Treatment of Unresectable Hepatocellular Carcinoma with Use of ^{90}Y Microspheres (TheraSphere): Safety, Tumor Response, and Survival

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PURPOSE: To present safety and efficacy results obtained in treatment of a cohort of patients with unresectable hepatocellular carcinoma (HCC) with use of ^{90}Y microspheres (TheraSphere).

PATIENTS AND METHODS: Forty-three consecutive patients with HCC were treated with ^{90}Y microspheres over a 4-year period. Patients were treated by liver segment or lobe on one or more occasions based on tumor distribution, liver function, and vascular flow dynamics. Patients were followed for adverse events, objective tumor response, and survival. Patients were stratified into three risk groups according to method of treatment and risk stratification (group 0, segmental; group 1, lobar low-risk; group 2, lobar high-risk) and Okuda and Child-Pugh scoring systems.

RESULTS: Based on follow-up data from 43 treated patients, 20 patients (47%) had an objective tumor response based on percent reduction in tumor size and 34 patients (79%) had a tumor response when percent reduction and/or tumor necrosis were used as a composite measure of tumor response. There was no statistical difference among the three risk groups with respect to tumor response. Survival times from date of diagnosis were different among the risk groups ($P < .0001$). Median survival times were 46.5 months, 16.9 months, and 11.1 months for groups 0, 1, and 2, respectively. Median survival times of 24.4 months and 12.5 months by Okuda scores of I and II, respectively, were achieved (mean, 25.8 months vs 13.1). Patients had median survival times of 20.5 months and 13.8 months according to Child class A and class B/C disease, respectively (mean, 22.7 months vs 13.6 months). Patients classified as having diffuse disease exhibited decreased survival and reduced tumor response. There were no life-threatening adverse events related to treatment.

CONCLUSIONS: Use of ^{90}Y microspheres (TheraSpheres) provides a safe and effective method of treatment for a broad spectrum of patients presenting with unresectable HCC. Further investigation is warranted.

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Abbreviations: ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization

HEPATOCELLULAR carcinoma (HCC) represents an end-stage event resulting from chronic inflammatory liver disease, which is largely caused by geographically varying etiologic factors. In the United States, the age-adjusted incidence rates have doubled during the past 20 years, primarily as a result of latent hepatitis C infection. It is estimated that, in 2004, between 8,500 and 11,500 new cases of HCC were diagnosed (1). As many as 50% of these patients receive no therapy for their HCC; however, most patients do receive palliative treatment for symptoms of pain, vascular and bile duct obstruction, bleeding or risk of bleeding associated with tumor progression, and liver failure and its sequelae (2). Historic reasons for lack of treat-

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ment in many patients are multifactorial and include the lack of safe and efficacious systemic therapies, presentation with end-stage liver disease, and/or high intrahepatic or extrahepatic tumor burden. HCC is known to be multidrug-resistant and, relative to liver parenchyma, radiation-resistant (3–6).

For patients who present with unresectable disease, adequate liver function, and no contraindications to treatment, a wide variety of local and regional therapies have been developed for the purpose of providing local control of liver tumors while sparing essential vascular structures, liver parenchyma, and adjacent organs. These treatments (eg, thermal or chemical ablation, embolization, and chemoembolization) are applied intraoperatively, percutaneously, or intraarterially with use of imaging and/or angiographic guidance, with the intent of inducing targeted tumor necrosis and cytoreduction (7–9). Ablation approaches target individual tumors whereas intraarterial approaches can be applied to individual tumors, segmentally, or in a targeted fashion for the treatment of tumors distributed throughout a lobe of the liver with a single administration.

^{90}Y microspheres (TheraSphere; MDS Nordion; Ottawa, ON, Canada) are pure β-emitters. When placed within the tumor vasculature, the microspheres can deliver high doses of radiation, providing lethal insult to HCC cells, destroying essential tumor vascular flow, and resulting in cell death and tumor necrosis (10,11). The microspheres are delivered intraarterially through a catheter placed in the hepatic artery that perfuses tumor(s) anatomically located within a liver segment, occupying multiple discrete liver segments, or spanning several contiguous segments (ie, regional). The ability to superselectively place a catheter, to take advantage of arterial blood flow dynamics, and to vary the amount of injected activity provides an opportunity for individualization of treatment, enabling the sparing of liver parenchyma and adjacent organs while delivering targeted tumoricidal radiation doses. The purpose of this article is to present phase II data on the safety and effectiveness of the use of ^{90}Y microspheres (TheraSphere) for first- or second-line treatment of 43 patients with unresectable HCC.

MATERIALS AND METHODS

Patients

Between July 2001 and January 2005, 43 prospectively enrolled patients with unresectable HCC were treated with ^{90}Y microspheres in this phase II study. The institutional review board approved the treatment protocol as well as research use of the data. Inclusion criteria for treatment included: (i) diagnosis of HCC by pathologic examination or by two imaging studies (computed tomography [CT] and magnetic resonance [MR] imaging) with increased α-fetoprotein levels (>400 ng/mL), (ii) ineligibility for liver resection or transplantation (iii,) and an Eastern Cooperative Oncology Group (ECOG) performance status of less than 3. Patients were not excluded based on age, presence of portal vein thrombosis, vascular invasion, portosystemic shunts, hepatofugal flow, or limited extrahepatic disease. This last criterion was defined as minimal extrahepatic disease that was deemed significantly less life-threatening than the HCC itself (eg, solitary lung, bone or adrenal metastases, and lymph node >2 cm).

^{90}Y Microsphere Treatment

^{90}Y microspheres consist of nonbiodegradable glass microspheres (mean diameter of 25 μm), in which the ^{90}Y is an integral constituent of the glass. ^{90}Y is a pure β-emitter with a physical half-life of 64.1 hours. The average energy of β-emission is 0.9367 MeV, with a mean tissue penetration of 2.5 mm and a maximum of 10 mm. One gigabecquerel (27 mCi) of ^{90}Y per kilogram of tissue provides a dose of 50 Gy (12). The microspheres were supplied in 0.5 mL of sterile, pyrogen-free water contained in a 0.3-mL V-bottom vial secured within a 12-mm clear acrylic vial shield.

Before treatment, angiography with selective visceral catheterization was performed. This procedure was performed to evaluate the vascular and tumor anatomy and blood-flow dynamics, enabling a determination of the optimal placement of the catheter for selective treatment (13). After correcting for risk of any gastrointestinal flow with coil embolization, a technetium Tc 99 macroaggregated albumin scan was performed to test for gastrointestinal flow and to estimate the percent of injected activity shunted to the lungs. The method of computing the required activity to be injected and the dose received by the liver and lungs has been published (12–14). CT or MR imaging was used to determine the liver volume to which ^{90}Y microspheres are delivered (ie, volume of distribution). With use of a conversion factor of 1.03 g/cm^3, the corresponding liver mass (in kg) was determined. The method for calculating the required activity for injection and the dose delivered to the target is:

$$\text{TheraSphere activity (in GBq)}$$

$$A = [D\ (\text{in Gy}) \times M\ (\text{in kg})]/50$$

where A is net activity delivered to the liver, **D** is the radiation absorbed dose to the target liver mass, and **M** is target liver mass.

When lung shunt fraction and residual activity in the vial after treatment are taken into account, the actual dose delivered to the target mass (Gy) becomes:

$$D\ (\text{in Gy}) = [A\ (\text{in GBq}) \times 50 \times (1 - [\text{LSF} - R])]/M\ (\text{in kg})$$

where A is net activity delivered to the liver, D is the radiation absorbed dose to the target liver mass, M is target liver mass, LSF is lung shunt fraction, and R is percentage residual activity in the vial.

