RESEARCH ARTICLE

Is Hepatectomy for Huge Hepatocellular Carcinoma (≥10cm in Diameter) Safe and Effective? A Single-center Experience

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Abstract

Background: This retrospective study aimed to validate the safety and effectiveness of hepatectomy for huge hepatocellular carcinoma (HCC). Materials and Methods: Data of patients who underwent hepatectomy for HCC between January 2006 and December 2012 were reviewed. The patients were divided into three groups: huge HCC(≥10cm in diameter), large HCC(≥5 but<10 cm in diameter) and small HCC(<5cm in diameter). Results: Characteristics of pre-operative patients in all three groups were homogeneously distributed except for alpha fetal protein (AFP)(p<0.001).The 30, 60, 90-day post-operative mortality rates were not different among the three groups (p=0.785, p=0.560, and p=0.549). Laboratory data at 1, 3, and 7 days after surgery also did not vary. The 5-year overall survival (OS) and 5-year disease-free survival (DFS) rates in the huge and large HCC groups were lower than that of the small HCC group (OS: 32.5% vs 36.3% *vs* 71.2%, p=0.000; DFS: 20.0% vs 24.8% *vs* 40.7%, p=0.039), but there was no difference between the huge and large HCC groups (OS: 32.5% *vs* 36.3%, p=0.667; DFS: 20.0% *vs* 24.8%, p=0.540). In multivariate analysis, five independent poor prognostic factors that affected OS were significantly associated with worse survival (p<0.05), namely, AFP level, macrovascular invasion, Edmondsone Steiner grade, surgical margin and Ishak score. AFP level, macrovascular invasion, microvascular invasion, and surgical margin influenced disease-free survival independently (p<0.05). Conclusions: The safety of hepatectomy for huge HCC is similar to that for large and small HCC; and this approach for huge HCC may achieve similar long-term survival and disease-free survival as for large HCC.

Keywords: Hepatocellular carcinoma - hepatectomy - safety - effectiveness - short-term results - long-term results

Asian Pac J Cancer Prev, **15 (17)**, 7069-7077

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide in men and the second most frequent cause of cancer death, with an annual incidence of 0.5 million worldwide. Half of these cases and deaths occur in China. (Jemal et al., 2011) The large population in China has partly caused the problem; and the problem is especially severe in the country's western region where socioeconomic development and healthcare services have lagged behind its eastern counterpart. Most healthcare system there is overburdened, and patients with HCC are not screened timely. As a result, patients are usually diagnosed to have huge or large HCC rather than small HCC when they come to the hospital.

Currently, the treatment options for HCC include liver resection, liver transplantation (orthotopic and live), regional ablative therapies, such radiofrequency or cryoablation, local transarterial infusion/embolizaton, external-beam radiotherapy, and systemic chemotherapy. Historically, the only proven potentially curative treatment for HCC is surgical treatment-either hepatic resection or liver transplantation. (Truty et al., 2010) Liver transplantation is considered in patients with small, early lesions and cirrhosis who are eligible according to the previously established Milan criteria or even the new extended University of California, San Francisco, guidelines because survival rates are low and recurrence rates are high in patients with much larger lesions (Mazzaferro et al., 1996; Ringe et al., 1989). Radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) have been proved to be effective only with smaller tumors (Lencioni, 2010), and transarterial chemoembo-lization (TACE) has not been considered as a curative modality but one of only local control (Abdalla et al., 2008). External-beam radiotherapy can offer advanced tumor downstaging and conversion to resectable or transplantable (Hoffe et al., 2010). Similarly, the current Barcelona Clinic Liver Cancer (BCLC) staging system excludes patients with HCC (≥10cm in diameter) from chemoembolization, and instead restricts them to sorafenib and supportive care (Forner et al., 2010). All these findings suggest that neither liver transplantation nor nonsurgical treatment are effective to treat HCC (>10cm in diameter),

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and that liver resection can be used as a first-line treatment for tumor of this size level.

Larger tumor size has been found to directly correlate with vascular invasion, which usually leads to poor outcomes (Jonas et al., 2001; Pawlik et al., 2005a). In addition, the considerable technical challenges associated with major resection of these massive cancers are well demonstrated and are correlated with higher perioperative complications such as heavy bleeding and tumor rupture. As a result, patients with larger tumors often refuse to accept aggressive curative therapy, and certain groups have even advocated that large tumor size (5 cm) be a contraindication to liver resection (Bruix et al., 2002). Nevertheless , tumor size alone should not be a contraindication to liver resection because hepatectomy is the only viable option for patients with large HCC (Truty et al., 2010). Recent study (Shrager et al., 2013) has revealed that patients with HCC (>10cm) achieved 3- and 5-year survival rates of 55.8% and 37.2%, respectively. This encourages us to continue the study on the rationality of liver resection for HCC (>10cm).

