for PTA. When a patient was indicated for both surgery and PTA, the modality of treatment was determined by patient choice after obtaining fully informed consent. PEIT was carried out under US guidance using a 15- or 20-cm-long needle (21 gauge) (Hakko, Chikuma, Japan) [35], PMCT was performed under US guidance using a 15-cm-long guide needle (14 gauge) according to the procedure described previously [37], and RFA was executed under US guidance using a 15- or 20-cm-long guide needle (16 gauge) (Tyco Healthcare Japan, Tokyo, Japan) [36]. PTA was repeated until complete necrosis of all HCC lesions was confirmed by dynamic CT. Treatment of HCC was considered curative, when no viable HCC lesions were detected on dynamic CT 3 months after completion of the treatment.

Of the 395 patients receiving curative treatment for HCC, 124 had received either human lymphoblastoid IFN, recombinant IFN-alpha 2a, or recombinant IFN-alpha 2b monotherapy for chronic HCV infection before the development of HCC (IFN-treated group), whereas 271 had not (IFN-untreated group) (Fig. 1). Patients received 6 million units of IFN by intramuscular injection three times weekly for 24 weeks as outpatients. If patients could not tolerate this dose, the IFN dose was reduced to 3 million units. SVR was defined as HCV RNA (as determined by RT-PCR; detection limit, 10^2 copies/ml) negativity for over 6 months after the termination of IFN therapy. SVR was achieved in 17 of the 124 patients (SVR group) and the remaining 107 were regarded as non-SVR (non-SVR group) (Fig. 1).

Follow-up of Patients

Patients attended a monthly medical consultation at the Okayama University Hospital outpatient clinic. Blood biochemical markers, including α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), were measured every 1–2 months; US was performed every 2–3 months, and dynamic CT was performed every 6 months. If HCC recurrence was suspected, further imaging examinations including dynamic CT, magnetic resonance imaging, abdominal angiography, or US-guided tumor biopsy were performed to confirm the diagnosis.

New HCC foci as well as local recurrent nodules at tumor, node, metastasis (TNM) stage I, II, and III, were mainly treated by a second course of PTA; local recurrent nodules at TNM stage IV were treated with transarterial chemoembolization or chemotherapy. Further development of HCC and survival of patients (tumor recurrence rate and survival rate) were analyzed in relation to the time interval after treatment of HCC.

Table 1 Demographic and clinical characteristics of patients with HCV-related HCC

Groups	IFN-treated		IFN-untreated (n = 271)	p^a	p^b
	SVR (n = 17)	Non-SVR (n = 107)			
Characteristics					
Sex (men/women), n	13/4	60/47	187/84	0.049	0.112
Age (years)	63 (52–71)	65 (46–82)	67 (33–85)	0.018	0.061
Laboratory data					
Total bilirubin (mg/dl)	0.74 (0.40–1.29)	0.85 (0.36–3.28)	0.91 (0.16–4.13)	0.194	0.171
Albumin (g/dl)	4.4 (3.7–4.8)	3.7 (2.5–4.8)	3.6 (2.2–4.7)	<0.001	<0.001
Prothrombin time (%)	93 (70–121)	85 (47–142)	85 (40–145)	0.355	0.023
ALT (IU/l)	22 (10–54)	55 (12–198)	60 (14–201)	0.058	<0.001
Platelet count ($\times 10^4/\mu l$)	16.6 (8.4–30.3)	9.2 (2.8–37.2)	10.1 (3.2–31.9)	0.980	<0.001
Child–Pugh stage (A/B/C), n	17/0/0	87/20/0	213/54/4	0.236	0.049
Tumor-related variables					
Number of tumors (single/multiple), n	15/2	76/31	192/79	0.603	0.136
Size of largest tumor (mm)	20 (8–40)	18 (10–53)	20 (9–74)	0.033	0.942
AFP (ng/ml)	13 (1.9–25,716)	24 (1.7–3,480)	20 (0.6–54,535)	0.956	0.297
DCP (mAU/ml)	34 (1–35,000)	46 (10–56,000)	46 (1–66,700)	0.294	0.195
Initial treatment of HCC					
PTA/surgical resection, n	6/11	79/28	207/64	0.100	0.002

Laboratory data and tumor-related variables are at the development of HCC. Continuous variables are given as medians with ranges

HCV hepatitis C virus, *HCC* hepatocellular carcinoma, *IFN* interferon, *SVR* sustained virological response, *ALT* alanine aminotransferase, *AFP* α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *PTA* percutaneous tumor ablation

