Initial Experience On a Real-Time Biologically-Guided Radiotherapy System

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Outline

- PET imaging
- PET based BGRT
- Stanford IDE study
- RefleXion system overview
- RefleXion X1 commissioning and QA

Positron emission tomography (PET)

- PET is a functional imaging technique that uses radiotracers to visualize changes in metabolic processes, and activities including blood flow, regional chemical composition, and absorption.
- A radiotracer is injected into the body as a tracer. The $e^-$ annihilation process emitted gamma rays and the signals are detected by detector arrays to form a 3D PET image.
- Tracers: 18F-FDG $\rightarrow$ cancer and GTV delineation, NaF-18 $\rightarrow$ bone formation, oxygen-15 $\rightarrow$ measure blood flow.

Beyer et al, 2020 Cancer imaging
**Biological Imaging in Radiation Therapy**

- CT and MRI improved structure visualization with enhanced spatial resolution.
- PET imaging visualize biological and molecular level in tumor.
- Wide spectrum of positron-emitting tracer to cover more disease sites with high sensitivity.

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**Why PET-based BGRT?**

- Oligometastatic disease -- 3 to 5 or fewer metastases.
- Clinical trial of 3 sited and 5 sited NSCLC shows the improved overall survival (6-24 months). (Gomez 2019 JCO, Iyengar JAMA 2018)
- Biologically tracking the oligometastases: Redefining the role for radiotherapy in metastatic cancer.
- PET imaging reveals tumor characteristics of tumors and biological response to treatment: perfect tools BGRT.

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**PET-based BGRT**

- Biology tracking zone (BTZ):
  - Encompass ITV + Setup Margin
- Biological Margin (BgM):
  - Tracking margin ~5mm (PET latency ~400ms)
  - PET to planning CT alignment margin
BGRT Planning Studies

- Lung BGRT studies by City of Hope: (Liang et al, ASTRO 2019)
- 6 lung SBRT patients.
- BGRT vs ITV-based SBRT, PTV volume reduced 21.8% in average.
- OAR sparing is better for the lungs, spinal cord, esophagus, and heart.
- Emory’s study to investigate stability of FDG F18 as a “fiducial” for SBRT (Tian et al, ASTRO 2019)
- 14 lung SBRT patients, 10 Gy x 5 fractions.
- 3 PET/CTs acquired before the 1, 2, and 5th fractions.
- mean SUVmax change from PET1-2 = -8.2%, from PET1-3 = -7.0%.
- [SUVmax/liver SUVmean] was stable over time; PET1-2 = -0.1%, PET1-3 = +1.8%.
- Reflection set SUVmax/SUVmean in BTZ threshold is 2.7 for simulation, 2.0 for treatment tracking.

BGRT Workflow

![BGRT Workflow Overview Diagram]

PET-based BGRT

- Full time PET – 300ms (half rotation) in 60 RPM
- Limited-time-sample (LTS) PET image to track tumor: 100ms per image.
- Phantom measurement validation performed.

![PET-based BGRT Image Diagram]
Stanford IDE Study

- **Primary Objectives:**
  - To identify the Recommended RefleXion FDG Dose (RRFD) that enables the use of biology-guided radiotherapy (BgRT) on the RefleXion system. (Cohort I: RRFD)
  - To determine whether BgRT dose distributions generated from Limited Time Sample (LTS) Positron Emission Tomography (PET) images obtained at the time of treatment delivery are consistent with the approved BgRT plan. (Cohort II: Emulated Delivery)

- **Design:**
  - Cohort I: RRFD: 6 to 12 subjects (3 to 6 bone lesions, 3 to 6 lung lesions)
  - Cohort II: Emulated Delivery: 3 to 12 subjects (4 or more bone lesions, 4 or more lung lesions)

- **Primary End Point:**
  - Cohort I: Recommended RefleXion FDG Dose (RRFD). The FDG dose that results in Activity Concentration necessary for BgRT functioning: 5 kBq/ml or higher.
  - Cohort II: The percent of radiotherapy fractions where the emulated BgRT dose distribution in silico is shown to be consistent with the approved BgRT treatment plan.

