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

Prostate Cancer Radiotherapy

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Disclosures

Research grants / Honoraria / Advisory Board:

Tomotherapy Inc.
Varian Medical
Siemens
Viewray Inc.
### PELVIC SITES

<table>
<thead>
<tr>
<th>Uncertainties matter more if:</th>
<th>Dose</th>
<th>High Dose Target Size</th>
<th>Current RT Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Small</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

#### Pelvic Sites / Diseases:

<table>
<thead>
<tr>
<th>Site</th>
<th>Dose</th>
<th>Target Size</th>
<th>Current Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>High</td>
<td>Small</td>
<td>Frequent</td>
</tr>
<tr>
<td>Lower GI (rectum / anus)</td>
<td>Low</td>
<td>Large</td>
<td>Infrequent</td>
</tr>
<tr>
<td>GYN (Cervix – with Brachy)</td>
<td>Low</td>
<td>Large</td>
<td>Infrequent</td>
</tr>
<tr>
<td>GYN (Cervix – Definitive IMRT)</td>
<td>High</td>
<td>Small</td>
<td>Rare</td>
</tr>
<tr>
<td>GYN (Endometrium)</td>
<td>Low</td>
<td>Large</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Bladder</td>
<td>High</td>
<td>Small</td>
<td>Rare</td>
</tr>
<tr>
<td>Testicular Ca</td>
<td>Low</td>
<td>Large</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>
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 Hypofractionation: 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, David Wilkins, Libni Eapen, Christopher Morash, Youssef Wassef, Lee Gerg

Department of Radiation Oncology, The Ottawa Hospital Regional Cancer Centre, Ottawa, Canada, Department of Physics, Carleton University, Ottawa, Canada, 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 Schechter, 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

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 VANDECAYEVE, 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

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

Prostate

Seminal Vesicles

Alignment on mid gland prostate

Prostate

Seminal Vesicles

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;

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 \( \sigma \sim 2-3\text{mm} \), 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. Melancon⁴, Jennifer C. O’Daniel⁴, Lifei Zhang⁴, Rajat J. Kudchadker⁴, Deborah A. Kuban⁵, Andrew K. Lee⁵, Rex M. Cheung⁵, Renaud de Crevoisier⁴,¹, Susan L. Tucker⁶, Wayne D. Newhauser⁴, Radhe Mohan⁴, Lei Dong⁴,∗

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

Areas of interest: Prostate+SV
Prostate
Peripheral Zone (tumor proxy)
Bladder / Rectum

8 mm margins

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 ($D_{\text{mean}}$) 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)
Challenge: Independent movement of prostate vs nodes


INTRAPROSTATIC TARGETS

SELECTIVE INTRAPROSTATIC BOOST VS FOCAL THERAPY
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 Vulpun, Marielle E.P. Philippens, Ulrike A. van der Heide

University Medical Center Utrecht, The Netherlands

Abstract

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.

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E stained sections – macroscopic slices (mm)</th>
<th>Stacking macroscopic slices (mm)</th>
<th>Rigid registration 3D stack – T2w image (mm)</th>
<th>Overall (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.18 mm</td>
<td>0.23 mm</td>
<td>1.67 mm</td>
<td>1.70 mm</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.91 mm</td>
<td>0.38 mm</td>
<td>1.93 mm</td>
<td>2.17 mm</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.78 mm</td>
<td>0.63 mm</td>
<td>1.65 mm</td>
<td>1.93 mm</td>
</tr>
<tr>
<td>Patient 4</td>
<td>0.38 mm</td>
<td>0.59 mm</td>
<td>2.93 mm</td>
<td>3.01 mm</td>
</tr>
<tr>
<td>Patient 5</td>
<td>0.27 mm</td>
<td>0.29 mm</td>
<td>2.32 mm</td>
<td>2.35 mm</td>
</tr>
</tbody>
</table>

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 all the registered MR images. (B) T2w image. (C) DW-MRI image. (D) ADC map. (E) $k_{max}$ map.
Tumor Regression in the Pelvis: Cervical Cancer

- Volumetric Imaging
- Monitor target coverage
- Adaptive RT?

Courtesy: AJ Mundt
14 cervical cancer patients
MRI prior to RT and after 30 Gy external beam
GTV decreased (on average) by 46%
Decrement 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
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

\[\text{Implemented simultaneously}\]

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

![Graph showing biochemical control rate over time after RT (years).](image1)

- Undistended: CSA ≤ 11.2 cm²
- Distended: CSA > 11.2 cm²
- P < 0.001

Dutch Trial

![Graphs showing freedom from failure over time (months).](image2)

- Treatment group III/IV, dose 67.9 Gy (a)
- Treatment group III/IV, 77.9 Gy (b)

References:

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

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 ??

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
Adjusting for Deformations Prostate versus Pelvic Lymph Nodes Clinical Impact?
NODAL RT:
IMAGE GUIDANCE IMPROVING TOXICITY?

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

| Toxicity | RTOG grade | | | | CTCAE grade | | | |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | 0 | 1 | 2 | | 0 | 1 | 2 | | 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.

