Unresectable Chemorefractory Liver Metastases:

Radioembolization with ^{90}Y Microspheres—Safety, Efficacy, and Survival[1]

Kent T. Sato, MD
Robert J. Lewandowski, MD
Mary F. Mulcahy, MD
Bassel Atassi, MD
Robert K. Ryu, MD
Vanessa L. Gates, MS
Albert A. Nemcek, Jr, MD
Omar Barakat, MD
Al Benson III, MD
Robert Mandal, MD
Mark Talamonti, MD
Ching-Yee O. Wong, MD, PhD
Frank H. Miller, MD
Steven B. Newman, MD
John M. Shaw, MD
Kenneth G. Thurston, MA
Reed A. Omary, MD
Riad Salem, MD, MBA

Purpose: To prospectively evaluate the safety, efficacy, and survival of patients with chemorefractory liver metastases who have been treated with yttrium 90 (^{90}Y) glass microspheres.

Materials and Methods: Institutional review boards from two institutions approved the HIPAA-compliant study; all patients provided informed consent. One hundred thirty-seven patients underwent 225 administrations of ^{90}Y microspheres by using intraarterial infusion. Primary sites (origins) included colon, breast, neuroendocrine, pancreas, lung, cholangiocarcinoma, melanoma, renal, esophageal, ovary, adenocarcinoma of unknown primary, lymphoma, gastric, duodenal, bladder, angiosarcoma, squamous cell carcinoma, thyroid, adrenal, and parotid. Patients underwent evaluation of baseline and follow-up liver function and tumor markers and computed tomographic or magnetic resonance imaging. Patients were observed for survival from first treatment. Median survival (in days) and corresponding 95% confidence intervals were computed by using the Kaplan-Meier method. The log-rank statistic was used for statistical significance testing of survival distributions between various subgroups of patients.

Results: There were 66 men and 71 women. All patients were treated on an outpatient basis. Median age was 61 years. The mean number of treatments was 1.6. The median activity and dose infused were 1.83 GBq and 112.8 Gy, respectively. Clinical toxicities included fatigue (56%), vague abdominal pain (26%), and nausea (23%). At follow-up imaging, according to World Health Organization criteria, there was a 42.8% response rate (2.1% complete response, 40.7% partial response). There was a biologic tumor response (any decrease in tumor size) of 87%. Overall median survival was 300 days. One-year survival was 47.8%, and 2-year survival was 30.9%. Median survival was 457 days for patients with colorectal tumors, 776 days for those with neuroendocrine tumors, and 207 days for those with noncolorectal, nonneuroendocrine tumors.

Conclusion: ^{90}Y hepatic treatments are well tolerated with acceptable toxicities; tumor response and median survival are promising.

Clinical trial registration no. NCT00532740.
http://clinicaltrials.gov/show/NCT00532740

[1] From the Department of Radiology, Section of Interventional Radiology (K.T.S., R.J.L., M.F.M., B.A., R.K.R., V.L.G., A.A.N., O.B., F.H.M., R.A.O., R.S.), Department of Medicine, Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center (M.F.M., A.B., S.B.N., J.M.S., R.S.), Department of Nuclear Medicine (V.L.G.), and Department of Surgery, Robert H. Lurie Comprehensive Cancer Center (M.T.), Northwestern University, 676 N Saint Clair St, Suite 800, Chicago, IL 60611; North Shore Oncology and Hematology Associates, Libertyville, Ill (R.M.); Department of Nuclear Medicine, Beaumont Hospital, Royal Oak, Mich (C.Y.O.W.); and West Grove, Pa (K.G.T.). Received November 28, 2006; revision requested January 24, 2007; revision received June 27; accepted August 1; final version accepted October 15. **Address correspondence to** R.S. (e-mail: *r-salem@northwestern.edu*)

Radioembolization has been shown to be effective in the treatment of unresectable hepatocellular carcinoma, as well as unresectable colon carcinoma metastases (1–4). Radioembolization is a local-regional liver-directed therapy that involves transcatheter delivery of particles embedded with the radioisotope yttrium 90 (^{90}Y). Particles are infused through a catheter into the hepatic artery where they travel distally and lodge at the tumor arteriolar level. ^{90}Y is a pure beta emitter that delivers a high dose of radiation to the tumor, which results in necrosis. One of the clinically available products for radioembolization is TheraSphere (MDS Nordion, Ottawa, Ontario, Canada). TheraSphere has received a humanitarian device exemption from the Food and Drug Administration for use in hepatocellular carcinoma. Investigators are directed to published Food and Drug Administration guidelines for the use of humanitarian device exemptions in disease conditions other than the approved indication. The use of this therapy for hepatocellular carcinoma, colorectal carcinoma, and mixed neoplasia has been previously reported (1–11). Although short-term results of radioembolization for metastatic liver disease are promising (response rates, 30%–60%), the purpose of our study was to prospectively evaluate the safety, efficacy, and survival of patients with chemorefractory liver metastases who have been treated with ^{90}Y glass microspheres.

Materials and Methods

One author (R.S.) is a consultant for MDS Nordion and has disclosed a potential conflict of interest. None of the other authors have disclosed a conflict. The data were controlled by all authors. No industry support for this study was provided.

