

Surgical Resection of Centrally Located Large Hepatocellular Carcinoma

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Background: Centrally located large hepatocellular carcinoma (HCC) is a difficult issue in surgery. These HCCs can be treated by hemi-/extended or central hepatectomies. The aim of this study was to analyze the results of hemi-/extended and central hepatectomies.

Methods: One hundred and four patients with centrally-located large tumors were retrospectively reviewed. Patients were divided into group 1 (n = 41) with hemi-/extended hepatectomies, and group 2 (n = 63) with central hepatectomies. Characteristics were analyzed between groups and survival rates were calculated.

Results: Parenchyma resection was limited in group 2. The resection margin in 92.6% of group 2 patients was < 1 cm, compared with 78.9% of group 1 patients ($p = 0.056$). The 1- and 5-year disease-free survival rates were 50% and 38.9% for group 1, and 50% and 15% for group 2 ($p = 0.279$). The 1-, 5-year overall survival rates were 89.5% and 66.2% for group 1 and 87.5% and 53.1% for group 2 ($p = 0.786$). Cirrhosis, the preoperative aspartate aminotransferase (AST) level and lower resected liver weight were independent factors impairing survival.

Conclusion: Hemi-/extended and central hepatectomies have comparable complication rates and long-term survival rates for patients with centrally located large HCC. Cirrhosis, the AST level and resected liver weight were independent factors determining long-term survival.

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Key words: hepatocellular carcinoma, central hepatectomy, hemi-hepatectomy

Hepatocellular carcinoma (HCC) ranks as the fifth most common malignancy in the world.⁽¹⁾ In Taiwan, HCC is strongly associated with hepatitis B infection and cirrhosis, and it is the second leading cause of cancer-related death.⁽²⁾ Although several therapeutic modalities are applied to treat HCC, surgical resection is still the treatment of choice. With

recent improvements in surgical techniques and post-operative management, hospital morbidity ranges from 10 to 25% and hospital mortality has approached zero.⁽³⁻⁵⁾

Centrally located HCCs (segments 4, 5, 8) may require extensive resections because of their relationship to major vascular structures and their deep loca-

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tion. Traditionally, these HCCs are resected by right, left, extended right or extended left hepatectomies. Extended or anatomically systematic hepatectomy is recommended based on HCC spread via portal flow. However, these kinds of resections carry a risk of not only significant blood loss but also postoperative liver failure in patients with cirrhosis or poor liver functional reserve.^(6,7) Surgical morbidity and mortality rates can be as high as 30% and 5%, respectively.⁽⁸⁻¹⁰⁾

The treatment for centrally located large tumors is still in embarrassed circumstances. Radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) are less effective against tumors greater than 5 cm than smaller tumors and access is sometimes difficult because of tumor location and adjacent large vessels. Similarly, transarterial chemoembolization (TACE) for centrally located tumors can be difficult because of dual blood supply from the right and left hepatic artery branches.^(11,12) Large tumors are poor candidates for liver transplantation and criteria expansion beyond the Milan or University of California at San Francisco criteria is still under evaluation.^(13,14) Therefore, limited resection of the central segments remains the choice of treatment, especially, when the tumors are associated with underlying cirrhosis.

Previous reports show that central hepatectomy may achieve the same complication rates and overall survival rates as conventional major hepatectomies.^(15,16) However, most reported series included tumors of different sizes and etiologies. The role of surgical resection for centrally -located large HCC is not really clarified. Therefore, the aim of this study is to analyze the early and long- term results of patients with centrally located large HCC, treated with central hepatectomy, or hemi-/extended hepatectomy.

METHODS

Patients

From 1999 to 2005, 344 patients with large HCC (maximum diameter > 5 cm) underwent curative liver resections at Chang-Gung Memorial Hospital. Among them, 104 patients had centrally located tumors which involved segments 4, 5 or 8. (Fig. 1). These patients were divided in two groups. Group 1 (n = 41) had hemi- or extended

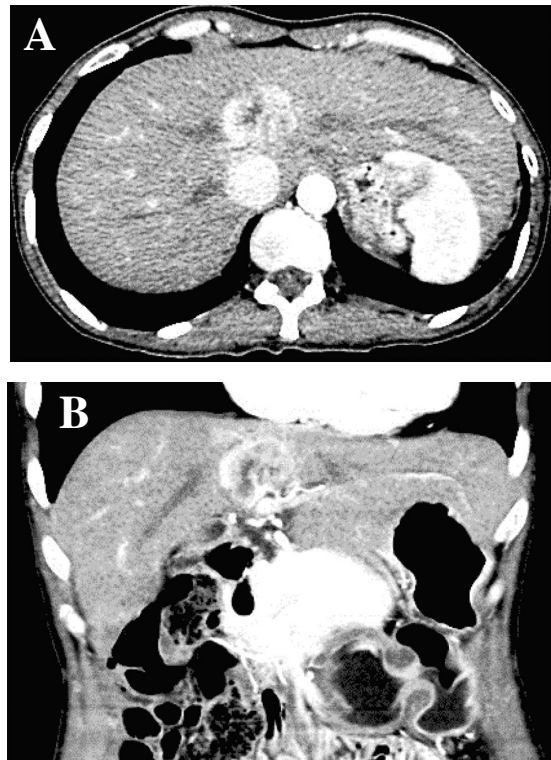


Fig. 1 Abdominal computed tomography images of a 6 cm tumor located in segment 4.

