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Long-term survival after surgical resection for huge HCC: comparison with TACE after propensity score matching

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ABSTRACT

Background/Aims: Surgical resection (SR) and transarterial chemoembolization (TACE) have been commonly applied for patients with huge hepatocellular carcinoma (HCC). However, optimal treatment has not been established. **Methods:** Between 2000 and 2009, 267 patients with huge HCC (≥10 cm) underwent TACE and 84 underwent SR as the first treatment. Propensity score matching generated a matched cohort composed of 152 patients. We investigated overall survival and possible prognostic factors. **Results:** At baseline, the surgery group showed a tendency to have solitary tumor (72.6% vs. 39.3%, $P<0.001$), less vessel invasion (29.8% vs. 51.3%, $P<0.001$), and unilobar tumor extent (77.4% vs. 50.9%, $P<0.001$) than TACE group. During median follow-up of 10 months (range: 0-103), the surgery group showed higher 1-, 3-, and 5-year overall survival rates than TACE group (73.8%, 54.8%, and 39.8% vs. 37.8%, 16.3%, and 9.7%, respectively, $P<0.001$). In the propensity score-matched cohort, baseline characteristics did not differ between the two groups. Surgery group showed higher 1-, 2-, and 3-year overall survival rates than TACE group (69.7%, 58.6%, and 51.7% vs. 40.2%, 33.9%, and 18.5%, respectively, $P<0.001$) during median follow-up of 14.5 months (range: 0-103). Multivariate analysis revealed that male (HR 1.90; 95% CI, 1.01-3.58; $P=0.048$), albumin (HR 0.54; 95% CI, 0.34-0.85; $P=0.008$), ascites (HR 1.77; 95% CI, 1.02-3.08; $P=0.044$), and SR (HR 0.44; 95% CI, 0.28-0.70; $P=0.001$) were the independent prognostic factors associated with survival. **Conclusion:** Comparing survival after SR and TACE, we showed that SR would be associated with better outcomes than TACE as the first treatment of huge HCC.

Key words: Huge hepatocellular carcinoma; Surgical resection; Transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is one of the most common causes of cancer death worldwide.[1] The introduction of surveillance in patients at high risk of HCC has allowed detection of small HCC.[2,3] Nevertheless, a substantial proportion of patients present with huge HCC (10 cm or more in diameter) with worse survival rates than with smaller tumors.[4-6] They are not eligible for radiofrequency ablation or liver transplantation.[7] Surgical resection (SR) and transarterial chemoembolization (TACE) are the generally accepted treatment options. SR is the treatment modality offering long-term survival in some patients with huge HCC.[8-11] However, resection of huge HCC is technically difficult and usually requires major hepatic resection, which can be associated with an increased risk of operative mortality.[12] On the other hand, TACE could be expected to extend life expectancy without a significant procedure-related mortality, although it is a non-curative treatment.[13,14] TACE was reported to provide survival benefit in patients with unresectable HCC larger than 10 cm in diameter. The 1-, 3-, and 5-year overall survival rates in TACE group were 42%, 13%, and 7% respectively.[14]

In a previous study, surgical treatment was reported to show longer mean survival in patients with huge HCC than nonsurgical multidisciplinary therapy including hepatic arterial infusion, transcatheter arterial embolization, and percutaneous acetic acid injection (17 months vs. 7 months, P=0.003).[15] However, these results do not definitively demonstrate superiority of surgery in survival because that may result from differences in patient selection. An ideal method to compare the outcome after SR and TACE would be a randomized controlled trial. However, no direct comparison between well balanced SR and TACE groups has been performed even in a retrospective design. Accordingly, superiority of SR for patients with huge HCC as compared with TACE remains to be determined.

The purpose of this study was to compare long-term results of SR and TACE in patients with huge HCC before and after propensity score matching and to investigate possible prognostic factors associated with survival.

Patients and Methods

Study population

Between 2000 and 2009, a total of 4,527 patients were diagnosed with HCC at Samsung Medical Center, Seoul, Korea. Of them, 586 patients had huge HCC (10 cm or more in diameter). One hundred and thirty three patients who had any metastasis at the time of diagnosis were excluded. Among remaining 453 patients, 84 underwent SR (surgery group), 267 underwent TACE (TACE group), 26 underwent other treatment including chemotherapy (n=19) and radiotherapy (n=3), and 76 received supportive care only as the first treatment. The diagnosis of HCC was based either on pathologic confirmation or on the clinical criteria based on typical image findings and/or elevated serum alpha-fetoprotein (AFP) levels in high risk group.[16,17]

The following clinical and laboratory information was collected from each patient: age, gender, etiology of liver disease, presence of liver cirrhosis, and Child-Pugh class. From the radiologic findings, tumor characteristics also were evaluated regarding size, number, extent, and presence of vessel invasion.

