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The Impact of Chemoembolization Endpoints on Survival in Hepatocellular Carcinoma Patients

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Abstract

OBJECTIVE—To investigate the relationship between angiographic embolic endpoints of transarterial chemoembolization (TACE) and survival in patients with hepatocellular carcinoma (HCC).

MATERIALS AND METHODS—This study retrospectively assessed 105 patients with surgically unresectable HCC who underwent TACE. Patients were classified according to a previously established subjective angiographic chemoembolization endpoint (SACE) scale. Only one patient was classified as SACE level 1 and thus excluded from all subsequent analysis. Survival was evaluated with Kaplan-Meier analysis. Multivariate analysis with Cox's proportional hazard regression model was used to determine independent prognostic risk factors of survival.

RESULTS—Overall median survival was 21.1 months (95% confidence interval [CI], 15.9–26.4). Patients embolized to SACE levels 2 and 3 were aggregated and had a significantly higher median survival (25.6 months; 95% CI, 16.2–35.0) than patients embolized to SACE level 4 (17.1 months; 95% CI, 13.3–20.9) ($p = 0.035$). Multivariate analysis indicated that SACE level 4 (Hazard ratio [HR], 2.49; 95% CI, 1.41–4.42; $p = 0.002$), European Cooperative Oncology Group performance status > 0 (HR, 1.97; 95% CI, 1.15–3.37; $p = 0.013$), American Joint Committee on Cancer stage 3 or 4 (HR, 2.42; 95% CI, 1.27–4.60; $p = 0.007$), and Child-Pugh class B (HR, 1.94; 95% CI, 1.09–3.46; $p = 0.025$) were all independent negative prognostic indicators of survival.

CONCLUSION—Embolization to an intermediate, sub-stasis endpoint (SACE levels 2 and 3) during TACE improves survival compared to embolization to a higher, stasis endpoint (SACE level 4). Interventional oncologists should consider targeting these intermediate, sub-stasis angiographic endpoints during TACE.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, and constitutes the 3rd leading cause of cancer death worldwide [1]. Surgical resection and liver transplantation represent potentially curative treatments [2,3]. Unfortunately 85% of HCC

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are diagnosed at advanced stages, beyond the criteria for surgical therapy [4]. For these patients, transarterial chemoembolization (TACE) has become an established treatment with demonstrated survival benefits over best supportive care [5].

The optimal embolic endpoint of TACE has not been elucidated [6], leading to significant variability in how the procedure is performed. During TACE, chemotherapy is initially injected via catheter using an oil-based emulsion, followed by embolization with polyvinyl alcohol (PVA), tris-acetyl gelatin microspheres, or gelatin sponge. The embolization has two aims: (a) to induce ischemic tumor necrosis by reducing blood flow to the targeted HCC, and (b) to increase dwell time of injected cytotoxic agents [7,8]. While under-embolization during TACE may inadequately treat the targeted tumor [9,10], over-embolization may increase liver toxicity [11] and expression of angiogenic growth factors [12–14]. The risk of accelerating liver failure may be even higher in Child-Pugh B/C patients due to their increased baseline liver dysfunction [15]. It is thus unknown if interventional oncologists should seek stasis to antegrade blood flow, or a lesser reduction in antegrade blood flow (i.e. sub-stasis), as their desired endpoint during TACE.

Digital subtraction angiography (DSA) is the primary method to guide TACE. A previously reported subjective angiographic chemoembolization endpoint (SACE) scale was developed in an effort to standardize the nomenclature of DSA endpoints of TACE [16]. The current study aims to determine the relationship of TACE endpoints with patient survival by classifying treated patients using this SACE scale. We hypothesized that an intermediate, sub-stasis embolization endpoint, associated with SACE levels 2 and 3, is associated with better patient survival than under- (SACE level 1) or over-embolization (SACE level 4). If so, then interventional oncologists could target these endpoints in future TACE procedures to improve clinical outcomes.

