

Baptist Health South Florida

Scholarly Commons @ Baptist Health South Florida

All Publications

11-17-2022

Overall survival and toxicity of Y90 radioembolization for hepatocellular carcinoma patients in Barcelona Clinic Liver Cancer stage C (BCLC-C)

Ripal Gandhi

Miami Cardiac & Vascular Institute, gandhi@baptisthealth.net

Follow this and additional works at: <https://scholarlycommons.baptisthealth.net/se-all-publications>

Citation

Goswami, P., Adeniran, O. R., K Frantz, S., Matsuoka, L., Du, L., Gandhi, R. T., Collins, Z. S., Matrana, M. R., Petroziello, M., Brower, J. S., Sze, D. Y., Kennedy, A. S., Goltzarian, J., Wang, E. A., & Brown, D. B. (2022). Overall survival and toxicity of Y90 radioembolization for hepatocellular carcinoma patients in Barcelona Clinic Liver Cancer stage C (BCLC-C). *BMC gastroenterology*, 22(1), 467. <https://doi.org/10.1186/s12876-022-02528-y>

This Article -- Open Access is brought to you for free and open access by Scholarly Commons @ Baptist Health South Florida. It has been accepted for inclusion in All Publications by an authorized administrator of Scholarly Commons @ Baptist Health South Florida. For more information, please contact Carrief@baptisthealth.net.

RESEARCH

Open Access



Overall survival and toxicity of Y90 radioembolization for hepatocellular carcinoma patients in Barcelona Clinic Liver Cancer stage C (BCLC-C)

Pulak Goswami¹, Oladapo R. Adeniran², Shelby K. Frantz², Lea Matsuoka³, Liping Du⁴, Ripal T. Gandhi⁵, Zachary S. Collins⁶, Marc R. Matrana⁷, Michael Petroziello⁸, Jayson S. Brower⁹, Daniel Y. Sze¹⁰, Andrew S. Kennedy¹¹, Jafar Golzarian¹², Eric A. Wang¹³ and Daniel B. Brown^{2*}

Abstract

Introduction: National Comprehensive Cancer Network HCC guidelines recommend Y90 to treat BCLC-C patients only in select cases given the development of systemic regimens. We sought to identify ideal candidates for Y90 by assessing survival and toxicities in this patient group.

Materials and methods: The Radiation-Emitting Selective Internal radiation spheres in Non-resectable tumor registry is a prospective observational study (NCT: 02,685,631). Patients with advanced HCC were stratified into 3 groups based on tumor location, Eastern Cooperative Oncology Group (ECOG) performance status, and liver function. Group 1: liver isolated HCC, ECOG 0 and Child Pugh (CP) A ($n = 12$, 16%), Group 2: liver isolated HCC, ECOG ≥ 1 or CP B/C ($n = 37$, 49%), and Group 3: extrahepatic HCC with any ECOG or CP score ($n = 26$, 35%). Patients in any group could have macrovascular invasion. Overall survival (OS) and progression-free survival (PFS) with 95% confidence intervals (95% CI) were calculated. Grade 3+ toxicities were tracked using Common Terminology Criteria for Adverse Events v5. Cox proportional hazard model was performed to determine factors affecting OS.

Results: Seventy-five BCLC-C patients treated between 2015 and 2019 were reviewed. The groups were similar in age, sex, race, and ethnicity (all $p > 0.05$). Bilobar disease was least common in Group 1 ($p < 0.001$). Median OS of the entire cohort was 13.6 (95% CI 7.5–16.1) months. Median OS of Groups 1–3 were 21.8, 13.1 and 11.5 months respectively ($p = 0.6$). Median PFS for the cohort was 6.3 (4.8–14.7) months. Median PFS for group 1 was not reached. Mean PFS for Group 1 was 17.3 ± 4.8 months. Median PFS for Groups 2 and 3 was 6.8 and 5.9 months ($X^2 = 1.5$, $p = 0.5$). Twenty-four Grade 3 or greater toxicities developed, most commonly hyperbilirubinemia (8/75, 11%) and thrombocytopenia (2/75, 3%). The incidence of toxicities between groups was similar (all $p > 0.05$). Cox Proportional Hazard analysis predicted shorter OS with CP class B/C ($X^2 = 6.7$, $p = 0.01$), while macrovascular invasion ($X^2 = 0.5$, $p = 0.5$) and ECOG score of ≥ 1 ($X^2 = 2.1$, $p = 0.3$) was not associated with OS.

*Correspondence: daniel.b.brown@vumc.org

² Division of Interventional Radiology, Vanderbilt University Medical Center, CCC-1118 Medical Center North, 1161 21st Ave S, Nashville, TN 37232, USA
Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Conclusions: OS of CPA patients with advanced HCC and performance status of 0 was 21.8 months following Y90. CP A cirrhosis is the best predictor of prolonged OS in advanced (BCLC-C) HCC.

Keywords: Carcinoma, hepatocellular carcinoma, Yttrium radioisotopes/ therapeutic use, Yttrium radioisotopes/ adverse events, Adult, Treatment outcome

Introduction

Hepatocellular carcinoma (HCC) is the sixth most diagnosed form of cancer and is the third leading cause of cancer death worldwide while continuing to increase in incidence [1–3]. Intra-arterial therapy with chemoembolization and trans-arterial radioembolization (TARE) are commonly used for patients with HCC [4, 5]. Survival by the Barcelona Clinic Liver Cancer classification (BCLC) decreases with advancing stage [6, 7]. Advanced/BCLC-C disease is defined by imaging criteria such as vascular invasion and/or extrahepatic disease in the setting of preserved liver function but also includes subjective criteria, including patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 1–2. A criticism of including ECOG score is that patients may have symptoms related to underlying cirrhosis rather than from cancer and the ECOG score may not reflect cancer symptoms [8].

