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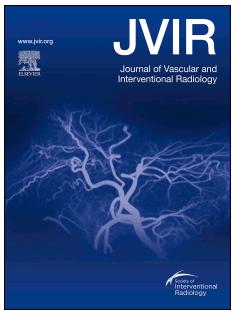

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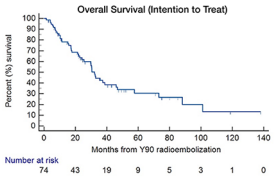

Radioembolization for Intermediate Stage Hepatocellular Carcinoma Maintains Liver Function and Permits Systemic Therapy at Progression

ABSTRACT

Purpose:

To assess the liver function trends in intermediate-stage (BCLC B) patients undergoing Y90-radioembolization (TARE) in response to a growing concern that that liver-directed therapies negatively impact liver function and prevent HCC patients from systemic therapy candidacy.

Methods:

A prospectively acquired HCC/TARE database (2004-2017) was retrospectively reviewed. BCLC B/Child-Pugh (CP)-A patients with laboratory tests/imaging at baseline and for at least 1-month post-TARE were included. Follow-ups were at 3-month intervals. CP was assessed at each timepoint. Endpoints included time-to-persistent CP-B, time-to-CP-C, and median overall survival (OS). Time-to-endpoint analyses were performed using Kaplan-Meier method.

Results:

74 patients (80% males with mean age 63 years) with mostly (62%) bilobar disease underwent 186 TARE treatments (median 2 (range[r]: 1-8)). Median time-to-2nd TARE was 2.3 months (r: 1.7-6.4), median time-to-3rd and 4th TARE was 11.7 (r: 7.5 – 15) and 17.3 (r: 11.5-23.1) months, respectively. 43 patients (58%) developed persistent CP-B at median time-to-persistent CP-B of 15.4 Months (CI: 9.2 – 25.3) months. 17 (23%) became CP-C at a median time-to-CP-C of 87.2 (CI: 39.8 – 136.1) months. Median OS censored

to transplantation was 30.4 (CI: 22.7-37.4) months. On univariate and multivariate analyses baseline albumin was significant prognosticator of OS, while baseline albumin and bilirubin were significant prognosticators of time-to-persistent CP-B, and time-to-CP-C.

Conclusion

In CP-A patients undergoing TARE for BCLC B HCC, the median time-to persistent CP-B is 15.4 months. These findings indicate that patients would be candidates for systemic therapy at progression if indicated.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed cancer and fourth leading cause of malignancy-related death worldwide.(1) Though only resection, ablation, and transplant are curative, many locoregional and targeted molecular therapies have demonstrated important roles in palliative care and survival.(2) Therapeutic options are diverse and depend on a variety of factors.

The Barcelona Clinic Liver Cancer staging classification (BCLC) is both a unique and widely used staging classification system, as it links staging to therapy. Approximately 25% of patients present with BCLC B (intermediate) stage disease, and management of these patients can be quite complex due to patient heterogeneity.(3) Locoregional therapy is usually recommended for intermediate stage patients with preserved liver function. First line therapy is typically transarterial chemoembolization (TACE), with a post-procedural median survival time of 2 - 5 years and an accepted median of 26-30 months(4). Over the last decade, transarterial radioembolization using yttrium-90 (^{90}Y, TARE) has become increasingly accepted as an alternative demonstrating comparable survival, longer time to progression as demonstrated in the PREMIERE Trial,(5) and better quality of life.(6, 7) Recently, TARE has been shown to improve OS compared to TACE.(8)

Critical to the choice of therapy for HCC is overall liver function. Locoregional therapy such as TACE and TARE are more widely recommended for earlier and intermediate stage disease, (4) while systemic therapy remains a mainstay for widely advanced and metastatic disease and patients with CP A status, although there is some data for its use

in patients with CP B status.(4) As systemic therapies continue to evolve and advance at a rapid pace, there has been increased enthusiasm for its use in intermediate stage disease as defined by Bolondi and Apple criteria.(9) However, for the most robust evidence and in order to qualify for clinical trials investigating its use in this population, patients need to sustain CP A status after undergoing locoregional therapies such as TARE.(4) Thus, while interest has continued to grow in bridging locoregional therapies to rapidly developing new systemic therapies and/or combining these methods, their interplay with regard to liver function is a complicating factor.(3) Along these lines, there has recently been a concern that locoregional therapy for patients impairs liver function and thus precludes them from the potential benefits of any subsequent systemic therapy.(10) This issue has been previously addressed with regards to hepatic function in CPA patients with portal venous thrombosis after radioembolization, demonstrating prolonged time to deterioration of liver function.(11) As a direct response to this concern, this study seeks to assess liver function trends in intermediate stage patients undergoing TARE.

