Assessment and Management of Uncertainties: Overview and Examples in the Pelvis

Prostate Cancer Radiotherapy

Patrick Kupelian, M.D.
James Lamb, Ph.D.

University of California Los Angeles
Department of Radiation Oncology

August 2011

Disclosures

Research grants / Honoraria / Advisory Board:

Tomotherapy Inc.
Varian Medical
Siemens
Viewray Inc.

PELVIC SITES

	Dose	High Dose Target Size	Current RT Use
Uncertainties matter more if:	*High*	*Small*	*Frequent*
Pelvic Sites / Diseases:			
Prostate	High	Small	Frequent
Lower GI (rectum / anus)	Low	Large	Infrequent
GYN (Cervix – with Brachy)	Low	Large	Infrequent
GYN (Cervix – Definitive IMRT)	High	Small	Rare
GYN (Endometrium)	Low	Large	Infrequent
Bladder	High	Small	Rare
Testicular Ca	Low	Large	Infrequent

Introduction

Current Outcomes (Disease control)

a. Depends on risk groups: Low versus Intermediate vs High
(mostly defined by Stage, PSA, Gleason score)

b. Low / Intermediate risk: High cure rates (90%+)

c. High risk: Lower cure rates (50-80%): Use Hormonal Therapy

d. Competition with surgery: Always need to improve local therapy

Introduction

Current Outcomes (toxicity)

a. Minimal radiotherapy-associated toxicity:
Rectal / Urinary / Sexual

b. Low / Intermediate risk patients:
Manage radiotherapy toxicity

c. High risk patients:
Manage hormonal therapy toxicity

Introduction

1. High RT doses needed for local control:
   a. Standard dose fractionation: 75-81 Gy @ 1.8-2.0 Gy
   b. Moderate Hypofractionation: 50-72 Gy @ 2-5 Gy
   c. Extreme Hypofrationation: 36-50 Gy @ 6-10 Gy

2. Modalities:
   a. Conformal / IMRT
   b. Protons
   c. Brachytherapy

3. Most important sources of uncertainty:
   a. Delineation of the target
   b. Localization of the prostate during treatment

Target Delineation Uncertainty

PROSTATE DELINEATION: CT

A study of prostate delineation referenced against a gold standard created from the visible human data

Zhanrong Gao[b,*], David Wilkins[a,b,c], Libni Eapen[a,c], Christopher Morash[c], Youssef Wassef[c], Lee Gerig[a,b,c]

[a]Department of Radiation Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Canada, [b]Department of Physics, Carleton University, Ottawa, Canada, [c]Department of Medicine, University Of Ottawa, Ottawa, Canada

Radiotherapy and Oncology, 2007

"…radiation oncologists are more concerned with the unintentional inclusion of rectal tissue than they are in missing prostate volume. In contrast, they are likely to overextend the anterior boundary of the prostate to encompass normal tissue such as the bladder".

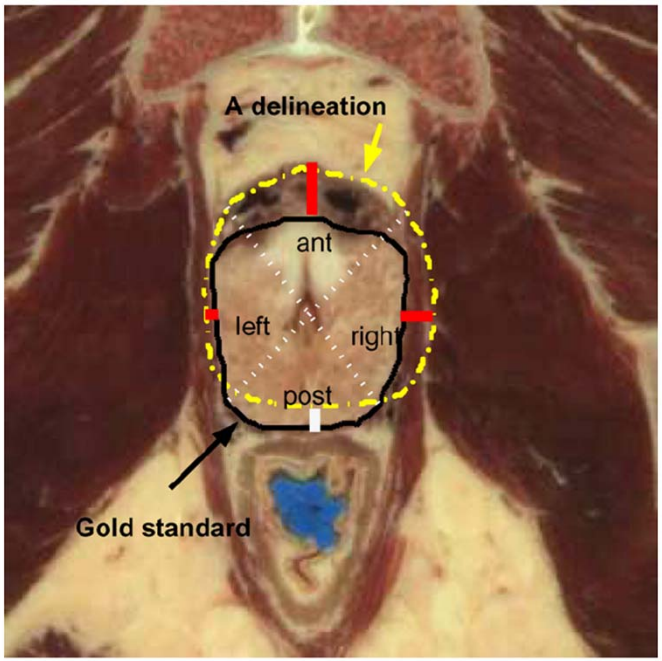


Fig. 2. An example of the difference between the gold standard contour and a representative CT based physician contour. Both are superimposed on the anatomical image and the ''Gap'' between the two in each of the four principal axes is shown.

PROSTATE DELINEATION: CT vs MRI vs US

MRI believed to be more accurate than by CT

MR-based contours are typically smaller than CT-based contours

Registration of CT to MR images is important:

- Use implanted fiducial markers if available.
- Do not use bony anatomy

Use of MRI images alone for planning?

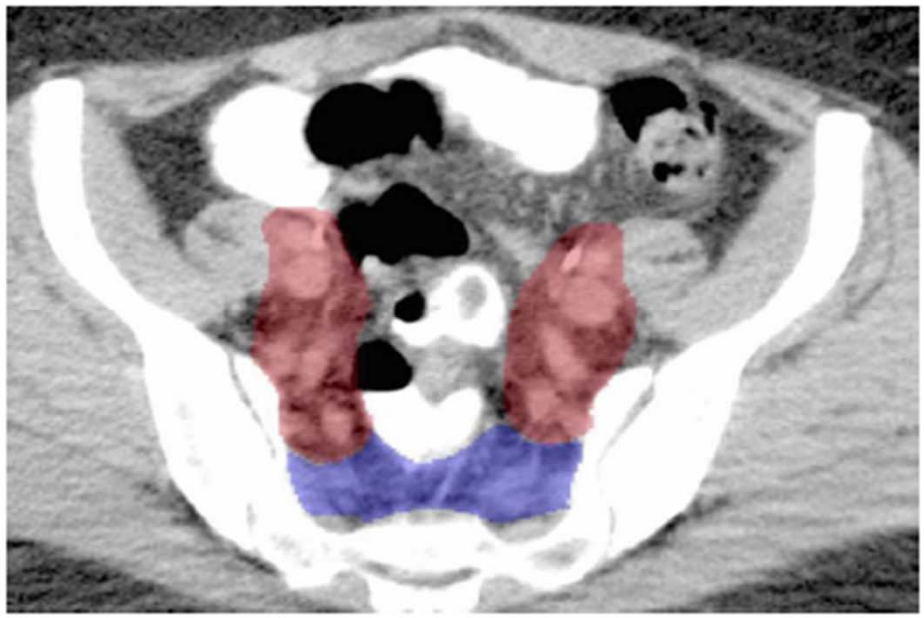
Ultrasound is routinely used in brachytherapy:

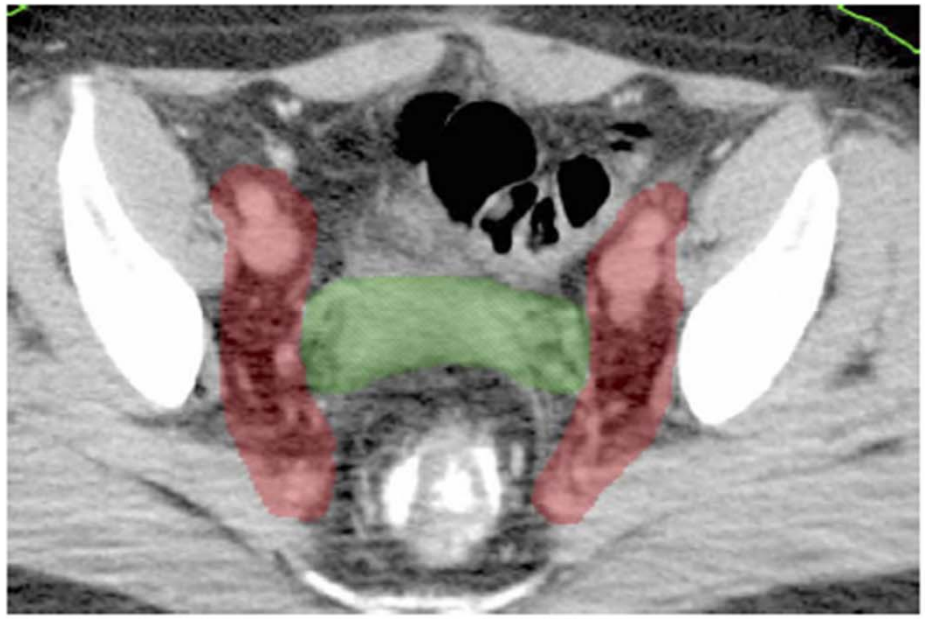
- Volumes closer to MRI?
- Definition of bladder/rectum volumes on US?

Rasch. IJROBP. **43**, 57-66,1999
Parker. IJROBP. **66**, 217-224, 2003

CONSENSUS GUIDELINES FOR DELINEATION OF CLINICAL TARGET VOLUME FOR INTENSITY-MODULATED PELVIC RADIOTHERAPY IN POSTOPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER

WILLIAM SMALL, JR., M.D.,* LOREN K. MELL, M.D.,† PENNY ANDERSON, M.D.,‡
CARIEN CREUTZBERG, M.D.,§ JENNIFER DE LOS SANTOS, M.D.,¶ DAVID GAFFNEY, M.D., PH.D.,‖
ANUJA JHINGRAN, M.D.,# LORRAINE PORTELANCE, M.D.,** TRACEY SCHEFTER, M.D.,††
REVATHY IYER, M.D.,‡‡ MAHESH VARIA, M.D.,§§ KATHRYN WINTER, M.S.,¶¶ AND ARNO J. MUNDT, M.D.‖‖





IJROBP 2008;71:428

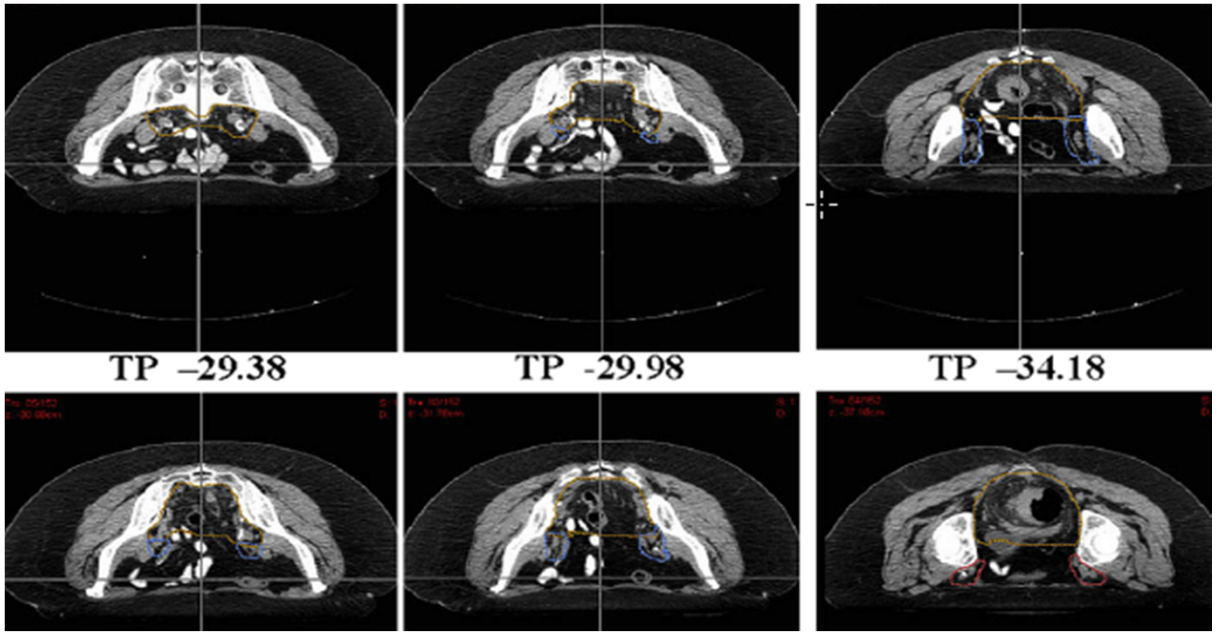
Courtesy: AJ Mundt

Consensus Target Delineation Guidelines

CLINICAL INVESTIGATION **Rectum**

ELECTIVE CLINICAL TARGET VOLUMES FOR CONFORMAL THERAPY IN ANORECTAL CANCER: A RADIATION THERAPY ONCOLOGY GROUP CONSENSUS PANEL CONTOURING ATLAS

ROBERT J. MYERSON, M.D., PH.D.,* MICHAEL C. GAROFALO, M.D.,† ISSAM EL NAQA, PH.D.,* ROSS A. ABRAMS, M.D.,‡ ADITYA APTE, PH.D.,* WALTER R. BOSCH, PH.D.,* PRAJNAN DAS, M.D.,§ LEONARD L. GUNDERSON, M.D.,‖ THEODORE S. HONG, M.D.,¶ J. J. JOHN KIM, M.D.,# CHRISTOPHER G. WILLETT, M.D.,** AND LISA A. KACHNIC, M.D.††



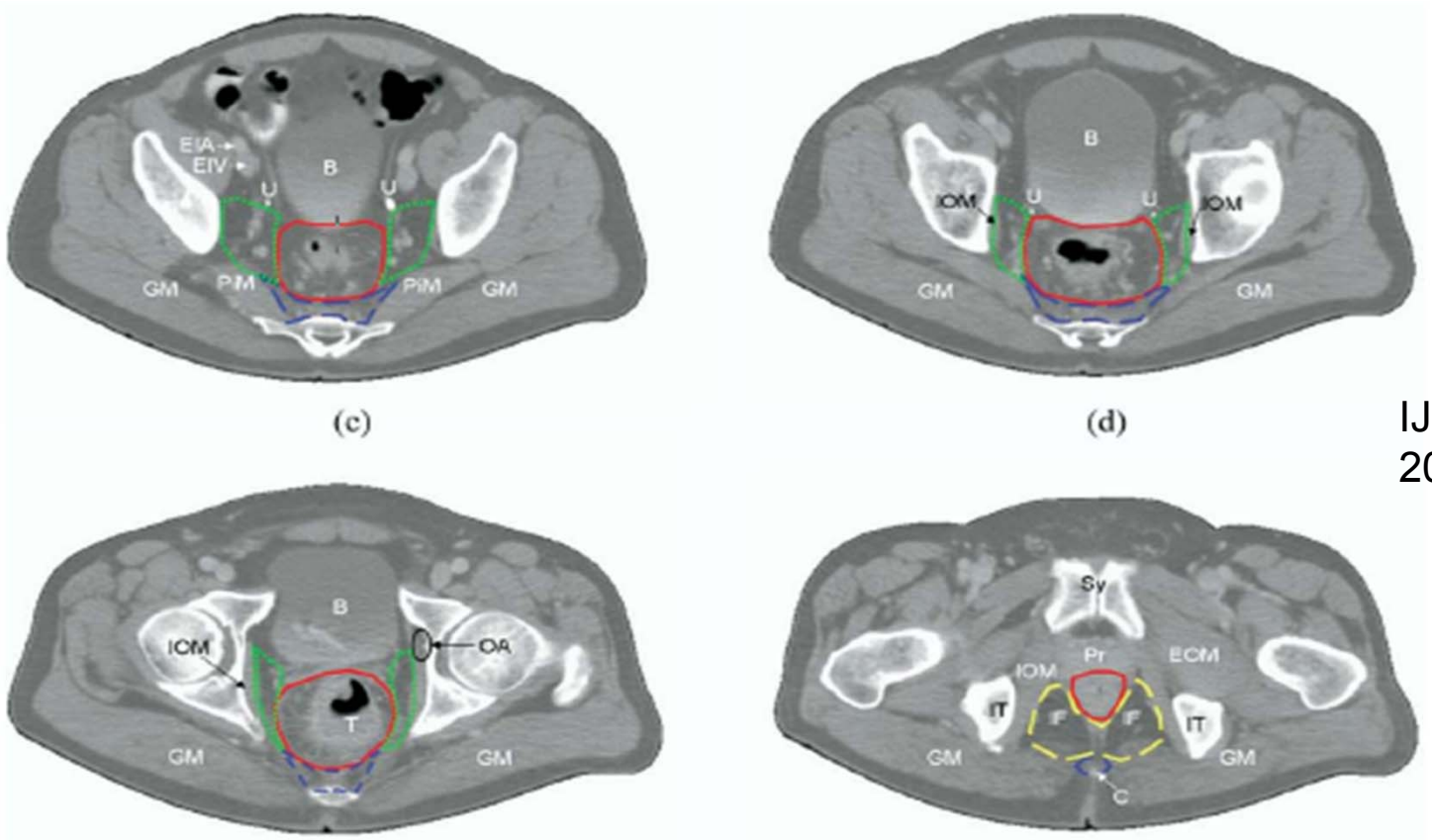
Myerson et al.
Red J 2009;74:824

Courtesy: AJ Mundt

DEFINITION AND DELINEATION OF THE CLINICAL TARGET VOLUME FOR RECTAL CANCER

SARAH ROELS, M.D.,* WIM DUTHOY, M.D.,§ KARIN HAUSTERMANS, M.D., PH.D.,* FREDDY PENNINCKX, M.D., PH.D.,† VINCENT VANDECAVEYE, M.D.,‡ TOM BOTERBERG, M.D.,§ AND WILFRIED DE NEVE, M.D., PH.D.§

Departments of *Radiotherapy, †Surgery, and ‡Radiology, University Hospital Gasthuisberg, Leuven, Belgium; and §Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium



IJROBP 2006;65:1129

Courtesy: AJ Mundt

Inter-Fraction Translations

Inter-fraction positional variations of the prostate with respect to bony anatomy are typically less than 5mm but with significant outliers above 5mm.

v. Herk. IJROBP. **33**, 1311-1320, 1995
Balter. IJROBP. **31**, 113-118, 1995
Schallenkamp. IJROBP. **63**, 800-811, 2005

Different approaches have been suggested to adjust for daily positional variations of the prostate, the residual errors exceeding 3 and 5 mm are still too frequent if daily adjustments are not made. This is due to the mostly random nature of such positional variations.

Setup adjustments should be performed using:

Images of the prostate (US, CT, MRI)
Surrogate of the prostate (markers or radiofrequency beacons)

Inter-Fraction Motion

Need for Daily Imaging?

74 patients, 2252 fractions, all IGRT with daily shifts.

Replay different alignment strategies;

Check residual errors vs actual daily shifts.

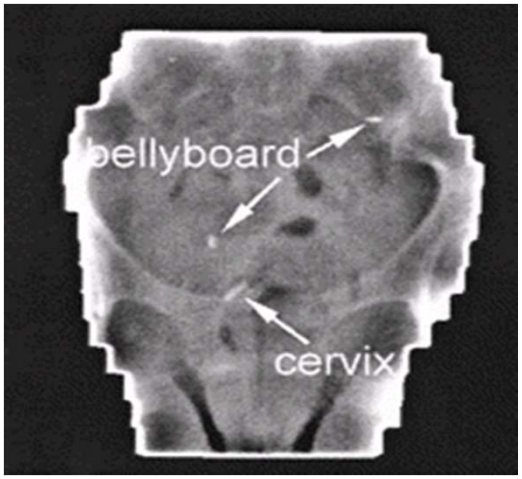
Significant proportions of residual errors with any scenario.

