Original Article

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Predictors of Response and Overall Survival for Selective Intraarterial Radiomicrosphere Therapy in Hepatocellular Carcinoma

Hepatosellüler Kanserde Selektif İntraarteriyel Radyomikroküre Tedavisi Sonrası Yanıt ve Genel Sağkalımın Belirleyicileri

Başak Soydaş Turan[1], Murat Fani Bozkurt[2], Gonca Eldem[3], Ferdi Çay[3], Şuayib Yalçın[4], Bora Peynircioğlu[3]*, Ömer Uğur[2], Bilge Volkan Salancı[2]

[1]*Hacettepe University Faculty of Medicine, Department of Nuclear Medicine, Kastamonu, Türkiye*
[2]*Hacettepe University Faculty of Medicine, Department of Nuclear Medicine, Ankara, Türkiye*
[3]*Hacettepe University Faculty of Medicine, Department of Interventional Radiology, Ankara, Türkiye*
[4]*Hacettepe University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye*
**Current affiliation: Acıbadem Maslak Hospital, Clinic of Interventional Radiology, Istanbul, Türkiye*

Abstract

Objectives: Data on the prognostic contribution of biomarkers reflecting hepatic fibrosis and systemic inflammation to outcomes following yttrium-90 selective internal radiation therapy (^{90}Y SIRT) in unresectable hepatocellular carcinoma (uHCC) remain limited. To evaluate the impact of baseline clinical, laboratory and tumor-related parameters including fibrosis- and inflammation-related biomarkers on radiological treatment response and overall survival (OS) in patients with uHCC undergoing ^{90}Y SIRT, and to develop a simple alternative risk-stratification approach.

Methods: This retrospective single-center study included 79 patients. Associations among baseline variables, radiological response, and OS were analyzed using binary logistic regression and Cox regression analyses.

Results: In multivariate logistic regression analysis, higher aspartate aminotransferase-to-platelet ratio (APRI) [odds ratio (OR)=7.75, p=0.023; cut-off: 0.33], larger target lesion size (OR=4.87, p=0.025; cut-off: 9 cm), and higher neutrophil-to-lymphocyte ratio (NLR) (OR=3.53, p=0.024; cut-off: 3.56) independently predicted non-response. Median OS was 11.2 months (95% confidence interval: 7.3-15.1). Multivariate Cox analysis identified albumin-bilirubin (ALBI) score [hazard ratio (HR)=3.73, p<0.001], extrahepatic metastasis (HR=3.27, p=0.001), and gamma-glutamyl transferase (GGT) level (HR=1.037 per 10-unit increase, p=0.001) as independent predictors of worse OS. Higher GGT levels in patients with preserved hepatic reserve were associated with poorer survival (23.2 months vs. 41.3 months; p=0.014), whereas lower GGT levels were associated with improved survival in those with impaired reserve (13.9 months vs. 7.8 months; p=0.037).

Conclusion: APRI and NLR may serve as useful predictors of treatment response, while ALBI score, extrahepatic metastasis, and GGT independently predict OS. Combined ALBI-GGT assessment may offer a risk-stratification approach, although further validation is required.

Keywords: Hepatocellular carcinoma, ^{90}Yttrium, survival

Address for Correspondence: Başak Soydaş Turan, Hacettepe University Faculty of Medicine, Department of Nuclear Medicine, Kastamonu, Türkiye
E-mail: basaksoydas@hotmail.com **ORCID ID:** orcid.org/0000-0003-3425-751X
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Öz

Amaç: Hepatik fibrozis ve sistemik inflamasyonu yansıtan biyobelirteçlerin, rezektabl olmayan hepatoselüler karsinomda (uHCC) itriyum-90 ile selektif internal radyasyon tedavisi (^{90}Y SIRT) sonrası sonuçlara prognostik katkısına ilişkin veriler sınırlıdır. ^{90}Y SIRT uygulanan uHCC hastalarında, hepatik fibrozis ve sistemik enflamasyonla ilişkili biyobelirteçler dahil olmak üzere başlangıçtaki klinik, laboratuvar ve tümör ilişkili parametrelerin radyolojik tedavi yanıtı ve genel sağkalım (GS) üzerindeki etkisini değerlendirmek ve alternatif risk sınıflandırma yaklaşımı geliştirmektir.

Yöntem: Bu retrospektif tek merkezli çalışmaya 79 hasta dahil edildi. Başlangıç değişkenleri ile radyolojik yanıt ve GS arasındaki ilişkiler lojistik regresyon ve Cox regresyon analizleriyle değerlendirildi.

Bulgular: Çok değişkenli lojistik regresyon analizinde, daha yüksek aspartat aminotransferaz-trombosit oranı (APRI) [odds oranı (OR)=7,75; p=0,023; eşik: 0,33)], daha büyük hedef lezyon boyutu (OR=4,87; p=0,025; eşik: 9 cm) ve daha yüksek nötrofil-lenfosit oranı (NLR) (OR=3,53; p=0,024; eşik: 3,56) yanıt alınamamasının bağımsız belirleyicileri olarak saptandı. Medyan GS 11,2 ay idi (%95 güven aralığı: 7,3-15,1). Çok değişkenli Cox analizinde albümin-bilirubin (ALBI) skoru [hazard oranı (HR) = 3,73; p<0,001], ekstrahepatik metastaz varlığı (HR = 3,27; p=0,001) ve gama-glutamil transferaz (GGT) düzeyi (her 10 birim artış için HR=1,037; p=0,001) daha kötü GS'nin bağımsız belirleyicileri olarak bulundu. Korunmuş hepatik rezervi olan hastalarda daha yüksek GGT düzeyleri daha kötü sağkalım ile ilişkiliyken (23,2 aya karşı 41,3 ay; p=0,014), bozulmuş rezervi olan hastalarda daha düşük GGT düzeyleri daha iyi sağkalım ile ilişkiliydi (13,9 aya karşı 7,8 ay; p=0,037).

Sonuç: APRI ve NLR tedavi yanıtının yararlı öngörücüleri olabilirken, ALBI skoru, ekstrahepatik metastaz ve GGT düzeyi GS'nin bağımsız belirleyicileri olarak bulundu. ALBI-GGT kombinasyonuyla değerlendirme, daha ileri doğrulama gerektirmekle birlikte, potansiyel bir risk sınıflama yaklaşımı sunabilir.

Anahtar Kelimeler: Hepatoselüler kanser, ^{90}Yttriyum, sağkalım

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and remains a major cause of cancer-related mortality worldwide (1,2). Curative treatment options such as surgical resection, liver transplantation, or local ablative therapies are feasible only in a minority of patients diagnosed at an early stage (3). Consequently, a substantial proportion of patients present with intermediate or advanced disease requiring locoregional or systemic treatment strategies (3).

