



Overall survival and toxicity of hepatocellular carcinoma Barcelona Clinic Liver Cancer B patients receiving Y90 radioembolization: analysis of the radiation-emitting SIR-spheres in non-resectable liver tumor (RESiN) registry

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Background: To evaluate overall survival (OS), progression-free survival (PFS) and toxicity after resin Yttrium-90 (Y-90) radioembolization in Barcelona Clinic Liver Cancer B (BCLC B) hepatocellular carcinoma (HCC) patients using the Bolondi subgroup classification.

Methods: A total of 144 BCLC B patients were treated between 2015–2020. Patients were broken into 4 subgroups by tumor burden/liver function tests with 54, 59, 8 and 23 in subgroups 1, 2, 3 and 4. OS and PFS were calculated with Kaplan-Meier analysis with 95% confidence intervals. Toxicities were assessed using Common Terminology Criteria for Adverse Events (CTCAE) v5.

Results: Prior resection and chemoembolization were performed in 19 (13%) and 34 (24%) of patients. There were no deaths within 30 days. Median OS and PFS for the cohort were 21.5 and 12.4 months. Median OS was not reached for subgroup 1 at a mean 28.8 months, and was 24.9, 11.0 and 14.6 months for subgroups 2–4 ($\chi^2=19.8$, $P=0.0002$). PFS by BCLC B subgroup was 13.8, 12.4, 4.5, and 6.6 months ($\chi^2=16.8$, $P=0.0008$). The most common Grade 3 or 4 toxicities were elevated bilirubin ($n=16$, 13.3%) and decreased albumin ($n=15$, 12.5%). Grade 3 or greater bilirubin (32% *vs.* 10%, $P=0.03$) and albumin (26% *vs.* 10%, $P=0.03$) toxicity were more common in the subgroup 4 patients.

Conclusions: The Bolondi subgroup classification stratifies OS, PFS and development of toxicity in patients treated with resin Y-90 microspheres. OS in subgroup 1 approaches 2.5 years and Grade 3 or greater

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hepatic toxicity profile in subgroups 1–3 is low.

Keywords: Radioembolization; hepatocellular carcinoma (HCC); Barcelona Clinic Liver Cancer (BCLC)

Submitted Oct 04, 2022. Accepted for publication Feb 10, 2023. Published online Mar 06, 2023.

doi: 10.21037/jgo-22-972

View this article at: <https://dx.doi.org/10.21037/jgo-22-972>

Introduction

Primary liver cancer is the sixth most common type of cancer and the third leading cause of cancer death worldwide, with hepatocellular carcinoma (HCC) comprising 75–80% of these tumors (1). The most widely accepted classification scheme is the Barcelona Clinic Liver Cancer (BCLC) system (2–5). BCLC has been validated as a predictor of overall survival (OS) and is endorsed both by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (6–12). BCLC intermediate-stage (BCLC B) patients have a diverse range of presentation regarding tumor burden and liver function (11–13).

Transarterial chemoembolization (TACE) is the first-line treatment recommendation for HCC in this group with a reported OS ranging from 14–45 months (7,11). Due to limited evidence-based and standardized treatment

recommendations across the spectrum of BCLC B patients, Bolondi *et al.* proposed a subclassification system for intermediate stage HCC focused on tumor burden and liver function (14). Given the common overlap of cirrhosis and HCC, both these factors are critical in treatment planning. Previous papers have demonstrated that stratifying patients by the Bolondi subclassification stratified OS with best supportive care, chemoembolization and other treatments (15–18).

Transarterial radioembolization (TARE) using Yttrium-90 (Y-90) is performed in BCLC B patients (19). The OS of BCLC B patients treated with TARE compares favorably with those treated with TACE (18). Additionally, patients maintain better health-related quality of life with TARE compared to TACE (20). The Radiation-Emitting Sir-Spheres in Non-resectable tumor (RESiN) registry (NCT 02685631) is a prospectively gathered observational study on patients treated with Y-90 embedded microspheres (Sirtex Medical, Woburn, MA, USA). Previously, outcomes of 448 HCC patients in the RESiN registry were reported (21). The purpose of the current analysis is to evaluate OS and toxicities of BCLC B patients broken down by the Bolondi sub-classification method. We present the following article in accordance with the STROBE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-972/rc>).

