Online Adaptive Radiotherapy: Are We Ready?

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AAPM Therapy Symposium
Aug. 4th 2011

Disclosure
- Sponsored Research Grants from
  - Varian
  - Philips
- Software Licensed to
  - Varian
- NIH/NCI Grants
  - Adaptive RT for H&N
  - Proton Therapy
- State of Texas Grant
  - Adaptive RT for Lung Cancer

Objectives
- Demonstrate advantages and limitations of adaptive radiotherapy
- Understand various forms of adaptive radiotherapy
- Discuss practical issues related to clinical implementation

Concept of Treatment Planning
Goal: To design a treatment plan based on an anticipated patient treatment

- Requirements
  - Accurate target delineation
  - Normal structure delineation and dose tolerance
  - Accurate model of the patient
  - CT or 4DCT of the patient in treatment position
  - Accurate margin prediction
  - Balance of risk and benefit
The initial simulation CT is perhaps the most biased representation of patient’s anatomy!

Is one DVH enough to accept the plan?


Significant Anatomic Variations

Planning CT During Treatment

CTV is in the air

Impact of Tumor Shrinkage on Proton Dose Distribution

Original Proton Plan Dose recalculated on the new anatomy

Bucci/Dong et al. ASTRO Abstract, 2007
A single plan designed before treatment is insufficient to describe the actual delivered doses, and often leads to suboptimal treatment.

Population margin is too big for highly conformal therapy

Margins are based on random and systematic uncertainties of population

\[
\begin{align*}
\tau_i &= \sum (s_i - s_{ref_i}) / N_i \\
\sigma_i &= \sqrt{\sum (s_i - s_{ref_i})^2 / N_i}
\end{align*}
\]

\[
\begin{align*}
\mu &= \sum \tau_i / N \\
\sigma &= \sqrt{\sum (\tau_i - \mu)^2 / N} \\
\sigma_{sys} &= \sqrt{\sum (\sigma_i^2 / N)}
\end{align*}
\]

“Definition”

“Online Adaptive radiotherapy” is defined as changing the radiation treatment plan delivered to a patient during a treatment session to account for temporal changes in anatomy (e.g. tumor shrinkage, weight loss or internal motion) or changes in tumor biology/function (e.g. hypoxia).
"Definition"

Online Adaptive Radiotherapy:
- online "near real-time" prior to a fraction
- In real time during a fraction

Image Guidance vs. Adaptive RT
- "Image Guidance" is commonly referred to a process to re-position the patient without modifying the initial treatment plan
- Adaptive RT involves the modification of the initial plan, including

Can't be corrected by simple couch shifts

Planning CT  
During Treatment

Non-rigid bony structure changes - Can't be corrected by simple couch

Planning CT  
Daily Cone-beam CT with planning contour overlay
Rapid changes can occur early 4 days after simulation.

Simulation CT

5 days after treatment

10 days after treatment

Target Volume Increases - Can't be corrected by simple couch shifts

Planning CT

2 weeks into treatment

Early Replan - Fraction #1!

Original Plan

1st Treatment Fraction

CTV70

CTV63

R Parotid

L Parotid

Early Adaptive Replan Case

1st plan 2nd plan
Anatomy Changes Along Beam Path in Proton Therapy

Original Plan

Daily CT

Benefits of Online Anatomy-based Adaptive Radiotherapy

- Correction for non-rigid anatomical changes beyond image guidance
- Further improvement in conformality of the delivered plan
- Reducing margin requirements for IGRT
- Reducing normal tissue dose
- Dose-guided, instead of anatomy based

Adaptive Radiotherapy with Emerging Biological/functional Imaging

- Bentzen (Lancet Oncol 2005)
  - A partial GTV boost may be even more appealing if we can determine the parts of the GTV at the highest risk of failure because of high clonogen density, proliferation rate, hypoxic content, or low cellular radiosensitivity.

- Geets et al. (Radiother Oncol 85 (2007))
  - FDG-PET-based and adaptive IMRT planning reduced the irradiated volumes by 15–40% compared to pretreatment CT planning.

Adaptive Boost Treatment of Biological Target Volume

C. Ling et al. IJROBP Vol. 47 No. 3 p551, 2000
Role of Functional Imaging

Dose Painting By Numbers
(More accurate imaging and targeting are required for non-uniform dose prescriptions)

Biologically targeted adaptive therapy
- Up-to-date treatment response information
- Further reduction in target volume

Limitations of Functional Imaging
Table 1. Summary of main provisions of the various categories of PET image segmentation techniques

