

Radioembolization with ⁹⁰Yttrium Microspheres: A State-of-the-Art Brachytherapy Treatment for Primary and Secondary Liver Malignancies

Part 1: Technical and Methodologic Considerations

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Microsphere and particle technology represent the next-generation agents that have formed the basis of interventional oncology, an evolving subspecialty of interventional radiology. One of these platforms, yttrium-90 microspheres, is rapidly being adopted in the medical community as an adjunctive therapeutic tool in the management of primary and secondary liver malignancies. Given the complexity of the treatment algorithm of patients who may be candidates for this therapy and the need for clinical guidance, a comprehensive review of the methodologic and technical considerations was undertaken. This experience is based on more than 900 ⁹⁰Y infusions performed over a 5-year period.

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Abbreviations: ECOG = Eastern Cooperative Oncology Group, FDA = Food and Drug Administration, GDA = gastroduodenal artery, HCC = hepatocellular carcinoma, LSF = lung shunt fraction, MAA = macroaggregated albumin, PET = positron emission tomography, PS = performance status, SPECT = single photon emission computed tomography, TACE = transcatheter arterial chemoembolization

YTTRIUM-90 microspheres are 20- to 40- μ m particles that emit β -radiation. Because the microspheres are delivered via the hepatic arterial route, the process can be considered as internal rather than external radiation. The treatment algorithm is analogous to that followed with transarterial chemoembolization (TACE). Clinical history, physical examination, laboratory values, and performance status (PS) are evaluated. Patients' conditions are initially evaluated and their disease is staged with cross-sectional imaging techniques: computed tomography

(CT), magnetic resonance (MR) imaging, and/or positron emission tomography (PET). When a patient is considered a possible candidate for therapy, evaluation with mesenteric angiography followed by treatment on a lobar basis is undertaken. Patients are followed up clinically to assess toxicities and response before treatment of the other lobe is undertaken.

TheraSphere (glass microsphere; MDS Nordion, Kanata, ON, Canada) was approved in 1999 by the U. S. Food and Drug Administration (FDA) under a humanitarian device exemption for the treatment of unresectable hepatocellular carcinoma (HCC) in patients who can have appropriately positioned hepatic arterial catheters (1). Medical professionals are directed to published FDA guidance documents on humanitarian device exemptions for uses in diseases other than HCC (2). SIR-Spheres (resin microsphere; Sirtex Medical, Lane Cove, Australia) were granted full premarketing approval in 2002 by the FDA for the treatment of colorectal metastases in conjunction with intrahepatic floxuri-

dine (3). Given the dearth of published literature on the technical and methodologic considerations required for proper ⁹⁰Y implementation and usage, this comprehensive overview was undertaken. For the purposes of this article, unless otherwise stated, ⁹⁰Y microspheres, radioembolization, and selective internal radiation therapy will refer to the use of TheraSphere and SIR-Spheres.

The use of ⁹⁰Y for the primary and secondary treatment of liver malignancies is not investigational or experimental (2). Given the FDA approval for both devices, their use in HCC and colorectal cancer represents their approved indication. For disease states other than the strict indication, the use of ⁹⁰Y represents the practice of medicine. This article is the first of a series of three that will be published on the topic of radioembolization. The first part will focus on the technical and methodologic considerations. The second will discuss special topics as they relate to ⁹⁰Y microspheres. The third will provide a comprehensive literature review on the topic of radioembo-

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lization and discuss future directions for this technology. It should be noted that some of the discussions presented in parts 1 and 2 represent the opinions of the authors, whereas part 3 represents a strict review of the literature. This experience is based on more than 900 ⁹⁰Y infusions performed over a 5-year period by a multidisciplinary team including investigators from medical oncology, hepatology, surgery, transplantation, and interventional radiology as the authorized users.

TECHNICAL AND METHODOLOGIC CONSIDERATIONS

Overview

Radioembolization is defined as the injection of micron-sized embolic particles loaded with a radioisotope by use of percutaneous transarterial techniques. There are two distinct aspects to the procedure. The first is the injection of embolic particles (ie, "embolization") as the vehicle; the second is the delivery and administration via this embolic vehicle of radiation ("radio-"). Fluoroscopic guidance, angiographic endpoints of embolization and stasis, and the need to modify this on the basis of angiographic findings make this treatment a true embolization procedure. In addition, dosimetry planning, the administration and delivery of radiation, modification of dose on the basis of tumor and hepatic volume, and the required knowledge of radiation effects on tissue make this a brachytherapy procedure as well. Although the term "selective internal radiation therapy" has also been used to describe this therapy, "radioembolization" more accurately describes the actual mode of action of ⁹⁰Y microspheres according to the rationale described. Hence, for technologies that require embolic particles to carry radioisotopes to the targeted tumors, we propose that the term "radioembolization" be formally recognized.

HCC represents one of the most common forms of cancer, with more than 1 million new cases estimated annually worldwide. In the United States, the incidence of HCC has steadily increased during the past two decades, an estimated 18,900 new cases having been diagnosed in 2004

(4). Traditionally, these patients have had few treatment options (5). The safety and therapeutic benefit of ⁹⁰Y microspheres for HCC is well documented in the literature (6–8).

The evaluation of unresectable HCC is significantly different from that of metastatic disease. Curative options include liver transplantation and resection (9). Unfortunately, only 10%–15% of patients are candidates for curative therapy (9). Ideal candidates for treatment with ⁹⁰Y microspheres include patients with a performance status (PS) of 0–2, intact liver function, and a patent portal vein. Unlike patients with metastatic disease to the liver, pathologic confirmation of HCC is not always necessary and may be established in patients with classic history (ie, alcohol or viral hepatitis), imaging findings (ie, hypervascular tumors, cirrhosis) and a serum α -fetoprotein level greater than 400 ng/mL (10). The benefits of radioembolization with ⁹⁰Y in patients with HCC has been previously described (7,11–19).

Patients with metastatic cancer to the liver often have complex medical histories. In cases of colon cancer, if the disease is detected in the early stages, resection of the primary tumor without lymph node involvement may obtain long-term cure. In some cases, patients with stage IV disease with liver metastases may be treated with surgical resection alone, also providing a chance for long-term cure. In patients with surgically unresectable liver disease with or without extrahepatic disease, systemic chemotherapy has become the standard for first- and second-line treatment (20,21). Combination therapy with angiogenesis inhibitors and surgical resection has now become an integral part of first- and second-line therapies (22). Patients with liver-dominant disease in which standard first- and second-line therapies have failed may be considered for treatment with ⁹⁰Y.

The liver is the most frequent site of metastases, primarily as a result of the spread of cancer cells through the portal circulation. In fact, approximately 60% of patients with colorectal carcinoma eventually have liver disease as the predominant site (23). Similarly to HCC, surgical resection of metastatic hepatic disease is the treatment of choice. However, surgical resection is feasible in fewer than 20% of patients

(23). The benefits of radioembolization with ⁹⁰Y in these patients has been reported in many studies (24–29).

PATIENT SCREENING AND SELECTION

Clinical Presentation and Imaging Correlates in HCC

The selection process for patients undergoing ⁹⁰Y treatment is multifactorial. Simply put, ideal patients should have liver-only or liver-dominant disease, minimal comorbidities, and normal liver function test results. Patients with HCC may have a clinical history of viral (hepatitis B or C virus) or alcoholic cirrhosis. In rare instances, patients may present with cirrhosis of uncertain cause, a condition often referred to as nonalcoholic steatohepatitis (30). Depending on the severity of the disease, patients can manifest other sequelae of cirrhosis such as encephalopathy, ascites, and portal hypertension with or without portal vein thrombosis. Patients with HCC may have varied surgical and therapeutic histories, including previous resection, radiofrequency ablation, or TACE. Clinical considerations in these patients include the degree of hepatic compromise and imaging findings.

Hepatoma findings on imaging are quite variable (31). If ultrasound (US) is the initial diagnostic modality, additional cross-sectional imaging should be performed. Other than operator dependence, altered hepatic echotexture can result in a high false-negative rate, especially for smaller lesions. Also, in some cases, infiltrative tumors can be misdiagnosed as peliosis hepatis (32). For patients with cirrhosis, any hepatic mass should be considered a hepatoma until proven otherwise, warranting further investigation. Triple-phase CT is highly sensitive in the detection of hepatoma (33). Because many of these tumors are hypervascular, scanning in the early phases allows for detection. Later-phase imaging is necessary to detect other less vascular lesions and multifocality, as well as to identify portal vein patency (33). Alternatively, MR imaging can also be used to identify and characterize HCC lesions, with specific attention to diffusion-weighted imaging sequences and oxygenation (34,35). The diagnosis of

Table 1
ECOG Performance Status and Karnofsky Score

ECOG Scale	Characteristics	Equivalent Karnofsky Score (%)
0	Asymptomatic and fully active	100
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity	80–90
2	Symptomatic; ambulatory; capable of self-care; >50% of waking hours are spent out of bed	60–70
3	Symptomatic; limited self-care; spends >50% of time in bed	40–50
4	Completely disabled; no self-care; bedridden	20–30

HCC can be confirmed by invasive means (ie, fine needle aspiration or core biopsy) or noninvasive means (ie, imaging criteria, α -fetoprotein level >400 ng/mL) (10). If HCC can be diagnosed according to imaging and biochemical criteria, biopsy should be avoided, given the risk of tract seeding after percutaneous needle procedures such as radiofrequency ablation (36). CT and MR imaging are useful in the posttreatment identification of necrosis and cell death, allowing assessment of tumor response to ^{90}Y therapy (10,37).

On the basis of a retrospectively performed review of historical data, Okuda et al (38) developed a staging system for patients with HCC. From this, historical controls were developed, and median survival for untreated HCC was estimated to be 3–6 months. The variability results in part from the late stage of disease with which many of these patients present. With proper screening of patients at high risk, it is possible to detect hepatoma at the point at which adequate hepatic reserve is present. The ideal patient for ^{90}Y therapy has less than 50% tumor burden, no ascites, normal bilirubin level, and albumin level greater than 3 g/dL, translating into Okuda stage 1. Although the lobar treatment approach increases the safety profile of ^{90}Y therapy, patients with increased liver function test results (>1.2 g/dL) should be treated cautiously (discussed later). In these patients, if the tumor can be isolated angiographically, segmental/subsegmental infusion (just as with TACE) should be undertaken to provide therapeutic benefit (such as downstaging for transplantation, radiofrequency

ablation, or resection) while minimizing the risk of hepatic decompensation (39). Recently, other staging systems have supplanted the Okuda system, such as the Cancer of the Italian Liver Program, Child-Pugh, or Barcelona Clinic Liver Cancer systems (40). In our center, we stage disease with the Okuda, Child-Pugh, Cancer of the Italian Liver Program, and Barcelona Clinic Liver Cancer scales.

In summary, HCC should be staged appropriately to provide valuable prognostic information. The patient's condition should be quickly assessed for possible resection or transplantation. If not, it is possible that the patient might be a candidate for downstaging of HCC (41). Because the majority of HCC patients have unresectable disease, palliative options such as TACE, drug-eluting microspheres, and ^{90}Y treatment may be considered.

Clinical Presentation and Imaging Correlates in Metastatic Disease

Metastatic disease to the liver is the most common form of hepatic malignancy (42). In particular, given the increasing incidence of colorectal cancer, percutaneous management will continue to play an increasingly important role in this disease (43). Patients with metastatic cancer usually have better PS than those with hepatoma and have successfully completed two or three different courses of chemotherapy. First- and second-line therapies usually include 5-fluorouracil/leucovorin, irinotecan, and oxaliplatin, with or without bevacizumab. The inherently rich blood supply of some metastatic tumors such as renal or

neuroendocrine tumors makes them ideal for intraarterial therapy.

Factors to consider in patients with metastatic disease to the liver include a history of chemotherapy, surgical resection, infusion pump placement with surgically altered vascularity, and imaging findings of liver-dominant disease. Of particular interest is the increasing pool of patients undergoing liver-directed therapy after failure of growth-factor inhibitors such as bevacizumab and cetuximab. However, in all patients, one of the most important factors in determining eligibility for ^{90}Y treatment is Eastern Cooperative Oncology Group (ECOG) PS. Patients presenting with clearly compromised functional status (ECOG 2–4) (Table 1) are at high risk for rapid onset of liver failure and treatment-related morbidity. Although each patient deserves individual consideration, careful thought should precede treatment of these clinically compromised patients.

Findings on cross-sectional imaging in patients with liver metastases are relatively consistent. Unlike HCC, in which a diagnosis can be made according to imaging criteria, these do not exist for metastatic lesions. Hence, when a mass is identified in a patient with metastatic disease, pathologic confirmation is usually necessary. PET should play an integral role in the disease staging and clinical follow-up of patients receiving ^{90}Y therapy. Given the recognized limitations of tumor size in the follow-up of patients receiving liver-directed therapy, PET appears to provide more salient information regarding functional improvement after treatment (28,42,44,45). The use of PET in this setting is analogous to its clinical use in patients with lymphoma (46).

Irrespective of the cause of the liver tumors, evaluation of a patient for possible treatment with ^{90}Y should be driven by the patient's ECOG PS rather than the clinical disease stage. In the current authors' experience, PS has been the most reliable indicator of a patient's ability to tolerate ^{90}Y treatment (16,42). From a practical standpoint, patients with an ECOG PS of 0–2 (equivalent to Karnofsky score of $\geq 60\%$) should be considered for therapy (Table 1). For patients who do not fulfill this criterion, the decision to treat should be based on individual patient evaluation and clinical judgment.

In summary, patients with metastatic disease to the liver should also have their disease staged appropriately. They should have liver-only or liver-dominant disease. Some may present with painful bulky tumors that require palliation. Unless contraindicated, patients should have completed standard-of-care chemotherapy. In such cases, palliative options such as TACE, bland embolization, and ⁹⁰Y therapy may be considered (42,47).

Liver Function Parameters and Tumor Markers in HCC and Metastatic Disease

As described in the oncologic literature, the best indicators of overall liver function include prothrombin time and levels of albumin and total bilirubin (48). This is particularly true of patients with HCC. Just as patients with normal findings in these three parameters have better outcomes of systemic chemotherapy, ⁹⁰Y patients will also have better long-term outcomes if these three biochemical factors are within normal range (48). Ideally, before treatment with ⁹⁰Y, patients should have recent determination of laboratory values, including liver function and complete blood count with differential. Patients with HCC should also have recent measurements of prothrombin time and International Normalized Ratio.

Other parameters that should be evaluated before treatment of liver cancers include tumor markers, most commonly α -fetoprotein for hepatoma (>400 ng/mL is usually diagnostic), carcinoembryonic antigen for colorectal malignancies, cancer antigen 19-9 for tumors of pancreaticobiliary origin, and serotonin/5-hydroxyindole acetic acid/chromogranin A for some neuroendocrine tumors. Although not all tumors produce these markers, they may be helpful during follow-up, when response to treatment is being assessed and quantified biochemically. If these tumor markers are measured immediately after treatment, a false increase caused by tumor lysis may be observed. Although nonspecific, other markers such as lactate dehydrogenase and C-reactive protein may be helpful in posttreatment monitoring. C-reactive protein has also

been shown to have prognostic value in patients with HCC (49).

VASCULAR ANATOMY, TARGET VASCULAR BED, PULMONARY SHUNT, AND GASTROINTESTINAL FLOW

Given the propensity for arterial variants and hepatic tumors to exhibit arteriovenous shunting, all patients being evaluated for ⁹⁰Y must undergo pretreatment mesenteric angiography (17,39,50). In summary, meticulous, detailed, and power-injection imaging of the hepatic and visceral vasculature should be performed in all patients before treatment. Vessels that must be interrogated include the celiac artery, common and proper hepatic arteries, gastroduodenal artery (GDA), and right and left hepatic arteries. Knowledge of the arterial anatomy allows for the administration of ⁹⁰Y, with one treatment to each target vascular bed (usually the hepatic lobe or segment) at 30- to 60-day intervals. However, when variants are present, treatment plans must be tailored to ensure safe and accurate delivery of ⁹⁰Y microspheres. For instance, in some cases, a middle hepatic artery may be present, usually arising from the right hepatic artery. Despite accurate catheter placement, this anatomy may preclude delivery of ⁹⁰Y to the segment supplied by the middle hepatic artery, given the flow dynamics. Therefore, three treatments (one each to the right, middle, and left hepatic arteries) may be necessary to cover the entire liver. Another example might include a patient with an accessory right hepatic artery, necessitating a third treatment (left hepatic [segments 2-4], right hepatic [segments 5/8], and accessory right hepatic [segments 6/7]) (50).

