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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

The Achievement of a Sustained Virological Response Either Before or After Hepatectomy Improves the Prognosis of Patients with Primary Hepatitis C Virus-Related Hepatocellular Carcinoma

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ABSTRACT

Background. Hepatitis C virus (HCV) infection is a major cause of hepatocellular carcinoma (HCC). Achieving a sustained virological response (SVR) is associated with a reduced risk of recurrence. The recent introduction of direct acting antivirals (DAAs) has resulted in SVR rates of nearly 100% in treated patients. The purpose of the present study was to clarify the outcomes in patients who underwent antiviral therapy and patients without antiviral therapy.

Methods. This retrospective study included 220 patients with primary HCV-related HCC who underwent hepatectomy. An SVR was defined as a serum HCV-RNA titer below the detection sensitivity limit at 6 months after the termination of antiviral therapy. Postoperative antiviral therapy was introduced after confirming that there was no early recurrence.

Results. Eighty-eight patients received antiviral therapy. Among these, 58 patients (66%) obtained an SVR. With the exception of one patient, all patients who received DAAs obtained an SVR. The overall survival rate of the pre-operative SVR group was significantly better than that of the preoperative untreated group ($P = 0.045$). Moreover, there was no recurrence at 3 years after surgery in the pre-operative SVR group. The achievement of an SVR was an independent predictor of overall survival [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.59–0.94, $P = 0.011$] and recurrence (HR 0.61, 95% CI 0.40–0.94, $P = 0.024$).

Conclusions. Obtaining an SVR either before or after surgery was associated with the suppression of HCC recurrence after hepatectomy in patients with primary HCV-related HCC.

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is the fifth leading cause of cancer-related death in Japan.[1] Hepatitis C virus (HCV) infection is a major cause of HCC; 40–60% at 5 years after hepatectomy has been obtained due to the development of surgical techniques and perioperative management, HCC is still difficult to cure due to its high recurrence rate.[2–4] Even when HCC is completely removed by surgery, it often recurs with intrahepatic metastasis and/or multicentric occurrence.[5–8] Although several studies have revealed the achievement of a sustained virological response (SVR) is associated with a reduced risk of multicentric recurrence after hepatectomy, few studies have shown the outcomes of nonresponders to antiviral therapy, because nonresponders have typically been assigned to a non-SVR group in the papers focused on this issue.[9–12]

In past decades, the treatment of chronic HCV with interferon (IFN)-based regimens led to a cure in approximately 50% of treated patients. The recent introduction of direct acting antivirals (DAAs) has resulted in SVR rates of nearly 100% in treated patients—irrespective of the stage of liver fibrosis—with an excellent safety profile.[13] However, the impact of DAA-based regimens on the occurrence of HCC in patients with cirrhosis and especially on the incidence of recurrence of HCC after hepatectomy is

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controversial. Reig et al.[14] described an unexpectedly high rate of recurrence after IFN-free DAA therapy in patients with a history of treatment for HCV-related HCC. Some studies supported similarly high rates of tumor recurrence after DAA, whereas other studies did not show such high rates or rapid recurrence.[13,15–19] Moreover, no reports have shown the benefit of introducing DAA treatment after hepatectomy.

The purpose of the present study was to clarify the outcomes in patients who receive antiviral therapy (assigned to two groups: SVR and nonresponder) and patients treated without antiviral therapy. Moreover, the patients in whom antiviral therapy was introduced after hepatectomy were analyzed to evaluate the rate at which DAA therapy is introduced and the impact of obtaining an SVR on the prognosis in patients with primary HCV-related HCC.

MATERIALS AND METHODS

A total of 514 patients underwent hepatectomy for primary HCC with curative intent at the Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center Hospital, between September 2002 and June 2017. Among 514 patients, 220 patients with HCV-related HCC were included in the present study. We retrospectively reviewed the database of this hospital until January 2018. This study was retrospective in nature, and we obtained approval from the Institutional Review Board of Shizuoka Cancer Center for the exception of patient consent (number: J2019-40-2019-1-3).

An SVR was defined as a serum HCV-RNA titer below the detection sensitivity limit at 6 months after the termination of antiviral therapy. The patients without preoperative SVR were indicated for antiviral treatment after surgery in principle, and postoperative antiviral therapy was promptly introduced after confirming that there was no recurrence at postoperative month 3. DAA therapy instead of an IFN-based regimen has been used for antiviral therapy in our hospital since 2014, when DAA was approved for coverage by Japanese health insurance.

