The Current Trajectory of Personalized Adaptive RT

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Motivation

- Presidential mandate for precision medicine
  - Image-guided, personalized, adaptive radiotherapy is the epitome of precision medicine
- Radiation therapy initiative to ensure safety
  - Active monitoring of the treatment delivery and evaluation of outcomes is an important piece of this process
- 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

Personalized Adaptive RT Trajectory

Design → Delivery → Outcomes
ASTRO Plenary Session 2005

Adaptive Planning and Delivery to Account for Anatomical Changes Induced by Radiation Therapy of Head and Neck Cancer

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- Set the stage for the importance of adaptive radiotherapy
- Promoted the role of Medical Physics
- Demonstrated the role of adaptive planning to eliminate the PTV
- Demonstrated the need to account for soft tissue changes in dose accumulation
- So what have we done since then…

Purpose: To present pilot toxicity and survival outcomes for a prospective trial investigating adaptive radiotherapy (ART) for oropharyngeal squamous cell carcinoma.

Conclusion: This is the first prospective evaluation of morbidity and survival outcomes in patients with locally advanced head-and-neck cancer treated with automated adaptive replanning. ART can provide dosimetric benefit with only one or two mid-treatment replanning events. Our preliminary clinical outcomes document functional recovery and preservation of disease control at 1-year follow-up and beyond.

Conventional

Reference Planning CT
Mask Alignment

Slide Courtesy of Lei Dong
SUMMARY

1. Images Obtained during Tx
   - Daily CT (CT on-rails)
2. (Auto) Segmentation
   - Auto-segmentation via DIR
3. Deformable Image Registration
   - Modified (dual force accelerated) Thirion’s Demons Algorithm
4. Dose Re-calculation & Summation
   - Calculation on Tx Fx CT, no summation
5. Decision Making Tools
   - Replan prompted by changes identified in patient
6. Plan Re-Optimization (including delivered dose)
   - Naïve, empirical adaptive PTV (1 mm)
Replan: Timing and Frequency

1 Replan:
Mean parotid dose sparing was improved by:
- 2.8% (p = 0.003) in the contralateral parotid
- 3.9% (p = 0.002) in the ipsilateral parotid

2 Replans:
Mean parotid dose sparing was improved by:
- 3.8% (p = 0.026) for the contralateral parotid
- 9% (p = 0.001) for the ipsilateral parotid

Role of Personalized Adaptive RT

- Localized Oral Cavity and Pharynx Cancer: 83.3% 5 year survival
- 2015 report from Zeng et al of 208 patients who received IMRT, where xerostomia was recorded in 80.8%, 66.3%, 56%, 40.9% and 40.9% of patients within 1, 2, 3, 4 and 5 years after RT, respectively.

https://seer.cancer.gov/statfacts/

How to Reduce Toxicity?

ClinicalTrials.gov

De-intensification of Radiation and Chemotherapy for Low-Risk Human Papillomavirus-related Oropharyngeal Squamous Cell Carcinoma

Search for studies: Advanced Search | Help | Studies by Topic | Glossary

ClinicalTrials.gov Identifier: NCT01339007
First posted: January 20, 2012
Last updated: July 1, 2014
Last viewed: May 2016
Method of Change
would be likely to benefit. In our study, the iPG was the only structure with an NTCP benefit (MCID >5%, approximately 40% of patients) with the dose reduced P60 plans. However, when the PTV was eliminated, the iPG and cSMG both benefited (approximately 40% of patients).
Methods and Materials

- 100 H&N (base of tongue) patients Tx with CBCT/VMAT evaluated.
- Phantom used to evaluate CBCT dose calc accuracy
- 4 cases selected for auto-segmentation assessment
- Deviations in the normal tissues were evaluated including:
  - Mean dose: superior (SC) and inferior constrictors (IC)
  - Mean dose: L and R parotid glands (PG)
  - Mean dose: L and R submandibular glands (SMG)
  - Max dose: spinal canal
  - CTV D95