[a] IFN-treated versus IFN-untreated

[b] SVR versus non-SVR

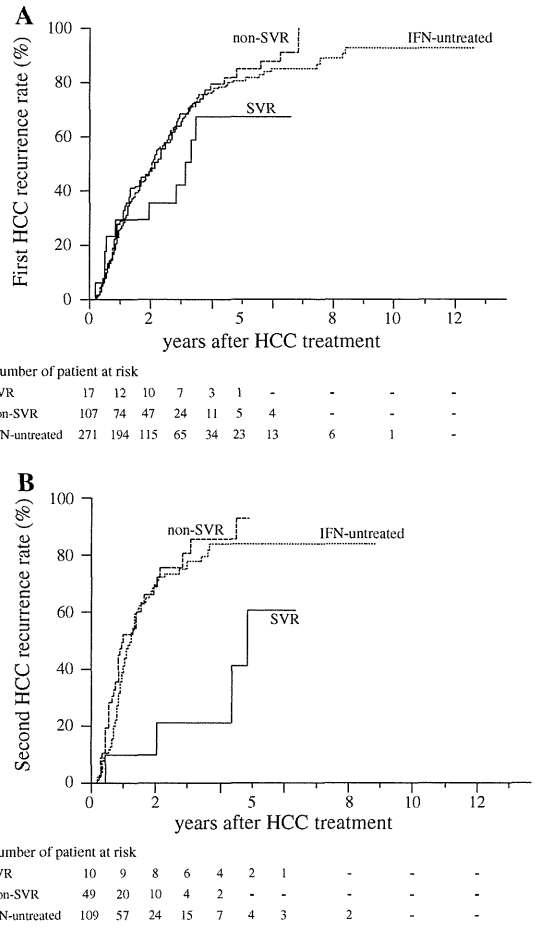

Fig. 2 Cumulative first (**a**, $n = 395$) and second (**b**, $n = 168$) HCC recurrence rates in patients with curative treatment of HCC according to the previous IFN treatment and response to the treatment. The first HCC recurrence rates were similar among SVR, non-SVR, and IFN-untreated groups (**a**). However, the second HCC recurrence rate in the SVR group at 2 years after HCC treatment was significantly lower than that in the non-SVR group (10 vs. 69%, $p = 0.003$) and the IFN-untreated group (10 vs. 70%, $p = 0.006$) (**b**)

Statistical Analysis

Statistical analysis was performed using JMP statistical discovery software, version 8.0 (SAS Institute Inc., Cary, NC). Differences between two groups were evaluated using the unpaired Student's t test or the Mann–Whitney U test. The Chi-square test or the Fisher's exact probability test was used to compare categorical data. Cumulative incidence curves were determined with the Kaplan–Meier method, and the differences between patient groups were assessed using the logrank test. Possible risk factors for recurrence of HCC and survival included both IFN-related variables and variables at the development and recurrence of HCC (age, total bilirubin level, albumin level, prothrombin time, ALT level, platelet count, number of tumors, largest tumor size, AFP level, and DCP level). Tumor associated variables, number of tumors and size of largest tumor, were transformed into categorical data consisting of two ordinal numbers by the median value. Variables exhibiting p values less than 0.10 in univariate analysis were subjected to a stepwise Cox proportional hazards regression analysis. A risk ratio with a 95% confidence interval was denoted for each analysis. p values less than 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics of patients at the development of HCC are shown in Table 1. The patient group comprised 260 men and 135 women (73 men and 51 women in the IFN-treated group), and median age was 58 years (65 years in the IFN-treated group). Of the 395 patients (80%), 317 were classified as Child–Pugh stage A. Significant differences were observed between IFN-treated and untreated patients in sex, age, albumin level, and size of largest tumor. On the other hand, significant differences were observed between IFN-treated patients with SVR and non-SVR in albumin level, prothrombin time, ALT level, platelet count, Child–Pugh stage, and initial treatment of HCC. This indicated better hepatic functional reserve in SVR patients than in non-SVR patients.

