

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

Part 3: Comprehensive Literature Review and Future Direction

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Treatment options for primary and secondary liver tumors that cannot be resected or ablated are based on transarterial techniques. Although the majority of these are based on bland and chemoembolization techniques, yttrium-90 microspheres represent an alternate transarterial option. Although the amount of literature on ^{90}Y does not rival that of bland or chemoembolization, there nevertheless are ample data that support its use for primary and metastatic liver tumors. A comprehensive review of the entire available literature dating from the early 1960s is presented, as is a discussion of the possibilities for future research with use of radioembolization as a platform.

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Abbreviations: AFP = α -fetoprotein, CEA = carcinoembryonic antigen, ECOG = Eastern Cooperative Oncology Group, FDG = [18F]fluorodeoxyglucose, 5-FU = 5-fluorouracil, GEP = gastroenteropancreatic, HAC = hepatic artery chemotherapy, HCC = hepatocellular carcinoma, PET = positron emission tomography, RECIST = Response Evaluation Criteria in Solid Tumors, RF = radiofrequency, SIRT = selective internal radiation therapy, TACE = transarterial chemoembolization

ALTHOUGH yttrium-90 microsphere therapy has only recently (within the past 5 years) gained increasing awareness and clinical use, investigations into ^{90}Y and other radioisotopes for the treatment of cancer date back to the 1960s (1,2). Initial studies of resin ^{90}Y in humans were reported in the late 1970s. The seminal work in a canine liver model demonstrating the safety and feasibility of ^{90}Y therapy for hepatic malignancies was reported in

the late 1980s (3,4). Human studies of ^{90}Y microsphere therapy in liver applications followed from the late 1980s through the 1990s (5–16). These investigations established the safety of ^{90}Y for intrahepatic applications and the optimal dosimetry for tumor radiation kill while minimizing exposure to normal liver tissue. The assessment of potential pulmonary shunt, particularly in patients with hepatocellular carcinoma (HCC), was reinforced in these studies. The importance of embolization of collateral vessels such as the gastroduodenal and right gastric arteries to prevent reflux to the gastric structures was also realized. Gastric ulceration requiring surgical intervention was routinely reported in many of these studies.

With improvements in technology permitting smaller vessels to be catheterized, as well as refinements in imaging techniques, the safety and efficacy of ^{90}Y microsphere delivery has improved significantly. During the

past 5 years, numerous studies involving larger cohorts, randomized trials, and ^{90}Y microspheres in combination with other systemic and liver-directed therapies have provided confirmatory evidence of the safety and efficacy of ^{90}Y therapy for the treatment of primary and metastatic (predominantly colorectal) liver disease (8,13,14, 17–27). New applications for ^{90}Y therapy in selective lobar/segmental infusion with the intent of preserving functional liver reserve and downstaging disease to permit resection, radiofrequency (RF) ablation, and liver transplantation are also being explored (5–10).

On the basis of encouraging preliminary results with ^{90}Y therapy in metastases other than those from colorectal cancer, such as breast and neuroendocrine metastases, several directions for future clinical applications are also warranted (11–20). ^{90}Y therapy in combination with radiation-sensitizing agents and growth factor

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inhibitors present opportunities to evaluate its application in combinatorial treatment paradigms. Other possible studies include randomized trials of ^{90}Y versus transarterial chemoembolization (TACE), bland embolization, drug-eluting beads, other radioactive spheres, and best supportive care. Finally, the potential application of ^{90}Y therapy to organs other than the liver via an intraarterially placed catheter presents several areas for future research.

This review concludes the three-part series on radioembolization and provides a comprehensive review of the historical development of ^{90}Y therapy, contemporary clinical results, and the direction for future research in clinical applications.

CONTEMPORARY CLINICAL RESULTS

Early Clinical Work

As early as 1963, researchers were investigating the utility of ^{90}Y microspheres in canine prostates (2). In 1967, Flynn (1) assessed the role of ^{90}Y microspheres for the treatment of lung malignancies. Ariel (21,22) and Ariel et al (23) described initial results of ^{90}Y microsphere treatment with indications, as well as the experience with intraarterial injection of microspheres for the treatment of unresectable pancreatic cancer. These agents have also been used for splenic injection in a patient with lymphoma, cerebral infusion for brain tumors, extremity infusions for osteogenic sarcomas, and synovial injection for pain (24–31). Seminal work performed by investigators established the proof of principle of radioactive intraarterial injection for the treatment of liver tumors with use of various radioconjugates including ^{90}Y , ^{32}P , rhenium, and holmium (29,32–43). Direct intratumoral injection and portal venous injection of ^{90}Y have been studied, with both techniques demonstrating antitumoral activity (44–46). Magnetically guided microspheres have also been investigated (47–49). Antitumor effects of ^{90}Y are well-established in patients with lymphoma, as well as in combination with bone tracers (50–52). Nonradioactive glass microspheres have been studied in rabbit kidneys (53). Finally, splenic radioembolization with ^{90}Y

has successfully been used for the treatment of hypersplenism and thrombocytopenia (54).

In 1987, Wollner and colleagues (4) studied the effects of radiosensitizers combined with ^{90}Y resin microspheres. Five dogs were treated with 50 Gy of ^{90}Y alone, whereas another five were treated with 50 Gy ^{90}Y with bromodeoxyuridine. The approximate radiation dose to the liver was 50 Gy. Dogs receiving ^{90}Y alone experienced no changes in aminotransferase levels, whereas those that received bromodeoxyuridine and ^{90}Y experienced transient changes. At necropsy, the type and degree of hepatic toxicity among the animals receiving radioactive microspheres was comparable with that previously described in patients receiving external-beam hepatic irradiation at conventional doses (20–30 rad). Resin microspheres were found in the lungs of some canines, causing radiation-induced granulomas and leading to the initiation of lung shunting calculation before the use of ^{90}Y microspheres. The authors concluded that bromodeoxyuridine could produce acceptable, nonlethal, and tolerable toxicities in this dog model, suggesting that clinical studies of this combination are not likely to be contraindicated by synergistic toxicity (4). The unexpected fragmentation of the resin spheres without myelosuppression led the authors to initiate work with glass microspheres that cannot leach.

In 1988, Wollner et al (3) studied the effects of ^{90}Y glass microspheres in a canine model. Hepatic arterial injection of radioactive glass microspheres was found to produce portal changes similar to those observed in humans after external-beam therapy. Although the extent of damage was proportional to absorbed dose, radiation exposures in excess of 300 Gy did not cause total hepatic necrosis and were compatible with survival. No microspheres distributed to the bone marrow, and no myelosuppression was encountered. The authors concluded that hepatic exposures to humans of 50–100 Gy by ^{90}Y microsphere injection appear to be feasible and tolerable (3).

Comprehensive Literature Review

^{90}Y glass microspheres or Therasphere in HCC.—In 1989, Houle et al (55) presented data on a pilot study of

seven patients with HCC. No toxicities were observed for absorbed doses of 50–100 Gy to the liver and as high as 320 Gy to the tumor itself. Tumor response was seen only at the higher absorbed doses. The authors concluded that ^{90}Y glass microspheres can safely deliver large doses of internal radiation to hepatic tumors as long as extrahepatic shunting can be excluded, and that extrahepatic shunting will be the main limitation to this form of radiation therapy.

In 1992, Shepherd et al (56) conducted a phase I dose-escalation study of ^{90}Y microspheres in 10 patients with primary HCC. The inclusion criteria included cytologically or histologically confirmed HCC and measurable hepatic lesions, a Karnofsky performance status of 60% or greater, normal bone marrow function, and adequate pulmonary status. Exclusionary criteria included compromised liver function, history of significant peripheral vascular disease, previous thromboembolism, bleeding diathesis, or allergy to contrast agents. Treatment was administered in a nuclear medicine laboratory through a previously placed hepatic artery catheter. Bremsstrahlung scans were obtained after dosing to assess distribution. Before injection of ^{90}Y , the presence of extrahepatic shunting was assessed with use of $^{99\text{m}}\text{Tc}$ macroaggregated albumin scanning. Scintigraphy was then performed, and ^{90}Y was not administered if there was significant shunting to the lungs, stomach, or bowel. Four patients were treated with 50 Gy, two patients received a 75-Gy dose, and three patients received a 100-Gy dose. Survival was not an endpoint but was reported in this series to range from 16 days to 1,050 days (median survival, 126 d). The patients who survived the longest had the greatest tumor-to-liver perfusion ratio and therefore the greatest estimated dose delivered to the tumor. None of the patients experienced myelosuppression. One patient experienced a duodenal ulcer 2 weeks after treatment, which ultimately required surgery. This seminal study provided the initial safety data to enable outcome studies with ^{90}Y in HCC and provided critical patient selection and technique refinement. For example, the study defined areas for excluding patients at risk for extrahe-

patatic shunting and suggested the importance of the assessment of peritumoral hepatic vasculature (56).

Direct intratumoral injection was performed by Dong et al (57) in a 1992 study in which 28 patients with HCC were treated with a percutaneous injection of ^{90}Y glass microspheres under ultrasound (US) guidance. In some patients, peritumoral ethanol and intraportal chemotherapy was also given. There was a 91% reduction in tumor size for the cohort. On follow-up Doppler imaging, there was a reduction and/or elimination in blood flow within the tumors. Eleven of 13 patients had a response as measured by α -fetoprotein (AFP) levels; six patients' condition completely normalized. Histopathologically, eight patients exhibited complete necrosis. The authors concluded that percutaneous ^{90}Y is an appropriate first-line treatment for patients with HCC (57).

Tian et al (46) performed another direct intratumoral injection of ^{90}Y glass microspheres in which 27 patients with HCC and six patients with liver metastases were treated with US-guided glass microsphere injection. The procedure was repeated at 3- to 4-week intervals as necessary. Follow-up consisted of US and clinical and laboratory assessments. Ninety-one percent of tumors decreased in size, with concomitant blood flow and sonographic changes observed. AFP in 10 of 13 patients returned to normal levels. The authors concluded that intratumoral administration of ^{90}Y glass microspheres under US guidance yielded a promising cure rate for liver tumors with no significant side effects. Radiation doses of 28,215–75,720 cGy were thought to explain the tumor response. The authors further postulated that these results demonstrated that direct, percutaneous, intratumoral radionuclide injection is feasible for treatment of malignant lesions (46).

Yan et al (58) published similar encouraging data with glass microspheres in 1993. Six rabbits were injected with 185–1,480 MBq of ^{90}Y glass microspheres. Three rabbits were injected with 35–300 mg of ^{90}Y glass microspheres for toxicity analysis. Pathologic examinations were performed on all rabbits. No toxicities were noted in the rabbits after injection of 114.1–845.2 Gy ^{90}Y glass microspheres. In the rabbit study, some ar-

tefacts of hepatocyte degeneration and portal fibrosis were seen pathologically. The authors concluded that rabbits could tolerate as much as eight times the upper limit of a clinical dose of 100 Gy. In a parallel clinical study, 18 patients received 2,442–5,550 MBq of 35- μm ^{90}Y glass microspheres for the treatment of HCC. Whole blood counts, liver function tests, and imaging examination were performed. The mean tumor-to-liver tissue ratio was 3:1. In some tumors, a 14:1 tumor-to-liver ratio was noted. Mean absorbed doses in the normal liver parenchyma and tumor liver tissue were 30 Gy and 88 Gy, respectively. Clinical follow-up demonstrated 50% reduction in tumor mass in 13 of 18 patients (72%), as well as a significant decrease in posttreatment AFP level. The authors concluded that ^{90}Y glass microspheres are safe and effective in large doses through the hepatic artery for internal radiation treatment of HCC, and that responses were a result of localized and hypervascular tumors (58).

Investigators reported on 22 patients to determine response parameters, survival, and toxicity after intraarterial injection of ^{90}Y microspheres (59). The conditions of 20 patients were evaluated for efficacy, including nine patients with Okuda stage I/II disease and 11 patients with Okuda stage III disease. The median dose delivered was 104 Gy (range, 45–145 Gy). There were 31 serious adverse events; the most common were liver enzyme increases and gastrointestinal ulceration. Treatment efficacy was measured by tumor response, duration of response, time to progression, and overall survival. One complete tumor response and three partial responses were reported. The median time to progression was 44 weeks, and the median survival was 54 weeks (range, 7–180 weeks). Total dose greater than 104 Gy, Okuda stage I disease, and tumor-to-liver uptake ratio greater than 2 were three factors associated with prolonged survival.