<table>
<thead>
<tr>
<th>Organ</th>
<th>Planning Constraint (Gy)</th>
<th>Dose Deviation Threshold (Gy)</th>
<th>Organs Included in Model* (N)</th>
<th>Organs Exceeding Deviation (n)</th>
<th>Deviation** at Completion of Tx (Gy)</th>
<th>Deviation** by Fx15 (Gy)</th>
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<tr>
<td>Inf. Constrictor Sup</td>
<td>20</td>
<td>3</td>
<td>12</td>
<td>1</td>
<td>5.62</td>
<td>5.86</td>
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<tr>
<td>Sup Constrictor Spinal Cord</td>
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<td>7.5</td>
<td>60</td>
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<td>High CTV Variable*</td>
<td>Variable*</td>
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<td>Variable*</td>
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<td>Oral Cavity</td>
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<td>4.5</td>
<td>56</td>
<td>1</td>
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<td>-4.84</td>
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<td>Left Parotid</td>
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<td>37</td>
<td>1</td>
<td>3.77</td>
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<tr>
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<td>4.5</td>
<td>179</td>
<td>7</td>
<td>8.22 (max)</td>
<td>3.5 (min)</td>
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*Started with 100 patients and only included organs in the evaluable region of the CBCT and without DIR failure
**Deviation = completed (accumulated) dose – planned dose
Changes in pharyngeal constrictor volumes during head and neck radiation therapy: Implications for dose delivery

Arie Kumaravelu, Cheng Li, Nima Kamali, Cagney Freeman, Stephen Brown, Justin J. Charly, Jia-Kun Kim, Farrah Subapalp
Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA

- 13 oropharyngeal cancer patients with daily cone beam computed tomography (CBCT) was retrospectively studied.
- Anterior-posterior PCM thickness was measured at the midline level of C3 vertebral body.
- Delivered dose to PCM was estimated by calculating dose on daily images and performing dose accumulation on corresponding planning CT images using a parameter-optimized B-spline-based deformable image registration algorithm.
- The mean and maximum delivered dose (D_{mean}, D_{max}) to PCM were determined and compared with the corresponding planned quantities.

Figure 1: Example case of cross-sections of physician-drawn pharyngeal constrictor in axial view:
(a-h) pharyngeal constrictor contours at C3 level on simulation computed tomography and cone beam computed tomography images of 5, 10, 15, 20, 25, 30, and 35 fractions,
i contours at simulation and at the last (#35) fraction overlaid on the simulation computed tomography with dose color wash, and
(j) the respective DVHs at simulation (dashed line) and at fraction 35 (solid line). For this case, D_{mean} increased from 62.4 to 63.0 Gy, whereas D_{max} remained unchanged.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>ΔV(%)</th>
<th>Δt(%)</th>
<th>ΔD_{mean}(Gy)</th>
<th>ΔD_{max}(Gy)</th>
<th>Replanned (Y/N)</th>
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<td>1</td>
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<tr>
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<td>76.7</td>
<td>84.6</td>
<td>2.2</td>
<td>1.4</td>
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<tr>
<td>5</td>
<td>18.5</td>
<td>75.1</td>
<td>2.4</td>
<td>1.2</td>
<td>24.2</td>
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<tr>
<td>6</td>
<td>48.6</td>
<td>03.9</td>
<td>0.3</td>
<td>0.2</td>
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<tr>
<td>7</td>
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<td>91.1</td>
<td>0.8</td>
<td>0.4</td>
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<tr>
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<td>0.5</td>
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<td>9</td>
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<td>15</td>
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<tr>
<td>11</td>
<td>109.7</td>
<td>111.1</td>
<td>5.1</td>
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<tr>
<td>12</td>
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<td>7.7</td>
<td>0.6</td>
<td>0.3</td>
<td>35.0</td>
</tr>
<tr>
<td>13</td>
<td>94.3</td>
<td>473.8</td>
<td>2.5</td>
<td>1.7</td>
<td>15</td>
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</table>
Figure 3: Correlations of (a) volume $\Delta V$, and (b) thickness increases $\Delta t$, to mean dose increases ($\Delta D_{\text{mean}}$). $R^2$ values from linear regression correlation are also shown.

PCM thickness at C3 predicted dose increase, however dose increase is minor to moderate.