Similarly, the fraction of liver treated was estimated by dividing the volume of liver used in the dose calculation by the whole liver volume. The estimated dose to the lungs was calculated, assuming the lungs to be 1 kg in mass (12,14). Estimated lung doses greater than 30 Gy on a single administration or greater than 50 Gy accumulated in multiple administrations, as well as any detectable flow to the gastrointestinal tract visualized on the ^{99m}Tc macroaggregated albumin scan that was uncorrectable using angiographic techniques, represent contraindications to treatment. Liver dose was defined as the dose from a single administration or the accumulated dose to that specific volume if the spe-

cific volume was treated multiple times (unique-volume treatment). A volume-weighted average was used to compute the liver dose when two separate liver volumes were treated. For example, if the left lobe (representing one treated region and a fraction of one fifth of the whole liver) was treated followed by the right lobe (representing one treated region and a fraction of four fifths of the whole liver), a volume-weighted average of these two regions was used to compute the dose delivered to the whole liver (ie, fraction of 1).

The patient's presenting ECOG performance status, angiographically determined profile of vascular anatomy, anomalies, flow dynamics, liver function, and imaging-derived tumor burden were all considered in formulating and carrying out the treatment plan. The therapeutic approach was to provide maximum radiation dose to the liver tumor burden while minimizing radiation exposure to liver parenchyma. This approach resulted in patients receiving a single segmental or lobar treatment or multiple segmental or lobar treatments on one or more occasions. Segmental versus lobar treatment was defined by catheter placement and arterial blood flow distribution. A treatment was classified as segmental when the catheter was placed in an artery that perfused no more than two Couinaud liver segments. Patients were classified as being treated segmentally only if all of their individual treatments were classified as segmental. Nonsegmental treatments were defined as lobar.

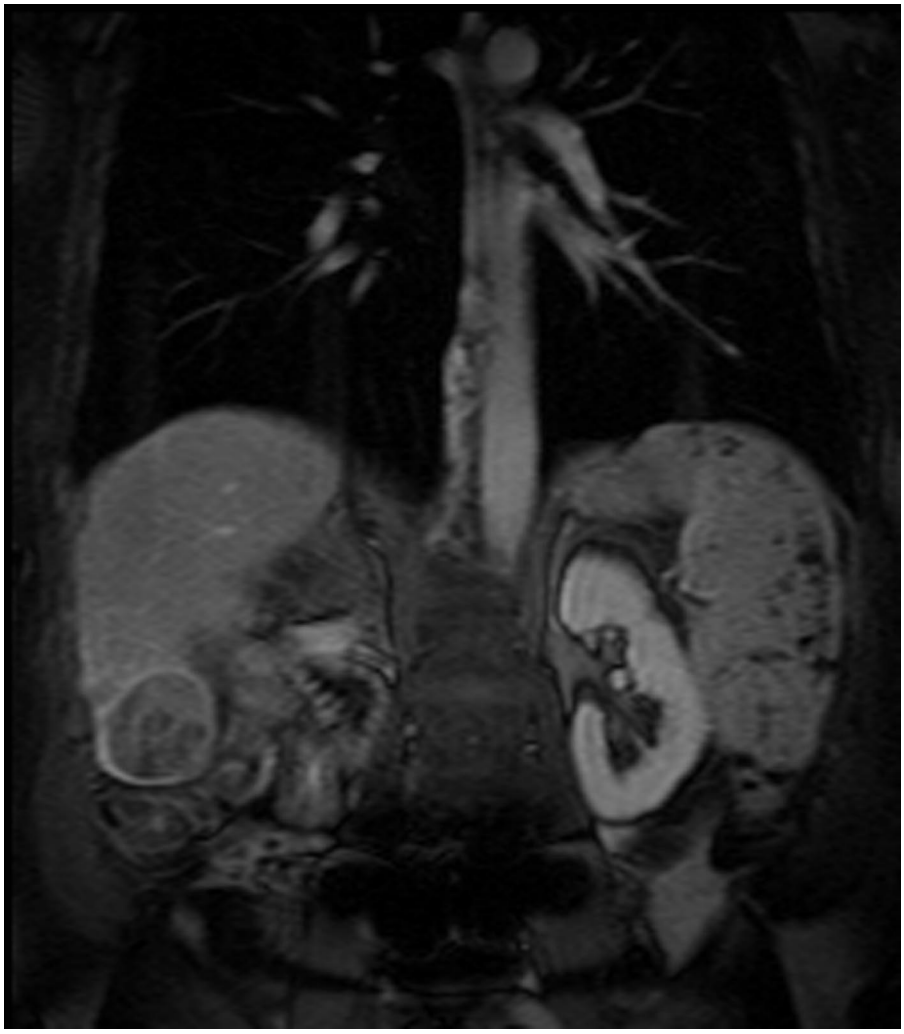

Figure 1. Example of a patient classified in group 0. Pretreatment contrast material–enhanced MR image demonstrates a right-lobe HCC measuring 6 cm × 7 cm. This patient had a solitary feeding vessel to this tumor such that segmental infusion of ^{90}Y microspheres could be performed.

Evaluations

After evaluation by a multidisciplinary tumor board comprised of personnel from medical oncology, hepatology, transplant surgery, and interventional radiology, patients were referred for treatment with ^{90}Y microspheres. Pretreatment evaluation included medical history, documenting demographics, HCC risk factors, comorbid diseases, previous cancer diagnoses and therapies, previous liver surgery, and previous systemic or regional treatments for HCC. Functional status was assessed by ECOG performance status. Patients had hematologic analysis (complete blood count and platelet count), chemistry analysis (including liver and renal function) and an α-fetoprotein assay. Pretreatment imaging included a triple-phase helical CT or contrast material–enhanced MR of the chest, abdomen, and pelvis; liver angiography with selective visceral catheterization; and a ^{99m}Tc macroaggregated albumin scan for assessment of lung shunting. Imaging studies were reviewed to document tumor burden and location, assess vascular anatomy and presence/absence of portal vein occlusion, and determine target liver volumes for use in dose calculations.

Patients were seen in clinical follow-up at 2 and 4 weeks after each treatment by the initial referring physician as well as the treating interventional radiologists. After completion of the initial treatment plan, follow-up visits were scheduled at 1-month or 3-month intervals, depending on the patient's condition. At each follow-up visit, evaluations included repeat CT/MR imaging, repeat laboratory assessments, and a clinical interview to identify and record adverse events that had occurred since the previous visit.

All patients underwent staging before treatment according to ECOG performance status, Child-Pugh class, Okuda score, and a previously published novel ^{90}Y risk-stratification system (15–21).

