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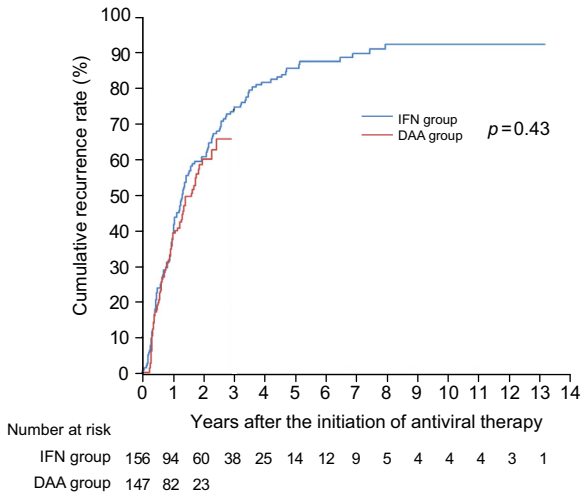
Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy

Graphical abstract



Highlights

- There was no significant difference in the early HCC recurrence rate and pattern between IFN-based and DAA therapy.
- High AFP-L3, short recurrence-free period, and history of multiple HCC treatments were risk factors for early recurrence.
- Eradication of HCV after curative HCC treatments could preserve liver function, regardless of antiviral therapy regimen.

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Lay summary

We detected no significant difference in early hepatocellular carcinoma (HCC) recurrence rates and patterns between patients who received interferon-based and direct-acting antiviral therapy after HCC treatment. High *lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein level, short recurrence-free period, and a history of multiple HCC treatments were independent risk factors for early HCC recurrence after the initiation of antiviral therapy.

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Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy

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Background & Aims: It remains controversial whether direct-acting antivirals (DAAs) accelerate the recurrence of hepatitis C-related hepatocellular carcinoma (HCC) after curative therapy. This study aimed to evaluate HCC recurrence after DAA treatment of chronic hepatitis C.

Methods: We enrolled patients with a history of successful radiofrequency ablation treatment for hepatitis C-related HCC who received antiviral therapy with DAAs (DAA group: 147 patients) or with interferon (IFN)-based therapy (IFN group: 156 patients). We assessed HCC recurrence rates from the initiation of antiviral therapy using the Kaplan-Meier method and evaluated risk factors for HCC recurrence by multivariate Cox proportional hazard regression analysis. The recurrence pattern was categorized as follows: intrahepatic recurrence with a single tumor <2 cm (stage 0), a single tumor or up to 3 tumors ≤3 cm (stage A), multinodular (stage B), and extrahepatic metastasis or macrovascular invasion (stage C).

Results: The recurrence rates at 1 and 2 years were 39% and 61% in the IFN group and 39% and 60% in the DAA group, respectively ($p = 0.43$). Multivariate analysis identified higher *lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein level, a history of multiple HCC treatments, and a shorter interval between HCC treatment and initiation of antiviral therapy as independent risk factors for HCC recurrence. HCC recurrence in stage 0, A, B, and C was found in 56 (41%), 60 (44%), 19 (14%), and 1 (0.7%) patients in the IFN group and 35 (44%), 32 (40%), 11 (14%), and 2 (2.5%) patients in the DAA group, respectively ($p = 0.70$).

Conclusions: HCC recurrence rates and patterns after initiation of antiviral therapy did not differ between patients who received IFN-based therapy and DAA therapy.

Lay summary: We detected no significant difference in early hepatocellular carcinoma (HCC) recurrence rates and patterns between patients who received interferon-based and direct-acting antiviral therapy after HCC treatment. High *lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein level, short recurrence-free period, and a history of multiple HCC treatments were independent risk factors for early HCC recurrence after the initiation of antiviral therapy.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and a leading cause of cancer-related death.[1] HCC usually develops in patients with chronic liver diseases, often related to hepatitis C virus (HCV) infection.[2,3] Although interferon (IFN)-based therapy after HCC treatment reportedly reduces the risk of HCC recurrence,[4–6] few patients were eligible for IFN therapy after HCC treatment because of aging or advanced liver fibrosis, and its antiviral effect was inversely associated with the rates of adverse effects.[7] Currently, with the development of direct-acting antivirals (DAAs), patients with a history of HCC can achieve a high sustained virologic response (SVR) rate with favorable tolerability.[8,9]

However, a high rate of early tumor recurrence has been reported in patients with a prior history of HCC treatment who were starting DAA treatment,[10,11] for which we have presented counterevidence.[12] Briefly, a retrospective study compared the HCC recurrence rates between patients with a prior history of HCC treatment who underwent DAA therapy, IFN-based therapy, and non-antiviral therapy. DAA use did not increase the early HCC recurrence rate compared with that in the other 2 groups. In that study, the interval between initial HCC treatment and initiation of antiviral therapy was limited to 2 years, and patients with HCC recurrence before antiviral therapy were excluded. Thus, selected patients among those we saw in daily clinical practice were enrolled.

In the current study, we expanded the enrollment criteria to those with a history of multiple HCC treatments, irrespective of the interval between HCC treatment and initiation of antiviral therapy to reflect actual antiviral use. We evaluated the HCC recurrence rates and patterns after the administration of IFN-based and DAA therapy.

Keywords: Hepatitis C; Direct-acting antivirals; Hepatocellular carcinoma recurrence.
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Materials and methods

Study design and participants

This retrospective cohort study was conducted in accordance with the ethical guidelines for epidemiological research of the Japanese Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor, and Welfare. The study design was included in a comprehensive protocol of retrospective studies at the University of Tokyo Hospital, Department of Gastroenterology, which was approved by the University of Tokyo Medical Research Center Ethics Committee (approval number 2058).

From 1990 to 2016, a total of 4,163 patients with treatment-naïve or recurrent HCC were admitted to the Department of Gastroenterology at the University of Tokyo Hospital. All patients were registered in a prospectively collected computerized database, and the study was based on data until the end of August 2017. All HCC treatment histories were stored in the database. Among the 4,163 patients, 2,559 were treated for HCC with radiofrequency ablation (RFA). We aimed to provide curative treatment in 2,435 of these patients and RFA treatment was successful in 2,420 patients (99.3%). We confirmed complete response based upon the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[13] by enhanced computed tomography (CT) or magnetic resonance imaging (MRI) before the initiation of DAA therapy. Of these patients, 1,691 were positive for HCV antibody and negative for hepatitis B surface antigen. Among them, 303 patients received antiviral therapy after HCC treatments. These patients were divided into 2 groups according to the initial antiviral therapy after HCC treatment: the IFN group (156 patients) and the DAA group (147 patients) (Fig. 1). Patients who were treated with DAAs after failure of IFN therapy were included in the IFN group.

