Treatment of Nonresectable Hepatocellular Carcinoma with Intrahepatic ^{90}Y-Microspheres

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Treatment for nonresectable hepatocellular carcinoma (HCC) is palliative. The relatively greater arteriolar density of hepatic tumors compared with normal liver suggests that intrahepatic arterial administration of ^{90}Y-microspheres can be selectively deposited in tumor nodules and results in significantly greater radiation exposure to the tumor than external irradiation. The purpose of this study was to determine the proportion (frequency) and duration of response, survival, and toxicity after intrahepatic arterial injection of ^{90}Y-microspheres in patients with HCC. **Methods:** Patients with documented HCC, Eastern Cooperative Oncology Group performance status 0–3, adequate bone marrow, and hepatic and pulmonary function were eligible for study. Patients who had significant shunting of blood to the lungs or gastrointestinal (GI) tract or who could not undergo cannulation of the hepatic artery were excluded. Patients received a planned dose of 100 Gy through a catheter placed into the hepatic artery. **Results:** Twenty-two patients were treated with ^{90}Y-microspheres; 20 of the treated patients (median age, 62.5 y) were evaluated for treatment efficacy. Nine patients were Okuda stage I, and 11 were Okuda stage II. The median dose delivered was 104 Gy (range, 46–145 Gy). All 22 treated patients experienced at least 1 adverse event. Of the 31 (15%) serious adverse events, the most common were elevations in liver enzymes and bilirubin and upper GI ulceration. The response rate was 20%. The median duration of response was 127 wk; the median survival was 54 wk. Multivariable analysis suggested that a dose $>$104 Gy ($P = 0.06$), tumor-to-liver activity uptake ratio $>$2 ($P = 0.06$), and Okuda stage I ($P = 0.07$) were associated with longer survival. **Conclusion:** Significantly higher doses of radiation can be delivered to a HCC tumor by intrahepatic arterial administration of ^{90}Y-microspheres than by external beam radiation. This treatment appears to be beneficial in nonresectable HCC with acceptable toxicity.

Key Words: hepatocellular carcinoma; ^{90}Y; intrahepatic arterial therapy

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Hepatocellular carcinoma (HCC) is one of the most lethal of malignancies. Although surgery is potentially curative in up to 25% of cases, it is an option for only 10%–20% of patients with HCC because of 3 interrelated factors: large tumor size, poor underlying liver function, and bilobar or metastatic disease at presentation (*1*,*2*). Most patients present with nonresectable disease or relapse after resection. Historically, the median survival for these groups of patients is $<$4 mo (*3*). However, recent clinical trials have reported median survivals in the nontreatment control arms of $\geq$1 y, suggesting marked heterogeneity in the prognosis of patients with nonresectable HCC (*4*,*5*). Treatment for most patients with nonresectable or recurrent disease is palliative. Currently available modalities include hepatic arterial embolization alone or with hepatic arterial chemotherapy, external irradiation, and systemic intravenous chemotherapy. Despite various treatment approaches that have been developed to treat nonresectable HCC, such therapies have not had significant impact on overall survival.

External beam irradiation results in palliation of symptoms in $>$50% of patients, although only 20% experience significant tumor shrinkage (*6*). These data suggest that HCC is radiosensitive. However, the dose that can be delivered is limited by normal tissue tolerance. Two factors suggest that the hepatic arterial administration of radiopharmaceuticals embedded in microspheres is a potential therapeutic option for patients with HCC: The tumor nodules are often more vascular compared with the surrounding normal liver, and the nodules receive their blood supply predominately from hepatic arterial rather than portal venous circulation. Administration of microspheres through hepatic artery branches with subsequent deposition in the tumor terminal vasculature could result in an $\sim$3-fold or greater radiation dose in tumor nodules relative to normal liver (*7*). ^{90}Y embedded into nonbiodegradable glass microspheres can be administered safely by intrahepatic arterial injection to patients with HCC and underlying cirrhosis at a dose of 100 Gy (*8*,*9*). We report an investigation of intrahepatic arterial ^{90}Y-microspheres at this dose in patients with nonresectable HCC designed to determine the proportion (frequency) and duration of response and survival and to consider the immediate and long-term toxicities of this treatment modality.

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MATERIALS AND METHODS

Patient Selection

Before study entry, patients with HCC underwent the following baseline determinations: complete blood count (CBC); prothrombin time (PT); activated partial thromboplastin time (APTT); serum creatinine; bilirubin; liver transferases; serum α-fetoprotein; chest radiography; liver sonography or CT (or both); pulmonary function tests including forced expiratory volume in 1 s, vital capacity, functional residual volume, and diffusion capacity of the lungs for carbon monoxide; and ^{99m}Tc–sulfur colloid liver scanning. Other radiologic investigations were performed incident to clinical management.