Several systemic therapy options including Atezolizumab-Bevacizumab, Nivolumab and Lenvatinib for patients with BCLC-C HCC have been developed in the last few years and are now accepted first-line therapy for advanced disease [4, 9–12]. Current National Cancer Cooperative Network recommendations state that patients with advanced HCC should be carefully evaluated prior to initiating locoregional therapy [4]. This statement reflects the relative lack of existing survival data when treating advanced HCC particularly with the development of efficacious systemic options [9]. These findings are compounded by the lack of success of Y90 to improve overall survival versus or in combination with sorafenib [13–15]. Findings in individual trials were reinforced by a meta-analysis which found no benefit when adding Y90 to sorafenib [16]. Treatment of advanced HCC varies regionally. In the United States and Europe, locoregional therapy is primarily considered when systemic options fail or are poorly tolerated [17]. In other countries such as China, chemoembolization is recommended in the setting of advanced disease [18]. Previous evaluations of outcomes with TARE in BCLC-C patients reported on the use of glass microspheres [19]. Outcomes using resin microspheres have not been widely reported [20]. The Radiation-Emitting SIR-Spheres in Non-Resectable (RESiN) liver tumor registry (NCT 02,685,631) was a national multicenter, prospective observational study capturing data on demographics, laboratory parameters,

treatment details, response and toxicities treated with resin microspheres. The registry captured real-world utilization of TARE outside the idealized scenario of clinical trials. The objectives of this study are to evaluate outcomes and toxicities from the registry in patients with BCLC-C HCC.

Methods

Registry/patients

The RESiN registry was an observational study collecting data on patients over 18 years of age with primary or secondary liver cancer scheduled to receive Y90 microsphere therapy as part of their treatment. The study was approved by the institutional review board at each of the 36 enrolling sites. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by each institution's human research committee. All patients signed written informed consent. Physicians at each of the institutions determined appropriateness for treatment, Y90 dosimetry, and follow-up imaging and laboratory examination per local practice guidelines. Patients were enrolled on the day of treatment and tracked afterward with enrollment from 2015–2020. Key exclusion criteria included age less than 18 years of age, an inability to provide informed consent and previous TARE. Other prior hepatic interventions, such as resection, chemoembolization, ablation, and stereotactic body radiotherapy were allowed. Data were entered utilizing a Research Electronic Data Capture online database.

In this analysis, all patients had HCC diagnosed by radiologic appearance and/or biopsy. Of the 1655 patients enrolled in RESiN, 448 had HCC. Seventy-five patients were BCLC-C. The subgroups were determined by the presence or absence of portal vein invasion, extrahepatic metastatic disease, Child–Pugh (CP) class and ECOG performance status as suggested by Bolondi [21]. These categories were designed to identify patients who have biologically different forms of advanced disease and include patients who have:

1. Portal venous invasion and are ECOG 0 and CP A without extrahepatic disease.
2. Portal venous invasion and are ECOG 1–2 and/or CP B-C without extrahepatic disease

3. Have extrahepatic disease with or without portal venous invasion and any ECOG CP score.

Procedures

Participants were treated by trained interventional radiologists to ensure minimal patient and operator radiation exposure [22]. Patients underwent mapping scintigraphy with technetium 99 m-labeled macroaggregated albumin to ensure lung dose < 30 Gray as well as absence of extrahepatic deposition. Based on these findings, therapeutic dose was calculated and patients then underwent TARE with resin ⁹⁰Y microspheres. The procedures were performed in accordance to the quality improvement guidelines of the Society of Interventional Radiology [23].

Imaging and Response Assessment:

Baseline and follow-up imaging consisted of multiphase contrast-enhanced CT or MRI scans. The tumor number, location and sizes were calculated along with the total tumor diameter in patients with measurable disease. Total tumor diameter was defined as the diameter of a single tumor or the sum of the maximal diameters in the setting of multifocal disease. Measurable disease was defined as tumors where margins could be accurately assessed to calculate greatest diameter. Portal vein patency and/or level of invasion was assessed as well. Timing of follow-up imaging was per institutional guidelines with response determined using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Studies were assessed by trained diagnostic radiologists to limit inter-operator variability described in other studies [24].

Data analysis

The Kruskal–Wallis test was used to calculate continuous variables and the Pearson test was used for discrete variables. Overall (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, respectively. Kaplan–Meier analysis was performed to compare OS and PFS with 95% confidence intervals reported. Data regarding the incidence of adverse events (AEs) was tracked using the Common Terminology Criteria for Adverse Events version 5 with grades 1–5. If a patient had multiple events of the same AE within the course of the study, then the highest grade was given and counted as a single event. A single patient could develop multiple AEs. A Cox Proportional Hazards model was performed to identify which baseline factors predicted longer OS.

Results

Demographics

The cohort and subgroup details are outlined in Table 1. The majority of patients were male ($n=56$, 75%), white ($n=56$, 75%), and non-Hispanic ($n=65$, 87%). Groups 1–3, had 12, 37, and 26 patients, respectively. The subgroups were similar in age ($p=0.921$), gender ($p=0.939$), race ($p=0.735$), and ethnicity ($p=0.499$). The baseline serum bilirubin was significantly higher in Group 2 compared to Groups 1 and 3 (median = 1.1 mg/dl versus 0.8 and 0.7 mg/dl, respectively, $p=0.023$) as was aspartate transaminase (median = 68.5 U/L versus 37.0 and 44.5 U/L respectively, $p=0.039$). The cause of cirrhosis was similar across all groups ($p=0.87$) with hepatitis C the most common etiology. Non-alcoholic steatohepatitis was more common in Group 1 (4/12, 33%) than in Groups 2 (3/26, 12%) or 3 (1/37, 3%) ($p=0.01$). The median Model for End-Stage Liver Disease (MELD) score of Group 2 [10, interquartile range (IQR) 8–12] was significantly higher ($p<0.001$) than Groups 1 (median 8, IQR 7–9.5) and 3 (median 7, IQR 6–9). The percentage of patients with Child B/C cirrhosis was significantly higher ($p<0.001$) in Group 2 (22/36, 61%) than Groups 1 (0/12, 0%) and 3 (4/22, 18%).