Methods

Registry/patients

The RESiN registry is an observational study collecting data on patients over 18 years of age with primary or secondary liver cancer scheduled to receive Y-90 microsphere therapy as part of their treatment. Patients were enrolled from 2015–2020. The decision to treat with Y-90 was made at an institutional level based on collaborative decision making with the treating IR and referring physician(s). Exclusion criteria included (I) prior treatment with arterial Y-90 therapy, even if new areas were being targeted, and (II) the

Highlight box

Key findings

- Bolondi subgroup classification predicts overall (OS) and progression-free survival (PFS) for Barcelona Clinic Liver Cancer (BCLC) Class B disease.
- Median OS for patients in subgroups 1 wasn't reached at a mean of 28.8 months. Median OS for subgroup 2 was 24.9 months.
- Hepatic function toxicities were most common in subgroup 4.

What is known and what is new?

- Chemoembolization is the standard of care for initial treatment of BCLC B disease.
- Previous research had demonstrated similar survival stratification with best supportive care and chemoembolization.
- Bolondi subgroup class can predict survival and toxicity following radioembolization.

What is the implication, and what should change now?

- Radioembolization is a reasonable treatment option for patients with intermediate-stage (BCLC B) hepatocellular carcinoma.
- Radioembolization should only be used for patients in subgroup 4 in patients that can be treated with segmental infusion.

Table 1 Bolondi B subgroup classification scheme. The Up to 7 Criteria is the sum of the total number of HCC and the diameter of the largest tumor

Variables	Subgroup B1	Subgroup B2	Subgroup B3	Subgroup B4
Child-Pugh score	5, 6, 7	5, 6	7	8–9
Up to 7 criteria	Within	Outside	Outside	Within or outside
Portal vein thrombosis	No	No	No	No

HCC, hepatocellular carcinoma.

need for consent from a surrogate in cases where patients were unable to consent on their own. This registry was an online collaboration between 43 hospitals across The United States utilizing a Research Electronic Data Capture online database. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study protocol was approved and reviewed by the Vanderbilt Ingram Cancer Center and Vanderbilt University Institutional Review Board (IRB) as GI 1523 (IRB No. 150407) and subsequently approved at the other sites. All patients signed informed consent to participate.

In this review, all patients had HCC diagnosed by radiologic appearance and/or biopsy. All tumors qualified as BCLC B. The subgroups were determined by liver function and whether tumor burden was within or beyond the “Up to 7” Criteria: the sum of the number of tumors plus the diameter of the largest tumor. The subgroups were determined as outlined by Bolondi in *Table 1*. All patients followed local imaging and laboratory follow-up guidelines given the observational nature of the registry. Follow-up imaging was interpreted at each institution by abdominal imagers. Baseline demographic values included age, sex, race, ethnicity, cause of cirrhosis, hepatic functions including ascites and encephalopathy, and previous arterial and surgical treatments. Patients were treated by trained interventional radiologists. The treated portion of the liver (whole liver, lobar, segmental), the delivered activity and dosimetry method were tracked.

Statistical analysis

Demographic differences between subgroups were assessed using Kruskal-Wallis and Pearson tests for continuous and discrete variables regarding liver function, cirrhotic etiology, tumor characteristics, and health status. OS and progression-free survival (PFS) were defined as the time from the date of treatment to death or confirmation of disease progression at any site at follow-up CT or MRI.

Kaplan-Meier analysis was performed to compare OS and PFS with 95% confidence intervals reported. Fifteen patients (7 in subgroup 1, 7 in subgroup 2, and 1 in subgroup 4) had no further data entered after their baseline. OS and PFS were calculated for the remaining 129 patients using modified Response Evaluation Criteria in Solid Tumors (mRECIST). For patients that were lost to follow-up, the last date of contact was used as a censoring point. Reasons for leaving the study were tracked, including the cause of death when available with differences compared using the Pearson test. Variables concerning the nature of intra- and extrahepatic progressive disease following treatment were analyzed by way of Pearson tests. Grade 3 or greater liver function toxicities and constitutional adverse events were tracked using the Common Terminology Criteria for Adverse Events version 5. If a patient had multiple events of the same toxicity within the course of the study, then the highest grade was given and counted as a single event. A single patient could develop multiple toxicities.

Results

Demographics

Cohort demographics are included in *Table 2*. Subgroups B1, B2, B3 and B4 had 54, 59, 8, and 23 patients respectively. Prior to treatment, 109/144 (76%) of the patients had a diagnosis of cirrhosis, most commonly in subgroups 1 (48/54, 89%) and 4 (23/23, 100%) compared to subgroups 2 (33/59, 56%) and 3 (5/8, 62%) ($P < 0.001$). Thirty-four patients (24%) had previous arterial therapy and 19 (14%) had previous resection. The subgroups were similar in age ($P = 0.30$), race ($P = 0.65$), ethnicity ($P = 0.45$), and gender ($P = 0.26$). Most of the patients were male ($n = 116$, 81%) and white ($n = 107$, 74%). The most common causes of cirrhosis were hepatitis C ($n = 68$, 47%) and alcohol ($n = 35$, 24%). Patients in subgroups 3 and 4 more commonly had hepatic encephalopathy (8/31,

