Functional Image-guided Thoracic and Hepatic Radiation Therapy: synergies between nuclear medicine and radiation oncology

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Synergy: Nuc Med Imaging for Precision Rad Onc

• Key premise is that therapeutic ratio (efficacy / toxicity) can be individually optimized
• Nuc med imaging as a biomarker to risk stratify rad onc patients
  – Select therapies, dosing, fractionation
  – Define target / organs-at-risk volumes + dose objectives
• Nuc med imaging as a biomarker to evaluate individual RT response
  – Adapt therapies, dosing, fractionation
  – Adapt target / organs-at-risk volumes + dose objectives
• Nuc med imaging to spatially optimize RT dose distribution
• Applications of nuc med imaging to radiation therapy for thoracic / hepatic cancers
FDG PET/CT for RT Target Definition

- Primary tumor + regional node definition
- CT
- PET/CT
- SD
- Disagreement 1 cm 0.4 cm 45% 1.6%
- Delineation time 16 min 12 min

Steenbakkers RJ et al. IJROBP 64: 435-448, 2006

FDG PET/CT for RT Target Definition

De Ruysscher 2012

Primary tumor + regional node definition

Mid-RT PET Response Outcome Stratification

- Outcome prediction improves with FDG PET mid-RT response measures relative to baseline FDG PET

Mid-RT PET Response Outcome Stratification

- 2 week mid-FDG PET
- 4 week mid-FDG PET
- 4 week mid-FDG PET

- Improved risk stratification on mid-PET within 4 weeks of RT start

Timing of PET Response Assessment during RT

- Metabolic Volume Tumor + Nodes
- Peak SUV Nodes

- Improved risk stratification on mid-PET within 4 weeks of RT start
FDG PET Predicts RT Failure Patterns

- FDG PET as spatial map of local treatment failure risk distribution
  Aerts, Radiother Oncol 2009, 2012

NM Imaging to Optimize RT Spatial Dose Distribution

- Dose painting by contours / Subvolume boosting
  - Biological target volumes (BTV) for uniform dose escalation
    Ling 2000, Tome 2003, Madani 2009
- Dose painting by numbers accounts for intratumoral variations in response to therapy

FDG PET-guided Lung Dose Painting Clinical Trials

- NKI+Maastricht: average dose increase to PET avid areas up to 65+ Gy in 24 fractions
- RTOG 1106: dose escalation based on mid Tx PET (up to 80.4 Gy in 30 fractions)
Nuc Med Lung Functional Imaging

- **Perfusion**
  - $^{99m}$Tc-MAA SPECT/CT
  - $^{68}$Ga-MAA PET/CT

- **Ventilation**
  - $^{99m}$Tc-DTPA SPECT/CT
  - $^{99m}$Tc-Technegas SPECT/CT
  - $^{68}$Ga-Galligas PET/CT

- **Inflammation**
  - FDG PET/CT

Functional Lung Dosimetry for Toxicity Prediction

- Patients with similar clinical characteristics & anatomic dosimetry (MLD)
  - Upper lobe primary tumors
  - Conventionally fractionated chemoRT
  - Anatomic mean lung dose 16.4 Gy (top) vs. 16.4 Gy (bottom)

- Different functional lung dosimetry (pMLD)
  - Top (pneumonitis): perfused mean lung dose 24.5 Gy
  - Bottom (no pneumonitis): perfused mean lung dose 8.6 Gy

- Combined MLD and pMLD best predict for Grade 2+ pneumonitis in initial (AUC = 0.92) and expanded patient cohorts (AUC = 0.94)

Functional Lung RT Dose-response Modeling

- Perfusion decline spatially correlates with increased inflammation in high dose regions
- Baseline high perfusion regions have steeper (more sensitive) dose-response curves

Owen et al. IJROBP 2018

Thomas et al. (under review)
Nuclear Medicine Basic Science Lectures
Stephen Bowen

Nuc Med Liver Functional Imaging

- PET/CT
  - FDG
  - FDG lactose
- SPECT/CT
  - GSA
  - HIDA
  - Sulfur colloid

<table>
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<tr>
<th>Uptake Type</th>
<th>Image</th>
<th>Description</th>
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<tr>
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<td>Untreated CP-A6</td>
<td>Untreated CP-B7</td>
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<tr>
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Bowen et al. EJNMMI Res 2016

