

past 11 years, 209 cases of single nodular HCC were subjected to the study. Twenty-four cases with more than one satellite nodules larger than 1 cm were defined as multinodular type and were excluded from the study. Preoperative tumoral staging is Stage 1: 69 cases, stage 2: 118 cases, stage 3: 22 cases [21]. Segmentectomy or subsegmentectomy were performed in 150 cases. Limited resection was performed in 59 cases. The 209 patients included 162 men and 47 women, ages 36–86 years (median = 63 years). Hepatitis B antigen (HBsAg) was detected in 21 of the 191 patients tested; antibody to the hepatitis C virus (anti-HCV) was detected 141 of 173 patients tested (Table 1). The resected liver specimens were fixed in 10% formalin, and their entirety were cut into 0.2–0.3 cm slices to facilitate careful gross and histological examinations. Each of the liver slices was divided into two or more blocks, embedded in paraffin, cut into 4- $\mu$ m sections, and stained with hematoxylin-eosin.

Gross classification was defined according to the definition of Kanai and Liver Cancer Study Group of Japan [5,6]. Histological grading was based on WHO classification [22]. According to Edmondson–Steiner's classification [23], well differentiated corresponds to grade I, and moderately differentiated corresponds to grade II and/or III, and poorly differentiated corresponds to grade III and/or IV.

Single nodular type was defined as those with gross appearance of clear round nodule. Single nodular type with extranodular growth was defined as those with gross appearance similar to the single nodular type, but this tumor demonstrates extranodular growth in varying degrees. Confluent multinodular type was defined as a nodule, which is formed by a cluster of small and confluent nodules. Vaguely nodular type was defined as a nodule, which has indistinct margins and contains portal tracts inside [7].

The following lesions was determined as intrahepatic metastasis according to the definition of the Liver Cancer Study Group of Japan [6]: (i) tumors which are clearly growing from portal vein tumor thrombi, (ii) tumors which surround a large main tumor with multiple satellite nodules, and (iii) small solitary tumors

which are located proximal to the main tumor and which are histologically similar to or less differentiated than the main tumor. However, some lesions are difficult to clarify as either principal tumors or metastasis. To clarify as either principal tumors or metastasis, tumors with satellite nodules larger than 10 mm were omitted in this study. When intrahepatic metastasis was histologically confirmed, the distance between the edges of the metastatic lesion and the main tumor were measured. Mann–Whitney test and Kruskal–Wallis test were used to evaluate statistical significance of pathological characteristics of HCC patients.

### 3. Results

#### 3.1. Macroscopic findings and histopathologic characteristics

Among the 209 HCCs, there were 22 cases of vaguely nodular type, 123 cases of single nodular type, 45 cases of single nodular type with extranodular growth, and 19 cases of confluent multinodular type. Tumor diameter was smaller in vaguely nodular type, i.e. mostly 15 mm or smaller, whereas the diameter of the other three types was usually 15 mm or larger, and there was no significant group difference in a tumor size between the three types. Histologic grade was solely well-differentiated cancerous tissue in 19 of the 22 vaguely nodular type, in six of the 123 single nodular type, and in none of the single nodular type with extranodular growth and confluent multinodular type (Table 2). Noncancerous liver tissues of all 209 cases were associated with chronic liver diseases, and it was liver cirrhosis or pre-cirrhosis in 150 (71.8%) cases, and chronic hepatitis in 59 (28.2%) cases. Degree of fibrosis was defined according to Ludwig classification [24], as grade 1 in 36 cases, grade 2 in 23 case, grade 3 in 48 cases and grade 4 in 102 cases. Table 3 summarizes frequencies of capsule formation, capsule invasion, septum formation, portal vein invasion and hepatic vein invasion according to macroscopic type of the nodules. All portal vein invasions, except one, were microscopic portal invasion. None of the vaguely nodular type showed portal vein invasion and intrahepatic metastasis. Among the nodular type HCCs, portal vein invasion and intrahepatic metastasis were found at a high frequency in single nodular type with extranodular growth and confluent multinodular type than in single nodular type.

#### 3.2. Intrahepatic metastatic lesions

In 22 cases with intrahepatic metastasis, number of metastatic lesions ranged mostly from one to two. Fifty-seven metastatic lesions were obtained in one case.

Table 1  
Patient profile

Number of patient	209
Age range in years (mean)	36–86 (63)
Male:female	162:47
<i>Virus markers in serum</i>	
HBsAg	21/191
Anti-HCV	141/173
Both HbsAg and anti-HCV	3/168
Neither HbsAg nor anti-HCV	17/168

Abbreviations: HBsAg, hepatitis B surface antigen; Anti-HCV, antibody to hepatitis C virus.

Table 2  
Relationship among gross type, histologic grade, and tumor size

	Well	Well+Mod	Mod	Mod+Poor	Total	Tumor size (mm)
Vaguely nodular type	19 (86.4%)	3 (13.6%)	0	0	22	13.6 ± 5.4
Single nodular type	6 (4.9%)	24 (19.5%)	92 (74.8%)	1 (0.8%)	123	22.8 ± 5.6*
Single nodular type with extranodular growth	0	5 (11.1%)	40 (88.9%)	0	45	23.1 ± 5.4*
Confluent multinodular type	0	6 (31.6%)	11 (57.9%)	2 (10.5%)	19	23.9 ± 5.3*

Tumor size is shown in mean ± S.D. Well: well-differentiated type. Mod: moderately differentiated type. Poor: poorly differentiated type. \*P < 0.001, vs. vaguely nodular type.

Macroscopic type of the primary nodule with metastasis was single nodular type in five cases (22.7%), single nodular type with extranodular growth in 12 (54.5%) cases, and confluent multinodular type in five (22.7%) cases. Tumor cell invasion into the portal vein was found in one (20%) case of single nodular type, 11 (91.7%) of single nodular type with extranodular growth, and three (60%) of confluent multinodular type. The largest diameter of metastatic lesion ranged from 0.5 to 9.7 mm (mean: 2.7 mm), and 62 nodules (41.6%) were less than 2 mm in diameter and 13 (8.7%) were larger than 5 mm in diameter. Distance between the closest edges of a metastatic lesion and its primary nodule ranged from 0.5 to 42.0 mm. Four metastatic lesions were unable to be accurately measured for the distance, because these metastatic lesions were not located in the slice containing the main HCC nodule, and the approximate distance between the edges of each of these four metastatic lesions and its primary nodule was 10 mm or longer. Overall, the distance was 2 mm or shorter in 56 nodules (37.6%), longer than 2 mm and shorter than 5 mm in 32 nodules (21.5%), longer than 5 mm and shorter than 10 mm in 30 nodules (20.1%), and 10 mm or longer in 31 nodules (20.8%). According to macroscopic type, the distance was 2 mm or shorter in six (66.7%) of the nine single nodular type with metastases, 23 (30.7%) of the 75 single nodular type with extranodular tumor growth, and 27 (41.5%) of the 65 confluent multinodular type. On the other hand, the distance was 5 mm or far away in two nodules (22.2%), 40 nodules (53.4%), and 19 nodules (29.2%), respectively (Tables 3 and 4, Figs. 1-4).



Fig. 1. Gross feature of vaguely nodular type. A nodular tumor (arrow head) with 0.7 cm in diameter shows an indistinct border between cancerous and noncancerous tissue.

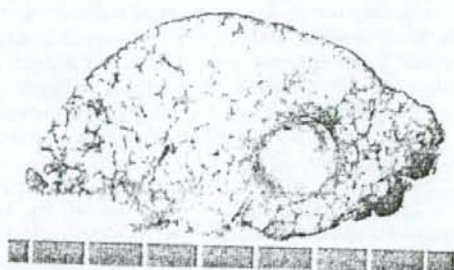


Fig. 2. Gross feature of single nodular. The tumor nodule is distinctly nodular with a thin fibrous capsule. The size is 1.4 × 1.4 cm.

Table 3  
Relationship among gross type, capsule and septum formation, capsule invasion, portal and vein invasion, and intrahepatic metastasis

	Number of cases	fc	fc-inf	sf	vp	vv	im
Vaguely nodular type	22	0	0	2 (9.1%)	0	0	0
Single nodular type	123	90 (73.2%)	79 (64.2%)	65 (52.8%)	23 (18.7%)	3 (2.4%)	5 (4.1%)
Single nodular type with extranodular growth	45	38 (84.4%)	35 (77.8%)	35 (77.8%)	20 (44.4%)	2 (4.4%)	12 (26.7%)
Confluent multinodular type	19	1 (5.3%)	1 (5.3%)	14 (73.7%)	12 (63.2%)	3 (15.8%)	5 (26.3%)

fc: presence of capsule formation. fc-inf: presence of cancerous infiltration to tumor capsule. sf: presence of fibrous septum within the tumor. vp: presence of portal vein invasion. vv: presence of hepatic vein invasion. im: presence of intrahepatic metastasis.