Eligibility Criteria

Between 2002 and 2006, 137 patients with chemorefractory liver-dominant metastases from various primary malignancies were treated at two institutions (Northwestern University and Beaumont Hospital) and were prospectively enrolled in this open-label phase II study. All patients underwent preprocedural imaging with computed tomography (CT). Magnetic resonance (MR) imaging was performed in the setting of contrast material allergies or renal dysfunction. Liver function and tumor markers were evaluated when appropriate. Positron emission tomography (PET) was used to assess response in patients with conditions commonly assessed by using PET, such as colorectal and breast cancers. Survival and follow-up data from both institutions were obtained and included in this analysis. The institutional review boards from both institutions approved our Health Insurance Portability and Accountability Act–compliant study, and all patients provided informed consent.

Inclusion criteria were as follows: *(a)* chemorefractory or progressive liver-dominant metastases; *(b)* being a nonsurgical candidate; *(c)* Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; *(d)* noncompromised pulmonary function; *(e)* the ability to undergo angiography and selective visceral catheterization; *(f)* adequate hematology (granulocyte count $\geq 1.5 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L) and renal function (creatinine level $\leq$ 2.0 mg/dL [176.8 μmol/L]); *(g)* adequate liver function (bilirubin level $\leq$ 2.0 mg/dL [34.2 μmol/L]); and *(h)* limited extrahepatic disease not deemed clinically important by the referring physician. Exclusion criteria were as follows: *(a)* other planned systemic or local-regional therapy for their cancer; *(b)* liver failure (bilirubin level > 2.0 mg/dL [34.2 μmol/L]); *(c)* evidence of any uncorrectable flow to the gastrointestinal tract observed at angiography or technetium 99m macroaggregated albumin imaging; and *(d)* greater than 30 Gy (16.5 mCi) estimated to be delivered to the lungs in a single administration or 50 Gy in multiple administrations.

Patient Referral and Work-up

Progression of liver metastases in patients was documented by using two consecutive imaging studies (CT or MR imaging), and patients were referred to interventional radiology for treatment by the attending medical or surgical oncologists (M.F.M., A.B., R.M., M.T., S.B.N., J.M.S.). After obtaining relevant laboratory test results (liver function tests, complete blood count, metabolic panel) and clinical history, patients underwent pretreatment angiography with selective visceral catheterization. Preprocedural angiography was performed to evaluate anatomy and identify vessels that required intervention such as embolization. The estimated shunt fraction of ^{90}Y to the lungs was also calculated at that time (1,12–17). Baseline images were evaluated for the percentage of tumor burden in the liver, presence of extrahepatic metastases, portal ve-

Advance in Knowledge

- The efficacy of radioembolization is demonstrated by an 87% radiologic response rate.

Implication for Patient Care

- Patients with good performance status and liver-dominant disease may obtain some clinical benefit from radioembolization.

Published online before print
10.1148/radiol.2472062029

Radiology 2008; 247:507–515

Abbreviations:
CI = confidence interval
ECOG = Eastern Cooperative Oncology Group

Author contributions:
Guarantor of integrity of entire study, R.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, K.T.S., R.J.L., M.F.M., B.A., A.A.N., C.Y.O.W., K.G.T., R.S.; clinical studies, K.T.S., R.J.L., M.F.M., B.A., R.K.R., V.L.G., O.B., R.M., M.T., C.Y.O.W., F.H.M., S.B.N., J.M.S., R.A.O., R.S.; statistical analysis, R.J.L., M.F.M., B.A., R.A.O., R.S.; and manuscript editing, R.J.L., B.A., R.K.R., A.B., F.H.M., K.G.T., R.A.O., R.S.

Clinical trial registration no. NCT00532740.

See Materials and Methods for pertinent disclosures.

nous occlusion, and the overall number of lesions.

Treatment and Follow-up Evaluation

Depending on the extent of disease within the liver at presentation, patients received either bilobar (right and left lobe) or unilobar treatment. For bilobar treatment, the first lobe treatment was followed by the second lobe treatment approximately 30 days later. No whole liver infusions were performed. Lobar treatment was targeted to deliver 120 Gy by using previously published dosimetry techniques (18). Infusion of ^{90}Y microspheres (TheraSphere) was performed by four interventional radiologists (R.S., R.K.R., K.T.S., and R.J.L. with 8, 8, 5, and 2 years of experience, respectively). Baseline imaging with spiral CT or dynamic gadolinium-enhanced MR imaging was performed prior to treatment for all patients. For those patients receiving bilobar treatment, imaging was repeated just prior to the second lobar treatment (30–45 days) and again at 3 months after first imaging. Patients undergoing unilobar treatment were scheduled for imaging every 30 days and then once every 3 months. Patients were followed up with imaging every 3 months until the patient died. Laboratory and clinical toxicity results (including lymphocytes) were assessed at each clinic visit and were classified by using the National Cancer Institute common toxicity criteria (version 3.0) (grade 0 = normal, grade 1 = more than upper limit normal [ULN] to 1.5 times ULN, grade 2 = more than 1.5 to three times ULN, grade 3 = more than three to 10 times ULN, grade 4 = more than 10 times ULN). Procedural complications were classified by using the standards established by the Society of Interventional Radiology (19). All patients were prescribed a 2-week course of proton pump inhibitors. Patients without diabetes received a 5-day methylpredisolone dose pack to counteract fatigue.

