Manuscript Impact on Prognosis of Different Anatomical Hepatectomy Approaches for Single Hepatocellular Carcinoma in Segment VI

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Abstract

Background. Liver resection is effective for hepatocellular carcinoma (HCC). For a single HCC in subsegment 6 (S6), segmentectomy of S6, S5 (S6+5) and segmentectomy of S6, S7 (S6+7) are the common anatomical surgical procedures. However, the benefit of the two resection methods has not been clarified in this patient subgroup. This study aimed to compare the outcomes of S6+5 resection and S6+7 resection for single, early HCC located on S6 of the liver. Methods. In total, 115 patients with single HCC in S6 without vascular invasion and distant metastasis were included in this study. The patients were divided into the S6+5 group (n=73) and S6+7 group (n=42). A one-to-one propensity score-matching analysis (PSM) was performed to minimize the effect of potential confounders. Results. Forty patients from each group were matched. The preoperative factors were balanced between the two groups. The 1-, 2-, and 3-year overall survival (OS) rates in the S6+5 group were 92.3%, 82.1%, and 76.8%, respectively, and in the S6+7 group were 94.5%, 91.6% and 88.6%, respectively (p=0.197). The 1-, 2-, and 3-year recurrence-free survival (RFS) rates in the S6+5 group were 71.9%, 61.6%, and 58.9%, respectively, and in the S6+7 group were 83.5%, 77.7% and 68.8%, respectively (p=0.432). There were no significant differences in the recurrence pattern and postoperative recovery of liver function. The surgical procedure was not a significant risk factor for the OS and RFS in both the uni- and multivariate analyses. Conclusion. S6+5 and S6+7 resection achieved similar outcomes for early-stage solitary HCC in S6.

Background

epatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related deaths worldwide[1]. Surgery is an effective treatment for early liver cancer, leading to the best outcomes of any treatment available[2]. For hepatectomy, anatomical resection was considered to have a better prognosis than non-anatomical resection in many previous studies[3-6]. However, the actual surgical procedures chosen depends on the tumour location in the liver and the intraoperative situation.

For single HCC in subsegment 6 (S6) without vascular invasion and distant metastasis, surgical resection is undoubtedly the most preferred treatment. When considering tumour factors, resection margins and liver function, the method of resection will be different. Simple S6 segmentectomy sometimes fails to achieve therapeutic goals. Commonly, the anatomical segmentectomy of S6 and S5 (S6+5), or segmentectomy of S6 and S7 (S6+7) will be applied, but the efficacy and benefits of segmentectomy of S6+5 and S6+7 remain unclear.

The purpose of the present study was to compare the true outcome of S6+5 segmentectomy with S6+7 segmentectomy for single, early-stage HCC in S6 using propensity score-matching (PSM) in real-world data.

Methods

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. The analysis of the patient data was reviewed and approved by the Institutional Review Board at the Sun Yat-sen University Cancer Center (B2019-057-01).

Patients

From January 2006 to December 2016, a total 409 patients with single HCC limited to the liver S6 underwent liver resection as the initial treatment with curative intent at the Sun Yat-sen University Cancer Center, Department of

Hepatobiliary Surgery, and these patients were retrospectively screened for eligibility.

Among the 409 patients, 297 were excluded from this study for the following reasons: not S6+5 or S6+7 resection (197 patients), non-anatomic resection (55 patients), pathological multiple lesions (20 patients), tumour thrombus (15 patients), extrahepatic metastasis (5 patients), and spontaneous tumour rupture (2 patients). The specific flow chart is shown in Figure 1. The remaining 115 patients were ultimately included in this study and divided into two groups: the S6+S5 (n=73) and S6+S7 (n=42) groups. All preoperative laboratory serum test was collected within 3 days before surgery. Preoperative imaging examinations included contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) within a week before surgery.