Patients were defined as cirrhotic when they had radiologic findings compatible with cirrhosis (nodular surface on computed tomography), thrombocytopenia (< 100,000/mm^3) and splenomegaly, or esophago-gastric varices on endoscopy.

To reduce the effect of treatment selection bias and potential confounding in this study, we performed rigorous adjustment for the differences in the baseline characteristics by using propensity score matching.[18] After matching by propensity scores composed of age, gender, etiology of liver disease, Child-Pugh class, tumor number, presence of vessel invasion, and tumor extent, 76 patient pairs were selected. The study protocol was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board at Samsung Medical Center, Seoul, Korea.

TACE procedure

After catheterization of the celiac artery, arteriography was initially performed to assess patient anatomy, tumor burden, vascularity, and portal vein patency. Then, superior mesenteric artery, or common hepatic artery with a 5-french (F) catheter, selective angiography was performed. Then, a coaxial superselective micro-catheter was inserted through the 5-F catheter as close to the tumor as possible. After the micro-catheter was positioned in the target branch, a mixture of doxorubicin hydrochloride (Adriamycin; Ildong, Seoul, Korea) and iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) was slowly injected through the catheter. The mixture of iodized oil and doxorubicin hydrochloride was prepared by vigorously pumping the solutions 10 to 20 times between two syringes interconnected with a three-way stopcock. The doses of adriamycin and lipiodol were determined based on the size and vascularity of the tumor, though we limited the maximum doses of adriamycin and lipiodol for one session of TACE to 70 mg and 25 mL, respectively. Infusion of the lipiodol mixture was followed by particulate embolization with 1- to 2-mm-diameter gelatin sponge pledgets (Cutanplast; MasciaBrunelli, Milan, Italy). The end-point of TACE was fluoroscopic observation of complete lipiodol uptake by the tumor or stagnation of blood flow in the tumor-feeding arteries, or the injection of the maximum dose of the lipiodol mixture allowed per session.

Treatments and follow-up

All patients who underwent surgery were followed-up every 3 months during the first 2 years, and every 6 months thereafter. During each visit, liver function tests, serum AFP level measurements, and dynamic liver computed tomography (CT) were performed for surveillance of recurrence.

For TACE group, two consecutive TACE sessions were routinely performed at intervals of one month. Patients visited the outpatient clinic one month after each cycle (before the next TACE). Patients were evaluated with liver function tests, serum AFP level measurements, and dynamic liver CT scans. TACE was repeated if clinically feasible and viable tumor was present on the dynamic liver CT. No further TACE was performed in the presence of complete radiological response. Contraindications for TACE were defined as clinical features obviating further TACE applications (occurrence of extrahepatic lesions, complete portal vein thrombosis, diffuse tumor growth and total bilirubin >3 mg/dL, deteriorations to ECOG performance status ≥3 or Child-Pugh class C).

Assessment

The baseline characteristics of the surgery and TACE groups were compared in all study subjects and propensity score matched-cohort. The primary endpoint was overall survival, which was defined as the time from the SR or TACE for HCC to death from any cause. Overall survival was compared between the two groups in all study subjects and propensity score matched-cohort. Prognostic factors for overall survival were explored using univariate and multivariate analysis in the propensity score matched-cohort.

Statistical analysis

The statistical results are presented as the mean ± standard deviation or percentages.

In all study subjects, continuous variables were compared parametrically using Student's *t*-test or non-parametrically using the Mann-Whitney *U*-test. Categorical variables were compared using the χ2-test or Fisher's exact test as appropriate. Overall survival was calculated using the Kaplan–Meier method and compared using the log-rank test.

The propensity scores were estimated regarding all variables presented in the baseline characteristics with parsimonious logistic regression model. The 1: 1 matching without replacement was performed within 25% of standard deviation of log-transformed propensity scores. In the propensity score-matched cohort, the two groups were compared in terms of the baseline characteristics. Continuous variables were compared using a paired *t*-test or the Wilcoxon signed-rank test, while categorical variables were compared using the McNemar test. The stratified Cox regression models were used to examine the association of baseline characteristics with all-cause mortality in the propensity score-matched cohort.