hepatectomies, and group 2 (n = 63) received central hepatectomies. A central hepatectomy involved resection of Couinaud's segments 4, 5, and 8 (Fig. 2). A right hemihepatectomy included segments 5, 6, 7, and 8, a left hemihepatectomy, segments 2, 3, and 4, an extended right hepatectomy, segments 4, 5, 6, 7, and 8 and an extended left hepatectomy, segments 2, 3, 4, 5, and 8. The caudate lobe or segment 1 was resected together with the right or left lobe whenever indicated.

Hepatectomy

Our algorithm for selecting patients for hepatectomy was based on Makuuchi's criteria.⁽¹⁷⁾ Before surgery, quantitative liver function was evaluated by the indocyanine green retention rate at 15 minutes (ICG R₁₅). The extent of liver resection was assessed according to the ICG R₁₅. The ICG R₁₅ was performed by injecting indocyanine green (0.5 mg/kg) into the patients' peripheral vein and blood samples (3 ml) were drawn from different sites before and fifteen minutes after ICG injection. Next, the ICG R₁₅

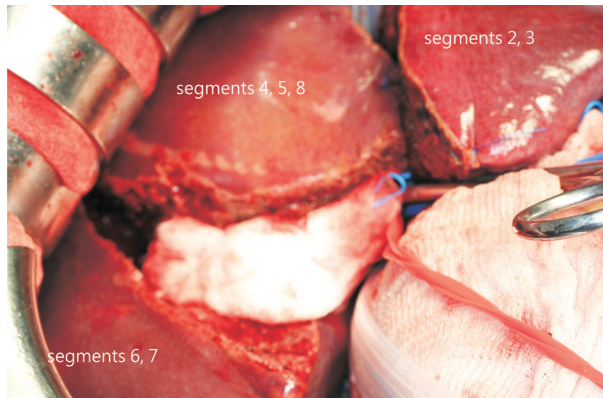


Fig. 2 Central hepatectomy involving segments 4, 5, and 8.

was calculated using spectrophotometric measurements. Both central hepatectomy and hemi or extended hepatectomy involve resection of more than three liver segments and therefore are considered major hepatectomies. The patients were carefully selected and according to our algorithm, and were included in the analysis if they had no ascites, a bilirubin level below twice the upper limit and an ICG clearance rate at 15 minutes of less than 20%. The selection criteria for central hepatectomy or hemi or extended hepatectomy was according to the surgeon's preference and the anatomic location of the tumor. For instance, if the tumor was located more on the right side and close to the right hepatic hilum, a right or extended right hepatectomy was preferred.

During surgery, the abdomen was explored through a subcostal incision with a midline xyphoid extension or through a Mercedes star incision. Intraoperative ultrasonography was routinely performed in order to confirm resectability and evaluate the relationship between the resection line and major vascular structures. Inflow control with the Pringle maneuver was commonly applied intermittently. Hemivascular control was performed in selected right or left hepatectomies. The liver parenchyma was divided according to the surgeon's preference using a clamp-crushing technique or ultrasonic dissector.

Follow up

Eighty patients were regularly followed up long-term at outpatient clinics and 16 patients were lost to follow-up. Follow-up examinations included liver

function tests, alpha-fetoprotein (AFP) levels and ultrasonography every 2-3 months. When tumor recurrence was suspected on ultrasonography, dynamic computed tomography (CT) or hepatic angiography was performed. Repeated hepatic resection, RFA or TACE were the treatments of choice in case of recurrence. The disease-free survival was calculated from the date of surgery to the date when disease recurrence was confirmed with abdominal CT. Overall survival was calculated from the day of surgery until the date of the last follow up.

Analysis of prognostic factors

To identify independent variables and compare the outcomes of patients who underwent central or conventional hepatectomies, clinical, surgical and pathological factors were analyzed. The clinical factors studied were gender, age, hepatitis B and C virus infections, alcohol abuse, liver function (including albumin level, total bilirubin level, transaminase levels, prothrombin time, platelet count, ICG R₁₅, Child-Pugh classification), and presence of esophageal varices and cirrhosis (defined by histopathological findings). The surgical factors included the method of hepatic resection (right/left hemi-/extended versus central hepatectomy), operative time, estimated blood loss and volume of intraoperative blood transfusions. The tumor factors included AFP level, tumor size, encapsulation of the tumor, presence of daughter nodules, vascular invasion, tumor differentiation (according to the Edmonson-Steiner grading system), surgical margin, TNM staging (according to the seventh edition of Cancer Staging Manual of the American Joint Committee on Cancer), and type and treatment of recurrence. The postoperative variables included length of hospital stay, hospital mortality (defined as mortality within 30 days), morbidity, presence of recurrence, and survival time.

