^{90}Y Radioembolization for Locally Advanced Hepatocellular Carcinoma with Portal Vein Thrombosis: Long-Term Outcomes in a 185-Patient Cohort

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We report survival outcomes for patients with advanced-stage hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) treated with ^{90}Y radioembolization. **Methods:** With institutional review board approval, we searched our prospectively acquired database for ^{90}Y patients treated between 2003 and 2017. Inclusion criteria were patients who had HCC with tumor PVT. Patients with metastases were excluded. Laboratory data were collected at baseline and 1 mo after ^{90}Y radioembolization. Toxicity grades were reported according to the Common Terminology Criteria for Adverse Events, version 4.0, and long-term survival outcomes were reported and stratified by Child–Pugh class (CP). Overall survival was calculated using the Kaplan–Meier method. Multivariate analysis was performed using Cox proportional hazards regression. A subanalysis for patients with a high level of α-fetoprotein (AFP) (>100 ng/dL) was conducted. **Results:** In total, 185 patients with HCC PVT underwent ^{90}Y radioembolization. Seventy-four (40%) were CP-A, 51 (28%) were CP-B7, and 60 (32%) were ≥CP-B8. New albumin, bilirubin, and alkaline phosphatase grade 3/4 toxicities were, respectively, 3%, 10%, and 0% for CP-A; 14%, 12%, and 6% for CP-B7; and 23%, 32%, and 3% for ≥CP-B8. Median overall survival for CP-A patients was 13.3 mo (95% confidence interval [CI], 8.7–15.7 mo). CP-B7 and ≥CP-B8 patients exhibited median overall survival of 6.9 mo (95% CI, 5.3–10.1 mo) and 3.9 mo (95% CI, 2.9–5.0 mo), respectively. Significant overall survival prognosticators on univariate analysis were albumin, bilirubin, ascites, tumor size 5 cm or smaller, focality, distribution, infiltration, Eastern Cooperative Oncology Group status, AFP level, and PVT extent. Multivariate analysis showed the prognosticators of overall survival to be bilirubin, no ascites, tumor size 5 cm or smaller, solitary lesion, baseline AFP level lower than 100 ng/dL, and Eastern Cooperative Oncology Group status. Of 123 patients with a high AFP level (>100 ng/dL), 12 patients achieved restored normal AFP levels (<13 ng/dL) and exhibited median overall survival of 23.9 mo (95% CI, 20.1–124.1 mo). AFP responders at 1 mo had better overall survival than nonresponders, at 8.5 mo versus 4.8 mo ($P = 0.018$); AFP responders at 3 mo had overall survival of 13.3 mo, versus 6.9 mo for nonresponders ($P = 0.021$). **Conclusion:** ^{90}Y radioembolization can serve as a safe and effective treatment for advanced-stage HCC patients with tumor PVT. Overall survival outcomes are affected by baseline liver function, tumor size, and AFP level.

Key Words: hepatocellular carcinoma (HCC); ^{90}Y radioembolization; portal vein thrombosis (PVT)

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, with a marked increase in prevalence in the United States within the past 50 y (*1,2*). It is the most common primary liver malignancy and the second most common cause of cancer-related mortality worldwide (*3*). Because of comorbidities, underlying poor liver function, large tumor size, and late-stage presentation, only 10% of HCC patients can receive curative treatments (*4*).

An estimated 7%–15% of HCC patients present with infiltrative disease (*5*). Most of those patients present with portal vein thrombosis (PVT). Therefore, they are not typically considered candidates for possible curative treatments (resection, transplantation), given that the presence of PVT significantly increases the chances of extrahepatic spread and decreases overall survival (*6*). ^{90}Y radioembolization has previously been found to be a safe and promising treatment for HCC patients with PVT. Because the treatment is microembolic, it maintains the hepatic vasculature intact (*7*).

