Selective Internal Radiation Therapy—Tackling the Tumor, Sparing the Organ

Primary liver cancer is the fifth most common cause of cancer in the world, with hepatocellular cancer (HCC) accounting for a large majority of cases. HCC has the highest incidence in East Asia and sub-Saharan Africa and is the fastest-growing cause of cancer-related death in the US. The liver is also a common site for metastases from other primary cancers, especially colorectal cancer because of portal venous drainage of the bowel. Approximately 20% of colon cancer patients are found to have stage IV disease at the time of initial diagnosis. In 40% of these cases metastases are confined to the liver, and most of these patients have no extra-hepatic metastases, even at the time of death.

The only curative therapy for liver cancer is surgical removal of the tumor. Surgery may prolong survival in well-selected patients with liver metastases from colon cancer, although only 10–20% of patients with liver metastases are reasonable surgical candidates. If surgery is not possible, local ablative therapies such as radiofrequency ablation are possible for some patients with a limited number of small tumors. For those with liver tumors who cannot be treated surgically or with ablative therapy, the prognosis is generally poor. Systemic chemotherapies can downsize some metastases to the point of resectability, but primary liver tumors do not generally respond to this treatment. External-beam radiation is limited by the relatively poor tolerance of the normal liver to standard radiation techniques.

The vascular supply of liver tumors offers a unique opportunity to selectively deliver therapeutic agents to liver tumors while sparing the rest of the organ. Liver tumors receive >80% of their blood supply via the hepatic artery, whereas the portal vein provides about 75% of the blood supply to the normal liver parenchyma. In addition, the microvascular density of liver tumors is three to 200 times greater than the surrounding liver parenchyma. These differences have been exploited in the development of treatments that are delivered via the hepatic artery, including transarterial chemoembolization, embolization to induce tumor ischemia, and embolization using drug-eluting microspheres or radiation-emitting microspheres.

Two types of selective internal radiation therapy (SIRT) radiolabeled microspheres are available, one of which is made of glass (TheraSphere®, MDS Norton Inc., Canada) and the second of which is made of resin (SIR-Spheres®, Sirtex Medical Inc., Australia). Both carry 90yttrium (Y), a beta emitter with a half-life of 64.1 hours and an average energy of 0.94 megaelectron volts (MeV), which corresponds to a maximum range of 1.1cm within tissue with a mean path of 2.5mm. The two formulations differ considerably in terms of particle size and average dose of radioactivity delivered. In 2002, the US Food and Drug Administration (FDA) gave pre-market approval of SIR-Spheres as a brachytherapy device for the treatment of metastases from colorectal cancer. TheraSphere is approved as a humanitarian device for use in patients with unresectable HCC.

Treatment with Sir-Spheres is considered to be the third-line option for patients with colorectal metastatic disease that is confined to the liver or with minimal extra-hepatic involvement. A few reports have suggested better long-term survival in patients with colorectal cancer when SIRT was used in conjunction with other chemotherapy. In most cases, patients have exhausted other treatment options and no longer respond to chemotherapy, cannot tolerate or refuse chemotherapy, or choose to receive both SIRT and chemotherapy.

**Patient Selection and Preparation**

The first step in evaluating a patient for SIRT is proper staging to confirm that metastatic disease is largely confined to the liver and ensure that the
patient meets the selection criteria in order to minimize the likelihood of life-threatening complications (see Table 1). A computed tomography (CT) (see Figure 1A) or magnetic resonance (MR) examination will establish tumor burden in the liver. A positron emission tomography (PET) (see Figure 1B) or PET/CT examination is helpful to evaluate the extent of metastasis as well as to provide a baseline measure of the metabolic activity of the tumors, which can be used to assess the response to SIRT. Only patients with few or no extra-hepatic metastases will benefit from SIRT.

