Journal of Surgical Oncology 2011;104:292–298

Outcomes of Hepatic Resection for Huge Hepatocellular Carcinoma (≥10 cm in Diameter)

YO-ICHI YAMASHITA, MD, PhD,[1,2]* AKINOBU TAKETOMI, MD, PhD,[1] KEN SHIRABE, MD, PhD,[1] SHINICHI AISHIMA, MD, PhD,[3] EIJI TSUIJITA, MD, PhD,[2] KAZUTOYO MORITA, MD,[1] HIROTO KAYASHIMA, MD,[1] AND YOSHIHIKO MAEHARA, MD, PhD, FACS[1]

[1]*Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan*
[2]*Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Naka-ku, Hiroshima, Japan*
[3]*Department Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan*

Background: The object of the current study was to review the outcomes of hepatic resection for hepatocellular carcinoma (HCC) ≥ 10 cm.
Methods: Between 1995 and 2007, fifty-three patients with HCC ≥ 10 cm underwent hepatic resection, and clinical data were compared to those of patients with non-surgical treatment (n = 12). Surgical results for HCC ≥ 10 cm were compared to those of patients with HCC < 10 cm (n = 412). The independent poor prognostic factors of the patients with HCC ≥ 10 cm were identified.
Results: Overall survival was significantly better in patients with hepatic resection for HCC ≥ 10 cm than in those with non-surgical treatment ($P < 0.01$). Survival rates of patients with hepatic resection for HCC ≥ 10 cm were 35% at 5 years. Morbidity and mortality rate were statistically equal. The independent poor prognostic factors of patients with hepatic resection for HCC ≥ 10 cm were revealed: T4 status, macroscopic tumor thrombus in portal vein (VP+), and the use of intra-operative transfusion.
Conclusion: Hepatic resections for HCC ≥ 10 cm are safe and efficacious. Minimizing intra-operative blood loss and the establishment of an effective systemic treatment for patients with HCC ≥ 10 cm in T4 appear to be critical.
J. Surg. Oncol. 2011;104:292–298. © 2011 Wiley-Liss, Inc.

KEY WORDS: huge hepatocellular carcinoma (larger than 10 cm in diameter; HCC ≥ 10 cm); hepatic resection; morbidity and mortality; poor prognostic factors

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with an annual occurrence of at least 1 million new cases [1]. The mainstay of treatment is hepatic resection, although patients with HCC are frequently treated non-surgically with radio frequency ablation, or transarterial chemoembolization (TACE). In patients with huge HCC (> or =10 cm in diameter; HCC ≥ 10 cm), TACE resulted in a 5-year survival rate of <10% [2,3], whereas hepatic resection has a 5-year survival rate of 16.7–54.0%, unsurpassed by other treatment modalities [4–17]. At present, hepatic resection is regarded as the most available treatment of choice for HCC ≥ 10 cm, provided the patient's hepatic functional reserve is acceptable for resection. However, there may be an increased risk of operative morbidity and mortality in the hepatic resection for HCC ≥ 10 cm because of its technical difficulties and the need for major hepatic resections [6,14]. The aim of this study is to determine whether hepatic resection carried out for HCC ≥ 10 cm is safe and effective, and to identify clinicopathologic features of prognostic value.

PATIENTS AND METHODS

Patients

Sixty-five patients with HCC ≥ 10 cm were admitted the Department of Surgery and Science, Kyushu University Hospital, between January 1995 and December 2007. Fifty-three patients (82%) underwent hepatic resection, and 12 (18%) were diagnosed to be inoperable because of accompanying liver dysfunction, advanced tumor stage, or distant metastasis. Nine patients were treated by lipiodolization [18] and TACE [2,3] with or without systemic chemotherapy using 5-fluorouracil or Tegafur/Uracil, but three patients could not be treated because of liver dysfunction and entered best supportive care. Surgical results of patients with HCC ≥ 10 cm were compared to those of patients with initial hepatic resection for HCC less than 10 cm in diameter (HCC < 10 cm) during the same periods (n = 412). The medical records of 65 and 412 patients (total 477 patients) were followed up through December 2008. The median follow-up period in this series was 38 months.

Surgical Techniques and Follow-Up Methods

Thorough intra-operative ultrasonography was performed to determine the extent of disease and the line of parenchymal transection. A decision was then made on the type of liver resection that would allow a clear margin around the tumor with maximum preservation of the hepatic parenchyma. In almost all hepatic resections, intermittent Pringle's maneuvers consisting of clamping the portal triad for 15 min and then releasing the clamp at 5-min intervals or hemivascular occlusions [19,20] were applied. A SONOP SUS201D dissector (Aloka, Tokyo, Japan) was used to transect the liver parenchyma in 1995, but since 1996, the CUSA system (Valley Lab, Boulder, CO, USA) has been used. Our standard skin incision for HCC ≥ 10 cm was an upper midline and bi-lateral subcostal incision (so-called

*Correspondence to: Yo-ichi Yamashita, MD, PhD, Department of Surgery, Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital, Senda-Machi 1-9-6, Naka-ku, Hiroshima 730-8619, Japan. Fax: +81-82-246-0676. E-mail: yamashi@surg2.med.kyushu-u.ac.jp

Received 14 October 2010; Accepted 14 March 2011

DOI 10.1002/jso.21931

Published online 4 April 2011 in Wiley Online Library (wileyonlinelibrary.com).

