The Efficacy of Surgery in Advanced Hepatocellular Carcinoma: A Propensity Score Analysis

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Research

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Abstract

Background There is still controversial that whether hepatocellular carcinoma (HCC) patients with lymph node invasion should receive surgery treatment. This study is to evaluate the efficacy of surgery in HCC patients with regional lymph node invasion.

Methods The study utilized data from the Surveillance, Epidemiology, and End Results-18 (SEER-18) cancer registry. 1434 patients were included in the analysis. Among them, 168 patients were treated surgically and 1266 received non-surgery treatment. Propensity Score Matching (PSM) model was used to reduce selection bias.

Results Before PSM, the median overall survival (mOS) and median cancer-specific survival (mCSS) of patients treated surgically were longer than in patients receiving non-surgery treatment (mOS: 20 months vs. 7 months, $P < 0.001$; mCSS: 21 months vs. 6 months, $P < 0.001$). Subgroup analysis did not detect a significant difference in mOS and mCSS between liver resection and non-liver resection surgery cohorts ($P > 0.05$). Similar results were obtained in the PSM analysis. The mOS and mCSS in the surgery group were longer than in the non-surgery group (mOS: 20 months vs. 7 months, $P < 0.001$; mCSS: 20 months vs. 6 months, $P < 0.001$). The multivariate analysis documented that surgery was an independent predictor for OS and CSS before and after PSM.

Conclusions HCC patients with invasion of regional lymph nodules may get more survival benefit from surgery than other types of treatment.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and lethal cancers[1, 2]. The incidence of HCC in the United States might be double by 2030[3]. Patients with early HCC can have a high 5-year survival rate after transplantation, or liver resection or ablation treatment[4–6]. However, typically, the patients are diagnosed with HCC in the intermediate or advanced stage of the disease since no obvious clinical symptoms are present in early stage HCC, and radical treatments are not suitable for these patients. HCC patients with intrahepatic vascular invasion, regional lymph nodules invasion, or metastases to distant organs, and patients with cancer-related symptoms (symptomatic tumors, Eastern Cooperative Oncology Group, ECOG 1–2) are diagnosed as advanced HCC according to the guideline and treatment with molecular target drugs is recommended[2]. The SHARP trial demonstrated that, in comparison with placebo, sorafenib prolongs the survival of advanced HCC patients by approximately four months[7]. However, only a small fraction of patients respond to the drug and many patients discontinue the therapy because they cannot bear the complications of the drugs, limiting the efficacy of pharmacologic treatment. Therefore, alternative therapeutic modalities that might prolong the survival of advanced HCC patients are worth considering.

The current guideline do not recommend surgery for the treatment of advanced HCC patients[2]. However, it has been proposed that patients with regional vascular, lymph nodes, or organs invasion, or limited

distant metastases should not be defined as patients with advanced cancer. Conversely, they should be considered as the stage between intermediate and late stage since they could get a better survival benefit from surgery[8]. Recent data indicate that HCC patients with regional lymph node invasion or several metastasizes might receive the survival benefit from liver resection, ablation, radiotherapy, or transarterial chemoembolization (TACE)[9–13]. Although these studies presented encouraging results regarding the efficacy of surgery in patients with advanced HCC, the insufficient number of cases included in the analysis limits the strength of the conclusions reached.

The benefit of surgery in HCC patients with regional lymph nodules invasion remains unclear. Moreover, no randomized controlled trial (RCT) was conducted to address this issue. Therefore, the goal of the present study was to analyze the efficacy of surgery on HCC patients with regional lymph nodules invasion based on record available in the Surveillance, Epidemiology, and End Results-18 (SEER-18) database.

Methods

The study utilized the information from a publicly-available cancer registry, SEER-18. This database includes approximately 28% of United States population (Connecticut, San Francisco, Iowa, Detroit, New Mexico, Alaska Native Registry, Seattle, Hawaii, Utah, Atlanta, San Jose-Monterey, rural Georgia, Los Angeles, Kentucky, New Jersey, California [excluding San Francisco, San Jose-Monterey, and Los Angeles], Louisiana and Georgia [excluding Atlanta and rural Georgia]). SEER-18 includes information on the site and extent of disease, treatment modality, patient survival, and demographic data.