There are several treatment options for HCC patients with PVT. The current standard of care for these patients is sorafenib (*8*). Regorafenib also has been proven to provide a survival benefit for HCC patients who progressed during sorafenib treatment (*9*). Other systemic treatments, such as erlotinib, have failed to provide improved survival when added to sorafenib (*10*). Although contraindicated for patients with PVT, transarterial chemoembolization is still used (*11–13*).

This study reports on the largest cohort of HCC patients with PVT (without metastases) treated with ^{90}Y radioembolization.

MATERIALS AND METHODS

This retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by the Northwestern University Institutional Review Board. All subjects gave written informed consent for the treatment. The study was a subset analysis of a 1,000-patient

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cohort of consecutive HCC patients who were treated with ^{90}Y radioembolization at our institution from December 2003 to March 2017. To isolate the appropriate cohort, we excluded patients who did not exhibit PVT at baseline, and to reduce the confounding effect of extrahepatic metastases on survival, we excluded patients who had them. This resulted in the identification of 185 patients who demonstrated PVT at baseline imaging. The sample was further subdivided by Child–Pugh class (CP) (CP-A, CP-B7, ≥CP-B8). In a prior analysis, we reported long-term outcomes for a 291-patent cohort that included 96 patients with PVT-only disease. In this study, we shed light on our experience in 185 PVT-only patients treated over a 14-y period (*14*).

Evaluation and Staging

The diagnosis of HCC was based on radiographic findings according to guidelines or biopsy (*15*). Portal vein tumor thrombus was diagnosed on the basis of enhancement during the arterial phase of contrast injection during cross-sectional imaging (*16*). The location of PVT was also assessed (segmental, lobar, main). Six patients with main PVT had tumor thrombus extending to the superior mesenteric vein. These were included in the main PVT group for the purposes of this study. Patients were classified by CP, the criteria of the United Network for Organ Sharing, and the Barcelona Clinic Liver Cancer Criteria.

Patients had prior cross-sectional imaging that elucidated tumor number, size, and location. Patient history, physical examination results, and Eastern Cooperative Oncology Group performance status were assessed during initial clinic visits. The decision to treat patients with ^{90}Y was made during a weekly meeting of a multidisciplinary tumor board.

^{90}Y Treatment

Tumor blood supply and lung shunt fraction were evaluated from planning angiography and ^{99m}Tc-macroaggregated albumin imaging. Radioembolization was then performed per standard methodology, delivering a radiation dose of 80–150 Gy to the hepatic parenchyma using glass microspheres (*17,18*).

AFP Producers

AFP producers within the cohort were defined as patients who had an AFP level higher than 100 ng/mL at baseline. Their laboratory AFP values were collected until their last day of follow-up. AFP responders were defined as patients who had more than a 50% decrease in their AFP level from baseline. Patients were also considered to have a normalized AFP level if they achieved an AFP level of 13 ng/mL or less.

Laboratory Toxicities

Clinical and laboratory assessment was performed at baseline, 1–3 mo after radioembolization, and every 3 mo thereafter. Laboratory toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4.0 (*19*). If patients already met these criteria at baseline and the grade of toxicity did not progress after ^{90}Y radioembolization, the toxicity was considered not attributable to ^{90}Y. Toxicities occurring up to 6 mo after treatment (irrespective of disease progression) were reported.

Statistical Analysis

Overall survival was estimated using the Kaplan–Meier method. Univariate analysis was conducted using the Kaplan–Meier method and the log-rank test. Multivariate analysis was conducted using Cox proportional hazards regression. All statistical analyses were conducted using IBM SPSS Statistics, version 24.

