Radioembolization for Hepatocellular Carcinoma Using Yttrium-90 Microspheres: A Comprehensive Report of Long-term Outcomes

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BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) has limited treatment options; long-term outcomes following intra-arterial radiation are unknown. We assessed clinical outcomes of patients treated with intra-arterial yttrium-90 microspheres (Y90). **METHODS:** Patients with HCC (n = 291) were treated with Y90 as part of a single-center, prospective, longitudinal cohort study. Toxicities were recorded using the Common Terminology Criteria version 3.0. Response rate and time to progression (TTP) were determined using World Health Organization (WHO) and European Association for the Study of the Liver (EASL) guidelines. Survival by stage was assessed. Univariate/multivariate analyses were performed. **RESULTS:** A total of 526 treatments were administered (mean, 1.8; range, 1–5). Toxicities included fatigue (57%), pain (23%), and nausea/vomiting (20%); 19% exhibited grade 3/4 bilirubin toxicity. The 30-day mortality rate was 3%. Response rates were 42% and 57% based on WHO and EASL criteria, respectively. The overall TTP was 7.9 months (95% confidence interval, 6–10.3). Survival times differed between patients with Child–Pugh A and B disease (A, 17.2 months; B, 7.7 months; $P = .002$). Patients with Child–Pugh B disease who had portal vein thrombosis (PVT) survived 5.6 months (95% confidence interval, 4.5–6.7). Baseline age; sex; performance status; presence of portal hypertension; tumor distribution; levels of bilirubin, albumin, and α-fetoprotein; and WHO/EASL response rate predicted survival. **CONCLUSIONS: Patients with Child–Pugh A disease, with or without PVT, benefited most from treatment. Patients with Child–Pugh B disease who had PVT had poor outcomes. TTP and overall survival varied by patient stage at baseline. These data can be used to design future Y90 trials and to describe Y90 as a potential treatment option for patients with HCC.**

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the sixth most common malignancy worldwide and the third most common cause of cancer-related mortality.[1,2] Transplantation and resection remain the only potentially curative options.[3] Locoregional therapies such as chemoembolization (TACE) and radiofrequency ablation have an established palliative role in select patients.[4–8] Targeted molecular therapies now have a recognized role, with sorafenib demonstrating improved survival in patients with advanced HCC.[9,10]

HCC has traditionally been regarded as a radioresistant tumor due to the limited ability to deliver lethal doses using external beam techniques.[11] Although the delivery of focused external beam radiation has improved, technical limitations persist.[12] Radioembolization with yttrium-90 (Y90) microspheres represents a new concept in radiation therapy for HCC; radiolabeled particles are injected through the hepatic artery, become trapped at the precapillary level, and emit lethal internal radiation. This mechanism limits exposure to the surrounding normal parenchyma, thereby permitting higher dose delivery than with an external beam.[13,14] However, long-term outcomes remain unknown. We report a comprehensive analysis of a cohort of 291 patients with HCC who were treated with Y90.

Three important clinical outcome parameters were assessed (response rate, time to progression [TTP], and survival). Because decrease in lesional size and amount of enhancing tissue have been shown to be prognosticators of survival, response rates using both methodologies are reported.[15,16] Also, given TTP as a measure of tumor control without the confounding effect of liver disease as well as its prognostic value in predicting survival, this was

Abbreviations used in this paper: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PR, partial response; PVT, portal vein thrombosis; TACE, transarterial chemoembolization; TTP, time to progression; UNOS, United Network for Organ Sharing; WHO, World Health Organization; Y90, yttrium-90 microspheres.

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also determined.[9,10,17] Finally, survival is also reported to capture the overall clinical outcome.

Patients and Methods

Patient Cohort

Between January 1, 2004, and December 31, 2008, 291 patients with HCC were treated with Y90 at one institution as part of a cohort study. A comprehensive review of toxicity, imaging, and survival outcomes was performed. Data were collected prospectively. The study was Health Insurance Portability and Accountability Act compliant, approved by the institutional review board, and registered (NCT00530010).

Pretreatment Evaluation and Staging

Patients underwent pretreatment assessment, including clinical history, physical examination, and laboratory and baseline imaging studies. Inclusion criteria included diagnosis of HCC by biopsy or imaging using accepted guidelines,[7,16,17] Eastern Cooperative Oncology Group (ECOG) score 0–2, and bilirubin level <3.0 mg/dL at protocol enrollment. Portal vein thrombosis (PVT) and/or limited extrahepatic metastases were not considered exclusionary. Patients were staged by Child–Pugh, United Network for Organ Sharing (UNOS) and Barcelona Clinic Liver Cancer (BCLC) scores (A, early; B, intermediate; C, advanced; D, end-stage).[18,19] Patients exhibiting cancer-related symptoms (eg, pain), PVT, or extrahepatic metastases were classified as BCLC stage C. Lymph nodes >2.0 cm were defined as extrahepatic metastases.[20] The decision to treat patients with Y90 as part of this study was made by consensus at our weekly multidisciplinary HCC conference composed of staff from hepatology, medical oncology, transplant surgery, and interventional radiology.

Treatment

Pretreatment mesenteric angiography and technetium-99m macroaggregated albumin scanning were performed to assess gastrointestinal flow and lung shunting.[21] The device used was glass based (TheraSphere; Ottawa, Ontario, Canada); this is a brachytherapy device approved by the Food and Drug Administration for HCC with or without PVT.[22] Technical and dosimetry considerations for Y90 have been described previously; target dose was 100–120 Gy.[23]

Posttreatment Imaging Evaluation

Per our institutional protocol, 4- to 6-week scans were obtained following each treatment and subsequently at 2- to 3-month intervals once all disease was treated.[16] During the interpretation of each scan, World Health Organization (WHO) and European Association for the Study of the Liver (EASL) responses were assessed as well as restaging, depending on the appearance of extrahepatic metastases or new lesions.[24]

Imaging Analysis: Quantifying Size Reduction and Necrosis

WHO response. Response rate by WHO criteria was assessed using the following definitions: complete response, 100% decrease in the sum of cross products; partial response (PR), ≥50% decrease in the sum of cross products; progressive disease, >25% increase in the sum of the cross products from maximum response. All others were defined as stable disease.[16,24]

EASL response. Assessing tumor size without also taking into consideration necrosis and enhancement has limitations in determining response for locoregional therapies.[16,25] EASL response was obtained based on the following: complete response, absence of any enhancing tissue; PR, >50% decrease in enhancing tissue; stable disease, <50% decrease in enhancing tissue.[16] Progressive disease was defined as any increase in enhancement of the treated tumor that clinically would translate into additional locoregional therapy (ie, repeat Y90).

