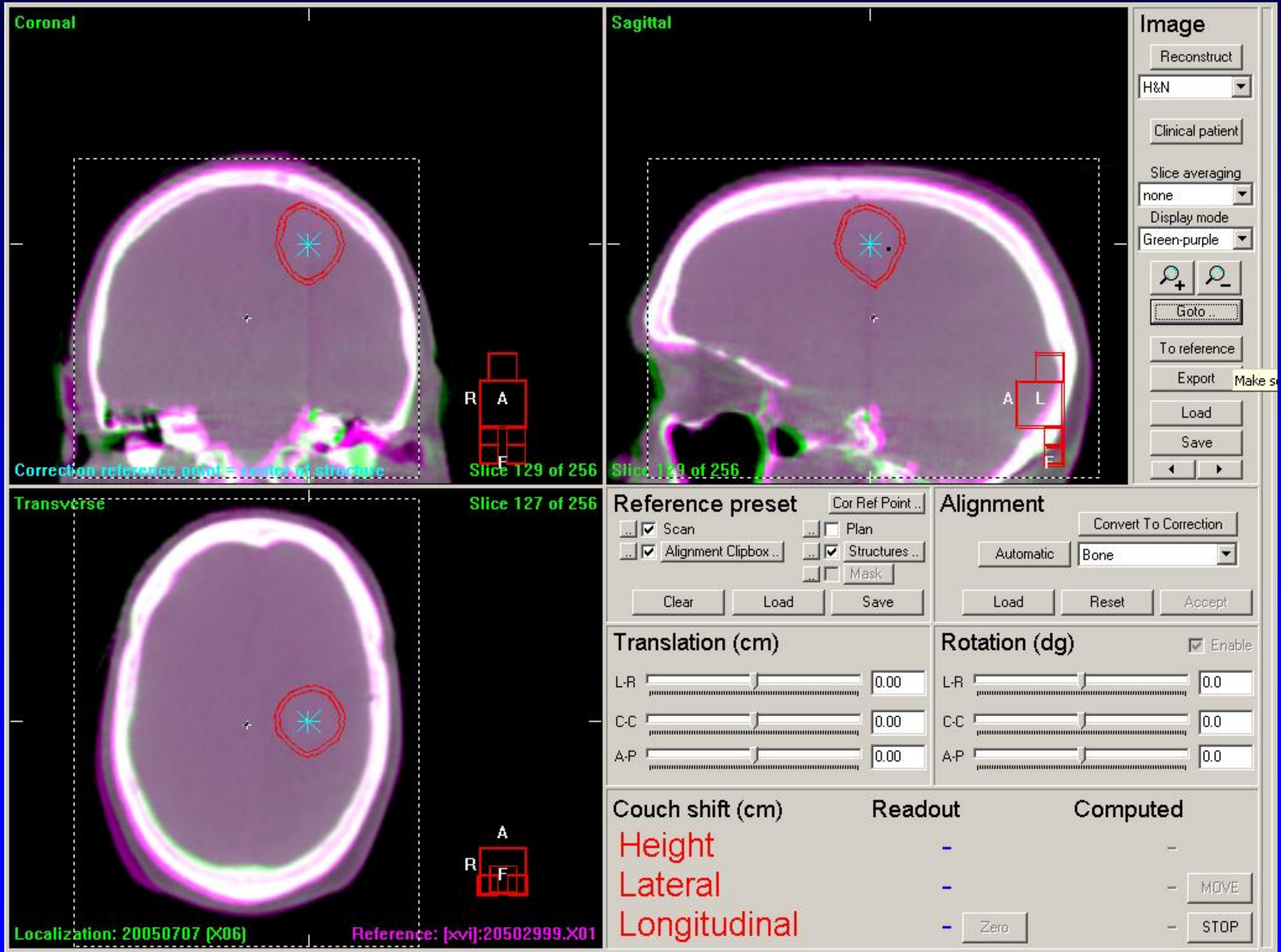


Match without rotations

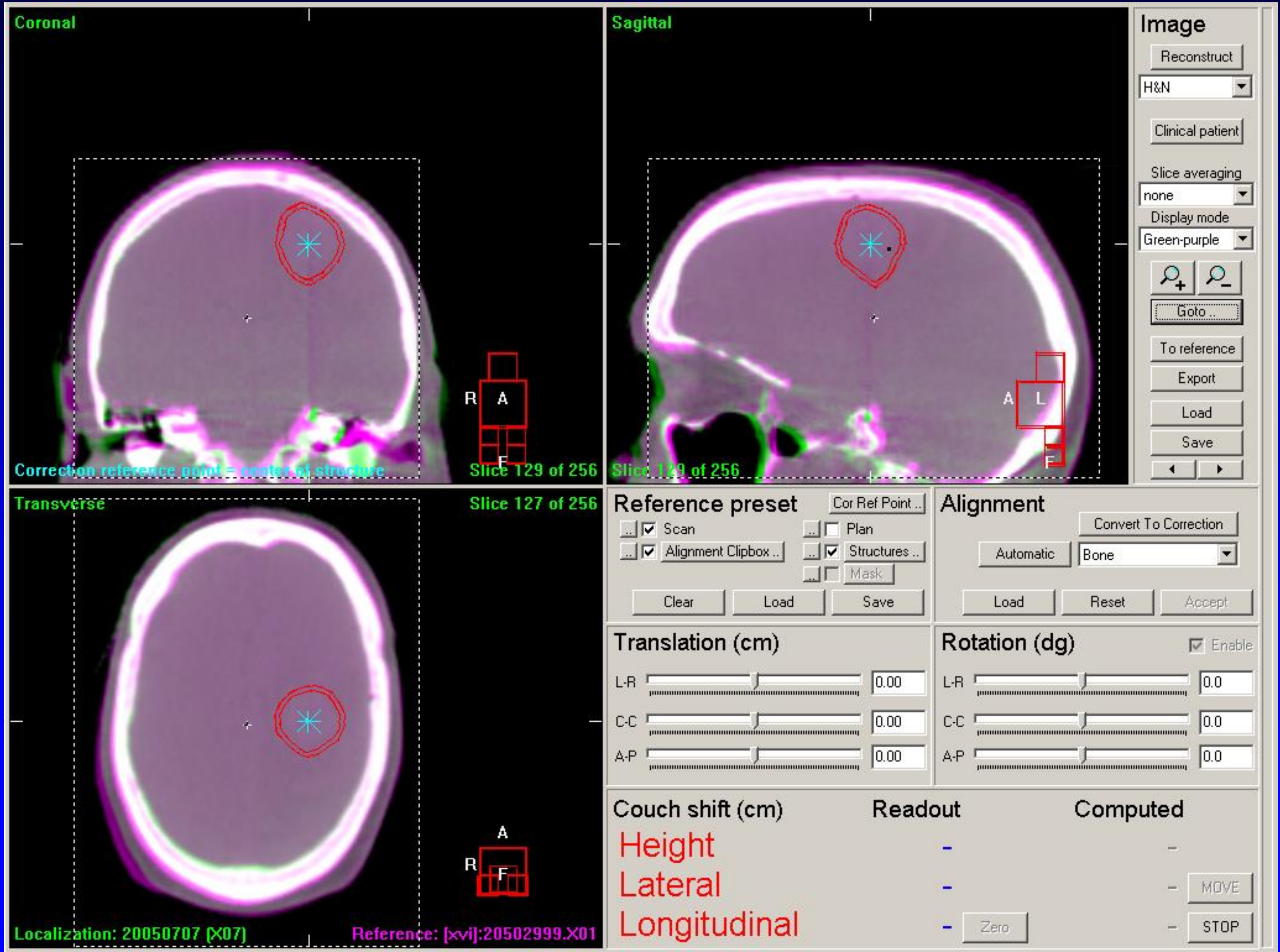
Match procedure – First scan, CTC



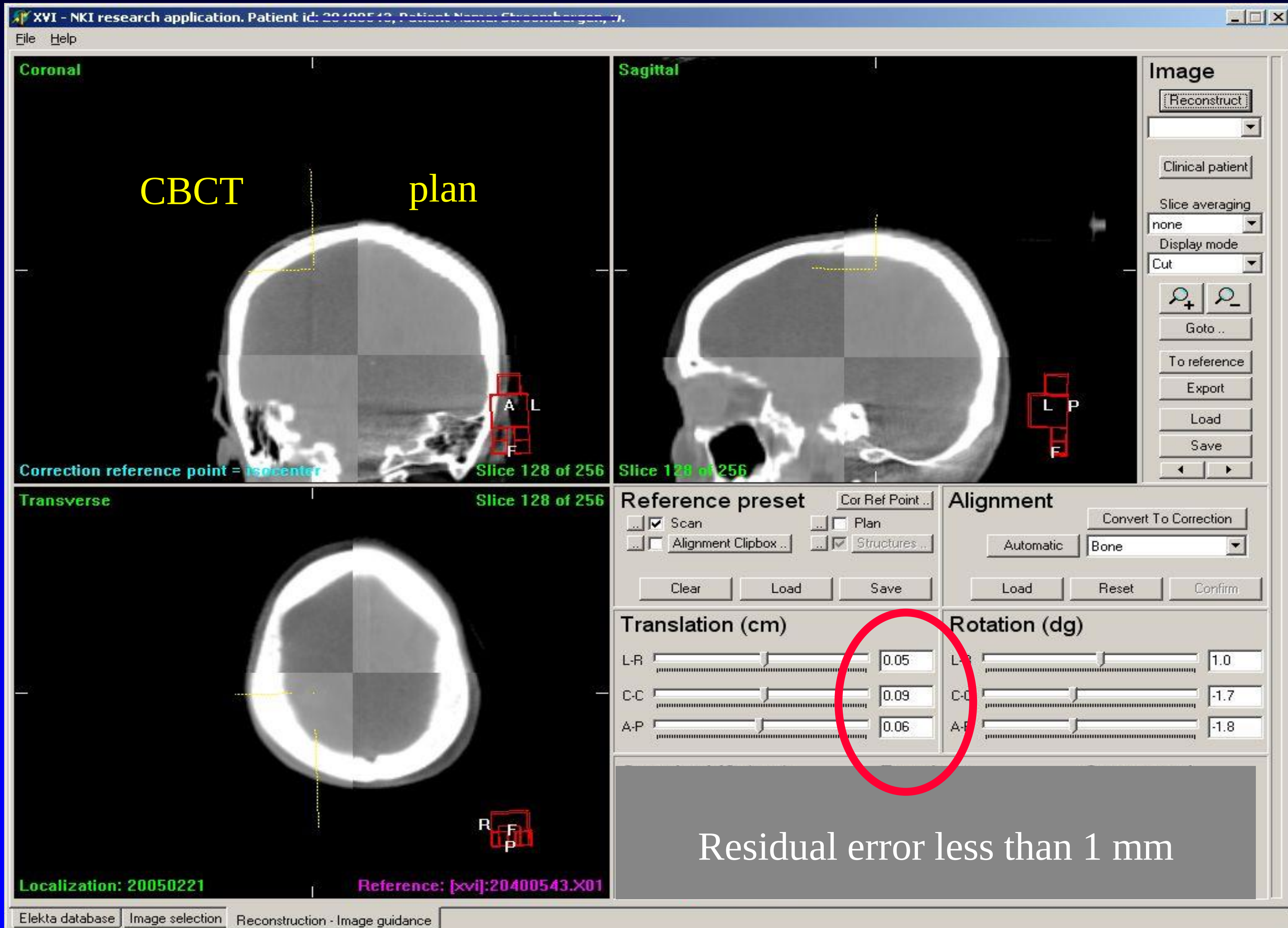
Match procedure – Pre-treatment scan



Match procedure – Post-treatment scan

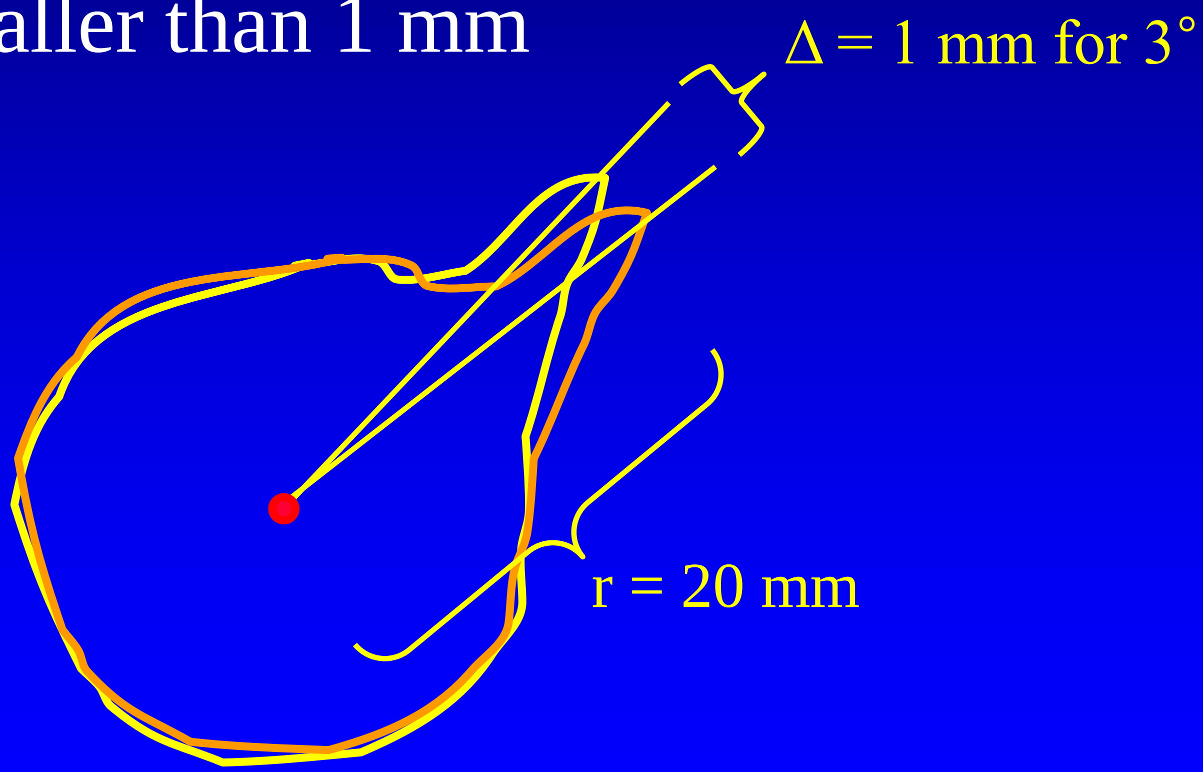


Post Treatment (and after couch shift)



Rotations

- Largest rotation found: 3 degrees (SD 1 degree)
- Errors will be smaller than 1 mm



Glioma delineation variation (Beijing 2008)

	SD (mm)	SD (mm) outliers removed	Margin (mm)
Homework	3.6	2.3	5.8
Groups	1.3	1.3	3.2
Validation	2.6	2.3	5.8

- Delineation uncertainty is a systematic error that should be incorporated in the margin
- Consistency is imperative to gather clinical evidence

Why is SD between observers important?

- Assume each group is equally skilled
- Let one group prepare plan
- Evaluate DVH of delineation other group given dose distribution of this plan
- Since one group is not more correct than another, this DVH should show adequate coverage
  - → Need to add SD between groups in CTV-PTV margin

CNS: single fraction IGRT for brain metastasis

all in cm	**systematic errors**	squared	**random errors**	squared	
delineation	**0.13**	0.0169		0	
organ motion	**0**	0		0	
setup error	**0.03**	0.0009		0	
CBCT accuracy	**0.02**	0.0004		0	
intrafraction motion			**0.02**	0.0004	
total error	**0.13**	0.02	**0.02**	0.0004	
	times 2.5		**times 0.7**		
error margin	**0.34**		**0.01**		
total error margin		**0.35**			

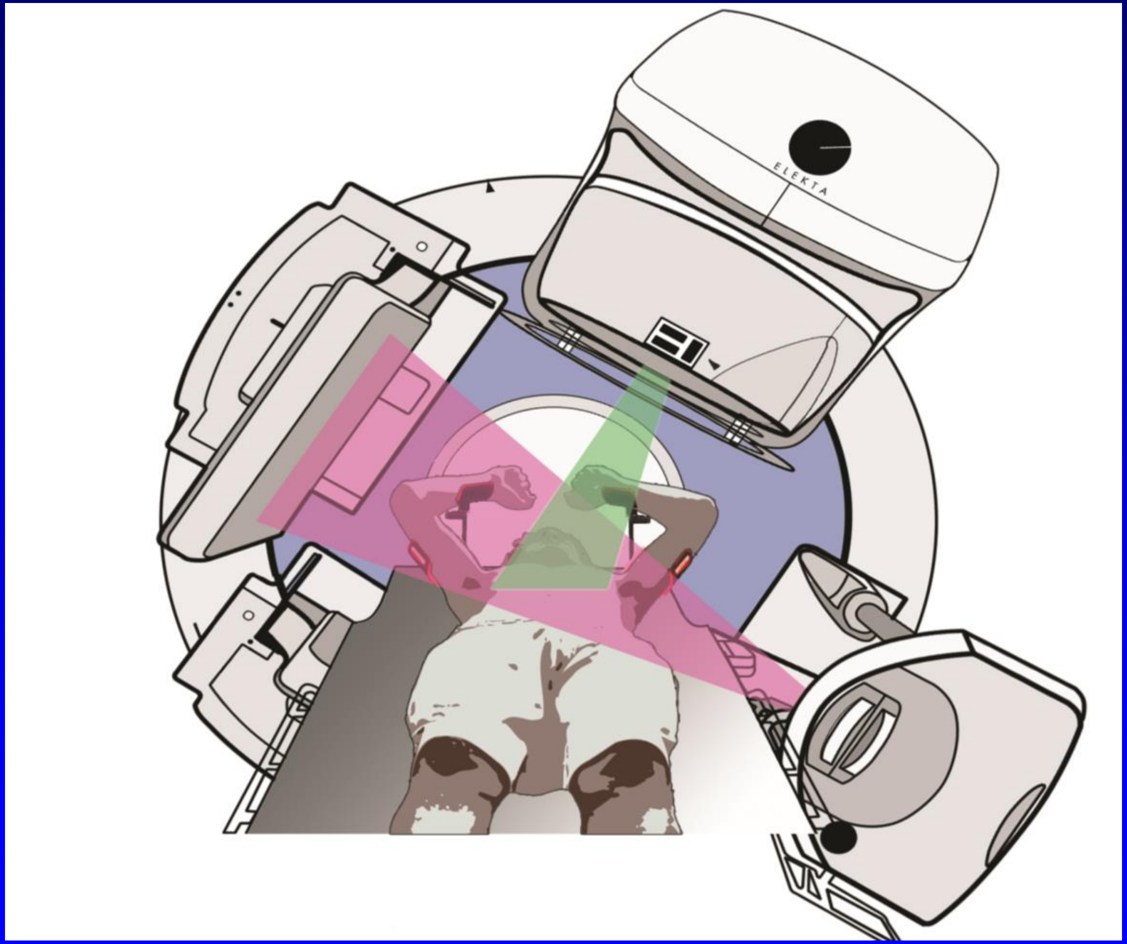
•Tightest margin achievable in EBRT ever due to very clear outline on MRI

Conclusions

- Intra-fraction movement in a mask is about 0.2 - 0.3 mm, registration accuracy comparable
- With automatic couch shift, the accuracy of IGRT is extremely high
- Rotational errors have a negligible effect for CTV coverage in most cases
- Cone-beam CT guidance of stereotactic treatments achieves comparable results to methods based on invasive frames
- Post treatment scan important to validate workflow

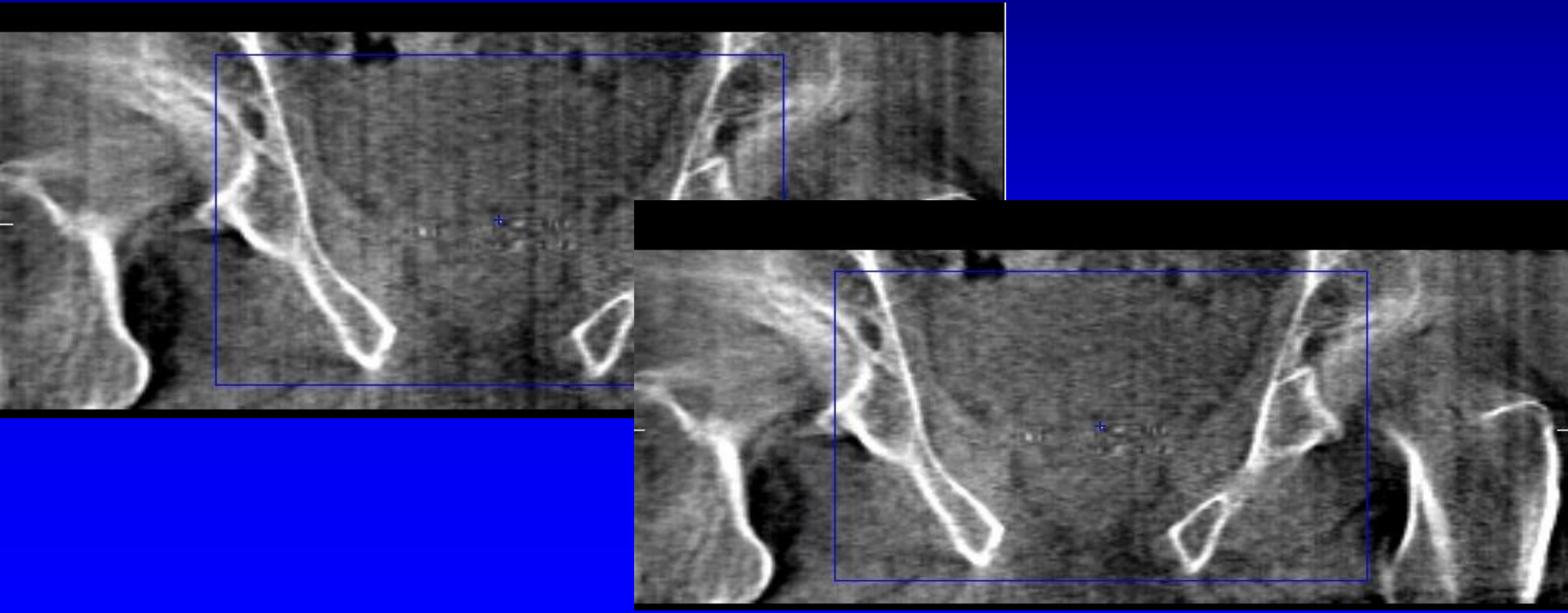
Intra-fraction monitoring

Simultaneous kV imaging with VMAT delivery

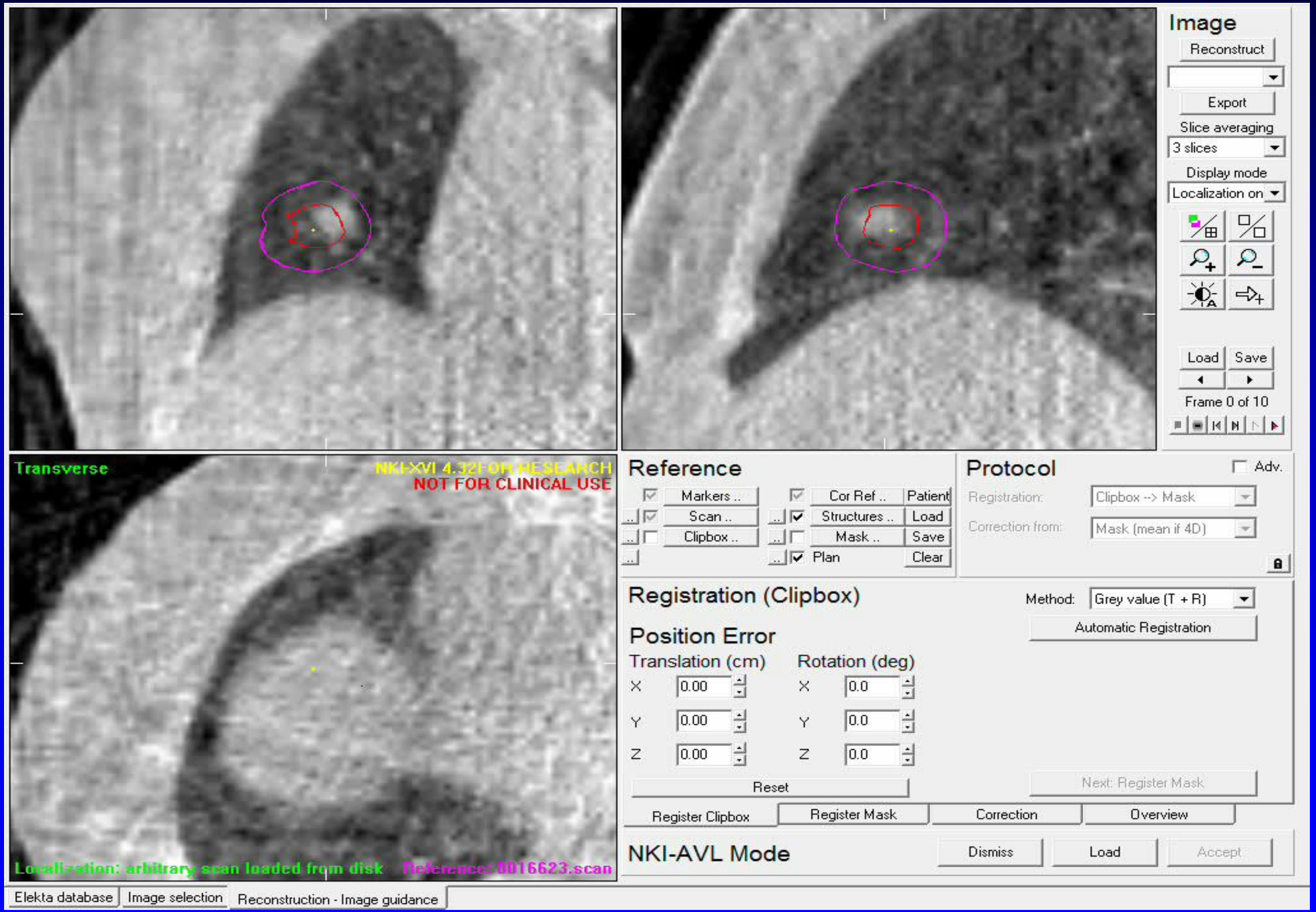


- Pulse line artifact
- Scattered MV dose
- 1-3 minutes per arc
- 300-1000 projection images per arc (1-1.5 cGy kV dose)

Pulse line artifact supression



Validation scan during first VMAT arc



•Image quality deteriorated somewhat by scatter

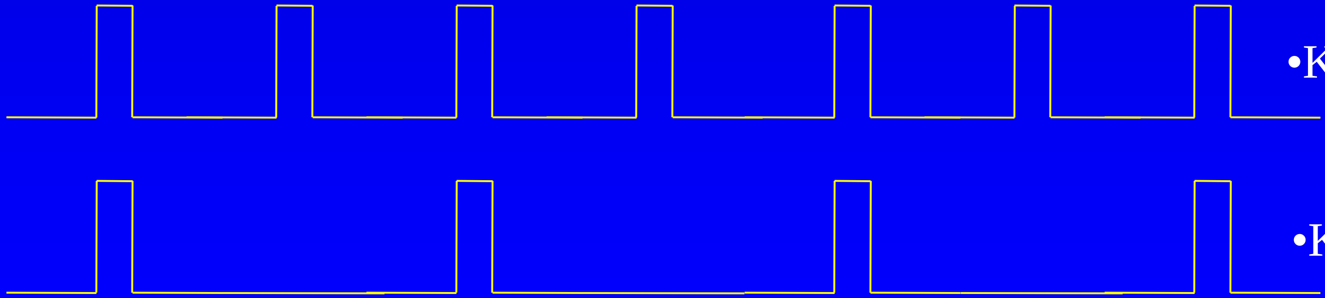
•This amount of intra-fraction baseline shift (4 mm) is rare

Alternating image acquisition for scatter correction

•Elekta DCB board

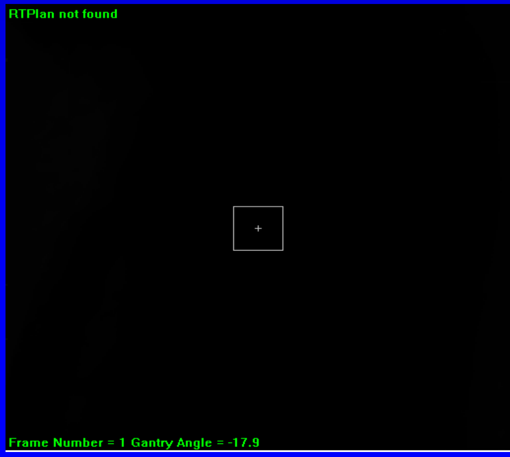
•Arduino microcontroller — •USB control

•KV generator

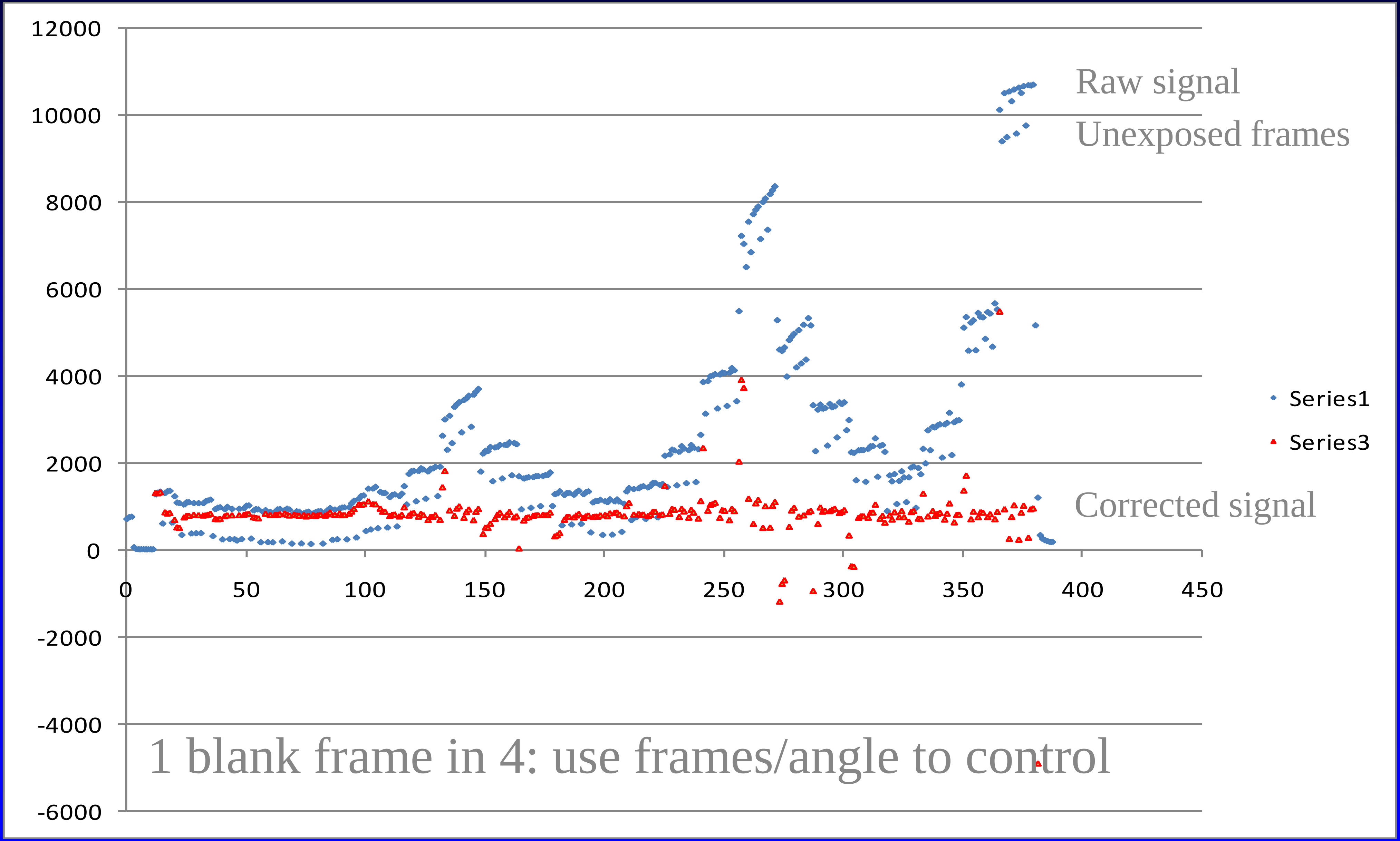


•KV control in

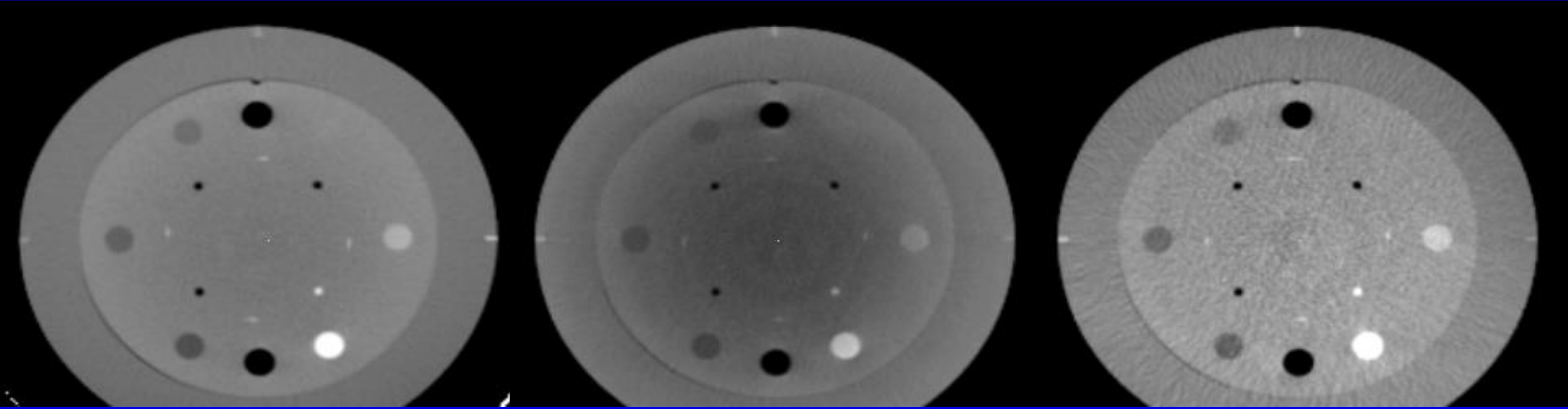
•KV control out



How much scatter from MV beam?



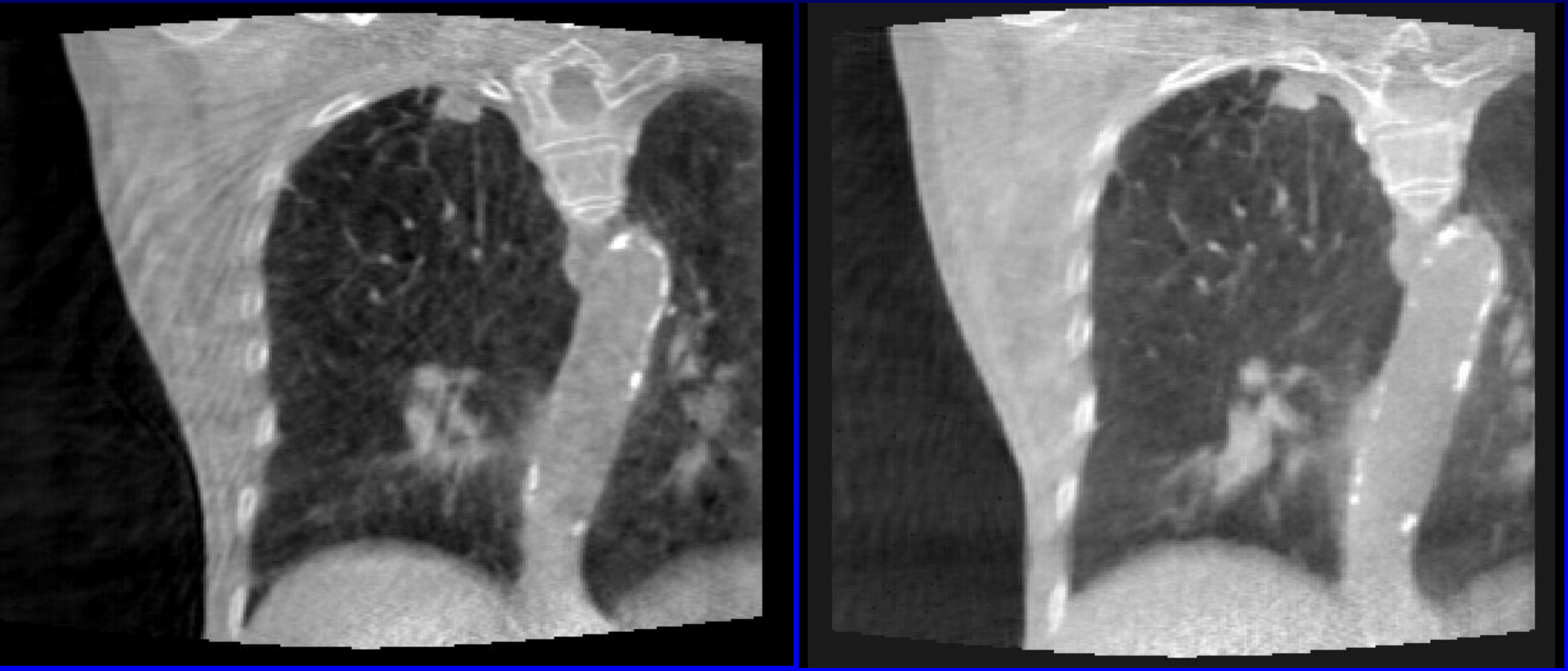
MV scatter correction
CAT Phantom



- Regular CBCT
- CBCT during VMAT
- Corrected CBCT

- MV scatter onto kV panel estimated from kV-off frames corrected for ghosting

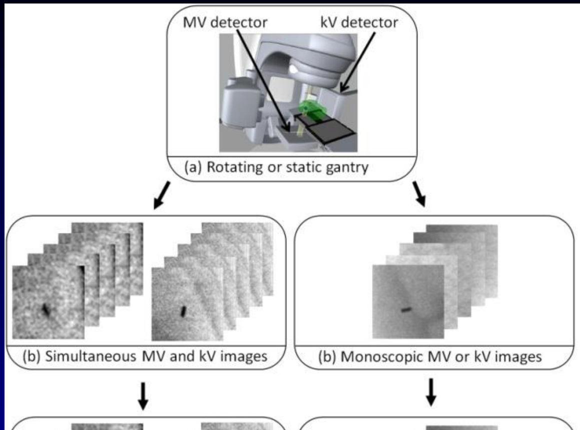
First patient result



•Regular CBCT

•During VMAT: corrected/uncorrected

Alternatively: use markers

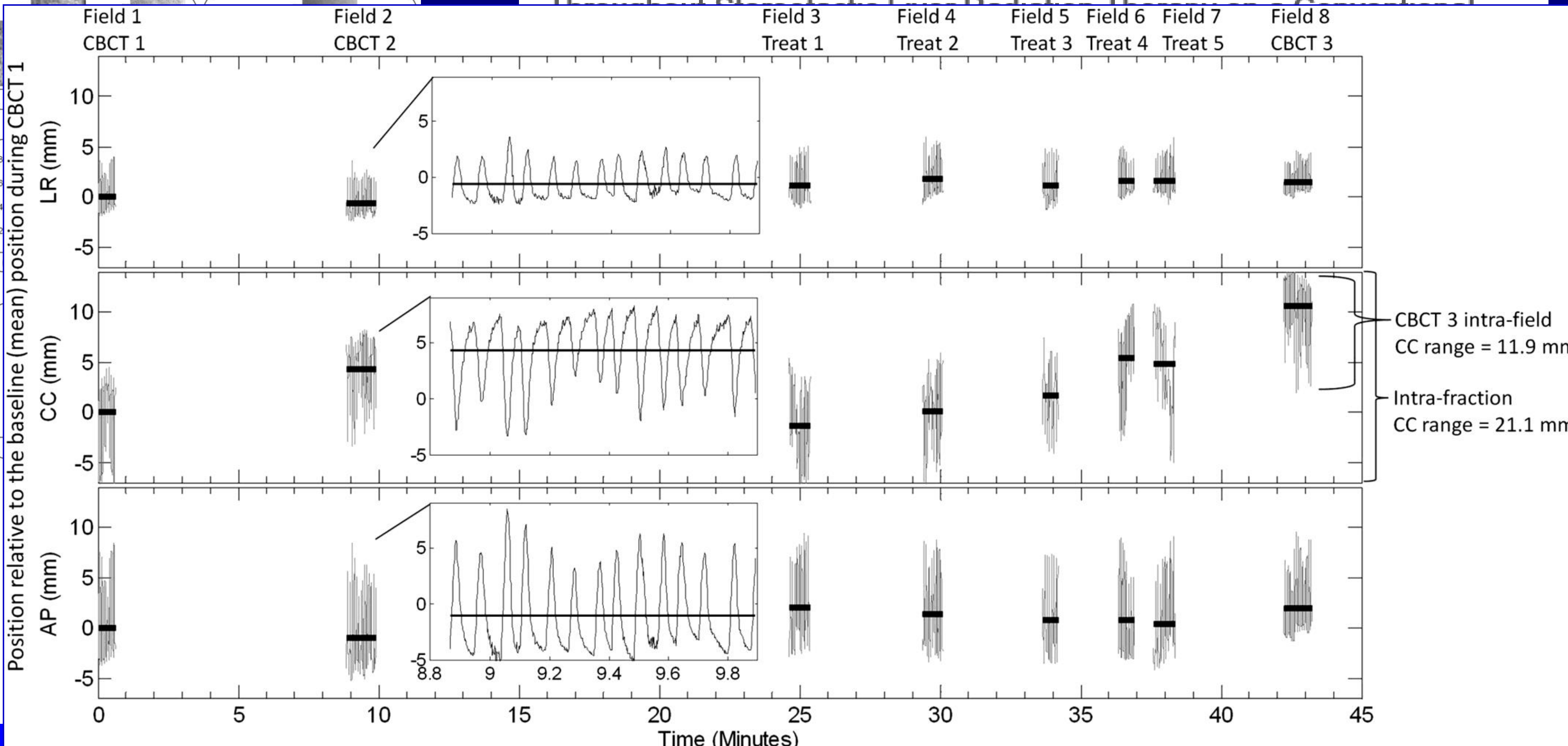


International Journal of Radiation Oncology*Biology*Physics

Volume 86, Issue 1, 1 May 2013, Pages 190–197

Physics Contribution

Three-dimensional, Time-Resolved, Intrafraction Motion Monitoring



Conclusions

- In stereotactic radiosurgery, patient stability is very important

- Methods to validate your radiotherapy procedure are:
  - CBCT after end of treatment
  - CBCT during VMAT delivery
  - Fluoroscopy during delivery

- Stability seems adequate unless treatment time too long

MR-guided radiotherapy: potential and current clinical practice

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Associate Professor of Radiation Oncology & Biomedical Engineering

Washington University School of Medicine

St. Louis, Missouri, USA

ESTRO School

Disclosures

Research Funding

Viewray Inc

Objectives

To understand that online MR guided radiation therapy is being clinically practiced at several institutions

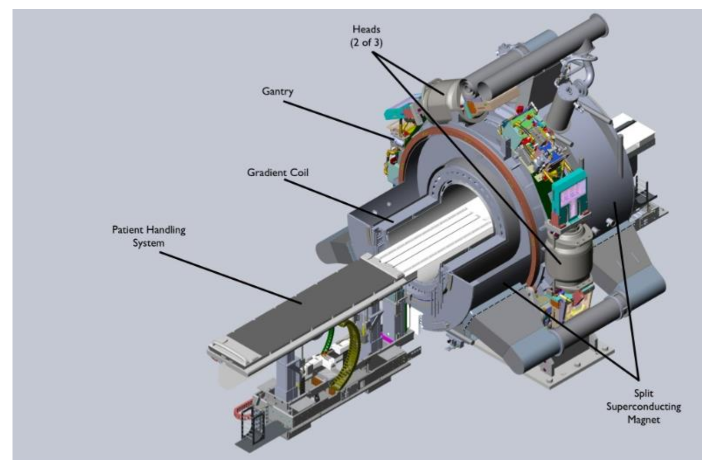
To understand the differences in soft tissue visualization between MR and CBCT

To get a taste of the different immobilization concerns needed for MRgRT

To be able to give two examples of current organ sites treated with MRgRT

First clinical implementation of MRgRT

- 0.35T MRI integrated with 3 Co-60 heads
  - ~550 cGy/min @ iso
- 3 fully divergent MLCs (minimized penumbra)
- Large imaging FOV (50 cm) and Tx volume (27cmx27cm)
- 4 frames / second saggital cine imaging during
- Integrated planning system
  – Monte Carlo dose calculation



Clinical MRgRT timeline

1/2014 -First patient treatment

9/2014 -First online adaptive treatment (Conventional fractionation)

1/2015 - First online adaptive SBRT

2/2015 - First online adaptive SBRT with MRTC (gating)

Today 9 clinical sites

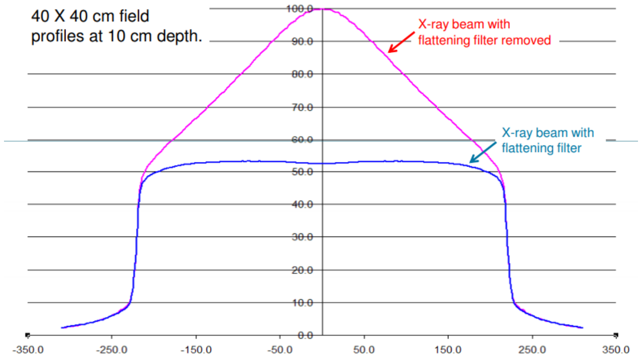
- Washington University, St. Louis, Missouri, USA
- UCLA, Los Angeles, California, USA
- University of Wisconsin, Madison, Wisconsin, USA
- University of Miami, Miami, Florida, USA
- Seoul National University Hospital, Seoul, South Korea
- VUMC, Amsterdam, Netherlands
- Gemelli, Rome, Italy
- National Cancer Center, Tokyo, Japan
- Henry Ford Medical Center, Detroit, Michigan, USA *

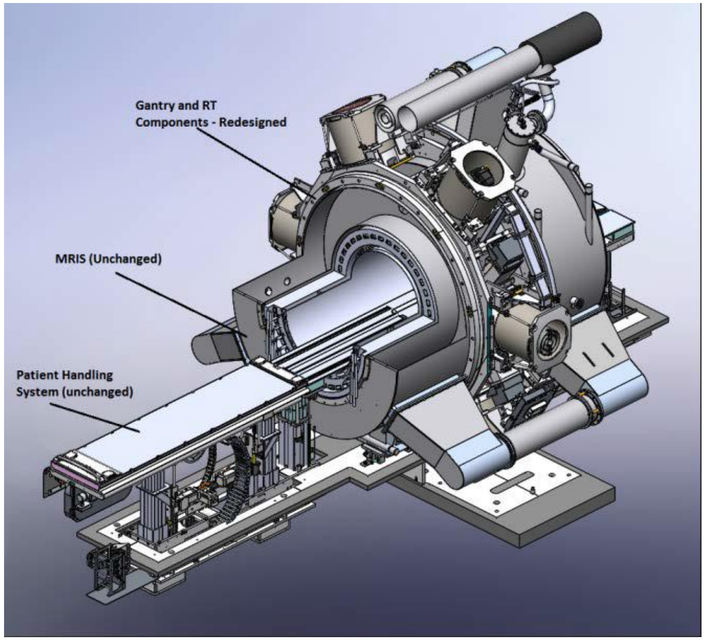
MR Linac – used by Henry Ford

6 MV FFF linear accelerator with dose rate of 600 cGy/min

90cm isocenter, matched to the isocenter of the magnet

Double stack, double focused 138-leaf MLC (8.3 mm) designed to project field sizes from 0.2 x 0.4 cm^2 up to 27.4 x 24.1 cm^2 at isocenter, capable of full over-travel and interdigitation.





Slide content courtesy of Maria Bellon of ViewRay, Inc.

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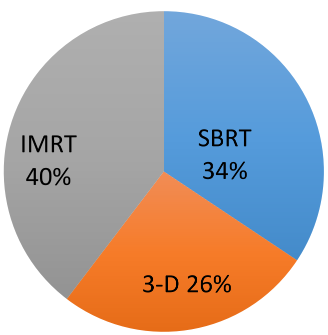
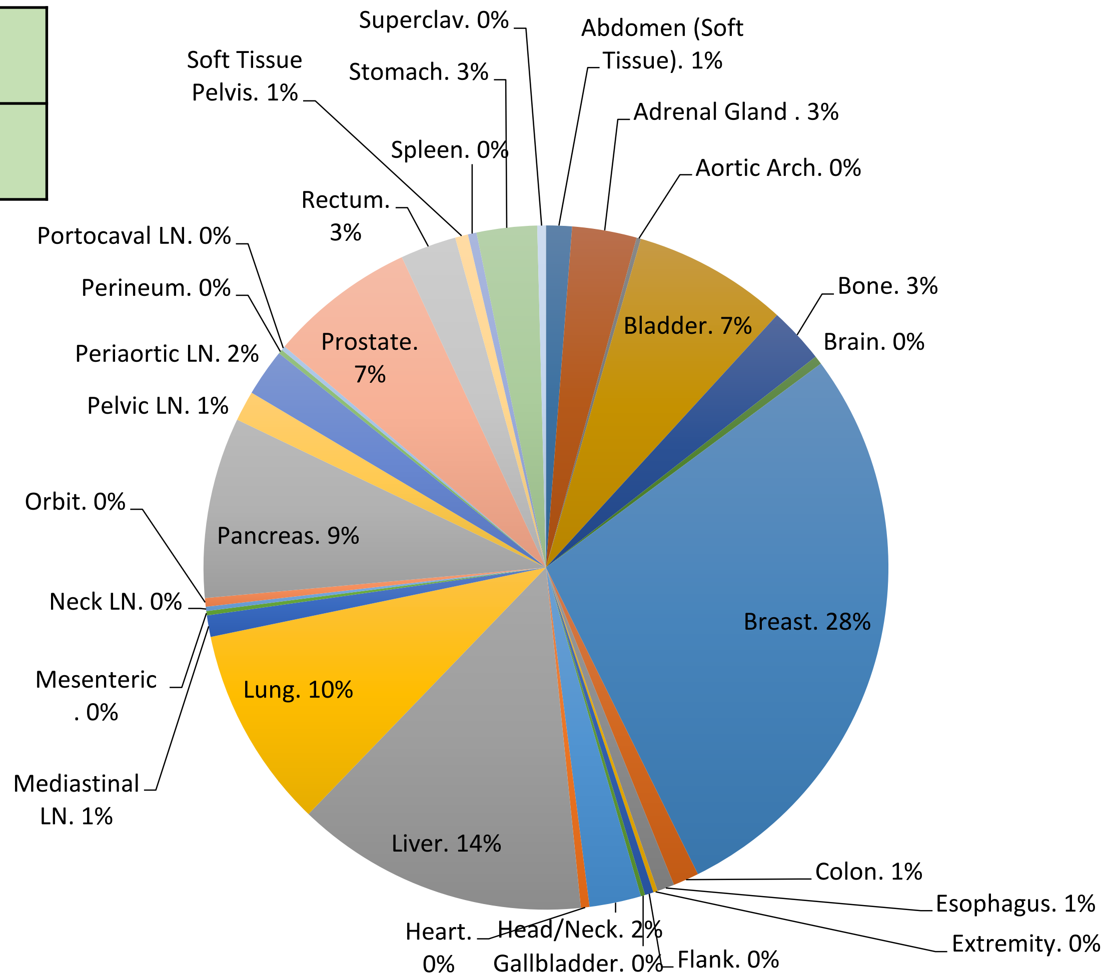
Washington University Clinical Dashboard 2014-2017

Total Patients Treated to Date	583
Total patients treated with ART	152

Treatment Type (%)



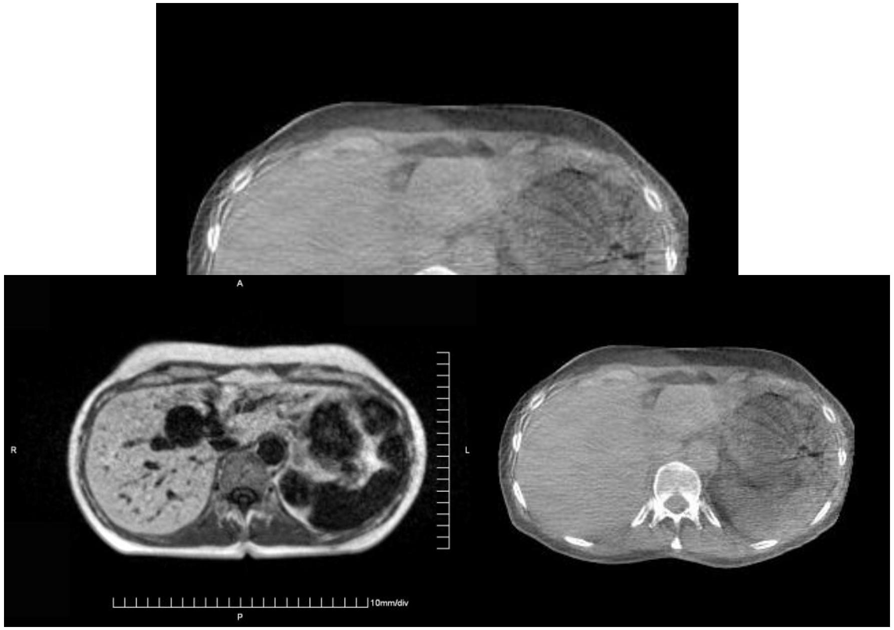


MRI imaging is better than CBCT

Onboard CT images used for routine treatment localization were collected

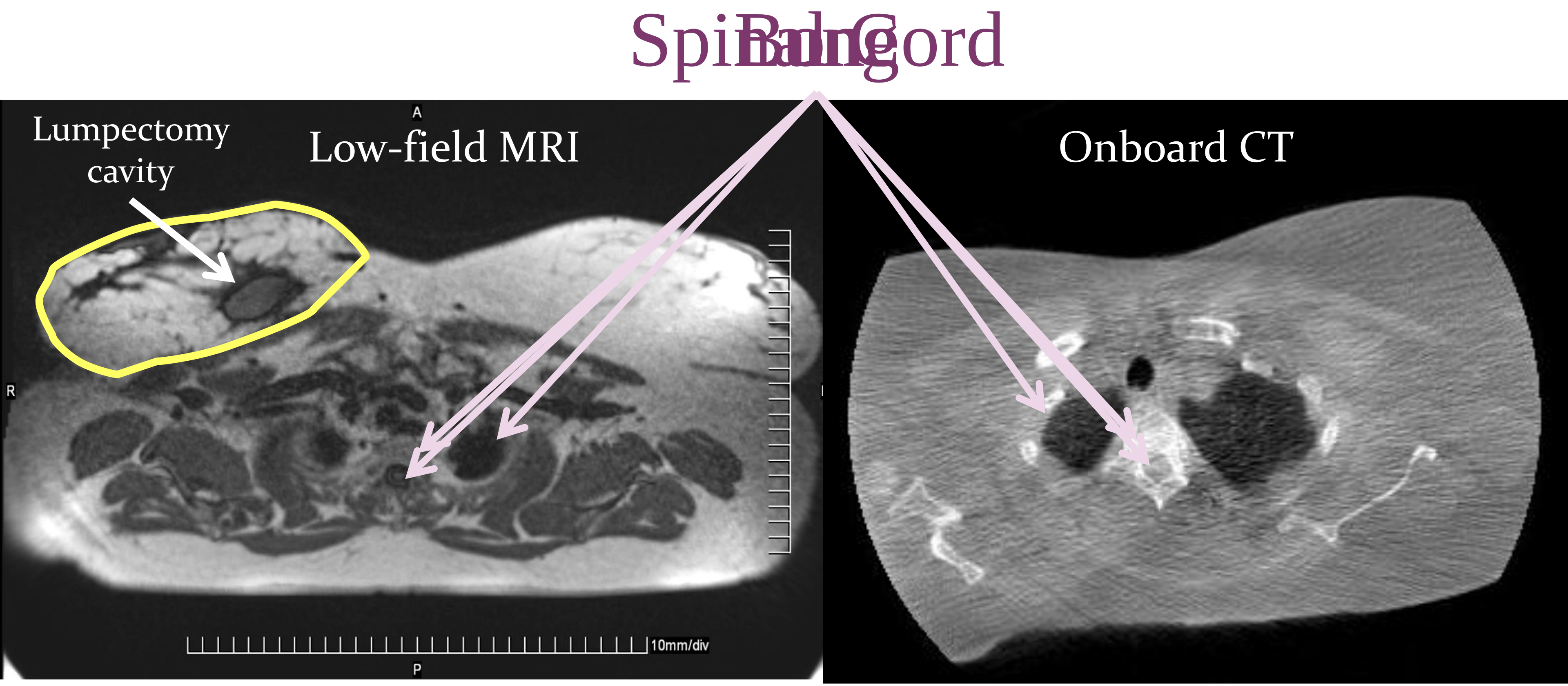
- MVCT or kVCT
- In-plane resolution: ~1-1.5mm
- Slice thickness: 2.5 - 4.0 mm

3 radiation oncologists evaluated the low-field MRI & onboard CT images side-by-side



Noel, Parikh et al, Acta Oncologica, 2015

Breast Cancer Patient



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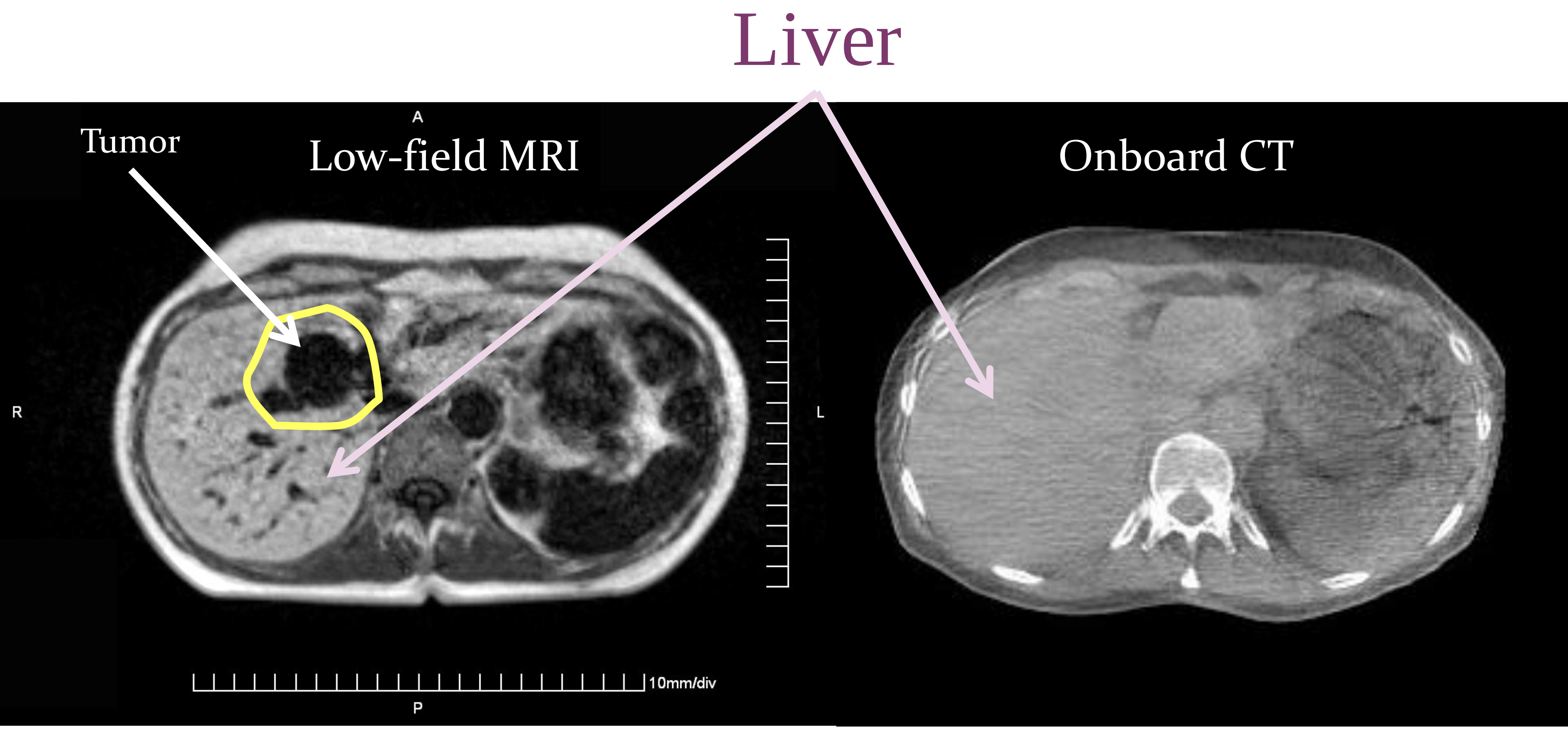
Liver Metastasis Patient

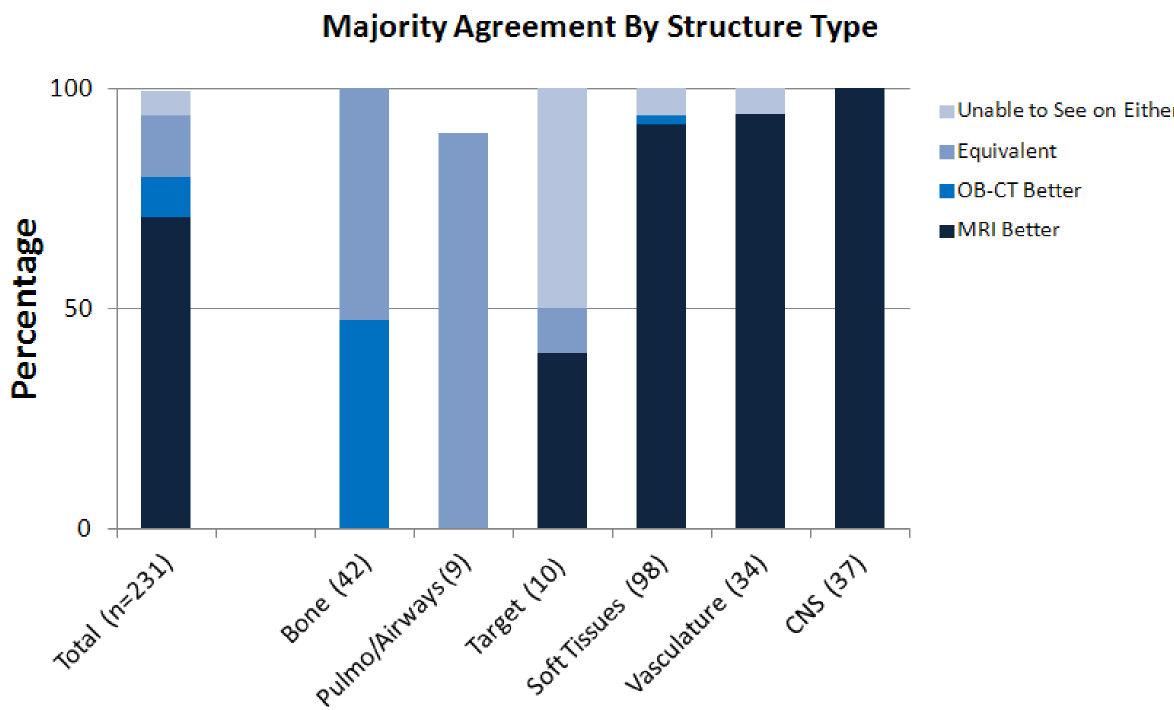


Noel, Parikh et al, Acta Oncologica, 2015

MRI vs CBCT Results

When examined by **structure type**, there were differences in which modality offered better visualization:

- **Bone:**
  OB-CT (48%) or Equivalent (52%)
- **Pulmonary Systems/Airways:** Equivalent (90%)
- **Target:**
  MRI (40%), Equivalent (10%)
- **Soft Tissues:** MRI (92%)
- **Vasculature:** MRI (94%)
- **CNS:** MRI (100%)



Noel, Parikh et al, Acta Oncologica, 2015

Accelerated partial breast radiation

CTV, PTV margins for APBI:

Brachytherapy (Mammosite, SAVI):

Preferred → Cavity + 1 cm = CTV = PTV

EBRT:

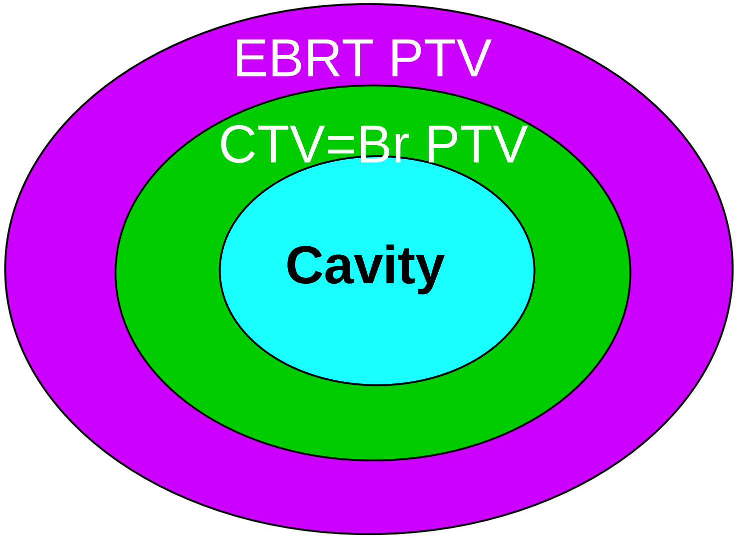
Alternative → Cavity + 1-1.5 cm = CTV.

CTV + 1 cm = PTV

PTV = Cavity + 2-2.5 cm

Larger PTV margins needed due to:

- Setup uncertainty
- Intra-fraction motion



We sought to evaluate MR-IGRT for delivery of APBI given easy localization of cavity on MRI (setup) and ability to monitor intra-fraction motion.

Courtesy of Maria Thomas, MD, PhD

MRG-RT: Breast

Patient characteristics: Women with Stage 0-1 breast cancer, status post lumpectomy, appropriate candidates for APBI, who were not eligible for brachytherapy. Enrolled on institutional registry. (N = 30 patients)

Treatment: MR-IGRT APBI, 38.5 Gy/10 fx BID

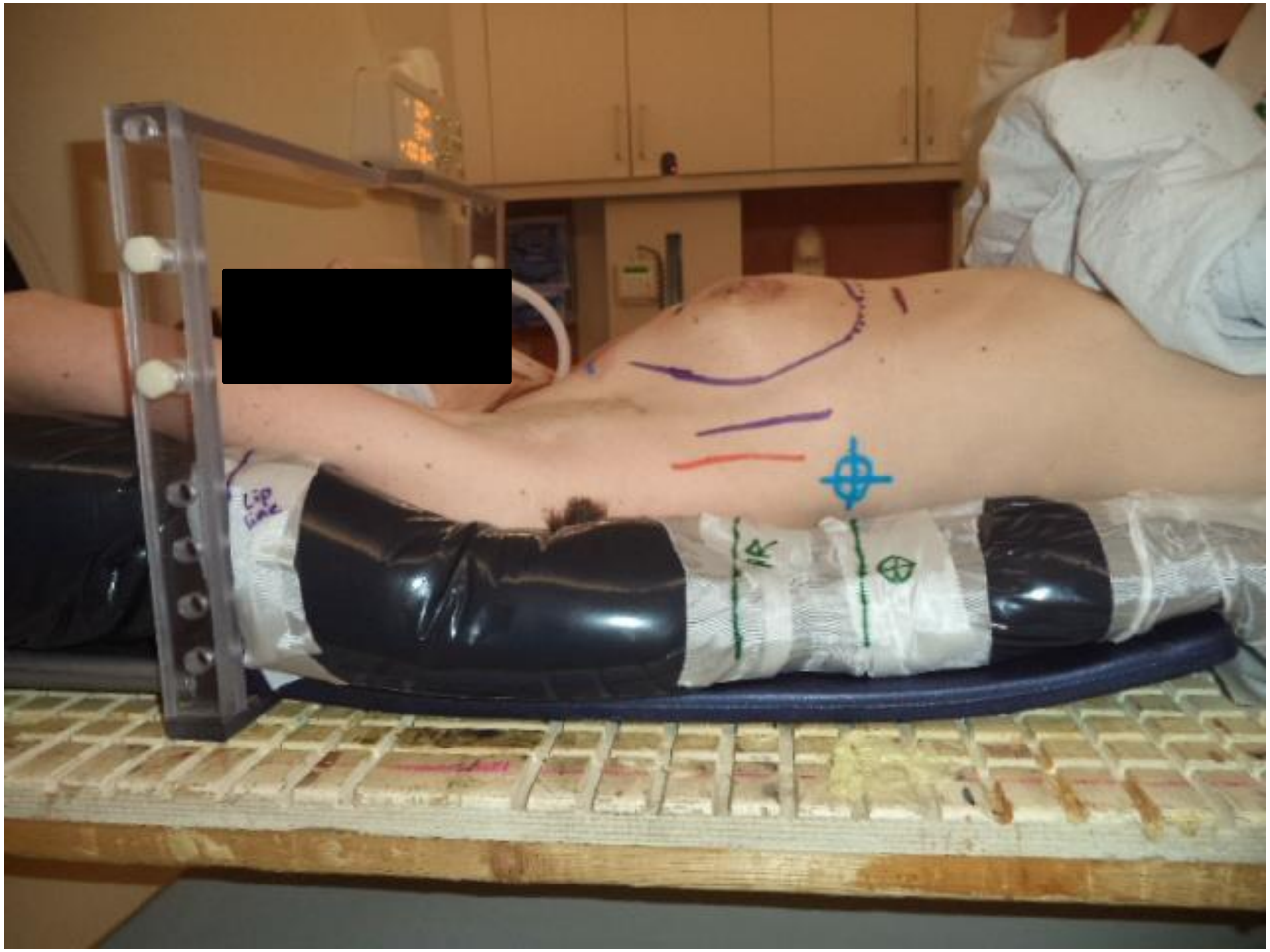
Treatment planning:

- CT and MRI simulation (Supine, arms up, AC, Lucite brackets)
- PTV = CTV = Cavity + 1 cm
- Cavity localization on volumetric MRI prior to each fraction
- Continuous cine acquisition during delivery of each fraction
- Patient time in room per fraction: mean 36 minutes

Courtesy of Maria Thomas, MD, PhD

MRG-RT: Breast

MRG-RT: Moderate Experience - Breast



MRG-RT: Breast

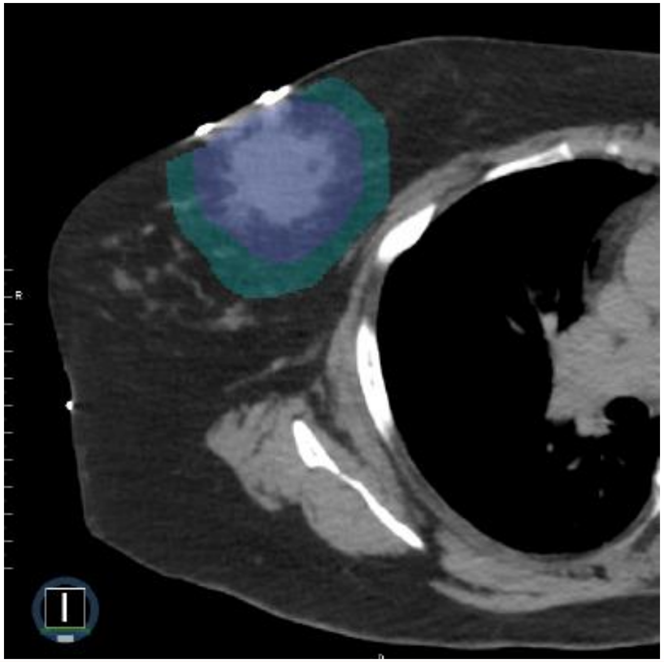
MRG-RT: Breast

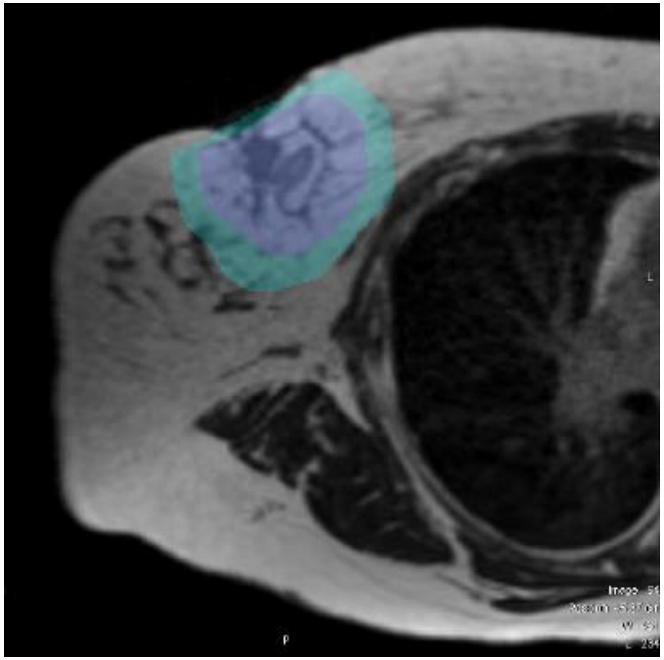
Comparison of PTV volumes:

3D-CRT: Mean PTV = 177 cc *Cyan colorwash*

MR-IGRT: Mean PTV = 85 cc *Dark blue colorwash*

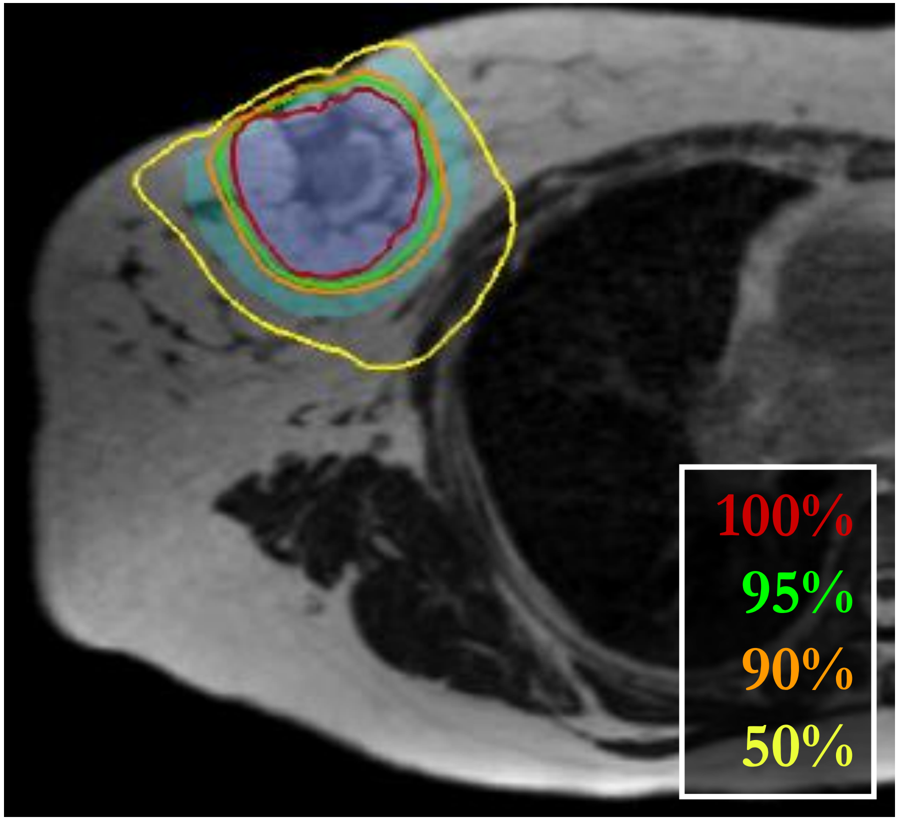
*52% reduction in volume with MR-IGRT





Courtesy of Maria Thomas, MD, PhD

MRG-RT: Breast



	MR-IGRT	3D-CRT
PTV:		
Volume	85 cc	177 cc
V(95%)	99.5%	99.5%
Ipsilateral Breast:		
V(20%)	51.7%	64.8%
V(50%)	31.3%	52.7%
V(75%)	17.6%	34.6%
V(90%)	12.6%	27.4%
V(100%)	11.7%	21.6%

Courtesy of Maria Thomas, MD, PhD

MRG-RT: Moderate Experience - Breast

Courtesy of Maria Thomas, MD, PhD

MRG-RT: Breast

Courtesy of Maria Thomas, MD, PhD

MRG-RT: Breast

Acute toxicity:

Well tolerated.

Minimal acute skin toxicity: Grade 0 - 1.

Ongoing evaluations:

Median follow up: < 1 year.

Outcomes: No recurrences to date.

Late toxicity: Grade 0-1 skin and subcutaneous tissue.

Cosmetic result: 100% Excellent/Good cosmesis scores to date.