The analysis included patients aged 30-84 years, diagnosed with HCC (International Classification of Diseases for Oncology, Third Edition (ICD-O-3), histology code 8170-8175, site code C22.0 (liver)) from 2004 to 2015. Patients for whom the treatment type was not clear and those with distant metastasis or without regional lymph nodules invasion were excluded. For survival analysis, patients with the survival months coded as 0 and 999 were excluded. A total of 1434 patients were included in the study; 168 of them were treated surgically, and 1266 received non- surgical treatment (**Supplementary Figure 1**). The characteristics of patients before PSM are listed in **Table 1**.

Study outcomes

The endpoint of this study was patient death. The overall survival (OS) of patients was defined from the time of HCC diagnosis to death. Cancer-specific survival was defined as the time from HCC diagnosis to death caused by cancer.

Statistical analysis

The data were extracted using the SEER*Stat software (version 8.3.6). Categorical variables were analyzed by the Chi-square test and Fisher's exact test. OS and CSS were plotted by the Kaplan-Meier method and compared by the log-rank test. Predictors for OS and CSS were analyzed by the Cox

proportional risk model. Multivariate analysis included the characteristics of gender, age, ethnicity, marital status, American Joint Committee on Cancer (AJCC) T stage, year of diagnosis, tumor size, number of tumors, and the type of treatment.

Propensity score matching (PSM) was used to reduce potential confounding effects and selection bias. The characteristics of gender, age, ethnicity, marital status, AJCC T stage, year of diagnosis, tumor size, number of tumors, and the type of treatment were included in PSM assessment. A total of 608 patients were generated by 1:4 ratio matching with an optimal caliper of 0.2. The characteristics of patients after PSM are listed in **Table 3**.

All tests were two-tailed, and the P value less than 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, San Diego, CA) and SPSS v24.0 (IBM, Chicago, IL, USA) software.

Results

Survival analysis

Before PSM, the mOS in the surgery group (20 months, 95%CI: 15.3-24.7) was longer than in the non-surgery group (7 months, 95%CI: 6.4-7.6) ($P<0.001$) (**Figure 1A**). In the surgery group, the subgroup analysis showed that the mOS in the liver resection group (16 months, 95%CI: 8.2-23.8) was similar to that in the non-liver resection group (22 months, 95%CI: 16.6-27.4) ($P=0.886$) (**Figure 2A**). In the liver resection subgroup, the mOS of patients with liver resection combined with the removal of regional lymph nodes (14 months, 95%CI: 9.5-18.5) was similar with patients treated with liver resection alone (24 months, 95%CI: 21.1-26.9) ($P=0.142$) (**Figure 2C**).

Similar results were obtained in the analysis of CSS. The mCSS of patients treated surgically (21 months, 95%CI: 15.5-26.5) was longer than in patients subjected to non-surgical treatment (6 months, 95%CI: 5.3-6.7) ($P<0.001$) (**Figure 1B**). In the subgroup analysis of the surgery group, the mCSS in patients with liver resection (18 months, 95%CI: 10-26) was slightly shorter than in patients treated without liver resection surgery (21 months, 95%CI: 15.4-26.6) but this difference did not reach statistical significance ($P=0.813$) (**Figure 2B**). The mCSS in patients with liver resection alone (25 months, 95%CI: 20-30) was longer than in patients with liver resection combined with lymph nodes removal (14 months, 95%CI: 9.5-18.5) but the difference was not statistically significant ($P=0.058$) (**Figure 2D**).

After PSM, the mOS and mCSS in the surgery group (mOS: 20 months, 95%CI: 15.1-24.9; mCSS: 20 months, 95%CI: 14.6-25.4) were longer than in the non-surgery group (mOS: 7 months, 95%CI: 5.9-8.1; mCSS: 6 months, 95%CI: 4.8-7.2) ($P<0.001$ for both mOS and mCSS) (**Figure 3A-3B**).

