Radioactive Microsphere Therapy of Hepatic Neoplasm

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What is Nuclear Medicine?

Traditionally, Nuclear Medicine is the specialty of medicine which uses non-sealed sources of radioactivity for the diagnosis and treatment of disease.
What is a Non-Sealed Source of Radiation?

Official Definition: …

Practical Definition: A source of radiation, other than external beam irradiation, which, once administered, can not be removed from the patient.
Who decides what is a sealed source of radiation (a “device”) vs. what is a non-sealed source (a “drug,” “radiopharmaceutical,” or “biological”)?

Officially: The FDA

Practically: The manufacturer has a great influence on the decision.
Is a Y-90 microsphere a drug or a device? Is it a sealed or a non-sealed RAM?

- **Tc-99m MAA**
  - Mostly gamma emitter
  - Diagnostic intent
  - Several hundred thousand particles
  - Human albumin
  - 20-90 micron
  - Intravenous injection
  - No realistic way to retrieve particles
  - Particles stay in the body until metabolized

- **Y-90 microspheres**
  - Beta emitter
  - Therapeutic intent
  - Millions of particles
  - Glass or resin
  - 20-60 microns
  - Intraarterial injection
  - No realistic way to retrieve particles
  - Particles stay in the body permanently unless organ removed at surgery
Is a Y-90 microsphere a device or a drug?
Is it a sealed or a non-sealed RAM?

• This is what the manufacturers knew.

JAMA 297:1304, 2007
SIRT

Selective Internal Radiation Therapy

(SIRTeX Medical®)
Regulatory Requirements

• Y-90 microspheres must be used in accordance with US NRC and/or State RAM requirements

• 10 CFR Part 35.1000 (Other Medical Uses of Byproduct Material)

• Authorized User (AU)
  – Radiation Oncology
  – Nuclear Medicine
  – Interventional Radiology
Why Yttrium-90?

Physical properties are:

• Pure beta emitter

• Half Life = 64.1 hours

• Energy of the beta particles:
  - Maximum = 2.27 MeV
  - Mean = 0.93 MeV

• Range:
  - Maximum in air = 9621 mm
  - Mean in air = 3724 mm
  - Maximum in tissue = 11 mm
  - Mean in tissue = 2.5 mm
Currently available commercial forms of Yttrium-90 microspheres:

1. SIR-Spheres®
2. TheraSpheres®
# Y-90 Microspheres Compared

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Glass</th>
<th>Resin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(TheraSpheres)</td>
<td>(Sir-Spheres)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>20-30 µm</td>
<td>20-60 µm</td>
</tr>
<tr>
<td><strong>Isotope</strong></td>
<td>Yttrium-90 in glass matrix</td>
<td>Yttrium-90 on resin surface</td>
</tr>
<tr>
<td><strong>Specific Gravity</strong></td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Activity/sphere</strong></td>
<td>2500 Bq</td>
<td>50 Bq</td>
</tr>
<tr>
<td>(at calibration)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong># of dose sizes</strong></td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>(3,5,7,10,15,20 GBq)</td>
<td></td>
<td>(3 GBq)</td>
</tr>
<tr>
<td><strong># spheres/dose</strong></td>
<td>1.2-8 Million</td>
<td>40-80 Million</td>
</tr>
<tr>
<td><strong># spheres/3GBq dose</strong></td>
<td>1.2 Million</td>
<td>40-80 Million</td>
</tr>
<tr>
<td><strong>US – FDA Approval</strong></td>
<td>HCC</td>
<td>CRC metastases with FUDR pump</td>
</tr>
</tbody>
</table>

*Salem et al. JVIR 2006;17(8):1251-1278*
US Regulatory Status

- SIR-Sphere: NDA
- TheraSphere designated as Humanitarian Use Device (HUD) (not NDA)
  - Legally marketed under Humanitarian Device Exemption (HDE)
  - “Demonstrated safety and probable clinical benefit”
- HDE Requirements:
  - IRB oversight and approval required
  - Use within approved labeling does not constitute research or investigational use
TheraSphere/Yttrium–90 Formulation

