World Journal of

Gastrointestinal Surgery

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ABOUT COVER

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AIMS AND SCOPE

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RESPONSIBLE EDITORS FOR THIS ISSUE

Observational Study

Liver resection for hepatocellular carcinoma larger than 10 cm: A multi-institution long-term observational study

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Abstract

BACKGROUND
The treatment of hepatocellular carcinoma (HCC) ≥ 10 cm remains a challenge.

AIM
To consolidate the role of surgical resection for HCC larger than 10 cm.

METHODS
Eligible HCC patients were identified from the Chang Gung Research Database, the largest multi-institution database, which collected medical records of all patients from Chang Gung Memorial Foundation. The surgical outcome of HCC ≥ 10 cm (L-HCC) was compared to that of HCC < 10 cm (S-HCC) (model 1). The survival of L-HCC after either liver resection or transarterial chemoembolization (TACE) was also analyzed (model 2). The long-term risks of all-cause mortality and recurrence were assessed to consolidate the role of surgery for L-HCC.

RESULTS
From January 2004 to July 2015, a total of 32403 HCC patients were identified from the Chang Gung Research Database. Among 3985 patients who received liver resection, 3559 (89.3%) had S-HCC, and 426 had L-HCC. The L-HCC patients had a worse disease-free survival (0.27 for L-HCC *vs* 0.40 for S-HCC) and overall survival (0.18 for L-HCC *vs* 0.45 for S-HCC) than the S-HCC after liver resection (both $P < 0.001$). However, the surgical and long-term outcome of resected L-HCC had improved dramatically in the recent decades. After adjusting for covariates, surgery could provide a better outcome for L-HCC than TACE (adjusted hazard ratio of all-cause mortality: 0.46, 95% confidence interval: 0.38-0.56 for surgery). Subgroup analysis stratified by different stages showed similar trend of survival benefit among L-HCC patients receiving surgery.

CONCLUSION
Our study demonstrated an improving surgical outcome for HCC larger than 10 cm. Under selected conditions, surgery is better than TACE in terms of disease control and survival and should be performed. Due to inferior survival, a subclassification within T1 stage should be considered. Future studies are mandatory to confirm our findings.

Key Words: Hepatocellular carcinoma; 10 cm; Liver resection; Transarterial chemoembolization; Chang Gung Research Database

Core Tip: By analyzing the data from one of the largest clinical databases worldwide, the current study demonstrated an improving surgical outcome for hepatocellular carcinoma ≥ 10 cm. Under selected conditions, surgery is better than transarterial chemoembolization in terms of disease control and survival. Due to inferior survival for HCC ≥ 10 cm, a subclassification within T1 stage should be considered.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a lethal malignancy of liver and ranks as one of the most common causes of cancer-related death globally[1-3]. Liver resection remains as an effective treatment for HCC, but the underlying chronic liver injury has hampered

the feasibility of surgery[4-11]. Fortunately, with improvements in preoperative preparation, operative techniques, surgical instruments, and perioperative care, the mortality rate of this challenging operation has been greatly reduced[4,12-14]. According to a recent study, the 30-d and in-hospital mortality rates after hepatectomy for HCC were both below 3%[15,16]. As a result, liver resection is recommended by most guidelines as one of the standard curative treatments for HCC.

Among published guidelines, the Barcelona Clinic Liver Cancer (BCLC) staging system is acknowledged by major academic societies worldwide. Both the Taiwan Liver Cancer Association, the American Association for the Study of Liver Diseases, and the European Association for the Study of Liver have recognized BCLC system to guide the treatment for patients with HCC[17-19]. According to BCLC, liver resection is the preferred treatment for patients with BCLC stage 0 and A diseases. Asymptomatic large (> 5 cm) HCC without major vascular invasion or extrahepatic spread, on the other hand, should receive transarterial chemoembolization (TACE) since it is categorized as intermediate stage disease (BCLC B)[20,21]. However, major guidelines have not excluded liver resection for HCC greater than 5 cm[17,18], and there were also studies addressing the surgical outcome of large HCC[22,23]. The best management for large HCC, particularly those greater than 10 cm, remains undetermined as a result. Studies comprising larger sample size and longer follow-up are therefore required to recommend treatment guidelines for these large HCC.

The Chang Gung Research Database contains all medical records of the Chang Gung Memorial Foundation since year 2000 and has become one of the largest clinical databases worldwide[24-26]. The current study, by utilizing the data from the Chang Gung Research Database (CGRD) and comparing them with our previous results, aimed to consolidate the role of liver resection for HCC ≥ 10 cm.

MATERIALS AND METHODS

Data source

The CGRD, which collected the clinical information from seven Chang Gung memorial hospitals in Taiwan, was the primary data source of the current study. With more than 280000 admissions by 10070 beds, 8500000 outpatient visits, and 500000 emergency visits each year, the CGRD has become an excellent database for various kinds of clinical studies[24-26]. For cancer patients, it contains comprehensive cancer registry maintained in a prospective manner. The information obtained from the cancer registry is manually validated with a high completeness rate[27,28]. Both the International Classification of Diseases, 9th and 10th revision, Clinical Modification codes and the International Classification of Diseases, 3rd edition are used in the CGRD. For personal privacy, the individual identity is protected by encryption. The medical information is prospectively digitalized and stored in the CGRD and is amenable for researchers to perform large-scale retrospective analysis.

