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ORIGINAL ARTICLE

Trends in long-term outcomes of patients with HCV-associated hepatocellular carcinoma after hepatectomy: A comparison before and after introduction of direct-acting antivirus therapy

Fumiaki Munekage | Tomoaki Yoh | Satoshi Ogiso | Takuya Kato | Nguyen Hai Nam | Kazuyuki Nagai | Yoichiro Uchida | Takashi Ito | Takamichi Ishii | Etsuro Hatano

Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence
Tomoaki Yoh, Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
Email: tomyoh@kuhp.kyoto-u.ac.jp

Abstract

Backgrounds: The success of direct-acting antiviral (DAA) therapy provides a cure for patients chronically infected with hepatitis C virus (HCV); however, outcomes after hepatectomy for HCV-associated hepatocellular carcinoma (HCC) before and after DAA introduction remain poorly studied.

Methods: Patients who underwent R0/R1 hepatectomy for HCV-associated HCC were retrospectively analyzed. Two time periods were defined: Pre-DAA (2007–2011, December 2013 was defined as the end of follow-up) and Post-DAA groups (2014–2018, December 2020 was defined as the end of follow-up). Propensity score matching (PSM) analyses were performed to highlight the effect of DAA therapy.

Results: A total of 155 patients with HCV-associated HCC were included in this study (Pre-DAA group, $n=103$ and post-DAA group, $n=52$). In the Post-DAA group, DAA therapy was performed in 26 patients (50.0%), and all of these patients achieved sustained virologic response (SVR) (preoperative SVR, $n=7$; postoperative SVR, $n=19$). There was no significant difference between the two groups regarding surgical settings and tumor pathology. There was no significant difference in the 5-year overall survival (OS) rate (61.1% and 64.8%, pre- and post-DAA group, respectively, $p=0.441$); meanwhile, the 5-year recurrence-free survival (RFS) rate in the post-DAA group was better than the pre-DAA group (21.1% and 40.2%, $p=0.073$) with a trend toward significance. After PSM except for the postoperative SVR status, there were no significant differences in OS ($p=0.586$) and RFS ($p=0.888$).

Conclusions: This study showed that survival outcomes were not changed in hepatectomized cases of HCV-associated HCC before and after the introduction of DAA therapy.

Fumiaki Munekage and Tomoaki Yoh contributed equally to this study.

KEYWORDS
DAA, direct-acting antivirals, HCC, HCV, hepatectomy, hepatitis C virus, hepatocellular carcinoma, survival

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, showing and its incidence is increasing worldwide.[1] Among the available treatment options, liver resection (LR) and liver transplantation can provide long-term survival in selected patients with HCC.[2] Among the several prognostic factors, hepatitis C virus (HCV) infection, the leading cause of HCC in the East-Asian population, represents the significant determinant of survival outcomes in resected and transplanted cases.[3] One possible explanation for these unsatisfactory outcomes is the high rate of multicentric occurrence and progressive liver dysfunction.[4] Therefore, HCV eradication has been considered as the key factor in achieving long-term survival in patients with HCC.[5]

Since 2014, the introduction of direct-acting antiviral (DAA) therapy has led to a paradigm shift in the treatment of patients with HCV infection.[6] While interferon (IFN) therapy was the primary treatment for HCV infection in the past, DAA therapy achieves a high rate of sustained virologic response (SVR), ranging from 76% to 100%.[7] It is currently established as the standard treatment for patients with HCV infection as an alternative to IFN therapy.[8] From an oncologic point of view, an association between DAA therapy and HCC development and recurrence was also initially discussed.[9,10] The introduction of DAA therapy after curative treatment for HCV-associated HCC has been reported to be equally effective in suppressing recurrence of IFN therapy.[11] Despite the possible benefit of DAA therapy, it remains to be fully investigated whether survival outcomes are improved in patients with HCV-associated HCC.

Therefore, the aim of this study was to investigate the trends in survival outcomes of patients with HCV-associated HCC who underwent hepatectomy before and after the introduction of DAA therapy at a tertiary referral center for hepatobiliary surgery.

2 | PATIENTS AND METHODS

2.1 | Study design

The protocol of this retrospective observational study was approved by the Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University (approval code: R1721-2). Based on the introduction of DAA therapy in 2014, clinical characteristics and outcomes were compared between the two time periods: Pre-DAA (2007–2011) and Post-DAA (2014–2018) groups. To reduce the bias of the length of follow-up time and impact of DAA therapy between the two groups, December 2013 was defined as the end of follow-up in the Pre-DAA group; December 2020 was defined as the end of follow-up in the Post-DAA group. Written informed consent was obtained from all study participants.

2.2 | Patients

We reviewed a prospectively maintained institutional database of consecutive patients with HCV-associated HCC who underwent initial hepatectomy at the Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Kyoto University, between January 2007 and December 2018. As mentioned above, the patients were divided into the two groups: the Pre- and Post-DAA groups.

Inclusion criteria were: (1) patients who underwent initial hepatectomy for HCV-associated HCC; (2) patients who tested positive for HCV antibody, and (3) patients with histologically diagnosed HCC. Exclusion criteria were: (1) patients with distant metastasis detected on imaging studies, such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-FDG-PET, or intraoperatively; (2) patients who underwent repeated hepatectomy during the study period; and (3) patients who underwent hepatectomy and concomitant ablative therapy. Clinicopathologic data, including sex, age, hepatitis virus markers, primary tumor characteristics, treatment-related variables, and survival data were retrieved from the database.