As a matter of fact, the aim of treatment many people ignore is to improve lifespan and thus, the course of treatment selection is to balance risks and benefits. We hypothesized that surgical resection for HCC (≥10cm in diameter) is safe and effective and that the first-line treatment for huge HCC is surgical resection in selected patients. To test this hypothesis, we conducted this study to evaluate the safety and efficacy of liver resection for HCC larger than 10cm in diameter compared to HCC less than 10cm in diameter based on short-term and long-term outcomes.

Materials and Methods

Patient population

We prospectively collected and retrospectively reviewed all partial hepatectomies with curative intent for primary HCC performed at the Liver Surgical Center of West China Hospital, Sichuan University between 1 January, 2006 to 31 December, 2012. The main inclusion criterion for our study was pathological verification of an HCC. Candidates eligible for partial hepatectomy were those whose radiologically evident diseased part of liver could be completely removed while retaining a sufficient future liver remnant (FLR) (Abdalla et al., 2006). Patient outcomes were followed until May 1, 2013.

Of the 1084 patients enrolled in the study, 876 were men and 208 were women ranging from 9 to 79 years. All patients were followed up until May 1, 2013 or until death if it occurred. The patients were categorized into three groups: patients with tumors ≥10 cm in greatest diameter (huge HCC; n=266), patients with tumors ≥5 but < 10 cm (large HCC; n=515), and patients with tumors<5cm (small HCC; n=303).

The study was approved by the Ethics Committee of West China Hospital of Sichuan University in accordance with the Helsinki Declaration of 1975.

Preoperative assessment

The diagnosis of HCC was based on the diagnostic criteria for HCC used by EASL (Bruix et al., 2001): 1) radiological criterion: at least two radiologic techniques including ultrasound, contrast-enhanced dynamic computed tomography (CT), magnetic resonance imaging (MRI), and hepatic arterial angiography demonstrating the concordant classical dynamic radiologic features of HCC; 2) combined criteria: an imaging technique showing typical features of HCC together with an increased serum alpha fetoprotein (AFP)level over 400 ng/mL; or 3) histopathologic identification by ultrasound-guided biopsy.

The preoperative work-up included blood tests, including AFP and other clinical data needed to calculate the CHILD score and the MELD score, and dual radiology modalities (thoracoabdominal computed tomography (CT) and liver magnetic resonance imaging (MRI) with liver volumetry. In addition, the indocyanine green retention (ICGR) test at 15 min was used to assess the liver functional reserve.

The surgical indications for all HCC patients were as follows:

1) Absence of tumor thrombosis in portal vein trunk or inferior vena cava, and attaining an en bloc removal of the invaded vessel and tumors with a competent tumor-free margin of 5 mm;

2) Patients with liver function of CHILD score A or B , a MELD score less than 9 points, and liver function reserve test indocyanine green clearance test (ICG) retention rate of less than 15% at 15 min;

3) Absence of extrahepatic metastasis;

4) No previous or simultaneous malignancies; and

5) No absolute contraindications for liver surgery by multidisciplinary evaluation.

In addition, a remnant liver volume of at least 40 % was suitable for HCC≥5cm. Patients with a liver remnant less than 40% or severe cirrhosis with CHILD C grade and MELD score more than 9 points were excluded from hepatectomy.

Surgical procedure

For this study, our standard skin incision for HCC was a right or bi-lateral subcostal incision (known as Benz incision). Hepatectomy included local hepatectomy, hemihepatectomy (right or left) and extended (right or left) hepatectomy. Thorough intraoperative ultrasonography (IOUS) was routinely performed to better confirm the number, size, and location of tumors as well as for intrahepatic vascular mapping of thrombosis and feeding vessels of the tumor which could determine the line of parenchymal transection. IOUS could also spot new metastatic lesions. After tumor data were confirmed, a hepatectomy with at least 5mm tumor-free margin was performed on the liver surface accordingly by the cavitron ultrasonic aspiration (CUSA; Valleylab, Boulder, Colorado) or water dissector (JET2; ERBE, Tuebingen, Germany). To control bleeding during the operation, dipolar electric coagulation, argon unit, suturing, and titanium were used. To further reduce bleeding, low central venous pressure (CVP<5cmH20) anesthesia was routinely practiced by restricting intravenous fluid administration (Melendez et al., 1998). Vascular clamping

methods, including Pringle maneuver, selective hepatic vascular occlusion, and total vascular isolation (TVI), were performed when necessary. In our study, resection of <3, 3-4, and >4 liver segments was defined for minor, major, and extended hepatectomy.

