Future Needs for Standards in $^{90}\text{Y}$ Microsphere Therapy

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Objectives

I. General Description
   – Microsphere Distribution
   – Product Comparison

II. Dosimetry Models
   – Shortcomings

III. Uncertainty Analysis
   – Y90 Assay
   – Activity Injected
   – NIST Standards and Needs
Liver Cancer

• Two types of liver cancer
  – Hepatocellular Carcinoma (HCC) = Primary
    • 28,720 new cases estimated for 2012 (ACS)
    • Resectable → curative
  – Hepatic Metastasis = Secondary
    • Colorectal – 150,000 cases estimated for 2006
    • Others
      • Nonresectable → palliative

• Microspheres approved for HCC and colorectal liver metastasis
I. General Description

• How does the treatment work?
  – $^{90}$Y-loaded microspheres
  – Insoluble device
    • 15 – 40 μm diameter
    • $^{90}$Y β emitter ($t_{1/2} = 64$ h)
      – $E_{\text{max}} = 2.28$ MeV
      – $E_{\text{ave}} = 0.93$ MeV
      – $X_{90} = 5.3$ mm
  – Injected via the femoral artery to the hepatic artery by the IR
  – Spheres preferentially deposit in tumors
Liver Blood Flow

- Normal supply
  - Hepatic artery $\rightarrow$ 20%
    - From celiac trunk
    - Oxygenated
  - Portal vein $\rightarrow$ 80%
    - From GI tract
    - Venous blood - branches

- Tumor supply
  - Hepatic artery $\rightarrow$ 80%
  - Portal vein $\rightarrow$ 20%
Patient Injection & Delivery Box
Microscopic Distribution

- Non-uniform sphere dist.
  - Spheres cluster
    - 1 – 20 spheres/cluster
    - Cluster extent of 0.5 – 1 mm
  - Tumor periphery
    - Surface = 175 spheres/mm$^3$
    - Core = 2.7 spheres/mm$^3$
  - Nontumorous tissue
    - 3.5 spheres/mm$^3$

- Tumor to Normal Ratio (T:N)
  - Range from 1:1 to 200:1
**In Vivo Assessment of Distribution**

- **99Tc-labeled Macroaggregated Albumin (MAA) scan**
  - Particle Size: 10 – 100 um
  - Degradeable
    - Particle size < 10 um
    - Inaccurate flow analysis
  - % Lung Shunt
  - Prescan
- **CT Scan**
# Product Comparison

<table>
<thead>
<tr>
<th></th>
<th><strong>Therasphere®</strong> (MDS, Nordion)</th>
<th><strong>SIR-Spheres®</strong> (SIRTex)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>15-35 um</td>
<td>20-40 um</td>
</tr>
<tr>
<td><strong>Material</strong></td>
<td>Glass (3.2 g/cc)</td>
<td>Resin (1.6 g/cc)</td>
</tr>
<tr>
<td><strong>Specific Activity</strong></td>
<td>2500 Bq/sphere</td>
<td>50 Bq/sphere</td>
</tr>
<tr>
<td><strong># of spheres injected</strong></td>
<td>1.2 – 20 million</td>
<td>20 – 60 million</td>
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II. Dose Estimation Models

- Intraoperative beta dosimetry
  - Direct measurement
    - Beta probe swept over liver surface
    - Determine mean count rate (cps)
    - Determine mean activity
      - Assume homogeneous sphere distribution
    - Calculate liver dose
  - Invasive
  - Difficult application to metastatic cancer
Dose Estimation Models Cont’d

• MIRD Formalism
  – Assumptions:
    • Homogeneous distribution in source (liver)
      – No distinction between normal liver and tumor
    • No dose to non-source organs
      – $\Phi = 0$ for target for beta emitting source
  – Overestimates dose to normal liver
  – Underestimates dose to tumor
Dose Estimation Models Cont’d

• Partition Model
  – Determine tumor-to-normal tissue ratio (T:N)

\[
T : N = \left( \frac{A_t}{M_t} \right) / \left( \frac{A_i}{M_i} \right)
\]

\[
D_{\text{liver}} = \frac{50 \text{Gy-kg}}{\text{GBq}} \frac{A_{\text{inj}} (1 - F_{\text{lung}})}{(T : N)M_t + M_l}
\]