Study population and protocol

Figure 1 is the flow diagram of the current study. The diagnosis of HCC in Taiwan is made when two of the following criteria are met: α-fetoprotein (AFP) ≥ 400 ng/mL, positive findings on multi-phasic magnetic resonance imaging or computed tomography liver scan, and pathological confirmation, according to the recommendations from the American Association for the Study of Liver Diseases and the Gastroenterological Society in Taiwan[17,19]. HCC patients diagnosed from January 2004 to July 2015 were retrieved from the CGRD database (*n* = 32403). The first date of definite diagnosis for HCC was set as the index date. These eligible subjects were followed until December 2017. Two models were designed for outcome analysis: Model 1, patients with HCC ≥ 10 cm (L-HCC) or HCC < 10 cm (S-HCC) receiving curative-intent liver resection; model 2, patients with HCC ≥ 10 cm receiving either curative-intent liver resection or TACE as the primary treatment. The surgical indications and techniques were based on our previous publications[15,16,29]. Patients who underwent liver transplantation for HCC were excluded from the current study. The primary outcome was overall survival (OS), while HCC-related survival and disease-free survival (DFS) were the secondary outcomes. OS was calculated from the index date to the date of death or the end of year 2017. HCC-related survival spanned the period between the index date and the date of liver-cause mortality. The liver-causes included tumor recurrence, metastasis, and complications of decompensated liver cirrhosis. DFS defined the period between the index date and the date of the first documented clinical recurrence or the end of year 2017. In addition, the evolution of
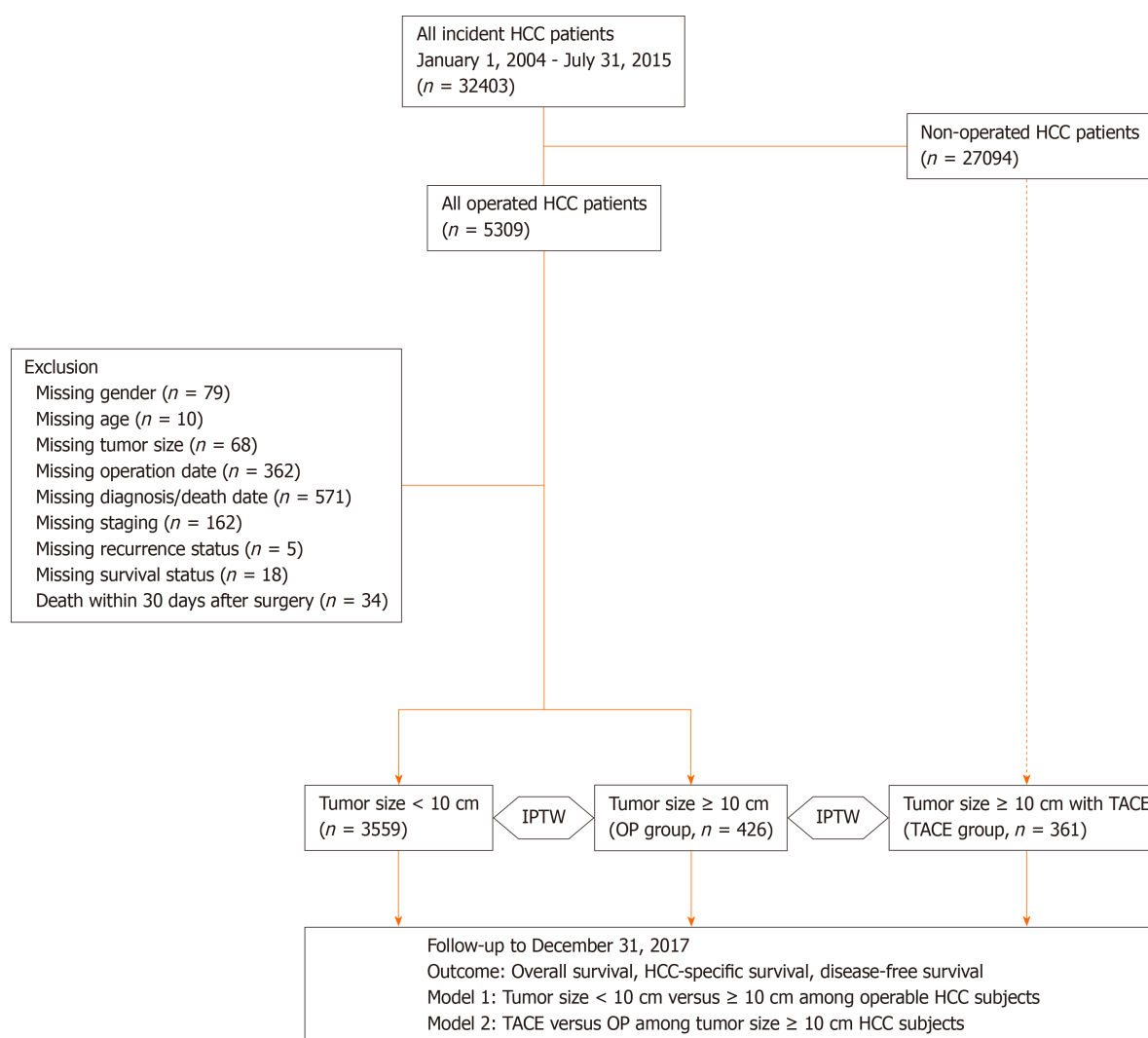
Figure 1 Flow diagram of the current study. Hepatocellular carcinoma (HCC) patients diagnosed from January 2004 to July 2015 were retrieved from the Chang Gung Research Database (CGRD; *n* = 32403). Two models were designed for analysis: model 1, patients with HCC ≥ 10 cm (L-HCC; 426 patients) or HCC < 10 cm (S-HCC; 3559 patients) receiving liver resection; model 2, patients with HCC ≥ 10 cm receiving either liver resection or transarterial chemoembolization (TACE; 361 patients) as the primary treatment. The primary outcome was overall survival (OS), while HCC-specific survival and disease-free survival (DFS) were the secondary outcomes.

surgical outcome for HCC ≥ 10 cm from separate cohorts of different era was also examined. Tumor was staged by the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis staging system for HCC, 6th and 7th edition[30-32]. The study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital, No. 202000608B0.

Statistical analysis

The demographic features were presented as either continuous numbers with mean ± SD or counts with proportion (in percentage), and all covariates were compared by either *t*-test or chi-square statistics according to the nature of the covariates. To eliminate the potential confounding bias originating from heterogeneous baseline features and disproportionate case numbers, inverse-probability of treatment weighting between different groups was adopted[33,34]. The following covariates were considered: Gender, age, lifestyle, co-morbidities, viral hepatitis, tumor size, tumor stage, BCLC stage, and biochemical profiles including AFP, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, indocyanine green retention test at 15 min, and prothrombin time with international normalize ratio. These covariates were selected to generate the propensity score. Then 1/ps was assigned as the weight of L-HCC subjects receiving liver resection (model 1 and 2), while 1/1-ps was assigned as the weight of S-HCC subjects receiving surgery (model 1) or L-HCC subjects receiving TACE (model 2). To estimate the survival, Kaplan-Meier curves with log-rank tests were used, and, after

applying inverse-probability of treatment weighting (IPTW) to each subject, cox-regression analysis was employed to assess the hazard ratio (HR). Both the unadjusted and adjusted HR were acquired. Subgroup analysis was performed to investigate further the outcome in different stages of HCC. All statistics were analyzed by STATA software version 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16, College Station, TX, USA: StataCorp LLC.), and the statistical significance was defined as a *P* value of less than 0.05.

RESULTS

Patient demographics

We first identified 32403 patients diagnosed to have HCC from the CGRD. Among them, 5309 patients received liver resection for their HCC. After excluding patients with missing data and 30-d surgical mortality, a total of 3985 patients were enrolled into our final analysis. Among them, 3559 (89.3%) patients had smaller HCC (S-HCC), and 426 (10.7%) had HCC larger than 10 cm (L-HCC). As for the remaining 27069 non-operated HCC patients, 361 (13.3%) patients underwent TACE-based treatment for their large HCC (Figure 1). Tables 1 and 2 summarized the demographic data of HCC patients receiving liver resection. The mean age of HCC diagnosis was 58.7-years-old, and 77% were male. Hepatitis B virus (HBV) infection was the most common cause (52%), followed by chronic hepatitis C virus (HCV) infection (28%). Earlier stage HCC (AJCC stage I and II) accounted for around 80% of all operated patients.