Example: Every other day imaging + apply running average;
Residual errors > 3 mm in ~40% of fractions
Residual errors > 5 mm in ~25% of fractions

→ Significant random component: Need daily imaging

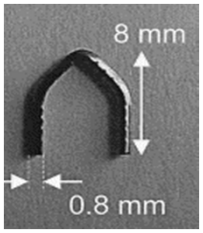
Kupelian et al., IJROBP, 70: 1146, 2008

Cervical Ca



Kaatee et al. IJROBP 2002;54:576

10 cervix pts with radiopaque tantalum markers
Track cervix position
Good image quality but lost ½ time before end of RT



Stroom et al. IJROBP 2000;46:499

14 gynecology patients
Based on boney landmarks
Action level > 4 mm

57% re-positioned
Average time ~ 3 minutes
↓PTV margins to 5 mm

Courtesy: AJ Mundt

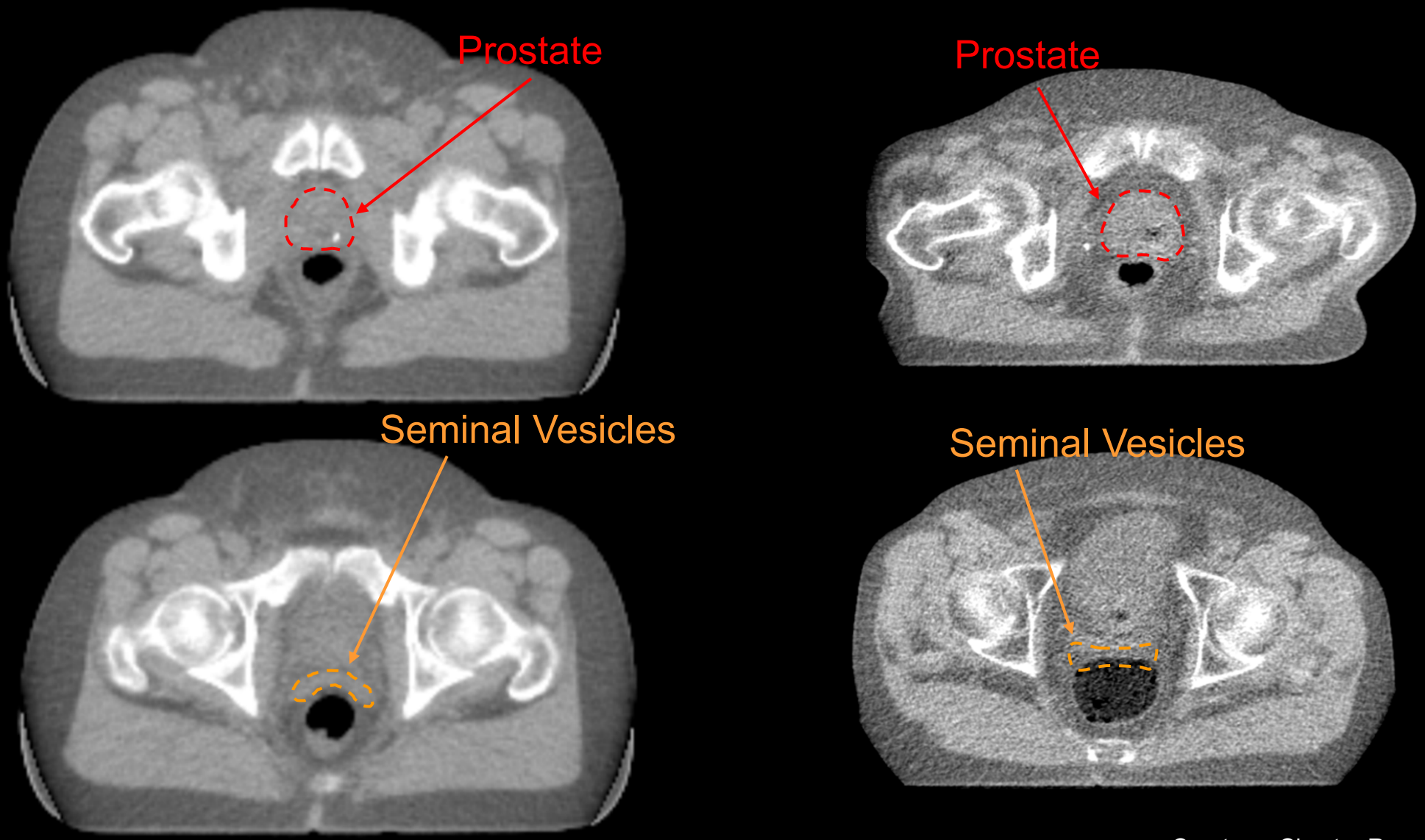
Interfraction Motion / Deformations

Geometry versus Dosimetry

Interfraction Anatomic Variations: Daily MVCTs

Alignment on markers

Alignment on mid gland prostate



Courtesy: Chester Ramsey

Inter-Fraction Deformation / Rotation

Target deformation includes deformation of the prostate gland itself and deformation of the seminal vesicles (SV) relative to the prostate gland, and the relative position of the prostate/SVs with respect to pelvic lymph node chains.

This deformation might or might not be detected with implanted fiducials (intermarker distance).

Kupelian. IJROBP, 62, 1291-1296, 2005
Kerkhof. PMB 53, 2008
v. d. Wielen. IJROBP. 72, 1604-1611, 2008
Mutanga. IJROBP, Article in Press, Corrected Proof, 2011
Deurloo. IJROBP, 61, 228-238, 2005
Smitsmans. IJROBP, Article in Press, Corrected Proof, 2011

PROSTATE;
Deformation of the gland itself probably has a negligible dosimetric effect on the prostate for conventionally-fractionated treatments.
Kerkhof PMB, 53, (2008).

SEMINAL VESICLES:
deformation of the SV relative to the prostate requires additional margins to avoid significant dosimetric errors.

Smitsmans et al IJROBP, 2011:13 patients with 296 CBCT,
Residual SV mis-alignment of the SVs [σ ~ 2-3mm], irrespective of whether rotational corrections based on marker registration were performed.
Margin requirement:

4.6mm in the left-right direction
7.6mm margin in the anterior-posterior direction

Is a 3-mm intrafractional margin sufficient for daily image-guided intensity-modulated radiation therapy of prostate cancer? ☆,☆☆

Adam D. Melancon[a,d], Jennifer C. O'Daniel[a], Lifei Zhang[a], Rajat J. Kudchadker[a], Deborah A. Kuban[b], Andrew K. Lee[b], Rex M. Cheung[b], Renaud de Crevoisier[b,1], Susan L. Tucker[c], Wayne D. Newhauser[a], Radhe Mohan[a], Lei Dong[a,*]

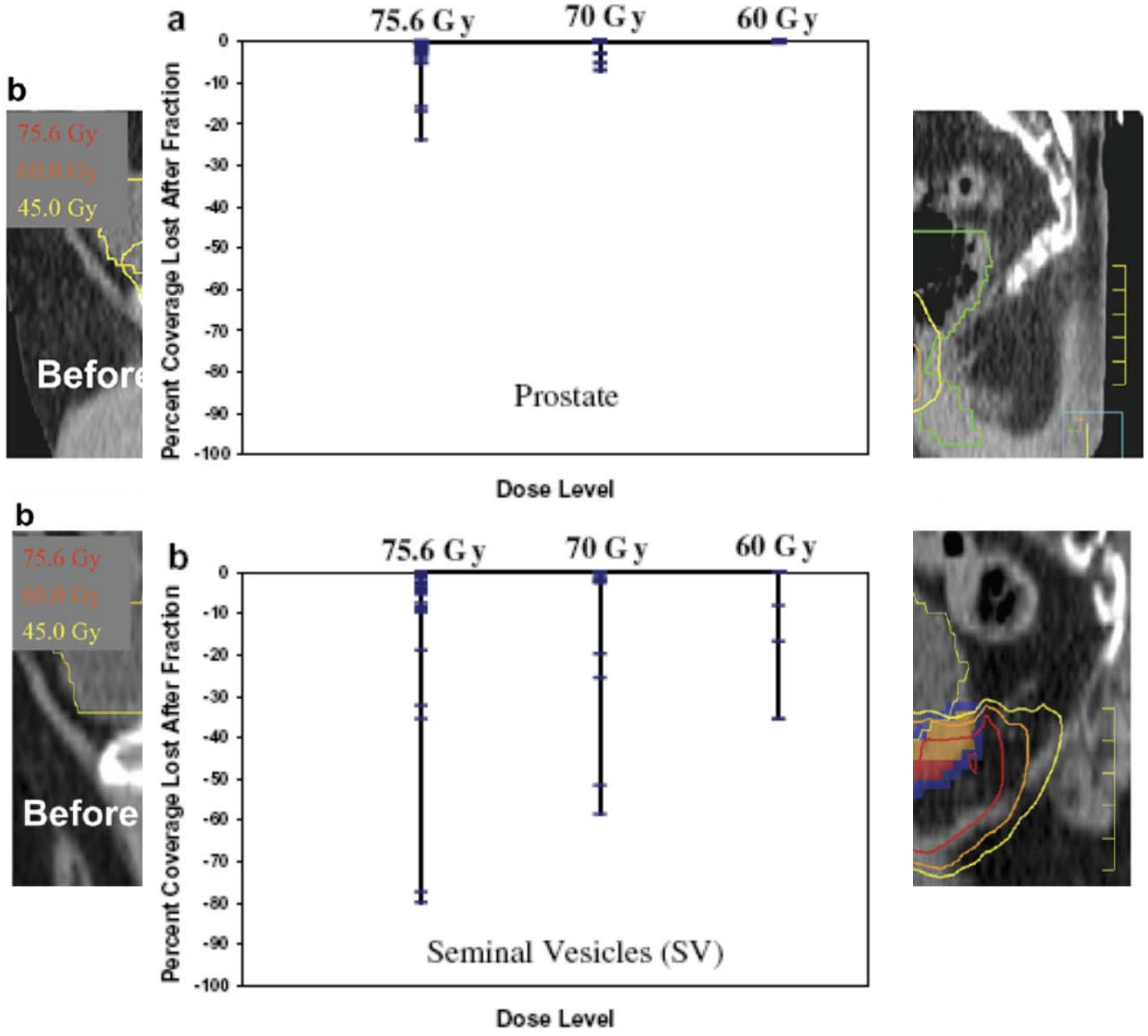
Melancon et al, Radiotherapy and Oncology, 85, 251-259, 2007

UT MDACC

N= 46 patients.
CT scan before and after delivery

3 mm margin was adequate for the prostate gland.

Coverage of the seminal vesicles was compromised.



Interfraction motion: Dosimetric Impact

van Haaren et al.: Univ Amsterdam / Univ Utrecht, 2009

217 patients, 35 fractions per patient
Daily shift data on implanted fiducials

Dose recalculation and accumulation:

Static	vs	Uncorrected	vs	Corrected
(plan)		(no shifts applied)		(shifts applied)

Areas of interest:
- Prostate+SV
- Prostate
- Peripheral Zone (tumor proxy)

} 8 mm margins

- Bladder / Rectum

van Haaren et al., RO, 90: 291, 2009

Interfraction motion: Dosimetric Impact - PTV 8 mm margin

van Haaren et al., RO, 90: 291, 2009

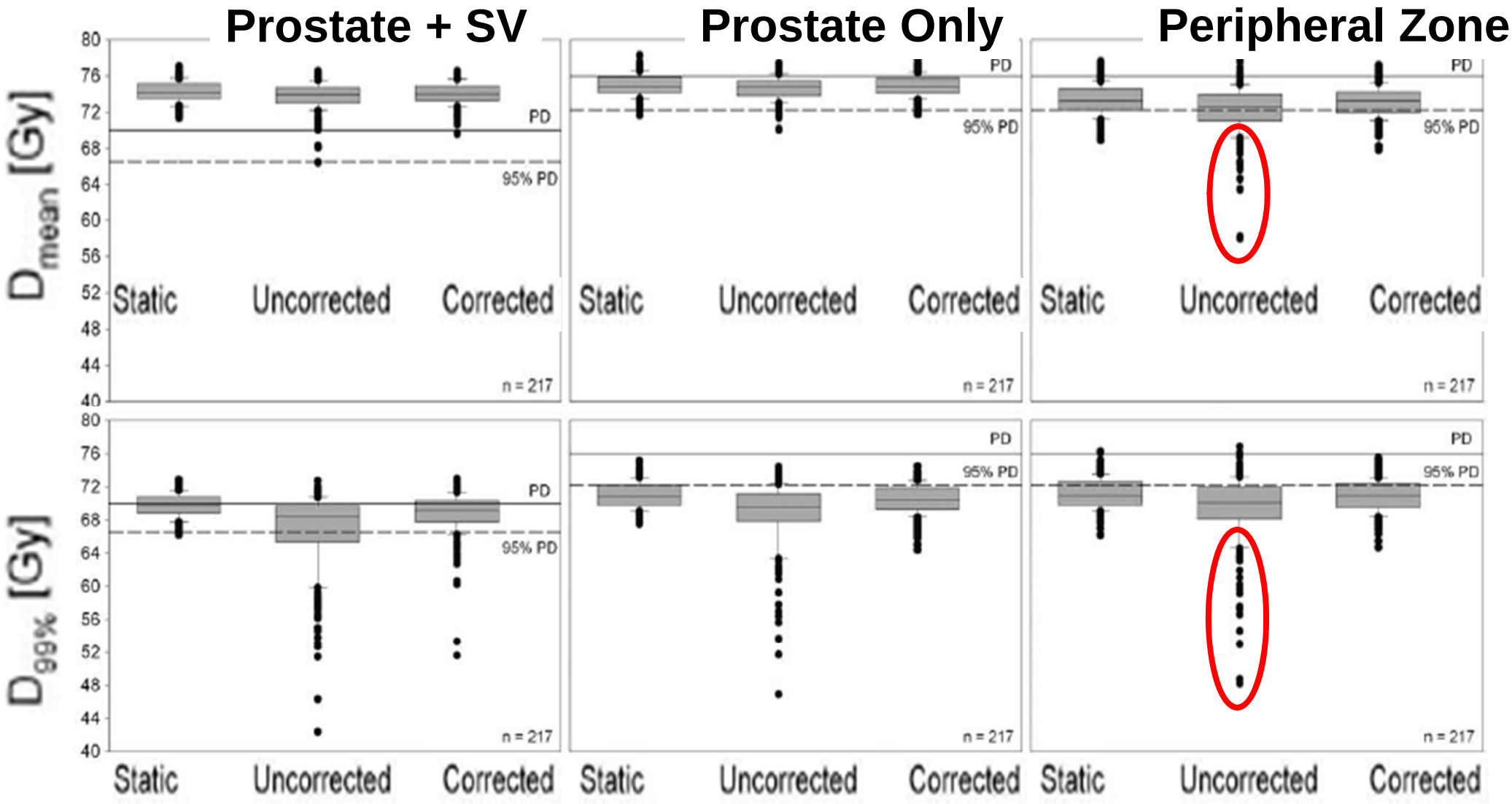
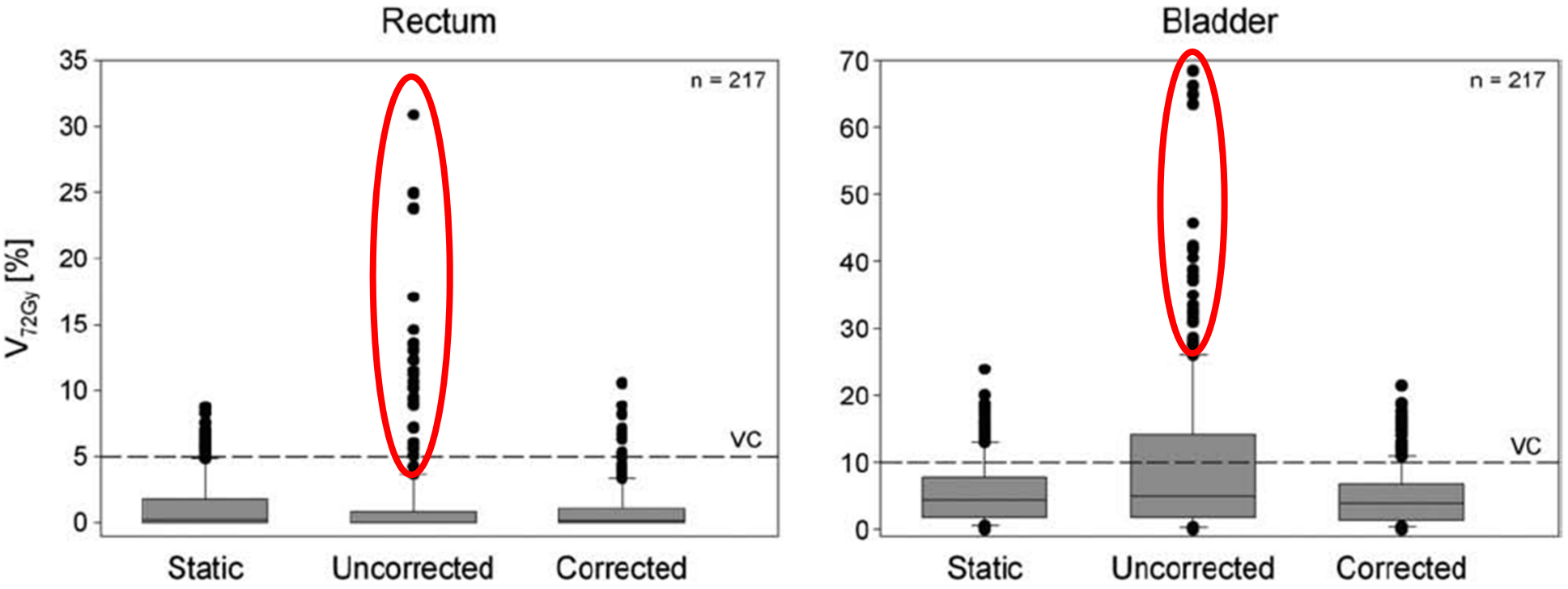


Fig. 2. Average dose (D_{mean}) and $D_{99\%}$ to CTV, boost volume and peripheral zone for the static, uncorrected and corrected plans, with respect to the prescription dose (PD) and 95% of PD. Box plots show medians, and 25th and 75th percentiles; whiskers are 10th and 90th percentiles; dots represent outliers.

Interfraction motion: Dosimetric Impact - Bladder / Rectum

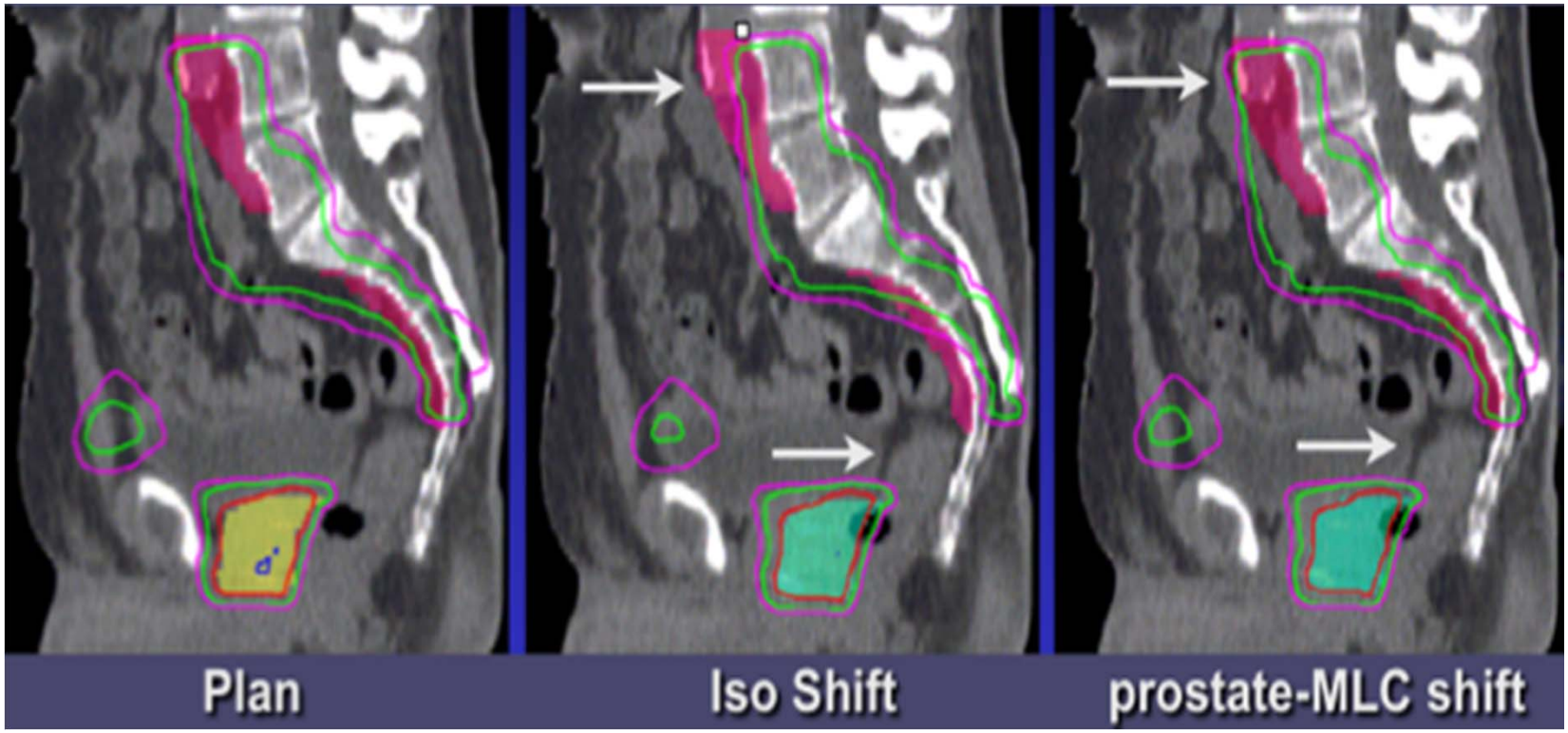
van Haaren et al., RO, 90: 291, 2009

Volumes receiving high doses (>72 Gy)



DEFORMATION

Challenge: Independent movement of prostate vs nodes



J. Pouliot, From Dose to Image to Dose: IGRT to DGRT, Panel on On-Board Imaging : Challenges and Future Directions, ASTRO 49th Annual Meeting in Los Angeles, Ca, Oct. 29, 2007.