All of the patients included in this study had undergone computed tomography (CT) and preoperative viral serological testing, tumor markers, such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), and a laboratory assessment of the liver function before surgery. The liver function was assessed using the Child–Pugh classification and liver damage criteria, including the indocyanine green retention rate at 15 min ($ICGR_{15}$).[20,21] All of the patients presented with a confirmed diagnosis of HCC after surgical pathology. The tumor stage was assessed based on the seventh edition of the Union Internationale Contra le Cancer classification.[22]

The surgical procedure and extent of hepatectomy in each patient were decided in a weekly surgical conference. The details of the surgical strategy and procedure have been reported previously.[23] The types of hepatectomy were defined according to the Brisbane 2000 terminology as minor (2 liver segments or less) or major (3 liver segments or more).[24]

The patients underwent physical examinations and blood tests every 3 months after surgery. Serial CT or liver ultrasonography was performed in each patient every 3–6 months. When recurrence of HCC was found, the most appropriate therapy, such as repeat hepatectomy, transcatheter arterial chemoembolization, radiofrequency ablation, sorafenib, or other therapies was applied, after considering the patient's liver function and tumor factors. For the analysis of the overall survival rate, the follow-up period ended at the time of death from HCC. The remaining patients were censored at the last follow-up visit before January 2018.

Statistical Analysis

Continuous variables are presented as the median and range and were compared using the Mann–Whitney *U* test. Categorical variables were compared using the Chi squared test or Fisher's exact test, as appropriate. The cumulative relapse-free and overall survival curves were analyzed using the Kaplan–Meier method and compared using the log-rank test. The cutoff points for the laboratory data were defined as the upper limit of normal applied at our institution, and the cutoff points for the age, $ICGR_{15}$ value, and tumor diameter were defined as the median value. A Cox proportional hazards model was used for the univariate and multivariate analyses, and all factors found to be significant predictors of relapse-free and overall survival ($P < 0.05$) in a univariate analysis were entered into a multivariate analysis. The multivariate analysis was performed using a backward stepwise selection model. All statistical analyses were performed using the SPSS 24.0 software package (SPSS, Inc., Chicago, IL), and two-tailed P values < 0.05 were considered to indicate statistical significance.

RESULTS

SVR Status Before Surgery

A perioperative flowchart is shown in Fig. 1. Fifty-seven (25.9%) of 220 patients received antiviral therapy with IFN-based ($N = 53$) or DAA ($N = 4$) therapy before hepatectomy, and 33 (57.9%) of 57 patients achieved an SVR, defined as the persistent disappearance of HCV-RNA. All patients who received DAA therapy obtained an SVR. The

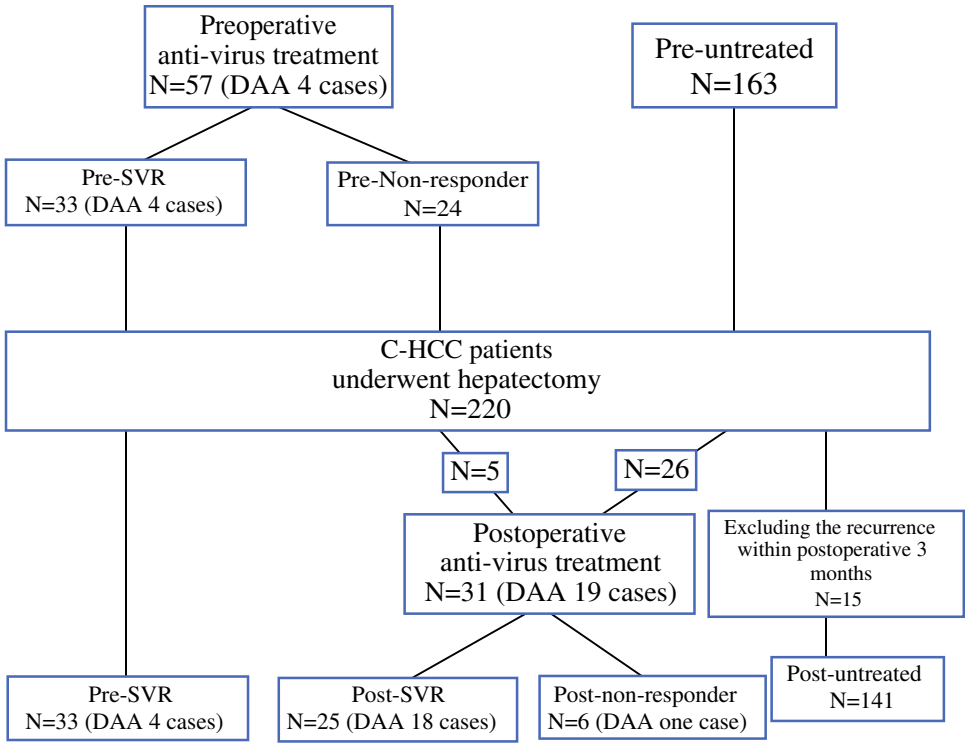

FIG. 1 Flow chart of the study population

patients were allocated into three groups according to the antiviral therapy and SVR status: Preoperative (Pre)-SVR, Pre-nonresponder and Pre-untreated.

