



Comparison of prognosis between surgical resection and transarterial chemoembolization for patients with solitary huge hepatocellular carcinoma

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Background: For patients with solitary huge (>10 cm in size) hepatocellular carcinoma (HCC) and without major vascular invasion, the treatment efficacy between surgical resection (SR) and transarterial chemoembolization (TACE) is not well studied. We aimed to compare the prognoses between SR and TACE for patients with solitary huge HCC.

Methods: We enrolled 143 patients with treatment-naïve, solitary HCC (>10 cm) who had received either SR or TACE treatment between 2007–2016. Factors of overall survival (OS) were analyzed by multivariate analysis. Propensity scores matching (PSM) method was adopted to adjust baseline demographic differences for further analysis.

Results: Ninety patients underwent SR and 53 patients received TACE. After a median follow-up of 17.0 (interquartile range 7.7–45.6) months, 83 patients had died. The cumulative 5-year OS rate was 44.7% and 11.7% for the SR group and the TACE group, respectively ($P < 0.001$). A multivariate analysis showed that TACE [hazard ratio (HR): 3.515, 95% confidence interval (CI): 2.202–5.610, $P < 0.001$], and albumin-bilirubin (ALBI) grade >1 (HR: 2.181, 95% CI: 1.343–3.543, $P = 0.002$) were the independent risk factors associated with poorer OS. After PSM, 37 pairs of matched patients were selected from each treatment arm. After matching, patients who underwent SR still evinced a significantly higher OS than did those who underwent TACE ($P = 0.010$).

Conclusions: SR provided a better OS than did TACE for patients with solitary huge (≥ 10 cm) HCC. As such, SR is recommended as the therapeutic priority for these patients.

Keywords: Hepatocellular carcinoma (HCC); prognosis; propensity score matching; surgical resection; transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the second most lethal malignancy after pancreatic cancer (1), being responsible for 745,500 deaths worldwide in 2012 and ranking as the second and sixth most common cause of cancer among men and women, respectively (2). According to the current standards of HCC management, treatments are classified as either curative or non-curative (3). Curative treatments include surgical resection (SR), liver transplantation, and local ablation therapies, which could provide a median overall survival (OS) of over five years for HCC patients after treatment (1). Non-curative treatments include transarterial chemoembolization (TACE), transarterial radioembolization, external beam radiotherapy, and systemic therapy (e.g., molecular target therapy, immune-based therapy). For patients with huge (>10 cm in diameter) HCC, local ablation is unfeasible because the tumor size exceeds physical limitation. Liver transplantation is also inapplicable given that the size exceeds the current criteria (4-6). Consequently, SR and TACE are more popular alternatives in this clinical context.

However, HCC patients with a larger tumor size displayed a higher incidence of vascular invasion and satellite nodules relative to those with a smaller tumor (7). Considering that vascular invasion is a major risk factor for tumor recurrence and poor OS after surgery (8-11), the indication and treatment efficacy of SR for patients with huge HCC is a topic of debate. Generally, Asian countries have adopted more liberal application of SR for HCC (12,13), whereas the current guidelines for the management of HCC set by the European Association for the Study of the Liver (EASL) limited SR to patients with solitary HCC, well-preserved liver function, normal portal pressure and serum bilirubin levels, good performance status, and without extra-hepatic metastasis or vascular invasion (14). However, there is a growing body of evidence suggesting that SR could yield favorable outcomes for HCC patients with portal hypertension, size exceeding 5 cm, multiple tumors, macroscopic vascular invasion, or even for those presenting with solitary extra-hepatic organ involvement (7,15-22). Another widely-applied classification system in Asia, Hong Kong Liver Cancer (HKLC), adopted more liberal criteria to SR (23).

Theoretically speaking, in the absence of distant metastasis and major vascular invasion, a clear-margin resection seems to serve as a curative therapy regardless of tumor size and number (16,21). We hypothesized that,

for patients with solitary huge HCC in addition to well-preserved liver function, SR may still provide a survival advantage over the guideline-endorsed treatment TACE. To test this hypothesis, the long-term prognoses between SR and TACE for patients with single huge HCC were compared.

Methods

Patients

A prospectively conducted and retrospectively analyzed cohort study was conducted. The diagnosis of HCC was established according to the criteria set forth by the American Association for the Study of Liver Disease (AASLD) (24). All patients newly diagnosed with HCC at Taipei General Veterans Hospital were discussed to determine treatment strategy by a weekly-convened, multi-discipline HCC panel meeting attended by an oncologist, gastroenterologist, surgeon, radiologist, pathologist, onco-radiologist, and nursing personnel (25,26). Following the meeting, treatment modality decision was shared with the patient and the physician after discussing the risks, benefits, complications, efficacies of the currently available treatments, and the multidisciplinary experts' recommendations. The demographic characteristics, treatment modalities, and prognoses of all patients with newly diagnosed HCC were prospectively recorded in the database for the multidisciplinary committee.

In this study, the inclusion criteria were as follows: (I) treatment-naïve HCC; (II) solitary tumor with size ≥ 10 cm; (III) well-preserved liver function with Child-Pugh grade A or B; (IV) absence of major portal branch invasion by computed tomography scan or magnetic resonance imaging; (V) absence of distant metastases; and (VI) SR or TACE as the first treatment for HCC.

The study was conducted in accordance with the Declaration of Helsinki and current ethical guidelines. It was approved by the Institutional Review Board (IRB) of the Taipei Veterans General Hospital. Informed consent was obtained before the patient underwent SR or TACE. Patient information was anonymized prior to the initiation of this study.

