

Table 2 Baseline analysis

Strategy	Total cost (US\$)	Incremental cost (US\$)	Expected life years (year)	QALY	Incremental QALY	ICER (US\$/QALY)
No surveillance	29 142	–	10.45	6.18	–	–
US surveillance	58 064	28 922	14.13	7.85	1.67	17 296†
CEUS surveillance	65 726	36 584	14.86	8.17	1.99	18 384† (24 250‡)

†Compared with the no surveillance group.

‡Compared with the US surveillance group.

CEUS, contrast-enhanced ultrasonography; ICER, incremental cost effective rate; QALY, quality-adjusted life-year.

Both the US group and the CEUS group could extend their additional life years as compared with the no US group, regardless of age. The CEUS group could also extend their additional life years as compared with the US group. The biggest difference in expected life years between the US and CEUS groups was 0.93 at an age of 40 years. The superiority of surveillance with CEUS over US was also seen in the 70 year-old patients group. If the sensitivity of US was lower than 50%, then CEUS could extend their additional life years by 2 years and more as compared with the US group.

In the no surveillance group, 55 year-old patients (base value) with compensated HCV-related cirrhosis are expected to live 10.45 life years. When surveillance for HCC with conventional US or CEUS was used in these patients, their expected life years increased by 3.68 years and 4.41 years, respectively. Since the discount rate and health-related utility should be considered in cost-effective analysis, we showed the results of the baseline cost-effectiveness analysis in Table 2. Even though the additional expected life years became small when the program was analyzed while considering the discount rate and health-related utility, in comparison to having no surveillance, the US and CEUS groups still showed an increase in QALYs, 1.67 and 1.99 QALYs, respectively.

Next, the incremental cost-effectiveness ratio (ICER) was estimated, which is a measure of the extra cost incurred to save one year of life. The ICER of the US and CEUS groups, as compared to the no surveillance group, were \$US 17 296/QALY and \$US 18 384/QALY, respectively. These values were well below \$US 50 000/QALY, which is commonly considered to be the cost-effective threshold. Even when the CEUS group was compared with the US group, the ICER of the CEUS group was \$US 24 250/QALY, and was also cost-effective.

Sensitivity analysis

The above results depended largely on the baseline values used in this model, but the estimates of these parameters vary in the published literature. We therefore

examined the effects of changing the value of each parameter through sensitivity analysis (Fig. 4). After performing the sensitivity analysis on all parameters in this model, three important parameters emerged in CEUS surveillance compared with US surveillance: the annual HCC incidence rates, and the CEUS sensitivity, and the US sensitivity.

Figure 5a shows the differences of ICERs in varying the US sensitivity. The ICERs of the US and CEUS groups were also less than US\$ 20 000, and cost-effective when compared with the no surveillance group. On the other hand, when the CEUS group was compared with the US group, the ICER of the CEUS group increased as the US sensitivity increased up to almost the CEUS sensitivity. However, if the US sensitivity was 80%, then the ICER was \$US 34 143, and still less than the threshold of \$US 50 000/QALY. If the US sensitivity was lower than 60%, then the ICER of the CEUS group was almost \$US 20 000, and thus was more cost-effective. On the other hand, CEUS sensitivity was especially affected when the CEUS group was compared with the US group, and the ICER rose sharply when the CEUS sensitivity was lower than 80% (Fig. 5b).

DISCUSSION

IN THE PRESENT study, we analyzed the cost-effectiveness of CEUS for HCC surveillance using Sonazoid in liver cirrhosis patients, and demonstrated that CEUS surveillance could cost effectively extend the expected life years, even compared with the US surveillance.

Currently, there are only two US contrast agents, Sonazoid and Levovist, which can be used for Kupffer imaging in the post-vascular phase. However, Levovist bubbles are very fragile, and are collapsed by US emissions easily. Therefore, Kupffer imaging in the post-vascular phase using Levovist needs to be performed by a single sweep scan of the liver, which is insufficient for surveillance.

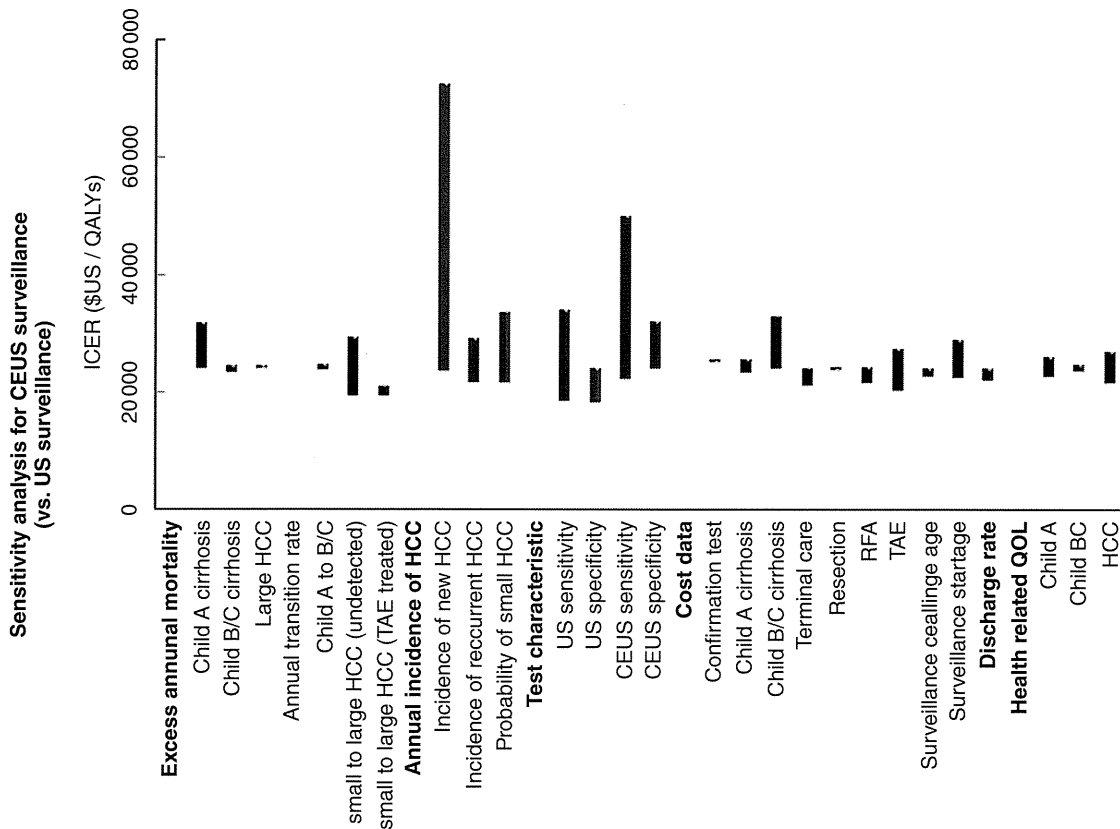


Figure 4 One way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) for the contrast-enhanced ultrasonography (CEUS) surveillance group. When the ICER of the CEUS group was compared with the ultrasonography (US) group, the annual incidence rate of hepatocellular carcinoma (HCC) and CEUS sensitivity were critical parameters in this model. QALY, quality adjusted life year; RFA, radio-frequency ablation; TAE, transcatheter arterial embolization.

