CLINICAL STUDY

Long-Term Hepatotoxicity of Yttrium-90 Radioembolization as Treatment of Metastatic Neuroendocrine Tumor to the Liver

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ABSTRACT

Purpose: To determine long-term hepatotoxicity of yttrium-90 (^{90}Y) radioembolization in patients treated for metastatic neuroendocrine tumor (mNET) and evaluate if imaging and laboratory findings of cirrhosis-like morphology are associated with clinical symptoms.

Materials and Methods: Retrospective review from 2003 to 2016 was performed for patients with mNET treated with ^{90}Y glass microspheres. Fifty-four patients with > 2 year follow-up were stratified into unilobar (n = 15) vs whole-liver (n = 39) treatment. The most common primary mNET sites were small bowel (19 of 54), pancreas (19 of 54), and unknown (8 of 54). Preradioembolization imaging and laboratory findings were compared with most recent follow-up for indications of worsening portal hypertension and decline in hepatic function.

Results: Among patients who underwent unilobar radioembolization, imaging follow-up at a mean of 4.1 years (range, 2.0–15.2 y) revealed cirrhosis-like morphology in 26.7% (4 of 15), ascites in 13.3% (2 of 15), varices in 6.7% (1 of 15), and a 21.9% increase in splenic volume. The respective incidences in patients treated with whole-liver ^{90}Y radioembolization were 56.4% (22 of 39), 41.0% (16 of 39), and 15.4% (6 of 39), with a 64.7% increase in splenic volume. Patients treated with whole-liver radioembolization exhibited significantly decreased platelet counts ($P = .023$) and lower albumin levels ($P = .0002$). Eight patients (20.5%) treated with whole-liver radioembolization who exhibited cirrhosis-like morphology showed clinical signs of hepatic decompensation; only 2 of 39 patients (5.1%) had no other causes of hepatotoxicity.

Conclusions: Whole-liver ^{90}Y radioembolization for patients with mNET results in long-term imaging findings of cirrhosis-like morphology and portal hypertension in > 50% of treated patients, but the majority remain clinically asymptomatic. Long-term hepatotoxicity solely attributable to ^{90}Y develops in a small percentage of patients.

ABBREVIATIONS

mNET = metastatic neuroendocrine tumor, ^{90}Y = yttrium-90

Yttrium-90 (^{90}Y) radioembolization is recognized by the National Comprehensive Cancer Network guidelines for the treatment of patients with metastatic neuroendocrine tumors (mNETs) to the liver (1). These tumors metastasize to the liver in 50%–95% of patients (1,2); local therapies such as radioembolization can mitigate bulk and hormonal symptoms and provide disease control (1,3,4).

Changes in liver size and appearance following radioembolization have been described, with radiation injury potentially developing into sinusoidal congestion and portal hypertension (4–8). There are limited data concerning the frequency and clinical impact of portal hypertension

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following radioembolization, especially at greater than 6 months of follow-up (7,9,10). The present study aims to evaluate the long-term (> 2 y after treatment) hepatotoxicity of radioembolization in patients with mNETs by reviewing imaging and laboratory findings and determining their correlation with clinical symptoms. Patients with mNETs have greater life expectancies than most other patients with unresectable hepatic metastases, allowing for long-term evaluation (11).

MATERIALS AND METHODS

Study Population and Demographics

This single-institution retrospective review was approved by the institutional review board and compliant with the Health Insurance Portability and Accountability Act. All patients provided written informed consent for treatment, and 154 patients with liver-dominant mNETs were treated with radioembolization between 2003 and 2014. Imaging, laboratory, and clinical data review was completed in 2016. Clinical selection criteria for ^{90}Y radioembolization have been published previously (12). Fifty-four of the 154 patients had > 2-year imaging and clinical follow-up from the date of first radioembolization and were stratified into 2 groups: unilobar ^{90}Y treatment (n = 15) and sequential lobar (ie, whole-liver) ^{90}Y treatment (n = 39). Patients who underwent unilobar treatment did not undergo treatment to the contralateral lobe during the follow-up period. Patients with initial unilobar disease who subsequently showed disease progression that required contralateral lobar treatment were grouped in the whole-liver radioembolization group. Repeat treatments were allowed. Mean patient age was 58 years (range, 27–85 y), and 52% of the cohort was female. The primary sites of mNETs were the stomach in 2% (1of 54), the colon in 2% (1 of 54), the small bowel in 35% (19 of 54), the pancreas in 35% (19 of 54), the lung in 11% (6 of 54), and an unknown primary lesion in 15% (8 of 54).

