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ORIGINAL ARTICLE

# Preoperative transcatheter arterial chemoembolization for surgical resection of huge hepatocellular carcinoma (≥ 10 cm): a multicenter propensity matching analysis

Chao Li[1] · Ming-Da Wang[1] · Lun Lu[2] · Han Wu[1] · Jiong-Jie Yu[1] · Wan-Guang Zhang[3] · Timothy M. Pawlik[4] · Yao-Ming Zhang[9] · Ya-Hao Zhou[5] · Wei-Min Gu[6] · Hong Wang[7] · Ting-Hao Chen[8] · Jun Han[1] · Hao Xing[1] · Zhen-Li Li[1] · Wan Yee Lau[1,10] · Meng-Chao Wu[1] · Feng Shen[1] · Tian Yang[1]

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## Abstract

**Background and Aims** Surgical resection for hepatocellular carcinoma (HCC) is potentially curative, but long-term survival remains unsatisfactory. There is currently no effective neoadjuvant or adjuvant therapy for HCC. We sought to evaluate the impact of preoperative transcatheter arterial chemoembolization (TACE) on long-term prognosis after surgical resection of huge HCCs (≥ 10 cm).

**Methods** Using a multicenter database, consecutive patients who underwent curative-intent resection for huge HCC without macrovascular invasion between 2004 and 2014 were identified. The association between preoperative TACE with perioperative outcomes, long-term overall survival (OS), and recurrence-free survival (RFS) was assessed before and after propensity score matching (PSM).

**Results** Among the 377 enrolled patients, 88 patients (23.3%) received preoperative TACE. The incidence of perioperative mortality and morbidity was comparable among patients who did and did not undergo preoperative TACE (3.4% vs. 2.4%, $p=0.704$, and 33.0% vs. 31.1%, $p=0.749$, respectively). PSM analysis created 84 matched pairs of patients. In examining the entire cohort as well as the PSM cohort, median OS (overall cohort: 32.8 vs. 22.3 months, $p=0.035$, and PSM only: 32.8 vs. 18.1 months, $p=0.023$, respectively) and RFS (12.9 vs. 6.4 months, $p=0.016$, and 12.9 vs. 4.1 months, $p=0.009$, respectively) were better among patients who underwent preoperative TACE vs. patients who did not. After adjustment for other confounding factors on multivariable analyses, preoperative TACE remained independently associated with a favorable OS and RFS after the resection of huge HCC.

**Conclusion** Preoperative TACE did not increase perioperative morbidity or mortality, yet was associated with an improved OS and RFS after liver resection of huge HCC (≥ 10 cm).

**Keywords** Hepatocellular carcinoma · Hepatectomy · Transcatheter arterial chemoembolization · Recurrence · Survival

**Abbreviations**

| | |
|---|---|
| HCC | Hepatocellular carcinoma |
| TACE | Transcatheter arterial chemoembolization |
| PSM | Propensity score matching |
| OS | Overall survival |
| RFS | Recurrence-free survival |
| RCT | Randomized controlled trial |
| RFA | Radiofrequency ablation |
| BMI | Body mass index |
| ASA | American society of anesthesiologists |
| INR | International normalized ratio |
| HBV | Hepatitis B virus |
| AFP | Alpha-fetoprotein |
| CT | Computed tomography |
| MRI | Magnetic resonance imaging |
| SD | Standard deviation |
| HR | Hazard ratio |
| 95% CI | 95 Percent confidence interval |

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✉ Feng Shen
fengshensmmu@gmail.com

✉ Tian Yang
yangtianehbh@smmu.edu.cn

Extended author information available on the last page of the article

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the third leading cause of cancer-related death [1]. In general, surgical resection is the standard option and treatment of choice for appropriate patients with localized HCC [2]. Unfortunately, among patients with HCC amenable to surgical resection, up to 50% will recur after a short recurrence-free interval especially patients with large (≥ 5 cm) or huge HCC (≥ 10 cm) [3–6]. The high incidence of recurrence typically manifests as intrahepatic recurrence and has been attributed to the presence of occult micro-metastases derived from the initial tumor at the time of resection, as well as the lack of effective neoadjuvant or adjuvant therapies [7].

Transarterial chemoembolization (TACE) is a locoregional therapy that has been extensively utilized in the palliative treatment of unresectable HCC [8]. More recently, TACE has been proposed as a potential form of neoadjuvant therapy prior to liver resection of HCC. Several observational studies [9–28] and a few randomized controlled trials (RCTs) [29–32] have previously sought to evaluate whether preoperative TACE was effective in preventing recurrence and prolonging survival after HCC resection. The conclusions of these studies are controversial and limited due to small sample size, potential selection bias, and unbalanced baseline characteristics among the groups. As such, consequent meta-analyses largely did not support a survival benefit for routine preoperative TACE for all patients undergoing resection of HCC [33–35]. Several authors have suggested, however, that TACE may benefit subgroups of patients with certain types of HCC tumors [9–28].

Large tumor size is a major risk factors associated with poor oncologic outcomes after the resection of HCC [36, 37]. Most huge HCCs (≥ 10 cm) have a rich blood supply from the hepatic artery and thereby may be better able to be targeted for TACE treatment [38, 39]. Patients with huge HCC tumors may not be candidates for surgical resection, and the long-term prognosis is poor even among those who undergo curative-intent resection [3–6, 37]. There is, therefore, a need in this subset of HCC patients to prevent postoperative recurrence and improve long-term prognosis. To this point, preoperative TACE may have a role in treating patients with huge HCC prior to surgical resection. The objective of the current study was to characterize the effect of preoperative TACE on long-term overall survival (OS) and recurrence-free survival (RFS) after curative resection of huge HCC using a large multicenter database. To define the relationship between preoperative TACE and postoperative oncologic prognosis after resection, propensity score-matching (PSM) analysis was used to balance the difference from baseline characteristics between the two groups.

## Patients and methods

### Patient cohort

Using a multicenter database, consecutive patients who underwent curative-intent liver resection for HCC from January 2004 to December 2014 at 7 Chinese hospitals (Eastern Hepatobiliary Surgery Hospital, Tongji Hosptial, Pu'er People's Hospital, Fourth Hospital of Harbin, Liuyang People's Hospital, Ziyang First People's Hospital and Meizhou People's Hospital) were identified. Patients were included in the analytic cohort who (1) had a huge HCC with maximum tumor size ≥ 10 cm, which were confirmed by histopathological examination of the resected specimens; (2) did not have portal/hepatic vein invasion or distant metastasis; (3) underwent curative liver resection of HCC, which was defined as complete resection of all microscopic and macroscopic tumors (R0 resection). Patients were excluded who (1) were under 18 years of age; (2) had HCC with maximum tumor size < 10 cm; (3) had recurrent HCC; (4) had received preoperative anti-HCC treatments other than TACE, including portal vein embolization, systematic chemotherapy or radiofrequency ablation (RFA); (5) had a palliative liver resection, i.e., microscopically positive (R1 resection) or grossly positive (R2 resection) resection margins; (6) were lost to follow-up within 90 days after liver resection; and (7) had had missing data on prognostic variables or follow-up information. Data in the study were censored on July 31, 2018.