Postoperative Evaluation

Tumor diagnosis, differentiation, satellites, and vascular invasion as well as tumor involvement of the resection margin were confirmed by a macroscopical and histological examination of resected specimens. Edmondson-Steiner criteria were used to assess tumor cell differentiation (Edmondson et al., 1954) and the criteria by Ishak et al to grade fibrosis or cirrhosis of nontumoral liver parenchyma (Ishak et al., 1995). Postoperative mortality (short-outcomes) was assessed at 30, 60, and 90 days after surgery. Surgical complication rate and laboratory data at 1, 3, and 7 days after surgery were also evaluated. Surgical complications were identified according to the Clavien classification of post-operative complications (Dindo et al., 2004).

Follow-up

All patients were followed up by the surgical team. The first endpoint was overall five-year survival, and the secondary endpoints were five-year disease-free survival and recurrence rate. The final follow-up evaluation was conducted on May 1, 2013. The surveillant outcomes were acquired by telephone interviews or the attending physicians. Follow-up included physical examination, laboratory tests with serum AFP assays, serological liver function tests, and conventional radiography of the chest and abdomen including liver ultrasonography, CT scan, and MRI. The first examination of radiography was performed about 1 month after surgery and repeated about every 3 to 4 months in the first year and every 6 months in subsequent years if no recurrence was detected. When serum AFP level increased abnormally, the patients should under abdominal ultrasonography, CT scan, and MRI; and if intrahepatic recurrence was not identified, a chest CT and bone scintigraphy were performed. Once a diagnosis of recurrence was confirmed, treatment strategies were proposed based on the decision of a multidisciplinary team consisting of surgeons, pathologists, and radiologists; however, priority was given to the patient's opinion.

Statistical analysis

Patients data of the three aforementioned groups, including 30-, 60-, and 90-day postoperative mortality, disease-free survival rate, over-all survival rate, and clinicopathological and follow-up data were compared. The follow-up time was defined as the number of months from surgical treatment of HCC to death, or to the last contact with the patient. Continuous data were expressed as a mean±standard deviation (SD). The X^2 test was used for categorical variables and the Student's t test for continuous variables. The data of patients lost to follow-up were treated as censored. Overall and disease-free survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. All variables with a P value <0.05 by univariate analysis were entered for multivariate analysis. Results of multivariate analysis were presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI). All statistical tests were two-sided, and the cut-off for statistically significant outcome was a p value less than 0.05. The statistical analyses of the data were performed using the SPSS 18.0 statistical software (SPSS Company, Chicago, IL).

Results

At the time of final analysis, patients lost to follow-up were censored at the time of the last visit. About 123 patients (11.3%) were lost to follow-up.

Patient Characteristics

In our study, 303 patients with small HCC, 515 with large HCC, and 266 with huge HCC underwent liver resection. To determine whether the clinical characteristics of these patients changed with tumor size, we compared the clinicopathological findings among the three groups (Table 1). Except for serum AFP, which was higher significantly in the large group and huge group (54685ug/ml vs 4868 ug/ml vs 920 ug/ml; p =0.00), no other significant differences were found among the three groups regarding preoperative parameters including age, gender, HBV, pain symptoms, Child classification, serum albumin, serum total bilirubin, prothrombin time (PT), international normalized ration (INR), platelets (PLT), and concomitant diseases. Comparison of postoperative parameters and pathological data showed that except for hospital stay (p=0.288), all parameters were found different among the three groups. However, only surgical margin and blood loss were significant difference between the large HCC and huge HCC groups (p<0.05) (Table 2).

Short-term Results

No significant differences among the three groups were observed regarding 30-, 60-, and 90-day postoperative mortality; at 30 days, the mortality rate was 0.38%, 0.58%, and 0.66% for small, large, and huge HCC groups, respectively (p=0.895); at 60 days, the mortality rate was 0.75%, 1.36%, and 1.32% for small, large, and huge HCC groups, respectively (p=0.742); and at 90 days, the mortality rate was 1.51%, 2.53%, and 2.65% for small, large, and huge HCC groups, respectively (p=0.602). There were not differences in surgical complication rate among the three groups (0.38% vs 0.19 vs 0.33, p=0.881) (Table 3). Meanwhile, laboratory data at 1, 3, and 7 days after surgery did not differ among the three groups, either (Table 4). Among patients with or without fibrosis or cirhosis who underwent major (3-4 segments) and extended hepatectomy (>4segments), 90-day mortality of major hepatectomy did not differ (p=0.787), but fibrosis or cirrhosis did affect the outcome of patients undergoing extended hepatectomy (p=0.045) (Table 5).