When comparing HCC of different sizes, L-HCC patients were significantly younger than their S-HCC counterparts (55.7 *vs* 59.1 years, *P* < 0.001). There were considerably more male and less diabetes mellitus in the L-HCC group (*P* = 0.031 and 0.006, respectively). While the prevalence of HBV infection was comparable between the two groups, there was significantly less HCV infection in the L-HCC group (L-HCC *vs* S-HCC, 10% *vs* 31%, *P* < 0.001). The non-viral cause, on the other hand, accounted for a remarkably greater proportion of L-HCC patients (40% *vs* 23%, *P* < 0.001). As for the underlying liver function, the serum levels of aspartate aminotransferase and alkaline phosphatase and prothrombin time were higher in the L-HCC group (All *P* < 0.05), while that of albumin was lower in the L-HCC group (*P* < 0.001). The serum level of AFP, on the other hand, was significantly higher in the L-HCC group *P* < 0.001). The levels of alanine aminotransferase and bilirubin were similar between the two groups. As for the disease severity, L-HCC was far more advanced in terms of AJCC stage in both eras (Table 1).

Surgical outcome and long-term survival of L-HCC after liver resection

The 30-d surgical mortality rate was 2.1% in the L-HCC group and 0.7% in the S-HCC group (*P* = 0.003). After excluding these patients with surgical mortality, the L-HCC (426 patients) and S-HCC (3559 patients) groups were followed for a mean of 1175 d and 1733 d, respectively. Around 60% of L-HCC patients developed tumor recurrence during postoperative follow-up, compared to 44% in the S-HCC group (*P* < 0.001). Local recurrence was the most common pattern of HCC recurrence in both groups (L-HCC, 51.2%; S-HCC, 70.7%); however, distant metastasis occurred more frequently in the L-HCC group (L-HCC, 18.4%; S-HCC, 5.5%, *P* < 0.001). The 1-, 3-, and 5-year DFS rate was 48.5%, 36.1%, and 31.1% in the L-HCC group and 78.3%, 61.7%, and 55.3% in the S-HCC group (all *P* < 0.001) (Table 3). Kaplan-Meier analysis found that the L-HCC group had a significantly worse DFS than the S-HCC group (median DFS, 329 d in the L-HCC and 1024 d in the S-HCC, log-rank *P* < 0.001) (Figure 2). At the end of this study, 41.1% of L-HCC patients were still alive, compared to 68.1% in the S-HCC group. Liver-related causes remained the most common reason of death in both groups (45.8% and 22.3% of total, respectively). The 1-, 3-, and 5-year OS rate was 75.8%, 53.3%, and 46.2% in the L-HCC group and 94.2%, 83.0%, and 75.6% in the S-HCC group (all *P* < 0.001) (Table 3). Kaplan-Meier analysis found that the L-HCC group had a significantly worse OS than the S-HCC group (median OS, 801.5 d in the L-HCC and 1579 d in the S-HCC, log-rank *P* < 0.001) (Figure 2, with IPTW; Supplementary Figure 1, without IPTW).

Risks of tumor recurrence and mortality after adjusting for covariates

Before applying IPTW, the L-HCC group had a significantly higher risk of tumor recurrence than the S-HCC group [adjusted HR (aHR), 1.85, 95% confidence interval (CI), 1.60-2.13, *P* < 0.001] (Table 4). The risk of tumor recurrence was still significantly higher in the L-HCC group after matched analysis by applying IPTW (aHR, 1.73,

Table 1 Demographic data (categorical) of hepatocellular carcinoma patients undergoing liver resection, *n* (%), *n* = 3985

Variables		Total	S-HCC, < 10 cm	L-HCC, ≥ 10 cm	*P* value
Number[1]		3985 (100)	3559 (89)	426 (11)	
Gender	Male	3061 (77)	2716 (76)	345 (81)	0.031
Age	≤ 20	9 (< 1)	4 (< 1)	5 (1)	< 0.001
	21-40	292 (7)	240 (7)	52 (12)	
	41-60	1668 (42)	1478 (42)	190 (45)	
	≥ 61	2016 (51)	1837 (52)	179 (42)	
Diabetes	Yes	831 (21)	764 (21)	67 (16)	0.006
Hypertension	Yes	1172 (29)	1053 (30)	119 (28)	0.480
HBV surface antigen	Positive	2074 (52)	1849 (52)	225 (53)	0.740
Anti-HCV antibody	Positive	1135 (28)	1091 (31)	44 (10)	< 0.001
Non-HBV non-HCV	Yes	986 (25)	815 (23)	171 (40)	< 0.001
Cigarette smoking	Yes	380 (10)	330 (9)	50 (12)	0.100
Alcohol consumption	Yes	322 (8)	277 (8)	45 (11)	0.047
Betel nut	Yes	109 (3)	93 (3)	16 (4)	0.170
AJCC 6th (2002-2009)		1771	1577	194	
	Stage I	1035 (58)	973 (62)	62 (32)	< 0.001
	Stage II	347 (20)	307 (19)	40 (21)	
	Stage III	364 (21)	279 (18)	85 (44)	
	Stage IV	25 (1)	18 (1)	7 (4)	
AJCC 7th (2010-2015)		2214	1982	232	
	Stage I	1064 (48)	1031(52)	33 (14)	< 0.001
	Stage II	783 (35)	717 (36)	66 (28)	
	Stage III	341 (15)	220 (11)	121 (52)	
	Stage IV	26 (1)	14 (1)	12 (5)	

[1]Number excluded surgical mortality (30-d mortality).

AJCC: American Joint Committee on Cancer; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; L-HCC: Hepatocellular carcinoma ≥ 10 cm; S-HCC: Hepatocellular carcinoma < 10 cm.

95%CI, 1.40-2.15, *P* < 0.001). Subgroup analysis revealed that, for patients in the same stage, the L-HCC group was associated with a significantly higher risk of tumor recurrence than the S-HCC group (aHR, 1.62, 95%CI, 1.02-2.56, *P* = 0.042 for stage I; aHR, 1.70, 95%CI, 1.28-2.27, *P* < 0.001 for stage II; aHR, 2.14, 95%CI, 1.74-2.63, *P* < 0.001 for stage III). As for the risk of death, the L-HCC group had a significantly higher risk of all-cause mortality than the S-HCC group both without and with IPTW analysis (aHR, 1.95, 95%CI, 1.68-2.26, *P* < 0.001, and aHR, 2.07 95%CI, 1.70-2.51, *P* < 0.001, respectively). In subgroup analysis, the risk of all-cause mortality was still significantly higher in the L-HCC group (stage I to stage III, all *P* < 0.05). Similarly, the risk of liver-cause mortality was significantly higher in the L-HCC group both without and with IPTW analysis (aHR, 2.16, 95%CI, 1.82-2.56, *P* < 0.001, and aHR, 2.15 95%CI, 1.73-2.67, *P* < 0.001, respectively). With IPTW analysis, all stage I to stage III L-HCC patients were found to have a significantly higher risk of liver-cause mortality than the S-HCC patients in the same stage (all *P* < 0.05).