Yttrium-90 selective internal radiation therapy (^{90}Y SIRT), also referred to as transarterial radioembolization, has emerged as an important locoregional treatment modality for patients with unresectable HCC (4). This technique delivers high dose beta radiation directly to tumor tissue through the hepatic arterial supply while relatively sparing the surrounding liver parenchyma (5). However, clinical outcomes after ^{90}Y SIRT remain heterogeneous, likely reflecting variations in tumor burden, hepatic functional reserve, systemic inflammatory status, and underlying hepatic fibrosis.

Several prognostic factors have been reported in previous studies, including albumin-bilirubin (ALBI) grade, tumor size, number of nodules (>5), bilobar involvement, presence of extrahepatic metastasis, ascites, portal vein thrombosis, serum alpha-fetoprotein (AFP) levels (6-10). In addition, biomarkers reflecting hepatic fibrosis and systemic inflammation, such as the aspartate aminotransferase (AST) -to-platelet ratio index (APRI), the fibrosis index based on four factors (FIB-4), and the neutrophil-to-lymphocyte ratio (NLR) have gained increasing attention. Nevertheless, data regarding the prognostic contribution of these parameters to radiological response and survival following ^{90}Y SIRT remain limited (11,12,13). In this retrospective single-center study, we aimed to evaluate baseline clinical, laboratory, and tumor-related parameters associated with radiological treatment response and overall survival (OS) in patients with unresectable HCC who were treated with ^{90}Y SIRT. Furthermore, we sought to investigate the impact of underlying hepatic fibrosis and of systemic inflammatory status, and to develop an alternative, simple, clinically applicable risk-stratification model.

Materials and Methods

Study Design and Patient Selection

This retrospective study at a single tertiary academic center included patients with unresectable HCC who underwent ^{90}Y SIRT at Hacettepe University between April 2008 and December 2018. Patients were excluded from the study if data were only available for <20% of the predefined clinical, laboratory, or imaging parameters.

Eligibility criteria for ^{90}Y SIRT at our center generally included an Eastern Cooperative Oncology Group performance status 0-2; total bilirubin ≤2 mg/dL; serum albumin ≥3 g/dL; alanine aminotransferase (ALT) and AST levels ≤5 times the upper limit of normal; and suitability for planning angiography. However, ^{90}Y SIRT was performed in a limited number of patients who did not fully meet these criteria at the time of treatment. Specifically, treatment was administered to one patient who had a serum albumin level of 2.2 mg/dL, two patients who had total bilirubin levels of 2.4 mg/dL, three patients who had AST levels

exceeding five times the upper limit of normal, and one patient who was receiving chronic hemodialysis.

Patients were deemed ineligible for ^{90}Y SIRT if hepatopulmonary shunt ratio ≥ 20% on technetium-99m macroaggregated albumin (Tc-99m MAA) scan or if uncorrectable leakage to the gastrointestinal tract was detected.

^{90}Y SIRT Procedure

At our institution, all cases were evaluated by a multidisciplinary tumor board consisting of surgeons, medical oncologists, interventional radiologists, and nuclear medicine physicians. Clinical and laboratory evaluations were performed prior to treatment.

Planning angiography was performed 1-3 weeks before ^{90}Y SIRT to evaluate tumoral arterial anatomy, identify anatomic variants, and determine optimal microcatheter positioning. The angiographic study was followed by the injection of Tc-99m MAA through the hepatic artery. Subsequently, a hepatic artery perfusion scan [whole-body planar views and abdominal single-photon emission computed tomography (CT)/CT] was obtained within 1 hour to assess tracer distribution in the tumoral and healthy liver tissue, calculate the hepatopulmonary shunt ratio, and detect extrahepatic leakage. Prophylactic embolization of the gastroduodenal, gastric, or other extrahepatic arteries was performed when necessary.

Once the procedure was deemed safe, patients were treated with either ^{90}Y resin microspheres or glass microspheres. The decision to use resin or glass microspheres for treatment depended on the type of radiomicrospheres supplied to the clinic. For resin microspheres, the activity was calculated according to the manufacturer's guidelines using the body surface area (BSA) method: activity (GBq) = (BSA-0.2) + (tumor volume/total liver volume) (14,15). For glass microspheres, activity was calculated using the target liver lobe or segment volume and hepatopulmonary shunt ratio, based on the following formula recommended by the manufacturer: activity (GBq) = desired dose (Gy) × (mass of target liver lobe/50) (16). For each patient, nuclear medicine physicians calculated the administered activity (GBq) using 120 Gy as the desired tumor dose. For both microsphere types, the administered activity was adjusted according to the hepatopulmonary shunt ratio.

Microspheres were administered via hepatic arterial catheterization, as performed during the planning angiography. Post-treatment Bremsstrahlung imaging was performed on the same day to confirm intrahepatic deposition of ^{90}Y microspheres. All procedures were carried out by experienced nuclear medicine physicians and interventional radiologists.

Data Collection

Clinical, laboratory, and imaging data were retrospectively collected. Recorded variables included age, gender, etiology of liver disease (viral hepatitis, alcohol use, etc.), prior HCC-directed therapies, Barcelona Clinic Liver Cancer (BCLC) stage (17) and Child-Pugh class (18).

Baseline laboratory parameters included a complete blood count, liver and renal function tests, international normalized ratio (INR), and serum AFP level. Liver function, fibrosis and systemic inflammation indices were calculated using the following formulas: 1) Model for end-stage liver disease (MELD) score = 6.43 + [loge creatinine (mg/dL) × 9.57] + [loge total bilirubin (mg/dL) × 3.78] + [loge INR × 11.2] (19). 2) ALBI score = [$\log_{10}$ bilirubin (μmol/L) × 0.66] + [albumin (g/L) × -0.0852] (20). 3) ALBI grade; grade 1 = ALBI score ≤-2.60, grade 2 = ALBI score >-2.60 to ≤-1.39, grade 3 = ALBI score >-1.39 (20). 4) APRI = [(patient AST level / upper limit of normal AST level) / platelet count (10^9/L)] × 100 (21). 5) FIB-4 = [age (years) × AST (IU/L)] / [platelet count (10^9/L) × √ALT (IU/L)] (22). 6) NLR = neutrophil count / lymphocyte count (absolute or %).

Baseline contrast-enhanced CT or magnetic resonance imaging (MRI) was reassessed to determine tumor location, size, and number, and to evaluate the presence of portal vein invasion, ascites, and extrahepatic metastases.

Treatment Characteristics and Response Assessment

Details regarding the date, number, route, microsphere type, and administered activity of each ^{90}Y SIRT were obtained from the patient records.

Follow-up imaging with contrast-enhanced CT or dynamic contrast-enhanced MRI was primarily performed 1-3 months after ^{90}Y SIRT and was subsequently re-evaluated to assess local therapy response. In a subset of patients, radiologic response was evaluated 4-6 months after treatment. Radiologic tumor response was assessed according to the modified Response Evaluation Criteria in Solid Tumors (23).

