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

Part 2: Special Topics

Riad Salem, MD, MBA, and Kenneth G. Thurston, MA

Yttrium-90 microspheres are increasingly being used as a treatment modality for primary and secondary liver tumors. As these therapies continue to be accepted, it is natural that their application in more complex clinical scenarios will become more common. This article is meant to introduce these controversies and to generate interest and dialogue by the interventional oncology community. This discussion is based on more than 900 ^{90}Y radioembolization procedures performed over a 5-year period.

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Abbreviations: GDA = gastroduodenal artery, HCC = hepatocellular carcinoma, MAA = macroaggregated albumin, PET = positron emission tomography, RECIST = Response Evaluation Criteria in Solid Tumors, TACE = transarterial chemoembolization, WHO = World Health Organisation

OUR previous article on methodologic and technical considerations (1) introduced the concept of yttrium-90 microsphere therapy and the principles of preferential hepatic arterial flow and hypervascularity of tumor relative to normal parenchyma. Given preferential distribution of the ^{90}Y microspheres to tumor, and the local (β) radiation emitted, high levels of radiation beyond that possible with external-beam radiation can be delivered with minimal exposure to normal liver parenchyma. The ^{90}Y treatment paradigm requires a multidisciplinary team comprising interventional radiology, nuclear medicine, radiation oncology, hepatology, medical oncology, and radiation safety personnel. Careful treatment planning with particular attention to patient selection, hepatic vascular mapping, embolization of collateral gastrointestinal vessels, assessment of pulmonary shunt, and optimal dosimetry will result in an optimal clinical outcome for the patient.

The current article extends the general principles of ^{90}Y therapy to additional considerations for treatment planning and approach. Patient selection for ^{90}Y therapy versus transarterial chemoembolization (TACE) and treatment-emergent complications and their management are issues that require some consideration. Other topics include treatment of patients with compromised functional reserve and ^{90}Y treatment after other intrahepatic therapies and surgical procedures. ^{90}Y therapy in the presence of vascular issues such as cystic artery and portal vein thrombosis are also considered. Special considerations for the treatment and follow-up procedures, such as planning mesenteric angiography, radiation segmentectomy, hypervascularity, and increased lung shunting, merit further discussion. Finally, imaging evaluation of tumor response and long-term follow-up for hepatocellular carcinoma (HCC) and metastatic disease are covered as they relate to radioembolization. The discussion of special topics that follows stems from observations made by the primary author after having completed more than 900 radioembolization procedures.

PATIENT SELECTION FOR ^{90}Y VERSUS TACE IN HCC

Patient selection is one of the most frequent areas of debate. The question often arises how to select a patient who might benefit from ^{90}Y versus TACE.

For years, TACE was assumed to provide a survival advantage over supportive care despite several randomized trials with results to the contrary (2–6). Secondary outcomes such as tumor response, lack of enhancement, and promising survival in comparison with historical untreated control individuals justified the use and adoption of this treatment modality for HCC. In 2002, two landmark articles were published supporting the

From the Department of Radiology (R.S.), Robert H. Lurie Comprehensive Cancer Center, 676 North St Clair, Suite 800, Chicago, Illinois 60611; and MDS Nordion (K.G.T.), Kanata, Canada. Received June 25, 2006; and accepted June 26. **Address correspondence to** R.S.; E-mail: r-salem@northwestern.edu

R.S. is a consultant for MDS Nordion (Kanata, ON, Canada) and has lectured for Sirtex Medical (Lane Cove, Australia). K.G.T. is Director of Clinical Affairs for MDS Nordion. No research support was provided for this manuscript, and neither manufacturer had any input in this document.

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statistical survival benefits of TACE in patients with unresectable HCC (7,8). Both studies established TACE as the treatment of choice and standard of care for selected patients with unresectable HCC. From these studies, the use of TACE has been definitively accepted as the treatment of choice for HCC. However, several observations should be made concerning the selection criteria, techniques, control groups, and conclusions of these studies.

Lo et al (8) performed a study randomizing patients into a TACE or control arm. Exclusion criteria included increased bilirubin level (2.9 mg/dL [converted from 50 μmol/L]), increased creatinine level (2.04 mg/dL [converted from 180 μmol/L]), previous treatment for HCC, previous rupture, increased prothrombin time by 4 seconds, capsular rupture, presence of extrahepatic disease, arterial invasion, main portal vein thrombosis, history of encephalopathy or variceal bleeding, and performance status of 4. Patients were then randomized into a treatment group and a control group. The control group received only supportive care, whereas those in the TACE arm received a mixture of cisplatin and iodized oil administered with standard transarterial techniques. Gelfoam pledgets (Pharmacia & Upjohn, Kalamazoo, MI) soaked in gentamycin were then injected. The angiographic endpoint was one at which retrograde flow was avoided during the infusion. Patients were treated again on a predetermined schedule at 2–3 months unless a contraindication to treatment developed or disease progression occurred. An intent-to-treat analysis was conducted, with survival from randomization as the primary endpoint and tumor response (World Health Organisation [WHO] criteria), patient tolerance, and hepatic toxicity as secondary endpoints. Eighty percent of the patients showed positive test results for hepatitis B surface antigen. Although the cutoff point for baseline bilirubin level was 50 μmol/L by protocol, none of the patients recruited in the study had bilirubin levels greater than 23 μmol/L (1.3 mg/dL). The TACE cohort received a median of 4.5 treatments (range, 1–15). Half the patients received at least four treatments, and one patient received 15 treatments. Forty-nine percent of the patients (49%) received TACE with a right or left lobe injection, which implied that the remaining 51% had whole-liver TACE. The median duration of hospitalization for limited postembolization syndrome was 2 days (range, 1–21 d). Of the 192 treatments given to the 40 patients in the treatment arm, there were 145 events of fever (76%) and a 38.5% incidence of abdominal pain or vomiting. Interestingly, the majority of patients were symptomatic at time of treatment (57 of 79). There was statistically significant improvement in survival in patients who underwent TACE compared with the untreated control group. Tumor progression was the cause of death in 20 of 31 patients (65%) and 34 of 37 patients (92%) in the treated and control groups, respectively. The estimated 1-, 2-, and 3-year actuarial survival rates were 57%, 31%, and 26%, versus 32%, 11%, and 3% for the treated and untreated arms, respectively. Survival times for patients with Okuda I and II disease, respectively, were 25.4 and 9.2 months in the TACE arm and 11.5 and 5.2 months in the untreated arm. The tumor response rates (WHO criteria) were 39% and 6% for the treated and untreated groups, respectively. α-Fetoprotein response rates were 72% and 10% for the treated and untreated groups, respectively.