The median follow-up period after curative treatment of HCC for patients with and without IFN treatment was 3.8 years and 3.5 years, respectively. In the IFN-treated group, patients underwent IFN therapy 7.2 (0.8–17.4) (median and range) years before development of HCC. Of the 395 patients, 277 (70%) had recurrence of HCC during a median follow-up period of 2.1 (1.8–2.4) years [including 86 of 124 IFN-treated patients (69%)]. Of the 168 patients receiving curative treatment for the first recurrence of HCC, 113 (67%) had a second HCC recurrence during a median follow-up period of 1.3 (1.0–1.4) years [including 38 of 59 IFN-treated patients (64%)] (Fig. 1).

HCC Recurrence Rates

The rates of the first and second HCC recurrence after curative treatment of primary HCC in each treatment group are shown in Fig. 2. In the IFN-treated group, 86 patients (10 with SVR and 76 with non-SVR) had the first HCC recurrence and 38 (four with SVR and 34 with non-SVR) had the second HCC recurrence during the follow-up period. The average times to the first and second HCC recurrence were 632 and 1,069 days, 661 and 401 days, and 666 and 428 days in SVR, non-SVR, and IFN-untreated groups, respectively. The rates of the first recurrence at 2 years in SVR, non-SVR, and IFN-untreated groups were 36, 47, and 48%, respectively. The differences between these rates were not statistically significant

($p = 0.410$) (Fig. 2a). However, the rates of the second HCC recurrence at 2 years were significantly lower in the SVR group than in the non-SVR group (10 vs. 69%, $p = 0.003$) and in the IFN-untreated group (10 vs. 70%, $p = 0.006$) (Fig. 2b). There was no significant difference in the second HCC recurrence rates between non-SVR and IFN-untreated groups ($p = 0.441$). In multivariate analysis, platelet count ($p = 0.033$) and number of tumors ($p = 0.001$) were independent factors associated with the first recurrence of HCC (Table 2), whereas SVR to previous IFN therapy ($p = 0.002$) was the only factor associated with lower risk for the second recurrence of HCC (Table 3).

Overall Survival

Survival rates after curative treatment of primary HCC in each group are shown in Fig. 3. A tendency was observed toward a higher survival rate in the IFN-treated group than in the IFN-untreated group but it was not significant ($p = 0.053$) (Fig. 3a). In contrast, survival rates at 5 years were higher in the SVR group (100%) than in non-SVR (73%) and IFN-untreated groups (62%) ($p = 0.004$) (Fig. 3b). No significant difference was observed in the survival rates between non-SVR and IFN-untreated groups ($p = 0.450$). In multivariate analysis, SVR to previous IFN therapy ($p < 0.001$), albumin level ($p = 0.006$), number of tumors ($p = 0.007$), and AFP level ($p = 0.046$) were independent factors associated with overall death after curative treatment of primary HCC (Table 4).

Discussion

In the present study, we have demonstrated that patients with SVR to previous IFN treatment before development of HCC showed lower risk for the second recurrence of HCC and better survival compared to patients with non-SVR to previous IFN treatment or IFN-untreated patients. Several studies have demonstrated that IFN therapy reduces the risk of HCC development among chronic hepatitis C patients. On the other hand, a few reports are available on the influence of previous IFN therapy before the development of HCC on patient outcomes after curative treatment of HCV-related HCC. It was initially reported that HCV-related HCC patients who received IFN therapy before development of HCC showed lower recurrence rates and better survival rates, independent of response to IFN therapy, compared to those without previous IFN therapy [29, 30]. It has recently been reported that patients showing

Table 2 Risk factors for the first recurrence of HCC ($n = 395$)

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Sex (male)	1.17 (0.91–1.51)	0.229	–	
IFN-related variables				
IFN-untreated	1			
Non-SVR	1.07 (0.82–1.39)	0.623	–	
SVR	0.68 (0.34–1.22)	0.209	–	
Variables at the development of HCC				
Age (≥60 years)	1.13 (0.84–1.56)	0.434	–	
Total bilirubin (≥1.0 mg/dl)	1.07 (0.83–1.37)	0.579	–	
Albumin (<3.5 g/dl)	1.34 (1.04–1.71)	0.022	1.24 (0.95–1.61)	0.108
Prothrombin time (<70%)	1.07 (0.79–1.43)	0.664	–	
ALT (≥40 IU/l)	1.09 (0.83–1.43)	0.542	–	
Platelet count(<10 × 10^4/μl)	1.37 (1.08–1.75)	0.009	1.34 (1.04–1.75)	0.026
Tumor-related variables				
Number of tumors (multiple vs. single)	1.66 (1.27–2.15)	<0.001	1.63 (1.24–2.14)	0.001
Size of largest tumor (≥20 mm)	1.24 (0.98–1.57)	0.074	1.22 (0.94–1.59)	0.140
AFP (≥100 ng/ml)	1.45 (1.07–1.92)	0.016	1.30 (0.96–1.74)	0.093
DCP (≥40 mAU/ml)	1.33 (1.02–1.75)	0.034	1.11 (0.85–1.44)	0.448
Initial treatment of HCC				
PTA/surgical resection	1.09 (0.84–1.43)	0.530	–	

