Patient Specific Dosimetry in TRT: To What Extent Can It be Simplified to Move from Research to The Clinic

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Targeted radionuclide therapy (TRT): why dosimetry?

- Current TRT: ‘one dose fits all’ or weight based adjustment
  - Convenient, but potential for under- or over-treatment
  - Variability in pharmacokinetics, anatomy, activity distribution not considered
  - Examples: $^{177}$Lu PRRT (‘one size’), $^{90}$Y RE (liver mass), $^{90}$Y RIT (body weight)

- Treatment planning based on absorbed dose:
  - Simplified protocols for clinical practice
    - Activity adjusted to keep absorbed dose to critical organ < MTD
  - Highly patient specific protocols
    - Taylor to deliver therapeutic absorbed dose to lesion at acceptable toxicity. Standard in EBRT but limited to research setting in TRT
Targeted radionuclide therapy: why do dosimetry?

• Pre-treatment dosimetry
  • For planning therapy to improve efficacy (theranostics)
  • Often using a surrogate

• Peri-therapeutic dosimetry (during treatment)
  • Dosimetry after each cycle to modify subsequent cycle, real time dosimetry to adjust activity during treatment

• Post-treatment dosimetry
  • Verification, early assessment of safety & response (additional therapies/interventions when needed), establish dose vs. effect
Benefit of pre-treatment dosimetry: example from 90Y RE

- Initial study (n=36): Tc-MAA SPECT/CT based tumor dosimetry, standard therapy (liver 120 Gy, lung < 30 Gy)
  - Established **205 Gy to tumor** as threshold for response

- Intensification study (n=41): Activity based on MAA dosimetry. Tumor >205 Gy, normal liver<120 Gy, lung<30 Gy
  - 37% received higher activity
  - **Improved Survival:** TD < 205 Gy, 4 mo
  - TD > 205 Gy, 18 mo \( (P = 0.005) \)
  - No increase in toxicity

Garin et al, JNM 2015;339-346
Benefit of dosimetry during treatment: examples from $^{177}$Lu PRRT

- **Sundlov et al, EJNMMI 2017**
  - Treatment based on renal dosimetry with BED < 27Gy

- **Sandstrom et al, ACTA ONCOL. 2018**
  - With BED < 38 Gy to kidney and AD < of 2 Gy to marrow
  - 95% could get > 4 cycles

# of cycles within the protocol specified BED and AD limits

# of cycles can be increased in most patients without reaching toxicity limits
Benefit of post-treatment dosimetry: example from Y-90 RE

- Dose maps can be used to plan EBRT (boost under-dosed region)

6 month after Y90: poor response

Increase in target and lesion minimum dose. They are now covered. Small increase in normal liver mean dose.

After 90Y

- Lesion
- Targeted Boost
- Normal Liver

EBRT 50 Gy Boost

- target minimum dose is ~ 50 Gy and very uniform.

90Y+EBRT

Normal Liver

Target

Courtesy of Justin Mikell, Radiation Oncology, University of Michigan
SPECT/CT or PET/CT based patient specific dosimetry

Can this process be simplified?

PET/CT or SPECT/CT Acquisition

CT reconstruction

PET/CT or SPECT/CT Acquisition

SPECT or PET reconstruction with AC, SC, RR,...

Attenuation map

Calibration Factor
cps/voxel -> MBq/mL

Density map

Activity map

Partial Volume Correction

AD, DVH, BED

Repeat at multi-time points (except Y-90 RE)
Patient specific dosimetry in TRT: simplification to move to clinic

- Do we need specialized reconstruction software & calibrations?
- Do we need a radiologist for target segmentation?
- Do we need multiple-imaging time points?
- Do we need Monte Carlo Dosimetry?

Two therapies will be discussed as examples: Y-90 Radioembolization (RE) and Lu-177 Peptide Receptor Radionuclide Therapy (PRRT)
Y-90 RE example: Reconstruction & calibration

- $^{90}$Y dosimetry is easy
  - Microspheres are trapped: only need one time point
  - No gamma-rays, so little cross dose

BUT

- Imaging is complex
  - Bremsstrahlung photons for SPECT
  - Low abundance positrons for PET

Dewaraja et al, Med Phys 2017;6363-6376
Y-90 PET reconstruction, quantification

- Commercial reconstruction tools sufficient, but need TOF+RR
  - Phantom studies to identify optimal reconstruction parameters
- Direct Bq/mL from $^{90}$Y PET, but need partial volume correction (PVC)
  - Quantification accuracies within 5% for healthy liver within 10% for ‘lesions’ with PVC. Similar results by others*

* Willowson et al, QUEST study, EJNMMI 2015  
D’Arienzo et al, EJNMMI Res 2017
Y-90 RE: Do we need a radiologist for segmentation?

