Dosimetry in radioembolization therapy of hepatic malignancies: value of post-therapy imaging-based dose estimates

Yuni K Dewaraja

Department of Radiology
University of Michigan

Dosimetry in Therapeutic Nuclear Medicine. IDOS 2019, IAEA, Vienna, Austria
Y-90 Radioembolization: why do dosimetry?

• Pre-treatment dosimetry
  • For therapy planning (theranostics) to improve efficacy/toxicity
    • Imaging surrogate used (e.g. Tc-99m MAA)
      - Mostly used to assess lung shunt
      - Potential differences between MAA and microsphere distribution

• Peri-(during) and post-treatment dosimetry
  • During
    • Real time dosimetry to adjust activity during treatment
  • Post
    • Verification: assess safety/response (early intervention)
    • Documentation: important when retreating with radiation
    • Establishing dose vs. effect for future
Current clinical approach to Y-90 RE treatment planning

• Glass:

\[ A_{\text{inj}}[^{\text{GBq}}] = D_{\text{liver}}[^{\text{Gy}}] \times \text{mass}_{\text{liver}}[^{\text{kg}}] / 49.4 \]

with LS * \( A_{\text{inj}} \) < 0.61 GBq and \( D_{\text{liver}} \) typically 100 - 120 Gy

• Resin:

BSA: \( A_{\text{inj}}[^{\text{GBq}}] = \text{BSA} - 0.2 + \text{Tumor Volume/Liver Volume} \)

Empiric: \( A_{\text{inj}}[^{\text{GBq}}] = \text{Liver involvement activity} \times \text{LSM} \times \text{LPM} \)

Partition model:

\[
D_{\text{NormalLiver}} = \frac{49.4 \times A_{\text{inj}}(1 - L)}{m_{\text{NormalLiver}} + \frac{T}{N} \times m_{\text{Tumor}}} 
\]

• Current approaches: promising response rate but poor survival

- Motivation for individualized dosimetry guided treatment

Patient specific dosimetry in Y-90 radioembolization

- Practical to implement clinical dosimetry
  - Microspheres do not re-distribute
    - Need only a single imaging time point. Can do while patient in recovery
  - No γ-rays and short β range relative to resolution
    - Voxel-level dosimetry assuming local energy deposition
  - Liver relative calibration option

But …

- Quantitative imaging is complex
  - Differences in MAA particles vs. microspheres
  - Y-90 ‘pure’ β emitter.
    - SPECT via bremsstrahlung photons
    - PET via low yield positron
Challenges of Y-90 SPECT and PET imaging for dosimetry

- **Bremsstrahlung SPECT:**
  - Downscatter of high energy photons
  - Cannot correct with simple energy windows

- **Y-90 PET:**
  - Low true coincidence counts, high randoms
  - Quantification improved with TOF
Y-90 SPECT vs PET

- SPECT: higher visibility lower resol.
  - w/o scatter corr.
  - w/ MC scatter corr.
- PET: higher resolution, high noise
  - w/o TOF and RR
  - w/ TOF and RR

Profile across lesion center

<table>
<thead>
<tr>
<th>Relative Counts</th>
<th>Pixel</th>
<th>TOF PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>30</td>
<td>SPECT w/o SC</td>
</tr>
<tr>
<td>0.4</td>
<td>60</td>
<td>SPECT w/ SC</td>
</tr>
<tr>
<td>0.6</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>0.8</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>-</td>
</tr>
</tbody>
</table>
Patient example: Y-90 PET vs. SPECT based dosimetry

<table>
<thead>
<tr>
<th></th>
<th>Mean Dose Gy</th>
<th>D10 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Y-90 SPECT</td>
<td>SPECT w/ SC</td>
</tr>
<tr>
<td>Lesion</td>
<td>269</td>
<td>335</td>
</tr>
<tr>
<td>Healthy Liver</td>
<td>77</td>
<td>61</td>
</tr>
</tbody>
</table>
Value of pre-treatment dosimetry
Why do dosimetry? Pre-treatment dosimetry for planning

- **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 planning based on MAA Tumor >205 Gy, non-tumoral liver<120 Gy, lung<30 Gy
  - 37% received higher activity
  - **Improved Survival:**
    - TD < 205 Gy, 4 mo (3–5 mo)
    - TD > 205 Gy, 18 mo (8–29 mo) ($P = 0.005$)

- No increase in toxicity

*Garin et al, JNM 2012:255-63*
Value of post-treatment dosimetry
Why post-RE dosimetry? Real-time to adjust activity

