

## Effects of a 24-week course of interferon- $\alpha$ therapy after curative treatment of hepatitis C virus-associated hepatocellular carcinoma

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related HCC occurred during persistent viral infection. Eradication of HCV is essential for the prevention of HCC recurrence and improvement of survival.

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**Key words:** Hepatitis C virus; Hepatocellular carcinoma; Recurrence; Survival; Sustained virological response

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### Abstract

**AIM:** To assess whether a 24-wk course of interferon (IFN) could prevent hepatocellular carcinoma (HCC) recurrence and worsening of liver function in patients with hepatitis C virus (HCV)-infected patients after receiving curative treatment for primary HCC.

**METHODS:** Outcomes in 42 patients with HCV infection treated with IFN- $\alpha$ , after curative treatment for primary HCC (IFN group), were compared with 42 matched curatively treated historical controls not given IFN (non-IFN group).

**RESULTS:** Although the rate of initial recurrence did not differ significantly between IFN group and non-IFN group (0%, 44%, 61%, and 67% vs 4.8%, 53%, 81%, and 87% at 1, 3, 5, and 7 years,  $P = 0.153$ , respectively), IFN group showed a lower rate than the non-IFN group for second recurrence (0%, 10.4%, 28%, and 35% vs 0%, 30%, 59%, and 66% at 1, 3, 5 and 7 years,  $P = 0.022$ , respectively). Among the IFN group, patients with sustained virologic response (SVR) were less likely to have a second HCC recurrence than IFN patients without an SVR, or non-IFN patients. Multivariate analysis identified the lack of SVR as the only independent risk factor for a second recurrence, while SVR and Child-Pugh class A independently favored overall survival.

**CONCLUSION:** Most intrahepatic recurrences of HCV-

### INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms worldwide. Chronic infection with hepatitis C virus (HCV) has been causally associated with HCC<sup>[1-3]</sup>. Recent advances in imaging and treatment have brought about some improvement in prognosis of patients with HCV-related HCC, but outcomes are still unsatisfactory. The 5-year survival rate is only 50%-70%, even after curative treatment such as hepatic resection or local ablation<sup>[4]</sup>. Reasons for this unfavorable prognosis are considered to include high intrahepatic tumor recurrence rates and sustained hepatic damage, both resulting from HCV infection<sup>[5]</sup>.

Even after curative hepatic resection for HCV-related HCC, the rate of intrahepatic tumor recurrence within 1 year is 20%-40%, rising to about 80% by 5 years<sup>[4,6-8]</sup>. Intrahepatic recurrence of HCC may result from intrahepatic metastasis originating from the primary HCC, or from ongoing multicentric carcinogenesis related to chronic HCV infection. Underlying HCV-related hepatic damage may also compromise hepatic functional reserve, and worsen clinical outcome. Thus prevention of HCC recurrence and preservation of liver function are both high priorities for improving prognosis of patients with HCV-

related HCC.

Interferon (IFN) therapy for patients with HCV infection is effective in reducing serum alanine transaminase (ALT) activity and in eradicating HCV<sup>[9,10]</sup>, and thus IFN could have value in minimizing hepatic necrosis, inflammation and fibrosis, as well as reducing the incidence of HCC. Several recent studies have reported that IFN therapy, even after curative treatment for HCV-related HCC, could prevent HCC recurrence and improve survival<sup>[11-17]</sup>. Unfortunately, since these studies are characterized by differing IFN regimens, definitions of IFN responses, and background characteristics of patients, results have varied and no standard IFN regimen has been established for after curative treatment of HCV-related HCC. As well, the mechanisms by which IFN suppresses HCC recurrence, including possible direct anti-tumor and anti-inflammatory effects, remain uncertain.

In the present study, recurrence and survival outcomes in matched historical controls were compared with those in patients receiving a 24-wk course of IFN- $\alpha$  therapy after receiving curative treatment for HCC.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed 495 consecutive patients treated for primary HCC associated with HCV infection at Hiroshima University Hospital from March 1992 to March 2004. Of these, 384 with HCC initially underwent therapeutic intervention with curative intent. Curative treatment was defined as complete tumor eradication, with no residual tumor visible by computed tomography, or resection of all evident tumor tissue. Medical treatment included percutaneous radiofrequency ablation (RFA), ethanol injection, and microwave coagulation therapy (MCT). Surgical treatment included hepatic resection and ablation during laparotomy.

