

The Efficacy of Surgery in Advanced Hepatocellular Carcinoma: A Cohort Study

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Research

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Abstract

Background It is still controversial that whether hepatocellular carcinoma (HCC) patients with lymph node invasion should receive surgery treatment. This study aimed to evaluate the efficacy of surgery (liver resection and local tumor destruction treatments[1]) in HCC patients with regional lymph node metastasis.

Methods The study utilized data from the Surveillance, Epidemiology, and End Results-18 (SEER-18) cancer registry. Patients for whom the treatment type was not clear or 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. [2] All 1434 patients were included in the analysis. Among them, 168 patients were treated surgically and the other 1266 received non-surgery therapy. 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 that of receiving non-surgery treatment (mOS: 20 months, 95%CI: 15.3-24.7 vs. 7 months, 95%CI: 6.4-7.6, $P < 0.001$; mCSS: 21 months, 95%CI: 115.5-26.5 vs. 6 months, 95%CI: 5.3-6.7, $P < 0.001$). Subgroup analysis found no significant differences in mOS and mCSS between liver resection and non-liver resection surgery cohorts ($P = 0.886$ and $P = 0.813$, respectively). [3] 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, about 70-80% of the patients are diagnosed with HCC in the intermediate or advanced stage for there are no obvious clinical symptoms in early stage HCC, and the radical treatments are not suitable for these people. HCC patients with intrahepatic vascular infiltration, 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 patients with advanced HCC by approximately 4 months[7]. However, many patients discontinue the therapy because they cannot bear the complications of the drugs, which limited the effectiveness, as a result, only a small fraction of

patients respond to pharmacologic treatment. Therefore, it is worth considering other treatments that may prolong the survival of patients with advanced HCC.

The current guideline does 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 advanced cancer. Conversely, they should be considered as the stage between intermediate and late stages since they could get a better survival benefit through surgery[8]. Recent data indicate that HCC patients with regional lymph node invasion or several metastases 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 records available in the Surveillance, Epidemiology, and End Results-18 (SEER-18) database.

Methods

This study utilized the information from a publicly-available cancer registry, SEER-18. The 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 or 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. In the research, the death or cancer specific death (patients be survival or lost follow-up when the deadline arrived were thought be censored) survival time were taken as dependent variables based on the model to analyze the influence of all of factors on survival. To reduce collinearity caused by some factor, we did not conduct univariate analysis, but conduct multivariate analysis directly. 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 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) and patients with surgery had higher survival rate than patients with non-surgery (HR: 0.476, 95%CI:0.397,0.571) (**Figure 1A**). In the surgery group, the subgroup analysis showed that mOS in the liver resection group (16 months, 95%CI: 8.2-23.8) was similar to that in the non-liver resection group (local tumor destruction: cryoablation, percutaneous ethanol injection, heat-radio-frequency ablation and other) (22 months, 95%CI: 16.6-27.4) (P=0.886) (**Figure 2A**). In the liver resection subgroup, 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 liver resection alone (24 months, 95%CI: 21.1-26.9) (P=0.142) (**Figure 2C**). The mOS in liver resection group was longer than non-surgery group (P<0.001) (**Supplementary Figure 2A**). However, the mOS in liver resection combined with the removal of regional lymph nodes was similar with non-liver resection group (P=0.354) (**Supplementary 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) and patients with surgery had lower cancer specific death rate than patients with non-surgery (HR: 0.475, 95%CI: 0.389,0.580)(**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) ($P=0.813$) (**Figure 2B**). The mCSS in patients with liver resection alone (25 months, 95%CI: 20-30) was longer than with liver resection combined with lymph nodes removal (14 months, 95%CI: 9.5-18.5) ($P=0.058$) (**Figure 2D**). The mCSS in liver resection group was longer than non-surgery group ($P<0.001$) (**Supplementary Figure 2B**). However, the mCSS in liver resection combined with the removal of regional lymph nodes was similar with non-liver resection group ($P=0.226$) (**Supplementary 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 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 (**Table 2**).

