CLINICAL STUDY

Long-Term Toxicity after Transarterial Radioembolization with Yttrium-90 Using Resin Microspheres for Neuroendocrine Tumor Liver Metastases

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ABSTRACT

Purpose: To evaluate long-term effects of yttrium-90 (^{90}Y) transarterial radioembolization (TARE) for unresectable hepatic metastases of neuroendocrine tumors (NETs).

Materials and Methods: Retrospective analysis of 93 patients (47 women, 46 men; mean age 59 y) who underwent resin-based ^{90}Y TARE was performed. Variables associated with overall survival were analyzed using univariate and multivariate models. Changes in serologic values and imaging characteristics were assessed with long-term follow-up.

Results: Unilobar TARE was performed in 48 patients, and staged bilobar TARE was performed in 45 patients. In multivariate analysis, ascites ($P = .002$) and extrahepatic metastases ($P = .038$) at baseline were associated with poor survival. Among 52 patients who had > 1 year of follow-up, significant increases in alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase were observed; however, only 4 patients experienced grade 3 serologic toxicities. Imaging signs of cirrhosis-like morphology and portal hypertension were observed in 15 of 52 patients, more frequently in patients treated with bilobar TARE compared with unilobar TARE. Patients treated with bilobar TARE exhibited significantly increased hepatobiliary enzymes and decreased platelet count. Sustained increases in liver enzymes were observed in patients with > 4 years of follow-up. No radioembolization-related liver failure or grade 4 toxicity was observed.

Conclusions: ^{90}Y radioembolization using resin microspheres demonstrated a high safety profile for NET liver metastases, with low-grade, although sustained, long-term liver toxicity evident > 4 years after treatment. Bilobar treatment suggested a trend for treatment-related portal hypertension. Ongoing research will help define parameters for optimizing durable safety and efficacy of radioembolization in this setting.

ABBREVIATIONS

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, HR = hazard ratio, NET = neuroendocrine tumor, TARE = transarterial radioembolization, ^{90}Y = yttrium-90

Neuroendocrine tumors (NETs) are relatively slow-growing neoplasms of neuroendocrine cell differentiation from a variety of origins (1). Although relatively rare, the incidence of NETs has increased over the past 3 decades with a prevalence of 35 per 100,000 patients (2). Of patients with NETs, 46%–93% have synchronous liver metastases at diagnosis (3), which is the most important prognostic factor affecting survival (4). Without treatment,

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5-year survival rate can be 20% in patients with NET liver metastases (5).

The management of NET liver metastases is clinically challenging. Surgical resection is preferred if > 90% of the disease can be safely removed. However, nearly 90% of patients present with multiple hepatic lesions not amenable to surgery (6). Alternative treatment options, such as thermal ablation (7,8), peptide receptor radionuclide therapy (9), external-beam radiation (10), systemic chemotherapy (11), and transarterial embolization and chemoembolization (12,13), have been explored for unresectable NET liver metastases.

Yttrium-90 (^{90}Y) transarterial radioembolization (TARE), also known as selective internal radiation therapy to distinguish it from external-beam radiation therapy, is an emerging treatment for unresectable NET liver metastases. TARE has been demonstrated to be safe and effective for treatment of NET liver metastases (14,15). The main advantages of TARE with ^{90}Y are its short half-life of 64 hours and low mean penetrance depth of 2–3 mm, which allows the radiation to be contained within the tumor bed with relative sparing of the surrounding parenchyma (16).

Data concerning long-term safety after ^{90}Y TARE are limited (17). Although previous retrospective reports have described biliary damage as a potential complication of therapy with ^{90}Y and chemoembolization, the potential long-term toxicity of ^{90}Y treatment is poorly understood. In many scenarios where radioembolization is performed in the salvage setting, long-term toxicity is not a major concern; however, because of the potential for longer survival in patients with NET liver metastases, the long-term toxicity of ^{90}Y therapy becomes more relevant. A previous report describing long-term hepatotoxicity in patients with NET liver metastases treated with ^{90}Y glass microspheres concluded that long-term hepatotoxicity solely attributable to ^{90}Y develops in a relatively small percentage of patients (18). The aim of the present study was to assess the prognostic factors and long-term (> 1 y after treatment) safety and toxicity of ^{90}Y TARE with resin microspheres for patients with NET liver metastases to further build on this experience.

