MR Guidance and Online Adaptation of Liver and Pancreas Patients

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Disclosure

• Employer: Miami Cancer Institute, Staff Medical Physicist
• Affiliate: Florida International University, Assistant Professor
• Co-founder: MR Guidance, LLC
• Research Agreement: ViewRay Inc.
Learning objectives

Understand the clinical rationale for MR-guided adaptive radiation therapy for pancreatic and liver cancers

Learn importance of planning technique and robustness in online adaptation of abdominal SBRT

Gain familiarity of current and future biological and AI initiatives in pancreas and liver ART
ART due to organ at risk changes
ART due to organ at risk changes
Abdominal SMART BED 100 Gy is safe and safe
Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer


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Online Adaptation: Overall Survival

2-yr OS 49% vs 30%

**FIGURE 1** Overall survival from start of radiation therapy stratified by biologically effective dose (BED$_{10}$). Standard error bars displayed at each 6-mo timepoint.
Prospective phase II Study of Stereotactic MR-guided on-table Adaptive Radiation Therapy (SMART) for Patients with Borderline or Inoperable Locally Advanced Pancreatic Cancer

Principal Investigators:

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Chief of Service, MR-IGRT  
Washington University  
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MRgRT offers superior soft tissue for simulation and each fraction.
MRgRT-BH may enable reduction target volume over CT-IGRT-FB and potentially reduce GI OARs dose in adaptive RT

Shallowing breathing
PTV=ITV+3mm
~140 cc

Breath hold
PTV=CTV+3mm
~120 cc

Role of real-time MR intrafraction motion management when delivering ablative dose near GI OARs

Ablative dose near critical GI likely benefit from real-time intrafraction management

MR sagittal plane real-time tracking in pancreas SBRT

MR sagittal plane real-time tracking in liver SBRT
Gadoxetic acid for target delineation in liver SMART

- Gadobenate dimeglumine (Gd-BOPTA; Eovist™/Primovist™) and gadoxetate disodium (Gd-EOB-DTPA; MultiHance™) are liver-specific gadolinium-based MR contrast agents.
- Mechanism: Gadoxetic acid distributes into hepatocytes and the biliary tract system in a late, hepatobiliary phase. This allows for a differentiation of hepatocytes from neoplastic cells, which do not show a gadoxetic acid uptake.
- Visualization for metastases as well as some primary HCC and CC
- Hepatobiliary phase targeted for MRgRT localization and real-time tracking—Wojcieszynski et al, 2016

Five phases:
1. T1W precontrast
2. late arterial (30-35 sec)
3. portal venous (~75 sec)
4. "transitional" (~3 min)
5. **Hepatobiliary (~20 min to 1 hour with Gadoxetate disodium and 1-3 hours for Gadobenate dimeglumine)**
Daily Gadoxetic contrast for liver SMART to enable accurate liver tumor delineation/localization/tracking

Wojcieszynski et al, 2016
On-table MR-guided ART clinical workflow

- **Positioning**
  - THERAPIST: Image and registration of scan of the day to initial to simulation scan

- **Deformation**
  - PHYSICIAN: Edit deformed contours

- **Contouring**
  - PHYSICIST: Evaluate deformed electron density; edit deformed contours; apply contour Boolean operations and margin expansion

- **Plan re-optimization**
  - PHYSICIST: Plan generation; compare adaptive plan to initial plan recalculated on anatomy of the day

- **Plan quality evaluation**
  - PHYSICIAN: Plan quality review

- **Treatment**
  - THERAPIST: Treatment delivery

Hill P and Mittauer K, “MR-guidance in radiation therapy,” AAPM Summer School, 2018
Intrafraction gastroduodenal peristalsis can result in overdose of GI OAR
Potential sources of error in MR-guided online ART

1. Scan FOV
2. Electron density
3. Segmentation
4. IMRT plan fidelity (non-measured based IMRT QA)
5. Out of date anatomy during ART replanning (i.e., intrafraction GI peristalsis)
6. Cumulative dose from summed ART fractions

- Overcome with checklists, workflow checks/hard stops, secondary observer
How to adapt robustly with large GI interfractional anatomical changes?