WHO guidelines describe tumor response for systemic chemotherapy treatments but provide no guidance for locoregional therapies.[24] These are addressed by recent guidelines.[16,17] As a result of these limitations with WHO, the following additional adjustments were made for the locoregional nature of this treatment: (1) the starting point for all parameters (response rate, TTP, survival) was the date of first Y90, and (2) TTP was defined as progression by WHO, EASL, and UNOS stage; PVT appearance or extension (if preexisting); or appearance of new lesions. Per guideline suggestions, an individual radiologic event, such as a new lesion, was adjudicated in retrospect as progression at the time it was first detected, even if strict criteria were only met on subsequent radiologic imaging. Imaging end points were censored to curative therapies (transplantation or resection).

Clinical and Laboratory Toxicities

Patients were followed up clinically for adverse events by following National Cancer Institute Common Terminology Criteria version 3.0. Toxicities were recorded at any time during follow-up and were censored to curative treatment. Conservatively, patients with preexisting laboratory toxicities were counted as toxicities at follow-up, even if there was no change in grade.

Statistical Analyses

The proportions were compared using the Fisher exact and χ^2 tests. Independent variables were compared using the Mann–Whitney *U* test, while dependent variables were compared using the Wilcoxon test. Time to response and TTP median overall survivals were calculated using the Kaplan–Meier method and were compared using the log-

Table 1. Baseline Characteristics

Demographics	n (%)
Age (*y*)	
Younger than 65	138 (47)
65 or older	153 (53)
75 or older	64 (22)
Sex	
Male	223 (77)
Female	68 (23)
Ethnicity	
White	208 (71)
Black	37 (13)
Asian	29 (10)
Hispanic	17 (6)
Etiology	
Hepatitis C virus	100 (34)
Alcohol	56 (19)
Cryptogenic	54 (19)
Hepatitis B virus	26 (9)
Hepatitis C virus and alcohol	23 (8)
Nonalcoholic steatohepatitis	6 (2)
Autoimmune	4 (1.3)
Hemochromatosis	4 (1.3)
Hepatitis C virus and hepatitis B virus	3 (1)
Primary biliary cirrhosis	1 (0.4)
Unknown	14 (5)
ECOG performance status	
0	162 (56)
1	104 (36)
2	25 (8)
Prior therapy	
None	253 (87)
Resection	16 (5)
Radiofrequency ablation	6 (2)
Chemoembolization	13 (5)
Orthotopic liver transplantation	3 (1)
Method of diagnosis	
Biopsy	148 (51)
Imaging	143 (49)
α-Fetoprotein level	18 (6)
Imaging findings	
Cirrhosis	
Present	254 (87)
Absent	37 (13)
Ascites	
Present	57 (19)
Absent	234 (81)
Portal hypertension (by imaging/platelet count)	
Present	202 (69)
Absent	89 (31)
Tumor characteristics	
Distribution	
Solitary	78 (27)
Multifocal	213 (73)
Tumor location	
Bilobar	139 (48)
Unilobar	152 (52)
Tumor vascularity by cross-sectional imaging	
Hypovascular	47 (16)
Hypervascular	244 (84)
Tumor burden	
0%–25%	223 (76.6)
26%–50%	48 (16)
51%–75%	19 (7)
76%–100%	1 (0.4)
PVT	
None	166 (57)
Branch	58 (20)
Main	67 (23)
Metastases	
None	245 (84)
Lymph nodes	29 (10)
Other	17 (6)
Largest tumor size	
Overall 291	(mean, 7 cm; range, 1.2–22 cm)
<5 cm 116 (40)	(mean, 3.4 cm; range, 1.2–4.9 cm)
5–10 cm 123 (42)	(mean, 7.1 cm; range, 5–10 cm)
>10 cm 52 (18)	(mean, 14.9 cm; range, 10.1–22 cm)
Laboratory data	
α-Fetoprotein level (*ng/mL*)	
≤200	157 (54)
>200	134 (46)
Total bilirubin level (*mg/dL*)	
<2	247 (85)
2–3	30 (10)
>3	14 (5)
Albumin level (*mg/dL*)	
>3.5	17 (6)
2.8–3.5	134 (46)
<2.8	140 (48)
Staging	
Child–Pugh	
A	131 (45)
B	152 (52)
C	8 (3)
BCLC	
A	48 (17)
B	83 (28)
C	152 (52)
D	8 (3)
UNOS	
T1 (1 tumor <2 cm)	1 (0.4)
T2 (1 tumor ≤5 cm, 2 or 3 tumors ≤3 cm)	49 (17)
T3 (1 tumor >5 cm, 2 or 3 tumors, at least one >3 cm)	48 (16)
T4a (≥4 tumors)	51 (18)
T4b (PVT)	96 (33)
N (lymph nodes >2 cm)	29 (10)
M (extrahepatic metastases)	17 (5.6)

rank test.[26] Because some patients underwent curative therapies following treatment response, censored survival is reported per previous investigators.[8,17]

The hazard ratios (HRs) were calculated by univariate and multivariate analyses. Univariate analyses were performed using the Kaplan–Meier method, and multivari-

ate analyses were performed using the Cox proportional model.[26] All variables studied in the univariate analyses were entered in the multivariate analysis with the following exceptions. (1) Because tumor distribution, tumor size, and presence of PVT and extrahepatic metastases were included to assess the independent effect of each, UNOS stage was not included in the multivariate model. (2) Because baseline bilirubin level, albumin level, and ascites were included in the multivariate model to assess the independent effect of each, Child–Pugh class was not included. These were excluded to eliminate the crossover effect of variables captured by one or more categories.

Results

Patient Population

Patient demographics, tumor characteristics, and stage are presented in Table 1. The median age was 65 years (range, 26–90 years), and 22% were 75 years of age or older. Most were male (77%), with hepatitis C (34%) and alcohol (19%) as the most common etiologies. A majority were ECOG 0 (56%) or 1 (36%) and were treatment naive (87%). A total of 51% were confirmed to have HCC by biopsy. Most patients were cirrhotic (87%) and had portal hypertension (69%). A total of 73% exhibited multifocal disease with tumor burden <25% (77%) and no vascular invasion (57%). Sixteen percent had extrahepatic metastases. The mean size of the largest tumor was 7.0 cm. A total of 52% were Child–Pugh B, and 52% were BCLC C. Seventeen percent were UNOS T2. Ninety-four (32%), 187 (64%), and 10 (4%) were Okuda stages I, II, and III, respectively.

Treatment and Follow-up

The 291 patients underwent 526 treatments (mean, 1.8; median, 1; range, 1–5), all as outpatients. The median dose was 103 Gy per treatment (95% confidence interval [CI], 99–108). The median lung dose per treatment was 8.8 Gy (95% CI, 7.9–9.6). Median follow-up time was 30.9 months (95% CI, 22.7–35.7). A total of 107 patients (37%) required coil embolization of extrahepatic vessels before treatment. Five patients, separate from the 291-patient cohort, were excluded from treatment during the study period because of elevated lung shunting and theoretical risk of excessive lung dose.