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 physical condition (ECOG 0) should be treated surgically (liver resection, liver transplantation or ablation for early HCC, and TACE) [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 treatment by a combination of sorafenib and hepatic arterial infusion chemotherapy with that of using sorafenib alone, which has found that patients with combined therapies had longer mOS than that of single treatment[25]. The usage of surgical treatment for patients with advanced HCC is limited because it might lead to 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 mOS of patients with surgical treatment was 20 months before PSM, which was longer than in patients treated non-surgically included in previous studies presented (mOS: 7.4- 7.9 months)[9, 27, 28]. Kokudo and collaborators compared the efficacy of HCC patients with portal vein tumor thrombosis who received liver resection with who received other treatments, and found that patients with liver resection had longer mOS than those not subjected to liver resection[29]. Similar results were obtained in present study; patients with liver resection had longer mOS than patients with non-surgical treatment. However, in a subgroup analysis, mOS in patients with liver resection was comparable to that in patients undergoing procedures (such as ablation), suggesting that liver resection might not be the preferred modality in patients with regional lymph nodes invasion. In the liver resection group, patients with liver resection and lymph nodes resection had no longer mOS than that of liver resection alone, and there was no difference of mCSS between the two groups. Our findings suggest that in patients treated with liver resection, it should be not recommended to remove regional lymph nodes. However, the findings are hypothesis generating rather than conclusive and further research in this area is required. After PSM and reduction of the selection biases and confounding effects, the mOS and mCSS in the surgery group were still longer than that of non-surgery group ($P < 0.001$), supporting the conclusion that surgical treatment for HCC patients with regional lymph nodes invasion could obtain a better survival benefit than 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, whether or not PSM was performed. Patients not treated with surgery would have more than 2-fold higher risk of overall death and cancer-specific death compared to patients undergoing surgery.

Liver function and physical condition of patients were not included in the current analysis as these characteristics were not recorded in the SEER database. The BCLC criteria defines that patients with ECOG 1 should be classified as advanced HCC and should receive molecular targeted drugs or optimal supportive care. These patients were not included in this study, which might affect 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. Patients included in this study might have good liver function and physical condition, but of all advanced HCC patients who had lymph node invasion, could get more survival benefits from surgery treatment. Thus, the study could still prove that surgery should be performed in advanced HCC patients who had good liver function and physical condition.

Although this analysis provided encouraging results, some limitations resulting from the historical 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 less 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 selection biases since there are no RCTs or prospective studies focus on the issue presented in this analysis. Third, liver function and physical condition that might influence the OS of patients were not incorporated in the current work, and the sample size was substantially smaller, which might lead to insufficient conclusion. Thus we hope that future high-quality studies can confirm the findings of this study. All in all, compared with other types of treatments, patients with advanced HCC could get a better survival benefit through surgery. Lastly, despite the inclusion of many known confounders in the analysis and use of PSM, residual confounding cannot be excluded.

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 benefit more from surgery than other treatments, therefore, surgery might be a better therapy 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

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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References

1. Siegel RL, Miller KD, Jemal A: **Cancer statistics, 2019**. *CA Cancer J Clin* 2019, **69**:7-34.
2. **EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma**. *J Hepatol* 2018, **69**:182-236.
3. Kamarajah SK, Frankel TL, Sonnenday C, Cho CS, Nathan H: **Critical evaluation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with Hepatocellular Carcinoma (HCC): A Surveillance, Epidemiology, End Results (SEER) analysis**. *J Surg Oncol* 2018, **117**:644-650.
4. Fonseca AL, Cha CH: **Hepatocellular carcinoma: a comprehensive overview of surgical therapy**. *J Surg Oncol* 2014, **110**:712-719.
5. Luo W, Zhang Y, He G, Yu M, Zheng M, Liu L, Zhou X: **Effects of radiofrequency ablation versus other ablating techniques on hepatocellular carcinomas: a systematic review and meta-analysis**. *World J Surg Oncol* 2017, **15**:126.
6. Duan C, Liu M, Zhang Z, Ma K, Bie P: **Radiofrequency ablation versus hepatic resection for the treatment of early-stage hepatocellular carcinoma meeting Milan criteria: a systematic review and meta-analysis**. *World J Surg Oncol* 2013, **11**:190.
7. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al: **Sorafenib in advanced hepatocellular carcinoma**. *N Engl J Med* 2008, **359**:378-390.

