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
- Calculation of the lung shunt fraction
- 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

90Y-microsphere Therapy

- Trans-arterial delivery of radioactive 90Y-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 90Y-microspheres are capable of delivering lethal radiation doses to (proximal) neoplastic tissue while sparing (more distal) surrounding normal tissue
90Y-microsphere Therapy

- 90Y-microsphere therapy usually target the liver
- 90Y-microsphere therapy takes advantage of the unique circulatory system in the liver
  - Portal vein (normal liver) & hepatic artery (tumor)
- Liver directed EB-RT are limited in scope
  - Radiation tolerance of normal hepatocytes < neoplastic tissue
  - Max. tolerated doses 30–40 Gy
- With 90Y-microspheres, total liver radiation doses up to 80 Gy were well tolerated with no hepatic radiation damage
- 90Y-microsphere therapy is approved by the FDA for the treatment of unresectable HCC and metastatic colorectal cancer

Properties of Yttrium-90

- Production: Y-89 (n,γ) Y-90
- Decay: Y-90 (β-, 64.1 hr) Zr-90; a pure β emitter
  - Y-90 also emits β+ at low yields (~32 ppm) via internal pair-production
- β energy: 0.937 MeV (mean) and 2.28 MeV (max)
- Tissue penetration depth: 2.5 mm (mean) and 11 mm (max)
- 90Y deposits >90% of its energy in the first 5 mm of tissue
- 90Y deposits >90% of its energy in the first 11 days
- Permanently implanted 90Y can deliver radiation absorbed doses of ~50 Gy per kilogram of tissue for 1 GBq of activity

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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 10^6 spheres
- Maximum activity available: 3 GBq (81 mCi)
- Indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant chemotherapy (FUDR)
- Liver is common site of metastases from a variety of neoplasms
- Clinical trials on management of metastatic liver disease

TheraSphere®
- MDS Nordion, Ottawa, Canada
- Insoluble, biocompatible glass matrix
- 20–30 μm glass spheres
- 3 GBq (81 mCi) activity = 1–2 x 10^6 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

Patient Imaging Prior to 90Y-TAR

- CT or MRI – Estimate target tumor mass
- IR – Selective embolize aberrant/hepatic vasculature
  - Int. Radiologist under fluoroscopic guidance in an angiography suite
- 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

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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>Reduction Factor</td>
</tr>
<tr>
<td>0 % - 10 %</td>
<td>No Reduction</td>
</tr>
<tr>
<td>10 % - 15 %</td>
<td>20 % reduction</td>
</tr>
<tr>
<td>15 % - 20 %</td>
<td>40 % reduction</td>
</tr>
<tr>
<td>&gt; 20 %</td>
<td>No Treatment</td>
</tr>
<tr>
<td>Lung dose per treatment &lt; 25 Gy</td>
<td></td>
</tr>
</tbody>
</table>

Example Lung Shunt Calculation

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

- SIR-Spheres:
  - LS < 20% (no modification)
  - 81 mCi 90Y activity limit
- TheraSphere:
  - 30 Gy lung dose limit
  - 222 mCi 90Y activity limit

90Y-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
**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

\[
\text{Activity Required (GBq)} = \frac{\text{Desired Dose (Gy) x Target Mass (kg)}}{50 \text{ (Gy - kg/GBq)}}
\]

**Dose Calculations: TheraSphere**

- Max Activity (mCi) = 30 (Gy) x M_{liver} (kg) / (LS x 0.037 (GBq/mCi) x 49.7 (Gy-kg/GBq))

- Lung Shunt
- Maximum Activity = 222 mCi, for lung dose = 30 Gy
- Liver dose (Gy) = 378 (Gy-kg) / M_{liver} (kg)
  - 198 Gy for M_{liver} = 1.91 kg (MIRD Std. Man)
  - 154 Gy for M_{liver} = 2.46 kg (Weight-based)
  - 137 Gy for M_{liver} = 2.76 kg (CT-based)

- Target liver dose = 120 Gy → 134.6 mCi of \( { }^{90} \text{Y} \) → Lung dose delivered = 18.2 Gy

**Radiation Absorbed Dose**

\[
\text{Dose}_{\text{tissue}} \text{ (Gy)} = \frac{A_{\text{tissue}} \text{ (GBq)} \times 49.7 \text{ (Gy-kg/GBq)}}{M_{\text{tissue}} \text{ (kg)}}
\]