QA Needs for online, adaptive MRgRT

Noel et al, Med Phys 2014

Reviewed each step in online adaptive process

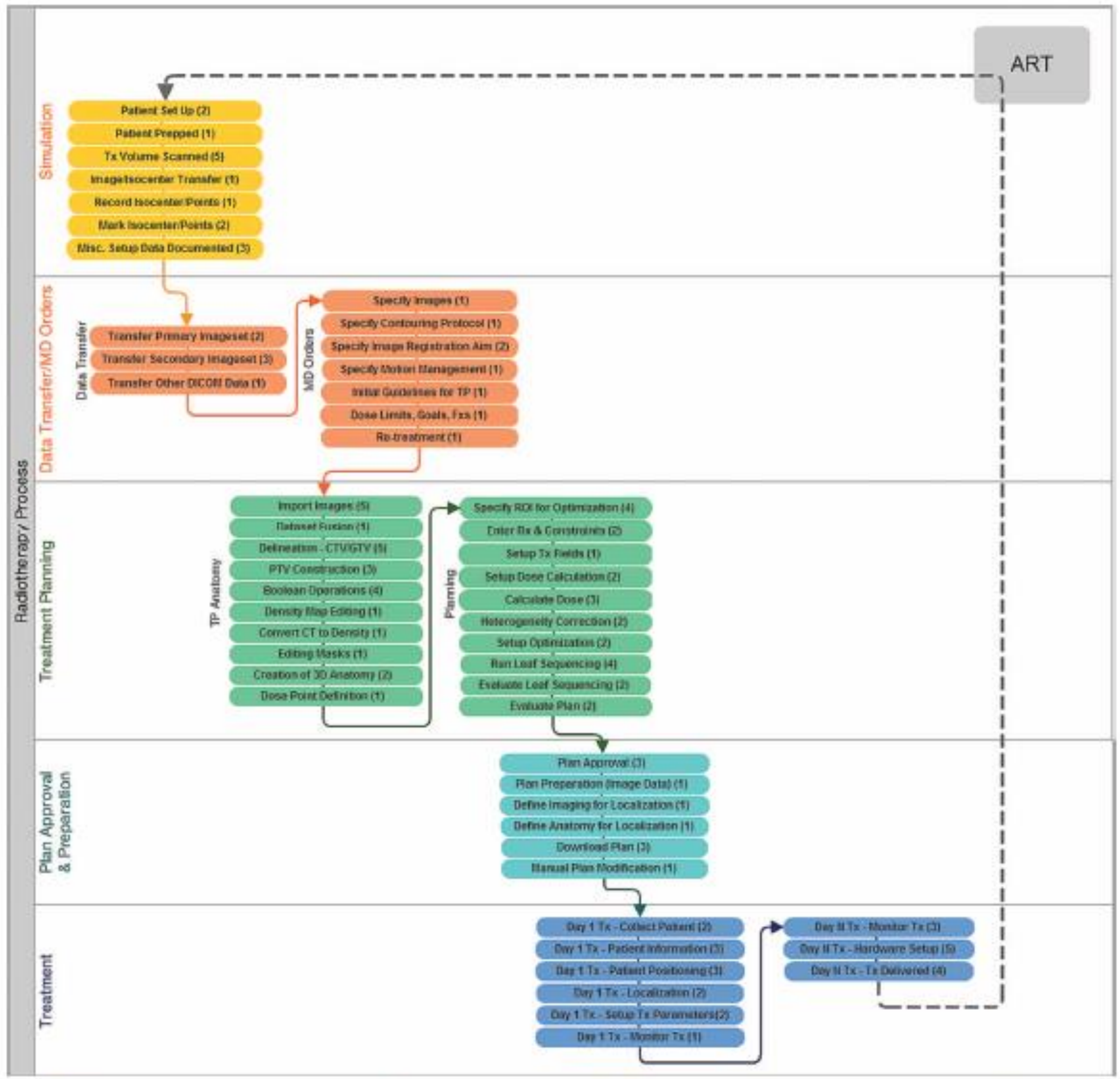
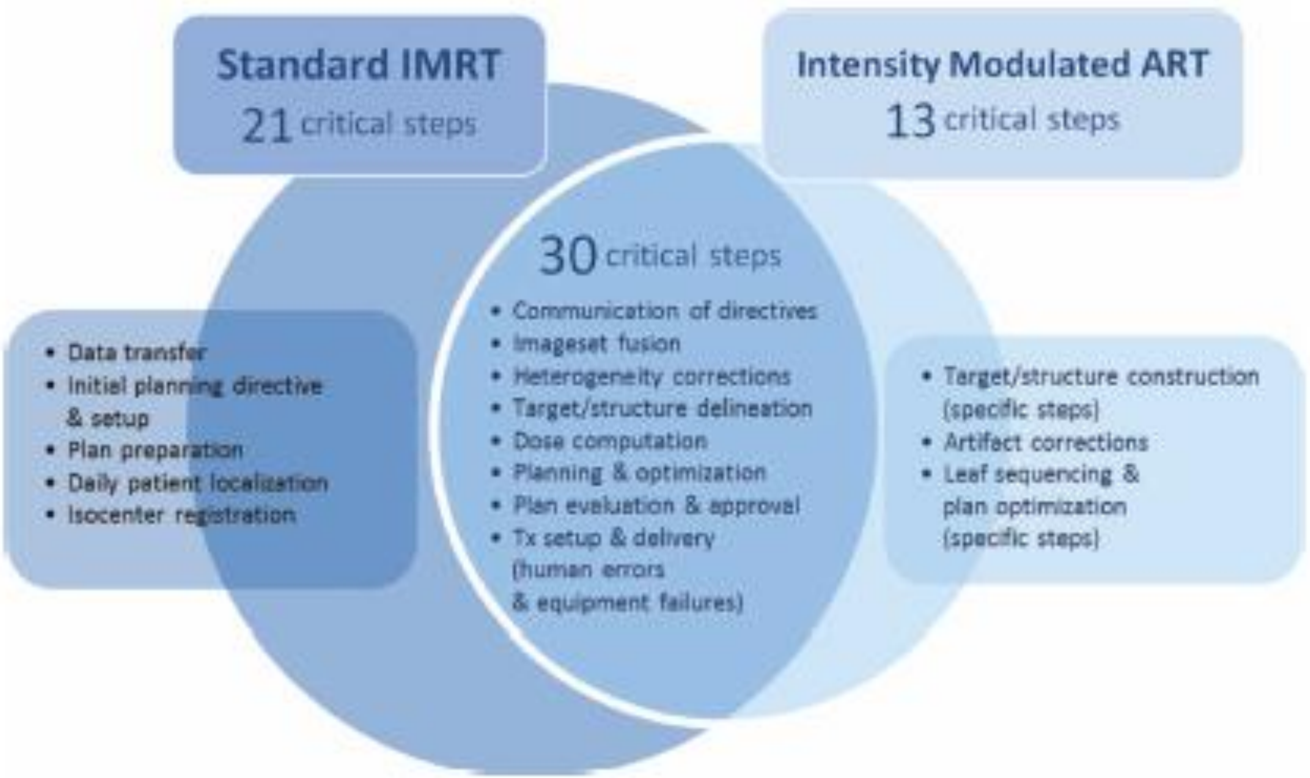


Fig. 1. Flow diagram of major intensity-modulated ART processes and subprocesses. The number of failure modes per subprocess is included in parenthesis.

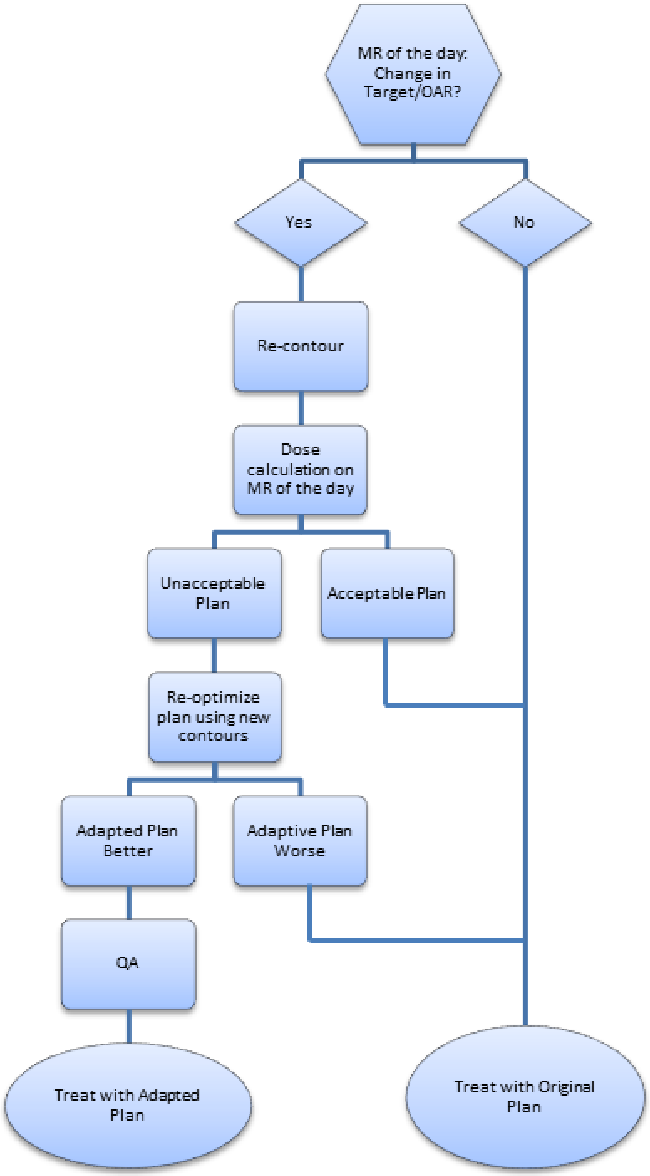
School

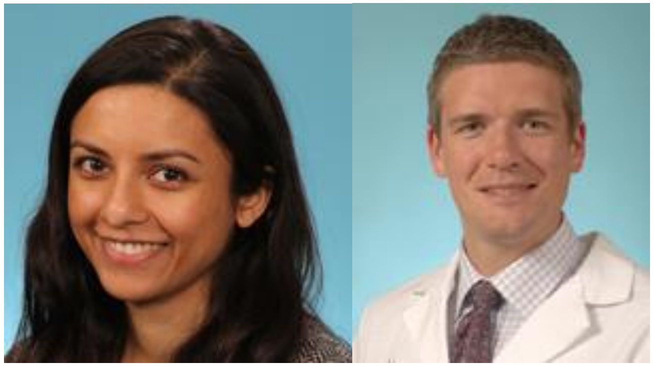
FMEA analysis of QA



Found unique points of failure in ART, but some issues in standard IMRT not found. Created processes to review contours and perform virtual QA

First clinical paper with adaptive MR guided radiation





Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications, Acharya, et al. IJROBP Vol. 94, No. 2, pp. 394e403

Online Adaptive SBRT Phase I Study

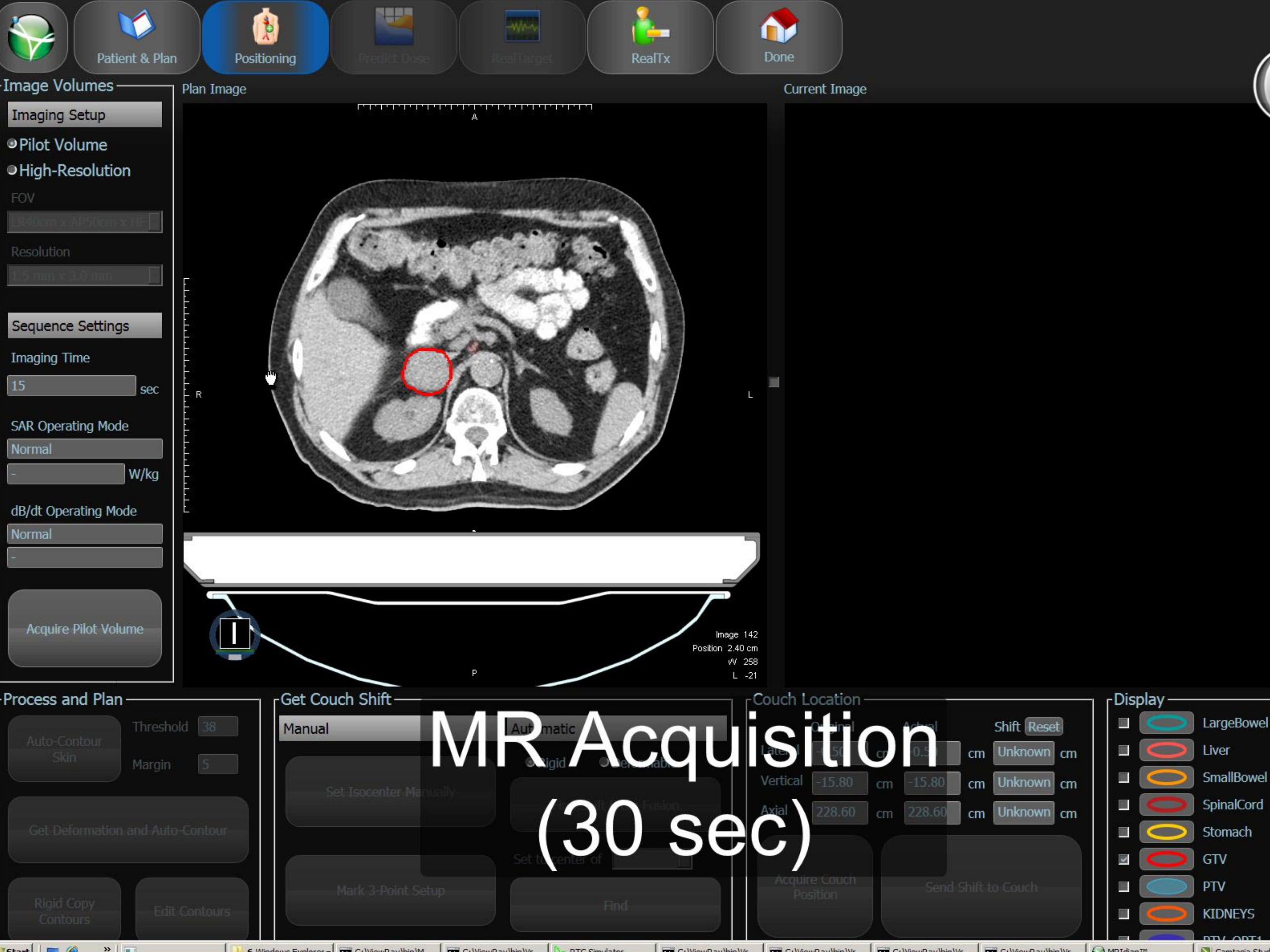
Co-PIs: Henke, Olsen, Parikh, Kashani

(NCI 02264886)

20 patients with unresectable primary or oligometastatic disease of the liver (n = 10) & non-liver (n=10) abdomen planned for SBRT

Prescription: 50Gy/5fx with online, adaptive MR-IGRT approach

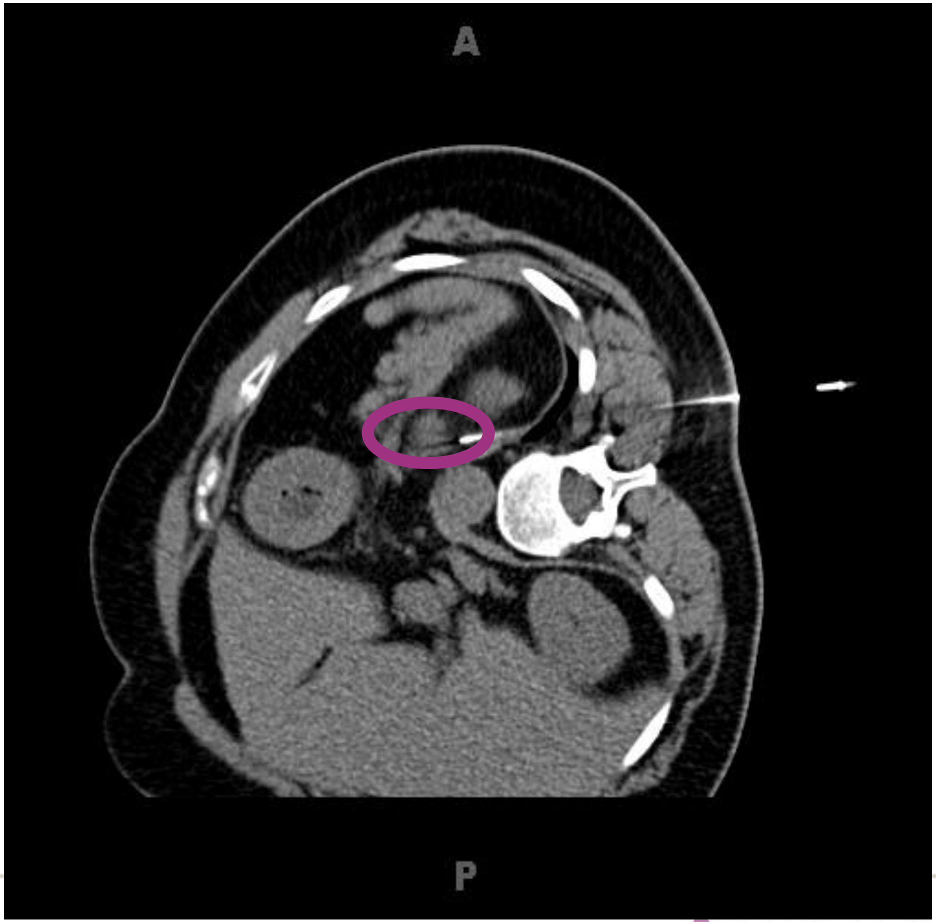
Isotoxicity approach, with dose escalation (or de-escalation) based on hard OAR constraints


Patient & Plan
Positioning
RealTx
Done
Image Volumes
Imaging Setup
Pilot Volume
High-Resolution
FOV
Resolution
Sequence Settings
Imaging Time
15
sec
SAR Operating Mode
Normal
W/kg
dB/dt Operating Mode
Normal
Acquire Pilot Volume
Plan Image
Current Image
A
R
L
P
Image 142
Position 2.40 cm
W 258
L -21
Process and Plan
Auto-Contour Skin
Threshold
38
Margin
5
Get Deformation and Auto-Contour
Rigid Copy Contours
Edit Contours
Get Couch Shift
Manual
Set Isocenter Manually
Mark 3-Point Setup
Find
Couch Location
Vertical
-15.80
Axial
228.60
Shift
Reset
Unknown
Send Shift to Couch
Display
LargeBowel
Liver
SmallBowel
SpinalCord
Stomach
GTV
PTV
KIDNEYS
MR Acquisition
(30 sec)

Phase I Trial Example Case

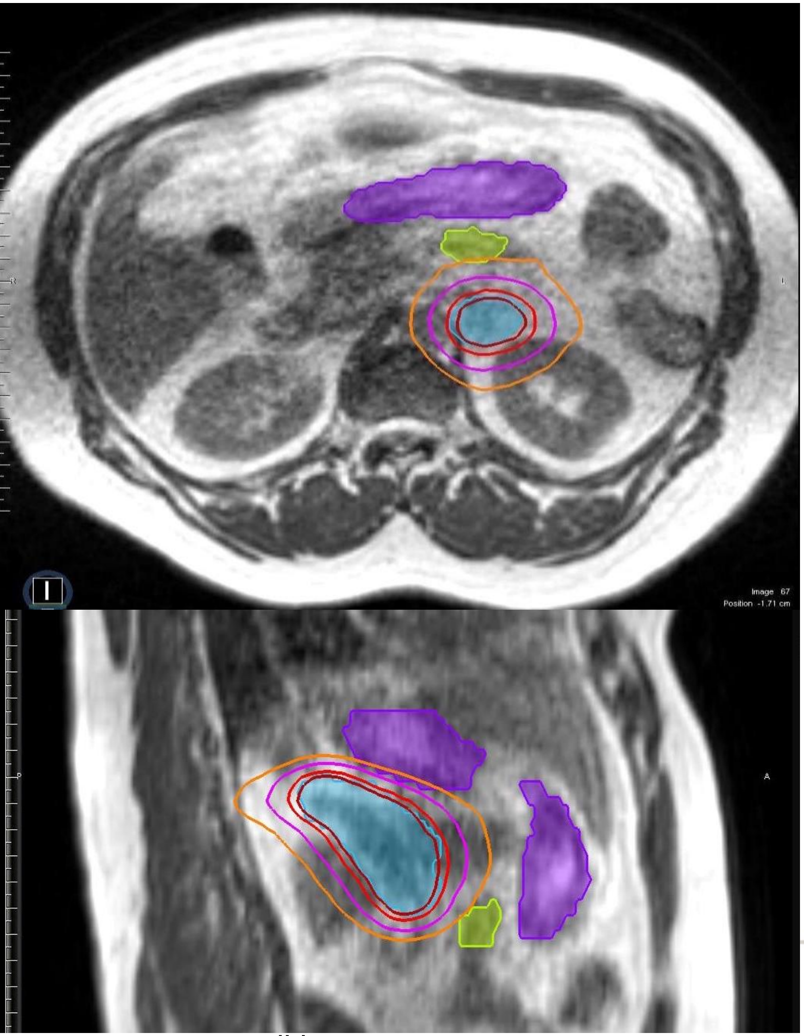
Solitary NSCLC Adrenal Metastasis

- 51yo woman, 1 year disease-free period
- Biopsy-proven, solitary 1.8cm adrenal ADC metastasis
- KPS 100%
- Preferred non-surgical option

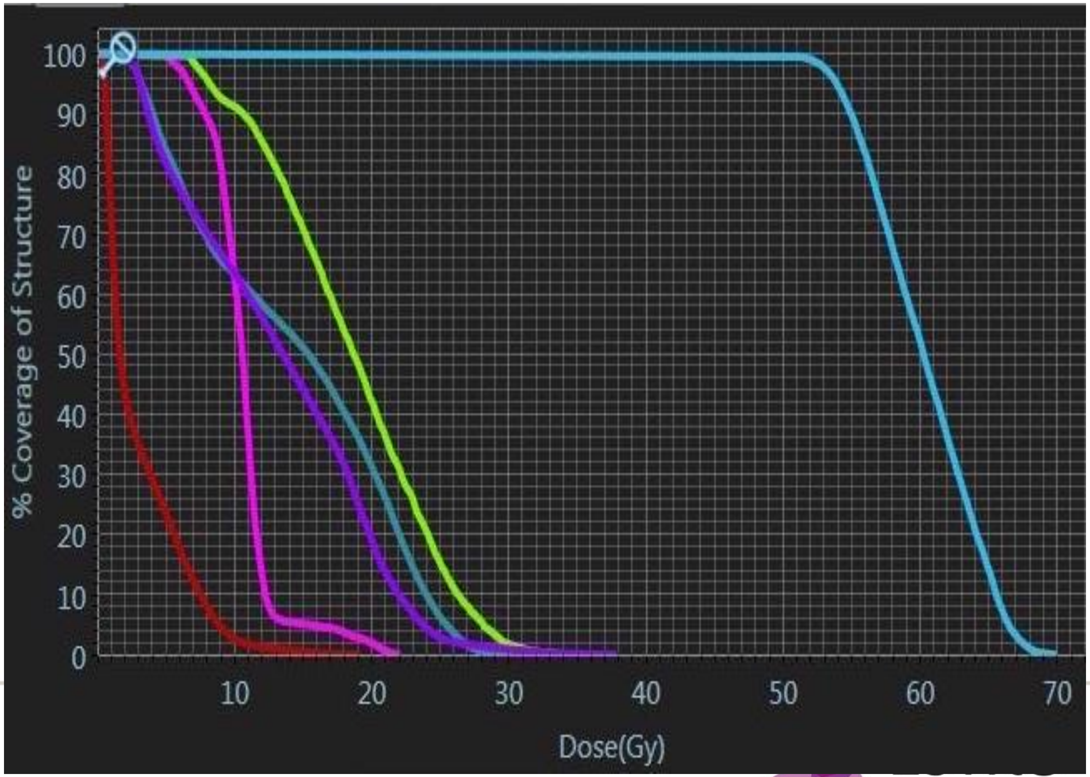


Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis



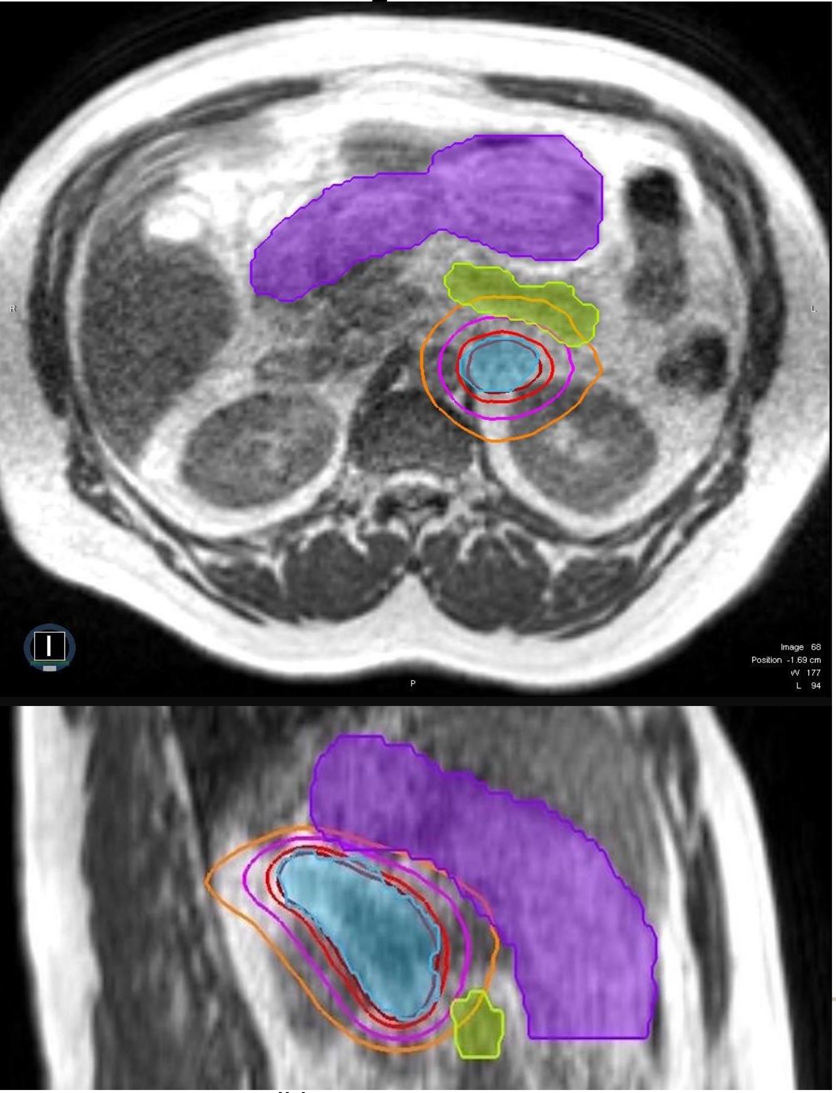
Day 1- All OAR constraints met, including small bowel & stomach



School

Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis



Day 2- Application of day 1 plan violates small bowel & stomach OAR constraints

Absolute
(% Isodose)
55 Gy (110%)
50 Gy (100%)
40 Gy (80%)
30 Gy (60%)

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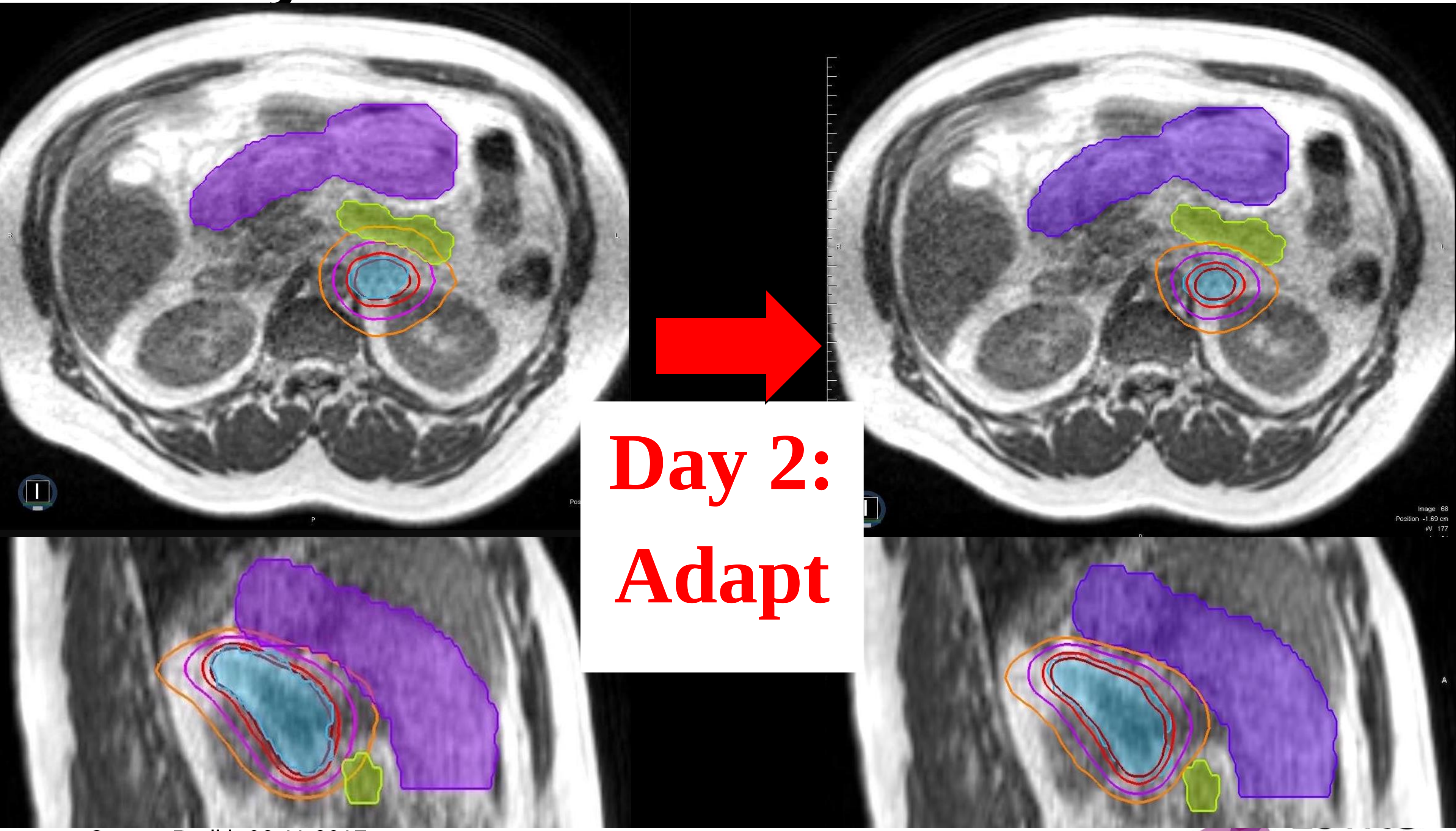
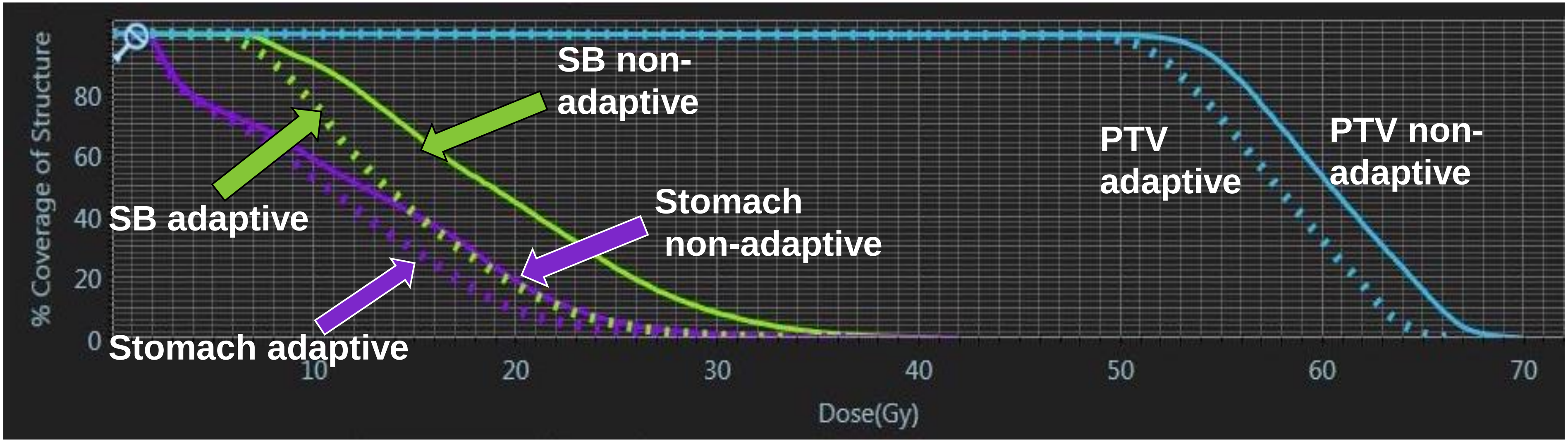
Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis



Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis



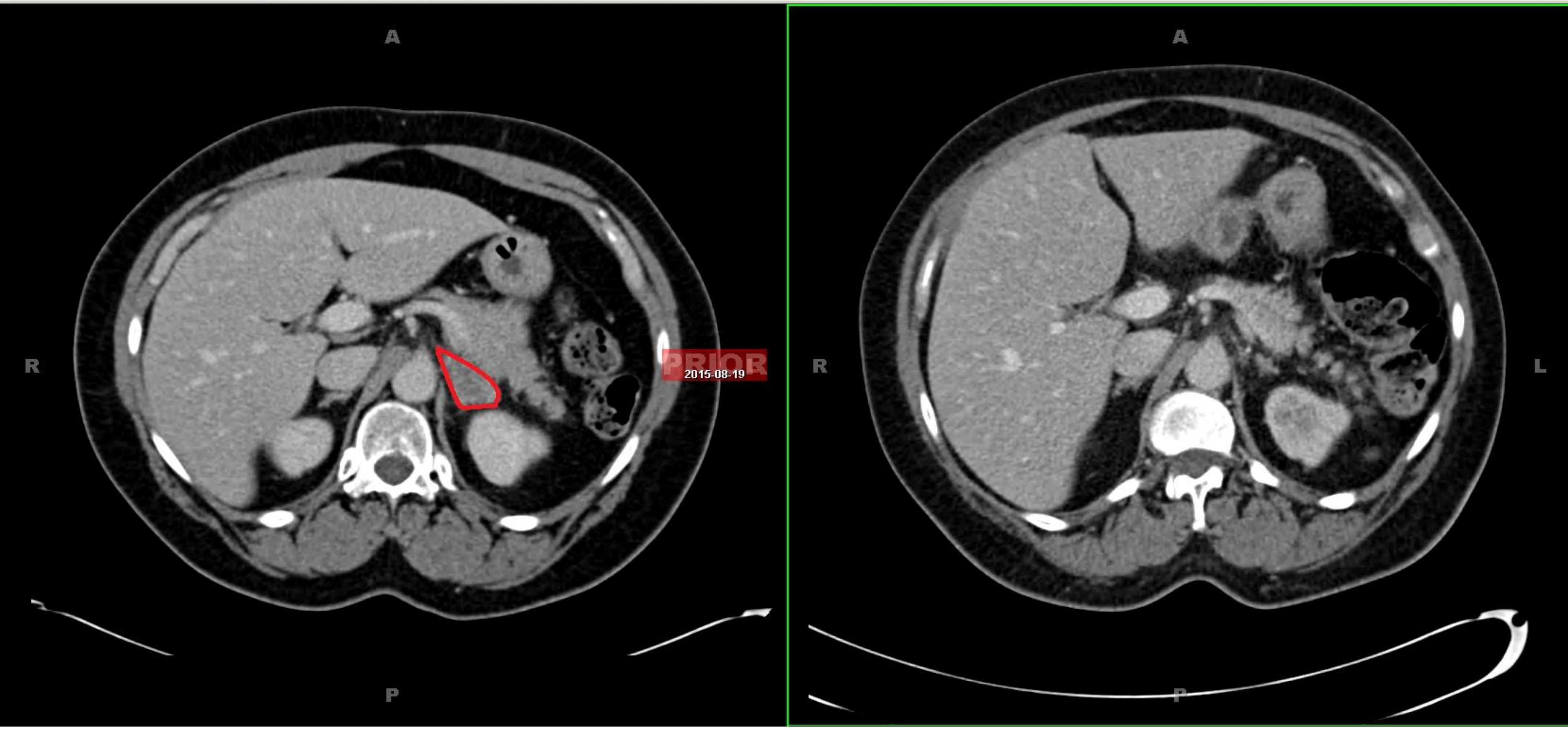
Adaptive plan reduces small bowel and stomach dose

PTV coverage minimally sacrificed

PTV coverage remains at goal 50Gy

Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis



Patient with zero reported acute or late toxicity

Radiographic CR at 3 and 6 months

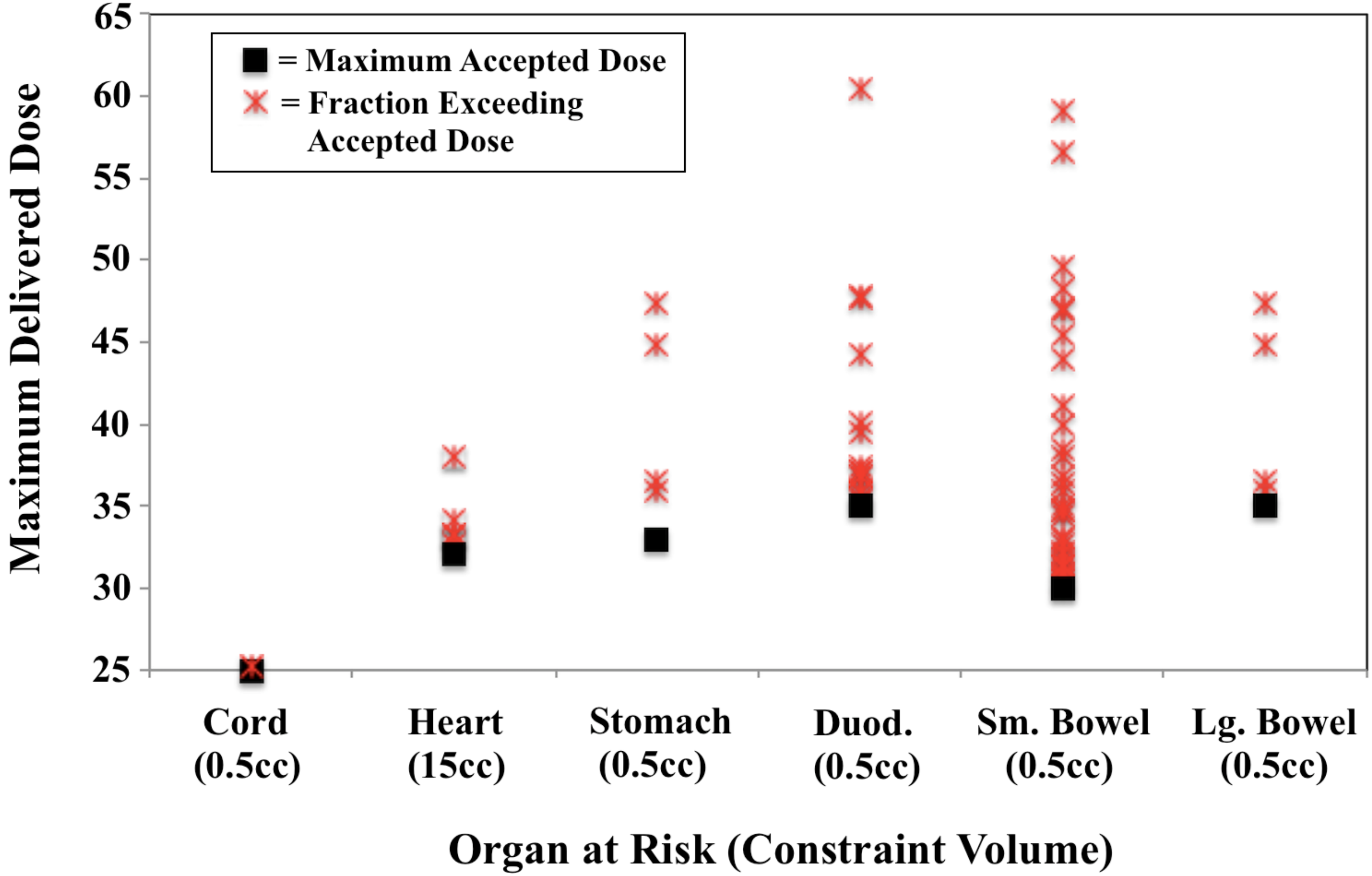
Phase I Results—Timing

- Median on table time: 79 minutes
- Median segmentation time: 9 min
- Median re-planning time: 10 min
- Median QA time: 5 min

Phase I Results—Plan Adaptation

- 83% (79/95) fx adapted—all patients had ≥1
- Plans adapted for 64% of liver & 98% of non-liver abdomen fx
- Initial plans would have violated OAR constraints in 70/95 fx
- 100% of OAR violations resolved with adaptive planning

Phase I Results—OAR Sparing

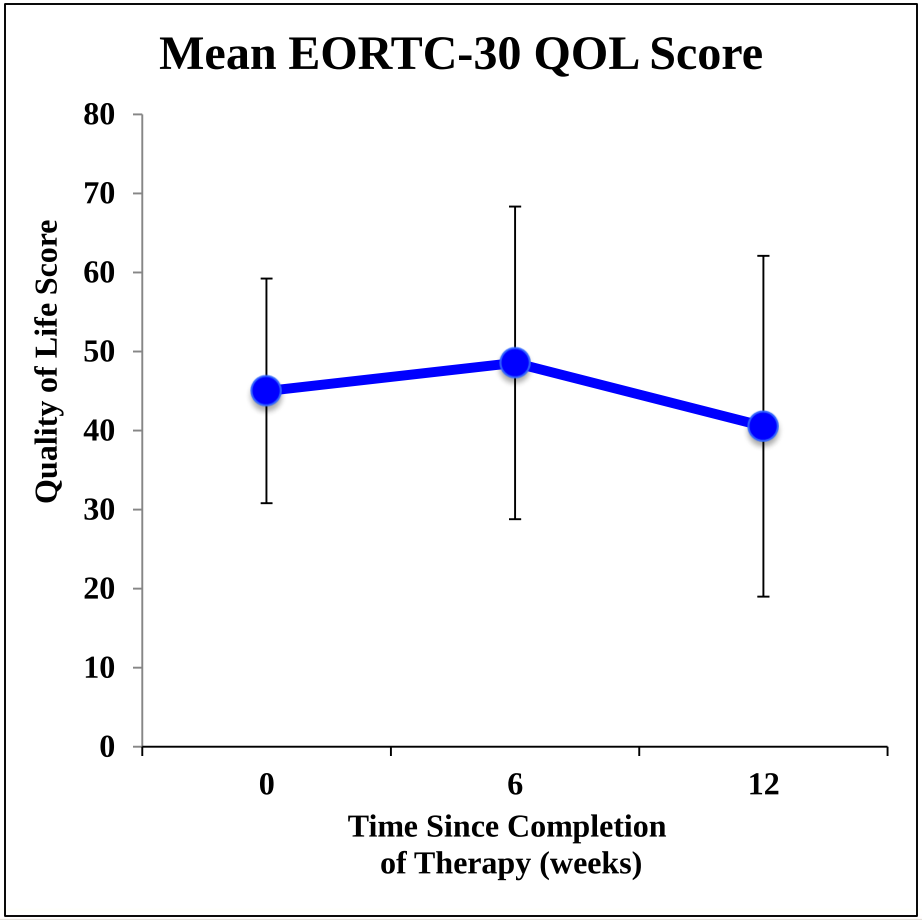


Phase I Results—Clinical Outcomes

No Grade 3 toxicity at median 11.8 mo f/u

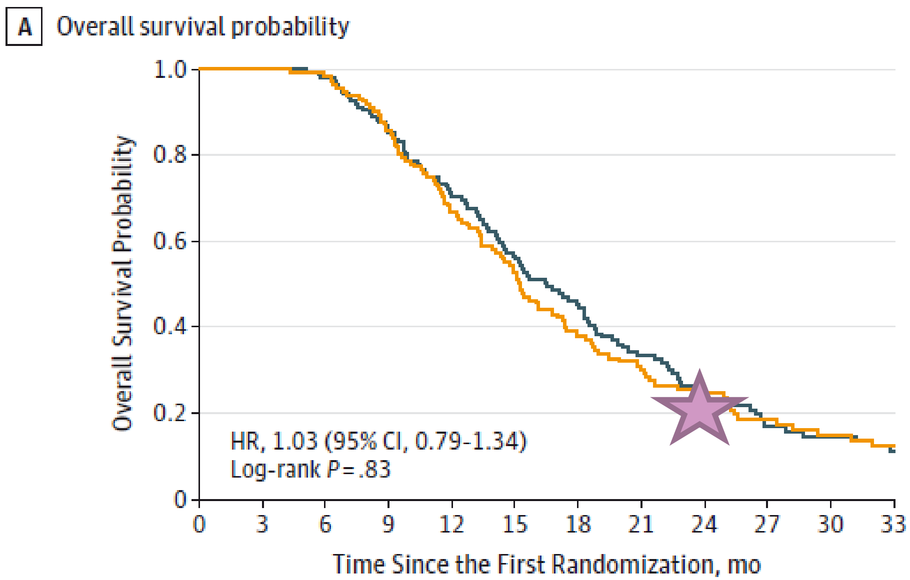
Expected 20-30% using aggressive dose regimen

No change in patient-reported EORTC-qlq 30 QOL scores (*P* = 0.29) at 0, 6, and 12wks.



My favorite topic: Pancreatic Cancer

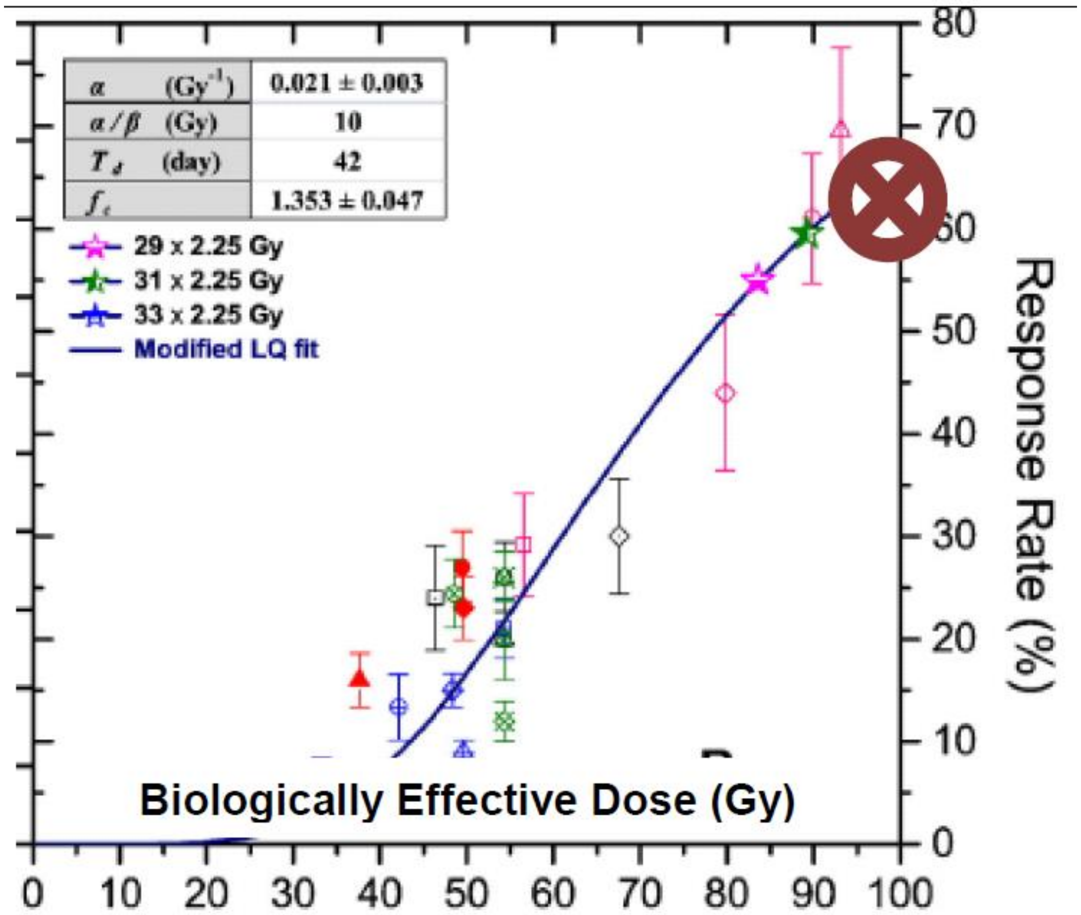
Locally Advanced Pancreatic Cancer is Bad



Chemotherapy												
No. at risk	136	136	133	117	94	70	55	39	24	14	12	8
No. of events	0	0	4	20	40	60	73	87	99	104	106	109
Chemoradiotherapy												
No. at risk	133	133	131	113	87	66	45	34	26	18	12	9
No. of events	0	0	3	20	45	63	80	89	96	101	105	106

“If cancer is the emperor of all maladies, then pancreatic adenocarcinoma is the ruthless dictator of all cancers” – Deborah Schrag

Could dose escalation help?



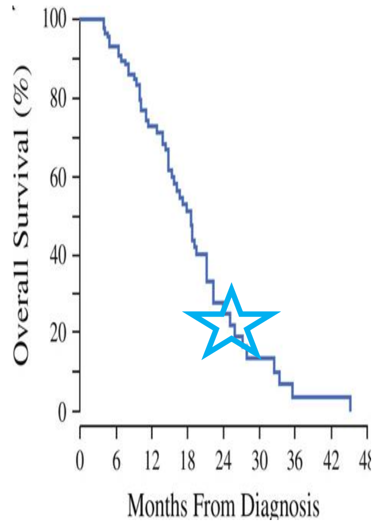
Dose escalation may improve SURVIVAL in Pancreatic Cancer

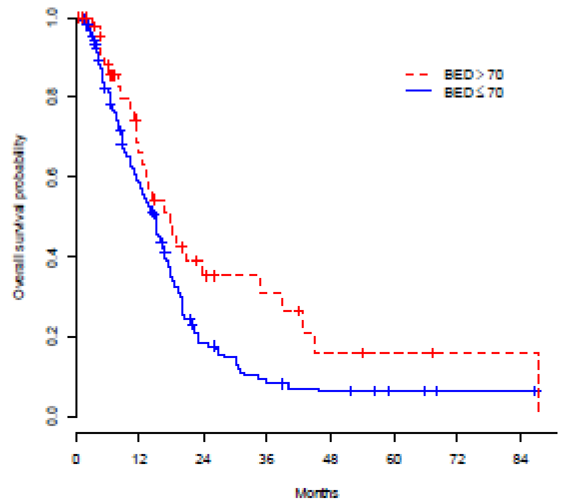
- Retrospective report from MD Anderson
- Tumors at least 1 cm from a GI structure (25% of patients) were considered for hypofractionated dose escalation
- Patients who received radiotherapy with BED > 70 Gy had an improved overall survival of 36% versus 19% at 2 years, and 31% versus 9% at 3 years

Table 1 Dose fractionation schedules, biologically effective dose, and dose-volume constraints

Dose and no. of fractions	Biologically effective dose (Gy)	No. of patients	Average stomach V50 (cm^3) or maximum point dose if V50 = 0 cm^3	Average duodenum V50 (cm^3) or maximum point dose if V50 = 0 cm^3
63 Gy in 28 fx	77.2	14	25.5	22.8
70 Gy in 28 fx	87.5	11	25	27.6
67.5 Gy in 15 fx	97.9	7	0; 44.8 Gy	0; 44.9 Gy
60 Gy in 10 fx	96.0	1	0; 41.3 Gy	0; 43 Gy
50 Gy in 5 fx	100.0	1	0; 26.3 Gy	0; 36.1
51.3-70.4 Gy in 13-39 fx	70.4-84.3	13	33.9	15.2

Abbreviations: fx = fractions; V50 = volume of organ receiving >50 Gy.
α/β = 10 for calculation of biologically effective dose.



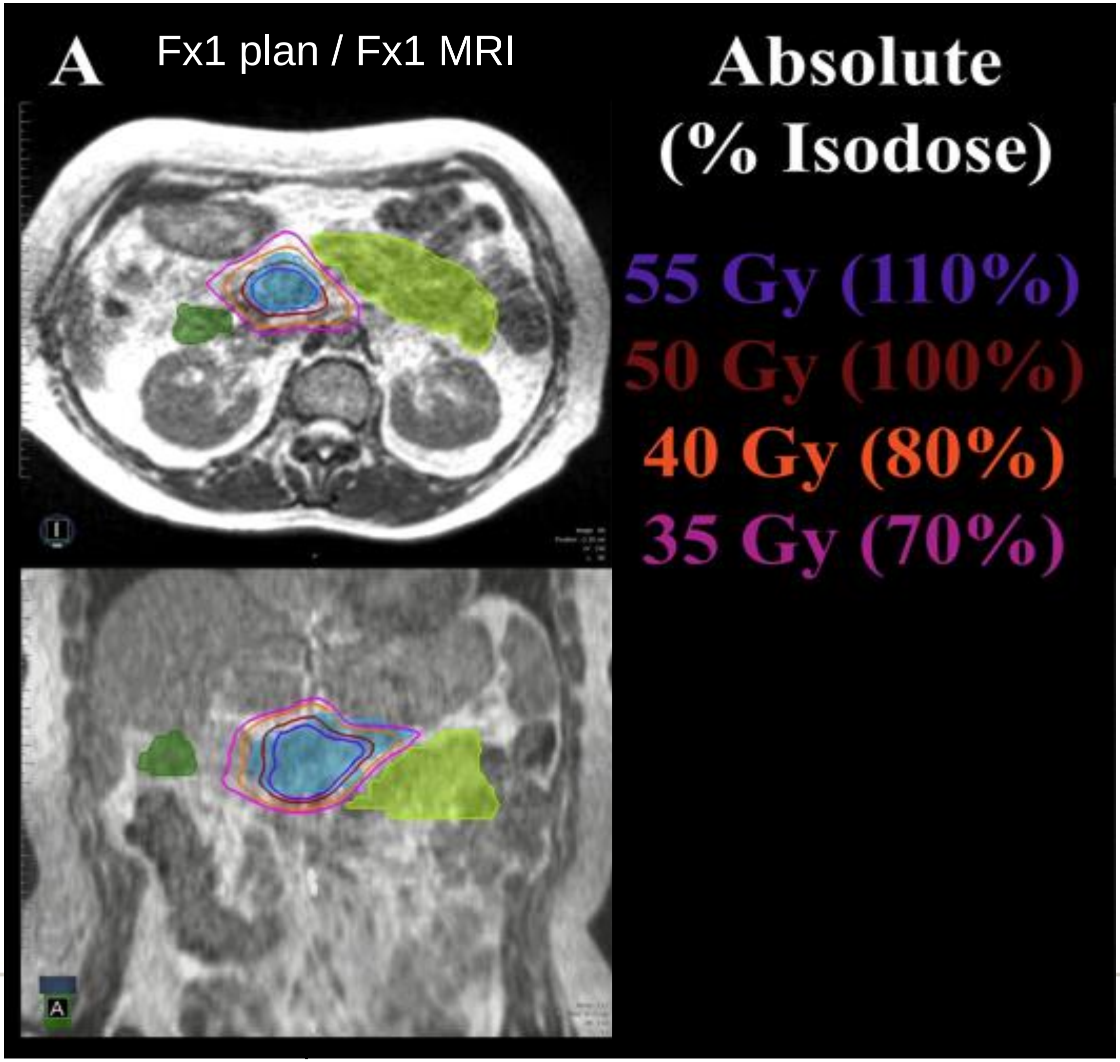


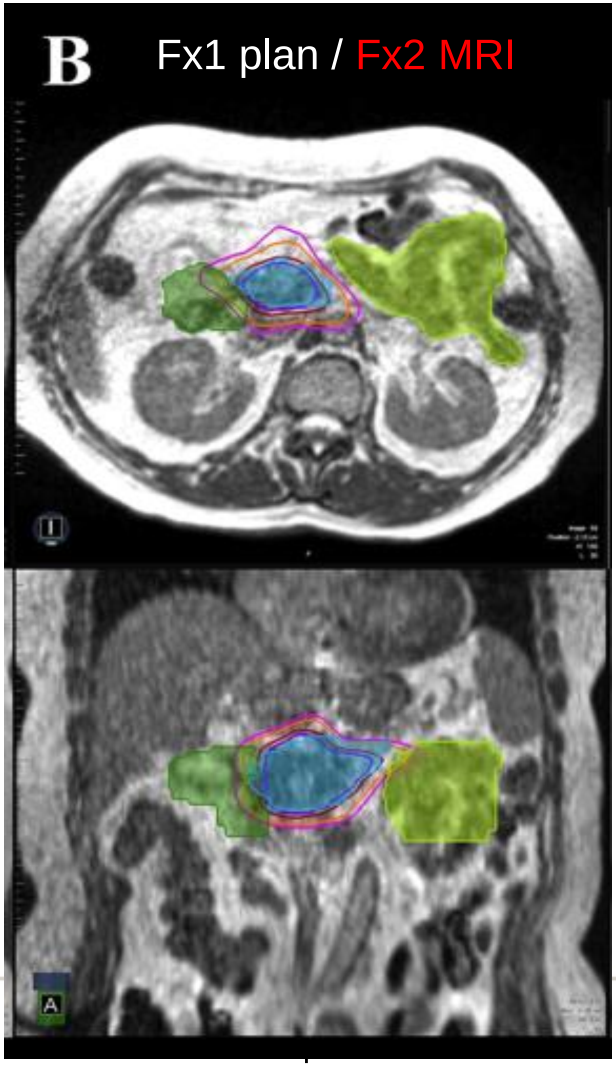
Patient Population

Pt ID	Oncologic History	Dose (Gy)/ Fx	Concurrent chemo	OARs for re-contouring	Additional OARs in replanning optimizer	Motion Management	Re-planning constraints
1	57 y/o with LAPC with continued encasement of celiac artery after gemcitabine/nab-paclitaxel and FOLFIRINOX. Planned for resection.	50.7/15	gemcitabine	Stomach Small Bowel Duodenum	Large Bowel Spinal Cord Kidneys	Expiratory gating with 3 mm boundary. 5 mm PTV.	Stomach - Re-plan if 0.5 cc > 40 Gy Small bowel - Re-plan if 0.5 cc > 40 Gy Duodenum - Re-plan if 0.5 cc > 40 Gy PTV - Re-plan if > 83% receives > 48.17 Gy Dmax - Re-plan if > 70 Gy
2	71 y/o with BRPC with SMV abutment after gemcitabine/nab-paclitaxel	60/15	gemcitabine /nab-paclitaxel	Stomach Small Bowel Duodenum	Large Bowel Spinal Cord Kidneys	Expiratory gating with 3 mm boundary. Pt with poor breath hold.	Stomach - Re-plan if 0.75 cc > 40 Gy Small bowel - Re-plan if 0.75 cc > 40 Gy Duodenum - Re-plan if 0.75 cc > 40 Gy GTV - Re-plan if > 70% receives > 57 Gy Dmax – no hot spot near GI tract
3	63 y/o with LAPC with SMA encasement after gemcitabine/nab-paclitaxel and FOLFIRINOX	60/15	capecitabine	Stomach Small Bowel Duodenum	Large Bowel Spinal Cord Kidneys	Expiratory gating with 3 mm boundary. 6 mm PTV.	Stomach - Re-plan if 0.75 cc > 40 Gy Small bowel - Re-plan if 0.75 cc > 40 Gy Duodenum - Re-plan if 0.75 cc > 40 Gy CTV - Re-plan if > 95% receives > 40 Gy Dmax – Re-plan if > 72 Gy
4	59 y/o with metastatic pancreatic cancer with response of hepatic metastasis to FOLFIRINOX and FOLFIRI and progression of primary tumor	60/15	gemcitabine	Stomach Small Bowel Duodenum	Large Bowel Spinal Cord Kidneys	Expiratory gating with 3 mm boundary. 6 mm PTV.	Stomach - Re-plan if 0.75 cc > 40 Gy Small bowel - Re-plan if 0.75 cc > 40 Gy Duodenum - Re-plan if 0.75 cc > 40 Gy GTV - Re-plan if > 95% receives > 40 Gy Dmax – no hot spot near GI tract

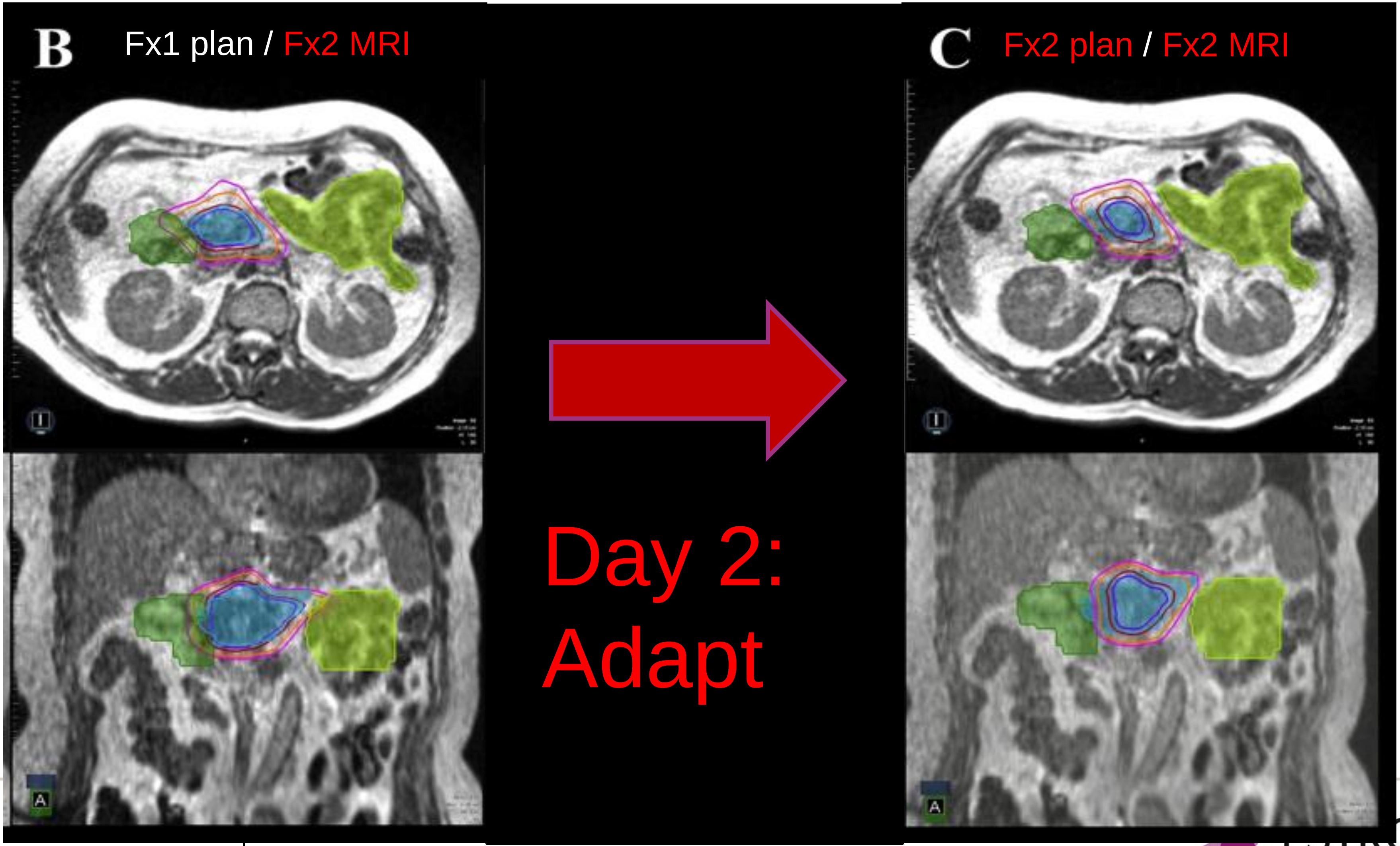
After chemo

Before chemo


A
Fx1 plan / Fx1 MRI
Absolute
(% Isodose)
55 Gy (110%)
50 Gy (100%)
40 Gy (80%)
35 Gy (70%)



Day 2 – Application of fraction 1 plan violates duodenal and small bowel OAR constraints


B
Fx1 plan / Fx2 MRI
Day 2:
Adapt
C
Fx2 plan / Fx2 MRI

Overall Tolerance

2/5 patients needed pain medication, anxiolytics or both to tolerate MRgRT

No acute GI toxicity!

Fatigue was present

Would normally expect ~22% rate of grade 3 acute GI toxicity with a dose of 55 Gy in 25 fractions! (Badiyan, AJCO, 2016)

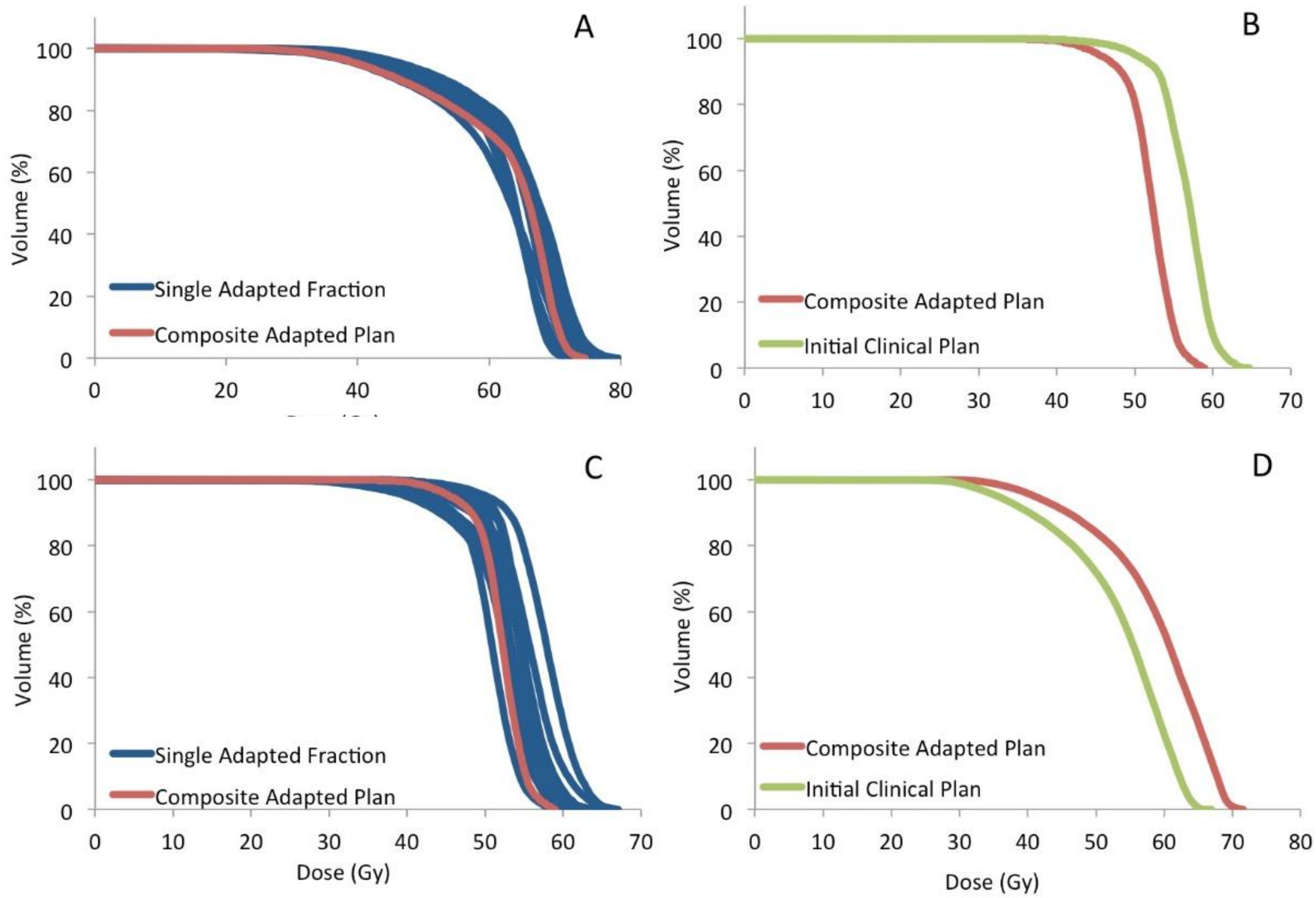
Plan adaptations

Pt ID	Adapted Fractions	Reason for Adaptation
1	13	Stomach – 9 Small bowel – 1 Stomach and small bowel – 2 Stomach and duodenum - 1
2	14	Target coverage – 2 Duodenum – 3 Large bowel – 3 Duodenum and small bowel – 3 Stomach and duodenum – 1 Small bowel – 1 Large bowel, small bowel, stomach - 1
3	10	Target coverage – 2 Duodenum – 6 Small bowel and duodenum – 1 Small bowel – 1
4	14	Target coverage – 2 Stomach – 2 Duodenum – 7 Small bowel and duodenum – 1 Small bowel – 1

Patients had plan adaptation for most of their fractions

Varied reasons, mostly for OAR constraints

Cumulative Target Dose



Reviewing MRgRT data to date

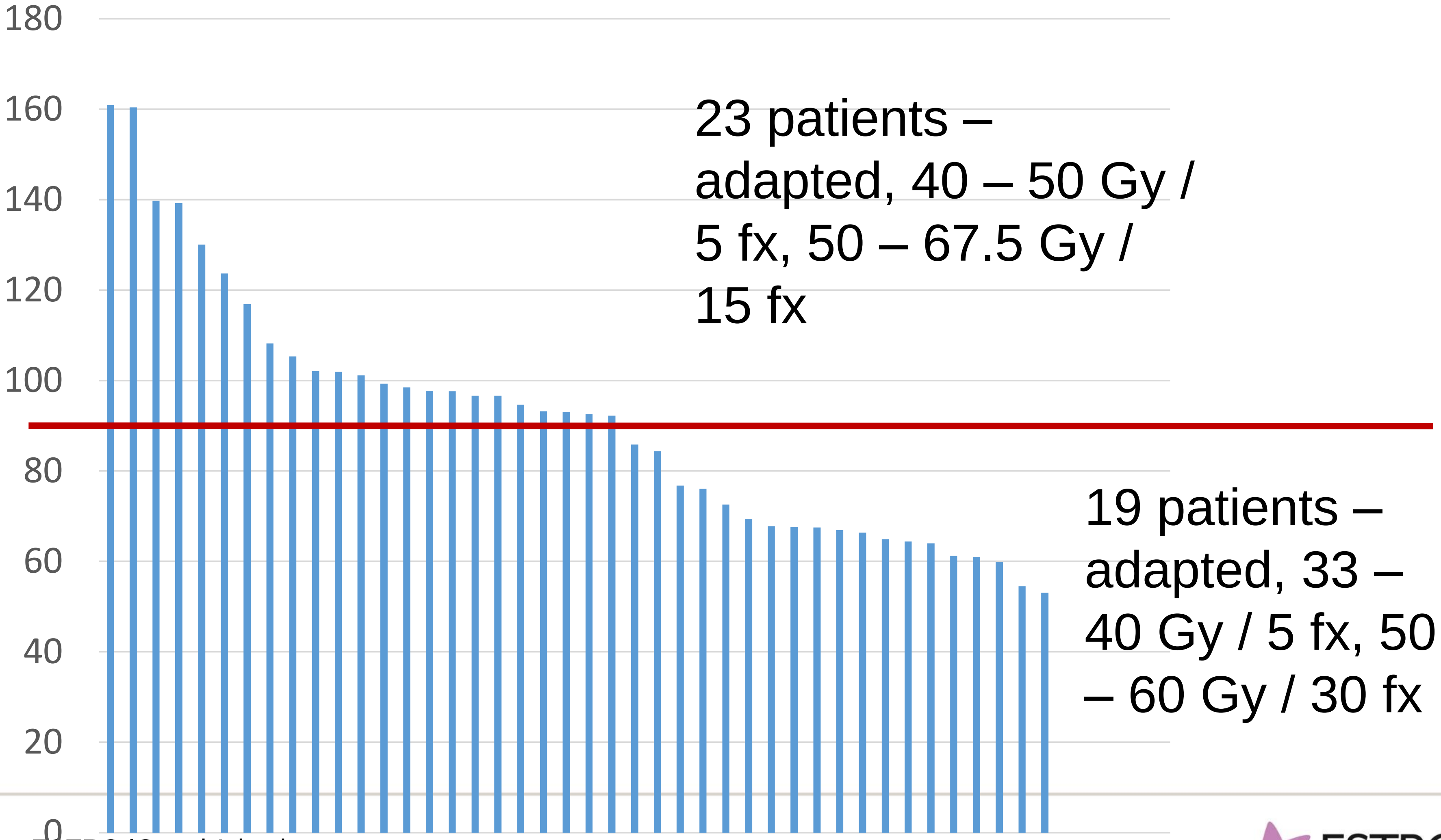
Reviewed four institutions' data for pancreas MRgRT (VUMC, Wisconsin, UCLA, Washington University)

Locally advanced, borderline resectable and medically inoperable pancreatic cancer patients treated up to 8/2016

Practices varied between dose, fractionation, technique between institutions

Looked at dose as a predictor of survival

Maximum BED > 90 Gy



Patient Characteristics	$maxBED_{10}>90$ N=23	$maxBED_{10}<90$ N=19	p-value
Age (median)	68	62	0.068
Sex:			
Male	14	12	0.879
Female	9	7	
Tumor Characteristics			
Location:			
Head	17	12	0.453
Tail	6	7	
Resectability:			
BRPC	4	6	0.409
LAPC	17	13	
Medically Inoperable	2	0	
Median CA 19-9 at diagnosis (U/mL)	263.4	82.5	0.099
Node positive	4	4	0.698

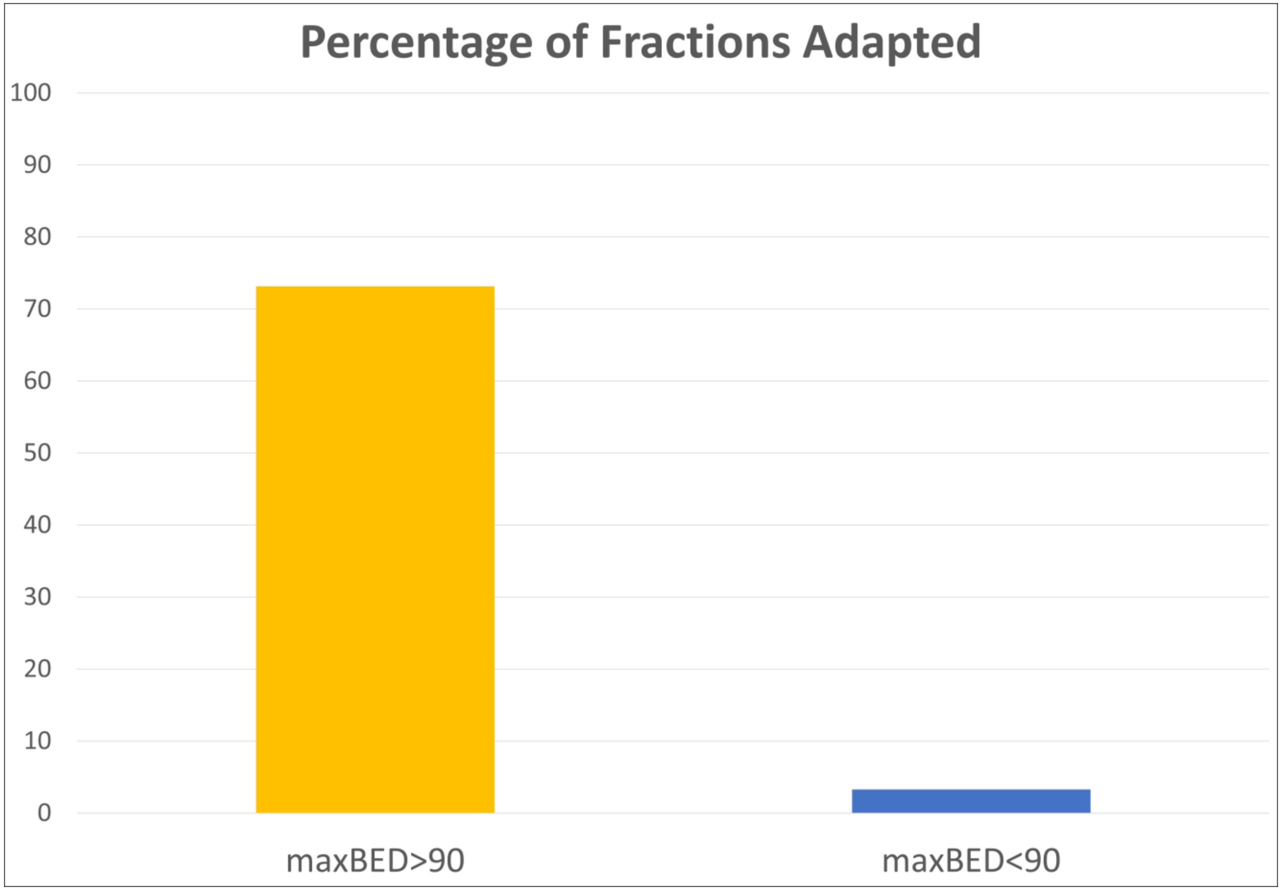
Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

Treatment Factors	$maxBED_{10}>90$ N=23	$maxBED_{10}<90$ N=19	p-value
Post – RT Surgery	3	2	1.000
Ind. Chemo:			
Gem-based	9	10	0.970
FOLFIRINOX	11	8	
FOLFOX	1	0	
None	2	1	
Conc. Chemo:			
Gem-based	4	9	0.094
Capecitabine	3	4	
None	16	6	
Radiation Factors			
BED_{10} of Rx (Gy)	72.0	59.5	<0.001
$maxBED_{10}$	101.1	66.9	<0.001
Median Fractions Adapted per patient	5	0	<0.001
GTV (cc)	38	36	0.714

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

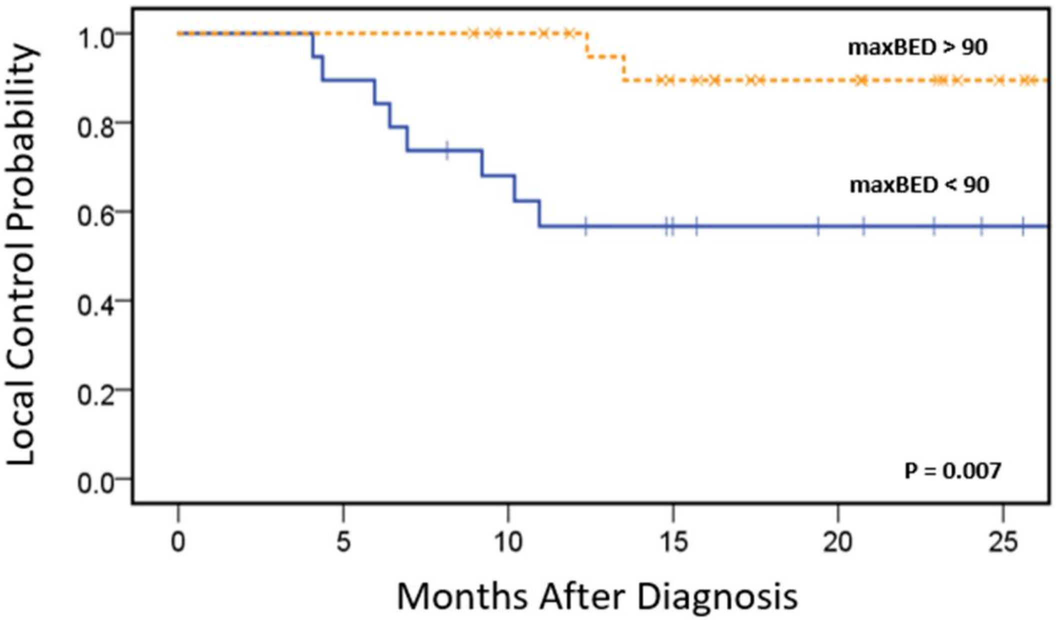
RT Technique	Dose and Fractionation	Number of Patients
Conventional	50.4 Gy in 28 Fractions	6
	40 - 55 Gy in 25 Fractions	7
Hypofractionated	50 - 67.5 Gy in 10-15 Fractions	8
SBRT ($maxBED_{10} < 90$)	30 – 40 Gy in 5 Fractions	6
SBRT ($maxBED_{10} > 90$)	40 – 52 Gy in 5 Fractions	15

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017



Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

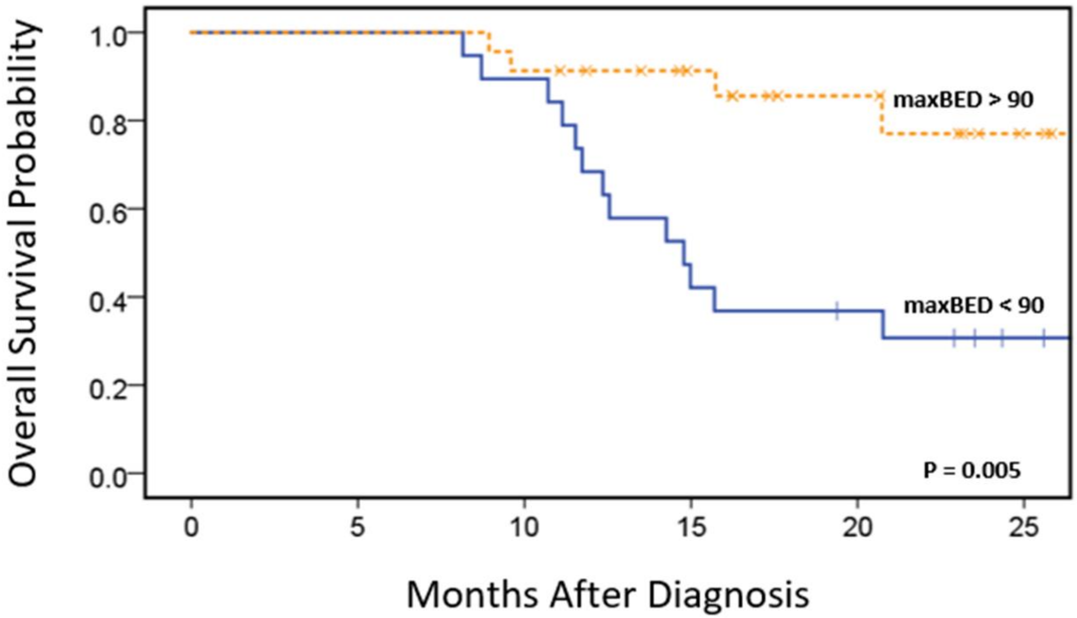
Local Control



No. at Risk						
maxBED > 90	23	23	21	15	10	4
maxBED < 90	19	17	12	7	5	2

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

Overall Survival



No. at Risk

maxBED > 90	23	23	21	16	11	5
maxBED < 90	19	19	17	8	6	2

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

Gr 3+ GI Toxicity	
$maxBED_{10}$>90	0%
$maxBED_{10}$<90	15.8%

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

Results

- Median follow-up for survivors is 21 months.