Adapting to Changing Anatomy

and Functional Changes

Adaptive Radiotherapy for Lung Cancer

Jan-Jakub Serke, PhD, and Joel Beldoros, MD, PhD

Adaptation to changing anatomy and functional changes involving the adaptive dosing to the changing CT simulation and freehand CT (red area) and functional changes are evident in both arms. Due to the changes in the anatomy the structure has an altered planning CT scan. Adapted and a shift of functional changes to the partial volume correction was on the CT scan. The correlation of the dose planning and the dose delivered to the patient is shown in the images above and below shows the dose delivered to the PTV and the percent isolation of normal lung dose spared.
Lung Tumor Regression

Tumor Regression: Anatomy Follows
Tumor Regression: Anatomy Stays

1.5 mm reduction of DIR error translated to >1 Gy differences in Dmin in up to 50% of a patient population with the following characteristics:
1. Dose homogeneity index > 15
2. DIR-induced Dice differences > 0.08

These characteristics were specific criteria but not highly sensitive since there were cases that met the criteria without resulting in >1 Gy differences (in accumulated dose).
Adaptive 4D PET Results

- 32 patients were recruited, 27 completing all scans.
- 25 patients (93%) were boosted successfully above the clinical plan doses at week 0, 23 (85%) at week 2 and 20 (74%) at week 4.
- The median dose received by 95% of the planning target volume (D95) at week 0, 2 and 4 to PET-T were 74.4 Gy, 75.3 Gy and 74.1 Gy and to PET-N were 74.3 Gy, 71.0 Gy and 69.5 Gy.

Conclusions: Using 18F-FDG-4DPET/4DCT, it is feasible to dose escalate both primary and nodal disease in most patients. Choosing week 0 images to plan a course with an integrated boost to PET-avid disease allows for more patients to be successfully dose escalated with the highest boost dose.
Clinical Relevance:
- Mean position PTV margins are smaller in volume than the standard ITV approach
- Reduction in volume will also reduce the overlap with luminal GI structures

• Purpose: Quantify the dosimetric improvement in liver SBRT delivery with mean position planning and targeting.


Dose-Escalated Liver SBRT @ Mean Position

Data:
- 20 patients, planned on exhale 4D CT for 27-49.8 Gy in 6 fractions
  - Treated free-breathing tumor amplitude: 1-21 mm (median: 8 mm)
  - Daily 3D CBCT registration of the liver (retrospective 4D sorting)

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

Mean Respiration Model

Breathing position:
- Exhale
- Mean
- Inhale

Internal target volume (ITV) + 5 mm

Dose-probability

Mean Δ tumor-PTV volume: -38 ± 3%

Dose-probability PTV* = 2.5* + 1.28(σ - σ_penumbra)

L: residual tumor error after liver alignment on CBCT(>3-5 mm)
Σ: residual Mean-position CT(≈1/5 breathing amplitude)
σ: residual CT(≈1/3 breathing amplitude)

van Herk. IJROBP 2000;84(4): 1121-1135

Dose-Escalated Liver SBRT @ Mean Position
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

Swaminath, Brock, Dawson, et al. IJROBP 2015

What about Normal Tissue?

- Simulation of the impact of using accumulated dose in toxicity models
- Under 22 Gy, acc-dose NTCP model using the planned dose yields a more accurate prediction of duodenal toxicity than the standard model:
  - Standard, planned-dose NTCP models:
    - Avg error 6.3%, SD 6.5%
    - Max error 16%

Work by Molly McCulloch

Summary

- This is a very exciting time for precision radiotherapy!
- Advances in treatment planning allows for the sculpting of dose around normal tissue to reduce toxicity risk and improve the probability of local control.
- The combination of volumetric imaging and anatomical modeling enables assessment of the delivery and potential adaptation of the treatment plan, based on anatomical and functional changes.
- Calculation of the delivered dose has the potential to improve our understanding of the impact of radiation dose on normal tissue toxicity and tumor control.
- Completing the loop, we can use this information to further advance the safe, optimization of radiotherapy.
Acknowledgement
Michael B. Sharpe, PhD, FAAPM: Friend, Mentor, Colleague

Mike taught me so much... state of the art image-guided treatment planning, how to engage in clinically meaningful translational research, but even more, that if you are very lucky, you will have amazing friends in your life, who will teach you and challenge you,

A friend that will remind you to not take a single day for granted and will make your life better through their friendship, even when that friendship becomes cherished memories.