Diagnosis of HCC and follow-up

HCC was diagnosed by dynamic CT or MRI; hyperattenuation in the arterial phase and washout in the late phase were considered diagnostic.[14] Dynamic CT or MRI was performed before the initiation of antiviral therapies to confirm the absence of viable HCC nodules. We monitored HCC recurrence by dynamic CT or MRI every 4 months and measurement of serum alpha-fetoprotein (AFP), *lens culinaris* agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3), and des-gamma-carboxy-prothrombin (DCP) levels. HCC recurrence was diagnosed using the same criteria as applied to the diagnosis of HCC. Liver biochemistry tests were also performed every 4 months to evaluate liver function.

Antiviral therapy

The IFN therapy regimens were as follows: IFN monotherapy for 24–48 weeks for genotypes 1 and 2, IFN plus ribavirin (RBV) for 48–72 weeks for genotype 1 and 24 weeks for genotype 2, peginterferon (PegIFN) monotherapy for 24–48 weeks for genotypes 1 and 2, PegIFN plus RBV for 48–72 weeks for genotype 1 and 24 weeks for genotype 2, and PegIFN plus RBV plus telaprevir or simeprevir for 12 weeks followed by 12 weeks of PegIFN plus RBV for genotype 1. The DAA therapy regimens were as follows: daclatasvir plus asunaprevir for 24 weeks for genotype 1, sofosbuvir plus ledipasvir for 12 weeks for genotype 1, sofosbuvir plus RBV for 12 weeks for genotype 2, ombitasvir and paritaprevir with ritonavir for 12 weeks for genotype 1, and elbasvir plus grazoprevir for 12 weeks for genotype 1. An SVR12 was defined as undetectable HCV RNA at 12 weeks after the cessation of antiviral therapy.

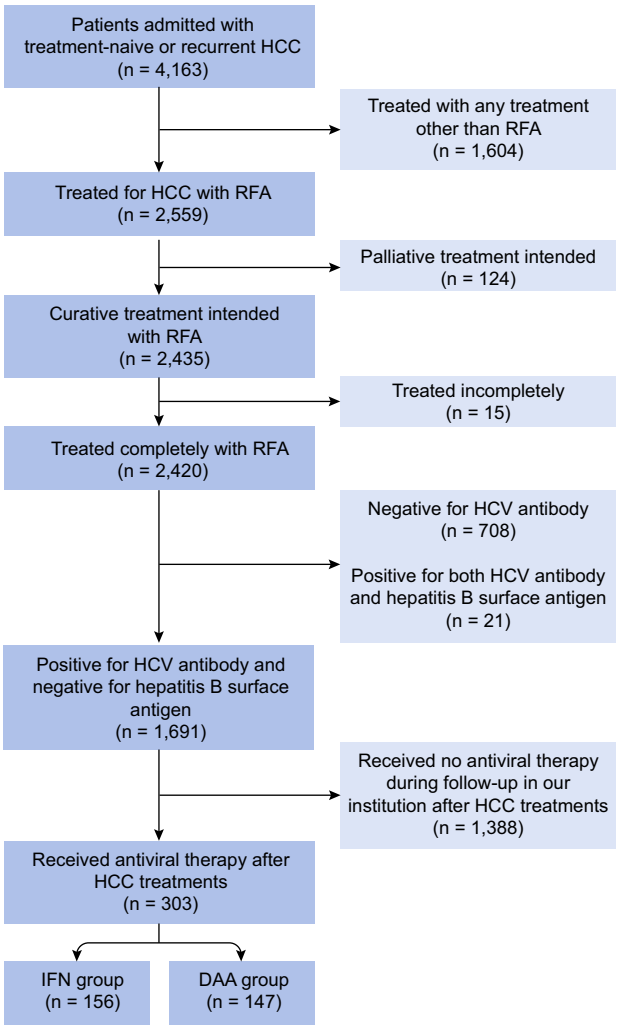

Fig. 1. Flow of patients in this study. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; RFA, radiofrequency ablation.

Outcomes

The primary endpoint was HCC recurrence after the initiation of antiviral therapy. Time to recurrence was defined as the interval between the initiation of antiviral therapy and the detection of HCC recurrence. The secondary endpoint was the HCC recurrence pattern. HCC recurrences were classified into the following 4 groups in reference to the Barcelona Clinical Liver Cancer (BCLC) staging system: intrahepatic recurrence of a single tumor and <2 cm in diameter (stage 0), intrahepatic recurrence of a single tumor and ≥2 cm in diameter, or up to 3 tumors and 3 cm in diameter (stage A), intrahepatic recurrence of more than 3 tumors or 2–3 tumors >3 cm in diameter (multinodular) (stage B), and extrahepatic metastasis or macrovascular invasion (stage C). Any patient with intrahepatic recurrence overlapping with extrahepatic metastasis or macrovascular invasion was included in stage C. In addition, the rates of hepatic decompensation at 48 weeks after the initiation of antiviral therapy were evaluated. Hepatic decompensation was defined as the occurrence of gastroesophageal varices hemorrhage, hepatic encephalopathy, ascites, jaundice (total bilirubin ≥3 mg/dl) or an increase in Child-Pugh score by 2 or more points from baseline.

Statistical analysis

Data are presented as medians and interquartile ranges for quantitative variables and numbers and percentages for qualitative variables. Differences between the IFN and DAA groups were evaluated using the Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables.

Recurrence rates from the initiation of antiviral therapy were assessed by the Kaplan-Meier method and compared using the log-rank test. Data were censored on August 31, 2017. Patients who were lost to follow-up or died without HCC recurrence were censored. We analyzed age, gender, total bilirubin, serum albumin, ALT, platelet count, AFP, AFP-L3, DCP, presence or absence of cirrhosis, tumor number, and size at the last HCC treatment, number of HCC treatments, interval between the last HCC treatment and initiation of antiviral therapy, achievement of an SVR, and antiviral regimen as risk factors for HCC recurrence by univariate and multivariate Cox proportional hazard regression analyses. The association of antiviral type with HCC recurrence was analyzed using multivariate Cox proportional hazard regression models adjusted for variables with a p <0.10 in the univariate analyses. When multiple collinearity existed between variables with a $p < 0.10$ in the univariate analyses, only 1 variable was included in the multivariate analyses. In addition, a matching analysis was performed to compare HCC recurrence rates because the baseline characteristics differed between the 2 groups. Patients were extracted to match age, gender, platelet count, and the number of HCC treatments. The chi-squared test was used to compare the HCC recurrence patterns of the 2 groups. All tests for differences were two-tailed, and p values of less than 0.05 were considered to indicate a significant difference. Statistical analyses were performed using R 2.13.0 (http://www.R-project.org).

For further details regarding the materials used, please refer to the CTAT table and supplementary information.

Results

Patient profiles

Baseline characteristics at the initiation of antiviral therapy are shown (Table 1).

Table 1. Baseline characteristics of the patients.