Sonazoid is composed of a hard shell containing bubbles, and produces stable, non-linear oscillations in the low-power acoustic field. Because of this feature, Sonazoid provides detailed perfusion features during vascular imaging in the vascular phase, and Kupffer imaging in the post-vascular phase at least 10 min after injection, without collapsing the bubbles. Specifically, Sonazoid CEUS is stable for at least 3 h after injection and allows for multiple and real time scans, because the Sonazoid microbubbles are phagocytosed by Kupffer cells.⁴⁴ In contrast, malignant hepatic tumors including HCC contain few or no Kupffer cells, which lead to clear negative contrast as a perfusion defect in Kupffer imaging.^{45,46} Thus, surveillance for HCC using Sonazoid is especially useful for LC patients whose liver parenchyma have become roughened by fibrosis. For these reasons, the trend towards the use of US contrast agents in Japan has changed dramatically from Levovist to Sonazoid after it became commercially-available in 2007.

A recent study on the cost-effectiveness of surveillance for HCC reported the sensitivity of US at only 28.6% for detecting middle-sized HCC (between 2 and 5 cm in diameter).⁴⁷ The sensitivity of US depends on the skill of the operator, especially in LC patients, in which the intrahepatic echo patterns become roughened with advanced fibrosis. In sensitivity analysis, the US sensitivity was an important factor. When the US sensitivity is expected to be low due to patient physiologic factors such as obesity, CEUS surveillance is recommended. US technicians whose skill may not achieve the average level are also advised to perform additional CEUS using Sonazoid.

Contrast-enhanced ultrasonography sensitivity was a critical factor for cost-effectiveness. When the CEUS group was compared with the US group, and CEUS surveillance was not cost-effective if CEUS sensitivity was lower than 75% (Fig. 5b). As noted earlier, CEUS using Sonazoid is effective for Kupffer imaging, and it

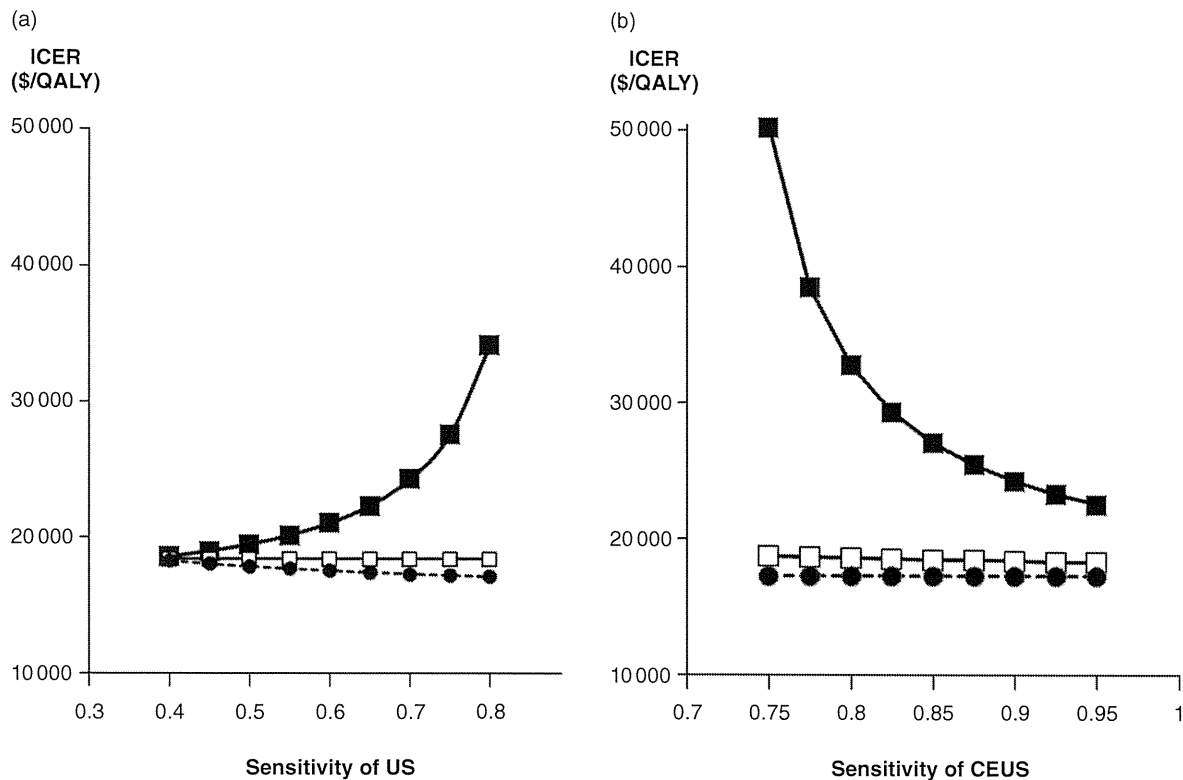


Figure 5 Effects of the sensitivity of ultrasonography (US) (A) and contrast-enhanced ultrasonography (CEUS) (B). When the incremental cost-effectiveness ratio (ICER) was compared with the no surveillance group, both US and CEUS surveillance groups were less than \$US 20 000/quality adjusted life year (QALY) in all ranges. The ICER of the CEUS surveillance group achieved \$US 50 000/QALY when the sensitivity of CEUS was lower than 0.75. —■—, CEUS (vs US surveillance); -□-, CEUS (vs no surveillance); -●-, US (vs no surveillance).

has been reported to have high sensitivity.⁷ This helps technicians to detect the HCC more easily. Thus, a greater than 75% sensitivity represents a reasonable value for Sonazoid CEUS.

The incidence of HCC is the most critical parameter in decision-making for the surveillance of patients with cirrhosis. In our baseline analysis, we selected 7% as a baseline value because most studies in Japan reported 5–8% as the incidence of HCC.^{6,26,48,49} This rate is slightly higher than the one in the United States and Europe, where incidence rates are reported from 1.5 to 4%.^{8,27} Figure 6 shows how the incidence rate affects the ICER. When the ICER of the CEUS group was compared with the US group, it increased as the rate decreased. However, when the rate was 2%, the ICER of the CEUS group was still less than \$50 000/QALY.

Although our results enable us to evaluate the effectiveness of CEUS surveillance, the study has some limitations. First, Sonazoid is available only in Japan. Thus, there are only Japanese published reports for analysis.

On the other hand, our baseline data of US sensitivity 70% could be affected by the regional difference, and might be estimated lower than in the Japanese one. However, even if the US sensitivity was as high as 80%, ICER was still lower than \$US 40 000 when CEUS surveillance was compared with US surveillance (Fig. 5a).

Similarly, our results were analyzed based on some hypothesis. Thus, the validation is desirable but is difficult because there are also ethical issues. For the solution of the problems, we performed the sensitivity analysis with the widest possible range using many representative reports. As the results of our analysis, we could indicate that the parameters except the HCC incidence rate, US sensitivity and CEUS sensitivity have little impact on cost-effectiveness.

In summary, our analysis suggests that surveillance for HCC in patients with compensated HCV-related cirrhosis by CEUS using Sonazoid was a cost-effective strategy. Since this cost-effectiveness decreased when the HCC incidence rate was low, this strategy should be selected

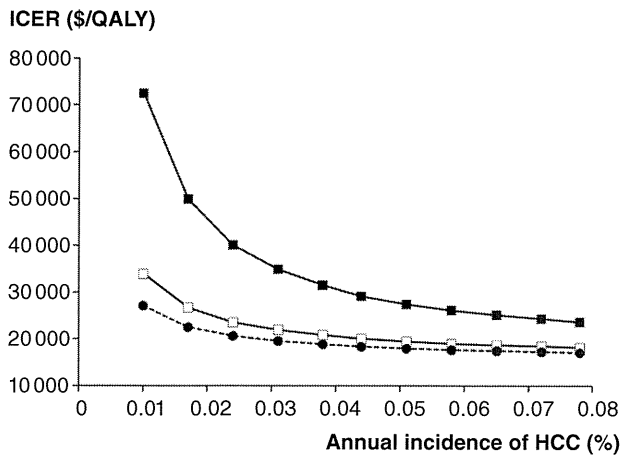


Figure 6 Effects of the annual incidence of hepatocellular carcinoma (HCC). The incremental cost-effectiveness ratio (ICER) values of the ultrasonography (US) and contrast-enhanced ultrasonography (CEUS) surveillance groups were less than \$US 35 000/ quality adjusted life year (QALY) in all ranges as compared with the no surveillance group. However, the ICER of the CEUS surveillance group achieved \$US 50 000/QALY as compared with the US surveillance group when the incidence was lower than 0.016. —■—, CEUS (vs no surveillance); —□—, CEUS (vs US surveillance); —●—, US (vs no surveillance).

considering of the influence of patient factors such as age, gender and fibrosis grade.