• Evaluate compartment activity and mass
  – Based on $^{99m}$Tc-MAA prescan

• Still assumes no dose to normal tissue from tumors

– Application to metastatic cancer
  • Difficult to determine tumor mass and uptake fraction
Determination of Tumor Mass
T:N Ratio
III. Microsphere Assay

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<th><strong>Therasphere®</strong></th>
<th><strong>SIR-Spheres®</strong></th>
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<tr>
<td><strong>Vial Geometry</strong></td>
<td>0.3 ml glass v-vial in</td>
<td>5 ml glass vial</td>
</tr>
<tr>
<td></td>
<td>acrylic shield</td>
<td></td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>3, 5, 7, 10, 15 or 20</td>
<td>3 GBq ± 10%</td>
</tr>
<tr>
<td></td>
<td>GBq ± 10%</td>
<td></td>
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</tbody>
</table>

- **Activity Standard**
  - Therasphere activity is traceable to NIST
  - SIR-Sphere activity is not traceable to NIST
    - Apparent activity is 25% greater than indicated

- **Transfer standard to local clinic**
SOURCE PREPARATION FOR CALIBRATION OF YTTRIUM-90

Bulk Material from Supplier
Yttrium-90 as YCl₃ in 0.5 N HCl

Dilute to 5 mL with 1 N HCl

1 mL V-Vial
0.05 mL soln
CRC 12 : 48 x 10

V-Vial in Hand Shield
0.05 mL soln
CRC 12 : 43 x 10

3 mL Syringe
1.1 mL soln
CRC 12 : 60 x 10

5 mL Syringe
1.2 mL soln
CRC 12 : 57 x 10

10 mL Serum Vial
5 mL soln
CRC 12 : 38 x 10

NIST Standard Ampoule
5 mL soln
CRC 12 : 48 x 10

British Standard Ampoule
3 mL soln

20 mL Serum Vial
10 mL soln
CRC 12 : 22 x 10

Gravimetric dilution 1:100

LS Vials
Cerenkov Vials
NaI(Tl) Samples
Y-90 Measurements at NIST

- Liquid scintillation - destructive
  - CIEMAT/NIST
  - Triple-to-Double coincidence method

- Therasphere calibration
  - Calibration for v-vial and v-vial in dose shield in 3 and 20 GBq activities
    - LS of Y90 standard to determine correct dial setting
    - Measure microspheres with dial settings in CRC-12
    - 6 mm change in height = 1% increase in signal
Assay Uncertainty: SIR-Spheres

- Proper Dose Calibrator Setting
  - Reference dose used to determine setting
    - Example: Setting variation was ± 18%

- Additional sources of uncertainty
  - Withdraw administered activity
  - Volume reduction → geometry variation
    - Changes in efficiency for a 0.2 ml sample compared to a 2 ml sample

- Activity in the syringe prior to treatment
Need 1

• Low uncertainty NIST traceable transfer standard for the vendor-specific injection geometry
  – Y90 positron emission calibration
    • Reduces geometry dependence
    • Chamber or source calibration (ADCL)
  – Sr90 calibration
    • Long-lived sample for routine calibration checks
Y90 Positron Emission

• Y90 emits a positron 31.86 ppm
  – Measured using a single high-purity germanium (HPGe) detector
  – More recently measured using a coincidence system (Paxton, UW-Madison)
    • HPGe and NaI
    • High SNR and reduced measurement time
  – 511 keV photon relatively insensitive to geometry differences, unlike beta measurements
Activity Injected

• Microspheres cluster
  – Lodge in 3-way valve, needle, and catheter
  – How much residual activity is trapped?
    • Equipment placed in Capintec
    • Or use radiac to measure dose rate
  – Residual activity in syringe

• Overall Uncertainty > 20%
  – Assumes manufacturer calibration is accurate
Need 2

- NIST traceable post-injection assay of residual activity and trapped activity