Statistical analysis

Continuous data were expressed as median (interquartile range). Differences in continuous variables between the two treatment groups were assessed using the Mann-Whitney *U* test. Categorical variables were expressed as percentages and analyzed by the chi square or Fisher exact test, as appropriate. Survival curves were established by the Kaplan-Meier method. Factors with $p < 0.2$ in

univariate analyses were included in multivariable analysis. The final multivariable model was determined using Cox proportional hazard regression in order to identify independent predictors of disease free survival and overall survival. $p < 0.050$ was considered statistically significant. All statistical analyses were performed using SPSS® version 13.0 (SPSS, Chicago, Illinois, U.S.A.).

RESULTS

Patients

Group 1 and 2 patients had similar age and sex distributions. Fifteen patients (36.6%) in group 1 and thirty (47.6%) in group 2 had liver cirrhosis. Between the two groups, there were no significant differences in preoperative liver function, ICG and AFP values, or percentage of patients with liver cirrhosis and viral hepatitis. Three patients (7.3%) in group 1 and seven patients (11.1%) in group 2 had TACE before the operations. The clinical features of the two patient groups are shown in Table 1.

Differences in surgical variables between groups

The operative time and estimated blood loss were less in group 2 than group 1 (Table 2). The resected liver weight in group 2 was less than in group 1 as well ($p < 0.0001$). However, there were no differences in intraoperative blood transfusions. Hemivascular control was mostly performed in group 1 and the intermittent Pringle maneuver was commonly used in group 2. The inflow control time for group 2 was longer than for group 1 (62 vs. 38 minutes, $p = 0.012$).

Characteristics of the tumors

The tumors in group 2 were a mean 7.23 ± 2.34 cm in diameter, compared with 8.49 ± 3.47 cm in group 1 ($p = 0.047$). Because central hepatectomies mostly consisted of limited resections, the resection margin was less than 1 cm in 92.6% of patients in Group 2, compared with 78.9% in group 1 ($p = 0.056$). There were no differences in terms of daughter nodules, tumor differentiation and vascular invasion (Table 3).

Outcomes after surgery

The demands of the surgical technique for hemi-

Table 1. Characteristics of Patients with Extended/Hemi-Hepatectomy (Group 1) and Central Hepatectomy (Group 2)

	Group 1 (n = 41)	Group 2 (n = 63)	<i>p</i> value
Age (years)	61.00 (50.00-68.50)	58.00 (50.00-66.00)	0.601
Gender			0.872
Male	32 (78.0%)	50 (79.4%)	
Female	9 (22.0%)	13 (20.6%)	
Alcohol	8 (19.5%)	14 (22.2%)	0.741
HBs Ag +	27* (73.0%)	43 (68.3%)	0.619
Anti-HCV +	8* (21.6%)	15*** (24.6%)	0.737
Cirrhosis	15 (36.6%)	30 (47.6%)	0.267
History of EV bleeding	0	4 (6.3%)	0.152
Albumin (mg/dL)	4.20 (3.60-4.40)	4.05 (3.50-4.40)	0.882
Total bilirubin (mg/dL)	0.80 (0.70-1.30)	0.80 (0.70-1.00)	0.622
AST (U/dL)	49.00 (30.75-87.25)	38.00 (28.00-62.00)	0.196
ALT (U/dL)	49.00 (32.25-71.75)	41.00 (24.00-73.00)	0.492
PT (sec)	11.90 (11.23-12.50)	11.80 (11.20-12.40)	0.520
Platelet ($10^3/uL$)	179.50 (149.25-232.25)	198.00 (148.00-235.00)	0.748
Creatinine (mg/dL)	1.00 (0.88-1.10)	1.00 (0.90-1.18)	0.321
ICG retention rate ₁₅	8.14 (5.88-14.48)	8.57 (5.20-13.53)	0.723
Child-Pugh			0.737
A	37* (92.50%)	56 (88.9%)	
B	3* (7.5%)	7 (11.1%)	
Pre-op treatment	3 (7.3%)	7 (11.1%)	0.736

Variables are expressed as median (interquartile range) or as number (n) and percent (%).

Abbreviations: HBsAg: hepatitis B viral surface antigen; HCV: hepatitis C virus; EV: esophageal varices; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; ICG: indocyanine green.