Xia et al., Comparison of three strategies in management of independent movement of the prostate and pelvic lymph nodes. Med Phys. 2010 Sep;37(9):5006-13.

INTRAPROSTATIC TARGETS

SELECTIVE INTRAPROSTATIC BOOST
VS
FOCAL THERAPY

Radiotherapy and Oncology 94 (2010) 145–150

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Functional imaging

Validation of functional imaging with pathology for tumor delineation in the prostate

Greetje Groenendaal *, Maaike R. Moman, Johannes G. Korporaal, Paul J. van Diest, Marco van Vulpen, Marielle E.P. Philippens, Uulke A. van der Heide

University Medical Center Utrecht, The Netherlands

A B S T R A C T

Introduction: A study was performed to validate magnetic resonance (MR) based prostate tumor delineations with pathology.

Material and methods: Five patients with biopsy proven prostate cancer underwent a T2 weighted (T2w), diffusion weighted MRI (DW-MRI) and dynamic contrast-enhanced MRI (DCE-MRI) scan before prostatectomy. Suspicious regions were delineated based on all available MR information. After prostatectomy whole-mount hematoxylin–eosin stained (H&E) sections were made. Tumor tissue was delineated on the H&E stained sections and compared with the MR based delineations. The registration accuracy between the MR images and H&E stained sections was estimated.

Results: A tumor coverage of 44–89% was reached by the MR based tumor delineations. The application of a margin of ~5 mm to the MR based tumor delineations yielded a tumor coverage of 85–100% in all patients. Errors created during the registration procedure were 2–3 mm, which cannot completely explain the limited tumor coverage.

Conclusions: An accurate tissue processing and registration method was presented (registration error 2–3 mm), which enables the validation of MR based tumor delineations with pathology. Reasonable tumor coverage of about 85% and larger was found when applying a margin of ~5 mm to the MR based tumor delineations.

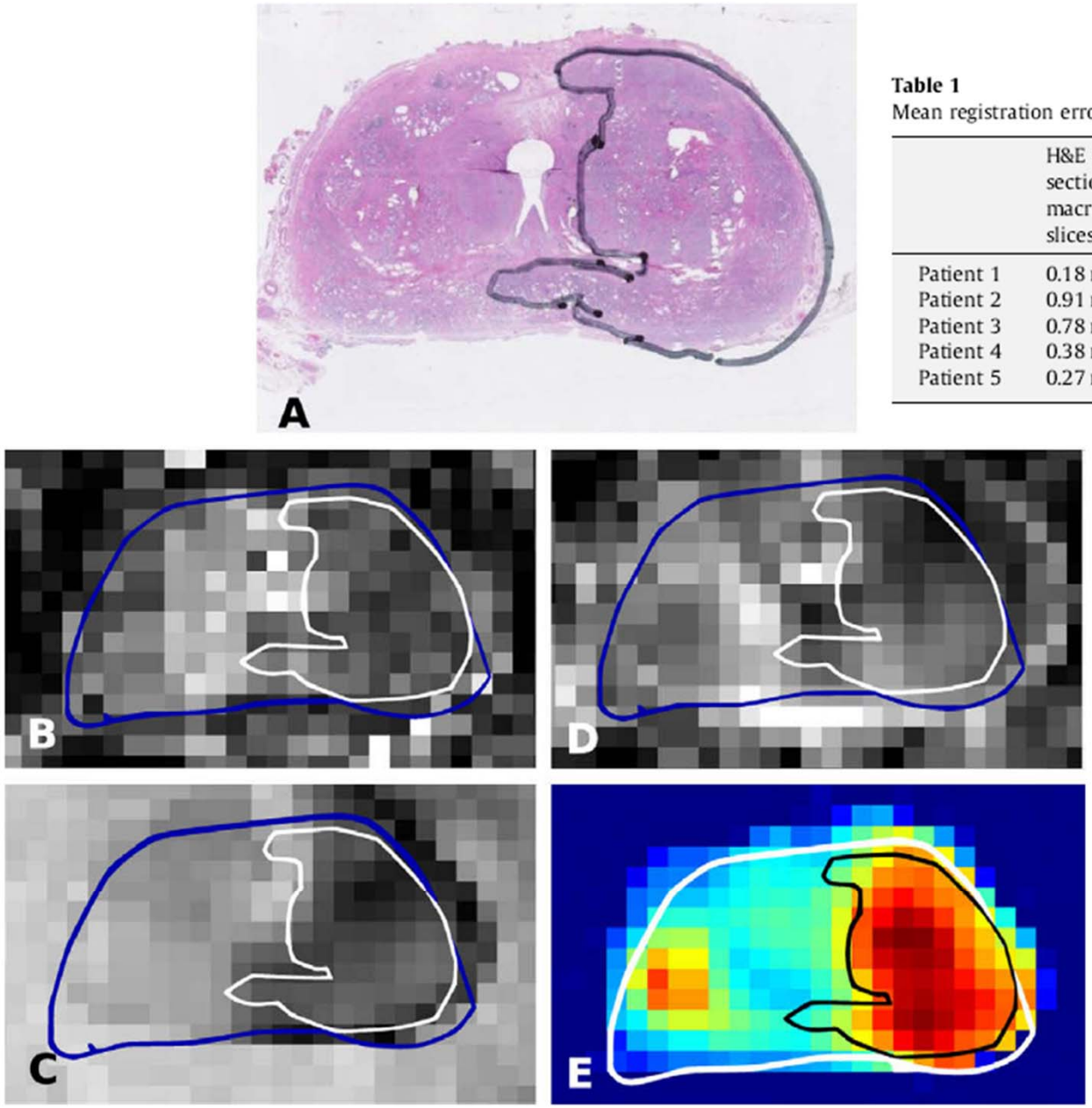


Table 1
Mean registration errors for the different registration steps.

	H&E stained sections – macroscopic slices (mm)	Stacking macroscopic slices (mm)	Rigid registration 3D stack – T2w image (mm)	Overall (mm)
Patient 1	0.18 mm	0.23 mm	1.67 mm	1.70 mm
Patient 2	0.91 mm	0.38 mm	1.93 mm	2.17 mm
Patient 3	0.78 mm	0.63 mm	1.65 mm	1.93 mm
Patient 4	0.38 mm	0.59 mm	2.93 mm	3.01 mm
Patient 5	0.27 mm	0.29 mm	2.32 mm	2.35 mm

Fig. 3. Comparison of the tumor delineated in an H&E stained section with the corresponding MR images. (A) H&E stained section with a delineation created by the pathologist. This delineation is copied to al the registered MR images. (B) T2w image. (C) DW-MRI image. (D) ADC map. (E) K^{trans} map.

Tumor Regression in the Pelvis: Cervical Cancer

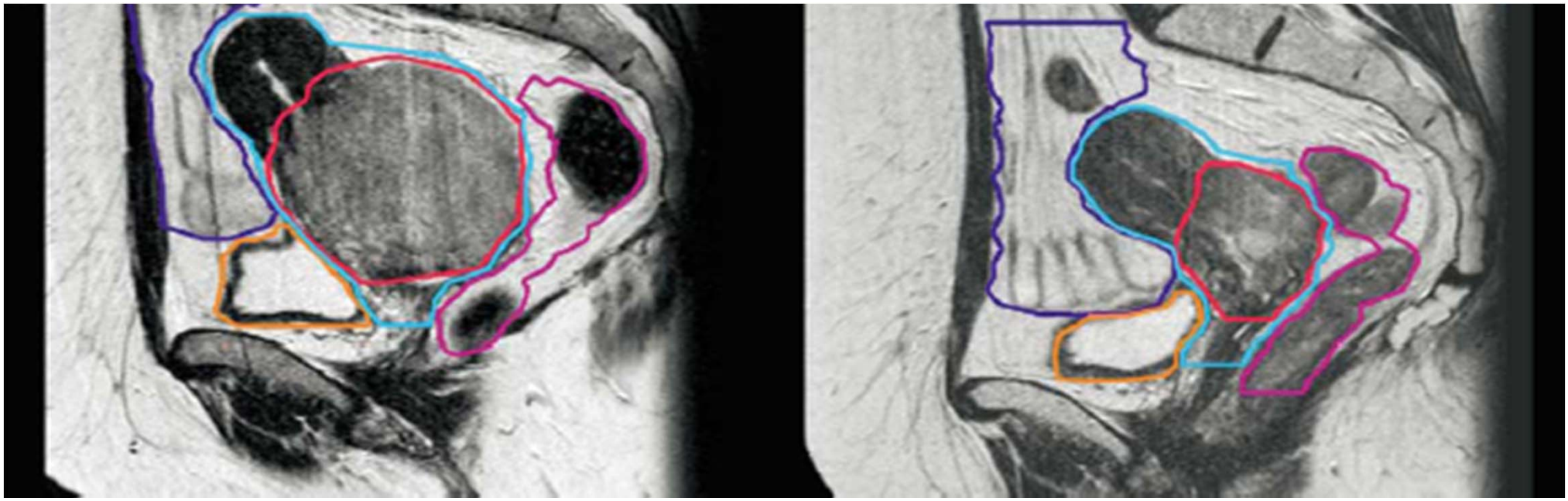
- Volumetric Imaging
- Monitor target coverage
- Adaptive RT?

Courtesy: AJ Mundt

CONVENTIONAL, CONFORMAL, AND INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLANNING OF EXTERNAL BEAM RADIOTHERAPY FOR CERVICAL CANCER: THE IMPACT OF TUMOR REGRESSION

LINDA VAN DE BUNT, M.D.,* UULKE A. VAN DER HEIDE, PH.D.,* MARTIJN KETELAARS, PH.D.,* GERARD A. P. DE KORT, M.D.,† AND INA M. JÜRGENLIEMK-SCHULZ, M.D., PH.D.*

Departments of *Radiation Oncology and †Radiology, University Medical Center Utrecht, Utrecht, The Netherlands



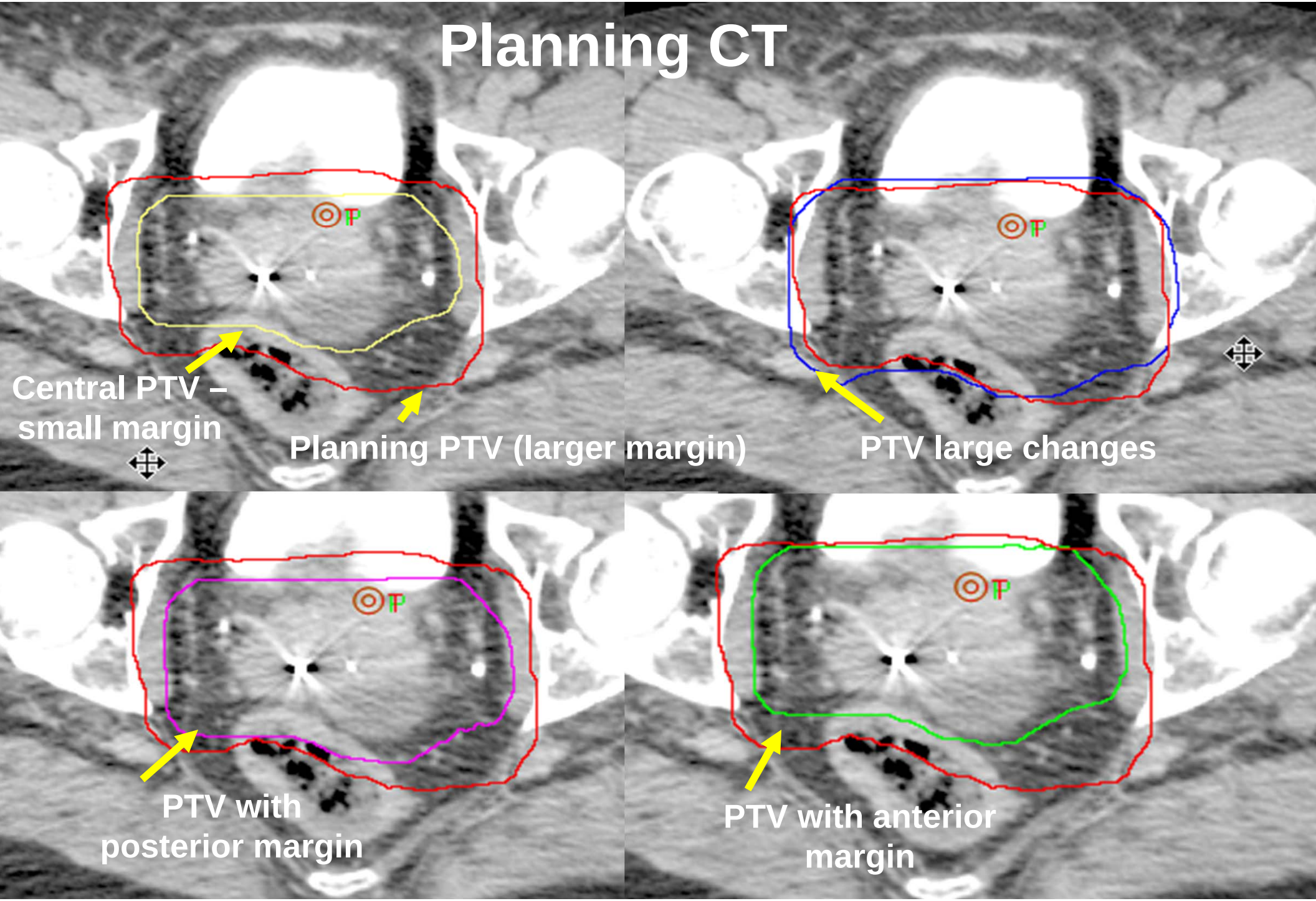
14 cervical cancer patients
MRI prior to RT and after 30 Gy external beam
GTV decreased (on average) by 46%
Decrements in CTV and PTV were 18% and 9%

Courtesy: AJ Mundt

Adaptive Gynecologic IGRT (AJ Mundt)

- Generate 4 plans for each patient with various asymmetrical margins
  - Tight margins (0.5 cm)
  - More generous anterior margin (1.2 cm)
  - More generous posterior margin (1.2 cm)
  - Very generous in all directions (1.5 cm)
- At the machine, the best plan is selected for treatment based on the CBCT
- So far, the breakdown is:
  - 40% tight margins
  - 25% generous anterior
  - 25% generous posterior
  - 10% very generous in all directions

Courtesy: AJ Mundt


Planning CT
Central PTV – small margin
Planning PTV (larger margin)
PTV large changes
PTV with posterior margin
PTV with anterior margin

Interfraction Motion / Deformation

Clinical Impact of Image Guidance

Clinical Impact

Challenges to document clinical impact:

Endpoints:

Cure; Long timeline, few events

Toxicity: Low number of significant events

Dose escalation
Decreasing margins
Image Guidance

} Implemented simultaneously

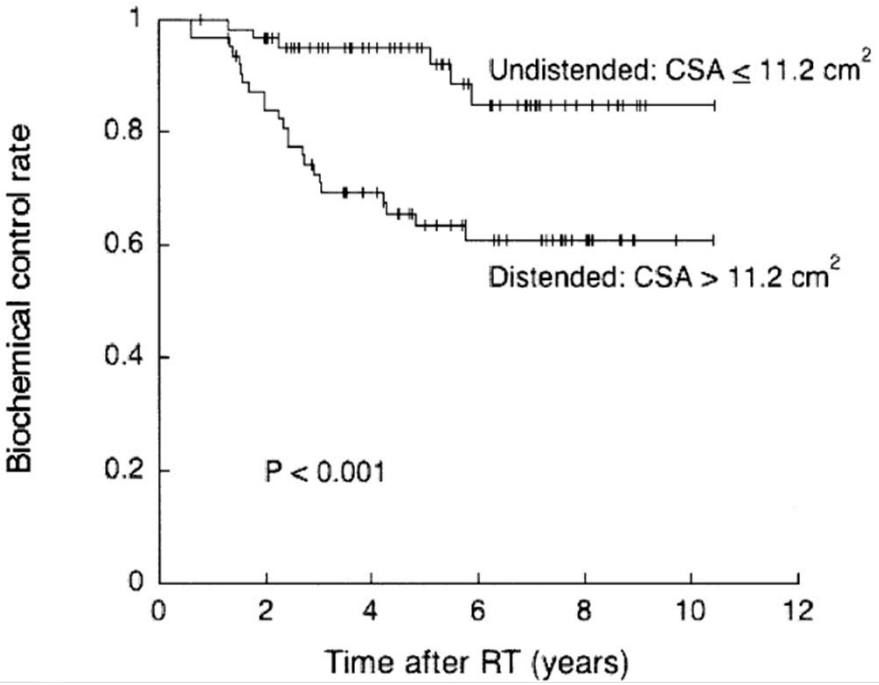
Independent effect of image guidance??

Image Guidance: Avoiding Systematic Errors

IMPACT ON CLINICAL OUTCOMES: TUMOR CONTROL

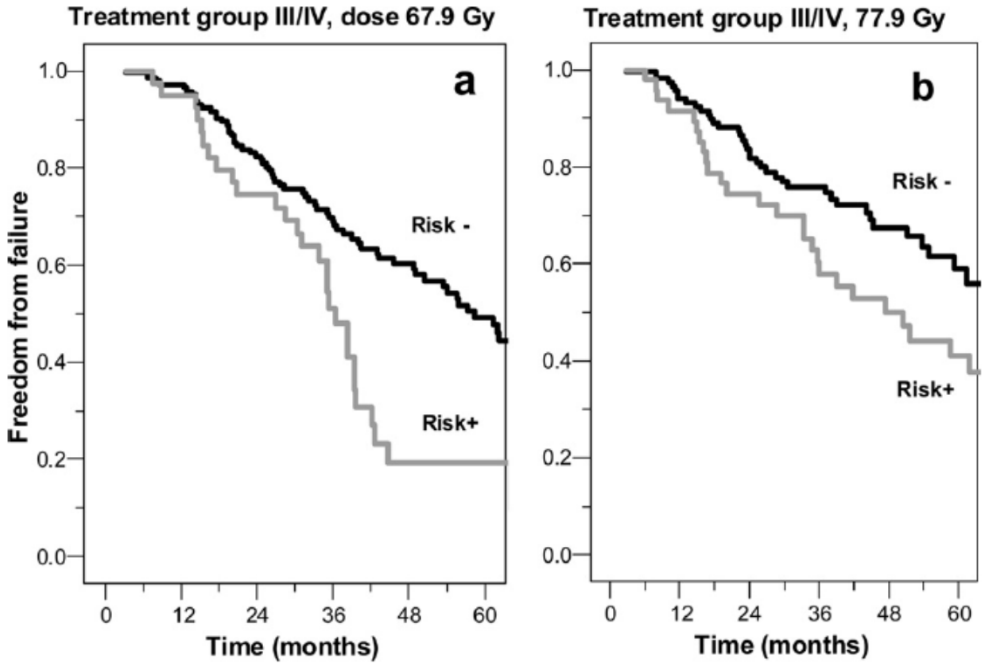
Impact of Rectal Distention at the Time of Initial Planning

MDACC



de Crevoisier et al, IJROBP, 62, 965-973, 2004

Dutch Trial



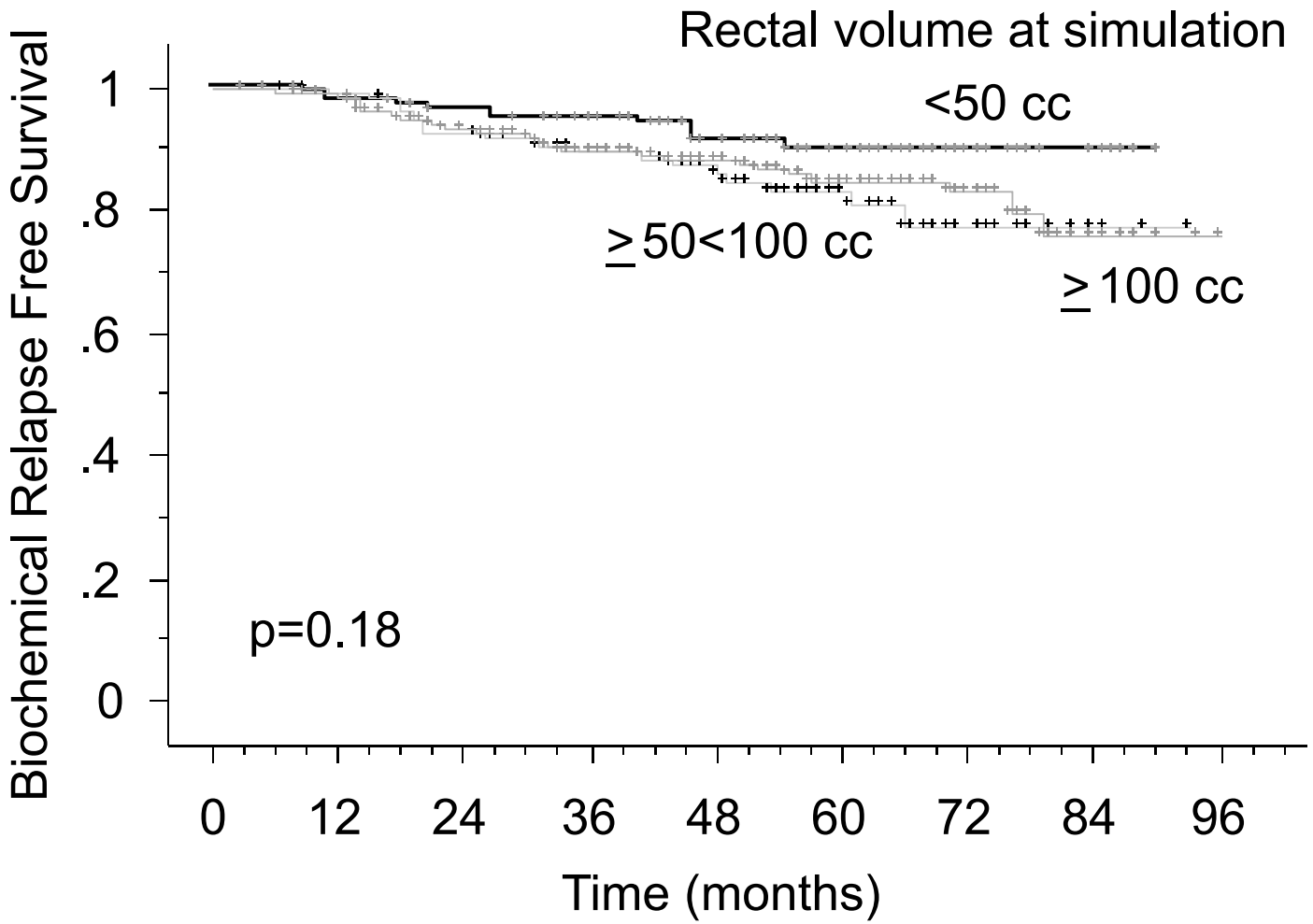
Heemsbergen et al., IJROBP, 67, 1418–1424, 2007

NO IMPACT OF RECTAL DISTENTION ON RELAPSE FREE SURVIVAL IN PATIENTS TREATED WITH IGRT

Cleveland Clinic
N=488
BAT
IMRT

Rectal volume
on Planning CT

Med FU: 60 mos



Kupelian, IJROBP (70), 1146, 2008

TREATMENT MARGINS TOO SMALL: INCREASED FAILURES ??

