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Table 1. Tumor node metastasis stage of Liver Cancer Study Group of Japan and Japan Integrated Soring (JIS) system

T factor* for TNM stage of LCSGJ 5th edition
T1: Fulfilling 3 factors
T2: Fulfilling 2 factors
T3: Fulfilling 1 factor
T4: Fulfilling 0 factors
TNM stages in LCSGJ 5th edition
Stage I: T1N0M0
Stage II: T2N0M0
Stage III: T3N0M0
Stage IVa: T4N0M0, or any TN1M0
Stage IVb: Any TN0-N1M1
JIS score/ALBI-T score
JIS/ALBI-T score 0: TNM stage I and Child-Pugh A/ALBI 1
JIS/ALBI-T score 1: TNM stage I and Child-Pugh B/ALBI 2
TNM stage II and Child-Pugh A/ALBI 1
JIS/ALBI-T score 2: TNM stage I and Child-Pugh C/ALBI 3
TNM stage II and Child-Pugh B/ALBI 2

TNM stage III and Child-Pugh A/ALBI 1
JIS/ALBI-T score 3: TNM stage II and Child-Pugh C/ALBI 3
TNM stage III and Child-Pugh B/ALBI 2
TNM stage IV and Child-Pugh A/ALBI 1
JIS/ALBI-T score 4: TNM stage III and Child-Pugh C/ALBI 3
TNM stage IV and Child-Pugh B/ALBI 2
JIS/ALBI-T score 5: TNM stage IV and Child-Pugh C/ALBI 3

ALBI: albumin-bilirubin grade, JIS: Japan Integrated Scoring, LCSGJ: Liver Cancer Study Group of Japan, TNM stage: tumor node metastasis stage, ALBI-T: scoring determined based on TNM stage as shown in the LCSGJ 5th edition and by ALBI grade
*The 3 factors are a single lesion, a lesion measuring <2 cm, and no vascular involvement.

Table 2. Clinical background of patients with hepatocellular carcinoma

Average age (years) (median, range)	69.0±9.8 (70, 21-96)
Sex (male:female)	1850:734
Etiology (HCV:HBV:HBV&HCV:alcohol:others	1723:308:26:149:378
Child-Pugh class A:B:C	1871:558:155
TNM stage of LCSGJ 5th (I:II:III:IVa:IVb)	594:1044:569:244:133
Milan criteria (within:beyond)	1637:947
Therapies (surgical resection:RFA:PEIT:TACE:RT:chemotherapy:BSC)	833:743:55:492:8:97:356

HCV: hepatitis C virus, hepatitis B virus, LCSGJ: Liver Cancer Study Group of Japan, RFA: radiofrequency ablation, PEIT: percutaneous ethanol injection therapy, TACE: transcatheter arterial chemoembolization, BSC: best supportive care

Table 3. Median survival time (months) with each prognostic scoring system

ALBI-T score	JIS score	CLIP score	BCLC stage	BALAD score
0 137.7	***0*** 97.6	***0*** 85.0	***0*** 85.0	***0*** 90.4
1 83.2	***1*** 74.9	***1*** 55.0	***A*** 77.0	***1*** 50.6
2 53.4	***2*** 39.7	***2*** 23.5	***B*** 40.7	***2*** 32.7
3 27.4	***3*** 15.0	***3*** 9.0	***C*** 23.5	***3*** 12.8
4 5.0	***4*** 4.0	***4*** 2.7	***D*** 8.2	***4*** 2.7
5 1.4	***5*** 1.0	***5*** 1.4	- -	***5*** 1.5
- -	- -	***6*** 0.9	- -	- -

ALBI-T: scoring determined based on TNM stage shown in the Liver Cancer Study Group of Japan 5th edition and albumin-bilirubin grade JIS: Japan Integrated Staging, CLIP: Cancer of the Liver Italian Program, BCLC: Barcelona Clinic Liver Cancer, BALAD: bilirubin, albumin, lens culinaris agglutinin A-reactive fraction of α-fetoprotein, α-fetoprotein and des-γ-carboxy prothrombin

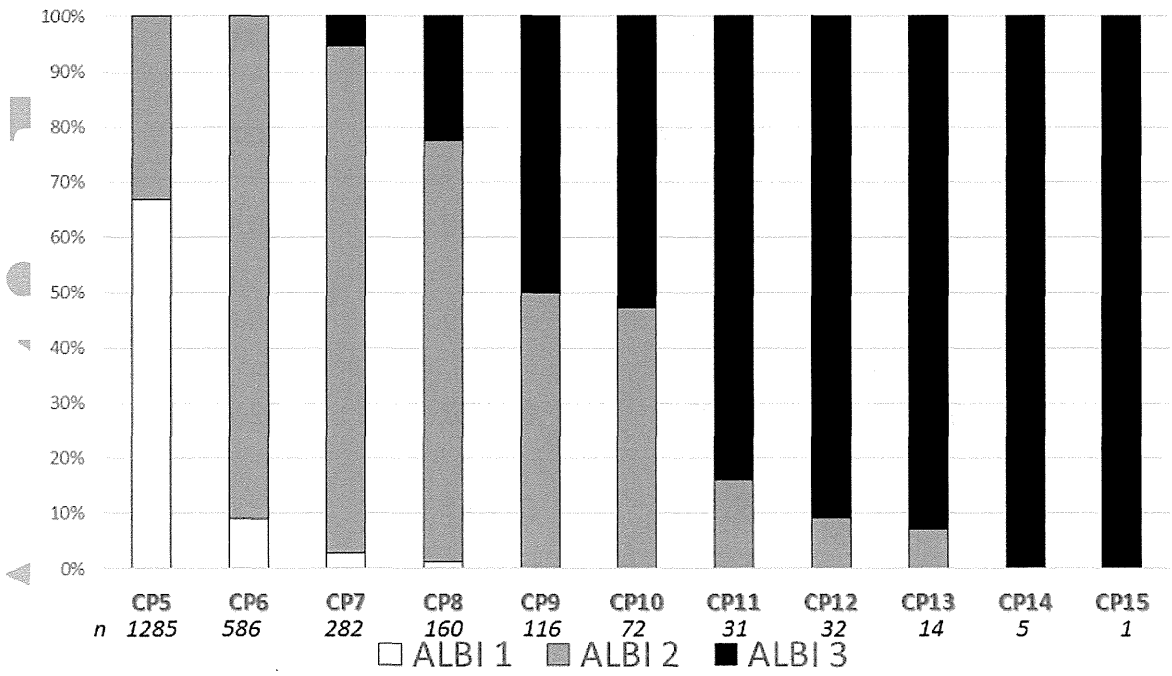
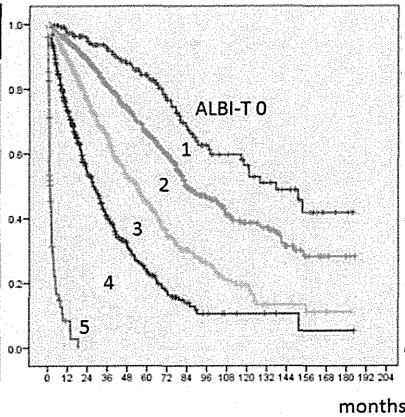