Llovet et al (7) performed a study randomizing patients to receive TACE, bland embolization, or supportive care. Rather than wait for disease progression for repeat treatment to be performed, patients were treated at regularly scheduled intervals (similarly to systemic chemotherapy), a deviation from previous TACE treatment protocols. Exclusion criteria included age greater than 75 years, Child-Pugh class C disease, encephalopathy, ascites, vascular invasion (including branch portal vein thrombosis), extrahepatic spread, portosystemic shunt, hepatofugal flow, and serum bilirubin level greater than 85.5 μmol/L (5.0 mg/dL). Patients were then randomized into TACE, bland embolization, and control groups. The control group received only supportive care, whereas those in the TACE and bland embolization arms received treatment at baseline, at 2 and 6 months, and every 6 months thereafter. Treatment was discontinued if any exclusion criteria developed. The TACE group received an emulsion of doxorubicin and iodized oil adjusted to bilirubin levels, followed by gelatin sponge particles. The bland embolization group received gelatin sponge embolization until flow stagnation was reached. Whole-liver embolization was performed at each session. No antibiotic prophylaxis was used. The primary endpoint was survival, and the secondary endpoint was tumor response. The majority of patients had hepatitis C cirrhosis (>81%). Although the cutoff level for baseline bilirubin measurements was 85.5 μmol/L according to the protocol, none of the patients recruited in the study had bilirubin levels greater than 29.1 μmol/L (1.7 mg/dL). Although the only difference between the groups in baseline characteristics was in serum bilirubin level, it did not reach significance. The mean numbers of treatments were 3.08 (range, 0–7) and 2.8 (range, 1–8) for the embolization and TACE groups, respectively. Tumor response rates were 35% in the TACE arm (14 of 40 patients) and 43% in the bland embolization arm (16 of 37 patients). Compared with the bland embolization arm, only TACE resulted in lower frequency of vascular invasion. One- and 2-year survival probabilities in the TACE arm were 82% and 63%, respectively; those in the bland embolization group were 75% and 50%, respectively; and those in the control arm were 63% and 27%, respectively. Hence, TACE demonstrated a statistical improvement in survival compared with control. Given the early stoppage of the trial, the investigators were unable to undertake a proper analysis or to test the rejection of the null hypothesis in the bland embolization group. The authors concluded that TACE should become the standard approach for a select group of candidates termed to have intermediate-stage disease (ie, unresectable HCC and preserved liver function) (7).

It is clear from these two investigations (7,8) that TACE appears to extend survival compared with supportive care in patients who meet the strict entrance criteria. However, since the publication of these two studies, patient selection criteria for TACE in clinical practice appear to have softened, and the survival benefits incurred by TACE are being assumed to

exist not only for intermediate-stage disease but for all cases of HCC (despite precautions against this generalization by the authors of these studies) (7). TACE has now evolved into use for the treatment of cases that differ significantly in baseline characteristics from those in the two randomized reports (7,8). Patients are treated in a segmental/lobar (rather than whole-liver) fashion, despite increased bilirubin levels, portal vein thrombosis, and minimal extrahepatic disease; without reaching stasis, with the use of triple (not single) drug regimens in addition to permanent embolic particles (instead of Gelfoam). In addition, the most common treatment model in clinical practice is that of initial treatment followed by repeat treatment only if progression occurs. This is in direct contradistinction to the treatment paradigm being advocated by these two excellent studies (7,8). In terms of the "bland" embolization group, controversy exists as to whether the mechanism of Gelfoam is comparable to that of true bland particle embolization. Finally, the long-term outcome of the patients undergoing bland embolization is not discussed in detail.

In summary, for the select cohort of patients with intermediate-stage disease in these two studies (7,8), TACE imparts a survival advantage compared with supportive care provided TACE is practiced as advocated by the randomized studies. However, for patients whose disease is categorized outside those selection criteria, there are no randomized data supporting the use of TACE. This having been said, it is important to state that, without question, TACE is the worldwide standard for the treatment of HCC. The amount of data on ^{90}Y does not rival that of TACE. With TACE, the goal has been achieved to establish the proof of principle of arterial therapy to deliver therapy to tumors. Because of the introduction and adoption of TACE, technical and angiographic considerations have been perfected; microcatheter systems have been developed, allowing for the highly selective delivery of therapeutic agents. The proof of principle of arterial-based therapy has now been conclusively demonstrated since its introduction in 1982, setting the stage for the next generation of innovative therapies, such as drug-eluting, drug-coated, biodegradable, and radioactive microspheres, as well as other products currently in development (9).

Ultimately, given the similar response rates, the differences between TACE and ^{90}Y therapy may be in the incidence of postembolization syndrome and clinical toxicities. Also, several analyses have shown that tumor response is the one variable that most consistently translates into a survival advantage (7,8,10). Hence, the 39%–47% response rates obtained with ^{90}Y treatment suggest a trend toward survival benefit (11,12). Just as with TACE, proper selection of patients who may benefit from ^{90}Y therapy is important. Investigators are directed to several recent studies that have demonstrated that selected patients may benefit from ^{90}Y therapy (12–15).

RATIONALE FOR USE OF ^{90}Y THERAPY VERSUS TACE IN METASTATIC DISEASE

Although no randomized data support the use of liver-directed therapies such as TACE for metastatic disease to the liver, abundant phase II studies support this indication (16–20). Response rates ranging from 35% to 100% dispel the notion that metastatic lesions do not respond to arterial treatment given their perceived hypovascularity.

The term "hypovascularity" in reference to metastatic lesions should be further explored. Although it is true that, relative to normal hepatic parenchyma, metastatic liver lesions do not exhibit significant contrast enhancement, studies have shown that there is preferential uptake of intraarterially injected ^{99m}Tc macroaggregated albumin (MAA) in metastatic tumors compared with normal parenchyma (21). These lesions may not be as vascular as metastatic renal or neuroendocrine lesions, but relative uptake of ^{99m}Tc-MAA suggests that they are more vascular than normal parenchyma. In other words, liver metastases may have a gradation of vascularity, starting from hepatic cysts that are avascular, followed by normal hepatic parenchyma, and followed then by less vascular metastatic lesions (ie, of the colon, breast, or pancreas), and finally hypervascular metastases (ie, renal, neuroendocrine, thyroid).

This concept of relative uptake of ^{99m}Tc-MAA over normal parenchyma (supporting relative hypervascularity) in liver metastases has been described previously (21,22). Relatively less flow to metastatic tumors may affect the ability to deliver drugs, especially in large particle format (>300 μm). However, with ^{90}Y microspheres, the high specific activity and small size (20–60 μm) of the particles offsets the "hypovascularity," which most likely accounts for the favorable response rates obtained with ^{90}Y for the treatment of metastatic liver disease. In other words, insufficient chemotherapy may penetrate metastatic tumors to provide very high response rates, whereas, for the same tumor, sufficient high-radiation microspheres may penetrate the tumor to yield a response. Therefore, intraarterial delivery of liver-directed therapy for metastatic disease in the form of TACE or ^{90}Y treatment appears to be justified by findings in the literature (14,17,19,21–27). Finally, a study involving more than 400 patients concluded the following: (i) there is no correlation between perceived vascularity on angiography (or lack thereof) with tumor versus normal tissue uptake ratio in HCC and liver metastases, (ii) HCC had higher ranges of tumor versus normal tissue uptake ratio, and (iii) there is no correlation between tumor size and tumor versus normal tissue ratio (23).

COMPLICATIONS OF ^{90}Y INFUSION

Other than the mild postembolization symptoms that may occur after administration of ^{90}Y, the most common complications of radioembolization include nontarget radiation (ie, gastrointestinal ulceration, pancreatitis), radiation pneumonitis, and radiation-induced liver disease (ie, radiation hepatitis) (12,24–29). The incidence of nontarget radiation should be minimized if the technical principles described earlier are followed, including aggressive embolization of collateral vessels and the use of fluoroscopic guidance. Aggressive prophylactic embolization is recommended because ^{90}Y-induced ulcers may be refractory to medical therapy (30).

