

Liver resection associated with better outcomes for single large hepatocellular carcinoma located in the same section

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Abstract

The influence of the anatomical location of single large hepatocellular carcinoma (HCC) on outcomes following hepatic resection (HR) is still unclear. This study examined the role of anatomical location profiles as prognostic markers for patients with single large HCC undergoing HR.

A total of 374 consecutive patients with single large HCC undergoing HR between January 2009 and July 2013 were included. They were divided into group same section (SS) group (n = 171) and different sections (DS) group (n = 203) according to their tumor's anatomical location. Short- and long-term outcomes were compared between the two groups.

More patients in group DS had intraoperative blood loss of >1000 mL and needed intraoperative blood transfusion than those in group SS. There were no significant differences regarding postoperative complications and 30- and 90-day mortality between the two groups. The overall survival (OS) and recurrence-free survival (RFS) rates were significantly higher in group SS than group DS. The subgroup analysis showed that tumor in the same section was associated with better prognosis than those in different sections for both patients with tumor of ≤8 cm and of > 8 cm. Multivariate analysis revealed that age <60 years, portal hypertension, alpha-fetoprotein ≥400 ng/mL, tumor in different sections, microvascular invasion and poorly differentiated tumor are independent predictors of poor prognosis in patient with single large HCC.

For patients with single large HCC, a tumor located in the same section may lead to better long-term survival and lower tumor recurrence rates than those in different sections following HR.

Abbreviations: AASLD = the American Association for the Study of Liver Diseases, AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CT = computed tomography, DS = different section group, EASL = the European Association for the Study of the Liver, HBV DNA = hepatitis B virus deoxyribonucleic, HCC = hepatocellular carcinoma, HR = hepatic resection, LT = liver transplantation, MRI = magnetic resonance imaging, OS = overall survival, PHT = portal hypertension, PT = prothrombin time, RFA = radio frequency ablation, RFS = recurrence-free survival, SS = same section group, TACE = transcatheter arterial chemoembolization, TB = total bilirubin.

Keywords: anatomical location, hepatocellular carcinoma, outcomes, resection, single large tumor

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WZ and YT contributed equally to this study and are co-first authors, they were coordinated the study, and wrote the article. LJ was responsible for conception and design and revised the article. JY and QL participated in the review of literature. WZ and LJ collected the data. LJ and YT analyzed the data. TW and BL provided critical revisions. All authors read and approved the final version of the article.

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1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and is the third cause of cancer-related deaths. In China, the estimated incidence of new cases is 22.3 per 100,000 and the mortality rate is 21.4 per 100,000 each year.^[1]

Among the several HCC staging systems proposed, the Barcelona Clinic Liver Cancer (BCLC) system is the only one recommended by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL),^[2,3] which recommends hepatic resection (HR) only for patients with early-stage HCC (BCLC stage A). In the most recent reviews concerning the BCLC staging system,^[4,5] patients with single tumor >5 cm in diameter are classified as having stage A disease and are considered as suitable candidates for HR. For multiple tumors, they are likely to be in the same hepatic section or different hepatic sections. Therefore, we investigated, in our recent serial studies,^[6,7] that the impact of the tumor anatomical location on HR outcomes in HCC patients with multifocal tumors meeting the Milan criteria. Similarly, as the tumor size increases, the chance of locating in different hepatic sections for the single HCC also increases. However, there are very few studies, to the best of our knowledge, investigating the tumor anatomical location on HR outcomes in HCC patients with a single tumor. The influence of the

anatomical location of single large HCC on outcomes following HR is still unclear.

To clarify this issue, we exclusively compared the short- and long-term outcomes of single large HCC patients after HR using tumors located in either same or different hepatic sections according to Couinaud's segmentation. In addition, we determined prognostic predictors and performed a subgroup analysis to assess the differential survival benefits associated with different locations for single tumor in these patients.

2. Methods

This study was approved by the West China Hospital Ethics Committee and in accordance with the ethical guidelines of the Declaration of Helsinki.

2.1. Diagnostic criteria and definitions

The HCC diagnosis was confirmed by a histopathological examination of the surgical samples.

