Joint EANM/AAPM Multi-disciplinary Scientific Symposium

Quantitative SPECT for Radionuclide and External Beam Treatment Planning: SPECT in Radionuclide and External Beam Treatment Planning

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Disclosures

- Research Grants
  - Sirtex Medical, Boston Scientific, GE Healthcare, ABK Biomedical
- Consultant
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Outline

- Introduction to Radiopharmaceutical therapy
- SPECT in Radiopharmaceutical therapy
  - $^{177}$Lu DOTATATE
  - $^{90}$Y SIRT
- SPECT in EBRT/PBR
  - LungTx
  - LiverTx

What is Radiopharmaceutical Therapy?

- Radiopharmaceutical uptake
  - Disease sites (Target)
  - Non-target organs (Organs at Risk)
- Tracer radiopharmaceutical administered to plan therapy
dose/activity
  
  **SAFETY**
  - Dose constraints on Organs at Risk (e.g., red marrow, lungs, liver, kidneys)

  **EFFICACY**
  - Dose constraints on tumors (e.g., planned mean dose > threshold dose for response)
Targeted Radionuclide Therapy

Radionuclide Imaging
- Radionuclide has $\gamma$ or $\beta^+$ emission used for in vivo imaging of biodistribution
- Exam with low activity (effective dose) to diagnose, stage, and assess treatment response

Radionuclide Therapy
- Radionuclide has energetic particle emission ($\beta^-$, $\alpha$, Auger e$^-$) used for in vivo radiation of tissue
- Exam with high activity (adsorbed dose) to induce cell death and generate response

Both involves a radiopharmaceutical (radioactive drug) that targets (binds or uptake) cancer cells via specific biological processes

Therapeutic + Diagnostic = Theranostic

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Therapeutic</th>
</tr>
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<tbody>
<tr>
<td>5 mCi</td>
<td>200 mCi</td>
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</table>

- I-131 NaI for differentiated thyroid cancers
  - I-131 NaI or I-123 NaI
- Y-90 Zevalin for NHL
  - In-111 Zevalin
- Y-90 microsphere SIRT liver cancers
  - Tc-99m MAA

Special considerations needed for planning agents with different radionuclide based on their half-life
RNT is Image-Guided Radiation Therapy

- Assessment of disease for treatment selection
- Evaluate patient-specific biodistribution of radiopharmaceutical for RNT treatment planning
- Develop patient-specific treatment plans: dose limits to targets & OAR
- Assessment of response
- Treat and Image based verification of RNT delivery

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Targeted Radionuclide Therapy

• Administer Tracer Drug
• Administer Therapeutic Dosage
• D/A for Targets & OAR

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RNT treatment schemas

Fixed Activity Treatment

Patient-specific Activity Treatment

• Almost all investigational trials and clinical approved RNT are based on either Fixed Activity or Maximum Dose to OAR

• Y90-SIRT is one of the exceptions where minimum dose to tumor and maximum dose to OAR is part of dosimetry schema
  – a recent development

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### Serial Quantitative SPECT/CT scans

#### Advantages
- More accurate assessment of TAC
- Patient-specific organ masses
- Patient-specific S-factors via Monte Carlo or GBBS
- More accurate tumor dosimetry
- Facilitates Voxel dosimetry

#### Disadvantages
- Increased patient time on the scanner (factor of 2 or more)
- Higher use of resources for clinical operation
- Increased complexity in data processing

#### Practical Approaches
- Integrate a single quantitative SPECT/CT scan within the sequence of serial whole-body planar imaging – 2.5D dosimetry
- Modified serial quantitative SPECT/CT scans
- Single-time point SPECT/CT

- $^{177}$Lu-DOTATATE/DOTATOC
**177Lu-DOTATATE (Lutathera)**

- Recent FDA-approval for use in GEP-NET tumors (NETTER-1 trial)
  - Expanding to use in all NET expressing SSR2
- Fractionated Schema: 4 cycles of 7.4 GBq (200 mCi) with 8 week interval
  - $^{68}$Ga-DOTATATE PET/CT scans to establish the patients disease expresses SSR2 and ensure adequate uptake (theranostic)

![PET/CT scans](image)

(Reference: Hope et al, JNM 60, 2019)

**177Lu-DOTATATE/DOTATOC**

- Dosimetry for approval based on planar multi-time point dosimetry
- NO patient specific dosimetry calculations for SOC treatment plans
  - Netter-1 Trial Objective Response Rates ~18%
- Need to develop practical schema for patient specific dosimetry to answer:
  - How do we safely prescribe more than 4 cycles of Tx? ← Track dose to OAR
  - Can we improve the objective response rates (NETTER-1 ~18%)? ← Track dose to tumors
  - Very challenging to perform multi-timepoint imaging for dosimetry spanning 0 to 168 h after each treatment cycle ← Simplified schema needed

![PET/CT scans](image)

(Case Report: $^{68}$Ga DOTATOC PET/CT scans of patient that underwent 7 cycles of Lu177 treatment in 5 year span illustrating the “waxing and waning” pattern of disease)

(Reference: Puranik et al, Case Reports 1, 2015)
177Lu-DOTATATE/DOTATOC dosimetry

- 20 patients, 4 cycles → 80 Tx
- 3 time-point SPECT/CT (4, 24, 96-120 h) after each Tx were acquired

Recommendations:
- 1st cycle multi-time point SPECT/CT for patient-specific kinetics
- Use single time-point SPECT/CT @ 24 h for uptake in subsequent cycles
- Error in residence times ~16%

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177Lu-DOTATATE/DOTATOC dosimetry

- 29 treatments, 4 cycles → 116 Tx
- 6 time-point SPECT/CT (24, 48, 72, 96, 120, and 144 h) after each Tx were acquired

