The Need for Quantitative Imaging in Radiation Oncology Treatment Guidance and Assessment

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Disclosure

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PA CURE

Objectives

- A summary of a myriad of imaging markers
- Discussions on the various challenges.
- Examples of quantitative imaging in clinical trials
- IROC As Quantitative Imaging Resource
Quantitative Imaging (QI)

- **Definition**
  - Extraction of quantifiable radiological biomarkers

- **Applications**
  - Diagnosis, staging
  - Treatment response assessment
  - Improve prognostication of response to RT
  - "Dose painting"
  - Adaptive treatments based on anatomic or functional responses

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**Table 1. Clinical Indicators for Which Imaging can be Performed in a Clinical Trial Setting**

<table>
<thead>
<tr>
<th>Role</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic and staging</td>
<td>To determine whether a lesion is positive or negative for malignancy</td>
<td>FDG-PET in lymphomas; nodal staging using FDG-PET in head and neck cancer (RCHOP+BE)</td>
</tr>
<tr>
<td>Prognostic biomarker</td>
<td>To determine the expected outcomes under standard therapy for the patient’s disease stage</td>
<td>Lesion size on anatomic imaging such as CT or MRI; high vs low Ki67 on FDG-PET in head and neck cancers (RCHOP+BE)</td>
</tr>
<tr>
<td>Predictive biomarker</td>
<td>To differentiate between patients expected to benefit clinically on one treatment relative to another from those not expected to experience such a benefit</td>
<td>FDG-PET in breast cancer; PET-CT in pancreatic cancer</td>
</tr>
<tr>
<td>Pharmacokinetic marker</td>
<td>To measure the effects of the drug on the body</td>
<td>PET-CT and DCE/DEXA MRI in anti-angiogenesis targeted therapy</td>
</tr>
<tr>
<td>Pharmacodynamic marker</td>
<td>To determine the expected ultimate outcome on a particular therapy regimen when changes in a tumor characteristic following a few cycles of treatment</td>
<td>FDG-PET response in gastric cancer after neoadjuvant chemotherapy (ACXRT)</td>
</tr>
<tr>
<td>Early response indicator</td>
<td>To determine whether a treatment responded to the subsequent Phase II investigations</td>
<td>FDG-PET in colon cancer</td>
</tr>
<tr>
<td>Outcome/clinical end point</td>
<td>A perc to posttreatment change measurement used to determine whether a patient is a candidate for a definitive clinical end point</td>
<td>Progression-free survival; SCC, squamous cell carcinoma; SUA, standardized uptake value</td>
</tr>
</tbody>
</table>

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**Quantitative Imaging Modalities**

**Anatomic-based imaging**

- **Tomography (CT)**
  - T1- and T2-weighted (MRI)

**Functional-based imaging**

- **Positron emission tomography (PET)**
  - Single photon emission computed tomography (SPECT)
  - Perfusion and Diffusion weighted imaging (DSC, DCE, DWI)

- **Magnetic resonance spectroscopy imaging (MRSI)**
Imaging Time Sequence

CT

- 3D CT: Anatomical
- 4D-CTs: Visualize respiratory motion; Ventilation guided avoidance
- Dual-energy CT (DECT): Accurate photon and proton dose calculation
- CT (DCE-CT): Target delineation; Assess response to therapies; Predict outcomes after RT
- CT-based radiomics: Diagnostic accuracy, prognostic capability, and response prediction

Challenges

CT Radiomics:
- Reproducibility of using test-retest analyses
- Robustness of image features
PET Tracers

FDA approved:

[18F]-fluorodeoxyglucose ([18F]-FDG)
Na[18F], 18F-fluciclovine
[11C]-Choline
[68Ga]-DOTATATE

FDG PET

Target delineation: HN, lung, lymphoma, pancreatic, anal, rectal
Predictive of RT response
Response assessment
Adaptive RT
Need for standardization to reduce variability

FDG-PET for Response Assessment
Early Response Predicts Long Term Outcome

NCCN Recommendations on Use of 18F-FDG PET/CT for Target Definition and Treatment Response Evaluation in Radiotherapy

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Target definition</th>
<th>Response evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Recommended</td>
<td>Optional</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Recommended</td>
<td>Optional</td>
</tr>
<tr>
<td>Head and neck</td>
<td>—</td>
<td>Optional</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>Optional</td>
<td>Recommended</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>Optional</td>
<td>Recommended</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>Recommended</td>
<td>—</td>
</tr>
<tr>
<td>Small cell lung</td>
<td>Recommended</td>
<td>—</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Recommended</td>
<td>—</td>
</tr>
</tbody>
</table>

Recommendations are as of 2015. No significant evidence to support use of 18F-FDG PET/CT at this point in non-small cell lung cancer, which does not mean that use of 18F-FDG PET/CT may not be beneficial but merely that evidence at this point is still insufficient.