Imaging

Baseline CT and MR findings are outlined in Table 2. Bilobar disease was most common in Group 2 (16/26, 62%) compared to Groups 1 (1/12, 8%) and 3 (8/37, 22%) ($p<0.001$). Both the number ($p=0.09$) and tumor diameter ($p=0.06$) were similar between groups. Thirty-eight patients (51%) had multifocal disease. Total tumor diameter was assessable in 49 patients (65%) with indistinct tumor margins limiting assessment in the remaining participants. Tumor thrombus was significantly more common in Groups 1 (12/12, 100%) and 2 (37/37, 100%) compared to Group 3 (6/20, 30%, $p<0.001$). Ascites was more common in Group 2 ($n=16/37$, 43%), than in Group 1 and Group 3 ($n=2/12$, 17% and $n=3/26$, 12% respectively, $p=0.014$).

Dosimetry

Dosimetry methodology was available in 51/75 (68%) patients: 11/12 (92%) in Group 1, 15/26 (58%) in Group 2, and 25/37 (68%) in Group 3. The most common method was body surface area method in 10/12 (83%) in Group 1, 13/15 (87%) in Group 2 and 23/25 (92%) in Group 3. The difference in dosimetry method was not significant by group ($p=0.5$). Median prescribed activity between groups was also not significantly different ($p=0.7$): 1.3 GBq (IQR: 1.2–1.5) in Group 1, 1.5 GBq (IQR: 1.1–1.8) in Group 2, and 1.5 (1.0–1.8) in

Table 1 Patient Demographics for group 1, 2, and 3

	N reported	Group 1 (N = 12)	Group 2 (N = 37)	Group 3 (N = 26)	Combined	P-value
<i>Age</i>	74	63.0 (58.2–68.2)	64.0 (58.0–68.0)	63.0 (59.0–69.0)	63.0 (58.2–69.0)	0.921
<i>Gender</i>	75					0.939
Female		3 (25%)	10 (27%)	6 (23%)	19 (25%)	
Male		9 (75%)	27 (73%)	20 (77%)	56 (75%)	
<i>Race</i>	75					0.735
American Indian /Alaska		0 (0%)	1 (3%)	0 (0%)	1 (1%)	
Asian		0 (0%)	2 (5%)	1 (4%)	3 (4%)	
Black		0 (0%)	4 (11%)	4 (15%)	8 (11%)	
Native Hawaiian		0 (0%)	1 (3%)	0 (0%)	1 (1%)	
Other		0 (0%)	1 (3%)	1 (4%)	2 (3%)	
Unknown		2 (17%)	1 (3%)	1 (4%)	4 (5%)	
White		10 (83%)	27 (73%)	19 (73%)	56 (75%)	
<i>Ethnicity</i>	75					0.499
Hispanic or Latino		1 (8%)	1 (3%)	2 (8%)	4 (5%)	
Non-Hispanic		9 (75%)	34 (92%)	22 (85%)	65 (87%)	
Unknown		2 (17%)	2 (5%)	1 (4%)	5 (7%)	
Other		0 (0%)	0 (0%)	1 (4%)	1 (1%)	
<i>Causes of Cirrhosis</i>						
<i>Alcohol</i>	75					0.094
Yes		2 (17%)	11 (30%)	2 (8%)	15 (20%)	
No		10 (83%)	26 (70%)	24 (92%)	60 (80%)	
<i>Hepatitis B</i>	75					0.508
Yes		0 (0%)	3 (8%)	1 (4%)	4 (5%)	
No		12 (100%)	34 (92%)	25 (96%)	71 (95%)	
<i>Hepatitis C</i>	75					0.869
Yes		5 (42%)	15 (41%)	9 (35%)	29 (39%)	
No		7 (58%)	22 (59%)	17 (65%)	46 (61%)	
<i>NASH</i>	75					0.011
Yes		4 (33%)	1 (3%)	3 (12%)	8 (11%)	
No		8 (67%)	36 (97%)	23 (88%)	67 (89%)	
<i>Other</i>	75					0.908
Yes		1 (8%)	2 (5%)	2 (8%)	5 (7%)	
No		11 (92%)	36 (97%)	23 (88%)	67 (89%)	
<i>Bilirubin</i>	74	0.800 (0.675–0.925)	1.05 (0.600–1.625)	0.700 (0.500–0.900)	0.800 (0.600–1.300)	0.023
<i>Albumin</i>	74	3.60 (3.18–3.92)	3.50 (3.20–3.68)	3.35 (3.08–3.60)	3.50 (3.10–3.70)	0.324
<i>Ascites</i>	75					0.014
Yes		2 (17%)	16 (43%)	3 (12%)	21 (28%)	
No		10 (83%)	21 (57%)	23 (88%)	54 (72%)	
<i>Hepatic Encephalopathy</i>	75					0.333
Yes		1 (8%)	1 (3%)	0 (0%)	2 (3%)	
No		11 (92%)	36 (97%)	26 (100%)	73 (97%)	
<i>MELD</i>	70	8.0 (7.0–9.5)	10.0 (8.0–12.0)	7.0 (6.0–9.0)	9.0 (7.0–11.0)	<0.001
<i>Child Pugh Class</i>	70					<0.001
Class A		12 (100%)	14 (39%)	18 (82%)	44 (63%)	
Class B/C		0 (0%)	22 (61%)	4 (18%)	26 (37%)	