MATERIALS AND METHODS

Study Population and Treatment Characteristics

With institutional review board approval, all patients with NET liver metastases treated with ^{90}Y TARE at a single institution between February 2007 and November 2015 were retrospectively reviewed. The following patients were included: (*a*) patients with NET liver metastases with available contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging and who were not surgical candidates, (*b*) patients with available details of radiation treatment planning and delivery, and (*c*) patients 18–99 years old. Patients who had undergone prior treatment for NET liver metastases, including liver resection, systemic chemotherapy, transarterial embolization and chemoembolization, and locally ablative techniques were included. Exclusion criteria included (*a*) unsafe treatment owing to collateral arterial flow to the gastrointestinal tract, (*b*) hepatopulmonary shunt fraction > 20%, or (*c*) previous external-beam radiation therapy to the liver. All patients had baseline serologic values including liver function tests and complete blood count and contrast-enhanced CT or MR imaging before ^{90}Y treatment to assess the status of liver disease, tumor burden, signs of portal hypertension, and extrahepatic metastases.

Characteristics of the patients (n = 93) and treatments are shown in **Table 1**. Successful delivery of ^{90}Y was achieved in all patients. The mean age at the time of first treatment was 58.6 years ± 13.7 (range, 22–88 y) with a male-to-female ratio of 1:1. Eastern Cooperative Oncology Group performance status was 0 in 47 patients, 1 in 41 patients, and 2 in 5 patients. The primary tumor was classified as carcinoid tumor in 66 patients and islet cell tumor in 27 patients. Of the 71 patients whose tumor differentiation was known, 56 patients had well-differentiated tumors, and 15 had low-grade tumors. At baseline evaluation, 32 patients had extrahepatic metastases, and 16 patients had ascites. Child-Pugh class was A in 75 patients, B in 17 patients, and C in 1 patient. Previous treatments included transarterial embolization and chemoembolization in 24 patients, liver resection in 21 patients, systemic chemotherapy in 15 patients, and ablative therapy in 10 patients. No previous therapy was administered in 35 patients. The mean time interval from diagnosis of liver metastases to ^{90}Y treatment was 27 months (range, 1–216 months). The median follow-up duration was 15.0 months (interquartile range, 7.0–31.0 months). Of 93 patients, 23 patients were lost to follow-up, and 18 patients died, leaving 52 patients with > 1 year of clinical follow-up after initial TARE; 11 patients had > 4 years of follow-up. The mean total administered activity of ^{90}Y microspheres was 1.92 GBq ± 0.91. Unilobar TARE was performed in 48 patients, and staged sequential bilobar TARE (ie, right lobe followed by left lobe at a later date) was performed in 45 patients. For bilobar treatment, the time between the 2 treatments was usually 4–6 weeks. A total of 168 treatments were administered; 160 were lobar, and 8 were segmental. No single-session, whole-liver treatment was performed except in 3 patients who had undergone prior lobar resection. The mean number of TARE treatments was 1.8 (range, 1–4).

Preprocedural Work-up

Before treatment, patients underwent mapping visceral angiography. Collateral arteries supplying the gallbladder, stomach, or bowel were identified, and approximately 4 mCi of technetium-99m-labeled macroaggregated albumin was injected into the hepatic arteries in the anticipated location of the planned ^{90}Y delivery. Whole-body gamma scintigraphy, with or without combined single photon emission computed tomography/CT, was then performed to assess extrahepatic activity (eg, gastrointestinal flow) and to

estimate the lung shunt fraction. This technique accurately estimates dose distribution, quantification of hepatopulmonary shunting, and expected lung dose (19–22).

