Online Adaptive Radiation Therapy
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- Involvement in ViewRay, Inc sponsored clinical trial (Pancreas ART)

What is ART?
- Changing treatment plan based on observed changes
  - Weight loss
  - Tumor response
  - OAR variations
  - Functional changes
- Strategies based on timeframe of adaptation

Figure credit: Keall et al., Hematology, Oncology and Palliative Medicine
Evidence for Online ART in Prospective Trials

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Study Design</th>
<th>ART Results</th>
<th>ART Clinical Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Daily kV imaging + fiducials, aperture adapted if shift &gt; 3 mm</td>
<td>Allowed 5 mm margins in 31/39 patients</td>
<td>Online ART based on prostate motion allowed for safe margin reduction</td>
</tr>
<tr>
<td>Central Lung</td>
<td>MR-linac, 5 SBRT patients</td>
<td>10/25 plans adapted, 70% due to OAR violations</td>
<td>No grade 3 or greater toxicities, excellent local control</td>
</tr>
<tr>
<td>Oligometastases</td>
<td>MR-linac, 20 SBRT patients</td>
<td>Coverage increased in 20/97 Fx, OAR reduced 61/97 Fx</td>
<td>Reduces dose to OARs, offers potential for dose escalation</td>
</tr>
</tbody>
</table>

Deutschmann, Red Journal, 2012; Henke et al., Advances in RadOnc 2019; Henke et al., Radiother Oncol, 2018

Low-Field MRI On-line ART Workflow

- Image: Evaluate skin external, electron density
- Re-contour: Deform OARs, 2-3 cm of PTV, rigid copy PTV
- Predict dose
- Treat
- Motion verification
- Re-optimize: Evaluate, Plan QA

Figure credit: Parag Parikh, MD

The Move to On-line Adaptive

- Major workflow development
  - Rapid contouring requirements (3 cm around PTV)
  - On-the-fly electron density & plan review
  - Defining physician directives + criteria to adapt (OARs and/or Targets)
  - Safety and plan checks
  - Associated documentation

- Major technical benchmarking
  - MR primary planning (deformable image registration (DIR) of CT/MR, electron density mapping) for a robust patient model
  - Online optimization/planning strategies
  - Validation of vendor-provided secondary dose calculation tool
MDA MRL Clinical Workflow - Online

- All patients
  - Patient arrival and Daily MR assessment (RTT)
  - Patient setup (RTT)
  - MR image acquisition (RTT)
  - Online adaptation (Physician)
  - Verification of adaptation (Physician)
  - Secondary MU calculation for adapted plan (Physics)
  - Verification scan acquisition (RTT) – to verify that patient hasn’t moved during plan adaptation
  - Adapted plan approval (Physician)
  - Verification of transfer of adapted plan parameters to Integrity console (Manually prior to delivery of each field using hard copy print out from secondary MU calc system) – AFS disabled (RTT)
  - Beam delivery (RTT)

Deformable Image Registration (DIR) for Online ART

INITIAL
- CT to MRI DIR to enable MRI primary planning

DAILY
- Deform electron density
- Contour propagation

OFFLINE
- Dose accumulation
Daily Electron Density Validation for Accurate Dose Calculation

Benchmarking Adaptive with PETE

- MR-compatible Pelvic End-to-End (PETE) phantom simulated changes in rectum volumes (Empty, medium, full)
- Imaged using clinical protocol and performed ART workflow
- Generated various ART plans, evaluated secondary calculation, conducted PSQA on ART plan (film & point dose)

J. Cunningham et al., JACMP, 2018
Online QA: Benchmarking 2ndary Monte Carlo Dose Calculation with PETE

Histogram of Gamma Values:

99.23% passed

<table>
<thead>
<tr>
<th>Patients</th>
<th>TPS (cGy)</th>
<th>Measurement (cGy)</th>
<th>DDIFF</th>
<th>2%/2mm Pass Rate</th>
<th>2%/2mm Pass Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Plan</td>
<td>1009.4</td>
<td>1011.8</td>
<td>0.2%</td>
<td>96.8%</td>
<td></td>
</tr>
<tr>
<td>Adapted Plan - Small Rectum</td>
<td>1015.6</td>
<td>1023.8</td>
<td>0.8%</td>
<td>94.3%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Adapted Plan - Medium Rectum</td>
<td>981.0</td>
<td>999.5</td>
<td>1.9%</td>
<td>98.4%</td>
<td>99.2%</td>
</tr>
<tr>
<td>Adapted Plan - Medium Rectum, Modified Bladder</td>
<td>1026.0</td>
<td>1035.0</td>
<td>0.9%</td>
<td>95.4%</td>
<td>98.6%</td>
</tr>
<tr>
<td><strong>MEAN</strong></td>
<td></td>
<td></td>
<td><strong>0.9%</strong></td>
<td><strong>96.2%</strong></td>
<td><strong>99.1%</strong></td>
</tr>
<tr>
<td><strong>STDEV</strong></td>
<td></td>
<td></td>
<td><strong>0.6%</strong></td>
<td><strong>1.6%</strong></td>
<td><strong>0.3%</strong></td>
</tr>
</tbody>
</table>

Data Credit: Josh Kim, PhD, HFCI

Example Online ART Physics Check
Post-Treatment ART PSQA Benchmarking

- SBRT: A26MR micro-ion chamber and gafchromic EBT3 film measured in a 15cm Solid Water stack
- Conventional: A26MR micro-ion chamber and ArcCheck measurements
- Both: Evaluated AQA results, conducted PSQA on ART plan (film & point dose)

Results: SBRT ART PSQA, Initial & ART Fx (15 Patients)

MR-Guided Adaptive Cases (10/2018-present)

- 54 Patients (50 SBRT, 4 Conventional)
- 290 total treatments
- 81% of treatments adapted; others did not meet clinical ART criteria
Clinical Case: MR-guided Pancreas ART

Retrospective Data

Prospective Trial

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

Actionable limits:
- Constraints violated for OARs (or)
- GTV/CTV coverage <85% by 47.5 Gy (or)
- Favorable shift GTV/OARs where ART increases coverage by 10% or more

Slide adapted from Parag Parikh, MD, HFCI

Benefit of ART: Resolve Small Bowel Dose Violation

ART Scenario: More Favorable Geometry for Isotoxic Approach
Target Dose Improvement: Solid = ART, Dashed = Base Plan

On-Line Adaptive Treatment Times

PANCREAS ADAPTIVE TIMING
113 SBRT FRACTIONS (24 PATIENTS)

PANCREAS TOTAL TIME = 71 ± 14 MIN
ART TIME = 25 ± 6 MIN

ART CRITERIA:
• Normal tissue out of tolerance
• Increase CTV/PTV >10% to OAR tolerance

MRgRT for Response Prediction

• H&N cancer patient, decreased ADC observed in GTV
• Longitudinal DWI is feasible with the 0.35T ViewRay MRI
Functional diffusion map: Darkened areas suggest treatment-resistant subregions

Yang et al., IM, 2016

0.35T Co60 Response: Rectal Cancer & Sarcoma

Shaverdian et al., BJIR, 2017

0.35T MR-linac Resolution of Fluid, Changes in T1/R2* Maps

Patient 3, Serial STAGE Imaging: Bifrontal Oligodendroglioma

- Improvement in FLAIR abnormalities, mass effect, resolved 5 mm node

Figure Credit: Siamak Nejad-Davarani, HFCI
Conclusions & Future Directions

- Establishing MRgART introduces new technical and workflow challenges
- Offers strong potential to improve targeting/accuracy for patient populations expected to benefit
- Despite added complexity, online ART offers significant potential for toxicity reduction or dose escalation when anatomy is favorable
- Next steps: to begin well-curated clinical trials to fully capture benefits of online MRI/MR-guided ART→NRG currently preparing for multi-institutional trial work.

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