Postembolization Syndrome

Given the embolic load of SIR-Spheres (Sirtex Medical, Lane Cove, Australia), it is not uncommon for patients to experience abdominal pain in the target organ. This often resolves within 30–60 minutes with the use of narcotics (31,32). This acute abdominal pain does not usually occur with TheraSphere (MDS Nordion, Kanata, ON, Canada) (12).

Postembolization syndrome may occur in as many as 50% of patients. This syndrome is not as severe as that observed with TACE and is usually dominated by fatigue and constitutional symptoms (12,31,33).

Radiation Gastritis, Gastrointestinal Ulcers, and Pancreatitis

Attenuated radiation to adjacent structures is another theoretical concern of ^{90}Y therapy. For example, segment 4, 5, or 6 lesions may impart a radiation effect to the right side of the colon or gallbladder after treatment. Also, treatment to the left lobe of the liver may cause radiation gastritis as a result of its proximity to the stomach. One final example of attenuated radiation effect is right pleural effusion, which is occasionally seen after right lobe treatment. Gastrointestinal ulceration and nontarget administration of microspheres should be minimized with use of angiographic techniques previously described (24,30,32,34). Nontarget administration of microspheres can result in pancreatitis (35,36).

Radiation Pneumonitis

Proper lung shunting studies and incorporation of this information in dosimetry models should be practiced universally. The risk of radiation pneumonitis is mitigated if cumulative lung dose is limited to 50 Gy (37).

Radiation Hepatitis

Another possible complication of radioembolization is radiation hepatitis. This mechanism involves the irradiation of normal parenchyma beyond that which is tolerated. Ingold et al (25) published the landmark series on radiation hepatitis in a cohort of patients treated with whole-abdomen external-beam radiation for gynecologic malignancies. The classical findings of anicteric ascites, increased alkaline phosphatase levels, thrombocytopenia, and venoocclusive disease occurred in patients who received doses of more than 30 Gy to the liver. More recently, investigators studied the tolerance of liver to external-beam radiation. Patients with HCC were able to tolerate 39.8 Gy, whereas patients with liver metastases could tolerate 45.8 Gy without the occurrence of radiation hepatitis (38).

Although the mechanism and dosimetry of selective "internal" microsphere radioembolization is distinctly different from that of external-beam radiation, liver failure in this unique form of radiation hepatitis is a possibility despite the previously published explanation of the safety of hepatic doses of 100–150 Gy (39). When radioembolization with microspheres is undertaken, the objective is to administer the microspheres to the tumor without affecting the normal parenchyma. However, if the normal parenchyma receives a threshold dose greater than a yet-undetermined amount for this mode of therapy, irreversible liver failure may ensue. Systemic steroid treatment may control the progression of radiation hepatitis. It must be stated that the true mechanism of radiation hepatitis from radioembolization is not currently understood. Any evidence of radiation hepatitis (eg, anicteric ascites and increased alkaline phosphatase and aminotransferase levels) represents an extension of the knowledge gained from external-beam radiation (32,40).

Lymphopenia

Lymphopenia is another possible clinical sequela of ^{90}Y infusion. This is not surprising, given the exquisite sensitivity of lymphocytes to radiation. Although lymphopenia tends to occur more commonly in patients treated with glass microspheres, opportunistic infection has not been reported (11,12).

Biliary Injury

It is well known that biliary complications may occur as a result of radiation therapy to the upper abdomen (41,42). Very little has been reported on biliary complications after treatment with ^{90}Y microspheres. Theoretically, given that the microsphere size of 20–60 μm is quite similar to the blood supply to the peribiliary plexus, microspheres may lodge in this plexus and cause microscopic injury (34). Possibilities include abscess formation, biliary necrosis, biloma, and radiation cholecystitis (43). Further investigation in this uncharted territory is warranted.

Hepatic Fibrosis and Portal Hypertension

The injection of ^{90}Y into the hepatic arterial system may cause hepatic fibrosis, resulting in portal hypertension. Investigators have reported this as a possible complication of ^{90}Y therapy (44) after surgical exploration before and after ^{90}Y infusion. At repeat laparotomy, increased portal pressures and venous congestion was noted. The authors concluded that ^{90}Y therapy might have contributed to this surgical finding (44).

It is important to note that the finding of hepatic fibrosis is not unique to ^{90}Y therapy. Systemic chemotherapies may also result in the same clinical findings of sinusoidal obstruction, perisinusoidal fibrosis, and venoocclusive disease of the normal hepatic parenchyma (45). These systemic chemotherapies may also cause steatohepatitis, resulting in higher perioperative mortality rates in patients who subsequently undergo hepatic resection (46).

For ^{90}Y, the findings of hepatic fibrosis seen in metastatic disease after treatment should not be referred to as cirrhosis. The hepatic parenchymal changes are a result of radiation effect and scarring to the hepatic interstitium, not a direct injury to the hepatocyte with the development of cirrhosis. Liver function in these patients is usually preserved, possibly supporting this explanation (47).

Radiation Cholecystitis

Radioembolization may cause radiation cholecystitis. Although clinically relevant radiation cholecystitis requiring cholecystectomy is not common, imaging findings of gallbladder injury (ie, enhancing wall, mural rent) are quite common (32,43). Patients who do not experience acute cholecystitis may have symptoms of chronic right

upper quadrant pain and biliary dyskinesia.

Miscellaneous Imaging Findings

Investigators may observe many imaging findings after radioembolization, which include tumor necrosis, ring enhancement, transient perivascular edema, biliary injury (as described earlier), hepatic fibrosis, pleural effusion, perihepatic fluid, and posttreatment lobar hypertrophy (eg, caudate) (32,48).

Idiosyncratic Reactions

Investigators should refer to the product inserts for a list of all possible adverse events and idiosyncratic reactions. These include periinfusional shaking or chills that can be seen in patients with HCC being treated with glass microspheres, and changes in gustatory sensation that may last for weeks or months (30,49).

PATIENTS WITH INCREASED BILIRUBIN LEVELS: ^{90}Y VERSUS TACE

It can be quite difficult to predict clinical toxicities that might be observed in a patient undergoing TACE. Although risk factors have previously been described, patients who have normal biochemical parameters may still experience treatment toxicities. This is also true of radioembolization.

In the absence of metabolic abnormalities, drug toxicities, or biliary obstruction, patients with increased bilirubin levels, by definition, have compromised hepatocyte function. In patients with HCC, this dysfunction may be a result of cirrhosis. In patients with metastatic disease, this dysfunction may be a result of tumor infiltration or chemotherapy toxicity.

The mechanism of embolic type therapy (ie, bland embolization or TACE) consists of the injection of 300- to 700-μm particles to induce ischemia and/or increase cytotoxic agent dwell time in the setting of TACE. The particles lodge proximal to the hepatocytes, usually at the 300- to 700-μm level. The fact that the embolic particles do not reach the hepatocyte level allows tumors and hepatocytes to recruit extrahepatic vessels as well as portal venous flow. This in turn maximizes the likelihood that the hepatocytes will maintain viability and hence intrinsic liver function. The ability of the hepatocyte to recruit blood flow demonstrates the ability to compensate for the embolic insult and maximize the likelihood that the patient will tolerate the therapy. If this occurs, intrinsic liver function may be preserved. This mechanism is one of the explanations for the finding of normal liver functions in the presence of occluded hepatic arteries, a scenario that is not uncommon after several TACE procedures.