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**RefleXion project timeline**

- RefleXion X1 FDA clearance for IGRT – Mar 2020.
- Construction start – May 2020
- Physics Training – July 2020
- Machine delivery – Aug 3, 2020
- Installation – Aug. 2020
- Acceptance testing – Sep 2020
- Commissioning Start – Oct 2020
- Software upgrades – Dec 2020, Feb 2021, Apr 2021
- First patient imaged using RefleXion PET on the IDE study – Apr 2, 2021
- First patient treated using RefleXion – IMRT – May 17, 2021

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**PET-based BgRT**

- biological mechanisms have not been consistently elucidated, early results have shown to be consistent with the approved BgRT treatment plan.
- Although these techniques have traditionally been explored in the setting of clinical trials, they are limited to aggregate changes rather than changes in tumor bulk, tumor heterogeneity, and tumor pace, and thus they are fundamentally limiting. Rather, adequate spatiotemporal resolution of the biological richness of the tumor requires the ability to track heterogeneous dose changes in real-time during an ongoing course of treatment based upon dynamic changes in the PET signal, in essence extending the concept of "modulated radiotherapy" to biology-modulated radiotherapy (Biology-Modulated RT).

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FUTURE POSSIBILITIES WITH BgRT

- Today, most applications of radiotherapy serve a single goal: to kill tumors by providing a uniform dose to some regions of the tumor based on biological knowledge of the tumor. However, as biology-modulated radiotherapy (Biology-Modulated RT) is beginning to emerge, the need for a more personalized approach to radiotherapy is becoming more apparent. One can envision an application of modifying dose at each fraction of a treatment course.

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The role of the Imaging-guided radiotherapy (IGRT) system is changing from a paradigm of off-line (and determine whether to move to next beam station) to an online approach (beginning at the time of treatment delivery and continuing even during the course of treatment). The potential for BgRT to be used in combination with immunotherapy is significant, as the ability to adaptively change the delivery of radiotherapy and immunotherapy can lead to improved outcomes for patients with metastatic cancer. As BgRT aims to enable multisite planning and treatment in a single treatment environment, it is expected that its adoption will increase as more institutions recognize the benefits of this innovative approach.
RefleXion X1 is a 6MV-FFF linac mounted on the 85cm O-ring gantry rotating at 60 rpm

- Axial step and shoot delivery: couch advances in 2.1mm increments
- The modulation is achieved via 50 firing positions with 64 binary MLCs (6.25mm at 85cm SAD) with either 1cm or 2cm jaws
- Maximum field sizes: 1x40cm; 2x40cm; Maximum IEC Y target size = 50cm
- 3 delivery modes: IMRT (1 pass SUP to INF), SBRT (4 passes), BGRT (4 passes)
- Dose calculation: Collapsed Cone Convolution reported to tissue with a dose calculation grid: 2.1mm
Source to Y-Jaw Alignment (V.B.1.a)

- Check that the source is centered in the collimated field by the y-jaws < 0.5 mm
- Setup A17 ion chamber to the beam center to measure a narrow-slit beam (1 mm y-jaw opening) that is moved in 15 steps along the y-direction (14 mm to +14 mm)
- Plot the Output-Y jaw sweep curve: The peak offset is 0.64 mm at the iso. Project back to the source location, the actual source misalignment is 0.049 mm

Source to X-alignment (V.B.1.b)

- Use the MLC tongue and groove (T&G) effect to check x-centering of the source: Out of focus < 2%
- Crossline water tank beam scan of fields: 40x2 open, all even-numbered MLC leaves opened, and all odd-numbered MLC leaves opened.
- Add odd and even profile -> T&G profile:
  \[ \text{Out of focus} = 100\% \times (1 - (a + b)/2). \]
- Out of focus = 0.66%
Y-jaw divergence and twist (V.B.1.c, V.B.1.d)

- To assure that the central transverse axis of the treatment beam intersects the rotational axis perpendicularly: Divergence at the isocenter = 0.5 mm
- To assure that the y-jaw be parallel to the plane of rotation: The jaw twist = 0.5°
- Position a film 21 cm below the isocenter (Z=21). Open right half of MLC leaves. Deliver the beam @ gantry 0 deg and 180 deg. Analyzed the film using RT.
- The jaw divergence is 0.3 mm < 0.5 mm. The jaw twist is 0.03° < 0.5°.