Carr (60) performed a critical study in 2004 supporting the safety and efficacy of TheraSphere for inoperable HCC. Sixty-five patients with biopsy-proven HCC received a median radiation dose of 134 Gy. Forty-two patients had Okuda stage I disease, and 23 had Okuda stage II disease. Toxicities included nine episodes of abdom-

inal pain (which did not fit criteria for postembolization syndrome), two episodes of cholecystitis, and transient increases in liver function in 25 patients. A finding previously unreported was lymphopenia in 75% of patients, none of which was associated with adverse clinical events or opportunistic infections. Median survival times were 649 days and 302 days for patients with Okuda I and Okuda II disease, respectively, compared with 244 days and 64 days, respectively, for historical control individuals.

A study presenting data in patients treated with TheraSphere in the presence of portal vein thrombosis was published in 2004 (61). Fifteen patients with unresectable HCC and portal vein thrombosis of one or both first-order and related segmental portal venous branches received a total of 29 infusions. Liver toxicity was assessed by serum total bilirubin level graded by severity according to the National Institutes of Health/National Cancer Institute Clinical Toxicity Criteria (version 2.0). Other adverse events were reported according to the standards established by the Society of Interventional Radiology. There were no procedural complications with delivery of microspheres, and treatment was well tolerated by all patients. Increased posttreatment bilirubin levels were observed in all treatments in five patients, four of whom had computed tomographic (CT) or AFP evidence of intrahepatic disease progression. After initial treatment, two patients experienced bilirubin toxicity (grades 1/2), one patient exhibited an increment in bilirubin toxicity grade (grades 1–3), and one patient had an improvement in grade after initial treatment. There were no new treatment-related toxicities in nine patients after a second treatment. The authors concluded that TheraSphere treatment was well tolerated and appears to be safe to use in patients with compromised portal venous flow in one or both first-order and related segmental portal venous branches. In patients who did not exhibit disease progression, there appeared to be no clinically significant change in bilirubin level (61). The efficacy of TheraSphere in this context was subsequently presented in 2006 (62), in which investigators introduced the concept of portal vein retraction as a secondary sign of tumor response.

In 2004, Liu et al (63) presented a retrospective review of 14 patients treated for unresectable HCC. Tumor response by CT/magnetic resonance imaging and AFP level was monitored after treatment. One patient had complete response by CT; however, this patient received TACE before TheraSphere treatment. Eight patients had a partial response, and two patients had tumor progression. AFP-producing HCC was seen in eight of the 11 patients treated. Five patients had decreased AFP after treatment. None of the patients treated experienced any serious adverse events, including liver toxicity.

Geschwind et al (64) reported on 80 patients from a relatively large database of 121 patients who were treated with TheraSphere. Patients' disease was staged with the Child-Pugh, Okuda, or Cancer of the Liver Italian Program scoring systems. Survival times were found to be 628 days and 324 days for Okuda I (68%) and II (32%) disease, respectively. These data were instrumental for delineating the essential components to conduct a large randomized controlled trial comparing TheraSphere versus a standard TACE regimen with potential endpoints of survival, tumor response, AFP reduction, and quality-of-life estimates.

To evaluate the cumulative HCC clinical experience with TheraSphere, data from patients in the original humanitarian device exemption application were combined with data from patients from the humanitarian device exemption clinical experience at three sites through February 2003. This provided a cohort of 121 patients for whom toxicity and survival data were analyzed to identify predictive factors associated with 3-month mortality rate (65). Patients were stratified into high and low risk categories on the basis of five liver reserve factors, including (i) tumor presentation (infiltrative vs focal), (ii) bulk disease (tumor volume $\geq 70\%$ vs $< 70\%$), (iii) increase in liver enzymes (aspartate or alanine aminotransferase level $> 5\times$ upper limit of normal vs $\leq 5\times$ upper limit of normal), (iv) a combination of tumor volume and albumin (tumor volume $\geq 50\%$ and albumin level < 3 g/dL versus other), and (v) bilirubin increase (≥ 2 mg/dL vs < 2 mg/dL). Two non-liver reserve factors were also iden-

tified, including a diagnosis of cholangiocarcinoma (one patient had received a misdiagnosis of HCC when, in fact, the correct diagnosis was cholangiocarcinoma) and a lung dose greater than 30 Gy. When these seven factors were taken into account, 33 of 121 patients were classified as high risk (at least one high risk factor) versus 88 patients classified as low risk (no high risk factor). As expected, the high-risk group had lower survival and a higher proportion of patients who experienced treatment-related adverse events ending in death. Sixteen of the 33 patients in the high-risk group (49%) did not survive the first 3 months after treatment, compared with six of the 88 patients in the low-risk group (7%; Fisher exact test; $P < .0001$). Median survival times for the low- and high-risk groups were 466 days and 108 days, respectively (hazard ratio, 6.0; $P < .0001$). There were a total of 25 serious adverse events ending in the death of the patient. Eleven of 12 patients experiencing a treatment-related serious adverse event ending in death were in the high-risk group. Moreover, if the high mortality risk criteria based on the seven liver reserve and non-liver reserve factors are taken into account, 16 of the patients (64%) would have been classified as having high mortality risk before treatment. Causes of death in these 16 patients included liver failure ($n = 8$), hepatitis ($n = 1$), hepatorenal failure ($n = 1$), gastric ulcer ($n = 1$), radiation pneumonitis ($n = 1$), not otherwise specified ($n = 2$), infection ($n = 1$), and gastrointestinal bleeding ($n = 1$). The results of this study suggested that the conditions of patients with HCC should be evaluated for the presence of the aforementioned risk factors, which include infiltrative tumor, at least 70% liver replacement by tumor, increase in liver enzyme levels (aspartate or alanine aminotransferase level $\geq 5\times$ upper limit of normal), a combination of tumor volume at least 50% and albumin level less than 3 g/dL, bilirubin level increase of at least 2 mg/dL, diagnosis of cholangiocarcinoma, or predicted lung dose of greater than 30 Gy. Patients with any of these characteristics would be expected to experience early death (< 3 months) and have an increased likelihood of treatment-related adverse events resulting in death. The absence

of these risk factors was predictive of improved survival (median, 466 days) compared with patients in the high-risk group (median, 108 days).

The patients in the low-risk group represented the group for whom the risk/benefit ratio of TheraSphere treatment was most favorable; that is, optimal survival (> 3 months) with minimal likelihood of treatment-related adverse events resulting in death. A subsequent analysis examined the relationship between the incidence of treatment-emergent liver toxicities and the factors influencing those events in this group (66). The purpose of this analysis was to characterize clinically significant (grade ≥ 3) liver toxicities observed after TheraSphere treatment and to identify factors associated with increased risk of these events. Because contemporary treatment approaches involved sequential lobar infusion of TheraSphere in more than one treatment cycle, treatment-emergent toxicities after first and second treatments were examined. The factors analyzed for association with the first treatment toxicities were tumor presentation (ie, unilobar, bilobar), presence of portal vein occlusion (yes vs no), presence of ascites (yes vs no), pretreatment total bilirubin value, percent of tumor replacing liver volume, treatment approach (lobar vs whole), and liver dose. The factors evaluated for second treatment toxicities were duration between treatments (in days), same liver volume treated as the first treatment (yes vs no), pretreatment (day of treatment) total bilirubin value, second-treatment liver dose and patient dose (accumulated for same volume or weighted average for different volumes). The median dose administered on first treatment (whole liver or lobar) for all 88 patients was 127 Gy (range, 34–153 Gy). Twenty-three patients (26%) received a second treatment at a median dose of 129 Gy (range, 27–146 Gy). Two patients received a third treatment (median, 138 Gy; range, 130–145 Gy). Thirty patients (34%) received whole-liver treatment in a single administration (median, 105 Gy; range, 46–151 Gy), two administrations (one patient; median, 100 Gy), or two sequential lobar administrations (median, 130 Gy; range, 89–139 Gy). Fifty-six patients received lobar treatment in a single treatment

to one lobe only (median, 133 Gy; range, 34–153 Gy) or repeated treatments to the same lobe (median, 246 Gy; range, 144–268 Gy). The median accumulated dose per patient for all 88 patients who received whole-liver or lobar treatment was 130 Gy (range, 34–268 Gy). Thirty-seven of 88 patients (42%) experienced 68 liver toxicities after first or second treatment, including increased bilirubin level ($n = 24$), ascites ($n = 11$), increased aspartate or alanine aminotransferase ($n = 7$), increased alkaline phosphatase ($n = 3$), hepatic encephalopathy ($n = 3$), liver failure ($n = 3$), and hemobilia ($n = 1$). Two patients experiencing liver failure underwent liver biopsies for possible radiation-induced liver disease, without confirmation of this condition. When the independent effect of the factors was examined, pretreatment bilirubin level was associated with the occurrence of liver toxicities for first ($P < .0001$) and second ($P = .04$) treatments, and the median bilirubin level in those patients experiencing at least one event was approximately two times higher than in patients who did not experience an event. There was also an association between liver dose and liver toxicities (first treatment medians, 123 Gy vs 133 Gy; $P = .08$; second treatment medians, 126 Gy vs 132 Gy; $P = .26$). There also appeared to be increased risk of liver toxicity with decreasing time interval between treatments (medians, 154 days vs 77 days; $P = .05$). Further analyses of the joint effects of the various factors with respect to first treatment indicated that bilirubin level and liver dose were linearly related ($P < .05$) with an increased risk (odds and hazard ratios) of patients experiencing liver toxicity. This trend remained for bilirubin on second treatment (three of 13 patients [23%] with bilirubin level <1.1 mg/dL experienced liver toxicity vs six of 10 patients [60%] with bilirubin level ≥ 1.1 mg/dL; $P = .10$). There was no association between increased liver dose and liver toxicities on second treatment ($P = .25$). Of note, despite the apparent relationship between bilirubin level, liver dose, and liver-related toxicities, the majority (53 or 78%) of the 68 observed liver toxicities resolved on follow-up. Of the remaining 15 events, four patients experienced toxicities resulting in death; however, none of the events were

judged to be treatment-related. One patient had an increased bilirubin level at 565 days after treatment and died 2 years later. Ten events in nine patients represented sustained grade 3 events (eight bilirubin, one alkaline phosphatase, and one aspartate or alanine aminotransferase) with onset from treatment ranging from 28 days to 119 days. Five of these events were judged to be unlikely or unrelated to treatment, and the five remaining patients had tumor progression in the untreated lobe.

In summary, this analysis indicated that, for patients who satisfy the eligibility criteria defined as low risk, approximately one third would experience at least one severe or life-threatening (grade 3/4) liver-related toxicity after treatment. The risk of these toxicities appears to be related to patients' pretreatment total bilirubin level, increasing treatment dose as high as 150 Gy per treatment, and the five liver-related risk factors (65,66). Most of these toxicities (78%) will resolve; however, some may persist as a result of tumor progression and/or advancing cirrhosis. These data confirmed that treatment-related liver toxicities increase with increasing pretreatment total bilirubin levels. In addition, in this patient population, radiation-induced liver disease was not seen, including in two patients whose liver biopsy results were negative for this condition. This promising treatment option was put in perspective by an editorial published by Dawson (67).

Rhee et al (9) reported on 14 patients with HCC treated with TheraSphere with use of a segmental approach. Dose vials intended for lobar infusion were administered at the segmental level, thereby increasing the effective dose to the tumor and minimizing radiation to the normal parenchyma. The range of absorbed dose to tumor was 105–857 Gy. There was no change in bilirubin level after treatment with this alternative approach. The authors concluded that subsegmental infusions are safe and feasible, with no alterations in liver functions, setting the stage for radiation segmentectomy.

Investigators reported on 43 consecutive patients treated with TheraSphere for unresectable HCC (10). Patients were stratified into three risk

groups according to the method of treatment and risk stratification (group 0, segmental infusion; group 1, lobar infusion/low risk; group 2, lobar infusion/high risk), as well as on the basis of the Okuda and Child-Pugh scoring systems. Patients were treated by liver segment or lobe on one or more occasions on the basis of tumor distribution, liver function, and vascular flow dynamics, with a volume-weighted average of 138 Gy. Patients were monitored for adverse events, objective tumor response, and survival. On the basis of follow-up data, 20 patients (47%) had an objective tumor response based on percent reduction in tumor size (World Health Organization), and 34 patients (79%) had a tumor response when percent reduction and/or tumor necrosis were used as a composite measure of tumor response. When patient risk stratification was used, median survival times were 46.5 months (group 0), 16.9 months (group 1), and 11.1 months (group 3). Median survival in all patients in non-high-risk groups (groups 0/1) was 20.8 months. There were no treatment-related life-threatening adverse events. The authors concluded that TheraSphere appears to be safe and effective in selected patients and represents a promising new therapy for HCC (10,67).

