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原　　著

The Outcomes of the Operated Hepatocellular Carcinoma Patients

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Summary

During the past 5 1/3 years, we have performed 521 hepatic resections, of which 308 cases were hepatocellular carcinomas (HCC). Two hundreds and sixty cases of the 308 HCC patients were studied on their outcomes. These patients included 198 males and 62 females, whose ages ranged from 29 to 84 years. Underlying cirrhosis of the liver was found in 66% of the patients. Hepatectomized patients were classified into 5 groups according to the curability as follows; Group A, the resection of the tumor-bearing segment and additional segment; Group B, the complete resection of the tumor with more than 1.0 cm free surgical margin; Group C, the complete resection of the tumor with less than 1.0 cm free surgical margin; Group D, the incomplete resection of the tumor; Group E, the surgical approach for advanced HCC with tumor thrombi in the main trunk or the 1st branch of the portal vein and/or the inferior vena cava, with multiple daughter nodules in both lobes and with tumor recurrence. The number of patients in Groups A, B, C, D and E was 14 (5.4%), 105 (40.4%), 61 (23.4%), 14 (5.4%) and 66 (25.4%), respectively. There were 5 death (2.6%) among the 194 patients of Group A–D within 30 days after operation and 12 death (18.2%) in Group E. The overall 5-year survival rate of all 249 patients except for 11 surgical death cases was 32%. Whereas, 5-year suvival rate for Group A and B were 100% and 47%, 4-year rate for Group C was 44%, respectively. One-year survival rate for Group E was 57% and we had 10% of cases survived for more than 3 years in this group.

Introduction

The long-term survival of hepatocellular carcimona (HCC) patients is unable to be expected with any treatment other than resection. The resection rate of HCC is much lower compared with those of the gastrointestinal tract cancers[1,7,15,16]. Its poor resectability is caused by its intrahepatic

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metastasis via the portal vein and the high incidence of associated cirrhosis. The invasion of HCC to the inflow and outflow vessels mostly restricts the resectability, although operative techniques have been developed to take invasion of the portal vein and inferior vena cava[2,3,6,28]. On the other hand, in Japan, most of the HCC occurs along with liver cirrhosis, a condition which restricts major hepatic resection. Recently we have shown that the extensive resection of the cirrhotic liver can be safely performed when the hepatic function is accurately monitored during operation by the serial measurement of arterial ketone body ratio (acetoacetate/β-hydroxybutyrate, AKBR), which reflects the hepatic mitochnodrial redox potential[19–27,29]. Improvements in surgical technique, so as not to cause a prolonged decrease in AKBR below the critical level, have further enabled us to perform ultimate operations for HCC[9,10].

The present study was undertaken to characterize the outcomes of 260 cases of 308 HCC patients in 521 hepatectomized patients during the past 5 1/3 years in our department.

Patients and Methods

We performed hepatic resections of 521 patients during the past 5 years and 4 months, from January 1, 1985 to April 30, 1990 at Second Department of Surgery, Kyoto University Hospital. During this period, we experienced the operations for 308 cases with HCC, 73 with bile duct carcinomas, 58 with metastatic liver cancer, 68 with benign diseases and 14 with other hepic ill conditions.

In hepatic resection, the intrahepatic invasion of HCC spreading via the portal blood stream, and the direct invasion to the surrounding liver tissue are important viewpoints to be focused. Thus, the larger the resected portal vein branching area, and the wider the surgical margin from the tumor, the higher the curability should be. In the present study, a 1.0 cm free surgical margin from the tumor edge was considered to be a safe margin against direct invasion of the tumor.