© 2011 Wiley-Liss, Inc.

Benz incision). In five patients (9.4%) with gross diaphragmatic involvement, the right subcostal incision was extended to the eighth or ninth intercostal space, and the diaphragm and costal arch were divided to improve exposure of the right hepatic vein and supra-hepatic vena cava [21]. Also, in four patients (7.5%) with a particularly large right-lobe tumor, we used the anterior approach, in which parenchymal transection was performed without earlier mobilization of the liver and extra-hepatic control of the hepatic veins [22]. A bile leakage test using indocyanine diluted green solution was routinely performed [23].

After discharge, all patients were examined for recurrence by ultrasonography and tumor markers such alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) every month, and by dynamic computed tomography (CT) every 3 months [24]. We treated recurrent HCC by repeat hepatectomy [25], ablation therapy, and lipiodolization [18] according to the previously described strategy [26].

Statistical Analysis

Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. To evaluate poor prognostic factors after hepatic resection for HCC ≥ 10 cm, we performed multivariate analysis with the Cox proportional hazard model, using a variable-selection method involving the backward-elimination procedure. A value of $P < 0.05$ was set as the cutoff for elimination. The following 19 clinical, surgical, and tumor-related variables were analyzed in accordance with the findings of previous reports [27–34]: age (≥ vs. <65 years); diabetes mellitus (present vs. absent); preoperative serum total bilirubin level (≥ vs. <1 mg/dl); ICG R15 (≥ vs. <20%); albumin level (≥ vs. <3.5 g/dl); Child-Pugh class (A vs. B/C); background liver status as assessed histologically (cirrhosis vs. non-cirrhosis); the gross classifications of HCC (single nodular vs. non-single nodular); macroscopic tumor thrombus in portal vein (VP; yes vs. no); macroscopic intra-hepatic metastasis as assessed histologically (IM; yes vs. no); preoperative AFP (≥ vs. <100 ng/ml); preoperative DCP (≥ vs. <100 IU/l); histological cancer spread including vascular invasion and intrahepatic metastasis (vp or im: yes vs. no); tumor cell differentiation (well/moderate vs. poor); primary tumor stage according to the latest criteria of the Liver Cancer Study Group of Japan (T2/T3 vs. T4) [35]; surgical time (≥ vs. <360 min); surgical blood loss (≥ vs. <2,000 ml); history of blood cell transfusion (yes vs. no); and surgical margin (≥ vs. <5 mm).

Continuous variables were expressed as means ± SE and compared using Student's *t*-test. Categorical variables were compared using either the chi^2 test or Fisher's exact test, as appropriate. All analyses were performed with Statview 5.0 software (Abacus Concepts, Berkeley, CA, USA). *P*-values of <0.05 were considered to indicate statistical significance.

RESULTS

Clinical Characteristics of Patients With Hepatic Resection for HCC ≥ 10 cm Compared to Those With Non-Surgical Treatment

The clinical characteristics of the two groups of 65 patients with HCC ≥ 10 cm are summarized in Table I. The hepatic resection group (n = 53) maintained liver function better than the non-surgical treatment group (n = 12) with lower total bilirubin level, higher albumin level, lower ICG R15 value, and better Child classification. In addition, the hepatic resection group was accompanied with earlier tumor stage than the non-surgical treatment group, with rare presence of VP, rare presence of IM, earlier Tumor-Node Metastasis (TNM) stage, and lower DCP level.

The overall survival curves of the two groups are illustrated in Fig. 1. Survival rates of the hepatic resection group were 74% at 1 year, 43% at 3 years, and 35% at 5 years. On the other hand, the survival rate of the non-surgical group was 17% at 1 year, and all 12 patients died within 2 years after treatment. The overall survival rate of the hepatic resection group was significantly better than that of the non-surgical treatment group ($P < 0.01$).