SUBJECTS AND METHODS

Clinical Setting and Patients

This retrospective study was approved by our local institutional review board, and complies with the Health Insurance Portability and Accountability Act. Between October 2000 and December 2008, we assessed 163 consecutive patients who underwent TACE at a single large university-affiliated hospital. These patients were considered unsuitable candidates for surgical resection or liver transplantation by an attending transplant surgeon because of: (a) concurrent comorbidities including cardiac or respiratory compromise, (b) recurrent or multilobar disease, (c) cirrhosis or portal hypertension, (d) vascular invasion, (e) high tumor burden, and/or (f) contraindications to general anesthesia. All TACE patients met the following inclusion criteria: (a) age > 18 years, (b) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , (c) Child-Pugh class A or B disease, (d) focal or multifocal HCC with measurable disease, and (e) informed consent. Patients were excluded from TACE if they had (a) life expectancy < 6 months, (b) ECOG performance status > 2, (c) Child-Pugh class C disease, (d) uncorrectable coagulopathy with an International Normalized Ratio > 1.5, (e) total bilirubin level > 4.0 mg/dL, (f) serum creatinine > 2.0 mg/dL, or (g) uncorrectable thrombocytopenia with a platelet count < 50,000/ μ L. Treatment for these patients was chosen at a weekly institutional multi-disciplinary liver tumor conference consisting of hepatologists, oncologists, transplant surgeons, and interventional oncologists. Patients were non-invasively diagnosed with HCC based on characteristic imaging findings and/or a rising alpha-feto-protein (AFP) level in the setting of cirrhosis [15]. Patients with equivocal imaging findings were diagnosed via image-guided percutaneous liver biopsy.

We excluded patients from this study if they (a) did not have pre-treatment diagnostic computed tomography (CT) or magnetic resonance (MR) imaging stored on an institutional

picture archive and communication system (PACS), (b) had inadequate procedural angiographic images stored on PACS, precluding our ability to assign a SACE level (inadequate images defined as ≤ 5 pre-TACE or post-TACE DSA images), or (c) did not have any follow up imaging. After incorporating exclusion criteria, 105 of the original 163 patients were included in this study.

Pre-Treatment Evaluation

All patients underwent a complete pre-treatment workup, including a clinical history, radiological imaging (contrast enhanced CT or MRI), serum AFP, and liver function tests. On the basis of pre-treatment workup, all patients were classified according to baseline ECOG performance status, as well as Child-Pugh, American Joint Committee on Cancer (AJCC), and Cancer of the Liver Italian Program (CLIP) staging systems [17,18].

Chemoembolization

TACE was performed using a standardized approach. Patients were prepared and draped in standard sterile fashion while supine. After arterial access was gained, a 5-F catheter (Simmons-1; Cook, Bloomington, Indiana) was used to perform initial mapping and visceral radiographic DSA. Typically, a 2-F microcatheter (Renegade Hi-Flo; Boston Scientific, Natick, Massachusetts) was advanced into either a lobar or segmental hepatic artery, depending on the location of the targeted tumor. DSA was performed with injection of iohexol (Omnipaque 300; Amersham Health, Princeton, New Jersey) using a power injector. Injection rates were typically 1–3 mL/s, with a total amount of 6–10 mL injected. These values were adjusted to best depict blood flow to the targeted tumor while minimizing reflux into non-target liver segments. All DSA images were recorded at a filming rate of 3 frames per second.