Treatment Procedure

All patients were treated with ^{90}Y resin microspheres (SIR-Spheres; Sirtex Medical Ltd, North Sydney, Australia) using body surface area to calculate liver mass according to a standard protocol. The radioembolization procedure was performed in accordance with institutional radiation safety guidelines. Treatment endpoints were defined as administration of the entire planned dose or observation of reduced arterial flow and anticipated risk of reflux. Patients were typically discharged home the same day.

Table 1. Patient and Treatment Characteristics (N = 93)

Characteristic	Value
Patients	
Age, y, mean ± SD	58.6 ± 13.7
Sex	
Male	46 (49.5%)
Female	47 (50.5%)
ECOG performance status	
0	47 (50.5%)
1	41 (44.1%)
2	5 (5.4%)
Tumor type	
Carcinoid	66 (71.0%)
Islet cell	27 (29.0%)
Previous treatments	
Transarterial embolization/chemoembolization	24 (25.8%)
Resection	21 (22.6%)
Systemic chemotherapy	15 (16.1%)
Ablation	10 (10.8%)
None	35 (37.6%)
Cell differentiation	
Well	56 (60.2%)
Moderate/poor	15 (16.1%)
Unknown	22 (23.7%)
Hepatic tumor burden	
< 25%	36 (38.7%)
25%–50%	31 (33.3%)
> 50%	26 (28.0%)
Ascites	
Present	16 (17.2%)
Absent	77 (72.8%)
Extrahepatic metastases	
Present	32 (34.4%)
Absent	61 (65.6%)
Follow-up duration	
< 1 y	41 (44.1%)
≥ 1 y	52 (55.9%)
Child-Pugh class	
A	75 (80.6%)
B	17 (18.3%)
C	1 (1.1%)
ALP NCI CTCAE grade at baseline	
0, 1	77 (82.3%)
2, 3	16 (17.7%)
Treatments	
Total administered activity, GBq, mean ± SD	1.92 ± 0.91
Treatment distribution	
Unilobar	48 (51.6%)
Bilobar (staged)	45 (48.4%)
Number of ^{90}Y treatments	
1	37 (39.8%)
2	43 (46.2%)
3	7 (7.5%)
4	6 (6.5%)

ALP = alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events; RE = radioembolization.

Follow-up and Assessment of Outcomes

Electronic health records were reviewed for clinical history and laboratory data. The primary outcome was all-cause mortality. Patients were evaluated from the date of initial TARE treatment to the date of either last clinical follow-up or death. Mortality data were obtained by searching the electronic records and the Social Security Death Index. Among patients with > 1 year of follow-up, changes in serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, albumin, and complete blood count were evaluated. Contrast-enhanced CT or MR imaging examinations performed 1 year after TARE were reviewed and compared with imaging performed before treatment to evaluate for signs of developing portal hypertension, defined as new ascites, varices, parenchymal surface nodularity (cirrhosis-like morphology), or emergence of splenomegaly (23). Independent review of CT and MR imaging was performed by 2 trained radiologists, with discordant reads resolved by consensus if needed. Treatment response was assessed using the Response Evaluation Criteria In Solid Tumors. All serologic toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (24). In this system, severe hepatotoxicity is defined as grade 3 (AST, ALT, or ALP elevation > 5 times the upper limit of the normal range or total bilirubin elevation > 3 times the upper limit of the normal range).

Statistical Analysis

Overall survival was summarized using a Kaplan-Meier survival table. Effects of clinicopathologic and treatment-related

Table 2. Predictors of Survival Based on Clinicopathologic and Treatment-Related Factors