Long-term Results

The overall survival at 1, 3, and 5 years was 88.2%, 80.0%, and 71.2% for small group, respectively; 70.9%, 50.2%, and 36.3% for large group, respectively; and 64.4%, 45%, and 32.5% for huge group, respectively.

Table 1. Preoperative Clinico-Demographic Data About Three Groups (n=1084)

Varible	Small(n=266)	Large(n=515)	Huge(n=303)	*p* value
Age(years)	50.27±11.55	50.07±13.15	85.86±610.23	0.246
AFP*	920.73±2679.40	4868.51±13379.56	54685.02±159902.00	<0.001
Serum albumin	41.06±3.30	41.12±4.10	41.20±4.22	0.915
Serum total bilirubin	16.21±7.39	16.97±15.54	15.91±6.34	0.435
INR**	1.09±0.11	1.09±0.09	1.09±0.11	0.807
PLT***	138.18±57.60	136.93±59.86	136.77±45.80	0.941
Gender				0.489
male	242	424	211	
female	62	91	55	
Concomitant diseases				0.923
hypertension(A)	15	25	14	
diabetes(B)	28	39	25	
A+B	4	8	2	
Hbs-Ag(+)				0.347
absent	51	107	52	
present	253	408	214	
Pain symptoms				0.293
absent	171	282	133	
present	133	233	133	
Child-pugh class				0.673
A	288	480	250	
B	16	35	16	

*AFP: Alpha fetal protein,**INR: international normalized ratio,***PLT:Platelets

Table 2. Postoperative and Pathological Data(n=1084)

Variable	Small(n=266)	Large(n=515)	Huge(n=303)	*P*	*P* (huge vs large)
bilateral lesions				0.001	0.488
absent	300	483	246		
present	4	32	20		
vascular invasion				<0.001	0.573
micro-	245	307	153		
macro-	59	208	113		
Edmondson-Steiner				0.01	0.115
poor	73	162	99		
moderate	186	292	130		
well	44	61	37		
tumor capsule				<0.001	0.502
absent	284	360	205		
present	20	155	98		
extent of hepatectomy			<0.001	0.096	
<3 segment	169	39	12		
3-4 segment	131	395	200		
>4 segment	0	81	54		
other organ invasion			<0.001	0.061	
absent	284	436	211		
present	19	79	55		
surgical margin				<0.001	0.004
<1 cm	252	455	252		
>1 cm	52	60	14		
Ishak score				<0.001	0.53
0-2	30	77	43		
3-4	237	297	160		
5-6	37	141	63		
blood loss	411.60±161.69	543.20±255.24	672.70±362.56	<0.001	<0.001
RBC*	0.05±0.38	0.36±0.93	0.67±1.41	<0.001	<0.001
plasma	12.01±97.64	38.06±145.05	46.99±153.73	0.005	0.401
hospital stay	9.33±5.05	9.54±3.59	9.92±5.41	0.288	0.842

*RBC, Red blood cell

Among them, the 5-year overall survival rate of the small group was almost two folds better than that of the other two groups (p=0.000). However, tumor size was not associated with1, 3, and 5 year overall survival rates between large and huge groups (p=0.082, p=0.352, and p=0.667) (Figure A-D). During the follow-up period, cancer recurred in some patients only, including metastatic disease, locoregional recurrence, or new intrahepatic malignancy. The disease-free survival rates at 1, 3, and 5 years were as follows: 62.5%, 50.3%, and 40.7% for

Table 3. Short-term outcomes

Variable	Small (n=266)	Large(n=515)	Huge (n=303)	*P* value	*P* (huge vs large)
30-day mortality,n(%)	1 (0.38)	3 (0.58)	2 (0.66)	0.895	0.891
60-day mortality,n(%)	2 (0.75)	7 (1.36)	4 (1.32)	0.742	0.963
90-day mortality,n(%)	4 (1.51)	13 (2.53)	8 (2.65)	0.602	0.917
complication rate,n(%)	88 (33.08)	195 (37.86)	130 (42.90)	0.055	0.154

Table 4. Laboratory Data of Postoperative 1,3,7-Day

Variable	Small(n=266)	Large(n=515)	Huge(n=303)	*P* value
Postoperative 1-day				
TB*	26.46±16.64	27.40±14.59	27.59±13.37	0.617
ALT**	424.27±404.70	464.68±430.72	503.87±524.94	0.108
PT***	15.06±2.30	15.20±2.21	15.41±2.30	0.207
Postoperative 3-day				
TB	29.95±15.16	30.09±20.28	31.43±20.18	0.539
ALT	327.14±312.72	333.05±375.55	334.29±302.27	0.956
PT	14.09±1.95	14.16±1.55	14.50±1.79	0.069
Postoperative 7-day				
TB	24.52±19.35	25.25±17.05	26.81±17.78	0.41
ALT	113.45±122.36	124.50±120.05	135.49±145.43	0.211
PT	13.00±2.26	13.30±2.12	13.47±2.12	0.103