Eligible patients had histologically confirmed nonresectable HCC confined to the liver and at least 1 measurable lesion. Other eligibility criteria were Eastern Cooperative Oncology Group performance status 0–3 (*10*); an estimated life expectancy ≥12 wk; absolute granulocyte count $\geq 2.0 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; PT and APTT within normal limits; bilirubin $< 1.5 \times$ upper normal limit; aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase $< 5 \times$ upper normal limit; and normal pulmonary function defined as no more than 30% greater or less than the expected normal for each parameter. Exclusion criteria included previous chemotherapy or radiation; any contraindication to hepatic artery catheterization such as vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis; or any medical or psychosocial condition that would not permit management of the patient according to the protocol. The protocol was approved by the university and hospital ethics review boards. All patients gave informed written consent.

To define the hepatic vascular anatomy, patients were assessed by hepatic arteriography. If this was normal, ^{99m}Tc-macroaggregated albumin (MAA) was injected through the hepatic artery catheter and planar scintigraphy of the abdomen and chest was performed to compare liver and tumor perfusion and detect shunting of blood to extrahepatic organs. Patients were excluded from treatment if, on the basis of quantitation of the MAA images, there was flow to the upper gastrointestinal (GI) tract that could not be corrected by angiographic techniques or if there was significant shunting of blood to the lungs that could result in delivery of >370 MBq (10 mCi) to the lungs (lung shunt fraction × the amount of injected activity). On the basis of our subsequent experience and that reported by others (*11*), the latter criterion was relaxed to allow treatment at the discretion of the treating physician. Immediately before treatment, CBC, PT, APTT, renal and hepatic serum biochemistries, hepatic angiography, and hepatic nuclear angiography were repeated. If all pretreatment criteria were again fulfilled, patients received treatment with ^{90}Y-microspheres. After treatment, CBC and biochemistry profiles were measured daily for the first week, weekly for the first month, and then bimonthly. Tumor response was assessed bimonthly by physical examination of the liver, sonography or CT scanning, and serum α-fetoprotein measurement.

Staging

Okuda's method was used to stage disease in patients (*3*). Briefly, the stage of disease is determined by the presence or absence of the following features: bilirubin >51 μmol/L, serum albumin <30 g/L, and the presence of ascites and tumor replacement of the liver by >50%. Patients without any of these features are stage I, patients with 1 or 2 features are stage II, and patients with >2 features are stage III. The percentage of liver replacement by tumor was estimated using CT scans. The presence of ascites was determined by both clinical examination and imaging results.

Administration

^{90}Y, a pure β emitter, decays to stable ^{90}Zr with a physical half-life of 64.2 h. Mean tissue penetration of its 0.94-MeV β is 2.5 mm, with a maximum of 10 mm. One gigabecquerel (27 mCi) ^{90}Y/kg of tissue provides a dose of 50 Gy (*12*). ^{90}Y embedded in insoluble glass microspheres (TheraSphere, mean 25-mm diameter with tolerances of <5% below 15 μm and <10% above 35 μm; MDS Nordion, Inc., Kanata, Canada) was supplied in 0.05 mL sterile pyrogen-free water contained in a 0.3-mL V-bottom vial secured within a 12-mm clear acrylic vial shield. The target dose was 100 Gy, and the amount of radioactivity required to deliver this to the liver was calculated using the following formula:

$$\text{activity required (GBq)} = \frac{(\text{target dose [Gy]})(\text{liver mass [kg]})}{50}.$$

The liver mass was determined using CT scans and assuming a conversion factor of 1.03 g/cm^3. After calculating the required activity to be injected, ^{90}Y-microspheres were allowed to physically decay to the appropriate activity before injection.

^{90}Y-microspheres were injected into a percutaneous catheter inserted into the femoral artery and directed to the hepatic artery under image intensification. The patency of the catheter was maintained by an infusion of normal saline and heparin administered through a continuous infusion pump. Immediately before injection of the microspheres, the presence of extrahepatic shunting was assessed by injecting ^{99m}Tc-MAA. Images of the liver, lungs, and stomach were obtained with a digital scintillation camera. The material was not administered if there was significant shunting to the lungs or flow to the GI tract. Bremsstrahlung scans were obtained at a photo peak of 80 keV with a 15% window immediately after the injection to evaluate the distribution of the microspheres.

Regions of interest were manually drawn around the liver and each of the tumoral areas on the anterior projection ^{99m}Tc-MAA images. The tumor-to-liver activity ratio (TNR) was calculated as follows:

$$\text{TNR} = \frac{\text{total tumor counts}}{\text{total hepatic counts} - \text{total tumor counts}}.$$

The dose delivered to the liver was calculated using the following formula:

$$\text{delivered dose (Gy)} = \frac{\text{delivered activity (GBq)} \times (1 - \text{lung shunt fraction}) \times 50}{\text{liver mass (kg)}}.$$

The radiation dose to the lungs was estimated assuming a uniform microsphere distribution using the formula of Berger (*13*):

$$\text{radiation dose (Gy)} = \frac{\text{activity (GBq)} \times \text{lung shunt fraction} \times 50}{\text{mass of lungs (kg)}}.$$

Total lung mass, including blood, was assumed to be 1 kg according to Synder et al. (*14*). The lung shunt fraction was based on the ^{99m}Tc-MAA images and computed as the number of counts in the lungs divided by the number of counts in the lungs plus the number of counts in the liver.

