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Is Salvage Liver Resection Necessary for Initially Unresectable Hepatocellular Carcinoma Patients Downstaged by Transarterial Chemoembolization? Ten Years of Experience

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Key Words. Transarterial chemoembolization • Hepatocellular carcinoma • Downstaging • Salvage surgery • Overall survival

ABSTRACT

Introduction. This study evaluated long-term outcomes of salvage surgery as additional therapy following downstaging of hepatocellular carcinoma (HCC) with transarterial chemoembolization (TACE) in patients with initially unresectable HCC.

Methods. A retrospective analysis was performed of 831 consecutive patients with unresectable HCC who underwent TACE as initial treatment between June 2004 and December 2014. Of these, 82 patients with downstaged resectable HCC were enrolled in this study: 43 received salvage surgery (S group) and the remaining 39, who refused salvage resection, were the control group (T group). The primary endpoint was overall survival (OS).

Results. The median OS in the S and T groups was 49 and 31 months, respectively ($p = .027$). The 2-, 4-, and 5-year survival rates were 93%, 47%, and 26% in the S group and 74%, 18%, and 10% in the T group, respectively ($p = .019$). Treatment modality (hazard ratio [HR], 0.337; 95% confidential interval [CI], 0.184–0.616; $p < .001$) and response to TACE (complete vs. partial; HR, 3.154; 95% CI, 1.709–5.822; $p < .001$) were independent prognostic factors for survival. The median OS for patients in the complete response and partial response (PR) subgroups was 50 and 49 months, respectively, in the S group and 54 and 24 months, respectively, in the T group ($p = .699$ and $p < .001$, respectively). The median OS for HCC patients with macroscopic vascular invasion (MVI) was 58 and 30 months in the S and T groups, respectively ($p = .024$).

Conclusion. Salvage surgery after downstaging of unresectable HCC had a survival benefit only for patients with MVI or a PR to TACE. ***The Oncologist*** 2016;21:1442–1449

Implications for Practice: The results of this study suggest that salvage liver resection after downstaging of unresectable hepatocellular carcinoma in patients with a complete response to transarterial chemoembolization (TACE) has a comparable long-term outcome in this good-prognosis group. Salvage liver resection may provide a better long-term outcome compared with TACE alone, but only in patients with macroscopic vascular invasion or those with a partial response to TACE.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related death in the world [1]. Complete tumor resection is the generally accepted potential curative modality for HCC. However, only 30%–40% of early-stage patients are amenable to such curative therapy, because greater than 50% of all HCCs are diagnosed at an unresectable tumor stage and have a poor prognosis. These patients, therefore, must rely on palliative therapy to prolong their survival [2–4]. Transarterial chemoembolization (TACE) is a valuable and commonly applied palliative treatment for most patients with unresectable HCC [2–7]. TACE procedures can sometimes result in downstaging of HCC, allowing some unresectable lesions to become resectable because tumors shrink, satellite lesions disappear, and nontumorous tissue appears in the liver hypertrophy [7–13].

There have been numerous reports indicating that salvage liver resection or liver transplantation for unresectable tumors