METHODS

With institutional review board approval and in compliance with the Health Insurance Portability and Accountability Act, an institutional prospectively acquired database of HCC patients who underwent TARE between 2004 and 2017 was reviewed. All patients were reviewed at a multidisciplinary tumor board, with treatment decisions reached as a consensus. Patients with BCLC stage B/CP A disease and who had follow-up at least one-month post-TARE were included. A total of 74 patients met these criteria.

Prior to all treatment, patient evaluation included history and physical examination, imaging and laboratory studies, and biopsy or imaging confirmed diagnosis of HCC. Patients were classified according to BCLC, CP, and United Network for Organ Sharing (UNOS) TNM staging. For all patients undergoing TARE, lung shunting was assessed via technetium-99 macroaggregated scanning and mesenteric angiography prior to treatment. Patients undergoing TARE were treated with glass-based microspheres (TheraSphere, Boston Scientific, Marlborough, MA). Dosimetry and technical considerations for TARE have been previously elaborated (2). The target dose for lobar infusions was 100 – 120 Gy, with modifications to > 190 and 150 Gy for radiation segmentectomy and lobectomy, respectively.(2, 12) Imaging and laboratory testing was obtained one month after treatment and at 3-month intervals thereafter. CP status was assessed at each time point. It was also noted if patients underwent systemic therapy post TARE. Treatment start dates, duration, and end dates were recorded. For these patients, laboratory testing including liver function tests were also noted at the time of receiving therapy.

Of the 74 patients meeting the inclusion criteria, 59 (80%) were male, with a mean age of 63 (range[r]:30 – 86) years. Most patients (62%) had bilobar disease, with a median tumor index size of 4.7 (r: 1.2 – 17.8) cm. A more detailed representation of baseline characteristics is provided in **Table 1**. Patients underwent a total of 186 TARE treatments (median 2 [r: 1-8]). The median time to 2nd, 3rd, and 4th TARE was 2.3 (r: 1.7 - 6.4), 11.7 (r: 7.5 – 15), and 17.3 (r: 11.5 - 23.1) months, respectively.

The endpoints of the study were as follows: time to development of initial CP B status; time to persistent CP B status (defined as CP B status at two sequential follow-up visits); time to CP C status; and median overall survival (OS). OS was calculated from first TARE until death or last follow-up. OS was additionally censored to transplant. Univariate analysis for all endpoints was performed using Kaplan-Meier method. Cox proportional hazards regression was used to conduct multivariate analysis for OS, time to development of initial CP B status, and time to persistent CP B status. P <0.05 was considered significant. All statistical analyses were performed using Medcalc software (MedCalc, Mariakerke, Belgium).

RESULTS

49 (66%) patients developed CP B status, with a median time to 1st development of CP B status of 10.5 (CI: 6.4 – 16.1) months post-TARE. Of this subset of patients, 16 (21%) exhibited transient fluctuations to CP B status that resolved at the next follow-up. Over time, 43 (58%) patients developed persistent CP B status, with a median time to persistent CP B status of 15.4 (CI: 9.2 – 25.3) months. In addition, 17 (23%) patients exhibited CP C status, with a median time to development of CP C status of 87.3 (CI: 35.7 – 136.1) months. The median intention-to-treat OS was 32.2 months (95% CI: 24.2-45.9). The median OS censored to liver transplant was 30.4 (CI: 22 - 37.4) months. (**Fig. 1**)

Of the cohort, 20 patients (27%) underwent systemic therapy subsequent to TARE. Two (10%) and 1 (5%) of this subset of patients underwent 2nd and 3rd line systemic treatments, respectively. Median time from TARE treatment to systemic therapy was 17.2 months (range: 1.2-96.8 months). Among these patients, 8 (20%) had progressed to CP B status prior to the start of systemic treatment. A comprehensive representation of the characteristics of patients receiving systemic therapy post-TARE is outlined in **Table 2**.

Univariate and Multivariate Analyses

Univariate survival analysis indicated significantly better survival outcomes in patients with baseline albumin >3.5 g/dL (P=0.002), which was confirmed by multivariate analysis to be the only significant prognosticator of survival. The full univariate and multivariate analyses for overall survival are described in **Table 3**.

Regarding time-to-development to initial CP B status, univariate analysis revealed significantly longer time-to-endpoint in patients with non-infiltrative tumor (P=0.01), baseline albumin > 3.5 g/dL (P=0.0004), and baseline bilirubin < 1.2 mg/dL (P=0.04). However, multivariate analysis demonstrated baseline albumin and bilirubin to be the only significant predictors of time to development to initial CP B. The full univariate and multivariate analyses for time-to-development to initial CP B status are outlined in **Table 4**. Among patients who developed persistent CP B status, univariate statistical significance was observed in baseline albumin and baseline bilirubin. Multivariate analysis confirmed baseline bilirubin and albumin as significant prognosticators of developing persistent CP B. The full univariate and multivariate analyses for time-to-development to persistent CP B status are outlined in **Table 5**.