### Baseline characteristics and operative variables

Information on baseline patient characteristics included age, sex, diabetes mellitus, body mass index (BMI), ASA score, etiology of liver diseases, cirrhosis, portal hypertension, Child-Pugh grade, preoperative platelets count, preoperative international normalized ratio (INR), preoperative HBV-DNA load, preoperative alpha-fetoprotein (AFP) level, the presence or absence of preoperative TACE, maximum tumor size, tumor number, microvascular invasion, satellite nodules, tumor differentiation, and tumor encapsulation. Cirrhosis was diagnosed histopathologically. Portal hypertension was defined as the presence of either esophageal varices, or splenomegaly along with a decline in platelet count ($\leq 100 \times 10^9$/L). Satellite nodules were defined as tumors less than 1 cm in diameter and located less than 1 cm from the main tumor. Operative variables included intraoperative blood loss, intraoperative blood transfusion, extent of liver resection, and type of liver resection. Minor liver resection was defined as resection of fewer than three Couinaud liver segments, while major liver resection was defined as resection of three or more liver segments. Non-anatomical liver resection included a limited resection or wedge resection;

anatomical resections were defined by the Brisbane 2000 system.

## Preoperative TACE

Given the retrospective nature of the study, the decision to utilize TACE before the operation was not controlled intentionally, but was determined by the treating physician at the time of care. A vascular catheter was inserted through the femoral artery using the Seldinger technique. Conventional mesenteric arteriography was performed first, and the coeliac artery was catheterized. After assessing the hepatic vascular anatomy, TACE was performed selectively through the left or right hepatic artery, or the tumor-feeding artery when technically possible. The chemotherapeutic regimens used included three combinations of 5-fluorouracil, mitomycin C, cisplatin, carboplatin, doxorubicin, or epirubicin; the embolization materials used were iodized oil and gelatin sponge cubes, or iodized oil only, which was mixed completely with these chemotherapeutic drugs as an emulsion and injected. Because TACE was performed at different hospitals, the amounts and combinations of chemotherapeutic agents varied. Embolization was performed using gelatin sponge cubes. Contrast-enhanced computed tomography (CT) scanning was routinely performed 3–6 weeks after TACE to demonstrate lipiodol uptake by the tumor tissue.

## Postoperative follow-up

Patients were regularly followed at each participating hospital. The postoperative surveillance strategy for recurrence was consistent at each participating hospital and consisted of physical examination, serum AFP level, ultrasonography, or contrast-enhanced CT/magnetic resonance imaging (MRI) of the abdomen at 2- or 3- monthly intervals for the first 6 months after resection, 3- or 4-monthly intervals for the next 18 months, and then 3- or 6-monthly thereafter. When the recurrence of HCC was suspected, CT and/or MRI, bone scanning or positron emission tomography were performed as indicated clinically. Tumor recurrence was defined as the new appearance of intrahepatic or extrahepatic tumor nodule(s), with or without a rise in serum AFP level, when the intrahepatic nodules had typical imaging features consistent with HCC on contrast-enhanced CT or MRI. Treatment options for patients with tumor recurrence included reoperation, liver transplantation, TACE, local ablation, sorafenib, or supportive therapy.

## Study endpoints

Study endpoints included postoperative 30-day mortality and morbidity, as well as overall survival (OS) and recurrence-free survival (RFS). Perioperative mortality was defined as death within 30 days after surgery or before discharge from the hospital. Perioperative morbidity within 30 days after surgery was graded according to the Clavien-Dindo classification, and major morbidity was defined as Clavien–Dindo Grade $\geq 3$. Hepatic dysfunction was defined as postoperative total bilirubin > 100 mmol/L accompanied with prolonged clotting time > 6 s or the occurrence of hepatoencephalopathy. OS was defined as time from surgery to death from any cause, while RFS was defined as time from the date of surgery to the date when HCC recurrence was first diagnosed for patients with recurrence, or from the date of surgery to the date of the last follow-up or death for patients without recurrence.

## Propensity score matching (PSM)

Propensity score-matching (PSM) analysis was used to reduce the bias of treatment selection. Patients who underwent preoperative TACE were matched with patients who were not treated with preoperative TACE using the propensity score-matching method as described by Rubin and Rosenbaum [40, 41]. Covariates entered into the propensity model included age, sex, diabetes mellitus, BMI, ASA score, etiology of liver disease, cirrhosis, portal hypertension, Child–Pugh grading, preoperative platelets count, INR, HBV-DNA load, and AFP levels, maximum tumor size, tumor number, microvascular invasion, satellite nodules, tumor differentiation, and tumor encapsulation. This model was used to provide a one-to-one match between the two groups. The matching procedure has been described previously [42].

## Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics version 25.0 (SPSS Inc., Armonk, NY, USA) and SAS 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (range). Categorical variables were reported as number (*n*) or proportion (%). The Student's *t* test was used for comparisons of continuous variables when applicable. Otherwise, the Mann-Whitney *U* test was applied. Categorical variables were compared with the $\chi^2$ test with the Yates correction or the Fisher's exact test, as appropriate. OS and RFS were compared among patients who did and did not undergo preoperative TACE before and after propensity matching using the Kaplan–Meier curves generated by the log-rank test. Multivariable Cox proportional hazard regression analyses were then performed to adjust for other prognostic factors which were associated with OS and RFS. $p$ values $< 0.05$ were considered statistically significant.