A single HCC tumor of >5 and ≤ 10 cm in diameter is defined as large HCC^[8] and a single tumor of >10 cm in diameter is defined as huge HCC.^[9]

Clinically relevant portal hypertension (PHT) is defined as the presence of esophageal varices and/or a platelet count of $<100,000$ per μL in association with splenomegaly.^[10]

By using the branches of the portal vein and the location of the hepatic veins, the right liver can be divided into the right anterior section (segments 5 and 8) and right posterior section (segments 6 and 7), the left liver can be divided into the left medial section (segment 4) and left lateral section (segments 2 and 3), and the caudate lobe (segment 1) can be considered as a separate section.^[11]

2.2. Patients

Figure 1 shows inclusion and exclusion criteria for the cohort. A total of 1926 consecutive patients with HCC (not including the patients with recurrent HCC) underwent HR from January 2009 to July 2013 in our center. Of these, 797 patients who had multiple tumors were excluded. Next, 498 patients who had single tumor of ≤ 5 cm were excluded, and 183 patients who had single tumor of >10 cm were also excluded. In addition, we

excluded 43 patients who had macrovascular invasion. After excluding 31 patients who were lost to follow-up, 374 patients with single large HCC who underwent HR were finally enrolled in this study. They were then divided into 2 groups according to the anatomical tumor locations (Couinaud's segmentation): group SS ($n=171$), which consisted of patients with tumor located in the same section; and group DS ($n=203$), which consisted of patients with tumor located in different sections. They were monitored until March 2016 or their death, and their medical records were retrospectively reviewed.

2.3. Indications for HR

The indications of HR for single large HCC were the presence of an appropriate residual liver volume evaluated by computed tomography (CT) or magnetic resonance imaging (MRI). For HCC patients without cirrhosis, we considered 40% remnant liver volume after HR to be adequate. However, for cases with intermediate or advanced cirrhosis, the remnant volume should be $>50\%$. We also required well-preserved liver function as another necessary condition for HR. If the patient had intermediate or advanced cirrhosis with Child-Pugh B or C liver function, the HR was not performed.

2.4. Follow-up and treatment of recurrence

The follow-up exam was routinely performed in the outpatient clinic. Alpha-fetoprotein (AFP) and hepatitis B virus deoxyribonucleic (HBV DNA) measurements and abdominal ultrasonography were performed every 3 months. A contrast-enhanced CT scan was performed every 6 months. When intrahepatic recurrence was difficult to ascertain, MRI or contrast-enhanced ultrasonography were performed. The tumor recurrence was mainly based on radiographic evidence and/or the AFP level. The patients who showed tumor recurrence were treated with the following alternatives: re-resection, radio frequency ablation (RFA), salvage liver transplantation (LT), transcatheter arterial chemoembolization (TACE), sorafenib, radiotherapy, and chemotherapy.

2.5. Statistical analysis

The statistical software SPSS 21.0 (SPSS, Inc.) was used to analyze relevant data. Categorical data were presented as number (percent) and compared using Pearson chi-square or Fisher's exact test. Continuous variables were expressed as the mean \pm SD and analyzed using the *t*-test. Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by the Kaplan-Meier method, and differences between the two groups were determined by the log-rank test. The Cox proportional hazards model was used to test potential predictor of survival after surgery. The statistically significant variables identified by univariate analysis were then included in the multivariate analysis with proportional hazard regression. A 2-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of all study patients

Baseline demographic and clinicopathologic data for all 374 patients are listed in Table 1. There were no significant differences in age, sex, tumor size, serum levels of total bilirubin (TB), alanine aminotransferase (ALT), aspartate aminotransferase (AST),