Patient Evaluation and Workup

All patients were seen in the interventional radiology clinic for consultation. They underwent history and physical examinations with baseline laboratory tests (complete blood count with differential and comprehensive metabolic panel) and imaging (triphasic liver computed tomography [CT] or magnetic resonance [MR] imaging of the abdomen with and without contrast medium). Laboratory tests were performed at baseline immediately before radioembolization and then at each clinic follow-up, whereas imaging was performed within a 2-week period before ^{90}Y radioembolization and then at each clinic follow-up.

Radioembolization Treatment

Two interventional radiologists with a mean of 13.5 years of experience (11 and 16 y, respectively) performed all radioembolization procedures. Technical aspects of the treatment have been described previously (13). Glass microspheres (TheraSphere; BTG International, West Conshohocken, Pennsylvania) were the radioembolic device employed. The use of TheraSphere was on an off-label basis for patients with mNET to the liver. All patients underwent lobar treatments, and the mean radiation dose to each hepatic lobe was calculated.

Data Collection and Clinical Follow-up

Patients were seen in follow-up (at medical oncology and/or interventional radiology clinic) approximately 4 weeks, 3 months, and 6 months after radioembolization. After this, patients maintained a minimum of 6-month interval follow-up. All patients underwent imaging, laboratory, and clinical follow-up 2 years after the first radioembolization. Mean and median follow-up intervals were 4.1 and 3.5 years after the first radioembolization, respectively (range, 2.0–15.2 y; standard deviation, 2.3 y). Patients were followed until death by using the Social Security Death Index or via direct family confirmation regarding the date of death. Otherwise, patients were censored at the time of the last known follow-up clinic visit.

Image interpretation was originally done by board-certified diagnostic radiologists; images were also independently reviewed by an interventional radiologist with 11 years of experience in performing radioembolization. Specifically, images were studied for development of a nodular cirrhosis-like morphology and/or signs of portal hypertension (ascites graded as trace, small, moderate, or large by the interpreting diagnostic radiologist; varices; and splenomegaly defined as > 12 cm in length) (14). The distinction was made between the classical "cirrhotic" appearance as a result of infection (hepatitis B or C) or alcohol and the "cirrhosis-like" morphology caused by the postulated long-term radiation-induced liver injury from ^{90}Y (7,8). This concept of "pseudocirrhosis" has been previously described in the literature to differentiate the underlying cause of liver morphology that describes drug-induced hepatotoxicity, resulting in a nodular shrunken liver pattern in patients with metastatic breast cancer (15).

Further analyses were performed by stratifying patients based on cirrhosis-like morphology and clinical symptoms of hepatic dysfunction into the following 3 groups: patients without cirrhosis-like morphology, patients with cirrhosis-like morphology without clinical implications, and patients with cirrhosis-like morphology with clinical implications. The mean radiation dose to each hepatic lobe was included in this analysis.

Liver and Spleen Volumes

Liver and spleen volumetric calculations were performed at baseline and at the most recent imaging follow-up by two radiology residents, each with 1.5 years of diagnostic radiology training in interpreting cross-sectional abdominal imaging. Findings were verified by an interventional radiologist with 11 years of experience in radioembolization. Whole-liver volumes were calculated; segmentation of

measurements was not done. In total, 108 scans were evaluated, which included a combination of MR imaging and CT. Nine patients had splenectomy at baseline and were not included in the spleen volumetric analysis on follow-up. Two patients had right lobectomy at baseline imaging before ^{90}Y radioembolization with subsequent left hepatic lobe ^{90}Y therapy and were classified as having undergone whole-liver ^{90}Y treatments.

Images were transferred to VITREA medical imaging software (Vital Images, Minnetonka, Minnesota). A computer-assisted manual volumetric drawing of hepatic lobes on the portal-venous phase of T1 postgadolinium MR sequences (sophisticated harmonic artifact reduction for phase data or volumetric interpolated breath-hold examination) or on CT (by contouring the right and left lobes) was performed. The hepatic hilum (main biliary ducts and vessels, eg, portal vein, hepatic artery), gallbladder, and inferior vena cava were excluded from the volumetric measurement.