Statistical analysis

The primary endpoint of this study was OS. All patients were followed up until either their final hospital visit,

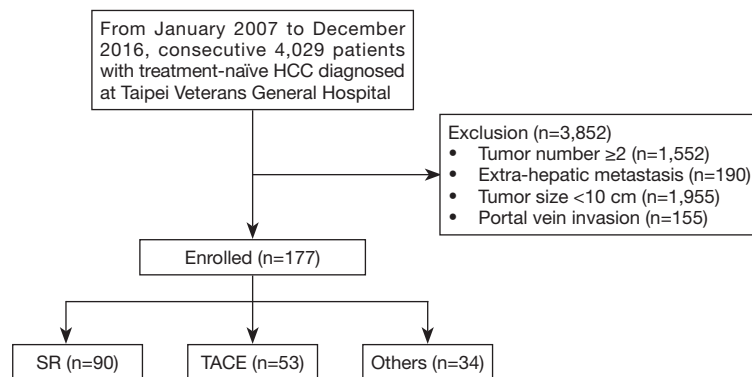


Figure 1 The study flow chart.

death, or December 31, 2017. Student's *t*-test and Mann-Whitney U test were adopted for parametric and non-parametric distributed continuous variables, respectively. χ^2 test and Fisher's exact test were applied for parametric and non-parametric nominal variables, respectively. Kaplan-Meier survival analysis was adopted for estimating OS after therapy. Cox proportional hazards model was employed to determine the factors associated with OS. Factors with a P value <0.05 in the univariate analysis were enrolled to multivariate analysis by a forward stepwise Cox's regression model.

We were aware that baseline demographic differences may confound OS analysis results. Therefore, a propensity-matched scoring (PSM) method was used to adjust for differences of demographic characteristics and tumor factors between the two groups of patients as previously described (27,28). Subsequently, a one-to-one match between the SR and TACE groups was obtained using the nearest-neighbor matching method. Survival analysis was repeated to compare the OS between SR and TACE amended from these confounding factors. A two-tailed P value <0.05 was defined as statistically significant. All statistical analyses were performed by IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline demographic characteristics

From January 2007 to December 2016, a total of 4,029 patients were diagnosed with HCC in our center. Among these, 177 presented with a solitary huge HCC with a characteristic tumor size ≥ 10 cm, and without main portal branch invasion or distant metastases. Ninety of these

patients underwent SR, 53 patients underwent TACE, and the remaining 34 patients received another treatment such as radiotherapy, chemotherapy, or best supportive treatments (Figure 1).

As shown in Table 1, patients who underwent SR were younger than their TACE counterparts ($P=0.001$). Regarding the viral etiology, although results were not statistically significant, patients who had undergone SR displayed a trend of higher rate of hepatitis B virus (HBV) infection and lower rate of antibodies against hepatitis C virus (HCV) in sera relative to those treated with TACE. Otherwise, gender, tumor size, and liver functional reserve did not differ significantly between the two groups.

Factors related to OS

There were two mortality cases within 30 days after TACE and no cases in the SR group. The 90 days mortality were six and two cases in the TACE group and in the SR group respectively. Following a median follow-up period of 17.0 (interquartile range IQR 7.7–45.6) months, 83 patients had died. As shown in Figure 2A, the 1-, 2-, 3-, and 5-year cumulative OS rate for patients who underwent SR and TACE were 78.1% vs. 45.1%, 67.5% vs. 27.6%, 58.3% vs. 20.7%, and 44.7% vs. 11.7%, respectively. The median OS was 55.7 (95% confidence interval CI: 23.4–88.1) months and 11.6 (95% CI: 8.5–14.6) months for patients receiving SR and TACE, respectively. Patients treated with SR displayed better survival relative to those treated with TACE ($P<0.001$).

A univariate analysis disclosed that TACE, low platelet count, prothrombin time (PT) international normalized ratio (INR) ≥ 1.15 , serum bilirubin ≥ 1.0 mg/dL, and albumin-bilirubin (ALBI) grade 2 or 3 (Figure 2B) were

