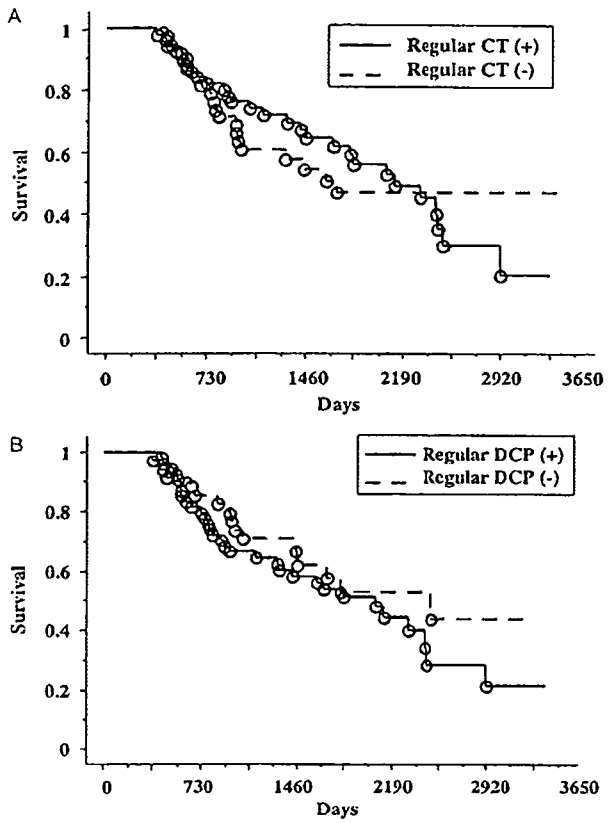

FIGURE 2. A, Kaplan-Meier survival curves of 91 patients with HCC detected at Kurume University School of Medicine. Survival was comparable between Regular CT (+) and (−) groups. B, Kaplan-Meier survival curves of 91 patients with HCC detected at Kurume University School of Medicine. Survival was comparable between Regular DCP (+) and (−) groups.

screening for HCC by AFP and US could identify tumors at an earlier stage, resulting in higher chance of receiving treatment. In the present study, the frequency of receiving promising treatment (HR or LAT) was significantly higher in group A (73%) than in groups B (52%) and C (26%), and significantly higher in group B than in group C (group A vs. group B: $P = 0.002$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$) (Table 2). Surveillance at specialized Department of Liver Disease could identify earlier stage of HCC than other institutions, resulting in higher chance of receiving promising treatment.

The cumulative survival rates of group A were significantly better than those of groups B ($P = 0.0157$) and C ($P < 0.0001$), and group B was significantly better than that of group C ($P < 0.0001$) (Fig. 1). These results are similar to those of Yuen et al,[9] Sangiovanni et al,[10] and Trevisani et al,[11] indicating that surveillance for HCC improved the survival of cirrhotic patients when effective treatment of HCC and management of liver cirrhosis were available. Surveillance at specialized Department of liver disease may prolong survival of patients with chronic liver disease compared with surveillance for HCC at other institutions. Randomized prospective trials are needed to confirm the survival benefits of surveillance of HCC between institutions.

Arguedas et al[15] reported that the screening for HCC by using CT is the most cost effective strategy in transplant-eligible patients with cirrhosis in the United States using Markov model. In the present study, we tested whether regular 3-phase CT or regular DCP in addition to regular US and AFP can detect early stage-HCC in 91 patients at Kurume University School of Medicine (Table 3). The regular CT (+) group tended to have smaller HCC than regular CT (−) group (mean tumor size: 18.7 vs. 22.4 mm; $P = 0.061$). However, the number of tumors, tumor markers, frequency of meeting UNOS T1-2 criteria, frequency of receiving promising treatment, and cumulative survival were not significantly different between the 2 types of HCC detection (Table 3, Fig. 2A). Furthermore, tumor characteristics, frequency of meeting UNOS T1-2 criteria, frequency of receiving promising treatment, and cumulative survival rate were comparable between regular DCP (+) and DCP (−) groups (Table 3, Fig. 2B). Regular CT and regular DCP in addition to conventional method of surveillance of HCC offered limited value of early detection of HCC at specialized Department of liver disease.

In conclusion, surveillance for HCC at specialized Department of liver disease can detect early-stage HCC, allowing a better chance of receiving promising treatment. Randomized prospective trials are needed to determine whether surveillance for HCC can improve survival of patients with chronic liver disease. Regular CT and regular DCP in addition to conventional methods of surveillance program of HCC seem to be of limited value in early detection of HCC.