Table 2 Baseline imaging findings

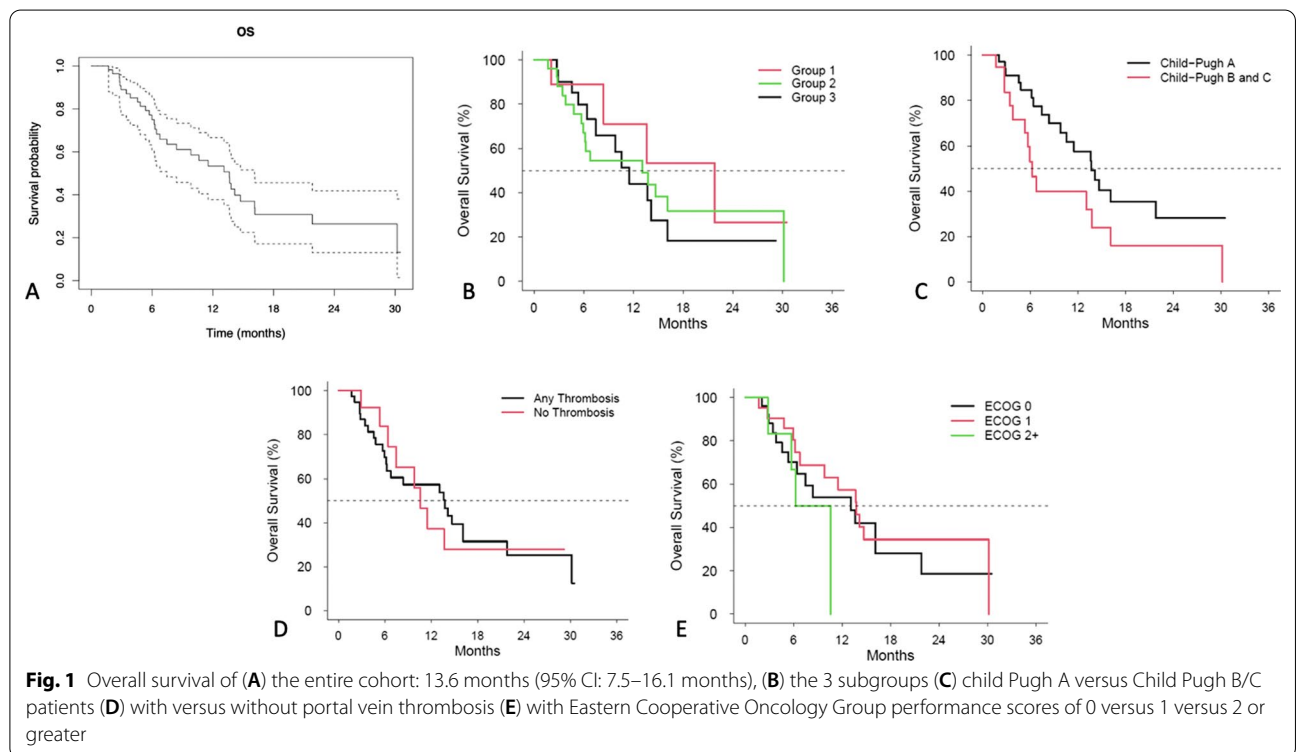
	N reported	Group 1 (N = 12)	Group 2 (N = 37)	Group 3 (N = 26)	Combined	p-value
<i>Tumor Number</i>	73					0.09
1		7	21	7	35 (48%)	
2–3		1	8	7	16 (21%)	
>4		4	6	12	22 (30%)	
<i>Tumor Location</i>	75					<0.001
Bilobar		1	8	16	25 (33%)	
One Lobe		11	29	10	50 (67%)	
<i>Total Tumor Diameter (cm)</i>	49	6.4 (3.2–13.6)	12.9 (7.5–16.1)	15.1 (10.6–22.3)	12.9 (7.0–20.0)	0.06
<i>Vascular Invasion</i>	69					<0.001
Patent		0 (0%)	0 (0%)	14 (70%)	14 (20%)	
Segmental Thrombosis		5 (42%)	11 (30%)	2 (10%)	18 (26%)	
Lobar Thrombosis		2 (17%)	12 (32%)	3 (15%)	17 (25%)	
Main Thrombosis		5 (42%)	14 (38%)	1 (5%)	20 (29%)	

Total tumor diameter refers to the diameter of a single tumor or the sum of the maximal measurable diameters in the setting of multifocal disease

Group 3. Treatment location was also similar between groups with lobar infusions most common: 10/12 (83%) in Group 1, 20/26 (77%) in Group 2 and 25/37 (68%) in Group 3 ($p=0.3$). No repeat therapies were reported.

Survival

Median OS of the entire cohort was 13.6 (95% CI 7.5–16.1) months (Fig. 1A). There were no deaths within 30 days of treatment. Median OS of Groups 1–3 were 21.8 (95% CI 2.1–Not Reached), 13.1(15% CI 5.7- Not Reached) and 11.5 (95% CI: 6.4–16.1) months respectively (Fig. 1B). These differences were not statistically



significant ($X^2=0.9$, $p=0.6$). The median OS for CP class A and CP class B/C were 13.67 (95% CI 8.4–21.8) and 6.28 (3.8–13.8) respectively ($X^2=3.8$, $p=0.05$) (Fig. 1C). The median OS with venous invasion (Fig. 1D) was 13.8 months (95% CI 6.2–16.2) and not significantly different than with a patent portal venous system with a median of 10.6 months (95% CI: 5.4–Not Reached, $X^2=0$, $p=1$). Similarly, a performance status (Fig. 1E) of 0 (median 13.1 months, 95% CI: 5.4–21.8), 1 (median 13.8 months, 95% CI: 6.2–Not Reached) and 2 (median 8.4 months, 95% CI: 2.8–Not Reached, $X^2=1.5$, $p=0.5$) did not affect OS.