Univariate analysis also showed that patients with baseline albumin > 3.5 g/dL and baseline bilirubin < 1.2 mg/dL had a significantly longer time-to-progression to CP C. Multivariate analysis was not conducted for time-to-CP C status because of insufficient endpoints at the time of data closure. The complete univariate analyses for time-to-development to CP C status are outlined in **Table 6**. **Figure 2** outlines significant findings of uni- & multivariate analyses in the study.

DISCUSSION

TARE has become an increasingly popular approach to therapy for patients with intermediate stage HCC in recent years, and the concurrent rapid development of new systemic therapies has vastly expanded the possible choices for therapy in these patients. Management of these patients, however, is inherently complicated by the need to choose the appropriate therapy within the context of liver function. While there is optimism for approaches combining TARE and systemic therapy, there is an unsubstantiated narrative that TARE may render patients unsuitable for systemic therapy and their mandated CP A requirement, and hence, may be denied the benefits of systemic therapy.

The data from the cohort provide several key insights into the trends of liver function status post TARE and indicate that TARE outcomes for BCLC B, CP A patients are favorable. For those patients who did convert to CP B or CP C status after TARE, they were able to maintain adequate hepatic function for a significant amount of time to allow for the initiation of systemic therapies, as the median time to progression to persistent CP B status was 15.4 months post TARE. It is also important to note that the median time to each endpoint did not vary significantly across different TARE-specific variable such as volumes of treatment in the first TARE session or the number of TARE treatments, suggesting that different aspects of TARE itself did not independently impact median survival time or time to CP status progression. The data additionally demonstrate that baseline patient characteristics and natural progression of the disease itself rather than the impact of undergoing TARE was associated with conversion CPB and CP C status

since despite multiple TARE sessions, only baseline liver function (assessed by serum albumin and bilirubin) were associated with progression of CP status for CP A/BCLC B patients receiving TARE. In addition, the median OS censored to liver transplant was 30.4 months in the cohort post-TARE, which very much aligns with the expected OS for BCLC B patients of 26-30 months.(13)

Patient with intermediate stage HCC comprise a heterogenous cohort.(9) Given the diversity and vast number of patients in this stage, there have been a number of initiatives such as the system proposed by Bolondi et al. to further subdivide this stage based on certain disease characteristics and risk factors in an effort to further tailor treatment approaches.(9) With the continued evolution of novel systemic therapies for HCC, there is an equally rapidly growing enthusiasm for the combination of these therapies with locoregional modalities for many patients who are at the higher risk end of the spectrum of intermediate stage disease.(3) Within the cohort, many patients would be qualified as being higher risk given their disease characteristics. For these patients, it is vital for their liver function to be maintained for adequate time for the initiation of systemic therapy and/or participation in clinical trials investigating new systemic modalities. As a whole, this study indicates that patients with intermediate stage disease and CP A status do not experience a rapid decompensation to CP B status, even despite some receiving whole liver therapy with TARE over their treatment course. In a broader sense, as combination therapy and new systemic therapies continue to be explored, these findings are thus important for demonstrating that similar patients with intermediate stage disease do not

experience rapid decompensation and can be eligible for treatment with systemic modalities and participation in clinical trials with novel agents.

Absent in the literature is a similar time-to-event analysis of systemic therapies in this patient population. While drug-induced liver injury is one of the most common adverse events in HCC patients undergoing systemic therapies, randomized controlled trials inherently provide short-term follow-up. It would be of interest to assess time to hepatic decompensation in a similar population treated with systemic agents, as the transition of HCC therapies can proceed from local-to-systemic or from systemic-to-local treatments.

Limitations of this analysis include the retrospective nature and small sample size. Though powered enough to still detect statistically significant differences, the small sample size and analyses of patients from a single center limit generalizability. Moreover, while the choice was made to analyze number of TARE treatments and volume of TARE treatment, it is important to recognize there are other subtle differences in TARE technique, approaches, materials, and practitioner skill that could impact overall liver function trends and survival in the long term that were not captured in this study. Another limitation is that progressive disease (either tumor progression or progression of underlying cirrhosis) and the impact of subsequent local or systemic therapies, both of which can impact hepatic function, was not studied, making the outcomes presented conservative. Finally, the analysis of patients progressing to CP C is limited given both the small sample size and insufficient endpoints at the time of data closure.

Despite these limitations, however, the results of this study are hypothesis-generating and demonstrate that CPA patients with intermediate stage HCC do not experience rapid hepatic decompensation to preclude them from receiving benefits of systemic therapy. Indeed, these results warrant further investigation of the relationship between TARE and systemic therapy in larger samples to re-demonstrate these trends with greater statistical power.

