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Surgical Intervention for Patients With Stage IV-A Hepatocellular Carcinoma Without Lymph Node Metastasis

Proposal as a Standard Therapy

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Objective
The aim of this study was to evaluate the effects of surgical treatments for patients with stage IV-A hepatocellular carcinoma (HCC) without lymph node metastasis.

Summary Background Data
Nonsurgical therapy for highly advanced HCC patients has yielded poor long-term survival. Surgical intervention has been initiated in an effort to improve survival.

Methods
The outcome of 150 patients who underwent hepatic resection was studied. Survival analysis was made by stratifying stage IV-A HCC patients into two groups—those with and those without involvement of a major branch of the portal or hepatic veins. Those with involvement were further divided into subgroups according to major vascular invasions.

Results
Patients who had multiple tumors in more than one lobe without vascular invasion had a significantly better 5-year survival rate (20%) than those with vascular invasion (8%) ($p < 0.01$). The survival rate of patients with hepatic vein tumor thrombi (10%) was better than the rate for those with tumor thrombi in the inferior vena cava (0%), in whom no patients survived more than 2 years, although the survival rate for those with portal vein tumor thrombi in the first branch (11%) was no different from the rate for that in the portal trunk (4%). The operative mortality decreased from 14.3% in the first 6 years to 1.4% in the following 5 years.

Conclusions
Surgical intervention for stage IV-A HCC patients brought longer survival rates for some patients. We recommend surgical intervention as an effective therapeutic modality for patients with advanced HCC.

There have been many treatments used for hepatocellular carcinoma (HCC). Percutaneous ethanol injection therapy (PEIT) is useful for patients with small HCC and for some patients with advanced HCC with poor hepatic functional reserve.[1] Transcatheter arterial chemoembolization (TACE) is performed both on patients with unresectable HCC and patients with multiple intrahepatic recurrent tumors.[2,3] Liver transplantation is another effective modality for small HCC with severe liver dysfunction.[4] However, there still remain many patients with highly advanced HCC for whom those modalities are not indicated because of vascular invasion and large tumor size. We believe that surgical intervention can be an effective therapeutic modality for improving the survival of those patients.

Improvements in preoperative evaluation of liver function and tumor character,[5–7] in surgical procedures,[8–12] and in perioperative management[13] have decreased the morbidity and mortality associated with hepatic resection in patients with chronic hepatitis or liver cirrhosis. Building on these advances, we have used hepatic resection with the aim of complete tumor resection or cytoreductive treatment for highly advanced HCC patients. Even if tumor resection is

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only palliative, tumor-mass reduction increases the efficacy of subsequent adjuvant therapies. The recanalization of the portal vein by the removal of portal vein tumor thrombi prevents life-threatening complications (*e.g.*, bleeding from esophageal varices, which is the cause of death in 9% of HCC patients).[14] It also enables postoperative TACE to be performed.

On the UICC TMN classification, stage IV-A HCC is defined by T_4, any N, and M_0. T_4 denotes multiple tumors in more than one lobe or a tumor or tumors involving a major branch of the portal or hepatic veins.[15] By this definition, stage IV-A patients may have tumors with several different characteristics, such as multiple tumors, vascular invasion of large vessels, and lymph node metastasis. In general, regional lymph nodes are not dissected routinely during surgical treatment of HCC in Japan because lymph node metastasis, both regional and distant, is found in only 1.6% of operated cases[16] (although it is found in 30.3% of autopsied cases[14]). However, multiple tumors are observed in 29% of operated cases; vascular invasion of the portal vein is found in 16.9% and of the hepatic vein in 4.9%.[14] In this study, we evaluate the surgical indications of stage IV-A HCC patients without lymph node metastasis.

