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TREATMENT OF HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN TUMORAL THROMBOSIS BY ^{90}Y RADIOEMBOLIZATION: SAFETY AND OUTCOME RESULTS.

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Abstract:
Purpose: Portal vein tumor thrombosis (PVT) is a late stage complication of infiltrative hepatocellular carcinoma (HCC), common in patients. Limited treatment options are available for patients with hepatocellular carcinoma with PVT. We present our initial experience treating such patients with ^{90}Y radioembolization.
Materials and Methods: From August 2011 to February 2013, 31 patients with hepatitis C and HCC with PVT treated by ^{90}Y radioembolization were retrospectively reviewed. Tumor involves the main portal vein in 5 (16.1%) patients, lobar PV in 16 (51.7%) patients, and segmental PV in 10 (32.3%) patients. 36 treatment sessions were performed on 31 patients. 8 patients (25.8%) received whole liver treatment, and the remainder received segmental or lobar treatment. Median dose delivered was 1.92 GBq (range, 0.21–4.96 GBq). 14 patients (45%) started sorafenib treatment one week after radioembolization. Clinical and biochemical toxicities were recorded. Tumor response was evaluated using RECIST and mRECIST criteria. Survival statistics were calculated.
Results: The main clinical toxicity was fatigue (54.8%). One patient experienced grade 3 bilirubin toxicity, and none experienced gastroduodenal ulcers. Overall and PVT response rates by RECIST were 56.5% and 60.9% and by mRECIST 73.9% each, respectively.
Overall mean and median survival were 16.2 months and 7 months. Mean survival stratified by the location of PVT was 21.5, 10.7 and 19.6 months for segmental, lobar and main PVT patients (p=0.256). Patients who died did so from progressive intrahepatic disease. Using univariate analysis, ECOG performance status (p=0.016, HR=3.262), lobar involvement (p=0.036, HR=2.689), serum bilirubin (p<0.0001, HR=6.971) and presence of extrahepatic metastasis (p=0.046, HR=2.896) correlated with survival
Conclusion: ^{90}Y radioembolization treatment for patients with HCC complicated by PVT is safe and results in a very high rate of radiologic response and very encouraging survival

statistics.

Keywords: Hepatocellular carcinoma, Portal vein thrombosis, radioembolization, liver tumor

INTRODUCTION:

In hepatocellular carcinoma (HCC), portal vein invasion is a negative prognostic factor present in up to 44% of patients with HCC at death (1) - those patients have a higher chance of extrahepatic spread and decreased overall survival (2). Portal vein invasion is suspected when HCC is accompanied by adjacent portal vein thrombosis (PVT). This occlusion of the potential main blood flow to the liver leads to diminished perfusion to normal healthy liver, potentially marginalizing the patient's ability to tolerate embolic trans arterial therapies (3). Yttrium-90 (^{90}Y) radioembolization is an established transarterial therapy that has been proven capable of inducing significant tumor necrosis and delaying disease progression (4-6). The minimally embolic nature of radioembolization has made the treatment of HCC with associated PVT an increasingly common indication for its use (7, 8).

Radioembolization delivers ^{90}Y-loaded microspheres into tumor feeding arteries from the hepatic artery. The injected microspheres emit radiation with mean range about 2.5 mm and destroy the tumor cells. Compared to sorafenib, ^{90}Y radioembolization has a higher chance of complete response with more tolerable toxicity profile (9-11).

Studies have shown that radioembolization also demonstrates lower toxicity rates when compared to transarterial chemoembolization (TACE) as well as longer time to progression (5). The advantage of performing radioembolization instead of TACE in HCC with PVT is that radioembolization has a lower risk of ischemic side effects due to minimal arterial occlusion (12). The aim of this study was to evaluate treatment safety and clinical benefit of radioembolization in patients with HCC with PVT.