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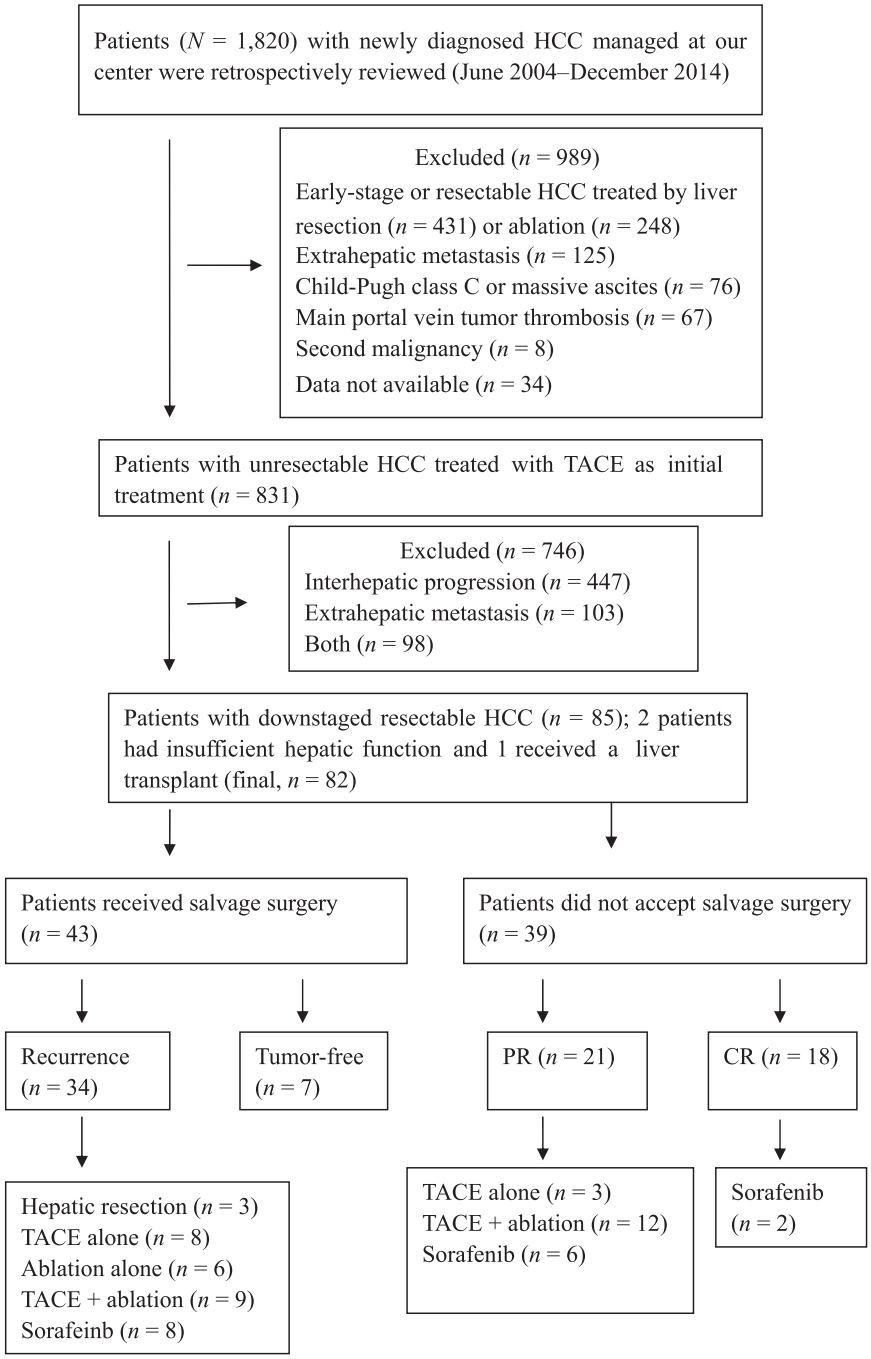

Figure 1. Flow diagram illustrating the patient selection process and treatment allocation. Two patients who received liver resection died during hospitalization.

Abbreviations: CR, complete response; HCC, hepatocellular carcinoma; PR, partial response; TACE, transarterial chemoembolization.

downstaged by TACE or other therapeutic modalities achieve excellent long-term outcomes [8–13]. However, the majority of these studies were single-arm trials and did not compare between therapeutic modalities nor did they identify the most appropriate candidates for their particular procedure. For example, patients who responded better to the treatment may have had tumors that are biologically less aggressive. Hence, results may not have reflected the true benefit of treatment. Similarly, there were some reports showing that patients who responded well to initial treatment and refused surgery had a comparable outcome to those treated with surgery [14, 15].