RTOG 1106/ACRIN 6687
RANDOMIZED PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE RADIOTHERAPY USING DURING-TREATMENT FDG-PET/CT AND MODERN TECHNOLOGY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

| No Failure | Randomized FDG-PET/CT scan within 36 or 72 hours prior to start of treatment, but not on same day as RT/GYRT/PT/CT scans

Additional information based on using RT/GYRT/PT/CT scans and information with CT scan with results accessible for a 15-day window prior to the day 29-30 dose fraction.

15-Day window prior to day 29-30 dose fraction of 8 weeks indicated as in the RT/20Gy.
Question set 3:

Which of the following is the primary objective for RTOG 1106-6697: To determine when an individualized adaptive radiation treatment (RT) plan is applied by the use of an FDG-PET/CT scan acquired during the course of fractionated RT in patients with inoperable or unresectable stage III NSCLC

a) whether tumor dose can be escalated to improve the LRPF rate at 2 years;

b) whether an individualized dose escalation improves overall survival (OS);

c) whether an individualized dose escalation improves progression-free survival (PFS);

d) whether the rate of severe (grade 3+ CTCAE, v. 4) radiation-induced lung toxicity (RILT) differs

Answer: a)

Literature:

Reference: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1106

PET with Other Tracers

FLT: Early response, differentiate progression

Hypoxia PET: [18F]-fluoromisonidazole (FMISO)

[18F]-fluoroazomycin arabinoside (FAZA)

[18F]-flortanidazole (HX4)

Cu-ATSM

Adaptive; Dose painting;

Standardization
Variability in Imaging and Sample Size

Effects of Injection-to-Acquisition Time Variability on Required Sample Size

MR

T1- and T2-weighted
Perfusion, DWI
Diffusion tensor imaging (DTI)
Spectroscopy

Tumor delineation
Prediction of RT response
Planning adaptation
Assessment of treatment response
Perfusion MR

Dynamic contrast enhanced (DCE) MRI
1) Ktrans; 2) Kep; 3) Vp and Ve
Dynamic susceptibility contrast (DSC) MRI
Cerebral blood volume (CBV); cerebral blood flow (CBF);
Mean transit time (MTT)

Differentiate tumor progression
Predict for survival outcomes e.g. ACRIN 6677/RTOG 0625; ECOG-ACRIN (NCT03115333)
DCE-MRI Ktrans values for targeting radio-resistance

DWI MR

Early response in Clinical Trials:
Esophageal cancer (NCT03151642); HNC (NCT02497573, NCT00581906); Prostate cancer (NCT02319239); Rectal cancer (NCT02233374); Pediatric sarcoma (NCT02419816), and Cervical cancer (NCT01992861)
3 T allows for higher b value
QA and standardization of ADC for segmentation and radiomics

MRS/MRSI

Diagnosis: Tumor grade
Response assessment: Differentiate tumor progression and radiation necrosis.
Target delineation and dose escalation
Example: Prostate: tumor id for brachy therapy guidance
Multi-parametric MR for Tumor Definition

EPSI for Tumor Delineation

MR for Outcome Prediction

<table>
<thead>
<tr>
<th>Type of measurement</th>
<th>Functional imaging method</th>
<th>Known as</th>
<th>What is measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion</td>
<td>Dynamic contrast enhanced</td>
<td>DCE, permeability</td>
<td>Gadolinium-enhanced shrinking of T1</td>
</tr>
<tr>
<td></td>
<td>Dynamic susceptibility contrast</td>
<td>DSC</td>
<td>Gadolinium-enhanced shrinking of T2</td>
</tr>
<tr>
<td></td>
<td>Arterial spin labeling</td>
<td>ASL</td>
<td>Intra-contrast enhancement generated from magnetization of arterial blood</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Diffusion-weighting imaging</td>
<td>DWI</td>
<td>Gradient-motions correlation of molecular diffusion</td>
</tr>
<tr>
<td>Metabolic function</td>
<td>Spectroscopy</td>
<td>MRSI</td>
<td>Chemical composition based on resonance frequency</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Blood-oxygen deposition</td>
<td>REDO, PWI</td>
<td>T2* differences in oxy- and deoxyhemoglobin</td>
</tr>
</tbody>
</table>
MRI Radiomics