Clinicopathologic Factors	Univariate Model		Multivariate Model*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Patient				
Age: > 60 y vs ≤ 60 y	1.19 (0.63–2.24)	.590		
Sex: male vs female	1.47 (0.80–2.70)	.214		
ECOG performance status: 0 vs ≥ 1	1.66 (0.89–3.10)	.112		
Tumor				
Histopathologic subtype: carcinoid vs islet cell	0.98 (0.51–1.89)	.948		
Cell differentiation: higher grades vs well-differentiated	1.53 (0.69–3.42)	.295		
Extrahepatic metastases: present vs absent	2.63 (1.40–4.92)	.003†	2.02 (1.04–3.91)	.038†
Hepatic tumor burden				
≥ 50% vs <5 0%	1.54 (0.79–3.03)	.203		
≥ 25% vs < 25%	1.43 (0.77–2.68)	.259		
Clinical				
Ascites: present vs absent	9.42 (3.87–22.95)	< .001†	5.25 (1.85–14.96)	.002†
Child-Pugh class: B, C vs A	3.55 (1.77–7.20)	< .001†	1.54 (0.58–4.10)	.387
ALP NCI CTCAE grade at baseline: 2, 3 vs 0, 1	2.46 (1.21–4.97)	.013†	1.87 (0.91–3.83)	.250
Pre-RE treatments				
Transarterial embolization/chemoembolization: yes vs no	0.98 (0.50–1.92)	.945		
Resection: yes vs no	0.87 (0.42–1.83)	.716		
Systemic chemotherapy: yes vs no	2.91 (1.32–6.40)	.008†	1.97 (0.82–4.78)	.131
Treatment				
RE treatment distribution: bilobar vs unilobar	0.88 (0.48–1.62)	.676		
Total administered activity: > 1.92 GBq vs ≤ 1.92 GBq	1.03 (0.54–1.98)	.926		

ALP = alkaline phosphatase; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events; RE = radioembolization.
*All clinicopathologic factors demonstrating a significant association with survival on univariate Cox regression analysis (defined by *P* value < .05) were incorporated as covariates in multivariate Cox regression analysis.
†Signifies statistically significant values.

factors on survival rates were analyzed by univariate and multivariate Cox regression models. To assess the variation in serologic values over consecutive assessments, one-way repeated measures analysis of variance was used. Univariate repeated measures analysis of variance models were additionally adjusted for baseline tumor burden by volume (< 25%, 25%–50%, or > 50% involvement). Fisher exact test was used to compare imaging changes between patients treated with unilobar versus bilobar TARE. IBM SPSS Version 24.0 (IBM Corp, Armonk, New York) was used for all statistical analysis. P values < .05 were considered statistically significant.

RESULTS

Overall Survival

During the study period, 42 (45.2%) patients died. Table 2 presents the results of Cox regression models. In univariate analysis, presence of ascites at baseline (hazard ratio [HR] 9.42, $P < .001$), extrahepatic metastases at baseline (HR 2.63, $P = .003$), previous systemic chemotherapy (HR 2.91, $P = .008$), high baseline ALP (toxicity grade ≥ 2) (HR 2.46, $P = .013$), and Child-Pugh class B or C (HR 3.55, $P < .001$) were significant predictors of worse survival. In multivariate analysis, extrahepatic metastasis (HR 2.02, $P = .038$) and ascites (HR 5.25, $P = .002$) remained significant predictors of poor survival after TARE. The overall median survival was 28.0 months (95% confidence interval [CI], 16.2–39.8). Median survival for patients without extrahepatic disease was 58.0 months (95% CI, 28.1–73.9) compared with 21.1 months (95% CI, 12.9–23.1) for patients with extrahepatic disease (Fig 1). Median survival of patients without baseline ascites was 53.8 months (95% CI, 9.3–58.7) compared with 7.3 months (95% CI, 3.8–10.2) for patients with baseline ascites (Fig 2). There was a significant interaction between ascites and extrahepatic metastasis ($P = .014$) for which the multivariate model was adjusted.

Long-Term Toxicity

The results of mean laboratory values and serologic toxicities obtained from the 52 patients with > 1 year of follow-up are summarized in Tables 3 and 4. Radiographically at 1 year, there were 13 patients (25%) with partial response, 35 patients (67%) with stable disease, and 4 patients (8%) with progressive disease. During 1-year follow-up, 9 patients received systemic chemotherapy (everolimus in 7 patients, capecitabine and