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A Decrease in AFP Level Related to Administration of Interferon in Patients with Chronic Hepatitis C and a High Level of AFP

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It is known that there is a very high incidence of hepatocellular carcinoma (HCC) among patients with type C chronic hepatitis and cirrhosis, and α-fetoprotein (AFP) has been widely used as a diagnostic marker for HCC. However, there are some patients showing continuous high AFP values but no evidence of HCC, and some studies have defined such patients as a high-risk group for HCC. In vitro study has shown that interferon (IFN) inhibits cell proliferation and enhances apoptosis as well as specific cytotoxic T lymphocytes against HCC, resulting in direct anticancer actions. In this study, we investigated the effect of IFN on AFP changes in chronic hepatitis C patients. Of 40 patients with chronic hepatitis C in whom diagnostic imaging confirmed the absence of HCC, 24 patients showed high pretreatment AFP values (high AFP group: AFP level > 10 ng/dl; mean ± SD, 46.3 ± 41.5 ng/dl) and 16 showed low pretreatment AFP values (low AFP group: pretreatment AFP level ≤ 10 ng/dl; mean ± SD, 5.3 ± 2.2 ng/dl). Pretreatment clinical parameters were statistically evaluated in relation to the AFP value. In the high AFP group, the platelet count, albumin level, and prothrombin (%) were significantly lower ($P = 0.047$, $P = 0.0002$, and $P = 0.044$, respectively), suggesting that AFP value increases with advancing liver disease. Subsequently 27 patients were administered IFN (IFN group), and the remaining 13 patients were administered Stronger Neo-minophagen C (SNMC), a glycyrrhizin preparation (SNMC group), as a control group receiving liver-protective therapy. Alanine aminotransferase was reduced in both the IFN and the SNMC group (mean, 132.56 to 60.07 mg/ml [$P < 0001$] and 147.85 to 56.23 mg/ml [$P = 0.0240$], respectively). AFP was significantly reduced in the IFN group (mean, 30.03 to 12.65 ng/ml; $P = 0.0034$), but there was no significant change in AFP in the SNMC group (mean, 29.70 to 39.17 ng/ml). AFP is useful for diagnosing HCC; however, some patients show a persistently high AFP level in the absence of HCC, and these patients have been described as a high-risk group for HCC. In this study, we found that IFN therapy but not SNMC universally reduced the AFP baseline. Since AFP is a significant predictor for HCC, therapeutic strategies for hepatitis C, e.g., long-term low-dose IFN treatment, may reduce hepatocarcinogenesis.

KEY WORDS: hepatitis C; interferons; hepatocellular carcinoma; α-fetoprotein.

Recently, combination therapy with pegylated interferon (IFN) and ribavirin for 48 weeks has achieved viral eradication in 54 to 56% of patients, and the occurrence of hepatocellular carcinoma (HCC) was prevented in these responders (1, 2). For nonresponders to IFN therapy, liver-protective therapy, such as oral administration of

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ursodeoxycholic acid or intravenous injection of Stronger Neo-minophagen C (SNMC), is commonly performed in Japan, and it is considered that these treatments may delay the progression of liver disease (3, 4). SNMC is a glycyrrhizin preparation that exhibits potent anti-inflammatory actions and has been used to treat allergic diseases and hepatitis in Japan for centuries. However, this agent is not considered to have any antiviral or anticancer ability (5), while IFN is considered to have antiviral, anti-inflammatory, and anticancer effects, and is employed in clinical practice to treat certain types of cancer, such as germ cell tumor and RCC (6, 7).

α-Fetoprotein (AFP) has been widely used as a diagnostic marker for HCC. However, there are some patients with a high AFP baseline but no evidence of HCC, although some papers have reported that AFP is a significant predictor of HCC in such patients (8, 9). This study investigated the clinical characteristics of such patients with a high AFP baseline and assessed the effect of IFN administration in terms of AFP changes, since AFP is suggested to be an important risk factor for HCC.

METHODS

Forty patients with type C chronic hepatitis and compensatory liver cirrhosis patients who were being followed at Kurume University Medical Center were retrospectively investigated. All patients were confirmed to be positive for serum hepatitis C virus (HCV)-RNA by polymerase chain reaction (PCR). HBs-Ag-positive, autoimmune, alcoholic, and drug-induced hepatitis patients were excluded from the study. Furthermore, the absence of HCC was confirmed by abdominal ultrasonography (US) or dynamic computed tomography (CT) in all subjects.