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Figure Legends

Figure 1a: Kaplan-Meier curve demonstrating Overall Survival on intention-to-treat basis for all patients.

Figure 1b: Kaplan-Meier curve demonstrating Overall Survival censored to transplant.

Fig 2. Flowchart summarizing the findings of univariate and multivariate analyses.

Table 1: Baseline Characteristics of Patients with BCLC Stage B/CP A Status Undergoing TARE

		N (%)
Age	< 65	40 (54)
	≥ 65	34 (46)
Gender	Male	59 (80)
	Female	15 (20)
Etiology	Alcohol	6 (8)
	Hepatitis C	28 (38)
	Hepatitis B	10 (14)
	Non-alcoholic steatohepatitis	4 (5)
	Cryptogenic	4 (5)
	Primary Biliary Cholangitis	1 (1)
	Autoimmune Hepatitis	1 (1)
	Hemochromatosis	3 (4)
	Unknown	16 (22)
	Other	1 (1)
Prior Liver Therapy (TACE, Resection, and/or Radiofrequency Ablation)	Yes	49 (66)
	No	25 (35)
Method of Diagnosis	Imaging	32 (43)
	Biopsy	42 (57)
Ascites	Yes	1 (1)
	No	73 (99)
Tumor Distribution	Unilobar	28 (38)
	Bilobar	46 (62)
Maximum Tumor Dimension (cm)	< 5.0	38 (51)
	5.0 – 10.0	28 (38)
Maximum Tumor Dimension (cm)	> 10.0	8 (11)
	> 100	25 (34)
Alpha Fetoprotein	< 100	48 (66)
Total Bilirubin (mg/dL)	< 1.0	43 (58)
	1.0 – 3.0	33 (42)
Albumin (mg/dL)	> 3.5	26 (35)
	2.8 – 3.5	47 (64)
Albumin (mg/dL)	< 2.8	1 (1)
INR	< 1.0	4 (6)
	1.0 – 1.3	59 (83)
INR	1.3 – 1.6	8 (11)
Alkaline Phosphatase	< 40.0	2 (3)
	40.0 – 140.0	58 (78)
Alkaline Phosphatase	> 140.0	14 (19)
Albumin-Bilirubin Grade	1	6 (8)
	2	68 (92)

UNOS Staging	T3 (2 or 3 lesions [1 > 3 cm])	30 (41)
	T4a (4 or more lesions)	44 (59)

Table 2. Characteristics of Patients Receiving Systemic Therapy Post-TARE

	N (%)
Modality	
First treatment	
Bevacizumab	1 (5.6)
Gemcitabine	1 (5.6)
Nivolumab	1 (5.6)
Sorafenib	14 (77.8)
Sorafenib/cixutumumab	1 (5.6)
Second treatment	
Brivanib (post-sorafenib)	1 (5.6)
Regorafenib (post-sorafenib)	1 (5.6)
Third treatment	
Nivolumab (post-sorafenib and regorafenib)	1 (5.6)
Duration (days)	
First treatment	
0-100	8 (44.4)
100-200	4 (22.2)
200-300	5 (27.8)
500-600	1 (5.6)
Second treatment	
0-20	1 (50.0)
60-80	1 (50.0)
Third treatment	
60-70	1 (100.0)
All treatments	
0-100	8 (44.4)
100-300	8 (44.4)
300-400	1 (5.6)
>400	1 (5.6)
CP Status	
Start of first treatment	
A	10 (56.6)
B	8 (44.4)
C	0 (0.0)
End of first treatment	
A	9 (50.0)

B	6 (33.3)
C	3 (16.7)
Start of second treatment	
A	1 (50.0)
B	1 (50.0)
C	0 (0.0)
End of second treatment	
A	1 (50.0)
B	0 (0.0)
C	1 (50.0)
Start of third treatment	
A	1 (100.0)
B	0 (0.0)
C	0 (0.0)
End of third treatment	
A	1 (100.0)
B	0 (0.0)
C	0 (0.0)
End of all treatments	
A	8 (44.4)
B	6 (33.3)
C	4 (22.2)