CLINICAL INVESTIGATION **Prostate**

CONFORMAL ARC RADIOTHERAPY FOR PROSTATE CANCER: INCREASED BIOCHEMICAL FAILURE IN PATIENTS WITH DISTENDED RECTUM ON THE PLANNING COMPUTED TOMOGRAM DESPITE IMAGE GUIDANCE BY IMPLANTED MARKERS

BENEDIKT ENGELS, M.D., GUY SOETE, M.D., PH.D., D. VERELLEN, PH.D., AND GUY STORME, M.D., PH.D.

Department of Radiotherapy, University Hospital Brussels, Brussels, Belgium

Engels, IJROBP, 74: 388-391, 2009

TREATMENT MARGINS TOO SMALL??

N=213	6 mm lateral, 10 mm otherwise	No guidance
N=25	3 mm lateral, 5 mm otherwise	Fiducial/Guidance

bNED at 5 years (median follow-up 53 months):

No guidance (large margins):	91%	
Guidance (small margins):	58%	p=0.02

On multivariate analysis, biochemical failure predictors were;

- High Risk Group
- Low RT Dose
- Rectal Distention
- Guidance (small margins)

Engels, IJROBP, 74: 388-391, 2009

Adusting for Deformations Prostate versus Pelvic Lymph Nodes

Clinical Impact?

NODAL RT:
IMAGE GUIDANCE IMPROVING TOXICITY?

CLINICAL INVESTIGATION **Prostate**

DOES IMAGE-GUIDED RADIOTHERAPY IMPROVE TOXICITY PROFILE IN WHOLE PELVIC-TREATED HIGH-RISK PROSTATE CANCER? COMPARISON BETWEEN IG-IMRT AND IMRT

HANS T. CHUNG, M.D., F.R.C.P.C.,* PING XIA, PH.D.,† LINDA W. CHAN, M.D.,†
EILEEN PARK-SOMERS, B.SC.(HONS),* AND MACK ROACH, III, M.D., F.A.C.R.†

*Department of Radiation Oncology, Cancer Institute, National University Hospital, Singapore; and †Department of Radiation Oncology, University of California, San Francisco, School of Medicine, San Francisco, CA

Chung et al., IJROBP, 73: 53-60, 2009

NODAL RT:
IMAGE GUIDANCE IMPROVES TOXICITY

Table 5. Acute rectal toxicities as scored by RTOG and CTCAE criteria between NUH (IMRT) and UCSF (IG-IMRT)

	RTOG grade			CTCAE grade		
Toxicity	0	1	2	0	1	2
Rectal						
IMRT	1 (10)	1 (10)	8 (80)	1 (10)	4 (40)	5 (50)
IG-IMRT	6 (40)	7 (47)	2 (13)	6 (40)	8 (53)	1 (7)
Bladder						
IMRT	1 (10)	3 (30)	6 (60)	2 (20)	4 (40)	4 (40)
IG-IMRT	0 (0)	13 (87)	2 (13)	0 (0)	14 (93)	1 (7)

Abbreviations: RTOG = Radiation Therapy Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; other abbreviations as in Table 1.

Chung et al., IJROBP, 73: 53-60, 2009

Intra-fraction Deformation and Rotation

Difficult to document

For prostate RT, given current treatment volumes and treatment margins, it is very unlikely that dosimetric and clinical implications will be significant.

With smaller targets (e.g. intraprostatic lesions), such deformations and rotations relative to the prostate (or fiducial surrogate) position might be important to understand.

Ghilezan et al: Cine-MRI study:
Magnitude of deformations is relatively small: within 2 mm.
IJROBP, 62, 406-417, 2005

Guidance Techniques

1. Transabdominal ultrasound

2. In-room Planar X-rays / CT

3. Implantable markers: radio-opaque

4. TRACKING: Electromagnetic
   Radioactive

4. ADAPTIVE RT
5. REAL TIME RADIOTHERAPY

Trans-abdominal ultrasound

Advantages:
Fast
non-invasive
no radiation dose

Disadvantages:
Accuracy?
Large inter-user variability

Newer ultrasound systems are currently available with 3D reconstruction capabilities which could improve the accuracy and variability issues

Langen et al., IJROBP, 57, 635 (2003)
Scarbrough et al. , IJROBP, 65, 378, (2006)

Fiducial Markers Using Planar X-ray

Advantages:
Fast
Minimal interpretation
Low inter-user variability

Disadvantages:
Invasive
Possible migration (rare and minimal)

The accuracy of marker-based registration of the prostate gland is estimated to be less than 1mm.

Fiducial Markers Using in-room CT (KV or MV CBCT, Helical MVCT)

Advantages:

Visualization of soft tissues (the prostate) versus Fiducials:

- Fiducial migration
- Target deformation
- Bladder/rectal filling
- Possibly adding dosimetric evaluations

Disadvantages:

- Higher imaging dose
- Longer time of acquisition
- Increased artifacts with motion / metal
- Lower resolution images versus helical KV CTs

KV or MV CBCT, Helical MVCTs WITHOUT FIDUCIALS

Smitsmans (IJROBP; 64, 975-984, 2005):
Rigid-registration method 83% successful in registering CBCT to planning CT based on visual verification, and successful registrations had a 1-4mm error as assessed by manually tracking prostate calcifications.

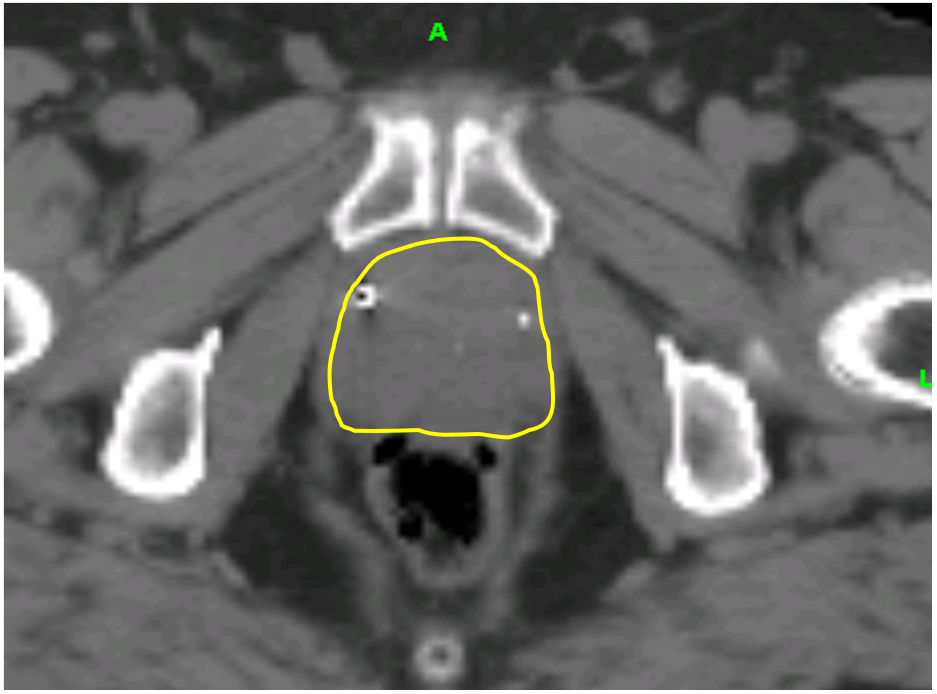
Moseley (IJROBP, 67(3), 942–953, 2007):
Manual translation registration kV CBCT images vs Fiducials

Agreement within +/- 3 mm:		
	LR	99%
	AP	70%
	SI	78%

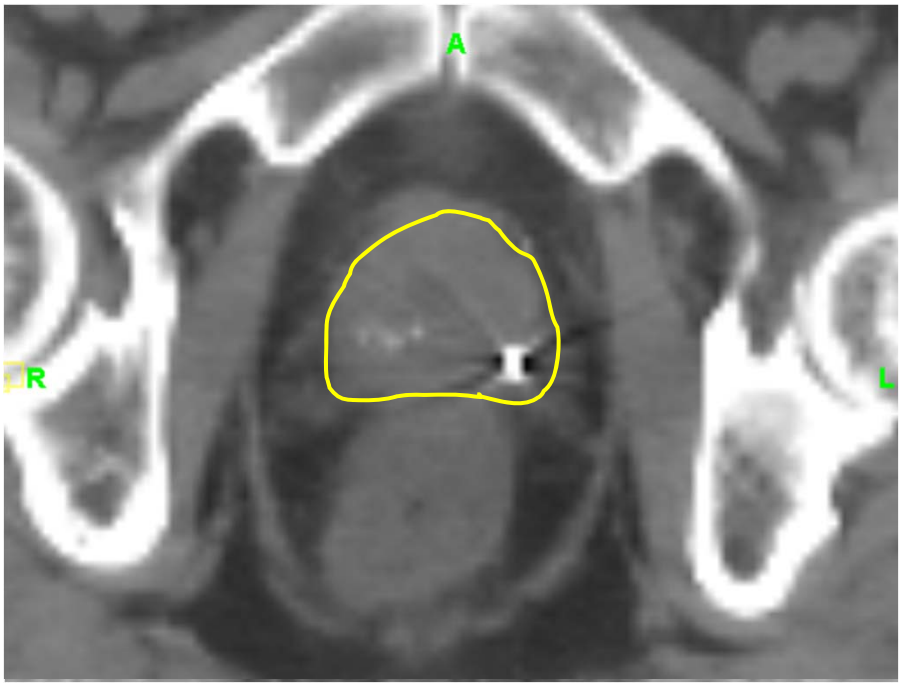
The general consensus is that implanted fiducials are necessary even when in-room CT scans are obtained.

Marker Location

Should be representative of relevant anatomy (prostate/rectum interface)

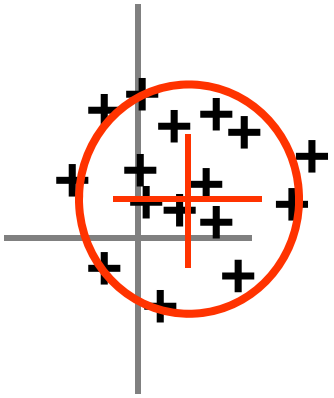


Inadequate Placement (Anterior)



Adequate Placement (Posterior)

Treatment Margins: On the van Herk Formula



- Probabilistic approach: e.g. van Herk formula

M = 2.5 S + 0.7s (S: Systematic error s: Random error)

Definition: Ensure that 90% of the patients have a minimum CTV dose > 95% of prescribed dose

Critical role in the quantitation of margins in the 3DCRT/IMRT era
Allowed critical-organ sparing approaches

PROSTATE CANCER	CURE RATES:	>85%
	COMPLICATIONS RATES:	<10%

For prostate cancer outcomes, these compromises are clinically difficult to make: Need daily localization / tracking

Guidance Techniques

1. Transabdominal ultrasound

2. In-room Planar X-rays / CT

3. Implantable markers: radio-opaque

4. TRACKING: Electromagnetic
   Radioactive

4. ADAPTIVE RT
5. REAL TIME RADIOTHERAPY

Prostate Real Time Motion Studies
Adapted from Ghilezan, IJROBP, 62, 406–417, 2005

Author (year)	Obs	Method	Sampling	Motion (mm)
Kupelian (2005)	1157	Calypso	9-11 min Continuous	≥3 mm motion for >30 secs in 41% ≥5 mm motion for >30 secs in 15%
Ghilezan (2005)	18	Cine MRI	1hr q 6 sec	Range S.D.: 0.7-1.7
Mah (2002)	42	Cine MRI	9 min q 20 s	Range S.D.: 1.5-3.4
Padhani (1999)	55	Cine MRI	7 min	≥5 mm motion in 29%
Khoo (2002)	10	MRI	6 min q 10 s	Range S.D.: 0.9 -1.7
Kitamura (2002)	50	Fluoro	2 min	Range S.D.: 0.1-0.5
Dawson (2000)	4	Fluoro	10–30 sec	Range S.D.: 0.9–5.3
Malone (2000)	40	Fluoro	q 20 s	≥4-mm motion AP 8% SI 23%
Nederveen (2002)	251	Fluoro	2–3 min	Range S.D.: 0.3-0.7
Shimizu (2000)	72	Fluoro	9 min	Median: AP 0.7, SI 0.9
Vigneault (1997)	223	EPID	--	No displacement
Huang (2002)	20	US (2)	15–20 min apart	Range S.D.: 0.4 – 1.3

TRACKING

FIDUCIAL (OR BONY ANATOMY) BASED:

In-room X-rays:

- Stereoscopic KV-Xrays
- On-board imagers (KV/MV)

Electromagnetic tracking

Implanted Radioactive Markers

VOLUMETRIC:

Ultrasound

In-room MRI

PRE AND/OR POST TREATMENT IMAGING DOES NOT DOCUMENT INTRAFRACTION MOTION

TRACKING

FIDUCIAL (OR BONY ANATOMY) BASED:

In-room X-rays:

- Stereoscopic KV X-rays
- On-board imagers (KV/MV)

Electromagnetic tracking

Implanted Radioactive Markers

VOLUMETRIC:

Ultrasound

In-room MRI

Real Time Motion: Stereoscopic KV X-rays
Intra-Treatment Verification

Tracking

Robot adjustment
Accuray Synchrony®

Courtesy Accuray

Gating

BrainLAB
ExacTrac ®

Courtesy BrainLAB

TRACKING

FIDUCIAL (OR BONY ANATOMY) BASED:

In-room X-rays:

- Stereoscopic KV X-rays
- On-board imagers (KV/MV)

Electromagnetic tracking

Implanted Radioactive Markers

VOLUMETRIC:

Ultrasound

In-room MRI

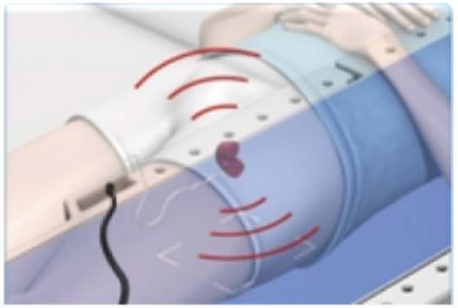
Intrafraction Motion

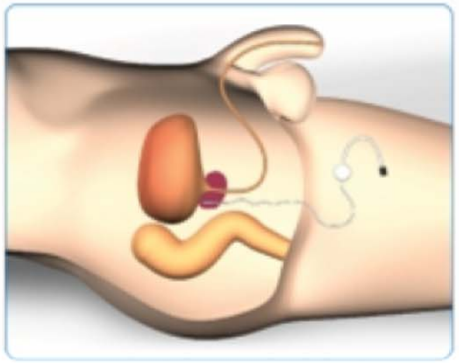
Electromagnetic Tracking (Prostate)

Calypso

Wireless
Permanent

Micropos





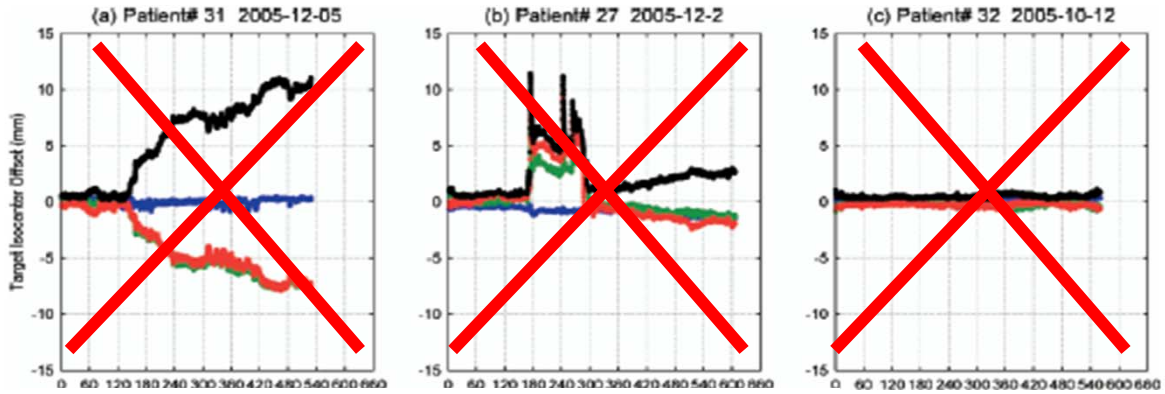
Wire
Removable

PROSTATE MOTION

Continuous Drift

Transient Excursion

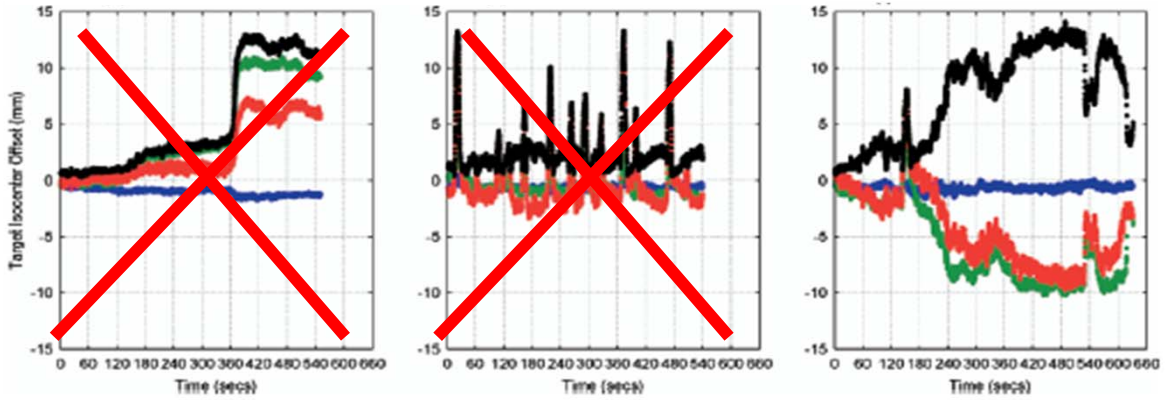
Stable



Persistent Excursion

High Frequency Excursion

Erratic



ARE THERE PATTERNS? NO

ARE PATTERNS PREDICTABLE? NO

Kupelian, IJROBP, 67: 1088-1098, 2007

Electromagnetic Tracking

35 patients
1157 sessions (mean 33 per patient)
Sessions 9-11 minutes long

	% of fractions with 3D offset outside limit >30 seconds	
	3 mm limit	5 mm limit
Weighted Average	**41%**	**15%**