Among these 384 patients, we administered IFN therapy to 42 who met the following eligibility criteria: age under 70 years; up to three tumors with none exceeding 30 mm in diameter, or a solitary tumor less than 50 mm in diameter; tumor-node-metastasis (TNM) stage I, II, or III; detectable serum HCV RNA; seronegativity for hepatitis B surface antigen; chronic hepatitis or compensated cirrhosis with a Child-Pugh class of A or B; platelet count above 70 000/ $\mu$ L; absence of local recurrence during the follow-up period; and absence of ectopic intrahepatic recurrence within 24 wk after treatment for primary HCC. We used the TNM classification system of the Liver Cancer Study Group of Japan as the staging system for HCC<sup>[18]</sup>. Underlying liver conditions such as hepatitis or cirrhosis were confirmed by laboratory, pathologic and radiologic examinations. We classified liver function in chronic hepatitis as Child class A because chronic hepatitis is a known pre-cirrhotic condition. There were only a few chronic hepatitis cases: three in the IFN group and four in the non-IFN group.

As historical control subjects, we selected 42 patients with no IFN therapy after treatment for primary HCC (non-IFN group). These 42 patients, who met the eligibility

Table 1 Patient characteristics

	IFN group ( <i>n</i> = 42)	Non-IFN group ( <i>n</i> = 42)	<i>P</i>
Median age in years (range)	62 <sup>1</sup> (45-69)	63 <sup>1</sup> (40-69)	NS
Gender (male/female)	36/6	29/13	NS
Alb (g/dL)	3.9 <sup>1</sup>	3.9 <sup>1</sup>	NS
PLT ( $\times 10000/\mu$ L)	12 <sup>1</sup>	11.5 <sup>1</sup>	NS
ICG R-15 (%)	17 <sup>1</sup>	18 <sup>1</sup>	NS
CH or Child A/B	35/7	35/7	NS
Size of main tumor (mm)	20 <sup>1</sup> (10-50)	15 <sup>1</sup> (10-50)	NS
AFP (ng/mL)	26 <sup>1</sup>	31.4 <sup>1</sup>	NS
No. of HCC (single/two or three)	30/12	36/6	NS
Stage (I / II or III)	14/28	23/19	NS
Treatment of HCC (medical/surgical)	18/24	20/22	NS

IFN: interferon; Alb: albumin; PLT: platelet; ICG-R15: indocyanine green retention at 15 min; CH: chronic hepatitis; AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma. <sup>1</sup>Median.

criteria noted above, were matched by age, gender, tumor size, TNM stage of HCC, serum albumin, platelet counts, and Child-Pugh class with patients who received IFN therapy (IFN group).

Thus, a total of 84 patients (42 in the IFN group and 42 in the non-IFN group) were enrolled. All agreed to participate in the research protocol, which was approved by the hospital research ethics board. Table 1 shows the baseline characteristics of the two groups, indicating no significant differences for age, gender, liver function, tumor characteristics, or therapeutic methods used against HCC.

### IFN therapy

In the IFN group, patients received 6 MIU of natural IFN- $\alpha$  (human lymphoblastoid IFN, Sumiferon; Dainippon Sumitomo Pharmaceuticals, Osaka, Japan) intramuscularly every day for 2 wk, followed by three times weekly for 22 wk. IFN therapy began within 24 wk after the initial treatment for HCC. All patients were evaluated every week in an outpatient setting during IFN treatment. Qualitative detection of HCV-RNA was performed by a standardized qualitative reverse transcription-polymerase chain reaction (RT-PCR) assay at every 4 wk during and after IFN treatment.

