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Long-term outcomes after hepatectomy of huge hepatocellular carcinoma: A single-center experience in China

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ABSTRACT

Background: Currently, hepatectomy remains the first-line therapy for hepatocellular carcinoma (HCC). However, surgery for patients with huge (>10 cm) HCCs is controversial. This retrospective study aimed to explore long-term survival after hepatectomy for patients with huge HCC.

Methods: The records of 188 patients with pathologically confirmed HCC who underwent curative hepatectomy between 2007 and 2017 were reviewed; patients were divided into three groups according to tumor size: huge (>10 cm; $n=84$), large (5–10 cm; $n=51$) and small (<5 cm; $n=53$) HCC. Kaplan-Meier analysis was used to assess overall survival (OS) and disease-free survival (DFS), and log-rank analysis was performed for pairwise comparisons among the three groups. Risk factors for survival and recurrence were analyzed using the Cox proportional hazard model.

Results: The median follow-up period was 20 months. Although the prognosis of small HCC was better than that of huge and large HCC, OS and DFS were not significantly different between huge and large HCC ($P=0.099$ and $P=0.831$, respectively). A family history of HCC, poor Child-Pugh class, vascular invasion, diolame, pathologically positive margins, and operative time ≥240 min were identified as independent risk factors for OS and DFS in a multivariate model. Tumor size (>10 cm) had significant effect on OS, and postoperative antiviral therapy and postoperative complications also had significant effects on DFS.

Conclusions: Huge HCC is not a contraindication of hepatectomy. Although most of these patients experienced recurrence after surgery, OS and DFS were not significantly different from those of patients with large HCC after resection.

Introduction

Hepatocellular carcinoma (HCC) is one of the predominant causes of cancer-related mortality worldwide, with an increasing trend in incidence in some Western countries, significantly contributing to the global burden of cancer. A recent epidemiological study revealed that liver cancer is the second most common cancer-related death in Brazil and the United States [1]. Although numerous treatments for liver cancer are available, including surgery, radiofrequency ablation, transhepatic arterial chemotherapy and embolization (TACE), and external radiation, surgical resection is still the preferred option and remains the only feasible curative therapy for HCC [2]. Due to advances in surgical techniques and perioperative management, surgical indications for advanced tumors have been gradually expanding, which has improved the long-term outcomes for patients with HCC in recent years [3]. Nevertheless, for patients with huge (>10 cm) HCC, the international guidelines for treatment remain controversial because these patients frequently have recurrence after resection accompanied by vascular invasion, satellite nodules and poor tumor differentiation [4–6], which correspond to more aggressive tumor biology, leading to a poor prognosis. Huge HCC is not described by the Milan criteria, and internationally, liver transplantation is not considered appropriate. Moreover, these patients are often in an advanced stage according to the BCLC staging system, and surgery is not recommended. Local treatment, such as radiofrequency ablation, is considered beneficial for small HCC (no larger than 3 cm) but is debatable for tumors that are 3–5 cm [7]. Although TACE is a good treatment choice, the long-term prognosis after TACE is unclear. Previously, surgery has been reported to be the ideal solution for the treatment of very large liver cancers (≥10 cm) [8], and guidelines published in the Asia-Pacific region recommend surgical resection as the primary treatment for patients with large,

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multiple HCCs and HCCs with vascular invasion [9,10]. Other studies commonly report similar findings. Lim et al. [11] suggested that patients with isolated HCC would obtain a benefit from surgical resection regardless of tumor size. Yang et al. [12] found no significant difference in overall survival (OS) between a huge HCC group and a large HCC group after surgery. Therefore, hepatectomy may remain a reasonable treatment for huge HCC. This study aimed to analyze the long-term outcomes of patients with HCC >10 cm who underwent curative hepatectomy and compare them with the outcomes of patients with HCC ≤10 cm and to identify risk factors related to the prognosis of HCC.

Methods

Selection of research subjects

A retrospective survey of patients who had undergone hepatectomy and had pathologically confirmed HCC postoperatively from 2007 to 2017 was conducted at the First Affiliated Hospital, Anhui Medical University. The study was approved by the institutional review committee of the First Affiliated Hospital, Anhui Medical University. Patients who underwent noncurative therapy, such as exploratory laparotomy, biopsy, radiofrequency ablation, or TACE, and those without HCC were excluded from our series. Ultimately, 188 patients were identified and included in the study. Relevant demographic, clinical, operative, and histopathological features of these patients and their long-term outcomes were extracted from the Kang Heng medical follow-up database. We divided these patients into three groups according to tumor size (based on the pathology report): less than 5 cm in diameter (small HCC), between 5 and 10 cm (large HCC), and greater than 10 cm (huge HCC).

