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Offline Adaptive RT

Conflict of Interest

• Funding from the NIH, NCI R01CA221971
• Funding from RaySearch Laboratories (including work in dose mapping and outcomes assessment)
• Research Agreement with Mirada Medical (including work in AI)
• Licensing Agreement with RaySearch Laboratories (deformable registration technology)

Acknowledgments

• Image Guided Cancer Therapy Research Program
• Morfeus Lab
  – Guillaume Cazoulat, PhD, Molly McCulloch, PhD, Bastien Rigaud, PhD
• Fuller Lab (PI: C. David Fuller, MD, PhD)
• Chung Lab (PI: Caroline Chung, MD)
• Koay Lab (PI: Eugene Koay, MD, PhD)
• Collaborators at Princess Margaret Hospital and University of Michigan
  – Michael Velec, PhD and Laura Dawson MD
  – James Balter, PhD, Marc Kessler, PhD, Randy Ten Haken, PhD
  – Avi Eisbruch, MD, Ted Lawrence, MD
• Geoff Hugo, PhD – Washington University St. Louis
Motivation

- Mandate for precision medicine
  - Image-guided, personalized, adaptive radiotherapy is the epitome of precision medicine
  - Increasing amount of imaging – for planning, delivery, and assessment
- Precision in design, delivery, and assessment of radiation may have an impact of trial design and outcomes assessment
- QUANTEC:
  - "To maximize the therapeutic ratio, models relating the true accumulated dose to clinical outcome are needed and robust methods must be developed to track the accumulation of dose within the various tissues of the body.
- Goal: Advance the design, delivery, and understanding of radiotherapy

Precision Delivery/Assessment

- Evaluation of biological influence on outcomes of treatment, need to ensure that all pts are tx precisely
- Integration of advanced imaging requires patient model and link to dose
- Accurate design and evaluation of clinical trials requires accurate dose assessment

Critical Impact of Radiotherapy Protocol Compliance and Quality of the Treatment of Advanced Head and Neck Cancer: Results from TROG 05.03
"Vision without action is a daydream. Action with without vision is a nightmare." — Japanese proverb

What is our Vision of Precision in Radiotherapy Design and Delivery?
Clinical Trial Design:
Importance of Dose Assessment and Outcomes Prediction

- 38 oropharyngeal cancer
- VMAT
- minimal clinically important benefit (MCID): mean change in NTCP of >5%

With Adaptive RT

- iPG was the only structure with an NTCP benefit (MCID >5%, ~40% of pts)
- PTV elimination: iPG and cSMG both benefited (approximately 40% of patients)

Can We Deliver What we Plan?
30 Patients – dose accumulation

21 patients (70%) had large dose deviations (>5%) to any tissue or GTV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD, % of Rx</th>
<th>Max, Min (Gy)</th>
<th>Max, Min (% of Rx)</th>
<th>Patients with ΔD &gt; 5% (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV (max to 0.5 cm³), n = 54</td>
<td>0.2 ± 1.0</td>
<td>-4.0, 2.3</td>
<td>(-15, 5)</td>
<td>10</td>
</tr>
<tr>
<td>Liver (mean), n = 30</td>
<td>0.2 ± 0.5</td>
<td>-6.0, 0.9</td>
<td>(-6, 2)</td>
<td>3</td>
</tr>
<tr>
<td>Large bowel (max to 0.5 cm³), n = 30</td>
<td>1.1 ± 1.5</td>
<td>-5.3, 1.5</td>
<td>(-15, 3)</td>
<td>33</td>
</tr>
<tr>
<td>Small bowel (max to 0.5 cm³), n = 15</td>
<td>-1.3 ± 2.2</td>
<td>-7.8, 1.1</td>
<td>(-26, 3)</td>
<td>20</td>
</tr>
<tr>
<td>Duodenum (max to 0.5 cm³), n = 30</td>
<td>1.5 ± 2.6</td>
<td>-12.6, 0.7</td>
<td>(-42, 3)</td>
<td>33</td>
</tr>
<tr>
<td>Esophagus (max to 0.5 cm³), n = 20</td>
<td>0.8 ± 0.8</td>
<td>-0.8, 2.4</td>
<td>(-3, 1)</td>
<td>7</td>
</tr>
<tr>
<td>Stomach (max to 0.5 cm³), n = 30</td>
<td>0.4 ± 1.5</td>
<td>-4.3, 1.6</td>
<td>(-14, 4)</td>
<td>17</td>
</tr>
<tr>
<td>Right kidney (mean), n = 30</td>
<td>-0.4 ± 0.7</td>
<td>-2.0, 0.6</td>
<td>(-5, 2)</td>
<td>10</td>
</tr>
<tr>
<td>Kidney (max to 0.5 cm³), n = 25</td>
<td>0.6 ± 1.0</td>
<td>-4.6, 0.6</td>
<td>(-11, 2)</td>
<td>8</td>
</tr>
<tr>
<td>Lung (NIETGZ, n = 30)</td>
<td>0.5 ± 2.5</td>
<td>-6.3, 14.7</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>
Can we more closely deliver the planned dose if we improved our technology at the Tx Unit?

