Yttrium-90 Radioembolization

- Yttrium-90 radioembolization is generally used as a palliative therapy for selected patients with unresectable tumors of the liver including:
  - Metastatic tumors from colorectal cancer, breast cancer, neuroendocrine cancer, or melanoma
  - Primary liver cancers including hepatocellular carcinoma and cholangiocarcinoma
- Two products are available for radioembolization treatment: resin microspheres (SIR-Spheres) and glass microspheres (TheraSpheres)
- Radioembolization is effective at prolonging survival and in improving quality of life

Applications of radiation therapy from an external source are limited for tumors in the liver, which can only tolerate between 30 to 50 Gy before the development of significant radiation-induced liver disease; 90 to 100 Gy is required for effective treatment of liver tumors. These limitations can be overcome through the use of microspheres carrying yttrium-90 (Y-90), which are introduced via a catheter inserted into the hepatic artery and lodge in the capillaries of the tumor. Using this technique, doses as high as 150 Gy can be delivered to the tumor, but the bulk of the liver is spared because the average range of radiation within tissue is 2.5 mm and the maximum range is 1.1 cm. The normal liver parenchyma is largely spared because it receives its blood primarily from the portal vein, whereas tumors are perfused primarily via the hepatic artery. In addition, the microvascular density of tumors is three to 200 times greater than the surrounding liver parenchyma.

Two products are available for radioembolization: SIR-Spheres (Sirtex, Australia) and TheraSpheres (BTG Medical, PA). SIR-Spheres were first approved in 2002 by the US Food and Drug Administration (FDA) for the treatment of colorectal metastases, and TheraSpheres were first approved in 1999 for the treatment of hepatocellular carcinoma (HCC). Neither treatment causes substantial ischemic embolization, allowing sufficient oxygen in the tumors to enable the generation of free radicals that drive cell death. As more particles are administered in SIR-Sphere treatments, the distribution may be more uniform than in TheraSphere treatments. However, TheraSpheres emit much more radiation per particle, and higher local doses may be obtained using TheraSpheres.

**Table 1. Comparison of Radioembolization Products**

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<tr>
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<th>SIR-Spheres</th>
<th>TheraSpheres</th>
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<tbody>
<tr>
<td>Year of FDA approval</td>
<td>2002 for treatment of colorectal</td>
<td>1999 for treatment of HCC</td>
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<tr>
<td></td>
<td>metastases</td>
<td></td>
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<tr>
<td>Microsphere material</td>
<td>Resin</td>
<td>Glass</td>
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<tr>
<td>Specific activity</td>
<td>50 Bq per microsphere</td>
<td>2500 Bq per microsphere</td>
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<tr>
<td>Microsphere size</td>
<td>20–60 µm</td>
<td>20–30 µm</td>
</tr>
<tr>
<td>Number of microspheres required for treatment</td>
<td>40–60 million</td>
<td>1–2 million</td>
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Figure 1. (A) MR image of a patient with metastases from colorectal carcinoma, showing several tumors. Those in the right lobe are color-coded blue and those in the left liver are color coded pink, which were traced using an image post-processing program. Post-processed 3D volume MR images of the same patient showing (B) total liver and right and left lobe volumes and (C) Tumor volumes in the right (blue) and left (pink) lobes.

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<tr>
<th>Region</th>
<th>Volume (ml)</th>
<th>Mean Value</th>
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<tr>
<td>Right Liver Volume</td>
<td>1500.67</td>
<td>452.3 ± 153.5</td>
</tr>
<tr>
<td>Left Liver Volume</td>
<td>771.05</td>
<td>449.8 ± 107.4</td>
</tr>
<tr>
<td>Total</td>
<td>2271.72</td>
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Figure 2. Scintigraphy showing the distribution of 99m Tc-MAA. (A) Right anterior LT abdomen, (B) LT Posterior LT abdomen, (C) RT anterior LT chest (D). LT posterior RT chest. The images indicate that 8.9% of the 99m Tc-MAA is shunted to the lungs.
Figure 3. Axial (A) and coronal (B) fusion images showing distribution of $^{99m}$ Tc-MAA, overlaid on MR images. The heterogeneous distribution corresponds to the location of the tumors.

**Indications for Radioembolization**

Radioembolization is a treatment option for patients with metastatic disease to the liver from colorectal cancer, breast cancer, melanoma, and neuroendocrine disease. In most cases, patients who receive radioembolization have exhausted other treatment options. In cases of primary liver cancer, including hepatocellular cancer, it may be considered a palliative therapy or a primary treatment for patients who are not candidates for surgery.

The first steps in evaluating patients for radioembolization are to establish that metastatic disease is largely confined to the liver and to determine that patients meet certain other criteria in order to avoid life-threatening complications. Patients must have adequate liver function, with a serum bilirubin of <2 mg/dL, Eastern Cooperative Oncology Group status <2, portal vein patency, and adequate renal function (eGFR >30 mL/min/m2). Patients who meet these criteria must then undergo both tumor (Figure 1) and vascular mapping (Figures 2 & 3) to establish the tumor burden and that safe delivery of the Y-90 microspheres is possible after protective embolization (Figure 4).

