Radioembolization With Selective Internal Radiation Microspheres for Neuroendocrine Liver Metastases

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BACKGROUND. There are limited effective treatment options available and a poor 5-year survival for patients with inoperable neuroendocrine liver metastases (NETLMs). In this study, the authors prospectively assessed the safety and efficacy of treatment with yttrium 90 (^{90}Y) radioactive microspheres for patients with unresectable NETLMs.

METHODS. Radioactive ^{90}Y resin microspheres (selective internal radiation [SIR-Spheres]) were administered through a temporarily placed percutaneous hepatic artery catheter concomitantly with a 7-day systemic infusion of 5-fluorouracil to patients with progressive, unresectable NETLMs. Patients were monitored prospectively, and the response to treatment was measured by using cancer markers and tumor size on computed tomography imaging studies.

RESULTS. Thirty-four patients (22 men) with a mean age 61 years (range, 32-79 years) who had unresectable NETLMs were treated between December 2003 and December 2005. The mean (±standard error) follow-up was 35.2 ± 3.2 months. The site of the primary neuroendocrine tumor was the bronchus in 1 patient, the medullary thyroid in 2 patients, gastrointestinal in 15 patients, the pancreas in 8 patients, and of unknown origin in 8 patients. The tumors were classified as vipoma (1 tumor), somatostatinoma (1 tumor), glucagonoma (2 tumors), large cell (3 tumors), carcinoid (25 tumors), and of unknown origin (2 tumors). Complications after ^{90}Y radioembolization included abdominal pain, which was mild to severe; nausea and fever; and lethargy that lasted from 1 week to 1 month. Two patients developed biopsy-proven radiation gastritis, 1 patient developed a duodenal ulcer, and there was 1 early death from liver dysfunction and pneumonia. Subjective changes from recorded baseline hormone symptoms were reported every 3 months. Symptomatic responses were observed in 18 of 33 patients (55%) at 3 months and in 16 of 32 patients (50%) at 6 months. Radiologic liver responses were observed in 50% of patients and included 6 (18%) complete responses and 11 (32%) partial responses, and the mean overall survival was 29.4 ± 3.4 months). In patients who had evaluable chromogranin A (CgA) marker levels, there was a fall in CgA marker levels after ^{90}Y radioembolization in 19 patients (26%) at 1 month, in 19 patients (41%) at 3 months, in 15 patients (43%) at 6 months, in 11 patients (42%) at 12 months, in 8 patients (38%) at 24 months, and in 3 patients (46%) at 30 months.

CONCLUSIONS. In this open study of 34 patients, the results demonstrated that radioembolization with ^{90}Y resin microspheres can achieve relatively long-term responses in some patients with nonresectable NETLMs. ***Cancer*** **2008;113:921–9.**

KEYWORDS: selective internal radiation spheres, radioembolization, unresectable neuroendocrine tumors, liver metastases, yttrium 90.

Although the recognition and treatment of primary gastroenteropancreatic neuroendocrine tumor (NET) has improved over the

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last decades, liver metastases (LMs) from NET (NETLMs) are common.[1] NETLMs frequently are responsible for symptoms because of hormone secretion, pressure on structures, or replacement of liver. Resection and ablation can be associated with long-term survival,[2,3] but the treatments seldom are curative, and the 5-year survival rate for patients who have unresected LMs is between 25% and 50%.[1] Ablative therapies (radiofrequency, laser therapy, or cryotherapy) are limited to the small proportion of patients with few tumors.[4,5,6]

Systemic chemotherapy with streptozotocin achieves modest response rates of limited duration, is better for pancreatic NETs compared with metastatic carcinoid tumors,[7] and frequently is accompanied by significant toxicity.[8] The Eastern Cooperative Oncology Group's randomized study of doxorubicin with fluorouracil or streptozocin with fluorouracil followed by dacarbazine at disease progression in patients with metastatic carcinoid demonstrated an 8.2% response rate but significant treatment-related toxicity.[9] Although chemoembolization can achieve a response in up to 79% of patients, the effects usually are of short duration, and a survival benefit has not been demonstrated.[10,11]

Patients with NETLMs can be affected variously by carcinoid syndrome or by endocrine symptoms that seriously can reduce quality of life. Somatostatin analogues can ameliorate hormone symptoms, but it is not clear that they have altered the survival of patients with metastatic carcinoid.[12]

