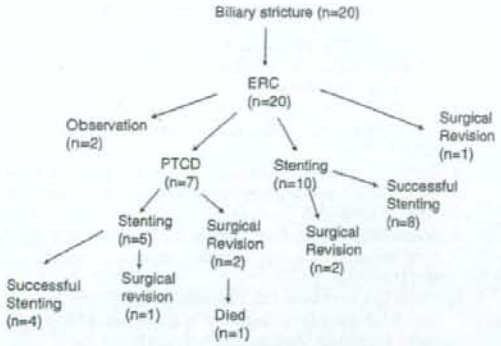

Fig. 5 Summary of the treatment modalities used for biliary stricture: endocsopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), and surgical revision

underwent LDLT with duct-to-duct biliary reconstruction. In previous reports the incidence of biliary stricture in patients who have undergone LDLT with duct-to-duct biliary reconstruction ranges from 20% to 60% [15, 16], whereas the reported incidence of biliary stricture in patients who have undergone cadaveric-donor liver transplantation with duct-to-duct biliary reconstruction is less than 30% [17–19]. Fan et al. reported that while the incidence of biliary leakage was comparable in the two groups, the incidence of biliary stricture was significantly higher in the LDLT group than in cadaveric whole-graft liver transplantation [20].

The present study sought to identify the risk factors for biliary leakage and stricture unique to duct-to-duct biliary reconstruction. We found that patients who developed biliary leakage were vulnerable to biliary stricture. Bile leakage after liver transplantation has previously been suggested as a risk factor for the development of anastomotic strictures [4, 21, 22]. It is likely that the leakage of bile causes local inflammation, thus increasing the risk of fibrosis. Further, the leakage of bile may merely represent ischemia of the extrahepatic bile duct, and in this manner, is associated with anastomotic stricture. The immunosuppressive regimes that included basiliximab were found to be a protective factor against anastomotic leakage. Biliary leakage developed less frequently in patients treated with the basiliximab-based immunosuppressive regimes than in those treated with the non-basiliximab-based ones. The initial 1-week doses of methylpredonisolone were significantly lower in the basiliximab-based immunosuppressive regimes than in those without basiliximab. In general, glucocorticosteroids impair fibroblast proliferation and collagen synthesis, and they delay wound healing [23]. Possibly, the steroid-sparing basiliximab-based immunosuppressive therapy contributed to protection against biliary leakage. Consequently, the development of biliary strictures tended to be less frequent in the basiliximab-based immunosuppressive therapy than in the non-basiliximab-based one. However, there was no significant difference in the incidence of biliary stricture with respect to the immunosuppressive therapies by using stepwise multivariate analysis.

In our series, 40% of the liver grafts had multiple bile duct orifices. The poor outcome might be related to the complicated procedures. The Kyoto Group has reported that they experienced a higher rate of biliary complications with the use of stents for biliary reconstruction; further, no difference was observed with respect to the presence of single or multiple biliary anastomoses [4]. Salvalaggio et al. studied the impact of multiple bile duct anastomoses on the development of biliary complications after liver transplantation in children. They demonstrated that patients with multiple ducts had a higher incidence of leaks as compared to those in the single duct group, but that the incidence of strictures, both early and late, was similar in the two groups [24]. Similarly, in our study, the presence of multiple or single hepatic ducts was not a significant risk factor for biliary stricture. The extensive dissection enabled us to overcome the technical difficulty encountered with multiple and widely separated bile ducts in the liver grafts, as the corresponding orifices in the recipient hilar plate could be freely selected. The use of a bile duct with a wide orifice might result in a good outcome. Hwang et al. reported that duct-to-duct biliary reconstruction involving a small-sized duct (diameter <4 mm) was a risk factor for anastomotic stenosis [25]. However, in our study, the diameter of the graft bile duct was not related to the incidence of biliary strictures.

Ischemic changes around the anastomosis are known to be a major cause of biliary stricture. In donor operations, particularly in cases of right lobe graft, the tissues surrounding the right hepatic duct at the bifurcation must be removed in order to correctly identify the anatomy of the anterior and the posterior segmental branches. The anterior branch of the hepatic duct might be more widely exposed than the posterior branch during the dissection. Dissecting these tissues might cause the biliary stump in the right-lobe graft to become ischemic, which may then facilitate formation of a biliary stricture. The arterial blood supply of the biliary system has been described by several investigators [26–29]. A fine arterial plexus covering the surface of the biliary tract is one of the main sources of the blood supply of the biliary system. Furthermore, the vascular supply for both hepatic ducts depends on an arterial network that is bilaterally fed by the plexus that is formed by the branches of both the right and left hepatic arteries. The blood supply to the bile duct of the graft tends to be tenuous. Shortening of the segment of the donor duct results in an improved circulatory status around the biliary anastomosis, and this technique is therefore suitable for LDLT with a limited length of the graft hepatic duct [9].

Our patients with biliary strictures were treated satisfactory by ERC, PTBD, surgery, or a combination of these. Hisatake et al. reported that 14 (73.4%) of their patients with strictures were treated endoscopically by inserting internal stents ranging from 7 to 12 Fr in size [13]. The complication of biliary stricture occurred only in one patient. Our initial treatment for duct-to-duct biliary reconstruction recipients was endoscopic stenting. Forty percent of our patients with anastomotic strictures failed to respond to endoscopic treatment because it was impossible to pass an endoscopic guidewire through the stricture because of the extreme narrowness of the duct. Those patients who failed to the respond to the endoscopic treatment were treated via a percutaneous transhepatic approach. The total success rate of stenting therapy was 60%. Surgical correction had been effectively performed in patients with recurrent symptoms of cholangitis after stent removal or in those patients for whom stenting was not possible. As demonstrated in several studies, balloon dilatation and stenting via either an endoscopic or percutaneous transhepatic approach were safe and effective. Nonetheless, surgical correction should be reserved for patients who fail to respond to nonsurgical treatment.