Following appropriate catheter placement, we injected 1–3 mL aliquots of a 1:1 mixture of iodized oil (Ethiodol; Savage Laboratories, Melville, New York) and a three-drug chemotherapy regimen. The chemotherapy regimen consisted of 100 mg of cisplatin, 30 mg of doxorubicin, and 30 mg of mitomycin-C. Chemotherapy infusion was continued until slowing of antegrade blood flow was visualized. TACE was completed by the infusion of either PVA particles (Contour; Boston Scientific, Natick, MA) or tris-acetyl gelatin microspheres (Embospheres; Biosphere Medical, Rockland, MA). One patient was treated with 150–250 μ m PVA particles, 2 patients were treated with 250–355 μ m PVA particles, 27 patients were treated with 355–500 μ m PVA particles, and 5 patients were treated with 500–710 μ m PVA particles. Twenty patients were treated with 300–500 μ m Embospheres, and 36 patients were treated with 500–700 μ m Embospheres. The specific embolization particle used for the remaining 14 patients is unknown or was unrecorded. At the discretion of the attending interventional oncologist, infusion of PVA particles or Embospheres was continued until a stasis or sub-stasis endpoint of antegrade blood flow was achieved. Following TACE, completion arteriography was performed via manual injection to minimize reflux into non-targeted areas.

Angiographic Embolic Endpoint

Selective angiographic images before and after TACE were recorded and stored in PACS. In batch fashion, three board certified interventional radiologists each independently reviewed these images. Together, these interventional radiologists have specialized in interventional oncology for an average of over 7 years. Each of these attending oncologists, blinded to the survival outcomes of the patients, classified the TACE endpoints according to the previously established SACE scale [16]. SACE levels range from 1 to 4, depending on the presence of residual antegrade blood flow and tumor blush on completion arteriography during TACE. Antegrade blood flow reaching the tumor on completion arteriography was compared to

antegrade blood flow reaching the tumor on pre-TACE angiography. This residual antegrade blood flow reaching the tumor was classified as either unchanged from pre-TACE imaging, reduced in intensity from pre-TACE imaging, or occluded proximal to the targeted tumor. Similarly, the presence of tumor blush on completion arteriography was compared to the tumor blush on pre-TACE angiography. The residual post-TACE tumor blush was classified as either unchanged from pre-TACE imaging, reduced in intensity or size from pre-TACE imaging, or completely eliminated. Table 1 demonstrates how a SACE score is derived based on the classification of these two considerations. In cases of multiple tumors, only the largest targeted tumor was considered when assigning a SACE rating. Each patient's final SACE classification was determined by that patient's majority SACE rating from the three radiologists. That is, a patient was assigned the specific SACE level that at least 2 of the 3 interventional oncologists assigned that patient.

Statistical Analysis

At the time of analysis, the survival status of all patients was obtained from hospital records as well as the Social Security Death Index, a national database of death records maintained by the United States Social Security Administration. Survival status was assessed on January 8, 2010, 12.3 months following the final TACE procedure. Baseline clinical information was compared between different SACE groups by using a one way analysis of variance (ANOVA) for continuous data, and chi-square (χ^2) analysis for ordinal data. Cumulative survival rates were expressed using Kaplan-Meier analysis. Differences in survival among groups were compared by using the log-rank test. Variables with $p < 0.10$ on univariate analysis were simultaneously entered into the multivariate analysis using the Cox proportional hazards model. Significance for all tests was determined at the $p < 0.05$ level. All computations were performed using a commercially available statistical software package (SPSS version 16.0, Chicago, Illinois).

RESULTS

SACE Level Groups

Only 1 patient, exhibiting negligible change between pre-TACE and post-TACE DSA, was assigned SACE level 1, and was therefore excluded from all further analysis. Figures 1–3 depict representative SACE level 2, 3, and 4 angiographic endpoints from our patient sample. Table 2 displays the baseline patient characteristics of patient groups, as defined by SACE levels. Baseline characteristics did not significantly differ between SACE level groups. In addition, SACE levels 2 and 3 were aggregated, and compared to SACE level 4 (Table 3). Characteristics of these groups also did not significantly differ.

