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ORIGINAL ARTICLE - HEPATOLOGY (CLINICAL)

Long-term assessment of recurrence of hepatocellular carcinoma in patients with chronic hepatitis C after viral cure by direct-acting antivirals

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Key words
direct-acting antivirals, hepatitis C virus, hepatocellular carcinoma, recurrence.

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Abstract

Background and Aim: Early hepatocellular carcinoma (HCC) recurrence is common, even after achieving hepatitis C virus (HCV) cure. This study was carried out to assess the long-term trends and predictors of recurrence after HCV cure by direct-acting antivirals (DAAs).

Methods: This retrospective, multicenter cohort study enrolled 365 consecutive patients with chronic hepatitis C who required HCC treatment following sustained viral response (SVR) by DAA administration. Patients with HCC recurrence before SVR were excluded. Late HCC recurrence and its predictors beyond the post-treatment early phase (24 weeks after SVR) were evaluated.

Results: The data of 326 patients were available for the final analysis. The median follow-up duration from SVR determination was 2.7 years. Median age was 74, and 220 (67.5%) were 70 or over. The corresponding 5-year cumulative HCC recurrence rates of previous curative and palliative treatment groups were 45.4% and 65.7%, respectively (log-rank test: $P < 0.001$). Cox regression multivariable analysis revealed that cirrhosis (hazard ratio [HR] 1.85, $P = 0.021$), the number of HCC nodules (≥ 2) (HR 1.52, $P = 0.031$), and previous palliative HCC treatment (HR 1.71, $P = 0.012$) were independent predictors of late recurrence, in addition to the predictors of early recurrence; AFP > 7 ng/mL at 12 weeks after DAA administration, time from HCC complete response (CR) to DAA initiation (< 1 year), and the number of HCC treatments necessary to achieve CR (≥ 2).

Conclusions: The evaluation of fibrosis and characteristics of the previous HCC would allow for better HCC recurrence stratification, which would be helpful for developing long-term surveillance strategies.

Introduction

Patients with chronic hepatitis C may have life-threatening complications, including hepatocellular carcinoma (HCC) and liver failure, mainly caused by progressive liver fibrosis.[1,2] Highly effective and well-tolerated direct-acting antivirals (DAAs) have the potential to contribute to amelioration of health-related quality of life.[3,4] In fact, sustained viral response (SVR) is associated with a similar reduction in HCC risk after treatment with either a DAA or interferon.[5–7] It is crucial to distinguish differences in the relation of DAAs to de novo HCC and HCC recurrence when assessing the hepatic benefits of potential DAA-induced viral cures.

With interferon-based regimens, SVR is associated with a significant decrease in HCC recurrence after curative treatment.[8] Unfortunately, most patients with advanced fibrosis are not able to tolerate interferon-based treatment because of severe adverse effects.[9] In contrast, DAAs improve liver function and hepatic reserve and have a good safety profile, even for patients with cirrhosis.[10,11] In two studies, the existence of active HCC was independently associated with lower SVR, although the SVR rate was still relatively high at approximately 85–90%.[12,13] Nevertheless, it remains to be clarified if HCV cure by DAAs has benefits for decreasing HCC recurrence, especially over the long-term.

Recent studies have reported that the risk of HCC recurrence for those treated with DAAs is not significantly reduced compared with untreated patients, although overall survival and the risk of decompensated cirrhosis were significantly improved.[14,15] However, the follow-up period of these studies was relatively short, from 1 to 3 years at most, which resulted only in the conclusion that the time from HCC treatment to DAA initiation has a great influence on HCC recurrence. More data on other potential risk factors for HCC recurrence over a longer follow-up duration would be useful for clinicians.

We conducted a real-world, multicenter study to assess the risk factors for HCC recurrence beyond 24 weeks after the achievement of SVR by DAA treatment. Additionally, we also evaluated the differences in predictors of HCC recurrence in the early phase and beyond and survival rates according to the previous HCC treatment regimen.

Patients and methods

Study design and patient population. The Kyushu University Liver Disease Study Group consists of hepatologists from Kyushu University Hospital and its affiliated hospitals located in the northern Kyushu area of Japan. This retrospective, multicenter cohort study analyzed the data of 356 consecutive Japanese patients with chronic HCV infection who were enrolled between September 2014 and December 2019 for treatment with an interferon-free DAA regimen and who had experienced a complete response (CR) to HCC treatment within 6 months of DAA initiation. CR was defined as the disappearance of all target lesions by dynamic computed tomography (CT) or magnetic resonance imaging (MRI) according to the modified RECIST criteria.[16] Exclusion criteria were (i) under age 18 at the initiation of treatment, (ii) decompensated cirrhosis, (iii) DAA treatment failure or unknown DAA treatment outcome, (iv) HCC recurrence before SVR determination, (v) suspected HCC by image assessments within 3 months before DAA initiation, (vi) α-fetoprotein (AFP) $>$ 200 ng/mL at DAA initiation, (vii) concomitant human immunodeficiency virus or hepatitis B virus infection, and (viii) history of organ transplantation.

This study was performed with the approval of the Ethics Committees of Kyushu University hospital and each study site and is registered as a clinical study on the University Hospital Medical Information Network (ID 000027342). Data were acquired from medical records from a prospectively maintained database of all patients who have been treated with a DAA.