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Review Article

Anticarcinogenic impact of interferon therapy on the progression of hepatocellular carcinoma in patients with chronic viral infection

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Hepatocellular carcinoma (HCC) is mainly caused by a persistent infection due to the hepatitis B or hepatitis C virus. The number of HCC cases is increasing in Asian and African countries, as well as in European and American countries. Interferon (IFN) therapy, used for type B chronic liver diseases, inhibits hepatic carcinogenesis in patients with compensated cirrhosis. However, there is insufficient evidence that IFN therapy inhibits hepatic carcinogenesis in patients with chronic hepatitis B. There are few cases of HCC due to chronic hepatitis B, and long-term follow-up periods verifying the inhibitory effect of IFN on hepatic carcinogenesis have not been obtained. To improve the prognosis of type B chronic liver diseases, it is important that hepatitis treatment follows guidelines in which a patient's age and the extent of hepatic fibrosis are taken into account. As for chronic hepatitis C,

since a sustained virological response (SVR) in IFN therapy inhibits hepatic carcinogenesis and improves prognosis, treatment that aims for an SVR while taking into consideration host-sided and virus-sided factors is recommended for patients with type C chronic liver diseases. In areas with low incidence of HCC (e.g. USA), a large number of cases and a long-term follow-up period are needed before it can be accepted that IFN therapy inhibits hepatic carcinogenesis. After locally curative treatment of HCC, IFN therapy suppresses recurrence and improves survival rates.

Key words: chronic hepatitis, hepatitis B virus, hepatitis C virus, hepatocellular carcinoma, interferon, prevention

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) ranks fifth in the number of patients worldwide who are diagnosed with cancer; its death toll ranks third.¹ Approximately 600 000 to 700 000 patients worldwide die of HCC each year; the number of HCC cases is increasing in Asian and African countries, as well as in European and American countries.^{2,3} HCC is mainly derived from a persistent infection due to the hepatitis B virus (HBV) or hepatitis C virus (HCV); thus, treating viral hepatitis inhibits hepatic carcinogenesis. In clinical and epidemiological studies of patients with chronic hepatitis B, active replication of HBV is linked to progression to cirrhosis and HCC.⁴ Cessation of HBV repli-

cation reduces complications and improves prognosis. If, as a result of interferon (IFN) therapy, seroclearance of hepatitis B e antigen (HBeAg) can be achieved and the patient is negative for HBV DNA, then this might reduce the chances of HCC developing.⁵ IFN therapy for chronic hepatitis C helps to reduce the risk of HCC developing in patients in whom a sustained virological response (SVR) has been achieved and that therapy also helps to reduce the risk of HCC developing in patients in whom viral clearance has proven difficult.^{6,7} This paper reviews clinical research studies that have focused on the inhibitory effect of IFN therapy on hepatic carcinogenesis.

THE ANTITUMOR ACTION OF IFN

INTERFERON IS A cytokine with varied forms of bioactivity including antiviral action as well as action to inhibit cell growth, angiogenetic activity, action to regulate the immune response, and action to inhibit

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telomerase activity. IFNs are generally grouped into type I IFNs, which include IFN- α , - β , and - ω , and type II IFN, which consists solely of IFN- γ .⁸⁻¹⁰ IFN- α and - β are widely used clinically to treat viral diseases such as chronic hepatitis B and C and neoplastic diseases such as renal cell carcinoma and glioblastoma. Evidence of IFN's direct antitumor action has been reported, i.e. IFN- α and - β have been found to inhibit growth of a hepatoma cell line in a concentration-dependent manner.¹¹ In addition, IFN has been found to exhibit antitumor action by inducing apoptosis of tumor cells via p53 and by stopping the progression of the cell cycle.¹² Similarly, an *in vivo* study noted that an IFN dose similar to that used clinically suppressed the growth of hepatic carcinoma cells.¹³ Moreover, alpha fetoprotein (AFP) levels decreased after administration of IFN to patients with chronic hepatitis C and consistently elevated AFP levels; the mechanism for this phenomenon may be antitumor action.¹⁴ In addition, IFN is also assumed to have indirect antitumor action by immunopotentialization via natural killer cells.¹⁵ Nevertheless, the current reality is that the mechanism of IFN's antitumor action has yet to be fully elucidated.

HBV-RELATED HCC

THERE ARE AN estimated 300 million or more HBV carriers in the world; many of them are concentrated in Asian and African areas.¹ About 15% of HCC cases in Japan are HBV-related.¹⁶ The annual incidence of HCC in patients with type B chronic hepatitis is 0.1% to 1.0% and in patients with type B cirrhosis, 2.2% to 4.3%; the incidence of HCC is higher in Asia than elsewhere in the world.¹⁷ A study of the natural history of HCC has reported that factors for a high risk of developing the condition are cirrhosis, being an elderly male, having genotype C or F1, having a double substitution (A1762T and G1764A) in the core promoter region, and high HBV DNA levels.⁴ Since it is difficult to completely eliminate HBV, the primary goals of treatment are to eliminate or reduce HBV DNA in the blood and to normalize the levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT).¹⁸

We searched the medical published reports and found that the inhibitory effect of IFN therapy on hepatic carcinogenesis in patients with type B chronic hepatitis and cirrhosis was first reported in 1996; we also found four randomized controlled trials (RCT) – three from Europe and one from Asia (Table 1).¹⁹⁻²² The paper from Asia indicated that IFN therapy inhibits hepatic carcinogenesis, but the papers from Europe did not have this

Table 1 Baseline characteristics of randomized control trials assessing effect of interferon (IFN) on hepatocellular carcinoma (HCC) development in hepatitis B virus (HBV)-infected patients

Study [reference]	Year	Sample size (n)	Male (%)	Mean age (years)	HBeAg positive (%)	Pre-existing cirrhosis (%)	IFN regimen	Mean follow-up (years)	VR (%)	Incidence of HCC (%)
Lampertico P <i>et al.</i> ²¹	1997	T21	T80	T44	T0	T19	α -2b: 6 MU 3 times a week for 24 months	3.8	T28	T5
Krogsgaard K <i>et al.</i> ¹⁹	1998	C21	C90	C47	C0	C14	α -2a: 2.5–18 MU 3 times a week for 12–24 weeks	4.7	C0	C0
		T210	81	36	T100	19			T24	T1
Mazzella G <i>et al.</i> ²⁰	1999	C98	T76	T36	C100	T0	α : 5 MU/m ² 3 times a week for 24 weeks	7.1	C20	C1
		T33			T100				T36	T3
Lin SM <i>et al.</i> ²²	1999	C31	C80	C40	C100	C0	α : 4–6 MU/m ² 3 times a week for 12 weeks	6.6	C0	C6
		T67	T100	T32	T100	T10			T42	T1.5
		C34	C100	C32	C100	C14		6.5	C24	C11.8

C, control group (no treatment); HBeAg, hepatitis B e antigen; MU, million units; T, IFN treated group; VR, virological response.