According to the pretreatment AFP value, the 40 subjects were divided into two groups: the high AFP group (AFP > 10 ng/dl; $n = 24$) and the low AFP group (AFP ≤ 10 ng/dl; $n = 16$). Then the pretreatment clinical background parameters were statistically investigated using the Mann-Whitney U-test and chi-square test to compare the high and low AFP groups.

These 40 subjects were divided into two groups, the IFN group ($n = 27$) and the SNMC group ($n = 13$). Six million units of recombinant IFNα-2b was injected intramuscularly three times a week or more in the IFN group. SNMC was administered intravenously three times a week at a dose of 40 to 100 ml in the SNMC group. Both alanine aminotransferase (ALT) and AFP values after 4 weeks of treatment were compared with the pretreatment values. Paired t-test was used, and $P < 0.05$ was regarded as significant.

RESULTS

Clinical Characteristics in Patients with High AFP Baseline (High AFP) vs. Low AFP Group. There were no significant differences in age, gender, ALT level, HCV genotype, or HCV-RNA level between the high and the low AFP groups; however, in the high AFP group, the platelet count, albumin level, and prothrombin (PT) value were significantly lower ($P = 0.0014$, $P = 0.0026$, and $P = 0.0041$) (Table 1). These results suggest that the AFP level increases with the progression of liver disease.

Pretreatment Backgrounds in IFN and SNMC Treatment Groups. There were no significant differences in the pretreatment background parameters such as AFP value, age, gender, ALT value, platelet count, albumin level, PT (%), and HCV-RNA level between the two groups (Table 2). Fourteen of the 27 IFN-treated patients (52%) showed a high pretreatment AFP value (>10 ng/ml), and 9 of the 13 SNMC-treated patients (69%) showed a high pretreatment AFP value (>10 ng/ml).

ALT Changes in IFN and SNMC Treatment Groups. With respect to changes in the ALT level, the AFP level was significantly decreased in the IFN group (132.6 ± 72.7 to 61.1 ± 43.3 U/L; $n = 27$; $P < 0.0001$). In the SNMC group, ALT levels were also significantly decreased (149.4 ± 17.2 to 83.0 ± 57.7 U/L; $n = 12$; $P = 0.019$) (Figure 1).

AFP Changes in IFN and SNMC Treatment Groups. As for AFP changes, the AFP value was significantly

TABLE 1. PRETREATMENT CLINICAL CHARACTERISTICS ACCORDING TO AFP VALUE

	High AFP (n = 24) (AFP > 10 ng/ml)	*Low AFP (n = 16) (AFP ≤ 10 ng/ml)*	P *value*
AFP (ng/ml)	46.264 ± 41.534	5.348 ± 2.229	—
Age (yr)	55.875 ± 9.252	52.938 ± 12.179	0.3914
Gender (M/F)	14/10	12/4	0.2790
ALT (U/L)	144.333 ± 88.122	125.813 ± 83.818	0.5108
PLT ($\times 10^4/\mu l$)	11.421 ± 4.997	14.550 ± 4.030	0.0467*
Albumin (g/dl)	3.617 ± 0.444	4.138 ± 0.238	0.0002*
PT (%)	72.368 ± 11.923	80.237 ± 10.796	0.0439*
HCV-RNA (KIU/mL)	472.667 ± 286.404	463.067 ± 323.334	0.9257

Note. Mann-Whitney U-test or chi-square test was used. $P < 0.05$ was considered significant.
Values are expressed as mean ± SD.

TABLE 2. PRETREATMENT PATIENT PROFILES IN THE SNMC AND IFN GROUPS

	SNMC (n = *13*)	*IFN* (n = *27*)	P *value*
AFP (ng/ml)	29.970 ± 35.229	30.030 ± 39.643	0.9798
Age (yr)	54.308 ± 10.427	54.889 ± 10.685	0.8719
Gender (M/F)	9/4	17/10	0.6071
ALT (U/L)	147.846 ± 110.816	132.556 ± 272.702	0.6039
Platelets (×104/μl)	11.015 ± 6.244	13.441 ± 3.870	0.1387
Albumin (g/dl)	3.738 ± 0.568	3.867 ± 0.408	0.4185
PT (%)	72.615 ± 13.775	77.615 ± 10.887	0.2607
HCV-RNA (KIU/mL)	502.900 ± 299.403	455.500 ± 302.124	0.6752

Note. Mann-Whitney *U*-test or chi-square test was used. $P < 0.05$ was considered significant.
Values are expressed as mean ± SD.

decreased in the IFN group (53.0 ± 44.3 to 20.3 ± 26.7 ng/ml; $n = 14$; $P = 0.0023$). Interestingly, all 27 IFN-treated patients showed a decrease in AFP value regardless of response to treatment. However, there was no significant change in the AFP value after SNMC administration (31.1 ± 36.4 to 39.0 ± 46.5 ng/ml; $n = 9$; $P = 0.11$) (Figure 2). Mean AFP value was slightly increased in the SNMC group.

