Quantitative SPECT and PET in Absorbed Dose Calculations for Radionuclide Therapy

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With a special shout-out to Stephen Graves, PhD who provides some critical content and perspective.
1. Context
External Beam Radiation Therapy

Start with CT and Prescription
Choose electrons or photons
Dial up simulated energy and current
Generate Treatment Plan

Energy
Current
Molecular Targeted Radionuclide Therapy

- **Theranostics**
  - Imaging (PET: Ga-68 PSMA
    - Quantitative
  - Therapeutic (Lu-177 PSMA, Ac-225 PSMA)
- **Beta particles**
  - Radiobiology
- **Alpha particles**
  - Radiobiology
- **Theranostics**
  - Therapeutic Imaging
  - Image-based dosimetry

Current Targeted Radionuclide Therapy Paradigm

Typically:
1. Imaging Study to confirm that tumors express target.
2. No dosimetry.
3. No dose modification.
2. Quantitative SPECT and PET Imaging
PET and SPECT Imaging

Inherently and Historically Quantitative

Historically Non-Quantitative... But great strides have been made recently

Positron-Emitting Radionuclides:
- Positron Emitters: Energy Dependent
- 511 keV Photons

Single Photon Emitters: Energy Radionuclide Dependent
Quantitative PET and SPECT Images: What does that mean?
Turning Quantitative Images into Dose Maps: DPKs

Radionuclide-Specific Dose Point Kernel

Absorbed Dose Distribution

Beta Spectra

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Absorbed Dose (Bq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>137 Bq</td>
<td>140 Bq</td>
</tr>
<tr>
<td>139 Bq</td>
<td>130 Bq</td>
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</tbody>
</table>

300 Bq
512 Bq
712 Bq
1219 Bq
1357 Bq
1322 Bq
1400 Bq
1353 Bq
1305 Bq
1498 Bq
410 Bq
511 Bq
698 Bq
1345 Bq
1305 Bq
498 Bq
522 Bq
410 Bq
Creation of Dose Rate Maps from Quantitative Images (SPECT or PET)

Activity Map

Radionuclide Specific "Dose Point Kernel"

= Image Based Dose Rate Map
Integrate Dose Rate Map Over Time for Actual Dose Estimate (Tumor and Normal Organs)

Dose Rate Image

\[ \text{Dose} = \int_{t=0}^{T} \text{Dose Rate}(t) \, dt \]

Dose Image
Using Quantitative Images to Generate Dose Maps for Radiotherapeutics

• Monte Carlo Approaches
  • Use the Activity Concentration Maps and Time Course
    • Highly Computationally Expensive
    • Analogous to EBRT, but more complex dimensionally

• Dose Point Kernel Approaches
  • Use radionuclide (and tissue?)-specific “dose point kernel”.
    • DPK based on a tissue specific Monte-Carlo simulation
    • Applied to the 3D image at large
    • Can determine both Tumor Dose (efficacy) and organ dose (toxicity)

• Organ or Tumor Based Approaches
  • Critical-Organs(s) dose measurement, or lindex Tumor
    • Simple VOI-based methods
    • Dose modification to avoid toxicity
Y-90 PET/CT SPECT/CT Kidney Dose Workflow

1. Generate Kidney regions on SPECT/CT over 4 time points.
2. Plot SPECT total kidney counts.
3. Calibrate SPECT curve 5.5 hour time point to 90Y PET/CT based activity measurement.
4. Calculate Kidney Dose (Must be less than 23 Gray(?)

Goal: Modify Administered Dose to subsequent Fraction (3X) to get Kidney Dose to approximately 23 Gray
### 90Y-DOTATOC MTRT Personalized Kidney Dose/Activity & Treatment Modifications

<table>
<thead>
<tr>
<th>Admin. Activity (GBq)</th>
<th>Kidney Dose/Activity (mGy/MBq)</th>
<th>Cumulative Kidney Dose (23 Gy Protocol Max)</th>
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<tbody>
<tr>
<td>Cycle 1</td>
<td>Cycle 2</td>
<td>Cycle 3</td>
</tr>
<tr>
<td>1</td>
<td>4.4</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>3.8</td>
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</tr>
<tr>
<td>22</td>
<td>4.5</td>
<td>4</td>
</tr>
</tbody>
</table>

**Patients that likely would have benefited from 2-3x the prescribed baseline therapeutic dose.**

**Patients that likely would have benefited from approx. 1.5X the prescribed baseline therapeutic dose.**

**Patients whose administered dose was reduced in subsequent administrations to keep kidney dose below limits.**

**Factor of 5X uptake differences to the critical organ!**
MTRT Tumor Dosimetry: In its infancy...

Tumor doses can be estimated using a similar approach to the kidney dose estimates using the PET data to calibrate the SPECT/CT clearance.


