Current status of surgical treatment for hepatocellular carcinoma

Shiro Yogita, and Seiki Tashiro

First Department of Surgery, The University of Tokushima School of Medicine, Tokushima, Japan

Abstract: The therapeutic modalities for hepatocellular carcinoma (HCC) have diversified during the past decades, and in particular, the treatment has mainly been concentrated on small HCC of 3 cm or less. Therefore, it has become very important for surgeons to be able to identify the clinical indications for liver resection in HCC.

We reviewed data on liver resection for HCC using the National Primary Hepatic Cancer follow-up survey report of the Liver Cancer Study Group of Japan, indicating problem associated with liver resection for HCC. As a result, the indications of surgical treatment for HCC are as follows : (1) In patients with HCC of 3 cm or less in diameter, a solitary HCC indicates liver resection. However, priority should be given to medical treatment such as percutaneous transhepatic ethanol injection therapy, microwave coagulative necrosis therapy for multiple HCC and patients with clinical states II or III. (2) HCC between 3 cm and 5 cm in diameter is a good indicator for liver resection. Solitary HCC indicates liver resection as a first choice. (3) HCC greater than 5 cm in diameter and cases with tumor stages II or III indicate liver resection. (4) There are limits to treating HCC with tumor thrombus in the second branch of the portal vein (Vp2) and tumor thrombus in the first branch, the trunk of the portal vein or in a branch on the opposite side (Vp3) only by liver resection. (5) HCC with tumor thrombus in the right, middle or left hepatic vein trunk, posterior inferior hepatic vein trunk or short hepatic vein (Vv2) and with tumor thrombus in the inferior vena cava (Vv3) are indicators for liver resection. A limited resection according to Glissons structure and with a negative surgical margin can be performed in HCC of 5 cm or less, however an extended resection is required for HCC greater than 5 cm. Furthermore, the extent of liver resection should be considered according to the hepatitis virus. Finally, it was emphasized that effective measures against the postoperative recurrence was essential in order to improve the outcome of HCC. J. Med. Invest. 47 : 91-100, 2000

Key words **:** *indication of liver resection, hepatocellular carcinoma, tumor size*

INTRODUCTION

Japan Soc. of Hepatology published a "Liver cancer white paper" in 1999. It reported that the whole aspect of hepatocellular carcinoma (HCC) in Japan has been significantly clarified during the past several decades, and in the future, to develop the promotion of HCC eradication is urgently needed (1). However, with regard to the treatment of HCC, the therapeutic modalities have diversified with the clarification of the characteristics of HCC, and the indication of surgical treatment (liver resection) for HCC have also changed (2).

In this paper, the treatment outcome of HCC at First Department of Surgery, The University of Tokushima School of Medicine was mainly described, with referrence to the national primary liver cancer follow up survey report (National Re-

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Address correspondence and reprint requests to Shiro Yogita, M.D., First Department of Surgery, The University of Tokushima School of Medicine, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-631-9698.

port) of the Liver Cancer Study Group of Japan, which indicated the problems associated with liver resection for HCC.

ABBREVIATIONS AND STATISTICAL ANALYSIS

The abbreviations and the definitions (tumor staging, clinical stage, operative curability etc.) used here were based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan (3). Statistical analysis was carried out using Student's t test for unpaired observations. Cumulative survival rates and curves were calculated using the Kaplan-Meier method. The log-rank test was used to compare the survival curves. P-values less than 0.05 were considered statistically significant.

I. Characteristics and the problem of HCC in Japan

Over 95% of HCC in Japan is associated with chronic liver disease (i.e. chronic hepatitis, liver cirrhosis) by persistent infection of hepatitis B virus (HBV) or hepatitis C virus (HCV), and development in the liver is considered to be multicentric. In recent years, over 80% of cases were related in HCV (1). In the treatment, the high recurrence rate after treatment has become a serious problem.

When it was reported in the 13th National Report, the recurrence rate within the 2 years investigation period was 27.5%, and 85.7% of those recurring within 1 year after treatment. The recurrence site was a remnant liver in 84.6% of cases (4).

This has become a problem even for liver transplantations for HCC in Europe and the United States of America. In the liver transplantations of 422 HCC patients was observed in the 1998 Registry Report, that the cumulative survival rates were 72.2% after 1 year, 63.4% after 2 years, 47.4% after 4 years, 44.4% after 5 years, and the recurrence rate was reported as 25.6% (108 of 422 patients) (5). Thus, because of the high recurrence rate after transplantation and the poor prognosis compared with the findings of liver transplantation for other diseases, the indications of liver transplantation for HCC have also been discussed.

II. Changes to the therapeutic modality for HCC

In the 13th National Report (1998), liver resection (Hr), transcatheter arterial embolization (TAE), Chemo-Lipiodolization (Chemo-Lp), Chemotherapy (Chemo), ethanol injection therapy (EIT), Microwave coagulative necrosis therapy (MCT) were all used as a therapy (4). The performed rates for HCC were Hr : 28.6%, TAE : 46.2%, Chemo-Lp : 60.0%, Chemo : 11.3%, EIT : 24.2% and MCT : 3.1%. The proportion of MCT in these modalities has doubled since the 12th National Report (1996) (6). Although it was 11.8% on EIT in the 10th National Report (1992) (7), it has greatly increased to 24.2% in the 13th National Report.