Among the patients who received IFN therapy, 28 were of HCV genotype 1 and 14 were of HCV genotype 2. These 42 patients had various pretreatment viral loads. Twenty patients (genotype 1, *n* = 11; genotype 2, *n* = 9) had high viral loads ( $\geq 100$  kIU/mL by PCR), and 22 (genotype 1, *n* = 17; genotype 2, *n* = 5) had low viral loads ( $\leq 100$  kIU/mL by PCR). The 42 patients were divided into two subgroups according to virologic response, i.e., patients with *vs* without a sustained virologic response (SVR). SVR was defined as the sustained absence of serum HCV RNA for more than 24 wk after completion of IFN treatment. Absence of SVR included both persistent viremia (no response) and transient viral disappearance (transient response) during or after IFN therapy. Biochemical response was defined as ALT activity declining to a value within the normal reference range in the presence of viremia.

### Follow-up

After curative treatment for primary HCC, all patients studied underwent liver function tests, serum tumor marker assays, such as those for  $\alpha$ -fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II) every month, abdominal ultrasonography every 3 mo, and dynamic computed tomography (CT) every 6 mo. If recurrence of HCC was suspected, additional examinations including CT during arteriography or tumor biopsy were performed. Recurrence of HCC was defined as any new nodules indicated by CT as hyperattenuation during hepatic arteriography or by hypoattenuation in CT performed during arteriportography. Hypovascular HCC was confirmed histopathologically after fine-needle aspiration biopsy. Patients with recurrent HCC were treated medically or surgically, with curative intent if possible.

In IFN patients, including those with or without SVR, and in the non-IFN group, we compared both the rate of HCC recurrence and the survival rate. We also sought to identify significant prognostic indicators for survival and recurrence after curative treatment of primary HCC.

### Statistical analysis

Chi-squared and Fisher exact tests were used for categorical variables, while Student's *t* test and the Mann-Whitney *U* test were used for continuous and ordinal variables, as appropriate. The Kaplan-Meier method was used to assess cumulative survival and recurrence rates, calculated from the date of diagnosis to the date of disease recurrence or death. Surviving patients and those who died of causes unrelated to the liver were defined as censored cases, while patients who died of causes related to the liver were defined as non-censored cases. The log-rank test was used to compare survival and recurrence curves. Univariate and multivariate predictors of survival or recurrence time were determined using the Cox proportional hazard model. Hazard ratios and their 95% confidence intervals (95% CI) were computed.  $P < 0.05$  was considered to indicate statistical significance. The JMP version 5.1 statistical software package (SAS Institute, Cary, NC, USA) was used for analysis of data.

## RESULTS

### Virologic and biochemical responses to IFN therapy and side effects

The 42 patients receiving IFN therapy included 29 in the SVR group and 13 in the group without SVR (10 transient virological responders, 3 with no virological response). In the group without SVR, 7 biochemical responders who had a normalized ALT included 5 with transient virological responses and 2 with no virological response. Although there was no significant difference in the population of patients with HCV genotype 1 between the SVR and non-SVR group, patients in the former had significantly lower pre-IFN viral loads than patients in the latter group. In the SVR group, 24 patients received full-dose IFN therapy without dose reduction, while five patients received a reduced dose of IFN until completion

of treatment. In the group without SVR, one patient with no response discontinued IFN treatment at 16 wk because of a recurrence of HCC, while three patients with a transient response discontinued treatment because of generalized fatigue. The remainder of the group without SVR received the full course of IFN therapy. Thus, most patients were able to complete the 24-wk course.