Predictors for OS and CSS

Before PSM, the multivariate logistic regression analysis demonstrated that the patient's age at diagnosis (age 45-59 at diagnosis: HR:1.493; 95%CI: 1.025,2.173, $P=0.037$; age 60-74 at HCC diagnosis: HR: 1.487;

95%CI: 1.023-2.162, $P=0.038$; age 75-84 at HCC diagnosis: HR:1.586; 95%CI: 1.068-2.357, $P=0.022$), AJCC T stage (stage T3: HR: 1.418; 95%CI: 1.217-1.652, $P<0.001$; stage T4: HR: 1.703; 95%CI: 1.294-2.240, $P<0.001$), tumor size (tumor size 3-5 cm: HR: 1.305; 95%CI: 1.080-1.577, $P=0.006$; tumor size larger than 5 cm: HR: 1.685; 95%CI: 1.392-2.039, $P<0.001$), radiotherapy (non-radiotherapy: HR: 1.664; 95%CI: 1.281,1.876, $P<0.001$), chemotherapy (non-chemotherapy: HR:1.64; 95%CI:1.485,1.865, $P<0.001$) and treatment (non-surgery: HR: 2.115; 95%CI: 1.789-2.501, $P<0.001$) were independent predictors for OS in advanced HCC patients. Older age, higher AJCC stage, larger tumor size, and without receiving radiotherapy, chemotherapy and surgical treatment were associated with worse outcome in all patients (**Table 2**). For CSS, Similar results were obtained in the multivariate logistic regression analysis for CSS. Older age, higher AJCC stage, larger tumor size, and without receiving radiotherapy, chemotherapy and surgical treatment were all correlated with a shorter CSS of the patients.

After PSM, the multivariate logistic regression analysis showed that older patients, patients with high AJCC T stage, larger tumor size, and without receiving radiotherapy, chemotherapy and surgical treatment had worse OS and CSS (**Table 4**).

Discussion

The most widely adopted HCC staging system is based on Barcelona Clinical Liver Cancer (BCLC) criteria[14]. BCLC staging is endorsed by the guidelines of the American Association for the Study of Liver Diseases (AASLD) and The European Association for the Study of the Liver (EASL) due to its ability to account for liver function, tumor burden, and prognosis prediction[2, 15]. The BCLC criteria recommend that early-intermediate HCC patients with good liver function (Child-Pugh A-B) and good physical condition (ECOG 0) should be treated surgically (liver resection, liver transplantation or ablation for early HCC, and TACE) for intermediate HCC patients[14]. However, accumulating evidence supports the conclusion that patients with intermediate HCC can obtain a better survival benefit from liver resection than from TACE[16–18], and patients with advanced HCC can get good efficacy from surgery alone or in combination with other treatments[19].

Patients with advanced HCC often have poor survival outcomes due to cancer-related impairment of liver function or physical condition. Previous studies documented that advanced HCC patients with lymph nodes invasion or metastases had median survival times of 6–8 months[20, 21]. However, the same group of patients treated with molecular targeted drugs, surgery alone, or a combination of both therapies could expect longer survival times of 7.0-20.4 months[7, 22–25]. In these analyses, the combination of surgery with molecular targeted drugs or with another surgery often resulted in longer mOS. Duffy and coworkers have found that patients with advanced HCC treated with the combination of tremelimumab and liver ablation had mOS of 12.3 months[26], which was longer than mOS of patients treated with sorafenib alone[27]. A randomized phase II trial compared the efficacy of the treatment by a combination of sorafenib combined and hepatic arterial infusion chemotherapy with the therapy using sorafenib alone. The study has found that patients with combined therapies had longer mOS than patients with single treatment ($P = 0.031$)[25]. The limited usage of surgical treatment in advanced HCC patients

because it might cause liver failure and early death. However, emergent new technologies, such as laparoscopic surgery, microwave ablation, and TACE with drug-eluting beads, limit the damage of surgery to patients and liver function. Therefore, patients with Child-Pugh A or B might get survival benefit from surgery.