The measured and calculated volumes were defined as follows. Liver volume change percentage was calculated by subtracting baseline liver volume from follow-up liver volume, dividing by baseline liver volume, and multiplying by 100. Spleen volume change percentage was calculated by subtracting baseline spleen volume from follow-up spleen volume, dividing by baseline spleen volume, and multiplying by 100.

Toxicity Analysis

Of the patients with new cirrhosis-like liver morphology after ^{90}Y radioembolization, those with progressive clinical signs of liver decompensation from their most recent clinical visits were identified. Clinical symptoms of progressive hepatic decompensation were defined as worsening hepatic encephalopathy, jaundice, upper gastrointestinal bleeding, ascites, anasarca, or lower-extremity edema. Relevant but nonspecific symptoms such as anorexia, weight loss, weakness, and fatigue were not included. Correlation of clinical symptoms with imaging findings of tumor progression was assessed. Exposure to potentially hepatotoxic systemic agents was recorded. Clinically significant hepatotoxicity was solely attributed to ^{90}Y only when patients showed imaging and laboratory findings of portal hypertension with associated clinical symptoms of hepatic decompensation in the absence of other potentially confounding hepatic insults (disease progression and/or exposure to hepatotoxic drugs).

Statistical Analysis

Univariate and multivariate statistical analysis with paired *t* test, Fisher exact test, analysis of variance, Cochran–Mantel–Haenszel test, and Kruskal–Wallis test were performed, with significance set at $P < .05$.

RESULTS

Imaging Results

Five patients were removed from imaging analysis because they presented with cirrhosis-like morphology at baseline. The median time to development of cirrhosis-like morphology on imaging was 1.8 years (range, 0.7–7.2 y). Imaging findings of cirrhosis-like liver morphology and portal hypertension were more common in the whole-liver cohort (Fig). Cirrhosis-like morphology developed in 22 of 39 patients (56.4%) who underwent whole-liver ^{90}Y radioembolization, ascites developed in 16 of 39 (41.0%; n = 6 large, n = 4 moderate, n = 5 small, and n = 1 trace), and varices developed in six of 39 (15.4%; Fig). Compared with baseline, tumor progression had developed at the most recent follow-up in 18 patients (46.2%) treated with whole-liver ^{90}Y radioembolization: 94.4% (17 of 18) had > 50% liver involvement, 66.7% (12 of 18) had > 75% liver involvement, including 2 patients with tumor invading the

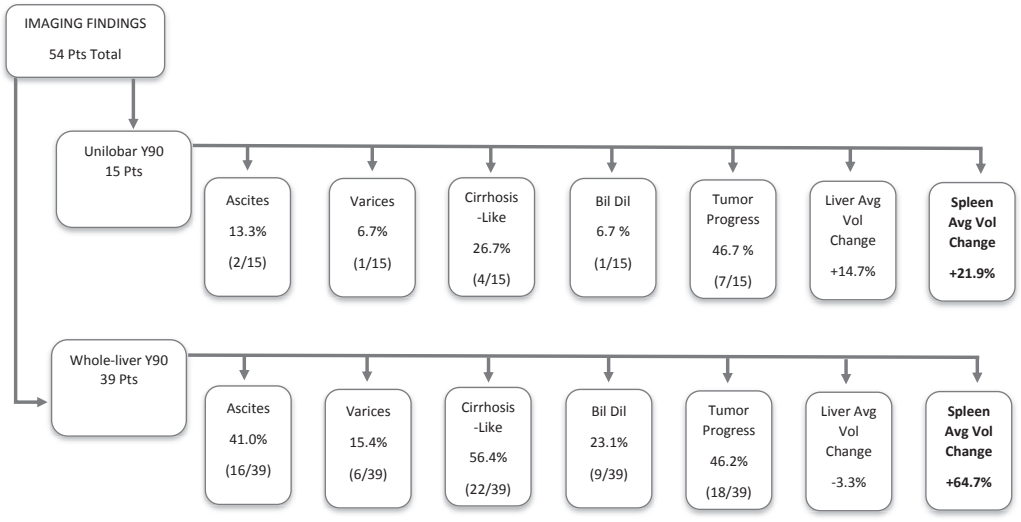

Figure. Imaging findings before and after ^{90}Y radioembolization in patients who underwent whole-liver versus unilobar treatment (bold text indicates $P \leq .05$; Table 1).