In addition, liver resection was carried out at 34.4% in the 12th National Report (1996) (6), but in the 13th National Report (4), it had decreased to 28.6% despite the increase in the number of registered patients. Also, in our department, the number of liver resections for HCC has decreased year by year since the peak year 1993 (Fig. 1a). The features of HCC themselves which refers to surgery have also changed.

The cases of our department were examined by dividing into prophase (before 1993, number of patients (n)=88) and later stages (after 1994, n=93). In the latter stage, tumor stage IV-A increased to 30.4%, and stage I decreased to 5.4% (Fig. 1b). That is to say, advanced HCC over 5 cm in diameter and with multiple nodules had increased. As a result, cases which required lobectomy (Hr2) also increased to 27.3%. Cases in which curative resection was possible decreased, and the proportion of non-curative resections increased. Differences appeared in the survival rate for tumors treated like this, the latter stage showed a poor cumulative survival rate (p= 0.1169) and disease-free survival rate (p=0.0037).

III. Results and indications for surgical treatment for HCC

1) The outcome of HCC patients treated surgically in our department

①Survival rate and cause of death

A total of 181 patients underwent liver resection for HCC between January, 1985 and December, 1999 at our department. The cumulative survival rate of all cases were 77.3% after 1 year, 57.8% after 3 years, 40.4% after 5 years, 36.0% after 7 years, 9.1% after 10 years, and the disease-free survival rates were 60.0% after 1 year, 29.8% after 3 years, 24.2% after 5 years, 10.3% after 7 years and 10.3% after 10 years. The operative mortality rate was 2.2% (4 patients). At the time of analysis, 102 patients had died : 64 (62.7%) died because of their tumors, 29 (28.4%) died due to liver failure, 3 died due to infection and 6 died by other causes. In the 13th National Report (4), the cumulative survival rate of all cases who underwent Hr (n=16728, 1978-1995) were 83.2% after 1 year, 62.6% after 3 years, 45.3% after 5 years and 21.2%

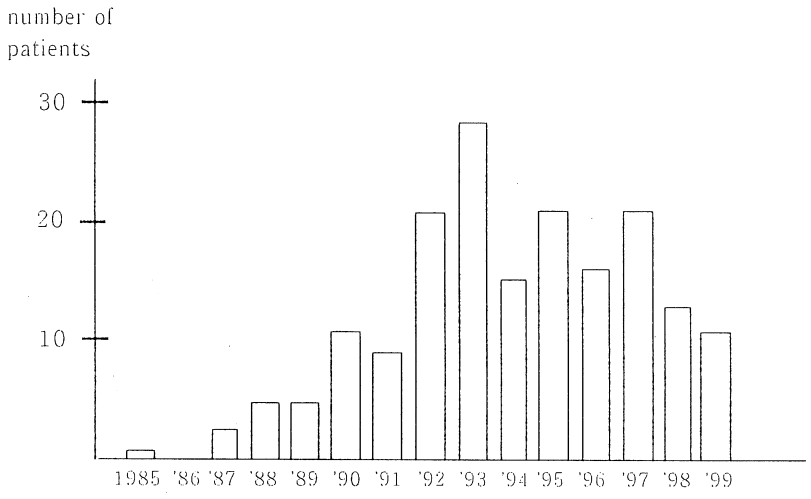

Fig. 1 a

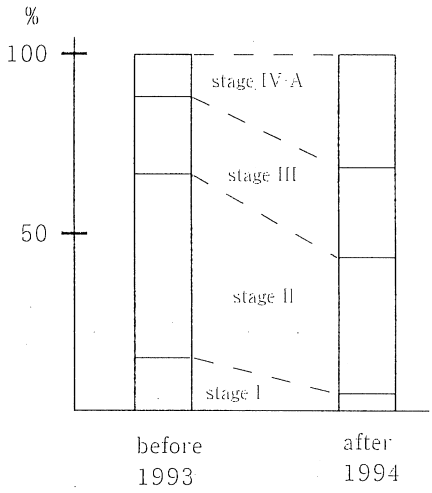

Fig. 1 b

Fig. 1 a. Yeary number of patients who underwent liver resection
1 b. Proprotion and comparison of tumor stage between prophse (before 1993, n=88) and later stage (after 1994, n=93) p=0.0077

after 10 years, and the operative mortality rate was 1.5%. In addition, the cumulative survival rate in patients treated by EIT (n=2080, 1988-1995) were 90.2% after 1 year, 63.1% after 3 years, 40.8% after 5 years, and in patients who underwent TAE were 60.4% after 1 year, 26.1% after 3 years, 13.3% after 5 years and 3.5% after 10 years .