In the setting of ^{90}Y treatment, the particles may have multiple effects in the patient with increased bilirubin level and resulting dysfunctional hepatocytes. For the minimally embolic TheraSphere particles, the particles lodge in the 20- to 30-μm sized arterioles, in relative proximity to hepatocytes. The β-irradiation from the ^{90}Y potentially affects the dysfunctional hepatocytes and may result in further compromise. Because ischemia is not induced (with a low number of spheres injected), any deleterious effect is caused by radiation (50).

For SIR-Spheres, not only do 20- to 60-μm particles reach the hepatocytes, analogous to TheraSphere, but the significantly larger number of spheres may induce embolization and initiate a response to hypoxia. Collateral vessels may be recruited from extrahepatic or portal venous sources as a response. The hepatocyte insult may be augmented from one of radiation alone to the synergistic effect of radiation and ischemia, which may further worsen hepatocyte dysfunction.

For these reasons, until studies are undertaken to prove the contrary, embolic-type therapies should be considered safer and more established than ^{90}Y microsphere therapy in patients with increased bilirubin levels (unless segmental infusions can be performed). This postulated mechanism of liver toxicity as a result of ^{90}Y in patients with increased bilirubin levels breaks down as the hypervascularity of tumor increases. Intuitively, as more microspheres are absorbed in the tumor, fewer are available to reach hepatocytes with consequent irradiation. Cautionary notes in the treatment of patients with increased bilirubin levels with ^{90}Y are supported by the literature as well as by the package labels for both devices (35,51–54). Treatment with steroids and antiinflammatory drugs should be considered in patients with increased bilirubin levels undergoing radioembolization.

LOBAR VERSUS WHOLE-LIVER TREATMENT

Although much of the early experience with ^{90}Y involved whole-liver infusion, this treatment paradigm is no longer recommended (55,56). Whole-liver treatment was undertaken because of the limitations in microcatheter technology and imaging. With the advent of 2.3-F and 3-F microcatheters, lobar and segmental infusions are recommended when possible. In addition, significant extrahepatic flow through small vessels can be avoided only with use of lobar or segmental infusions (34,57). In our practice, we recommend a treatment paradigm that parallels TACE (ie, lobar or segmental infusions).

If an authorized user insists on treating the entire liver at once, a "bilobar lobar" infusion is recommended. This involves placement of the catheter in one hepatic artery (right or left) followed by the other hepatic artery, where infusions are performed. Infusion of ^{90}Y via the proper hepatic artery should be avoided, given the possibility of unrecognized small perforating vessels (34). Infusion of ^{90}Y via the common hepatic artery should be avoided altogether even if the gastroduodenal artery (GDA) has been embolized. Several small perforating vessels exist between the common hepatic artery and the gastrointestinal tract (30). Infusion from the common hepatic artery increases the risk of nontarget embolization. Prophylactic embolization of the GDA does not justify the infusion of ^{90}Y at the common hepatic artery. Ultimately, the infusion of microspheres at the lobar/segmental level rather than the whole liver is justified by the observation that most of the reports of ulcerations in the literature have come from centers that practice whole-liver infusion with or without prophylactic embolization of vessels (12,31,33,58,59). In the authors' opinion, although segmental or lobar infusions may at times obviate prophylactic embolization of certain vessels before infusion of glass microspheres, this is never the case with resin microspheres. Given the embolic

load of resin microspheres and the clinical insignificance of coil embolization, all extrahepatic vessels should be embolized with coils before resin infusion irrespective of infusion site or approach (ie, lobar or segmental).

TREATING PATIENTS AFTER RESECTION OR RADIOFREQUENCY ABLATION

The most common scenario involving resection in patients with HCC or colorectal metastases likely involves patients who have already undergone right hepatic lobectomy and in whom disease in the left lobe has now developed. In such cases, the left hepatic artery (and remnant of the right hepatic artery) has usually hypertrophied. The liver should be treated by a lobar approach, with embolization of all collateral vessels, as would be performed in other patients. In this case, the lobes include the left lateral segment (segments 2/3) and left medial segment (segments 4a/b) (30). The corresponding target volume should be determined when the activity required to deliver the dose is calculated. In such cases, whole left lobe infusion is not recommended.

Patients who have had hepatic wedge resections or other needle-based liver therapies (eg, radiofrequency [RF] ablation or percutaneous ethanol injection) can be treated according to the standard principles described throughout this article and require no special precautions as long as tumor vascularity is present.

TREATING PATIENTS AFTER TACE

The treatment of patients after TACE is an area of very frequent inquiry. The principles of TACE involve the slow and deliberate infusion of a mixture of oil and chemotherapeutic agent, followed by an embolic agent to (i) increase chemotherapy dwell time within the tumor and (ii) minimize systemic toxicity (60). Ideally, if superselective TACE is performed, the tumor vascular bed is saturated with oil/chemotherapy/embolic material while much of the normal parenchyma has been spared. The same is true if a lobar infusion has been performed, except for the degree of normal parenchyma spared.

The principles of tumor hypervascularity and blood supply from the hepatic arterial system apply as much to ^{90}Y as to TACE, if not more so. This is because the very nature of ^{90}Y involves the infusion of 20- to 60-μm β-emitting radioactive particles. For this to have an effect, the microvascularity of the tumor must be accessible.

Patients who have previously undergone TACE may undergo ^{90}Y infusion given the following conditions: (i) enough time has lapsed and the vessels to the tumor have recanalized; (ii) TACE was not performed to the extent of obliteration of tumor vasculature, chemical vasculitis, or induction of parasitizing flow to the tumor; and (iii) the performance status and liver function have not significantly deteriorated (61). In our institution, if a patient has received previous TACE therapy, a hepatic angiogram is obtained to assess patency of the vasculature to the tumor. In addition, assessment of extrahepatic blood supply to the tumor is performed, close attention being paid to the right inferior phrenic, right adrenal, and right internal mammary arteries. Other vessels adjacent to previously embolized tumors might also be assessed, including the left gastric artery for left lobe tumors, as well as the gastroduodenal, omental (ie, epiploic), superior mesenteric, and intercostal arteries for right lobe tumors. Despite several attempts by our group to treat patients after TACE and the perceived "patency" of the vessels to the tumor, our responses have been suboptimal. This likely relates to the fact that, despite large vessels to the tumor being seen on angiography, the microvasculature has been obliterated, precluding microspheres from entering that same vascular bed.

COMBINATION CHEMOTHERAPY AND ^{90}Y THERAPY

Ample data have been published describing the use of chemotherapy with SIR-Spheres for colorectal liver metastases. Phase I, II, and III studies have been completed and have demonstrated the safety and efficacy of combination therapy (62–68). Further investigations are under way (64,66, 69). It is recommended that investigators refer to those publications and the package insert when undertaking combination therapy with SIR-Spheres. In particular, investigators should exercise extreme caution when catheterizing the hepatic vasculature in patients receiving combination chemotherapy and SIR-Spheres (as described later).

