Research Article

Hepatocellular carcinoma and Y90-radioembolization treatment

HEPATOLOGY FORUM

doi: 10.14744/hf.2022.2022.0036

Is the Y90-radioembolization treatment effective on the intermediate-advanced stage of hepatocellular carcinoma and what is the albumin-bilirubin score's prediction factor for survival?

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Abstract

Background and Aim: Radioembolization (RE) is a one of the palliative treatments that have been used to down stage and/or increase the survival time in intermediate-advanced stages of HCC. We aimed to evaluate the clinical impact of RE and the clinical use of the albumin-bilirubin (ALBI) score as a predictor for survival in HCC patients.

Materials and Methods: Fifty-nine unresectable hepatocellular carcinoma (HCC) patients were enrolled. RE was performed in 28 of them (group 1) and 31 patients were followed up in the natural course (NC) (group 2). Patients were classified according to the Child-Pugh score (only cirrhotic patients), Barcelona clinic liver cancer (BCLC) staging, and ALBI scores were also calculated.

Results: All patients in Group 1 were cirrhotic and their BCLC stages were as follows: 60.7% stage B and 39.3% stage C. In Group 2, 83.9% of patients were cirrhotic and their BCLC stages were as follows: 9.7% stage B, 51.6% stage C, and 38.7% stage D. Mortality rates were 82% and 100% in Groups 1 and 2, respectively. The median overall survival (OS) was 13.5 months (95% CI: 10.4–16.6 months) and 4.5 months (95% CI: 3.5–5.5 months) in Groups 1 and 2, respectively (p=0.000). When RE was applied to patients with ALBI Grade 1 and 2, the median OS was statistically higher than in the NC group, respectively (p<0.001, p<0.001).

Conclusion: RE is an effective treatment method at the advanced stages of HCC. The ALBI score is a more useful and practical than the other prognostic tools.

Keywords: ALBI score; hepatocellular carcinoma; natural course; radioembolization.

How to cite this article: Evirgen S, Cavus B, Gokturk S, Iliaz R, Ozkan ZG, Baran B, et al. Is the Y90-radioembolization treatment effective on the intermediate-advanced stage of hepatocellular carcinoma and what is the albumin-bilirubin score's prediction factor for survival? Hepatology Forum 2023; 4(3):103–107.

Received: December 14, 2022; **Accepted:** March 13, 2023; **Available online:** June 16, 2023

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Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Hepatocellular cancer (HCC) is the most common primary liver malignancy, and it is also the fifth ranking cause of cancer-related deaths in males and seventh in females worldwide.[1] The annual incidence and mortality rates of HCC are 800,000 and 750,000, respectively, in the world.[2,3] HCC is a complication of chronic liver diseases, especially after the development of cirrhosis; hence, it is important to detect chronic liver diseases at early stages and follow-up periodically. Surveillance guidelines recommend HCC screening with ultrasound (US) and/or alfa-fetoprotein (AFP) every 6 months for patients with hepatitis B-related chronic liver diseases or cirrhosis.[3,4] Unfortunately, only 30% of patients are currently detected in and given curative treatments in the early stages despite appropriate screening recommendations.[5] Patients usually are diagnosed at advanced stages of HCC due to the use of inappropriate screening techniques, patient noncompliance for screening, or undiagnosed chronic liver diseases at early stages. Any acute deterioration in liver function, acute decompensation of previously compensated liver cirrhosis with the development of ascites, hepatic encephalopathy, variceal bleeding, or any new symptoms, such as fever, abdominal pain, or weight loss, should alert the physician that further work-up must be done to rule out HCC.[6] After the diagnosis of HCC, liver function tests for the severity of cirrhosis, tumor size, vascular structures (portal and hepatic artery/vein), and metastatic disease as well as the patient's performance score are important factors to determine the treatment pathway. The Barcelona classification was created in the light of these factors and is being used for HCC management in Europe and America.[7] The most common cause of mortality is the development of liver failure due to disease progression rather than distant metastasis, which makes local control of the tumor more important, especially for patients in advanced stages of HCC.[8] Treatment options such as radioembolization (RE), Sorafenib, and TACE are helpful to increase downstaging and for symptom palliation and survival in the intermediate-advanced stage of the disease.[9–14] They are not recommended for patients who have terminal stage HCC.

The aims of this study were to compare the survival of patients with intermediate-advanced stage HCC who were treated with RE with Y-90 microspheres to patients who were not treated for various reasons and to investigate the effectiveness of RE on survival for the intermediate-advanced stage of the disease.

