Direct-acting antivirals reduce the risk of tumour progression of hepatocellular carcinoma after curative treatment

Hiroko Ikenaga, Sawako Uchida-Kobayashi, Akihiro Tamori, Naoshi Odagiri, Kanako Yoshida, Kohei Kotani, Hiroyuki Motoyama, Ritsuzo Kozuka, Etsushi Kawamura, Atsushi Hagihara, Hideki Fujii, Masaru Enomoto, Norifumi Kawada

Highlights	◇C 型肝炎ウイルスの感染があり初期の肝がんを根治した患者に対し、がんの治療後に経口治療薬（DAA）治療を使用して C 型肝炎ウイルスを排除することの有益性を検討。 ◇DAA 治療は、肝がんの再発リスクを低下させなかったもののがんの進行リスクを大きく低下。 ◇肝臓病による死亡リスクや、がんが進行するまでに行った肝がんの治療頻度も低下した。
概　要	研究グループは、C 型肝炎ウイルスの感染がある初期の肝がん患者に対して、がんの治療後に経口治療薬（DAA）治療により C 型肝炎ウイルスを排除することで、肝がんの進行リスクを低下させることを初めて明らかにしました。さらに、肝がんの治療頻度、死亡リスクも低下させることを明らかにしました。本研究成果により、DAA 治療が肝がん治療後の患者にも有益性が高いことが示されました。 C 型肝炎ウイルス感染症は肝がんの原因となる感染症で、DAA 治療は C 型肝炎ウイルスに直接作用して増殖を抑える飲み薬です。肝がんになったことのない患者に DAA 治療を行うと、肝がんが発生しにくくなることが明らかとなっていますが、肝がん根治後の患者にもがんを抑える効果があるかどうかははっきりしていませんでした。 今回、本研究グループは、初発で初期の肝がんを根治した患者 165 例を対象とし、がんの治療後に DAA 治療で C 型肝炎ウイルス感染症を治すことにより、肝がんの再発リスク、がんの進行リスク、がんの治療頻度、肝臓病による死亡リスクがどのように変化するか調査しました。その結果、DAA 治療をした患者としなかった患者では、再発リスクはすでにいくつもの研究で報告されているのと同じく差が見られませんでした。しかし、がんの進行リスクは、DAA 治療をした患者で 72%も低下しました。さらに、肝臓病による死亡リスクは 88%も低下し、治療頻度も 1 年で 59%も低下しました。 【補足説明】 DAA 治療： C 型肝炎ウイルスに直接作用して増殖を抑える薬で、日本では 2014 年に承認されました。飲み薬だけの治療で副作用がほとんどなく、多くが 2～3 ヶ月程度の短期間で治療が完了します。治療成功率は 95%以上と高く、殆どの患者さんでウイルスを排除することができます。薬の価格は高額ですが、日本には本治療に対して医療費を助成する制度があります。 ‘C 型肝炎ウイルスの経口治療薬が肝がん治療後のがんの進行リスクを低下させることを明らかに’. 大阪市立大学. https://www.osaka-cu.ac.jp/ja/news/2021/211108. (参照 2021-11-08)

Direct-Acting Antivirals Reduce the Risk of Tumor Progression of Hepatocellular Carcinoma after Curative Treatment

Hiroko Ikenaga[1], Sawako Uchida-Kobayashi[1], Akihiro Tamori[1], Naoshi Odagiri[1], Kanako Yoshida[1], Kohei Kotani[1], Hiroyuki Motoyama[1], Ritsuzo Kozuka[1], Etsushi Kawamura[1], Atsushi Hagihara[1], Hideki Fujii[2], Masaru Enomoto[1], Norifumi Kawada[1]

[1]Department of Hepatology, Graduate School of Medicine, Osaka City University, Osaka, Japan
[2]Department of Premier Preventive Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan

Short running title

DAAs reduce the risk of HCC progression

Corresponding Author

Norifumi Kawada, MD & PhD
Department of Hepatology, Graduate School of Medicine, Osaka City University, Osaka, Japan
1-4-3, Asahi-machi, Abenoku, Osaka, 545-8585, Japan.
Phone: +81-6-6645-3905
E-mail: kawadanori@med.osaka-cu.ac.jp

Funding statement

The present study was supported in part by a Research Grant from the Japan Agency for Medical Research and Development (no.21fk0210058h0003).

Conflict of interest disclosure

N.K. received lecture fees and research funding from Gilead, and received a scholarship donation from AbbVie. All other authors have no conflict of interest.

Ethics approval statement

This study protocol was approved by the Ethics Committee of Osaka City University Hospital (No.2021054).

Authors' contributions

HI and SUK conceived the project, participated in data analysis, and drafted the manuscript. NO, KY, KK, HM, RK, EK, AH, HF, ME and AT were involved in the clinical data analysis and data interpretation. NK supervised the project, was involved in data interpretation, and drafted the manuscript. All authors critically revised the report, commented on the drafts of the manuscript, and approved the final report.

Acknowledgements

We thank Ms. Yoko Yasuhara, Sanae Deguchi, Ayano Fujikawa and Rie Yasuda for their assistance with data/sample collection, and Dr. Satoko Ohfuji for her advice on statistical analysis. We would like to thank Editage (www.editage.com) for English language editing.

Abbreviations

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; SVR, sustained virological response; DAA, direct-acting antivirals; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; CI, confidence interval; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; IFN, interferon; CT, computed tomography; MRI, magnetic resonance imaging; TACE, transarterial chemoembolization; ALBI score, Albumin-Bilirubin score; FIB-4 index, fibrosis-4 index; AFP, α-fetoprotein; BMI, body mass index; PLT, platelet count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alb, albumin; Cr, creatinine; INR, prothrombin time-international normalized ratio; PY, person-year; AASLD, American Association for the Study of Liver Disease.