finding. In a study involving 308 patients with HBe antigen (HBeAg)-positive chronic hepatitis and cirrhosis, Krogsgaard *et al.*¹⁹ administered a 2.5 to 10 million unit (MU)/m² dose of IFN- α 2a three times weekly for 12 to 24 weeks to 210 patients (i.e. the treatment group). During a mean follow-up period of 4.7 years, HCC occurred in two patients in the treatment group and in one patient in the control group. In a study involving 64 patients with HBeAg-positive chronic hepatitis, Mazzella *et al.*²⁰ administered a 5 MU/m² dose of IFN- α three times weekly for 24 weeks to 33 patients (i.e. the treatment group). During a mean follow-up period of 7.1 years, HCC occurred in three patients whose chronic hepatitis had progressed to cirrhosis (one patient in the treatment group and two patients in the control group). In a study involving 42 patients with HBeAg-negative chronic hepatitis, Lampertico *et al.*²¹ administered a 6 MU dose of IFN- α 2b three times weekly for 96 weeks to 21 patients (i.e. the treatment group). During the mean follow-up period of 3.8 years, HCC occurred in one patient in the treatment group. In a study involving 101 patients with HBeAg-positive chronic hepatitis, Lin *et al.*²² administered a 4–6 MU dose of IFN- α three times weekly for 12 weeks to 67 patients (i.e. the treatment group). During a mean follow-up period of 7 years, HCC occurred in one patient in the treatment group and in four patients in the control group ($P=0.043$). They believed that IFN therapy had an inhibitory effect on hepatic carcinogenesis.

On the other hand, reports from a study involving patients with HBeAg-positive cirrhosis²³ and several studies involving patients with HBeAg-positive chronic hepatitis and HBeAg-negative chronic hepatitis^{19,20,24,25} deny that IFN therapy inhibits hepatic carcinogenesis. Based on their meta-analysis of seven non-randomized controlled trial (NRCT) studies involving patients with cirrhosis,^{20,23,26–30} Cammà *et al.*³¹ believe that IFN therapy inhibits hepatic carcinogenesis (risk difference [RD], –6.4%; confidence interval [CI], –2.8 to –10; $P < 0.001$). However, their analyses of subgroups with small variations showed no significant differences and they found that IFN therapy did not inhibit hepatic carcinogenesis. Sung *et al.*³² in a meta-analysis of 12 papers (which included an RCT study)^{5,19,20,23–26,28–30,33,34} concluded that, compared with patients in the control group, patients in the IFN therapy group had a 34% reduced risk of developing HCC. This effect was especially beneficial for patients with cirrhosis. However, in a recent meta-analysis based on two RCT studies,^{20,22} Zhang *et al.*³⁵ concluded that IFN therapy does not necessarily reduce the development of HCC.

At the current point in time, previous reports offer conflicting results with regard to whether or not IFN therapy suppresses hepatocarcinogenesis when used to treat hepatitis B virus-related chronic liver disease. Reasons for this conflict are presumably related to discrepancies in IFN's suppression of carcinogenesis brought about by differences in the clinical characteristics of the patients studied. In other words, numerous factors, such as: (i) patient age; (ii) sex; (iii) liver function tests; (iv) differences in the mode of infection (vertical or horizontal infection); (v) stage of liver fibrosis and grade of necroinflammatory activity; (vi) positivity or negativity for HBeAg; (vii) HBV genotype; (viii) levels of HBV DNA; (ix) treatment protocol; (x) therapeutic efficacy; and (xi) follow-up period, may affect study results. In a NRCT involving 313 patients with cirrhosis due to hepatitis B, Ikeda *et al.*²⁶ administered 6 MU IFN- α three times a week for 40 weeks to 94 patients in a treatment group (including 61 patients who were positive for HBeAg). A follow-up lasting an average of 7 years revealed 10 patients in the treatment group and 51 of 219 patients in an untreated group developed HCC; this finding indicated that use of IFN decreased the rate of carcinogenesis. In addition, Lin *et al.*⁵ reported a case-control study matching for age, sex, HBeAg, ALT, and levels of HBV DNA. Their results revealed that five patients in a group receiving IFN therapy and 16 in an untreated group developed HCC ($P=0.025$) in a mean follow-up of 6.8 years. A follow-up of 15 years indicated that the cumulative rate of hepatocarcinogenesis was significantly lower for patients who had cirrhosis and were receiving IFN therapy in comparison to the control group, but differences between the control group and patients who did not have cirrhosis and were receiving IFN therapy were not noted. Multivariate analysis indicated that independent risk factors for the progression of HCC were age, not having undergone IFN therapy, pre-existing cirrhosis, carrying HBeAg, and having the HBV genotype C (in comparison to genotype B). Based on previous studies, IFN therapy for patients with compensated cirrhosis B should be able to suppress hepatocarcinogenesis.^{5,22,23,26,31,32,36} However, the inhibitory effect of IFN therapy on hepatic carcinogenesis for patients with type B chronic hepatitis has not yet gained a sufficient consensus. One reason is that there are few cases of hepatic carcinogenesis that develop from type B chronic hepatitis; thus, researchers cannot obtain either a sufficient number of cases or long-term follow-up periods to verify that IFN therapy inhibits hepatic carcinogenesis. An HBV carrier who has a high level of HBV DNA

rapidly progresses to cirrhosis, which is associated with a high rate of HCC.³⁷ In patients with HBeAg seroconversion and reduced levels of HBV DNA due to IFN therapy, the progression of cirrhosis slows and development of HCC is inhibited.⁵ When serum transaminase returns to normal and HBV DNA falls below detection limits due to IFN therapy given to HBeAg-negative European patients, an improved prognosis is noted but IFN therapy has not been found to suppress hepatocarcinogenesis.³⁸ Miyake *et al.* reported that IFN therapy has been found to suppress hepatocarcinogenesis in Asians; they also reported that IFN has an effect in populations with a 10% or greater incidence of HCC that have not undergone IFN therapy and study populations with 70% or more subjects that are positive for HBeAg.³⁹

Compared with the standard IFN, pegylated-IFN (PEG-IFN) has been reported as more effective in the elimination of HBeAg, reducing HBV DNA, and normalizing the serum ALT level.³⁶ However, there is no report on whether PEG-IFN (in comparison with the standard IFN and nucleos(t)ide analogs such as lamivudine) more greatly reduces the risk of developing HCC. Future research is needed.

In addition, IFN for type B cirrhosis is not price-listed in Japan, and the IFN administration period for type B chronic hepatitis is 6 months. Price-listing of IFN for type B cirrhosis, the extension of the administration period, and the approval of using PEG-IFN are pending.

HCV-RELATED HCC

THE HCV WOULD not be naturally eliminated when an infection is passed to humans. About 70% of persistently infected people become carriers and necro-inflammatory reactions continue; as a result, hepatic fibrosis progresses to cirrhosis.⁴⁰ However, hepatic fibrosis progression rates in persistently HCV-infected people differ significantly among individuals and are influenced by the person's age when infected, the amount of alcohol intake, gender, and the extent of liver function abnormality. It has been demonstrated that, in people who have insulin resistance and fatty livers, the hepatic fibrosis progression rate is rapid and the sustained virological response (SVR) ratio in IFN therapy is reduced.^{41,42} HCC incidence rates increase in relation to the progression of hepatic fibrosis.⁴³ The annual incidence of HCC from type C compensated cirrhosis is reportedly 7.1% in Japan and 3.7% in both Europe and America; and the annual incidence of HCC from chronic hepatitis is 1.8% in Japan and 0% in both Europe and America.¹⁷ When such natural courses are taken into

account, the treatment goals for type C chronic hepatitis are to prevent the progression to cirrhosis and to inhibit hepatic carcinogenesis.