②Survival based on tumor size

In comparison of tumor diameters 2 cm or less (n=31) and 2 cm to 3 cm (n=50), the patients profiles and features of HCC did not differ between them, and there was no significant difference in cumulative survival rate and disease-free survival rate. Therefore, all cases (n=177) were divided into three groups ; small-sized HCC (tumor size≦3.0 cm, n=81), middle-sized HCC (3.0<tumor size≦5.0 cm, n=54), and large-sized HCC (tumor size>5.0 cm, n=42).

Cumulative survival rates at 3 cm or less in diameter were 86.2% after 1 year, 66.7% after 3 years, 48.9% after 5 years, 41.8% after 7 years, and there was no difference between the 3 cm to 5 cm groups ; 81.3% after 1 year, 67.6% after 3 years, 46.6% after 5 years, 46.6% after 7 years. However, the disease-free survival rate of 3 cm or less were 63.4% after 1 year, 28.2% after 3 years, 20.7% after 5 years, 5.3% after 7 years, and in the 3 cm to 5 cm group, they were 77.9% after 1 year, 45.9% after 3 years, 39.9% after 5 years, 25.1% after 7 years, and in cases of 3 cm or less it was significantly poorer (p=0.0350).

The cumulative survival rates of 5 cm and over was 51.9% after 1 year, 25.7% after 3 years, 14.7% after 5 years, and the disease-free survival rate was 35.7% after 1 year, 8.8% after 3 years, 8.8% after 5 years, which were significantly poorer than the other 2 groups (p<0.0001) (Fig. 2 a, b).

③Characteristics of patients with small-sized HCC (tumor size≦3 cm)

Despite the cumulative survival rate being almost equal between the cases of 3 cm or less and the cases of 3 to 5 cm in our data, the disease-free survival rate of cases of 3 cm or less was poorer than in cases of 3 to 5 cm. The reason for this was studied by comparing several factors influencing the survival rates of patients and the postoperative recurrence of HCC. As a result, the characteristics of patients with HCC 3 cm or less were as follows (Tab. 1) ; In the tumor-related factors, the incidence of solitary HCC was low at 61.7% (p=0.123), and that of multicentric HCC were high at 24.7% (p=0.0123), and well differentiated HCC was 50.0% (0.0021). In host-related factors, concomitant liver cirrhosis (Z2) was 65.8% (p=0.02), indocyanine-green retention ratio at 15 min (ICGR 15) was 21.7% ± 11.3% (p=0.0030). In hepatitis virus, no difference was recognized. In surgery-related factors, subsegmentectomy (HrS) or less was 88.8% (p=0.0001). However despite small ranged liver resections, no difference was recognized for intraoperative blood loss (p=0.3181). Although the proportion of absolute curative resection was high for 3 cm or less cases in operative curability,

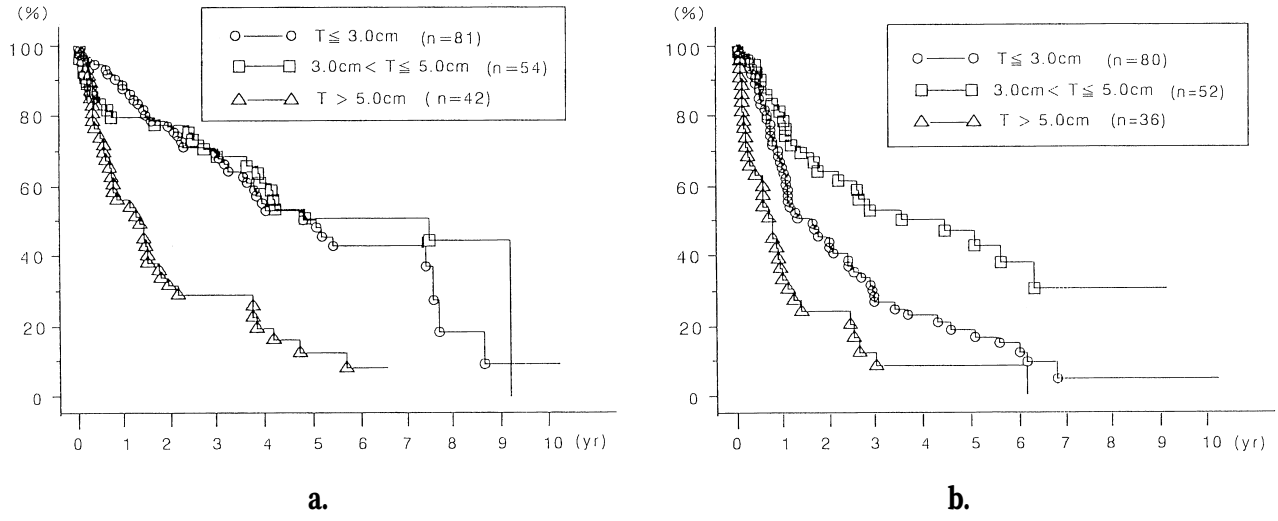

Fig. 2. Cumulative survival rate based on tumor size. T : tumor size n : number of patient
a. Cumulative survival rate.
survival rate of HCCs greater than 5 cm is poorer than the other 2 groups ($p<0.0001$).
b. Disease-free survival rate.
there are significant differences among the 3 groups ($p=0.0350$).