Data Collection and Outcome Measures

All medical, laboratory, and clinical data were prospectively collected. Because use of ^{90}Y microspheres is a liver-directed therapy, tumor response was limited to an assessment of hepatic lesions. Tumor response at CT or MR imaging was determined for a maximum of four measurable lesions (>1 cm) per patient in terms of the product of the greatest cross-sectional tumor length and the length of the corresponding orthogonal projection (cross product). Corresponding lesions from baseline and posttreatment studies were compared during venous and arterial contrast phases to assess tumor morphology and size changes. Complete response was defined as a change in the sum of the cross products to zero (ie, a 100% reduction); partial response, as a decrease in the sum of cross products by at least 50%; stable disease, as a decrease in the sum of cross products by less than 50% or an increase less than 25%; and progression, as an increase in the sum of cross products by at least 25% (20). Posttreatment studies were compared side by side on a computer display with pretreatment images and were assessed simultaneously by three board-certified radiologists (R.S.; R.J.L.; and F.H.M., who had 14 years of experience). The primary end point was survival. Survival was calculated for the entire group and was then stratified by age, tumor vascularity, tumor number, and tumor type. Secondary end points included clinical and laboratory toxicities, as well as tumor response.

Statistical Analysis

All statistical analysis was performed by using software (SAS, version 8.2; SAS Institute, Cary, NC). The treated-patient sample was assessed relative to demographics, functional ECOG performance status, tumor burden, and liver function laboratory measurements before treatment. Median, minimum, and maximum values were used to describe the doses (in grays) delivered to the treated liver, which was categorized by the location (bilobar, right lobe, or left lobe) of tumor burden at presentation. Lung dose (in grays) was accumulated during treatments, which was based on the percentage of activity estimated to flow to the lungs at technetium 99m macroaggregated albumin imaging.

Survival analyses were conducted by using time from the first treatment until death or by censoring at the last follow-up date. Median survival (in days) and corresponding 95% confidence intervals (CIs) were computed by using the Kaplan-Meier method (21). The log-rank statistic was used for statistical significance testing of survival distributions between the various subgroups of patients (22). A P value of less than .05 indicated a significant difference.

Results

Demographics

One hundred thirty-seven patients underwent a total of 225 administrations of ^{90}Y microspheres by using transcatheter intraarterial infusion (Table 1). The median age of patients was 61 years, and there were 66 men and 71 women. Primary sites (origins) of malignancy included colon (n = 51), breast (n = 21), neuroendocrine (n = 19),

Table 1

Patient Demographics and Treatment

Parameter	Datum
Age (y)	
< 65	80 (58)
≥ 65	57 (42)
Sex	
Men	66 (48)
Women	71 (52)
ECOG score	
0	82 (60)
1	40 (29)
2	14 (10)
3	1 (<1)
No. of treatments	
Total	225
Mean	1.6
Range of number of treatments	
1	69 (50)
2	52 (38)
3	14 (10)
4	1 (<1)
5	0 (0)
6	1 (<1)

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

cholangiocarcinoma ($n = 7$), pancreas ($n = 6$), lung ($n = 5$), melanoma ($n = 5$), renal ($n = 4$), esophageal ($n = 3$), adenocarcinoma unknown primary ($n = 3$), ovary ($n = 2$), adrenal ($n = 1$), angiosarcoma ($n = 1$), bladder ($n = 1$), cervical ($n = 1$), duodenal ($n = 1$), gallbladder ($n = 1$), gastric ($n = 1$), lymphoma ($n = 1$), parotid ($n = 1$), squamous cell carcinoma ($n = 1$), and thyroid ($n = 1$). All patients were considered to have unresectable disease, and none responded to standard-of-care polychemotherapy (Table 2). All patients' performance status was evaluated by using the ECOG criteria (Table 3). Patients received a mean number of 1.6 treatments (range, 1–6), and all were released from the hospital within 6 hours of the procedure.

Baseline Imaging Characteristics

Baseline tumor burden before therapy is shown in Table 4. Eighty percent of patients had a tumor burden of 25% or less, 15% had 26%–50% tumor replacement, and 5% had 51%–75% tumor burden. No patients had greater than 76% tumor replacement. The presence of any prior treatments to the liver was also noted. Eighty-four percent of patients had not previously undergone any liver-directed therapies, such as radiofrequency ablation or transarterial chemoembolization. Limited extrahepatic metastases were noted in 50% of all