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very simple to use. Tools to transfer RT objects to treatment planning systems available from most vendors</td>
<td></td>
</tr>
<tr>
<td>Thresholding techniques</td>
<td>Most frequently used due to their simplicity in implementation and high efficiency</td>
<td>Hard decision making. Too sensitive to PET uptake heterogeneity and motion artifacts. Some methods volume, others focus on intensity differences.</td>
</tr>
<tr>
<td>Unsupervised</td>
<td>Subtracted accuracy, boundary continuity and relatively efficient. They are mathematically well developed and allow for incorporation of priors such as shape</td>
<td>Sensitivity to image noise. As a Gaussian blur, intensity could be subject to numerical fluctuations, especially parameters are not properly selected</td>
</tr>
<tr>
<td>Learning methods</td>
<td>Utilize pattern recognition power. Two main types: supervised (classification) and unsupervised (clustering)</td>
<td>Computational complexity especially in supervised setting which requires time-consuming training. Parameter tuning and user-identified intensity is a flexibility that is a challenge</td>
</tr>
<tr>
<td>Stochastic models</td>
<td>Exploit statistical differences between tumor uptake and surrounding tissues. Most similar to deal with the noisy nature of PET</td>
<td>Effect of initialization and convergence to local optima solutions are unclear, especially, when compared to improved efficiency</td>
</tr>
</tbody>
</table>

Functional Imaging is rarely tumor specific
- Neither FDG nor FLT are tumor specific
- Nonspecific uptake has been seen with virtually all PET tracers
- Particularly in post-radiation therapy setting, the infiltration of FDG avid macrophages, inflammation, reactive lymph nodes,…
- Image processing techniques from raw signals to biological signals

<table>
<thead>
<tr>
<th>Segmentation method</th>
<th>Max diameter (mm)</th>
<th>Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>6.5</td>
<td>98</td>
</tr>
<tr>
<td>PET_Tmax</td>
<td>7.5</td>
<td>80</td>
</tr>
<tr>
<td>RG</td>
<td>6.5</td>
<td>65</td>
</tr>
<tr>
<td>Neblet et al.</td>
<td>7.5</td>
<td>135</td>
</tr>
<tr>
<td>Black et al.</td>
<td>6.5</td>
<td>117</td>
</tr>
<tr>
<td>SMB</td>
<td>6.5</td>
<td>65</td>
</tr>
<tr>
<td>FCM</td>
<td>4.8</td>
<td>32</td>
</tr>
<tr>
<td>FCM-S</td>
<td>5.5</td>
<td>45</td>
</tr>
<tr>
<td>FCM-SW</td>
<td>6.5</td>
<td>76</td>
</tr>
</tbody>
</table>
One should still realize that no form of biological imaging is capable of showing tumor deposits that are small relative to the resolution of the scanners (which is, for instance, at best 5 mm for PET). This means that tumor deposits on a microscopical level cannot be visualized and may be missed, and moreover that dose painting based upon biological images showing radioresistant areas (i.e. hypoxia) at a low resolution may be suboptimal. In addition, the complexity of the tumor biology makes the interpretation of molecular images far from trivial.
An automatic on-line CT-guided adaptive radiation therapy technique for prostate cancer – Court et al.

On-line modification of MLC leaf pairs for adaptive prostate radiotherapy
Court et al.

Couch-shift ART
Slice (a)
75.6 Gy
70.0 Gy
60.0 Gy
50.0 Gy

Slice (b)
75.6 Gy
70.0 Gy
60.0 Gy
50.0 Gy

Couch-shift ART

(a) Seminal vesicles
PTV
Prostate

(b) (c)
Adaptive Radiotherapy: Correction Techniques

Use of Deformed Intensity Distributions for On-Line Modification of Image-Guided IMRT to Account for Inter-Fractional Anatomic Changes

Radhe Mohan, Ph.D., Xiaodong Zhang, Ph.D., He Wang, Ph.D., Yixiu Kang, Ph.D., Xiaochun Wang, Ph.D., Helen Liu, Ph.D., K. Kian Ang, M.D., Debora Kuban, M.D., Lei Dong, Ph.D.
Example of deformed intensity maps

Practical Challenges

- Time for imaging
- Time in Planning
  - Auto-segmentation
  - Correction strategies
  - Efficient replanning
- Time for plan-verification (QA)
- Approval process
- R & V
- Adapting intra-fractional changes

How much time do you need?
Prostate Intra-Fractional Variations

Before Treatment

After Treatment (20 minutes)

Contours overlaid from before treatment CT images after bony registration

Melancon et al. IJROBP (in press)

Volume Change of the Rectum for 45 patients

-20
0
20
40
60
80

1
4
7
10
13
16
19
22
25
28
31
34
37
40
43

Patient #

Volume Change of Rectum in cc

Gaseous Build-up

Melancon et al. IJROBP (in press)

Real-time tracking of prostate positions

- Motion is unpredictable
- 15% patients had >5mm shifts

KUPELIAN et al. IJROBP vol.67 pp1088 -2007

Variations in prostate position during treatment measured by Calypso Markers

35 pts

Li et al. IJROBP 2008; 71(3): 801-812
Image Quality is the Limiting Factor For IGRT

My wish list

- Magic imaging techniques that can see “CTV”

My wish

- Imaging-on-rails in treatment room

I am still waiting