DISCUSSION

AFP is a fetal protein that is not normally present in the serum of adults and is commonly used as a tumor marker for HCC. However, serum AFP is also elevated during pregnancy and in chronic hepatitis patients (10, 11). In this study, a considerable number of type C chronic hepatitis and compensated cirrhosis patients demonstrated persistently elevated AFP levels in the absence of HCC. In addition, the AFP level decreased significantly after IFN administration. Furthermore, the AFP decrement was universally observed regardless of treatment response to IFN therapy. Transient AFP elevation has been observed after a rise in transaminase in acute hepatitis and fulminant hepatitis (12–14). This type of AFP elevation is explained as a result of hepatocyte regeneration accompanied by necroinflammatory change. In this study, AFP was not changed in the SNMC group despite significant improvement in transaminase, suggesting that the AFP elevation was not caused by hepatocyte regeneration in chronic hepatitis patients.

AFP production is supposed to regulate the transcription level of hepatocytes (15). Among HCV-infected patients, the HCV-coding core protein is regarded to be one of the proteins responsible for hepatocarcinogenesis, up-regulating several molecules resulting in activation of the cell cycle and cell proliferation at the transcriptional level in hepatocytes (16). The HCV-coding core protein may also upregulate AFP production at the transcriptional

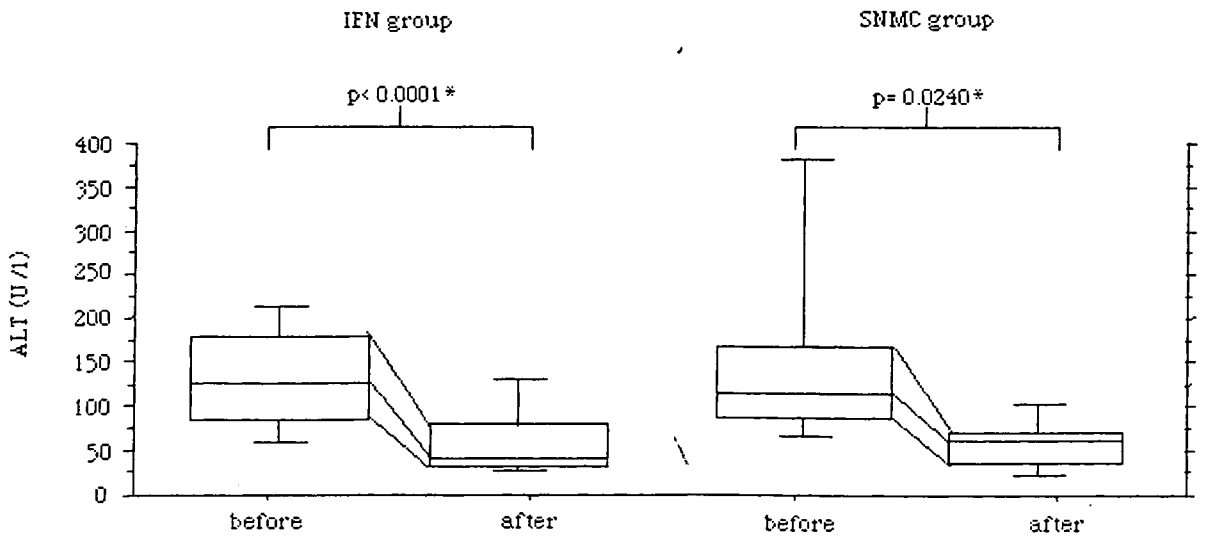

Fig 1. Changes in alanine aminotransferase (ALT) after IFN and SNMC administration. Paired *t*-test was used. *$P < 0.05$ was regarded as significant.