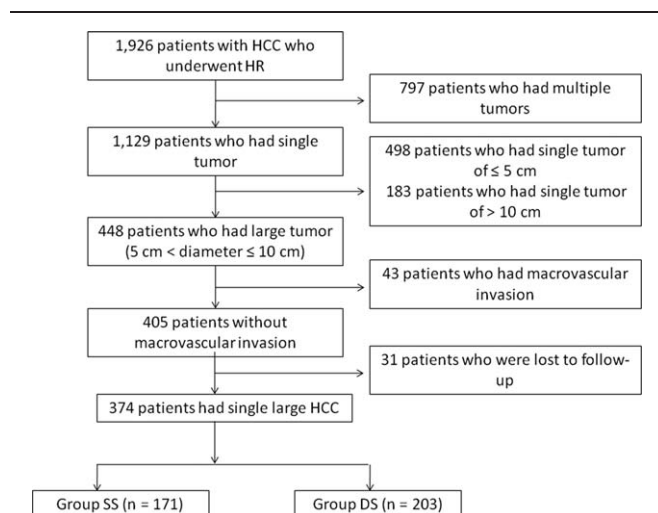


Figure 1. Flow chart of study participants. DS=different sections, HCC=hepatocellular carcinoma, HR=hepatic resection, SS=same section.

Table 1**Preoperative characteristics of single large hepatocellular carcinoma patients who underwent HR.**

Variables	Group SS (n=171)	Group DS (n=203)	P value
Age, mean±SD (range), y	53.9±12.1 (24.1–79.6)	51.4±13.2 (19.2–81.8)	0.062
Male, n (%)	143 (83.6)	169 (83.3)	0.923
Tumor size, mean±SD (range), cm	7.6±1.4 (5.1–10)	7.9±1.5 (5.4–10)	0.060
HBsAg positivity, n (%)	165 (96.5)	195 (96.1)	0.826
HBV DNA ≥1000 IU/mL, n (%)	39 (22.8)	47 (23.2)	0.937
Serum AFP ≥400 ng/mL, n (%)	74 (43.3)	95 (46.8)	0.495
TB level, mean±SD (range), μmol/L	14.2±5.6 (4.5–35.8)	15.0±6.2 (3.3–34.9)	0.239
ALT level, mean±SD (range), IU/L	54.3±48.0 (18–366)	51.3±49.7 (10–572)	0.551
AST level, mean±SD (range), IU/L	52.8±41.4 (16.4–310)	54.7±54.7 (13–668)	0.715
Albumin level, mean±SD (range), g/L	41.4±4.6 (30.6–59.7)	41.1±4.9 (30.2–61.7)	0.547
PT level, mean±SD (range), seconds	11.7±1.2 (9.6–17.3)	11.8±1.4 (9.5–17.9)	0.297
Platelet level, mean±SD (range), 10 ⁹ /L	152.5±67.8 (42–412)	160.1±77.6 (35–500)	0.320
Child–Pugh class A, n (%)	167 (97.7)	200 (98.5)	0.540
PHT, n (%)	59 (34.5)	81 (39.9)	0.283

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DS = different sections, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus deoxyribonucleic, HR = hepatic resection, PHT = portal hypertension, PT = prothrombin time, SD = standard deviation, SS = same section, TB = total bilirubin.

albumin, prothrombin time (PT) and platelet count, and the percentage of serum hepatitis B surface antigen positivity, HBV DNA of >1000 IU/mL, AFP level of >n 400 ng/mL, the patients with Child–Pugh class A, and the patients with clinical PHT between group SS and DS (all $P > 0.05$).

3.2. Short-term outcomes of all study patients

Short-term results after surgery are summarized in Table 2. There were more patients with intraoperative blood loss of >1000 mL

Table 2**Short-term outcomes of single large hepatocellular carcinoma patients who underwent HR.**