Recommendations:
- Population-based S-values can be used (kinetics)
- Single SPECT/CT at 4 d (96 h) P.I. to measure the uptake
- Error in residence times < 10%-20%

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(Willowson et al, EJNMMI Phys 5, 2018)
- **90Y-radioembolization or SIRT**

SIRT treatment planning uses 99mTc-MAA as a surrogate for 90Y-microspheres:
- Access extra-hepatic shunting
- Lung dose from arterio-venous shunting
- Tumor & Normal Liver dosimetry

**Imaging for Therapy Planning**
- CT or MR Lab work
- Angiography, C-arm CT, 99mTc SPECT/CT

**Imaging for Therapy Delivery and Verification**
- Angiography, 90Y SPECT/CT
- 99mTc-MAA SPECT/CT For Planning Dosimetry
- 90Y SPECT/CT For Verification Dosimetry
**SIRT Timeline**

- **1980’s and 90’s**
  - Initial studies in human

- **1999**
  - TheraSphere Y90 – HDE

- **2002**
  - SIR-Spheres Y90 – FDA

- **2002**
  - TheraSphere Y90 – FDA

- **2015**
  - QuiremSpheres Ho166 – CE

- **Present**
  - Intervention for Disease Control

**Driving Factors**
- Improved dosimetry models
- Tumor dose-response models
- Clinical benefits of SIRT realized
- SIRT well positioned in IR toolkit

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**90Y-SIRT TCP for HCC with 90Y SPECT/CT**

<table>
<thead>
<tr>
<th>Dose Metric</th>
<th>Responder (median)</th>
<th>Non-Respond (median)</th>
<th>Threshold Dose (D50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dmean (Gy)</td>
<td>209</td>
<td>138</td>
<td>160 (123-196)</td>
<td>0.002</td>
</tr>
<tr>
<td>BEDmean (Gy)</td>
<td>259</td>
<td>178</td>
<td>214 (146-280)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

(Chiesa et al, EJNMMI 42, 2015)

(Kappadath et al, Int J Rad Onc Phys Bio 102, 2018)
Role of SPECT in EBRT

- Use functional NM imaging to assess normal organ function and its spatial distribution during EBRT/PBRT treatment planning dosimetry
  - Goal is to preserve organ function after intervention

**Assessment & Dosimetry**
**Planning Phase**
- Radiopharmaceutical imaging
- FDA approved tracer
- SOC imaging
- Assess normal tissue function and distribution
- Functional considerations included for Planning Dosimetry

**Treatment & Verification**
**Dosimetry**
- SBRT/PBRT/IMRT
- Image processing; fusion; dosimetry; etc.
- Voxel dosimetry; DVH; D, BED, other metrics

**Follow-up Imaging & Labs**
- Toxicity assessments
- Response assessments
- Follow-Up duration

**Lung EBRT/PBRT**

- $^{99m}$Tc-MAA to assess perfused lung tissue for RT planning of lung cancer patients
Functional Lung Perfusion Imaging

(Shioyama et al, Int J Rad Onc Phys Bio 68, 2007)

(Thomas et al, BJR, 2019)
Liver EBRT/PBRT

- $^{99m}$Tc-Sulfur Colloid and $^{99m}$Tc-mebrofenin to assess functioning normal liver tissue for RT planning of liver cancer patients

Functional Liver in RT Plans

Fig. 1. Observed radiation dose-response or longitudinal SC SPECT/CT for a patient with Child-Pugh A5 hepatocellular carcinoma. (A) Three-field proton radiotherapy planning CT and dose color scale overlay; (B) pretreatment SC SPECT coregistered to dose overlay; and (C) 1-month posttreatment SC SPECT coregistered to dose overlay. SC SPECT window/level normalized to out-of-field integral uptake. Regions within the treatment-field show reductions in uptake that are correlated with radiation dose magnitude and spatial distribution. Abbreviation: CT = computed tomography; SC = sulfur colloid; SPECT = single photon emission tomography.

(Price et al, Radiotherapy & Oncol 115, 2015)

[\[^{99m}\text{Tc}\] SC SPECT/CT $\rightarrow$ FLY$_{4.3X-10}$ ROI $\rightarrow$ DHART]

(Bowen et al, Radiotherapy & Oncol 115, 2015)

Functional Liver in RT Plans

Fig. 3. Conventional radiotherapy vs. SPECT/CT for an example HCC patient. Pretreatment RT dose distributions in an anteroposterior (A-C) but not other anatomic liver subregions (D) or functional liver subregions (E) with the resulting dose difference distribution (F). Plots show the dose distribution in the same anteroposterior (A-F) but not other anatomic liver subregions (G) or functional liver subregions (H) with the resulting dose difference distribution (I). (Color figure online) Abbreviations: PTV, planning target volume; FLV, functional liver volume; TLD, thermoluminescent dosimeter; CT, computerized tomography.

(Bowen et al., Radiotherapy & Oncol 115, 2015)

Summary

Quantitative SPECT/CT has come to maturity

Role of SPECT/CT in RNT

- Central to the development and advancement of new and existing RNT
- Time to focus on the personalized treatment planning based on patient-specific physiology and tumor characteristics
- Need to demonstrate improvement in treatment efficacy with patient-specific dosimetry
  - Prospective clinical studies that incorporate dosimetry measurements
- Need for standardization and consistency in practice

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Summary
Quantitative SPECT/CT has come to maturity

Role of SPECT/CT in Radiation Therapy

- Adjust treatment plan based on spatial information of normal tissue function to decrease OAR dose and improve therapeutic ratio
- Need to characterize the quantitative changes in normal tissue function based on dose delivered
- Need to demonstrate mitigation of risk associate with toxicity when treatment plans include functional information