Radioembolization with yttrium 90 (^{90}Y) has been used for well over a decade to treat patients with nonresectable LMs from primary and secondary liver cancers and had produced encouraging results.[13-18] Yttrium 90 is a pure β emitter that has average range of penetration that is 5 mm with the standard dose of 2 gigabecquerel (GBq) contained in 50 million resin microspheres. In 7 patients with nonresectable hepatocellular carcinoma, Lau et al reported a 50% tumor response in 27% of patients who received ^{90}Y.[15] In patients with colorectal LMs, a decrease in serum carcinoembryonic (CEA) levels was achieved in >90% of patients, and 82% of patients had some decrease in tumor size as measured by computed tomography (CT) imaging.[13,14]

It is recognized that NETLMs are hypervascular tumors, and this characteristic has been used to obtain therapeutic benefit with hepatic artery ligation, intermittent occlusion, and embolization treatments.[20] In this, we prospectively assessed the safety and efficacy of ^{90}Y radioactive resin microspheres in patients with unresectable NETLMs.

MATERIALS AND METHODS

Methods

Thirty-four patients with NETLMs were treated with ^{90}Y microspheres (selective internal radiation spheres [SIR-Spheres]; Sirtex, Sydney, Australia) between December 2003 and December 2005. All patients who were treated were enrolled in a prospective study with Human Research Ethics Committee approval (South East Sydney Area Health Service Ethics Committee Approval No. 03/173; D.L.M.), and the study was conducted at St. George Hospital, Sydney.

All patients who were considered for study entry were current, single-institution patients with progressive, unresectable NET. Inclusion criteria stipulated that all patients had radiologically proven LMs from primary neuroendocrine origin with NETLMs that were not amenable to curative surgical resection; CT evidence of demonstrated liver disease progression within the last 6 months; a patent right or left portal vein; adequate hematologic, renal, and hepatic function; no portal hypertension; prior surgery, ablation, or chemotherapy for LMs was allowed; signed informed consent; a World Health Organization performance status from 0 to 2; aged 18 years to 85 years; and an expected survival >3 months. ^{90}Y radioembolization was permitted for patients with extrahepatic disease (EHD). All 34 patients who were considered for entry fulfilled the study criteria for ^{90}Y after clinical assessment by the chief investigator and a multidisciplinary team.

Patients had a liver CT studies obtained and were reviewed clinically within 10 days before ^{90}Y treatment. A hepatic angiogram with 99m technetium-labeled macroaggregated albumin (^{99m}Tc-MAA) scintigraph also was obtained to demonstrate any aberrant hepatic anatomy, distribution of isotope within the liver, and the percentage of pulmonary shunting. High-percentage shunting can cause radiation pneumonitis. Only patients who had <20% arteriovenous lung shunting on the ^{99m}Tc-MAA scan and a tumor/normal liver uptake ratio >2:1 were eligible. The tomographic regions were determined as regions of interest around the tumor compared with normal parenchyma, and the tumor volume/normal liver area was assessed by the nuclear medicine department, which coregistered the pre-^{90}Y CT liver scan and the ^{99m}Tc-MAA scan. The ^{90}Y GBq dose was adjusted for tumor volume and lung shunt fraction. The systemic 5-fluorouracil dose was based on patient body surface area, and a systemic, continuous, 5-fluorouracil infusion (225 mg/m^2) was administered as a radiosensitizer concurrently for 7 days through a peripherally inserted central catheter the day before ^{90}Y radio-

embolization. The baseline serum marker CgA level was collected.

The ^{90}Y resin microspheres (29-35 microns in diameter with a half-life of 64 hours) were injected over 10 minutes through a temporary hepatic artery catheter that was placed percutaneously through the femoral or brachial artery. Whole liver treatments were administered for bilobar NETLMs with a divided dose of 2 separate injections (two-thirds to the right lobe and one-third to the left lobe of liver). The catheter was placed into the right hepatic artery, proximal to the junction with the gastroduodenal artery, and a two-thirds dose was infused over 5 minutes. Then, the catheter was withdrawn partially and repositioned into the left hepatic artery, again avoiding the gastroduodenal junction for infusion of the remaining one-third ^{90}Y dose.

Aberrant vessels were not embolized before radioembolization. The dose of ^{90}Y resin microspheres (between 1.4 GBq and 2.6 GBq) was titrated to the extent of disease (according to User Manual guidelines). All patients had prophylaxis against carcinoid crisis. An H2 antagonist was taken for 1 month after ^{90}Y with oral analgesia as required. All patients were hospitalized overnight. Blood and biochemical levels were obtained weekly for 4 weeks then every 3 months, and tumor marker levels and CT scans were obtained monthly and then every 3 months.