Tumor dose–response relationship for patients with PNETs treated with PRRT using 177Lu-DOTATATE, including tumors larger than 2.2 cm (A) and only tumors larger than 4 cm (B). Ezgi Ilan et al. J Nucl Med 2015;56:177-182

Why don’t we routinely perform dosimetry?

- “Sophisticated” dosimetry tools have only recently become available (~3 years)
  - MIM (SurePlan)
  - Hermes (Voxel Dosimetry)
  - Velocity (RapidSphere)
  - DOSIsoft (Planet DOSE)
  - OLINDA 2.0
  - Mirada (Simplicit\textsuperscript{90}Y)
- “Trained” physicists are scarce.
- Currently, neither formal training programs nor credentialing programs exist in this area.
- Convincing prospective clinical trial data proving that “dosimetry matters” is scarce.
3. Radionuclide Therapy Applications
### VERY partial list of radiotherapeutics approved and in development

<table>
<thead>
<tr>
<th>Therapeutic Radiopharmaceutical</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>131-I-radioiodine</td>
<td>Jubilant Draximage</td>
<td>Thyroid Ca</td>
</tr>
<tr>
<td>131-I-MIBG</td>
<td>Progenics</td>
<td>Adrenergic+ tumors</td>
</tr>
<tr>
<td>212Pb-trastuzumab</td>
<td>OranoMed</td>
<td>HER2+ tumors</td>
</tr>
<tr>
<td>212Pb-PRIT</td>
<td>OranoMed/Roache</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>212Pb-antisomatostatin</td>
<td>OranoMed/Radiomedix</td>
<td>Somatostatin+ tumors</td>
</tr>
<tr>
<td>212Pb-aTEM1</td>
<td>OranoMed/Morphotek</td>
<td>TEM1+ tumors</td>
</tr>
<tr>
<td>212Pb-aCD37</td>
<td>Oranomedi/NordicNanovecto</td>
<td>Leukemia</td>
</tr>
<tr>
<td>131-I-aCD45</td>
<td>Actinium Pharma</td>
<td>BM xplant prep</td>
</tr>
<tr>
<td>225Ac-aCD33</td>
<td>Actinium Pharma</td>
<td>Leukemia</td>
</tr>
<tr>
<td>90Y-microspheres</td>
<td>Varian/Sirtex</td>
<td>Hepatic tumors</td>
</tr>
<tr>
<td>90Y-microspheres</td>
<td>BTG</td>
<td>Hepatic tumors</td>
</tr>
<tr>
<td>177Lu-Pentixather</td>
<td></td>
<td>Multiple Myeloma</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Therapeutic Radiopharmaceutical</th>
<th>Company</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>177Lu-Lutathera</td>
<td>Novartis/AAA</td>
<td>Neuroendocrine Tumor</td>
</tr>
<tr>
<td>177Lu-PSMA-R2</td>
<td>Novartis/AAA</td>
<td>Prostate</td>
</tr>
<tr>
<td>177Lu-NeoBOMB1</td>
<td>Novartis/AAA</td>
<td>Bombasin+ Tumors</td>
</tr>
<tr>
<td>177Lu-PSMA-617</td>
<td>Endocyte/Novartis/AAA</td>
<td>Prostate</td>
</tr>
<tr>
<td>223Ra-Xofigo</td>
<td>Bayer</td>
<td>Bone Mets</td>
</tr>
<tr>
<td>227Th-HER2-TTC</td>
<td>Bayer</td>
<td>HER2+ Tumors</td>
</tr>
<tr>
<td>227Th-PSMA-TTC</td>
<td>Bayer</td>
<td>Prostate</td>
</tr>
<tr>
<td>227Th-MSLN-TTC</td>
<td>Bayer</td>
<td>Mesothelin+ Tumors</td>
</tr>
<tr>
<td>227Th-CD22-TTC</td>
<td>Bayer</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>225Ac-FPX-01</td>
<td>J&amp;J/Fusion</td>
<td>NSCLC/Pancreatic Cancer</td>
</tr>
<tr>
<td>177Lu-DOTATOC</td>
<td>ITM</td>
<td>Neuroendocrine Tumor</td>
</tr>
<tr>
<td>177Lu-FAP2286</td>
<td>Clovis</td>
<td>FAP+ (Fibroblast Act) Tumors</td>
</tr>
</tbody>
</table>

Adapted from G. Sgouros
The Case for Dosimetry in Alpha-Emitter Therapy 2019
Examples of Therapy Applications: Phase 1-3 to Approved...