Option 1: MR in the Room & Online
Next!

Option 2: Better Tools with CBCT

Methods:
1. DIR between exh CT and CBCT
2. Compare 3 alignments:
   - Clinical
   - Liver
   - Tumors
3. Reconstruct the delivered dose for each
Advanced IGRT

- Results, Accumulated – Predicted dose:
  - The magnitude of min GTV decreases with clinical IGRT (max: -14%) were reduced by up to 7% (Liver IGRT) and 6% (Tumor IGRT)
  - Dose deviations for normal tissues (within 2Gy of max constraint) with the clinical IGRT (range: -38, 10%), were reduced with Liver IGRT (range: -21, 8%) and Tumor IGRT (range: -21, 8%)

Better delivery of the intended dose!

Can we design a better treatment?

- Data:
  - 20 patients, 27-49.8 Gy in 6Fx
  - Tumor motion: 1-21 mm (median: 8 mm)
  - 4D CBCT Daily

- Methods:
  - Optimized new SBRT plans, dose-escalated up to 60 Gy, for an equivalent risk of liver complication and PTV dose-coverage:
    1. Exhale 4D CT and ITV based PTV (ITV + 5 mm)
    2. Mid position CT and Dose probability PTV
How can we determine if we are not ‘on track’ to deliver the intended dose?

How do we know if the deviation is acceptable?
Developing Predictive Model

Clinically defined deviation threshold: 15% of dose constraint

100 Patients Retrospective Accumulation of Dose

8 SGs
$\Delta \geq 4.5\ Gy$

Deviation at $F = 15$
To Identify Deviations

$\Delta \geq 3.5\ Gy$
1 False +
100% Sens., 98.7% Specif.

Independent Validation
52 Patients

Sensitivity: 100%
Specificity: 98%

Materials and methods: 47 patients treated for locally advanced cervical cancer. EBRT + with 2 individually planned 3D IG-adaptive BT $F_x$. $D_{2cm}^3$ and $D_{0.1cm}^3$ were estimated by DVH parameter addition vs dose accum.

Results: DIR-based DVH analysis was possible in 42/47 patients. DVH parameter addition resulted in mean dose deviations relative to DIR of $4.4 \pm 0.3\ Gy (1.5 \pm 1.8\%)$ and $1.9 \pm 1.6\ Gy (5.2 \pm 4.2\%)$ for $D_{2cm}^3$ and $D_{0.1cm}^3$, respectively. Dose deviations greater than 5% occurred in 2% and 38% of the patients for $D_{2cm}^3$ and $D_{0.1cm}^3$, respectively. Visual inspection showed that hotspots were located in the same region of the bladder during both BT $F_x$ for the majority of patients.

Conclusion: DVH parameter addition provides a good estimate for $D_{2cm}^3$, whereas $D_{0.1cm}^3$ is less robust.

What about complex deformation?
Problems with Traditional DIR

- Need high DIR accuracy
  - near the PTV for dose mapping
  - At structure boundaries for contour mapping

- ‘Traditional’ DIR algorithms rely on assumption of corresponding features between the images to be registered

- Atelectasis appearance in CT challenges this assumption.

- Goal: To develop a DIR algorithm that can handle missing/incomplete correspondence in the lung.