Response to treatment was reported as the change from baseline measurement in tumor volume and serum CgA marker after treatment. The Response Evaluation Criteria in Solid Tumors was used to measure liver response and to assess overall disease progression.[21]

The distribution of ^{90}Y microspheres within the liver was imaged the day after treatment by measuring the Bremsstrahlung radiation emitted as the ^{90}Y β rays decelerated within the tissue. Single-photon emission CT imaging was performed, and tomographic reconstruction was achieved by using an iterative algorithm[22] that incorporated corrections for attenuation losses and resolution recovery. The reconstructed images were analyzed by classifying voxels into 3 groups—liver, tumor, and other—and the total counts in liver and tumor regions were measured. By assuming that all of the administered activity was trapped in the liver/tumor system, it was possible to calculate the initial activity distribution and, hence, to estimate the radiation-absorbed dose to both liver and tumor by using the method of voxel dose kernel convolution.[23]

Statistical Analysis

SPSS 14.0 for Windows software (SPSS Inc., Chicago, Ill) was used for data management and statistical analysis. A P value of .05 was considered significant and was used with the Kaplan-Meier product method and the log-rank test.

RESULTS

Patient Details

There were 34 patients (22 men), the mean patient age was 61 years (range, 32-79 years), and the mean follow-up (±standard error [SE]) after ^{90}Y microspheres was 35.2 ± 3.2 months. The primary NET site was the bronchus in 1 patient, the stomach in 1 patient, the medullary thyroid in 2 patients, the small bowel in 11 patients, the colon/rectum in 3 patients, the pancreas in 8 patients, and of unknown origin in 8 patients. The primary NETs were classified as vipoma in 1 patient, somatostatinoma in 1 patient, glucagonoma in 2 patients, large cell in 3 patients, carcinoid in 25 patients, and unknown in 2 patients. All patients had histologic evidence of NET, and prior treatments included liver surgery in 10 patients, systemic chemotherapy in 5 patients, and thyroid surgery in 2 patients. Twenty-five patients were receiving a somatostatin analogue at study entry.

The mean (±SE) interval from the diagnosis of primary NET to ^{90}Y treatment was 55.9 ± 11.8 months, and the mean interval from diagnosis of NETLMs to treatment with SIR therapy (SIRT) was 36.61 ± 6.72 months. At study entry, 20 patients (59%) had histologic or documented CT evidence of EHD (Tables 1, 2). The estimated percentage shunting to the lungs on ^{99m}Tc-MAA scans was 6.3% (SE, ±0.7%). The mean dose of ^{90}Y was 1.99 GBq (SE, ±0.6 GBq; range, 0.92-2.80 GBq). One patient had a 40% reduced dose of SIR-Spheres because of 17% lung shunting.

Safety

During ^{90}Y treatment, 4 patients experienced severe pain and vomiting, which were alleviated by intravenous narcotics and antiemetics. All patients reported some degree of mild-to-severe abdominal pain from 1 week to 1 month after treatment. Variable symptoms of nausea, lethargy, anorexia, and fever persisted for 1 week to 1 month for all patients and generally required nonopioid analgesia.

Three patients developed radiation gastritis demonstrated on endoscopy/biopsy at 1 month, 2 months, and 6 months after treatment because of malperfusion of ^{90}Y microspheres.[24,25] Ulceration was self-limiting in 2 patients who remained well and asymptomatic after ^{90}Y treatment with stable disease (SD) at 44 months and with a complete response (CR) at 27 months on CT imaging. The other patient, whose gastritis persisted, died at 12 months with

TABLE 1
Characteristics of Patients the With Best Liver Response to Yttrium-90 Radioembolization by Response Evaluation Criteria in Solid Tumors

CT Response in Liver	Primary Site	Prior Liver Treatments	Prior Extrahepatic Disease	% Hepatic Replacement	Follow-up, mo	SIR-Spheres: Dose Delivered, GBq	Yttrium 90 Estimated Tumor Dose, Gy	CgA Fall, %
CR	Pancreas	LR	Nil	30	42	1.9	79	−93
CR	Small bowel	LR	Nil	1	42	1.6	62	−63
CR	Small bowel	Nil	+	10	33	2	16	−48
CR	Medullary thyroid	Nil	Nil	50	48	2	46	−60
CR	Small bowel	Nil	Nil	10	28	0.9	19	−70
PR	Small bowel	Nil	Nil	60	26	2.3	18	−23
PR	Small bowel	Nil	Nil	50	4*	1.9	45	Nil baseline
PR	Small bowel	Nil	Nil	40	8*	1.9	60	−31
PR	Unknown	Nil	Nil	50	11*	2.3	40	−14
PR	Small bowel	IV	+	30	24*	1.9	55	−68
PR	Pancreas	LR	Nil	10	45	1.5	65	−77
PR	Glucagonoma	Nil	Nil	10	41	2	125	−63
PR	Unknown	Nil	+	30	41	2.1	36	−20
PR	Unknown	Nil	+	20	35	1.6	55	−25
PR	Somatostatinoma	LR	Nil	10	39	1.8	50	−12.5
PR	Pancreas	Nil	+	25	29	2.1	61	−25
PR	Small bowel	Nil	Nil	40	12*	2	52	Nil baseline
SD	Bronchus	Nil	Nil	10	8	2	105	−55
SD	Small bowel	LR	+	20	20*	2.3	52	−86
SD	Small bowel	IV	+	50	39*	2.1	65	−79
SD	Vipoma	LR	+	20	18*	2.1	89	No change
SD	Small bowel	LR	+	25	24*	1.9	40	−75