HCC hepatocellular carcinoma, *IFN* interferon, *SVR* sustained virological response, *ALT* alanine aminotransferase, *AFP* α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *PTA* percutaneous tumor ablation, *CI* confidence interval

Table 3 Risk factors for the second recurrence of HCC ($n = 168$)

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Sex (male)	1.07 (0.73–1.61)	0.719	–	
IFN-related variables				
IFN-untreated	1		1	
Non-SVR	1.17 (0.77–1.74)	0.447	1.09 (0.68–1.72)	0.718
SVR	0.27 (0.08–0.65)	0.002	0.10 (0.01–0.50)	0.002
Variables at the development of HCC				
Age (≥60 years)	1.50 (0.91–2.61)	0.115	–	
Total bilirubin (≥1.0 mg/dl)	1.08 (0.72–1.60)	0.701	–	
Albumin (<3.5 g/dl)	1.04 (0.68–1.57)	0.847	–	
Prothrombin time (<70%)	1.18 (0.70–1.89)	0.529	–	
ALT (≥40 IU/l)	1.30 (0.86–2.01)	0.220	–	
Platelet count ($<10 \times 10^4/\mu l$)	1.00 (0.69–1.47)	0.984	–	
Number of tumors (multiple vs. single)	1.57 (1.04–2.32)	0.033	1.51 (0.93–2.42)	0.098
Size of largest tumor (≥20 mm)	0.91 (0.63–1.32)	0.613	–	
AFP (≥100 ng/ml)	0.65 (0.38–1.06)	0.084	0.77 (0.39–1.39)	0.391
DCP (≥40 mAU/ml)	0.81 (0.54–1.23)	0.331	–	
Initial treatment of HCC				
PTA/surgical resection	1.12 (0.75–1.69)	0.595	–	
Variables at the first recurrence of HCC				
Age (≥60 years)	0.97 (0.46–2.39)	0.950		
Total bilirubin (≥1.0 mg/dl)	0.94 (0.59–1.46)	0.785	–	
Albumin (<3.5 g/dl)	1.67 (1.06–2.61)	0.029	1.47 (0.90–2.36)	0.125
Prothrombin time (<70%)	1.24 (0.60–2.30)	0.531	–	
ALT (≥40 IU/l)	1.49 (0.95–2.40)	0.083	1.21 (0.75–2.01)	0.452
Platelet count ($<10 \times 10^4/\mu l$)	1.13 (0.74–1.73)	0.573	–	
Number of tumors (multiple vs. single)	2.09 (1.37–3.13)	<0.001	1.47 (0.91–2.34)	0.112
Size of largest tumor (≥20 mm)	0.96 (0.62–1.45)	0.840	–	
AFP (≥100 ng/ml)	0.72 (0.32–1.41)	0.355	–	
DCP (≥40 mAU/ml)	1.05 (0.67–1.63)	0.842	–	

HCC hepatocellular carcinoma, *IFN* interferon, *SVR* sustained virological response, *ALT* alanine aminotransferase, *AFP* α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *PTA* percutaneous tumor ablation, *CI* confidence interval

biochemical response, with or without SVR to previous IFN therapy, showed higher tumor-free survival rates after surgery than those without such a response to IFN or those without previous IFN therapy [31, 32]. In these previous reports, a biochemical response as well as SVR to previous IFN therapy was associated with favorable outcome, demonstrating the importance of response to previous IFN therapy for the outcome after surgery of HCV-related HCC.

However, in the present study, patients with non-SVR showed similar recurrence and survival rates as IFN-untreated patients. Furthermore, no difference was observed in the recurrence and survival rates among non-SVR patients with and without biochemical response to previous IFN therapy (data not shown). In fact, only patients with SVR to previous IFN therapy showed better outcome than those with non-SVR or IFN-untreated patients. Therefore, the present data indicate that SVR but not biochemical response without SVR to previous IFN treatment is a predictor of favorable outcome in patients who have developed HCC.

