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Optimizing Survival Benefit by Surgical Resection by the Seven-Eleven Criteria in Barcelona Clinic Liver Cancer Stage A/B Hepatocellular Carcinoma beyond the Milan Criteria

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Keywords

Barcelona Clinic Liver Cancer · Surgical resection · Transarterial chemoembolization · Overall survival · Tumor burden · Up-to-7 criteria

Abstract

Introduction: Optimal treatment of hepatocellular carcinoma (HCC) beyond the Milan criteria is in debate. We aimed to identify candidates for surgical resection (SR) in Barcelona Clinic Liver Cancer (BCLC)-A/B HCC beyond the Milan criteria with survival benefit. ***Methods:*** Patients with BCLC-A/B HCC beyond the Milan criteria at the National Taiwan University Hospital during 2005 and 2019 were screened, and those who received transarterial chemoembolization (TACE) or SR were consecutively included. The tumor burden was classified by the seven-eleven criteria into low (≤7), intermediate (7–11), or high (>11). Multivariable Cox proportional hazard regression analysis was used for outcome prediction. ***Results:*** Overall, 474 patients who received SR (n = 247) and TACE (n = 227) were enrolled. Patients who underwent SR were significantly younger with better liver reserve. There were 76 (31%) and 129 (57%) deaths in the SR and TACE groups after a median follow-up of 3.9 and 2.1 years, respectively. The seven-eleven criteria could distinguish median overall survival (OS) among low (n = 149), intermediate (n = 203), and high (n = 122) tumor burden groups (7.7 vs. 6.9 vs. 2.8 years, respectively, $p < 0.001$). Patients receiving SR had a significantly higher median OS compared with TACE in those with intermediate (8.2 vs. 2.6 years, $p < 0.001$) and high (5.6 vs. 1.5 years, $p = 0.001$) tumor burden. After adjustment for age, sex, and liver reserve, SR was predictive for better OS in intermediate (adjusted hazard ratio [aHR]: 0.45, 95% confidence interval [CI]: 0.27–0.75) and high tumor burden groups (aHR: 0.54, 95% CI: 0.32–0.92). The survival benefit of SR especially confines to patients within 3 tumors.

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Conclusions: In patients with BCLC-A/B HCC beyond the Milan criteria with tumor burden beyond the up-to-7 criteria but within 3 tumors, SR has better OS than TACE and should be considered in resectable patients.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death worldwide in 2020 [1]. HCC beyond the Milan criteria include single large tumor (>5 cm) and multinodular HCCs (>3 nodules, or 2–3 nodules with size >3 cm). According to the Barcelona Clinic Liver Cancer (BCLC) classification, single large tumor is classified as BCLC-A and is recommended to receive surgical resection (SR), whereas multinodular HCCs are classified as BCLC-B and the standard therapy is transarterial chemoembolization (TACE).

Several studies suggested single large HCC (>5 cm) should be considered as BCLC-B because its prognosis was more similar to that of BCLC-B HCC and the prognosis was worse than BCLC-A HCC within the Milan criteria [2–7]. The efficacy of TACE compared to SR for single large HCC demonstrated inconsistent results [8–11]. Besides, several studies demonstrated that SR achieved better survival than TACE in selected patients with BCLC-B HCC [12–18]. According to the National Comprehensive Cancer Network (NCCN) guideline, SR is a potentially curative therapy for carefully selected patients, based on patient characteristics including performance status, comorbidity, as well as liver reserve and the tumor location [19]. Moreover, according to Asian Pacific Association for the Study of the Liver (APASL) guideline, SR should be considered in the BCLC-A/B patients in a multidisciplinary setting as a potentially curative therapy, regardless of tumor burden or liver function status [20].

Several BCLC-B subclassification systems have been proposed by using tumor burden and liver reserve to improve the outcome of HCC [21]. Recently, the seven-eleven criteria had been introduced, which is simply calculated by the sum of the total number of tumors and the diameter of the largest tumor. The seven-eleven criteria were shown to be most discriminative in predicting radiologic response and overall survival (OS) in patients with BCLC-B HCC undergoing TACE than the up-to-7 criteria and the up-to-11 criteria [22].

Since patients with BCLC-A/B HCC beyond the Milan criteria comprise a heterogeneous population with various tumor burden and liver reserve, therefore, not all patients benefit from the treatment recommendations by the BCLC guideline [23, 24]. In this study, we aimed to compare the efficacy between SR and TACE and further identify optimal candidates for SR in BCLC-A/B HCC beyond the Milan criteria according to the tumor burden defined by the seven-eleven criteria.

Materials and Methods

Patients

We conducted this retrospective cohort study to screen patients older than 20 year old with a diagnosis of HCC from the cancer registry of the Integrative Medical Database of National Taiwan University Hospital (NTUH-iMD), a tertiary medical center in Taiwan. Diagnosis of HCC is based on histological confirmation or at least one typical imaging study according to the recommendations of the American Association for the Study of Liver Diseases (AASLD) [25]. We included patients of BCLC-A/B HCC beyond the Milan criteria who received TACE or SR as the first treatment. The treatment modality was jointly decided by the patient and our tumor board by multidisciplinary experts.