Survival Rates by SACE Level

The mean follow-up period for the 105 patients was 25.4 months (range, 2–105 months). Of these, 64 patients reached a terminal event. Figure 4 displays the cumulative survival curve of all patients. Overall median survival was 21.1 months (95% confidence interval [CI], 15.9–26.4). The probabilities of survival at 1, 2, and 3 years were 77%, 46%, and 36%, respectively. Figure 5 compares the Kaplan-Meier survival curves of SACE levels 2, 3, and 4. Median survival was 24.2 months (95% CI, 10.8–37.6) for SACE level 2, 25.6 months (95% CI, 14.2–37.0) for SACE level 3, and 17.1 months (95% CI, 13.3–20.9) for SACE level 4 ($p = 0.081$). Compared to each other, SACE levels 2 and 3 were not associated with significantly different survival functions ($p = 0.955$). Although SACE level 2 was not associated with survival improvement over SACE level 4 ($p = 0.151$), SACE level 3 was associated with a significant survival benefit over SACE level 4 ($p = 0.046$). When patients classified as SACE level 2 and 3 were aggregated, and compared to patients classified as

SACE level 4, significant differences in survival rate were also identified ($p = 0.035$) (Figure 6).

Survival Rates Stratified by Child-Pugh Score

When stratified by Child-Pugh scores, differences in survival between different SACE levels became more significant. In this setting, when pooled over both Child-Pugh A and B disease, SACE levels 2, 3, and 4 were associated with significant differences in survival rate ($p = 0.030$). Differences in survival rate between these SACE levels were more apparent in Child-Pugh B patients ($p = 0.018$) than Child-Pugh A patients ($p = 0.518$). This trend was also seen when aggregating SACE level 2 with SACE level 3 (Table 3). SACE level 2/3 was associated with better survival than SACE level 4 when pooled over both Child-Pugh A and B disease ($p = 0.008$). However when analyzed over individual Child-Pugh scores, this survival advantage was only significant in Child-Pugh B patients ($p = 0.006$), and not in Child-Pugh A patients ($p = 0.372$).

Multivariate Analysis

Table 4 presents the univariate and multivariate analyses. Variables with $p < 0.10$ on univariate analysis were incorporated into the multivariate analysis, and included ECOG performance status, AJCC staging, Child-Pugh score, and SACE level. Multivariate analysis indicated the following individual negative prognostic factors for patient survival in our cohort of patients: ECOG performance status > 0 (Hazard ratio [HR], 1.97; 95% CI, 1.15–3.37; $p = 0.013$), AJCC stage > 2 (HR, 2.42; 95% CI, 1.27–4.60; $p = 0.007$), Child-Pugh score B (HR, 1.94; 95% CI, 1.09–3.46; $p = 0.025$), and SACE level 4 (HR, 2.49; 95% CI, 1.41–4.42; $p = 0.002$).

DISCUSSION

This study retrospectively analyzed a sample of 105 patients and assessed survival as a primary endpoint. Among this cohort, those treated to SACE level 2 or 3 (an intermediate level sub-stasis angiographic endpoint) demonstrated a significant survival advantage over patients treated to SACE level 4 (a high level stasis angiographic endpoint). This survival advantage was more pronounced in patients with Child-Pugh score B than Child-Pugh score A. In fact, the median survival of SACE level 2 or 3 patients was over twice as long as SACE level 4 patients among those with Child-Pugh B disease, suggesting that patients with worse underlying liver function may be at an increased risk from over-embolization. In addition, multivariate survival analysis demonstrated that reaching a SACE level 4 embolic endpoint was independent of all other baseline factors, including Child-Pugh score, as a negative prognostic indicator of survival.

Although TACE is an established treatment for unresectable HCC, significant variability exists in procedural protocol related to choice of chemotherapy, embolic agent, and endpoint. Because embolic endpoint is the most variable and subjective of these procedural choices, we think that it is the most important of these items to study. Additionally, previous research suggests that embolic endpoints may affect tumor response. For example, injection of embolic particles during TACE improves tumor response over chemotherapy infusion alone [10]. This finding suggests that inadequate embolization may lead to suboptimal patient outcomes. In contrast, induction of tumor hypoxia after TACE has been associated with increased expression of hypoxia inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF). The increased expression of these angiogenic proteins may in turn be associated with greater rates of local recurrence and reduced survival [12–14,19,20]. Therefore, over-embolization during TACE may inadvertently promote tumor progression or else accelerate liver failure by inducing ischemia of normal liver tissues. This ischemia