Preoperative evaluation

All patients underwent complete laboratory assessments of liver function, virus serological detection, abdominal ultrasound, abdominal enhanced CT and abdominal enhanced MRI to evaluate tumor characteristics and cirrhosis. If viral replication was considered high, antiviral therapy was administered. The Child-Pugh score [13] (prothrombin time, bilirubin, albumin, ascites, and encephalopathy) and indocyanine green (ICG) clearance [14] were routinely used to assess hepatic reserve. Patients categorized as Child-Pugh class A and with an ICG clearance of less than 15% were considered to have adequate reserves. Patients with poor liver function were preoperatively administered hepatoprotective therapy. In patients with huge HCC, three-dimensional reconstruction of the liver was used to delineate the tumor and the peripheral blood vessels.

Surgical techniques

Anatomical resection of the liver was performed whenever possible because the incidence of local recurrence is significantly higher after non-anatomical resection than that after anatomical resection [15]. Because the anterior approach can prolong the survival of patients with large-size liver cancer compared to the conventional approach [16], we routinely used an anterior approach to perform hepatectomy for large tumors located in the right lobe of the liver.

Follow-up

All patients were followed up regularly at the outpatient clinic. Alpha-fetoprotein (AFP) was routinely assessed because it is a critical factor for determining recurrence. Menahem et al. [17] constructed the AFP score to assess patient prognosis and to develop a valid tool for patient selection after hepatectomy for solitary HCC (HCC <6 cm). Of note, the AFP score was developed for chronic liver disease, and patients "in AFP score" typically exhibited better survival compared with those "out AFP score". Ultrasonography results were reviewed every 3 months, and computed tomography or MR of the liver were performed every 6 months. HCC recurrence was considered when either new lesions with typical features associated with HCC were observed on imaging or AFP levels began to increase. For atypical lesions, biopsy was recommended. The treatments for patients who experienced recurrence included repeat operation, TACE, locoregional ablation, and sorafenib administration.

Independent variables

The independent variables investigated that could affect prognosis included patient demographics (age, sex, family history, symptoms, and viral hepatitis status), disease characteristics (preoperative liver function, AFP level, degree of liver cirrhosis, and preoperative vascular invasion), pathologic specimens [the number and size of the tumor(s), satellite nodule(s), histological grade of tumor differentiation, pathological vascular invasion, diolame, margin, and tumor stage] and classification of surgical complications as described by Dindo et al. [18]. According to the results of a previous study [19], which reported that the long-term survival of HCC patients was significantly prolonged by a wide surgical margin (≥1 cm), we defined a margin ≥1 cm as a negative margin. The tumor stage was based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for HCC [20]. Postoperative therapy included TACE, nucleoside analogue therapy or repeat resection; the nucleoside analogues administered included lamivudine, entecavir or telbivudine, which are recommended for treatment of chronic HBV infection [21].

Dependent variables

The dependent variables were OS and disease-free survival (DFS). OS was defined as the interval between the date of the first operation and patient death, and data for individual survival status, including the date and cause of death, were obtained from records at the public security bureau. DFS was defined as the interval between the first operation and the date of the first recurrence.

Statistical analysis

SPSS version 19 (IBM Corp., Armonk, NY, USA) was used for data processing. Continuous variables were compared using Student's *t* test or a Mann-Whitney Wilcoxon test, and categorical variables were compared by Chi-square test. Survival estimates were calculated by Kaplan-Meier analysis, and the log-rank test was used to identify significant differences in pairwise comparisons among groups. A univariate log-rank test was used to evaluate all variables, and those with a $P < 0.1$ or that possibly affected the prognosis were entered into a multivariate Cox model, with $P < 0.05$ considered significant.

Results

The demographic, clinical, histopathological and interventional characteristics of the study population are shown (Table 1); the patients were allocated into three groups based on tumor size. The patient ages ranged from 23 to 78 years with a mean of 54.3 (±12.1) years. All groups included more elderly patients than younger patients. The ratio of men to women was 5.96 (161/27),

Table 1
Comparison of clinical features of patients who underwent resection of HCC.