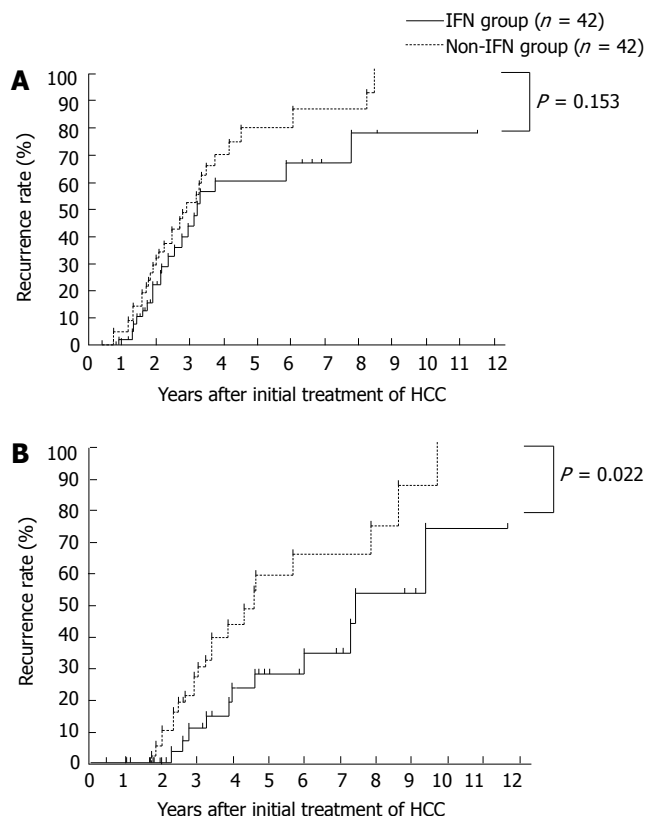
### Recurrence of HCC

In the IFN group, first recurrences of HCC developed in 20 patients after the initial treatment for HCC during a median follow-up period of 32 mo. Of these recurrences, 10 were in patients with SVR (10/29) and 10 in patients without SVR (10/13), including 7 transient virological responders and 3 with no virological response. For the 7 biochemical responders without SVR, HCC recurred in 6 patients, including 5 transient virological responders and 1 with no virological response. Of these 20 patients with recurrence, 18 were treated with local ablation therapy or surgical resection without leaving any residual tumor. The remaining 2 patients developed uncontrolled multiple HCC and were excluded from the subsequent study concerning the next recurrence. One died of HCC, while the other was treated repeatedly with hepatic arterial infusion, and has survived. Three patients in the SVR group and 7 in the group without SVR (5 transient virological responders and 2 with no virological response) had a second recurrence of HCC. Of these 10 patients with a second recurrence, 3 (2 transient virological responders and one with no virological response) developed uncontrolled HCC, while others were treated curatively with hepatic resection or local ablation therapy. In the non-IFN group, a first recurrence of HCC occurred in 30 patients during a median follow-up period of 31 mo. HCC recurred in 11 of the 17 who had a normal ALT level. Among the 30 patients with recurrent HCC, 25 were treated with local ablation therapy or surgical treatment, with no residual tumor. The remaining 5 patients who did not undergo curative therapy were treated repeatedly with transarterial chemoembolization. A second recurrence developed in 15 of the 25 patients who had curative treatment for a first recurrence. Among these 15 patients, 10 were treated curatively (9 with local ablation and 1 with hepatic resection). The remaining 5 patients had uncontrolled multiple HCC as their second recurrence.

Overall cumulative rates for first and second recurrence of HCC were compared between the groups. The 1-, 3-, 5- and 7-year rates for first recurrence in the IFN and non-IFN group were 0% *vs* 4.8%, 44% *vs* 53%, 61% *vs* 81%, and 67% *vs* 87%, respectively (Figure 1A,  $P = 0.153$ ; no significant difference between groups). However, the 1-, 3-, 5-, and 7-year rates for second recurrence in the IFN and non-IFN group were 0% *vs* 0%, 10.4% *vs* 30%, 28% *vs* 59%, and 35% *vs* 66%, respectively (Figure 1B,  $P = 0.022$ ). Thus, the second-recurrence rate was significantly lower in the IFN group than in the non-IFN group.

Next, the recurrence rates of HCC were compared between the SVR group, the non-SVR group and the non-IFN group. The rate of first recurrence was significantly lower in the SVR group than in the non-SVR and non-IFN group (Figure 2A). The rate of second recurrence in the





**Figure 1** Cumulative recurrence rates after curative treatment of HCC. **A:** Rates of first recurrence compared between IFN and non-IFN groups, showed no significant difference ( $P = 0.153$ ); **B:** Rates of second recurrence compared between IFN and non-IFN groups. The second recurrence rate for the IFN group was lower than that for the non-IFN group ( $P = 0.022$ ).