2.3 | Surgical strategy and perioperative management

Treatment decisions were determined in a comprehensive matter, taking into account the size or the number of tumors, the anatomical location of the tumors, the availability of other treatment options, and the performance status of the patients. Treatment decisions were discussed in a weekly cancer board meeting.[12] Indications for LR included a Child–Pugh (CP) grade of A or B and an indocyanine green (ICG) clearance of the remnant liver (ICG-Krem) >0.03.[13] Volumetric computed tomography (CT) was routinely performed for volume assessment.[13] Open surgical procedures of LR were standardized, as previously reported[14]; meanwhile, the indication and technique of laparoscopic LR were chronologically changed as previously reported.[15] In patients with macrovascular invasion, pre- and/or post-adjuvant HAIC was performed when possible.[16] The extent of liver resection was classified according to the Brisbane 2000 terminology.[17] Patients were carefully monitored on a daily basis until their hospital discharge. A CT assessment was routinely performed around postoperative Day 7 or in cases of suspected abdominal or pulmonary complications. Complications were defined according to the Clavien–Dindo classification.[18]

2.4 | Postoperative follow-up

The follow-up protocol, recurrence criteria, definition of recurrence patterns, and treatment strategy for tumor recurrence have been described elsewhere.[13,19] Indication for DAA therapy was determined according to the Japanese guidelines.[20] Principally, postoperative antiviral therapy for HCV infection was initiated after confirmation of the absence of tumor recurrence at least at postoperative month 3. All patients who did not achieve SVR before curative hepatectomy were eligible for DAA therapy. However, patients who were not overcoming perioperative complications, early recurrent cases, liver failure, and others could not administer DAA. SVR was defined as a serum HCV-RNA titer below the detection sensitivity limit at 6 months after cessation of antiviral therapy.[21] As our center is a tertiary referral center for hepatobiliary surgery, the patient was transferred back to the hospital of origin for follow-up. Postoperative DAA therapy was performed at the originating hospital of origin whenever possible. SVR status was confirmed in the case report.

2.5 | Statistical analyses

Categorical variables were analyzed using the chi-squared test and Fisher's exact test when appropriate. Continuous variables were analyzed using the Mann–Whitney *U* test. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or the date of last follow-up. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence or death from any cause. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

To emphasize the influence of DAA therapy between the Pre- and Post-DAA groups, a propensity score matching (PSM) analysis was performed.[22] A propensity score was calculated using a logistic regression model. The variables that could potentially influence the choice of DAA therapy and long-term outcomes were included in the model.[23] After the propensity score was generated, patients in the Pre- and Post-DAA groups underwent 1:1 nearest-available matching of the logit of the propensity score with a caliper width of 0.20 of the standard deviation of the score.[24] Patients who did not meet the matching criteria were excluded.

All *p* values were two-sided, and values less than 0.050 were considered statistically significant, while values less than 0.100 were considered a trend toward statistical significance. Statistical analyses were performed with JMP Pro 16.2 software (SAS Institute Inc.). PSM was performed using the JMP add-in program.

3 | RESULTS

Figure 1 shows a flow diagram of the present study. From 2007 to 2018, 253 hepatectomies were performed for HCV-associated HCC. According to the study criteria, a total of 155 patients were included. Of these, 103 and 52 patients were included in the Pre- (2007–2011) and Post-DAA (2014–2018) groups, respectively.

3.1 | Patients demographics

The overall patient characteristics are shown in Table 1. Of the 155 patients included, 112 were men (72.3%) and 43 were women (27.7%). The median patient age of the patients was 71 years (range, 46–87 years). Among the patients, five had an HCV-RNA titer below

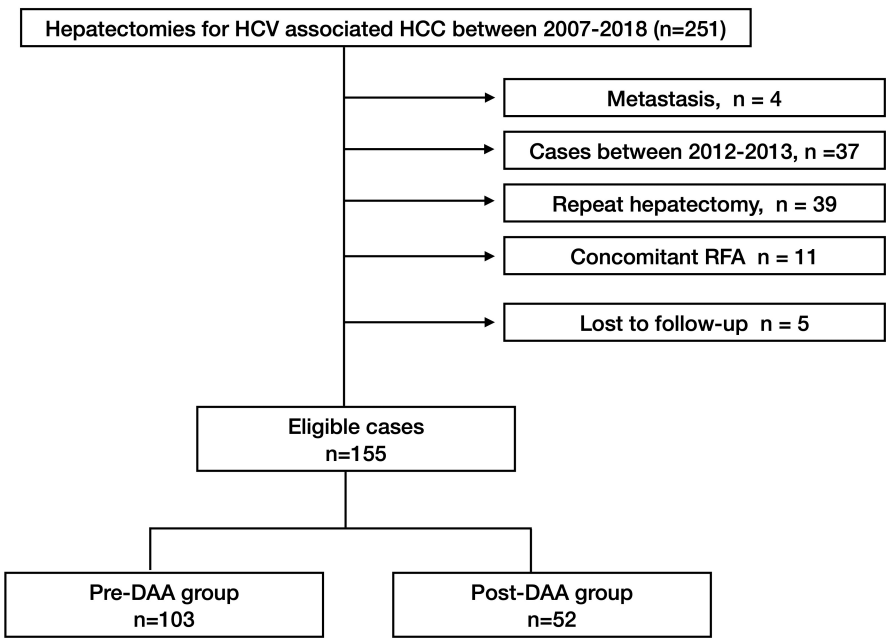


FIGURE 1 Flow chart of the study. DAA, direct-acting antivirus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

TABLE 1 Clinicopathological characteristics of patients with HCV-associated HCC before and after introduction of DAA therapy.