Variable	Overall cohort			Matched cohort		
	IFN group n = 156	DAA group n = 147	*p* value	IFN group n = 61	DAA group n = 61	*p* value
Age (years)	65.3 (60.9–70.7)	74.4 (67.9–80.0)	<0.001	67.2 (62.4–71.5)	67.8 (60.8–74.4)	0.71
Male gender, n (%)	117 (75)	87 (59)	0.005	47 (77)	40 (66)	0.23
Total bilirubin (mg/dl)	0.9 (0.6–1.2)	0.9 (0.7–1.2)	0.81	0.9 (0.6–1.2)	1.0 (0.7–1.3)	0.23
Albumin (g/dl)	3.7 (3.4–3.9)	3.7 (3.3–3.9)	0.51	3.6 (3.3–3.9)	3.6 (3.2–3.9)	0.83
ALT (IU/L)	60 (40–89)	47 (32–70)	<0.001	59 (39–86)	50 (34–76)	0.13
Platelet count ($\times 10^4/\mu l$)	11.6 (9.6–15.0)	11.0 (7.5–14.3)	0.03	11.3 (9.6–14.3)	11.5 (7.3–14.8)	0.22
Liver cirrhosis, n (%)*	119 (76)	109 (74)	0.69	47 (77)	48 (79)	1
Child Pugh class, n (%)			0.73			0.61
A	153 (98)	144 (98)		60 (98)	58 (95)	
B	3 (1.9)	3 (2.0)		1 (1.6)	3 (4.9)	
Ascites, n (%)	0 (0)	0 (0)	1	0 (0)	0 (0)	1
AFP (ng/ml)	11.7 (4.8–29)	11.8 (5.2–27)	0.64	12.9 (5.0–37)	11.0 (4.9–27.1)	0.79
AFP-L3 (%)	0.5 (0.5–0.5)	3.7 (0.5–5.8)	<0.001	0.5 (0.5–3.7)	3.7 (0.5–5.5)	0.004
DCP (mAU/ml)	15 (12–20)	16 (11–22)	0.66	15 (12–21)	18 (14–32)	0.07
Tumor number >1 at the last HCC treatment, n (%)	69 (44)	44 (30)	0.01	25 (41)	21 (34)	0.58
Tumor size at the last HCC treatment (mm)	19 (16–25)	16 (13–21)	<0.001	18 (13–25)	17 (14–22)	0.27
Number of HCC treatments(1 / 2 / ≥3)	94 / 33 / 29	60 / 31 / 56	<0.001	35 / 12 / 14	27 / 14 / 20	0.33
Interval between the last HCC treatment and initiation of antiviral therapy (years)	0.45 (0.18–1.11)	0.56 (0.21–1.56)	0.29	0.44 (0.21–1.33)	0.46 (0.18–1.51)	0.85
Interval between the last imaging evaluation and initiation of antiviral therapy (years)	0.12 (0.07–0.19)	0.10 (0.05–0.19)	0.18	0.12 (0.08–0.20)	0.11 (0.05–0.19)	0.36
Genotype 1 / 2	115 / 41	124 / 23	0.02	47 / 14	52 / 9	0.35
Antiviral therapy						
IFN monotherapy	12	–		6	–	
IFN/RBV	11	–		5	–	
PegIFN monotherapy	24	–		12	–	
PegIFN/RBV	106	–		36	–	
PegIFN/RBV/DAA	3	–		2	–	
DCV/ASV	–	38		–	16	
SOF/LDV	–	81		–	35	
OBV/PTV/ritonavir	–	2		–	1	
EBR/GZR	–	3		–	0	
SOF/RBV	–	23		–	9	

Values are medians (interquartile ranges) or numbers (%). *Liver cirrhosis was defined as cases who had at least 1 of the following features: liver biopsy with F4, fibroscan value above 15 kPa, platelet count less than $10 \times 10^4/\mu l$, gastroesophageal varix and splenomegaly. The Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables were used to compare them between the IFN and DAA groups.

AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT, alanine aminotransferase; ASV, asunaprevir; DAA, direct-acting antiviral; DCP des-gamma-carboxy prothrombin; DCV, daclatasvir; EBR, elbasvir; GZR, grazoprevir; HCC, hepatocellular carcinoma; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; PegIFN, peginterferon; RBV, ribavirin; SOF, sofosbuvir.

Patients in the DAA group were significantly older than those in the IFN group (74.4 *vs.* 65.3 years, p <0.001). The proportion of females was higher in the DAA group (41 *vs.* 25%, p = 0.005). The proportion of cirrhotic patients was similar in the 2 groups (76% in the IFN group *vs.* 74% in the DAA group, p = 0.69). Patients in the DAA group had lower ALT levels, lower platelet counts, and higher AFP-L3 levels than those in the IFN group. Patients in the DAA group had smaller tumors and a higher proportion of single tumors at the last HCC treatment. The proportion of patients with a history of multiple HCC treatment was higher in the DAA group. Among the enrolled patients, 57 (37%) and 135 (92%) achieved an SVR12 in the IFN and DAA groups, respectively.

Recurrence according to antiviral agent

During the median observation period of 7.2 years in the IFN group and 1.8 years in the DAA group, HCC recurrence developed in 136 patients in the IFN group and 80 patients in the DAA group. The tumor recurrence rates at 1 and 2 years were 39% and 61% in the IFN group and 39% and 60% in the DAA group, respectively (Fig. 2A). There was no significant difference in HCC recurrence rates between the 2 groups (p = 0.43 by log-rank test). A matching analysis was performed with the following baseline variables: age, gender, platelet count, and the number of HCC treatments. Sixty-one patients were extracted in each group and there was no significant difference between the matched groups (p = 0.68 by log-rank test) (Fig. 2B).

Risk factors for recurrence in the DAA group and in the entire cohort

In univariate analyses of patients in the DAA group, the following factors were associated with HCC recurrence (p <0.10): higher total bilirubin level, lower albumin level, higher AFP-L3 level, higher DCP level, larger number of HCC treatments, and short interval between last HCC treatment and initiation of antiviral therapy. A multivariate analysis, adjusted for factors with a p <0.10 in univariate analyses, identified larger number of HCC treatments, and shorter interval between the last HCC treatment and initiation of antiviral therapy as independent risk factors for HCC recurrence after DAA therapy (Table 2). In univariate analyses of the entire cohort, the following factors were associated with HCC recurrence (p <0.10): lower albumin level, higher AFP level, higher AFP-L3 level, higher DCP level, presence of liver cirrhosis, larger number of tumors at the last HCC treatment, larger number of HCC treatments, shorter interval between last HCC treatment and initiation of antiviral therapy, and achievement of an SVR. A multivariate analysis adjusted for factors with a p < 0.10 in univariate analyses, excluding AFP level because of multiple collinearity with AFP-L3 level, showed no significant difference between the IFN and DAA groups (p = 0.71), and identified a higher AFP-L3 level, larger number of HCC treatments, and shorter interval between the last HCC treatment and initiation of antiviral therapy as independent risk factors for HCC recurrence (Table 2).