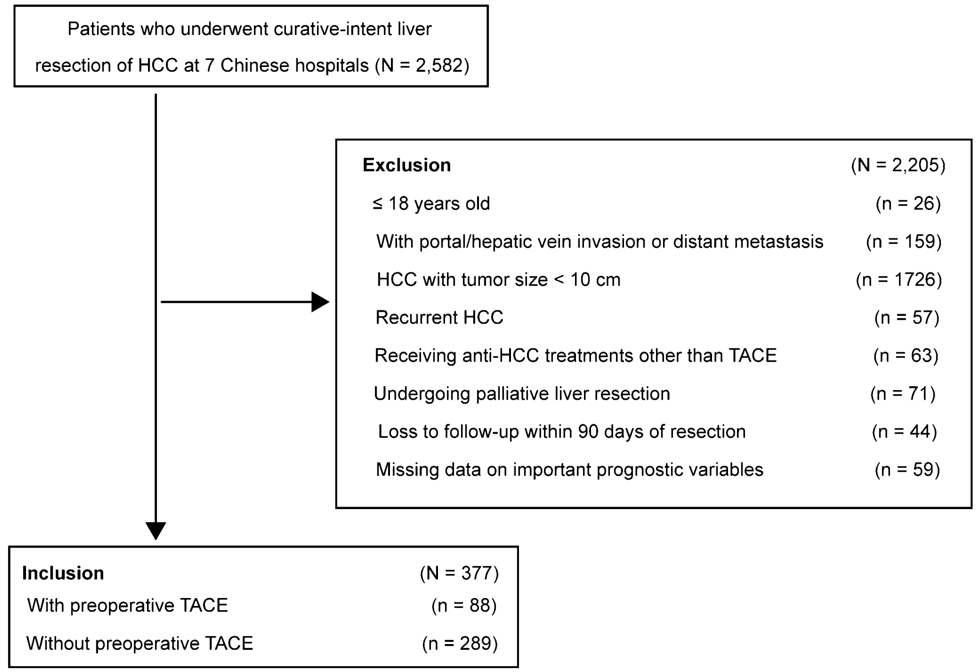


**Fig. 1** Selection of the study population. *HCC* hepatocellular carcinoma, *TACE* transarterial chemoembolization

## Results

During the study interval, 2582 patients underwent liver resection with curative intent for HCC among whom 377 had a huge HCC and comprised the analytic cohort (Fig. 1). Among these 377 patients, 88 patients underwent preoperative TACE at least one time (median 1; range 1–6) before surgical resection. The median interval between the first TACE and surgery was 6 weeks (range 2–36), while the median interval between the last TACE and surgery was 4 weeks (range 2–6). PSM created 84 pairs of patients who did or did not undergo preoperative TACE.

### Comparisons of clinicopathological variables and perioperative outcomes

Comparison of the patient baseline characteristics, operative variables, and perioperative outcomes among patients who did and did not undergo preoperative TACE before and after PSM is noted in Table 1. In the entire cohort, compared with patients who did not undergo preoperative TACE, patients who had preoperative TACE were more often male (95.5% vs. 85.8%, $p=0.015$), had a lower preoperative AFP level (AFP > 400 μg/L, 52.3% vs. 64.4%, $p=0.041$), and less often had microvascular invasion (71.6% vs. 82.7%, $p=0.022$). There were no differences in other baseline characteristics and operative variables between the two groups. In addition, in the entire cohort, for patients with preoperative TACE, the median AFP level at the first diagnosis of HCC was 612 μg/L, which was significantly decreased to 486 μg/L at the last examination before surgery ($p=0.03$). Among the entire cohort, patients who underwent preoperative TACE had similar perioperative 30-day mortality (2.4% vs. 3.4%, $p=0.704$) and perioperative 30-day morbidity (31.1% vs. 33.0%, $p=0.749$); the incidence of different types of postoperative complications was also comparable among patients who did vs. did not undergo preoperative TACE (all $p>0.05$).

As suspected, all the clinicopathological variables were balanced among patients who did vs. did not undergo preoperative TACE after PSM (all $p>0.2$). Similar to the analysis of the entire cohort, perioperative morbidity (31.0% vs. 27.4%, $p=0.611$) and the incidences of various postoperative complications (all $p>0.05$) were comparable among the TACE vs. no TACE PSM cohorts.

### Comparisons of long-term outcomes

Comparison of the long-term outcomes among patients who did and did not undergo preoperative TACE before and after PSM is shown in Table 2. With a median follow-up of 25.5 months, death and recurrence were observed in 77.3% (218/282) and 80.9% (228/282) of patients who did not undergo preoperative TACE, respectively; in contrast, death and recurrence occurred in 68.2% (58/85) and 76.5% (65/85) of patients who underwent preoperative TACE in the entire cohort, respectively ($p=0.090$ and 0.378, respectively). In analyzing the entire cohort, the median OS and RFS among patients who underwent preoperative TACE were 32.8 and 12.9 months, which were longer than patients who did not undergo TACE (22.3 and 6.4 months, $p=0.035$ and 0.016, respectively). Among all patients in the study, OS and RFS

**Table 1** Comparisons of patients' baseline characteristics, operative variables and perioperative outcomes between patients with and without preoperative transarterial chemoembolization (TACE) before and after propensity score matching (PSM)