SR was indicated in patients with adequate remnant liver volume, preserved liver function, with adequate tumor-free resection margins following Makuuchi's criteria [26]. Resection is generally not suitable for tumors involving both lobes of the liver, >3 nodules, and deeply located or with hilar involvement [27]. However, there are no limitations precluding resection regarding tumor size, number, or involvement of portal vein in patients without cirrhosis according to the management guideline in Taiwan [27].

After HCC treatment, a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) would be arranged within 2 months to confirm the responses of treatment. Abdominal ultrasound, CT, or MRI would be arranged every 3–6 months afterward for the surveillance of recurrent HCC. Repeated HCC treatment would be performed according to current guidelines and the multidisciplinary discussion of the HCC tumor board.

Data Collection

The clinical characteristics of patients were collected from electronic medical records, including sex, birth date, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, platelet (PLT) count, alpha-fetoprotein (AFP) level, status of hepatitis B virus and hepatitis C virus infection, status of cirrhosis, tumor numbers, maximum tumor size, BCLC staging, treatment for first tumor recurrence, and date of HCC diagnosis, mortality, or last follow-up. Cirrhosis was diagnosed clinically by the appearance of nodular liver surface, coarse liver parenchymal texture, narrowed vessels with irregular intrahepatic vessel contour, and enlarged spleen size in abdominal ultrasound or CT [28]. Tumor numbers and tumor size were mostly determined based on radiologic findings or by pathologic findings if appropriate.

The tumor burden was calculated by the sum of diameter of the largest tumor and the total number of tumors and was classified into low (≤7), intermediate (7–11), or high (>11) according to the

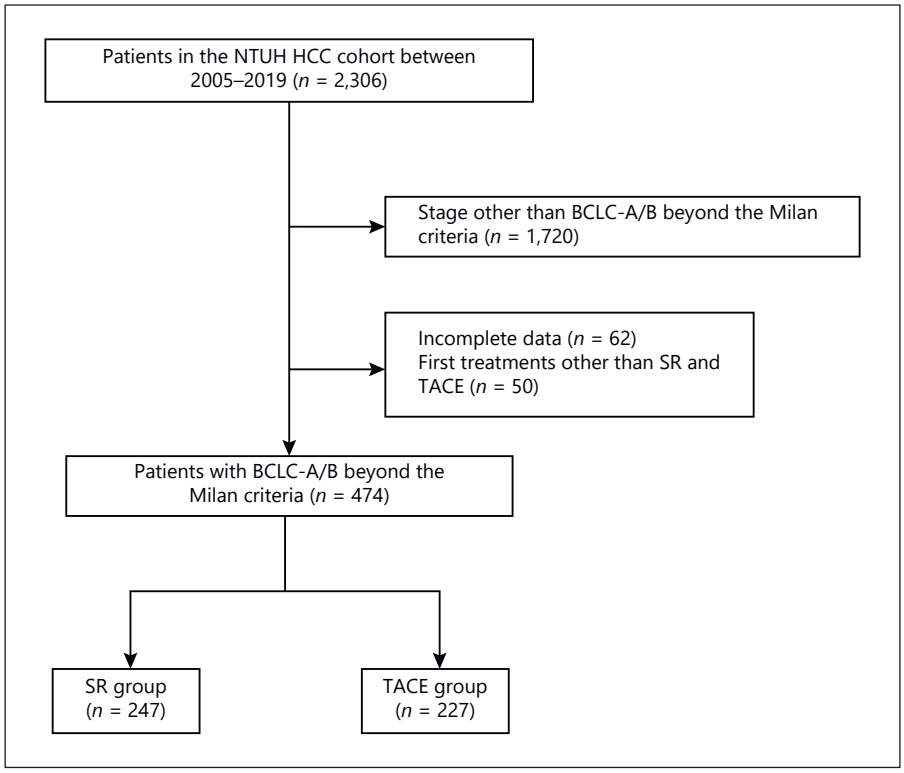

Fig. 1. Study flowchart.

seven-eleven criteria [22]. The liver reserve measurement in our cohort included albumin-bilirubin (ALBI) score ($\log_{10}$ bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.085) and fibrosis-4 (FIB-4) index (age [years] × AST [U/L])/(PLT [10^9/L] × ALT [U/L]$^{1/2}$).

Statistical Analysis

All statistical analysis was performed by STATA (version 16.0; Stata Corp., College Station, TX, USA). All tests were two sided, and p values <0.05 were considered significant. The continuous variables are reported as median (interquartile range) and the categorical data as a number (percentage). Differences between groups were evaluated by Wilcoxon rank-sum test or the χ^2 test as appropriate. The survival time was defined from the diagnosis date of HCC to the date of mortality or last follow-up. The OS between SR and TACE in the three tumor burden groups was compared using Kaplan-Meier (KM) curve analysis and the logrank test. Independent predictors of OS were determined by multivariable Cox proportional hazard regression analysis after adjustment for relevant factors and factors with statistical significance in univariable analysis.