RESULTS

Baseline Characteristics

Table 1 demonstrates demographics and baseline characteristics on the date of the first ^{90}Y treatment. Seventy-four patients (40%)

TABLE 1
Baseline Characteristics

Characteristic	Variable	Data
Age (y)	<65	104 (56.2)
	≥65	81 (43.8)
Sex	Male	148 (80)
	Female	37 (20)
Largest tumor size	<5 cm	50 (27)
	≥5 cm	135 (73)
PVT	Segmental	43 (23)
	Lobar	65 (35)
	Main	77 (42)
Distribution	Solitary	53 (28.6)
	Multifocal	132 (71.4)
Tumor infiltration	Noninfiltrative	80 (43)
	Infiltrative	105 (57)
Tumor location	Unilobar	107 (57.8)
	Bilobar	78 (42.2)
Method of diagnosis	Imaging	121 (65.4)
	AFP	6 (3.2)
	Biopsy	58 (31.4)
ECOG performance status	0	77 (41.6)
	1	93 (50.3)
	2	15 (8.1)
Underlying liver disease	ETOH	26 (14.1)
	HCV	94 (50.8)
	HBV	17 (9.2)
	NASH	6 (3.2)
	Unknown	22 (11.9)
	Cryptogenic	14 (7.6)
	Other	6 (3.2)
Imaging cirrhosis	Present	164 (88.6)
	Absent	21 (11.4)
Ascites	Absent	123 (66.5)
	Moderate	54 (29.2)
	Severe	8 (4.3)
CP	A	74 (40)
	B7	51 (28)
	≥B8	60 (32)
Bilirubin (mg/dL)	<2	156 (84.3)
	2–3	17 (9.2)
	>3	12 (6.5)
Prior liver-directed therapy	None	170 (92)
	Resection	4 (2.2)
	Chemoembolization	8 (4.3)
	Radiofrequency ablation	3 (1.6)
AFP (ng/mL)	≤100	62 (33.5)
	>100	123 (66.5)
Albumin (mg/dL)	>3.5	20 (10.8)
	2.8–3.5	93 (50.3)
	<2.8	72 (38.9)

ECOG = Eastern Cooperative Oncology Group; ETOH = ethanol; HCV = hepatitis C virus; HBV = hepatitis B virus; NASH = nonalcoholic steatohepatitis.
Data are *n* followed by percentage in parentheses; total *n* = 185.

were CP-A, 51 (28%) were CP-B7, and 60 (32%) were ≥CP-B8. Forty-three patients (23%) had segmental PVT, 77 (42%) had main PVT, and 65 (35%) had branch PVT.

Laboratory Toxicities

Data on laboratory toxicities are presented in Table 2.

CP-A. At baseline, grade 1/2 toxicities were noted: bilirubin in 28% ($n = 21$), albumin in 66% ($n = 49$), and alkaline phosphatase in 45% ($n = 61$). The new toxicities noted after treatment were grade 1/2 bilirubin in 8% ($n = 6$), grade 3/4 bilirubin in 10% ($n = 7$), grade 3/4 albumin in 3% ($n = 2$), and grade 1/2 alkaline phosphatase in 10% ($n = 7$).

CP-B7. At baseline, grade 1/2 toxicities were noted: bilirubin in 31% ($n = 16$), albumin in 49% ($n = 25$), and alkaline phosphatase in 55% ($n = 28$). New toxicities noted after treatment were grade 1/2 bilirubin in 8% ($n = 4$), grade 3/4 bilirubin in 12% ($n = 6$), grade 3/4 albumin in 14% ($n = 7$), grade 1/2 alkaline phosphatase in 24% ($n = 12$), and grade 3/4 alkaline phosphatase in 6% ($n = 3$).

≥CP-B8. At baseline, grade 1/2 toxicities were noted: bilirubin in 20% ($n = 12$), albumin in 57% ($n = 34$), and alkaline phosphatase in 73% ($n = 44$). New toxicities noted after treatment were grade 1/2 bilirubin in 32% ($n = 19$), grade 3/4 bilirubin in 32% ($n = 19$), grade 1/2 albumin in 12% ($n = 7$), grade 3/4 albumin in 23% ($n = 14$), grade 1/2 alkaline phosphatase in 12% ($n = 7$), and grade 3/4 alkaline phosphatase in 3% ($n = 2$).