CT indicates computed tomography; SIR, selective internal radiation; GBq, gigabecquerel; Gy, grays; CgA chromogranin A; CR, complete response; LR, liver resection; +, positive; PR, partial response; IV, systemic chemotherapy; SD, stable disease.
*Deceased.

progressive liver disease. In those 3 patients, we had reassessed the screening angiogram/^{99m}Tc-MAA scans, but no aberrant anatomy was evident before ^{90}Y treatment in the 2 patients who developed radiation gastritis or in the 1 patient who had a duodenal ulcer.

Two patients developed jaundice at 2 weeks that resolved in 1 patient. The second patient, who died at 1 month after ^{90}Y treatment, presented 7 months previously with abdominal pain only. The patient was diagnosed with large cell NET of unknown primary site, 50% bilobar hepatic metastases, ascites, and a large portacaval lymph node (3.7 × 3.9 cm) within gall bladder lumen. There were no adverse events at the time of ^{90}Y infusion with two-thirds of the dose delivered to the right lobe and one-third of the dose delivered to the left lobe. The patient had jaundice and raised bilirubin at 2 days after ^{90}Y infusion. Endoscopy revealed normal duodenoscopy but a short, possibly inflammatory stricture proximal to the hepatic confluence. A stent was inserted, and the jaundice resolved. The patient who lived alone and had longstanding cerebral ischemia was discharged to a nursing home for recuperation, where she increasingly became confused, developed pneumonia, and died. A CT scan at 3 weeks after ^{90}Y treatment revealed decreased liver tumor bulk.

Retreatment and Differential Response in Liver Lobes

The routine study treatment was ^{90}Y infusion to the whole liver. Three patients had an initial partial response (PR)/SD on CT scans in the right liver but had progressive disease (PD) in the left lobe only and were retreated at 2 months, 7 months, and 8 months. All patients had progressive liver disease, and 1 patient died. No chemotherapy was given to any patient who was retreated with ^{90}Y radioembolization. An additional 4 patients who had symptomatic, bilobar PD had a second whole liver ^{90}Y dose at 17 months, 18 months, 22 months, and 26 months. Two patients with extensive liver and bone metastases died, and the third patient, who had progressive liver disease at 15 months, had SD at 11 months after the second ^{90}Y treatment. The fourth patient (aged 38 years with an unknown primary carcinoid who underwent liver resection in 2000) received ^{90}Y treatment in December 2003 and had a PR/SD for 18 months until June 2005, when a new liver lesion developed, which was resected at 19 months after ^{90}Y treatment. The patient developed symptomatic,

TABLE 2
Characteristics of Patients Without Liver Response to Yttrium-90 Radioembolization by Response Evaluation Criteria in Solid Tumors Criteria

CT Response in Liver	Primary Site	Prior Liver Treatments	Prior Extrahepatic Disease	% Hepatic Replacement	Follow-up, mo	SIR-Spheres: Dose Delivered, GBq	Yttrium 90 Estimated Tumor Dose, Gy	CgA Fall, %
Died at 1 mo	Unknown	Nil	Nil	50	1*	2.2	61	Nil baseline
PD	Small bowel	IV	+	60	28	1.9	12	−72
PD	Small bowel	Nil	+	60	8*	2.8	81	Nil baseline
PD	Medullary thyroid	Nil	+	60	14*	2	48	−65
PD	Small bowel	LR	+	25	14*	1.4	40	−38
PD	Unknown	IV	+	30	15*	1.5	14	−48
PD	Unknown	LR	+	40	28*	2.1	49	−17
PD	Small bowel	Nil	+	40	21	2.3	46	−63
PD	Pancreas	Nil	+	30	28	2.2	51	No change
PD	Pancreas	IV	+	40	30	2.1	42	−7
PD	Unknown	LR	+	40	44	2	40	−41
PD	Unknown	Nil	+	20	44	2	63	−63