Variables	Overall patients ($n = 155$)	Pre-DAA ($n = 103$)	Post-DAA ($n = 52$)	p-Value
Preoperative findings				
Age (years), median (range)	71 (46–87)	71 (46–83)	71 (52–87)	0.390
Sex (men), *n*, %	112 (72.3)	75 (72.8)	37 (71.2)	0.827
ASA-PS ≥ III	13 (8.4)	6 (5.8)	7 (13.5)	0.129+
Treated for HCV before hepatectomy, *n*, %	61 (39.4)	39 (37.9)	22 (42.3)	0.593
IFN therapy, *n*, %	54 (34.8)	39(100)	15 (68.2)	
DAA therapy, *n*, %	2 (3.3)	0	2 (9.1)	
DAA (failure of IFN therapy), *n*, %	5 (8.2)	0	5 (22.7)	
SVR before hepatectomy, *n*, %	28 (18.0)	15 (14.6)	13 (25.0)	0.111
IFN therapy, *n*, %	21 (13.5)	15 (83.3)	6 (40.0)	
DAA therapy, *n*, %	7 (8.5)	0	7 (17.1)	
DAA (failure of IFN therapy), *n*, %	2 (2.4)	0	2 (4.9)	
HCV-RNA titer below the detection	5 (3.2)	3 (2.9)	2 (3.9)	1.000+
Positive for HBs antigen, *n*, %	4 (2.6)	2 (1.9)	2 (3.9)	0.602+
Child–Pugh B, *n*, %	21 (13.6)	14 (13.6)	7 (13.5)	0.982
ICG-15R (%), median (range)	16 (3–83)	17 (3–83)	14 (5–55)	0.131
Platelet count, median (range)	118 (6.6–428)	123 (6.6–374)	103.5 (10.8–428)	0.276
Serum AFP (ng/mL), median (range)	19.6 (1.2–185 800)	24.5 (1.2–185 800)	13.7 (1.7–57 465)	0.637
History of ablative therapy, *n*, %	3 (1.9)	3 (2.9)	0	0.551+
History of TACE, *n*, %	32 (20.6)	29 (28.2)	3 (5.8)	0.001*
Perioperative findings				
Major hepatectomy, *n*, %	46 (29.7)	32 (31.1)	14 (26.9)	0.594
Laparoscopic hepatectomy, *n*, %	37 (23.9)	23 (22.3)	14 (26.9)	0.527
Blood loss (mL), median (range)	640 (0–6540)	726 (0–4467)	447 (0–6540)	0.105
Complications (CD grade ≥ II)	54 (34.8)	35 (34.0)	19 (36.5)	0.752
Postoperative morality <90 days, *n*, %	5 (3.2)	5 (4.9)	0 (0)	0.169†
Pathological findings				
Vascular invasion, *n*, %				
Vp0/Vv0	119 (76.8)	78 (75.7)	41 (82.0)	
Vp1/Vv1	26 (16.8)	18 (17.5)	8 (15.4)	0.952+
Vp2-4/Vv2-3	10 (6.5)	7 (6.8)	3 (5.8)	
Multiple tumors, *n*, %	36 (23.2)	24 (23.3)	12 (23.1)	0.975
Tumor number, median (range)	1 (1-5)	1 (1–5)	1 (1–4)	0.904
Tumor diameter (cm), median (range)	3.2 (0.7–20)	3.3 (0.7–20)	3.1 (0.8–13.5)	0.513
Poorly/un differentiation, *n*, %	33 (21.3)	18 (17.5)	15 (28.9)	0.103
Negative surgical margins, *n*, %	139 (89.7)	90 (87.4)	49 (94.2)	0.186
F3/F4 fibrosis, *n*, %	94 (60.7)	61 (59.2)	33 (63.5)	0.610
Clinical findings after hepatectomy				
Early recurrence/death (<1 year)	56 (36.1)	41 (39.8)	15 (28.8)	0.180
Treated for HCV after hepatectomy, *n*, %	28 (18.1)	9 (8.7)	19 (36.5)	<0.001*
IFN therapy, *n*, %	9 (8.7)	9 (100)	0 (0)	0.028*
DAA therapy, *n*, %	19 (12.3)	0 (0)	19 (100)	<0.001*
SVR after surgery, *n*, %	24 (15.5)	5 (4.9)	19 (36.5)	<0.001*
IFN therapy, *n*, %	5(3.2)	5 (100)	0	
DAA therapy, *n*, %	19 (12.3)	0	19 (100)	
Overall treated for HCV, *n*, %	81 (52.3)	46 (44.7)	35 (67.3)	0.008*
Overall SVR, *n*, %	52 (33.6)	20 (19.4)	32 (61.5)	<0.001*

Abbreviations: AFP, alfa feto protein; AS-PS, American Society of Anesthesiologist Physical Status; DAA, direct-acting antivirus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICG-15R, indocyanine green retention rate at 15 min; IFN, interferon; SVR, sustained virologic response; TACE, transcatheter arterial chemoembolization.