	Group SS (n=171)	Group DS (n=203)	P value
Intraoperative blood loss, mL			
<100	31 (18.1%)	42 (20.7%)	0.534
100–500	87 (50.9%)	102 (50.2%)	0.903
501–1000	50 (29.2%)	47 (23.2%)	0.181
>1000	3 (1.8%)	12 (5.9%)	0.041
Intraoperative blood transfusion	5 (2.9%)	16 (7.9%)	0.038
Duration of postoperative hospital stay, mean ±SD (range), d	10.6±10.7 (3–114)	10.9±9.9 (4–106)	0.792
Complications			
Grade I	35 (20.5%)	42 (20.7%)	0.958
Grade II	19 (11.1%)	26 (12.8%)	0.615
Grade IIIa	8 (4.7%)	13 (6.4%)	0.470
Grade IIIb	6 (3.5%)	10 (4.9%)	0.500
Grade IVa	7 (4.1%)	11 (5.4%)	0.551
Grade IVb	3 (1.8%)	4 (2.0%)	1.000
Grade V	2 (1.2%)	2 (1.0%)	1.000
30-day mortality	2 (1.2%)	2 (1.0%)	1.000
90-day mortality	5 (2.9%)	4 (2.0%)	0.737
Resection margins, mean±SD (range), cm	1.8±0.7 (0.3–3)	1.7±0.7 (0.2–4)	0.136
Microvascular invasion	58 (33.9%)	84 (41.4%)	0.139
Tumor grade			
G1–G2	49 (28.7%)	48 (23.6%)	0.271
G3	85 (49.7%)	94 (46.3%)	0.512
G4	37 (21.6%)	61 (30.0%)	0.065

DS = different sections, HR = hepatic resection, SD = standard deviation, SS = same section.

in group DS than that in group SS (5.9% vs 1.8%, $P=0.041$). Similarly, more patients in group DS needed intraoperative blood transfusion than those in group SS (7.9% vs 2.9%, $P=0.038$). No difference was found in duration of postoperative hospital stay between the group SS and DS. Both the 30-day mortality rate (1.2% vs 1.0%, $P=1.000$) and 90-day mortality rate (2.9% vs 2.0%, $P=0.737$) were not statistically different between the group SS and DS.

R0 resection was confirmed in all patients in each group, with a mean margin width of 1.8 ± 0.7 cm in the group SS and 1.7 ± 0.7 cm in the group DS, respectively ($P=0.136$). Postoperative complications were evaluated using the Clavien–Dindo classification.^[12] Most postoperative complications were grade I or II (Table 2) and there were no significant differences between group SS and DS regarding the grades of postoperative complications. The degree of pathological differentiation of HCC was identified using Edmonson–Steiner classification.^[13] Most tumors were grade G3 and there were no significant differences between group SS and DS regarding the tumor grades. In addition, there was no statistical difference in microvascular invasion between the two groups.

3.3. Long-term outcomes of all study patients

During a mean follow-up period of 41.4 ± 21.6 months (range 0.7–86.1 months), 103 (60.2%) patients in the group SS and 149 (73.4%) patients in the group DS died, respectively. OS rates were significantly better in the group SS than in the group DS: 1-, 3-, and 5-year OS rates were 91.8%, 70%, and 39.1%, respectively, for patients in the group SS versus 84.6%, 54.2%, and 27.9%, respectively, for those in the group DS ($P=0.001$, Fig. 2A). Similarly, the 1-, 3-, and 5-year RFS rates were significantly higher in group SS than that in group DS (86.2%, 51.1%, and 26.9% vs 71.4%, 36.2%, and 17.7%, respectively, $P=0.002$; Fig. 2B)

3.4. Subgroup analysis by tumor size

All patients were divided into 2 subgroups according to the tumor size: SG1 ($n=246$), which consisted of tumor of >5 and ≤8 cm; and SG2 ($n=128$), which consisted of tumor of >8 and ≤10 cm. In SG1, the OS rates were significantly higher in the patients with