A two-sided *P* value <0.05 was taken as statistically significant. Statistical analyses were conducted using PASW Statistics 18 for Windows (SPSS, Inc, Chicago, IL) and the open source statistical language and platform, R, version 2.12.1 (R Development Core Team, 2010), with the package "Matching".

Results

Baseline characteristics of the study population before matching

The baseline characteristics of the two groups in all study subjects are shown in Table 1. There were no significant differences between the two groups with regard to age, gender, etiology of liver disease, Child-Pugh class, and tumor size. However, the surgery group showed a tendency to have a solitary tumor (72.6% vs. 39.3%, $P<0.001$), less vessel invasion (29.8% vs. 51.3%, $P<0.001$), and unilobar tumor extent (77.4% vs. 50.9%, $P<0.001$) compared to the TACE group.

Procedure-related mortality

Two patients who underwent SR died of liver failure during the same hospital admission. One patient who underwent TACE died of lipiodol-induced acute lung injury. The in-hospital mortality of SR group did not differ from that of TACE group (2.4% vs. 0.4%, $P=0.14$).

Overall survival of the study population before matching

During median follow-up of 10 months (range: 0-103), the surgery group showed higher 1-, 3-, and 5-year overall survival rates than TACE group (73.8%, 54.8%, and 39.8% vs. 37.8%, 16.3%, and 9.7%, respectively, $P<0.001$; Figure 1).

Baseline characteristics of the propensity score-matched cohort

In the propensity score-matched cohort, there were no significant differences between the two groups regarding age, gender, etiology of liver disease, Child-Pugh class, serum total bilirubin, serum albumin, prothrombin time, presence of ascites, tumor size, tumor number, vessel invasion, and tumor extent (Table 2).

Overall survival of the propensity score-matched cohort

After propensity score matching, the surgery group showed higher 1-, 2-, and 3-year overall survival rates than TACE group (69.7%, 58.6%, and 51.7% vs. 40.2%, 33.9%, and 18.5%, respectively, P<0.001; Figure 2) during median follow-up of 14.5 months (range: 0-103).

Predictive factors for overall survival in the propensity score-matched cohort

To adjust for the simultaneous impact of potential confounders even after propensity score matching, stratified Cox proportional hazards regression was conducted (Table 3).In the univariate analysis, hazard ratio (HR) of surgery group was 0.29 (95% confidence interval (CI), 0.14-0.59; P<0.001). Multivariate analysis revealed that male gender (HR 1.90; 95% CI, 1.01-3.58; P=0.048), serum albumin (HR 0.54; 95% CI, 0.34-0.85; P=0.008), presence of ascites (HR 1.77; 95% CI, 1.02-3.08; P=0.044), and surgical resection (HR 0.44; 95% CI, 0.28-0.70; P=0.001) were the independent prognostic factors associated with survival in propensity score matched-cohort with huge HCC.

Discussion

Although SR and TACE are generally applied to patients with huge HCC, it is not clear which is the optimal treatment modality. To date, no randomized trial, a theoretically ideal method to compare two treatment modalities, has been performed regarding this topic. Although Luo et al.[19] compared hepatic resection with TACE as the initial treatment for large, multiple, and resectable HCC in prospective design, patients were not randomly allocated and large HCC was defined as 5 cm or larger. One retrospective study reported the results of comparing hepatectomy and nonsurgical multidisciplinary therapy, but had possible selection bias.[15] Therefore, we compared the long-term results of SR and TACE as the first treatment for patients with huge HCC before and after propensity score matching and investigated possible prognostic factors associated with survival.

In our results, the overall cumulative 1-, 3-, and 5-year survival rates were 38.5%, 21.7%, and 13.3% respectively. Surgery group showed higher 1-, 3-, and 5-year overall survival rates than TACE group (73.8%, 54.8%, and 39.8% vs. 37.8%, 16.3%, and 9.7%, respectively, $P<0.001$). In the previous study, surgical treatment group was reported to show higher 1-, 3-, and 5-year overall survival rates than nonsurgical treatment group (60.7%, 24.5%, and 24.5% vs. 23.3%, 9.6%, and 8.2%, respectively, $P<0.001$).[15] However, the surgical treatment group had less patients with liver cirrhosis and less patients with portal vein or hepatic vein invasion than the nonsurgical treatment group. Therefore, it remains possible that patient selection factors may have influenced the results, which limits the usefulness of the study. In our study, the differences in the baseline characteristics were noticed in the study populations before matching. Hence, we performed rigorous adjustment through propensity score matching to reduce the effect of treatment selection bias and potential confounding. This produced 76 patient pairs selected after matching by propensity scores composed of age, gender, etiology of liver disease, Child-Pugh class, tumor number, presence of vessel invasion, and tumor extent. Even after propensity score matching, surgery group showed higher 1-, 2-, and 3-year overall survival rates than TACE group (69.7%, 58.6%, and 51.7% vs. 40.2%, 33.9%, and 18.5%, respectively).