Table 1 Baselines demographics of enrolled patients

	All patients (n=143)	SR (n=90)	TACE (n=53)	P
Age (years)	65.0, 54.0–76.0	62.0, 52.0–72.0	73.0, 61.5–79.0	0.001
Gender (M/F) (%)	117/26 (81.8/18.2)	75/15 (83.3/16.7)	42/11 (79.2/20.8)	0.540
BMI (kg/m ²)	23.6, 21.5–25.9	24.0, 21.9–26.2	23.0, 20.9–25.4	0.283
AFP (ng/mL)	92.0, 5.2–6,595.3	87.7, 4.3–6,944.2	123.7, 9.0–6,309.8	0.583
Tumor size (cm)	12.4, 11.0–14.4	12.4, 11.0–14.3	12.4, 10.8–15.0	0.665
HBsAg (+/-) (%)	82/54 (60.3/39.7)	57/30 (65.5/34.5)	25/24 (51/49)	0.097
Anti-HCV (+/-) (%)	15/110 (12/88)	6/72 (7.7/92.3)	9/38 (19.1/80.9)	0.056
MELD	8.3, 7.2–9.7	8.0, 7.1–9.7	8.7, 7.3–10.1	0.746
ALBI	-2.46, -2.79–2.11	-2.49, -2.87–2.11	-2.31, -2.67–1.96	0.053
ALBI (1/2/3) (%)	53/82/7 (37.3/57.7/4.9)	36/51/3 (40/56.7/3.3)	17/31/4 (32.7/59.6/7.7)	0.386
Child-Pugh class (A/B) (%)	122/5 (96.1/3.9)	78/4 (95.1/4.9)	44/1 (97.8/2.2)	0.655
Albumin(mg/dL)	3.7, 3.4–4.1	3.7, 3.4–4.2	3.6, 3.3–4.0	0.215
Bilirubin (U/L)	0.80, 0.58–1.15	0.74, 0.57–1.06	0.92, 0.63–1.51	0.080
Platelet (/mm ³)	217,000, 160,000–284,000	226,000, 167,000–297,000	196,000, 148,000–256,000	0.129
PT INR	1.07, 1.02–1.14	1.07, 1.01–1.14	1.07, 1.02–1.18	0.340
Hgb (mg/dL)	12.5, 10.9–14.1	12.8, 11.4–14.5	11.9, 10.0–13.6	0.167
BUN (mg/dL)	16, 12–19	15, 11–19	17, 12–20	0.062
Creatinine (mg/dL)	0.91, 0.75–1.12	0.90, 0.74–1.10	0.95, 0.76–1.17	0.594
ALT (U/L)	43, 28–71	39, 26–72	46, 32–71	0.795
GGT (U/L)	87, 54–151	82, 50–124	114, 58–214	0.457
ALKP (U/L)	112, 82–161	103, 79–133	138, 96–191	0.054

Continuous variables are expressed as the median with 25th and 75th percentiles. SR, surgical resection; TACE, transarterial chemoembolization; BMI, body mass index; AFP, α -fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; PT INR, prothrombin time/international normalized ratio; HgB, hemoglobin; ALT, alanine aminotransferase; GGT, γ -glutamyl transferase; ALKP, alkaline phosphatase.

associated with poorer OS for patients with a solitary huge HCC (Table 2). Multivariate analysis showed that TACE (HR: 3.515, 95% CI: 2.202–5.610, $P < 0.001$) and ALBI grade 2 or 3 (HR: 2.181, 95% CI: 1.343–3.543, $P = 0.002$) were the independent factors predicting poorer OS. Subgroup analysis further revealed that, in the majority of patient subgroups, patients who underwent SR had a better OS than those who had received TACE, with the exception of female patients and patients with a PT INR ≥ 1.15 (Figure 2C).

Comparison of OS between SR and TACE after PSM analysis

Because the baseline demographic characteristics were dissimilar between patients who underwent SR of TACE, a PSM analysis was performed to adjust for the differences between both of these groups. Subsequently, 74 patients (37 per group) were selected. As shown in Table 3, following the PSM, baseline demographics between both groups were well-matched, and survival analysis still indicated that SR