Contrast-enhanced CT or MR imaging of the chest, abdomen, and pelvis is performed to determine whether the tumors are primarily confined to the liver. Volumetric analysis is performed to calculate the tumor volume, total liver volume, and liver reserve from the same CT or MRI scans (Figure 1). This information will determine whether the patient is a suitable candidate for radioembolization.

As it is important to ensure that the Y-90 microspheres do not cause damage to other organs, the gastroduodenal artery and the right gastric arteries are generally coil-embolized (Figure 5) to prevent reflux of the Y-90 microspheres into the stomach, which could result in serious non-healing radiation-induced gastric ulcers. In addition, perfusion scintigraphy is performed with $^{99m}$Tc-macro aggregated albumin (MAA) infused into the proper hepatic artery. MAA particles are similar in size to Sir-Spheres and provide information about blood flow from the hepatic artery, in particular to the lungs and gastrointestinal tract (Figure 2). Radioembolization is contraindicated if scintigraphy shows that the radiation dose to the lungs would exceed 30 Gy per treatment.

**Radioembolization Procedure**

Radioembolization is carried out with close coordination of an interventional radiologist who performs the procedure and is authorized to administer the dose, a nuclear pharmacist who calculates and prepares the appropriate dose, and a radiation safety officer. Patients may not eat or drink for eight hours prior to the procedure, which is performed under conscious sedation with local anesthesia at the catheter insertion site. It is usually performed as an outpatient procedure.
Under image guidance, an angiographic catheter is inserted and placed into the proper hepatic artery, and the Y-90 microspheres are infused. In some cases, if there are many small tumors scattered throughout the liver, two treatments can be given with infusions into the right hepatic artery in one session and the left hepatic artery in the second session. Once the infusion is completed, the microcatheter is withdrawn into the angiographic catheter prior to its removal to prevent unwanted deposition of radioactivity.

After the procedure is completed, patients are required to lie flat for two to six hours. For a few days following the procedure, patients should avoid close contact with others, especially pregnant women and children, to prevent secondary radiation exposure. The half-life of Y-90 is 64.1 hours.

**Complications**

Radioembolization is well tolerated, and post-procedural symptoms are generally milder than those following chemoembolization. Postembolization syndrome has been reported in 2–5% of patients. Typical symptoms include low-grade fever, mild abdominal pain, mild nausea and vomiting, and fatigue. Although hepatic injury and biliary dysfunction are feared complications, the incidence of radiation-induced liver disease has been reported to be in the range of 0–4%, and biliary complications are seen in <10% of patients. Gastric and small bowel injuries have been documented, including radiation-induced gastric ulcers that may result from unrecognized collateral circulation. These injuries and pneumonitis are minimized by thorough pre-procedure preparation.
Follow-up
PET is more sensitive than CT for the assessment of early response in some tumors such as colorectal metastasis, and MRI is used in other tumors such as HCC. Therefore, PET-CT (Figure 6) or MRI, together with laboratory tests for tumor markers, is used to assess response four to six weeks after initial treatment, and at subsequent three-month intervals for the first year and every six months thereafter to detect recurrence or spread of disease. If liver tumors recur with no metastases elsewhere, it is possible to retreat with radioembolization.

Outcomes after Radioembolization
Radioembolization alone or combined with chemotherapy for colorectal metastases has been studied extensively. When used as a salvage therapy in patients with chemorefractory disease, median survival has been reported to be eight to 16 months, compared to 3.5 to six months for supportive care or conventional therapy. When used in conjunction with chemotherapy in first-line treatment, median survival has been reported to be 29 to 38 months, compared to 12 months for chemotherapy alone.

Radioembolization has also been shown to be beneficial for patients with HCC, with the largest study showing a response rate of 49%, compared to 36% in the chemoembolization group. Similarly, patients who have been treated for intrahepatic cholangiocarcinoma have a longer median survival (15 to 16 months) than those who receive conventional treatment (three to eight months). Complications requiring hospitalization were less frequent in the group receiving radioembolization than those receiving chemoembolization, and they scored higher for functional well-being and health-related quality of life. In a small number of patients, the tumor burden has been downsized sufficiently to allow for definitive therapy, such as liver transplantation or resection.

In patients with neuroendocrine metastatic disease to the liver, radioembolization results in a high overall response rate (65 to 100%) and most patients (55 to 95%) experience symptomatic relief. Liver metastases are also common in patients with breast cancer, although metastases are often widespread in this disease. Radioembolization has been explored in these patients, usually in those with end-stage disease and a history of systemic therapies. One study reported that the median survival of breast cancer patients after radioembolization was 13.6 months, compared with a life expectancy of 4.2 months. Uveal melanoma is another cancer that frequently metastasizes to the liver, and death is often due to liver failure. When radioembolization is used to treat these patients, median overall survival is longer than anticipated compared to conventional treatment.

Further Information
For further information on radioembolization, please contact Suvranu Ganguli, MD, Interventional Radiology, Department of Radiology, Massachusetts General Hospital, at 617-726-3937.

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Janet Cochrane Miller, D. Phil., Author
Raul N. Uppot, M.D., Editor