PATIENTS AND METHODS

The clinical records of all patients who had undergone hepatic resection for HCC at the Department of Gastroenterological Surgery, Kyoto University Hospital, were reviewed. Between January 1985 and December 1995, 585 patients with HCC underwent hepatic resection. The male/female ratio was 3.8:1. The mean age was 60.5 years. One hundred fifty patients in stage IV-A without lymph node metastasis were entered in this study.

Preoperative liver dysfunction was evaluated using the clinical stage classification of the Liver Cancer Study Group of Japan.[17] The determinations were made using ascites, serum total bilirubin level, serum albumin level, indocyanine green retention rate at 15 minutes ($ICGR_{15}$), and prothrombin time (%). The preoperative clinical features of our 150 patients are given in Table 1. There were 135 men and 15 women; the mean age was 60.1 years (range 18–85 years). The patients were divided into two groups: those with vascular invasion of the first branch of the portal or hepatic veins and those without. One hundred five patients had multiple tumors in more than one lobe; of these, 79 had no vascular invasion. The other 71 patients had tumor thrombi in the first branch of the portal or hepatic veins.

Operative procedures for hepatic resection consisted of 16 trisegmentectomies, 86 right or left lobectomies, 8 medial bisegmentectomies, 13 segmentectomies, and 27 partial resections of the liver (Table 2).[18] Sixty-seven of the 71 patients with tumor thrombi in a major branch of the portal or hepatic vein underwent more than hepatic lobectomy. In 49% (39/79) of patients without vascular invasion and in 72% (51/71) of patients with vascular invasion, tumors were

Table 1. PATIENT PROFILES AND TUMOR CHARACTERS OF STAGE IV-A HCC WITHOUT LYMPH NODE METASTASIS

	Without Vascular Invasion (n = 79)	With Vascular Invasion (n = 71)
Gender (Male:Female)	(74:5)	(61:10)
Age range	18–85	36–84
(mean ± SD)	(60.8 ± 9.7)	(57.7 ± 10.4)
Clinical stage I	43	41
Clinical stage II	36	29
Clinical stage III	0	1
$ICGR_{15} \leq 15\%$	39	42
$15\% < ICGR_{15} \leq 25\%$	28	15
$25\% < ICGR_{15} \leq 35\%$	9	12
$35\% < ICGR_{15}$	3	2
Solitary (IM0)	0	25
Multiple (IM1)	0	6
Multiple (IM2)	40	23
Multiple (IM3)	39	17
Vp0	74	9
VP1	2	1
Vp2	3	3
Vp3a	0	29
Vp3b	0	29
Vv0	78	38
Vv1	1	5
Vv2	0	18
Vv3	0	10

IM0, No intrahepatic metastasis; IM1, Intrahepatic metastasis to the segment in which the main tumor is located; IM2, Intrahepatic metastases to two segments; IM3, Intrahepatic metastases of three or four segments; Vp0, No tumor thrombus into the portal vein; VP1, Tumor thrombus distal to the second branch of the portal vein; Vp2, Tumor thrombus in the second branch of the portal vein; Vp3a, Tumor thrombus in the first branch of the portal vein; Vp3b, Tumor thrombus in the portal trunk or extending to a branch on the opposite side; Vv0, No tumor thrombus in the hepatic vein; Vv1, Tumor thrombus in a branch of the hepatic vein; Vv2, Tumor thrombus in the hepatic vein trunk or the short hepatic vein; Vv3, Tumor thrombus in the inferior vena cava.

macroscopically removed during the operation. In the other patients, in whom tumors remained in the remnant liver, multidisciplinary treatments were undertaken, with treatment depending on the number, size, and location of the residual tumors and on liver function. As a general principle, intraoperative ethanol injection to the residual tumors was performed. Then, when computed tomography (CT) at 3 weeks after hepatic resection showed viable tumors, TACE using doxorubicin (50 mg/body) was performed within 1 month.