Surgical Outcomes of Patients With HCC ≥ 10 cm Compared With Those of HCC < 10 cm

Clinicopathological features of patients with hepatic resection for HCC ≥ 10 cm (n = 53) and for HCC < 10 cm (n = 412) are summarized in Table II. The HCC ≥ 10 cm group maintained liver function better than the HCC < 10 cm group with higher albumin level, lower ICG R15 value, and better Child classification. The HCC ≥ 10 cm group was accompanied with hepatitis B infections more frequently than the HCC < 10 cm group, and with hepatitis C

TABLE I. Clinical Features Between Patients Undergoing Hepatic Resection and Patients With Non-Surgical Treatment for HCC ≥ 10 cm

Va1uab1es	Hepatic resection (n = 53)	Non-surgical (n = 12)	*P*-value
Backgrounds characteristics			
Age (years)	60 ± 2	62 ± 3	0.89
Ma1e:fema1e	48:5	10:2	0.56
T-bil (mg/dl)	0.8 ± 0.2	2.1 ± 2.1	<0.01
Alb (g/dl)	3.8 ± 0.1	3.4 ± 0.3	0.02
Child A:B:C	38:15:0	2:8:2	0.02
ICG R15 (%)	13.9 ± 1.4	25.1 ± 5.3	<0.O1
HBV infection (%)	18 (34%)	4 (34%)	0.91
HCV infection (%)	22 (42%)	6 (50%)	0.41
Tumor-related factors			
Maximum tumor size (cm)	13.2 ± 0.4	14.9 + 1.2	0.63
Stage II/III/IV	14/10/29	0/1/11	<0.01
Vp (%)	24 (45%)	9 (75%)	0.02
IM (%)	29 (55%)	12 (100%)	0.03
AFP (ng/ml)	3,194 ± 1,138	3,983 ± 1,237	0.15
DCP (mAU/L)	6,386 ± 5,274	7,246 ± 5,147	0.04

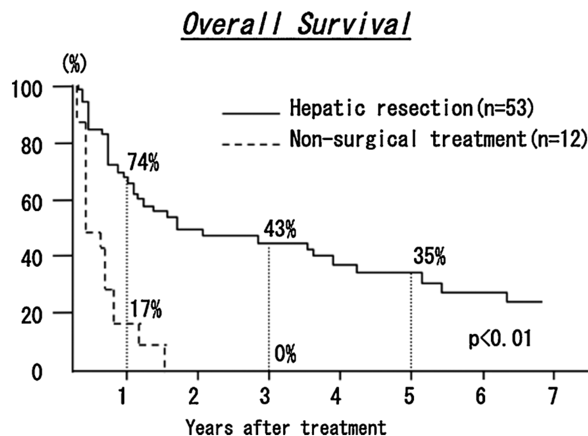

Fig. 1. Overall survival curves of patients with hepatic resection for HCC ≥ 10 cm (n = 53) and of those with non-surgical treatment for HCC ≥ 10 cm (n = 12) are illustrated. Survival rates of the hepatic resection group were 74% at 1 year, 43% at 3 years, and 35% at 5 years.

infection less frequently than the HCC < 10 cm group. The HCC ≥ 10 cm group was accompanied with advanced tumor stage more than the HCC < 10 cm group with frequent VP+, frequent IM+, advanced T stage, and higher AFP and DCP level.

Surgical outcomes in the HCC ≥ 10 cm group and HCC < 10 cm groups are compared in Table III. Surgical stresses of the HCC ≥ 10 cm group such as surgical time (369 vs. 295 min), surgical blood loss (2,430 vs. 1,017 g), intra-operative transfusion rates (58 vs. 25%), resected liver volume (1,048 vs. 212 g), and the ratio of major hepatic resection (62 vs. 23%) were significantly higher than those of the HCC < 10 cm group. Irrespective of the higher operative stresses, the ratio of cases in which tumor margin was maintained at more than 5 mm was significantly lower in the HCC ≥ 10 cm group than in the HCC < 10 cm group (17% vs. 39%). But hospital mortality rate (3.8% vs. 2.4%), postoperative complication rate (24.5% vs. 22.3%), and the mean duration of hospital stay (28 vs. 25 days) were statistically the same in the two groups.

The recurrence-free and overall survival curves of the two groups are illustrated in Fig. 2. The recurrence-free and overall survival rates of the HCC ≥ 10 cm group were significantly lower than those of the HCC < 10 cm group ($P < 0.01$), but both the 5-year recurrence-free survival rate (24%) and the survival rate (35%) of the HCC ≥ 10 cm group were relatively high.