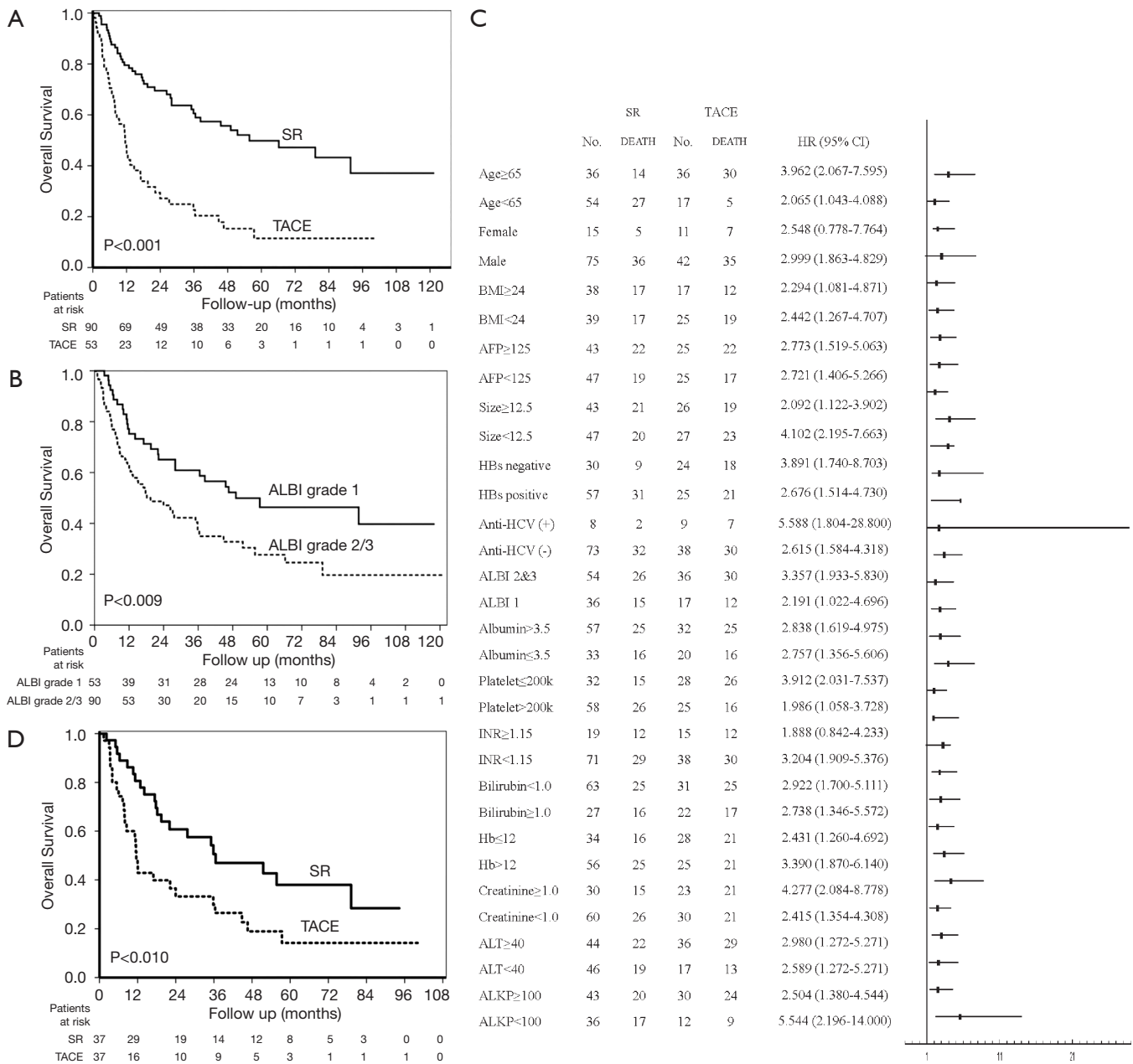


Figure 2 Comparison of OS rates between different treatment modalities, ALBI grades, and demographic characteristics and tumor factors. (A) Comparison of OS rates between patients having undergone SR and TACE before PSM. (B) Comparison of OS rates between patients with ALBI grade 1 and those with ALBI grade 2 or 3. (C) Subgroup analysis for the comparison of OS rates between patients having undergone SR or TACE. (D) Comparison of OS rates between patients having undergone SR or TACE after PSM. OS, overall survival; ALBI, albumin-bilirubin; SR, surgical resection; TACE, transarterial chemoembolization; PSM, propensity scores matching.

Table 2 Factors associated with poor overall survival in HCC

Variable	N (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
TACE/SR	53/90 (37.1/62.9)	3.022 (1.952–4.680)	<0.001	3.515 (2.202–5.610)	<0.001
Age (y/o) >65/≤65	68/75 (47.6/52.4)	1.310 (0.851–2.018)	0.220		
Gender F/M	26/117 (18.2/81.8)	0.731 (0.396–1.350)	0.317		
BMI (kg/m ²) ≥24/<24	55/63 (46.6/53.4)	0.957 (0.586–1.562)	0.859		
AFP (ng/mL) ≥125/<125	68/72 (48.6/51.4)	1.536 (0.988–2.389)	0.056		
Size (cm) >12.5/≤12.5	67/76 (46.9/53.1)	0.817 (0.530–1.259)	0.360		
HBsAg, N/Y	54/82 (39.7/60.3)	0.644 (0.404–1.026)	0.064		
Anti-HCV, N/Y	110/15 (87.7/12.3)	0.804 (0.399–1.619)	0.541		
ALBI 2 & 3/1	89/53 (62.7/37.3)	1.873 (1.173–2.990)	0.009	2.181 (1.343–3.543)	0.002
MELD >8/≤8	79/64 (55.2/44.8)	2.206 (1.398–3.481)	0.001		
Albumin (mg/dL) ≤3.5/>3.5	88/53 (37.6/62.3)	1.438 (0.921–2.247)	0.110		
Platelet (/mm ³) >200,000/≤200,000	82/60 (57.7/42.3)	1.603 (1.042–2.466)	0.032		
PT INR ≥1.15/<1.15	34/108 (23.9/76.1)	1.904 (1.181–3.069)	0.008		
Bilirubin (mg/dL) ≥1.0/<1.0	49/92 (34.8/65.2)	1.652 (1.061–2.573)	0.026		
Hgb (mg/dL) ≤12/>12	62/80 (43.7/56.3)	1.064 (0.690–1.642)	0.778		
BUN (mg/dL) ≥20/<20	33/106 (23.7/76.3)	0.951 (0.568–1.592)	0.848		
Creatinine (mg/dL) ≥1.0/<1.0	53/89 (37.3/62.7)	1.339 (0.864–2.075)	0.192		
ALT (U/L) ≥40/<40	80/62 (56.3/43.7)	1.202 (0.772–1.872)	0.415		
ALKP (U/L) ≥100/<100	73/47 (60.8/39.2)	1.235 (0.758–2.010)	0.396		

CI, confidence interval; SR, surgical resection; TACE, transarterial chemoembolization; BMI, body mass index; AFP, α -fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; PT INR, prothrombin time/international normalized ratio; Hgb, hemoglobin; ALT, alanine aminotransferase; ALKP, alkaline phosphatase.

resulted in better OS than did TACE ($P=0.010$; *Figure 2D*).

Comparison of OS between SR and TACE stratified by ALBI grade

As treatment modality and ALBI grade were the independent factors correlated with poorer OS according to multivariate analysis, we further compared the prognoses between patients receiving SR or TACE by stratification by ALBI grade. In our cohort, although most patients were in Child-Pugh class A liver functional reserve (96.1%), the proportion of ALBI grade was 37.3%, 57.7%, and 4.9% for grade 1, 2, and 3, respectively. The distribution of ALBI grades in SR and TACE groups did not present statistically significant differences ($P=0.386$). Survival analysis showed

that SR had better survival than TACE, both in terms of ALBI grade 1 (*Figure 3A*, $P=0.030$) and ALBI grade 2 or 3 (*Figure 3B*, $P<0.001$). For patients with ALBI grade 1, the 1-, 2-, 3-, and 5-year cumulative OS rate for patients having undergone SR vs. TACE were 83.2% vs. 58.8%, 77.3% vs. 39.2%, 71.1% vs. 39.2%, and 58.0% vs. 24.5%, respectively. For those with ALBI grade 2 or 3, the 1-, 2-, 3-, and 5-year cumulative OS rate for patients having undergone SR vs. TACE were 77.1% vs. 38.1%, 64.1% vs. 21.8%, 52.2% vs. 14.5%, and 43.8% vs. 5.4%, respectively.

