Yttrium-90 Microsphere Therapy Planning and Dose Calculations

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Educational Objectives

- To understand the imaging sequence for Yttrium-90 microsphere therapy
- To understand calculation of lung shunt fraction and estimation of absorbed dose for lung and liver
- To become familiar with radiation safety and regulations surrounding Yttrium-90 microsphere therapy

Outline

- Overview of 90Y-microsphere therapy
- Patient imaging prior to 90Y-microsphere therapy
- Lung shunt fraction and lung dose calculations
- 90Y-microsphere therapy dose calculations
- Patient imaging post 90Y-microsphere therapy
- Three-compartment partition model
- Measurement of 90Y activity and admin. activity
- Radiation Safety
- Challenges and Summary
Trans-arterial delivery of radioactive \(^{90}\)Y-labeled microspheres via a catheter directly at disease sites (targeted infusion)

- Microspheres (20-30 µm) trapped in tumor capillary vessels due to their embolic size and targeted delivery

- \(\beta\) emissions from trapped \(^{90}\)Y-microspheres are capable of delivering lethal radiation doses to (proximal) neoplastic tissue while sparing (more distal) surrounding normal tissue

\(^{90}\)Y-microsphere Therapy

- \(^{90}\)Y-microsphere therapy usually target the liver

- \(^{90}\)Y-microsphere therapy takes advantage of the unique circulatory system in the liver
  - Portal vein (normal liver) & hepatic artery (tumor)

- Liver directed XRT are limited in scope
  - Radiation tolerance of normal hepatocytes < neoplastic tissue
  - Max. tolerated doses 30–40 Gy (Emami et al., IJROBP 21, 1993; McGinn et al., J Clin Onc 16, 1998)

- With \(^{90}\)Y-microspheres, total liver radiation doses up to 80 Gy were well tolerated with no hepatic radiation damage (Gray et al., Annals Oncology 12, 2001; Burton et al., Radiology 175, 1990)

- \(^{90}\)Y-microsphere therapy is approved by the FDA for the treatment of unresectable HCC and metastatic colorectal cancer

Properties of Yttrium-90

- Decay: \(^{90}\)Y (9.6, 64.1 hr) Zr-90; a pure \(\beta\) emitter
  - \(^{90}\)Y also emits \(\beta^+\) at low yields (~32 ppm) via internal pair-production

- \(\beta\) energy: 0.937 MeV (mean) and 2.28 MeV (max)

- Tissue penetration depth: 2.5 mm (mean) and 11 mm (max)

- \(^{90}\)Y deposits >90% of its energy in the first 5 mm of tissue

- \(^{90}\)Y deposits >90% of its energy in the first 14 days

- Permanently implanted \(^{90}\)Y can deliver radiation absorbed doses of ~50 Gy for 1 GBq of activity per kilogram of tissue
Commercial 90Y-microsphere Products

- SIR-Spheres®
  - Sirtex Medical, Sydney, Australia
  - Insoluble, biocompatible resin matrix
  - 30–35 µm glass spheres
  - 3 GBq (81 mCi) activity = 30–60 x 10⁶ spheres
  - Maximum activity available: 1 GBq (28 mCi)
  - Indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant chemotherapy (FUDR)

- TheraSphere®
  - MDS Nordion, Ottawa, Canada
  - Insoluble, biocompatible glass matrix
  - 20–30 µm glass spheres
  - 3 GBq (81 mCi) activity = ~1.2 x 10⁶ spheres
  - Maximum activity available: 20 GBq (540 mCi)
  - Indicated for radiation treatment or as a neoadjuvant for surgery or transplantation in patients with unresectable HCC

Liver is common site of metastases from a variety of neoplasms

Clinical trials on management of metastatic liver disease

Patient Imaging Prior to 90Y Therapy

- CT or MRI – Estimate target tumor mass
- IR – Set Int. (Interventional Radiology) – Selective embolize aberrant/hepatic vasculature
- NM – ⁹⁹mTc-MAA Planar and/or SPECT imaging
  - MAA used as a surrogate for microspheres
  - Assess TA catheter placement and perfusion of targeted tumors
  - Calculate lung shunt factor and lung dose
  - Determine treatment dose/activity