Pretreatment angiography allows for accurate calculation of the target volumes. Although discussed in later sections, target volume deserves special attention. Irrespective of the ⁹⁰Y agent used, it is imperative that dosimetry calculations be based on the volume of the target vascular bed supplied by the artery to be catheterized. For instance, the simplest scenario might include a patient with standard anatomy, with single right and left hepatic arteries. In this case, if the lesions to be treated are located within the right lobe, the target volume includes

the entire right lobe, with the middle hepatic vein (or gallbladder) as the separator between the right and left lobes (see Treatment Process section). In the case of a patient with right and accessory right hepatic arteries, techniques in target volume calculations will have to be altered. Usually, the accessory right hepatic artery will supply the posterior segment of the right lobe (segments 6/7). The right hepatic artery branching off the proper hepatic artery will supply the anterior segment of the right lobe (segments 5/8), and the left hepatic artery will supply the left lobe (segments 2-4). Knowledge of this vascular anatomy permits accurate lobar volume calculations for prescribing the correct activity to deliver the optimal ⁹⁰Y dose. To summarize, the volume used for dose calculation is determined by the volume of the liver segment(s) being supplied by the artery to be infused. In addition, the determination of target volume is best performed by the interventional radiologist who performed the initial angiographic assessment of the patient. It is the interventional radiologist who can optimally correlate the CT findings (ie, location of tumors, burden) and angiographic findings (ie, standard vs variant anatomy). Hence, it is highly recommended that calculations of volumes be determined by the interventional radiologist who has performed the diagnostic mesenteric angiogram on the patient to be treated.

Pulmonary Shunting and Technetium-99m Macroaggregated Albumin Scanning

In contrast to metastatic tumors to the liver, one of the angiographic characteristics of HCC, other than portal vein thrombosis, is direct arteriovenous shunting bypassing the capillary bed (51). As a result, one of the concerns with administration of 20- to 40- μ m ⁹⁰Y microspheres is direct shunting to the lungs, possibly resulting in radiation pneumonitis (52). When the catheter is placed in the proper hepatic artery, 4- to 5-mCi ^{99m}Tc macroaggregated albumin (MAA) is administered intraarterially. Because the size of ^{99m}Tc-MAA particles closely mimics that of ⁹⁰Y microspheres, it is assumed that the distribution of the microspheres will be

identical with that of ^{99m}Tc -MAA, and this distribution is used in the planning process. Lung shunting is assessed with planar and/or single photon emission CT (SPECT) γ -cameras. In our experience, we have used planar and fixed dual-head image acquisition techniques to assess shunting immediately after injection. Single-projection anterior planar techniques have the advantage of speed and ease of use. SPECT γ -camera techniques in two or three projections have the theoretical advantage of higher resolution and sensitivity. However, for SPECT to be performed, patients must be transferred from the angiography suite to the nuclear medicine department. The transfer time may allow for the normal degradation of ^{99m}Tc -MAA with time and may falsely increase the degree of shunting to the lungs. In our experience, we have found no clinically significant difference in the degree of lung shunting as measured by planar or SPECT techniques (53). Either technique with the use of a portable γ -camera or fixed dual-head SPECT imaging in the nuclear medicine department is acceptable for the accurate assessment of shunting. Lung shunting fraction is described in the package inserts for glass and resin microspheres (1,3) and is determined by the following equation:

$$\text{Lung shunt fraction} = \frac{\text{total lung counts}}{\text{total lung counts} + \text{liver counts}}$$

However, there are several technical nuances to the assessment of shunting. If a patient has a solitary HCC and if only one treatment is planned, injection of the ^{99m}Tc -MAA into the artery that is planned for injection is indicated (in lobar or segmental infusion). However, if the diagnosis is multifocal bilobar HCC, ^{99m}Tc -MAA injection and lung shunting should be assessed before each treatment at the lobar level. This is because HCC tumors located in different lobes may shunt to varying degrees. Without this information, the total cumulative pulmonary dose may be inadvertently exceeded.

In patients with metastatic disease, significant shunting is rare unless the tumor burden is very high. Hence, lung shunting can be assessed once

with catheter placement and ^{99m}Tc -MAA injection within the proper hepatic artery at the time of planning visceral arteriography. Overall, in our institution, we have found the incidence of significant lung shunting with HCC or metastatic disease to be well below 10%. As a result, we have now adopted injection of the ^{99m}Tc -MAA within the proper hepatic artery for all disease states (ie, HCC, metastases) unless gross arteriovenous/portal shunting is noted angiographically. If angiographic shunting is observed, lobar ^{99m}Tc -MAA imaging is performed.

Timing of imaging after injection of ^{99m}Tc -MAA is also important. There are three potential causes of the overestimation of lung shunt. First, given that ^{99m}Tc -MAA represents a radioisotope/protein structure, there is a time-dependent breakdown into smaller particles of the proteinaceous ^{99m}Tc -MAA, with subsequent migration of these smaller fragments via the normal capillary bed to the lungs. This may be a problem if too much time elapses between the injection of ^{99m}Tc -MAA in the angiography suite and the time of imaging in the nuclear medicine department. As a result, it is important that patients undergo imaging as quickly as possible after injection of ^{99m}Tc -MAA. Second, although the normal manufactured size of ^{99m}Tc -MAA particles is 30–90 μm , statistically, a small percentage of these particles will fall outside of this range. Particles that are initially manufactured smaller than 8–10 μm will shunt through the normal capillary system, which will result in an increase in perceived lung shunt. According to most manufacturers, fewer than 10% of the MAA particles are smaller than 10 μm (54). Third, free technetium may result in an inaccurate estimation of lung shunt. The interpretation of the lung shunt fraction and gastrointestinal uptake must take into consideration the presence of ^{99m}Tc -MAA. Uptake in the thyroid and salivary glands and kidneys, as well as diffuse gastric mucosal uptake, should not be considered shunting. Uptake in the gastric mucosa, the small bowel, or pancreas in the absence of salivary and thyroid uptake should be interpreted with caution because it may represent true gastrointestinal shunting.

In patients with variant anatomy in

which whole liver shunting assessment is planned, fractionated injection of ^{99m}Tc -MAA is recommended. For example, a patient with a replaced left hepatic artery should receive 1–2 mCi of ^{99m}Tc -MAA in the replaced left hepatic artery, with the other 2–3 mCi injected in the right hepatic artery. Depending on the variant anatomy that is identified, the 4- to 5-mCi vial of ^{99m}Tc -MAA should be fractionated during the planning angiography procedure in such a manner that the entire liver is imaged in one setting.

Finally, it should be stated that the injection of ^{99m}Tc -MAA should be used to absolutely determine lung shunting fraction only. An authorized user should not rely solely on the SPECT images of the upper abdomen tract to absolutely exclude gastrointestinal shunting. Rather, it should be considered an adjunctive imaging modality of the gastrointestinal tract. Exclusion of gastrointestinal flow should be accomplished by use of the combined information obtained from meticulous hepatic angiography, three-dimensional CT angiography, and SPECT imaging. Fusion of CT and ^{99m}Tc -MAA SPECT images may also be helpful in the identification of extrahepatic flow of ^{99m}Tc -MAA.

The lungs can tolerate 30 Gy per treatment session and 50 Gy cumulatively (55). Therefore, when treatment planning is undertaken and lung shunting is identified, the total cumulative pulmonary dose must be calculated. Patients may be treated if their cumulative pulmonary dose will not exceed 50 Gy for all planned infusions of ^{90}Y . However, in patients with compromised pulmonary function, such as that resulting from chronic obstructive pulmonary disease or previous lung resection, caution must be taken as total cumulative doses are approached. In these instances, the decision to treat must be individualized and based on overall clinical status. In some ^{90}Y treatment practices, conservative values of 15 Gy per treatment and 30 Gy cumulatively are used as dose limitations.

Gastrointestinal Flow via Extrahepatic Vessels

The final consideration in the angiographic evaluation of HCC and metastatic disease is the presence of

flow to the gastrointestinal tract. During each step of visceral angiography, assessment for potential gastric or small-bowel flow must be made. The celiac arteriogram is used to detect the presence of arterial variants such as replaced left hepatic artery or double hepatic arteries, as well as parasitization of blood flow to the liver tumors (50,56,57). Depending on the proximity of the left gastric branch to the other hepatic branches (such as with a gastrohepatic trunk), coil embolization of this vessel may be warranted, because this will minimize the risk of reflux during ⁹⁰Y infusion. The GDA should be identified and prophylactically embolized, particularly if the more embolic SIR-Spheres are being considered. The right gastric artery should also be identified during angiography. Although this vessel is often seen to arise from the left hepatic artery, it can also arise from the common, proper, or right hepatic artery as well as the GDA (50,57,58). Depending on the anatomic location of this vessel and the relative ease with which distal catheterization may be achieved for infusion, prophylactic coil embolization should be undertaken to minimize inadvertent deposition of ⁹⁰Y into the gastric bed. Other vessels that should be searched for include the cystic, supraduodenal, retroduodenal, falciform, accessory left gastric, and right and left inferior phrenic arteries (50,57).

Given all the complexities of angiographic assessment and the absolute requirement for the prevention of gastrointestinal flow of microspheres, the threshold for prophylactic embolization of the GDA, right gastric artery, and other extrahepatic arteries should be low, irrespective of the proximity of the intended infusion site (50). Prophylactic embolization of these vessels is of no clinical consequence, because this represents the analogue to surgically placed pumps for floxuridine infusion in patients with colorectal cancer. Surgeons placing such pumps routinely ligate the GDA and right gastric artery and interrupt any vascular communication between the liver and stomach, small bowel, or diaphragm. Reflux of microspheres into gastroduodenal or gastric circulation will almost always result in grave clinical consequences, including severe ulceration, gastrointestinal bleeding, or

pancreatitis. Given the serious clinical risks of microsphere reflux into non-target organs when prophylactic embolization is not performed versus the lack of clinical consequences of prophylactic embolization of the GDA, right gastric artery, and/or other extrahepatic vessels, the latter approach is strongly favored (50,57,58).

The use of balloon occlusion techniques for liver-directed therapy has been described previously (59). This approach to ⁹⁰Y infusion should be discouraged for several reasons. First, balloon occlusion techniques were used historically, given catheter size and fluoroscopic imaging limitations. Imaging techniques have improved significantly since then, and microcatheters and microcoils are now available. Second, the use of relatively large balloon occlusion systems may cause vessel injury, spasm, or dissection. Also, administration of ⁹⁰Y is a flow-dependent therapy. If the vessels flowing to tumor are patent, tumor hypervascularity will permit the microspheres to be "absorbed." When balloon occlusion is used, hypervascular tumor flow dynamics are eliminated, and microspheres are "pushed" within the target tissue and tumor. This may result in inadequate distribution. Finally, balloon occlusion physiology may facilitate the "layering" of microspheres, given that they are pushed into the target bed.

ALTERING VASCULAR ANATOMY TO OPTIMIZE ⁹⁰Y DELIVERY

The topic of alteration in vascular anatomy to optimize ⁹⁰Y delivery is quite complex. This complexity reinforces the importance of highly trained and dedicated interventional radiologists as an integral part of the team to safely perform ⁹⁰Y therapy. As described earlier, the proper identification of vessels involved in the hepatic and gastric distribution is crucial to successful treatment. Interventional radiologists with proper training should be able to perform the basic tasks of catheter placement and coil embolization when necessary in 95% of potential candidates. However, there are instances when patients could have vascular anatomy that may be altered percutaneously to achieve more favorable anatomy. The simplest of these examples includes coil embolization of the right gastric artery,

thereby minimizing the possibility of gastrointestinal toxicity. However, more complex alterations may be required. This topic has been extensively addressed by other investigators (50,57,58,60).

The GDA and right gastric arteries represent the two most common vessels that will require angiographic attention and evaluation. Although TheraSphere and SIR-Spheres represent significantly different embolic loads, the prophylactic embolization of the GDA and right gastric arteries is advocated. As described earlier, the clinical sequelae of this are nonexistent, whereas the potential clinical safety benefits are enormous. With respect to the small-sized right gastric artery, despite difficulty in its identification, infusion of microspheres into this vessel almost invariably leads to gastrointestinal ulceration. At times, significant difficulty in catheterization of the right gastric artery may be encountered. In such circumstances, the normal right/left gastric anastomotic arcade should permit successful embolization of the right gastric artery in a retrograde fashion via the left gastric artery (50,57).

The topic of redistribution of hepatic flow deserves special mention. In some cases, such as small hepatic vessels, redistribution of blood flow may be considered. This is accomplished by the prophylactic embolization of a main vessel (eg, left hepatic artery arising off the left gastric artery) or the embolization of a small middle hepatic artery to convert the vascular bed into a standard or whole lobe to simplify the ⁹⁰Y infusion. Although hepatic vessels such as the left hepatic artery are routinely ligated in preparation for intraarterial pump placement and floxuridine administration, this has not been definitively shown to be applicable to ⁹⁰Y with use of percutaneous techniques (61). Although floxuridine infused into a pump placed in the GDA with a ligated left hepatic artery will perfuse the entire liver, it remains to be determined whether this phenomenon is replicated with the infusion of 20- to 60- μ m ⁹⁰Y particles. It is not clear whether ⁹⁰Y microspheres will travel through the hepatic sinusoids as effectively as floxuridine. Nevertheless, investigators infusing ⁹⁰Y through surgical pumps have con-

		Yes	No
TOTAL BILIRUBIN	Normal	Lobar infusions (scenario A)	Lobar or segmented infusions (scenario B)
	Elevated	Uncertain (scenario C)	Segmented infusions only (scenario D)

sistently observed positive tumor responses (25,26). Further investigation on flow distribution and the effect on tumor response as it relates to ^{90}Y infusion is necessary.

SELECTION OF TREATMENT APPROACH: SIMPLIFIED TREATMENT MATRIX

Despite a growing body of literature clarifying the pathophysiology of HCC and metastatic disease to the liver, there remains an element of uncertainty in determining which patients should receive treatment with ^{90}Y microspheres. In addition, after the patient has been selected, the safest and most effective technique may not be obvious to the operator who is not well versed in ^{90}Y microsphere use.

HCC

We have adopted a simplified approach to the treatment of patients with unresectable HCC who are not candidates for transplantation or resection. This approach involves two variables: tumor presentation (ie, unifocal or multifocal/bilobar disease) and total bilirubin level. For patients with unifocal tumors and normal bilirubin levels, treatment may be conducted via a lobar or angiographically isolatable vessel(s) (ie, segmental infusion). For patients with unifocal tumor and increased bilirubin levels, treatment with ^{90}Y should proceed only if a segmental feeding vessel may be isolated, resulting in a high dose delivered to the tumor and no radiation to the normal parenchyma. The intent in these patients would be definitive therapy or downstaging of disease to permit transplantation. For patients with multifocal tumor and normal bilirubin levels, staged and lobar infusions should be undertaken, analo-

gous to the classical TACE paradigm. For patients with multifocal disease and increased bilirubin levels, the risks of ^{90}Y treatment in this setting may be unacceptably high (as discussed later).

Table 2 displays a simplified 2-by-2 decision matrix that has been created to simplify and guide the user on the use of ^{90}Y in unresectable HCC. This simple table describes the most commonly encountered clinical scenarios in patients with HCC. The management of these four scenarios is dependent on the following assumptions: (i) ^{90}Y microspheres, if administered on a lobar basis, will preferentially flow to the tumor but will invariably result in some irradiation of normal hepatic parenchyma; (ii) segmental/subsegmental infusions will result in microsphere delivery to the target vascular bed only, with no irradiation of the remaining noninfused parenchyma; (iii) multifocal disease is defined by the presence of multiple tumors within a hepatic lobe that derive their blood supply from the artery feeding the lobe; (iv) increased bilirubin levels are caused by liver failure itself and not an obstructive process; and (v) in the absence of biliary obstruction and/or metabolic conditions causing an increased total bilirubin level (eg, Gilbert syndrome), the definition of increased bilirubin levels should be tailored appropriately. At the present authors' institution, increased total bilirubin level is defined as greater than 1.3 mg/dL. Given these assumptions, it is possible to appropriately tailor the treatment plan for each clinical scenario.