The current study demonstrated that the mOS and CSS of patients with surgical treatment was 20 months and 21 months before PSM, which was longer than in patients treated non-surgically included in previous studies presented³⁻⁹. Kokudo and collaborators compared the efficacy of portal vein tumor thrombosis in patients who received liver resection and patients who received other treatments, and found that patients with liver resection had longer mOS than patients not subjected to liver resection[28]. Similar results were obtained in the present study; patients with liver resection had longer mOS than patients with non-surgical treatment ($P < 0.001$). However, in the subgroup analysis, the mOS of patients with liver resection comparable to that of patients treated with other surgery (such as ablation) ($P = 0.886$), suggesting that liver resection might not be the preferred modality in patients with regional lymph nodes invasion. In the liver resection group, patients treated with liver resection combined with the removal of lymph nodes had no longer mOS than patients with liver resection alone, and there was no significant difference of mCSS between the two groups. This finding indicates that in patients treated with liver resection treatment, removal of regional lymph nodes should not be recommended as the mean to prolong the survival time and reduce the damage of surgery to patients. After PSM and reduction of the selection biases and confounding effects, the mOS and mCSS in the surgery group were still longer than in the non-surgery group ($P < 0.001$), supporting the conclusion that HCC patients with regional lymph nodes invasion could obtain a better survival benefit from surgery than from non-surgical approaches.

In multivariate logistic regression analysis, age at diagnosis, year of diagnosis, AJCC T stage, tumor size, radiotherapy treatment, chemoembolization treatment and utilization of surgery were included in the analysis to reduce mutual influence among the variables. This approach documented that non-surgical treatment was an independent unfavorable factor for OS and CSS, regardless of whether PSM was performed or not. Patients not treated with surgery would have more than 2-fold higher risk of overall death and cancer-specific death than patients subjected to surgery.

Liver function and physical condition of patients were not included in the current analysis because these characteristics were not recorded in the SEER database. The BCLC criteria defines that patients with ECOG 1 should be classified advanced HCC and should receive molecular targeted drugs treatment or best support care. These patients were not included into this study, which might influence the accuracy of the results. However, patients with regional lymph nodes invasion were defined as having an advanced disease independently of liver function and physical condition. The patients included in the study might have good liver function and physical condition, but all of patients have lymph node invasion, which showed they had advanced HCC and they could get more survival benefits from surgery treatment. Thus, the study could still prove that surgery should be used in advanced HCC patients treatment if the patients had good liver function and physical condition.

Although this analysis provided encouraging results, some limitations resulting from the retrospective design of the study should be acknowledged. First, the analysis utilized the SEER database which does not include the laboratory and imaging results; these variables might represent more precise predictors for OS and CSS. Second, selection biases may persist despite the use of the PSM model. However, PSM might be the best option to reduce the selection biases since there are no RCTs or prospective studies focused on the issue presented in this analysis. Third, liver function and physical condition which might influence the OS of patients were not incorporated in the current work, which needed future high-quality studies to confirm the results of the study. Thus, patients with advanced HCC could get a better survival benefit from surgery than from other types of treatment.

Conclusions

In conclusion, although the guidelines recommend molecular targeted drugs as the first-line treatment for advanced HCC patients, among them, patients with regional lymph nodes invasion might get more survival benefit from surgery than from other treatments, and, therefore, surgery might be the better treatment option for these patients.

Abbreviations

HCC
Hepatocellular Carcinoma
SEER
Surveillance, Epidemiology, and End Results
mOS
median Overall Survival
mCSS
median Cancer-Specific Survival
PSM
Propensity Score Matching
ECOG
Eastern Cooperative Oncology Group
TACE
Transarterial Chemoembolization
AJCC
American Joint Committee on Cancer

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Supplementary Material Information

Figure 1: The flowchart of patients inclusion

Declarations

Ethical approval and consent to participate: The research do not need to be reviewed by the ethics committee because the data were from SEER database and the written informed consent was exempted. However, the data used in the research was permitted by the SEER database management department.