Figure 1. Re-evaluation of hepatic reserve function using ALBI grade. We divided 1285 patients with 5 points in the Child-Pugh classification into 858 (66.8%) with ALBI grade 1 and 427 (33.2%) with grade 2, as well as 586 with 6 points into 53 (9.0%) with ALBI grade 1 and 533 (91.0%) with grade 2. None were found with ALBI grade 3. The ratio of ALBI grade 2 among patients with a Child-Pugh score of 6 points (class A) was 91.0%, which was similar to that of those with 7 points (class B) (91.8%). The ratio of ALBI grade 3 among patients with a Child-Pugh score of 9 points (class B) was 50.0%, which was similar to that of those with 10 points (class C) (52.8%).

a. Correlation of JIS and ALBI-T scores

JIS \ ALBI-T	0	1	2	3	4	5
0	234	245	-	-	-	-
1	3	519	391	-	-	-
2	-	12	337	260	-	-
3	-	-	5	199	153	-
4	-	-	-	15	115	25
5	-	-	-	-	19	52

b. ALBI-T score
N=2584



c. JIS score
N=2584

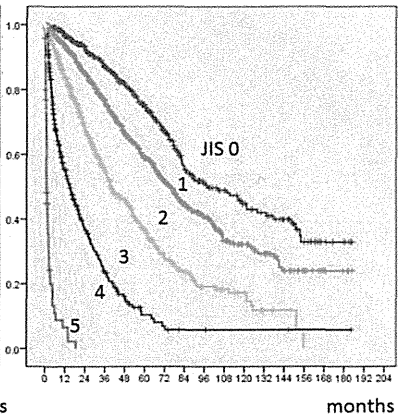


Figure 2. Survival rates according to JIS and ALBI-T scores. Correlation of Japan Integrated Scoring (JIS) and ALBI-T scores (a). Patients with a lower ALBI-T score of 0, 1, 2, 3, 4, or 5 (b) showed better prognosis than those with a corresponding lower JIS score (0, 1, 2, 3, 4, 5) (c) [median survival time (MST): ALBI-T score =137.7 : 83.2 : 53.4 : 27.4 : 5.0 : 1.4 vs. MST for JIS score =97.6 : 74.9 : 39.7 : 15.0 : 4.0 : 1.0 months].

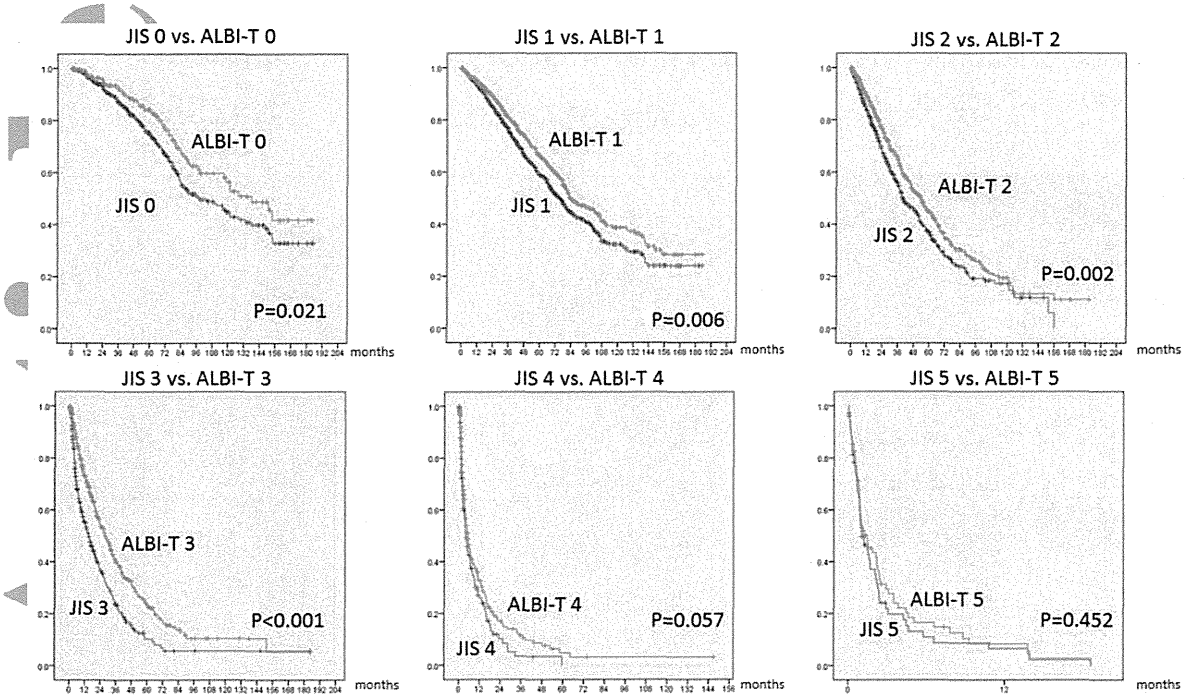


Figure 3. Comparison of each score of ALBI-T and JIS scores. ALBI-T score 0, 1, 2, 3 show better prognosis than those with corresponding JIS score significantly (P values of 0, 1, 2 and 3: 0.021, 0.006, 0.002 and <0.001).