Recurrence sites after hepatic resection of the two groups are compared in Table IV. In all, 32 patients (62%) of the HCC ≥ 10 cm group and 225 patients (54%) of the HCC < 10 cm group had HCC recurrences. The rate of multiple liver recurrence of the HCC ≥ 10 cm group (59%) was significantly higher than that of the HCC ≤ 10 group (33%; $P = 0.04$). In addition, the rate of extrahepatic recurrence—i.e., recurrence in lung, bone, brain, or

TABLE II. Clinicopathologic Features Between Patients With Hepatic Resection for HCC ≥ 10 cm and for HCC ≤ 10 cm

Valuables	HCC ≥ 10 cm (n = 53)	HCC ≤ 10 cm (n = 412)	*P*-value
Clinical characteristics			
Age (years)	60 ± 2	64 ± 3	0.21
Male: female	48:5	328:84	0.56
T-bil (mg/dl)	0.8 ± 0.2	0.9 ± 0.3	0.19
Alb (g/dl)	3.8 ± 0.1	3.6+0.3	0.03
Child A:B:C	38:15:0	246:164:2	<0.01
1CGR15 (%)	13.9 ± 1.4	18.9 ± 5.3	<0.01
HBV infection (%)	18 (34%)	60 (15%)	0.03
HCV infection (%)	22 (42%)	311 (75%)	0.02
Tumor-related factors			
Maximum tumor size (cm)	13.2 ± 0.4	3.8 ± 2.2	<0.01
T 1/2/3/4	0/14/10/29	43/177/121/71	<0.01
Well/mod/poor	1/14/38	53/298/61	<0.01
Vp (%)	24 (45%)	45 (11%)	0.02
1M (%)	29 (55%)	57 (14%)	0.03
AFP (ng/ml)	3,194 + 1,138	9,486 ± 2S33	0.02
DCP (mAU/L)	6,386 + 5,274	1,298 + 6,123	<0.01

TABLE III. Surgical Outcomes of Patients With HCC ≥ 10 cm

Variables	HCC ≥ 10 cm (n = 53)	HCC ≤ 10 cm (n = 412)	*P*-value
Operative outcomes			
Surgical time (min)	369 ± 16	295 ± 18	<0.01
Surgical blood loss (g)	2,430 ± 382	1,017 ± 212	<0.01
Transfusion (%)	31 (58%)	103 (25%)	<0.01
Resected kiver volume (g)	1,048 ± 67	212 ± 35	<0.01
Major hepatic resection (%)	33 (62%)	95 (23%)	<0.01
Surgical margin >5 mm (%)	9 (17%)	160 (39%)	<0.01
Short-term outcomes			
Mortality (%)	2 (3.8%)	10 (2.4%)	0.45
Morbidity (%)	13 (24.5%)	92 (22.3%)	0.55
Hospital stay (days)	28 ± 2	25 ± 5	0.49

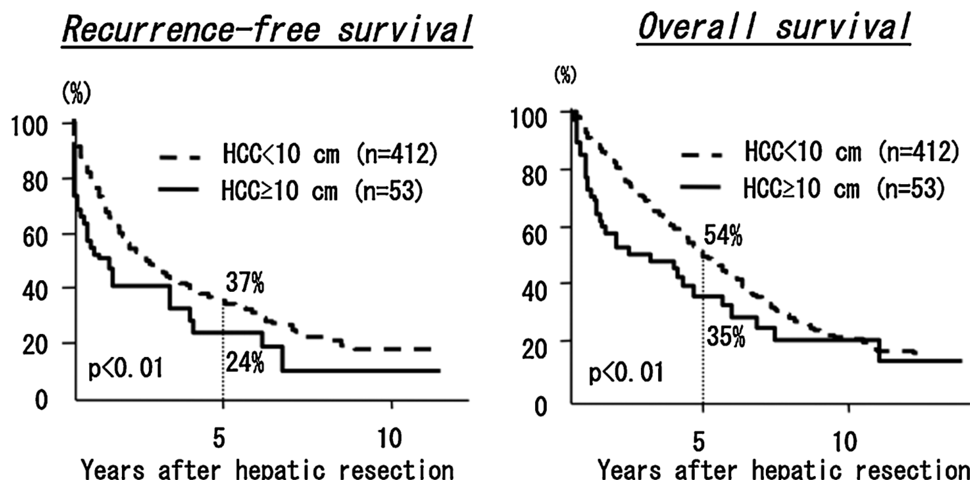

Fig. 2. The recurrence-free and overall survival curves of patients with hepatic resection for HCC ≥ 10 cm (n = 53) and for HCC < 10 cm (n = 412) are illustrated. Both 5-year recurrence-free survival rate (24%) and survival rate (35%) of the HCC ≥ 10 cm group were relatively high.

peritoneum—of the HCC ≥ 10 cm group (38%) was significantly higher than that of the HCC < 10 group (10%; $P = 0.02$).

Poor Prognosis Factors of Patients With Hepatic Resection for HCC ≥ 10 cm

The results of multivariate analysis with the Cox proportional hazard model using a variable-selection method involving a backward-elimination procedure among the 19 clinical, surgical and tumor-related variables listed in the Patients and Methods section above are summarized in Table V. The analysis revealed two independent poor prognostic factors in recurrence-free survival: T4 status (hazard ratio; HR 5.12) and VP+ (HR 3.29). In overall survival, the independent poor prognostic factors were T4 status (HR 4.13) and the use of intra-operative transfusion (HR 2.76).

