Risk Factors for Different Patterns of Recurrence after Resection of Hepatocellular Carcinoma

MASAKI KAIBORI, YOICHI MATSUI, TAKAMICHI SAITO and YASUO KAMIYAMA

Department of Surgery, Hirakata Hospital, Kansai Medical University, Hirakata, Osaka 573-1191, Japan

Abstract. *Background: Long-term survival of patients with hepatocellular carcinoma after hepatectomy is unsatisfactory because of the high recurrence rate. Patients and Methods: Among 396 patients who underwent curative resection of hepatocellular carcinoma, there were 228 patients with clinical recurrence: 85 with solitary intrahepatic recurrence (group A), 109 with two or more intrahepatic recurrences (group B), and 34 who had extrahepatic recurrence (group C). The clinical and pathological factors for each group were investigated for association with long-term survival of each group. Results: The survival rate of group C was significantly lower than that of the other groups. Patients in group C were significantly younger than those in groups A or B, with higher levels of protein induced by absence/antagonism of vitamin K-II, larger tumors, more poorly differentiated tumors, intravascular invasion and a lower incidence of cirrhosis than the other groups. Group A showed a significantly longer period until recurrence and maintained good liver function at recurrence. In group B, the survival rate of Child-Pugh class A patients was significantly higher than that of class B and C patients. Class A patients received significantly more treatments for recurrence than patients in the other classes. Conclusion: Postoperative adjuvant chemotherapy should be performed as early as possible after hepatectomy if the patient is younger, has a large tumor and/or has a high level of protein induced by absence/antagonism of vitamin K-II. Patients with solitary intrahepatic recurrence and adequate liver function should receive further curative therapy. It is important to maintain the postoperative nutritional status of patients with multiple intrahepatic recurrences in order to allow repeated and aggressive therapy to be performed.*

Correspondence to: Masaki Kaibori, Department of Surgery, Hirakata Hospital, Kansai Medical University, 2-3-1 Shinmachi, Hirakata, Osaka 573-1191, Japan. Tel: +81 72 804 0101 (ext. 56130), Fax: +81 72 804 0170, e-mail: kaibori@hirakata.kmu.ac.jp

Key Words: Hepatocellular carcinoma, patterns of recurrence, risk factors.

Advances in surgical techniques and perioperative management have transformed the resection of hepatocellular carcinoma (HCC) into a relatively safe operation with a low mortality rate (1). However, the long-term survival of these patients is still unsatisfactory because of the high recurrence rate of HCC after curative hepatectomy (2). Prevention and effective management of recurrence are the most important methods for improving the long-term survival of these patients. Numerous studies have investigated the risk factors for recurrence of HCC after surgical resection (3-16), but the postoperative recurrence rate (especially intrahepatic recurrence) remains high and is the main cause of death (6, 10, 17-20). Recurrence is thought to have two main mechanisms: one is metastasis from the primary tumor *via* the portal system and the other is metachronous development of multicentric tumors. Multiple intrahepatic recurrences, as well as extrahepatic recurrence, are the main patterns of metastatic recurrence (21) and the prognosis of such patients is worse than that of patients with nodular recurrence (22).

We classified patients with recurrence of HCC into 3 groups on the basis of the site of the recurrence and the number of recurrent tumors, and then analyzed the clinical and pathological factors for each pattern of recurrence. The aim of this study was to investigate the main risk factors for each pattern of recurrence after resection of HCC in terms of the long-term survival rate.

Patients and Methods

Patients. Between February 1992 and June 2005, a total of 411 patients with HCC underwent curative resection at our institution. A curative operation was defined as one during which all of the tumors were macroscopically resected. Fifteen patients died in hospital prior to discharge and the remaining 396 patients were followed at our outpatient clinics. Ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) was performed at least every 3 months. In addition, various laboratory parameters were monitored, including the serum levels of alanine transaminase (ALT), total bilirubin and albumin, as well as the prothrombin time, platelet count, α-fetoprotein (AFP) and protein induced by absence/antagonism of vitamin K-II (PIVKA-II). When recurrence of HCC was detected based on tumor marker

levels or imaging findings, treatment was provided. As of December 2005, a total of 228 (58%) of the 396 patients had suffered from clinical recurrence and were included in this study. Informed consent was obtained from all of the patients.

Clinicopathological variables and surgery. Before surgery, each patient underwent measurement of the indocyanine green retention rate at 15 min (ICGR15) and conventional liver function tests. Hepatitis screening was performed by detection of hepatitis B surface antigen and hepatitis C antibody, while AFP and PIVKA-II were also measured in all patients. Our operative procedures have been reported previously (23, 24). The method of hepatectomy was largely chosen according to the criteria of Makuuchi (25, 26) and the procedures were classified according to conventional terminology with respect to the eight liver subsegments of Couinaud (27). Anatomic resection was defined as lobectomy (resection of one liver lobe), extended lobectomy (lobectomy plus removal of additional contiguous segments), or segmentectomy (resection of two Couinaud subsegments). All of the other non-anatomic procedures were classified as limited resection. A senior pathologist reviewed each specimen for histological confirmation of the diagnosis. The maximum tumor diameter was recorded and the resection margin width was measured as the distance from the tumor edge to the resection line.