In this study, Child-Pugh class was used to correct liver function status between the two groups. However, noncirrhotic patients also were included in this study and cirrhotic patients who have clinically significant portal hypertension can have Child-Pugh class A. We, therefore, performed subgroup analysis of the overall survival rates after surgery and TACE according to the cirrhosis status of the population. The surgery group showed a higher survival rate than TACE group in non-cirrhotic patients (*P*=0.01, Figure 3A). However, the surgery group showed a marginally higher survival rate than TACE group in cirrhotic patients, which did not reach to the statistical significance (*P*=0.06, Figure 3B).

We investigated possible prognostic factors associated with survival in propensity score matched-cohort with huge HCC. In multivariate analysis, treatment modality was the strongest prognostic factor associated with survival. HR of surgery group was 0.44 as compared with TACE group (95% CI, 0.28-0.70; *P*=0.001). Accordingly, SR would provide more survival benefit in patients with huge HCC than TACE.

The present study had some limitations. First, the retrospective design may have introduced selection bias. Despite we minimized selection bias and potential confounding using the propensity score matching, bias because of imbalance on unmeasured baseline characteristics remained possible, as in any observational study. Second, the patient series was rather small. Nevertheless, this comparative study was performed in the well-designed propensity score-matched cohort. In addition, to the best of our knowledge, this is the first study to report superiority of SR to TACE as the first treatment in patients with huge HCC. Lastly, we included the presence or absence of vessel invasion into matching regardless of the extent of invasion, since vessel invasion was noted in a minority of the surgery group and major vascular invasion was observed in the very limited number of patients undergoing surgery. Further studies comparing two groups according to the extent of vessel invasion in detail might provide some more useful information on the role of major and minor vessel invasion.

In conclusion, comparing the survivals after SR and TACE in overall patients and propensity score-matched cohort, we showed that SR would be associated with better outcome than TACE in the treatment of huge HCC.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Figure legends

Figure 1. Kaplan-Meier survival curves showing overall survival rates in 351 patients with huge hepatocellular carcinoma after surgery (n=84) and TACE (n=267). Surgery group showed higher 1-, 3-, and 5-year survival rates than TACE group (73.8%, 54.8%, and 39.8% vs. 37.8%, 16.3%, and 9.7%, respectively; $P<0.001$).

TACE, transarterial chemoembolzation

Figure 2. Kaplan-Meier survival curves showing overall survival rates in propensity score matched-cohort (76 matched pairs) with huge hepatocellular carcinoma after surgery and TACE. Surgery group showed higher 1-, 2-, and 3-year survival rates than TACE group (69.7%, 58.6%, and 51.7% vs. 40.2%, 33.9%, and 18.5%, respectively; $P<0.001$).

TACE, transarterial chemoembolzation

Figure 3. Kaplan-Meier survival curves showing overall survival rates cirrhosis after surgery and TACE in propensity score matched-cohort (76 matched pairs) according to the presence of cirrhosis: a) in non-cirrhotic patients and b) in cirrhotic patients.

TACE, transarterial chemoembolzation

Table 1. Comparison of baseline characteristics between patients undergoing surgery and transarterial chemoembolzation for huge hepatocellular carcinoma before propensity score matching (n=357)

Variables	Surgery (n=84)	TACE (n=267)	*P* value
Age	52.7 ± 11.7	53.7 ± 10.9	0.46
Male	70 (83.3%)	229 (85.8%)	0.58
Etiology of liver disease			0.34
HBV	62 (73.8%)	209 (78.3%)	
HCV	3 (3.6%)	9 (3.4%)	
HBV+HCV	1 (1.2%)	0 (0.0%)	
non-B non-C	18 (21.4%)	49 (18.4%)	
Child-Pugh class			0.20
A	75 (89.3%)	223 (83.5%)	
B	9 (10.7%)	44 (16.5%)	
Tumor size			0.10
10-15 cm	72 (85.7%)	245 (91.8%)	
>15 cm	12 (14.3%)	22 (8.2%)	
Tumor number			<0.001
Solitary	61 (72.6%)	105 (39.3%)	
Multiple	23 (27.4%)	162 (60.7%)	
Vessel invasion	25 (29.8%)	137 (51.3%)	<0.001
Tumor extent			<0.001
One lobe	65 (77.4%)	136 (50.9%)	
Both lobes	19 (22.6%)	131 (49.1%)	

TACE, transarterial chemoembolization

Data are shown as the mean ± SD or number (%) of patients.