Results

Baseline Characteristics

From 2005 to 2019, a total of 2,306 patients with HCC were screened from the NTUH-iMD as the NTUH HCC cohort. Among them, 1,720 patients were excluded due to BCLC stage 0, C, D, and BCLC stage A within the Milan criteria. We further excluded 62 patients with incomplete data and excluded 50 patients receiving first treatment other than SR or TACE, such as radiofrequency ablation (RFA) and systemic therapy. Finally, 474 patients were included in this study (shown in Fig. 1).

Of these patients, 247 (52%) received SR, whereas 227 (48%) underwent TACE. The baseline clinical data for the 474 patients are shown in Table 1. Patients in the SR group were significantly younger (64 vs. 68 years, p = 0.004) and had lower FIB-4 index (2.17 vs. 3.98, p < 0.001), ALBI score (−3.01 vs. −2.89, p < 0.001), AFP (20.9 vs. 40.8 ng/mL, p < 0.001), less cirrhosis (40 vs. 73%, p < 0.001), larger maximum tumor size (7.0 vs. 5.6 cm, p < 0.001), less HCV infection (19 vs. 36%, p < 0.001), and mostly had single tumor (75 vs. 26%, p < 0.001). There were no significant differences in tumor burden according to the seven-eleven criteria (p > 0.05). After a median follow-up of 3.9 and 2.1 years in the SR group and TACE group, respectively, the mortality rate is significantly lower in SR group than TACE group (31 vs. 57%, p < 0.001).

The detailed information of tumor numbers (1, 2, or 3, and >3) and treatment modalities in different tumor burden groups is shown in online Supplementary

Table 1. Characteristics of 474 patients with BCLC-A/B HCC beyond the Milan criteria receiving SR or TACE

Variables	SR (n = 247)	TACE (n = 227)	p value
Age, years	64 (55–75)	68 (58–75)	0.004
Sex			
Male	200 (81)	161 (71)	0.010
Female	47 (19)	66 (29)	
FIB-4 index	2.17 (1.50–3.24)	3.98 (2.29–6.85)	<0.001
ALBI score	−3.01 (−3.22–-2.79)	−2.89 (−2.49–-1.98)	<0.001
AFP, ng/mL	20.9 (4.1–526.5)	40.8 (9.1–373.2)	0.030
HBV positive	136 (55)	112 (49)	0.213
HCV positive	46 (19)	81 (36)	<0.001
Cirrhosis	99 (40)	166 (73)	<0.001
Seven-eleven criteria			
Low (≤7)	76 (31)	73 (32)	0.062
Intermediate (7–11)	117 (47)	86 (38)	
High (>11)	54 (22)	68 (30)	
Tumor number			
1	186 (75)	59 (26)	<0.001
2 or 3	53 (22)	115 (51)	
>3	8 (3)	53 (23)	
Maximum tumor size, cm	7.0 (5.6–9.8)	5.6 (3.7–8.9)	<0.001
Follow-up duration, years	3.9 (2.2–5.2)	2.1 (1.0–4.1)	<0.001
Death	76 (31)	129 (57)	<0.001

Data are expressed as median (interquartile range) or number (percentage). BCLC, Barcelona Clinic Liver Cancer classification; HCC, hepatocellular carcinoma; SR, surgical resection; TACE, transarterial chemoembolization; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000529143). Generally, patients who received SR mostly had single tumor, while those who received TACE mostly had 2 or 3 tumors.

Survival Analysis

We first compared the OS of 474 patients, and the median OS in the SR group was 8.2 years which was significantly longer than 2.8 years in the TACE group (logrank $p < 0.001$) (shown in Fig. 2a). According to the seven-eleven criteria, there were 149 (31%), 203 (43%), and 122 (26%) patients having low, intermediate, and high tumor burden, respectively. The KM curve analysis revealed significant nonoverlapping survival curves of low, intermediate, and high tumor burden groups (logrank $p < 0.001$). The median OS in low, intermediate, and high tumor burden group were 7.7, 6.9, and 2.8 years, respectively (shown in online suppl. Fig. 1).

We then investigated the OS according to the tumor burden. In patients with low tumor burden, the KM curve analysis showed significant overlap of survival curves in the first 2 years post SR or TACE (shown in Fig. 2b). To identify the predictor of OS, univariable analysis showed that high FIB-4 index, high ALBI score, and SR (vs. TACE) were significant predictors of survival (shown in Table 2). The multivariable Cox regression analysis revealed SR had no survival benefit compared with TACE in the low tumor burden group (adjusted hazard ratio [aHR]: 0.82, 95% confidence interval [CI]: 0.43–1.55, $p = 0.532$).

In the intermediate tumor burden group, the KM survival curves revealed SR had a significantly better OS than TACE (8.2 vs. 2.6 years, $p < 0.001$) (shown in Fig. 2c). The univariate analysis showed that age, FIB-4 index, ALBI score, cirrhosis, and SR (vs. TACE) were significant predictors of survival (shown in Table 3). The multivariable Cox regression analysis revealed that SR reduced 55% risk of mortality compared with TACE (aHR: 0.45, 95% CI: 0.27–0.75, $p = 0.002$).