- Self dose from β emission: > 90% energy deposit in <5mm
- 49.7 (Gy-kg/GBq) = equilibrium accumulated dose constant
- Bremsstrahlung dose << β dose

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

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

- Error in liver mass propagates into liver dose calculation
- Model estimates average dose to target volume assuming uniform microsphere uptake within volume

**Dose Calculations: SIR-Spheres**

- Basic model: 2.5 GBq (67.5 mCi)
- BSA model: \( \text{BSA(m^2)} = 0.2 + \text{Tumor involvement (TI)}/100 = 1.85 \text{ GBq (50.1 mCi)} \)

- Liver Dose (Gy) = \( A \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 \times \text{LS} \times 49.7 \text{ (Gy-kg/GBq)}}{M_{\text{liver}} \text{ (kg)}}
  - 6.8 Gy (< 25 Gy)

\[ M, 53 \text{ kg, 174.5 cm} \rightarrow \text{BSA} = 1.60 \text{ m^2} \]

\[ \text{Tumor involvement (TI)} = 45\% \rightarrow \text{Dose modification YES} \]

\[ \text{Lung Shunt (LS)} = 7.35\% \rightarrow \text{Dose modification NO} \]
Patient imaging day of $^{90}$Y-Therapy

- Intervventional Radiologist - Angiography suite
  - verify catheter placement, assess flow
  - deliver $^{90}$Y-microspheres
- NM Planar & SPECT $^{90}$Y-bremsstrahlung imaging
  - 79keV/26% window, MELP collimation, 128x128 matrix, 4.8 mm² pixels, 128 views/360°, 28 s/view, non-circular step-shoot
  - Assess delivery and distribution of $^{90}$Y-microspheres
- Follow-up evaluations at 2-3 months – CT or MRI

Prior to $^{90}$Y-microsphere Therapy

SPECT Concordance: $^{99m}$Tc-MAA & $^{90}$Y

Prior to $^{90}$Y-microsphere Therapy

SPECT Concordance: $^{99m}$Tc-MAA & $^{90}$Y
SAM Question 1

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 max. 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


SAM Question 2

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

Pre and Post $^{90}$Y-microsphere Therapy

CT 3-June-2008  
CT 5-Sept-2008

Tc-99m MAA SPECT/CT 24-June-2008  
Tc-99m MAA SPECT/CT 2-Sept-2008
SAM Question 2: Answer

- The most common route of $^{90}$Y-microsphere administration for liver-directed therapy is:
  A. Peritumoral injection
  B. Implantation of $^{90}$Y-brachytherapy seeds
  C. Systematic administration via intravenous injection
  D. Trans-hepatic arterial administration via catheter


SAM Question 3

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.
  - Lung Shunt Fraction (%)
  - Lung Counts
  - Liver Counts

- B.
  - Lung Shunt Fraction (%)
  - Lung Counts
  - Liver Counts

- C.
  - Lung Shunt Fraction (%)
  - Lung Counts
  - Liver Counts
  - Liver Counts

- D.
  - Lung Shunt Fraction (%)
  - Lung Counts
  - Liver Counts


SAM Question 4

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

- A. 40–60 cGy
- B. 40–60 Gy
- C. 80–120 cGy
- D. 80–120 Gy

SAM Question 4: Answer

- The typical range of planned absorbed doses to target liver tissue in \(^{90}\text{Y}\)-microsphere internal radionuclide therapies is around:
  
  A. 40 – 60 cGy
  B. 40 – 60 Gy
  C. 80 – 120 cGy
  D. 80 – 120 Gy


Limitations of \(^{90}\text{Y}\)-microsphere 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 (Ho et al., EJNM 23, 947-52, 1996)
  - Tumor burden (\(M_{\text{tumor}}\)) and Tumor uptake ratio (R)

- Estimation of fractional Tumor Involvement (TI)
  - \(M_{\text{tumor}} = M_{\text{liver}} + M_{\text{tumor}}\)
  - \(M_{\text{tumor}} = \text{TI} \times M_{\text{liver}}\) and \(M_{\text{liver}} = (1-\text{TI}) \times M_{\text{total}}\)