Table 3. Uni/Multivariate Analyses for Overall Survival

	Univariate analysis				Multivariate analysis	
Predictor	Category	OS (95% CI)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age	<65	38.7 (22-101)	0.6 (0.3-1.1)	0.1	N/A	N/A
	≥65	30.3 (17.3-37.3)	1		N/A	
Sex	Female	35.7 (5.9-35.7)	0.6 (0.3-1.4)	0.3	N/A	N/A
	Male	30.4 (21.4-38.7)	1		N/A	
Albumin	>3.5 g/dl	73.1 (45.9-88.1)	0.3 (0.2-0.7)	**0.002**	0.2 (0.1-0.6)	**0.001**
	≤3.5 g/dl	24.1 (17.1-32.2)	1		1	
Bilirubin	<1.2 mg/dL	35.7 (29.7-88.1)	0.6 (0.3-1.2)	0.2	1	
	≥1.2 mg/dL	24.2 (15.7-38.7)	1		1.8 (0.9-3.6)	0.07
Baseline Tumor Size	≤5 cm	35.7 (29.3-73.1)	0.5 (0.2-1)	0.1	1	
	5-10 cm	22 (15.2-45.9)	1		1.7 (0.8-3.5)	0.1
	>10 cm	22.7 (9.6-37.3)	0.6 (0.2-1.7)		0.9 (0.2-2.7)	0.8
Infiltration	Non-infiltrative	30.4 (22.7-38.7)	1	0.5	N/A	N/A
	Infiltrative tumor	29.7 (3.9-29.7)	0.7 (0.2-2)		N/A	
Tumor distribution	Unilobar	38.7 (17.1-88.1)	0.8 (0.4-1.6)	0.6	N/A	N/A

	Bilobar	30.4 (21.4-37.3)	1		N/A	
AFP	<100	30.3 (22-38.7)	1	0.2	N/A	N/A
	≥100	46.7 (17.3-101)	0.6 (0.3-1.2)		N/A	
Systemic therapy	No	30.4 (17.3-46.7)	0.9 (0.5-1.8)	0.8	N/A	N/A
	Yes	32.8 (22.7-57.6)	1		N/A	
Volume treated in the first Y90 session*	<50%	32.5 (25.4-46.7)	1	0.9	N/A	N/A
	≥50	30.4 (15.2-57.6)	0.9 (0.5-1.8)		N/A	
Number of Treatments	≥3 sessions	35.7 (29.7-46.7)	0.8 (0.4-1.5)	0.8	0.4 (0.1-1.1)	0.07
	2 sessions	25.4 (11.3-57.6)	1		0.8 (0.3-2)	0.6
	1 session	32.8 (7-73.1)	0.8 (0.4-2)		1	

* Volume was based on visual estimate.

Table 4. Uni/Multivariate Analyses for progression to Child-Pugh B

	Univariate analysis				Multivariate analysis	
Predictor	Category	Progression to CPB (95% CI)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age	<65	10.5 (6-27.3)	0.8 (0.4-1.5)	0.6	N/A	N/A
	≥65	9.5 (2.8-16.4)	1		N/A	
Sex	Female	7.2 (2.1-37.1)	1	0.9	N/A	N/A
	Male	11.8 (7.6-16.4)	0.9 (0.4-1.9)		N/A	
Albumin	>3.5 g/dl	34.1 (11.8-72.7)	0.3 (0.1-0.6)	**0.0004**	0.2 (0.1-0.4)	**0.0002**
	≤3.5 g/dl	6.4 (3.5-9.7)	1		1	
Bilirubin	<1.2 mg/dL	13 (7.2-25.3)	0.4 (0.2-0.9)	**0.04**	1	
	≥1.2 mg/dL	6 (1.4-12.5)	1		2 (1.1-3.8)	**0.02**
Baseline Tumor Size	≤5 cm	11.8 (5.8-18.4)	0.6 (0.2-1.7)	0.5	N/A	N/A
	5-10 cm	9.7 (5.5-27.3)	0.7 (0.2-2.1)		N/A	
	>10 cm	3.5 (1.9-35.6)	1		N/A	
Infiltration	Non-infiltrative	11.8 (7.2-16.4)	0.1 (0.03-0.7)	**0.01**	1	
	Infiltrative tumor	2.3 (0.9-16.3)	1		1.6 (0.6-4.3)	0.3
Tumor distribution	Unilobar	12.5 (6.4-16.4)	0.8 (0.4-1.4)	0.5	N/A	N/A
	Bilobar	9.5 (3.7-25.3)	1		N/A	
AFP	<100	12.5 (6.4-25.3)	0.6 (0.3-1.1)	0.1	N/A	N/A
	≥100	9.7 (3.3-15.6)	1		N/A	
Systemic therapy	No	8 (4.6-16.1)	1	0.6	N/A	N/A
	Yes	15.6 (5.8-35.6)	0.8 (0.4-1.5)		N/A	

Volume treated in the first Y90 session	<50%	12.5 (6-16.4)	1	0.5	1	
	≥50%	8 (3.5-35.6)	0.8 (0.4-1.5)		0.9 (0.4-1.7)	0.8
Number of Treatments	≥3 sessions	12.5 (7.2-25.3)	0.9 (0.4-1.7)	0.8	N/A	N/A
	2 sessions	9.7 (2.3-18.4)	1		N/A	
	1 session	8 (3.6-37.1)	0.7 (0.3-1.6)		N/A	