In the high tumor burden group, the KM survival curves revealed SR had significantly better OS than TACE (5.6 vs. 1.5 years, $p = 0.001$) (shown in Fig. 2d). Besides, FIB-4 index, ALBI score, and SR (vs. TACE) were significant predictors of survival in the univariable analysis

Table 2. Cox regression analysis for prediction of OS in 149 patients with low tumor burden

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, 1 year increase	1.00 (0.98–1.03)	0.818	1.00 (0.97–1.02)	0.839
Male (vs. female)	0.77 (0.43–1.39)	0.392	0.81 (0.43–1.51)	0.503
FIB-4 index, 1 point increase	1.07 (1.02–1.13)	0.006	1.01 (0.94–1.09)	0.779
ALBI score, 1 point increase	2.41 (1.50–2.44)	<0.001	2.13 (1.13–4.00)	0.019
AFP, 1 ng/mL increase	1.00 (1.00–1.00)	0.660		
HBV positive (vs. negative)	1.02 (0.59–1.75)	0.943		
HCV positive (vs. negative)	1.37 (0.79–2.38)	0.261		
Cirrhosis (vs. no)	1.79 (0.97–3.22)	0.063		
SR versus TACE	0.54 (0.31–0.94)	0.029	0.82 (0.43–1.55)	0.532

OS, overall survival; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Table 3. Cox regression analysis for prediction of OS in 203 patients with intermediate tumor burden

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, 1 year increase	1.02 (1.01–1.04)	0.011	1.01 (0.99–1.03)	0.193
Male (vs. female)	0.85 (0.50–1.45)	0.557	0.98 (0.57–1.67)	0.938
FIB-4 index, 1 point increase	1.06 (1.02–1.11)	0.005	0.96 (0.90–1.03)	0.256
ALBI score, 1 point increase	2.71 (1.89–3.89)	<0.001	2.19 (1.30–3.68)	0.003
AFP, 1 ng/mL increase	1.00 (1.00–1.00)	0.840		
HBV positive (vs. negative)	1.10 (0.71–1.71)	0.678		
HCV positive (vs. negative)	1.07 (0.66–1.73)	0.794		
Cirrhosis (vs. no)	1.88 (1.18–3.00)	0.008	1.26 (0.74–2.15)	0.388
SR versus TACE	0.29 (0.18–0.46)	<0.001	0.45 (0.27–0.75)	0.002

OS, overall survival; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

(shown in Table 4). The multivariable Cox regression analysis again revealed SR was predictive of better OS compared with TACE (aHR: 0.54, 95% CI: 0.32–0.92, p = 0.022).

Subgroup Analysis Based on Tumor Numbers

Since BCLC-A/B HCC beyond the Milan criteria composed of single large tumor (BCLC-A) and multinodular tumors (BCLC-B), we stratified our patients into two subgroups: single large HCC (n = 245) or multinodular HCCs (n = 229). The baseline characteristics were shown in online supplementary Table 2. Besides, the actual number of HCC is a major determinant for the selection of SR or TACE by physicians, so we also stratified our patients by tumor number in each different tumor burden group.

Single Large HCC

The median OS was significantly better in the SR group (n = 186) than in the TACE group (n = 59) (8.2 vs. 2.7 years, p < 0.001) (shown in Fig. 3a). According to the seven-eleven criteria, there were 74 (30%), 119 (49%), and 52 (21%) patients having low, intermediate, and high tumor burden, respectively. After adjusting for age, sex, and liver reserve, the multivariable analysis showed ALBI score, high tumor burden (vs. low), and SR (vs. TACE) were significant predictors of OS (shown in Table 5). SR reduced 43% risk of mortality compared with TACE (aHR: 0.57, 95% CI: 0.35–0.93, p = 0.023).

Multinodular HCCs

The median OS was significantly better in the SR group (n = 61) than in the TACE group (n = 168) (6.3 vs. 2.8