Classification of recurrent tumors. Patients with recurrence were assigned to 1 of 3 groups on the basis of the site of recurrence and the number of recurrent tumors. Group A consisted of 85 patients with solitary intrahepatic recurrence, group B of 109 patients with two or more intrahepatic recurrences, and group C of 34 patients who had extrahepatic recurrence with or without intrahepatic recurrence. The sites of extrahepatic recurrence in group C were the lung, bone, lymph node, adrenal gland, skin and brain in 15 (44%), 7 (21%), 5 (15%), 3 (9%), 2 (6%), and 2 (6%) patients, respectively. Concomitant recurrence in the liver remnant and an extrahepatic organ was seen in 14 patients.

Group B was divided into Child-Pugh class A and class B/C at the time of recurrence. Group B patients were also classified into four categories according to the location of recurrence in the liver remnant (13), which were marginal recurrence, recurrence in an adjacent segment, recurrence in a distant segment and multisegmental recurrence. The size of the recurrent tumor was defined as the initial diameter of the recurrent lesion on US, CT, and/or MRI. In patients with multiple recurrent tumors, the size of the largest lesion was used for classification. Portal venous invasion at the time of recurrence was detected on angiography as protrusion of the tumor into the first and/or second branches of the portal vein or into the main trunk.

Treatment of recurrent HCC. On the basis of liver function and tumor factors, either transcatheter hepatic artery infusion of anticancer agents (lipiodolization) or transcatheter arterial chemoembolization (TACE) was selected for intrahepatic recurrence in 146 patients. Eleven of the 14 patients with concomitant recurrence in the liver remnant and extrahepatic organs underwent lipiodolization or TACE for their intrahepatic tumors. Other treatments were used in 30 patients, including 17 patients who underwent repeat hepatic resection and 13 patients who underwent percutaneous ethanol injection therapy (PEIT). Percutaneous microwave coagulation therapy and radiofrequency ablation under US guidance were performed in 11 and six patients, respectively, while four patients each underwent radiation therapy and systemic chemotherapy, respectively. Twenty-seven patients did not receive any treatment for recurrence because they had a poor hepatic functional reserve or refused treatment. Patients with two or more recurrences usually received TACE or PEIT.

Statistical analysis. Continuous variables were used to divide the subjects into 2 categories by the median value. The significance of differences among the three groups of patients was assessed by the chi-square test. The significance of differences between Child-Pugh class A and class B/C in group B was also assessed by the Chi-square test. The Kaplan-Meier life table method was used to calculate the survival rate after recurrence as of December 2005, and the significance of differences in survival was estimated using the generalized log-rank test. In all analyses, $p<0.05$ was considered to indicate statistical significance.

Results

Perioperative characteristics. The perioperative characteristics of each group of patients with recurrent HCC are shown in Table I. Compared with those in groups A and B, patients in group C were significantly younger, had lower ICGR15 and serum alanine aminotransferase (ALT) levels, and had a higher platelet count and a higher serum PIVKA-II level. In addition, patients in group C were significantly more likely to have anatomic resection, larger tumors, poorly differentiated histology, intravascular invasion and an advanced disease stage compared with those in the other two groups. Examination of the resected nontumorous liver tissue demonstrated a significantly lower incidence of cirrhosis in group C.

Clinical characteristics at recurrence and subsequent survival. The clinical characteristics of the three groups at the time of recurrence are summarized in Table II. Patients in group A had a significantly longer period until recurrence, had higher serum albumin levels and were more often in Child-Pugh class A compared with patients from groups B or C. Patients in group A were also significantly more likely to receive curative therapy (such as repeat hepatectomy or local ablation) for their recurrent HCC. Patients in group C had significantly higher serum AFP and PIVKA-II levels compared with patients from the other groups. In addition, group C patients were significantly more likely to receive no treatment for recurrence and had fewer treatments for recurrent HCC after the initial recurrence.

Figure 1 compares the survival rate after recurrence of HCC among the three groups. The survival rate of group A was significantly higher than that of the other groups (both $p<0.0001$), while the survival rate of group B was significantly higher than that of group C ($p<0.005$). In group A, the survival rate was 93.3% at 1 year, 63.9% at 3 years, and 39.1% at 5 years, whereas the survival rates for