Given that the majority of research with TheraSphere has been as a monotherapy, studies combining it with chemotherapy have yet to be completed. Research that has been published in indications other than HCC have routinely been performed in salvage settings in patients in whom chemotherapy has failed (56,70). Despite this, there may be instances when investigators are considering treating patients with metastatic disease who are receiving systemic chemotherapy with TheraSphere or are considering temporary suspension of chemotherapy for the patient to recover from any adverse events. In such cases, chemotherapy should be discontinued a minimum of 2–4 weeks before TheraSphere administration (34). After completion of therapy, another 2–4 weeks should elapse before the resumption of systemic therapy. The one exception to this guideline is the presence of neuroendocrine disease. Patients with neuroendocrine cancers should continue to receive octreotide throughout their course of therapy with ^{90}Y (71,72). Just as with other liver-directed therapies, a 100- to 200-μg intramuscular octreotide bolus on the day of ^{90}Y treatment is recommended to minimize the risk of inducing a carcinoid crisis (20,73–80).

The complicating technical aspects of catheterization and embolization should also be reinforced. Patients receiving chemotherapy are at higher risk of arterial spasm, dissection, and rupture. Extreme caution should be exercised during the technical portions of radioembolization in these high-risk cases (34). Patients with a recent history of exposure to any chemotherapeutic agent (particularly radiosensitizing agents) such as 5-fluorouracil, irinotecan, oxaliplatin, and capecitabine should be treated with caution. The advent of new growth factor inhibitors (eg, bevacizumab, cetuximab) will likely affect the ability to deliver these microspheres with use of transarterial techniques. The vascu-

larity and flow dynamics of patients receiving growth factor inhibitors is altered, potentially making liver-directed therapies less effective.

Murthy et al (81) recently described a cohort of nine patients who had received a mean of six treatments with cetuximab and/or bevacizumab with a mean follow-up time of 5 months. The median delivered dose was 33.2 mCi (range, 16–54 mCi). Four of seven patients had a decrease in carcinoembryonic antigen, whereas three of seven had stable disease on imaging. The authors concluded that treatment with SIR-Spheres after cetuximab and bevacizumab is feasible. Limitations of the analysis included small sample size, no definition of the time interval between chemotherapy and intraarterial infusion, and no control arm. Hence, despite this pilot report, the effectiveness of ^{90}Y after administration of these agents remains unclear.

COMBINATION RF ABLATION AND ^{90}Y

Just as with TACE, there is much interest in combining ^{90}Y therapy with RF ablation. The theory behind this might be to downstage tumors to sizes amenable to RF ablation (≤3 cm) or to create a multimodality approach in the management of liver tumors. Some have advocated the use of RF ablation before radioembolization in an attempt to create a zone of hyperemia and enhanced microsphere uptake. Others have suggested treating the tumors with radioembolization and then administering RF ablation after the tumor has shrunk to a size at which RF ablation might be feasible. Both are plausible theories. Combining modalities is the logical next evolution of this therapy and should warrant investigation in a manner similar to the combination of TACE and RF ablation. The principles of downstaging tumors with use of ^{90}Y to allow the performance of RF ablation, surgical resection, or transplantation have been previously described (13,14,69,82,83).

HEPATICOENTERIC ANASTOMOSES AND BILIARY STENTS

The treatment of patients with previous biliary surgery, hepaticoenteric anastomoses, or biliary stents deserves special mention. It is well recognized that these patients are at high risk for infection after embolic and ablative therapies (84–86). Given that blood supply to the biliary tree is via the 30-μm peribiliary plexus, ^{90}Y microspheres may potentially flow into and have an effect on the biliary tree. When a patient has received a stent or has undergone surgery with violation and disruption of the ampulla of Vater, the biliary tree is colonized, creating a nidus for infection. In our experience, despite the use of segmental and low-dose infusion as well as pretreatment antibiotics, biliary sepsis, abscess formation not only remains a distinct possibility but is highly probable. Decompressing the biliary tree with endoscopic stents or percutaneous transhepatic cholangiography should not be assumed to reduce the risks associated with ^{90}Y use. Therefore, until further controlled studies are complete, the use of ^{90}Y in these patients should be discouraged, considering the high risk for infection, sepsis, and biliary complications. Aggressive pretreatment antibiotic therapy should not be assumed to mitigate the risks of infectious biliary complications.

CYSTIC ARTERY

The cystic artery may occasionally need to be addressed in the treatment of patients with ^{90}Y. The cystic artery may arise from the right, left, proper hepatic artery, or GDA (34). Although the need for prophylactic embolization has never been advocated, our recent experience suggests that prophylactic cystic artery embolization may be considered. This approach is a reaction to two cases of radiation cholecystitis we have encountered among more than 400 patients treated (one case with each type of ^{90}Y microsphere). Although a previous report has suggested that the incidence of radiation cholecystitis without coil embolization of the vessel is clinically acceptable, we have adopted this enhanced approach when necessary (43). In our institution, we may consider embolizing the cystic artery before infusion of microspheres if (i) blood flow into the cystic artery is significant on angiography, suggesting that ^{90}Y microspheres will flow into the gallbladder, or (ii) catheterization and radioembolization distal to the cystic artery may lead to inadequate distribution of microspheres, given the hepatic branching pattern and the proximity of the cystic artery to the right hepatic artery bifurcation. As an example of the latter scenario, it is possible that advancing the catheter distal to the cystic artery will lead to flow into only one of the two right hepatic artery branches (ie, anterior or posterior branch). In this case, if the patient has multifocal right lobe disease, infusion distal to the cystic artery will result in incomplete distribution of microspheres. Finally, temporary occlusion with Gelfoam may also be considered, although it is technically difficult to accomplish.

One possible strategy to deal with the cystic artery, should embolization be essential for proper ^{90}Y infusion, relates to the approach to the GDA. The blood supply to the gallbladder may come from the cystic artery, perforating vessels from the liver parenchyma, or vessels arising from the GDA. If embolization of the GDA is being considered for ^{90}Y infusion, embolization with as few coils as possible very close to the origin of the GDA may be in order. This may permit branches from the GDA distal to the coils to receive retrograde blood from the gastroepiploic artery and provide flow to the gallbladder when the cystic artery is embolized.

TREATING PATIENTS ON THE SAME DAY AS PLANNING MESENTERIC ANGIOGRAPHY

Several clinicians have addressed the possibility of treating patients on the same day as the planning mesenteric angiography. For this to be successful, a vial of ^{90}Y (SIR-Spheres or TheraSphere) would have been ordered for that day, and the patient would undergo angiography with coil embolization of vessels, injection of ^{99m}Tc-MAA, and imaging in nuclear medicine, and would then return to the angiography suite for ^{90}Y infusion. The shunting fraction and dosimetry calculations would be determined in a "just-in-time" manner, followed by ^{90}Y infusion in one setting. Although some centers have attempted to streamline this process, further discussion is warranted (87).

Although this approach is poten-

tially attractive, its use is fraught with potential pitfalls. First, the mesenteric angiography may take 1–3 hours, depending on the complexity of the case, the number of vessels that require embolization, and the experience of the operator with ^{90}Y. The ^{99m}Tc-MAA would then need to be infused and the patient transferred to the nuclear medicine suite for assessment of lung and gastrointestinal shunting with the arterial catheters stabilized in place. Nursing support would be required for continuous observation of the patient, given the arterial sheaths and conscious sedation. The lung shunting fraction and dosimetry determinations would then need to be performed in a just-in-time manner. The patient would then need to be returned to the interventional radiology laboratory for ^{90}Y infusion. Given different institutional efficiencies, this entire process may take 3–5 hours. A predetermined dose of ^{90}Y would have been ordered in advance in anticipation of treatment. Although this does not pose a problem for SIR-Spheres (given the ability to custom dispense in the nuclear pharmacy), it does pose a problem for TheraSphere. When a vial of TheraSphere has been ordered for a patient, the entire vial must be infused. Unlike with SIR-Spheres, a fraction of the TheraSphere dose vial cannot be infused. Also, given arterial variants that are often seen during initial angiographic evaluation, the location, vessel to be injected, and dosimetry considerations are often impossible to predict in a reliable manner.