Recurrence pattern

Recurrence patterns are shown (Table 3). There was no significant difference in recurrence pattern between the 2 groups (p = 0.70 by chi-squared test). Intrahepatic recurrence with a single tumor or up to 3 tumors and tumors of <3 cm diameter (stage 0 and A) was found in most patients in both groups (116 patients [85%] in the IFN group and 67 patients [84%] in the DAA group). Extrahepatic metastases were found in 1 patient (para-aortic and hilar lymph nodes metastasis) in the IFN group and 2 patients (bile duct invasion in 1 patient and portal vein tumor thrombosis and multiple lung metastasis in the other) in the DAA group. No patient exhibited extrahepatic metastases overlapping with intrahepatic recurrence. With regard to tumor markers, the AFP and ΔAFP values were not different between the 2 groups. The AFP-L3 value at the diagnosis of HCC recurrence was higher in the DAA group and the ΔAFP-L3 value was not different between the 2 groups. The DCP and ΔDCP values were higher in the IFN group.

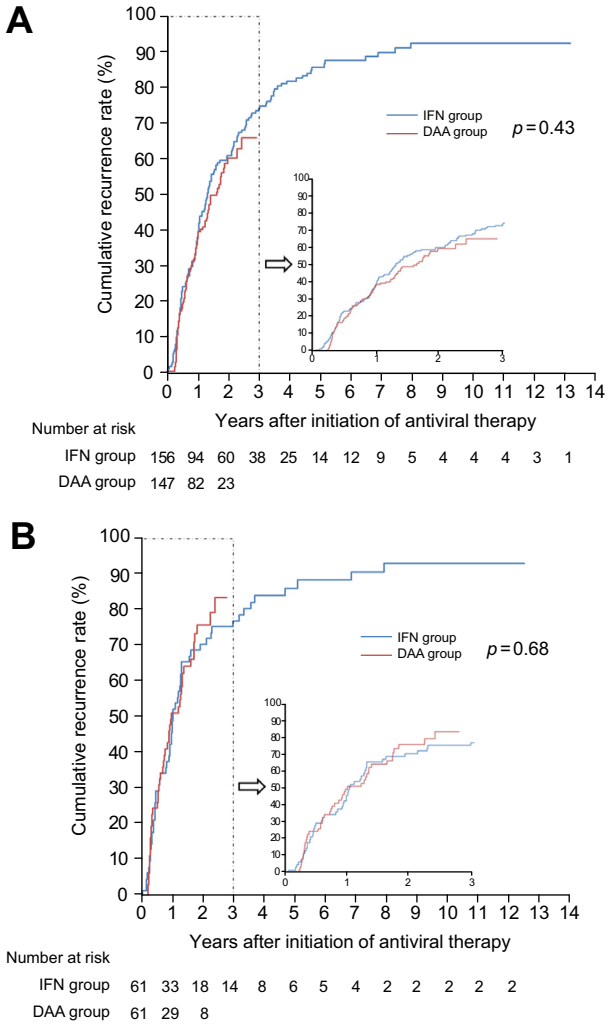

Fig. 2. Cumulative HCC recurrence rates according to antiviral agent. (A) Cumulative HCC recurrence rates according to antiviral agent in the overall cohort. The tumor recurrence rates at 1 and 2 years were 39% and 61% in the IFN group and 39% and 60% in the DAA group, respectively. The Kaplan-Meier method was used to assess cumulative recurrence rates, and the log-rank test was used to compare them. (B) Cumulative HCC recurrence rates according to antiviral agent in the matched cohort. The following baseline variables were matched: age, gender, platelet count, and number of HCC treatments. The tumor recurrence rates at 1 and 2 years were 46% and 70% in the matched IFN group and 51% and 76% in the matched DAA group, respectively. The Kaplan-Meier method was used to assess cumulative recurrence rates, and the log-rank test was used to compare them. DAA, direct-acting antiviral; IFN, interferon; HCC, hepatocellular carcinoma. (This figure appears in colour on the web.)

Recurrence according to virological response and antiviral agent

The cumulative recurrence rate in patients who achieved an SVR12 was not significantly diferrent from that in those who

Table 2. Univariate and multivariate analyses of HCC recurrence after antiviral therapy.

Variable	The DAA group				The entire cohort			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age per 1 year	0.99 (0.96–1.01)	0.27			0.99 (0.97–1.01)	0.28		
Male gender	0.95 (0.61–1.48)	0.82			0.88 (0.66–1.17)	0.37		
Total bilirubin per 1 mg/dl	1.59 (1.03–2.45)	0.04	1.05 (0.76–1.47)	0.75	1.23 (0.92–1.64)	0.17		
Albumin per 1 g/dl	0.50 (0.29–0.85)	0.01	0.70 (0.47–1.05)	0.09	0.55 (0.39–0.78)	<0.001	0.74 (0.49–1.11)	0.14
ALT per 1 IU/L	1.00 (0.99–1.00)	0.43			1.00 (1.00–1.00)	0.34		
Platelet count per 1x10^4/μl	0.98 (0.94–1.02)	0.27			0.98 (0.95–1.01)	0.17		
AFP >10 ng/ml	1.36 (0.87–2.13)	0.17			1.35 (1.04–1.79)	0.03		
AFP-L3 >5%	1.68 (1.07–2.64)	0.02	1.41 (0.99–2.00)	0.06	1.62 (1.17–2.22)	0.003	1.47 (1.02–2.11)	0.04
DCP >40 mAU/ml	2.20 (1.13–4.31)	0.02	1.24 (0.73–2.10)	0.42	1.88 (1.14–3.10)	0.01	1.21 (0.71–2.05)	0.49
Liver cirrhosis	1.00 (0.60–1.66)	1.00			1.32 (0.96–1.82)	0.09	1.09 (0.76–1.57)	0.64
Child Pugh A	0.82 (0.20–3.33)	0.78			1.52 (0.48–4.76)	0.48		
Tumor number >1 at the last HCC treatment	1.33 (0.83–2.13)	0.23			1.28 (0.97–1.68)	0.08	1.14 (0.85–1.52)	0.39
Tumor size >20 mm at the last HCC treatment	1.18 (0.73–1.89)	0.49			1.02 (0.77–1.34)	0.86		
Number of HCC treatments								
1	1	–	1		1	–	1	–
2	1.42 (0.77–2.60)	0.26	1.50 (0.81–2.80)	0.20	1.42 (1.01–2.01)	0.04	1.33 (0.94–1.89)	0.11
≥3	2.05 (1.24–3.39)	0.005	1.92 (1.13–3.27)	0.02	1.95 (1.41–2.69)	< 0.001	1.65 (1.16–2.35)	0.007
Interval between the last HCC treatment and initiation of antiviral therapy >2 years	0.41 (0.21–0.79)	0.008	0.47 (0.23–0.96)	0.04	0.41 (0.26–0.64)	< 0.001	0.51 (0.31–0.83)	0.007
SVR *vs.* non-SVR	0.76 (0.35–1.65)	0.48			0.75 (0.57–0.98)	0.04	0.81 (0.57–1.14)	0.22
DAA group *vs.* IFN group	–	–	–	–	0.89 (0.67–1.19)	0.43	0.93 (0.64–1.35)	0.71

Independent risk factors for HCC recurrence were analyzed using Cox proportional hazard regression analyses.
AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; ALT, alanine aminotransferase; DAA, direct-acting antiviral; DCP, des-gamma-carboxy prothrombin; HCC, hepatocellular carcinoma; HR, hazard ratio; IFN, interferon; SVR, sustained virologic response.