Table I. *Perioperative clinical characteristics of the three groups.*

	Group A (n=85)	Group B (n=109)	Group C (n=34)	*P*-value
Gender (male/female)	70/15	91/18	27/7	NS
Age >67 years	42 (49.4%)	52 (47.7%)	8 (23.5%)	$p<0.01$ (C *vs.* A), $p<0.05$ (C *vs.* B)
HBsAg	10 (11.8%)	23 (21.1%)	7 (20.6%)	NS
HCVAb	70 (82.4%)	79 (72.5%)	23 (67.6%)	NS
Alcohol abuse	39 (45.9%)	49 (45.0%)	15 (44.1%)	NS
ICGR15 >17.0%	45 (52.9%)	56 (51.4%)	10 (29.4%)	$p<0.05$ (C *vs.* A and B)
Platelets $<13.0x10^4/\mu l$	50 (58.8%)	51 (46.8%)	9 (26.5%)	$p<0.005$ (C *vs.* A), $p<0.05$ (C *vs.* B)
Total bilirubin >0.9 mg/dl	34 (40.0%)	41 (37.6%)	12 (35.3%)	NS
Albumin <3.7 g/dl	33 (38.8%)	53 (48.6%)	13 (38.2%)	NS
Prothrombin time <89%	43 (50.6%)	52 (47.7%)	14 (41.2%)	NS
Cholinesterase <99 U/l	44 (51.8%)	52 (47.7%)	16 (47.1%)	NS
AST >46 IU/l	39 (45.9%)	57 (52.3%)	14 (41.2%)	NS
ALT >47 IU/l	46 (54.1%)	56 (51.4%)	10 (29.4%)	$p<0.05$ (C *vs.* A and B)
Child-Pugh class: A/B/C	80/5/0	98/11/0	32/2/0	NS
α-Fetoprotein >26 ng/ml	33 (38.8%)	57 (52.3%)	22 (64.7%)	$p<0.05$ (C *vs.* A)
PIVKA-II >106 mAU/ml	30 (35.3%)	59 (54.1%)	26 (76.5%)	$p<0.0001$ (C *vs.* A), $p<0.01$ (B *vs.* A and C)
Preoperative TACE	40 (47.1%)	50 (45.9%)	15 (44.1%)	NS
Hepatic resection (limited/anatomic)	72/13	82/27	14/20	$p<0.0001$ (C *vs.* A), $p<0.0005$ (C *vs.* B)
Operative blood loss >983 ml	36 (42.4%)	57 (52.3%)	21 (61.8%)	NS
Blood transfusion	35 (41.2%)	59 (54.1%)	20 (58.8%)	NS
Number of patients with complications	20 (23.5%)	23 (21.1%)	9 (26.5%)	NS
Tumor size >3.2 cm	33 (38.8%)	50 (45.9%)	28 (82.4%)	$p<0.0001$ (C *vs.* A), $p<0.0005$ (C *vs.* B)
Histology (well or moderately/poorly)	81/4	102/7	26/8	$p<0.005$ (C *vs.* A and B)
TW	12 (14.1%)	30 (27.5%)	10 (29.4%)	NS
VP and VV	28 (32.9%)	66 (60.6%)	28 (82.4%)	$p<0.0001$ (C *vs.* A), $p<0.05$ (C *vs.* B), $p<0.0005$ (A *vs.* B)
Number of tumors (single/multiple)	62/23	66/43	19/15	NS
Associated liver disease (normal or fibrosis or hepatitis/cirrhosis)	44/41	57/52	25/9	$p<0.05$ (C *vs.* A and B)
Tumor stage (I/II/III/IVA)	22/42/16/5	7/52/32/18	3/6/15/10	$p<0.0001$ (C *vs.* A), $p<0.05$ (C *vs.* B), $p<0.0005$ (A *vs.* B)

Data represent the number of patients. NS, not significant; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 min; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PIVKA-II, protein induced by absence/antagonism of vitamin K-II; TACE, transcatheter arterial chemoembolization; fc, microscopic capsule formation; TW, microscopic surgical margin <5 mm from the tumor; VP, microscopic invasion of the portal vein; VV, microscopic invasion of the hepatic vein.

groups B and C were 74.7% *versus* 36.5% at 1 year, 33.2% *versus* 20.0% at 3 years, and 13.8% *versus* 4.0% at 5 years, respectively.

Clinical characteristics of the two Child-Pugh subgroups at recurrence and subsequent survival. Group B was classified into patients who were in Child-Pugh class A or class B and C at recurrence (Table III). Patients in classes B and C had a significantly shorter period until recurrence, lower serum albumin level, longer prothrombin time and higher serum bilirubin level compared with those in class A. There were no differences between the two subgroups with respect to the pattern of intrahepatic recurrence, tumor size, or presence of portal venous invasion at recurrence. Patients in class A received significantly more treatment for recurrence of HCC after the initial recurrence compared with those in class B and C.

The survival rate of patients in class A was significantly higher than that of those in class B and C (Figure 2), with the rates being 89.0% *versus* 38.2% at 1 year and 43.0% *versus* 3.8% at 3 years, respectively ($p<0.0001$).

Discussion

The long-term survival of patients with HCC is still unsatisfactory after curative hepatectomy because of the high recurrence rate (2). Therefore, the present study was performed to identify the characteristics of patients with single, multiple, or extrahepatic recurrence and to assess the clinical significance of such variables. Our aim was to identify patients who required intervention to prevent recurrence following initial hepatectomy so that effective treatment can be provided as early as possible after surgery.