TABLE 2
Toxicities

Toxicity	Grade	CP	Present at baseline*	Newly present after ^{90}Y*
Albumin	1/2	A	49 (66)	0 (0)
		B7	25 (49)	0 (0)
		≥B8	34 (57)	7 (12)
	3/4	A	0 (0)	2 (3)
		B7	0 (0)	7 (14)
		≥B8	0 (0)	14 (23)
Bilirubin	1/2	A	21 (28)	6 (8)
		B7	16 (31)	4 (8)
		≥B8	12 (20)	19 (32)
	3/4	A	0 (0)	7 (10)
		B7	0 (0)	6 (12)
		≥B8	0 (0)	19 (32)
Alkaline phosphatase	1/2	A	45 (61)	7 (10)
		B7	28 (55)	12 (24)
		≥B8	44 (73)	7 (12)
	3/4	A	0 (0)	0 (0)
		B7	0 (0)	3 (6)
		≥B8	0 (0)	2 (3)

*Data are *n* followed by percentage of baseline CP in parentheses. (At baseline, cohort was substratified on the basis of their CP score. New onset ^{90}Y radioembolization toxicities were compared in each class with respective comparable cohort at baseline and were presented in percentages.)

Survival Stratified by CP

Table 3 shows survival stratified by CP.

CP-A patients ($n = 74$) had a median overall survival of 13.3 mo (95% confidence interval [CI], 8.7–15.7 mo). When substratified by location of PVT, survival was 14.3 mo (95% CI, 12.0–17.8 mo) for segmental, 14.2 mo (95% CI, 7.3–19.5 mo) for lobar, and 7.7 mo (95% CI, 4.6–13.8 mo) for main ($P = 0.78$). Patients with an AFP level of more than 100 ng/mL had a survival of 7.8 mo (95% CI, 6.9–15 mo), compared with 15.6 mo (95% CI, 13.2–20.7 mo; $P = 0.16$) for an AFP level of 100 ng/mL or less. A baseline tumor size of 5 cm or less had a survival of 14.2 mo (95% CI, 11.4–24 mo), and a baseline tumor larger than 5 cm had a survival of 11.7 mo (95% CI, 7.8–17.7 mo; $P = 0.27$) (Supplemental Fig. 1; supplemental materials are available at http://jnm.snmjournals.org).

CP-B7 patients ($n = 51$) had a median overall survival of 6.9 mo (95% CI, 5.3–10.1 mo). When substratified by location of PVT, survival was 6.5 mo (95% CI, 3.4–38 mo) for segmental, 6.9 mo (95% CI, 4.6–13.3 mo) for lobar, and 7.7 mo (95% CI, 4.8–11.1 mo) for main ($P = 0.82$). Patients with an AFP level of more than 100 ng/mL had a survival of 6.4 mo (95% CI, 4.6–10.4 mo), compared with 7.9 mo (95% CI, 6.4–14.4 mo; $P = 0.94$) for an AFP level of 100 ng/mL or less. A baseline tumor size of 5 cm or less had a survival of 14.4 mo (95% CI, 6.9–20.1 mo), compared with 6.4 mo (95% CI, 4.8–8.1 mo; $P = 0.04$) for a baseline tumor larger than 5 cm (Supplemental Fig. 2).

≥CP-B8 patients ($n = 60$) had a median overall survival of 3.9 mo (95% CI, 2.9–5.0 mo). When substratified by location of PVT, survival was 8.4 mo (95% CI, 1.2–75.2 mo) for segmental, 4.4 mo (95% CI, 2.5–9.7 mo) for lobar, and 3.4 mo (95% CI, 2.5–4.6 mo) for main ($P = 0.015$). Patients with an AFP level of more than 100 ng/mL had a survival of 3.3 mo (95% CI, 2.3–4.8 mo), compared with 4.8 mo (95% CI, 4.1–9.5 mo; $P = 0.09$) for an AFP of 100 ng/mL or less. A baseline tumor size of 5 cm or less had a survival of 12.6 mo (95% CI, 2.3–21.7 mo), and a baseline tumor larger than 5 cm had a survival of 3.6 mo (95% CI, 2.3–4.8 mo; $P = 0.01$) (Supplemental Fig. 3).