Investigators reported on 140 patients with HCC who underwent 238 administrations to the right and/or left hepatic artery with TheraSphere on an outpatient basis (68). All patients were stratified by Okuda, Child-Pugh, and low/high risk stratification as previously described. Patients had baseline liver function tests on the day of treatment, as well as at clinical follow-up at 30- to 90-day intervals. Follow-up CT/MR images of the liver were obtained at 30 days and subsequently at 90-day intervals. Patients were followed up until death. The median lobar volume, activity delivered, and absorbed dose were 838 mL, 1.61 GBq, and 110 Gy, respectively. The cause of liver disease was hepatitis C (30%), alcohol (24.3%), combined hepatitis C and alcohol (8.6%), cryptogenic etiology (23.5%), hepatitis B (6.4%), hemochromatosis (3.6%), and other (3.6). There were 54, 85, and one patient, respectively, with Okuda class I, II, and III disease. There were 69, 66, and five patients, respectively, with

Child-Pugh class A, B, and C disease. There were 97 and 43 patients in low- and high-risk groups, respectively. There was an 11% incidence of grade 3 bilirubin toxicities at 3 months after the last treatment, most of which were attributed to cirrhosis and tumor progression. Tumor response rates in patients with complete 3- to 6-month data were 32% according to RECIST and 68% according to European Association for the Study of the Liver criteria. Median survival for patients with Okuda I and II/III disease were 800 days versus 368 days ($P < .0001$). Median survival times for Child class A and B/C disease were 800 days versus 368 days ($P < .0001$). Median survival times for low- and high-risk groups were 800 days versus 258 days ($P < .0001$). The authors concluded in this large cohort that TheraSphere unilobar infusion for HCC appears to represent an efficacious therapy with acceptable toxicity and promising survival data (68).

Therasphere in HCC in downstaging to permit liver transplantation, resection, or RF ablation.—The use of TheraSphere as a bridge to transplantation was recently described (6,69). The patient was initially excluded from transplantation by size criteria. The patient was treated with TheraSphere and underwent a successful transplantation 42 days after treatment. Pathologic explants demonstrated complete necrosis of the tumor with no viable cells.

Kulik et al (5) recently described a large cohort of 35 patients who were not candidates for transplantation, resection, or RF ablation and were treated with TheraSphere. Sixty-six percent of these patients had their disease successfully downstaged to permit transplantation, resection, or RF ablation. Eight patients received a transplant, and one underwent resection. Five of seven explants in the transplanted patients demonstrated complete necrosis by pathologic examination. Tumor partial response rate was 50% by World Health Organisation criteria. Median time to partial response was 75 days, and median time to maximum response was 120 days. One-, 2-, and 3-year survival rates were 84%, 54%, and 27%, respectively. Median survival for the entire cohort was 800 days.

Tumor viability on explants after

TheraSphere and other liver-directed therapies such as TACE and RF ablation have been previously described (5,70,71).

Therasphere in colorectal cancer.—In 1992, Anderson et al (72) performed a small study with TheraSphere in patients with colorectal cancer. A maximum of 150 Gy was administered with glass ⁹⁰Y microspheres administered via the hepatic artery and targeted to tumor with use of angiotensin II in seven patients. The authors observed no toxicities, and hepatic metastatic progression was delayed in six patients. Median survival was 11 months (range, 5 to >25 months).

Goin et al (73) performed a dose-escalation study with TheraSphere in 43 patients with colorectal metastases. The study assessed dose-related effects on survival, tumor response, and toxicity. There were no life-threatening or fatal toxicities. The median survival was 408 days (95% CI, 316–565 d). Tumor response was evaluated by decrease in tumor size assessed by cross-sectional imaging. By these criteria, two patients had a complete response, eight had a partial response, and 35 (81%) had at least stable disease. Higher doses were associated with greater tumor response and increased survival ($P = .05$). In addition, tumor hypervascularity ($P = .01$), greater baseline performance status ($P = .002$), and less liver involvement ($P = .004$) were associated with enhanced response or survival. Clinical toxicities included duodenal/gastric ulcers in six patients (14%), which resolved with medical management. These were most likely caused by inadvertent deposition of microspheres into the gastrointestinal tract via unappreciated collateral vessels. Other related complications included single occurrences of mild fever and fatigue. No dose relationship to toxicities was observed in the study.

Wong et al (74) presented data on TheraSphere treatment of eight patients with unresectable colorectal liver metastases. Tumor response was evaluated with imaging (CT/MR imaging) and metabolic evaluation via [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) and serum carcinoembryonic antigen (CEA). Five of the eight patients had an improvement in their tumor activ-

ity, as assessed by a decrease in ¹⁸F-FDG-PET metabolic activity and confirmed by parallel changes in serum CEA level. However, as observed in other studies, the use of imaging by CT/MR illustrated that only some of the tumors that responded by metabolic criteria showed a corresponding decrease in size. This study suggested that the use of tumor size as an indication of treatment response would lead to underestimation of the effect of TheraSphere. The authors concluded that there was a significant metabolic response to TheraSphere treatment in patients with unresectable colorectal liver metastases. This treatment appeared to provide significant palliation for patients with otherwise incurable disease. In a subsequent study, Wong et al (75) presented data on TheraSphere treatment of 27 patients with metastatic colorectal cancer to the liver. Tumor response was evaluated via ¹⁸F-FDG-PET and serum CEA measurement. The study evaluated the use of ¹⁸F-FDG-PET to quantify the metabolic response to treatment, comparing visual estimates with standardized hepatic uptake values. Visual estimates were graded as indicative of progression; no change; or mild, moderate, or dramatic improvement. Visual estimates indicated that 20 patients showed a response to treatment, whereas seven patients experienced progression or no change in their disease. In the response group, there was a significant correlation ($r = 0.75$; $P < .0001$) between the responses identified through visual estimation and those determined by hepatic standardized uptake values. No significant correlation was observed with CEA values ($P = .13$), which was attributed to the effect of extrahepatic lesions. The authors concluded that treatment significantly reduced hepatic tumor metabolism and appeared to be palliative in patients with unresectable liver metastases.

In a recent article, Lewandowski et al (76) reported on 27 patients with unresectable colorectal cancer treated with TheraSphere. The targeted absorbed radiation dose was 135–150 Gy. They found that TheraSphere provided stabilization of liver disease in patients in whom chemotherapy had failed. Tumor response measured by PET imaging exceeded that of CT imaging for first (88% vs 35%) and sec-

ond (73% vs 36%) treated lobes, respectively. Tumor replacement less than 25% (vs >25%) was associated with a significant increase in median survival (339 days vs 162 days). Treatment-related toxicities included mild fatigue (48%), nausea (15%), and vague abdominal pain (19%). There was one case of radiation-induced gastritis from inadvertent deposition of microspheres to the gastrointestinal tract (4%). Interestingly, the response rate in this study duplicates the 35% rate obtained in 1978 in a similar cohort treated with intraarterial chemotherapy and microspheres (77).

Atassi et al (78) described a 71-patient cohort with metastatic colorectal cancer treated with TheraSphere at a targeted dose of 120 Gy on a lobar basis. The median lobar volume, activity administered, and net dose were 825 mL, 127 Gy, and 2.16 GBq, respectively. Treatment-related toxicities included mild fatigue ($n = 28$; 39%) and transient vague abdominal discomfort ($n = 14$; 20%). Grade 3/4 bilirubin toxicity occurred in three patients (4%), all of whom had documented tumor progression. There were no cases of radiation-induced gastritis/ulceration, hepatitis, or pneumonitis. The partial tumor response rate by RECIST was 35%. Survival rates from first treatment at 1 and 2 years were 39.1% and 22.1%, respectively. Factors associated with prolonged survival included baseline Eastern Cooperative Oncology Group (ECOG) performance status, number of tumors, and presence or absence of extrahepatic disease. ECOG scores of 0/1 were associated with median survival times of 566 days and 219 days, respectively ($P < .0001$). The number of tumor nodules (≤ 4 vs > 4) was associated with median survival times of 566 days and 216 days, respectively ($P < .0001$). The presence or absence of extrahepatic disease was related to median survival of 187 and 407 days, respectively ($P < .003$).

The authors concluded that, in selected patients with liver-dominant colorectal metastatic disease, TheraSphere appears to provide a viable treatment alternative (78).

Therasphere in mixed neoplasia.—In 1988, Herba et al (15) treated 15 patients, 12 with metastatic colorectal cancers, one with a carcinoid tumor, one with an islet-cell tumor, and one

with a hepatoma, with three dose levels: 5,000 cGy ($n = 10$), 7,500 cGy ($n = 3$), and 10,000 cGy ($n = 2$). Mean follow-up time was 7 months (range, 2–12 months). Stable disease in the liver was seen in 10 patients, four of whom had concurrent progression of extrahepatic disease, which resulted in two deaths. Two additional deaths were not directly related to the malignant process. Progression of liver disease was found in five patients, with three deaths occurring at 7–8 months. No procedural, hematologic, or pulmonary complications occurred. Late gastroduodenal ulceration occurred at 6–8 weeks in three patients who had histories of chronic alcohol abuse. This method of therapy seems to be feasible and efficient. Caution is necessary with high doses or with patients with a history of, or predisposition to, gastroduodenal ulcers.

In 1989, Blanchard et al (79) described the use of ^{90}Y microspheres as monotherapy in 14 liver metastases and one case of HCC. Twenty additional patients were screened but were found to be unsuitable for this therapy. Five patients exhibited a response by World Health Organisation criteria (33%). Treatment was complicated by gastric ulceration in six patients (40%). Survival in the treated group was 62 weeks, whereas it was 30 weeks for the untreated cohort. The authors concluded that ^{90}Y monotherapy might be effective in reducing tumor size in properly selected patients.

Andrews et al (11) presented data on 24 patients including 17 with colorectal metastases to the liver, six with metastatic neuroendocrine tumors, and one with HCC. Imaging at week 16 indicated a partial response in five patients, minimal response in four, stable disease in seven, and progressive disease in the remaining eight. Other than mild gastrointestinal symptoms in four patients (unrelated to TheraSphere treatment), no hematologic, hepatic, or pulmonary toxicities were observed. The authors considered the hepatic tolerance to radiation delivered by ^{90}Y to be excellent at doses as high as 150 Gy used in the study.

Herba and Thirlwell (80) performed a prospective dose-escalation study with TheraSphere starting at 50 Gy and escalating in 25-Gy increments to

150 Gy. There were 37 patients with liver metastases, 33 of whom had colorectal metastases to the liver. The authors observed no major hematologic or pulmonary complications but did observe some gastroduodenal ulceration, which occurred early in their clinical experience with TheraSphere, as a result of inadvertent deposition of spheres in the gastrointestinal tract. A beneficial response was observed by CT in cases in which tumors could be resolved. Stabilization or decrease in tumor size was observed in 22 of 30 patients (73%). Because of the small sample size of the study, no statistically significant relationship between dose and clinical or radiologic beneficial effects was observed. The authors concluded that TheraSphere treatment was a feasible and safe technique with beneficial effects.

Lewandowski et al (81) reported on a large cohort of patients with liver metastases treated with TheraSphere. One hundred thirteen patients underwent 171 administrations. Primary tumors included colon ($n = 43$), breast ($n = 18$), neuroendocrine ($n = 11$), pancreatic ($n = 7$), lung ($n = 5$), cholangiocarcinoma ($n = 5$), melanoma ($n = 4$), renal ($n = 4$), esophageal ($n = 3$), ovarian ($n = 2$), adenocarcinoma with unknown primary tumor ($n = 2$), and lymphoma, gastric, duodenal, bladder, angiosarcoma, squamous-cell carcinoma, thyroid, adrenal, and parotid ($n = 1$ each). Standard-of-care multiple-agent chemotherapy had failed in all patients. Patients underwent baseline and follow-up liver function tests, tumor markers, CT/MR imaging, and PET imaging. They were followed up for survival from time of first treatment. The median age of patients was 62 years. The mean activity and dose infused were 2.4 GBq and 117 Gy, respectively. All patients were discharged within 6 hours after the procedure. Clinical toxicities included fatigue (54%), abdominal pain (11%), and nausea/vomiting (11%). There were no ulcers. Follow-up CEA measurements in patients with colorectal cancer demonstrated a mean 61% decrease after therapy. On imaging follow-up, RECIST, European Association for the Study of the Liver, and PET response rates of 29%, 67%, and 79% were obtained, respectively. Median survival from first treatment for all patients was 10 months. The au-

thors concluded that TheraSphere hepatic treatments can be performed safely on an outpatient basis in patients with unresectable liver neoplasia. Treatments are well tolerated, with acceptable toxicities. Response to ⁹⁰Y in these patients is supported by the decrease in metabolic activity on PET and tumor markers (81).

SIR-Spheres in HCC.—The earliest reports of the use of resin microspheres were in the late 1970s (82–86). Since then, there has not been a significant body of literature discussing the use of resin microspheres in this clinical setting.

