Predictive dosimetry: BSA vs. Partition Model

S. Gnesin
Institute of Radiation Physics,
Lausanne University Hospital, Lausanne, Switzerland

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• Which dosimetry ?
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Introduction to Y-90 Radioembolization

Yttrium-90 microsphere radioembolization is a valuable therapeutic option in unresectable hepatocellular carcinoma (HCC).

Tumor vs. non-tumor differential vascularization

Radioembolization of hepatic tumors, A. Kennedy, J Gastrointest Oncol 2014;5(3):178-189
Two devices are clinically available

**glass-spheres**
Therasphere®
- Similar size (~ 30 μm)
- Different specific activity
  - $4 \times 10^5$ glass-spheres/GBq

**Resin-Spheres**
SIRTeX SIR-Spheres®
- Similar size (~ 30 μm)
- Different specific activity
  - $2 \times 10^7$ resin-spheres/GBq

→ Different microsphere density

! Differences in activity deposition heterogeneity and embolic effect!
Therapy preparation via Tc-99m MAA administration

**Catheter fluoroscopy guided procedure**

Tc-99m MAA SPECT/CT acq.

Tumour (TV) and non-tumour volume (NTV) delineation

Average signal in:
TV ($S_{TV}$) and NTV ($S_{NTV}$)

Tum. to Non-Tum. Ratio (TNR)

$$\text{TNR} = \frac{S_{TV}}{S_{NTV}}$$

**Post-treatment 90Y TOF PET acq.**

Post-treatment;
- **90Y Bremmsstrahlung SPECT/CT acq.**
  For target deposition and possible extrahepatic shung assessment
Why dosimetry?

The aim is to **treat the tumor** while **preserving the liver function**

- Radiobiological effects are dose dependent
- Response to treatment:
  - Lesion response (**efficacy**): dose/response correlation
  - Spare healthy tissue and/or avoid/limit toxicity (**safety**)

Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study


Joint Hepatocellular Carcinoma Study Group, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong.

Scientific evidences (1)

- HCC patients
- Resins spheres

- the treatment was well tolerated
- Tumour regression was found to be dose related.
- Progressive or static disease occurred in a higher proportion of patients whose tumours received 120 Gy

We conclude that yttrium-90 microsphere therapy is:
- safe
- tumour response is dose related.

- A tumour dose of > 120 Gy is recommended.
Efficacy: Dose-response correlation (HCC/glass spheres)

EASL response
Increase with dose to the lesion

Safety: Normal Tissue Complication Probability (HCC/glass spheres)

Normal tissue complication probability (NTCP) as a function of the mean absorbed dose $D$ (target volume)

Acceptable LD risk of 15 % corresponds to the main planning limit of 75 Gy to whole parenchyma
Scientific evidences (3)

SIRT 90Y on HCC: Time to progression (TTP) and overall survival (OS)

Response (TTP, OS) stratification according to lesion delivered dose

Conclusion: **Dosimetry based on MAA SPECT/CT was able to accurately predict response and survival in patients treated with glass microspheres**

Dose–Response correlation in colorectal cancer liver metastases
(Resin spheres, administered activity according to BSA)

FIGURE 3. Survival curves stratified on metabolic liver response and average liver tumor dose.
(A) Patients with (blue line) metabolic liver response (50% decrease in TLG* at 1 mo after treatment) showed significantly longer median OS than nonresponders (red line). (B) Patients with average liver tumor dose exceeding 60 Gy (blue line) showed trend of longer median OS than those with lower liver tumor dose (red line).

Insights into the Dose–Response Relationship of Radioembolization with Resin 90Y-Microspheres:
A Prospective Cohort Study in Patients with Colorectal Cancer Liver Metastases
Conclusions: Lesions receiving an average dose greater than 50 Gy are likely to have a significant response.
Dosimetry of 90Y (self S-Factor from Olinda)

\[ T_{1/2}[h] = 64.1[h] \]

\[ TIAC_s = \frac{T_{1/2}[s]}{\ln(2)} \]

\[ S_{Liver} = 7.83 \times 10^5\,[mGy\times MBq^{-1}\times s^{-1}] \]

\[ m_{Liver} = 1.91[Kg] \]

\[ m_{Liver} = 1.91[Kg] \]

\[ E_{mean} = 0.94[MeV] \]

\[ |e| = 1.602 \times 10^{-19}[C] \]

\[ TIAC_s \times E[J] = 92.5[h] \times 3.6[Msi\times h^{-1}] \times 0.94[MeV] \times 0.16[J\times EeV^{-1}] = ? \]

\[ \overline{D}_{[GY]}(r_T) = \frac{A_0[GBq]}{m_{rT}[Kg]} \times 50[J\times GBq^{-1}] \]
90Y radioembolization: Which dosimetry?