Table 2. Baseline characteristics between patients undergoing surgery and transarterial chemoembolization for huge hepatocellular carcinoma after propensity score matching (76 matched pairs)

Variables	Surgery (n=76)	TACE (n=76)	*P* value
Age	53.0 ± 12.0	54.8 ± 10.5	0.28
Male	63 (82.9%)	64 (84.2%)	1.00
Etiology of liver disease†			0.71
HBV	57 (75.0%)	54 (71.1%)	
HCV	3 (4.0%)	2 (2.6%)	
non-B non-C	16 (21.1%)	20 (26.3%)	
Child-Pugh class			0.66
A	67 (88.2%)	64 (84.2%)	
B	9 (11.8%)	12 (15.8%)	
Total bilirubin (mg/dL)	0.9 ± 0.5	1.0 ± 0.6	0.76
Albumin (g/dL)	3.8 ± 0.6	3.8 ± 0.5	0.99
Prothrombin time (INR)	1.1 ± 0.1	1.1 ± 0.1	0.72
Ascites	11 (14.5%)	20 (26.3%)	0.07
Tumor size			0.58
10-15 cm	68 (89.5%)	65 (85.5%)	
>15 cm	8 (10.5%)	11 (14.5%)	
Tumor number			0.72
Solitary	23 (30.3%)	25 (32.9%)	
Multiple	53 (69.7%)	51 (67.1%)	
Vessel invasion	24 (31.6%)	20 (26.3%)	0.42
Tumor extent			1.00
One lobe	57 (75.0%)	56 (73.7%)	
Both lobes	19 (25.0%)	20 (26.3%)	

TACE, transarterial chemoembolization

Data are shown as the mean ± SD or number (%) of patients.

†HBV+HCV infection was excluded from analysis because the number of patients was too small to match between the two groups.

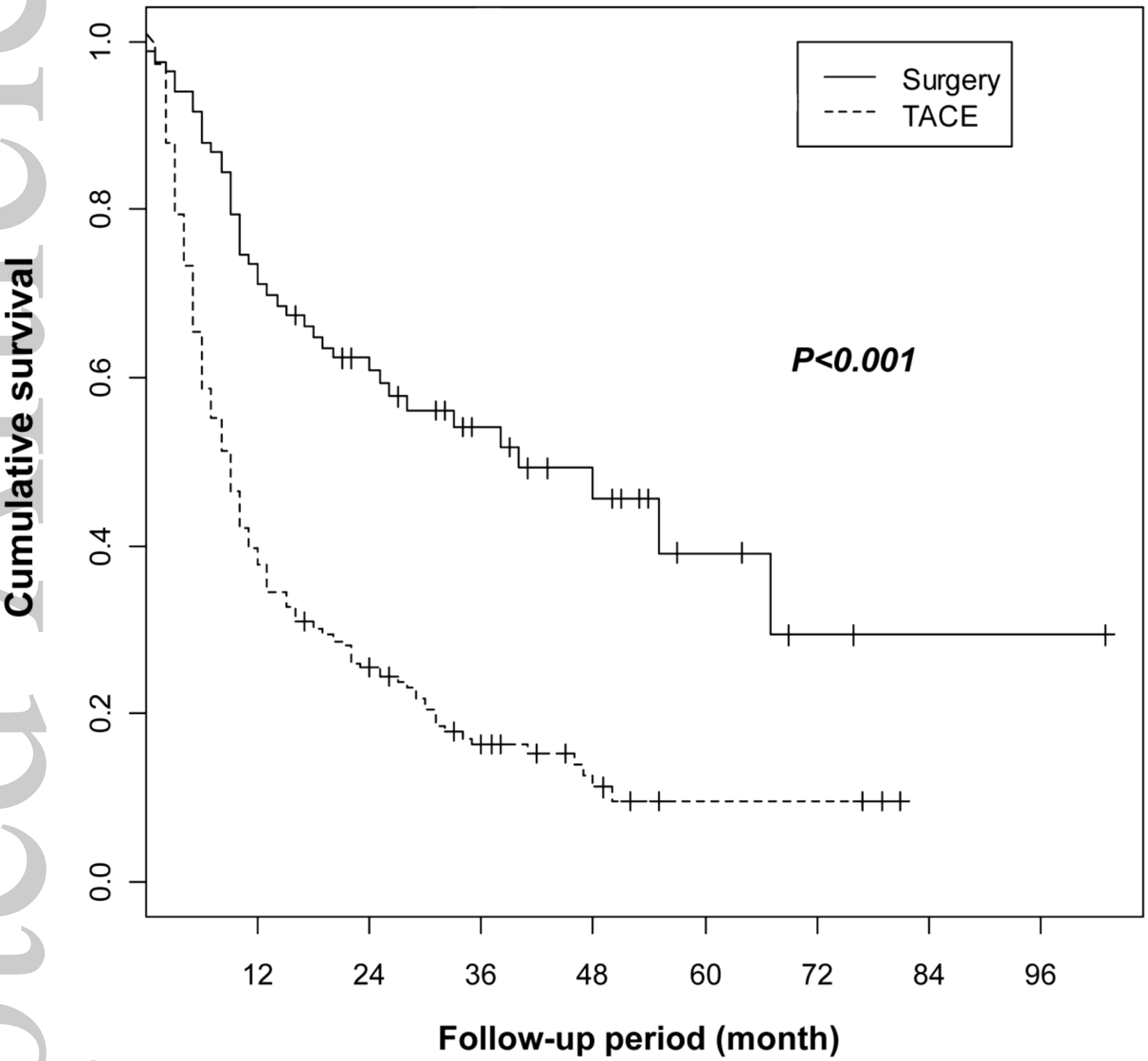
Table 3. Prognostic factors associated with overall survival in propensity score matched-cohort with huge hepatocellular carcinoma (76 matched pairs)