SVR group was also lower than that in the non-SVR and non-IFN groups; this decrease was significantly greater than that for the rate of first recurrence (Figure 2B). No significant difference was seen in cumulative rates for first or second recurrence between the non-SVR and non-IFN groups. We also confirmed that biochemical responders in the non-SVR and non-IFN groups showed similar Kaplan-Meier curves for cumulative recurrence (data not shown). Recurrence curves were similar between the non-SVR group, including biochemical responders, and the non-IFN group, therefore, we defined these two groups as "non-SVR status" for statistical analysis. Factors found to be significantly associated with first recurrence by univariate analysis were tumor size ( $\geq 20$  mm) and non-SVR status ( $P = 0.019$ ,  $P = 0.0067$ , respectively). Multivariate analysis showed that no independent risk factor was associated with the first recurrence of HCC (data not shown), although non-SVR status tended to be associated with first recurrence ( $P = 0.0657$ ). As shown in Table 2, univariate analysis indicated that non-SVR status, low platelet count ( $< 100\,000$ ) and high indocyanine green retention ( $\geq 20\%$ ) were significantly associated with second recurrence. Multivariate analysis identified only SVR status as a significant independent inhibiting factor for second recurrence of HCC.

### Survival of patients

During the observation period, 13 of the total patients

studied died of liver disease. Nine died of HCC and 4 of liver failure. When we compared cumulative survival rates between the IFN and the non-IFN groups (Figure 3A), the respective rates were 100% *vs* 95% at 3 years, 100% *vs* 72% at 5 years, and 86% *vs* 63% at 7 years. The cumulative survival rate was significantly higher in the IFN group than in the non-IFN group ( $P = 0.039$ ). Median survival time following the first treatment of HCC was 52.3 mo (range, 12-158) in the IFN group and 51.8 mo (range, 11-126) in the non-IFN group. In the IFN group, 2 patients died of advanced HCC, 1 with an SVR and the other without. No patients in the IFN group died of hepatic failure. In the non-IFN group, 7 patients died of HCC and four of hepatic failure.

Figure 3B shows cumulative survival curves for the SVR, non-SVR and non-IFN groups. The rate of survival in the SVR group was significantly better than that in the non-IFN group ( $P = 0.029$ ), while no significant difference was evident between the non-SVR and non-IFN group ( $P = 0.248$ ).

Pretreatment factors found to be significantly associated with survival by univariate analysis subsequently were evaluated by Cox regression analysis to determine independent factors. Multivariate analysis showed that SVR status and Child-Pugh class A were independent factors favorably associated with long survival (Table 3).

### Liver function

Compared with the non-IFN group, patients who received IFN therapy were less likely to have worsening of hepatic dysfunction. For the SVR, non-SVR and non-IFN groups, we compared the average score for Child-Pugh classification at initial treatment of HCC with that at the time of data analysis. Median observation time was 59.8 mo in the SVR group, 45 mo in the non-SVR group, and 51.8 mo in the non-IFN group. There were no significant differences in the Child-Pugh classification score among these three groups at the time of initial treatment of HCC; however, at the time of data analysis, scores in the non-IFN group were significantly worse than in the SVR group ( $P = 0.003$ ). No significant difference was seen between the non-SVR and non-IFN groups (Figure 4).

## DISCUSSION

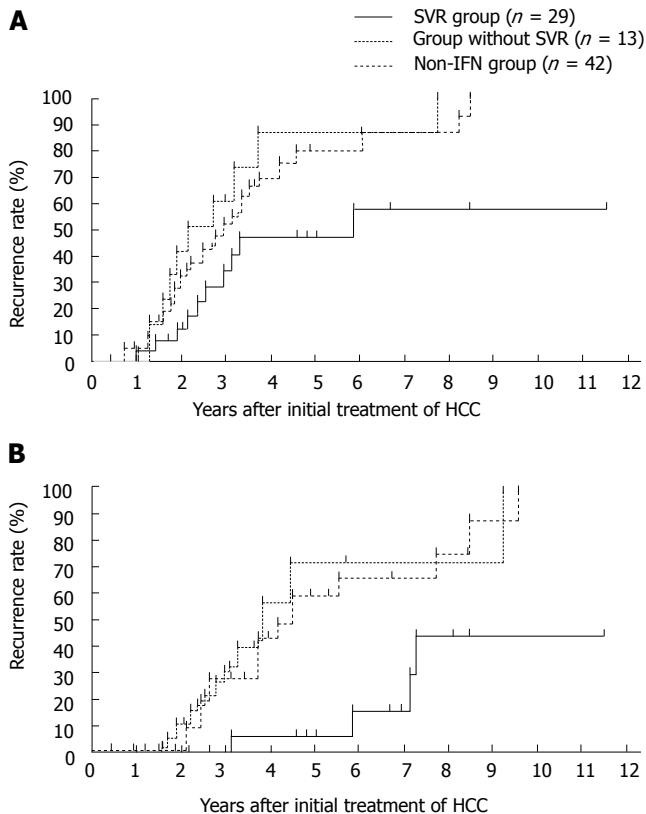
The present study compared historical control subjects with no IFN treatment with other subjects who were treated with IFN. Background characteristics showed no significant difference between the groups. IFN and non-IFN group did not differ significantly in their rate of first recurrence, but did differ significantly in their rate of second recurrence. According to IFN response, the recurrence rate in the SVR group was significantly lower than that in the non-SVR and non-IFN group, while recurrence rates in the non-SVR and non-IFN group did not differ significantly. Thus, SVR (i.e., HCV eradication) was the most important, and only, inhibiting factor for decreasing risk of HCC recurrence, associated with a 24-wk course of IFN- $\alpha$  therapy following HCC treatment.