Table 1. Proprtion and comparison of patients by tumor size

Factor	Tumor size (T)		p-value
	T≦3.0 cm	3.0 cm < T ≦ 5.0 cm	
Tumor factor			
well	50.0%	20.0%	0.0021
solitary	61.7%	81.5%	0.1230
multicentric	24.7%	3.0%	0.0123
vp positive	25.3%	33.9%	0.0426
Host factor			
clinicalstage II + III	72.7%	59.2%	0.1498
Z2	65.8%	43.3%	0.0200
ICGR15	21.7±11.3%	16.2±8.7%	0.0030
HCV positive	70.3%	66.7%	0.4133
Operative factor			
absolute non-curative resection	16.3%	3.7%	0.0009
blood loss	882±801g	1032±834g	0.3181
Cause of death			
liver failure	41.8%	30.0%	0.6046
Recurrence			
solitary	62.5%	56.6%	0.0585
multicentric	28.6%	13.3%	0.1692

% : number of patients with factor/total number of each group, well : well diferrentiated HCC, multicentric : HCC of multicentric occurrence, VP positive : tumor thrombus exists in the portal vein., Z 2 : liver cirrhosis, ICGR15: indocyanine green retention ratio at 15 min., HCV postive : patient with HCV antibody, clinical stage and absolute non-curative resection : criteria used The General Rules for the Clinical and Pathological Study of Primary Liver Cancer

Table 2. Survival rates and recurrence rates at 5 years after EIT at the leading 2 institutions in Japan and the our findings by liver resection for small-sized HCC (tumor size≦3 cm, tumor number≦3 nodules).

institute	modality	number of patients	survival rates					recurrence rates at 5yrs
			1yr	3yrs	5yrs	7yrs	10yrs	
our cases	Hr	181	86.0%	66.3%	48.2%	41.2%	8.8%	80.5%
Univ. of Tokyo	EIT	349	93%	74%	47%	38%	26%	75%
Univ. of Chiba	EIT	245	97.4%	72.0%	54.2%	34.8%	16.0%	86.1%

Univ. of Tokyo : Digestive Medicine, The University of Tokyo School of Medicine ; Univ. of Chiba : 1st Department of Medicine, The University of Chiba School of Medicine Hr : liver resection, EIT : Ethanol injection therapy

the proportion of absolute non-curative resection due to the tumor being deep in the liver, etc. was also high at 16.3% (0.0009). For the cause of death, liver failure was 41.8% (p=0.6046). However there was no significant difference in intrahepatic recurrence modes, and the incidence of the multicentric recurrence tended to be high at 28.6% (0.1692).

As described above, in HCC of 3 cm or less, the incidence of concomitant liver cirrhosis was high, and the hepatic functional reserve was lowered in the majority of cases. Accordingly, patients appeared to have similar degrees of enforced operative load with respect to large liver resection despite small liver resection, and some developed deterioration of hepatic function after surgery. It was suggested that multicentric recurrence, in addition to metastatic recurrence, was related in the disease-free survival rate after surgery.

2) The indications of liver resection for HCC based on tumor size

①Surgery for HCC with 3 cm or less

Various medical congresses have examined which therapy is chosen for the small HCC (3 cm or less) as a first treatment such as the 53rd Japanese Soc. of Gastroenterological Surgery general meeting, February, 1999 : workshop "the surgical treatment policy for the small liver cancer", The 35th Japan liver cancer workshop, June, 1999 : symposium "the treatment strategy for the small liver cancer", and The 3rd Japan Soc. of Hepatology : October, 1999 : panel discussion "Re-examination of the treatment selection in the small Hepatoma". However a fixed consensus has not been obtained because research results have been equivocal. However, in the 13th National Report (4), 80.1% of EIT was carried out for HCC of 3 cm or less, and, 96.1% was for HCC with less than three nodules. MCT was indicated in similar to EIT, and 78.9% of MCT was carried out for HCC of 3 cm or less and with less than three nodules. Thus, it is general practice to perform EIT and MCT for HCCs of 3 cm or less and tumor numbers of three or fewer.

In the results of EIT for small HCC (tumor size ≦3 cm, tumor number≦3 nodules) at the leading 2 institutes in Japan, The Univ. of Tokyo (digestive medicine) was 47.0% after 5 years and 26% after 10 years on the cumulative survival rate (8), and they were 54.2% after 5 years, 16% after 10 years at The Univ. of Chiba (1st Dep. of Medicine) (9). The cumulative survival rate of our cases by liver resection were 86.0% after 1 year, 66.3% after 3 years, 48.2% after 5 years, 41.2% after 7 years and 8.8% after 10 years. The 5-year recurrence rate was 75% in the Univ. of Tokyo, 86.1% in The Univ. of Chiba, and 80.5% in our department. Thus, our data were similar to the results of the 2 institutes mentioned above (Tab. 2).