Table II. *Clinical characteristics of the three groups at recurrence.*

	Group A (n=85)	Group B (n=109)	Group C (n=34)	*P*-value
Period until recurrence				
<1 year	24 (28.2%)	55 (50.5%)	20 (58.8%)	$p<0.005$ (A *vs.* C), $p<0.005$ (A *vs.* B)
1-2	27 (31.8%)	30 (27.5%)	8 (23.5%)	
>2 years	34 (40.0%)	24 (22.0%)	6 (17.6%)	
Albumin <3.6 g/dl	29 (34.1%)	55 (50.5%)	22 (64.7%)	$p<0.005$ (A *vs.* C), $p<0.05$ (A *vs.* B)
Bilirubin >0.9 mg/dl	43 (50.6%)	50 (45.9%)	15 (44.1%)	NS
ALT >54 IU/dl	39 (45.9%)	49 (45.0%)	15 (44.1%)	NS
Platelets $<11.6x10^4/\mu l$	47 (55.3%)	49 (45.0%)	20 (58.8%)	NS
Prothrombin time <85%	40 (47.1%)	53 (48.6%)	19 (55.9%)	NS
α-Fetoprotein >35 ng/ml	35 (41.2%)	58 (53.2%)	25 (73.5%)	$p<0.005$ (C *vs.* A), $p<0.05$ (C *vs.* B)
PIVKA-II >52 mAU/ml	28 (32.9%)	55 (50.5%)	32 (94.1%)	$p<0.0001$ (C *vs.* A and B)
Child-Pugh class: A/B/C	79/5/1	78/29/2	27/6/1	$p<0.0001$ (A *vs.* C), $p<0.001$ (A *vs.* B)
Treatment of initial recurrence				
None	2 (2.4%)	9 (8.3%)	16 (47.1%)	$p<0.0001$ (C *vs.* A and B), $p<0.05$ (A *vs.* B)
Other	28 (32.9%)	20 (18.3%)	7 (20.6%)	
Hepatectomy	11	6	0	
PEIT	8	5	0	
PMCT	6	5	0	
PRFA	3	3	0	
Radiation	0	1	3	
Chemotherapy	0	0	4	
TACE/LPD	55 (64.7%)	80 (73.4%)	11 (32.4%)	
>3 treatments after initial recurrence	41 (48.2%)	49 (45.0%)	8 (23.5%)	$p<0.05$ (C *vs.* A and B)

The variables were determined at recurrence. Data represent the number of patients. NS, not significant; ALT, alanine aminotransferase; PIVKA-II, protein induced by absence/antagonism of vitamin K-II; PEIT, percutaneous ethanol injection therapy; PMCT, percutaneous microwave coagulation therapy; PRFA, percutaneous radiofrequency ablation; TACE, transcatheter arterial chemoembolization; LPD, lipiodolization.

Extrahepatic recurrence of HCC after hepatectomy is not infrequent, especially in patients with advanced disease (28, 29). Nakashima *et al*. studied 225 HCC patients at autopsy and found lung metastases and lymph node metastases in 51.6% and 26.7%, respectively (30). In the present study, the survival rate of group C (extrahepatic recurrence) was significantly lower than that of groups A or B (intrahepatic recurrence). Patients in group C were more likely to have large tumors, poorly differentiated histology, and intravascular invasion. They also had a relatively young age, good preoperative liver function, lower incidence of cirrhosis in the nontumorous liver, and higher PIVKA-II levels. Among the patients with advanced HCC, only those who had well-preserved liver function were candidates for anatomic resection. If a patient is aged ≤67 years, has a tumor larger than 3 cm in diameter and has a preoperative plasma level of PIVKA-II >100 mAU/ml, we recommend postoperative adjuvant regional chemotherapy or lipiodolization (31-33). In addition, more careful follow-up (including bone scintigraphy and chest CT) may be necessary to detect extrahepatic recurrence as early as possible after curative hepatectomy in such patients.

The survival rate after recurrence was significantly higher in group A than in the patients with multiple intrahepatic

Table III. *Clinical characteristics of Child-Pugh class A or class B/C patients in group B.*