Laboratory evaluations are essential in order to determine whether patients have adequate liver function (bilirubin <2mg/dl) and renal function (epidermal growth factor receptor [eGFR] >30ml/minute/m²). Patient performance status should be graded according to the Eastern Co-operative Oncology Group (ECOG) scheme. Patients with compromised performance (score of two to four) have an increased risk for treatment-related morbidity. The next step is an angiographic examination to assess the anatomy of the celiac, superior mesenteric, and hepatic arteries. A detailed, meticulous angiography (see Figure 2A) of the hepatic arteries is important. First, it is useful to determine whether a whole-liver or lobar approach is appropriate for infusion of ⁹⁰Y microspheres, second, to isolate the arterial supply to one or two arteries by embolizing the multiple feeders so as to simplify the treatment, and third, to occlude extra-hepatic arteries such as the gastroduodenal artery (GDA), right gastric artery (RGA) (see Figure 2B), and others to prevent non-target embolization because this would result in radiation-induced gastroduodenal ulcers. In addition, portal vein patency should be assessed because of the danger of acute liver failure if there is an occlusion. However, patients with a thrombosis in a first-order branch of the portal vein appear to tolerate SIRT.

The fourth step in treatment planning is to determine the degree of hepatopulmonary shunting due to the tumor. This phenomenon is more common with HCC. The assessment is accomplished by infusing macro-aggregated albumin (MAA) particles labeled with ⁹⁹mTc 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, that to the lungs and abdominal organs. Planar scintigraphy is used to assess the distribution of radioactivity: if >20% of the radioactivity reaches the lungs (see Figure 3A), SIRT is contraindicated because of the risk of developing radiation pneumonitis: if 10–20% reaches the lungs, it is possible to perform SIRT with a reduced dose of ⁹⁰Y; if <10% reaches the lungs (see Figure 3B), the procedure can be conducted using the standard protocol.

The dose is calculated on the assumptions that the deposition of SIR-Spheres is influenced by the extent of the tumor burden and that the resulting deposition will not be uniform. Two methods of dose calculation are used, one based on body surface area and the other on empirical data. The former uses the equation A=body surface area [BSA] -0.2 + tumor volume [TV]/(TV plus liver volume [LV]), where A is the activity of the ⁹⁰Y content of the microspheres in gigabecquerel (GBq). The latter method assumes that if the tumor involves <25% of the total liver volume, the nominal dose is 2GBq. This rises to 5GBq if the tumor burden is 25–50%, and 3GBq if the tumor involves >50% of the total liver. These doses are reduced to 80% of the nominal dose if the hepatopulmonary shunt fraction is 10–15%, and 60% of the nominal dose if the hepatopulmonary shunt fraction is 15–20%.

### Table 1: Patient Selection Criteria for Selective Internal Radiation Therapy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>Non-resectable liver tumors and ineligible for other local/regional therapies</td>
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<tr>
<td>Previously treated unsuccessfully with intravenous chemotherapy</td>
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<tr>
<td>No prior external-beam radiation</td>
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<tr>
<td>Little or no extra-hepatic malignancy</td>
<td></td>
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<tr>
<td>No significant hepatopulmonary shunting</td>
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<tr>
<td>No recent (within past 2 months) treatment with capcitabine</td>
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<tr>
<td>Serum bilirubin ≤2mg/dl</td>
<td></td>
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<tr>
<td>Creatinine ≤1.8mg/dl</td>
<td></td>
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<tr>
<td>Platelet count ≥50,000µl</td>
<td></td>
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<tr>
<td>No portal vein occlusion with hepato-fugal flow</td>
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<td>Low risk for microsphere implantation in non-occludable vessels to other organs</td>
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<td>Life expectancy &gt;6 weeks</td>
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<td>Eastern Co-operative Oncology Group performance status ≤3</td>
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### Figure 1: Imaging of the Liver in a Patient with Colon Cancer

A: Axial computed tomography (CT) of the liver in a patient with colon cancer shows metastasis (arrows) in segment eight of the liver; B: Positron emission tomography (PET) image of same patient showing high focal uptake (arrow) of ¹⁸F-fluoro-deoxy-glucose in the tumor. With permission from Kalva et al.

### Figure 2: Detailed Angiography of the Hepatic Arteries

A: Pre-treatment angiogram shows normal celiac artery; B: Angiogram after coil embolization of the gastroduodenal artery (GDA) (single arrows) and right gastric artery (RGA) (two arrows) shows successful embolization with no flow into these vessels. Coil embolization is performed to prevent accidental reflux of SIR-Spheres from the hepatic artery to the gut vessels.