Table 5. Uni/Multivariate Analyses for persistent Child-Pugh B

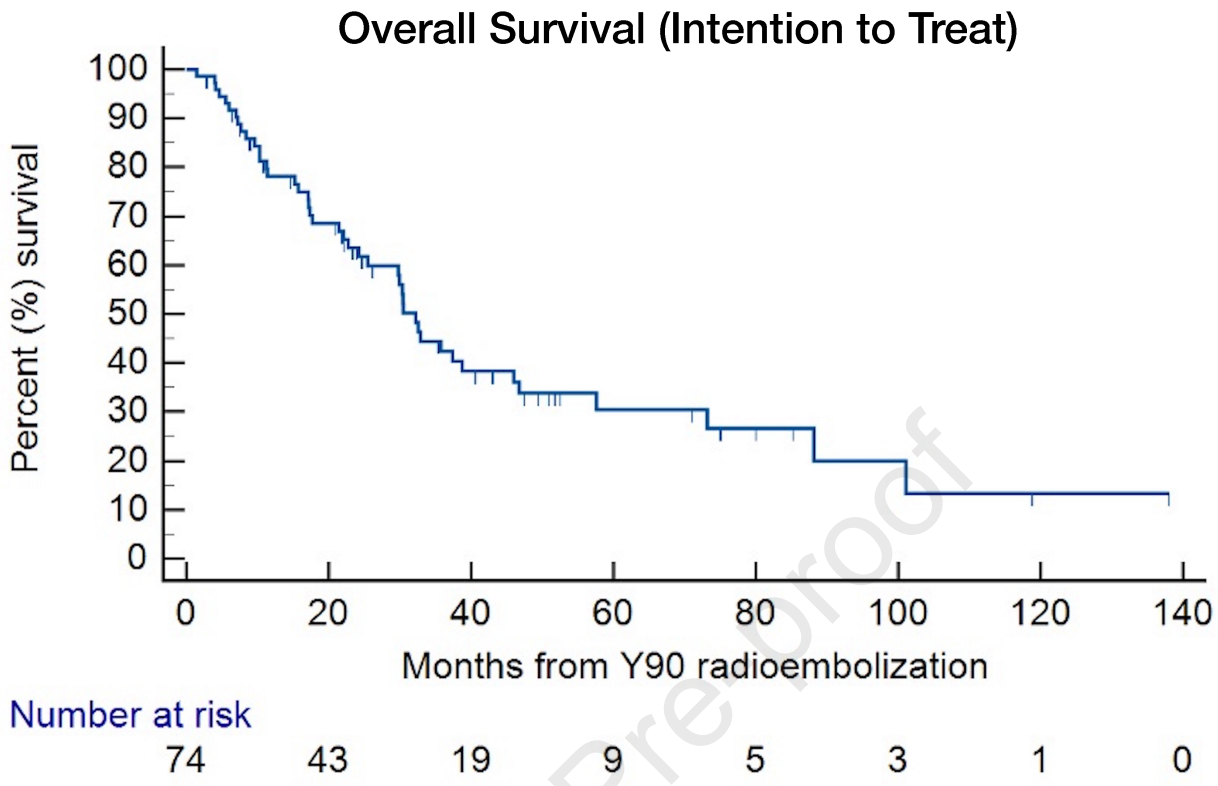
	Univariate analysis				Multivariate analysis	
Predictor	Category	Persistent CPB (95% CI)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age	<65	15.3 (8-37.8)	0.7 (0.4-1.4)	0.4	N/A	N/A
	≥65	15.6 (6.7-21.7)	1		N/A	
Sex	Female	15.4 (2.1-37.1)	0.8 (0.4-1.7)	0.6	N/A	N/A
	Male	15.3 (9.1-25.3)	1		N/A	
Albumin	>3.5 g/dl	43.9 (21.7-72.7)	0.3 (0.1-0.6)	**0.0005**	0.1 (0.07-0.4)	**<0.0001**
	≤3.5 g/dl	9.2 (5.5-13)	1		1	
Bilirubin	<1.2 mg/dL	16.3 (9.7-37.8)	0.4 (0.2-0.9)	**0.04**	1	
	≥1.2 mg/dL	9.1 (3.3-21.7)	1		2.6 (1.3-5.2)	**0.003**
Baseline Tumor Size	≤5 cm	16.1 (8-37.1)	0.8 (0.3-2.3)	0.9	N/A	N/A
	5-10 cm	12.5 (6.4-43.9)	0.9 (0.3-2.6)		N/A	
	>10 cm	13 (1.9-35.6)	1		N/A	
Infiltration	Non-infiltrative	15.4 (9.2-35.6)	0.8 (0.2-2.5)	0.7	N/A	N/A
	Infiltrative tumor	15.3 (0.9-16.3)	1		N/A	
Tumor distribution	Unilobar	15.3 (7.2-72.7)	0.9 (0.4-1.7)	0.7	N/A	N/A
	Bilobar	15.4 (8-37.1)	1		N/A	
AFP	<100	16.1 (9.1-37.8)	0.7 (0.3-1.5)	0.4	N/A	N/A
	≥100	11.9 (3.5-37.1)	1		N/A	
Systemic therapy	No	12.5 (7.2-37.1)	1	0.8	N/A	N/A