Patients were followed up at the outpatient ward of Kyoto University Hospital or at the hospitals from which they had been referred every 2 weeks after surgery. Serum alpha-fetoprotein levels were measured once a month and ultrasonography or CT was done once every 3 months. As to the treatment of recurrent tumors, first every effort was made to resect the tumors in the liver as completely as possible. Then, PEIT and TACE were given to patients for whom re-resection was not indicated. Systemic chemotherapy was

Table 2. OPERATIVE PROCEDURES OF HEPATIC RESECTION IN STAGE IV-A HCC PATIENTS

Segments	Without Vascular Invasion (n = 79)	With Vascular Invasion (n = 71)
Partial resection	26	1
Segmental resection	10	3
Medial bisegmentectomy	5	3
Lobectomy	30	56
Trisegmentectomy	8	8

Segments were defined according to the Healey's Classification.

not used when extrahepatic recurrent tumors were not observed.

All deaths occurring within 30 days after hepatic resection were counted as operative deaths. Survival rates were determined by the Kaplan-Meier method, and the differences in the rates between the groups were compared by the log-rank test. A p value <0.05 was considered statistically significant.

RESULTS

The 1-, 3- and 5-year survival rates for the 585 patients overall were 73.2%, 51.7%, and 33.9%, respectively. The 5-year survival rate was 63% for stage I patients (n = 78), 41% for stage II (n = 209), 32% for stage III (n = 124), 15% for stage IV-A without lymph node metastasis (n = 150), and 0% for stage IV-B and for patients with lymph node metastasis (n = 24) (Fig. 1). There were significant differences in the survival rates of patients in the various stages, except between stage IV-A and IV-B.

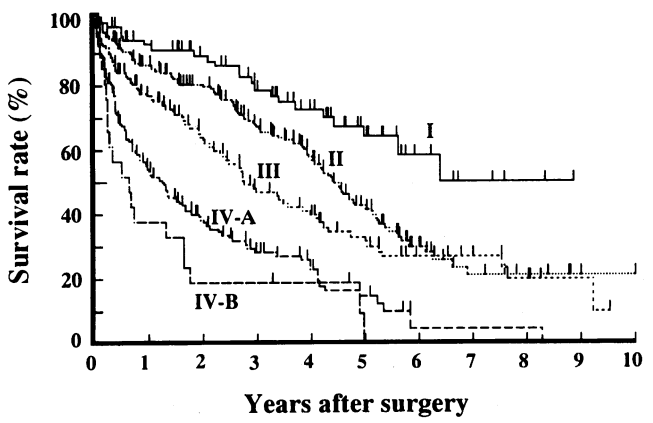

Figure 1. Survival of patients with hepatocellular carcinoma who underwent hepatic resection according to the macroscopic staging classification. There were 78 patients in stage I, 209 in stage II, 124 in stage III, 150 in stage IV-A, and 24 in stage IV-B. There were significant differences in the survival rates of patients in the various stages except between stage IV-A and IV-B ($p < 0.05$).

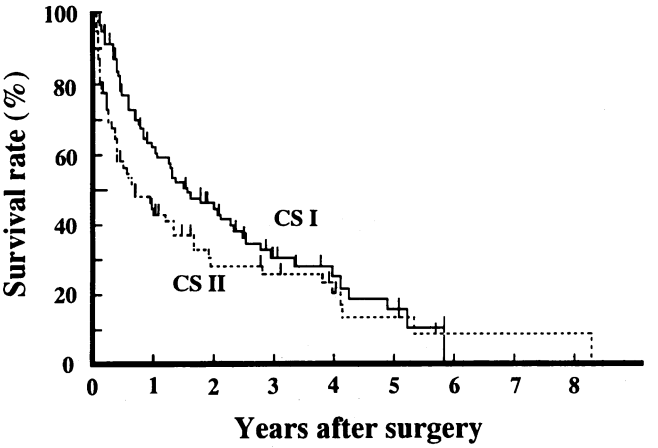

Figure 2. Survival of stage IV-A hepatocellular carcinoma patients according to the clinical stage classification of the Liver Cancer Study Group of Japan. There was no significant difference between the survival rate of patients in clinical stage I (CS I, n = 84) and clinical stage II (CS II, n = 65).