Patients or treatments achieving complete or partial responses were classified as responders, whereas those with stable or progressive disease were classified as non-responders. In the per-patient analysis, patients were classified as nonresponders if disease progression occurred in the untreated contralateral hepatic lobe despite a response in the treated lobe or if a mixed response was observed during sequential or repeated ^{90}Y SIRT sessions. In contrast, in the per-treatment analysis, each treatment session was evaluated independently, and a treatment was classified as a responder if a radiological response was observed in the treated hepatic lobe, irrespective of disease status elsewhere in the liver.

Definition of Survival Endpoint

OS was defined as the time interval between the date of ^{90}Y SIRT and the date of death. Patients confirmed to be alive at the time of analysis were censored on the date of analysis. OS was analyzed per patient.

Statistical Analysis

Statistical analyses were performed using SPSS v23.0 (IBM, NY, USA), and a p-value of <0.05 was considered statistically significant. Continuous variables were expressed as mean ± standard deviation for normally distributed data or median (minimum-maximum) for non-normally distributed data. Categorical variables were summarized as frequencies (percentages). Normality was tested using the Kolmogorov-Smirnov test.

Predictors of radiologic tumor response were analyzed using binary logistic regression, while factors associated with OS were evaluated using Cox proportional hazards regression. Initially, univariate analyses were performed for binary logistic regression and Cox regression. For clinical interpretation, optimal cut-off values of significant continuous variables were determined based on the maximum Youden's index. Variables with p<0.10 in univariate analyses were considered for inclusion in multivariate models. To avoid multicollinearity, pairwise correlations between variables were assessed using Spearman's correlation test. When a strong correlation was observed (r>0.7), the variable with the highest area under the curve (AUC) on receiver operating characteristic (ROC) analysis was selected for inclusion in the multivariate model using backward elimination. In addition, Kaplan-Meier survival curves were generated, and group differences were assessed using the log-rank test.

Binary logistic regression analyses were performed on treatments for which radiological response assessment was available within 1-3 months after ^{90}Y SIRT. Patients who died before the first radiological response assessment and patients whose first response assessment was performed between 3 and 6 months after ^{90}Y SIRT were excluded from the binary logistic regression analysis but remained included in the OS analyses.

Ethical Statement

This study was approved by the Institutional Ethics Board of Hacettepe University Faculty of Medicine (approval number: 2021/10-11, date: 04.05.2021).

Results

Patient Population and Treatment Characteristics

Between 2008 and 2018, ^{90}Y SIRT was performed in 103 HCC patients. Twenty-four patients were excluded from the final analysis due to insufficient clinical or laboratory data (n=2), lack of radiological response assessment (n=21), or cardiac arrest on the day of treatment (n=1). The final cohort, therefore, comprised 79 patients, representing a total of 100 ^{90}Y SIRT procedures. After excluding procedures with insufficient data, 94 treatments were eligible for analysis (Figure 1).

Comparison of available baseline characteristics between included and excluded patients revealed no significant differences in age, BCLC stage, Child-Pugh class, extrahepatic metastasis, ALBI score, albumin, bilirubin, ALT, AST, or INR (Supplementary Table 1).

The mean age at the time of the first ^{90}Y SIRT was 63 years, and 85% of the patients were male. Baseline demographic, disease, and treatment characteristics are summarized in Table 1. Hepatitis B virus was the most common etiology. According to the BCLC staging system, most patients were classified as stage B, and the majority had compensated liver disease, as reflected by Child-Pugh class A and a

Table 1. Demographics, disease and treatment characteristics

Variables	n*	
Age at first ^{90}Y SIRT, mean ± SD	79	63.1±9.2 years
Male, n (%)	79	67 (84.8)
Cirrhosis, n (%)	79	50 (63.3)
HCC etiology, n (%)	79	
Hepatitis B		33 (41.8)
Hepatitis C		10 (12.7)
Alcohol		4 (5.1)
Alcohol + viral hepatitis		4 (5.1)
NASH		2 (2.5)
Cryptogenic		23 (29.1)
Other¶		3 (3.9)
BCLC stage, n (%)	79	
B		43 (54.4)
C		36 (45.6)
Child-pugh score, n (%)	73	
A		63 (79.7)
B		10 (12.7)
Bilobar disease, n (%)	79	44 (55.7)
Portal vein invasion, n (%)	79	31 (39.2)
Ascites, n (%)	79	8 (10.1)
Extrahepatic metastasis, n (%)	79	15 (19)
Target lesion size, median (min-max)	94	6.5 (0.5-17) cm

Table 1. Continued

Variables	n*	
Number of hepatic lesions, n (%)	94	
<5		36 (38.3)
5-9		29 (30.9)
≥10		29 (30.9)
Laboratory values, median (min-max)		
Alpha-fetoprotein	69	235.8 (2.4-229006.4) ng/mL
Albumin, mean ± SD	94	3.7±0.5 g/dL
Total bilirubin	94	0.8 (0.3-2.4) mg/dL
ALT	94	32 (8-260) U/L
AST	94	43.5 (13-248) U/L
ALP	94	159 (60-1018) U/L
GGT	94	141.5 (14-876) U/L
Creatinine	93ɤ	0.7 (0.4-1.5) mg/dL
INR	81	1.1 (0.8-1.5)
Hemoglobin	94	13.2 (8.5-18) g/dL
Platelet	94	176.5 (30-748) x10^3/µL
Liver function, fibrosis and systemic inflammation indices, median (min-max)		
MELD score	81	8 (6-23)
ALBI score, mean ± SD	94	-2.36±0.49
APRI	94	0.81 (0.12-7.49)
FIB-4	94	2.96 (0.43-13.60)
NLR	93	3.42 (1.10-22.75)
Previous treatments, n (%)	79	
None		34 (43)
TACE		12 (15.2)
Chemotherapy		8 (10.1)
Resection		4 (5.1)
RFA		3 (3.8)
TACE + chemotherapy		7 (8.9)
TACE + RFA		2 (2.5)
Resection + chemotherapy		2 (2.5)
Resection + RFA		1 (1.3)
Resection + TACE + chemotherapy		3 (3.8)
Resection + RFA + chemotherapy		3 (3.8)
Time from HCC diagnosis to ^{90}Y		4.43 (0.95-105.36) months

Table 1. Continued

Variables	n*	
Number of ^{90}Y SIRT, n (%)		
1		60 (75.9)
2		18 (22.8)
4		1 (1.3)
Type of microsphere, n (%)	94	
Glass		55 (58.5)
Resin		39 (41.5)
Route of treatment, n (%)	94	
Right lobe		57 (60.6)
Left lobe		27 (28.7)
Bilobar		5 (5.3)
Right lobe + segment IV		5 (5.3)
Administered activity, median (min-max)		
Right lobe	53	1.75 (0.53-7.28) GBq
Left lobe	23	1 (0.45-2.97) GBq
Bilobar	5	3.41 (1.73-3.95) GBq
Right lobe + segment IV	4	1.24 (0.90-4.05) GBq

*Size and number of hepatic lesions, laboratory values, indices of liver function, fibrosis and systemic inflammation, and ^{90}Y SIRT-related variables are presented on a per-treatment basis, as these parameters could vary between sequential/repetitive ^{90}Y SIRT sessions in the same patient. ¶, "other" includes autoimmune hepatitis, Wilson disease, and Wilson disease combined with hepatitis B. ɤ, A patient undergoing chronic dialysis with a high serum creatinine level (6.7 mg/dL) was not included. HCC: Hepatocellular carcinoma, ^{90}Y SIRT: Yttrium-90 selective internal radiation therapy, NASH: Non-alcoholic steatohepatitis, BCLC: Barcelona Clinic Liver Cancer, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, MELD: Model for end-stage liver disease, ALBI: Albumin-bilirubin, APRI: AST-to-platelet ratio index, FIB-4: Fibrosis-4 index, NLR: Neutrophil-to-lymphocyte ratio, TACE: Transarterial chemoembolization, RFA: Radiofrequency ablation, SD: Standard deviation

median MELD score of 8. Regarding ALBI grading, 52 patients (66%) were classified as ALBI grade 2, 26 patients (33%) were classified as ALBI grade 1, and one patient (1%) was classified as ALBI grade 3.