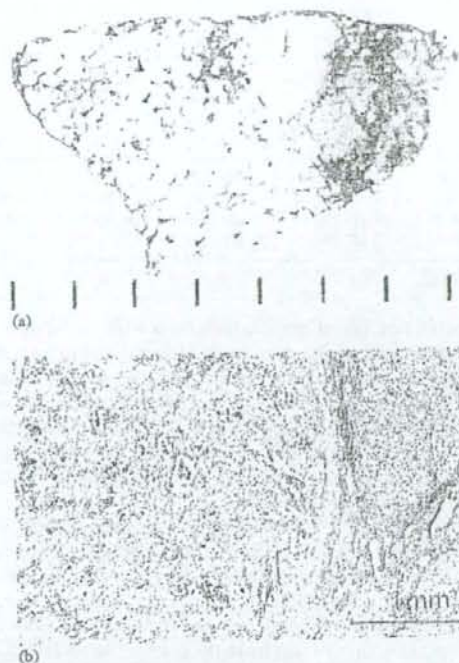


Fig. 3. (a) A minute intrahepatic metastasis (arrow heads) was observed 1.5 cm away from a nodular tumor with extranodular growth. (b) Histological findings of the metastatic lesion. The metastatic lesion consists of moderately differentiated HCC with pseudoglandular arrangement.

#### 4. Discussion

HCC recurs at a high frequency even if the patient received surgical resection or ablation therapies at an early stage, and this results in poor outcomes [18]. Recurrence could occur due to intrahepatic metastasis or multicentric occurrence of nodules [3,4]. It has been known that intrahepatic metastasis occurs at an early postoperative period, and multicentric occurrence occurs at a later postoperative period [25]. Some researchers reported the presence of portal vein invasion and intrahepatic metastasis within surgically resected liver tissues as predictive factors of metastasis or patient's outcome [2,9,10,15], but there has not yet been enough information on the relationship between metastasis/portal vein invasion and macroscopic type of small HCCs.

Clinicopathologic studies on those small HCCs brought a new macroscopic classification system for relatively small nodules. In addition, macroscopic features of quite small HCCs have been revealed, and small HCC with indistinct margin (i.e. vaguely nodular type)

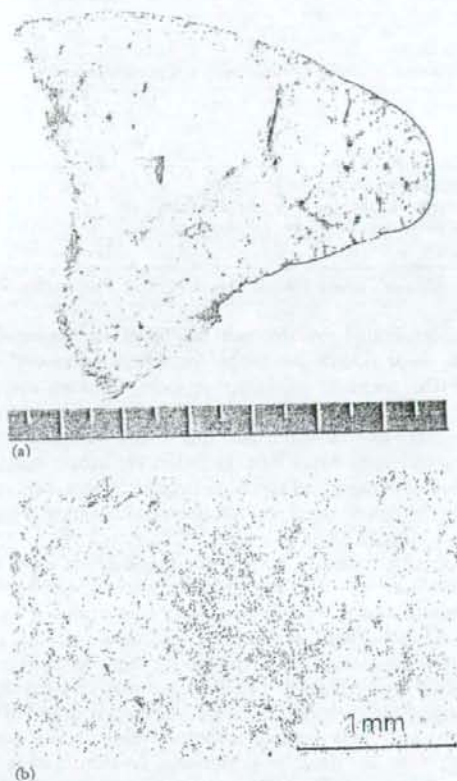


Fig. 4. (a) Gross feature of confluent multinodular type. The size is 1.8 × 1.5 cm. (b) Histologically, micrometastasis is less than 1 mm in diameter and consists of moderately differentiated HCC with pseudoglandular arrangement.

is nowadays regarded as the major characteristic of early-stage HCC [5–7].

In the present study, vaguely nodular type had smaller tumor diameter than the other three types of nodules, most of them were consisted solely of well-differentiated HCC tissues, and did not have portal vein invasion or intrahepatic metastasis. Therefore, this type of tumor nodule could be regarded as 'carcinoma in situ' in the liver, and expected to be completely cured after surgical resection [26]. The other three types of nodules, i.e. single nodular type, single nodular type with extranodular growth, and confluent multinodular type, did not have remarkable group differences on histological grade and tumor diameter, but single nodule type and the other two types had remarkable differences in the frequencies of intrahepatic metastasis and portal vein invasion.

Confluent multinodular type presents several minute nodules, which are confluent, each other, and a capsule

Table 4  
Distance between metastatic lesion and primary nodule

	Distance (mm)				Total
	≤2	2.1–5	5.1–10.0	> 10.1	
Single nodular type	6 (66.7%)	1 (11.1%)	0 (0.0%)	2 (22.2%)	9
Single nodular type with extra nodular growth	23 (30.7%)	12 (16.0%)	17 (22.7%)	23 (30.7%)	75
Confluent multinodular	27 (41.5%)	19 (29.2%)	13 (20.0%)	6 (9.2%)	65
Total	56 (37.6%)	32 (21.5%)	30 (20.1%)	31 (20.8%)	149

Figures represent number of nodules. Total: total number of nodules examined.

is generally not observed. Kanai et al. suggested this type of nodule would be formed when several small HCC nodules, which are replacing lobules, are fused together [5]. This type of HCC has a high frequency of portal vein invasion, and this would be because many portal veins could be engulfed in the tumor when they are confluent, and this high frequency would also result in its high frequency of intrahepatic metastasis. Kanai et al. classified nodular type HCCs into Type 1, 2 or 3. These groups correspond to single nodular type, single nodular type with extranodular growth, and confluent multinodular type, respectively. They reported Types 2 and 3 had frequent intrahepatic metastasis and portal vein invasion, and also had poor prognosis [5]. Hui et al. also reported those two type tumors were statistically significant risk factors for tumor recurrence and disease-specific death by univariate and multivariate analysis [27]. At the point of portal vein invasion and intrahepatic metastasis, we also supported their study. In the present study, single nodular type with extranodular growth showed a higher frequency of intrahepatic metastasis, and this type of nodule could have metastatic lesions at a place located further away than confluent multinodular type does.

Selection of local ablation therapy (e.g. ethanol injection, radio-frequency) or surgical resection has been a matter of concern in the treatment of small HCC [28–30]. Makuuchi et al. [31] reported that small intrahepatic metastatic lesions could be resected at surgical treatment for the primary nodule, and this could result in better outcome. In our 209 primary HCC cases, intrahepatic metastasis was found in 22 cases (10.5%), and 91.3% of the entire metastatic lesions were 5 mm or smaller. Utsunomiya et al. [32] reported that 60% of the metastatic lesions with 5–10 mm of diameter were depictable by preoperative image diagnosis, but smaller lesions were hardly depicted. This indicates that metastatic lesions were undetectable before surgery in majority of our patients. Among our 22 cases with intrahepatic metastasis, and whose primary nodules were either single nodular type with extranodular growth or confluent multinodular type, the distance of metastatic lesion was 5 mm or far away in 53.4 or 29.2%, respectively. Our findings (Table 4) showed there was

small number of metastatic lesions with 5 mm or larger diameter, and the frequency of intrahepatic metastasis and the distance from the primary nodule were different among the three macroscopic types. Surgical treatment could resected those small intrahepatic metastatic lesions. However, local ablation therapy (e.g. ethanol injection, radio-frequency) could left some of those intrahepatic metastatic lesions.

Therefore, it is important to precisely determine the gross type of small HCC by diagnostic imaging in order to predict portal vein invasion and micrometastasis, and to select therapeutic modalities. In addition, because approximately 80% of intrahepatic micrometastasis are located within 1.0 cm from the primary small HCCs, it is important to ablate the tumor with enough surrounding tissue (1 cm in width at least) in order to prevent the recurrence form those micrometastasis. Conversely, since their applicability in resection is less relevant since most of the term currently perform subsegmentectomy or segmentectomies.

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# Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

## Analysis of 48 Cases

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**BACKGROUND.** The prognosis of patients with hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is extremely poor. The aim of this study was to elucidate the efficacy of hepatic arterial infusion chemotherapy (HAIC) for patients with advanced HCCs.

**METHODS.** Forty-eight HCC patients with PVTT were treated by HAIC via a subcutaneously implanted injection port. Of these, 14 had PVTT in the second portal branch and 34 patients had PVTT in the first portal branch or in the main portal trunk. One course of chemotherapy consisted of daily cisplatin (7 mg/m<sup>2</sup> for 1 hour on Days 1-5) followed by 5-fluorouracil (170 mg/m<sup>2</sup> for 5 hours on Days 1-5). Patients were scheduled to receive four serial courses of HAIC. Responders were defined as having either a complete response (CR) or partial response (PR) and nonresponders were defined as exhibiting stable disease or progressive disease. The prognosis after HAIC and factors related to survival were analyzed.