Our patients with biliary leakages were treated satisfactory by ENBD, percutaenous drainage, or surgery. We preferred interventional treatment rather than surgery as mentioned by Hwang et al [25]. All patients with biliary leakages were successfully treated by ENBD or percutaneous drainage, except one patient who was treated by surgery.

In summary, our experiences revealed that biliary stricture was associated with biliary leakage and that steroid-sparing basiliximab-based immunosuppressive therapy contributed to the decreased incidence of biliary leakage. The incidence of biliary stricture was not associated with the type or method of biliary reconstruction. The radiological, endoscopic, or surgical treatment for biliary complications was effective and satisfactory. However, the incidence rate of biliary stricture after LDLT is still high. Further improvements in surgical modalities and postoperative management should contribute to the decrease in the incidence of biliary complications.

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ORIGINAL ARTICLE

Microsurgical hepatic artery reconstruction during living-donor liver transplantation by using head-mounted surgical binocular system

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Keywords
hepatic artery reconstruction, living-donor liver transplantation, microsurgery, surgical telescope.

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Summary

We have described our experience with arterial reconstruction during living-donor liver transplantation by using Varioscope® AF3 – a head-mounted surgical binocular system with automatic focusing and continuous zoom magnification from 3.6× to 7.2×. From July 1996 to December 2006, 91 grafts were implanted in 89 living-donor liver transplantation recipients, including two that required retransplantation. For microsurgical reconstruction of the graft hepatic artery, a conventional operating microscope was used in the first 10 transplants and Varioscope, in the subsequent 81. The time required to complete arterial reconstruction while using a conventional operating microscope and Varioscope was 78.6 ± 44.6 min and 35.5 ± 15.5 min, respectively. No arterial complications, including hepatic artery thrombosis, occurred in any of the 89 patients during the observation period. In living-donor liver transplantation, successful hepatic artery reconstruction can be safely carried out using Varioscope.

Introduction

Hepatic artery thrombosis after liver transplantation is a life-threatening event and is associated with high mortality. It has been reported that the incidence of hepatic artery thrombosis varies widely (approximately 2–15%); however, because of recent technical advances, it has generally decreased, even in the case of split liver transplantation or living-donor liver transplantation [1–7]. One of the most important advances in hepatic artery reconstruction is the introduction of microsurgical techniques involving an operating microscope. Generally, a conventional operating microscope comprising a binocular head, counterbalanced pantographic arm, and floor stand is used for microsurgical hepatic artery reconstruction. However, this type of operating microscope has certain drawbacks: it is bulky, requires tilting, and presents difficulties for focusing in the abdominal cavity. As a substitute for this device, we used Varioscope® AF3 (Varioscope; Life Optics®, Vienna, Austria) – a head-mounted surgical binocular system with automatic focusing and continuous zoom magnification from 3.6× to 7.2×. It is operated using a footswitch and can provide a wide field of view at any working distance (300–600 mm) and any magnification (Fig. 1). Here, we describe our experience of hepatic artery reconstruction by using Varioscope in a series of 91 living-donor liver transplantations for 89 adult patients; we have focused on the microsurgeon's perspective.

Patients and methods

Patient population

From July 1996 to December 2006, 91 grafts were implanted in 89 living-donor liver transplantation recipients

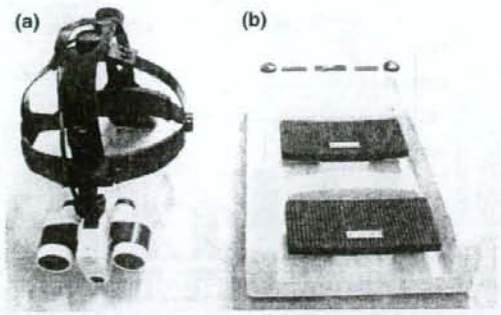

Figure 1 The Varioscope® AF3 is a head-mounted surgical telescope with automatic focusing and continuous zoom magnification from 3.6× to 7.2× that can be operated using a footswitch. This device refocuses if the working distance changes, and the surgeon has almost unlimited mobility without any corresponding loss of sharpness in the obtained three-dimensional images. (a) Head-mounted surgical telescope. (b) Footswitch for focusing and zoom magnification.

comprising 52 men and 37 women whose age ranged from 20 to 69 years (mean age 50). The indications for living-donor liver transplantation included hepatitis virus-related cirrhosis in 52 patients, cholestatic liver disease including primary biliary cirrhosis and autoimmune hepatitis in 14, fulminant hepatitis in 10, retransplantation in two, and others in 13. Of 41 patients with hepatocellular carcinoma, 22 had a history of transcatheter arterial chemoembolization prior to living-donor liver transplantation. The types of liver grafts included those of the right liver lobe ($n = 72$), left liver lobe ($n = 18$), and right lateral sector ($n = 1$).

Surgical technique

Prior to microsurgical hepatic artery reconstruction, the implanted graft was reperfused in the recipients after the portal veins were reconstructed [8]. For microsurgical reconstruction of the graft hepatic artery, a conventional operating microscope was used for the first 10 transplants and Varioscope, for the subsequent 81. The recipient artery was selected according to its patency, extent of intimal damage, and caliber consistency with the graft artery caliber. End-to-end vessel anastomosis was carried out between the recipient and graft hepatic arteries with interrupted 8-0 monofilament nylon sutures. In all 91 implants, we used microvascular double clamp type A-II comprising two bulldog clamps fitted to a sliding bar; it can be used to anastomose vessels of diameters ranging from 0.5 to 5.0 mm without injuring the vessel wall (Fig. 2) [9]. After reconstruction, the intrahepatic arterial signals were verified using color Doppler ultrasonography. Postoperative anticoagulation management was carried out via heparin infusion (the target activated clotting time was 150–200 s for 2 weeks). To determine the adequacy of blood flow and velocity during the first two post-transplant weeks, color flow Doppler ultrasound was performed daily, on alternate days in the third week, and once a week thereafter until discharge.