At baseline, 44 patients had bilobar disease, 31 had portal vein invasion, 15 had extrahepatic metastases, and 8 had mild ascites.

Overall, 45 of 79 patients (57%) received at least one HCC-directed therapy before ^{90}Y SIRT, whereas ^{90}Y SIRT was the first treatment modality for 34 patients (43%). Most patients (n=60, 76%) underwent a single ^{90}Y SIRT session. Among the 94 analyzed treatments, 55 (58%) were performed using glass microspheres. Among patients with bilobar disease, 19 underwent ^{90}Y SIRT to both lobes, either in a single session or in staged procedures.

Treatment Response Assessment

Radiological treatment response was evaluable in 61 of the 79 patients within 1-3 months after ^{90}Y SIRT. Based on per-patient analysis, 24 patients were classified as responders and 37 as non-responders, including 12 with stable disease. On a per-treatment basis, local radiological response was observed in 34 treatments, whereas 36 were classified as non-responders, including 19 that resulted in stable disease.

In 10 patients, radiological response assessments were performed between 3 and 6 months after ^{90}Y SIRT. Among these patients, 2 were classified as responders and 8 as non-responders, including 3 with stable disease.

Eight patients died within 3 months after ^{90}Y, before radiological response assessment could be performed.

Treatment Response Predictors

To evaluate the biological conditions at the time of ^{90}Y administration, tumor- and laboratory-related predictors of local radiological response, assessed at 1-3 months, were analyzed on a per-treatment basis.

In univariate binary logistic regression analyses, demographic and clinical variables were not significantly associated with radiological treatment response (Table 2). Among tumor-related variables, target lesion size was significantly associated with treatment response. Treatments targeting lesions larger than 9 cm were associated with a significantly higher likelihood of non-response compared with those targeting lesions ≤9 cm (OR=3.75, p=0.039).

With respect to laboratory parameters, elevated cholestatic enzymes were associated with an unfavorable tumor response. Higher ALP (>138 IU/L) and GGT (>95 IU/L) levels were significantly associated with non-response (OR=2.88, p=0.035, and OR=3.95, p=0.015, respectively).

Among indices reflecting liver function, fibrosis, and systemic inflammation, lower APRI levels (≤0.338) were associated with a six times higher probability of achieving radiological response compared to higher APRI levels

Table 2. Results of univariate and multivariate binary logistic regression analyses for treatment response

Variables	Categories or cut-offs	OR	%95 CI	p
Univariate				
Age (years)	Per unit	0.983	0.933-1.036	0.527
Gender	Female vs. male	0.524	0.131-2.088	0.359
Cirrhosis	Absence vs. presence	0.522	0.178-1.528	0.235
Etiology	Viral vs. other etiologies	0.812	0.285-2.312	0.696
BCLC	B vs. C	2.091	0.792-5.522	0.137
Child-pugh	A vs. B	2.001	0.339-11.817	0.444
Number of lesions	<5 vs. ≥5	0.987	0.384-2.535	0.978
Size of lesions (cm)	≤9 vs. >9	3.750	1.072-13.121	**0.039***
Portal vein invasion	Absence vs. presence	1.920	0.715-5.157	0.196
Ascites	Absence vs. presence	1.941	0.168-22.445	0.595
Laboratory values				
Alpha-fetoprotein	Per 100-unit	0.999	0.996-1.002	0.618
Albumin	Per unit	0.678	0.261-1.762	0.425
Total bilirubin	Per unit	0.802	0.294-2.189	0.667
ALT	Per 10-unit	1.054	0.928-1.197	0.416
AST	Per 10-unit	1.060	0.948-1.186	0.307
ALP	Per 10-unit	1.055	0.994-1.120	0.076
ALP	≤138 vs. >138	2.879	1.080-7.673	**0.035***
GGT	Per 10-unit	1.026	0.995-1.059	0.103
GGT	≤95 vs. >95	3.947	1.304-11.948	**0.015***
Haemoglobin	Per unit	1.007	0.780-1.298	0.960
Platelet	Per unit	0.998	0.994-1.003	0.466

Table 2. Continued

Variables	Categories or Cut-offs	OR	%95 CI	p
Liver function, fibrosis, systemic inflammation indices				
MELD	Per unit	0.827	0.619-1.104	0.198
MELD	≤7 vs. >7	1.067	0.384-2.965	0.902
ALBI	Per unit	1.319	0.497-3.501	0.578
ALBI	≤-2.231 vs. >-2.231	1.640	0.628-4.287	0.313
APRI	Per unit	1.465	0.849-2.526	0.170
APRI	≤0.338 vs. >0.338	6.120	1.215-30.828	**0.028***
FIB-4	Per unit	1.117	0.937-1.333	0.217
FIB-4	≤1.908 vs. >1.908	2.900	0.993-8.466	0.051*
NLR	Per unit	0.987	0.858-1.137	0.861
NLR	≤3.568 vs. >3.568	2.614	0.987-6.921	0.053*
Type of radiomicrosphere	Resin vs. glass	1.100	0.423-2.864	0.845
Administered activity (GBq)	Per unit	0.961	0.605-1.527	0.866
Multivariate (backward elimination)				
APRI	≤0.338 vs. >0.338	7.759	1.322-45.542	**0.023**
Size of lesions	≤9 vs. >9 cm	4.877	1.225-19.423	**0.025**
NLR	≤3.568 vs. >3.568	3.533	1.181-10.573	**0.024**

Values shown in bold represent statistically significant results. "*" indicates variables entered into the multivariable model. Cut-off values were determined using the maximum Youden's index. Odds ratios represent the likelihood of radiological non-response. BCLC: Barcelona Clinic Liver Cancer, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, MELD: Model for end-stage liver disease, ALBI: Albumin-bilirubin, APRI: AST-to-platelet ratio index, FIB-4: Fibrosis-4 index, NLR: Neutrophil-to-lymphocyte ratio, OR: Odds ratio, CI: Confidence interval

(p=0.028). Higher FIB-4 (>1.908) and NLR (>3.568) values were also associated with a trend toward non-response (OR=2.90, p=0.051; OR=2.61, p=0.053, respectively).