Table 1  Organ at risk constraints for 5-fraction pancreas stereotactic magnetic resonance image guided adaptive radiation therapy

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Dose constraint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach, duodenum, small bowel</td>
<td>V35 &lt;0.5 mL</td>
</tr>
<tr>
<td></td>
<td>V40 &lt;0.03 mL</td>
</tr>
<tr>
<td>Large bowel</td>
<td>V38 &lt;0.5 mL</td>
</tr>
<tr>
<td></td>
<td>V43 &lt;0.03 mL</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Mean &lt;10 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean &lt;15 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>V25 &lt;0.03 mL</td>
</tr>
</tbody>
</table>

Rx Dose = 50.00 Gy

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Rx (%)</th>
</tr>
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<tbody>
<tr>
<td>60.00</td>
<td>120.0</td>
</tr>
<tr>
<td>50.00</td>
<td>100.0</td>
</tr>
<tr>
<td>45.00</td>
<td>90.0</td>
</tr>
<tr>
<td>35.00</td>
<td>70.0</td>
</tr>
<tr>
<td>33.00</td>
<td>66.0</td>
</tr>
<tr>
<td>25.00</td>
<td>50.0</td>
</tr>
<tr>
<td>15.00</td>
<td>30.0</td>
</tr>
</tbody>
</table>
How to adapt robustly?

• Adequate # of beam angles. Enables degrees of freedom for dynamic changes to fluence based on anatomical geometry of the day
• Optimization structures that auto-populate, particularly in regions of target and OAR overlap
• Optimization objectives based on these overlapped regions with differential gradients based on spatial position
• Conformality is king. Rings can eliminate dose spillage
• A hotspot driver away from overlap region of the OAR. Eliminates hotspot being in unsafe location on anatomy of the day
• Simple is better. Elimination of potential conflicting objectives for future adaptive anatomical geometries.
• Standardization is key. Allows for ease and feasibility for cross-coverage of users and ability to apply manual updates to optimization objectives without a priori plan knowledge
• A class solution is ideal. A set of optimization objectives and geometric beam arrangements that are sufficiently robust to produce a clinically acceptable dose distribution regardless of the patient anatomy, target volume or organs at risk

Chow et al 2021, O. Bohoudi et al 2017, J.E. van Timmeren 2020, Clark et al 2017
Defining the gradient with OAR intersection of rings and ANN-based optimization objectives — the AUMC approach

Plan quality: baseline plan versus adaptive plan — AUMC approach

<table>
<thead>
<tr>
<th></th>
<th>Baseline plans</th>
<th>Plans Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SMART$_{3CM}$-baseline</td>
<td>FULLOAR-baseline</td>
</tr>
<tr>
<td></td>
<td>mean (range)</td>
<td>mean (range)</td>
</tr>
<tr>
<td>PTV V$_{95%}$ (Gy)</td>
<td>89.4 (74.0–95.1)</td>
<td>89.4 (74.0–95.1)</td>
</tr>
<tr>
<td>PTV D$_{\text{mean}}$ (Gy)</td>
<td>43.7 (42.4–44.8)</td>
<td>43.1 (41.7–43.9)</td>
</tr>
<tr>
<td>PTV D$_{1%}$ (Gy)</td>
<td>50.6 (49.4–53.2)</td>
<td>50.0 (48.6–51.3)</td>
</tr>
<tr>
<td>HI</td>
<td>1.28 (1.24–1.34)</td>
<td>1.26 (1.22–1.31)</td>
</tr>
<tr>
<td>CI</td>
<td>1.18 (0.91–1.34)</td>
<td>1.17 (0.91–1.32)</td>
</tr>
<tr>
<td>Beam-on time *</td>
<td>9.16 (7.85–11.3)</td>
<td>9.20 (8.48–10.5)</td>
</tr>
<tr>
<td>Segments</td>
<td>52 (36–79)</td>
<td>50 (31–80)</td>
</tr>
<tr>
<td>Optimizations **</td>
<td>4 (2–6)</td>
<td>18 (12–22)</td>
</tr>
</tbody>
</table>

ART robustness and stability—the MCI approach
Automation of spatial gradient based on GI OAR of the day—the MCI approach
Future direction in MR-guided ART including biological and AI opportunities
Simulation-free workflow in MR-guided adaptive RT is feasible

- Our prior study showed ART can be collapsed down to same day consult-to-treat for palliative RT for a simulation-free workflow.
- Eliminating initial plan creation may improve start time, simulation and planning resources, and clinical efficacy for pancreas SBRT.
- In abdominal sites, the anatomy at the time of simulation is likely out of date by the first fraction.
- Can we do this for complex adaptive sites e.g., 50Gy/5 fraction SBRT pancreas?
Planning-free workflow in MR-guided adaptive RT is feasible

• “SMART ART” = a class solution of a pre-plan template for pancreas SBRT built on sim anatomy of 38 pancreas SMART patients and evaluated on 66 pancreas SMART patients.