In individual patients:
Range % fractions with ≥3 mm displacements: 3 – 86%
Range % fractions with ≥5 mm displacements: 0 – 56%

Kupelian, IJROBP, 67(4): 1088-1098, 2007

MONITORING INTRAFRACTION MOTION IN THE CLINIC
Calypso, Electromagnetic tracking

Clinical protocol: 3 mm threshold
Realignment only between beams

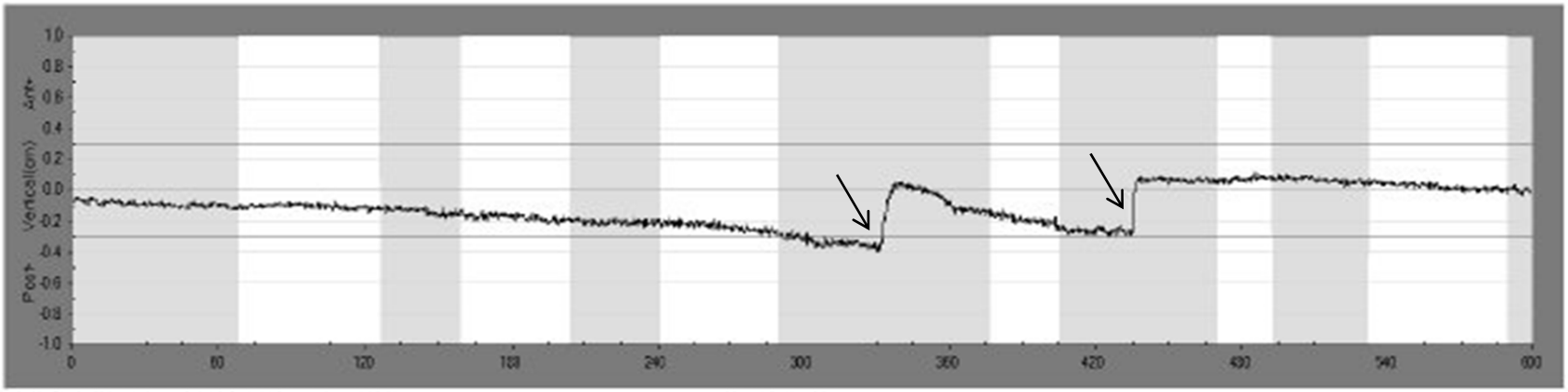
Patients N=29 Fractions: N=963, mean= 33 /patient

Events:	Mean Frequency	Range (indiv pt)
No motion >3 mm, no intervention	59%	10-100%
Motion >3 mm, transient, no intervention	14%	0-42%
Motion >3 mm, realignment between beams	25%	0-85%
MD disagree with therapist intervention (interuser variability)	1%	0-8%

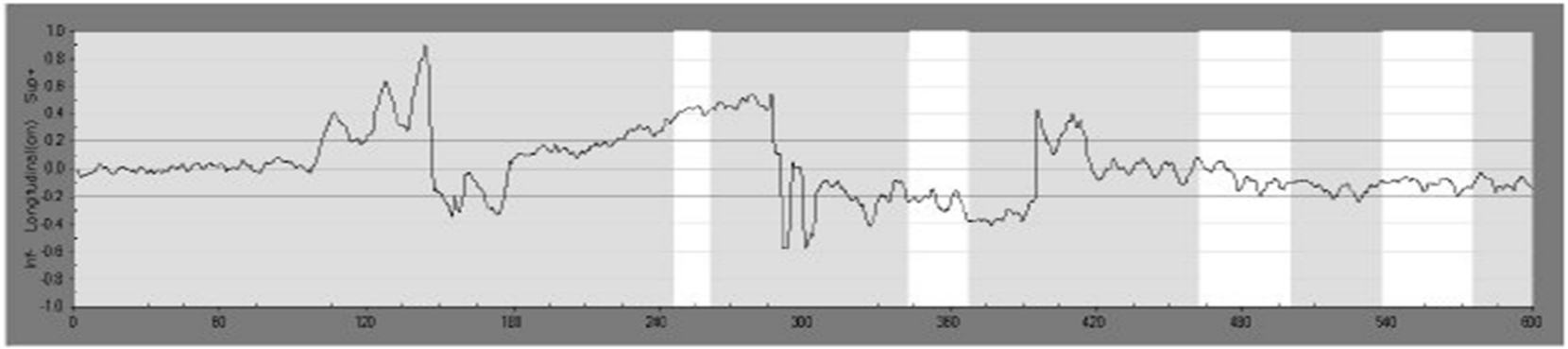
Kupelian 2009

MONITORING INTRAFRACTION MOTION – Clinical Examples

Persistent drift; corrections twice in one fraction - Vertical motion

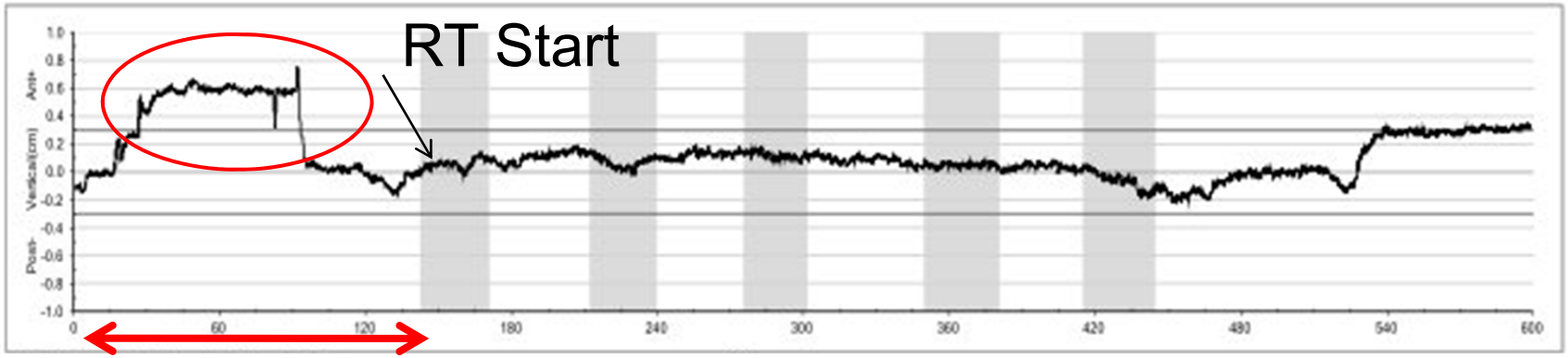


Patient motion versus prostate motion (pt with Parkinson's) - Longitudinal motion

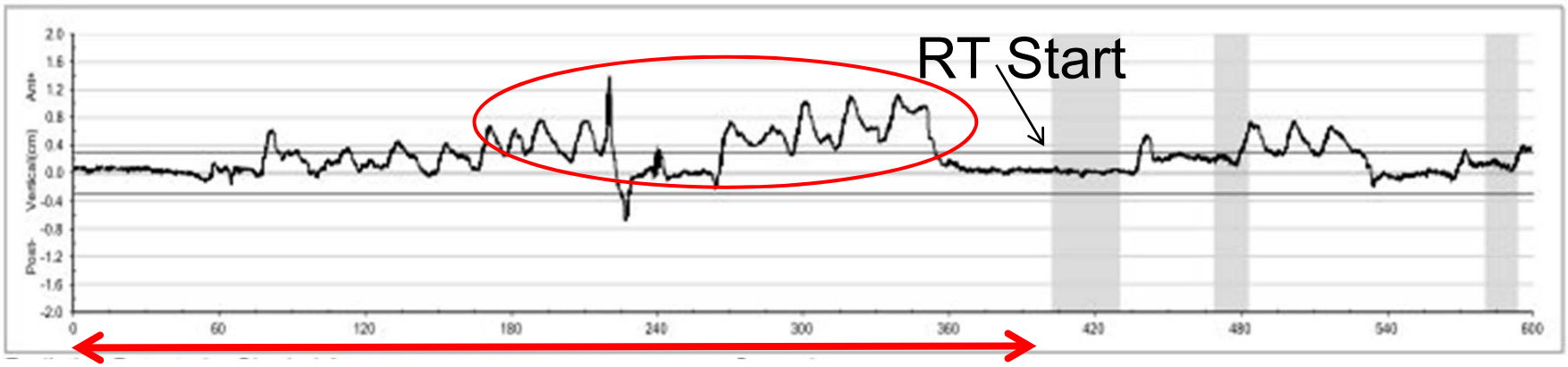


MONITORING INTRAFRACTION MOTION – Clinical Examples

Motion prior to start of radiation delivery - Vertical



~2 mins



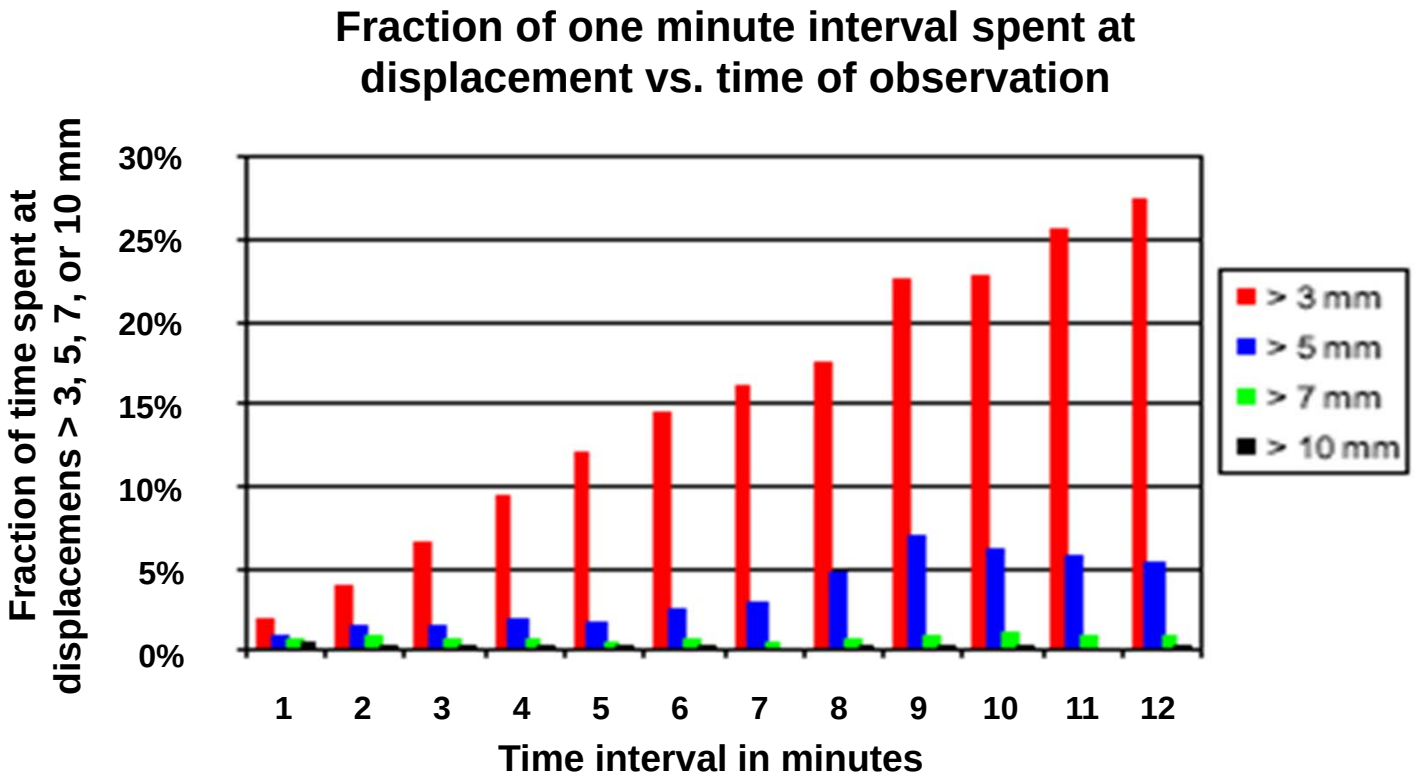
~6 mins

Prostate displacement increases with time after patient positioning

17 patients

550 Real time tracking sessions

Mean: 32 tracks per patient



Langen et al, PMB, 53, 7073, 2008

Treat as soon and as quickly as possible after imaging.
Verification during treatment is beneficial.

Dosimetric Consequence Of Intrafraction Motion

4D dosimetry

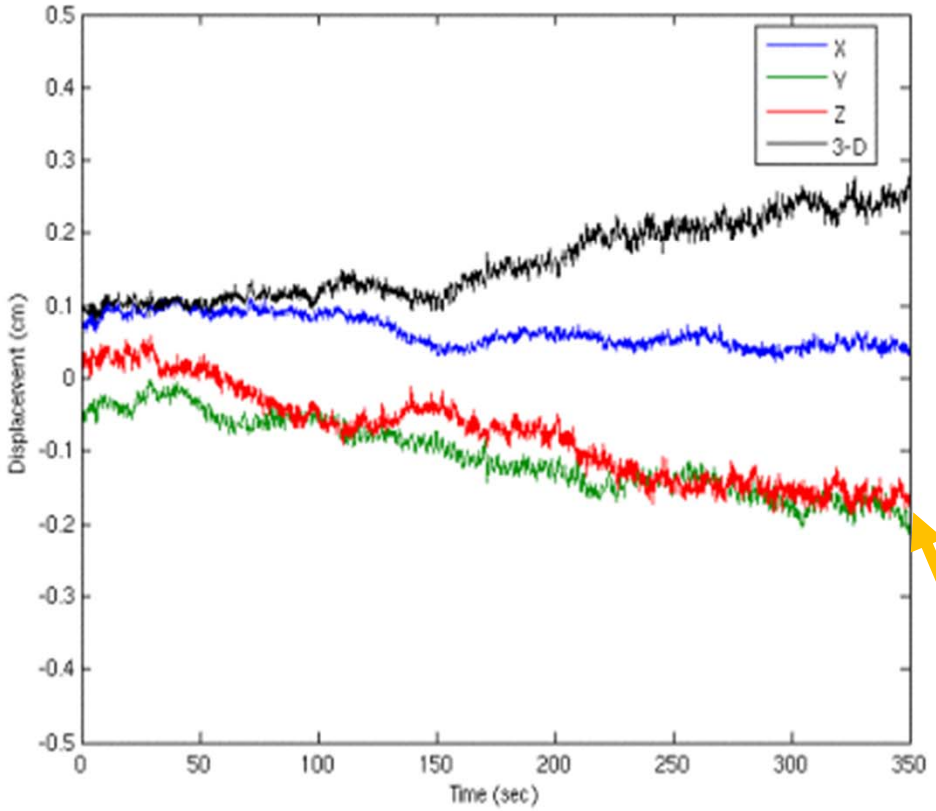
Static Field IMRT Delivery: Pierburg et al, IJROBP, ASTRO 2007
Li et al. IJROBP, 71, 801, 2008

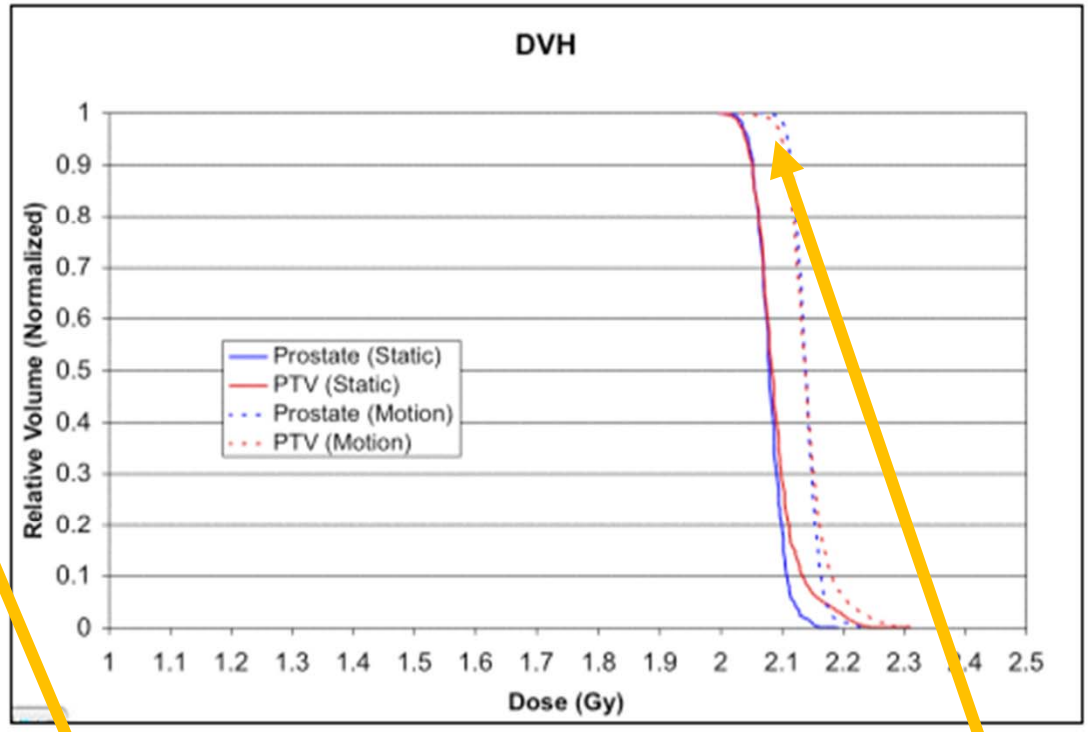
Helical Tomotherapy Delivery: Langen et al, PMB, 53, 7073, 2008
Langen et al, IJROBP, 2009