Variables	Multivariate analysis	
	HR (95% CI)	***P***
Age	0.99 (0.98-1.01)	0.52
Gender		
Female	1	
Male	1.90 (1.01-3.58)	0.048
Etiology of liver disease		
HBV	0.65 (0.40-1.06)	0.08
HCV	0.89 (0.26-3.10)	0.85
non-B non-C	1	
Total bilirubin	0.87 (0.56-1.34)	0.52
Albumin	0.54 (0.34-0.85)	0.008
Prothrombin time	1.79 (0.19-16.7)	0.61
Ascites	1.77 (1.02-3.08)	0.044
Tumor number		
Solitary	1	
Multiple	0.66 (0.39-1.11)	0.12
Vessel invasion		
No	1	
Yes	0.70 (0.42-1.16)	0.22
Tumor extent		
One lobe	1	
Both lobes	0.69 (0.38-1.25)	0.17
Treatment		
Surgical resection	0.44 (0.28-0.70)	0.001
TACE	1	

HR, hazard ratio; CI, confidence interval.

The other abbreviations are the same as those defined in Table 1.

†Child-Pugh class was replaced with its detailed measurements in multivariate analysis. Tumor size was excluded from this analysis because it was highly correlated with other variables and interfered with proper interpretation of multiple regression results.



Surgery
TACE
P<0.001
Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
12
24
36
48
60
72
84
96
Follow-up period (month)