Factors of OS and recurrence-free survival in SR group

Among the 90 patients who underwent SR, 75 patients (83.3%) reached R0 resection (no cancer cells were found

Table 3 Demographic data of HCC patients after propensity score matching

Variable	Overall (n=74)	SR (n=37)	TACE (n=37)	P
Age (years)	67.5, 54.0–76.0	67.0, 55.0–74.0	68.0, 54.0–77.5	0.889
Gender (M/F) (%)	58/16 (78.4/21.6)	29/8 (78.4/21.6)	29/8 (78.4/21.6)	1.000
BMI	22.7, 20.7–25.4	22.9, 20.9–26.0	22.6, 20.3–24.9	0.624
AFP (ng/mL)	57.8, 4.6–1907.7	17.9, 3.9–1907.7	97.9, 5.8–4485.6	0.511
Tumor size (cm)	12.9, 11.0–15.0	12.9, 11.0–14.3	12.8, 10.9–16.5	0.465
HBsAg (+/-) (%)	39/34 (53.4/46.6)	18/18 (50/50)	21/16 (56.8/43.2)	0.731
Anti-HCV (+/-) (%)	9/65 (12.2/87.8)	5/32 (13.5/86.5)	4/33 (10.8/89.2)	0.469
MELD	8.5, 7.3–10.0	8.0, 7.1–10.1	8.7, 7.3–10.2	0.712
ALBI	-2.39, -2.68 to -1.89	-2.40, -2.63 to -1.97	-2.38, -2.69 to 1.71	0.493
ALBI (1/2/3) (%)	22/46/6 (29.7/62.2/8.1)	9/26/2 (24.3/70.3/5.4)	13/20/4 (35.1/54.1/10.8)	0.334
Albumin (mg/dL)	3.6, 3.3–4.1	3.6, 3.3–4.1	3.7, 3.3–4.1	0.948
Platelet ($1,000 \mu\text{L}^{-1}$)	213, 160.7–270	223, 159.5–277	209, 162.5–262	0.935
PT INR	1.07, 1.02–1.16	1.07, 1.02–1.14	1.10, 1.06–1.22	0.473
Bilirubin (U/L)	0.91, 0.60–1.52	0.80, 0.58–1.36	0.95, 0.64–1.60	0.328
HgB (mg/dL)	12.0, 10.4–14.0	11.6, 10.9–14.3	12.3, 10.3–13.8	0.681
BUN (mg/dL)	16, 12–19	15, 11.5–19.5	16, 11.8–19.0	0.329
Creatinine (mg/dL)	0.86, 0.69–1.05	0.88, 0.69–1.02	0.85, 0.70–1.08	0.858
ALT (U/L)	45.5, 30–81	45, 27.5–88	47, 32–76	0.914
GGT (U/L)	104, 61–151.5	91, 61–122.5	119.5, 58.8–216	0.634

Continuous variables are expressed as the median with 25th and 75th percentiles. SR, surgical resection; TACE, transarterial chemoembolization; BMI, body mass index; AFP, α -fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; PT INR, prothrombin time/international normalized ratio; HgB, hemoglobin; ALT, alanine aminotransferase; GGT, γ -glutamyl transferase.

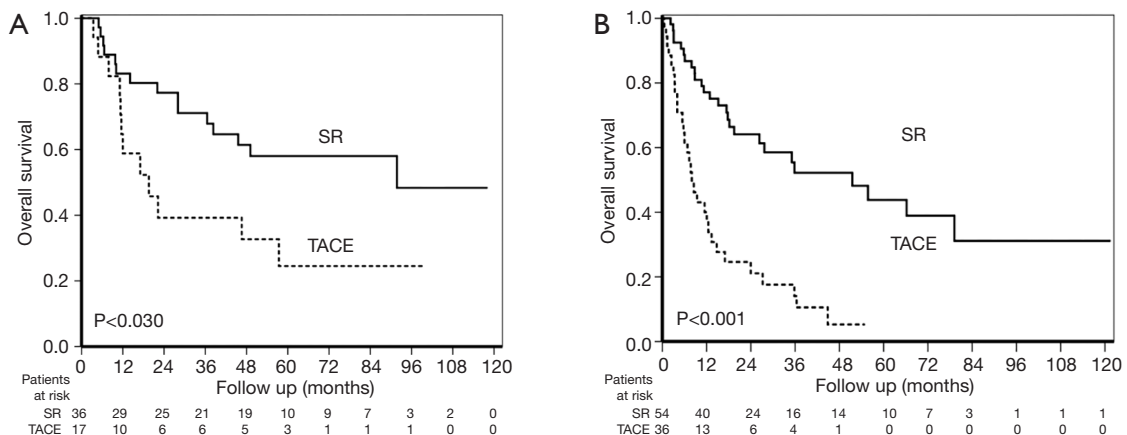


Figure 3 Comparison of OS rates between SR and TACE stratified by the ALBI grades. (A) ALBI grade 1; (B) ALBI grade 2 or 3. OS, overall survival; SR, surgical resection; TACE, transarterial chemoembolization; ALBI, albumin-bilirubin.