inferior vena cava and 1 patient with tumor invading the extrahepatic bile ducts, and the remaining 5.6% (1 of 18) had 25%–50% liver involvement. Nine of 39 patients (23.1%) showed new findings of intrahepatic biliary ductal dilation. None were related to radioembolization: 5 developed in the setting of tumor progression compressing bile ducts, 2 were transient and remote from treatment, 1 patient had extraanatomic liver surgery that resulted in biliary injury, and 1 was remote from the ^{90}Y treatment site.

One of the 26 patients in whom cirrhosis-like liver morphology developed exhibited a distinct imaging pattern. This patient, who had been treated with whole-liver ^{90}Y radioembolization, was diagnosed with ethanol-related cirrhosis following radioembolization. Imaging of this patient revealed multiple lobulations and conspicuous nodular contours on a background of heterogeneous liver parenchyma; the remaining 25 patients had a mildly undulating liver surface contour with minimally heterogeneous parenchyma, termed cirrhosis-like for the present study.

Table 1 reports liver and spleen volume changes. There was no statistically significant change in whole liver volume for patients undergoing whole-liver ($P = .433$) or unilobar ($P = .213$) radioembolization. There was a significant increase in spleen volume (whole-liver, 64.7%, 335 cm^3 vs 223 cm^3, $P = .0009$; unilobar, 21.9%, 275 cm^3 vs 224 cm^3, $P = .0464$).

Laboratory Results

For patients who were treated with whole-liver ^{90}Y radioembolization, there was a significant serum platelet count reduction (from 255 × 10^9/L to 201 × 10^9/L; $P = .023$), decrease in serum albumin level (from 3.4 g/dL to 2.9 g/dL; $P = .0002$), increase in aspartate aminotransferase level (from 27 U/L to 53 U/L; $P = .0014$), and increase in alkaline phosphatase level (from 110 U/L to 359 U/L; $P < .00001$; Table 2). There were no statistically significant abnormalities in laboratory values for patients treated with unilobar ^{90}Y radioembolization (Table 3). At the most recent follow-up, 14 of 54 total patients had more severe hyperbilirubinemia (> 1 mg/dL) compared with baseline. Of these 14 patients, 21.4% (n = 3) had developed biliary obstruction, 57.1% (n = 8) were exposed to systemic therapies, and 78.6% (n = 11) had tumor progression.

Table 1. Liver and Spleen Volume Changes before and after Unilobar and Whole-Liver ^{90}Y Radioembolization

Measurement	Whole-Liver		Unilobar	
	Volume	*P* Value	Volume	*P* Value
Liver (mL)				
Baseline	1,874 ± 658	–	1,764 ± 960	–
Recent	1,802 ± 821	–	2,061 ± 1,616	–
Spleen (mL)				
Baseline	223 ± 94	–	224 ± 85	–
Recent	335 ± 220	–	275 ± 129	–
Change (%)				
Liver	−3.34 ± 31.9	.4334	14.7 ± 53	.2129
Spleen	64.7 ± 110.6	.0009	21.9 ± 29	.0464

^{90}Y = yttrium-90.
Note–Values presented as mean ± standard deviation.

Table 2. Mean Laboratory Findings before and after Whole-Liver ^{90}Y Radioembolization

Measurement	Baseline	Follow-up	*P* Value*
Platelets (1 × 10^9/L)	255.4	200.9	.0230
Albumin (g/dL)	3.4	2.9	.00024
ALT (U/L)	26.9	56.2	.0934
AST (U/L)	27.2	53.2	.0014
Tbil (mg/dL)	1.1	2.2	.0566
ALP (U/L)	110.2	359.2	< .00001

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin; ^{90}Y = yttrium-90.
*Calculated by *t* test.

Table 3. Laboratory Findings before and after Unilobar ^{90}Y Radioembolization

Measurement	Baseline	Follow-up	*P* Value*
Platelets (1 × 10^9/L)	256.9	250.7	.7957
Albumin (g/dL)	3.5	3.6	.4997
ALT (U/L)	22.8	41.5	.0266†
AST (U/L)	22.3	33.9	.0733
Tbil (mg/dL)	0.8	0.7	.4054
ALP (U/L)	77.2	240.3	.0603

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin; ^{90}Y = yttrium-90.
*Calculated by *t* test.
†Although significantly different, these values are both within normal limits.