• Yttrium-89 oxide powder (yttrium is part of glass formulation)
• Molten glass made into microspheres (25 µm)
• Reactor activation:
  – Y-89 becomes Yttrium-90 (one week)
  – Byproducts from reactor activation: Eu-152, 154

• Benefits:
  – Yttrium-90 is an integral part of glass, which enables:
    • higher specific activity with minimal particles
    • no Y-90 leaching from the surface
Microspheres are intended for use on the day of calibration. At the date and time of calibration, the activity in the vial matches the activity printed on the label ($3\text{GBq}^{+/-10\%}$). The microspheres may be used for up to 24 hours after calibration.
Calibration Time

SIR-Spheres are typically manufactured about 48 hours prior to the treatment or calibration date to allow time for shipping. The calibration time also serves as a lockout time, before which the microspheres cannot be implanted. The time from shipping to calibration provides a window for product recall. The calibration time, date and reference time is on the attached label.
Calibration Time

- Beyond 24 hours after calibration, the number of microspheres required to provide sufficient activity increases by at least 30% and this may exceed the vascular capacity of the tumors in some patients (primarily with Sir-Spheres, less so with TheraSpheres).
Radiofrequency Ablation

- Accepted as best therapeutic choice for nonsurgical patients with early stage HCC
- Patient selection:
  - Single tumor < 5 cm, or < 3 nodules smaller than 3 cm each
  - No vascular invasion
  - No extrahepatic spread
  - Performance status of 0
  - Liver cirrhosis in Child-Pugh class A or B
- Considerations for use:
  - Avoid lesions located near gastrointestinal tract
  - Lesions located near gallbladder are at risk to injury of biliary tract
- Most common complications:
  - Intraperitoneal bleeding, hepatic abscess, bile duct injury, hepatic decompensation, and grounding pad burns

1Lencioni, R. et al. Techniques in Vascular and Interventional Radiology. 2006;38-46
## Systemic Chemotherapy - Sorafenib

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient selection</strong></td>
<td>Child A/B = 284/14</td>
<td>Child A/B = 297/6</td>
</tr>
<tr>
<td></td>
<td>BCLC B/C = 54/244</td>
<td>BCLC B/C = 51/252</td>
</tr>
<tr>
<td><strong>Median overall survival</strong></td>
<td>10.7 months</td>
<td>7.9 months</td>
</tr>
<tr>
<td><strong>Median time to symptomatic progression</strong></td>
<td>4.1 months</td>
<td>4.9 months</td>
</tr>
<tr>
<td><strong>Median time to radiologic progression</strong></td>
<td>5.5 months</td>
<td>2.8 months</td>
</tr>
<tr>
<td><strong>Tumor response (RECIST)</strong></td>
<td>211 (71%) SD; 7 (2%) had PR; 0 CR</td>
<td>204 (67%) SD; 2 (1%) had PR; 0 CR</td>
</tr>
<tr>
<td><strong>AE</strong></td>
<td>80%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>52%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>Rate of Discontinuation due to AE</strong></td>
<td>38%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Dose Interruption due to AE</strong></td>
<td>44%</td>
<td>30%</td>
</tr>
</tbody>
</table>

# Particle Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Y-90 Glass Microsphere (TheraSphere)</th>
<th>Transarterial Chemoembolization (TACE)</th>
<th>Drug Eluting Beads (DEB – DC Bead)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Particle Size</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>25µm</td>
<td>300 - 700 µm</td>
<td>100 - 700 µm</td>
</tr>
<tr>
<td><strong>Mode of Action &amp; No. of Treatment</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Beta Radiation Y-90) + minimal embolization (Avg 1.8/pt)</td>
<td>Chemotherapy + Embolization (variable cycles/pt)</td>
<td>Delayed chemo release + embolization (Treat every 3-4 wks)</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>Standardized &amp; Reproducible</td>
<td>Variable Regimens</td>
<td>Variable Regimens</td>
</tr>
<tr>
<td><strong>Indications</strong>&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>- Unresectable HCC (FDA)</td>
<td>- Not approved (FDA)</td>
<td>- Not approved (FDA)</td>
</tr>
<tr>
<td><strong>Follow-up Tx Options</strong></td>
<td>Any therapy (TACE/RFA/Y-90, etc.)</td>
<td>Limited options; must wait for recanalization</td>
<td>Limited options; must wait for recanalization</td>
</tr>
</tbody>
</table>

<sup>1</sup>Salem et al. JVIR (Part 1) 2006;17(8):1251-1278  
<sup>2</sup>www.Biocompatibles.com (accessed December 1 2008)
Vascular Delivery

Hypervascular Tumor (3:1) – preferentially delivered to tumor
Radiolabeled Microspheres
Does Size of the Microspheres Matter?