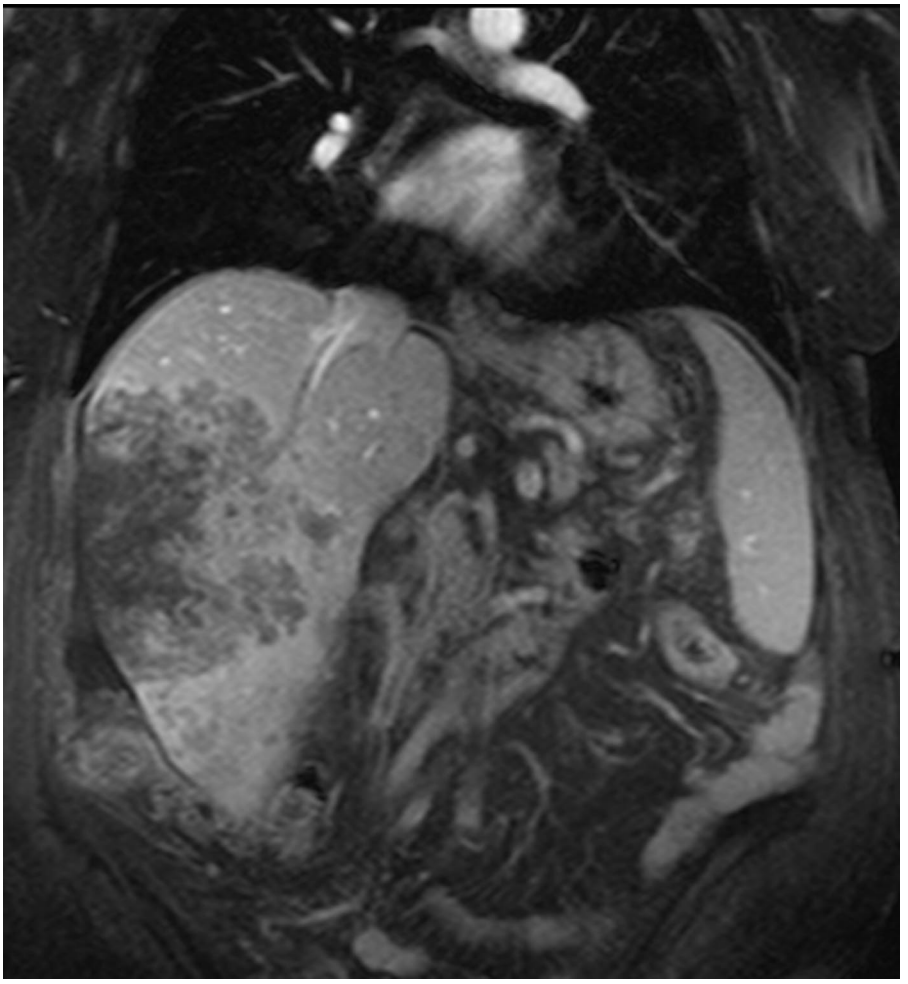

Figure 2. Example of a patient classified in group 2, high risk. Contrast material–enhanced MR image demonstrates a large right-lobe HCC with more than 70% replacement, aspartate aminotransferase and alanine aminotransferase levels greater than five times the normal limit, and bilirubin level greater than 2.0 mg/dL. Note hepatic vein thrombus.

Endpoints

Imaging-derived objective tumor response and survival are presented as efficacy measures, wherein tumor response was evaluated for as many as five measurable lesions. After treatment, lesions were measured serially and the best response in terms of size reduction and/or tumor necrosis was used. Tumor response was computed with use of the product of the longest diameter and length of the perpendicular diameter for each of the measurable lesions (ie, cross-products) and summed to represent tumor size. A tumor response was assigned to those patients who demonstrated a decrease of greater than 50% in the sum of the cross-products after treatment compared with before treatment (22). Tumor response also was evaluated by rating the presence and extent of tumor necrosis. Tumors were classified as demonstrating treatment-related necrosis when the tumor located on pretreatment imaging demonstrated decreased vascularity and greater than a 50% increase in necrosis after treatment. This approach allowed each measurable lesion to be classified with respect to treatment response based on tumor shrinkage alone or based on a composite measure of tumor shrinkage and/or necrosis (23). Lesions assigned to the necrosis-only category provided surrogate responses. These lesions were assigned a 50% reduction in size, which allowed necrotic and nonnecrotic lesion results to be combined for computing individual patient response rates. Because treatment of individual lesions varied over time, lesions were measured again before each treatment for pretreatment evaluation. Seventeen new lesions developed during the follow-up period; 14 of these were measured, treated, and evaluated for tumor response.

Survival was computed from the date of diagnosis until death or May 1, 2005, whichever occurred first. Adverse experiences were coded according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (24). Adverse experiences were recorded from day of treatment through death, alternative treatment, or 90 days after last treatment, whichever came first. When an alternative therapy was given after completion of treatment with TheraSphere, no further ^{90}Y was administered.

^{90}Y Risk Stratification

When the data were retrospectively reviewed, patients were allocated to one of three risk-stratification groups based on previously published reports (15). Segmentally treated patients (n = 10) had hypervascular focal nodules (n = 7 of 10), low tumor burden (<25% replacement), and vascular anatomy facilitating delivery of high radiation doses to tumor via a selective feeding hepatic artery (group 0; **Fig 1**). The remaining 33 patients were treated in a lobar fashion in a single lobe for unilobar disease (n = 12) or both lobes for bilobar disease (n = 21). These patients were divided into low-risk and high-risk groups (groups 1 and 2, respectively) based on previously published risk factors described herein (15,20). Patients presenting with ascites, diffuse disease (which includes infiltrating tumor type and disease with nodules too numerous to count on pretreatment imaging), greater than 70% replacement of liver by tumor, aspartate aminotransferase or alanine aminotransferase levels greater than five times the upper limit of normal (0–40 U/L and 0–48 U/L, respectively), or total serum bilirubin level greater than 2 mg/dL (normal range, 0–1.3 mg/dL) were classified in the lobar high-risk group (group 2; **Fig 2**). Patients treated in a lobar fashion without any of these criteria were classified in the lobar low-risk group (group 1; **Fig 3**).

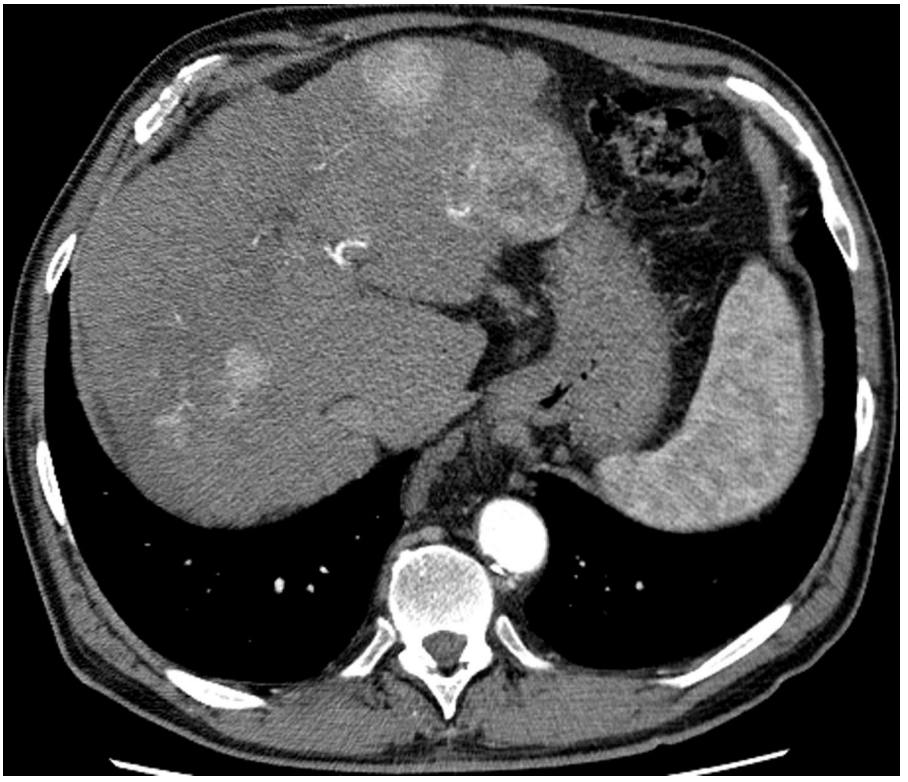

Figure 3. Example of a patient classified in group 1, low risk. Contrast material–enhanced CT image demonstrates multifocal, bilobar HCC (normal bilirubin level, low tumor burden).