Clinical and Laboratory Toxicities

Table 2 lists the clinical and laboratory toxicities. The most common findings posttreatment included fatigue (57%), pain (23%), and nausea/vomiting (20%). There were no ulcers or pulmonary toxicities. Bilirubin toxicities included grade 1/2 (55%) and grade 3/4 (19%). Baseline bilirubin levels as classified by Common Terminology Criteria in the 19% (n = 54) of patients who experienced posttreatment grade 3/4 toxicities were as follows: 19 (35%), grade 0; 13 (24%), grade 1; 13 (24%), grade 2; and 9 (17%), grade 3.

Table 2. Toxicities

Clinical toxicities (grade 1/2)	n (%)
Fatigue	167 (57)
Abdominal pain	67 (23)
Nausea/vomiting	57 (20)
Anorexia	45 (15)
Diarrhea	7 (2)
Fever/chills	10 (3)
Weight loss	4 (1)
Biochemical toxicities	
Bilirubin	
Grade 1/2	161 (55)
Grade 3/4	54 (19)
Albumin	
Grade 1/2	223 (77)
Grade 3/4	53 (18)
Alanine aminotransferase	
Grade 1/2	169 (58)
Grade 3/4	14 (5)
Aspartate aminotransferase	
Grade 1/2	208 (71)
Grade 3/4	55 (19)
Alkaline phosphatase	
Grade 1/2	219 (75)
Grade 3/4	11 (4)

The rates of grade 3/4 bilirubin toxicities stratified by time from first treatment were: <30 days, 5%; <90 days, 14%; <180 days, 11%. Thirty-day mortality was 3% (n = 9). All of these patients (n = 9) had PVT; 7 of 9 had Child–Pugh B disease, and one had Child–Pugh C disease.

Imaging Outcomes

Response rate. A total of 273 patients had imaging follow-up (94%). Overall, 1250 scans were reviewed, translating into 4.3 scans per patient. Tables 3 and 4 list the response and TTP stratified by stage. WHO response rate (n = 273) varied by stage; overall, it was 42%. EASL response rate was 57% (complete response, 23%; PR, 34%). In responding patients, the time to PR was 6.6 months (95% CI, 5.6–7.6) by WHO criteria and 2.1 months (95% CI, 1.3–2.6) by EASL criteria. Response rates were better in patients with Child–Pugh A disease (WHO, 49%; EASL, 66%) than patients with Child–Pugh B disease (WHO, 36%; EASL, 51%). WHO response rates varied by baseline largest tumor size: <5 cm, 44%; 5–10 cm, 42%; and >10 cm, 33%.

TTP. TTP for the entire cohort (n = 273) was 7.9 months (95% CI, 6–10.3). TTP for patients with Child–Pugh A and B disease without PVT was 15.5 months (95% CI, 10.7–25.9) and 13.0 months (95% CI, 8.4–18.1), respectively (P = .759). TTP for patients with Child–Pugh A and B disease who had PVT was 5.6 months (95% CI, 2.3–7.6) and 5.9 months (95% CI, 4.2–7.9), respectively (P = .685).

Survival Analysis

A total of 34 patients (12%) underwent treatment with curative intent following Y90 (transplantation, n =

Table 3. Imaging/Survival Analyses for Patients Without Extrahepatic Metastases

			N (no. of patients with imaging follow-up)	EASL PR, n (%)	WHO PR, n (%)	TTP median (95% CI)	Survival median (95% CI)	No. who underwent transplantation (%)
Child–Pugh class								
A	Overall Child–Pugh A		116 (113)	78 (69)	59 (52)	10.8 (7.4–14)	17.2 (14.9–24)	18 (16)
	PVT absent	Overall no PVT	81 (79)	61 (77)	42 (53)	15.5 (10.7–25.9)	22.1 (17.2–32.5)	16 (20)
		T1/T2	27 (25)	22 (88)	13 (52)	27.1 (8–n.c.)	20.5 (14.9–27.4)	9 (33)
		T3	27 (27)[a]	24 (89)	17 (63)	21.9 (10.9–25.8)	35.7 (18.3–44.4)	5 (19)
		T4a	27 (27)	15 (56)	12 (44)	8.6 (6–n.c.)	14.9 (7.3–22.2)	2 (7)
	PVT present	Overall PVT (T4b)	35 (34)	17 (50)	17 (50)	5.6 (2.3–7.6)	10.4 (7.2–16.6)	2 (6)
		Branch PVT	19 (19)	11 (58)	11 (58)	5.6 (3.7–13.6)	16.6 (8.8–24)	2 (11)
		Main PVT	16 (15)[a]	6 (40)	6 (40)	5.8 (1–7.5)	7.7 (3.3–13.2)	0
B	Overall Child–Pugh B		122 (114)	59 (52)	44 (39)	8.4 (5.9–12.3)	7.7 (6.5–11.2)	14 (11)
	PVT absent	Overall no PVT	65 (64)	43 (67)	30 (47)	13.0 (8.4–18.1)	14.8 (11.8–29.1)	12 (19)
		T1/T2	22 (22)	15 (68)	8 (36)	13.0 (6.3–25)	29.1 (17.1–n.c.)	5 (23)
		T3	21 (21)	18 (86)	12 (57)	17.4 (8.4–33.9)	38.3 (6.9–41.7)	4 (19)
		T4a	22 (21)	10 (48)	10 (48)	8.8 (3.6–18.1)	11.8 (6.2–19)	3 (14)
	PVT present	Overall PVT (T4b)	57 (50)	16 (32)	14 (28)	5.9 (4.2–7.9)	5.6 (4.5–6.7)	2 (4)
		Branch PVT	27 (25)	10 (40)	7 (28)	5.1 (4.2–8.9)	6.5 (5–8.5)	1 (4)
		Main PVT	30 (25)	6 (24)	7 (28)	6.0 (2.3–10.4)	4.5 (2.9–6.6)	1 (4)
C			7 (5)	1 (20)	0	2.1 (n.c.–2.3)	2.5 (1–3.7)	0
BCLC								
A	Overall BCLC A		48 (46)	36 (78)	21 (46)	25.1 (8–27)	26.9 (17–30.2)	14 (29)
	Child–Pugh A		27 (25)	22 (88)	13 (52)	27.1 (7.5–n.c.)	20.5 (15–27.4)	9 (33)
	Child–Pugh B		21 (21)	14 (67)	8 (38)	13 (6.4–25.2)	29.1 (17–n.c.)	5 (24)
B	Overall BCLC B		83 (82)	57 (70)	42 (51)	13.3 (4.4–18.1)	17.2 (13.5–29.6)	13 (16)
	Child–Pugh A		48 (48)	34 (71)	24 (50)	13.3 (8–25.9)	17.3 (13.7–32.5)	7 (15)
	Child–Pugh B		35 (34)	23 (68)	18 (53)	17.4 (5.8–18.2)	13.5 (6.4–25.4)	6 (17)
C	Overall BCLC C		107 (99)	44 (44)	40 (40)	6.0 (4.6–8.8)	7.3 (6.5–10.1)	5 (5)
	Child–Pugh A	Overall	41 (40)	22 (55)	22 (55)	6.2 (3.7–11.7)	13.8 (8.8–17.7)	2 (5)
		PVT Absent	6 (6)	5 (83)	5 (83)	23.8 (10.8–n.c.)	47.4 (n.c.)	0
		PVT present	35 (34)	17 (50)	17 (50)	5.6 (2.3–7.6)	10.4 (7.2–16.6)	2 (6)
	Child–Pugh B	Overall	66 (59)	22 (37)	18 (31)	6.0 (4.5–8.8)	6.4 (4.9–7.7)	3 (5)
		PVT absent	9 (9)	6 (67)	4 (44)	13.7 (n.c.–23.6)	11.8 (n.c.–34)	1 (11)
		PVT present	57 (50)	16 (32)	14 (28)	5.9 (4.2–7.9)	5.6 (4.5–6.7)	2 (4)
	Non-(Child–Pugh B + PVT)		50 (49)	28 (57)	26 (53)	6.9 (4.2–13.6)	13.8 (10.2–20.4)	3 (6)
D (Child–Pugh C)			7 (5)	1 (20)	0	2.1 (n.c.–2.3)	2.5 (1–3.7)	0