Table 2. Surgical Variables for Group 1 and Group 2

	Group 1 (n = 41)	Group 2 (n = 63)	<i>p</i> value
Operative time (min)	316.00 (250.00-381.50)	230.00 (180.00-294.00)	< 0.0001
Estimated blood loss (mL)	750.00 (300.00-1700.00)	500 (100.00-750.00)	0.004
Intraoperative blood transfusion (mL)	600.00 (300.00-900.00)	600.00 (375.00-900.00)	0.899
Resected liver weight (g)	590.00 (367.50-995.00)	226.50 (178.75-363.75)	< 0.0001

Variables are expressed as median (interquartile range).

Table 3. Characteristics of Tumors in Group 1 and Group 2

	Group 1 (n = 41)	Group 2 (n = 63)	<i>p</i> value
AFP (ng/mL) (median)	82 (7.00-989.50)	58 (8.00-925.00)	0.760
Tumor size (cm)	8.00 (5.50-10.25)	6.50 (5.50-8.50)	0.156
Encapsulation	26 (63.4%)	45 (71.4%)	0.391
Daughter nodules	16 (39.0%)	20 (31.7%)	0.446
Vascular invasion			0.153
Macro	13 (31.7%)	12 (19.0%)	
Micro	6 (14.6%)	18 (28.6%)	
Absent	22 (53.7%)	33 (52.4%)	
Tumor differentiation			0.569
I-II	14 (34.1%)	25 (39.7%)	
III-IV	27 (65.9%)	38 (60.3%)	
Section margin			0.056
≤ 1 cm	30 (78.9%)	50 (92.6%)	
> 1 cm	8 (21.1%)	4 (7.4%)	
TNM			0.165
Stage 1	18 (43.9%)	24 (38.1%)	
Stage 2	2 (4.9%)	10 (15.9%)	
Stage 3a	8 (19.5%)	14 (22.2%)	
Stage 3b	13 (31.70%)	12 (19%)	
Stage 3c	0	3 (4.8%)	

Variables are expressed as median (interquartile range) or as number (n) and percent (%).

Abbreviation: AFP: alpha-fetoprotein.

/extended right or left hepatectomy and central hepatectomy were different. The preservation of liver volume after hemi-/extended hepatectomy and central hepatectomy was also totally different. To compare the outcomes of group 1 and 2 patients, the complication rates and survival rates of both groups were calculated. The mean postoperative hospital stay was 11.2 ± 4.2 and 10.0 ± 6.6 days for groups 1 and 2, respectively. Six complications occurred in group 1 and eight in group 2. These complications included immediate liver failure after hepatectomy ($n = 4$), biliary leakage ($n = 2$), upper gastrointestinal bleeding ($n = 2$), intraabdominal hematoma ($n = 2$), intraabdominal bleeding ($n = 1$), pneumonia ($n = 1$), intraabdominal abscess ($n = 1$) and surgical site infection ($n = 1$). Both groups had two patients with liver failure and one with biliary leakage. All of them died of subsequent multiorgan failure because the surgical complications were superimposed on infection. Overall hospital mortality was 7.3% for group 1 and 7.9% for group 2 (Table 4). After excluding patients with hospital mortality, the duration of follow-up ranged from 1.2 to 99.7 months with a median of 30.6 months. The survival rates for the two groups were calculated and the results showed that the disease-free and overall survival curves were comparable between groups. The cumulative 1- and 5-year disease-free rates were 50%, and 38.9% for group 1, and 50% and 15% for group 2 (Fig. 3, $p =$

Table 4. Postoperative Complications and Tumor Recurrence for Group 1 and 2

	Group 1 (n = 41)	Group 2 (n = 63)	<i>p</i> value
Postoperative hospital stay (days)	10.00 (8.00-12.00)	8.00 (7.00-9.00)	0.001
Postoperative complications	6 (14.6%)	8 (12.7%)	0.777
Hospital mortality	3 (7.3%)	5 (7.9%)	1.000
Recurrence	17 (41.5%)	39 (61.9%)	0.094
Recurrence type			0.768
Single	4 (23.5%)	14 (35.9%)	
Multiple	9 (52.9%)	19 (48.7%)	
Intraabdominal	1 (5.9%)	2 (5.1%)	
Distant metastasis	3 (17.6%)	4 (10.3%)	

Variables are expressed as median (interquartile range) or as number (n) and percent (%).

0.279). The 1- and 5-year overall survival rates were 89.5% and 66.2% for group 1 and 87.5% and 53.1% for group 2 (Fig. 4, $p = 0.786$). Among the patients with tumor recurrence, 82.1% of the recurrences were within the liver, of which 39.3% were in the same lobe or near the resection margin and 60.7% developed in other lobes. The difference in the recurrence pattern and type of treatment for recurrences was not statistically significant between groups. Of the patients with recurrence, 58.9% were treated with TACE, 5.4% received RFA or PEI, and 7.1% underwent another resection. The four patients with opera-

tions for tumor recurrence were in group 2. In univariate analysis, age above 65 years, cirrhosis, an aspartate aminotransferase (AST) level less than 34 U/L, and an albumin level less than 3.5 g/dL were significant predictors for recurrence. Age above 65 years, cirrhosis, an AST level less than 34 U/L, an albumin level less than 3.5 g/dL, tumor encapsulation, tumor grading, tumor more than 6.5 cm in diameter, resected liver weight more than 330 g and method of inflow control were all significant factors predicting poor overall survival. In multivariate analysis, cirrhosis, a low AST level and low resected liver weight were independent factors contributing to overall survival (Tables 5 and 6).