Results

The details and sizes of the graft/recipient hepatic arteries used for anastomosis are shown in Tables 1 and 2. Double arterial reconstructions were performed in three transplant patients. In one of the right lobe grafts, the

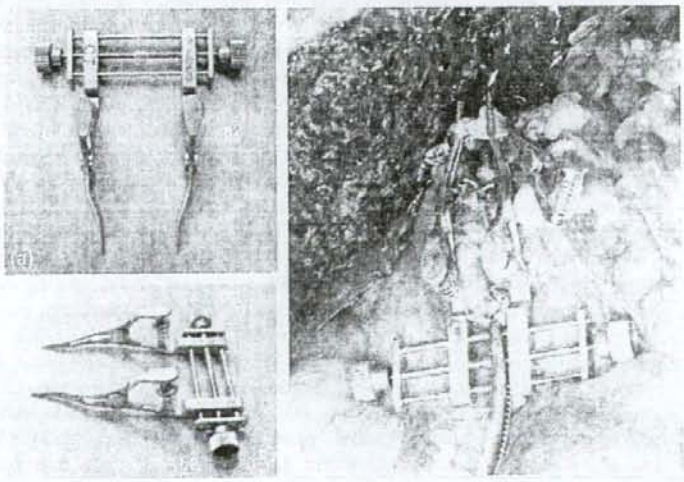

Figure 2 The microvascular double clamp type A-II device comprising 4.2 cm long bulldog clamps and weighing 17 g. By rotating b1 or b2, the distance of the two tips can be freely adjusted from 0 to 25 mm. By rotating a1 and a2, the pressure required to open the tips can be adjusted from approximately 40–250 g. (a) Frontal view. (b) Oblique view. (c) Use of the device during end-to-end anastomosis of the hepatic artery for living-donor liver transplantation with a right lobe.

Table 1. Details of graft/recipient hepatic arteries anastomosed.

Graft	Recipient	No
Right lobe graft		
RHA	RHA	60
RHA	LHA	7
RHA	CHA	2
RHA	Paramedian branch b of RHA	2
Lateral branch of RHA	Lateral branch of RHA	2
Paramedian branch b of RHA	Paramedian branch of RHA	1
Paramedian branch b of RHA	LHA	1
Left lobe graft		
LHA	LHA	13
LHA	RHA	4
LHA	CHA	1
MHA	RGEA	1
Total		94

RHA, right hepatic artery; CHA, common hepatic artery; LHA, left hepatic artery; RGEA, right gastroepiploic artery; MHA, middle hepatic artery.

Table 2. Diameters of hepatic arteries anastomosed (n = 94).

Diameters	Graft	Recipient
2 mm and less	42 (44.7)	26 (27.7)
2–3 mm	39 (41.9)	48 (51.1)
Over 3 mm	13 (13.8)	20 (21.3)
Mean	2.72 mm	2.92
SD	0.95 mm	0.75

Values indicated in parentheses are percentage.

paramedian and lateral branches of the donor's right hepatic artery were anastomosed to those of the recipient's right hepatic artery, respectively. In another right lobe graft, these branches were anastomosed to the recipient's left and right hepatic arteries, respectively. In one of the left lobe grafts, the left hepatic artery and middle hepatic artery were anastomosed to the recipient's left hepatic artery and right gastroepiploic artery, respectively. Vascular interposition grafts were not used in this series.

Figure 3 shows the chorographical comparison of the time required to complete arterial reconstruction. Overall, the time required for hepatic artery reconstruction by using a conventional operating microscope and Varioscope was 78.6 ± 44.6 min (n = 10) and 35.5 ± 15.5 min (n = 81), respectively. All the anastomoses were patent and yielded a 100% patency rate. Twenty-six patients died postoperatively of multiple organ failure, sepsis, recurrence of hepatic tumor, and chronic rejection. However, arterial complications did not develop even in these 26 patients. In the remaining 63 (74.2%) patients, the hepatic artery anastomoses remained patent during a mean follow-up period of 28.7 ± 19.4 months. Thus, no arterial

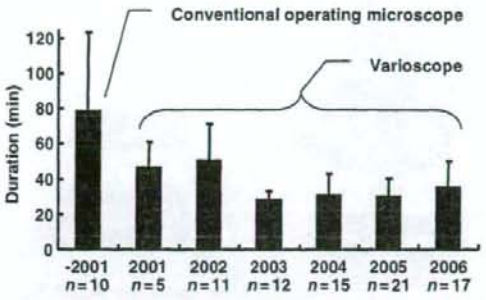

Figure 3 Chorographical comparison of the time required to complete arterial reconstruction. Average values ± SD in each year from 1996 to 2006 are shown.

complications, including hepatic artery thrombosis and hepatic artery stenosis, occurred in any of the 89 patients during the observation period.