Comparison of Patients According to the Preoperative SVR Status

The preoperative patient background data and blood examination results are shown in Table 1. Although the rate of hyperlipidemia in the Pre-SVR group was significantly higher than that in the Pre-untreated group ($P = 0.008$), there were no significant differences among the three groups. Regarding the blood examination results, the levels of albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and $ICGR_{15}$ in Pre-SVR group were significantly better than those in Pre-nonresponder and Pre-untreated groups. In contrast, there were no significant differences in the liver function values of the Pre-nonresponder and Pre-untreated groups.

The tumor diameter of the Pre-nonresponder group was significantly smaller than that of the Pre-SVR and Pre-untreated groups ($P = 0.001$ and $P < 0.001$, respectively).

In the Pre-SVR group, 2 patients (6.1%) died of recurrent HCC, 1 (3.0%) died of other causes, and 12 (36.4%) remain alive with recurrent HCC. In contrast, in the Pre-non-responder and Pre-untreated groups, 8 (33.3%) and 60 patients (36.8%) died of recurrent HCC, 1 (4.2%) and 14 patients (8.6%) died of other causes, and 7 (29.2%) and 51 patients (31.3%) remain alive with recurrent HCC, respectively.

The cumulative overall survival rate of Pre-SVR group was significantly better than that of Pre-untreated group (Fig. 2a, $P = 0.045$), whereas there were no significant differences of the overall survival rate between Pre-SVR and Pre-nonresponder groups, and Pre-nonresponder and Pre-untreated groups (Fig. 2a, $P = 0.112$, and $P = 0.695$, respectively). There was a marginal difference of the relapse-free survival rate between Pre-SVR and Pre-untreated groups (Fig. 2b, $P = 0.061$).

The recurrence rate of the Pre-SVR group in the early phase until postoperative year 2 was significantly better than that of the Pre-nonresponder and Pre-untreated groups (Fig. 3a, $P = 0.028$, and $P = 0.012$, respectively). In contrast, there was no significant difference of the recurrence rate in the late phase between the Pre-nonresponder and Pre-untreated groups (Fig. 3a, $P = 0.679$). After 3 years, there were no decreases in the overall or relapse-free survival curves of the Pre-SVR-group (Fig. 2a, b).

SVR Status After Surgery

Thirty-three patients who obtained a pre-SVR and 17 patients who suffered from recurrence within postoperative 3 months were excluded from the postoperative survival analyses. Thirty-one (16.6%) of 187 patients had received antiviral therapy with IFN-based ($N = 12$) or DAA ($N = 19$) therapy after hepatectomy, and 25 (80.6%) of 31

TABLE 1 Comparisons of clinical characteristics, operation procedure and pathological findings among the HCC patients with SVR or non-responder after antiviral therapy and the patients without antiviral therapy before surgery