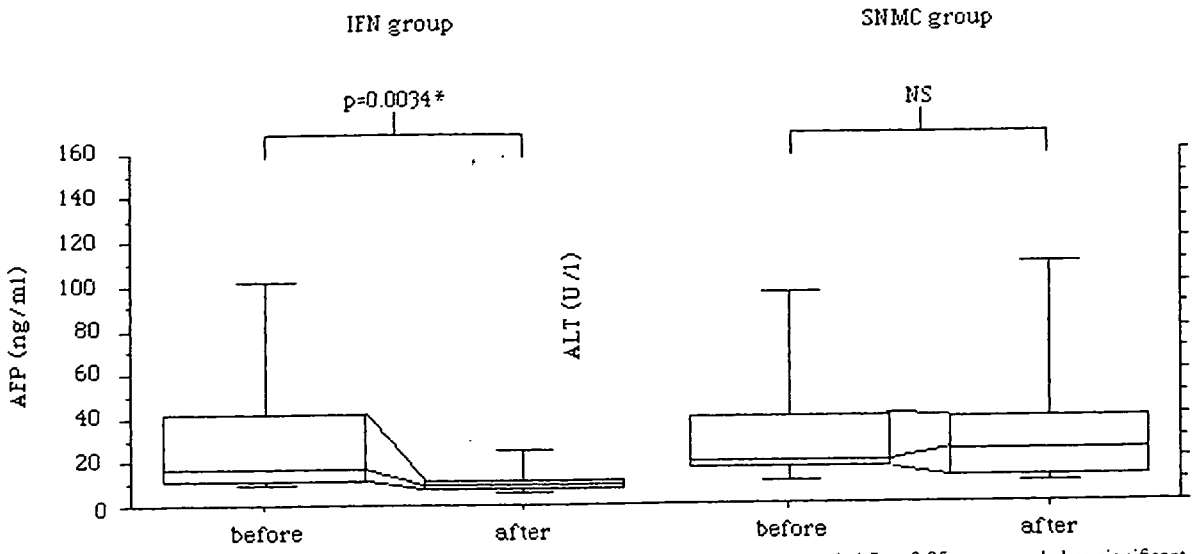

Fig 2. α-Fetoprotein (AFP) changes with IFN and SNMC administration Paired *t*-test was used. $*P < 0.05$ was regarded as significant. NS, not significant.

level. In contrast, IFN is considered to down-regulate cell cycle progression at the transcriptional level and induce apoptosis via the IFN receptor-mediated JAK-STAT signaling pathway (17). This competing action of IFN against HCV-related protein may be a direct anticancer mechanism that inhibits HCC. Actually, a clinical study has demonstrated anticancer effects of IFN administration against intrahepatic recurrence after resection of HCC (18), and IFN has also been used to treat HCC in combination with anticancer agents such as 5-fluorouracil (19).

Many reports have cited elevated AFP baselines as an independent HCC risk factor (8, 9) along with age, gender, liver histology stage, and ethnicity in HCV-infected patients. In the present study, the AFP baseline was decreased in all IFN-treated patients, even IFN nonresponders. This indicates that IFN therapy, rather than liver-protective therapy, universally reduces the risk factors of HCC in HCC high-risk subjects with high AFP values and advanced liver disease. Therefore, therapeutic strategies, such as long-term administration of low-dose IFN, may inhibit HCC in patients who have failed to respond to routine IFN treatment. Further investigation is needed to evaluate IFN effect in relation to AFP production and hepatocarcinogenesis.

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Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type

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Abstract

Background/aims: Recurrence due to clinically undetectable intrahepatic metastasis and portal vein invasion of HCC cells is not 'uncommon' even in small HCCs. The present study investigated the relationship between these factors and macroscopic types of HCC. *Methods:* Surgically resected 209 cases of small HCC less than 3 cm in diameter were examined. Macroscopically, 209 cases were divided into 'vaguely nodular type', 'single nodular type', 'single nodular type with extranodular growth' and 'confluent multinodular type'. *Results:* None of the vaguely nodular type had intrahepatic metastasis or portal vein invasion, and their diameter was significantly smaller than the other three types. 'Single nodular type with extranodular growth' and 'confluent multinodular type' show higher frequency of portal vein invasion and intrahepatic metastases than 'single nodular type'. Among 149 metastatic lesions, the distance was 10 mm or shorter in 118 (79.2%). *Conclusions:* It is important to precisely determine the gross type of small HCC by diagnostic imaging in order to predict portal vein invasion and micrometastasis. It is also important to ablate the tumor with enough surrounding tissue 1 cm in width at least to prevent the recurrence from those micrometastasis.

Keywords: Hepatocellular carcinoma; Gross classification; Intrahepatic metastasis; Portal vein invasion; Hepatic resection

1. Introduction

Along with remarkable advance in imaging diagnosis, increasing numbers of small hepatocellular carcinoma (HCC) have been detected and successfully treated [1]. However, recurrence of these HCCs occurs at a high frequency after ablation therapies and/or surgical resection [2]. Most probable cause of these recurrences is multicenteric occurrence (second primary tumor), but it is also presumed that clinically undetectable intrahepatic metastasis participates in a certain proportion of the recurrence [3,4]. Many of the resected small HCCs are nodular type, and they were well demarcated from surrounding liver tissue. The Liver Cancer Study Group of Japan classified nodular type HCCs into three types, i.e. 'single nodular type', 'single nodular type with extranodular growth' and 'confluent multinodular type'. Furthermore, single nodular type HCC has a sub-category of vaguely nodular type, which is known as a macroscopic characteristic of early-stage small HCCs [5–7].