Discussion

The introduction of microsurgical techniques in living-donor liver transplantation has resolved the problem associated with the high risk of hepatic artery thrombosis, enabled the reconstruction of arteries of different calibers, and reduced the incidence of arterial complications because of the delicate manipulation required in living-donor liver transplantation. The widely used operating microscope, which needs to be covered with a sterile plastic bag and adjusted depending on the operator's position, provides an operating field of view at a certain prefixed angle (usually a vertical view) but does not allow the operating field to be viewed sideways. This takes time and occasionally causes difficulties in the precise observation of the hepatic artery intima that are sequestered by the outer tunica. An additional problem is the movement of the vessels due to ventilation; the upper abdominal organs together with the recipient artery move in accordance with ventilation. During suturing performed with the aid of an operating microscope, it is occasionally difficult to adjust continuously the operative field of view. Therefore, when required, respiration needs to be withheld during suture placement. Because of this inconvenience, high-power surgical loupes are sometimes preferred to operating microscopes. It has been reported that microvascular hepatic artery reconstruction with 4× or 6× loupe magnification can yield results as good as those obtained with an operating microscope [10,11]. We employed the Varioscope – a device that is more sophisticated than surgical loupes; this instrument combines a miniature high-end microscope with a flexible head-

mounted system. The Varioscope can simply be mounted on the head, thereby saving setup time. It enables the surgeon to easily adapt to the motion of the operative field due to respiration. Temporary termination of artificial respiration to prevent motion of the operative field was not required when the Varioscope was used.

Previously, a liver graft with a fine hepatic artery of diameter <2 mm was regarded as a risk factor for hepatic artery thrombosis. As shown in Table 2, approximately 45% of the graft hepatic arteries and 28% of the recipient hepatic arteries were of diameter ≤2 mm. Our procedure using Varioscope enables the reconstruction of such relatively small arteries. Microvascular double clamp type A-II was used in most transplants in the present series. Both ends of the graft and recipient hepatic arteries were immobilized using the clamps, and the distance between the tips of the two clamps was adjusted such that the ends of the arteries were in contact. After the anterior wall of the hepatic artery had been anastomosed using interrupted sutures, the double clamp was rotated, and the posterior wall was then similarly anastomosed. In two cases wherein the graft hepatic artery was short, we employed the posterior-wall-first anastomotic technique using smaller single-clamp devices. In this technique, microsutures are first placed in the posterior wall of the vessel, and turning over of the microclamp is thereby eliminated; it is known to have significant advantages for such short hepatic artery reconstruction in living-donor liver transplantation [6]. For both anastomotic techniques, Varioscope could provide sufficient magnification at an appropriate working distance. Although vascular interposition grafts for hepatic artery reconstruction were not used in this series, they may be occasionally required when a suitable recipient's artery is not available for reconstruction [12,13]. The utility of the Varioscope in such cases remains to be tested.

In conclusion, we have described our experience with the successful use of Varioscope for arterial reconstruction in living-donor liver transplantation, instead of using a convectional microscope that has positioning and tilting problems.

Authorship

HO and HT performed hepatic artery reconstruction; HO, HT, KI, KI, MS, TI, MO, HT, TI and TA performed recipient transplantation; TI and T.A performed donor hepatectomy; HO analyzed the data and wrote the paper.

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Surveillance Program for Early Detection of Hepatocellular Carcinoma in Japan

Results of Specialized Department of Liver Disease

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Objective: Surveillance of cirrhotic patients enables early detection of hepatocellular carcinoma (HCC) and possibly prolongs survival. The aim of this study was to explore whether early-stage HCC can be detected earlier at a specialized department of liver disease than in other institutions.

Methods: The study subjects were 574 patients with HCC. Patients were subdivided into 3 groups according to the manner of HCC detection: group A, HCC was detected in 91 patients during periodic examination at Kurume University School of Medicine; group B, HCC was detected in 301 patients during periodic examination at other institutions; group C, HCC was detected incidentally or because of symptoms in 182 patients.

Results: The HCC detected in group A was significantly of smaller size (20.4 mm) compared with groups B (27.1 mm, $P < 0.0001$) and C (57.8 mm, $P < 0.0001$). The frequency of receiving treatment (surgery or local ablation therapy) was significantly higher in group A (73%) than in groups B (52%, $P = 0.002$) and C (26%, $P < 0.0001$). The 5-year survival rates were 52% for group A, 40% for group B, and 23% for group C, respectively. The survival of group A was significantly better than that of groups B ($P = 0.0157$) and C ($P < 0.0001$).

Conclusions: Surveillance for HCC at specialized Department of Liver Disease can detect early-stage HCC, resulting in a higher chance of receiving promising treatment.

Key Words: hepatocellular carcinoma, surveillance, ultrasonography, computed tomography, tumor markers

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Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death.[1] HCC has become the leading cause of death among patients with liver cirrhosis.[2] The incidence of HCC has increased in the United States over the past 2 decades.[3] HCC commonly occurs in patients with chronic liver diseases related to hepatitis C virus (HCV) or hepatitis B virus (HBV) and the incidence of HCC in patients with HCV was reported to be 1.5% to 8% per annum.[4–7] Several studies have shown that surveillance with ultrasonography (US) and α-fetoprotein (AFP) for patients with liver cirrhosis can detect early-stage HCC, resulting in higher chance of receiving early treatment.[4–11] However, some studies showed that surveillance for HCC has a limited value in prolonging survival of patients with HCC including cost effectiveness,[12,13] and there is no randomized controlled trial to establish the value of surveillance of HCC in increasing survival of patients with chronic liver disease. Nowadays, such a study is almost impossible for ethical reasons. Discrepancies in the results of surveillance of HCC are related to differences in the incidence of HCC, target population of surveillance, frequency of surveillance, effective treatment of HCC, management of liver cirrhosis, and possibly also US equipment and skill of US examiner. The improvement of US equipment and increased proficiency of US examiner for surveillance of HCC have allowed early diagnosis of HCC, and resulted in prolonging survival of patients with liver cirrhosis over 3 quinquennia.[10] US equipment and skill of US examiner vary among institutions. However, no controlled trial has compared the results of surveillance of HCC among institutions.