Although several recent studies have reported the

Table 2 Factors associated with second recurrence

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
SVR	0.454	0.246-0.728	0.0005	0.457	0.243-0.757	0.0015
PLT > 100 000/ $\mu$	0.553	0.373-0.814	0.003	0.694	0.445-1.069	0.0973
ICG R-15 (< 20%)	0.667	0.450-0.965	0.032	0.685	0.447-1.035	0.0721

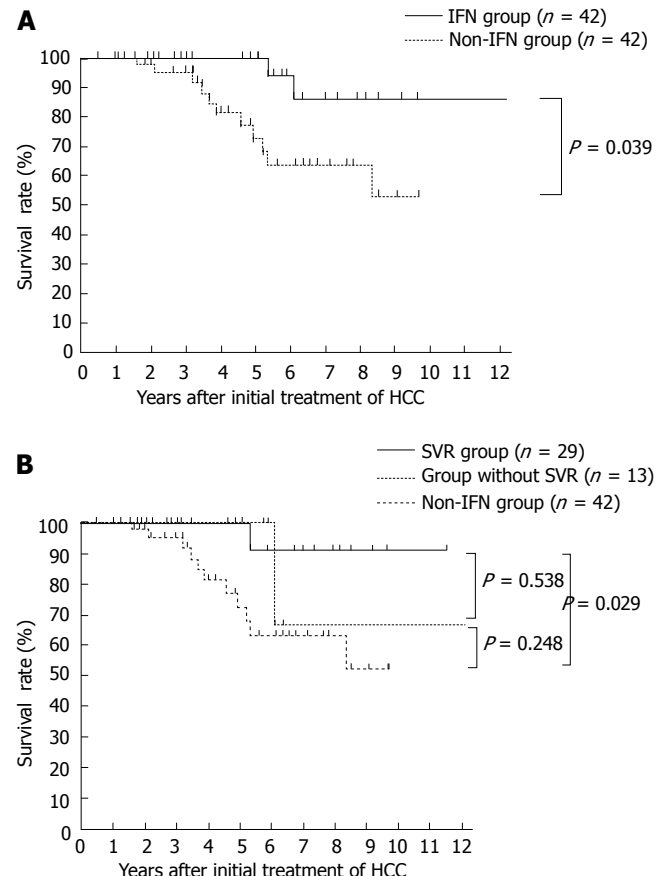
Cox's proportional hazards model was used.



**Figure 2** Cumulative recurrence rates according to SVR to IFN therapy after curative treatment of HCC. **A:** Rates of first recurrence compared among SVR, non-SVR and non-IFN groups. The rate of first recurrence of HCC in the SVR group was significantly lower than in the non-SVR and non-IFN groups ( $P = 0.002$ ,  $P = 0.016$ , respectively). No significant difference in first recurrence rate was seen between the non-SVR and non-IFN groups ( $P = 0.381$ ); **B:** Rates of second recurrence compared among the three groups. Second recurrence of HCC was suppressed in the SVR group compared with the non-SVR and non-IFN groups ( $P = 0.0037$ ,  $P = 0.0019$ , respectively), and to a more pronounced degree than for the first recurrence rate. No significant difference in second recurrence rate was seen between the non-SVR and non-IFN groups ( $P = 0.90$ ).