**RESULTS.** Following HAIC, 4 and 19 patients exhibited a CR and PR, respectively (response rate = 48%). The 1, 2, 3, and 5-year cumulative survival rates of 48 patients treated with HAIC were 45%, 31%, 25%, and 11%, respectively. Median survival periods for 23 responders and 25 nonresponders were 31.6 (range, 8.3-76.9) months and 5.4 (1.9-29.0) months, respectively. Therapeutic effect ( $P < 0.001$ ) and hepatic reserve capacity ( $P = 0.021$ ) were identified as significant prognostic factors by univariate analysis. Multivariate analysis identified only therapeutic effect as being significantly related to survival.

**CONCLUSIONS.** HAIC using low-dose cisplatin and 5-fluorouracil may be a useful therapeutic option for patients with advanced HCC with PVTT. HCC patients with PVTT who respond to HAIC could certainly have survival benefits. *Cancer* 2002;95:588-95. © 2002 American Cancer Society.

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**KEYWORDS:** hepatocellular carcinoma, tumor thrombosis, hepatic arterial infusion chemotherapy (HAIC), prognosis, biochemical modulation, cytoreduction.

The incidence of hepatocellular carcinoma (HCC) has increased during the past decade and HCC has become the leading cause of death among patients with cirrhosis.<sup>1,2</sup> Recent technologic advances in imaging modalities and therapeutic procedures have facilitated early diagnosis and curative treatment in patients with HCC.<sup>3-17</sup> Despite this marked progress in medical science, the prognosis for HCC patients remains unsatisfactory. Surgical resection or liver transplantation for these patients is limited due to coexistent cirrhosis or the limited availability of suitable donor livers.<sup>10-12</sup> Furthermore, HCC

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TABLE 1  
Clinical Profile of 48 Patients with Hepatocellular Carcinoma

Patient characteristics		Tumor characteristics	
Gender (male/female)	41/7	Tumor location (unilobular/bilobular)	12/36
Age (younger than 65 yrs/65 yrs and older)	27/21	Macroscopic finding (nodular/infiltrative)	12/36
HCV (+/-)	46/2	Maximum tumor size (< 50 mm/≥ 50 mm)	12/36
T-bilirubin (mg/dL; mean ± SD)	1.24 ± 0.74	Tumor extent (E1/E2/E3/E4) <sup>b</sup>	3/17/16/12
Albumin (g/dL; mean ± SD)	3.52 ± 0.44	Tumor stage (1/2/3/4) <sup>c</sup>	0/0/4/44
Child (A/B/C) <sup>a</sup>	19/22/7	Grade of portal invasion (Vp1/Vp2/Vp3) <sup>d</sup>	0/14/34
Previous treatment (yes/no)	29/19	Completion of protocol (yes/no)	40/8
Plasma concentration of AFP (< 1,000 ng · mL <sup>-1</sup> /≥ 1,000 ng · mL <sup>-1</sup> )	21/27		
Plasma concentration of DCP (< 1,000 mAU · mL <sup>-1</sup> /≥ 1,000 mAU · mL <sup>-1</sup> )	23/25		

HCV: hepatitis C virus; AFP:  $\alpha$ -fetoprotein; DCP: des-gamma-carboxy prothrombin; Vp: portal vein tumor thrombosis.

<sup>a</sup> Child stage.<sup>29</sup>

<sup>b</sup> Tumor extent.<sup>33</sup> Tumor replacement of liver parenchyma: E1, < 20%; E2, 20–40%; E3, 40–60%; E4, > 60%.

<sup>c</sup> TNM classification.<sup>34</sup>

<sup>d</sup> Portal invasion.<sup>33</sup> Vp1: in a third or more of the peripheral branch; Vp2: in the second branch; Vp3: in the first branch or trunk.

has a high recurrence rate even after "curative" surgery and these tumors progress to an advanced stage.<sup>11,12</sup> The survival rates of patients with advanced HCC, with complications such as portal vein tumor thrombosis (PVTT) or distant metastasis, remains extremely poor.<sup>10–20</sup> Previous studies have reported that patients with diffuse HCC involving PVTT survive only 1–2 months if effective treatment is not administered.<sup>21</sup> For patients with advanced HCCs, an effective therapy that maintains a satisfactory quality of life is required. Surgery is considered the most effective treatment in HCC patients with PVTT,<sup>19</sup> although the number of suitable cases is limited because of dissemination of the tumor throughout the liver or coexistence of cirrhosis. Transcatheter arterial embolization (TAE), systemic chemotherapy, hormonal therapy, and interferon (IFN) therapy have been used in patients with advanced HCC, although no survival benefit for these modalities has been reported in various randomized controlled trials (RCT).<sup>22–24</sup>

Advances in the biotechnology of implantable drug delivery systems have facilitated repeated arterial infusion of chemotherapeutic agents. Hepatic arterial infusion chemotherapy (HAIC) with several anticancer agents,<sup>25–27</sup> using combinations of obstructive agents<sup>28</sup> and antiproliferative agents,<sup>29</sup> provide a useful option for patients with advanced HCC. We have reported the usefulness of HAIC using low-dose cisplatin and 5-fluorouracil (5-FU) in patients with advanced HCC.<sup>30,31</sup> The aim of this study was to elucidate the efficacy of this therapy by analyzing the clinical results of 48 HCC patients with PVTT treated in this manner.

## MATERIALS AND METHODS

### Patients

From April 1, 1990 to March 31, 2000 at the Department of Medicine II, Kurume University School of

Medicine, and its affiliated hospitals, 142 patients with unresectable HCC underwent HAIC using low-dose cisplatin and 5-FU, via a subcutaneously implanted injection port. Due to the progression of HCC or co-existent cirrhosis, these patients were not suitable candidates for either surgical resection<sup>11,12</sup> or nonsurgical treatments, including microwave coagulation therapy (MCT),<sup>13</sup> radiofrequency ablation (RFA),<sup>14</sup> percutaneous ethanol injection (PEI),<sup>15</sup> or TAE.<sup>17</sup> Of the initial 142 patients, 48 with PVTT were enrolled in the current study. Informed consent was obtained from all patients before commencement of the study. The diagnosis of HCC was made by histopathology and/or imaging studies. Of these 48 patients, 7 were confirmed histopathologically and 41 were confirmed clinically using imaging studies, consisting of ultrasonography (US), computed tomography (CT) scan, angiography, and magnetic resonance imaging, and/or high plasma levels of tumor markers such as  $\alpha$ -fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP). Recent studies have reported the usefulness of serum DCP levels at initial treatment for detecting the development of PVTT.<sup>32</sup> The presence of PVTT was confirmed in all cases by demonstration of one of the following: 1) a low-attenuation intraluminal mass that expanded the portal vein or portal branch on US or enhanced CT scan<sup>5,6</sup>; 2) the "thread-and-streaks" sign or arteriportal shunts on hepatic angiography<sup>7,8</sup>; or 3) filling defects in the portal vein or in the portal branch on an indirect portogram obtained from a venous phase angiogram of the superior mesenteric artery.

Table 1 summarizes the clinical profile of 48 HCC patients with PVTT treated by HAIC. They included 41 males and 7 females with an average age of 64.7 years

(range, 49–79 years). Forty-five patients were infected with hepatitis C virus (HCV), one patient was infected with both HCV and hepatitis B virus (HBV), and the remaining two patients were not infected with either HCV or HBV. Twenty-nine patients had a history of treatment of HCC with surgery, PEI, MCT, TAE and/or chemolipiodolization. PVTT grading and tumor extent rating were determined according to the criteria of the Liver Cancer Study Group of Japan.<sup>33</sup> PVTT grading was based on the location of the tumor thrombus in the peripheral portal vein: Vp1, tumor thrombus in a third or more of the peripheral branch of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branch or trunk of the portal vein. Tumor extent rating was determined by imaging studies. The rating system was based on the percentage of the tumor extent (E): E1, less than 20% of the whole liver; E2, 20–40% of the whole liver; E3, 40–60% of the whole liver; E4, greater than 60% of the whole liver. Tumor stage was graded according to the TNM classification.<sup>34</sup>

#### Technique of Catheter Placement

The catheter was inserted through the femoral artery using the Seldinger method. After detection of HCC, an indwelling 4 or 5-Fr catheter was sited. The tip of the catheter was placed at the common hepatic artery or proper hepatic artery. The other end of the catheter was connected to the injection port and the device was implanted in a subcutaneous pocket in the right lower abdominal quadrant.<sup>30</sup> The gastroduodenal artery and the right gastric artery were occluded using steel coils to prevent gastroduodenal injury from anticancer agents. The entire procedure was performed under local anesthesia.<sup>26,27,30</sup> To prevent occlusion of the catheter, 5 mL (5000 U) of heparin solution was infused biweekly via the injection port.