Three-phase computed tomography (CT) and magnetic resonance imaging (MRI) might be potentially more sensitive and specific for the diagnosis of HCC.[14] Studies from the United States indicated that the screening for HCC with CT could be a cost effective strategy in transplant-eligible patients with cirrhosis.[15] Des-γ-carboxy prothrombin (DCP), a new tumor marker of HCC is more specific or equally specific to AFP.[16,17] However, surveillance studies using 3-phase CT, MRI, and DCP have not been reported.

The aims of the present study were (1) to determine differences in detecting early-stage HCC among various departments of liver disease, (2) if such differences have an impact on survival of patients with chronic liver disease, and (3) compare the values of regular 3-phase CT or regular DCP and conventional method of surveillance program of HCC in the detection of early-stage HCC.

PATIENTS AND METHODS

Patients

The study subjects were 574 Japanese patients with HCC diagnosed at Kurume University School of Medicine between January 1995 and December 2000. The diagnosis of HCC was established by histopathology and/or imaging studies (US, CT, angiography, CT-angiography, and MRI), and/or based on high plasma levels of tumor markers such as AFP and DCP. Patients were subdivided into 3 groups according to the manner of HCC discovery: group A, 91 patients were found to have HCC during periodic follow-up examination at Kurume University School of Medicine; group B, 301 patients were found to have HCC during periodic follow-up examination in other institutions; and group C, 182 patients were found to have HCC incidentally or because of symptoms.

Surveillance Program

Surveillance of 91 patients of group A included patients with chronic liver disease irrespective of age, liver cirrhosis, or etiology (HCV, HBV, alcoholic and other chronic liver diseases). Regular surveillance program of 91 patients of group A was as follows: US + AFP, 20 patients; US + AFP + DCP, 20 patients; US + AFP + CT, 15 patients; and US + AFP + CT + DCP, 36 patients. The frequency of monitoring using US, AFP, CT, DCP were 3, 6 to 12, and 3 to 6 months, respectively. During the subsequent surveillance period, imaging studies and tumor markers, together with physical examination and routine biochemical test, were repeated every 3 months. If 1 diagnostic modality indicated possible HCC, the other modalities were then performed on an out-patient basis. When nodular liver lesion was depicted by US or CT in such patients, they were admitted to Kurume University School of Medicine, and the diagnosis of HCC was confirmed by histopathology and/or imaging studies conducted based on high plasma levels of tumor markers.

The 301 patients of group B were found to have nodular liver lesions during periodic follow-up examination at other institutions at least 6-month interval by means of direct interview of the patients. The surveillance program of the 301 patients of group B was unknown. Classification of 182 patients as group C was based on finding a nodular liver lesion incidentally or at examination for symptoms and interview of patients but not at periodic follow-up examination.

Treatment Strategy

When a diagnosis of HCC was established at Kurume University School of Medicine, the following treatment options were assessed. Liver transplantation (LT)[18,19] was not considered because of very small number of donor resources and insurance system in Japan from January 1995 to December 2000. (1) Hepatic resection (HR)[20] was assessed especially for patients with localized HCC and preserved hepatic reserve capacity. (2) Nonsurgical treatments, such as percutaneous ethanol injection (PEI),[21] microwave coagulation therapy (MCT),[22] radiofrequency ablation (RFA),[23,24] transarterial chemoembolization (TACE),[25] hepatic arterial infusion chemotherapy (HAIC),[26] and systemic chemotherapy[27] were assessed when HR was contraindicated or the patient refused surgical treatment. The most appropriate therapeutic procedure was selected according to the tumor status and the underlying liver cirrhosis. Local ablation therapies (LAT) such as, PEI, MCT, and RFA were considered in patients with 1-3 tumor nodules, each measuring ≤ 30 mm in diameter that were devoid of vascular invasion and not associated with extrahepatic metastasis. (3) TACE, HAIC, or systemic chemotherapy was considered in patients with maximum tumor size of > 30 mm, number of tumors > 3, presence of vascular invasion and/or presence of extrahepatic metastasis. (4) Best supportive care was assessed when patient had little hepatic reserve capacity or patient refused any treatment of HCC.

Outcome Measures

Outcome measures were analyzed retrospectively in groups A to C as follows: (1) tumor characteristics including size and number of HCC nodules, presence of vascular invasion, and presence of extrahepatic metastasis; (2) UNOS (The United Network for Organ Sharing) criteria for HCC[28]; (3) treatment of HCC; and (4) cumulative survival of patients with HCC.

Differences of Surveillance Program at Kurume University School of Medicine

In 91 patients of group A, 51 patients underwent regular CT (15 US + AFP + CT and 36 US + AFP + CT + DCP) and 56 patients underwent regular DCP (20 US + AFP + DCP and 36 US + AFP + CT + DCP) in addition to US and AFP for surveillance program of HCC, respectively. (1) Tumor characteristics; (2) UNOS criteria for HCC; (3) treatment of HCC; and (4) cumulative survival of patients with HCC was also compared in 51 patients with regular CT [regular CT (+) group] and 40 patients without regular CT [regular CT (−) group], and in 56 patients with regular DCP [regular DCP (+) group] and 36 patients without regular DCP [regular DCP (−) group].