From these considerations, the hepatectomized patients were classified into 5 groups according to their curability as follows. Group A (absolute radical resection): adopted in the case of the tumor localized within one segment. This is the resection of one tumor-bearing segment and one additional segment. Group B (relative radical resection): the complete resection of the tumor with more than 1.0 cm free surgical margin. Group C (relative non-radical resection): the complete resection of the tumor with less than 1.0 cm free surgical margin. Group D (absolute non-radical resection): the incomplete resection of the tumor. Group E (palliative resection): the aggressive surgical approach for advanced liver cancer. Two hundreds and sixty cases of HCC patients were studied on their outcomes, which were ascertained. Among the 260 hepatectomized HCC patients, the number of patients for Groups A, B, C, D, and E was 14 (5.4%), 105 (40.4%), 61 (23.4%), 14 (5.4%), and 66 (25.4%), respectively. There were 5 deaths (2.6%) among the 194 patients of Group A–D within 30 days after operation (surgical death) and 12 deaths (18.2%) in Group E. The long-term survival rate after discharge from hospital was obtained from the record of our out-patient clinic. Follow-up on some patients by other clinics was ascertained by the referring doctors, the patients, or their families.

All results are shown as means±SEM. Student's t test, was used for statistical analysis. Survival curves after hepatic resection were obtained using the Kaplan-Meier method[8], and the comparison of survival curves was done using the generalized Wilcoxon test[5]. A value of $P<0.05$ was considered significant.

Table 1 Relationship between Operative Method, Liver Cirrhosis and Clinical Data

Operative method	No. of cases	Liver Cirrhosis#	K-ICG	ChE $\times 10^2$ IU/L	Total Bilirubin (mg/dl)	RTI
Enucleation or Partial resection	68	(+) 55	0.09±0.03+	1.76±0.57	1.25±0.55	0.26±0.04*
		(−) 13	0.12±0.08	1.66±0.60	1.00±0.40	0.98±0.09
Subsegmentectomy	11	(+) 6	0.10±0.06*	1.45±0.25	0.91±0.33	0.33±0.03*
		(−) 5	0.12±0.04	2.24±2.32	1.01±0.33	0.93±0.22
Segmentectomy	65	(+) 44	0.106±0.038*	2.05±0.85	0.99±0.32*	0.49±0.06*
		(−) 21	0.134±0.046	2.55±1.21	0.77±0.24	0.93±0.09
Lobectomy	67	(+) 44	0.145±0.20	2.10±1.01*	1.08±0.78	0.56±0.05*
		(−) 23	0.134±0.04	2.88±1.20	0.91±0.60	0.95±0.14
Extended lobectomy	29	(+) 16	0.111±0.043	2.50±0.81	1.39±0.60**	0.56±0.08*
		(−) 13	0.135±0.048	1.85±0.74	0.66±0.22	1.04±0.07
Tri-segmentectomy	20	(+) 7	0.139±0.044	2.55±0.55	1.21±0.43	0.59±0.06*
		(−) 13	0.148±0.069	2.06±0.86	1.07±0.57	0.99±0.08

#) diagnosed microscopically

+) Mean±SEM.

* $p<0.05$ ** $P<0.01$, compared with non-cirrhotic liver

Results

Two hundreds and sixty cases of 308 patients who underwent hepatic resection for the treatment of HCC were involved in this study. Their ages ranged from 29 to 84 years. The patients were composed of 198 males and 62 females. Incidence of HCC was the highest in the 6th and 7th decades. Major resections of more than two segmentectomy were performed on 116 patients (45%) (Table 1), of which 67 (58%) had histologically confirmed cirrhosis. Minor resection of less than one segmentectomy was performed on 144 patients (55%), of which 105 (73%) had cirrhosis (Table 1). Hepatic resections of less than one segmentectomy were mainly performed in cirrhotic patients with markedly decreased K-ICG and RTI[14]. Simultaneous operations for esophageal varices were performed on seven patients. All of these operations were prophylactic, and were done only when preoperative endoscopic examinations revealed the red color sign on the varices. Distal spleno-renal (Warren) shunt was performed in six patients and transabdominal esophageal transection in one patient. Postoperative sclerotherapy was performed in four patients.