DISCUSSION

The treatment of patients with centrally located HCCs remains under debate.⁽¹⁸⁾ Hemi- or extended hepatectomies are the traditional approaches. With these major hepatectomies, a large volume of functional liver parenchyma is sacrificed and it is well known that the number of resected segments has a negative impact on perioperative morbidity and mortality.⁽¹⁹⁻²¹⁾ This is especially critical in cirrhotic patients, where excessive resections may lead to postoperative liver failure and associated complications. In our study, only two patients (4.9%) in group 1 died of immediate postoperative liver failure and this was comparable to the reported rate of 6-10% in the literature.⁽¹⁰⁾

Central hepatectomy, the other surgical alternative, preserves more liver parenchyma and theoretically is associated with a better recovery in the short term. However, central hepatectomy is a technically demanding surgery. The presence of two hepatic parenchymal transections with proximity to important vascular structures makes it technically more complex than hemihepatectomies. Moreover, large tumors located in the central portion of the liver are associated with an increased risk of intraoperative bleeding. To reduce the operative blood loss, we routinely employed the Pringle maneuver to control the blood inflow. The middle hepatic vein was carefully evaluated by CT scan preoperatively and ultrasound intraoperatively. During parenchymal dissection, care was especially taken with the middle hepatic vein to reduce blood loss. In this series, only 12% of patients required blood transfusions intraoperatively.

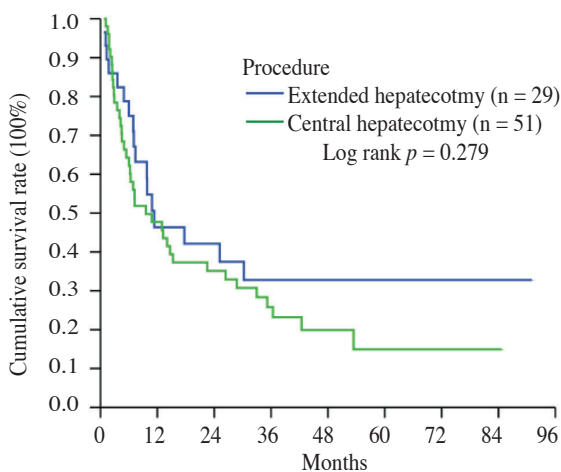


Fig. 3 Disease-free survival rates for patients with hemi-/extended or central hepatectomy for centrally located large HCC.

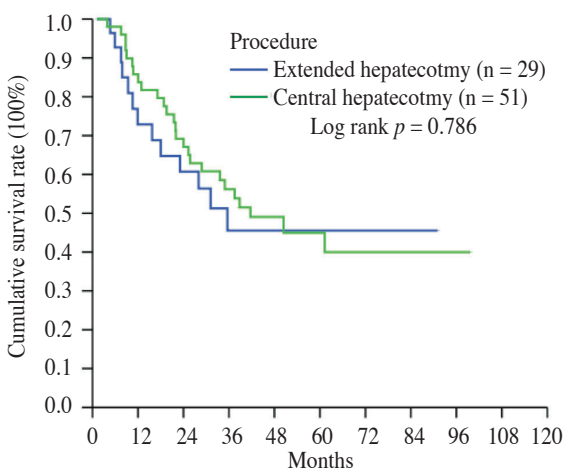


Fig. 4 Overall survival rates for patients with hemi-/extended or central hepatectomy for centrally located large HCC.

Table 5. Univariate and Multivariate Analysis of Risk Factors for Disease-free Survival