The reason for the difference between the present and previous studies in the outcome of non-SVR patients with biochemical response to previous IFN therapy is currently unknown. In patients with HCV-related chronic hepatitis and cirrhosis, who received IFN therapy and showed normalization of ALT levels, suppression of primary HCC development and better survival rates have been independently demonstrated of eradication of HCV infection by the IFN therapy [10, 11, 13, 39]. However, this

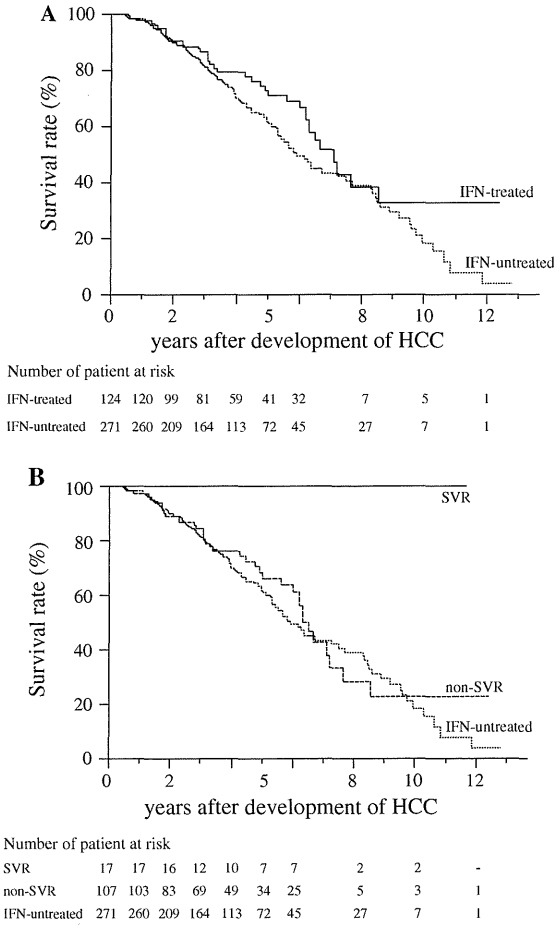

Fig. 3 Overall survival rates of HCV-related HCC patients ($n = 395$) according to their previous IFN treatment before development of HCC (**a**) and their response to the treatment (**b**). A tendency was observed toward a higher survival rate in the IFN-treated group than in the IFN-untreated group but it was not significant ($p = 0.053$) (**a**). On the other hand, the survival rate of the SVR group was significantly higher than those of non-SVR and IFN-untreated groups ($p = 0.004$) (**b**)

suppression observed for primary carcinogenesis in non-SVR patients with biochemical response to IFN therapy does not appear to be the case for secondary carcinogenesis in the present study. The period after IFN therapy was much longer in the present study than in the previous reports on primary carcinogenesis. The IFN therapy had preceded to the HCC development, that should have required long incubation after the termination of IFN treatment, and in the present study the observation of HCC recurrence and survival started with the curative treatment of the primary HCC. In patients who had sustained biochemical response but had not eradicated HCV infection, we and others demonstrated that platelet count transiently increases following IFN therapy but decrease over the following 3 years after the termination of IFN therapy. On the other hand, in patients with SVR an increase followed by persistence in platelet counts was observed [40, 41]. These observations suggest the progression of fibrosis during a longer incubation period after IFN therapy, even in the non-SVR patients with biochemical response to the therapy. Therefore, the suppressive effect of IFN therapy on development of HCC may not persist beyond the development of primary HCC particularly in these patients.

It has also been demonstrated that HCV core transgenic mice can develop HCC without apparent hepatitis [42]. Therefore, besides active hepatitis, which involves persistent hepatocyte death and regeneration, and should result in both genetic and epigenetic disorders as well as increased oxidative stress, the presence and persistence of HCV infection and viral products such as core protein may themselves play an important role in the development of HCC in non-SVR patients with biochemical response. Thus, patients with SVR who had eradicated HCV infection should have a lower incidence of HCC recurrence and higher survival rates than non-SVR patients with biochemical response.

In the present study, patients with SVR showed a better overall survival rate than other groups. However, although patients with SVR showed lower rates of the second HCC recurrence, this was not the case for the first HCC recurrence. Although both SVR and non-SVR groups have a carcinogenic background during the development of primary HCC, the carcinogenic potential in SVR patients may be gradually attenuated because of the eradication of HCV infection, whereas it may increase in those with non-SVR because of persistence of HCV infection and relapse of hepatitis, finally leading to progression of fibrosis over a longer period. However, a substantial time may be required before differences between patients with and without SVR become apparent, and these differences eventually become significant in the second recurrence of HCC.