Variables	Pre-SVR $N = 33$	Pre-nonresponder $N = 24$	P*	Pre-untreated $N = 163$	$P^{\$}$	$P^{\&}$
Patient characteristics						
Age (years)[#]	68 (58–86)	70 (54–79)	0.382	71 (42–87)	0.431	0.151
Gender (men/women)	25/8	17/7	0.765	135/28	0.332	0.167
Alcohol intake history (80 g/day over)	7 (21.2%)	2 (8.3%)	0.277	21 (12.9%)	0.272	0.744
Child–Pugh grade (B)	0 (0%)	0 (0%)		7 (4.3%)	0.604	0.598
Liver damage (B)	4 (12.1%)	9 (37.5%)	0.052	45 (27.6%)	0.077	0.339
ASA-PS (1/2/3)	1/30/2	1/21/2	0.918	7/129/27	0.269	0.578
Hypertension (present)	24 (72.7%)	18 (75.0%)	0.494	102 (62.6%)	0.316	0.467
Hyperlipidemia (present)	4 (12.1%)	2 (8.3%)	0.687	5 (3.1%)	***0.008***	0.172
Diabetes mellitus (present)	11 (33.3%)	9 (37.5%)	0.784	34 (20.9%)	0.171	0.115
Body mass index (kg/m^2)[#]	22.1 (16.6–32.8)	23.5 (18.4–32.9)	0.710	22.1 (14.5–28.6)	0.570	0.125
Preoperative blood examinations						
Albumin (g/dL)[#]	4.3 (3.6–5.6)	4.1 (3.3–4.7)	***0.014***	4.0 (2.7–5.0)	< ***0.001***	0.792
PT (%)[#]	92 (67–109)	83 (61–103)	0.099	86 (55–117)	0.050	0.840
Total serum bilirubin (mg/dL)[#]	0.7 (0.3–1.2)	0.7 (0.4–1.9)	0.378	0.6 (0.2–1.7)	0.777	0.239
Platelet count ($\times 10^4$/μl)[#]	15.5 (7.3–30.3)	11.8 (6.1–25.3)	***0.028***	13.4 (4.8–42.9)	0.050	0.259
AST (U/L)[#]	31 (20–110)	46 (18–136)	***0.009***	49 (17–143)	< ***0.001***	0.282
ALT (U/L)[#]	30 (14–106)	46 (16–97)	***0.009***	47 (9–281)	< ***0.001***	0.762
$ICGR_{15}$ (%)[#]	10.5 (2.2–27.0)	20.5 (4.3–31.0)	< ***0.001***	16.8 (5.2–36.0)	< ***0.001***	0.135
AFP (ng/mL)[#]	9.9 (2.8–6960)	16.0 (1.4–2813)	0.204	20.4 (1.5–168,895)	0.142	0.934
DCP (mAL/mL)[#]	55 (17–124,000)	37 (8–2860)	***0.013***	136 (1–134,000)	0.587	***0.001***
Operation procedures						
Major resection (present)	8 (24.2)	1 (4.2%)	0.064	40 (24.5)	1.000	***0.031***
Anatomical resection (present)	17 (51.5)	6 (25.0%)	0.058	82 (50.3)	1.000	***0.027***
Pathological findings						
Tumor diameter (mm)[#]	30 (11–128)	19 (6–50)	***0.001***	33 (11–180)	0.552	< ***0.001***
Tumor number (multiple)	5 (15.2%)	9 (37.5%)	0.067	48 (29.4%)	0.131	0.478
Tumor differentiation (well/moderately/poorly)	6/26/1	3/20/1	0.831	36/120/7	0.818	0.553
Vp (present)	5 (15.2%)	1 (4.2%)	0.384	34 (20.9%)	0.633	0.052
Vv (present)	3 (9.1%)	1 (4.2%)	0.631	20 (12.3%)	0.772	0.485
Im (present)	6 (18.2%)	0	***0.034***	22 (13.5%)	0.584	0.083
Surgical margin (mm)	4 (0–25)	5 (0–25)	0.140	5 (0–43)	0.322	0.229
Tumor margin (positive)	1 (3.0%)	1 (4.2%)	1.000	6 (3.7%)	1.000	1.000
Cirrhosis (present)	7 (21.2%)	12 (50.0%)	***0.045***	50 (30.7%)	0.298	0.104
Tumor stage (I/II/III)	21/9/3	13/9/2	0.712	86/54/23	0.494	0.723

Bold and italic values indicate significant differences

HCC hepatocellular carcinoma, *SVR* sustained virological response, *ASA-PS* American Society of Anesthesiologists Performance Status, PT prothrombin time, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, $ICGR_{15}$ indocyanine green retention15, AFP alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin, *Vp* portal vein thrombosis, *Vv* venous vein thrombosis, *Im* intrahepatic metastasisis

Values in parentheses are percentages unless indicated otherwise; [#]Value is expressed as the median (range)

*P value pre-SVR versus pre-non-SVR; $^{\$}P$ value pre-SVR versus pre-un-treatment; and P value pre-non-SVR versus un-treatment

patients had achieved an SVR. IFN-based and DAA achieved SVR rates of 58% and 95%, respectively. The patients were allocated into three groups according to the antiviral therapy and SVR status: Postoperative (Post)-SVR, Post-nonresponder, and Post-untreated (Fig. 1).

Comparison of the Prognoses According to the Postoperative SVR Status

There were no significant differences of the overall survival rates between the Post-SVR and Post-untreated