| *N* (%) | The entire cohort | | | The PSM cohort** | | |
|---|---|---|---|---|---|---|
| | Without preoperative TACE (*N* = 289) | With preoperative TACE (*N* = 88) | *p* | Without preoperative TACE (*N* = 84) | With preoperative TACE (*N* = 84) | *p* |
| Age, years* | 49.1 ± 10.9 | 49.5 ± 10.8 | 0.779 | 48.0 ± 11.5 | 49.5 ± 10.6 | 0.392 |
| Sex | | | | | | |
| Male | 248 (85.8) | 84 (95.5) | 0.015 | 77 (91.7) | 80 (95.2) | 0.349 |
| Female | 41 (14.2) | 4 (4.5) | | 7 (8.3) | 4 (4.8) | |
| Diabetes mellitus | 18 (6.2) | 5 (5.7) | 0.851 | 3 (3.6) | 5 (6.0) | 0.720 |
| BMI | 23.9 ± 3.6 | 24.2 ± 3.5 | 0.480 | 23.7 ± 3.7 | 24.1 ± 3.4 | 0.506 |
| ASA score | | | | | | |
| ≤ 2 | 262 (90.7) | 78 (88.6) | 0.577 | 78 (92.9) | 74 (88.1) | 0.293 |
| > 2 | 27 (9.3) | 10 (11.4) | | 6 (7.1) | 10 (11.9) | |
| Etiology of liver diseases | | | | | | |
| HBV | 260 (90.0) | 81 (92.0) | 0.836 | 75 (89.3) | 77 (91.7) | 0.895 |
| HCV | 4 (1.4) | 1 (1.1) | | 0 (0) | 1 (1.2) | |
| HBV + HCV | 1 (0.3) | 0 (0) | | 1 (1.2) | 0 (0) | |
| Others | 24 (8.3) | 6 (6.8) | | 8 (9.5) | 6 (7.1) | |
| Cirrhosis | 186 (64.4) | 61 (69.3) | 0.392 | 51 (60.7) | 57 (67.9) | 0.334 |
| Portal hypertension | 64 (22.1) | 24 (27.3) | 0.319 | 17 (20.2) | 21 (25.0) | 0.461 |
| Child–Pugh grade | | | | | | |
| A | 253 (87.5) | 79 (89.8) | 0.572 | 81 (96.4) | 78 (92.9) | 0.496 |
| B | 36 (12.5) | 9 (10.2) | | 3 (3.6) | 6 (7.1) | |
| Preoperative platelets count, $\times 10^9$/L | 170 ± 67 | 164 ± 83 | 0.436 | 173 ± 59 | 167 ± 83 | 0.609 |
| Preoperative INR | 1.08 ± 0.11 | 1.07 ± 0.12 | 0.418 | 1.07 ± 0.11 | 1.06 ± 0.11 | 0.594 |
| Preoperative HBV-DNA load | | | | | | |
| $\leq 10^5$ copies/ml | 181 (62.6) | 51 (58.0) | 0.430 | 55 (65.5) | 50 (59.5) | 0.426 |
| $> 10^5$ copies/ml | 108 (37.4) | 37 (42.0) | | 29 (34.5) | 34 (40.5) | |
| Preoperative AFP level | | | | | | |
| ≤ 400 ug/L | 103 (35.6) | 42 (47.7) | 0.041 | 40 (47.6) | 42 (50.0) | 0.758 |
| > 400 ug/L | 186 (64.4) | 46 (52.3) | | 44 (52.4) | 42 (50.0) | |
| Maximum tumor size, cm* | 12.6 ± 2.4 | 12.7 ± 2.1 | 0.517 | 12.4 ± 2.3 | 12.6 ± 2.1 | 0.654 |
| Tumor number | | | | | | |
| Solitary | 173 (59.9) | 46 (52.3) | 0.207 | 46 (54.8) | 45 (53.6) | 0.877 |
| Multiple | 116 (40.1) | 42 (47.7) | | 38 (45.2) | 39 (46.4) | |
| Microvascular invasion | 239 (82.7) | 63 (71.6) | 0.022 | 65 (77.4) | 59 (70.2) | 0.292 |
| Satellite nodules | 143 (49.5) | 48 (54.5) | 0.405 | 51 (60.7) | 45 (53.6) | 0.350 |
| Tumor differentiation | | | | | | |
| Well or moderate | 16 (5.5) | 7 (8.0) | 0.407 | 3 (3.6) | 7 (8.3) | 0.329 |
| Poor | 273 (94.5) | 81 (92.0) | | 81 (96.4) | 77 (91.7) | |
| Tumor encapsulation | | | | | | |
| Complete | 45 (15.6) | 16 (18.2) | 0.560 | 11 (13.1) | 15 (17.9) | 0.394 |
| Incomplete | 244 (84.4) | 72 (81.8) | | 73 (86.9) | 69 (82.1) | |
| Intraoperative blood loss | | | | | | |
| ≤ 400 ml | 80 (27.7) | 30 (34.1) | 0.247 | 23 (27.4) | 28 (33.3) | 0.401 |
| > 400 ml | 209 (72.3) | 58 (65.9) | | 61 (72.6) | 56 (66.7) | |
| Intraoperative blood transfusion | 141 (48.8) | 38 (43.2) | 0.356 | 41 (48.8) | 35 (41.7) | 0.352 |
| Extent of liver resection | | | | | | |
| Major liver resection | 212 (73.4) | 59 (67.0) | 0.249 | 62 (73.8) | 56 (66.7) | 0.311 |
| Minor liver resection | 77 (26.6) | 29 (33.0) | | 22 (26.2) | 28 (33.3) | |
| Type of liver resection | | | | | | |

**Table 1** (continued)

| *N* (%) | The entire cohort | | | The PSM cohort** | | |
|---|---|---|---|---|---|---|
| | Without preoperative TACE (*N*=289) | With preoperative TACE (*N*=88) | *p* | Without preoperative TACE (*N*=84) | With preoperative TACE (*N*=84) | *p* |
| Anatomical | 121 (41.9) | 33 (37.5) | 0.465 | 39 (46.4) | 32 (38.1) | 0.274 |
| Non-anatomical | 168 (58.1) | 55 (62.5) | | 45 (53.6) | 52 (61.9) | |
| Perioperative mortality | 7 (2.4) | 3 (3.4) | 0.704 | 0 | 0 | 1.000 |
| Perioperative morbidity | 90 (31.1) | 29 (33.0) | 0.749 | 23 (27.4) | 26 (31.0) | 0.611 |
| Minor morbidity | 62 (21.4) | 17 (19.3) | 0.667 | 16 (19.0) | 18 (21.4) | 0.701 |
| Major morbidity | 28 (9.7) | 12 (13.6) | 0.292 | 7 (8.3) | 8 (9.5) | 0.787 |
| Perioperative complications | | | | | | |
| Hepatic dysfunction | 19 (6.6) | 6 (6.8) | 0.936 | 5 (6.0) | 3 (3.6) | 0.720 |
| Abdominal hemorrhage | 6 (2.1) | 1 (1.1) | 1.000 | 2 (2.4) | 0 (0) | 0.497 |
| Bile leakage | 7 (2.4) | 1 (1.1) | 0.687 | 2 (2.4) | 1 (1.2) | 1.000 |
| Incisional infection | 15 (5.2) | 6 (6.8) | 0.596 | 3 (4.8) | 4 (4.8) | 1.000 |
| Organ/space infection | 14 (4.8) | 4 (4.5) | 1.000 | 2 (2.4) | 3 (3.6) | 1.000 |
| Respiratory infection | 5 (1.7) | 2 (2.3) | 0.667 | 0 (0) | 2 (2.4) | 0.497 |
| Pleural effusion | 36 (12.5) | 10 (11.4) | 0.784 | 7 (8.3) | 8 (9.5) | 0.787 |
| Ascites | 28 (10.5) | 7 (8.0) | 0.624 | 6 (7.1) | 5 (6.0) | 0.755 |
| Other complications | 9 (3.1) | 1 (1.1) | 0.464 | 1 (1.2) | 0 (0) | 1.000 |

*AFP* alpha-fetoprotein, *ASA* American Society of Anesthesiologists, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *BMI* body mass index, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *INR* international normalized ratio, *PSM* propensity score matching

*Values are mean ± standard deviation or median (range) unless otherwise indicated