Many researchers have pointed out the close relationship among clinical outcomes and intrahepatic metastasis and portal vein invasion [8–20]. The present study investigated the frequency of intrahepatic micrometastasis and portal vein invasion of tumor cells in surgically resected small HCCs according to the gross type.

2. Materials and methods

Among 233 consecutive cases of HCC less than 3 cm in diameter, which were curatively ressected at Kurume University Hospital or its affiliated hospitals during the

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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 histolological examinations. Each of the liver slices was divided into two or more blocks, embedded in paraffin, cut into 4-μm 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.

Table 1
Patient profile

Number of patient	209
Age range in years (mean)	36–86 (63)
Male:female	162:47
Virus markers in serum	
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.

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 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).

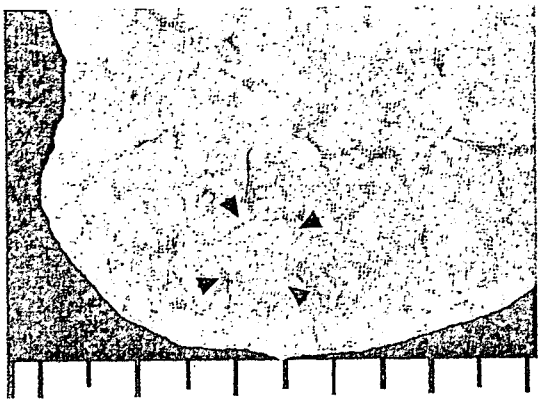

Fig. 1. Gross feature of vaguely nodular type. A nodular tumor (arrow head) with 0.7 cm in diameter shows an indistinct border between cancerous and noncancerous tissue.

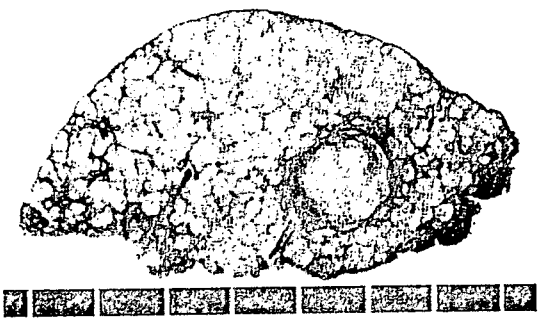

Fig. 2. Gross feature of single nodular. The tumor nodule is distinctly nodular with a thin fibrous capsule. The size is 1.4 × 1.4 cm.

Table 3
Relationship among gross type, capsule and septum formation, capsule invasion, portal and venus 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.

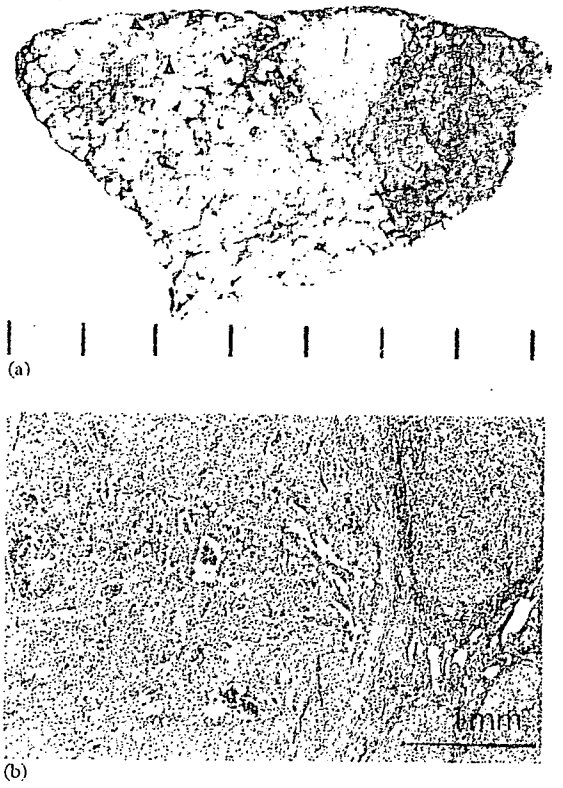

Fig. 3. (a) A minute intrahepatic metastasis (arrow heads) was observed 1.5 cm away from a nodular tumor with extranodular growth. (b) Histological findings of the metastatic lesion. The metastatic lesion consists of moderately differentiated HCC with pseudoglandular arrangement.