The recurrence-free and overall survival curves of T2/T3 patients (n = 24) and T4 patients (n = 29) are illustrated in Fig. 3. The recurrence-free and overall survivals of the T4 group were significantly worse than those of the T2/T3 group ($P < 0.01$). The recurrence-free 2-year survival rates were 73% in the T2/T3 group, and 8% in the T4 group. The overall 5-year survival rates were 56% in the T2/T3 group, and 17% in the T4 group. The prognosis of patients with hepatic resection for HCC ≥ 10 cm in T2/T3 could be concluded to be relatively good, and statistically the same as that of patients with hepatic resection for HCC < 10 cm.

DISCUSSION

The prognosis of the hepatic resection group for HCC ≥ 10 cm (n = 53) proved considerably better than that of the non-surgical treatment group (n = 12). Patients with hepatic resection for HCC ≥ 10 cm have been reported to have 5-year survival rates of 16.7–54.0% [4–17]; in our series their 5-year survival rate was 35%. In previous reports, TACE for HCC ≥ 10 cm resulted in a 5-year

TABLE IV. Recurrence Sites After Hepatic Resection

Recurrence sites	HCC ≥ 10 cm (n = 32)		HCC < 10 cm (n = 225)		*P*-value
Liver					
Solitary	1 (3%)		129 (57%)		
Multiple	19 (59%)		74 (33%)		$P = 0.04$
Lung	8 (25%)	12 (38%)	18 (8%)	22 (10%)	$P = 0.02$
Bone	2 (6%)		4 (2%)		
Brain	1 (3%)		0 (0%)		
Peritoneum	1 (3%)		0 (0%)		

TABLE V. Multivariate Analysis for the Poor Prognostic Factors in Patients With Hepatic Resection for HCC ≥ 10 cm

Variables	Hazard ratio	95% Confidence interval	*P*-value
Recurrence-free survival			
T4	5.12	1.31–20.0	0.02
VP (+)	3.29	1.03–10.4	0.04
Overall survival			
T4	4.13	1.12–10.7	0.01
Intra-operative transfusion	2.76	1.05–6.80	0.03

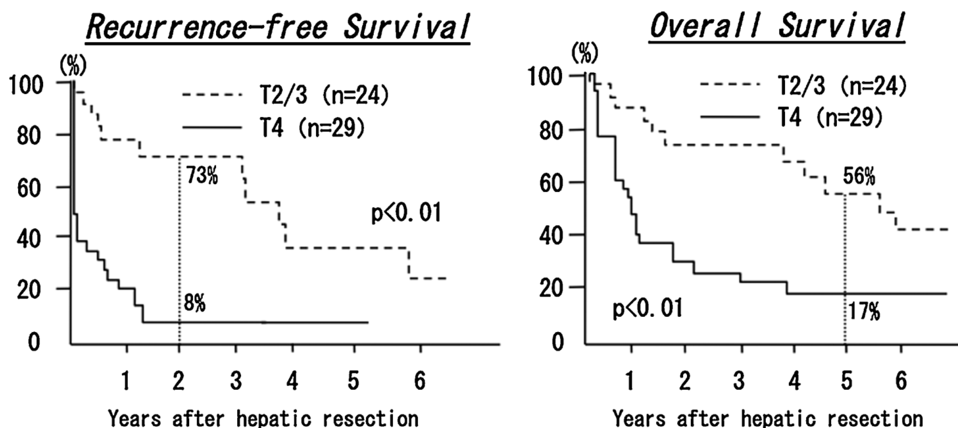

Fig. 3. The recurrence-free and overall survival curves of T2/3 patients (n = 24) and T4 patients (n = 29) with hepatic resection for HCC ≥ 10 cm are illustrated. In the T4 group, the recurrence-free 2-year survival rate was 8%, and the overall 5-year survival rate was 17%.

survival rate of <10% [2,3]. In our series, the 1-year survival rate of the non-surgical treatment group was 17%, and all patients died within 2 years of treatment. On the other hand, Mok et al. [4] reported that the advantage of hepatic resection for HCC ≥ 10 cm is marginal, and overall survival curves were similar between the hepatic resection group and the non-surgical treatment group. Of course, treatment effects of the hepatic resection and the non-surgical treatment such as lipiodolization and TACE for HCC ≥ 10 cm could not be directly compared, because of the patients' background differences such as tumor stage and remnant liver function. Generally speaking, the non-surgical treatment group for HCC ≥ 10 cm had comparative disadvantages in treatment such as more advanced tumor stage and more severe liver dysfunction. Also in our series, the non-surgical group had more severe liver function (higher total bilirubin level, lower albumin level, higher ICG R15 value, and worse Child classification) and more advanced tumor stage (frequent VP+, frequent IM+, more advanced TNM stage, and higher DCP level). Therefore, according to our results, we can only say that patients with HCC ≥ 10 cm who were diagnosed as operable and underwent hepatic resection had better prognosis than those who were diagnosed as inoperable and treated with non-surgical modalities.