Multidisciplinary treatment of liver cancer was established at our institution in 2005. The team consists of surgeons, radiologists, and oncologists. Every case is discussed to decide the optimal treatment. TACE is the first-line treatment for unresectable HCC, and when downstaged, resectable HCC is observed, salvage surgery is recommended if the patient's general condition permits. However, in our clinical practice, some patients with unresectable HCC downstaged by TACE, who refused to receive salvage resection because of unease with surgery or other reasons, underwent TACE alone. Interestingly, we found that some

Table 1. Comparison of baseline patient characteristics

Characteristics	S group ($n = 43$)	T group ($n = 39$)	p value
Age (years)	54.9 ± 11.1	51.2 ± 9.2	.095
Sex			
Male	41 (95)	37 (95)	1.000
Female	2 (5)	2 (5)	
HBV infection			.602
Yes	42 (98)	37 (95)	
No	1 (2)	2 (5)	
Cirrhosis			.271
Yes	38 (88)	31 (79)	
No	5 (12)	8 (21)	
Child-Pugh class			.665
A	41 (95)	36 (92)	
B	2 (5)	3 (8)	
Indocyanine green retention rate in 15 min (%)	7.3 ± 3.4	7.5 ± 4.4	.761
AFP (ng/mL)			.120
<20	7 (16)	12 (31)	
>20	36 (84)	27 (69)	
Reasons for initially unresectable HCC			.871
Bilobar involvement	34 (79)	31 (79)	
Hepatic vein involvement	2 (5)	1 (3)	
Insufficient hepatic remnant	7 (16)	7 (18)	
Macroscopic vascular invasion			.419
Absent	38 (88)	32 (82)	
Present	5 (12)	7 (18)	
No. of tumors			.101
1–4	38 (88)	29 (74)	
≥5	5 (12)	10 (26)	
Size of main tumor (cm)	9.5 ± 3.2	9.1 ± 4.1	.645
ECOG performance status		0.730	
0–1	39 (91)	34 (87)	
2	4 (9)	5 (13)	

Data are presented as mean ± SD or *n* (%).
Abbreviations: AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; S group, patients who received salvage surgery; T group, control group.

of these TACE-only patients also had good long-term outcomes.

Therefore, the survival benefit of salvage surgery after TACE-induced downstaging of HCC compared with TACE treatment alone for patients with unresectable HCC is unclear and controversial. The criteria for selecting patients in whom salvage surgery would most likely be of benefit are also unknown. We conducted a retrospective analysis of 82 initially unresectable HCC patients who were treated with TACE during a 10-year period to determine whether salvage surgery offers an additional overall survival (OS) benefit. We also sought to define the critical factors influencing treatment outcomes.

Patients and Methods

Patient Selection

The protocol was approved by the ethics committees of the First Affiliated Hospital, Sun Yat-sen University. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Between June 2004 and December 2014, 1,820 consecutive patients with newly diagnostic HCC managed at our center were retrospectively reviewed. The diagnosis of HCC was based on the diagnostic criteria used by the European Association for the Study of the Liver [3]. Of these patients, 679 (37%) were assessed as having early stage or resectable disease and were treated by liver surgery or local ablation; 1,141 (73%) were initially considered as unresectable. We also excluded patients exhibiting any of the following: extrahepatic metastasis and main portal vein tumor thrombosis, Child-Pugh class C or massive ascites, secondary malignancy, and unavailability of data. These unresectable HCC patients were treated by TACE as a first-line treatment and were prospectively reviewed after every course of TACE by the same multidisciplinary team. Resectability of the tumor was assessed by the same liver surgeon (L.L., who has more than 20 years of experience) and

Table 2. Treatment outcome in the S and T groups

Parameter	S group ($n = 43$)	T group ($n = 39$)	p value
Treatment response after downstaging[a]			.412
Complete response	16 (37)	18 (46)	
Partial response	27 (63)	21 (54)	
Types of hepatectomy			
Anatomic hemihepatectomy	33		
Extended hemihepatectomy	8		
Debulking surgery	2		

Data are presented as *n* or *n* (%).
[a]Treatment response evaluated according to radiology and α-fetoprotein.
Abbreviations: S group, patients who received salvage surgery; T group, control group.

radiologist (J.L., who has more than 15 years of experience). Liver surgery was reconsidered every time a documented response to TACE was observed.