Table 3. Recurrence patterns.

	IFN Group n = 136	DAA Group n = 80	*p* value
Recurrence pattern			0.70
Stage 0: Single <2 cm, n (%)	56 (41)	35 (44)	
Stage A: Single ≥2 cm, or ≤3 nodules and ≤3 cm, n (%)	60 (44)	32 (40)	
Stage B: >3 nodules or 2–3 tumors >3 cm, n (%)	19 (14)	11 (14)	
Stage C: Extrahepatic metastasis or macrovascular invasion, n (%)	1 (0.7)	2 (2.5)	
Tumor marker at HCC recurrence			
AFP (ng/ml)	11 (5–32)	10 (5–37)	0.92
AFP-L3 (%)	0.5 (0.5–7.1)	3.4 (0.5–12.4)	0.004
DCP (mAU/ml)	22 (14–38)	17 (13–38)	0.08
Tumor marker increase from the initiation of the antiviral therapy			
ΔAFP (ng/ml)	–0.2 (–8.6–6.7)	–1.4 (–11.5–8.4)	0.83
ΔAFP-L3 (%)	0 (0–3.5)	0 (–0.7–2.6)	0.68
ΔDCP (mAU/ml)	5 (0–23.3)	2 (–3–10)	0.01

Values are medians (interquartile ranges) or numbers (%). The Mann-Whitney U-test for continuous variables and the chi-squared test for categorical variables were used to compare them between the IFN and DAA groups.
AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein; DAA, direct-acting antiviral; DCP des-gamma-carboxy prothrombin; HCC, hepatocellular carcinoma; IFN, interferon.

did not in the IFN group ($p = 0.08$ by log-rank test) and in the DAA group ($p = 0.48$ by log-rank test). Among those who achieved an SVR12, the tumor recurrence rates at 1 and 2 years were 35% and 53% in the IFN group and 37% and 60% in the DAA group, respectively (Fig. 3A). There was no significant difference in HCC recurrence rates between the 2 groups ($p = 0.85$ by log-rank test).

Recurrence according to the number of HCC treatments and antiviral agent

The cumulative recurrence rate in patients with a history of 1 HCC treatment was significantly lower than that in those with a history of multiple HCC treatments in the IFN group ($p = 0.004$ by log-rank test) and in the DAA group ($p = 0.01$ by log-rank test). Among those with a history of 1 HCC treatment, the 1- and 2-year tumor recurrence rates were 35% and 54% in the IFN group and 26% and 51% in the DAA group, respectively. There was no significant difference in HCC recurrence rates between the 2 groups ($p = 0.19$ by log-rank test). Among those with a history of multiple HCC treatments, the 1- and 2-year tumor recurrence rates were 45% and 71% in the IFN group and 49% and 66% in the DAA group, respectively (Fig. 3B). There was no significant difference in HCC recurrence rates between the 2 groups ($p = 0.57$ by log-rank test).