Characteristics	Small HCC (<5 cm, $n=53$)	Large HCC (5–10 cm, $n=51$)	Huge HCC (>10 cm, $n=84$)	P value
Age (yr)				**0.037**
20–39	7 (13.2%)	2 (3.9%)	14 (16.7%)	
40–60	25 (47.2%)	37 (72.5%)	42 (50.0%)	
>60	21 (39.6%)	12 (32.5%)	28 (33.3%)	
Sex (male/female)	40/13	45/6	76/8	0.420
Family history of HCC (yes/no)	14/39	12/39	28/56	0.431
HBsAg (positive/negative)	45/8	39/12	60/24	0.193
Symptoms (yes/no)	18/35	29/22	69/15	<**0.001**
Child-Pugh class (A/B)	52/1	49/2	77/7	0.264
AFP (ng/mL)				**0.007**
0–399	34 (64.2%)	26 (51.0%)	39 (46.4%)	
400–800	7 (13.2%)	4 (7.8%)	2 (2.4%)	
>800	12 (22.6%)	21 (41.2%)	43 (51.2%)	
Liver cirrhosis				<**0.001**
No	6 (11.3%)	5 (9.8%)	12 (14.3%)	
Mild	10 (18.9%)	10 (19.6%)	38 (45.2%)	
Moderate	27 (50.9%)	18 (35.3%)	26 (31.0%)	
Severe	10 (18.9%)	18 (35.3%)	8 (9.5%)	
Satellite nodules (yes/no)	7/46	11/40	24/60	0.108
Tumor differentiation				**0.031**
Well	11 (20.8%)	5 (9.8%)	7 (8.3%)	
Moderate	30 (56.6%)	24 (47.1%)	55 (65.5%)	
Poor	12 (22.6%)	22 (43.1%)	22 (26.2%)	
Vascular invasion (yes/no)	6/47	19/32	25/59	**0.008**
Diolame (yes/no)	42/11	29/22	58/26	**0.048**
Margin (positive/negative)	0/53	2/49	5/79	0.200
AJCC T stage				<**0.001**
T1	41 (77.4%)	22 (43.1%)	42 (50.0%)	
T2	9 (17.0%)	12 (23.5%)	2 (2.4%)	
T3	1 (1.9%)	12 (23.5%)	21 (25.0%)	
T4	2 (3.8%)	5 (9.8%)	19 (22.6%)	
Complications (Clavien-Dindo grade)				**0.028**
I	26 (49.1%)	16 (31.4%)	49 (58.3%)	
II	26 (49.1%)	33 (64.7%)	31 (36.9%)	
III	1 (1.9%)	2 (3.9%)	3 (3.6%)	
IV	0	0	1 (1.2%)	
Postoperative antiviral therapy (yes/no)	23/30	22/29	30/54	0.575
Postoperative TACE (yes/no)	15/38	24/27	53/31	<**0.001**

HBV: hepatitis B virus; AFP: alpha-fetoprotein; TACE: transhepatic arterial chemotherapy and embolization; AJCC: American Joint Committee on Cancer.

and 28.7% of patients had a family history of HCC. Among patients with small HCC, asymptomatic presentation was more frequent than symptomatic presentation; however, the opposite was true among patients with large and huge HCC ($P < 0.001$). A total of 76.6% of patients had chronic HBV infection, and 87.8% had cirrhosis of the liver. AJCC stage T1, T2, T3 and T4 disease were diagnosed in 55.9%, 12.2%, 18.1% and 13.8% of the cohort, respectively. Only 7 patients were confirmed to have a positive margin by postoperative pathology. Patients who received antiviral therapy and TACE after resection accounted for 39.9% and 48.9% of the cohort, respectively. Importantly, we found that larger tumors were more likely to have poor tumor differentiation, vascular invasion and absence of diolame, resulting in a worse prognosis.

The median follow-up period was 20 months. The 5- and 10-year OS rates of these patients were 56.0% and 34.1%, respectively. The OS rates for patients with small, large and huge HCC were 94.0%, 75.2%, and 72.5% at 1-year; 88.6%, 60.1%, and 47.6% at 3-year; 88.6%, 51.6%, and 41.1% at 5-year; and 88.6%, 51.6%, and 16.0% at 10-year, respectively. The 5- and 10-year DFS rates of these patients were 46.3% and 20.1%, respectively. The DFS rates for patients with small, large and huge HCC were 77.2%, 64.6%, and 62.6% at 1-year; 64.9%, 48.9%, and 44.4% at 3-year; 59.0%, 39.9%, and 42.2% at 5-year; and 44.4%, 19.9%, and 15.5% at 10-year, respectively. At the last follow-up, 72 (38.3%) patients had died due to tumor recurrence, and of the remaining 116 patients who were still alive, 94 were disease-free. Kaplan-Meier survival curves of different HCC subgroups were illustrated in Fig. 1.