*Significant difference.

+Fisher exact test.

the detection. Before hepatectomy, anti-HCV therapy was administered to 61 patients, with 54 receiving IFN therapy, two receiving DAA therapy, and five receiving DAA therapy as a result of IFN therapy failure. After hepatectomy, anti-HCV therapy was administered to 28 patients, with nine receiving IFN therapy and 19 receiving DAA therapy. Among the 52 patients who achieved SVR, 26 received IFN therapy, and 26 received DAA therapy. Additionally, 74 patients did not receive any antiviral therapy. Prior to hepatectomy, 28 patients achieved SVR, and after hepatectomy, 24 patients achieved SVR.

3.2 | Comparison of clinicopathologic characteristics between the pre- and post-DAA groups

Table 1 also summarizes the clinicopathologic data between the Pre- and Post-DAA groups. Regarding the treatment for HCV infection, a higher proportion of patients who were treated for HCV infection was found in the Post-DAA group (44.7% vs. 67.3%, Pre- vs. Post-DAA groups, respectively, $p=0.008$). In the Post-DAA group, DAA therapy was indicated in 26 patients (50.0%). In both the overall and postoperative setting, a significantly higher proportion of patients achieving SVR were found in the Post-DAA group (overall setting, 19.4% vs. 61.5%, $p<0.001$; postoperative setting, 4.9% vs. 36.5%, $p<0.001$). Meanwhile, SVR status before surgery was not significantly different between the two groups (14.6% vs. 25.0%, $p=0.111$). As shown in Table 2, 26 patients in the Post-DAA group were not indicated for DAA therapy for the following reasons: (i) comorbidity/older age ($n=9$); (ii) recurrence of HCC ($n=8$); (iii) preoperative SVR ($n=6$); (iv) HCV-RNA titer below the detection before hepatectomy ($n=2$); and (v) liver failure ($n=1$). Regarding the pre-and postoperative outcomes, there were no significant differences between the two groups. In addition, there were no significant differences in pathological factors between the two groups.

TABLE 2 Causes of ineligibility for DAA therapy in the Post-DAA group.

Variables	($n=26$)
Comorbidity/older age	9
Liver cirrhosis	2
Older age	1
Older age with comorbidity	4
Other comorbidities	2
Recurrence of HCC	8
Preoperative SVR	6
HCV-RNA titer below the detection before hepatectomy	2
Liver failure	1

Abbreviations: DAA, direct-acting antivirus; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

3.3 | Trends in survival outcomes of patients with HCV-associated HCC after hepatectomy

Overall, median follow-up in the Pre- and Post-DAA groups was 46.4 (range, 0.5–84.8 months); 45.2 (range, 0.5–84.8 months) and 49.1 months (range, 4.6–84.3 months), respectively ($p=0.208$). Twenty-one patients (16 and five patients in the Pre- and Post-DAA groups, respectively) died without tumor recurrence. The survival analysis is shown in Figure 2. There was no significant difference in OS between the two groups; the median OS of both groups was not reached, and the 1-, 3-, and 5-year OS rates were 86.4%, 76.5%, and 61.1%, and 92.2%, 84.0%, and 64.8% in the Pre- and Post-DAA groups, respectively ($p=0.441$). Meanwhile, median RFS and the 1-, 3-, and 5-year RFS rates were better in the Post-DAA group than in the Pre-DAA group (18.5 months, and 60.2%, 31.6%, and 21.1%, vs. 26.8 months, and 76.7%, 46.5%, and 40.2%, $p=0.073$) with a trend toward significance.