*TB, total bilirubin, **ALT, Alanine transaminase, ***PT, Prothrombin time

Table 5. 90-day Mortality and 5-year Survival Rate according to Extent of Liver Resection and Underlying Chronic Liver Disease

Extent of liver resection	Fibrosis/cirhosis absent	present	*P* value
major hepatectomy(n=634)	35%	65%	
90-day mortality rate(%)	2	2.5	0.787
5-years survival rate(%)	41	37	0.502
extented hepatectomy(n=169)	38%	62%	
90-day mortality rate(%)	1	6	0.045
5-years survival rate(%)	35	21	0.009

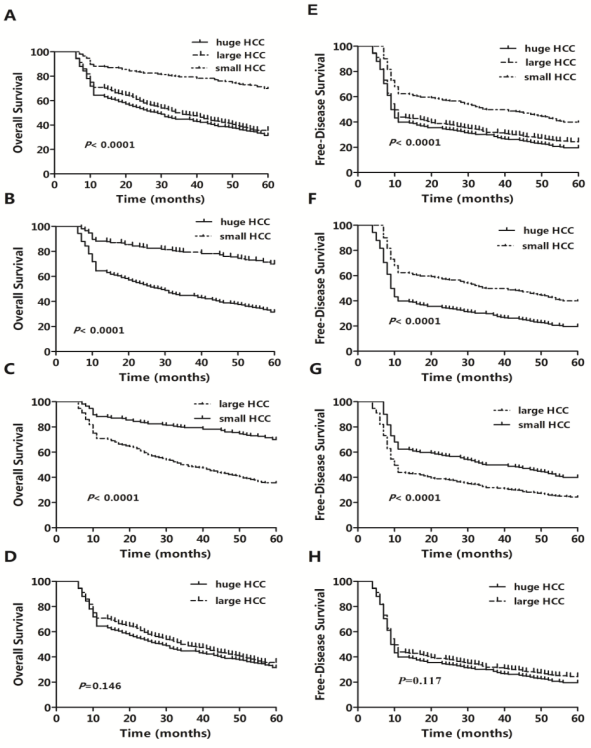

Figure 1. A-D Indicate Overall-Survival after Hepatectomy for HCC of three Groups; E-H Indicate Free-Disease Survival for HCC of Three Groups.

Table 6. Predictors of Overall Survival after Hepatectomy for HCC (N=1084)

Variable	Survival(%)	Univariate Analysis *P*	Multivariate Analysis *P*	HR	95%CI
Age(years)		0.661			
<60	39.59				
≥60	36.71				
Gender		0.884			
male	38.08				
female	39.13				
AFP(ng/ml)		0.003	0.002	1.58	1.17-2.64
>1000	23.14				
≤1000	43.81				
HBV		0.703			
absent	36.92				
present	34.88				
Pain symptoms		0.912			
absent	36.77				
present	36.97				
Serum total bilirubin		0.896			
≤0.7mg	34				
>0.7mg	33.24				
Serum albumin		0.763			
≤3.9g	35.63				
>3.9g	37.27				
Platelets		0.698			
≤100	36.89				
>100	38.84				
Surgical margin		0.005	0.002	2.04	1.48-2.83
>1 cm	44.82				
<1 cm	25.98				
Transfusion		0.009	NS		
absent	24.86				
present	42.59				
Vascular invasion		0.006	0.008	2.28	1.43-3.01
micro-	25.9				
macro-	43.97				
Extent of hepatectomy			0.547		
<3 segment	36.63				
3-4 segment	35.64				
>4 segment	33.78				
Multiple lesions		0.476			
absent	39.41				
present	36.7				
Tumor capsule		0.369			
absent	39.3				
infilitration	35.26				
Other organ invasion		0.01	NS		
absent	42.13				
present	26.08				
Edmondson-Steiner		0.003	0.028	1.27	1.13-2.32
poor	24.48				
moderate	36.53				
well	45.52				
Ishak score		0.014	0.019	1.46	1.12-2.49
0-2	44.75				
3-4	37.24				
5-6	28.59				

small group, respectively; 44.0%, 32.1%, and 24.8% for large group, respectively; and 39.7%, 30.0%, and 20.0% for huge group, respectively. Likewise, the 5-year disease-free survival analysis indicated that small group was better than other two groups (p=0.039) whi le 1, 3, and 5 years DFS rates did not differ between large and