	Class A (n=78)	Classes B/C (n=31)	*P*-value
Period until recurrence			
<1 year	28 (35.9%)	26 (83.9%)	$p<0.0001$
1-2 years	27 (34.6%)	4 (12.9%)	
>2 years	23 (29.5%)	1 (3.2%)	
Age >67 years	41 (52.6%)	11 (35.5%)	NS
Albumin <3.6 g/dl	25 (32.1%)	30 (96.8%)	$p<0.0001$
Bilirubin >0.9 mg/dl	30 (38.5%)	20 (64.5%)	$p<0.05$
ALT >51 IU/dl	42 (53.8%)	12 (38.7%)	NS
Platelets $<11.9x10^4/\mu l$	35 (44.9%)	15 (48.4%)	NS
Prothrombin time <85%	23 (29.5%)	27 (87.1%)	$p<0.0001$
α-Fetoprotein >37 ng/ml	35 (44.9%)	19 (61.3%)	NS
PIVKA-II >78 mAU/ml	36 (46.2%)	17 (54.8%)	NS
Classification of intrahepatic recurrence marginal/adjacent segment/distal segment/ multisegment	2/24/2/50	0/5/2/24	NS
Tumor size >2.0 cm	30 (38.5%)	13 (41.9%)	NS
PVI	4 (5.1%)	4 (12.9%)	NS
>3 treatments after initial recurrence	45 (57.7%)	4 (12.9%)	$p<0.0001$

The variables were determined at recurrence. Data represent the number of patients. NS, not significant; ALT, alanine aminotransferase; PIVKA-II, protein induced by absence/antagonism of vitamin K-II; PVI, portal venous invasion.

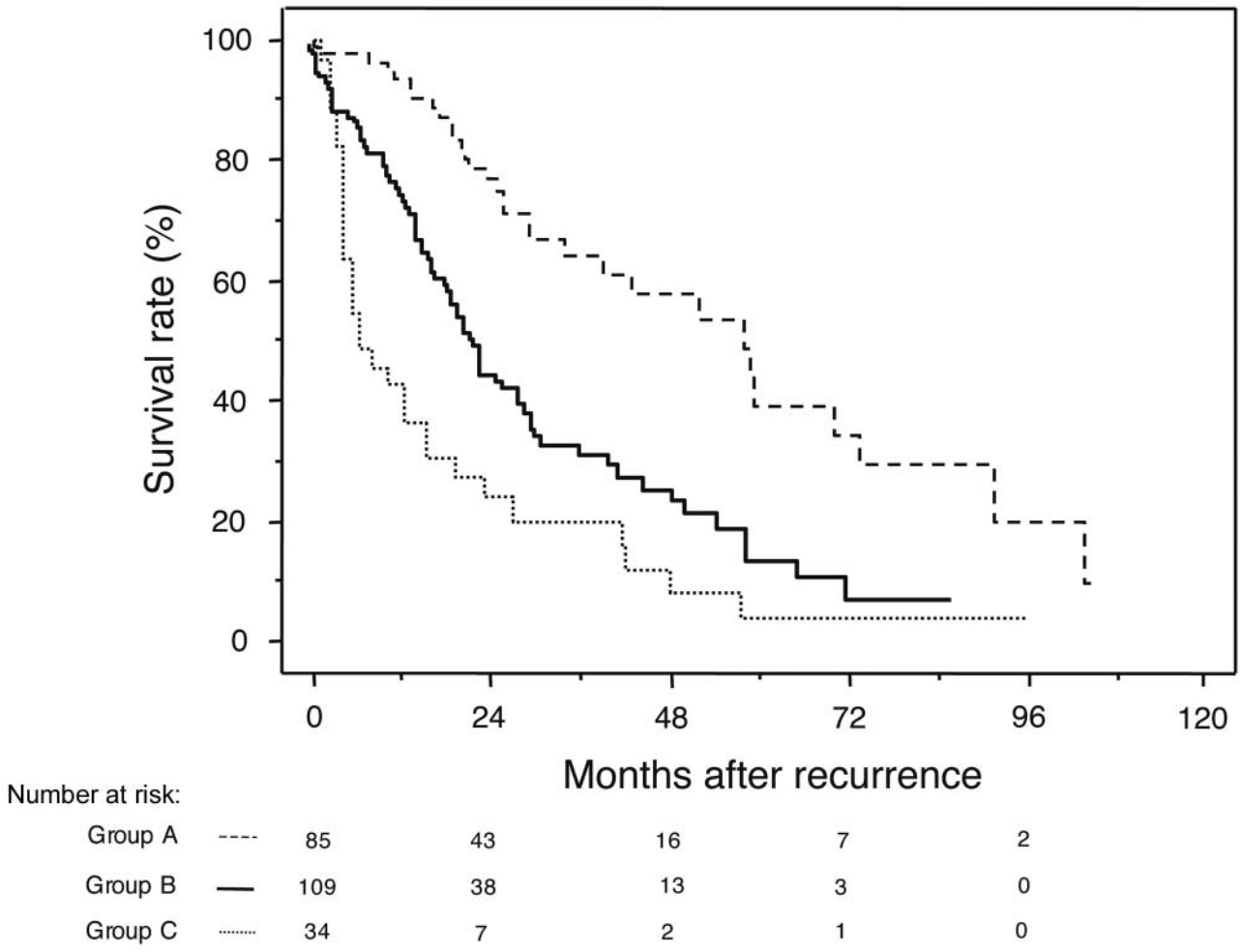

Figure 1. *Survival rate after recurrence of hepatocellular carcinoma (HCC) in each group. The survival rate of group A (broken line) was significantly higher than that of the other two groups (both $p<0.0001$) and the survival rate of group B (unbroken line) was significantly higher than that of group C (dotted line) ($p<0.005$). The number of patients at risk is shown below the graph.*