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*

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Langen et al., IJROBP, 57, 635 (2003)
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.

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

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Obs</th>
<th>Method</th>
<th>Sampling</th>
<th>Motion (mm)</th>
</tr>
</thead>
</table>
| 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 INTRAFACTION 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

Gating

Robot adjustment
Accuray Synchrony®

BrainLAB ExacTrac ®

Courtesy Accuray

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
ARE THERE PATTERNS? NO
ARE PATTERNS PREDICTABLE? NO

Electromagnetic Tracking

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

<table>
<thead>
<tr>
<th></th>
<th>% of fractions with 3D offset outside limit &gt;30 seconds</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3 mm limit</td>
</tr>
<tr>
<td>Weighted Average</td>
<td>41%</td>
</tr>
</tbody>
</table>

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

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 INTRAFOCUSION MOTION – Clinical Examples

Persistent drift; corrections twice in one fraction - Vertical motion

Patient motion versus prostate motion (pt with Parkinson’s) - Longitudinal motion
MONITORING INTRAFACTION 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

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

Langen et al, PMB, 53, 7073, 2008
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

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, $D_{95\%}$

MDACC: WORST CASE (WORST INTRAFRACTION MOTION)

Langen, IJROBP, 2009
CORRECTION OF INTRAФRACTION MOTION

CLINICAL IMPACT
Intrafraction Monitoring Correction – Clinical Impact?

Assessing the Impact of Margin (AIM) Reduction Study

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

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2 (Historical control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EM tracking (Calypso)</strong></td>
<td>Guidance method, if any, not reported</td>
</tr>
<tr>
<td>(2 mm threshold)</td>
<td>“Institutional norms”</td>
</tr>
<tr>
<td>3 mm post margins</td>
<td>Varying margins “5-10 mm”</td>
</tr>
<tr>
<td>81 Gy</td>
<td>~ 75-80 Gy</td>
</tr>
<tr>
<td>N=64 patients</td>
<td>N=153 patients</td>
</tr>
<tr>
<td>IMRT, no hormones</td>
<td>IMRT, no hormones</td>
</tr>
<tr>
<td>Realignment in 60% of fractions</td>
<td></td>
</tr>
</tbody>
</table>

Sanda et al., NEJM 2008 358(12) 1250-61
## Intrafraction Monitoring Correction – Clinical Impact?

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

Assessing the Impact of Margin (AIM) Reduction Study
Intrafraction Monitoring Correction – Clinical Impact?

Assessing the Impact of Margin (AIM) Reduction Study

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</tr>
<tr>
<td>81 Gy</td>
<td>~ 75-80 Gy</td>
</tr>
</tbody>
</table>

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

Reducing anatomic variations: Abdominal Compression

Interfraction and intrafraction prostate motion not affected 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.
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

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\textsuperscript{a,b,d}, Fok-Ching Chong\textsuperscript{a}, Ming-Kuen Lai\textsuperscript{b,c,d}, Yeong-Shiau Pu\textsuperscript{c},
Jian-Kuen Wu\textsuperscript{b}, Jason Chia-Hsien Cheng\textsuperscript{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

Good:
Posterior rectum sparing

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

With balloon

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

<table>
<thead>
<tr>
<th></th>
<th>Shift [mm]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray Correction</td>
<td>-4.86</td>
<td>-6.42</td>
</tr>
<tr>
<td>X-ray Verification 1</td>
<td>0.33</td>
<td>0.43</td>
</tr>
<tr>
<td>X-ray Verification 2</td>
<td>-2.07</td>
<td>-3.58</td>
</tr>
<tr>
<td>X-ray Verification 3</td>
<td>1.82</td>
<td>3.34</td>
</tr>
<tr>
<td>X-ray Verification 4</td>
<td>-1.13</td>
<td>0.83</td>
</tr>
<tr>
<td>X-ray Verification 5</td>
<td>-1.03</td>
<td>0.57</td>
</tr>
</tbody>
</table>
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

Balloons 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
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

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

Real-Time Radiotherapy
Evolution of Adaptive Radiotherapy

- Triggered Off-line Adaptation
- Planned Off-line Adaptation
- Triggered On-line Adaptation
- Daily On-line Adaptation
- Real-Time Radiotherapy

No adaptation
On-line Adaptive Techniques: Prostate
Speed versus Quality

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…

On-line replanning scheme for interfractional variations
Deformable registration / reoptimization - 2 mins…

On-line Deformable registration, dose accumulation
No replanning – 5-6 mins…
# Adaptive RT – Anatomic Sites

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head &amp; Neck</strong></td>
<td>Adaptive radiotherapy of head and neck cancer. Castadot et al. Semin Radiat Oncol. 20:84, 2010</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>Role of Adaptive Radiotherapy During Concomitant Chemoradiotherapy for Lung Cancer: Analysis of Data From A Prospective Clinical Trial. IJROBP. 75(4):1092-7, 2009</td>
</tr>
</tbody>
</table>
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


(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 techniques Daily 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