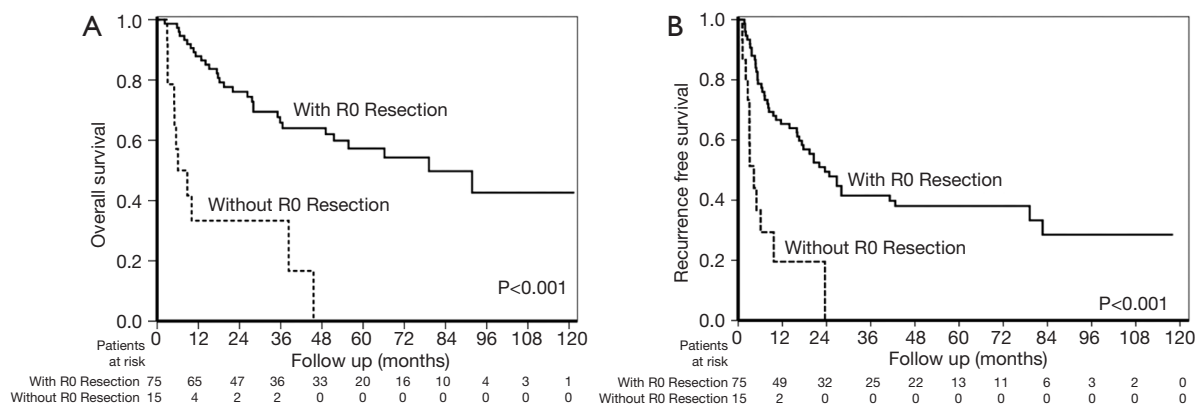


Figure 4 Comparison of prognoses between patients with and without R0 resection in the SR group. (A) OS rates; (B) RFS rates. SR, surgical resection.

in surgical margin, and tumor was completely resected). Pathological examination showed that 9 (10%) patients had macrovascular invasion, and 79 patients (87.8%) had microvascular invasion in their surgical specimen. When stratified by the status of R0 resection, the cumulative 1-, 2-, 3-, and 5-year cumulative OS rates were 87.9% vs. 33.3%, 76.1% vs. 33.3%, 65.9% vs. 33.3% and 57.3% vs. 0% in the R0 resection group and in the non-R0 resection group, respectively (Figure 4A, $P < 0.001$).

As shown in Table 4, a multivariate analysis disclosed the independent prognostic factors to poorer OS included ALBI grade 2 or 3 (HR: 4.252, 95% CI: 1.998–9.049, $P < 0.001$) and no R0 resection (HR: 6.341, 95% CI: 2.903–13.851, $P < 0.001$).

Besides, 46 patients developed tumor recurrence after tumor resection. The median recurrence time was 5.7 (IQR 3.2–14.4) months. The median recurrence free survival (RFS) was 19.4 (IQR 13.1–25.7) months. The cumulative 1-, 2-, 3-, and 5-year cumulative RFS rates were 65.3% vs. 19.6%, 49.4% vs. 0%, 41.5% vs. 0% and 38.1% vs. 0%, respectively in the R0 resection group and in the non-R0 resection group, respectively (Figure 4B, $P < 0.001$).

A multivariate analysis showed that age > 65 years (HR: 2.004, 95% CI: 1.106–3.636, $P = 0.022$), serum alpha-fetoprotein (AFP) level ≥ 125 ng/mL (HR: 1.772, 95% CI: 1.024–3.067, $P = 0.041$), ALBI grade 2 or 3 (HR: 5.055, 95% CI: 2.687–9.511, $P < 0.001$) and no R0 resection (HR: 5.458, 95% CI: 2.644–11.264, $P < 0.001$) were the independent factors predicting poorer RFS (Table 5).

Discussion

Our study reports several major findings. First, for patients with a solitary huge HCC, SR yielded a better long-term OS than did TACE, which was further substantiated by multivariate analysis, PSM analysis, and subgroup analysis. SR was found to be safe and may be served as the front-line treatment modality for such patients given that they are not contraindicated for the operation. Second, ALBI grade possessed a discriminatory capability to predict prognosis for patients with solitary huge HCC. It suggested that liver functional reserve still played a crucial role in determining the outcomes of patients with huge HCC, and it could provide an important reference to predict prognosis in this clinical setting.

Regarding evaluation of SR's suitability for patients with HCC, Eastern and Western medicinal perspectives might differ. For the Eastern world, large size, microscopic portal vein invasion, and presence of clinically significant portal hypertension (CSPH) do not alter surgeons' judgement on carrying out resection once a clear-cut margin is attainable and liver function is well-reserved (12,16,29,30). Conversely, SR is discouraged in such clinical contexts by their Western counterparts (6). The present study showed that, for patients with solitary huge HCC in which the tumor size exceeded the Milan criteria, the median OS and 5-year cumulative OS rate in those having undergone SR were 55.7 months and 44.7%, respectively. The results appeared satisfactory when compared to the previous results (31–33),

Table 4 The univariate and multivariate with poor overall survival of patients in the SR group