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Treatment Field Centering (V.B.1.e)

- To check if all clinical treatment fields share a common center: agree within 0.5 mm
- Setup a film perpendicular to the beam axis at an 85 cm source-to-film distance
- Gantry 90 deg. Deliver different rectangular fields to the film and check the center variation = 0.03 mm
- The y-jaw divergence/beam centering test can be used in this instance.

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MLC Alignment Test (V.B.1.f)

- To test: the lateral alignment of the MLC relative to the center of rotation < 1.5 mm, and the MLC aligned parallel to the rotational plane < 0.5°.
- A film is positioned at isocenter and two central MLC leaves (31 and 32) are opened in addition to two off-center leaves (26 and 27). The film is exposed with the gantry at 0°. The gantry is moved to 180° and only the two off-center leaves (26 and 27) are opened.
- The MLC offset is 0.5 mm < 1.5 mm. The MLC twist is 0.15° < 0.5°.
Synchronicity Test (V.B.1)

- Designed to test the accurate transmission of beam through the MLC to the isocenter within tolerance of angular deviation and offset (0.5 mm, 0.5 degrees at isocenter)

Starshot with gantry rotation

- Sandwich a film in between two 50x50x5cm³ solid water blocks, deliver 1.25x2cm beam at the following angles: 0, 72, 144, 216, 288 degrees.
- The minimum tangent circle radius is 0.67mm < 1mm.

Equipment

- IBA Blue Phantom Helix 3D Water Scanning System
- Field detector: Edge Diode detector, Exradin A14 ion chamber, W2 1x1 scintillator
- Reference detector: High sensitivity reference diode and Exradin A17 ion chamber
TPS Beam Input Measurements

- 16 Air scans with Edge diode detector
- Tongue and groove leaf crossline X profile scans: 8 single leaf scans/8 double leaf
- Open field profile X & Y scans: 40x2 and 40x1 cm open fields
- 2 water PDD scans with Edge diode detector

TPS Beam Input Measurements

- 2 water PDD scans with Edge diode detector
- 40x2 and 10x2 cm open fields

Measurement Vs. TPS: PDD

- PDD: TG-148 suggested the measured and TPS modeled PDDs for each jaw width agrees within 1%. For the 40x2 cm² field and 40x1 cm² field, the differences are 0.2% and -0.3%.
Measurement Vs. TPS: Transverse Profile

- TG-148 suggested transverse (crossline) profile difference in the field core (80% of the nominal field) is within 1% for each jaw width.

<table>
<thead>
<tr>
<th>Depth (cm)</th>
<th>1.5</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Mean profile difference (%) in the field core:

Depth (cm) | 1.5 | 5 | 10 | 15 | 20 |
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>40x2cm</td>
<td>0.75</td>
<td>0.67</td>
<td>0.47</td>
<td>0.47</td>
<td>0.37</td>
</tr>
<tr>
<td>40x1cm</td>
<td>0.93</td>
<td>0.96</td>
<td>0.72</td>
<td>0.66</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Measurement Vs. TPS: Longitudinal Profile

- RefleXion suggested slice width (FWHM) between the measure and TPS modeled longitudinal profiles for each jaw width <0.5mm.

<table>
<thead>
<tr>
<th>Y-jaw (mm)</th>
<th>Field size X (mm)</th>
<th>Depth (mm)</th>
<th>TPS FWHM (mm)</th>
<th>Measured FWHM (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20m</td>
<td>40x1.0</td>
<td>15.0</td>
<td>15.0</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.0</td>
<td>21.1</td>
<td>21.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150.0</td>
<td>23.8</td>
<td>23.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200.0</td>
<td>25.0</td>
<td>24.6</td>
</tr>
<tr>
<td>10m</td>
<td>40x1.0</td>
<td>15.0</td>
<td>10.5</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100.0</td>
<td>10.1</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150.0</td>
<td>11.9</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200.0</td>
<td>12.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>

TPS Commissioning: dosimetric tests
Reproducibility of dose output and symmetry with gantry angle

- Tomodose diode array was mounted to the gantry head perpendicular to the beam axis. Set field size to 40 cm x 2 cm and take measurement at the gantry positions of 0°, 90°, 180° and 270°. The dose and symmetry vs. gantry angle variation <2%.