Published surgical results such as operative mortality and 5-year survival rate for HCC ≥ 10 cm including more than 50 patients are summarized in Table VI [4–7,9–11,14,16,17]. Resection of HCC ≥ 10 cm is technically challenging because of difficulty in mobilization, especially if the tumor is located in the right lobe. A large tumor can also hamper the control of the hepatic veins before

TABLE VI. Comparison of Published Surgical Results of Hepatic Resection Against HCC ≥ 10 cm Including More Than 50 Patients

Reference	Country	No. of patients	Mortality (%)	5-year survival rate (%)	Year
Poon et al. [16]	China	120	3.3	28	2002
Mok et al. [4]	Taiwan	56	2.0	25	2003
Yeh et al. [5]	Taiwan	211	4.3	17	2003
Zhou et al. [6]	China	621	4.5	26	2003
Chen et al. [7]	China	525	2.7	17	2004
Liau et al. [9]	USA	82	2.0	33	2005
Pawlik et al. [10]	International	300	5.0	27	2005
Lee et al. [11]	Korea	100	2.0	31	2006
Chen et al. [17]	China	780	2.2	35	2006
Shah SA et al. [14]	Canada	189	8.3	54	2007
Present study	Japan	53	3.8	35	2010

TABLE VII. Tumor Stage of HCC Presented by Liver Cancer Study Group of Japan

Variables of primary tumor	
① Solitary tumor	
② Maximum tumor diameter ≤ 2 cm	
③ Absence of macroscopic vessel or bile duct invasion (VpO, VvO, BO)	
Primary tumor stage	**Tumor stage**
T1: All variables fit	Stage I: T1 NO MO
T2: Two variables fit	Stage II: T2 NO MO
T3: One variable fits	Stage III: T3 NO HO
T4: No variable fits	Stage IVA: T4 NO MO
	Stage IVB: T1–4 N1 MO
	T1–4 NO-1 M1

or during transection of the liver parenchyma. This would contribute to the longer surgical time, higher surgical blood loss, and transfusion requirement in the HCC ≥ 10 cm group compared with those of the HCC < 10 cm group [5,8,15,16]. Although there are a few reports that hepatic resections in cases of HCC ≥ 10 cm increase operative morbidity [6,14] and mortality [6], almost all reports including ours have demonstrated that hepatic resections for HCC ≥ 10 cm did not increase operative risks of hepatic resection [5,8,9,15,16]. Hepatic resection for HCC ≥ 10 cm could be summarized as having an operative mortality rate of 2.0–14.0% [4–10,12–17]; therefore, hepatic resections for HCC ≥ 10 cm could be concluded to be relatively safe. Almost all reports including ours have demonstrated that the survival of patients with hepatic resection for HCC ≥ 10 cm is significantly worse than that for HCC < 10 cm [5,6,8,15,16], whereas hepatic resections for HCC ≥ 10 cm have been reported to have 5-year survival rate of 16.7–54% [4–17]. Also in our series, the 5-year survival rate of patients with hepatic resection for HCC ≥ 10 cm reached 35%. With the consideration that the 5-year survival after hepatic resections for HCC ≥ 10 cm exceeded 25% in almost reports, hepatic resection could be concluded to be an effective treatment for HCC ≥ 10 cm.

There are only two studies that have reported in detail the recurrence pattern after hepatic resection for HCC ≥ 10 cm. Mok et al. [4] reported that extrahepatic recurrence occurred in 43.4% patients, and Poon et al. [16] reported that extrahepatic recurrence was significantly more frequent in patients with hepatic resection for HCC ≥ 10 cm (31.9%) than those for HCC < 10 cm (12.8%). Also in our series, extrahepatic recurrence such as that in the lung (8/32; 25%), bone (2/32; 6%), brain (1/32; 3%), and peritoneum (1/32; 3%) was significantly more frequent in patients with hepatic resection for HCC ≥ 10 cm (total 12/32; 38%) than those for HCC < 10 cm (total 22/225; 10%). From consideration of these results, routine follow-up targeted to extrahepatic recurrence after hepatic resection using CT for lung and brain metastasis and bone scintigraphy for bone metastasis should be important for patients with hepatic resection for HCC ≥ 10 cm.