In patients with normal bilirubin levels and multifocal/bilobar disease (scenario A) (**Table 2**), a TACE-like paradigm should be followed, because this will allow for optimal and complete tumor coverage. In patients with

normal bilirubin and localized or unifocal disease (scenario B), a lobar or segmental infusion is appropriate. However, in this scenario, the authorized user must realize that performing a lobar infusion in a case in which a segmental infusion could technically be performed will result in the unnecessary irradiation of normal parenchyma. Given the propensity for new tumors to develop in cirrhotic liver, we will perform segmental infusions when possible, sparing the normal parenchyma and thereby allowing for future ^{90}Y infusion to nonirradiated parenchyma. In cases of localized disease with increased bilirubin levels (scenario D), patients should be assessed for possible treatment with use of a segmental approach only. The increased bilirubin level implies intrinsic hepatocyte dysfunction or failure, with a tumor that has developed within the diseased liver. In such a case, if angiographic factors permit and a segmental feeding vessel is identified on angiography, a patient may be a candidate for palliative therapy with ^{90}Y without injury to normal parenchyma (41). In some cases, patients may have liver failure with a liver tumor that exceeds the size criteria for liver transplantation. These patients should, at minimum, undergo diagnostic mesenteric angiography in a search for a segmental vessel to the tumor. If such a vessel is found, these patients can undergo segmental/subsegmental infusion without risk of non-target radiation or alteration in Child-Pugh score (39). Treatment with ^{90}Y in such cases may result in sufficient downstaging of disease to allow transplantation (62).

The management of the last category may represent end-stage liver disease and is clearly the most difficult (scenario C) (**Table 2**). Patients with multifocal disease and increased bilirubin level are clearly at high risk for hepatic decompensation after any treatment. In such cases, and in the recognition that an infusion of ^{90}Y microspheres will irradiate some normal parenchyma and may further worsen the liver failure, treatment should probably be withheld (as discussed later). In cases in which treatment is sought, hepatic artery chemoembolization or bland particle embolization in a lobar or preferably segmental

manner might be considered if the bilirubin level is 3.0 mg/dL or lower (63).

Metastatic Disease to the Liver

Table 2 may also be used to describe the most commonly encountered clinical scenarios in patients with metastatic disease to the liver and can also be used to guide users on the use of ⁹⁰Y in such patients. The management of the four scenarios in the 2-by-2 matrix, just as with HCC, is dependent on the following assumptions, with some modifications: (i) ⁹⁰Y microspheres, if administered on a lobar basis, will preferentially flow to the tumor but will also result in some irradiation of normal hepatic parenchyma; (ii) segmental/subsegmental infusions will result in microsphere delivery to the target vascular bed only, with no irradiation of the remaining noninfused parenchyma; (iii) multifocal disease is defined by the presence of multiple tumors within a hepatic lobe that derive their blood supply from the lobar artery; (iv) as opposed to HCC, patients with metastatic disease to the liver with increased bilirubin levels are more likely to have an obstructive process such as portal lymphadenopathy; (v) increased bilirubin level, in the absence of biliary obstruction, is very uncommon *de novo* in these patients and is more likely to be the result of chemotherapy toxicity (eg, from capecitabine) and/or infiltrative, end-stage metastatic disease within the liver that may or may not be apparent on imaging studies; and (vi) in the absence of biliary obstruction and/or metabolic conditions causing an increased total bilirubin level (eg, Gilbert syndrome), the definition of increased bilirubin level should be tailored appropriately. At this authors' institution, increased total bilirubin is defined by a level greater than 1.3 mg/dL. Given these assumptions, it is possible to appropriately tailor the treatment plan for each clinical scenario.

In patients with normal bilirubin levels and multifocal/bilobar disease (scenario A), lobar infusions should be performed, because this will allow for optimal and complete tumor coverage. In patients with normal bilirubin level and localized or unifocal disease (scenario B), a lobar or segmental infusion is appropriate. However, just as with HCC, the treating physician must re-

alize that performing a lobar infusion in a case in which the blood supply can be isolated and performed on a segmental basis will lead to irradiation of normal, non-tumor-containing parenchyma. Because new tumors may develop in patients with metastases as their disease progresses, the ability to repeatedly treat portions of liver that have never been irradiated may prove to be beneficial for the patient. In our institution, given the propensity for new tumors to develop in patients with metastatic disease, we will perform segmental infusions when possible, sparing the normal parenchyma, thereby allowing for future infusion to nonirradiated parenchyma. However, scenario B is uncommon in patients with metastatic disease, because they usually present with bilobar multifocal metastases.

The scenario of localized disease with elevated bilirubin (scenario D) (Table 2) is also quite uncommon in patients with metastatic disease to the liver. Nevertheless, these patients may be assessed for possible treatment with a segmental approach only. In this scenario, the increased bilirubin level implies compromised liver function. In such a case, if other factors permit (eg, PS), a patient might be a candidate for ⁹⁰Y treatment with segmental techniques without injury to the normal parenchyma. In the present authors' experience, follow-up imaging in this clinical scenario usually demonstrates the development of liver lesions in previously unsuspected portions of the liver (ie, micrometastases). If this develops and the bilirubin level continues to be increased (scenario C), treatment with ⁹⁰Y is not advocated, given the inevitable radiation of some of the remaining functional parenchyma and deterioration of liver function. In such cases, embolic therapy with or without chemotherapy (ie, TACE/bland embolization) may be considered (as discussed in the second part of this three-part series).

THE TREATMENT PROCESS

The Interdisciplinary Team: Referral Patterns and "Drivers"

The development and establishment of an interdisciplinary team is crucial to the success of a radioembolization with ⁹⁰Y brachytherapy

program. The team should be well represented with members from interventional radiology; medical, radiation, and surgical oncology; transplant surgery; nuclear medicine; hepatology; medical physics; and radiation safety. Patients may be referred for therapy from various sources. In patients with hepatoma, the initial diagnosis may be made by the hepatologist. Depending on the tumor size and location, patients may then be referred to surgical or transplant oncology departments for possible resection. If the patient is not a surgical candidate, he or she may be seen by medical oncologists for possible treatment under a clinical trial, systemic therapy, embolic-type therapy (eg, TACE), or ⁹⁰Y therapy. In general, patients with HCC are usually referred by a team composed of hepatology, transplant surgery, and HCC-focused medical oncology personnel. For patients with metastatic disease to the liver, the referrals may come directly from the medical oncology or surgical oncology departments because the surgical options may have been exhausted. Alternatively, given the limited ability to deliver external-beam therapy to the liver, the radiation oncologist may refer the patient for ⁹⁰Y treatment in an attempt to maximize the therapeutic effect of intraarterial brachytherapy. It is essential that interventional radiology play an integral role in all of these teams.

The drivers of the ⁹⁰Y process may come from any of the aforementioned medical subspecialties. Medical and surgical oncologists, interventional radiologists, or radiation oncologists may oversee the process. Irrespective of the driver, the complexity of the treatment planning process necessitates adequate representation from all disciplines. Interventional radiologists are experts in radiation physics and contribute the technical and imaging expertise, all of which is crucial for successful therapy. Radiation oncologists have expertise in brachytherapy, dosimetry, and radiation biology and treatment, and a sound understanding of radiation effects on tissue. Surgical and medical oncologists provide the treatment backbone for all malignancies. Nuclear medicine specialists have well-established expertise in handling radiopharmaceuticals, as well as nuclear and functional imaging. Radia-

Table 3
Couinaud Segments Based on Angiographic Findings

Angiographic Findings	Corresponding Target Segments	
	Right	Left
Standard right and left hepatic arteries	1, 5, 6, 7, 8	2, 3, 4
Replaced right hepatic with flow to medial segment left lobe	1, 4, 5, 6, 7, 8	2, 3
Replaced right hepatic artery without flow to middle lobe, left hepatic artery with flow to medial and lateral segments left lobe	1, 5, 6, 7, 8	2, 3, 4
Replaced left hepatic artery without flow to medial lobe		2, 3
Replaced left hepatic artery with flow to medial lobe		2, 3, 4
Accessory right hepatic artery	6, 7	
Right hepatic artery in the presence of an accessory right hepatic	5, 8	
Middle hepatic artery (irrespective of origin)		4

Note.—Vascular anatomy subject to variation. There is an assumption that caudate lobe (segment 1) derives blood supply from right hepatic artery. Among the caudate lobe (segment 1), right anterior lobe (segments 5/8), right posterior lobe (segments 6/7), left medial lobe (segment 4), left lateral lobe (segments 2 and 3), depending on tumor location, these variants will guide the volume calculation process.

tion safety specialists oversee the proper and safe use of ^{90}Y under the regulations dictated by the Nuclear Regulatory Commission or local state boards.

Clinical and Diagnostic Evaluation

The first step in the evaluation of patients for therapy includes collecting a history and conducting a physical examination. Patients should be able to tolerate treatment, as best assessed by Okuda, ECOG, and Karnofsky score evaluation. Total bilirubin level and prothrombin time are important predictors of which patients will tolerate treatment. Relevant information to be elicited includes a history of renal or hepatic failure, as well as pulmonary compromise such as chronic obstructive pulmonary disease. Tumor markers such as α -fetoprotein should be measured and may be used in the assessment of treatment response. If patients are receiving chemotherapy, it is important to discontinue the treatments 2–3 weeks before the beginning of treatment with ^{90}Y to clearly identify the agent responsible for any subsequent therapeutic response. More important, it is essential to identify those patients receiving agents known to be radiation sensitiz-

ers, such as 5-fluorouracil, capecitabine, and gemcitabine. Radiation hepatitis, a potentially fatal complication, is a theoretical concern for patients receiving ^{90}Y microspheres, particularly if it is used concurrently with radiation sensitizers.

From a diagnostic imaging standpoint, careful review of recent CT or MR imaging (with 2–4 weeks) is warranted. Controversy exists about the diagnostic pathway of a patient with cirrhosis and a liver mass. In many institutions, including the authors', a biopsy for the diagnosis of hepatoma is usually performed. Although bypassing this step might prevent bleeding, tract seeding, and false-negative results, these potential complications have not been observed clinically (36). For metastatic disease to the liver, by the time the patient is referred for ^{90}Y therapy to the liver, a diagnostic biopsy of the liver has been performed. When the cross-sectional imaging modality has been reviewed and the patient has been deemed a candidate, liver volume calculations are obtained.

Calculation of Liver Volumes: The Lobar Approach

Triple-phase CT provides the fastest and most reproducible imaging of

the liver for volume (TheraSphere) and tumor burden (SIR-Spheres) calculation. Because the treatment approach for ^{90}Y is most commonly lobar, proper imaging and volume calculation is essential for dosimetry purposes. The ability to understand hepatic anatomy relies on the sound understanding of the Couinaud hepatic segments (64). Anatomically, the middle hepatic vein separates the right and left lobes. When regions of interest are drawn and lobar volumes are calculated, it is the middle hepatic vein that should be used as the anatomic delineator between the right and left lobes. If the middle hepatic vein cannot be seen, the gallbladder fossa and its axis relative to the liver may be used. This technique assumes standard arterial anatomy with single right and left hepatic arteries. If variants are observed angiographically (eg, an accessory right hepatic artery), accurate angiographic correlations must be performed when the regions of interest for lobar or segmental volumes are drawn. This will ensure that accurate volumes are obtained and three or more treatments are administered.

The most common angiographic findings and variants, with their associated target segments (and hence required volumes), are listed in **Table 3** (50,58). It is incumbent on the interventional radiologist to have a sound knowledge of these anatomic variants and their effects on dosimetry and microsphere distribution. The following case illustrates typical anatomy and the middle hepatic vein as the landmark used for volume calculation. In **Figure 1**, Ethiodol (Savage Laboratories, Melville, NY) was injected into the left hepatic artery as part of a TACE procedure. The venous system is not visualized, because no intravenous contrast medium has been administered. The area that is highlighted by the Ethiodol is the left lobe of the liver: segments 2, 3, 4A, and 4B, and part of segment 1. Regions of interest around the right and left lobes in the same patient who received intravenous contrast medium are depicted in **Figures 2** and **3**. This demonstrates conclusively the location of the middle hepatic vein and its role as the separator between the right and left lobe by CT. **Figures 4** and **5** represent coronal maximum-intensity projection views



1.

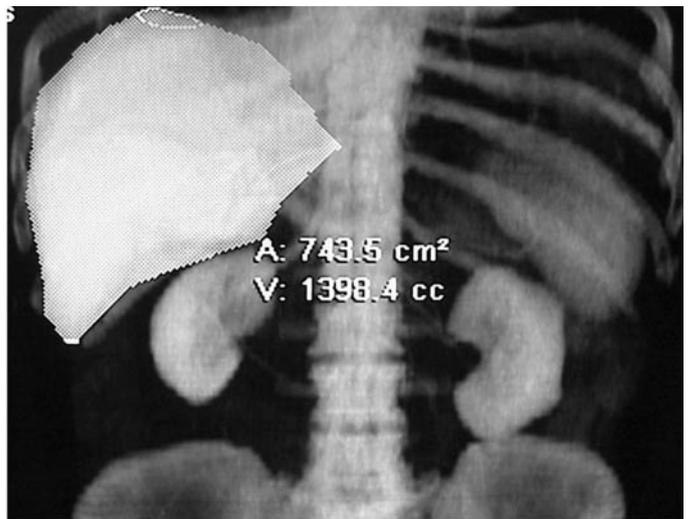


2.

Figures 1, 2. 1. Noncontrast CT of the liver in a patient with standard anatomy after TACE to the left lobe illustrates the middle hepatic vein as the anatomic separator between the right and left lobes. 2. Regions of interest drawn around the right lobe to calculate volume (segments 5, 6, 7, 8, and a portion of segment 1). The middle hepatic vein is used as the delineator between the right and left lobes.



3.



4.

Figures 3, 4. 3. Regions of interest drawn around the left lobe to calculate the volume (segments 2, 3, 4, and a portion of segment 1). In patients with standard hepatic arterial anatomy, the middle hepatic vein separates the right and left lobes. 4. Three-dimensional CT reconstruction following regions of interest around the right lobe determine the right lobe volume (1,398.4 mL). This volume is now used to calculate the activity of TheraSphere required.

of the three-dimensional reconstruction of the right and left lobes, with each respective calculated volume.

The dosimetry for SIR-Spheres is based on (i) body surface area and percentage tumor burden or (ii) percentage tumor burden alone. The latter dosimetry model is based on tumor burden with respect to the entire liver. As an example, **Figures 6** and **7** illustrate the right (937.3 mL) and left (972.6 mL) lobe volumes for a patient

to be treated with SIR-Spheres. **Figure 8** demonstrates three-dimensional reconstruction of tumor volume (311.2 mL). If tumor burden model is used, SIR-Spheres dosimetry is then based on a whole liver tumor burden of 16.3% ($311.2 / [937.3 + 972.6]$).