Second, the possibility of increased lung shunting, potentially excluding the patient from treatment, should be anticipated. If this occurs, the preordered vial of ^{90}Y may go unused, resulting in an unnecessary and preventable expense.

Third, because ^{90}Y represents therapy that relies on hypervascular flow to the tumor, injection of ^{99m}Tc-MAA proteinaceous particles may occlude the very microvasculature of the tumor being targeted. One to 2 hours between ^{99m}Tc-MAA and ^{90}Y injection may not be a sufficient amount of time to allow normal physiologic breakdown of the ^{99m}Tc-MAA.

In addition, vessels, after they are coil embolized, require hours to days for complete occlusion. This suggests that mesenteric angiography with coil embolization should be separated by days before radioembolization. Therefore, coil embolization and immediate radioembolization is discouraged, given the chance that microspheres may migrate through recently embolized vessels (eg, GDA, right gastric artery). This does not pose a problem for TheraSphere, given the minimal embolic nature of the therapy, but it does pose a problem for SIR-Spheres, given the significant embolic load (31,50).

Ultimately, treatment of liver tumors with ^{90}Y on the same day as diagnostic angiography is discouraged because it exposes the authorized user and treating physician to many complex decisions that may be made without sufficient time for thought, reflection, and planning. Ideally, mesenteric angiography and ^{90}Y infusion should not be separated by more than 2–3 weeks.

All these issues discussed, with the exception of blocking the target arterioles by ^{99m}Tc-MAA, are mitigated if ^{90}Y is performed with a surgically placed port. Performing the ^{99m}Tc-MAA lung shunt study and treating at close intervals through an implanted arterial port has still been shown to be quite effective (22). The complexities of percutaneous ^{90}Y therapy—vessel embolization and anatomic distribution—are eliminated when a surgically implanted port has been placed during a previous admission. This having been said, in today's environment of enhanced fluoroscopic tools, microcatheters, embolization techniques, and the possibility of residual microspheres in the port, treatment through surgically implanted ports is no longer recommended.

RADIATION SEGMENTECTOMY: DOSIMETRY FOR SEGMENTAL OR SUBSEGMENTAL INFUSIONS

As described earlier, the activity of TheraSphere is based on dose required (in Gy) and target volume (in kg). There are cases in which the target tissue is small, there is a feeding vessel to the tumor only, and the 3-GBq activity of TheraSphere is not low enough to deliver 80–150 Gy to the tissue after decay. In such cases, radiation "segmentectomy" is advocated (57,88). An example best illustrates this. On the basis of the dose decay curve, the lowest activity of TheraSphere available for patient use is approximately 0.75 GBq, representing a 3-GBq vial decayed to Friday. For a 100-Gy dose, this corresponds to a target tissue of 0.375 kg. However, if the target tissue is 0.1 kg and a segmental infusion through a feeding vessel is planned, infusion of 0.75 GBq is an option corresponding to an absorbed dose of 375 Gy to that target. Therefore, the principle of radiation segmentectomy is that small volumes of liver may be radiated with very high doses without an adverse effect on normal parenchyma if an isolated feeding vessel is identified. This technique of infusing high radiation doses to small segments of liver has been previously been described, with doses as high as 5,000 Gy administered (14,57,88).

Radiation segmentectomy may also be achieved with the use of SIR-Spheres. The lower limit of available activity vial does not exist with SIR-Spheres. The standard activity of the vial that is shipped is 3 GBq. Therefore, the nuclear pharmacist can dispense as little radiation as clinically required, based on the written directive. This small activity can then be infused in the vessel of interest. The only limitation with radiation segmentectomy and SIR-Spheres is the limitation in microsphere number (and therefore dose) that can be infused, given its embolic effect. Radiation segmentectomy may be limited in select cases with SIR-Spheres because the feeding vessel may become saturated with microspheres before infusion of the entire intended activity.

HYPERVASCULARITY AND TUMOR-TO-NORMAL UPTAKE RATIO

The therapeutic effect of ^{90}Y microsphere therapy for treatment of liver cancers involves two fundamental principles: (i) most of the tumor blood supply (90%–95%) is derived from the hepatic artery, and (ii) blood flow is preferentially distributed to the tumor relative to normal liver tissue (89–91). As previously described, this preferential flow permits maximum concentration of the microspheres in the arterioles within the tumor while minimizing radiation exposure to the normal tissue that may be supplied by the

hepatic system. The extent to which preferential flow is directed to the tumor can be described as the hypervascularity ratio. A hypervascularity ratio of 7:1 is defined as seven eighths (87.5%) of hepatic blood flowing preferentially to tumor, with the remaining one eighth (12.5%) flowing to normal tissue. Russell et al (92) described a perfusion factor *N* (varying between 2 and 6) that determines the degree to which ^{90}Y dose is increased as a result of higher perfusion of the tumor. Preferential flow to tumor as measured by deposition of ^{99m}Tc-MAA particles has been quantified in numerous studies. Tumor-to-normal uptake ratios for a series of 24 patients with colorectal, neuroendocrine, or hepatocellular lesions ranged between 2 and 4.5 (55). In another series of 17 patients with unresectable colorectal cancer and HCC, the ratios ranged from 3 to 14 (26). A high correlation was observed between radiation doses to tumor and normal tissue predicted on the basis of ^{99m}Tc-MAA scanning and direct measurement of actual doses delivered using intraoperative β-probe detection (tumor r, 0.862; normal r, 0.804; $P < .001$).

It should be noted that tumor-to-normal uptake ratios as measured by ^{99m}Tc-MAA scanning might not correlate directly with hypervascularity ratio. The former is a quantitative measure of radioactive particle deposition as the result of preferential flow, whereas the latter is a discrete assessment of dynamic blood flow via contrast medium–enhanced imaging techniques such as hepatic angiography, computed tomography (CT), or magnetic resonance (MR) imaging (23). Finally, it should also be noted that there is no correlation between tumor-to-normal uptake ratio as assessed by ^{99m}Tc-MAA and clinical response as measured by carcinoembryonic antigen levels and CT (22).

TREATING A PATIENT WITH INCREASED LUNG SHUNTING

The basic assumption of ^{90}Y infusion and dosimetry is the homogeneous distribution of microspheres throughout the hepatic parenchyma resulting in the same radiation dose to the volume targeted for treatment. However, because tumors are fed almost exclusively by hepatic vasculature and are hypervascular relative to normal parenchyma, this assumption breaks down in a favorable direction. Consequently, hypervascular tumors receive higher doses while normal parenchyma is exposed to minimal radiation. If this premise is recognized and accepted, it is possible to treat patients with increased lung shunting.

The package insert for TheraSphere dictates that patients receive no more than 16.5 mCi or 30 Gy cumulative radiation absorbed dose (54). The SIR-Spheres package insert provides guidance on dose reduction for elevated lung shunting; patients with lung shunt fractions greater than 20% should not be treated (35). In the authors' opinion, these recommendations should be viewed as guidelines because the peer-reviewed published lung limitation is 30 Gy per treatment and 50 Gy cumulative lung dose (37). There are also methods of modifying the approach to dosimetry to all patients with increased lung shunt to be treated in a clinically safe and appropriate manner.