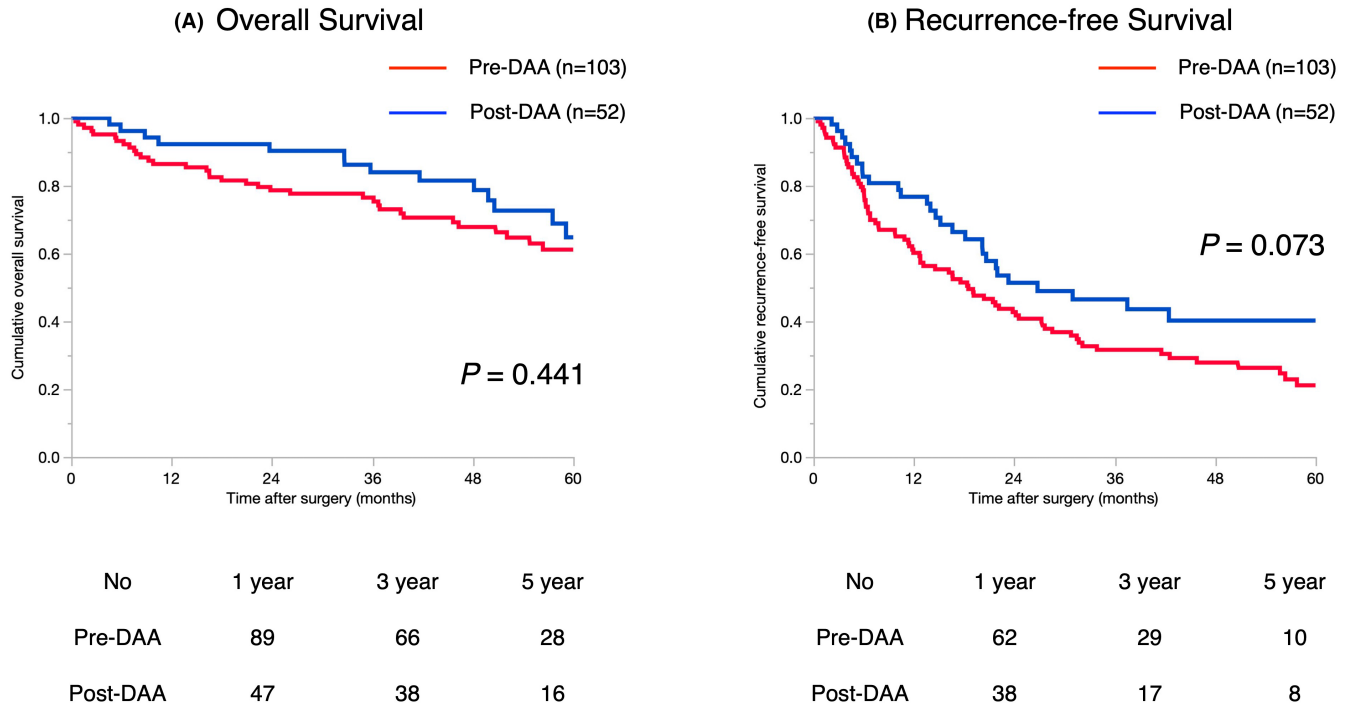
3.4 | Comparison of clinical characteristics at tumor recurrence in patients with HCV-associated HCC after hepatectomy

To further assess the clinical characteristics between the two groups, we analyzed the clinical data at the time of tumor recurrence in patients with HCV-associated HCC after hepatectomy. During the defined follow-up period, 69 patients in the Pre-DAA group and 27 patients in the Post-DAA group showed tumor recurrence. As shown in Table 3, there were no significant differences in terms of age, gender, time to recurrence, recurrence pattern, and treatment variables.

3.5 | Propensity score matching analyses

The main difference between the two groups was the status of postoperative SVR. To highlight the influence of postoperative DAA therapy, PSM analyses were performed. Fourteen variables (age, gender, American Society of Anesthesiologist Physical Status (ASA-PS) classification, preoperative SVR status, Child–Pugh grade, serum AFP levels, history of TACE, postoperative complications, tumor diameter, pathological tumor multiplicity, microvascular invasion, tumor differentiation, surgical margin, and early recurrence/death) (<1 year) were included in the logistic model. Using the propensity score, 84 patients with HCV-associated HCC were matched into either the Pre-DAA group ($n=42$) or the Post-DAA group ($n=42$). After PSM, there was no difference between the two groups except for the postoperative SVR status and related variables (Table 4).

Survival analyses were performed in the matched cohort (Figure 3). There was no significant difference in OS and RFS between the two groups; the median OS of both groups was not



No	1 year	3 year	5 year
Pre-DAA	89	66	28
Post-DAA	47	38	16

No	1 year	3 year	5 year
Pre-DAA	62	29	10
Post-DAA	38	17	8

FIGURE 2 Comparison of (A) cumulative overall survival and (B) recurrence-free survival after hepatectomy in patients with HCV-associated HCC between Pre-DAA and Post-DAA groups. DAA, direct-acting antivirus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

TABLE 3 Clinical characteristics of patients with recurrent HCV-associated HCC before and after introduction of DAA therapy.

Variables	Pre-DAA ($n=69$)	Post-DAA ($n=27$)	p-value
Age, years, median (range)*	70 (50–83)	73 (54–87)	0.697
Gender, male, n (%)	53 (76.8)	22 (81.5)	0.619
Time to recurrence, months, median (range)	12.8 (1.1–65.5)	16.6 (2.2–69.1)	0.648
Recurrence pattern			
Intrahepatic recurrence	63 (91.3)	23 (95.8)	0.639+
Extrahepatic recurrence	6 (8.7)	1 (4.2)	
Main treatment			
Ablative therapy	21 (33.3)	7 (25.9)	0.499+
Repeat hepatectomy	4 (6.3)	1 (4.8)	
TACE	34 (54.0)	11 (52.4)	
Systemic chemotherapy	1 (1.6)	2 (9.5)	
Others	3 (4.8)	0	

Abbreviations: DAA, direct-acting antivirus; HCC, hepatocellular carcinoma; SVR, sustained virologic response; TACE, transcatheter arterial chemoembolization.

*Findings at recurrence.