Study assessments and hepatocellular carcinoma surveillance. Clinical parameters were measured by standard laboratory techniques at a commercial laboratory at baseline (within the 3 months before DAA initiation), every 4 weeks from DAA treatment completion to 12 weeks after (pw12), then every 12 weeks after achieving SVR, which was defined as undetectable HCV RNA (target not detected) at pw12. HCV RNA was measured using a real-time reverse transcriptase PCR assay (COBAS TaqMan HCV assay, Version 2.0) (Roche Molecular Diagnostics, Tokyo, Japan) that has a lower limit of quantitation of 15 IU/mL. FIB-4 index was calculated as a serological fibrosis marker at the time of DAA initiation.[17] Cirrhosis was determined by transient elastography (FibroScan; Echosens, Paris, France) (cut-off value: 14.9 kPa)[18] or the presence of clinical, histological, radiologic, or endoscopic evidence of cirrhosis and/or portal hypertension (nodular contour on imaging, splenomegaly, and presence of varices). Curative HCC treatment was by radiofrequency ablation or resection.

In principle, HCC surveillance was performed every 6 months with abdominal ultrasonography if the patient had achieved a CR after over 2 years of a prior HCC treatment (high-risk group). Dynamic CT or MRI was performed every 6 months for patients who achieved CR in 2 years or under (extremely high-risk group). AFP level was examined every 3 months. The surveillance protocols were mainly based on the Japanese guidelines.[19] HCC recurrence was diagnosed on the basis of abnormal findings on abdominal ultrasonography plus one additional finding on dynamic CT or MRI.[20]

End-points. The primary end-points were HCC recurrence beyond 24 weeks after SVR and its predictors after achieving SVR by DAA treatment. The follow-up period reflects the time between the date of SVR determination (index date) and the date of the last image assessment or first imaging showing HCC recurrence. For patients with HCC recurrence, we collected data on the Barcelona Clinic Liver Cancer (BCLC) stage and on their treatment method. Secondary end-points were differences in predictors of HCC recurrence between the early and late (beyond 24 weeks after SVR) phases. Moreover, deaths that occurred during follow-up, even after the development of HCC and whether or not they were liver-related, were obtained from the medical records of each hospital.

Statistical analysis. Standard descriptive and comparative statistics were performed for all demographic and clinical variables. Categorical variables are described using proportions (%) and continuous variables as the median (first-third quartile). The Kaplan–Meier method was used to estimate the cumulative risks of HCC recurrence and death. The log-rank test was used to compare differences between the groups in HCC recurrence and death. Multivariable Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the variables associated with HCC recurrence during the follow-up period. An additional predefined analysis included patients with the censoring criteria of early HCC recurrence within 6 months of SVR determination. Multivariable regression analysis was used to identify variables associated with early HCC recurrence, with the results expressed as odds ratio (OR) and their 95%CI. All statistical analyses were conducted using SPSS Statistics Version 25.0

(IBM SPSS Inc, Chicago, IL, USA). Statistical significance was defined using a two-tailed P value < 0.05.

Results

Demographics. Three hundred and sixty-five patients with chronic hepatitis C and a history of HCC who were treated with a DAA were enrolled. Thirty-nine were excluded according to the criteria, leaving the data of 326 available for the final analysis (Fig. 1). Patient characteristics classified by recurrence status after DAA treatment are provided in Table 1. Overall median age was 74, 220 (67.5%) were 70 or over, and 76 (23.3%) were 80 or over at DAA initiation. Of the total patients, 55.2% were men, 77.0% had cirrhosis, 39.6% were treatment-naïve, and 33.7% had a diagnosis of diabetes. The median time from previous HCC treatment to the initiation of a DAA was 1.2 years (range 0.3–15.7 years). Approximately 30% had more than one HCC nodule, 40% had required HCC treatment to CR more than once, and 75% were treated with curative procedures.

Hepatocellular carcinoma recurrence after sustained viral response determination. During the follow-up after SVR, 171 patients (52.5%) had a recurrence of HCC. HCC recurrence within 6 months after SVR determination (early recurrence) was seen in 46 patients, whereas recurrence was beyond the early phase in 125 (Table 2). In both groups, approximately half of the patients who developed HCC recurrence were in the BCLC 0/A stage. However, the rate of curative treatment for patients in the later period was higher than that for those with early recurrence (49.6% *vs* 36.9%). Almost all patients were again treated for HCC, but the number of patients with the best supportive care was very small (n = 9, 5.3%).

Primary analysis: hepatocellular carcinoma recurrence beyond the first 6 months after hepatitis C virus cure. The median follow-up duration from SVR determination was 2.7 years (range 0–5.4 years). After excluding patients with early HCC recurrence, the corresponding 3-year and 5-year cumulative HCC recurrence rates in the previous curative treatment group were 33.6% and 45.4%, respectively. In contrast, the rates in the previous palliative treatment group were significantly higher, at 56.2% and 65.7%, respectively (log-rank test: $P < 0.001$) (Fig. 2a).