- **68Ga and 177Lu DOTATATE NET**
- **68Ga images of FAP (Fibroblast Activation Protein) Candidate Target**
- **68Ga-DOTATOC images post-$^{213}$Bi-DOTATOC, Ac-225 DOTATOC NET**

- **68Ga PSMA-11 and 177Lu - PSMA617 Prostate Ca**
90Y-microspheres for Hepatocellular Carcinoma (Radio-Embolization)

- Two agents in clinical use:
  - Y-90 SIR-Spheres (Sirtex, 20-60 µM Resin)
  - Y-90 Theraspheres (Boston Scientific, 25 µM Glass)

- 80% of Hepatic tumors fed by the hepatic artery.
- Y-90 infused spheres are administered via angio-access via femoral artery.
- PRIOR to Y-90 treatment, a Tc-99m MAA (15-150 µM) imaging study is performed to assess lung shunting.

The Hepatic Vein provides blood to the healthy liver.
Branches of the Hepatic Artery feed the tumors.
Using the Tc-99m MAA Scan for Dosimetry Estimate for Y-90 Embolization

(A and B) 99mTc-MAA SPECT (A) and 90Y TOF PET (B) images of liver treated with glass spheres, with treated volume delimited by green lines and tumors by blue lines. (C and D) Dose–volume histograms (DVH) of tumors 1 (C) and 2 (D), with blue lines corresponding to 90Y dosimetry based on 99mTc-MAA SPECT spatial distribution and red lines to 90Y TOF PET (posttreatment dosimetry). Silvano Gnesin et al. J Nucl Med 2016;57:1672–1678.

Figure 5. Receiver operating characteristic (ROC) curve showing the optimum value of the estimated tumor-specific radiation dose predicting treatment response.
90Y-microspheres for Hepatocellular Carcinoma

- 2016 study on tumor dosimetry as predicted by 99mTc-MAA SPECT/CT
  \[N = 85 \text{ patients}\]
- The only factor which was found to correlate with overall survival was tumor dose (TD)
  \[6.5 \text{ months vs 21 months for above/below 205 Gy (p=0.005)}\]
- Response rate with TD < 205 Gy = 9.1%
- Response rate with TD >205 Gy = 89.7%

90Y-microspheres for Heptocellular Carcinoma

4. Quantitative Challenges
Quantitative Challenges:

1. SPECT Quantitation is still in early phases.
   - low sensitivity due to the necessary use of a collimator (more so than PET)
   - complicated scatter and attenuation correction (more so than PET)
   - lower resolution creating partial volume effects (more so than PET)
   - Uncertain how quantitation from one SPECT/CT system to another actually compare.

2. Multiple imaging time points over several days are necessary to characterize the radionuclide washout. Inconvenient for patient.
   - Might be able to be simplified to single time-point imaging if the shape of the washout curve is consistent across patients.
Quantitative Challenges: Partial Volume Effect (PET and Particularly SPECT)

Vendor Specific Reconstructions demonstrate both dramatic
• Quantitative Bias
• Quantitative Variability

A Bq/mL needs to be reasonably consistent across imaging systems. Absorbed dose is being estimated based upon this measurement. It is not yet consistent.

Variability in Lutetium-177 SPECT quantification between different state-of-the-art SPECT/CT systems. EJNMMI Physics volume 7:9 (2020)
Quantitative Variability Between SPECT/CT Systems

Variability in Lutetium-177 SPECT quantification between different state-of-the-art SPECT/CT systems. EJNMMI Physics volume 7:9 (2020)
Other Quantitative Challenges

- Quantitation tuned to Tc-99m, which is not necessarily relevant to the therapeutic radionuclide. Gamma energy matters.
- SPECT scanners physically designed for lower energy gammas (collimators and crystal thickness). This is being re-thought.
- Attenuation correction using CT is difficult because different look-up attenuation coefficients for different gamma mixes for different radionuclides.
Quantitative Challenges: The Challenge of Multiple Time Points

The field is sensitive to patient inconvenience, and the reimbursement situation associated with multiple timepoint scans.

Radionuclide clearance can typically be well estimated by a bi-exponential. How many points are needed to accurately estimate the area under the curve (total decays)?

**FIGURE 1.** $^{177}$Lu-PSMA I&T whole-body scintigraphy images obtained at 2, 20, 43, 69, and 165 h after administration. Regions of interest were drawn on liver, kidneys, parotid glands, submandibular glands, lacrimal glands, and lesions in right humerus, thoracic vertebrae, and right femur.