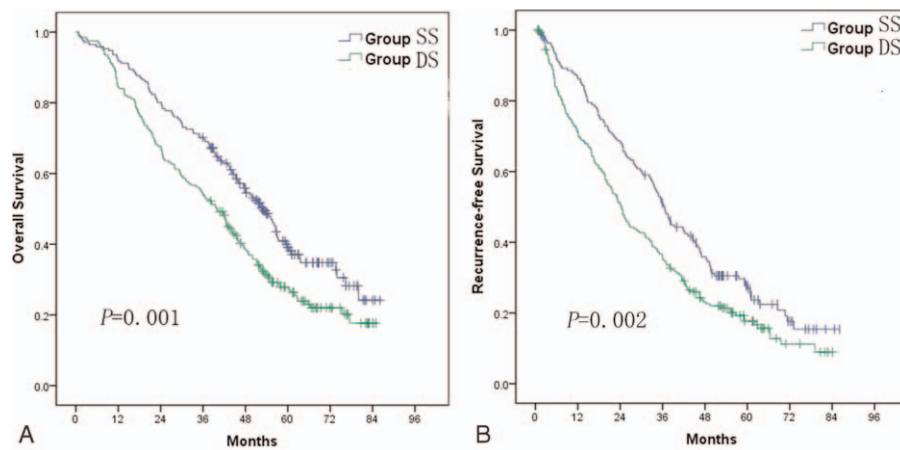


Figure 2. The OS and RFS for patients with single large HCC located in same and different sections according to Couinaud's segmentation following HR. (A) The OS for patients with single large HCC located in same and different sections. (B) The RFS for patients with single large HCC located in same and different sections (log-rank test). HCC=hepatocellular carcinoma, HR=hepatic resection, OS=overall survival, RFS=recurrence-free survival.

tumor located in the same section than in those with tumor located in different sections (1-, 3-, and 5-year OS rates of 89.7%, 66.7%, and 37.6% in the patients with tumor in the same section vs 82.8%, 50.0%, and 29.9% in those with tumor in different sections, respectively, $P=0.018$; Fig. 3A). Similarly, for patients in SG1, the 1-, 3-, and 5-year RFS rates were significantly higher in those with tumor located in the same section than that in those with tumor located in different sections (85.0%, 51.3%, and 24.0% vs 66.4%, 36.7%, and 18.8%, respectively, $P=0.028$; Fig. 3B).

In SG2, the patients with tumor located in the same section had better OS and RFS rates than those with tumor located in different sections: the 1-, 3-, and 5-year OS rates were 96.3%, 77.8%, and 42.8%, respectively, for patients with tumor in the same section versus 87.7%, 61.6%, and 24.0%, respectively, for those with tumor in different sections ($P=0.029$; Fig. 4A), and the 1-, 3-, and 5-year RFS rates were 88.7%, 50.8%, and 33.2%, respectively, for those with tumor in the same section versus 80.3%, 33.8%, and 15.4%, respectively, for those with tumor in different sections ($P=0.021$; Fig. 4B).

3.5. Risk factor analysis for survival

In univariate analysis, significant risk factors for postoperative survival were age of <60 years, PHT, AFP ≥ 400 ng/mL, tumor located in different sections, microvascular invasion, and tumor grade of G4 (all $P < 0.05$; Table 3). In multivariate analysis, the variables including age of <60 years, PHT, AFP ≥ 400 ng/mL, tumor located in different sections, microvascular invasion, and tumor grade of G4 were also found to be independent predictive factors for poor postoperative survival (Table 4).

4. Discussion

To focus on clinical HR outcomes relating to the anatomical location of single large HCC, we excluded patients who had macrovascular invasion, which could lead to poor prognosis. In addition, all patients enrolled in this study had the initial HCCs not the recurrent HCCs. We believe that the inclusion and exclusion criteria in this study could keep baseline data consistent between the two groups and may result in a more accurate analysis for outcomes. As shown in Table 1, we found that