In this example, the TheraSphere dose calculation would be based on the lobar volume to be infused (937.3 mL) and would be independent of tumor burden. For TheraSphere dosim-

etry, the following statement is always true and should be remembered when dosimetry calculations are performed: the volume that is entered in the formula is the volume of liver tissue that is perfused by the vessel that will be infused. In other words, it is the volume of the liver segments being perfused by the vessel of interest. For example, if the right lobe is to be infused with standard hepatic arterial anatomy, the volume to be entered is that

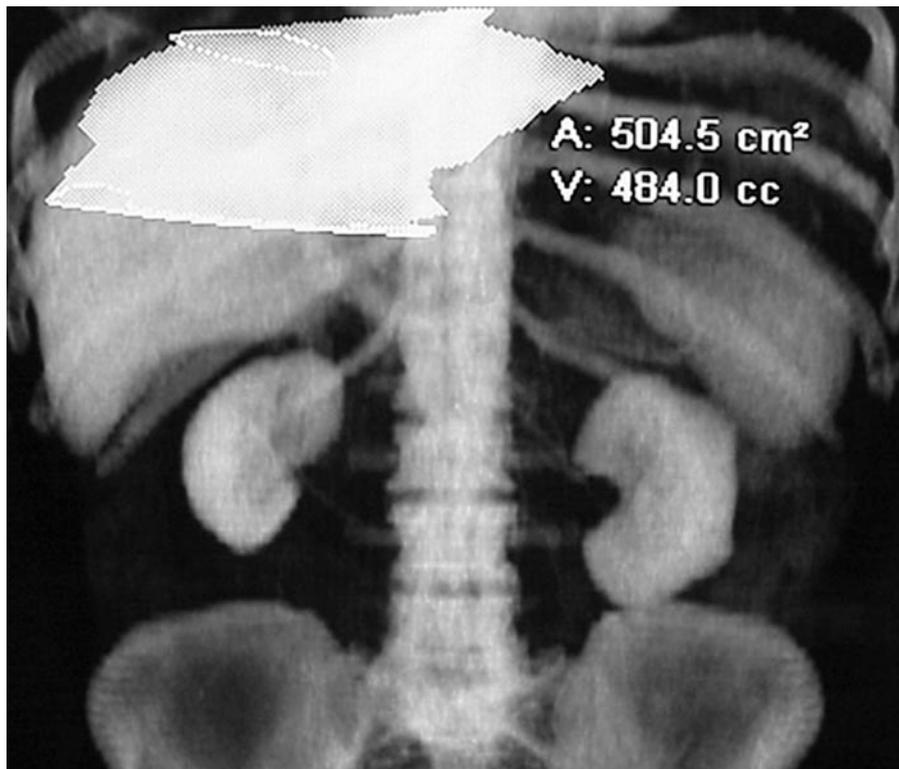


Figure 5. Three-dimensional CT reconstruction following regions of interest around the left lobe determine the left lobe volume (484.0 mL). This volume is now used to calculate the activity of TheraSphere required.

of segments 1, 5, 6, 7, and 8. If the middle hepatic artery is the vessel to be infused, the volume to be entered is that of segment 4. If the accessory right hepatic artery is to be infused, segments 6 and 7 represent the volume to be entered. These concepts are further described later in the article.

Dose Calculation, Ordering, and Infusion

TheraSphere.—As described in the product insert, TheraSphere consists of insoluble glass microspheres in which ^{90}Y is an integral constituent of the glass (65). The mean sphere diameter ranges from 20 to 30 μm . Each milligram contains 22,000–73,000 microspheres. TheraSphere is supplied in 0.05 mL of sterile, pyrogen-free water contained in a 0.3-mL v-bottom vial secured within a 12-mm clear acrylic vial shield. TheraSpheres are dispensed weekly by the manufacturer (MDS Nordion) on Wednesdays, are calibrated for 12:00 noon (Eastern Standard Time) of the following Sunday, and are available in the follow-

ing six activity sizes: 3 GBq (81 mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi), and 20 GBq (540 mCi) (1). The corresponding number of microspheres per vial is 1.2 million, 2 million, 2.8 million, 4 million, 6 million, and 8 million, respectively. The activity per microsphere is approximately 2,500 Bq (66).

The recommended activity of TheraSphere that should be delivered to a lobe of the liver-containing tumor is between 80 Gy and 150 Gy. This wide range exists to give the treating physician clinical flexibility. Patients with significant cirrhosis should be treated more conservatively (80–100 Gy), whereas patients without cirrhosis may be treated more aggressively (100–150 Gy). In our institution, the most commonly used dose range is 100–120 Gy, a range that balances safety and efficacy. If there is any uncertainty as to the tolerability of treatment, the approach of dose fractionation should be considered, such as two doses of 50–75 Gy rather than a single dose of

100–150 Gy. Dose fractionation is a well-accepted principle in radiation oncology and should be considered as one of the treatment options for patients undergoing treatment with ^{90}Y . The one caveat to repeat infusion is the principle of augmentation of hepatopulmonary shunting after treatment with ^{90}Y (67). In our institution, we have observed that relative shunting may increase after treatment with TheraSphere or SIR-Spheres. Therefore, if treatment according to a fractionation model is to be followed, repeat assessment of lung shunting should be undertaken before the second treatment to ensure that the dose to the lung will remain below the threshold of 50 Gy cumulative absorbed dose (52). Assuming that TheraSphere ^{90}Y microspheres distribute in a uniform manner throughout the liver and ^{90}Y undergoes complete decay in situ, radioactivity required to deliver the desired dose to the liver can be calculated according to the following formula (17):

$$\text{TheraSphere: } A \text{ (GBq)} = [D \text{ (Gy)} \times M \text{ (kg)}] / 50, \text{ or}$$

$$\text{Activity required (GBq)} =$$

$$[\text{desired dose (Gy)}] \times$$

$$[\text{target liver mass (kg)}] / 50$$

Given that a fraction of the microspheres will flow into the pulmonary circulation without lodging in the arterioles, when lung shunt fraction (LSF) and vial residual is taken into account, the actual dose delivered to the target volume after the vial is infused becomes (17):

$$D \text{ (Gy)} = [A \text{ (GBq)} \times$$

$$50 \times (1 - \text{LSF} - R)] / M \text{ (kg)}, \text{ or}$$

$$\text{Dose (Gy)} = 50 [\text{measured pre-infusion activity (GBq)} * (1 - \text{LSF}) * (1 - R)] / \text{target liver mass (kg)}$$

where A is activity infused to the target liver, D is the absorbed delivered dose to the target liver mass, and M is target liver mass. Liver volume (in cm^3) is estimated with CT and then converted to mass with a conversion factor of 1.03 mg/mL.

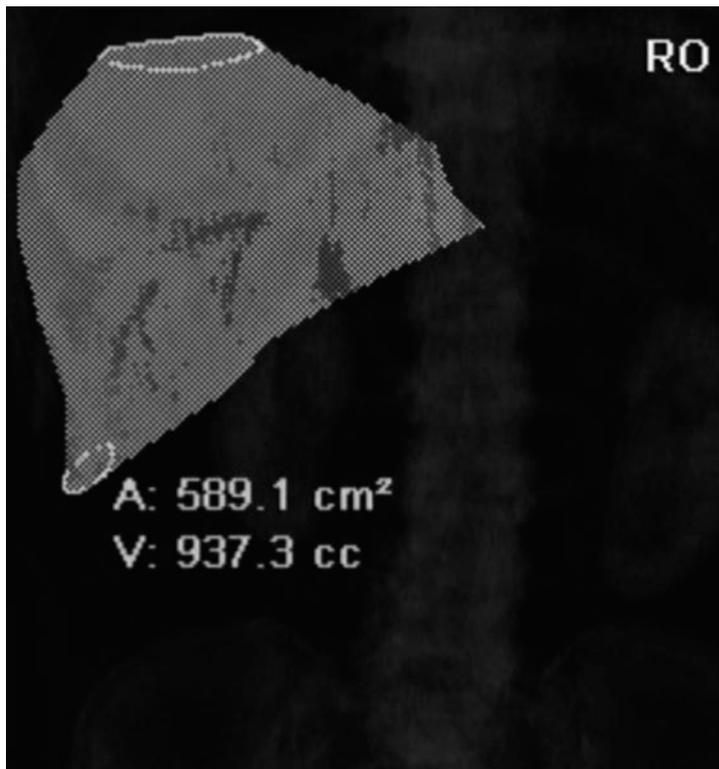


Figure 6. Right lobe volume in a patient being treated with SIR-Spheres.

For example, an authorized user wishes to treat a patient with TheraSphere with the following characteristics: standard hepatic arterial anatomy, target vascular volume (ie, right lobe, segments 1, 5, 6, 7, and 8) of 1,000 mL (1.030 kg), desired dose of 120 Gy, LSF of 5%, and vial residual of 2%. The tumor(s) is in the right lobe.

Activity required for treatment =

$$(120 \times 1.030)/50 = 2.47 \text{ GBq}$$

The patient receives an infusion of 2.47 GBq to the target volume. Given 5% LSF and 2% residual in the vial, the actual delivered dose to the target liver (right lobe) would be:

$$D (\text{Gy}) = [2.47 \times 50 \times$$

$$(1 - 0.05) \times (1 - 0.02)]/1.030 = 112 \text{ Gy}$$

The lung dose calculation (see sections on Calculation of Lung Dose and Calculation of Residual Activity and Proportional Activity Delivered) is as follows:

$$D (\text{lung}) = 50 * \text{infused activity}$$

corrected for residual in vial * LSF

$$D (\text{Gy}) = 50 \times (2.47 [1 - 0.02] \times 0.05) = 6.1 \text{ Gy}$$

Note that the dosimetry for TheraSphere is independent of tumor burden and is dependent on the mass of the targeted/infused liver tissue (in this case, 1.030 kg). In this scenario, the dose received by the left lobe was 0 Gy and the dose received by the right lobe (segments 1, 5, 6, 7, and 8) was 112 Gy. Finally, because the LSF is a known variable, it is possible to use the aforementioned formulas to compensate for this and to prescribe a higher overall dose that will correspond to 120 Gy to the targeted liver tissue. In this case, prescribing 129 Gy, assuming the same 5% LSF and 2% residual, would result in the desired dose to the right lobe of 120 Gy. The lung dose would be 6.5 Gy.

In a second example, an authorized user wishes to treat a patient with TheraSphere with the following characteristics: variant anatomy (accessory right hepatic artery), target vascular volume (ie, posterior segment of the

right lobe, segments 6 and 7) of 650 mL (0.670 kg), desired dose of 136 Gy, LSF of 8%, vial residual of 1%. The tumor(s) is in the posterior segment of the right lobe.

Activity required for treatment =

$$(136 \times 0.670)/50 = 1.82 \text{ GBq}$$

The patient receives an infusion of 1.82 GBq to the target volume. Given 8% LSF and 1% residual in the vial, the actual delivered dose to the target liver (posterior segment right lobe, segments 6 and 7) is:

$$D (\text{Gy}) = [1.82 \times 50 \times$$

$$(1 - 0.08) \times (1 - 0.01)]/0.670 = 124 \text{ Gy}$$

The lung dose calculation (see sections on Calculation of Lung Dose and Calculation of Residual Activity and Proportional Activity Delivered) is as follows:

$$D (\text{Gy}) = 50 \times (1.82 \times [1 - 0.01]$$

$$\times 0.08) = 7.2 \text{ Gy}$$

Note again that the dosimetry for TheraSphere is independent of tumor burden and is dependent on the mass of the targeted/infused liver tissue (in this case 0.670 kg). In this scenario, the dose received by the anterior segment of the right lobe and the left lobe was 0 Gy, and the dose received by the posterior segment of the right lobe (segments 6 and 7) was 124 Gy. In this case, prescribing 149 Gy and assuming the same 8% LSF and 1% residual would result in the desired dose to the posterior segment of the right lobe of 136 Gy. The lung dose would be 7.9 Gy.

TheraSphere administration/physics.— Because TheraSphere is not shipped as a specific patient unit dose, the appropriate vial must be ordered and the activity decayed to the required treatment activity. The usable shelf life of a TheraSphere dose is 7 days from the dose calibration date. Doses are scheduled to arrive on the day before the scheduled treatment date. If an institution plans to perform more than four administrations per week, a license possession limit of 240 GBq is recommended. This possession limit allows for the storage of the highest dose ordered and the residual activity from

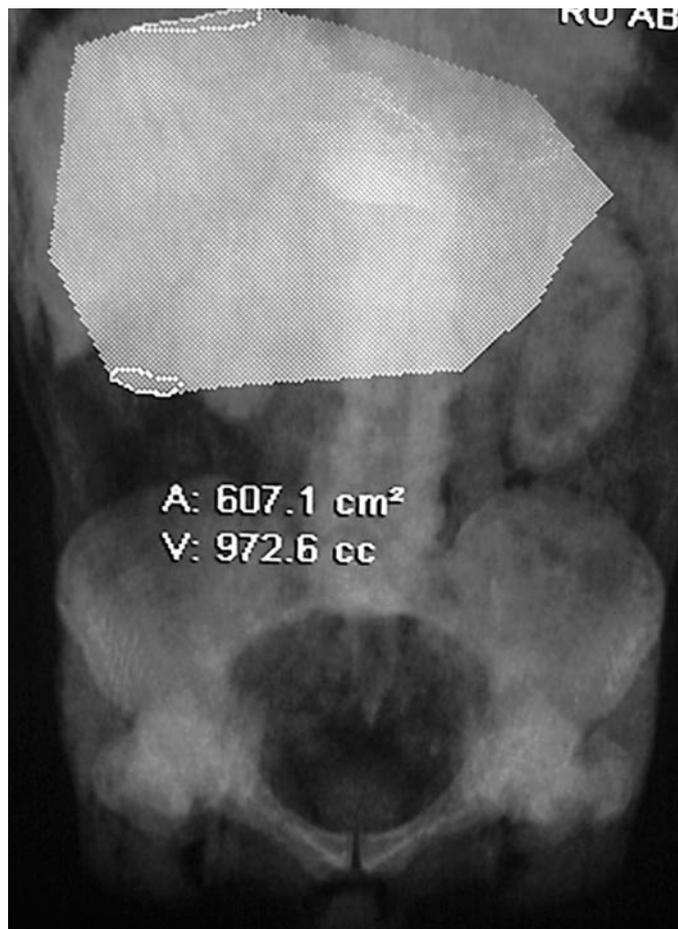


Figure 7. Left lobe volume in a patient being treated with SIR-Spheres.

administrations. A clinical treatment dose range of 80–150 Gy also allows for a 12-hour flexible schedule for most patients. Most patients can be treated earlier in the week with the lower-activity vials (3, 5, or 7 GBq) or later in the week with higher-activity vials (7, 10, 15, or 20 GBq).

Before administration, the vial activity can be verified with two different techniques. The dose can be measured in a standard dose calibrator. The dose calibrator must be calibrated for the TheraSphere vial configuration, which includes the acrylic shield. Asaying the first dose and adjusting the reading until it is equal to the manufacturer's decayed activity is the standard method of obtaining the calibration correction factor. The other method confirms the dose vial activity by measuring the dose rate with a portable ionization chamber (ie, a "cutie pie") that is placed at a calibrated distance in such a manner that 1 mrem/h

is equal to 1 GBq. The center of the portable ionization chamber is positioned approximately 30 cm from the center of the acrylic-shielded vial. Again, the reading is only accurate at best to within 10%. If the facility has multiple dose vials at hand, it is crucial to use both methods just before infusion to avoid a potential misadministration or medical event caused by confusion with dose vials. Because human error is a possibility, an individual other than the one using the ionization chamber for dose verification should measure the dose in the dose calibrator.

The TheraSphere administration set consists of one inlet set, one outlet set, one empty vial, and two interlocking units consisting of a positioning needle guide, a priming needle guide, all contained behind a Lucite shield. A Monarch 30-mL syringe (Merit Medical, South Jordan, UT) is used to infuse saline solution through the system.

The saline solution containing the TheraSphere ^{90}Y microspheres is infused through a catheter placed in the hepatic vasculature. When the catheter is positioned at the treatment site and the authorized user verifies the integrity of the delivery system, the catheter is connected to the outlet tubing. Delivery of TheraSphere is accomplished by pressurizing the Monarch syringe. For 3-F catheter systems, the infusion pressure should range from 20 to 40 psi, whereas for 5-F systems, the infusion pressure usually should not exceed 20 psi (use of 5-F systems for infusion is discussed later). It is essential that, irrespective of the infusion pressure used, the flow of microspheres must closely mimic that observed angiographically. This can be accomplished with a gentle hand injection of contrast medium followed by a column of saline solution. At this point, it is important that the authorized user become familiar with the actual flow dynamics of the vessel being infused and use a correspondingly lowered TheraSphere infusion pressure where necessary, such as might be seen in patients with decreased cardiac output. Given the small volume of microspheres contained in a given dose of TheraSphere (typically 27–90 mg), the volume of saline solution required to infuse a vial of TheraSphere is low; the majority of the microspheres have been infused after the first 20 mL of saline solution. In addition, given the low number of microspheres infused with TheraSphere (typically 1.2–4.0 million), the entire vascular bed is never completely saturated. Hence, although the infusion must be performed in the interventional radiology catheterization laboratory, continuous and live fluoroscopic guidance while the infusion is occurring is not necessary. A complete infusion usually requires 20–60 mL and usually requires 5 minutes to complete.