Patients with increased lung shunting should be treated individually depending on vessel anatomy, tumor burden, hypervascularity, and liver volume, with lung shunting playing an important but secondary role. Lung shunting fraction alone should not be used to exclude a patient from possible treatment with ^{90}Y microspheres. An example illustrates this point. Assume that a patient has metastatic neuroendocrine cancer to the liver, with a hypervascularity ratio of 7:1 (ie, seven eighths of all hepatic flow is to the tumor and one eighth is to normal parenchyma). This ratio is estimated by using the results from the nuclear medicine hepatic ^{99m}Tc-MAA scan, tumor enhancement on CT or MR imaging, and the principle of preferential flow to tumor that has been previously published (21,93–96).

Further assume that lung shunting is 25%, that the prescribed activity of ^{90}Y is 3.0 GBq, that target tumor volume is 0.30 kg, and that the entire lobar volume is 1.50 kg. Ignoring hypervascularity and lung shunting, and assuming uniform distribution throughout the liver, the dose to tissue D is as follows (97):

$$D(Gy) = \frac{50\ [A\ (GBq)][1 - F]}{M\ (kg)}$$

$$50\ [3.0]\ (1 - 0)\ /\ 1.5 = 100\ \text{Gy}$$

where A is the injected activity, F is the fraction of injected activity localizing in the lungs as measured by ^{99m}Tc-MAA scintigraphy, and M is the target liver mass treated.

Assuming a 25% lung shunt fraction, dose to the target tissue with no hypervascularity would be as follows:

$$50\ [3.0]\ [1 - 0.25]\ /\ 1.5 = 75\ \text{Gy}$$

Correspondingly, dose to lung, assuming pulmonary mass of 1.0 kg, would be as follows (98):

$$\text{D (Gy) (lung)} = 50 * \text{A (GBq)} * \text{LSF}$$

where A is the injected activity (corrected for residual in vial) and LSF is the lung shunt fraction.

$$\text{D (Gy) (lung)} = 50 * 3 * 0.25 = 37.5\ \text{Gy}$$

These calculations assume that there is homogeneous distribution of ^{90}Y microspheres to the target liver mass of 1.5 kg. However, it is known that the microspheres are preferentially distributed to tumor tissue as a result of the hypervascularity of tumor relative to normal liver parenchyma (21,99). For this example, assume that the tumor-to-normal uptake ratio is estimated to be 7:1. The tumor burden estimated via the CT scan is 20% (0.3/1.5 kg = 20%) of the target liver mass. Hence, the normal parenchyma constituted a fraction of 1 minus 0.2, or 0.8 of the entire liver.

If the uptake ratio of tumor to normal is 7:1 (0.875 vs 0.125) and the activity infused to the target liver mass is 3.0 GBq, an estimate of the dose delivered to tumor and normal parenchyma, taking into account the proportional mass of tumor to normal tissue (0.20 vs 0.80), may be determined as follows:

$$\text{Dose (Gy) tumor} = \frac{50\ [3.0\ (0.875)]\ [1 - 0.25]}{0.2\ (1.5)} = 328\ \text{Gy}$$

$$\text{Dose (Gy) normal} = \frac{50\ [3.0\ (0.125)]\ [1 - 0.25]}{0.8\ (1.5)} = 12\ \text{Gy}$$

Therefore, by incorporating hypervascularity and proportional tumor to normal tissue, the dose to tumor would be 328 Gy and the dose to normal parenchyma would be 12 Gy. However, either ^{90}Y product would be contraindicated in this setting, because 37.5 Gy would reach the lungs in a single setting (TheraSphere contraindication is >30 Gy; SIR-Spheres contraindication is 20% lung shunting), and the patient showed 25% lung shunting. Given that a dose of 120 Gy is accepted as tumoricidal, the theory of preferential uptake of microspheres to tumor may be used to reduce the activity injected to minimize pulmonary radiation exposure (26,100). In this example, if the activity administered was reduced to 1.5 GBq with the same 25% lung shunt fraction, this would result in a tumor dose of 164 Gy, a normal tissue dose of 6 Gy, and a lung dose of 18.75 Gy. Tumor dose is well above the 120-Gy tumoricidal dose, and 18.75 Gy is well below the threshold dose of 30 Gy for radiation pneumonitis. Therefore, by modifying and individualizing dosimetry, patients with increased lung shunts may be treated safely with tumoricidal doses.

In the authors' opinion, the principle of treating patients who show increased lung shunt fraction with lower-activity ^{90}Y may apply more to glass than to resin microspheres. This is because of the significantly greater number of resin spheres that are needed for a given specific activity. When patients are treated with resin spheres and high shunting, the pulmonary complication may stem not only from the radioactive properties but also from the embolic properties of the microspheres trapped in lung tissue. Investigators have previously stated that patients with more than 13% lung shunting should not be treated with resin microspheres (101). With glass microspheres, the embolic load is significantly lower, and therefore the risk to the lungs in such a setting is purely from a radiation, not an embolic, standpoint (50). To summarize, an absolute percentage cutoff in lung shunting fraction should not be used to ultimately decide whether a patient should be treated with ^{90}Y. This decision should be made in view of overall cumulative lung dose (not percent shunting), performance status, and history of pulmonary disease.

Complications have been described in patients undergoing hepatic artery embolization with small particles (102). In addition, although attempts have been made to reduce lung shunt fraction to allow for TACE, this has not been demonstrated to be directly applicable to ^{90}Y microsphere infusion (103). Reducing lung shunting to permit ^{90}Y treatment represents an area that requires further investigation.

PORTAL VEIN THROMBOSIS: AN EXCLUSIONARY CRITERION?

Increased alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase, and total bilirubin levels before TACE are associated with increased relative risk for hepatic decompensation (60,104–106). In addition, the presence of portal vein thrombosis without cavernous transformation and hepatopetal flow is a well-accepted relative contraindication for percutaneous embolization of liver tumors, despite reports to the contrary (107–109). Controversy exists concerning whether the same portal venous exclusionary criteria should be applied to the selection of patients for treatment with ^{90}Y microspheres.

The mechanism of action for ^{90}Y is more related to that of a device/drug infusion than a complete embolization, with its subsequent induction of ischemia. Although the spheres are lodged in the arteriolar bed measuring 20–60 μm, the relative percentage of arterioles that become obliterated is small. Effectively, there is minimal alteration in vascularity and minimal to moderate embolic phenomena (50). Therefore, the administration of ^{90}Y in patients with portal vein thrombosis should be well tolerated (110). In a cohort of 15 patients treated with ^{90}Y, no case of hepatic decompensation or significant alteration in liver function was observed. Mean follow-up was more than 12 weeks (110). However, the important technical point in these cases is that particular care must be taken not to injure, dissect, or cause thrombosis in the hepatic artery during treatment, because hepatic artery compromise combined with portal vein thrombosis may result in hepatic infarction. Dose fractionation may also be used to avoid reaching an embolic state in the tumor bed in those cases in which there is a concern regarding the potential for hepatic decompensation, particularly with SIR-Spheres. It should be noted that portal vein thrombosis is currently contraindicated according to the package inserts of both ^{90}Y devices (35,54). Finally, portal vein retraction has also been described as a secondary sign of tumor response in HCC (111).