Using Cox regression multivariable analysis, cirrhosis (HR 1.85, 95%CI 1.10–3.14, P = 0.021), AFP $>$ 7 ng/mL at pw12 (HR 2.09, 95%CI 1.38–3.17, $P < 0.001$), number of HCC nodules ($\geq$ 2) (HR 1.52, 95%CI 1.04–2.23, P = 0.031), time from HCC CR to DAA initiation ($<$ 1 year) (HR 1.70, 95%CI 1.16–2.49, P = 0.007), number of HCC treatments necessary to achieve CR ($\geq$ 2) (HR 2.02, 95%CI 1.37–2.97, $P < 0.001$), and previous palliative HCC treatment (HR 1.71, 95%CI 1.13–2.60, P = 0.012) were extracted as independent predictors of late HCC recurrence (Table 3, right panel).

Next, we analyzed the predictors of late HCC recurrence according to the prior HCC treatment procedure. In the previous curative treatment group, multivariable analysis extracted cirrhosis (HR 2.08, 95%CI 1.09–3.98, P = 0.027), AFP $>$ 7 ng/mL at pw12 (HR 2.26, 95%CI 1.34–3.76, P = 0.002), and number of HCC treatments necessary to achieve CR ($\geq$ 2) (HR 2.50, 95%CI 1.55–4.03, $P < 0.001$) as independently associated with late HCC recurrence (Table 4, left panel). In the previous palliative treatment group, multivariable analysis extracted serum albumin $\leq$ 3.5 g/dL (HR 3.09, 95%CI 1.18–8.06, P = 0.021), number of HCC nodules ($\geq$ 2) (HR 2.66, 95%CI 1.24–5.72, P = 0.012), and time from HCC CR to DAA initiation ($<$ 1 year) (HR 2.78, 95%CI 1.29–6.02, P = 0.001) as independently associated with late HCC recurrence (Table 4, right panel).

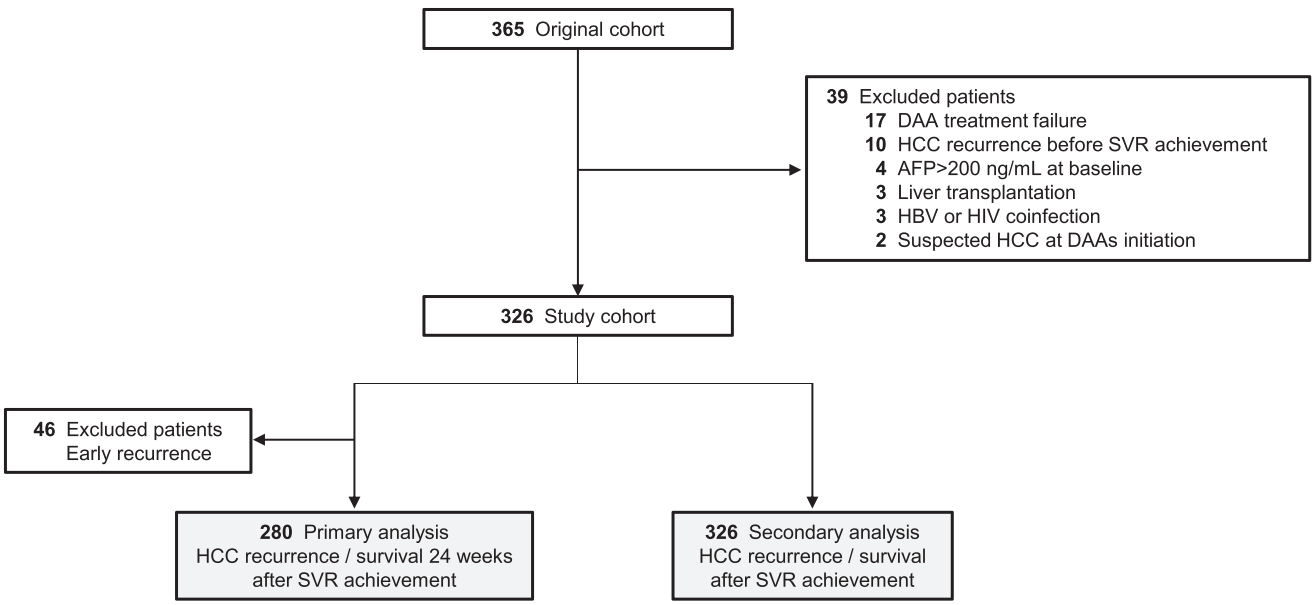

Figure 1 Study flowchart. AFP, α-fetoprotein; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; SVR, sustained viral response.