- Current semi-automatic segmentation tools sufficient for organs, but typically need radiologist guidance for lesions

Lesion defined by Radiologist on MR: 30 cc

Radiologist defined lesion: 30 cc
- SPECT 3% threshold: 1100 cc
- SPECT 6% threshold: 807 cc
- SPECT 40% threshold: 16 cc
- SPECT 20% threshold: 44 cc
- PET Gradient based: 30 cc

Lesion defined by Radiologist on MR: 30 cc
Y-90 RE dosimetry: Do we need Monte Carlo?

- Comparison of estimates from MC with estimates from voxel S value kernels and local energy deposition (LDM)

<table>
<thead>
<tr>
<th></th>
<th>DPM* Monte Carlo Absorbed Dose (Gy)</th>
<th>Difference compared with Local Energy Deposition</th>
</tr>
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<tbody>
<tr>
<td>8 mL sphere</td>
<td>191</td>
<td>2.5%</td>
</tr>
<tr>
<td>16 mL sphere</td>
<td>246</td>
<td>1.6%</td>
</tr>
<tr>
<td>29 mL ovoid</td>
<td>249</td>
<td>0.8%</td>
</tr>
<tr>
<td>Healthy liver</td>
<td>59</td>
<td>-1.6%</td>
</tr>
<tr>
<td>L Lung</td>
<td>4.5</td>
<td>-144% (-10%)</td>
</tr>
<tr>
<td>R Lung</td>
<td>4.8</td>
<td>-144% (-6%)</td>
</tr>
</tbody>
</table>

TRUE DOSE-MAP
90Y PET/CT DOSE-MAP (MONTE CARLO)
90Y PET DOSE-MAP (LOCAL ENERGY DEP.)

Y-90 RE patient dosimetry example

- **Segmentation:**
  - Lesion (radiologist), liver (semi-auto)
- **Registration & transfer contours**
  - Commercial software
- **Activity map:** direct PET Bq/mL
- **Voxel-level dosimetry (LDM)**
  \[ D(\text{Gy}) = 49.3 \times \frac{A \text{ (GBq)}}{M \text{ (kg)}} \]
- **Mean value PVC using RCs**
- **Uncertainty**

\[
\frac{u(D_{VOI})}{D_{VOI}} = \sqrt{\left(\frac{u(A_{VOI})}{A_{VOI}}\right)^2 + \left(\frac{u(M_{VOI})}{M_{VOI}}\right)^2 - 2 \frac{u(A_{VOI}, M_{VOI})}{A_{VOI}M_{VOI}}} 
\]

* Gear et al, EJNMMI 2018
Lu-177 PRRT example: reconstruction and quantification

- Image acquisition: ME collimator, typically using 208 keV peak (10%). Also 113 keV peak (6%)
- SPECT reconstruction: standard OS-EM
- Quantification:
  - Point source or phantom based calibration
  - Some new systems have ‘in-built’ Lu-177 calibration
    - Image in units of Bq/mL
  - RC still needed

Ljungberg et al, MIRD 26. JNM 2016
Calibration factor for absolute SPECT quantification

- NIST recommendation\(^1\) (0.9 % uncertainty)
  - 3 mL \(^{177}\text{Lu}\) in a 10 mL Schott vial: CRC-15R setting 449x10
- Transferring calibration to a new geometry (10 mL syringe)
- With the syringe in the dose calibrator adjust setting to get correct reading
  - for 3 mL in syringe: 480 x 10
- Calibration Factor
  - 12.9 cps/MBq (head 1), 13.4 cps/MBq (head 2)
  - within 1 % of manuf. specified value

Lu-177 PRRT patient example: time-activity

- SPECT/CT day 0, 1, 4, 5
- Co-registered time-points
- Activity directly from SPECT or apply calibration
- Apply RCs for PVC
- Mono- or bi-exponential fit