Downstaged, resectable HCC was defined as disease of any stage in which all gross tumors were deemed potentially resectable with a clear margin, as observed radiologically [8, 10]. Among the 831 local, unresectable HCC patients, 85 were significantly downstaged by TACE; 2 of these had insufficient liver function reserve and 1 received a liver transplant. The remaining 82 patients formed the population of the study. Patients were divided into 2 groups according to the pursued therapeutic strategy: 43 patients who underwent salvage surgery after downstaging of HCC (S group) and 39 patients who refused salvage liver resection and underwent only TACE treatment (T group).

Methods

TACE Procedure

TACE was performed using techniques previously described [16, 17]. Briefly, 10–20 mL of lipiodol (Guerbet, Paris, France, http://www.guerbet.com) was mixed with 20–40 mg of epirubicin (Pfizer, New York, NY, http://www.pfizer.com/) to create an emulsion. Depending on the tumor size and liver function, 2–20 mL of the emulsion was then infused into the liver tumor through a catheter. Subsequently, embolization using Gelfoam (Pfizer, Hangzhou, China, http://www.pfizer.com.cn) was performed. When blood flow slowed or a vascular cast was observed, the injection was stopped. We preferentially targeted the lobar, segmental, or subsegmental tumor-feeding artery, depending on the tumor distribution. Repeated TACE was performed at a 4- to 6-week interval on an "on-demand" basis without deterioration of liver function.

Hepatic Resection Procedure

Hepatic resection [18] was performed at 4–6 weeks after successful downstaging TACE. Anatomic resection of the liver was based on the Couinaud segments, and aimed at a gross resection margin of 1 cm from the edge of the lesions. Nonanatomic resection was performed when the tumor was at the edge of the liver. If the residual lesion was considered not resectable during surgery because of the discovery of additional lesions that were not visible on preoperative imaging, a debulking surgery was performed. The aim of the debulking surgery was to remove all macroscopic tumors while leaving behind microsatellite lesions to be treated later by locoregional therapy.

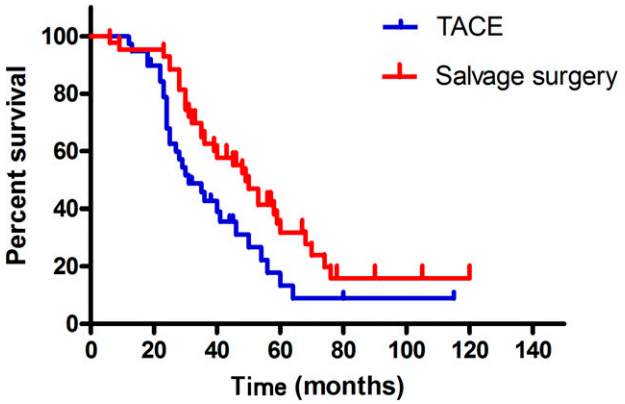

Figure 2. Kaplan-Meier curves for patients with downstaged unresectable hepatocellular carcinoma in the salvage surgery and TACE groups. The median overall survival (OS) for the salvage surgery group ($n = 43$) was 49 months and the median OS for the TACE group ($n = 39$) was 31 months ($p = .027$).
Abbreviation: TACE, transarterial chemoembolization.

Follow-Up and Additional Treatment

Contrast-enhanced computed tomography (CT) scanning of the chest and abdomen, liver function tests, and α-fetoprotein (AFP) measurements were performed 1 month after TACE to evaluate its effect and check for lung metastases. Additional TACE was performed for patients who did not achieve a downstaging of HCC. If downstaging of the tumor was observed, salvage surgery was recommended to every patient by the attending physician and was performed in patients who accepted. Additional treatment was performed in patients who did not accept the surgery recommendation if they still had residual viable tumors.