Radiation Dose and Multivariate Analyses

Mean radiation dose for each lobar treatment session was 114 Gy (range, 11–340 Gy). For patients who underwent repeated treatments, the mean cumulative radiation doses were 254 Gy (range, 109–524 Gy) to the right hepatic lobe and 375 Gy (range, 175–762 Gy) to the left hepatic lobe. Additional analysis was performed by stratifying patients into three groups based on cirrhosis-like imaging findings and clinical implications of hepatic dysfunction (Table 4). Confirming the initial univariate analysis, there were significant between-group differences in the development of new ascites ($P < .0001$), tumor progression ($P < .0001$), albumin level ($P = .0035$), aspartate aminotransferase level ($P = .032$), total bilirubin level ($P = .023$), and alkaline phosphatase level ($P = .042$). There were no significant between-group differences in the development of varices ($P = .168$), liver volume ($P = .795$), spleen volume

Table 4. Analysis Based on Cirrhosis-Like Imaging Findings and Clinical Implications of Hepatic Dysfunction

Variable	Group 1	Group 2	Group 3	*P* Value
Tumor progression (%)	39.1	47.1	55.6	< .0001
Per-patient incidence (%)				
Development of ascites	13.0	35.3	88.9	< .0001
Development of varices	8.7	11.8	33.3	.1679
Development of biliary obstruction	26.1	23.5	0.0	.0857
Liver volume (mL)	1,840.8	1,821.5	1,758.9	.7947
Spleen volume (mL)	272.4	281.1	265.7	.9472
Platelets (1×10^9/L)	225.0	258.7	201.2	.6072
Albumin (g/dL)	3.45	3.32	2.68	.0035
Alanine aminotransferase (U/L)	33.6	34.2	65.5	.8001
Aspartate aminotransferase (U/L)	29.8	38.1	53.6	.0321
Total bilirubin (mg/dL)	1.32	1.16	2.22	.0232
Alkaline phosphatase (U/L)	159.3	193.5	293.5	.0416
Right hepatic lobe cumulative radiation dose (Gy)	174.1	182.9	194.7	.8126
Left hepatic lobe cumulative radiation dose (Gy)	226.6	256.6	223.6	.5119
Whole-liver ^{90}Y treatment (%)	60.9	82.4	88.9	.1999
Repeat ^{90}Y treatment (%)	54.2	41.2	44.4	.9282

Note–group 1, patients without cirrhosis-like features on imaging; group 2, patients with cirrhosis-like features on imaging without clinical implications of hepatic dysfunction; group 3, patients with cirrhosis-like features on imaging with clinical implications of hepatic dysfunction.
^{90}Y = yttrium-90.

Table 5. Specific Symptoms of Patients with Clinical Progression of Hepatic Decompensation after ^{90}Y Radioembolization

Pt. No.	Radioembolization	Symptoms of Progressive Hepatic Decompensation (Interval after ^{90}Y Radioembolization)
1	Whole-liver	Refractory ascites with worsening lower-extremity edema (2.03 y)
2	Whole-liver	Refractory ascites (2.46 y), worsening lower-extremity edema (2.34 y), GI bleeding (2.58 y) with EGD showing portal hypertensive gastropathy
3	Whole-liver	Large pleural effusion (3.19 y), worsening ascites and lower-extremity edema (3.12 y), GI bleeding (2.75 y) with EGD showing esophageal ulceration but no varices
4	Whole-liver	Worsening anasarca and lower-extremity edema (2.1 y)
5	Whole-liver	Progressive lower-extremity edema (3.87 y), GI bleeding (3.05 y), EGD negative
6	Whole-liver	Increasing ascites (8.75 y), worsening lower-extremity edema (8.79 y), GI bleeding (7.26 y), EGD negative
7	Whole-liver	Worsening ascites and lower-extremity edema (3.40 y)
8	Whole-liver	Worsening lower-extremity edema (3.58 y)
9	Unilobar	Progressive abdominal swelling with worsening lower-extremity edema (3.07 y)

EGD = esophagogastroduodenoscopy; GI = gastrointestinal; ^{90}Y = yttrium-90.