may be particularly adverse in the 80% [21] of patients with HCC who have underlying cirrhosis. An additional consideration is that excessive embolization during TACE may permanently occlude feeding vessels to the tumor, precluding the ability for future TACE procedures to be successfully performed. An inability to perform subsequent TACE procedures may in turn negatively impact survival. These important clinical issues motivated us to determine the ideal embolic endpoint during TACE.

Interventional oncologists rely on DSA to guide TACE, with C-arm angiographic CT and intraprocedural MR perfusion scans serving as accessory imaging tools in some instances [22–25]. The ubiquitous use of DSA to guide therapy was our rationale to investigate angiographic endpoints of embolization. To date, the SACE scale has been the only published angiographic endpoint scale used for TACE [16]. The SACE scale uses residual tumor blush and antegrade blood flow to the targeted tumor to rate DSA embolic endpoints of TACE on a 4-point scale. A SACE level of 1 represents a minimal or no changes to tumor blush and antegrade flow on DSA following TACE, and is most likely to be associated with under-embolization. A SACE level of 4, on the other hand, represents elimination of both tumor blush and antegrade blood flow. Because complete stasis of antegrade blood flow has also been achieved, SACE level 4 would be expected to maximize ischemic tissue hypoxia. Our findings in this study supported our hypothesis that SACE levels 2 and 3 – equivalent to intermediate levels of sub-stasis embolization – are associated with improved survival over SACE level 4.

This study used an intention to treat analysis and did not censor patients to transplantation. TACE has been reported as an established method of both bridging and down-staging HCC patients to transplantation [26]. Moreover, successful TACE treatment has also been reported with improved outcomes following transplantation [27,28]. Therefore survival results, even following transplantation, were considered to be outcomes affected by the TACE procedure.

Our study contained several limitations. First, it was a retrospective analysis of patient angiographic embolic endpoints and survival, rather than a randomized controlled trial. Second, the lack of patients classified as SACE level 1 precluded an analysis of outcomes related to potential under-embolization. Instead, our study was restricted to comparing intermediate with high levels of angiographic embolization. Third, we used all cause mortality in our survival analysis. This approach prohibited us from distinguishing between cancer progression, advanced liver failure, or other underlying mechanisms as the primary cause of death. Fourth, SACE levels were assigned to patients retrospectively based upon their DSA procedural images stored in PACS. Therefore patients with missing or incompletely archived images could not be assigned SACE levels and were excluded from our analysis. Fifth, all patients in this study were treated using either PVA or tris-acetyl gelatin microspheres as the embolic agent. Thus our results may not be generalizable to TACE protocols which employ gelatin sponge, or other embolic agents. Finally, classifying embolic endpoints based on DSA is intrinsically subjective. Overcoming this limitation of subjective SACE quantification will require developing objective approaches to quantifying perfusion reductions [25,29,30]. Determining the impact of these quantitative perfusion reductions on patient outcomes will be needed in order to validate our subjective angiographic findings.

In conclusion, our study investigated the potential relationship between angiographic embolic endpoints of TACE and overall survival as the primary clinical outcome. We found that embolizing to SACE level 4 was a significant independent prognostic factor for reduced patient survival. This result suggests that when performing TACE, rather than striving for complete stasis of antegrade blood flow (SACE level 4), interventional oncologists should

consider targeting an intermediate, sub-stasis embolization endpoint (SACE levels 2 or 3), especially in patients with underlying poor liver function. Future studies should aim to validate these results prospectively. They should also seek to develop more objective quantitative procedural endpoints that can be correlated with patient survival.