MATERIALS AND METHODS

Patient selection

31 patients with unresectable HCC presenting with segmental, lobar or main PVT treated between August 2011 and February 2013 were retrospectively reviwed, all patients with HCC were ineligible for radical treatments (surgery, liver transplantation, or percutaneous ablation) or chemoembolization as a result of the presence of PVT were evaluated for ^{90}Y radioembolization.

Inclusion criteria for treatment included (1) HCC by imaging as outlined by the European Association for the Study of the Liver (EASL) or The American Association for the Study of Liver Diseases (AASLD) criteria; (2) nonsurgical candidate; (3) Eastern Cooperative Oncology Group (ECOG) 0 to 2; (4) able to undergo angiography and selective visceral catheterization; (5) adequate hematology (platelets $\geq 50 \times 10^9$/L), renal function (creatinine < 1.5 mg/dL); (6) liver function (bilirubin < 2.0 mg/dL). Exclusion criteria were (1) liver failure (bilirubin > 2.0 mg/dL); (2) evidence of any uncorrectable flow to the gastrointestinal tract observed on angiography and (3) high lung shunt >20%.

Treatment Protocol

The protocol for ^{90}Y microsphere therapy is discussed elsewhere (12, 13). In summary, patients underwent a preparatory angiographic study to (i) identify vascular anatomy, tumor feeding vessels, aberrant vessels and any extrahepatic vessels feeding, and the presence of intrahepatic or intratumoral arterioportal shunting; and (ii) evaluate the direction of portal blood flow (hepatopetal or hepatofugal). Aberrant hepatic vessels and extrahepatic vessels were embolized either by coils or other embolizing materials to prevent the inadvertent misplacement of ^{90}Y microspheres into the gastrointestinal tract or pancreas.).

Technetium Tc 99m–labeled MAA (^{99m} Tc-MAA) particles were then injected with the microcatheter in the intended position for ^{90}Y microsphere infusion. All the patients underwent ^{99m} Tc-MAA planar imaging and SPECT-CT to assess pulmonary shunt and any flow to other extrahepatic organs and to calculate tumor/normal liver ratio. Dosimetry was calculated using modified body surface area to maximize the therapeutic activity to tumorous tissue and minimize exposure of nontumoral parenchyma and lung tissue. The week next to the preparatory angiography study, the prescribed activity of ^{90}Y microspheres was administered by placing the tip of the delivery catheter in the same anatomic position as that used for the ^{99m} Tc-MAA injection.

Data Collection and Follow-up

Biochemical data were obtained at baseline and at 2 weeks, 4 weeks, 8 weeks, and 12 weeks after treatment. Clinical follow-up was obtained at 1 month and 3 months and approximately every 3 months thereafter. Cutoff for the safety and toxicity was taken at a period of 6 months. This is because radiation induced liver disease caused by treatment most probably occur within this time interval. Toxicities occurring beyond this time were not considered to be treatment-related.

Data was collected on demographics, tumor characteristics, radiation dosimetry, grades of toxicity and response. Baseline data were stratified by age (<60 or ≥60), sex (Male or Female), ECOG, Child-Pugh, lobar involvement (unilobar or bilobar), tumor distribution, tumor burden (<25% or 26-50% or 51-75%), PVT location (segmental or lobar or main), total bilirubin (≤1.3 or > 1.3 mg/dL), presence of extrahepatic metastasis, previous liver directed therapy, Anti-angiogenic agents after treatment and tumor response

The dosing information consisted of the dose delivered for the first treatment cycle and the total cumulative dose delivered for all subsequent treatment cycles. Outcome data after treatment included clinical adverse events (AEs), biochemical AEs, imaging response, and overall survival.

Toxicity, response, and survival analyses were censored at time of last clinic visit or call or death. All adverse events were classified for severity using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Any grade 3 or greater adverse events occurring within 6 months following first treatment was considered to be a possibly related adverse event and are therefore reported herein without definite attribution to treatment.