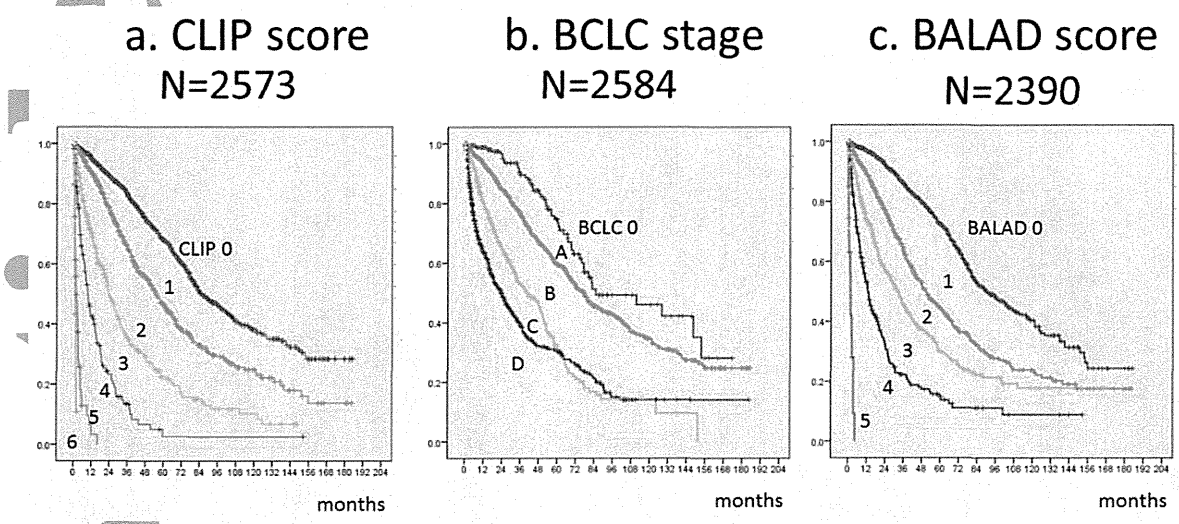


Figure 4. Survival rates according to CLIP score, BCLC stage, and BALAD score. The median survival time (MST) of patients with a Cancer of the Liver Italian Program (CLIP) score of 0, 1, 2, 3, 4, 5, and 6 was 85.0, 55.0, 23.5, 9.0, 2.7, 1.4, and 0.9 months, respectively, while that of those classified as Barcelona Clinic Liver Cancer (BCLC) stage 0, A, B, C, and D was 85.0, 77.0, 40.7, 23.5, and 8.2 months, respectively, and of those with a bilirubin, albumin, lens culinaris agglutinin A-reactive fraction of α-fetoprotein, α-fetoprotein and des-γ-carboxy prothrombin (BALAD) score of 0, 1, 2, 3, 4, and 5 was 90.4, 50.6, 32.7, 12.8, 2.7, and 1.5 months, respectively. BCLC stage B and C could not be separated. Cases lacking data for each score were excluded from analysis.

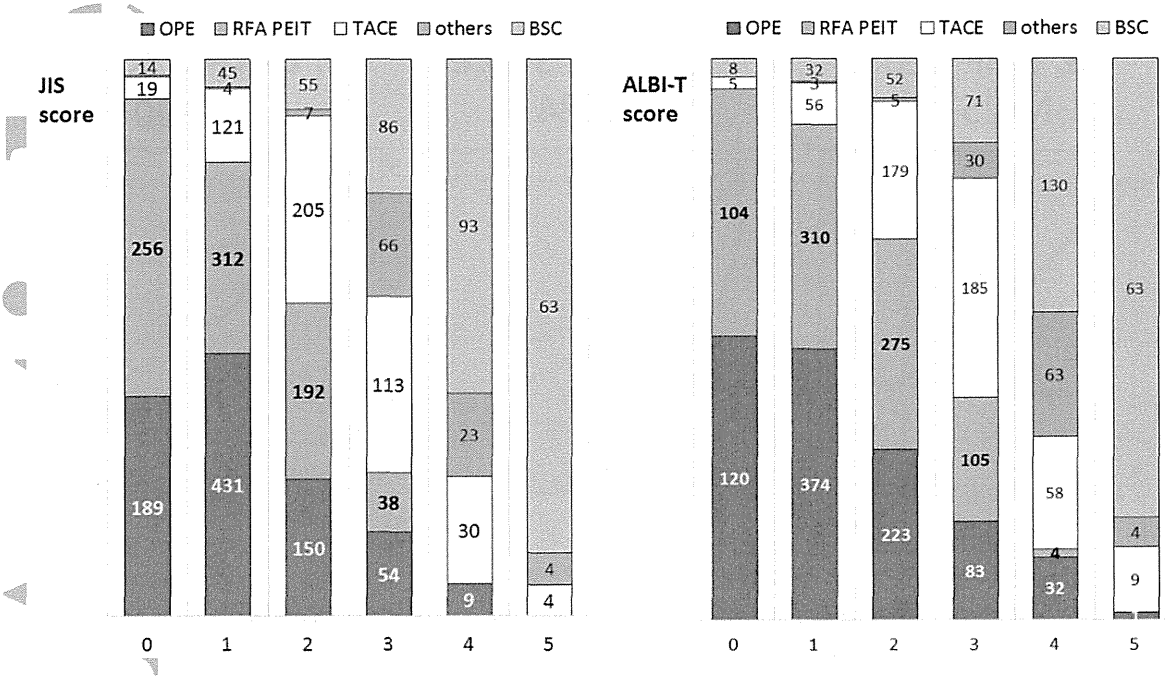


Figure 5. Frequency of each therapy for each grade of JIS score and corresponding ALBI-T score. The percentage of patients who underwent surgical resection or radiofrequency ablation (RFA) was higher with an ALBI-T score of 0, 1, 2, 3, 4 and 5 as compared to the corresponding Japan Integrated Scoring (JIS) score (94.5% vs. 92.9%, P=0.159; 88.3% vs. 81.4%; P<0.001; 67.8% vs. 56.2%; P<0.001; 40.0% vs. 25.8%, P=0.001; and 12.5% vs. 5.8%, P=0.165, and 7.1 vs. 0.0%, P=0.439 respectively).