In stage IV-A patients, there were no significant differences between the survival rates of patients in clinical stage I and II (Fig. 2). However, stage IV-A patients who had intrahepatic multiple tumors without vascular invasion showed a significantly better survival than patients who had vascular involvement in a major branch of the portal or hepatic veins ($p < 0.01$) (Fig. 3). The 3- and 5-year survival rates of patients without vascular invasion were 41.9% and 20%, respectively; those of patients with vascular invasion were 12.8% and 7.7%. However, neither group's prognosis was affected by whether their tumors were resected completely or not. The 3-year survival rate in patients without vascular invasion who underwent complete tumor resection

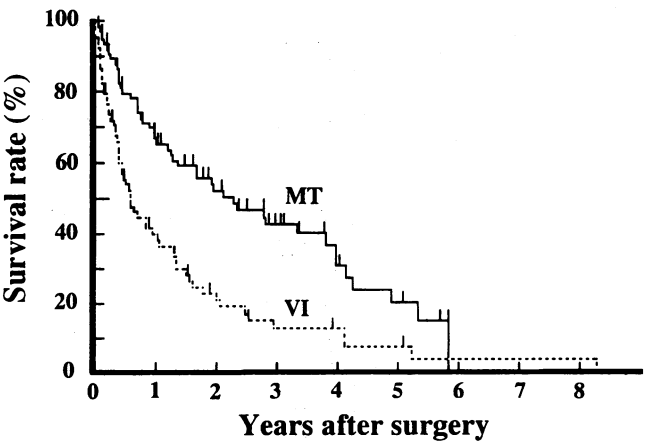

Figure 3. Survival of stage IV-A hepatocellular carcinoma patients with and without vascular invasion. Patients without vascular invasion (MT, n = 79) showed a significantly better survival than those with vascular invasion (VI, n = 71) ($p < 0.01$).

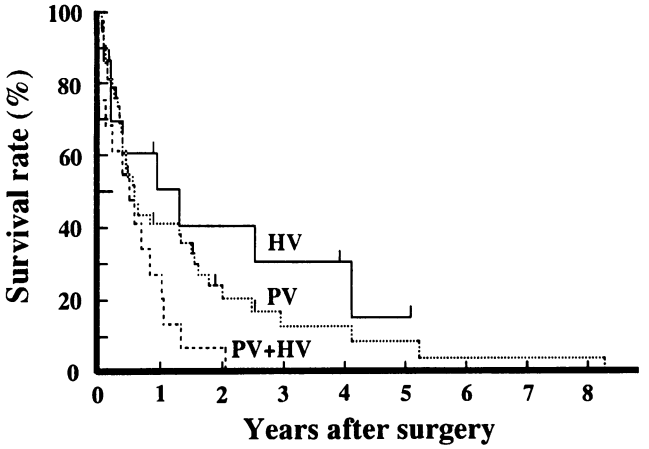

Figure 4. Survival rates of stage IV-A hepatocellular carcinoma patients with tumor thrombi in the major vessels. There were significant differences in the survival rates between patients with tumor thrombi only in the hepatic vein (HV, n = 13) and those in both the portal and hepatic veins (PV + HV, n = 15) ($p < 0.05$). However, patients with tumor thrombi only in the portal vein (PV, n = 43) showed no significant difference in survival rate when compared with patients with hepatic vein tumor thrombi only or when compared with patients with tumor thrombi in both the portal and hepatic veins.

was 42.8% (n = 39), and that for patients undergoing palliative resection was 40.9% (n = 40). For those with vascular invasion, the 3-year survival rates for complete resection and palliative resection were 12.5% (n = 51) and 13.5% (n = 20), respectively.