Various poor prognostic factors of patients with hepatic resection for HCC ≥ 10 cm have been reported; high AFP value [4,5,10], curative resection [6,11,14,16], large amount of intra-operative blood loss [5,7,9,17], VP+ [4,6–11,14,16,17], IM+ [5–8,10,16,17], Stage IV [13,15], T4 [15], the absence of tumor capsule [6,7,17], the presence of liver cirrhosis [10,13,15], the gross classification of HCC [33,34], and poor tumor differentiation [4,14]. We found three poor prognostic factors; T4 status, VP+, and the use of intra-operative transfusion. The primary tumor stage according to the latest criteria of the Liver Cancer Study Group of Japan are summarized in Table VII [35]. T4 of HCC ≥ 10 cm might mean the coexistence of both VP and IM. There are no patients with hepatic resection for HCC ≥ 10 accompanied with lymph nodes metastasis (N) and distant metastasis (M) in our series, therefore primary tumor stage should be directly connected to the total tumor stage (T4 → Stage IVA). According to previous reports and our results, the prognosis of patients with hepatic resection for HCC ≥ 10 cm in T4 [15] or Stage IV [13] should be poor. Therefore, neoadjuvant or adjuvant systemic chemotherapy is important for patients with hepatic resection for HCC ≥ 10 cm in T4, but there is no established systemic neoadjuvant or adjuvant chemotherapy regimen for HCC [36]. Sorafenib, an oral multikinase inhibitor, has been recently reported to be effective for the treatment of advanced HCC in a SHARP trial [37] and in a phase III trial of Asia-Pacific regimen [38]; therefore, Sorafenib should be one of the most important drugs for establishing systemic adjuvant treatment regimen for HCC ≥ 10 cm in T4. On the contrary, the prognosis of patients with hepatic resection for HCC ≥ 10 cm in T2/3 is significantly equal for that for HCC < 10 cm from our results; therefore, patients with HCC ≥ 10 cm in T2/3 should be indicated for aggressive hepatic resection.

There are some reports that intra-operative blood transfusion promotes the recurrence of HCC after hepatic resections [39–41]. In many reports, a large amount of intra-operative blood loss was concluded to be a poor prognostic factor in patients with hepatic resection for HCC ≥ 10 cm; in our series, as well, intra-operative blood transfusion was an independent poor prognostic factor. Therefore, minimizing intra-operative blood loss to avoid intra-operative transfusion should be essential in patients with HCC ≥ 10 cm.

In conclusion, hepatic resections for HCC ≥ 10 cm are safe and efficacious. Minimizing intra-operative blood loss to avoid transfusion and the establishing an effective systemic treatment regimen for T4 patients with HCC ≥ 10 cm appear to be critical for more favorable long-term outcomes in patients with HCC ≥ 10 cm.

REFERENCES

1. Lau WY: Management of hepatocellular carcinoma. J R Coll Surg Edinb 2002;47:389–399.
2. Poon RTP, Ngan H, Lo CM, et al.: Transarterial chemoembolization for inoperable hepatocellular carcinoma and postresection intrahepatic recurrence. J Surg Oncol 2000;73:109–114.
3. Huang YH, Wu JC, Chen SC, et al.: Survival benefit of transcatheter arterial chemoembolization in patients with hepatocellular carcinoma larger than 10 cm in diameter. Aliment Pharmacol Ther 2006;23:129–135.
4. Mok KT, Wang BW, Lo GH, et al.: Multimodality management of hepatocellular carcinoma larger than 10 cm. J Am Coll Surg 2003;197:730–738.
5. Yeh CN, Lee WC, Chen MF: Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: Two decades of experience at Chang Gung memorial hospital. Ann Surg Oncol 2003;10:1070–1076.
6. Zhou XD, Tang ZY, Ma ZC, et al.: Surgery for large primary liver cancer more than 10 cm in diameter. J Cancer Res Clin Oncol 2003;129:543–548.
7. Chen XP, Qiu FZ, Wu ZD, et al.: Chinese experience with hepatectomy for huge hepatocellular carcinoma. Br J Surg 2004;91:322–326.
8. Nagano Y, Tanaka K, Togo S, et al.: Efficacy of hepatic resection for hepatocellular carcinomas larger than 10 cm. World J Surg 2005;291:66–71.
9. Liau KH, Ruo L, Shia J, et al.: Outcome of partial hepatectomy for large (>10 cm) hepatocellular carcinoma. Cancer 2005;104:1948–1955.
10. Pawlik TM, Poon RT, Abdalla EK, et al.: Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 2005;140:450–457.
11. Lee SG, Hwang S, Jung JP, et al.: Outcome of patients with huge hepatocellular carcinoma after primary resection and treatment of recurrent lesions. Br J Surg 2007;94:320–326.
12. Furuta T, Sonoda T, Matsumata T, et al.: Hepatic resection for a hepatocellular carcinoma larger than 10 cm. J Surg Oncol 1992;51:114–117.
13. Hanazaki K, Kajikawa S, Shimozawa N, et al.: Hepatic resection for hepatocellular carcinoma in diameter of > or =10 cm. Hepatogastroenterology 2002;49:518–523.
14. Shah SA, Wei AC, Cleary SP, et al.: Prognosis and results after resection of very large (> or =10 cm) hepatocellular carcinoma. J Gastrointest Surg 2007;11:589–595.
15. Taniai N, Yoshida H, Tajiri T: Adaptation of hepatectomy for huge hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 2008;15:410–416.
16. Poon RTP, Fan ST, Wong J: Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J Am Coll Surg 2002;194:592–602.