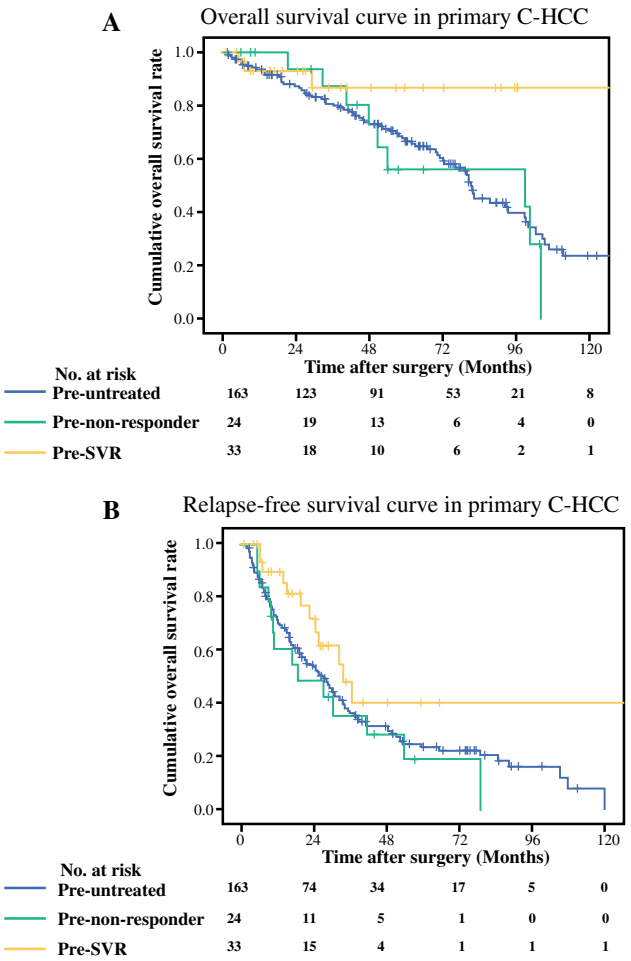

FIG. 2 Survival curves of primary HCV-related HCC patients who underwent hepatectomy classified by the pre-operative status using the Kaplan–Meier method. **a** Overall survival curve classified according to antiviral therapy and the SVR status. The 5-year cumulative overall survival rate of Pre-SVR, Pre-nonresponder, and Pre-untreated was 86.8%, 56.3%, and 66.9% respectively. **b** Relapse-free survival curve classified according to antiviral therapy and the SVR status. The 5-year cumulative relapse-free survival rate of Pre-SVR, Pre-nonresponder, and Pre-untreated was 39.9%, 18.8%, and 23.5%, respectively

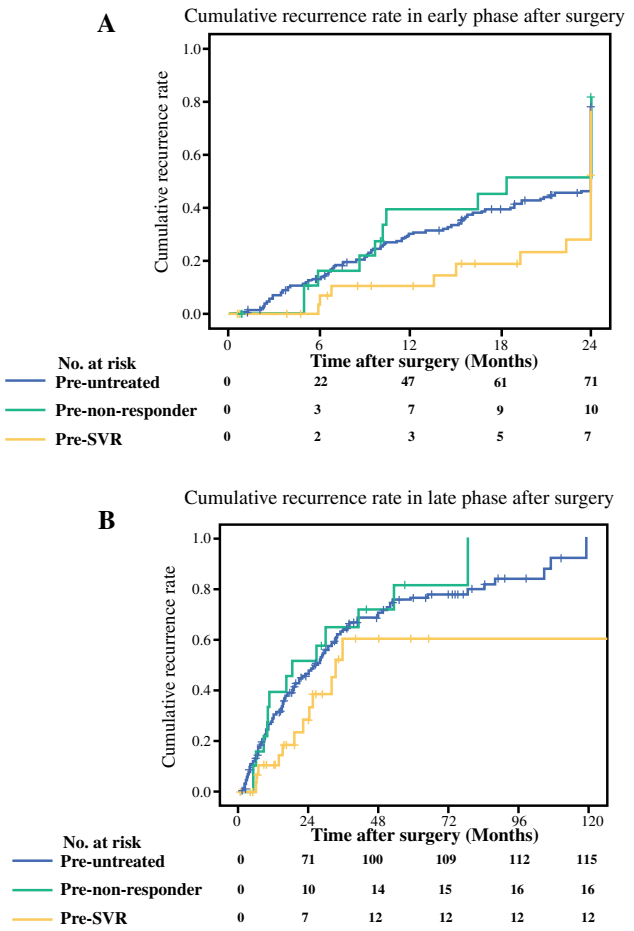

FIG. 3 Cumulative recurrence rate after hepatectomy. **a** Early phase after surgery. **b** Late phase after surgery

groups (Fig. 4a, $P = 0.073$), and between the Post-SVR and Post-nonresponder groups (Fig. 4a, $P = 0.104$). Moreover, there was no significant difference in the relapse-free survival rates of the Post-SVR and Post-untreated groups (Fig. 4b, $P = 0.112$), whereas a comparison between the Post-SVR and Post-nonresponder groups revealed a marginal difference in the relapse-free survival rate ($P = 0.052$).

Prognostic Factors for Relapse-Free and Overall Survival in 220 Primary HCV-Related HCC Patients

In the multivariate analysis, the achievement of a Pre- or Post-SVR [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.59–0.94, $P = 0.011$] and prothrombin time (PT) $<$ 70% (HR 1.96, 95% CI 1.11–3.46, $P = 0.021$) among the liver function-related factors, and AFP $>$ 10 g/dL (HR 1.61, 95% CI 1.11–2.35, $P = 0.012$) and DCP $\geq$ 40 mAL/mL (HR 1.74, 95% CI 1.20–2.51, $P = 0.003$) among the tumor-related factors remained significant independent predictors of recurrence (Table 2).

In the multivariate analysis, the achievement of a Pre- or Post-SVR (HR 0.61, 95% CI 0.40–0.94, $P = 0.024$), age $\geq$ 71 years (HR 2.62, 95% CI 1.57–4.37, $P < 0.001$), PT $<$ 70% (HR 3.02, 95% CI 1.54–5.91, $P = 0.001$), and platelet count $< 13.1 \times 10^4/\mu l$ (HR 1.64, 95% CI 1.05–2.59, $P = 0.032$) among the liver function- or patient background-related factors, and DCP $\geq$ 40 mAL/mL (HR 1.90, 95% CI 1.18–3.06, $P = 0.009$) among the tumor-related factors, remained significant independent predictors of survival (Table 2).