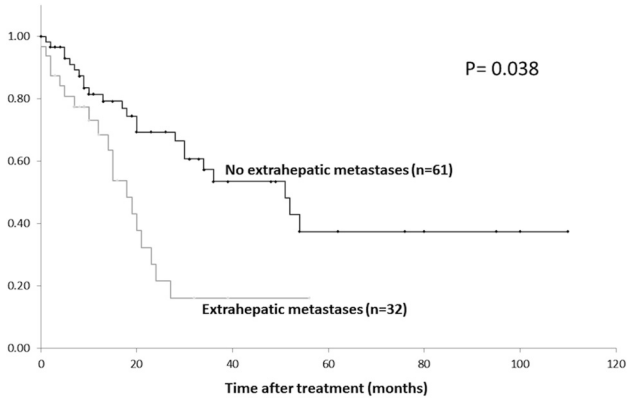

Figure 1. Comparison of overall survival with vs without extrahepatic metastases at baseline.

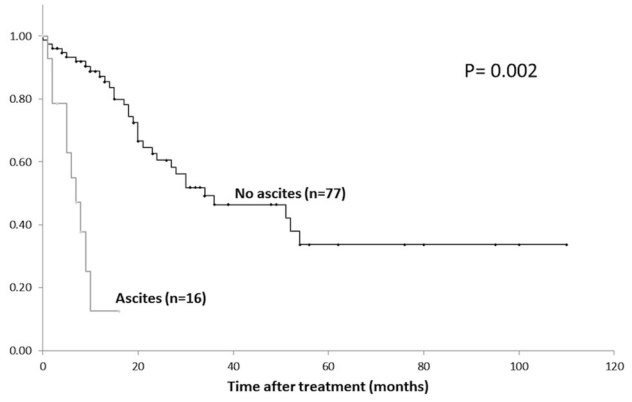

Figure 2. Comparison of overall survival with vs without ascites at baseline.

temozolomide in 2 patients), and 1 patient received hepatic arterial infusion. Values obtained at baseline before treatment, at 6 months after ^{90}Y treatment, and at 1 year after ^{90}Y treatment were reviewed. Levels of ALP, AST, and ALT over the 1-year period showed a significant increasing trend (one-way repeated measures analysis of variance, $P = < .001$, $P = < .001$ and $P = .003$). The trends remained statistically significant after adjusting for baseline tumor burden. There were no significant changes in albumin, total bilirubin, hemoglobin, platelet count, or leukocyte count over the 1-year follow-up period.

The most common serologic toxicity was grade 2 elevation in alkaline phosphatase levels, which was experienced by 13 patients; however, 6 of these patients had grade 2 elevations at baseline. Grade 2 serologic toxicity was experienced by 36 of 52 patients (69%), and grade 3 serologic toxicity was experienced by 4 of 52 patients (8%) during the 1-year period following ^{90}Y therapy. Grade 3 serologic toxicities included elevation in total bilirubin levels (n = 2), elevation in ALP levels (n = 1), and decrease in serum albumin levels (n = 1). Six patients experienced new-onset ascites. No patient experienced grade 4 toxicity. Laboratory follow up data > 4 years after ^{90}Y treatment were available for 11 patients (21.2%). Elevations in ALP and AST over the 4-year period remained statistically significant compared with baseline ($P = 0.017$ and $P = 0.037$) (Table 5). CTCAE grade toxicities observed were grade 3 (n = 1; 9%), grade 2 (n = 1; 9%), and grade 1 (n = 6; 54%) elevation in ALP and grade 1 (n = 4; 36%) elevation in AST.

Comparison of Unilobar versus Bilobar TARE

Serial changes in serologic values of unilobar and bilobar TARE therapy are shown in Table 3. Significant sustained increases in serum ALP, AST, and ALT levels and decreases in platelet counts were observed in patients receiving bilobar therapy. By comparison, after adjusting for baseline tumor burden, patients receiving unilobar therapy demonstrated a significant upward trend of only ALP levels (Table 3). Changes in follow-up imaging 1 year after TARE are shown in Table 6. Imaging changes of cirrhosis-like morphology or portal hypertension were seen in 15 of 52 patients (29%) and more frequently in patients receiving bilobar therapy compared with unilobar therapy. Of 29 patients with bilobar treatment, cirrhosis-like morphology developed in 6 (20.7%), ascites developed in 5 (17.2%), splenomegaly developed in 6 (20.7%), and varices developed in 2 (6.9%), although this did not reach statistical significance.