Surgical procedures

Surgical procedures were classified according to conventional terminology derived from the eight segments[7]. Hepatic resection was performed using the previously described technique[8, 9]. Intraoperative ultrasound was routinely performed to evaluate the tumour burden, remnant liver, and possibility of a negative resection margin. Anatomical resection was defined as hepatic segmentectomy or combined resection for adjacent liver segments. Anatomical S6+5 and S6+7 segmentectomy was verified according to the surgical records.

Follow-up

Postoperative follow-up ended on May 31, 2019. The first visit of most patients after hospital discharge occurred 4 weeks after surgery. The next follow-up sessions were performed every 3 months for the first 2 years and then once every 6 months after 2 years. Each follow-up session included a detailed medical history, physical examination, laboratory tests, and one of ultrasonography, contrast-enhanced CT, or MRI. Recurrence was defined as the appearance of a new lesion with typical imaging features of HCC confirmed by at least two imaging modalities. The proper subsequent treatment was performed as clinical routine.

Statistical Analysis

The clinical characteristics between the S6+S5 and S6+S7 groups were compared. Categorical variables were compared using Pearson's $\chi 2$ test or Fisher's exact test. The variable distribution was described using the mean ± standard error (S.E.) for normally distributed values, and median and range for non-normally distributed values. Continuous variables were compared using Student's t-test for normally distributed values or the Mann-Whitney test for skewed distributed values. To minimize the influence of selection bias produced by preoperative factors between the two groups, PSM was conducted using a logistic regression model[10, 11]. Preoperative variables were entered into PSM, including age (≤/>50 years old), sex (male/female), hepatitis B DNA copies (≤10E2/>10E2), AFP (≤/>400 ng/ml) level, Child-Pugh score (5/>5) and tumour size (≤5/>5 cm). PSM was performed by a 1:1 matching method with a calliper width of 0.1. The survival analysis was calculated using the Kaplan-Meier method, and differences in the survival curves were analysed with the log-rank test. All variables that yielded a P value of < 0.1 in the univariate analysis were subjected to a multivariate analysis using Cox's proportional hazards models. The hazard ratio (HR) and confidence intervals (CI) were calculated. A value of two-tailed $P < 0.05$ was considered statistically significant. All data analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL).

Results

Preoperative characteristics of the S6+5 and S6+7 groups

The clinical preoperative characteristics of the patients in the S6+5 and S6+7 groups are summarized in Table 1. The two groups were comparable in terms of basic characteristics, liver function, tumour burden and surgical factors. After PSM, the Child-Pugh score and tumour size were more consistent in the two groups.

Postoperative Survival of the S6+5 and S6+7 Groups

In the overall cohorts, the 1-, 2-, and 3-year overall survival (OS) rates in the S6+5 group were 95.7%, 89.9%, and 84.9%, respectively, and in the S6+7 group were 94.8%, 92.0%, and 89.2%, respectively (p=0.188). The 1-, 2-, and 3-year recurrence-free survival (RFS) rates in the S6+5 group were 74.8%, 64.7%, and 61.6%, respectively, and in the S6+7 group were 84.4%, 78.9% and 70.5%, respectively (p=0.288). In matched cohorts, the 1-, 2-, and 3-year OS rates in the S6+5 group were 92.3%, 82.1%, and 76.8%, respectively, and in the S6+7 group were 94.5%, 91.6% and 88.6%, respectively (p=0.197). The 1-, 2-, and 3-year RFS rates in the S6+5 group were 71.9%, 61.6%, and 58.9%, respectively, and in the S6+7 group were 83.5%, 77.7% and 68.8%, respectively (p=0.432). Survival graphs are shown in Figure 2. It seemed that the S6+7 group might have better survival than the S6+5 group, but the difference was not statistically significant.