A significant difference in OS was observed among the three groups ($P < 0.001$), but the difference in DFS was not significant ($P=0.082$) (Fig. 1). Subgroup analysis according to tumor size revealed that patients with larger tumors were more likely to have worse OS. The 5-year OS was better in patients with small HCC (<5 cm) than in those with large HCC (5–10 cm) (88.6% versus 51.6%, $P=0.001$) and huge HCC (>10 cm) (88.6% versus 41.1%, $P < 0.001$). However, the difference in 5-year OS was not significant between the large HCC and huge HCC groups (51.6% versus 41.1%, $P=0.194$). OS was significantly different between patients with small HCC and large HCC ($P=0.001$) as well as between patients with small HCC and huge HCC ($P < 0.001$), but no significant difference was found between patients with large HCC and huge HCC ($P=0.099$) (Table 2). Subgroup analysis showed that 5-year DFS and overall DFS were significantly different between small and huge HCC groups; small to large, large to huge comparisons did not show significance (Table 3).

In multivariate analysis (Tables 4 and 5), the significant prognostic factors that affected OS and DFS included a family history of HCC, Child-Pugh class B, no vascular invasion, diolame, positve surgical margin and operative time ≥240 min. Other factors, such as tumor size (>10 cm), was significant in the multivariate analysis of OS; postoperative antiviral therapy and complications

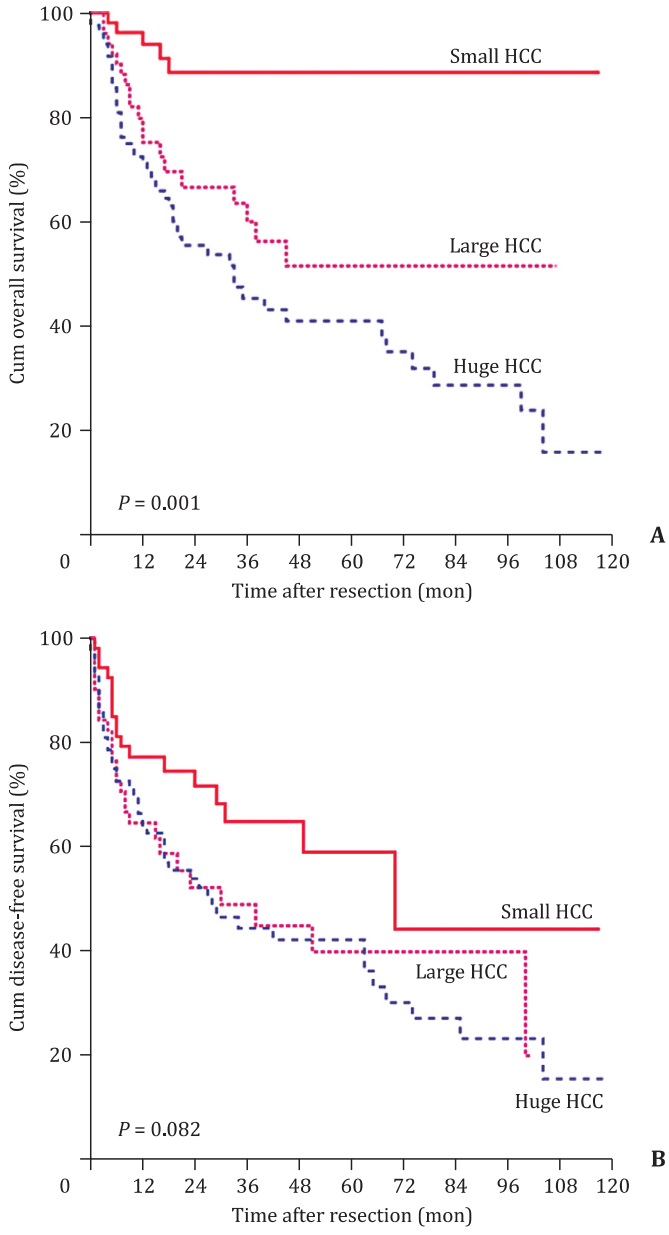

Fig. 1. Kaplan-Meier curves showing overall survival (**A**) and disease-free survival (**B**) according to tumor size.

(Clavien-Dindo grade ≥ class III) were also significant in the multivariate analysis of DFS.