DISCUSSION

Reported median survival rates for patients with NET liver metastases treated with ^{90}Y radioembolization are varied, ranging from 15 to 70 months (14,15,25,26). Factors associated with overall survival in patients treated for NET liver metastases include hepatic tumor burden, previous surgery, size of target lesions, baseline serologic values, presence of extrahepatic metastases, and Child-Pugh class (26–29). In the studied cohort, patients with extrahepatic metastases or ascites at baseline had a significantly worse prognosis, with baseline ascites representing the greatest predictor of poor survival. A statistical interaction between extrahepatic metastases and ascites was observed, possibly representing malignant ascites with ensuing worse prognosis.

Serologic toxicity is a major concern after any interventional treatment for liver metastases. This issue has been addressed by several studies within the context of ^{90}Y radioembolization for hepatic tumors (16,17,19–21,26–30). Almost all studies have shown an acceptable level of serologic toxicity in the short-term; however, patients with NET liver metastases have a relatively longer median survival than most other patients with liver metastases or patients with primary liver malignancy. As such, the impact of long-term toxicities for treatments in this patient population becomes more important. In the present study, only 4 patients (8%) experienced grade 3 serologic toxicities during 1-year follow-up. There were low-grade, but statistically significant, increases in ALP, AST, and ALT levels in the bilobar treatment group and ALP and AST levels in the unilobar treatment group 1 year after initial treatment. Moreover, these observed liver enzyme elevations persisted in patients

Table 3. Changes in Serologic Values during 1-Year Follow-up after ^{90}Y Treatment

	Serologic Value	Baseline Mean (SD)	6-Month Mean (SD)	1-Year Mean (SD)	*P* Value (rANOVA)	Adjusted *P* Value* (rANOVA)
Total (n = 52)	Albumin, g/dL	3.5 (0.4)	3.5 (0.4)	3.4 (0.5)	.069	.294
	ALP, IU/L	143.1 (89.3)	152.1 (83.5)	250.8 (141.6)	< .001†	< .001†
	AST, IU/L	30.5 (13.8)	35.6 (18.5)	43.2 (20.2)	< .001†	.003†
	ALT, IU/L	32.5 (19.5)	34.3 (18.5)	40.5 (18.3)	.003†	.031†
	Bilirubin, mg/dL	0.7 (0.3)	0.7 (0.4)	0.8 (0.5)	.352	.440
	Hemoglobin, g/dL	12.4 (1.4)	12.3 (1.5)	12.3 (1.8)	.964	.862
	Platelets, 10^9/L	238.3(101.7)	222.3 (80.2)	217.2 (116.8)	.197	.326
	Leukocytes, 10^9/L	6.8 (2.2)	6.1 (2.5)	6.4 (2.9)	.241	.284
Unilobar ^{90}Y (n = 23)	ALP, IU/L	136.9 (84.9)	151.3 (66.8)	246.7 (128.9)	< .001†	.002†
	AST, IU/L	29.3 (12.3)	33.4 (13.3)	39.8 (17.6)	.012†	.179
	ALT, IU/L	33.3 (23.6)	31.3 (17.2)	37.6 (20.5)	.251	.631
	Platelets, 10^9/L	246.6 (125.5)	226.1 (93.2)	256.0 (154.8)	.393	.252
	Bilirubin, mg/dL	0.8 (0.4)	0.9 (0.4)	0.7 (0.2)	.276	.425
Bilobar ^{90}Y (n = 29)	ALP, IU/L	148.1(93.8)	152.7 (96.2)	254.1 (153.1)	< .001†	< .001†
	AST, IU/L	31.4 (15.1)	37.3 (21.8)	45.9 (22.0)	.001†	.003†
	ALT, IU/L	31.8 (15.9)	36.7 (19.5)	42.7 (16.3)	.002†	.002†
	Platelets, 10^9/L	231.7 (79.7)	219.2 (69.8)	186.4 (61.6)	< .001†	.002†
	Bilirubin, mg/dL	0.6 (0.2)	0.7 (0.4)	0.8 (0.6)	.075	.103

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; rANOVA = repeated measures analysis of variance; ^{90}Y = yttrium-90.
*Adjusted for baseline hepatic tumor burden.
†Signifies statistically significant values.