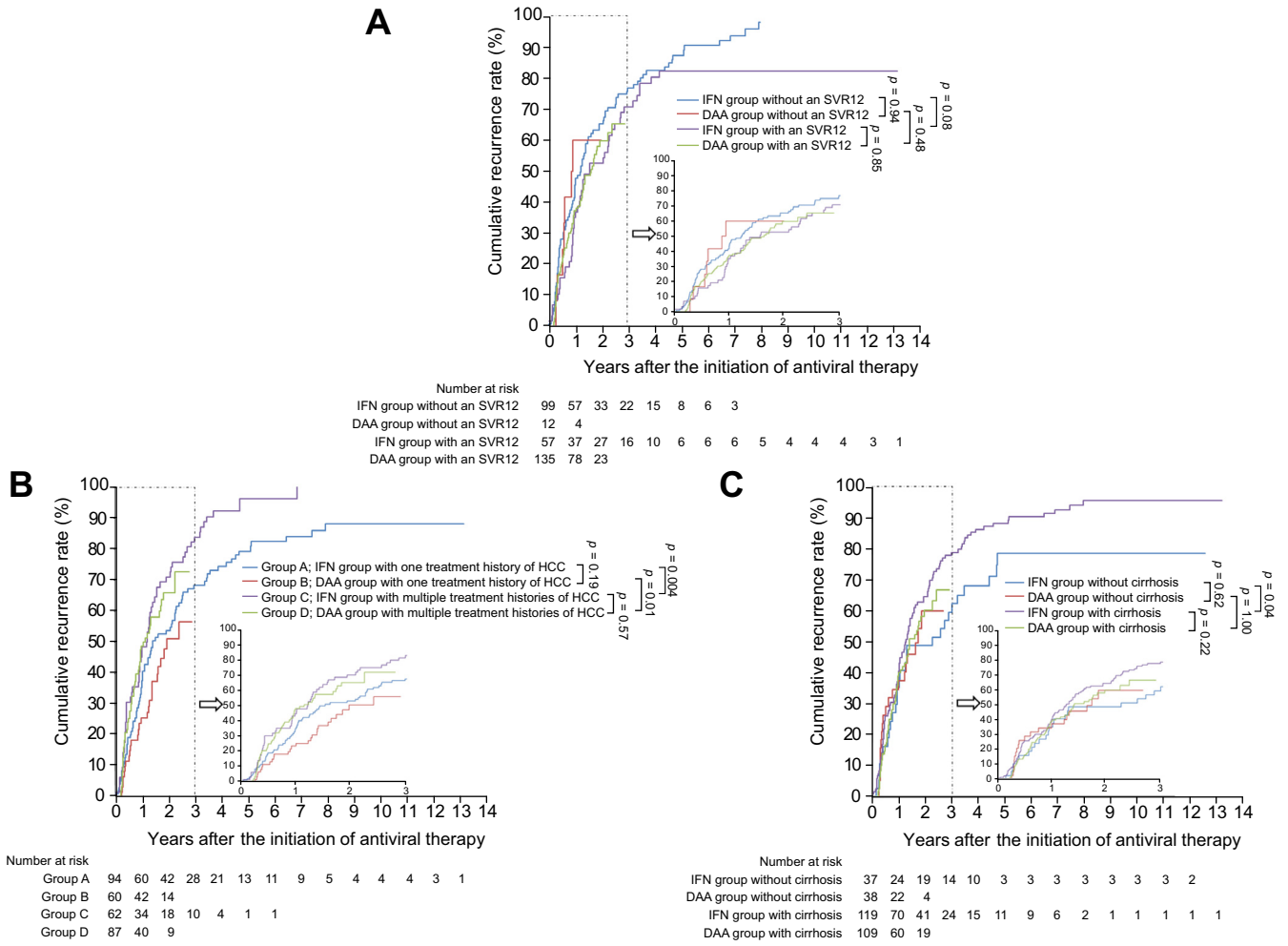

Fig. 3. Subgroup analysis of HCC recurrence. (A) Cumulative recurrence rates according to virological response and antiviral agent. The tumor recurrence rates at 1 and 2 years were 35% and 53% in the IFN group with an SVR12, 37% and 60% in the DAA group with an SVR12, 42% and 65% in the IFN group without an SVR12, and 60% and N/A in the DAA group without an SVR12, respectively. The Kaplan-Meier method was used to assess cumulative recurrence rates, and the log-rank test was used to compare them. (B) Cumulative recurrence rates according to the number of HCC treatments and antiviral agent. Eligible patients were divided into the following 4 groups: Group A, patients with history of 1 HCC treatment in the IFN group; Group B, patients with history of 1 HCC treatment in the DAA group; Group C, patients with history of multiple HCC treatments in the IFN group; and Group D, patients with history of multiple HCC treatments in the DAA group. The tumor recurrence rates at 1 and 2 years were 35% and 54% in Group A, 25% and 51% in Group B, 45% and 71% in Group C, and 49% and 66% in Group D, respectively. The Kaplan-Meier method was used to assess cumulative recurrence rates, and the log-rank test was used to compare them. (C) Cumulative recurrence rates according to the presence or absence of cirrhosis and antiviral agent. The tumor recurrence rates at 1 and 2 years were 41% and 65% in the IFN group with cirrhosis, 40% and 60% in the DAA group with cirrhosis, 35% and 49% in the IFN group without cirrhosis, and 37% and 60% in the DAA group without cirrhosis, respectively. The Kaplan-Meier method was used to assess cumulative recurrence rates, and the log-rank test was used to compare them. DAA, direct-acting antiviral; IFN, interferon; HCC, hepatocellular carcinoma; SVR12, sustained virologic response at 12 weeks. (This figure appears in colour on the web.)

Recurrence according to the presence or absence of cirrhosis and antiviral agent

The cumulative recurrence rate in patients with cirrhosis was significantly higher than that in those without cirrhosis in the IFN group ($p = 0.04$ by log-rank test) and not significantly different in the DAA group ($p = 1.00$ by log-rank test). Among those with cirrhosis, the 1- and 2-year tumor recurrence rates were 41% and 65% in the IFN group and 40% and 60% in the DAA group, respectively. There was no significant difference in HCC recurrence rates between the 2 groups ($p = 0.22$ by log-rank test). Amont those without cirrhosis, the 1- and 2-year tumor recurrence rates were 35% and 49% in the IFN group and 37% and 60% in the DAA group, respectively (Fig. 3C). There was no significant difference in HCC recurrence rates between the 2 groups ($p = 0.62$ by log-rank test).

Hepatic decompensation

The rates of hepatic decompensation at 48 weeks after the initiation of antiviral therapy were 0% in the IFN group with an SVR and 7.3% in the IFN group without an SVR, and 0% in the DAA group with an SVR and 8.3% in the DAA group without an SVR (Fig. 4). None of the patients who achieved an SVR in either group had hepatic decompensation at 48 weeks.

Discussion

Previous studies have reported conflicting results on the early HCC recurrence rate after the initiation of DAA therapy.[8–12,15–22] We referred to a previous summary table written by Kushner *et al.*[23] and created Table 4 based on the

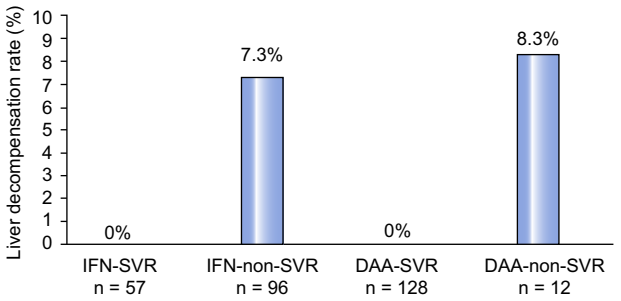

Fig. 4. The rates of hepatic decompensation within 48 weeks after the initiation of antiviral therapy. The rates of hepatic decompensation were 0% (0/57) in the IFN group with an SVR12 (IFN-SVR) and 7.3% (7/96) in the IFN group without an SVR12 (IFN-nonSVR), and 0% (0/128) in the DAA group with an SVR12 (DAA-SVR) and 8.3% (1/12) in the DAA group without an SVR12 (DAA-nonSVR). Seven patients in the DAA group and 3 patients in the IFN group were censored. In the DAA group, observational periods less than 48 weeks in 2 patients, changing hospital in 1 patient, death of sepsis due to liver abscess within 48 weeks in 1 patient, peritoneal cancer progression in 1 patient, and obstructive jaundice in 2 patients due to cystic duct cancer or HCC. In the IFN group, death due to HCC progression within 48 weeks in 1 patient and changing hospital in 2 patients. DAA, direct-acting antiviral; IFN, interferon; HCC, hepatocellular carcinoma; SVR12, sustained virologic response at 12 weeks.

recent reports. These conflicting results occurred in part because of differences in tumor stage, HCC treatment modalities, interval between HCC treatment and DAA initiation, and indirect comparison of the DAA and control groups. Furthermore, to compare HCC recurrence rates between 2 groups, it was considered necessary to adjust for tumor number, tumor size, and tumor marker levels, which are associated with HCC recurrence.[5,24]

In this study, there was no significant difference in the early HCC recurrence rate after adjustment for tumor factors (Table 2). A high AFP-L3 level, a history of multiple HCC treatments, and short recurrence-free period were independent risk factors for early HCC recurrence after the initiation of antiviral therapy. This is clinically plausible for the following reasons. First, an increase in the level of AFP-L3, a fucosylated variant of AFP that reacts with *lens culinaris* agglutinin A, is highly specific to HCC.[25,26] High AFP-L3 levels after HCC treatment strongly indicate residual cancer that cannot be detected by imaging.[24] Second, recurrent HCC has an increased risk of subsequent recurrence after curative treatment,[27] which could explain the high risk of HCC recurrence in patients with a history of multiple HCC treatments. In Table 4, recurrence rates in the current study seemed higher than those in other studies, probably because the majority of patients underwent multiple treatments for tumor recurrence before the initiation of DAA treatments.

Third, early HCC recurrence was considered to be associated with tumor dissemination.[5] Patients with a short recurrence-free period before the initiation of antiviral therapy were in the possible state of early recurrence, which is associated with a higher risk of HCC recurrence than a long recurrence-free period.