Median PFS for the cohort was 6.3 (95% CI: 4.8–14.7) months (Fig. 2A). Median PFS for Group 1 was not reached at 17.3 months mean. PFS for Groups 2 and 3 was 6.8 (95% CI 4.83–Not Reached) and 5.9 (2.96, 16.1) months ($X^2=1.5$, $p=0.5$) (Fig. 2B).

Response/progression

Six-month imaging was performed in 38 patients (51%) with 35 patients (47%) having response assessment. Fourteen percent had complete response (5/35), 17% had a partial response (6/35), 37% had stable disease (13/35), and 31% had progressive disease (11/35). The objective response rate was 31% (11/35 patients) and the disease control rate was 68% (24/35 patients).

Details of progressive disease were available in 25 patients (33.3%) from the entire cohort. All 25 patients developed intrahepatic progression and 12% (3/25) also developed extrahepatic disease. Regarding intrahepatic progression, 28% (7/25) developed progression outside and 72% (18/25) developed progression within the treated region. The incidence of progressive disease was similar between the groups (all $p>0.05$).

Off-study

Fifty (67%) of the 75 patients left the study. Seventy eight percent (39/50) died, 12% (6/50) were lost to follow up, and 10% (5/50) entered hospice. The cause of death was available for 24 of the 39 (62%) who expired. Eighty four percent (20/24) died from tumor progression or worsening cirrhosis. The remaining 17% (4/24) died of other causes.

Toxicity

Twenty-seven Grade 3 or greater toxicities developed and are outlined in Table 3. There were 16 Grade 3 or greater hepatic function toxicities in 12 patients with hyperbilirubinemia (8/58, 14%) and elevated alanine aminotransferase (3/58, 5%) being the most common. There were no liver function adverse events within 30 days. Thirteen of the 16 events developed in patients with progressive disease, leaving only 3 hepatic function toxicities that were directly attributable to the procedure: 1 (2%) Grade 3 hyperbilirubinemia and 2 (3%) alanine transaminase elevations. Four percent of patients developed thrombocytopenia (3/75). The incidence of toxicities between groups was similar (all $p>0.05$). There was one Grade 5 event which was reported as a death with no additional information.

Cox proportional hazards model

The full Cox Proportional Hazard model is shown in Table 4. Only one factor, CP class A versus CP class B/C predicted shorter OS ($X^2=6.7$, $p=0.01$), whereas macrovascular invasion ($X^2=0.5$, $p=0.5$) and ECOG score of ≥ 1 ($X^2=2.1$, $p=0.3$) were not associated with OS.

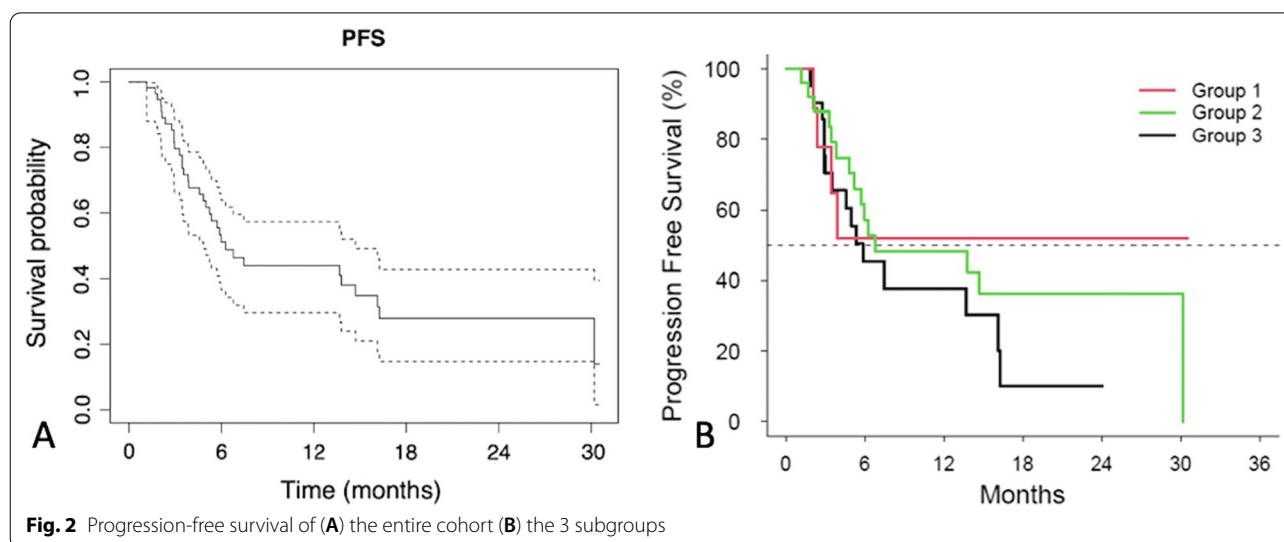


Table 3 Summary of grade 3–4 toxicities

Toxicity	Grade 3	Grade 4	Total
<i>Liver Function Adverse Events</i>			
Bilirubin (N=58)	7	1	8
Albumin (N=58)	1	0	1
AST (N=58)	1	1	2
ALT (N=58)	2	1	3
INR (N=48)	0	0	0
<i>Other Laboratory Adverse Events</i>			
Thrombocytopenia	3	0	3
Leukopenia	1	0	1
<i>Constitutional Adverse events</i>			
Fever	1	0	1
Abdominal Pain	1	0	1
Flank Pain	1	0	1
Abdominal Distention	1	0	1
Nausea	1	0	1
Non-cardiac chest pain	1	0	1
Stomach Pain	1	0	1
Tumor lysis Syndrome	1	0	1
Urinary tract infection	1	0	1
Total:	24	3	27