NOTE. Imaging outcomes are based on 232 patients, and survival analyses are based on 245 patients. T1/T2/T3/T4a/T4b refer to UNOS stages.
n.c., not calculable.
[a]Two patients underwent resection.

32; resection, n = 2). Tables 3 and 4 report survival outcomes. Survival between patients with Child–Pugh A disease and patients with Child–Pugh B disease was significantly different (Child–Pugh A, 17.2 months; Child–Pugh B, 7.7 months; $P = .002$). Survival in patients with BCLC B trended to favor patients with Child–Pugh A disease over patients with Child–Pugh B disease (17.3 months vs 13.5 months; $P = .27$). Figure 1 displays the Kaplan–Meier curves for TTP and survival stratified by Child–Pugh, UNOS, and BCLC classification systems. At the time of study closure, 183 patients had died (114 [62%] with disease progression, 56 [31%] with stable disease and grade ≥1 bilirubin toxicity, and 13 [7%] with stable disease and no bilirubin toxicities).

For patients with Child–Pugh A disease, WHO responders had higher median survival than nonresponders (23.9 months [95% CI, 18.2–30.4] vs 11.4 months [95% CI, 8.2–15], respectively; $P = .0003$), with an HR of 0.40 (95% CI, 0.25–0.66) for responders compared with nonresponders. For patients with Child–Pugh B disease, WHO responders had higher median survival than WHO nonresponders (18.9 months [95% CI, 12.8–29.1] vs 5.2 months [95% CI, 4.3–6.3], respectively; $P < .0001$), with an HR of 0.21 (95% CI, 0.13–0.32) for responders compared with nonresponders. In patients with Child–Pugh A disease, the HRs for survival in WHO responders compared with nonresponders substratified by BCLC stage were as follows: BCLC A, 0.24 (95% CI, 0.05–1.08; $P = .06$); BCLC B, 0.51 (95% CI, 0.23–1.17; $P = .11$); BCLC C, 0.26 (95% CI, 0.13–0.53; $P = .0002$). In patients with Child–Pugh B disease, the HRs for survival in WHO responders compared with nonresponders substratified by BCLC stage were as follows: BCLC A, 0.16 (95% CI, 0.02–1.32; $P = .09$); BCLC B, 0.08 (95% CI, 0.02–0.29; $P = .0001$); BCLC C, 0.29 (95% CI, 0.17–0.47; $P < .0001$).

For patients with early HCC (BCLC A), WHO responders had a higher median survival than nonresponders (30.2 months [95% CI, 27.4–not calculable] vs 17.0 months [95% CI, 14.2–26.8], respectively; $P = .003$), with an HR of 0.15 (95% CI, 0.05–0.53) for responders compared with nonresponders. For patients with intermediate HCC (BCLC B), WHO responders had a higher median survival than nonresponders (29.6 months [95% CI, 18.4–37.4] vs 9.6 months [95% CI, 6.3–15.7], respectively;

Table 4. Imaging/Survival Analyses for Patients with Extrahepatic Metastases

			N (no. of patients with imaging follow-up)	EASL PR, n (%)	WHO PR, n (%)	TTP median (95% CI)	Survival median (95% CI)
Child–Pugh class							
A	Overall Child–Pugh A		15 (14)	6 (43)	4 (29)	3.7 (1.1–5.1)	8.7 (6–11.3)
	PVT absent	Overall no PVT	10 (10)	5 (50)	3 (30)	3.9 (1.3–17.2)	9.5 (8.4–13)
		T1/T2	2 (2)	1 (50)	0	2.4 (n.c.)	11.3 (n.c.)
		T3	4 (4)	3 (75)	1 (25)	17.1 (n.c.)	13 (n.c.–22.4)
		T4a	4 (4)	1 (25)	2 (50)	2.9 (n.c.)	5.6 (n.c.–9.5)
	PVT present	Overall T4b	5 (4)	1 (25)	1 (25)	3.7 (1.1–5.2)	6.3 (n.c.–12.9)
B	Overall Child–Pugh B		30 (26)	12 (46)	7 (27)	2.3 (1.2–7.9)	3.2 (2.4–6)
	PVT absent	Overall no PVT	7 (7)	4 (57)	3 (43)	—	6.4 (2.1–14.1)
		T1/T2	0	—	—	—	—
		T3	1 (1)	0	0	—	6 (n.c.)
		T4a	6 (6)	4 (67)	3 (50)	—	8.8 (2.1–14.1)
	PVT present	Overall PVT (T4b)	23 (19)	8 (42)	4 (21)	1.4 (1.1–6.3)	2.7 (2.4–3.6)
		Branch PVT	8 (6)	4 (67)	3 (50)	3.6 (n.c.–7.9)	2.6 (1.1–28.9)
		Main PVT	15 (13)	4 (31)	1 (8)	1.4 (1.2–3.1)	2.9 (2.4–3.6)
C			1 (1)	0	0	0.63 (n.c.)	2.33 (n.c.)
BCLC							
A	Overall BCLC A		—	—	—	—	—
B	Overall BCLC B		—	—	—	—	—
C	Overall BCLC C		45 (40)	18 (45)	11 (28)	3.1 (1.2–5.1)	5.4 (2.7–7.5)
	Child–Pugh A	Overall	15 (14)	6 (43)	4 (29)	3.7 (1.1–5.2)	8.7 (6.3–11.3)
		PVT absent	10 (10)	5 (10)	3 (30)	3.9 (1.3–17.2)	9.5 (8.4–13)
		PVT present	5 (4)	1 (25)	1 (25)	3.7 (1.1–5.2)	6.3 (n.c.–12.9)
	Child–Pugh B	Overall	30 (26)	12 (46)	7 (27)	2.3 (1.2–7.9)	3.2 (2.4–6)
		PVT absent	7 (7)	4 (57)	3 (43)	—	6.4 (2.1–14.1)
		PVT present	23 (19)	8 (42)	4 (21)	1.4 (1.1–6.3)	2.7 (2.4–3.6)
D (Child–Pugh C)			1 (1)	0	0	0.63 (n.c.)	2.33 (n.c.)