Comparison of treatment outcome between different eras

Table 5 compared the treatment results between the current study and those of the same institute conducted more than 20 years ago[22]. Between 1982 and 2001, which was the first era, there were 211 patients operated for their L-HCC. The mean age of diagnosis was 47.8 years in the first era, which was a lot younger than that of the

Table 2 Demographic data (continuous) of hepatocellular carcinoma patients undergoing liver resection, *n* = 3985

Variables		Total	S-HCC, < 10 cm	L-HCC, > 10 cm	*P* value
		Mean ± SD	Mean ± SD	Mean ± SD	
Tumor size	cm	4.41 ± 3.98	3.36 ± 2.14	13.14 ± 4.95	< 0.001
Age	yr	58.7 ± 12.4	59.1 ± 12.1	55.7 ± 14.3	< 0.001
Alpha-fetoprotein	ng/mL	6156.3 ± 60012	2400.7 ± 19087	40531.8 ± 178925	< 0.001
Albumin	g/dL	3.8 ± 0.6	3.8 ± 0.6	3.5 ± 0.7	< 0.001
Alkaline phosphatase	U/L	97.9 ± 104.4	90.1 ± 75.6	161.1 ± 221.4	< 0.001
AST	U/L	81.3 ± 158.1	76.4 ± 140.0	121.8 ± 261.2	< 0.001
ALT	U/L	85.1 ± 144.8	84.2 ± 133.5	92.2 ± 217.0	0.290
Bilirubin-direct	mg/dL	0.4 ± 0.8	0.4 ± 0.8	0.4 ± 0.6	0.400
Bilirubin-total	mg/dL	1.1 ± 1.3	1.1 ± 1.4	1.1 ± 1.0	0.680
ICG-15	%	9.7 ± 7.9	9.9 ± 8.1	8.0 ± 5.8	< 0.001
PT	seconds	11.8 ± 2.1	11.7 ± 2.0	12.0 ± 2.6	0.019

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HCC: Hepatocellular carcinoma; ICG-15: Indocyanine green retention test at 15 minutes; L-HCC: Hepatocellular carcinoma ≥ 10 cm; PT: Prothrombin time; SD: Standard deviation; S-HCC: Hepatocellular carcinoma < 10 cm.

current study (55.7 years, the second era). Male patients constituted the majority of these L-HCC in both eras (around 80%). Interestingly, while the proportion of chronic HCV infection remained similar (11.6% and 10.3% in the first and second eras, respectively), HBV infection declined dramatically from 81.9% in the first era to 52.8% in the second era. The 30-d, or surgical mortality rate, improved from 4.3% in the first era to 2.1% in the second era. As for the oncological outcome, the 1-, 3-, and 5-year DFS rates improved from 32.9%, 18.8%, and 12.7%, respectively, in the first era to 48.5%, 36.1%, and 31.1%, respectively, in the second era. The 1-, 3-, and 5-year OS rates were also much prolonged in the second era (48.1%, 24.0%, and 16.7%, respectively, in the first era, and 75.8%, 53.3%, and 46.2%, respectively, in the second era).

Surgery vs TACE for HCC larger than 10 cm
A total of 361 patients received TACE as the primary treatment for their large HCC (TACE group). As shown in Supplementary Table 2, the TACE group was significantly older with more HCV infection than the hepatectomy group (all *P* < 0.05). While the gender distribution (male, 81%) and tumor size (13.1 cm) were comparable between the two groups, the TACE group was far more advanced than the hepatectomy group in terms of AJCC staging and BCLC staging (*P* < 0.001). Furthermore, the degree of liver impairment in terms of liver biochemistry was also more severe in the TACE group. Supplementary Table 4 summarizes the treatment outcome of L-HCC after either hepatectomy or TACE. The 30-d and 90-d mortality rates were significantly higher in the TACE group than in the hepatectomy group (30-d, 6.5% *vs* 2.1%, *P* = 0.002; 90-d, 27.5% *vs* 7.8%, *P* < 0.001). More than 90% of patients in the TACE group could not achieve disease-free during their treatments, as compared to only 16.2% in the hepatectomy group (*P* < 0.001). At the end of this study, 41.1% of hepatectomy group were still alive, compared to 13.9% in the TACE group. Liver-related causes remained the most common cause of death in both groups (45.8% and 72.3% of total, respectively). The 1-, 3-, and 5-year OS rate was 75.8%, 53.3%, and 46.2% in the hepatectomy group and 36.0%, 17.5%, and 15.0% in the TACE group (all *P* < 0.001) (Supplementary Table 4). Kaplan-Meier analysis found that the TACE group had a significantly worse OS than the hepatectomy group (median OS, 801.5 d in the hepatectomy group and 243 d in the TACE group, *P* < 0.001) (Figure 3, with IPTW; Supplementary Figure 2, without IPTW). Subgroup analysis showed that the hepatectomy group still enjoyed a significantly better OS than the TACE group in either BCLC stage B/C patients or AJCC stage I to stage IV patients (Figure 4 and Supplementary Figure 3, respectively). Regarding the risk of death, the hepatectomy group had a significantly reduced risk of all-cause mortality than the TACE group both without and with IPTW matched analysis (aHR, 0.37, 95%CI, 0.30-0.47, *P* < 0.001, and aHR, 0.38 95%CI, 0.30-0.48, *P* < 0.001, respectively). In subgroup analysis, the risk

Table 3 Surgical and oncological outcome of patients with hepatocellular carcinoma, *n* (%)			
	S-HCC, < 10 cm	**L-HCC, ≥ 10 cm**	***P*-value**
Surgical mortality at 30-d	25 (0.7)	9 (2.1)	0.003
Patient number[1]	3559 (100)	426 (100)	
Follow-up times in d, mean ± SD	1733.1 ± 1071.5	1175.3 ± 1034.2	< 0.001
Recurrence status			< 0.001
Yes	1568 (44.1)	256 (60.1)	
No	1735 (48.7)	101 (23.7)	
Never disease free	256 (7.2)	69 (16.2)	
Recurrence pattern			< 0.001
Local[2]	1109 (70.7)	131 (51.2)	
Regional[3]	88 (5.6)	10 (3.9)	
Combined[4]	63 (4.0)	36 (14.1)	
Distant	87 (5.5)	47 (18.4)	
Death without recurrence	221 (14.1)	32 (12.5)	
Disease free survival in d, median (IQR)	1024 (413-1907)	329 (121-1244)	< 0.001
1-yr DFS rate	2585 (78.3)	173 (48.5)	< 0.001
3-yr DFS rate	2037 (61.7)	129 (36.1)	< 0.001
5-yr DFS rate	1828 (55.3)	111 (31.1)	< 0.001
Final status			< 0.001
Alive	2424 (68.1)	175 (41.1)	
Death - liver cause	795 (22.3)	195 (45.8)	
Death - other cause	340 (9.6)	56 (13.1)	
Overall survival (d) [median (IQR)]	1579 (871-2455)	801.5 (362-1818)	< 0.001
1-yr OS rate	3354 (94.2)	323 (75.8)	< 0.001
3-yr OS rate	2954 (83.0)	227 (53.3)	< 0.001
5-yr OS rate	2689 (75.6)	197 (46.2)	< 0.001

[1]Number excluded surgical mortality (30-d mortality).

[2]Local recurrence include resection margin/remnant liver or trocar site.

[3]Regional recurrence include adjacent organs/regional LNs, or both.

[4]Combined recurrence include local and regional recurrence.