**Resin-spheres dosimetry: BSA**

Body Surface Area (BSA)

\[
A_{BSA} (GBq) = \left[(BSA - 0.2) + \frac{V_{tum}}{V_{tum} + V_{non\,tum}}\right] \times \left(\frac{V_{target\,liver\,(tum+non\,tum)}}{V_{total\,liver}}\right)
\]

fractional tumor burden

Liver involvement (mBSA)

**Target: right liver (RL)**

Patient of 1.8m and 80 kg \(\rightarrow\) Patient BSA = 2m²

- \(V_{tot\,liver} = 2000\) mL
- \(V_{RL} = 1500\) mL (75% of total liver)
- \(V_{TV} = 450\) mL (30% of the target volume =RL)
- \(V_{NTV} = 1050\) mL

\[
A_{BSA} = ( (2-0.2) + (450/1500) ) \times 0.75 = 1.575\ GBq
\]

\[
D_{mean,RL} = (50\ Gy/GBq.kg \times 1.575\ GBq)/(1.5\times1.04\ kg) = 50.5\ Gy
\]

\[
D_{TV} = 94\ Gy
\]

\[
D_{NTV} = 31.3\ Gy
\]
\[ A_{PM}(GBq) = \frac{D_{NTV}(Gy) \times M_{TV}(g)}{49670} \times \frac{R_{TV/NTV} \times (V_{tum}/V_{non-tum})}{(1 - L)} \]

\[ D_{TV}(Gy) = \frac{49670 \times A_{TV}(GBq)}{M_{TV}(g)} \]

\[ D_{NTV}(Gy) = \frac{49670 \times A_{NTV}(GBq)}{M_{NTV}(g)} \]

Target: right liver (RL)

\[ V_{tot \ liver} = 2000 \ mL \]

\[ V_{RL} = 1500 \ mL \ (75\% \ of \ total \ liver) \]

\[ V_{TV} = 450 \ mL \ (30\% \ of \ the \ target \ volume =RL) \]

\[ V_{NTV} = 1050 \ mL \]

\[ A_{PM} \ with \ a \ limit \ of \ 40 \ Gy \ to \ NTV \]

\[ A_{PM,40Gy} = 2.01 \ GBq \]

\[ D_{TV} = 120 \ Gy \quad D_{NTV} = 40 \ Gy \quad D_{mean,RL} = 64 \ Gy \]
**Glass-sphere dosimetry**

\[
A_{\text{Target}}(\text{GBq}) = \frac{D_{\text{Target}} \times M_{\text{Target}}(\text{kg})}{50}
\]

only morphologic input data (CT, MR)

Recommended \( D_{\text{Target}} = [80-150] \) Gy not account for TV, NTV and \( R_{\text{TV/NTV}} \)

Target: right liver (RL)

\[ V_{\text{tot liver}} = 2000 \text{ mL} \]
\[ V_{\text{RL}} = V_{\text{Target}} = 1500 \text{ mL (75\% of total liver)} \]
\[ V_{\text{TV}} = 450 \text{ mL (30\% of the target volume = RL)} \]
\[ V_{\text{NTV}} = 1050 \text{ mL} \]

\[
A_{\text{Target},120\text{Gy}} = 120 \times 1500 \times 1.03/50 = 3.71 \text{ GBq}
\]
\[ D_{\text{Target}} = 120 \text{ Gy} \quad D_{\text{NTV}} = 75 \text{ Gy} \quad D_{\text{TV}} = 225 \text{ Gy} \]

\[
A_{\text{Target},80\text{Gy}} = 80 \times 1500 \times 1.03/50 = 2.47 \text{ GBq}
\]
\[ D_{\text{Target}} = 80 \text{ Gy} \quad D_{\text{NTV}} = 50 \text{ Gy} \quad D_{\text{TV}} = 150 \text{ Gy} \]
\[ \text{TNR} = \frac{S_{TV}}{S_{TV}} = 3 \]