- Tailoring based on patient’s physiology at treatment time
- **Single day** procedure: time ~ 4 h
  - Initial $^{90}\text{Y}$ infusion based on BSA model (33 mCi)
  - $^{90}\text{Y}$ PET/CT dosimetry
    - liver: 6 Gy, tumor: 52 Gy
  - Repeat to deliver a total 120 Gy to tumor based on PET estimate
- Technically challenging
Why voxel-level post-treatment dosimetry? Verification

Baseline: Lesion with necrotic center, enhancing rim

PET based dose map

Under dosed < 20 Gy

6 month follow-up: poor response

DVH for PET based contour (240 mL) mean 253 Gy

DVH for CT contour (525 mL) mean 83 Gy
Why voxel-level post-RE dosimetry?
Intervention: boost under-dosed voxels with EBRT

EBRT target minimum dose is ~50 Gy and uniform.

Necrotic core now covered. Small increase in non-tumoral liver mean dose: 21 Gy to 31 Gy

After 90Y

EBRT 50 Gy Boost

90Y+EBRT

• Courtesy of Justin Mikell, Radiation Oncology, University of Michigan
Why post-therapy dosimetry? dose-effect studies

• Absorbed dose - effect relationships seldom investigated

  The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy

  Lidia Strigari · Mark Konijnenberg · Carlo Chiesa · Manuel Bardies · Yong Du · Katarina Sjögreen Gleisner · Michael Lassmann · Glenn Flux

• Pub Med search: dose-effect correlation in 48 out of 79 studies
• However, small sample sizes and different dosimetry methods
• Post-therapy imaging should be used for dose-effect
# Dose - effect in $^{90}$Y microsphere RE of liver cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Imaging</th>
<th>Endpoint</th>
<th>Threshold dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garin</td>
<td>36</td>
<td>TcMAA SPECT</td>
<td>PFS, EASL (PR+CR)</td>
<td>205 (lesion)</td>
</tr>
<tr>
<td>Mazzaferro</td>
<td>52</td>
<td>TcMAA SPECT</td>
<td>EASL (PR+CR)</td>
<td>500 (tumor)</td>
</tr>
<tr>
<td>Chiesa</td>
<td>52</td>
<td>TcMAA SPECT</td>
<td>EASL (PR+CR) liver decomp 50% TCP 15% NTCP</td>
<td>250, 1000 Gy (small, large tumor), 75 (liver)</td>
</tr>
<tr>
<td>Chansanti</td>
<td>15</td>
<td>TcMAA SPECT</td>
<td>mRECIST (PR+CR)</td>
<td>191 (tumor)</td>
</tr>
<tr>
<td>Chang</td>
<td>35</td>
<td>90Y PET/CT</td>
<td>mRECIST (PR+CR)</td>
<td>225 (tumor)</td>
</tr>
<tr>
<td>Kappadath</td>
<td>34</td>
<td>90Y SPECT/CT</td>
<td>mRECIST 50% TCP</td>
<td>160 (tumor)</td>
</tr>
<tr>
<td>Strigari</td>
<td>73</td>
<td>90Y SPECT</td>
<td>50% TCP (PR+CR) 5% &gt; G2 toxicity</td>
<td>150 (tumor), 50 Gy BED (liver)</td>
</tr>
<tr>
<td>Sangro</td>
<td>45</td>
<td>REILD</td>
<td></td>
<td>40 (liver)</td>
</tr>
<tr>
<td>Campbell</td>
<td>12</td>
<td>TcMAA SPECT</td>
<td>FDG res. &gt; 50%</td>
<td>260 (tumor)</td>
</tr>
<tr>
<td>Flamen</td>
<td>8</td>
<td>TcMAA SPECT</td>
<td>FDG res. &gt; 50%</td>
<td>46 (tumor)</td>
</tr>
<tr>
<td>Song</td>
<td>23</td>
<td>90Y PET/CT</td>
<td>PFS, RECIST</td>
<td>200 (tumor)</td>
</tr>
</tbody>
</table>

90Y PET/CT dose - outcome study at Univ. Michigan

• Goal: Construct tumor control probability (TCP) models for future treatment planning. Also evaluate non-tumoral liver dose-toxicity
• Glass microspheres. Standard activity.
• 90Y PET/CT imaging. Parameters optimized using phantoms
• Lesions defined on baseline CT, MR by radiologist
• Monte Carlo based voxel-level absorbed dose, BED, EUD
• RECIST, mRECIST at first follow-up
• Initial results reported in Dewaraja et al, JNM 2019 (in press)
  • 89 lesions (28 treatments) dose - shrinkage
  • 42 lesions (14 treatments) TCP analysis with mRECIST (both primary liver cancer and mets combined for analysis)
90Y PET/CT dose - effect study: optimizing imaging parameters

