Stereotactic MR-Guided Adaptive Radiation Therapy: It’s the SMART thing to do!

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Disclosures

•Research Funding
  –Viewray Inc

Low field MRgRT implementation
Clinical MRgRT timeline

- 1/2014 - First patient treatment
- 9/2014 - First online adaptive treatment
- 1/2015 - First online adaptive SBRT
- 9/2015 - First online adaptive SBRT with automated MR image based gating
- 5/2018 - MR-linac comes online
- 7/2018 - First online adaptive SBRT on MR-linac

Over 10 clinical sites:
- Seoul National University Hospital, Seoul, South Korea
- Washington University, St. Louis, Missouri, USA*
- UCLA, Los Angeles, California, USA
- University of Wisconsin, Madison, Wisconsin, USA*
- University of Miami, Miami, Florida, USA
- Heidelberg*
- Miami Cancer Institute*
- NYP / Weill
- Sheikh Khalifa, Dubai
- VUMC, Amsterdam, Netherlands
- Gemelli, Rome, Italy
- National Cancer Center, Tokyo, Japan
- Henry Ford Medical Center, Detroit, Michigan, USA *

Washington University Clinical Dashboard 2014-2018

Disease Sites Treated Over 4.5 Years

Henke, Contreras et al. Clinical Oncology, in submission

MRI imaging is better than CBCT

- Onboard CT images used for routine treatment localization were collected
  - MVCT or kVCT
  - In-plane resolution: ~1-1.5mm
  - Slice thickness: 2.5 - 4.0 mm

- 3 radiation oncologists evaluated the low-field MRI & onboard CT images side-by-side

MRI vs CBCT Results

When examined by structure type, there were differences in which modality offered better visualization:

- **Bone:**
  - OB-CT (48%) or Equivalent (52%)
  - CBCT (48%) or Equivalent (52%)

- **Pulmonary Systems/ Airways:**
  - Equivalent (90%)

- **Target:**
  - MRI (40%), Equivalent (10%)

- **Soft Tissues:**
  - MRI (92%)

- **Vasculature:**
  - MRI (94%)

- **CNS:**
  - MRI (100%)

Noel, Parikh et al, Acta Oncologica, 2015
First clinical paper with adaptive MR guided radiation


FMEA analysis of QA

Noel et al, Med Phys 2014

- Found unique points of failure in ART, but some issues in standard IMRT not found. Created processes to review contours and perform virtual QA, no physical QA!

Online Adaptive SBRT Phase I Study

Radiother Oncol. 2017 Dec 22. pii:

Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen.

Henke L1, Kashani R1, Robinson C1, Curcuru A1, DeWees T1, Bradley J1, Green O1, Michalski J1, Mutic S1, Parikh P2, Olsen J1.
Online Adaptive SBRT Phase I Study

- 20 patients with unresectable primary or oligometastatic disease of the liver (n = 10) & non-liver (n=10) abdomen planned for SBRT
- Prescription: 50Gy/5fx with online, adaptive MR-IGRT approach
- Isotoxicity approach, with dose escalation (or de-escalation) based on hard OAR constraints

Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis

- 51yo woman, 1 year disease-free period
- Biopsy-proven, solitary 1.8cm adrenal ADC metastasis
- KPS 100%
- Preferred non-surgical option

Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis

- Day 1: All OAR constraints met, including small bowel & stomach
Day 2 - Application of day 1 plan violates small bowel & stomach OAR constraints.

- Absolute (Isodose) 55 Gy (110%) 50 Gy (100%) 40 Gy (80%) 30 Gy (60%)

Day 2:
• Adapt

- Adaptive plan reduces small bowel and stomach dose
- PTV coverage minimally sacrificed
- PTV coverage remains at goal 50Gy

Henke et al, R&O, 2017
**Phase I Trial Example Case**

**Solitary NSCLC Adrenal Metastasis**

- Patient with zero reported acute or late toxicity
- Radiographic CR at 3 and 6 months

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**Phase I Results—Timing**

- Median on table time: 79 minutes
- Median segmentation time: 9 min
- Median re-planning time: 10 min
  - Median QA time: 5 min

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**Phase I Results—Plan Adaptation**

- 83% (79/95) fx adapted—all patients had ≥1
- Plans adapted for 64% of liver & 98% of non-liver abdomen fx
- Initial plans would have violated OAR constraints in 70/95 fx
- 100% of OAR violations resolved with adaptive planning

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**Phase I Results—OAR Sparing**

- No Grade 3 toxicity at median 11.8 mo f/u
- Expected 20-30% using aggressive dose regimen
- No change in patient-reported EORTC-qol 30 QOL scores ($P = 0.29$) at 0, 6, and 12wks.