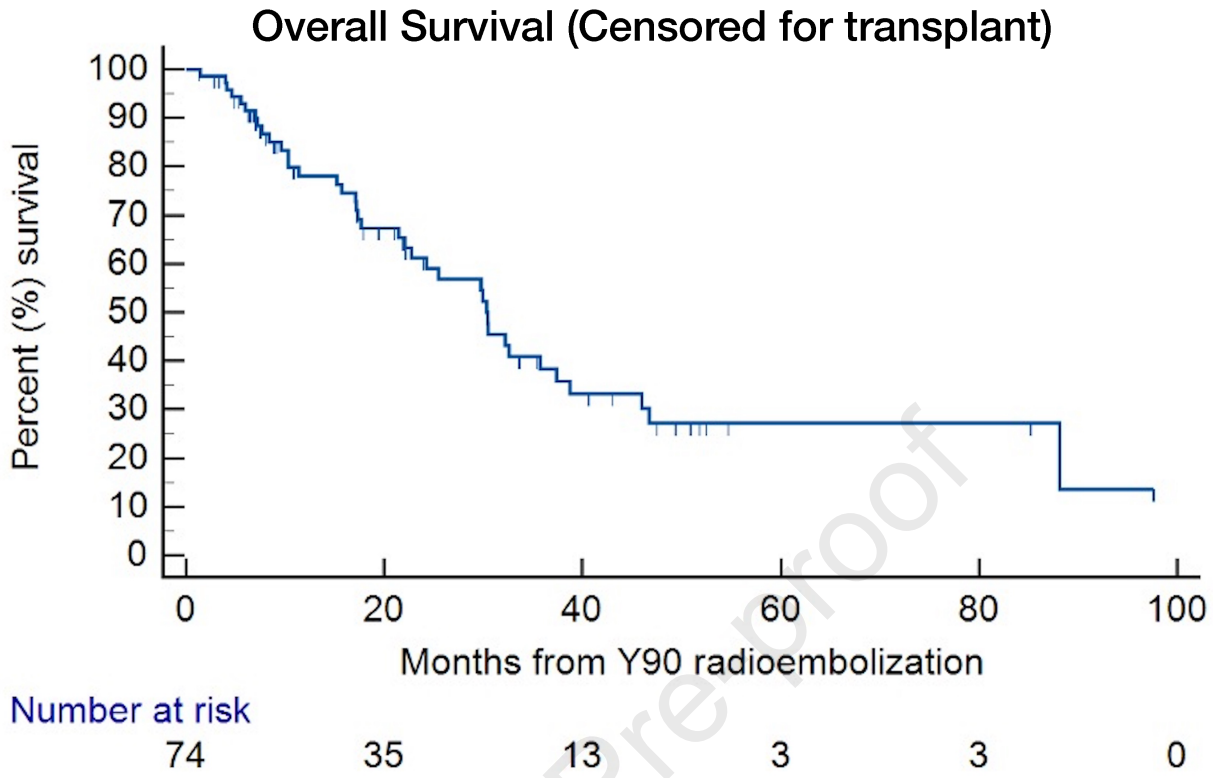
	Yes	15.6 (9.1-35.6)	0.9 (0.4-1.7)		N/A	
Volume treated in the first Y90 session	<50%	16.1 (8-25.3)	1	0.5	1	
	≥50%	13 (5.5-35.6)	0.8 (0.4-1.5)		0.6 (0.3-1.3)	0.2
Number of Treatments	≥3 sessions	16.3 (9.1-35.6)	0.8 (0.4-1.7)	0.8	0.4 (0.1-1.1)	0.1
	2 sessions	13 (5.8-37.8)	1		0.7 (0.3-1.9)	0.6
	1 session	37.1 (5.5-37.1)	0.7 (0.3-1.7)		1	