- Median OS for patients with maxBED10 > 90 and maxBED10 < 90 was 27.8 months vs. 14.8 months (p = 0.005)

- LC at 18 months for patients with maxBED10 > 90 and maxBED10 < 90 was 87% vs 57% (p = 0.007)

- Number of fractions adapted, maxBED and BED of Rx were predictive of survival on univariate analysis

- No tumor, patient or other therapy factor was related to outcome

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

Results in Context

Study	Median OS (months)
LAP07 – 3DCRT	15.2
MDACC – mostly 3DCRT	15*
MDACC – IMRT	17.8*
MRgRT – standard IMRT & SBRT	14.8
MSKCC – IMRT	23
Harvard[11] – SBRT	20
JHU – SBRT	18.4
MRgRT – Hypofrac/High dose SBRT	**27.8**

Next Step for Pancreas MRgRT

VUmc VU University Medical Center Amsterdam

UCLA

Washington University in St. Louis

WISCONSIN UNIVERSITY OF WISCONSIN–MADISON

Inoperable Pancreas Cancer after >= 3 months of chemotherapy → 50 Gy / 5 fractions MR guided, adapted and tracked

ViewRay Launches Clinical Trial Following Compelling Early Pancreatic Cancer Data with MRIdian System

First Initiative Based on Retrospective Study That Suggests Potential for Significantly Prolonged Survival

September 25, 2017

Primary endpoint: Toxicity at 90 days

Secondary endpoints: Disease related outcomes

Goal: 100 patients

Gemelli Fondazione Policlinico Universitario A. Gemelli Università Cattolica del Sacro Cuore

UNIVERSITY OF MIAMI

Henry Ford HEALTH SYSTEM

Challenges

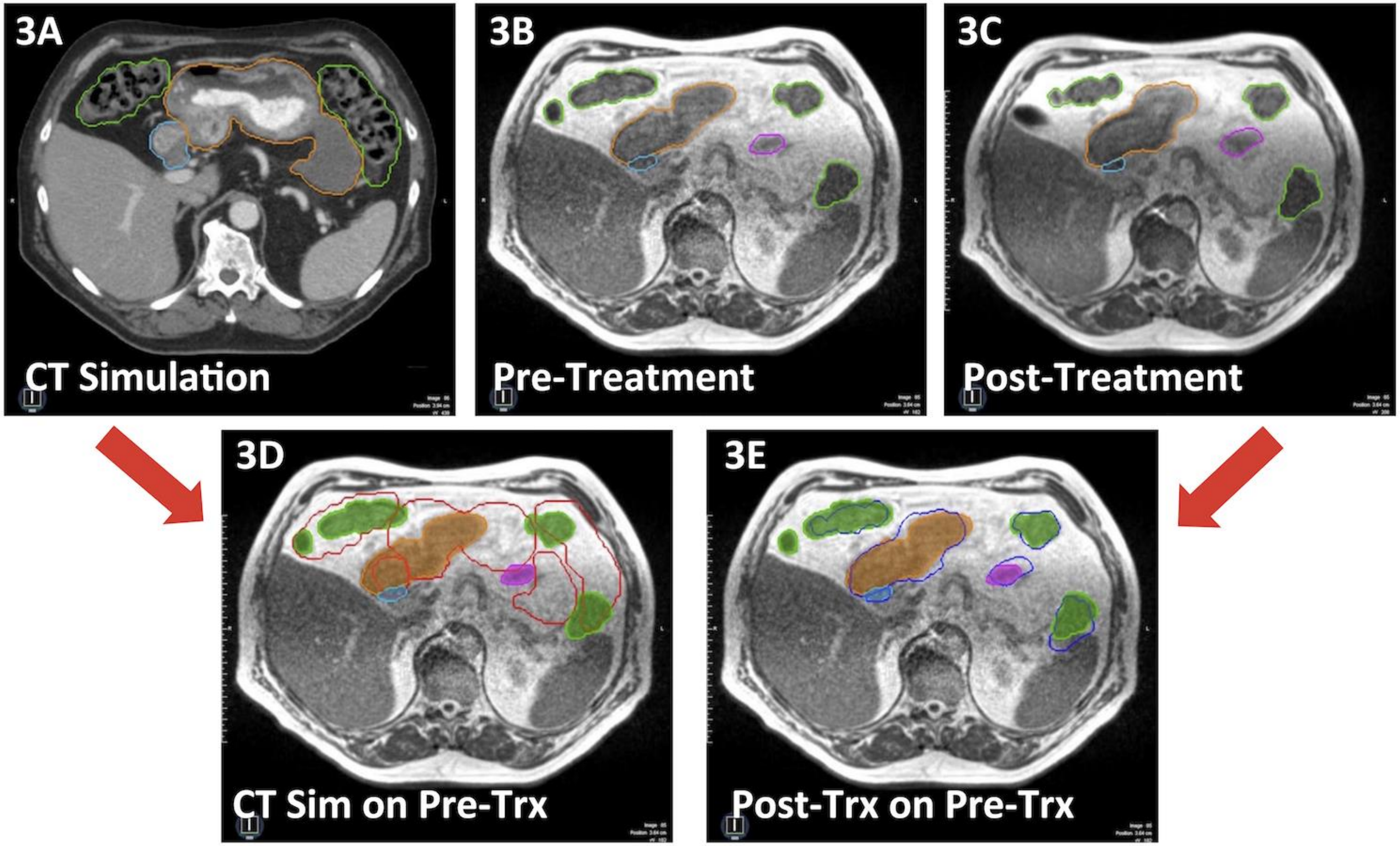
Assessing Intrafraction Motion during Plan Adaptation

Patients received 2 sets of images on a delivery day due to machine errors or patient intolerance

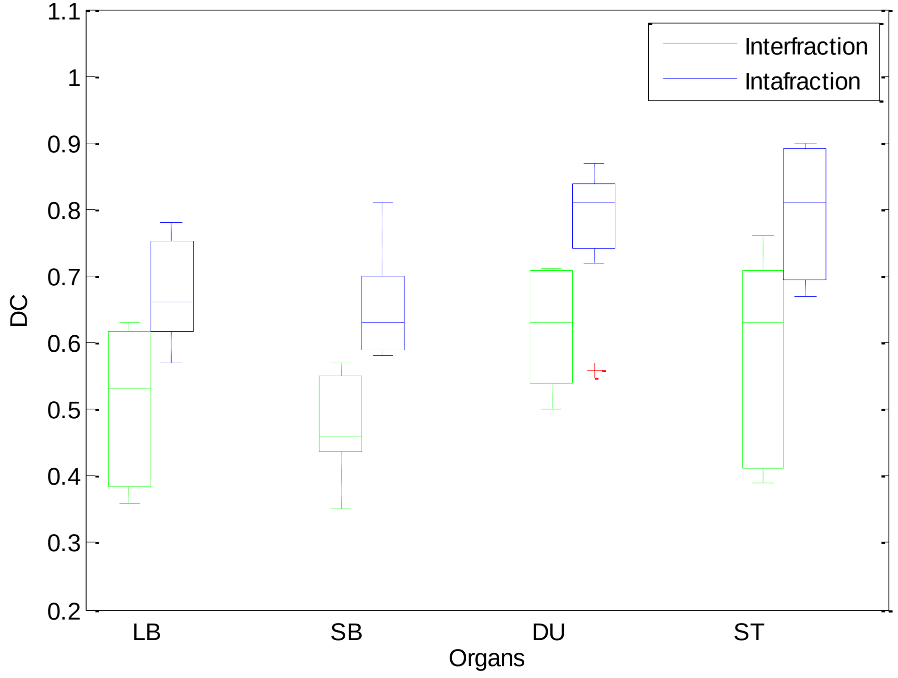
Images compared with simulation images taken at the beginning of therapy

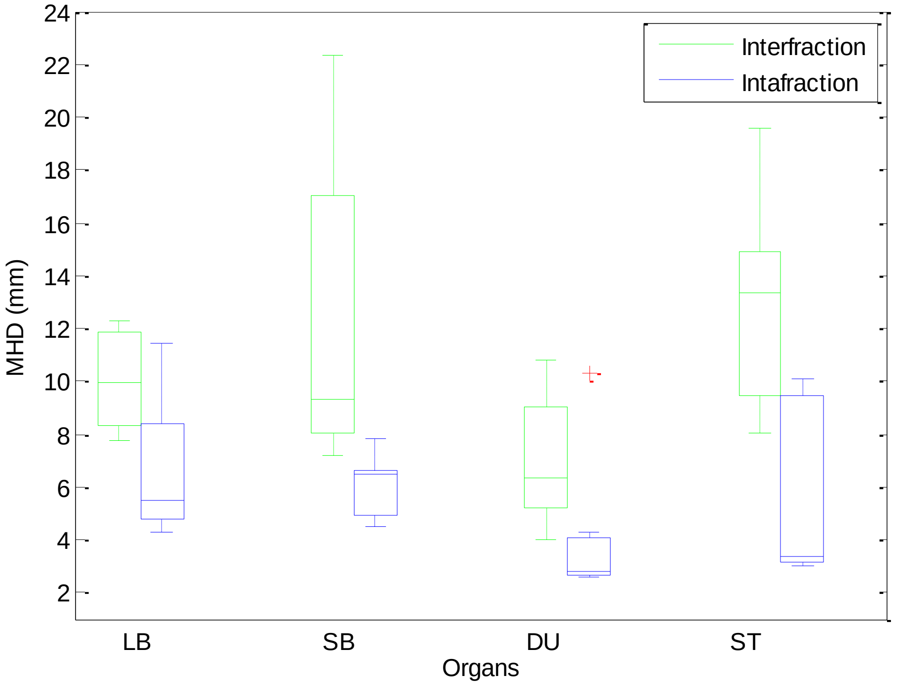
The viscous GI structures – stomach, duodenum, small intestine and large intestine were contoured on each image

Patient example (intrafx motion)



Early image analysis





Meaningful dose constraints

Current dose constraints based on non-adaptive plans (ie 45 Gy maximum dose to GI structures in hypofractionated regimen; 33 Gy to proximal GI structures in SBRT regimen)

These are not necessarily applicable to a ‘plan of the day’ regimen

There are residual errors in the ‘plan of the day’ regimen

We will need to increase these tolerances to make a ‘real’ dose constraint

Therapist change in requirements

Therapists already had to learn MR based localization and safety

Now learning MR based segmentation for normal tissue structures

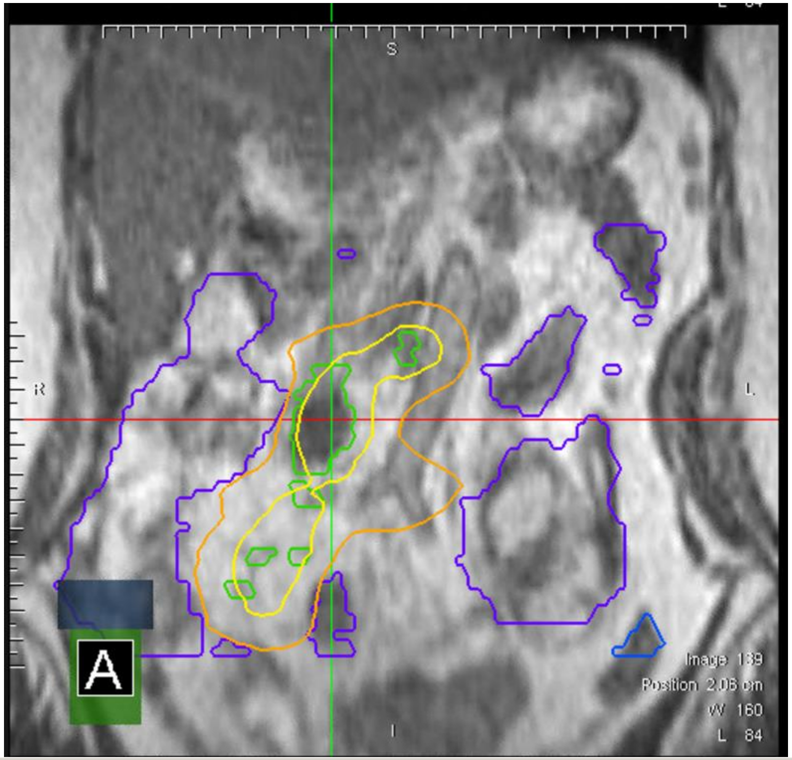
Not common skills in US based radiation therapists!

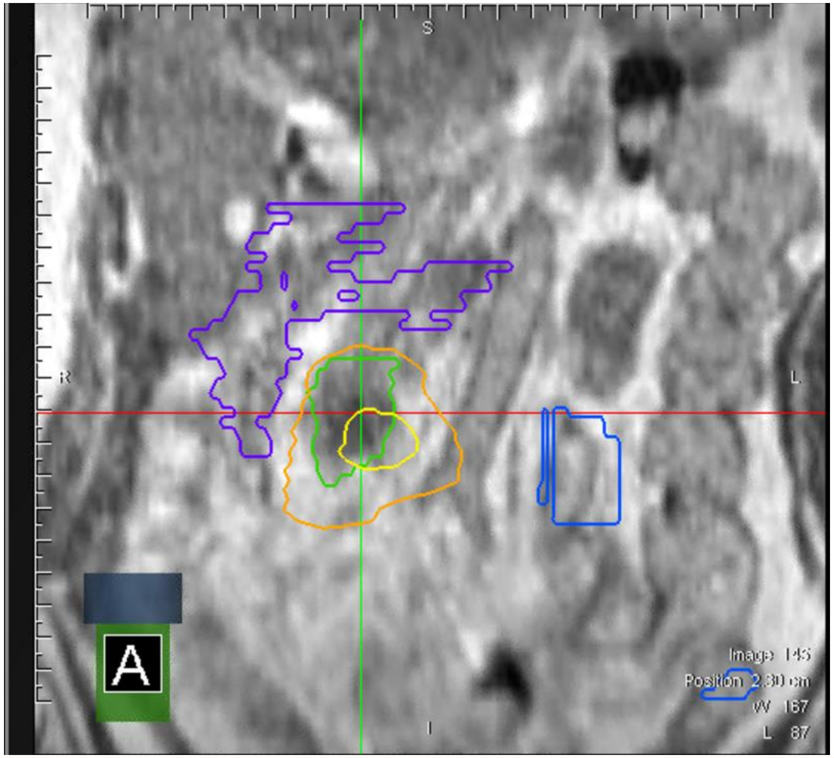
We are creating two ‘Advanced Practice Radiation Therapists’ who will start leading on-table segmentation and plan generation!

Physician contouring on demand – not good at it

Changing targets

2 MD can mean 2 gold standard segmentation





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- Sasa Mutic, PhD
- Jeff Michalski, MD

- Soumon Rudra, MD
- Jeff Bradley, MD
- Jeff Olsen, MD
- Cliff Robinson, MD
- Ben Fischer-Valluck, MD
- Sahaja Acharya, MD

www.siteman.wustl.edu

Additional Publications

Henke et al, Simulated Online Adaptive Magnetic Resonance-Guided Stereotactic Body Radiation Therapy for the Treatment of Oligometastatic Disease of the Abdomen and Central Thorax: Characterization of Potential Advantages. Int J Radiat Oncol Biol Phys. 2016 Aug 31

Mazur TR et al, SIFT-based dense pixel tracking on 0.35 T cine-MR images acquired during image-guided radiation therapy with application to gating optimization. Med Phys. 2016 Jan;43(1):279.

Acharya S et al, Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications. Int J Radiat Oncol Biol Phys. 2016 Feb 1;94(2):394-403.

Noel CE et al, Comparison of onboard low-field magnetic resonance imaging versus onboard computed tomography for anatomy visualization in radiotherapy. Acta Oncol. 2015;54(9):1474-82.

Noel CE et al, Process-based quality management for clinical implementation of adaptive radiotherapy. Med Phys. 2014 Aug;41(8):081717.

Safety and procedures

Helen McNair, DCR(T), PhD

Research lead Radiographer

Royal Marsden NHS Foundation Trust and Institute of Cancer Research

The ROYAL MARSDEN
NHS Foundation Trust

ICR The Institute of Cancer Research

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Understanding errors - What type of errors occur

active failures: 'unsafe acts'	Committed by those working at the sharp end of a system Usually short-lived and often unpredictable
latent conditions:	Can develop over time and lie dormant before combining with other factors or active failures to breach a system's safety defences. Long-lived and, unlike many active failures, can be identified and removed before they cause an adverse event

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Understanding errors - What type of errors occur

Active failure	Error	
Slips	Lack of attention Skilled	
Lapses	Memory failure- Omitting planned action Skilled	
Mistakes	Conscious control Skilled	
Violations	Deliberate deviation Skilled	

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Understanding errors - What type of errors occur

Latent conditions	Error	Example
time pressures targets, understaffing, inadequate equipment, inexperienced staff	**Lead to error and violation**	Incorrect registration and action
unworkable procedures design problems	**Create weaknesses in the defences**	Ad hoc pathway

Understanding errors - What type of errors occur

Systematic	Random
Incorrect protocol input into management system	Incorrect image acquisition selected on one day

Understand radiotherapy pathway

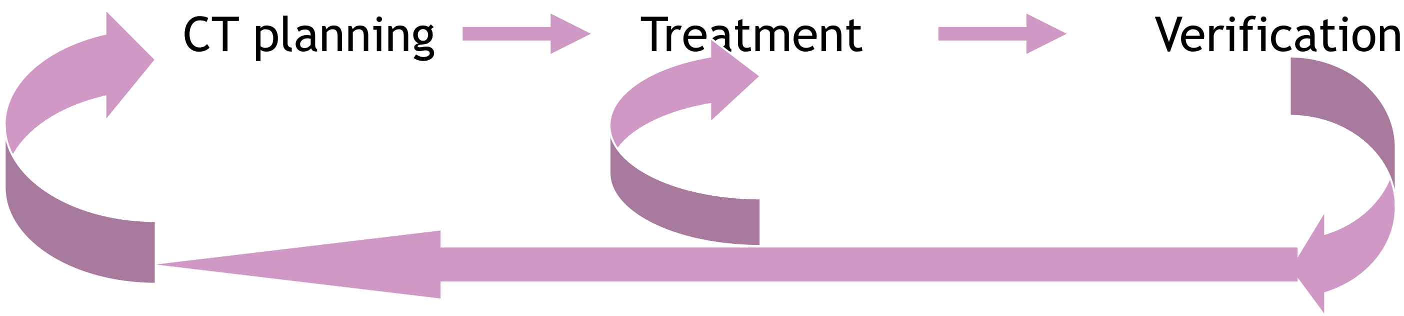
Reasons 'swiss cheese' model

Safety considerations for IGRT: Executive summary

"The safe application of IGRT technology is not limited to the operation of the technology at the treatment unit "

Practical Radiation Oncology
Volume 3, 2013, Pages 167–170

CT planning → Treatment → Verification



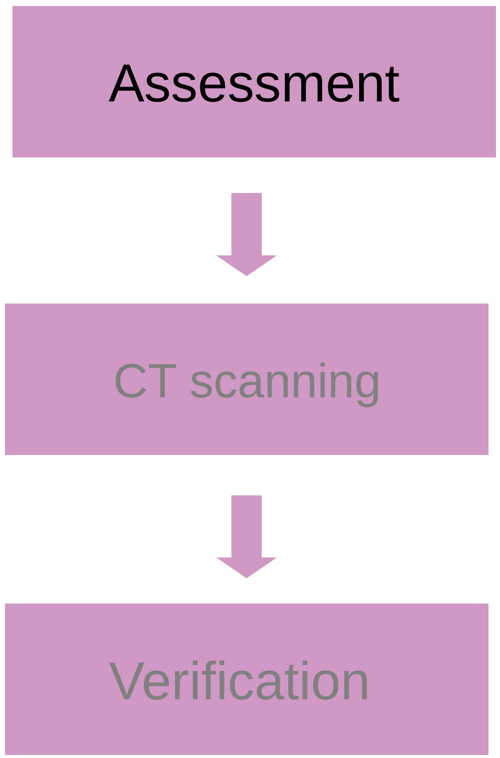
Assessment

↓

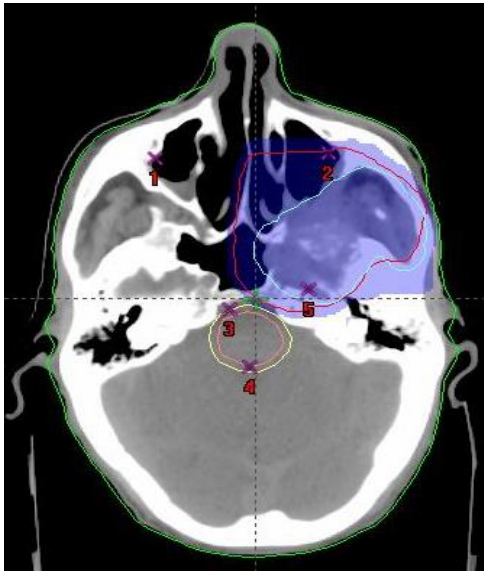
CT scanning

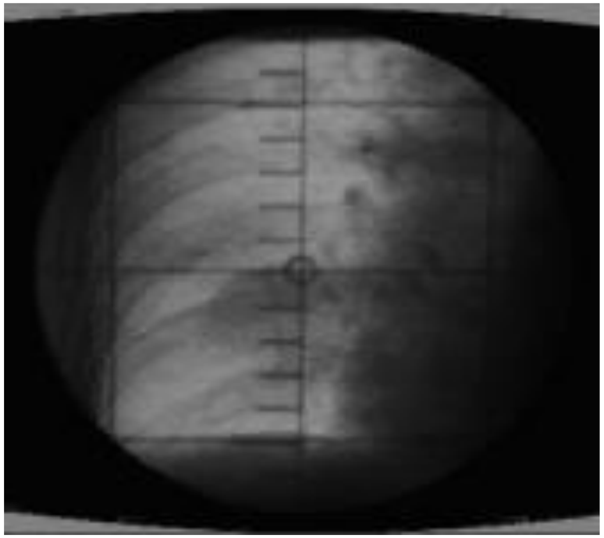
↓

Verification


Assessment
CT scanning
Verification

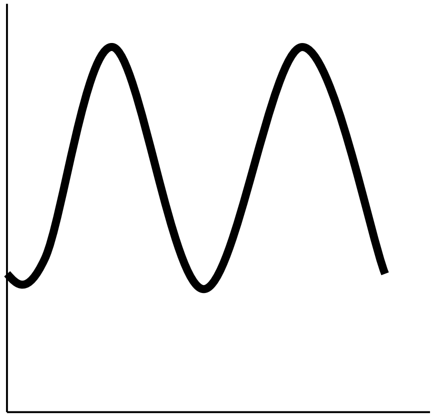
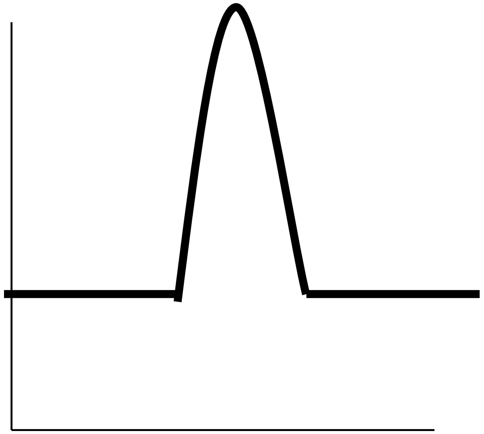
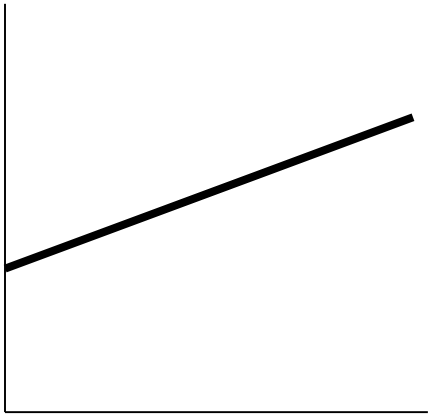
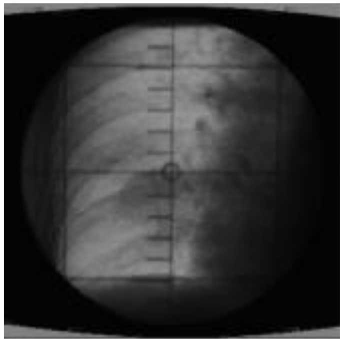
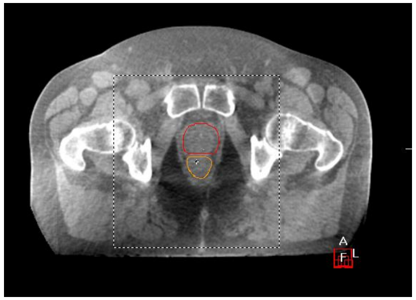
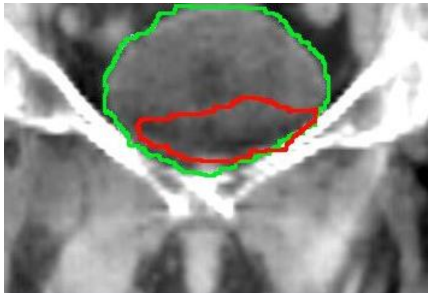
Assessment: Understanding patient tumour and motion





Magnitude of movement

Assessment

Risk- Incorrect planning or margins

	No markers	Implanted markers
No of patients	213	25
Margins (mm)	6 mm right left (RL) 10 mm anterior posterior (AP) and cranial–caudal (CC)	3 mm LR and 5 mm AP and CC.
5-year freedom from biochemical failure	91%	58%

Engels IJROBP 2009

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Referral

The ROYAL MARSDEN
NHS Foundation Trust

Radiotherapy Planning Referral

GENERAL / PALLIATIVE

Patient Name: ....

Address : ....(first line)

PLEASE ATTACH PATIENT STICKER

Hospital Number: ...........................D.O.B: ....

Consultant *The Practitioner justifying this referral is the above named consultant	*Referrer	OP / IP give ward:

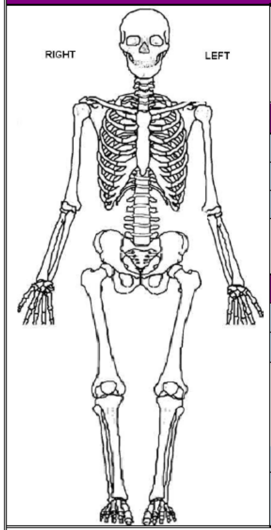
STAGING DETAILS: specify site / diagnosis / stage / laterality : right or left

Clinical Trial CCR No	Consent obtained YES / NO	Female patients: Pregnancy included in consent	YES / N/A	Previous RT YES / NO	Previous RT Details:

Other information: Including relevant other medical / allergy / pacemaker/ personal / transport / mobility / bariatric details / chemo / surgery / hormone trt / ECAD / lung function:

PROPOSED TREATMENT DETAILS

AREA 1 Anatomical volume to be irradiated	Proposed Prescription (dose and fractionation)



Anatomical site:

(Indicate approximate area on diagram)

TREATMENT PLANNING TECHNIQUE (tick all boxes which apply) :

Virtual Sim Single direct field		Clinical Mark up (M.O.S)	
Virtual Sim Parallel opposed pair		Other (specify:	
Radiographer led Virt sim			

Specific planning requirements:

PRE-TREATMENT CT PREPARATION (tick all boxes which apply):

Position:	Supine		Prone		Thermoplastic mask	
Bolus:	YES		Specify thickness & area:			

Specific scan levels (NB* Spine & Ribs as per protocol unless specified):

Additional treatment area?		Signed	Dated
YES (DOCUMENT OVERLEAF)	NO	*Operator	

Confirm audit review and changes made at audit	*Practitioner	

Justification by practitioner for off – protocol / retreatments & mould room requests plus additional areas / phases see overleaf

in compliance with Ionising Radiation (Medical Exposure) Regulations 2000 Page 1 of 3 J-RP-001-06 (04.15)

Legible
Filled in correctly

Electronic request

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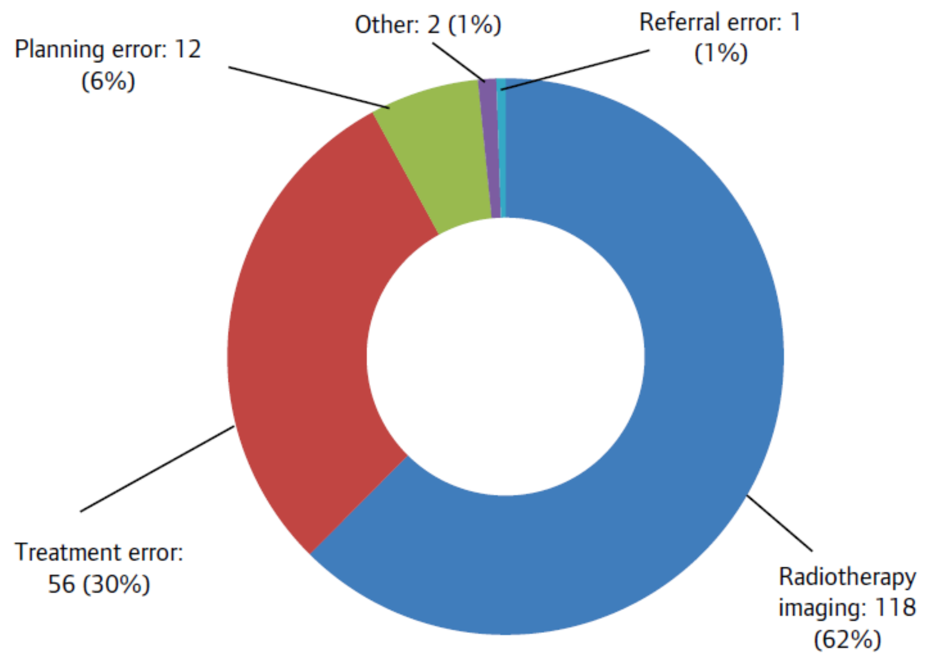
Risk

Poor assessment		
Patient unable to procedure	Breathing controls/ 4D motion/ Deaf	delay for treatment Ineffective use of resources
Incorrect pathway booked	Upper limb- Sarcoma patient too large for CT	delay for treatment Ineffective use of resources
Incorrect planning or margins		irradiation of normal tissue miss the target

Type of errors- ‘much greater than intended ‘

Care Quality Commission

Figure 13: Type of error (radiotherapy 2016)



Source: CQC notifications data.

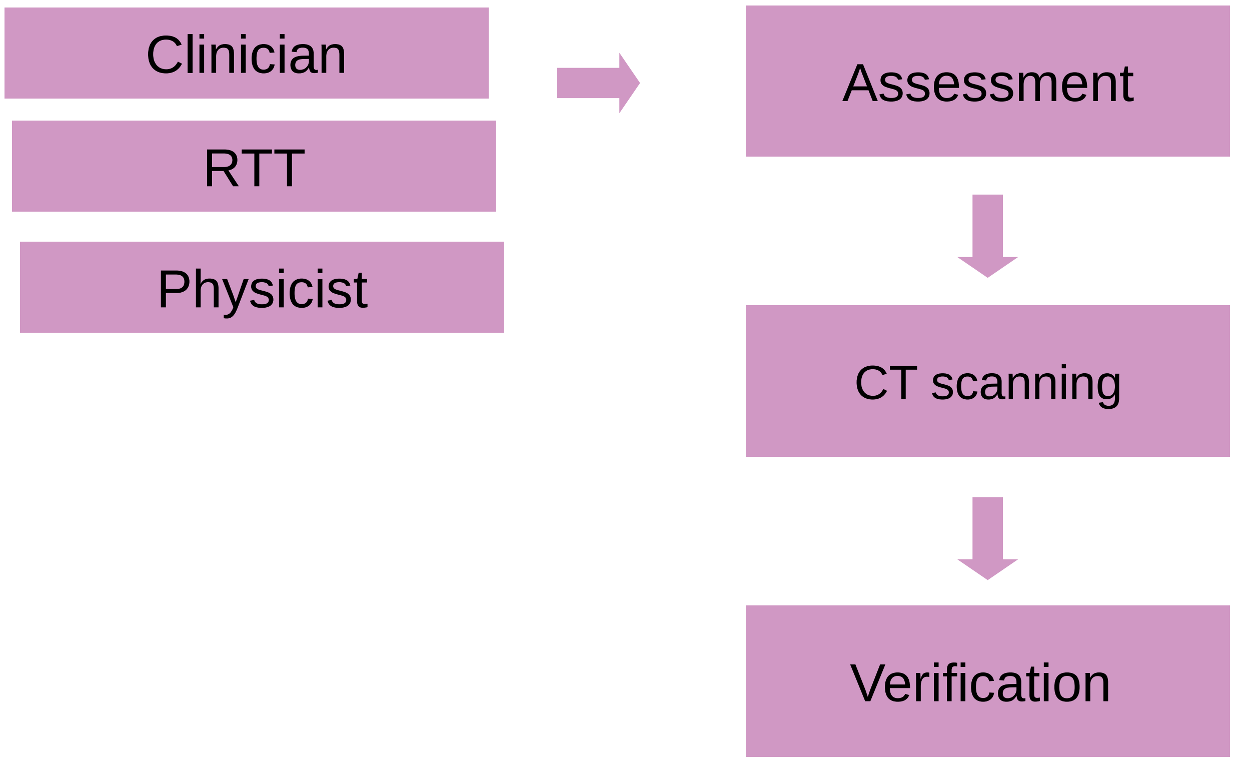
Care Quality Commision IR(ME)R annual report 2016 released October 2017

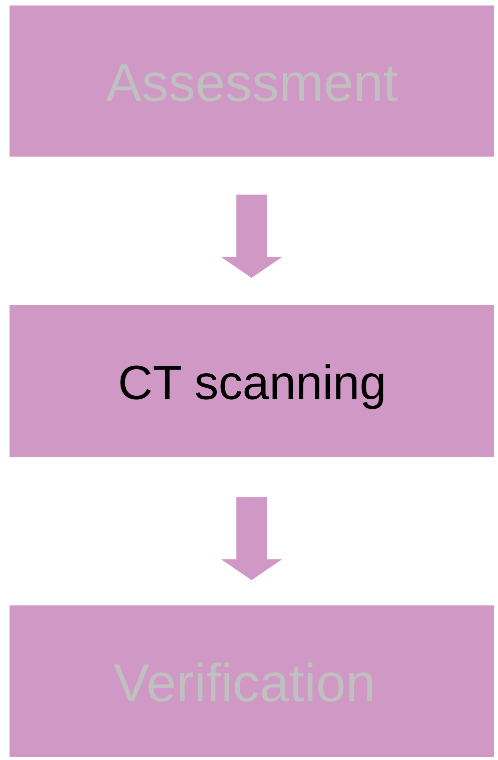
Type of errors- ‘much greater than intended ‘

118 imaging notifications
2/3 were Radiotherapy planning imaging

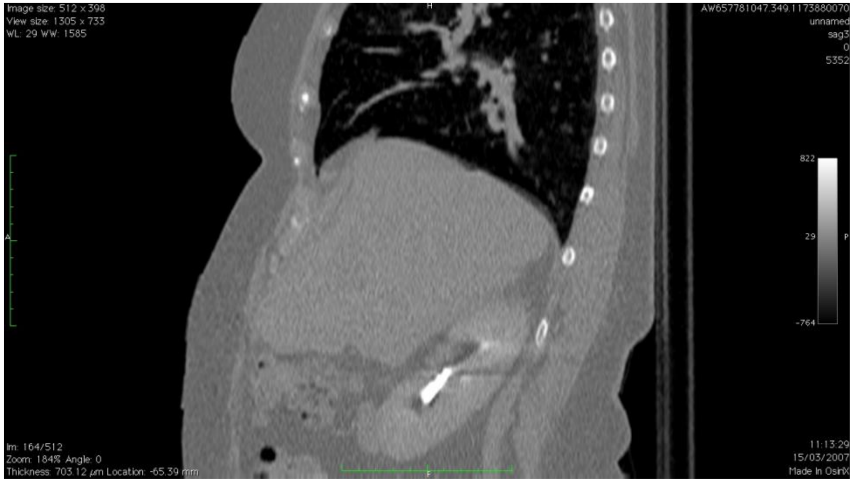
- incorrect patient positioning
- operator selecting incorrect or too restrictive scan limits
- operator selecting the wrong imaging protocol
- operator misinterpreting or making a mistake in reading the request, or miscommunication between the operator and referrer
- clinical oncologist providing inadequate or incorrect clinical information.

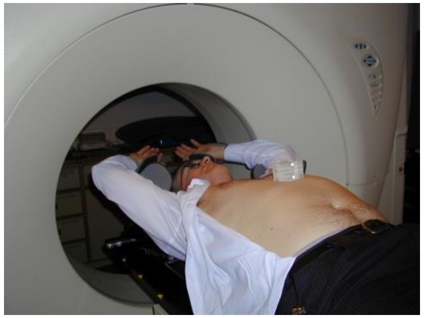
Care Quality Commision IR(ME)R annual report 2016 released October 2017

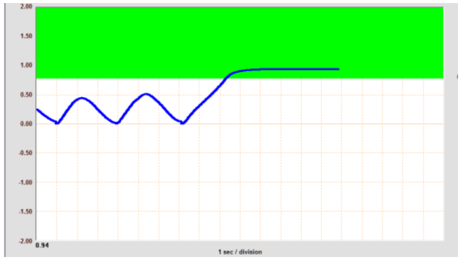

Clinician
RTT
Physicist
Assessment
CT scanning
Verification


Assessment
CT scanning
Verification

CT planning

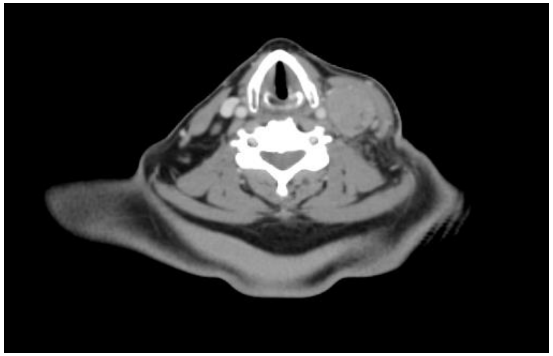


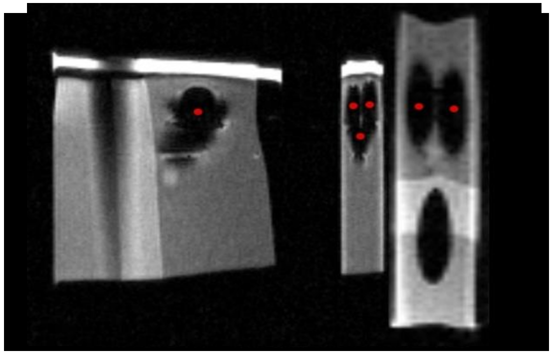




Courtesy of M Hawkins

Image Quality



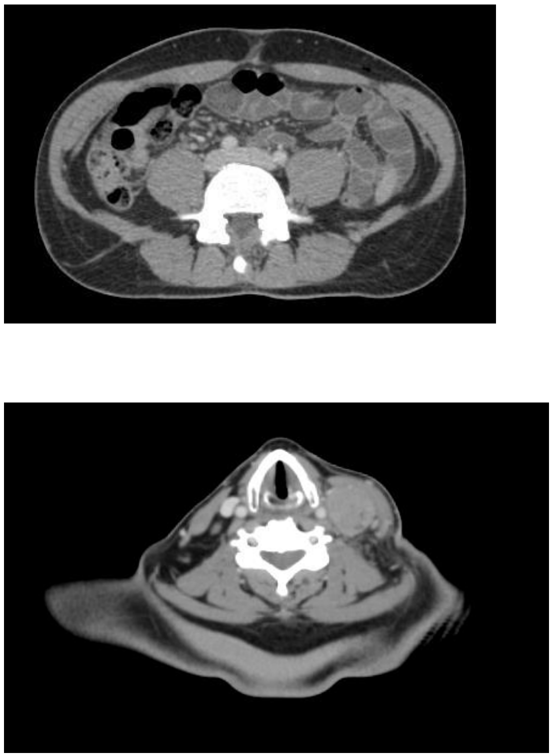


Contrast

Markers

Courtesy of C Ockwell

Image Quality

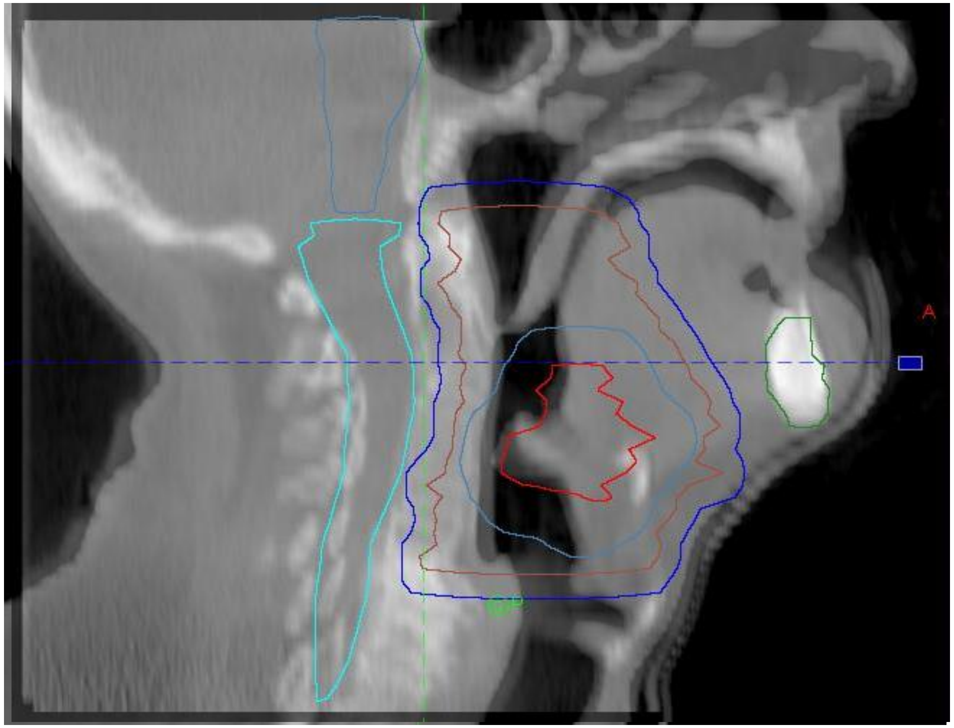


Contrast

Slice thickness

Courtesy of C Ockwell

Risk

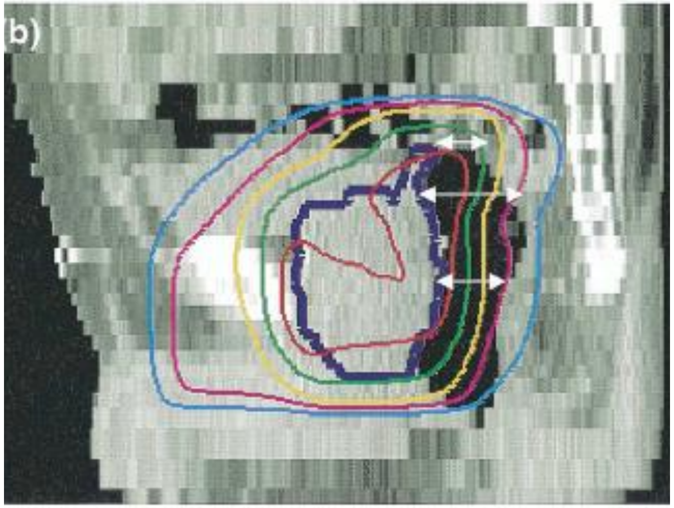


Reference image not reproducible

Courtesy of A Baker

Risk

Rectal distension at CT = poor outcome



	p value
(1) CSA >11.2cm²	0.0009
(2) CSA ≥ 8cm² + (2) Diarrhoea ≥ 25% RT time	0.02

Reference image not reproducible

(1) De Crevoisier IJROBP 2005
(2) Heemsbergen IJROBP 2007

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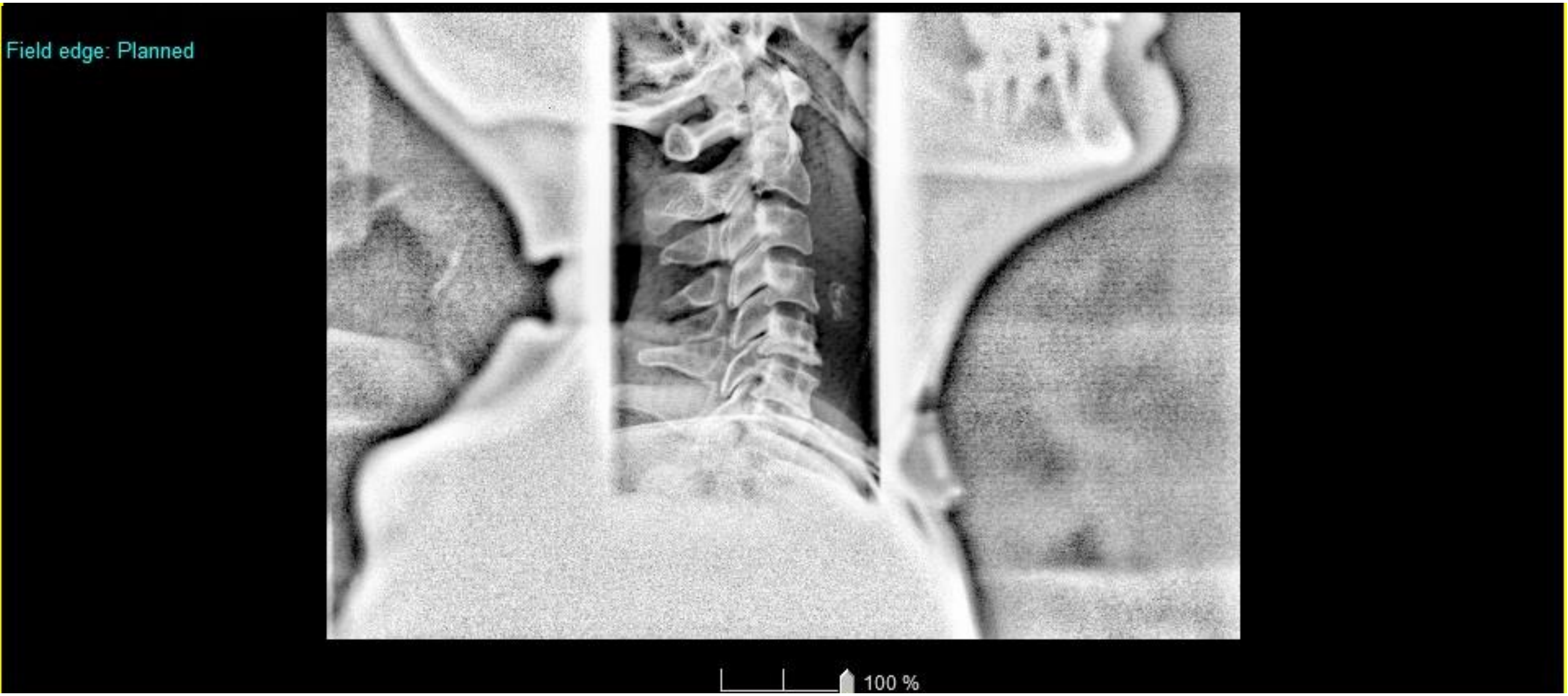

Field edge: Planned
100 %

Helical TomoTherapy

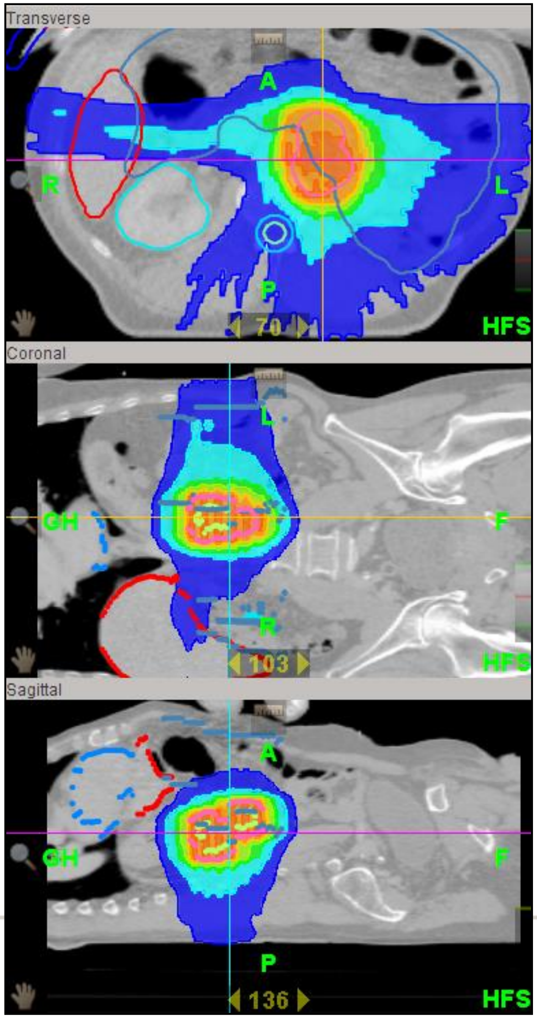
Near-incidents related to IGRT @ UZB

"Pure" image-guided

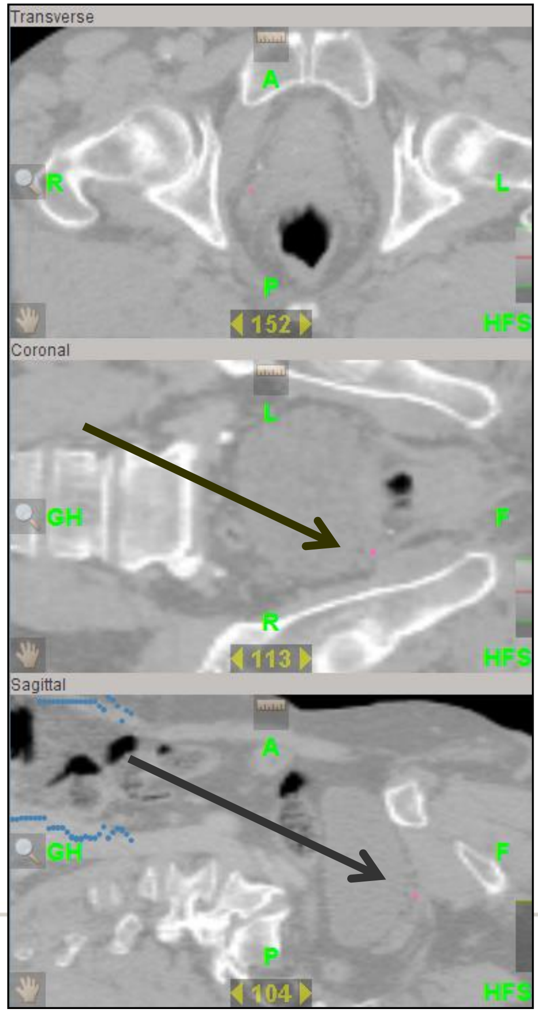
- No visual control of beam alignment
- Patient slides into the boar for treatment, once properly positioned.
- TomoTherapy treats all voxels that are designed "target"

Helical TomoTherapy

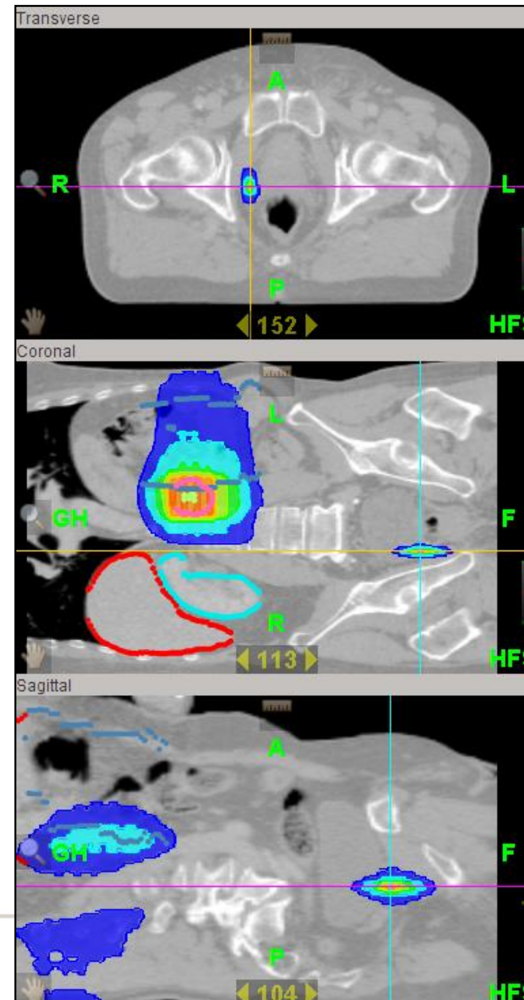
Intended treatment



"Little" delineation problem

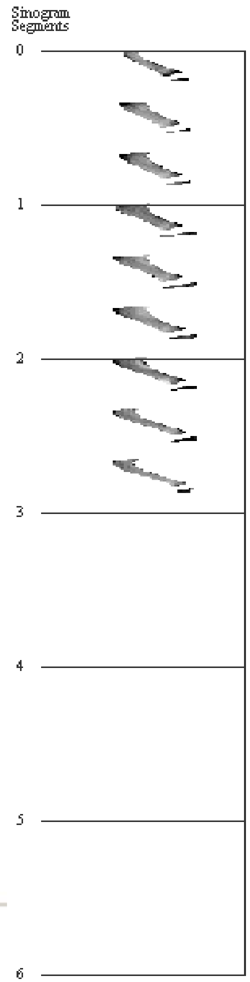


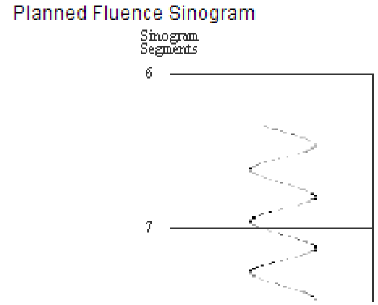
"serious" consequences



Helical TomoTherapy

Sinogram, reveals problem



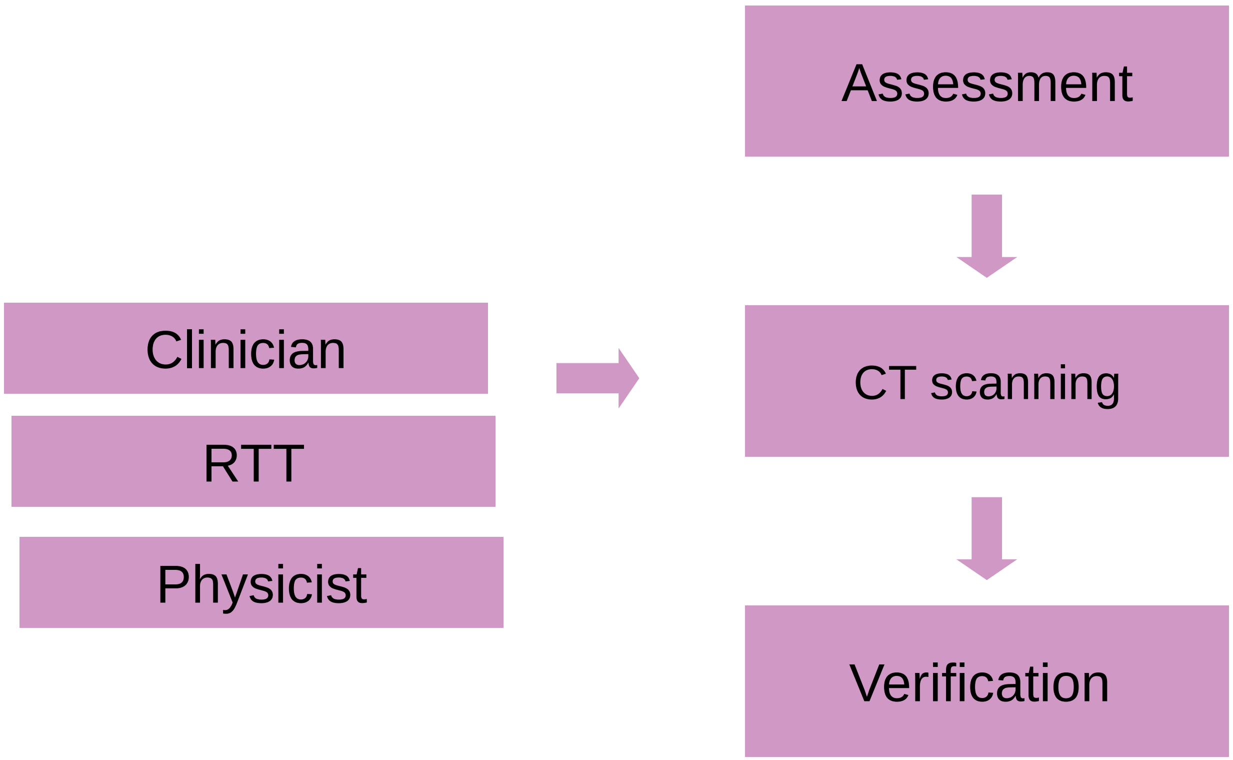


Universitair
Ziekenhuis
Brussel

ESTRO School

Risk

CT scan not representative		
Poor organ position	Systematic error	delay for treatment Ineffective use of resource
Not reproducible	difficult set up	delay for treatment Ineffective use of resources



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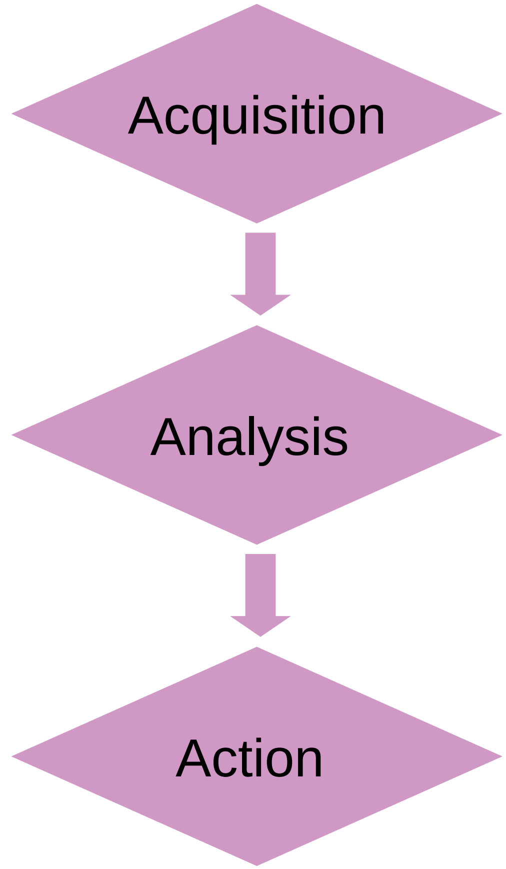
Assessment

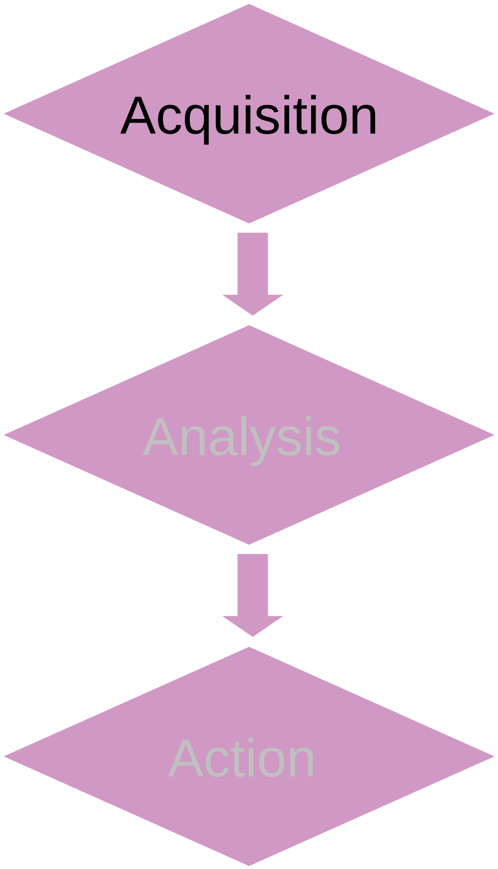
↓

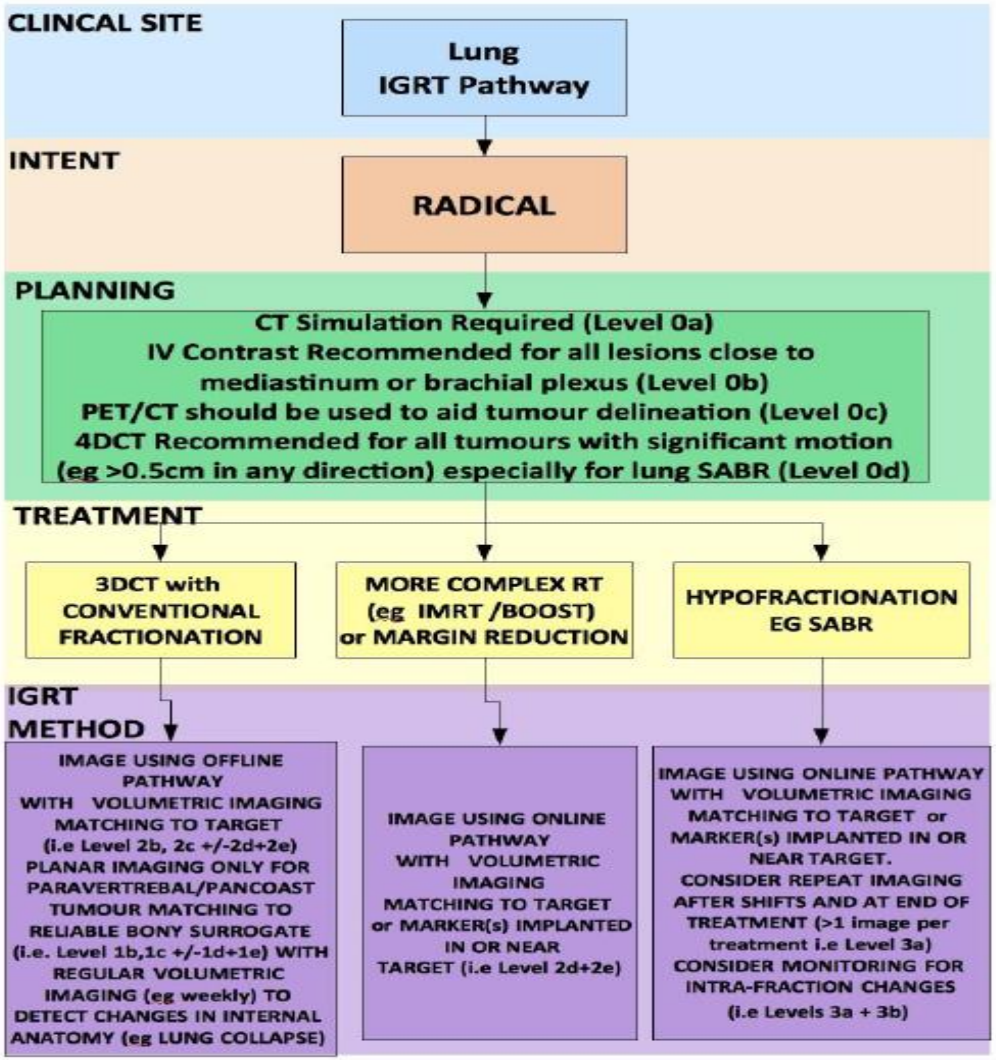
CT scanning

↓

Verification


Acquisition
Analysis
Action

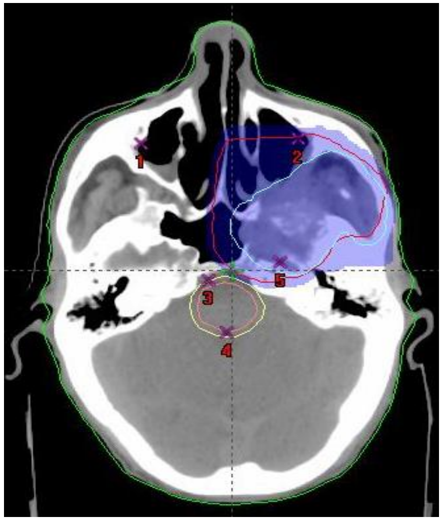

Acquisition
Analysis
Action

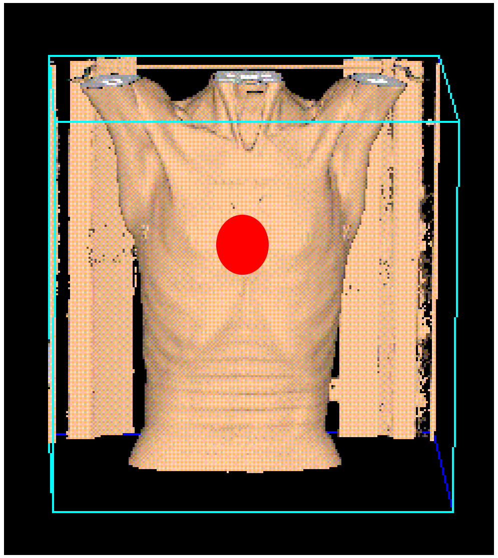


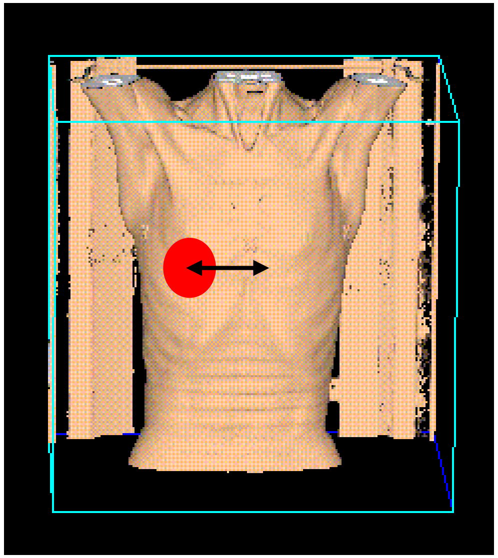
National Radiotherapy Implementation Group Report
Image Guided Radiotherapy (IGRT).
Guidance for implementation and use.
August 2012 UK

Acquisition

Factors affecting protocol choice







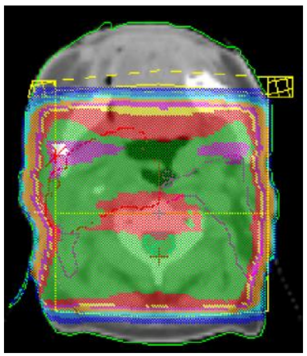
Tumour site

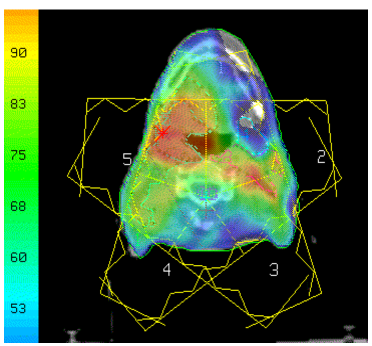
Tumour location

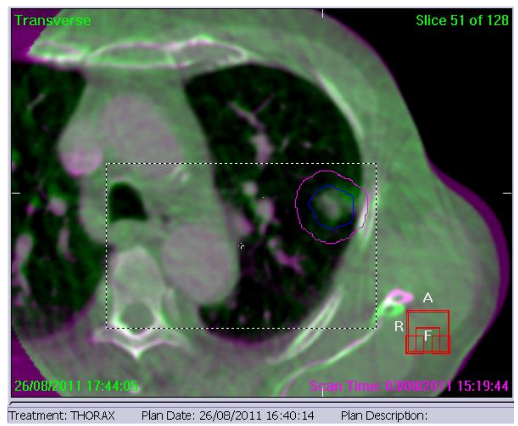
Tumour location

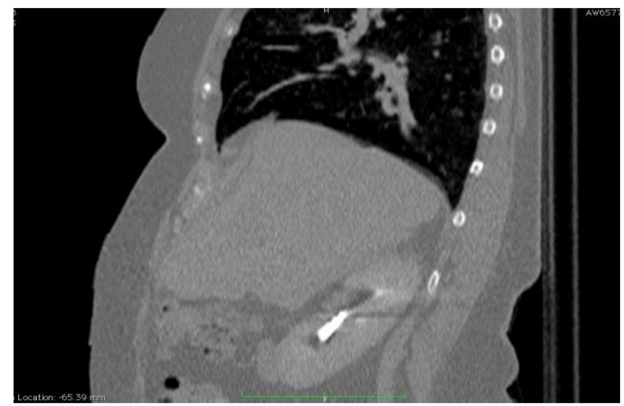
Acquisition

Factors affecting protocol choice









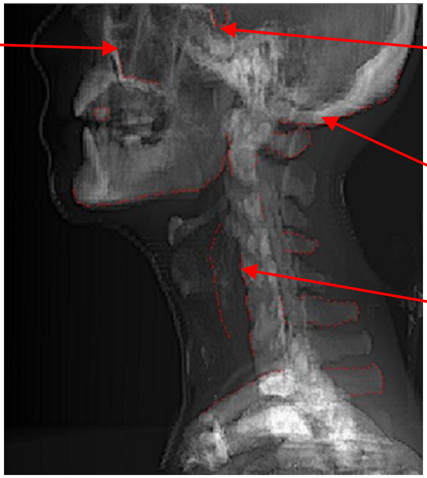
Technique Technique Technique

Acquisition

Anatomy for template

Preparation – Protocols

Stable anatomy



http://www.rcr.ac.uk/docs/oncology/pdf/BFCO(08)5_On_target.pdf

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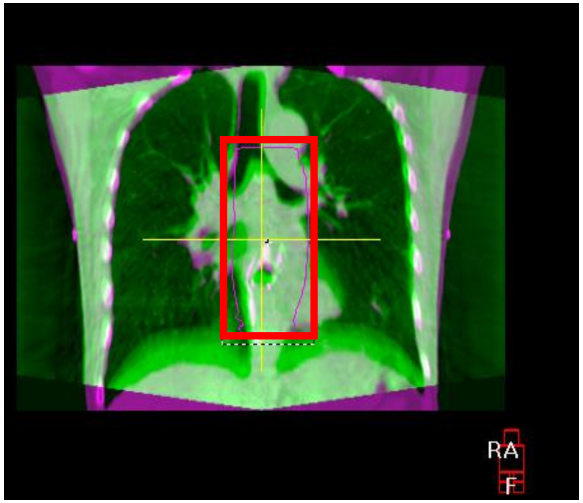
Acquisition

Preparation – Protocols

Region/Volume of Interest



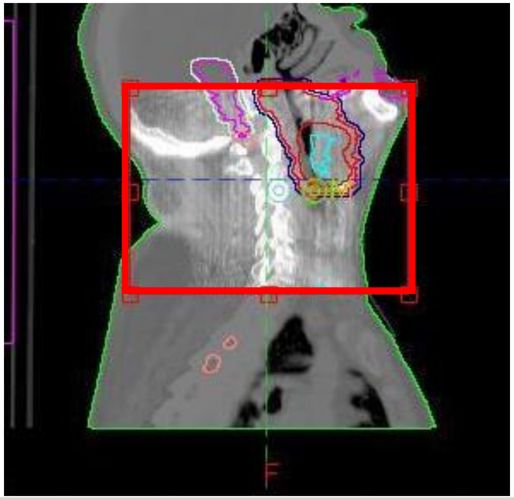
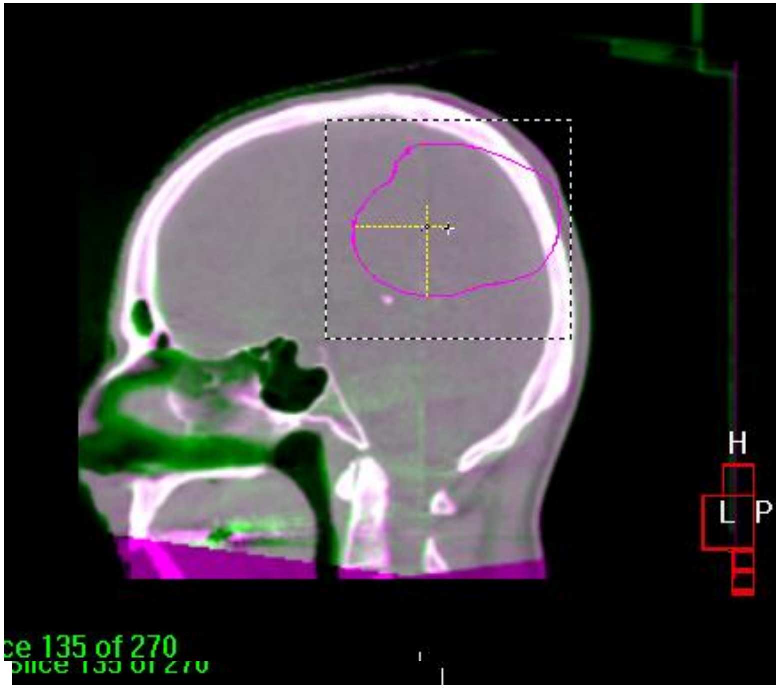


Image Registration

Preparation – Protocols

Region/Volume of Interest

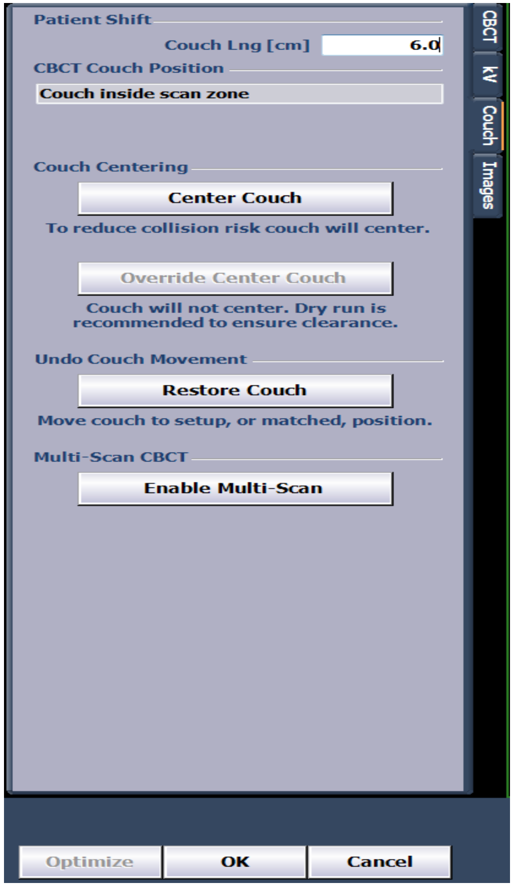


Acquisition

Off set
True Beam example

Preparation

Length/Field of View



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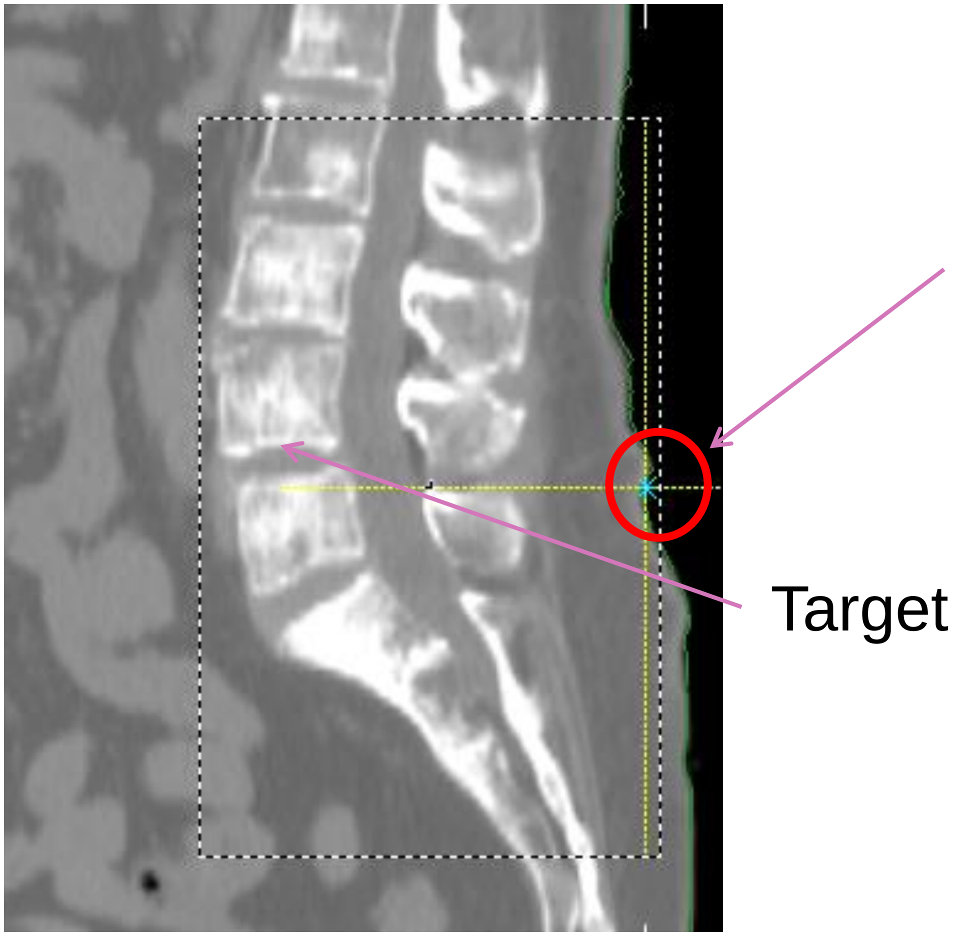
Incorrect preparation

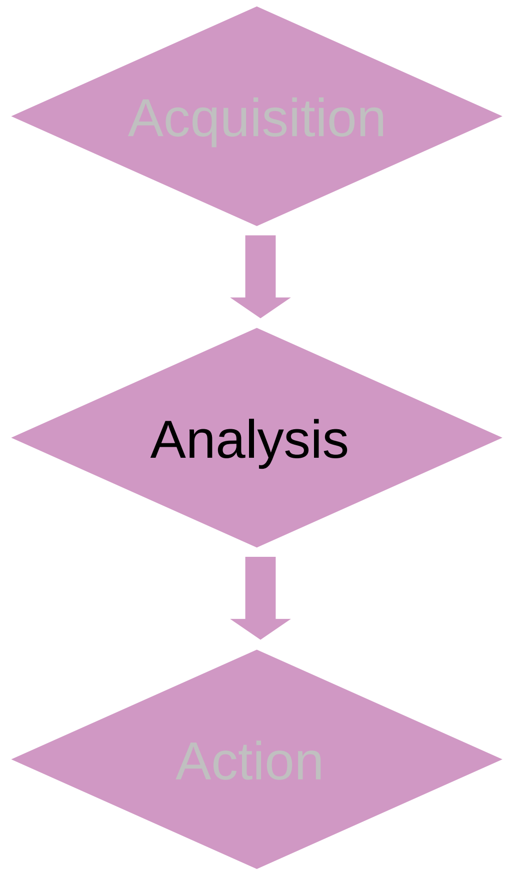


Courtesy of Rianne de Jong

correct jaw sizes input but
Patient feet first towards the gantry
Incorrect orientation of the Y jaw setting.