Pros and cons of TheraSphere dosimetry and physical characteristics.—There are several advantages to the TheraSphere empiric dosimetry model and the physical characteristics of the delivery system. First, the microspheres are shipped in a v-bottom vial that contains a fixed volume of sterile water. The v-bottom vial containing the microspheres is sealed within an acrylic shield with a removable cap for septum access. This configuration

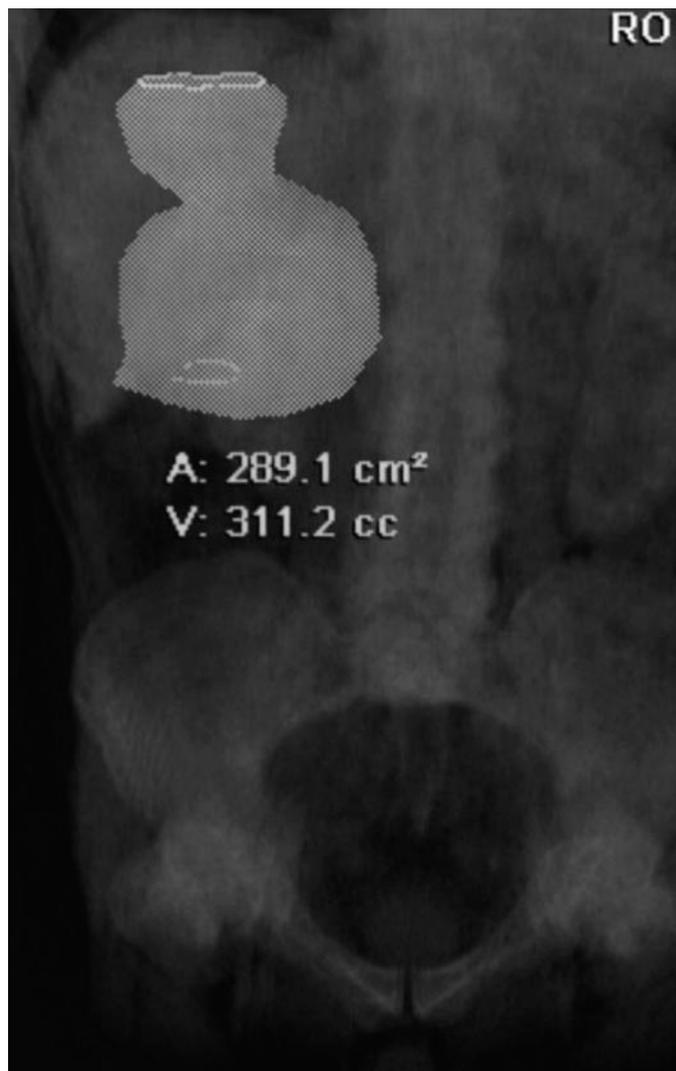


Figure 8. Three-dimensional reconstruction outlining volume of tumor burden.

ensures that most of the microspheres are confined to a fixed volume within the sealed vial. Because the activity of the microspheres is determined with use of a dose calibrator that measures the Bremsstrahlung radiation produced by the β -interaction with the shielding, the accuracy of the measurement depends on the volume of the microspheres. For the TheraSphere dose vials, the shielding is fixed and the volume of the suspended microspheres is limited to less than 0.5 mL. Both these conditions ensure that the accuracy in dose calibrator calibration and the dose assay will be reproducible from one facility to another. Moreover, this configuration requires no physical manipulation, such as decanting,

thereby reducing the potential of a dosing error caused by staff transferring the dose from one vial to another. The fixed shielding and lack of manipulation of the microspheres also reduces the radiation exposure to staff who assay the dose vials.

Second, because the target radiation absorbed dose is dependent on the target vascular volume, which is calculated with three-dimensional software, dosimetry calculations among different users for any given volume are reproducible. That is, this dosimetry is independent of tumor burden, further simplifying the determination of the required activity. The relatively low number of microspheres results in more than 95% delivery in nearly all cases without reaching stasis or com-

plete vessel occlusion, allowing the administration of extremely high radiation dose or radioactivity (2,500 Bq per sphere) with (relatively) few microspheres. Because embolic effects are limited to only the smallest capillaries within the target tissue, high oxygenation is maintained and radiation dose responses are improved (50,68). Moreover, this lack of significant embolic effect suggests potentially safe applications in patients with compromised portal venous flow or portal vein thrombosis, and also correlates with low clinical toxicities compared with embolic therapies (15,69).

The shelf life of a TheraSphere dose vial is 7 days, further adding to the clinical flexibility of patient treatment and scheduling. Given this shelf life, the same activity may be administered with different numbers of microspheres infused. Therefore, this device may be used and altered with various degrees of desired embolic effect (see previous discussion of decay curve). Finally, the manufacturer has appropriately recommended that, in cases of very high tumor burden (>70%), treatment should likely be withheld (70,71). This guidance is consistent with other types of liver-directed treatments.

There are also several disadvantages of TheraSphere glass microspheres. The dosimetry model lacks a variable for tumor burden. By considering only the target volume, one ignores the fact that more activity (and hence microspheres) may be required to treat greater tumor burden (this limitation is overcome with strategies described later in this article). Moreover, the high specific activity per microsphere may result in radiation dosages that prevent dose fractionation if maximum hepatic radiation tolerance is reached. The specific gravity of TheraSphere microspheres is high compared with SIR-Spheres and may theoretically limit microsphere distribution. TheraSphere doses have a relatively low number of microspheres compared with SIR-Spheres that may result in inadequate tumor coverage for large tumors. Also, although this is clinically inconsequential, the manufacturing process may result in long-lived radioactive contaminants such as europium ^{152}Eu and ^{154}Eu . These contaminants are found in other reactor-produced products used in medicine,

such as strontium Sr 89, used for bone pain, or ⁹⁰Y antiB1, used for lymphoma. However, the glass microspheres are placed directly in the reactor to activate the ⁹⁰Y, which increases the amount of contaminant to less than 30 uCi per dose vial. Finally, there is room for improvement in the administration set.

SIR-Spheres.—As described in the product insert, SIR-Spheres consist of biocompatible resin-based microspheres containing ⁹⁰Y with a size between 20 μm and 60 μm in diameter. SIR-Spheres constitute a permanent implant and are provided in a vial with water for injection. Each vial contains 3 GBq of ⁹⁰Y (at the time of calibration) in a total of 5 mL water for injection. Each vial contains 40–80 million microspheres (3). Consequently, the activity per microsphere for SIR-Spheres is much lower than that of TheraSphere (50 Bq vs 2,500 Bq) (66). SIR-Spheres are dispensed three times per week by the manufacturer (Sirtex) and are calibrated for 6:00 PM (Eastern Standard Time) on the date of treatment. The shelf-life is 24 hours after the calibration date and time.

Just as with TheraSphere, assuming SIR-Spheres ⁹⁰Y microspheres distribute in a uniform manner throughout the liver and undergo complete decay in situ, radioactivity delivered to the liver can be calculated by one of two available methods:

The first method incorporates body surface area and estimate of tumor burden, as follows (3,72):

$$\text{SIR-Spheres: A (GBq)} = \frac{\text{body surface area (m}^2\text{)}}{1.73} - 0.2 + (\% \text{ tumor involvement}/100)$$

The second method is based on a broad estimate of tumor burden as described in **Table 4**. The larger the tumor burden, the higher the recommended activity in increments of 0.5 GBq per 25% tumor burden. For either SIR-Spheres dosimetry model, A (in GBq) is decreased depending on the extent of LSF (<10% LSF, no reduction; 10%–15% LSF, 20% reduction; 15%–20% LSF, 40% reduction; >20% LSF, no treatment).

As an example, an authorized user wishes to treat a patient with the fol-

Table 4
SIR-Spheres Dosimetry Based on Tumor Burden

Tumor Involvement in the Liver (%)	Recommended Activity (GBq)
>50	3.0
25–50	2.5
<25	2.0

lowing characteristics: total weight of 91 kg, height of 1.83 m (6 feet), liver volume of 1,000 mL, tumor volume of 300 mL, LSF of 5%.

According to the first method, the formula for BSA as described by Dubois and Dubois (73,74) is as follows:

$$\text{Body surface area} = 0.20247$$

$$\times \text{height}^{0.725} \text{ (m)} \times \text{weight}^{0.425} \text{ (kg)}$$

Therefore:

$$A \text{ (GBq)} = 2.13 - 0.2$$

$$+ (30/100) = 2.23 \text{ GBq}$$

would be required according to the body surface area formula.

Alternatively, given the tumor burden of 25%–50%, the patient could be prescribed 2.5 GBq in activity, on the basis of the calculations described (3). Given the 5% LSF, no reduction in activity would be required. It should be noted that, for SIR-Spheres, the dosimetry described in the product insert is based on whole liver infusion. If a lobar infusion is intended, the infused activity should be calculated assuming whole liver volume and then “corrected” to the proportional volume of the target lobe that is to be infused. For example, if the right lobe is the target and represents 70% of the entire liver volume, the calculated activity (in this case 2.23 GBq) to be delivered should be multiplied by 0.7. Correcting SIR-Spheres dosimetry that is based on whole liver infusion and applying it to lobar therapy requires an understanding of percentage mass of the right and left lobes as well as the differing tumor burdens in each lobe.

The lung dose calculation assuming 2.23 GBq activity infused with no residual (see sections on Calculation of Lung Dose and Calculation of Resid-

ual Activity and Proportional Activity Delivered) is as follows:

$$D \text{ (Gy)} = 50 \times (2.23 \times 0.05) = 6 \text{ Gy}$$

Note that SIR-Spheres body surface area dosimetry is based on tumor burden and liver mass (larger liver mass with higher body surface area). Empiric SIR-Spheres dosimetry is dependent only on tumor burden and is independent of liver mass.

SIR-Spheres administration and physics.—Before administration, the SIR-Spheres dose is assayed in a dose calibrator but should be verified with a different technique. The dose calibrator must be calibrated for the vial configuration and the volume of the dosing vial as well as the shipping vial. The standard method for obtaining the calibration factors for ⁹⁰Y requires obtaining a National Institute of Standards and Technology–calibrated source in the smallest volume of sterile water that will be used for patient dosing. This vial will be assayed and the reading adjusted until it agrees within 10% of the decayed activity. To obtain the calibration factor for greater volumes, simply add the desired amount of sterile water and repeat the measurements. Because this technique is based on the Bremsstrahlung radiation, it is important to use a vial for the calibration source that is constructed of the same material used for the shipping vial and the v-bottom vial. It is also important to use a vial of the same shape, such as a v-bottom vial or a flat surface bottom vial. The manufacturer recommends that the activity of the dose vial be determined from the difference between the assays of the shipping vial before and after decanting. The dose vial activity should be confirmed by assaying the acrylic-shielded dose vial in the dose calibrator with the calibration factors for a shielded dose. This reading should be within 10% of the reading obtained according to the manufacturer’s method. Readings that differ by more than 10% indicate that a significant amount of the SIR-Spheres may be in the transfer needle. The dose should also be verified by measuring the dose rate with a portable ionization chamber that is placed at a calibrated distance in such a manner that 1 mrem/h is equal to 1 GBq.

The center of the portable ionization chamber is positioned approximately 30 cm from the center of the acrylic-shielded vial. Again, the reading is only accurate at best to within 10%. If the facility has multiple dose vials at hand, it is crucial to use both methods just before infusion to avoid a potential misadministration or medical event caused by confusion with dose vials. Because human error is possible, an individual other than the one using the ionization chamber for the dose verification should measure the dose in the dose calibrator. Because the treatment vial does not have a label, a label describing the contents, radioactive sign, activity, and procedure or patient identification should be placed on the shield or vial. This label must not obscure the view of the contents.

The SIR-Spheres administration set consists of a Perspex shield, the dose vial, and inlet and outlet tubing with needles. Standard 10-mL or 20-mL injection syringes preloaded with sterile water are required to infuse the microspheres into the delivery catheter. Pressure gauges are not available when SIR-Spheres are infused. Usually, slow and deliberate hand-injection of the SIR-Spheres through the 3-F or 5-F catheter systems is adequate (use of 5-F systems for infusion is discussed later). Care should be taken when performing the infusion because the infusion setup is composed of several connection tubings in series, thereby increasing the pressure required to infuse the microspheres. Care should be taken not to allow too vigorous an injection rate, because this may result in leaks at points of potential weakness (eg, septum, tubing connections). Just as with TheraSphere, the infusion rate used must closely mimic the blood flow rate observed angiographically. The blood flow dynamics should dictate the pace at which infusion occurs. If the authorized user is not an interventional radiologist, the proper communication of this information to the authorized user becomes crucial. Depending on the activity infused, an amount of 20–40 mL is usually sufficient for infusion of the intended dose.

Pros and cons of SIR-Spheres dosimetry and physical characteristics.—There are advantages to the SIR-Sphere dosimetry model and the characteristics

of the resin microspheres. The dependence of activity required for treatment on tumor burden is inherently logical. The activity vial may be manipulated and the specific activity decanted in the nuclear medicine pharmacy tailored for the patient. The infusion may be done with alternating injections of sterile water and contrast medium, thereby allowing monitoring specifically with the use of fluoroscopy to ensure that stasis is not reached. The lower specific gravity theoretically makes for better suspension. The lower specific activity per microsphere (50 Bq per microsphere) allows for the possibility of dose fractionation. Dose fractionation is a well-accepted principle in radiation oncology (75). Finally, the administration kit is simple.

There are limitations to the dosimetry and physical characteristics of resin microspheres. The shelf-life of the device is 24 hours, restricting clinical flexibility and patient scheduling. The need to physically decant although, on the surface, potentially advantageous introduces further human technical manipulation that may result in spills requiring radiation containment or, more critically, result in the wrong activity administered. There are several formulas for dose calculation, potentially resulting in several different prescribed doses for the same patient. This lack of uniformity makes interuser variability very high. If one were to use the tumor burden formula described earlier in this article, a patient with 1% tumor burden would receive the same prescribed activity as someone with 24% tumor burden. A patient with 51% tumor burden would receive the same activity as someone with 99% tumor burden. Unlike the dosimetry model for glass microspheres, this dosimetry model does not account for patients with the highest tumor burdens. Withholding treatment from patients with extremely high tumor burdens should be considered (70). In addition, vessel stasis and premature termination of the infusion has been described in 35% of cases, bringing into question the reproducibility of dosimetry and the ability to administer sufficient radiation (29). Embolic effect may cause hypoxia, potentially limiting the effect of the radiation (76,77). Also, given the

large number of microspheres, it is difficult to determine whether any therapeutic effect is a result of radiation or embolic effects.

Comparison between TheraSphere and SIR-Spheres.—TheraSphere and SIR-Spheres are distinctly different products. Although both are ⁹⁰Y embolic brachytherapy devices (ie, radioembolization devices), the differences far exceed the similarities. TheraSphere is a minimally embolic brachytherapy device consisting of 20- to 30- μ m particles with specific activity of 2,500 Bq, higher specific gravity, and lower number of microspheres (approximately 2–4 million microspheres per treatment). The infusion can proceed without concern for vascular stasis, given the lower embolic load (68). Because of these characteristics, the median percentage activity infused per vial is well above 95%.

This is in direct contradistinction with SIR-Spheres, which are a moderately embolic brachytherapy device consisting of 20- to 60- μ m particles with specific activity of 50 Bq, lower specific gravity, and higher number of microspheres (approximately 40–80 million microspheres per treatment) (Table 5). Given these characteristics, it is not unusual for the vascular bed to become saturated and angiographic stasis to be reached (29). Hence, the median percentage of microspheres infused is usually lower in comparison with TheraSphere.