Tumor Response

Tumor response following ^{90}Y radioembolization was assessed at 3 and 6 months by cross sectional imaging. In the evaluation of tumor response, the PVT and overall intrahepatic components of disease were assessed. Response were assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) and modified RECIST criteria (14) in those patients with measurable disease, and the development of new lesions was assessed in all patients which is considered a progressive disease.

Statistical Analysis

Descriptive statistics for nominal, ordinal, and continuous variables, including frequency, mean, median, and range, were used as appropriate. univariate analysis applied the chi-square test with $p < 0.05$ considered as statistically significant. Survival from date of treatment was calculated with the Kaplan-Meier method. A *P* value lower than .05 was considered statistically significant. A commercial statistical software package (SPSS version 22; SPSS, Chicago, Illinois) was used for data analysis.

RESULTS

Patient Characteristics and Treatment

The baseline characteristics of the 31 patients (mean age, 59 years) with PVT who received ^{90}Y microsphere treatment are presented in Table 1. Most patients were men (97%) and have Child-Pugh stage A (83.9%), Two patients received anti-angiogenic agent treatment (6.5%), 13 patients had history of previous chemoembolization while three patients had history of radiofrequency ablation. 12 patients (38.7%) were ECOG 0, 14 patients (45.2%) were ECOG 1 while five patients (16.1%) were ECOG 2. Median bilirubin range was 0.89 mg/dL (0.43 – 3.97) and median alfa-fetoprotein (AFP) was 2218.5 ng/mL (2 – 18,1011)

Table 1. Demographics and Baseline characteristics of the study patients

Characteristic	Patients, *n* (%)
Sex, Male / Female	30 / 1
Age, year: mean (range)	59 (41 – 78)
Previous systemic treatment	
Anti-angiogenic agents	2 (6.5%)
Previous liver-directed treatment	
Radiofrequency ablation	3 (9.7%)
Trans-arterial embolization	13 (41.9%)
ECOG performance status	
0	12 (38.7%)
1	14 (45.2%)
2	5 (16.1%)
Child-Pugh stage	
A	26 (83.9%)
B	5 (16.1%)
Baseline laboratory values: median (range)	
Serum total bilirubin, mg/dL	0.89 (0.43 – 3.97)
Serum AST, IU/L	61 (20 – 180)
Serum ALT, IU/L	38 (11 – 132)
Serum albumin, g/dL	3.6 (2.6 – 4.4)

Platelet count, 10^9/L	140 (44 – 396)
AFP, ng/mL	2218.5 (2 – 18,1011)

Table 2 presents the tumor characteristics for the patients, 48.4% had bilobar disease. Most patients presented by infiltrative tumor disease (58.1%), while 9 patients (29%) had multifocal disease and four patients (12.9%) had unifocal disease. 8 patients (25.8%) presented by high tumor burden >50%, while in 14 patients (45.2%) the tumor burden was 26-50%, <25% tumor burden was found in 9 patients (29%). Portal vein tumoral thrombus was identified in the main portal vein in 5 (16.1%) of patients and in the right or left lobar branches in 16 (51.6%) of patients. Ten patients (32.3%) presented with segmental portal vein occlusion. Three patients (9.7%) were found to have right hepatic vein invasion by the tumor while the left hepatic vein or the left and middle hepatic veins were found invaded in one patient each. 10 patients (32.2%) had lymph node metastases and four patients (12.9%) had extrahepatic metastases to other sites mostly bone.

Table 2. Tumor characteristics of the study patients

Characteristic	Patients, *n* (%)
Tumor location	
Unilobar	16 (51.6%)
Bilobar	15 (48.4%)
Tumor Distribution	
Unifocal	4 (12.9%)
Multifocal	9 (29%)
Infiltrative	18 (58.1%)
Tumor Burden	
< 25%	9 (29%)
26 - 50%	14 (45.2%)
51 - 75%	8 (25.8%)
Portal vein tumor thrombosis	
Segmental	10 (32.3%)
Lobar (right or left)	16 (51.6%)
Main (± lobar)	5 (16.1%)
Hepatic Venous Invasion	
RHV	3 (9.7%)
LHV	1 (3.2%)
LHV&MHV	1 (3.2%)
Metastases	
LN	10 (32.2%)
other	4 (12.9%)