CT indicates computed tomography; SIR, selective internal radiation; GBq, gigabecquerel; Gy, grays; CgA chromogranin A; PD, progressive disease; IV, systemic chemotherapy; +, positive; LR, liver resection, *Deceased.

progressive liver disease at 38 months and received a second ^{90}Y infusion. A left eye/orbital mass (NET/carcinoid with the same histology as the liver lesion) was resected in August 2007. At 5 years after the first radioembolization, the patient was treated with radiotherapy and radiolabeled octreotide for PD in the liver and bone.

Difficulty in the administration of ^{90}Y spheres was recorded in 2 patients because of vessel spasm during the procedure. Both patients, who had similar celiac axis anomalies documented on screening angiograms/^{99m}Tc-MAA scans, had separate ^{90}Y treatments to the right lobe only and the left lobe only 1 week apart. The first patient, who had multifocal EHD, had a liver PR at 6 months but died at 12 months with overall PD. The second patient, who had no prior EHD, had an overall CR at 27 months.

Survival

The mean survival (±SE) was 27.6 ± 2.3 months. Fourteen patients (41%) died from progressive metastatic disease at 1 to 28 months, and the mean survival was 14.6 ± 2.2 months, and 20 patients remained alive with a mean survival of 36.7 ± 1.8 months.

Symptomatic Response

A subjective hormone response to ^{90}Y radioembolization was observed in this study. Twenty-four patients (71%) had symptoms of diarrhea, flushing, or rash at the baseline assessment. Eighteen of 33 patients (55%) at 3 months and 16 of 32 patients (50%) at 6 months who previously were symptomatic reported improvement. No patient reported de novo hormone symptoms. Two patients with EHD had increased tricuspid disease at 29 months after ^{90}Y treatment.

Radiology

Data for patients who demonstrated a hepatic response after ^{90}Y radioembolization are shown in Table 1, and data on hepatic progression are shown in Table 2. In the liver, a CR was observed in 6 patients, 11 patients had a PR, 5 patients had SD, and 11 patients had PD.

Tumor Marker Response

To assess the CgA marker response to ^{90}Y radioembolization, 33 of 34 patients who had baseline CgA and serial data available were divided into 2 groups: 18 patients with EHD at study entry and 15 patients without EHD at study entry. The CgA values were categorized as no change from baseline, <25% decrease, ≤0% decrease, >25% decrease, and ≥50% increase. In the non-EHD group, all the patients had a decrease in CgA levels. Four patients (27%) had a decrease <25%, 9 patients (60%) had a decrease <50%, and 1 patient each (7%) had an increase >25% and >50% in CgA levels.

In the EHD group, there were 3 patients (17%) without CgA changes from baseline, 4 patients (22%) had a decrease <25%, 6 patients (33%) had a decrease <50%, and 5 patients (28%) had an increase >50% in CgA levels.

For the EHD group (n = 18 patients), the mean CgA nadir (±SE) was 328.4 ± 109.7 U/L; and, for the non-EHD group (n = 15 patients), the mean CgA