Consent for publication: All authors approved for publication of the manuscript for the journal.

Availability of data and materials: The data could be found in SEER database (<https://seer.cancer.gov/data/>).

Competing interests: The authors declare that they have no competing interests.

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Authors' Contributions: Chuansheng Zheng and Fan Yang designed the research; Lei Chen and Tao Sun extracted the data from SEER database; Lei Chen, Tao Sun and Shi Chen made statistical analysis; Lei Chen, Tao Sun, Shi Chen and YanQiao Ren written the manuscript; Chuansheng Zheng and Fan Yang reviewed the manuscript.

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Tables

Table 1: The baseline characteristics of patients before PSM.

Characteristics	All patients (No, %)		P value
	1434(100)		
	Surgery (168, 11.7)	Non-surgery (1266,88.3)	
Gender			0.363
Male	135 (80.4)	1053 (83.2)	
Female	33 (19.6)	213 (16.8)	
Age at diagnosis			0.225
30-44	7 (4.2)	27 (2.1)	
45-59	72 (42.8)	499 (39.4)	
60-74	71 (42.3)	563 (44.5)	
75-84	18 (10.7)	177 (14)	
Ethnicity			0.373
White	119 (70.8)	871 (68.8)	
Black	23 (13.7)	225 (17.8)	
Other	26 (15.5)	170 (13.4)	
Marital status			0.022
Married	103 (61.3)	638 (50.4)	
Single	57 (33.9)	571 (45.1)	
Other	8 (4.8)	57 (4.5)	
AJCC T stage			<0.001
T1	58 (34.5)	289 (22.8)	
T2	51 (30.4)	270 (21.3)	
T3	56 (33.3)	627 (49.5)	
T4	2 (1.2)	65 (5.1)	
TX	1 (0.6)	15 (1.2)	
Year of diagnosis			<0.001
2004-2006	49 (29.2)	178 (14.1)	
2007-2009	49 (29.2)	249 (19.7)	
2010-2012	28 (16.6)	393 (31)	
2013-2015	42 (25)	446 (35.2)	
Tumor size			0.01
≤3 cm	38 (22.6)	181 (14.3)	
3-5 cm	39 (23.2)	274 (21.6)	
>5 cm	91 (54.2)	811 (64.1)	
Tumor number			0.428
1	142 (84.5)	1104 (87.2)	
2	19 (11.3)	135 (10.7)	
3	6 (3.6)	23 (1.8)	
>3	1 (0.6)	4 (0.3)	
Radiotherapy			0.115
Yes	11 (6.5)	132 (10.4)	
No	157 (93.5)	1134 (89.6)	
Chemotherapy			0.046
Yes	77 (45.8)	684 (54)	
No	91 (54.2)	582 (46)	

Table 2: Multivariate analysis of predictors for mortality and cancer-specific death before PSM.