Of the 66 Group E patients, there were 40 cases with tumor thrombi in the main trunk or the 1st branch of the portal vein and/or the inferior vena cava, 18 cases with multiple small daughter nodules in both lobes and 8 cases with tumor recurrence.

Of the 40 patients with tumor thrombi of the portal vein, hepatic vein and/or inferior vena cava, there were 8 hepatectomy alone (tumor thrombus of the 1st branch of the portal vein), 24 hepatectomy concomitant with thrombectomy, and 8 hepatectomy with reconstruction of the inferior vena cava.

In 15 out of 40 patients, tumor thrombi developed from the main tumor to occlude the portal vein trunk and the portal vein of the opposite side. In such patients, extended hepatic resection was performed together with the removal of the tumor thrombus in the portal vein of the residual liver or with resections of the portal vein segments, including tumor thrombus, according to one of the following techniques: (1) balloon catheter method for removal of portal vein tumor thrombus, (2) bypass

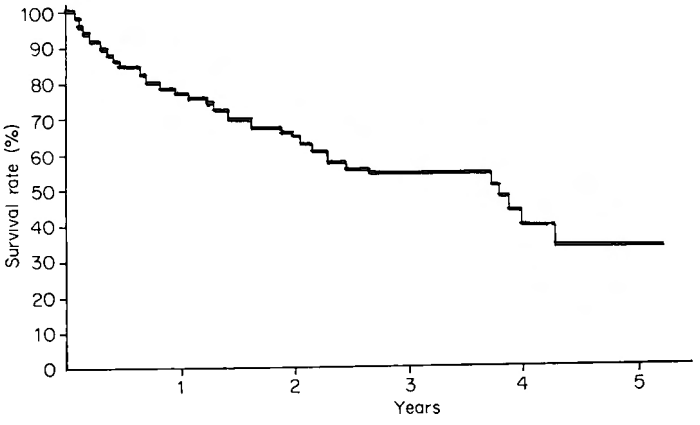

Fig. 1 The overall survival rate curve of 249 patients, except for surgical death who were operated on for hepatocellular carcinoma during the past 5 1/3 years

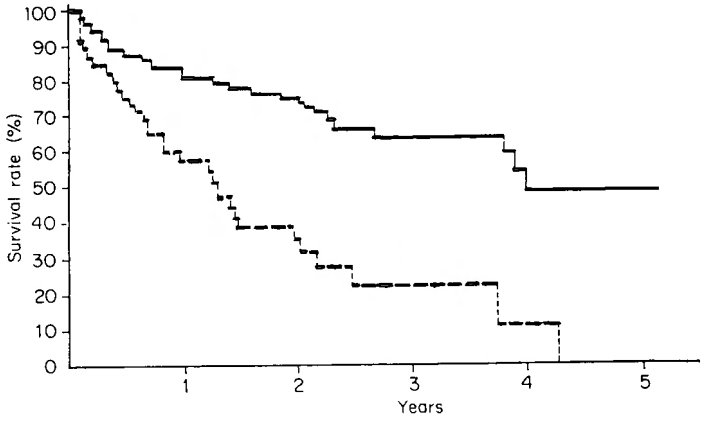

Fig. 2 The survival rate curve of 194 patients performed conventional hepatic resections (Groups A–D) (represented by continual line), and of 66 patients performed aggressive operation (Group E) (represented by interrupted line)

grafting between the umbilical part of the left portal vein (or the confluence of the right secondary branches) and the intact portal vein trunk by autogenous right external iliac vein, and then the removal of the portal vein including tumor thrombus, (3) portal vein reconstruction by end to end anastomosis and (4) removal of tumor thrombus through portal vein incision by hepatic vascular exclusion method associated with temporary triad clamping and occlusion of the inferior vena cava below and above the liver, using a centrifugal pump driven bypass. Two of 15 cases died of hepatic failure within 40 days after operation. The survival of the other 13 operated patients ranged from 5 months to 3 years and 6 months. In ten of the patients, we began TAE two weeks after the operation.