**Remove the cases of perioperative mortality (*n* = 10)

**Table 2** Comparisons of long-term oncological outcomes between patients with and without preoperative transarterial chemoembolization (TACE) before and after propensity score matching (PSM)

| *N* (%) | The entire cohort | | | The PSM cohort | | |
|---|---|---|---|---|---|---|
| | Without preoperative TACE (*N*=282) | With preoperative TACE (*N*=85) | *p* | Without preoperative TACE (*N*=84) | With preoperative TACE (*N*=84) | *p* |
| Postoperative adjuvant TACE | 158 (55.4) | 40 (48.8) | 0.287 | 47 (54.0) | 40 (49.4) | 0.548 |
| Period of follow-up, months* | 22.5 (2.5–163.6) | 31.7 (3.5–132.8) | 0.120 | 19.1 (2.7–162.2) | 32.2 (3.5–132.8) | 0.135 |
| Recurrence during the follow-up | 228 (80.9) | 65 (76.5) | 0.378 | 72 (85.7) | 64 (76.2) | 0.116 |
| Site of initial recurrence | | | | | | |
| Intrahepatic | 176 (62.4) | 50 (58.8) | 0.551 | 53 (63.1) | 49 (58.3) | 0.527 |
| Extrahepatic | 14 (5.9) | 5 (5.0) | 0.781 | 6 (7.1) | 5 (6.0) | 0.755 |
| Intrahepatic and extrahepatic | 38 (13.5) | 10 (11.8) | 0.682 | 11 (13.1) | 10 (11.9) | 0.816 |
| Death during the follow-up | 218 (77.3) | 58 (68.2) | 0.090 | 68 (81.0) | 57 (67.9) | 0.052 |
| Median OS, 95% CI, months | 22.3 (16.9–27.7) | 32.8 (25.5–40.1) | 0.035 | 18.1 (8.0–28.3) | 32.8 (25.6–40.1) | 0.023 |
| 1-year OS rate, % | 64.2 | 78.8 | | 58.3 | 78.6 | |
| 3-year OS rate, % | 37.2 | 45.6 | | 34.5 | 46.2 | |
| 5-year OS rate, % | 26.2 | 34.8 | | 24.5 | 35.3 | |
| Median RFS, 95% CI, months | 6.4 (4.0–8.8) | 12.9 (7.8–17.9) | 0.016 | 4.1 (1.1–7.0) | 12.9 (7.7–18.1) | 0.009 |
| 1-year RFS rate, % | 39.7 | 54.1 | | 35.7 | 53.6 | |
| 3-year RFS rate, % | 19.8 | 31.8 | | 17.7 | 32.1 | |
| 5-year RFS rate, % | 14.6 | 21.3 | | 13.7 | 21.6 | |

*CI* confidence interval, *OS* overall survival, *PSM* propensity score matching, *RFS* recurrence-free survival, *TACE* transarterial chemoembolization

*Values are median and range

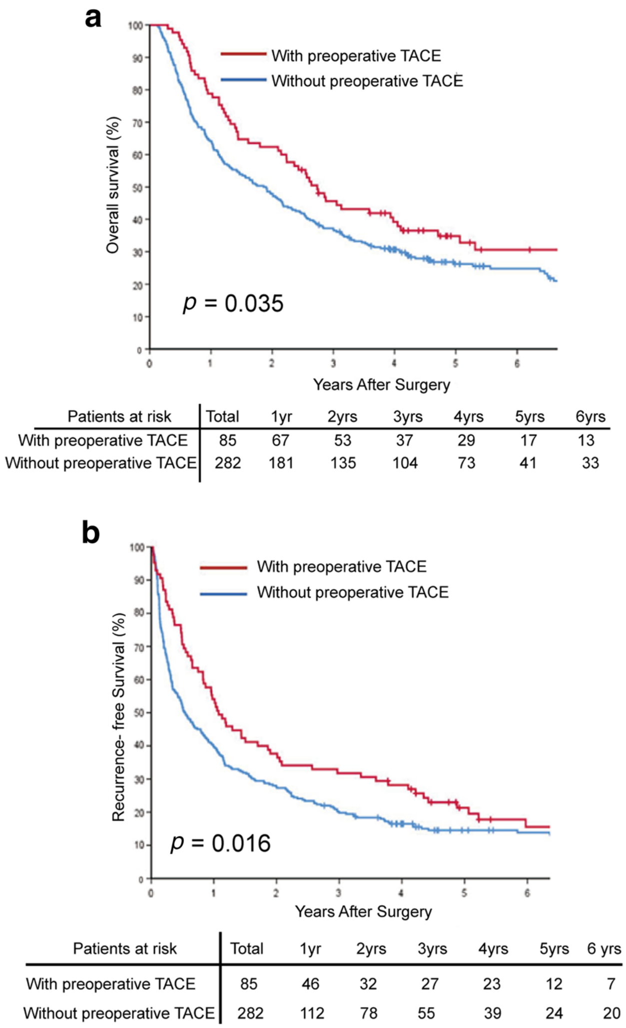


**Fig. 2** Cumulative incidence of overall survival **a** and recurrence-free survival **b** curves comparisons between patients with and without preoperative transarterial chemoembolization (TACE) in the entire cohort

among patients who underwent preoperative TACE vs. patients who did not are shown in Fig. 2a, b.

After PSM, the incidence of death and recurrence among the 84 patients who had preoperative TACE was lower vs. the matched 84 patients in the no TACE group (67.9% vs. 81.0% and 76.2% vs. 85.7%, respectively) ($p = 0.052$ and 0.116, respectively). On PSM, median OS and RFS among patients who underwent preoperative TACE were 32.8 and 12.9 months, which were also better than patients who did undergo TACE (18.1 and 4.1 months, $p = 0.023$ and 0.009, respectively) (Fig. 3a, b).