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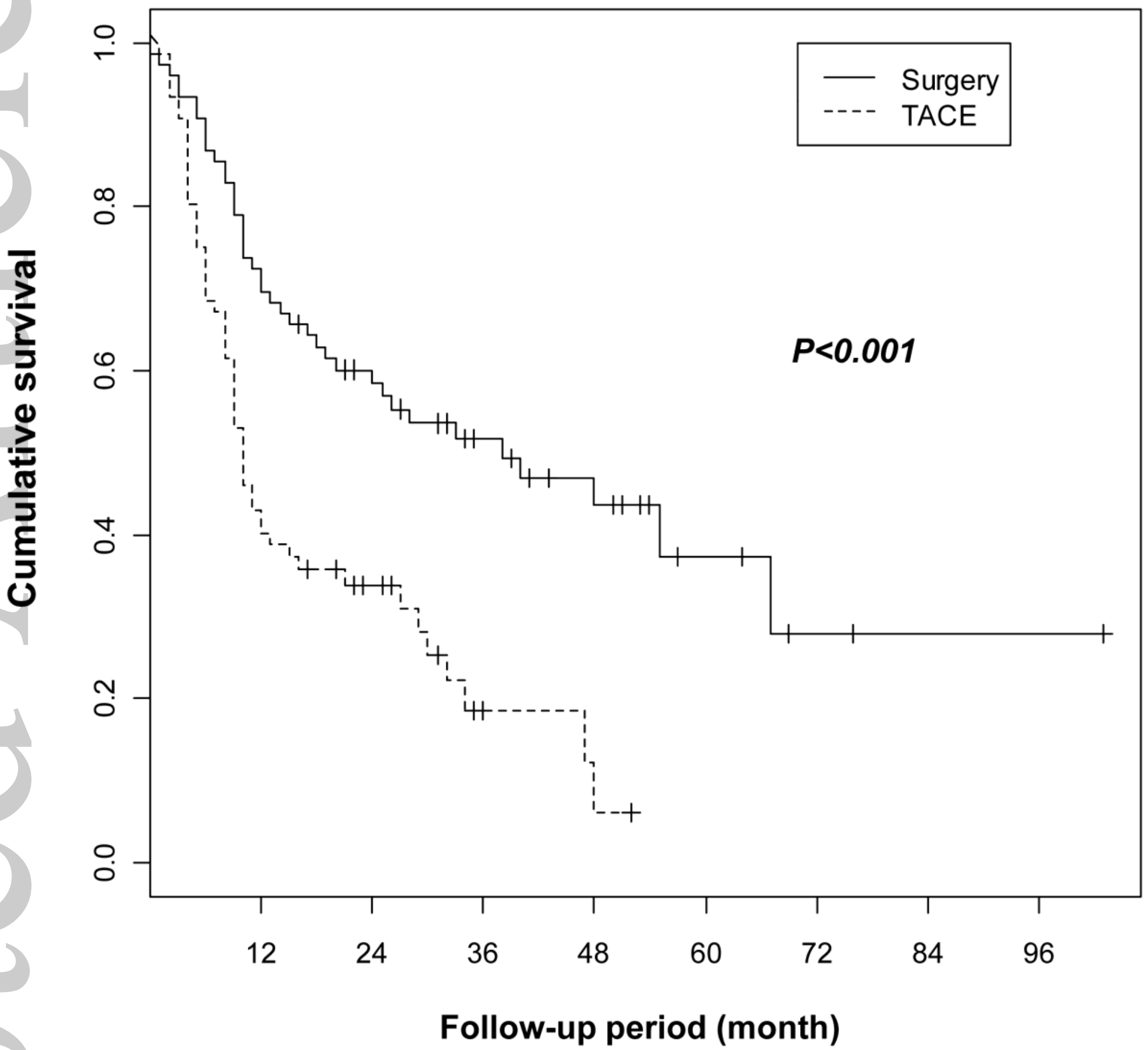
Cumulative survival
1.0
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0.2
0.0
Surgery
TACE
P<0.001
12
24
36
48
60
72
84
96
Follow-up period (month)