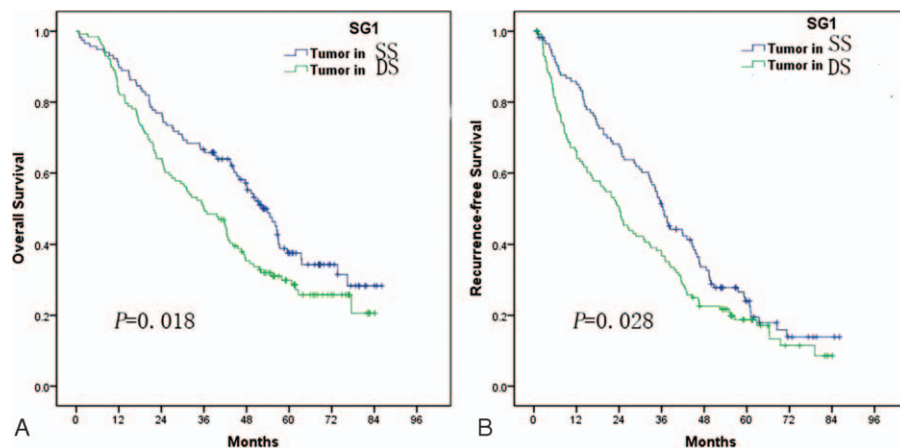


Figure 3. The OS and RFS for SG1 (consisted of tumor of >5 and ≤ 8 cm) patients with tumor in same and different sections after HR. (A) The OS for SG1 patients with tumor located in same and different sections after HR. (B) The RFS for SG1 patients with tumor located in same and different sections after HR (log-rank test). HR=hepatic resection, OS=overall survival, RFS=recurrence-free survival.

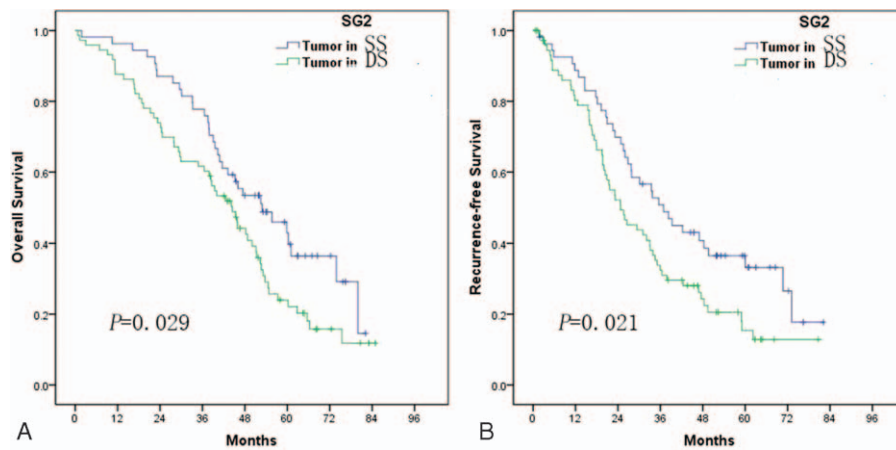


Figure 4. The OS and RFS for SG2 (consisted of tumor of >8 and ≤ 0 cm) patients with tumor in same and different after HR. (A) The OS for SG2 patients with tumor locating in same and different sections after HR. (B) The RFS for SG2 patients with tumor locating in same and different sections after HR (log-rank test). HR = hepatic resection, OS = overall survival, RFS = recurrence-free survival.

patients with single large HCC located in same or different hepatic sections did not show any significant baseline differences.

With improvements in surgical technique and perioperative care, HR can be safely performed on patients whose tumors lie in any part of liver. Our study showed that there was no significant difference between the two groups in regard to various grades of postoperative complications (Table 2). However, the rates of intraoperative blood loss of >1000 mL and intraoperative blood transfusion were higher in patients with tumor located in different sections than in those with tumor in the same section. We think it may be attributed to mesohepatectomy, which facilitates en bloc resection with preservation of more functional parenchyma but may be associated with more intraoperative blood loss and transfusion because of high technical demanding and 2 transaction surfaces.^[14,15]

Our data suggested that patients with single large tumor located in the same hepatic section had significantly better OS and RFS than patients with tumor in different hepatic sections (all $P < 0.05$, Fig. 2). The similar findings have been reported by our recent serial studies of early HCC patients with multifocal tumor meeting the Milan criteria.^[6,7] However, the influence of anatomical location for single large HCC on outcomes following HR, to our knowledge, has not been reported to date. To explore further

whether tumor size makes a difference to the above results, we performed a subgroup analysis by tumor size. The similar results, that patients with tumor located in the same section had better OS and RFS rates than those with tumor located in different sections, were found in the tumor of >5 and ≤ 8 cm and the tumor of >8 and ≤ 10 cm (all $P < 0.05$, Figs. 3 and 4).