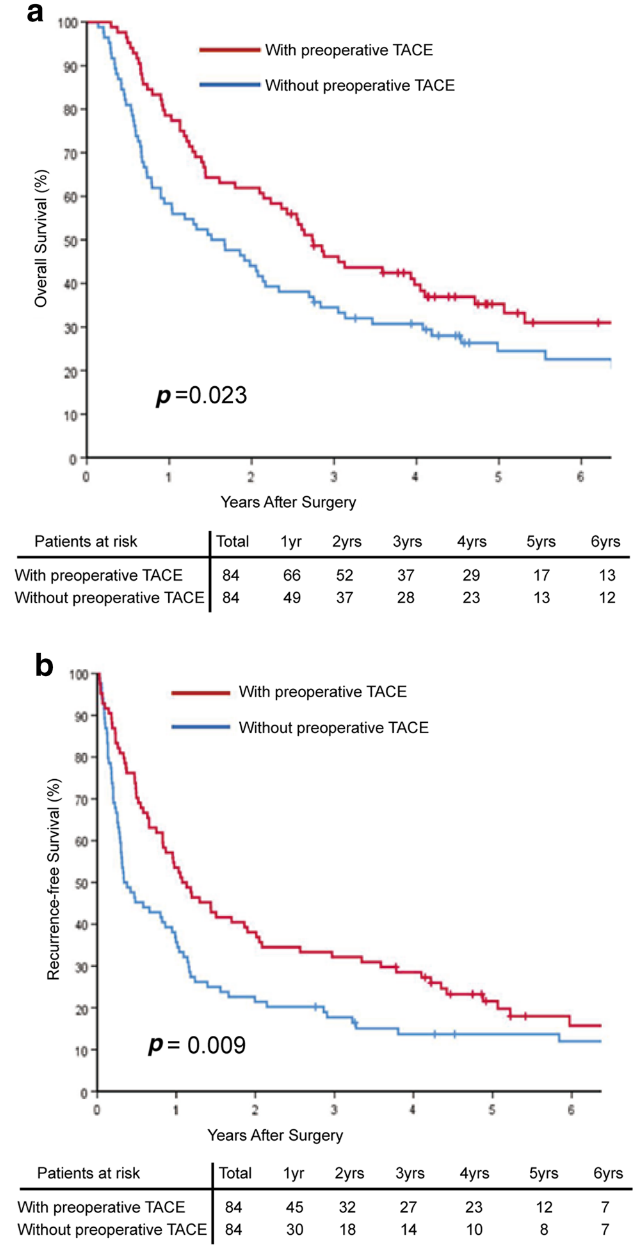


**Fig. 3** Cumulative incidence of overall survival **a** and recurrence-free survival **b** curves comparisons between patients with and without preoperative transarterial chemoembolization (TACE) in the propensity score-matching (PSM) cohort

## Univariable and multivariable analyses of OS and RFS in the PSM cohort

Additional univariable and multivariable Cox-regression analyses with robust estimator were performed in the PSM cohort. Univariable and multivariable analyses of OS and RFS after curative liver resection for huge HCC in the PSM cohort are shown in Tables 3 and 4. On multivariable analyses, preoperative TACE remained independently associated

**Table 3** Univariate and multivariate Cox-regression analyses predicting overall survival in the propensity score-matching (PSM) cohort

| Variables | HR comparison | UV HR (95% CI) | UV *p* | MV HR (95% CI) | MV *p** |
|---|---|---|---|---|---|
| Preoperative TACE | No vs. yes | 1.503 (1.056–2.138) | **0.023** | 1.565 (1.083–2.262) | **0.017** |
| Age | ≤ 60 vs. > 60 years | 1.060 (0.657–1.711) | 0.811 | | |
| Sex | Male vs. female | 0.707 (0.358–1.395) | 0.317 | | |
| Diabetes mellitus | Yes vs. no | 0.917 (0.403–2.086) | 0.836 | | |
| Preoperative BMI | ≤ 24.0 vs. > 24.0 | 1.273 (0.882–1.838) | 0.197 | | |
| ASA score | ≤ 2 vs. > 2 | 0.966 (0.533-1.753) | 0.910 | | |
| Etiology of liver diseases | HBV vs. non-HBV | 1.022 (0.535–1.954) | 0.947 | | |
| Cirrhosis | Yes vs. no | 1.281 (0.887–1.850) | 0.187 | | |
| Portal hypertension | Yes vs. no | 1.319 (0.885–1.966) | 0.174 | | |
| Child–Pugh grade | *A* vs. *B* | 1.823 (0.923–3.601) | **0.084** | NS | 0.541 |
| Preoperative platelets count | ≤ 100 vs. > 100 × $10^9$/L | 1.687 (1.041–2.734) | **0.034** | 1.858 (1.125–3.068) | **0.015** |
| Preoperative INR | ≤ 1.15 vs. > 1.15 | 1.468 (0.960–2.243) | **0.076** | NS | 0.597 |
| Preoperative HBV load | ≤ $10^5$ vs. > $10^5$ copies/ml | 1.614 (1.130–2.306) | **0.008** | 1.625 (1.127–2.344) | **0.009** |
| Preoperative AFP level | ≤ 400 vs. > 400 ug/L | 1.620 (1.135–2.314) | **0.008** | 1.514 (1.059–2.166) | **0.023** |
| Maximum tumor size | 10.0–15.0 cm vs. > 15.0 cm | 1.530 (1.033–2.267) | **0.034** | 1.804 (1.196–2.720) | **0.005** |
| Tumor number | Solitary vs. multiple | 2.098 (1.469–2.995) | **< 0.001** | NS | 0.452 |
| Microvascular invasion | Yes vs. no | 2.278 (1.429–3.631) | **0.001** | 1.713 (1.053–2.787) | **0.030** |
| Satellite nodules | Yes vs. no | 3.044 (2.067–4.483) | **< 0.001** | 2.821 (1.881–4.230) | **< 0.001** |
| Tumor differentiation | Well or moderate vs. Poor | 1.535 (0.674–3.493) | 0.307 | | |
| Tumor encapsulation | Complete vs. incomplete | 2.200 (1.182–4.096) | **0.013** | NS | 0.364 |
| Intraoperative blood loss | ≤ 400 vs. > 400 ml | 1.767 (1.144–2.729) | **0.010** | NS | 0.502 |
| Intraoperative blood transfusion | Yes vs. no | 1.900 (1.328–2.719) | **< 0.001** | NS | 0.507 |
| Extent of liver resection | Major vs. minor | 1.390 (0.907–2.132) | 0.131 | | |
| Type of resection | Anatomical vs. non-anatomical | 0.968 (0.679–1.381) | 0.859 | | |
| Postoperative adjuvant TACE | No vs. yes | 0.801 (0.563–1.139) | 0.215 | | |

*AFP* alpha-fetoprotein, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *CI* confidence interval, *HBV* hepatitis B virus, *HR* hazard ratio, *INR* international normalized ratio, *MV* multivariable, *NS* not significant, *PSM* propensity score matching, *TACE* transcatheter arterial chemoembolization, *UV* univariable

*Those variables found significant at $p < 0.1$ in univariable analyses were entered into multivariable Cox-regression analyses

with a better OS (HR 1.565, 95% CI 1.083–2.262; $p = 0.017$) and RFS (HR 1.550, 95% CI 1.101–2.180; $p = 0.012$).

## Discussion

TACE remains one of the safest and effective therapeutic modalities for unresectable HCC by inducing tumor necrosis and tumor shrinkage. The safety and efficacy of preoperative TACE for resectable HCC remain, however, controversial [33–35]. Some studies have reported that patients with resectable HCC did benefit from preoperative TACE [9, 16, 31]. Patients included into these studies often had resectable tumors that were less than 5 cm in diameter or early/intermediate-stage HCC. In contrast, some investigators suggested that preoperative TACE may preferentially benefit patients with large HCC [11, 18], advanced HCC [16], and HCC with portal vein tumor thrombus [26]. In the current study, we analyzed a large multicenter cohort of patients with huge HCC (≥ 10 cm). Of note, preoperative TACE was not associated with differences in postoperative 30-day mortality and morbidity among patients who did vs. did not undergo preoperative TACE. Rather, preoperative TACE seemed to provide an OS and RFS survival benefit both in assessing the entire cohort, as well as the PSM groups. In addition, multivariable Cox-regression analyses identified that preoperative TACE remained associated with better OS and RFS among patients undergoing curative resection of huge HCC (≥ 10 cm).