Next, the survival rate of solitary and multiple HCCs with 3 cm or less in diameter was analyzed in our department. The cumulative survival rate of patients with solitary HCC was 83.5% after 1 year, 72.5% after 3 years, 61.5% after 5 years, 54.2% after 7 years and 18.1% in 10 years. In addition, that of patients with multiple HCCs was 90.0% after 1 year, 57.3% after 3 years, 28.9% after 5 years, 19.3% after 7 years, which showed no significant difference, although it tended to be poorer in patients with multiple HCCs (p=0.1691). Furthermore, the disease-free survival rate of solitary HCC were 74.6% after 1 year, 37.9% after 3 years, 25.6% after 5 years, 9.3% after 7 years and 9.3% after 10 years, and those of multiple HCCs were 47.1% after 1 year, 13.2% after 3 years, 13.2% after 5 years. The survival rate of solitary HCC was significantly better than for multiple HCCs (p=0.008) (Fig. 3a, b). The 5 year survival rate of solitary HCC was better than the 41.8% for the EIT for solitary HCC in the 13th National Report (4), and it was also better than the 53.6% reported at the Univ. of Chiba (9).

Ryu *et al*. examined the 3,225 cases of multiple

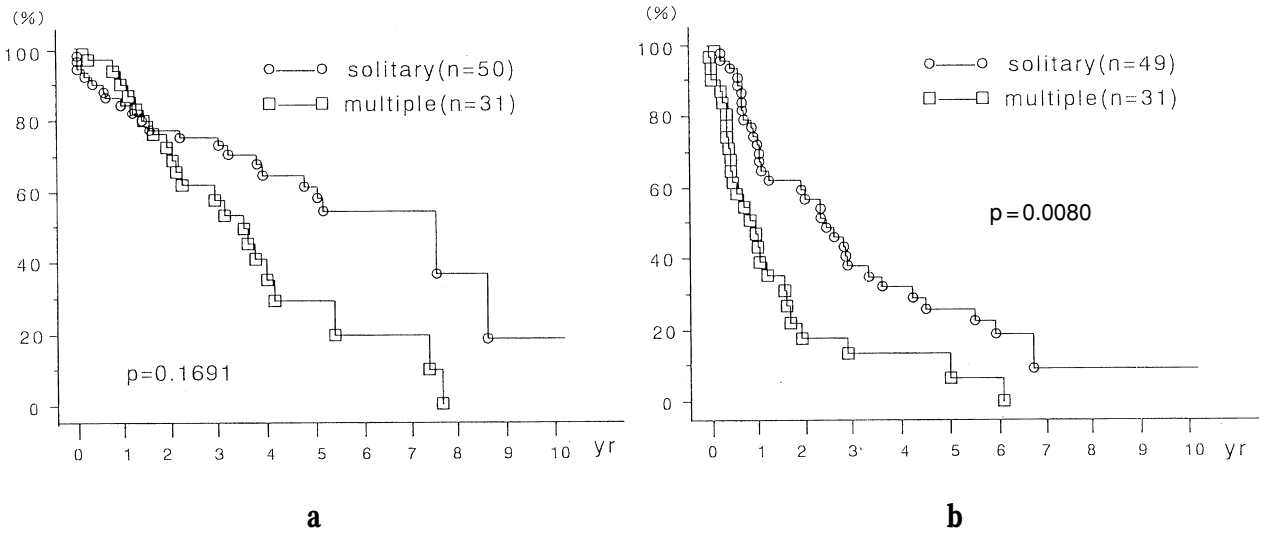

Fig. 3. Cumulative survival rate (a) and disease-free sruvival rate (b) of patients with solitary or multiple HCC (tumor size≦3 cm)

facilities retrospectively, and reported that resection or EIT should be performed in patients with Clinical Stage I (CSI) disease with tumors≦3 cm and≦3 in number, but in patients with CSII, EIT should be performed. Since the operative mortality rate of patients with CSII was significantly worse than those with CSI, resection should be selected taking the site of the tumor into consideration in patients with CSII (10). When the survival rate was compared by Clinical Stage in our cases, the 3-and 5-year survival rates in patients with CSI were 78.5% and 60.4%, respectively. In patients with CSII, the 3-and 5-year survival rates were 62.2% and 51.6% and those rates in patients with CSIII were 62.5% and 0%, respectively. Although survival was poor in patients with CSIII, there was no significant difference among 3 groups (p=0.2507). The 3-and 5-year disease-free survival rates in patients with CSI were 47.9% and 35.9%, respectively. In patients with CSII, the 3-and 5-year disease-free survival rates were 21.9% and 15.0%, and in patients with CSIII, those rates were 12.5% and 0%, respectively. The disease-free survival rate of patients with CSII or III was significantly worse than that of patients with CSI (p=0.0042).

Therefore, in patients with HCC of 3 cm or less, there is no significant difference between liver resection or EIT for solitary HCC. We used liver resection as the first selection for solitary HCC with CS I. However, it is suggested that priority should be given to topical treatments such as EIT or MCT in multiple HCCs and for patients with clinical stage II or III.