Factors	Univariate analysis		<i>p</i> value	Multivariate analysis	
	n	Median survival (m) (95% CI)		Hazard ratio (95% CI)	<i>p</i> value
Age			0.092		
≤ 65	56	11.34 (4.79-17.88)		1	
> 65	24	10.81 (4.94-16.69)		1.028 (0.532-1.985)	0.935
Cirrhosis			0.011		
Present	33	5.98 (2.91-9.05)		1	
Absent	47	14.69 (0.57-28.81)			0.011
Child-Pugh status			0.602		
A	75	10.88 (6.45-15.30)			
B	5	4.93 (1.80-8.06)			
ICG retention rate			0.843		
≤ 15	56	9.79 (5.63-13.95)			
> 15	12	11.34 (0-35.99)			
AST (U/L)			0.078		
≤ 34	34	9.56 (5.07-14.06)		2.481 (1.259-4.889)	0.009
> 34	43	13.21 (0-28.04)		1	
ALT (U/L)			0.771		
≤ 36	29	9.86 (2.60-17.12)			
> 36	44	10.88 (3.89-17.86)			
Albumin (g/dL)			0.002		
≤ 3.5	20	6.34 (3.19-9.49)		2.053 (1.1080-3.903)	0.028
> 3.5	57	14.69 (0-31.13)		1	
Estimated blood loss (L)			0.569		
< 500	39	7.36 (0.08-14.64)			
500-1000	25	10.88 (2.63-19.13)			
> 1000	16	11.34 (0-22.92)			
AFP (ng/mL)			0.301		
> 400	49	11.34 (6.48-16.20)			
≤ 400	30	10.81 (1.62-20.00)			
Capsule			0.300		
Present	53	13.21 (0-29.94)			
Absent	27	7.36 (2.94-11.78)			
Vascular invasion			0.347		
Macro	20	7.16 (3.90-10.43)			
Micro	21	9.56 (3.76-15.36)			
Absent	39	22.52 (2.39-42.64)			
Daughter nodules			0.583		
Present	27	9.86 (4.41-15.30)			
Absent	53	13.21 (6.70-19.72)			
Tumor grading			0.402		
I-II	32	14.69 (0-33.07)			
III-IV	48	7.36 (2.67-12.05)			
Tumor size (max. diameter in cm)			0.740		
≤ 6.5	39	15.28 (0-30.94)			
> 6.5	41	9.56 (6.30-12.83)			

Table 5. Univariate and Multivariate Analysis of Risk Factors for Disease-free Survival (continued)

Factors	Univariate analysis		<i>p</i> value	Multivariate analysis	
	n	Median survival (m) (95% CI)		Hazard ratio (95% CI)	<i>p</i> value
Resected liver weight (g)			0.767		
≤ 330	38	14.03 (0.94-27.12)			
> 330	41	9.79 (5.74-13.84)			
Margin (cm)			0.348		
≤ 1	70	10.88 (6.12-15.64)			
> 1	10	7.36 (0.00-16.79)			
Inflow control			0.630		
Pringle maneuver	36	15.28 (0-35.73)			
Hemivascular	15	7.03 (4.73-9.34)			
None	27	12.98 (5.64-20.32)			
TNM			0.280		
Stage 1	30	25.15 (10.83-39.47)		1	
Stage 2	10	4.50 (0-13.77)		0.902 (0.351-2.318)	0.830
Stage 3a	18	9.86 (2.20-17.51)		1.251 (0.606-2.581)	0.545
Stage 3b	20	7.16 (3.90-10.43)		1.999 (0.914-4.371)	0.083
Stage 3c	2	4.43		2.412 (0.477-12.199)	0.287
Procedure			0.279		
Extended hepatectomy	29	11.34 (2.21-20.46)		1	
Central hepatectomy	51	9.56 (2.44-16.68)		1.128 (0.579-2.196)	0.724

Abbreviations: ICG: indocyanine green; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein.

Table 6. Univariate and Multivariate Analysis of Risk Factors for Overall Survival

Factors	Univariate analysis		<i>p</i> value	Multivariate analysis	
	n	Median survival (m) (95% CI)		Hazard ratio (95% CI)	<i>p</i> value
Age			0.087		
≤ 65	56	–		1	
> 65	24	34.91 (16.19-53.64)		2.153 (0.576-3.662)	0.110
Cirrhosis			0.082		
Present	33	28.83 (13.67-43.99)		3.152 (1.302-7.627)	0.011
Absent	47	–		1	
Child-Pugh status			0.368		
A	75	41.65 (14.32-68.98)			
B	5	21.46 (0-48.62)			
ICG retention rate			0.759		
≤ 15	56	33.63 (17.78-49.47)			
> 15	12	61.24 (16.66-105.83)			
AST (U/L)			0.088		
≤ 34	34	24.03 (10.84-37.21)		3.400 (1.356-8.522)	0.009
> 34	43	61.25 (–)		1	
ALT (U/L)			0.740		
≤ 36	29	37.47 (12.98-61.97)			
> 36	44	35.57 (5.73-69.41)			
Albumin (g/dL)			0.005		
≤ 3.5	20	21.99 (4.99-38.99)		2.153 (0.841-5.507)	0.110
> 3.5	57	–		1	

Table 6. Univariate and Multivariate Analysis of Risk Factors for Overall Survival (continued)