recurrence (group B) or extrahepatic recurrence (group C) (Figure 1). Group A showed a longer time until recurrence, as well as maintenance of good liver function at recurrence. Lu *et al*. (34) reported that local ablation of recurrent tumors with radiofrequency or microwave energy is a efficient and safe procedure in patients with relatively good function of the liver remnant after hepatectomy. Nakajima *et al*. (35) reported that intrahepatic recurrence of HCC can be treated safely by repeat resection in the same way as the primary tumor, provided that an adequate hepatic functional reserve can be maintained. It was also reported that re-resection is the best treatment for solitary recurrence due to multicentric carcinogenesis in Child-Pugh class A patients (36). Therefore, patients with a solitary intrahepatic recurrence who have well-preserved liver function should receive further curative therapy such as repeat hepatectomy or local ablation.

Multiple intrahepatic recurrences after resection of HCC may be the result of intrahepatic metastasis or may be due to multicentric development of new tumors in the liver remnant and controversy exists about the relative contribution of each mechanism (6, 10, 36, 37). In our patients, early recurrence and multinodular recurrence were associated with intravascular invasion, suggesting that intrahepatic metastasis was the mechanism involved rather than multicentric carcinogenesis. Shimada *et al*. (22) reported that nodular recurrence ($\leq$3 nodules) was associated with a better prognosis than was multiple recurrence ($\geq$4 nodules) and that the main prognostic factor in patients undergoing repeat resection of recurrent HCC was venous invasion by the primary tumor at the time of initial resection (38). These findings support the concept that multiple recurrence is due to intrahepatic metastasis, and thus the prognosis is poor. In