DFS: Disease-free survival; HCC: Hepatocellular carcinoma; IQR: Interquartile range; L-HCC: Hepatocellular carcinoma ≥ 10 cm; OS: Overall survival; SD: Standard deviation; S-HCC: Hepatocellular carcinoma < 10 cm.

of all-cause mortality was still significantly lower for the hepatectomy group in both BCLC stage B/C patients and AJCC stage I to IV patients (all $P < 0.05$). Similarly, the risk of liver-cause mortality was significantly reduced in the hepatectomy group both without and with IPTW analysis (aHR, 0.35, 95%CI, 0.27-0.44, $P < 0.001$, and aHR, 0.35 95%CI, 0.28-0.45, $P < 0.001$, respectively). With IPTW matched analysis, the hepatectomy group could achieve a significantly lower risk of liver-cause mortality in both BCLC stage B and C patients (all $P < 0.001$) (Table 6).

DISCUSSION

The best treatment strategy for HCC larger than 10 cm has not been clearly defined. Due to its large size, both liver transplantation and radiofrequency ablation are not recommended. TACE has become the suggested primary treatment for these unfavorable diseases as a result[17-20]. Nevertheless, the response of these large HCC

Table 4 Analyses of survival outcome with and without IPTW between the two groups: HCC ≥ 10 cm *vs* < 10 cm

| | Without IPTW | | | | With IPTW | | | |
| | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | |
	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value	Hazard ratio (95%CI)	P value
Recurrence								
Entire cohort	2.24 (1.96-2.56)	< 0.001	1.85 (1.60-2.13)	< 0.001	1.60 (1.28-2.01)	< 0.001	1.73 (1.40-2.15)	< 0.001
Within stage I					1.43 (0.87-2.37)	< 0.001	1.62 (1.02-2.56)	0.042
Within stage II					1.64 (1.23-2.20)	0.160	1.70 (1.28-2.27)	< 0.001
Within stage III					1.98 (1.61-2.43)	0.001	2.14 (1.74-2.63)	< 0.001
Within stage IV					1.46 (0.56-3.83)	< 0.001	1.93 (0.63-5.91)	0.251
All-cause mortality								
Entire cohort	2.70 (2.36-3.10)	< 0.001	1.95 (1.68-2.26)	< 0.001	1.99 (1.59-2.48)	< 0.001	2.07 (1.70-2.51)	< 0.001
Within stage I					2.34 (1.49-3.67)	< 0.001	2.47 (1.64-3.74)	< 0.001
Within stage II					1.81 (1.22-2.69)	0.003	1.80 (1.31-2.49)	< 0.001
Within stage III					1.78 (1.44-2.20)	< 0.001	1.89 (1.52-2.35)	< 0.001
Within stage IV					0.71 (0.27-1.86)	0.490	1.31 (0.58-2.96)	0.510
Liver-cause mortality								
Entire cohort	3.16 (2.70-3.70)	< 0.001	2.16 (1.82-2.56)	< 0.001	2.09 (1.61-2.72)	< 0.001	2.15 (1.73-2.67)	< 0.001
Within stage I					2.36 (1.31-4.26)	0.004	2.15 (1.43-3.24)	< 0.001
Within stage II					1.95 (1.21-3.15)	0.006	1.88 (1.29-2.72)	0.001
Within stage III					2.00 (1.58-2.55)	< 0.001	2.12 (1.67-2.69)	< 0.001
Within stage IV					0.67 (0.24-1.92)	0.460	0.96 (0.37-2.48)	0.932

CI: Confidence interval; HCC: Hepatocellular carcinoma; IPTW: Inverse-probability of treatment weighting.

to TACE is generally poor[35-37]. Liver resection for HCC larger than 10 cm is thus still preserved by surgeons worldwide. However, most articles regarding surgical treatment for HCC larger than 10 cm had limited case numbers[22,38-49]. To our knowledge, the current study is one of the largest series in the literature to address the efficacy of surgery for HCC larger than 10 cm.

According to the current study, more than 30% of L-HCC patients still remained disease-free and more than 45% of them were still alive at 5 years after the operation. This group of patients, although shorter than the S-HCC group, can survive for a median of more than 2.2 years after the curative operation. Even though the surgical mortality rate for L-HCC was higher than that of the S-HCC group, it was still in the acceptable range of around 2%. Furthermore, when compared to the patients receiving TACE, patients with large HCC undergoing surgery were much more likely to achieve disease-free and enjoyed a significantly longer OS. To eliminate further the influence imposed by various confounding factors, we have applied the IPTW method in subgroup analysis and found that, for patients with comparable liver functional reserve, liver resection led to a significantly lower risk of death than TACE for either solitary HCC larger than 10 cm (AJCC stage I and II), HCC larger than 10 cm with daughter nodules or major vascular invasion, or ruptured HCC larger than 10 cm (AJCC stage III). Since the BCLC staging system is also prognostic for HCC and is adopted by various treatment guidelines[17-19], we compared surgery with TACE in subgroup analysis and discovered that liver resection is still remarkably better than TACE in terms of death in BCLC B patients. This finding is similar to previous articles showing that surgery would be a better treatment modality for large HCC; furthermore, instead of dealing with HCC larger than 5 cm[50,51], we compared and confirmed that surgery is better for HCC larger than 10 cm.

Table 5 Comparison of current study with our previous report

	Yeh *et al*[27]: 1st era	Current study: 2nd era
Number of HCC ≥ 10 cm	211	426
Study period	1982-2001	2002-2015
Study design	Retrospective	Institutional-based cohort with IPTW
Age in yr	47.8 ± 14.3	55.7 ± 14.3
Gender, male %	78%	81%
HBV infection, positive	81.9%	52.8%
HCV infection, positive	11.6%	10.3%
Size in cm	13.9 ± 3.4	13.14 ± 4.95
Surgical mortality at 30-d	4.3%	2.1%
1-yr DFS rate	32.9%	48.5%
3-yr DFS rate	18.8%	36.1%
5-yr DFS rate	12.7%	31.1%
1-yr OS rate	48.1%	75.8%
3-yr OS rate	24.0%	53.3%
5-yr OS rate	16.7%	46.2%

DFS: disease-free survival; HCC: Hepatocellular carcinoma; IPTW: Inverse-probability of treatment weighting; OS: Overall survival.

Moreover, the current study has demonstrated the evolutional surgical outcome of HCC larger than 10 cm between two different eras. Since the surgeries were operated by the same group of surgeons, the results should be rather representative. We have shown that the risk of death from surgery had improved dramatically from 4.3% in late 1990s to only 2% in year 2000s. The long-term oncological outcome is also improving. This may be attributed to the advancement of preoperative preparation, surgical technique, perioperative care, and postoperative surveillance. In addition, we discovered that there was less HBV infection in the second era. It may be due to our nationwide HBV vaccination, effective antiviral therapy, and increasing incidence of non-alcoholic fatty liver disease. As a result, with acceptable performance status and liver functional reserve (*i.e.* European Cooperative Oncology Group 0-1, Child-Pugh A, indocyanine green retention test at 15 min < 10%, absence of Vp4 invasion, and future liver remnant > 30%), we suggest liver resection should be performed for single huge HCC larger than 10 cm or huge HCC with limited daughter nodules confined in the same lobe.