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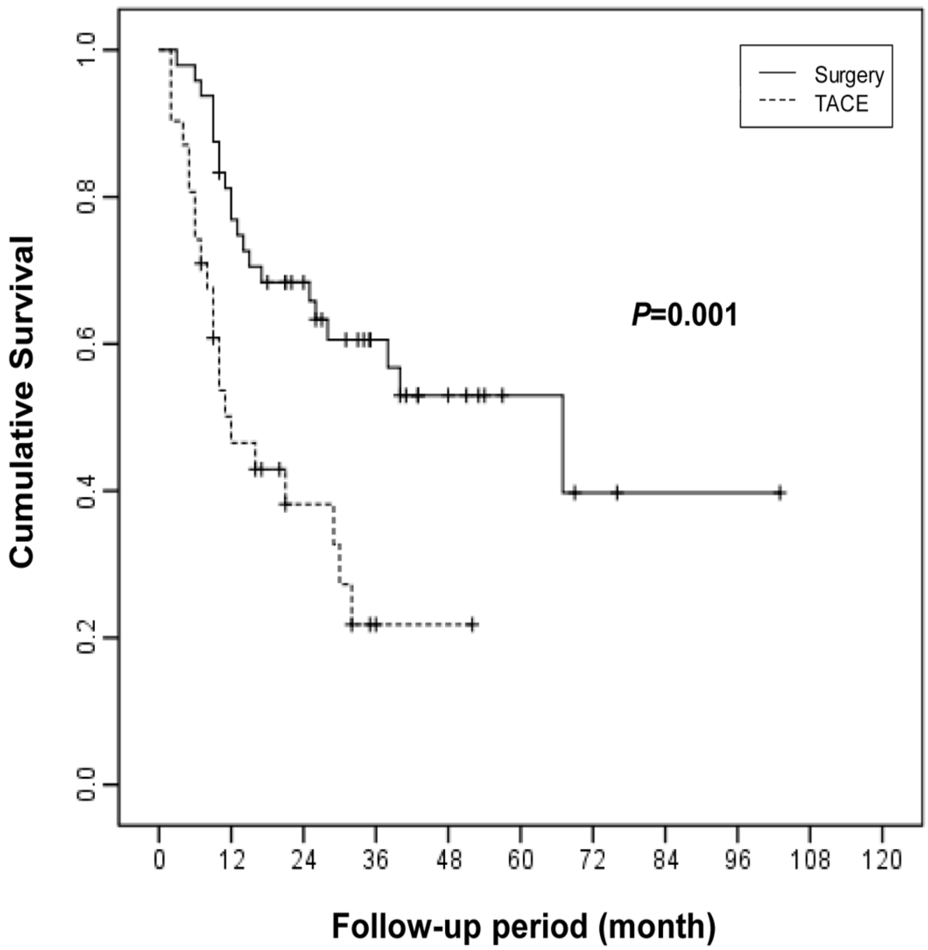

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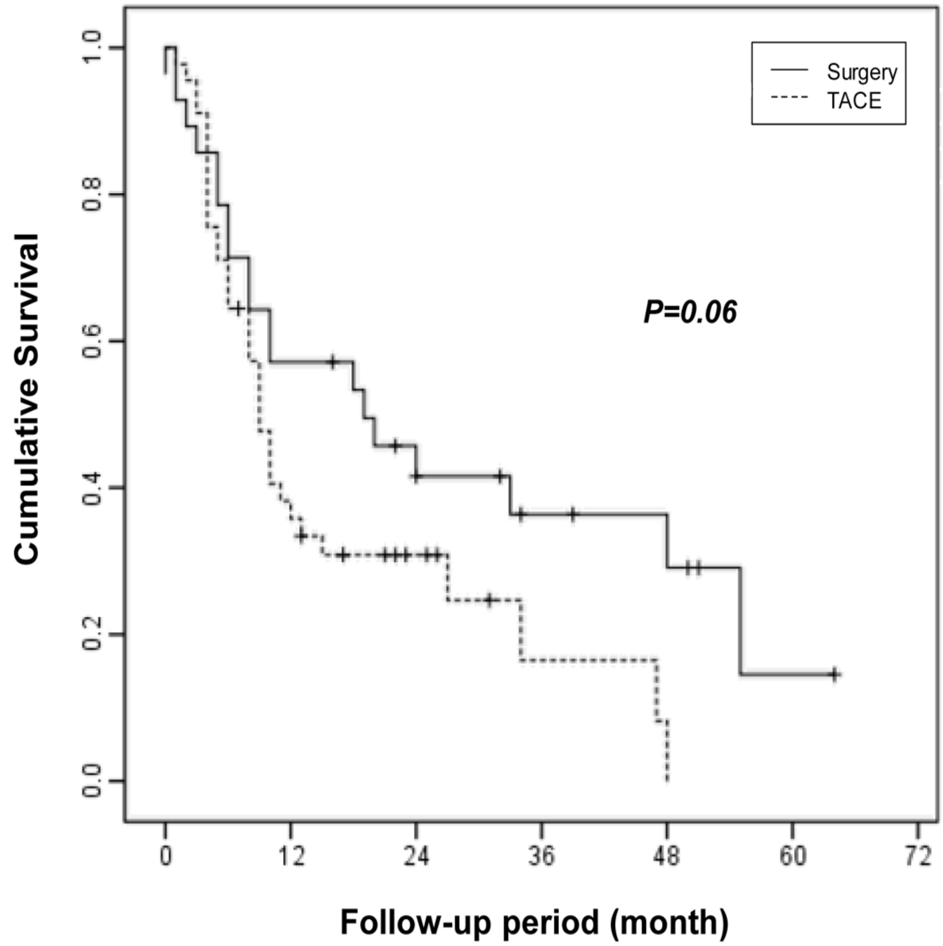

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