($P = .947$), right or left hepatic lobe cumulative radiation dose ($P = .813$ and $P = .512$, respectively), whole-liver ^{90}Y treatment ($P = .200$), or repeat ^{90}Y treatment ($P = .928$).

Clinical Progression of Hepatic Decompensation

Eight of 22 patients treated with whole-liver ^{90}Y radioembolization (20.5%) with new cirrhosis-like morphology on recent follow-up imaging exhibited worsening clinical symptoms of progressive hepatic decompensation (Table 5). Six of 8 patients (75%) with clinical progression correlating with imaging and laboratory findings of liver decompensation showed the development of hepatic tumor progression; all had > 50% tumor progression, and 4 had > 75% liver involvement. These 6 patients were subsequently exposed to hepatotoxic systemic therapies, including capecitabine (Xeloda; Genentech, South San Francisco, California), everolimus (AFINITOR; Novartis, Basel, Switzerland), temozolomide (TEMODAR; Merck, Kenilworth, New Jersey), sunitinib (Sutent; Pfizer, New York, New York), pazopanib (VOTRIENT; Novartis), streptomycin sulfate (Merck), doxorubicin (Adriamycin; Pfizer), etoposide (Etopophos; Bristol-Myers Squibb, New York, New York), carboplatin (Paraplatin; Bristol-Myers Squibb), and lutetium-177–labeled somatostatin analogues. Only 2 patients (5.1%) treated with whole-liver ^{90}Y radioembolization exhibited clinical progression of hepatic decompensation without another potential confounding cause. One patient died at 4.7 years, and the other at 3.8 years, after first ^{90}Y treatment. Four patients treated with unilobar ^{90}Y radioembolization had exhibited cirrhosis-like liver morphology on recent imaging, one of whom (25%) had clinical symptoms of hepatic decompensation. This patient had severe disease progression (> 90% liver involvement) with tumor invasion of the IVC.

DISCUSSION

The long-term impact of radioembolization on hepatic function is not well known. This is important when considering therapeutic options in patients with long life expectancy (ie, those with low-grade mNET) or when considering this therapy earlier in the disease course for patients with metastatic disease (eg, in first-line treatment of metastatic colorectal cancer [16]). In the present study, it

was found that more patients with mNET who underwent whole-liver ^{90}Y radioembolization showed long-term (> 2-y follow-up) imaging and laboratory signs of hepatic decompensation compared with patients who underwent unilobar ^{90}Y radioembolization. However, only 5.1% of patients treated with whole-liver ^{90}Y radioembolization exhibited clinical symptoms of hepatic decompensation that could be solely attributed to ^{90}Y. There was no clinically significant hepatotoxicity attributable to ^{90}Y in patients who had undergone unilobar treatments.

Imaging findings of portal hypertension following radioembolization have been described (7,8,10). Radiation to the liver can produce liver injury and fibrosis secondary to radiation-induced fibrotic tissue remodeling, resulting in increased portal pressures and splenic enlargement (7,8,10). In the present study, we found significant increases in splenic volume over the study period: a 64.7% increase (P = .0009) for patients treated with whole-liver ^{90}Y radioembolization and a 21.9% increase (P = .0464) for patients treated with unilobar ^{90}Y radioembolization. This change in splenic volume is likely a gradual event, as this phenomenon has been described in studies with longer-term follow-up (8,9,17) but not in those with shorter follow-up periods (7,18). There was no significant change in whole-liver volume following radioembolization. This is in accordance with previous studies by Seidensticker et al (8) and Ahmadzadehfar et al (18), who investigated patients with liver metastases of different origins undergoing bilobar or sequential lobar ^{90}Y radioembolization. In comparison, several other studies with longer follow-up (7,19) have demonstrated statistically significant reductions in whole-liver volumes along with splenic volume increases after whole-liver ^{90}Y radioembolization. There are a few possible explanations for the fact that the whole liver volume did not change significantly in the present study. First, the sequential lobar approach (vs bilobar) might impart a protective benefit, as the originally untreated hepatic lobe might undergo hypertrophy before radioembolization of that lobe. Second, 46% of the patients who underwent whole-liver ^{90}Y radioembolization showed hepatic tumor progression, and liver expansion by tumor involvement could have confounded volumetric analysis.