Hepatology Research

Hepatology Research 2015 doi: 10.1111/hepr.12613

Original Article

Characteristics and prognosis of hepatocellular carcinoma detected in patients with chronic hepatitis C after the eradication of hepatitis C virus: A multicenter study from Japan

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Aim: We investigated the characteristics and prognosis of patients with hepatocellular carcinoma (HCC) diagnosed after sustained virological response (SVR) to antiviral therapy for chronic hepatitis C virus (HCV) infection, namely, the eradication of HCV, according to surveillance status after SVR.

Methods: In this multicenter study, liver function at HCC diagnosis and progression of HCC among patients with HCC diagnosed after SVR were compared. Outcomes were also investigated.

Results: In patients not under surveillance after SVR, HCC was significantly more advanced at diagnosis, with tumors that were larger in size and of higher stage than in patients who continued under surveillance after SVR. Survival rates were significantly lower in patients not under surveillance ($P < 0.0001$). Among patients who were under surveillance, those with a 6-month surveillance interval had larger and higher stage HCC than patients with a 3-month interval. Recurrence rates in patients with a 6-month surveillance interval were significantly higher than in patients with a 3-month surveillance interval ($P = 0.0417$).

Conclusion: Lack of surveillance after SVR was obviously associated with more advanced HCC at detection, resulting in poor prognosis. More importantly, there may be a difference in the severity of HCC at diagnosis and prognosis based on the surveillance interval after SVR. Establishing guidelines how to survey patients with chronic hepatitis C after SVR is necessary.

Key words: chronic hepatitis C, hepatocellular carcinoma, interval, prognosis, surveillance, sustained virological response

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is one of the most prevalent cancers worldwide.[1] It is the third leading cause of cancer death among men and the sixth among women worldwide. In Japan, HCC is the third and fifth most common cause of death from cancer in men and women, respectively,[2] and its incidence is predicted to increase in the USA.[3,4] Chronic hepatitis C is one of the major causes of HCC;[4–6] the main purpose of antiviral therapy to eradicate hepatitis C virus (HCV) infection is to prevent HCC in chronically infected patients.

Sustained virological response (SVR), defined as the eradication of HCV with antiviral therapy, has been reported to prevent the progression of chronic hepatitis and associated complications.[7] Several studies have confirmed that the incidence of HCC was lowered by the achievement of SVR.[8–12] However, the risk of HCC remains even after the eradication of HCV; HCC is

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Conflict of interest: There is no conflict of interest on this study. Financial support: No grant or other financial support was received for this study. Received 28 July 2015; revision 29 September 2015; accepted 21 October 2015.

sometimes observed in patients who have achieved SVR.[13–17] The emergence of new direct-acting antiviral drugs against HCV will dramatically increase the number of patients who achieve SVR. Given the marked increase expected in the number of patients who will achieve SVR, there will be an increase in the number of patients who develop HCC after SVR in the near future.

There have been several studies that investigated risk factors for HCC after HCV eradication,[14–18] but very few that have studied the characteristics of HCC diagnosed after SVR and the associated prognosis.

In this multicenter study, we investigated the characteristics and outcomes of HCC in patients with chronic HCV infection who achieved SVR, namely, HCV eradication, according to the type of surveillance for HCC after SVR.

METHODS

Patients and analysis

IN THIS MULTICENTER study, we recruited patients in whom initial, non-recurrent HCC was diagnosed after the confirmation of SVR following interferon-based antiviral therapy between the years 1998 and 2014 at one of the following eight liver centers: Ehime Prefectural Central Hospital, Kagawa Prefectural Central Hospital, Teine Keijinkai Hospital, Saiseikai Niigata Daini Hospital, Asahi Chuo Hospital, Komaki City Hospital, Isesaki Municipal Hospital and Ogaki Municipal Hospital. Patients who had had a history of HCC before the start of the antiviral therapy that resulted in SVR were excluded. SVR was defined as the absence of serum HCV RNA at 24 weeks after the completion of antiviral therapy.

Data on the characteristics of HCC at diagnosis, including tumor size, number of tumors, portal vein invasion, tumor stage (the Barcelona Clinic Liver Cancer [BCLC] classification[19] and tumor–node–metastasis (TNM) stage according to the Liver Cancer Study Group of Japan [LCSGJ] classification),[20] tumor marker levels, degree of differentiation (in patients who underwent surgical resection) and treatment were collected by medical record review. The type of HCC surveillance patients underwent after SVR and before HCC diagnosis was also investigated. The recurrence and survival rates after HCC diagnosis were calculated. The characteristics and prognosis of HCC at the time of HCC diagnosis were compared based on surveillance status.

The study protocol was in compliance with the Declaration of Helsinki and was approved by the institutional review board of each participating institution.

Surveillance after SVR and HCC diagnosis

Patients under surveillance principally underwent ultrasonography and laboratory testing including aspartate aminotransferase, alanine aminotransferase, platelet count, α-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive AFP and des-γ-carboxyprothrombin every 3 or 6 months. When a liver tumor was detected or suspected by ultrasonography, or tumor marker elevation was found, an additional imaging study (usually computed tomography or magnetic resonance imaging) was conducted to verify the presence of HCC. The diagnosis of HCC was based on appropriate imaging characteristics according to LCSGJ consensus guidelines.[21] In patients who underwent surgical resection as a treatment, the diagnosis of HCC was also confirmed based on pathological findings in the resected specimen. Decisions regarding treatment for each individual patient were principally based on the Japanese guidelines.[22]

Statistical analysis

Differences in percentages between groups were analyzed using the χ^2-test. Differences in numerical values were analyzed using the Mann–Whitney *U*-test. The date of HCC diagnosis was defined as time zero when calculating recurrence and survival rates. In the analysis of survival, patients who were alive were censored, and those who died were not censored. In the analysis of recurrence, patients without HCC recurrence were censored, and patients who had HCC recurrence were not censored. The Kaplan–Meier method[23] was used to calculate recurrence and survival rates, and the log–rank test[24] was used to analyze differences. The Cox proportional hazards model[25] was used for univariate and multivariate analysis of factors related to survival and recurrence. Variables that reached $P < 0.10$ in the univariate analysis were subsequently included in the multivariate analysis. Statistical analysis was performed using JMP statistical software, version 6.0 (Macintosh version; SAS Institute, Cary, NC, USA). All *P*-values were derived from two-tailed tests, with $P < 0.05$ accepted as statistically significant.