Prognostic Factors for the Overall and Recurrence-free Survival after PSM

The risk factors of the OS and RFS were analysed using the Cox regression hazards model in matched cohorts (Table 2). The univariate analysis identified platelet (PLT) and tumour size as two significant prognostic factors for OS. Only PLT were identified as an independent prognostic predictor in the multivariate analysis (HR 0.238, 95% CI 0.079-0.719, P=0.011). For RFS, Age, PLT, and tumour size were identified as independent prognostic predictors in the univariate analysis. Multivariate analysis identified age (HR 3.173, 95% CI 1.518-6.631, P=0.002) and tumour size (HR 4.205, 95% CI 2.045-8.648, P<0.001) as significant factors. In matched cohorts, the method of resection was not a significant predictor for OS and RFS.

Postoperative Liver Function Recovery of the S6+5 and S6+7 Groups after PSM

The serum level changes of the liver function indicators 3 days, 7 days and 1 month after the operation were compared between the S6+5 and S6+7 groups (Table 3). All indicators returned to normal over time, and there was no significant difference between the two groups.

Initial Recurrence Pattern of the S6+5 and S6+7 Groups after PSM

Patients with a recurrence of HCC were screened for analysis (Table 4). The initial recurrence site of the liver was as follows: surgical margin (within 2 cm of the cut edge), proximal part (right lobe), distal (left lobe), whole liver, and extrahepatic organ. In two of those patients, the specific recurrence sites could not be tracked until death. No significant difference in the recurrence pattern was found between the two groups.

Discussion

Clinically, HCC in segment 6 of the liver is common. Because the location is close to the edge, HCC in segment 6 tends to be easier to remove than that in other inner liver segments, which makes surgery the first choice most of the time when it is at an early stage. In the past few years, despite the controversy, anatomical resection has been

widely applied as a rational surgical procedure for its potential ability to prevent the development of intrahepatic metastases through the portal vein[12-14]. When the tumour is small, local tumour removal or S6 anatomical resection is often used. When the tumour is large or close to the edge of the adjacent segment of the liver, the common excisional methods are the anatomical resection of S6+5 and S6+7. There is no previous research report on the prognosis of these two methods of resection. Therefore, we designed this study and initially showed that the two surgical procedures resulted in a similar prognosis for the HCC patients.

The baseline characteristics were almost identical in the two groups. Limited by the potential selection bias of retrospective studies, one-to-one PSM was still performed. There was no difference in survival between the S6+5 group and the S6+7 group. It seemed that patients in the S6+7 group had better data statistics for OS and RFS, but there was no significant difference. Moreover, the two resection methods had no effect on the recovery of postoperative liver function and the recurrence rate and pattern. This further verified the same prognosis in the two groups. In these early-stage HCC patients, the OS and RFS were consistent with previous scientific reports, indicating the practical universality of the patients included in this study[15-17].

In univariate and multivariate analyses, segment resection was not an independent predictor. PLTs were identified as a significant prognostic predictor for OS. This result was consistent with previous studies[18, 19]. Tumour size was reasonably the unique risk factor in the univariate and multivariate analyses for RFS. Notably, AFP and the shortest margin were not associated with survival. This might be due to the limited number of cases. However, the resection margin width had no influence on survival, according to some previous studies[20, 21]. All the patients in the studies were in the early stage of HCC, with most of the tumour diameter was within 5 centimetres, which weakens the effect of AFP on the prognosis of these patients.

We acknowledge some limitations in our study. First, although PSM was used to control the imbalance of the preoperative factors, a retrospective study inevitably identifies bias. The number of cases was small. Second, the patients were selected from January 2006 to December 2016. Over a 10-year period, the technique of the surgery itself had been changed or improved. The study focused on early liver cancer patients, and the impact on the OS was relatively small. Third, our study is from a single centre. The advantage is that the perioperative management of the preoperative diagnosis, surgical technique and postoperative care is relatively consistent, which can effectively control other variables outside the scope of resection, making the conclusion credible.