Most baseline characteristics among patients who did and did not undergo preoperative TACE were comparable except for male sex, AFP level, and the presence of microvascular invasion. These baseline characteristics imbalances were likely related to inherent selection bias due to the retrospective nature of this study—as care providers were more likely to use preoperative TACE among patients with high AFP in particular. Several retrospective studies [43, 44] and a RCT [45] had indicated that postoperative adjuvant TACE could

**Table 4** Univariate and multivariate Cox-regression analyses predicting recurrence-free survival in the propensity score-matching (PSM) cohort

| Variables | HR comparison | UV HR (95% CI) | UV *p* | MV HR (95% CI) | MV *p** |
|---|---|---|---|---|---|
| Preoperative TACE | No vs. yes | 1.549 (1.112–2.157) | **0.009** | 1.550 (1.101–2.180) | **0.012** |
| Age | ≤ 60 vs. > 60 years | 0.852 (0.531–1.368) | 0.499 | | |
| Sex | Male vs. female | 0.649 (0.340–1.237) | 0.189 | | |
| Diabetes mellitus | Yes vs. no | 0.806 (0.377–1.725) | 0.578 | | |
| Preoperative BMI | ≤ 24.0 vs. > 24.0 | 1.231 (0.871–1.740) | 0.240 | | |
| ASA score | ≤ 2 vs. > 2 | 0.746 (0.413–1.348) | 0.331 | | |
| Etiology of liver diseases | HBV vs. non-HBV | 1.076 (0.595–1.945) | 0.808 | | |
| Cirrhosis | Yes vs. no | 0.904 (0.640–1.277) | 0.567 | | |
| Portal hypertension | Yes vs. no | 1.158 (0.790–1.696) | 0.452 | | |
| Child–Pugh grade | A vs. B | 1.447 (0.735–2.847) | 0.285 | | |
| Preoperative platelets count | ≤ 100 vs. > $100 \times 10^9$/L | 1.378 (0.865–2.195) | 0.178 | | |
| Preoperative INR | ≤ 1.15 vs. > 1.15 | 1.503 (1.105–2.227) | **0.042** | NS | 0.396 |
| Preoperative HBV load | ≤ $10^5$ vs. > $10^5$ copies/ml | 1.607 (1.149–2.248) | **0.006** | 1.668 (1.184–2.349) | **0.003** |
| Preoperative AFP level | ≤ 400 vs. > 400 ug/L | 1.577 (1.131–2.197) | **0.007** | 1.585 (1.335–1.942) | **0.015** |
| Maximum tumor size | 10.0–15.0 cm vs. > 15.0 cm | 1.372 (0.976–1.999) | **0.088** | NS | 0.159 |
| Tumor number | Solitary vs. multiple | 1.953 (1.397–2.730) | **< 0.001** | 1.466 (1.048–2.050) | **0.025** |
| Microvascular invasion | Yes vs. no | 1.995 (1.308–3.043) | **0.001** | 1.548 (1.003–2.387) | **0.048** |
| Satellite nodules | Yes vs. no | 3.025 (2.113–4.332) | **< 0.001** | 2.726 (1.916–3.983) | **< 0.001** |
| Tumor differentiation | Well or moderate vs. poor | 0.992 (0.505–1.951) | 0.982 | | |
| Tumor encapsulation | Complete vs. incomplete | 1.879 (1.097–3.218) | **0.022** | NS | 0.899 |
| Intraoperative blood loss | ≤ 400 vs. > 400 ml | 1.438 (0.973–2.124) | **0.068** | NS | 0.805 |
| Intraoperative blood transfusion | Yes vs. no | 1.642 (1.179–2.289) | **0.003** | NS | 0.512 |
| Extent of liver resection | Major vs. minor | 1.448 (0.975–2.150) | **0.066** | | |
| Type of resection | Anatomical vs. non-anatomical | 0.997 (0.715–1.391) | 0.987 | | |
| Postoperative adjuvant TACE | No vs. yes | 0.902 (0.648–1.254) | 0.538 | | |

*AFP* alpha-fetoprotein, *ASA* American Society of Anesthesiologists, *BMI* body mass index, *CI* confidence interval, *HBV* hepatitis B virus, *HR* hazard ratio, *INR* international normalized ratio, *MV* multivariable, *NS* not significant, *PSM* propensity score matching, *TACE* transcatheter arterial chemoembolization, *UV* univariable

*Those variables found significant at $p < 0.1$ in univariable analyses were entered into multivariable Cox-regression analyses

effectively reduce recurrence and prolong OS and RFS after curative resection in patients with HCC and microvascular invasion. As such, it was reasonable to be skeptical for the effect of preoperative TACE on reducing the positiveness of microvascular invasion, thus potentially improving the long-term progress after resection, especially for those huge HCCs, considering the proportion of microvascular invasion is relatively high. Actually, for the differences of preoperative AFP level and the presence of microvascular invasion between two groups in the entire cohort, we hypothesized to be due to the effect of TACE itself but not the selection bias, although we have not found the relevant theoretical or clinical evidence in the previous studies. As we think, it deserves further research or exploration in the future.

Previous studies suggested that hepatic inflammation after TACE might result in more intraoperative bleeding and increase operative difficulties when HCC resection is performed after TACE [10]. However, some authors have proposed that TACE has little influence on subsequent surgery if the interval between the last TACE and resection was long enough. Nagasue et al. reported that a mean interval between the last TACE and surgery of 130 day resulted in similar operating times and rates of bleeding as patients who did not have preoperative TACE [46]. Similarly, in the current study, among nearly all 88 patients who received preoperative TACE, the interval between the last TACE and liver resection was at least 4 weeks (the median interval was 6 weeks). Whereas in the entire cohort or the PSM cohort, intraoperative blood loss and the intraoperative blood transfusion rates were comparable among patients who did and did not undergo preoperative TACE; meanwhile, perioperative mortality and morbidity (including minor and major morbidity) were also comparable. In our clinical experience, although the perihepatic inflammatory adhesion may still exist in a few patients at several weeks after TACE, it did not have a very negative effect on the procedure and short-term outcomes of HCC resection.