+Fisher exact test.

reached, and 1-, 3-, and 5-year OS rates were 88.1%, 83.3%, and 76.7%, and 92.8%, 85.2%, and 62.4% in the Pre- and Post-DAA groups, respectively ($p=0.586$); the median RFS was 24.4 and 23.4 months, and 1-, 3-, and 5-year RFS rates were 66.7%, 40.2%, and 26.5%, and 76.1%, 38.7%, and 35.5% in the Pre- and Post-DAA groups, respectively ($p=0.888$).

4 | DISCUSSION

This study aimed to investigate the trends in outcomes of patients with HCV-associated HCC who underwent hepatectomy before and after the introduction of DAA therapy. The number of hepatectomy cases for HCV-associated HCC has decreased over time, and DAA

TABLE 4 Clinicopathological characteristics of patients with HCV-associated HCC before and after introduction of DAA therapy after propensity-score matching.

Variables	Overall patients ($n=84$)	Pre-DAA ($n=42$)	Post-DAA ($n=42$)	p-value
Preoperative findings				
Age (years), median (range)	70.5 (52–87)	71.5 (54–83)	70 (52–87)	0.697
Sex (men), *n*, %	58 (69.1)	29 (69.1)	29 (69.1)	1.000[+]
ASA-PS ≥ III	9 (10.7)	5 (11.9)	4 (9.5)	1.000[+]
Treated for HCV before hepatectomy, *n*, %	35 (41.7)	18 (42.9)	17 (40.5)	0.825
IFN therapy, *n*, %	32(91.4)	18(100)	14 (82.4)	
DAA therapy, *n*, %	4 (11.4)	0	4 (23.5)	
DAA (failure of IFN therapy), *n*, %	1 (2.9)	0	1 (5.9)	
SVR before hepatectomy, *n*, %	19 (22.6)	11 (26.2)	8 (19.1)	0.434
IFN therapy, *n*, %	15 (78.9)	11 (100)	4 (50.0)	
DAA therapy, *n*, %	3 (15.8)	0	3 (75.0)	
DAA (failure of IFN therapy), *n*, %	1 (5.3)	0	1 (25.0)	
HCV-RNA titer below the detection	3 (3.6)	1 (2.4)	2 (4.8)	1.000[+]
Positive for HBs antigen, *n*, %	2 (2.4)	1 (2.4)	1 (2.4)	1.000[+]
Child–Pugh B, *n*, %	11 (13.1)	6 (14.3)	5 (11.9)	0.746
ICG-15R (%), median (range)	15 (4–83)	15.5 (4–83)	14.5 (5–55)	0.622
Platelet count, median (range)	122.5 (10.8–374)	125.5 (13.1–374)	104 (10.8–261)	0.428
Serum AFP (ng/ml), median (range)	12.6 (1.2–167 928)	10.5 (1.2–167 928)	15.3 (1.7–23 586)	0.744
History of ablative therapy, *n*, %	0	0	0	
History of TACE, *n*, %	9 (10.7)	6 (14.3)	3 (7.2)	0.483[+]
Perioperative findings				
Major hepatectomy, *n*, %	23 (27.4)	12 (28.6)	11 (26.2)	0.807
Laparoscopic hepatectomy, *n*, %y	21 (25.0)	10 (23.8)	11 (26.2)	0.801
Blood loss (mL), median (range)	510 (0–6077)	600 (0–3250)	457 (0–6077)	0.519
Complications (CD grade ≥ II)	30 (35.7)	14 (33.3)	16 (38.1)	0.649
Postoperative morality <90 days, *n*, %	3 (3.6)	3 (7.1)	0 (0)	0.241[+]
Pathological findings				
Vascular invasion, *n*, %				
Vp0/Vv0	67 (79.8)	33 (78.6)	34 (80.1)	0.325[+]
Vp1/Vv1	15 (17.9)	9 (21.4)	6 (14.3)	
Vp2-4/Vv2-3	2 (2.4)	0	2 (4.8)	
Multiple tumors, *n*, %	25 (29.8)	14 (33.3)	11 (26.2)	0.474
Tumor number, median (range)	1 (1–5)	1 (1–5)	1 (1–4)	0.429
Tumor diameter (cm), median (range)	3.3 (0.8–20)	3.5 (0.9–20)	3.1 (0.8–10)	0.148
Poorly/un differentiation, *n*, %	20 (23.8)	11 (26.2)	9 (21.4)	0.608
Negative surgical margins, *n*, %	82 (97.6)	42 (100)	40 (95.2)	0.494[+]
F3/F4 fibrosis, *n*, %	49 (58.3)	23 (54.8)	26 (61.9)	0.507
Clinical findings after hepatectomy				
Early recurrence/death (<1 year)	26 (31.0)	14 (33.3)	12 (28.6)	0.637
Treated for HCV after hepatectomy, *n*, %	19 (22.6)	2 (4.8)	17 (40.5)	<0.001[*]
IFN therapy, *n*, %	2 (10.5)	2 (100)	0 (0)	
DAA therapy, *n*, %	17 (89.5)	0 (0)	17(100)	
SVR after surgery, *n*, %	18 (21.4)	1 (2.4)	17 (40.5)	<0.001[*]
IFN therapy, *n*, %	1 (5.6)	1 (100)	0	
DAA therapy, *n*, %	17 (94.4)	0	17 (100)	

