Nuclear imaging in Yttrium-90 Radioembolization: what, why and how

Cicero Habito, M.D., FPCR
• Vascular and Interventional Radiology

• Nuclear Medicine and Molecular Imaging

• Abdominal Imaging
"Now, you all know me, I like to call a spade a vegetable plot preparation solution..."
Selective Internal Radioembolization Therapy (SIRT)
OVERVIEW

• What is Y90 Radioembolization?
• What nuclear imaging is involved?
• Why do we perform nuclear imaging?
• What baseline knowledge is essential for image acquisition and interpretation?
WHAT IS Y90 RADIOEMBOLIZATION?
WHAT IS RADIOEMBOLIZATION?

• Interventional procedure in which blood vessels are occluded with radioactive material.

• Falls under the umbrella of embolization procedures, for which an interventional radiologist utilizes any combination of liquid, gel, metal/coils or particulate material.

• Selective Internal Radiation Therapy
WHAT IS YTTRIUM-90?

- An isotope of Yttrium with 51 neutrons and 39 protons.
- Undergoes $\beta^-$ decay to zirconium-90 with a half-life of 64 hours and a decay energy of 2.28 MeV.
- Mean penetration in tissue of 2.5 mm (9 m in air).
- “Pure beta emitter” – misnomer (also a weak positron emitter, <50 per million).
- Yttrium-90 is a decay product of strontium-90 which makes up about 5% of the nuclear daughter isotopes when uranium is fissioned (nuclear reactor).
<table>
<thead>
<tr>
<th></th>
<th>Theraspheres</th>
<th>Sirspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition</strong></td>
<td>Glass</td>
<td>Resin</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>HCC under a Humanitarian Device Exemption</td>
<td>liver metastasis from colorectal primary</td>
</tr>
<tr>
<td><strong>Diameter</strong></td>
<td>20-30 μm</td>
<td>20-40 μm</td>
</tr>
<tr>
<td><strong>Activity per microsphere (Bq)</strong></td>
<td>2500</td>
<td>50</td>
</tr>
<tr>
<td><strong>Specific gravity/microsphere</strong></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Dose variation with tumor volume</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Number (million) of microspheres per dose</strong></td>
<td>3-8</td>
<td>40-70</td>
</tr>
<tr>
<td><strong>Maximum prescribed dose (GBq)</strong></td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td><strong>Average dose (GBq)</strong></td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td><strong>Relative embolic potential</strong></td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td><strong>Contrast injection during infusion</strong></td>
<td>Not possible</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>Relative pressure of infusion</strong></td>
<td>Higher</td>
<td>Lower</td>
</tr>
</tbody>
</table>
TheraSpheres®

Photomicrograph (original magnification, 200) shows glass microspheres.

SIR-Spheres®

Photomicrograph (original magnification, 1000) shows resin microspheres.

Murthy et al, 2005
WHERE DOES SIRT STAND CURRENTLY?

- Worldwide: ~10,000 treatments/annum
- Nonroutine, palliative therapy for liver tumors
  - Hepatocellular Carcinoma
  - Cholangiocarcinoma
  - Colorectal adenocarcinoma
  - Melanoma
  - Breast
  - Neuroendocrine tumors
- Limited reports of use for extrahepatic tumors
WHERE DOES SIRT STAND CURRENTLY?

• HCC: 5\textsuperscript{th} most common malignancy worldwide

• Colorectal cancer: third most common worldwide and the fourth most common cause of death
PAYOR REIMBURSEMENT FOR SIRT

POLICY STATEMENT:
I. Based upon our criteria and assessment of peer-reviewed literature, selective internal radiation therapy (SIRT) has been medically proven to be effective and is considered medically appropriate as a treatment for:
A. Primary hepatocellular carcinoma that is unresectable and limited to the liver (See Policy Guidelines);
B. Hepatic metastases from neuroendocrine tumors with diffuse and symptomatic disease when systemic therapy has failed to control symptoms;
C. As a bridge to transplant for patients with hepatocellular carcinoma who meet liver transplant criteria and are waiting liver transplantation; or
D. Unresectable hepatic metastases from colorectal carcinoma, in patients with liver-dominant disease who are refractory to chemotherapy or who are not candidates for chemotherapy (see Policy Guidelines).
II. Based upon our criteria and assessment of peer-reviewed literature, selective internal radiation therapy (SIRT) has not been medically proven to be effective and is considered investigational as a treatment for all other metastatic or primary tumors of the liver.