Variables with p<0.10 in univariate analyses were entered into a multivariate model using backward elimination. In the final model, APRI, target lesion size, and NLR remained independent predictors of radiological treatment response (Table 2).

OS

At the time of analysis, survival status was available for 77 of the 79 patients, 74 of whom had died. The median OS was 11.2 months (95% CI, 7.3-15.1), with estimated 1-, 3-, and 5-year survival rates of 46%, 19%, and 5%, respectively. Median OS was comparable between the analyzed cohort and patients excluded from the study cohort (11.2 vs. 11.8 months, p=0.07).

Kaplan-Meier Analyses

Kaplan-Meier survival analyses identified several variables that were significantly associated with OS (Figure 2). Patients with advanced disease and impaired liver function had markedly shorter survival. Specifically, patients with BCLC stage C had significantly worse OS than patients with stage B [5.8 months (95% CI, 2.3-9.4) vs. 17.9 months (95% CI: 8.5-27.4), p<0.001; Figure 2a]. Similarly, Child-Pugh class B was associated with substantially reduced survival compared with class A [3.1 months (95% CI: 0.7-5.5) vs. 11.5 months (95% CI: 5.8-17.2), p=0.001; Figure 2b].

The larger target lesion size, presence of portal vein invasion, ascites and extrahepatic metastasis was also associated with significantly shorter OS [>9 cm vs. ≤9 cm: 5.3 months (95% CI: 1.7-8.7) vs. 16.4 months (95% CI: 12.2-20.6), p=0.001; portal vein invasion: 5.5 months (95% CI: 4.4-6.7) vs. 15.1 months (95% CI: 9.1-21.1), p=0.001; ascites: 3.1 months (95% CI: 0.001-8.826) vs. 13.5 months (95% CI: 8.2-18.9), p=0.003; extrahepatic metastasis: 8.3 months (95% CI: 2.8-13.8) vs. 14.8 months (95% CI: 7.6-21.9), p=0.001; Figure 2c-f].

A stepwise deterioration in OS with worsening ALBI grade was observed (p<0.001; Figure 2g). Patients with ALBI grade 1 had the most favorable survival outcomes, with a median OS of 28.2 months (95% CI, 14.9-41.4). In contrast, patients with ALBI grade 2 exhibited significantly shorter survival, with a median OS of 7.9 months (95% CI: 5.7-10.2). Only one patient was classified as ALBI grade 3, with an observed OS of 2.3 months.

Among prior treatments, resection, either as a standalone or in combination with other treatments, was associated with longer survival [37.3 months (95% CI: 23.1-51.5) vs. 9.1 months (95% CI: 6.8-11.3), p<0.001; Figure 2h]. However, OS did not differ significantly between patients who received ^{90}Y SIRT as first-line therapy and those who had undergone prior treatment [9.4 months (95% CI: 7.2-11.6) vs. 11.5 months (95% CI: 5.2-17.8), p=0.165]. Likewise, the number of lesions [<5 vs. ≥5: 10.1 months (95% CI: 4.3-15.9) vs. 11.3 months (95% CI: 2.2-20.5), p=0.108], lesion distribution [unilobar vs. bilobar: 13.9 months (95% CI: 7.4-20.4) vs. 9.7 months (95% CI: 5.8-13.6), p=0.460] and radiomicrosphere type [resin vs. glass: 14.7 months (95% CI: 5.6-23.9) vs. 10.1 months (95% CI: 6.9-13.3), p=0.772] were not significantly associated with OS.

Cox Regression Analyses

To identify independent predictors of OS, univariate and multivariate Cox regression analyses were performed. In univariate analyses, several clinical, tumor-related, and laboratory-related parameters were significantly associated with prognosis (Table 3). Advanced disease stage was strongly predictive of worse survival, with BCLC stage C showing a more than twofold increased risk of death compared with stage B (HR=2.47, p<0.001). Similarly, impaired liver function was associated with poor outcomes, as patients with Child-Pugh class B had a significantly higher mortality risk than those with Child-Pugh class A (HR=3.01, p=0.002).

Tumor-related features, including larger tumor size (HR=1.07 per unit increase, p=0.010), portal vein invasion (HR=2.16, p=0.002), ascites (HR=2.96, p=0.005), and extrahepatic metastasis (HR=2.57, p=0.002), were also significantly associated with reduced OS. In contrast, lesion number and distribution (lobar vs. bilobar) were not significantly associated with survival in this cohort.

Among baseline laboratory parameters, higher serum albumin levels were strongly protective, whereas higher total bilirubin and liver enzyme levels [(AST, ALT, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT)] were associated with increased mortality. AFP showed a modest but significant association with survival (Table 3).

Indices reflecting liver function, fibrosis, and systemic inflammation demonstrated strong prognostic value. Higher MELD (HR=1.50, p=0.002), ALBI (HR=5.05, p<0.001), APRI (HR=1.32, p=0.001), and FIB-4 scores (HR=1.11, p=0.002)

Table 3. Results of univariate and multivariate Cox regression analyses for overall survival

Variables	Categories or Cut-offs	HR	%95 CI	p
Univariate				
Age (years)	Per unit	1.011	0.986-1.037	0.384
Gender	Female vs. male	1.197	0.629-2.278	0.583
Cirrhosis	Absence vs. presence	1.301	0.809-2.091	0.278
Etiology	Viral vs. other	0.915	0.576-1.453	0.706
BCLC	B vs. C	2.470	1.526-3.996	**<0.001***
Child-Pugh	A vs. B	3.010	1.501-6.038	**0.002***
Number of lesions	<5 vs. ≥5	0.679	0.423-1.092	0.111
Location of lesions	Lobar vs. bilobar	1.189	0.751-1.882	0.462
Size of lesions (cm)	Per unit	1.077	1.018-1.139	**0.010***
Size of lesions (cm)	≤9 vs. >9	2.285	1.368-3.814	**0.002**
Portal vein invasion	Absence vs. presence	2.169	1.341-3.509	**0.002**
Ascites	Absence vs. presence	2.960	1.382-6.341	**0.005***
Extrahepatic metastasis	Absence vs. presence	2.570	1.409-4.688	**0.002***
Baseline laboratory values				
Alpha-fetoprotein	Per 100-unit	1.001	1.000-1.002	**0.011***
Albumin	Per unit	0.251	0.154-0.408	**<0.001**
Total bilirubin	Per unit	2.108	1.291-3.442	**0.003***
Alanine aminotransferase	Per 10-unit	1.072	1.009-1.140	**0.024**