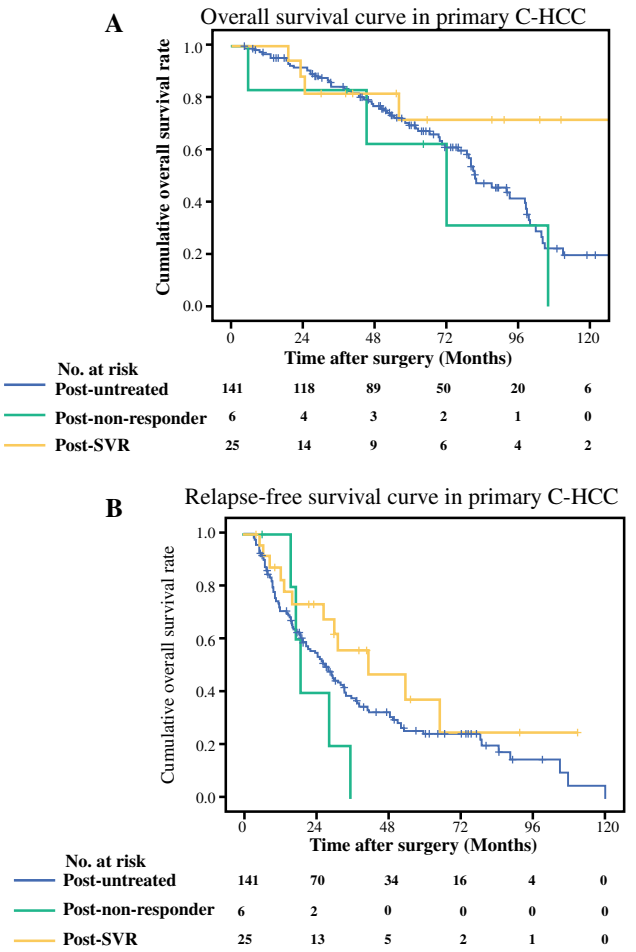

FIG. 4 Survival curves of primary HCV-related HCC patients who underwent hepatectomy classified by the post-operative status using the Kaplan–Meier method. **a** Overall survival curve classified according to antiviral therapy and the SVR status. The 5-year cumulative overall survival rate of Post-SVR, Post-nonresponder and Post-untreated was 71.6%, 62.5%, and 69.4% respectively. **b** Relapse-free survival curve classified according to antiviral therapy and the SVR status. The 5-year cumulative relapse-free survival rate of Post-SVR, Post-nonresponder, and Post-untreated was 37.3%, zero, and 24.4%, respectively

Prognostic Factors for Relapse-Free and Overall Survival in 88 Primary HCV-Related HCC Patients Who Received Antiviral Therapy

A univariate analysis revealed that the achievement of a Pre- or Post-SVR had a significant impact on overall and relapse-free survival (Table 3). However, a multivariate analysis showed that the achievement of a Pre- or Post-SVR was not a significant predictor of survival or recurrence despite identifying a marginal difference (HR 0.62, 95% CI 0.37–1.05, $P = 0.073$ and HR 0.72, 95% CI 0.52–1.01, $P = 0.057$, respectively). The introduction of DAA therapy was a favorable predictor of recurrence in a univariate analysis.

DISCUSSION

The present study showed that the achievement of an SVR either before or after surgery was associated with the suppression of HCC development and demonstrated an improvement in overall and relapse-free survival after hepatectomy in patients with primary HCV-related HCC.

This study contains several suggestive results. First, although some studies revealed that the achievement of an SVR suppresses the occurrence of HCC, a few reports have shown the outcomes after surgery in patients who could not obtain an SVR.[12] Koda et al.[12] showed that the overall survival rate of a Pre-nonresponder group was significantly higher than that of a Pre-untreated group. In contrast, the present study showed that there were no significant differences in overall or relapse-free survival between the Pre-nonresponder and Pre-untreated groups. Although it was difficult to discuss the reason for this discrepancy, because there were no data on the patient background or tumor factors in the Pre-nonresponder group in the previous report, the present study showed that there were no significant differences in the liver function between the Pre-nonresponder and Pre-untreated groups, whereas the tumor factors of the Pre-nonresponder group were favorable in comparison to the Pre-untreated group.[9] These results suggest that the Pre-non-responder group was followed firmly for HCC occurrence as the high-risk group but that the early detection of HCC did not contribute to the prognosis.