The treatment parameters for the patient cohort are outlined in Table 3. Most of the patients (48.4%) were injected from the right hepatic artery, and left hepatic artery injected in two patients (6.5%), Whole liver treatment with ^{90}Y microspheres was performed in 8 patients (25.8%): one patient received ^{90}Y microsphere infusion from the proper hepatic artery and the other seven received either right and left hepatic artery infusion at the same time in 5 patients or sequential infusions into the right and left hepatic branches with a 3-4 week interval in 2 patients, respectively. The median activity administered was 1.91 GBq (range, 0.21–4.96 GBq). All patients successfully received most of the dose prescribed, without stasis during infusion. This wide range in administered activity relies on the different tumor burden treated in each patient.

The median lung shunt fraction was 4.9% and no patient received an excessive (ie,>30 Gy) radiation dose to the lung.

Table 3. Treatment parameters

Characteristic	Patients, *n* (%)
Number of treatment	
1	27 (87.1%)
2	3 (9.7%)
3	1 (3.2%)
First treatment dose (n=31)	
Calculated activity in GBq: median (range)	1.99 (0.21 – 5.01)
Calculated lung shunt in %: median (range)	4.9 (0 – 19.5)
Administered activity in GBq: median (range)	1.92 (0.21 – 4.96)
Target treatment	
Whole liver	8 (25.8%)
Proper hepatic artery single administration	1 (3.2%)
Two lobar administrations during same procedure	5 (16.1%)
Two lobar administrations sequentially	2 (6.5%)
Right	15 (48.4%)
Left	2 (6.5%)
Right & segment IV	5 (16.1%)
Left & segment IV	1 (3.2%)

Clinical and Biochemical Adverse Events

Table 4 illustrates biochemical AEs classified by CTCAE v5.0. Although there is transient elevation of the liver functions but all of them were grade 1/2 except 1 patient experienced a bilirubin toxicity, which was medically controlled.

Table 4. Main procedure related biochemical and clinical adverse events

Characteristic	Patients, *n* (%)
Biochemical adverse events	
Bilirubin	
Grade 1 / 2	11 (35.5%)
Grade 3 / 4	1 (3.2%)
Albumin	
Grade 1 / 2	14 (45.2%)
Grade 3 / 4	–
Alanine aminotransferase	
Grade 1 / 2	10 (32.2%)
Grade 3 / 4	–
Aspartate aminotransferase	
Grade 1 / 2	8 (25.8%)
Grade 3 / 4	–
Alkaline phosphatase	
Grade 1 / 2	5 (16.1%)
Grade 3 / 4	–
Clinical adverse events (grade1/2)	
Fatigue	17 (54.8%)
Fever	9 (29%)
Abdominal pain	7 (22.6%)

Nausea and/or vomiting	6 (19.4%)
Weight loss	2 (6.5%)

Clinical AEs were classified into gastrointestinal, hematologic, pulmonary and renal. The most common clinical toxicity was fatigue which was present in about 55% of the cases, most of them were mild and disappeared after 4 weeks of treatment, other clinical toxicities was fever, abdominal pain, nausea and/or vomiting and weight loss were seen in less than 30% of the cases. There were no cases of radiation-induced gastritis or pneumonitis. No significant complications or mortalities secondary to the technical aspects of radioembolization e.g. gastrointestinal ulceration.

Treatment responses

Responses to radioembolization treatments are summarized in Table 5. Among the 23 patients who reached the follow up and were evaluated for response, 2 patients (8.7%) showed complete response of the portal venous thrombus by RECIST and 9 patients (39.1%) by mRECIST (Figure 1,2). 14 (60.9%), and 17 (73.9%) patients showed responding disease by RECIST and mRECIST respectively for the portal venous thrombus component. The overall response of the disease by RECIST and mRECIST was 56.5% and 73.9% respectively while the overall disease control was 82.6% by RECIST and mRECIST.