To explore further the influence of different co-variables on survival, a multivariable logistic regression analysis was conducted on the entire cohort of patients. The analysis also confirmed a single large tumor locating in different hepatic sections as an independent risk predictor of postoperative survival (Table 4). Couinaud’s segmentation was proposed based on the distribution of the portal pedicles and the location of the hepatic veins, which is widely used in our clinical practice.^[16,17] The portal vein acts an important blood supply of tumor and efferent tumor vessel in the intrahepatic spread of HCC.^[18,19] Therefore, if one single large tumor is located in different hepatic sections dominated by different branches of the portal vein, then there may be more blood supplies and more chance of developing potential intrahepatic spread that could lead to more recurrence and poorer outcomes.

Our multivariate Cox modeling to identify other prognostic factors in HCC patients following HR came to similar conclusions as previous studies: patients with serum AFP levels >400 ng/mL,^[20,21] PHT,^[22–24] microvascular invasion,^[25–27] and poor tumor differentiation^[28,29] had significantly worse outcomes than did other patients after HR. With the improvements in surgical technique and strict section standard, many

Table 3
Univariate analysis of prognostic factor for survival.

Variables	Number	Chi-square	P value
Sex (M/F)	314/60	0.944	0.331
Age (≥60/<60 years)	119/255	17.977	<0.001
Child-Pugh score (5/>5)	299/75	0.004	0.948
PHT (Yes/No)	140/234	16.263	<0.001
HBV DNA (≥1000/<1000 IU/mL)	86/288	0.558	0.455
AFP (≥400/<400 ng/mL)	169/205	23.922	<0.001
Tumor size (>8/≤8 cm)	128/246	0.002	0.964
Tumor location (same/different sections; Couinaud’s segmentation)	171/203	10.654	0.001
Microvascular invasion (Yes/No)	142/232	29.830	<0.001
Tumor grade = G4 (Yes/No)	98/276	102.449	<0.001

AFP = alpha-fetoprotein, F = female, HBV DNA = hepatitis B virus deoxyribonucleic, M = male, PHT = portal hypertension.

Table 4
Multivariate analysis of prognostic factors for survival.

Variables	Hazard ratio	95% CI	P value
Age ≥60 years	0.563	0.419–0.757	<0.001
PHT (yes)	1.645	1.271–2.130	<0.001
AFP ≥400 ng/mL	1.935	1.491–2.512	<0.001
Tumor location (same section; Couinaud’s segmentation)	0.682	0.530–0.879	0.003
Microvascular invasion (yes)	1.603	1.242–2.070	<0.001
Tumor grade = G4 (yes)	4.203	3.173–5.568	<0.001

AFP = alpha-fetoprotein, CI = confidence interval, PHT = portal hypertension.

centers have believed that HR can be performed safely on elderly patients and can provide a comparable curative effect to that in young patients.^[30–32] Furthermore, some studies showed that the elderly patients with HCC possibly had a better OS and/or RFS than that of the younger patients.^[33,34] Our modeling also identified the age of < 60 years as an independent predictor of poor long-term survival.

This study is mainly limited by its retrospective nature and a single-center experience. However, this study, to the best of our knowledge, represents the first and largest cohort to exclusively investigate the role of anatomical location profile for single large HCC on outcomes following HR, and some new findings may be vital for guiding the surgeon in choosing the optimal therapeutic strategy for the single large HCC according to the anatomical distribution of tumor. However, well-designed, long-term, randomized, controlled, prospective trials are still necessary to further confirm this new point proposed in this study.

In conclusion, this study demonstrates that the single large HCC patients who have tumor located in the same hepatic section according to Couinaud's segmentation may have better long-term survival and lower HCC recurrence rates than those with tumor located in different hepatic sections following HR. Some factors were observed to be associated with postoperative poor survival, such as patient with tumor located in different hepatic sections, AFP levels >400 ng/mL, PHT, and tumor with microvascular invasion, and poor tumor differentiation.

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