In 1998, Lau et al (87) reported on 71 patients with HCC treated with SIR-Spheres. Patients were treated with percutaneous techniques or intrahepatic ports. Response was measured by AFP measurements and/or cross-sectional imaging. Patients were administered activities ranging from 0.8 to 5.0 GBq (21.6–135.1 mCi; median, 3.0 GBq or 81.1 mCi). Partial response rate as measured by 50% reduction in tumor volume occurred in 19 patients (26.7%) after the first treatment. Overall objective response in terms of changes in AFP level was 89% (partial response, 67%; complete response, 22%) among the 46 patients with increased pretreatment AFP levels. Treatment was repeated in 15 patients. The maximum number of treatments was five, and the maximum total activity was 13.0 GBq (351.4 mCi) given in three treatments. Four patients underwent resection after treatment. In two cases, complete histologic remission was noted, and in the other two, occasional viable tumor cells were found in the necrotic centers. The median survival of the 71 patients was 9.4 months (range, 1.8–46.4 months). Treatment was well tolerated, and there was no bone marrow toxicity or clinical evidence of radiation hepatitis or pneumonitis. The authors concluded that (i) selective internal radiation therapy (SIRT) with ⁹⁰Y microspheres is effective in selected cases of unresectable HCC and is well tolerated, (ii) objective response rate in terms of decrease in AFP is higher than that based on reduction in tumor volume shown by CT, (ii) nontumorous liver appears more tolerant to internal radiation than to external-beam radiation, and (iv) selective internal ra-

diation treatment may make some unresectable tumors resectable (87).

In 2001, Lau et al (88) reported results from data during a treatment period from 1992 through 1996 in which 82 patients with unresectable HCC were treated with ⁹⁰Y. Analyses of outcomes were used to classify patients as “short survivors” (died within 1 year; $n = 51$; 62%), or “long survivors” (lived for ≥ 1 year from treatment; $n = 31$; 34%). Comparisons between groups suggested that low pretreatment AFP levels and high tumor-to-liver uptake ratios favored longer survival.

Szeto et al (89) reported on a hepatitis B surface antigen–positive patient who experienced HCC 7 years after cadaveric kidney transplantation. The patient was treated with SIR-Spheres. Serum AFP levels normalized within 2 weeks. Follow-up imaging demonstrated significant necrosis of the tumor and compensatory hypertrophy of the normal parenchyma. The treatment was well tolerated except for transient liver function deterioration. The patient died of liver failure after 15 disease-free months.

SIR-Spheres in downstaging to permit liver transplantation, resection, or RF ablation.—In 2004, Lau et al (7) reported on salvage hepatic surgery in 49 patients with HCC treated with downstaging procedures. Thirty-two patients had combination chemotherapy alone (65.3%), eight patients had single-agent chemotherapy alone (16.3%), four patients received intraarterial SIR-Spheres alone (8.2%), and five patients received sequential therapy (10.2%). Twenty-eight patients (57.1%) underwent major hepatic resection. Thirteen patients (26.5%) had complete necrosis of the tumor after treatment. Twenty-one patients (42.9%) had recurrence after surgery, and 14 of these were intrahepatic recurrence. The median survival time was 85.9 months. The 1-year, 3-year, and 5-year survival rates were 98%, 64%, and 57%, respectively.

⁹⁰Y resin microspheres or SIR-Spheres in colorectal cancer.—In 1989, investigators reported on dosimetry work in 10 patients with metastatic colorectal cancer (90). The microspheres were concentrated in the microvasculature of the tumor nodules by the concurrent administration of

angiotensin II. The radiation dose delivered to liver parenchyma was measured at the time of operation by an intraoperative radiation detection probe. The investigators concluded that intraoperative dosimetry confirmed the poor correlation between total radioactivity used and radiation dose received by normal liver parenchyma.

In 1992, investigators published their experience in the treatment of 29 patients with metastatic colorectal cancer with a surgically implantable hepatic artery pump (91). Vasoactive agents were used to enhance tumor flow of microspheres. The overall mean decrease in CEA level was 70% of pretreatment levels, with 88% of patients (23 of 26) experiencing more than a 50% decrease in pretreatment CEA levels. In 48% of patients, there was a decrease in tumor volume by more than 50%. The authors concluded that SIR-Spheres treatment was effective in causing tumor regression in patients with liver metastases secondary to large bowel cancer.

Gray et al (92) published a phase III randomized clinical trial of 74 patients conducted to assess whether a single injection of SIR-Spheres in combination with intrahepatic floxuridine could increase the tumor response rate, time to disease progression in the liver, and survival compared with floxuridine alone. Treatment-related toxicities and changes in quality of life were also examined. All patients had undergone complete surgical resection of a primary adenocarcinoma of the large bowel, and only those with unresectable metastases limited to the liver and lymph nodes in the porta hepatis were included in the study. In addition, patients were required to have World Health Organisation performance status of 0–2, adequate hematologic and hepatic function, and no evidence of cirrhosis or ascites. Both treatment arms received 12-day cycles of continuous-infusion floxuridine at 0.3 mg/kg at four weekly intervals, which was continued for 18 cycles or until there was evidence of tumor progression, extrahepatic metastases requiring a systemic chemotherapy change, unacceptable toxicity, or port failure, or the patient requested cessation of treatment. The SIR-Spheres treatment arm also received a predetermined quantity of ⁹⁰Y that

varied (2 GBq, 2.5 GBq, or 3 GBq) depending on the size of the tumor. ^{90}Y microspheres were administered one time only, within 4 weeks of insertion of the hepatic artery access port. The mean SIR-Spheres dose administered was 2.156 ± 0.32 GBq. There was no difference between the ^{90}Y arm and control arm in the mean floxuridine dose ($1,863 \pm 1,735$ mg vs $1,822 \pm 1,323$ mg) or the mean number of cycles of chemotherapy (8.7 ± 5.6 vs 8.0 ± 5.0). Six of 34 patients in the hepatic artery chemotherapy (HAC) arm (18%) had at least a partial response, whereas 16 of 36 patients in the HAC/ ^{90}Y arm (44%) had at least a partial response. The partial plus complete response rate was significantly greater for patients receiving SIR-Spheres when measured by tumor area (44% vs 17.6%; $P = .01$) tumor volume (50% vs 24%; $P = .03$), and CEA level (72% vs 47%; $P = .004$). The median time to disease progression in the liver was significantly longer for patients who received SIR-Spheres than in those who received HAC alone when measured by tumor area (9.7 months vs 15.9 months; $P = .001$), tumor volume (7.6 months vs 12.0 months; $P = .04$), or CEA level (5.7 months vs 6.7 months; $P = .06$). The 1-, 2-, 3-, and 5-year survival rates for patients treated with SIR-Spheres were 72%, 39%, 17%, and 3.5%, respectively, compared with 68%, 29%, 6.5%, and 0 for HAC alone. Cox regression analysis suggested an improvement in survival for patients treated with SIR-Spheres who survived more than 15 months ($P = .06$). There was no increase in grade 3/4 treatment-related toxicity and no loss of quality of life for patients treated with SIR-Spheres compared with patients treated with HAC alone.

The authors concluded that the combination of a single injection of SIR-Spheres plus HAC was substantially more effective in increasing tumor response and progression-free survival than the same regimen of HAC alone (92).

Investigators reported on a 50-patient cohort with extensive colorectal liver metastases not suitable for resection or cryotherapy (93). The study compared experience with ^{90}Y alone ($n = 7$) and in combination with 5-fluorouracil (5-FU; $n = 43$). For all patients, ^{90}Y microspheres were admin-

istered as a single treatment within 10 days of hepatic artery port placement. The dose was titrated to the estimated extent of disease (<25% liver replacement, 2 GBq; 25%–50% liver replacement, 2.5 GBq; >50% liver replacement, 3 GBq) and given over a period of 10 minutes a few minutes after administration of 50 μg angiotensin II. Forty-three of the 50 enrolled patients also received 5-FU given at the time of ^{90}Y continuously over a period of 4 days (1 g/d) every 4 weeks. Acute pain and/or nausea were experienced by 14 patients (28%) at the time of administration of SIR-Spheres and were managed with narcotics and antiemetic agents. Six patients (12%) experienced an acute duodenal ulcer within 2 months after SIR-Spheres therapy and the initial cycle of 5-FU as a result of misperfusion of the duodenum by ^{90}Y , 5-FU, or both. Median CEA levels were reduced to 25% of baseline values at 1 month after treatment with ^{90}Y and remained at less than 30% of baseline levels when monitored for 6 months. Among all patients with liver metastases, median survival from the time of diagnosis was 14.5 months (range, 1.9–91.4 months), and median survival from the time of treatment was 9.8 months (range 1.0–30.3 months).

The same group (94) described 38 patients with extensive colorectal liver metastases who received SIR-Spheres. Liver involvement was less than 25% in 19 patients, 25%–50% in nine patients, and greater than 50% in 10 patients. Patients received ^{90}Y in the hepatic artery via an arterial port and subsequent every-4-week cycles of HAC with 5-FU. The treatments were well tolerated, and no treatment-related mortality was observed. Response to SIR-Spheres therapy, as indicated by decreasing tumor markers and serial CT every 3 months, was seen in more than 90% of patients. Estimated survival rates at 6, 12, and 18 months were 70%, 46%, and 46%, respectively, and were principally driven by the development of extrahepatic metastases. The authors concluded that SIR-Spheres treatment was well tolerated in patients with extensive colorectal liver metastases and achieved encouraging liver tumor responses that are well maintained by HAC.

Van Hazel et al (18) reported a ran-

domized study of 21 patients in which 11 patients received SIR-Spheres plus 5-FU/leucovorin and 10 received 5-FU/leucovorin alone. The mean administered radiation dose in those receiving SIR-Spheres was 2.25 GBq. The authors concluded that the administration of SIR-Spheres along with a standard chemotherapeutic regimen significantly increased treatment-related response (10 vs zero patients showed a partial response on follow-up CT), time to disease progression (18.6 months vs 3.6 months), and survival (29.4 months vs 12.8 months) in comparison with chemotherapy alone. Even though more toxicities were associated with the combination therapy, there was no difference in quality of life over a 3-month period (18).

Geller et al (95) described a group of 19 patients with chemotherapy-refractory colorectal cancer treated with SIR-Spheres. One hepatic lobe was treated through the right or left hepatic artery at any treatment session. Patients received 40 Gy \pm 20%. There were no toxicities that were greater than grade 2. Eighty percent of patients had grade 1 granulocyte or platelet decrease, 50% had grade 1/2 lymphocyte decrease, and only one case of grade 1 elevation in bilirubin level was seen. The conditions of 13 patients could be evaluated for response at 2 months at the lobar level. There were six minor responses (46%), three cases of stable disease (23%), two mixed responses, and two patients with progressive tumors. The authors concluded that these represented encouraging initial results for heavily pretreated patients with advanced-stage colon metastases in the liver.

Coldwell et al (14) presented an abstract describing 84 patients receiving 127 infusions of SIR-Spheres for colorectal metastases to the liver. The target dose was 90 Gy to the tumor and 30 Gy to the normal parenchyma. Objective response rates were 35% by CT, 70% by CEA, and 90% by FDG-PET. Mean follow-up time was 12 months, with median survival not having been reached at the time of presentation. No life-threatening toxicities were noted. All patients who showed fluoroscopic cessation of blood flow (ie, stasis) during ^{90}Y infusion experienced post-embolization syndrome. The authors concluded that radioembolization pro-

vided encouraging response rates with an improvement in overall survival and acceptable toxicity in the group of patients treated.

Van Hazel et al (20) presented results of a phase I/II dose-escalation study combining SIR-Spheres with systemic chemotherapy. Seventeen patients with liver metastases from colorectal cancer, who had not received previous chemotherapy for metastatic disease, were entered into the study. Chemotherapy consisted of the FOLFOX4 regimen (oxaliplatin/5-FU/leucovorin) modified with an oxaliplatin dosage escalated from 30 mg/m² to 85 mg/m² to assess safety and tolerability. SIR-Spheres were implanted by injection into the hepatic arterial system on day 3 or 4 of the first chemotherapy cycle. Most patients experienced nausea or abdominal pain within 48 hours of ^{90}Y administration. Mild peripheral neuropathy was evident in six of the first 11 patients, appearing between cycles 10 and 12. Grade 3/4 transient neutropenia was seen in five of 11 patients. Three grade 3 events were documented in two of three patients treated at the 30-mg/m² tier (diarrhea, nausea/vomiting, fever). Six grade 3 events were seen in four of eight patients treated at the 60-mg/m² tier (diarrhea, nausea/vomiting, abdominal pain, fever, leukopenia, anemia). Only one grade 3 event has been shown to date in one of six patients at the 85-mg/m² tier (nausea/vomiting). Partial responses (by RECIST criteria) were seen in all of the first 11 patients. The median time to liver progression at the time of presentation was 11 months. The authors concluded that SIR-Spheres therapy in combination with oxaliplatin appears to possess an acceptable toxicity profile. Further trials are under way (20).