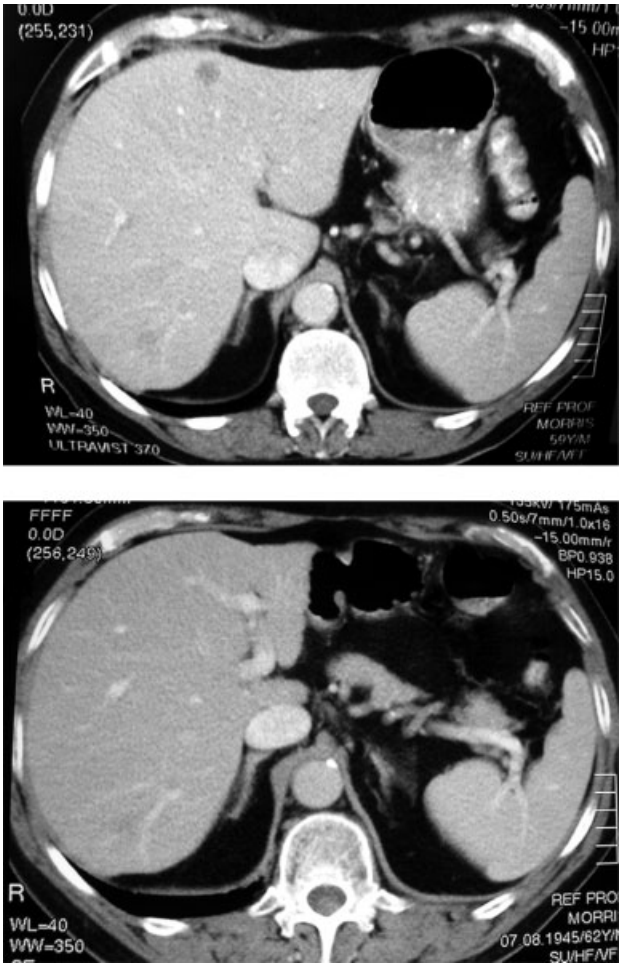

FIGURE 1. Computed tomography scans before (*Top*) and 27 months after (*Bottom*) ^{90}Y radioembolization in a patient who had a complete response in the liver.

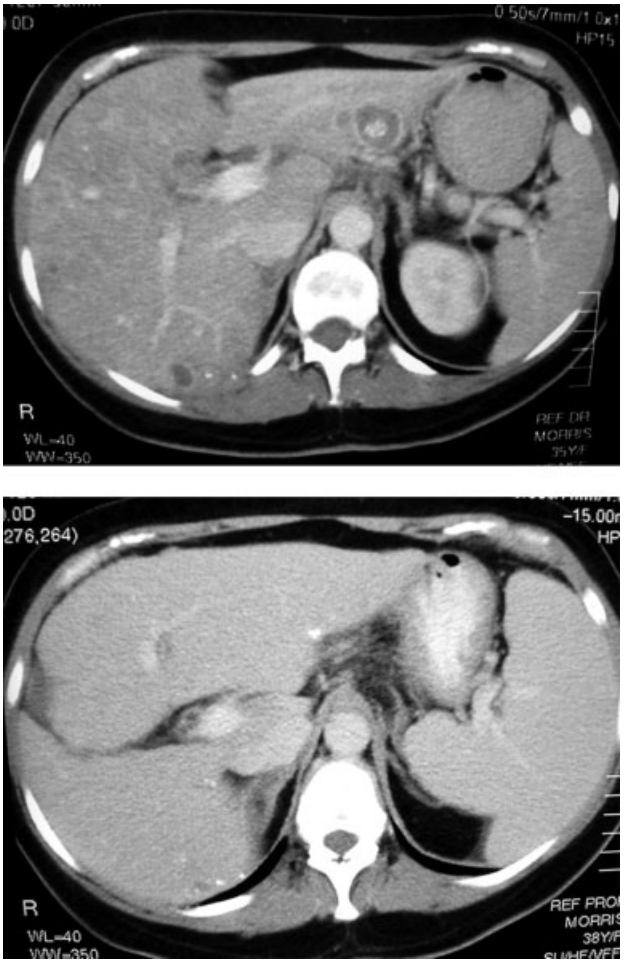

FIGURE 2. Computed tomography scans before (*Top*) and 36 months after (*Bottom*) ^{90}Y radioembolization in a patient who had a complete response in the liver.

nadir was 146.2 ± 50.2 U/L. For the EHD group, the mean time to CgA nadir was 5.1 ± 1.5 months; and, for the non-EHD group, the mean time to CgA nadir was 8.6 ± 2.4 months.

Factors Affecting Response

Tumor volume replacement, ^{90}Y dose, and estimated ^{90}Y dose to tumor are shown in Tables 1 and 2 for responders and nonresponders. The most important finding of this study was that 12 patients (35%) remained alive for mean (±SE) of 33.3 ± 2.3 months with no recurrence of liver disease after treatment with Y.[90] In those 12 patients, there was no obvious contributing factor evident that could account for the good to excellent response to ^{90}Y, except perhaps for less hepatic volume replacement. Radiologic CRs in the liver achieved by 3 patients after ^{90}Y treatment are illustrated in Figures 1 through 3.

There was a trend toward a difference in the mean percentage (±SE) of hepatic tumor replacement in patients who had a radiologic responses to ^{90}Y treatment: The hepatic tumor placement was 26.8% ± 9.8% in 6 patients who had a CR, 28.6% ± 4.6% in 11 patients who had a PR, and 25% ± 6.7% in 5 patients who had SD compared with 41.2% ± 4% in 12 patients who had PD. Two of the patients who had a CR had >50% hepatic replacement. There was no difference in the mean GBq dose (±SE) of microspheres delivered, which was 1.8 GBq for patients who had a CR, 1.9 GBq for patients who had a PR, 2.1 GBq for patients who had SD, and 2 GBq for patients who had PD. The mean estimated ^{90}Y megabecquerel (MBq) dose delivered (±SE) to the liver tumors was 40 ± 10.9 MBq for patients who had a CR, 58.5 ± 7.2 MBq for patients who had a PR, 70.2 ± 11.9 MBq for patients who had SD, and 45.6 ± 5.5 MBq for patients who had PD.

