IGRT Solution for the Living Patient and the Dynamic Treatment Problem

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Learning Objectives:

• Identify common site-specific anatomic changes during the course of external beam radiotherapy using conventional fractionation schemes.
• Illustrate dosimetric consequences due to changed anatomy or the positions of the targets.
• Suggest correction strategies based on observed patterns of site-specific anatomic variations.

Conventional Workflow

• An implied assumption is that the shapes, volumes, and positions of an anatomic structure of interest will not change throughout entire radiotherapy treatment.
  – Even if these changes exist, wide margins can be used to correct for them (ICRU #50 & #62).
• But, this may not be enough:
  – IMRT is more sensitive to organ variations
  – Further treatment optimization requires more careful considerations of site-specific or patient-specific anatomic variations.
Outline

- Review: types of uncertainties
- Site-specific issues in prostate
- Site-specific issues in head & neck
- Site-specific issues in thorax or abdomen
- Image-guided adaptive radiotherapy

Why do we need to worry?

- The dose response curves are quite steep. There is a clinical evidence that a small change (7% to 10%) in dose can result in a change in tumor control probability (ICRU Report #24, 1976).
- With highly conformal radiotherapy (such as IMRT), the probability of geographic miss increases significantly.

How to quantify inter- and intra-fraction organ “motion” or “variations”

- Systematic
  - Group statistics
- Random
  - Day-to-day variations
- Shape Variations
  - Volume
  - Deformation
- Trends
  - Time-dependent variations
Random and Systematic Uncertainties

Individual Patient Statistics
\[ \tau_i = \frac{\sum (x_i - \mu)}{N} \]
\[ \sigma_i = \sqrt{\frac{\sum (x_i - \mu)^2}{N}} \]

Group Statistics
\[ \mu = \frac{\sum \tau}{N} \]
\[ \Sigma = \sqrt{\frac{\sum (\tau - \mu)^2}{N}} \]
\[ \sigma_{\text{sys}} = \sqrt{\frac{\sum \sigma_i^2}{N}} \]

Margin Considerations
• Marcel van Herk
  - Errors and Margins in Radiation Therapy. Seminars in Radiation Oncology, Vol 14, No.1, 2004
  - 2.5 \Sigma + 0.7 \sigma

• Di Yan et al.
  - CT-guided Management of Inter-fractional Patient Variation. Seminars in Radiation Oncology
  - Large \Sigma and small \sigma: more beneficial for off-line correction
  - Large \sigma: more beneficial for on-line correction

How big is the population margin?

Margin = 2.5 * \Sigma + 0.7 * \sigma

\[ \Sigma (\text{mm}) \quad \sigma (\text{mm}) \quad \text{Margins (mm)} \]

<table>
<thead>
<tr>
<th>ROIs</th>
<th>AP</th>
<th>SI</th>
<th>RL</th>
<th>AP</th>
<th>SI</th>
<th>RL</th>
<th>AP</th>
<th>SI</th>
<th>RL</th>
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<tbody>
<tr>
<td>C2</td>
<td>2.3</td>
<td>1.6</td>
<td>2.6</td>
<td>1.7</td>
<td>1.8</td>
<td>1.5</td>
<td>6.9</td>
<td>5.3</td>
<td>7.8</td>
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<tr>
<td>C6</td>
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<td>2.0</td>
<td>3.2</td>
<td>2.0</td>
<td>2.2</td>
<td>2.3</td>
<td>7.7</td>
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<tr>
<td>PPM</td>
<td>2.4</td>
<td>4.2</td>
<td>1.5</td>
<td>1.7</td>
<td>2.9</td>
<td>1.1</td>
<td>7.2</td>
<td>12.5</td>
<td>4.5</td>
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</tbody>
</table>
Population-derived margin will not work well (too conservative)

The danger of systematic errors

- Consistently wrong
  - Example

Effect of Rectal Distension

**Hypothesis:**
If prostate motion is not taken into account, rectal distension on the planning CT may result in a systematic target miss and therefore an increased risk of biochemical failure.
Measures of Rectal Distension:

Cross-Section Area (CSA) = rectal volume / length

Study Population

- Distribution of Risk Groups
  - Low Risk: N=26 (21%)
  - Intermediate Risk: N=60 (47%)
  - High Risk: N=41 (32%)
- > 2-yr follow-up (median 7 yrs; up to 10 yrs)
- No enema
- Setup with skin marks + weekly PF