Goldstein et al (96) presented a phase I dose-escalation study with irinotecan in which 25 patients whose previous chemotherapy had failed but who were irinotecan naive had been entered into the study. Irinotecan was given weekly twice every 3 weeks starting the day before ^{90}Y administration for a maximum of nine cycles. Irinotecan dosage was escalated from 50 mg/m² to 100 mg/m² to assess safety and tolerability and to identify a maximum tolerated dosage. If no grade 3/4 toxicity was experienced after two cycles, patients could have

their irinotecan dosages escalated to 75 mg/m² and then 100 mg/m². Early-stage acute and self-limiting nausea, vomiting, and liver pain were experienced by most patients. Mild lethargy and anorexia was also common. Grade 3/4 toxic events were seen in four of six patients treated at a dosage of 50 mg/m² (jaundice, $n = 1$; ascites, $n = 1$, thrombocytopenia, $n = 1$; increased ALP level, $n = 1$), four of 13 treated at 75 mg/m² (ascites, $n = 1$; thrombocytopenia, $n = 1$; abdominal pain, $n = 1$; fatigue, $n = 1$), and two of six (at the time of publication) treated at 100 mg/m² (deep vein thrombosis, $n = 1$; abdominal pain, $n = 1$). Partial responses were seen in nine of 17 patients, median time to liver progression was 7.5 months, and median survival time was 12 months. The authors concluded that the use of SIR-Spheres in combination with irinotecan was associated with acceptable toxicity. Trials of first-line therapy with irinotecan and 5-FU/leucovorin combinations were then initiated (96).

In the same group, Sharma et al (97) presented another phase I dose-escalation study of oxaliplatin. The objective was to determine the MTD of oxaliplatin with infusional 5-FU in combination with ^{90}Y in the first-line treatment of patients with inoperable liver metastases from colorectal cancer. Secondary objectives included efficacy as demonstrated by response rate, time to progression, and overall survival. Oxaliplatin dosages were escalated at 30 mg/m², 60 mg/m², and 85 mg/m². If no grade 3/4 toxicity was experienced after two cycles, individual patients could have their dosages escalated to 85 mg/m². Chemotherapy treatment commenced 2 days before ^{90}Y therapy. Fourteen patients were enrolled in the study. Five patients had extrahepatic metastases. Acute, mild, self-limiting nausea, vomiting, and liver pain were experienced by most patients. Mild lethargy and anorexia was also common. Grade 3/4 toxic events were reported in one of three patients treated at a dosage of 30 mg/m² (neutropenia and diarrhea), four of eight patients treated at 60 mg/m² (neutropenia, $n = 2$; diarrhea and neutropenia, $n = 1$; neutropenia, $n = 1$). Recruitment of three of six patients occurred at a dosage of 85 mg/m². Partial responses were seen in 10 of 11 patients whose conditions were

evaluable. The authors concluded that SIR-Spheres in combination with FOLFOX4 (oxaliplatin/5-FU/leucovorin) is associated with acceptable overall toxicity. Although the MTD was not reached, it is expected to be 85 mg/m² (19). Since the publication of these initial data, the authors have updated their findings (97). A total of 20 patients were enrolled in the study. The mean dose of SIRT administered was 1.7 GBq. National Cancer Institute grade 1–3 abdominal pain within 48 hours of SIRT was noted in eight patients, one of whom had microspheres detected in the gastric mucosa by endoscopy. Grade 3/4 neutropenia was seen in 12 patients, seven of whom were treated at the highest dose level, thereby defining the dose-limiting toxicity. The nadir in mean leukocyte levels was noted 2 months after SIRT. Although one episode of transient grade 4 hepatotoxicity occurred, there was no radiologic evidence of radiation hepatitis in any of the patients treated. Partial responses by RECIST criteria were seen in 18 patients, and stability was noted in the remaining two patients. Two patients underwent hepatic surgery after protocol therapy, with no significant postoperative complications. Pathologic examination of hepatic samples revealed small amounts of viable adenocarcinoma with small foci of necrosis and extensive surrounding fibrosis. In the subset of patients with no extrahepatic metastases, mean time to progression was 14.2 months. The authors closed their study and concluded that the maximum tolerated dose for SIRT with concomitant chemotherapy with FOLFOX4 (oxaliplatin/5-FU/leucovorin) is 60 mg/m² of oxaliplatin for the first three cycles. They also noted that downstaging of disease should be considered in selected patients after treatment (97).

Murthy et al (98) reported on 12 patients with advanced unresectable colorectal hepatic metastases treated with SIR-Spheres. A total of 17 infusions were administered. The average median prescribed dose was 39.6 mCi. The delivered dose in six infusions (35%) was less than the prescribed dose as a result of embolic arterial occlusion. Radiologic response was stable disease in five of nine patients (56%), and CEA levels decreased in four of seven patients (57%). Median

survival times from diagnosis and treatment were 24.6 and 4.5 months, respectively. In seven of the 17 infusions (41%), the patient experienced transient abdominal pain and nausea. One patient experienced a gastric ulcer that was managed nonoperatively (98).

Lim et al (99) reported on a 30-patient cohort composed of patients with liver metastases from colorectal origin in which 5-FU-based therapies had failed. There was a 33% response rate, with median response duration of 8.3 months and a time to progression of 5.3 months. Response rate and progression-free survival rates were lower in patients in whom earlier chemotherapy had failed (21% and 3.9 months, respectively). Four cases of late gastrointestinal ulcers were noted.

Kennedy et al (100) recently reported on a seven-center study in which 208 patients in whom irinotecan and/or oxaliplatin-based chemotherapy had failed were treated with SIR-Spheres on a lobar and whole-liver basis. All were monitored for clinical and laboratory toxicities, anatomic and functional response, and overall survival. The most common clinical toxicities were constitutional (eg, fatigue, fever, weight loss), gastrointestinal (eg, nausea, vomiting, gastric ulcers), and bilirubin level increases, which occurred in 45%, 30%, and 4.5% of patients, respectively. Five percent of patients experienced gastrointestinal ulceration. There were no cases of radiation-induced liver disease. The response rate on imaging was 35%, whereas the PET response rate was 91%. Survival rates were 10.5 months and 4.5 months for responders and nonresponders, respectively. The authors concluded that, for patients with metastatic colorectal cancers, resin microspheres provide acceptable clinical toxicities, significant objective imaging responses, and promising survival rates (100).

One group presented the preliminary results in a 50-patient ongoing phase II study (101). Seventeen patients had been enrolled at the time of the initial report. Nine patients had a tumor burden less than 25%, whereas the remaining eight had a 25%–50% tumor burden. The majority had bilobar disease; the mean dose administered was 1.6 GBq. Three months after treatment, there was one complete re-

sponse by necrosis criteria, three patients had stable disease, two had disease progression, and two others underwent resection. The authors concluded that SIRT may be used as a downstaging procedure for surgical resection in selected patients and that RF ablation may play a complimentary role (101).

SIR-Spheres in mixed neoplasia.—Rubin et al (17) presented a case report of a patient with metastatic breast cancer to the liver treated with SIR-Spheres. The authors concluded that the use of an integrative approach to cancer treatment including SIR-Spheres was successful in the performance of palliative therapy in a patient with metastatic breast cancer.

Coldwell et al (12) reported on 34 women with unresectable breast cancer metastatic to the liver treated with SIR-Spheres. Inclusion criteria included only those patients with an ECOG performance score of 0/1 with an expected survival of at least 3 months. The average dose of radiation administered was 1.75 GBq. Although all patients showed a response to treatment with a reduction of the number and size of the hepatic lesions on PET, all patients also experienced mild to moderate postembolization syndrome.

Lim et al (102) reported on 46 patients with unresectable hepatic malignancies (colorectal cancer, $n = 32$; hepatocellular carcinoma, $n = 5$; other disease, $n = 9$) treated with SIR-Spheres. These selected patients had ECOG performance scores of 2 or less, life expectancy of more than 3 months, and no brain metastases at the time of treatment. Follow-up data were available for 43 of the patients. Of these, 12 patients (27%) showed partial response to therapy (10 with metastatic colorectal cancer and one with hepatoma), whereas another 12 patients (27%) had stable disease. The median duration of response for all patients was 8.6 months (range, 2–21 months). Early toxicities were minimal, and four patients experienced delayed gastric ulceration (102).

The use of SIR-Spheres for metastatic neuroendocrine cancers is of particular interest. The high embolic load coupled with low specific activity makes this an ideal therapeutic option for this condition. An 84-patient cohort was described in 2005 (13). Tumor

dose was 1,000 Gy to tumor volume. There were 14 cases (17%) of grade 3 gastrointestinal toxicity. Sixty-seven percent of patients experienced response on follow-up PET, with disease stabilization in the remaining patients. Eighty percent of patients who experienced symptoms reported relief of the symptoms. The authors concluded that the administration of ^{90}Y SIR-Spheres is a viable treatment option for metastatic neuroendocrine disease (13). Another cohort was presented in 2006 in which investigators used 24 fractions to treat 18 patients (103). The investigators observed an 89% objective tumor response rate by imaging and chromogranin A measurement. There were no treatment-related deaths and no significant toxicities. Median survival had not been reached by the time of publication (103).

Pöpperl et al (104) recently reported on 23 patients with unresectable hepatic malignancies (21 with metastatic disease and two with HCC) treated with SIR-Spheres. The mean activity of treatment was 2,270 MBq. Follow-up data in 13 of 23 patients showed a marked decrease of FDG uptake, a decrease in tumor marker levels, and unchanged or slightly decreasing lesion size (on CT) in 10 of 13 patients (one of whom had HCC). Disease stability was found in two patients, whereas another patient experienced progressive disease. Long-term follow-up investigations were available in two of 23 patients, in whom hepatic and extrahepatic progression was seen 6 and 9 months after ^{90}Y therapy. Minor side effects included abdominal pain and fever. Pancreatitis and gastric ulceration were also observed (104).

Wong et al (105) described 19 patients with unresectable chemotherapy-refractory hepatic metastatic disease of various origins treated with SIR-Spheres. The median absorbed dose for the tumor was 76 Gy. PET was used to monitor patients at 3-month intervals. By PET criteria, 15 of patients (79%) showed response to therapy, whereas four (21%) showed no response. The authors concluded that there is a significant reduction of hepatic metastatic load as evaluated by PET after radioembolization (105).

Murthy et al (101) described a cohort of patients with metastatic lung cancer treated with SIRT. Six patients with unresectable hepatic metastases

were treated with eight infusions of SIR-Spheres after failed systemic chemotherapy, RF ablation, or arterial embolization. SIRT was administered as second- to sixth-line therapy. The median interval from diagnosis to SIR-Spheres treatment was 20.5 months (range, 6–51 months). A median dose of 36.1 mCi (range, 12.9–54 mCi) was delivered. Single-photon emission CT/CT fusion Bremsstrahlung scans after therapy confirmed preferential deposition of SIR-Spheres within metastases. Responses to therapy included a decrease in the size of the hepatic metastases in one patient and stable disease in two patients. One patient had a mixed response, and two patients had progression of disease. One grade 3 liver toxicity and one grade 4 liver toxicity occurred. All patients experienced grade 1/2 fatigue. Time to progression of liver disease ranged from 3 months to 9 months. The authors concluded that administration of SIR-Spheres is a feasible alternative to systemic therapy for patients with liver-dominant metastases from lung cancers (101). Although serious hepatic toxicity was noted in patients with advanced liver metastases, the treatment was tolerated with only reversible fatigue in the majority of patients. Finally, the authors concluded that, when the treatment was deemed effective, the duration of local disease control after one treatment equaled or exceeded what would be expected with chemotherapy (101).

Investigators reported on 49 patients who underwent 78 administrations of SIR-Spheres via intraarterial infusion in the left or right hepatic artery (106). Of these patients, 26 had a diagnosis of colorectal cancer metastatic to the liver. Pancreatic, breast, carcinoid, lung, thyroid, squamous-cell, renal-cell, gastrointestinal stromal tumor, and endometrial cancer were among the other primary malignancies with hepatic metastases. All patients had undergone previous multiple-agent chemotherapy, which had failed. The median target volume was 993 mL. The mean dose of resin microspheres administered was 0.83 GBq, which translates to 42 Gy absorbed dose. Forty-seven of 49 patients received treatment on an outpatient basis. Clinical toxicities included fatigue ($n = 18$; 37%), vague abdominal pain ($n = 10$; 20%), and nausea/vomiting (n

$= 10$; 20%). Three patients (6%) experienced ascites and/or leg edema after treatment as a consequence of liver failure in advanced-stage metastatic disease. Follow-up CEA measurement in patients with colorectal cancer demonstrated a mean 59% decrease after therapy over a mean period of 62 days. On CT/MR imaging follow-up, a RECIST response rate of 29% and a PET response rate of 79% were noted. Mean and median survival times were 305 days and 175 days, respectively (106).