Univariate and Multivariate Analyses

Univariate survival analysis using the Kaplan–Meier method and the log-rank test showed a statistically significant survival benefit in patients with a baseline albumin level of more than 3.5 g/dL ($P = 0.002$), a baseline bilirubin level of less than 2 mg/dL ($P < 0.0001$), absence of ascites ($P = 0.0015$), a tumor size of 5 cm or less ($P = 0.0007$), a solitary lesion ($P = 0.001$), unilobar disease ($P = 0.0015$), noninfiltrative tumors ($P = 0.01$), Eastern Cooperative Oncology Group status 0 or 1 ($P = 0.0001$), and a baseline AFP level of less than 100 ng/dL ($P = 0.05$). Patients who had either segmental or lobar PVT had better survival outcomes than patients with PVT involving the main portal vein ($P = 0.008$).

Multivariate analysis using Cox proportional hazards regression showed a bilirubin level of less than 2 mg/dL, a bilirubin level of 2–3 mg/dL, absence of ascites, a tumor size of 5 cm or less, a solitary lesion, a baseline AFP level of less than 100 ng/dL, and Eastern Cooperative Oncology Group status 0 or 1 to be significant prognosticators of survival (Table 4).

Patients who were AFP producers ($n = 123$) were also analyzed. At 1 mo after ^{90}Y radioembolization, 101 patients were followed up; AFP nonresponders ($n = 52$) had a median overall survival of 4.8 mo (95% CI, 3.7–7.7 mo), versus 8.5 mo (95% CI, 6.5–14.3 mo; $P = 0.018$) for AFP responders ($n = 49$). At 3 mo after ^{90}Y radioembolization, 65 patients had follow-up laboratory tests; AFP nonresponders ($n = 22$)

TABLE 3
Overall Survival Stratified by CP

CP	Factor	Variable	No. of patients*	Median survival†	*P*	Overall survival†
A ($n = 74$)	Age (y)	≥65	30 (41)	17.7 (8.7–19.5)	0.32	13.3 (8.7–15.7)
		<65	44 (59)	11.7 (7.3–14.2)		
	Sex	Male	54 (73)	13.7 (8–19.1)	0.35	
		Female	20 (27)	13.2 (7.7–17.7)		
	PVT	Segmental	24 (32)	14.3 (12.0–17.8)	0.78	
		Lobar	27 (37)	14.2 (7.3–19.5)		
		Main	23 (31)	7.7 (4.6–13.8)		
	AFP	>100 mg/dL	27 (37)	7.8 (6.9–15)	0.16	
		≤100 mg/dL	47 (63)	15.6 (13.2–20.7)		
	Size‡	≤5 cm	25 (34)	14.2 (11.4–24.0)	0.27	
		>5 cm	49 (66)	11.7 (7.8–17.7)		
B7 ($n = 51$)	Age (y)	≥65	24 (47)	6.4 (4.5–8.1)	0.11	6.9 (5.3–10.1)
		<65	27 (53)	7.9 (5.8–13.3)		
	Sex	Male	43 (84)	6.9 (5.0–9.1)	0.60	
		Female	8 (16)	6.5 (3.4–11.0)		
	PVT	Segmental	11 (22)	6.5 (3.4–38)	0.82	
		Lobar	17 (33)	6.9 (4.6–13.3)		
		Main	23 (45)	7.7 (4.8–11.1)		
	AFP	>100 mg/dL	36 (71)	6.4 (4.6–10.4)	0.94	
		≤100 mg/dL	15 (29)	7.9 (6.4–14.4)		
	Size‡	≤5 cm	9 (18)	14.4 (6.9–20.1)	0.04	
		>5 cm	42 (82)	6.4 (4.8–8.1)		
≥B8 ($n = 60$)	Age (y)	≥65	27 (45)	3.5 (2.5–5.0)	0.34	3.9 (2.9–5.0)
		<65	33 (55)	4.1 (2.9–6.7)		
	Sex	Male	51 (85)	3.9 (2.7–5.0)	0.45	
		Female	9 (15)	4.1 (2.7–9.5)		
	PVT	Segmental	8 (13)	8.4 (1.2–75.2)	0.015	
		Lobar	21 (35)	4.4 (2.5–9.7)		
		Main	31 (52)	3.4 (2.5–4.6)		
	AFP	>100 mg/dL	41 (68)	3.3 (2.3–4.8)	0.09	
		≤100 mg/dL	19 (32)	4.8 (4.1–9.5)		
	Size‡	≤5 cm	16 (27)	12.6 (2.3–21.7)	0.01	
		>5 cm	44 (73)	3.6 (2.3–4.8)		