Table 7. Predictors of Free-Disease Survival after Hepatectomy for HCC (N=1084)

Variable	Survival(%)	Univariate Analysis *P*	Multivariate Analysis *P*	HR	95%CI
Age(years)		0.584			
<60	17.52				
≥60	14.43				
Gender		0.832			
male	15.89				
female	16.41				
AFP(ng/ml)		0.005	0.013	1.47	1.05-2.38
>1000	25.38				
≤1000	10.07				
HBV		0.765			
absent	12.11				
present	14.38				
Pain symptoms		0.964			
absent	14.21				
present	14.48				
Serum total bilirubin		0.991			
≤0.7mg	10.93				
>0.7mg	11.03				
Serum albumin		0.792			
≤3.9g	14.85				
>3.9g	13.39				
Platelets		0.627			
≤100	16.78				
>100	14.68				
Surgical margin		0.007	0.011	1.92	1.17-2.63
>1 cm	10.74				
<1 cm	24.29				
Transfusion		0.535			
absent	12.15				
present	15.76				
Vascular invasion		0.005	0.006	2.08	1.23-2.94
micro-	10.64				
macro-	23.94				
Extent of hepatectomy			0.568		
<3 segment	12.4				
3-4 segment	14.36				
>4 segment	15.98				
Multiple lesions		0.526			
absent	13.89				
present	16.61				
Tumor capsule		0.315			
absent	12.88				
infilitration	17.25				
Other organ invasion		0.016	NS		
absent	11.19				
present	22.46				
Edmondson-Steiner		0.023	NS		
poor	22.76				
moderate	16.9				
well	10.39				
Ishak score		0.026	NS		
0-2	11.37				
3-4	17.18				
5-6	23.5				

huge groups (p=0.809, p=0.178, and p=0.540) (Figure E-H). Among patients with or without fibrosis or cirrhosis who underwent major (3-4segment) and extended hepatectomy (>4segment), overall survival did not differ in accordance with major liver resection (p=0.502;), but fibrosis or cirrhosis resulted the worse outcome of patients undergoing extended hepatectomy (p=0.009) (Table 5).

Prognostic Factors Affecting OS and DFS of patients having HCC

Univariate analysis identified AFP, tumor size, macrovascular invasion, microvascular invasion, other organ invasion, surgical margin, Edmondson-Steiner grade, and fibrosis/cirrhosis as factors predictive for both overall and disease-free survival of HCC; OS was also associated with intraoperative transfusion. Other variables evaluated were not prognostic. In Cox regression test, AFP (hazard ratio 1.58, 95%CI: 1.17-2.64, p=0.002), vascular invasion (hazard ratio 2.28, 95%CI: 1.43-3.01, p=0.008), surgical margin (hazard ratio2.04, 95%CI: 1.48-2.83, p=0.002), Edmondson-Steiner grade (hazard ratio1.27, 95%CI: 1.13-2.32, p=0.028), and Ishak score (hazard ratio 1.46, 95%CI: 1.12-2.49, p=0.019) were of independent prognostic significance for overall survival (Table 6), and AFP (hazard ratio1.47, 95%CI: 1.05-2.38, p=0.013), vascular invasion (hazard ratio2.08, 95%CI: 1.23-2.94, p=0.006), and surgical margin (hazard ratio1.92, 95%CI: 1.17-2.63, p=0.011) for disease-free survival (Table 7). The analysis revealed three poor independent prognostic factors in recurrence-free survival.

Discussion

Tumor size is one of the important factors of tumor staging systems in hepatocellular carcinoma and criteria in liver transplantation. Many studies from the 1990s reported that patients with HCC ≥10 cm had poor outcome after liver resection (Lai et al., 1990; Belghiti et al., 1991; Lee et al., 1998). As a result, the BCLC staging system, the best staging system and treatment algorithm for HCC by the European Association for the Study of Liver Disease (EASL), and the American Association for the Study of Liver Disease (AASLD) (Bruix et al., 2001; Bruix et al., 2011) the mainstay treatment for HCC ≥10 cm was TACE (Llovet et al., 1999). With these dissatisfactory long-term results, validity about resection of such huge tumors will remain controversial. From an ethical perspective, every patient should get the appropriate treatment based on the state of their illnesses. Fortunately, recent study by Pierre A et al (Allemann et al., 2013) suggests that surgical outcome did not differ for HCC≥10cm and HCC<10cm, even if more complex surgery was performed in huge HCC. Tumor size alone did not correlate with survival (Liau et al., 2005; Pawlik et al., 2005b; Shah et al., 2007; Young et al., 2007), and so tumor size per se should not be used as the sole criterion to exclude patients from partial hepatectomy who have an otherwise resectable tumor (Pawlik et al., 2005b). Therefore, it is necessary to update the therapeutic recommendations for patients with HCC≥10cm.