#### Chemotherapeutic Regimen

After insertion of the drug delivery system in situ, patients received repeated arterial infusion of chemotherapeutic agents via the injection port. One course of chemotherapy consisted of daily administration of cisplatin (7 mg/m<sup>2</sup> on Days 1–5) followed by 5-FU (170 mg/m<sup>2</sup> on Days 1–5). Days 6 and 7 were rest days. Both cisplatin and 5-FU were administered by a mechanical infusion pump set at 1 and 5 hours, respectively.<sup>30</sup> In principle, patients were to receive four serial courses of chemotherapy and these patients were considered to have had "completion" of HAIC. Patients whose chemotherapy was suspended before the completion of the four serial courses because of adverse reactions or complications were considered to have had "incompletion" of HAIC. One or 2 months

after the completion of the initial four courses of HAIC, the patients were to receive a supplemental two to four courses of chemotherapy based on tumor response, performance status, hepatic function, adverse reactions, and complications. The serotonin antagonist ondansetron hydrochloride was administered intravenously as an antiemetic. A saline infusion (500 mL) was administered during chemotherapy.

#### Response Criteria

Local response to treatment was classified following the World Health Organization criteria.<sup>35</sup> Complete response (CR) is the complete disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart. Partial response (PR) is a greater than 50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart. Stable disease (ST) does not qualify for CR/PR or progressive disease (PD). PD is a greater than 25% increase in the size of one or more measurable lesions or the appearance of new lesions.

#### Additional Therapy

Additional therapies were designed on the basis of performance status, hepatic reserve capacity, tumor responses to HAIC, adverse reactions, and complications. Before January 1996, all patients were followed up without additional therapies until recurrent HCC was detected. After January 1996, patients received additional therapies. For example, patients whose residual tumors were relatively small and localized with disappearance of PVTT received radical local therapies such as surgery, RFA, MCT, and PEI as cytoreduction therapy<sup>36,37</sup> and patients who were unsuitable candidates for local therapy received interventional radiology on an outpatient basis (additional chemotherapy). The protocol for additional chemotherapy included weekly HAIC with cisplatin and 5-FU (cisplatin 7 mg/m<sup>2</sup>/day and 5-FU 170 mg/m<sup>2</sup>/day, weekly or biweekly), weekly HAIC with cisplatin (cisplatin 7 mg/m<sup>2</sup>/day, weekly or biweekly), weekly HAIC with epirubicin (epirubicin 7 mg/m<sup>2</sup>/day, weekly or biweekly), monthly chemolipiodolization with epirubicin (epirubicin 14–20 mg/m<sup>2</sup>/day with lipiodol 3 mL, monthly), and monthly chemolipiodolization with carboplatin (carboplatin 100 mg/m<sup>2</sup>/day with lipiodol 3 mL, monthly).

#### Statistical Analysis

Baseline data for patients were expressed as mean  $\pm$  SD or as medians and ranges. Univariate analysis to identify predictors of survival was performed by the Kaplan–Meier method<sup>38</sup> and compared by the log rank



test. Fifteen variables were assessed, including gender, age (younger or older than 65 years), presence of hepatitis-C antibody (HCV-Ab), hepatic reserve capacity (Child A, B, or C classification),<sup>39</sup> presence of pretherapy of HCC, AFP levels (< 1000 or > 1000 ng/mL), DCP levels (< 1000 or > 1000 mAU/mL), tumor location (unilobular, bilobular), maximum tumor size (< 50 or > 50 mm), tumor extent (E1 or E2, E3 or E4),<sup>33</sup> tumor stage (T3, T4),<sup>34</sup> macroscopic findings (nodular, infiltrative), PVTT rating (Vp2 / Vp3),<sup>33</sup> therapeutic effect after HAIC (responders, nonresponders), and completion of protocol. The multivariate analysis was investigated by the Cox proportional hazard model.<sup>40</sup> Survival was confirmed up to April 30, 2001. Statistical significance was defined as a *P* value less than 0.05.

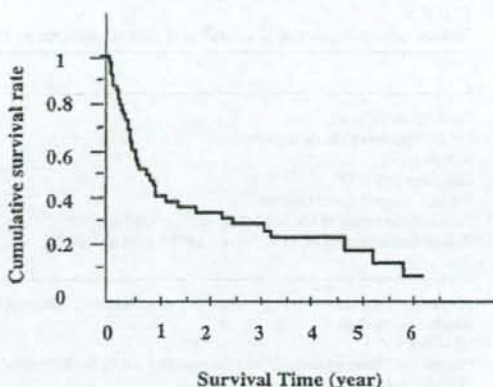
## RESULTS

### Response to Therapy

Patients received 1.8–8.0 (median, 4.0) courses of chemotherapy. HAIC was delivered over more than four serial courses in 40 patients (completion of protocol) and it was suspended in 8 patients within four serial courses (incompletion of protocol). Of the 48 patients, 4 (8%), 19 (40%), 14 (29%), and 11 (23%) patients exhibited CR, PR, ST, and PD, respectively (response rate [CR and PR/ST and PD] = 48%). Of the 19 PR patients, 4 patients had residual tumors which were recognized as necrotic areas.

### Additional Therapy

Twenty-two patients were treated with HAIC after January 1996. Of these, 13 patients received additional therapies. One patient was treated with MCT after a marked decrease in the size of HCC and disappearance of PVTT had been achieved by HAIC. Twelve patients underwent additional chemotherapy after HAIC: two patients received weekly HAIC with cisplatin and 5-FU, five patients received weekly HAIC with cisplatin, one patient received weekly HAIC with epirubicin, three patients received monthly chemolipiodolization with epirubicin, and one patient received monthly chemolipiodolization with carboplatin. Of 13 patients, 4 exhibited disappearance of viable HCC after additional therapy: 1 patient was treated with MCT after HAIC and 3 patients were treated with additional chemotherapy (1 treated with weekly HAIC with cisplatin and 5-FU, 2 treated with HAIC with cisplatin). All four cases had exhibited PR after HAIC. Following the additional therapies, 12 (25%) of 48 patients (4 CR patients, 4 PR patients with necrotic tumor, and 4 PR patients who had effective additional therapies) exhibited disappearance of viable HCC.



**FIGURE 1.** Cumulative survival of 48 hepatocellular carcinoma patients with portal vein tumor thrombosis treated with hepatic arterial infusion chemotherapy. The 1, 2, 3, and 5-year cumulative survival rates of 48 patients, including both responders and nonresponders, were 45%, 31%, 25%, and 11%, respectively.

### Survival and Prognostic Factors

The cumulative survival of 48 patients is shown in Figure 1. The 1, 2, 3, and 5-year cumulative survival rates of the 48 patients were 45%, 31%, 25%, and 11%, respectively. The median survival duration of 48 patients treated with HAIC was 10.2 (range, 1.9–76.9) months.

Two of the 15 factors analyzed by univariate analysis showed prognostic significance: Child stage ( $P = 0.021$ ) and therapeutic effect ( $P < 0.001$ ; Table 2). Tumor extent and PVTT grading were not significant prognostic factors. Multivariate analysis showed only one variable, therapeutic effect, to be an independent predictor of mortality ( $P < 0.001$ ).

The median survival times in 23 responders and 25 nonresponders were 31.6 (range, 8.3–76.9) months and 5.4 (range, 1.9–29.0) months, respectively. Of 23 responders, the 1, 2, 3, and 5-year cumulative survival rates of 12 patients with disappearance of viable HCC were 100%, 91%, 81%, and 40%, respectively. The 1, 2, 3, and 5-year disease-free survival rates of 12 patients were 75%, 50%, 50%, and 8%, respectively.

### Adverse Reactions and Complications

Table 3 shows the adverse reactions and complications in 48 patients treated with HAIC. The most common adverse reaction was nausea and loss of appetite (35%). Most of these adverse reactions were controllable by medical treatment and/or suspension of HAIC. However, deterioration of liver function forced

TABLE 2  
Factors Influencing Cumulative Survival of Patients Analyzed by Univariate analysis

	P value		P value
Gender (males/females)	0.559	Tumor location (unilobular/bilobular)	0.057
Age (younger than 65/65 yrs and older)	0.282	Maximum tumor size (< 50 mm/≥ 50 mm)	0.154
HCV-Ab (+/-)	0.283	Tumor extent (E1 or E2/E3 or E4) <sup>b</sup>	0.093
Child stage (A/B or C) <sup>a</sup>	0.021	Tumor stage (3/4) <sup>c</sup>	0.165
Previous treatment (present/absent)	0.058	Macroscopic finding (nodular/infiltrate)	0.616
Plasma concentrations of AFP (< 1,000 ng · mL <sup>-1</sup> /≥ 1,000 ng · mL <sup>-1</sup> )	0.961	Grade of portal invasion (Vp2/Vp3) <sup>d</sup>	0.422
Plasma concentrations of DCP (< 1,000 ng · mL <sup>-1</sup> /≥ 1,000 ng · mL <sup>-1</sup> )	0.373	Therapeutic effect (PR or CR/ST or PD)	0.001
		Completion of protocol (yes/no)	0.114

HCV-Ab: hepatitis C virus antibody; AFP:  $\alpha$ -fetoprotein; DCP: des-gamma-carboxy prothrombin; Vp: portal vein tumor thrombosis; CR: complete remission; PR: partial remission; ST: stable disease; PD: progressive disease; NS: not significant.