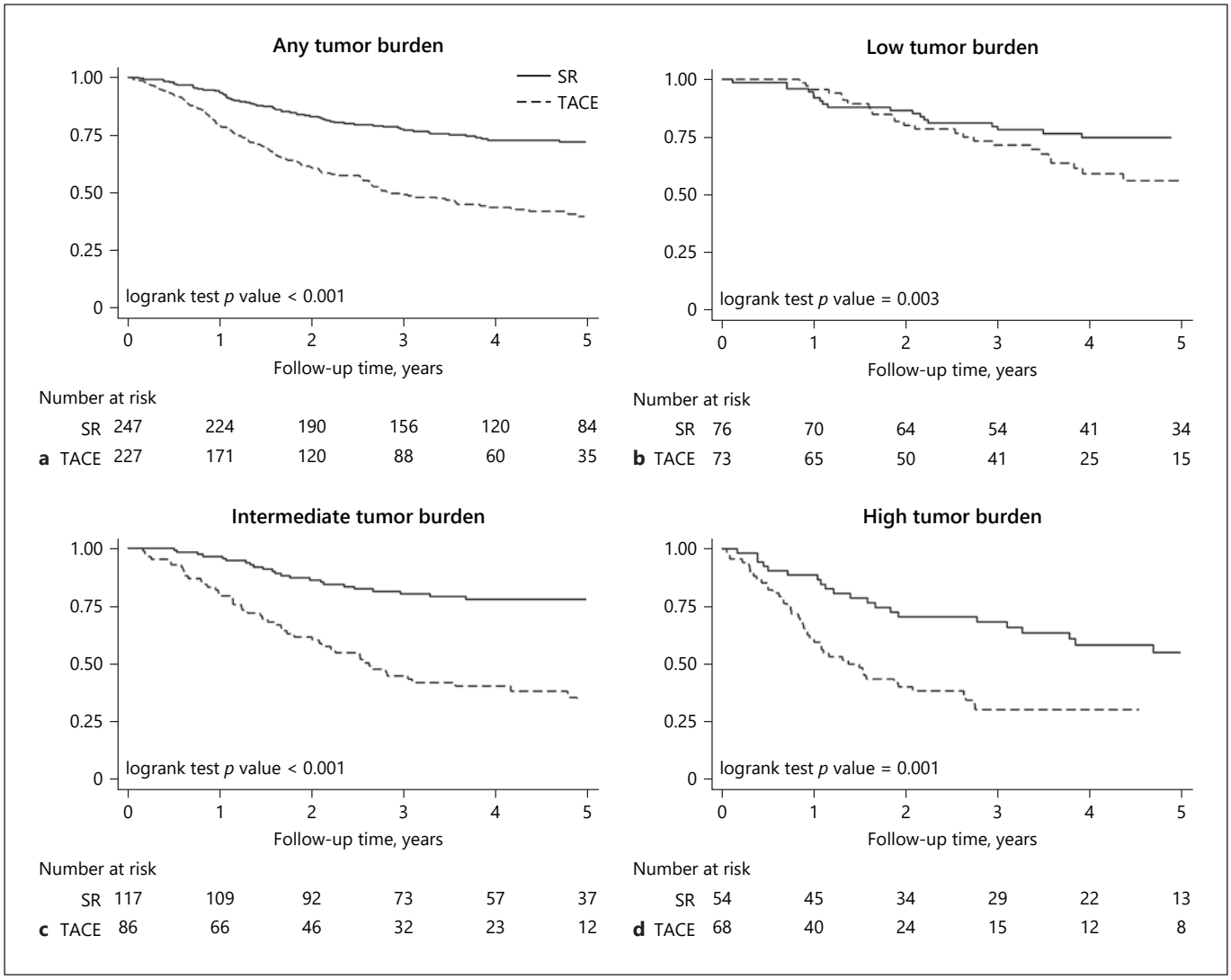

Fig. 2. Kaplan-Meier survival curves between surgical resection (SR) and transarterial chemoembolization (TACE) in patients with BCLC-A/B HCC beyond the Milan criteria with any tumor burden (**a**), low tumor burden (**b**), intermediate tumor burden (**c**) and high tumor burden (**d**) defined by the seven-eleven criteria.

years, $p = 0.008$) (shown in Fig. 3b). According to the seven-eleven criteria, there were 75 (33%), 84 (37%), and 70 (30%) patients having low, intermediate, and high tumor burden, respectively. After adjusting for age, sex, and liver reserve, the multivariable analysis showed age, ALBI score, high tumor burden (vs. low), and SR (vs. TACE) were significant predictors of survival (shown in Table 6). SR reduced 43% risk of mortality compared with TACE (aHR: 0.57, 95% CI: 0.35–0.93, $p = 0.024$).

SR is generally not suitable for tumor number >3, so we further stratify the tumor numbers of ≤3 and >3 in the intermediate and high tumor burden groups. In the intermediate tumor burden group, 176 patients had 1–3 nodule(s). After adjusting for age, sex, FIB-4 index, ALBI score, and treatment modality, the multivariable analysis showed SR reduced 64% risk of mortality compared with TACE (aHR: 0.36, 95% CI: 0.21–0.61, $p < 0.001$) (shown in online suppl. Table 3). However, there was no survival benefit for SR compared with TACE in those with >3 nodules ($n = 27$) because only 4 patients received SR in this subgroup (shown in online suppl. Table 4).

In the high tumor burden group, 102 patients had 1–3 HCC(s). There was a trend that SR had survival benefit compared with TACE after multivariable analysis (HR: 0.58, 95% CI: 0.33–1.01, $p = 0.056$) (shown in online suppl. Table 5). There was no survival benefit for SR