Table 2 Baseline characteristics

Variables	N	Group 1 (N=54)	Group 2 (N=59)	Group 3 (N=8)	Group 4 (N=23)	Combined (N=144)	P value
Age, years	144	65 [62–70]	67 [62–73.5]	68 [64–74.5]	64 [60.5–68]	62.0 [66.0–71.0]	0.3 ¹
Sex	144						0.26 ²
Female		12 (22%)	13 (22%)	6 (75%)	22 (96%)	28 (19%)	
Male		42 (78%)	46 (78%)	2 (25%)	1 (4%)	116 (82%)	
Race	144						0.65 ²
American Indian/Alaska		0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (1%)	
Asian		1 (2%)	5 (8%)	0 (0%)	0 (0%)	6 (4%)	
Black		8 (15%)	6 (10%)	3 (38%)	4 (17%)	21 (15%)	
White		42 (78%)	42 (71%)	5 (62%)	18 (78%)	107 (74%)	
Other		0 (0%)	3 (5%)	0 (0%)	0 (0%)	5 (3%)	
Unknown		1 (2%)	2 (3%)	0 (0%)	1 (4%)	4 (3%)	
Ethnicity	144						0.45 ²
Hispanic/Latino		9 (17%)	5 (8%)	0 (0%)	4 (17%)	18 (12%)	
Non-Hispanic		43 (80%)	48 (81%)	7 (88%)	17 (74%)	115 (80%)	
Other		0 (0%)	3 (5%)	0 (0%)	0 (0%)	3 (2%)	
Unknown		2 (4%)	3 (5%)	1 (12%)	2 (9%)	8 (6%)	
Cirrhosis present	144						<0.001 ²
Yes		48 (89%)	33 (56%)	5 (62%)	23 (100%)	109 (76%)	
No		6 (11%)	26 (44%)	3 (38%)	0 (0%)	35 (24%)	
Alcohol	144						0.003 ²
Yes		14 (26%)	8 (14%)	1 (12%)	12 (52%)	35 (24%)	
No		40 (74%)	51 (86%)	7 (88%)	11 (48%)	109 (76%)	
Hepatitis B	144						0.76 ²
Yes		1 (2%)	2 (3%)	0 (0%)	0 (0%)	3 (2%)	
No		53 (98%)	59 (100%)	8 (100%)	22 (96%)	141 (98%)	
Hepatitis C	144						0.076 ²
Yes		32 (59%)	21 (36%)	3 (38%)	12 (52%)	68 (47%)	
No		22 (41%)	38 (64%)	5 (62%)	11 (48%)	76 (53%)	
NASH	144						0.96 ²
Yes		6 (11%)	5 (8%)	0 (0%)	2 (9%)	13 (9%)	
No		48 (89%)	54 (92%)	8 (100%)	21 (91%)	131 (91%)	
Bilirubin	144	0.80 [0.6–1.2]	0.80 [0.5–1.1]	0.8 [0.6–0.9]	1.9 [1.4–2.5]	0.9 [0.6–1.3]	<0.001 ¹
Albumin	144	3.85 [3.5–4.1]	3.7 [3.4–4.1]	3.1 [2.6–3.3]	2.9 [2.6–3.2]	3.7 [3.2–4.0]	<0.001 ¹
Previous embolization	139						0.11 ²
Yes		15 (28%)	8 (14%)	3 (38%)	8 (36%)	34 (24%)	
No		38 (72%)	48 (86%)	5 (62%)	14 (64%)	105 (76%)	

Table 2 (continued)

Table 2 (continued)

Variables	N	Group 1 (N=54)	Group 2 (N=59)	Group 3 (N=8)	Group 4 (N=23)	Combined (N=144)	P value
Previous resection	135						0.83 ²
Yes		10 (21%)	9 (16%)	0 (0%)	0 (0%)	19 (14%)	
No		38 (79%)	49 (84%)	8 (100%)	21 (100%)	116 (86%)	
Ascites	144						<0.001 ²
Yes		2 (4%)	2 (3%)	5 (62%)	15 (65%)	24 (17%)	
No		52 (96%)	57 (97%)	3 (38%)	8 (35%)	120 (83%)	
Hepatic encephalopathy	144						<0.001 ²
Yes		2 (4%)	1 (2%)	1 (12%)	7 (30%)	11 (8%)	
No		52 (96%)	58 (98%)	7 (88%)	16 (70%)	133 (92%)	
MELD	143	9 [7–11]	8 [6–9]	7 [6–9.5]	13 [11.5–15]	9 [7–11]	<0.001 ¹
Child-Pugh class	144						<0.001 ²
Class A		44 (81%)	59 (100%)	0 (0%)	0 (0%)	103 (72%)	
Class B/C		10 (19%)	0 (0%)	8 (100%)	23 (100%)	41 (28%)	

Values are presented as n (%) or median value with interquartile range. Baseline differences were assessed with the Kruskal-Wallis test (¹) or the Pearson test (²). MELD, Model for End-Stage Liver Disease.