Table 2

Patient Demographics according to Primary Disease

Parameter	Datum
Colon	
Men	33 (65)
Women	18 (35)
Mean age (y)	63.1
Age < 65 years	27 (53)
Age ≥ 65 years	24 (47)
Breast	
Men	0 (0)
Women	21 (100)
Mean age (y)	52.3
Age < 65 years	16 (76)
Age ≥ 65 years	5 (24)
Neuroendocrine	
Men	10 (53)
Women	9 (47)
Mean age (y)	57.2
Age < 65 years	13 (68)
Age ≥ 65 years	6 (32)
Cholangiocarcinoma	
Men	5 (71)
Women	2 (29)
Mean age (y)	64.7
Age < 65 years	3 (43)
Age ≥ 65 years	4 (57)
Other locations	
Men	18 (46)
Women	21 (54)
Mean age (y)	64.4
Age < 65 years	21 (54)
Age ≥ 65 years	18 (46)

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

Table 3

ECOG Performance Status in Patients according to Tumor Groups

Status	Colon	Breast	Neuroendocrine	Cholangiocarcinoma	Other Locations
0	34 (67)	12 (57)	15 (79)	4 (57)	17 (44)
1	12 (24)	6 (29)	3 (16)	3 (43)	16 (41)
2	5 (10)	3 (14)	1 (5)	0 (0)	5 (13)
3	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)

Note.—Data are numbers of patients, with percentages in parentheses.

Table 4

Baseline Imaging Results and Laboratory Characteristics of Patients

Parameter	Men ($n = 66$)	Women ($n = 71$)	Total ($n = 137$)
Tumor burden			
0%–25%	54 (82)	55 (77)	109 (80)
26%–50%	7 (11)	14 (20)	21 (15)
51%–75%	5 (8)	2 (3)	7 (5)
≥76%	0 (0)	0 (0)	0 (0)
Distribution			
Unilobar	14 (21)	13 (18)	27 (20)
Bilobar	52 (79)	58 (82)	110 (80)
Total bilirubin level			
Grade 0 (normal)	57 (86)	66 (93)	123 (89.8)
Grade 1	5 (8)	3 (4)	8 (5.8)
Grade 2	4 (6)	2 (3)	6 (4.4)
Previous liver directed therapy			
Yes	13 (20)	9 (13)	22 (16)
No	53 (80)	62 (87)	115 (84)
Extrahepatic metastases			
Yes	25 (38)	43 (61)	68 (50)
No	41 (62)	28 (39)	69 (50)
Portal vein occlusion			
Yes	2 (3)	3 (4)	5 (4)
No	64 (97)	68 (96)	132 (96)
More than four metastatic lesions			
Yes	39 (59)	52 (73)	91 (66)
No	27 (41)	19 (27)	46 (34)
Standard mesenteric anatomy			
Yes	36 (55)	41 (58)	77 (56)
No	30 (45)	30 (42)	60 (44)

Note.—Data are numbers of patients, with percentages in parentheses.

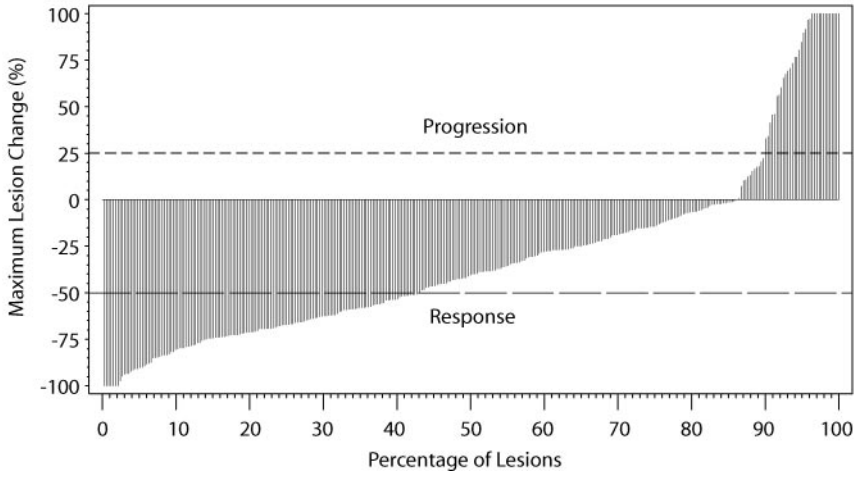
patients. The portal vein was occluded in 4% of patients. Sixty-six percent of patients had more than four liver lesions at their initial evaluation. Forty-four percent of patients had mesenteric anatomy that required some transarterial intervention, such as coil embolization prior to treatment (eg, gastroduodenal, right gastric, falciform, or accessory left gastric artery embolization). Sixty-eight of 137 patients underwent baseline PET.

Tumor Response

A total of 332 lesions in 137 patients were measured. The median number of follow-up studies was two (range, 1–10). The mean imaging follow-up time was 159 days (95% CI: 22, 758). The mean and median lesion size was 4.2 and 2.8 cm, respectively (range, 1.0–16.2 cm). The time to partial response was 133 days (95% CI: 120, 170). A complete response was demonstrated in 2.1% of lesions, and 40.7% of lesions had a partial response, for an overall World Health Organization response rate of 42.8%. Forty-seven percent of lesions had stable disease, and 10.2% had progression according to World Health Organization criteria. When looking at radiologic criteria alone (ie, any decrease in tumor size after treatment), there was an 87% tumor response to treatment and a 13% rate of progression (Figure). The median time to progression was 462 days (95% CI: 422, 541). The median duration of response was 433 days (95% CI: 341, 541). There was a 50% decrease in tumor markers in 20 (37%) of 54 patients with available pre- and posttreatment data. Of the 68 patients with initial PET scans, the response assessment at PET was as follows: complete response, 9; partial response, 52; and progressive disease, 12. Some patients underwent more than one PET scan; however, the overall response rate was 90% (61 of 68 patients).