RESULTS

Characteristics, treatments and outcomes of patients with HCC after SVR according to surveillance status

THERE WERE 83 patients from one of eight liver centers who developed HCC after the achievement of SVR among a total of 2152 SVR patients, and these patients were included in the analysis. Table 1 shows the characteristics of all patients at HCC diagnosis and based on whether surveillance was performed or not after SVR. The

Table 1 Characteristics of patients who developed HCC after SVR based on surveillance status ($n = 83$)

	Total	Under surveillance at the time of HCC diagnosis		
		Yes ($n = 66$)	No ($n = 17$)	*P*
Age at SVR24 (years)	60.1 ± 6.9	60.6 ± 7.0	58.1 ± 6.2	0.1930
Age at HCC diagnosis (years)	66.7 ± 7.4	66.6 ± 7.7	67.4 ± 6.0	0.9376
Sex (male/female)	65 (78.3)/18 (21.7)	51 (77.3)/15 (22.7)	14 (82.4)/3 (17.6)	0.8988
Interval between SVR and HCC (years)	6.7 ± 4.5	6.4 ± 4.3	7.9 ± 5.0	0.2852
Liver histology at the diagnosis of HCC* (F1/F2/F3/F4)	7 (16.7)/9 (21.4)/11 (26.2)/15 (35.7)	5 (15.6)/6 (18.8)/8 (25.0)/13 (40.6)	2 (20.0)/3 (30.0)/3 (30.0)/2 (20.0)	0.6782
ALT (IU/L)	26.7 ± 14.4	25.7 ± 14.5	30.5 ± 13.9	0.1203
Albumin (g/dL)	4.22 ± 0.48	4.25 ± 0.44	4.09 ± 0.58	0.3884
Bilirubin (mg/dL)	0.91 ± 0.57	0.91 ± 0.49	0.93 ± 0.84	0.3907
Platelet counts ($\times 10^3/\mu L$)	161 ± 56	153 ± 51	192 ± 65	0.0065
Tumor size (cm)	3.2 ± 2.5	2.4 ± 1.4	6.3 ± 3.2	<0.0001
No. of tumors (single/multiple)	62 (74.7)/21 (25.3)	54 (81.8)/12 (18.2)	8 (47.1)/9 (52.9)	0.0085
Portal vein invasion (absent/present)	74 (89.2)/9 (10.8)	63 (95.5)/3 (4.5)	11 (64.7)/6 (35.3)	0.0014
BCLC class (0/A/B/C or D)	30 (36.1)/21 (25.3)/22 (26.5)/10 (12.1)	30 (45.5)/20 (30.3)/13 (19.7)/3 (4.5)	0/1 (5.9)/9 (52.9)/7 (41.2)	<0.0001
Tumor stage (I/II/III or IV)**	30 (36.1)/35 (42.2)/18 (21.7)	30 (45.5)/29 (43.9)/7 (10.6)	0/6 (35.3)/11 (64.7)	<0.0001
AFP (ng/dL, mean [range])	7.8 (0.8–305 000)	5.5 (0.8–63 750)	108.4 (3.6–305 000)	0.0051
AFP-L3 (%, mean [range])	0 (0–79.0)	0 (0–49.0)	21.0 (0–79.0)	0.0059
DCP (mAU/mL, mean [range])	50 (7–59 900)	35.5 (7–41 800)	1815 (20–59 900)	<0.0001
Differentiation (well/moderately or poorly)*	12 (28.6)/30 (71.4)	11 (34.4)/21 (65.6)	1 (10.0)/9 (90.0)	0.2764
Treatment (resection/RFA/TACE/none)	42 (50.6)/30 (36.2)/6 (7.2)/5 (6.0)	32 (48.5)/29 (43.9)/5 (7.6)/0	10 (58.8)/1 (5.9)/1 (5.9) /5 (29.4)	<0.0001

AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive AFP; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; DCP, des-γ-carboxyprothrombin; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; SVR24, sustained virological response confirmed 24 weeks after the completion of antiviral therapy; TACE, transarterial chemoembolization.

Data are expressed as means ± standard deviation or median (range). Percentages are shown in parentheses.

*Among patients who underwent surgical resection and a liver specimen was available.

**Based on the tumor–node–metastasis staging of the Liver Cancer Study Group of Japan.[19]

patients consisted of 65 men and 18 women, with a mean age of 66.7 ± 7.4 years at HCC diagnosis. The mean duration from the confirmation of SVR to HCC diagnosis was 6.7 ± 4.5 years. All but one patient had Child–Pugh class A liver function[26] at HCC diagnosis. At the diagnosis of HCC, 17 patients did not undergo surveillance for HCC and the other 66 patients continued surveillance. Among patients who underwent surveillance, 50 patients visited the hospital for surveillance with 6-month intervals and the remaining 16 patients visited with 3-month intervals. There were no differences in the distribution of patients by surveillance across the participating hospitals. All surveyed patients underwent ultrasonography and laboratory tests at every visit in both 6- and 3-month interval groups. HCC was diagnosed 5.3 ± 3.1 years after the dropout from surveillance in patients who did not undergo surveillance after SVR, and they had significantly larger tumors and there was a higher proportion of patients with multiple HCC and portal vein invasion than those who had been under surveillance. The BCLC classification and TNM stage at diagnosis was significantly more advanced in patients who did not undergo surveillance; none of the patients were diagnosed with BCLC class 0 and TNM stage I HCC, more than 40% had BCLC class C or D and more than 60% had TNM stage III or IV HCC at diagnosis.