Table 1. Patients demographic characteristics

	Overall (n=59)		RE (n=28)		Natural course (n=31)		p
	n	%	n	%	n	%	
Median age			60	48–72	58	48–69	0.866
Male	81	48	79	22	84	26	0.6
Viral etiology	72	42	61	17	81	25	NC
Chirrhosis	92	54	100	28	84	26	NC
BCLC-B	34	20	85	17	10	3	0.000
BCLC-C	46	27	41	11	52	16	0.56
BCLC-D	20	12	0	0	38	12	
AFP <400* ng/ml	29		52	15	48	14	0.6
AFP >400* ng/ml	28		43	12	57	16	0.343
Albumin (g/dl)			3.9±0.07		3.97±0.71		0.9
Bilirubin (mg/dl)			1.15±0.1		2.82±0.55		0.005
Portal venous invasion absent	53	31	57	16	48	15	0.45
Portal venous invasion present	47	28	43	12	52	16	0.3
ALBI grade 1	34	20	46	13	22	7	0.003
ALBI grade 2	49	29	54	15	45	14	0.97
ALBI grade 3	17	10	0	0	33	10	

RE: Radioembolization; BCLC: Barcelona clinic liver cancer; AFP: Alfa-fetoprotein; ALBI: Albumin-bilirubin; *: Missing data not included.

Materials and Methods

A total of 59 patients diagnosed with HCC admitted to our tertiary care hospital were reviewed retrospectively. Of these patients, 28 underwent RE (group 1) and 31 HCC were not treated and left to pursue a natural course (NC) (group 2). The institutional ethics board approved the study (2554-24).

Patient Selection

The decision to treat HCC patients was evaluated by a multidisciplinary team including a hepatologist, nuclear medicine specialist, interventional radiologist, and transplant surgeon in our hospital during a weekly tumor board. HCC was diagnosed with dynamic computed tomography (CT)/ magnetic resonance imaging (MRI), liver lesion biopsy, or a combination of these modalities. This committee decided to pursue RE or NC according to the following criteria. Patients who had a Child-Pugh score ≤7, sufficient liver reserve (albumin ≥3 g/dL, total bilirubin ≤2 mg/dL, transaminase levels <5 times x ULN), neutrophils >1.5 × 109/L, platelets >50 × 109/L, good Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, Barcelona clinic liver cancer (BCLC) staging B-C, limited extrahepatic disease (lymph node <2 cm, lung nodule <1 cm, and bone metastasis) were included in Group 1 (RE group). Patients who did not meet these criteria, had a high shunt in the lung or gastrointestinal system, significant extrahepatic disease, had a tumor localization not suitable for RFA or who were not eligible for other treatment options were included in Group 2 (NC group). Furthermore, patients who refused RE and the other treatments were also included in the second group. Five patients left on NC group were non-cirrhotic with extrahepatic metastasis and AFP >400 ng/mL. The patients who were unsuitable for TACE (tumor localization, ECOG performance status 3, or Child B-C) or who started Sorefenib and could not tolerate the drug due to side effects (GIS intolerance, skin reactions vs.) and stopped the treatment in a short time

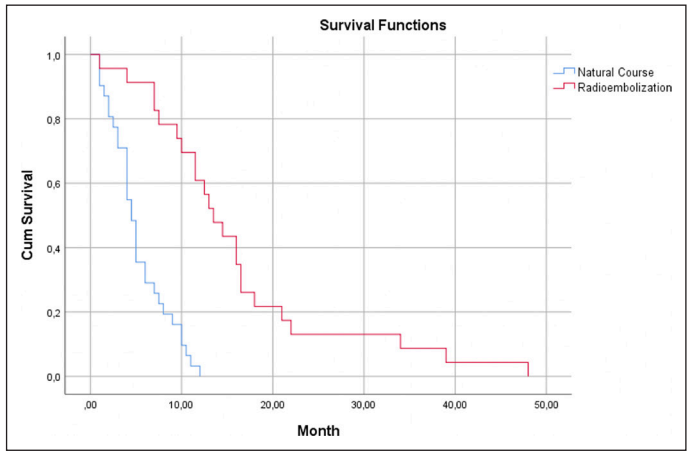

Figure 1. Median Overall Survival graphic of patients who underwent RE versus to NC.

or had contraindications for Sorafenib treatment (ECOG performance status ≥2 and Child B-C) were included in the both study group. The ECOG performance evaluation, BCLC staging, and albumin-bilirubin (ALBI score of all patients were recorded. Child-Pugh classification could not be calculated for each patient, since physical examination data required for calculation could not be obtained in some patient file. For this reason, BCLC classification was based on tumor spread, performance score, and portal invasion criteria. Patients who underwent RE were followed up and post-procedure records were kept regarding changes in blood values (AFP, bilirubin, albumin, and PT) and side effects. The response to treatment was evaluated with imaging methods of CT/MRI and/or F-18 fluorodeoxyglucose-positron emission tomography (FDG PET-CT). None of the patients with bone or lung metastases who received RE treatment used systemic therapy after the procedure.