Refer to Corporate Medical Policy #7.01.03 regarding Cryosurgical Tumor Ablation.
Refer to Corporate Medical Policy #7.01.49 regarding Transcatheter Arterial Chemoembolization of Hepatic Tumors.
Refer to Corporate Medical Policy # 7.01.78 regarding Peptide Receptor Radionuclide Therapy.
Refer to Corporate Medical Policy #7.02.32 regarding Radiofrequency Tumor Ablation.
Refer to Corporate Medical Policy #11.01.10 regarding Clinical Trials.
Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES:
I. In general, SIRT is used for unresectable HCC that is greater than 3 cm.
II. SIRT should be reserved for patients with adequate functional status (ECOG 0-2), adequate liver function and reserve, Child Pugh score A or B, and liver-dominant metastases. Patients should also have a life expectancy of greater than 3 months.
III. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.
BCLC STAGING SYSTEM

From AASLD
CURRENT EVIDENCE


CURRENT CLINICAL TRIALS

- **SIR-Spheres microsphere**
  - Pre-clinical: Current product is approved
  - First in Human: SIRFLOX (n = 450)
  - Pre-market: FOXFIRE (n = 490)
  - Post-market: SIRveNIB (n = 360)
  - 1st Line HCC vs sorafenib
    - 1st Line HCC +/- sorafenib
      - 1st Line mCRC
        - 1st Line HCC vs sorafenib
          - 1st Line mCRC
            - Renal Cancer
              - New technologies
                - Radioprotector
                  - Microspheres evolution
                    - Imaging and Delivery
  
  - RESIRT (n = 15 - 24)
## CURRENT CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Objective</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP-HCC</td>
<td>Evaluate the safety and efficacy of TheraSphere in the treatment of inoperable hepatocellular carcinoma (HCC)</td>
<td># of patients: ~400 patients&lt;br&gt;# of sites: Up to 40&lt;br&gt;Patients receive TheraSphere prior to receiving standard protein kinase inhibitor therapy vs. protein kinase inhibitor&lt;br&gt;&lt;br&gt;&lt;strong&gt;Primary endpoint:&lt;/strong&gt; Overall survival</td>
</tr>
<tr>
<td>EPOCH</td>
<td>Evaluate safety and efficacy of TheraSphere in the treatment of liver metastases in colorectal cancer patients</td>
<td># of patients: ~360 patients&lt;br&gt;# of sites: Up to 30&lt;br&gt;Patients receive TheraSphere + second-line chemotherapy vs. chemotherapy&lt;br&gt;&lt;br&gt;&lt;strong&gt;Primary endpoint:&lt;/strong&gt; Progression-free survival</td>
</tr>
<tr>
<td>YES-P</td>
<td>Evaluate in treatment of HCC, in a subset with portal vein thrombosis</td>
<td>Design &amp; protocol in planning</td>
</tr>
<tr>
<td><strong>Total estimated cost</strong></td>
<td></td>
<td>$15 million to $20 million per trial over approx. six years</td>
</tr>
</tbody>
</table>
RADIOEMBOLIZATION: A MULTIDISCIPLINARY EFFORT
Medical Oncologist
- treatment coordination

Diagnostic Radiologist
- baseline and follow up imaging

Interventional Radiologist
- deliver microspheres

Nuclear Medicine
- image microspheres
OVERVIEW

• What is Y90 Radioembolization?

What nuclear imaging is involved?

• Why do we perform nuclear imaging?
• What baseline knowledge is essential for image acquisition and interpretation?
RADIOEMBOLIZATION:
A TWO SESSION PROCEDURE
OVERVIEW OF SIRT PROCEDURE

- Typically a 2-stage process
- Work-up procedure:
  - Hepatic angiogram
  - Occlusion of extra-hepatic vessels
  - Injection of $^{99m}$Tc-MAA for lung-shunt study
- Treatment procedure:
  - 1–3 weeks later
  - Reassessment of occlusion
  - Injection of SIR-Spheres dose
  - Nuclear imaging study to confirm implantation
WHAT ARE THE RISKS OF SIRT?

- Liver failure
- Tumor Lysis Syndrome
- Infection
- Contrast Nephropathy
- Allergic Reactions
- Vessel Damage
- Non-target embolization
  - radiation pneumonitis
  - pancreatitis
  - intractable ulcers
RADIATION INDUCED GASTRIC ULCER
HOW DO WE AVOID NON-TARGET EMBOLIZATION?

PRE-SIRT SIMULATION
PRE-SIRT PROCEDURE

- Performed at least 1 day prior to SIRT
- Embolization of gastroduodenal artery, right gastric artery, cystic artery and any other significant collateral vessels
- Administration of Tc-99 MAA through a catheter within target vessel: 4-5 mCi (148 MBq) in 3 ml
- Gamma camera imaging
PRE-SIRT NUCLEAR IMAGING
OVERVIEW

• What is Y90 Radioembolization?
• What nuclear imaging is involved?

• **Why do we perform nuclear imaging?**
  
  • What baseline knowledge is essential for image acquisition and interpretation?
PURPOSES OF NUCLEAR IMAGING IN CONJUNCTION WITH SIRT

Pre-SIRT
- Calculate hepatopulmonary shunt fraction
- Identify patterns of extrahepatic activity which may pose contraindications to SIRT
- Assist in prognostication of response to therapy?