Table 1 Baseline characteristics and previous HCC data

Baseline characteristic[†]	Overall (n = 326)	Recurrence[‡] (n = 171)	Non-recurrence[‡] (n = 155)	P value
Age	74 (68–79)	74 (68–80)	74 (67–79)	0.38
Male	180 (55.2)	100 (58.5)	80 (51.6)	0.21
Body mass index (kg/m^2)	22.1 (20.4–24.3)	22.2 (20.6–24.2)	21.8 (20.1–24.9)	0.67
Cirrhosis	251 (77.0)	148 (86.6)	103 (66.5)	< 0.001
Diabetes	110 (33.7)	56 (32.7)	54 (34.8)	0.69
Treatment-naïve	129 (39.6)	75 (43.9)	54 (34.8)	0.10
FIB-4 index	5.26 (3.47–7.94)	5.78 (4.12–8.35)	4.67 (3.00–6.66)	0.009
Total bilirubin (mg/dL)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.13
Albumin (g/dL)	3.7 (3.3–4.0)	3.7 (3.3–3.9)	3.8 (3.4–4.0)	0.12
AST (U/L)	50 (37–70)	53 (40–72)	49 (35–67)	0.17
ALT (U/L)	42 (29–63)	42 (29–63)	42 (29–63)	0.66
γGTP (U/L)	38 (26–65)	36 (26–62)	40 (26–68)	0.56
eGFR (mL/min/1.73 m^2)	67 (56–78)	69 (56–79)	67 (57–79)	0.56
Platelet count (10^3/μL)	111 (80–149)	101 (75–145)	125 (85–156)	0.052
α-Fetoprotein (ng/mL)	7.7 (4.6–17.0)	8.0 (5.1–19.4)	6.8 (3.9–15.2)	0.09
HCV RNA (logIU/mL)	6.0 (5.5–6.4)	6.0 (5.5–6.3)	6.1 (5.6–6.4)	0.73
HCV Genotype				
Genotype 1	280 (85.9)	146 (85.4)	134 (86.5)	0.78
Genotype 2	46 (14.1)	25 (14.6)	21 (13.5)	
History of interferon treatment	123 (37.7)	71 (42.5)	52 (33.5)	0.14
DAA regimen				
LDV/SOF	135 (41.4)	69 (40.4)	66 (42.6)	0.72[§]
ASV + DCV	88 (27.0)	52 (30.4)	36 (23.2)	
SOF + RBV	32 (9.8)	17 (9.9)	15 (9.7)	
EBR + GZR	30 (9.2)	11 (6.4)	19 (12.3)	
GLE/PIB	25 (7.7)	14 (8.2)	11 (7.1)	
2D	16 (4.9)	8 (4.7)	8 (5.2)	
Previous HCC data				
HCC nodules at diagnosis				
1	224 (70.2)	103 (61.7)	121 (79.6)	< 0.001
2	63 (19.7)	40 (24.0)	23 (15.1)	
≥ 3	32 (10.0)	24 (14.4)	8 (5.3)	
Missing	7	4	3	
Maximum HCC diameter (cm)	1.7 (1.3–2.5)	1.6 (1.3–2.4)	1.7 (1.4–2.5)	0.22
Time from HCC CR to DAA treatment				
Median (year)	1.2 (0.6–3.2)	0.8 (0.3–2.0)	1.8 (0.6–3.9)	< 0.001
< 1 year	154 (48.3)	97 (58.1)	57 (37.5)	
1–3 year	81 (25.4)	46 (27.5)	35 (23.0)	
> 3 year	84 (26.3)	24 (14.4)	60 (39.5)	
Missing	7	4	3	
HCC treatment required to achieve CR				
1	189 (59.2)	72 (43.6)	117 (76.0)	< 0.001
2	63 (19.7)	41 (24.8)	22 (14.3)	
≥ 3	65 (20.4)	52 (31.5)	13 (8.4)	
Missing	7	6	1	
HCC treatment procedure				
Curative	237 (74.3)	109 (65.3)	128 (84.2)	< 0.001
RFA	116	68	48	
Resection	114	36	78	
Resection + RFA	7	5	2	
Palliative	82 (25.7)	58 (34.7)	24 (15.8)	
TACE	53	40	13	
TACE + RFA/Resection	24	15	9	
Particle radiotherapy	3	2	1	
PEIT	2	1	1	
Missing	7	4	3	

Data are expressed as median (first-third quartiles) or number (%).

[†]Baseline data were determined at the time of DAA initiation.

[‡]Evaluation of HCC recurrence after DAA treatment.

[§]Comparison of SOF-based and non-SOF-based treatment.

2D, ombitasvir/paritaprevir/ritonavir; γGTP, gamma-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASV, asunaprevir; CR, complete response; DAA, direct-acting antiviral; DCV, daclatasvir; EBR, elbasvir; eGFR, estimated glomerular filtration rate; GLE, glecaprevir; GZR, grazoprevir; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDV, ledipasvir; PEIT, percutaneous ethanol injection therapy; PIB, pibrentasvir; RBV, ribavirin; RFA, radiofrequency ablation; SOF, sofosbuvir; TACE, transarterial chemoembolization.

Table 2 HCC recurrence staging and treatment

Parameter	Early recurrence	Late recurrence
Number	46	125
BCLC tumor stage		
0/A	22 (47.8)	67 (53.6)
B	16 (34.8)	48 (38.4)
C	5 (10.5)	5 (4.0)
D	3 (6.5)	5 (4.0)
Treatment of HCC recurrence		
Resection	6 (13.0)	30 (24.0)
RFA	11 (23.9)	32 (25.6)
TACE	21 (45.7)	53 (42.4)
Biologics[†]	3 (6.5)	2 (1.6)
Radiation	2 (4.3)	2 (1.6)
Liver transplantation	0	0
Best supportive care	3 (6.5)	6 (4.8)

Data are expressed as number (%).
[†]Biologics: lenvatinib or sorafenib.
BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Secondary analysis: early hepatocellular carcinoma recurrence after sustained viral response. Including patients with both early and late HCC recurrence, the corresponding 3-year and 5-year cumulative HCC recurrence rates of the previous curative treatment group were 40.8% and 51.4%, respectively, significantly lower than the rates of the previous palliative treatment group, 66.5% and 73.7%, respectively (log-rank test: $P < 0.001$) (Fig. 2b).