<table>
<thead>
<tr>
<th>RC</th>
<th>Activity (Uncert.) MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>Lesion</td>
<td>0.93</td>
</tr>
<tr>
<td>R kidney</td>
<td>0.96</td>
</tr>
<tr>
<td>L kidney</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Baseline MRI, Ga-68 PET/CT, Defined on CT of SPECT/CT, dose map (Gy)

lesion time-activity
kidney time-activity
Do we need multi-time points? single-point dosimetry

• Recently reported by Madsen for Y-90 DOTATOC & Hanscheid et al, for Lu-177 PRRT

• The time integrated activity estimated from a single activity measurement and population mean kinetics parameters

\[ \hat{A}^* = A(T)e^{\hat{k}T}/\hat{k} \]

ideal sampling point \( T = \tau \ (1/k) \)

For Lu-177 DOTATATE ~ 96 h
Lu-177 DOTATATE: Do we need multiple time points?

- University of Michigan pilot study: absorbed doses from SPECT/CT at 4 time points vs. at a single time point.
Do we need to image after each cycle?

- Comparison of dosimetry performed after 2 consecutive cycles
Lu-177 PRRT dosimetry simplification: ignore cross dose?

- How important is cross dose?
  - Betas have short path length, gammas have low intensity

- 500 patients with NETs treated with Lu-177 DOTATATE
  - Kidney self-dose from SPECT/CT. Cross dose from WB imaging

- Kidney self-dose 4.2 Gy (1.0 - 9.8) cross-dose 0.1 Gy (0.0 - 0.5)
  - < 10% cross dose in 97% of patients
  - > 10% only in patients with high tumor burden

- Important for tumor?
  - Simulation study showed minimal differences between MC and local energy absorption

Lu-177 PRRT simplification of dosimetry: AD vs. BED?

• BED was calculated as

\[
\text{BED} = \sum D_i + \frac{\beta}{\alpha} \frac{t_{rep}}{t_{1/2}} + \frac{t_{eff}}{t_{1/2}} \sum D_i^2
\]

- \(D_i\) is absorbed dose for cycle \(i\)
- \(\alpha/\beta = 2.6\) Gy and \(t_{rep} = 2.8\) h

• Results should be considered as approximations

- \(\alpha/\beta\) values used not specific to kidney and NETs

• 500 patients: BED only slightly higher than AD. Difference increases with absorbed dose

‘The use of a refined absorbed dose methodology led to the finding of a clear kidney dose-response relationship in patients treated with 90 Y-DOTATOC. Our data provide evidence that patient-specific anatomy and dose-rate effects cannot be neglected. The BED model appears to be a reliable predictor of toxicity and could thus be helpful in implementation of individual treatment planning’
Several software options now available that facilitate patient specific dosimetry

Characterization of Noise and Resolution for Quantitative 177Lu SPECT/CT with xSPECT Quant

Sequential xSPECT Quant study following 177Lu DOTATATE therapy in metastatic NET for dosimetry

Dosimetry methods and clinical applications in peptide receptor radionuclide therapy for neuroendocrine tumours: a literature review

Validation of post-treatment PET-based dosimetry software for hepatic radioembolization of Yttrium-90 microspheres

Phantom and clinical evaluation of the effect of full Monte Carlo collimator modelling in post-SIRT yttrium-90 Bremsstrahlung SPECT imaging
Summary: Translating Patient Specific Dosimetry to the Clinic

• Do we need specialized reconstruction software & calibrations?
  - Commercial software sufficient in several cases. Choose parameters.

• Do we need a radiologist for target segmentation?
  - Commercial tools sufficient for organs, but typically not for lesions

• Do we need multiple-imaging time points?
  - Single point methods possible, but must validate for each application

• Do we need Monte Carlo?
  - LDM sufficient for soft tissue and pure β emitters or low intensity Photon emitters.
  - Consider voxel size, noise

<table>
<thead>
<tr>
<th></th>
<th>β (Mev) Max</th>
<th>β (Mev) Avg.</th>
<th>Max β range (mm)</th>
<th>γ (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-131</td>
<td>0.6</td>
<td>0.18</td>
<td>2</td>
<td>364 (82%) 637 (7%)</td>
</tr>
<tr>
<td>Y-90</td>
<td>2.3</td>
<td>0.94</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Lu-177</td>
<td>0.5</td>
<td>0.13</td>
<td>1.5</td>
<td>208 (10%) 113 (6%)</td>
</tr>
</tbody>
</table>
Thank You
To patients who volunteered for the presented clinical studies.

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