②Surgery for HCC of 3 to 5 cm

In the 13th National Report (4), the cumulative survival rate of EIT for 3 to 5 cm (n=240) were 78.5% after 1 year, 43.3% after 3 years, 24.3% after 5 years. The cumulative survival rate of TAE for HCC (all cases, n=13,228) were 60.4% after 1 year, 26.1% after 3 years, 13.3% after 5 years. Beppu et al. reported that the 3-year survival rate of HCC for 3.1-5.0 cm in diameter by TAE was 49.0% (11). The our data of liver resection for HCC of 3 to 5 cm was better than both therapies. Especially, the survival rates of solitary HCC by liver resection which were 54.7% after 5 years and 47.9% after 10 years. The disease-free survival rate was 44.0% after 5 years and 27.7% after 10 years. This showed solitary HCC was very good for survival over long terms.

In the investigation of multiple facilities by Seki *et al.*, the cumulative survival rates of liver resection for a solitary HCC of 3 to 5 cm were 60.2% after 5 years, 26.4% after 10 years in patients with clinical stage I. Liver resection showed good results in comparison with TAE of the same clinical stage. Similar results were seen even in patients with clinical stage II (12). Accordingly, HCC with 3 to 5 cm in diameter should have liver resection as the first selection, and especially a patient with solitary HCC it is regarded as the best indication of liver resection.

③Surgery for HCC of over 5 cm in diameter

The cumulative survival rates of HCC of over 5 cm by liver resection were 51.9% after 1 year, 25.7% after 3 years and 14.7% after 5 years in our department, and the disease-free survival rates were 25.7% after 1 year, 8.8% after 3 years, 8.8% after 5 years. This must be regarded as poor prognosis. Beppu et al. reported 5-year survival rate of HCC greater

than 5.1 cm in TAE of 13.1% (11). Seki *et al.* reported that the cumulative survival rates of TAE for over 5.0 cm was 32.7% after 3 years and 23.3% after 5 years in a solitary HCC (12). Thus, it is unclear whether liver resection or TAE for HCC of greater than 5 cm is best.

In our data of HCCs greater than 5 cm by tumor stage, the cumulative survival rates were 50.3% after 3 years and 33.6% after 5 years in patients with tumor stage II, and 50.0% after 3 years and 25.0% after 5 years in patients with tumor stage III, which were comparatively good results. However, in patients with tumor stage IV-A, the survival rate was 16.8% after 1 year, and no patient was alive after 2 years postoperatively (Fig. 4a). In addition, the difference could not be seen in the survival rates by clinical stage. When survival rate by operative curability was observed, cumulative survival rates of relative curative resection were 37.5% after 3 years and 18.8% after 5 years, and those with relatively non-curative resection were 29.0% after 3 years and 17.4% after 5 years. In absolute non-curative resections, the cumulative survival rates were 12.5% after 1 year, and no patient was alive after 2 years postoperatively (Fig. 4b), of which 87.1% died of cancer recurrence. The mode of recurrence was mostly metastatic intrahepatic recurrence with distant metastasis to lungs, bone etc.

Thus, in HCCs greater than 5 cm, liver resection is the first choice for patients with tumor stage II or III. However the surgical indication for patients with tumor stage IV-A and/or a patient becoming an absolute non-curative resection should be prudent.

IV. The apporpriate liver resection with special reference to recurrence after surgery

For recurrence after liver resection, there are two well documented modes ; metachronous multicentric recurrence and metastatic recurrence. In the 12th National Report, multicentric recurrence was 8.9% after hepatectomy. Probable multicentric recurrence was 27.8%, metastatic recurrence was 37.6%, and indistinctness was 25.9% (6). In our data, recurrence was 16.6%, which showed multicentric recurrence histologically (13). it was clarified that most HCC arises in chronic liver disease (i.e. liver cirrhosis) and cancerates via a multistep process (14).Therefore, it appears that there is a limit in pursuing the higher radicality by only extending the extent of liver resection as long as the metachronous multicentric recurrence exists after surgery. In other words, it is only metastatic recurrence that we can be prevented surgically.

When factors influencing the metastatic recurrence of HCC postoperatively were analyzed, tumor size, portal vein invasion (Vp), hepatic vein invasion (Vv), α-feto protein (AFP), and intrahepatic metastasis (IM), cancer-related factors were mainly related (13). So, the extent of liver resection was examined by tumor size as an independent factor by multivariate analysis using a stepwise forward Cox regression model. Since the details have already been reported (13, 15, 16), only the conclusion is

