Evolving Role of Physics in Radiation Therapy
--- Technology and Beyond

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  – T McNutt, E Tryggestad, K Wang, T Roland, …

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• *JHU Physics & Astronomy*
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Disclosure

- Small animal platform
  - NCI R01 CA158100
  - Gulmay Medical Inc. (Xstrahl) Research Agreement
    Tech transfer and Consultancy
- Integrated x-ray CBCT and Ultrasound imaging
  - NCI R01 CA 161613
  - Elekta Research Agreement and Royalty
- Philips Research Agreement
- QA Box --- MD Biotech, MD TEDCO, JPLC Associates
Technology Challenge: TG 142 QA

- 1.4 Mixels, 16-bit, CCD camera to provide 0.2 mm x 0.2 mm per pixel resolution for a 20 cm x 20 cm image
- CCD operates at integration mode
- Optical / Laser imaging *without* buildup on phosphor
- Radiation imaging *with* buildup on phosphor
An Unified QA System for TG 142

- A mirror system that allows capturing images at the isocenter plane with a stationary camera

Semi-transparent phosphorus screen
Neutron/x-ray shielding
CCD camera
Optical path
1st prototype

Suspended setup for gantry rotation measurements
Radiation Isocenter QA

- Results of isocentricity
  - Gantry Starshot diameter
  - Collimator Starshot diameter

- The use of *Center Of Mass (COM)* calculations of a small field (2x2 cm) for collimator, table and gantry rotation

- For collimator:
  
  \[
  \text{COM diameter} = 0.3 \text{ mm} \\
  \text{Film star-shot,} \\
  \text{diameter} = 0.7 \text{ mm}
  \]

Method can be applied to gantry rotation instead of gantry star-shot
Raven QA: Product-Grade Prototype
### Technology Challenges: IGRT of Soft Tissue Targets

#### Inter-fraction methods: Cone beam CT, MV CT

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Radiation Therapy</td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td></td>
<td>Image Quality</td>
</tr>
</tbody>
</table>

#### Inter-fraction methods: Intra-modal ultrasound imaging

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue information</td>
<td>Snap Shot (at present)</td>
</tr>
<tr>
<td>Non-ionizing</td>
<td>Expertise/operator dependence</td>
</tr>
</tbody>
</table>

#### Intra-fraction methods: Implanted Markers

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-time monitoring</td>
<td>Invasive</td>
</tr>
<tr>
<td>Non-ionizing option</td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td></td>
<td>Soft tissue surrogate (truth?)</td>
</tr>
</tbody>
</table>

- Emergence of MRI-Radiation Machines
Phase 1 Prototype MRI-GRT

Room height 3.5m

1m

Confidential To be used only for the purpose supplied
MRI-GRT project: Current Status

- MRI Magnet full on at 1.5T and able to image
- Linac able to radiate
- MLC able to move leaves
- Gantry able to rotate

At the same time!
Cine MRI on MRI-GRT concept platform

- 2 frames per second
- Kidneys, liver and spleen can be followed in real time

Courtesy UMC Utrecht
Integrated 3D ultrasound/CBCT imaging for soft tissue IGRT

**Hypothesis:**

- US-CBCT offers an non-ionizing, non-invasive inter- and intra-fraction solution for soft tissue targets
- Prostate, liver, pancreas
<table>
<thead>
<tr>
<th>Challenges of US imaging</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproducibility / operator dependence</td>
<td>Robotic placement of a 3D probe</td>
</tr>
<tr>
<td>Deformation of anatomy</td>
<td>Keep US probe in place during irradiation while avoiding beams → Intra-fraction monitoring</td>
</tr>
<tr>
<td>Soft tissue registration</td>
<td>By definition, auto-fusion of CBCT and real-time US</td>
</tr>
<tr>
<td>Require simulation/planning of patient in treatment position with the ultrasound/CBCT system in place</td>
<td></td>
</tr>
</tbody>
</table>
Passive robotic arm and gel phantom

- A passive robotic arm with 1D linear (vernier scale) actuator
- Deformable gel phantoms with embedded 12 PMMA beads (1.2, 2.8, 3.2 mm in diameter)
- CT scans of repeat cycles compress/release to determine reproducibility
- Intra-, inter-fraction reproducibility all within 1 mm
Ex-vivo Bovine Liver in gel phantom