Biochemical Control by Risk Group:
Biochemical Control by Rectal Distension:

For Intermediate Risk Patients:

![Graph showing biochemical control rate over time for intermediate risk patients with and without distension.](image)

- Undistended: CSA < 11.2 cm²
- Distended: CSA > 11.2 cm²

P = 0.001

Time after RT (years)

Biochemical control rate

For High Risk Patients:

![Graph showing biochemical control rate over time for high risk patients with and without distension.](image)

- CSA ≤ 11.2 cm²
- CSA > 11.2 cm²

P = 0.034

Time after RT (years)

Biochemical control rate
Multivariate Analysis:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>High Risk Disease</td>
<td>2.28</td>
<td>0.028</td>
</tr>
<tr>
<td>CSA &gt; 11.2 cm²</td>
<td>3.12</td>
<td>0.018</td>
</tr>
<tr>
<td>Rectal Diameter &gt; 6cm</td>
<td>2.44</td>
<td>0.043</td>
</tr>
</tbody>
</table>

No correlation between rectal distension (CSA) and:

- Risk group
- PSA
- T-stage
- Gleason score

Conclusion of this study

- There is clinical evidence that rectal distension on the treatment planning CT scan decreased the probabilities of biochemical control, local control and rectal toxicity in patients who are treated without daily image-guided prostate localization, presumably due to geographic misses. Therefore, an empty rectum is warranted at the time of simulation.
N=549
78 Gy vs. 68 Gy
Tumor control was significantly decreased in a subgroup of patients with a large rectum filling visible on the planning CT scan and who had an estimated risk of SV involvement of 25%.

Example of setup error and organ variation during the course of prostate radiotherapy

- Contours from treatment planning CT are overlaid as reference
- Patient aligned with BBs

Prostate Position Relative to Skin Marks

- Systematic 1SD = 3.7 mm
- Random 1SD = 3.3 mm
Comparison of Bony and Direct Target Localization

Bony Registration  Direct Target Localization

“freezing” the prostate!

Dosimetric Impact of Varying Anatomy
(Patient Averages Rectal Wall DVH +/- 1SD)

Error bar (+/- 1SD) was calculated based on 24 serial CT images.

Time-Trend for Bladder Volume

90% of daily bladder volumes are smaller than the volume at the simulation!
Dosimetric Impact of Varying Anatomy
(Pat07, Average Bladder DVH +/- 1SD)

Can I use 0-margin for PTV when I use IGRT?

Anatomic and Dosimetric Analysis of Intra-fractional Motion during an IMRT Treatment Fraction
A Melancon*, R de Crevoisier, L Zhang, J O'Daniel, D Kuban, R Cheung, A Lee, R Mohan, L Dong,
Univ. of Texas M. D. Anderson Cancer Center, Houston, TX
Effect of Bladder Filling to Prostate Positions

- MICHAEL PINKAWA et al. from Department of Radiotherapy, Rheinisch-Westfälische Technische Hochschule Aachen, Aachen, Germany.
- 30 patients CT scanned with full and empty bladder at the beginning, middle, and the end of RT.
- Prostate position is barely affected by the bladder filling.
- Rectum volume has the major influence on prostate position.
- Support to treat patients in supine position with full bladder.
Summary for prostate patients

- Systematic uncertainties are similar or greater than random uncertainties
  - Off-line correction protocol may be beneficial.
  - Daily IGRT would be ideal.
- The planning CT may not be a typical CT during treatment
  - Large uncertainties in DVHs for both rectum and bladder
- The volumetric change of prostate gland during the course of radiotherapy is small and may not have significant clinical impact.

Setup Uncertainties In Head & Neck Treatment

19 Treatment CT scans acquired during the course of head & neck radiotherapy

An example of increasing room inside a thermoplastic facemask due to tumor shrinkage as treatment progressing. Near the end of treatment, the lower neck was not centered on the headrest, presumably due to patient's self-adjustment to the relatively “roomier” mask.
Figure 8. Examples of anatomy rotation between the planning CT (first row) and the daily CT (second row). The axial CT images shown on the left indicate a roll in the patient’s head; the coronal CT images on the right show yaw (rotation of the spinal column).