It was hypothesized that the rapid control of inflammation could impact anti-tumoral immune control, allowing the emergence of tumor clones; IFN does not result in this emergence because of its anti-tumoral immune effect.[11] The SVR rate was 91% with DAA therapy and 37% with IFN-based therapy. However, achievement of an SVR was not significantly associated with the risk of early HCC recurrence in a multivariate analysis (Table 2). A subgroup analysis of patients who achieved an SVR showed no significant difference in the early HCC recurrence rate between the IFN and DAA groups (Fig. 3A). These results suggest that early HCC recurrence was not associated with viral state or the antiviral regimen. Furthermore, a subgroup analysis of patients with a history of multiple HCC treatments showed no significant difference in early HCC recurrence rate between the 2 groups (Fig. 3B). If the hypothesis were true, HCC recurrence may occur in patients with a history of multiple HCC treatments, who are at high risk of HCC recurrence,[27] due to the introduction of DAA therapy. However, our data do not support this hypothesis.

This study has several limitations. First, there was no control arm (*i.e.*, patients who did not receive antiviral therapy after HCC treatment). We are unable to state that antiviral therapy, regardless of regimen, reduced HCC recurrence. However, in a recently published meta-analysis,[28] the 1- and 2-year recurrence rates were 20% (95% CI 12.7–27.4%) and 47 % (95% CI 39.5–54.4), respectively, in an HCV-untreated arm after curative treatment of HCV-related HCC.

In our study, among patients with history of 1 HCC treatment, considering the median interval between HCC treatment and the initiation of antiviral therapy of 0.6 years in the IFN group and 0.8 years in the DAA group, the 14% and 48% 0.4- and 1.4-year recurrence rates in the IFN group and 0% and 26% 0.2- and 1.2-year recurrence rates in the DAA group were not high compared with the 1- and 2-year recurrence rate in HCV-untreated arm (data not shown). Regarding patients with a history of multiple HCC treatments, establishing an appropriate control group for patients undergoing antiviral therapy after multiple treatments for HCC would be problematic. Second, the observational period of the DAA group was relatively short. Therefore, long-term follow-up studies are required to investigate late recurrences of HCC and the effect on prognosis. However, none of the patients who achieved an SVR had hepatic decompensation at 48 weeks after the initiation of antiviral therapy. Eradication of HCV after curative HCC treatments could preserve liver function, which might improve overall survival.[29] Third, the baseline characteristics of the IFN group and the DAA group were different. However, in the multivariate analysis and the matched-control analysis there was no significant difference in the early HCC recurrence rate between the IFN group and the DAA group. Although tumor markers were not successfully matched, being higher in the DAA group, there was no significant difference between the matched groups. That is, it could be said that DAAs did not promote HCC recurrence compared to IFN in the matched analysis. Fourth, patients treated with DAAs after failure of IFN therapy were included in the IFN group, which could have caused a bias. However, the number of those patients was small (n = 7) and there was no significant difference between patients treated with DAAs after failure of IFN therapy and those treated with only IFN (data not shown).

In conclusion, we found no significant difference in the early HCC recurrence rate and pattern between patients who received IFN-based and DAA therapy after HCC treatment. Recurrence at an advanced stage was infrequent in both groups. A high AFP-L3 level, short recurrence-free period, and history of multiple HCC treatments were independent risk factors for early HCC recurrence after the initiation of antiviral therapy.

Table 4. Summary of the articles about HCC recurrence after DAA therapy.

Study	Method	Number of patients, n		Last treatment of HCC	Median observation period (months)	HCC recurrence, n (%)		Conclusion: Did DAAs accelerate recurrence?
		DAA	Control			DAA	Control	
Reig, 2016[11]	Retrospective	58	0	Resection, ablation, or TACE	5.7	16 (27.6)	–	Yes
ANRS CO22, 2016[8]	Retrospective	189	78 (no treatment)	Resection or ablation	21.6 (DAA), 26.1 (no treatment)	24 (12.7)	16 (20.5)	No
ANRS CO12, 2016[8]	Retrospective	13	66 (no treatment)	Resection or ablation	21.3 (all patients)	1 (7.7)	31 (47.0)	No
ANRS CO23, 2016[8]	Retrospective	314	0	Transplantation	7 (mean)	7 (2.2)	–	No
Conti, 2016[10]	Retrospective	59	0	Resection, ablation, PEI, or TACE	37 (with Rec.*),12 (without Rec.†)	17 (28.8)	–	Yes
Minami, 2016[12]	Retrospective	27	38 (IFN), 861 (no treatment)	Ablation	16 (DAA), 36 (IFN, no treatment)	8 (29.6)	26 (68.4) (IFN), 553 (64.2) (no treatment) at 3 years	No
Torres, 2016[15]	Prospective	8	0	Resection, ablation,or proton therapy	12	0 (0)	–	No
Zeng, 2016[16]	Retrospective	8	0	Ablation	15	0 (0)	–	No
Cabibbo, 2017[9,‡]	Prospective	143	0	Resection, ablation, or TACE	8.7	29 (20.3)	–	No
Ikeda, 2017[17,‡]	Retrospective	177	89 (no treatment)	Resection, ablation, TACE or PRT	20.7 (DAA, No treatment)	30.1% (12 months) 38.9% (24 months)	25% (12 months), 46.5% (24 months)	No
Kolly, 2017[18]	Retrospective	47	0	Resection, ablation,or TACE	9.6	Disease-free rate 77% (6 months), 58% (12 months)	–	No
Nagata, 2017[19]	Retrospective	83	60 (IFN)	Resection or ablation	28 (SVR DAA§), 74 (SVR IFN‖)	22.9% (SVR), 40% (Non–SVR) at 3 years	47.1% (SVR), 77.1% (Non–SVR) at 5 years	No
Petta, 2017[20]	Retrospective	58 (SVR DAA§)	57 (SVR IFN‖) 328 (HCV active¶)	Resection or ablation	18 (SVR DAA§), 34 (SVR IFN‖), 17 (HCV active¶)	16 (27.6)	22 (38.6) (SVR IFN†), 142 (43.3) (HCV active‡)	No
Virlogeux, 2017[21]	Retrospective	23	45 (no treatment)	Resection, ablation, TACE, or combination	17.4 (DAA with Rec.*), 10.1 (No treatment with Rec.†), 35.7 (DAA without Rec.*), 15.4 (No treatment without Rec.†)	11 (47.8)	33 (73.3)	No
Zavaglia, 2017[22]	Retrospective	31	0	Resection, ablation, or TACE	8	1 (3.2)	–	No
Kinoshita (The current study)‡	Retrospective	147	156 (IFN)	Ablation	22 (DAA), 86 (IFN)	80 (54.4)	136 (87.2)	No

*With Rec. means patients who had HCC recurrence. †Without Rec. means patients who did not have HCC recurrence. ‡Patients with a history of multiple HCC treatments were included. §SVR DAA means patients who achieved SVR by DAA therapy. ‖SVR IFN means patients who achieved SVR by IFN therapy. ¶HCV active means patients who had active HCV infection.
ANRS, France REcherche Nord and sud Sida-vih Hépatitis; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; PEI, percutaneous ethanol injection; PRT, particle radiation therapy; SVR, sustained virologic response; TACE, transcatheter arterial chemoembolization.