Contrast-enhanced CT of the chest and abdomen, as well as liver function and AFP tests, were performed 1 month after liver salvage surgery to evaluate the outcome. In patients who achieved a complete response (CR) or who were tumor free, follow-up was performed every 2 months for the first 2 years. The follow-up interval was extended to every 6 months between the 2nd to 4th years after treatment, and to every 12 months after 5 years. At each follow-up session, contrast-enhanced CT scanning of the abdomen and chest, as well as liver function and AFP tests, were performed. Patients in whom recurrence or metastasis was detected were recommended for local ablation, TACE, systemic therapy, or conservative treatment was recommended, depending on the Barcelona clinic liver cancer (BCLC) staging system.

Assessments

Tumor response was assessed based on radiological evaluation according to the modified Response Evaluation Criteria in Solid Tumors guideline [19]. AFP response was classified as either CR (normalization) or partial response (PR; a decrease by >50% of the baseline value) [17]. In HCC

Table 3. Univariate and multivariate analysis of prognostic factors

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Treatment		.027		<.001
TACE	1.000		1.000	
Salvage surgery	0.633 (0.030–1.235)		0.337 (0.184–0.616)	
Response type		.010		<.001
CR	1.000		1.000	
PR	1.767 (1.175–2.358)		3.154 (1.709–5.822)	
No. of tumors		.056		NA
1–4	1.000			
≥5	1.533 (0.992–2.074)		—	
Size of main tumor, cm		.371		NA
<10	1.000			
≥10	0.976 (0.374–1.577)		—	
Macroscopic vascular invasion				NA
Absent	1.000			
Present	0.988 (0.513–1.463)		—	

Abbreviations: —, empty value in multivariate analysis; CI, confidence interval; CR, complete response; NA, not applicable; PR, partial response; TACE, transarterial chemoembolization.

patients positive for AFP (a baseline AFP level >20 ng/mL), CR was assessed based on radiological evaluation and AFP normalization. Treatment complications that occurred within 4 weeks were recorded according to Common Terminology Criteria for Adverse Events, version 3.0 [20]. OS was defined as the time from the start of treatment until death or the last follow-up.

Statistical Analysis

All statistical analyses were performed using SPSS software version 16.0 (IBM Corp., Chicago, IL, https://www.ibm.com). For baseline characteristics, continuous variables are described as median ± SD, and categorical variables are expressed as frequencies and percentages. The *t* test was used to compare continuous variables between the two groups. The chi-square test was used to compare categorical variables between the two groups. The Kaplan-Meier method was used to calculate the OS between groups. Univariate analyses were performed with the log-rank test. Variables with $p < .1$ on univariate analysis were subjected to a multivariate analysis. The multivariate Cox model was used to identify risk factors that affected OS. All statistical tests were two-sided, and $p < .05$ was considered statistically significant.

Results

Study Population

Between June 2004 and December 2014, a total of 1,820 consecutive, naïve HCC patients were retrospectively analyzed, and 1,141 patients were diagnosed as having unresectable tumors. A total of 310 patients were excluded from the first analysis. Then, 831 patients with local, unresectable HCC (intermediate, $n = 411$; advanced, $n = 420$) who were initially treated by TACE were analyzed. Of these, 85 patients were significantly downstaged by TACE; 2 of these patients had insufficient liver function reserve and 1 patient received a liver transplant. The remaining 82 patients with downstaged, resectable HCC were enrolled in the study; 43 of these received salvage surgery therapy, and the remaining 39, who refused salvage resection, underwent TACE and ablation treatment (Fig. 1). The baseline characteristics of all patients are shown in Table 1. None of the variables, including the reason for initial unresectability, the cause of liver disease, or liver function, differed significantly between the two groups. The main reason for initial unresectability of tumors was bilobar involvement. The majority of the patients were male, and hepatitis B and cirrhosis were the most common underlying diseases.