Misconceptions about TheraSphere and SIR-Spheres.—With both microsphere devices, fluoroscopic guidance is used, no blind infusions are performed, individually determined patient-specific doses are used, and patients are treated in a lobar fashion. The idea that resin spheres suspend better than glass, resulting in better tumor coverage, has never been validated. In fact, a previous report has described the opposite, in which no difference in tumor distribution was found between glass and resin microspheres (66). Gravitational flow to more dependent areas has been documented (78,79). Also, studies have correlated distribution of microspheres with blood flow (80). Hence, flow in a dependent region is likely the result of normal physiologic flow and gravity, not the specific gravity of the microsphere infused. It should therefore be assumed that the distri-

Table 5
Comparison of TheraSphere and SIR-Spheres

Characteristic	TheraSphere	SIR-Spheres
Isotope	⁹⁰ Y	⁹⁰ Y
Half-life (h)	64.2	64.2
Time to near-complete decay (3% residual activity), days	13	13
Particle size (μm)	20–30	20–60
Range of spheres per vial	1.2–8.0 million	40–80 million
Activity per sphere (Bq)	2,500	50
Specific gravity	High	Low
Activities available (GBq)	3, 5, 7, 10, 15, 20	3
Requires handling for dispensing	No	Yes
Modern delivery route	Transcatheter, intraarterial (hepatic)	Transcatheter, intraarterial (hepatic), hepatic ports (rare)
Embolic effect	Mild	Moderate
Indication for use	Hepatocellular carcinoma with appropriately positioned catheter	Colorectal metastases with intrahepatic floxuridine
Special radiation precautions upon discharge*	None	Possible urine contamination

* Refer to package insert and to institutional, state, and federal regulations for radiation safety considerations.

butions of glass and resin microspheres are comparable until this is proved otherwise.

The other major misconception is the idea little if any dosimetry work has been completed on either agent. This is misleading, given that many authors have performed validation of the dosimetry models (37,50–63). Although dosimetry remains a work in progress for both ⁹⁰Y devices, sufficient data are available to allow widespread use of ⁹⁰Y with clinical benefit. It should be noted that, although the empiric nature of the dosimetry for ⁹⁰Y microspheres is a fair criticism, empiric models are the standard and are routinely used in medicine, such as dosimetry for TACE, ⁹⁰Y-labeled antibodies for lymphoma, and systemic chemotherapy. Empiric dosimetry is the standard in medical practice rather than the exception.

Calculation of Lung Dose

Radiation pneumonitis is a theoretical concern with ⁹⁰Y treatment. Previous preclinical and clinical studies with ⁹⁰Y microspheres demonstrated that as much as 30 Gy to the lungs could be tolerated with a single injection, and as much as 50 Gy could be tolerated for multiple injections (55). For this reason, patients with ^{99m}Tc-MAA evidence of potential pulmo-

nary shunting resulting in lung doses greater than 50 Gy should not be treated.

The absorbed lung radiation dose is the total cumulative dose of all treatments (81):

Cumulative absorbed lung radiation

$$\text{dose} = 50 \times \text{lung mass} \sum_{i=1}^n = A_i * \text{LSF}_i$$

where A_i represents activity infused (correcting for residual in vial), LSF_i represents LSF during infusion, n represents number of infusions, and approximate lung mass (for both lungs, including blood) is 1 kg (82).

This dose should not exceed the limit of 30 Gy per single infusion and 50 Gy cumulatively. In patients who require more than two treatments to achieve tumor coverage or in patients being treated repeatedly in the same target volume after progression, repeat ^{99m}Tc-MAA LSF assessment may be necessary (67).

Variations in Activity in Relation to Number of Microspheres

TheraSphere.—As described previously, TheraSphere doses are dispensed weekly by the manufacturer on Wednesdays and are calibrated on Sunday, 4 days later, at 12:00 noon Eastern Standard Time. All microspheres carry the same specific ac-

tivity. The only difference between the various activities at the moment the different vials are dispensed is the number of microspheres per vial. The numbers of microspheres per vial are 3 GBq (1.2 million), 5 GBq (2 million), 7 GBq (2.8 million), 10 GBq (4 million), 15 GBq (6 million), and 20 GBq (8 million). Knowledge of radiation physics, activities, number of microspheres per vial, and required volume for microspheres is important in the ordering and treatment planning process. The fact that the microsphere number alone differentiates the various activities dispensed by the manufacturer must be taken into consideration when dosimetry calculations are performed. **Figures 9** and **10** illustrate the dose decay curves of the manufactured activity vials to a certain activity.

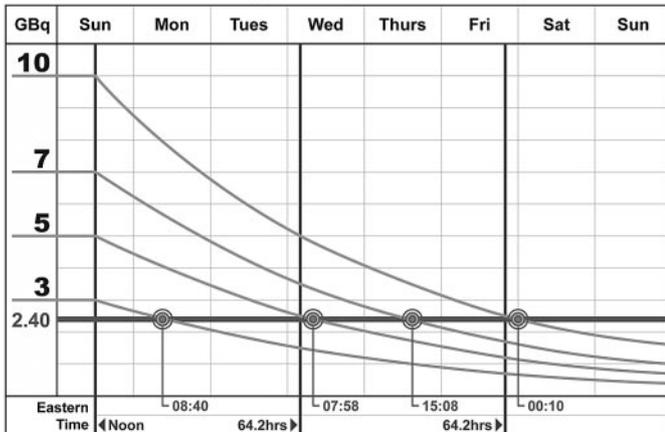
An example best illustrates this principle. An authorized user wishes to treat a patient with a 971-mL right lobe volume with a dose of 120 Gy. Assuming zero lung shunt, this would imply the need for the following of activity to treat the patient:

$$(971 \text{ mL} * 1.03 \text{ g/mL} * 0.001 \text{ kg/gm}$$

$$* 120 \text{ Gy})/50 = 2.4 \text{ GBq}$$

This would translate into 2.4 GBq of activity generated by a 3-GBq vial Monday at 08:40 AM, a 5-GBq vial Wednesday at 07:58 AM, a 7-GBq vial

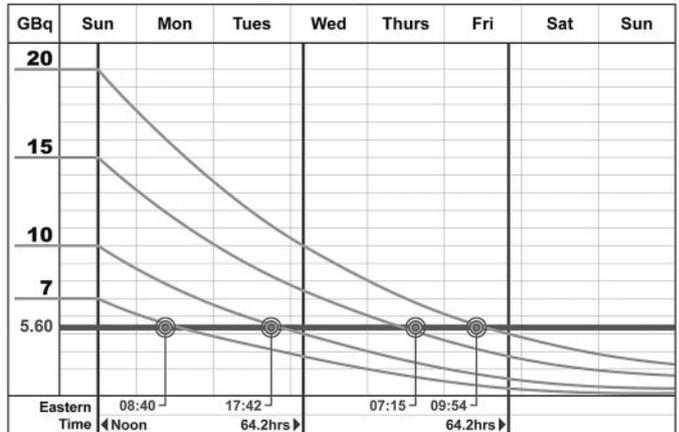
Treatment Window 1kg X 120Gy / 50 = 2.40GBq



9.

Figures 9, 10. 9. Decay curve of 3-, 5-, 7-, and 10-GBq vials of TheraSphere. The day of the week and time at which each vial has decayed to 2.4 GBq is illustrated. 10. Decay curve of 7-, 10-, 15-, and 20-GBq vials of TheraSphere. The day of the week and time at which each vial has decayed to 5.6 GBq is illustrated.

Treatment Window 2kg X 140Gy / 50 = 5.60GBq



10.

Thursday at 15:08 PM, or a 10-GBq vial Saturday morning 12:10 AM (Fig 9). Hence, depending on the dose selected and patient treatment scheduling, different numbers of microspheres would be administered. If treatment is scheduled for Monday, a 3-GBq vial decayed to 2.4 GBq Monday at 08:40 AM will be required, and the patient will receive 1.2 million microspheres. If the same patient receives a 5-GBq vial decayed to 2.4 GBq on Wednesday at 07:58 AM, 2 million microspheres will be administered. A treatment with a 7-GBq vial decayed to 2.4 GBq will be performed on Thursday at 3:08 PM, translating into 2.8 million microspheres. The use of a 10-GBq vial is unlikely in this example, because this would require a Saturday 12:10 AM injection time. An understanding of this principle is extremely important when dosimetry with TheraSphere is considered, because the authorized user may want to take into account tumor size and vascularity. For example, a tumor with densely packed vascularity (eg, HCC or neuroendocrine tumor) may best be treated with a higher number of spheres than one without such dense vasculature. In addition, large bulky lesions may also be better treated with higher-activity vials later in the week, translating into a higher number of microspheres administered and enhanced tumor coverage. Therefore, it is encouraged that this flexibility in microsphere number for any given ac-

tivity be recognized and factored in treatment planning.

In summary, it is important that authorized users recognize the significant difference in number of microspheres depending on the vial manufactured. Larger, more vascular lesions may be treated later during the week to enhance coverage, whereas smaller tumors may be treated with lower-activity vials early in the week. Figure 10 demonstrates another example of this concept of modifying the number of TheraSphere particles injected for a given activity.

SIR-Spheres.—Variation in microsphere number also exists with SIR-Spheres. SIR-Spheres are always delivered in 3-GBq activity vials. According to the package insert (3), a 3-GBq vial might contain between 40 and 80 million microspheres. Given this variation, a patient receiving the entire 3-GBq vial might receive 40 million microspheres, whereas the following week, an identical patient might receive 80 million microspheres with less specific activity. Given this variation and the inability to reliably estimate the number of microspheres being infused, the necessity for slow and deliberate infusion of the microspheres with continuous fluoroscopic observation is further reinforced. In addition, given the need for constant fluoroscopic observation during the infusion, the assessment for an angiographic endpoint (ie, stasis), the infusion of ⁹⁰Y

(especially SIR-Spheres) represents a true embolization procedure.

The Treatment Procedure

Room preparation.—Standard room preparations for interventional procedures are used. A large 6-foot × 6-foot drape should be placed on the floor near the fluoroscopy unit in such a manner that when the ⁹⁰Y delivery system is brought in proximity to the patient, any potential contamination or leak on the floor will be contained. For the administration of ⁹⁰Y microspheres, at least two different radiation detectors should be available in the room. A survey meter with a thin window Geiger-Müller detector capable of detecting radiation levels less than 0.1 mR/h should be available near the exit from the room. This meter will be used to detect possible radioactive contamination of the staff, in the waste, and on the fixed equipment in the room. A portable ionization chamber capable of detecting radiation doses as low as 1 mrem/h should be available. This survey meter is used to measure the radiation doses emanating from the Bremsstrahlung within the patient. A surface measurement with the ionization chamber will give a crude estimate of the dose delivery site. The ionization chamber is also used to measure residual activity that may be in the dose vial. To locate TheraSphere

microspheres along the catheter and tubing connected to the dose vial, a high count rate ionization chamber with a thin-window β -detector is very useful (eg, Eberline R07). Because the TheraSphere delivery system has two solid-state radiation detectors to determine radiation levels at the dose vial and the catheter connection point, the high count rate ionization chamber is not necessary to deliver 90% of the dose.

To ensure delivery of the SIR-Sphere, a visual indicator should be confirmed with a radiation level measurement of the dose vial. Use of the exposure rate at a fixed distance from the device before and after infusion provides a positive determination of the dose delivered in addition to surface measurements of the patient.

In addition to the supplied TheraSphere and SIR-Sphere administration sets, a Nalgene container and an acrylic Nalgene shield are required. The dose vial, attached tubing, and the catheter are placed in the Nalgene container immediately after infusion of the spheres. Residual activity is determined with use of the ionization chamber and the shielded Nalgene in the same geometry as the ionization chamber and dose vial before administration.

Patient preparation and catheterization.—Access to the vascular system is achieved in the standard fashion. Because planning visceral angiography and embolization of extrahepatic vessels has already been accomplished, the choice of catheters should be kept consistent and readily available in the procedural report. Catheterization of the celiac trunk with 4-F or 5-F systems is recommended (hydrophilic catheters may be used). Subsequently, a 3-F coaxial system (≥ 0.0325 inches) is recommended for infusion rather than 4-F or 5-F catheters. This will permit administration of ^{90}Y at low and consistent pressures. In addition, consistency in pressure and flow will maintain the spheres in suspension, allowing unimpeded passage through the catheter to the intended target volume. The use of 0.018-inch systems is not encouraged for routine ^{90}Y injection because there may be excessive outflow resistance to injection, preventing adequate flow rates and particle suspension. Exceptions may be made

if the vascular anatomy does not permit the placement of catheter systems larger than 0.018 inches. If 0.018-inch systems are used, higher pressures may be required to achieve proper microsphere suspension. Caution should be exercised if such pressures are used, because points of weakness (eg, septum, catheter connection point) may result in microsphere leakage.

Infusion of ^{90}Y microspheres through 4-F or 5-F catheters is not recommended. The rationale for this is twofold: (i) larger catheters advanced deep in the hepatic vascular bed, although technically feasible for the experienced angiographer, may cause vessel spasm, limiting the ability to infuse microspheres that rely on flow dynamics for optimal delivery; and (ii) the resistance to injection of the microspheres through 4-F or 5-F catheters may be too low, thereby increasing the risk of reflux of microspheres to nontarget areas, particularly in the case of an overly vigorous injection. By virtue of their smaller overall caliber, luminal size, and length, use of 3-F catheters is less likely to result in vessel spasm and microsphere reflux.

Administration set preparation (TheraSphere, SIR-Sphere).—It is crucial to assemble the microsphere delivery kit carefully because any error during the setup may lead to incorrect administration. Significant errors during critical steps in the setup and delivery of microspheres should be addressed at dose termination points. To increase consistency and limit errors, three individual team members should check all steps. For TheraSphere infusions, it is very important to ensure that the connections to the saline solution bag, syringe, and inlet and outlet catheters are tight to ensure that the system is sealed and a constant pressure can be maintained. For SIR-Spheres infusions, it is very important that needles are within the septum and that the septum has not been damaged during setup and manipulation (eg, excessive punctures). The microsphere administration kits for TheraSphere and SIR-Spheres should be assembled according to objective, reproducible, and repeatable checklists. The manufacturers routinely provide these checklists. If any of the steps in the assembly pro-

cess fails, consideration should be made of terminating the procedure without attempting to infuse the microspheres.

Microsphere infusion technique.—The technical aspects of radioembolization are quite complex and should not be undertaken lightly. The infusion technique varies depending on the ^{90}Y agent being used, the size and location of the catheter, and the vessel undergoing infusion. In addition, the deliveries of TheraSphere and SIR-Spheres are distinctly different. Given this, it is recommended that institutions beginning a ^{90}Y program commit to having the same authorized user and/or interventional radiologist perform the first 10–15 cases. This allows for the learning curve to be reached quickly, as well as allowing individual institutional inefficiencies to be identified and remedied rather than repeated with different authorized users.

Unlike SIR-Spheres, the embolic effects of 20- to 30- μm TheraSphere ^{90}Y particles are angiographically minimal (68). As previously published and further reinforced in this article, the presence of unrecognized collateral vessels with consequent infusion of radioactive microspheres is certain to result in clinical toxicities if proper angiographic techniques are not adopted (1,3,29,50,57,58,83). These might include gastrointestinal ulceration, pancreatitis, skin irritation, and other nontarget radiation. For this reason, aggressive prophylactic embolization of vessels before therapy, in such a manner that all hepaticocenteric arterial communications are completely eliminated, is highly recommended. These vessels include the GDA, right gastric artery, esophageal artery, accessory phrenic artery, falciform artery, and variant arteries such as the supra- or retroduodenal artery. At our institution, where over 900 radioembolization procedures have been performed, we have found our gastrointestinal toxicity rate to be well below 1%. This is because of our standard practices of (i) aggressive prophylactic embolization of GDA/right gastric artery and other variant vessels; (ii) use of minimally embolic TheraSphere in a lobar and segmental fashion; (iii) use of SIR-Spheres in a lobar, segmental, and dose-fractionated method (ie, several small doses

rather than one larger dose) without reaching a completely static and embolic state; and (iv) routine prophylactic use of a 2-week course of anti-ulcer medications.

TheraSphere infusion technique.—Most infusions should be performed with use of 3-F systems. This includes standard lobar infusions as well as cases with difficult anatomy, small vessels (eg, left hepatic artery), and subselective catheterizations. In these instances, the required pressures are greater, usually 20–40 psi. The delivery of TheraSphere is dependent on blood flow through the hepatic vasculature distal to the catheter tip. Therefore, it is necessary to make certain that the catheter does not occlude the vessel in which it is placed, because doing so will result in vessel spasm and reflux as the infusion proceeds. Flushing should be continued until optimal delivery of TheraSphere is achieved. A minimum flush of 60 mL is recommended with 3-F systems.