Post SIRT
- Document delivery of microspheres to target region
- Assist in prognostication of response to therapy?
PRE-SIRT IMAGING

- MAA injected by interventional radiologist in angiography suite
- Planar and Fused SPECT/CT imaging as soon as possible following MAA delivery
  - Energy window: 140 KeV with 20% window
- Planar: anterior and posterior images of the abdomen and chest
  - Abdomen: liver centered in FOV, 256x256 matrix for 1k
  - Chest: same amount of time as abdomen
- SPECT using single bed position including the pancreas and liver inferiorly, and as much of the lungs as possible superiorly
MINIMIZE INTERVAL BETWEEN MAA INTRODUCTION AND IMAGING

Acquisition

• Both planar and Fused SPECT/CT imaging
• SPECT before scintigraphy useful in certain scenarios
• Patient closely monitored during imaging
• Cross sectional imaging of upper abdomen and entire thorax

Interpretation

• Optimally reviewed on workstation
• Ensure acceptable ROIs for shunt calculation
• Origin/nature of all extrahepatic activity MUST be interrogated
• Immediate alert to IR if SIRT contraindicated
HEPATO-PULMONARY SHUNT QUANTIFICATION

Planar Method

13.5% SHUNTING TO THE LUNGS
SPECT/CT ROLE IN DETECTING NONTARGET EMBOLIZATION
Advantages of fused SPECT/CT over SPECT and planar nuclear imaging

- SPECT/CT reveals extrahepatic $^{99m}$Tc-MAA particle deposition missed on angiography, SPECT and planar nuclear imaging

- A review of 90 $^{99m}$Tc-MAA studies by Ahmadzadehfar, et al. reported extrahepatic accumulation detected by planar imaging, SPECT, and SPECT/CT in 12%, 17%, and 42% of examinations, respectively

Denecke et al. performed SPECT/CT on 13 patients with colorectal cancer and found gastrointestinal $^{99m}$Tc-MAA uptake in 31% using SPECT/CT, versus 15% using SPECT alone
ADVANTAGES OF FUSED SPECT/CT OVER SPECT
AND PLANAR NUCLEAR IMAGING

• CT fusion can distinguish ominous periportal or duodenal $^{99m}$Tc-MAA deposition from otherwise acceptable GB activity

• Fused SPECT/CT best depicts heterogenous patterns of particle deposition within tumor. The significance of radioembolic particle deposition patterns and their effect on treatment response is currently being studied: CT fusion is required for reliable identification of areas of tumor devoid of radioembolic particles
LIMITING FACTORS

• Addition of CT imaging provides an incremental radiation dose (of minimal significance when utilizing low dose protocols)

• Fused SPECT/CT capable machines are either unavailable or have restricted availability at some centers, requiring prior coordination to ensure patient is slotted into dedicated SPECT/CT room.

• Rarely, coregistration errors may result in marginal left hepatic activity being interpreted as focal gastric wall uptake

• Micron diameter: 10-90 (MAA) vs 20-60 (Sirspheres)
SPECT FOR LUNG SHUNT QUANTIFICATION
DOSE CALCULATION

☐ Theraspheres
  - Activity Required (GBq):
    \[
    \frac{\text{[Desired Dose (Gy)]} \times \text{[Liver Mass (kg)]}}{50}
    \]
  - Do not exceed 610 MBq to the lungs
  - 30 Gy single session or 50 Gy cumulative

☐ Sirspheres
  - empiric, BSA and partition models
  - less than 10% lung shunting: no reduction
  - 10-15%: 20% reduction
  - 15-20%: 40% reduction
% Shunt = 100 x \((\text{Lung Counts} / \text{total Liver and Lung Counts})\)

*geometric mean of anterior & posterior lung and liver counts

\[
\text{SIR-Spheres activity in GBq}= (\text{BSA}-0.2) + \frac{\% \text{ of tumor involvement}}{100}
\]

<table>
<thead>
<tr>
<th>% Lung Shunting</th>
<th>% Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 %</td>
<td>0 %</td>
</tr>
<tr>
<td>10-15 %</td>
<td>20 %</td>
</tr>
<tr>
<td>15-20 %</td>
<td>40 %</td>
</tr>
</tbody>
</table>

\[
\text{Lung dose (Gy)} = \frac{[49670 \times \text{lung activity (GBq)}]}{\text{lung mass (grams)}}
\]
SIRT IMAGING
Y90 IMAGING

- Bremsstrahlung scans possible due to high-energy β-emission interacting with tissue.
- Bremsstrahlung emissions represent a broad spectrum of energy, which results in poor spatial resolution.
Y90 IMAGING

• SPECT performed with single bed position centered on liver; CT fusion optional
  • Medium energy collimators
  • 20 sec/frame, 180 degree rotation
• Patients are imaged on same day following SIRT
Post-SIRT Imaging: Key Points

Immediate imaging not required

Acquisition
- Planar and SPECT imaging in any sequence
- If imaged immediately, patient closely monitored

Interpretation
- Check angiography for vessel into which microspheres were introduced
- Radioactivity must predominate in distribution of same vessel
- Described distribution pattern of radioactivity
POST SIRT IMAGING: PET

PET images the primary emission not a secondary emission
PET images have improved spatial resolution but with low sensitivity - more noisy data
PET produces quantifiable images
OVERVIEW

• What is Y90 Radioembolization?
• What nuclear imaging is involved?
• Why do we perform nuclear imaging?
• What baseline knowledge is essential for image acquisition and interpretation?
THOUGHTS?

chabito@mgh.harvard.edu