Table 3 Baseline tumor burden by group

Variables	N	Group 1 (N=54)	Group 2 (N=59)	Group 3 (N=8)	Group 4 (N=23)	Combined (N=144)	P value
Tumor number	141						0.002 ²
1		27 (50%)	15 (25%)	3 (38%)	5 (25%)	50 (35%)	
2–3		18 (33%)	20 (34%)	0 (0%)	9 (45%)	47 (33%)	
4–5		9 (17%)	7 (12%)	2 (25%)	2 (10%)	20 (14%)	
>5		0 (0%)	17 (29%)	3 (38%)	4 (20%)	24 (17%)	
Largest tumor diameter (cm)	144	2.5 (1.8–4.3)	6.7 (4.7–10.3)	8.2 (6.9–11.9)	4.2 (3.8–5.4)	4.6 (2.7–6.8)	<0.001 ¹
Total tumor diameter (cm)	114	4.6 (3.2–6.3)	14.1 (9.6–20.0)	13.9 (11.0–21.9)	7.3 (5.7–12.8)	7.8 (4.8–14.4)	<0.001 ¹

Values are presented as number (%) or median value with interquartile range. Differences were assessed with the Kruskal-Wallis test (¹) or the Pearson test (²).

26% compared to 3/109, 3%, $P < 0.001$) and pre-treatment ascites (20/31, 65% compared to 4/109, 37%, $P < 0.001$). Ten of the 11 (91%) patients with encephalopathy had Grade 1 disease at baseline. All patients responded to intervention for their encephalopathy and ascites. Patients in subgroup 4 also had a higher bilirubin (median 1.9 *vs.* 0.8 in the other subgroups, < 0.001) and lower albumin (2.9 *vs.* > 3 in the other subgroups, $P < 0.001$).

Baseline imaging

Baseline imaging findings are included in *Table 3*. Ninety-seven patients had 1 ($n = 50$, 35%) or 2–3 tumors ($n = 47$, 33%). Patients in subgroup 1 had the smallest diameter index tumor (median 2.5 cm, IQR: 1.8–4.3 cm) and total tumor diameter (median 4.6 cm, IQR: 3.2–6.3 cm). Patients in subgroup 4 had the next lowest burden of disease, followed

Table 4 Delivered activity and targeted treatment zone by subgroups

Variables	N	Group 1 (N=54)	Group 2 (N=59)	Group 3 (N=8)	Group 4 (N=23)	Combined	P value
Activity (GBq)	144	1.0 (0.8–1.4)	1.4 (1.1–1.7)	1.4 (1.2–1.8)	1.2 (1.0–1.5)	1.2 (0.9–1.6)	0.02 ²
Treatment zone	144						0.06 ¹
Whole liver		10 (19%)	14 (24%)	2 (25%)	3 (13%)	29 (20%)	
Lobar		34 (63%)	45 (76%)	6 (75%)	18 (78%)	103 (72%)	
Segmental		10 (19%)	0 (0%)	0 (0%)	2 (9%)	12 (8%)	
Dosimetry method	98						0.6 ¹
BSA		34 (87%)	33 (89%)	6 (100%)	15 (94%)	88 (90%)	
Empiric		0	1 (3%)	0	1 (6%)	2 (2%)	
Partition		5 (13%)	3 (8%)	0	0	8 (8%)	

Values are presented as n (%) or median value with interquartile range. Baseline differences were assessed with the Kruskal-Wallis test (¹) or the Pearson test (²). GBq, Gigabecquerel; BSA, body surface area.

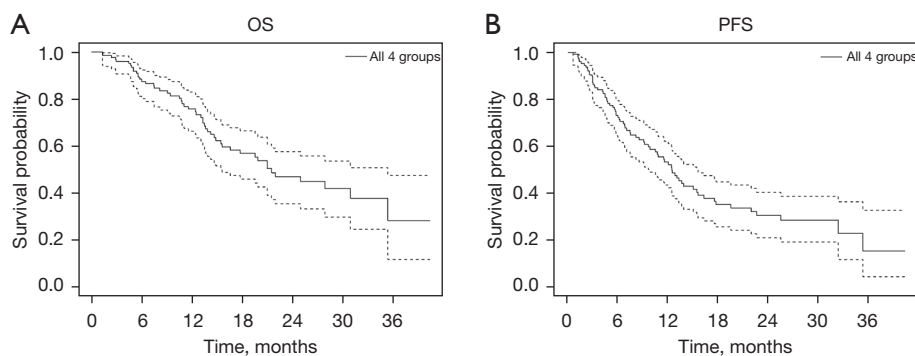


Figure 1 Overall and Progression-Free survival of the entire group. (A) Kaplan-Meier analysis of OS of the entire cohort. Median OS was 21.5 months (95% CI: 15.6–35.4 months). (B) Kaplan-Meier analysis of PFS of the entire cohort. Median PFS was 12.4 months (95% CI: 9.8–15.4 months). OS, overall survival; PFS, progression-free survival.