*Data are *n* followed by percentage in parentheses.
†Data are months followed by 95% CI in parentheses.
‡Size of tumor at baseline.

had a median survival of 6.9 mo (95% CI, 5.3–8.9 mo), whereas AFP responders ($n = 43$) had a survival of 13.3 mo (95% CI, 8.7–17.7 mo; $P = 0.021$). AFP producers with a normalized AFP level at any follow-up time ($n = 12$) had a survival of 23.9 mo (95% CI, 20–124 mo), whereas nonnormalized AFP producers ($n = 89$) had a survival of 6.4 mo (95% CI, 4.9–7.8 mo; $P < 0.0001$) (Supplemental Table 1).

DISCUSSION

HCC patients presenting with PVT have limited treatment options because the tumor and underlying liver cirrhosis are further complicated by the development of PVT. Further, unless they have preserved liver function (CP-A), they are precluded from most clinical trials and systemic agents (*15*). Our results indicate that ^{90}Y radioembolization brought about a clinically meaningful increase in overall survival for HCC patients with PVT (predominantly those with preserved liver function), when compared with published outcomes with systemic agents.

Many treatments have been implicated in palliating or providing a survival benefit for patients with advanced-stage HCC. Sorafenib, a small-molecule multikinase inhibitor, remains the systemic treatment of choice for advanced-HCC patients. A

TABLE 4
Univariate and Multivariate Analyses

Predictor	Univariate analysis				Multivariate analysis	
	Category	Overall survival	Hazard ratio	*P*	Hazard ratio	*P*
Age (y)	<65	7.8 (5.8–11)	0.9 (0.6–1.2)	0.49	NA	NA
	≥65	7.5 (5–9.4)	1		NA	
Sex	Female	9.5 (5.3–13.7)	0.9 (0.6–1.3)	0.6	NA	NA
	Male	7.3 (5.8–8.5)	1		NA	
Albumin	>3.5 g/dL	11.7–21	0.4 (0.2–0.7)	0.002	0.7 (0.4–1.4)	0.3
	2.8–3.5 g/dL	7.8 (6.4–11.4)	0.7 (0.5–0.9)		0.7 (0.5–1)	0.07
	<2.8 g/dL	4.8 (4–7.7)	1		1	
Bilirubin	<2 mg/dL	8 (7.3–11)	0.15 (0.03–0.6)	<0.0001	0.16 (0.07–0.3)	<0.0001
	2–3 mg/dL	5 (2.2–9.7)	0.24 (0.05–1.2)		0.18 (0.07–0.43)	0.0001
	>3 mg/dL	2 (1.2–3)	1		1	
Cirrhosis	Absent	6.8 (6.2–8.9)	0.95 (0.6–1.6)	0.86	NA	NA
	Present	7.7 (5–20)	1		NA	
Ascites	Absent	8.8 (7.7–12)	0.6 (0.4–0.85)	0.0015	0.6 (0.4–0.9)	0.01
	Present	4.6 (3.5–6.4)	1		1	
Baseline tumor size	≤5 cm	13.9 (11–20)	0.5 (0.4–0.75)	0.0007	0.64 (0.42–0.97)	0.037
	>5 cm	6.4 (5–7.8)	1		1	
Number of lesions	Solitary	12.6 (7.7–19)	0.6 (0.4–0.78)	0.001	0.62 (0.4–0.98)	0.04
	Multifocal	6.5 (5–7.9)	1		1	
Infiltration	Noninfiltrative	12.6 (7.7–14)	0.67 (0.5–0.9)	0.01	1 (0.7–1.5)	0.9
	Infiltrative tumor	6.2 (4.6–7.7)	1		1	
Tumor distribution	Unilobar	9.4 (7.7–13.3)	0.6 (0.4–0.8)	0.0015	0.68 (0.46–1)	0.068
	Bilobar	5 (4.5–6.5)	1		1	
AFP	<100	11.4 (7.9–13.9)	0.7 (0.5–0.9)	0.05	0.67 (0.5–0.96)	0.03
	≥100	6.5 (5–7.7)	1		1	
ECOG	0	8 (6.7–13.8)	0.32 (0.14–0.78)	0.0001	0.44 (0.24–0.8)	0.01
	1	7.7 (5.2–9.5)	0.35 (0.15–0.8)		0.39 (0.22–0.7)	0.001
	2	2.5 (2–4.6)	1		1	
PVT extent	Segmental	13.8 (8.5–15.7)	0.54 (0.36–0.8)	0.008	0.8 (0.5–1.3)	0.4
	Lobar	7.7 (5.3–10.4)	0.7 (0.5–1)		0.8 (0.5–1.2)	0.2
	Main	5 (4–7.7)	1		1	