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Fig. 1. 58-year-old male with hepatocellular carcinoma treated with TACE to a SACE level 2 angiographic endpoint. **A**, DSA performed prior to injection of chemoembolic materials. **B**, Completion maximum enhancement DSA image obtained immediately following injection of chemoembolic materials. There is slight reduction of both antegrade blood flow (arrow) to the tumor as well as angiographic tumor blush (star) following TACE.

Fig. 2. 76-year-old female with hepatocellular carcinoma treated with TACE to a SACE level 3 angiographic endpoint. **A**, DSA performed prior to injection of chemoembolic materials. **B**, Completion maximum enhancement DSA image obtained immediately following injection of chemoembolic materials. There is reduction of antegrade blood flow to the tumor (arrow) as well as elimination of angiographic tumor blush (star) following TACE.

Fig. 3. 68-year-old male with hepatocellular carcinoma treated with TACE to a SACE level 4 angiographic endpoint. **A**, DSA performed prior to injection of chemoembolic materials. **B**, Completion maximum enhancement DSA images obtained immediately following injection of chemoembolic materials. There is elimination of both antegrade blood flow supplying the tumor (arrow), as well as angiographic tumor blush (star).

Fig. 4. Kaplan-Meier curve displays the overall survival of the 105 patients included in this study

Survival by SACE Level

Figure 5.
Kaplan-Meier curve displays the survival stratified by SACE level.

SACE 2/3 vs SACE 4: Overall **SACE 2/3 vs SACE 4: Child-Pugh A**

SACE 2/3 vs SACE 4: Child-Pugh B

Figure 6.

Kaplan-Meier curve displays the survival rates of the patients with SACE level 2/3 compared to patients with SACE level 4. **A**, Survival curve of all patients. **B**, Survival curve of only patients with Child-Pugh A disease. **C**, Survival curve of only patients with Child-Pugh B disease.

Table 1

Subjective Angiographic Chemoembolization Endpoint (SACE) Scale originally proposed by Lewandowski et al [16].

Level	Residual Antegrade Arterial Flow	Residual Tumor Blush
I	Normal	Normal
II	Reduced	Reduced
III	Reduced	None
IV	None	None

Table 2

Baseline Patient Characteristics of Patients in all SACE Levels

	All Patients (n = 105)	SACE 1 (n = 1)	SACE 2 (n = 19)	SACE 3 (n = 60)	SACE 4 (n = 25)	p Value
Sex						0.87
Male	84 (80)	1	16 (84)	48 (80)	19 (76)	
Female	21 (20)	0	3 (16)	12 (20)	6 (24)	
Age						
Average $\pm$ SD (y)	60.6 $\pm$ 10.4	54.9	59.7 $\pm$ 10.7	60.2 $\pm$ 10.4	62.2 $\pm$ 10.5	0.78
≤ 65	66 (63)	1	12 (63)	39 (65)	14 (56)	
> 65	39 (37)	0	7 (37)	21 (35)	11 (44)	
Ethnicity						0.31
Caucasian	62 (59)	1	11 (58)	37 (62)	13 (52)	
African American	14 (13)	0	0 (0)	11 (18)	3 (12)	
Hispanic	13 (12)	0	2 (11)	8 (13)	3 (12)	
Asian	9 (9)	0	4 (21)	1 (2)	4 (16)	
Other	7 (7)	0	2 (11)	3 (5)	2 (8)	
Etiology						0.63
HCV	57 (54)	0	11 (58)	34 (57)	12 (48)	
HBV	12 (11)	0	2 (11)	6 (10)	4 (16)	
Alcohol	16 (15)	1	3 (16)	9 (15)	3 (12)	
Other/Unknown	20 (19)	0	3 (16)	11 (18)	6 (24)	
Distribution						0.49
Solitary	43 (41)	1	8 (42)	22 (37)	12 (48)	
Multifocal	62 (59)	0	11 (58)	38 (63)	13 (52)	
Targeted Tumors						0.24
1	61 (58)	1	13 (68)	30 (50)	17 (68)	
> 1	44 (42)	0	6 (32)	30 (50)	8 (32)	
Tumor Diameter						0.61
≤ 4 cm	53 (50)	1	11 (58)	30 (50)	11 (44)	
> 4 cm	52 (50)	0	8 (42)	30 (50)	14 (52)	