by subgroups 2 and 3, respectively. The differences in index and overall tumor burden between subgroups was significant (both $P < 0.001$). There were no patients with portal vein thrombosis as this study addresses BCLC B patients.

Delivered activity

The median prescribed activity was 1.2 [interquartile range (IQR), 0.9–1.6] Gigabecquerel (GBq). Delivered activity and treatment location by subgroup is included in *Table 4*. The highest activities were prescribed for patients in subgroups 2 and 3. One hundred thirty-two treatments were lobar or greater. All 12 (8%) of patients that underwent segmental therapy were in the subgroups that included patients that

met the Up to 7 Criteria: 10/54 patients (19%) of subgroup 1 and 2/23 patients (9%) of subgroup 4. Median activity delivered for whole liver, lobar and segmental treatments was 1.7 (IQR, 1.4–2.2), 1.2 (IQR, 0.9–1.5), and 0.7 (IQR, 0.4–1.0) GBq. This difference was significant ($P < 0.001$).

Survival

The median OS (*Figure 1A*) for the cohort was 21.5 months (95% CI: 15.6–35.4 months). There were no deaths within 30 days of treatment. The median PFS (*Figure 1B*) for the cohort was 12.4 months (95% CI: 9.8–15.4 months). Subgroup analysis for OS is demonstrated in *Figure 2A*. Median OS was not reached for subgroup 1 at a mean of 28.8 months, while it was 24.9 months (95% CI: 16.5–not reached) for

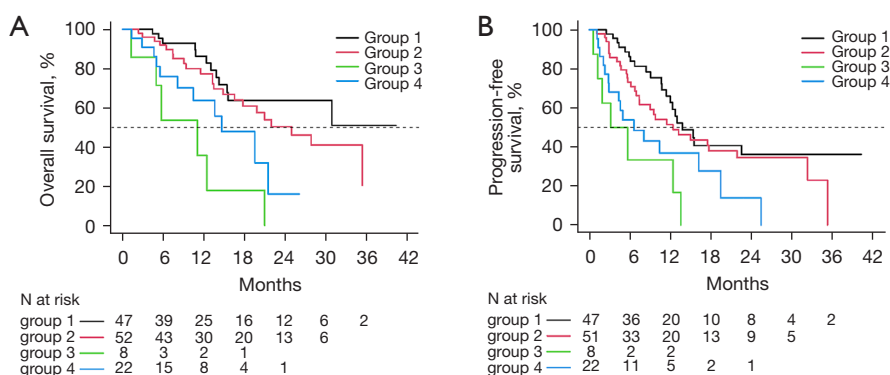


Figure 2 OS and PFS by BCLC subgroups. (A) OS by BCLC subgroups. Subgroup 1 did not reach median survival at a mean of 28.8 months. Differences in OS between subgroups were statistically significant using the log-rank test ($\chi^2=19.8$, $P=0.0002$). (B) PFS by BCLC subgroups. PFS ranged from 4.5–13.8 months. Differences in PFS were statistically significant using the log-rank test ($\chi^2=16.8$, $P=0.0008$). OS, overall survival; PFS, progression-free survival; BCLC, Barcelona Clinic Liver Cancer.

subgroup 2 and 11.0 months (95% CI: 1.3–not reached) for subgroup 3 and 14.6 months (95% CI: 8.1–21.5 months) for subgroup 4. These differences were statistically significant ($\chi^2=19.8$, $P=0.0002$). Median PFS by subgroup is in *Figure 2B*. Subgroup 1 had the longest median PFS (13.8 months, 95% CI: 11.4–not reached). Subgroup 2 median PFS was 12.4 months (95% CI: 7.4–21.9), subgroup 3 was 4.5 months (95% CI: 0.6–not reached) and subgroup 4 was 6.6 months (95% CI: 2.9–19.5). The differences in PFS by subgroup were statistically significant as well ($\chi^2=16.8$, $P=0.0008$).