Tumor thrombi sometimes exist both in the portal and hepatic veins. In our series, 43 of the 71 patients with vascular invasion (61%) had tumor thrombi only in the portal vein, 13 (18%) only in the hepatic vein, and the other 15 (21%) in both the portal and hepatic veins. There were significant differences in the survival rate of patients with hepatic vein tumor thrombi when compared with those with tumor thrombi in both the portal and hepatic veins. However, patients with tumor thrombi only in the portal vein showed no significant difference in survival rate when compared with patients with hepatic vein tumor thrombi only or when compared with patients with tumor thrombi in both the portal and hepatic veins (Fig. 4).

Of the 58 patients with vascular involvement in the portal vein, 29 patients had tumor thrombi in the first branch and 29 patients in the portal trunk. In 18 of the 28 patients with hepatic vein tumor thrombi, tumor thrombi existed in the hepatic vein, and the tumor invaded the inferior vena cava (IVC) in 10. Figure 5 shows the cumulative survival rates of patients with tumor thrombi. There were no significant differences in the survival rates between patients with tumor thrombi in the first branch of the portal vein and those with tumor thrombi in the portal trunk (Fig. 5a). However, the outcome of patients with IVC tumor thrombi was extremely poor; no patients survived more than 2 years. Patients with hepatic vein tumor thrombi showed a significantly better survival rate than those with tumor thrombi invading the IVC ($p < 0.01$) (Fig. 5a).

Major postoperative complications were liver failure, intraabdominal bleeding, and intraabdominal infection. The overall morbidity was 51%, and the postoperative mortality was 8.4% (Table 3). In 12 patients, death was directly related to hepatic resection, resulting from intra-abdominal bleeding in 4 and from postoperative liver failure or multiorgan failure in 8. One patient died of heart failure. When the first 6 years were compared with the following 5 years, fatal complications and the mortality rate decreased, especially in the group with vascular invasion. In the last 5 years, the mortality rate was 1.4%.

DISCUSSION

Improvements in diagnostic imaging and clinical screening for HCC in high-risk patient populations have made it possible to diagnose small, asymptomatic HCC. They have led to better survival for HCC patients treated with surgical and nonsurgical therapies.[14,19,20] In patients with advanced