Abstract

Background and Aim: Hepatocellular carcinoma (HCC) has high recurrence rates. HCC sometimes progresses from early-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage 0/A) to advanced-stage HCC after repeated recurrences and treatments. HCC progression deteriorates the quality of life and prognosis. However, the effect of direct-acting antiviral (DAA)-induced sustained virologic response (SVR) on HCC progression remains uninvestigated.

Methods: We conducted a retrospective cohort study of patients with hepatitis C virus-related HCC with BCLC stage 0/A diagnosed for the first time and treated by curative resection or ablation. Using a time-varying method, we estimated the risk of tumor progression (defined as progression to BCLC stage B-D) and liver-related death and the characteristics of repeated recurrence.

Results: Overall, 165 patients were enrolled. Following curative HCC treatment, 72 patients received DAA therapy (DAA-treated group), whereas 93 did not (untreated group). Approximately 75% of the recurrences were at an early stage and expected to be disease-free by retreatment. We recorded 56 tumor progressions, of which 60.7% were observed after second recurrence. Multivariate adjusted time-varying Cox regression analysis showed that the DAA-induced SVR significantly reduced the risk of tumor progression (hazard ratio [HR] 0.28; $p=0.001$) and liver-related death (HR 0.12; $p<0.001$). The annual incidence of HCC treatment until tumor progression was 82.8% and 23.9% in the untreated and DAA-treated groups, respectively (HR 0.30; $p<0.001$).

Conclusions: DAA-induced SVR significantly reduced the risk for tumor progression and liver-related death and the frequency of HCC treatment following curative treatment for HCC at BCLC stage 0/A.

Keywords

neoplasm, DAA, Sustained Virologic Response, hepatitis C virus, survival

Introduction

The hepatitis C virus (HCV) infection affects 71 million people worldwide,[1] and is a major risk factor for hepatocellular carcinoma (HCC). HCC is the sixth most common tumor worldwide and the fourth leading cause of cancer-related death.[2] Approximately 31% of the HCC cases can be attributed to HCV infection, and this increases up to 64% in Japan.[3,4] HCC is well known for its high recurrence rate, with nearly 70% of the patients developing recurrence within 5 years of curative HCC resection.[5]

Direct-acting antiviral (DAA) therapy regimens are effective at eradicating HCV infections.[6] DAA-induced sustained virologic response (SVR) results in reduced HCC incidence, risk of liver-related, and all-cause death.[7,8] However, evidence for the benefit of DAA therapy for HCC recurrence is deemed low or inconclusive.[9] Furthermore, recent multicenter prospective cohort studies reported no significant difference in the HCC recurrence rates between DAA-treated and DAA-untreated patients.[10,11]

The Barcelona Clinic Liver Cancer (BCLC) staging system is recommended for prognostic prediction and treatment allocation.[3] In BCLC stage 0/A, curative treatment (resection, ablation, and transplantation) is recommended, and median survival surpasses more than 5 years following curative treatment. However, curative treatment is not recommended following progression to BCLC stage B; when the median survival reduces to below 2 years. The progression of BCLC stage strongly affects the patients' quality of life and prognosis.

Although the risk of HCC recurrence following DAA therapy has been investigated in many previous studies, the timing of progression remains uninvestigated. According to previous reports, most HCC recurrences were BCLC stage 0/A, which were expected to be disease-free after retreatment following HCC recurrence. Some HCC recurrences are treated several times without progression. Therefore, assessment of the risk of tumor progression is important. Thus, this study aimed to assess the impact of DAA-induced SVR on the HCC progression and the frequency of HCC treatment following curative treatment for HCC at BCLC stage 0/A.

Materials and Methods

Study design and Patient population

We conducted a retrospective cohort study of patients with HCV-related HCC who were admitted to the Department of Hepatology at Osaka City University Hospital from 2010 to 2019. HCC was diagnosed based on the American Association for the Study of Liver Disease (AASLD) criteria.[12,13] HCV infection was diagnosed by positive HCV-RNA or positive HCV core antigen. Patients were included if HCC was diagnosed for the first time, in BCLC stage 0/A, cured with resection or ablation (curative treatment), with Child-Pugh class A, and if they were followed up for more than 90 days after HCC treatment. Patients were excluded if they were positive for hepatitis B surface antigen, had autoimmune hepatitis (AIH) or primary biliary cholangitis (PBC), achieved SVR with interferon (IFN)-based therapy, failed HCV treatment with DAA therapy, or received DAA therapy before HCC diagnosis (Figure 1). Cured HCC was defined as the presence of no residual tumor by computed tomography (CT) or magnetic resonance imaging (MRI) after curative treatment.

We classified the patients into untreated and DAA-treated groups. The untreated group included patients who did not receive DAA therapy after HCC treatment. The DAA-treated group included patients who received DAA therapy and achieved SVR after HCC treatment.

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Osaka City University Hospital.

Follow-up

Patients were followed up with three-monthly physical examinations and laboratory evaluations and abdominal ultrasonography, dynamic computed tomography (CT), or magnetic resonance imaging (MRI) every 3–6 months following HCC treatment. HCC recurrence was diagnosed using dynamic CT/MRI, contrast-enhanced ultrasonography, or histological examination. HCC recurrences were treated per the AASLD guidelines.[13]

Outcomes

The main outcome of this study was the estimation of the risk of tumor progression. Tumor progression was defined as progression of HCC to BCLC stage B-D, which is characterized by more than 4 nodules of HCC, portal invasion, or extrahepatic metastasis on follow-up imaging, or by Child-Pugh C hepatic reserve.

We also estimated the risk of liver-related death, recurrence at new foci, and the frequency of HCC treatment until tumor progression. Recurrence at new foci was defined as the appearance of a

new HCC lesion at a different part from the HCC lesion that was initially diagnosed. The frequency of HCC treatment until tumor progression was calculated from the number of treatments performed for recurrent HCC during the follow-up period. We counted the combination therapy, such as ablation following transarterial chemoembolization (TACE), as one treatment.