Safety Assessment

All patients were treated on an outpatient basis and hence released on the same day as treatment. The most common clinical toxicity was fatigue (56%), followed by nonspecific self-limiting abdominal pain (26%), nausea (23%), fever (6%), anorexia (6%), diarrhea (6%), transient gustatory change (1.5%), groin hematoma (1.5%), and chills (1.5%). Of all patients, 89.8% had a normal bilirubin level at baseline, 5.8% had grade 1 bilirubin toxicity, and 4.4% had grade 2 toxicity (Table 5). After treatment, 100 patients (76.3%) showed no change in serum total bilirubin level after therapy. Six patients had grade 3 or 4 bilirubin toxicity; four improved from baseline levels (Table 5). There was no significant difference in bilirubin toxicities on the basis of tumor type. Twenty-nine percent had no clinical complaints after treatment.



Waterfall plot demonstrates maximum change from baseline in cross product of 332 lesions after therapy.

Table 5

Bilirubin Toxicity 90 Days after Baseline

Bilirubin Level	Men	Women	Total
No change	47	53	100
Worsened from baseline			
Grade 0 to 3	1	5	6
Grade 0 to 4	1	0	1
Grade 2 to 3	0	1	1
Improved from baseline			
Grade 1 to 0	2	0	2
Grade 2 to 0	2	0	2

Note.—Data are numbers of patients. Follow-up laboratory data were available in 131 patients.

Follow-up data on lymphocytes was available in 131 patients. Eighty-six (62.8%) patients had a normal lymphocyte count prior to treatment. At follow-up, 44.5% remained unchanged from their preprocedural values. Sixty-eight (49.6%) had a decrease in their lymphocyte counts after treatment (Table 6).

Five patients had complications that required subsequent interventions. These were classified as major complications. There was one case of gastrointestinal ulceration (biopsy proved) and one case of radiation-induced cholecystitis requiring surgery. Two patients developed bilomas requiring percutaneous external drainage. One pa-

Table 6

Lymphocyte Data

Parameter	Men ($n = 66$)	Women ($n = 71$)	All Patients ($n = 137$)
Baseline			
Low	25 (38)	26 (37)	51 (37.2)
Normal	41 (62)	45 (63)	86 (62.8)
Follow-up			
Low	58 (88)	57 (80)	115 (83.9)
Normal	6 (9)	10 (14)	16 (11.7)
Missing	2 (3)	4 (6)	6 (4.4)
Results from baseline to follow-up			
Low to >low	25 (38)	22 (31)	47 (34.3)
Low to >normal	. . .	2 (3)	2 (1.5)
Normal to >low	33 (50)	35 (49)	68 (49.6)
Normal to>normal	6 (9)	8 (11)	14 (10.2)
Missing	2 (3)	4 (6)	6 (4.4)
Cumulative days of lymphocyte depression			
Mean	223.8	220.3	222.0
Median	173.0	172.0	172.0
Minimum	17	1	1
Maximum	964	954	964
Patients returning to normal lymphocyte level	12 (36)	12 (34.3)	24 (35.3)
Days to return to normal level			
Mean	82.1	130.5	106.3
Median	69.5	105.0	87.0
Minimum	15	29	15
Maximum	268	392	392

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

Table 7

Yttrium 90 Dosing Parameters

Parameter	Men	Women	All Patients
No. of treatments	107	118	225
Lobe volume (cm^3)			
Mean	1033	826	924
Median	931	800	840
Minimum	250	300	250
Maximum	2700	1800	2700
Activity at time of infusion (GBq)			
Mean	2.34	1.97	2.15
Median	1.86	1.80	1.83
Minimum	0.7	0.8	0.7
Maximum	6.9	4.4	6.9
Lung shunt fraction (%)			
Mean	5.54	5.00	5.26
Median	4.00	3.30	3.70
Minimum	1.00	0.00	0.00
Maximum	26.6	22.4	26.6
Lung dose per treatment (Gy)			
Mean	5.98	4.58	5.23
Median	3.54	2.79	3.18
Radiation dose to site (Gy)			
Mean	105.5	109.4	107.5
Median	108.4	114.1	112.8

tient with previous hepaticojejunostomy developed a hepatic abscess requiring external drainage.

Treatment Dosimetry

The median volume of the treated lobes was 840 cm^3 (range, 250–2700 cm^3). The median activity at the time of infusion in the dose vial was 1.83 GBq (range, 0.7–6.9 GBq). The median residual activity in the vial was 1.8% (0%–30.7%). The median lung shunt fraction was 3.7% (range, 0%–26.6%). The median lung dose was 3.18 Gy. The mean radiation absorbed dose per site was 112.8 Gy (range, 27–180 Gy) (Table 7).