<table>
<thead>
<tr>
<th>Deviation in average</th>
<th>Dose %</th>
<th>Symmetry %</th>
<th>Symmetry V %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gantry 0°</td>
<td>1.01</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Gantry 90°</td>
<td>1.02</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Gantry 180°</td>
<td>1.00</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Gantry 270°</td>
<td>1.01</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Multi-Leaf-Test</td>
<td>1.01</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Relative Output Factor Measurement

- Detectors: Edge Diode, Exradin W2 1x1 scintillator, Film, MC simulation.
- Smallest field measured 0.625 cm x 1 cm (single leaf field).

Absolute Beam Calibration

- AAPM TG-51: IAEA TRS398, MV Beam calibration. (PDD10/TPR20,10)
  \[ D_{\text{ref}} = M_{\text{ref}} N_{\text{ref}} k_{\text{ref}} \]
- IAEA TRS443: small machine-specific reference (SMR) field calibration
  \[ D_{\text{msr}} = M_{\text{msr}} N_{\text{msr}} k_{\text{msr}} \]
  - furnished the quality factor required for the differences between the conventional reference field of quality (Q0) (e.g. 6MV) and the SMR field (e.g. some (Qmax) ~6MV.
Absolute Beam Calibration

- Varian A14 ion chamber:
  - Collector Volume: 0.015 cm³
  - Collector Diameter: 0.1 mm
  - Collector Diameter: 0.1 mm
- MSR field: 10 x 3 cm²
- Reference Clinical Field A: 10 x 2 cm²
- Calibrate machine output to 100 cGy/MU for Clinical Field at Nominal dmax = 1.5 cm.
- Considering PDD = 0.575, and OF = 0.952
- Seal at 10 cm Depth of MSR field expected value 0.664 cGy/MU.

Laser Vs. kVCT Vs. Radiation Center

- Setup UMA phantom to laser: Perform kVCT scan and 3D-3D match. The offset laser to kVCT is: X = 0.8 mm, Y = 0.8 mm, Z = -0.3 mm.
- Re-Setup UMA phantom to laser. Move the couch sup 1 m. Take 0 and 90 deg MV image pair. The offset laser to radiation center is: X = 0.9 mm, Y = -0.2 mm, Z = -0.2 mm.

MV image at Gantry 0 degree.

MV image at Gantry 90 degree.

kVCT Commissioning

- kVCT scans of Catphan 504 in different dose and couch speed: Comparable to simulation CT.

Geometric Distortion = 0.12 mm
Slice thickness = 1.38 (vendor’s tolerance: 1.25 mm - 0.5 mm)
Low contrast visibility: 0.734.
KVCT Tube Voltage, Current and Imaging Dose

- RTI MAS-2 and Piranha are used to verify the mA and voltage
- The CTDI phantom was set up with a Standard Imaging A101 pencil chamber with a protocol of 120kVp, 150mA and 1.25mm slice thickness.
- The voltage and current are within 5% of the setting of 120 kV and 150 mA.
- CTDI(00century) = 3cGy.
- CTDI periphery = 3.6cGy.
- The CTDIw = 1.4cGy (body) and 3cGy (head).

Monthly QA

- kVCT using normal and fast couch speed – Catphan504
- Output calibration / Beam Quality: TG51 in solid water or 1D water tank
- Tomodose measurement for profile constancy checks
- Mechanical checks: laser, imaging and MV center, couch

Daily QA

- Tomodose measurement of 20cm x 2cm conformal Arc field:
Summary

- Reviewed PET imaging and PET based BGRT
- Introduced Stanford IDE study
- Overviewed RefleXion X1 system
- Presented results of RefleXion X1’s commissioning and QA

Acknowledgment

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  - John White
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