Eight patients were operated on by the above hepatic vascular exclusion method, using a centrifugal pump driven bypass. Four of 8 patients had liver cirrhosis. The major hepatic resections were performed in all patients, using an EPTFE graft (Gore-Tex^{R}, 24 mm in diameter) for the resected part of the inferior vena cava in 3 patients, the removal of the tumor thrombi in the portal

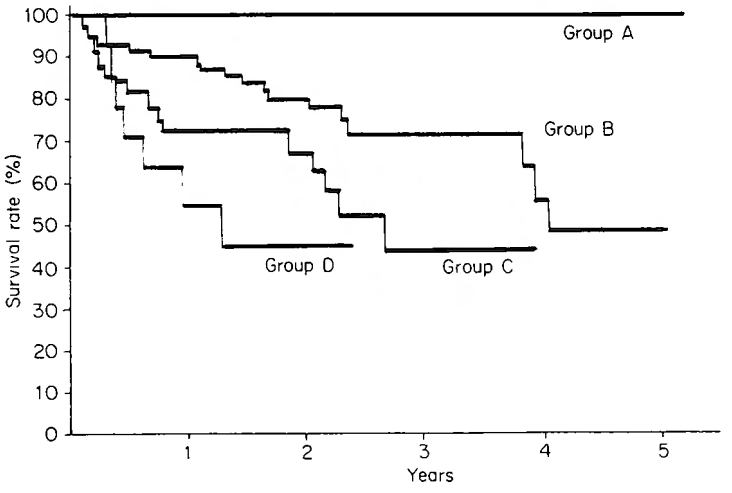

Fig. 3 The survival rate curve of the each group patient perfomed conventional hepatic resection

vein in one patient and a partial resection of the inferior vena cava wall in 3 patients. The operative mortality rate was nil.

In 18 patients with main tumor and multiple small nodules, the main tumor was resected with percutaneous and intraoperative ethanol injection therapy (PEIT) for small nodules in 10 cases, and for enucleations of small nodules in 8 cases.

Eight patients were reoperated for tumor recurrence within 1 year after 1st operation. All patients are alive from 200 days to 2300 days after the reoperation.

Fig. 1 illustrates the overall survival curve of all 249 patients except for 11 surgical death cases. The 1-year survival rate was 76%, 2-year rate 64%, 3-year rate 53%, 4-year rate 38% and 5-year rate 32%. Fig. 2 shows 2 survival curves in comparison between convevtional hepatic resection and aggressive operation. Even in the latter group, the 1-year survival was 57% and we had more than 3-year survived patients (10%). Fig. 3 shows the survival curve of each patient group, who undergone conventional hepatic resections. One-year survival rates were 100%, 88%, 71% and 55% for Groups A, B, C and D; 2-year rates 100%, 78%, 64% and 46% for Groups A, B, C and D; 3-year rates 100%, 72%, and 44% for Groups A, B and C; 4-year rates 100%, 48% and 44% for Groups A, B and C; 5-year rates 100% and 47% for Groups A and B, respectively.

There were significant differences between Group A–B and Groups C, D and E during all periods ($p<0.05$), but there was no significant difference between Groups C and E.

Discussion

Surgical resection is the surely curable way for HCC, which other adjunctive means such as transcatheter arterial chemoembolization (TAE) cannot be expected to provide. The aim of this study is to improve the degree of resectability and curability and to prevent the recurrence of HCC. The resectability rate of primary liver cancer varied widely from 7.3% to 35.6%. NAGASUE *et al.*[17] reported a high rate of 63%. In our series hepatic resection was performed in 308 of the 346 total patients with HCC (89% resectability). However, this is the hepatic resection rate for patients who were selected for operation at our outpatient clinic or referred to us by some other clinic. Only