Survival

Seventy (51.1%) patients died during follow-up (Table 8). Mean clinical follow-up was 287 days. The median survival for all patients was 300 days (95% CI: 234, 591). The 1-year survival rate for the group was 47.8%, and 2-year survival rate was 30.9%. Fifty-five percent of patients were younger than 65 at initial treatment. The median survival rate for those younger than 65 was 255 days, compared with 591 days for those older than 65 years old. Patients with hypervascular tumors at angiography had a median survival time of 300 days, whereas those with hypovascular tumors had a median survival of 261 days. Similarly, patients with tumors that were hypervascular at cross-sectional imaging had a median survival of 306 days, compared with 284 days for those with hypovascular tumors. Patients with four or fewer lesions had a median survival rate of 632 days, but those with more than four lesions had a median survival rate of 234 days. A subset analysis of colorectal, neuroendocrine, and noncolorectal, nonneuroendocrine tumors in patients demonstrated median survival rates of 457 (15.2 months), 776 (25.9 months), and 207 (6.9 months) days, respectively.

Discussion

A large number of patients with metastatic disease of the liver either initially

Table 8

Survival Analysis

Parameter	No. of Patients	No. of Patients Who Died*	Mean Survival (d)	Median Survival (d)	1-year Survival (%)	2-year Survival (%)	*P* Value
Patients	137	70 (51.1)	418	300	47.8	30.9	.434
Men	66	39 (59)	393	264	43.4	24.4	
Women	71	31 (44)	438	562	53.1	40.6	
Age (y)							.211
<65	80	44 (55)	386	255	40.9	25.6	
≥65	57	26 (46)	449	591	57.2	38.6	
Primary diagnosis							.021
Colon	51	25 (49)	416	457	53.7	26.7	
Neuroendocrine	19	6 (32)	591	776	69.3	69.3	
Noncolorectal, nonneuroendocrine	67	39 (58)	341	207	36.8	26.5	
ECOG category							<.001
0	82	23 (28)	592	731	75.3	51.9	
>0	55	47 (85)	169	137	9.6	0	
ECOG category (colon)							<.001
0	34	9 (26)	553	657	82.1	43.6	
>0	17	16 (94)	195	160	8.8	0	
ECOG category (neuroendocrine)							.012
0	15	3 (20)	678	776	83.3	83.3	
>0	4	3 (75)	181	219	25.0	25.0	
ECOG category (noncolorectal, nonneuroendocrine)							<.001
0	33	11 (33)	534	731	64.8	51.8	
>0	34	28 (82)	144	124	8.3	0	
Angiographic vascularity							.955
Hypervascular	108	56 (51.9)	420	300	48.5	25.9	
Hypovascular	29	14 (48)	382	261	47.9	32.8	
CT vascularity							.671
Hypervascular	24	15 (63)	408	306	47.6	30.5	
Hypovascular	113	55 (49)	384	284	48.3	31.1	
Tumor burden							.001
0%–25%	109	49 (45.0)	457	506	54.6	35.8	
26%–50%	21	14 (67)	300	181	33.2	22.1	
51%–75%	7	7 (100)	147	158	0	0	
≥76%	0	0 (0)	. . .	. . .	. . .	. . .	
Tumor burden (colon)							.001
0%–25%	41	16 (39)	458	562	64.8	38.1	
26%–50%	7	6 (86)	271	151	21.4	0	
51%–75%	3	3 (100)	141	158	0	0	
≥76%	0	0 (0)	. . .	. . .	. . .	. . .	
Tumor burden (neuroendocrine)							.094
0%–25%	14	3 (21)	666	776	81.8	81.8	
26%–50%	3	1 (33)	52	. . .	66.7	66.7	
51%–75%	2	2 (100)	234	234	0	0	
≥76%	0	0 (0)	. . .	. . .	. . .	. . .	
Tumor burden (noncolorectal, nonneuroendocrine)							.016
0%–25%	54	30 (56)	355	234	39.2	22.4	
26%–50%	11	7 (64)	137	181	31.2	31.2	
51%–75%	2	2 (100)	70	70	0	0	
≥76%	0	0 (0)	. . .	. . .	. . .	. . .	
More than four lesions							.013
Yes	91	51 (56)	370	234	37.4	28.4	
No	46	19 (41)	504	632	68.6	38.1	

* Data in parentheses are percentages.

do not respond to systemic chemotherapy or ultimately have disease that becomes chemorefractory. For these patients, liver-directed therapies aimed at treating liver metastases directly provide an effective alternative. The purpose of this open-label phase II study was to assess the safety and efficacy of radioembolization in this patient population.

The number of men and women in our cohort was similar, as was the number of patients younger than age 65 and those 65 and older. Half the patients received only one treatment, while the remainder required multiple radioembolizations. Given that the therapy used has been shown to be minimally embolic, multiple repeated treatments through the same artery are possible given the preserved vascular patency (23). This is because the end point of this therapy is not complete macrovascular occlusion and embolization. Rather, the primary modes of action of this therapy are tissue radiation, not tissue ischemia, and microvascular embolization without reaching stasis.