Statistical Analysis

Kaplan-Meier and Cox regression methods were used for analysis of survival data, with censoring at the date of last follow-up for which the patient was known to be alive (25,26). The Kruskal-Wallis test was used for testing of differences in distributions in lesion characteristics (number of lesions, lesion distribution, and sum of longest diameters) among risk groups before treatment (27). Testing for patient-level tumor response among risk groups is based on application of a generalized linear model involving the logit link function. Testing for lesion-level tumor response among risk groups is based on application of generalized estimating equations with use of the logit link function to accommodate the correlation within a patient across lesions (28–30). This model is applied to evaluate the association of tumor response with previous treatment, number of measurable lesions, tumor involvement, percent of liver replaced by tumor, diffuse disease, portal vein occlusion, and α-fetoprotein level. All analyses were carried out with use of SAS software, version 8.2 (SAS, Cary, NC), and all reported P values are two-sided, without adjustment for multiple testing. Statistical model assumptions were verified for all reported results with use of standard methods. A least-squares model was used to fit the data corresponding to dose (D) and fraction (F) of liver treated (**Fig 4**):

$$[D = \alpha F + (1 - F)10{,}000\exp(\beta F^{\gamma})]$$

This model was empirically determined, and the solid exponential curve is presented (**Fig 4**) to emphasize the relation between these two variables.

RESULTS

Patient Demographics

Tables 1 and 2 provide a description of the patient population. None of the 43 patients treated with ^{90}Y microspheres were candidates for surgical treatment or transplantation because of one or more of the following factors: advanced age, comorbid health conditions, inadequate liver function, extrahepatic disease, portal vein thrombosis, previous liver surgery, high tumor burden, or tumor location not amenable to surgery. Fourteen patients (33%) had documented alcohol abuse, and three patients (7%) and 13 patients (30%) had a history of hepatitis B and C infection, respectively. Fifteen patients (35%) had diabetes, seven patients (16%) had a history of gastrointestinal bleeding, 10 patients (23%) had a history of thrombocytopenia, and three patients (7%) had a history of chronic renal insufficiency. Twenty-six patients (60%) had portal hypertension, 20 patients (46%) had portal vein thrombosis, and 13 patients (30%) had limited extrahepatic disease. All patients in group 0 had less than 25% of their liver replaced by tumor, whereas groups 1 and 2 included two patients (12%) and six patients (38%) with more than 50% of their liver replaced by tumor, respectively. All patients with main portal vein thrombosis were in group 2. Two patients (20%) in group 0 and nine patients (56%) in group 2 presented with at least mild ascites as determined on pretreatment imaging. For groups 0, 1, and 2, the numbers of patients with ECOG performance status of 0 were nine (90%), 11 (65%), and eight (50%). Child-Pugh class A disease was seen in seven (70%), 14 (82%), and six patients (38%), respectively. Okuda score of I was seen in seven (70%), 12 (71%), and two patients (13%), respectively. The median time from diagnosis of HCC to treatment was 2 months.

Treatments

All patients were treated on an outpatient basis and were discharged 6 hours following the procedure. **Table 3** provides a description of the applied treatments. Of 10 patients who received segmental treatment, five patients received one treatment, three received two treatments, one received three treatments, and one received five treatments. One segmentally treated patient received two treatments on the same day to two separate segments. The mean and median numbers of treatments per patient were 1.7 and 2, respectively. Two patients received more than one treatment to the same

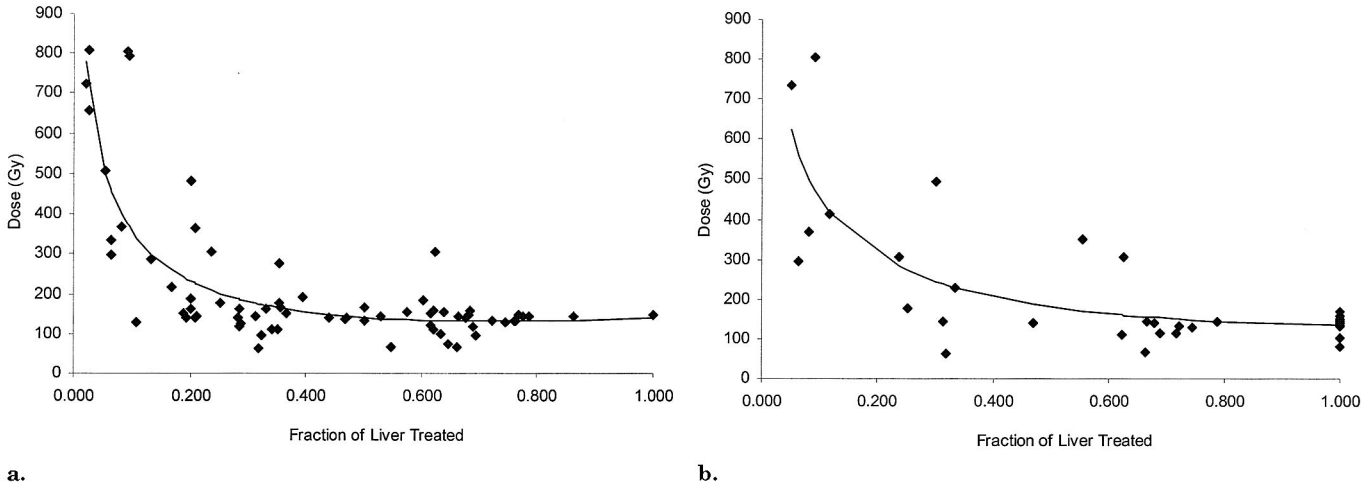

Figure 4. Plots of liver dose (in Gy) and corresponding fraction of liver treated: **(a)** unique-volume treatments (n = 70) and **(b)** volume-weighted treatments (n = 43). Estimated solid exponential line is obtained by fitting the equation $D = \alpha F + (1 - F)10{,}000\exp(\beta F^{\gamma})$, where D represents dose (in Gy); F represents fraction of liver treated; and α, β, and γ are estimated parameters.

liver volume (ie, unique-volume). Half the patients who received two treatments had their second treatment approximately 1 month after the first treatment. Three patients received chemotherapy for extrahepatic disease progression, including one patient who received inhaled doxorubicin therapy for lung metastases. Three patients were found to be in violation of the lung shunt safety criterion at the time of evaluation for a second treatment and subsequently received embolization as an alternative treatment. Embolization or chemoembolization was also used to control spontaneous HCC tumor bleeding (n = 2) and to control pain (n = 1) or intrahepatic progression (n = 1). When an alternative therapy was given after completion of treatment with ^{90}Y microspheres, no further ^{90}Y was administered.

Figure 4 displays the radiation doses (in Gy) and associated fraction of liver treated for unique-volume and volume-weighted average doses by patient. The estimates of α are 141 Gy for unique volumes and 138 Gy for the volume-weighted averages, which corresponds to whole-liver treatment (fraction, 1). Of 30 unique-volume treatments in which more than 50% of the liver was exposed, eight patients (27%) received radiation doses greater than 150 Gy (151, 153, 155, 158, 158, 167, 182, and 305 Gy). Seven were single treatments and one patient received two treatments (135 Gy and 170 Gy) to the right lobe 6 months apart. The patient in **Figure 4**a, representing a fraction of 1, had a previous left lobectomy and received a single treatment via the right hepatic artery. Twenty patients received treatment to their whole liver (via left and right hepatic arteries), which is indicated in **Figure 4**b (fraction of 1). The median radiation doses to exposed liver for groups 0, 1, and 2 were 359 Gy, 141 Gy, and 142 Gy, respectively. The median cumulative lung dose was 9 Gy per patient. There were no misadministrations. All patients received the prescribed dose.