- Estimation of Tumor Uptake Ratio (R)
  - \(A_{\text{liver}} [\text{mCi}] = A [\text{mCi}] \times (1-\text{LS}) \times M_{\text{liver}} / (M_{\text{liver}} + R \times M_{\text{tumor}})\)
  - \(A_{\text{tumor}} [\text{mCi}] = A [\text{mCi}] \times (1-\text{LS}) \times R \times M_{\text{tumor}} / (M_{\text{liver}} + R \times M_{\text{tumor}})\)
  - \(\text{Dose}_{\text{organ}} [\text{Gy}] = A_{\text{organ}} [\text{GBq}] \times 49.7 [\text{Gy-kg/GBq}] / M_{\text{organ}} [\text{kg}]\)

Example Dose Calculation: 3-compartment

- LS = 7.35%
- Total Activity = 222 mCi
- Total liver = 2.76 kg
- TI = 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 = 284.5 Gy

- Prior estimate of liver dose = 137 Gy with T/N=1
Three Compartment Model: Normal Liver Dose

- Quantify differences of 3 dosimetry models
  - Empirical model (STD)
  - Weight-based 3-compartment model (WTB)
  - CT-based 3-compartment model (CTB)
- Differences in lung mass, liver mass, T/N Ratio, Ti

- Median ± 1σ difference, t-test p-values
  - WTB < STD: -27.7 ± 20.5 Gy; p<0.001
  - CTB < STD: -28.2 ± 19.3 Gy; p<0.001
  - CTB ~ WTB: -0.7 ± 5.5 Gy; p>0.10

- Linear correlation, r
  - WTB & STD: r = 0.26; p>0.10
  - CTB & STD: r = 0.37; p>0.10
  - CTB & WTB: r = 0.92; p=0.004

(Kappadath et al., JNM 50, 2009)

Three Compartment Model: Tumor Dose

- Quantify differences of 3 dosimetry models
  - Empirical model (STD)
  - Weight-based 3-compartment model (WTB)
  - CT-based 3-compartment model (CTB)
- Differences in lung mass, liver mass, T/N Ratio, Ti

- Median ± 1σ difference, t-test p-values
  - WTB > STD: 80.1 ± 52.1 Gy; p<0.0002
  - CTB > STD: 48.3 ± 38.0 Gy; p<0.0005
  - CTB ~ WTB: -10.2 ± 37.3 Gy; p>0.10

- Linear correlation, r
  - WTB & STD: r = 0.19; p>0.10
  - CTB & STD: r = 0.26; p>0.10
  - CTB & WTB: r = 0.80; p=0.011

(Kappadath et al., JNM 50, 2009)

Assay of 90Y Activity

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

<table>
<thead>
<tr>
<th>Dose Calibrator S/N</th>
<th>Calibration Number</th>
<th>M Ci</th>
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<tr>
<td>15769</td>
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</tbody>
</table>

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

Assay of 90Y Activity

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

TheraSphere Activity

<table>
<thead>
<tr>
<th>Activity Delivered</th>
<th>Dose Delivered</th>
<th>Dose Delivered</th>
<th>Target Volume (mL)</th>
<th>Target Liver Mass (g)</th>
<th>Target Liver Mass (g)</th>
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<tr>
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<tr>
<td>120</td>
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<td>120 g</td>
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<tr>
<td>160</td>
<td>160</td>
<td>160</td>
<td>160 mL</td>
<td>160 g</td>
<td>160 g</td>
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(Kappadath et al., JNM 50, 2009)
**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

\[
\text{Activity Delivered [\%]} = 100 \times \frac{1 - \text{Dose vial measurement before therapy}}{\text{Waste measurement after therapy}}
\]

- Activity delivered to patient

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

**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 the 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** $^{91}$Y and $^{89}$Y may be present with reactor production of $^{90}$Y
  - Long-lived radioactive by-products may not be a problem using carrier free $^{99m}$Tc 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 \(\rightarrow\) free $^{99m}$Tc-pertechnetate
  - Free $^{99m}$Tc biodistribution differs from MAA; thyroid & stomach uptakes free $^{99m}$Tc \(\leftarrow\) introduce error in LSF
  - Non-spherical shape; Size range 10–100 μm
- **Additional objective measures of response**
  - 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 (Jensen et al, IJROBP 55, 2008)
Summary

- ^90^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.