	All Patients (n = 105)	SACE 1 (n = 1)	SACE 2 (n = 19)	SACE 3 (n = 60)	SACE 4 (n = 25)	p Value
ECOG PS						0.95
0	44 (42)	0	8 (42)	25 (42)	11 (44)	
> 0	61 (58)	1	11 (58)	35 (58)	14 (56)	
Child Pugh						0.29
A	39 (37)	1	7 (37)	19 (32)	12 (48)	
B	66 (63)	0	12 (63)	41 (68)	13 (52)	
AJCC Stage						0.78
1	42 (40)	1	9 (47)	21 (35)	11 (44)	
2	38 (36)	0	5 (26)	24 (40)	9 (36)	
> 2	25 (24)	0	5 (26)	15 (25)	5 (20)	
CLIP Stage						0.87
0	12 (11)	0	3 (16)	5 (8)	4 (16)	
1	37 (35)	1	7 (37)	20 (33)	9 (36)	
2	38 (36)	0	5 (26)	25 (42)	8 (32)	
> 2	18 (17)	0	4 (21)	10 (17)	4 (16)	
Subsequent TACE Procedures						0.749
0	56 (53)	1	9 (47)	32 (53)	14 (56)	
> 0	49 (47)	0	10 (53)	28 (47)	11 (44)	

Note. — Values in parentheses represent percentages. SACE = Subjective Angiographic Chemoembolization Endpoint; SD = standard deviation; HCV = hepatitis C virus; HBV = hepatitis B virus; ECOG PS = Eastern Cooperative Oncology Group Performance Status; AJCC = American Joint Committee on Cancer; CLIP = Cancer of the Liver Italian Program

Table 3

SACE 2/3 vs SACE 4 Baseline Characteristics and Survival Rate Comparison

	SACE 2/3 (n = 79)	SACE 4 (n = 25)	p Value
Sex			0.586
Male	64 (81)	19 (76)	
Female	15 (19)	6 (24)	
Age			0.387
Average $\pm$ SD (y)	60.1 $\pm$ 10.4	62.2 $\pm$ 10.5	
$\leq$ 65	51 (65)	14 (56)	
> 65	28 (35)	11 (44)	
Ethnicity			0.656
Caucasian	48 (61)	13 (52)	
African American	11 (14)	3 (12)	
Hispanic	10 (13)	3 (12)	
Asian	5 (6)	4 (16)	
Other	5 (6)	2 (8)	
Etiology			0.713
HCV	45 (57)	12 (48)	
HBV	8 (10)	4 (16)	
Alcohol	12 (15)	3 (12)	
Other/Unknown	14 (18)	6 (24)	
Distribution			0.373
Solitary	30 (38)	12 (48)	
Multifocal	49 (62)	13 (52)	
Targeted Tumors			0.231
1	42 (54)	17 (68)	
> 1	36 (46)	8 (32)	
Tumor Diameter			0.491
$\leq$ 4cm	41 (52)	11 (44)	
> 4cm	38 (48)	14 (56)	
ECOG PS			0.844
0	33 (42)	11 (44)	
> 0	46 (58)	14 (56)	
Child Pugh			0.172
A	26 (33)	12 (48)	
B	53 (67)	13 (52)	
AJCC Stage			0.818
1	30 (38)	11 (44)	
2	29 (37)	9 (36)	
> 2	20 (25)	5 (20)	