The upper size limit allows delivery to the tumors via the hepatic artery. The lower size limit prevents the microspheres passing from the arterial circulation through the tumor vasculature and into the venous (and systemic) circulation.
Radiolabeled Microspheres
Microsphere Benefits Overview

Targeted Therapy:
Sparing Healthy Tissue

- Low toxicities: well tolerated
- Outpatient procedure
- Minimal embolic syndrome
  (TACE vs. microsphere)
- Promising survival data
- Post-microsphere patients eligible for further therapeutic options due to preserved liver vascularity
Tumor Vascularity

- Pretreatment angiogram demonstrating hepatic vein (hyperdynamic) flow


- 45 day post-treatment angiogram demonstrating elimination of tumor vascularity while preserving normal parenchymal flow
Addressing Common Adverse Events

• Fatigue
  – Usually lasts 10 – 12 days
  – Can be offset by Medrol dose pack

• Mild abdominal pain or discomfort
  – Bloating/nausea
  – Relieved by conservative measures

• Fever/Night Sweats
  – Bulky disease
  – Cytokine release from tumor necrosis
  – Rule-out other causes
  – Relieved by conservative measures
Radiolabeled Microspheres

• Serious Side Effects
  – Nausea/Vomiting
  – Abdominal Pain

• Serious Distant Tissue Effects
  – Pneumonitis due to intrahepatic shunting from hepatic arterial circulation to the hepatic venous system
  – Mucosal damage in stomach and gut due to GDA perfusion
  – Pancreatitits due to pancreatic arterial perfusion
Treatment Approach & Patient Selection
Multidisciplinary Team

Similar for many oncology patients

- Interventional Radiologist
- Tumour Board
- Hepatology
- Radiation Oncology
- Surgical Oncology
- Medical Oncology
- Clinical Coordinator
- Radiation Safety
- Physics
- Nuclear Medicine
- Administration
- Transplant Surgeon

Patient
Patient Selection

The ideal candidate for microspheres presents with:

• Non-infiltrative tumor type
• tumor nodules that are not too numerous to count
• AST/ALT < 5 x ULN
• Tumor volume ≤ 50% and Albumin > 3 g/dL
• Bilirubin ≤ 2 mg/dL

TheraSphere US Package Insert
Importance of Bilirubin in Patient Selection
(n = 80)

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Censor</th>
<th>N</th>
<th>Median</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.6</td>
<td>△</td>
<td>30</td>
<td>637</td>
<td>492-984</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt; 0.6 - 1.2</td>
<td>□</td>
<td>35</td>
<td>513</td>
<td>256-1259</td>
<td></td>
</tr>
<tr>
<td>&gt;1.2</td>
<td>◊</td>
<td>15</td>
<td>190</td>
<td>113-331</td>
<td></td>
</tr>
</tbody>
</table>

Geschwind et al, Gastroenterology 2004;127:S194-S205
Patient Planning

TheraSphere Dosimetry Planning

- Obtain liver volume from CT scan / angiogram
- Perform Tc-99m MAA scan
- Determine required TheraSphere dose
  
  \( (3, 5, 7, 10, 15 \text{ or } 20 \text{ GBq}) \)

- Based on:
  - optimal therapeutic dose
  - liver mass
  - physical decay of Y-90 and resulting activity at time of treatment
  - treatment time window
  - written directive
Volume analysis: CT Imaging

Salem et al. JVIR (Part 1) 2006;17(8):1251-1278
Pretreatment Angiogram & Tc-99m MAA Scan

- **Hepatic angiogram** with placement of intra-hepatic catheter to assess vasculature and microsphere delivery route

- **Technetium-99m Macro-aggregated Albumin** (Tc-99m MAA) study to assess extrahepatic flow to GI tract and/or pulmonary shunting
Clinical Outcomes
Large Lesion

Large right lobe HCC

- Patient treated with 1 dose of TheraSphere

Images provided by Riad Salem, Interventional Radiologist, Northwestern University, Chicago, Illinois
Multiple Lesions
HCC post downstaging to transplantation
• Arrows point to enhancing capsule following treatment.