Table 4. Toxicity over Time after ^{90}Y Treatment (NCI CTCAE) (n = 52)

Value	Baseline		6 Months		1 Years	
	Grade 2	Grade 3	Grade 2	Grade 3	Grade 2	Grade 3
Albumin	2	0	3	0	11	1
ALP	6	0	5	0	13	1
AST	0	0	1	0	1	0
ALT	4	0	1	0	3	0
Bilirubin	1	0	2	0	0	2
Hemoglobin	3	0	3	0	4	0
Platelets	0	0	0	0	2	0
Leukocytes	1	0	1	0	2	0
Ascites	1	0	1	1	1	6

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI CTCAE = National Cancer Institute Common Toxicity Criteria for Adverse Events; ^{90}Y = yttrium-90.

with > 4 years of follow-up, suggesting sustained hepatotoxicity from the treatment. Other serologic values did not significantly change, and there were no cases of grade 4 toxicity or radioembolization-induced liver failure despite a patient cohort with significant additional treatments. Thus, although low-level sustained hepatotoxicity can be observed after ^{90}Y radioembolization with resin microspheres, overall, this treatment was very well tolerated.

^{90}Y microspheres deliver targeted radiotherapy to tumors while sparing viable hepatic tissue, owing to the predominant arterial supply of liver metastases compared with the predominantly portal venous blood supply of uninvolved liver parenchyma. Despite this fact, the uninvolved liver parenchyma is also irradiated and at risk for liver injury, fibrotic changes, and portal hypertension. This notion is supported by radiographic studies assessing volume changes of the liver and spleen after ^{90}Y treatment. In a series of 17 patients treated with bilobar TARE, a mean decrease in liver volume of 11.8% and a mean increase in splenic volume of 27.9% was noted, accompanied by increases in portal vein diameter (31). In another series of 45 patients, liver volumes were shown to decrease in lobes treated with TARE by up to 45% at 12 months after treatment (32). Despite recorded changes in liver and spleen volume, there was no clinical evidence of liver failure.

In the examined cohort, 15 of 52 (29%) patients developed imaging signs of cirrhosis-like morphology or portal hypertension after 1 year of follow-up, including all 4 patients who experienced grade 3 serologic toxicity. Moreover, a trend toward treatment-related portal hypertension was observed in patients receiving bilobar TARE compared with unilobar TARE. Because of the small sample size, there were no significant differences in imaging changes between unilobar and bilobar treatment; however, decline of platelet counts, a serologic marker of portal hypertension, was significant only in patients receiving bilobar treatment. For patients receiving unilobar TARE, the untreated liver lobe can theoretically compensate for any putative loss of parenchymal function from the treated lobe. In a previous study on unilobar TARE, a mean decrease in treated lobar volume of 8.9% and contralateral lobar hypertrophy of 21.2% without increases in splenic volume were seen (31). There are 4 reported de novo cases of severe cirrhosis following bilobar TARE, 2 of which were confirmed pathologically

Table 5. Patients with Follow-up Data > 4 Years after ^{90}Y Treatment (n = 11)