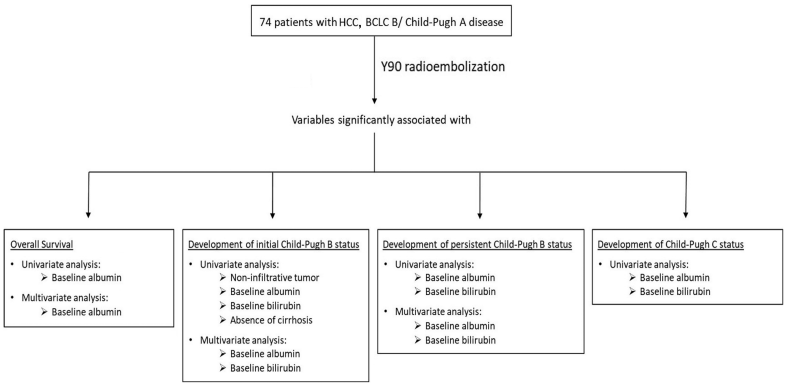
Table 6. Univariate Analyses for progression to Child-Pugh C

	Univariate analysis			
Predictor	Category	Progression to CPC (95% CI)	Hazard Ratio (95% CI)	P-value
Age	<65	51.1 (17.7-51.1)	1	0.2
	≥65	87.3 (35.7-136.1)	0.5 (0.1-1.4)	
Sex	Female	Median Not Reached	0.3 (0.1-1.1)	0.08
	Male	51.1 (31.2-136.1)	1	
Albumin	>3.5 g/dl	87.3 (51.1-87.3)	0.3 (0.1-0.9)	**0.04**
	≤3.5 g/dl	35.7 (17.7-136.1)	1	
Bilirubin	<1.2 mg/dL	87.3 (39.8-136.1)	0.2 (0.08-0.9)	**0.03**
	≥1.2 mg/dL	Median Not Reached	1	
Baseline Tumor Size	≤5 cm	Median Not Reached	0.3 (0.1-1.1)	0.1
	5-10 cm	39.8 (17.1-87.3)	1	
	>10 cm	136.1	0.3 (0.08-1.4)	
Infiltration	Non-infiltrative	87.3 (35.7-136.1)	0.9 (0.1-7.6)	0.9
	Infiltrative tumor	Median Not Reached	1	
Tumor distribution	Unilobar	87.3 (17.7-87.3)	0.7 (0.2-2.1)	0.6
	Bilobar	51.1 (31.2-136.1)	1	
AFP	<100	51.1 (31.2-136.1)	1	0.3
	≥100	Median Not Reached	0.5 (0.1-1.8)	
Systemic therapy	No	87.3 (39.8-87.3)	0.5 (0.1-1.6)	0.2
	Yes	35.7 (17.7-136.1)	1	

Volume treated in the first Y90 session	<50%	51.1 (31.2-87.3)	1	0.6
	≥50%	136.1	0.8 (0.2-2.2)	
Number of Treatments	≥3 sessions	87.3	0.8 (0.3-2.4)	0.9
	2 sessions	51.1 (22.1-136.1)	1	
	1 session	Median Not Reached	0.7 (0.1-3.2)	







Research Highlights / Take Home Points:

- Intermediate stage (BCLC B) HCC comprises a broad range of patients with multifocal tumors. These are often treated with locoregional therapies (LRTs). Patients often require multiple treatments before moving to the next line of treatment that may involve systemic therapy.
- Baseline liver function currently plays a rule in systemic therapy candidacy, especially in the setting of new clinical trials.
- In BCLC B patients, despite the multifocality, and multiple treatment that may include the whole liver, the rate of hepatic decompensation post-TARE is relatively slow.
- Further studies exploring hepatic decompensation after systemic agents are needed.

	Item No	Recommendation	✔ (N/A)
Title and abstract			
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✔
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✔
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✔
Objectives	3	State specific objectives, including any prespecified hypotheses	✔
Methods			
Study design	4	Present key elements of study design early in the paper	✔
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✔
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	✔
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	(N/A)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✔
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✔
Bias	9	Describe any efforts to address potential sources of bias	✔
Study size	10	Explain how the study size was arrived at	✔
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	(N/A)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✔
		(*b*) Describe any methods used to examine subgroups and interactions	✔
		(*c*) Explain how missing data were addressed	✔
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	✔
		(*e*) Describe any sensitivity analyses	(N/A)

Results			✔ **(N/A)**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✔
		(b) Give reasons for non-participation at each stage	(N/A)
		(c) Consider use of a flow diagram	(N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✔
		(b) Indicate number of participants with missing data for each variable of interest	✔
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	✔
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✔
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*(N/A)*
		Cross-sectional study—Report numbers of outcome events or summary measures	*(N/A)*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✔
		(*b*) Report category boundaries when continuous variables were categorized	(N/A)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(N/A)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✔
Discussion			
Key results	18	Summarise key results with reference to study objectives	✔
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✔
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✔
Generalisability	21	Discuss the generalisability (external validity) of the study results	✔
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A (No Funding)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*N/A stands for not applicable and may be a reasonable choice depending on the type of study performed