NA = not applicable; ECOG = Eastern Cooperative Oncology Group.
Data in parentheses are 95% CI.

randomized controlled trial of sorafenib for advanced-HCC patients found that it increased overall survival and median time to radiologic progression by almost 3 mo, when compared with the placebo group (*20*). Another phase III trial found that sorafenib demonstrated improved survival in HCC patients with both macrovascular invasion and metastatic disease (*21,22*). Recently, Bruix et al. found that regorafenib, another multikinase inhibitor, provided a survival benefit for HCC patients with PVT who tolerated sorafenib but progressed while on therapy (*9*). The study population included only CP-A patients. The regorafenib group showed an overall survival of 10.6 mo, in comparison to 7.8 mo for the placebo group (*9*). Johnson et al. found that brivanib, a tyrosine kinase inhibitor, demonstrated overall survival and time to progression similar to sorafenib as a first line of treatment, but sorafenib was better tolerated than brivanib (*23*). Nivolumab, a programmed cell death protein 1–blocking antibody, has shown promising preliminary results as both a first-line and a second-line systemic therapy for advanced-stage HCC (*24*).

^{90}Y radioembolization has proved to be the locoregional treatment of choice in cases with portal vein invasion (*25*). The small size of ^{90}Y glass microspheres (30 μm) allows for deep infiltration into the tumor without ischemia of the hepatic parenchyma (*7*). Occluding arterial flow to a hepatic region that has no portal venous flow because of malignant portal vein invasion could result in complete loss of blood supply and unfavorable outcomes. Moreover, for most late-stage HCC patients, maintenance of hepatic blood flow is a priority to preserve liver function. Theoretically, this makes a microembolic therapy appealing in such a scenario (*26*).

Until recently, there were no studies comparing ^{90}Y radioembolization and sorafenib as a sole treatment for advanced-stage HCC. However, a new clinical study comparing ^{90}Y resin microspheres to sorafenib found that the median overall survival for the ^{90}Y radioembolization arm was not improved over the sorafenib arm. Additionally, there was no significant difference in progression-free survival between the 2 groups (*27*). There were, however, significant differences between the 2 groups with regard to therapy safety, toxicity profile, and quality of life. Patients treated with ^{90}Y radioembolization had fewer and less severe treatment-related side effects and displayed toxicity and tolerability advantages. ^{90}Y patients also sustained their health status, whereas sorafenib patients had a significant decline in quality of life (*27,28*). The low toxicity profile makes ^{90}Y radioembolization a promising therapy for treatment-naïve late-stage HCC patients.