Discussion

In the present study, we retrospectively analyzed data from a group of patients with pathologically confirmed HCC who had undergone hepatectomy at a single-center. We found that the prognosis of small HCC (< 5 cm) was significantly better than that of large and huge HCC (≥ 5 cm), which was similar to the results of a study by Dai et al., who reported that a tumor size ≥ 5 cm might be a risk factor for death and early recurrence [22]. However, our analysis revealed no significant difference in either OS or DFS of patients with large HCC compared to those with huge HCC, which was similar to previous findings [11,12]. Although earlier studies [23,24] reported a lower 5-year survival rate for huge HCC patients after hepatectomy, recent studies [25–27] have reported a higher 5-year survival rate, which may be related to improvements

Table 2
Comparison of 5-year OS and overall survival among different HCC subgroups.

Groups	*P* value	
	5-year OS	Overall survival
Small HCC versus Large HCC	**0.001**	**0.001**
Small HCC versus Huge HCC	<**0.001**	<**0.001**
Large HCC versus Huge HCC	0.194	0.099

Table 3
Comparison of 5-year DFS and overall DFS among different HCC subgroups.

Groups	*P* value	
	5-year DFS	Overall DFS
Small HCC versus Large HCC	0.069	0.088
Small HCC versus Huge HCC	**0.041**	**0.029**
Large HCC versus Huge HCC	0.951	0.831

in surgical techniques and multidisciplinary treatment for HCC. All of these studies, however, were based on survival outcomes of patients with huge HCC who were treated in Asian countries, and the geographical differences between Western and Eastern countries were not considered. Allemann and colleagues [28] reported that the median survival and 5-year survival for huge HCC patients were better than those for large HCC patients, which might be due to less aggressive tumor biology. Therefore, for patients with estimated resectable HCC and adequate hepatic reserve, hepatectomy should be performed regardless of the size of the tumor.

In our study, we identified six significant predictors of both OS and DFS: a family history of HCC, Child-Pugh class B, vascular invasion, diolame, positive margin, and operative time ≥ 240 min; some of these results were consistent with previous findings [29–32]. In addition, we found that tumor size (> 10 cm) had a significant effect on OS and postoperative antivival therapy and complications (Clavien-Dindo grade ≥ class III) played significant roles in DFS. Although the incidence of postoperative complications was high, it did not appear to affect OS in the multivariate analysis, which was similar to the results of Shah et al. [8]. In view of the high morbidity of HBV in China and the high HBV infection rate in most patients with HCC, antiviral therapy plays an effective role in these patients, which is consistent with the conclusion of Wei et al. and Nishikawa et al. [33,34]. Previous studies [35–37] demonstrated that bleeding and transfusions led to a poor prognosis, but we did not include blood loss as a variable in our analysis because of the inaccuracy of blood loss estimation. In contrast to other studies [38–41], satellite nodules and the number of tumors were not significant factors in our study, which may have occurred because patients had fewer tumors, and the tumors tended to be more concentrated in the liver lobes. Golse et al. [42] revealed that the degree of fibrosis did not impact OS or DFS, which was similar to the results of our analysis.

Our study had several limitations. As with any retrospective study, selection bias was inevitable. The study had a small sample size and lacked some important preoperative variables; thus, multicenter studies should be conducted. Another limitation is that some patients underwent multiple treatments such as radiofrequency ablation and TACE, which might affect the outcome. Other factors, such as nonuniformity of both the tumor biology and patient characteristics among the groups, may impact the results.

In conclusion, surgical operation is safe and feasible for individuals with huge HCC and sufficient residual liver volume. A family history of HCC, vascular invasion, Child-Pugh class B, the absence of diolame, a positive surgical margin, and longer operative time were independent risk factors for a poor prognosis.

Table 4
Univariate and multivariate Cox regression analyses of prognostic factors for overall survival.