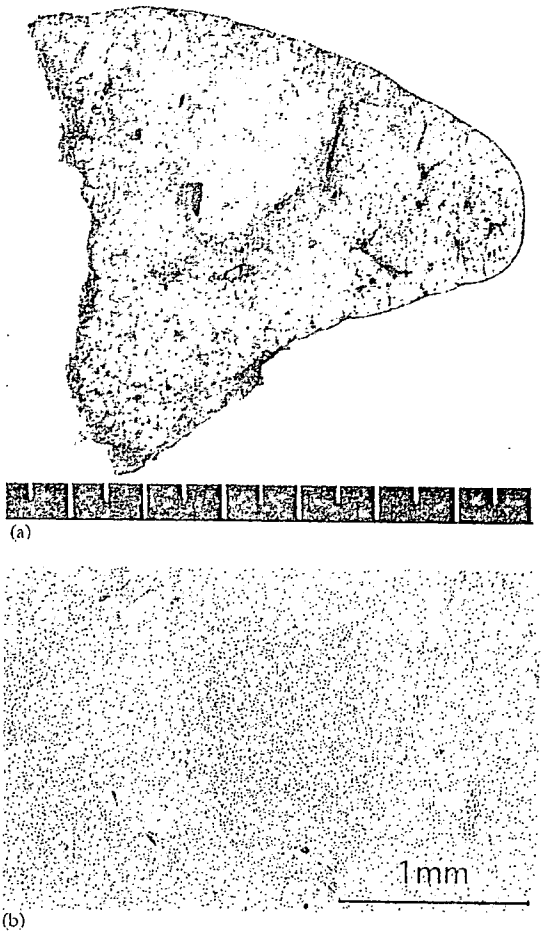

Fig. 4. (a) Gross feature of confluent multinodular type. The size is 1.8 × 1.5 cm. (b) Histologically, micrometastasis is less than 1 mm in diameter and consists of moderately differentiated HCC with pseudoglandular arrangement.

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 multicenteric occurrence of nodules [3,4]. It has been known that intrahepatic metastasis occurs at an early postoperative period, and multicenteric 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) 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)				
	≤ 2	2.1–5	5.1–10.0	> 10.1	Total
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 undepictable 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^2 for 1 hour on Days 1–5) followed by 5-fluorouracil (170 mg/m^2 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.[1,2] Recent technologic advances in imaging modalities and therapeutic procedures have facilitated early diagnosis and curative treatment in patients with HCC.[3–17] 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.[10–12] 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/66 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)[b]	3/17/16/12
Albumin(g/dL; mean ± SD)	3.52 ± 0.44		
Child (A/B/C)[a]	19/22/7	Tumor stage (1/2/3/4)[c]	0/0/4/44
Previous treatment (yes/no)	29/19	Grade of portal invasion (Vp1/Vp2/Vp3)[d]	0/14/34
Plasma concentration of AFP (< 1,000 ng · mL^{-1}/≥ 1,000 ng · mL^{-1})	21/27	Completion of protocol (yes/no)	40/8
Plasma concentration of DCP (<1,000 mA.U.mL^{-1}/≥ 1,000 mAU.mL^{-1}	23/25		

HCV: hepatitis C virus; AFP: α-fetoprotein; DCP: des-gamma-carboxy prothrombin; Vp: portal vein tumor thrombosis.
[a] Child stage.[39]
[b] Tumor extent.[33] Tumor replacement of liver parenchyma: E1, < 20%; E2, 20–40%; E3, 40–60%; E4, > 60%.
[c] TNM classification.[34]
[d] Portal invasion.[33] 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.[11,12] The survival rates of patients with advanced HCC, with complications such as portal vein tumor thrombosis (PVTT) or distant metastasis, remains extremely poor.[18–20] Previous studies have reported that patients with diffuse HCC involving PVTT survive only 1–2 months if effective treatment is not administered.[21] 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,[19] 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).[22–24]

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,[25–27] using combinations of obstructive agents[28] and antiproliferative agents,[29] 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.[30,31] 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 coexistent cirrhosis, these patients were not suitable candidates for either surgical resection[11,12] or nonsurgical treatments, including microwave coagulation therapy (MCT),[13] radiofrequency ablation (RFA),[14] percutaneous ethanol injection (PEI),[15] or TAE.[17] 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 α-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.[32] 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[5,6]; 2) the "thread-and-streaks" sign or arterioportal shunts on hepatic angiography[7,8]; 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.[33] 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.[34]