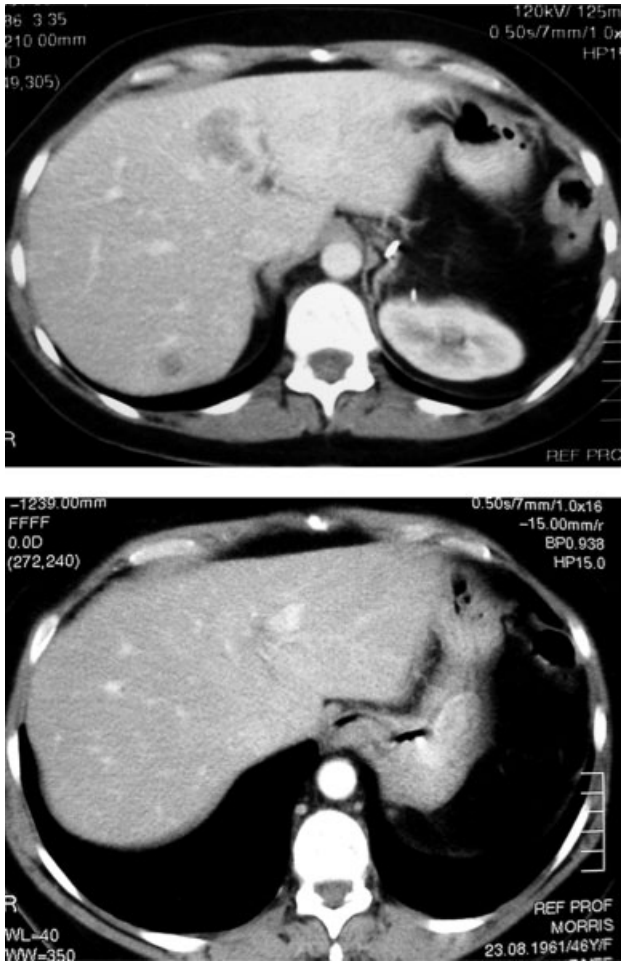

FIGURE 3. Computed tomography scans before (*Top*) and 36 months after (*Bottom*) ^{90}Y radioembolization in a patient who had a complete response in the liver.

There was no clear relation between radiologic response and the maximum percentage decrease in CgA (CR, 50.6% ± 22.9%; PR, 33.6% ± 21.3%; SD, 57.6% ± 31.3%; and PD, 29.4% ± 26.4%).

DISCUSSION

The results of the current study demonstrate that some patients can achieve a CR in their NETLMs after treatment with ^{90}Y microspheres for ≥2 years and that an additional proportion of patients may attain a response of SD. To date, the long-term duration of response to ^{90}Y is not clear, but it is most encouraging; because patients who achieve a CR in the liver survive from 26 months to 48 months after radioembolization.

It is questionable whether any other therapy previously has achieved such useful results in patients with inoperable disease. Although the morbidity associated with ^{90}Y radioembolization is well known,[24,25] a CR assessed by CT scan has been described in only 2 of >500 patients who underwent by hepatic arterial embolization or hepatic arterial chemoembolization in the last 20 years (Table 3).[20,26-38] Two other patients reportedly had a CR, but that assessment was on the basis of angiographic assessment, and not CT assessment. Four other CRs were reported in 2003 by Loewe et al, who used a different and experimental technique of permanent hepatic artery occlusion with cyanoacrylate.[34] Although we accept that a CR occur can after hepatic arterial embolization alone, it is uncommon; whereas we observed a CR in 6 of 34 patients after ^{90}Y treatment. Radioembolization/hepatic arterial embolization combined or chemotherapy postradioembolization does not appear to have been studied previously in patients with NETLMs, but this may offer an additional benefit. A report indicated the effectiveness of ^{90}Y radioembolization, even in patients with refractory metastatic disease who were treated with previous nonradioactive embolization procedures.[39]