Two reports by the same group (107,108) were presented in which laboratory toxicities and midterm results of the use of SIR-Spheres were discussed. Thirty-four patients with extensive hepatic metastases were treated, and their toxicities were assessed by Southwest Oncology Group criteria. Twenty-two patients (65%) experienced 33 liver toxicities. At 3-month follow-up, 17 grade 0 and 16 grade 1 toxicities were observed. No toxicities of grade 3 or greater were recorded. At 6-month follow-up, six grade 0, 15 grade 1, four grade 2, and one grade 3 toxicities were noted. The most frequent toxicity was increased aminotransferase levels, followed by increased alkaline phosphatase levels and increased bilirubin levels. Eight of the 33 toxicities resolved on follow-up, whereas five patients had disease progression. The case of grade 3 toxicity was attributed to tumor progression. It was concluded that whole-liver treatment with intraarterial injection of ⁹⁰Y microspheres in a single session is a safe palliative treatment option in patients with extensive hepatic metastases. No life-threatening liver-related toxicities were observed. The same group discussed the clinical follow-up of the 34-patient cohort (108). Two major adverse events were observed (gastric ulcers). Mean follow-up time was 242 days (range, 62–586 days). Two patients died within 90 days after treatment. One patient underwent RF ablation of residual metastases. The mean hepatic tumor volume of all patients increased by 2% after 3 months of 5-FU therapy, decreased by 5% after 6 months, and increased again by 26% after 9 months. According to RECIST criteria, partial response was detected in 11, four, and two patients at 3, 6, and 9 months, respectively. Stable disease was seen in six, four, and two

patients at 3, 6, and 9 months, respectively. Progressive disease was noted in five patients at 3- and 6-month follow-up. No complete remission was observed. Initially, in almost all patients, a significant decrease in tumor markers was recorded, supporting the clinical benefit of the therapy (107,108).

Jakobs et al (109) presented midterm results on 88 patients who received 118 administrations of SIR-Spheres. Forty-five of these patients had colorectal cancer, whereas the remaining cases comprised pancreatic, breast, neuroendocrine, lung thyroid, squamous-cell, gastrointestinal stromal, thymus, melanoma, and endometrial cancers, and HCC. All patients had undergone chemotherapy that failed. The mean dose infused was 0.83 GBq for lobar and whole-liver treatments. The mean absorbed dose was 42 Gy. Sixty-seven of 88 patients were treated on an outpatient basis. There were two cases of gastric ulceration and one case of pancreatitis, which were likely a result of nontarget embolization. The mean CEA decrease was 32% for the entire cohort of patients with colorectal cancer. The imaging response rate according to RECIST criteria was 18%, whereas the functional response rate according to PET was 62%. Mean and median survival times were 285 days and 180 days, respectively. The authors concluded that SIR-Spheres could be performed safely on an outpatient basis and that the device was safe and effective for a variety of metastatic tumors as evidenced by functional imaging (ie, PET) and tumor markers (ie, CEA) (109).

Cianni et al (110) reported on 29 patients with liver metastases that had shown progression despite multiple-agent chemotherapy treated with SIR-Spheres. Primaries included colon, pancreas, breast, esophagus, and stomach cancers. Patients with bilirubin levels greater than 1.8 mg/dL and greater than 20% lung shunting were excluded. One patient died of hepatic failure 30 days after treatment. Two patients with more than 60% tumor burden died within 4–6 months of microsphere implantation. The investigators obtained a response in all cases by imaging or tumor markers. The authors concluded that radioemboliza-

tion was safe and effective for this pretreated population (110).

Wang et al (111) reported on 34 patients with liver metastases treated with SIR-Spheres. The mean activity infused was 2.2 GBq (range, 0.7–6.1 GBq). There were two cases of gastritis, two cases of peptic ulcer disease, and one case of radiation cholecystitis. Surprisingly, no patient had coil embolization (eg, gastroduodenal artery, right gastric artery) before administration of SIR-Spheres. Twenty-two patients showed complete initial response, four showed partial initial response, and eight showed disease progression. Average times to progression were 8 months and 4 months in responders and nonresponders, respectively. Survival times were 16 months and 7 months in responders and nonresponders, respectively. The authors concluded that this therapy was a safe and effective therapy, with most patients showing no complications (111).

King et al (112) described their experience in 34 patients with metastatic neuroendocrine tumors treated with SIRT and systemic 5-FU. Patients received whole-liver infusion, and clinical toxicities and imaging follow-up were obtained. The median follow-up time was 9.8 months. Complications included three ulcers, one case of pancreatitis, and two cases of self-limiting jaundice. All patients had abdominal pain, fatigue, and lethargy for 4 weeks. Of 30 patients whose conditions were evaluable at 3-month follow-up, there were six partial responders (20%), 19 with stable disease (63%), and five with progressive disease (17%). Chromogranin A levels decreased in 60% of patients. The authors concluded that SIRT appears to be safe and effective for neuroendocrine tumors (112).

Coldwell et al (113) described 33 patients with nodular cholangiocarcinoma treated with SIR-Spheres. All patients had received two chemotherapy regimens that had failed. The median age was 47 years; 18 patients received one treatment, and five patients had two treatments each. The mean activity infused was 1.5 GBq, with a mean tumor dose of 150 Gy. Mean follow-up time was 14 months. Median survival was not reached, with 19 of 23 patients alive at the time of analysis. Response rates by PET and cross-sectional imaging were 90% and 45%,

respectively. The authors concluded that the lack of response to systemic chemotherapy, the slow growth of this tumor type, and their hypervascular nature make these tumors ideal for locoregional therapy (113).

Studies combining Therasphere and SIR-Spheres.—Lewandowski et al (8) presented findings of a novel technique (“radiation segmentectomy”) with use of intraarterially infused ^{90}Y to deliver tumoricidal doses ranging from 163 Gy to 4,993 Gy with minimal radiation exposure to normal tissue. Eighteen patients with a median age of 65 years (range, 41–80 y) underwent TheraSphere or SIR-Spheres treatment for unresectable hepatoma ($n = 12$) or metastatic liver disease ($n = 6$). Patients presented with good performance status (ECOG stage 0/1) and normal liver function test results at baseline. All patients received selective infusion of ^{90}Y microspheres to segments within the right ($n = 13$), left ($n = 4$), or both ($n = 1$) lobes. The median segmental mass treated was 231.8 g (range, 108–1,236), median activity of ^{90}Y infused was 1.4 GBq (range, 0.8–3), median absorbed tumor dose was 925.9 Gy (range, 163–4,993), and median dose to normal segmental parenchyma was 14.1 Gy (range, 0.2–124). Other than reported symptoms of fatigue at 7–10 days after treatment, there were no clinical adverse effects. Liver function test results remained within normal limits for all patients for a median follow-up time of 60 days (range, 20–200). No patient had signs or symptoms of radiation hepatitis during the follow-up period. The authors concluded that tumoricidal radiation doses approaching 5,000 Gy could be achieved to portions of the liver with virtually no adverse clinical events. Radiation segmentectomy using selective and nonembolic infusion of ^{90}Y microspheres to targeted hepatic segments appears safe with minimal toxicity in a patient population whose disease is refractory to other forms of treatment. This approach permits the safe delivery of extremely high doses of radiation that cannot be achieved with use of traditional external-beam therapy (8).

Kennedy et al (114) described a cohort of 243 patients with unresectable colorectal cancer who were treated

with TheraSphere or SIR-Spheres. All patients had received first- and second-line chemotherapy that had failed, including irinotecan and/or oxaliplatin. Patients were treated without concurrent chemotherapy in a single outpatient treatment to the whole liver or on a lobar basis. The target dose was 60–150 Gy to the tumor and less than 30 Gy to the normal parenchyma. Follow-up regarding toxicities, response, progression, and survival was available for all patients: 243 patients were reviewed (127 treated with TheraSphere, 116 treated with SIR-Spheres), with follow-up times ranging from 3 to 34 months. Patients in the TheraSphere group received doses of 36–150 Gy (median, 147 Gy; 171 infusions). TheraSphere objective response rates at 3 months were 35% by CT, 70% by CEA, and 90% by PET, with median survival times of 11.0 months versus 5.8 months historically. Patients in the SIR-Spheres group received 40–85 Gy over 140 infusions. Response rates were similar to those with TheraSphere, but the median survival had not yet been reached by the time of publication. The most common grade 3 toxicities were nausea, pain, and fatigue in 30% of cases. There were no reports of radiation hepatitis. Repeat treatment of 18 patients was successful 8–33 months after initial microsphere therapy. The authors concluded that ^{90}Y microsphere treatment for salvage therapy of colorectal liver metastases is encouraging regarding response rate, safety profile, and possible improvement in survival (114).

Kennedy et al (16) also presented a cohort of 40 patients (median age, 56 years) with neuroendocrine tumors who underwent 64 treatments with TheraSphere or SIR-Spheres. The median number of treatments per person was 2 (range, 1–4), and treatments were administered on a lobar ($n = 31$) and whole-liver ($n = 9$) basis. Fourteen patients received TheraSphere, with a median dose of 143 Gy (range, 131–281 Gy), whereas 26 patients received SIR-Spheres, with a median activity of 36.69 mCi (range, 9–64.2 mCi). Follow-up times ranged from 2 months to 48 months. At the time of presentation, 33 of 40 patients were still alive. There were three complete responses, three cases of stable diseases, and 34 partial responses on serial CT and OctreoScan. There were no

grade 3/4 toxicities, no cases of radiation hepatitis, and no life-threatening events. Five patients (13%) were able to discontinue palliative octreotide therapy because of regression of paraneoplastic carcinoid symptoms after microsphere therapy. Only three patients had not had previous chemotherapy or liver-directed procedures. The authors concluded that intraarterial brachytherapy is an effective treatment for liver-dominant neuroendocrine disease, with an excellent safety profile, wide patient applicability, consistent palliative results, and significant debulking (16).

Wong et al (115) recently described a study to assess the safety and tumor response of intraarterial TheraSphere and SIR-Spheres for the treatment of surgically unresectable and chemotherapy-refractory liver metastases. Forty-six patients with metastatic cancer to the liver from various solid tumors with tumor progression despite multiple-agent chemotherapy were included. All patients had baseline CT, PET, hepatic angiography, and intraarterial ^{99m}Tc macroaggregated albumin scan for assessment of extrahepatic aberrant perfusion and lung shunting fraction. Treatment on a lobar basis was undertaken in 27 patients with glass microspheres and in 19 patients with resin microspheres. Patients were monitored over a period of 3 months after the last treatment with use of dedicated attenuation-corrected PET. The results demonstrated a significant decrease in total liver standardized uptake value after treatment by glass or resin-based microspheres ($P = .027$ and $P = .014$, respectively). There was no significant difference in the amplitudes of the mean percentage reduction of tumor metabolism between these two agents ($20\% \pm 25\%$ vs $10\% \pm 30\%$ for glass vs resin-based microspheres; $P = .38$). None of the patients in the glass-based microsphere group experienced complications, whereas three patients had complications related to hyperbilirubinemia (one transient and two permanent) in the resin-based microsphere group. The authors concluded that there is significant mean reduction of hepatic metastatic tumor load (ie, metabolism) as evaluated objectively by PET after radioembolization for the treatment of unresectable metastatic disease to the liver. Radioem-

bolization represents a safe and effective therapy for metastatic cancer to the liver by arresting disease progression and decreasing standardized uptake value (115).

Two review articles and two book chapters have recently been published on the topic of ⁹⁰Y therapy for the treatment of hepatic malignancies (116–119). The authors discussed the role of ⁹⁰Y in patients with HCC and metastatic disease to the liver and reviewed the available literature. In addition, a discussion of the future direction of ⁹⁰Y was presented, including questions that remain on timing and optimal dose for ⁹⁰Y, the ideal mode of administration (percutaneous vs intrahepatic ports), factors that might predict successful outcomes, and the comparison of ⁹⁰Y therapy with other regional therapies (116–119). These will continue to form the basis of further investigations.

FUTURE DIRECTION

Potential Role of ⁹⁰Y in Treatment of Liver-dominant Breast and Colorectal Metastases

There have been significant advances in the treatment of primary breast and colorectal carcinoma with the thymidylate synthase inhibitors (eg, 5-FU, floxuridine, capecitabine) that are known to be radiation sensitizers (120). The typical treatment paradigm involves resection of the primary tumor followed by chemotherapy (in the case of positive lymph nodes) or radiation (in the case of positive margins) for breast carcinoma or radiation of the surgical bed in the case of local recurrence of colorectal malignancy. The most typical sites of distant metastases after breast cancer resection include the liver, bone, and brain, and those for colorectal cancer include the liver and lungs. The natural course of disease appears to be improved and altered by improved chemotherapy agents, with liver metastases representing the life-threatening condition.