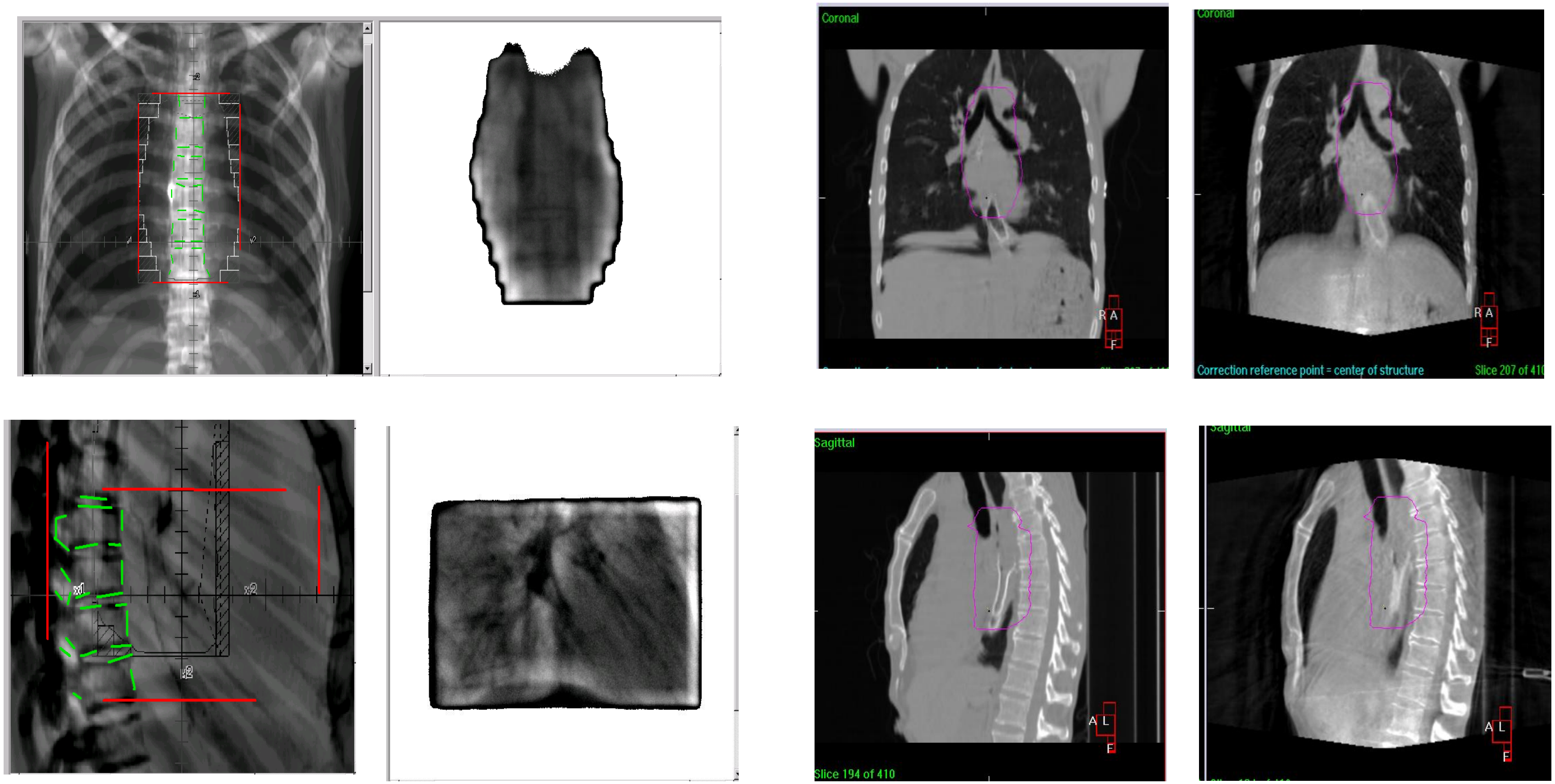
Risk

Incorrect protocol	Repeat imaging	Increase dose Increase time
Incorrect imaging modality	Repeat imaging	Increase dose Increase time
Incorrect preparation	Incorrect registration	Incorrect shift


Acquisition
Analysis
Action

Analysis

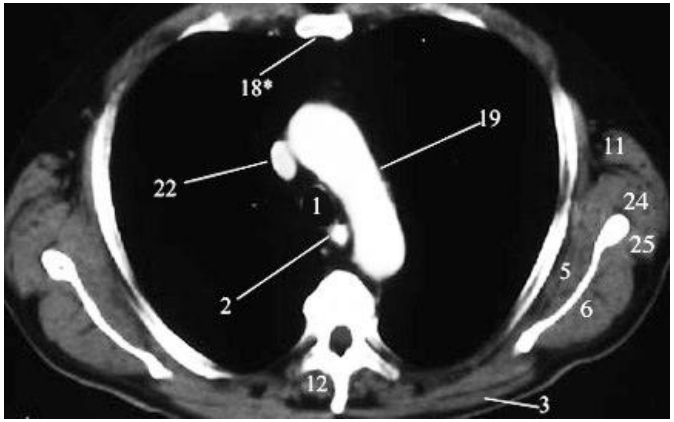
CT anatomy

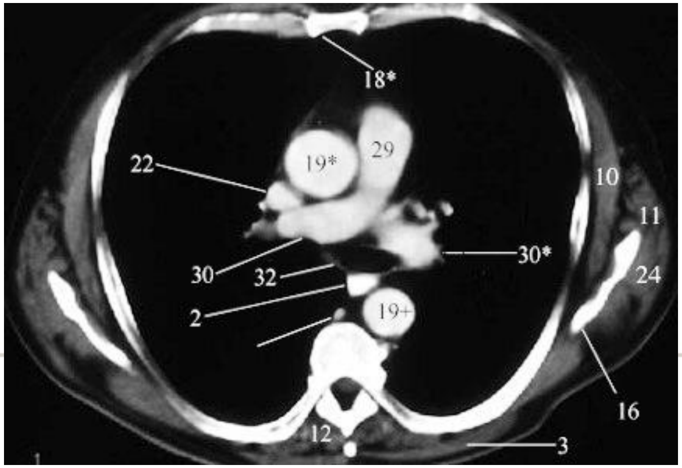


DRR MV EPI Planning CT CBCT

Analysis

CT anatomy

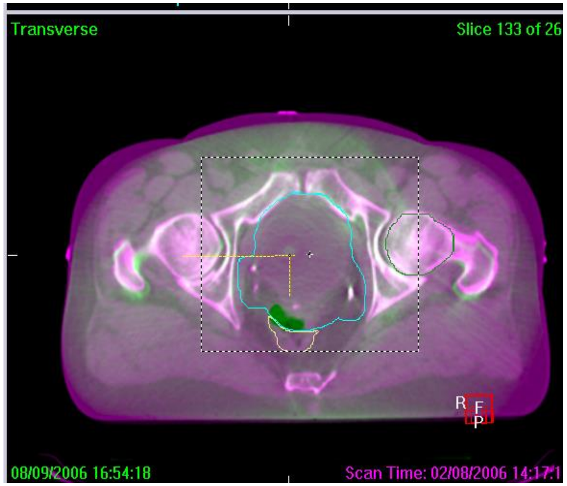


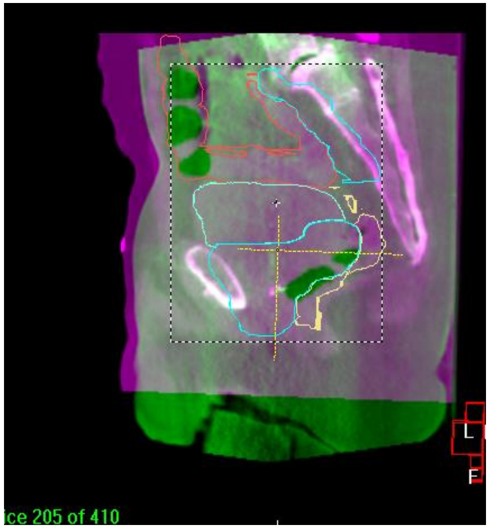


1 Trachea
2 Oesophagus
3 Trapezius Muscle
5 Subscapularis
6 Infraspinatus
10 Serratus Anterior
11 Latissimus Dorsi
12 Erector spinae
16 Scapula
18* Body of sternum
19* Ascending aorta
19+ Descending aorta
22 SVC
24 Teres major muscle
25 Teres minor
30 RT Pulmonary Artery
30* LT Pulmonary Artery
32 Carina

Analysis

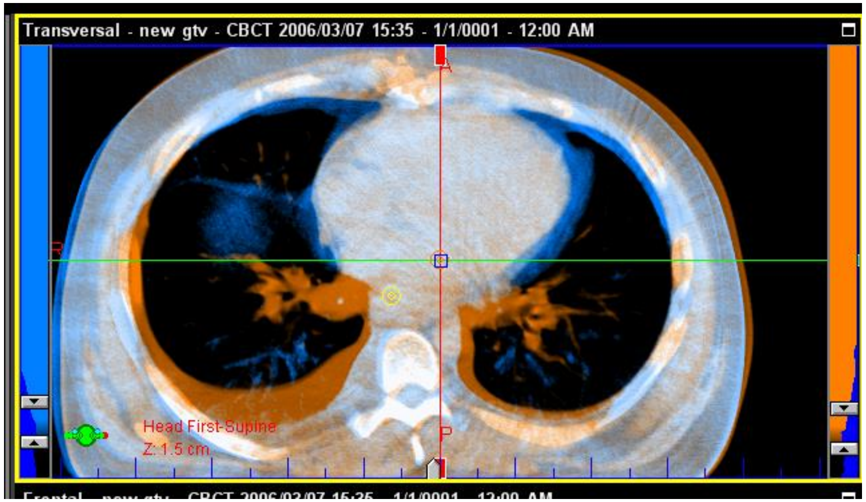
Gross error

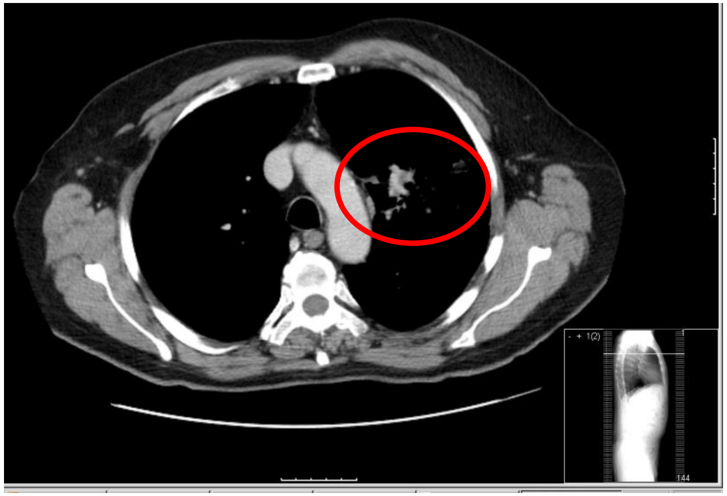


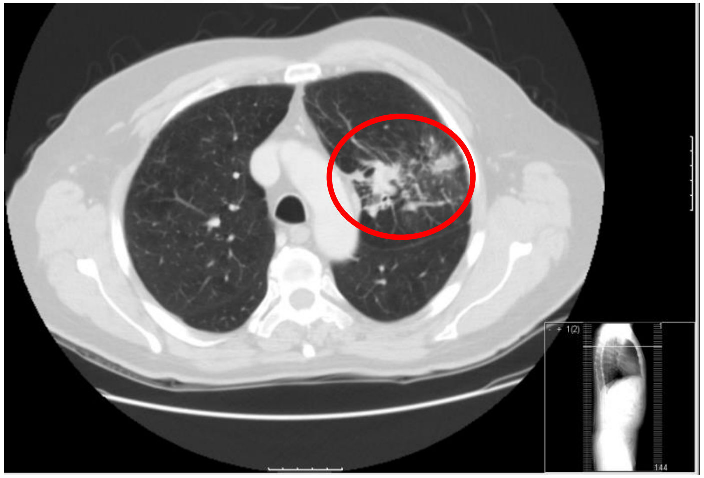


Analysis

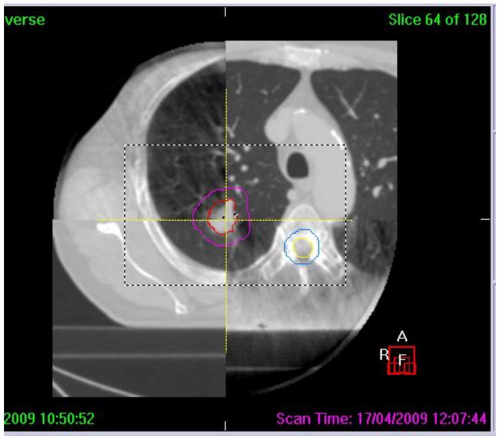
Window levels







Analysis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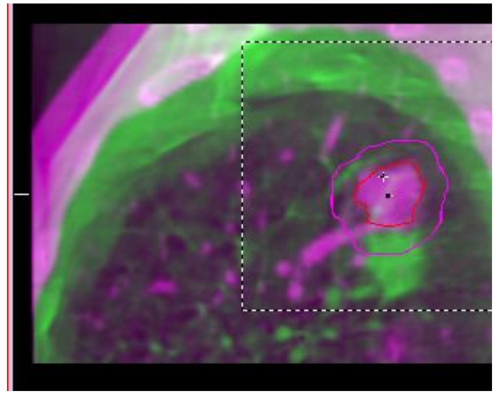
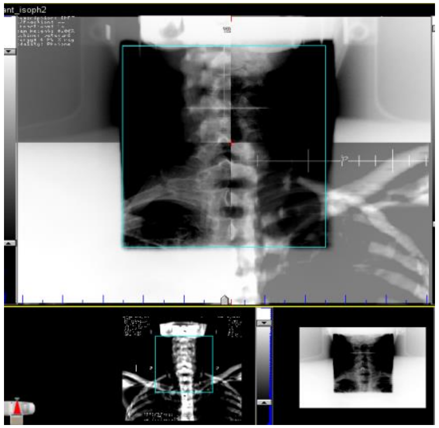
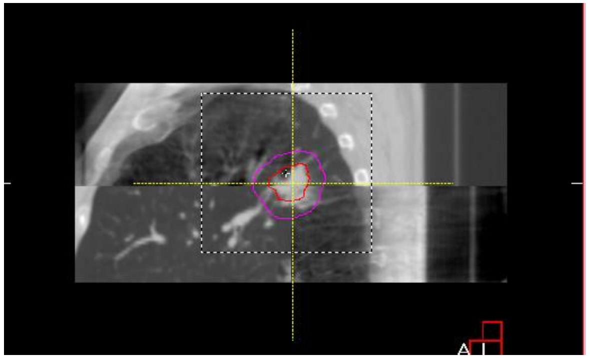
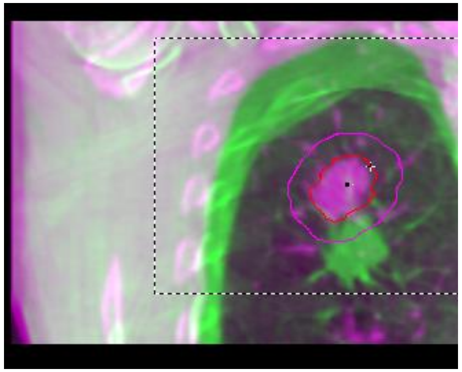
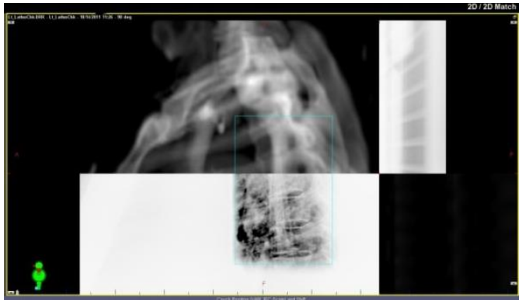
2009 10:50:52
Scan Time: 17/04/2009 12:07:44



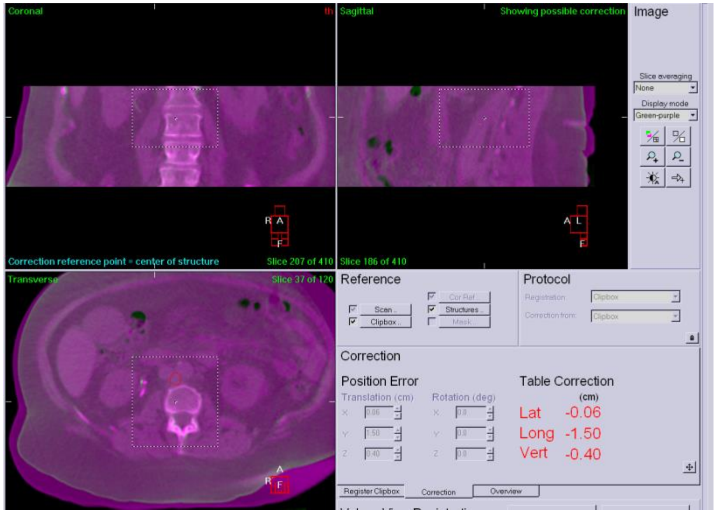







2D / 2D Match

Analysis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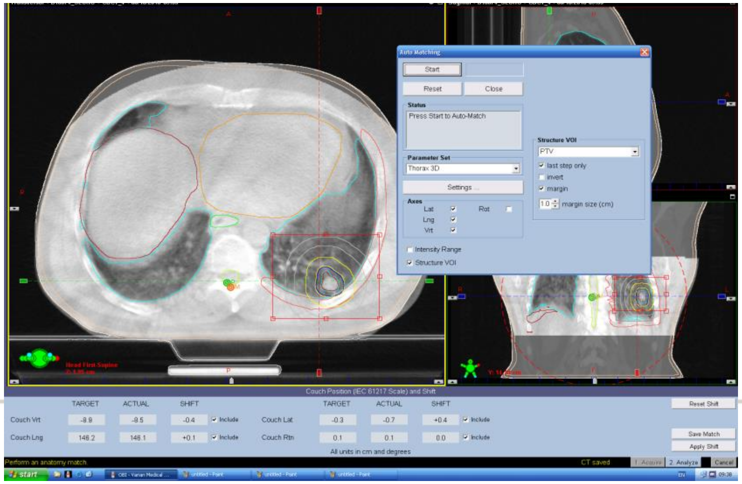
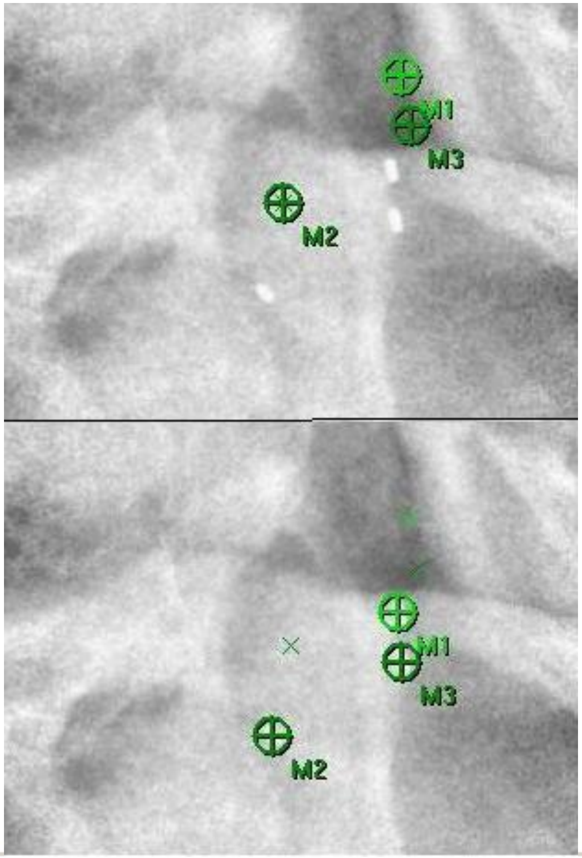
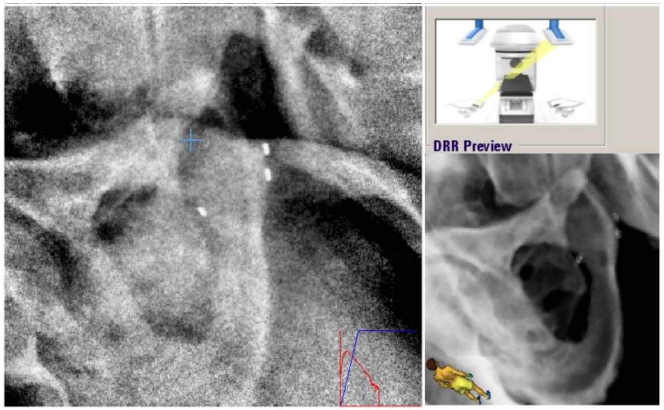
Sagittal
Showing possible correction
Image
Slice averaging
None
Display mode
Green-purple
Correction reference point = center of structure
Slice 207 of 410
Slice 186 of 410
Transverse
Slice 37 of 120
Reference
Scan
Clipbox
Cor Ref
Structures
Mask
Protocol
Registration
Correction from
Clipbox
Correction
Position Error
Translation (cm)
Rotation (deg)
Table Correction
(cm)
Lat -0.06
Long -1.50
Vert -0.40
Register Clipbox
Correction
Overview


Auto Matching
Start
Reset
Close
Status
Press Start to Auto-Match
Parameter Set
Thorax 3D
Settings
Axes
Lat
Lng
Vrt
Rot
Intensity Range
Structure VOI
PTV
last step only
invert
margin
margin size (cm)
Couch Position (IEC 61217 Scale) and Shift
TARGET
ACTUAL
SHIFT
Couch Vrt
Couch Lng
Couch Lat
Couch Rtn
Include
Reset Shift
Save Match
Apply Shift
All units in cm and degrees

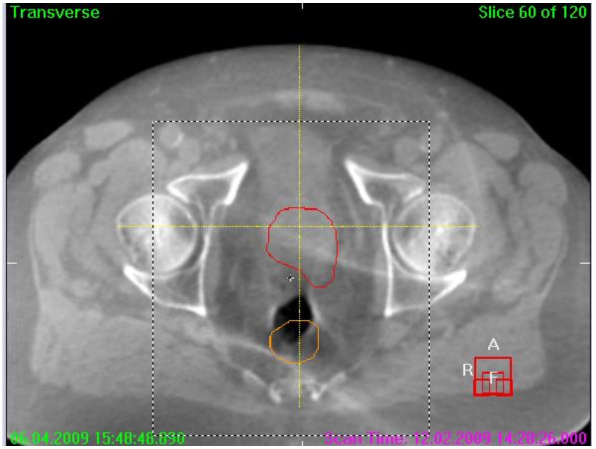

M1
M3
M2
M1
M3
M2

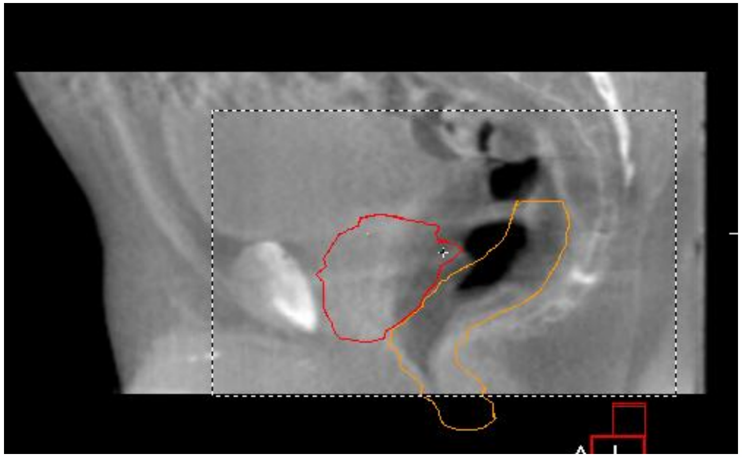
Analysis



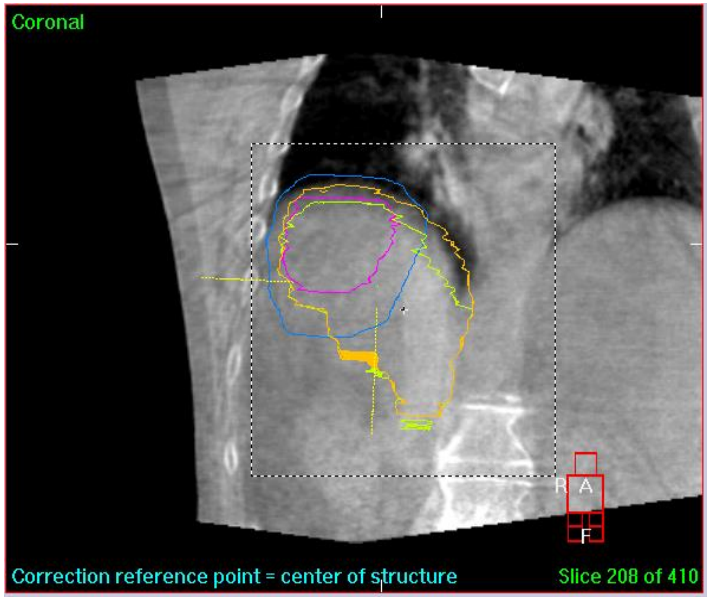
Interpretation

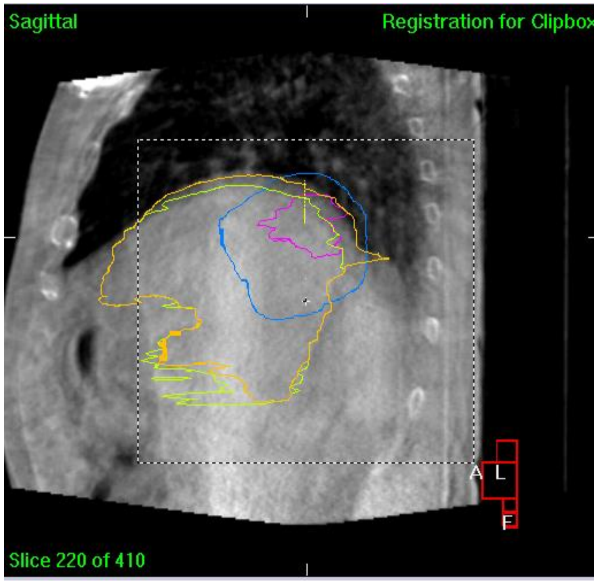
Decision





Analysis

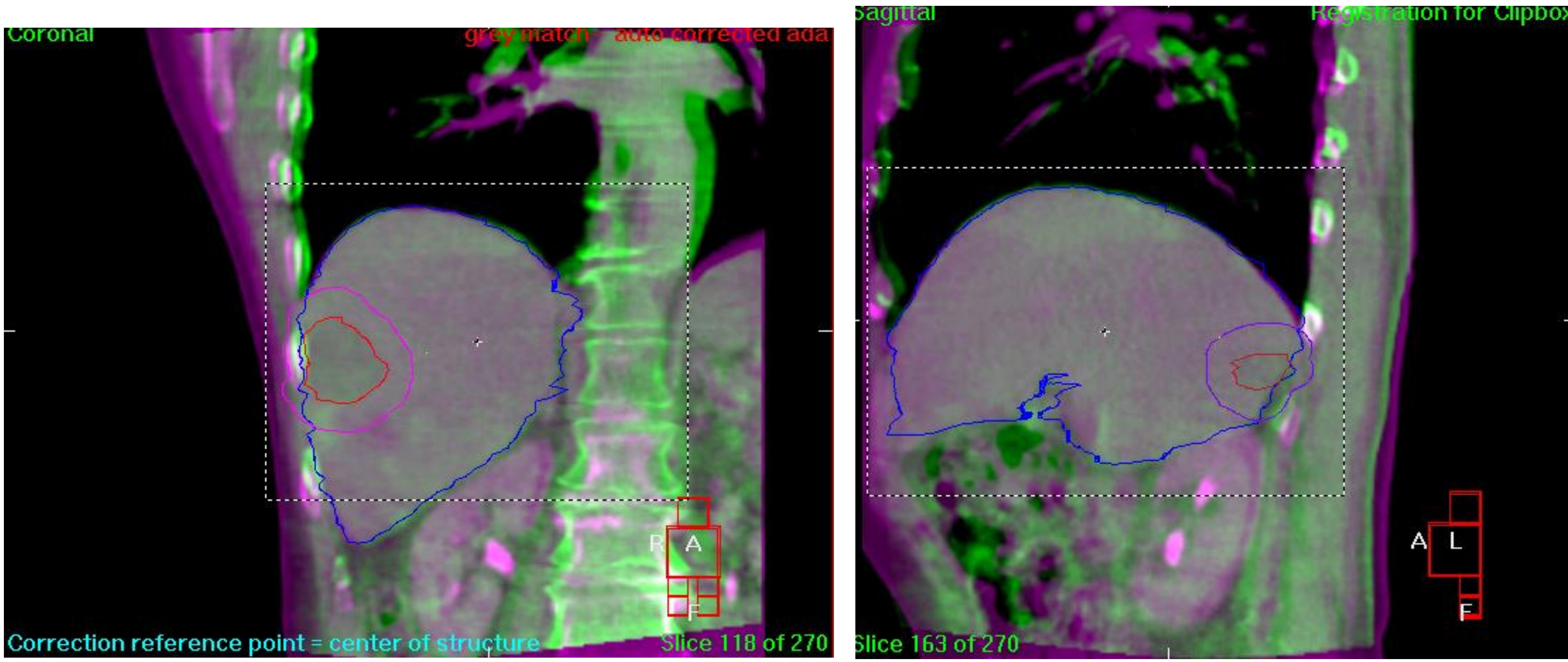




Free Breathing

Courtesy of M Hawkins

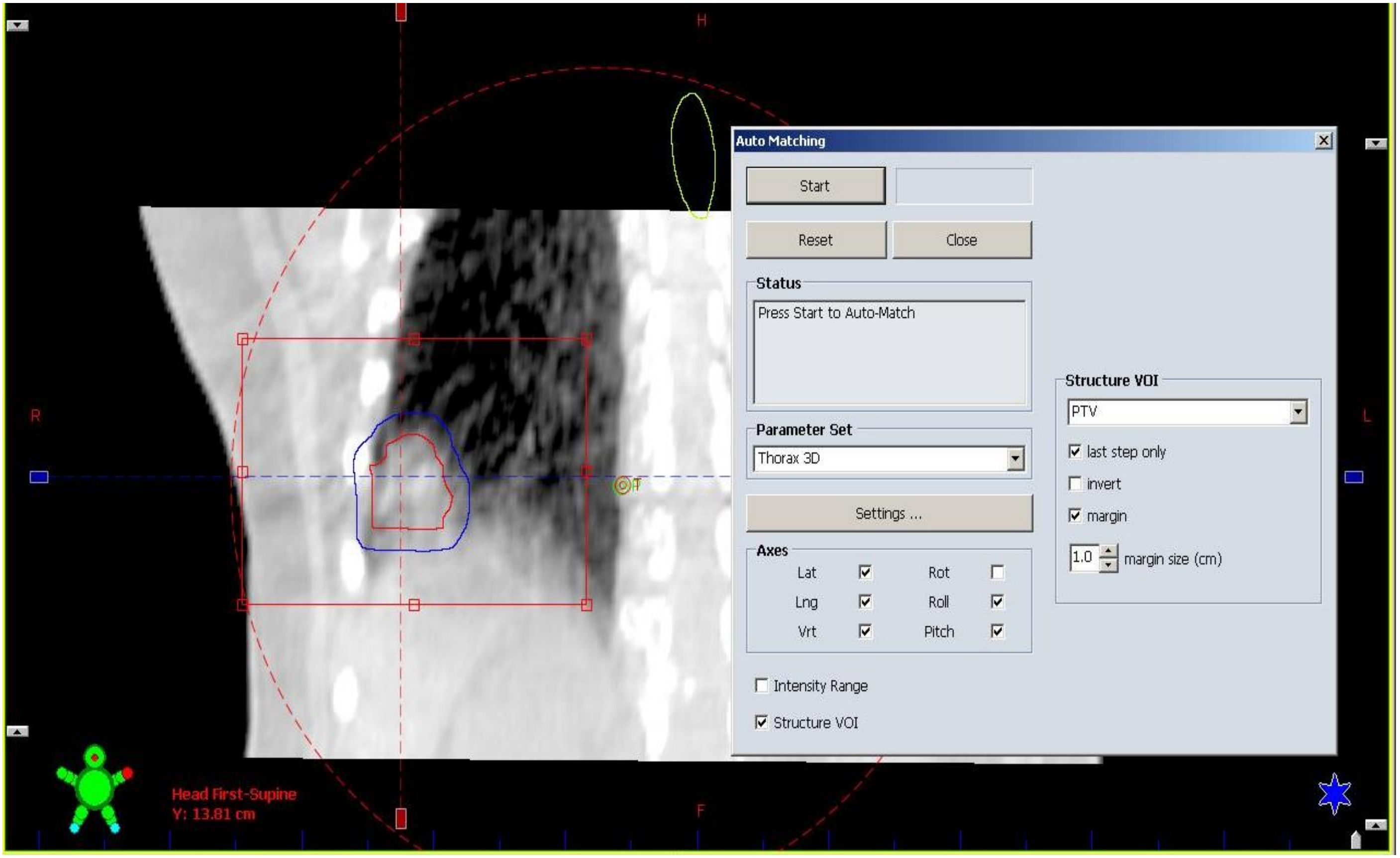
Analysis



Breath hold

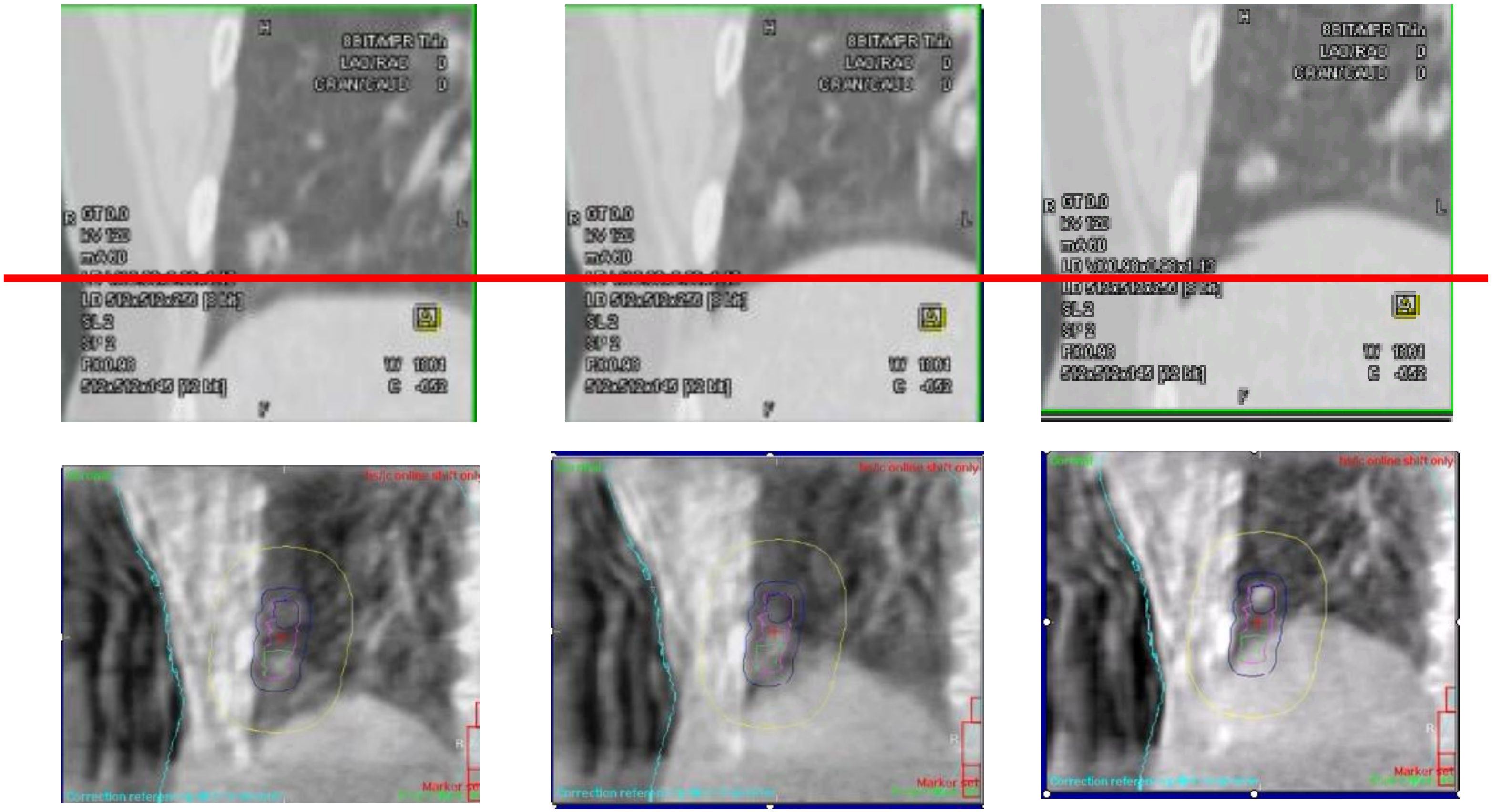
Courtesy of M Hawkins

Analysis



Courtesy of A Baker

Analysis



4DCT

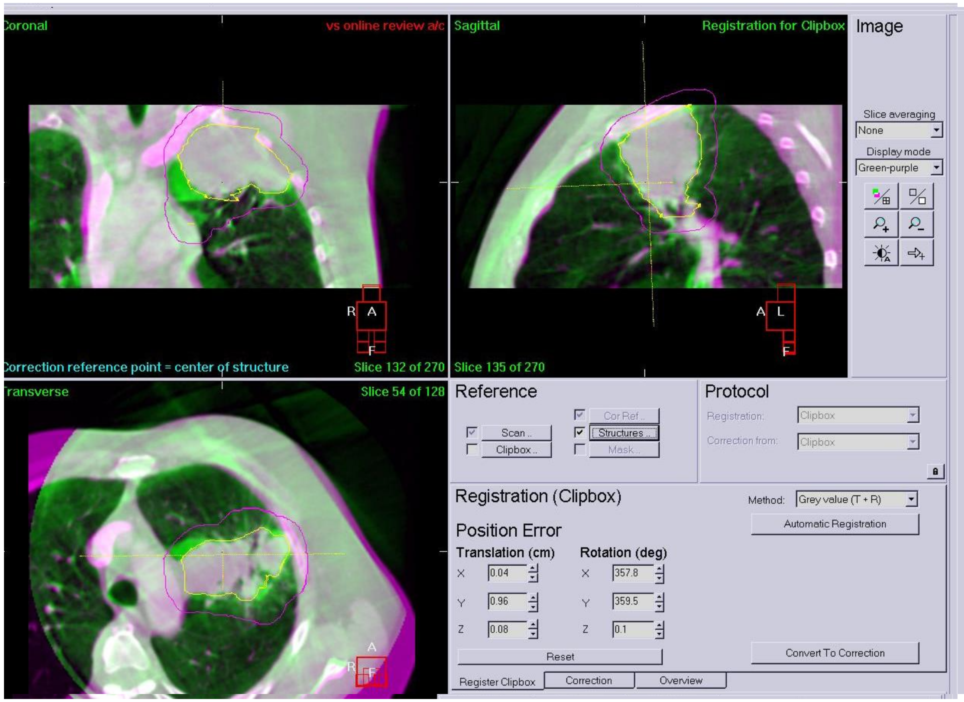
4D
Cone Beam
CT

Coronal View

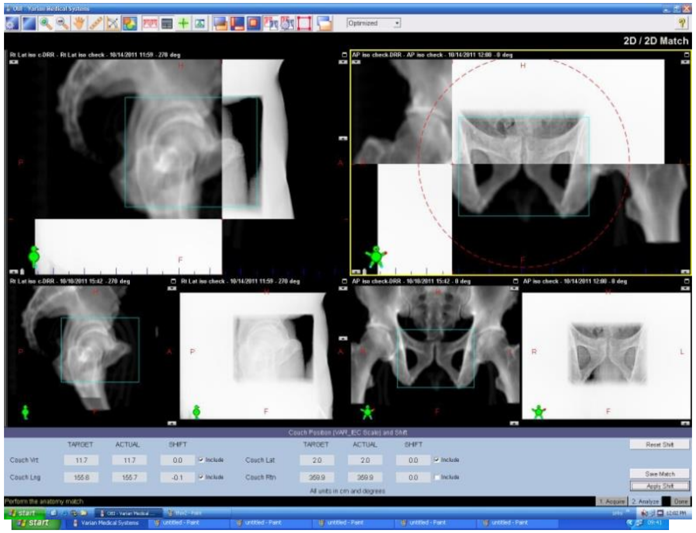
Courtesy of J Lilley, Leeds

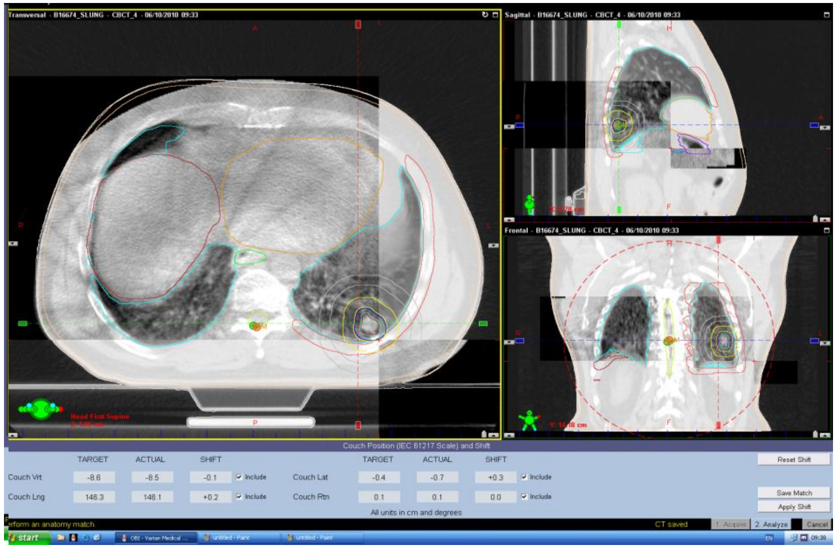
Analysis

Detecting changes anomalies

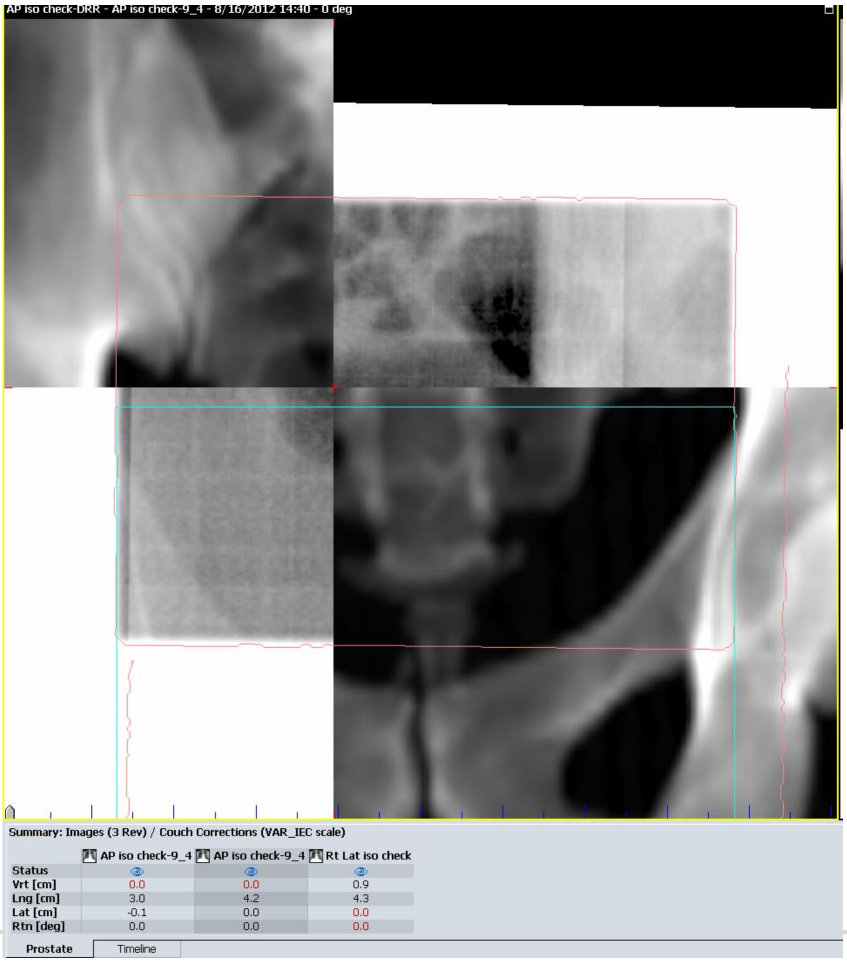


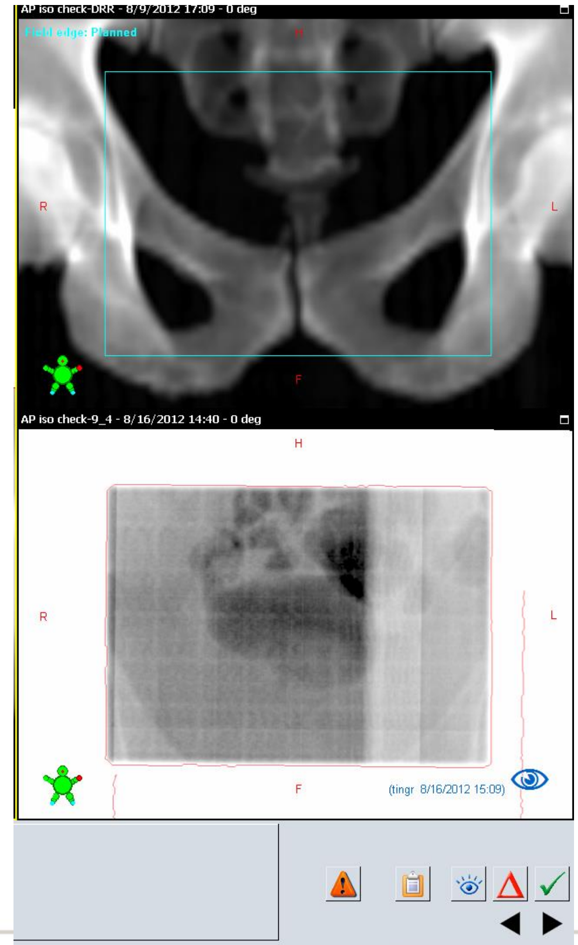
Acquisition





Risk - Misinterpretation of structures





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<table>
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<tr><td>Misinterpretation of structures</td><td rowspan="3">incorrect adjustment

incorrect decision</td><td></td></tr>
<tr><td>Incorrect visualisation</td><td></td></tr>
<tr><td>Inadequate knowledge</td><td></td></tr>
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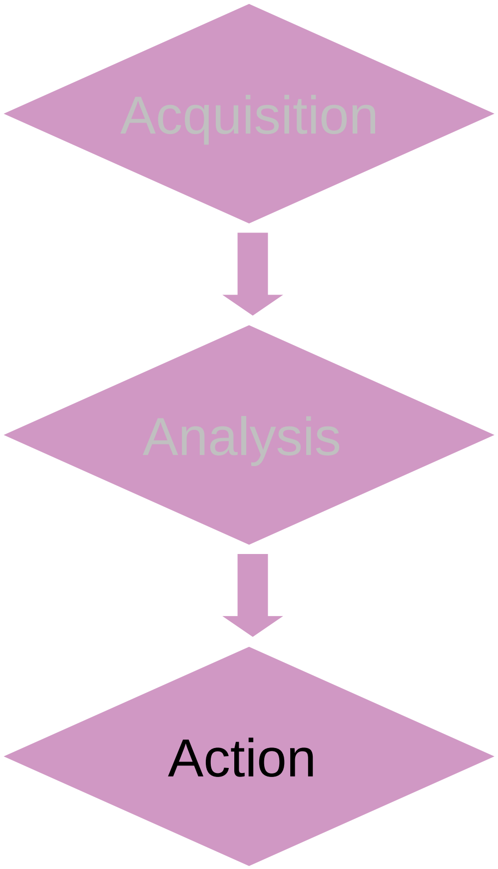
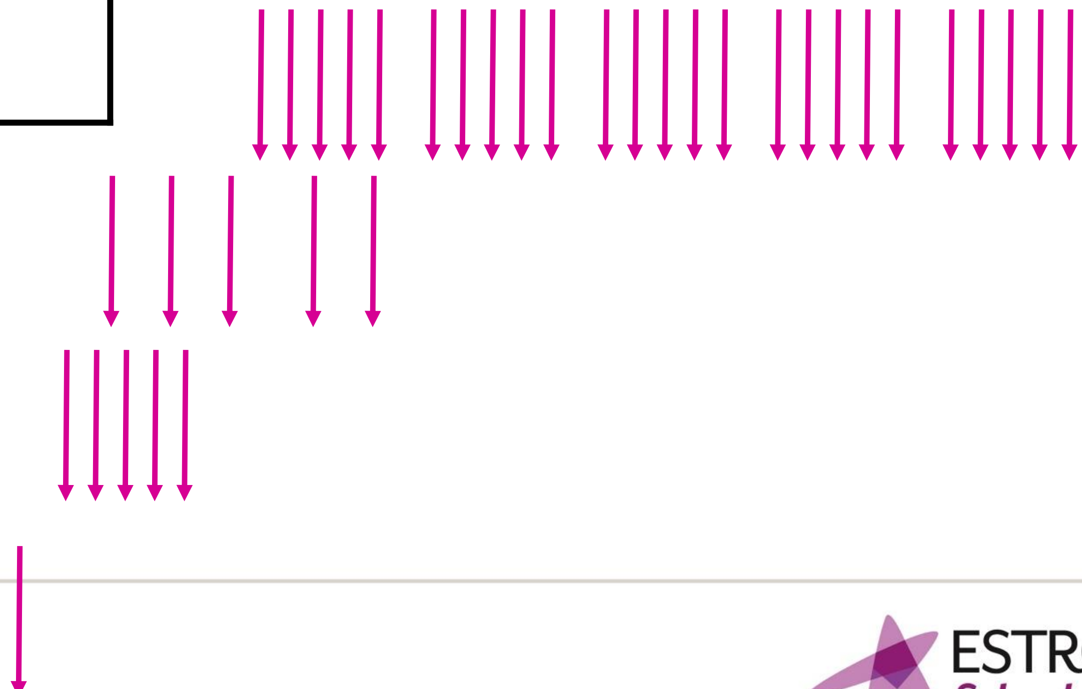
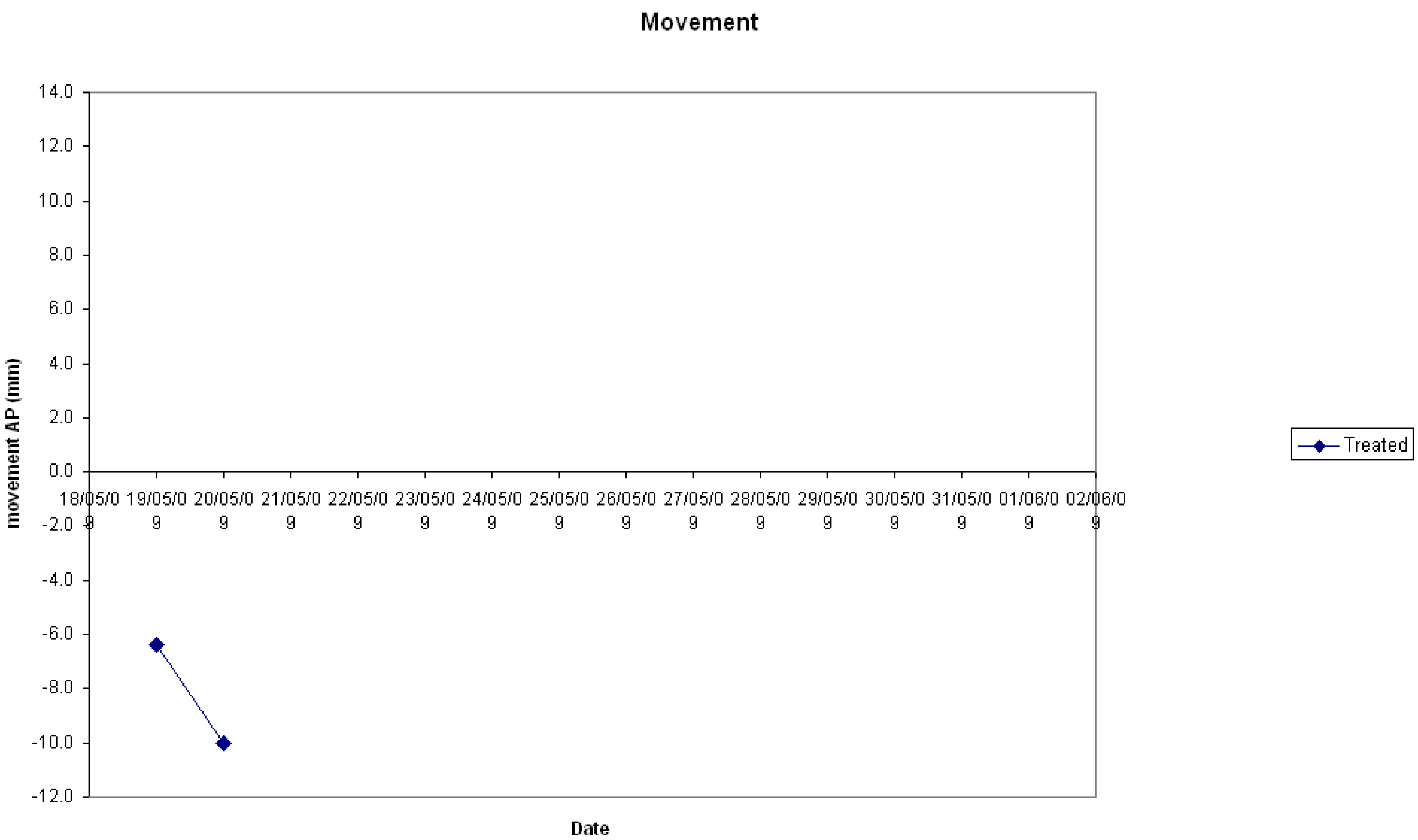

Acquisition
Analysis
Action

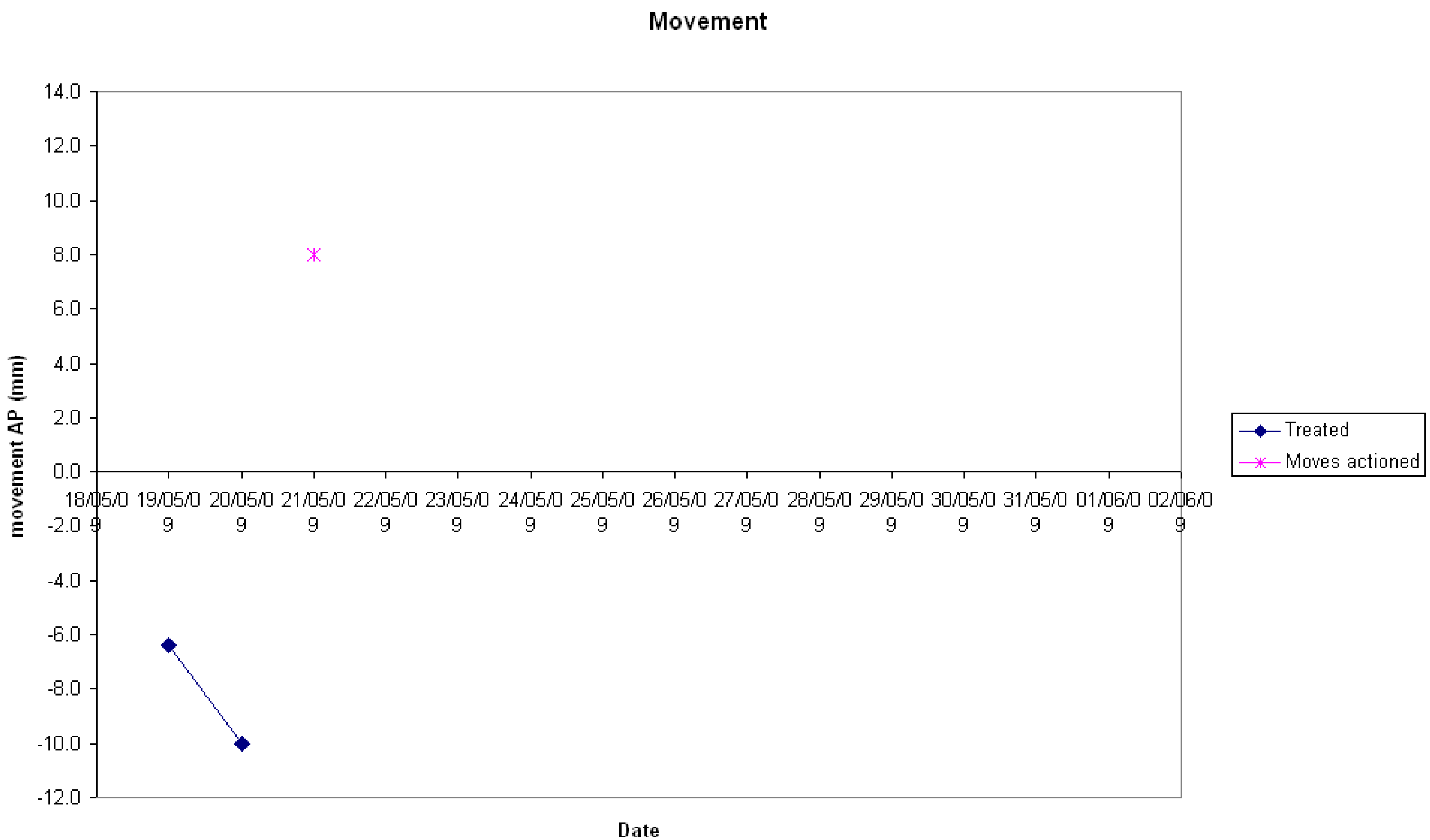
Off line/On line

On line	Off line
Immediate	Time for review
Random and Systematic	Systematic
Audit?	Audit?

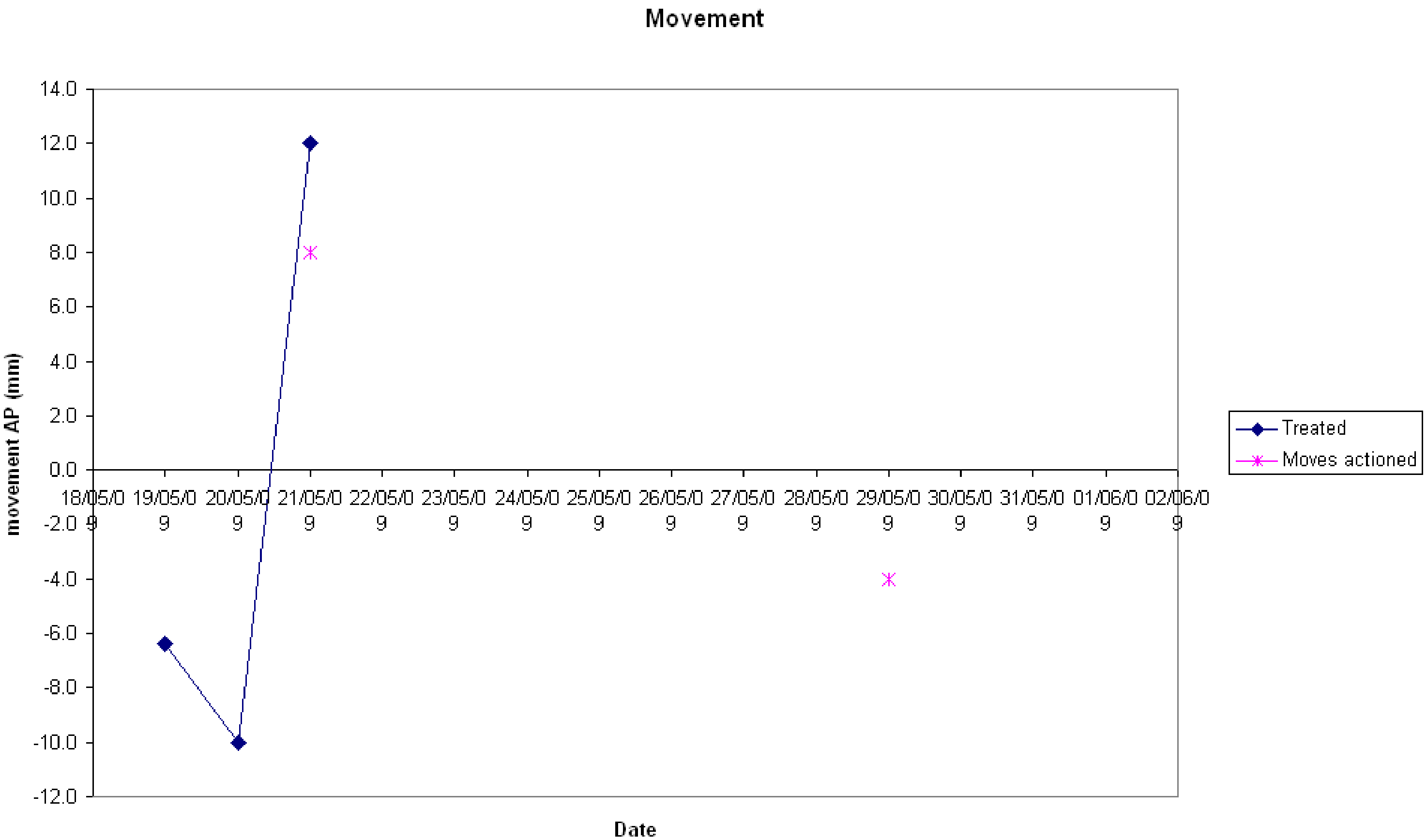




Movement
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
movement AP (mm)
18/05/09
19/05/09
20/05/09
21/05/09
22/05/09
23/05/09
24/05/09
25/05/09
26/05/09
27/05/09
28/05/09
29/05/09
30/05/09
31/05/09
01/06/09
02/06/09
Date
Treated



Movement
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
movement AP (mm)
18/05/09
19/05/09
20/05/09
21/05/09
22/05/09
23/05/09
24/05/09
25/05/09
26/05/09
27/05/09
28/05/09
29/05/09
30/05/09
31/05/09
01/06/09
02/06/09
Date
Treated
Moves actioned



Movement
movement AP (mm)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
18/05/09
19/05/09
20/05/09
21/05/09
22/05/09
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25/05/09
26/05/09
27/05/09
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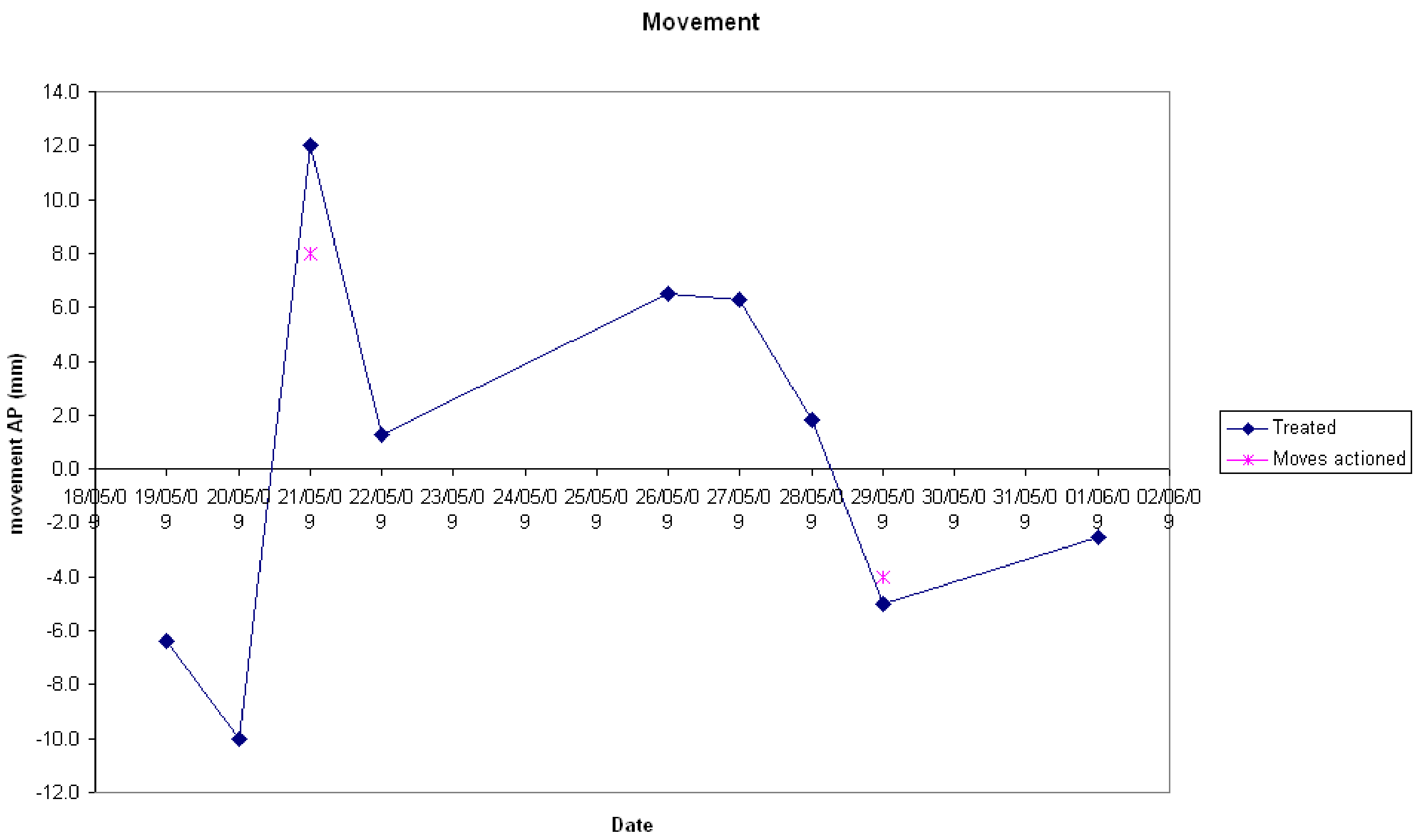
31/05/09
01/06/09
02/06/09
Date
Treated
Moves actioned



Movement
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
movement AP (mm)
18/05/09
19/05/09
20/05/09
21/05/09
22/05/09
23/05/09
24/05/09
25/05/09
26/05/09
27/05/09
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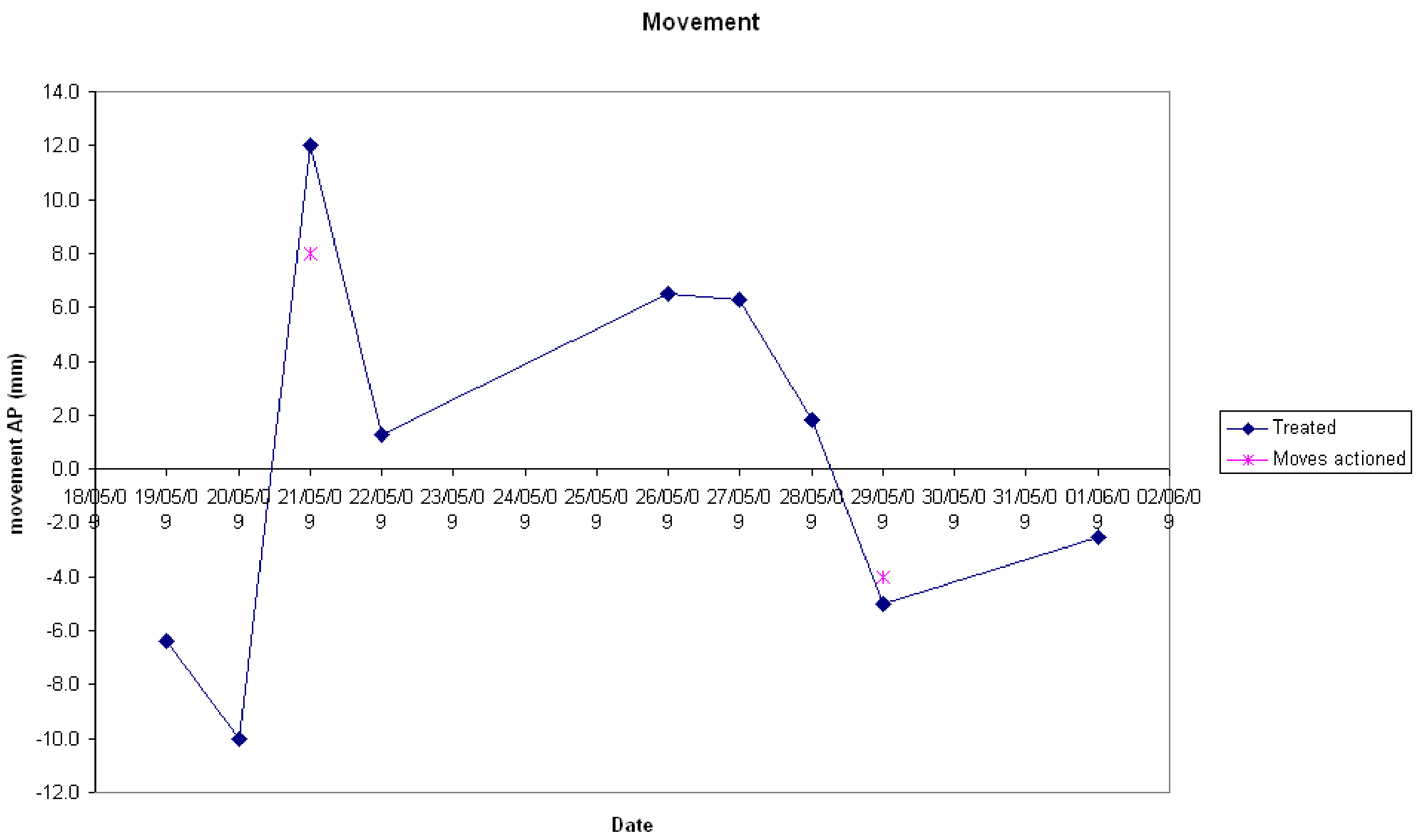
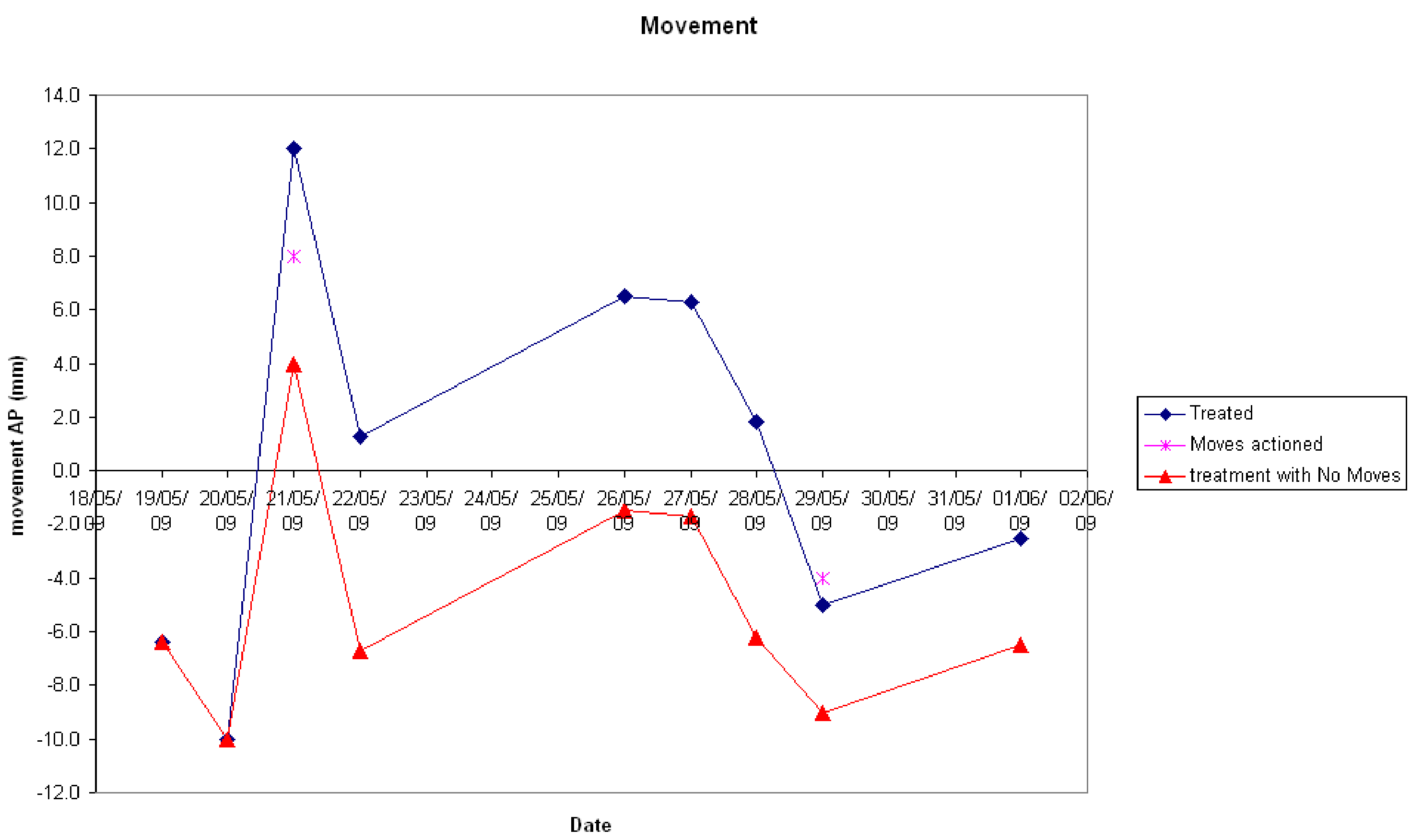
30/05/09
31/05/09
01/06/09
02/06/09
Date
Treated
Moves actioned

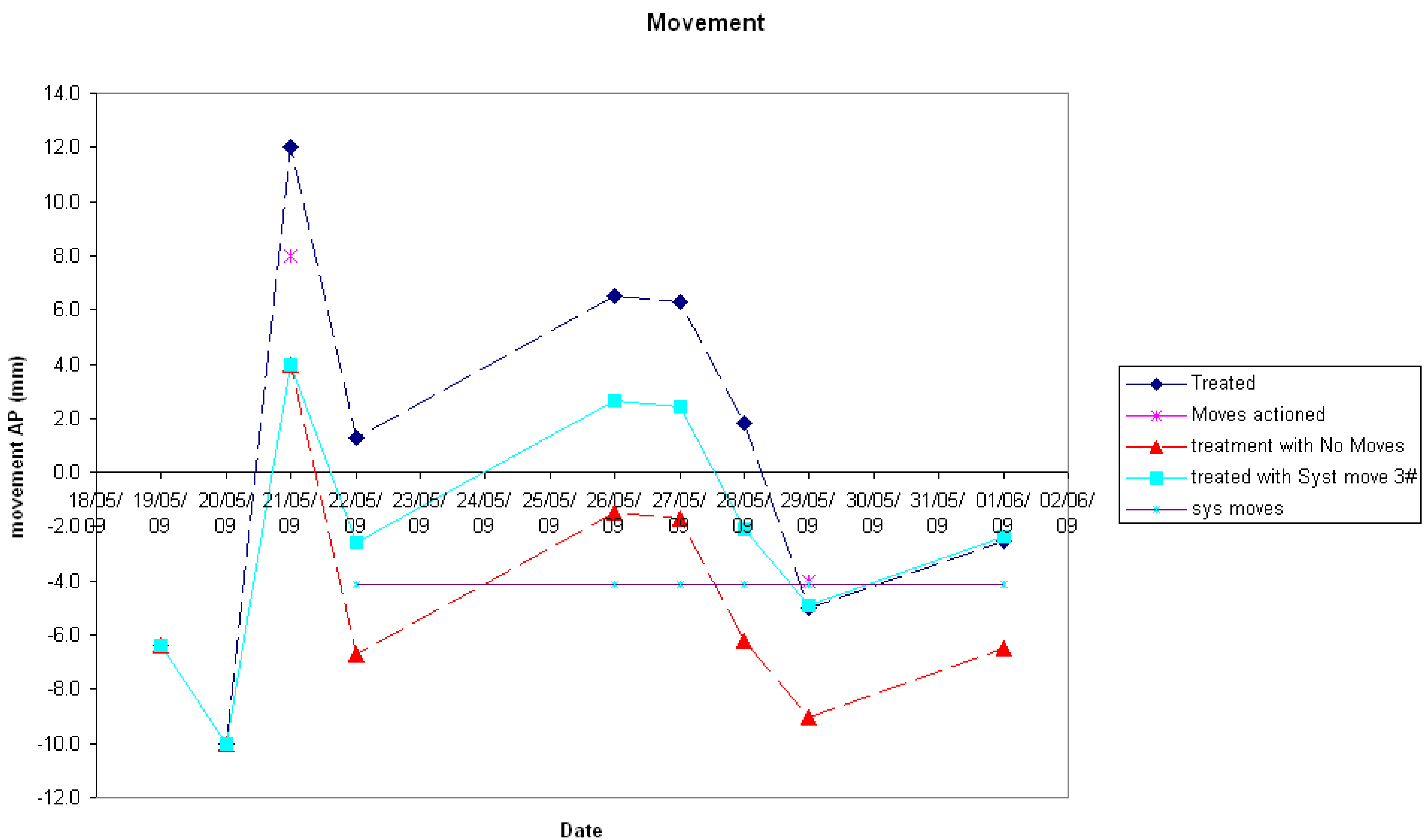


Movement
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
movement AP (mm)
18/05/09
19/05/09
20/05/09
21/05/09
22/05/09
23/05/09
24/05/09
25/05/09
26/05/09
27/05/09
28/05/09
29/05/09
30/05/09
31/05/09
01/06/09
02/06/09
Date
Treated
Moves actioned



Movement
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
movement AP (mm)
18/05/09
19/05/09
20/05/09
21/05/09
22/05/09
23/05/09
24/05/09
25/05/09
26/05/09
27/05/09
28/05/09
29/05/09
30/05/09
31/05/09
01/06/09
02/06/09
Date
Treated
Moves actioned
treatment with No Moves

Risk - Off line protocol not followed



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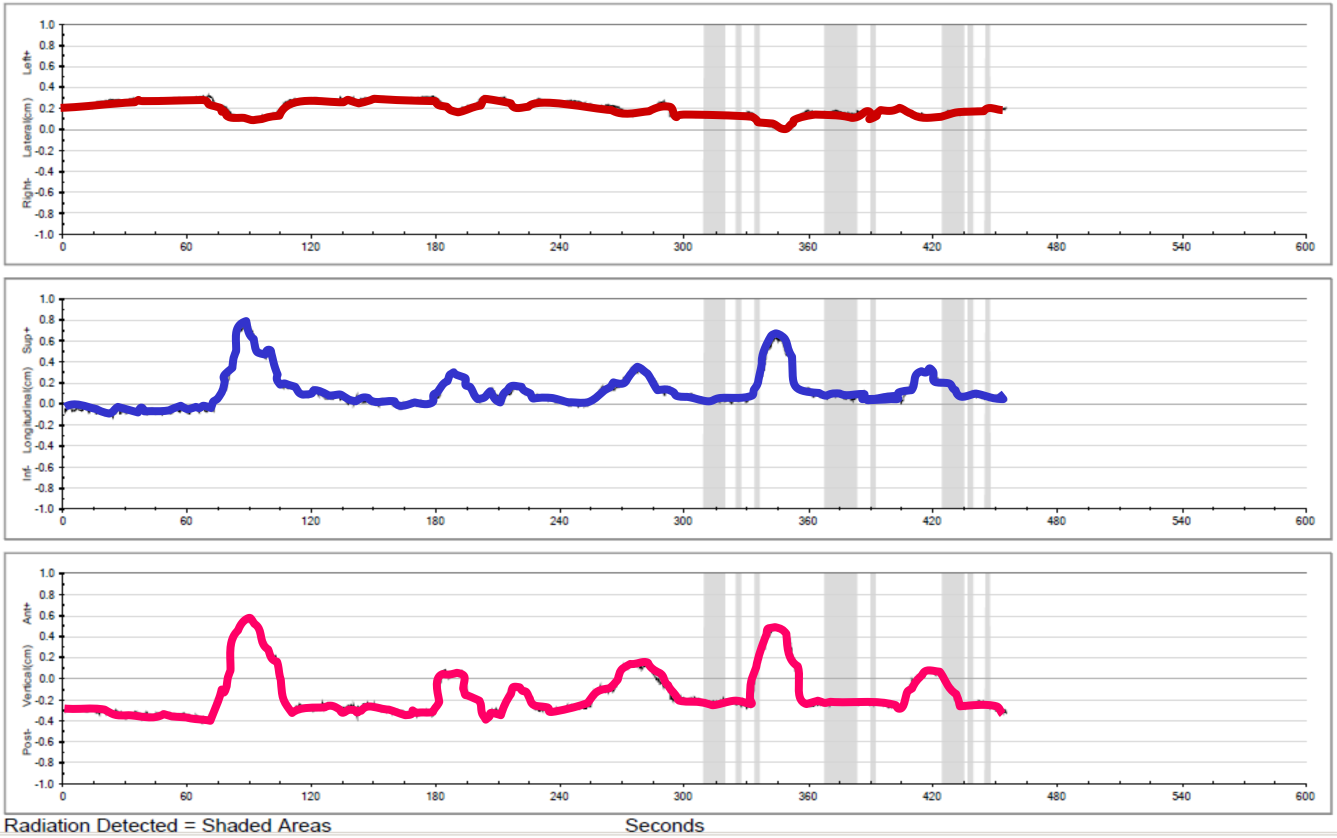
Risk

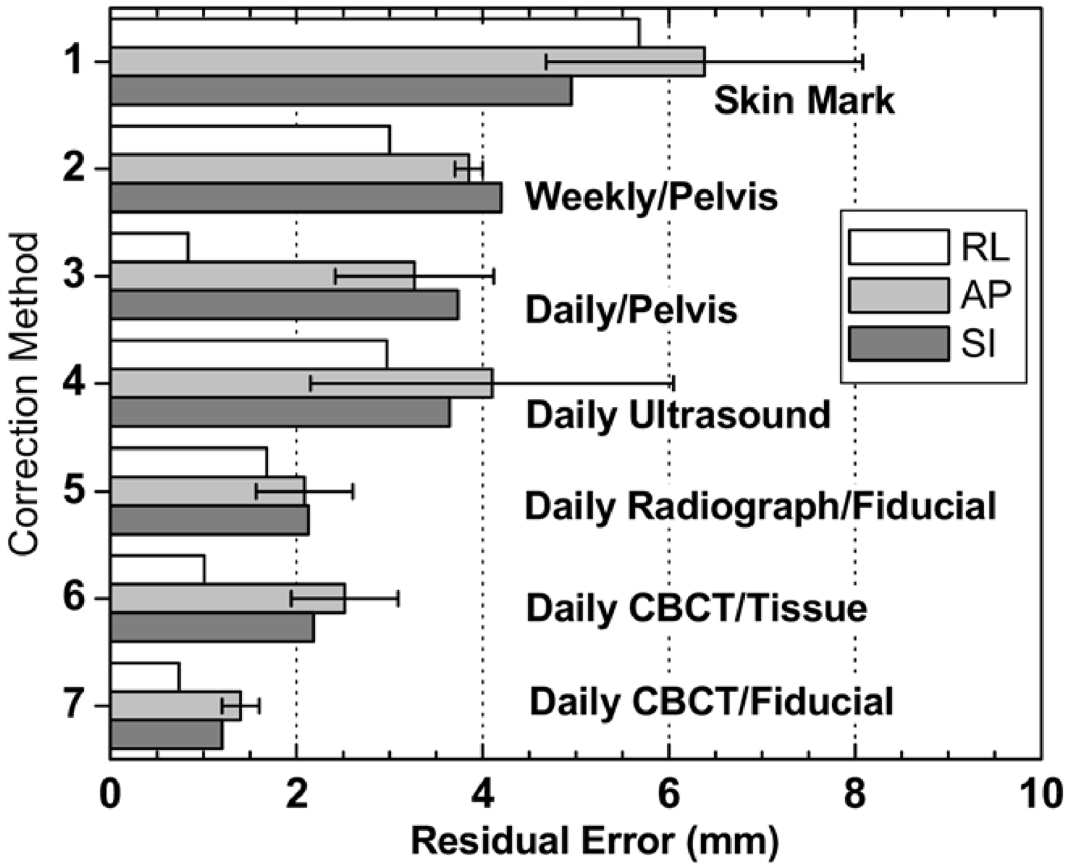
Unawareness of lack of knowledge	**Incorrect protocol/ frequency of imaging**	Increase dose to patient Geographic miss target
	Incorrect decision	move or incorrect 'NOT' move

Risk – underestimate intrafraction motion

Intra fraction motion – prostate

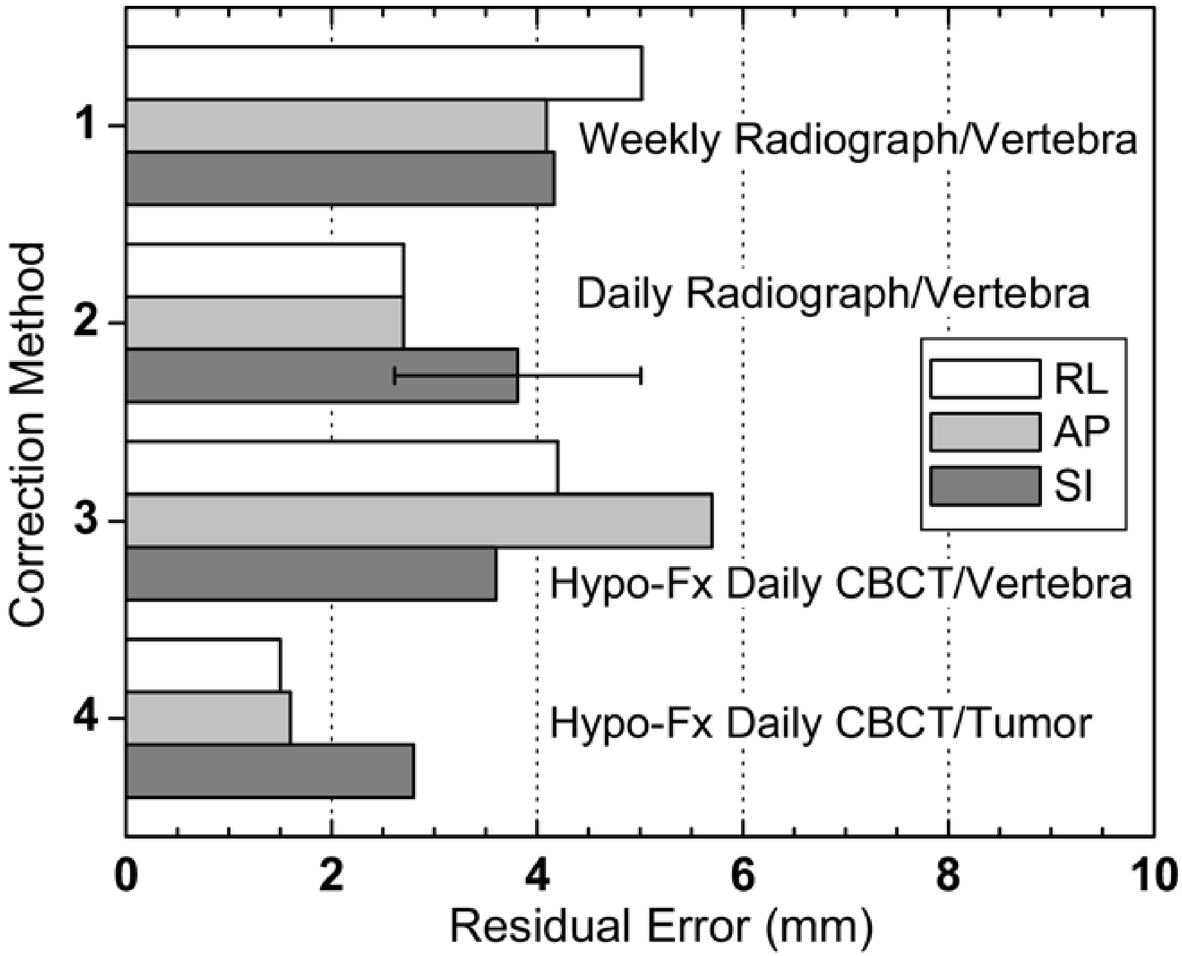


Risk – underestimate residual errors



Mageras Sem Rad Onc 2007

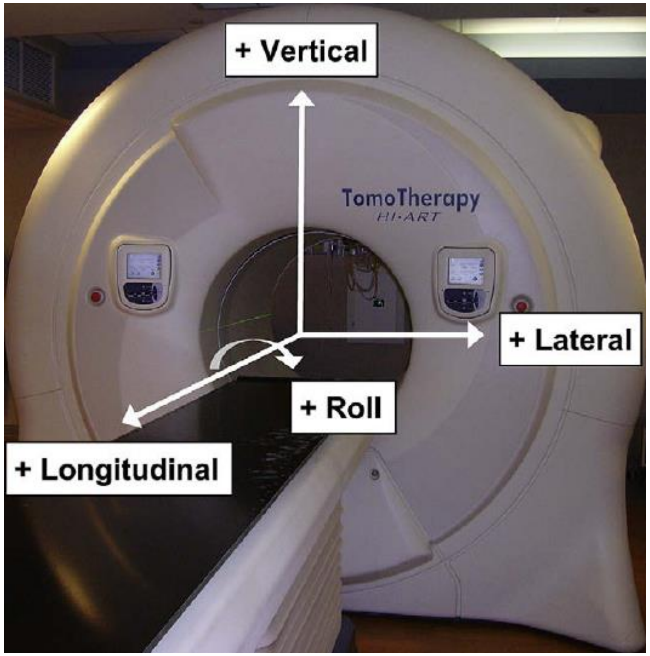
Risk – underestimate residual errors



Mageras Sem Rad Onc 2007

Risk- belief in 'new' technology

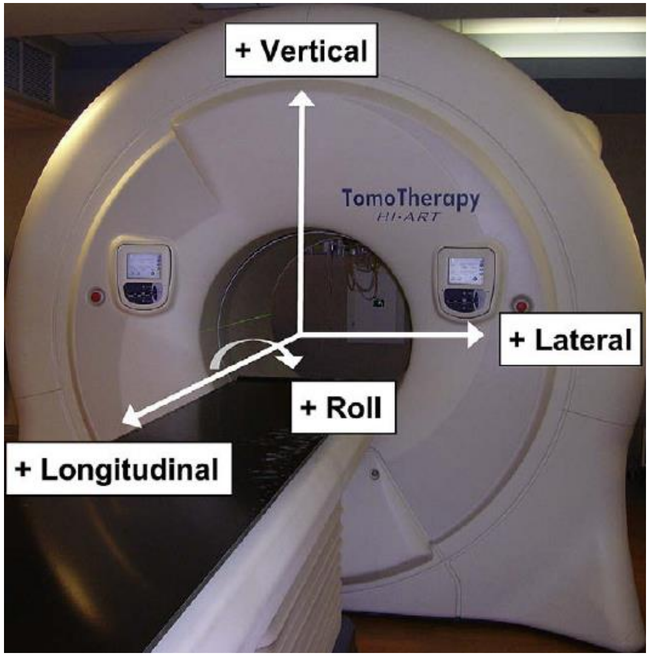
Prostate
Mean error
AP 4.7mm (p<0.001)
SI 2.3 mm



Schubert 2009

Risk- belief in 'new' technology

Head and Neck
Mean error
AP 3.0mm (-2.3 to 5.8mm)
SI -2.8mm (-5.6mm to 0.8mm



Recommended activities for assuring quality in IGRT practice within a clinical program

Safety considerations for IGRT: Executive summary
Practical Radiation Oncology
Volume 3, 2013,

Houghton 2009

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Risk – inadequate training

Recommended Activities	Comments	Refs.
1. Assure RTT curriculum includes IGRT theory and practice.	Technology awareness is not sufficient. RTTs also need to understand concepts of margin design, residual uncertainty, and inter-observer variability to knowledgeably apply IGRT.	None
2. Assure DP curriculum includes IGRT theory and practice, dose reconstruction, normal tissue delineation, and understanding of ART concepts.	Understanding concepts of margin design, residual uncertainty, and inter-observer variability are relevant to DP's practice. Future adaptive processes will be coordinated by this profession and this requires curriculum expansion.	None
3. Assure MP residency training in imaging (eg, CT, MR, US), IGRT theory, and process management.	Imaging technologies need to be understood if they are to be properly applied. In addition, the MP has a leadership role in margin design and the link to planning. Curriculum extensions are needed.	None
4. Assure RO residency curricula explicitly include IGRT theory and practice.	PTV/PRV margin approval requires a sound understanding of IGRT concepts. Target delineation is another critical area for dedicated training. Physicians in practice need to access CME opportunities.	None
5. Facilitate cross-profession engagement between RTTs, DPs, MPs, and ROs for decision-making and delegation issues.	Clarity in decision-making role is critical for safe IGRT. Educational programs that reinforce this engagement are desirable.	11
6. Facilitate the generation of a lexicon for IGRT practice.	ICRU has provided powerful tools for dose prescription and the airline industry has demonstrated the value of consistent language to communicate in complex situations. Furthermore, the development of ART will challenge our current lexicon.	34,42,43,45
7. Include testing on IGRT in the board certification process for all professions.	Including margin design, correction strategies, and quality assurance practices.	39

Abbreviations: IGRT (Image Guided Radiation Therapy); RTT (Radiation Therapist); DP (Medical Dosimetrist and Other Qualified Planner); ART (Adaptive Radiation Therapy); MP (Medical Physicist); CT (Computed Tomography); MR (Magnetic Resonance); US (Ultrasound); RO (Radiation Oncologist); PTV (Planning Target Volume); PRV (Planning Organ at Risk Volume); CME (Continuing Medical Education); ICRU (International Commission on Radiation Units).