Regarding treatment for HCC, eight of 30 patients with TNM stage I HCC (26.7%) underwent surgical resection, 21 (70.0%) underwent radiofrequency ablation (RFA) and the remaining one patient (3.3%) underwent transarterial chemoembolization (TACE). In contrast, 26 of 35 patients with stage II HCC (74.3%) underwent surgical resection, eight (22.9%) underwent RFA and the remaining one (2.8%) underwent TACE, due to the large size of HCC for RFA. In 18 patients with stage III or IV HCC, eight patients (44.4%) underwent surgical resection, one (5.6%) underwent RFA, four (22.2%) underwent

TACE and the remaining five (27.8%) did not receive treatment. Whereas more than 90% of patients who underwent surveillance for HCC after SVR could undergo curative treatment (surgical resection or RFA), nearly 30% of patients who did not undergo surveillance could not receive any treatment for HCC due to advanced disease. Of note, RFA could be performed as a treatment for HCC in only one patient who was not under surveillance; most of the other patients had tumors that were too large to be treated using RFA.

Figure 1 compares the survival rates of patients with HCC based on whether they were under surveillance for HCC. Patients who were not under surveillance had a significantly lower survival rate than patients who had been under surveillance ($P < 0.0001$). Univariate and multivariate analyses were conducted for factors related to survival including factors other than tumor progression that are closely associated with surveillance status before HCC diagnosis. In univariate analysis, lower platelet count at HCC diagnosis and absence of surveillance were significantly associated, and age at HCC diagnosis tended to be associated with lower survival rates. In multivariate analysis, only absence of surveillance was significantly associated with lower survival rates (Table 2).

Characteristics, treatments and outcomes of patients with HCC after SVR based on the surveillance interval

Table 3 compares the characteristics of patients at HCC diagnosis in patients who had continued surveillance for HCC after SVR based on the surveillance interval. Although there were no differences in the proportion of patients with multiple HCC or portal vein invasion at diagnosis and levels of tumor markers, tumors were significantly larger in patients who underwent surveillance at 6-month intervals compared with those with 3-month intervals. Whereas HCC was BCLC class 0 and TNM stage I in 75% of patients with a 3-month interval, there were three patients (6.0%) diagnosed with BCLC class C or D HCC and seven patients (14.0%) with TNM stage III or IV HCC with a 6-month interval even through surveillance. In 32 patients who underwent surgical resection to treat HCC, the proportion of patients with well-differentiated HCC was significantly higher among those with 3-month surveillance than those with 6-month surveillance ($P = 0.0053$).

In both groups, curative treatment for HCC was possible in more than 90% of patients. Figures 2 and 3 compare the survival and recurrence rates of patients after HCC diagnosis based on the surveillance interval after SVR. No significant differences in survival rates were found between patients who underwent 3- or 6-month surveillance ($P = 0.1979$). In contrast, the recurrence rate was significantly higher in patients with 6-month surveillance than those with 3-month surveillance ($P = 0.0373$). In univariate analysis, the 6-month surveillance was significantly associated with higher recurrence rates, and lower platelet count and lower serum albumin level at HCC diagnosis tended to be associated with higher recurrence rates. In multivariate analysis, only 6-month surveillance was significantly associated with higher recurrence rates (Table 4).

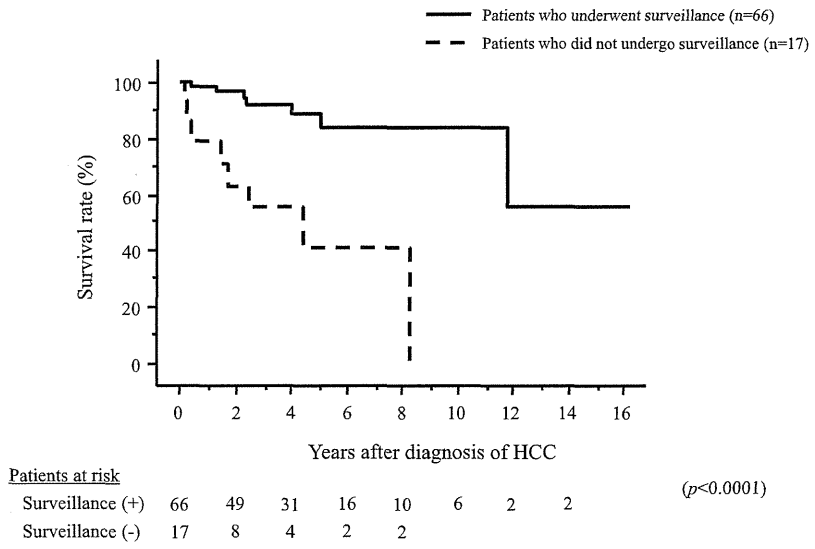


Figure 1 Survival rates after the diagnosis of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) infection who achieved a sustained virological response (SVR) to the antiviral therapy for HCV based on whether they underwent surveillance for HCC after SVR. The survival rate of patients who did not undergo surveillance after SVR was significantly lower than that of patients who continued surveillance after SVR ($P < 0.0001$).

Table 2 Univariate and multivariate analysis for factors associated with survival of patients in whom HCC was diagnosed after SVR ($n = 83$)

Factor		Univariate analysis	HR (95% CI)	Multivariate analysis	HR (95% CI)
Age at HCC		0.0874	1.06 (0.99–1.15)	0.1338	1.06 (0.99–1.16)
Sex	Male				
	Female	0.5654		—	
Interval between SVR and HCC (years)		0.7313		—	
ALT (IU/L)		0.3503		—	
Albumin (g/dL)		0.2462		—	
Bilirubin (mg/dL)		0.7746		—	
Platelet counts ($\times 10^3/\mu L$)		0.0178	1.11 (1.02–1.22)	0.5501	1.04 (0.92–1.15)
Surveillance at the time of	Present				
HCC diagnosis	Absent	0.0001	2.74 (1.66–4.60)	0.0009	2.54 (1.47–4.54)

ALT, alanine aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; SVR, sustained virological response.