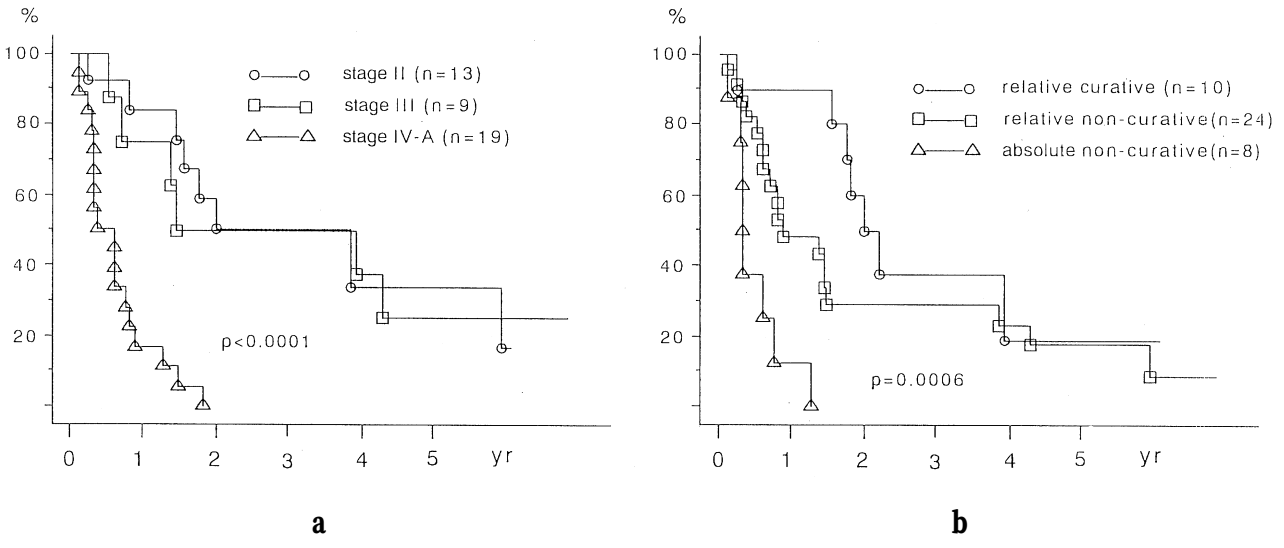

Fig. 4. Survival rate of patients with tumor sizes greater than 5 cm in diameter.
a : Cumulative survival rate by tumor stage
b : Cumulative survival rate by operative curability

described here.

In HCC of 5 cm or less in diameter, it does not always necessary to resect greater than the extent of the tumor (Hr≧H) by curative resection according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, and a limited resection according to Glissons structure and with a negative surgical margin (TW-) can be performed. HCC with multiple nodules can also be treated with limited resection as described above for each nodule. However, an extended liver resection in the possible range of the liver functional reserve is required for the treatment of HCCs greater than 5 cm. Since the prognostic factor in HCCs greater than 5 cm was not the clinical stage of patient but rather cancer-related factors, This suggested that the patients, in which the curative resection is possible, should be chosen.

The extent of liver resection should be considered according to the hepatitis virus. Since patients with hepatitis B showed a smaller decrease in liver function, and often recurred from the primary tumor to the remnant liver via the portal vein, systemic resection should be offered as far as possible in the initial operation. In contrast, because metachronous multicentric recurrence is dominant in patients with hepatitis C postoperatively, limited resection according to Glissons structure should be performed (17).

V. Challenge and limits of surgical treatment for HCC

①HCC with tumor thrombus in the portal vein (Vp 2, 3)

In the 13th National Report, the incidence of patients in which tumor thrombus existed in the second branch of the portal vein (Vp2) and the first branch, or trunk of the portal vein or in a branch on the contralateral side (Vp3) were 3.1% and 3.3% each (4). The number of patients with Vp2,3 together reached 16 (8.8%) in our department. The cumulative survival rates of these cases were 22.3% after 1 year, 7.4% after 3 years, 0% after 4 years, which were significantly poorer than patients with Vp0,1 ($p<0.0001$). All cases with Vp 2,3 recurred approximately 1 year postoperatively, and 73.3% of the patients died of the cancer recurrence. Several major efforts have been attempted to deal with tumor thrombus in the portal vein by aggressive treatment (18). Also in our department,, priority was given to the dissection of the hepatic hilum prior to the hepatic parenchymal transection, and the portal vein tumor thrombus was removed first as a contrivance of operative method. However, there has been no notable improvement in the treatment outcome. Yamaoka et al. was also reported that the cumulative survival rates with Vp3 were 31% after 1 year, 6% after 3 years, 6% in 5 years and the prognosis was equally bad even in Vp2, and there was a limit to attempting an improvement in the treatment outcome only by liver resection for the Vp2,3 cases (19). This suggested that adjuvant therapy should be performed after surgery, although a universal and effective treatment has not yet been reported.

②HCC with Tumor thrombus in the Inferior Vena Cava (IVC)

When combining the Vv3 cases (tumor thrombus in the IVC) with the Vv2 cases (tumor thrombus in the main hepatic vein, or short hepatic vein), they were 10 cases (Vv 2 : 6 cases, Vv 3 : 4 cases). A total of 5.5% of patients underwent liver resection in our department. There were tumor thrombi in the right hepatic vein in 3 of 6 patients with Vv2, which removed together with the main tumor. However, 3 remaining cases with Vv2 and 4 cases of patients with Vv3 required clamping of the inferior vena cava (IVC) to remove the tumor thrombus (Tab. 3).