It should also be noted that IFN-treated patients enrolled in the present and previous studies are a selected cohort, since the incidence rates of HCC development in patients treated with IFN should be lower than in those untreated with IFN [13]. This is particularly the case for patients with SVR to previous IFN treatment, whose risk for development of HCC is less than one fifth of that for IFN-untreated patients [13]. Reported risk factors for HCC development in patients who received IFN therapy include advanced fibrosis, lower platelet count, advanced age, male gender, and regular drinking [8, 9, 12, 13, 43]. Therefore, in the present study, HCC patients who received IFN therapy before the development of HCC may have demonstrated many of these characteristics, making them more prone to develop HCC than those not developing HCC after IFN therapy and not included in this study. Furthermore, it has been suggested that cirrhotic patients who develop primary

Table 4 Analysis of factors associated with overall death after curative treatment for primary HCC ($n = 395$)

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Sex (male)	1.02 (0.73–1.44)	0.911	–	
IFN-related variables				
IFN-untreated	1		1	
Non-SVR	0.86 (0.59–1.24)	0.445	1.05 (0.71–1.54)	0.794
SVR	<0.01 (0–0.17)	<0.001	<0.01 (0–0.26)	<0.001
Variables at the development of HCC				
Age (≥60 years)	1.06 (0.72–1.63)	0.773	–	
Total bilirubin (≥1.0 mg/dl)	1.45 (1.04–2.01)	0.028	1.21 (0.82–1.76)	0.332
Albumin (<3.5 g/dl)	2.07 (1.49–2.89)	<0.001	1.70 (1.16–2.49)	0.007
Prothrombin time (<70%)	1.44 (0.99–2.06)	0.059	0.97 (0.65–1.43)	0.874
ALT (≥40 IU/L)	1.12 (0.78–1.67)	0.531	–	
Platelet count (<10 × 10^4 μl)	1.72 (1.23–2.41)	0.001	1.35 (0.93–1.96)	0.118
Tumor-related variables				
Number of tumors (multiple vs. single)	1.59 (1.10–2.26)	0.014	1.71 (1.16–2.46)	0.007
Size of largest tumor (≥20 mm)	1.15 (0.83–1.60)	0.395	–	
AFP (≥100 ng/ml)	1.71 (1.17–2.45)	0.006	1.50 (1.00–2.18)	0.047
DCP (≥40 mAU/ml)	1.33 (0.91–1.98)	0.145	–	
Initial treatment of HCC				
PTA/surgical resection	1.69 (1.16–2.53)	0.006	1.03 (0.68–1.60)	0.882

HCC hepatocellular carcinoma, *IFN* interferon, *SVR* sustained virological response, *ALT* alanine aminotransferase, *AFP* α-fetoprotein, *DCP* des-γ-carboxy prothrombin, *PTA* percutaneous tumor ablation, *CI* confidence interval

HCC may already be at a "carcinogenic stage" and have a higher potential to develop intrahepatic multicentric carcinogenesis than those without HCC [15]. Patients who have already developed HCC may have background features such as greater age and impaired liver function because of more advanced fibrosis. Therefore, the observed recurrence and survival rates in the present study are those of selected patients who were already at the carcinogenic stage, and are thus biased in comparison to previous observations on primary prevention of HCC development in patients who had received IFN therapy. Recently, Imai et al. reported that an inhibitory effect of IFN therapy on development of HCC in older patients was limited to patients with SVR [44]. This also supports the notion that patients already at a carcinogenic stage or with risk factors associated with HCC development, such as greater age or advanced fibrosis, require eradication of HCV infection in order to achieve a significantly better prognosis.

The present observation highlights the importance of eradication of HCV in order to prevent HCC recurrence and to achieve better survival in this patient group. Plenty of reports are available that demonstrated the favorable effect of IFN therapy on the recurrence of HCC and survival particularly in patients who achieved SVR [21–28]. Therefore, re-treatment with more potent IFN therapies, such as combination therapy of PEGylated IFN plus ribavirin [45], should be recommended for patients who previously underwent IFN treatment without achieving SVR.