(Continues)

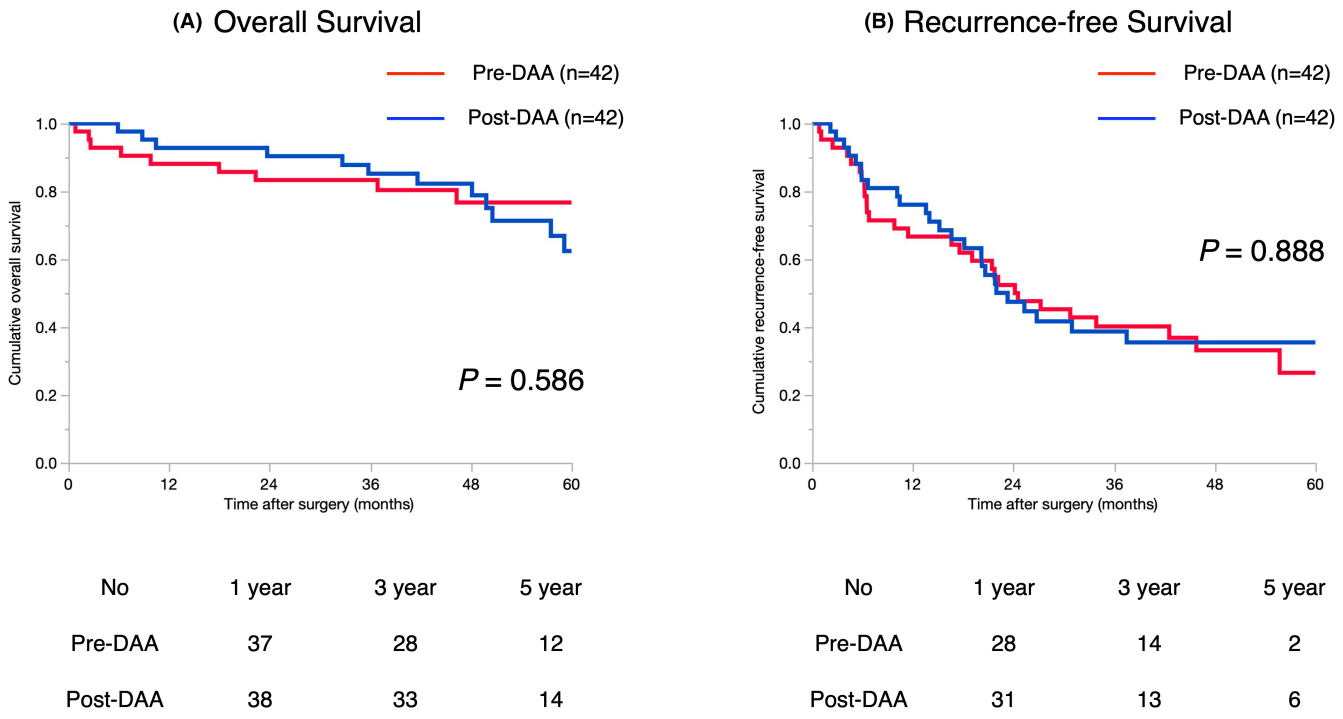
TABLE 4 (Continued)

Variables	Overall patients ($n=84$)	Pre-DAA ($n=42$)	Post-DAA ($n=42$)	p-value
Overall treated for HCV, *n*, %	48 (57.1)	20 (47.6)	28 (66.7)	0.078
Overall SVR, *n*, %	37 (44.1)	12 (28.6)	25 (59.5)	0.004*

Abbreviations: AFP, alfa feto protein; AS-PS, American Society of Anesthesiologist Physical Status; DAA, direct-acting antivirus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IFN, interferon; ICG-15R, indocyanine green retention rate at 15 minutes; SVR, sustained virologic response; TACE, transcatheter arterial chemoembolization.

*Significant difference.

+Fisher's exact test.



No	1 year	3 year	5 year
Pre-DAA	37	28	12
Post-DAA	38	33	14

No	1 year	3 year	5 year
Pre-DAA	28	14	2
Post-DAA	31	13	6

FIGURE 3 Comparison of (A) cumulative overall survival and (B) recurrence-free survival after hepatectomy in patients with HCV-associated HCC between Pre-DAA and Post-DAA groups after propensity score matching. DAA, direct-acting antivirus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

therapy was indicated for selected patients ($n=26$, 50.0%) in the Post-DAA period. As with the overall results, the introduction of DAA therapy significantly improved the SVR rate. In this study, the use of DAA therapy in the postoperative setting was biased. In this setting, the better RFS with a trend toward statistical significance was found in the Post-DAA time frame, yet, a comparable OS was observed between the two groups. To further highlight the influence of DAA therapy, PSM analyses were performed. According to PSM except for postoperative SVR status and related variables, both OS and RFS were not stratified by the time period.

The benefit of DAA therapy for patients with HCV infection has been well-reported[6]; the use of DAA was associated with the improvement in hepatic functional reserve, regardless of the stage of liver fibrosis.[25] Older studies reported that SVR by IFN therapy was associated with the development of HCC,[26] and DAA therapy might have the same effect in patients with HCV infection.[27] Therefore, it has been suggested that the incidence of HCV-associated HCC has been reduced in part by the introduction of DAA therapy.[28] In line with this trend, DAA therapy might have influenced the reduced cases of hepatectomy for HCV-associated HCC.