<sup>a</sup> Child stage.<sup>29</sup>

<sup>b</sup> Tumor extent.<sup>33</sup> Tumor replacement of liver parenchyma: E1, < 20%; E2, 20–40%; E3, 40–60%; E4, > 60%.

<sup>c</sup> TNM classification.<sup>24</sup>

<sup>d</sup> Portal invasion.<sup>23</sup> Vp2, in the second branch; Vp3, in first branch or trunk.

TABLE 3  
Adverse Reactions and Complications Related to HAIC

Adverse reactions	No. of patients (%)	Complications	No. of patients (%)
Nausea, loss of appetite	17 (35)	Obstruction of catheters	5 (10)
Peptic ulcers	6 (13)	Hematoma around injection port	4 (8)
Leukopenia, thrombocytopenia	6 (13)	Infection around catheter (sepsis)	2 (4)
Deterioration of hepatic function	6 (13)	Dislocation of the tip of catheter	1 (2)
Renal damage	1 (2)	Obstruction of hepatic artery	1 (2)
Auditory disturbance	1 (2)		

HAIC: hepatic arterial infusion chemotherapy.

the discontinuation of HAIC in four patients and led to death due to irreversible liver dysfunction in one patient.

Complications related mainly to technical problems associated with the indwelling catheter. The majority of patients with these technical problems continued HAIC after implantation of another catheter. Infection around the catheter (sepsis) occurred in two patients: one patient continued HAIC after reimplantation of another catheter and the other patient died of infection caused by methicillin-resistant *Staphylococcus aureus*. Hepatic artery occlusion, which interfered with continuation of HAIC, occurred in one patient.

#### Cause of Death

Ten patients were still alive during the observation period and 38 patients had died. Twenty-three patients (61%) had died of cancer-related disease. Of these, 21 patients (56%) had died of tumor extension and 2 patients (5%) had died of tumor rupture. Eight patients (21%) had died of gastrointestinal bleeding and four patients (10%) had died of liver failure, including one patient who died of liver injury associated

with HAIC. Three patients (8%) died of other causes, including sepsis due to catheter infection (one), pneumonia (one), and cerebral bleeding (one).

#### DISCUSSION

HCC is associated with a high risk of portal vein involvement, which is reportedly observed in 64.7% of cases at autopsy.<sup>9</sup> PVTT is an important prognostic factor in patients with HCC and multivariate analyses have shown it to be a significant clinicopathologic variable that influences survival.<sup>11,19,20,41</sup> However, this vascular involvement is generally refractory to treatment. Surgery is considered the most effective treatment in HCC patients with PVTT. Fujii et al.<sup>19</sup> reported the efficacy of surgical treatment in HCC patients with PVTT. In 104 patients with HCC with PVTT, the survival rates in the surgical ( $n = 32$ ) and nonsurgical groups ( $n = 72$ ) were 72% and 25% at 1 year, 59% and 9% at 2 years, and 54% and 5% at 3 years ( $P < 0.001$ ), respectively. However, the number of suitable cases for surgery is limited because of dissemination of the tumor throughout the liver or coexistence of cirrhosis. PEI is indicated when the throm-

bus is located segmentally (Vp2) or subsegmentally (Vp1).<sup>16</sup> TAE is contraindicated because of the risk of necrosis of the noncancerous portion of the liver and deterioration of the hepatic reserve capacity.<sup>17</sup> Liver transplantation is suitable for small HCCs.<sup>10</sup> Systemic chemotherapy, hormonal therapy, and IFN therapy are all of limited value and only a few patients benefit from tumor regression.<sup>22-24,41</sup> Despite marked progress in medical science and technology, none of the previous therapies has been effective for these patients.

Regional HAIC is a reasonable drug delivery system for patients with advanced HCCs because the tumors derive most of their blood supply from the hepatic artery, whereas the portal vein supplies the normal liver parenchyma.<sup>42</sup> HAIC may provide higher concentrations of chemotherapeutic agents to HCCs. Moreover, hepatic extraction of chemotherapeutic agents results in minimal systemic concentrations of these agents, potentially minimizing systemic toxicity.<sup>43</sup> In a previous study,<sup>30</sup> we reported the usefulness of HAIC with low-dose cisplatin and 5-FU in nine patients with advanced HCC with PVTT. Patt et al.<sup>25</sup> reported the usefulness of HAIC with the FLAP regimen, comprising cisplatin, doxorubicin, flurouridine, and leucovorin. They treated 31 patients with advanced HCC, including 15 patients with PVTT. Fourteen patients had greater than 50% liver replacement of the tumor. The response rate and the median survival duration were 41% and 15 months, respectively. However, patients positive for HBV antigen and/or HCV-Ab showed an increased susceptibility to myelotoxic drugs and median survival duration among these patients was significantly shorter (7.5 months) than among hepatitis nonreactive patients. In an RCT, Chung et al.<sup>29</sup> demonstrated the efficacy of adjuvant systemic IFN therapy in HAIC using a cisplatin regimen. The study included 68 patients with advanced HCC with major PVTT or extrahepatic metastasis. The patients were divided into three groups. The first group received combination therapy of IFN and HAIC with cisplatin ( $n = 19$ ), the second group received HAIC with cisplatin alone ( $n = 23$ ), and the third group was treated conservatively ( $n = 26$ ). Their results revealed a significantly higher survival rate among patients in the first group, compared with survival rates among patients in the second and third groups. However, the response rate and median survival duration of the first group were only 27% and 4.8 months, respectively.<sup>29</sup> In the current study, the response rate and median survival duration of 48 patients with PVTT were 48% and 10.2 (range, 1.9-76.9) months, respectively. Moreover, 12 patients exhibited disappearance of viable HCC (4 CR patients, 4 PR patients with necrotic tumor, and 4 PR patients who

had effective additional therapies). These patients had a favorable result. Their 1, 2, 3, and 5-year cumulative and disease-free survival rates were 100%, 91%, 81%, 40%, and 75%, 50%, 50%, 8%, respectively.

The rationale of this treatment regimen is that cisplatin and 5-FU have an antitumor effect,<sup>44,45</sup> cisplatin has a synergistic effect as a modulator for 5-FU,<sup>46-48</sup> and cisplatin and 5-FU can be administered in low doses to reduce adverse reactions. This combination is used widely to treat various malignancies, including breast, ovarian, and colorectal carcinoma,<sup>46-48</sup> as well as HCC.<sup>27,36</sup>

Univariate analysis demonstrated that two factors, namely, therapeutic effect ( $P < 0.001$ ) and hepatic reserve capacity ( $P = 0.021$ ), influenced the prognosis (Table 2). Patients with Child A cirrhosis were suitable candidates for HAIC using this regimen, irrespective of previous therapy for HCC, high plasma levels of tumor markers, degree of tumor involvement of the liver, and degree of portal vein invasion. Several investigators have reported that the hepatic reserve capacity is an independent prognostic factor in patients with HCC.<sup>11,18-20,41</sup> We presume that patients with good hepatic reserve capacity are more tolerant to adverse reactions induced by anticancer agents compared with patients with poor hepatic reserve capacity, thus allowing continuation of HAIC. In the current study, all of the patients with Child A cirrhosis received HAIC for more than four serial courses (completion of HAIC). However, completion of the protocol was not a significant prognostic factor in this study. Multivariate analysis revealed that only the therapeutic effect was an independent prognostic factor of survival. The median survival intervals in 23 responders and 25 nonresponders were 31.6 (range, 8.3-76.9) months and 5.4 (range, 1.9-29.0) months, respectively. Llovet et al.<sup>20</sup> reported the natural history of patients with untreated nonsurgical HCC and revealed that the median survival duration of patients with PVTT was only 2.4 months. Okuda et al.<sup>18</sup> reported similar results. A statistically significant prognostic advantage for HAIC in patients with PVTT should be evaluated by a properly conducted RCT. However, in view of the studies demonstrating that the postdiagnostic median survival period of HCC patients with PVTT was only a few months,<sup>18,20</sup> the survival periods of responders in our current study were longer compared with those previously reported. It is noteworthy that the nonresponders in our study also exhibited slightly longer median survival intervals than those previously reported,<sup>18,20</sup> although most patients in the study (61%) died of cancer-related disease. Starting in January 1996, we administered additional therapies in patients with residual tumors after HAIC. One patient subse-

quently exhibited disappearance of viable HCC after cytoablation therapy (MCT)<sup>36,37</sup> and three patients had disappearance of viable HCC after additional chemotherapy. Of the initial 142 patients with advanced HCC treated with this HAIC chemotherapy regimen, additional therapies were significant prognostic factors (data not shown). Additional therapies following HAIC might be an option for prolongation of survival in these patients.