8. Weichselbaum RR, Hellman S: **Oligometastases revisited.** *Nat Rev Clin Oncol* 2011, **8**:378-382.
9. Pan T, Xie QK, Lv N, Li XS, Mu LW, Wu PH, Zhao M: **Percutaneous CT-guided Radiofrequency Ablation for Lymph Node Oligometastases from Hepatocellular Carcinoma: A Propensity Score-matching Analysis.** *Radiology* 2017, **282**:259-270.
10. Mu L, Sun L, Pan T, Lyu N, Li S, Li X, Wang J, Xie Q, Deng H, Zheng L, et al: **Percutaneous CT-guided radiofrequency ablation for patients with extrahepatic oligometastases of hepatocellular carcinoma: long-term results.** *Int J Hyperthermia* 2018, **34**:59-67.
11. Wu H, Liu S, Zheng J, Ji G, Han J, Xie Y: **Transcatheter arterial chemoembolization (TACE) for lymph node metastases in patients with hepatocellular carcinoma.** *J Surg Oncol* 2015, **112**:372-376.
12. Xiaohong S, Huikai L, Feng W, Ti Z, Yunlong C, Qiang L: **Clinical significance of lymph node metastasis in patients undergoing partial hepatectomy for hepatocellular carcinoma.** *World J Surg* 2010, **34**:1028-1033.
13. Kaizu T, Karasawa K, Tanaka Y, Matuda T, Kurosaki H, Tanaka S, Kumazaki T: **Radiotherapy for osseous metastases from hepatocellular carcinoma: a retrospective study of 57 patients.** *Am J Gastroenterol* 1998, **93**:2167-2171.
14. Forner A, Reig ME, de Lope CR, Bruix J: **Current strategy for staging and treatment: the BCLC update and future prospects.** *Semin Liver Dis* 2010, **30**:61-74.
15. Bruix J, Sherman M: **Management of hepatocellular carcinoma: an update.** *Hepatology* 2011, **53**:1020-1022.
16. Yin L, Li H, Li AJ, Lau WY, Pan ZY, Lai EC, Wu MC, Zhou WP: **Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT.** *J Hepatol* 2014, **61**:82-88.
17. Yang B, Zheng B, Yang M, Zeng Z, Yang F, Pu J, Li C, Liao Z: **Liver resection versus transarterial chemoembolization for the initial treatment of Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma.** *Hepatol Int* 2018, **12**:417-428.
18. Hyun MH, Lee YS, Kim JH, Lee CU, Jung YK, Seo YS, Yim HJ, Yeon JE, Byun KS: **Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies.** *Hepatology* 2018, **68**:977-993.
19. Zhao Y, Wang WJ, Guan S, Li HL, Xu RC, Wu JB, Liu JS, Li HP, Bai W, Yin ZX, et al: **Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients.** *Ann Oncol* 2013, **24**:1786-1792.
20. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Camma C: **A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma.** *Hepatology* 2010, **51**:1274-1283.
21. Llovet JM, Bruix J: **Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival.** *Hepatology* 2003, **37**:429-442.
22. Suzuki E, Kaneko S, Okusaka T, Ikeda M, Yamaguchi K, Sugimoto R, Aramaki T, Asagi A, Yasui K, Sano K, et al: **A multicenter Phase II study of sorafenib in Japanese patients with advanced**