Assessment of Response

Imaging characteristics and tumor response evaluations for measurable lesions by group are provided in **Table 4**. As expected, a decreasing percentage of unilobar measurable disease was observed for groups 0, 1, and 2, respectively. No association of tumor response (on a lesion or patient level) with group was observed, with 47% of patients and 51% of lesions demonstrating greater than 50% reduction in tumor size. Imaging follow-up time was longer for those patients who had greater than a 50% size reduction (median, 196 days vs 69 days). When necrosis was incorporated into the tumor response evaluation, 79% of lesions and patients were classified as exhibiting a response to treatment. The median time to partial response (50% reduction) for the cohort was 82 days.

An analysis of the association of tumor response with several variables was performed. Of these variables, only diffuse disease was negatively associated with tumor response, with one of eight patients (13%) exhibiting greater than a 50% decrease in tumor size and three patients (38%) exhibiting a response when necrosis was incorporated into the definition of response. Six of the eight patients with greater than 50% of their liver replaced by tumor had diffuse disease. There was no statistical association between tumor response and percent tumor replacement after adjustment for diffuse disease.

Figures 5–7 illustrate the effect of ^{90}Y microsphere treatment and supports the use of necrosis as a surrogate measure of tumor response. The patient illustrated presented with a hypervascular focal tumor nodule (MR imaging in arterial phase, 5.6 cm × 5.1 cm) in the caudate lobe, occupying approximately half the segment volume (**Fig 5**). Infusion of 1.6 GBq radiation was performed segmentally, resulting in a computed dose of 306 Gy. Ten weeks later (**Fig 6**), the tumor (5.1 cm × 5.1 cm) demonstrated decreased vascularity and marked necrosis. One year after treatment (**Fig 7**), necrosis and complete lack of enhancement persist. In addition, there has been a 56% size reduction in cross-products

Table 1
Overall Population Description

Demographics and previous treatments	N (%)
Age (y)	
< 69	21 (49)
≥ 69	22 (51)
Ethnic group	
White	34 (79)
Black	4 (9)
Hispanic	1 (2)
Asian	2 (5)
Other	2 (5)
Sex	
Male	28 (65)
Female	15 (35)
Failed previous treatments	
None	30 (70)
Systemic	6 (14)
Regional	5 (12)
Systemic and regional	2 (5)
Prior HCC surgery	
None	39 (90)
Resection	2 (5)
Lobectomy	2 (5)
Tumor characteristics	
Lesion distribution (measurable)	
Unilobar	23 (53)
Bilobar	11 (26)
Spanning*	9 (21)
Measurable lesions	
1	21 (49)
2	8 (19)
3	9 (21)
4	2 (5)
5	3 (7)
Replacement by tumor (%)	
0–25	29 (67)
26–50	6 (14)
51–75	7 (16)
>75	1 (2)
Morphology	
Uninodular and <50%	17 (39)
Multinodular and <50%	18 (42)
Massive or >50%	8 (19)
Portal vein thrombosis	
None	23 (54)
Unilobar	16 (37)
Main	4 (9)
α-Fetoprotein level (ng/mL)†	
<400	33 (79)
≥400	9 (21)
Liver function	
Ascites	
No	32 (74)
Yes	11 (26)
Bilirubin (total)	
≥ULN	30 (70)
>ULN	13 (30)
Albumin	
≥LLN	16 (37)
<LLN	27 (63)
Aspartate aminotransferase level†	
≤ULN	10 (24)
>ULN	31 (76)
Alanine aminotransferase level†	
≤ULN	20 (49)
> ULN	21 (51)
Portal hypertension	
No	17 (40)
Yes	26 (60)
Portosystemic shunt	
No	32 (74)
Yes	11 (26)
Hepatofugal flow	
No	23 (54)
Yes	20 (46)
Staging	
ECOG performance status	
0	28 (65)
1	13 (30)
2	2 (5)
Extrahepatic disease‡	
No	30 (70)
Yes	13 (30)
Lymph nodes	
None	15 (35)
< 2 cm	23 (53)
> 2 cm	5 (12)
Child-Pugh class	
A	27 (63)
B	15 (35)
C	1 (2)
Okuda score	
I	21 (49)
II	22 (51)
90-Day risk (15)	
Low	30 (70)
High	13 (30)

Note.—LLN = lower limit of normal; ULN = upper limit of normal.
* At least one mass involved both lobes.
† One unknown α-fetoprotein level; two unknown aspartate and alanine aminotransferase levels.
‡ Lymph nodes < 2 cm were not classified as extrahepatic disease

(3.4 cm × 3.7 cm) versus before treatment.

Adverse Events

Treatment-related laboratory adverse events of grade 3 or worse were compiled (**Table 5**). Twenty-two of the 23 patients with follow-up lymphocyte counts (96%) had a reduction graded as mild to moderate ($n = 14$) or severe ($n = 8$). This phenomenon is characteristic of the sensitivity of lymphocytes to radiation and the half-life of the ^{90}Y microspheres. There were six grade 3 bilirubin-related toxicities, five of which were in high-risk group 2, ie, in patients with large tumor burden, portal vein invasion, infiltrative disease, and increased liver function test results at baseline. Three of the patients had pretreatment bilirubin levels greater than 2.0 mg/dL (2.5 mg/dL, 2.8 mg/dL, and 3.2 mg/dL); one patient had pretreatment ascites with left, right, and main portal vein occlusion; and one patient had pretreatment ascites with hepatofugal flow. Three of 16 patients in the high-risk group developed grade 3 ascites. Two of these patients had mild pretreatment ascites, and one patient had an increased bilirubin level before treatment (2.5 mg/dL), greater than 75% liver replacement by tumor, main portal vein occlusion, and hepatofugal flow. The development of ascites in these patients coincided with disease progression.

Survival

Survival results for this cohort using several different classifications are provided in **Table 6**. Median survival for Okuda stage I and II patients was 24.4 and 12.5 months respectively. Child-Pugh A and B/C patients exhibited a median survival of 20.5 and 13.8 months. When patient risk stratification for ^{90}Y TheraSphere was used, median survival was 46.5, 16.9, and 11.1 month for groups 0, 1 and 2 respectively. Median survival in all non high-risk patients (groups 0/1) was 20.8 months. Survival stratified by tumor burden is also listed (1: 0–25%, 2: 26%–50%, 3: 51%–75%, 4: >75%). Factors associated with lower survival included high-risk designation (group 2), presence of ascites, ECOG performance status > 0, presence of extrahepatic disease, > 25% tumor burden, infiltrative disease, main portal vein thrombosis and α-fetoprotein > 400 ng/mL.

DISCUSSION

Systemic therapy, including chemotherapy, hormonal therapy, and immunotherapy, is ineffective in treating unresectable HCC. Randomized controlled trials have failed to demonstrate consistent survival benefit with the use of these therapies, and it is

Table 2
Population Description by Group

	Group (N %)			
	0	1	2	Total
ECOG performance status				
0	9 (90)	11 (65)	8 (50)	28 (65)
1	1 (10)	5 (29)	7 (44)	13 (30)
2	–	1 (6)	1 (6)	2 (5)
Okuda score				
I	7 (70)	12 (71)	2 (13)	21 (49)
II	3 (30)	5 (29)	14 (87)	22 (51)
Child-Pugh class				
A	7 (70)	14 (82)	6 (38)	27 (63)
B	3 (30)	3 (18)	9 (56)	15 (35)
C	–	–	1 (6)	1 (2)
90-Day risk stratification				
Low	8 (80)	17 (100)	5 (31)	30 (70)
High	2 (20)	–	11 (69)	13 (30)
Extrahepatic disease				
No	8 (80)	11 (65)	11 (69)	30 (70)
Yes	2 (20)	6 (35)	5 (31)	13 (30)

Note.—Values in parentheses are percentages.