Safety considerations for IGRT: Executive summary
Practical Radiation Oncology
Volume 3, 2013,

Risk-assessment

IGRT Process	Description of risk	What factors may cause this risk to occur	Existing control measures for each potential hazard	Risk Level (1 low -5 high)
Acquisition	Gantry collision with patient	Off set isocentre	Safety check for gantry clearance before each acquisition	3
	Treated with Incorrect isocentre	Isocentre has to be moved for CBCT	Record and verify system	3
Analysis process	Anatomy changes missed	Lack of training/awareness	Training	4
	Potential for geographical miss if on line matching	Lack of training	Training Clinician to be present if staff not trained to advanced level	4
	Incorrect target surrogate i.e. seed outlined	Poor image quality on reference images	Seeds marked on TPS by planner then marked with cross on DRR by treatment staff.	1
	Seed position inconsistent	Marker migration	Training regarding risk of migration and effect of rotations	2
Action	Potential for geographic miss	Lack of understanding of protocols	Training regarding protocol action levels	2
	Potential for geographic miss	Individual patient anatomy anomalies	Training with specific case examples	2

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Risk-assessment

Table 2: Recommendations to establish a foundation for safe and effective IGRT practices

Recommendation	Comments	Refs.
1. Establish a multi-professional team responsible for IGRT activities.	MP, DP, RTT, and RO membership; responsible for leading IGRT initiatives. Collectively, this team has deep expertise on IGRT. The program should make educational investments in this team.	37
2. Establish and monitor a program of daily, monthly, and annual QA for all new or existing IGRT sub-systems.	Led by MPs with participation by RTTs. Reporting and results should be transparent to other professions and administrators. See AAPM Task Group reports for test frequency.	12,13
3. Provide device- and process-specific training for all staff operating IGRT systems or responsible for IGRT delivery.	Applications training needs to be augmented by internal process-specific training with competency testing for all professions and supported by the IGRT team (see Recommendation1, above).	13
4. Perform end-to-end testing for all new IGRT procedures (from simulation to dose delivery) and document performance prior to clinical release.	The combination of various sub-systems is typically not certified by vendors and needs to be tested before use. Tests should be specific to the process and include staff that will be performing the procedure in the clinical setting.	13

Safety considerations for IGRT: Executive summary
Practical Radiation Oncology
Volume 3, 2013,

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Protocols

The ROYAL MARSDEN **STANDARD CT SCANNING FOR RADIOTHERAPY PLANNING – SUTTON**

NEURO	PATIENT POSITON	SLICE/ FEED (mm)	Sur-View	Field Of View	SCANNING LEVELS	CONTRAST	COMMENTS
BRAIN PALLIATIVE	Shell	1.5/1.0	Lat	450	Vertex to below mandible	NONE	
BRAIN RADICAL ADULT	Supine in cast (3 point)	AXIAL 1.5/6	Lat	500	Vertex to below mandible (scan lock bar if necessary)	50ml IV contrast if requested. Hand Inject – minimum of 8 minute delay, maximum 3 hours.	
BRAIN PEADIATRIC	Supine in cast (3 point)	AXIAL 1.5/6	Lat	500	Vertex to below mandible	IV contrast if	+/- GA
STEREO BRAIN in cast	Supine in cast (3 point)	AXIAL 1.5/6	Lat	5			

The ROYAL MARSDEN

TREATMENT VERIFICATION PROTOCOLS (ROUTINE)

Site	Modality	Justification	Frequency	Correction Strategy	Scan	Preset	Match	Tolerance	Dose /Image
WHOLE CNS	EPI	For whole CNS verification refer to the chart S-CH-266		Offline					
BRAIN or SPINE	XVI	Confirm Isocentre Pos^n	At least fractions 1-3 => Apply syst corr =>Weekly	Offline	Half	13 OR 15 FAST L DOSE H&N S10 OR S20 F0	Bone	≤3mm Rot^n ≤3°	0.45mGy
STEREO BRAIN	XVI	Confirm Isocentre Pos^n	Each fraction	Online	Half	13 OR 15 FAST L DOSE H&N S10 OR S20 F0	Bone	ON-Line couch corr	0.45mGy

Admin | Logout |

Incidents

Datix

Helen McNair

The Royal Marsden NHS Foundation Trust Red Flag & Incident investigation form.

This form should be used fo

The investigators user guide

For further assistance with t

TO REPORT A NEW INCI

What are you reporting?

A near miss is any incident that had the potential to cause harm but was prevented

* Are you reporting an incident / near miss or a red flag?	Incident / Near miss
* Is this a Near Miss?	No

Was a patient involved / affected by this incident?

* Was a patient involved / affected by this incident?	Yes

Incident details

Date incident reported (dd/MM/yyyy)	17/10/2017
* Date incident occurred (dd/MM/yyyy)	12/10/2017
* Time incident occurred (hh:mm) If the time was unknown, it is recorded as **12:34**	14:00
* What happened? **Do not mention:** Names, dates of birth, hospital numbers, or any other personal identifiable information here. Use job titles or the word patient to describe people involved/affected.	TSRT Level 3 10E, 13AA, 13O. Right Thigh 50Gy/25# incident occurred #9. An anterior Kv image was taken for the first time on the patient (usually a CBCT is scheduled - this followed protocol as weekly CBCT was out of tolerance). The Kv image was taken of the patient with correct jaw sizes inputted, however radiographers
* Action taken at the time of the incident or to prevent re-occurrence. **Do not mention:** Names, dates of birth, hospital numbers, or any other personal identifiable information here. Use job titles or the word patient to describe people involved/affected.	orientation and a Kv image was taken resulting in concomitant exposure for the repeat anterior Kv image which was annotated in the patient journal by a practitioner radiographer. This event is unlikely to reoccur as MV iso images are now scheduled that pre-define the jaw field size and
Additional information Additional information which could not be added anywhere on the report, and could contain **vital information**.	

ary

TRO

ool

2012, 2014 and 2016 reported error trends.

	Number of reports	Percentage of IGRT errors
2012	65	2.0
2014	302	3.5
2016	825	6.9

Process code	Activity code	Example
13i	Use of on-set imaging	Imaging according to protocol
13z	On-set imaging: production process	Inappropriate exposure used Image not captured CBCT filter left in for kV image
13aa	On-set imaging: approval process	Image review not done Image review inaccurate Image matched to inappropriate reference image
13bb	On-set imaging: recording process	Recording of image review not undertaken Actions following image review not undertaken

ukpha

Radiotherapy Errors and Near Misses Data Report (December 2013 to November 2015)
Public Health England , UK

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Pause and check- pre treatment

January - March

Check all following correlate with Planning referral:
Review specific requests of clinician
Dentures / Wax
Technique (e.g. VIBH)
ID and Pregnancy Status
Previous Tattoos
Scanning protocol
Position and Orientation
CT + Anatomical Markers
Consent
Patient Data entry
SURVIEW / SCOUT
Correct scanning levels FOV
Select Contrast Delay

Diagnostic Radiology -2015

National patient safety agency
‘Pause and check’ reduces errors

Now coming into radiotherapy

Pause and check-treatment

The ROYAL MARSDEN

Have you 'PAUSED & CHECKED'?

P	Patient	• ID • Patient set-up *(eg black mattress)*
A	Anatomy	• Site • Laterality
U	User checks	• Breath-hold (VIBH / ABC) • Wax
S	Schedule	• Fraction number / phase • Verification schedule & modality
E	Exposure	• No amendments to treatment / dose to be delivered
D	Draw to a close	• Clinic day? Bloods? • End of treatment letter?

Page 1 of 1 J-CH-081-01 (04.16)

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Reports

Imaging for Treatment Verification Work Group Task Group #179

Quality assurance for image-guided radiation therapy utilizing CT-based technologies: A report of the AAPM TG-179. Medical Physics, Vol 39, Issue 4

http://www.rcr.ac.uk/docs/oncology/pdf/BFCO(08)5_On_target.pdf

National Radiotherapy Implementation Group Report

Image Guided Radiotherapy (IGRT). Guidance for implementation and use. August 2012 UK

The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy (ESTRO-EIR) report on 3D CT-based in-room image guidance systems: a practical and technical review and guide.

Korreman S, Rasch C, McNair H, Verellen D, Oelfke U, Maingon P, Mijnheer B, Khoo V. Radiother Oncol. 2010 Feb;94(2):129-44.

Safety considerations for IGRT:Executive summary

Practical Radiation Oncology. 2013:3(3):167-170

Acknowledgements

CANCER RESEARCH UK

Radiotherapy department RMH

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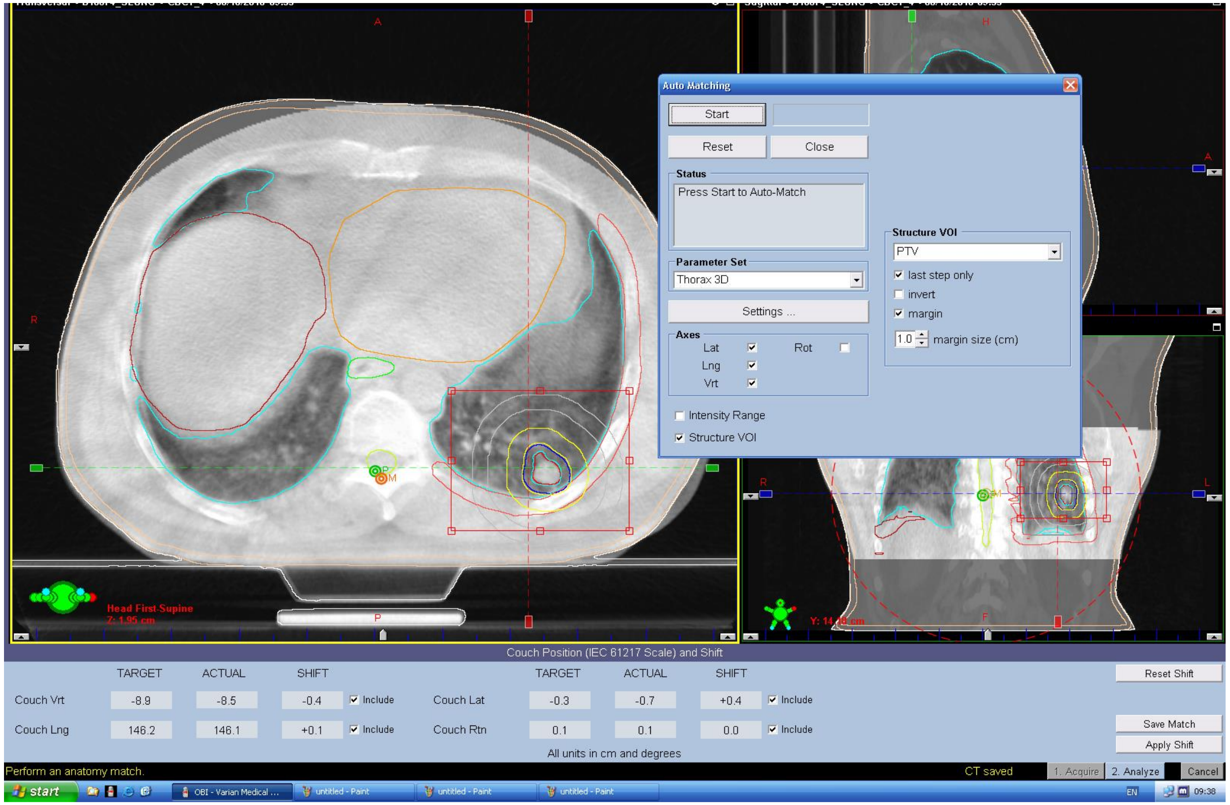
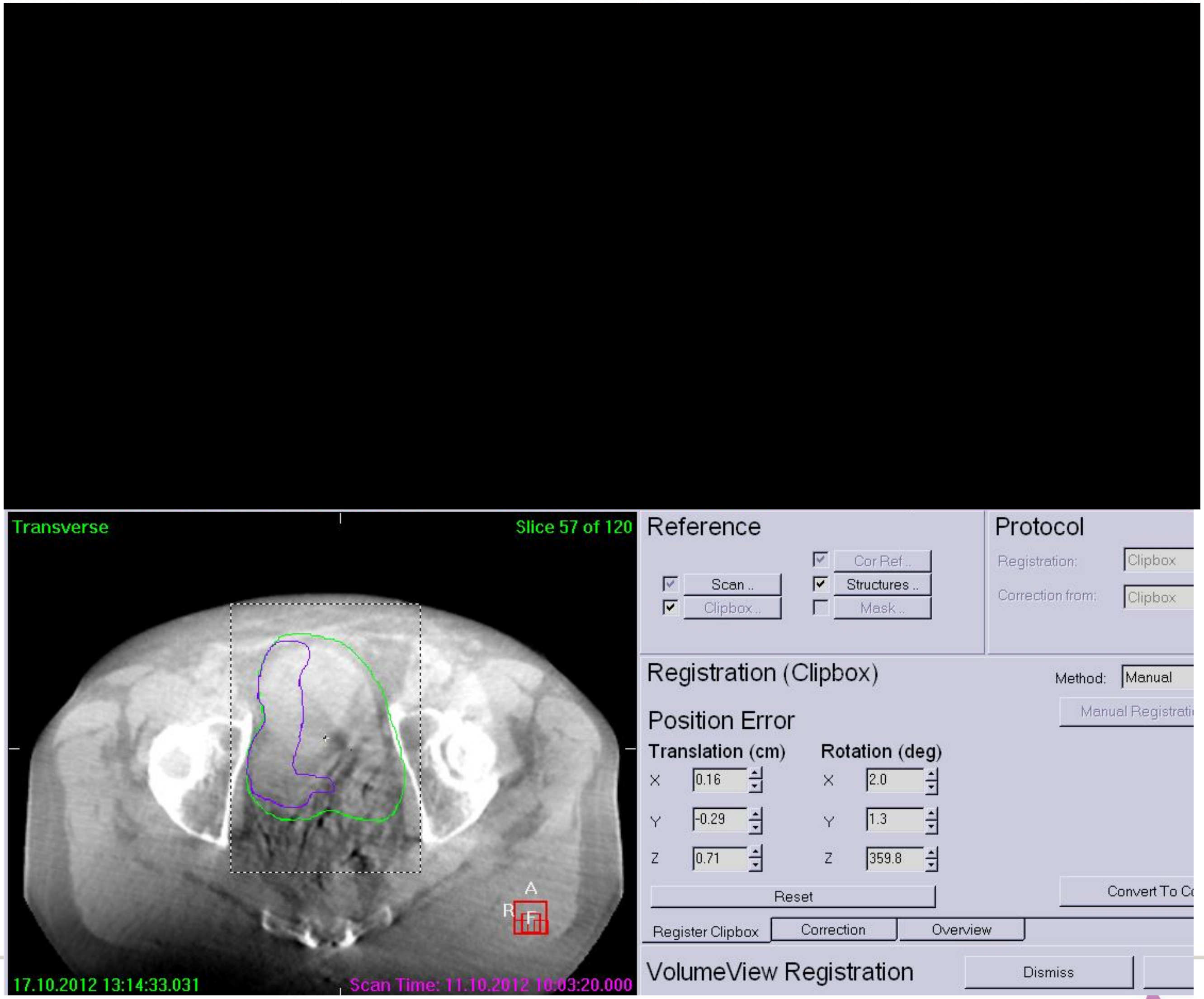
Action

Hypofractionated lung– on line



Risk



Transverse
Slice 57 of 120
17.10.2012 13:14:33.031
Scan Time: 11.10.2012 10:03:20.000
Reference
Scan ..
Clipbox ..
Cor Ref ..
Structures ..
Mask ..
Protocol
Registration:
Clipbox
Correction from:
Clipbox
Registration (Clipbox)
Method:
Manual
Position Error
Translation (cm)
Rotation (deg)
X 0.16
Y -0.29
Z 0.71
X 2.0
Y 1.3
Z 359.8
Reset
Register Clipbox
Correction
Overview
VolumeView Registration
Dismiss

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Patient Preparation and Positioning

Rianne de Jong *RTT*,
Academic Medical Centre, Amsterdam
Athens

m.a.j.dejong@amc.uva.nl

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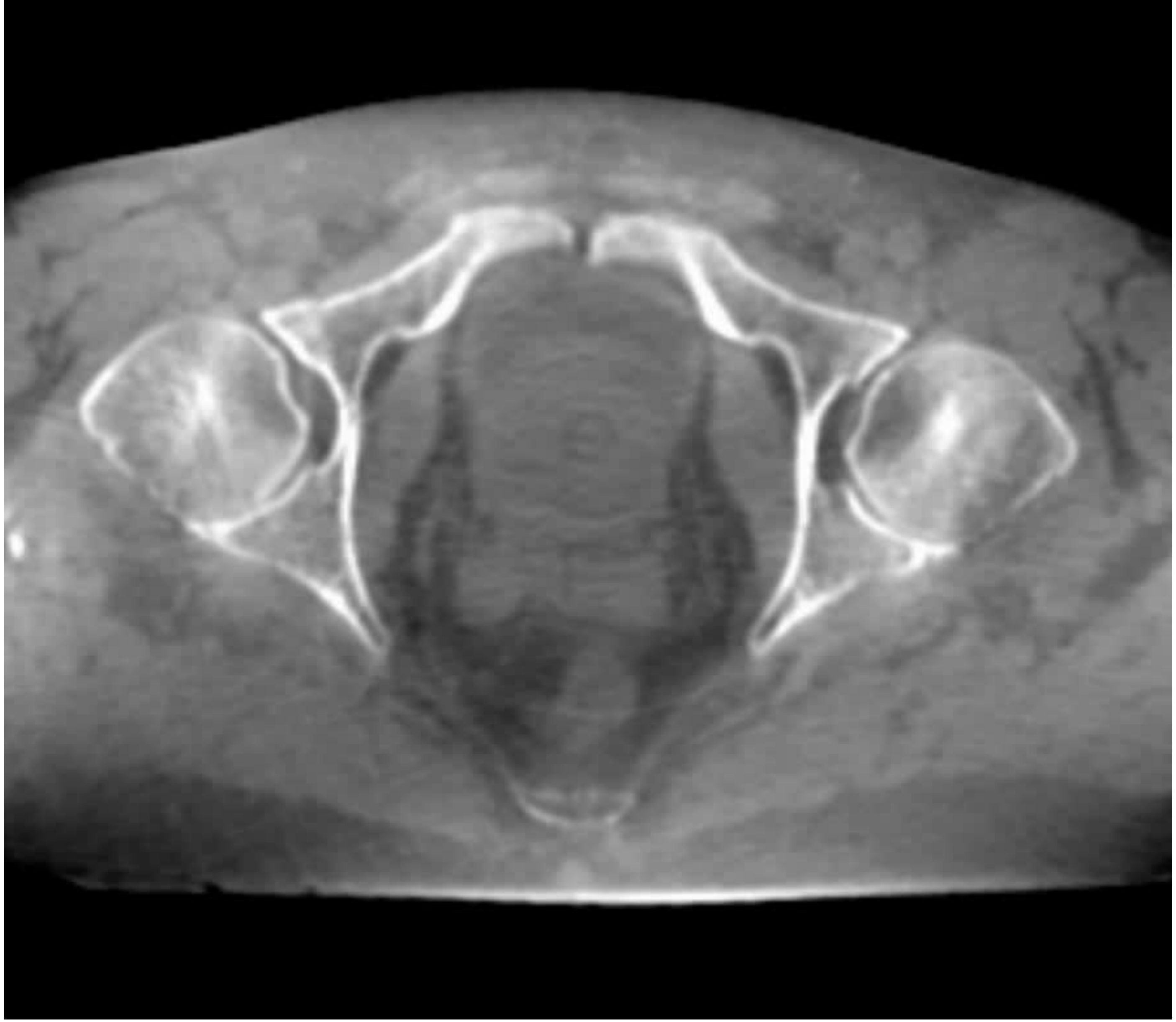

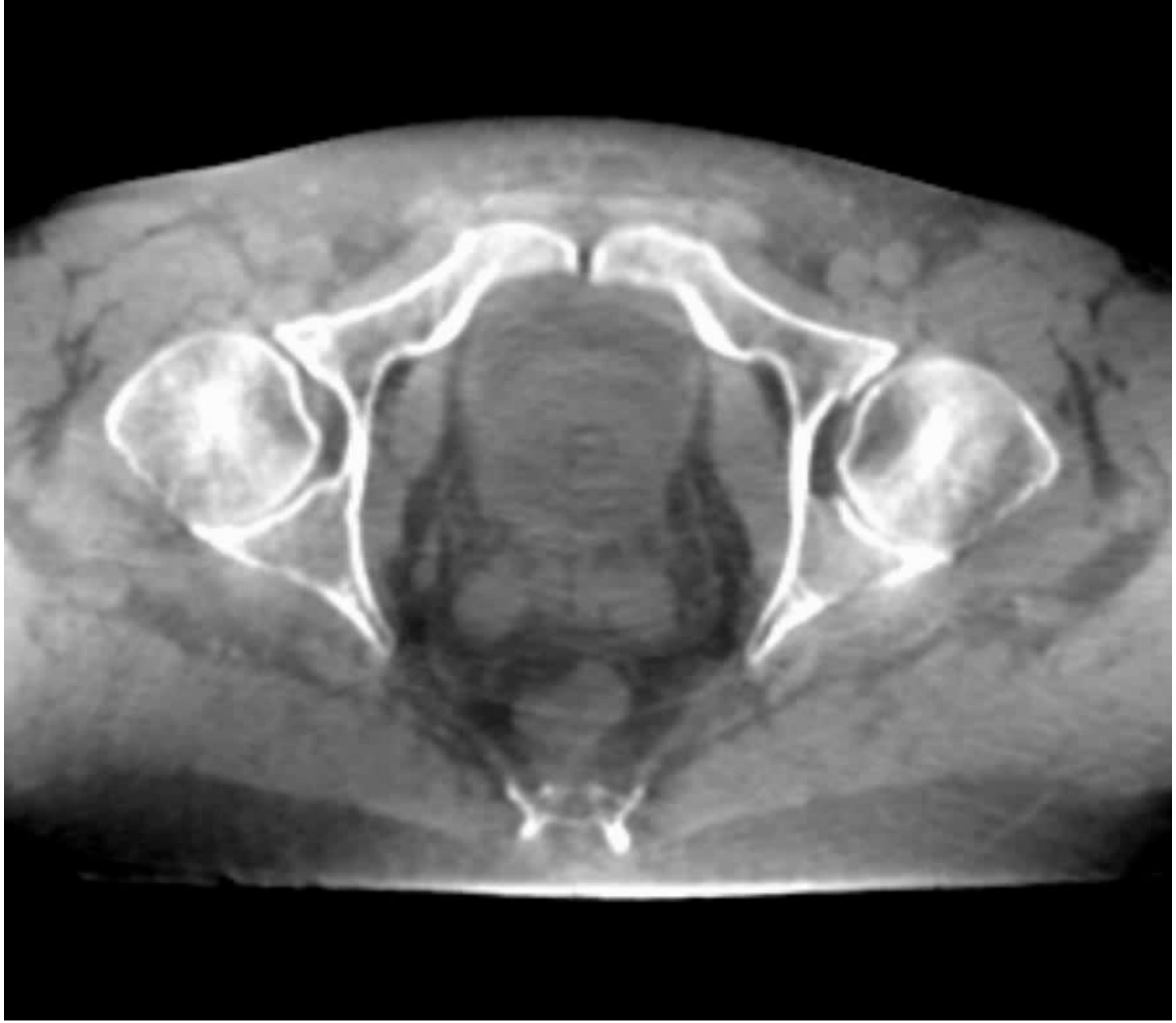

Introduction

- ✓ In-room imaging enables the visualization of the target just prior to treatment.
- ✓ On-line image guidance minimizes target position variability.

Is there still a need for patient immobilisation and preparation?

Aim of Patient preparation and positioning

→ **Minimize the difference in patient position**

- between simulation and treatment sessions
- during the treatment session

→ **Maximize the distance between target volume and organs at risk**

How?

1. Patient compliance
2. Immobilization and fixation

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Aim of Patient preparation and positioning

→ Patient compliance

- Information and education
  - Using photo books, DVD's, folders etc.
  - Tour through department
- Psychological support to minimize fears
- Medication
  - Pain control

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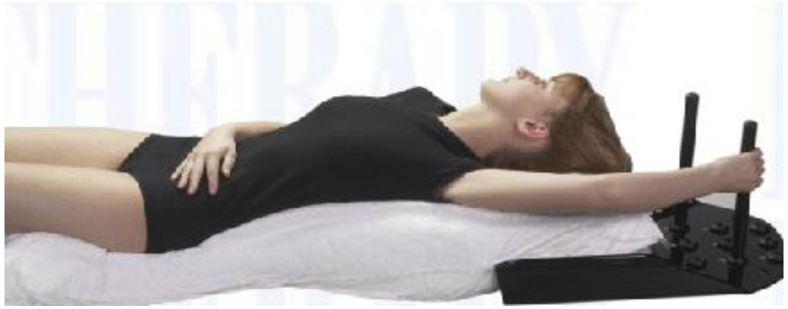
Aim of Patient preparation and positioning

→ Immobilization

Daily set-up reproducibility and stability through the use of fixation or aiding devices





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Aim of Patient preparation

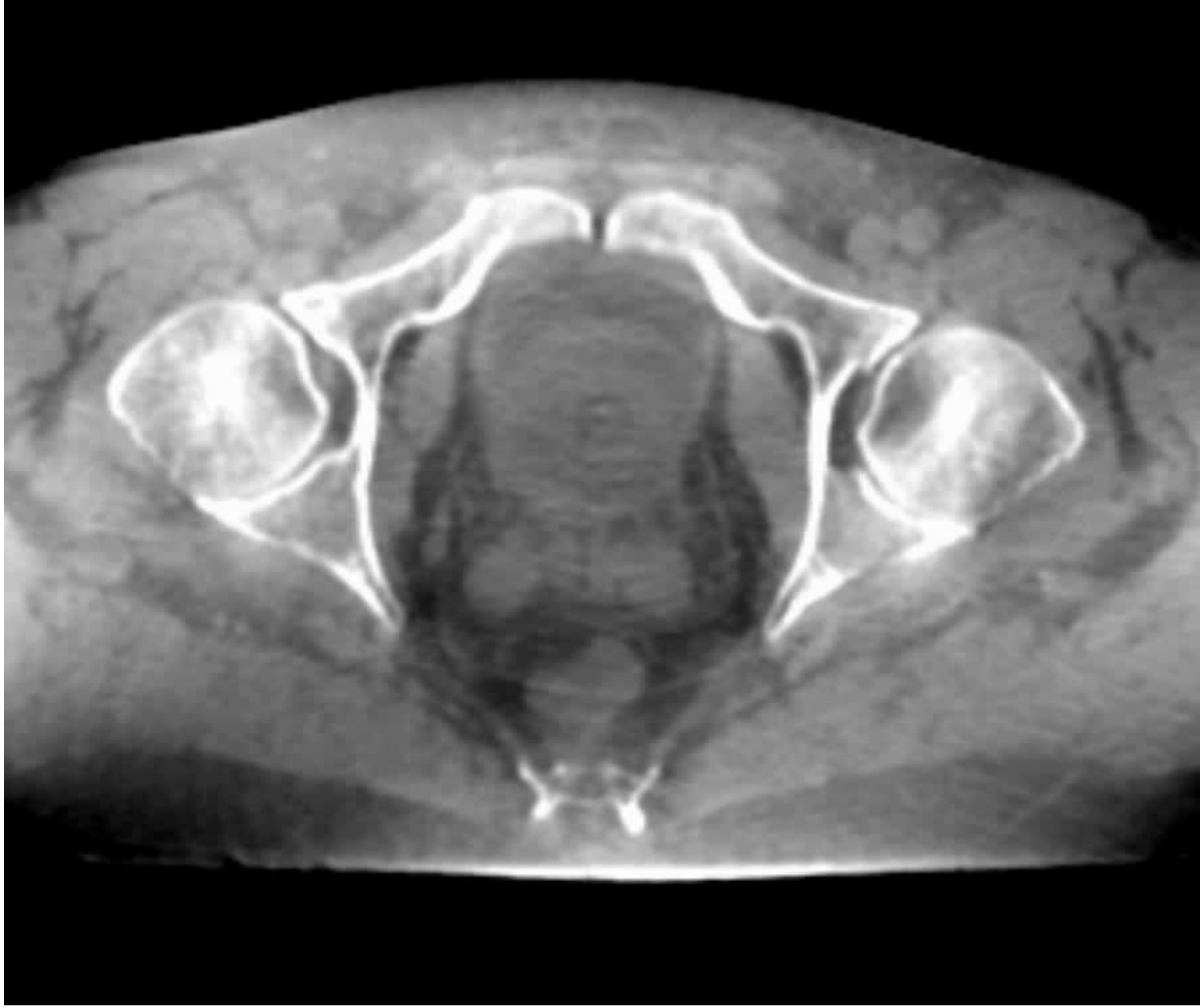
- Prostate patients
- Rectum patients

Prostate patients

- ✓ Off-line correction on bony anatomy with SAL protocol
  - Portal imaging
    - Kilo voltage CBCT

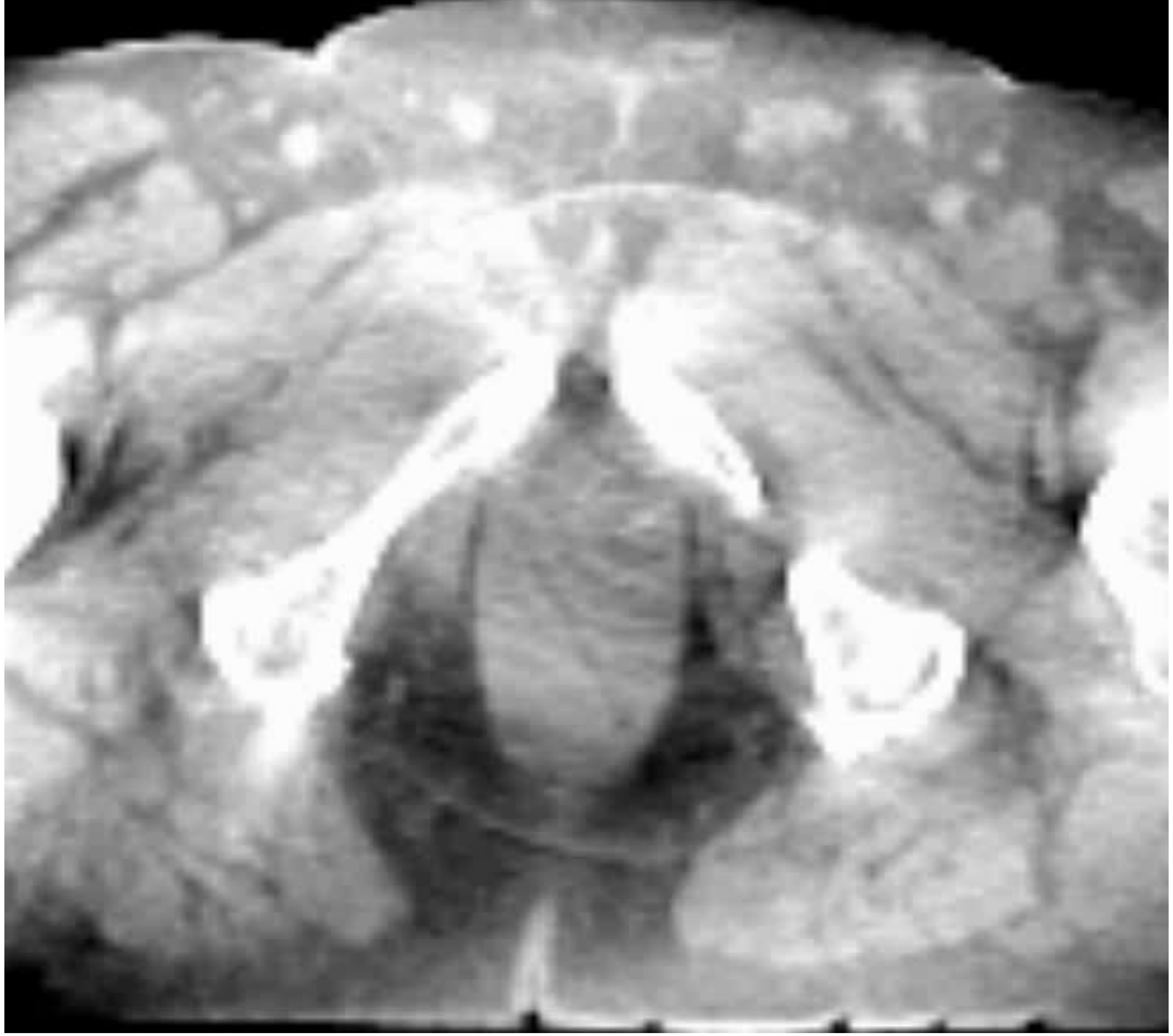
? Soft tissue registration on prostate?

(no markers)



Projection images

CBCT



Reconstructed

CBCT

Prostate patients

To improve image quality:

- ✓ Dietician
  - Mild regimen of laxatives
  - Diet
- ✓ Fixed treatment times

Prostate patients

	gas	faeces	moving gas
no diet	68%	61%	45%
with diet	42%	23%	22%

- Improved image quality for registration and delineation
- Reduced intra fraction motion

For all prostate patients

Courtesy Josien de Bois

Prostate patients

Lips et al. Ijrobp 2011

739 patients without diet, 205 patients with diet

Diet instructions on leaflet

No reduction of **intrafraction** movement

McNair et al. 2011

22 patients using questionaires

Rectal filling consistency not improved

Diet + fixed treatment times, **no laxatives**

McNair and van Vulpen 2013

Rectum patients

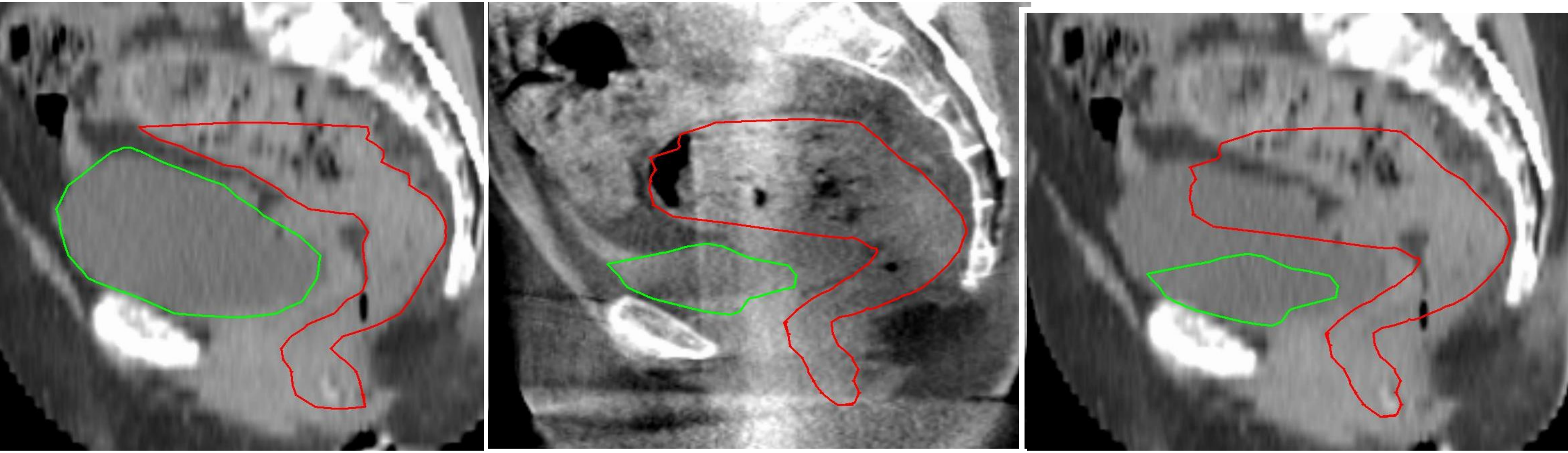
Series of repeated CT scans

Bladder filling and rectal filling over different fractions

With drinking protocol

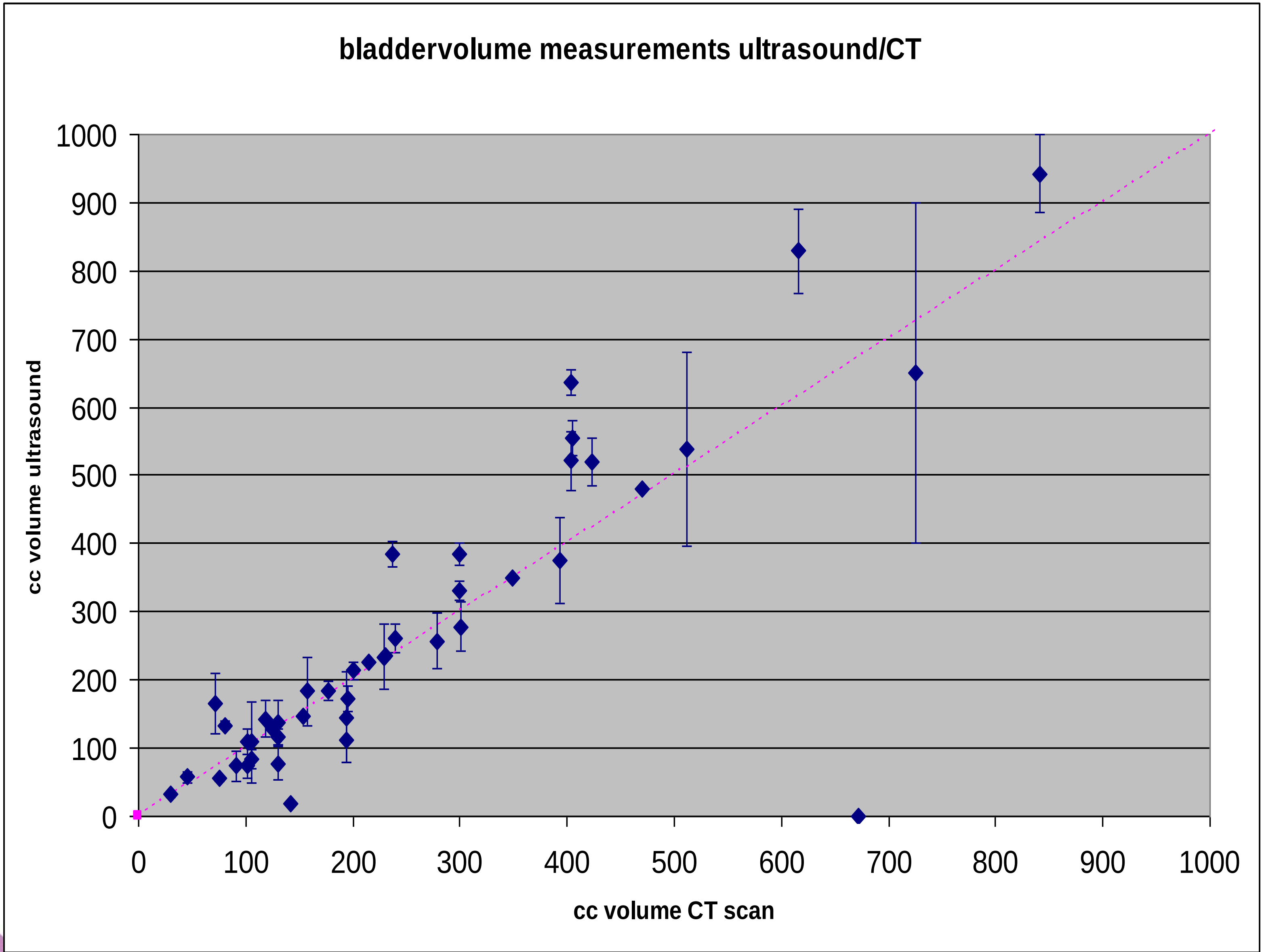
No bowel prep

Rectum patients



Influence of bladder filling on CTV of rectum, with equal rectal filling

Rectum patients



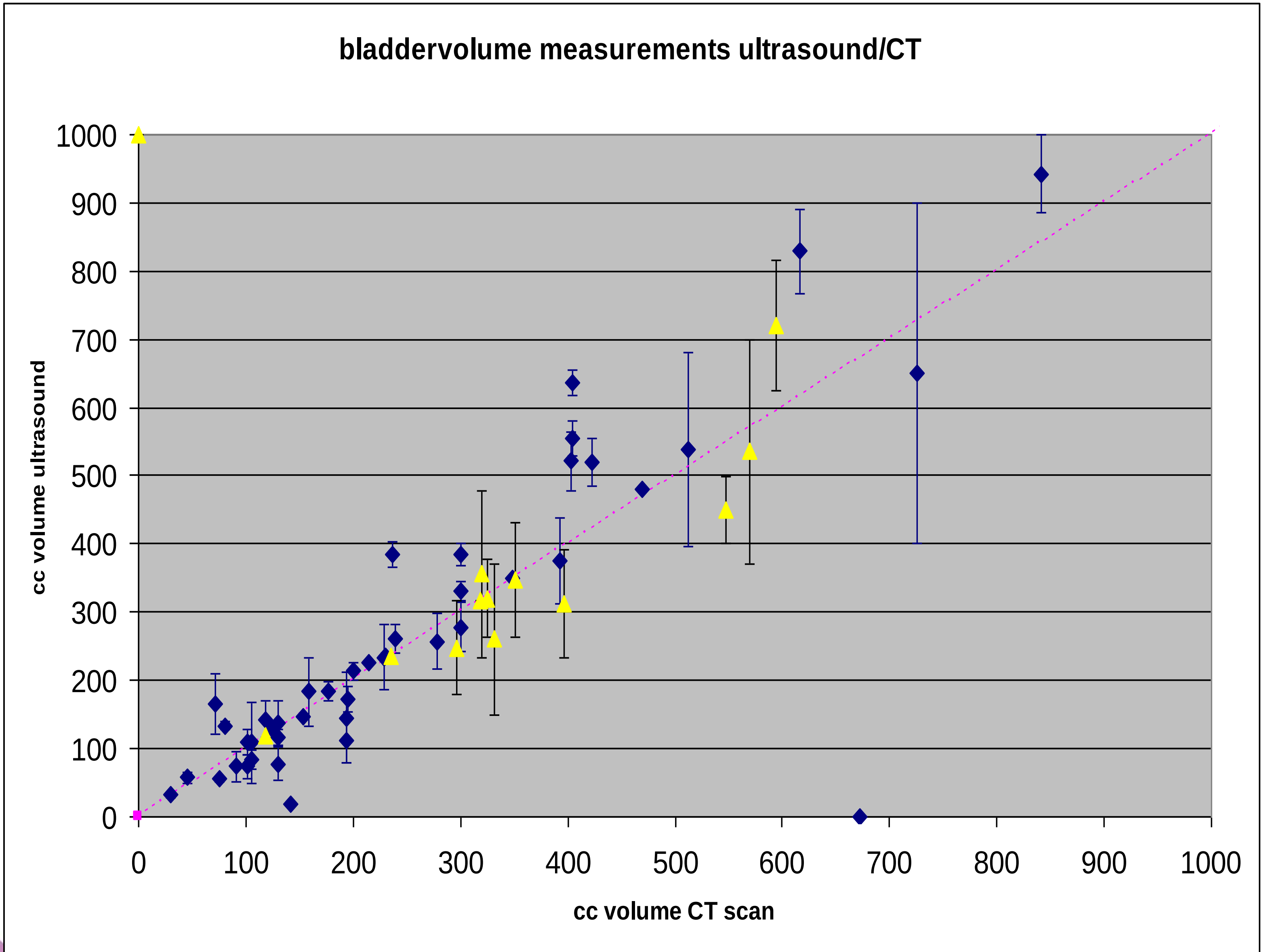
Drinking protocol:

30 min prior to treatment

+

250 cc water

Rectum patients



Drinking protocol:

60 min prior to treatment

+

350 cc water

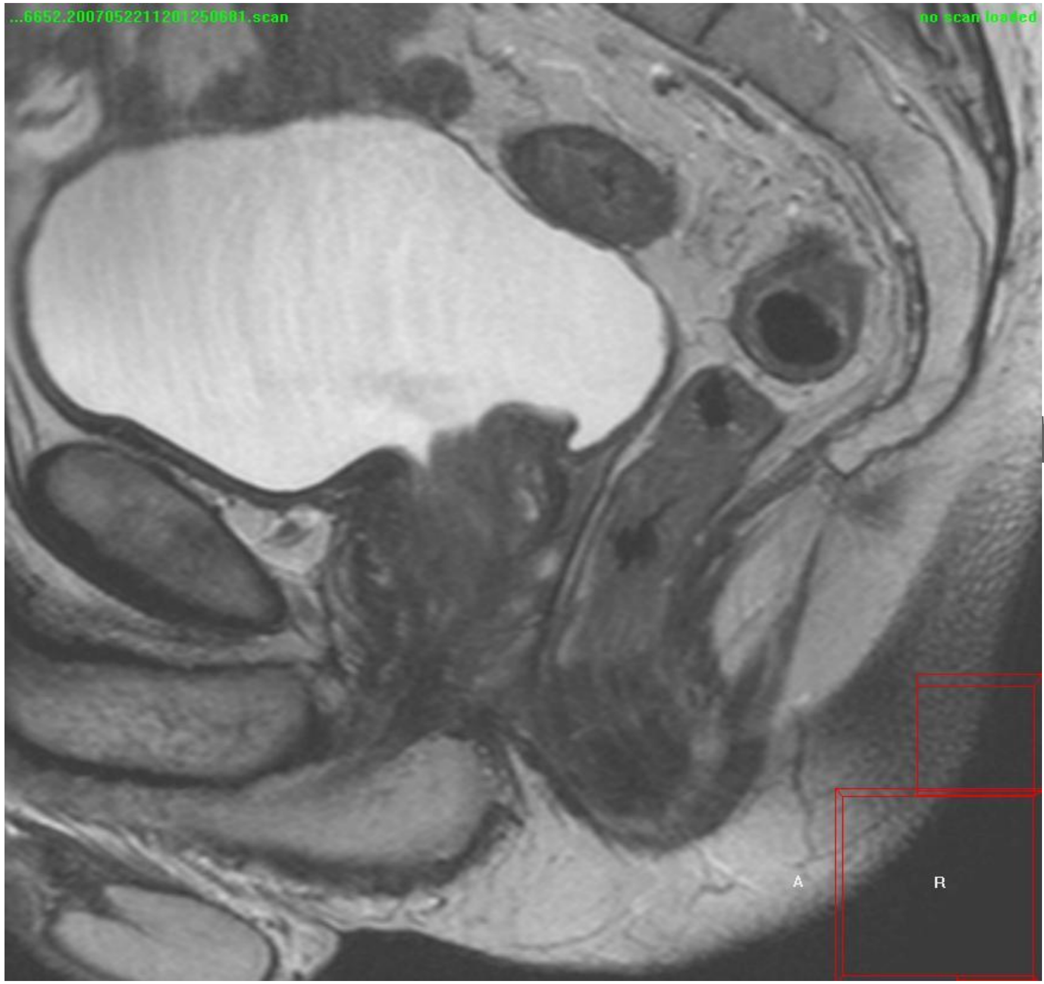
+

total 2 liter water during day

Contents

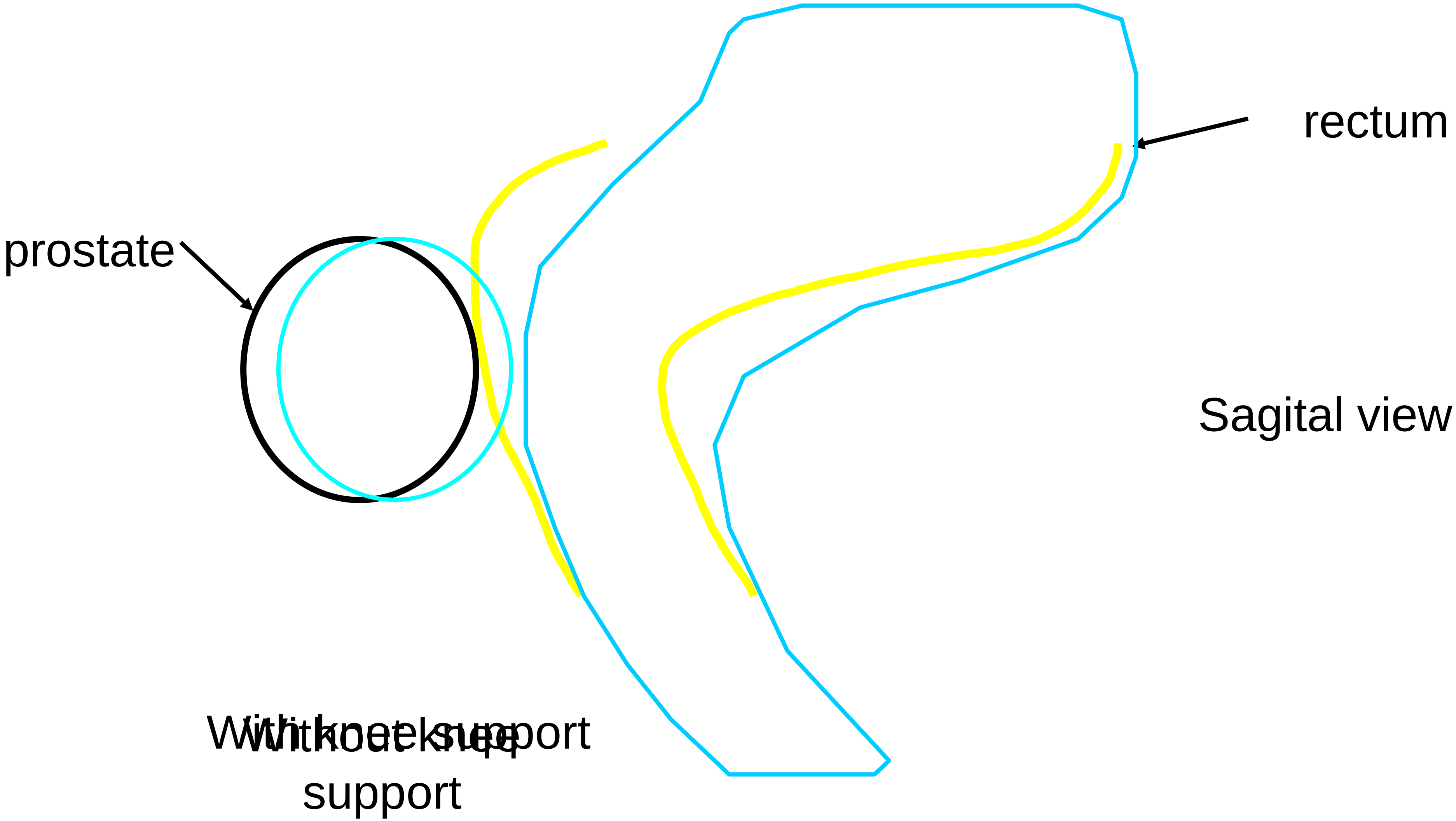
Patient Positioning

- Prostate patients
- Rectum patients
- Pelvic patients
- Lung patients



Steenbakkers et al. Int J Radiat Oncol Biol Phys. 1997

Steenbakkers et al. Int J Radiat Oncol Biol Phys. 1997



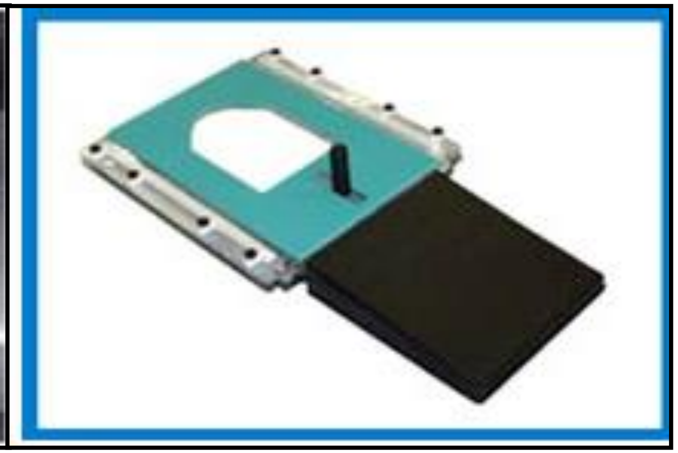
Steenbakkers et al. Int J Radiat Oncol Biol Phys. 1997

Rectum patients

Prone position

- Belly board
- Intra fraction stability prone/supine

Rectum patients



Belly board

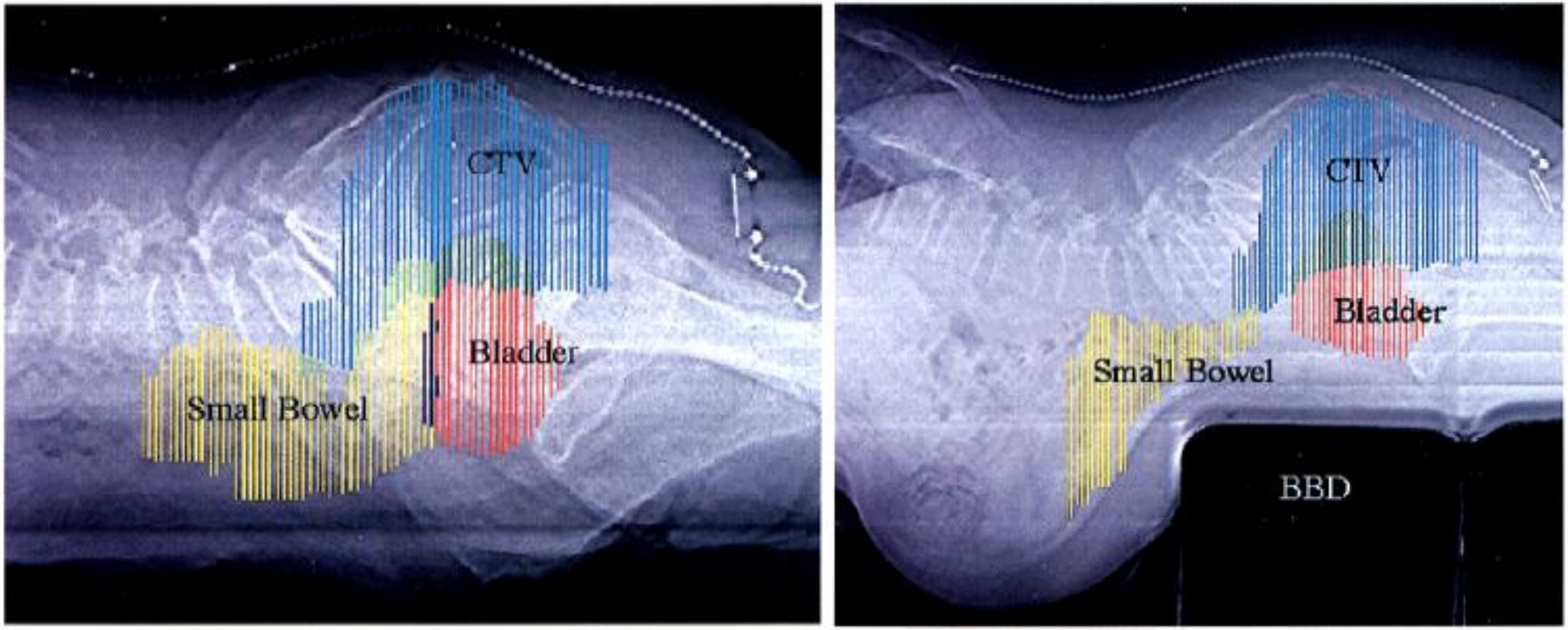


Fig. 2. Pilot localization, lateral view is shown (a) for simulation without BBD and (b) with BBD. The clinical target volume (CTV), small bowel, and bladder are shown. Note a dramatic shift in small bowel in the cephalic direction with the BBD.

Das *et al,* 1997

Rectum patients

On-line bony anatomy registration 5x5 Gy

Introduction of IMRT

RTT in the clinic: impression prone not as stable as supine

- Kilo voltage CBCT
- Prone versus supine

Rectum patients

Prone position

Supine position

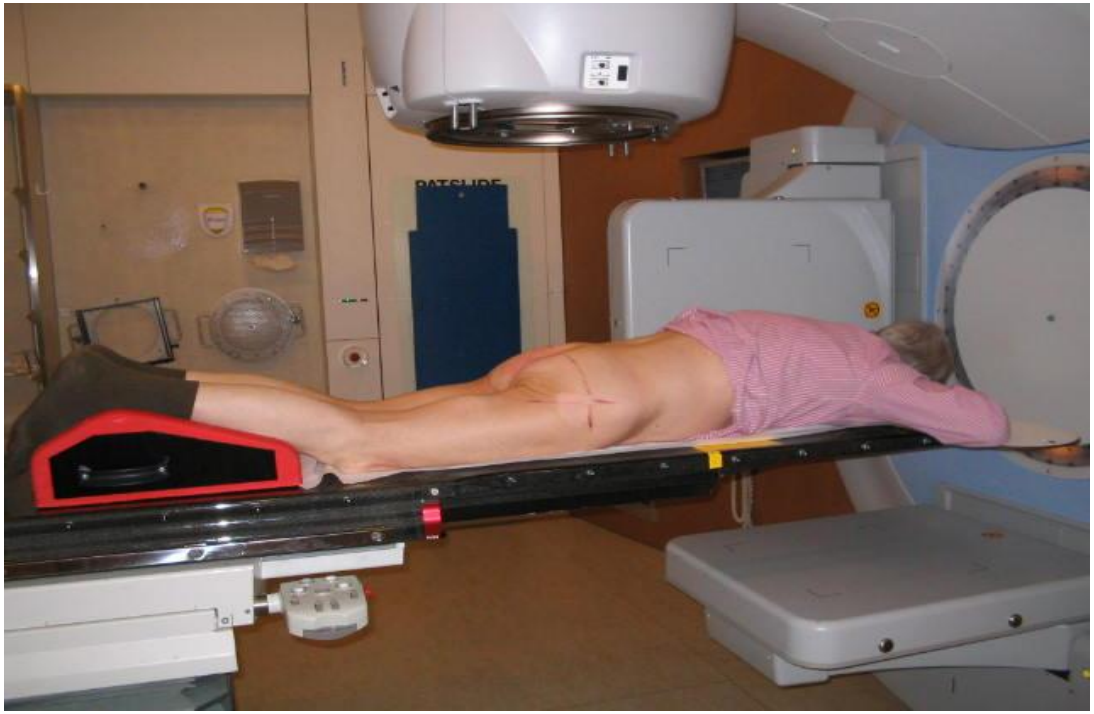
Image quality of CBCT

Rectum patients

- Arms over chest
- Knee support
- Pillow under head

✓ No interventions

Rectum patients



- Hands under forehead
- No turning of the head
- Ankle support

✓ Tape over back side of patient:	60%
✓ Repositioning on lasers between fields:	5%
✓ Additional support (like pillow):	5%
✓ No intervention:	40%

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Rectum patients

prone	Translations (mm)			Rotations (dg)		
	L-R	C-C	A-P	L-R	C-C	A-P
Mean	-0.3	0.4	-0.8	1.3	0.6	-0.1
Σ	**2.1**	**0.8**	**1.3**	**1.2**	**1.0**	**0.5**
σ	2.5	1.1	1.0	0.7	0.8	0.4
Supine	Translations (mm)			Rotations (dg)		
	L-R	C-C	A-P	L-R	C-C	A-P
Mean	0.1	-0.4	-0.5	-0.5	0.2	0.0
Σ	**0.5**	**0.4**	**0.5**	**0.7**	**0.3**	**0.3**
σ	0.9	0.6	0.6	0.8	0.4	0.3

$P<0.05$

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Rectum patients

prone	Translations (mm)			Rotations (dg)		
	L-R	C-C	A-P	L-R	C-C	A-P
Mean	-0.3	0.4	-0.8	1.3	0.6	-0.1
Σ	2.1	0.8	1.3	1.2	1.0	0.5
σ	**2.5**	**1.1**	**1.0**	0.7	**0.8**	0.4
Supine	Translations (mm)			Rotations (dg)		
	L-R	C-C	A-P	L-R	C-C	A-P
Mean	0.1	-0.4	-0.5	-0.5	0.2	0.0
Σ	0.5	0.4	0.5	0.7	0.3	0.3
σ	**0.9**	**0.6**	**0.6**	0.8	**0.4**	0.3

P<0.05

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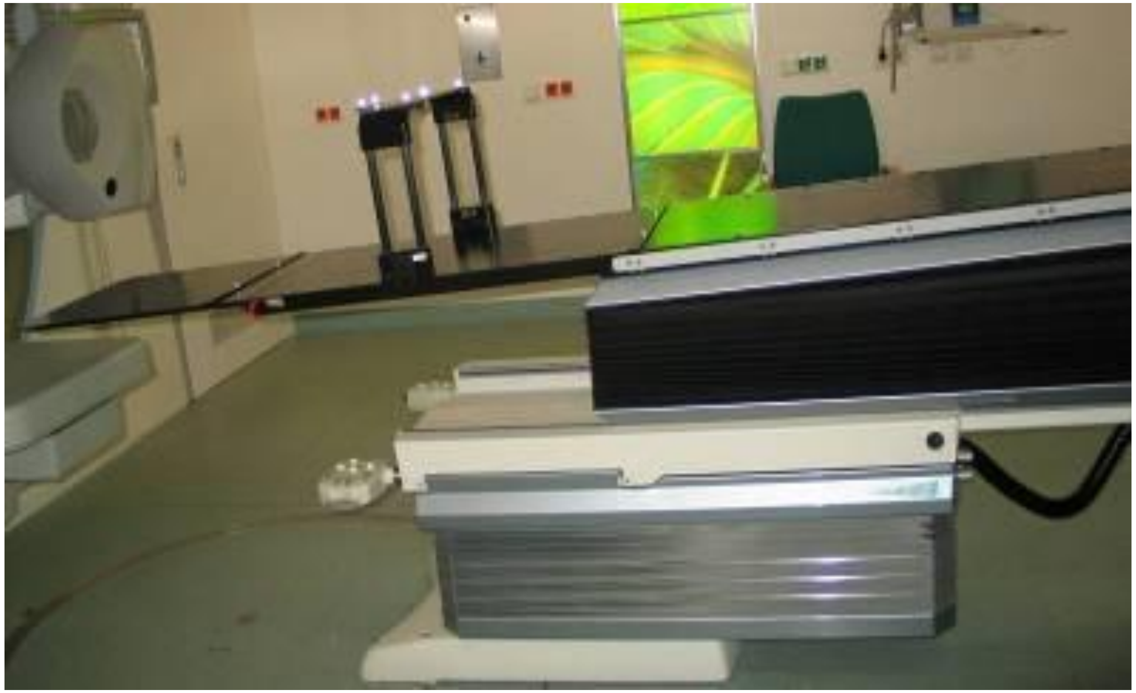
Rectum patients

Intra fraction motion in prone is around a factor of 2 or more larger than supine

(with this immobilisation)

Pelvic patients and hexapod



Without proper fixation:

Correction of 3° rotational error

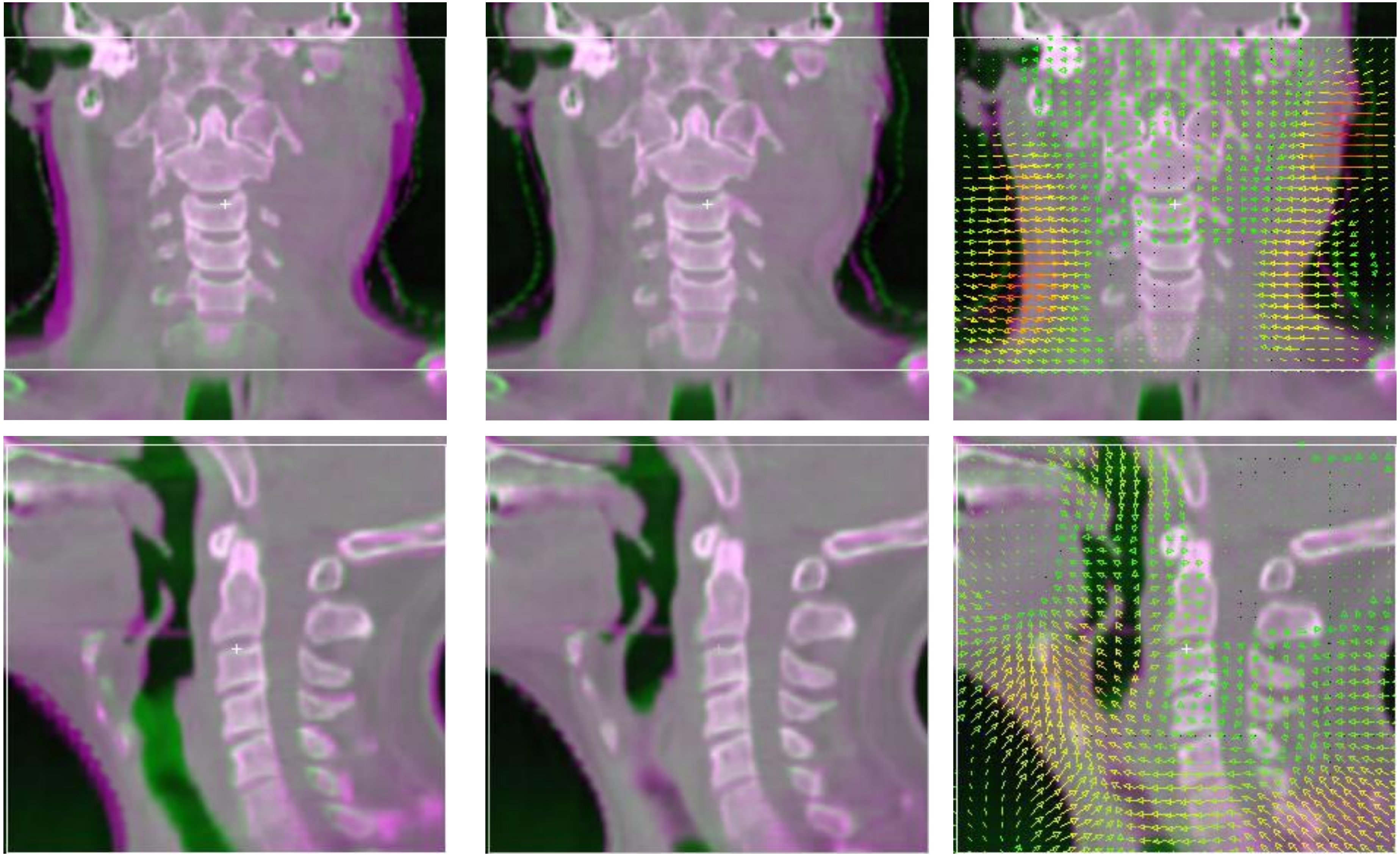
→ displacement of ~ 2mm

Courtesy Matthias Guckenberger, Wuerzburg

Rigid registration | BSpline registration | Deformation field

Coronal

Sagittal



Deformable registration to asses anatomy changes

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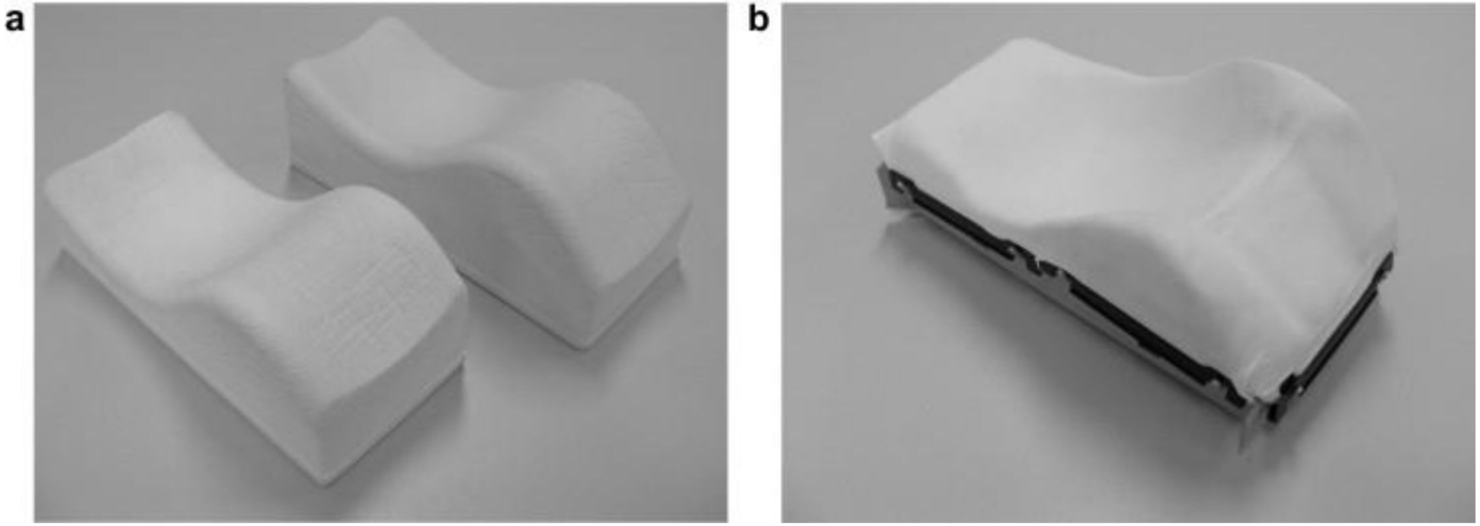
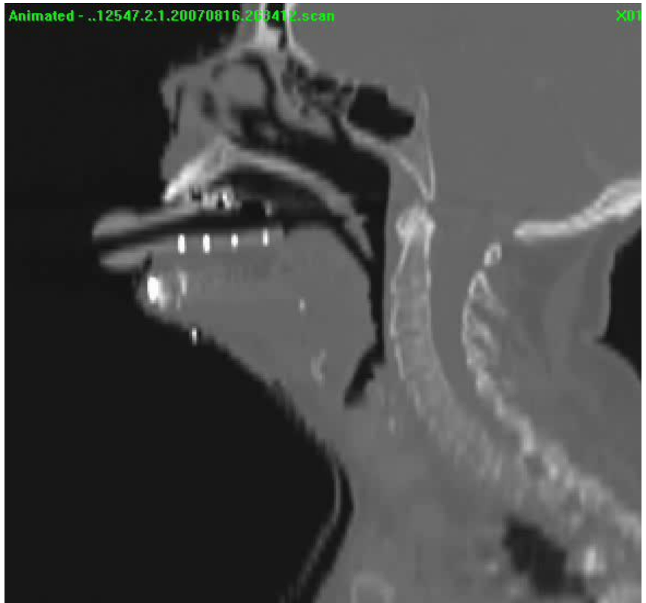
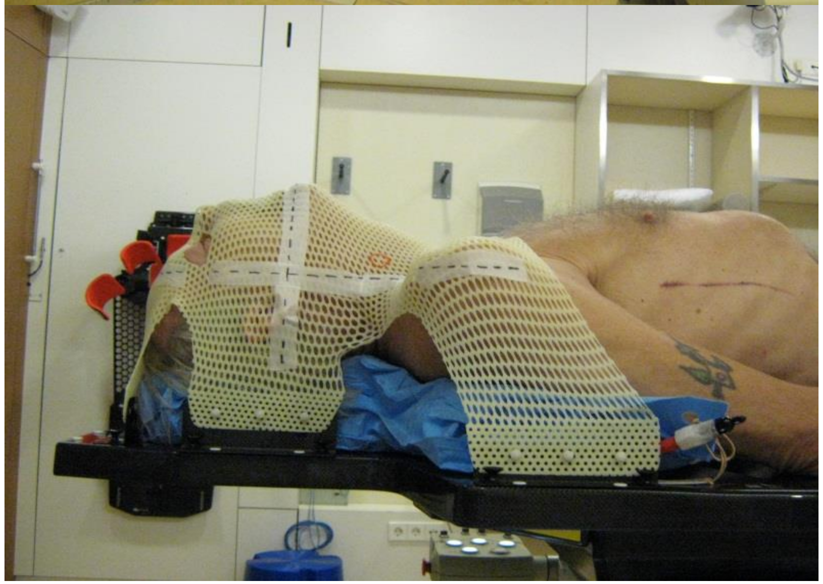


- ✓ Reduction of systematic error for inter and intra fraction motion.
- ✓ Reduction of deformations.