The follow-up began from the date of curative treatment for HCC and continued until the date of death or date of last follow-up.

Statistical analysis

Baseline characteristics of the patients just before the first HCC treatment were analyzed using a $\chi 2$ test for categorical variables and the Mann-Whitney U test for continuous variables. We estimated the cumulative incidence using the Kaplan-Meier method and hazard ratio (HR) using time-varying Cox regression. We used multivariate analysis to adjust for the following variables: the variables in multivariate 1 analysis included age, number of tumors, Child-Pugh score, fibrosis-4 (FIB-4) index, α-fetoprotein (AFP), and type of treatment (resection or ablation), and the variables in multivariate 2 analysis included age, number of tumors, ALBI score, FIB-4 index, AFP, and type of treatment (resection or ablation). The ALBI score was calculated using serum albumin and total bilirubin: (log10 bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.085), which assesses liver function in HCC.[14] FIB-4 index was calculated using age, platelet, aspartate aminotransferase (AST), and alanine aminotransferase (ALT): age (year) × AST (IU/L)/(platelet count [10^9/L] × √ALT [IU/L]), which is an accurate marker of fibrosis in HCV infection.[15] Event rates were reported as annual incidence rates. The timing of DAA therapy after HCC treatment differed among patients, which means the status could change during the follow-up period. Therefore, we assigned DAA therapy as a time-varying covariate, by which the time from HCC treatment to the initiation of DAA therapy was statistically treated as the untreated group (Supplementary Figure 1).[16] All data analyses were performed using R statistical software (version 3.6.0). All reported P values were two-sided, and a P value of less than 0.05, was considered statistically significant.

Results

Patient Characteristics

We identified 558 patients with HCV-related HCC diagnosed for the first time. After adjusting for the inclusion and exclusion criteria, 165 patients were included in the analysis. After curative treatment for HCC, 72 patients received DAA therapy (DAA-treated group) and 93 patients did not (untreated group). Baseline characteristics are listed in Table 1. The median age was 72 years (interquartile range [IQR], 67-77), and 96 patients (58.2%) were men. Surgical resection for HCC was performed in 32.1% of patients. Patients in the DAA-treated group had lower FIB-4 index ($p=0.001$) and ALBI score ($p=0.03$), higher platelet level ($p=0.003$), and were more likely to undergo surgical resection ($p<0.001$). Most patients (84.2%) had genotype 1 HCV infection.

The median follow-up period was 27.2 (IQR 11.0-49.4) months: 21.2 (IQR 7.7-43.7) months in the untreated group and 39.4 (IQR 20.9-58.9) months in the DAA-treated group. The median time from the HCC treatment to the initiation of DAA therapy was 8.0 (IQR, 5.4-30.8) months, wherein 33.3% were treated within 6 months, 29.2% were treated within 6-12 months, 9.7% were treated within 1-2 years, and 27.8% were treated for more than 2 years after HCC treatment.

Tumor progression

We recorded 47 incidences of tumor progression in the untreated group and nine in the DAA-treated group. Among them, 29 (51.8%) involved more than 4 nodules in the liver, 13 (23.2%) were due to portal invasion, 8 (14.3%) were due to extrahepatic metastasis, and 6 (10.7%) were due to deterioration of hepatic reserve. A total of 22 (39.3%) cases were detected at first recurrence, 17 (30.4%) were at second recurrence, and 17 (30.4%) had more than three recurrences. The one-year, 3-year-, and 5-year tumor progression rates were 7.1%, 35.7%, and 54.5% respectively in the untreated group and 5.9%, 9.2%, and 17.1% respectively in the DAA-treated group (Figure 2A). The annual incidence rate of recurrence was 14.0% in the untreated group and 4.1% in the DAA-treated group (Table 2).

Liver-related mortality

A total of 31 and 3 liver-related deaths were detected in the untreated and DAA-treated groups, respectively. The 1-year, 3-year, and 5-year liver-related mortality rates were 0.7%, 13.7%, and 40.2%, respectively, in the untreated group and 1.5%, 3.5%, and 10.0%, respectively, in the DAA-treated group (Figure 2B). The annual incidence of liver-related death was 6.42% in the untreated group and 1.05% in the DAA-treated group (Table 2).

Recurrence at new foci

A total of 67 and 29 recurrences at new foci were detected in the untreated and DAA-treated groups, respectively. In the untreated group and the DAA-treated group, 48/67 (71.6%) and 24/29 (82.8%) recurrences at new foci were detected as BCLC stage 0/A. The 6-month, 1-year, and 2-year recurrence at new foci probabilities were 4.0%, 21.4%, and 42.9%, respectively, in the untreated group and 6.6%, 18.7%, and 25.3%, respectively, in the DAA-treated group (Supplementary Figure 2).

The frequency of HCC treatment

Until tumor progression, 278 HCC treatments were performed in the untreated group (66 resection, 166 ablation, and 46 TACE) and 52 HCC treatments were performed in the DAA-treated group (7 resection, 30 ablation, and 15 TACE). The annual incidence of HCC treatment was 82.8% in the untreated group and 23.9% in the DAA-treated group (HR 0.30; $p<0.001$) (Table 2).