Table 5. Treatment response

Characteristic	Patients, *n* (%)
PVT response	
RECIST	
CR	2 (8.7%)
PR	12 (52.2%)
SD	5 (21.7%)
PD	4 (17.4%)
Responding disease (CR+PR)	14 (60.9%)
Disease control (CR+PR+SD)	19 (82.6%)
mRECIST	
CR	9 (39.1%)
PR	8 (34.8%)
SD	2 (8.7%)
PD	4 (17.4%)
Responding disease (CR+PR)	17 (73.9%)
Disease control (CR+PR+SD)	19 (82.6%)
Overall response	
RECIST	
CR	-
PR	13 (56.5%)
SD	6 (26.1%)
PD	4 (17.4%)
Responding disease (CR+PR)	13 (56.5%)
Disease control (CR+PR+SD)	19 (82.6%)
mRECIST	
CR	7 (30.4%)
PR	10 (43.5%)
SD	2 (8.7%)
PD	4 (17.4%)

Responding disease (CR+PR)	17 (73.9%)
Disease control (CR+PR+SD)	19 (82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

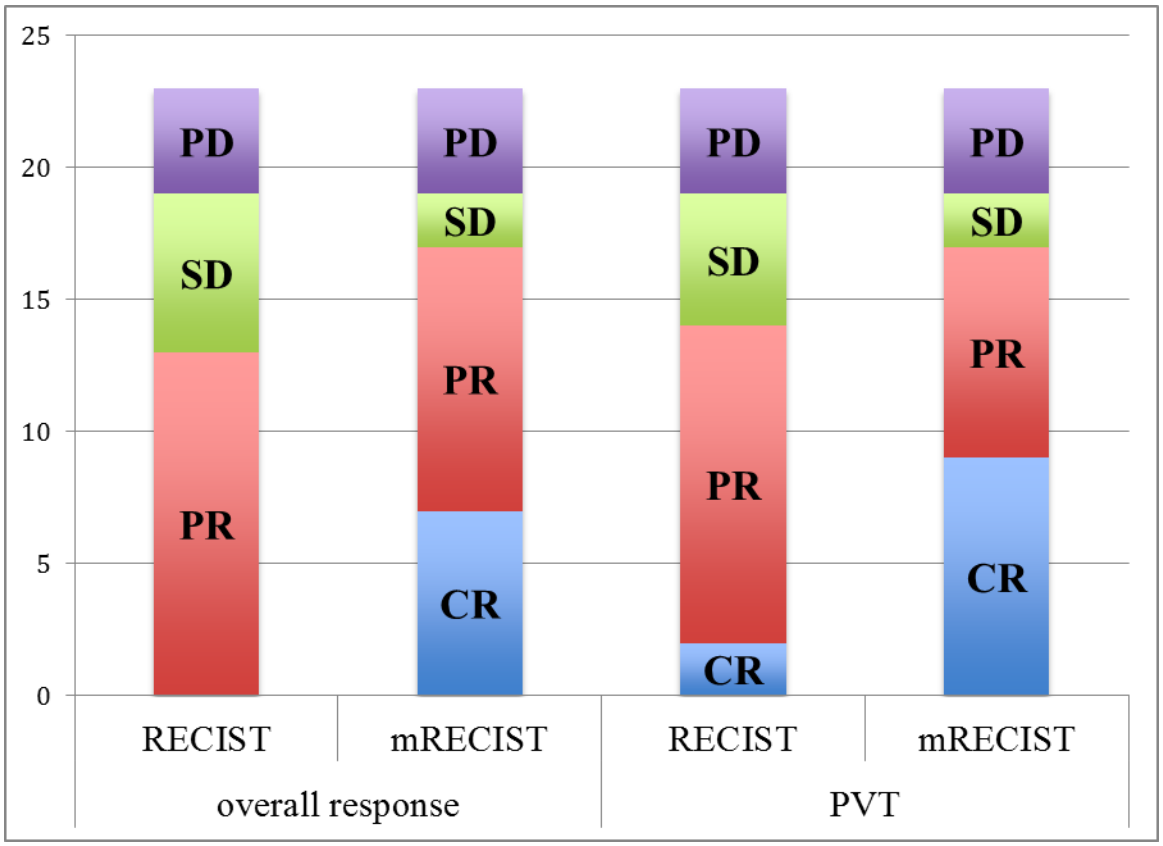

Figure 1: Overall and PVT response by RECIST and mRECIST criteria