Using multivariable analysis, AFP $>$ 7 ng/mL at pw12 (OR 4.32, 95%CI 1.94–9.62, $P < 0.001$), time from HCC CR to DAA initiation ($<$ 1 year) (OR 2.39, 95%CI 1.07–5.35, $P = 0.034$), and the number of HCC treatments necessary to achieve CR ($\geq$ 2) (OR 2.66, 95%CI 1.23–5.78, $P = 0.013$) were extracted as independent predictors of early HCC recurrence (Table 3, left panel). Unlike in the case of late recurrence, fibrosis status, the number of HCC nodules, and HCC treatment procedure were not associated with early recurrence.

Survival rate and causes of death. Fifty-eight patients (17.8%) died during the timeframe after the recurrence of HCC. Among them, 42 (72.4%) died of liver-related complications mainly due to HCC, six died due to infections such as pneumonia, five died due to non-liver cancer, and three died due to heart failure.

In the group that excluded patients with early HCC recurrence, the 3-year and 5-year survival rates for those with previous curative treatment (92.2% and 87.2%) were significantly higher than those of patients with previous palliative treatment (83.2% and 70.6%) (log-rank test: $P = 0.009$) (Fig. 3a). In the group that included patients with early HCC recurrence, the 3-year and 5-year survival rates for those with previous palliative treatment were lower than those in the above analysis (75.4% and 58.8%) (Fig. 3b).

Discussion

Direct-acting antiviral treatment has been shown to be beneficial for patients with a history of HCC treatment in regards to the improvement of survival; however, it did not have positive impact on early recurrence when comparison was performed with untreated patients.[14,15] We believe this real-world multicenter study provides further insight into differences in the predictors of HCC recurrence over a long period of time after SVR. To our knowledge, this is the longest follow-up study performed to elucidate HCC recurrence and survival after HCV cure by a DAA. Our main findings revealed that predictors of HCC recurrence differed between the early and later phases, which would be useful for developing HCC surveillance strategies. In our survival analysis, the 5-year overall survival rate after the achievement of SVR of those who had palliative HCC treatment before DAA treatment (58.8–70.6%) was significantly lower than that of those who had curative HCC treatment before DAA treatment (84.1–87.1%). Over the long run, curative HCC treatment would contribute to lowering the frequency of recurrence and lengthening survival after HCV cure.

Early HCC recurrence patterns following DAAs were identified a systematic meta-analysis[21]: a shorter interval between HCC CR and DAA initiation and prior HCC recurrence were associated with early recurrence. Consistent with previous findings, our analysis demonstrated that time from HCC CR to DAA initiation ($<$ 1 year) and prior HCC recurrence are significantly associated with early recurrence. However, we should consider the possibility that delaying DAA treatment can lead to the creation of a longer time to verify HCC CR, thereby minimizing the chance of misclassification. There is a very small possibility of HCC lesions that have not been detected by dynamic CT or MRI before the initiation of DAA treatment. Therefore, this association does not necessarily mean that DAA treatment should be delayed more than 1 year after HCC CR. The AFP level pw12 had a huge impact on early recurrence and was also significantly associated with de novo HCC[6,22]; thus, the measurement of AFP level is an essential item for monitoring both de novo HCC and HCC recurrence. However, we found totally different predictors of late HCC recurrence according to the prior HCC treatment procedure. For patients treated with curative methods, the predictors of recurrence (cirrhosis and AFP level) were very similar to those of de novo HCC. In contrast, for patients treated with palliative methods, the degree of loss of liver function (serum albumin level at post-treatment) and prior HCC characteristics were strongly associated with late HCC recurrence. In particular, the number of HCC nodules might be related to an increased likelihood of local recurrence over a long period of follow-up. Another crucial finding of our study is that patient characteristics, such as age, sex, body mass index, and diabetes, were not associated with recurrence despite the fact that many elderly patients were enrolled, unlike for the development of de novo HCC.[5,6,22,23] Once HCC has occurred, it would be best to shift the surveillance strategy to HCC-related factors rather than to patient parameters, irrespective of the time of monitoring. In fact, two-thirds of the patients treated with palliative measures and half with curative procedures experienced late recurrence over 5 years after achievement of SVR.

We have shown the BCLC staging and HCC treatment regimens of patients with HCC recurrence after HCV cure. Although