Serologic Value	Baseline Mean (SD)	1-Year Mean (SD)	2-Year Mean (SD)	3-Year Mean (SD)	4-Year Mean (SD)	*P* Value (rANOVA)
Albumin, g/dL	3.7 (0.5)	3.7 (0.5)	3.7 (0.4)	3.7 (0.4)	3.6 (0.6)	.983
ALP, IU/L	101 (48.1)	196.9 (148.1)	158.8 (106.3)	184 (140.5)	224.6 (195.1)	.017*
AST, IU/L	28.3 (14.1)	37.9 (15.2)	39.4 (16.3)	37.1 (17.7)	40.7 (17.9)	.037*
ALT, IU/L	28.5 (14.8)	39.4 (16.6)	43.9 (23.7)	37.5 (14.2)	38.4 (18.8)	.201
Bilirubin, mg/dL	0.9 (0.6)	0.7 (0.3)	0.8 (0.4)	1.0 (0.6)	1.0 (0.5)	.377
Hemoglobin, g/dL	13.1 (0.9)	13.1 (1.9)	13.3 (1.0)	13.2 (0.9)	12.6 (2.0)	.570
Platelets, 10^9/L	226.5 (77.5)	245.1 (178.1)	201 (65.9)	198.7 (79.2)	184.9 (114.6)	.263
Leukocytes, 10^9/L	5.9 (2.5)	5.4 (2.6)	5.2 (2.3)	5.0 (1.8)	5.0 (2.2)	.323

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; rANOVA = repeated measures analysis of variance; ^{90}Y = yttrium-90.
*Signifies statistically significant values.

Table 6. Cross-Sectional Imaging Changes 1 Year after ^{90}Y Treatment

Imaging Change	Total (n = 52)	Unilobar RE (n = 23)	Bilobar RE (n = 29)	*P* Value
Ascites	6	1	5	.158
Cirrhrosis-like morphology*	7	1	6	.093
Splenomegaly†	9	3	6	.366
Varices	2	0	2	.306

*Cirrhrosis-like morphology defined as hepatic surface nodularity and enlargement of caudate lobe.
†Craniocaudal length > 10 cm (23).

(25,33–35). Thus, severe cirrhosis can represent a potential long-term complication of bilobar ^{90}Y treatment. Additional research is needed to better understand risk factors for developing cirrhosis or portal hypertension in this setting, including examination of patient baseline characteristics, history of prior therapy, and absorbed liver doses by tumor and nontumor tissue. Patients receiving bilobar TARE may require ongoing surveillance for treatable signs of portal hypertension and cirrhosis, such as the development of gastroesophageal varices or ascites.

A report describing long-term hepatotoxicity in patients with NET liver metastases treated with glass ^{90}Y microspheres (TheraSphere; BTG International Ltd, London, UK) found low rates of hepatotoxicity using this delivery device (18). Consistent with the findings of the present study, more patients who underwent whole-liver radioembolization showed imaging and laboratory signs of portal hypertension compared with patients who underwent unilobar radioembolization. Rates of cirrhosis-like morphology or portal hypertension were higher in their cohort compared with our observation. Whether this is due to differences in devices, dosimetry, or duration of follow-up requires further investigation. The present analysis thus provides additional data supporting the relative long-term safety of ^{90}Y in the liver and specifically with resin microspheres.

This study has some limitations. Because this was a retrospective single-center study, inherent selection bias must be considered. Furthermore, the influence of tumor progression on serologic toxicities was not taken into account; however, as only 4 patients in this study had progressive disease, the influence of tumor progression on the overall observed serologic toxicities was likely low. In addition, therapies received before or after ^{90}Y radioembolization may have contributed to long-term toxicities. Assessment of the precise influence of these additional therapies on long-term toxicity from TARE remains challenging. Lastly, some information on the 42 patients who died was lacking, as most died at outside hospitals, and cause of death for all could not be definitively determined.

In conclusion, ^{90}Y radioembolization is a safe and promising treatment option for unresectable NET liver metastases that is associated with low rates of severe long-term serologic toxicities. Patients treated with ^{90}Y radioembolization for NET liver metastases demonstrated sustained, although low-grade, long-term liver toxicity evident > 4 years after treatment. Bilobar treatment was associated with more frequent toxicity and suggested a trend for treatment-related portal hypertension. Baseline ascites and extrahepatic metastases predicted significantly poor outcomes, but patients in whom these features were not present had a median survival of up to 58 months. It is challenging to differentiate normal radiographic changes following radioembolization from true cirrhosis. Although prospective investigation is not easy to conduct owing to the rarity of the disease and the heterogeneity of the patients, another potential avenue for future research might be following these patients with the correlation between imaging and pathologic findings by liver biopsy.

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