The present study has limitations as it is retrospective in nature, and thus, patients enrolled were biased in favor of experience of IFN treatment, and also HCC patients with previous IFN treatment were a selected population from a large cohort of patients who had undergone IFN treatment. Also, information on the histological data that may have influence on the outcome of HCC patients was not available in the present study. Further prospective studies are required to address these issues.

In conclusion, the present study demonstrated that patients with SVR to IFN treatment before the development of HCV-related HCC showed lower second HCC recurrence rates and higher survival rates than those with non-SVR to previous IFN treatment or IFN-untreated patients. Therefore, treatment with potent antiviral therapy is recommended for patients in the latter groups in order to suppress recurrence and improve survival by eradicating HCV infection.

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References

1. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Semin Liver Dis.* 1995;15:64–69. doi:10.1055/s-2007-1007263.
2. Shiratori Y, Shiina S, Imamura M, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. *Hepatology.* 1995;22:1027–1033.
3. Tanaka K, Hirohata T, Koga S, et al. Hepatitis C and hepatitis B in the etiology of hepatocellular carcinoma in the Japanese population. *Cancer Res.* 1991;51:2842–2847.
4. Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med.* 1991;325:675–680. doi:10.1056/NEJM199109053251002.
5. Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med.* 1993;328:1797–1801. doi:10.1056/NEJM199306243282501.
6. Shiratori Y, Imazeki F, Moriyama M, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med.* 2000;132:517–524.
7. International Interferon-alpha Hepatocellular Carcinoma Study Group. Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. *Lancet.* 1998;351:1535–1539.
8. Imai Y, Kawata S, Tamura S, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. *Ann Intern Med.* 1998;129:94–99.
9. Kasahara A, Hayashi N, Mochizuki K, et al. Risk factors for hepatocellular carcinoma and its incidence after interferon treatment in patients with chronic hepatitis C. Osaka Liver Disease Study Group. *Hepatology.* 1998;27:1394–1402. doi:10.1002/hep.510270529.
10. Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet.* 1995;346:1051–1055.
11. Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. *Lancet.* 2001;357:196–197. doi:10.1016/S0140-6736(00)03595-9.
12. Okanoue T, Itoh Y, Minami M, et al. Interferon therapy lowers the rate of progression to hepatocellular carcinoma in chronic hepatitis C but not significantly in an advanced stage: a retrospective study in 1148 patients. Viral Hepatitis Therapy Study Group. *J Hepatol.* 1999;30:653–659.
13. Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. *Ann Intern Med.* 1999;131:174–181.
14. Belghiti J, Panis Y, Farges O, Benhamou JP, Fekete F. Intrahepatic recurrence after resection of hepatocellular carcinoma complicating cirrhosis. *Ann Surg.* 1991;214:114–117.
15. Ikeda K, Arase Y, Kobayashi M, et al. Significance of multicentric cancer recurrence after potentially curative ablation of hepatocellular carcinoma: a long-term cohort study of 892 patients with viral cirrhosis. *J Gastroenterol.* 2003;38:865–876. doi:10.1007/s00535-003-1163-2.
16. Lam VWT, Ng KKC, Chok KSH, et al. Risk factors and prognostic factors of local recurrence after radiofrequency ablation of hepatocellular carcinoma. *J Am Coll Surg.* 2008;207:20–29. doi:10.1016/j.jamcollsurg.2008.01.020.
17. N'Kontchou G, Mahamoudi A, Aout M, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology.* 2009;50:1475–1483. doi:10.1002/hep.23181.
18. Okada S, Shimada K, Yamamoto J, et al. Predictive factors for postoperative recurrence of hepatocellular carcinoma. *Gastroenterology.* 1994;106:1618–1624.
19. Shiina S, Tagawa K, Niwa Y, et al. Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. *AJR Am J Roentgenol.* 1993;160:1023–1028.
20. Kubo S, Nishiguchi S, Shuto T, et al. Effects of continuous hepatitis with persistent hepatitis C viremia on outcome after resection of hepatocellular carcinoma. *Jpn J Cancer Res.* 1999;90:162–170.
21. Breitenstein S, Dimitroulis D, Petrowsky H, Puhan MA, Mullhaupt B, Clavien PA. Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. *Br J Surg.* 2009;96:975–981. doi:10.1002/bjs.6731.
22. Ikeda K, Arase Y, Saitoh S, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor-A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology.* 2000;32:228–232. doi:10.1053/jhep.2000.9409.
23. Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg.* 2002;89:418–422. doi:10.1046/j.0007-1323.2001.02054.x.
24. Kubo S, Nishiguchi S, Hirohashi K, et al. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med.* 2001;134:963–967.
25. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology.* 2006;44:1543–1554. doi:10.1002/hep.21415.
26. Shen YC, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. *J Hepatol.* 2010;52:889–894. doi:10.1016/j.jhep.2009.12.041.
27. Shiratori Y, Shiina S, Teratani T, et al. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med.* 2003;138:299–306.
28. Singal AK, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. *Aliment Pharmacol Ther.* 2010;32:851–858. doi:10.1111/j.1365-2036.2010.04414.x.
29. Komorizono Y, Sako K, Yamasaki N, et al. Outcome of patients with hepatitis C virus-related hepatocellular carcinoma occurring after interferon therapy. *Anticancer Res.* 2002;22:3573–3578.
30. Kubo S, Nishiguchi S, Hirohashi K, et al. Influence of previous interferon therapy on recurrence after resection of hepatitis c virus-related hepatocellular carcinoma. *Jpn J Cancer Res.* 2001;92:59–66.
31. Uenishi T, Kubo S, Hirohashi K, et al. Relationship between response to previous interferon therapy and postoperative recurrence of hepatitis C virus-related hepatocellular carcinoma. *Hepatol Res.* 2002;24:404–412.
32. Uenishi T, Nishiguchi S, Tamori A, et al. Influence of interferon therapy on outcome after surgery for hepatitis C virus-related hepatocellular carcinoma. *Hepatol Res.* 2006;36:195–200. doi:10.1016/j.hepres.2006.07.011.