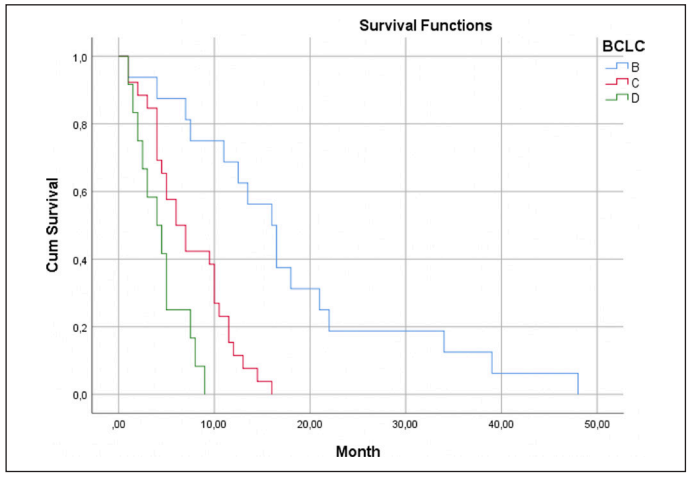

Figure 2. Median Overall Survival graphic according to Barcelona classification.

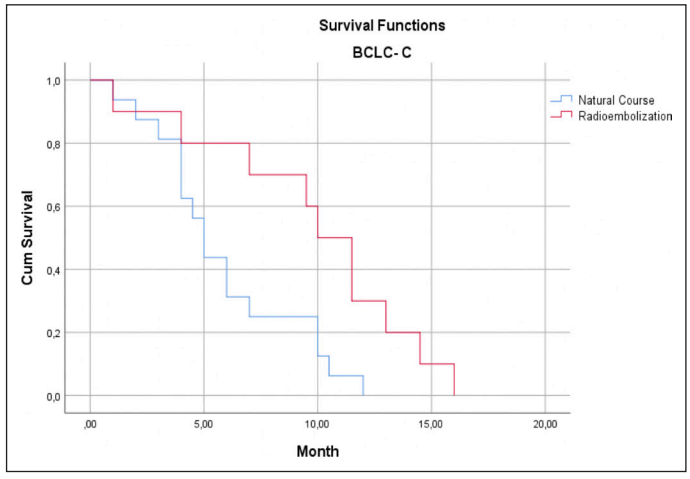

Figure 3. Median Overall Survival graphic of patients in BCLC-C patients who underwent RE versus to NC.