Treatment Outcome

The mean number of TACE procedures per patient before downstaging in the S and T groups was 2.7 (range, 1–4) and 3.0 (range, 1–5), respectively. Based on CT measurements, the median main tumor diameter was 9.5 cm and 9.1 cm in the S and T groups before treatment, respectively. The corresponding main tumor diameters after treatment were reduced to 6.5 cm and 6.2 cm, respectively. Serum AFP levels decreased by varying extents in the 63 patients in whom levels were initially positive Table 1. AFP levels returned to normal in 13 and 14 patients in the S and T groups, respectively. After downstaging, 16 patients achieved a CR and 27 had a PR in the S group. The main reasons that tumors were deemed resectable were disappearance of some lesions, complete tumor necrosis, and shrinkage of large HCCs. The details of the treatment outcomes are shown in Table 2. Among the 39 patients in the T group, 18 patients had a CR, and 21 had a PR and received further treatment (Fig. 1).

Correlation Between Treatment and Pathologic Response

Among the 43 patients who underwent salvage liver resection, 16 had a CR with no residual tumor enhancement and achieved

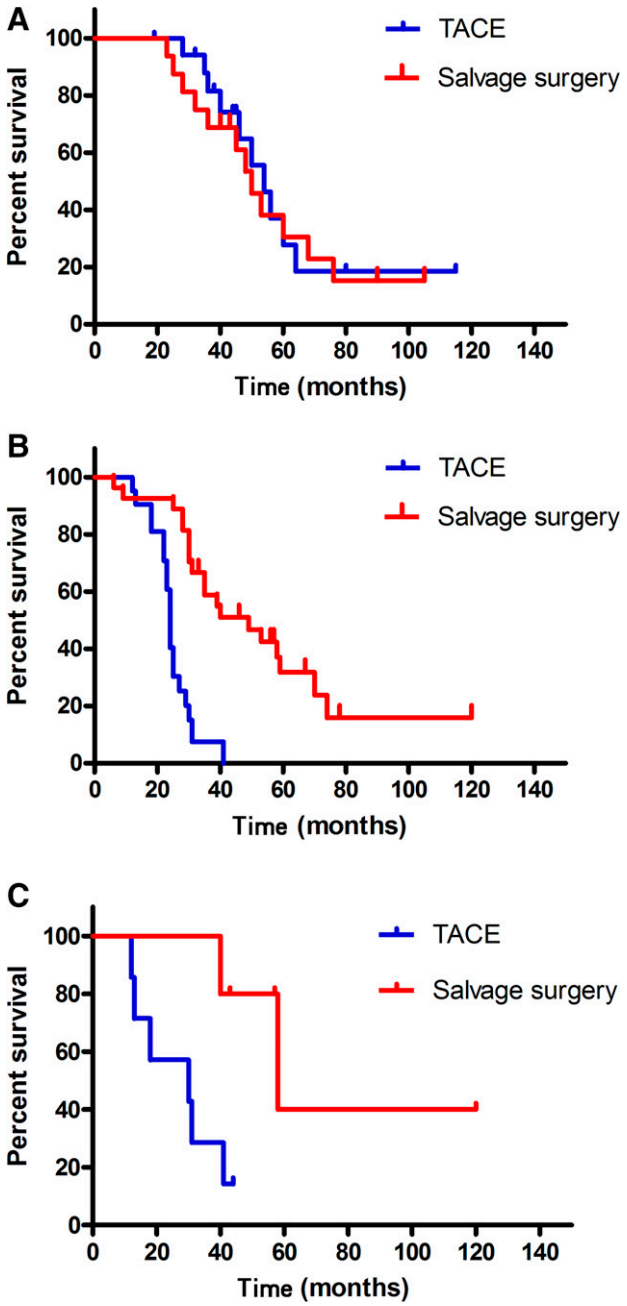

Figure 3. Kaplan-Meier curves for patients with downstaged unresectable hepatocellular carcinoma in the salvage surgery and TACE groups. **(A):** Patients with a complete response. The median overall survival (OS) for the salvage surgery group ($n = 16$) was 50 months and that of the TACE group ($n = 18$) was 54 months ($p = .669$). **(B):** Patients with a partial response. The median OS for the salvage surgery group ($n = 27$) was 49 months and that of the TACE group ($n = 21$) was 24 months ($p < .001$). **(C):** Patients with macroscopic vascular invasion. The median OS for the salvage surgery group ($n = 5$) was 58 months and that of the TACE group ($n = 7$) was 30 months ($p = .024$).

Abbreviation: TACE: transarterial chemoembolization.

AFP normalization before surgery. Seven patients showed complete tumor necrosis pathologically, while the remaining nine patients showed fewer residual, viable tumor cells. The 27 patients with a PR had viable tumors.

Survival

At the end of the follow-up period (August 2015), 31 patients (72%) in the S group and 29 patients (74%) in the T group had died. The mean follow-up time for these patients was 42.2 ± 22.7 months (range, 6–120 months) and the total follow-up time after initial therapy was over 10 years. Of the 43 patients who underwent liver resection, 2 died during their hospitalization. Seven patients had a tumor-free survival and 34 had a tumor recurrence, which