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.[30] 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.[26,27,30] 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^2 on Days 1–5) followed by 5-FU (170 mg/m^2 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.[30] 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.[35] 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[36,37] 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^2/day and 5-FU 170 mg/m^2/day, weekly or biweekly), weekly HAIC with cisplatin (cisplatin 7 mg/m^2/day, weekly or biweekly), weekly HAIC with epirubicin (epirubicin 7 mg/m^2/day, weekly or biweekly), monthly chemolipiodolization with epirubicin (epirubicin 14–20 mg/m^2/day with lipiodol 3 mL, monthly), and monthly chemolipiodolization with carboplatin (carboplatin 100 mg/m^2/day with lipiodol 3 mL, monthly).

Statistical Analysis

Baseline data for patients were expressed as mean ± SD or as medians and ranges. Univariate analysis to identify predictors of survival was performed by the Kaplan–Meier method[38] 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),[39] 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),[33] tumor stage (T3, T4),[34] macroscopic findings (nodular, infiltrative), PVTT rating (Vp2 / Vp3),[33] therapeutic effect after HAIC (responders, nonresponders), and completion of protocol. The multivariate analysis was investigated by the Cox proportional hazard model.[40] 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.

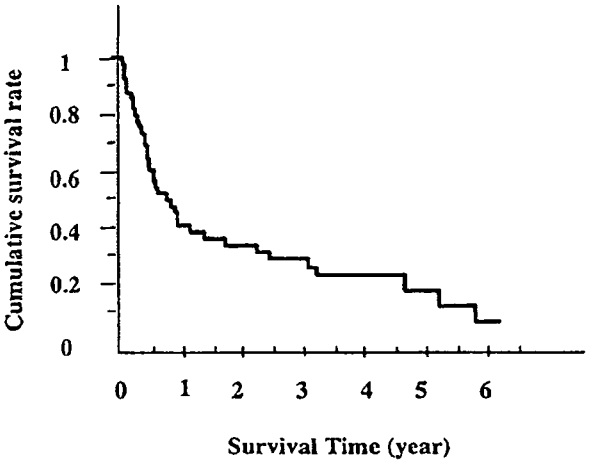

FIGURE 1. Cumulative survival of 48 hepatocellular carcinoma patients with portal vein tumor thrombosis treated with hepatic arterial infusion chemotherapy. The 1, 2, 3, and 5-year cumulative survival rates of 48 patients, including both responders and nonresponders, were 45%, 31%, 25%, and 11%, respectively.

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)[b]	0.093
Child stage (A/B or C)[a]	0.021	Tumor stage (3/4)[c]	0.165
Previous treatment (present/absent)	0.058	Macroscopic finding (nodular/infiltrate)	0.616
Plasma concentrations of AFP (< 1,000 ng · mL^{-1}/≥ 1,000 ng · mL^{-1}	0.961	Grade of portal invasion (Vp2/Vp3)[d]	0.422
Plasma concentrations of DCP (< 1,000 ng · mL^{-1}/≥ 1,000 ng · mL^{-1})	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: α-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.
[a] Child stage.[39]
[b] Tumor extent.[33] Tumor replacement of liver parenchyma: E1, < 20%; E2, 20–40%; E3, 40–60%; E4, > 60%.
[c] TMN classification.[34]
[d] Portal invasion.[33] 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.[9] 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.[11,19,20,41] However, this vascular involvement is generally refractory to treatment. Surgery is considered the most effective treatment in HCC patients with PVTT. Fujii et al.[19] 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).[16] TAE is contraindicated because of the risk of necrosis of the noncancerous portion of the liver and deterioration of the hepatic reserve capacity.[17] Liver transplantation is suitable for small HCCs.[10] Systemic chemotherapy, hormonal therapy, and IFN therapy are all of limited value and only a few patients benefit from tumor regression.[22-24,41] 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.[42] 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.[43] In a previous study,[30] we reported the usefulness of HAIC with low-dose cisplatin and 5-FU in nine patients with advanced HCC with PVTT. Patt et al.[25] reported the usefulness of HAIC with the FLAP regimen, comprising cisplatin, doxorubicin, fluxuridine, 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.[29] 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.[29] 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,[44,45] cisplatin has a synergistic effect as a modulator for 5-FU,[46-48] 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,[46-48] as well as HCC.[27,36]

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.[11,18-20,41] 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.[20] 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.[18] 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,[18,20] 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,[18,20] 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 cytoreduction therapy (MCT)[36,37] 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.[25–29] In the current study, myelotoxicity was less frequent than previously reported for HAIC.[25,26] 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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