The long-term and short-term outcomes of patients with HCC underwent liver resection have been our focus of research. To this day, patients with HCC ≥10 cm have generally received passive treatment instead of aggressive treatment (Llovet et al., 1999; Bruix et al., 2004; Forner et al., 2010). Nevertheless, the expansion of indication for liver resection for HCC has increased the proportion of patients who are ready to receive aggressive treatment. Currently, research results support that outcomes of liver resection for HCC≤5cm were better than HCC>5cm, including large and huge HCC (Llovet et al., 1999), which has left liver resection both for HCC>5cm, and for HCC≥10cm in particular, controversial. Unfortunately,

information on huge HCC has been little, which makes it difficult for us to conclude whether liver resection for HCC ≥10cm is an optimal treatment.

Because surgery cannot benefit all patients, safety is a factor affecting the reluctance to offer aggressive surgical resection to patients with HCC ≥10 cm. Previous studies reported that postoperative liver failure occurs in about 3-10 % of patients after resection for HCC (Kubo et al., 2004; Osada et al., 2004). Liver failure is the most common cause of mortality after liver resection in patients with cirrhotic liver (Wu et al., 1996). Biological and morphological assessments are the two important factors influencing liver resection safety. Normal liver function including liver functional reserve and sufficient remnant liver volume are the basic conditions of patients who undergo the liver resection. Like other studies (Lau et al., 1997; Ishizawa et al., 2008; Uchiyama et al., 2008; Allemann et al., 2013), our results also suggest that functional reserve of the remnant liver parenchyma, more than size of the lesion, may be an important factor in candidates for liver resection. To assess and improve selection criteria, our patients underwent an elaborate preoperative assessment that included indocyanine green retention time and liver volumetric evaluation.

The ICG clearance test is widely used to predict the risk factor of postoperative liver failure in patients with cirrhosis and to reflect the liver functional reserve (Imamura et al., 2003; Lau et al., 1997). An ICG retention at 15 minutes of less than 14% was found to be the safety limit of major hepatic resection (Lau et al., 1997). Like biological assessment, morphological assessment is also important. Even if the patient has an ICG retention value of less than 14% at 15 minutes, liver failure would still occur if the future liver remnant (FLR) is not adequate. In resection of huge HCC, a large amount of liver parenchyma has to be removed. The volume and function of the FLR closely correlate with post-operation liver failure. Adequate FLR volume after liver resection likely conduces to optimized selection of surgical candidates, particularly in the group of patients with limited hepatic functional reserve. A recent study showed that liver resection can be performed safely if standardized FLR is >20 % in patients with normal liver and >40 % in patients with liver cirrhosis (Kubota et al., 1997; Azoulay et al., 2000; Zorzi et al., 2007). The ratio of 30-, 60-, and 90-day post-operative mortality and surgical complication rate in our study did not differ significantly among the three groups, suggesting that LR in patients with huge HCC was as safe as LR for patients with large and small HCC. Among the three groups, post-operation parameters that reflect liver function, including prothrombin time activity, ALT, and T-Bil, did not differ significantly, either. These findings also indicate that current management practices for surgical complications have improved and helped prevent operative mortality. A multicentered, retrospective cohort of patients resected for HCC indicate that 90-day mortality rates was 2.7% for HCC>5cm (Torzilli et al., 2013). This finding confirmed our study result that partial hepatectomy in patients with huge HCC was safe in the short term. By refining the criteria in our study, including ICG <14%, FLR >40%, strengthening the management of hepatocellular carcinoma and improving the surgical techniques, deaths associated with liver resection decreased significantly. Most patients in our study were graded as CHILD A and a few as CHILD B, which also ensured operation safety.