In 1995, we examined (using an RCT) the inhibitory effect of IFN therapy on hepatic carcinogenesis for type C cirrhosis.^{44,45} Ninety patients with type C cirrhosis were divided into two groups: the IFN treatment group and the untreated group. We examined the long-term clinical effects of IFN therapy. In the IFN treatment group, an SVR occurred in seven patients and a biological response (BR) occurred in six patients. In the untreated group, the spontaneous disappearance of the HCV and sustained normalization of ALT level did not occur. During the mean follow-up period of 8.2 years, the cumulative incidence rate of HCC was significantly lower in the IFN treatment group than in the untreated group (27% vs. 73%, respectively) ($P = 0.001$). The relative risk (RR) was 0.256. A multicenter Japanese study – the Inhibition of Hepatocarcinogenesis by Interferon Therapy (IHIT) study – showed that, compared with the untreated group, the risk of hepatic carcinogenesis was inhibited by 0.51-fold in the IFN treatment group; the RR of hepatic carcinogenesis was 0.197 in patients who achieved SVR with IFN therapy.⁴⁶ To our knowledge, seven RCT papers have been published since 1995 that investigated the inhibitory effect of IFN therapy on hepatic carcinogenesis (Table 2).^{44,47–52} In a study involving 99 patients with compensated cirrhosis, Valla *et al.*⁴⁷ administered a 3 MU dose of IFN- α 2b three times weekly for 48 weeks to 52 patients (i.e. the treatment group). A mean follow-up period of 3.3 years showed that HCC occurred in five patients in the treatment group and in nine patients in the control group; however, there was no statistically significant difference between the groups. On the other hand, the results of a meta-analysis by Cammà *et al.*³¹ confirmed that IFN therapy inhibits hepatic carcinogenesis in patients with type C cirrhosis. Their investigation of 3109 patients in three RCT studies^{44,47,53} and 11 NRCT studies^{28,30,46,54–61} showed that the risk of developing HCC in the IFN treatment group was reduced by 12.8% (95% CI, –8.3% to –17.2%), compared with the risk in the untreated group. They reported that, especially in patients who obtained a SVR, there was a marked inhibition of hepatic carcinogenesis (as indicated by an RD of –19.1%). Even in people who did not have a SVR, the RD was significantly reduced (at –11.8%). Miyake *et al.*⁶² reported that hepatic carcinogenesis was inhibited in the IFN-treated group, compared with the untreated group (RR, 0.45; 95% CI, 0.31–0.65), based on their meta-analysis of three RCT studies^{47–49} and six

Table 2 Baseline characteristics of randomized control trials assessing effect of interferon (IFN) on hepatocellular carcinoma (HCC) development in hepatitis C virus (HCV)-infected patients

Study [reference]	Year	Sample size (n)	Male (%)	Mean age (years)	Pre-existing cirrhosis (%)	IFN regimen	Mean follow-up (years)	SVR (%)	Incidence of HCC (%)
Nishiguchi S <i>et al.</i> ⁴⁴	1995	T45	T62	T55	T100	α : 6 MU 3 times a week for 24 weeks	T4.4	T16	T4
		C45	C51	C57	C100		C5.5	C0	C38
Valla DC <i>et al.</i> ⁴⁷	1999	T45	T73	T57	T100	α -2b: 3 MU 3 times a week for 48 weeks	3.3	NA	T11
		C49	C65	C56	C100				C18
Bernardinello E <i>et al.</i> ⁴⁸	1999	T38	T50	T56	T100	β : 6 MU 3 times a week for 24 weeks followed by 3 MIU for another 24 weeks	5	T3	T5
		C23	C61	C58	C100				C4
Francesco A <i>et al.</i> ⁵⁰	2004	T30	T57	T55	T100	α -2b: 6 MU daily for 1 month followed by 3 MIU daily for 11 months plus ribavirin 1 g daily for 12 months	5	T43	T0
		C30	C60	C57	C100				C30
Soga K <i>et al.</i> ⁴⁹	2005	T103	T49	T52	T0	α , α -2a or α -2b: 3-10 MU daily for 2-4 weeks and 3 times a week for total of 14-28 weeks or β ; 3-6 MU daily for 6-8 weeks	7.8	T32	T5
		C30	C43	C54	C0				C0
Fartoux L <i>et al.</i> ⁵¹	2007	T51	T45	T60.5	T100	α -2a: 3 MU 3 times a week for 2 years	2	T0	T12
		C51	C45	C60.5	C100				C12
Lok AS <i>et al.</i> ⁵²	2009	T495	T71	T50	T40	PEG-IFN α -2a: 90 μ g weekly for 3.5 years	T4.6	T0	T4.6
		C510	T79	C53	C41				C4.9

C, control group (no treatment); MU, million units; NA, not available; PEG-IFN, pegylated interferon; SVR, sustained virological response; T, IFN treated group.

NRCT studies^{50,55,58,63–65} published between 1989 and 2009.

The inhibitory effect of IFN is furthermore demonstrated in non-responders (NRs) to IFN therapy (RR, 0.48; 95% CI, 0.26–0.66). Zhang *et al.*³⁵ recently performed a meta-analysis on the effect of non-maintenance IFN therapy on hepatic carcinogenesis. They used only four RCT papers (in three papers, the subjects were patients with type C cirrhosis).^{45,47–49} The results indicated that IFN therapy inhibited hepatic carcinogenesis in the IFN treatment group, compared with the untreated group (RR, 0.39; 95% CI, 0.26–0.59). The results of IFN therapy, when focusing only on patients with cirrhosis, also showed the same inhibitory effect (RR, 0.44; 95% CI, 0.28–0.68). In one study, patients who were initially NR to IFN therapy were divided into two groups: a maintenance IFN treatment group and an untreated group.^{51,52} An analysis of the results showed that IFN therapy has no inhibitory effect on hepatic carcinogenesis.

In the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial,⁵² 1005 patients had cirrhosis and had chronic hepatitis that progressed to fibrosis (i.e. bridging fibrosis). Of these, patients who were unresponsive to a combination therapy with PEG-IFN and ribavirin (RBV) were divided into two groups – the maintenance treatment group (PEG-IFN α -2a, 90 μ g) and the untreated group. The incidence of HCC in each group was investigated. During a mean follow-up period of 4.6 years, there was no difference between the two groups in the incidence of HCC. In a continuation of the HALT-C report,⁷ the mean follow-up period was extended to 6.1 years. The results showed that IFN therapy inhibited hepatic carcinogenesis in patients with cirrhosis in the maintenance IFN treatment group, compared with its inhibitory effect in the untreated group (HR, 0.45; 95% CI, 0.24–0.83). On the negative side, maintenance IFN therapy insufficiently inhibited hepatic carcinogenesis in patients with chronic hepatitis that had progressed to fibrosis. However, the incidence of HCC was reduced in these patients if their liver had a histological improvement with IFN therapy.

One report shows that maintenance IFN therapy reduces the incidence of HCC in elderly patients with chronic hepatitis, compared with patients in the untreated group.⁶⁶ Kumada *et al.* state that the administration of IFN therapy is important in normalizing serum ALT level or reducing the AFP level, even if HCV does not disappear.⁶ For non-SVR patients receiving IFN therapy, a patient's age is an important risk factor for hepatic carcinogenesis, and the annual incidence of

HCC in patients with chronic hepatitis and hepatic fibrosis is significantly higher in aged people than in young people.⁶⁷ It can be accordingly conjectured that the reason for a higher complication rate of HCC among HCV carriers in Japan than among HCV carriers in the USA is that Japanese carriers have a higher mean age and a higher extent of hepatic fibrosis.⁶⁸ These factors may be responsible for the difference in the inhibitory effect of IFN therapy on hepatic carcinogenesis noted between patients in Japan and patients in the USA.