Treatment Efficacy

Treatment efficacy was measured by tumor response, duration of response, time to progression, and survival. Complete response was defined as the disappearance of all clinical and radiologic evidence of tumor determined by 2 observations not less than 4 wk apart. The patient had to be free of all tumor-related symptoms. Partial response was defined as a 50% or greater decrease in the overall sum of the product(s) of the longest diameter and its perpendicular of all measurable lesions determined by 2 observations not less than 4 wk apart. No simultaneous increase in the size of any lesion or the appearance of any new lesions was allowed. Stable disease was defined as a steady state of disease less than the partial response or less than the progressive disease documented to be present for at least 8 wk from the start of therapy. Progressive disease was an unequivocal increase of at least 25% in the overall sum of measurable lesions compared with baseline or the appearance of new lesions. Response duration was measured from the time that the complete response or partial response criteria were first met until disease progression. Time to progression was measured in patients with complete response, partial response, and stable disease from the initiation of therapy until disease progression. Survival was calculated from the date of treatment to the date of death or the date of last follow-up.

Statistical Analysis

Survival curves were generated by the Kaplan-Meier technique (*15*). Multivariable stratified Cox regression (*16*) was used to evaluate the influence of liver dose, TNR, and Okuda's staging on survival time. The reported results for each of these variables are based on stratifying by the remaining 2 variables. Relative risk (RR) estimates were used to quantify the strength of association with survival. Model assumptions were verified using standard techniques. Median duration of response and time to progression were estimated accommodating right censoring. Two-sided *P* values without adjustment for multiplicity are reported. The analyses were performed using SAS version 6.11 software (SAS Institute, Cary, NC).

RESULTS

Between March 1992 and March 1996, 22 patients were treated with ^{90}Y-microspheres, with survival follow-up ending in February 1997. However, 2 patients were later deemed ineligible because of a lack of a confirmed diagnosis of HCC. Characteristics of the 20 eligible, treated patients are given in Table 1.

TABLE 1
Baseline Patient Characteristics

Characteristic	Statistic* (n = 20)
Age (y)	
Median	62.5
Range	32–74
Gender	
Male	14 (70)
Female	6 (30)
Prior hepatic surgery	
Left lobectomy	0 (0)
Right lobectomy	3 (15)
α-Fetoprotein (ng/mL)	
≤5	2 (10)
5–250	10 (50)
250–500	1 (5)
500–1000	0 (0)
1000–10,000	3 (15)
>10,000	4 (20)
Liver replacement	
≤50%	13 (65)
>50%	7 (35)
Okuda stage	
I	9 (45)
II	11 (55)
Current status†	
Alive	2 (10)
Dead	18 (90)

*Values in parentheses are percentages.
†February 14, 1997.

Administered Activity and Organ Doses

Administered activity, lung shunting percentages, and organ doses are given in Table 2. The median activity administered was 3.9 GBq (range, 2.0–9.2 GBq). The median dose delivered to the liver was calculated to be 104 Gy (range, 46–145 Gy). Eleven patients received >100 Gy, 5 received 80–100 Gy, and 4 received <80 Gy to the liver. Reasons for receiving less than the planned dose were technical error, lung shunting, and delay in administration, which led to excessive radioactive particle decay. The median calculated activity delivered to the lungs was 0.26 GBq (range, 0.04–1.13 GBq), resulting in a median dose to the lungs of 13.0 Gy (range, 1.8–56.5 Gy). Two patients were treated a second time, resulting in total liver doses of 100 and 209 Gy and lung doses of 43 and 36 Gy, respectively. Five (25%) patients had a TNR ≤ 1.0, 10 (50%) patients had a TNR < 2.0 (median), and 15 (74%) patients had a TNR ≤ 4.0.

Treatment Efficacy

Nineteen patients were evaluated for response (Table 3). One complete response and 3 partial responses were seen among patients for an objective response rate of 20%. The median duration of response was 127 wk. Table 4 provides the survival in days for each patient, with treatment dose, TNR, Okuda stage, and censored status. The median time to progression was 44 wk (95% confidence limits, 12–100 wk). The median survival for all patients was 54 wk (range, 7–180 wk). A trend toward improved survival was associated with doses >104 Gy versus <104 Gy (RR = 0.28; P = 0.06), TNR >2.0 versus <2.0 (RR = 0.26; P = 0.06), and Okuda stage I versus Okuda stage II (RR = 0.29; P = 0.07). Survival curves for all 20 patients and for patients receiving ≤104 Gy versus >104 Gy are shown in Figures 1 and 2, respectively.