- hepatocellular carcinoma and Child Pugh A and B class. *Jpn J Clin Oncol* 2018, **48**:317-321.
23. Cosgrove DP, Reyes DK, Pawlik TM, Feng AL, Kamel IR, Geschwind JF: **Open-Label Single-Arm Phase II Trial of Sorafenib Therapy with Drug-eluting Bead Transarterial Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma: Clinical Results.** *Radiology* 2015, **277**:594-603.
24. Zhang Y, Fan W, Wang Y, Lu L, Fu S, Yang J, Huang Y, Yao W, Li J: **Sorafenib With and Without Transarterial Chemoembolization for Advanced Hepatocellular Carcinoma With Main Portal Vein Tumor Thrombosis: A Retrospective Analysis.** *Oncologist* 2015, **20**:1417-1424.
25. Ikeda M, Shimizu S, Sato T, Morimoto M, Kojima Y, Inaba Y, Hagihara A, Kudo M, Nakamori S, Kaneko S, et al: **Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial.** *Ann Oncol* 2016, **27**:2090-2096.
26. Duffy AG, Ulahannan SV, Makorova-Rusher O, Rahma O, Wedemeyer H, Pratt D, Davis JL, Hughes MS, Heller T, ElGindi M, et al: **Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma.** *J Hepatol* 2017, **66**:545-551.
27. Palmer DH: **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008, **359**:2498; author reply 2498-2499.
28. Abou-Alfa GK, Qin S, Ryou BY, Lu SN, Yen CJ, Feng YH, Lim HY, Izzo F, Colombo M, Sarker D, et al: **Phase III randomized study of second line ADI-PEG 20 plus best supportive care versus placebo plus best supportive care in patients with advanced hepatocellular carcinoma.** *Ann Oncol* 2018, **29**:1402-1408.
29. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, Kudo M, Ku Y, Sakamoto M, Nakashima O, et al: **Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion.** *J Hepatol* 2016, **65**:938-943.

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 HR (95%CI)	P value	Cancer specific survival HR (95%CI)	P value
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

Supplementary Material

Figure 1: The flowchart of patients inclusion

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-surgery treatment; B: the cancer-specific survival of