Progression

Seventy of the 144 patients (49%) developed progressive disease. The majority of patients with progression (66/70, 94%) had new disease in the liver, while 10/70 (14%) developed extrahepatic metastases. Six of 70 patients with new disease (8.6%) developed both intrahepatic and extrahepatic metastases. Of the 60/144 patients (42%) with isolated intrahepatic progression, 52/144 (36%) were in an area of previous treatment. By subgroup, 16/50 (32%) patients in subgroup 1, 21/52 (40%) in subgroup 2, 6/8 (75%) in subgroup 3 and 9/23 (39%) in subgroup 4 developed progression in a previous treatment zone ($P=0.5$). The most common extrahepatic sites were the lungs ($n=5$, 3.5%) and skeletal system ($n=4$, 2.8%). BCLC subgroup did not predict whether progression would occur in the liver or extrahepatically ($P=0.28$), or the specific location where extrahepatic metastases would develop ($P=0.31$).

Off study

Eighty-five patients left the study as demonstrated in *Table 5*. The most common reason was death (63/85, 74%) followed by loss to follow-up (11/85, 13%) and entry to hospice (6/85, 7%). The cause of death was known in 41/63 (65%) patients. The most common cause of death was tumor progression (23/41, 56%). There was no difference between the subgroups in reasons to leave the study or cause of death (both $P=0.1$).

Toxicity

A total of 62 Grade 3 or 4 toxicities were reported. These are outlined in *Table 6*. Fifty-two liver function tests and 10 constitutional events were identified. While hepatic function toxicities were negligible one month after treatment, more elevations were identified later in follow-up. *Table 7* outlines toxicities at one month and at any point afterward. The most common Grade 3 or 4 liver function toxicities were elevated bilirubin ($n=16$, 13%) and decreased albumin ($n=15$, 12%). A higher proportion of significant bilirubin toxicities occurred in subgroup 4 (6/19, 32% *vs.* 10/101, 10%, $P=0.03$). Five patients in subgroup 4 (26%) developed Grade 3 albumin toxicity compared to 10/119 (10%) in subgroups 1–3 ($P=0.03$). Other liver function toxicities were less common and without significant difference between subgroups for aspartate aminotransferase (AST) ($P=0.7$), alanine aminotransferase (ALT) ($P=0.5$) and international normalized ratio (INR) ($P=0.2$). There was no identifiable

Table 5 Off-study reasons and causes of death for BCLC B patients

	Combined (n=144) [%]	Subgroup 1 (n=54) [%]	Subgroup 2 (n=59) [%]	Subgroup 3 (n=8) [%]	Subgroup 4 (n=23) [%]	P value
Off study reason	85/144 [59]	25/54 [46]	35/59 [59]	6/8 [75]	19/23 [83]	0.1
Death	63/85 [74]	16/54 [64]	27/35 [77]	6/6 [100]	14/19 [74]	
Lost to follow-up	11/85 [13]	4/54 [16]	7/35 [20]	0/6 [0]	0/19 [0]	
Hospice	6/85 [7]	3/54 [12]	0/35 [0]	0/6 [0]	3/19 [16]	
Withdrew consent	3/85 [4]	2/54 [8]	1/35 [3]	0/6 [0]	0/19 [0]	
Treatment elsewhere	1/85 [1]	0/54 [0]	0/35 [0]	0/6 [0]	1/19 [5]	
Other	1/85 [1]	0/54 [0]	0/35 [0]	0/6 [0]	1/19 [5]	
Cause of death	41/63 [65]	11/16 [69]	18/27 [67]	5/6 [83]	7/14 [50]	0.1
Progressive disease	23/41 [56]	7/11 [56]	13/18 [72]	1/5 [20]	2/7 [29]	
Hepatic decompensation	5/41 [12]	0/11 [0]	2/18 [11]	2/5 [40]	1/7 [14]	
Other	13 [32]	4/11 [36]	3/18 [17]	2/5 [40]	4/7 [57]	

No differences between the subgroups were identified. BCLC B, Barcelona Clinic Liver Cancer B.

Table 6 Summary of Grade 3–4 toxicities by liver function tests and constitutional events

Toxicity	30 days Grade 3 (n=35)	30 days Grade 4 (n=35)	Total Grade 3 (n=120)	Total Grade 4 (n=120)	Total
Bilirubin	0	0	13	3	16
Albumin	0	0	15	0	15
AST	0	0	5	5	10
ALT	0	0	7	3	10
INR	0	0	1	0	1
Abdominal pain	1	0	3	0	3
Abdominal distension	1	0	1	0	1
Encephalopathy	1	0	1	0	1
Fatigue	1	0	1	0	1
Fever	1	0	1	0	1
Hyperglycemia	0	1	0	1	1
Nausea	1	0	1	0	1
Renal disorder, other	1	0	0	1	1
Total	7 (20%)	1 (3%)	49 (41%)	13 (11%)	62

AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

difference in hepatic toxicity rates when comparing whole liver, lobar and segmental infusion (*Table 8*).