The current study discovered that patients with L-HCC were generally younger with less HCV infection and diabetes mellitus. Since younger HCC patients have been demonstrated to have lower rates of HCV infection and cirrhosis, it may explain the demographic differences observed[22]. However, it is also likely that the carcinogenesis of L-HCC is different from that of the smaller ones. The non-viral cause, such as non-alcoholic fatty liver disease, might have significant roles in the pathogenesis of L-HCC. This assumption can be supported by our finding that non-viral cause accounted for 40% of L-HCC in the present study, as compared to only 23% of S-HCC (*P* < 0.001). Further studies are warranted to unravel the causal relationships between these associations.

Despite acceptable outcome, the current study still identified inferior surgical results of L-HCC than that of S-HCC. The L-HCC patients had significantly higher risks of tumor recurrence and death than the S-HCC patients in all stage I to III patients. There was also more distant recurrence in the L-HCC group. We believe this inferior outcome may be due to either capsular invasion, absent or incomplete capsule, or occult metastasis when the L-HCC was going to be resected. Frequent postoperative follow-up is thus mandatory and routine adjuvant TACE or even systemic therapy should be considered for L-HCC after surgery. Furthermore, the findings discovered in the current study also prompt the necessity to stratify further the Tumor Node Metastasis staging system, since there was an apparent survival difference among stage I HCC patients with different tumor sizes. As suggested by a recent study,

Table 6 Analyses of survival outcome with and without inverse-probability of treatment weighting between the two groups (hepatectomy *vs* transarterial chemoembolization) - TNM and Barcelona Clinic Liver Cancer stage

	Without IPTW				With IPTW			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
All-cause mortality								
Entire cohort	0.33 (0.28-0.40)	< 0.001	0.46 (0.38-0.55)	< 0.001	0.49 (0.39-0.61)	< 0.001	0.46 (0.38-0.56)	< 0.001
Within stage I					0.39 (0.20-0.80)	0.009	0.37 (0.19-0.73)	0.004
Within stage II					0.30 (0.16-0.54)	< 0.001	0.24 (0.13-0.45)	< 0.001
Within stage III					0.50 (0.41-0.62)	< 0.001	0.50 (0.40-0.62)	< 0.001
Within stage IV					0.31 (0.14-0.67)	0.003	0.30 (0.09-0.93)	0.037
Liver-cause mortality								
Entire cohort	0.32 (0.26-0.39)	< 0.001	0.45 (0.37-0.56)	< 0.001	0.48 (0.37-0.61)	< 0.001	0.46 (0.37-0.56)	< 0.001
Within stage I					0.33 (0.16-0.71)	0.004	0.27 (0.12-0.60)	0.001
Within stage II					0.30 (0.16-0.56)	< 0.001	0.22 (0.10-0.47)	< 0.001
Within stage III					0.50 (0.39-0.63)	< 0.001	0.50 (0.40-0.63)	< 0.001
Within stage IV					0.30 (0.13-0.70)	0.005	0.29 (0.09-1.00)	0.050
All-cause mortality								
Entire cohort	0.33 (0.28-0.40)	< 0.001	0.37 (0.30-0.47)	< 0.001	0.38 (0.30-0.48)	< 0.001	0.38 (0.30-0.48)	< 0.001
BCLC stage A					NA	NA	NA	NA
BCLC stage B					0.33 (0.23-0.48)	< 0.001	0.30 (0.20-0.44)	< 0.001
BCLC stage C					0.40 (0.30-0.53)	< 0.001	0.41 (0.31-0.54)	< 0.001
BCLC stage D					NA	NA	NA	NA
Liver-cause mortality								
Entire cohort	0.32 (0.26-0.39)	< 0.001	0.35 (0.27-0.44)	< 0.001	0.36 (0.28-0.45)	<0 .001	0.35 (0.28-0.45)	< 0.001
BCLC stage A					NA	NA	NA	NA
BCLC stage B					0.32 (0.21-0.47)	< 0.001	0.29 (0.19-0.43)	< 0.001
BCLC stage C					0.37 (0.27-0.49)	< 0.001	0.38 (0.28-0.51)	< 0.001
BCLC stage D					NA	NA	NA	NA

BCLC: Barcelona Clinic Liver Cancer; CI: Confidence interval; HCC: Hepatocellular carcinoma; IPTW: Inverse-probability of treatment weighting; NA: Not applicable; TACE: Transarterial chemoembolization.

patients with a single HCC between 5 cm and 8 cm can be allocated into a new BCLC stage between early and intermediate stage, while patients with a single HCC larger than 8 cm can be ascribed to intermediate stage[44], we recommend there should be a subcategory within T1 stage to precisely predict patient outcome. The exact cutoff value warrants further investigations.

Despite remarkable findings, the current study still has several limitations. As mentioned above, since the most appropriate treatment modality for huge HCC has not been established, the management disposition (*i.e.* surgery or TACE for L-HCC) was based on the discretion of individual physician in the current study. As a result, the background demographics and biochemical profiles were heterogeneous between the surgical and TACE group. This heterogeneity was a significant weakness and rendered the statistics biased. Secondly, since the current study was generated from the hospital-based database and cancer registry, more descriptive variables such as
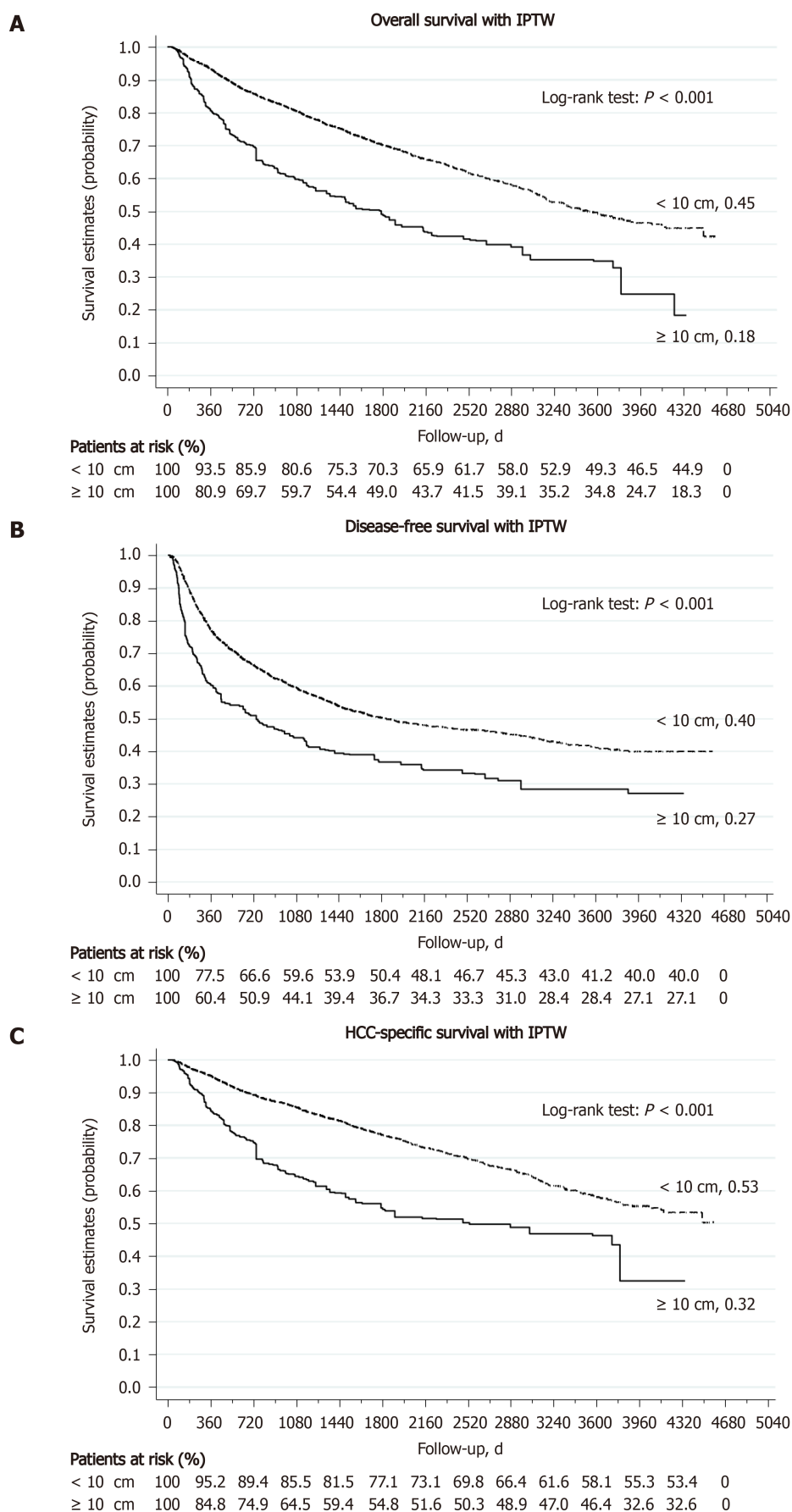
A