Functional Liver Dosimetry for Outcome Stratification

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (days)</th>
<th>1 year OS (%)</th>
<th>Log rank</th>
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<tbody>
<tr>
<td>CP A</td>
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<td>90%</td>
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<tr>
<td>CP B/C</td>
<td>292</td>
<td>39%</td>
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CP A FLV V20 < 20%
CP B/C FLV V20 > 20%
CP A FLV V20 > 20%
CP B/C FLV V20 < 20%

Schaub et al. IJROBP 2018

Functional Liver RT Dose-response Modeling

A

B

C

Price et al. IJROBP 2018

++ Toxicity
+ Toxicity
- Toxicity
### Functional Liver Avoidance Clinical Trials

Differential Hepatic Avoidance Radiation Therapy (DHART) Planning (U Wash)

- Conventional RT
- Functional Avoidance RT
- Dose Difference

Functional liver image-guided hepatic therapy (FLIGHT) trial (Indiana)

- HIDA SPECT/CT
  - Maximize functional liver volume receiving < 15 Gy
- Inter-patient variability in benefit

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### Functional Lung Avoidance Clinical Trials

- IMRT plans adapted to avoid perfused lung on 4D MAA PET/CT
- Ongoing functional lung avoidance trials using NM imaging
  - 4D MAA PET/CT (Peter MacCallum)
  - MAA SPECT/CT (U. Washington, U. Michigan)

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### Functional Lung Avoidance & Response-adaptive Escalation (FLARE) RT

- FDG PET/CT
- MAA SPECT/CT
- FLARE RT Plan

Lee et al. Med Phys 2017
FLARE-RT Phase II Trial
(NCT02773238, R01CA204301, PI: Bowen, Zeng)

- All patients get functional lung avoidance RT: potential quality of life benefit
- Only high local failure risk patients get FDG PET-guided dose escalation: potential survival benefit
- 1° endpoint: 2 yr overall survival vs. RTOG 0617 60 Gy arm
- 2° endpoints: 1 yr local control, grade 2+ pneumonitis incidence vs historical rates

FLARE-RT Mid-Tx PET Response Assessment

- PET Responders: $\text{SSUV}_{\text{peak}}$ decrease 40% (32-48%), $\text{MTV}$ decrease 40% (32-62%)
- PET Non-responders: $\text{SSUV}_{\text{peak}}$ decrease 13% (8-23%), $\text{MTV}$ decrease 9% (5-21%)

FLARE-RT Plan Adaptation Decisions

- PET Responder: required anatomic adaptation to 60 Gy in 30 fx
- PET Non-responder: required functional adaptation to 74 Gy in 30 fx
FLARE-RT Boost to PET Non-responders

- 13/34 (38%) have received FLARE RT boost
  - 3 weeks RT non-responders & no evidence distant mets
  - 74 Gy to PTV$_{mid}$t [90+ Gy to SUV$_{peak}$]

- Well tolerated
  - 2 Grade 3+ esophagitis
  - 2 Grade 2+ pneumonitis

Future: Multiscale Imaging Response Prediction

- Multiscale imaging response prediction uses information from individual image voxels combined with regional, tumor, and patient factors

- Voxel Forecast Tool: custom generalized least squares (GLS) regression to predict tumor voxel response on mid-RT PET
  - Matérn model variogram to account for spatially correlated voxel data
  - Jack-knife bias-corrected estimator validated on simulations of known voxel response patterns

Voxel Forecast Tool: PET Voxel Response Prediction for Rad Onc Decision Support

- PET Responder NED 491 days
  - 14% under responding tumor voxels
  - MAE = 1.1 SUV

- PET Non-responder Died 323 days
  - 34% under responding tumor voxels
  - MAE = 3.3 SUV
Future: Personalizing NM+RO for HCC management

- Favorable planned dosimetry: personalize $^{90}$Y-microsphere prescriptions to achieve isotoxicity in liver
  verify on $^{90}$Y-SPECT/PET dosimetry

- Unfavorable planned dosimetry: modify $^{90}$Y-microsphere injection site
  boost any remaining cold $^{90}$Y-SPECT/PET dosimetry regions with SBRT

Summary: Synergies between Nuc Med and Rad Onc

- Nuc Med imaging to personalize Rad Onc
  - Risk stratify patients
  - Define targets and functional normal tissues
  - Optimize prescriptions and planned radiation dose distributions
  - Assess early response for adaptive therapy

- Future: combined NM image-guided RT with NM therapies
  - RT + targeted radionuclide therapy (TNT) + immunotherapy (IO)
  - NM imaging for targeting / avoidance / dosimetry / verification / response
  - Radiomics / machine learning of NM imaging to personalize NM + RO Tx

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