Toxicities

All 22 treated patients were evaluated for toxicity. Toxicities were coded using the Southwest Oncology Group (SWOG; Operations Office, San Antonio, TX) grading

TABLE 2
Treatment Summary

Treatment	Median	Statistic* (n = 20)	Range
No. of treatments			
1		18 (90)	
2		2 (10)	
Artery occlusion procedures			
None		15 (75)	
1		3 (15)	
2		2 (10)	
Radiation administration			
Activity administered (GBq)	3.9		2.0–9.2
Liver dose (Gy)	104		46–145
Lung shunting (%)	6.4		0.8–39
Lung activity (GBq)	0.26		0.04–1.13
Lung dose (Gy)	13.0		1.8–56.5
Dose to liver (Gy)			
<80		4 (20)	
80–100		5 (25)	
100–120		8 (40)	
>120		3 (15)	

*Values in parentheses are percentages.

system (last revision, December 1994): grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life threatening; and grade 5, lethal (fatal). If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1%–50% increase from baseline; a grade 2 toxicity (moderate), as a 51%–200% increase from baseline; and a grade 3 toxicity (severe), as a >200% increase from baseline. Most (85%) of the adverse events were graded as mild or moderate in severity (Table 5). Serious (i.e., graded as severe, life threatening, or fatal) adverse events occurred in 14 patients. Of the serious adverse events, the most commonly reported were elevations in liver enzymes and bilirubin, and GI toxicities, including ulcers, ileus, and nausea. Most of the serious adverse events did not require treatment or resolved either spontaneously or with treatment. The deaths of 3 patients were attributed to hepatitis, liver failure, and radiation pneumonitis.

TABLE 3
Response to Treatment

Response	Statistic* (n = 20)
Complete	1 (5)
Partial	3 (15)
Stable	11 (55)
Progression	4 (20)
Not available	1 (5)

*Values in parentheses are percentages.

TABLE 4
Patient Survival in Days from Treatment by Liver Dose, TNR, Okuda Stage, and Censored Status

Dose (Gy)	Survival (d)
<104	64*, 113†, 144‡, 209‡, 316†, 331*, 378‡, 471‡, 719‡, 1259§
>104	49*, 193§, 218†¶, 256*, 515*, 635†, 719†¶, 778†, 1247‡, 1265§

*Stage II, TNR < 2.0.
†Stage I, TNR < 2.0.
‡Stage II, TNR > 2.0.
§Stage I, TNR > 2.0.
¶Censored.

One eligible patient, and an ineligible patient with cholangiocarcinoma, developed persistent hyperbilirubinemia and progressive hepatic failure after treatment with yttrium. The eligible patient had a preceding history of cirrhosis associated with hepatitis C virus. At baseline she had grade 2 elevations of bilirubin, AST, and ALT. Activity administered was 3 GBq, and the corresponding estimated dose to the liver was 90 Gy. Liver function tests repeated 1, 2, and 3 wk after treatment showed a progressive elevation of AST and ALT to grade 4 levels. Five weeks after treatment, AST and ALT improved to grade 2 levels, but the bilirubin level began to rise. Liver function tests continued to wax and wane over the following weeks. Follow-up tumor measurements by sonography showed a modest reduction in the size of the liver lesions, and serum α-fetoprotein fell from 3003 to 74 U/L. Because of persistent elevation in liver function tests that did not appear to be related to tumor progression, the patient underwent a liver biopsy 17 wk after treatment with ^{90}Y-microspheres. This showed severe cirrhosis with an inflammatory infiltrate consistent with chronic active hepatitis caused by hepatitis C virus. The patient's condition gradually deteriorated, with worsening ascites, peripheral edema, and generalized weakness, and death 5.5 mo after treatment. The cause of her death was thought to be hepatic failure associated with hepatoma, cirrhosis, and hepatitis C viral infection. The patient with cholangiocarcinoma had a preceding history of cirrhosis associated with a long-time, heavy ethanol abuse and hepatitis C virus infection associated with intravenous drug abuse, as well as a history of peptic ulcer disease. Baseline AST was grade 1, and ALT and bilirubin were grade 2. He received 4.2 GBq ^{90}Y-microspheres, and the total dose to the liver was 107 Gy. Over the next 3 wk, bilirubin and AST levels rose to grade 4, and ALT reached grade 3 levels without a simultaneous increase in alkaline phosphatase. The patient was admitted to the hospital 19 d after receiving ^{90}Y-microspheres with a 10-d history of epigastric burning; discomfort with progressive nausea, vomiting, diarrhea; and a low-grade fever. The patient refused to have an upper endoscopy but underwent a transjugular liver biopsy, which showed cirrhosis with