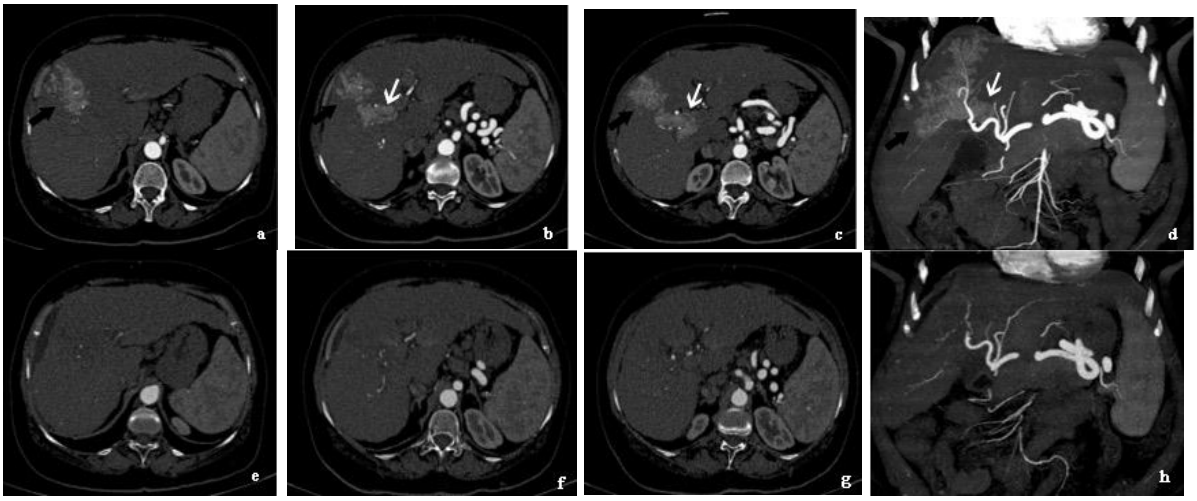

Figure 2: Baseline diagnostic CT scan in axial (a,b,c) and coronal reconstruction (d) views showed infiltrative hypervascular tumor in the right hepatic lobe mainly in segment VIII (black arrows) invading the right and main portal vein (white arrows).

Follow-up CT scan after 12 months of ^{90}Y radioembolization treatment in axial (e,f,g) and coronal reconstruction (h) views showed complete resolution of the tumors with disappearance of the tumor in the right and main portal vein.

Patient Survival

A Kaplan-Meier survival analysis was performed from the day of first treatment (Figure 3).

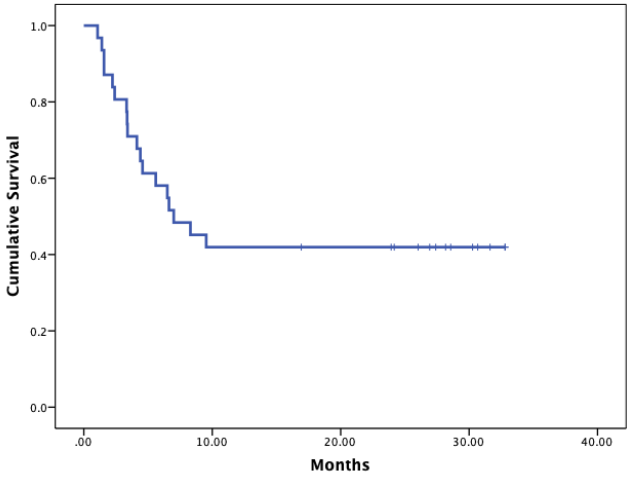

Figure 3. Kaplan-Meier curve showing overall survival for the all patients treated by Y^{90} radioembolization