17. Chen XP, Qiu FZ, Wu ZD, et al.: Hepatectomy for huge hepatocellular carcinoma in 634 cases. World J Gastroenterol 2006;12: 4652–4655.
18. Kanematsu T, Furuta T, Takenaka K, et al.: A 5-year experience of lipiodolization: Selective regional chemotherapy for 200 patients with hepatocellular carcinoma. Hepatology 1989;10: 98–102.
19. Makuuchi M, Mori T, Gunvén P, et al.: Safety of hemihepatic vascular occlusion during resection of the liver. Surg Gynecol Obstet 1987;164:155–158.
20. Lanois B: The intrahepatic Glissonian approach to liver resection. In: Blumgart LH, Fong Y. Surgery of the liver and biliary tract, 3rd edition, Vol. 2. London: WB Saunders; 2000. pp. 1698–1703.
21. Takenaka K, Fujiwara Y, Gion T, et al.: A thoracoabdominal hepatectomy and a transdiaphragmatic hepatectomy for patients with cirrhosis and hepatocellular carcinoma. Arch Surg 1998; 133:80–83.
22. Liu CL, Fan ST, Cheung ST, et al.: Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: A prospective randomized controlled study. Ann Surg 2006;244:194–203.
23. Yamashita Y, Hamatsu T, Rikimaru T, et al.: Bile leakage after hepatic resection. Ann Surg 2001;233:45–50.
24. Takenaka K, Kawahara N, Yamamoto K, et al.: Results of 280 liver resections for hepatocellular carcinoma. Arch Surg 1996; 131:71–76.
25. Shimada M, Takenaka K, Taguchi K, et al.: Prognostic factors after repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg 1998;227:80–85.
26. Shimada M, Takenaka K, Gion T, et al.: Prognosis of recurrent hepatocellular carcinoma: A 10-year surgical experience in Japan. Gastroenterology 1996;111:720–726.
27. Imamura H, Matsuyama Y, Miyagawa Y, et al.: Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. Br J Surg 1999;86:1032–1038.
28. Hasegawa K, Kokudo N, Imamura H, et al.: Prognostic impact of anatomic resection for hepatocellular carcinoma. Ann Surg 2005;242:252–259.
29. Yamashita Y, Taketomi A, Itoh S, et al.: Long term favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 years of experience. J Am Coll Surg 2007; 205:19–26.
30. Shirabe K, Kanematsu T, Matsumata T, et al.: Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: Univariate and multivariate analyses. Hepatology 1991;14:802–805.
31. Fan ST, Ng IO, Poon RT, et al.: Hepatectomy for hepatocellular carcinoma: The surgeon's role in long-term survival. Arch Surg 1999;134:1124–1130.
32. Fuster J, Garcia-Valdecasas JC, Grande L, et al.: Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series. Ann Surg 1996;223:297–302.
33. Yang LY, Fang F, Ou DP, et al.: Solitary large hepatocellular carcinoma: A specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. Ann Surg 2009;249:118–123.
34. Choi GH, Han DH, Kim DH, et al.: Outcome after curative resection for a huge (> or =10 cm) hepatocellular carcinoma and prognostic significance of gross tumor classification. Am J Surg 2009;198:693–701.
35. The Liver Cancer Study Group of Japan: The general results for the clinical and pathological study of primary liver cancer, 5th edition. Tokyo: Kanehara Shuppan; 2009.
36. Schwartz JD, Schwartz M, Mandeli J, et al.: Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: Review of the randomised clinical trials. Lancet Oncol 2002;3: 593–603.
37. Llovet JM, Ricci S, Mazzaferro V, et al., SHARP Investigators Study Group: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
38. Cheng AL, Kang YK, Chen Z, et al.: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10: 25–34.
39. Matsumata T, Ikeda Y, Hayashi H, et al.: The association between transfusion and cancer-free survival after curative resection for hepatocellular carcinoma. Cancer 1993;72:1866–1871.
40. Yamamoto J, Kosuge T, Takayama T, et al.: Perioperative blood transfusion promotes recurrence of hepatocellular carcinoma after hepatectomy. Surgery 1994;115:303–309.
41. Asahara T, Katayama K, Itamoto T, et al.: Perioperative blood transfusion as a prognostic indicator in patients with hepatocellular carcinoma. World J Surg 1999;23:676–680.