Characteristics	Multivariate analysis			
	Overall survival HR (95%CI)	P value	Cancer specific survival HR (95%CI)	P value
Gender				
Male	Reference		Reference	
Female	1.104 (0.950,1.282)	0.196	0.982 (0.826,1.167)	0.833
Age at diagnosis				
30-44	Reference		Reference	
45-59	1.493 (1.025,2.173)	0.037	1.725 (1.132,2.627)	0.011
60-74	1.487 (1.023,2.162)	0.038	1.768 (1.160,2.692)	0.008
75-84	1.586 (1.068,2.357)	0.022	1.842 (1.176,2.884)	0.008
Ethnicity				
White	Reference		Reference	
Black	0.955 (0.823,1.109)	0.548	0.914 (0.772,1.084)	0.302
Other	0.914 (0.773,1.082)	0.914	0.946 (0.788,1.136)	0.551
Marital status				
Married	Reference		Reference	
Single	1.010 (0.898,1.135)	0.869	1.040 (0.913,1.186)	0.554
Other	0.988 (0.749,1.303)	0.931	1.066 (0.793,1.433)	0.674
AJCC T stage				
T1	Reference		Reference	
T2	1.165 (0.980,1.385)	0.084	1.230 (1.09,1.500)	0.040
T3	1.418 (1.217,1.652)	<0.001	1.412 (1.189,1.677)	<0.001
T4	1.703 (1.294,2.240)	<0.001	1.881 (1.398,2.529)	<0.001
TX	1.443 (0.868,2.400)	0.157	1.343 (0.729,2.474)	0.344
Year of diagnosis				
2004-2006	Reference		Reference	
2007-2009	0.948 (0.791,1.137)	0.564	0.973 (0.794,1.191)	0.789
2010-2012	1.197 (1.009,1.421)	0.039	1.175 (0.970,1.424)	0.100
2013-2015	1.109 (0.930,1.322)	0.251	1.070 (0.878,1.303)	0.503
Tumor size				
≤3 cm	Reference		Reference	
3-5 cm	1.305 (1.080,1.577)	0.006	1.432 (1.151,1.781)	0.001
>5 cm	1.685 (1.392,2.039)	<0.001	1.857 (1.487,2.318)	<0.001
Tumor number				
1	Reference		Reference	
2	0.872 (0.727,1.046)	0.141	0.740 (0.461,1.186)	0.210
3	0.577 (0.368,0.904)	0.016	N	0.879
>3	1.528 (0.631,3.702)	0.348	N	N
Radiotherapy				
Yes	Reference		Reference	
No	1.550 (1.281,1.876)	<0.001	1.524 (1.230,1.888)	<0.001
Chemotherapy				
Yes	Reference		Reference	
No	1.664 (1.485,1.865)	<0.001	1.772 (1.559,2.015)	<0.001
Surgery				
Yes	Reference		Reference	
No	2.118 (1.756,2.555)	<0.001	2.115 (1.789,2.501)	<0.001

Table 3: The baseline characteristics of patients after PSM.

Characteristics	All patients 608 (No, %) (100)		P value
	Surgery (165, 27.1)	Non-surgery (443, 72.9)	
Gender			0.977
Male	135 (81.8)	362 (81.7)	
Female	30 (18.2)	81 (18.3)	
Age at diagnosis			0.765
30-44	7 (4.2)	12 (2.7)	
45-59	69 (41.8)	179 (40.4)	
60-74	71 (43.1)	201 (45.4)	
75-84	18 (10.9)	51 (11.5)	
Ethnicity			0.511
White	116 (70.3)	324 (73.1)	
Black	23 (13.9)	65 (14.7)	
Other	26 (15.8)	54 (12.2)	
Marital status			0.284
Married	100 (60.6)	257 (58)	
Single	57 (34.5)	174 (39.3)	
Other	8 (4.9)	12 (2.7)	
AJCC T stage			0.635
T1	55 (33.4)	145 (32.7)	
T2	51 (30.9)	121 (27.3)	
T3	56 (33.9)	159 (35.9)	
T4	2 (1.2)	14 (3.2)	
TX	1 (0.6)	4 (0.9)	
Year of diagnosis			0.228
2004-2006	46 (27.9)	107 (24.2)	
2007-2009	49 (29.7)	116 (26.2)	
2010-2012	28 (17)	109 (24.6)	
2013-2015	42 (25.4)	111 (25)	
Tumor size			0.532
≤3 cm	37 (22.4)	84 (19)	
3-5 cm	38 (23)	117 (26.4)	
>5 cm	90 (54.6)	242 (54.6)	
Tumor number			0.208
1	141 (85.5)	402 (90.7)	
2	18 (10.9)	34 (7.7)	
3	5 (3)	5 (1.1)	
>3	1 (0.6)	2 (0.5)	
Radiotherapy			0.796
Yes	11 (6.7)	27 (6.1)	
No	154 (93.3)	416 (93.9)	
Chemotherapy			0.950
Yes	77 (46.7)	208 (47)	
No	88 (53.3)	235 (53)	

Table 4: Multivariate analysis of predictors for mortality and cancer-specific death after PSM.