Statistical Analysis

We used the χ^2, Fisher exact, and Mann-Whitney tests, where appropriate, to evaluate differences in clinical features of patients and in tumor characteristics. Survival was analyzed by the Kaplan-Meier method[29] and survival curves were compared by the log-rank test. Survival was

TABLE 1. Clinical Profile of 572 Patients With HCC

	Group A	Group B	Group C
No. patients	91	301	182
Age (y, mean ± SD)	65.4 ± 7.4	65.2 ± 8.8	63.5 ± 9.3
Sex			
Male (%)	54 (59)	214 (71)	158 (87)
Female (%)	37 (41)	87 (29)	24 (13)
		$P = 0.035$	$P < 0.0001$
			$P < 0.0001$*
Etiology			
HCV-positive (%)	82 (90)	258 (86)	135 (74)
HBV-positive (%)	4 (4)	30 (10)	31 (17)
HCV-negative and HBV-negative (%)	5 (6)	13 (4)	16 (9)
			$P = 0.006$
			$P = 0.006$*
Total bilirubin (mg/dL: mean ± SD)	1.27 ± 0.64	1.22 ± 0.78	1.12 ± 0.86
Albumin (g/dL: mean ± SD)	3.39 ± 0.49	3.45 ± 0.47	3.50 ± 0.45
Child pugh class			
A (%)	53 (58)	186 (62)	126 (69)
B or C (%)	38 (42)	115 (38)	56 (31)
AFP (ng/mL)			
0 to 100 (%)	68 (75)	181 (60)	91 (50)
> 100 (%)	23 (25)	120 (40)	91 (50)
		$P = 0.011$	$P = 0.030$
			$P < 0.0001$*
DCP (mAU/mL)			
0 to 40 (%)	70 (77)	188 (62)	55 (30)
> 40 (%)	21 (23)	113 (38)	127 (70)

*Group B versus group C.

confirmed up to September 30, 2004. The statistical software package SPSS for Windows (version 10.0, SPSS Inc, Chicago, IL) was used for data analysis. A P value of < 0.05 was considered significant.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical profile of 574 patients with HCC. The 3 groups were comparable for age, serum levels of total bilirubin and albumin, and Child Pugh class, whereas they significantly differed for sex (group A vs. B: $P = 0.035$; group A vs. C: $P < 0.0001$; group B vs. C: $P < 0.0001$) and etiology of liver disease (group A vs. C: $P = 0.006$; group B vs. C: $P = 0.006$). Serum levels of AFP (> 100 ng/mL) and DCP (> 40 mAU/mL) were significantly higher in group C than in groups A and B, and significantly higher in group B than in group A (AFP; group A vs. group B: $P = 0.011$, group A vs. group C: $P < 0.0001$, group B vs. group C: $P = 0.030$. DCP; group A vs. group B: $P = 0.011$, group A vs. group C: $P < 0.0001$, group B vs. group C: $P < 0.0001$).

HCC Features

The characteristics of HCC in the three groups are listed in Table 2. Significantly smaller size and fewer HCC nodules were detected in group A than in groups B and C, and significantly smaller in group B than in group C (tumor size: A, B, C; 20.4, 27.1, 57.8 mm, respectively, group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$. Number of tumors; group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). A significantly higher proportion of tumors showed vascular invasion in group C than in groups A and B, and significantly higher in group B than in group A (group A vs. group B: $P = 0.020$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). Extrahepatic metastasis was noted in 9 patients. A significantly higher proportion of extrahepatic metastasis was noted in group C than in groups A and B (group A vs. group C: $P = 0.042$; group B vs. group C: $P = 0.001$).

UNOS Criteria and Treatment

Of the 574, 334 patients (58%) presented with HCC within UNOS T2 criteria (Table 2). A significantly higher proportion of patients presented with HCC within UNOS T2 criteria in group A (91%) compared with group B (68%) and group C (26%), and in group B compared with group C (group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). With regard to treatment, 10 (11%), 20 (7%), and 16 (9%) of groups A, B, and C were treated with HR, respectively. Furthermore, 56 (62%), 137 (45%), and 31 (17%) of group A, B, and C were treated with LAT including PEI, MCT, and RFA, respectively. In addition, 21 (23%), 132 (44%), and 122 (67%) of groups A, B, and C were treated with interventional radiology including TACE and HAIC, respectively. For other therapies, 2 of group C were treated with systemic chemotherapy, and 4 (4%), 12 (4%), and 13 (7%) of groups A, B, and C were

TABLE 2. Tumor Characteristics and Treatment of 572 Patients With HCC

	Group A	Group B	Group C
No. patients	91	301	182
Tumor size (mm; mean ± SD)	20.4 ± 9.5	27.1 ± 17.8 $P < 0.0001$	57.8 ± 34.0 $P < 0.0001$ $P < 0.0001$*
Tumor number			
1 (%)	57 (63)	133 (44)	43 (23)
2 (%)	30 (33)	100 (33)	54 (30)
> 3 (%)	4 (4)	68 (23) $P < 0.0001$	85 (47) $P < 0.0001$ $P < 0.0001$*
Vascular invasion			
Yes (%)	0 (0)	17 (6)	44 (24)
No (%)	91 (100)	284 (94) $P = 0.020$	138 (76) $P < 0.0001$ $P < 0.0001$*
Extrahepatic metastasis			
Yes (%)	0 (0)	1 (1)	8 (4)
No (%)	91 (100)	300 (99)	174 (96) $P = 0.042$ $P = 0.001$*
UNOS criteria			
T1-2 (%)	83 (91)	204 (68)	47 (26)
T3-4 (%)	8 (9)	97 (32) $P < 0.0001$	135 (74) $P < 0.0001$ $P < 0.0001$*
Treatment			
Surgery or local ablation (%)	66 (73)	157 (52)	47 (26)
TACE, HAIC, or systemic chemotherapy (%)	21 (23)	132 (44)	122 (67)
Supportive care (%)	4 (4)	12 (4)	13 (7)

*Group B versus group C.

followed-up conservatively without any specific treatment for HCC because of hepatic failure or patient refusal of any treatment for HCC. The frequency of receiving promising treatment (HR or LAT) was significantly higher in group A (73%) than groups B (52%) and C (26%), and significantly higher in group B than group C (group A vs. group B: $P = 0.002$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$).