The toxicity of chemotherapy was a substantial problem in all treatment arms.<sup>25-29</sup> In the current study, myelotoxicity was less frequent than previously reported for HAIC.<sup>25,26</sup> The most common adverse reactions and complications were early gastrointestinal symptoms and technical problems related to the indwelling catheter. The majority of these problems were resolved by medical treatment or reimplantation of the catheter (Table 3). However, two patients (4%) died of deterioration of hepatic function or catheter-related sepsis and four patients could not continue HAIC due to deterioration of hepatic function. Caution should be exercised in preventing and monitoring adverse reactions or complications, especially with respect to deterioration of hepatic function.

In conclusion, this chemotherapeutic regimen may potentially be a basic protocol for HCC patients with involvement of the portal vein. Patients with PVTT who respond to HAIC could certainly exhibit survival benefits. Suitable candidates for this chemotherapy included patients with preserved hepatic reserve capacity. Therefore, hepatic function should be monitored carefully during administration of HAIC.

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## 大血管内進展を伴う進行再発肝細胞癌に対する外科治療

Surgical treatment for recurrent hepatocellular carcinoma with invasion to major vessels

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●要旨●門脈や下大静脈内に腫瘍栓を形成する高度進行肝細胞癌（肝癌）は大型肝癌が多く、また、再発例では癒着や解剖学的な偏位がみられる場合があるので、術前に遠隔転移を含めた肝癌進展範囲と外科解剖を十分把握しておく。門脈腫瘍栓例では門脈本幹と左右1次分枝を遮断後、腫瘍栓を摘出する。下大静脈内腫瘍栓が右心房内に進展している場合は人工心肺下に、肝上下大静脈内に腫瘍栓が存在し、その頭側にテーピングが可能な場合、全肝血流遮断（THVE）下に腫瘍栓を摘出する。肝静脈流入部尾側で下大静脈にテーピングが可能であれば、下大静脈のクランプのみで腫瘍栓を摘出し得る。大血管内進展を伴う進行再発肝癌の手術は侵襲の大きな治療であるので、慎重な手術適応決定と心臓外科などとの協力体制が重要である。

● key words : 肝細胞癌, 門脈腫瘍栓, 下大静脈内腫瘍栓, 人工心肺, 全肝血流遮断 (total hepatic vascular exclusion : THVE)

### はじめに

肝細胞癌（肝癌）は進行すると門脈に浸潤、腫瘍栓（Vp）を形成、しばしば門脈本幹や反対側の肝内門脈枝に進展する。また、肝静脈に浸潤、形成された腫瘍栓（Vv）が下大静脈内に進展し、時にその腫瘍栓が右心房内に達することがある。初発例のみならず、肝癌切除後の肝内再発例においても再発部位によっては早期に門脈腫瘍栓や下大静脈内腫瘍栓を形成する。さらに、近年、マイクロウェーブ凝固療法やラジオ波焼灼術などの治療後に急速に門脈や肝静脈内に進展し、腫瘍栓を形成する症例も経験されるようになった。

このような大血管内に進展した局所高度進行肝癌の手術適応は慎重でなければならないが、症例によってはほぼ完全に切除できる場合や、術後リザーブ動注や5-FU・インターフェロン療法併用などにより長期生存が期待できる症例がみられることから、再発例であっても外科的治療が適応となる症例がみられる。

本稿ではこのような大血管内進展を伴う進行再発肝癌に対する外科的治療手技や問題点について概説する。

### 大血管内進展を伴う進行再発肝癌に対する手術の注意点

一般に肝切除後再発例に対する再肝切除においては、肝切除部や肝門部の高度な癒着や解剖学的偏位がしばしばみられる。そのため、術前の画像診断において肝癌の進展範囲や主要血管との位置関係をしっかりと把握しておくことが重要である。VpやVv症例では術前肝内転移巣や食道静脈瘤の検索を行う。また、下大静脈内腫瘍栓を伴う肝癌症例は容易に肺転移をきたすため、肺転移を含めた遠隔転移がないことを術前に確認する。大血管内進展を伴う症例では一般に大型肝癌の場合が多いので、十分な視野を得るため、正中切開に加えて同肋弓下切開を行う。肝静脈根部の確保が困難な場合は躊躇なく右第8あるいは第9肋間へと切開を延長し、開胸操作を加える。術中、逐次超音波検査を行い、腫瘍の位置と尿管の走行を確認しつつ手術を進め、尿管や周囲臓器の不用意な損傷を避ける。マイクロウェーブ凝固療法やラジオ波焼灼術などの局所治療や肝動脈塞栓術などが繰り返行われていた場

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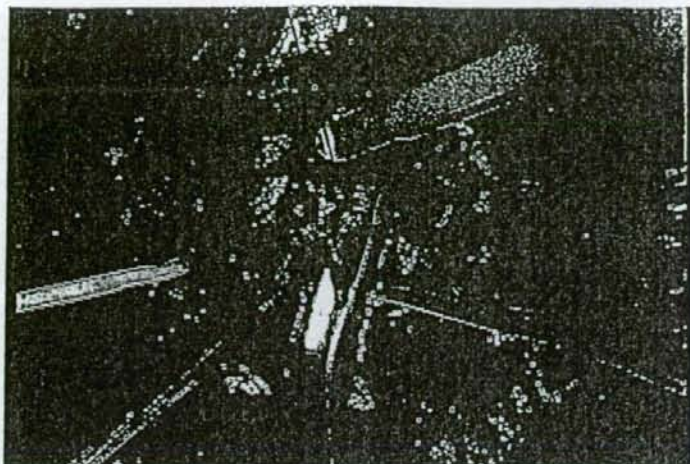


図1 Vps症例では鉗子などを用いて門脈本幹と対側門脈1次分枝を遮断した後、腫瘍側の門脈1次分枝に支持糸をかけ、メスで切開を加えて、門脈腫瘍栓を摘出する

合、発達した側副血行路や瘻痕、胆汁貯留などに注意を要する。

大血管内進展を伴う進行再発肝癌の予後は通常きわめて悪く、下大静脈内腫瘍栓を伴う場合、突然死の危険性がある。そこで、遠隔転移がなく、基本的に全肝内病巣を摘出できる場合で、肝機能が保たれており、全身状態が良好であれば手術適応となる。術後の化学療法併用の目的とした減量手術も行われる。

大血管内進展を伴った高度進行肝癌に対する手術では、大出血や血流遮断による循環不全や肝障害など過大侵襲が加わる可能性がある。また、術後比較的早期に再発をきたすことが少なくない。そこで、患者および家族には疾患の重症度、手術や再発の危険性とともな術後化学療法を含めた治療プランを十分に説明、理解していただくことが重要である。

#### 門脈腫瘍栓形成例に対する外科的治療

肝内病巣から肝内門脈枝を経て門脈1次分枝(Vps)や門脈本幹(Vp)に腫瘍栓を形成する。腫瘍栓が対側葉の門脈枝末梢、上腸間膜静脈や脾静脈に及ぶ場合は一般的に切除の適応はない。開腹後、腹腔内精査を行い、次いで術中超音波検査により肝内病巣と門脈腫瘍栓の進展度を把握する。通常、肝門部処理後、門脈腫瘍栓を摘出し、最後に肝切除を行う。すなわち、総胆管をテーピング後、担癌側の肝動脈を結紮・切離す

る。担癌側の胆管が確認できれば切離しておく、門脈の全容を確認しやすくなる。門脈本幹のテーピングを行い、左右門脈1次分枝を確保、テーピングする。Vps症例では腫瘍栓より尾側まで十分に剝離しておくが、側副血行路が発達している場合が多いため注意を要する。Vps症例では鉗子などを用いて門脈本幹と反対側の門脈1次分枝を遮断した後、腫瘍側の門脈1次分枝に支持糸をかけ、メスで門脈を切開、門脈腫瘍栓を摘出する(図1)。その後、門脈枝を離断し、断端を縫合閉鎖する。Vps症例で腫瘍栓が門脈本幹を占居するような症例では門脈本幹と対側門脈1次分枝を遮断し、門脈本幹に切開を加え、門脈腫瘍栓を摘出する(図2)。時には鉗子や吸引器を用いて腫瘍栓を摘出する(図3)。さらに門脈本幹の遮断を時々開放して、腫瘍栓を切開口から噴出させる。対側門脈枝に腫瘍栓がみられる場合、Fogartyカテーテルなどを用いて腫瘍栓を摘出する(図4)。その腫瘍栓が摘出されると、対側門脈枝より血液の逆流がみられるようになる。門脈腫瘍栓処理後、肝切除を行うが、尾状葉門脈枝に腫瘍栓がみられる場合は尾状葉合併切除を併施する。