Lung Dose Consideration

- Prevention of radiation pneumonitis
  - Arterio-venous shunting in neoplastic vasculature
  - Tc-99m MAA scans used to assess lung shunt fraction and lung dose
  - Exclude patients with lung shunting that could result in lung radiation dose >25-30 Gy per treatment or >50 Gy cumulative

<table>
<thead>
<tr>
<th>SIR-Spheres</th>
<th>TheraSphere</th>
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</thead>
<tbody>
<tr>
<td>Lung Shunting</td>
<td>Lung Dose Limit</td>
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<tr>
<td>Reduction Factor</td>
<td>Gy</td>
</tr>
<tr>
<td>~30 %</td>
<td>No Reduction</td>
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<tr>
<td>10 % - 15 %</td>
<td>20 % reduction</td>
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<tr>
<td>15 % - 20 %</td>
<td>40 % reduction</td>
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<tr>
<td>&gt; 20 %</td>
<td>No Treatment</td>
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<tr>
<td>Lung dose per treatment &lt; 25 Gy</td>
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[Ho et al., EJNM 24, 1997]
Lung Shunt (LS) Fraction

- 2.4 mCi of \(^{99m}\)Tc-MAA delivered trans-arterially in IR suite
- Planar scintigraphy of Thorax and Abdomen (AP and PA)
- Calculate Lung Shunt (LS) using the following formula

\[
\text{Lung Shu}(\%) = \frac{\text{Lung Counts}}{\text{Liver Counts} + \text{Lung Counts}} \times 100
\]

- SIR-Spheres: geometric-mean images
- TheraSphere: not specified

Example Lung Shunt Calculation

\[
\text{LS} (\%) = \frac{\text{Lung GM-counts}}{(\text{Lung GM-counts} + \text{Liver GM-counts})} \times 100
\]

- SIR-Spheres:
  - LS < 10% (no modification)
  - 81 mCi \(^{90}\)Y activity limit
- TheraSphere:
  - 30 Gy lung dose limit
  - 222 mCi \(^{90}\)Y activity limit

\[
\text{LS} (\%) = \frac{77278}{(77278 + 973962)} \times 100 = 7.35\%
\]

\(^{90}\)Y-Therapy Planning: SIR-Spheres

- SIR-Spheres therapy doses are based on activity (not target radiation dose) – maximum activity of 81 mCi
- Empirical dosimetry models
  - Basic: Activity based on maximum activity & tumor fraction
  - BSA: Activity based on BSA & tumor involvement in liver
  - Lung Shunt modification: No treatment for LS > 20%
- Average liver dose < 80 Gy and lung dose < 25 Gy

<table>
<thead>
<tr>
<th>Tumor Fraction Modification</th>
<th>Recommended (^{90})Y activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Activity</td>
</tr>
<tr>
<td>&gt; 50 %</td>
<td>3.0 GBq (81 mCi)</td>
</tr>
<tr>
<td>25 - 50%</td>
<td>2.5 GBq (75 mCi)</td>
</tr>
<tr>
<td>&lt; 25%</td>
<td>2.0 GBq (67.5 mCi)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung Shunt Fraction Modification</th>
<th>Reduction Factor</th>
</tr>
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<td>Lung Shunting</td>
<td>Reduction Factor</td>
</tr>
<tr>
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</tr>
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Lung dose per treatment < 25 Gy
TheraSphere therapy doses are based on desired radiation dose to target mass, typically 120 to 150 Gy. Target mass = whole liver or liver lobe or liver segment. Patient-specific vasculature and catheter approach (common or left or right hepatic artery) to target mass defines target mass. Therapy must maintain lung dose lower than 30 Gy. Maximum activity depends on the Lung Shunt fraction.

**Dose Calculations: TheraSphere**

Max Activity (mCi) = $10 \times (\text{Gy}) \times \frac{\text{M}_{\text{lung}} \times \text{kg}}{49.7 \times \text{GBq/mCi}}$.