### The Procedure

For each procedure, the SIR-Spheres are delivered in a kit that includes apparatus that shields the radiation and provides a closed circuit to prevent spills (see Figure 3). Patients are not allowed to eat or drink anything for six hours prior to the procedure, which is performed under conscious sedation and local anesthesia at the catheter insertion site. An angiographic catheter is inserted into the femoral artery and guided into the arteriolar circulation of the liver. If the entire liver is to be treated, the microspheres are infused from a microcatheter into the proper hepatic...
artery. In some cases, especially if there are many small tumors scattered throughout the liver, the microspheres are administered in two treatment sessions, with an infusion into the right hepatic artery in the first session and into the left hepatic artery in the second treatment session. Once the infusion is completed, the microcatheter is withdrawn into the angiographic catheter prior to its removal to prevent unwanted deposition of radioactivity.

Immediately after completion of the procedure, planar scintigraphy or single photon emission CT (SPECT) is used to assess the distribution of $^{90}$Y in the liver and to detect misplacement of the microspheres in the gastrointestinal tract. Patients are required to lie flat for two to six hours after the procedure and generally stay in hospital overnight for observation. Precautions to prevent unnecessary exposure to radiation in people other than the patient include avoiding contact with pregnant women and not permitting children to sit on the patient’s lap for a few days following the procedure.

### Follow-up

Patients should be evaluated at approximately one and three months after the procedure, and at three-monthly intervals thereafter. Both laboratory tests for liver function and imaging tests for tumor burden are necessary to assess tumor response. Two weeks after SIRT, the level of carcinoembryonic antigen (CEA) is often higher than at the time of treatment, but it declines by six weeks after treatment. CEA reduction from the pre-treatment value within two months of SIRT confers significant survival benefit. Although the standard method for determining tumor response is measuring tumor size, size alone is not reliable because necrosis, hemorrhage, and edema can cause an initial increase in size in a tumor that is responding. Despite this limitation, the majority of patients have a partial response or stable disease after SIRT by CT criteria (see Figure 4A), and most die as a result of extra-hepatic disease. In some cases, new liver tumors develop. Provided that there are no significant metastases elsewhere, patients can be re-treated with SIRT.