Variables	Univariate *P* value	Multivariate analysis	
		P value	Hazard ratio
Age (versus <40 yr)	0.892	0.892	
40–60 yr	0.883	0.636	0.782 (0.283–2.162)
>60 yr	0.842	0.852	0.929 (0.431–2.007)
Female	0.101	0.284	0.567 (0.200–1.603)
Family history of HCC	**<0.001**	**<0.001**	6.306 (3.277–12.138)
Child-Pugh class B	**0.012**	**<0.001**	7.806 (2.722–22.389)
AFP (versus >800 ng/mL)	**0.006**	0.297	
<400 ng/mL	0.146	0.134	0.284 (0.055–1.476)
400–800 ng/mL	**0.011**	0.909	1.044 (0.497–12.195)
Tumor size (versus <5 cm)	**<0.001**	**0.033**	
5–10 cm	**0.003**	0.119	2.564 (0.785–8.374)
>10 cm	**<0.001**	**0.012**	4.119 (1.361–12.472)
Liver cirrhosis	0.982	0.172	0.787 (0.557–1.110)
Tumor number (≥2)	**0.004**	0.211	0.323 (0.055–1.901)
No vascular invasion	**0.028**	**0.004**	0.252 (0.098–0.652)
Satellite nodules	**0.011**	0.526	1.727 (0.319–9.368)
Diolame	**<0.001**	**<0.001**	0.255 (0.126–0.520)
Operative time ≥240 min	**<0.001**	**0.001**	3.733 (1.766–7.891)
Blood loss volume ≥1000 mL	**0.003**	0.083	3.033 (0.864–10.652)
Positive margin	**<0.001**	**<0.001**	9.229 (2.711–31.411)
AJCC T stage (versus T1)	**<0.001**	0.198	
T2	0.068	0.365	0.583 (0.181–1.874)
T3	**0.002**	0.191	2.033 (0.702–5.888)
T4	**<0.001**	0.571	1.289 (0.536–3.097)
Tumor differentiation (versus well)	0.088	**0.047**	
Moderate	0.289	0.462	1.557 (0.478–5.069)
Poor	0.059	0.067	3.153 (0.924–10.759)
Postoperative antiviral therapy	0.654	0.458	0.775 (0.395–1.521)
Postoperative TACE	**0.034**	0.290	1.400 (0.750–2.641)
Complications (Clavien-Dindo grade ≥class III)	0.270	0.364	1.232 (0.785–1.933)

Table 5
Univariate and multivariate Cox regression analyses of prognostic factors for disease-free survival.

Variables	Univariate *P* value	Multivariate analysis	
		P value	Hazard ratio
Age (versus <40 yr)	0.885	0.753	
40–60 yr	0.701	0.039	0.292 (0.090–0.941)
>60 yr	0.929	0.421	0.779 (0.423–1.433)
Female	0.025	0.093	0.447 (0.174–1.145)
Family history of HCC	**<0.001**	**<0.001**	4.139 (2.458–6.971)
Child-Pugh class B	**0.005**	**<0.001**	6.073 (2.337–15.851)
AFP (versus >800 ng/mL)	0.097	0.109	
<400 ng/mL	0.140	0.039	0.292 (0.090–0.941)
400–800 ng/mL	0.212	0.421	0.779 (0.423–1.433)
Tumor size (versus <5 cm)	0.094	0.053	
5–10 cm	0.086	0.502	1.298 (0.607–2.776)
>10 cm	**0.033**	0.750	0.887 (0.424–1.854)
Liver cirrhosis	0.468	0.439	0.891 (0.665–1.193)
Tumor number (≥2)	**0.004**	0.473	0.570 (0.122–2.652)
No vascular invasion	0.101	**0.046**	0.425 (0.183–0.986)
Satellite nodules	**0.015**	0.594	1.481 (0.350–6.275)
Diolame	**0.004**	**0.022**	0.497 (0.273–0.902)
Operative time ≥240 min	**0.002**	**0.035**	2.030 (1.050–3.927)
Blood loss volume ≥1000 mL	**0.031**	0.155	2.323 (0.726–7.428)
Positive margin	**<0.001**	**0.001**	6.768 (2.294–19.967)
AJCC T stage (versus T1)	**0.003**	0.518	
T2	**0.047**	0.975	0.985 (0.377–2.575)
T3	**0.003**	0.191	1.843 (0.737–4.608)
T4	**0.003**	0.785	1.122 (0.490–2.567)
Tumor differentiation (versus well)	0.567	0.939	
Moderate	0.393	0.751	0.869 (0.365–2.070)
Poor	0.287	0.872	0.926 (0.363–2.365)
Postoperative antiviral therapy	0.168	**0.041**	0.566 (0.327–0.978)
Postoperative TACE	**0.002**	0.137	1.495 (0.880–2.540)
Complications (Clavien-Dindo grade ≥class III)	0.385	**0.025**	1.565 (1.057–2.317)

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Contributors

GXP and LFB proposed the study. FQ collected data and wrote the first draft. XQS, CJM, SSL, and XK analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts and approved the final version to be published. LFB is the guarantor.

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Ethical approval

The study was approved by the institutional review committee of the First Affiliated Hospital, Anhui Medical University.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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