Intrafraction Motion: Dosimetric Consequence

4D Dosimetry: Tomotherapy Delivery

SINGLE FRACTION





2 mm

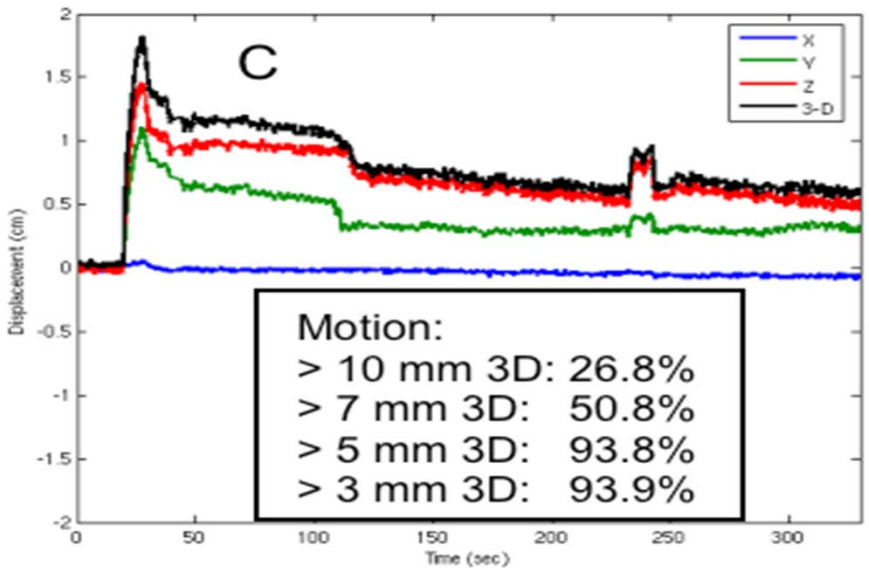
D95:+3.3%

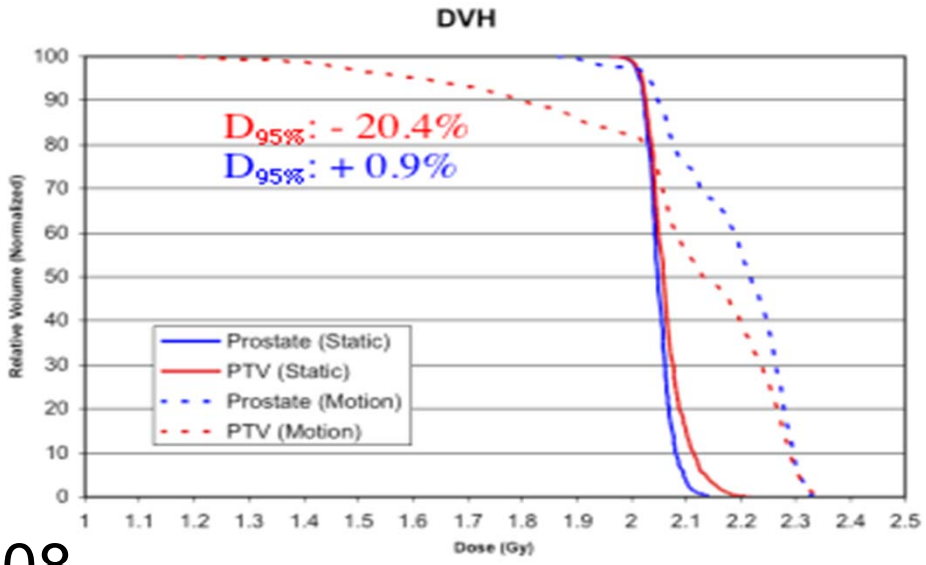
Langen et al, PMB, 53, 7073, 2008

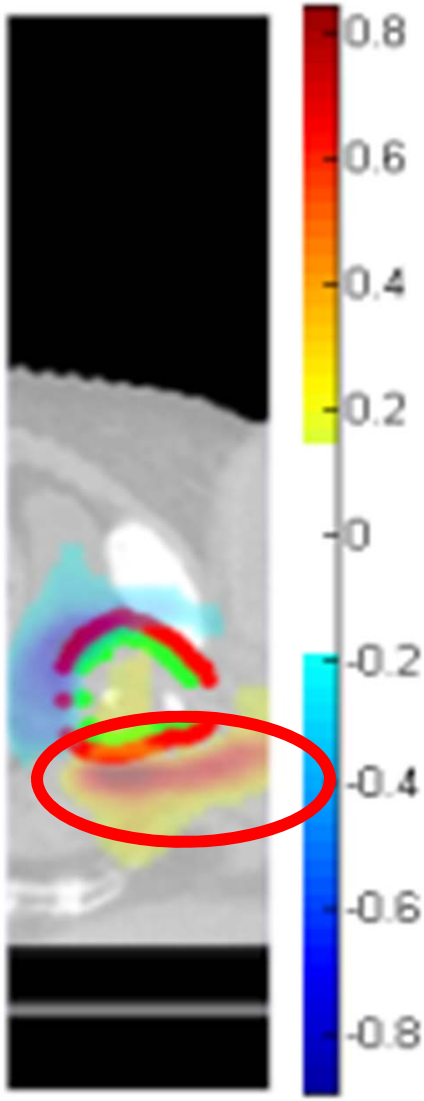
Intrafraction Motion: Dosimetric Consequence

4D Dosimetry: SINGLE FRACTION

WORST FRACTION





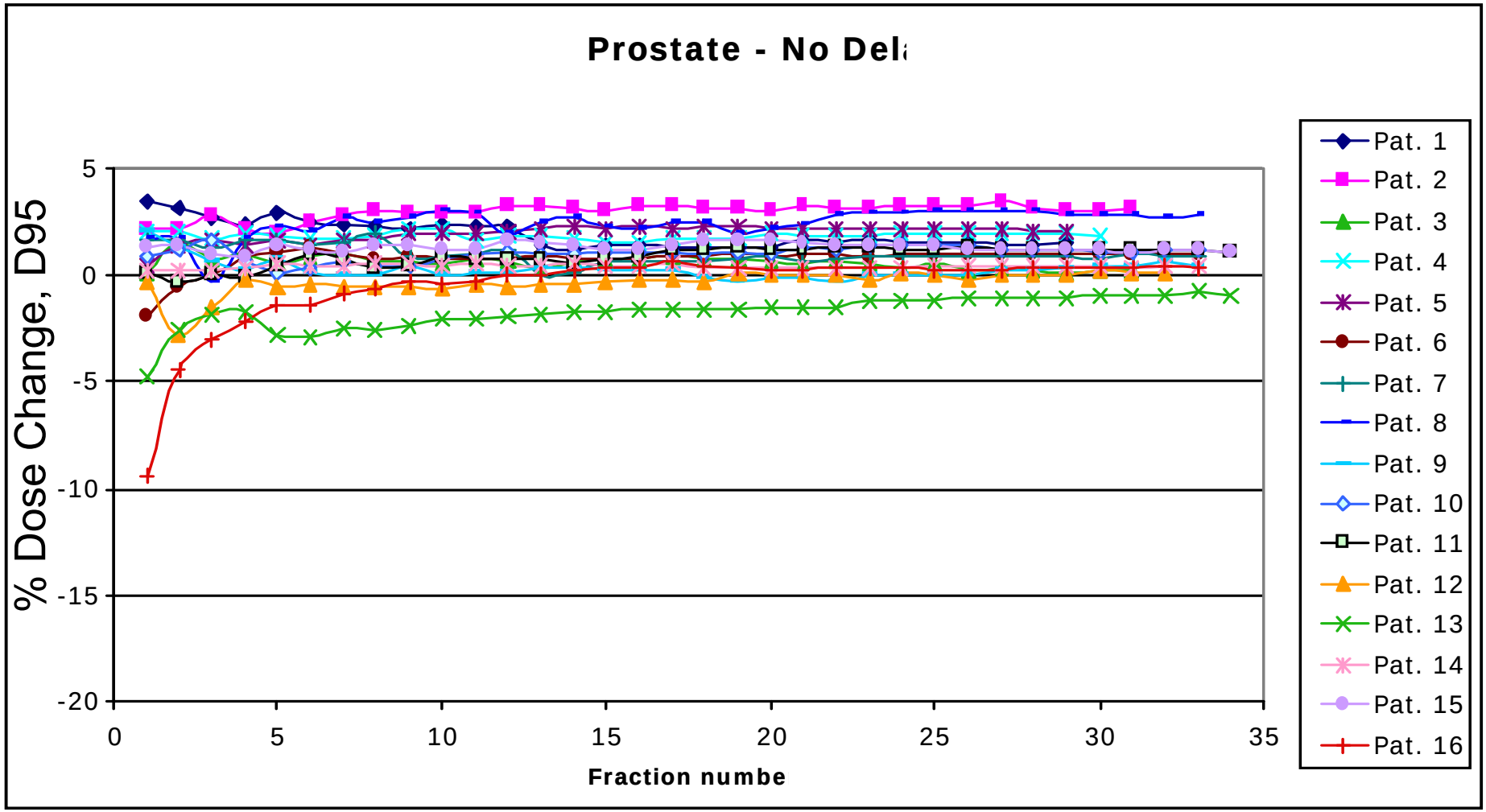


Langen et al,
PMB, 53, 7073, 2008

Intrafraction Motion: Dosimetric Consequence

FRACTIONATION, Cumulative doses, $D_{95\%}$

MDACCO: N=16 patients, full course

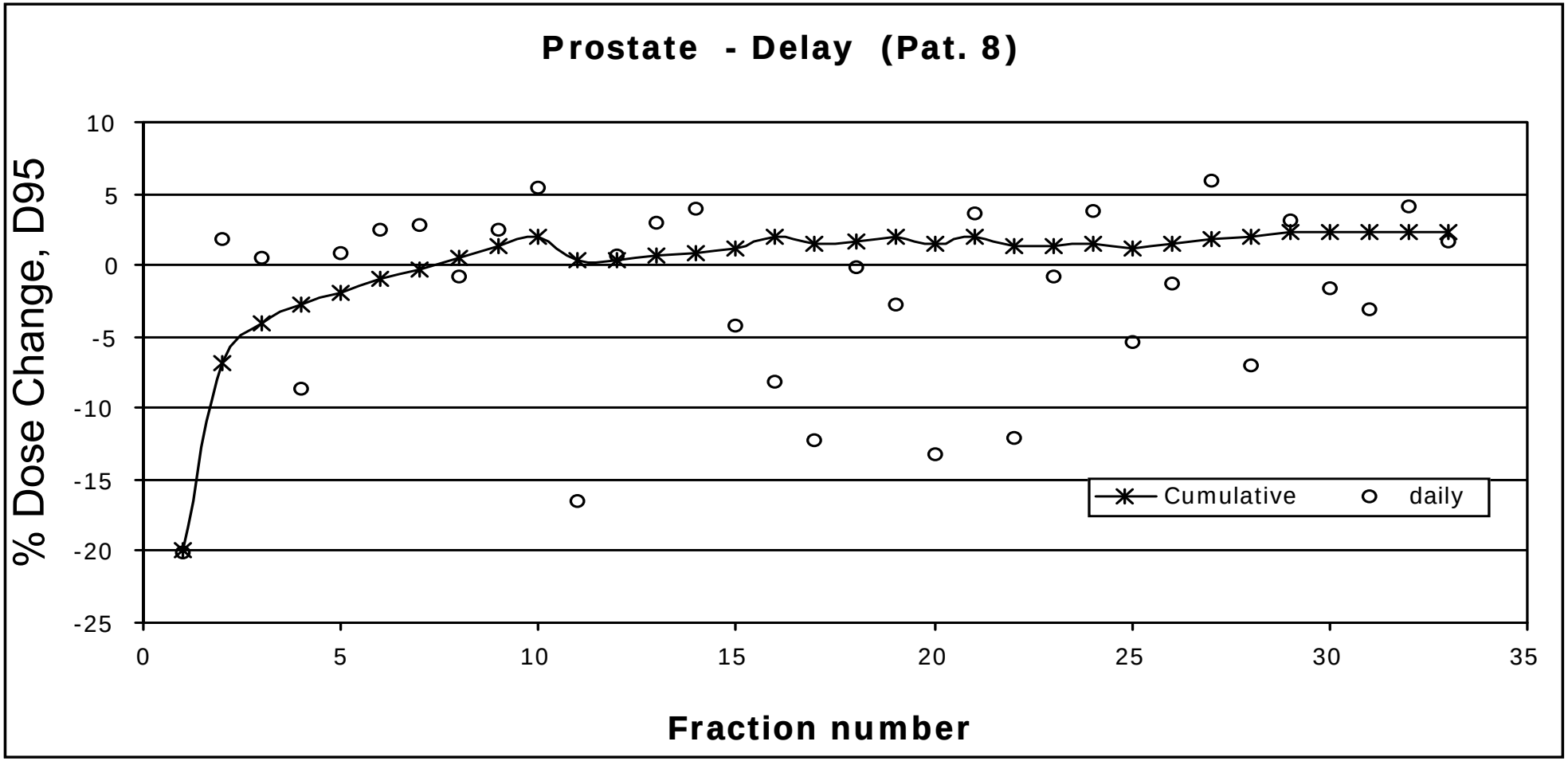


Langen, IJROBP, 2009

Intrafraction Motion: Dosimetric Consequence

FRACTIONATION, Cumulative doses, $D_{95\%}$

MDACCO: WORST CASE (WORST INTRAFRACTION MOTION)



Langen, IJROBP, 2009

CORRECTION OF INTRAFRACTION MOTION

CLINICAL IMPACT

Intrafraction Monitoring Correction – Clinical Impact?

Assessing the Impact of Margin **(AIM)** Reduction Study
Sandler, et al. Urology:75(5):1004-8, 2010

Acute toxicity comparison (PreRT and End of treatment QOL scores):

Group 1	Group 2 (Historical control) Sanda et al., NEJM 2008 358(12) 1250-61
EM tracking (Calypso) (2 mm threshold) 3 mm post margins 81 Gy	Guidance method, if any, not reported "Institutional norms" Varying margins "5-10 mm" ~ 75-80 Gy
N=64 patients IMRT, no hormones 2008-2009	N=153 patients IMRT, no hormones 2003-2006

Realignment in 60% of fractions

Intrafraction Monitoring Correction – Clinical Impact?

EPIC Domain	Study	PreRT Mean EPIC Score	PostRT Mean EPIC Score	Difference (Post – Pre)	
				Difference	95% CI on Difference
Bowel / rectal	AIM	91.8	89.8	-1.9	[-9.0, 5.1]
	NEJM Control	94.4	78.5	-16.0	[-19.4,-12.5]
Urinary irritation / obstruction	AIM	84.5	80.6	-4.0	[-10.0, 2.1]
	NEJM Control	86.6	70.1	-16.5	[-19.8, -13.3]

Assessing the Impact of Margin **(AIM)** Reduction Study
Sandler, et al. Urology:75(5):1004-8, 2010

Intrafraction Monitoring Correction – Clinical Impact?

Assessing the Impact of Margin **(AIM)** Reduction Study
Sandler, et al. Urology:75(5):1004-8, 2010

Group 1	Group 2 (Historical control)
EM tracking	"Institutional norms"
3 mm post margins	Varying margins "5-10 mm"
81 Gy	~ 75-80 Gy

Conclusions:

Technical changes will result in benefits.

Unclear if benefit is due to smaller margins or due to continuous tracking.

Adaptive Therapy Solutions?

Reducing the impact of anatomic variations

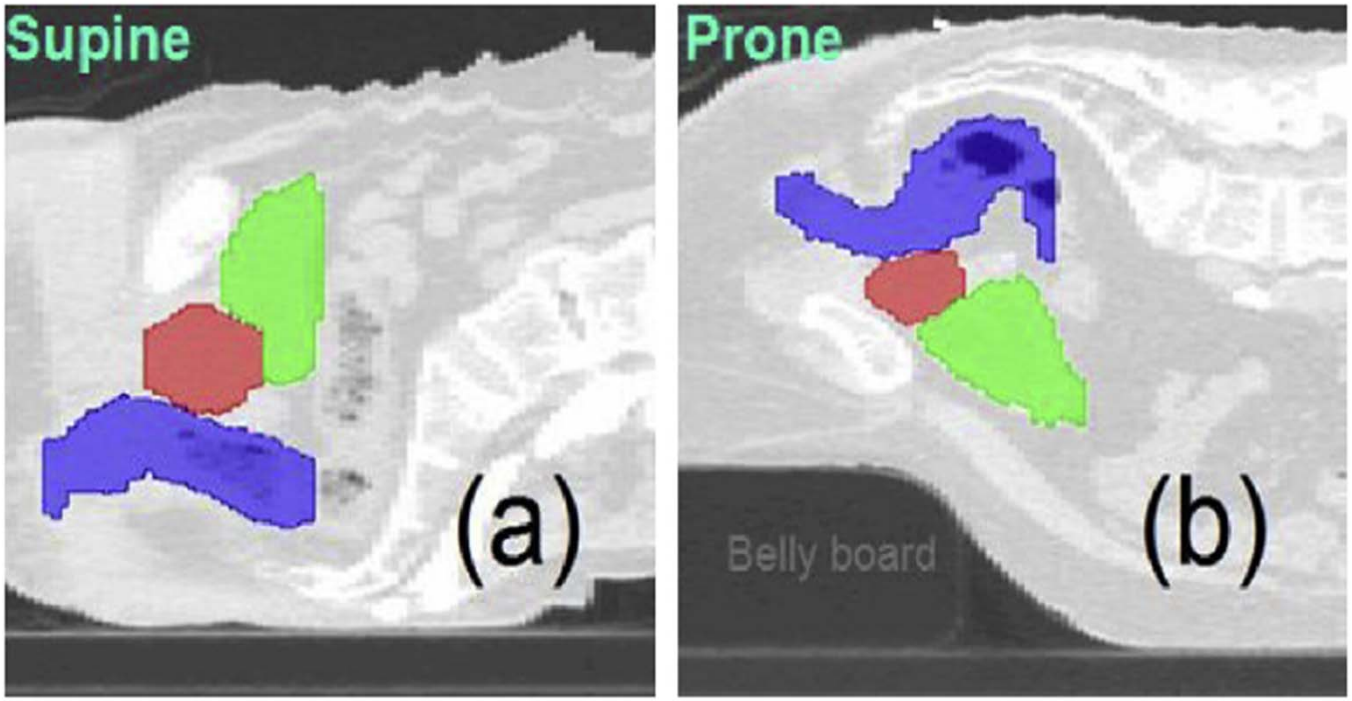
TREATMENT POSITION: Prone vs Supine

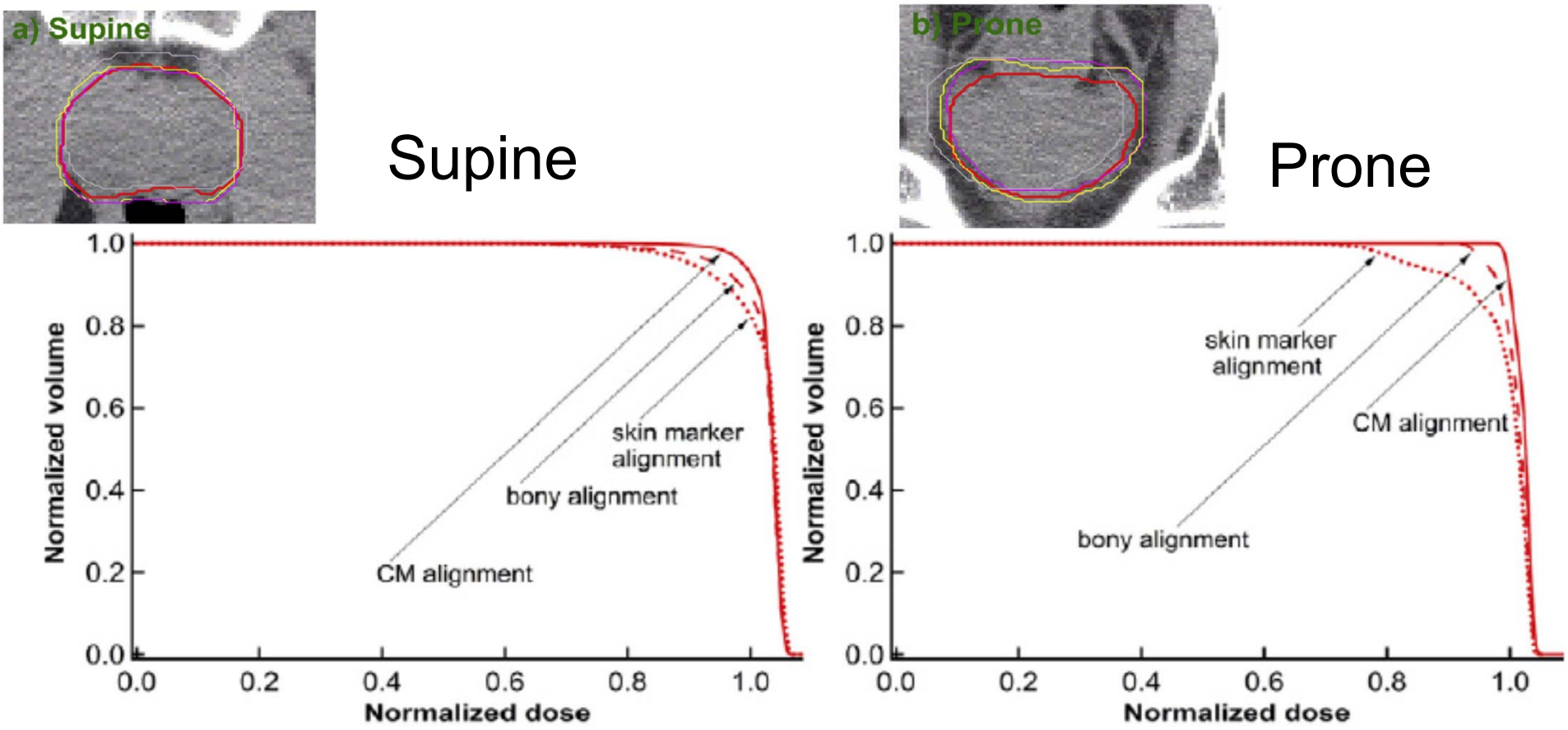
University of Maryland

Liu et al, Radiotherapy and Oncology, 2008

N=20 patients. Repeat CT scans; 10-11 scan per patient.

Dosimetry: Prone v supine
Skin v Bone v Prostate COM





Supine vs Prone:

-Skin alignments yield worse dosimetry than bony alignments.

-If aligned on bones; prone was better than supine for PTV coverage.

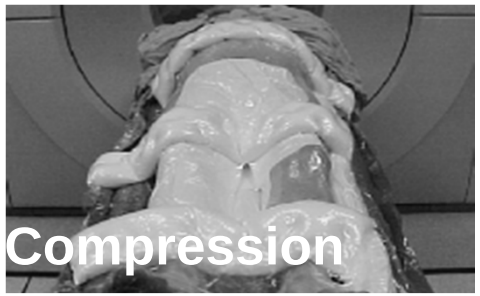
-No large differences in bladder and rectal doses with either position and alignment method.