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Conflict of interest
Kazuhiko Koike has received research funding from Merk Sharp & Dorme, Chugai Pharmaceutical Co., Ltd, Bristol-Meyers Squibb, Giliad Sciences, Abbvie GK, Jansen Pharmaceutical K.K. and Mitsubishi Tanabe Pharma Corporation. Ryosuke Tateishi has received lecture fee from Merk Sharp & Dorme, Chugai Pharmaceutical Co., Ltd, Bristol-Meyers Squibb, Giliad Sciences, Abbvie GK, and Mitsubishi Tanabe Pharma Corporation. Tatsuya Minami has received lecture fee from Merk Sharp & Dorme and Giliad Sciences.

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Authors' contributions
Conception and design: Mizuki Nishibatake Kinoshita, Tatsuya Minami, Ryosuke Tateishi. Acquisition of the data: Mizuki Nishibatake Kinoshita, Tatsuya Minami, Ryosuke Tateishi, Taijiro Wake, Ryo Nakagomi, Masaya Sato, Koji Uchino, Kenichiro Enooku, Hayato Nakagawa, Yoshinari Asaoka, Shuichiro Shiina. Analysis and interpretation of the data: Mizuki Nishibatake Kinoshita, Tatsuya Minami, Ryosuke Tateishi. Drafting of the manuscript: Mizuki Nishibatake Kinoshita, Tatsuya Minami, Ryosuke Tateishi. Statistical analysis: Mizuki Nishibatake Kinoshita, Tatsuya Minami, Naoto Fujiwara, Ryosuke Tateishi. Study supervision: Ryosuke Tateishi, Kazuhiko Koike. Final approval: All of the authors. Agreement to be accountable for all aspects of the work: All of the authors.

Supplementary data
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References
Author names in bold designate shared co-first authorship

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Simonetti RG, Camma C, Fiorello F, Cottone M, Rapicetta M, Marino L, et al. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case-control study. Ann Intern Med 1992;116:97–102.
[3] El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142, 1264–1273 e1261.
[4] Shiratori Y, Shiina S, Teratani T, Imamura M, Obi S, Sato S, 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.
[5] Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology 2006;44:1543–1554.
[6] **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.
[7] Minami T, Tateishi R, Shiina S, Nakagomi R, Kondo M, Fujiwara N, et al. Comparison of improved prognosis between hepatitis B- and hepatitis C-related hepatocellular carcinoma. Hepatol Res 2015;45:E99–E107.
[8] Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol 2016;65:734–740.
[9] Cabibbo G, Petta S, Calvaruso V, Cacciola I, Cannavo MR, Madonia S, et al. Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study. Aliment Pharmacol Ther 2017;46:688–695.
[10] **Conti F**, **Buonfiglioli F**, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727–733.
[11] Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719–726.
[12] Minami T, Tateishi R, Nakagomi R, Fujiwara N, Sato M, Enooku K, et al. The impact of direct-acting antivirals on early tumor recurrence after radiofrequency ablation in hepatitis C-related hepatocellular carcinoma. J Hepatol 2016;65:1272–1273.
[13] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.
[14] Torzilli G, Minagawa M, Takayama T, Inoue K, Hui AM, Kubota K, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. Hepatology 1999;30:889–893.
[15] Torres HA, Vauthey JN, Economides MP, Mahale P, Kaseb A. Hepatocellular carcinoma recurrence after treatment with direct-acting antivirals: first, do no harm by withdrawing treatment. J Hepatol 2016;65:862–864.
[16] Zeng QL, Li ZQ, Liang HX, Xu GH, Li CX, Zhang DW, et al. Unexpected high incidence of hepatocellular carcinoma in patients with hepatitis C in the era of DAAs: too alarming?. J Hepatol 2016;62:1068–1069.
[17] Ikeda K, Kawamura Y, Kobayashi M, Kominami Y, Fujiyama S, Sezaki H, et al. Direct-acting antivirals decreased tumor recurrence after initial treatment of hepatitis C virus-related hepatocellular carcinoma. Dig Dis Sci 2017;62:2932–2942.
[18] Kolly P, Waidmann O, Vermehren J, Moreno C, Vogeli I, Berg T, et al. Hepatocellular carcinoma recurrence after direct antiviral agent treatment: A European multicentre study. J Hepatol 2017;67:876–878.
[19] Nagata H, Nakagawa M, Asahina Y, Sato A, Asano Y, Tsunoda T, et al. Effect of interferon-based and -free therapy on early occurrence and recurrence of hepatocellular carcinoma in chronic hepatitis C. J Hepatol 2017;67:933–939.
[20] Petta S, Cabibbo G, Barbara M, Attardo S, Bucci L, Farinati F, et al. Hepatocellular carcinoma recurrence in patients with curative resection or ablation: impact of HCV eradication does not depend on the use of interferon. Aliment Pharmacol Ther 2017;45:160–168.
[21] Virlogeux V, Pradat P, Hartig-Lavie K, Bailly F, Maynard M, Ouziel G, et al. Direct-acting antiviral therapy decreases hepatocellular carcinoma recurrence rate in cirrhotic patients with chronic hepatitis C. Liver Int 2017;37:1122–1127.
[22] Zavaglia C, Okolicsanyi S, Cesarini L, Mazzarelli C, Pontecorvi V, Ciaccio A, et al. Is the risk of neoplastic recurrence increased after prescribing direct-acting antivirals for HCV patients whose HCC was previously cured? J Hepatol 2017;66:236–237.
[23] Kushner T, Dieterich D, Saberi B. Direct-acting antiviral treatment for patients with hepatocellular carcinoma. Curr Opin Gastroenterol 2018;34:132–139.
[24] Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, et al. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. Hepatology 2006;44:1518–1527.
[25] Sato Y, Nakata K, Kato Y, Shima M, Ishii N, Koji T, et al. Early recognition of hepatocellular carcinoma based on altered profiles of alpha-fetoprotein. N Engl J Med 1993;328:1802–1806.
[26] Taketa K, Endo Y, Sekiya C, Tanikawa K, Koji T, Taga H, et al. A collaborative study for the evaluation of lectin-reactive alpha-fetoproteins in early detection of hepatocellular carcinoma. Cancer Res 1993;53:5419–5423.
[27] Yamashiki N, Yoshida H, Tateishi R, Shiina S, Teratani T, Kondo Y, et al. Recurrent hepatocellular carcinoma has an increased risk of subsequent recurrence after curative treatment. J Gastroenterol Hepatol 2007;22:2155–2160.
[28] Cabibbo G, Petta S, Barbara M, Missale G, Virdone R, Caturelli E, et al. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver Int 2017;37:1157–1166.
[29] Cabibbo G, Petta S, Barbara M, Attardo S, Bucci L, Farinati F, et al. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. J Hepatol 2017;67:65–71.