Although discouraged, the use of 4-F or 5-F systems should allow for constant low-pressure (10–20 psi) infusion throughout the administration. The radioactivity is monitored as the spheres travel through the blue stopcock. At times, it may be necessary to slightly “tap” or “vibrate” the inlet and outlet sides of the blue stopcock while the administration is under way. It is possible for a very small percentage of the microspheres to remain lodged in the potential spaces that exist at catheter connection sites (eg, in three-way connections), necessitating a tapping process that will resuspend the spheres as the injection proceeds. Flushing should be continued until optimal delivery of TheraSphere is achieved. Just as with 3-F systems, a minimum flush of 60 mL is recommended with 4-F or 5-F catheter systems.

Irrespective of the size of the catheter system, it is necessary to ensure that the rate of infusion mimics the rate of hepatic arterial flow. This rate is assessed by visual inspection of a test dose of contrast material infused before TheraSphere administration. In some patients (eg, elderly patients with diminished cardiac function or celiac stenoses), slower hepatic arterial flow may be apparent. In such

cases, the infusion rate of TheraSphere must mimic this slower flow.

The process of placing a 0.035-inch (4-F or 5-F) catheter system into the artery designated for TheraSphere infusion is not always easy. Patients who have recently received chemotherapy have vessels prone to dissection and spasm (50). In addition, as stated previously, diminished cardiac output in elderly patients may result in slower than expected hepatic arterial flow. Although larger catheter systems with low resistance may result in easier infusion of TheraSphere, the combination with diminished hepatic arterial flow may result in the reflux of microspheres. Therefore, in cases in which a large 4-F or 5-F catheter is placed into the hepatic artery and reflux is of concern, placement of a 3-F catheter coaxially within the base catheter is recommended. This will create higher resistance to infusion and will minimize the risk of reflux. A typical TheraSphere infusion requires less than 5 minutes to complete.

Radiation monitoring of the TheraSphere administration set and catheter must be used to establish the timing of optimal delivery. It is important to correlate the flow of TheraSphere generated by the syringe with the normal blood flow through the hepatic artery. The interventional radiologist best estimates flow through the vessel being treated. Therefore, if the authorized user is not an interventional radiologist, it is essential that the interventional radiologist clearly communicate to the authorized user the vessel size and flow dynamics. The individual tailoring of the administration process is dependent on the information obtained from the interventional radiologist. Injecting TheraSphere at an infusion rate faster than the vessel will tolerate can result in reflux and administration to nontarget sites.

SIR-Sphere infusion technique.—Just as with TheraSphere, most SIR-Spheres infusions should be performed through 3-F catheter systems. Although the use of smaller catheter systems results in the need to generate higher pressures for microsphere delivery, they create a safety mechanism to prevent the forceful and unimpeded advancement of microspheres that might occur with larger

5-F catheters. There is no pressure gauge on the SIR-Spheres delivery kit, and hence pressure cannot be monitored. The delivery of SIR-Spheres is also dependent on blood flow through the hepatic vasculature distal to the catheter tip. Given the embolic load of SIR-Spheres, it is even more necessary to make certain that the catheter does not occlude the vessel in which it is placed to prevent reflux. Flushing should be continued until optimal delivery is achieved. A minimum flush of 60 mL is recommended with 3-F systems, depending on the activity infused.

The technical aspects of SIR-Spheres infusion are quite complex. The objective is to percutaneously achieve microsphere delivery in a manner analogous to that achieved with use of a surgically implanted pump. It is essential that the vascular bed providing blood flow to the liver be altered in a manner comparable to that achieved with surgical techniques. Because the surgical procedure would involve skeletonization of the common hepatic artery and ligation of the right gastric artery, as well as identification and exposure of hepatic vessels flowing in an extrahepatic direction, the percutaneous equivalent must be accomplished. This includes prophylactic embolization of the GDA and right gastric artery as well as the supraduodenal, falciform, accessory left gastric, and accessory inferior phrenic (ie, extrahepatic) arteries (50). When this is achieved, given the fact that metastatic cancer is usually multifocal and bilobar, treatment by a lobar approach is favored, thereby minimizing the risk of hepatic decompensation.

Given the larger number of microspheres (40–80 million) and lower activity of SIR-Spheres (50 Bq per microsphere) compared with TheraSphere, the delivery of SIR-Spheres is distinctly different from that of TheraSphere. When the catheter is in place and the authorized user is ready for to perform delivery, the catheter is connected to the outlet tubing. Given the very large number of SIR-Spheres required to deliver the intended dose, if the dosimetry formulas are strictly followed, it is not uncommon for the entire vascular bed to become saturated with mi-

rospheres and an embolic state to be reached. For this reason, fluoroscopic guidance is essential during the infusion. The technique of SIR-Spheres infusion involves the alternating infusion of sterile water and contrast medium, never allowing direct contact between the SIR-Spheres and contrast medium. This allows the authorized user to adequately monitor the injection and ensure that vascular saturation has not been reached. In cases in which unrecognized vascular saturation occurs and microsphere infusion continues, reflux of microspheres and nontarget radiation becomes a distinct possibility. The infusion is complete if (i) the entire intended dose has been infused without reaching stasis or (ii) stasis has been reached and only a portion of the dose has been infused. Given the risk of reflux and nontarget radiation after stasis has been reached, the continued infusion of SIR-Spheres is not recommended.

Monitoring of the SIR-Spheres infusion, as well as estimation of the percentage infused at any time, may be performed with use of an ionization chamber (minimum detection, 1 mrem/h) placed adjacent to the SIR-Spheres kit. Keeping the ionization chamber at a fixed distance from the vial and measuring baseline preinfusion dose can provide a live assessment of percentage infused. The dose reading should decrease as the infusion percentage increases. This may be helpful in cases in which an authorized user wishes to infuse a certain portion of the microspheres in one vascular territory, move the catheter position, and continue the infusion. The use of the ionization chamber can provide this information. Assessing percentage infused by visual estimates is fraught with error and is not recommended.

The final 1%–2% of SIR-Spheres may be expelled from the tubing by loading the 20-mL injection syringe with air. Pressuring the system with a column of air will result in the slow expulsion of the remaining microspheres. When this air column reaches the three-way valve, it should be turned off to prevent the intraarterial injection of air. A typical SIR-Sphere infusion requires 10–20 minutes to complete.

The technical aspects of SIR-

Spheres infusion for HCC deserve special mention. Unlike colorectal cancer, HCC has a propensity for unifocality and significant hypervascularity, despite being bilobar. Given this, the usual cirrhotic nature of patients with HCC, and the high embolic load of SIR-Spheres, administration of microspheres in these patients requires a delicate approach. In such cases, segmental/subsegmental infusion and dose reduction is recommended to (i) minimize the risk of reflux into nontarget organs, (ii) minimize the risk of microsphere flow into the normal parenchyma, (iii) minimize the risk of radiation-induced liver disease, and (iv) maximize the concentration of microspheres into the tumor bed (83,84).

General Radiation Safety Considerations

Radiation safety is an important consideration in this procedure, given the potentially high exposure from handling therapeutic amounts of ^{90}Y . ^{90}Y is a β -emitter; therefore, the primary concern is exposure to the eyes, skin, and hands. β -emissions from ^{90}Y can travel more than a meter in air but are significantly reduced by less than 1 centimeter of acrylic. Although the dose vial is shielded in acrylic, the inlet and outlet catheters are not shielded.

Because ^{90}Y microspheres are not metabolized, they are registered as a sealed source. However, the microspheres are delivered with use of saline solution or sterile water and should therefore be handled by the same techniques as those for radiopharmaceuticals. If the system becomes compromised, radioactive contamination is a concern, and steps should be taken to prevent the spread of contamination. ^{90}Y microspheres (resin and glass) contain trace amounts of long-lived radioactive contaminants such as ^{152}Eu . If significant amounts of residual dose are present (>1% of the dose), these contaminants may be detected with a GM meter after 30 days of decay. Disposal of this radioactive material should be addressed according to the facilities governing regulations (ie, Agreement State, Environmental Protection Agency, Nuclear Regulatory Commission).

Typical surface radiation dose rates

from the patient range between 4 and 12 mrem/h. This dose range is well within the accepted radiation levels for outpatient radiation treatments. Regardless of whether the patient is an inpatient or an outpatient, no special precautions are necessary.

In summary, to avoid inaccurate dose administration or termination, the following are recommended during treatment: (i) procedural checklist, (ii) two or three dose verification techniques, and (iii) team approach with defined roles for individuals from radiation oncology, nuclear medicine, interventional radiology, and medical physics or radiation safety departments. Both manufacturers provide authorized users with strict procedural checklists. This checklist allows for the deliberate setup and infusion of microspheres, thereby minimizing human error. Any portion of the checklist that cannot be completed during the setup should be considered an abort point. In such instances, rather than risk a misadministration, the procedure should be terminated.

When the infusion is complete, authorized users should be aware of the possibility of contamination and microsphere deposition in the base catheter while the microcatheter is being removed. Hence, if backbleeding is observed from the base catheter on microcatheter removal, contamination is a possibility. Caution should therefore be exercised during removal and handling of the base catheters. Although this can occur with glass and resin microspheres, we have observed this more commonly with the resin microspheres.

In accordance with basic radiation safety precaution, all personnel in the room at the time of ^{90}Y infusion must be measured for any possible contamination on their exit.

Radiation Safety Considerations in Patients Undergoing Transplantation or Surgical Resection

In several instances, patients undergoing ^{90}Y microspheres therapy become candidates for surgical resection or liver transplantation. Although investigators should follow their own institutional guidelines for elapsed time from ^{90}Y treatment to time of surgery or transplantation, this should be

balanced against the medical needs of the patient. In our institution, we recommend monitoring the patient surface dose rate to determine what precautions should be followed at the time of surgery. Generally, a patient skin surface dose rate of less than 20 $\mu\text{Sv/h}$ does not require special handling by the surgeon at the time of operation. That is, lead gloves, special instruments, and extremity radiation monitors (eg, ring badge) are not necessary. Radiation safety personnel should be notified for transportation and storage of the explanted specimen. In our institution, most of our patients treated with ⁹⁰Y microspheres have surface dose rates of less than 20 $\mu\text{Sv/h}$ at 30 days regardless of administered activity.

After resection or transplantation surgery, the explanted liver should be placed in a formaldehyde solution for storage in a leak-proof container. The container should be refrigerated while in storage. Because the explanted liver may contain radioactive microspheres, the container should be monitored with an energy-compensated Geiger-Müller detector or a portable ionization chamber. If the dose rate at the surface of the container exceeds 50 $\mu\text{Sv/h}$, the container should be placed behind lead shielding for decay in storage. While in storage, the explanted liver container should be labeled as radioactive material per federal and state radiation safety guidelines. Institutions should also follow federal and state guidelines for room posting of areas containing radioactive material or designated radiation areas. After the container has decayed for 60 days, the surface exposure rate will usually be less than 5–10 $\mu\text{Sv/h}$ with the use of a portable ionization chamber. At that time, the specimen may be handled by the pathologist in the laboratory according to standard precautions and techniques. However, when pathologic analysis is complete, all tissue should be placed in the original storage container and returned to radioactive material storage. All areas in which the liver specimen was handled should be surveyed with a radiation detection instrument such as a Geiger-Müller thin-window detector. Readings should be less than 0.1 mR/h.

In our institution, explanted livers from patients who received several treatments with ⁹⁰Y microspheres were

obtained. We measured the container, slice specimens, and the grossing laboratory equipment and workspaces (ie, surgical pathology department). The liver containers had been stored for at least 60 days. With use of a portable ionization chamber, the surface dose rate measured approximately 4 $\mu\text{Sv/h}$. The sliced specimens containing the treated site were measured with a Geiger-Müller pancake probe and exposure rates of 3–5 mR/h were obtained. Slices of explanted tissue that did not contain microspheres were at background levels (0.02 mR/h). The specimen-slicing work area, slicing equipment, and documentation area were also surveyed with the Geiger-Müller pancake probe. No contamination was present, and all readings were at background levels (0.02 mR/h).

Calculation of Residual Activity and Proportional Activity Delivered

After administration of ⁹⁰Y microspheres, the dose vial, inlet and outlet catheters, and towels beneath the delivery device are placed in the Nalgene container. This container fits into a cylindrical acrylic shield provided in the accessory kit. With the same configuration of the ionization chamber with the dose vial, the residual activity in the assembly can be determined. For determination of the actual dose (in Gy) delivered to the target liver after injection, the following formula is used:

$$\text{Dose (Gy)} = 50 [(\text{measured activity (GBq)} \times (1 - \text{LSF}) \times (1 - R)] / \text{liver mass (kg)}$$

where LSF is the fraction of injected radioactivity localizing in the lungs, as measured by ^{99m}Tc-MAA scintigraphy, and R is the fraction of injected radioactivity remaining in the dose vial, outlet catheter, and catheter as measured by the ionization chamber.

Authorized User Status

The technical aspects of microsphere delivery constitute an interventional radiology procedure almost in their entirety. Therefore, it is important that interventional radiologists play a leading role in the future evolution and development of this technology, including angiographic delivery, dosimetry, and overall technical

enhancements in radioembolization. Depending on institutional policies and hospital radiation safety committees, interventional radiologists should function in a collegial manner with authorized users of brachytherapy devices such as radiation oncology or nuclear medicine physicians. This having been said, although local regulatory bodies may impose some hurdles that limit the ability of interventional radiologists to perform radioembolization independently, this model should not be discouraged. Many successful radioembolization practices involving the interventional radiologists as authorized users have been established, supporting the practice model of the interventional radiologist as the authorized user of ⁹⁰Y.

Interventional radiologists are certified by the American Board of Radiology. Their specialized training is certified by the American Board of Medical Specialties. During their radiology residency and specialty fellowship training, interventional radiologists receive formal didactic training in radiation biology, radiation physics, and radiation safety, making them fully able to undertake roles and responsibilities of authorized users. Along with radiation oncologists, interventional radiologists undergo written examinations administered by the American Board of Radiology. In most clinical or hospital settings, radiologists, radiation oncologists, and nuclear medicine physicians are the most knowledgeable in matters regarding radiation and radiation safety. Interventional radiologists also provide the full spectrum of patient clinical care services, including consultation and initial patient evaluation, actual performance of the procedure, postoperative care, and follow-up care. Finally, one of the most compelling arguments in support of interventional radiologists as authorized users is that as of completion of this manuscript, all vendor training of physicians beginning ⁹⁰Y use was being performed by interventional radiologists, with the exception of one radiation oncologist. Therefore, interventional radiologists are ideally suited for authorized user status for radioembolization. This having been said, institutions are directed to individual state rules regarding authorized user status. At the time of manuscript completion, the Nuclear Regula-

tory Commission was considering changing the guidelines, which would permit interventional radiologists to become independent authorized users.

Postprocedural Care and Follow-up

Postprocedural considerations and discharge.—Because ^{90}Y therapy has a low toxicity profile, the treatment can be performed on an outpatient basis. Given the possibility of small unrecognized arterial vessels coursing to the gastrointestinal system, our protocol recommends the routine use of prophylactic antiulcer medications in all patients at the time of discharge to minimize the risks of gastrointestinal irritation (85). Gastric coating agents may also be used. In some cases, unless contraindicated (eg, diabetes), a tapering 5-day steroid dose pack is also given to counteract fatigue. After the procedure, patients recover and are discharged within 6 hours (2 hours if an arterial closure device is used). There are selected and idiosyncratic reactions that may occur in the immediate postprocedural time period. Aside from the transient temporary burning that patients may experience during ^{90}Y injection, they may also experience transient, sudden-onset chills, shaking, and fever. These symptoms are short lived and respond to meperidine, diphenhydramine, and acetaminophen. They may occur immediately after the procedure and through the first week. At our institution, the first five patients in whom these symptoms were observed were admitted for standard fever workup including blood cultures, chest radiography, and urinalysis. The results were noncontributory in all cases. Overall, we have seen this reaction in 10 patients. All responded to the implementation of the standard protocol described earlier. Most patients who experienced this reaction had arterioportal (ie, not arteriohepatic vein) shunting or portal vein thrombosis and all were being treated with TheraSphere for HCC (86). We now routinely administer diphenhydramine and meperidine immediately before infusion of ^{90}Y in patients who exhibit the aforementioned angiographic findings.