Conclusions

There is no significant difference in the prognosis of patients with single, early-stage S6 HCC undergoing anatomical S6+5 segmentectomy and S6+7 segmentectomy. A reasonable surgical procedure should be chosen between the two procedures based on tumor location, liver function and safety cutting edge in routine clinical practice. The results need to be confirmed in further prospective studies.

Abbreviations

HCC, hepatocellular carcinoma; PSM, propensity score-matching; OS, overall survival; RFS, recurrence-free survival

Declarations

Informed consent statement

Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed verbally to undergo treatment. Individuals cannot be identified based on the data presented.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest Statement

All authors declared no conflicts of interest.

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Authors' Contributions

Guo RP and Wei Wei designed the study; Lu LH, Anna Kan collected the data; Wang QX analyzed and Li SH interpreted the data; Mei Jie drafted the manuscript. All authors were involved in the initial drafting, review, and approval of the manuscript and the decision to submit it for publication.

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none

Institutional review board statement

This study was approved by the institutional review board (IRB) of Sun Yat-sen University Cancer Center. The approval number is B2019-057-01. The experiments were carried out in accordance with the approved guidelines.

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Tables

Table 1. Baseline characteristics and operative variables of patients before and after matching.

aracteristic	ALL patients			Propensity score-matched patients		
	S6+S5 Group (*n*=73)	S6+S7 Group (*n*=42)	*P* Value	S6+S5 Group (*n*=40)	S6+S7 Group (*n*=40)	*P* Value
demiology						
ge (y) *	49.5±11.2	50.2±10.1	0.742	48.8±12.4	50.8±10.0	0.423
ender (Male/female) **	68/5 (93.2/6.8)	38/4 (90.5/9.5)	0.722	37/3 (92.5/7.5)	38/2 (95.0/5.0)	1.000
iology						
epatitis B carrier s/no)	66/7 (90.4/9.6)	39/3 (92.9/7.1)	0.744	38/2 (90.0/10.0)	37/3 (92.5/7.5)	1.000
epatitis B DNA ies(≤10E2/>10E2)	40/33(54.8/45.2)	27/15 (64.3/35.7)	0.320	22/18 (55.0/45.0)	25/15 (62.5/37.5)	0.496
OG performance (0/1)	70/3 (95.9/4.1)	40/2 (95.2/4.8)	1.000	39/1 (97.5/2.5)	39/1 (97.5/2.5)	1.000
er function						
iver cirrhosis (yes/no)	44/29 (60.3/39.7)	26/16 (61.9/38.1)	0.863	25/15 (65.0/35.0)	25/15 (65.0/35.0)	1.000
hite blood cell count ^{9}/L) ***	6.1 (3.25-15.9)	5.8 (3.0-10.6)	0.242	6.1 (4.0-11.2)	6.0±1.7	0.296
aemoglobin (g/L)	148.0 (89.0-174.0)	144.5±16.0	0.692	144.3±13.1	145.6±15.6	0.864
latelet count (10^9/L)	184.3±57.9	168.9±53.5	0.164	179.7±54.8	169.0±54.8	0.377
rothrombin time (sec)	11.8 (10.0-15.0)	11.6 (9.6-14.5)	0.274	12.2±1.1	11.8±1.0	0.102
lanine aminotransferase L)	36.8 (13.0-134.4)	38.6 (9.3-172.8)	0.763	30.5 (14.0-93.4)	38.6 (9.3-172.8)	0.550
spartate notransferase (U/L)	30.2 (15.0-109.8)	30.9 (11.5-115.7)	0.981	28.4 (15.0-100.1)	34.3 (11.5-115.7)	0.247
erum albumin (g/L)	43.9±4.0	43.3±3.3	0.447	43.5±3.8	43.5±3.2	0.903
otal bilirubin (mmol/L)	14.1 (4.8-41.9)	14.1 (9.2-44.2)	0.897	13.5 (5.0-29.6)	15.0 (9.2-44.2)	0.791
hild-Pugh score (5/6/7)	62/10/1 (84.9/13.7/1.4)	40/2/0 (95.2/4.8/0)	0.089	38/2 (95.0/5.0)	38/2 (95.0/5.0)	1.000
nour burden						
umour size (≤5/>5 cm)	45/28 (61.6/38.4)	32/10 (76.2/23.8)	0.110	30/10 (75.0/25.0)	30/10 (75.0/25.0)	1.000
lpha-fetoprotein 00/>400 ng/ml)	46/27 (63.0/37.0)	30/12 (71.4/28.6)	0.359	28/12 (70.0/30.0)	28/12 (70.0/30.0)	1.000