Based on past studies investigating the inhibitory effect of IFN therapy on hepatic carcinogenesis in patients with type C chronic liver diseases, a consensus has been reached concerning the following three points:

- Point 1: Patients achieving SVR with IFN therapy have a reduced HCC incidence rate and an improved HCC prognosis.^{46,69,70}
- Point 2: Because of the use of combination therapy (e.g. PEG-IFN and RBV) in recent years, the treatment outcome has improved and the SVR ratio is about 50% to 80%.⁷¹ However, for patients with chronic hepatitis that has progressed to fibrosis and for patients with compensated cirrhosis, IFN therapy alone reduces the SVR ratio and reduces the incidence of complications associated with the liver (including hepatic carcinogenesis).⁶⁹
- Point 3: IFN therapy reduces the incidence rate of HCC when a BR is achieved or when there is a histological improvement.^{66,72}

Further examinations are needed to determine whether maintenance IFN therapy inhibits hepatic carcinogenesis and whether there is any difference between IFN therapy NR patients and IFN-untreated patients in the rate of hepatic carcinogenesis. Studies are needed that take into account the amount of IFN administered, the administration period, and the use of RBV and novel concurrent drugs. In addition, we expect that combination therapy with PEG-IFN and RBV for patients with compensated cirrhosis will be promptly price-listed in Japan.

RECURRENCE INHIBITION AFTER LOCALLY CURATIVE TREATMENT FOR HCC

EVEN IF LOCALLY curative treatment for HCC is performed, HCC relapses occur at an annual rate of 15% to 20%. This high rate is not caused by any other malignant neoplasms, and it results in a high mortality.⁷³ To improve the prognosis of patients with HCC, measures are needed that advance HCC treatment and inhibit recurrence.

Basic investigations reveal that IFN has anti-viral activity and it inhibits the growth of HCC.^{74,75} In a retrospective examination, Someya *et al.* reported that singlevariate and multivariate analyses showed that IFN therapy inhibits recurrence in patients with HCC-complicated type B cirrhosis after locally curative treatment.⁷⁶ Lo *et al.*⁷⁷ performed an RCT, using as subjects 40 patients who had undergone a radical hepatic resection because of HBV-related HCC. On examining the IFN treatment group (in which patients were administered 10 MU/m² of IFN- α 2b three times weekly for 12 weeks) and the untreated group, they found that the one-year and 5-year survival rates were 97% and 79%, respectively, in the IFN treatment group and 85% and 61%, respectively, in the untreated group. Therefore, the IFN treatment group had a better prognosis ($P = 0.137$). A multivariate analysis demonstrated that IFN therapy may reduce the risk of death (HR, 0.42; 95% CI, 0.17–1.05; $P = 0.063$). In the examination of subgroups, there was no difference between the IFN treatment group and the untreated group in the 5-year survival rate in patients at stage I/II; however, in patients at stage III/IV A, IFN therapy inhibited the early recurrence of HCC and improved the 5-year survival rate from 24% to 68% ($P = 0.038$). Sun *et al.*⁷⁸ in their RCT also reported that IFN therapy was useful after an operation for HCC and that the median overall survival time and median disease-free time were significantly longer in treated patients, compared with the untreated patients.

We found six RCT studies that examined the inhibitory effect of IFN therapy on recurrence after locally curative treatment for HCV-related HCC.^{79–84} Ikeda *et al.*⁷⁹ and Kubo *et al.*⁸⁰ showed that IFN therapy significantly inhibits the recurrence of HCC. Shiratori *et al.*⁸¹ reported no difference between the IFN-treated group and the control group with the first relapse of HCC, but noted that IFN therapy inhibits a second or later recurrence of HCC. Only Mazzaferro *et al.*⁸³ reported that IFN therapy shows no significant difference between the IFN treatment group and the control group; however, at the first relapse of HCC, IFN therapy inhibits recurrence in patients having a single tumor that is free from vascular invasion and has a diameter of less than 3 cm. An examination of NRCT, which were performed in Japan, also showed that IFN therapy significantly inhibits the relapse of HCC (especially in patients who receive IFN treatment aimed at eliminating HCV), achieves an SVR,^{85–87} and improves survival rates.⁸⁸ Maintenance IFN therapy after the locally curative treatment of HCC reportedly inhibits recurrence.^{85,89,90} Kudo *et al.*⁸⁹ reported that IFN therapy inhibits the first relapse (as

well as a second or third relapse) and improves the prognosis. We also demonstrated that long-term maintenance IFN therapy, given after the combination therapy with PEG-IFN and RBV, effectively inhibits HCC recurrence and improves prognosis.⁹¹ Singal *et al.*⁹² performed a meta-analysis of five RCT papers^{79,81–83,93} and five NRCT papers.^{87,89,94–96} They reported that IFN therapy inhibits HCC recurrence (odds ratio [OR], 0.31; 95% CI, 0.26; $P < 0.0001$) and significantly extends the overall survival time. Furthermore, Zhang *et al.*⁹⁷ conducted a meta-analysis of six RCT papers (Two papers focused on HBV-related HCC and four papers focused on HCV-related HCC).^{77,78,80–83,93} Their meta-analysis showed that IFN therapy inhibits early recurrence (OR, 0.62; 95% CI, 0.42–0.93; $P = 0.02$) and improves the one-year survival rate (OR = 3.14; 95% CI = 1.79–5.52; $P = 0.0001$). Shen *et al.*⁹⁸ similarly performed a meta-analysis of 13 papers on HBV-related and HCV-related HCC (nine papers involved RCT^{77–84,93}, and four papers involved NRCT^{87,89,94,99}). From this, they concluded that IFN therapy improved the one-year, 2-year, and 3-year recurrence-free survival rates in the IFN treatment group, compared with the control group.

Based on past studies investigating the inhibitory effect of IFN therapy on HCC recurrence after locally curative treatment, HCC recurrence is reduced through HCV clearance. Thus, IFN therapy for viral eradication is recommended for patients with hepatitis C if possible. Meanwhile, in patients with hepatitis B, IFN therapy after locally curative treatment may improve their prognosis. Further examinations are needed to determine whether IFN therapy after locally curative treatment reduces HCC recurrence in patients with hepatitis B.

FINAL COMMENTS

FOR PATIENTS WITH chronic hepatitis B, IFN therapy reduces the risk of hepatic events (including the inhibitory effect for developing HCC) particularly among responders to treatment in Asian, but not in European patients. The progression to cirrhosis and a high level of HBV DNA (greater than 10⁵ copies/mL) are strong risk factors for hepatic carcinogenesis from type B chronic liver diseases.³⁷ Liaw *et al.*¹⁰⁰ reported that therapy with lamivudine, a nucleos(t)ide analog, significantly reduces the progression to non-compensated cirrhosis and inhibits the development of HCC. Matsumoto *et al.*¹⁰¹ also had similar results in a multicenter study of Japanese patients with type B chronic hepatitis. As for inhibition of hepatic carcinogenesis from type B chronic liver diseases, measures for hepatitis

are important, after taking age, amount of HBV DNA, extent of background liver disorder, HBV genotype, and others into account, according to guidelines, use of IFN or nucleos(t)ide analogs needs to be determined.^{18,37}

It is important that IFN-based therapy obtains SVR to inhibit the development of hepatic carcinogenesis from type C chronic liver diseases. Thus, IFN therapy is recommended for patients with chronic hepatitis C. Tanaka N *et al.*¹⁰² reported single nucleotide polymorphisms (SNPs) in the IL28B locus. These polymorphisms are extremely effective for estimating the effects of IFN therapy; they provide a novel indicator to help determine a patient's therapy, and will be used clinically.¹⁰³ New anti-viral drugs are being developed for treating type C chronic hepatitis. Combination therapy using PEG-IFN, RBV, and a protease inhibitor reportedly improves the SVR rate.⁶⁸ In addition, the acyclic retinoid, studied and developed in Japan, is expected to show a strong inhibitory effect on hepatic carcinogenesis.¹⁰⁴

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Long-term interferon therapy after radiofrequency ablation is effective in treating patients with HCV-associated hepatocellular carcinoma

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Abstract

Purpose This study investigates the usefulness of long-term interferon (IFN) therapy following radiofrequency ablation (RFA) for HCV-associated hepatocellular carcinoma (HCC).