Radiation Dosimetry for $^{177}$Lu-PSMA I&T in Metastatic Castration-Resistant Prostate Cancer: Absorbed Dose in Normal Organs and Tumor Lesions

*J Nucl Med* 2017; 58:445–450

Each scan will take 15-75 minutes
The Challenge of Multiple Time Points

Technical Note: Single time point dose estimate for exponential clearance

Mark T. Madsen, Yusuf Menda, Thomas M. O’Dorisio, M. Sue O’Dorisio

Kidney Dosimetry in $^{177}$Lu and $^{90}$Y Peptide Receptor Radionuclide Therapy: Influence of Image Timing, Time-Activity Integration Method, and Risk Factors


90 Y-DOTATOC Dosimetry-Based Personalized Peptide Receptor Radionuclide Therapy

March 2018 - Journal of Nuclear Medicine 59(11) jnumed.117.202903
DOI: 10.2967/jnumed.117.202903

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John Sunderland - $M^38.04$ - University of Iowa

Original research | Open Access | Published: 23 January 2020

Dosimetry after peptide receptor radionuclide therapy: impact of reduced number of post-treatment studies on absorbed dose calculation and on patient management

Alexandre Chicheportiche, Simona Ben-Haim, Simona Grozinsky-Glasberg, Kira Oleinikov, Amichay Meirovitz, David J. Gross & Jeremy Godefroy

Kidney Dosimetry During $^{177}$Lu-DOTATATE Therapy in Patients With Neuroendocrine Tumors: Aspects on Calculation and Tolerance

Mattias Sandström, Ulfike Garska-Román, Silvia Johansson, Dan Granberg, Anders Sundin, Nanette Freedman

Minimizing the clinical requirements for kidney dosimetry in $^{177}$Lu-DOTATATE with reduced timepoint imaging and neural network segmentation

JNM May 2020

David Miranda, Yuni Dewaraja, Stephen Graves, Katherine Krawiec and Aaron Nelson
Dosimetry Through Quantitative Imaging: Clinical Trials
SPECT/CT QC and Quantitative Scanner Validation for Clinical Trials and Clinical Practice

• No standard phantom(s)
  • PET Phantoms features generally too small
  • Ad Hoc phantoms too simple to challenge systems

• No quantitative SPECT scanner validation programs

• No recommended quantitative SPECT validation tests with any historical boundaries for acceptance. We just don’t know variability.

• No formal physicist qualification, accreditation programs, internships, residency requirements for Targeted Radionuclide Therapy.
Quantitative SPECT Phantoms?

- Custom with spheres 13-60 mm diameter
  - But
    - Small
    - Symmetric
    - No attenuation or scatter challenges

- NEMA PET phantom with spheres 10-37 mm
  - But
    - Spheres too small
    - Scatter and attenuation challenge minimum to moderate.

- SNMMI CTN PET phantom with spheres 10-37 mm
  - But
    - Spheres too small
    - Available, but not ubiquitous
Acceptance Testing for SPECT, but Quantitation IGNORED...
SPECT Quantitation QC?

Not included:
- Sensitivity calibration for qSPECT
- Isotope-specific SPECT phantom
- SPECT phantom quantitation (e.g. uniformity and calibration check)
- CT to density calibration
- Image transfer integrity to TPS or analysis workstation
- Isotope-specific count rate performance
- Spatial resolution with real reconstruction parameters and isotopes other than Tc-99m
- Measurement of recovery coefficients as a function of:
  - Isotope
  - Tumor to background ratio
  - Camera orbit diameter
- Dose calibrator QC?
- Auto-well counter QC? (blood/marrow dosimetry)
- Radiation safety recommendations?
Conclusions: The MTRT Future - What does it look like?

Cycle 1
200 mCi
Acute Tox?
Yes
Imaging?
Yes
Stop

Cycle 2
200 mCi
Acute Tox?
Yes
Imaging?
Yes
Stop

Cycle 3
200 mCi
Acute Tox?
Yes
Imaging?
Yes
Stop

Cycle 4
200 mCi
Acute Tox?
Yes
Imaging?
Yes
Stop

Stop Stop Stop
Yes Yes Yes Yes
Imaging? Imaging? Imaging?
Conclusions: The MTRT Future - What does it look like?

**Quantitative Imaging**
1. Easy to use, validated dosimetry software
2. Improved quantitative SPECT reconstructions
3. SPECT phantoms to validate quantitative performance
4. Quality control standards for quantitative SPECT
5. Simplified imaging protocols minimizing time points

**Training and Accreditation**
1. A trained physicist workforce
2. Formal accreditation programs for physicists
3. A trained physician workforce
4. Formal accreditation programs for physicians
5. A Network of “Centers of Excellence” for training

**Dosimetry & Clinical Trials**
1. Prospective trials using dosimetry showing improved outcome.
2. Understanding low-dose rate organ limits for kidney & marrow
3. Organ- and RP-specific dose limits for alpha emitters
4. Understanding interplay with other systemic therapies (chemo, immunotherapies)
5. Simplified data-supported radiobiological reporting formalisms (e.g. Biological Effective Dose – dose rate, total dose, total time)