gery factors						
hortest margin (≤2/>2	54/19 (74.0/26.0)	33/9 (78.6/21.4)	0.580	30/10 (75.0/25.0)	32/8 (80.0/20.0)	0.592
lood loss (≤400/>400	61/12 (83.6/16.4)	38/4 (90.5/9.5)	0.406	35/5 (87.5/12.5)	36/4 (90.0/10.0)	1.000
lood transfusion (yes/no)	0/73 (0/100)	1/41 (2.4/97.6)	0.365	0/40 (0/100.0)	1/39 (2.5/97.5)	1.000
urgery time (min)	150.0 (65.0-510.0)	150.0 (90.0-300.0)	0.908	150.0 (65.0-400.0)	150.0 (90.0-300.0)	0.612
ortal vein block time n)	15.0 (0-28.0)	15.0 (0-30.0)	0.507	13.0 (0-28.0)	14.6 ± 8.2	0.279

*Mean ± SD; **Number (%); ***Median (Range)

ECOG: Eastern Cooperative Oncology Group

Table 2. Univariate and multivariate analysis of risk factors for overall survival and recurrence-free survival.

Variables	Overall survival						Recurrence-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P*	HR	95% CI	*P*
Age (y), (≤/>50)	1.964	0.783-4.928	0.151				2.160	1.086-4.297	0.028	3.173	1.518-6.631	0.002
Gender, (Female/male)	1.439	0.192-10.755	0.723				0.750	0.229-2.458	0.635			
Liver cirrhosis, (no/yes)	1.459	0.559-3.804	0.440				1.019	0.515-2.009	0.957			
PLT (10^9/L), (≤/>100),	0.238	0.079-0.719	0.011	0.238	0.079-0.719	0.011	0.342	0.118-0.992	0.048			
PT (sec), (≤/>14)	0.048	0-5829.225	0.610				2.303	0.548-9.680	0.255			
ALT (U/L), (≤/>50)	1.191	0.398-3.565	0.755				1.710	0.799-3.658	0.167			
AST (U/L), (≤/>40)	1.563	0.599-4.073	0.361				1.847	0.902-3.782	0.093			
ALB (g/l), (≤/>40)	0.715	0.209-2.455	0.595				0.527	0.229-1.211	0.131			
TBIL (mmol/L), (≤/>20)	2.152	0.775-5.982	0.142				1.688	0.730-3.899	0.211			
AFP (ng/ml), (≤/>400)	1.068	0.410-2.782	0.892				0.836	0.391-1.788	0.643			
Child-Pugh score, (5/6)	3.883	0.855-17.637	0.079				3.068	0.913-10.313	0.070			
Tumor size (≤/>5), (cm)	2.777	1.148-6.716	0.023				2.928	1.496-5.729	0.002	4.205	2.045-8.648	<0.001
Shortest margin (cm), (≤2/>2)	0.474	0.139-1.618	0.233				0.782	0.362-1.737	0.549			
Blood loss (ml), (≤400/>400),	1.255	0.286-5.513	0.763				1.267	0.304-5.275	0.745			

Surgery time (min), (≤180/>180)	1.058	0.303-3.691	0.929	0.744	0.236-2.352	0.615
Portal vein block time (min), (≤15/>15)	0.541	0.196-1.489	0.234	0.877	0.436-1.762	0.712
Subsequent radical treatment (no/yes)	0.507	0.543-3.448	0.507	-	-	-
Segment resection, (S5+6/S6+7)	0.550	0.219-1.381	0.203	0.765	0.391-1.496	0.434