included 3 patients with early, 18 with intermediate, 11 with advanced, and 2 with terminal disease, according to the BCLC staging system. Subsequent treatments after recurrence are shown in Figure 1. The median OS was 49 months (95% confidence interval [CI], 40.1–57.9) in the S group and 31 months (95% CI, 22.0–39.9) in the T group (Fig. 2). The difference between the two groups was significant ($p = .027$). The 2-, 4-, and 5-year survival rates were 93%, 47%, and 26% in the S group and 74%, 18%, and 10% in the T group, respectively ($p = .019$).

On univariate analysis, only treatment modality and response to TACE (CR or PR) after downstaging were significantly associated with survival. The number of tumors, tumor size, and presence of macroscopic vascular invasion (MVI) were not significantly associated with survival. On multivariate Cox analysis, treatment modality (hazard ratio [HR], 0.337; 95% CI, 0.184–0.616; $p < .001$) and response type (complete versus partial; HR, 3.154; 95% CI: 1.709–5.822; $p < .001$) were independent prognostic factors for OS (Table 3). Therefore, we further analyzed the OS rates between the CR and PR patient subgroups. The median OS times for patients in the CR and PR subgroups were 50 months (95% CI, 41.2–58.8) and 49 months (95% CI, 27.8–70.2), respectively, in the S group; and 54 months (95% CI, 44.8–63.2) and 24 months (95% CI, 22.9–25.1), respectively, in the T group (Fig. 3A, 3B).

MVI is a known negative predictor for OS. Therefore, we further compared the OS rates of patients with MVI between the S group and T group. The OS times were 58 months (95% CI, 31.8–84.2) and 30 months (95% CI: 0–60.8) in the S group and T group, respectively (Fig. 3C).

Complications

Two patients in the S group (5%) died within 4 weeks after the surgery (1 each of liver failure and sepsis). There were no deaths related to TACE. The most common adverse events after treatment were postembolization syndrome, pleural effusions, ascites, liver abscesses, bile leaks, and liver failure. Complications observed after treatment are detailed in Table 4.

Discussion

We assessed the long-term outcome of post-TACE salvage surgery compared with TACE alone for a specific group of patients with unresectable HCC who were downstaged by TACE. Furthermore, we defined the factors that influenced the treatment outcomes. To our knowledge, this is the first study to date that compares the outcomes of salvage surgery versus TACE alone for patients with initially unresectable HCC that were downstaged by TACE.

We observed that salvage surgery produced a more favorable long-term outcome than TACE alone for our patients.