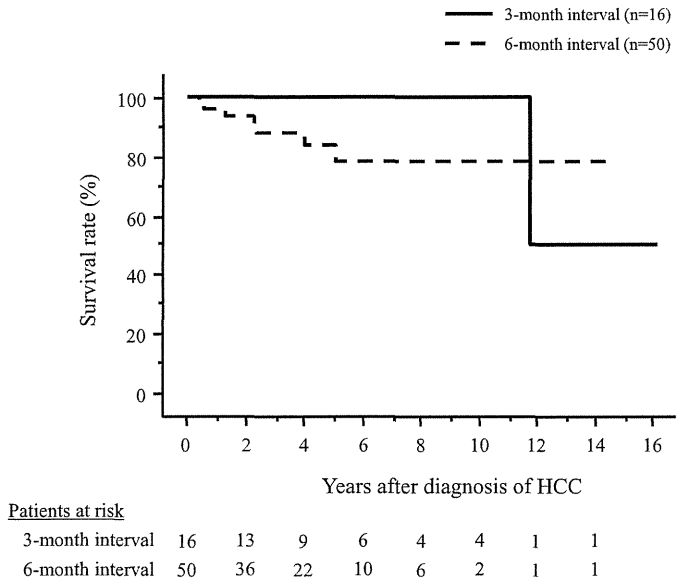
Table 3 Characteristics of patients with HCC based on the surveillance interval ($n = 66$)

	3 months ($n = 16$)	6 months ($n = 50$)	*P*
Age at SVR24 (years)	59.2 ± 8.8	61.0 ± 6.3	0.6311
Age at HCC development (years)	63.1 ± 10.1	67.7 ± 6.4	0.0935
Sex (male/female)	12 (75.0)/4 (25.0)	39 (78.0)/11 (22.0)	0.8032
Interval between SVR and HCC (years)	5.0 ± 4.8	6.9 ± 4.1	0.0453
ALT (IU/L)	26.5 ± 13.3	25.4 ± 15.0	0.6248
Albumin (g/dL)	4.11 ± 0.47	4.30 ± 0.43	0.1415
Bilirubin (mg/dL)	0.93 ± 0.76	0.90 ± 0.38	0.3261
Platelet counts ($\times 10^3/\mu L$)	141 ± 58	157 ± 48	0.2401
Tumor size (cm)	1.8 ± 0.7	2.6 ± 1.5	0.0085
Tumor number (single/multiple)	15 (93.8)/1 (6.2)	39 (78.0)/11 (22.0)	0.2940
Portal vein invasion (absent/present)	16 (100)/0	47 (94.0)/3 (6.0)	0.7540
BCLC class (0/A/B/C or D)	12 (75.0)/3 (18.8)/1 (6.2)/0	18 (36.0)/17 (34.0)/12 (24.0)/3 (6.0)	0.0484
Tumor stage (I/II/III or IV)*	12 (75.0)/4 (25.0)/0	18 (36.0)/25 (50.0)/7 (14.0)	0.0181
AFP (ng/dL, mean [range])	9.9 (1.6–7086)	4.7 (0.8–63 750)	0.3291
AFP-L3 (%, mean [range])	0.5 (0–21.9)	0 (0–49.0)	0.6842
DCP (mAU/mL, mean [range])	40 (11–268)	35.5 (7–41 800)	0.9195
Differentiation (well/moderately or poorly)**	6 (85.7)/1 (14.3)	5 (20.0)/20 (80.0)	0.0053
Treatment (resection/RFA/TACE/none)	7 (43.8)/8 (50.0)/1 (6.2)/0	25 (50.0)/21 (42.0)/4 (8.0)/0	0.8508

AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive AFP; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; DCP, des-γ-carboxyprothrombin; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; SVR24, sustained virological response confirmed 24 weeks after the completion of antiviral therapy; TACE, transarterial chemoembolization.
Data are expressed as means ± standard deviation or median (range). Percentages are shown in parentheses.
*Based on the tumor-node-metastasis (TNM) staging of the Liver Cancer Study Group of Japan.[19]
**Among patients who underwent surgical resection and a liver specimen was available.

DISCUSSION

HEPATOCELLULAR CARCINOMA USUALLY develops in the cirrhotic liver, and the deterioration of liver function and resultant liver failure is an important factor that influences prognosis of HCC patients as well as progression of HCC. When HCV is eradicated, however, further deterioration of liver function secondary to liver injury due to HCV will stop, and the influence of declining liver function on the survival of patients with HCC will diminish. Indeed, in the present study, all but one patient had Child-Pugh class A liver disease at the time of HCC diagnosis, because HCV was eradicated. Consequently, most patients could undergo curative therapy such as

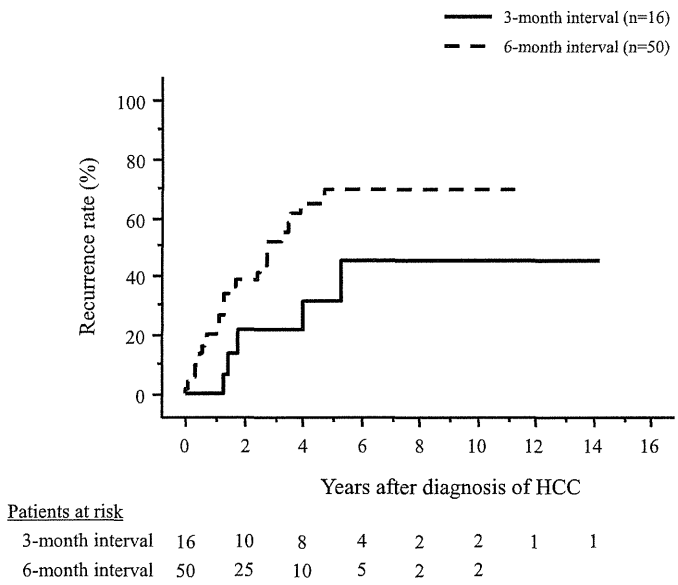


Patients at risk

3-month interval	16	13	9	6	4	4	1	1
6-month interval	50	36	22	10	6	2	1	1

(p=0.1979)

Figure 2 Survival rates after the diagnosis of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) infection who achieved a sustained virological response (SVR) and continued surveillance for HCC after SVR based on the surveillance interval. There was no significant difference in the survival rate between patients who underwent surveillance every 3 months versus every 6 months (P = 0.1979).