PLT, platelet count; PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, Total bilirubin, AFP, alpha-fetoprotein; HR, hazard ratio, CI, Confidence intervals

Table 3. Postoperative serum level changes of liver function indicators

Time after surgery	S6+S5 Group (n=40)	S6+S7 Group (n=40)	P Value
3 days			
White blood cell (10^9/L)	12.5 (5.0-72.8)	12.7 (6.1-124.0)	0.925
Haemoglobin (g/L)	124.7 ± 17.1	126.8 ± 12.2	0.536
Platelet count (10^9/L)	123.2 ± 44.6	127.0 ± 50.2	0.731
Prothrombin time (sec)	14.0 (12.6-16.9)	14.6 (13.5-18.4)	0.071
Alanine aminotransferase (U/L)	291.4 (46.0-1265.0)	320.9 (114.4-997.2)	0.739
Aspartate aminotransferase(U/L) (U/L)	123.0 (24-750.7)	154 (44.1-530.6)	0.566
Serum albumin (g/L)	36.6 ± 3.6	36.1 ± 3.4	0.542
Total bilirubin (mmol/L)	24.1 (8.7-107.8)	24.7 (9.2-111.0)	0.486
7 days			
White blood cell (10^9/L)	9.0 (4.4-16.9)	8.4 (3.4-13.9)	0.536
Haemoglobin (g/L)	119.3 ± 14.5	119.5 ± 11.1	0.961
Platelet count (10^9/L)	165.7 ± 54.9	174.8 ± 76.1	0.553
Prothrombin time (sec)	13.2 ± 0.7	13.4 (12.0-17.7)	0.448
Alanine aminotransferase (U/L)	109.3 (29.7-378.3)	113.5 (36.2-364.7)	0.987
Aspartate aminotransferase (U/L)	40.0 (18.9-104.6)	43.0 (15.5-127.1)	0.306
Serum albumin (g/L)	38.2 ± 3.8	38.0 (26.6-66.3)	0.703
Total bilirubin (mmol/L)	20.2 ± 9.3	22.1 (10.8-80.9)	0.257
1 month			
White blood cell (109/L)	6.74 ± 2.0	5.9 ± 2.2	0.237
Haemoglobin (g/L)	138.5 ± 9.6	137 (116.0-157.0)	0.783
Platelet count (109/L)	162.7 ± 56.1	169.9 ± 55.3	0.696
Prothrombin time (sec)	13.1 ± 0.5	12.3 ± 1.3	0.800
Alanine aminotransferase (U/L)	27.3 (15.0-55.0)	30.8 (7.6-128.1)	0.527
Aspartate aminotransferase (U/L)	28.3 ± 6.9	31.4 (15.6-73.7)	0.164
Serum albumin (g/L)	45.2 (37.1-76.2)	44.4 ± 3.4	0.475
Total bilirubin (mmol/L)	11.8 ± 3.7	11.8 (6.3-27)	0.639

Table 4. Initial recurrence of hepatocellular carcinoma after liver resection in propensity score-matched patients

Recurrence location	S6+S5 Group (N=20)	S6+S7 Group (N=12)	*P* Value
Within 2 cm of cut edge cm	3	4	
Right lobe	6	4	
Left lobe	4	2	
Whole liver	4	1	
Extrahepatic organ	4	2	0.754