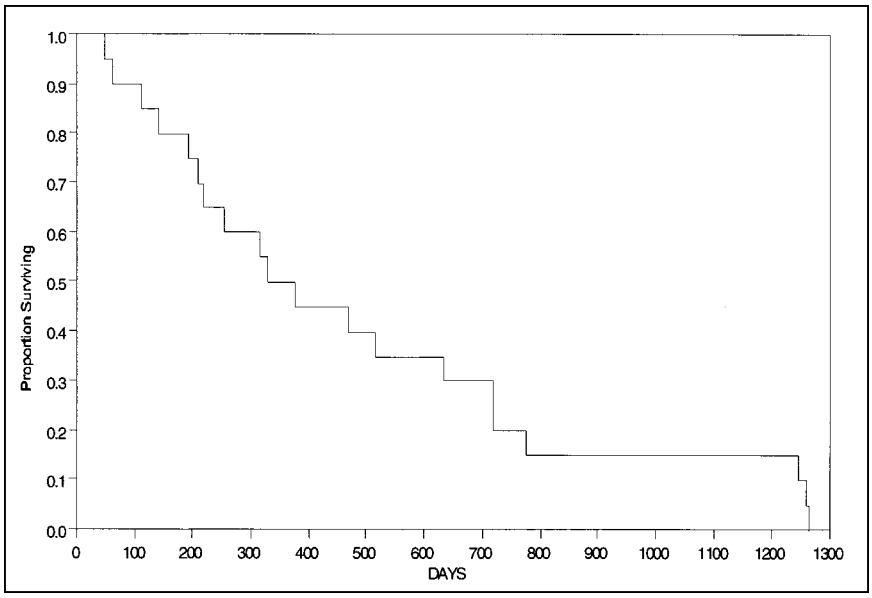

FIGURE 1. Kaplan-Meier survival plot (n = 20). Plot shows time from treatment with ^{90}Y-microspheres to death for all 20 eligible patients.

extensive and severe canalicular cholestasis with evidence of injury to most bile duct cell nuclei. There was no evidence of active hepatitis C viral infection. The patient was discharged with a diagnosis of gastric ulcers and cholestasis, possibly related to radiation injury, on ranitidine, sulcrafate, and prednisone. The patient was readmitted to the hospital and died of aspiration pneumonia and liver failure 8 wk after treatment with ^{90}Y-microspheres. Postmortem examination of the liver revealed extensive replacement of the liver by cholangiocarcinoma with necrosis of liver tumor nodules, possibly related to primary treatment with ^{90}Y-microspheres, as well as micronodular cirrhosis with gross ascites and splenomegaly. Multiple gastric ulcers with a maximum dimension of 4 cm were seen. There was evidence of bilateral bronchopneumonia. The cause of death was attributed to liver failure with cholangiocarcinoma, cirrhosis, GI hemorrhage from bleeding gastric ulcers, and bronchopneumonia. Both of these patients with hepatic malignancies, severe cirrhosis, and hepatitis C infections died of complications of hepatic failure. It is not possible to exclude completely treatment with ^{90}Y-microspheres as a contributing factor to the liver failure through the additive effect of radiation injury; however, there is no direct evidence that these patients had radiation hepatitis.

The patient whose death was attributed to radiation pneumonitis had a rapidly progressing tumor and 39% pulmonary shunting. With this degree of shunting to the lungs, it is questionable whether this patient should have been eligible for treatment; however, he was treated because of the rapid progression of his disease and the absence of other therapies. Unfortunately, treatment resulted in an estimated dose of 56 Gy to the lungs, progressive bilateral

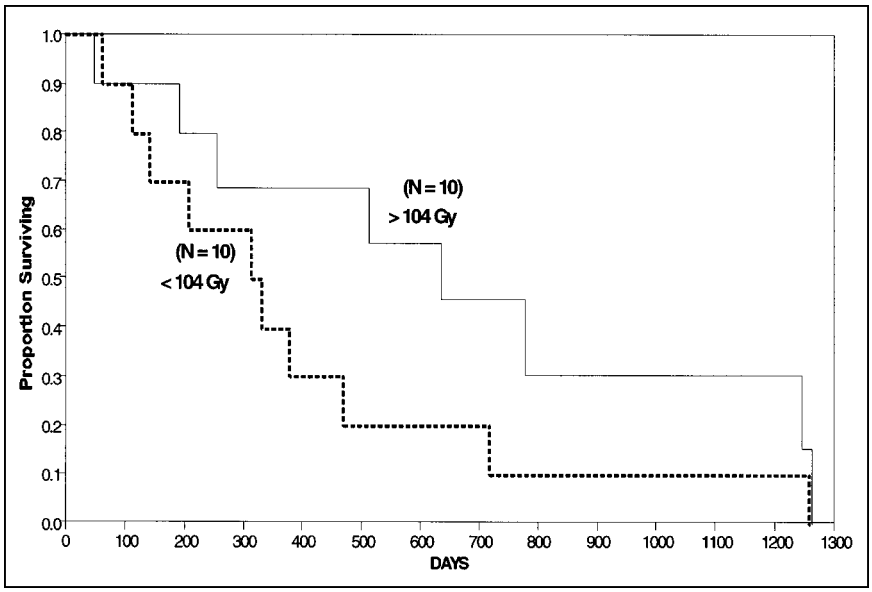

FIGURE 2. Kaplan-Meier survival plots by liver dose (n = 20). Plots show time from treatment with ^{90}Y-microspheres to death for patients treated with <104 Gy (n = 10; dashed line) and patients treated with >104 Gy (n = 10; solid line) ($P = 0.07$).