Predictors of the tumor progression, liver-related mortality, and recurrence at new foci

DAA-induced SVR was associated with a reduction in the risk of tumor progression in univariate analysis (HR 0.27, 95% confidence interval [CI] 0.13-0.57, $p<0.001$) and multivariate analysis (HR 0.28, 95% CI 0.13-0.61, $p=0.001$) after adjusted for age, number of tumors, Child-Pugh score, FIB-4 index, AFP, and type of HCC treatment (Table 3). DAA-induced SVR was also associated with a reduction in the risk of liver-related death in univariate analysis (HR 0.11, 95% CI 0.03-0.38, $p<0.001$) and multivariate analysis (HR 0.12, 95% CI 0.04-0.40, $p<0.001$) (Table 4). On the other hand, DAA-induced SVR was not associated with a decrease in the risk of recurrence at new foci by univariate (HR 0.69, 95% CI 0.45-1.06, $p=0.09$) and multivariate analysis (HR 0.68, 95% CI 0.43-1.08, $p=0.10$) (Supplementary Table 1).

The FIB-4 index was associated with the risk of tumor progression (HR 1.10, $p=0.004$), liver-related mortality (HR 1.14, $p=0.004$), and recurrence at new foci (HR 1.06, $p=0.02$).

Discussion

To our knowledge, this is the first study to investigate the effect of DAA therapy on the progression of HCC and describe the details of repeated recurrences in patients with HCC at BCLC stage 0/A using a tailored statistical method. We observed that the DAA-induced SVR significantly reduced the risk of tumor progression, and the rate of HCC treatment until tumor progression.

DAA therapy should benefit patients infected with HCV.[9] DAA-induced SVR reduces HCC incidence by approximately 70%,[7,17,18] and is expected to revert fibrosis, decrease portal hypertension,[19,20,21] and reduce the risk of liver-related and all-cause death.[8] However, the benefits of DAA-induced SVR for HCC recurrence are controversial. Two small uncontrolled studies with short follow-up periods reported a high recurrence rate in patients with DAA therapy, which indicated that DAA therapy unexpectedly made HCC more aggressive.[22,23] Large controlled prospective studies showed no increased risk of HCC recurrence following DAA therapy.[10,24,25] On the other hand, other studies showed that DAA therapy reduced the risk of recurrence.[26,27]

The results among previous studies were different because of the unique HCC characteristics, and varied types of HCC treatment and statistical methods used. Some studies included patients with recurrent HCC, HCC with BCLC stage B, or patients who received palliative treatment for HCC. In some studies, the effect of different timings of DAA therapy was not considered because the authors performed time-fixed analysis. To assess the impact of DAA-induced SVR clearly, we limited our selection criteria to patients with HCC in BCLC stage 0/A, diagnosed at first time and managed by curative treatment and analyzed the risk using a time-varying analysis. In our study, DAA-induced SVR was not associated with recurrence at new foci.

A meta-analysis demonstrated that 77.8% of HCC recurrences were detected at an early stage,[28] whereas in our study cohort, 75% of recurrences at new foci were in the BCLC stage 0/A. Even after the detection of HCC recurrence, most cases were expected to be cured again. Therefore, we investigated a new outcome, tumor progression, which was defined as HCC in BCLC stage 0/A progressing to BCLC stage B-D. We believe this outcome to be important because if HCC progresses to BCLC stage B-D, the median survival time is decreased to less than 2 years and[29,30] because tumor progression directly worsens the patients' quality of life and survival.[31]

Our study noted an interesting finding that DAA-induced SVR resulted in a 72% reduction in the risk of tumor progression ($p=0.001$), whereas DAA-induced SVR did not reduce the risk of recurrence at new foci ($p=0.10$). To assess the rate of repeated recurrence until tumor progression, we investigated the rate of HCC treatment until tumor progression. We found that DAA-induced SVR resulted in a 58.9% reduction in the annual incidence of HCC treatment ($p<0.001$).

Usually, cancer cells grow over long time-periods into a tumor mass that can be detected on imaging. Hence, cancer cells could already be present when DAA therapy is initiated, which could explain the different recurrence rates obtained after DAA therapy in previous studies. Our study showed that DAA-induced SVR strongly reduced the risk of tumor progression and dramatically decreased the rate of HCC treatment until tumor progression, indicating that DAA-induced SVR suppresses the tumorigenesis and metastasis. We also found that DAA-induced SVR strongly reduced the risk of liver-related death. Some recent multicenter studies reported that DAA therapy reduces the risk of death.[32,33] We suggest that a reduction in the risk of tumor progression contributes to this survival.

Our study had several limitations. First, this was a single-center retrospective study, and there could be some bias and confounding factors. Multivariate analysis was used to adjust for the factors that were suggested to affect outcomes. There was a selection bias since doctors would prescribe DAAs only for patients who could have a long survival. Thus, to reduce the selection bias, we collected data before the DAA regimen was permitted. Patients who survived longer without recurrence had more chances to receive DAA therapy; this introduced the immortal time bias. Thus, it was important to apply the timing of DAA therapy as a time-varying covariate.[16] Second, we excluded patients with Child-Pugh class B/C, because DAA therapy was not permitted for patients with Child-Pugh class B/C until February 2019 in Japan. Therefore, we were not able to assess the impact of DAA-induced SVR in patients with Child-Pugh class B/C. Lastly, the data on the patient's alcohol consumption was lacking, and we were not able to assess the effect of alcohol consumption on outcomes.

In summary, DAA-induced SVR significantly reduced the risk for tumor progression and liver-related death and the frequency of HCC treatment following curative treatment for HCC at BCLC stage 0/A.