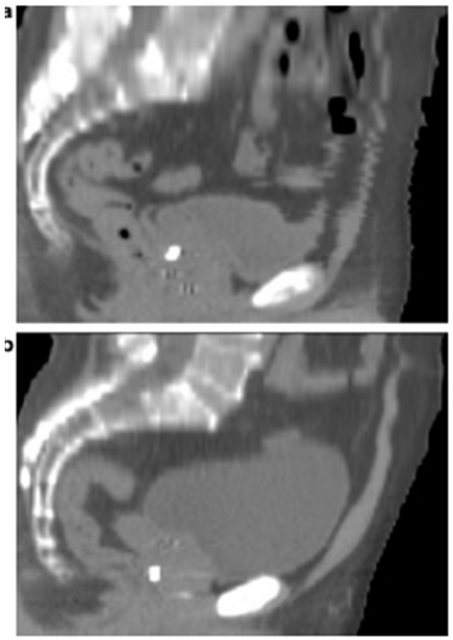
Liu et al, Radiotherapy and Oncology, 2008

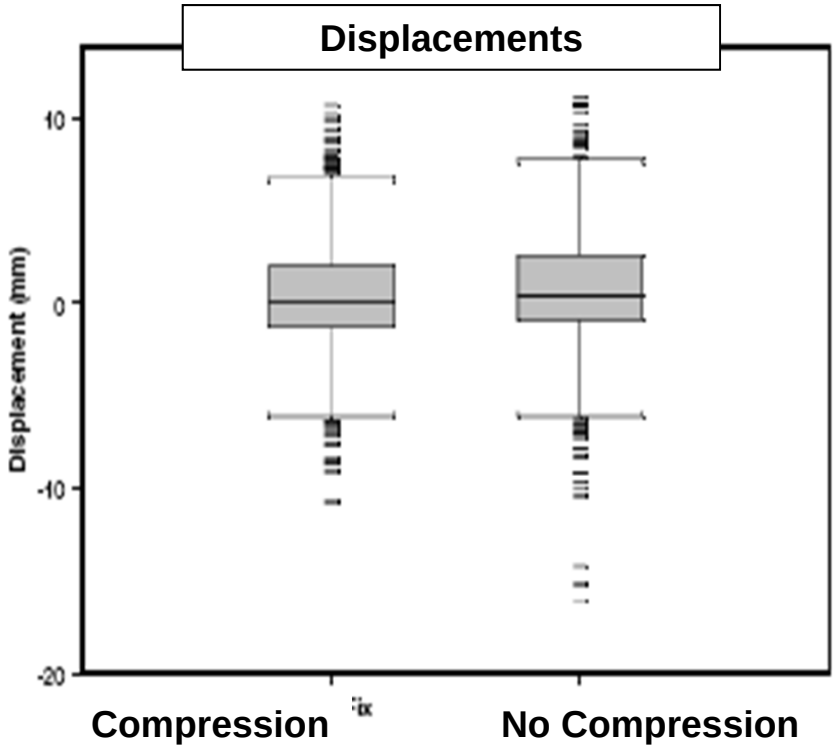
Reducing anatomic variations: Abdominal Compression

Rosewall et al (PMH), Radiotherapy and Oncology, 88, pp 88–94, 2008

N=32 patients. Randomized; with vs without and compression
Fiducials within prostate. EPIs daily, before and after delivery.







Interfraction and intrafraction prostate motion
<u>not affected</u> by abdominal compression.

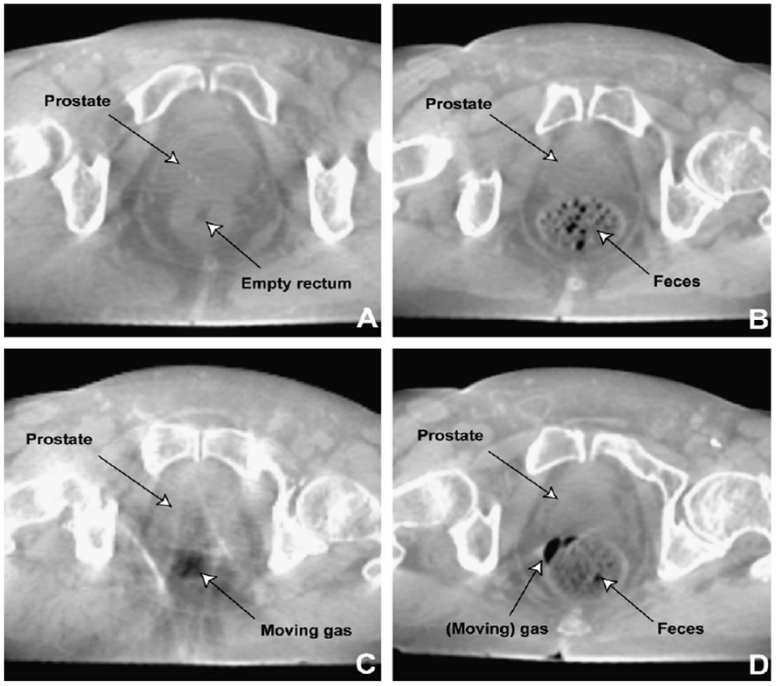
Reducing anatomic variations: Dietary Modifications

Smitmans et al, IJROBP, 71,1279–1286, 2008

26 patients (336 CBCT scans) - follow dietary protocol
23 patients (240 CBCT scans) – no protocol

Tracked: Feces and (moving) gas occurrence in the CBCT scans
The success rate of alignments
Statistics of prostate motion data

Dietary protocol decreased incidence of feces and (moving) gas.
CBCT image quality increased.
Success rate of guidance with CBCT images increased.



DIETARY PROTOCOL

Dietary guidelines

* Start one week before acquisition of planning CT scan
* Continue until the end of treatment

To obtain regular bowel movements

- Eat regularly and avoid skipping meals
- Increase physical activity
- Drink 1.5 - 2 liters of liquid per day

Avoid the following foods

- Whole wheat bread (except for fine grained)
- Cereals: Cruesli and muesli
- Nuts and peanuts
- Vegetables: peas, beans, cabbage, onions, garlic, red/green peppers, asperges
- Fruits: oranges, ananas, prunes, dried fruits
- Hot and spicy foods
- Carbonated beverages and beer
- Coffee; avoid > 4 cups per day

Avoid swallowing air

- Eat slowly and chew food well
- Chew with your mouth closed
- Avoid chewing gum
- Sip beverages rather than gulping

Magnesium oxide tablets (500 mg)

Intake scheme - 2 tablets per night

* On 2 consecutive days before acquisition of planning CT scan
* On 2 consecutive days before start treatment
* Continue intake each night during course of treatment

Treatment time

* Treatments after 10:00 A.M.

Reducing anatomic variations: Dietary Modifications Intrafraction Motion

Nichol et al, IJROBP, 2010

42 patients
Voided bladder and rectum before
3 cine MRIs scans
(1 before, 2 during RT course);
q 9 s for 9 min

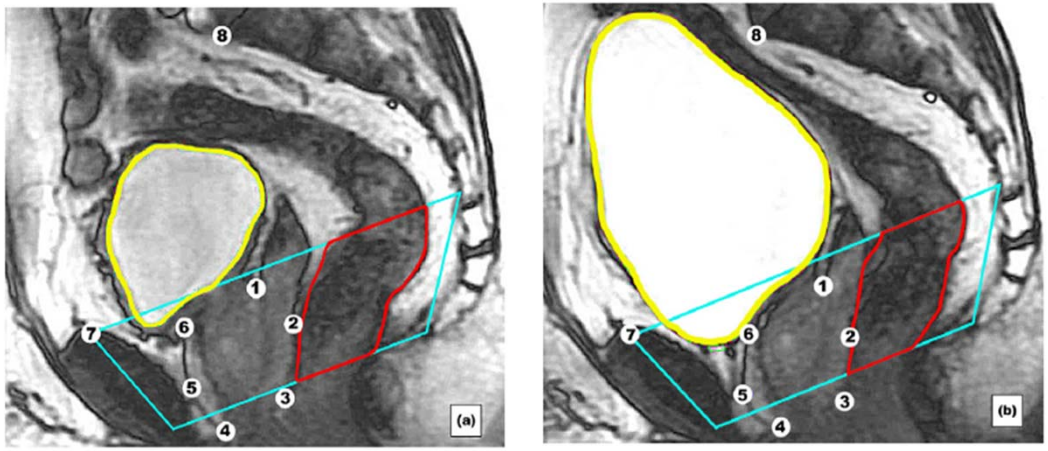
Conclusion:

No impact of diet and MoM on intrafraction motion.

For fractions of <9-min duration, intrafraction prostate motion can be managed with 2-mm margins.

Table 2. Guidelines for managing gas

Types of food	Specific foods to avoid
Vegetables	Peas, beans, lentils, broccoli, cauliflower, brussel sprouts, cabbage, sauerkraut, cucumber, turnip, rutabaga, onions, garlic
Fruits	Apples, bananas, prunes, melons
High-fat foods	Pastries, pies, deep-fried foods
Carbonated drinks	Soda, beer



Reducing anatomic variations: Intrarectal balloon

Immobilization? Unclear

van Lin et al, IJROBP, 61, 278, 2005
Court et al, RO, 81, 184, 2006
Wang et al, RO, 84, 177, 2007
Heijmink et al, IJROBP, 73, 1446, 2009

Improve rectal dosimetry / Decrease late rectal bleeding

Patel et al, RO, 67, 285, 2003
Teh et al, Med Dosim, 30, 25, 2005
van Lin et al, IJROBP, 67, 799, 2007

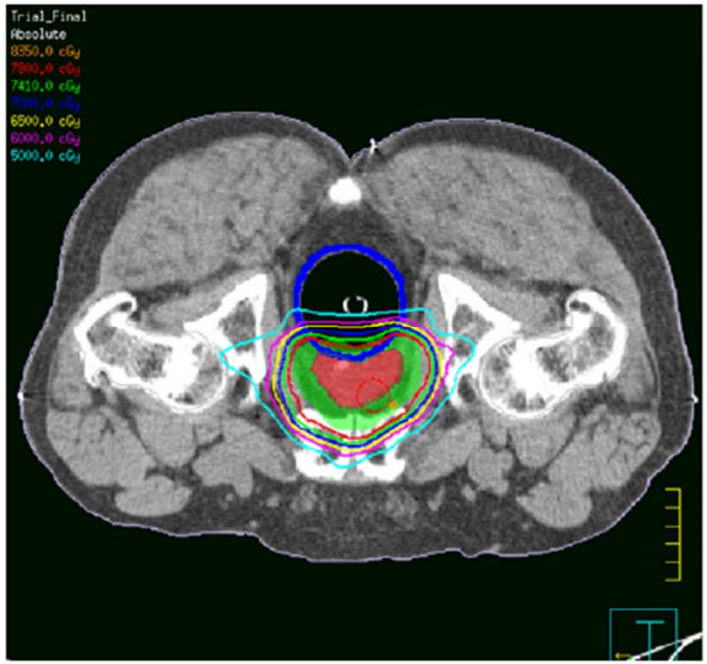
Set-up errors due to endorectal balloon positioning in intensity modulated radiation therapy for prostate cancer

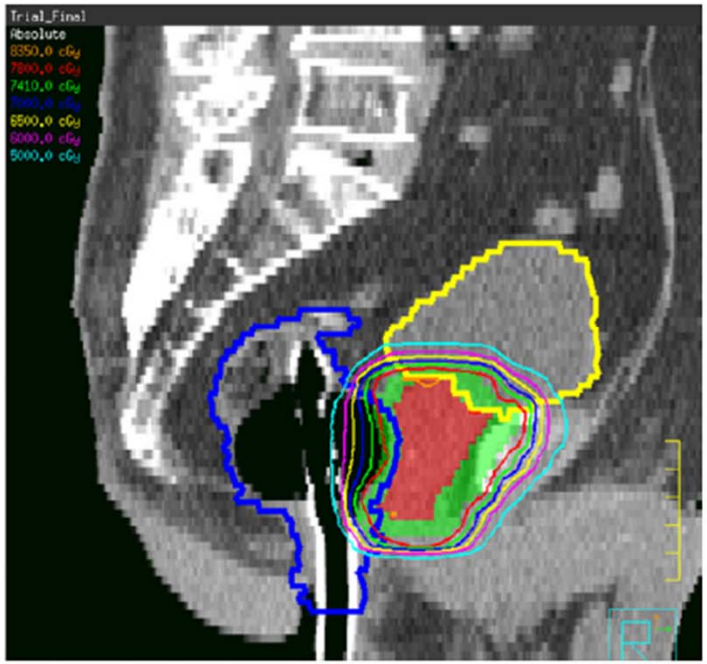
Chun-Wei Wang[a,b,d], Fok-Ching Chong[a], Ming-Kuen Lai[b,c,d], Yeong-Shiau Pu[c], Jian-Kuen Wu[b], Jason Chia-Hsien Cheng[b,d,e,*]

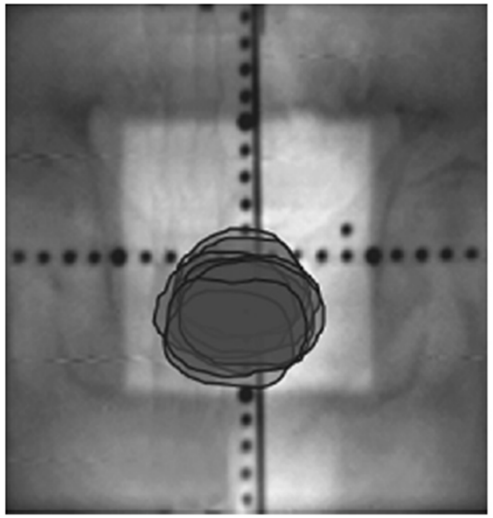
National Taiwan University

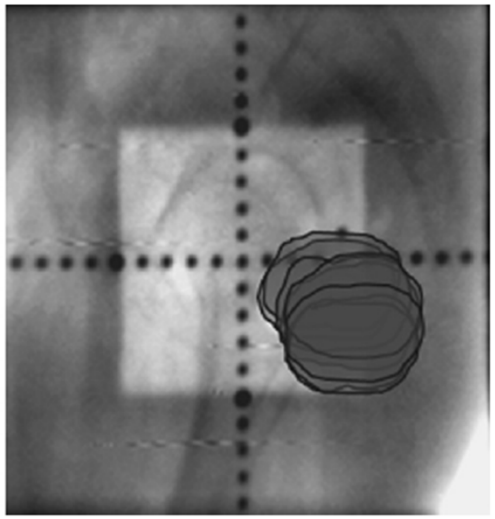
Radiotherapy and Oncology 84 (2007) 177–184

N=20 patients. Weekly EPIs. 154 EPIs.



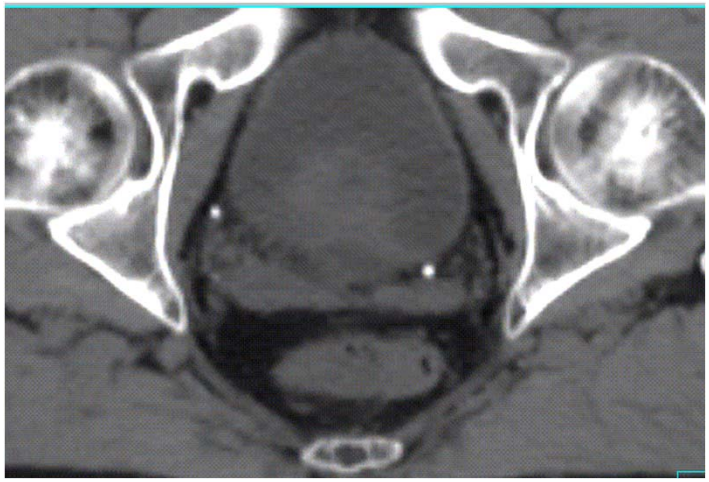


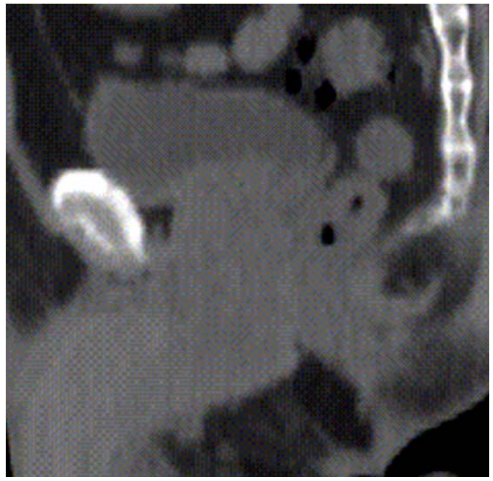




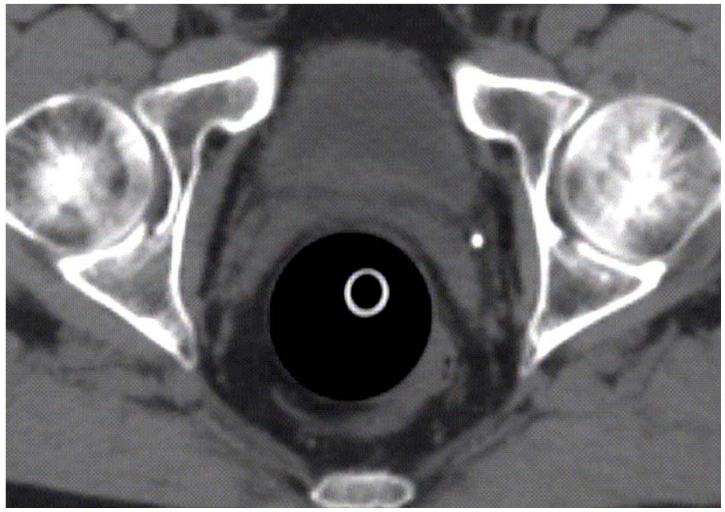
BALLOON: INTRODUCING DEFORMATION

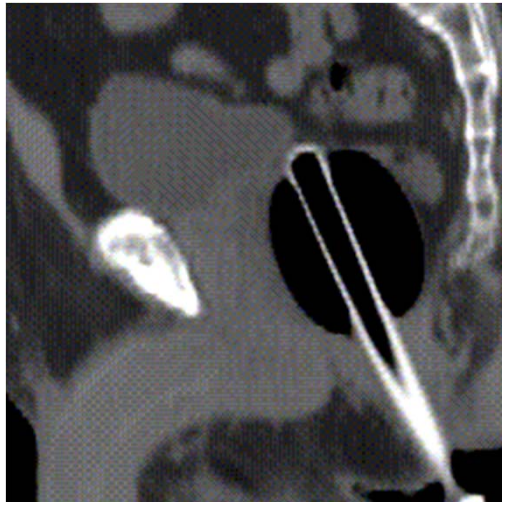
Without balloon





With balloon





<u>Good:</u>
Posterior rectum sparing

<u>Bad:</u>
Increased length of rectum irradiated?
Superior and inferior parts of the rectum get closer to high dose areas.

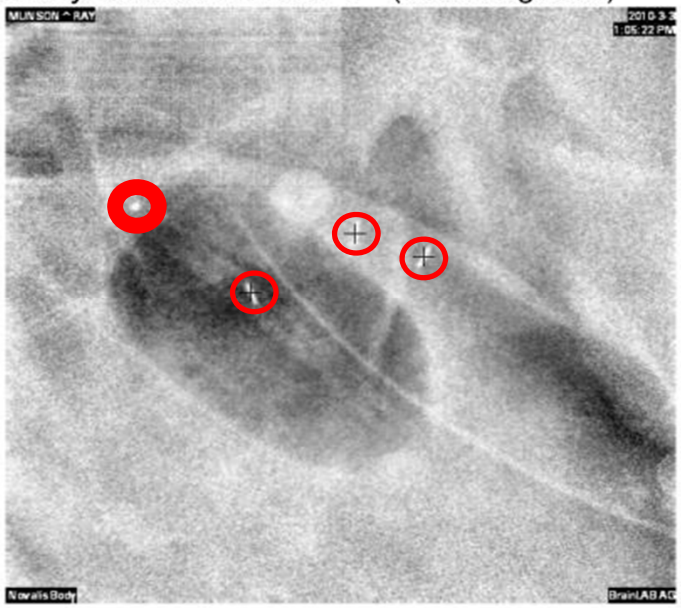
Anal canal:
Increased doses?

Beware of SV coverage;
Increase rectal doses superiorly?