TABLE 5
Incidence of Treatment-Emergent Adverse Events, SWOG Toxicity Grading System (n = 22)

Adverse event*	Grade†					Total†
	1, mild	2, moderate	3, severe	4, life threatening	5, lethal (fatal)	
↑ SGOT/SGPT‡	7 (31.8)	9 (40.9)	5 (22.7)	0 (0.0)	0 (0.0)	21 (95.5)
↑ ALP	15 (68.2)	2 (9.1)	2 (9.1)	0 (0.0)	0 (0.0)	19 (86.4)
↑ LDH	12 (54.5)	2 (9.1)	2 (9.1)	0 (0.0)	0 (0.0)	16 (72.7)
↑ Bilirubin	0 (0.0)	8 (36.4)	2 (9.1)	3 (13.6)	0 (0.0)	13 (59.1)
Abdominal pain	5 (22.7)	5 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	10 (45.5)
↓ Hemoglobin	6 (27.3)	2 (9.1)	2 (9.1)	0 (0.0)	0 (0.0)	10 (45.5)
↓ White blood cells	7 (31.8)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	9 (40.9)
M/F/L	3 (13.6)	5 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	8 (36.4)
↑ Creatinine	5 (22.7)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (31.8)
Nausea	4 (18.2)	2 (9.1)	1 (4.5)	0 (0.0)	0 (0.0)	7 (31.8)
Other pain§	4 (18.2)	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (31.8)
Anorexia	6 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (27.3)
↑ PT	4 (18.2)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	5 (22.7)
Fever, no infection	1 (4.5)	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)
Gastrointestinal§	2 (9.1)	1 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)	4 (18.2)
↓ Platelets	4 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)
Weight gain	2 (9.1)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (18.2)
Anxiety/depression	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Constipation	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Diarrhea	2 (9.1)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Dyspnea	0 (0.0)	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Edema	1 (4.5)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Gastric ulcer	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	1 (4.5)	3 (13.6)
Insomnia	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Vomiting	1 (4.5)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Cough	1 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)
Hemorrhage	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	0 (0.0)	2 (9.1)
Infection	1 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)
Other liver§	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	1 (4.5)	2 (9.1)
Pneumonia	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	2 (9.1)
Sweating	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)

*For each patient, highest severity of adverse event was counted once. Adverse events that were reported by at least 2 patients in total population are summarized.

†Values in parentheses are percentages.

‡If patient's transaminase was above normal at baseline and patient experienced further increase during study, SWOG grading was not applied; rather, grade 1 toxicity (mild) was defined as 1%–50% increase from baseline, grade 2 toxicity (moderate) as 51%–200% increase from baseline, and grade 3 toxicity (severe) as >200% increase from baseline.

§Other pain included pain in back (n = 1), epigastric (n = 1), chest (n = 1), legs (n = 1), shoulder (n = 1), stomach (n = 1), and toe (n = 1). Other gastrointestinal included abdominal discomfort (n = 1), early satiety (n = 1), heartburn (n = 1), and duodenal ulcer (n = 1). Other liver included hepatitis (n = 2).

SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ALP = alkaline phosphatase; LDH = lactic dehydrogenase; M/F/L = malaise/fatigue/lethargy; PT = prothrombin time; Hemorrhage = hemorrhage (clinical).

pulmonary infiltrates developed, and he died of respiratory failure within 6 wk after treatment.

DISCUSSION

Treatment for nonresectable HCC is palliative. Systemic chemotherapy is only modestly effective, and literature reviews suggest that no single drug or combination of drugs given systemically leads to reproducible response rates of >25% or has any significant effect on survival (*17–19*). Doxorubicin results in a median survival of only 12–20 wk. Other agents such as 5-fluorouracil or mitomycin are inconsistently effective when given systemically (*20*). Cisplatin results in an objective tumor response rate of 6%–17% (*21–23*). Consistently higher objective response rates have been reported with intrahepatic arterial administration of chemotherapy with or without embolizing agents. However, no survival advantage was found in randomized trials that compared intravenous with intra-arterial administration (*24*) or conservative management with intra-arterial chemoembolization (*5,25*).

Patients with nonresectable tumors may benefit from percutaneous hepatic artery embolization or ligation, which produces ischemic necrosis of the tumor. Although this may result in dramatic tumor shrinkage, side effects include fever

in >95% of patients, abdominal pain in >60% of patients, and increased ascites or transient elevation of transaminases in 20% of patients (*1*,*26*). In addition, this treatment almost always requires at least 24 h of hospitalization. Pleuroperitonitis, cystic artery spasm, and cholecystitis are not uncommon (*26*). Although embolizing agents administered with chemotherapy increase response rates, there is a significant risk of hepatocellular decompensation with their use (*25*).