Table 3
Treatment Description

Treatment Characteristics	No. of Patients
Number of treatments per patient	
1	17 (40)
2	23 (53)
3	2 (5)
4	0 (0)
5	1 (2)
Type of Treatment	
Segmental	10 (23)
Regional	33 (77)
Time between treatments	
First to second (n = 26)	
Median	34
Minimum	0*
Maximum	203
Second to third (n = 3)	
Median	204
Minimum	14
Maximum	224
Lung dose (Gy) per patient (n = 43)	
Median	9
Minimum	0.3
Maximum	29
Alternative Treatments	
None	32 (74)
(Chemo)embolization	8 (19)†
Systemic chemotherapy	2 (5)‡
Regional chemotherapy	1 (2)‡

Note.—Values in parentheses are percentages.
* One patient received two segmental treatments on the same day
† Bland or chemoembolization was used to control tumor bleeding (n = 2), control pain (n = 1), control progression (n = 1).
‡ Three patients received chemotherapy for extrahepatic disease progression, including one who received inhaled doxorubicin for lung metastases.

generally accepted that only 20% of patients undergoing single-agent or combination systemic therapy will have an objective tumor response on imaging studies (31,32). These therapies also can be clinically challenging to administer safely in this population as a result of the narrow therapeutic window and failing liver reserve (33). In contrast to those with other forms of cancer, patients diagnosed with HCC generally die of liver failure rather than as a result of advancing metastatic disease. The lack of an effective systemic therapy, combined with the certainty of progressive liver failure in unresectable HCC, has led to a variety of liver-directed treatments to reduce tumor burden. Such treatments provide palliation, improve the prospects for resection, prolong liver function to increase the likelihood of transplantation, and/or provide the potential for increased survival through treatment-directed tumoricidal effects.

Choosing an appropriate liver-directed treatment and individualizing therapy is a complex task that includes consideration of the patient's presenting tumor burden, liver function, and vascular anatomy; the patient's overall health status and preferences; and the treating physician's expertise and skill with the available treatments (17). Given that liver-directed treatments are applied repeatedly, consideration of the appropriate liver-directed treatment is an ongoing process that evolves over time for each patient. Because of advancing liver failure and its sequelae, supportive-care interventions to palliate and prolong overall patient health are critically important with the use of any liver-directed treatment for unresectable HCC.

The results reported here represent those obtained with ^{90}Y microspheres in a heterogeneous group of patients with unresectable HCC in a single institution. The treatments were tailored to the presenting clinical scenario, as characterized by type of treatment (segmental vs lobar), prescribed dose, number and interval of repeat treatments, and the use of alternative treatments when appropriate. Based on this careful approach to treatment and adherence to accepted warnings and contraindications for ^{90}Y microsphere treatment, no gastrointestinal or pulmonary adverse events were observed, including gastric ulcer and radiation pneumonitis, as previously reported with ^{90}Y microsphere treatment (14,17). In addition, treatment-related hepatic adverse events graded as severe were associated with pretreatment conditions predictive of increased risk. Although 22 of 23 patients with follow-up lymphocyte data exhibited lymphopenia, there were no clinical manifestations indicating increased risk of infection or reactivation of latent viral infection.

Patients were retrospectively assigned to one of three risk-stratification groups (groups 0, 1, and 2). Those who were able to undergo segmental treatment (group 0) had less-advanced disease, and, from the time of their first treatment, exhibited longer survival without severe treatment-related adverse events. This group is the beneficiary of screening tests, as their increased survival likely represents an

Table 4
Imaging Characteristics and Tumor Response for Measurable Lesions by Group

Characteristic	Group 0	Group 1	Group 2	Total	*P* Value*
Number of lesions (*n* = 43)					.98
1	5 (50)	8 (47)	8 (50)	21 (49)	
2–3	4 (40)	7 (41)	6 (38)	17 (40)	
4–5	1 (10)	2 (12)	2 (12)	5 (11)	
Lesion distribution (*n* = 43)					.04
Unilobar	7 (70)	10 (59)	6 (38)	23 (53)	
Bilobar†	3 (30)	7 (41)	10 (62)	20 (47)	
Lesion longest diameter (*n* = 43)					
Median	6.1	6.2	5.9	6.1	.76
Minimum	1.3	1.4	1.1	1.1	
Maximum	8.7	17.5	17.7	17.7	
Sum of longest diameters (*n* = 43)					.51
Median	7.8	7.1	10.0	8.2	
Minimum	3.6	1.4	2.0	1.4	
Maximum	13.0	19.9	24.4	24.4	
Patient response (*n* = 43)					
>50% decrease	4 (40)	10 (59)	6 (38)	20 (47)	.42
>50% decrease/necrosis	9 (90)	14 (82)	11 (69)	34 (79)	.39
Lesion response (*n* = 87)					
>50% decrease	11 (55)	19 (56)	14 (42)	44 (51)	.54
>50% decrease/necrosis	18 (90)	28 (82)	23 (70)	69 (79)	.18

Note.—Values in parentheses are percentages.
* Number of lesions, lesion distribution (bilobar and spanning combined), lesion longest diameter, and sum of longest diameters are based on Kruskal-Wallis test; patient level response is based on generalized linear model using logit link; and lesion level response is based on a generalized estimating equation implementation of the patient level generalized linear model for multiple lesion response measurements within patients.
† Includes tumors spanning both lobes.

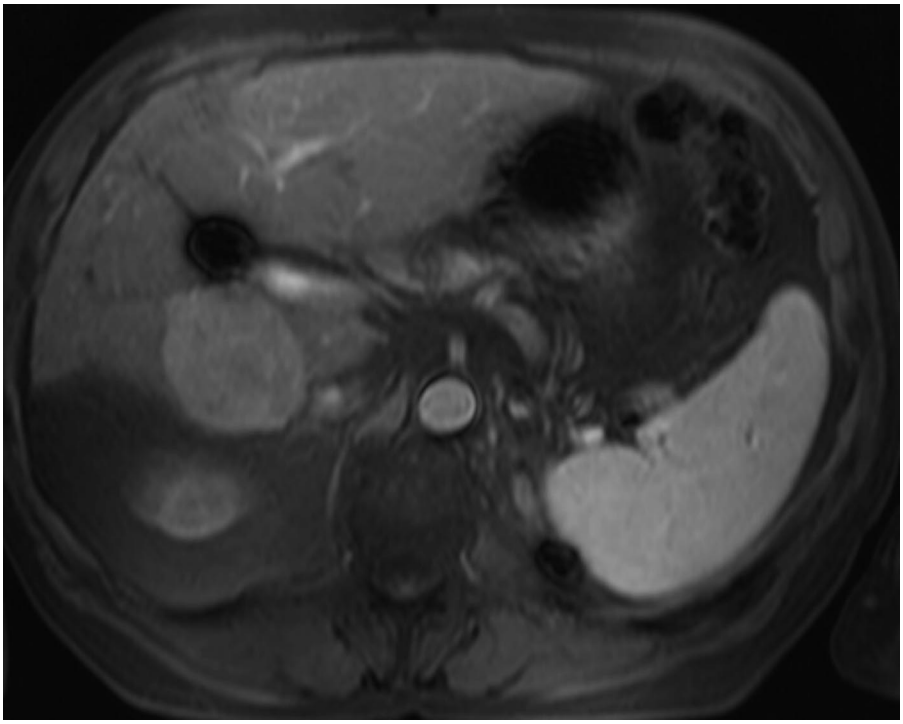

Figure 5. Contrast material–enhanced MR image demonstrates a 5.6-cm × 5.1-cm mass in caudate lobe.

element of early detection bias. Patients who required lobar treatment have more advanced disease. These patients were assigned to low (group 1) and high (group 2) mortality and adverse experience risk groups based on tumor and liver function characteristics. The survival results are clearly different among the three groups, which are uniquely defined herein. However, this experience can be placed in perspective by comparing the results versus literature-derived survival estimates reported for transcatheter arterial chemoembolization (TACE) with Okuda staging for risk stratification.