Houweling et al. 2010





Head and Neck

Hypofractionated lung treatment

On-line lung tumor match with CBCT: 3 x 18 Gy (old protocol without arc therapy and inline scanning)

Aligning the patient:	5 min
First CBCT scan:	4 min
Registration:	5 min
Manual table shift:	3 min
Second CBCT scan:	4 min
Evaluation CBCT scan:	1 min
Beam delivery:	25 min
Post treatment CBCT scan:	4 min

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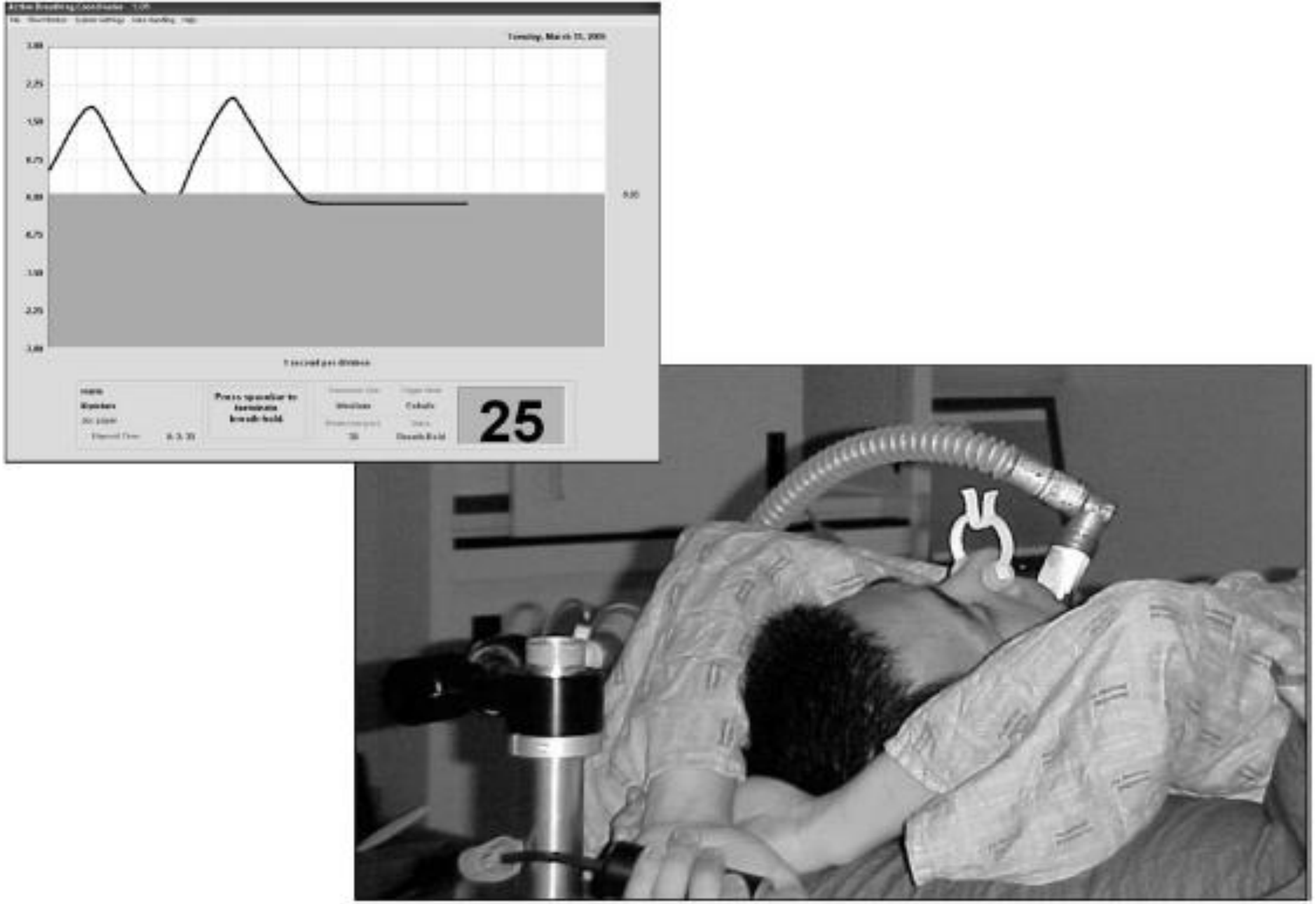
100x real speed

- Comfortable ‘camping matras’

Comfortable 'camping matras'
Intra fraction monitoring for outliers
Try-out session

Managing breathing motion

- Breath hold techniques
- Respiratory monitoring system
- Coaching



Courtesy to Laura Dawson

CC Reproducibility of ABC Breath Hold

	No. Images	Inter-fract. Reprod. (σ)	Intra-fract. Reprod. (σ)
Michigan	262	4.4 mm	2.5 mm
Toronto	257	3.4 mm	1.5 mm

IGRT required for maximal PTV reduction

Courtesy to Laura Dawson

Dawson LA. IJROBP 2001
Eccles, C, IJROBP, 2005

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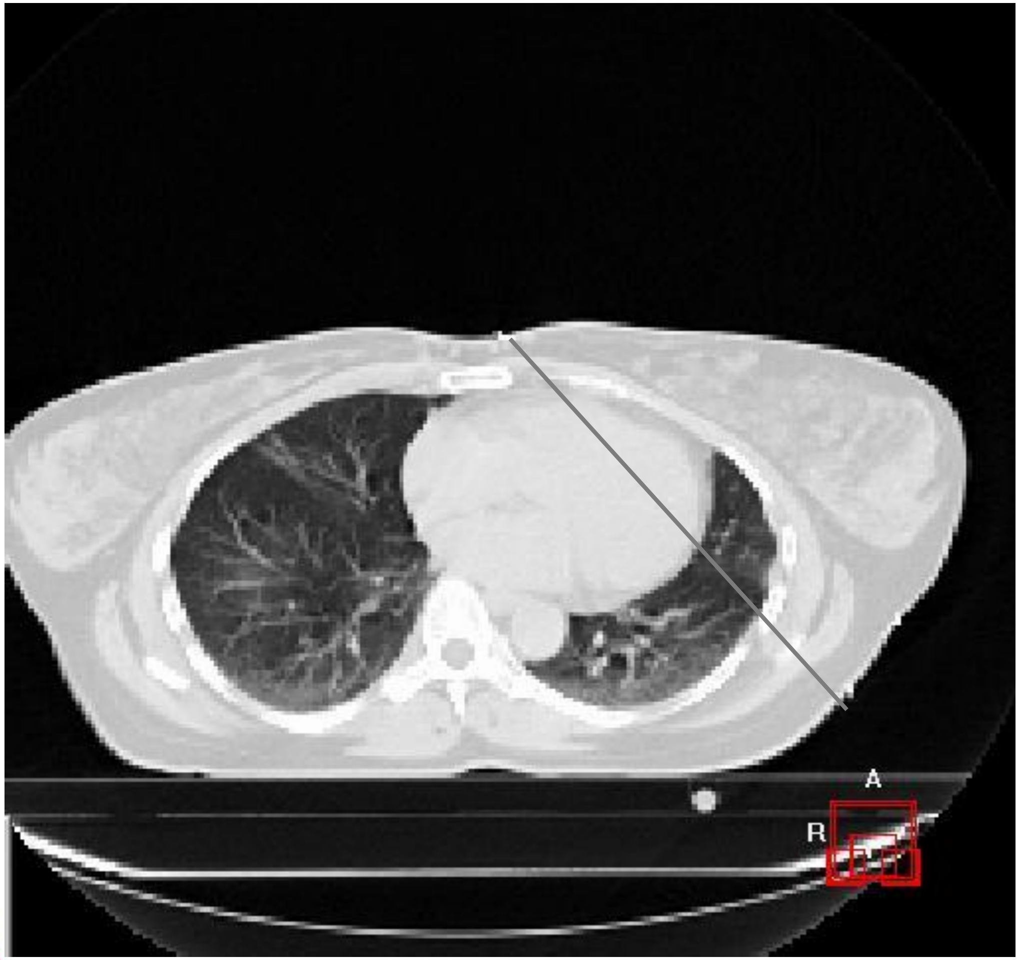
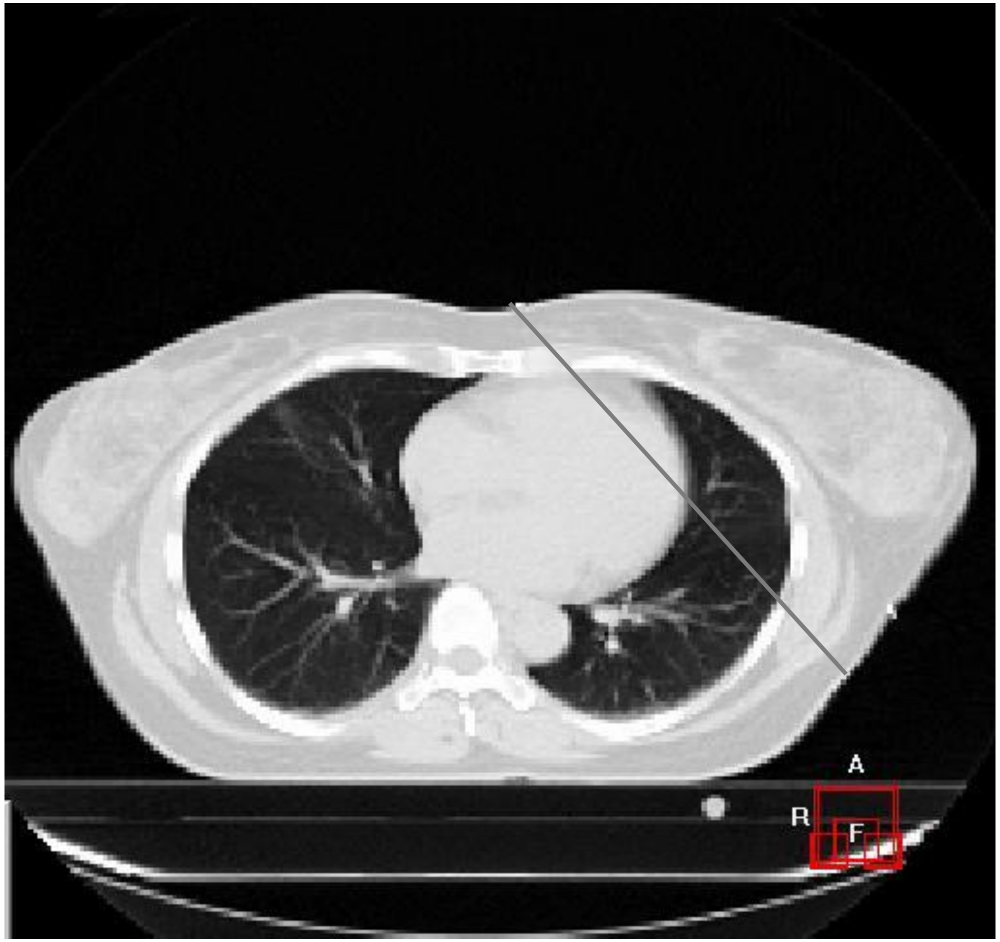
Breath hold

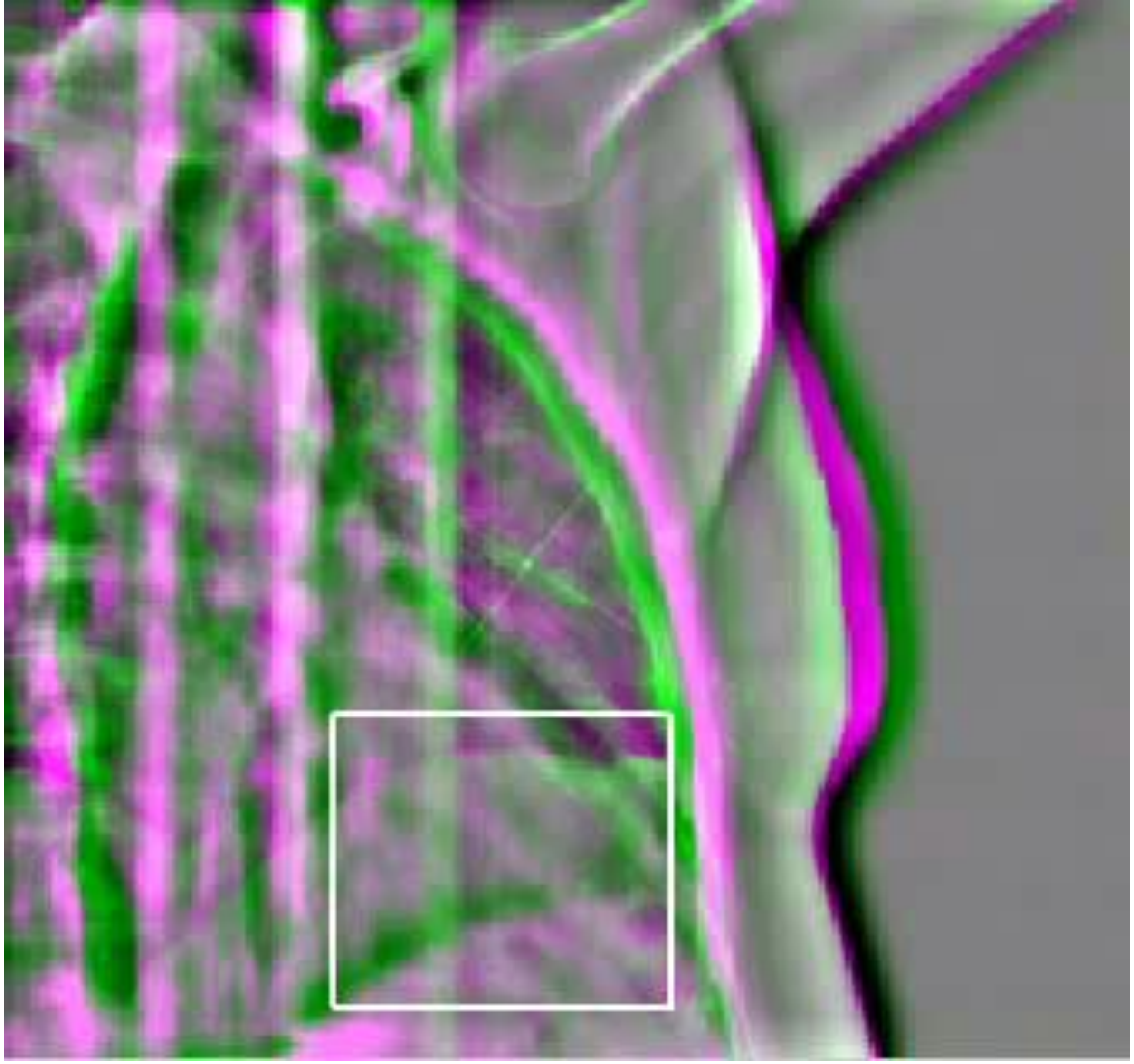
Normal inspiration



Deep inspiration



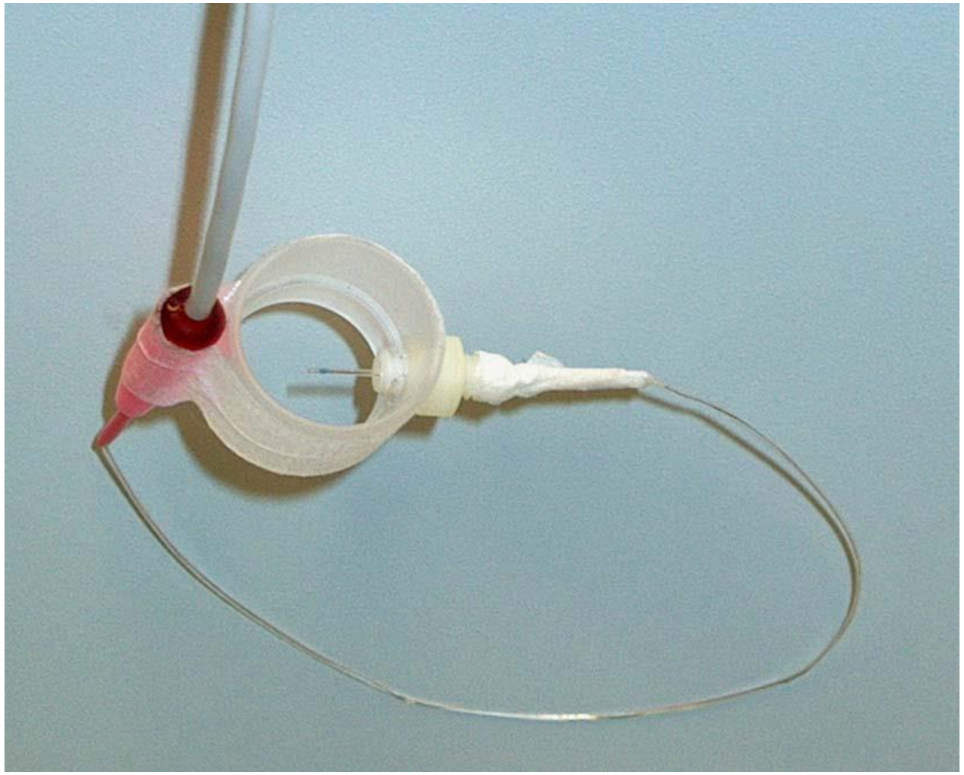
Jan-Jakob Sonke

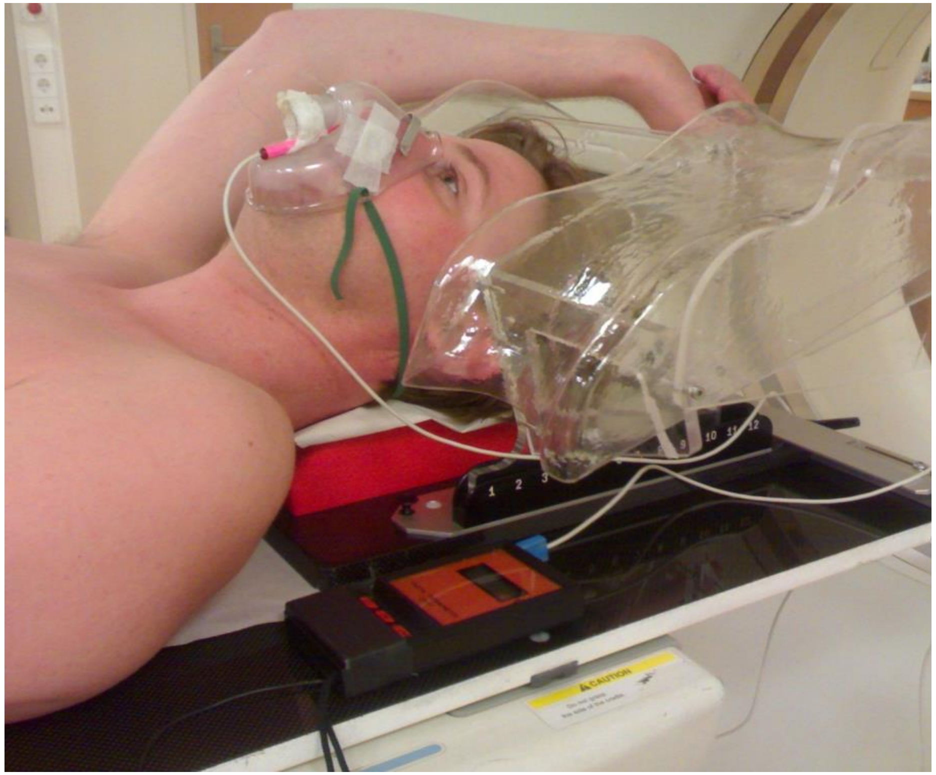


Imaging for reproducible breathhold,

- kV is the tool
- ✓ BH is moving the OAR away from target volume

Respiratory monitoring system





- 4D CBCT scans with and without oxygen mask
- 3D tumor motion was assessed for tumor mean position and amplitude

Respiratory monitoring system

With oxygen mask

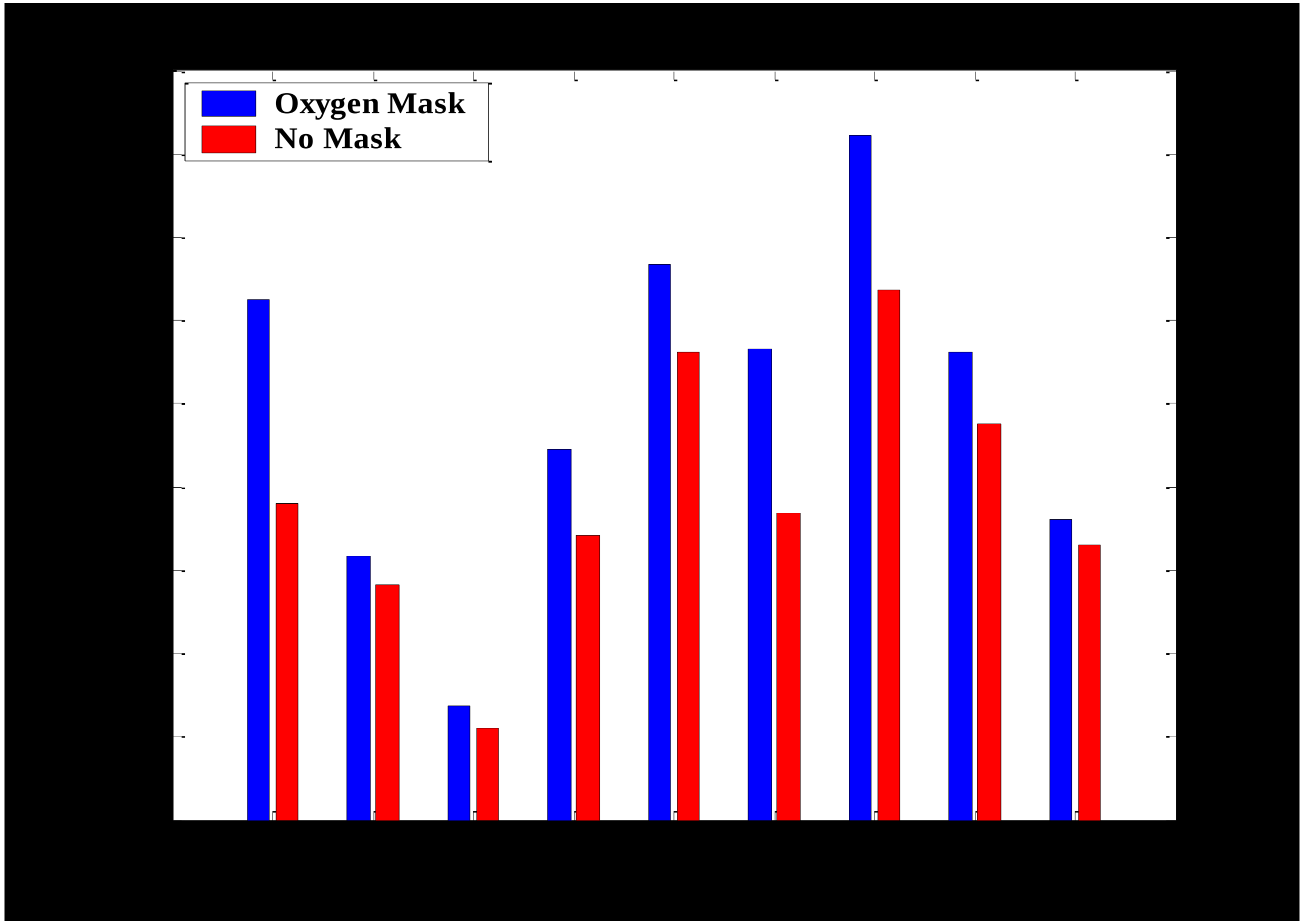
	LR (cm)	CC (cm)	AP (cm)
Σ	0.18	0.23	0.23
σ	0.16	0.19	0.19
Mean	0.06	0.03	0.00

Without oxygen mask

	LR (cm)	CC (cm)	AP (cm)
Σ	0.15	0.21	0.22
σ	0.18	0.17	0.20
Mean	0.04	0.08	-0.09

No significant difference in tumor mean position

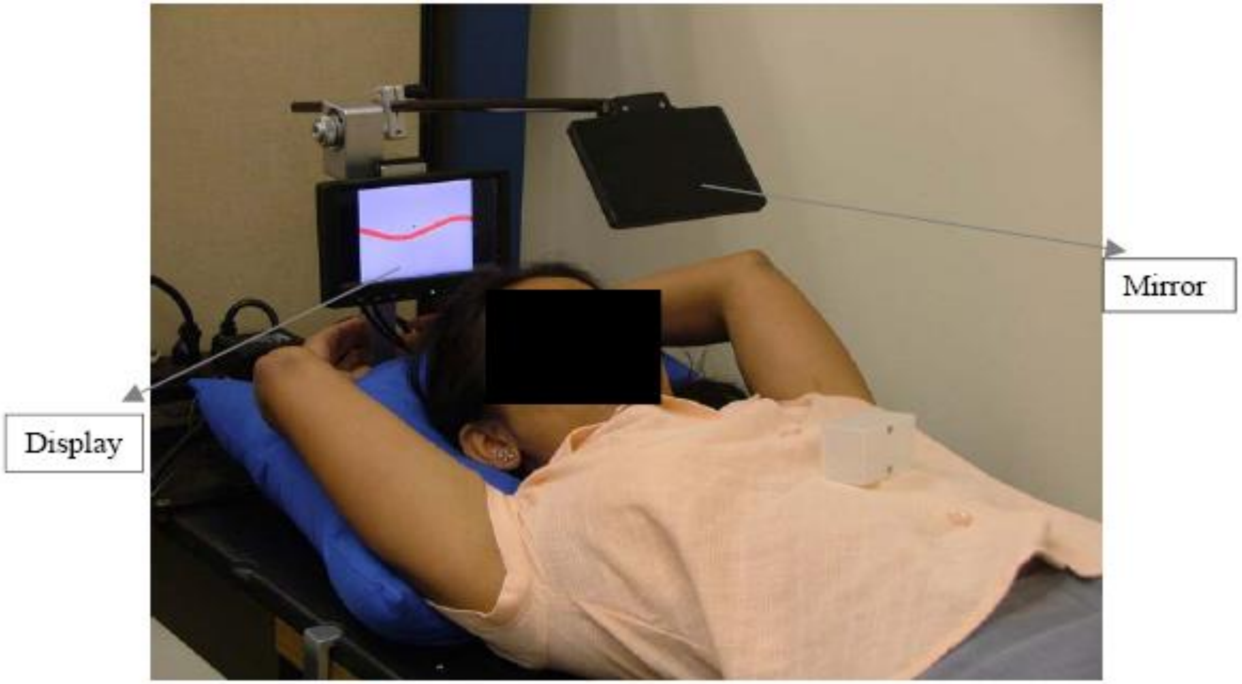
Respiratory monitoring system

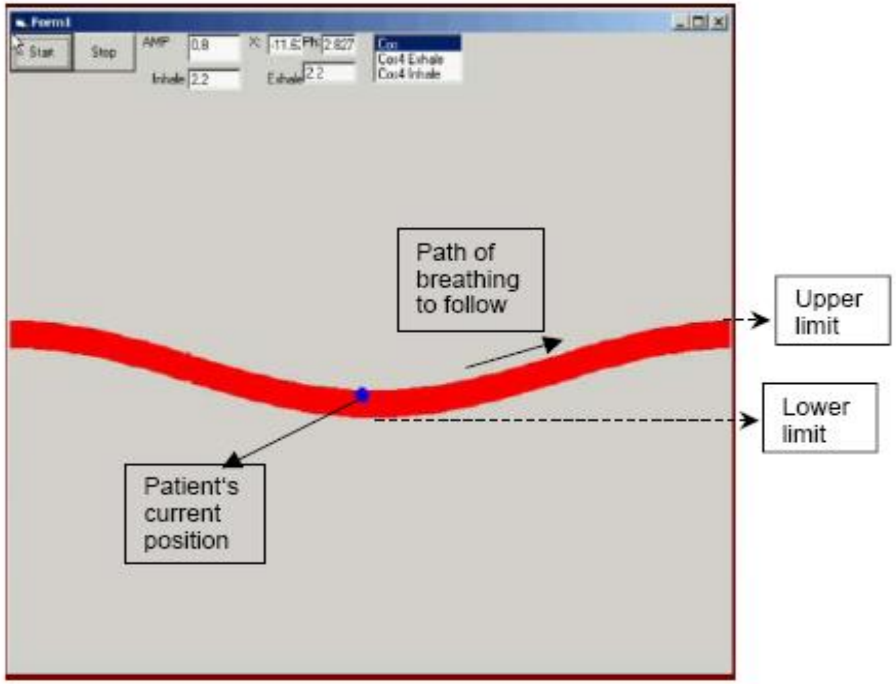


M = 29%, SD = 19%, p = 0.0017

Relative change in breathing amplitude

Coaching


Mirror
Display


Path of breathing to follow
Upper limit
Lower limit
Patient's current position

Coaching

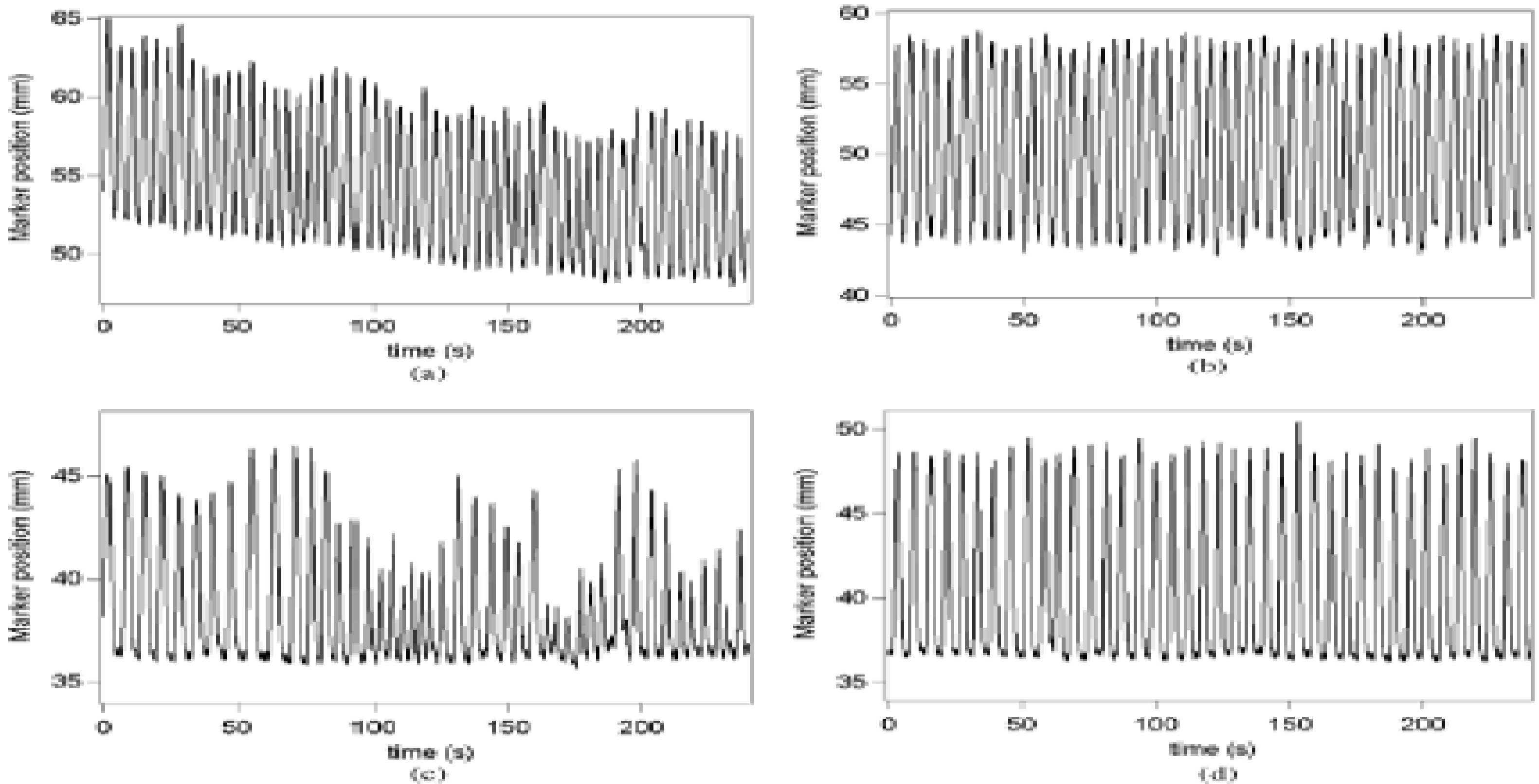
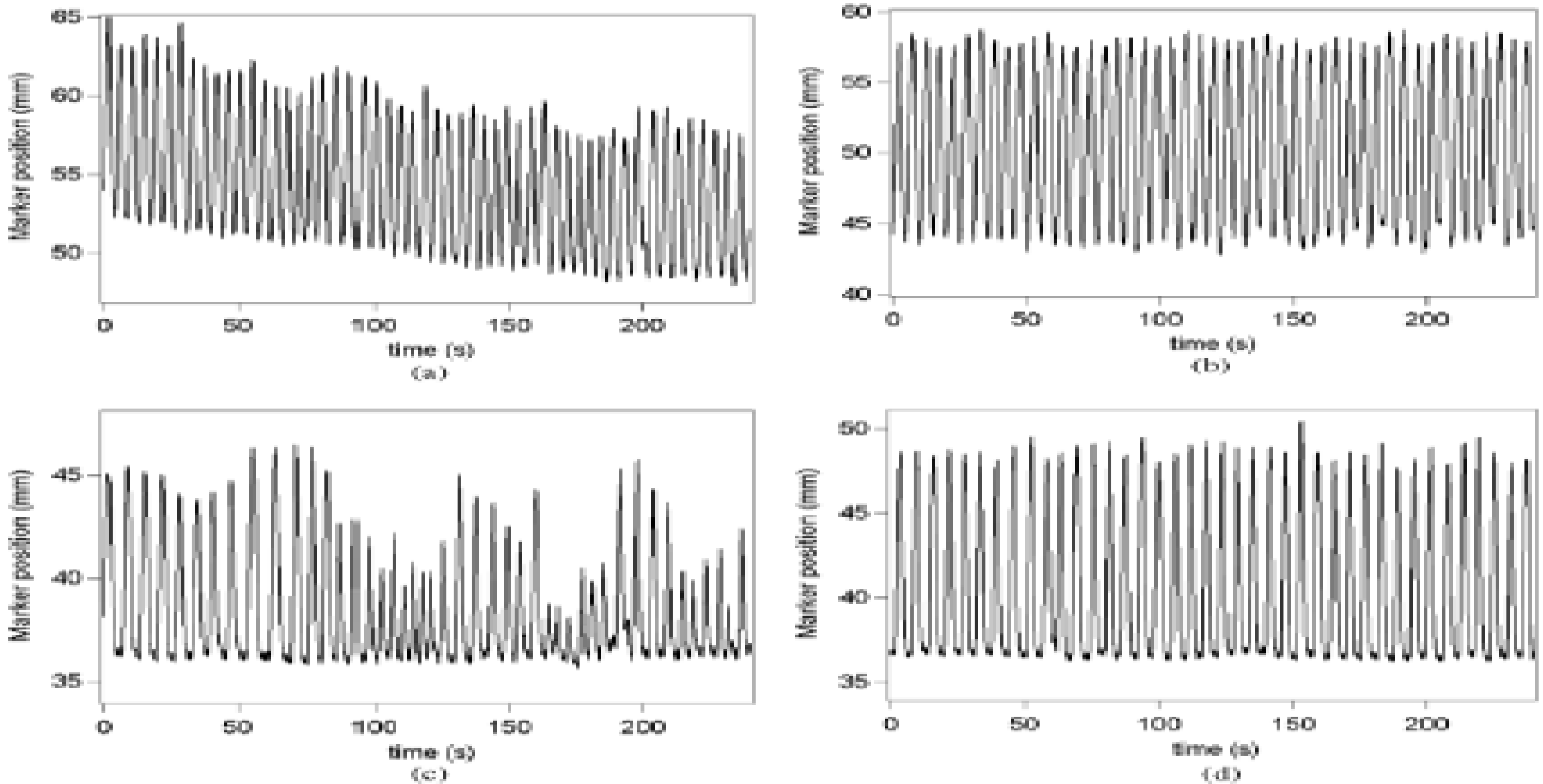


Figure 2. Example of time dependence of breathing trace acquired during free breathing (a) and (c) and audio–visual coaching (b) and (d). Data sets (a) and (b) belong to one volunteer while (c) and (d) belong to another. The free breathing data exhibit baseline shifts (a) and irregular breathing (c). Those problems were eliminated with breath coaching (b, d).

Neicu *et al. 2006*

Coaching

Again some caution: same procedure for CT and treatment planning



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Neicu *et al. 2006*

Conclusie

IGRT does **not** make patient positioning and preparation obsolete

- **Intra-fraction motion**
- Rotational and deformation errors
- Off-line protocols
- Moving the organs at risk away from target volume

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- **Moving the organs at risk away from target volume**

Conclusie

https://espace.cern.ch/ULICE-results/Shared%20Documents/D.JRA_5.1_public.pdf

‘Recommendations for organ depending optimized fixation systems’

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Image Guided Proton Therapy

Jan-Jakob Sonke

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Acknowledgements

- Martijn Engelsman
- Tony Lomax
- Hanne Kooij
- Coen Rasch

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Proton Therapy

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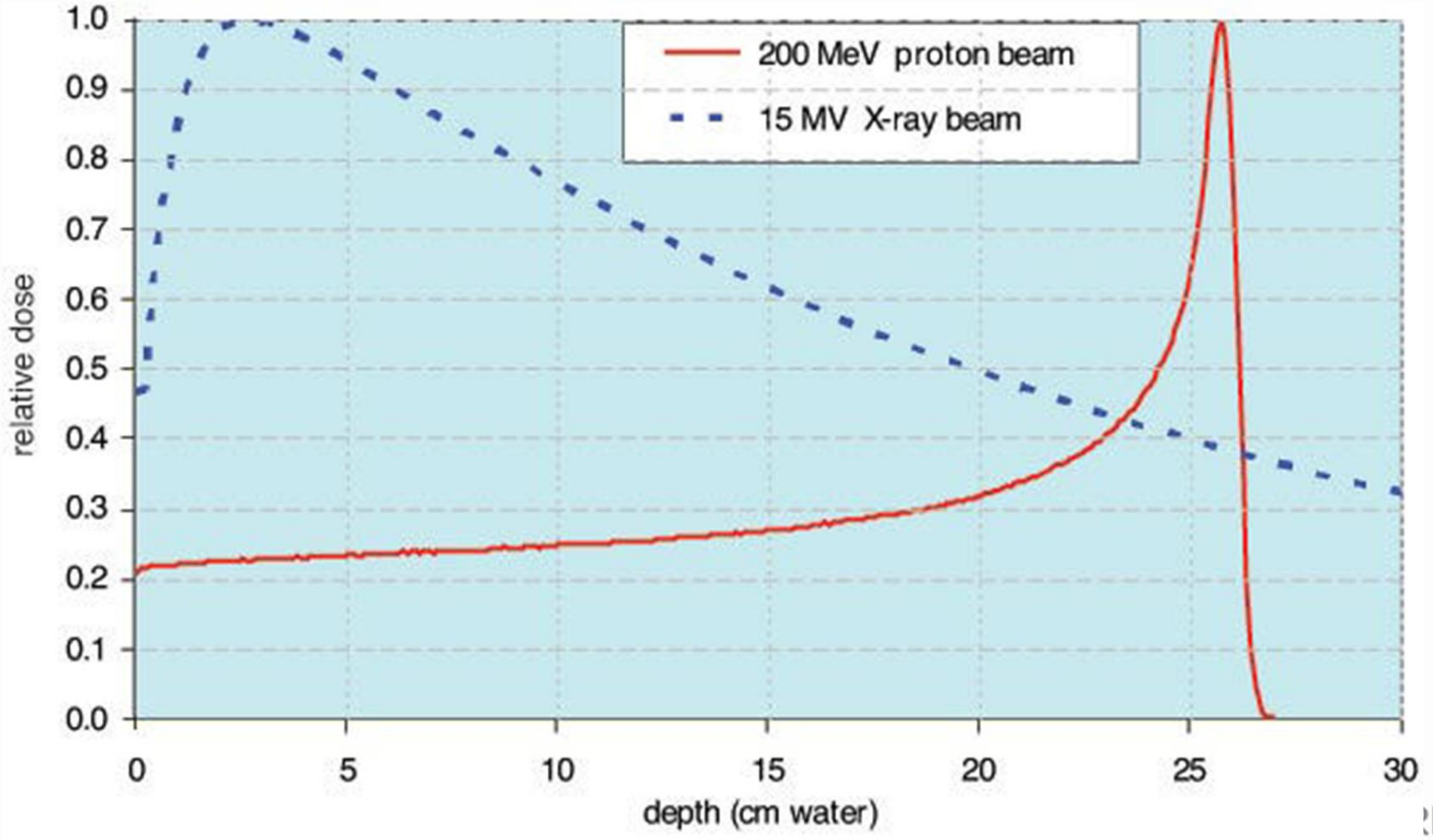
Protons versus photons
Favorable beam properties: Bragg peak



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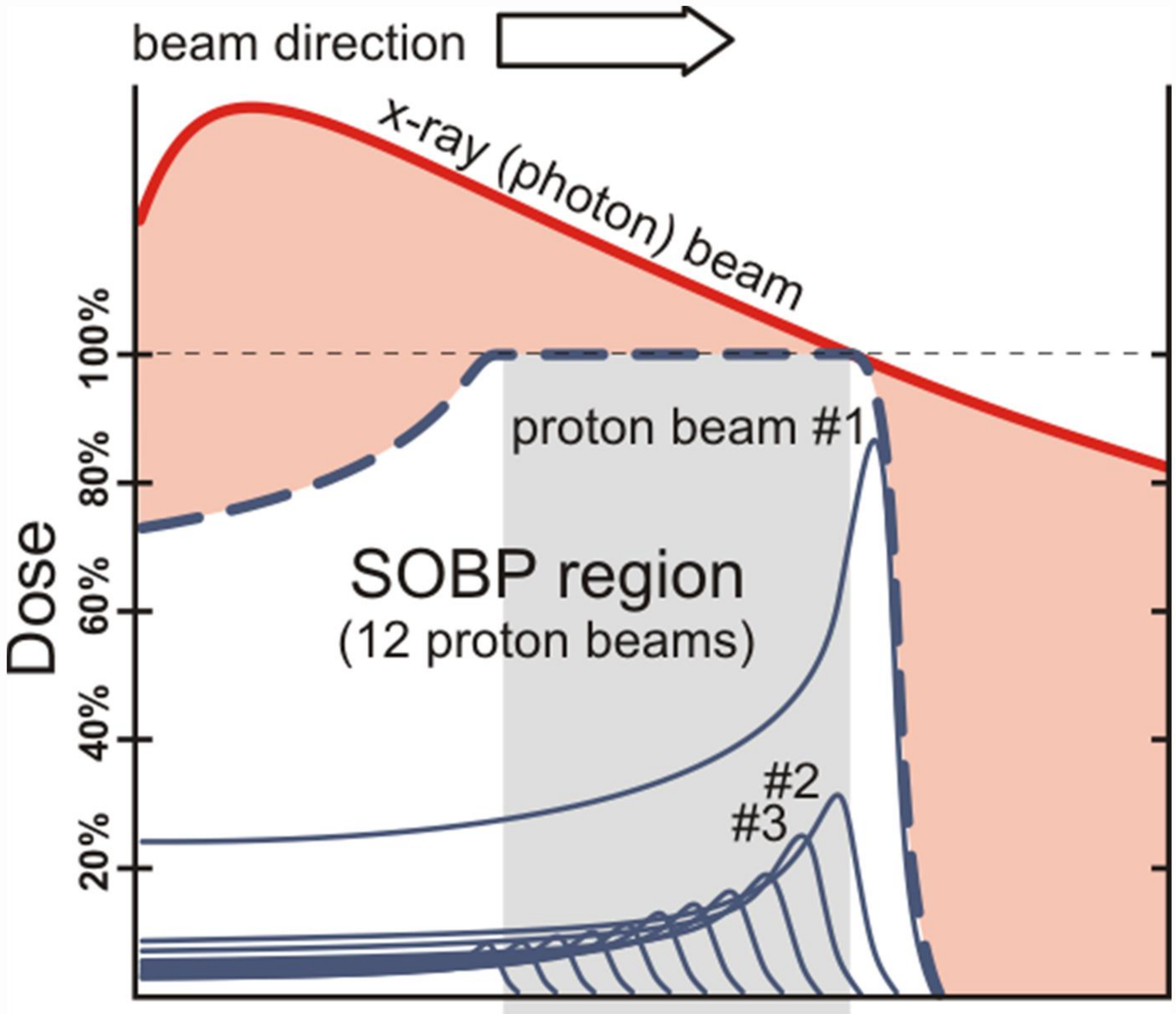
medicalphysicsweb.org

Protons versus photons
Favorable beam properties: Bragg peak



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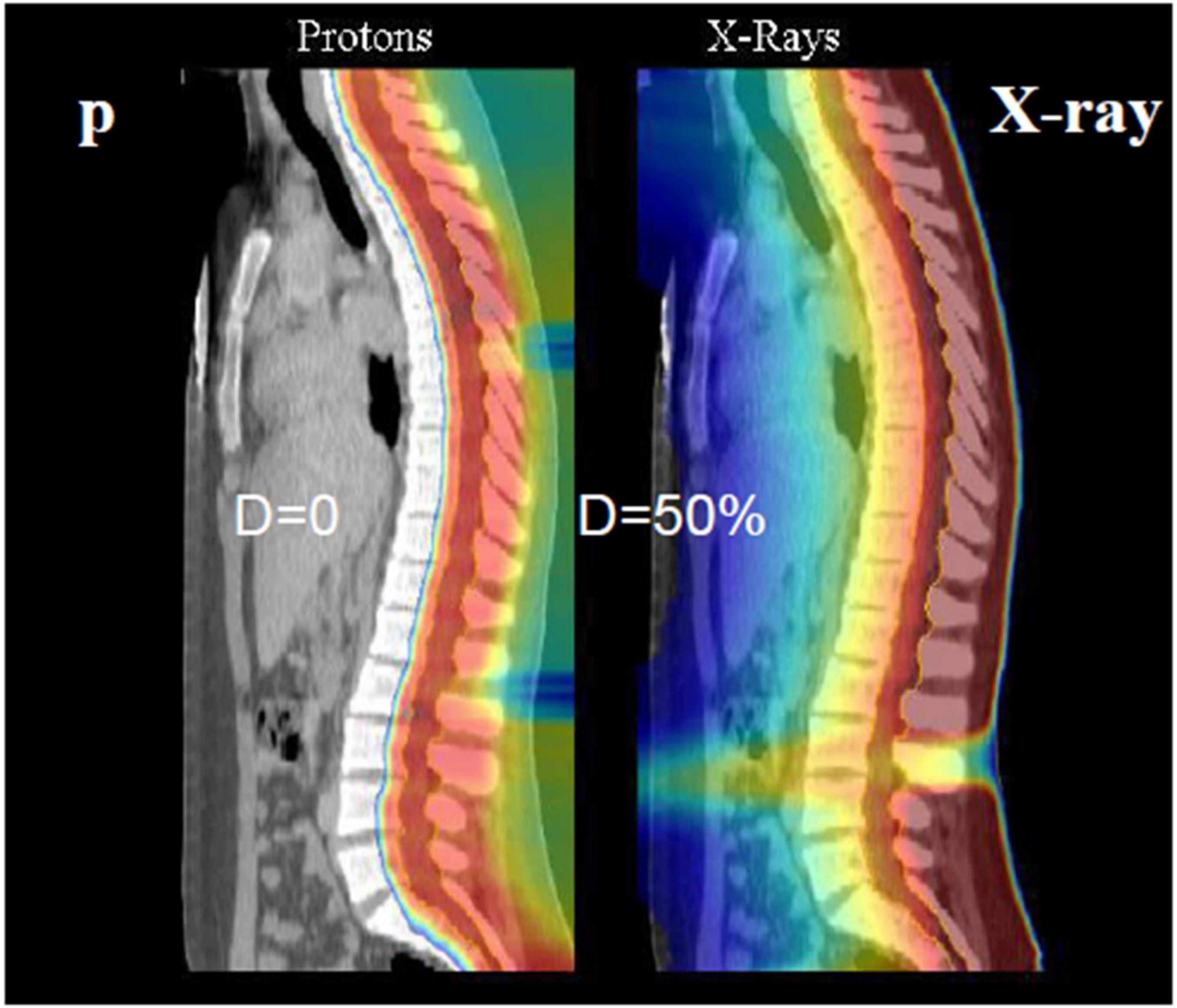
en.wikipedia.org/wiki/Proton_therapy

Craniospinal irradiation



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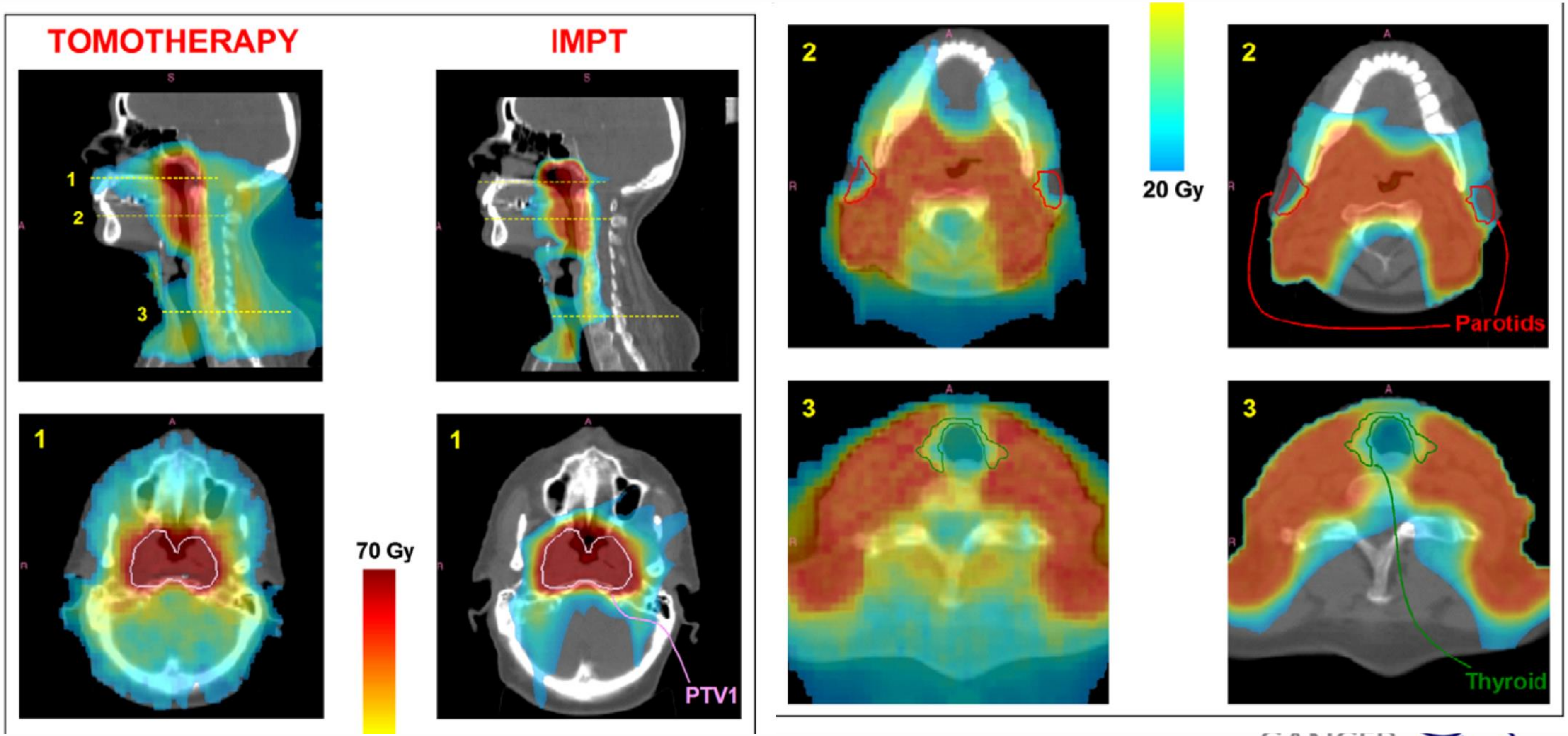
Tomo vs Proton nasopharynx



Widesott et al. 2009

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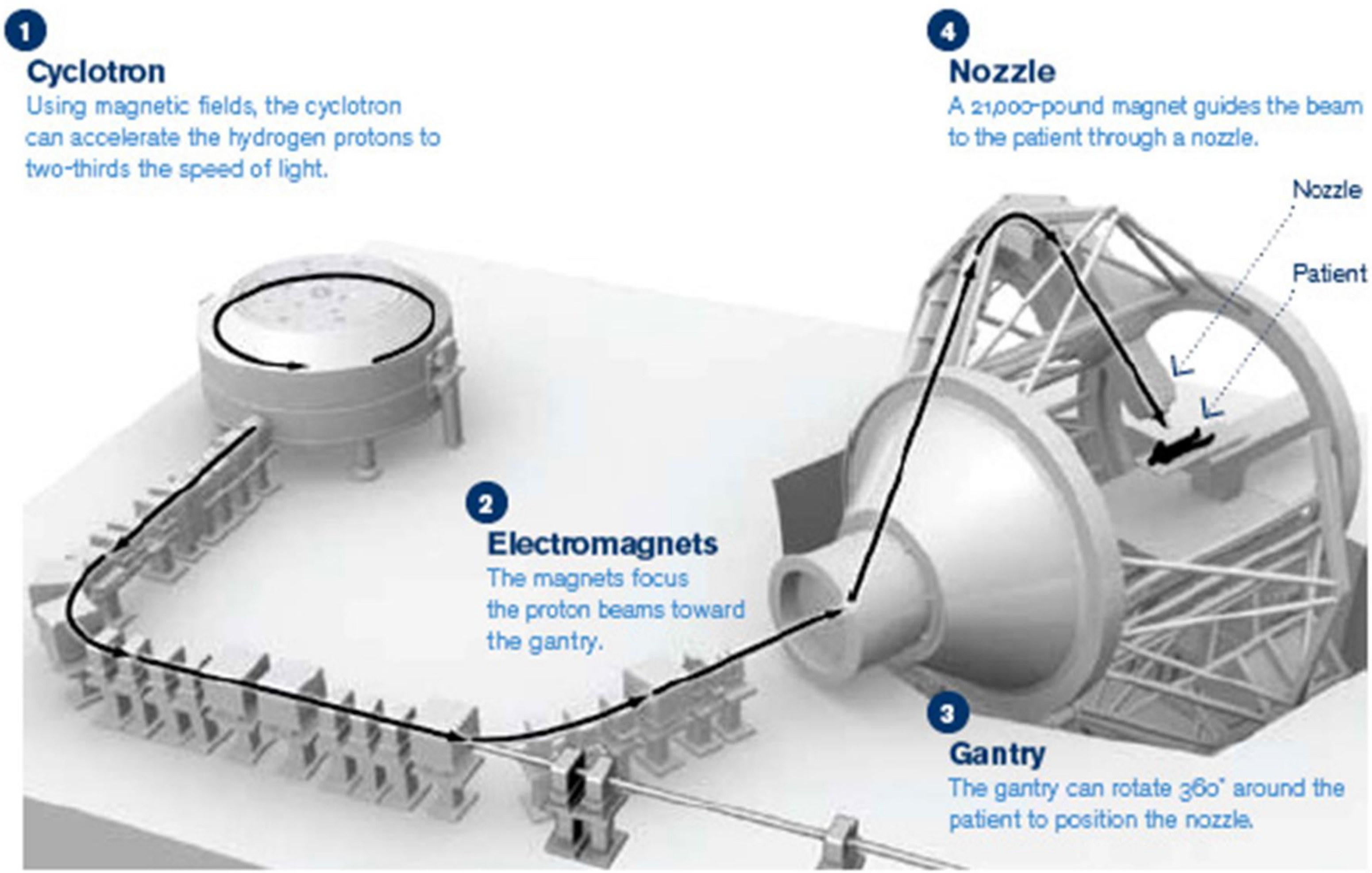
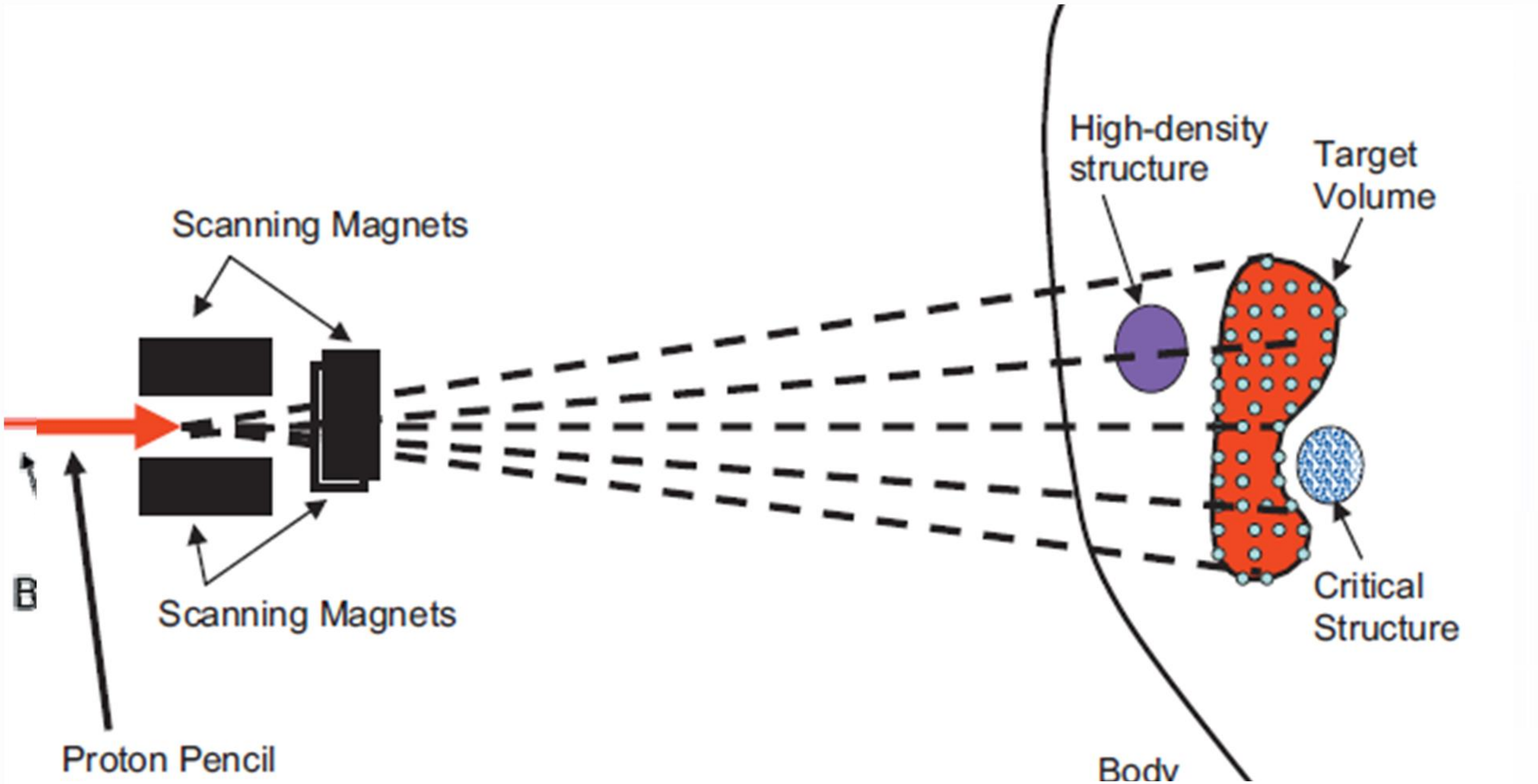
Large Facilities



symmetrymagazine.org

Proton Delivery Systems



Pencil Beam Scanning

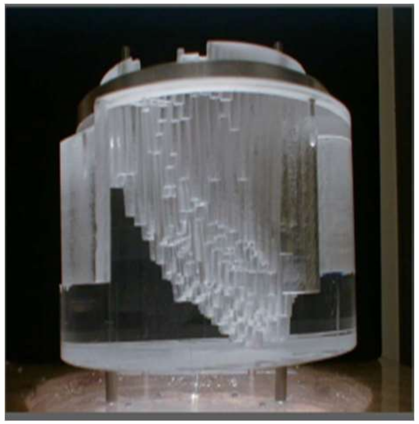
Double scattering versus Scanning

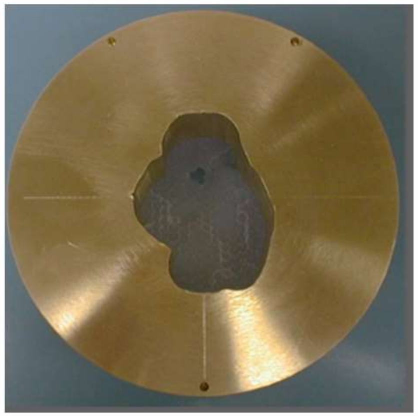
Double Scattering

- Distal conformality
- No intensity modulation
- Difficult for dose painting
- Time consuming
- Adaptation cumbersome

Scanning

- Distal + proximal conformality
- Intensity Modulation
- Dose painting
- Faster to deliver
- Easier to adapt





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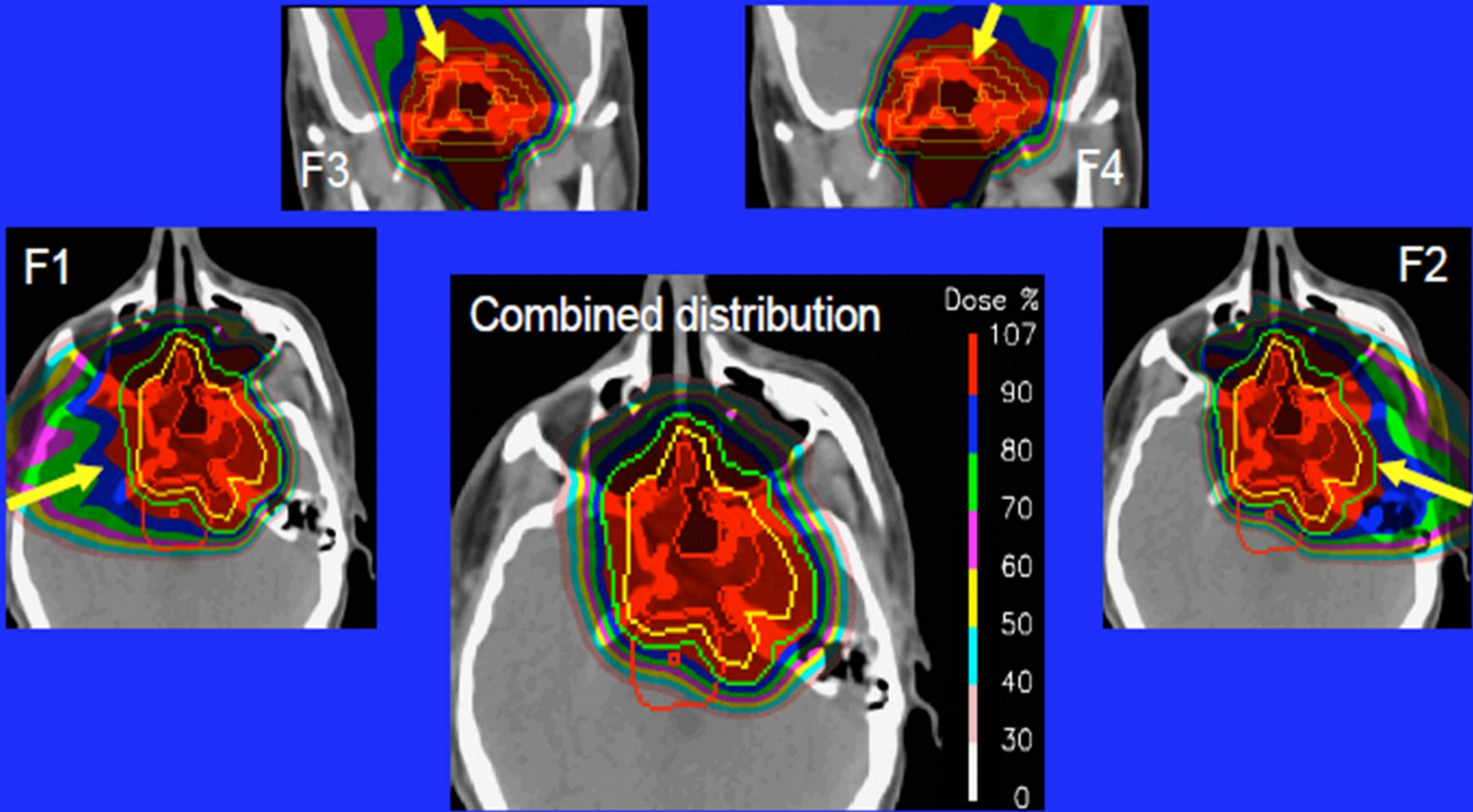
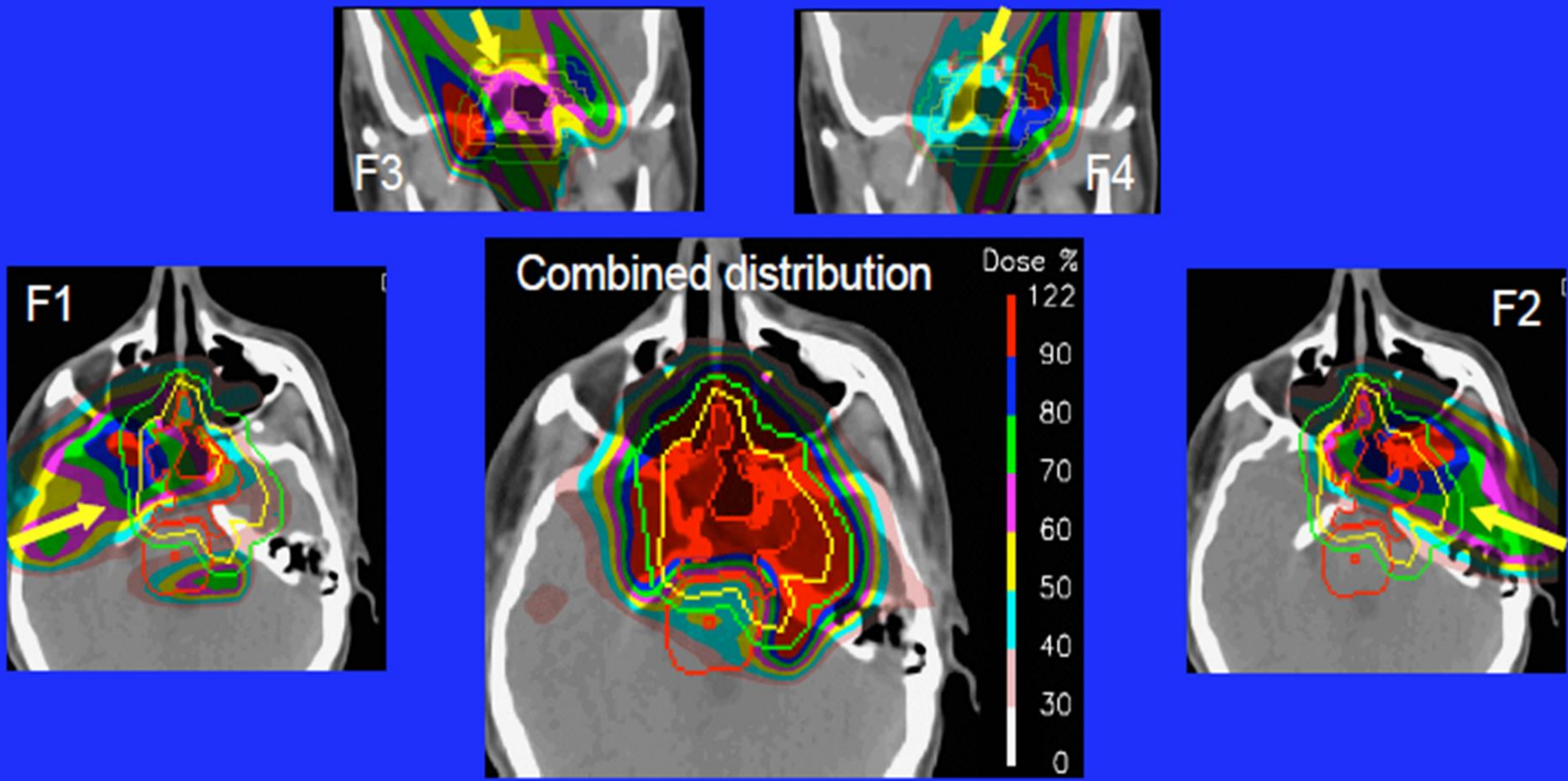
Single Field, Uniform Dose (SFUD)

A SFUD plan consists of the addition of one or more individually optimised fields.



Note, each individual field is homogenous across the target volume

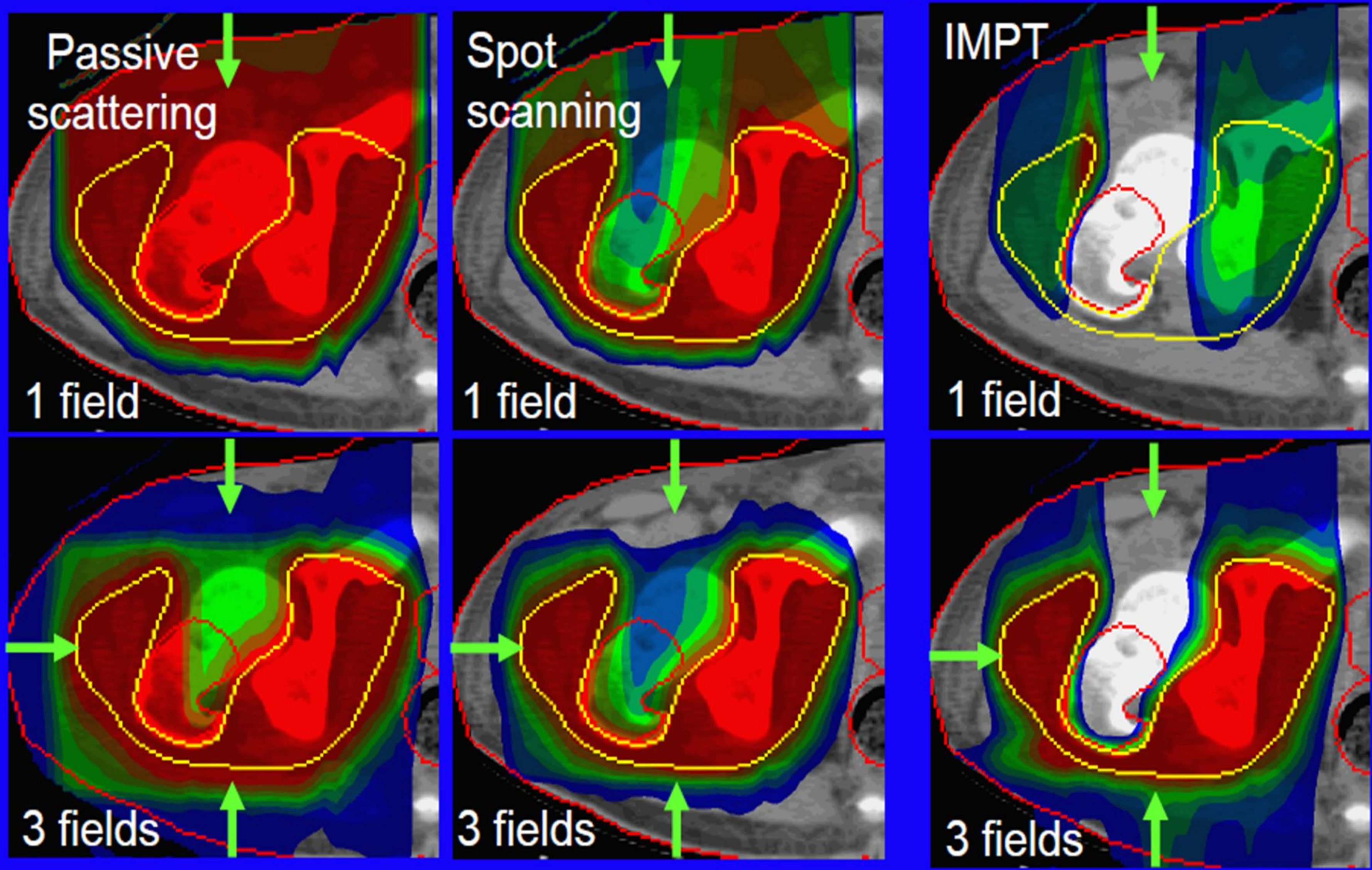
The simultaneous optimisation of all Bragg peaks from all incident beams. E.g..