To better compare the long-term outcomes among patients who did and did not have preoperative TACE, we used the PSM method to adjust for potential confounding factors and to reduce the selection bias between the two groups. The results demonstrated that long-term OS and RFS after curative resection of huge HCC among patients who had preoperative TACE were better compared with patients who did not have preoperative TACE (median OS and RFS in the entire cohort: 32.8 and 12.9 months vs. 22.3 and 6.4 months, $p = 0.035$ and 0.016, respectively; median OS and RFS in the PSM cohort: 32.8 and 12.9 months vs. 18.1 and 4.1 months, $p = 0.023$ and 0.009, respectively). Most previous studies that included all resectable HCC lesions had reported no effect of preoperative TACE on long-term outcomes, with only a small set of studies specifically focusing on a subset of resectable HCC [11, 16, 18, 26]. In considering only huge HCCs that often have a rich blood supply from hepatic artery and thus grow faster, preoperative TACE may give rise to massive necrosis of HCC tissue and lead to a preferential benefit to this subset of patients. Consistent with our findings, Lu et al. [11] reported that, among patients with very large HCC (> 8 cm), preoperative TACE was associated with a better 1-, 2-, and 3-year OS and RFS vs. the non-preoperative TACE group ($n = 19$) ($p = 0.017$ and 0.01, respectively). In our opinion, what kind of patients could get survival benefit from preoperative neoadjuvant or postoperative adjuvant therapy to improve the postoperative prognosis of HCC, it is still worthwhile to conduct some clinical prediction models, such like nomograms, to reveal possible beneficial population. In addition, RCTs are also needed for a specific patient group with one or some combined certain characteristics.

In the present study, in addition to the absence of preoperative TACE, other independent risk factors associated with poorer OS and/or RFS after curative liver resection of huge HCC included large tumor size (> 15 cm), high preoperative HBV load, high preoperative AFP level, microvascular invasion, and satellite nodules. These risks have also been demonstrated by many previous studies on liver resection for HCC [3, 4, 7, 42].

The present study has several limitations. This was a retrospective study that lacked randomization. One of the purpose of preoperative TACE is to increase the resectability rate of HCCs by down-staging tumors that are either initially borderline resectable or unresectable [11, 19]. However, we could not get information of all enrolled patients, whose initial HCC was resectable or unresectable before TACE. There may have been a selection bias regarding the treatment of patients. In addition, more than 90% of the patients with HCC had HBV infection. As such, these data may not be applicable to western countries, where HCC is more commonly caused by HCV and alcohol use. The inclusion of multiple hospitals also did not allow for the standardization of operative approach or protocols related to TACE. Although the overall sample size of patients with huge HCC was more than 300 (including 88 patients with preoperative TACE), it still was relatively small and did not allow us to perform some statistical analyses of subgroups.

In conclusion, the results of the current study provide valuable information to guide the management of patients with huge HCC. Preoperative TACE did not increase perioperative morbidity or mortality, yet was associated with an improved OS and RFS after liver resection of huge HCC (≥ 10 cm).

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**Author contributions** CL, M-DW, LL, HW, J-JY, and W-GZ contributed equally to this work. Dr. TY and FS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: CL, M-DW, FS, and TY. Acquisition, analysis, or interpretation of data: CL, M-DW, HW, W-GZ, Y-MZ, Y-HZ, W-MG, HW, T-HC, JH, J-JY, HX, and Z-LL. Drafting of the manuscript: CL, M-DW, HW, J-JY, Z-LL, and TY. Critical revision of the manuscript for important intellectual content: LL, TMP, CL, WYL, TY, and FS. Statistical analysis: HX, J-JY, CL, M-DW, and TY. Obtained funding: TY and M-DW. Administrative, technical, or material support: WYL, W-GZ, Y-MZ, Y-HZ, W-MG, HW, T-HC, FS, and TY. Study supervision: WYL, M-CW, FS, and TY.

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## Compliance with ethical standards

**Conflict of interest** Chao Li, Ming-Da Wang, Lun Lu, Han Wu, Jiong-Jie Yu, Wan-Guang Zhang, Timothy M. Pawlik, Yao-Ming Zhang, Ya-Hao Zhou, Wei-Min Gu, Hong Wang, Ting-Hao Chen, Jun Han, Hao Xing, Zhen-Li Li, Wan Yee Lau, Meng-Chao Wu, Feng Shen and Tian Yang declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of Eastern Hepatobiliary Surgery Hospital of Shanghai.

**Informed consent** The study protocol was approved by the Institutional Review Board of all participating hospitals, and informed consent from the patients was waived. Written, informed consent for the data to be used for clinical researches was obtained from all enrolled patients.

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## Affiliations

**Chao Li[1] · Ming-Da Wang[1] · Lun Lu[2] · Han Wu[1] · Jiong-Jie Yu[1] · Wan-Guang Zhang[3] · Timothy M. Pawlik[4] · Yao-Ming Zhang[9] · Ya-Hao Zhou[5] · Wei-Min Gu[6] · Hong Wang[7] · Ting-Hao Chen[8] · Jun Han[1] · Hao Xing[1] · Zhen-Li Li[1] · Wan Yee Lau[1,10] · Meng-Chao Wu[1] · Feng Shen[1] · Tian Yang[1]**

Chao Li
lichaoehbh@smmu.edu.cn

Ming-Da Wang
wangmdehbh@smmu.edu.cn

Lun Lu
drlulun@sina.com

Han Wu
wuhanehbh@smmu.edu.cn

Jiong-Jie Yu
yujiongjieehbh@smmu.edu.cn

Wan-Guang Zhang
dr_zhangwg@163.com

Timothy M. Pawlik
tim.pawlik@osumc.edu

Yao-Ming Zhang
zhangyaoming666@163.com

Ya-Hao Zhou
zyhpuer@163.com

Wei-Min Gu
weimingu66@163.com

Hong Wang
drwanghong111@163.com

Ting-Hao Chen
tinghaochen@163.com

Jun Han
hanjunehbh@smmu.edu.cn

Hao Xing
xinghaoehbh@smmu.edu.cn

Zhen-Li Li
xinghaoehbh@smmu.edu.cn

Wan Yee Lau
wy_lau@protonmail.com

Meng-Chao Wu
mengchao_wu@sina.com

1 Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), No. 225, Changhai Road, Shanghai 200438, China

2 Department of Radiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China

3 Department of Hepatic Surgery, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China

4 Department of Surgery, Wexner Medical Center, Ohio State University, Columbus, OH, USA

5 Department of Hepatobiliary Surgery, Pu'er People's Hospital, Yunnan, China

6 The 1st Department of General Surgery, The Fourth Hospital of Harbin, Heilongjiang, China

7 Department of General Surgery, Liuyang People's Hospital, Hunan, China

8 Department of General Surgery, Ziyang First People's Hospital, Sichuan, China

9 The 2nd Department of Hepatobiliary Surgery, Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital to Sun Yat-sen University, Meizhou, China

10 Faculty of Medicine the Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T.,, Hong Kong, SAR, China