Table 4. Comparison of complications between the S and T groups

Complication	S group ($n = 43$)	T group ($n = 39$)	*p* value
Abdominal pain			.924
Grade 1–2	28 (65)	25 (64)	
Fever (>38.5°C)			.808
Grade 1–2	22 (51)	21 (54)	
Vomiting			.939
Grade 1–2	18 (42)	16 (41)	
Temporary elevation of transaminase			.369
Grade 1–2	33 (77)	33 (85)	
Pleural effusion			.028
Grade 1–2	11 (26)	3 (8)	
Ascites			.026
Grade 1–2	13 (33)	4 (10)	
Liver abscess			.223
Grade 3–4	0	2 (5)	
Bile leaks			.243
Grade 3–4	3 (7)	0	
Sepsis			1.000
Grade 3–4	1 (2)	0	
Liver failure			.589
Grade 1–2	3 (7)	2 (5)	
Grade 3–4	1 (2)	0	
GI bleeding			1.000
Grade 1–2	2 (5)	2 (5)	

Data are presented as *n* (%).
Abbreviations: GI, gastrointestinal; S group, patients who received salvage surgery; T group, control group.

This was likely because of the complete tumor necrosis, which, as shown histopathologically, occurred in only 16% of patients (7 of 43) after downstaging treatment. Most patients have residual viable tumors that will regrow or metastasize if they are not surgically resected. Therefore, salvage surgery may potentially extirpate such residual tumors, resulting in survival benefits. We confirmed results of previous studies that showed that salvage surgery or transplantation for downstaged tumors produces excellent outcomes in HCC [8–13], as well as colorectal liver metastases and hepatoblastoma [21, 22]. In our study, the median OS of 50 months and the 5-year survival rate of 26% are consistent with other reported outcomes (5-year survival rate ranged from 24.9% to 57%) [8].

In this study, the treatment modality and response type were identified as the independent prognostic factors for OS. Therefore, we further compared the OS between the CR and PR patient subgroups. Interestingly, we found that the OS of the S group was comparable to that of the T group in the CR subgroup. This was similar to findings of a previous study that reported the survival rates of patients who underwent initial TACE and subsequent liver resection were comparable to that of patients who responded well to TACE but refused resection [15]. On the other hand, the difference between the 2 treatments among PR patients was significant and the difference persisted for 25 months. The most likely interpretations are that (a) patients in the CR subgroup of the T group may have achieved true complete necrosis (multiple lesions in three patients all disappeared after treatment) or a very low number of residual viable tumors that can be treated further if recurrence is observed radiologically, and this resulted in patients living longer; or (b) for the PR subgroup patients, the residual viable tumors were resected, which, likewise, could have prolonged the survival time. However, MVI was not identified as a predictor of OS in our study, and subgroup survival analysis for patients with MVI demonstrated a significant difference between the S and T group (OS was 58 vs. 30 months, respectively). The most likely interpretations for this observation are (a) the small sample sizes ($n = 5$ and 7, respectively) did not adequately reflect the OS, and (b) we found that all patients with unresectable HCC and MVI achieved a PR to TACE, and such patients may thus be potentially cured after salvage surgery. This is consistent with the fact that the response type was an independent prognostic factor for OS in our study.

This study has some limitations. First, it is a retrospective analysis, and the data were based on patients at a single center. The reason we analyzed data from a single center is that the success of TACE strongly depends on the operator's experience. Second, the sample size is relatively small; however, salvage surgery following tumor downstaging is possible only in a small proportion of patients with unresectable HCC (reportedly 8%–18% of patients) [8]. Third, the therapeutic options depended on the patients' individual preferences, which likely led to bias in our population. However, the bias was

limited by the fact that patients in both groups had similar baseline characteristics.

In conclusion, in patients with downstaged, resectable HCC, salvage liver resection may prolong the survival of patients with MVI or a PR to TACE. For patients with downstaged, resectable HCC and a complete response to TACE, salvage liver resection may not provide any additional survival benefits. Larger prospective studies are required to confirm this observation.

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Disclosures

The authors indicated no financial relationships.

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