NOTE. Imaging outcomes are based on 41 patients, and survival analyses are based on 46 patients. No patients with metastases underwent transplantation. T1/T2/T3/T4a/T4b refer to UNOS stages.
n.c., not calculable.

$P = .003$), with an HR of 0.36 (95% CI, 0.19–0.71) for responders compared with nonresponders. For advanced HCC without extrahepatic metastases (BCLC C), WHO responders had a higher median survival than WHO nonresponders (14.1 months [95% CI, 10.5–20.1] vs 5.3 months [95% CI, 4.4–6.3], respectively; $P < .0001$), with an HR of 0.26 (95% CI, 0.17–0.38) for responders compared with nonresponders. Figure 2 displays these findings and confirms WHO response as a significant prognosticator of survival.

Univariate/Multivariate Analyses

Table 5 presents the HRs by category of various predictors of survival in HCC. The following variables were significant prognosticators of survival on multivariate analysis: age; sex; performance status; portal hypertension; tumor distribution; baseline bilirubin, albumin, and α-fetoprotein levels; WHO response; and EASL response.

Discussion

Significant progress has been made in surgical, locoregional, and systemic treatment options for HCC. Our study includes a comprehensive analysis of TTP using strict imaging criteria in 291 patients with HCC who were treated with Y90. Given that PR and TTP are both prognosticators for survival, our analyses included both parameters.[10,15] Such imaging outcomes of Y90 for HCC obtained in a systematic manner have not been reported and represent the largest reported experience to date. Although it is recognized that comparative analyses to other treatments are difficult, these are cautiously undertaken to provide context relative to other options for unresectable HCC.

Safety

The safety of Y90 was found to be acceptable. We used a conservative approach in reporting all laboratory toxicities as potentially related to Y90 (even when present at baseline), recognizing that such toxicities may have been attributed to disease progression and background cirrhosis. Grades 3–4 bilirubin toxicities were noted in 19% of patients, consistent with previous findings as well as the natural biology of the disease.[27–29] The most common symptom was development of transient fatigue in >50% of patients. Some developed diarrhea, a side effect more prevalent with sorafenib.[10] There were no gastric ulcers, as has been reported by earlier series.[30]

Response Rate

Imaging response has been shown to predict survival benefit following locoregional therapies.[15] WHO response rate was 42% in our study, in line with previous

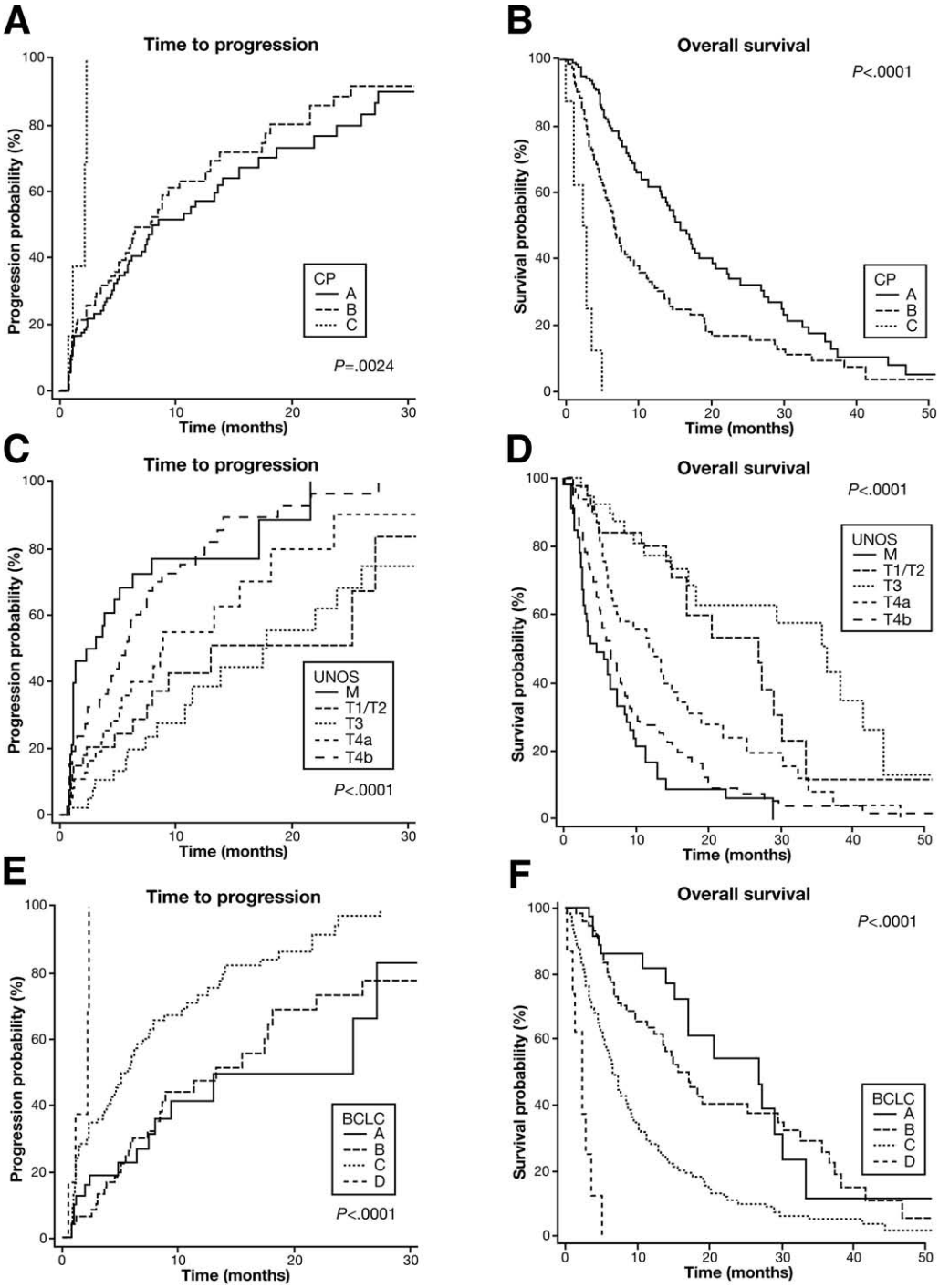

Figure 1. Kaplan–Meier curves demonstrating TTP and survival using Child–Pugh (CP), UNOS, and BCLC classification systems.