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

Table 4 Cox Proportional Hazard regression of baseline risk factors predicting survival events

Value	Coefficient	Z	Hazard ratio	p-value
Child–Pugh B/C	1	0.4	2.6	0.009
ECOG 1	− 0.1	0.4	− 0.3	0.8
ECOG 2+	0.5	0.4	1.2	0.2
Portal Vein Invasion	0.3	0.4	0.7	0.5

Child–Pugh B or C status was associated with survival events

Discussion

The current work demonstrates that treatment of BCLC-C patients with resin Y90 microspheres is safe and effective. The patients most likely to benefit from resin Y90 microsphere therapy were patients who were ECOG 0 and CP class A with disease confined to the liver. This group lived a median of 21.8 months. CP class A cirrhosis was the primary predictor of longer OS in a Proportional Hazard model that also included ECOG and venous invasion. No deaths occurred within 30 days and the toxicity profile was not severe with attributable Grade 3 or greater hepatic function toxicities in 5% (3/58) of patients and other toxicities in 14% (8/58) of patients. TARE should be considered in patients who are intolerant of or who progress on systemic therapy.

The 21.8-month OS of ECOG 0, CP A patients with advanced HCC in the current trial is similar to Atezolizumab/Bevacizumab from the Imbrave150 trial (9). The drug combination is currently the recommended first-line treatment for CP A patients with advanced HCC with a median OS of 19.2 months (2;9). The study group in Imbrave150 were all CP A and included 18% with BCLC A or B disease compared to 45% CP A and 0% BCLC A or B in the current study. The PFS in the current cohort (7.5 months) was similar to the Imbrave150 study group (6.9 months). The current results also compare favorably to Lenvatinib and Nivolumab (7;8). The Lenvatinib and Nivolumab trials included 18% and 21.8% BCLC A and B patients and also only enrolled CP A patients. This approach resulted in median OS of 13.6 and 16.4 months for Lenvatinib and Nivolumab, respectively, compared to the whole group OS of 13.7 months in the current study. The rate of tumor vascular invasion in the current trial (81%) was higher than Imbrave150 (38%), Lenvatinib (20.9%) and Nivolumab (23%). Despite these baseline differences, the Grade 3 or greater toxicity rates were no greater with radioembolization than with the current standard of care therapies for advanced HCC. Differences between these trials are outlined in Table 5.

The current cohort also is comparable to a previous evaluation of radioembolization using glass microspheres in patients with advanced HCC [8]. Ali, et al. reported whole group OS of 10.7 months. Their group included 202 patients (36.9%) with multiple reasons for BCLC-C status and also 345 patients (63.1%) with a single source for BCLC-C diagnosis. The single etiology group was separated into 233 patients with ECOG score related BCLC-C and 112 patients with vascular invasion or extrahepatic disease. They described a longer median OS (12.9 months) with an ECOG score of 1 compared to 0 (8.7 months) and 2 (4.3 months). Group 2 in the current study included 37 patients who had ECOG scores of 1–2. All 37 patients had vascular invasion as well. The absence of single component causes in the current study group makes it difficult to directly compare the current results to the results from Ali, et al. [8]. Choi, et al. reported use of chemoembolization alone or combined with chemo-infusion in patients with advanced HCC and reported a median OS of 15.5 months [25]. They noted improved outcomes noted when chemoinfusion was added to chemoembolization.

The incidence of grade ≥ 3 AE in our study were comparable to treatment with Nivolumab ($n=82/367$, 22%) and less than Lenvatinib ($n=270/476$, 56.7%), and Atezolizumab/Bevacizumab ($n=207/329$, 63%) [10–12]. Concerns about toxicity with radioembolization for advanced HCC should not preclude therapy when compared to the other treatment options.

Table 5 Summary of the differences in OS, PFS, toxicities, number of BCLC A or B patients, and number of patients without vascular invasion or extrahepatic metastasis

	Current study	Atezolizumab – bevacizumab	Nivolumab	Lenvatinib
Number of BCLC A or B patients (proportion)	0 (0%)	60 (18%)	68 (18%)	104 (21.8%)
Number of patients with no vascular invasion (proportion)	13 (19%)	91 (62%)	247 (77%)	755 (79.1%)
Child Pugh A	34 (45%)	336 (100%)	371 (100%)	478 (100%)
Overall Survival in months (95% CI)	13.7 (8.41–21.8)	19.2 (17.0 – 23.7)	16.4 (13.9–18.4)	13.6 (12.1–14.9)
Progression free survival in months (95% CI)	7.46 (3.55–16.26)	6.9 (5.7–8.6)	3.7 (3.1–3.9)	7.4 (6.9–8.8)
≥3 Toxicities	12 (16%)	143 (43%)	81 (22%)	270 (56.7%)

HCC screening prior to diagnosis was not tracked as part of the current study. The current HCC screening recommendations in the United States include ultrasound imaging with alpha-feto protein measurement [26]. Even in the setting of optimal surveillance utilization, some HCC's are sonographically undetectable, particularly in patients with non-alcoholic steatohepatitis (11% of the current group) [27]. Radioembolization has longer OS when diagnosed at earlier stages: Frantz, et al. did not reach median OS at 30 months for BCLC A patients and reported a median OS of 19.5 months in BCLC B patients [7]. As screening with MRI undergoes further evaluation, a higher rate of early detection may be possible employing either non-contrast or liver-contrast specific MRI [28, 29]. Additionally, as dosimetry methods for Y90 evolve with use of multicompartiment partition dosing, survival may increase further. This outcome is currently being investigated in an ongoing prospective trial [30].