Variable	N (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age (y/o) >65/≤65	33/57 (36.7/63.3)	0.839 (0.439–1.601)	0.594		
Gender F/M	15/75 (16.7/83.3)	0.672 (0.623–1.716)	0.406		
BMI (kg/m ²) ≥24/<24	38/38 (50/50)	1.074 (0.545–2.115)	0.836		
AFP (ng/mL) ≥125/<125	43/47 (47.8/52.2)	1.453 (0.786–2.689)	0.233		
Size (cm) >12.5/≤12.5	43/47 (47.8/52.2)	1.107 (0.598–2.049)	0.746		
Macrovascular invasion Y/N	9/81 (10/90)	1.801 (0.752–4.310)	0.187		
Microvascular invasion Y/N	79/11 (87.8/12.2)	9.345 (1.280–66.667)	0.028		
R0 resection N/Y	15/75 (16.7/83.3)	5.649 (2.720–11.732)	<0.001	6.341 (2.903–13.851)	<0.001
HBsAg N/Y	32/56 (36.4/63.6)	0.475 (0.232–0.975)	0.032		
Anti-HCV N/Y	72/6 (92.3/7.7)	1.784 (0.426–7.468)	0.428		
ALBI 2 & 3/1	54/36 (60/40)	3.063 (1.506–6.240)	0.002	4.252 (1.998–9.049)	<0.001
MELD >8/≤8	43/47 (44.2/63.8)	2.176 (1.156–4.096)	0.016		
Albumin (mg/dL) ≤3.5/>3.5	34/56 (37.8/62.2)	1.406 (0.377–1.339)	0.290		
Platelet (/mm ³) >200,000/≤200,000	33/57 (36.7/63.3)	1.060 (0.561–2.004)	0.856		
PT INR ≥1.15/<1.15	20/70 (28.6/71.4)	2.115 (1.074–4.165)	0.030		
Bilirubin (mg/dL) ≥1.0/<1.0	62/28 (68.9/31.1)	1.647 (0.877–3.092)	0.121		
Hgb (mg/dL) ≤12/>12	35/55 (38.9/61.1)	1.006 (0.536–1.889)	0.985		
BUN (mg/dL) ≥20/<20	21/69 (23.3/76.7)	0.595 (0.263–1.345)	0.212		
Creatinine (mg/dL) ≥1.0/<1.0	31/59 (34.4/65.6)	1.075 (0.567–2.038)	0.825		
ALT (U/L) ≥40/<40	45/45 (50/50)	1.047 (0.565–1.941)	0.885		
ALKP (U/L) ≥100/<100	44/35 (55.7/44.3)	1.118 (0.582–2.147)	0.738		

CI, confidence interval; SR, surgical resection; BMI, body mass index; AFP, α -fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; PT INR, prothrombin time/international normalized ratio; Hgb, hemoglobin; ALT, alanine aminotransferase; ALKP, alkaline phosphatase.

and they were significantly better than those for patients who underwent TACE. Although major vascular invasion was excluded from our study, microscopic vascular invasion was expected in the majority of enrolled patients due to the tumor size surpassing 10 cm in diameter (7). Indeed, by pathological examination, macroscopic and microscopic vascular invasion were found in 10.0% and 87.8% of the patients in the SR group, respectively. However, both macroscopic and microscopic vascular invasion were not associated with poorer OS and RFS by multivariate analysis. By stead, ALBI grade and R0 resection could determine the outcomes of patients with solitary huge HCC after

SR. It implied that microscopic vascular invasion did not appear to hinder SR effectiveness relative to TACE if liver function was well preserved and R0 resection could be achieved. However, more prospective studies are warranted to elucidate the impact of microscopic vascular invasion on the outcomes of patients with solitary huge HCC and on the selection of the treatment modality for these patients.

The HKLC system classifies patients with HCC size exceeding 5 cm, numbers less than 3, and good liver functional reserve (Child-Pugh class A) as IIb (23). In their cohort, SR and TACE comprised the most common treatment modalities in this tumor stage. Moreover, SR

Table 5 The univariate and multivariate with poor recurrence-free survival of patients in the SR group

Variable	N (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Age (y/o) >65/≤65	33/57 (36.7/63.3)	1.686 (0.964–2.949)	0.067	2.004 (1.106–3.636)	0.022
Gender F/M	15/75 (16.7/83.3)	0.463 (0.199–1.078)	0.074		
BMI (kg/m ²) ≥24/<24	38/38 (50/50)	1.108 (0.632–1.940)	0.721		
AFP (ng/mL) ≥125/<125	43/47 (47.8/52.2)	1.750 (1.041–2.941)	0.035	1.772 (1.024–3.067)	0.041
Size (cm) >12.5/≤12.5	43/47 (47.8/52.2)	1.208 (0.721–2.025)	0.472		
Macrovascular invasion Y/N	9/81 (10/90)	1.789 (0.808–3.953)	0.151		
Microvascular invasion Y/N	79/11 (87.8/12.2)	3.344 (1.199–9.346)	0.021		
R0 resection N/Y	15/75 (16.7/83.3)	3.861 (1.977–7.542)	<0.001	5.458 (2.644–11.264)	<0.001
HBsAg N/Y	32/56 (36.4/63.6)	0.739 (0.416–1.311)	0.301		
Anti-HCV N/Y	72/6 (92.3/7.7)	0.982 (0.352–2.741)	0.973		
ALBI 2 & 3/1	54/36 (60/40)	3.645 (1.992–6.673)	<0.001	5.055 (2.687–9.511)	<0.001
MELD >8/≤8	43/47 (44.2/63.8)	1.385 (0.826–2.322)	0.217		
Albumin (mg/dL) ≤3.5/>3.5	34/56 (37.8/62.2)	1.712 (1.011–2.907)	0.045		
Platelet (/mm ³) >200,000/≤200,000	33/57 (36.7/63.3)	1.122 (0.651–1.933)	0.679		
PT INR ≥1.15/<1.15	20/70 (28.6/71.4)	1.477 (0.795–2.746)	0.217		
Bilirubin (mg/dL) ≥1.0/<1.0	62/28 (68.9/31.1)	1.471 (0.858–2.523)	0.161		
Hgb (mg/dL) ≤12/>12	35/55 (38.9/61.1)	0.720 (0.415–1.251)	0.244		
BUN (mg/dL) ≥20/<20	21/69 (23.3/76.7)	0.673 (0.348–1.300)	0.238		
Creatinine (mg/dL) ≥1.0/<1.0	31/59 (34.4/65.6)	0.983 (0.570–1.694)	0.950		
ALT (U/L) ≥40/<40	45/45 (50/50)	0.991 (0.588–1.699)	0.972		
ALKP (U/L) ≥100/<100	44/35 (55.7/44.3)	0.982 (0.558–1.726)	0.982		