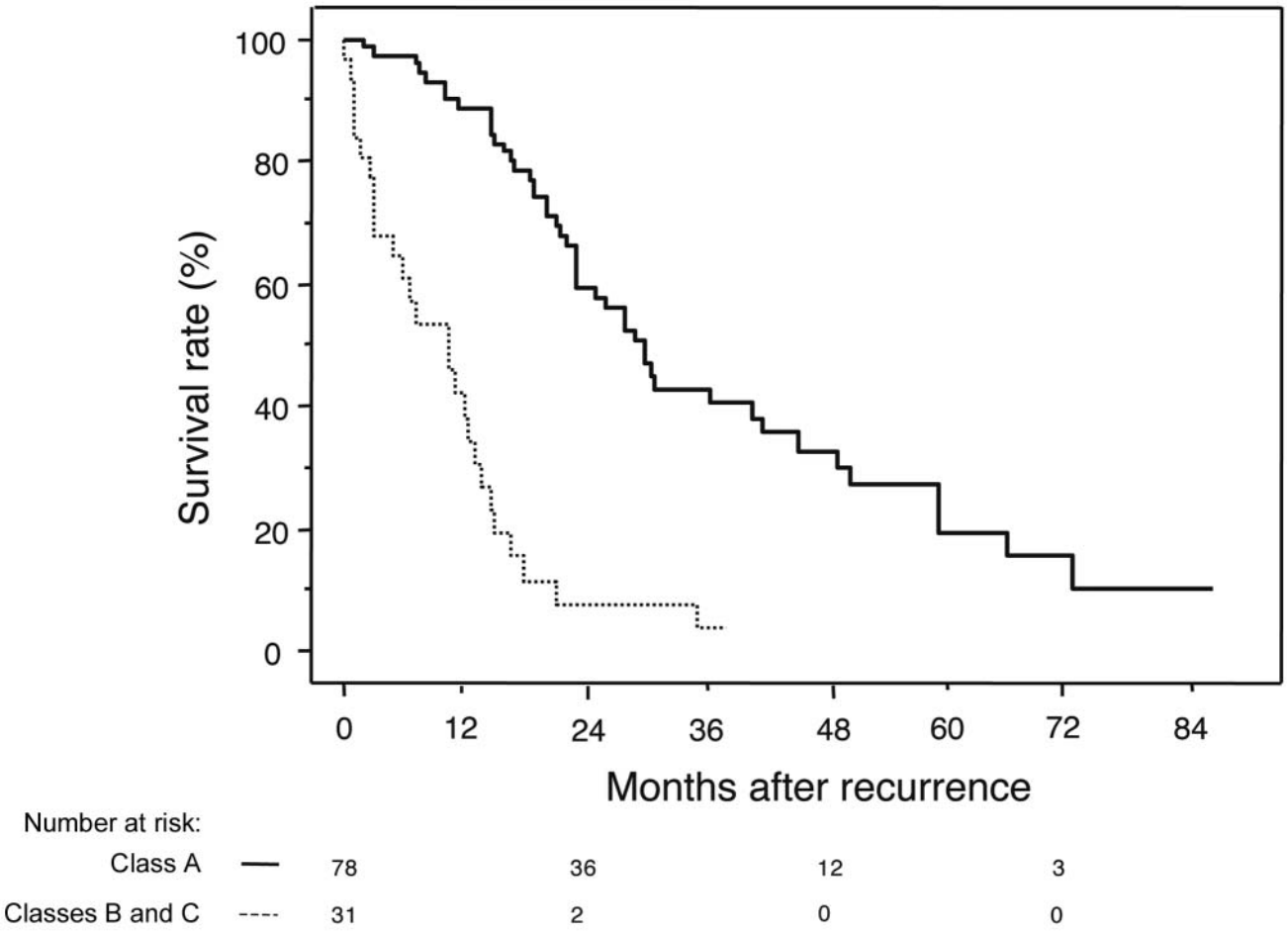

Figure 2. *Survival rate after recurrence of hepatocellular carcinoma (HCC) in group B patients from Child-Pugh class A or class B and C. The survival rate of class A patients (unbroken line) was significantly higher than that of class B/C patients (dotted line) ($p<0.0001$). The number of patients at risk is shown below the graph.*

group B, the survival rate of patients in Child-Pugh class A was significantly higher than that of patients in classes B and C (Figure 2). Patients in class A received significantly more treatment after initial recurrence compared with those in the other two classes (Table III). We and others have reported that the albumin level at the recurrence of HCC is an independent prognostic factor (22, 24, 36). Because liver function was well preserved in the class A patients with multiple intrahepatic recurrence, more aggressive therapy was feasible and this was more likely to be effective.

Conclusion

Postoperative adjuvant chemotherapy should be commenced as early as possible after curative hepatectomy for HCC if the patient is younger, has a large tumor and/or has a high PIVKA-II level. Patients with solitary intrahepatic recurrence who have adequate liver function should receive curative therapy for recurrent HCC such as repeated hepatectomy or local ablation. It is important to maintain the postoperative nutritional status of patients with multiple intrahepatic recurrences in order to allow performance of repeated and aggressive therapy. Thus, surgeons need to be extremely careful to maintain adequate liver function after hepatectomy for HCC and must closely follow-up their patients to detect recurrence.

References

1 Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C *et al*: Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. Ann Surg *229*: 322-330, 1999.

2 Tung-Ping Poon R, Fan ST and Wong J: Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg *232*: 10-24, 2000.

3 Shimada M, Takenaka K, Fujiwara Y, Gion T, Kajiyama K, Maeda T *et al*: Des-gamma-carboxy prothrombin and alpha-fetoprotein positive status as a new prognostic indicator after hepatic resection for hepatocellular carcinoma. Cancer *78*: 2094-2100, 1996.

4 Takenaka K, Kawahara N, Yamamoto K, Kajiyama K, Maeda T, Itasaka H *et al*: Results of 280 liver resections for hepatocellular carcinoma. Arch Surg *131*: 71-76, 1996.

5 Arii S, Tanaka J, Yamazoe Y, Minematsu S, Morino T, Fujita K *et al*: Predictive factors for intrahepatic recurrence of hepatocellular carcinoma after partial hepatectomy. Cancer *69*: 913-919, 1992.

6 Jwo SC, Chiu JH, Chau GY, Loong CC and Lui WY: Risk factors linked to tumor recurrence of human hepatocellular carcinoma after hepatic resection. Hepatology *16*: 1367-1371, 1992.

7 Otto G, Heuschen U, Hofmann WJ, Krumm G, Hinz U and Herfarth C: Survival and recurrence after liver transplantation *versus* resection for hepatocellular carcinoma: a retrospective analysis. Ann Surg *227*: 424-432, 1998.

8 Kosuge T, Makuuchi M, Takayama T, Yamamoto J, Shimada K and Yamasaki S: Long-term results after resection of hepatocellular carcinoma: experience of 480 cases. Hepatogastroenterology *40*: 328-332, 1993.

9 Adachi E, Maeda T, Kajiyama K, Kinukawa N, Matsumata T, Sugimachi K *et al*: Factors correlated with portal venous invasion by hepatocellular carcinoma: univariate and multivariate analyses of 232 resected cases without preoperative treatments. Cancer *77*: 2022-2031, 1996.

10 Nagasue N, Uchida M, Makino Y, Takemoto Y, Yamanoi A, Hayashi T *et al*: Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. Gastroenterology *105*: 488-494, 1993.

11 Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N *et al*: Hepatic resection for hepatocellular carcinoma in the elderly. J Am Coll Surg *192*: 38-46, 2001.

12 Ko S, Nakajima Y, Kanehiro H, Hisanaga M, Aomatsu Y, Kin T *et al*: Significant influence of accompanying chronic hepatitis status on recurrence of hepatocellular carcinoma after hepatectomy. Results of multivariate analysis. Ann Surg *224*: 591-595, 1996.

13 Poon RT, Fan ST, Ng IO and Wong J: Significance of resection margin in hepatectomy for hepatocellular carcinoma. A critical reappraisal. Ann Surg *231*: 544-551, 2000.