efficacy of chemoprevention with IFN after treatment of HCV-related HCC, the basis of this benefit has not been determined, since IFN has a variety of biologic effects, including antiviral, antiproliferative, immunomodulatory<sup>[19-22]</sup> and anti-fibrogenic<sup>[23,24]</sup> activities; growth inhibition through changes in signal transduction<sup>[19,25,26]</sup>; and activation of natural killer cells<sup>[27]</sup> and T cells<sup>[28,29]</sup>. Through these various effects, IFN therapy is thought to suppress tumor recurrence directly and/or indirectly.

Sakaguchi *et al.*<sup>[15]</sup> have reported that low-dose, long-term, intermittent IFN- $\alpha$  therapy can, by a direct anti-cancer effect, inhibit intrahepatic metastasis but not



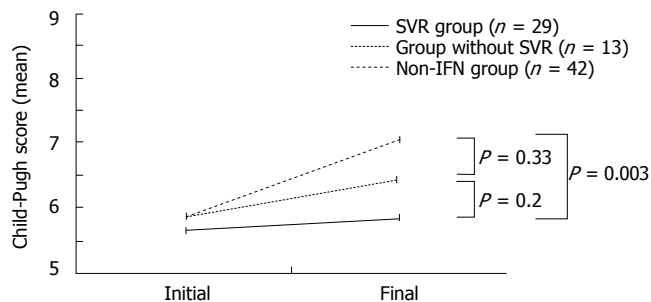
**Figure 3** Cumulative survival rates after curative treatment of HCC. **A:** Comparison of cumulative survival rates in the IFN and non-IFN groups. The cumulative survival rate was significantly higher in the IFN group than in the non-IFN group ( $P = 0.039$ ); **B:** Comparison of cumulative survival rates in the SVR, non-SVR and non-IFN groups. Although no significant overall difference was found between the SVR and non-SVR groups ( $P = 0.538$ ), the SVR group had a particularly high survival rate compared with the non-IFN group ( $P = 0.029$ ).

multicentric occurrences. Lai *et al.*<sup>[29]</sup> have reported that IFN- $\alpha$  therapy is effective in advanced HCC. Several experimental studies have shown that IFN inhibits the growth of a human hepatoma cell line<sup>[11,15]</sup>. In partial disagreement, however, Nishiguchi *et al.*<sup>[12,14]</sup>, Suou *et al.*<sup>[16]</sup> and Shiratori *et al.*<sup>[17]</sup> have reported that the rate of HCC recurrence was not different between IFN and non-IFN group during the first few years, but later became significantly lower in the IFN group. They suggested that IFN reduced HCC recurrence in the later period of observation by suppressing multicentric occurrence, as an indirect anti-tumor effect that was related to sustained hepatic inflammation. Although the present study did not have a randomized controlled design, and details of the

Table 3 Factors associated with survival

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
SVR	0.409	0.096-0.922	0.028	0.329	0.076-0.761	0.006
Child-Pugh class A	0.521	0.299-0.922	0.027	0.463	0.238-0.875	0.019
ICG R-15 (< 20%)	0.551	0.286-0.968	0.038	0.724	0.351-1.429	0.350

Cox's proportional hazards model was used.



**Figure 4** Influence of IFN therapy after curative treatment of HCC on Child-Pugh scores. IFN-treated patients were less likely to show deterioration of hepatic function. In particular, liver function scores in the SVR group were significantly better preserved than in the non-IFN group ( $P = 0.003$ ). Median observation time was 59.8 mo in the SVR group, 45 mo in the non-SVR group, and 51.8 mo in the non-IFN group.

IFN protocol differed from those of others, the long-term results appear to be similar among studies. Recurrence during the first few years might involve undetectable intrahepatic metastasis, or a potential malignant tumor already existing at the time of treatment of the primary HCC; afterward, HCC might recur as multicentric new liver tumor, accompanied by sustained hepatic necrosis and inflammation. Although a direct anti-cancer effect of IFN might to some extent have directly inhibited HCC recurrence, our IFN doses were insufficient to suppress intrahepatic metastatic tumors because there was only a 24-wk treatment. Therefore, in our study, we believe that IFN therapy suppressed HCC recurrence less by a direct anti-tumor effect than by an indirect effect through inhibition of the chronic inflammation associated with HCV infection in the later period of observation.