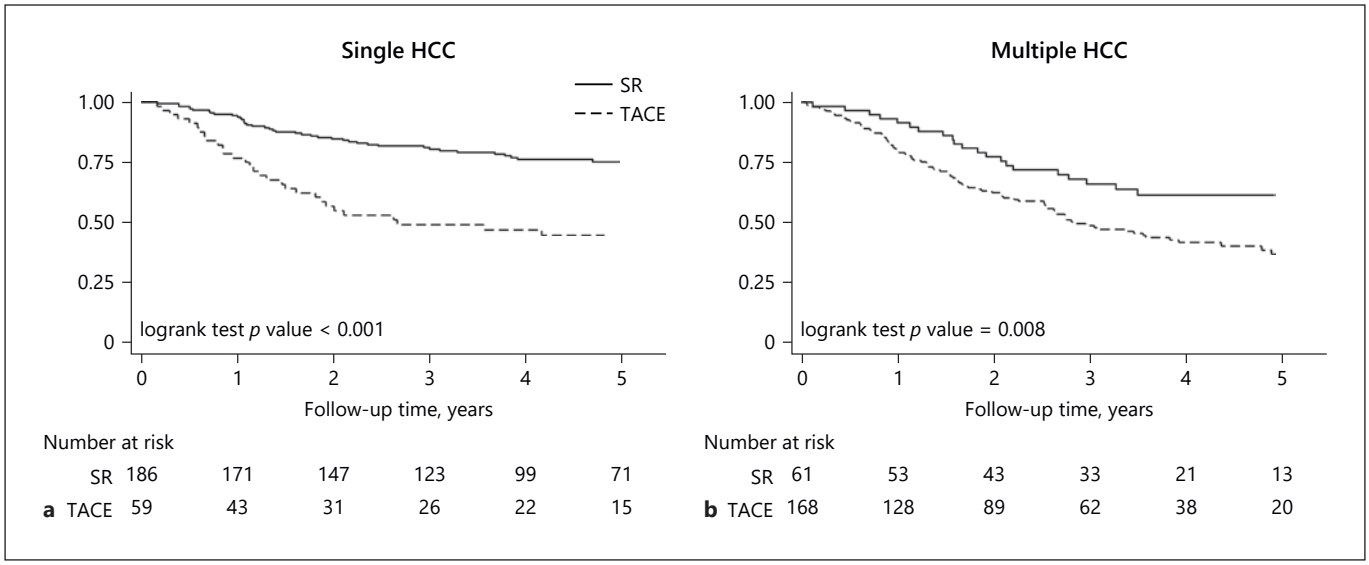

Fig. 3. Kaplan-Meier survival curves between surgical resection (SR) and transarterial chemoembolization (TACE) in patients with single large HCC (**a**) and multinodular HCCs (**b**).

Table 4. Cox regression analysis for prediction of OS in 122 patients with high tumor burden

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, 1 year increase	1.01 (0.99–1.03)	0.265	1.01 (0.99–1.03)	0.259
Male (vs. female)	0.86 (0.48–1.55)	0.624	1.04 (0.57–1.90)	0.891
FIB-4 index, 1 point increase	1.13 (1.05–1.21)	0.005	1.06 (0.97–1.16)	0.190
ALBI score, 1 point increase	1.67 (1.15–2.44)	0.007	1.28 (0.80–2.04)	0.299
AFP, 1 ng/mL increase	1.00 (1.00–1.00)	0.422		
HBV positive (vs. negative)	1.28 (0.80–2.05)	0.296		
HCV positive (vs. negative)	1.72 (0.98–3.03)	0.058		
Cirrhosis (vs. no)	1.00 (0.62–1.59)	0.965		
SR versus TACE	0.46 (0.28–0.75)	0.002	0.54 (0.32–0.92)	0.022

OS, overall survival; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

compared with TACE in those with >3 nodules (n = 20) because only 4 patients received SR in this subgroup (shown in online suppl. Table 6).

Subsequent Treatment after Tumor Recurrence

Subsequent curative treatment after tumor recurrence might affect the OS, especially in the TACE group. The types of the second treatment (n = 135) for the first tumor recurrence after SR included SR (n = 16, 11.9%), TACE (n = 78, 57.8%), RFA (n = 16, 11.9%), chemotherapy (n = 9, 6.7%), radiotherapy (n = 4, 3.0%), cryotherapy (n = 1, 0.7%), supportive care (n = 5, 3.7%), and loss of follow-up (n = 6, 4.4%). In the TACE group (n = 227), 159 patients had recurrence of HCC. The second treatment after first tumor recurrence included SR (n = 2, 1.3%), TACE (n = 126, 79.2%), RFA (n = 24, 15.1%), supportive care (n = 4, 2.5%), percutaneous ethanol injection (n = 1, 0.6%), and loss of follow-up (n = 2, 1.3%). Another 4 patients receiving SR for the second recurrence and 2 patients for de novo HCC at different lobe of liver. The median OS of these 8 patients in the TACE group who had further SR was 4.2 years, and the median OS of the remaining 219 patients of the TACE group was 2.8 years (p = 0.423).

Table 5. Cox regression analysis for prediction of OS in 245 patients with single large HCC

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, 1 year increase	1.01 (0.99–1.02)	0.262	1.00 (0.98–1.02)	0.944
Male (vs. female)	1.04 (0.61–1.78)	0.880	1.10 (0.63–1.92)	0.730
FIB-4 index, 1 point increase	1.14 (1.07–1.21)	<0.001	1.05 (0.97–1.14)	0.201
ALBI score, 1 point increase	3.60 (2.46–5.26)	<0.001	2.49 (1.52–4.07)	<0.001
AFP, 1 ng/mL increase	1.00 (1.00–1.00)	0.607		
HBV positive (vs. negative)	1.19 (0.78–1.81)	0.415		
HCV positive (vs. negative)	1.28 (0.79–2.07)	0.319		
Cirrhosis (vs. no)	1.39 (0.91–2.11)	0.124		
Seven-eleven criteria				
Low tumor burden	1		1	
Intermediate tumor burden	1.20 (0.71–2.01)	0.493	1.27 (0.75–2.15)	0.372
High tumor burden	2.05 (1.17–3.57)	0.012	1.86 (1.01–3.41)	0.046
SR versus TACE	0.35 (0.23–0.54)	<0.001	0.57 (0.35–0.93)	0.023