#### 下大静脈内腫瘍栓形成例に対する外科的治療

肝癌の場合、下大静脈内腫瘍栓は直接浸潤によるものはまれで、左・中・右肝静脈、短肝静脈、下右肝静

図2 Vp症例で腫瘍栓が門脈本幹を占居するような症例では門脈本幹と対側門脈1次分枝を遮断し、門脈本幹に切開を加えて腫瘍栓を摘出する

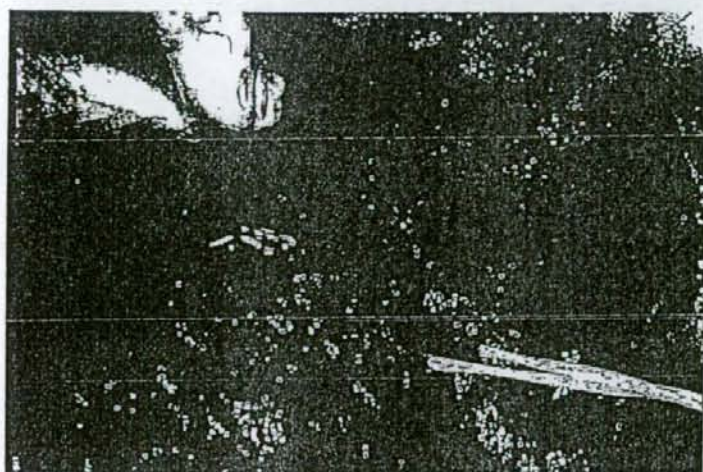
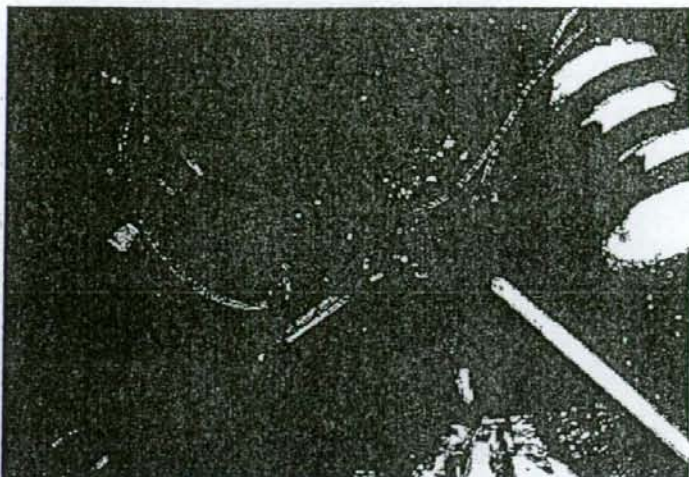
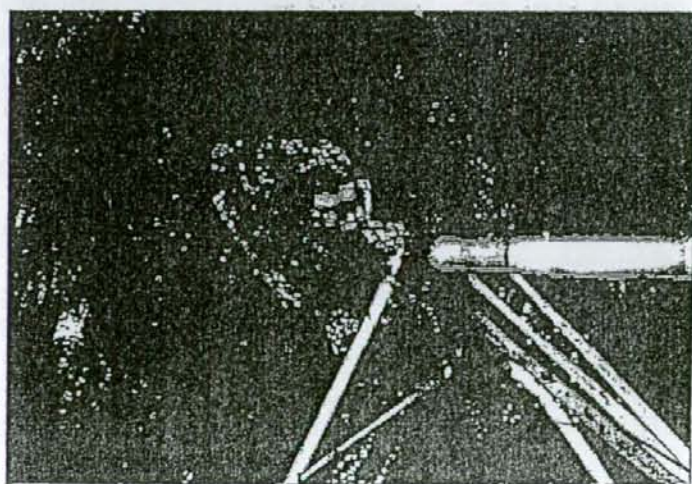


図3 必要に応じて鉗鉗や吸引器を用いて門脈腫瘍栓を摘出する

図4 対側門脈枝に腫瘍栓がみられる場合、Fogarty カテーテルなどを用いて腫瘍栓を摘出する





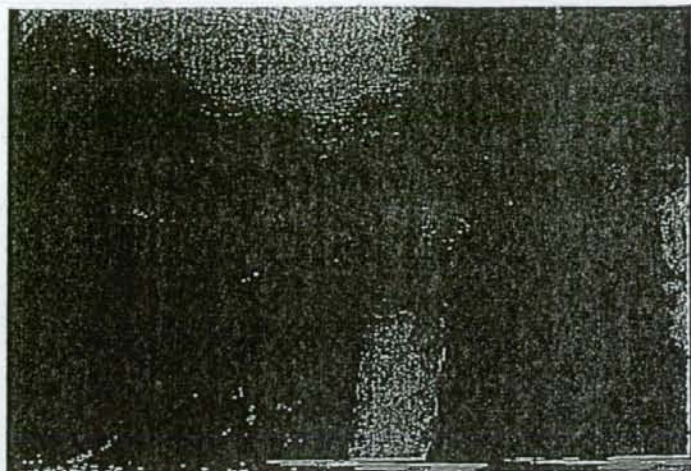


図5 下横隔静脈を介して下大静脈内に腫瘍栓を形成した症例における  
下大静脈内腫瘍栓抽出



図6 腫瘍栓が肝静脈流入部から肝上部下大  
静脈内に存在する症例の術中超音波像

脈を介して腫瘍栓が下大静脈内に進展する。筆者らは  
肝癌の再発病巣から下横隔静脈を介して下大静脈内に  
腫瘍栓を形成した症例を経験している(図5)。

下大静脈内腫瘍栓を伴う症例に対する手術方法は腫  
瘍栓の進展部位によって異なる。すなわち、腫瘍栓が

右心房内に進展している場合は人工心肺装置が必要と  
なる。肝上部下大静脈内に腫瘍栓が存在し(図6)、  
その頭側にテーピングが可能な場合、全肝血流遮断  
(total hepatic vascular exclusion: THVE, 図7)  
下に腫瘍栓を抽出し得る。下大静脈腫瘍栓が小さく、  
肝静脈流入部尾側で下大静脈にテーピングが可能であ  
れば、THVEをせずに抽出が可能である。

THVEを使用する場合、THVEの際のバイパス用  
に右(左)大伏在静脈、左腋窩静脈を露出できるように  
術野を設定しておく。開腹後、腹腔内の精査を行い、  
術中超音波検査によって肝内病巣とともに下大静脈内  
腫瘍栓の進展度を確認する。腫瘍栓が心房内に達する  
場合は、経食道超音波検査によって腫瘍栓を確認する  
(図8)。右心房内に腫瘍栓が進展している場合は、胸  
骨縦切開を加え、心臓外科の協力の下に人工心肺装置  
を装着する。この際、肝切除を先行し、人工心肺装着  
による心停止下に下大静脈から右心房内に進展した腫  
瘍栓を一塊として切除する方法と、あらかじめ人工心  
肺下に心停止し、下大静脈から右心房に進展した腫瘍  
栓を抽出後(図9)、肝切除を行う方法が考えられる。

THVE下に切除可能な場合、Kocherの授動術を行  
い、腎静脈頭側で下大静脈をテーピングする。次いで、  
肝上部下大静脈のテーピングを行う。この際、必要が  
あれば下横隔静脈を結紮・切離しておく。横隔膜下で  
テーピングが困難な場合、経横膈膜のあるいは右開胸  
を加え、心嚢内でテーピングを行う。経横膈膜の心嚢  
切開は下大静脈の正中線上で横膈膜に縦切開を加えて