Kulik, et al. Liver Transplantation 2005;11(9):1127-1131

Explant demonstrates complete necrosis of the tumor (42 days post Tx).
Technical Issues
Patient Dose Calculation

Activity required to administer 150 Gy to the right lobe:

\[
\text{Activity Required} = 50 \times [1 - F] \text{ (GBq)}
\]

Liver Mass = 1301 cc * 1.03 g/cc * 1 kg/1000g = 1.340 kg

\[
\text{Activity Required} = 50 \times [1 - F] \text{ (GBq)}
\]

\[
= 4.02 \text{ GBq}
\]
## Dose Scheduling

### Delivered Dose for Ordered Activity (GBq) = 7

<table>
<thead>
<tr>
<th>Time</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>211</td>
<td>162</td>
<td>125</td>
<td>97</td>
<td>75</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>202</td>
<td>156</td>
<td>120</td>
<td>92</td>
<td>71</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>193</td>
<td>149</td>
<td>115</td>
<td>89</td>
<td>68</td>
</tr>
<tr>
<td>8:00 PM</td>
<td>185</td>
<td>143</td>
<td>110</td>
<td>85</td>
<td>66</td>
</tr>
</tbody>
</table>

### Delivered Dose for Ordered Activity (GBq) = 5

<table>
<thead>
<tr>
<th>Time</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>150</td>
<td>116</td>
<td>89</td>
<td>69</td>
<td>53</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>144</td>
<td>111</td>
<td>86</td>
<td>66</td>
<td>51</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>138</td>
<td>106</td>
<td>82</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>8:00 PM</td>
<td>132</td>
<td>102</td>
<td>79</td>
<td>61</td>
<td>47</td>
</tr>
</tbody>
</table>
Radiolabeled Microspheres

• Dose varies depending on
  – User philosophy
  – Tumor burden
  – Degree of hepatic-to-systemic shunting
• Maximum dose (SIR-Spheres®) in US is 3 GBq (81 mCi)
  – But rarely use more than 2 GBq (54 mCi)
• Doses of up to 8 GBq have been used, with significantly increased side effects
Activity Calculations

• The activity of the microspheres implanted will usually be in the range of 1.0-2.5 GBq
Site Dose Measurement

• The use of a dose calibrator must follow manufacturer instructions, there must be a comprehensive program to evaluate geometry, repeatability, linearity, NIST Program

• The holder used has a very important effect on geometry and the accuracy of the activity measurement.

• Unique site factor determination
Administration Set Up
Radiation Safety

Monitoring should occur at two levels:

• the environment
• the staff.
Radiation Safety

• The treatment of patients using microspheres requires the standard shielding, protective clothing, gloves, radiation surveys, and training of personnel involved in the procedure as well as the staff nurses.
Radiation Safety

• Acceptable levels for the **environment** are established using a beta counter and anything above background should be considered contaminated.
Radiation Safety

- Items that may become contaminated with Yttrium-90 must be bagged, labeled, and returned to the nuclear medicine/radiation therapy department or other designated areas to decay for a period of ten half-lives (long-lived contaminants) i.e. until the measured activity does not exceed background levels.
Radiation Safety Instructions for the Patient

Instructions for the patient should be based on measured or typical exposure readings.

For example, for a 1.5 GBq (40 mCi) dosage:

typical exposures have been:

- surface = 1.0 mR/hr
- 1 meter = 0.1 mR/hr
Conclusions
Radiolabeled Microspheres

• According to FDA, these are **devices**
• Labeled with beta emitting Y-90
• TheraSpheres and SIR-Spheres differ by size, composition, and **specific activity**
• Only fully “approved” use is SirSpheres for colorectal cancer metastatic to liver
• Generally well tolerated but **serious** adverse effects of **improper** deposition
• Good clinical outcomes in difficult patient group
• Expensive, but cheaper than chemotherapy