Meanwhile, despite the potential benefit of DAA therapy, the "actual" trends in outcomes in patients with HCV-associated HCC who underwent hepatectomy remain poorly understood. In this before–after study, we have taken several efforts to highlight the impact of DAA therapy. As a result, the use of DAA therapy was skewed to the postoperative setting; it should be acknowledged that DAA therapy was not indicated for all the patients mainly due to HCC recurrence and comorbidities (Table 2). Actually, the postoperative induction of DAA therapy was 51.4% (19 patients out of 37 patients) excluding patients with preoperative SVR or HCV-RNA titer below the detection. Consequently, the use of DAA therapy was strongly associated with patients who might have favorable outcomes (i.e., less aggressive tumors or patients with relatively well-condition [Table 2]). In this setting, RFS was better in the Post-DAA group than the Pre-DAA group with a trend toward significance, but OS was comparable between the two groups. To further emphasize the

influence of DAA therapy, PSM analyses were performed. According to PSM except for postoperative SVR status and related variables, both OS and RFS were not stratified by time period. In addition to the high SVR ratio achieved by DAA therapy, equivalence between IFN and DAA therapy has been recognized in terms of their antitumor effects.[11] Therefore, the introduction of DAA therapy following curative hepatectomy for HCV-associated HCC was anticipated to improve survival outcomes, as previous studies predominantly reported the prognostic benefits of DAA therapy in patients who underwent curative treatment.[6,29,30] However, the findings in this before–after study suggested that the influence of DAA therapy on survival outcomes in patients who underwent hepatectomy might be limited. One possible explanation for the results of this present study was that hepatectomized cases represented relatively better liver function in the first place, and the prognostic impact of liver function recovery by DAA therapy might be limited. Another possible explanation was that the proportion of patients who achieved SVR postoperatively was low to influence the survival outcomes in the entire study population. Additionally, it is worth noting that the benefits of DAA therapy may become more apparent over a longer-term follow-up period,[30] which could explain the lack of observed significance within the limited duration of the follow-up period in this study.

In patients with HCV-associated HCC, hepatectomized cases would be divided into three groups: (i) antiviral treatment naive group, (ii) antiviral treatment failure group, and (iii) antiviral treatment success group. Considering the expansion of DAA therapy and its excellent results in the context of achieving SVR, the vast majority of patients with HCV-associated HCC will show an antiviral treatment success group at the time of surgery. Furthermore, the requirement of long-term follow-up after antiviral therapy[31] may allow the identification of early-stage HCC cases with SVR status. Considering the results of the present study, the role of DAA therapy for hepatectomized cases may be identification of early-stage HCC cases rather than improving survival outcomes.

This study had several unavoidable limitations. First, because of the retrospective design, the true value of DAA therapy remains inconclusive. To compensate for this limitation, we conducted PSM analyses adjusting for selected factors. Although prospective studies are ideal, conducting them would be challenging due to ethical issues related to the high SVR rate of DAA therapy. Even with PSM analysis, there may still be residual historical bias that could not be avoided, such as variations in indications, treatment strategies, surgical techniques, postoperative care, and recurrence management. Second, because our center is a tertiary hospital it was difficult to collect the detailed regimen of postoperative DAA therapy for all patients. Third, because of the single institutional analysis, sample size was limited. Further studies using multicenter data would be required to provide more comprehensive insights. Despite these limitations, this study was one of the largest-sized studies in Japan, and we have presented real-world data of survival outcomes in patients with HCV-associated HCC who underwent hepatectomy before and after the introduction of DAA therapy.[23,29,32] Actual data on long-term outcomes after hepatectomy for HCV-associated HCC would be of interest to clinicians and surgeons.

5 | CONCLUSIONS

This study showed that survival outcomes were not changed in hepatectomized cases of HCV-associated HCC before and after the introduction of DAA therapy.

AUTHOR CONTRIBUTIONS

Tomoaki Yoh developed the main concept and designed the study. Etsuro Hatano was the supervisor of this study. Fumiaki Munekage, Tomoaki Yoh, Takuya Kato, Nguyen Hai Nam, and Satoshi Ogiso were responsible for acquisition of clinicopathological data. Fumiaki Munekage, Tomoaki Yoh, and Etsuro Hatano performed data analysis, interpretation, and drafted the manuscript. All authors contributed to editing and critical revision for important intellectual content.

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The authors have no funding to declare.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

ETHICS STATEMENT

Approval of the research protocol: The present study was approved by Ethics Committee of the Graduate School and Faculty of Medicine, Kyoto University (approval code: R1721-2) and was carried out in compliance with the Helsinki Declaration.
Informed consent: Informed consent was obtained from all individual participants included in the study.
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ORCID

Fumiaki Munekage https://orcid.org/0009-0004-7325-8640
Tomoaki Yoh https://orcid.org/0000-0001-6518-2077
Satoshi Ogiso https://orcid.org/0000-0002-9577-330X
Yoichiro Uchida https://orcid.org/0000-0003-2266-7722

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