Compared with those who underwent unilobar ^{90}Y radioembolization, patients treated with whole-liver ^{90}Y radioembolization were more likely to exhibit cirrhosis-like liver morphology (56.4% vs 26.7%) following treatment, in addition to imaging findings of portal hypertension such as ascites (41.0% vs 13.3%) and varices (15.4% vs 6.7%). This is plausible given the nonradiated liver's ability for compensatory hypertrophy (7,8,17). Also, there was more significant spleen enlargement in patients treated with whole-liver ^{90}Y radioembolization than in those treated with unilobar ^{90}Y radioembolization (64.7% vs 21.9%).

Unilobar ^{90}Y radioembolization had no significant long-term impact on hepatic function as assessed by changes in serum laboratory values. Whole-liver ^{90}Y radioembolization significantly reduced serum platelet count (P = .023) and albumin level (P = .0002). These results are consistent with the biochemical hepatotoxicity after radioembolization reported in many previous publications (5,12,17,20,21). In these studies with limited follow-up periods, most toxicities were low-grade and more pronounced for whole-liver therapy versus unilobar treatments. There is a paucity of data regarding long-term (> 6 mo follow-up) hepatotoxicity of ^{90}Y. Gaba et al (22) described three of 20 patients with primary liver tumors with grade 1/2 bilirubin toxicities (defined per Common Terminology Criteria for Adverse Events) at greater than 12 months' follow-up after unilobar ^{90}Y radioembolization. Loree et al (23) published a case report of a patient who underwent sequential lobar ^{90}Y radioembolization for pancreatic neuroendocrine tumor metastatic to the liver and had imaging and clinical findings of pathologic confirmation of progressive hepatic failure and cirrhosis at 35 months after radioembolization, which was attributed as a complication of ^{90}Y.

Radioembolization is postulated to cause hepatic fibrosis, resulting in contraction of hepatic parenchyma with subsequent portal hypertension (4,20,23,24). In 32 patients with chemotherapy-refractory metastatic liver disease of various origins, Jakobs et al (7) showed that, despite the imaging findings of portal hypertension, no patients exhibited symptoms of liver failure at a mean follow-up of 139 days after ^{90}Y radioembolization. Although many patients in the present study exhibited imaging signs of portal hypertension, particularly in the whole-liver ^{90}Y radioembolization group, progressive clinical symptoms of portal hypertension developed in only 20.5% at a minimum 2-year follow-up. In most of these patients, the clinical symptoms could not be solely attributed to radioembolization. These patients had hepatic tumor progression with > 50% liver involvement, which could impact hepatic function. All patients with disease progression received systemic therapies with known hepatotoxic potential. Studies have demonstrated that toxins from chemotherapy and drugs are more damaging to sinusoidal endothelial cells than to hepatocytes, causing hepatic sinusoidal obstruction, centrilobular vein fibrosis, and liver injury (25,26). Only 2 patients in the present study exhibited clinical signs of hepatic dysfunction without other potential confounding factors. Both patients received whole-liver radioembolization, and both died of progressive hepatic dysfunction despite transjugular intrahepatic portosystemic shunt creation.

There are several limitations to the present study. First, this is a single-institution study from a tertiary-level center reporting on a relatively small patient cohort. Second, volume changes after radioembolization did not take into account the tumor burden. Third, the difficulty with the use of volume changes and liver texture to define outcomes following radioembolization lies in differentiating normal radiographic changes following radioembolization from cirrhosis-like morphology. Fourth, even though 61% of patients in the study had previous or concurrent systemic therapy, details regarding these therapies are incomplete because many of the patients (> 50%) were treated at outside hospitals.

In conclusion, whole-liver ^{90}Y radioembolization for patients with neuroendocrine tumors results in long-term imaging findings of cirrhosis-like morphology and portal hypertension in > 50% of treated patients, with additional imaging and laboratory manifestations of hepatic decompensation that are more pronounced than those in patients treated with unilobar ^{90}Y radioembolization. A majority of these patients will remain clinically asymptomatic. This knowledge is important, as patients with mNETs have longer life expectancies than patients with other unresectable hepatic metastases. Although this practice may translate into improved tumor response rates and overall survival, there may conceivably be manifestations of long-term hepatotoxicity from ^{90}Y.

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