Table 3. Continued				
Variables	**Categories or Cut-offs**	**HR**	**%95 CI**	**p**
Aspartate aminotransferase	Per 10-unit	1.120	1.070-1.173	**<0.001***
Alkaline phosphatase	Per 10-unit	1.040	1.025-1.055	**<0.001**
GGT	Per 10-unit	1.028	1.015-1.041	**<0.001***
Haemoglobin	Per unit	0.934	0.819-1.064	0.305
Platelet	Per unit	0.999	0.997-1.001	0.373
Liver function, fibrosis, systemic inflammation indices				
MELD score	Per unit	1.150	1.052-1.257	**0.002***
ALBI score	Per unit	5.057	2.927-8.738	**<0.001***
APRI	Per unit	1.322	1.113-1.571	**0.001**
FIB-4	Per unit	1.116	1.042-1.194	**0.002***
NLR	Per unit	1.062	0.993-1.137	0.079*
Previous treatments				0.082*
No prior treatment (reference)				
Radiofrequency ablation		0.178	0.024 -1.321	0.091
Resection		0.364	0.126-1.051	0.062
TACE		1.055	0.530-2.101	0.879
Chemotherapy		1.565	0.714-3.433	0.263
Combined		0.645	0.357-1.165	0.146
Type of radiomicrosphere	Resin vs. glass	1.069	0.699-1.634	0.759
Administered activity (GBq)		1.034	0.851-1.256	0.740
Multivariate (backward elimination)				
ALBI score	Per unit	3.733	1.842-7.565	**<0.001**
Extrahepatic metastasis	Absence vs. presence	3.276	1.584-6.776	**0.001**
GGT	Per-10 unit	1.037	1.015-1.059	**0.001**

Bold values represent statistically significant results. "*" indicates variables entered into the multivariable model. BCLC: Barcelona Clinic Liver Cancer, GGT: Gamma-glutamyl transferase, MELD: Model for end-stage liver disease, ALBI: Albumin-bilirubin, APRI: AST-to-platelet ratio index, FIB-4: Fibrosis-4 index, NLR: Neutrophil-to-lymphocyte ratio, TACE: Transarterial chemoembolization, HR: Hazard ratio, CI: Confidence interval

were significantly associated with poorer OS; NLR showed a borderline association (p=0.079).

Neither the type of microsphere used (resin vs. glass) nor the administered activity was significantly associated with OS.

Variables with p<0.10 in univariate analyses were further assessed for multicollinearity prior to inclusion in the multivariate Cox regression model. Strong correlations (r>0.70) were observed between the following variable pairs: BCLC stage and portal vein invasion; serum albumin and ALBI score; ALT and AST; AST and APRI; ALP and GGT; and APRI and FIB-4. To minimize collinearity, variables with higher AUC values in ROC analysis were selected for multivariate modeling. Accordingly, BCLC stage, ALBI score, AST, GGT, and FIB-4 were entered into the multivariate analysis together with other eligible variables.

Using backward elimination, the ALBI score, extrahepatic metastasis, and GGT remained independent predictors of OS. This finding was consistent in both the model including AFP (n=56) and in the model excluding AFP (n=67).

ALBI-GGT Risk-stratification

To further explore the combined prognostic impact of ALBI grade and GGT level, a composite risk-stratification model was constructed. Patients were categorized into four groups: group I, defined as patients with ALBI grade 1 and GGT ≤52 IU/L (n=8); group II, comprising patients with ALBI grade 1 and GGT >52 IU/L (n=18); group III, consisting of patients with ALBI grade 2-3 and GGT ≤52 IU/L (n=4); and group IV, including patients with ALBI grade 2-3 and GGT >52 IU/L (n=47). Median OS decreased stepwise across groups, with median values of 41.3 months (95%

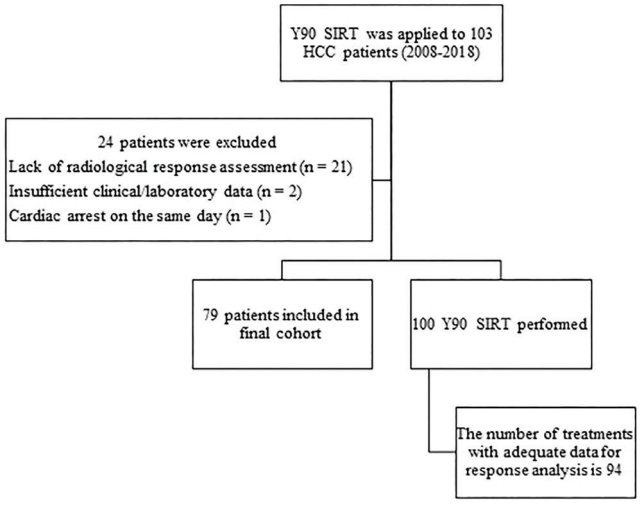


Figure 1. Flow diagram illustrating patient exclusion, final cohort formation, and treatment-level eligibility for response analysis
^{90}Y SIRT: Yttrium-90 selective internal radiation therapy, HCC: Hepatocellular carcinoma

CI: 6.5-76.2) in group I, 23.2 months (95% CI: 0-49.2) in group II, 13.9 months (95% CI: 0-50.8) in group III, and 7.8 months (95% CI: 5.7-9.9) in group IV (log-rank p<0.001; Figure 2i). Pairwise comparisons demonstrated that among patients with ALBI grade 1, those with lower GGT levels had significantly better median survival (group I vs. group II; p=0.014). Similarly, among those with ALBI grade 2-3, lower GGT levels were associated with longer survival (group III vs. IV; p=0.037).

To quantify the magnitude of risk associated with this stratification, univariate Cox regression analysis was performed using group I as the reference category. Patients in group II had a significantly higher risk of mortality (HR=3.19, 95% CI: 1.15-8.80, p=0.026). In contrast, patients in group III did not demonstrate a statistically significant increase in risk (HR=1.46, 95% CI: 0.36-5.85, p=0.596). Group IV exhibited the highest mortality, with an eightfold increased risk of death (HR=8.07, 95% CI: 2.99-21.77; p<0.001).

Discussion

Predictors of Radiological Treatment Response

In the present study, APRI, target lesion size (>9 cm), and NLR emerged as independent predictors of radiological treatment response following ^{90}Y SIRT. APRI, a composite index derived from AST levels and platelet count, serves as a marker of hepatic fibrosis and portal hypertension (24). Patients with lower APRI values (≤0.338) demonstrated a significantly higher likelihood of treatment response, suggesting that preserved hepatic microarchitecture and lower fibrotic burden may facilitate more homogeneous microsphere distribution and effective radiation delivery.

NLR, which has been associated with survival outcomes across multiple malignancies (25), is thought to reflect the balance between a pro-tumoral inflammatory state and the anti-tumoral immune response (26). The existence of pro-tumoral tumor-associated neutrophils is regulated by molecules within the tumor microenvironment and this neutrophil type can promote pro-tumor microenvironment by secreting angiogenic factors (27), while low levels of circulating lymphocyte levels may indicate decreased tumor-infiltrating lymphocytes and impaired anti-tumor immunity (28). Consequently, elevated NLR values, considered a biomarker of an immunosuppressive tumor microenvironment, may contribute to treatment resistance, thereby explaining the higher likelihood of non-response observed in patients with NLR >3.568.