Promising results have been reported using conformal radiation therapy and intrahepatic arterial chemotherapy. Three-dimensional radiation treatment planning excludes as much normal liver as possible from the treatment volume, allowing patients with nondiffuse hepatobiliary tumors to safely receive doses of twice the traditional whole-liver tolerance. In a single-institution study of 22 patients, including 11 with HCC, objective responses were seen in 10 of 11 patients who were evaluated, and the median survival was 16 mo (*27*). Although promising, this technique requires further evaluation to determine its role in the management of HCC.

In this study, treatment with ^{90}Y-microspheres was associated with a 20% response rate with less toxicity than with hepatic arterial embolization or high-dose external beam radiotherapy. In addition, 8 patients had durable stable disease. Our results confirm those of Lau et al. (*11*), who found 8 partial responses in 18 patients with inoperable HCC. However, their definition of tumor response included decreases in α-fetoprotein or ferritin levels (or both) as well as a 50% reduction in tumor volume. In their larger follow-up series, objective tumor regression of >50% in tumor volume was seen in 26% (19/71) of patients (*28*). We found fewer objective responses because of either our stricter response criteria or a lower dose; however, many of our patients had prolonged stable disease and survival suggesting that treatment with ^{90}Y-microspheres does have antitumoral effects that may be dose related.

In this study, we attempted to determine the distribution of microspheres and to estimate activity delivered to liver, tumor, and lungs. The values obtained for dose, TNR, and shunting should be regarded as estimates. We used ^{99m}Tc-MAA to determine regional perfusion and to detect extrahepatic shunting. Although we assumed that this technique accurately predicted the behavior of the glass microspheres, they are rigid and denser than ^{99m}Tc-MAA particles. Thus, dose and perfusion calculations are estimates. Microspheres with the same physical characteristics as the ^{90}Y-microspheres but labeled with γ emitters would be more suitable for imaging and would allow more accurate dosimetry (*29*). Despite these potential technical deficiencies, we found that higher dose and higher TNRs were associated with improved survival and confirm the results reported by Lau et al. (*11*) and those obtained in our previous study (*8*,*9*). Collectively, these studies suggest that treatment with ^{90}Y-microspheres is potentially beneficial for patients with HCC and that the response rate, prolonged stable disease, and extended survival we observed are in part attributed to treatment efficacy rather than selection of patients with already favorable prognoses. These results also imply that the relative distribution of ^{99m}Tc-MAA in tumor-bearing and nontumorous liver appears to be similar to that of ^{90}Y-microspheres and that the activities of ^{90}Y-microspheres in the lungs, tumor, and nontumorous liver can be estimated from the ^{99m}Tc-MAA scan. Ho et al. (*30*) found a close correlation between estimated doses to tumor-bearing and normal liver on the basis of the ^{99m}Tc-MAA scan with the radiation doses measured with a small, calibrated β probe during laparotomy in 17 patients with hepatic cancer treated with ^{90}Y-resin microspheres. A major limitation of our study is the lack of detailed hepatic dosimetry information. This partition model could potentially allow the determination of the quantity of ^{90}Y-microspheres to be administered to optimize the doses to the tumor and normal liver.

We found that the most common adverse events experienced by patients with HCC were hepatic and GI. The absence of severe hepatic toxicity despite the putatively high radiation doses to the liver suggests that permissible doses may be higher than the 100 Gy we used. The maximum dose that may be delivered to the liver by external beam radiotherapy without excessive risk of radiation hepatitis is 30–35 Gy (*31*,*32*). In contrast, no dose-limiting organ toxicity has been observed in patients who have received nominal absorbed radiation doses (NARDs) of up to 150 Gy by intrahepatic infusion of ^{90}Y-microspheres (*29*,*33*–*36*). The discrepancy between the tolerable dose of external beam radiation and that of hepatic arterial administration is likely associated with the preferential delivery of the radiopharmaceutical to tumor nodules as well as the low tissue penetration of β radiation. The NARD calculation assumes that microspheres are distributed evenly throughout the entire liver. However, the rationale for administration through the hepatic artery is the selectively greater perfusion of liver tumors from the hepatic artery. The NARD calculation underestimates the true radiation dose delivered to tumors and overestimates the dose delivered to normal liver. Lau et al. (*11*) determined liver and tumor counts with β probe and liquid scintillation counting. They showed that the nontumor-bearing cirrhotic liver was able to tolerate about 70 Gy of radiation without evidence of radiation hepatitis. They also reported that those patients in whom all tumors received radiation doses >120 Gy did better than those in whom at least 1 tumor nodule received <120 Gy. These data support the view that ^{90}Y-microspheres injected into the hepatic artery or its branches can be selectively deposited in tumor vasculature and that the efficacy of therapy depends on the delivered tumor dose. The disposition of ^{90}Y-microspheres into tumor compared with nontumorous liver tissue is clearly an important determinant of therapeutic index. More vascular tumors are likely to receive greater deposition of ^{90}Y-microspheres and radiation dose compared with normal liver tissue. Given that patients with HCC usually have underlying cirrhosis, there is an obvious risk of hepatic decompensation if they then develop radiation hepatitis.