Methods This is a retrospective observational study. Patients underwent pegylated IFN- α /ribavirin combination therapy for 48 weeks and then were maintained on IFN- α administration on average for 68 weeks (mean total duration 116 weeks). Patients who underwent IFN monotherapy were maintained on IFN administration on average for 78 weeks.

Results There were biases in the background factors between the IFN and non-IFN groups. Therefore, a covariate adjustment was performed using the propensity score. An analysis of 20-matched patients from each group showed the 5-year cumulative survival rate was higher in the IFN group than in the non-IFN group (100 and 76%, respectively), and the 3-year cumulative recurrence rate

was significantly lower in the IFN group than in the non-IFN group (38.0 and 64.2%, respectively). In 14 patients (i.e., IFN responders), the serum alanine aminotransferase (ALT) level remained normalized at 30 IU/mL or lower, regardless of disappearance of serum HCV RNA. In these patients, the cumulative recurrence rate was low, the hazard ratio was 0.158 (95% confidence interval = 0.045–0.561, $P = 0.004$), and the serum albumin level was retained.

Conclusion These results show the importance of maintaining the liver function and suggest that long-term IFN administration after RFA inhibits recurrence and contributes to an improved outcome in patients (in particular, IFN responders) who initially develop HCC.

Keywords Hepatitis C virus · Interferon · Hepatocellular carcinoma · Prevention · Radiofrequency ablation

Introduction

More than 500 million people in the world are infected with hepatitis B and C viruses (HBV and HCV, respectively). Persistent infection with these hepatitis viruses is strongly associated with the development of hepatocellular carcinoma (HCC). The HCC patient is ranked fifth among cancer patients throughout the world and the number of deaths from HCC is ranked at third [1]. Its pathogenesis is being progressively elucidated; in most instances, HCC develops in patients who have a background of HBV- and HCV-induced chronic hepatitis and hepatic cirrhosis [2]. Advances in the early detection of and therapy for HCC have increasingly led to curative treatment. However, HCC is likely to recur and the incidences of intrahepatic metastasis and multicentric recurrences are high and are a

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major problem in improving the treatment outcomes [3, 4]. There have been marked advancements recently in interferon (IFN) therapy for chronic hepatitis C. The incidence of HCC is, according to reports, significantly reduced in patients who achieved a sustained viral response (SVR) with IFN therapy and in patients for whom IFN therapy normalizes liver function. This indicates the importance of IFN therapy as a primary prevention against developing HCC [5–9]. IFN therapy after curative treatment of HCV-associated HCC is reportedly useful as secondary prevention against carcinogenesis [10–14]. There are reports that long-term IFN administration inhibits recurrence [15], but the evaluation of this has not been fully established [16]. In this study, after administering radical radiofrequency ablation (RFA), we performed long-term IFN therapy in patients with the initial development of HCV-associated HCC. We retrospectively investigated the recurrence-inhibitory effect of the treatment.

Patients and methods

Patients

Between April 2001 and March 2008, there were 226 patients who underwent RFA at the Division of Hepatobiliary and Pancreatic Diseases, Hyogo College of Medicine. Of these, 135 patients were negative for the HBs antigen and positive for HCV RNA, with tumor diameter ≤ 3 cm, with three or fewer tumors, and underwent RFA alone for the initial development of HCC. These 135 patients were selected for subjects. There were 71 male and 64 female patients who ranged from 39 to 85 years old (the median age was 68 years). The background liver was clinically and histologically evaluated. HCC was diagnosed using abdominal ultrasonography, dynamic computed tomography (CT), and magnetic resonance imaging (MRI). Markedly enhanced tumors were noted in the early phase of contrast imaging on CT or MRI in all patients and washout was observed in the portal phase or late phase 3 min after injection of the contrast medium. RFA was performed with ultrasonographic guiding using the Cool-tip Radiofrequency Ablation system (Tyco Healthcare Group LP, Burlington, MA). The lesions were evaluated by dynamic CT or MRI 1 and 8 weeks after RFA. The treatment was considered markedly effective when the intensely stained tumors disappeared and a treated area was sufficiently maintained.

IFN therapy was indicated for patients meeting the following conditions: (1) platelet count $\geq 70,000 \mu\text{L}^{-1}$, (2) white blood cell count $\geq 1,500 \mu\text{L}^{-1}$, (3) hemoglobin ≥ 10 g/dL, (4) Child-Pugh classification stage A, and (5) age ≤ 80 years. IFN therapy was performed in 20 patients for whom RFA was markedly effective. Nineteen

of 20 patients requested IFN therapy and met the criteria. One patient with Child-Pugh classification stage B underwent IFN therapy because of the patient's strong desire for this therapy. One hundred and fifteen patients did not undergo IFN therapy. Fifty-one of 115 patients did not meet the criteria. IFN therapy was not performed in 64 patients because of their unwillingness to undergo this therapy (despite meeting the indications for treatment) or because ursodeoxycholic acid or strong neominophagen C were being administered instead of IFN because the patients had complications such as hypertension and diabetes (Table 1).

Since this was a retrospective study, covariate adjustment using the propensity score was performed to adjust for between-group confounding factors [17, 18]. The following ten factors were adopted as matching covariates: age, gender, platelet count, serum alanine aminotransferase (ALT) level, α -fetoprotein (AFP) level, protein induced by vitamin K absence or antagonist-II (PIVKA-II) level, Child-Pugh classification, tumor diameter, number of tumors, and the Japanese tumor, node, and metastasis (TNM) stage [19]. Based on the results of the adjustments, 20 patients with IFN therapy and 20 patients without IFN therapy (i.e., IFN and non-IFN groups, respectively) were assessed. Recurrence of HCC was classified as a local tumor progression or as an ectopic recurrence. A local tumor progression was defined as recurrence in an area previously treated with RFA and an ectopic recurrence was defined as a recurrence outside this area.