References

1. Blach S, Zeuzem S, Manns M, Altraif I, Duberg AS, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. Lancet Gastroenterol Hepatol 2017; 2: 161-176.
2. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncology 2017; 3: 524-548.
3. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69: 182-236.
4. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen P et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015; 35: 2155-2166.
5. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of Hepatocellular Cancer after Resection: Patterns, Treatments, and Prognosis. Ann Surg 2015; 261: 947-955.
6. Persico M, Aglitti A, Aghemo A, Rendina M, Lleo A, Ciancio A, et al. High efficacy of direct-acting anti-viral agents in hepatitis C virus-infected cirrhotic patients with successfully treated hepatocellular carcinoma. Aliment Pharmacol Ther 2018; 47: 1705-1712.
7. Singal AG, Lim JK, Kanwal F. AGA Clinical Practice Update on Interaction Between Oral Direct-Acting Antivirals for Chronic Hepatitis C Infection and Hepatocellular Carcinoma: Expert Review. Gastroenterology 2019; 156: 2149-2157.
8. McDonald SA, Pollock KG, Barclay ST, Goldberg DJ, Bathgate A, Bramley P, et al. Real-world impact following initiation of interferon-free hepatitis C regimens on liver-related outcomes and all-cause mortality among patients with compensated cirrhosis. J Viral Hepat 2020; 27: 270-280.
9. Ioannou GN, Feld JJ. What Are the Benefits of a Sustained Virologic Response to Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection? Gastroenterology 2019; 156: 446-460.e2.
10. Singal AG, Rich NE, Mehta N, Branch A, Pillai A, Hoteit M, et al. Direct-Acting Antiviral Therapy Not Associated With Recurrence of Hepatocellular Carcinoma in a Multicenter North American Cohort Study. Gastroenterology 2019; 156: 1683-1692.e1.

11. Cabibbo G, Celsa C, Calvaruso V, Petta S, Cacciola I, Cannavò MR, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol 2019; 71: 265-273.
12. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD Guidelines for the Treatment of Hepatocellular Carcinoma. Hepatology 2018; 67: 358-380.
13. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68: 723-750.
14. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach-The ALBI Grade. J Clin Oncol 2014; 33: 550-558.
15. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and FibroTest. Hepatology 2007; 46: 32-36.
16. Shintani AK, Girard TD, Eden SK, Arbogast PG, Moons KGM, Ely EW. Immortal time bias in critical care research: Application of time-varying cox regression for observational cohort studies. Crit Care Med 2009; 37: 2939-2945.
17. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018; 68: 25-32.
18. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. Gastroenterology 2017; 153: 996-1005.e1.
19. Bachofner JA, Valli P V, Kröger A, Bergamin I, Künzler P, Baserga A et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017; 37: 369-376.
20. Lens S, Alvarado-Tapias E, Mariño Z, Londoño MC, LLop E, Martinez J, et al. Effects of All-Oral Anti-Viral Therapy on HVPG and Systemic Hemodynamics in Patients With Hepatitis C Virus-Associated Cirrhosis. Gastroenterology 2017; 153: 1273-1283.e1.
21. Mandorfer M, Kozbial K, Schwabl P, Freissmuth C, Schwarzer R, Stern R et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016; 65: 692-699.
22. Cammà C, Cabibbo G, Craxì A. Direct antiviral agents and risk for HCC early recurrence:

Much ado about nothing. J Hepatol 2016; 65: 861-862.

23. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016; 65: 727-733.
24. ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER CC and CC cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol 2016; 65: 734-740.
25. Huang AC, Mehta N, Dodge JL, Yao FY, Terrault NA. Direct-acting antivirals do not increase the risk of hepatocellular carcinoma recurrence after local-regional therapy or liver transplant waitlist dropout. Hepatology 2018; 68: 449-461.
26. Ikeda K, Kawamura Y, Kobayashi M, Kominami Y, Fujiyama S, Sezaki H, et al. Direct-Acting Antivirals Decreased Tumor Recurrence After Initial Treatment of Hepatitis C Virus-Related Hepatocellular Carcinoma. Dig Dis Sci 2017; 62: 2932-2942.
27. Imai K, Takai K, Hanai T, Suetsugu A, Shiraki M, Shimizu M. Sustained virological response by direct-acting antivirals reduces the recurrence risk of hepatitis C-related hepatocellular carcinoma after curative treatment. Mol Clin Oncol 2020; 12: 111-116.
28. Ochi H, Hiraoka A, Hirooka M, Koizumi Y, Amano M, Azemoto N, et al. Direct-acting antivirals improve survival and recurrence rates after treatment of hepatocellular carcinoma within the Milan criteria. J Gastroenterol. 2021; 56: 90-100.
29. Saraiya N, Yopp AC, Rich NE, Odewole M, Parikh ND, Singal AG. Systematic review with meta-analysis: recurrence of hepatocellular carcinoma following direct-acting antiviral therapy. Aliment Pharmacol Ther 2018; 48: 127-137.
30. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006; 44: 723-731.
31. Vitale A, Saracino E, Boccagni P, Brolese A, D'Amico F, Gringeri E et al. Validation of the BCLC Prognostic System in Surgical Hepatocellular Cancer Patients. Transplant Proc 2009; 41: 1260-1263.
32. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut 2014; 63: 844-855.
33. Dang H, Hui Yeo Y, Yasuda S, Huang C-F, Iio E, Landis C, et al. Cure With Interferon-Free Direct-Acting Antiviral Is Associated With Increased Survival in Patients With Hepatitis C Virus-Related Hepatocellular Carcinoma From Both East and West. Hepatology. 2020; 71:

1910-1922.

34. Singal AG, Rich NE, Mehta N, Branch AD, Pillai A, Hoteit M, et al. Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection Is Associated With Increased Survival in Patients With a History of Hepatocellular Carcinoma. Gastroenterology 2019; 157: 1253-1263.e2.

Tables

Table 1. Baseline Characteristics of the Patients.