B

C

Figure 2 Hepatocellular carcinoma ≥ 10 cm patients had worse outcome than Hepatocellular carcinoma < 10 cm patients after surgery. A: Overall survival; B: Disease-free survival; C: Hepatocellular carcinoma (HCC)-specific survival. Estimated with inverse-probability of treatment weighting (IPTW).

A

Overall survival with IPTW

Log-rank test: *P* < 0.001

OP, 0.07

TACE, 0.11

Survival estimates (probability)

Follow-up, d

Patients at risk (%)

	0	360	720	1080	1440	1800	2160	2520	2880	3240	3600	3960	4320
OP	100	70.0	51.6	44.0	39.0	35.7	32.5	30.2	27.5	26.1	23.5	19.5	7.0
TACE	100	41.6	27.9	19.8	15.2	14.9	11.4	10.7	10.7	10.7	0	0	0

B

HCC-specific survival with IPTW

Log-rank test: *P* < 0.001

OP, 0.24

TACE, 0.13

Survival estimates (probability)

Follow-up, d

Patients at risk (%)

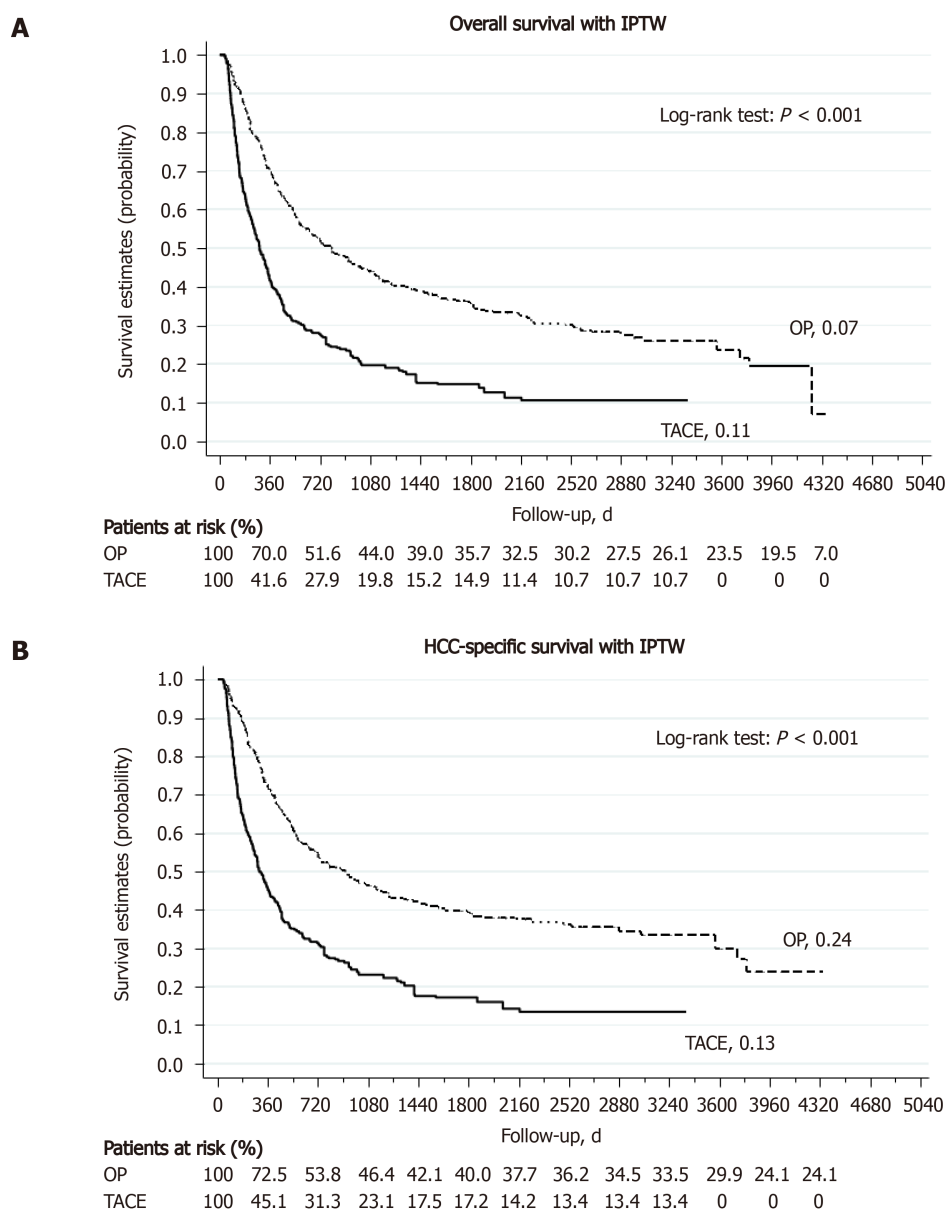|	0	360	720	1080	1440	1800	2160	2520	2880	3240	3600	3960	4320
OP	100	72.5	53.8	46.4	42.1	40.0	37.7	36.2	34.5	33.5	29.9	24.1	24.1
TACE	100	45.1	31.3	23.1	17.5	17.2	14.2	13.4	13.4	13.4	0	0	0

Figure 3 Liver resection, when comparing to transarterial chemoembolization, can provide a better long-term outcome for selected hepatocellular carcinoma ≥ 10 cm. A: Overall survival; B: Hepatocellular carcinoma (HCC)-specific survival. Estimated with inverse-probability of treatment weighting (IPTW). TACE: Transarterial chemoembolization.

performance status, ascites, encephalopathy, bilobar involvement, major vessel involvement, the volume of future liver remnant, and pathologic details were inaccessible. It may thus interfere with the final analysis. Our interpretation should therefore be rather cautious and not be extrapolated. Thirdly, since the current study was conducted in the largest tertiary care center in Taiwan, referral bias could be encountered. Further larger scale nationwide cohort studies are thus warranted to validate our findings.