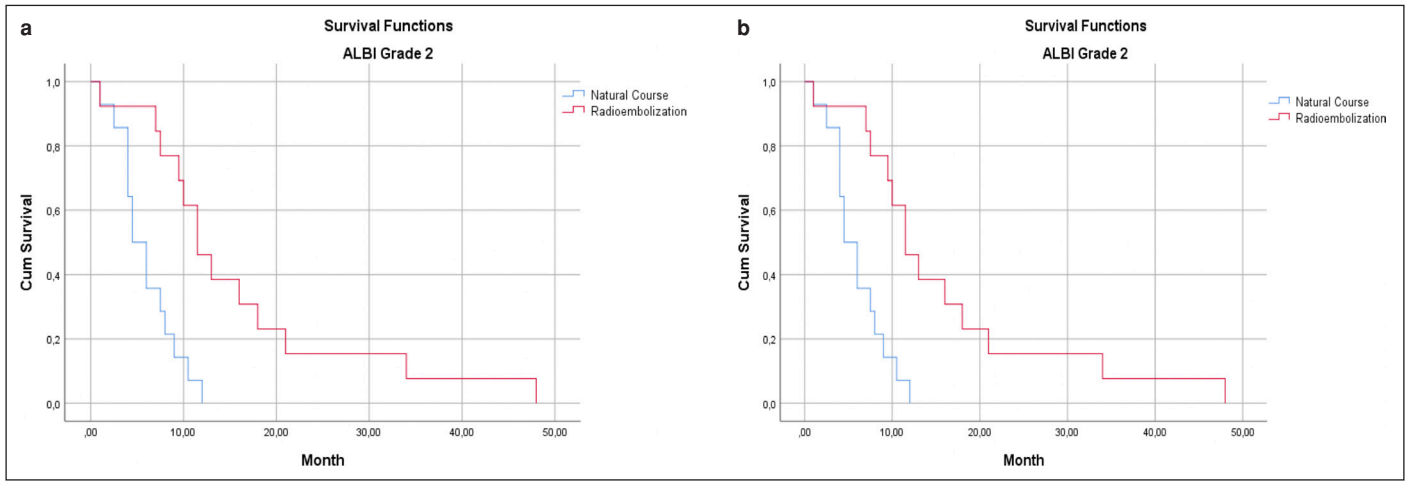

Figure 4. Median overall survival graphic of patients with ALBI grade 1 who underwent RE versus to NC **(a)**, Median overall survival graphic of patients with ALBI grade 2 who underwent RE versus to NC **(b)**.

Techniques

Comprehensive angiographic evaluation was performed in all patients eligible for RE. Coil embolization was applied to patients with aberrant hepatic vessels and extrahepatic collaterals to prevent extrahepatic leakage. Then, Tc-99-macro-aggregated albumin (MAA) was administered through the hepatic artery, and the whole body was scanned with SPECT-CT fusion imaging. Tc-99-MAA distribution in the body and the shunt rate in the lungs were assessed. The resin microspheres doses were calculated using the body surface area method, but for the glass microsphere treatment, manufacturer instructions were used. RE was applied to all patients within 1–2 weeks from MAA.

Statistics

Baseline demographics and clinical characteristics were compared using a χ^2 test for categorical variables and a nonparametric Wilcoxon rank sum test for continuous variables. A Kaplan-Meier survival curve was carried out for overall survival (OS). The log-rank test was used to examine the statistical significance of the differences observed between the groups. The authors applied a significant p level of 0.05 for each statistical test. All statistical analyses were carried out using the Statistical Package for the Social Sciences version 21.

Results

Demographic characteristics were similar in both groups (Table 1). Eighty-one percent of the patients were male. The mean age was 60.3±12 years and 58.8±10.7 years in the RE and NC groups, respectively. Among the etiologies of liver disease, the most common cause was hepatitis B virus (50%). All patients in Group 1 were cirrhotic, and according to BCLC, 60.7% were Stage B and 39.3% were Stage C. In Group 2, 83.9% of patients were cirrhotic, and according to BCLC, 9.7% stage B, 51.6% stage C, and 38.7% stage D. Mortality rates were 82% and 100% in groups 1 and 2, respectively. The median OS was 13.5 months (95% CI: 10.4–16.6) and 4.5 months (95% CI: 3.5–5.5) in Groups 1 and 2, respectively ($p<0.000$) (Fig. 1). The median OS in BCLC-B/C/D patients was 16, 6, and 4 months, respectively ($p<0.000$) (Fig. 2). The median OS in Groups 1 and 2 in BCLC-C patients was 10±1.1 months and 5±0.5 months, respectively ($p<0.013$) (Fig. 3).

The median OS in patients with ALBI Grades 1-2-3 was 10, 8, and 3 months, respectively ($p<0.003$). The median OS for patients with ALBI Grade 1 in the RE and NC groups was 14.5±1.2 months and 5±0.6 months, respectively, and it was statistically higher in the RE

group than the NC group (p<0.001). Similarly, for patients with ALBI Grade 2, the median OS was 11.5±1.8 months and 4.5±0.9 months for the RE and NC groups, respectively, and was statistically higher in the RE group (p<0.001) (Fig. 4).

The rate of portal vein thrombosis (PVT) was 43% (12/28) in Group 1 and 51% (16/31) in Group 2. The survival time was shorter in patients with PVT than without PVT, but it was not statistically significant (7±2.1 months, 9.5±2.6 months, p=0.519).

Y-90 resin (SIR-Spheres) was used in 23 patients and Y-90 glass (TheraSphere) microspheres were used in five patients during RE. The average dose was 1.5 GBq (range: 1–2.2 GBq) for resin microsphere treatment and 2.6 GBq (range: 1.6–3 GBq) for glass microsphere treatment. The right hepatic artery was used in 25 patients and the left hepatic artery in three patients. Approximately 58% of the patients developed abdominal pain and nausea after RE. There was a transient increase in bilirubin in 19 patients. AFP levels trended down in 12 patients after the procedure.

Response to RE was assessed between 6 weeks and 6 months after the treatment with CT/MRI and/or F-18 fluorodeoxyglucose-positron emission tomography (FDG PET-CT). Sixteen patients were recorded as responding to treatment with decreased mass size, increased necrosis, and decreased metabolic activity accepted as indications of response to treatment. Five patients had no significant changes and were considered to have stable disease. The response to treatment could not be evaluated in seven patients (18%) who underwent RE because they did not follow-up.