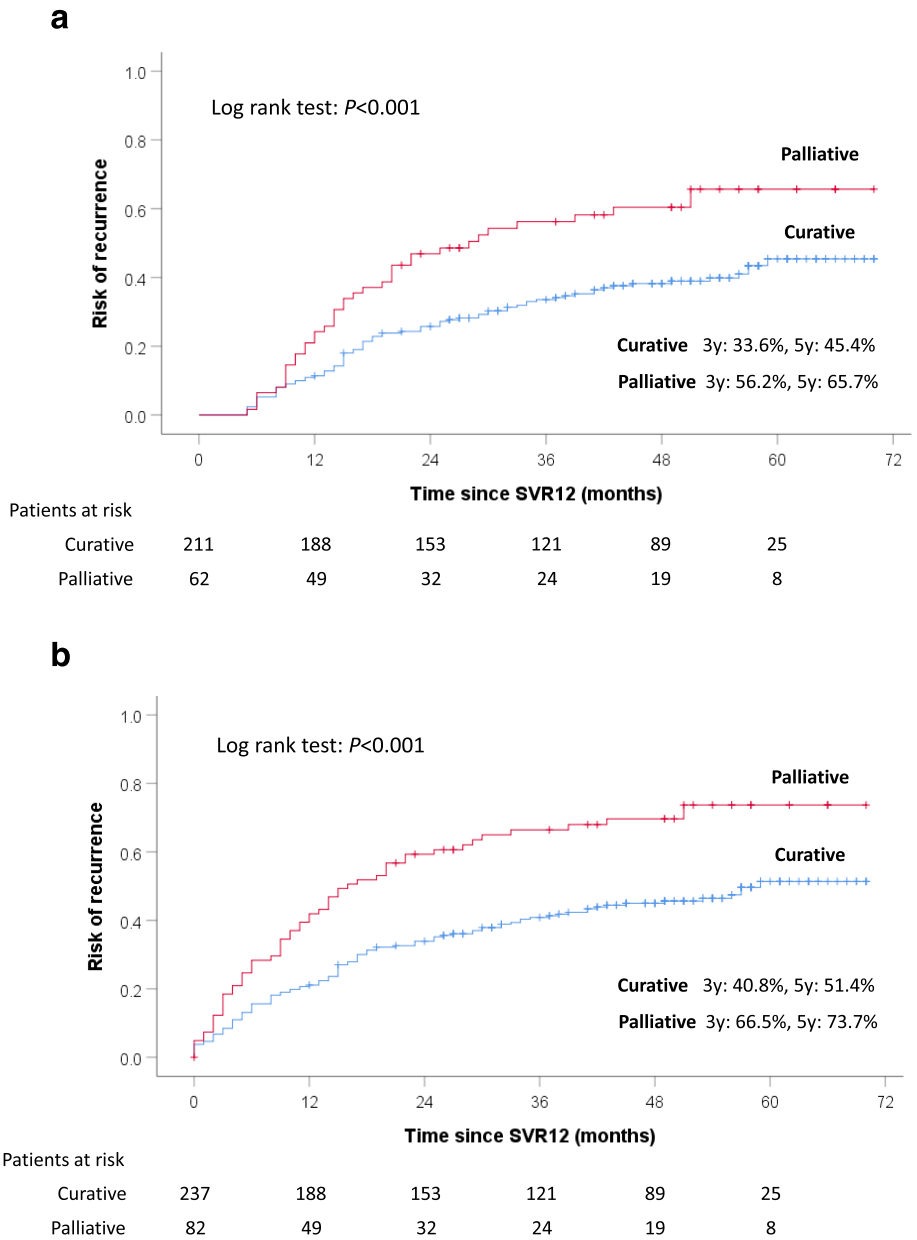

Figure 2 Cumulative development of hepatocellular carcinoma (HCC) recurrence after the determination of sustained viral response stratified by methods of previous HCC treatment. (a) HCC late recurrence and (b) HCC recurrence including the early phase.

approximately half of the patients in both the early and late recurrence groups were BCLC stage 0/A according to our strict strategy of HCC surveillance, the rate of late recurrence (49.6%) with curative treatment was higher than that of early recurrence (36.9%), probably because the hepatic reserve improved with time, but the difference did not reach significance ($P = 0.14$). Nevertheless, almost all patients except for BCLC stage D had some sort of HCC treatment. The monitoring methods and surveillance intervals require further consideration.

Our data provide the survival rate according to the previous HCC treatment procedure. The 5-year survival rate was reduced to 70.6% for patients treated with a palliative procedure before DAA treatment and to 58.8% when including patients with early recurrence mainly due to the liver-related complications. In contrast, the 5-year survival rate was maintained at over 80% for patients treated with a curative procedure before DAA treatment, even when those with early recurrence were included. We speculate that DAAs maintain or improve the survival rate through the improvement liver function, resulting in a higher likelihood of having to again receive curative treatment (49 of 84, 58.3%), even in cases of recurrence.

The strengths of this study include the large patient population with a history of HCC treatment who were consecutively enrolled, a consistent and systematic protocol of evaluation of clinical data,

Table 3 Predictors of HCC recurrence according phase (early or late)