cm, centimetre

Figures

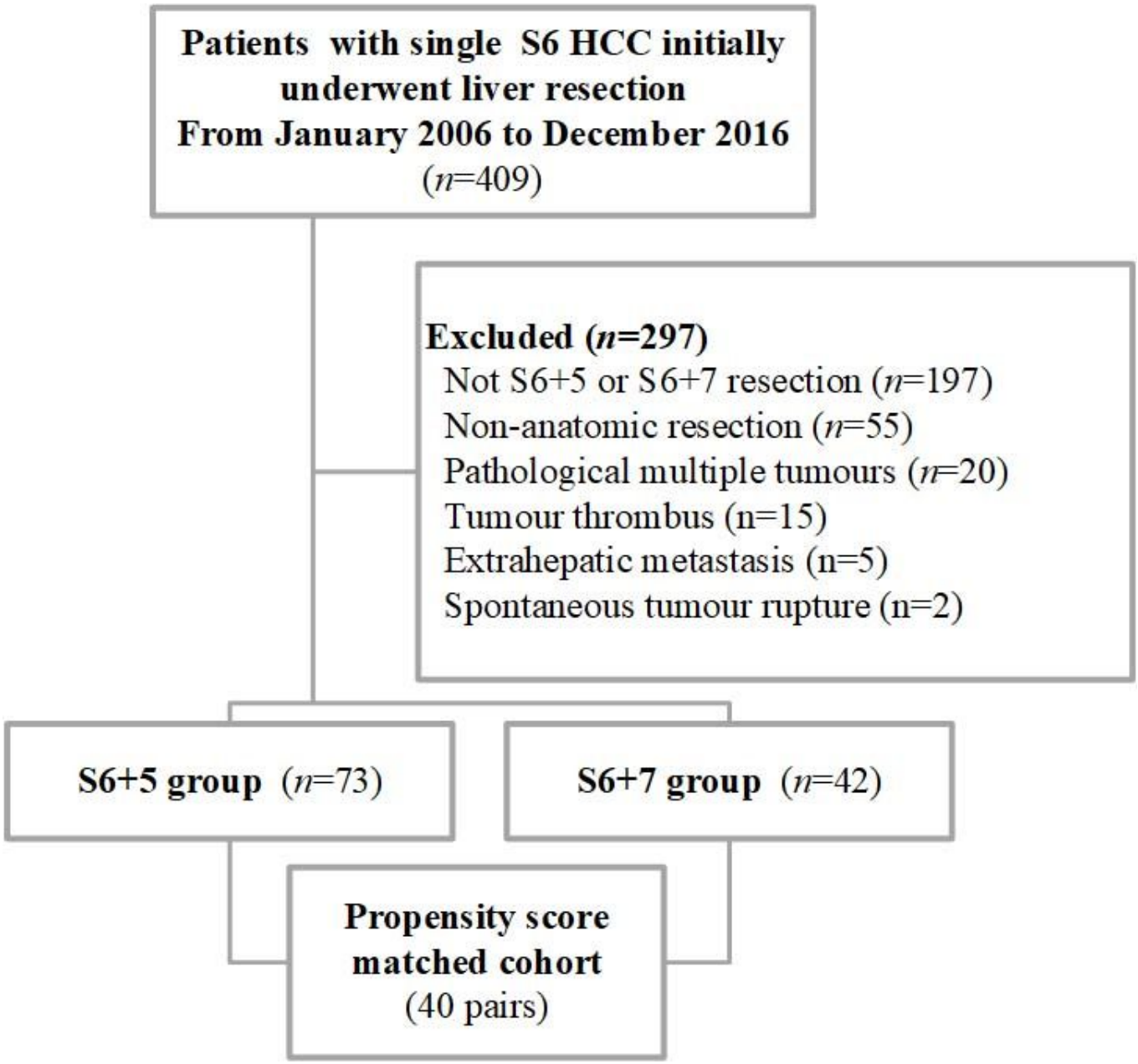

Figure 1

Patient selection algorithm chart

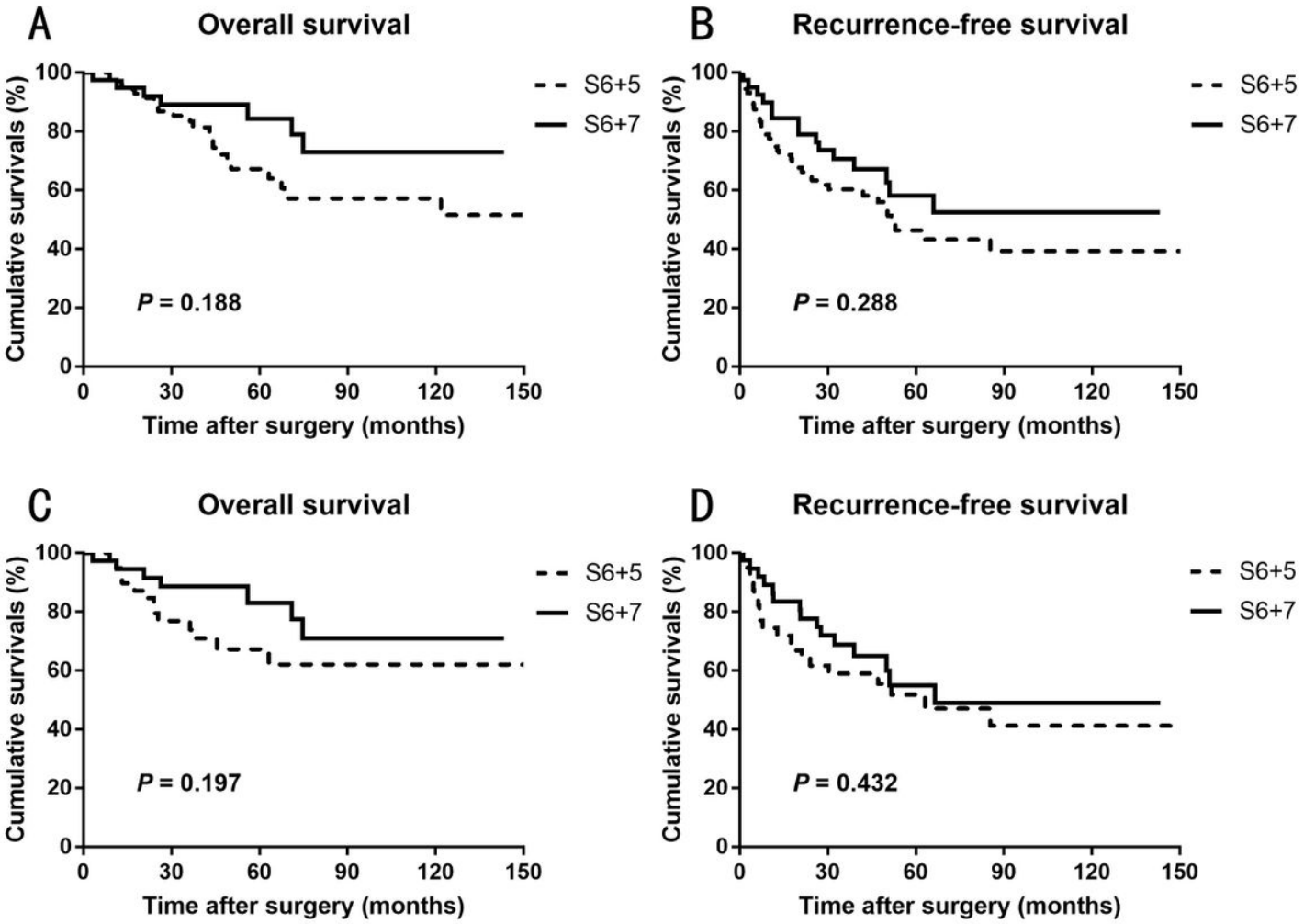

Figure 2

Kaplan-Meier curves of survival outcomes after hepatectomy of segment 6 hepatocellular carcinoma. (A) overall survival (OS) and (B) recurrence-free survival (RFS) in overall cohorts. (C) OS and (D) RFS in matched cohorts by PSM