As mentioned in the *Introduction*, intrahepatic recurrence is classified into intrahepatic metastasis and multicentric recurrence.[25] Intrahepatic metastasis arise from primary cancer, whereas multicentric recurrence is considered to be another tumor due to chronic hepatitis or liver cirrhosis.[25,26] The achievement of an SVR generally leads to the suppression of multicentric recurrence. Consistent with previous reports, the present study showed that the achievement of an SVR before surgery strongly suppressed the form of multicentric recurrence because there was no recurrence at 3 years after surgery.[9–11] Moreover, the preoperative achievement of an SVR led to the suppression of intrahepatic metastasis, because the rate of early recurrence in the Pre-SVR group was significantly lower than that in the Pre-nonresponder and Pre-untreated groups. Thus, there is a possibility that the achievement of an SVR suppressed the form of intrahepatic metastasis (early recurrence) as well as multicentric recurrence (late recurrence).

Ikeda et al.[27] showed the anticancer effects of IFN therapy without the achievement of an SVR after curative treatment for HCC. However, the results of the current study did not suggest that the anticancer effects of IFN therapy for HCC.

TABLE 2 Prognostic factors for the overall survival and relapse-free survival in primary C-HCC patients by univariate and multivariate analyses

Variables	Overall survival				Relapse-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*
Age (≥ 71 years)	1.94 (1.25–3.02)	***0.003***	2.62 (1.57–4.37)	***< 0.001***	1.18 (0.85–1.64)	0.336		
Gender (male)	0.80 (0.48–1.35)	0.408			1.03 (0.67–1.57)	0.900		
Pre- or Post-SVR (achievement)	0.25 (0.11–0.57)	***0.001***	0.61 (0.40–0.94)	***0.024***	0.49 (0.31–0.77)	***0.002***	0.75 (0.59–0.94)	***0.011***
Pre-nonresponder	1.16 (0.58–2.32)	0.671			1.41 (0.81–2.45)	0.671		
Albumin (< 40 g/L)	1.18 (0.76–1.81)	0.461			1.12 (0.80–1.57)	0.506		
PT (< 70%)	2.80 (1.59–4.93)	***0.001***	3.02 (1.54–5.91)	***0.001***	2.57 (1.49–4.45)	***0.001***	1.96 (1.11–3.46)	***0.021***
AST (> 40 IU/L)	1.27 (0.81–1.99)	0.303			1.53 (1.07–2.18)	***0.019***		
ALT (> 40 IU/L)	1.15 (0.74–1.78)	0.538			1.54 (1.09–2.18)	***0.014***		
Platelet count	(< 13.1 × 10^4/μl)	1.76	(1.15–2.70)	***0.009***	1.64 (1.05–2.59)	***0.032***	1.03 (0.74–1.44)	0.842
$ICGR_{15}$ (> 16%)	1.28 (0.83–1.99)	0.262			1.10 (0.79–1.53)	0.562		
AFP (> 10.0 ng/mL)	1.81 (1.11–2.94)	***0.017***			1.90 (1.34–2.70)	***< 0.001***	1.61 (1.11–2.35)	***0.012***
DCP (≥ 40 mAL/mL)	1.73 (1.08–2.75)	***0.022***	1.90 (1.18–3.06)	***0.009***	1.85 (1.28–2.67)	***0.001***	1.74 (1.20–2.51)	***0.003***
Child–Pugh classification (B)	1.54 (0.70–3.39)	0.278			1.20 (0.53–2.71)	0.669		
Cirrhosis (present)	1.45 (0.93–2.24)	0.099			1.33 (0.94–1.88)	0.105		
Anatomical resection (present)	0.82 (0.53–1.26)	0.360			0.91 (0.66–1.27)	0.592		
Tumor diameter (≥ 30 mm)	1.19 (0.78–1.83)	0.423			1.06 (0.76–1.47)	0.747		
Tumor number (multiple)	1.26 (0.81–1.96)	0.301			1.63 (1.15–2.30)	***0.006***		
Tumor margin (positive)	1.67 (0.52–5.31)	0.386			1.17 (0.43–3.16)	0.764		

Bold and italic values indicate significant differences

HCC hepatocellular carcinoma, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

In the past decades, it has been difficult for the elderly patients to be introduced to antiviral therapy after surgery due to the adverse events and low rate of viral elimination of IFN therapy. IFN-free DAA treatment can easily eradicate HCV with 3–6 months of administration, even in postoperative patients with old age and/or advanced fibrosis; however, the suppressive effect on HCC recurrence has not been elucidated.[13–19] The present study therefore analyzed the impact of introducing antiviral therapy after surgery and DAA therapy on the prognosis retrospectively. Although the achievement of an SVR was an independent predictor of overall survival and recurrence in the patients with primary HCV-related HCC patients, it was not a significant predictor in the patients who received an antiviral therapy. This discrepancy may be due to the facts that the background characteristics, such as the age, liver function and performance status, in the patients who received antiviral therapy better than those in all of the cohorts in the present study, so the factor of an SVR was not left as an significant prognostic factor in the patients who received antiviral therapy. However, the multivariate analysis revealed marginal differences in both the overall