Characteristic	Early recurrence		Late recurrence	
	Multivariable analysis		Multivariable analysis	
	Adjusted OR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
Age				
< 75	1 (Referent)	0.79	1 (Referent)	0.82
≥ 75	1.11 (0.52–2.38)		1.05 (0.71–1.55)	
Sex				
Female	1 (Referent)	0.25	1 (Referent)	0.10
Male	1.56 (0.72–3.38)		1.38 (0.94–2.02)	
Body mass index (kg/m^2)				
< 25	1 (Referent)	0.09	1 (Referent)	0.24
≥ 25	2.42 (0.88–6.70)		1.36 (0.82–2.25)	
Fibrosis status				
Non-cirrhosis	1 (Referent)	0.27	1 (Referent)	0.021
Cirrhosis	1.84 (0.62–5.48)		1.85 (1.10–3.14)	
Diabetes				
No	1 (Referent)	0.69	1 (Referent)	0.66
Yes	1.17 (0.54–2.52)		1.10 (0.72–1.66)	
History of interferon treatment				
Yes	1 (Referent)	0.055	1 (Referent)	0.73
No	2.22 (0.98–5.03)		1.07 (0.72–1.60)	
Serum albumin (g/dL) at pw12				
> 3.5	1 (Referent)	0.13	1 (Referent)	0.41
≤ 3.5	1.95 (0.83–4.59)		1.22 (0.76–1.96)	
ALT (U/L) at pw12				
< 30	1 (Referent)	0.054	1 (Referent)	0.56
≥ 30	2.45 (0.98–6.09)		1.17 (0.69–1.98)	
α-Fetoprotein (ng/mL) at pw12		< 0.001		< 0.001
≤ 7	1 (Referent)		1 (Referent)	
> 7	4.32 (1.94–9.62)		2.09 (1.38–3.17)	
HCV genotype				
Genotype 1	1 (Referent)	0.29	1 (Referent)	0.74
Genotype 2	0.59 (0.22–1.57)		0.91 (0.51–1.61)	
Pretreatment HCV RNA level (logIU/mL)				
< 6.0	1 (Referent)	0.96	1 (Referent)	0.76
≥ 6.0	0.98 (0.47–2.05)		0.94 (0.64–1.39)	
DAA treatment regimen				
Sofosbuvir-based	1 (Referent)	0.63	1 (Referent)	0.56
Non-sofosbuvir-based	0.83 (0.39–1.77)		0.89 (0.60–1.32)	
HCC nodules at previous diagnosis				
1	1 (Referent)	0.91	1 (Referent)	0.031
≥ 2	1.05 (0.47–2.32)		1.52 (1.04–2.23)	
Time from HCC CR to DAA treatment (year)				
≥ 1	1 (Referent)	0.034	1 (Referent)	0.007
< 1	2.39 (1.07–5.35)		1.70 (1.16–2.49)	
HCC treatment required to achieve CR				
1	1 (Referent)	0.013	1 (Referent)	< 0.001
≥ 2	2.66 (1.23–5.78)		2.02 (1.37–2.97)	
Previous HCC treatment procedure				
Curative	1 (Referent)	0.23	1 (Referent)	0.012
Palliative	1.63 (0.73–3.66)		1.71 (1.13–2.60)	

ALT, alanine aminotransferase; CI, confidence interval; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HR, hazard ratio; OR, odds ratio; pw12, 12 weeks after the end of DAA treatment.

and the long-term follow-up. Limitations include the retrospective design and that we had no controls without DAA treatment. However, DAA treatment has been accepted worldwide as the standard of care, even for patients with decompensated cirrhosis and a history of HCC; therefore, it is not feasible to design studies for direct comparison of patients who did *versus* did not receive DAAs.

Table 4 Predictors of late HCC recurrence according to prior HCC treatment procedure

Characteristic	Curative HCC treatment		Palliative HCC treatment	
	Multivariable analysis		Multivariable analysis	
	Adjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
Age				
< 75	1 (Referent)	0.55	1 (Referent)	0.95
≥ 75	1.16 (0.71–1.90)		0.97 (0.41–2.28)	
Sex				
Female	1 (Referent)	0.089	1 (Referent)	0.93
Male	1.51 (0.94–2.42)		1.03 (0.47–2.26)	
Body mass index (kg/m^2)				
< 25	1 (Referent)	0.69	1 (Referent)	0.076
≥ 25	1.14 (0.61–2.12)		2.33 (0.92–5.93)	
Fibrosis status				
Non-cirrhosis	1 (Referent)	0.027	1 (Referent)	0.66
Cirrhosis	2.08 (1.09–3.98)		1.30 (0.40–4.27)	
Diabetes				
No	1 (Referent)	0.67	1 (Referent)	0.64
Yes	1.12 (0.67–1.87)		1.25 (0.49–3.19)	
History of interferon treatment				
Yes	1 (Referent)	0.53	1 (Referent)	0.32
No	1.18 (0.71–1.94)		1.53 (0.66–3.51)	
Serum albumin (g/dL) at pw12				
> 3.5	1 (Referent)	0.87	1 (Referent)	0.021
≤ 3.5	1.06 (0.56–2.00)		3.09 (1.18–8.06)	
ALT (U/L) at pw12				
< 30	1 (Referent)	0.47	1 (Referent)	0.80
≥ 30	1.29 (0.64–2.61)		1.12 (0.47–2.68)	
α-Fetoprotein (ng/mL) at pw12				
≤ 7	1 (Referent)	0.002	1 (Referent)	0.70
> 7	2.26 (1.34–3.76)		1.19 (0.49–2.91)	
HCV genotype				
Genotype 1	1 (Referent)	0.25	1 (Referent)	0.59
Genotype 2	0.68 (0.35–1.32)		0.67 (0.16–2.85)	
Pre-treatment HCV RNA level (logIU/mL)				
< 6.0	1 (Referent)	0.62	1 (Referent)	0.99
≥ 6.0	0.89 (0.55–1.43)		1.00 (0.43–2.34)	
DAA treatment regimen				
Sofosbuvir-based	1 (Referent)	0.29	1 (Referent)	0.62
Non-sofosbuvir-based	0.77 (0.48–1.24)		0.81 (0.36–1.83)	
HCC nodules at previous diagnosis				
1	1 (Referent)	0.34	1 (Referent)	0.012
≥ 2	1.26 (0.78–2.03)		2.66 (1.24–5.72)	
Time from HCC CR to DAA treatment (year)				
≥ 1	1 (Referent)	0.27	1 (Referent)	0.001
< 1	1.31 (0.81–2.10)		2.78 (1.29–6.02)	
HCC treatment required to achieve CR				
1	1 (Referent)	< 0.001	1 (Referent)	0.58
≥ 2	2.50 (1.55–4.03)		1.24 (0.58–2.66)	

ALT, alanine aminotransferase; CI, confidence interval; CR, complete response; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HR, hazard ratio; pw12, 12 weeks after the end of DAA treatment.