reports of 40%–50% with Y90.[4,31,32] Although response rate has traditionally been used as an end point in phase 2 studies before advancing to phase 3, this concept is being challenged with the advent of molecular targeted therapies, with survival benefit being noted with marginal response but extended TTP.[17,33,34] Despite this observation, it is not clear that response as an end point can be entirely replaced by TTP for cytotoxic therapies. Clinical trials with early HCC where the natural history of disease and TTP are prolonged would be impossible without the use of response rate. In our cohort, the HR's for survival were comparable in Child–Pugh A (HR, 0.40) and B (HR, 0.21) disease, suggesting therapeutic benefit in responders irrespective of underlying liver disease. In our cohort, the HR for survival in WHO responders compared with nonresponders was significant in BCLC A

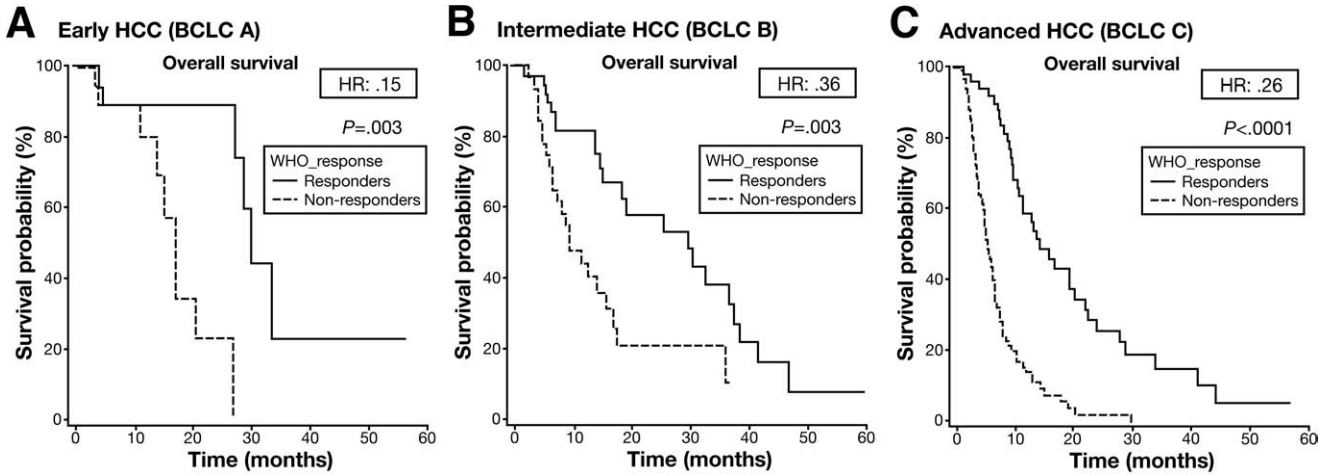

Figure 2. Kaplan–Meier curves of WHO nonresponders versus responders stratified by BCLC stage.

(HR, 0.15), BCLC B (HR, 0.36), and BCLC C (HR, 0.26), again demonstrating therapeutic benefit in responders (Figure 2). Similarly, EASL criteria demonstrated improved overall survival in responders compared with nonresponders that persisted despite differences in baseline Child–Pugh class. The combination of a decrease in size and degree of enhancement may be a superior assessment of treatment response than either alone.[35]

Patients With Child–Pugh A and B Disease

TACE is the established standard of care for selected patients with BCLC intermediate Child–Pugh A disease (without PVT or metastases), with survival ranging from 16 to 22 months.[8,36] In our cohort, survival of comparable patients with Child–Pugh A disease was 17.2 months. Although patients with Child–Pugh A disease may be candidates for various treatments, patients with more advanced disease are often precluded from clinical trials due to risk of hepatic decompensation. In this study, >50% of patients without evidence of extrahepatic metastases had Child–Pugh B disease. In patients with Child–Pugh B disease without PVT or extrahepatic disease, survival was 14.8 months. Specifically, patients with T3 Child–Pugh B disease had a median survival of 38.3 months, comparing favorably with 26 months in an equivalent group treated with TACE.[25] Although the number of patients is relatively small, our data show that patients with HCC who have advanced liver disease may have a potential treatment option in Y90, which may lead to successful downstaging and transplantation not only in patients with Child–Pugh A disease but also patients with Child–Pugh B disease.

Of note, there was no significant survival difference between T3 and T1/T2 disease. Previous investigators have shown similar survival in the setting of transplantation in patients meeting expanded T3A criteria compared with T2.[37] Because relatively few patients underwent transplantation, censoring for curative treatment does not explain this finding. Alternatively, this may be explained by the treatment effect of Y90 and potentially support the expanded transplantation criteria. As seen in the univariate analysis, it is also possible that UNOS staging may have limited discriminatory ability in predicting survival differences between UNOS T1, T2, or T3 patients when treated with locoregional therapies (Table 5). Further investigations of these concepts are under way.

Patients With Child–Pugh B Disease Who Have PVT

The role of Y90 in patients with BCLC advanced Child–Pugh B disease becomes questionable once there is evidence of PVT (survival, 5.6 months) or metastatic disease (survival, 6.4 months without PVT and 2.6 months with PVT). The competing risk of death due to underlying liver disease without tumor progression is apparent in the overall Child–Pugh B disease survival of 7.7 months despite a TTP of 8.4 months, highlighting the impact of liver dysfunction on overall survival.[17]

Comparison With Targeted Therapies

The results from 2 randomized studies (SHARP, Asia-Pacific) have shown a survival benefit in advanced patients treated with the oral targeted agent sorafenib compared with placebo.[9,10] Unlike these 2 trials in which >95% of the patients had Child–Pugh A disease, our cohort included 52% of patients with Child–Pugh B disease, leading to an overall survival of 7.3 months in the advanced group, inferior to SHARP but superior to the Asia-Pacific trial. This may potentially be explained by the fact that 17% of the patients in SHARP were determined to be intermediate rather than advanced stage at final analysis, making a survival comparison with our group difficult. In this cohort study, in patients with advanced Child–Pugh A disease and PVT without extra-