For CP-A and CP-B7, there was no significant difference in survival among segmental, branch, and main PVT. This finding is interesting because previous studies have repeatedly shown that patients with branch PVT had a significantly longer survival than those with main PVT (*29*). For CP-A patients, baseline tumor size was not a prognosticator of survival. This result could indicate that as long as PVT patients display preserved liver function, ^{90}Y radioembolization can be an effective treatment for such patients. For CP-B7 and ≥CP-B8 patients, tumor size was related to survival. Patients with tumors smaller than 5 cm had significantly longer survivals than patients with larger tumors, indicating that the 5-cm mark is significant in assessing tumor size before treatment.

AFP responders (baseline AFP level > 100 ng/mL) had significantly better survival at the 1-mo and 3-mo landmarks than AFP nonresponders, irrespective of CP. Patients with high AFP levels that became normalized after ^{90}Y radioembolization had a large survival benefit when compared with nonnormalized AFP producers. It has been found that AFP response after locoregional therapy can be used as a tool to assess tumor response, survival, and progression (*30*). More specifically, AFP was correlated with the imaging response and survival criteria of the European Association for the Study of the Liver (*31*). Future studies should investigate whether changes in AFP level can predict survival in PVT patients.

Previous studies have shown that a significant number of CP-A PVT patients treated with ^{90}Y radioembolization eventually progressed to CP-B/C (*29*). This finding suggests that CP-A patients have a limited interval after ^{90}Y radioembolization but before disease progression during which they are still eligible for systemic agents by CP. The concept of ^{90}Y radioembolization followed by adjuvant systemic treatment should be investigated (*32*).

A few comments about the recently reported SARAH and SIRVENIB trials are warranted, given that their focus was on "advanced disease." First, the definition of *advanced* is clear in guidelines and is meant to incorporate PVT, performance status 1 or 2, or extrahepatic metastases (*6*). These trials loosened that definition to include intermediate-stage (and even early-stage) patients, potentially diluting any effect ^{90}Y radioembolization might have over sorafenib. The studies should be interpreted as not meeting their endpoint, and with the statistical design, one can conclude that in those patients ^{90}Y radioembolization was no better and no worse than sorafenib. The studies were not powered for noninferiority, and a declaration that they provide the same survival cannot be made. The studies may also have been limited by the lack of modern dosimetry and boost techniques, currently becoming standards of care in this patient population (*33,34*). Although the analyses were appropriately by intention to treat, this has the secondary effect of biasing in favor of sorafenib, since many more patients are able to start therapy in pill form than those who pass the lung shunt fraction study. Despite designs that favored sorafenib, the secondary endpoints (response, quality of life) all favored ^{90}Y radioembolization, factors that are relevant to patients when considering treatment options. Also, although these 2 studies did not meet their endpoint, it does not mean there is no clinical effect of ^{90}Y radioembolization in this patient population. Demonstrating the benefit of ^{90}Y may require trial designs that are more finely tuned, with more detailed and homogeneous inclusion criteria. It would not be the first time an evolving treatment required several trials and different designs before a positive one was illustrated; several of the early chemoembolization studies were negative before the seminal studies establishing it as a standard of care in intermediate HCC. The same approach may be required for ^{90}Y radioembolization (*35*).

Unique strengths of this analysis include its being the largest homogeneous patient cohort of PVT patients without the confounder of metastases and with long-term 10-y follow-up. These data can be used to help design future studies. Limitations include its being retrospective and lacking a control arm.

CONCLUSION

^{90}Y radioembolization for HCC patients with PVT appears to have an acceptable safety profile, with better survival in CP-A patients than in CP-B patients. This study confirms prior reports of survival in PVT patients treated with ^{90}Y radioembolization, and survival after ^{90}Y radioembolization appears to exceed that in similar patients treated with systemic therapies. Despite the negative studies recently reported, ^{90}Y radioembolization is a reasonable treatment option in properly selected PVT patients. Further controlled studies are needed to compare it with systemic therapies or other locoregional treatments for advanced-stage HCC.

DISCLOSURE

Riad Salem and Robert J. Lewandowski are advisors to BTG. No other potential conflict of interest relevant to this article was reported.

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