Historical approaches to treatment of liver metastases have included administration of thymidylate synthase inhibitors in an attempt to delay further disease progression. Stabilization of disease has shown durations of 6–8 months; however, inevitably, all pa-

tients experience progression when these regimens are used (121). Preliminary data in the application of ⁹⁰Y microspheres for liver-dominant colorectal and breast metastases are very encouraging according to RECIST and FDG-PET imaging criteria (12,17–20). Given the low toxicity profile for ⁹⁰Y relative to the standard of care chemotherapy regimens, patients tolerate the therapy exceedingly well. Other than slight fatigue and flulike symptoms for approximately 2 weeks after treatment, there are virtually no clinical toxicities.

As mentioned previously, the systemic chemotherapy regimens in patients eligible for ⁹⁰Y treatment who present with liver-dominant metastatic disease are currently suspended at least 30 days before ⁹⁰Y therapy. This is because of the known radiation-sensitizing properties of the thymidylate synthase inhibitors and the potential for radiation-induced liver toxicity caused by the synergistic effect of the agent combined with ⁹⁰Y therapy. However, it is this synergism that may present some interesting opportunities to further extend the therapeutic benefit of ⁹⁰Y therapy in combination with radiation-sensitizing agents. There is precedent for this approach in the treatment of breast, pancreatic, colon, liver, and other malignancies. The principle of enhanced tumor response and time to disease progression with use of a combination of radiation-sensitizing agents and external-beam ionizing radiation is well established (122). Clearly, additional assessment of toxicity, maximum tolerated dose (ie, dose escalation), and optimal therapeutic window will need to be explored by carefully controlled studies before widespread clinical application is considered.

Other studies to be considered include the combination of liver-directed therapy, such as ⁹⁰Y, with current standards of care, including bevacizumab and cetuximab. Although growth factor inhibitors may indeed play a role in controlling tumor growth, the vascular effects may affect the applicability of transarterial therapies. Growth factor inhibitors (eg, bevacizumab, cetuximab) may inhibit the ability to treat liver tumors by deleteriously affecting the vasculature. Studies combining chemotherapy agents (ie, FOLFOX [5-FU/leucovor-

in/oxaliplatin], FOLFIRI [5-FU/leucovorin/irinotecan]) with and without ^{90}Y (first- or second-line treatment) may show promise in further extending survival, which is currently reported as longer than 20 months (120).

Potential Role of ^{90}Y in Treatment of Neuroendocrine Liver Metastases

Neuroendocrine tumors typically arise in the endocrine glands and cells that are located throughout the body. The most common types include carcinoid, gastroenteropancreatic (GEP), and adrenal. The most common primary sites for carcinoid tumors include the gastrointestinal tract or the lungs; they may also arise in the pancreas. Other neuroendocrine tumors may originate from anywhere in the body. GEP tumors that most commonly originate in the cells of the stomach, intestines, or pancreas may be further categorized into gastrinomas, glucagonomas, insulinomas, vasoactive intestinal polypeptide tumors, and somatostatinomas. There is also a class of multiple endocrine neoplasia syndromes that are usually genetically based, and their presence increases the likelihood of development of GEP. Carcinoid tumors, particularly if they metastasize to the liver, may result in the excessive production of serotonin and produce carcinoid syndrome. This condition is characterized by diarrhea, flushing of the skin, and asthma-like breathing difficulties. Loss of appetite and weight loss may also result.

The intent of neuroendocrine treatments is to reduce tumor burden, eliminate or reduce the symptoms resulting from excessive production of hormones when necessary, and prolong life. Classic treatments for neuroendocrine tumors that have metastasized to the liver include surgery (ie, resection) or transplantation and the administration of somatostatin analogues such as octreotide or lanreotide. Other approaches include ablative techniques (ie, cryoablation and RF ablation), bland embolization, TACE, and, more recently, ^{90}Y microsphere therapy.

The primary goals of surgical intervention in neuroendocrine disease are complete removal of the tumor, reduction of bulk disease, and elimination of carcinoid syndrome when present.

Liver transplantation has been attempted with mixed results. Five-year survival rates were reported at 36% and 47% in two transplant studies (123,124). Reported recurrence-free survival rates at 5 years were less than 24% for 103 patients studied (124). Surgical intervention, including local resection and more radical hepatectomy, has resulted in the elimination of carcinoid symptoms, with 5-year survival rates of 60%–80% (125–127). The samples reported in the majority of surgical trials are low ($n < 50$), with no prospective randomization versus untreated control individuals; therefore, any survival data are to be interpreted with caution. Moreover, patients amenable to surgical resection are most likely self-selected for less tumor burden than that experienced by those with more advanced stages of the disease. Despite initial apparent curative effect, recurrence rates of 50%–60% within 4–5 years have been reported (128). Two studies involving larger cohorts (120 and 144 patients) reported palliation or control of carcinoid symptoms, with survival rates of 61% at 5 years in one study and 91% and 68% at 3 years and 6 years, respectively, in the other (129,130).

Less invasive alternatives to surgery, such as RF ablation and cryoablation, have also been used in cases of unresectable disease, with limited success. These treatments involve the administration of extreme heat (ie, RF ablation) or cold (ie, cryoablation) to achieve tumor kill. In one study of 34 patients, immediate symptom relief was achieved in 95% of patients, with control in 80% for a mean of 10 months (131). New liver lesions appeared in 28% of cases, with local liver recurrence in 13%. Mean survival from diagnosis was 5.5 ± 0.8 years; survival from treatment was 1.6 ± 0.2 years. Cryoablation studies have reported median survival times of 13–24 months, with mostly asymptomatic results after treatment (132,133). Although RF ablation and cryoablation result in some reduction of tumor burden and symptom relief, disease recurrence and return of symptoms is inevitable.

Transarterial embolization and TACE involve the intrahepatic administration of particles (300–500 μm) or a combination of particles and cytotoxic agents to compromise blood supply to

the tumor and/or deliver a tumoricidal dose. Modest tumor response rates (ie, reduction or stabilization) ranging from 40% to 60% have been reported, with 5-year survival rates of 50%–65% (134,135). Tumor type affects tumor response and survival. Transarterial embolization and TACE were used to treat metastatic carcinoid tumors ($n = 69$) and pancreatic islet-cell cancers ($n = 54$). Clinical outcome was superior for carcinoid tumors versus pancreatic tumors with respect to tumor response (66.7% vs 35.3%), progression-free survival (22.7 months vs 16.1 months), and survival (overall survival, 33.8 months vs 23.2 months). TACE was also found to be superior to transarterial embolization in terms of tumor response (50% vs 25%) and survival (31.5 months vs 18.2 months) (134).

The classic treatment of GEP tumors has involved the administration of somatostatin analogues such as octreotide and lanreotide to control tumor growth and the symptoms of excessive hormonal production. Delanoit et al (136) conducted a comprehensive review of somatostatin analogues in the treatment of GEP tumors from 1970 to 2003. Median objective tumor response, stable disease, biochemical response, and symptomatic response rates among patients treated with octreotide were 4.5% (range, 0–28.6%), 40.0% (range, 21.4%–87.5%), 72.5% (range, 28.6%–81%) and 71.0% (range, 58%–100%), respectively. Corresponding values for the longer-acting lanreotide were 5.0% (range, 0–8%), 70.0% (range, 37%–87.5%), 42.0% (range, 18%–62.5%) and 50.0% (range, 30%–100%), respectively. Therefore, although biochemical and symptomatic responses were favorable, there was no evidence of objective tumor response for either agent (4.5% and 5.0%, respectively). The authors noted a scarcity of data regarding survival benefit of the somatostatin analogues in GEP and the fact that there were no prospective randomized trials of patients with GEP treated with these agents (136). The lack of tumor response to somatostatin analogues has been shown in other studies, with tumor responses of 3%–10%, in contrast to high biochemical (range, 53%–78%; mean, 77%) and symptom response rates (73%) (137,138). Other agents such as interferon with or with-

out octreotide have failed to improve tumor response (range, 0–11%), even in a large cohort of patients receiving the therapy ($n > 350$) (139). Although the somatostatin analogues provide palliative relief from the symptoms of hormone overproduction, their benefit in tumor reduction is negligible. This phenomenon is further supported by a thorough review of the literature from 1966 to 2000 regarding somatostatin analogues in the treatment of numerous cancer types. The authors attributed the lack of consistent results regarding objective tumor regression to several factors, including nonrandomized trials in patients with highly disseminated disease who had been pretreated, bias in reporting positive results, and unreliability of anecdotal data. However, they did suggest that the concept of receptor radiation therapy, particularly indium In 111 octreotide or ⁹⁰Y DOTA lanreotide, showed promising results in preliminary studies with somatostatin receptor-positive malignancies.

Although published data on the treatment of neuroendocrine tumors with ⁹⁰Y microspheres are limited, preliminary results based on its use in clinical practice are encouraging. The therapy showed an excellent safety profile, consistent palliative results, and significant debulking. The majority of patients showed a partial response on imaging follow-up (13,16). Therefore, on the basis of this early work, ⁹⁰Y microspheres appear to provide a low-toxicity alternative with some clinical benefit as measured by tumor response and symptom reduction.

Potential Clinical Investigations and Extrahepatic Applications

On the basis of the extensive clinical data for ⁹⁰Y microspheres accumulated to date, it is clear that the modality offers an attractive alternative in the available therapies for liver disease. Given careful patient selection and proper angiographic technique, the therapy offers patients a minimally invasive, low-toxicity treatment with very favorable tumor response and potential survival benefit, even in the context of extrahepatic disease (10,18,140).

Given the encouraging safety and therapeutic benefit of ⁹⁰Y in primary

and metastatic liver disease, there is an opportunity to explore its application in combination with other available therapies. Studies to assess the potential synergistic therapeutic benefit of ⁹⁰Y and known radiation sensitizers in metastatic breast and colorectal cancer are warranted. Combinatorial capecitabine and ⁹⁰Y presents a low-toxicity option for breast cancer. The potential to improve hepatic tumor response via the synergistic action of selective uptake of 5-FU in the presence of radiation warrants further investigation. ⁹⁰Y in combination with 5-FU, floxuridine, and capecitabine in colorectal metastases to the liver requires further study. Given the potential for “super irradiation” of liver parenchyma in the presence of these agents, carefully controlled phase I dose-escalation studies, particularly in breast cancer metastases, are required.

Combinatorial applications of ⁹⁰Y and ablative techniques such as RF and cryoablation may provide an option for patients who would otherwise require surgical resection but who are at high surgical risk as a result of comorbidities or prefer less invasive means of treatment for their disease. ⁹⁰Y has been shown to reduce tumor burden in downstaging to permit transplantation or resection for HCC (5–7,69). In patients with tumors that are not amenable to ablative therapy because of excessive size (6–8 cm), ⁹⁰Y microspheres could be used to reduce these lesions (<3 cm), followed by the use of ablative therapy to effect further response. This presumes that viable tissue is still present after ⁹⁰Y therapy. There is strong evidence that ⁹⁰Y treatment typically results in complete necrosis of the lesion(s) treated (5,141). A prospective randomized study comparing time to progression or progression-free survival of patients treated with ⁹⁰Y versus RF ablation in lesions 3–5 cm in size would provide important information concerning this question.

Combinatorial ⁹⁰Y and TACE presents an interesting opportunity to assess the cumulative effect of these modalities in effecting tumor kill. Intraarterial infusion of ⁹⁰Y in an aerobic environment (ie, nonstasis) could be followed by TACE after the radioactive effect diminishes to subtherapeutic levels (approximately 2 weeks after ⁹⁰Y treatment). TACE administra-

tion with cytotoxic tumor exposure in a hypoxic environment would then address any viable (ie, radioresistant) cells that remained.

The recently published American Association for the Study of Liver Disease practice guideline for the management of HCC has identified a subgroup of patients within the Barcelona Clinic Liver Cancer staging system who present with advanced-stage disease characterized by clinical symptoms and vascular invasion, including portal vein thrombosis (142). The challenge in treating patients with portal vein thrombosis with use of embolotype therapy is the risk of liver failure resulting from compromise of portal and hepatic flow. Preliminary studies have shown that ⁹⁰Y can be safely administered in patients with portal vein thrombosis if microsphere infusion is not pursued to the endpoint of angiographic stasis of the tumor bed (61). Moreover, in the case of single portal branch occlusion in the absence of main occlusion, the use of embolic agents may be considered if patients are selected carefully and hepatopetal flow is present. This presents an opportunity to assess the relative safety and efficacy of ⁹⁰Y therapy versus a number of agents in a prospective randomized paradigm. This could include, but not be limited to, ⁹⁰Y versus TACE, ⁹⁰Y versus bland embolization, ⁹⁰Y versus drug-eluting beads, ⁹⁰Y versus other radioactive spheres, and ⁹⁰Y versus best supportive care. Although investigators have suggested that ⁹⁰Y effects on tumor are the result of radiation rather than macroembolic effect, a study of ⁹⁰Y therapy versus bland 20- to 40- μ m microsphere treatment would be of interest (143).