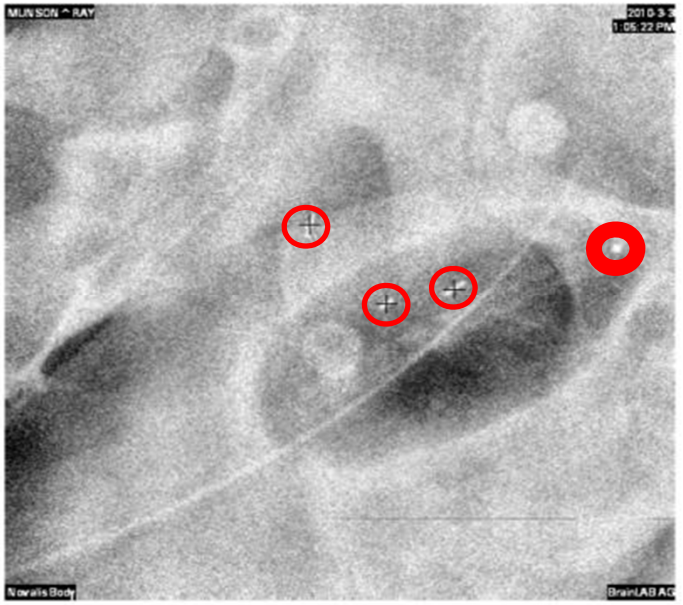
DAILY POSITIONAL VARIATION
BALLOON VERSUS PROSTATE GLAND

Day 5

X-ray Verification Run 1 (Table Angle: 0°)



X-ray Image (Tube 1)

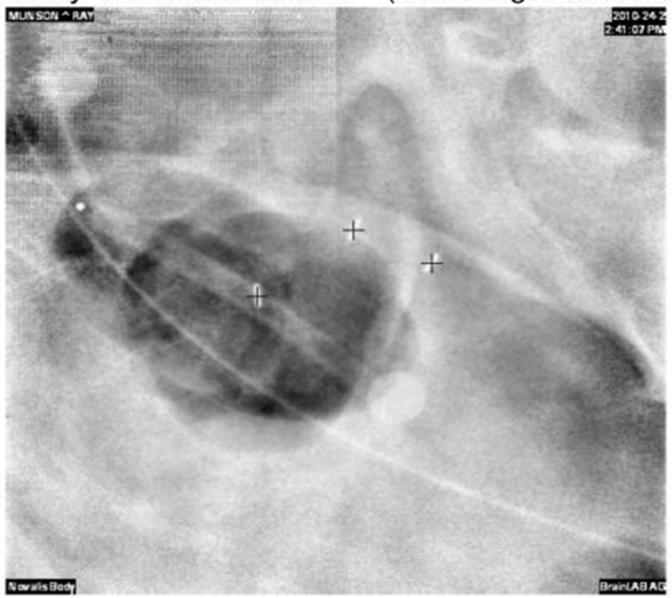


X-ray Image (Tube 2)

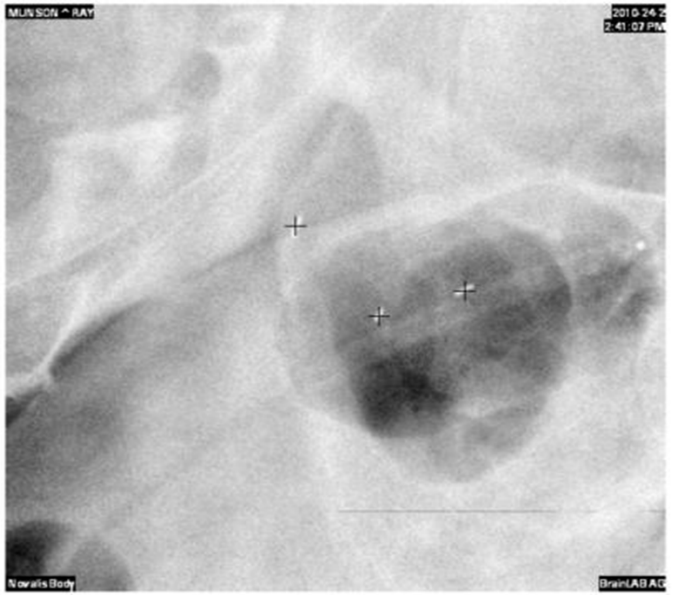
BALLOON: INTRAFRACTION MOTION
DURING PROSTATE SBRT

Time +38 mins

X-ray Verification Run 5 (Table Angle: 5.94683°)



X-ray Image (Tube 1)

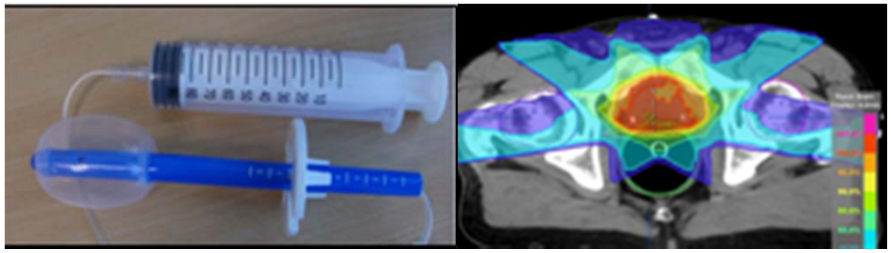


X-ray Image (Tube 2)

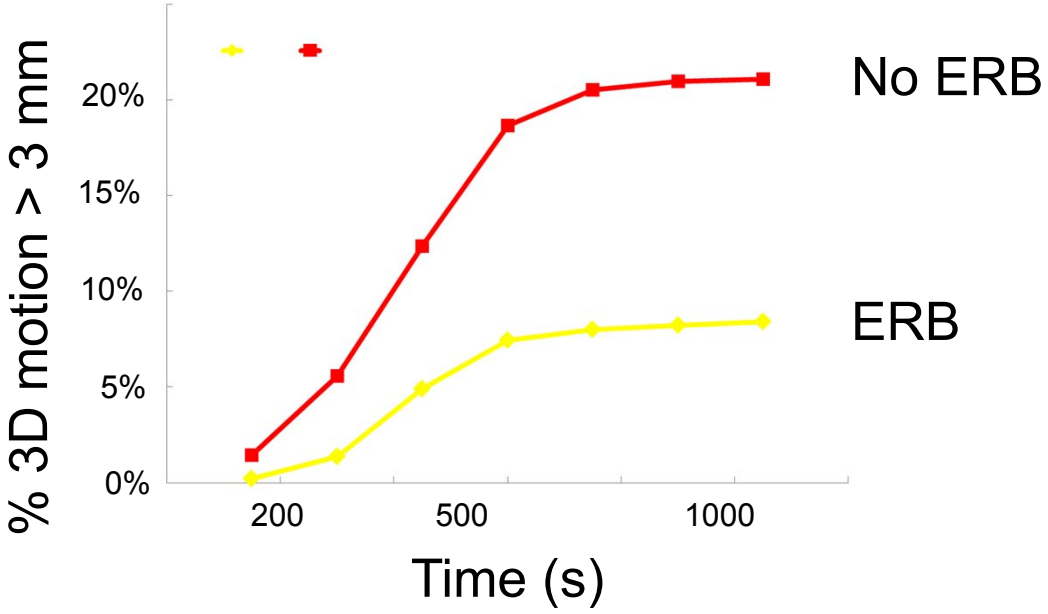
	Shift [mm]			Angle [°]		
	Lat.	Long.	Vert.	Lat.	Long.	Vert.
X-ray Correction	-4.86	-6.42	20.04	0.1	4.5	1.1
X-ray Verification 1	0.33	0.43	-0.41	-0.5	3.7	1.2
X-ray Verification 2	-2.07	-3.58	-5.43	-1.5	2.9	9.0
X-ray Verification 3	1.82	3.34	2.77	0.0	0.0	0.0
X-ray Verification 4	-1.13	0.83	0.16	0.0	0.0	0.0
X-ray Verification 5	-1.03	0.57	-0.23	0.0	0.0	0.0

ENDORECTAL BALLOON: DECREASE IN INTRAFRACTION MOTION?

Nijmegen + MDACC Orlando: Smeenk et al. ASTRO 2010.



Electromagnetic tracks in 30 patients
1143 tracks available for analysis
15 patients without balloon
15 patients with balloon



Balloon decreases but does not eliminate intrafraction motion

TRACKING

FIDUCIAL (OR BONY ANATOMY) BASED:

In-room X-rays:

- Stereoscopic KV X-rays
- On-board imagers (KV/MV)

Electromagnetic tracking

Implanted Radioactive Markers

VOLUMETRIC:

Ultrasound

In-room MRI

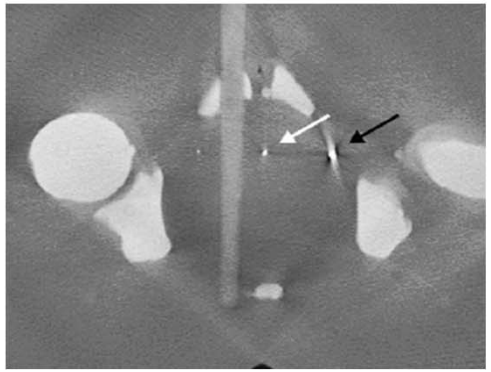
Radioactive Fiducial Tracking

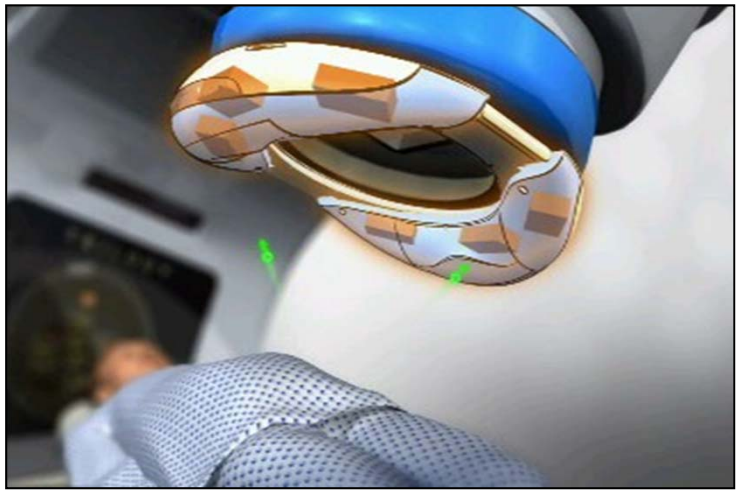
PHYSICS CONTRIBUTION

STABILITY, VISIBILITY, AND HISTOLOGIC ANALYSIS OF A NEW IMPLANTED FIDUCIAL FOR USE AS A KILOVOLTAGE RADIOGRAPHIC OR RADIOACTIVE MARKER FOR PATIENT POSITIONING AND MONITORING IN RADIOTHERAPY

David Neustadter, Ph.D.,* Michal Tune, B.S.,* Asaph Zaretsky, D.V.M.,† Rona Shofti, Ph.D.,† Arnon Kushnir, D.V.M., Tami Harel, Ph.D.,* Dafna Carmi-Yinon, M.D.,* and Ben Corn, M.S.‡

*Navotek Medical Ltd., Yokneam, Israel; †Technion Israel Institute of Technology, Haifa, Israel; and ‡Tel Aviv Medical Center, Tel Aviv, Israel





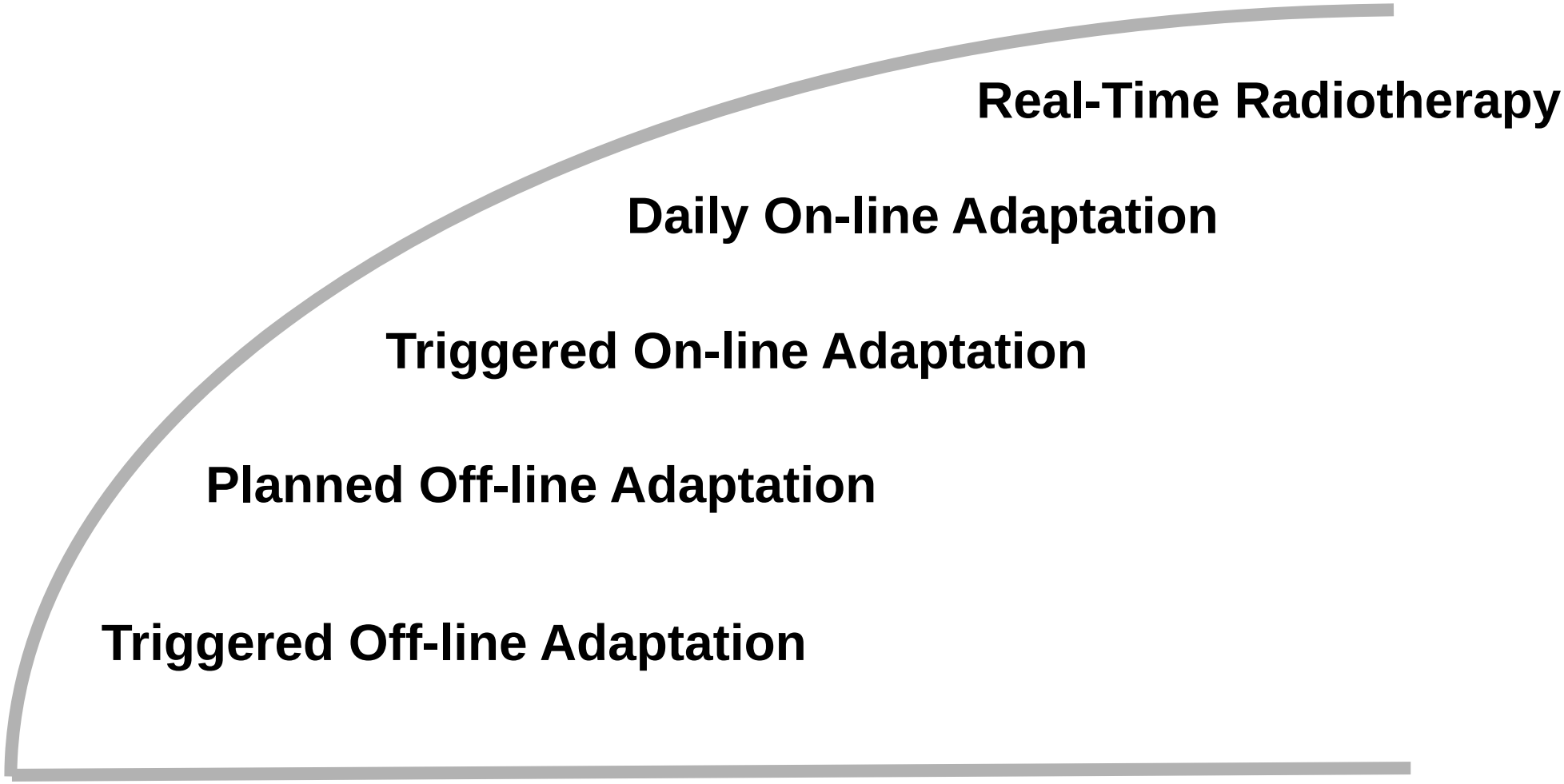
Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 4, pp. 1240–1247, 2010

	Electromagnetic tracking Calypso	Radioactive implant tracking Navotek
Number of Implants	3	1
Implantation Needle Size	14 Gauge	23 Gauge
Implant Stability	Stable	Stable
Update Rate	10Hz	10Hz
Positioning Accuracy	0.5±0.1mm (phantom) 1.9±1.2 mm in humans	0.3±0.2mm (phantom) 1.1±0.4 mm in dogs
MRI image distortion	Yes	No
Real-Time tracking	With any beam	Only with <10 MV Inter-beam with >10 MV

Adaptive Radiotherapy

Real-Time Radiotherapy

Evolution of Adaptive Radiotherapy



On-line Adaptive Techniques: Prostate

Speed versus Quality

UCSF: Ludlum et al. Med Phys. 2007;34(12):4750-6.
On-line prostate vs pelvic LN adjustment
Shifting MLC shapes

MCW: Ahunbay et al. Med Phys. 2008 ;35(8):3607-15
On-line replanning scheme for interfractional variations
Recontour / reoptimize – 10 mins…

Duke: Wu et al. Phys Med Biol. 2008 ;53(3):673-91
On-line replanning scheme for interfractional variations
Deformable registration / reoptimization - 2 mins…

UMDNJ: Zhou et al. Med Phys. 2010, 37(3):1298-308.
On-line Deformable registration, dose accumulation
No replanning – 5-6 mins…

Adaptive RT – Anatomic Sites

Head &Neck	Adaptive radiotherapy of head and neck cancer. Castadot et al. Semin Radiat Oncol. 20:84, 2010
	Adaptive radiation therapy for head and neck cancer-can an old goal evolve into a new standard? Schwartz et al. J Oncol. 2011;2011. pii: 690595. Epub 2010 Aug 18.
Lung	Role of Adaptive Radiotherapy During Concomitant Chemoradiotherapy for Lung Cancer: Analysis of Data From A Prospective Clinical Trial. IJROBP. 75(4):1092-7, 2009
	Potential of adaptive radiotherapy to escalate the radiation dose in combined radiochemotherapy for locally advanced non-small cell lung cancer. Guckenberger et al. IJROBP, 79, 901–908, 2011
Bladder	Offline adaptive radiotherapy for bladder cancer using cone beam computed tomography. Foroudi et al. J Med Imaging Radiat Oncol. 2009;53(2):226-33.
Cervix	MRI assessment of cervical cancer for adaptive radiotherapy. Dimopoulos et al. Strahlenther Onkol. 2009;185(5):282-7.

Real-Time Radiotherapy (Volumetric)

Real-Time Radiotherapy: In-room MRI

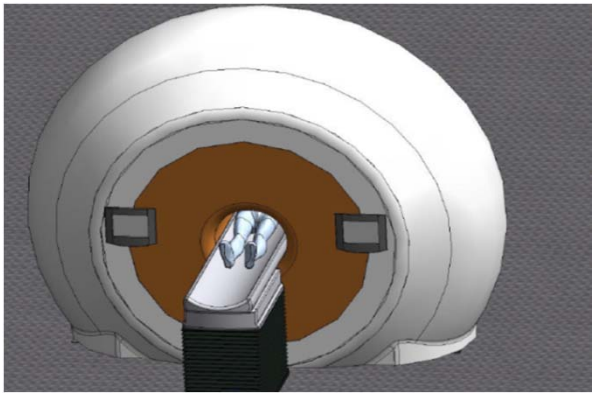
Intrafraction motion/deformation assessment
Functional imaging; e.g. tumor response ??

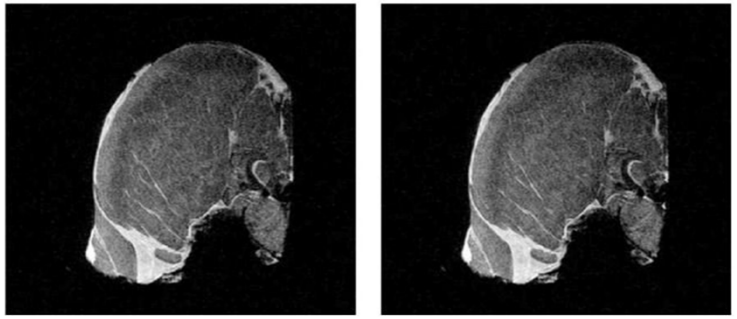
In-room MRI / Cobalt IMRT

ViewRay Inc.

(not approved for clinical use)

In-room MRI / Linac





Phys Med Biol. 2009 Jun 21;54(12):N229-37
Phys Med Biol. 2009 Sep 21;54(18):N409-15

(not approved for clinical use)

Intrafraction motion documented by MRI: Anatomic Gating
ViewRay – not approved for clinical use

Recommendations for Best Practices

1. Segmentation:
   Maintain internal consistency.
   Consider strongly the use of MRI in the planning process.
   Ensure quality of MR to CT registration.
   Do not compromise rectal sparing for wide-margin coverage of the entire extent of the seminal vesicles.

2. PTV Margins and Prescription Dose:

Tight margins (3-5 mms) around the prostate and seminal vesicles allows delivery of doses in the 80 Gy range.

Recommendations for Best Practices

3. Daily Guidance is required;
Random prostate motion necessitates daily guidance.
Inter-user variability is reduced and accuracy is increased with the use of intra-prostatic fiducials.
Soft tissue imaging (e.g. CBCT) is useful but not necessary.

4. Hypo-fractionation and SBRT:
Tight margins / Multiple beams or rotational techniquesDaily imaging is required.
Repeat alignment as frequently as necessary.
Intra-fraction motion check : Check at least every 5 mins

Assessment and Management of Uncertainties: Overview and Examples in the Pelvis

Prostate Cancer Radiotherapy

Patrick Kupelian, M.D.
James Lamb, Ph.D.

University of California Los Angeles
Department of Radiation Oncology

August 2011