### Table 2: Response to Selective Internal Radiation Therapy

<table>
<thead>
<tr>
<th>Patients (Number)</th>
<th>Primary Tumor (Number)</th>
<th>Trial Design</th>
<th>Response to Treatment</th>
<th>Major Complications of SIRT (Number)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>CRC</td>
<td>Prospective, randomized, SIRT + HAC versus HAC</td>
<td>Median time to progression: 15.9 versus 9.7 months (p&lt;0.001)$^a$</td>
<td>None reported</td>
<td>Gray et al. $^1$</td>
</tr>
<tr>
<td>21</td>
<td>CRC</td>
<td>Prospective, randomized: chemotherapy + SIRT versus chemotherapy</td>
<td>Median survival: 29.4 versus 12.8 months</td>
<td>Liver abscess (1) Radiation-induced cirrhosis (1)</td>
<td>Van Hazel et al. $^2$</td>
</tr>
<tr>
<td>39</td>
<td>CRC (17) BC (7) HCC (4) Other (6)</td>
<td>SIRT alone</td>
<td>Median time to progression: 6.5 months 8.5 months &gt;8$^b$ months 8$^b$ months</td>
<td>Gastric ulcer (2) Pancreatitis (1)</td>
<td>Jacobs et al. $^3$</td>
</tr>
<tr>
<td>100</td>
<td>CRC</td>
<td>SIRT alone</td>
<td>Median survival: Group 1: 8.7 months Group 2: 18.5 months</td>
<td>Gastric ulcer (8) Radiation hepatitis (1 fatal) Pancreatitis (1 fatal) Liver abscess (1)</td>
<td>Stubbs et al. $^4$</td>
</tr>
<tr>
<td>208</td>
<td>CRC</td>
<td>Multicenter study, SIRT alone</td>
<td>Median survival: Responders (90%): 10.5 months Non-responders (10%): 4.5 months</td>
<td>Gastric ulcer (12) Pulmonary embolus (1)</td>
<td>Kennedy et al. $^5$</td>
</tr>
<tr>
<td>30</td>
<td>CRC</td>
<td>SIRT alone; previously treated with fluorouracil</td>
<td>Median time to progression: All: 5.3 months Partial responders: 9.2 months</td>
<td>Gastric ulcer (4)</td>
<td>Lim et al. $^6$</td>
</tr>
<tr>
<td>21</td>
<td>CRC (10) Primary liver (3) Other (8)</td>
<td>SIRT alone</td>
<td>Median survival: Group 1: 5 months Group 2: 10 months</td>
<td>Cholecystitis, fibrosis, and portal hypertension (1) Gastric ulcer (1) Radiation hepatitis (2)</td>
<td>Jiao et al. $^7$</td>
</tr>
<tr>
<td>12</td>
<td>CRC</td>
<td>SIRT alone (7) SIRT and chemotherapy (6) SIRT and radiofrequency ablation (1)</td>
<td>Median survival: 4.5 months</td>
<td>Gastric ulcer (1)</td>
<td>Murthy et al. $^8$</td>
</tr>
<tr>
<td>24</td>
<td>HCC</td>
<td>SIRT alone</td>
<td>Median survival: 7 months</td>
<td>Jaundice (2)</td>
<td>Sangro et al. $^9$</td>
</tr>
<tr>
<td>20</td>
<td>CRC</td>
<td>SIRT + FOLFOX</td>
<td>Median time to progression: Group 1: 12.3 months (13/20) Group 2: 14.2 months (7/20)</td>
<td>Gastric ulcer (2)</td>
<td>Sharma et al. $^{10}$</td>
</tr>
<tr>
<td>24</td>
<td>CRC (7) HCC (7) Other (10)</td>
<td>SIRT alone</td>
<td>Median survival: 9 months 3.5 months 5.8 months</td>
<td>Gastric ulcer (1)</td>
<td>Rowe et al. $^{11}$</td>
</tr>
</tbody>
</table>

$^a$ Treated with SIRT and intra-HAC. $^b$ Control group, treated with intra-HAC alone. $^c$ Two patients died before first follow-up (within two to three months after SIRT) and were not included in analysis. $^d$ Group 1, with extra-hepatic disease; Group 2, no extra-hepatic disease. $^e$ No progressive disease in four patients at time of report; 15–18 months after SIRT, 53% of patients with progressive disease developed lung metastases, two patients were downstaged, and liver tumors were surgically resected.
PET is more sensitive than CT for the assessment of early response (see Figure 4B), and in one study 12 of 14 patients had a drop in standardized uptake value (SUV) on fluoro-deoxy-glucose (FDG)-PET imaging after six weeks, whereas only two of 15 patients had smaller lesions on CT at this time. In addition, there is some evidence that an increase in apparent diffusion constant, measured by diffusion-weighted MRI, may be a useful indicator of early response and the development of tumor necrosis. Early evidence of response may be useful in guiding further treatment.

**Patient Outcome**

There have been two prospective, randomized clinical trials of SIRT, one of which compared SIRT with hepatic artery chemotherapy (HAC), while the other compared SIRT alone with SIRT and systemic chemotherapy. Both showed that SIRT prolonged the lives of patients with liver metastases from colorectal cancer (see Table 2). Since then, there have been a number of reports on patient outcome following SIRT alone or combined with other treatments (see Table 2).

**Summary**

For the most part, complications are not serious. Low-grade fever, loss of appetite, lethargy, and fatigue are common for up to six weeks after the procedure. Acute abdominal/epigastric pain and/or nausea has been reported to occur in 30% of patients. The most common major complication is radiation-induced gastric ulcer (see Table 2), which can occur if any microspheres lodge in the blood vessels of the stomach. Unfortunately, radiation-induced ulcers do not heal well and can be distressing, and are best avoided by aggressive embolization of collateral vessels that supply the gut. Rare complications include radiation-induced pancreatitis and jaundice. The latter is more likely to occur in patients with HCC. These complications can be minimized by meticulous patient selection and preparation procedures.

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