Radioembolization with this therapy has been shown to be clinically well tolerated (1,4,24). Our study results confirm this finding because only two patients experienced the major complications of radiation cholecystitis and ulceration. Clinically, the most common complaints were fatigue, pain, and nausea. Almost 30% of patients had no complaints after treatment. Patients were all treated on a same-day basis with minimal restrictions after the procedure. In the majority of patients (76.3%), there was no change in serum bilirubin level at 90 days. Seven patients had grade 3 or 4 bilirubin toxicity; all of these toxicities were attributed to disease progression. Four patients actually had an improvement in their bilirubin toxicities after treatment. One possible explanation for this phenomenon is that the initial elevated bilirubin level was caused by mild biliary compression by the tumor, resulting in obstruction. After treatment, a decrease in tumor size may result in improvement of the microscopic obstruction. In 44.3% of patients, there was no change in the lymphocyte count from preprocedural levels; however, 49.6% decreased from normal levels. Despite this lymphopenia, this finding was of no clinical consequence, because no patients had signs or symptoms of opportunistic infections.

Tumors treated had a mean diameter of 4.2 cm. Median time to partial response was 133 days. This is slightly longer than previous reports of 75–82 days with this therapy (25,26). Overall, there was a response rate of 42.8% at the lesional level (2.1% complete response, 40.7% partial response). However, because the World Health Organization criteria for response require at least a 50% decrease in size of the lesion, many tumors that had a radiologic response were still classified as stable disease. The actual biologic response rate of treated tumors was 87%, with those lesions showing at least some decrease in size after therapy. Although the progression rate for this group was 10.2% by using World Health Organization criteria, the actual radiologic progression rate was 13% (any increase in size). Functional response rate was supported by the 90% response at PET observed in this cohort of patients. Twenty (37%) of 54 patients had a 50% decrease in tumor marker levels after treatment.

Differences in survival were seen with different tumor type, ECOG performance status, tumor burden, imaging findings (hypovascular or hypervascular tumors at angiography and cross-sectional imaging), and number of tumors. Median survival rate for patients with colorectal cancer, neuroendocrine tumors, and noncolorectal, nonneuroendocrine tumors were 457, 776, and 207 days, respectively. This subset analysis into three categories has set the stage for further investigation in these patient cohorts.

Patients with an ECOG performance status of 0 had a median survival time of 731 days, while those with an ECOG performance status of more than 0 had a median survival of 137 days. This trend was maintained across all tumor types and reached statistical significance, supporting the notion of poor prognosis once cancer-related symptoms appear (ECOG $>$ 0). A similar phenomenon was noted with stratification according to tumor burden. Patients with greater tumor burden appear to have a significantly lower survival rate than patients with a tumor burden of 0%–25% (506 days). Not surprisingly, this difference was also maintained for patients with colorectal cancer but not for those with neuroendocrine tumors or other tumor types. Patients with neuroendocrine tumors classically have prolonged survival rates despite significant disease burden.

At cross-sectional imaging, 82.5% of patients had hypovascular lesions in the liver, while at angiography 78.8% of tumors appeared hypervascular. All patients were treated in the same manner, and there was no significant difference in the median survival rate or the 1- and 2-year survival rates. Patients with hypervascular tumors at angiography had a median survival time of 300 days, whereas those with hypovascular tumors had a median survival of 261 days. Similarly, patients with tumors that were hypervascular at cross-sectional imaging had a median survival time of 306 days, compared with 284 days for those with hypovascular tumors. These findings suggest the following: *(a)* significant discrepancy exists in the perceived vascularity of liver metastases as assessed at cross-sectional imaging compared with that at the reference standard (angiography) and *(b)* the degree of vascularity is not predictive of survival. This implies that the radiologic appearance of tumors may not affect the delivery of microspheres and should not be used to include or exclude patients for this type of therapy. A statistically worse survival rate was noted in patients with more than four liver lesions (234 days) compared with those with four or fewer (632 days), a finding consistent with the surgical literature for colorectal cancer.

There were limitations to our study. First, this is a heterogeneous cohort treated and observed longitudinally without a true comparator arm. However, given that these are patients with chemorefractory disease who have pre-

viously not responded to standard-of-care therapies, no such control arm exists. The closest comparison of patients who did not respond to systemic therapy and were treated with supportive care demonstrated an overall survival of 6 months (27). Second, many of these patients were treated prior to the clinical availability of growth factor inhibitors, which made the impact of new chemotherapeutic agents difficult to assess. Third, this was an open-label phase II study with a heterogeneous population, which limits the ability to generalize the findings. However, surgical treatment in similarly heterogeneous patients has been previously reported to be beneficial (28–31). For radioembolization, subset analyses of these data are now being used to identify specific patients who might definitively benefit from this treatment. This study was performed at two institutions and warrants independent validation.

In conclusion, radioembolization represents a treatment option in patients with chemorefractory liver metastases. This therapy was able to halt or reverse progression at imaging in 87% of lesions with acceptable toxicity. Functional response was 90% at PET. Our study results suggest that radioembolization may benefit patients with chemorefractory liver metastases and may potentially affect overall or progression-free survival compared with that of supportive care. Given the demonstration of anatomic and functional response confirming tumoricidal effects from radioembolization, controlled studies in specific patient subsets in combination with chemotherapeutics or biologics are now being initiated.