Variable	Untreated group n = 93	DAA-treated group n = 72	*p* value
Age (y)	74 [67, 79]	71 [67, 75]	0.18
Sex: Male	55 (59.1)	41 (56.9)	0.78
BMI (kg/m^2)	22.8 [20.3, 24.6]	23.1 [20.7, 25.5]	0.41
Child-Pugh score 5/6	68 (73.1) / 25 (26.9)	59 (81.9) / 13 (18.1)	0.18
ALBI score	−2.52 [−2.73, −2.28]	−2.69 [−2.83, −2.38]	0.03*
PLT (10^3/μL)	102 [69, 139]	128 [97, 152]	0.003**
FIB-4 index	5.96 [4.11, 8.55]	4.14 [2.89, 6.36]	0.001**
ALT (U/L)	41 [28, 57]	42 [28, 65]	0.62
Bilirubin (mg/dL)	0.7 [0.5, 0.9]	0.6 [0.5, 0.9]	0.46
Alb (g/dL)	3.8 [3.5, 4.0]	3.9 [3.6, 4.1]	0.052
Cr (mg/dL)	0.76 [0.62, 0.90]	0.75 [0.63, 0.83]	0.46
INR	1.04 [0.99, 1.11]	1.03 [0.99, 1.07]	0.45
Treatment for HCC			
Resection	18 (19.4)	35 (48.6)	<0.001***
Ablation	75 (80.6)	37 (51.4)	
BCLC staging			
0	42 (45.2)	30 (41.7)	0.65
A	51 (54.8)	42 (58.3)	
Size of tumor (cm)	2.0 [1.5, 2.5]	2.0 [1.6, 2.5]	0.42
Number of tumors			
1 nodule	72 (77.4)	62 (86.1)	0.16
2–3 nodules	21 (22.6)	10 (13.9)	
AFP (ng/mL)	16.4 [6.7, 39.0]	12.7 [5.8, 72.6]	0.78
Genotype 1 / 2 / unknown	62 / 13 / 17	61 / 10 / 1	0.59
Time to DAA therapy			
< 6 months	N/A	24 (33.3)	N/A
6–12 months		21 (29.2)	
1–2 years		7 (9.7)	
2–3 years		6 (8.3)	
> 3 years		14 (19.4)	

Values are reported as n (%) or median [interquartile ranges].
* p<0.05, ** p<0.01, *** p<0.001
Abbreviation: BMI, body mass index; ALBI score, Albumin-Bilirubin score; PLT, platelet count; FIB-4 index, fibrosis-4 index; ALT, alanine aminotransferase; Alb, albumin; Cr, creatinine; INR, prothrombin time-international normalized ratio; HCC, hepatocellular carcinoma; BCLC stage, Barcelona Clinic Liver Cancer stage; AFP, α-fetoprotein.

Table 2. Incidence of Tumor progression, Liver-related death, Recurrence at new foci, and HCC treatment.

Event	PY	event (n)	Event rate per 1000PY	Annual incidence (%)
Tumor progression				
Untreated group	335.9	47	11.7	14.0
DAA-treated group	217.2	9	3.5	4.1
Liver-related death				
Untreated group	402.4	31	6.42	7.7
DAA-treated group	237.7	3	1.05	1.3
Recurrence at new foci				
Untreated group	273.1	67	20.4	24.5
DAA-treated group	156.5	29	15.4	18.5
HCC treatment				
Untreated group	335.9	278	69.0	82.8
DAA-treated group	217.2	52	19.9	23.9

Incidence of HCC treatment was calculated by the number of HCC treatment events until tumor progression.
The incidence of HCC treatment was calculated as the number of HCC treatments until tumor progression.
Abbreviation: PY, person-year; DAA, direct-acing antiviral.

Table 3. Univariate and Multivariate time-varying Cox regression analyses for Tumor progression.

		univariate		multivariate 1		multivariate 2	
Variable		HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
DAA therapy	DAA-treated	0.27 (0.13–0.57)	<0.001***	0.28 (0.13–0.61)	0.001**	0.28 (0.13–0.61)	0.001**
Age	per 10 years	1.26 (0.85–1.88)	0.26	1.13 (0.73–1.74)	0.60	1.16 (0.76–1.76)	0.50
Sex	Male	0.67 (0.40–1.14)	0.14				
BCLC stage	A	0.84 (0.49–1.42)	0.51				
Number of tumors	2–3 nodules	1.28 (0.68–2.44)	0.45	1.21 (0.65–2.22)	0.55	1.13 (0.61–2.07)	0.70
Size of tumor	per 1 cm	0.77 (0.55–1.09)	0.14				
Child-Pugh score	6	1.56 (0.85–2.88)	0.15	1.01 (0.46–2.22)	0.97		
ALBI score	per 1	2.39 (1.15–4.95)	0.02*			1.81 (0.75–4.36)	0.18
Platelet	under 100 10^3/μL	1.30 (0.77–2.20)	0.33				
FIB-4 index	per 1	1.10 (1.05–1.16)	<0.001***	1.10 (1.03–1.18)	0.004**	1.09 (1.03–1.16)	0.005**
AFP	over 40 ng/mL	0.80 (0.41–1.55)	0.50	0.68 (0.33–1.41)	0.30	0.65 (0.31–1.38)	0.26
Treatment	Resection	1	0.06	1	0.63	1	0.73
	Ablation	1.82 (0.97–3.41)		1.19 (0.59–2.42)		1.13 (0.55–2.34)	
BMI	per 1 kg/m^2	0.98 (0.91-1.06)	0.68				

* p<0.05, ** p<0.01, *** p<0.001

Tumor progression was defined as HCC in BCLC stage 0/A progressing to BCLC stage B-D.

Variables in multivariate 1 analysis included DAA therapy, age, number of tumors, Child-Pugh score, FIB-4 index, AFP, and type of treatment, and those in multivariate 2 included DAA therapy, age, number of tumors, ALBI score, FIB-4 index, AFP, and type of treatment.

Abbreviation: DAA, direct-acing antiviral; BCLC stage, Barcelona Clinic Liver Cancer stage; ALBI score, Albumin-Bilirubin score; FIB-4 index, fibrosis-4 index; AFP, α-fetoprotein; BMI, body mass index.