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

Figures

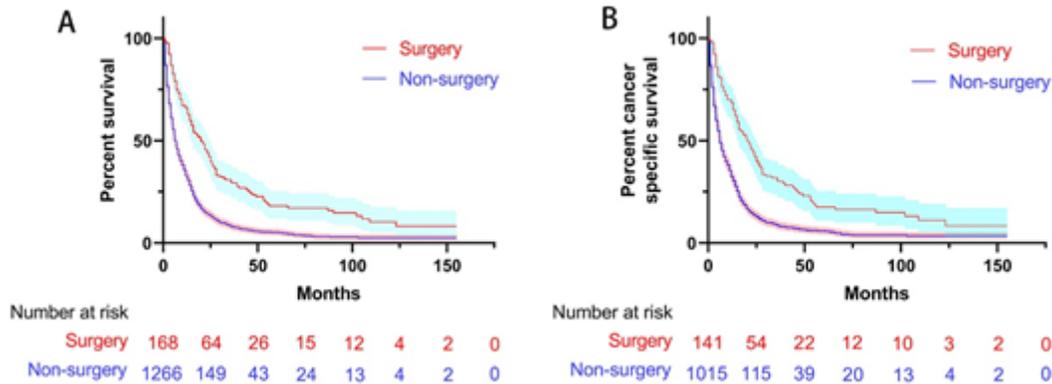


Figure 1

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

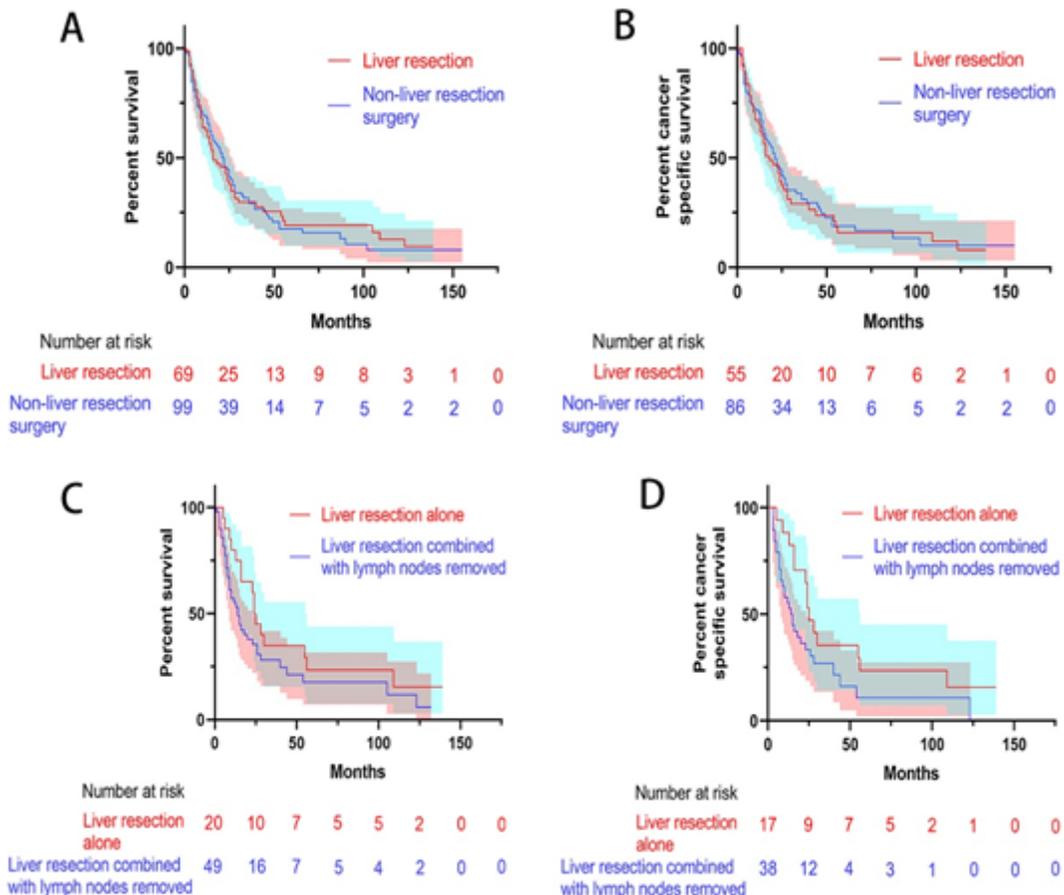


Figure 2

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

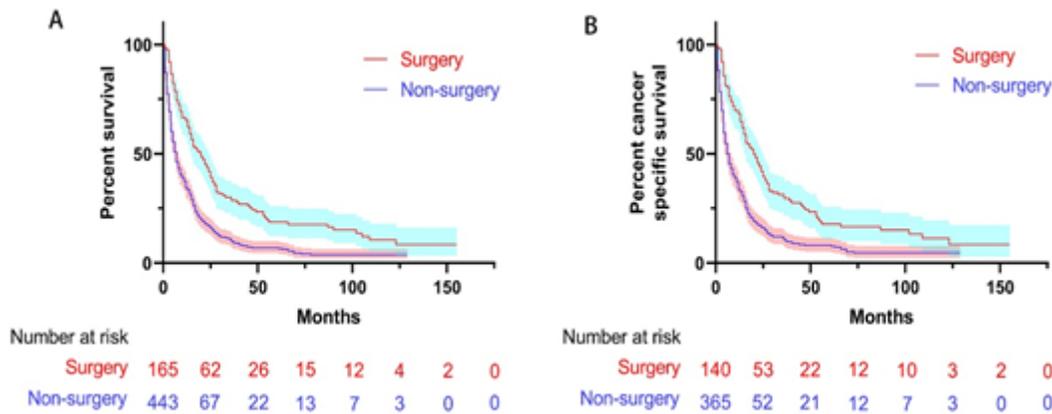


Figure 3

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

Supplementary Files

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- [Supplementarymaterials.pdf](#)