<table>
<thead>
<tr>
<th></th>
<th>Vol target</th>
<th>RTF = 3</th>
<th>Aadmin</th>
<th>D TV</th>
<th>D NTV</th>
<th>D target</th>
<th>A PM/A BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TV=5%</td>
<td>75</td>
<td>mL</td>
<td>mL</td>
<td>mL</td>
<td>mL</td>
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<tr>
<td>BSA (2m²)</td>
<td>1.38</td>
<td>120</td>
<td>40</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM 40</td>
<td>1.38</td>
<td>120</td>
<td>40</td>
<td>44</td>
<td></td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Glass 80</td>
<td>2.47</td>
<td>218</td>
<td>73</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass 120</td>
<td>3.71</td>
<td>327</td>
<td>109</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
\[
TNR = \frac{S_{TV}}{S_{TV}} = 6
\]

| BSA (2m²) | 1.38 | 121 | 35 | 44 | 1.14 |
| PM 40 | 1.57 | 240 | 40 | 50 |
| Glass 80 | 2.47 | 384 | 64 | 80 |
| Glass 120 | 3.71 | 576 | 96 | 120 |

This table shows the Vol target mL values for different conditions:

- TV = 5%: 75 mL
- TV = 10%: 150 mL
- TV = 30%: 450 mL
- TV = 50%: 750 mL
Tumour to Non-tumour liver Ratio (TNR)

CHUV cohort
50 treatment sessions
Mean: 4.4
Median: 3.5

A_{PM} / A_{BSA}

CHUV cohort
85 treatment sessions
Mean: 1.47
Median: 1.39
Y-90 Liver Radioembolisation: Predictive vs. post-treatment dosimetry

Predictive dosimetry based on $^{99m}$Tc-MAA SPECT/CT is used to predict:

- Dose to target volume: tumor and non tumor volumes
- dose-response in TV
- safety of the treatment $\rightarrow D_{NTV}$ vs. Toxicity

Quantitative agreement between **predictive dosimetry** based on $^{99m}$Tc-MAA SPECT/CT and **post-treatment dosimetry** based on $^{90}$Y TOF PET/CT for both TV and NTV in HCC patients

Experience with both resin- and glass-sphere devices
Concordance: predictive vs. post-treatment dosimetry in TV and NTV

**TV**

**Efficacy**

(A) Glass spheres

$r = 0.549, P = 0.08$

(B) Resin spheres

$r = 0.737, P < 0.001$

**NTV**

**Safety**

(A) Glass spheres

$r = 0.99, P < 0.001$

(B) Resin spheres

$r = 0.93, P < 0.001$

Concordance: predictive vs. post-treatment dosimetry in TV and NTV

**Tumor volumes**: On average good agreement for tumor dose deposition. But some cases showed important discrepancy.

**Non-tumor volumes**: Very good agreement (safety).

Conclusions

Scientific evidence support the need of dosimetry in Y-90 radioembolisation

**Dosimetry aims**

- **Efficacy**: tumoricidal effect of radiation → response in tumors
- **Safety**: Preserve hepatic function and avoid/limit toxicity

**Dosimetry approaches:**

- **BSA**: safely used in many clinical trials
  - Easy to implement (only radiology data are needed)
  - Tends to underdosage large tumors and large livers and overdose small tumors and small livers.

- **mBSA**: Incorporates the treated lobe volume (including tumor) into the formula.
  - suited for lobar/segmental treatment approach

- **Partition model:**
  - Includes emission data from Tc-99m MAA SPECT/CT (Tumor-to-nontumor ratio and lung shunt)
  - Need clear tumor/non tumor delineation
  - Results on average higher administered activities (compared do BSA and mBSA)
  - Potential benefits in terms of efficacy on tumors with simultaneous dose control on non-tumor parenchyma

\[
A_{BSA} (\text{GBq}) = \left[ (BSA - 0.2) + \frac{V_{tum}}{V_{tum} + V_{non\,tum}} \right]
\]

\[
A_{PM} (\text{GBq}) = \frac{D_{NTV} (\text{Gy}) \times M_{TV} (g)}{49670} \times \frac{R_{TV/NTV}}{(1 - L)} \times \frac{V_{tum}}{V_{non-tum}}
\]
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