about 20% of all cases diagnosed as HCC are subjected to hepatic resection in Japan. In view of these facts, we have been making efforts to increase the resectability rate by taking an aggressive surgical approach. On the other hand, the long-term survival of patients with HCC after resection is determined mainly by the biologic features of the tumor itself. This is connected with the fact that the main cause of death after discharge from the hospital is the recurrence of HCC. Therefore, it is recommended that the operative procedure by which the recurrence rate is the lowest be selected in order to achieve long-term survival. For technical reasons such as the size or location of the tumor or vascular invasion, and other attendant factors such as coexisting liver cirrhosis, conventional liver resection tends to be of limited value. In the present study, liver cirrhosis existed in the 67% of HCC patients, as same incidence as the former histological investigation[13]. Undetectable minute tumors are frequently found in the resected specimen surrounding the tumor. We have proposed that an additional one segment resection should be performed for patients with HCC localized within one segment. When an additional one segment resection cannot be performed, such as in patients whose tumors are large or associated with severe liver cirrhosis, the hepatic resection should include more than 1 cm of free surgical margin from the tumor. Unilobular multiple tumors or multiple bilobular tumors should be resected by removing sufficient surrounding hepatic parenchyma to encompass the tumor nodules as well. HCC often involves the portal vein and/or hepatic vein. An advanced tumor thrombus sometimes grows into the lumen towards the portal vein trunk and/or the contralateral branch across the confluence. Such terminal stage tumors usually exclude patients from surgery and furthermore contraindicate TAE. In our study, 40 patients with tumor thrombi in the portal vein trunk, hepatic vein and/or inferior vena cava were operated on. In such patients, extended hepatic resection was performed together with the removal of the tumor thrombus in the portal vein of the residual liver or with resections of the portal vein segments, including tumor thrombus, by vascular reconstructin of the residual liver.

NAGAO *et al.*[15] proposed that the more extensive the resection, the lower the recurrence rate would be, since, in small tumors less than 5 cm in diameter, the recurrence rate after segmentectomy was lower than that after local excision of the liver. OKAMOTO *et al.*[18] reported 26.7% and 13.3% survival rates for 3 years and 5 years, respectively, while NAGAO *et al.*[15] reported 42% and 25%, respectively. FORTNER *et al.*[4] reported an 88% three year survival rate after apparently curative resection. It would be inconclusive to compare our results directly with these results, since these various studies used different methods of patient selection, employed different curative rates after operation, and so on. But to our knowledge there has never been any group instituting a program of aggressive surgical treatment such as ours, aimed specifically at extending the limits of indication for hepatic resection[11,12]. Operative mortality rate after HCC resection was reported by NAGASUE *et al.*[17], NAGAO *et al.*[15], and IWATSUKI *et al.*[7], as 7.6%, 10% and 13.8%, respectively. In our conventional hepatectomy group, the operative mortality was 2.6%, compared to 18.2% for Group E. We think that the operative death of the latter group can be further kept to a minimum by intensive metabolic care. The aggressive surgical approach should be allowed to extend the limits of conventional hepatic resection. Multimodality treatment protocols combining aggressive surgical approach with other preoperative or postoperative techniques such as TAE and/or PEIT will also contribute to the improvement of the present results.

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和文抄録

肝切除施行肝細胞癌症例の予後

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われわれは，1985年1月から1990年4月までの間に521例の肝切除術を施行したが，そのうち308例が肝細胞癌であった．308例のうち260例について術後の予後について検討した．症例の内訳は男198例，女62で，66%の例に肝硬変を合併していた．われわれは，その根治性から A: 絶対治療切除14例（5.4%），B: 相対治療切除105例（40.4%），C: 相対非治療切除61例（23.4%），D: 絶対非治療切除14例（5.4%），E: 延命手術66例（25.4%）の5群に分類すると，術後30日以内の死亡は A-D 群の194例中5例（2.6%），E 群の12例（18.2%）にみられた．全症例について全体の5年生存率は32%であったが，A 群では100%，B 群では47%であった．C 群の4年生存率は44%であった．E 群では1年生存が57%にえられ，3年以上生存したものが10%にみられた．