The median and mean overall survival were 7 months (95% CI, 2.7–11.3 months) and 16.2 months (95% CI, 11.2–21.2 months) respectively. Mean survival stratified by the location of PVT was 21.5, 10.7 and 19.6 months for segmental, lobar and main PVT patients (p=0.256) (Figure 4).

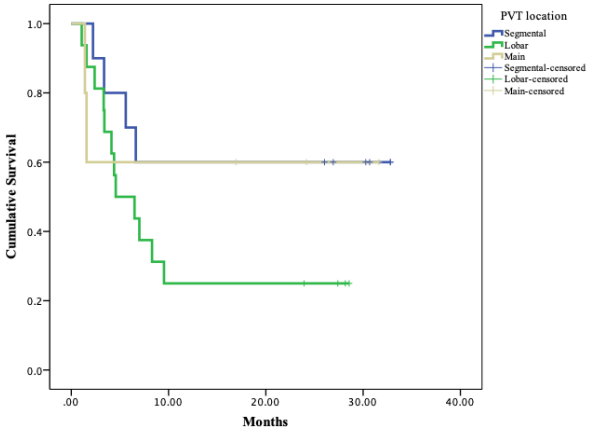

Figure 4. Kaplan-Meier curve showing overall survival for the all patients treated by Y^{90} radioembolization stratified by the PVT location

Patients who died did so from progressive intrahepatic disease. In the univariate analysis, the OS was significantly associated with the age, performance status, tumor morphology, bilirubin level (>1.3mg/dL), extrahepatic metastases, overall tumor response by mRECIST and PVT response by RECIST and mRECSIT (Table 6). We used these variables in a multivariate Cox analysis,

which revealed that a performance status ≥ 2 (hazard ratio [HR], 0.094; 95% confidence interval [CI], 0.011– 0.798; P = 0.03), bilobar tumor involvement (HR, 0.107; 95% CI, 0.014– 0.838; P = 0.033), and progression of the PVT by RECIST (HR, 0.054; 95% CI, 0.005– 0.563; P = 0.033) were associated with worse survival.

Table 6. Univariate and multivariate analyses

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P* value
Age (y)				
<60	4.209(1.627-	.002	0.75(0.047-	.838
>60				
Sex				
Male	1.158(0.134-	.886		
Female				
ECOG PS				
0-1	3.262(0.725-	.016	0.094(0.011-	.030
> 2				
Child-Pugh score				
A	1.729(0.460-	.326		
B				
Lobar involvement				
Unilobar	2.689(1.057-	.036	0.107(0.014-	.033
Bilobar				
Distrubution				
Unifocal		.808		
Multifocal				
Infiltrating				
Tumor Burden				
< 25%		.808		
26 - 50%				
51 - 75%				
PVT location				
Segmental		.247		
Lobar (right or left)				
Main (± lobar)				
Increased bilirubin (>1.3mg/dL)				
No	6.971(0.423-	<.000	----------	
yes				
LN metastases				
No	1.501(0.547-	.395		
Yes				
Extrahepatic metastases				
No	2.896(0.576-	.046	0.112(0.006-	.134
Yes				
Previous liver-directed treatment				
No	1.417(0.561-	.458		
Yes				
Anti-angiogenic agents after treatment				
Yes	0.780(0.309-	.598		
No				
Tumor response (overall RECIST,				
Yes	2.741(0.749-	.097		
No				
Tumor response (overall mRECIST,				
Yes	3.473(0.643-	.035	2.015(0.128-	.619
No				
Tumor response (PVT RECIST, n=23)				
Yes	4.569(1.086-	.008	0.054(0.005-	.015