33. Kato N, Yokosuka O, Omata M, Hosoda K, Ohto M. Detection of hepatitis C virus ribonucleic acid in the serum by amplification with polymerase chain reaction. *J Clin Invest.* 1990;86: 1764–1767. doi:10.1172/JCI114903.
34. Farmer DG, Rosove MH, Shaked A, Busuttil RW. Current treatment modalities for hepatocellular carcinoma. *Ann Surg.* 1994;219:236–247.
35. Lee MJ, Mueller PR, Dawson SL, et al. Percutaneous ethanol injection for the treatment of hepatic tumors: indications, mechanism of action, technique, and efficacy. *AJR Am J Roentgenol.* 1995;164:215–220.
36. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology.* 1999;210:655–661.
37. Seki T, Wakabayashi M, Nakagawa T, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer.* 1994;74:817–825.
38. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology.* 2000;32:1224–1229. doi: 10.1053/jhep.2000.20456.
39. Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. *Gastroenterology.* 2002;123:483–491.
40. Moriyama M, Matsumura H, Aoki H, et al. Long-term outcome, with monitoring of platelet counts, in patients with chronic hepatitis C and liver cirrhosis after interferon therapy. *Intervirology.* 2003;46:296–307. doi:10.1159/000073209.
41. Taniguchi H, Iwasaki Y, Fujiwara A, et al. Long-term monitoring of platelet count, as a non-invasive marker of hepatic fibrosis progression and/or regression in patients with chronic hepatitis C after interferon therapy. *J Gastroenterol Hepatol.* 2006;21: 281–287. doi:10.1111/j.1440-1746.2006.04201.x.
42. Moriya K, Fujie H, Shintani Y, et al. The core protein of hepatitis C virus induces hepatocellular carcinoma in transgenic mice. *Nat Med.* 1998;4:1065–1067. doi:10.1038/2053.
43. Iwasaki Y, Takaguchi K, Ikeda H, et al. Risk factors for hepatocellular carcinoma in Hepatitis C patients with sustained virologic response to interferon therapy. *Liver Int.* 2004;24:603–610. doi:10.1111/j.1478-3231.2004.0956.x.
44. Imai Y, Tamura S, Tanaka H, et al. Reduced risk of hepatocellular carcinoma after interferon therapy in aged patients with chronic hepatitis C is limited to sustained virological responders. *J Viral Hepat.* 2010;17:185–191. doi:10.1111/j.1365-2893.2009.01163.x.
45. Huang JF, Yu ML, Huang CF, et al. The efficacy and safety of pegylated interferon plus ribavirin combination therapy in chronic hepatitis c patients with hepatocellular carcinoma post curative therapies—a multicenter prospective trial. *J Hepatol.* 2011;54:219–226. doi:10.1016/j.jhep.2010.07.011.