The number of studies investigating the role of hepatic fibrosis and systemic inflammatory parameters in predicting radiological response after ^{90}Y SIRT is limited. In a recent study (11), APRI did not reach statistical significance in predicting treatment response; however, the authors attributed this finding primarily to a small sample size (n=35). In the same study, NLR was significantly associated with treatment response in univariate analysis but demonstrated only a trend toward significance in the multivariate model. In another study including 86 HCC patients identified elevated NLR (>3) as the strongest predictor of progressive disease following intra-arterial therapies, including radioembolization and chemoembolization (12). Further studies with larger cohorts are warranted to validate these results and clarify the potential relevance of APRI and NLR as predictors of treatment response following ^{90}Y SIRT.

Although a recently published study demonstrated higher rate of complete radiological response in patients receiving higher doses (29), precise tumor-absorbed dose calculations were not feasible in our cohort. Nevertheless, our findings suggest that underlying liver parenchymal status and host inflammatory milieu may also play a role in treatment efficacy.

Prognostic Factors of OS

We examined the effects of various baseline factors on survival. In the multivariable model, ALBI score, presence of extrahepatic metastasis, and GGT level emerged as independent predictors of OS.

Our study is not the first to demonstrate the prognostic utility of the ALBI score in patients undergoing ^{90}Y SIRT. In line with prior publications (6,9,13,30,31), our findings support ALBI

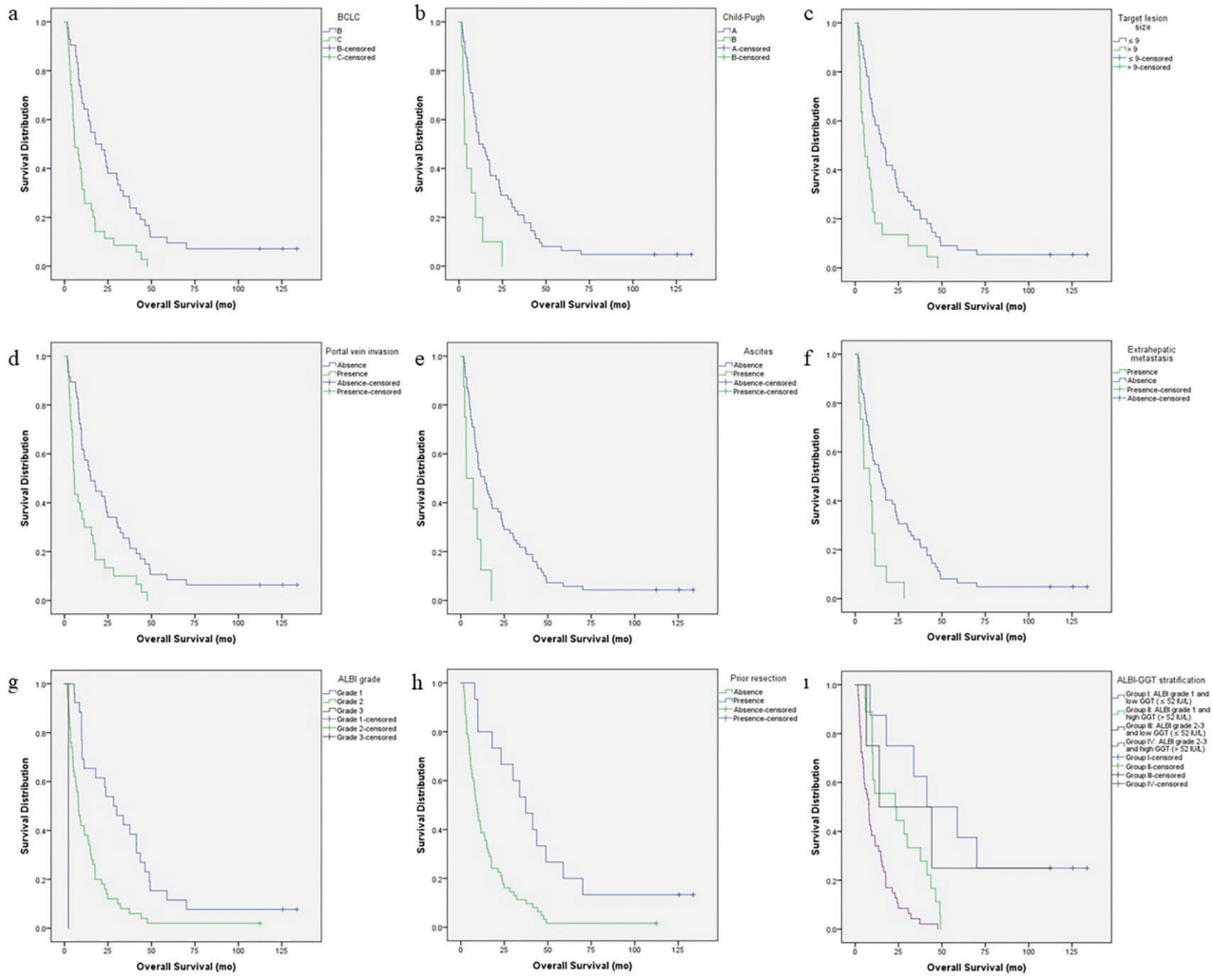


Figure 2 (a-i). Kaplan-Meier curves illustrating the association between clinical and tumor-related parameters and overall survival (OS) in HCC patients. (a) Patients with BCLC stage C had significantly worse OS compared with those with stage B (estimated 3-year OS: 8% vs. 28%, p<0.001). (b) Child-Pugh class B was associated with reduced survival compared with class A (estimated 3-year OS: 0% vs. 21%, p=0.001). (c) Larger target lesion size (estimated 3-year OS: 9% vs. 23%, p=0.001), (d) presence of portal vein invasion (estimated 3-year OS: 10% vs. 25%, p=0.001), (e) ascites (estimated 3-year OS: 0% vs. 22%, p=0.003), and (f) extrahepatic metastasis (estimated 3-year OS: 0% vs. 24%, p=0.001) were associated with significantly worse OS. (g) OS deteriorated in a stepwise manner with worsening ALBI grade (estimated 3-year OS: 42% vs. 8% vs. 0%, p<0.001). (h) Prior resection was associated with longer survival (estimated 3-year OS: 53% vs. 11%, p<0.001). (i) OS curves for risk groups I-IV defined by ALBI grade and GGT level: 3-year OS rates for groups I-IV were 63%, 33%, 50%, and 4%, respectively

HCC: Hepatocellular carcinoma, BCLC: Barcelona Clinic Liver Cancer, ALBI: Albumin-bilirubin, GGT: Gamma-glutamyl transferase

as a robust marker of hepatic reserve and OS and indicate that it may offer superior prognostic discrimination. Gui et al. (30) reported significantly longer survival in patients with ALBI grade 1 compared those with ALBI grade 2, while failing to demonstrate a significant survival difference between Child-Pugh class A and B patient. Mohammadi et al. (31) further supported the superior sensitivity of the ALBI score, concluding that ALBI outperformed the Child-Pugh classification, particularly in mild liver impairment. Antkowiak et al. (6) also demonstrated that ALBI was a stronger predictor of survival than Child-Pugh class in HCC patients treated with ^{90}Y SIRT. Likewise, other retrospective HCC series undergoing ^{90}Y SIRT identified ALBI as an independent prognostic factor for survival in multivariate analyses (9,13). Taken together, these findings, along with our results, underscore the prognostic value of the ALBI score and the importance of preserved hepatic reserve in determining survival outcomes.