14 Tsai TJ, Chau GY, Lui WY, Tsay SH, King KL, Loong CC *et al*: Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. Surgery *127*: 603-608, 2000.

15 Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S *et al*: Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol *38*: 200-207, 2003.

16 Poon RT, Fan ST, Ng IO, Lo CM Liu CL and Wong J: Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer *89*: 500-507, 2000.

17 Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M *et al*: Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology *18*: 1121-1126, 1993.

18 Okada S, Shimada K, Yamamoto J, Takayama T, Kosuge T, Yamazaki S *et al*: Predictive factors for postoperative recurrence of hepatocellular carcinoma. Gastroenterology *106*: 1618-1624, 1994.

19 Izumi R, Shimizu K, Ii T, Yagi M, Matsui O, Nonomura A *et al*: Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. Gastroenterology *106*: 720-727, 1994.

20 Adachi E, Maeda T, Matsumata T, Shirabe K, Kinukawa N, Sugimachi K *et al*: Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. Gastroenterology *108*: 768-775, 1995.

21 Matsumata T, Kanematsu T, Takenaka K, Yoshida Y, Nishizaki T and Sugimachi K: Patterns of intrahepatic recurrence after curative resection of hepatocellular carcinoma. Hepatology *9*: 457-460, 1989.

22 Shimada M, Takenaka K, Gion T, Fujiwara Y, Kajiyama K, Maeda T *et al*: Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. Gastroenterology *111*: 720-726, 1996.

23 Kaibori M, Matsui Y, Kitade H, Kwon AH and Kamiyama Y: Hepatic resection for hepatocellular carcinoma in severely cirrhotic livers. Hepatogastroenterology *50*: 491-496, 2003.

24 Kaibori M, Matsui Y, Yanagida H, Yokoigawa N, Kwon AH and Kamiyama Y: Positive status of alpha-fetoprotein and des-gamma-carboxy prothrombin: important prognostic factor for recurrent hepatocellular carcinoma. World J Surg *28*: 702-707, 2004.

25 Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S *et al*: Surgery for small liver cancers. Semin Surg Oncol *9*: 298-304, 1993.

26 Imamura H, Sano K, Sugawara Y, Kokudo N and Makuuchi M: Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg *12*: 16-22, 2005.

27 Couinaud C: Les hepatectomies elargies. *In*: Le Foie: Etudes Anatomiques et Chirurgicales. Couinaud C (ed.). Paris: Masson, pp. 400-409, 1957.

28 Adachi E, Maehara S, Tsujita E, Taguchi K, Aishima S, Rikimaru T *et al*: Clinicopathologic risk factors for recurrence after a curative hepatic resection for hepatocellular carcinoma. Surgery *131*: S148-152, 2002.

29 Utsunomiya T, Shimada M, Shirabe K, Kajiyama K, Gion T, Takenaka K *et al*: Clinicopathological characteristics of patients with extrahepatic recurrence following a hepatectomy for hepatocellular carcinoma. Hepatogastroenterology *48*: 1088-1093, 2001.

30 Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K *et al*: Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer *51*: 863-877, 1983.

31 Lau WY, Leung TWT, Ho SKW, Chan M, Machin D, Lau J *et al*: Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. Lancet *353*: 797-801, 1999.

32 Huang YH, Wu JW, Lui WY, Chau GY, Tsay SH, Chiang JH *et al*: Prospective case-controlled trial of adjuvant chemotherapy after resection of hepatocellular carcinoma. World J Surg *24*: 551-555, 2000.

33 Takenaka K, Yoshida K, Nishizaki T, Korenaga D, Hiroshige K, Ikeda T *et al*: Postoperative prophylactic lipiodolization reduces the intrahepatic recurrence of hepatocellular carcinoma. Am J Surg *169*: 400-405, 1995.

34 Lu MD, Yin XY, Xie XY, Xu HX, Xu ZF, Liu GJ *et al*: Percutaneous thermal ablation for recurrent hepatocellular carcinoma after hepatectomy. Br J Surg *92*: 1393-1398, 2005.

35 Nakajima Y, Ko S, Kanamura T, Nagao M, Kanehiro H, Hisanaga M *et al*: Repeat liver resection for hepatocellular carcinoma. J Am Coll Surg *192*: 339-344, 2001.

36 Poon RTP, Fan ST, Lo CM, Liu CL and Wong J: Intrahepatic recurrence after curative resection of hepatocellular carcinoma-Long term results of treatment and prognostic factors-. Ann Surg *229*: 216-222, 1999.

37 Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Ozaki H *et al*: Recurrence of hepatocellular carcinoma after surgery. Br J Surg *83*: 1219-1222, 1996.

38 Shimada M, Takenaka K, Taguchi K, Fujiwara Y, Gion T, Kajiyama K *et al*: Prognostic factors after repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg *227*: 80-85, 1998.

Received February 26, 2007
Accepted April 30, 2007