Our study is limited as a single arm cohort which has a modest sample size, a factor that is most apparent in the subgroup analyses. A larger sample size may have identified other differences between the three subgroups. Additionally, our analysis of PFS is challenging due to the difficulty in assessing response to Y90 in advanced HCC due to the incidence of amorphous tumor boundaries and challenges in assessing changes with vascular invasion. This challenge may be a reason PFS wasn't reported in other radioembolization studies [8]. There was also less than 100% data entry. Despite these limitations, we were able to report OS and toxicity rates that are similar to other therapies recommended by NCCN.

Conclusion

The current study found that BCLC-C patients treated with resin Y90 had OS comparable to those identified with Lenvatinib and Nivolumab. Additionally, patients

with CP A cirrhosis and performance status of 0 had OS of almost 22 months, similar to the outcomes of Atezolizumab and Bevacizumab. These findings were achieved with a reasonable toxicity profile. TARE with resin microspheres remains a reasonable option for patients with advanced HCC.

Abbreviations

AE: Adverse events; BCLC: Barcelona clinic liver cancer stage; ECOG: Eastern cooperative oncology group; HCC: Hepatocellular carcinoma; IQR: Interquartile range; MELD: Model for end-stage liver disease; OS: Overall survival; PFS: Progression-free survival; RESiN: Radiation-emitting SIR-spheres in non-resectable liver tumor; TARE: Trans-arterial radioembolization.

Acknowledgements

The authors would like to acknowledge Donna D'Souza, Islam Shahin, Ryan O'Hara, Nicholas Fidelman, Roshan Shrestha, Brian Kouri, Charles Hennemeyer, James Meeck, Prasoon Mohan, Gary Siskin, Justin Lee, Ricky Tong, Islam Shahin, Mark A. Sultenfuss, Suvranu Ganguli, Aravind Arepally, and Kirubahara Vaheesan, MD for their contributions to the manuscript.

Authors' contribution

PG interpreted the data and drafted the work. PG, ORA, SF, LD, LM, DYS, ASK, DBB contributed to study design. RTG, ZSC, MRM, MP, JSB, DYS, JG, EAW, DBB acquired data. LD performed statistical analysis. PG, DBB, LM, DYS and ASK performed data interpretation. PG, ORA and DBB drafted the manuscript. LD, LM, DYS and ASK provided critical revisions. All authors read and approved the final manuscript.

Funding

This study was funded by Sirtex Medical. Acquisition of data, review of data and manuscript preparation was performed by the authors.

Data availability and materials

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethical approval and consent to participate

This study protocol was approved and reviewed by the Vanderbilt Ingram Cancer Center and Vanderbilt University Institutional Review Board (IRB) as GI 1523 (IRB number 150407) and subsequently approved at the other sites. All patients signed informed consent to participate. This study was performed in accordance with the Declaration of Helsinki.

Consent for publications

Not applicable.

Competing interests

Ripal T. Gandhi is a consultant and speaker for Sirtex Medical and serves as a proctor for Sirtex Medical. Zachary S. Collins has received an institutional research grant from Sirtex Medical and serves as a speaker and consultant for Sirtex Medical. Jaysun S. Brower is a consultant for Sirtex Medical. Daniel Y. Sze has received institutional research grants from Sirtex Medical and Boston Scientific. He was a consultant and has received support for travel/hotel/meals for meetings with Sirtex Medical and Boston Scientific. Andrew S. Kennedy has received institutional support from Sirtex Medical. Jafar Golzarian is a consultant for Sirtex Medical and Boston Scientific. He has also received institutional grant support from Sirtex Medical. Eric A. Wang is a proctor for Sirtex Medical. Daniel B. Brown 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 other authors do not have a conflict to report.

Author details

¹Vanderbilt University School of Medicine, Nashville, TN, USA. ²Division of Interventional Radiology, Vanderbilt University Medical Center, CCC-1118 Medical Center North, 1161 21st Ave S, Nashville, TN 37232, USA. ³Division of Hepatobiliary Surgery and Liver Transplantation, Vanderbilt University Medical Center, Nashville, TN, USA. ⁴Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA. ⁵Miami Cardiac and Vascular Institute/Miami Cancer Institute, Miami, FL, USA. ⁶Division of Interventional Radiology, University of Kansas, Kansas City, KS, USA. ⁷Division of Hematology/Oncology, Ochsner Medical Center, New Orleans, LA, USA. ⁸Division of Interventional Radiology, Roswell Park Medical Institute, Buffalo, NY, USA. ⁹Department of Radiology, Sacred Heart Medical Center, Spokane, WA, USA. ¹⁰Division of Interventional Radiology, Stanford University, Palo Alto, CA, USA. ¹¹Department of Radiation Oncology, Sarah Cannon Research Institute, Nashville, TN, USA. ¹²Division of Interventional Radiology, University of Minnesota, Minneapolis, MN, USA. ¹³Department of Radiology, Carolinas Medical Center, Charlotte, NC, USA.