Factors	Univariate analysis		<i>p</i> value	Multivariate analysis	
	n	Median survival (m) (95% CI)		Hazard ratio (95% CI)	<i>p</i> value
Estimated blood loss (L)			0.710		
< 500	39	50.40 (-)			
500-1000	25	34.91 (0-84.83)			
> 1000	16	35.57 (20.47-50.67)			
AFP (ng/mL)			0.260		
> 400	49	34.91 (11.36-58.46)			
≤ 400	30	-			
Capsule			0.005		
Present	53	-		1	
Absent	27	23.07 (17.74-28.41)		1.596 (0.537-4.744)	0.400
Vascular invasion			0.211		
Macro	20	23.07 (15.84-30.31)			
Micro	21	41.65 (-)			
Absent	39	61.24 (-)			
Daughter nodules			0.556		
Present	27	37.47 (26.38-48.57)			
Absent	53	61.24 (-)			
Tumor grading			0.191		
I-II	32	-		1	
III-IV	48	33.63 (18.25-49.01)		2.165 (0.849-5.523)	0.106
Tumor size (max. diameter in cm)			0.017		
≤ 6.5	39	-		1	
> 6.5	41	25.74 (16.69-34.78)		2.237 (0.799-6.259)	0.125
Resected liver weight (g)			0.012		
≤ 330	38	-		1	
> 330	41	25.31 (14.79-35.83)		3.425 (1.038-11.301)	0.043
Margin (cm)			0.617		
≤ 1	70	38.79 (9.78-67.80)			
> 1	10	50.40 (-)			
Inflow control			0.125		
Pringle maneuver	36	61.24 (-)		1	
Hemivascular	15	23.07 (3.78-42.37)		3.659 (0.657-20.378)	0.139
None	27	50.40 (-)		1.584 (0.517-4.852)	
TNM			0.314		
Stage 1	30	-		1	
Stage 2	10	28.83 (-)		1.785 (0.399-7.989)	0.448
Stage 3a	18	34.47 (27.72-47.23)		0.907 (0.292-2.817)	0.866
Stage 3b	20	23.07 (15.84-30.31)		1.226 (0.360-4.175)	0.744
Stage 3c	2	12.92 (-)		3.870 (0.474-31.605)	0.207
Procedure			0.786		
Extended hepatectomy	29	35.57 (-)		1	
Central hepatectomy	51	41.65 (21.70-61.60)		3.160 (0.714-13.985)	0.129

Abbreviations: ICG: indocyanine green; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein.

Giuliante et al. demonstrated that preliminary control of the hepatic veins during central hepatectomy was associated with reduced operative bleeding and a lower blood transfusion rate.⁽²²⁾ Extrahepatic outflow control of the main hepatic veins and the infrahepatic vena cava could reduce the risk of hemorrhage from backflow bleeding. However, complete mobilization of the right lobe and retraction of the central segments may be difficult with big tumors. Alternatively, an anterior approach has been shown to reduce blood loss,⁽²³⁾ and this technique is already employed in central hepatectomies in our institution.⁽²⁴⁾

Bile leakage and liver failure are the most common complications in central hepatectomy. In our series, one patient had postoperative bile leakage (1.5%) and two patients died of liver failure (3.1%) after central hepatectomies. However, 47.6% of the patients in the central hepatectomy group had liver cirrhosis and the mean tumor size was 7.24 ± 2.35 cm. These two characteristics per se may carry a considerable risk of postoperative liver failure and complications.⁽²⁵⁾ In the literature, the incidence of complications after central hepatectomy ranges from 17 to 26.3% and the reported surgical mortality is between 0 and 6.25%.⁽¹⁸⁾ Our results are compatible with those of previous reports. Furthermore, the central hepatectomy group had a shorter postoperative hospital stay than the extended/hemi-hepatectomy group.

Centrally located tumors are often close to the hepatic hilum and the main hepatic veins. Therefore, surgical resection of these tumors is likely to be associated with small margins, especially if the tumors are larger than 5 cm. In our experience, extended hepatectomy only provides a slightly higher proportion of patients with a resection margin > 1 cm (21.1% versus 7.4%, $p = 0.056$). As mentioned previously, there is currently a trend toward limited hepatic resections to prevent postoperative liver failure. The number of hepatic segments resected is considered to have a negative impact on perioperative morbidity and mortality and the preservation of liver function is a priority.⁽¹⁹⁻²¹⁾ This was particularly reflected in the multivariate analysis, where a resected liver weight more than 330 g was a significant factor for poor long term survival.⁽²⁶⁻²⁸⁾

Additionally, it is also believed that most intrahepatic recurrences arise from multicentric carcinogenesis

and are distant from the resection margin. Therefore, although it is better to obtain a resection margin > 1 cm, the importance of a wide margin for centrally located large tumors still needs to be evaluated.^(27,29-31)

At present, patients with large HCC represent poor candidates for liver transplantation and partial hepatectomy remains the only treatment to provide consistent disease-free and overall survival. Portal vein embolization is an optional procedure that increases the remaining liver reserve and the safety of major hepatectomy without compromising long-term outcomes.^(32,33) However, with centrally located large tumors; it is difficult to wait for liver hypertrophy after either side of the portal vein is embolized. Direct surgical resection remains the mainstay of treatment. Because cirrhosis and poor hepatic reserve are often associated with HCC, this surgical strategy is the only one which allows for preservation of adequate residual liver volume and function. Thus, careful patient selection and surgical experience is mandatory.