Activity (mCi) = $D_{\text{max}} \times \text{M}_{\text{lung}} \times \text{kg} / (1 - \text{LS}) \times 0.037 \text{ [GBq/mCi]}$ $\times 49.7 \text{ [Gy-kg/GBq]}$.

- Lung Shunt = 0.0735
- Maximum Activity = 222 mCi for lung dose = 30 Gy
- Liver dose [Gy] = 378 [Gy-kg] $\div \text{M}_{\text{lung}} \times \text{kg}$
  - 198 Gy for $\text{M}_{\text{lung}} = 1.91$ kg (MIRD Std. Man)
  - 154 Gy for $\text{M}_{\text{lung}} = 2.46$ kg (Weight-based)
  - 137 Gy for $\text{M}_{\text{lung}} = 2.76$ kg (CT-based)

Target liver dose = 120 Gy

$\Rightarrow$ 134.6 mCi of $^{90}$Y $\Rightarrow$ Lung dose delivered = 18.2 Gy
Dose Calculations: SIR-Spheres

<table>
<thead>
<tr>
<th>Tumor involvement (TI)</th>
<th>45%</th>
<th>Dose modification YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Shunt (LS)</td>
<td>7.35%</td>
<td>Dose modification NO</td>
</tr>
</tbody>
</table>

Basic model: 2.5 GBq (67.5 mCi)

BSA model: \(\text{BSA}(\text{m}^2) - 0.2 + \frac{\text{TI}(\%)}{100} = 1.85 \text{ GBq (50.1 mCi)}\)

Liver Dose (Gy) = \(A \text{ (GBq)} \times (1-\text{LS}) \times 49.7 \text{ (Gy-kg/GBq)} / M_{\text{liver}} \text{ (kg)}\)

= 44.7 Gy (< 80 Gy)

Lung Dose (Gy) = \(A \text{ (GBq)} \times \text{LS} \times 49.7 \text{ (Gy-kg/GBq)} / M_{\text{lung}} \text{ (kg)}\)

= 6.8 Gy (< 25 Gy)

Patient imaging on day of \(^{90}\)Y-Therapy

- Interventional Radiologist in Angiography suite
  - Verify catheter placement, assess flow
  - Deliver \(^{90}\)Y-microspheres

- NM Planar & SPECT \(^{90}\)Y-bremsstrahlung imaging
  - 70keV/200k window, MELL collimation, 228x228 matrix, 4.8 mm\(^2\) pixels, 128 views/360°, 28 s/view, non-circular step-shot
  - Assess delivery and distribution of \(^{90}\)Y-microspheres

- Follow-up evaluations at 2-3 months – CT or MRI

Pre and Post \(^{90}\)Y-microsphere therapy

<table>
<thead>
<tr>
<th>PRIOR</th>
<th>THERAPY</th>
<th>POST</th>
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<tbody>
<tr>
<td>CT 3-June-2008</td>
<td>Y-90 SPECT/CT 2-July-2008</td>
<td>CT 5-Sept-2008</td>
</tr>
<tr>
<td>Tc-99m MAA SPECT/CT 2-July-2008</td>
<td>Tc-99m MAA SPECT/CT 2-July-2008</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up evaluations at 2-3 months – CT or MRI
The physical properties of Yttrium-90 that makes it well suited for internal radionuclide therapy are that $^{90}$Y is a pure $\beta^-$ emitter with a maximum energy of 2.28 MeV corresponding to a:

- A. maximum tissue penetration depth of ~0.1 mm
- B. maximum tissue penetration depth of ~1 mm
- C. maximum tissue penetration depth of ~10 mm
- D. maximum tissue penetration depth of ~100 mm

The most common route of $^{90}$Y-microsphere administration for liver-directed therapy is:

- A. Peri-tumoral injection
- B. Implantation of $^{90}$Y-brachytherapy seeds
- C. Systematic administration via intravenous injection
- D. Trans-hepatic arterial administration via catheter


The lung shunt fraction (LSF) based on $^{99m}$Tc-MAA Planar images, used to estimate lung absorbed doses from $^{90}$Y-microsphere therapy, is calculated as:

- A. $\frac{\text{Lung Counts}}{\text{Liver Counts}} \times 100$
- B. $\frac{\text{Liver Counts}}{\text{Lung Counts}} \times 100$
- C. $\frac{\text{Liver Counts}}{\text{Lung Counts}} \times 100$
- D. $\frac{\text{Lung Counts}}{\text{Liver Counts}} \times 100$
The lung shunt fraction (LSF) based on $^{99m}$Tc-MAA Planar images, used to estimate lung absorbed doses from $^{90}$Y-microsphere therapy, is calculated as:

\[
\text{LSF} = \frac{\text{Lung Counts}}{\text{Liver Counts}} \times \frac{100}{\text{Lung Counts}}
\]


SAM Question 3: Answer

The typical range of planned absorbed doses to target liver tissue in $^{90}$Y-microsphere internal radionuclide therapies is around:

25% A. 40 – 60 cGy
24% B. 80 – 120 cGy
27% C. 40 – 60 Gy
25% D. 80 – 120 Gy

Limitations of Planning Dosimetry

- Not intended to calculate dose to individual tumors
- Uses conservative assumptions to ensure safety
- Assumes uniform uptake of microspheres in tumor and normal liver compartments

- Three-compartment model: lung, liver, and tumor
  - Accounts for differential uptake of microspheres in liver versus tumor
  - All tumors, independent of their sizes or locations, grouped into the tumor compartment with a single uptake value

Three-compartment Partition model

- Additional information needed
  - Tumor burden ($M_{\text{tumor}}$) and Tumor uptake ratio ($R$)

- Estimation of fractional Tumor Involvement ($T_I$)
  - $M_{\text{tumor}} = M_{\text{tumor}} + M_{\text{normal}}$
  - $M_{\text{tumor}} = T_I \times M_{\text{total}}$

- Estimation of Tumor Uptake Ratio ($R$)

  \[
  A_{\text{liver}} [\text{mCi}] = A [\text{mCi}] \times (1-LS) \times M_{\text{liver}} / (M_{\text{liver}} + R \times M_{\text{tumor}})
  \]

  \[
  A_{\text{tumor}} [\text{mCi}] = A [\text{mCi}] \times (1-LS) \times R \times M_{\text{tumor}} / (M_{\text{liver}} + R \times M_{\text{tumor}})
  \]

- Dose [Gy] = $A_{\text{organ}} [\text{GBq}] \times 49.7 \text{ [Gy-kg/GBq]} / M_{\text{organ}} [\text{kg}]$

Example Calculation: Dose

- $LS = 7.35$
- Total Activity = 222 mCi
- Total liver = 2.76 kg
- $T_I = 45$
- $T/N: R = 632.9/32.8 = 19.3$

- Normal Liver
  - Mass = 1.52 kg
  - Activity = 12.3 mCi
  - Dose = 14.7 Gy

- Tumor
  - Mass = 1.24 kg
  - Activity = 193.4 mCi
  - Dose = 294.5 Gy

- Prior estimate of liver dose = 137 Gy with $T/N=1$
Three Compartment Model Dose Estimates

- 3CM doses are relatively insensitive to tumor uptake threshold levels
- 3CM yielded higher doses to tumor and lower doses to normal liver compared to BSA for both $^{99m}$Tc-MAA and $^{90}$Y-bremsstrahlung SPECT/CT
- Differences in calculated dose between the 3CM and BSA models are larger for the $^{99m}$Tc-MAA scans than with the $^{90}$Y scans

Significant correlation (p<0.001 @75% isocount threshold) was observed between the $^{90}$Y and $^{99m}$Tc-MAA tumor dose estimates but not for normal liver dose estimates

The $^{90}$Y images yielded lower estimates for tumor doses (72% on average at 75% threshold) and higher normal liver doses (150% on average at 75% threshold)

$^{90}$Y-PET/CT Images

- $^{90}$Y also emits $\beta^+$ at low yields (31.9 ±0.5 ppm) via internal pair-production of $0^–0^+$ transition of $^{90}$Zr