Discern benign from malignant lesions
Identify radiation necrosis after RT
Generate automatic tumor segmentation algorithms
Improve prognostic capabilities
Deep learning to correlate with genomic phenotypes

Challenge:
Validate robustness radiomic features
Imaging processing platforms that facilitate the discovery and validation of radiomic biomarkers

DWI MR Blurring and Distortion

Question set 1:

Extracting quantitative transport parameters from DCE-MRI acquisitions is challenging. The selection of different perfusion analysis software corresponded to within-subject coefficient variation for $k_{trans}$, in the range,

a) 28.3% - 48.8%
b) 48.3% - 68.8%
c) 68.3% - 88.8%
d) 38.3% - 58.8%

Answer: b)

Literature:
Imaging Variability & Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scale 1 (12 of 12)</th>
<th>Scale 2 (11 of 12)</th>
<th>Scale 3 (10 of 12)</th>
<th>Scale 4 (9 of 12)</th>
<th>Scale 5 (Score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity variation</td>
<td>Normal, not affecting image</td>
<td>Normal, not affecting image</td>
<td>Normal, not affecting image</td>
<td>Normal, not affecting image</td>
<td>No intensity variation</td>
</tr>
<tr>
<td>ADC (1000) (1000)</td>
<td>Moderate, normal physiological range</td>
<td>Moderate, normal physiological range</td>
<td>Moderate, normal physiological range</td>
<td>Moderate, normal physiological range</td>
<td>Moderate, normal physiological range</td>
</tr>
<tr>
<td>ADC (1000)</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
</tr>
<tr>
<td>Ratio of ADC, tumor-to-nontumor ratio</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
<td>Normal, no intensity variation</td>
</tr>
</tbody>
</table>

123 available, 84 (68%) >=3, 58 (47%) = 5

Overall Survival by QC Score

Diagram depicting the importance of optimizing imaging performance based on the fundamental objectives of radiotherapy (outer circle).
Question set 2:

Major impediments to broad adoption of molecular imaging include:

a) Lack of clinical evidence, immature technology, tracer scarcity, and inadequate recommendation.

b) Lack of clinical evidence, immature technology, lack of reimbursement models, and inadequate recommendation.

c) Lack of clinical evidence, inadequate training, lack of reimbursement models, and inadequate recommendation.

d) Lack of clinical evidence, lack of analysis tools, tracer scarcity, and inadequate recommendation.

Answer: c)

Literature:

IROC Mission

Provide integrated radiation oncology and diagnostic imaging quality control programs in support of the NCI’s NCTN Network thereby assuring high quality data for clinical trials designed to improve the clinical outcomes for cancer patients worldwide
IROC As a QI Resource

**IROC As a QI Resource**

**IROC**
- Contact PI: D. Followill
- Co-Pis: D. Followill, Houston (R7) and M.V. Knopp, Ohio (Imaging)
- Sub-awards to:
  - IROC Ohio
    - Dir.: M.V. Knopp
  - IROC Philadelphia
    - Dir.: Y. Xiao & M. Rosen
  - IROC Houston
    - Dir.: D. Followill
  - IROC Rhode Island
    - Dir.: T.J. Fitzgerald

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**IROC, CIRO, EIC and NCTN groups**

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**IROC’s Five Core Services**

1. **Site Qualification (SQ) (SQ)**
   - (FQs, ongoing QA, proton approval, resources)

2. **Trial Design Support/Assistance (TD) (TD)**
   - (protocol review, templates, help desk, key contact QA centers)

3. **Credentialing (CD) (CD)**
   - (tiered system to minimize institution effort)

4. **Data Management (DM)**
   - (pre-review, use of TRIAD, post-review for analysis)

5. **Case Review (CR)**
   - (Pre-, On-, Post-Treatment, facilitate review logistics for clinical reviews)
Summary

- QI essential for radiation therapy and have been incorporated in clinical trials
- Many challenges face appropriate usage of QI
- IROC as a resource for QI

Thank you