Another possible area of investigation includes the prophylactic radioembolization of remnant liver tissue in patients undergoing hepatic resection for HCC or colorectal metastases. Although initially attractive, this approach may hinder and limit the ability for future ⁹⁰Y to the prophylactically radioembolized lobe. In addition, the blood supply to small metastases is derived from the portal vein, not the hepatic artery, bringing into question whether prophylactic treatment would yield any radiation effect to microscopic metastases (144). Therefore, if such a study is undertaken, improved survival or decreased time to disease re-

currence would represent the endpoints, because imaging of lesions is not feasible. It is clear that further research is needed to address possible treatment options for advanced-stage HCC. Any studies in this patient population require careful consideration of the risk of therapy-induced liver failure versus the benefit of lesion stabilization.

Given the tremendous hypervascularity of neuroendocrine hepatic tumors relative to normal parenchyma, ^{90}Y represents an ideal therapy for palliative reduction of bulk disease and carcinoid syndrome when this condition is present. Limited studies with ^{90}Y in neuroendocrine disease suggest that these benefits may result (11,13,16,80). Randomized controlled studies of ^{90}Y versus current standard of care (ie, surgical resection or somatostatin analogues) are warranted.

One of the most fruitful areas for further research is the application of ^{90}Y in the downstaging of disease for liver transplantation. One study has shown that patients with stage T3 HCC lesions can have their disease downstaged to T2 (on Milan criteria) in more than 50% of cases (5). Larger prospective randomized controlled studies comparing ^{90}Y with other available therapies (eg, RF ablation and TACE) are also warranted. Given the increasing incidence of hepatitis C in the United States, the incidence of HCC in this country is expected to increase sharply in the next several years (145). Given earlier detection of HCC, with the intent of curative liver transplantation, there will be a significant need for alternative downstaging options. The ultimate question that remains unanswered is whether survival would be significantly extended for patients with downstaged disease treated with transplantation compared with patients who initially present with stage T2 disease. Only large prospective randomized controlled studies of well-established therapies will begin to provide the answers to this question.

Improved dosimetry planning (translating into enhanced efficacy) for ^{90}Y should be the focus of research in the next few years (9,146). This could come in the form of enhanced $^{99\text{m}}\text{Tc}$ macroaggregated albumin particles or in the development of planning resin or glass microspheres. This would al-

low the direct calculation of tumor and normal parenchymal exposure after ^{90}Y treatment. Direct knowledge of this would allow administration of sufficient ^{90}Y radioactivity to result in tumoricidal doses with minimal exposure to normal parenchyma. This might then evolve into the ability to perform repeated and scheduled ^{90}Y treatments in a manner analogous to TACE, but without the associated risks of radiation hepatitis. The ability to image the microspheres (cold or hot) with imaging techniques such as MR imaging would also prove clinically useful in the dose-planning and clinical follow-up stages.

One final area worthy of future investigation is in the treatment of non-colorectal, nonneuroendocrine cancers metastatic to the liver. Often referred to as mixed neoplasia, these terms refer to liver-dominant metastatic disease to the liver from various primary tumors (eg, breast, melanoma, pancreas, and lung). Although several reports have been described, controlled phase II studies that have studied time to progression, tumor response, or progression-free survival outcomes would be clinically relevant, given the dearth of options for some of these patients (11,15,16,80).

Survival is the gold standard by which the efficacy of any liver-directed therapy would ideally be measured. However, the resource costs and lengthy studies required to achieve this endpoint in a constantly evolving state-of-the-art paradigm make this a daunting task. There is clearly a need to develop surrogate measures of efficacy pending the refinement of technology, treatment techniques, and operator expertise so the treatment effect in randomized studies is validated to the satisfaction of scientists, statisticians, and clinicians. Tumor response provides a quantitative measure that has been historically touted as a viable alternative; however, correlative studies linking tumor response to extended survival have not been forthcoming. Quality of life has gained increasing awareness as a potentially useful measure of treatment efficacy. For patients who undergo systemic chemotherapy and external radiation as part of the treatment regimen, quality of life with respect to time commitment and side effects certainly affect their quality of

life during the finite time they have available. The incorporation of carefully designed and validated quality-of-life measures in prospective randomized controlled trials of ^{90}Y is another fruitful area of investigation. Time to progression and progression-free survival represent alternative endpoints that may balance the need for clinically relevant data with the options of patients who have disease progression despite therapy to try other experimental agents. Finally, although new and evolving treatments might ideally be compared with a no-treatment control arm, the ethical and moral issues in an increasingly aware patient base make the likelihood of this quite low.

The potential applications of ^{90}Y therapy to areas outside the liver are numerous. Any site in the body that is angiographically accessible may potentially be considered for ^{90}Y therapy, potentially permitting treatment of meningiomas, glioblastoma multiforme, renal-cell carcinomas, head/neck tumors, and lung tumors. Given that skin necrosis after ^{90}Y has been described, the cutaneous contribution of the extrahepatic vasculature being examined would have to be taken into consideration (28). Clearly, very carefully controlled *in vitro*, animal, and phase I safety studies with small patient cohorts are required before widespread clinical applications in these areas are explored.

SUMMARY

As with any oncologic therapy, the disease presentation, patient performance status, and functional liver reserve must be taken into account when a patient is considered for ^{90}Y microsphere therapy. In patients with primary HCC, treatment planning is often complicated by the trade-off between exposing functional (but cirrhotic) liver parenchyma to radiation while maximizing radiation exposure to malignant tissue to achieve complete kill. Although patients with liver-dominant metastatic disease present with good liver function, they have typically undergone multiple systemic chemotherapy regimens that may have compromised hepatic reserve and vascular supply. After the decision to treat with ^{90}Y therapy is made, the clinical outcome relative to

patient risk and benefit is the paramount consideration.

On the basis of the currently available data for ⁹⁰Y therapy in the treatment of liver disease, it is clear that the modality provides a favorable risk/benefit profile for the patient. Numerous studies have demonstrated that ⁹⁰Y therapy can effectively reduce or stabilize primary and metastatic liver disease with a minimal toxicity profile. The early clinical results indicated that ⁹⁰Y could be safely delivered to the tumor bed while minimizing insult to normal liver parenchyma. Subsequent studies have shown that, with appropriate patient selection, lobar administration, and careful attention to the embolization of collateral gastrointestinal vessels, complications of radiation to gastrointestinal structures are minimized. Despite these findings and the consensus among investigators supporting lobar infusions and prophylactic embolization of the gastroduodenal artery and right gastric arteries, practitioners continue to resist this approach and incorrectly assume that superselective infusion of microspheres completely eliminates the risk of nontarget administration. Hence, avoidable complications of ulceration and pancreatitis continue to be reported (98,111,147–149). These specialized interventional techniques have also minimized the risk of treatment-emergent liver failure caused by excessive exposure of functional liver reserve. Screening patients for potential pulmonary shunt via ^{99m}Tc macroaggregated albumin scanning has virtually eliminated the risk of radiation pneumonitis. Refinements in angiographic and imaging technology have further improved the safety and efficacy of ⁹⁰Y therapy in selectively directing microspheres to the target area. With improvements in catheter delivery technology, more selective delivery to the tumor bed (ie, radiation segmentectomy) has enabled the treatment of patients with increased bilirubin levels who otherwise would have been at risk of liver failure as a result of excessive radiation exposure of functional reserve.

Contemporary research in ⁹⁰Y therapy is extending its application in HCC to new areas including downstaging to permit orthotopic liver transplantation, resection, and RF ablation. It is common that, at some

point in the cancer disease process, patients present with life-threatening liver-dominant disease. Preliminary studies of ⁹⁰Y administration as monotherapy in patients with liver-dominant metastatic disease in whom standard-of-care systemic chemotherapy had failed are encouraging. Reduction and stabilization of advancing hepatic tumors provide the patients with a “chemotherapy break,” stabilize performance status, and in many cases permit patients to proceed to undergo other systemic or regionally directed therapies. This introduces the concept of the use of ⁹⁰Y as a “bridge” to chemotherapy.

However, there are continuing challenges and opportunities in the ⁹⁰Y treatment of liver disease. Several phase I studies of ⁹⁰Y microspheres in combination with infusional chemotherapy regimens in metastatic colorectal cancer to the liver have demonstrated very effective tumor response and stabilization of disease. However, the use of these regimens must be tempered against the neurologic, hematologic, and gastrointestinal toxicities that result. Whether the synergistic effect of ⁹⁰Y and radiation sensitizers outweighs the risk of increased toxicity remains to be determined. Clearly, the final determination of safety and efficacy will await the completion of randomized controlled trials comparing combinatorial ⁹⁰Y and chemotherapy versus chemotherapy alone.

Expanding ⁹⁰Y therapy to the treatment of other liver metastases such as breast and neuroendocrine tumors is also being explored. Preliminary studies indicate that ⁹⁰Y therapy can effectively reduce or stabilize disease and virtually eliminate the symptoms associated with carcinoid syndrome in the case of functional neuroendocrine tumors. Finally, the potential applications of ⁹⁰Y therapy to extrahepatic areas are numerous. It is clear that the modality provides a versatile tool in the array of therapeutic possibilities available to the interventional oncologist.

CONCLUSION

Advancements in liver-directed therapies continue to be of particular interest. With the advent of sophisticated improvements in techniques of

TACE such as drug-eluting microspheres, other technologies have begun to emerge. Administration of ⁹⁰Y microspheres represents a technology that continues to expand into the treatment of patients with liver malignancies. More than 100 publications, 50 posters, and innumerable presentations on ⁹⁰Y have been published or presented to scientific and clinical audiences. Worldwide, this therapy is used in more than 80 centers, with several interested in adding ⁹⁰Y treatment to their offerings. This comprehensive literature review clearly supports the conclusion that the administration of ⁹⁰Y microspheres is safe and effective for the treatment of liver tumors.

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CME TEST QUESTIONS

The following questions are based on the three-part series on radioembolization for liver malignancies found in the August, September, and current (October) 2006 issues of *JVIR*. Examination available at <http://directory.sirweb.org/jvircme>

1. You are an authorized user who plans to treat a hepatocellular carcinoma with TheraSphere radioembolization. Your goal is to treat the right lobe of the liver, which has a calculated volume of 900 mL. The patient has cirrhosis with borderline liver function and you plan to deliver approximately 80 Gy to the target volume. Assume that the lung shunt fraction is 0%. What is the radioactivity required to deliver the desired dose to the liver?
 - a. 0.48 GBq
 - b. 1.48 GBq
 - c. 2.53 GBq
 - d. 5.24 GBq
2. In question 1, assume instead that the lung shunt fraction is 50%. Which of the following statements is false?
 - a. A history of chronic obstructive pulmonary disease should be taken into account for treatment planning.
 - b. The patient is at risk for pulmonary toxicity if the planned 80 Gy dose is delivered in a single treatment session.
 - c. Dose fractionation is a treatment option.
 - d. Coil embolization of the hepatocellular carcinoma is a reasonable step before embolization.
3. You are an authorized user of SIR-spheres and would like to treat colorectal cancer metastases to the liver. The whole liver volume is 2000 cm³. The tumor volume is 350 cm³. According to the dosimetry model based on burden, what is the radioactivity required to treat the patient?
 - a. 1.0 GBq
 - b. 2.0 GBq
 - c. 2.5 GBq
 - d. 3.0 GBq
4. Which of the following statements regarding complications of ⁹⁰Y radioembolization is false?
 - a. Postembolization syndrome is more common with SIR-spheres than with TheraSphere.
 - b. Patients who develop lymphopenia following radioembolization are at high risk for opportunistic infection.
 - c. ⁹⁰Y-induced ulcers can occur with both TheraSphere and SIR-spheres and may prove refractory to medical therapy.
 - d. Liver failure may occur due to the irradiation of non-neoplastic liver parenchyma.
5. There is existing literature supporting all of the following conclusions regarding ⁹⁰Y radioembolization *except*:
 - a. Okuda stage I and II patients with unresectable hepatocellular carcinoma exhibit increased survival compared with historical controls following TheraSphere radioembolization.
 - b. Factors associated with early (3-month) mortality include liver replacement by tumor of 70% or more, albumin less than 3 g/dL, and bilirubin elevation of 2 mg/dL or more.
 - c. SIR-spheres radioembolization for colorectal cancer has been shown to improve tumor response and time to progression when combined with 5-fluorouracin.
 - d. Treatment-related liver toxicity decreases with increased pretreatment total bilirubin levels.