- Gel phantom was overly simplistic with uniform deformation
- A more realistic ex-vivo liver phantom was devised
- Comparison of deformation was made between ultrasound and model probe.
Reproducibility of Deformation

- Significant compression force differences between gel and liver phantom
- Suitability of phantom material is of concern

Contact forces lower with model probe
The robotic arm needs to be stiffened

Ex vivo bovine liver embedded in gelatin

Imaging Probe
(Force = 1.3 ± 0.13 N)

Model Probe
(Force = 0.3 ± 0.01 N)
Prostate (Force = 14 N)
Prostate Images

Ultrasound

CT with real probe

CT with model probe
Prostate (Force = 14 N; 10 N ~ 1 kg):
Marker Position Reproducibility in Interquartile Range

Real Probe: 3D mean error = 0.6 mm

Model Probe: 3D mean error = 0.7 mm

No Probe: 3D mean error = 0.4 mm
Prostate:
Probe-Induced Marker Displacement (from no probe)

3D mean error = 0.2mm
Liver at Breath-hold (Force = 40 N)
Liver CT and Ultrasound Images
Liver (at Breath-hold):
Probe-Induced Marker Displacement

3D mean error = 4.1 mm
Model of Elekta-Resonant 4D prostate system: Novel transperineal (TPUS) scan
Analytic database for personalized medicine and data sharing in radiation oncology

Radiation Oncology and Molecular Radiation Sciences
Johns Hopkins University
Re-engineering the Cooperative Research Model

- < 3% of patients treated are enrolled in cooperative clinical trials
- Required data submission for QA and approval – “big problem”
- Average duration to complete a clinical trial
  - > 5 years
  - Outpaced by advances
- No feedback from community practice
- Data limited for re-use
  - Data/Knowledge lost

Present (RTOG)
JHU: Re-engineering the Cooperative Research Model

- Keep data local and available in an active database
- Send queries to data, extracting only answers
  - e.g. Validate the PTV margin prescribed for lung SBRT
- Facilitate data-reuse, decision support and education
- Promote data sharing for CER
- *Tools for data capture to populate OncoSpace*
OncoSpace: Radiation Oncology Model for Data Sharing and Decision Support

14M Infrastructure

Institute 1
JHU

Analytic Database
Shape and Change Tools
Decision Support
Data-mining

I4M : Integration of Imaging, Information and Intervention in Medicine
1. Integration of clinical workflow with data collection to populate OncoSpace.
   - *Enable Mosaiq/Aria and TPS to capture data*

2. Optimize database architecture for secured distributed web-access

3. Tools for query, analysis, navigation and decision support

4. Data mining, decision support and bio-statistic research
Database organization

Tumor and Disease

Isolated PHI

History

Toxicity

Lab values

 Radiation dosimetry

Geometry and transformations

Tumor – OAR and relationships

Patient

Medication-Chemotherapy
MOSAIQ RO information system
Mobile devices for specific tasks

Plan Approval
Patient summary
Clinical assessment
Clinical notes
Patient Quality of Life

Monthly Utilization

0 400 800 1200 1600 2000
• How to ask questions of the data?
  - Given this DVH, what is the risk of toxicity?
Safety and Quality
Oncospace: Query & Analysis

- How to ask questions of the data?
  - Given this DVH, what is the risk of toxicity?
JHU & UCD
Physics to engage Biology in Radiation Therapy

- Questions and Challenges:
  - The validity of EUD, NTCP, ..............
  - Validation and optimization of biological image guided or molecular targeted radiation therapy
  - Others questions: biological target volume???