Characteristics	Multivariate analysis			
	Overall survival	P value	Cancer specific survival	P value
	HR (95%CI)		HR (95%CI)	
Gender				
Male	Reference		Reference	
Female	1.121 (0.890,1.411)	0.332	0.912 (0.696,1.194)	0.501
Age at diagnosis				
30-44	Reference		Reference	
45-59	2.384 (1.369,4.153)	0.002	2.874 (1.539,5.365)	0.001
60-74	2.397 (1.382,4.158)	0.002	3.055 (1.645,5.674)	<0.001
75-84	2.631 (1.456,4.757)	0.001	3.059 (1.562,5.993)	0.001
Ethnicity				
White	Reference		Reference	
Black	0.913 (0.706,1.181)	0.490	0.844 (0.634,1.121)	0.844
Other	0.8886 (0.675,1.162)	0.380	0.959 (0.709,1.296)	0.959
Marital status				
Married	Reference		Reference	
Single	0.968 (0.800,1.172)	0.741	1.026 (0.832,1.264)	0.812
Other	1.323 (0.792,2.209)	0.285	1.429 (0.837,2.442)	0.191
AJCC T stage				
T1	Reference		Reference	
T2	1.324 (1.044,1.679)	0.021	1.381 (1.054,1.811)	0.019
T3	1.316 (1.024,1.691)	0.032	1.359 (1.031,1.790)	0.030
T4	1.766 (1.028,3.034)	0.039	1.682 (0.941,3.008)	0.079
TX	1.462 (0.588,3.633)	0.413	1.322 (0.478,3.661)	0.591
Year of diagnosis				
2004-2006	Reference		Reference	
2007-2009	0.903 (0.711,1.147)	0.219	0.852 (0.655,1.108)	0.232
2010-2012	1.027 (0.798,1.322)	0.834	0.932 (0.701,1.239)	0.627
2013-2015	0.976 (0.748,1.274)	0.858	0.886 (0.659,1.192)	0.423
Tumor size				
≤3 cm	Reference		Reference	
3-5 cm	1.355 (1.040,1.767)	0.025	1.556 (1.149,2.107)	0.004
>5 cm	1.940 (1.462,2.575)	<0.001	2.173 (1.557,3.032)	<0.001
Tumor number				
1	Reference		Reference	
2	0.746 (0.538,1.035)	0.499	0.927 (0.450,1.906)	0.927
3	0.307 (0.125,0.754)	0.010	N	0.923
>3	1.546 (0.483,4.954)	0.463	N	N
Radiotherapy				
Yes	Reference		Reference	
No	1.765 (1.194,2.607)	0.004	1.931 (1.262,2.953)	0.002
Chemotherapy				
Yes	Reference		Reference	
No	1.660 (1.383,1.991)	<0.001	1.852 (1.510,2.271)	<0.001
Surgery				
Yes	Reference		Reference	
No	2.150 (1.750,2.641)	<0.001	2.213 (1.760,2.781)	<0.001

Figures

Figure 1

Kaplan-Meier curve of overall survival (A) and cancer-specific survival (B) of patients with surgery and non-surgery treatment before PSM, the shaded area indicates the 95% Confidence Interval

Figure 2

Kaplan-Meier curve of overall survival and cancer-specific survival of patients; A: the overall survival of patients with liver resection and non-liver resection treatment; B: the overall survival of patients with liver resection combined with lymph nodes removed treatment; C: the cancer-specific survival of patients with liver resection and non-liver resection treatment; D: the cancer-specific survival of patients with liver resection combined with lymph nodes removed treatment; the shaded area indicates the 95% Confidence Interval

Figure 3

Kaplan-Meier curve of overall survival (A) and cancer-specific survival (B) of patients with surgery and non-surgery treatment after PSM, the shaded area indicates the 95% Confidence Interval

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