Survival Rates

The cumulative survival rates according to the modality of HCC discovery are shown in Figure 1. The 3, 5, and 7-year cumulative survival rates were 67%, 52%, and 36% for group A; 60%, 40%, and 22% for group B; and 38%, 23%, and 9% for group C, respectively. The cumulative survival rates of group A were significantly better than those of groups B ($P = 0.0157$) and C ($P < 0.0001$), and those of group B were significantly better than those of group C ($P < 0.0001$).

Differences in Surveillance Program at Kurume University School of Medicine

The detected HCC in the regular CT (+) group tended to be smaller than the regular CT (−) group (mean tumor size: 18.7 mm vs. 22.4 mm; $P = 0.061$). However, the number of tumors, serum levels of AFP and DCP, frequency of meeting UNOS T1-2 criteria and frequency of receiving promising treatment were not significantly different between the 2 types of HCC discovery (Table 3). Furthermore, cumulative survival was comparable between regular CT (+) and CT (−)

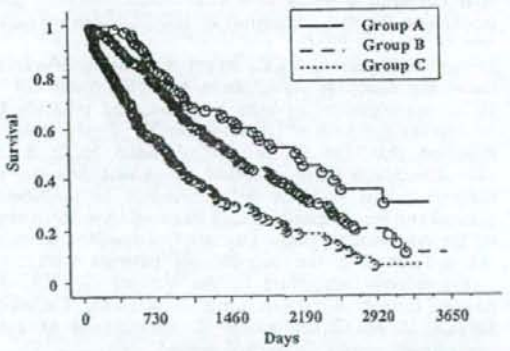

FIGURE 1. Kaplan-Meier survival curves of 574 patients with HCC according to the HCC diagnosis. The cumulative survival of group A was significantly better than that of groups B ($P=0.0157$) and C ($P<0.0001$), and group B was significantly better than that of group C ($P<0.0001$).

TABLE 3. Tumor Characteristics and Treatment of 91 Patients With HCC With Regular CT and DCP

	Regular CT (+)	Regular CT (−)	P	Regular DCP (+)	Regular DCP (−)	P
No. patients	51	40		56	35	
Tumor size (mm; mean ± SD)	18.7 ± 8.5	22.4 ± 10.1	0.0610	19.6 ± 8.7	21.5 ± 10.3	NS
Tumor size (mm)			0.0439			NS
0 to 20 (%)	35 (69)	18 (45)		35 (63)	18 (32)	
21 to 30 (%)	9 (17)	16 (40)		14 (25)	11 (31)	
> 31 (%)	7 (14)	6 (15)		7 (12)	6 (17)	
Tumor number			NS			NS
1 (%)	34 (67)	23 (58)		35 (63)	22 (63)	
2 (%)	15 (29)	15 (38)		17 (30)	13 (37)	
> 3 (%)	2 (4)	2 (5)		4 (7)	0 (0)	
AFP (ng/mL)			NS			NS
0 to 100 (%)	39 (76)	29 (73)		40 (71)	28 (80)	
> 100 (%)	12 (24)	11 (27)		16 (29)	7 (20)	
DCP (mAU/mL)			NS			NS
0 to 40 (%)	9 (18)	12 (30)		13 (23)	8 (23)	
> 40 (%)	42 (82)	28 (70)		43 (77)	27 (77)	
UNOS criteria			NS			NS
T1-2 (%)	47 (92)	38 (95)		51 (91)	34 (97)	
T3-4 (%)	4 (8)	2 (5)		5 (9)	1 (3)	
Treatment			NS			NS
Surgery or local ablation (%)	40 (78)	26 (65)		40 (72)	26 (74)	
TACE, HAIC, or supportive care (%)	11 (22)	14 (35)		16 (28)	9 (26)	

groups (Fig. 2A). Tumor size, number of tumors, serum levels of AFP and DCP, frequency of meeting UNOS T1-2 criteria, frequency of receiving promising treatment, and cumulative survival were comparable between regular DCP (+) and DCP (−) groups (Table 3, Fig. 2B).

DISCUSSION

HCC commonly occurs in patients with chronic liver diseases related to HCV or HBV.[4–7] Six months interval of surveillance including US and AFP for Child A-B cirrhotic patients is a conventional method used worldwide for early detection of HCC.[8–12] However, the results of surveillance are conflicting because of the annual incidence of HCC, target population of surveillance, frequency of surveillance, available treatment for HCC, management of liver cirrhosis, and possibly US equipment and skill of US examiner.[4–13] Trevisani et al[11] reported that the center that detected HCC during surveillance was an independent prognostic indicator for elderly Italian patients with cirrhosis in multicenter clinical studies. A small sample size could also contribute to the conflicting results. Our study attempted to define the difference in the outcome of patients with HCC retrospectively according to the manner of HCC discovery (group A, surveillance at Kurume University School of Medicine; group B, surveillance at other institutions; group C, control group).

The 3 groups were comparable for age, serum total bilirubin level, serum albumin level, and Child Pugh class (Table 1). Patients with symptomatic HCC had poorer hepatic reserve capacity than patients with HCC detected by surveillance, on the basis of the larger size of the tumors that exert a space-occupying effect despite the high proportion of patients without cirrhosis.[9,11] Variation of hepatic reserve capacity depends on the balance between existence of cirrhosis and tumors exerting a space-occupying effect.

A significantly higher proportion of patients unrelated to HCV (HBV-positive or HBV-negative and HCV-negative) were observed in group C compared with groups A and B (Table 1). Surveillance for HCC in patients with HCV-related chronic liver disease is commonly conducted across Japan.[5] HCC tends to be detected during surveillance in patients with HCV-related liver disease.