We used three methods for clamping the IVC. The first method was clamping only the retrohepatic IVC. In the cranial method, the IVC clamp was placed on the IVC below the orifice of the hepatic vein to the IVC and another clamp was put on the infrahepatic IVC. It is advantageous to carry out the dissection of the IVC without interrupting of the hepatic inflow, such as Pringle's maneuver. This technique was used in cases 1,2 and 3. In case 3, the tumor invaded the wall of IVC directly, so the retrohepatic IVC was resected, and was replaced using Gore-Tex with a ring.

The second method is Total Hepatic Vascular Exclusion (THVE) (20, 21). An IVC clamp was put on the suprahepatic and infrahepatic IVC in addition to interruption of the hepatic inflow. This procedure completely isolates the liver from the circulation and primarily aims at preventing bleeding. It was used in case 4. To shorten the hepatic ischemia time, the liver parenchymal transection is carried out in advance, and the dissected liver is connected with the tumor thrombus in the IVC only by the hepatic vein. Then the IVC is incised, and the tumor thrombus in the IVC is extracted together with the resected liver.

Table 3. Patients with Vv 2,3 requiring clamping of the IVC to remove tumor embolus

Pt.	Age/ gender	Location	Vv	Vp	Hepatic resection	Hepatic vascular clamping (time)	blood loss	Outcome
1.	71/F	PAMc	2	1	Hr3 + (APMc)	IVC only (8' 30")	3700	lung met ; 7m died
2.	48/M	PA	2	0	Hr2 + (PAc)	IVC only (5' 0")	4200	liver met, 4y10m alive
3.	62/M	CPAM	2	3	Hr3 + (CAPm)	IVC only (31' 55")	3210	mult. Liver met. 10m died
4.	64//M	MLA	3	2	Hr2 (LM)	THVE (35' 0")	7800	mult. Liver met. 7M died
5.	51/M	M	3	1	Hr3 (LMC)	THVE (25') + Ex. Cir.	2910	Lung met' 4y7m died
6.	67/M	PAL	3	2	Hr3 (PAC)	THVE (54') + Ex. Cir.	4600	no rec. 6m died
7.	43/M	LM	3	3	Hr3 (LMC)	THVE (25') + Ex. Cir.	4400	mult. Liver met. 4m alive

Pt : patient, F : female, M of gender : male, liver segment (A : anterior segment, P : posterior segment, M of location : medial segment, L : lateral segment, C : caudate lobe of the liver). Hr : extent of liver resection : Hr2, resection of two segments, Hr3, resection of three segments. IVC only : clamping only the retrohepatic IVC without Pringle's maneuver, THVE : total hepatic vascular exclusion, Bypass : Cardiopulmonary bypass. met, : metastasis, multi, : multiple. no rec : no recurrence after surgery. Vascular invasion (Vp and Vv) are described in the text.

The third method is for extracting the tumor thrombus in the IVC with the transected liver under the extracorporeal circulation using a cardiopulmonary bypass (22). This was done at cases 5, 6 and 7. Still, in case 6, it was cannulated via the portal vein to considerately lengthen the extracorporeal circulation time, and core cooling was done using a Lactate-Ringer solution cooled at 4°C in addition to topical cooling. The ischemic time of each case is shown in Table 3. They had few ascites and pleural effusion postoperatively, but patients left hospital without serious complications, such as liver failure.

When the outcome of patients with Vv2,3 were observed by the existence of Vp, one case (case 6) of 4 cases with Vp 2,3 died of another cause within 6 months postoperatively, but no patient had recurrence. Another 2 cases (cases 3 and 4) died of multiple liver metastasis 10 months and 7 months after surgery, respectively. one remaining patient (case 7) had multiple liver metastasis 2 months after surgery, but is doing well 4 months postopratively.

One patient (case 1) of three cases with Vp0,1 showed lung metastasis and multiple liver metastasis 2 months postoperatively, and died of cancer 7 months after surgery. However, One case (case 2) of 3 cases with Vp0,1 also recurred in the remnant liver 3 months after surgery, but arterial injection chemotherapy of stylene maleic acid neocarcinostatin (SMANCS) and treatment by EIT were undertaken, and cancer bearing survival was progress 4 years and 10 months postoperatively. Case 5 with tumor thrombus in the right atrium had multiple lung metastasis 1 year and 3 month after surgery. Systemic chemotherapy with cisplatin (CDDP) +5-fluorouracil (5FU) and radiation were enforced, and survival at 4 years and 7 months after surgery was obtained.

Thus, most of the patients with Vv2 or 3, had a tumor greater than 5 cm in diameter and showed recurrence in lungs and/or liver after early postoperatively. The cumulative survival rates were 57.1% after 1 year and 28.6% after 3 years, and the prognosis is poor. However, patients with Vv2,3 showed cardiac insufficiency, pulmonary embolism and inferior vena caval syndrome. And, there is no other effective method of treatment. In patients with Vp0,1, long term survival may be obtained. It is possible to carry out the operation safely. For the reasons described above, it is suggested as a indication of positive surgery, even if it is Vv.

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