Yttrium-90 Radioembolization for the Treatment of Unresectable Hepatocellular Carcinoma in Patients with Transjugular Intrahepatic Portosystemic Shunts

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ABSTRACT

Purpose: To evaluate the toxicity and response to radioembolization with yttrium-90 (^{90}Y) glass microspheres in patients with hepatocellular carcinoma (HCC) and existing transjugular intrahepatic portosystemic shunts (TIPS).

Materials and Methods: For treatment of unresectable HCC, 12 patients with a patent TIPS underwent a total of 21 infusions of ^{90}Y. Toxicity within 90 days of treatment was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0). Imaging response within the index lesion was assessed using the World Health Organization (WHO) and European Association for the Study of the Liver (EASL) guidelines. Survival was calculated using the Kaplan-Meier method.

Results: All patients had a patent TIPS on imaging before treatment. Clinical toxicities included fatigue (83%), encephalopathy (33%), and abdominal pain (25%). Three patients (25%) experienced new grade 3 or 4 bilirubin toxicity. Imaging response was achieved in 50% and 67% of patients according to WHO and EASL criteria. Six patients (50%) went on to liver transplantation. Median survival censored for liver transplantation was 498 days (95% confidence interval [CI],100–800 d), and uncensored median survival was 827 days (95% CI, 250–2,400 d).

Conclusions: ^{90}Y radioembolization may be a safe and effective treatment for patients with unresectable HCC and existing TIPS. This minimally embolic therapy may be particularly useful as a bridge to curative liver transplantation.

ABBREVIATIONS

CI = confidence interval, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma, SD = standard deviation, TIPS = transjugular intrahepatic portosystemic shunt, WHO = World Health Organization, ^{90}Y = yttrium-90

Advanced cirrhosis and portal hypertension often limit treatment options in patients with hepatocellular carcinoma (HCC). Because of extent of disease or advanced underlying cirrhosis and portal hypertension, 84% of patients presenting with advanced intrahepatic HCC do not undergo any potentially curative therapy (ie, transplant, operative resection, or ablation) (1,2). As a consequence, the overall annual survival rate of newly diagnosed HCC is $< 50\%$ (3).

Transcatheter intraarterial therapies, such as arterial embolization, chemoembolization, and radioembolization, have emerged as palliative treatment options for patients with unresectable HCC (4–8). These therapies take advantage of the dual blood supply of the liver. Typically, HCC is perfused by the hepatic artery, whereas the hepatic parenchyma obtains its blood supply from the portal vein (9). This portal venous perfusion enables embolization of the hepatic artery without concern for ischemic necrosis of the liver. However, advanced cirrhosis and resultant portal hypertension may mitigate this anatomic advantage of the liver.

Portal hypertension is an independent risk factor for the development of HCC, and these consequences of cirrhosis

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are often concomitant (10). Esophageal varices are present in 63% of patients with HCC (11) and have been associated with increased mortality (12,13). Creation of a transjugular intrahepatic portosystemic shunt (TIPS) can palliate complications of portal hypertension such as bleeding varices or refractory ascites; however, diversion of portal flow may increase complications from intraarterial therapies for HCC.

Retrospective studies have suggested that chemoembolization may be safe in patients with TIPS and adequate hepatic function (14,15). Studies of ^{90}Y treatment of HCC have not reported the presence of TIPS; therefore, information on the safety and efficacy of radioembolization in these patients is lacking. The purpose of this study is to present safety and early outcome data from cirrhotic patients with existing TIPS treated with yttrium-90 (^{90}Y) radioembolization for unresectable HCC.

MATERIALS AND METHODS

Patients

Between October 2004 and March 2011, 12 patients with a patent TIPS and a diagnosis of unresectable HCC were treated with ^{90}Y microspheres using a protocol approved by our institutional review board. Patients were referred for treatment after discussion at a multidisciplinary tumor board composed of hepatology, medical oncology, transplant surgery, and interventional radiology clinicians. This retrospective study complies with reporting standards established by the Society of Interventional Radiology (16).

Patient selection criteria included (*i*) diagnosis of unresectable HCC as defined by the American Association for the Study of Liver Diseases guidelines (17), (*ii*) the presence of TIPS that was patent on imaging before treatment, (*iii*) Eastern Cooperative Oncology Group performance status 0–2 (18), (*iv*) and ability to undergo arterial catheterization and angiography. Patients were excluded from treatment if they had significantly abnormal laboratory values before treatment (absolute granulocyte count $\leq$ 1,500/μL, platelet count $\leq$ 40,000/μL, serum creatinine $\geq$ 2.0 mg/dL, bilirubin $>$ 3.0 mg/dL), active uncontrolled infection, significant extrahepatic disease representing an imminent fatal outcome, or any other significant underlying medical or psychiatric illness. Two patients outside of the exclusion criteria (bilirubin 3.1 and 8.2 mg/dL) underwent superselective radioembolization after discussion at a multidisciplinary conference.

Table 1 summarizes descriptive details of the patient population. Nine patients (75%) had prior TIPS creation for variceal hemorrhage, and three patients (25%) received TIPS for refractory ascites. Seven patients (58%) had known VIATORR stent grafts (W. L. Gore & Associates, Flagstaff, Arizona), and five patients (42%) had bare metal stents. The mean time from TIPS creation to initial radioembolization was 666 days (standard deviation [SD], 480 d; range, 19–1,408 d). One patient received a second parallel TIPS for recurrent variceal hemorrhage in the

Table 1. Patient Population

Demographics and Previous Treatments	No. (%)
Age (y)	
$<$ 63	6 (50)
$\geq$ 63	6 (50)
Ethnic group	
White	6 (50)
Black	1 (8)
Hispanic	5 (42)
Sex	
Male	9 (75)
Female	3 (25)
Previous treatments	
None	10 (83)
Radiofrequency ablation	1 (8)
Resection	1 (8)
Tumor Characteristics	
Lesion distribution	
Unilobar	8 (67)
Bilobar	4 (33)
Measurable lesions	
1	6 (50)
2	4 (33)
$\geq$ 3	2 (17)
Replacement by tumor (%)	
0–25	8 (67)
26–50	3 (25)
51–75	1 (8)
$>$ 75	0
AFP level (ng/mL)	
$<$ 200	8 (67)
$\geq$ 200	4 (33)
UNOS stage	
I	0 (0)
II	6 (50)
III	4 (33)
IVA1	1 (8)
IVA2	1 (8)
Liver Function	
Cause of cirrhosis	
Alcohol	1 (8)
HCV	3 (25)
HCV + alcohol	2 (17)
Primary biliary cirrhosis	3 (25)
Nonalcoholic steatohepatitis	2 (17)
Cryptogenic	1 (8)
Time from TIPS placement (d)	
$>$ 730	5 (42)
$\leq$ 730	7 (58)
Portal vein thrombosis*	
No	11 (92)
Yes	1 (8)
Ascites	
No	8 (67)
Yes	4 (33)

(Continued)