Discussion

The current work reports a statistically significant

correlation between individual patient BCLC B Bolondi subgroup and OS and PFS following TARE. Tumor diameter is not incorporated in assessment scores such as albumin-bilirubin (ALBI) grade or Child-Pugh and the BCLC score doesn't account for liver function. The Bolondi subgroups provide value by combining tumor size as well

Table 7 Grade 3 or greater hepatic function toxicities by subgroups

	Subgroup 1 (n=47) [%]	Subgroup 2 (n=48) [%]	Subgroup 3 (n=6) [%]	Subgroup 4 (n=19) [%]	Total (n=120) [%]	P value
Bilirubin						0.03
Grade 3	4 [8]	5 [10]	0 [0]	4 [21]	13 [11]	
Grade 4	0 [0]	1 [2]	0 [0]	2 [10]	3 [2]	
Albumin						0.03
Grade 3	7 [15]	3 [6]	0 [0]	5 [26]	15 [12]	
AST						0.7
Grade 3	2 [4]	2 [4]	0 [0]	1 [5]	5 [4]	
Grade 4	2 [4]	1 [2]	0 [0]	2 [10]	5 [4]	
ALT						0.5
Grade 3	2 [4]	3 [6]	0 [0]	2 [10]	7 [6]	
Grade 4	2 [4]	0 [0]	0 [0]	1 [5]	3 [3]	
INR						0.2
Grade 3	1 [2]	0 [0]	0 [0]	0 [0]	1 [0.8]	

Significant differences were identified for bilirubin and albumin. AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

Table 8 Grade 3 or greater hepatic function toxicities by the level of selection

	Whole liver (n=26) [%]	Lobar (n=86) [%]	Segmental (n=8) [%]	Total (n=120) [%]	P value
Bilirubin					0.1
Grade 3	3 [12]	9 [10]	1 [12]	13 [11]	
Grade 4	1 [4]	2 [2]	0 [0]	3 [3]	
Albumin					0.1
Grade 3	1 [4]	14 [16]	0 [0]	15 [12]	
AST					0.5
Grade 3	2 [8]	3 [3]	0 [0]	5 [4]	
Grade 4	2 [8]	2 [2]	1 [12]	5 [4]	
ALT					0.5
Grade 3	2 [8]	4 [5]	1 [12]	7 [6]	
Grade 4	1 [4]	1 [1]	0 [0]	3 [3]	
INR					0.1
Grade 3	0 [0]	1 [1]	0 [0]	1 [0.8]	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio.

as liver function to predict outcome in this heterogeneous patient group with tumor involvement extending from just outside Milan criteria to multifocal diffuse disease (7). Median OS in subgroups B1 and B2 were longer than

subgroups B3 and B4. The median OS time was not reached for subgroup B1 at a mean follow-up time of 28.8 months while median OS of subgroup 2 was 24.9 months compared to 11.0 and 14.6 months for subgroups 3 and 4. There were

no deaths within 30 days of treatment. Additionally, the classification scheme demonstrated significant differences between subgroups by tumor size and liver function measure. Bilirubin and albumin toxicities occurred at a significantly higher rate in patients from subgroup 4. The majority of the hepatic function toxicities developed more than a month after treatment, making separation of treatment effect from progression of cirrhosis challenging. Subgroup 3 had the largest tumor burden and shortest OS. This study completed enrollment prior to the publication of the DosiSphere study which demonstrated OS benefit with personalized dosimetry using higher tumor doses (19). The outcomes in subgroup 3 would likely have improved with personalized dosimetry.

Our survival breakdown between subgroups is similar to previous studies evaluating best supportive care and chemoembolization for BCLC B patients (15-17). Giannini *et al.* described survival with best supportive care in 269 patients (15). They reported OS by subgroup of 25, 16, 9, and 5 months. Like our study, Giannini's B3 subgroup had the smallest proportion of patients (8.2% of the 269 in the study). This finding may reflect the requirement of a single Child-Pugh score, B7, in the setting of a tumor burden beyond the Up to 7 Criteria.