Table 5. Univariate/Multivariate Analyses

		Univariate analysis (Kaplan–Meier)		Multivariate analysis (Cox proportional hazards model)	
Predictor	Category	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (*y*)	Younger than 65	1.75 (1.31–2.36)	.0002	1.57 (1.10–2.23)	.0137
	65 or older	1.00		1.00	
Sex	Female	1.05 (0.75–1.46)	.7971	1.88 (1.24–2.83)	.0027
	Male	1.00		1.00	
Ethnicity	Black	1.06 (0.71–1.58)	.7745	0.79 (0.49–1.25)	.3075
	Hispanic	1.04 (0.55–1.98)	.8963	1.38 (0.70–2.69)	.3494
	Asian	0.65 (0.37–1.15)	.1422	0.70 (0.37–1.36)	.2951
	White	1.00		1.00	
Baseline bilirubin level (*mg/dL*)	<2	0.22 (0.13–0.39)	<.0001	0.37 (0.17–0.79)	.0111
	2–3	0.26 (0.13–0.52)	.0002	0.19 (0.08–0.47)	.0003
	>3	1.00		1.00	
Baseline albumin level (*mg/dL*)	>3.5	0.24 (0.11–0.52)	.0003	0.52 (0.22–1.23)	.1359
	2.8–3.5	0.55 (0.41–0.73)	<.0001	0.67 (0.46–0.97)	.0345
	<2.8	1.00		1.00	
Cirrhosis	Absent	0.76 (0.50–1.14)	.1839	0.97 (0.54–1.74)	.9241
	Present	1.00		1.00	
Portal hypertension	Absent	0.70 (0.52–0.95)	.022	0.61 (0.38–0.97)	.0347
	Present	1.00		1.00	
PVT	Absent	0.36 (0.27–0.47)	<.0001	0.73 (0.51–1.04)	.0826
	Present	1.00		1.00	
Metastases	Absent	0.39 (0.28–0.56)	<.0001	0.67 (0.44–1.01)	.0550
	Present	1.00		1.00	
Distribution	Solitary	0.41 (0.28–0.61)	<.0001	0.56 (0.36–0.88)	.0118
	Multifocal	1.00		1.00	
ECOG performance status	0	0.20 (0.13–0.32)	<.0001	0.31 (0.15–0.63)	.0012
	1	0.44 (0.28–0.69)	.0004	0.57 (0.31–1.07)	.0816
	2	1.00		1.00	
UNOS stage[a]	N/M	4.99 (2.83–8.82)	<.0001	—	—
	T4b (PVT)	3.47 (2.05–5.86)	<.0001	—	—
	T4a	2.07 (1.17–3.68)	.013	—	—
	T3	0.72 (0.36–1.41)	.3334	—	—
	T1/T2	1.00		—	—
Child–Pugh class[a]	A	0.08 (0.04–0.17)	<.0001	—	—
	B	0.15 (0.07–0.32)	<.0001	—	—
	C	1.00		—	—
Ascites	Absent	0.44 (0.32–0.61)	<.0001	0.72 (0.46–1.15)	.1687
	Present	1.00		1.00	
WHO response	Yes	0.29 (0.21–0.41)	<.0001	0.29 (0.20–0.43)	<.0001
	No	1.00		1.00	
EASL response	Yes	0.25 (0.18–0.34)	<.0001	0.47 (0.32–0.69)	.0001
	No	1.00		1.00	
α-Fetoprotein level (*ng/mL*)	≤200	0.52 (0.39–0.70)	<.0001	0.62 (0.44–0.87)	.0061
	>200	1.00		1.00	
Maximum baseline dimension (*cm*)	<5	0.49 (0.33–0.73)	.0003	1.13 (0.65–1.97)	.6642
	5–10	0.77 (0.54–1.12)	.1688	1.08 (0.68–1.72)	.7376
	>10	1.00		1.00	

[a]Because UNOS stage and Child–Pugh class are composite variables, they were not included in the multivariate model.

hepatic metastases, survival was 10.4 months and TTP was 5.6 months, which is comparable to the overall results from SHARP. Once stratified by branch or main PVT, survival with Y90 was 16.6 and 7.7 months, respectively. Furthermore, patients with advanced BCLC C who did not have combined Child–Pugh B disease and PVT survived a median of 13.8 months. In the SHARP subanalyses, survival in patients with PVT and/or extrahepatic spread was 8.9 months in those treated with sorafenib compared with 6.7 months in the placebo group. Further comparison is not possible because the location of PVT and its relation to survival were not reported. Additionally, there may be confounding secondary to imaging technique. To our knowledge, worsening PVT by imaging was not considered progression in SHARP, whereas we recorded enlarging PVT despite stable tumor size or en-

hancement as progression. Hence, in this study, TTP in patients with PVT may be artificially reduced by both imaging and reporting methodologies.

Patients With Extrahepatic Disease

Sixteen percent of our patients presented with metastatic disease and hence were categorized as BCLC C advanced. The liver-dominant disease was deemed to require therapy by multidisciplinary consensus. Extrahepatic metastases are often regarded as exclusionary criteria for locoregional therapy; systemic therapy is usually recommended. In patients with Child–Pugh A disease with metastases, survival was 8.7 months and TTP was 3.7 months. Not unexpectedly, those with metastatic disease and PVT had worse survival of 6.3 months, whereas those without PVT survived 9.5 months. Again, a direct comparison to SHARP is difficult due to the contribution of intermediate patients (17%). However, in analyzing only patients with metastatic disease and/or PVT in SHARP, the results become less discrepant with an overall survival of 8.9 months and TTP of 4.1 months. Similar results were reported in a phase 2 trial of sorafenib in patients with treatment-naive advanced HCC; overall survival was 9.2 months and TTP was 4.2 months.[34] Additional studies are required to assess the effect of combination local and systemic therapies. Combined approaches may provide synergistic effects potentially leading to longer survival in Child–Pugh A disease and/or PVT and/or metastases than with either therapy alone.

Multivariate Analyses

In the multivariate analysis, prognosticators of overall survival were age; sex; performance status; portal hypertension; tumor distribution; baseline bilirubin, albumin, and α-fetoprotein levels; WHO response; and EASL response. Some findings were unexpected. Female gender was found to be a negative prognostic factor with an HR of 1.88. Reasons for this are unclear. A recent study reported that female patients are less likely to undergo transplantation.[38] However, our analysis was censored to curative therapy and hence cannot explain this finding. The sex distribution of male patients to female patients in our cohort was typical at 3:1. Animal models of chemically induced hepatocarcinogenesis have suggested that the gender discrepancy in HCC is mediated via interleukin-6, which is inhibited by estrogens.[39] Gender differences in prognosis once HCC has developed are not known. Further analyses will be needed to explore if female patients fare worse with Y90.