Patients at risk

3-month interval	16	10	8	4	2	2	1	1
6-month interval	50	25	10	5	2	2		

(p=0.0373)

Figure 3 Rates of hepatocellular carcinoma (HCC) recurrence after treatment in patients with hepatitis C virus (HCV) infection who achieved a sustained virological response (SVR) and continued surveillance after SVR based on the surveillance interval (3 vs 6 months). The recurrence rate in patients who underwent surveillance every 6 months after SVR was significantly higher than that of patients who underwent surveillance every 3 months (P = 0.0373).

surgical resection or RFA unless HCC was not very advanced. Therefore, controlling HCC will become more important for achieving a good prognosis in patients who developed HCC after SVR than in those with persistent HCV infection. As a result, the importance of early detection and curative treatment of HCC will grow, especially for patients who have achieved SVR.

However, patients have been less likely to participate in HCC surveillance after HCV eradication than patients with persistent HCV infection,[27] owing to the decreased risk of HCC development in patients who achieve SVR. This may result in a failure to detect small HCC, allowing tumors to enlarge before detection and diagnosis at an advanced stage. Currently, most patients with HCV

Table 4 Univariate and multivariate analysis for factors associated with recurrence after treatment for HCC in patients in whom HCC was diagnosed after SVR ($n = 66$)

Factor		Univariate analysis	HR (95% CI)	Multivariate analysis	HR (95% CI)
Age at HCC		0.1721		—	
Sex	Male				
	Female	0.1628		—	
Interval between SVR and HCC (years)		0.8891		—	
ALT (IU/L)		0.7238		—	
Albumin (g/dL)		0.0702	2.07 (0.94–4.65)	0.3289	1.52 (0.66–3.55)
Bilirubin (mg/dL)		0.8141		—	
Platelet counts ($\times 10^3/\mu L$)		0.0589	1.07 (0.99–1.14)	0.1603	1.06 (0.98–1.14)
Surveillance interval at the time of	3 months				
HCC diagnosis	6 months	0.0263	1.63 (1.05–2.80)	0.0365	1.59 (1.03–2.74)

ALT, alanine aminotransferase; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; SVR, sustained virological response.

continue to undergo surveillance even after the eradication of HCV.[28]

Several previous studies have identified risk factors for HCC development after the eradication of HCV, such as advanced age, male sex, advanced fibrosis and persistent AFP elevation.[14–18,29] However, there are only a few studies that have investigated the characteristics of HCC detected and diagnosed after SVR and their prognosis after diagnosis in a small number of patients.[30,31] The results of the present study clearly demonstrate that the lack of surveillance after SVR is a disadvantage with regards to HCC development. HCC in patients who did not undergo surveillance after SVR was significantly more advanced, and associated with larger tumor size and higher stage at diagnosis. Accordingly, many patients could not undergo curative therapy, despite the fact that all but one patient had Child–Pugh class A liver disease. This resulted in significantly lower survival rates among patients who did not undergo surveillance compared with patients who continued to undergo surveillance after SVR. The importance of surveillance for HCC in patients at high risk of HCC development has been established,[32,33] and this effect would be the same in patients after SVR.

More importantly and surprisingly, HCC in patients who underwent surveillance for HCC after SVR every 6 months had more progressive disease than those who underwent surveillance for HCC after SVR every 3 months; tumors were larger and of a more advanced stage at diagnosis. It seemed difficult to detect and diagnose stage I HCC when patients underwent 6-month surveillance. As a result, the recurrence rate was higher in patients with 6-month surveillance. Although no significant differences were found in the survival rate, it might have been due to the small number of study patients. In the future, studies on whether survival rates will differ or not between these two groups with longer observation are necessary.

Another important finding in the present study is the considerably higher rate of recurrence even in patients who underwent surveillance after SVR and treatment with curative intent, especially during the first 5 years after treatment. Although several studies have reported that the incidence of HCC is lower in patients with chronic hepatitis C after SVR,[8–12] the short-term recurrence rate of HCC in patients who achieved SVR was not lower than that in HCC patients with persistent HCV infection once HCC developed, even they received treatment with curative intent. This emphasizes the importance of early detection of HCC for higher cure rates. In contrast, HCC did not recur 5 years after curative treatment, which may indicate that multicentric recurrence is rare if HCC is controlled completely.

There are several limitations in this study. This is a retrospective, multicenter study. Therefore, patients were not randomly assigned for non-surveillance, 6-month interval surveillance and 3-month interval surveillance groups, and the quality of surveillance and treatment was not completely homogenous across institutions. In addition, analysis of cost-effectiveness of continuing surveillance after HCV eradication will be necessary in the future. Finally, the present study lacks the analysis of the baseline characteristics before antiviral therapy of patients in whom HCC developed after SVR, the characteristics with which patients may have to be surveyed closely after SVR, because the present study focused on the characteristics of HCC at diagnosis and the prognosis after diagnosis. All patients who achieved SVR may not have to be surveyed in the same fashion. Although there are several reports that studied the characteristics of patients in whom HCC developed

after SVR,[14–18,29] further studies will be needed for the precise assessment of the risk of HCC development after SVR.

In conclusion, chronic hepatitis C patients who did not undergo surveillance for HCC after HCV eradication with antiviral therapy were at an obvious disadvantage compared with those who did; HCC stage was more advanced at diagnosis and survival rates were lower in patients who did not undergo surveillance. In addition and more importantly, there may be a difference in the progression of HCC at diagnosis and prognosis according to the surveillance interval, namely, 3 months versus 6 months. Surveillance with a 6-month interval may not be always sufficient to detect early stage HCC after SVR. Surveillance for HCC in high-risk patients remains controversial in Japan and Western countries; a previous study by Trinchet *et al.* reported that surveillance with ultrasonography every 3 months did not improve the detection of small HCC.[34] According to Japanese guidelines, in contrast, extremely high-risk patients should undergo surveillance for HCC every 3–4 months and high-risk patients should be surveyed every 6 months.[21] The appropriate interval of the surveillance for HCV-related HCC remains controversial, even in patients with persistent HCV infection. It also should be verified whether patients with HCV infection who achieved HCV eradication should be considered at high-risk or extremely high-risk, although the risk of HCC development will vary even among patients after SVR. In addition, the establishment of guidelines for HCC surveillance in chronic hepatitis C patients after SVR, including how to assess the risk of HCC for determining the intensity of surveillance, is necessary in the near future.

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