Discussion

RE is an effective and reliable locoregional treatment method with long-term results, as published recently.[15] In our study, the median OS was 13.5 months in the RE group and 4.5 months in the NC group (p<0.000). In our study, the median OS in BCLC-B/C was 16.5 and 10 months after treatment with RE. Considering the number of patients, only the BCLC-C group was statistically comparable in both groups. At BCLC-C stage, although the number of BCLC-C patients was higher in NC group, patients who received RE treatment were shown to do better overall survival than who were not treated (10 months vs. 5 months [p<0.0013], respectively). These results were similar to those of previous studies. In the study by Mazzaferro et al.,[16] the median OS was 15 months in HCC patients (BCLC-B/C) who were treated with RE. In the study by Sangro et al.,[17] the median OS was 24.4, 16.9, and 10 months for BCLC-A/B/C stages, respectively. In the study by Hilgard et al.[18] (BCLC-B/C), the median OS was 16.4 months. Similarly to our study, D'Avola et al.[19] compared patients who underwent RE and those who were technically unable to undergo RE in terms of survival, and median OS was found to be statistically higher in patients who underwent RE than those left to NC (16 months vs. 8 months [p<0.05], respectively).

Antkowiak et al.[20] investigated the prognostic effect of albumin, bilirubin, and ALBI staging on survival in 1000 patients with HCC after treatment with RE. The median OS was 46.7, 19.1, and 8.8 months in patients with ALBI stages 1-2-3 (p<0.001). In our study, the median OS was 10, 8, and 3 months in patients with ALBI stage 1-2-3 (p<0.001). Longer median OS durations were detected in patients who underwent RE in ALBI stage 1–2 compared to patients left to NC (p<0.001, p<0.001, respectively). The larger patient population[15,17,19] compared to our study will explain the difference in survival times. However, despite the different number of patients in both studies, the ALBI's prediction of on survival continues to be significant. ALBI scoring is a staging method that requires only simple laboratory examination. In contrast, for Child-Pugh classification, subjective data such as hepatic encephalopathy and ascites are required in addition to laboratory data, which can make staging difficult. Thus, in contrast to ALBI, Child-Pugh suffers from information loss, duplication, and subjectivity.

Sorafenib can be used in patients with good liver function (Child A), but unfortunately, very few advanced stage HCC patients are Child A. This suggests that a significant number of patients may remain without treatment according to the recommended guidelines. In addition, in the studies mentioned above,[15–20] the injected Y-90 radiation dose was calculated, but no calculations were made about the actual tumor dose, which is what determines the treatment response. More reliable results are likely to be obtained with a good dosimetric study.

Most patients with HCC are diagnosed at an advanced stage and a tolerable and effective treatment such as RE is likely to be included in future guidelines. However, RE is not yet included in the standard approach in the recent European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases guidelines. RE can be used as an alternative treatment method at every stage of the BCLC guideline. Many studies highlight the efficacy and safety of treatment with RE on a scale from symptomatic-palliative use to curative use with complete tumor necrosis. Some studies show that the RE can be effective in treating HCC not only in the advanced stages but also in early-intermediate stages.[21–28]

The limitations of this study are its retrospective nature and some missing data on some key factors (such as AFP levels and Child-Pugh). In addition, as we shared in the data, all of the patients in the RE group are BCLC-B/C; on the other hand, approximately 60% of the patients in the NC group are BCLC-B/C. As it is known, alternative treatment options such as TACE or systemic treatments (such as Sorafenib) could be used in this group of patients. However, it was not used for the reasons mentioned in the methods section above. Our goal in creating such a population was to eliminate the treatment factors that could affect the survival rates of both populations, compare the RE and NC patient groups one-on-one, and increase the scientific value of the study.

Conclusion

Our study showed that RE improves the survival of advanced stage HCC patients compared with patients that who not treated and that the ALBI score is very useful as a simple, effective prognostic marker for guiding HCC treatment.

Ethics Committee Approval: The Istanbul University Clinical Research Ethics Committee granted approval for this study (date: 18.09.2013, number: 2554-24).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – SE, FA; Design – SE, FA; Supervision – SE, BC; Fundings – SE, BC, SG, RI, ZGO, BB, ACO, OMS; Materials – SE; Data Collection and/or Processing – SE, BC, SG, RI, ZGO, BB, ACO, OMS, CK, KD, SFB, AP, FA, SK; Analysis and/or Interpretation – SE, FA; Literature Search – SE; Writing – SE; Critical Reviews – SE, FA.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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