Moreover, we enrolled consecutive patients treated with a DAA in each hospital, carefully reviewed every medical chart, and used objective criteria that included laboratory results, radiology reports, and physician notes, to determine cirrhosis and HCC status. Second, there is a lack of generalizability of our results to different ethnic groups and settings, such as age, clinical features, and comorbidities. Further studies of other ethnic groups and countries are needed to generalize our findings.

In conclusion, HCC recurrence commonly occurred long after the achievement of SVR. According to our long-term cohort study,

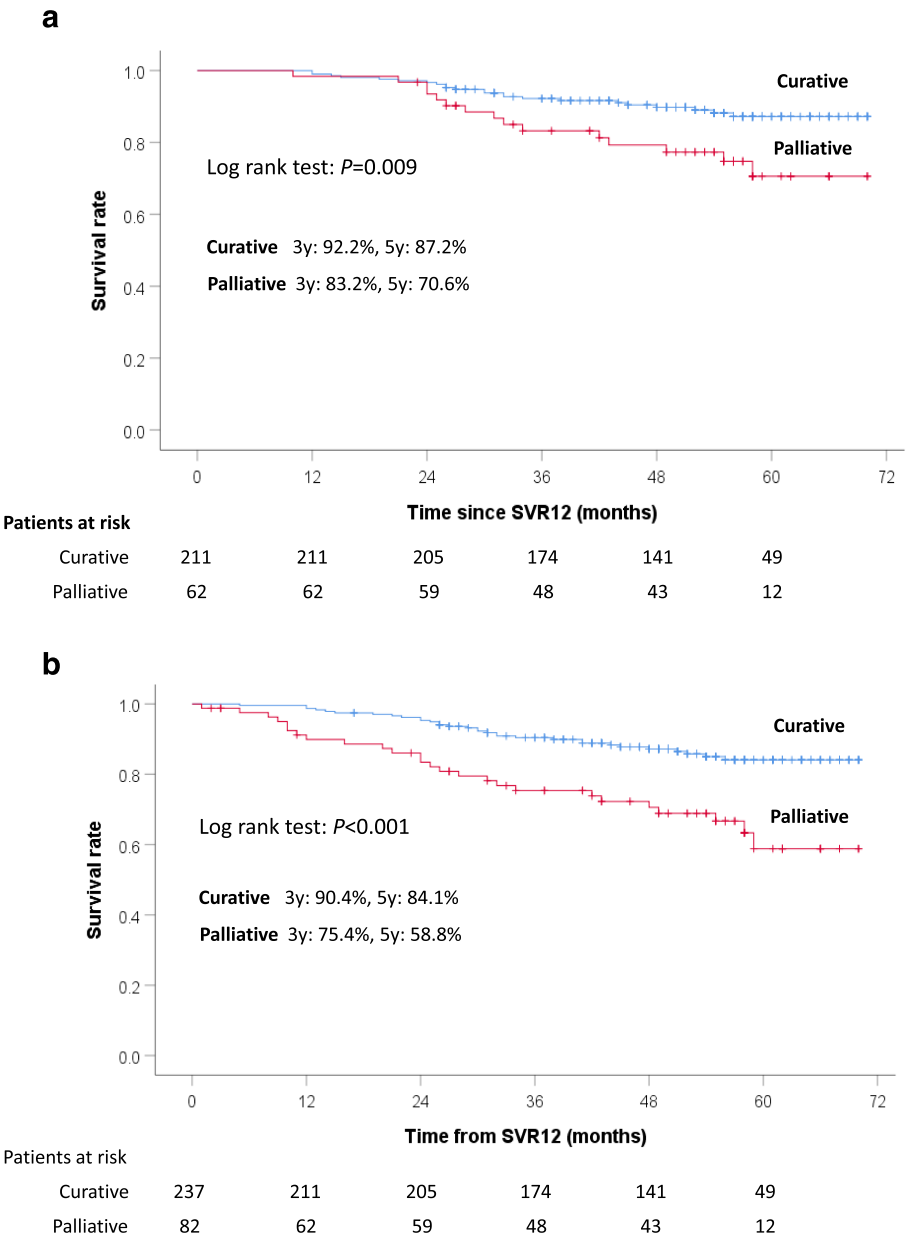

Figure 3 Survival rates stratified by methods of previous hepatocellular carcinoma (HCC) treatment. (a) Excluding those with HCC recurrence during the early phase, (b) including those with HCC recurrence during the early phase.

predictors of recurrence were partly different between the early and late phases; moreover, they were completely different according to the previous treatment procedure. The combination of fibrosis markers, previous HCC characteristics, and method of HCC treatment would allow for better HCC recurrence stratification and the development of individualized surveillance strategies.

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