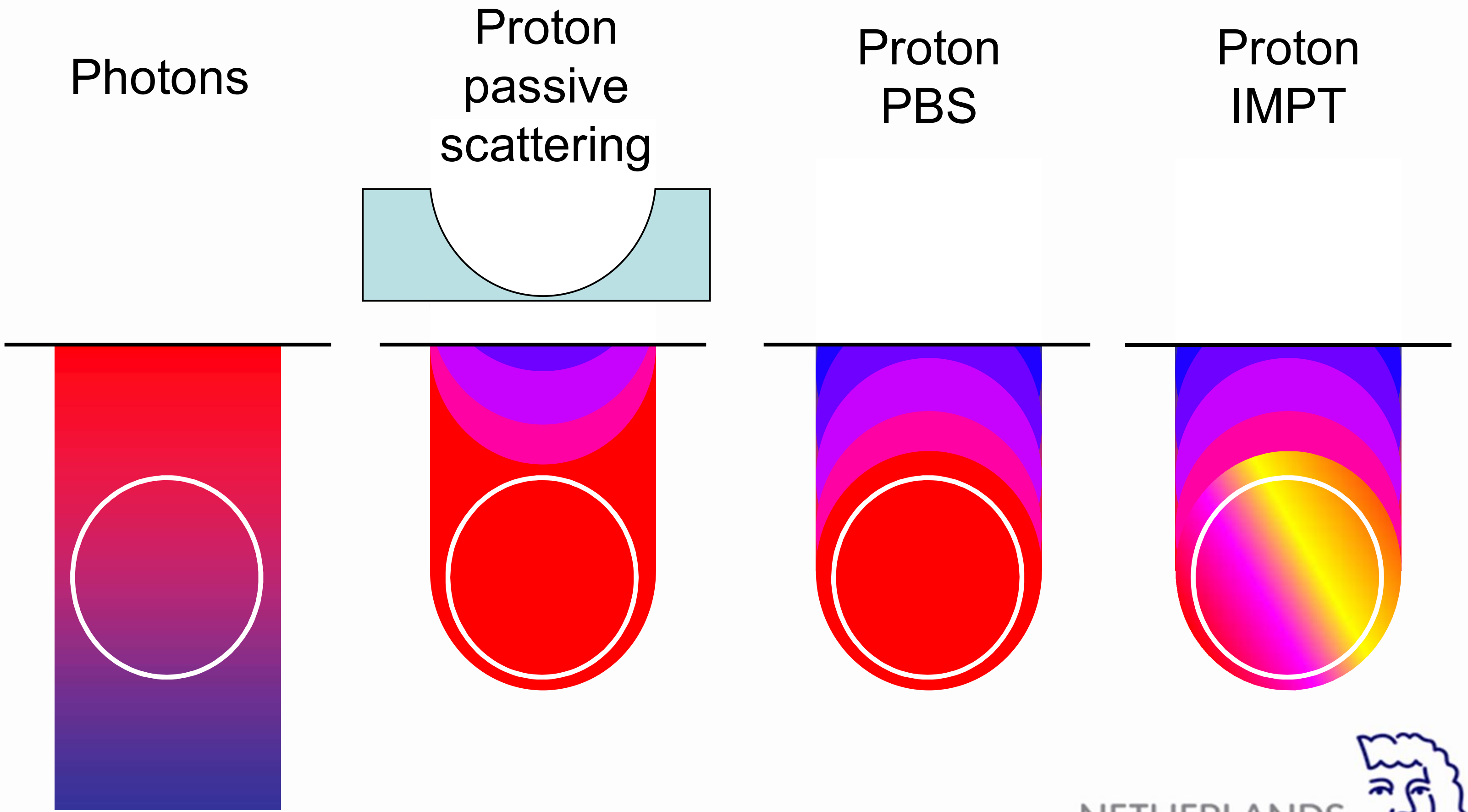
Lomax 1999, PMB 44: 185-205

Intensity Modulated Proton Therapy (IMPT)

The three 'orders' of proton therapy compared



Dosimetric Advantage



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Courtesy of Martijn Engelsman

Proton Penumbra

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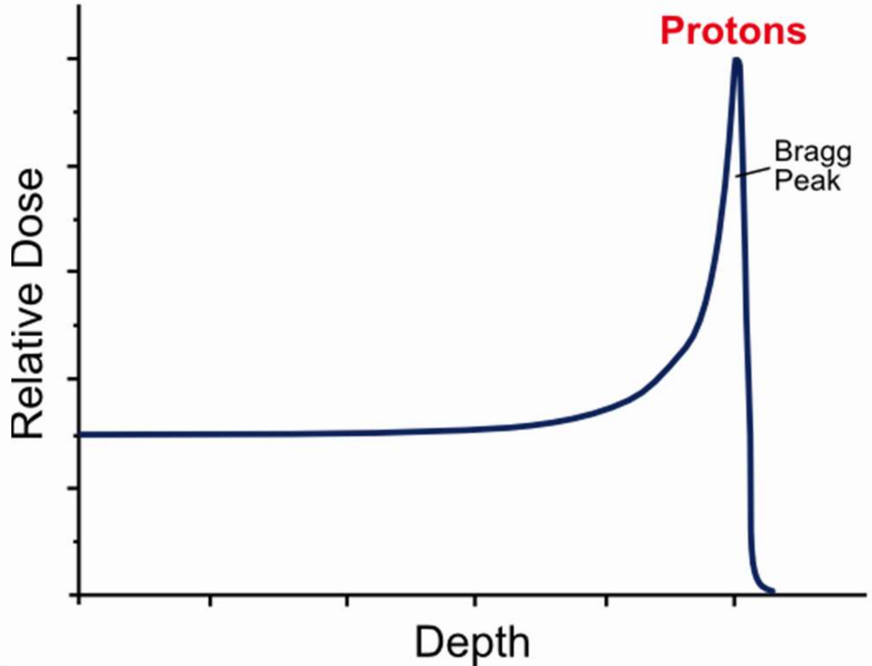
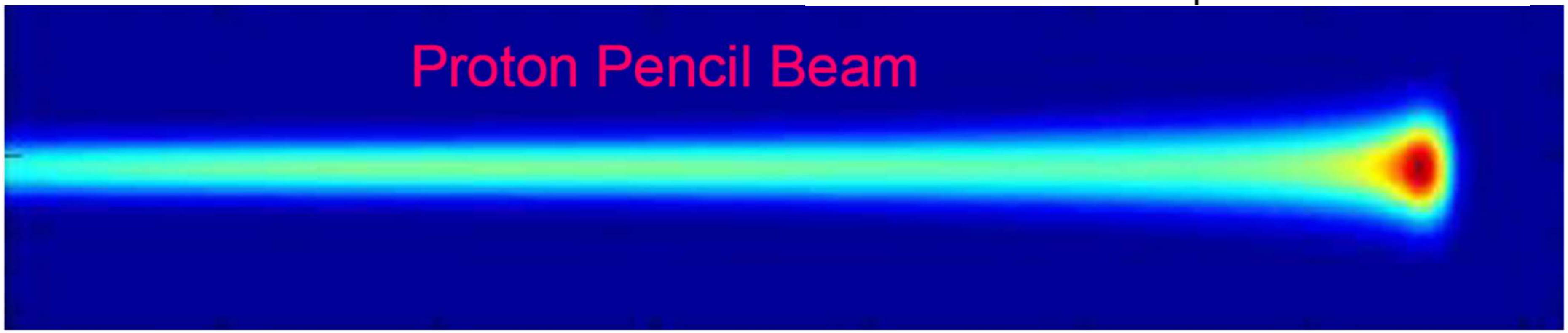
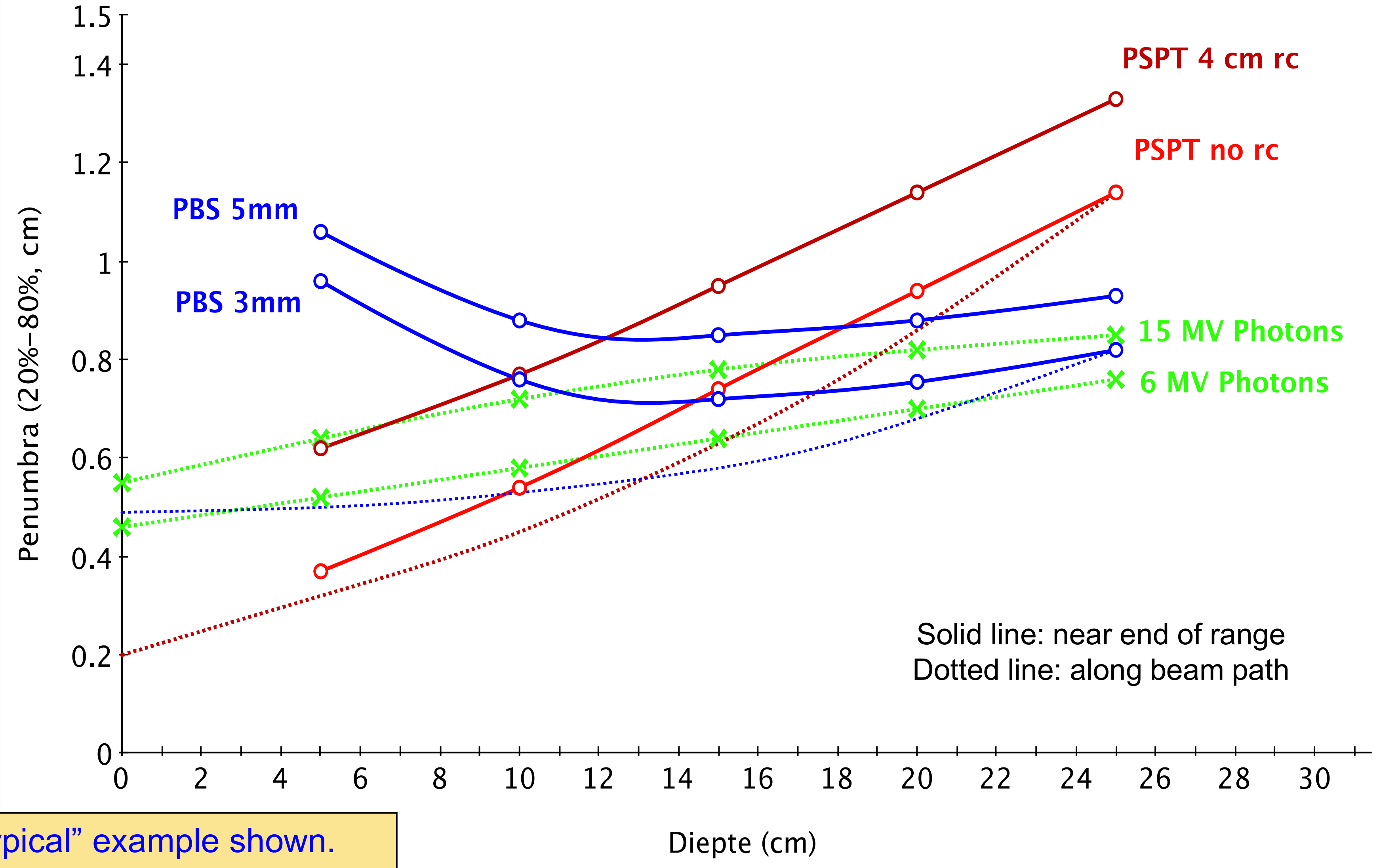
Lateral Penumbra





Paganetti, Physics of Particles, PTCOG 52

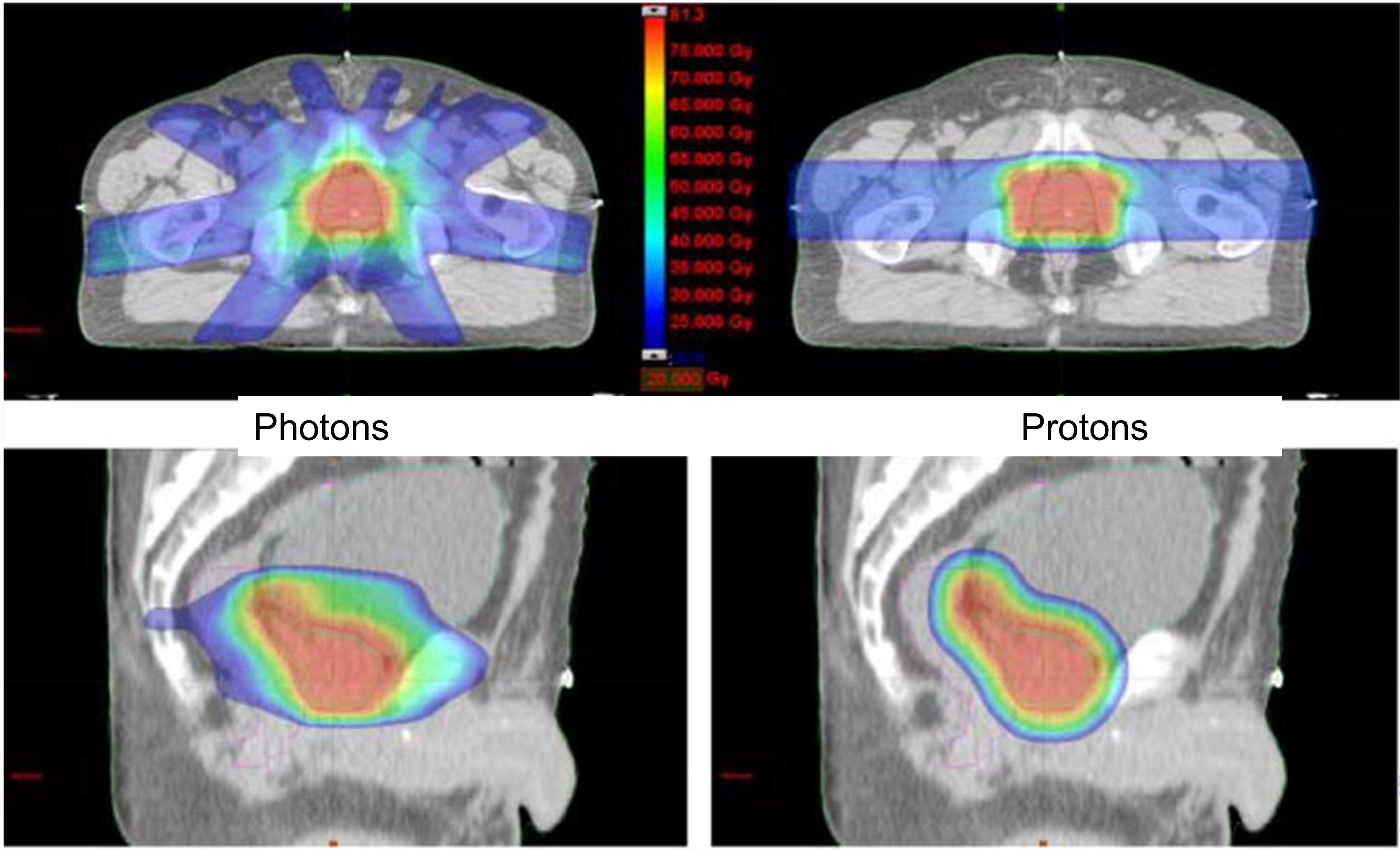
Lateral dose fall-off



"Typical" example shown. Penumbra depends heavily on beam-line layout/optics.

Courtesy of Martijn Engelsman

IMRT vs Proton, prostate



Zhang et al., IJROBP, 2007

Proton Benefit

- Proton penumbra not steeper than photons
  - Dose distribution in high dose region not superior than photons
  - OAR near target with max dose constraint not spared
- Advantage manifested in intermediate and low dose levels
- Model based advantage most likely in OAR with considerable volume effects:

  +Lung, Liver, Parotids

  - Spinal Cord, Rectum, Brainstem

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Range Uncertainties

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Protons Stop

Protons Stop … somewhere

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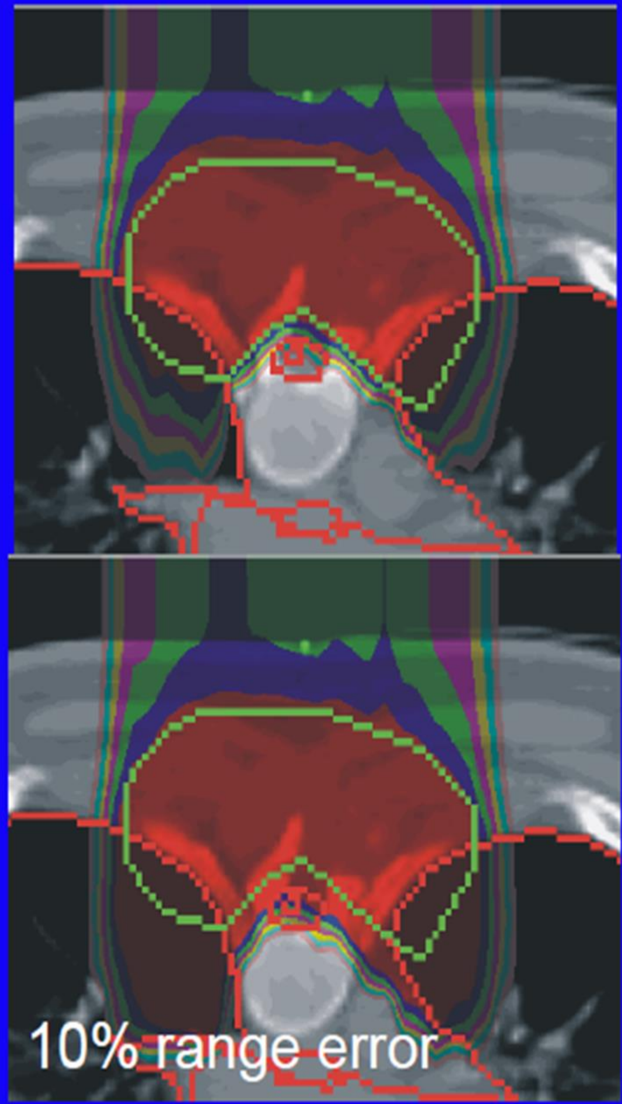
Dealing with uncertainties – range uncertainties.

The advantage of protons is that they stop.



The disadvantage of protons is that we don't always know where…

Range uncertainty will generally be systematic!

Sources of Range Uncertainty

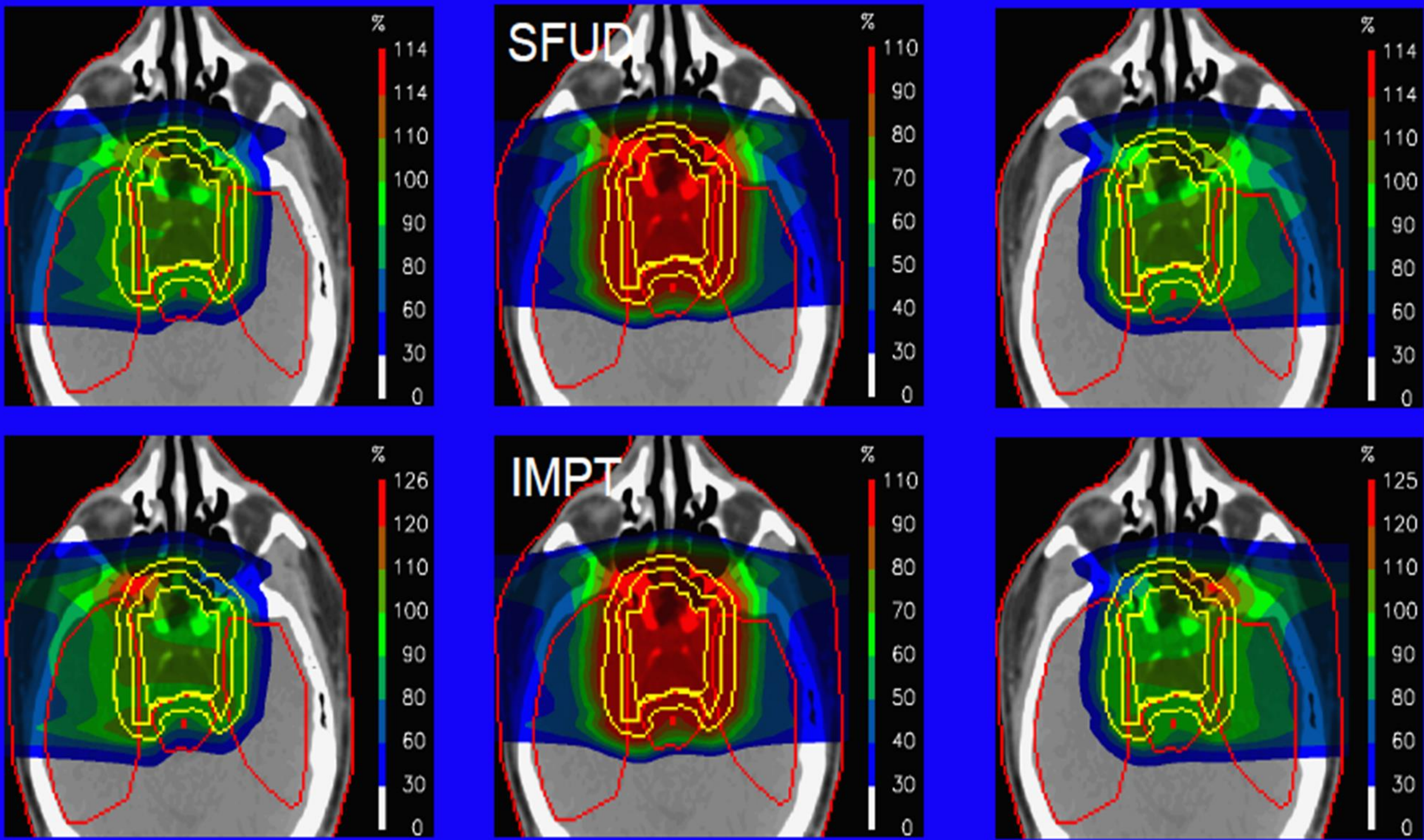
Table 1. Estimated proton range uncertainties and their sources and the potential of Monte Carlo for reducing the uncertainty. Paganetti and Goitein (2000), Robertson *et al* (1975) and Wouters *et al* (1996). The estimations are average numbers based on 1.5 standard deviations. Extreme cases, such as lung treatments, might show bigger uncertainties.

Source of range uncertainty in the patient	Range uncertainty without Monte Carlo	Range uncertainty with Monte Carlo
Independent of dose calculation		
Measurement uncertainty in water for commissioning	± 0.3 mm	± 0.3 mm
Compensator design	± 0.2 mm	± 0.2 mm
Beam reproducibility	± 0.2 mm	± 0.2 mm
Patient setup	± 0.7 mm	± 0.7 mm
Dose calculation		
Biology (always positive) ^	+~0.8%	+~0.8%
CT imaging and calibration	± 0.5% [a]	± 0.5% [a]
CT conversion to tissue (excluding I-values)	± 0.5% [b]	± 0.2% [g]
CT grid size	± 0.3% [c]	± 0.3% [c]
Mean excitation energy (I-values) in tissues	± 1.5% [d]	± 1.5% [d]
Range degradation; complex inhomogeneities	−0.7% [e]	± 0.1%
Range degradation; local lateral inhomogeneities *	± 2.5% [f]	± 0.1%
Total (excluding *, ^)	2.7% + 1.2 mm	2.4% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm	2.4% + 1.2 mm

Paganetti, PMB, 2012

Dealing with uncertainties – range uncertainties.

Range uncertainty for SFUD and IMPT plans

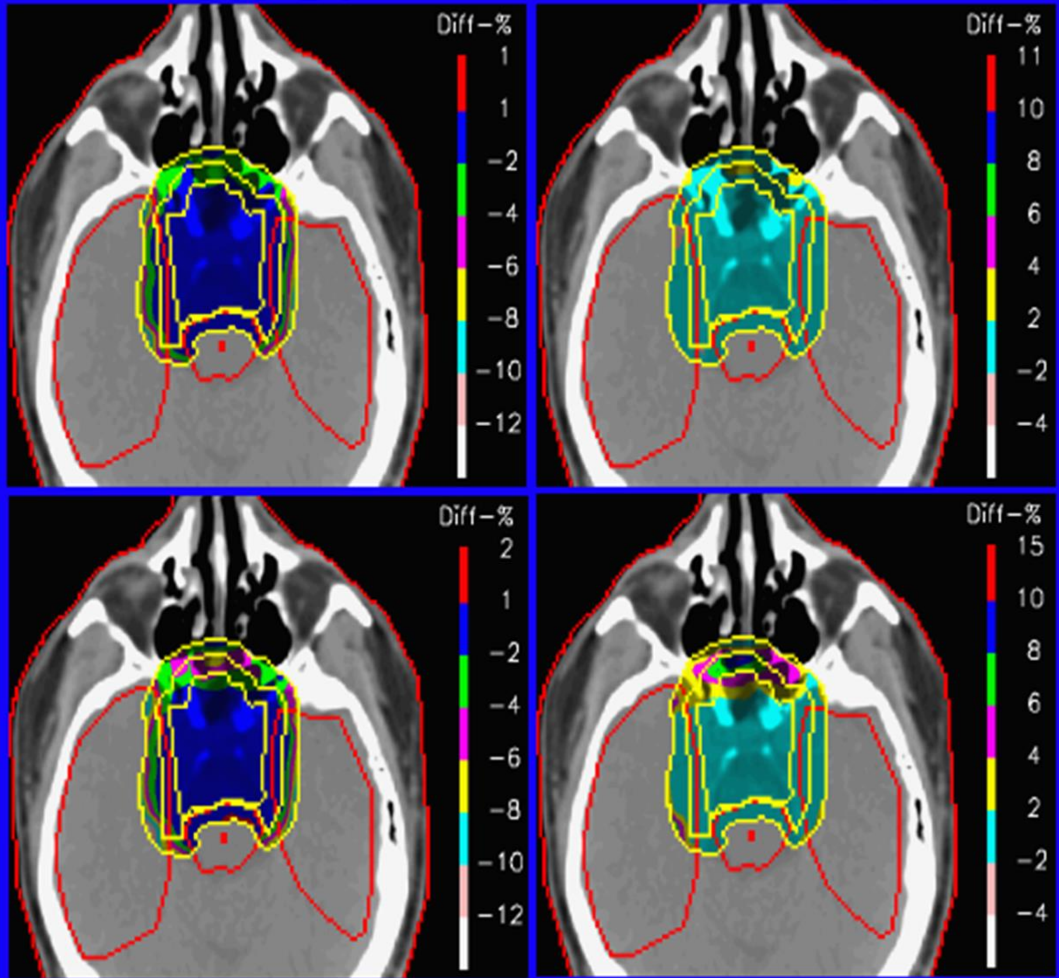


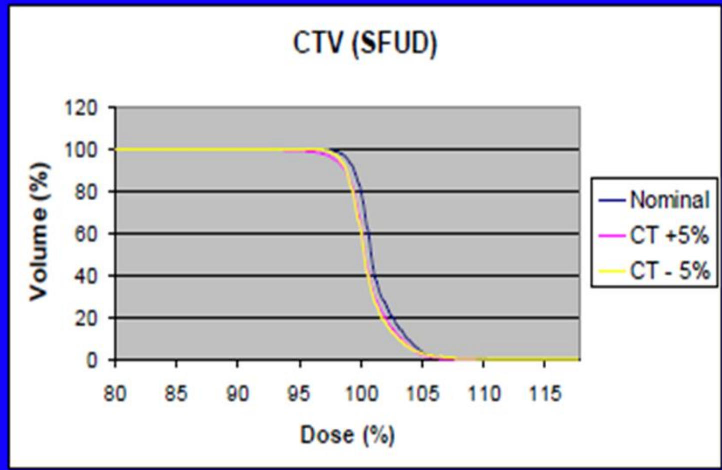
Lomax AJ (2007) in 'Proton and charged particle Radiotherapy', Lippincott, Williams and Wilkins

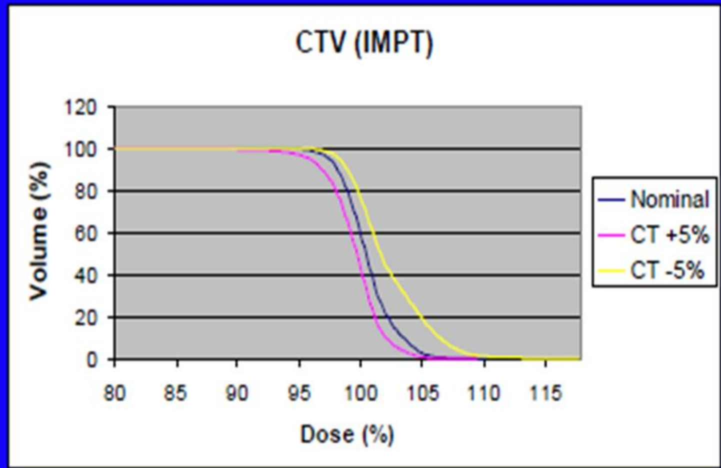
Dealing with uncertainties – range uncertainties.

Range uncertainty for SFUD and IMPT plans

+5% CT　　　　-5% CT

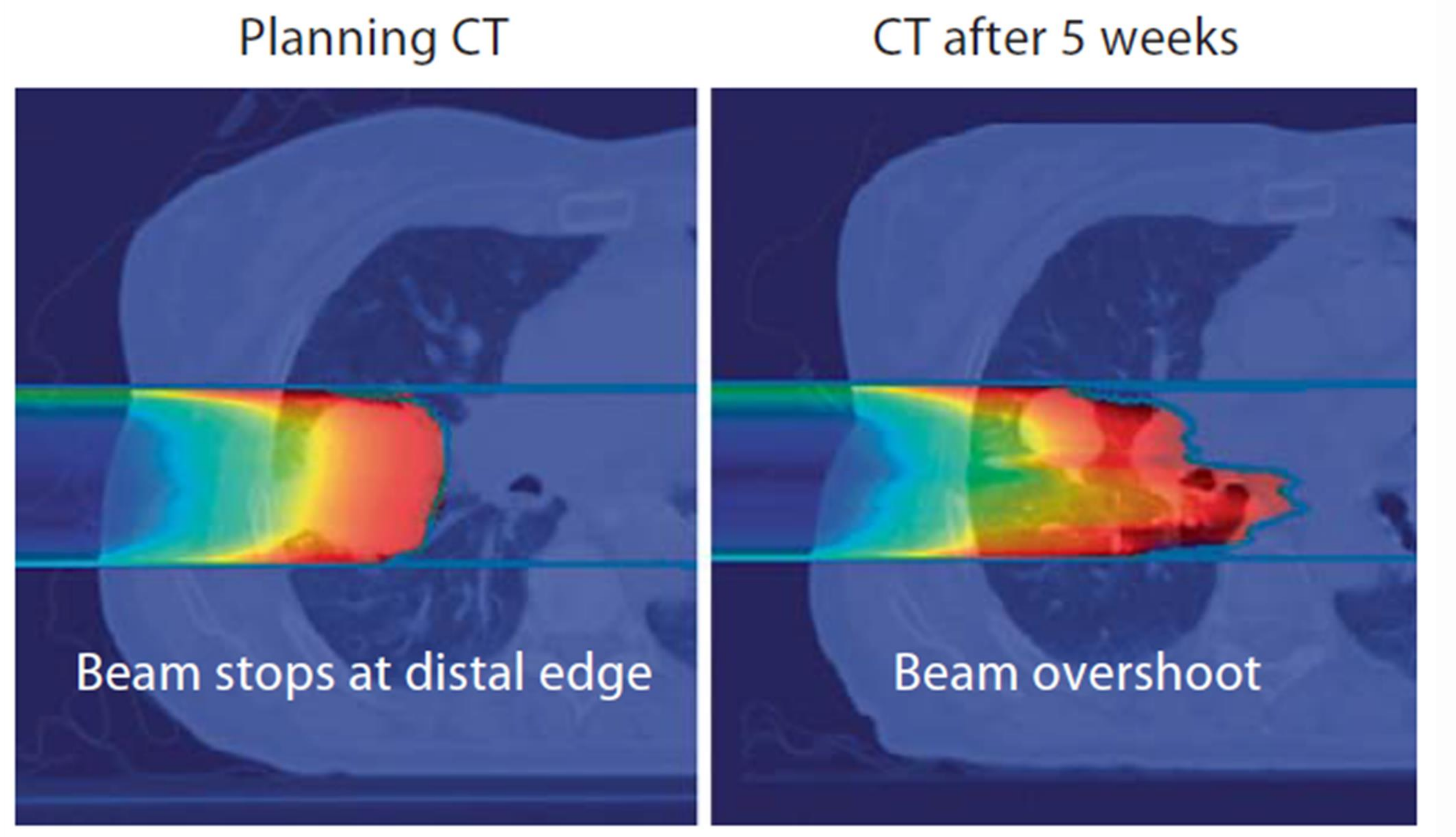






Lomax AJ (2007) in 'Proton and charged particle Radiotherapy', Lippincott, Williams and Wilkins

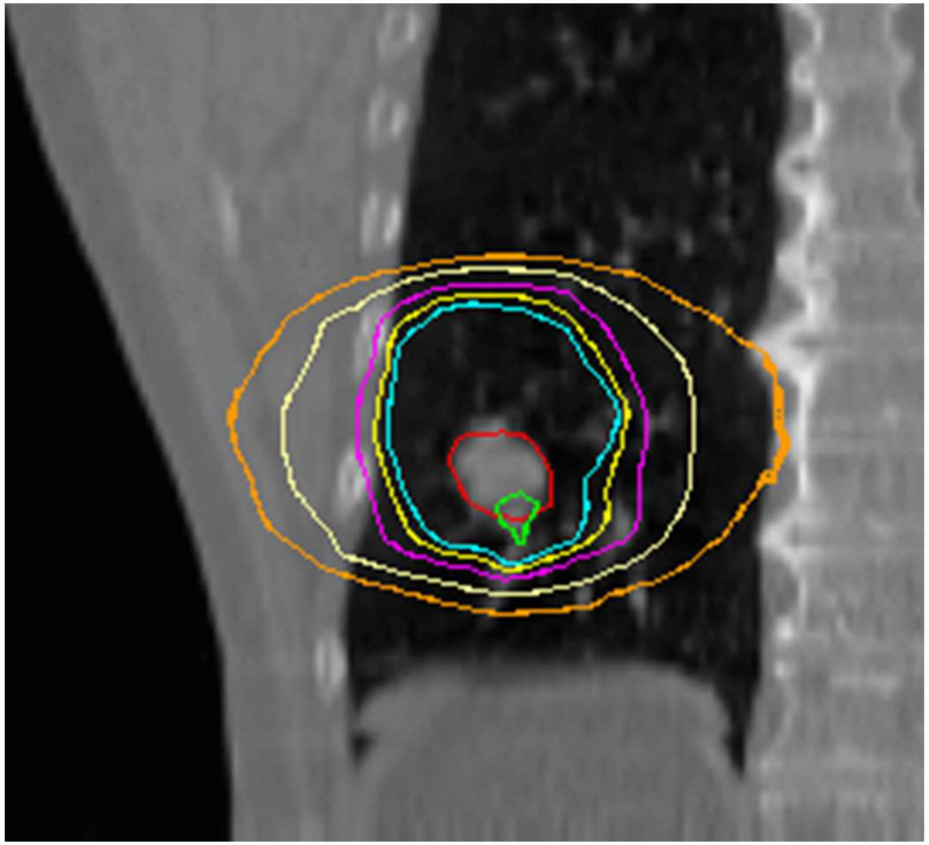
Anatomical Changes



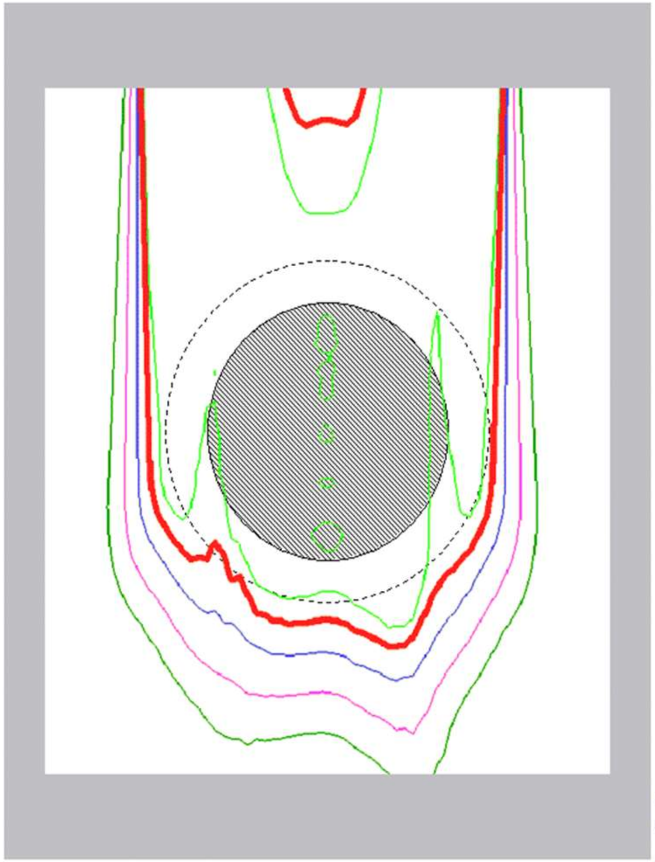
Mohan et al. Front Radiat Ther Oncol, 2011

Respiratory Motion

Photons



Protons



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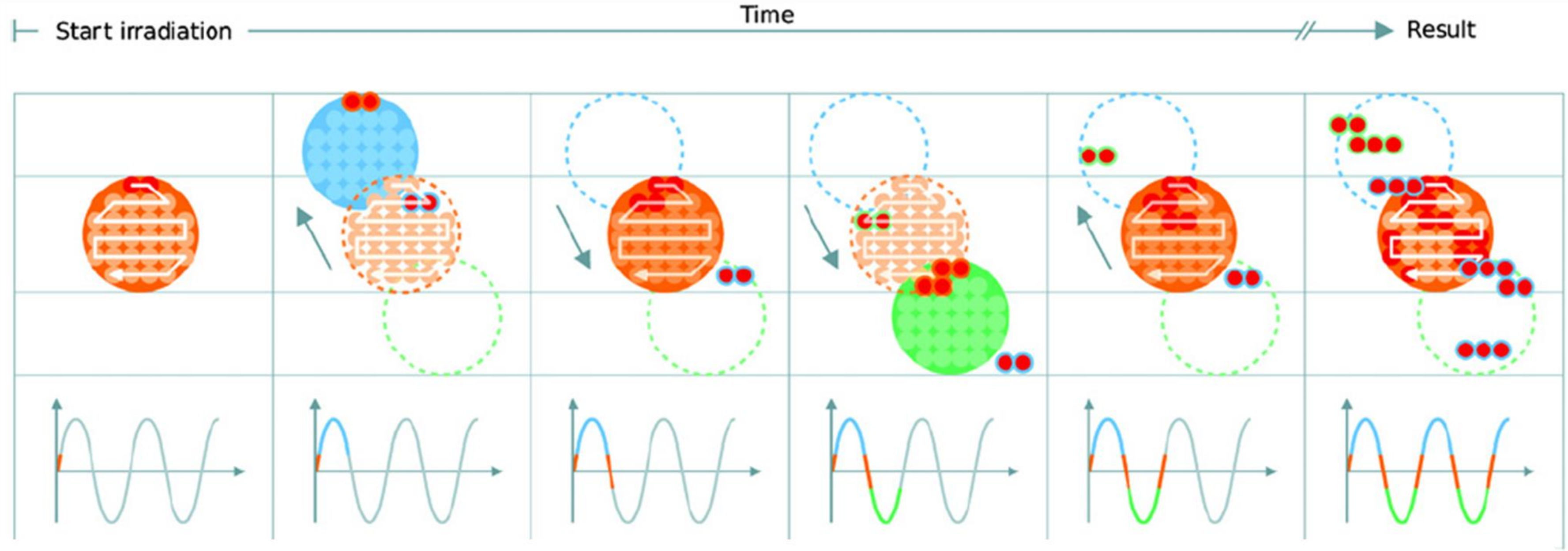
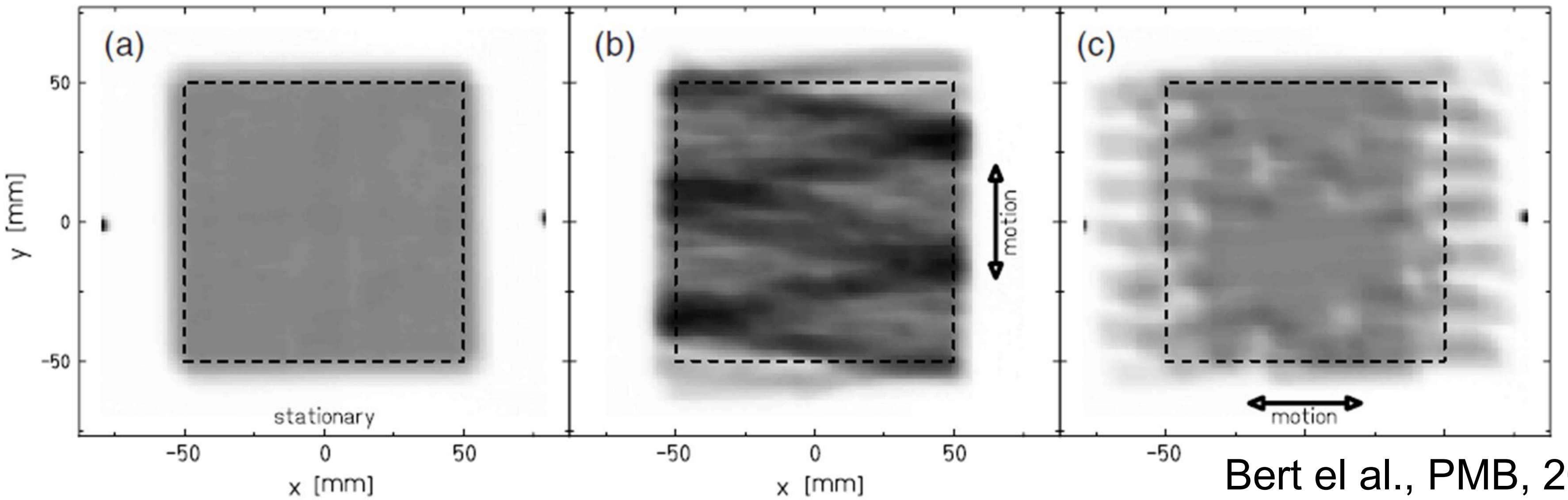
Courtesy of Martijn Engelsman

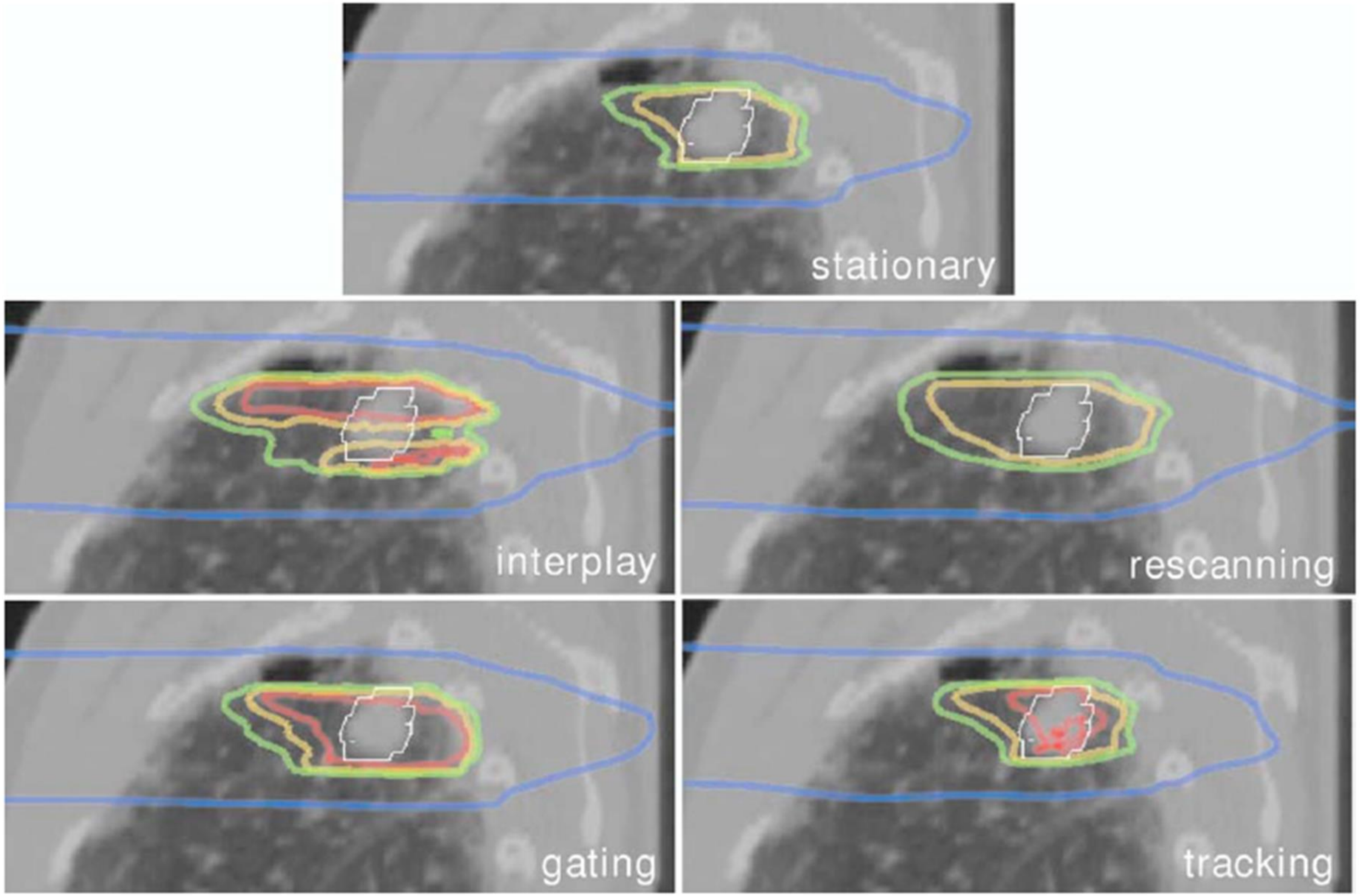
Interplay Effect





Bert el al., PMB, 2008

Motion Management

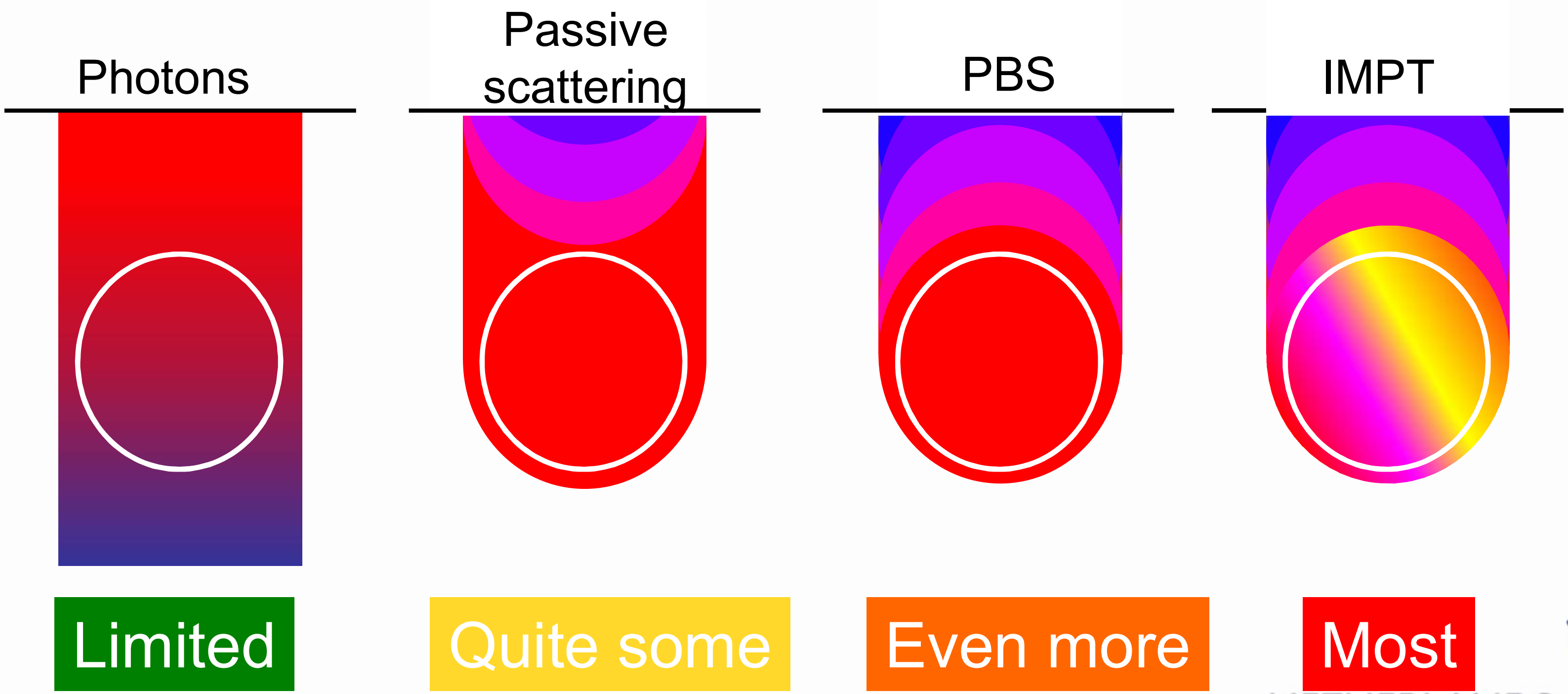


NHOEK

Rietzel et al, Med Phys, 2010

Sensitivity

To anatomical (density) changes, setup errors, interplay effect, etc.



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Courtesy of Martijn Engelsman

Margins

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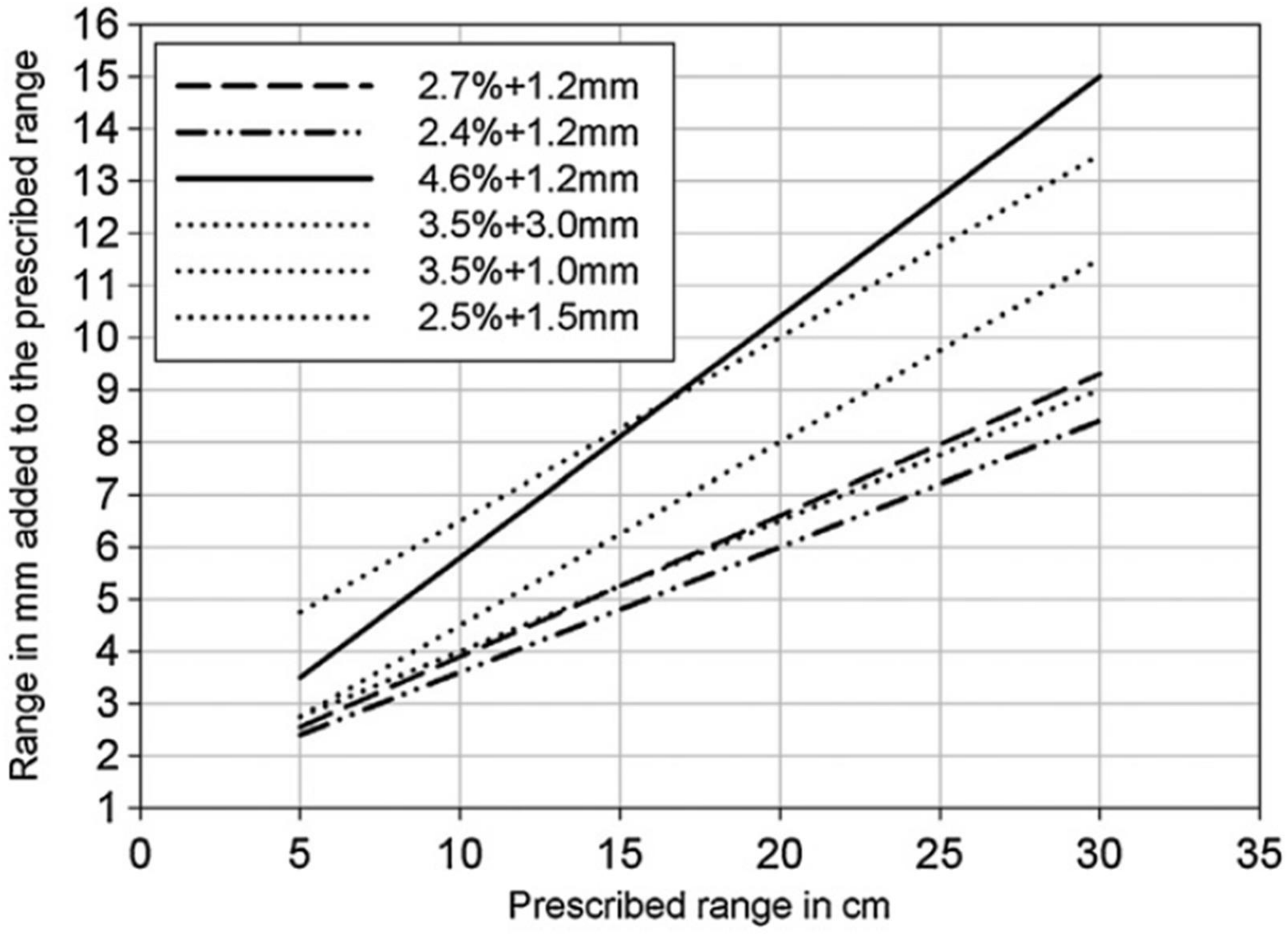
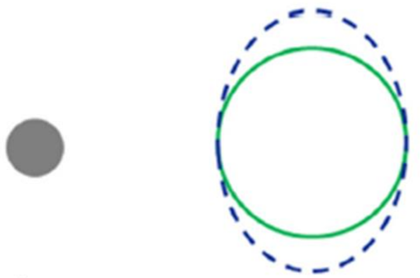
Margin for range uncertainties



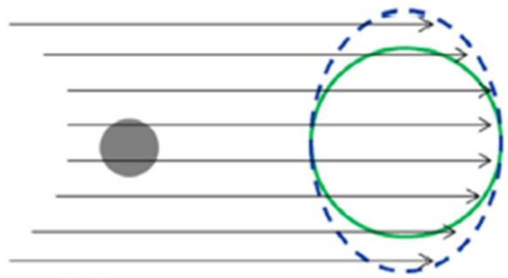
LEEUWENHOEK

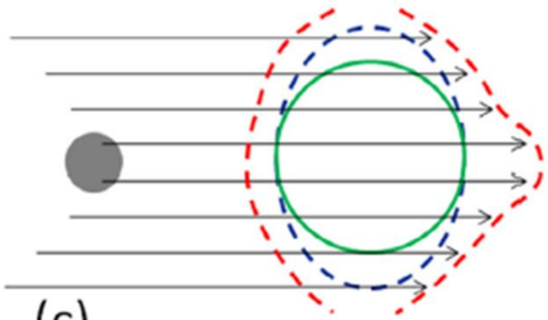
Paganetti, PMB, 2012

Beam Specific PTV

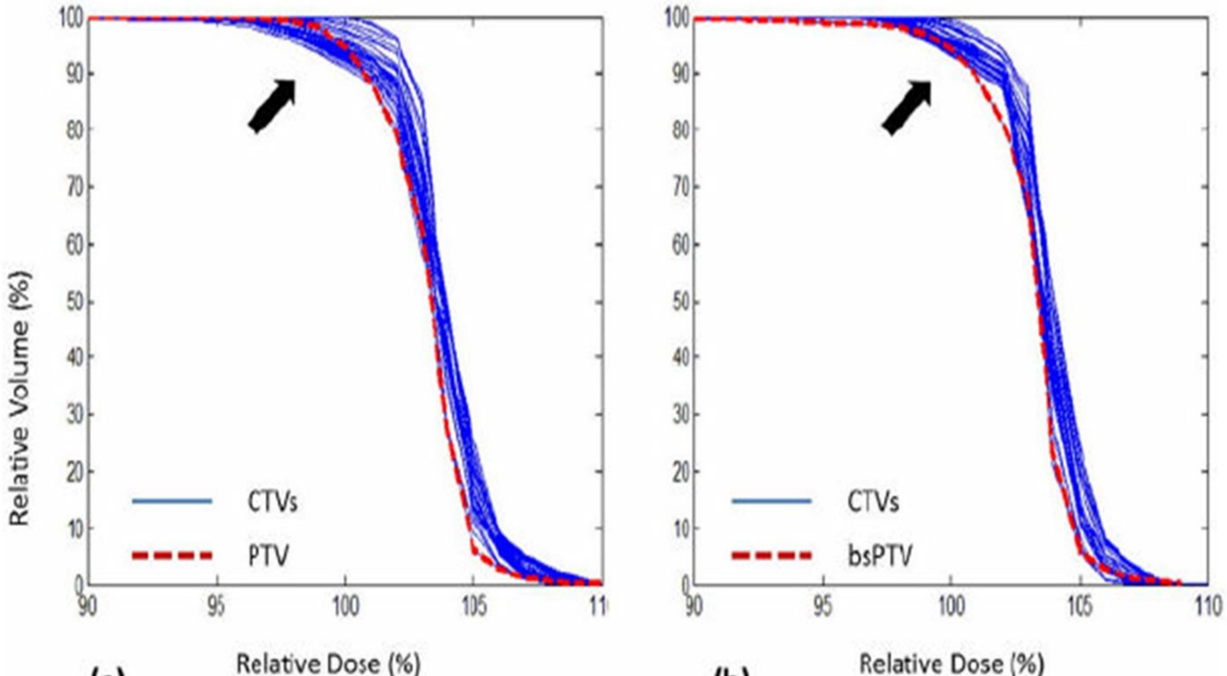


(a)





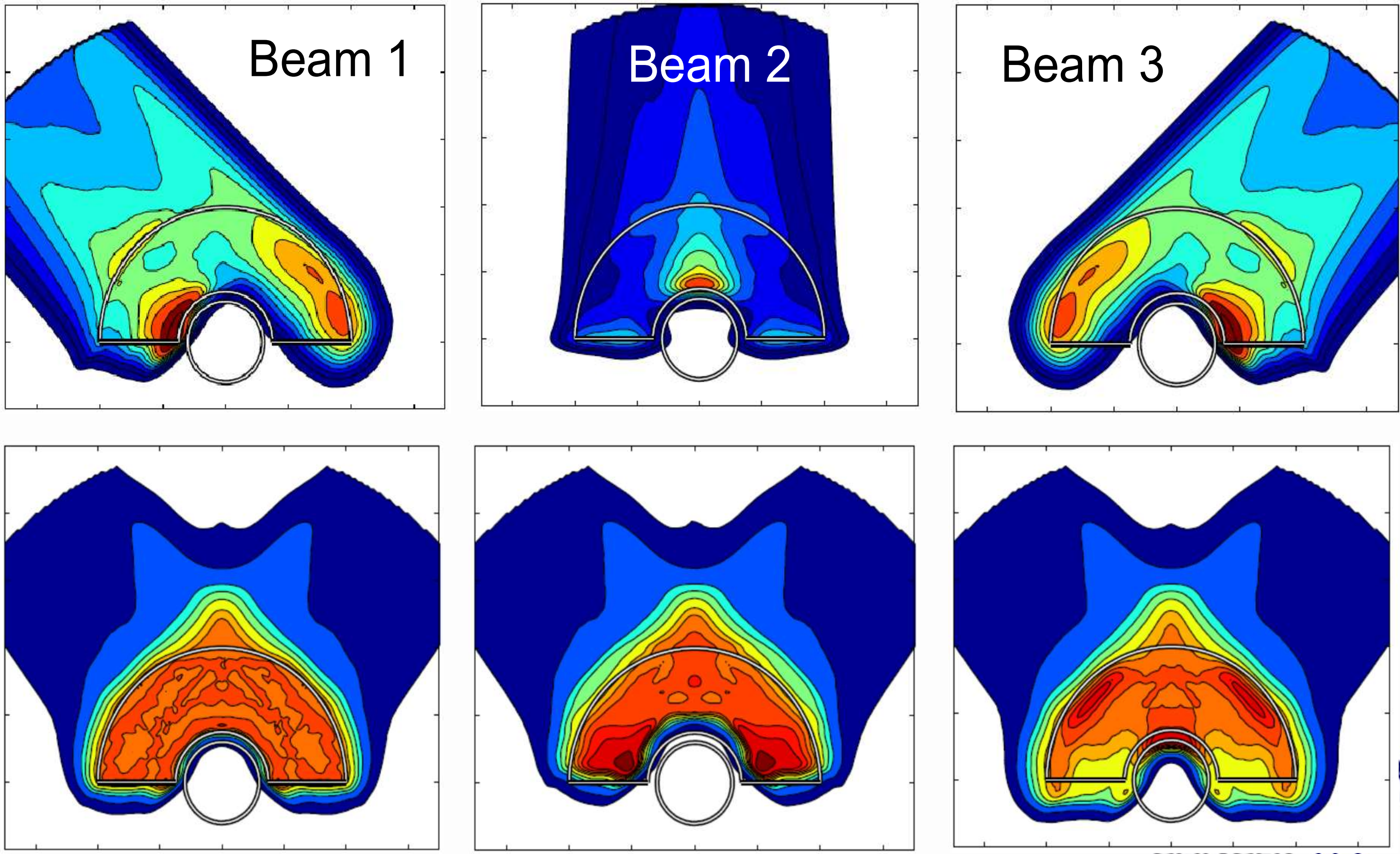
(c)



(a) (b)

Parks et al., IJROBP, 2012

Standard optimization



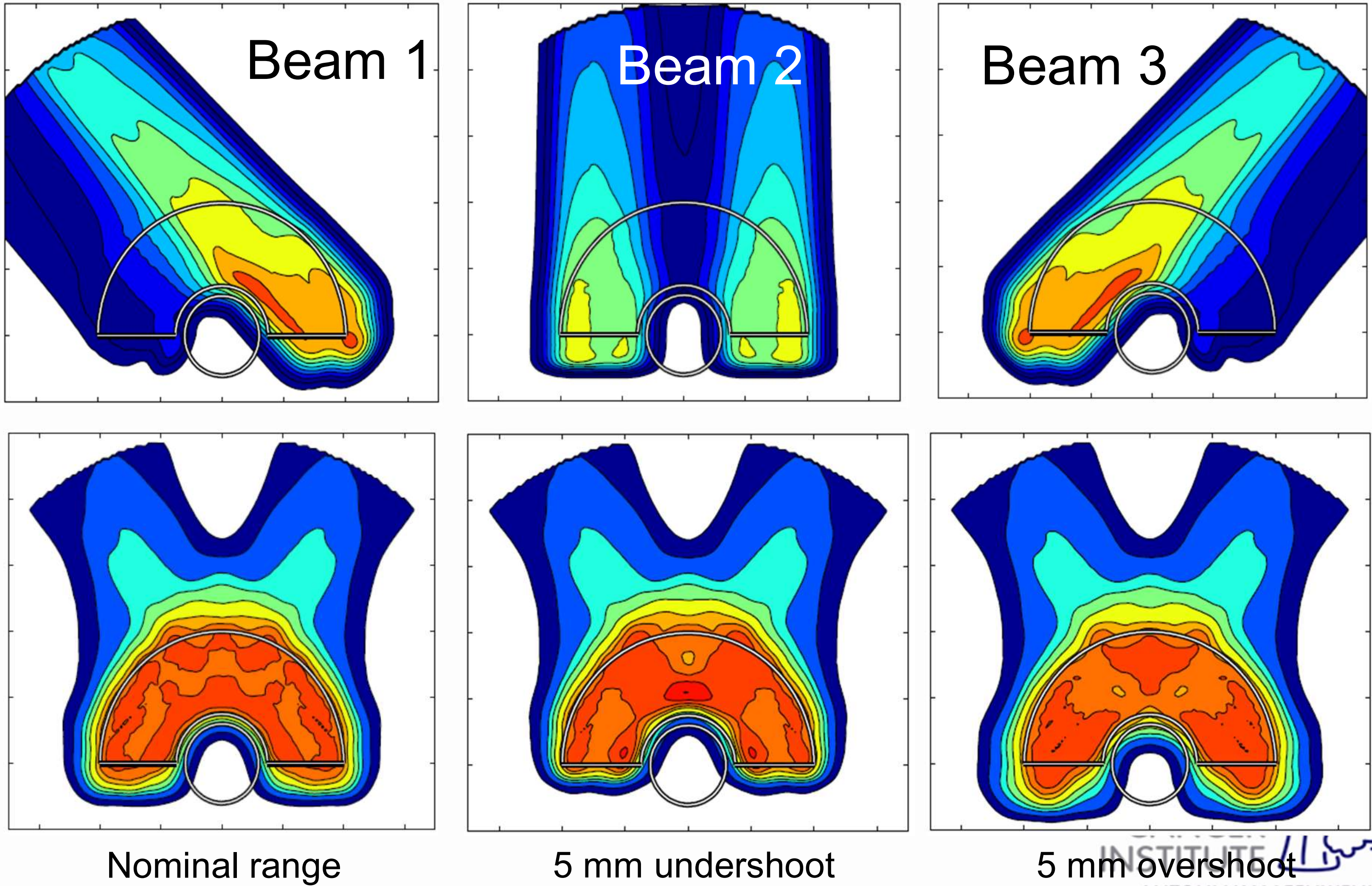
Nominal range

5 mm undershoot

5 mm overshoot

Unkelbach et al. Med Phys. 2009;36(1):149-63.

Robust optimization



Unkelbach et al. Med Phys. 2009;36(1):149-63.

Image Guidance

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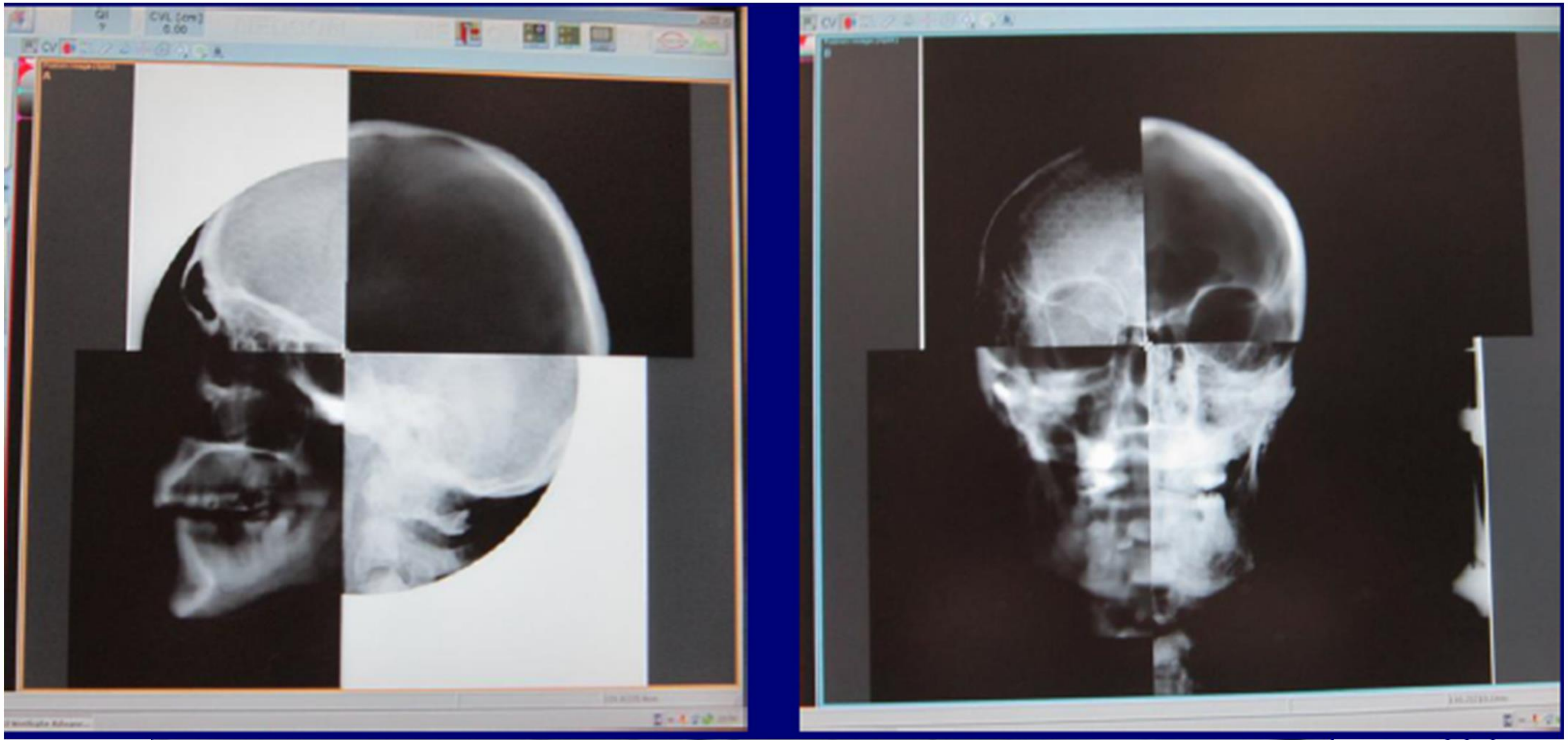
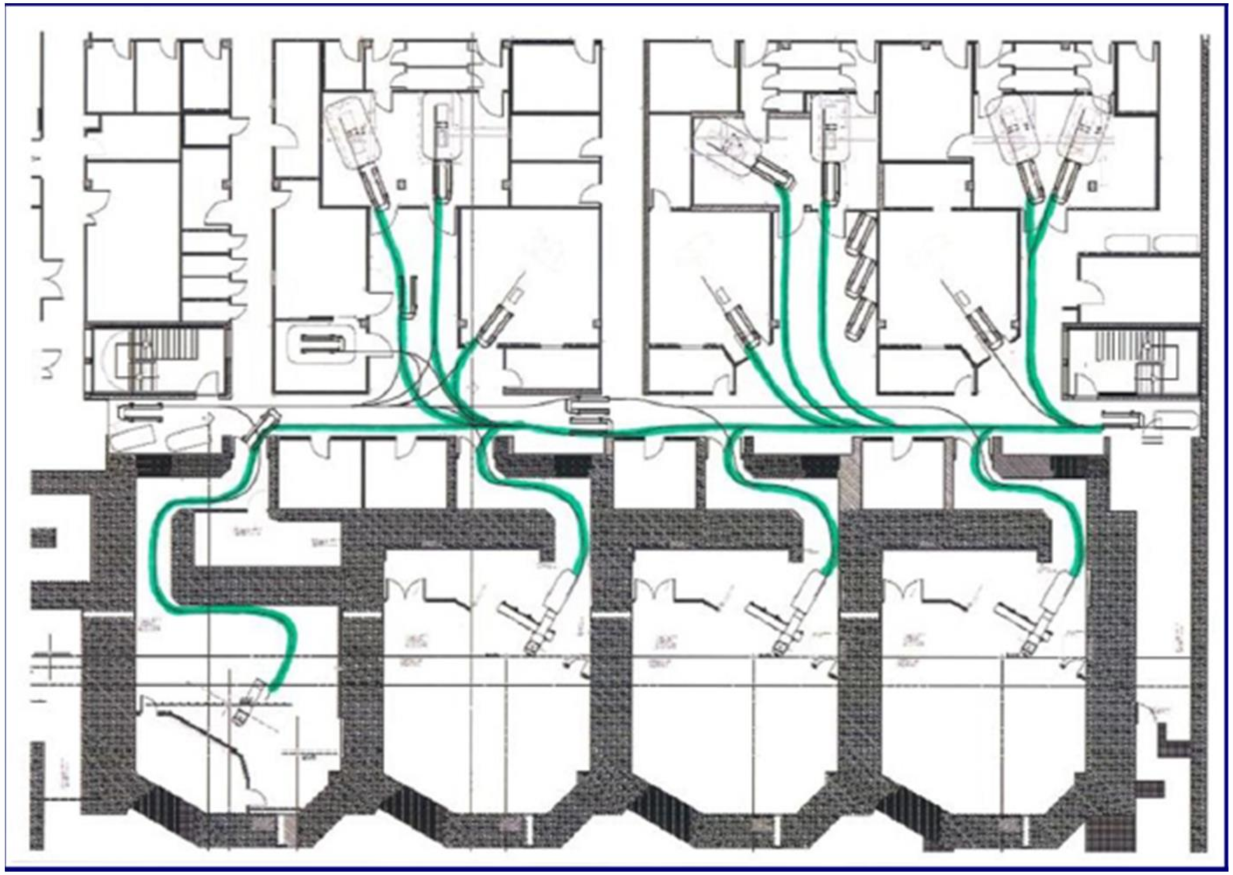
State of the art in room imaging



2D/3D Registration

Courtesy of Lamberti, WPE

Near room imaging



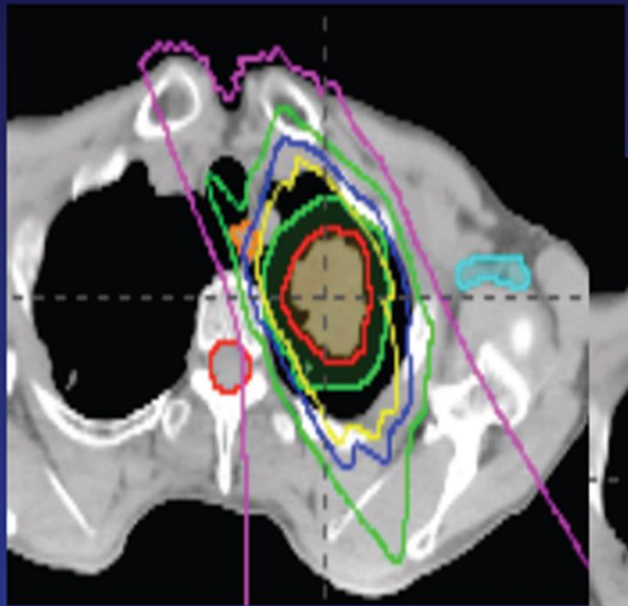
Oncolog Trolley System

Courtesy of Lamberti, WPE

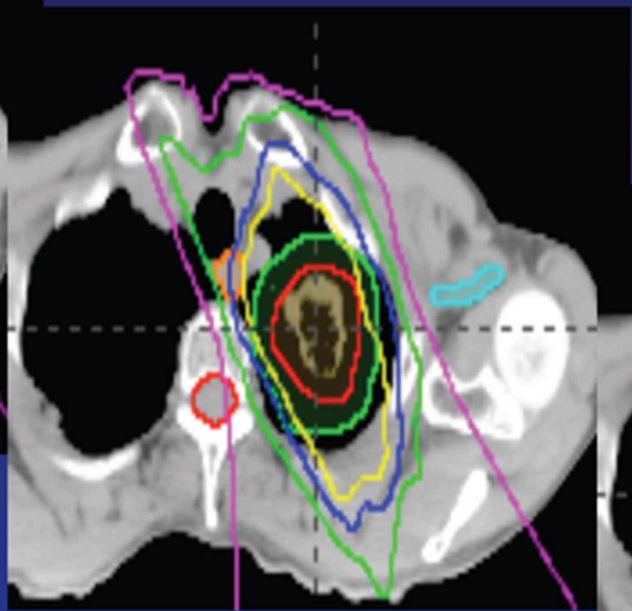
Adapted proton therapy

87.5 CGE in T2N0M0 NSCLC

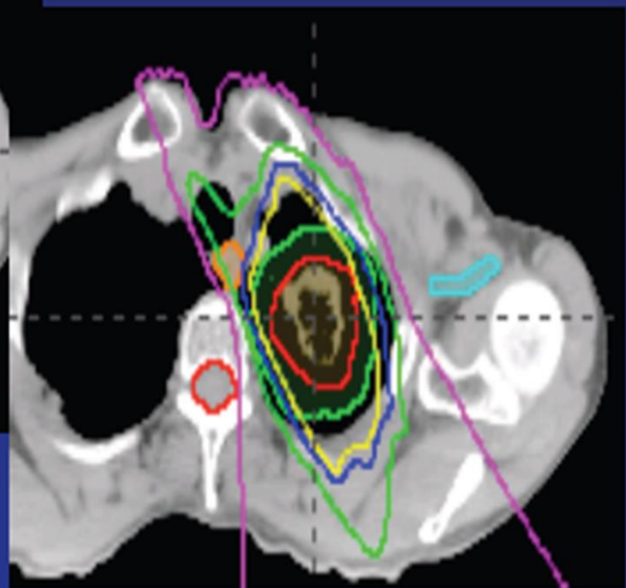
Initial plan



Initial plan
recalculated based on
CT after 5 wks TX



Re-plan based on
CT after 5 wks
TX



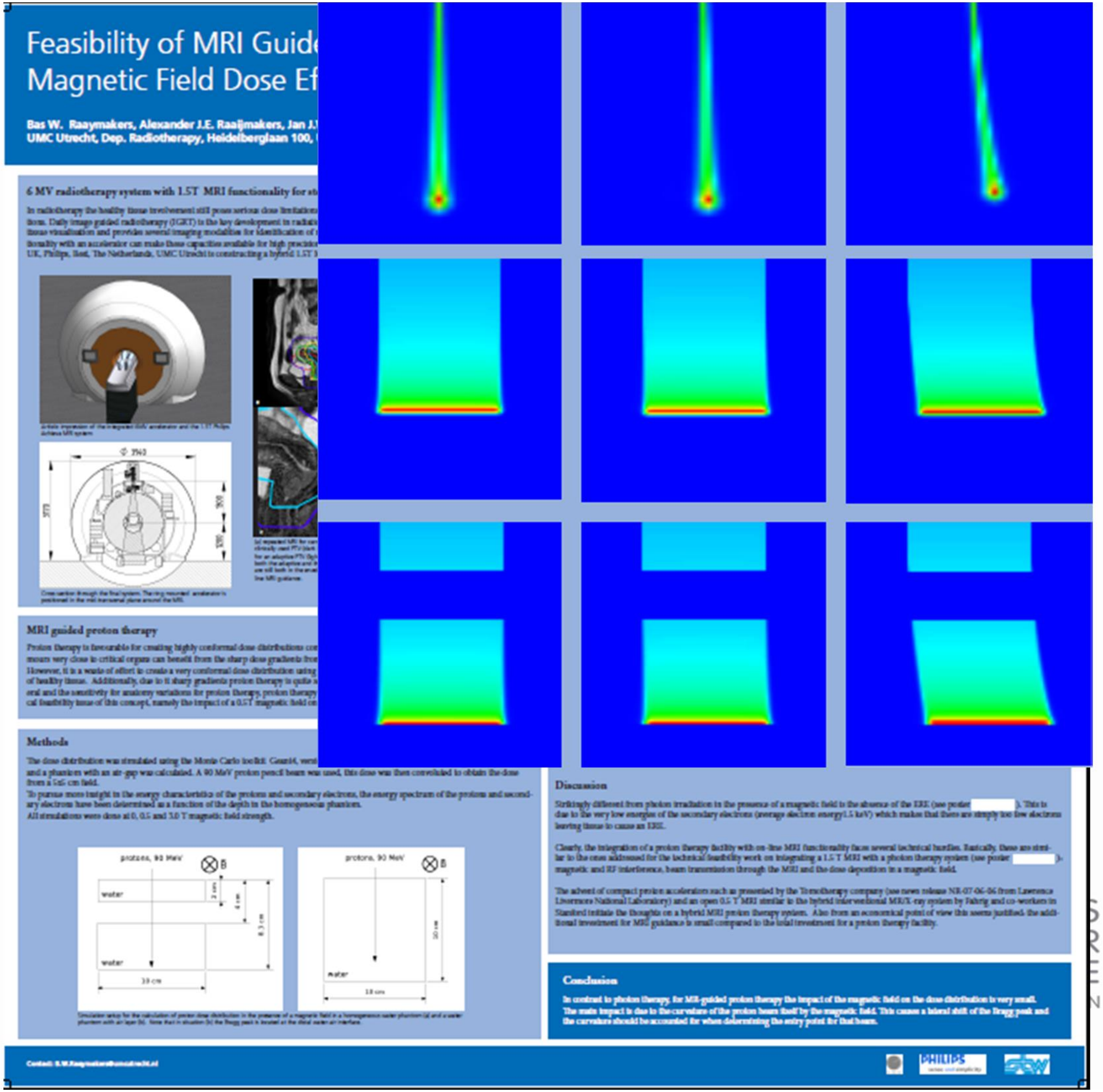
Courtesy of Joe Y Chang, MD Anderson

‘Future’ - In Room Imaging

Integrated CBCT

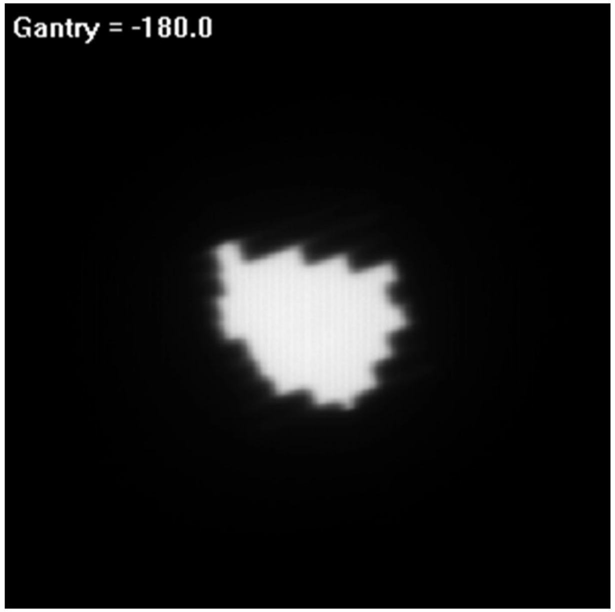
IHOEK

In room CT



N LEEUWENHOEK

3D EPID Dose reconstruction prostate VMAT plan



EPID movie

Dose per frame

Accumulated dose

axial slice through isocentre

- Energy: 10 MV
- 243 frames
- delivery time: 96 s

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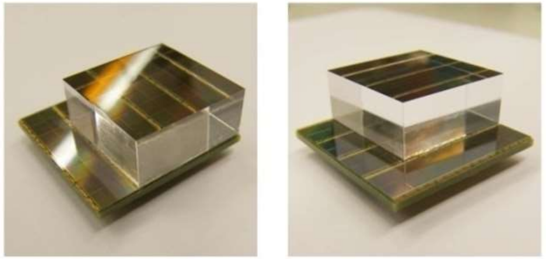
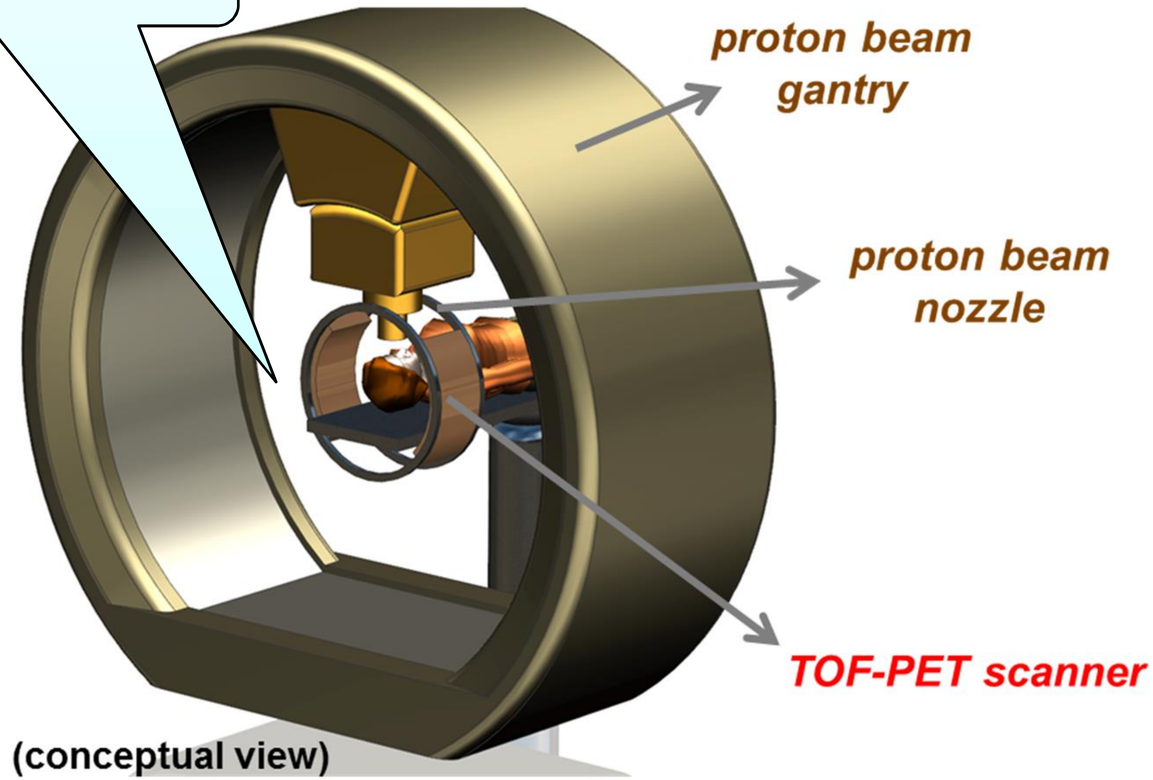
Example: in-situ dose imaging