**Phase I Results—Clinical Outcomes**

**Locally Advanced Pancreatic Cancer is Bad**

- “If cancer is the emperor of all maladies, then pancreatic adenocarcinoma is the ruthless dictator of all cancers” — Deborah Schrag

**Locally Advanced Pancreatic Cancer is Bad**

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Reviewing MRgRT data to date

- Reviewed five institutions’ data for pancreas MRgRT (VUMC, Wisconsin, UCLA, Washington University, University of Miami)
- Locally advanced, borderline resectable and medically inoperable pancreatic cancer patients treated up to 8/2016
- Practices varied between dose, fractionation, technique between institutions
- Looked at dose as a predictor of survival

Maximum BED > 90 Gy

![Graph showing dose distribution with 23 patients adapted, 40 – 50 Gy / 5 fx, 50 – 67.5 Gy / 15 fx and 19 patients adapted, 33 – 40 Gy / 5 fx, 50 – 60 Gy / 30 fx]

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>maxBED &gt; 90 Gy</th>
<th>maxBED ≤ 90 Gy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>68</td>
<td>62</td>
<td>0.068</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>12</td>
<td>0.879</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Tumor Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>17</td>
<td>12</td>
<td>0.453</td>
</tr>
<tr>
<td>Tail</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Histology:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSPC</td>
<td>4</td>
<td>6</td>
<td>0.806</td>
</tr>
<tr>
<td>LPC</td>
<td>17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Medically Inoperable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median CA 125-9 at</td>
<td>762.4</td>
<td>548.0</td>
<td>0.796</td>
</tr>
<tr>
<td>Diagnosis (LUMA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive</td>
<td>4</td>
<td>4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

### Treatment Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>maxBED&lt;90</th>
<th>maxBED&lt;90</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-RT Surgery</td>
<td>3</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>Ind. Chemotherapy</td>
<td>9</td>
<td>10</td>
<td>0.570</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>POYDIA</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>4</td>
<td>9</td>
<td>0.096</td>
</tr>
<tr>
<td>Hypofractionated</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Late toxicity risk</td>
<td>16</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

### RT Technique

<table>
<thead>
<tr>
<th>Technique</th>
<th>Dose and Fractionation</th>
<th>Number of Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>50.4 Gy In 28 Fractions</td>
<td>6</td>
</tr>
<tr>
<td>Hypofractionated</td>
<td>40 - 55 Gy In 25 Fractions</td>
<td>7</td>
</tr>
<tr>
<td>SBRT (maxBED₉₀ &lt; 90)</td>
<td>50 - 67.5 Gy In 10-15 Fractions</td>
<td>8</td>
</tr>
<tr>
<td>SBRT (maxBED₉₀ &gt; 90)</td>
<td>30 - 40 Gy In 5 Fractions</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>40 - 52 Gy In 5 Fractions</td>
<td>15</td>
</tr>
</tbody>
</table>

### Percentage of Fractions Adapted

![Percentage of Fractions Adapted](image)
Overall Survival – median follow-up

22 months

Continued high local control

No change in distant metastases
Gr 3+ GI Toxicity

| maxBED > 90 | 0% |
| maxBED < 90 | 15.8% |


Results in Context

<table>
<thead>
<tr>
<th>Study</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAP07 – 3DCRT</td>
<td>15.2</td>
</tr>
<tr>
<td>MDACC – mostly 3DCRT</td>
<td>15*</td>
</tr>
<tr>
<td>MDACC – SBRT</td>
<td>17.8*</td>
</tr>
<tr>
<td>MSKCC – IMRT</td>
<td>14.8</td>
</tr>
<tr>
<td>Harvard – SBRT</td>
<td>23</td>
</tr>
<tr>
<td>JHU – SBRT</td>
<td>20</td>
</tr>
<tr>
<td>MSkRT – hypofrac/high dose SBRT</td>
<td>Not reached - 27.8</td>
</tr>
<tr>
<td>MDACC</td>
<td>15*</td>
</tr>
<tr>
<td>MSKCC</td>
<td>17.8*</td>
</tr>
<tr>
<td>Harvard</td>
<td>23</td>
</tr>
<tr>
<td>JHU</td>
<td>20</td>
</tr>
<tr>
<td>MRgRT – standard IMRT &amp; SBRT</td>
<td>18.4</td>
</tr>
<tr>
<td>MRgRT</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Open Questions

- Hypofractionation vs SBRT?
  - Current technology and MD time commitment at the machine makes hypofractionation difficult.
  - No clear data on whether patients receiving 67.5 Gy / 15 fractions are doing better, worse or same at 50 Gy / 5 fractions.
  - We don’t have much surgery data after 50 Gy / 5 fractions, will need to acquire.
Open Questions

- Do the intestinal contents move during the plan adaptation process?
  - Anecdotal imaging (i.e., imaging redone during treatment due to patient/machine issues) suggest some motion, but less than motion from prior fraction to today
  - This needs to be investigated formally to create action levels on plan adaptation, and engineering goals for industry

Patient example (intrafx motion)

Does the adaptation work with intrafx motion?
Open Questions

• What is the correct organ at risk constraint for GI structures at risk?
  – We do not have cumulative dose technology
  – First prospective multi-institutional study will have more conservative dose constraints since primary aim is safety
    • 33 Gy to no more than 1 cc of stomach, duodenum, small and large bowel

Physician contouring on demand – not good at it, slows down pt flow

Changing targets

• 2 MD can mean 2 gold standard segmentations
New Radiographer requirements

- Radiographers already had to learn MR based localization and safety
- Now learning MR based segmentation for normal tissue structures
- We created two ‘Advanced Practice Radiation Therapists’ who lead on-table segmentation and plan generation.
- Have increased to 8 adapted patients / day!

Next Step for Pancreas MRgRT

Inoperable Pancreas Cancer after >= 3 months of chemotherapy

50 Gy / 5 fractions MR guided, adapted and tracked

Primary endpoint: Toxicity at 90 days
Secondary endpoints: Disease related outcomes
Goal: 100 patients

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Siteman Cancer Center

www.siteman.wustl.edu