TABLE 3 Prognostic factors for the overall survival and relapse-free survival in primary C-HCC patients who received an antiviral therapy by univariate and multivariate analyses

Variables	Overall survival				Relapse-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*	Hazard ratio (95% confidence interval)	*P*
Age (≥ 71 years)	2.57 (0.89–7.46)	0.082			1.19 (0.60–7.46)	0.611		
Gender (male)	0.78 (0.27–2.24)	0.639			1.15 (0.56–2.35)	0.710		
Pre- or Post-SVR (achievement)	0.57 (0.34–0.95)	***0.030***	0.62 (0.37–1.05)	0.073	0.70 (0.51–0.96)	***0.027***	0.72 (0.52–1.01)	0.057
Pre-nonresponder	2.92 (1.03–8.33)	***0.045***			1.79 (0.94–3.41)	0.074		
Antiviral therapy (after surgery)	0.27 (0.83–0.85)	***0.027***	0.31 (0.95–1.02)	0.055	0.61 (0.32–1.16)	0.129		
Antiviral therapy (DAA)	0.21 (0.23–1.55)	0.125			0.39 (0.16–0.94)	***0.035***		
PT (< 70%)	6.58 (1.39–31.3)	***0.018***			2.71 (0.64–11.5)	0.177		
AST (> 40 IU/L)	0.97 (0.35–2.68)	0.850			1.41 (0.76–2.64)	0.280		
ALT (> 40 IU/L)	1.43 (0.49–4.19)	0.517			1.43 (0.75–2.72)	0.274		
Platelet count (< 13.1×10^4/μl)	1.85 (0.69–4.94)	0.219			0.91 (0.50–1.85)	0.964		
$ICGR_{15}$ (> 16%)	1.00 (0.36–2.74)	0.995			1.24 (0.64–2.37)	0.526		
AFP (> 10.0 ng/mL)	1.32 (0.45–3.87)	0.613			1.33 (0.70–2.51)	0.381		
DCP (≥ 40 mAL/mL)	1.93 (0.69–5.37)	0.209			2.47 (1.24–4.92)	***0.010***	2.68 (1.35–5.35)	***0.005***
Cirrhosis (present)	1.33 (0.48–3.69)	0.578			1.05 (0.53–2.07)	0.894		
Tumor diameter (≥ 30 mm)	1.11 (0.40–3.08)	0.845			1.14 (0.60–2.14)	0.696		
Tumor number (multiple)	1.74 (0.61–4.93)	0.299			1.59 (0.81–3.15)	0.181		
Tumor margin (positive)	0.05 (0–14450)	0.634			0.46 (0.63–3.37)	0.445		

Bold and italic values indicate significant differences

HCC hepatocellular carcinoma, *AFP* alpha-fetoprotein, *DCP* des-gamma-carboxy prothrombin

survival ($P = 0.073$) and relapse-free survival ($P = 0.057$) and these results support the importance of obtaining an SVR either before or after surgery. On the other hand, there were no adverse effects of DAA therapy from the present study, and it was a rather favorable factor for relapse-free survival in a univariate analysis. Moreover, aggressive recurrence or unexpected early recurrence was not found in the patients who received DAA in the present study. Thus, the postoperative administration of DAA therapy might be suitable for patients with primary HCV-related HCC patients who undergo curative surgery because of the high SVR rate. However, some studies have shown that patients with a history of repeated HCC therapy in previous develop aggressive recurrence due to IFN-free DAA therapy; thus, attention is required when treating such patients.[28]

The present study was associated with several limitations. First, this study was retrospective in nature and was performed at a single center, and there was little information available on the initial or pre-therapy HCV-RNA value and its impact on the outcomes, as most HCC patients who underwent surgery were referred from other hospitals due to the characteristics of our hospital. Thus, the influence of a selection bias cannot be ruled out. Further prospective multi-institutional studies are therefore needed to objectively validate the results of the present study. However, the results of the present study, which were based on a relatively large study population (> 200 patients) and a long follow-up period (median, 50.3 months), were reliable. Second, the rate of introducing antiviral therapy before and after surgery in the present study (25.9% and 14.1%) was relatively low because there were no

hepatologists in the author's institution. However, the rate at which antiviral therapy using DAA is introduced has been increasing and it is possible for patients with HCV-related HCC to obtain an SVR rate of approximately 100% in the near future.

CONCLUSIONS

The achievement of an SVR either before or after surgery is associated with the suppression of HCC recurrence and leads to an improvement in overall and relapse-free survival after hepatectomy in patients with primary HCV-related HCC. With the advent of DAA, the administration of DAA therapy might be suitable for patients who seem tolerant of such therapy after surgery as they can obtain a high SVR rate.

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