IFN therapy

IFN therapy that was initiated 1 month after RFA was markedly effective in treating the initial HCC. In the IFN group, 19 patients had the genotype 1b and a high viral load. In Japan, pegylated IFN- α /ribavirin (PEG-IFN/RBV) combination therapy was approved at the end of 2004, and we have planned to give PEG-IFN/RBV combination therapy since 2005. IFN therapy was administered after requests from individual patients who gave informed consent. Twelve patients underwent PEG-IFN/RBV combination therapy. The therapy regimen consisted of PEG-IFN- α -2b (Peg-Intron, Schering Plough Corporation, Kenilworth, NJ) administered at a dose of 1.5 $\mu\text{g}/\text{kg}/\text{week}$; PEG-IFN- α -2a (Pegasys, Hoffman La Roche, Nutley, NJ) administered at a dose of 180 $\mu\text{g}/\text{week}$; and RBV administered for 48 weeks at a dose based on body weight (600 mg for ≤ 60 kg, 800 mg for 60–80 kg, and 1,000 mg for >80 kg). Two of the 12 patients achieved SVR, which was defined as the persistent negative conversion of serum HCV RNA after the 24th week of IFN therapy. After the combination therapy, nine patients underwent IFN- α (Sumiferon, Dainippon Sumitomo Pharma Co., Ltd.,

Table 1 Demographic and baseline characteristics of the patients

Variable	IFN group	Non-1 FN group	<i>P</i>
Patients (<i>n</i>)	20	115	
Age (range), years	65 (52–76)	67 (39–85)	0.06
Gender (<i>n</i>)			0.04
Male	15	56	
Female	5	59	
White blood count ($\times 10^2 \mu\text{L}^{-1}$)	40 (38, 50)	37 (28, 46)	0.08
Hemoglobin (g/dL)	12.9 (11.7, 13.9)	12.8 (11.3, 13.5)	0.35
Platelet count ($\times 10^4 \mu\text{L}^{-1}$)	9.7 (8.7, 11.9)	9.7 (8.0, 12.2)	0.36
Prothrombin activity (%)	80.9 (79.5, 88.9)	81.9 (77.5, 84.2)	0.80
Total bilirubin (mg/dL)	0.8 (0.6, 1.2)	0.9 (0.5, 1.2)	0.51
Albumin level (g/dL)	3.9 (3.5, 4.1)	3.7 (3.3, 3.9)	0.006
AST (IU/L)	60 (33, 82)	57 (45, 86)	0.42
ALT (IU/L)	50 (37, 83)	53 (39, 72)	0.71
AFP (ng/mL)	11 (6, 41)	27 (6, 79)	0.03
PIVKA-II (mAU/mL)	25 (17, 60)	37 (21, 137)	0.95
Child-Pugh classification (<i>n</i>)			0.41
A	19	96	
B	1	18	
C	0	1	
Tumor size (mm)	21 (17, 24)	20 (19, 29)	0.75
Number of tumors (<i>n</i>)			0.17
Solitary	18	88	
Multiple	2	27	
Japanese TNM stage (<i>n</i>)			0.044
I	6	43	
II	13	45	
III	1	27	
Follow-up period (month)	37 (19, 57)	31 (17, 69)	0.13

Except where indicated, data are expressed as the median (25th, 75th percentile)

Osaka, Japan) monotherapy (300 MU, 3 times/week) for a mean duration of 68 weeks (mean total duration 116 weeks).

Eight patients underwent IFN monotherapy. One patient had the genotype 2a, one patient had the hemoglobin of 11.1 g/dL and six patients had low levels of the platelet count ($<100,000 \mu\text{L}^{-1}$). In accordance with Japan package insert of PEG-IFN- α -2b, we planned to undertake IFN monotherapy in eight patients on enough informed consent. Treatment was initiated with PEG-IFN- α -2a monotherapy (90 $\mu\text{g}/\text{week}$ or 90 $\mu\text{g}/2$ weeks) in five patients, and IFN- α monotherapy (300–600 MU, 3 times/week) was initiated in three patients. The therapies were continued in these patients, except for one patient who ultimately achieved SVR. The mean duration of PEG-IFN- α -2a or IFN- α monotherapy was 78 weeks.

Follow-up procedure

After RFA for HCC, liver function testing and tumor marker measurement (AFP, PIVKA-II) were performed

every month in all patients. Abdominal ultrasonography was performed every 3 months and dynamic CT or MRI was performed every 6 months. Histological examination was performed on suspected hypovascular HCC using fine-needle aspiration biopsy. When a recurrence occurred, the patient was admitted for appropriate therapy.

Statistical analysis

For between-group comparisons, the Mann–Whitney *U* test was used for continuous variables and the Chi-square and Fisher exact tests were used for categorical variables. The survival time and HCC recurrence were evaluated using the Kaplan–Meier method and between-group comparisons were performed using the log-rank test. The influence of IFN administration on recurrence after RFA was investigated using the Cox proportional hazards model. Covariate adjustment was performed using the propensity score, as previously reported [17, 18]. The *C*-statistic (ROCKIT software, Kurt Rossmann Laboratories, University of Chicago, Chicago, IL) [20] was used for the goodness-of-fit

index of patients matched using the propensity score. Analysis was performed using statistical software SPSS ver. 16.0 (SPSS, Inc., Chicago, IL) and SAS ver. 9.13 (SAS Institute, Inc., Cary, NC). A two-sided *P* value of less than 5% was regarded as significant.

Results

The virological and adverse effects of IFN therapy

Two of the 19 patients with the genotype 1b who had a high viral load and one patient with the genotype 2a achieved SVR. HCV RNA did not become negative in 14 patients. HCV RNA disappeared in the remaining three patients, but assessing SVR was difficult since the patients were undergoing IFN therapy. Normalization of the serum ALT level to 30 IU/mL or lower occurred in 11 of the 17

non-SVR patients. Since there were no severe adverse events, IFN therapy was continued in 12 patients who underwent PEG-IFN/RBV combination therapy and in eight patients who underwent IFN monotherapy. IFN therapy was suspended due to recurrence of HCC in two patients who underwent IFN monotherapy, but the treatment was resumed after a second RFA treatment in the patients. In the non-IFN group, normalization of the serum ALT level to 30 IU/mL or lower did not occur in any patient.

Recurrence of HCC

After radical RFA in 135 patients, the 1- and 3-year cumulative recurrence rates were 5.0 and 38.0%, respectively, in the IFN group, and 25.0 and 68.6%, respectively, in the non-IFN group. The lower rate in the IFN group was statistically significant (*P* = 0.007). A comparison of the

Table 2 Demographic and baseline characteristics of the matched patients

Variable	IFN group	Non-IFN group	<i>P</i>
Patients (<i>n</i>)	20	20	
Age (range), years	66 (52–76)	67 (56–73)	0.30
Gender (<i>n</i>)			1.00
Male	15	15	
Female	5	5	
White blood count ($\times 10^2 \mu\text{L}^{-1}$)	40 (38, 50)	39 (29, 46)	0.14
Hemoglobin (g/dL)	12.9 (11.7, 13.9)	13.3 (11.9, 14.2)	0.67
Platelet count ($\times 10^4 \mu\text{L}^{-1}$)	9.7 (8.7, 11.9)	10.9 (7.8, 14.6)	0.49
Prothrombin activity (%)	80.9 (79.4, 88.9)	83.8 (74.3, 90.1)	0.89
Total bilirubin (mg/dL)	0.8 (0.6, 1.2)	1.0 (0.7, 1.2)	0.30
Albumin level (g/dL)	3.9 (3.5, 4.1)	3.7 (3.3, 4.0)	0.08
AST (IU/L)	60 (33, 82)	62 (41, 87)	0.19
ALT (IU/L)	50 (37, 83)	52 (35, 67)	0.69
AFP (ng/mL)	11 (6, 41)	18 (8, 69)	0.29
PIVKA-II (mAU/mL)	25 (17, 61)	33 (18, 47)	0.75
Child-Pugh classification (<i>n</i>)			1.00
A	19	20	
B	1	0	
Tumor size (mm)	21 (17, 24)	21 (18, 26)	0.67
Number of tumors (<i>n</i>)			1.00
Solitary	18	18	
Multiple	2	2	
Japanese TNM stage (<i>n</i>)			0.46
I	6	9	
II	13	9	
III	1	2	
HCV genotype			1.00
1b	19	18	
2a	1	2	
Viral load (kIU/mL)	900 (370, 1,600)	850 (270, 1,250)	0.76
Follow-up period (month)	37 (19, 57)	28 (17, 39)	0.24

Except where indicated, data are expressed as the median (25th, 75th percentile)