SR, surgical resection; CI, confidence interval; BMI, body mass index; AFP, α -fetoprotein; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MELD, model for end-stage liver disease; ALBI, albumin-bilirubin; PT INR, prothrombin time/international normalized ratio; Hgb, hemoglobin; ALT, alanine aminotransferase; ALKP, alkaline phosphatase.

could provide a survival benefit relative to TACE. Hence, SR is the recommended treatment in this clinical setting. Our study further validated that, even for patients with HCC tumor size exceeding 10 cm, SR could proffer better survival than could TACE. A further liberal step beyond current guideline-charted territory of SR may be justified.

Conventional assessment of liver reserve, the Child-Pugh classification, is not sufficiently accurate because the extents of ascites and encephalopathy were subjective variables (34). Furthermore, Child-Pugh class was originally designed for cirrhotic patients, and its use in

patients with HCC prognosis may be inaccurate (35). Accordingly, Johnson recently proposed that ALBI scores, which incorporated both serum albumin and bilirubin levels, could provide a simple, objective, and evidence-based method for the evaluation of liver function for patients with liver cirrhosis or HCC (36). Moreover, it has been validated to accurately predict the prognoses of patients with HCC across different tumor stages and treatment modalities (34–41).

In our cohort, although most patients fell in the Child-Pugh class A (96.1%), only 37.3% of the patients were

classified as ALBI grade 1. For these patients, ALBI grade still presented as an excellent predictor of prognosis. For patients with ALBI grade 1, the 5-year OS rate after SR was as high as 58.0%. This suggests that, for patients with solitary huge HCC and ALBI grade 1 liver reserve, SR could be encouraged as the front-line treatment rather than be restricted to guideline-endorsed treatment, given that resection is highly likely to yield favorable long-term outcomes.

By the current concept, SR is a curative treatment modality while TACE is regarded as a non-curative local regional therapy for the treatment of HCC. Nevertheless, for patients with solitary huge HCC, substantial patients received TACE because of the concerns of safety and treatment efficacy of SR due to large tumor burden and the presence of microvascular invasion. In our cohort, no patient died within 30 days after the operation in the SR group. Moreover, the 90-day mortality rates were also lower in the SR group when compared to that in the TACE group. Besides, the OS rate was also better in the SR group even given in the fact that most of the patients who underwent SR had microscopic invasion. It is suggested that SR could be served as the front-line therapy for solitary huge HCC if the patients with a well-preserved liver function and R0 resection could be achieved.

There were some limitations to our study. First, the study was retrospective and, second, our institution is a tertiary referral medical center. Hence, selection bias cannot be ruled out. Third, SR is—at minimum—a partially operator-dependent intervention. Our institutional experience may deviate from that of other institutions. Fourth, approximately 60% of patients had chronic HBV infection. In Taiwan, HBV is the major viral factor attributed to HCC carcinogenesis. On the other hand, chronic HCV infection accounts for the majority of HCC in Western countries, as patients with HBV-induced HCC might have a lower rate of cirrhosis and better liver functional reserve relative to HCV-related HCC (42,43). Conversely, regarding tumor factors, patients with HBV-related HCC seemed to have a higher rate of harboring gene signatures in the proliferation class, which was associated with poor prognosis compared to HCV-related HCC (1). Consequently, whether different initial carcinogenic factors resulted in identical disease course and prognosis remains to be elucidated. Hence, generalizations of our results should remain conservative, with external validation from other cohorts highly encouraged. Fifth, several new treatment modalities, such as drug-eluting beads TACE, selective internal radiation

therapy, molecular target therapy, and immune checkpoint inhibitors have been applied for patients with large HCC (1). Further prospective studies are warranted to assess the treatment efficacy and prognosis of these new treatment modalities for patients with solitary huge HCC.

In conclusion, for patients with solitary huge HCC, absence of major portal vein invasion, and no extra-hepatic metastasis, SR resulted in better survival than did TACE.

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Footnote

Conflicts of Interest: Chien-Wei Su: Speakers' bureau: Gilead Sciences, Bristol-Myers Squibb, AbbVie, Bayer, and Roche. Advisory arrangements: Gilead Sciences. Other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and current ethical guidelines. It was approved by the Institutional Review Board (IRB) of the Taipei Veterans General Hospital. Informed consent was obtained before the patient underwent SR or TACE.

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