No				
Tumor response (PVT mRECIST,				
Yes	3.473(0.643-	.035	----------	
No				

DISCUSSION

PVT is a poor prognostic factor for HCC limiting options for treatment such surgery or intra-arterial therapy as transarterial chemoembolization. According to the Barcelona Clinic Liver Disease (BCLC) classification (15), the only available treatment option is sorafenib that has improvement in survival with median OS 8.1 months versus 4.9 with placebo for BCLC C patients with macrovascular invasion. The objective response rate with sorafenib is very low, less than 3% with the RECIST criteria (16).

Our data showed that ^{90}Y radioembolization in patients with HCC complicated by PVT showed very high radiological response rate for both the overall and PVT components. The RECIST and mRECIST response for the PVT component reached up to 61% and 74% respectively and overall disease control for both was 83%, however the overall response rate by RECIST and mRECIST reached up to 57% and 74% respectively, and the disease control rate was 83%. This is comparable to the data published to date on the use of radioembolization for palliative purposes in HCC patients with PVT which have demonstrated a very high response rate (50–70%) (17). The safety profile appears to be similar to that observed in patients without PVT, especially for the embolic risk (18).

The median survival reported in our study was 7 months which is comparable with other studies. Few studies have reported that radioembolization can have positive outcomes in HCC patients with PVT, with median OS ranging from 5.6 to 13.8 months (4, 19-22). The extent of PVT and Child Pugh classification are the main prognostic factors that affect survival in HCC. Ours showed that the increased bilirubin level >1.3md/dL, performance status, lobar involvement by the tumor as well as the presence of extrahepatic metastasis are prognostic factors that may affect the survival.

Patients with Child-Pugh A disease has a better prognosis than those patients with Child-Pugh B7 disease (13.8 vs 6.5 months, respectively) a reported by previous study which shown also that patients with branch PVT had better OS of 10.7 months compared to patients with main PVT 9.7 months (17), other studies showed that patients with HCC and macrovascular invasion treated by ^{90}Y radioembolization had median OS of 8.1 (23) and 5.6 (24) months, respectively.

Patients with locally advanced HCC may have extrahepatic spread of the disease, and the use of sorafenib as a systemic control of the disease has gained acceptance duo to overall survival benefit, however controlling the disease locally by intraarterial therapy should be attempted whenever the patients are eligible for such therapy as sorafenib alone rarely control this advanced disease. Patients with locally advanced HCC with no extrahepatic metastasis have favorable outcomes compared to patients with HCC with extrahepatic metastasis (25), This may suggest that, PVT can be treated in a locoregional manner using ^{90}Y radioembolization . The lower overall survival of our study when compared to some other studies can be attributed to more patients we included (about 30%) that had extrahepatic metastases in which we treated

most of them after by sorafenib (about 45%). The rationale of TACE is to induce macroembolization to the feeding arteries, so when used for treatment of patients with PVT, acute decompensation mostly occur, this mechanism of occlusion is totally different from ^{90}Y treatment, in which the smaller microsphere does not induce macroembolization but the embolization is in the sinusoidal level promoting the patency of the feeding arteries and thus lower risk of post-embolization syndrome and a better safety profile than sorafenib (12). Accordingly, in our study, the radioembolization group showed significantly less severe adverse events, and no cases of acute hepatic decompensation occurred.

One of the drawbacks of our study is its retrospective design and the lack of control group. Second, the study population was relatively small to reach the median overall survival between patients based on the location of the PVT. Based on the results of the our study, it appears that radioembolization with ^{90}Y microspheres offers a favorable safety profile for patients presenting with unresectable HCC and PVT, also results in a very rate of radiographic response and very encouraging survival statistics. Unlike other embolic therapies such as chemoembolization, ^{90}Y radioembolization appears to be an effective treatment for patients who otherwise have limited treatment options and present with a poor prognosis.

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