Table 4. Univariate and Multivariate time-varying Cox regression analyses for Liver-related mortality.

		univariate		multivariate 1		multivariate 2	
Variable		HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
DAA therapy	DAA-treated	0.11 (0.03–0.38)	<0.001***	0.12 (0.04–0.40)	<0.001***	0.12 (0.04–0.41)	<0.001***
Age	per 10 years	1.26 (0.85–1.88)	0.22	1.34 (0.72–2.50)	0.35	1.44 (0.78–2.66)	0.24
Sex	Male	0.56 (0.29–1.11)	0.10				
BCLC stage	A	0.94 (0.48–1.86)	0.87				
Number of tumors	2–3 nodules	1.67 (0.75–3.71)	0.21				
Size of tumor	per 1 cm	0.77 (0.55–1.09)	0.29				
Child-Pugh score	6	1.80 (0.83–3.88)	0.13	1.03 (0.39–2.73)	0.95		
ALBI score	per 1	2.39 (1.15–4.95)	0.01*			2.17 (0.58–8.11)	0.25
Platelet	under 100 10^3/μL	1.42 (0.72–2.79)	0.31				
FIB-4 index	per 1	1.10 (1.05–1.16)	<0.001***	1.14 (1.04–1.24)	0.004**	1.12 (1.04–1.21)	0.004**
AFP	over 40 ng/mL	0.68 (0.28–1.65)	0.40				
Treatment	Resection	1	0.06				
	Ablation	2.26 (0.98–5.19)					
BMI	per 1 kg/m^2	0.98 (0.91–1.06)	0.64				

* p<0.05, ** p<0.01, *** p<0.001

Tumor progression was defined as HCC in BCLC stage 0/A progressing to BCLC stage B-D.

Variables in multivariate 1 analysis included DAA therapy, age, Child-Pugh score, and FIB-4 index; those in multivariate 2 included DAA therapy, age, ALBI score, and FIB-4 index.

Abbreviation: DAA, direct-acing antiviral; BCLC stage, Barcelona Clinic Liver Cancer stage; ALBI score, Albumin-Bilirubin score; FIB-4 index, fibrosis-4 index; AFP, α-fetoprotein; BMI, body mass index.

Figure legends

Figure 1.

Flowchart showing the study design for a retrospective cohort of patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). Overall, 165 patients were analyzed; 72 received direct-acting antivirals (DAA) after HCC treatment (DAA-treated group) and 93 did not (untreated group).

Figure 2.

Cumulative incidence of tumor progression (A) and liver-related mortality (B) by Kaplan-Meier analysis. Tumor progression was defined as when HCC in Barcelona Clinic Liver Cancer (BCLC) stage 0/A progressed to BCLC stage B–D.

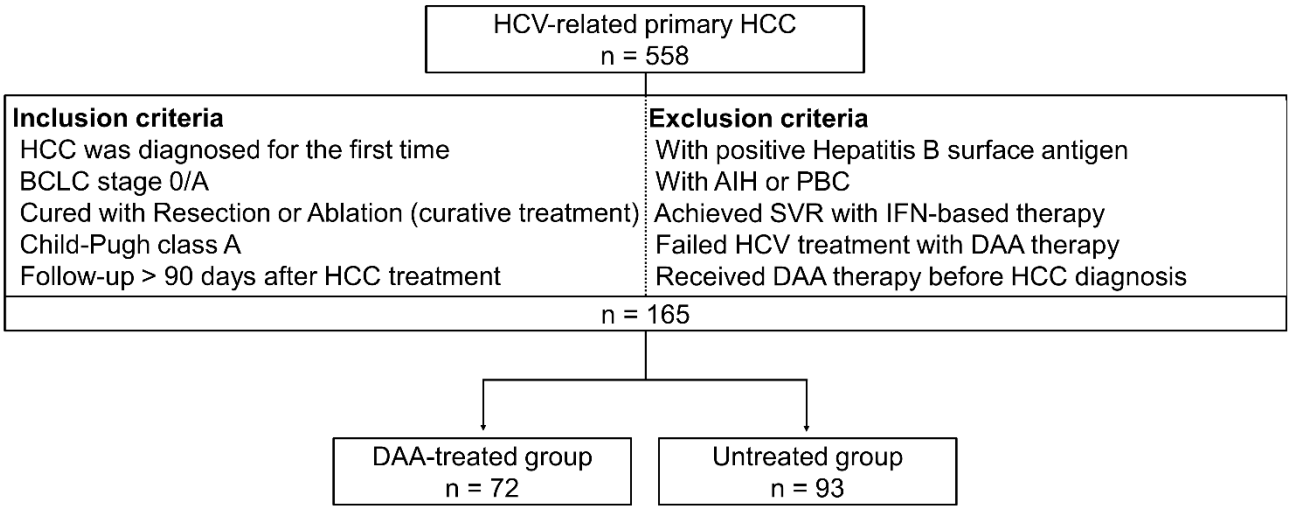
Supplementary Figure 1.

In the DAA-treated group, the time from HCC treatment to the initiation of direct-acting antiviral (DAA) therapy was considered as the untreated group (DAA unexposed period). The time-varying method is a tailored method to be used when the exposure is altered during follow-up. Using this method, the DAA unexposed period in the DAA-treated group was statistically analyzed similar to that of the untreated group.

Supplementary Figure 2.