Several studies have reported that recurrence was suppressed not only in virologic responders to IFN, but also in biochemical responders, even though HCV was not eradicated<sup>[12-14]</sup>. However, the recurrence rates in our study did not differ significantly between biochemical responders and the non-IFN group. HCV eradication appeared to stand alone as an IFN effect capable of inhibiting recurrence, with eradication having a stronger influence against second recurrence than the first. The differences between the results of the various studies might be due to several reasons. In most previous studies, IFN therapy was given for more than 48 wk, compared with our 24 wk. Differences may also have been present in underlying hepatic inflammatory conditions such as chronic hepatitis and cirrhosis. Although such differences introduce some uncertainty to the conclusions, several recent studies suggest that HCV core protein might directly participate in hepatocarcinogenesis<sup>[28,29]</sup>, which supports the importance

of virus eradication.

Although some other recent studies have reported that IFN therapy following HCC treatment also improves liver function and survival of patients with HCV-related HCC, which of the specific IFN actions is important for these benefits remains unknown. We found that overall survival rate and preservation of liver function were significantly better in the SVR group than in the other groups, even including biochemical responders, with all subgroups without SVR resembling non-IFN patients. Favorable independent factors associated with survival by multivariate analysis were SVR and Child-Pugh class A. Thus, with a 24-wk course of IFN- $\alpha$  therapy, HCV eradication appears necessary for prolonging survival, suppressing HCC recurrence, and preserving liver function.

As stated above, effective management of HCV infection is needed, as well as direct treatment of the primary HCC. Although our study had limitations, such as the use of historical controls and a small number of patients, we could demonstrate a clear requirement for HCV eradication to improve survival after a short-course IFN- $\alpha$  therapy. Ribavirin combination or pegylated IFN therapy are considered more effective in HCV eradication than conventional IFN monotherapy<sup>[32-34]</sup>. Several studies have indicated that pegylated IFN therapy is superior to conventional IFN when administered for 48 wk<sup>[34-41]</sup>. Pegylated IFN therapy, with or without ribavirin, may improve prognosis in selected patients with no sustained initial response to conventional IFN. For patients who cannot undergo standard-dose IFN therapy because of limited hepatic reserve or thrombocytopenia, low-dose IFN therapy for a longer course might be effective. Nonetheless, further studies with larger controlled groups and long-term follow-up need to be performed to establish what constitutes optimal management of HCV infection after HCC treatment.

## COMMENTS

### Background

Risk of multicentric recurrence of hepatocellular carcinoma (HCC) and liver function deterioration remains high in hepatitis C virus (HCV)-infected patients even after receiving curative treatment for primary HCC. Most intrahepatic recurrences occurred during persistent viral infection. Although several recent studies have reported the efficacy of chemoprevention with interferon (IFN) therapy after treatment of HCV-related HCC, there was no standard IFN regimen. We investigated whether 24-week course of IFN- $\alpha$  therapy following curative treatment for primary HCC associated with HCV infection could suppress HCC recurrence and improve prognosis.

### Research frontiers

To obtain sustained virological response (SVR) was important for suppression of HCC recurrence and for long-term survival in a 24-week course of IFN- $\alpha$  therapy.

### Innovations and breakthroughs

Our study demonstrated that only SVR status by a 24-wk IFN- $\alpha$  therapy was the most important factor for decreasing risk of HCC recurrence in the later period of observation including second recurrence.

### Applications

This study demonstrated that compared with non-IFN and non-SVR group, SVR group decreased the rate of recurrence, preserved liver function, and prolonged survival time in a 24-wk course of IFN- $\alpha$  therapy.

### Peer review

This is a matched historical case controlled study concerning about the effect of 24-week short course IFN- $\alpha$  therapy after receiving curative treatment for primary HCC. The paper is well written and the results show that the most important factor associated with the improvement of prognosis is the SVR status.

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