In the current study, vessel spasm was noted during the ^{90}Y infusion in 2 patients who had variant hepatic anatomy, as demonstrated at screening angiogram/^{99m}Tc-MAA scan. Both patients received separate right lobe and left lobe ^{90}Y treatments 1 week apart. In this study, we did not embolize aberrant vessels prophylactically, and we do not know whether doing so could have optimized delivery and/or decreased symptoms. It was reported in 2006 that 45% of 68 patients who had LMs treated by SIRT had abnormal arterial anatomy.[40] A recent review advised that, because of the large degree of variant hepatic arterial anatomy, aberrant vessels should be embolized prophylactically at CT angiography before the ^{99m}Tc-MAA scan for patients who receive ^{90}Y, and whole liver radioembolization at a single procedure no longer is advised.[41] It is feasible that more focused delivery of radiation to a smaller area of the liver or access to previously unattainable vessels can be attained now with microcatheter technology. This may decrease damage to normal liver and can take advantage of tumor vascularity.[40] We had re-examined the angiograph/^{99m}Tc-MAA scans of the 3 patients who had developed radiation gastritis and the 1 duodenal ulcer, but we observed no evidence of aberrant anatomy before ^{90}Y treatment.

The symptomatic responses observed in 55% of patients and the greater CgA reduction in responding patients also support our belief that ^{90}Y is an active therapy. The finding of an observed response in 1 side of the liver and disease progression in the other with a response attained after a second dose administered through the missed vessel (usually the accessory left hepatic artery from the left gastric artery) is good evidence of a biologic effect.

TABLE 3
Clinical Studies of Neuroendocrine Tumor Liver Metastases

Reference	HAE/HACE	CR, No.	PR, No.	Mean No. of Treatments	Median Survival Posttreatment, mo	Comments
Carrasio 1983[26]	18 Mix	0	11	1.6		Short follow-up
Ajani 1988[27]	22 HAE	0	12	4	33	Islet cell
Hajarizadeh 1992[28]	9 HACE	0	1		16	
Therasse 1993[29]	23 HACE	2	4		24	Angiography; CR
Ruszniewski 1993[20]	24 HACE	2	4	2	24	Median response, 14 mo; CR
Mavligit 1993[30]	5 HACE	0	4	2		Islet cell
Moertel 1994[31]	III mix	0	60%			Response duration: HAE, 4 mo; HACE, 18 mo
Eriksson 1998[32]	41 HAE	0	21	1.3	80	
Gupta 2003[33]	81 Mix	0	46	2	31	Median response, 17 mo
Loewe 2003[34]	22 HAE, CYA*	4	12	3.3	69	Permanent CYA
Roche 2003[35]	14 HACE	0	12	3.6	47	
Gupta 2005[36]	69 Mix	0	46, 19	2	33, 23	Carcinoid, islet cell
Osborne 2006[37]	59	NR	5	2.5	24	
Ho 2007[38]	46	0		2	36	

HAE indicates hepatic arterial embolization; HACE, hepatic arterial chemoembolization; CR, complete response; PR, partial response; CYA, cyanoacrylate; NR, not reached.
*Permanent embolization with CYA.

We can only speculate regarding why some patients achieve such excellent results whereas others do not respond. In this study, we examined the percentage of liver tumor replacement, the type of NET, and the ^{90}Y dose delivered. We observed no difference between the responders and nonresponders with respect to either the ^{90}Y dose delivered to the liver ($P = .3$) or the estimated dose taken up by the tumors ($P = .8$). We did not study the tumor kinetic index in this work, and we did not attempt to measure the vascularity of tumors. There may be a relation between ^{99m}Tc-MAA uptake and the disease response,[42] but we did not quantify the ^{99m}Tc-MAA uptake ratio in this study. Pancreatic NETs appear to be a little more likely to respond than other NETs.

The distribution of ^{90}Y microspheres assessed by nuclear imaging to estimate the radiation dose to tumor and liver (target to nontarget-ratio [TNT]) can only be estimated. This is because it is known that different tumor classes demonstrate different TNT ratios, even within the same patient; there is no method to assess small individual tumors; the distribution of ^{90}Y microspheres is fixed after administration, and there is no proof that all radioactivity drawn up is administered into the liver/tumor and that none escapes elsewhere or remains in the delivery apparatus.

We chose to use the pre-existing protocols involving systemic 5-fluorouracil at the time of ^{90}Y infusion. Whether this is necessary or not in patients with NETs is speculative.

These very good results suggest that long-term control of unresectable NETLMs by ^{90}Y microspheres is possible. Response of at least some magnitude may be expected in a significant population of patients. The favorable clinical response to radioembolization and the effect on long-term survival are limited by the presence and extent of significant EHD. Preliminary results indicate significant hepatic tumor response and amelioration of symptoms with low treatment-related toxicity.

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