	SACE 2/3 (n = 79)	SACE 4 (n = 25)	<i>p</i> Value
CLIP Stage			0.804
0	8 (10)	4 (16)	
1	27 (34)	9 (36)	
2	30 (38)	8 (32)	
> 2	14 (18)	4 (16)	
Subsequent TACE Procedures			0.720
0	41 (52)	14 (56)	
> 0	38 (48)	11 (44)	
Median Survival (months) (95% CI)			
Overall	25.6 (16.2 – 35.0)	17.1 (13.3 – 20.9)	0.035
Child-Pugh A	26.0 (0 – 67.9)	18.9 (13.5 – 24.3)	0.372
Child-Pugh B	24.1 (17.6 – 30.7)	11.3 (3.9 – 18.8)	0.006
Pooled over all Child-Pugh scores	25.6 (16.2 – 35.0)	17.1 (13.3 – 20.9)	0.008

Note. – Values in parentheses represent percentages. Survival calculated by Kaplan-Meier analysis. *P* values in bold denote statistical significance. SACE = Subjective Angiographic Chemoembolization Endpoint; SD = standard deviation; HCV = hepatitis C virus; HBV = hepatitis B virus; ECOG PS= Eastern Cooperative Oncology Group Performance Status; AJCC = American Joint Committee on Cancer; CLIP = Cancer of the Liver Italian Program; CI = confidence interval

Table 4

Univariate and Multivariate Survival Analysis

Kaplan-Meier and Log-Rank Univariate Analysis				Cox Proportional Hazards Multivariate Analysis			
Characteristic	No.	Median	95% CI	p	HR	95% CI	p
Age (y)				0.643			
< 65	65	20.4	13.6–27.2				
≥ 65	39	21.1	15.5–26.7				
Sex				0.672			
Male	83	21.1	14.9–27.3				
Female	21	22.5	15.7–29.2				
Ethnicity/Race				0.841			
Caucasian	61	22.3	17.9–26.7				
African-American	14	18.4	3.8–33.0				
Hispanic	13	18.4	10.2–26.5				
Asian	9	21.3	2.7–39.9				
Other	7	12.6	6.4–18.7				
Distribution				0.162			
Unifocal	42	25.6	14.8–36.5				
Multifocal	62	17.7	13.0–22.3				
Targeted Tumors				0.125			
1	60	24.2	18.7–29.8				
> 1	44	16.0	12.8–19.2				
Tumor Diameter				0.260			
≤ 4cm	52	22.3	13.8–30.8				
> 4cm	52	20.4	13.4–27.3				
Subsequent TACE Procedures				0.985			
0		38.5	29.0–48.0				
> 0		36.8	26.7–46.9				
ECOG PS				0.008			

Kaplan-Meier and Log-Rank Univariate Analysis				Cox Proportional Hazards Multivariate Analysis			
Characteristic	No.	Median	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Characteristics							
0	44	44.8	19.0–75.0		1.00		
1/2	60	17.7	13.4–21.9		1.97	1.15–3.37	0.013
AJCC Stage				0.046			
1	41	31.0	3.6–58.4		1.00		
2	38	18.4	13.8–22.9		1.79	0.97–3.30	0.063
3/4	25	15.4	11.1–19.7		2.42	1.27–4.60	0.007
CLIP Stage				0.315			
0	12	71.6	20.3–123.0				
1	36	21.1	12.0–30.2				
2	38	22.5	12.1–32.8				
> 2	18	14.9	5.0–24.9				
Child-Pugh Class				0.058			
A	38	24.2	15.0–33.5		1.00		
B	66	18.4	11.5–25.4		1.94	1.09–3.46	0.025
SACE Level				0.035			
2/3	79	25.6	16.2–35.0	1.00			
4	25	17.1	13.3–20.9	2.49	1.41–4.42	0.002	

Note. – Factors were included in multivariate analysis if $p < 0.10$ on univariate analysis. *P* values in bold denote statistical significance. CI = Confidence Interval; HR = Hazard Ratio; ECOG PS = European Cooperative Oncology Group Performance Status; AJCC = American Joint Committee on Cancer; CLIP = Cancer of the Liver Italian Program; SACE = Subjective Angiographic Chemoembolization Endpoint