Atelectasis / large tissue change

- Atelectasis (partial collapse)
- Pleural effusion (fluid)
- Large volume changes in atelectasis (~150cc) during RT
- Associated with large tumor shifts (> 3mm in 83% of pts)
- Associated with large dose changes to OARs (5-10 Gy single fx change in cord max, MLD, MLD)

Dose recalculated on mid-treatment image

- Aligned to both bone and carina
- Compared to planned dose

Worst-case estimate

Dose changes can be significant

Highlights need for ART/DIR
**Lung DIR Algorithm**

- Multi-resolution B-spline framework (elastix)
- Mass-preserving metric within healthy lung
- Intensity-based similarity metric within atelectasis
- Co-registration of lobe label images
- Co-registration of vesselness measure images

Chris Guy (VCU) & Geoff Hugo (WashU)

**Lung DIR Algorithm**

- Landmark registration error / mm
- Unregistered
- Intensity (CT) only
- Intensity + Lobes
- Intensity + Vessels
- Intensity + Lobes + Vessels

Chris Guy (VCU) & Geoff Hugo (WashU)

**Anatomical variability in brachytherapy**

- Radiotherapy
- Delivery (2*15 Gy = 30 Gy)
- Planning
- Brachytherapy
- Delivery (25*1.8 Gy = 45 Gy)
- Planning
- With intraoperative applicator

- Monitoring the dose for the whole treatment

Bastien Rigaud, PhD
**Data: 20 patients**

### Radiation Therapy vs. Brachytherapy

- **Data set:** 20 patients
- **Radiation therapy**
  - CT planning
  - CT simulation
  - RT dose
- **Brachytherapy**
  - CT planning
  - CT simulation
  - BT dose

**Post-EBRT CT**

**With applicator**

**Without applicator**

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**Study workflow**

1. **Rigid registration alignment**
2. **Deformable registration**
   - Diffeomorphic Demons
   - ANACONDA (1)
   - ANACONDA (2)
   - MORFEUS
3. **Deformation vector field**
4. **Geometric evaluation**
5. **Qualitative evaluation**
   - Hausdorff distance
   - Distance to agreement
   - Dice similarity coefficient

**Translation and rotation**

**Deformable registration methods**

**Diffeomorphic Demons**
- **Intensity**
  - Metric: sum of squared difference
  - Gaussian regularization
  - Fast convergence
  - Theoretically invertible

**ANACONDA**
- **Combined information**
  - Non-linear optimization
  - Metric: correlation coefficient
  - Jacobian constraint
  - Mesh regularization (contour and grid)
  - Contours constraint

**MORFEUS**
- **Biomechanical model**
  - Surface mesh
  - Boundary conditions
  - Finite element model
  - Mechanical properties
  - Discontinuities between organs
Biomechanical model-based DIR

DiR methods comparison

Qualitative evaluation: BT dose deformation
“However beautiful the strategy, you should occasionally look at the results.” —Sir Winston Churchill

Advancing our understanding of outcomes

Does Improved Accuracy in Dose Matter for Outcomes?

- 81 patients, 142 liver metastases
- accGTV calculated using DIR and daily CBCTs
- accGTV dose is a better predictor of TTLP compared to minPTV dose for liver metastases SBRT
- Univariate HR for TTLP for increases of 5 Gy in accGTV versus minPTV was 0.67 versus 0.74

Hypothesis: The use of accumulated dose will change NTCP models
Results

- **Lyman NTCP**
- Mean NTCP based on simulations with accumulated dose
- Mean NTCP based on simulations with planned dose

For the duodenal toxicity model:
- Under 22 Gy, the planned dose under-predicts toxicity and above 22 Gy over-predicts toxicity
- Average deviation of 6%, max error of 18%

Little difference between planned and acc dose models for the stomach.

Liver Response to Radiotherapy: Understanding Radiation Effects

- Patients with oligometastases often have multiple courses of SBRT
  - Need: map previously delivered dose
- Advancements in functional imaging (e.g. DCE-MRI) can predict/describe function
  - Need: correlate the delivered dose
- Challenging due to the volumetric response of the tissue to radiation
  - Often variable across the tissue as a function of dose

Hypothesis

Results Summary – TREs for the six methods
Addition of Volumetric Response

Addition of Internal Structures
Summary

• This is a very exciting time for DIR, dose accumulation, and adaptive RT!
• We need to proceed, but proceed with caution, education, and safety
• Adaptive is not just about advanced technology, but also about improving our understanding of the impact of radiation on tumor and normal tissue
• Data shows that what we plan is NOT what we deliver and this has the potential to impact correlation with outcomes
  – Need to move toward including dose accumulation in clinical trials
• As we seek to understand the biological aspects of the treatment and design and evaluate novel clinical trials, we need to ensure that we are
  – Planning the optimal therapy
  – Precisely delivering and tracking the delivered dose
  – Linking the delivered dose to retreatments, functional imaging, and outcomes
• Need to continue to advance predictive modeling and correlation with outcomes
  – Enable improved treatment and link with re-treatment and imaging outcomes