The 5-year disease-free and overall survival rates after central hepatectomy for large HCCs were comparable to those of hemi-/extended hepatectomies. One possible explanation is their similar recurrence pattern and use of aggressive treatment with TACE, RFA and even repeat resection. The cumulative 5-year disease-free rates were 38.9% for patients with extended resections and 15% for patients with central resections ($p = 0.279$). Although it was not statistically significant, this represented a trend. The patients' baseline characteristics, surgical factors and tumor factors were not different between groups, but one possible factor may be the higher proportion of patients with liver cirrhosis and Child B status in the central hepatectomy group. Cirrhosis is associated with higher recurrence rates⁽³⁴⁾ because of strong hepatic inflammatory activity and progressive liver disease,⁽³⁵⁾ which may be associated with continuing carcinogenesis.^(19,36)

Cirrhosis and low preoperative AST and albumin levels were other independent factors for tumor recurrence and overall survival. Mild to moderate elevations of liver enzymes are commonplace in patients with cirrhosis and HCC. They are sensitive indicators of the presence of liver disease and may lead to prompt examinations and earlier tumor diagnosis. Conversely, we presume that a low preopera-

tive AST level was a negative factor affecting survival because it may be associated with delayed diagnosis and treatment. Hypoalbuminemia has been reported to be a risk factor for perioperative morbidity⁽³⁷⁻⁴⁰⁾ or recurrence after resection.⁽⁴¹⁾ It is a multifactorial indicator for the degree of liver disease, nutritional status or a stress response. It is also associated with impairment of macrophage activation and a decreased innate immune response.⁽⁴²⁾ The presence of cirrhosis further worsens the state of protein-calorie malnutrition and increased catabolism. Liver resection in these patients further decreases the functional liver mass, and postoperative sepsis, nutritional deprivation and compromised immunity tend to cause further deterioration of liver function. The deterioration of liver function associated with a low regeneration capacity and impaired immune response may a posteriori contribute to tumor recurrence.

The long term survival for the central hepatectomy group was comparable with those in previous series and even with those treated with other types of minor resections. The debate still remains whether patients with large central tumors should receive a central hepatectomy even with its technical difficulties. The conservation of more nontumor liver parenchyma a priori is presumed to be important for patient survival, but at present, most series have failed to confirm this assumption. In our experience, a central hepatectomy preserves more liver parenchyma and finally the resected liver weight was an independent prognostic factor for survival. However, a central hepatectomy in cirrhotic patients with large tumors still carries a high risk of postoperative complications. We believe that this procedure requires extensive experience in liver surgery in a high-volume center.

Conclusion

The surgical strategy for centrally located large-sized HCC is still controversial. In this study, the overall surgical complication rate, hospital mortality, and long-term disease-free and survival rates for central hepatectomy and extended/hemi-hepatectomy were comparable. Cirrhosis, a low preoperative AST level and a low resected liver weight were independent factors determining long-term survival.

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中央區巨大肝細胞癌之手術治療

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- 背景：** 中央區巨大肝細胞癌是外科手術中一個困難棘手的病症，通常是以半／擴大或中央肝切除術來治療。這個研究主要是探討半／擴大或中央肝切除術的治癒成效。
- 方法：** 將於我院進行肝切除的 104 位中央區巨大肝細胞癌病患區分為 2 組，群組 1 有 41 位病患進行擴大的半肝切除；群組 2 有 63 位病患進行以中央肝切除術，針對 2 個群組的群組特徵以及手術治療進行研究分析。
- 結果：** 針對群組 2 的病患進行肝切除手術，其中群組 2 中有 92.6% 的人切緣小於 1 公分，而群組 1 中則有 78.9% 的人切緣小於 1 公分 ($p = 0.056$)。群組 1 的 1 年及 5 年存活率分別為 50% 及 38.9%；群組 2 的 1 年及 5 年存活率分別為 50% 及 15% ($p = 0.279$)。群組 1 的 1 年及 5 年存活率分別為 89.5% 及 66.2%；群組 2 的 1 年及 5 年存活率分別為 87.5% 及 53.1% ($p = 0.786$)。肝硬化、血清麩胺酸苯醋酸轉氨基酶數值及切除肝臟重量為影響病患存活率的獨立因素。
- 結論：** 擴大的半肝切除與中央肝切除的術後併發症及長期存活率相似。肝硬化、血清麩胺酸苯醋酸轉氨基酶數值及切除肝臟重量與長期存活率具有顯著的關聯性。
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關鍵詞： 肝癌，中央肝切除手術，半肝切除手術

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