• We demonstrated adapting a generic pre-plan to the anatomy-of-the-day is equivalent to the plan quality of adapting a patient-specific initial plan to the anatomy-of-the-day in pancreas SBRT.
First experience of autonomous, un-supervised treatment planning integrated in adaptive MR-guided radiotherapy and delivered to a patient with prostate cancer

Luisa A. Künzel, Marcel Nachbar, Markus Hagmüller, Simon Boeke, Daniel Zips, Daniela Thorwarth

Published: April 01, 2021 • DOI: https://doi.org/10.1016/j.radonc.2021.03.032

Highlights

• First-in-human: Integration and delivery of autonomous planning as basis for online adaptive MRgRT.

• Autonomous plan generation, including OAR segmentation, target generation and optimization.

• First checkpoint for human interaction at the time of clinical online adaptation at the MR-Linac.

The overall time from simulation to MR-Linac treatment was reduced to less than six hours, where no human interaction was required. Consequently, such an approach could enable the use of online adaptive MRgRT in more patients.

Fig. 1. Flowchart of the autonomous planning workflow and daily adaptation for online adaptive MRgRT (AI: artificial intelligence, CT: computed tomography, DL: deep learning, MRgRT: magnetic resonance-guided radiotherapy).
• Current barriers in ART
  • Manual steps
  • Human error
  • Checklist and real-time observer required
Presentation #: 1095
Abstract Title: Establishing the Gastroduodenal Maximum Tolerated Dose for Ablative 5-Fraction Stereotactic MR-guided Online Adaptive Radiation Therapy (SMART) in a Novel Swine Model
Presenter: Kathryn Mittauer
Author Block: Kathryn Mittauer, Michael Bassetti, Jennifer Meudt, Melissa Graham, Michael Wood, Jessica Miller, Michael Lawless, Jennifer Frank, Russ Ward, Albert Van Der Kogel, Dhanansayan Shanmuganayagam, John Bayouth
Scientific Session Title: Phys 7 - Dose Response Analysis and Novel Treatment Technology
Session Date/Time: TBD
MRgRT adaptive dose escalation liver trial to assess maximum tolerated dose bowel $D_{0.5\text{cc}}$ and liver $D_{700\text{cc}}$. 

Figure 3

Trial schematic for our organs at risk-based dose escalation liver SI

Patients will be dose-escalated on the basis of increasing doses to the liver or bowel, followed by a subsequent phase 1b expansion cohort. SBRT=stereotactic body radiotherapy.
SMART ultra-hypofractionation: single fraction SMART in pancreas/liver

- Delivery time
- Potential for > GI peristalsis
- BH reproducibility/stability
  - Supplemental O2
  - In-room monitor--visual real-time feedback on BH position
- Patient tolerability/stamina for 90 min
  - screening for compliance (i.e., performance status, claustrophobia, etc.)
  - Establish patient education and expectations
BIGART (biological image-guided adaptive radiotherapy): role of MRI for predictor of tumor response and normal tissue toxicities

MINI REVIEW ARTICLE

Quantitative Magnetic Resonance Imaging for Biological Image-Guided Adaptive Radiotherapy

Petra J. van Houdt, Yingli Yang and Uulke A. van der Heide

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2Department of Radiation Oncology, University of California, Los Angeles, CA, United States
Summary: Needs/future direction of MR-guided ART

1. Planning approach is critical for robust online adaptive RT in which interfraction OAR to target motion is anticipated.
2. Users should be cautious of on-table adaptation time due to GI peristalsis (i.e., MR anatomy “decaying away”)
3. Simulation and initial planning may no longer be necessary with the integration of AI solutions into adaptive RT workflow.
4. Prospective multi-institutional studies with daily on-treatment qMRI is needed for assessment of biomarkers for future integration.
THANK YOU