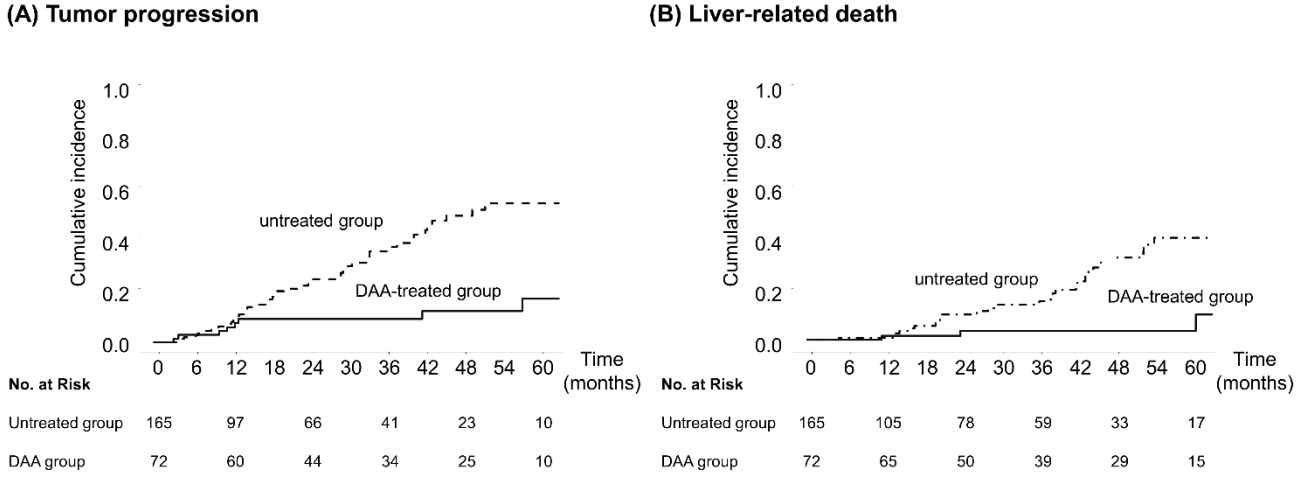
Cumulative incidence of recurrence at new foci by Kaplan-Meier analysis. Recurrence at new foci was defined as the appearance of a new HCC lesion at a different part of the liver than the HCC lesion that was diagnosed initially.

Figure 1.



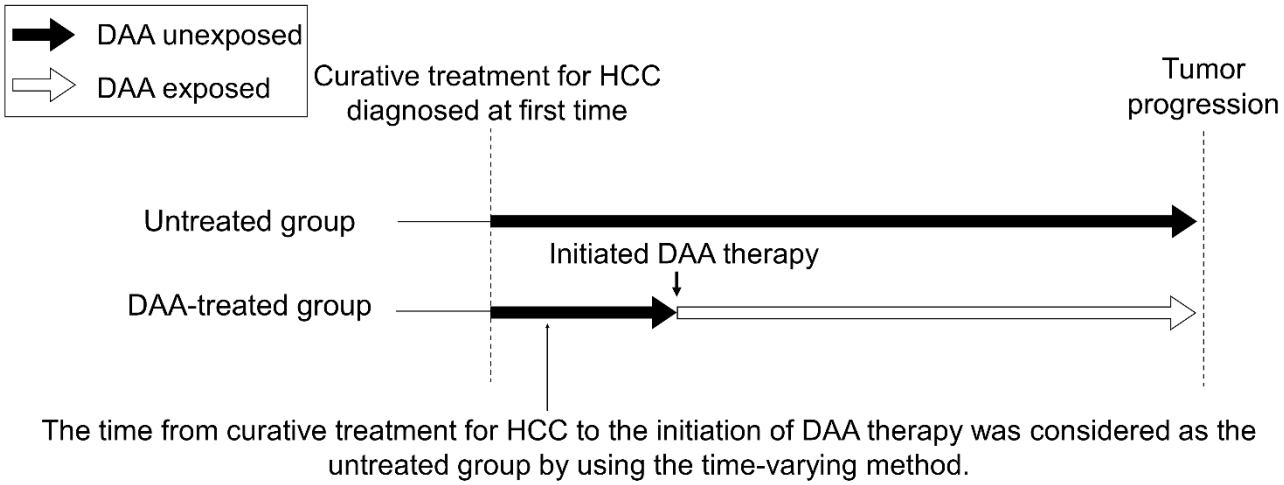
Flowchart showing the study design for a retrospective cohort of patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC). Overall, 165 patients were analyzed; 72 received direct-acting antivirals (DAA) after HCC treatment (DAA-treated group) and 93 did not (untreated group).

Figure 2.



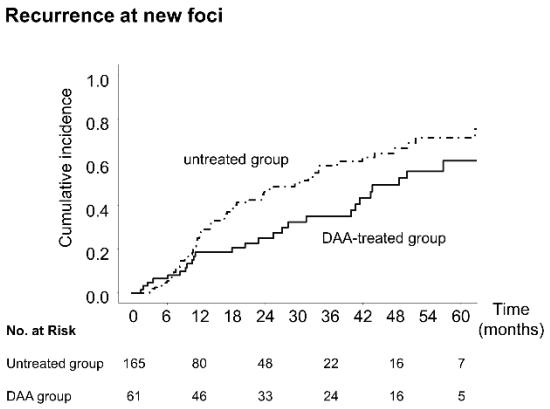
Cumulative incidence of tumor progression (A) and liver-related mortality (B) by Kaplan-Meier analysis. Tumor progression was defined as when HCC in Barcelona Clinic Liver Cancer (BCLC) stage 0/A progressed to BCLC stage B–D.

Supplementary Figure 1.



In the DAA-treated group, the time from HCC treatment to the initiation of direct-acting antiviral (DAA) therapy was considered as the untreated group (DAA unexposed period). The time-varying method is a tailored method to be used when the exposure is altered during follow-up. Using this method, the DAA unexposed period in the DAA-treated group was statistically analyzed similar to that of the untreated group.

Supplementary Figure 2.



Cumulative incidence of recurrence at new foci by Kaplan-Meier analysis. Recurrence at new foci was defined as the appearance of a new HCC lesion at a different part of the liver than the HCC lesion that was diagnosed initially.