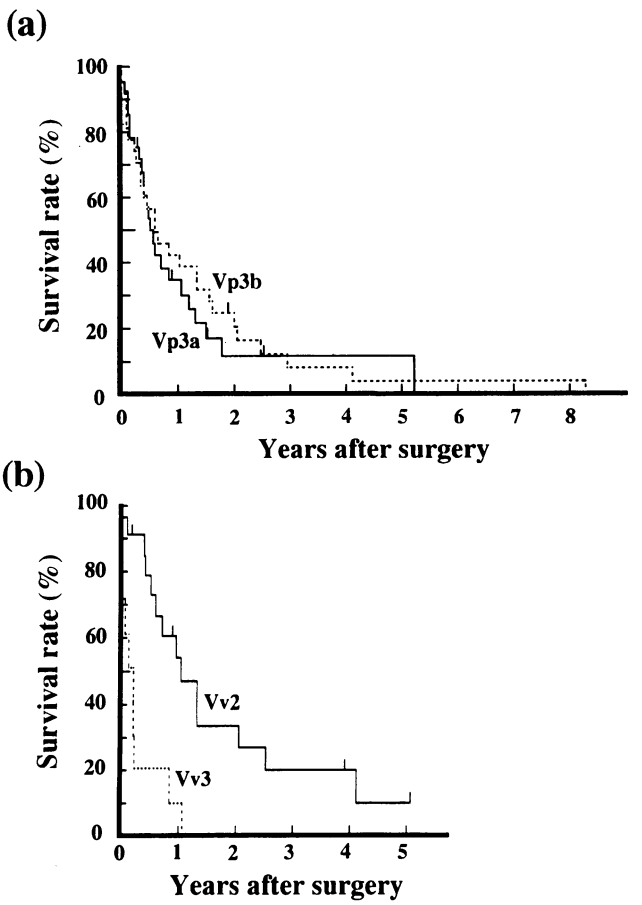

Figure 5. Survival of stage IV-A hepatocellular carcinoma patients with tumor thrombi in the portal vein (a) and the hepatic vein (b). There were no significant differences in the survival rates between patients with tumor thrombi in the first branch of the portal vein (Vp3a, n = 29) and those with tumor thrombi in the portal trunk (Vp3b, n = 29). Patients with hepatic vein tumor thrombi (Vv2, n = 18) had a significantly better survival rate than those with tumor thrombi invading the inferior vena cava (Vv3, n = 10) ($p < 0.01$).

Table 3. POSTOPERATIVE COMPLICATIONS IN STAGE IV-A HCC PATIENTS

Period	Without Vascular Invasion		With Vascular Invasion	
	1985–1990 (n = 36)	1991–1995 (n = 43)	1985–1990 (n = 46)	1991–1995 (n = 25)
Liver failure	6 (3)	2 (1)	8 (4)	1
IA bleeding	2	0	6 (4)	0
IA infection	6	2	8	0
Pleural effusion	6	5	5	3
Massive ascitis	2	14	0	5
Sepsis	1	1	1	1
GI bleeding	2	2	2	1
Heart failure	0	0	1 (1)	0
Bile leakage	0	2	1	0
Others	1	3	2	1
Morbidity	47.2%	51.2%	54.3%	40.0%
Mortality	8.3%	2.3%	19.5%	0.0%

Number in parentheses shows operative death.
Some patients had multiple complications.
IA bleeding, intraabdominal bleeding; IA infection, intraabdominal infection; GI bleeding, gastrointestinal bleeding.

HCC, however, the possibilities of surgical cure were sometimes disregarded due to vascular invasion or to the extensiveness of tumor.[21] Only a few investigators have studied the surgical indications for patients with highly advanced HCC. Recently, Shimada et al.[22] reported that the survival rate of stage IV patients undergoing a "curative" operation (one in which all the tumors were macroscopically resected) is similar to that of patients in stage I to III. However, patients in that study seemed to have undergone strict preoperative selection. Only 1 of the 15 patients who underwent curative resection had portal vein tumor thrombi, no patients had intrahepatic metastasis in more than three segments, and all were in Child A classification. In this study, we analyzed stage IV-A patients with diverse tumor characteristics, such as vascular invasion to a major branch of the portal or hepatic veins and intrahepatic multiple tumors spreading to more than one lobe, and with mild and moderate liver dysfunction, although we did exclude patients with severe liver dysfunction.

Approximately 80% of HCC patients in Japan have associated liver cirrhosis,[14] which increases the difficulty of a major hepatic resection. For HCC patients with severe liver dysfunction, liver transplantation offers the theoretical appeal of both complete removal of the tumor-bearing liver and restoration of normal liver function for those with small HCC,[4] and sometimes for those with advanced HCC.[23,24] Ringe et al.[23] reported that the 5-year survival rate of stage IV-A HCC patients was 5.6% for those treated by hepatic resection and 14.1% for those who underwent liver transplantation. The prognosis for those treated by liver transplantation in the Hannover group was similar to that of patients undergoing hepatic resection in our study. Iwatsuki et al.,[24] however, showed that there were no 3-year survivors after subtotal hepatic resection or liver transplantation among patients with stage IV-A HCC in the cirrhotic liver. These bleak outcomes do not encourage liver transplantation for advanced HCC patients, given the serious shortage of donor organs.

In many reports, liver dysfunction is one of the most important predictive prognostic factors for HCC patients.[20,24,25] However, accompanying liver dysfunction did not affect the survival rate in the stage IV-A patients in our study of patients who had mild or moderate hepatic dysfunction. This suggests that the character of the tumor has more of an effect on the prognosis of patients with highly advanced HCC than accompanying liver dysfunction, provided that liver function was sufficient for a major hepatic resection.