For patients with unresectable HCC, survival benefit attributed to TACE treatment has been controversial; however, two recent randomized controlled trials have provided evidence of a survival advantage for TACE versus supportive care in selected patients (34,35). Two additional informative randomized controlled trials, one evaluating TACE versus supportive care and the other evaluating TACE versus radioactive iodine I 131 therapy, have also been reported (36,37). These four trials were conducted on patients with various underlying etiologies, predominately hepatitis B and C and alcohol abuse. As described by Geschwind et al (17), the majority of the patients treated in these randomized controlled trials were classified as having Okuda stage I disease, and this allows comparisons with similarly stratified results for patients treated with ^{90}Y microspheres. Based on the results reported in these randomized controlled trials, the estimated 1-year survival rate for patients with Okuda stage I disease treated with TACE ranges from 56% to 62%. Geschwind et al (17) reported a median survival rate in 54 patients with Okuda stage I disease who underwent first-line ^{90}Y microsphere treatment of 20.9 months, or a 1-year survival estimate of 63%. In these patients, ^{90}Y microsphere treatment appeared to yield similar survival duration as that obtained with use of TACE, which has been shown to improve survival in randomized controlled trials. The estimated 1-year survival rate for patients with Okuda stage II disease was 51% and the median survival time was 12.8 months. In our sample, patients with Okuda stage I disease (n = 21) had an

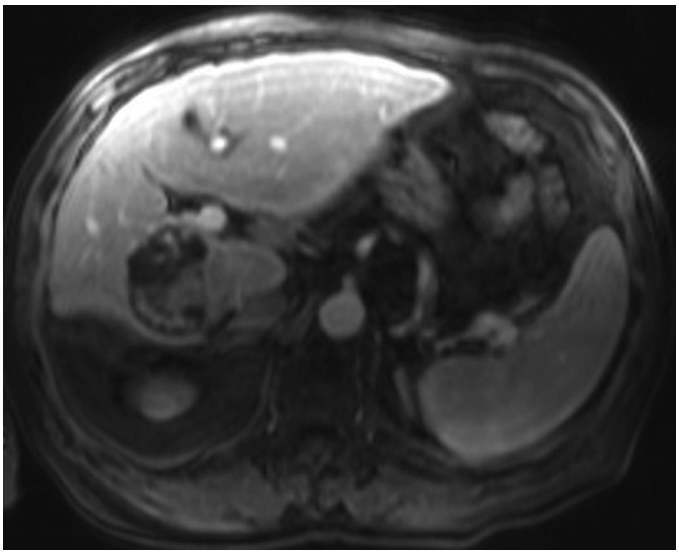

Figure 6. The patient received 1.6 GBq (306 Gy) radiation to the tumor. Ten-week follow-up contrast material–enhanced MR image demonstrates little tumor shrinkage (5.1 cm × 5.1 cm) but significant necrosis.

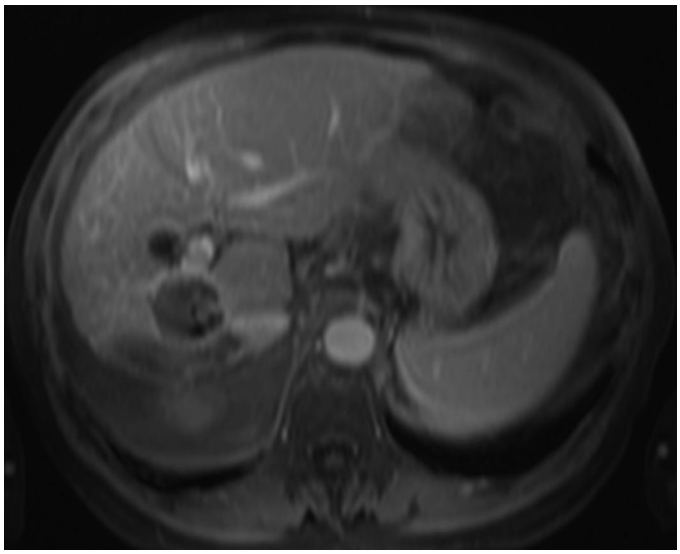

Figure 7. One-year follow-up contrast material–enhanced MR image demonstrates significant tumor shrinkage (56%) and persistent decreased vascularity and necrosis.

estimated 1-year survival rate of 80.9% and a median survival time of 24.4 months. This is similar to previous reports of 82% 1-year survival rates in patients treated with TACE (38). Our results demonstrated a 12.5-month median survival time and estimated 1-year survival probability of 54.5% for patients with Okuda II disease (n = 22). These results compare favorably with the results in patients with Okuda stage II disease reported by Raoul et al (37), who reported 1-year estimated survival rates of 21% and 15% for ^{131}I treatment (n = 30) and TACE (n = 27), respectively. Previous investigators of ^{90}Y therapy reported median survival times in patients with Okuda I and II disease of 21.6 months and 10.1 months, respectively (39).

The apparent survival benefit is supported by the ^{90}Y microspheres' effect on tumor, as measured by the individual lesion and patient level tumor response data. Of the 87 lesions treated, 44 (51%) had greater than a 50% reduction in size. Incorporating necrosis into the definition, as suggested by European Association of the Study of the Liver, provided an increase of 28% in response rate, yielding 69 lesions (79%) that responded to treatment. Twenty patients (47%) were classified as having a tumor response by exhibiting a greater than 50% reduction in the sum of cross-products. This is similar to previously reported response rates of 38% with this treatment technique (39). Patients treated with TACE or bland embolization have exhibited a 39% response rate (34,35).

The incidence of response in this study was increased to 34 patients (79%) when including tumor necrosis. These results appear to be slightly better than those reported for TACE by Eibed and colleagues (38) with use of related methodology to determine tumor response in individual lesions and tumor response at the patient level. The authors reported on 186 lesions in 72 patients, with 75 lesions (40%) exhibiting greater than a 25% reduction in size and 52 lesions (28%) exhibiting at least a 50% increase in tumor necrosis. Applying size reduction, increase in necrosis, and the failure to develop new lesions, the authors reported 38 patients who showed a response (53%). These authors used a more liberal definition of size reduction (25% vs 50%) and a similar definition of necrosis response.

Tumor necrosis is widely accepted as a valid measure of objective tumor response and "cytoreduction" with the use of liver-directed treatment in HCC (2,8,11,22,40,41). Clearly, necrosis reflects a reduction in viable tumor tissue and has been promoted as reducing intrahepatic tumor progression (42). In addition, tumor shrinkage in the cirrhotic liver may not be observed, or a prolonged follow-up time may be required to demonstrate size reduction (2,38). Unfortunately, for many cases of unresectable HCC, "prolonged follow-up time" is an oxymoron. The results reported herein are commensurate with this biologic treatment phenomenon, whereby patients who exhibit at least a 50% size reduction were followed (via imaging) for a median of 196 days, compared with a median follow-up time of only 69 days for patients who did not satisfy this criterion. Mistakenly, many authors use the biased reverse-logical construct to support their survival findings; that is, that patients who exhibit unadjusted tumor response have longer survival (43).