Because ^{90}Y is a β -emitter, most

patients will have surface readings of less than 1 mrem/h after implantation. Therefore, standard biohazard precautions are sufficient to protect from exposure to others after they have been discharged. With resin microspheres, trace amounts (25–50 kBq/L per GBq) of urinary excretion are a possibility in the first 24 hours after implantation (83). Investigators should refer to the product inserts, institutional radiation safety committees, and state and federal regulatory agencies for guidance on ^{90}Y use and patient discharge instructions.

Follow-up care and side effects.—The most common side effect of treatment is fatigue. The majority of patients will experience transient fatigue with vague flulike symptoms. This is likely related to the effects of short-lived, low-dose radiation on the normal hepatic parenchyma (16,42,57). It is also not unusual for shaking, chills, and fever to occur days after treatment. One possible explanation for delayed shaking, chills, and fever is the paraneoplastic fever syndrome, with the release of various pyretic agents and acute phase reactants such as tumor necrosis factor and C-reactive protein. This is not unlike what may be observed after TACE, and it is common in patients with neuroendocrine and other highly vascular tumors such as HCC. The majority of these symptoms resolve on their own. However, if they persist, infection should be a concern, and proper steps should be undertaken to exclude an infectious cause. Other possible side effects include abdominal pain, nausea, vomiting, and radiation cholecystitis. If the patient presents with chronic abdominal pain, nausea, vomiting, or bleeding, endoscopic evaluation may be indicated to exclude gastrointestinal ulceration. Despite the use of prophylactic drug regimens, the patient may experience radiation gastritis and ulceration, both of which may require surgery for definitive treatment. Radiation-induced liver disease is a possibility, particularly in patients with compromised liver function at initial treatment. Response to steroids in this condition is variable. There has been some success in treating patients with radiation hepatitis by the creation of transjugular intrahepatic portosystemic shunts (Bilbao I, personal communication).

Because the majority of microsphere radioactivity has decayed by 12 days (ie, four half-lives), all patients should be seen clinically at 14 days. This clinic visit is highly recommended, particularly for the treating physician during the early phase of the ^{90}Y program, because it provides the treating physician with a clinical assessment and rapid learning curve of the patient's tolerance for the treatment. The clinician can also evaluate the patient for a second treatment to the other lobe at 30–60 days follow-up if required. In addition, this clinic visit permits monitoring of adverse sequelae such as fatigue (most common); tumor lysis or paraneoplastic syndrome; or hepatic, gastrointestinal, or pulmonary toxicity. Ultimately, the visit is most important to confirm that the patient's ECOG PS has not deteriorated. Significant worsening in PS should be taken seriously and warrants delay in further therapy. If patients tolerate the first treatment, they should be scheduled for the second administration as required. Performing laboratory tests in patients in clinically stable condition during the 14-day visit is left to the discretion of the treating physician, as most patients will exhibit a transient increase in aminotransferase and tumor marker levels. The majority of patients do experience a sustained lymphopenia that is not associated with opportunistic infections (16). This phenomenon appears to occur more frequently with glass than with resin microspheres.

Treatment of the Second Lobe

Follow-up Evaluation of the First Lobe.—Thirty days after the first treatment, assessment of response to the first infusion must be undertaken, and overall clinic status of the patient must be assessed. Liver function tests, complete blood count with differential, tumor marker analysis, and cross-sectional imaging are performed. In the majority of cases, overall liver function (ie, total bilirubin) should be unchanged. Depending on the presence or absence of extrahepatic disease, tumor marker levels may increase, remain unchanged, or decrease compared with baseline, making interpretation difficult. If they are increased, tumor lysis, tumor progres-

sion in the liver, or the presence of extrahepatic disease sites may be implicated. If they are unchanged, an argument could be made that there has been interval stabilization and/or improvement in tumor burden. As a result of the uncertainty in interpretation of tumor markers at 30 days, their use in the assessment of clinical response should be reserved for long-term follow-up. Finally, because radiation may be implicated in thrombocytopenia and bone marrow suppression, it is important to obtain a complete blood count with differential. Lymphocyte suppression without clinical sequelae has been observed in many patients undergoing ^{90}Y therapy (11). The follow-up imaging modality used to assess tumor response should be consistent with that used for baseline imaging. If MR imaging is used, diffusion-weighted imaging permits the documentation of necrosis and cell death (37). CT may limit the ability to definitively document tumor necrosis. However, other indirect criteria can be used, such as size of the lesion and relative alterations in vascularity and enhancement. Follow-up functional imaging such as MR imaging or PET may be helpful (28,37,44,45).

The 4-week follow-up scan has a different purpose depending on whether primary or metastatic disease is treated. For HCC, the 4-week scan determines the degree of tumor shrinkage and necrosis. Progression to the point of alteration of the clinical liver-directed therapy plan is unusual in HCC at 30 days after the first treatment. For metastatic disease, the 30-day follow-up scan assesses tumor response and the presence of necrosis. Most importantly, given the greater likelihood of tumor progression (as opposed to HCC) in patients with liver metastases patients being treated with liver-directed therapy, the purpose of the 30-day scan is to search for failure of response to ^{90}Y treatment in the treated lobe or extrahepatic progression. Either of these scenarios may result in the discontinuation of ^{90}Y treatment. Tumor progression in the untreated lobe does not represent a reason for discontinuation of treatment with ^{90}Y if a positive result of the first treatment has been achieved. Positive results that support continued ^{90}Y treatment to the other lobe at

day 30 include (i) stability in tumor size, (ii) tumor shrinkage, (iii) necrosis within the tumor with or without tumor shrinkage, (iv) improvement on PET in the treated area, (v) improvement in liver function test results, (vi) improvement in PS or pain, and (vii) improvement in tumor markers if applicable. Results at day 30 that may result in the discontinuation of ^{90}Y treatment include (i) progression in the treated area implying radiation resistance, (ii) development of significant extrahepatic disease, (iii) worsening in liver function test results precluding further treatment, and (iv) worsening of PS.

Treatment of the second (or additional) lobe(s).—From an angiographic and technical standpoint, the administration to the second (or other) lobe should be straightforward, because it is the patient's third (or more) catheterization. Therefore, optimal catheters and guide wires will have been established during the planning visceral arteriography and first treatment session. If the first treatment was performed with lobar $^{99\text{m}}\text{Tc}$ -MAA evaluation (as might be done for HCC), a second $^{99\text{m}}\text{Tc}$ -MAA administration and calculation of shunting may be required. If whole-liver $^{99\text{m}}\text{Tc}$ -MAA was performed during planning mesenteric angiography, a repeat $^{99\text{m}}\text{Tc}$ -MAA scan is not necessary. The cumulative dose of ^{90}Y administered must not exceed a total lung exposure of 50 Gy (55).

Clinically, patients tolerate the second treatment similarly as they do the first, although there is usually less fatigue. This may simply be a phenomenon of the smaller left lobes being treated second. Therefore, the degree of fatigue varies, most of this effect occurring during treatment of the larger lobe, usually the right. There may also be a relationship between dose received and the manifestation of fatigue. Interestingly, the sensation of burning, fever, and chills is often reproduced in the same patient.

Repeat treatment of a lobe/segment.—Repeat injection of ^{90}Y may be necessary in a previously treated vascular bed (ie, lobe), such as recurrent disease or incompletely treated disease. However, it is important to recognize that the mode of action of ^{90}Y is distinctly different from that of embolic-

type therapy such as TACE or drug-eluting microspheres.

TACE involves the infusion of high-dose chemotherapy, followed by ischemia-inducing particles at the 300- to 700- μm level. When ischemia is induced, hepatocytes may still recruit blood flow from the portal vein or extrahepatic arterial vessels such as the right inferior phrenic or intercostal and thereby maximize the chance of cellular viability. Repeat treatment with TACE is therefore possible because this mechanism of hypoxia induction is independent of tumor presence and hypervascularity. Normal hepatocytes will continue to recruit vascularity with each embolization procedure.

The mechanism of ^{90}Y involves absorption of the microspheres by hypervascular tumors. The greater the hypervascularity, the more microspheres are absorbed in the tumor, and the lower the corresponding dose to normal parenchyma. Theoretically, if blood flow to a lobe were 100% to tumor and zero to normal parenchyma, the entire ^{90}Y dose would be absorbed by the tumor and normal parenchyma would receive no exposure. Given this mechanism of action, hypervascular tumors become necrotic and obliterated from an angiographic standpoint after treatment (58). This mechanism of action breaks down if retreatment is undertaken and tumor hypervascularity is not present, given the significant reduction in tumor blood flow that occurs after treatment with ^{90}Y . Therefore, during subsequent treatments, if tumor hypervascularity is not present, fewer microspheres are absorbed by tumor, and the corresponding normal parenchymal dose is increased. The limitation described herein lies in the inability to definitively calculate normal parenchymal dose with ^{90}Y microspheres. Therefore, until this limitation is corrected, repeat treatment with ^{90}Y should be considered only when tumor hypervascularity persists after initial treatment, and in such cases, segmental infusions should be performed if angiographically feasible. Little phase I/II work has been done with repeated treatment of ^{90}Y ; caution should be exercised in such cases.

In cases in which repeat treatment is initiated, several steps should be

undertaken to minimize the risks of radiation hepatitis and pneumonitis. First, it is essential that repeat ^{99m}Tc -MAA shunting fraction be evaluated. This is necessitated by the principle of hyperaugmentation of pulmonary shunting (67). Previously treated segments or lobes of liver may have altered microvascularity flow dynamics at the tumor level, requiring a repeat ^{99m}Tc -MAA scan. If shunting is not re-evaluated, the actual lung shunting may be underestimated, placing the patient at undue risk for lung injury. Second, depending on the angiographic findings of tumor vascularity, a lowered dose should be considered until phase I/II dose-escalation studies are complete. Finally, unless contraindicated (eg, in cases of diabetes), we advocate the use of a 14-day low-dose steroid regimen as well as antiinflammatory drugs in patients undergoing repeat treatment for HCC or metastases. This may theoretically reduce the risk of radiation-induced liver disease. Caution should be exercised in the use of nonsteroidal antiinflammatory drugs in patients with cirrhosis who have esophageal varices (87).

In summary, as long as there is significant tumor hypervascularity acting as a receptacle and sump for microspheres, repeat treatment may be considered if all other factors are appropriate (eg, repeat lung shunt fraction, as discussed earlier). If a large avascular necrotic lesion was created after initial treatment, repeat treatment should be considered with caution because microspheres will no longer be absorbed by tumor but will rather result in the irradiation of normal parenchyma. If significant tumor hypervascularity persists after an initial course of ^{90}Y , the cautionary note regarding repeat treatment become less valid. As long as there is tumor vascularity to absorb the microspheres, repeat treatment may be considered, provided the precautions listed earlier (eg, hyperaugmentation of lung shunt) are recognized.

SUMMARY

Radioembolization with ^{90}Y microspheres represents an innovative approach that has gained increasing awareness and clinical use during the

past 5–10 years. As described in this article, two ^{90}Y radioembolization devices are available today. Although both use ^{90}Y as the radioisotope, their modes of action are distinctly different. A thorough understanding of these differences should help decipher which device might best be applied to certain patients.

The minimal toxicity of radioembolization and the ability to discharge the patient on an outpatient basis make the therapy an attractive alternative in the treatment of primary and metastatic liver malignancies. Patients are able to resume normal activities shortly after treatment, with minimal side effects, in contrast to the postembolization syndrome often associated with current chemoembolic techniques.

Treatment planning requires a multidisciplinary team with clear leadership (ie the driver, as discussed earlier) and accountability to ensure that the screening, diagnostic, and treatment procedures are conducted in a seamless fashion. The essential steps include (i) calculation of target liver mass to be infused and tumor burden, (ii) visceral angiography to map tumor-perfusing vessels and embolize collateral vessels, (iii) assessment of pulmonary shunt, (iv) determination of the optimal therapeutic dose, (v) room preparation, (vi) radiation monitoring and safety procedures, and (vii) calculation of residual activity and efficiency of ^{90}Y delivery.

Careful patient selection and preparation for ^{90}Y liver-directed therapy will result in an optimal risk/benefit ratio for the patient. For patients with HCC, the treatment of advancing disease must be balanced against the often-compromised functional liver reserve caused by underlying cirrhosis. Selection of patients with adequate hepatic reserve and good functional status will maximize the beneficial therapeutic effect of ^{90}Y therapy with minimal risk to normal liver parenchyma. ^{90}Y therapy has also been shown to be beneficial for patients with metastatic disease who have intrahepatic progression despite standard-of-care chemotherapy.

When a patient is being considered for treatment with ^{90}Y therapy, lesion presentation (focal or diffuse), hepatic and renal function, previous therapies

(systemic and intrahepatic), and PS will all affect the prognostic outcome. Careful imaging and angiographic evaluation to assess tumor distribution, vascular anatomy, contribution to intra- and extrahepatic vessels, and pulmonary shunt is essential for (i) accurate delivery of the microspheres to the intended target lesion(s) (ie, safety) and (ii) the efficacy of ^{90}Y in selectively targeting high radiation dose to effect tumor kill while minimizing radiation exposure to normal parenchyma.

Depending on the cause, functional status, hepatic anatomic vasculature, and presentation of liver lesions, several factors need to be considered in treatment planning. If repeat treatment of the same target area is anticipated, cumulative radiation exposure to the target area should be determined and the radiation dose adjusted accordingly to minimize the risk of radiation-induced hepatitis. If vascularity permits, selective infusion of a segment or lesion (ie, “radiation segmentectomy”) will mitigate the risk of radiation exposure to normal tissue. Dose reduction may also be required if estimated pulmonary shunt exceeds 50 Gy among cumulative infusions of ^{90}Y or if hyperaugmentation of lung shunt is identified. Prophylactic administration of antiulcer medication (for 2 weeks) and steroids (for 5–7 days) after treatment will mitigate the risk of pain from nontarget radiation into the gastrointestinal tract and provide relief from fatigue, respectively.

Postprocedural follow-up of the patient to assess any treatment-emergent side effects and tumor response is conducted at 30 days and then at 2- to 3-month intervals thereafter. Other than mild to moderate constitutional symptoms, the side effects of radioembolization include nontarget radiation, radiation pneumonitis, and radiation hepatitis. Diligent vascular mapping during the treatment planning angiography with embolization of the GDA and right gastric arteries, as well as other perforating vessels, will minimize the likelihood of inadvertent deposition to gastric structures. As mentioned earlier, dose reduction and careful consideration of functional liver reserve will mitigate the occurrence of radiation pneumonitis and radiation hepatitis, respectively.

CONCLUSION

There are inherent advantages to the use of radioactive microspheres for the treatment of liver cancers. Delivery to small target volumes, the ability to effect much higher doses of radiation compared with external-beam radiation, the relatively low toxicity profile, and the tumoricidal effect of radiation irrespective of tumor origin make this mode of therapy particularly more attractive in comparison with disease-specific targeted microspheres. Doxorubicin-coated microspheres may have activity on HCC but not on colorectal cancer. Slow-release irinotecan or oxaliplatin microspheres may have an effect on colorectal cancer, but not on melanoma. Radioembolization, in the form of ⁹⁰Y, rhenium, phosphorous P 32, or holmium, eliminates the need for specificity of a therapeutic device. If delivered at the correct activity to the intended location, radioembolization will have a tumoricidal effect on all neoplastic tissue. This is the basis of radiation oncology: radiation delivered to tumor at scheduled and sufficiently increased levels will have a tumoricidal effect, irrespective of cellular origin. Therefore, radiation microparticles are particularly attractive as a therapeutic device.

The unique aspects of ⁹⁰Y therapy are its minimal toxicity profile and highly effective tumor kill with minimal exposure to normal liver tissue in properly selected patients. These unique characteristics in conjunction with the minimally invasive nature provide an attractive option for patients for whom there are few alternatives. The technical and clinical demands of patient selection, treatment planning, ⁹⁰Y administration, and clinical follow-up require a dedicated interdisciplinary team willing to work cooperatively to achieve the best result for the patient. The clinical benefit and potential for enhancing quality of life for the patient, given this commitment, present an exciting opportunity for the field of interventional oncology.

This article is the first of a three-part series that represents the culmination of years of effort in introducing and developing ⁹⁰Y therapy into clinical practice and is meant to spark interest in the future development of this and other radioembolization tech-

niques. The authors sincerely hope that this goal has been accomplished and that the medical community can continue to scientifically advance this promising therapy.

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