Recent advances in gene analysis have showed that intrahepatic multiple tumors sometimes arise from intrahepatic metastases consisting of monoclonal tumor cells and multicentric occurrences consisting of polyclonal tumor cells.[26,27] Yamamoto et al.[28] reported that stage IV-A HCC had a greater likelihood of containing slowly growing intrahepatic tumor clusters and that the removal of any rapidly growing tumors from such clusters should be undertaken by reduction surgery followed by subsequent multidisciplinary treatment for any residual tumor cells.[28] We performed cytoreductive surgery on patients with multiple tumors in bilateral lobes whose residual tumors were treated by intraoperative ethanol injection and postoperative PEIT and TACE. The survival rates of stage IV-A patients without vascular invasion, whether they underwent complete tumor resection or not, were better than those of patients with vascular invasion. Postoperative adjuvant therapies such as PEIT and TACE were sometimes effective for residual

tumors in the remnant liver after the resection of a main tumor. These results indicate that the character of the tumor in patients without vascular invasion differed from that in patients with vascular invasion, although all of them belong to stage IV-A.

Vascular invasion is one of the most important prognostic factors for HCC patients.[20,24,29] HCC patients with vascular invasion have a poor prognosis, whether they receive systemic or intra-arterial chemotherapy, intra-arterial radiotherapy, or nonspecific treatments. The 1-year survival rate is poor, ranging from 7% to 18%.[14,30–33] Such patients are unsuitable for TACE because of the high risk of hepatic infarction.[2] Moreover, tumor thrombi in the portal trunk sometimes result in intrahepatic metastasis and portal hypertension, which occasionally induces esophageal variceal bleeding, a life-threatening complication. To avoid this serious complication, patients require cytoreductive surgery combined with the removal of tumor thrombi in the portal vein, which recanalizes the portal vein and leads to the possibility of postoperative TACE.

Patients with tumor thrombi in the hepatic vein had a better prognosis only than those with IVC tumor thrombi. Surgical treatment was indicated for the former because hepatic vein tumor thrombi can be removed by anatomic hepatic resection. However, no patients with tumor thrombi invading the IVC survived more than 2 years, due to early distant organ metastasis, especially lung metastasis. Patients with tumor thrombi in both the portal and hepatic veins are at high risk for intrahepatic metastasis through portal vein tumor thrombi and for distal organ metastasis through hepatic vein tumor thrombi. For these patients, postoperative multidisciplinary treatments including local and systemic adjuvant chemotherapy are required in addition to hepatic resection.

For patients with vascular invasion, a major hepatic resection was required to resect the main tumor and tumor thrombi. Nagasue et al.[34] recommended that a major hepatic resection should be performed only in selected patients with Child A status. Fan et al.[35] suggested that a major hepatic resection should not be performed if $ICGR_{15}$ exceeded 14%. However, these indications are not always appropriate for patients with a major vascular invasion on evaluation of hepatic functional reserve. In 40% of the patients in this study who had major vascular invasion, the $ICGR_{15}$ was >15% and in clinical stage II.

Improvements in surgical technique and perioperative management have also decreased fatal complications markedly in the last 5 years, although morbidity is still 40%. The mortality rate in the last 5 years is 1.4% overall and 0% in patients with vascular invasion. Surgical procedures for patients with tumor thrombi have been established.

In conclusion, improvements in surgical procedures and perioperative management have allowed us to carry out hepatic resection in patients with highly advanced HCC. We have seen some patients with highly advanced HCC surviving longer. These patients have had not only multiple tumors but also tumor thrombi in the major vessels. However, the prognosis of HCC patients with tumor thrombi in the major vessels is still poor. To improve their survival rates, new multidisciplinary treatments including surgery, interventional radiology, chemotherapy, and radiation are required.

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