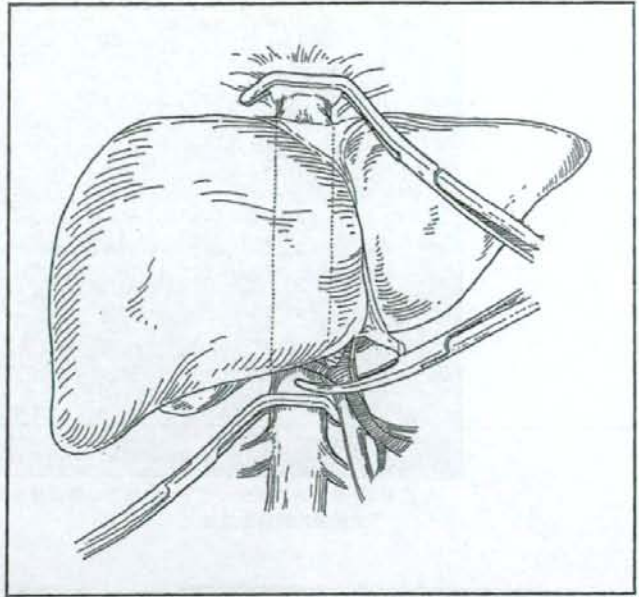


図7 全肝血流遮断 (total hepatic vascular exclusion) の模式図

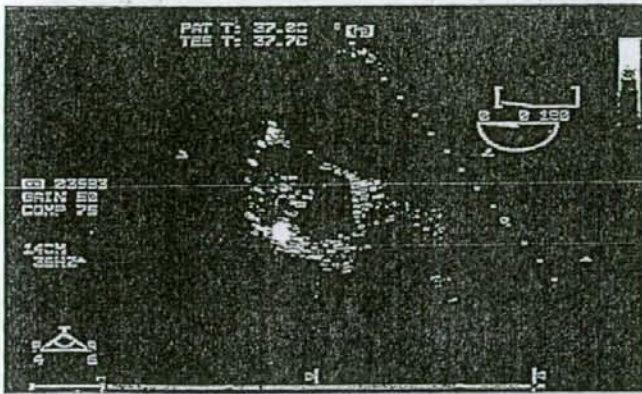


図8 右心房内腫瘍栓の経食道超音波像

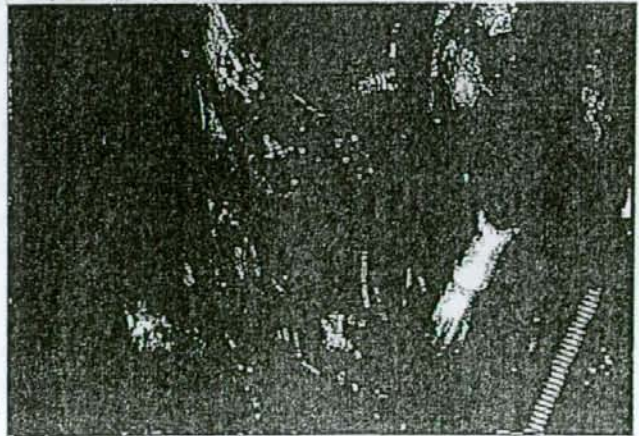


図9 人工心肺下, 右心房切開による右心房および下大静脈内腫瘍栓の抽出



図10 肝上部下大静脈, 肝下部下大静脈および肝門部で血流が遮断され, 全肝血流遮断が行われている

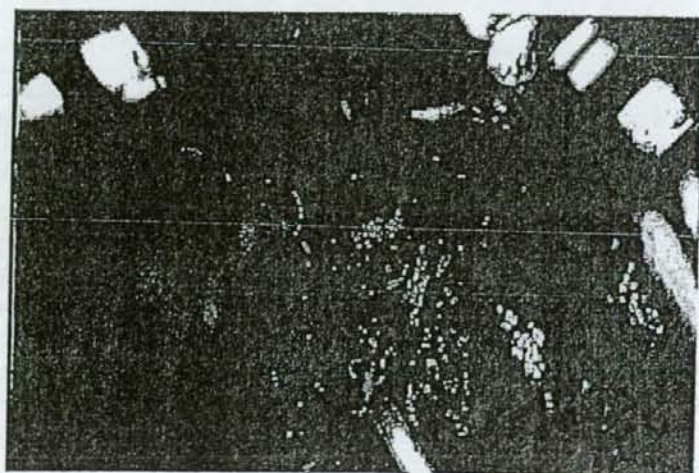


図11 THVE下, 下大静脈切開による腫瘍栓抽出

心嚢を開放し, 心嚢内肝上部下大静脈をテーピングする。肝門部処理に引き続いて肝を脱転し, 下大静脈に流入する短肝静脈を可能なかぎり結紮・切離する。右肝静脈や中・左肝静脈共通幹の下大静脈流入部にテーピングを行うが, 腫瘍側の肝静脈の頭側と反対側の肝静脈の尾側に斜めにテーピングしておくことができると, THVEの時間を短縮できる。肝切離を行った後, THVE下に肝静脈や下大静脈を切開し, 腫瘍栓を抽出する方法(図10, 11)と, THVE下に肝切離およ

び腫瘍栓抽出を行う方法がある。

THVEに際して, まず十分な輸液を行い, 中心静脈圧を維持しておく。さらにTHVEに先立ってテストクランプを行う。遮断後5分以内に血圧が低下しなければ基本的にバイパスなしにTHVEは可能である。逆にテストクランプ後, 血圧が30%以上低下する場合はバイパスを用意する。正常肝ではバイパスなしで60~90分間のTHVEに耐え得ると報告されている<sup>10)</sup>。一方, 肝硬変例においてバイパスの設置により

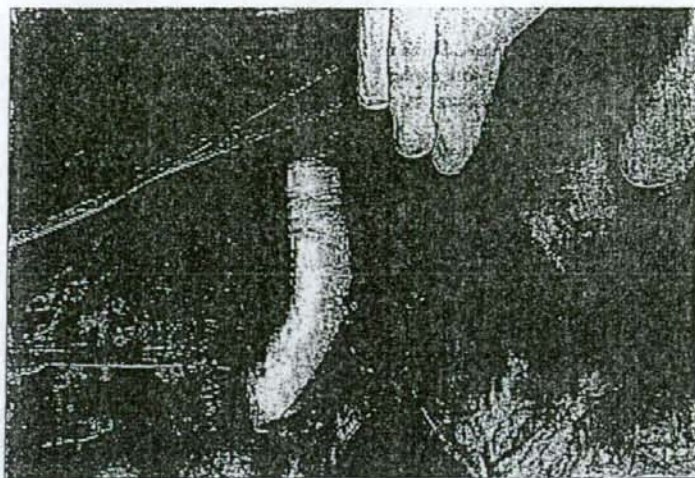


図12 リング付人工血管 (EPTFE) を用いた下大静脈の再建

60分間の THVE が可能と考えられている<sup>9)</sup>。バイパスには下大静脈血のみのシングル・バイパスと下大静脈血と門脈血をバイパスするダブル・バイパスがある。血圧維持と腸管のうっ血防止のためにはダブル・バイパスが行われる。また、バイパス方法には血流ポンプを用いるアクティブ・バイパスと血流ポンプを用いないパッシブ・バイパスがあるが、通常ヘパリン化を必要としないバイオポンプを用いたアクティブ・バイパスが選択されることが多い。前述のように、THVE 下に腫瘍栓を摘出した後に、肝静脈頭側の肝上部下大静脈で血流遮断している血管鉗子を、健側肝静脈尾側あるいは肝静脈流入部尾側へかけ直すことができれば、全肝の血流遮断を解除することが可能になり肝血流遮断時間を短縮できる。

下大静脈内腫瘍栓が肝静脈流入部付近に存在し、右肝静脈のみで肝右葉が下大静脈と連続している状況であり、肝右葉の尾側への牽引により腫瘍栓が横隔膜より尾側下大静脈内に引っ張れば、腹腔内操作のみで摘出可能である。さらに肝静脈流入部付近まで移動できれば、下大静脈のサイドクランプのみで摘出可能となる。

肝癌の浸潤により下大静脈合併切除を行う場合、欠損部が小範囲の場合が多く、欠損部が半周程度までであれば直接縫合を行う。欠損部が大きい場合、パッチを用いて縫合閉鎖を行うが、そのパッチには大伏在静脈、下腸間膜静脈、卵巣(精巣)静脈、心臓、人工血管などを用いる。下大静脈を再建する場合、径 2 cm

のリング付人工血管 (EPTFE) を用いて再建する (図 12)。

### 大血管内進展を伴う進行再発肝癌の併用療法

筆者らは Vps あるいは Vps 症例に対しては切除後に low dose FP 療法を中心とした肝動注療法を施行し、再発予防に努めている。また、高度進行肝癌に対する減量手術後の化学療法施行例の成績も報告され、長期生存例もみられるようになった<sup>10)</sup>。今後、これらの総合的な治療戦略の確立により、大血管内進展を伴う進行再発肝癌の治療成績の向上が期待される。

### おわりに

大血管内進展を伴う進行再発肝癌に対する手術は、術中大出血をきたす可能性や全身循環や肝障害がみられるなど侵襲がきわめて大きい治療であるので、慎重な手術適応決定と心臓外科などとの協力体制が重要である。

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