The effect of radiation dose on survival and tumor response is confounded by the method of treatment. Patients with smaller fractions of liver treated, on a single occasion or on multiple occasions, received higher radiation doses but only to the fraction of liver treated. **Figure 4** provides a vehicle for comparing the manner in which patients were treated. The actual dose to tumor and liver parenchyma are not presented. For example, the patient represented in **Figures 5–7** received a dose of 306 Gy, assuming uniform distribution of the ^{90}Y micro-

Table 5
Grade 3/4 Adverse Events Occurring within 90 days after Last Treatment

Adverse Event	No. of Patients
Lymphopenia*	**22 (96)**
Group 0	10 (100)
Group 1	7 (88)
Group 2	5 (100)
Increased alkaline phosphatase level	**0**
Group 0	0
Group 1	0
Group 2	0
Fatigue	**1 (2)**
Group 0	0
Group 1	1 (6)
Group 2	0
Increased total serum bilirubin level	**6 (14)**
Group 0	0
Group 1	1 (6)
Group 2	5 (31)
Ascites, nonmalignant	**3 (7)**
Group 0	0
Group 1	0
Group 2	3 (19)
Aminotransferase levels†	**2 (5)**
Group 0	0
Group 1	2 (12)
Group 2	0
Chills/rigor	**0**
Group 0	0
Group 1	0
Group 2	0
Fever, without infection	**0**
Group 0	0
Group 1	0
Group 2	0
Pain, abdominal	**0**
Group 0	0
Group 1	0
Group 2	0

Note.—Values in parentheses are percentages.
* Based on 23 patients with posttreatment measurements, all adverse events for lymphopenia (grades 1–4).
† Increased aspartate aminotransferase or alanine aminotransferase levels.

Table 6
Survival Statistics

Parameter	N	Mean Survival (days)	Median Survival (d)	95% Confidence Limits (days)	*P* Value†
Child-Pugh					
A	27	681	615	417–777	0.0061
B/C	16	409	414	286–516	
ECOG performance status					
0	26	720	619	516–777	<.0001
1/2	17	366	360	257–451	
Group					
0	10	1062	1394	615‡	<.0001
1	17	535	507	380–731	
2	16	349	332	257–451	
Risk group*					
0/1 (non–high-risk)	27	714	623	507–777	<.0001
2 (high- risk)	16	349	332	257–451	
Okuda stage					
I	21	774	731	534–853	<.0001
II	22	394	374	286–507	
Tumor burden (%)					
0–25	28	678	559	496–777	.0028
26–50	7	499	462	367–731	
51–75	4	321	323	257–383	
>75	4	307	289	73–577	

* Group 0 and 1 combined. *P* value compares group 0/1 (non–high-risk) versus 2 (high-risk).
† Log-rank test.
‡ Upper limit not reached.

spheres throughout the liver volume (ie, fraction) for which dose is computed. However, for this patient, it is estimated that half the caudate segment was occupied by tumor, which exhibited a 5:1 ratio in terms of blood flow to tumor compared with the surrounding liver parenchyma. Typically, tumor-to-normal blood flow ratios are in the range of 7:2 (44,45). In light of these data, a more accurate estimate of the tumor dose is 588 Gy, with an average dose over the entire liver parenchyma of 18 Gy (11). These calculations, and the fact that ^{90}Y microspheres represent discrete point sources of radiation with a distinct biologic effective dose (compared with external-beam radiation), exemplify the tumor-targeting and liver-sparing potential for treatment with ^{90}Y microspheres. This potentially explains the observed high level of patient tolerance, absence of life-threatening adverse effects of treatment in select patients, increased therapeutic effect when combining tumor size reduction and necrosis in estimating tumor response, and encouraging survival results (1–12).

Diffuse disease was found to be highly negatively associated with survival and tumor response. Eight patients (19%) were classified as having diffuse disease, five (12%) with infiltrating-type disease and three (7%) with widely distributed multifocal disease. Only one of these patients had a greater than 50% reduction in tumor size. This lack of response may be related to limitations of the duration of follow-up imaging, the evaluation methodology, treatment, liver biology, or a combination of these factors. Patients with diffuse disease often have vascular invasion of the portal system and are known to be at higher risk of early mortality and adverse events that are potentially related to treatment (15,46,47). Treating these patients requires careful consideration of the risk versus the benefit of any liver-directed treatment.

Patients classified at high-risk (ie, group 2) before receiving treatment with ^{90}Y microspheres deserve special mention. These patients presented with advanced infiltrative or multinodular disease with high tumor burden and compromised liver reserve. Although they were recognized as being at high risk before they received therapy, all patients elected to proceed with treatment as a palliative measure. Despite adequate tumor response (ie, stability of disease) after treatment, these patients accounted for the majority of the severe grade 3 bilirubin in-

creases after treatment. Although these toxicities were determined to be secondary to tumor progression and advancing end-stage liver disease, they are reported herein given their temporal relationship to treatment (<90 days).

There are limitations to this analysis. The lack of randomization to another treatment such as TACE makes any survival benefit difficult to confirm. Also, this type of prospectively acquired data makes the retrospective categorization of patients necessary to analyze patient groups. Although other centers active in this type of therapy have also published their results (17,39), this experience from a single center also requires further independent validation. Also, these data are clearly confounded by multiple variables, such as portal vein thrombosis, infiltrative disease, presence of limited extrahepatic disease, survival from time of diagnosis, and alternative treatments. In addition, only 37% of patients in this cohort had hepatitis B and/or C, whereas more than 80% had hepatitis B and/or C in previous reports of TACE treatment for HCC (34,35), making comparison between these cohorts difficult. Future work with this technology will require further refinement in patient selection and standardization before treatment.

However, there are advantages to this type of analysis. This was a prospective study in which all patients were enrolled without significant entry criteria bias, such as age, bilirubin level, and presence or absence of significant extrahepatic metastases or portal vein thrombosis. These entry criteria make this cohort reflect the actual overall population with HCC. Unlike other studies in which patient entry criteria were strict, all patients were treated with this therapy with palliative intent and the cohort was observed longitudinally. Grouping patients then permitted analysis and stratification based on these groups. This is no different than Okuda's original classification or the multitude of various other classifications (eg, Cancer of the Italian Liver Program, Child-Pugh, Japan Integrated Staging, Barcelona Clinic Liver Cancer), in which patient parameters were reviewed retrospectively and a prognostic index was created, intended for prospective use. It is clear that this type of retrospective analysis and methodology has played an instrumental role in the creation of prognostic indexes that are used prospectively, such as the aforementioned Child-Pugh, Cancer of the Italian Liver Program, Japan Integrated Staging, and Barcelona Clinic Liver Cancer indexes. Although this is a small series in which 43 patients were prospectively treated and 3 prognostic groups were created (segmental, lobar low-risk, lobar high-risk), it is a valuable addition to the refinement of patient selection criteria for patients undergoing ^{90}Y microsphere treatment. Finally, these types of data and analyses further reinforce the notion that ^{90}Y microspheres represent a promising therapeutic agent that must be included in the transarterial treatment armamentarium. Studies comparing ^{90}Y microsphere treatment versus other liver-directed therapies (eg, TACE, bland embolization, radiofrequency ablation, percutaneous ethanol injection, drug-eluting beads, phosphorous P 32 microparticles) in selected patients require serious consideration.

CONCLUSIONS

Similar to other liver-directed therapies such as TACE or radiofrequency ablation, ^{90}Y microsphere treatment in properly selected patients can be performed safely, provides clear evidence of reduced tumor viability, and demonstrates encouraging survival results. Randomized controlled trials should be undertaken to compare survival with ^{90}Y microspheres versus that with other forms of liver-directed treatment, and, when possible, with supportive care alone. These trials would provide quantification of survival benefit versus treatment risk on a larger group of patients with unresectable HCC and further refine the application of this technology to individual patients. In addition, as we approach the asymptote of the survival benefit curve being achieved by ^{90}Y and other liver-directed therapies for HCC, variables other than survival will need to be used to measure the clinical and economic benefit of a particular therapy. These might include objective and validated measures such as quality of life, incidence of postembolization syndrome, pain, days of hospitalization, time to progression, progression-free survival, objective tumor response, and cost.

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