(Greenberg & Deutsch 1956, Selwyn et al, 2007)
**Assay of ⁹⁰Y Activity**

- Dose calibration setting determined on-site with calibrated ⁹⁰Y activity

<table>
<thead>
<tr>
<th>Dose Calibration S/N</th>
<th>Calibration Number</th>
</tr>
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<tbody>
<tr>
<td>3172</td>
<td>47 x 10</td>
</tr>
<tr>
<td>3173</td>
<td>47 x 10</td>
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<tr>
<td>3174</td>
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<td>3176</td>
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<tr>
<td>3177</td>
<td>47 x 10</td>
</tr>
<tr>
<td>3178</td>
<td>47 x 10</td>
</tr>
</tbody>
</table>

- SIR-Spheres
  - Activity delivered as 81 mCi microspheres in water, 5 ml total volume
  - Draw microsphere solution by volume to desired activity

1. Check activity, by the number of ⁹⁰Y to calculate net activity
2. Calculate volume required for the prescribed dose:
   - Dose: Prescribed dose = 16 mCi
   - Concentration = 3 ml required
   - Original activity = 34 mCi
   - Residual 34 mCi in dose vial = 46 mCi in syringe

**Assay of ⁹⁰Y Activity**

- TheraSphere
  - Modification of the delivered activity is not allowed
  - Ordered activity would account for day/time of therapy

**Calculation of Administered Activity**

- Percentage of activity delivered to the patient can be based on ion-chamber exposure rate measurements
  - Before administration: dose vial in acrylic shield
  - After administration: the 2L Nalgene jar with beta shield containing waste and residual activity

- The percentage of activity delivered to the patient

\[
\text{Activity Delivered (%)} = \frac{\text{Activity Delivered (mCi)}}{\text{Dose Vial Activity (mCi)}} \times \frac{100}{1}
\]

- Activity delivered to patient

\[
\text{Activity Delivered (mCi)} = \text{Dose Vial Activity (mCi)} \times \text{Activity Delivered (%)} \times \frac{100}{1}
\]
Radiation Safety

- **Transport**
  - Acrylic shield will stop all beta emission and keep exposure rate low
  - ≤2 mR/hr at 1 m for up to 300 mCi of activity in acrylic shield

- **During administration**
  - Highest potential for exposure is to administering staff in IR suite when spheres are located in catheter between vial and patient
  - Stand behind shield and maintain distance

- **Survey personnel leaving the room with GM survey meter**

- Store radioactive material until the container surface radioactivity cannot be distinguished from background

- Long-lived contaminants $^{90}$Y and $^{88}$Y may be present with reactor production of $^{90}$Y
  - Long-lived radioactive by-products may not be a problem using carrier free $^{90}$Y from a $^{90}$Sr generator

Some Challenges for $^{90}$Y-Therapy

- **ROIs on 2D Planar images introduce uncertainties**
  - Estimate lung shunt fraction and lung dose
  - Split dose calculation – lobar separation of liver not visualized

- **MAA is a sub-optimal surrogate for microspheres**
  - Biologic degradation time 1–3 hours → free $^{99m}$Tc-pertechnetate
  - Free $^{99m}$Tc biodistribution differs from MAA; thyroid & stomach uptakes free $^{99m}$Tc → introduce error in LSF
  - Non-spherical shape; Size range 10 to 100 µm

- **Additional objective measures of response**
  - Tumor volume reduction is the mainstay (Gray et al., Aus & NZ J Surgery 62, 1992; Van Hazel et al., J Sur Onc 88, 2004; Lau et al., IJROBP 40, 1998; Sangro et al., IJROBP 66, 2006)
  - Metabolic response: observed in higher proportion than an CT-based anatomical response for mCRC (p<0.0002) (Wong et al., EJNMMI 29, 2002)
  - Functional response: >50% change in TLG at 6 weeks for mCRC lesions with tumor doses >46 Gy (Flamen et al., PMB 53, 2008)
Summary

- *Y*-microsphere therapy is a promising and an increasingly popular treatment option for palliative care of patients with metastatic liver disease and unresectable HCC
- Decreased tumor volumes and increased time to tumor progression have been reported
- New objective measures of response are under investigation
- Improved imaging and dosimetry are beginning to yield more accurate dose estimates