LT, HR, and LAT are promising therapeutic options for HCC[18–23] and suitable candidates for LT[18,19] and LAT[21–23] include HCC within UNOS T2 criteria[19,28] (single tumor; ≤5 cm in diameter and multiple tumors; no more than three tumor nodules, each ≤3 cm in diameter without vascular invasion or extrahepatic metastasis). Sangiovanni et al[10] concluded that a shift of more patients from HR toward LAT was favored by the application of strict criteria for patient selection to HR and that LAT contributed to prolongation of survival of patients with HCC over 3 quinquennia. In the present study, significantly smaller and fewer HCC were detected in group A than in groups B and C, and significantly smaller in group B than in group C. Moreover, a significantly higher proportion of patients of group A (91%) presented with HCC within UNOS T2 criteria than groups B (68%) and C (26%) and significantly higher proportion of group B than group C (group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). Yuen et al[9] reported that

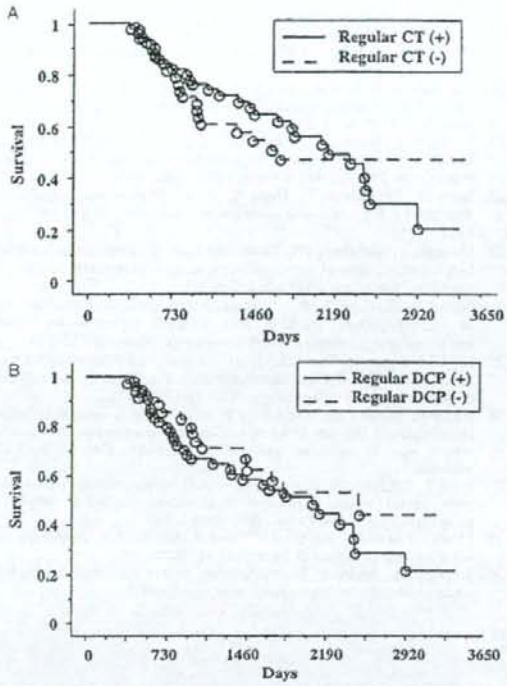

FIGURE 2. A, Kaplan-Meier survival curves of 91 patients with HCC detected at Kurume University School of Medicine. Survival was comparable between Regular CT (+) and (−) groups. B, Kaplan-Meier survival curves of 91 patients with HCC detected at Kurume University School of Medicine. Survival was comparable 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[13] 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

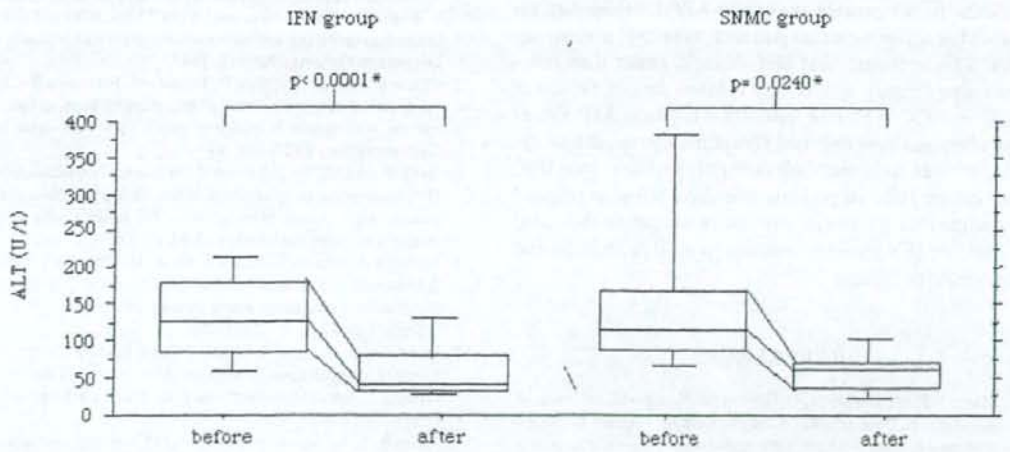

Fig 1. Changes in alanine aminotransferase (ALT) after IFN and SNMC administration. Paired *t*-test was used. *$P < 0.05$ was regarded as significant.

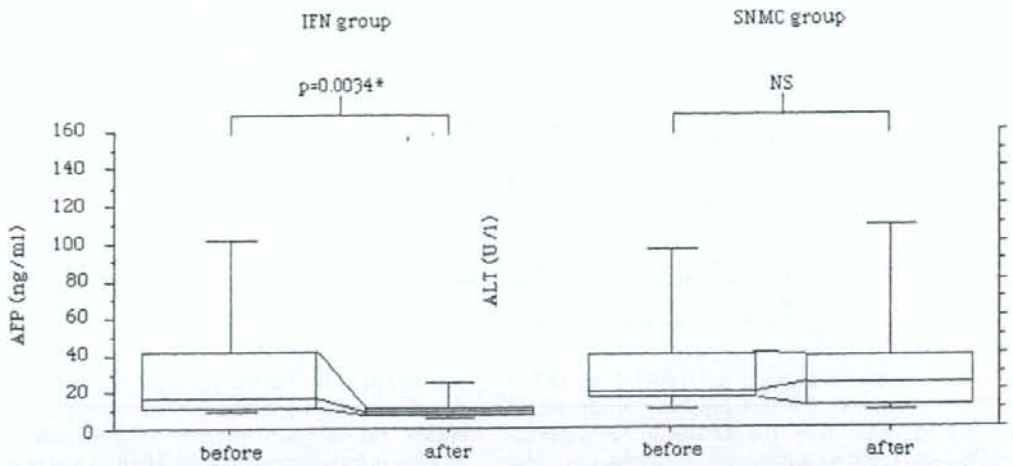

Fig 2. α-Fetoprotein (AFP) changes with IFN and SNMC administration Paired *t*-test was used. $*P < 0.05$ was regarded as significant. NS, not significant.

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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