Comparing the three groups, we observed that overall survival in huge and large HCC groups were poorer than that of small group, but it did not differ between huge and large HCC groups. At first glance, our study suggested that the 1-, 3-, and 5-year OS rates in huge group were 64.4%, 45.0%, and 32.5%, respectively. This result was better than most previous studies (Wang et al., 2010b). Although some studies (Shah et al., 2007; Wang et al., 2010a) show satisfactory long-term outcomes with 5-year survival rates being reported to be as high as 50%, outcomes varied by studies, and are even contradictory, with 5-year survival rates in some study lower than 25 % (Chen et al., 2006; Mok et al., 2003; Wang et al., 2010b; Zhou et al., 2012). In the present study, the survival rate was significantly poorer in the large and huge HCC groups. This may be caused by the fact that our patient population in the large and huge HCC groups included more with cirrhosis or CHILD B diseases. As observed in many other series (Ng et al., 2005; Pandey et al., 2007; Wang et al., 2010a; Wang et al., 2010b), the presence of cirrhosis seems to influence negatively overall survival, regardless of the lesion size. Subgroup analysis showed that patients with fibrosis or cirrhosis who underwent extended hepatectomy resulted in poorer short-term and long-term survival than patients without fibrosis or cirrhosis, but major hepatectomy did not associate with outcomes. Patients who had underlying liver disease and received extended hepatectomy remain superior to patients receiving nonsurgical treatments (e.g., transarterial chemoembolization) (Ruzzenente et al., 2009; Sotiropoulos et al., 2009). These findings emphasize the importance of patient selection for liver resection.

With regard to survival rate, surgical treatments outdo non-surgical treatment in most studies. Huang et al reported that patients with advanced-stage HCC who underwent nonsurgical therapies did not survive longer than 2 years, with 1-and 2-years OS rates being 29% and 0%, respectively (Huang et al., 2012). In previous reports, TACE for HCC ≥10 cm resulted in a 5-year survival rate of <10% (Huang et al., 2006; Poon et al., 2000). Yamashita et al (Yamashita et al., 2011) reported that the 1-year survival rate of the non-surgical treatment for HCC ≥10 cm was 17%, and all patients died within 2 years of treatment. Poon et al (Poon et al., 2000) analyzed a cohort of 384 HCC patients receiving TACE as their primary treatment, and reported a 3-year survival of 20%; and the median survival their subgroup of 117 patients with tumor size >10 cm was only 5.6 months, not as good as the 21.7 months as seen in our cohort. Besides, two prospective randomized trials revealed that TACE is superior to supportive care for large (>5 cm) and/or multinodular tumors, recording 3-year survival rates in the respective chemoembolization arms of 26% and 29% (Llovet et al., 2002; Lo et al., 2002). This result is far poorer than the 3-year survival rate of our surgical cohort, and these patients had smaller tumors size than those registered in our study. Finally, a propensity score analysis comparing TACE to resection

for tumors outside of the Milan criteria found TACE to be clearly poor in terms of survival (29% vs. 68% at 3 years, $p<0.001$) (Hsu et al., 2012). This result strongly suggests that patients in receivng liver resection can benefit from this surgical treatment. In addition, our study showed no difference in prognostic factors between huge and large HCC, which indicates that huge HCC, like large HCC, should be the candidate for liver resection.

Nevertheless, long-term outcomes such as the DFS rates were not as good as the OS rates. The 1-, 3- and 5-year disease-free survival rates in the three groups were 62.5%, 50.3%, and 40.7% for small group, respectively; 44.0%, 32.1%, and 24.8% for large group, respectively; and 39.7%, 30.0%, and 20.0% for huge group, respectively. No difference was found between huge and large HCC groups. According to a meta analysis (Tsoulfas et al., 2012), 5-year DFS rates ranged between 15% and 35%. Our 5-year DFS rate of 20% seems in line with them, but controversy seems to linger.

In the present study, survival was poorer in the huge and large HCC group than in the small HCC group. Multivariate analysis with the Cox proportional hazard model revealed that level of AFP, major vascular invasion, microvascular invasion, and surgical margin were independent predictors of inferior survival after liver resection. It is generally accepted that the less than satisfactory long-term results following resection of huge HCC is not due to the tumor size, but rather a result of the unfavorable pathological features with which large or huge tumor size is associated (Tsai et al., 2000; Zhou et al., 2001; Schwartz, 2004; Ng et al., 2005; Pawlik et al., 2005a). Hence, the surgeon should accept the challenge to perform surgical treatment as possible in order to improve the outcomes of patients with huge HCC.

Our study has two limitations. First, our study may have selective bias because it was single-centered rather than multi-centered. As a matter of fact, enters vary in methods to assess respectability and select surgical candidates, and this study represents the experience of a single specialized center only, thus leading to selective bias. Second, we analysed patients data retrospectively, but the number of patients in our study has been the relatively bigger reports on huge HCC. This limitation seems difficult to deal with, because liver resection for HCC is used less frequently than before. However, except for OLT and interventional radiology for small lesions, the number of patients with huge HCC recommended for liver resection may be increasing.

In conclusion, tumor size itself does not appear to be a significant contraindication to liver resection, both major and extended hepatectomy, when the patients are appropriately selected. Our results reveal that the safety of liver resection in huge HCC is similar to that in large and small HCC, and that this radical surgical approach may achieve similar long-term survival and disease-free survival to the treatment of large HCC.

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