CONCLUSION

In conclusion, our institutional-based observational study based on the CGRD had demonstrated an improving surgical outcome for HCC larger than 10 cm. With acceptable performance status and liver functional reserve, we suggest liver resection should be conducted for single huge HCC larger than 10 cm or huge HCC with limited daughter nodules confined in the same lobe. Due to its inferior survival, we suggest a subclassification within T1 stage to predict precisely patient outcome. Future studies are mandatory to confirm our findings.
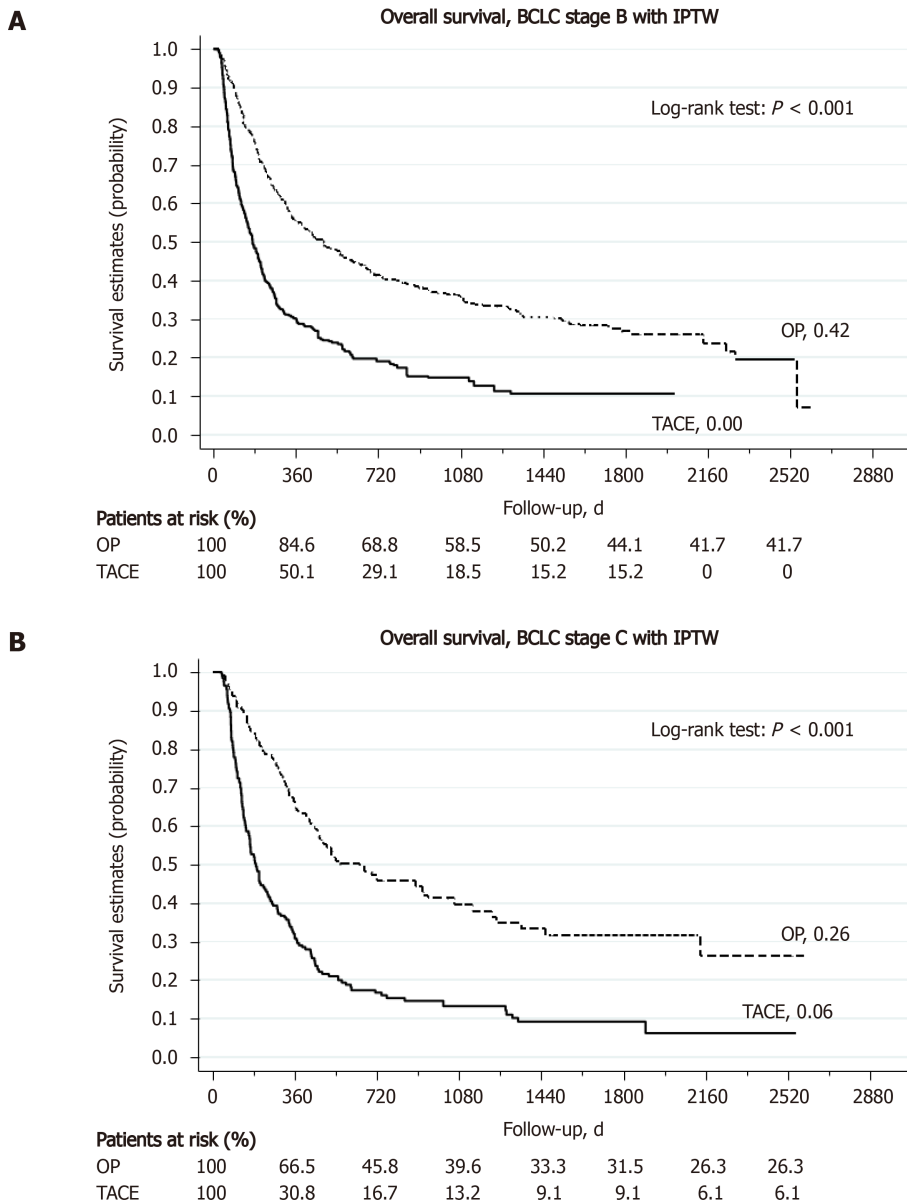
A

B

Figure 4 Liver resection is better than transarterial chemoembolization for selected Barcelona Clinic Liver Cancer stage B and Barcelona Clinic Liver Cancer stage C hepatocellular carcinoma ≥ 10 cm patients. A: Overall survival; B: Hepatocellular carcinoma-specific survival. Estimated with inverse-probability of treatment weighting (IPTW). BCLC: Barcelona Clinic Liver Cancer; TACE: Transarterial chemoembolization.

ARTICLE HIGHLIGHTS

Research background

The treatment of hepatocellular carcinoma (HCC) larger than 10 cm remains challenging. The Chang Gung Research Database (CGRD) contains all medical records of the Chang Gung Memorial Foundation and has become one of the largest clinical databases worldwide. By utilizing the data from CGRD, we attempted to analyze the outcome of HCC larger than 10 cm.

Research motivation

Owing to advancement in surgical technique and perioperative care, the surgical risks associated with liver resection are decreasing in the recent decades. However, the surgical outcome regarding HCC larger than 10 cm has not been updated.

Research objectives

We aimed to consolidate the role of surgical resection for HCC larger than 10 cm. The survival outcomes between surgery and transarterial chemoembolization (TACE) were also compared.

Research methods

Eligible HCC patients were identified from the CGRD, and two models were adopted: The surgical outcome between HCC ≥ 10 cm (L-HCC) and HCC < 10 cm (S-HCC) (model 1); the survival of L-HCC after either liver resection or TACE (model 2). To eliminate the potential confounding bias originating from heterogeneous baseline features and disproportionate case numbers, inverse-probability of treatment weighting between different groups was adopted.

Research results

Although worse than the S-HCC, the surgical and long-term oncological outcome of L-HCC had improved in the recent decades. Moreover, surgery could provide a better survival outcome for L-HCC than TACE.

Research conclusions

With acceptable performance status and liver functional reserve, we suggest liver resection should be conducted for HCC larger than 10 cm. Due to its inferior survival, T1 stage should be further sub-divided to predict precisely patient outcome.

Research perspectives

The current study demonstrated the inferior survival of L-HCC. The necessity of adjuvant therapy following liver resection for L-HCC should thus be determined by further randomized controlled trials.

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