Ideally, patients selected for treatment should not have severe cirrhosis and should have well-perfused tumors (hence, higher TNRs by ^{99m}Tc-MAA scanning) to minimize the risk of hepatic decompensation and maximize the potential for therapeutic benefit.

One of the most appealing aspects of intrahepatic arterial ^{90}Y-microsphere therapy is selective deposition in tumor vasculature with sparing of normal tissue. In theory, parenteral administration of ^{131}I- or ^{90}Y-labeled monoclonal antibodies to antigens such as ferritin and α-fetoprotein could provide selective tumor deposition with ease of intravenous administration. Unfortunately, heterogeneity of antigen expression on tumor cells, poor tumor localization, lack of penetration of antibody into larger tumors, inadvertent extrahepatic deposition resulting in toxicity, and the development of human-antimouse antibodies that prevent repeated treatments have all limited the development of monoclonal antibody therapies for solid tumors (*37*). In the only prospective, randomized controlled trial of radiolabeled antibody therapy in HCC patients reported to date, ^{131}I-antiferritin and chemotherapy led to equivalent response and survival rates compared with chemotherapy alone (*38*).

Although pulmonary and GI toxicities may result from treatment with ^{90}Y-microspheres, the likelihood of their occurrence can be markedly reduced by carefully selecting patients. In this study, only 1 treated patient developed pneumonitis. In retrospect, this patient should not have been treated because of the presence of significant shunting to lungs detected on a pretreatment ^{99m}Tc-MAA perfusion scan. Although this patient did not have histologic confirmation of the diagnosis, the clinical presentation of dyspnea, pulmonary infiltrates, and absence of an infectious or cardiovascular etiology within 6 wk of receiving ^{90}Y-microspheres favors the diagnosis of radiation pneumonitis. Leung et al. (*39*) reported that 5 of 80 patients treated with intra-arterial ^{90}Y, receiving tumor doses >120 Gy, developed progressive restrictive ventilatory function without an identifiable infectious or cardiovascular cause. The histopathologic appearance of lung specimens and the presence of microspheres in the lung tissue favored the diagnosis of radiation pneumonitis. These patients exhibited chest radiographic and CT changes comprising extensive consolidation with well-defined lateral margins from 1 to 6 mo after internal radiation treatment. All 5 patients were treated with corticosteroids, with 2 improving and 3 dying of respiratory failure. In their most recent analysis of 95 patients, 21 of whom were treated more than once, this group reported that patients with lung doses >30 Gy in a single treatment or >50 Gy in multiple treatments are at high risk of developing radiation pneumonitis, but this was not seen in any patients who were treated with doses below these levels (*40*). The risk of developing pulmonary toxicity was reduced only slightly if partial hepatic embolization was attempted to reduce lung shunting before ^{90}Y administration. Clearly, care must be taken to exclude patients with shunting to the lungs resulting in at least 30 Gy.

Upper GI ulceration is also a potential complication of inadvertent deposition of ^{90}Y-microspheres. Acute complications of hemorrhage and perforation as well as chronic atrophic and contracted stomach may develop (*41*). Despite careful evaluation before treatment and attempts to reduce ^{90}Y-microsphere exposure, gastroduodenal ulcers developed in 3 of our patients. These ulcers were within the area of distribution of the gastroduodenal artery and likely reflect backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce GI exposure, their effectiveness is uncertain and patients who have any flow to the GI tract should not be treated with ^{90}Y-microspheres.

CONCLUSION

Although this was an uncontrolled investigation with a limited number of patients, our study showed that significantly higher doses of radiation could be delivered to the liver by intrahepatic ^{90}Y-microsphere arterial administration than by external beam radiation. This approach appears to cause less toxicity than systemic or hepatic arterial chemotherapy or hepatic arterial chemoembolization. Given its ability to induce durable tumor regression or stabilization in patients with HCC, a disease that is notoriously resistant to standard therapies, ^{90}Y-microsphere administration appears to be a reasonable therapeutic alternative for patients who are deemed candidates for these locoregional approaches. Although patients were admitted to the hospital for treatment according to our protocol, it may be possible to perform this procedure safely on selected patients in an outpatient setting because pure β emitters do not require medical confinement of patients for radiation protection (*42*). Patients with significant shunting of blood to the pulmonary vasculature that would lead to >30 Gy to the lungs or any detectable flow to the GI tract should not receive intrahepatic arterial injection of ^{90}Y-microspheres. Future investigations will likely focus on methods to improve delivery of ^{90}Y-microspheres to tumor nodules, to map the distribution of ^{90}Y-microspheres more accurately, and to quantify the radiation dose more accurately. Further studies using ^{90}Y-microspheres in repeated doses and in combination with radiosensitizing agents might also be undertaken to optimize the efficacy of this treatment.

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