IMAGING EVALUATION OF TUMOR RESPONSE IN PATIENTS WITH HCC AND METASTATIC DISEASE: CAUTIONS REGARDING INTERPRETATION

The clinical treatment of patients with metastatic cancer receiving ^{90}Y is different from that for patients with HCC. Aside from demographics, other differentiating features include liver function, tumor markers, chemotherapy, and surgical history, as well as differences in the appearance of tumors within the context of background liver on imaging.

Hepatomas usually arise in diseased liver, a condition characterized by intrinsic hepatocyte dysfunction, often in a background of chronic hepatitis or alcohol consumption. These patients are often of Asian or Mediterranean descent. Patients with metastatic liver cancer usually do not have those predisposing factors and no intrinsic hepatocyte dysfunction. In other words, patients with metastatic cancer to the liver have normal liver parenchyma with tumor contained within, whereas patients with hepatoma have abnormal liver parenchyma, some portions of which have undergone malignant degeneration. The degree of background cirrhosis may prevent tumor shrinkage after successful ^{90}Y therapy.

The initial imaging of the patient with metastatic cancer is identical with that in the patient with hepatoma, with one exception. Given the difficulty in evaluating tumor response by CT or MR imaging, positron emission tomography (PET) has emerged as an integral imaging modality in the assessment of treatment response to ^{90}Y. Whereas CT provides anatomic information of tumor burden, PET is better at characterizing the functional status of the tumor before and after treat-

ment. In several studies published by Wong et al (112–114), metastatic colorectal liver lesions were evaluated with CT and PET before and after successful ^{90}Y treatment. PET was found to be consistently superior at assessing tumor response to therapy compared with CT (112–114). Moreover, reduction in metabolic activity measured by PET was correlated with a reduction in carcinoembryonic antigen levels. Portal vein retraction has also been described as a secondary sign of response of HCC to ^{90}Y therapy (111).

Traditional methods for the evaluation of tumor response to therapy have been size reduction on CT through the application of the WHO or Response Evaluation Criteria in Solid Tumors (RECIST) criteria (116,117). However, some pitfalls may occur when methods based on CT dimensional changes are applied to ^{90}Y therapy. First, RECIST or WHO criteria do not allow for the use of PET scanning in the follow-up evaluation, and the functional nature of the residual tissue is thereby ignored. In addition, because ^{90}Y treatment is a highly targeted form of radiation therapy, it may at times lead to tumor necrosis, edema, and peritumoral hemorrhage, resulting in an increase in tumor size. By RECIST or WHO criteria, this might suggest stabilization of tumor or progression rather than response. However, on closer analysis and correlation to PET findings, Wong et al (112–114) found the reverse to be true. In addition, some have shown that traditional CT techniques can be misleading and underestimate the true metabolic response associated with ^{90}Y administration (113,114,118,119). In fact, the conclusions of the Barcelona 2000 European Association for the Study of the Liver conference (117) noted that extensive tumor necrosis is not typically paralleled by a reduction in tumor diameter. The recommendations from this expert panel suggested that the estimation of tumor response after ablative therapies should include necrosis and lack of enhancement. This is also true for radioembolization.

Therefore, in patients being treated with ^{90}Y, standard evaluation and follow-up should include liver function, tumor marker measurement, and CT or MR imaging with assessment of lack of enhancement and necrosis. However, in patients with secondary malignancies such as colon cancer, the importance of a sound knowledge of CT findings and imaging pitfalls after ^{90}Y therapy, as well as the necessity of including PET, cannot be understated. The applicability of functional imaging in the follow-up care of the patient treated with ^{90}Y is undergoing further investigation, including study of diffusion-weighted MR imaging (120).

LONG-TERM FOLLOW-UP

Standard treatment response is assessed and reviewed with the patient 3 months after treatment. At that time, a repeat series of laboratory tests is performed, including liver function, tumor marker measurements, and complete blood count. Cross-sectional imaging including CT or MR imaging, as well as PET, is repeated to assess overall response on the basis of changes in lesion size, enhancement characteristics, or reduction in standard uptake values (112,113). Although transient changes in cytokines have been identified after treatment with ^{90}Y, they have not been shown to correlate with response (121).

In cases of significant tumor shrinkage and downstaging, other treatment options may be considered for the patient, such as surgical resection or RF ablation. Alternatively, some patients may wish to undergo additional chemotherapy. In our experience, oncologists prefer the advantage of minimally embolic ^{90}Y therapy compared with TACE, because the vascular supply to the tumor is not obliterated. Theoretically, this may enhance the ability of subsequently administered systemic or intraarterial chemotherapy to reach the tumor bed. Synergistic effects have been noted in patients receiving chemotherapy after ^{90}Y therapy (62,63). Finally, some patients may wish to attempt TACE as an alternative method of treatment for hepatic malignancy if clinical benefit was not obtained from ^{90}Y therapy. Imaging follow-up should be performed with techniques that take into account the localized nature of ^{90}Y as well as the potential lack of tumor reduction that may be observed after locoregional therapy. As previously mentioned, PET has emerged as an integral tool in the assessment of response after ^{90}Y therapy (112–114,118,119). However, these strategies should also include well-accepted and validated measures of tumor response, such as RECIST and WHO criteria (116). Ultimately, on the basis of the discussion herein and the abundant inconsistencies in the literature, investigators should follow the standards previously published and explicitly state their definition of response after the application of a therapy (122). This would include reporting dose, drug, device, and clinical endpoints (eg, survival from first treatment or diagnosis, response rate according to RECIST, WHO, or European Association for the Study of the Liver criteria). Such standardization will help improve the quality of research of interventional oncology and permit comparisons among therapeutic modalities (eg, TACE, RF ablation, ^{90}Y therapy, drug-eluting microspheres), investigators, and centers.

SUMMARY

In most cases of ^{90}Y treatment, patient selection, treatment planning, treatment, and clinical follow-up are relatively straightforward. However, as with any therapeutic endeavor, there are exceptions to the routine. Gastrointestinal and liver-related treatment-emergent complications, although infrequent, should be managed accordingly. Lobar or segmental ^{90}Y infusion beyond major collateral vessels is recommended to minimize deposition of microspheres to nontarget tissue. Prophylactic antiulcer medication will mitigate radiation gastritis resulting from possible deposition of microspheres in unappreciated gastric perforators. Gastrointestinal ulceration is a rare but serious condition that usually requires surgical intervention. Treating the patient with compromised liver function (ie, increased bilirubin levels) may be accomplished safely by selective infusion (ie, radiation segmentectomy) to a segment or tumor bed. In cases of increased pulmonary shunting, lowering the prescribed dose to lessen potential lung exposure will mitigate the likelihood of radiation pneumonitis. Treatment of patients with portal vein thrombosis may be considered if steps are taken to assure that hepatic flow is not compromised. CT and/or PET evaluation of tumor response in patients with HCC and metastatic disease provide useful indicators of treatment response. However, the interpretation of imaging with the poten-

tial for underreporting or misinterpreting results must be recognized. Classic measures of size reduction on MR imaging and CT are not the only indicators of response. Tumor necrosis, lack of enhancement, and functional imaging findings (ie, on PET) should be considered as useful correlates of response in appropriate cases. Finally, long-term follow-up of the treatment response should be undertaken at standard-of-care 3-month intervals with functional performance evaluation, imaging, and laboratory assessments.

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