Acknowledgments: The authors thank Suzanne Hackett, MS, and the team from StatWorks (Carrboro, NC) for managing the data and validating its integrity.

References

1. Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro B. Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical follow-up. J Nucl Med 1994;35(10):1637–1644.
2. Herba MJ, Illescas FF, Thirlwell MP, et al. Hepatic malignancies: improved treatment with intraarterial Y-90. Radiology 1988;169(2):311–314.
3. Herba MJ, Thirlwell MP. Radioembolization for hepatic metastases. Semin Oncol 2002;29(2):152–159.
4. Lewandowski RJ, Thurston KG, Goin JE, et al. 90Y microsphere (TheraSphere) treatment for unresectable colorectal cancer metastases of the liver: response to treatment at targeted doses of 135–150 Gy as measured by [18F] fluorodeoxyglucose positron emission tomography and computed tomographic imaging. J Vasc Interv Radiol 2005;16(12):1641–1651.
5. Carr BI. Hepatic arterial 90Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients. Liver Transpl 2004;10(2 suppl 1):S107–S110.
6. Georgiades CS, Salem R, Geschwind JF. Radioactive microspheres for the treatment of HCC. In: Golzarian J, ed. Vascular embolotherapy: a comprehensive approach. New York, NY: Springer, 2005; 141–148.
7. Geschwind JF, Salem R, Carr BI, et al. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. Gastroenterology 2004;127(5 suppl 1):S194–S205.
8. Liu MD, Uaje MB, Al-Ghazi MS, et al. Use of Yttrium-90 TheraSphere for the treatment of unresectable hepatocellular carcinoma. Am Surg 2004;70(11):947–953.
9. Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival. J Vasc Interv Radiol 2005;16(12):1627–1639.
10. Goin JE, Salem R, Carr BI, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. J Vasc Interv Radiol 2005;16(2 pt 1):205–213.
11. Goin JE, Salem R, Carr BI, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: a risk-stratification analysis. J Vasc Interv Radiol 2005;16(2 pt 1):195–203.
12. Gray B, Van Hazel G, Hope M, et al. Randomised trial of SIR-spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001;12(12):1711–1720.
13. Gray BN, Anderson JE, Burton MA, et al. Regression of liver metastases following treatment with yttrium-90 microspheres. Aust N Z J Surg 1992;62(2):105–110.
14. Gray BN, Burton MA, Kelleher DK, Anderson J, Klemp P. Selective internal radiation (SIR) therapy for treatment of liver metastases: measurement of response rate. J Surg Oncol 1989;42(3):192–196.
15. Lau WY, Ho S, Leung TW, et al. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90yttrium microspheres. Int J Radiat Oncol Biol Phys 1998;40(3):583–592.
16. Lau WY, Leung WT, Ho S, et al. Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. Br J Cancer 1994;70(5):994–999.
17. Salem R, Thurston KG, Carr BI, Goin JE, Geschwind JF. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. J Vasc Interv Radiol 2002;13(9 pt 2):S223–S229.
18. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. I. Technical and methodologic considerations. J Vasc Interv Radiol 2006;17(8):1251–1278. [Published correction appears in J Vasc Interv Radiol 2006;17(10):1594.]
19. Omary RA, Bettmann MA, Cardella JF, et al. Quality improvement guidelines for the reporting and archiving of interventional radiology procedures. J Vasc Interv Radiol 2003;14(9 pt 2):S293–S295.
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205–216.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457.
22. Cox DR, Oaks D. Analysis of survival data. London, England: Chapman & Hall, 1984.
23. Sato K, Lewandowski RJ, Bui JT, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. Cardiovasc Intervent Radiol 2006;29(4):522–529.
24. Wong CY, Salem R, Qing F, et al. Metabolic response after intraarterial 90Y-glass microsphere treatment for colorectal liver metastases: comparison of quantitative and visual analyses by 18F-FDG PET. J Nucl Med 2004;45(11):1892–1897.
25. Salem R, Lewandowski R, Roberts C, et al. Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. J Vasc Interv Radiol 2004;15(4):335–345.
26. Kulik LM, Atassi B, van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol 2006;94(7):572–586.
27. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352(9138):1413–1418.
28. Ercolani G, Grazi GL, Ravaioli M, et al. The role of liver resections for noncolorectal, nonneuroendocrine metastases: experience with 142 observed cases. Ann Surg Oncol 2005;12(6):459–466.
29. Harrison LE, Brennan MF, Newman E, et al. Hepatic resection for noncolorectal, nonneuroendocrine metastases: a fifteen-year experience with ninety-six patients. Surgery 1997;121(6):625–632.
30. Schwartz SI. Hepatic resection for noncolorectal nonneuroendocrine metastases. World J Surg 1995;19(1):72–75.
31. Weitz J, Blumgart LH, Fong Y, et al. Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. Ann Surg 2005;241(2):269–276.