Solution: in-situ imaging

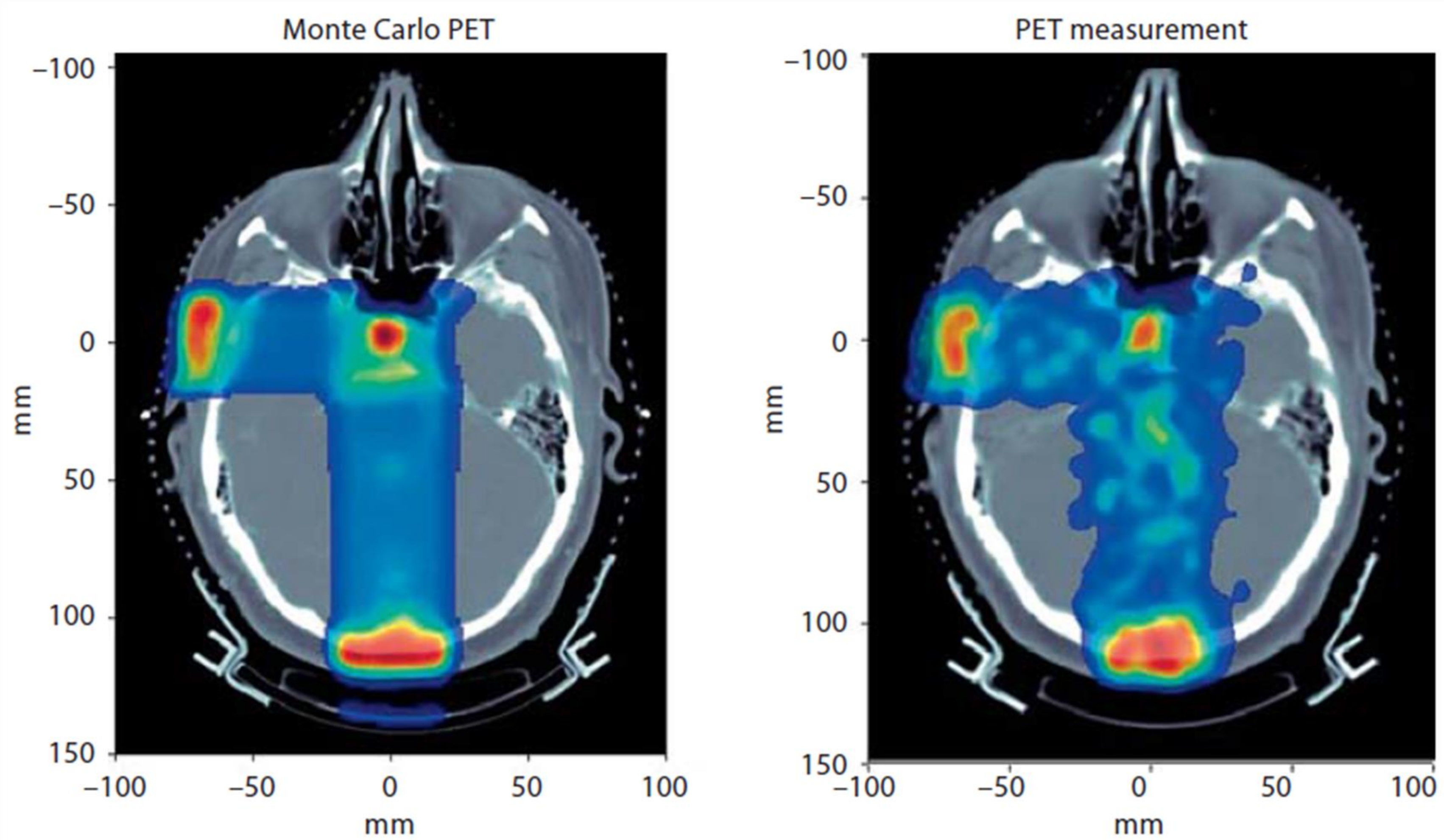
Incentive
Use revolutionary detection technology, under development for PET-MRI by TU Delft and Philips, to realize clinically useful in-situ dose imaging device



www.sublima-pet-mr.eu



Range Verification: PET



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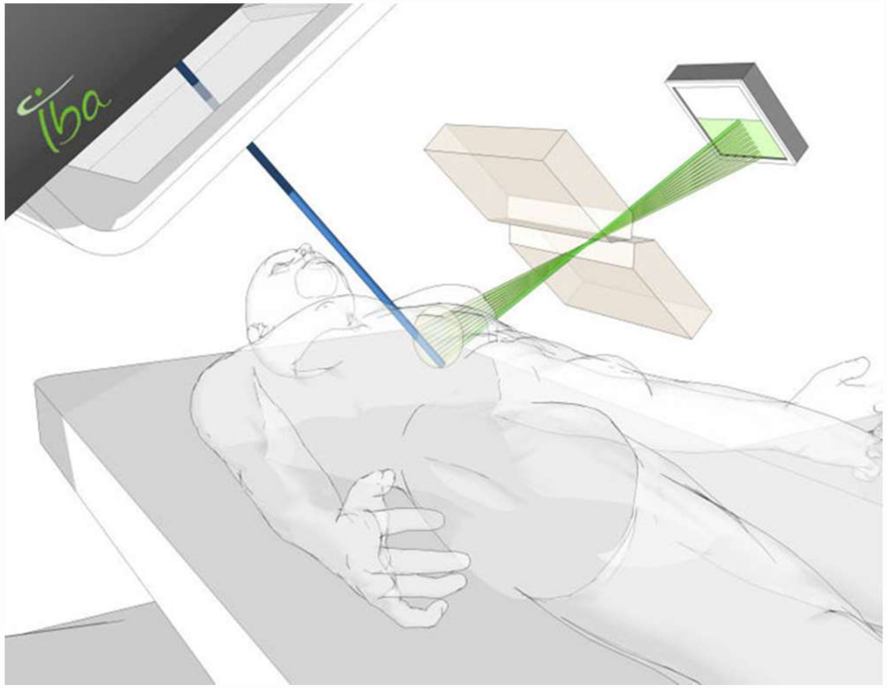
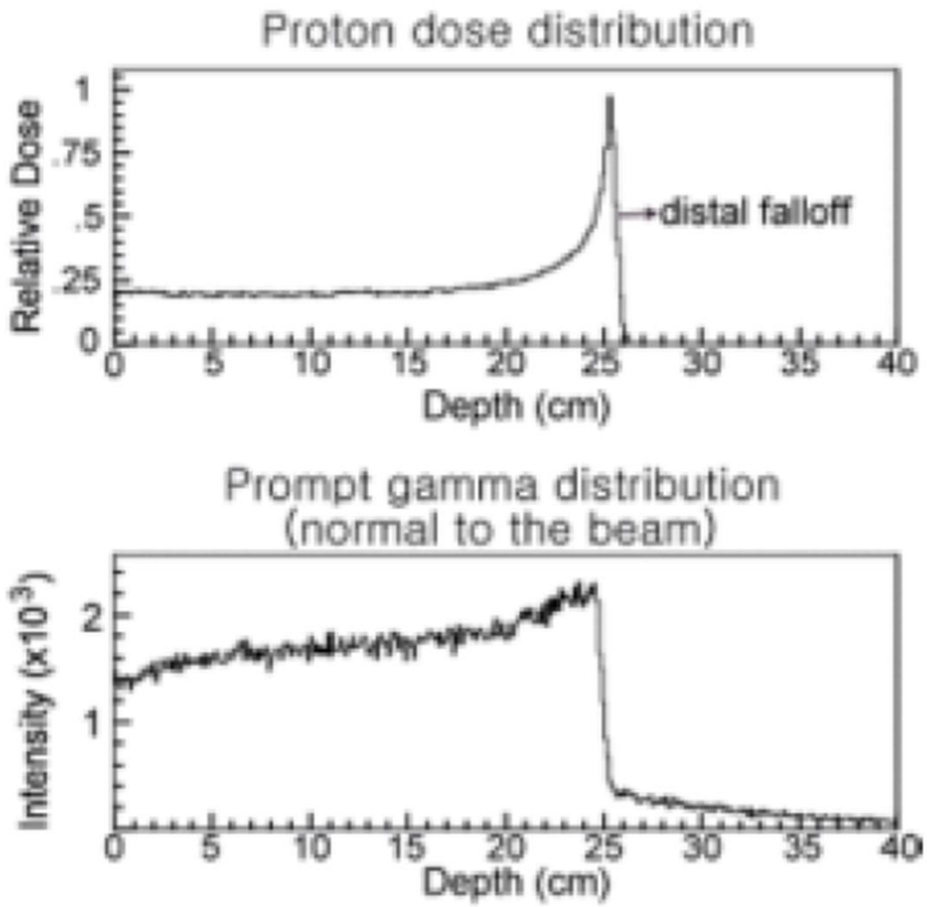
Courtesy of Martijn Engelsman

Range Verification: Prompt Gamma





B. Kang, J. Kim, IEEE Nucl. Sci. 2009

Thought experiment

	PROTONS	PHOTONS
Intensity modulation	Yes	Yes
3D/4D on-line alignment	Rare	Integrated
In-vivo dosimetry	No	Yes
Dose distribution sensitivity	High	Non-existent
Integral dose	Very low	Somewhat higher
Price per patient	€25,000	Cheaper: 2x to 3x

Conclusions

- Protons stop, providing great potential for organ at risk sparing
- Range uncertainties require larger 'margins' for target/OAR and/or more advanced correction strategy
- IGRT is currently underdeveloped for proton therapy

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CBCT for replanning

Marcel van Herk

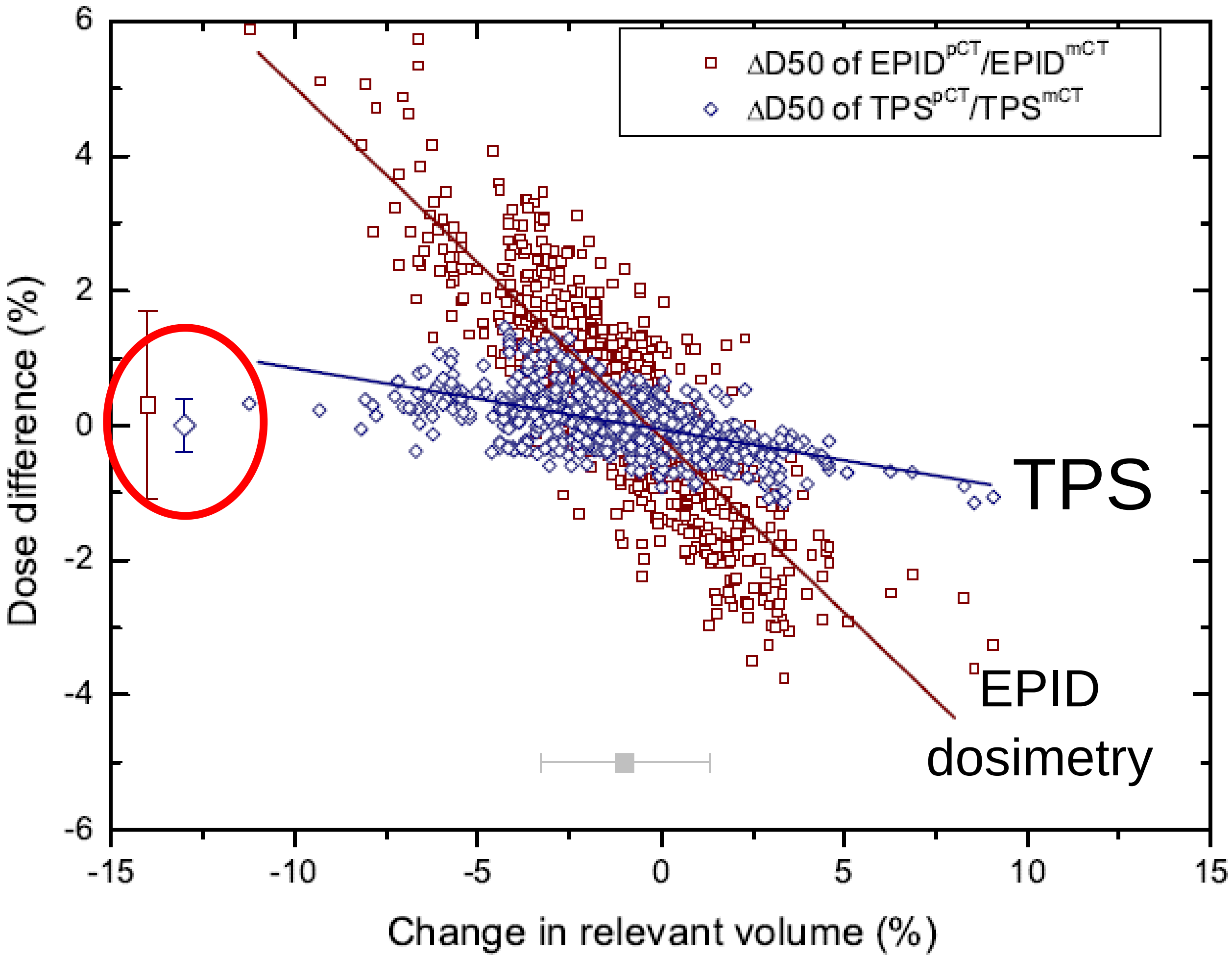
University of Manchester

Effects of anatomical changes

- Dosimetric effect
  - Extremely minor for photons

- Geometric effect
  - Organs and targets move relative to the dose distribution

Effect of weight loss on dose



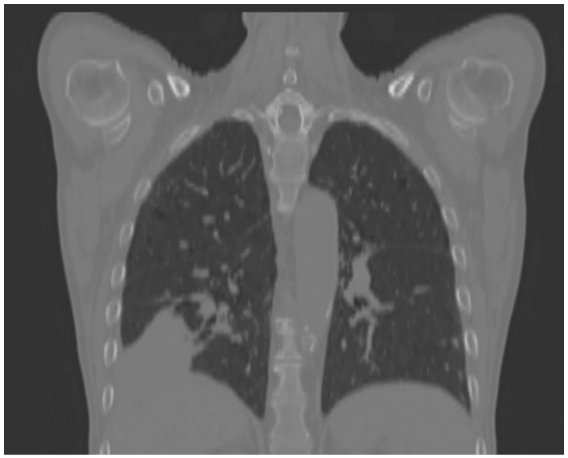
- Rozendaal et al, R&O 2015

Make localisation image suitable for dose calculation

- Density override
- Deform planning CT to CBCT
- Shading correction
  - Local patch histogram based
  - Differentiate soft tissue, bone and lung

Modify CT to CBCT anatomy

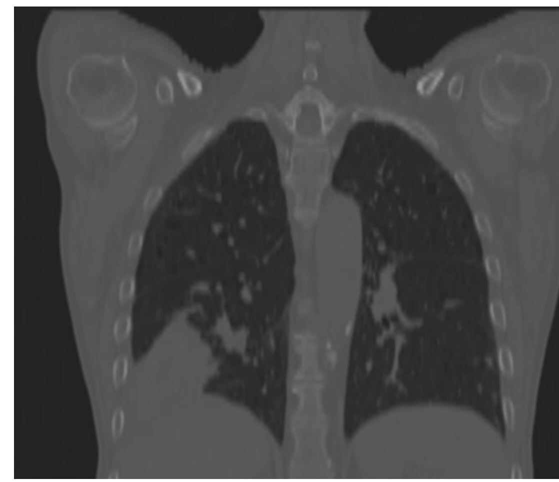
CT



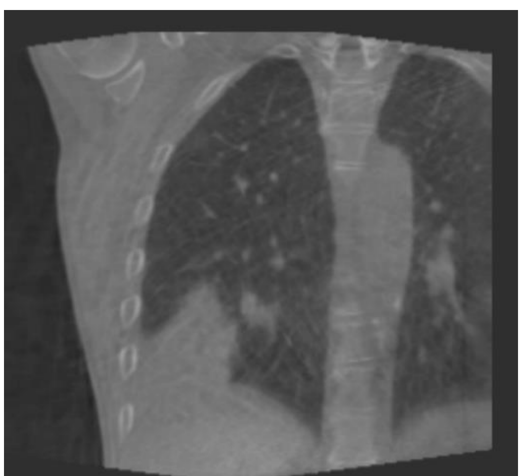
Deformable image registration

modified CT (mCT)

(CT numbers + CBCT anatomy)



CBCT

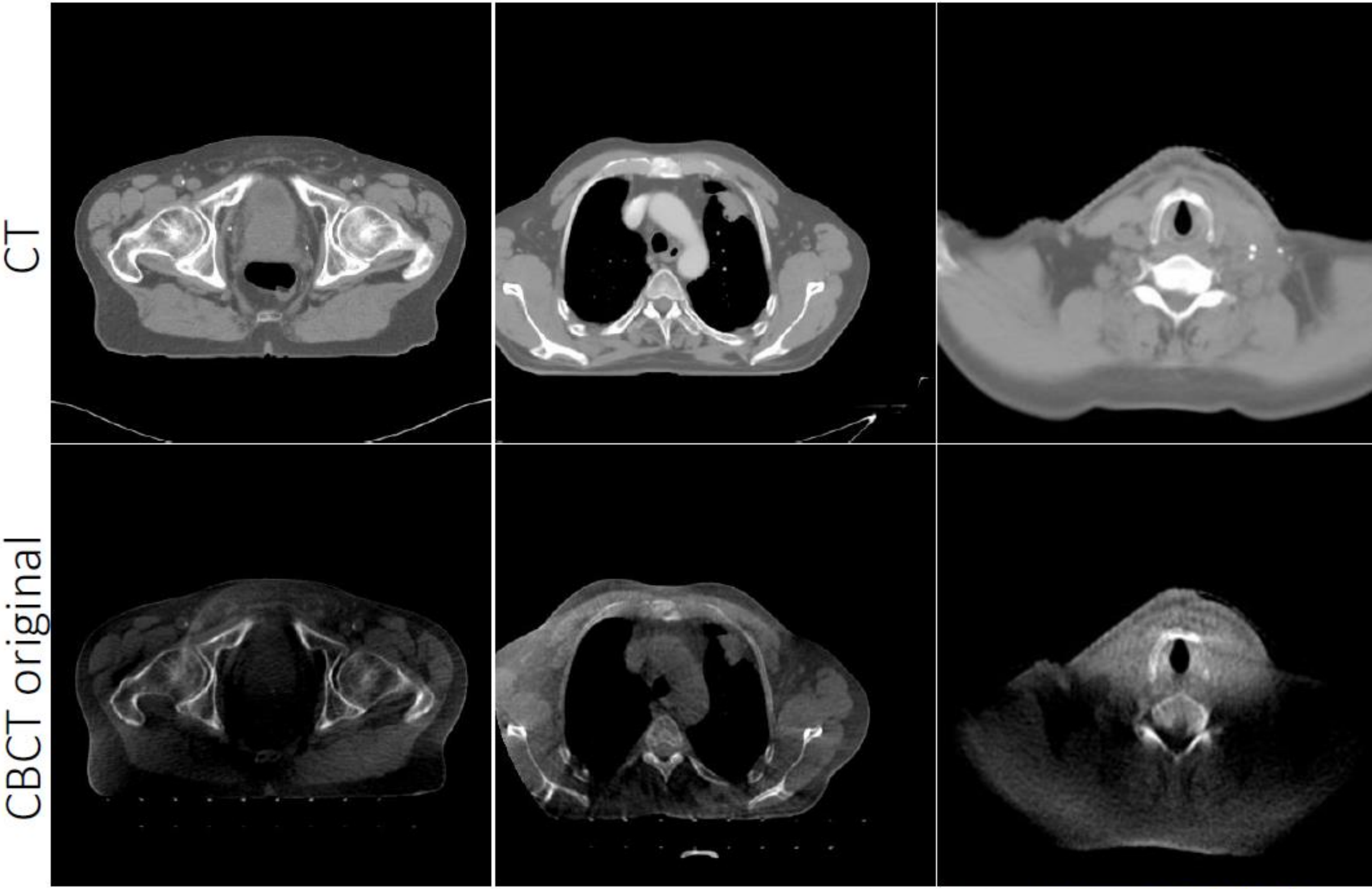


Make CBCT suitable for dose calculation

Szeto et al, NKI 2016

The Christie NHS
NHS Foundation Trust

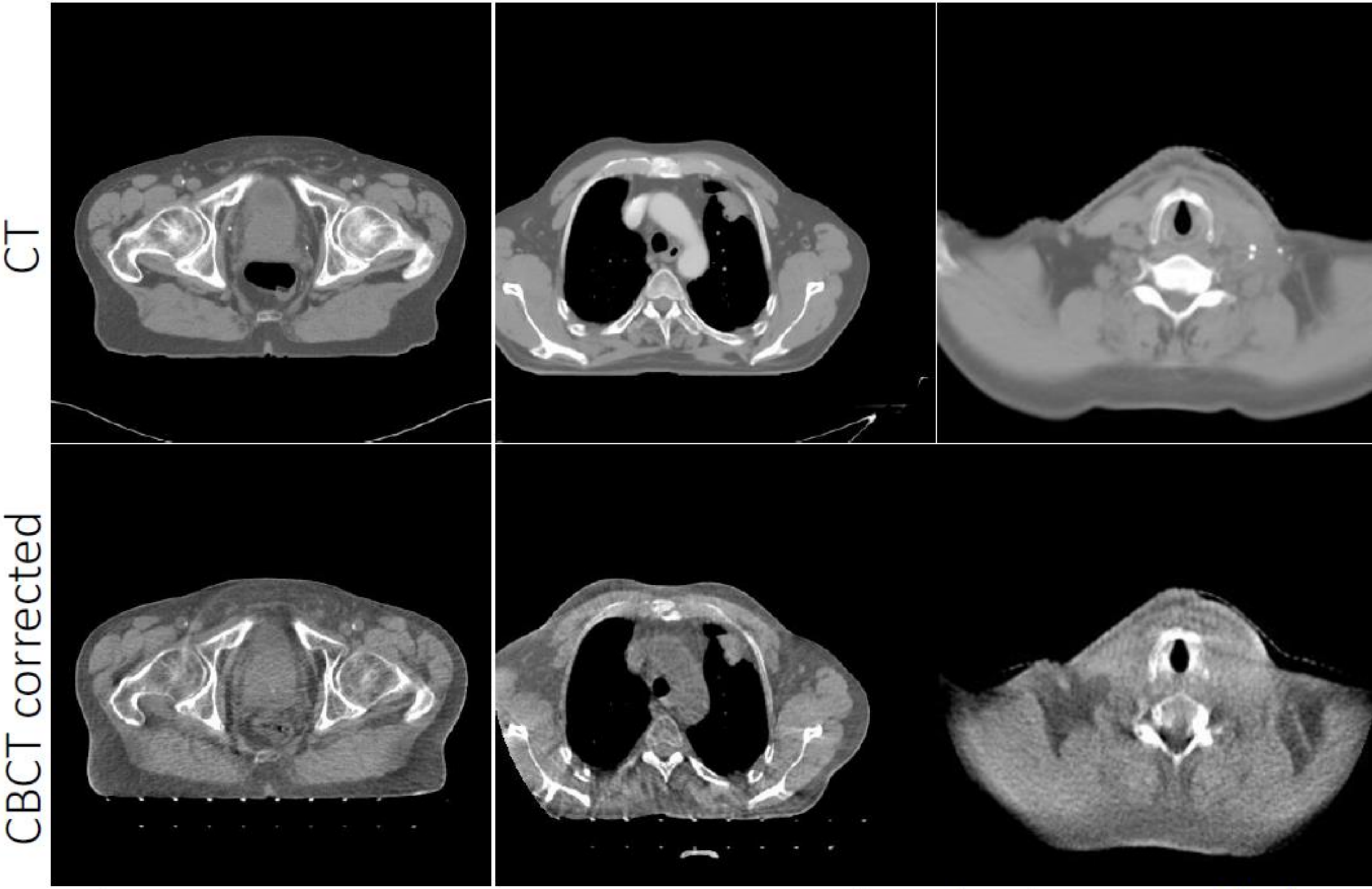
Shading correction examples



•Marchant and Yoshi, SPIE 2017

Examples at www.cscart.tech

Shading correction examples



• Marchant and Yoshi, SPIE 2017

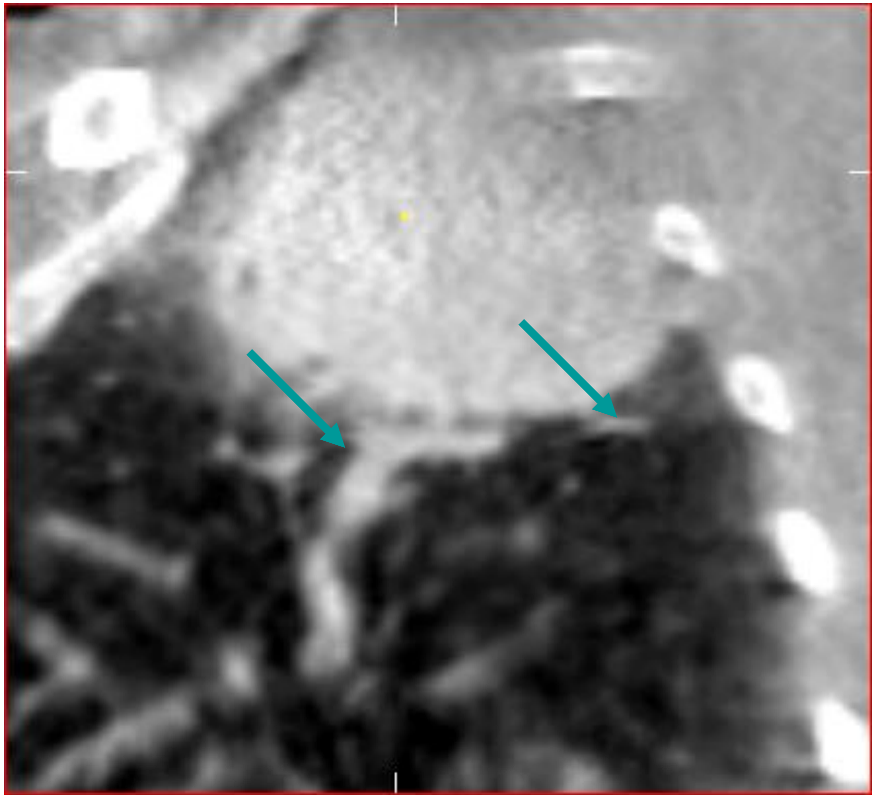
Examples at www.cscart.tech

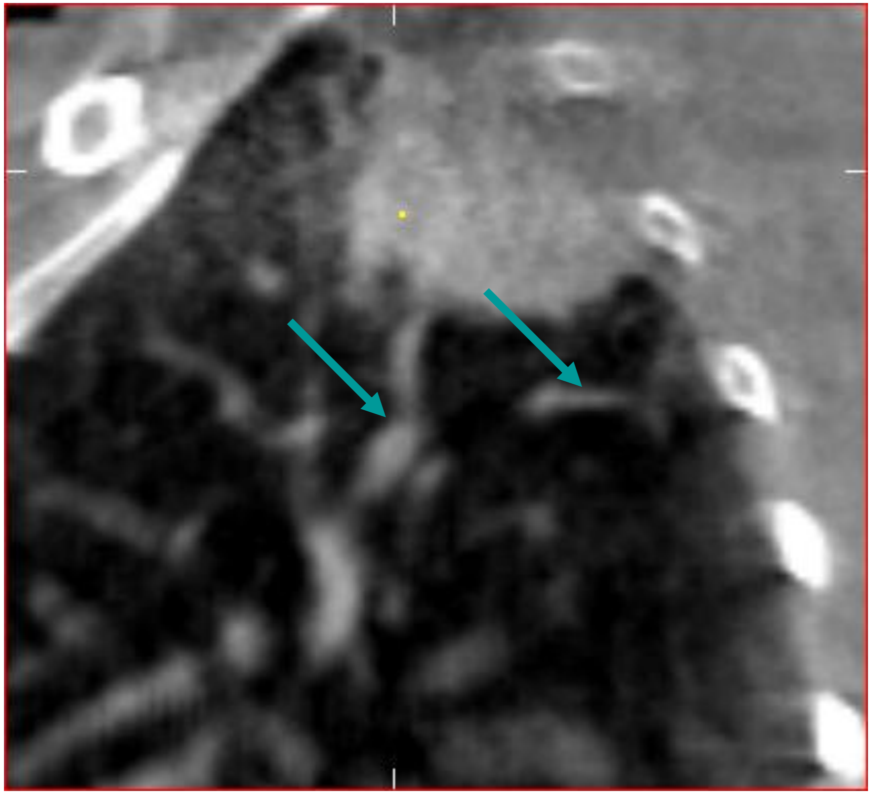
Contour propagation

- Based on deformable registration between planning CT and repeat CT
- May be useful for OAR contours
    - Editing often needed
- Take extreme care with GTV and CTV contours
    - Use rigid propagation if unsure

The Christie NHS
NHS Foundation Trust

Non-elastic tumour regression





JJ Sonke NKI

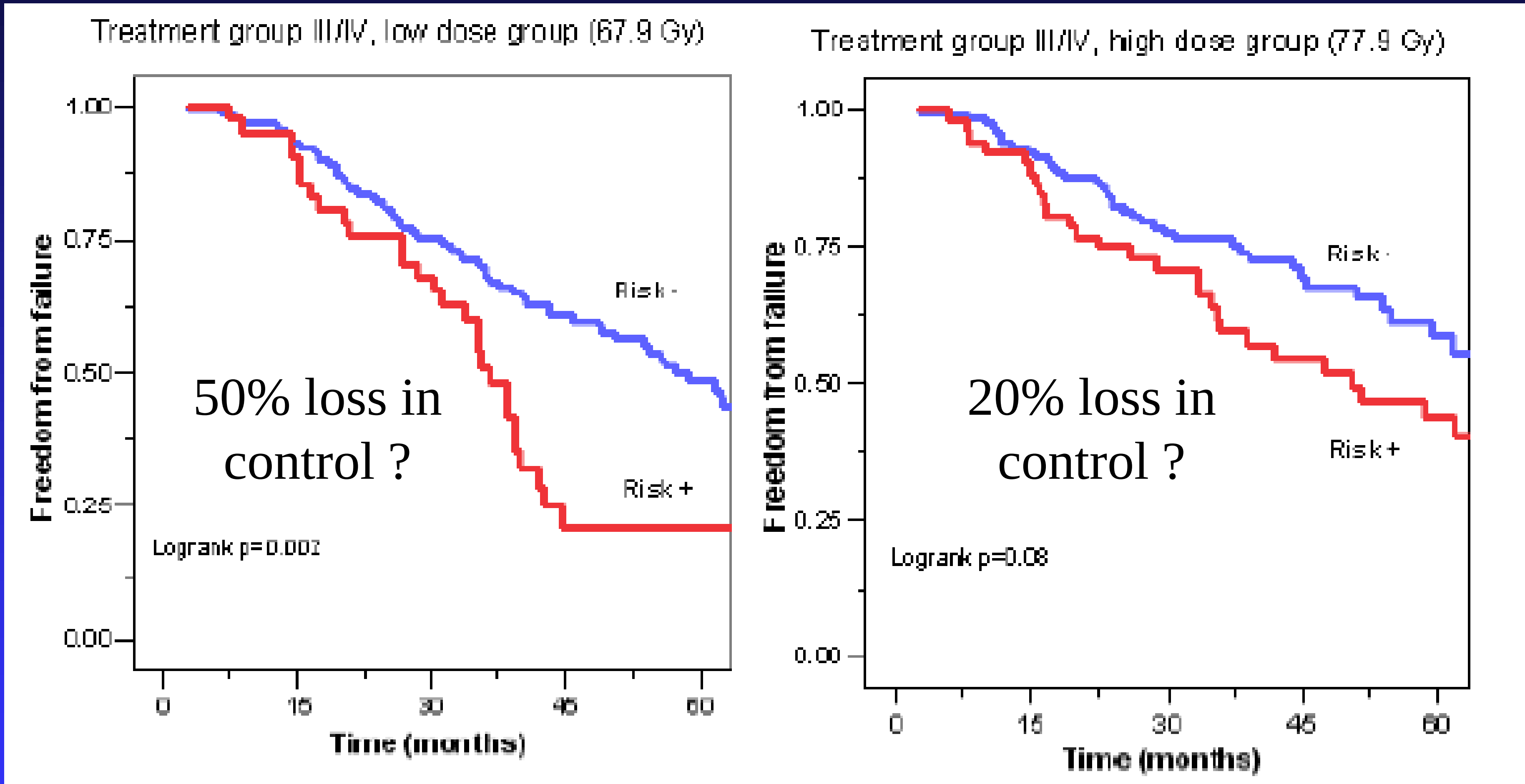
Have we forgotten about the ALARA principle in IGRT ? (2007 presentation)

Marcel van Herk

Radiotherapy Department

Netherlands Cancer Institute

IGRT important: prostate trial data (660 patients without IGRT)



Risk+: initial full rectum, later diarrhea

Heemsbergen at al, 2006

ALARA

- As Low As Reasonably Achievable
  - Refers to diagnostic imaging dose
  - Minimize risk of inducing cancer

ALARA in radiotherapy ?

☹ ☹ ☹ ☹ ☹

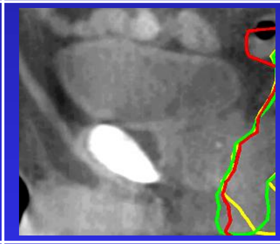
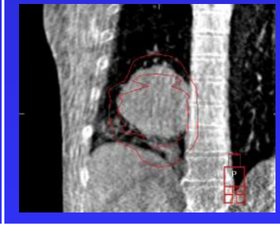
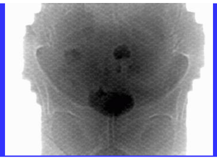
- Do not treat the patients → † † † † †
- Treat them with a low dose → † † † † ☺
- Treat without imaging (may miss) → † ☹ ☺ ☺ ☺
- Treat with imaging to the right place → ☺ ☺ ☺ ☺ ☺
- Imaging dose induced cancer → ?
  - Depends on protocol used, organs, age, predisposition, life expectancy

Cone beam CT - Elekta Synergy system

- 1997: proposed by David Jaffray and John Wong
- 2003: installation and software development at NKI
- 2004: prototype in routine clinical use at NKI
- July 2005: Released for clinical use in Europe (4 systems in NKI)

Over 20000 scans made at NKI – 25 GByte per machine per week

Selected dose levels for cone beam CT versus EPID at NKI

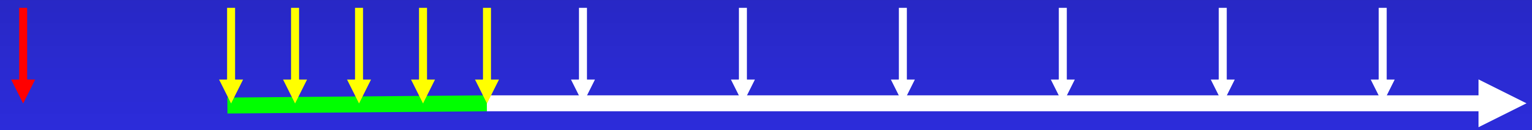
	Center dose	Skin dose	Sample image
Head and neck / 25 cm field of view (320 frames, 65 sec)	0.1 cGy - 1.0 cGy	0.15 cGy 1.5 cGy	
Prostate / 40 cm field of view (640 frames, 120 sec, bowtie filter)	≈ 3 cGy	≈ 3 cGy	
4D Lung / 25 cm field of view (640 frames, 240 sec)	≈ 2.2 cGy	≈ 3 cGy	
EPID – 2 x 5 MU	≈ 8 - 9 cGy	≈ 2 - 4 cGy	

Example ‘high’ imaging dose protocol

Adaptive radiotherapy (ART) for prostate:

Conventional plan, 10 mm

Average prostate & rectum adaptive plan, 7 mm *



CBCT first *5* days
3 cGy per scan

weekly monitoring treatment
(bony anatomy set-up protocol)

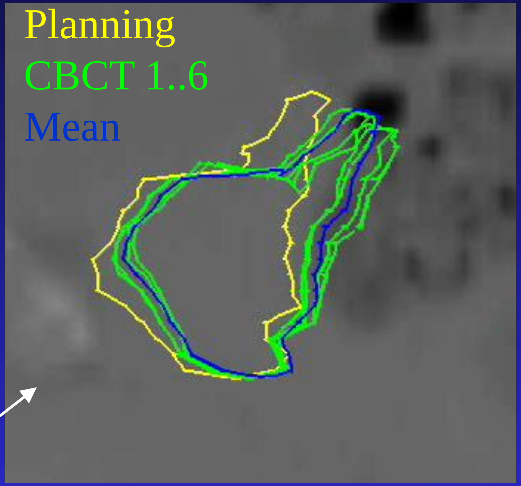
Until May 2007, 67 patients treated **

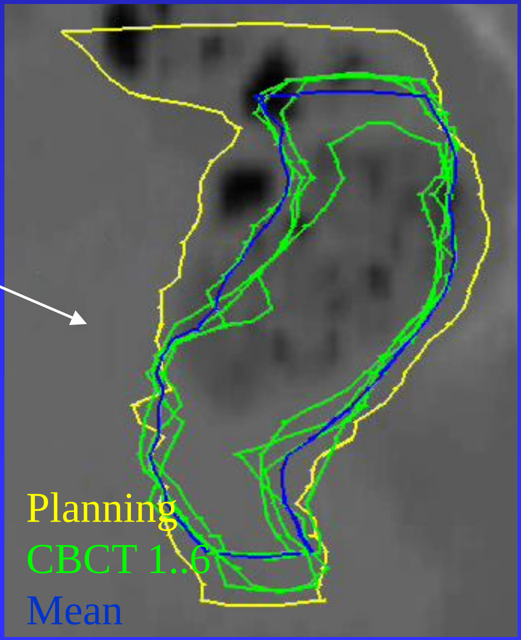
** Nuver et al. IJROBP 67 (2007)*

*** Nijkamp et al. IJROBP 2007*

Prostate adaptive RT

- Mild laxation to reduce rectal gas
- SIB plan (78 Gy) with 10 mm margin for first 6 fractions
  - 6 cone beam scans
- Automatically detect prostate motion and delineate rectum in cone beam scans
  - Generate prostate in mean position
  - Generate mean rectum
- Replan using mean prostate / rectum with 7 mm margin and treat remaining fractions
- Results in better GTV coverage and rectum sparing (≈ 30% less rectum NTCP)

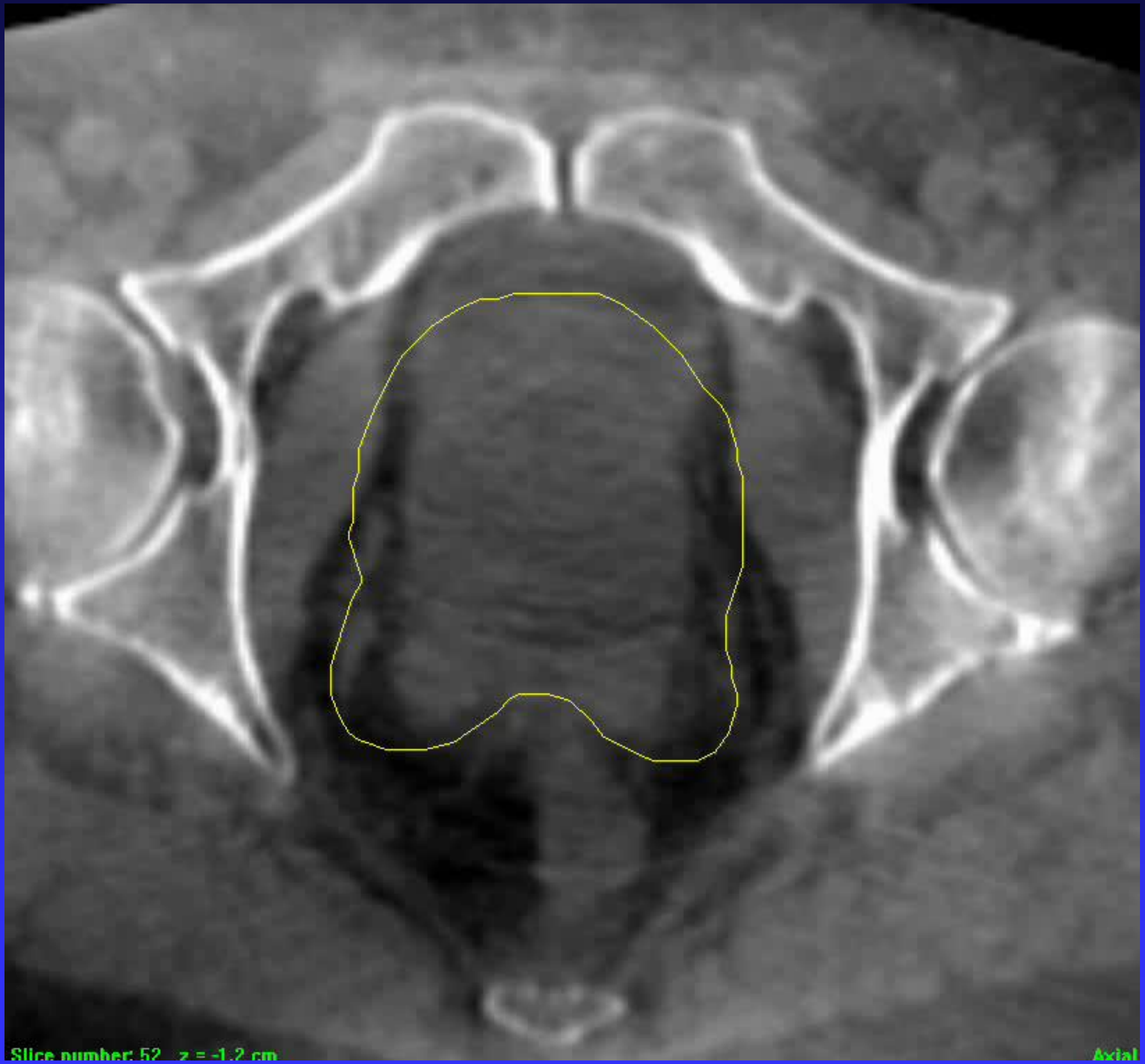




Weekly scans (3 cGy) to monitor treatment

average CTV +

7 mm margin



Out of 67 patients, only 6 showed marginal miss

The rectum is spared, but what about the dose to other normal tissues ?

- Described by integral dose (Gy . kg = J)

- Dose due to imaging ≈ 3 J for:
  - 10 scans
  - Soft tissue imaging (3 cGy)
  - 40 x 25 x 12 cm^3 scan volume

- Dose due to treatment ≈ 100 J for:
  - Tumor size: ≈ 6 cm for prostate
  - Margin: 10 mm
  - Dose: 78 Gy
  - Treatment technique: photon IMRT

Imaging dose in more detail (10 scans)

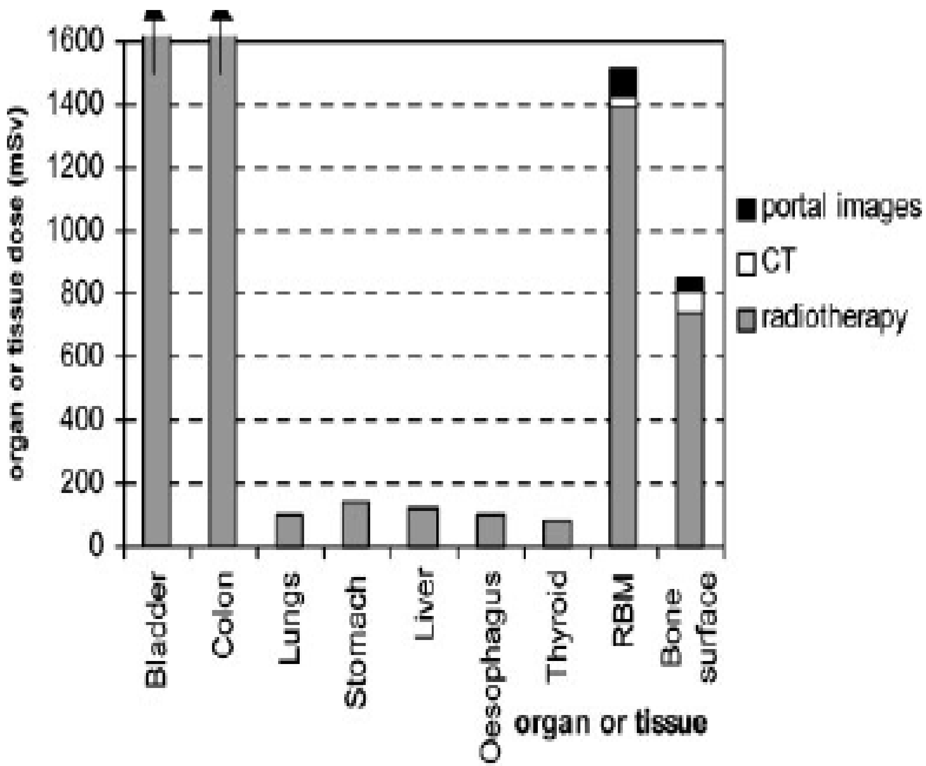
The British Journal of Radiology, *79* (2006), 487–496

Organ doses from prostate radiotherapy and associated concomitant exposures

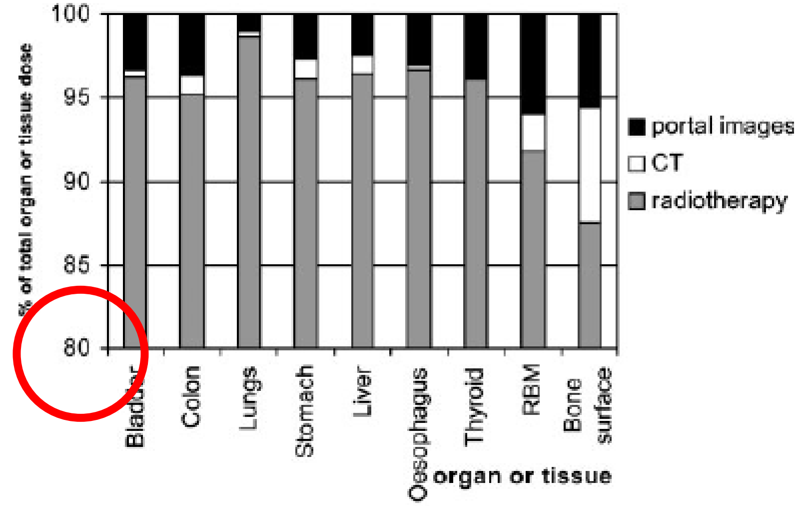
[1]R M HARRISON, PhD, [1]M WILKINSON, DCR(T), [1]A SHEMILT, BSc, [1]D J RAWLINGS, MPhil, [1]M MOORE and [2]A R LECOMBER, PhD

[1]Regional Medical Physics Department, Newcastle General Hospital,

absolute dose (prostate)



relative dose



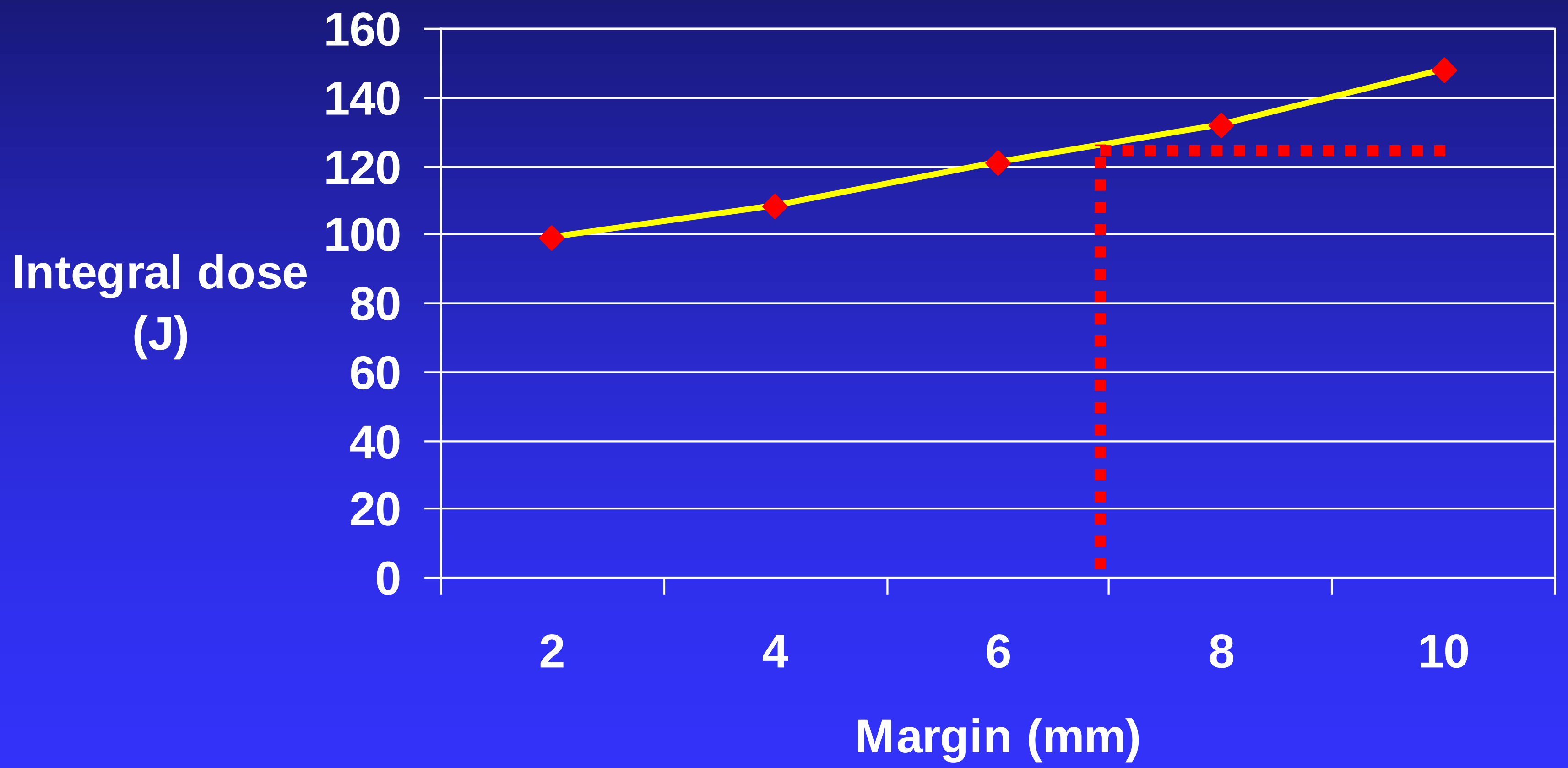
(b)

Figure 4. Organ doses from radiotherapy (photons and neutrons), 10 CT scans and 36 portal images for each organ or tissue (a) total doses for each organ and (b) % contribution of radiotherapy, CT scanning and portal imaging. Mean bladder, colon and rectal doses were 29.9 Gy, 2.8 Gy and 25 Gy, respectively.

So, we added a few % extra dose for imaging

- We may have improved outcome by as much as 20%
- Do organs now get more dose?
- No: we reduced their dose because we reduced the margin from 10 to 7 mm

Integral dose versus margin (prostate IMRT)



21 J integral dose reduction going from 10 mm to 7 mm margin

So, we added a few % extra dose for imaging

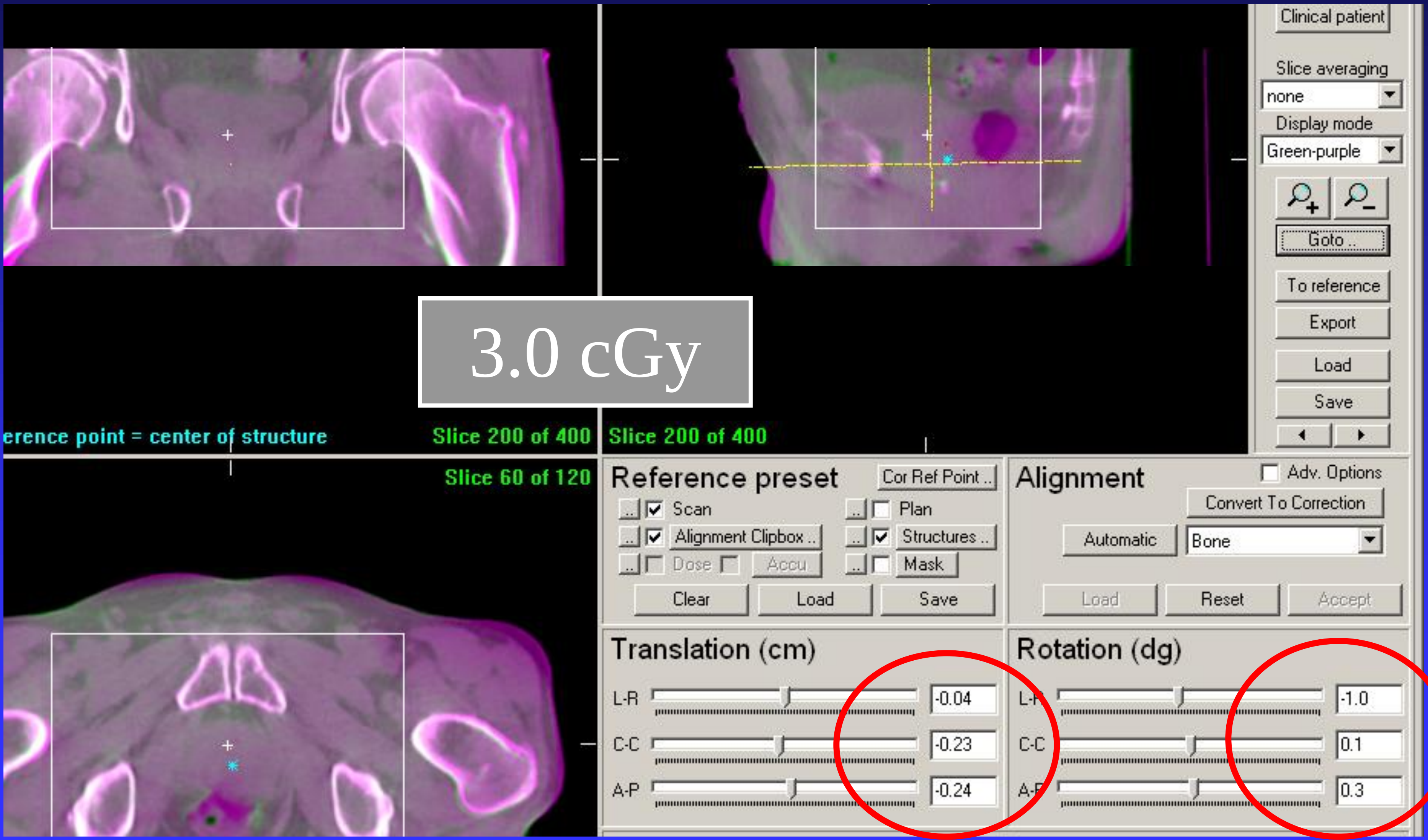
- We have improved outcome
- Spurious dose reduced by 21 - 3 J = 18 J
- Could we have used even lower dose imaging and markers ?

Sure: markers are good

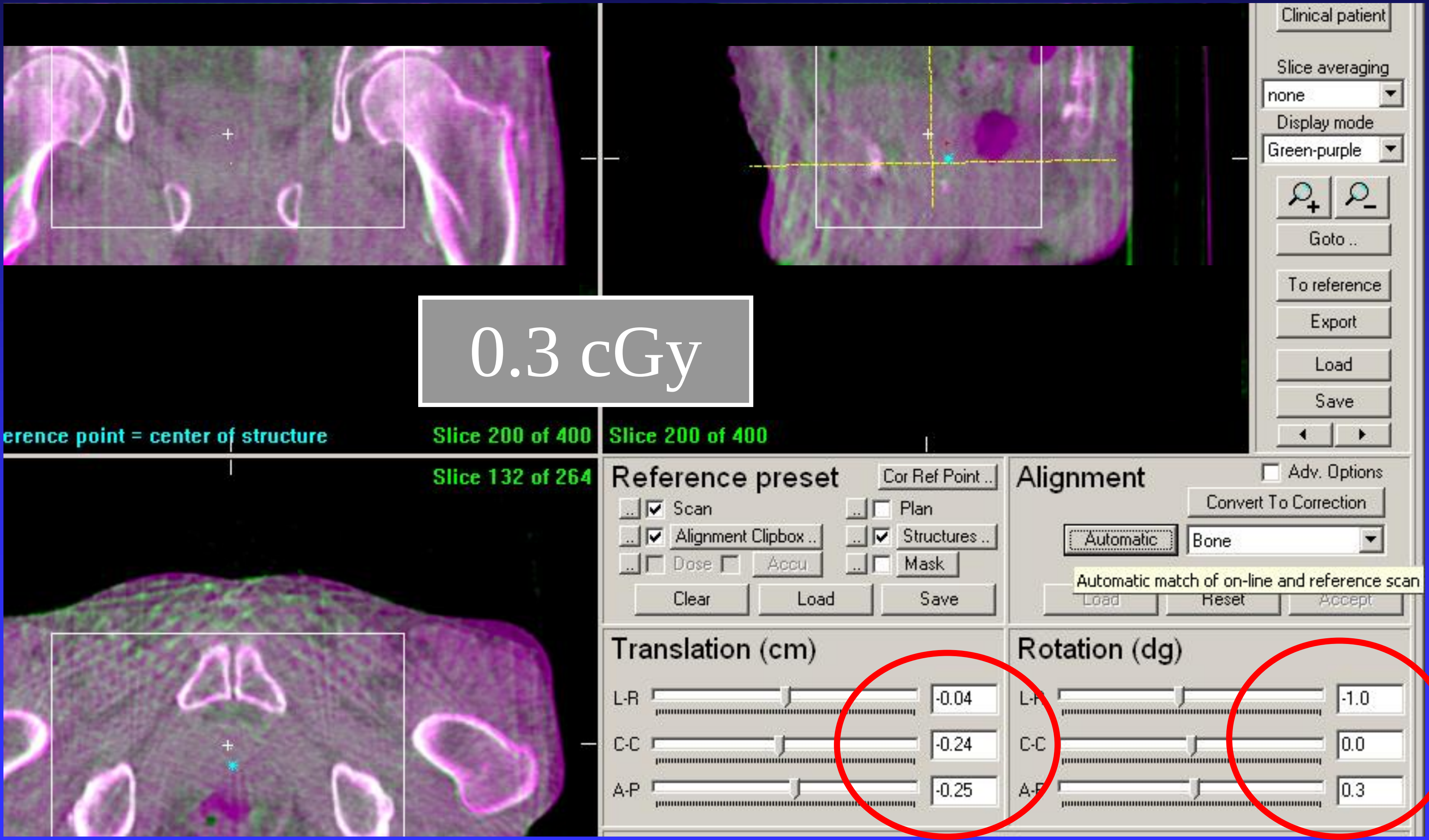
- Markers increase image contrast
- But: they do not tell you where the rectum is
- Don’t shoot the messenger: CBCT is just a way to visualize contrast just like X-ray
- CBCT and X-ray require same dose for same task

→ Best: markers + lower dose cone beam CT

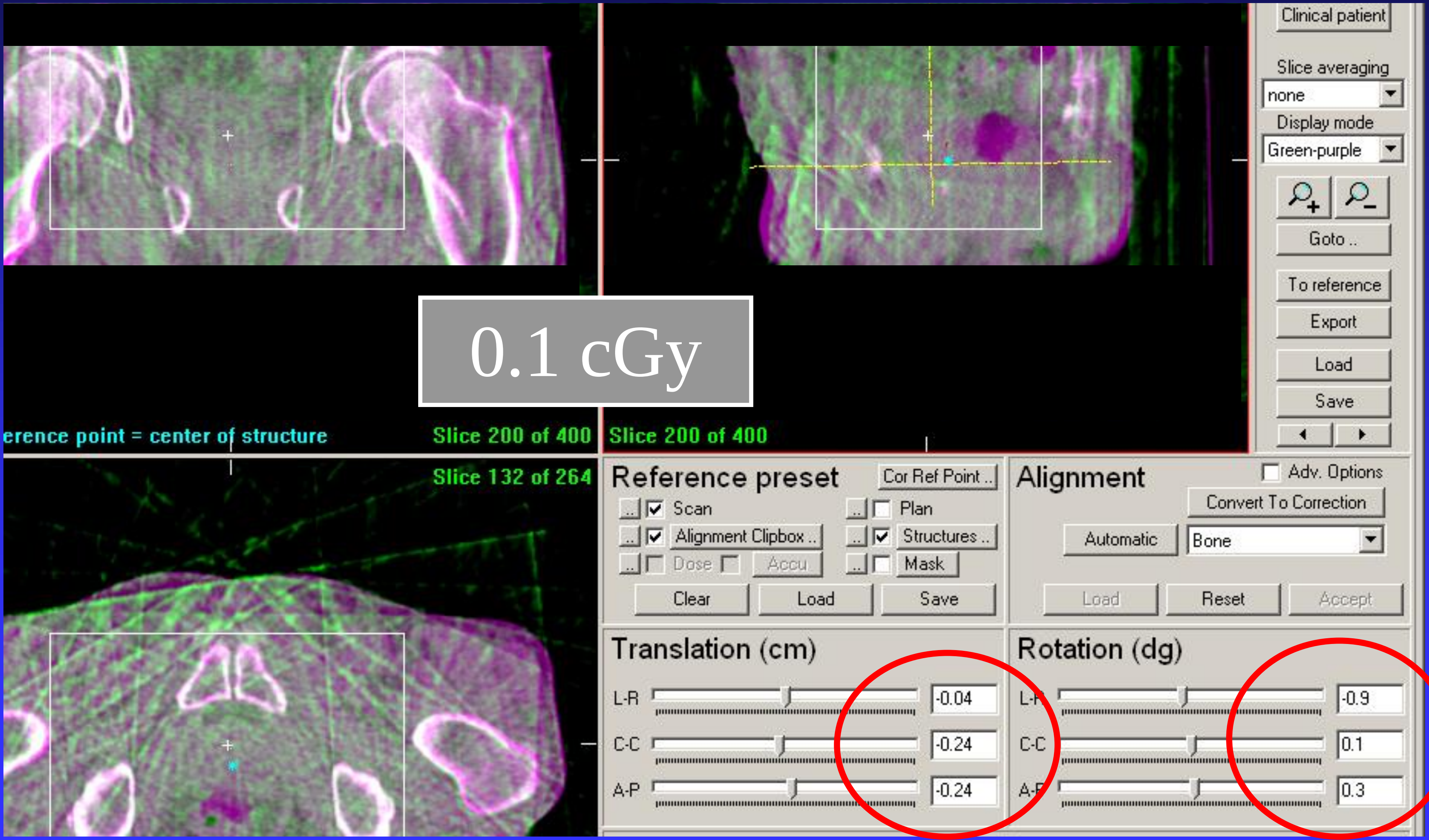
Dose required to localize bone with CBCT



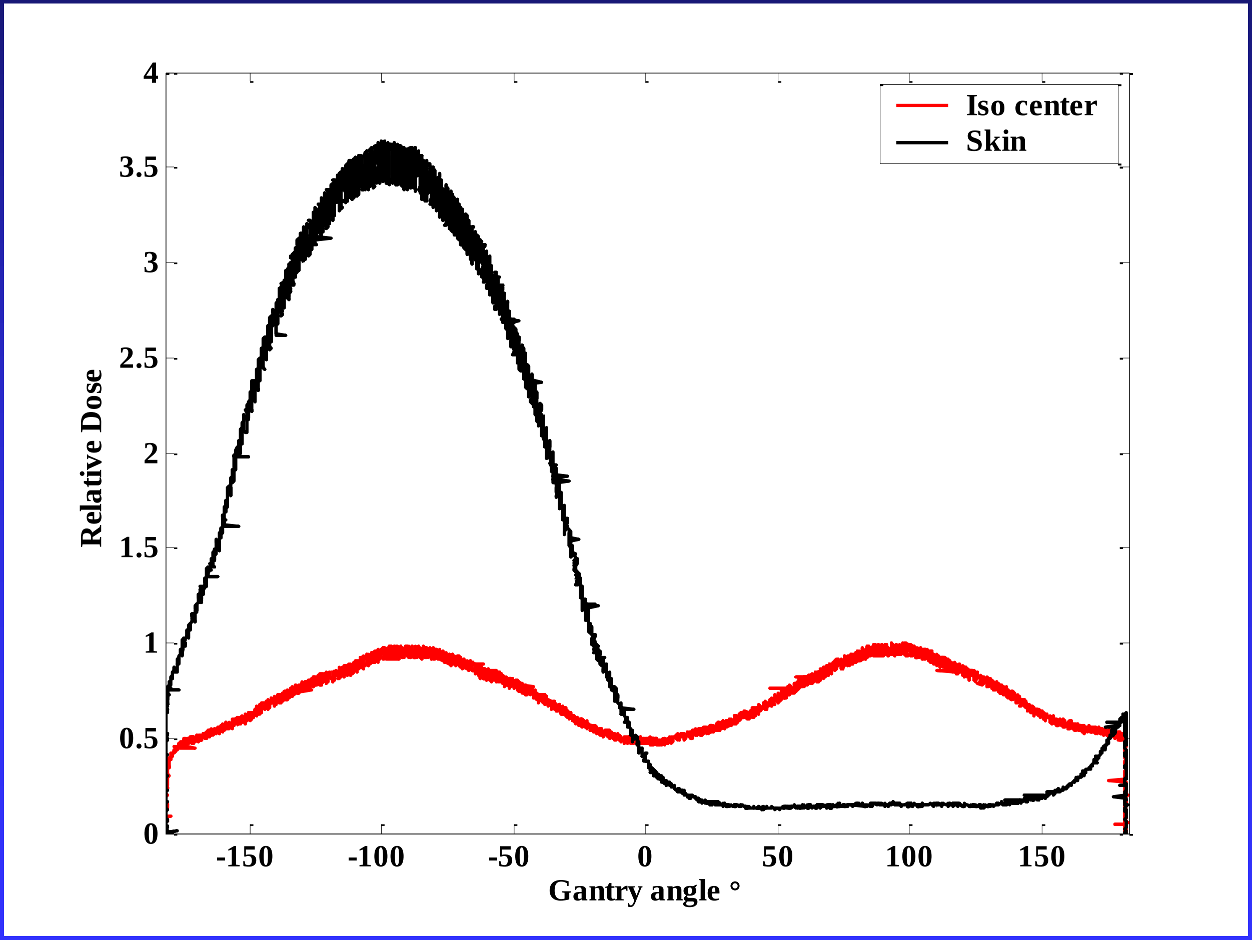
Dose required to localize bone with CBCT



Dose required to localize bone with CBCT



With a half rotation scan, you can spare half the patient: eyes, gonads, contralateral breast etc



The AHARA principle

- Make patient cure As High As Reasonably Achievable
  - Kill tumor and ….
  - limit complications by precisely delivering the treatment
  - Reduce secondary cancer by reducing the margin
- Imaging (dose) is required to:
  - Eliminate geometric miss → improve outcome
  - Lower dose to adjacent organs at risk like rectum
  - Smaller margins → lower integral dose
- Imaging dose contributes a few % to organs that already receive a fairly high dose due to radiotherapy: → order of magnitude less important than having good treatment

Acknowledgements

- Jonathan Sykes (Manchester)
  - Tuesday 1240, auditorium: effect of imaging dose on image registration
- Jan Jakob Sonke and Peter Remeijer
  - CBCT dose measurements
- Erik-Jan Rijkhorst
  - Analysis of margin and integral dose
- Wilma Heemsbergen, Joos Lebesque and Peter Koper (Erasmus)
  - Trial data

ESTRO School

Break-up session RTT on BreathHold

Prague 2015

Rianne de Jong
Academic Medical Centre, Amsterdam

Helen McNair
Rms.nhs, London

ESTRO School

Workshop on BreathHold

As interactive as possible!

1. Powerpoint introduction
2. Panel discussion guided by questionnaire

ESTRO School

Workshop on BreathHold

Why BH? *- In 1 image -*

CT scanning - free breating and BH?

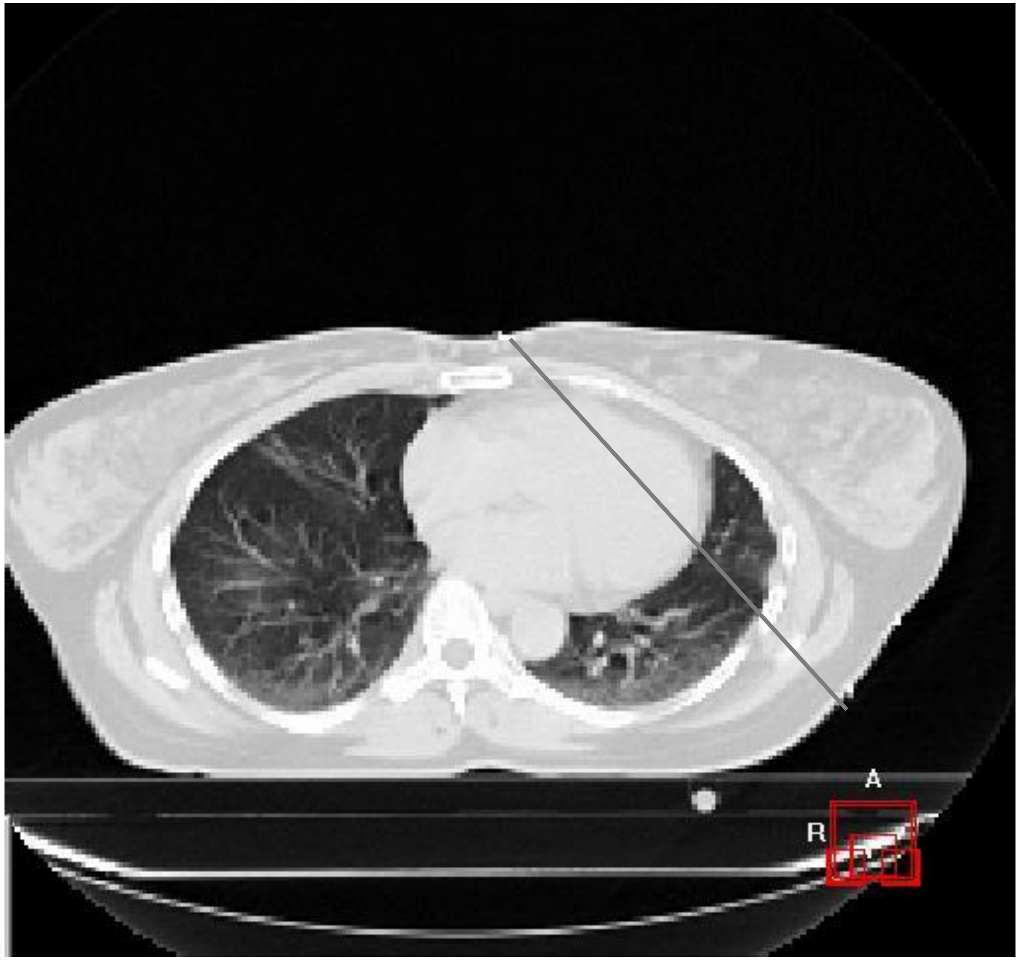
Setting up the patient - inspiration or expiration?

Imaging modalities - EPID or CBCT?

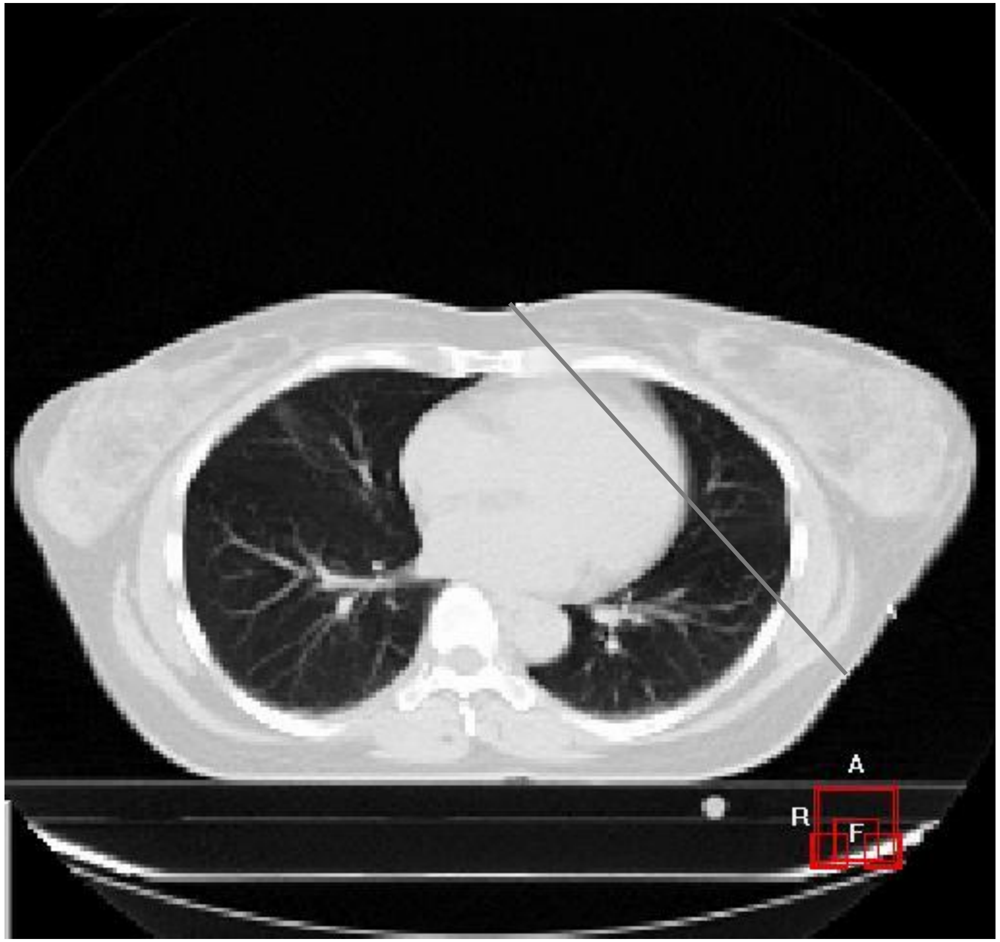
Monitoring intrafraction motion?

Breath hold

Normal inspiration



Deep inspiration



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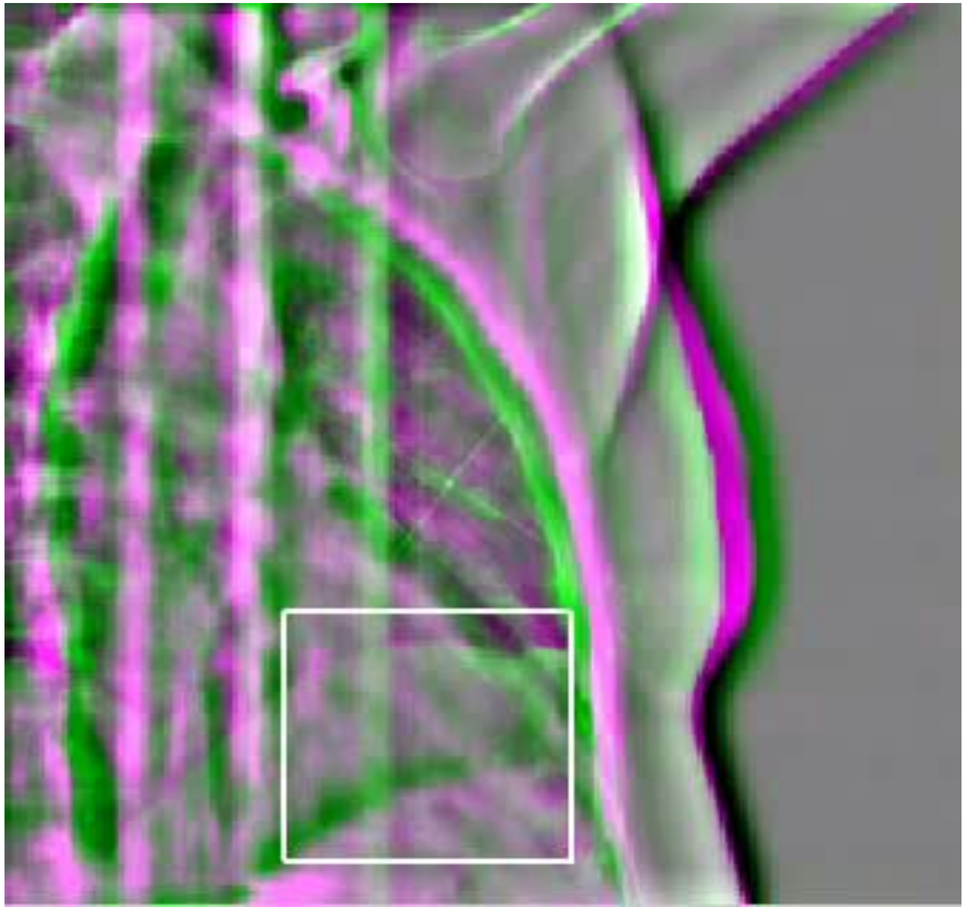
Setting up the patient

Inpiration

Expiration

kV movie loop before acquisition



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CC Reproducibility of ABC Breath Hold

	No. Images	Inter-fract. Reprod. (σ)	Intra-fract. Reprod. (σ)
Michigan	262	4.4 mm	2.5 mm
Toronto	257	3.4 mm	1.5 mm

IGRT required for maximal PTV reduction

Courtesy to Laura Dawson

Dawson LA. IJROBP 2001
Eccles, C, IJROBP, 2005

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Set-up error voluntary breath-hold

	Translations		
	LR (cm)	CC (cm)	AP (cm)
M	0.20	0.18	0.10
Σ	0.26	0.28	0.45
σ	0.25	0.28	0.38

Set-up error voluntary breath-hold

	Chest Wall			Diaphragm
	LR (cm)	CC (cm)	AP (cm)	CC (cm)
M	0.20	0.18	0.10	0.08
Σ	0.26	0.28	0.45	0.88
σ	0.25	0.28	0.38	0.58

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Monitoring Intra fraction Motion during BH

Automatic Breathing Coordination

- software feedback using a thresh-hold

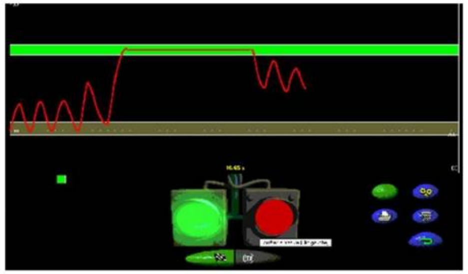
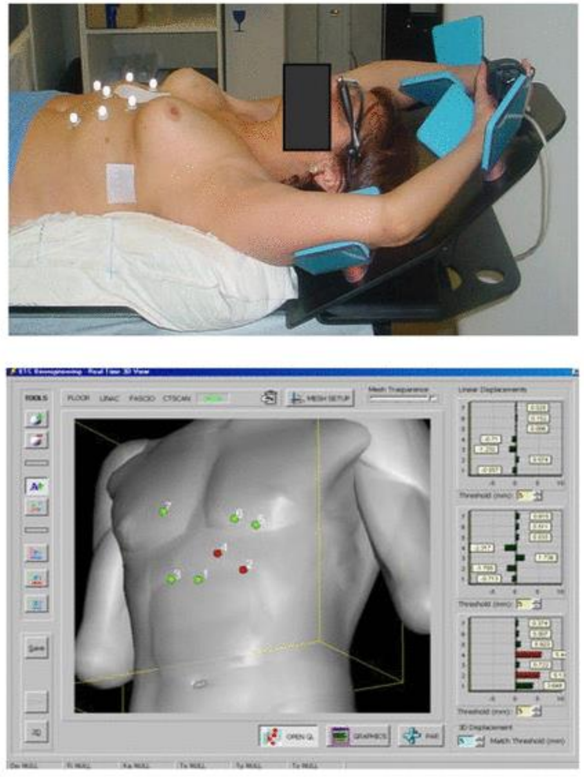


Figure 3: Diagram of the respiratory trace visualized by the patient in goggles screen and the therapist with the SDX device during a self-held breath-hold. The patient sees the evolution of his lung volume over time (yellow curve) and its breathing amplitude (green zone) predetermined during the training session. After three cycles of free-breathing, the patient is asked to reach this amplitude and to maintain its breath-hold (yellow plateau of the curve). During this period the CT scan acquisition or irradiation is done. He then resumed his normal breathing.

Monitoring Intra fraction Motion during BH

Voluntary BreathHold (deep or moderate):

- Visual monitoring with lines that mark the treatment fields
- Visual with pin that mark the chestwall height
- Using RPM feedback
- Using exactrac feedback
- Using movie loop of portal images with structure overlay
- Using surface rendering system feedback



(a) (b)