OS, overall survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Table 6. Cox regression analysis for prediction of OS in 229 patients with multinodular HCCs

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, 1 year increase	1.01 (0.99–1.03)	0.281	1.02 (1.00–1.04)	0.021
Male (vs. female)	0.78 (0.51–1.17)	0.232	0.91 (0.60–1.38)	0.645
FIB-4 index, 1 point increase	1.02 (0.98–1.06)	0.382		
ALBI score, 1 point increase	1.56 (1.16–2.11)	0.004	1.57 (1.13–2.17)	0.007
AFP, 1 ng/mL increase	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001
HBV positive (vs. negative)	1.05 (0.73–1.52)	0.792		
HCV positive (vs. negative)	0.89 (0.60–1.31)	0.546		
Cirrhosis (vs. no)	0.78 (0.52–1.18)	0.236		
Seven-eleven criteria				
Low tumor burden	1		1	
Intermediate tumor burden	1.58 (0.98–2.53)	0.493	1.44 (0.88–2.33)	0.143
High tumor burden	2.95 (1.83–4.75)	<0.001	2.95 (1.79–4.85)	<0.001
SR versus TACE	0.55 (0.35–0.86)	0.009	0.57 (0.35–0.93)	0.024

OS, overall survival; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; FIB-4 index, fibrosis-4 index; ALBI score, albumin-bilirubin score; AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; SR, surgical resection; TACE, transarterial chemoembolization.

Discussion

According to the BCLC classification, SR is indicated only for those patients with very early (BCLC-0) or early-stage (BCLC-A) HCC, while patients with intermediate-stage (BCLC-B) HCC are generally recommended to receive TACE [29]. Because BCLC-B stage comprises a heterogenous patient population, several BCLC-B subclassification systems have been proposed for better outcomes. Bolondi et al. [30] proposed a subclassification of BCLC-B HCCs in 2012. This substaging system incorporates the Child-Pugh score and the "beyond Milan and within up-to-7" criteria. TACE or systemic therapy is recommended when the tumor is beyond the up-to-7 criteria. Kudo et al. [31] proposed the Kinki criteria in 2015. Curative treatments such as resection and ablation are

only recommended in tumors within the up-to-7 criteria. When the tumors are beyond the up-to-7 criteria, patients are suggested to receive noncurative treatment. However, improvements in surgical technique and perioperative care in recent decades have reduced the morbidity and mortality associated with liver resection.

Several studies have shown that SR may provide better survival compared with TACE in patients with HCC beyond the Milan criteria in solitary large tumor or multiple tumors [9, 12–18]. Hsu et al. selected 146 pairs of patients with intermediate-stage HCC with similar baseline characteristics who underwent SR and TACE. Patients who underwent SR had significantly better 1-, 3-, and 5-year OS rates than patients who underwent TACE (82% vs. 65%, 68% vs. 29%, and 46% vs. 22%, respectively, $p < 0.001$) [12]. Zhong et al. enrolled 61 pairs of BCLC-B HCC patients undergoing SR and TACE. Patients who underwent SR had significantly better 1-, 3-, and 5-year survival rates than patients who underwent TACE. The further subgroup analysis of BCLC-B patients with a single large-sized tumor and with multiple tumors revealed that SR still offer better OS than TACE in both types of patients, which indicated large tumor size and multiple tumors should not exclude patients from SR [13]. A multicenter study recruited a total of 2,090 BCLC-A, -B, and -C HCC patients who underwent SR, locoregional therapy such as TACE and ablation, and best supportive care. Overall, SR confirmed higher median OS than TACE in BCLC stages 0, A, and B. After the subgroup analysis, SR had a large positive survival benefit over locoregional therapy in well-selected HCC patients [16]. Lin et al. enrolled 428 BCLC-B patients who received SR ($n = 140$), TACE+RFA ($n = 57$), and TACE ($n = 231$). The OS was significantly better in the SR group than in the TACE+RFA group (HR: 1.78, 95% CI: 1.15–2.75, $p = 0.009$) and in the TACE group (HR: 3.17, 95% CI: 2.31–4.36, $p < 0.001$) [18]. Therefore, it is important to define the criteria of choosing appropriate candidates to receive SR other than TACE in BCLC-A/B patients beyond Milan criteria.

Recently, the seven-eleven criteria were introduced to be most discriminative in predicting radiologic response and OS in patients with BCLC-B HCC undergoing TACE than the up-to-7 criteria and the up-to-11 criteria [22]. Our study demonstrated that SR had better OS than TACE in patients with BCLC-A/B HCC beyond the Milan criteria, and the seven-eleven criteria selected optimal candidates to receive SR. We found that in patients with intermediate to high tumor burden (beyond the up-to-7 criteria), SR had better OS than TACE for resectable tumors with tumor numbers ≤3.