Patients older than 65 years of age fared better than their younger counterparts. The effect of age on survival in HCC has been conflicting.[40,41] Portal hypertension resulted in inferior survival and likely reflected more advanced liver disease. Investigators have identified thrombocytopenia and portal hypertension as independent risk factors for the development of HCC in patients with hepatitis C virus.[42]

The presence of multifocal tumor distribution was associated with inferior survival, whereas PVT, metastases, and size of the largest lesion were not significant factors. Although it could be hypothesized that this finding is due to a positive treatment effect of Y90 in selected patients (Child–Pugh A disease), this is speculative given the available data.

Strengths and Limitations

Until well-designed prospective studies are completed, caution should be exercised in analyzing cohort studies such as the one presented herein. We minimized potential bias by reporting most conservatively. All variables (imaging, TTP, survival) were calculated from the time of first Y90 rather than protocol enrollment or time of HCC diagnosis. The patient sample is confounded by the inclusion of patients with PVT, advanced disease, and metastases, usually exclusionary criteria for studies using locoregional therapies. Other biases were corrected by establishing strict imaging criteria based on WHO that were modified for locoregional therapy. Progression by enhancement was recorded at first observation when any increase in tumoral enhancement was noted rather than waiting for a 30% increase as suggested by guidelines.[17] EASL consensus guidelines were used for the response analysis; a newer approach has been recently reported and will be used in future analyses.[17] The number of patients in this study (291) is small compared with other cohort studies. However, in context, although the incidence of this rare condition is increasing in the United States, this is the largest report of Y90 for HCC. Finally, given the variability in reporting based on stage, we reported outcomes stratified by the most commonly used HCC staging systems (Child–Pugh, UNOS, BCLC) to permit comparisons with other published series. This also permitted individualized prognostication of patient outcome following Y90 by stage. The lack of a control group is recognized; randomized studies to an appropriate control are being initiated at our institution and worldwide.

Future Studies

There are growing data that support the therapeutic role of Y90 in HCC. In accordance with the BCLC algorithmic approach to recommended treatment based on stage, randomized controlled studies comparing Y90 with established standard therapies will be required.[17] However, although Y90 may play a role in HCC at various stages of disease (early, intermediate, advanced), several

potential issues become apparent when trying to establish its role in HCC.

First, it should be recognized that not all patients defined by each stage of BCLC are ultimately candidates for the suggested treatment modality. As an example, an 85-year-old patient with Child–Pugh A disease who has thrombocytopenia and a 2.5-cm HCC located in the hilum may not be deemed the optimal candidate for potentially curative therapies (ablation, resection, transplantation). Although these patients are currently treated with TACE or sorafenib off study, given the higher level of evidence for these 2 options, they may also potentially benefit from Y90. Prior studies have reported inferior results in TACE for early HCC compared with surgical and ablative therapy; outcomes in early disease treated with Y90 are preliminarily presented herein.[43] Also, TTP in early disease is lacking given the lack of active research into this parameter, thus making the design and powering of any trial compared with or combined with curative therapies challenging and the results at risk for speculation. Because TTP is being proposed as potentially more relevant than tumor response by cross-sectional imaging in HCC, this becomes problematic when considering studies in which the TTP of the natural history of disease is long (such as early HCC).[17] As a result, survival studies of Y90 compared with standard therapies for early HCC would be required, resulting in lengthy follow-up and large sample sizes.[17]

Second, the potential role of Y90 in intermediate disease is suggested in a recent retrospective comparison with TACE, showing superior downstaging rates and longer TTP with Y90. Randomized studies of Y90 versus TACE in the treatment of intermediate HCC, where TACE is currently the standard of care, would be timely. Several issues arise when considering this approach. (1) As with early HCC, TTP for intermediate disease treated with TACE is unavailable, also resulting in speculative TTP estimates. (2) Comparable survival rates of TACE and Y90 create the need for prohibitively large trials to detect any difference. This inherent statistical barrier plus the relatively few centers familiar with Y90 (compared with TACE), create significant hurdles in trial feasibility. (3) TACE (as opposed to Y90) is well known to be heterogeneous in methodology and technique, resulting in difficult standardization between centers. Apparent quality-of-life differences as well as the fewer number of treatments needed with Y90 potentially represent an area of future investigation; however, these tools are difficult to apply in cirrhotic patients and are not universally accepted.[17] As a result of these limitations, centers unable to perform inpatient TACE given limited bed availability have implemented Y90 as a therapy given its outpatient nature.

Finally, although sorafenib is currently the standard of care for patients with advanced HCC, previous reports (as well as this cohort analysis) have demonstrated an antitumoral effect of Y90 worthy of further investigation. Patients with advanced disease, particularly those with Child–Pugh A disease and PVT, may represent a select cohort in which combinatorial therapy of Y90 with sorafenib (or other targeted therapy) may significantly improve outcome. It is rational to postulate that the cytotoxic effect of Y90 combined with the cytostatic effect of a targeted therapy could translate into a positive tumor response and prolonged TTP exceeding that reported in SHARP, both end points having been shown to improve survival.[10,15] Here again, certain trial design issues become apparent. (1) While the importance of TTP has now been established, the design of a randomized trial of Y90 compared with or combined with targeted therapies would need to address the confounding effects of crossover at the time of progression, particularly if survival is the end point; this would create ethical and treatment difficulties for patients being taken off study. (2) Although intuitive, the mere combination of biologic agents does not necessarily imply improved and synergistic results, as shown by the negative interaction of combined bevacizumab with panitumumab or cetuximab in colorectal cancer.[44,45] With properly designed studies, patients with Child–Pugh A BCLC who have PVT represent an ideal target whereby Y90 could become one of the standards of care. Given the promising antitumoral effects of Y90, one interesting clinical trial design might include Y90 versus Y90/sorafenib to capitalize on the cytotoxic effect of Y90 (response rate: WHO, 52%; EASL, 69%) and the cytostatic effect of sorafenib (TTP, 5.5 months).[10,17,46]

Ultimately, the demands for a higher level of evidence for Y90 in HCC should be tempered against the realities of existing standards of care that are based on a mixture of cohort and randomized trials, as well as the technical, ethical, and statistical feasibility of performing such studies.

Conclusions

The role of Y90 for the treatment of HCC continues to be defined. In properly selected patients, Y90 can be used safely with encouraging survival. We report the results of a large 291-patient cohort with substratification analyses to gain insight into which patients appear to potentially benefit from this therapy. The intricate interaction between tumor factors and degree of hepatic dysfunction is highlighted. Y90 in patients with Child–Pugh A disease (with or without PVT) and patients with Child–Pugh B disease (without PVT or metastases) is of particular interest and requires further exploration. Controlled studies comparing (1) Y90 with alternative locore-

gional therapies in early (radiofrequency ablation) and intermediate (TACE) disease and (2) Y90 in various combinations with systemic targeted therapies in advanced disease are of clinical and practical interest and are currently under way.

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Conflicts of interest

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