Received: 26 March 2022 Accepted: 4 October 2022

Published online: 17 November 2022

References

- Arnold M, Abnet C, Neale R, Vignat J, Giovannucci E, McGlynn K, Bray F. Global burden of 5 major types of gastrointestinal cancer. *World Health Organ*. 2020;159(1):335–349.e15.
- Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019; pp. 1941–1953.
- Globocan 2020. Section of cancer surveillance, international agency for research on cancer, World Health Organization; 2020. [Online]. Available: <https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf>. [Accessed 17 March 2022].
- Benson BA, D'Angelica IM, Abbott DE, Anaya DA, Anders R, Are C, Bachini M, Borad M, Brown D, et al. Hepatobiliary cancers, version 2.2021, NCCN clinical practice guidelines in oncology. *J Nat Compr Cancer Netw JNCCN*. 2021;19(5):541–65.
- Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchard J, Richard S, Rodes J, Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002;359(9319):1734–9.
- Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, Hickey R, et al. (2018) "Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience." *Hepatology*. 2018;68(4):1429–40.
- Frantz S, Matsuoka L, Vaheesan K, Petroziello M, Golzarian J, Wang E, Gandhi R, Collins Z, Brower J, Rachakonda VM, Du L, Kennedy AS, Sze DY, Lee J, Brown DB. multicenter evaluation of survival and toxicities of hepatocellular carcinoma following radioembolization: analysis of the RESIN registry. *J Vasc Interv Radiol JVIR*. 2021;32(6):845–52.
- Ali R, Gabr A, Abouchaleh N, Al Asadi A. Survival analysis of advanced HCC treated with radioembolization: comparing impact of clinical performance status versus vascular invasion/metastases. *Cardiovasc Interv Radiol*. 2018;41(2):260–9.
- Finn RS, Qin S, Ikeda M, Gale PR, Ducreux M, Kim T-Y, Kudo M, Breder V, Merle P, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–905.
- Yau T, Park J-W, Finn R, Cheng A-L, Mathurin P, Edeline J, Kudo M, Harding JJ, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77–90.
- Kudo M, Finn RS, Shukui Q, Han K-H, Ikeda K, Piscaglia F, Baron A, Park J-W, Han G, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–73.
- Chend A-L, Qin S, Ikeda M, Gale PR, Ducreux M, Kim T-Y, Lim HY, Kudo M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2021;S0168–8278(21):02241–8.
- Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasbazar A, Ong J, Choo SP, Cheow PC, Chotipanich C, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in asia-pacific patients with hepatocellular carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol*. 2018;36(19):1913–21.
- Vilgrain V, Pereira H, Assenet E, Gui B, Ilonca AD, Pageaux G-P, Sibert A, Bouattour M, Lebtahi R. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18(12):1624–36.
- Ricke J, Klumpen HJ, Amthauer H et al., Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma, *J Hepatol*. pp. 1164–1174; 2019.
- Facciorusso A, Paolillo R, Tartaglia N, et al. Efficacy of combined transarterial radioembolization and sorafenib in the treatment of hepatocellular carcinoma: a meta-analysis. *Dig Liver Dis*. 2022. <https://doi.org/10.1016/j.dld.2021.06.003>.
- European Association for the Study of the Liver. European association for the study of diabetes and european association for the study of obesity, "EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease." *J Hepatol*. 2016;64(6):1388–402.
- Xie D-Y, Ren Z-G, Zhou J, et al. Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr*. 2020;9(4):452.
- Mazzaferro V, Spostio C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchiano A, Bongini M, Lanocita R, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology*. 2013;57(5):1826–37.
- Spreato C, Maccauro M, Mazzaferro V, Chiesa C. The dosimetric importance of the number of 90Y microspheres in liver transarterial radioembolization. *Eur J Nucl Med Mol Imaging*. 2014;41(4):634–8.
- Bolondi L, Burroughs A, Dufour J-F, Gale PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis*. 2012;32(4):348–59.
- Compagnone G, Gimpalma E, Domenichelli S, et al. Calculation of conversion factors for effective dose for various interventional radiology procedures. *Med Phys*. 2012;39(5):2491–8.
- Padia SA, Lewandowski RJ, Johnson GE, et al. Radioembolization of Hepatic Malignancies: Background, Quality Improvement Guidelines, and Future Directions. *J Vasc Interv Radiol* 2017;28(1):1–15.
- Tovoli F, Renzulli M, Negrini G, et al. Inter-operator variability and source of errors in tumour response assessment for hepatocellular carcinoma treated with sorafenib. *Eur Radiol*. 2018;28(9):3611–20.
- Choi JW, Kim H-C, Lee J-H et al. Transarterial chemoembolization of hepatocellular carcinoma with segmental portal vein tumour thrombus. *Eur Rad*, pp. 1148–1458; 2017.
- Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of hepatocellular carcinoma surveillance: an assessment of benefits and harms. *Am J Gastroenterol*. 2020;115(10):1642–9.
- Fetzer DT, Browning T, Xi Y, et al. Associations of ultrasound LI-RADS visualization score with examination, sonographer, and radiologist factors:

retrospective assessment in over 10,000 examinations. *Am J Roentgenol.* 2022;218(6):1010–20.

28. Park HJ, Jang HY, Kim SY, et al. Non-enhanced magnetic resonance imaging as a surveillance tool for hepatocellular carcinoma: comparison with ultrasound. *J Hepatol.* 2020;72(4):718–24.
29. Renzulli M, Golfieri R, Bologna Liver Oncology Group. Proposal of a new diagnostic algorithm for hepatocellular carcinoma based on the Japanese guidelines but adapted to the Western world for patients under surveillance for chronic liver disease. *J Gastroenterol Hepatol.* 2016;31(1):69–80.
30. Mahvash A, Chartier S, Mark T, et al. A prospective, multicenter, open-label, single-arm clinical trial design to evaluate the safety and efficacy of 90 Y resin microspheres for the treatment of unresectable HCC: the DOORwaY90 (Duration Of Objective Response with arterial Yttrium-90) study. *BMC Gastroenterol.* 2022;22(1):151.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