- Present small animal radiation research methods bear little resemblance to human treatment

- A pressing need to down-size human treatment to bridge small animal laboratory research
Small Animal Radiation Research Platform

- Hopkins-Xstrahl partnership
- Integrated 3D-Slicer-GPU based treatment planning system
- Computer controlled
  - 360° gantry rotation
  - Non-coplanar delivery
SARRP CBCT: “Pancake” geometry
Small Animal Treatment Console
SARRP Slicer- 3D RTP: GPU Dose – CBCT Engine

Prescribed dose: 100 cGy

Set Iso
Assign Wt

3 x 3 collimator

Set Gantry,
Couch angle
Depth dose (SET2, double)

- Dose to aluminum in aluminum
- Dose to water in aluminum
Comparison of SC to Monte Carlo

Monte Carlo (Tsiamas, Harvard)
SC (Cho, JHU)
Comparison of SC with MC
Correcting for density scaling
On-board BLI/BLT for Beam’s Eye View Irradiation with the SARRP (R01 CA158100)
BLT reconstructed with only one wavelength (630nm). Accurate in vertical position, but 1-2mm error along axial direction. Multi-spectral recon would improve the accuracy.
Combining Stereotactic Radiation and Anti-PD1 Therapy in an Orthotopic Mouse Glioma Model (Zeng et al)
## Experimental Design

<table>
<thead>
<tr>
<th>Day</th>
<th>No Tx</th>
<th>RT only</th>
<th>PD-1 only</th>
<th>RT+PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>Tumor Implantation</td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>Bioluminescent Imaging</td>
<td></td>
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<tr>
<td>10</td>
<td></td>
<td>Radiation</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; antibody dose</td>
<td>Radiation; 1&lt;sup&gt;st&lt;/sup&gt; antibody dose</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12</td>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; antibody dose</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; antibody dose</td>
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<td>3&lt;sup&gt;rd&lt;/sup&gt; antibody dose</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; antibody dose</td>
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</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td>Bioluminescent Imaging</td>
<td></td>
</tr>
</tbody>
</table>

Radiation = 10 Gy in 3 mm beam
Antibody = anti-PD-1 antibody, 200 µg/mouse
Flank Re-challenge

Naïve Mice

"Cured" Mice

Tumor Volume (mm³)

Days Post-Re-challenge

Cured (0/8 tumors growing)
- Naïve 1
- Naïve 2
- Naïve 3
- Naïve 4
- Naïve 5
- Naïve 6
- Naïve 7
- Naïve 8
What do we do for the next 5 years?

• Medicine (and radiation oncology) is undergoing tremendous changes driven by technologies and information
• Treatment strategies will employ multiple therapeutic agents with radiation
• Personalized medicine will be based on genetics, treatment response, functional/anatomic ....
• Physics need to expand beyond technologies:
  – Technology, Informatics, Biology, ....
  – We must innovate
4D MRI (JHU/Siemens)

- 4D CT is a 2 min snapshot, not often re-evaluated
- Long duration (15 – 30 min) MRI to represent treatment
4D MRI – Tracked Motion

a) sagittal ROI

b) coronal ROI
4D MRI – Characterization of Motion

- med.-lat. (from coronal)
- ant.-post. (from sagittal)
- sup.-inf. (avg. from cor. & sag.)
- PMU resp. trace

2\textsuperscript{nd} breathing mode
4D MRI – Characterization of Motion

- % volume portion of full ITV “missed” by snippet ITV
- % volume ratio of snippet ITV to full ITV

--- * --- 1.5 cm diam. GTV
--- o --- 3.0 cm diam. GTV

--- D95<0.95*D_{Rx} ---
--- D95<0.95*D_{Rx} & D_{min}<0.90*D_{Rx} ---

Time snippet for mock ITV (sec)
Motion Management: A case for Breath-hold

- Breath hold imaging is the gold standard
- *Breath-hold and gating are not mutually exclusive*
- Active Breathing Control for reproducible breath-hold
  - Integrate the ABC process to maximize compliance
  - Short, normal or deep inspiration BH (ABC/gating)
  - Gate the accelerator with the ABC device
OncoSpace: Adapting the SkyServer Approach

SDSS is a collaborative effort to map 25% of the sky
SkyServer publishes data from the SDSS
>> 100’s of new discoveries in astrophysics
Increased scale and scope for research

Shared resources
– Methodology
– Software
– Expertise
– Experience
New opportunities
– Analysis
– Visualization
– User experience

Skyserver.sdss.org

Alex Szalay PhD - JHU
Jim Gray PhD - Microsoft