The benefit of SR in patients with intermediate and high tumor burden is probably because of poor TACE responses in these scenarios. The overall response rate to first TACE in patients within the up-to-7 criteria was significantly higher than that in patients beyond the up-to-7 criteria [32]. A recent study showed a higher propensity of TACE refractoriness in patients with BCLC-B HCC beyond the Milan and the up-to-7 criteria [33]. Other studies also demonstrated that tumors beyond the up-to-7 criteria were significantly related to early TACE refractoriness in patients with BCLC-B HCC [32, 34]. Second, liver function reserve tends to deteriorate after TACE in patients with HCC beyond the up-to-7 criteria [33, 35] because they may need multiple cycles of TACE. A decrease in the ALBI score is positively associated with the number of TACE sessions [36]. Thus, TACE seems unsuitable for patients with intermediate and high tumor burden. Poor liver function impacts patients' eligibility for subsequent systemic therapy. Our in-depth analyses demonstrated the survival benefit of SR confines to tumor numbers ≤3. For tumor numbers >3, they are traditionally regarded as SR ineligible and should consider other systemic therapies.

There is a paradigm shift in the treatment options in recent years [37]. For the patients with higher tumor burden but resectable HCC, SR offered more survival benefit than TACE and was recommended as the treatment of choice under careful patient selection [12, 14]. For the patients with higher tumor burden and unresectable HCC, receiving systemic treatment such as lenvatinib as the initial therapy was associated with longer OS, longer progression-free survival, higher objective response rate, and more stationary liver function compared with the patients receiving the standard-of-care of TACE [38, 39]. Thus, initiating systemic therapy first, followed by TACE when needed, was considered as the first-line treatment in the patients with unresectable HCC and high risk of TACE refractoriness in order to preserve liver function and improve OS [37].

Interestingly, the survival benefit of TACE in patients with low tumor burden is comparable to that of SR in our study. Our additional analyses showed that in patients with low tumor burden and single nodule, SR reduced 76% risk of mortality compared with TACE (aHR: 0.24, 95% CI: 0.07–0.78, $p = 0.018$) (shown in online suppl. Table 7). However, in 75 patients with multiple tumors, there was no survival benefit for SR compared to TACE (aHR: 2.01 95% CI: 0.76–5.29, $p = 0.158$) (data not shown). A recent study showed that complete response by initial TACE was the most important variable for OS in patients

with intermediate-stage HCC. "Tumor within the up-to-7 criteria," "<3 liver segments with nodule," and "simple nodular type" were associated with a higher complete response rate. Thus, "within the up-to-7" criteria are considered as one of TACE-eligible criteria [40]. A retrospective study found that HCC within the up-to-7 criteria had better prognosis, higher possibility to downstage to within the Milan criteria, and less Child-Pugh grade deterioration than HCC beyond the up-to-7 criteria in patients who underwent conventional TACE [35]. Therefore, TACE is also an effective treatment for patients with low tumor burden and preserved liver function.

The subsequent curative treatment of HCC would improve the OS, even in patients receiving TACE as the initial treatment. There were 8 patients to receive SR after relapse from TACE and the median OS was 4.2 years, which was 2.8 years in their counterparts. The benefit of initial TACE for downstaging, followed by curative therapy, should be further explored.

There are several limitations to our study. First, this was a retrospective study and the patients were from single center, which may cause some bias between the selection for SR and TACE. In addition, important variables such as tumor extent (unilobar or bilobar) were not included in the analysis. Further prospective studies are required to validate the role of SR for patients with BCLC-A/B HCC beyond the Milan criteria. In conclusion, in patients with BCLC-A/B HCC beyond the Milan criteria with intermediate to high tumor burden (beyond the up-to-7 criteria), SR may offer better OS than TACE in resectable HCC with tumor number ≤3.

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Statement of Ethics

This study was approved by the Institutional Review Board of National Taiwan University Hospital (201808090RINA) and conformed to the ethical principles for medical research involving human subjects of the Declaration of Helsinki updated in 2013. The need for informed consent was waived by the Institutional Review Board of National Taiwan University Hospital.

Conflict of Interest Statement

T.-H.S. received research grant from Gilead Sciences and was on speaker's bureaus for AbbVie, Bayer, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp and Dohme, and Takeda. J.-H.K. has served as a consultant for AbbVie, Gilead Sciences, Merck Sharp and Dohme, and Roche and on speaker's bureaus for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp, and Dohme. Others declare no conflict of interests.

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Author Contributions

Chian-Tzu Huang contributed to study concept and design, analysis and interpretation of data, and drafting the manuscript; Yu-Long Chu contributed to study concept and design, acquisition of data, analysis and interpretation of data, and drafting the manuscript; Tung-Hung Su contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, and obtain funding; Shang-Chin Huang, Tai-Chung Tseng, Shih-Jer Hsu, Sih-Han Liao, Chun-Ming Hong, Chen-Hua Liu, Hung-Chih Yang, and Chun-Jen Liu contributed to analysis and interpretation of data; Pei-Jer Chen contributed to study supervision and analysis and interpretation of data; and Jia-Horng Kao contributed to study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision. All authors contributed substantially to critically reviewing or revising the manuscript for important intellectual content and approved the final manuscript.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request and approved by the Institutional Review Board. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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