- Phantom with clinically relevant 90Y distribution, count-rates

- RCs

- Considering noise and AR, chose 1i (21ss) OSEM with filter

Dewaraja et al. JNM 2019 (in press)
Patient example: Y90 PET/CT based dosimetry

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Volume (cc)</th>
<th>Max Dose (Gy)</th>
<th>Min Dose (Gy)</th>
<th>Mean Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion 1</td>
<td>11</td>
<td>1256</td>
<td>23</td>
<td>488</td>
</tr>
<tr>
<td>Lesion 2</td>
<td>1</td>
<td>504</td>
<td>99</td>
<td>313</td>
</tr>
<tr>
<td>Lesion 3</td>
<td>2</td>
<td>674</td>
<td>177</td>
<td>407</td>
</tr>
<tr>
<td>Lesion 4</td>
<td>5</td>
<td>825</td>
<td>69</td>
<td>404</td>
</tr>
<tr>
<td>Healthy Liver</td>
<td>1140</td>
<td>780</td>
<td>0</td>
<td>33</td>
</tr>
</tbody>
</table>
Y90 PET-CT study: Dose - Shrinkage

```
<table>
<thead>
<tr>
<th></th>
<th>Mean [Range]</th>
<th>Mean [Range]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responding* lesions</td>
<td>Nonresponding* lesions</td>
<td></td>
</tr>
<tr>
<td>AD (Gy)</td>
<td>559 [90 - 1271]</td>
<td>183 [2 - 574]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BED (Gy)</td>
<td>1129 [102 - 4337]</td>
<td>255 [2 - 809]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* mRECIST criteria

Dewaraja et al. JNM 2019 (in press)
Y90 PET/CT study: TCP analysis of clinical response data

- Logit link function for (empiric) TCP model

- mRECIST binary outcome

- AD, BED, EUD covariates
  - $\alpha$ from ML

- AUC used to evaluate predictive accuracy

Dewaraja et al. JNM 2019 (in press)
**TCP Analysis: Results for EU(BED)**

- EU(BED) performed best in terms of AUC
- But, AD was comparable (AUC 0.88 vs 0.90)
## Y90 PET/CT study: TCP analysis results

<table>
<thead>
<tr>
<th>Dose Metric</th>
<th>AUC</th>
<th>TCP50 (Gy)</th>
<th>TCP90 (Gy)</th>
<th>Sensitivity [Specificity]**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean AD</td>
<td>0.88</td>
<td>292</td>
<td>554</td>
<td>0.75 [0.89]</td>
</tr>
<tr>
<td>EUD, $\alpha = 0.0002^*$</td>
<td>0.88</td>
<td>290</td>
<td>551</td>
<td>0.75 [0.89]</td>
</tr>
<tr>
<td>Mean BED</td>
<td>0.87</td>
<td>441</td>
<td>953</td>
<td>0.76 [0.89]</td>
</tr>
<tr>
<td>EUBED, $\alpha = 0.0005^*$</td>
<td>0.90</td>
<td>442</td>
<td>856</td>
<td>0.75 [0.89]</td>
</tr>
</tbody>
</table>

*Maximum likelihood estimate of $\alpha$

**Calculated using predicted TCP of 50% as threshold for predicted response

• TCP50/90 = dose corresponding to predicted TCP of 50% or 90%
Non-tumoral liver ADs: exploratory analysis

• Median non-tumoral liver AD was 38 Gy (range 8-63) for cirrhotic livers and 51 Gy (range 10 to 83) without cirrhosis

• No grade 4 toxicities. New grade 3 toxicity at 3 months: AST (0/21), ALT (0/21), ALP (1/21, cirrhotic liver), bilirubin (2/21, both cirrhotic). Similar at 6 months.

• No statistically significant correlation between non-tumoral liver AD and the liver function test levels, CTCAE classifications, or ascites classification, controlling for cirrhosis.

Dewaraja et al. JNM 2019 (in press)
Conclusion: value of dosimetry in Y-90 RE

• Pre-treatment dosimetry:
  - Garin et al: clear improvement in OS with planning ✅
  - Concordance between MAA and microspheres: mixed results ❌
    • Need better surrogate

• Post-treatment dosimetry: Activity and image (mostly) done
  Just do dosimetry calculation ...
    - Allows verification and early intervention (e.g. SBRT) ✅
    - Documenting ADs, important when re-treating with radiation
    - Dose - outcome for future planning ✅
Thank You

Funding from NIH(NIBIB) R01EB022075 is acknowledged

yuni@umich.edu