The presence of extrahepatic metastasis reflects advanced systemic tumor dissemination. Its independent association with survival emphasizes that beyond intrahepatic disease control, systemic tumor burden remains a critical determinant of prognosis. Consistent with our findings, it has been previously mentioned that extrahepatic disease is a significant predictor of survival in patients undergoing ^{90}Y SIRT (32).

GGT has traditionally been used as a serological marker for alcohol-related liver disease and hepatobiliary disorders (33). More recent evidence suggests that the enzymatic activity of GGT contributes to the generation of reactive oxygen species, thereby promoting oxidative stress (34). In this context, the implication of GGT in the pathogenesis of several diseases, including cardiovascular disorders, malignancies, pulmonary inflammation, and neurological diseases, is being researched (35). In our study, elevated GGT levels were independently associated with worse OS. This observation suggests that GGT may reflect more than cholestasis alone and has led us to consider that it could act as a marker of oxidative stress, unfavorable tumor biology, or a permissive microenvironment for tumor progression.

Further stratification combining ALBI grade and GGT level suggested that these two markers may provide complementary prognostic information for OS. Among patients with preserved hepatic reserve (ALBI grade 1), those with higher GGT levels had significantly shorter median survival. Similarly, among patients with impaired hepatic reserve (ALBI grade 2-3), lower GGT levels were associated with improved OS. Notably, patients with ALBI grades 2-3 but low GGT levels did not have a significantly increased risk compared with patients with ALBI grade 1 and similarly low GGT levels, despite their reduced hepatic reserve. This finding suggests that low GGT levels may partially mitigate the adverse prognostic impact of impaired liver function. However, given the small number of patients within these subgroups, these results should be interpreted as hypothesis-generating.

Tumor Burden, Prior Treatments and Technical Factors

Several independent prognostic factors for OS have been reported in previous studies, including tumor size, number of nodules (>5), bilobar involvement, presence of ascites, portal vein thrombosis, serum AFP levels, and partition model-based dosimetry (7,8,9,10,32).

In our cohort, tumor burden-related variables, including size, presence of ascites, portal vein invasion, and elevated serum AFP levels, were significantly associated with OS in univariate analyses. However, these associations did not remain statistically significant in the multivariate model. The number of hepatic lesions was not significantly associated with OS in our study. A similar finding has been reported previously (7), where the authors suggested that because ^{90}Y SIRT is typically delivered at the lobar level, the number of tumor nodules within the treated lobe may be less relevant for survival outcomes. Although a non-significant trend toward worse survival was observed in patients with fewer lesions, which may appear contradictory, this finding can be explained by the presence of dominant, large, or infiltrative tumors in patients with a limited number of lesions. In the setting of ^{90}Y SIRT, tumor size and vascular characteristics may play a more critical role than lesion count, as bulky disease can impair homogeneous microsphere distribution and effective radiation delivery. Consistent with the overall influence of tumor burden, patients with bilobar disease had a shorter median OS compared with those with unilobar involvement (9.7 vs. 13.9 months), although this difference did not reach statistical significance.

In the current study, OS did not differ significantly between patients who underwent any prior treatment and those who received ^{90}Y SIRT as first-line therapy, consistent with prior studies (9,36). Notably, a separate analysis of prior treatment modalities revealed that patients who had undergone surgical resection experienced longer survival.

Finally, our institution has the opportunity to obtain resin and glass microspheres, allowing a comparison. No significant association was found between the type of microsphere used (resin vs. glass) and OS. Consistent with our result, a single-center study comparing both microspheres (n; resin=41, glass=36) in HCC patients using partition model-based dosimetry demonstrated no survival difference between the groups (37).

Study Limitations

The retrospective and single-center design represents an inherent limitation of this study. Although comparison of available baseline characteristics and OS between included and excluded patients did not reveal significant differences, excluding patients without evaluable radiological follow-up may nevertheless have introduced selection bias. In addition, the retrospective design may have resulted in unmeasured confounding factors. Most notably, data on post-treatment systemic and locoregional therapies were incomplete for a subset of patients, which may have influenced survival outcomes. Another important limitation was the lack of detailed dosimetric data, precluding an assessment of dose-outcome relationships. Without dosimetry, predictors may represent residual confounding. Furthermore, longitudinal imaging follow-up after the initial radiological response was not consistently available until death for all patients. Progression-free survival analyses could not be

performed to avoid underestimation of progression events. In addition, the proposed ALBI-GGT risk-stratification approach was not validated either internally or externally. Therefore, the model should be considered exploratory and hypothesis-generating until validated in future studies. Taken together, these limitations underscore the need for prospective studies that include standardized follow-up protocols, comprehensive treatment data, advanced dosimetric assessment, and validation of the proposed risk-stratification model.

Conclusion

Two important findings can be drawn from the present study. First, APRI and NLR may play a meaningful role in predicting radiological response to ^{90}Y SIRT, underscoring the influence of underlying hepatic fibrosis and systemic inflammation on treatment efficacy. Second, with respect to OS, ALBI score, extrahepatic metastasis, and GGT levels emerged as independent prognostic factors. The combined use of ALBI grade and GGT level may represent a risk-stratification approach for patients undergoing ^{90}Y SIRT and requires prospective validation.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Board of Hacettepe University Faculty of Medicine (approval number: 2021/10-11, date: 04.05.2021).

Informed Consent: This retrospective study at a single tertiary academic center included patients with unresectable HCC who underwent ^{90}Y SIRT at Hacettepe University between April 2008 and December 2018.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.E., F.Ç., Ş.Y., B.P., Ö.U., B.V.S., Concept: M.F.B., Ş.Y., B.P., Ö.U., B.V.S., Design: M.F.B., Ş.Y., B.P., Ö.U., B.V.S., Data Collection or Processing: B.S.T., G.E., F.Ç., Analysis or Interpretation: B.S.T., B.V.S., Literature Search: B.S.T., Writing: B.S.T., M.F.B., Ö.U., B.V.S.

Conflict of Interest: Murat Fani Bozkurt is the Editor-in-Chief of Molecular Imaging and Radionuclide Therapy. However, he was not involved in any stage of the editorial evaluation or decision-making process for this manuscript. The manuscript was evaluated by editors from institutions different from those of the authors. The remaining authors declared no conflicts of interest.

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Supplementary Table Link: https://d2v96fxpocvxx.cloudfront.net/beb8919b-f013-4ea1-b1c8-40332e840fe1/content-images/c849f06d-f0aa-475b-a334-b62b44e2c66e.pdf

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