Kim *et al.* reported chemoembolization outcomes in 821 BCLC B patients broken down by the Bolondi criteria (16). Only 5% of their patients were Bolondi subgroup 4, compared to 16% in the current study. Their survivals decreased by patient subgroup from a median of 51 months for subgroup 1 to 14.8 months for subgroup 3. Kim *et al.* also reported longer OS in subgroup 4 versus subgroup 3 (25 *vs.* 14.8 months, respectively); this finding was similar to the current study: 14.6 months for subgroup 4 *vs.* 11.0 months for subgroup 3. One potential reason for longer OS in subgroup 4 may be that although this subgroup is primarily defined by poor liver function (Child-Pugh score 8-9) it includes any tumor burden. Patients with lower tumor burden may be treated more selectively, with less liver toxicity. Segmental treatment in our cohort was performed only in subgroups 1 and 4. In our cohort, subgroup 4 had smaller median index tumor (4.2 *vs.* 8.2 cm) and total tumor diameter (7.2 *vs.* 13.9 cm) than subgroup 3. One difference between the current study and Kim's report is that 2% of our patients had hepatitis B virus compared to 75.9%. Hepatitis B positive patients with HCC and viral control can have prolonged survival (22). Given the higher rate of hepatic function toxicities in the current study, we

would caution against treating patients in subgroup 4 unless segmental treatment could be performed.

Nouso *et al.* compared BCLC B patient outcomes with radiofrequency ablation versus chemoembolization using the Bolondi subgroups (23). The majority of patients with B1 disease were treated with ablation, compared to 19.7% of the chemoembolization group. While this study documented that BCLC B patients could successfully be treated with ablation, tumor size greater than 3.0 cm adversely affected survival. Kariyama *et al.* later reviewed outcomes of different therapies in BCLC B patients, including resection, ablation, and chemoembolization (24). Resection patients were almost exclusively (159/165, 96%) from the B1 and 2 subgroups, with 155 (94%) Child-Pugh A and significantly fewer tumors: 136/165 patients (82%) had 3 or fewer HCC. Resection patients had the longest median OS of any group in the study at 5.6 years compared to 4.2 years for ablation and 2.5 years for chemoembolization. Resection remains a valuable option for these highly selected BCLC B patients.

The current study contains limitations. Sites entered data at self-monitored time points, resulting in less than 100% entry. *Tables 2-4* include a column outlining the available and missing data for each measure. This study was performed prior to the era of personalized dosimetry which involved use of glass, rather than resin microspheres. The subgroups are not evenly matched. However, the purpose of the study was to demonstrate differences in outcomes based by stratification into the subgroups that were used. The results of this multicenter study should be validated by a larger cohort. It is encouraging that the OS breakdown by subgroup closely tracked with best previous research on supportive care and chemoembolization in BCLC B patients.

Conclusions

In summary, the current study found that the Bolondi BCLC B subclassification predicts OS and PFS. A high percent of the Grade 3 or greater adverse events were clustered in subgroup 4. Patients in this subgroup should be carefully selected prior to treatment with Y-90. Radioembolization of BCLC B subgroup 1-3 patients can be done with acceptable safety and efficacy.

Acknowledgments

Funding: This work was supported by Sirtex Medical.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-972/rc>

Data Sharing Statement: Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-972/dss>

Peer Review File: Available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-972/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroupp.com/article/view/10.21037/jgo-22-972/coif>). All authors report that the study was supported by Sirtex Medical. RTG is a consultant and speaker for Sirtex Medical and serves as a proctor for Sirtex Medical. Sirtex Medical has funded travel related to these roles. ZSC has received an institutional research grant from Sirtex Medical and serves as a speaker and consultant for Sirtex Medical. JSB is a consultant for Sirtex Medical. DYS has received institutional research grants from Sirtex Medical. He is a consultant and has received support for travel/hotel/meals for meetings with Sirtex Medical. ASK has received institutional support from Sirtex Medical, Bard Medical and ABK Biomedical. JG is a consultant for Sirtex Medical and Boston Scientific. He has also received institutional grant support from Sirtex Medical. EAW is a proctor for Sirtex Medical. DBB has received institutional research support from Sirtex Medical and Guerbet. He has served as a speaker for Cook Medical and a Data Safety Monitor for Bard Medical. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved and reviewed by the Vanderbilt Ingram Cancer Center and Vanderbilt University Institutional Review Board (IRB) as GI 1523 (IRB No. 150407) and subsequently approved at the other sites. All patients signed informed consent to participate.

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Cite this article as: Adeniran OR, Nguyen CN, Perez TH, Frantz SK, Matsuoka L, Du L, Gandhi RT, Collins ZS, Matrana MR, Petroziello M, Brower JS, Sze DY, Kennedy AS, Golzarian J, Wang EA, Brown DB. Overall survival and toxicity of hepatocellular carcinoma Barcelona Clinic Liver Cancer B patients receiving Y90 radioembolization: analysis of the radiation-emitting SIR-spheres in non-resectable liver tumor (RESiN) registry. *J Gastrointest Oncol* 2023;14(2):874-885. doi: 10.21037/jgo-22-972