**Change in Neck Curvature**

Planning CT

Daily Cone-beam CT with planning contour overlay

**2D planar x-rays = volume alignment?**
- Traditional alignment assumes rigid-body for the entire H&N region
- Can you combine multiple 2D ROI for a 3D ROI?
- $2 \times 2D = 3D?$

<table>
<thead>
<tr>
<th>Correlation on absolute setup shifts between C2 and C6 and between C2 and PPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2C6AP</td>
</tr>
<tr>
<td>-1.50</td>
</tr>
<tr>
<td>-0.50</td>
</tr>
<tr>
<td>0.50</td>
</tr>
</tbody>
</table>

PPM did not match after C2 alignment

Daily Treatment CT  Planning CT
C6 did not match after C2 alignment

Evidence of Anatomic Variations During Treatment Course

Significant Anatomic Variations
Summary for H&N patients

- Setup uncertainties were found larger than traditionally expected with portal films.
  - A collection of bones is not a rigid body.
  - Need to worry about residual shifts at different parts of the H&N anatomy.
  - Immobilization technique is important.
  - Systematic uncertainties appear to be larger than random setup uncertainties.
  - Offline correction strategy is beneficial.

- Trends in volumetric and positional variations
  - Adaptive radiotherapy strategy
Squamous Cell Ca NOS T4 N2 M0

Planning CT

One Month Into Treatment

4D CT Imaging

Coronal

Sagittal

Non-ITV Approach (IMRT-8mm)

10 Gy 20 Gy 35 Gy 50 Gy 70 Gy
Impact of Organ Motion To Proton Dose Distributions

Free breathing Treatment

Proton vs. IMRT (motion effect to dose distribution)

Impact of Organ Motion on Proton Dose Distributions

Treatment planned based on single Free-breathing (FB) CT image (conventional approach)

The same treatment plan calculated on 4D CT images

Workflow of IGRT and Adaptive Radiotherapy

A workflow diagram for in-room CT-guided adaptive radiotherapy

In-Room Imaging

Related Technologies
- RPM gating-4DCT
- Optical-guided Approaches

Ultrasonography
- BAT
- shave
- transducer

Video-Beam
- Video subtraction
- Photogrammetry
- AirWt
- Real-Time Video-Guided IMRT

Planar X-Ray
- EPID
- CyberKnife
- Needle
- IGRT

Volumetric
- In-Room CT
- Focal, MEKCC
- CT on-Rails
- On-Board
- Varian Excel/EXACT
- Tomotherapy
- MV Cone Beam CT
- Siemens
- kV Cone Beam CT
- Mobile
- Varian OBI
- Elekta Synergy
- Siemens In-Line
Why Adaptive Radiotherapy (ART)?

- Live patient and dynamic treatment
- ART = Adapting to changes (anatomy, dose distributions, biology…)
- Corrections beyond simple translation shifts

Image-guided Adaptive Radiotherapy Schemes

- Prospective Correction
  - Auto-segmentation
  - Re-planning
  - On-line
  - Off-line

- Final Dose Map

- Deforming doses

- Retrospective Evaluation

- Deformable image registration to quantify anatomic changes
- Auto-segmentation
- Cumulating doses

Example
H&N CT-on-rails Studies

How to evaluate and approve these deformed contours?

Auto-Segmentation of H&N Anatomy

Benefit of IGRT Alone

Mask Setup vs. C2-bone Setup

Patient #2
Evaluation of Cumulative Dose Distributions Fraction-by-Fraction

Patient #1

Dose Volume Histogram

Dose (cGy)

Fx01
Reducing CTV/GTV Uncertainties

- Target delineation uncertainties
  - Better knowledge about the disease and spread pathway.
  - Multi-modality imaging (PET, SPECT, fMRI etc.)
  - Inter-observer variations

CT only

CT + PET + SPECT

Summary and Discussion

- The living patient and the dynamic treatment problem
  - A computer treatment plan is not "WYSIWYG"
- Reducing systematic errors
  - Improving simulation techniques
  - Designing better immobilization devices
  - Off-line correction
- Reducing day-to-day variations
  - On-line image guidance
  - Better immobilization devices
- Trends
  - Volume effect
  - Mid-course correction
  - Adaptive Radiotherapy