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## **Absence of impact of direct acting antivirals for hepatitis C virus on recurrent hepatocellular carcinoma tumor growth in the AFEF/ANRS CO22 Hepather cohort**

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Full title: Absence of impact of direct acting antivirals for hepatitis C virus on recurrent hepatocellular carcinoma tumor growth in the AFEF/ANRS CO22 Hepather cohort

Short Title: No impact of DAAs for hepatitis C virus on recurrent hepatocellular carcinoma tumor growth

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## Highlights

Our blinded analysis of HCC recurrence following “curative” treatment:

- argues against the “curative” efficacy of the first treatment of HCC in one third of patients
- evidences that DAA therapy has no significant impact on the severity or progression of HCC recurrence.
- evidences that DAA therapy does not impact overall survival and could be considered in cirrhotic patients with prior history of HCC

## Abstract

**Background:** Although it has now been excluded that direct-acting antivirals (DAA) are associated with a significant risk of hepatocellular carcinoma (HCC) in HCV-infected patients, a possible effect of DAA on tumor growth is still a subject of debate. We performed a blind comparison of the kinetics of HCC recurrence in patients after HCV treatment with or without DAA to evaluate the potential aggressiveness of HCC after DAA treatment.

**Basic procedures:** Thirty-nine HCV-infected patients from the AFEF/ANRS CO22 Hepather cohort who experienced HCC recurrence after so-called curative treatment were evaluated. Contrast-enhanced CT and/or MR images were read blindly 6 months before HCC recurrence and during the follow-up period. Seventeen patients who received DAA (DAA+) before HCC recurrence were compared to the 22 who did not receive (DAA-), according to the LiRads and mRECIST criteria.

**Main findings:** There were 28 men and 11 women, median age 62 years old, 37 (95%) with cirrhosis. DAA+ patients had a lower median MELD score ( $8 \pm 2$  vs  $10 \pm 4$ ,  $p=0.0286$ ) than DAA- patients. The median time to HCC recurrence (time from the date of curative treatment to the diagnosis of recurrence) was not different (20 vs 18 months)( $p=0.73$ ) between the two groups.

There was no difference between the 2 groups in the overall survival and/or transplantation-free survival ( $p=0.71$ ) and for the mRECIST time to progression ( $p=0.25$ ).

Conclusion: This blinded analysis of HCC recurrence after HCC treatment does not support any negative impact of DAA therapy on the severity or progression of recurrent HCC.

Key words:

direct-acting antivirals

hepatitis C virus

hepatocellular carcinoma recurrence

tumor growth

Abbreviations

DAA: Direct Acting Antivirals

HCC: Hepatocellular Carcinoma

AFEF: Association Française pour l'Etude du Foie

ANRS : Agence Nationale de Recherche sur le Sida et les Hépatites

LT: Liver Transplantation

CT: Computer Tomography

MR: Magnetic Resonance

mRECIST: modified Response Evaluation Criteria in Solid Tumor

TACE: transarterial chemoembolization

SVR: Sustained Virological Response

BCLC: Barcelona Clinic Liver Cancer

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## Trial registration number

NCT019553458

## **Introduction**

In 2016, it was suggested that there was a higher risk of more rapidly progressing hepatocellular carcinoma (HCC) with the use of oral direct-acting antivirals (DAA) in hepatitis C virus (HCV)-infected patients (1). This unexpected high rate and pattern of HCC associated with HCV clearance could be explained by a disruption in immune surveillance which could facilitate the emergence of local or metastatic clones. While some methodologically limited studies (2-4) suggested a higher risk of both de novo and recurrent HCC, as well as greater tumor aggressiveness (5-7), this was not confirmed in several retrospective (8-12) and prospective studies (13-21) or in a meta-analysis (22-23). Because of the heterogeneity of treated and untreated patient populations at least in countries with treatment prioritization, we applied weighting methodologies (IPTW, Cox models) and showed a decreased risk of de novo HCC in the former compared to the latter (15). Thus, although the DAA-associated risk of HCC is no longer an issue (24), the impact of DAA on tumor growth is still a subject of debate.

Further study is needed to evaluate the influence of DAA therapy on the timing (early or late), frequency and aggressiveness of HCC recurrence after so-called “curative” treatment. Well-designed and blinded studies with robust comparisons are needed to determine the actual effect of DAA on the early and late recurrence of HCC, on tumor progression and on mortality. Thus, we performed a blinded comparison of HCC recurrence kinetics after “curative” treatment in HCV patients who were treated or not with DAA to assess tumor growth, overall survival and transplantation-free survival. Contrast-enhanced computer tomography (CT) and magnetic resonance (MR) imaging examinations were analyzed according to the recommended methodology for liver tumors (25). The mRECIST classification was used to define the patient as a complete responder, partial responder, with stable disease or progressive disease (26-27).

## **Materials and Methods**

The Association Française pour l’Etude du Foie (AFEF)/Agence Nationale de Recherche sur le Sida et les Hépatites Agence Nationale de Recherche sur le Sida et les Hépatites (ANRS) CO22 HEPATHER cohort « Therapeutic option for hepatitis B and C: a French cohort » is a national,



multicenter, prospective, observational cohort study of patients with hepatitis B or C virus infection (this study is registered with ClinicalTrials.gov, number NCT01953458). The cohort has been extensively described elsewhere (15, 18, 28). In this cohort as well as in two other prospective cohorts (ANRS CO12 CirVir cohort of 1345 patients with biopsy-proven compensated cirrhosis and ANRS CO23 Cupilt cohort of 345 patients with HCV-related HCC who were given DAA after liver transplantation) we previously reported the absence of impact of DAA on HCC recurrence in patients who were DAA-treated or not, according to the physician's decision (18).

In this study the radiological results of 40 patients with recurrent HCC following a first treatment considered to be curative, were first analyzed (18) (Figure 1A). Contrast-enhanced CT and/or MR images were reviewed by two experts (a hepatologist and a radiologist) beginning 6 months before HCC recurrence and during the follow-up period. The two reviewers (AVP and JMC) were blinded to patient information (including clinical history, DAA treatment or not, prior HCC treatment). They blindly reviewed all imaging modalities, regarding the medical history of each patient especially HCV treatment with or without DAAs and virological response, first HCC treatment, type of HCC recurrence and medical evolution after the recurrence.

In a second time, we had all medical informations for each patient. We decided to distinguish 2 cohorts: the whole cohort with all patients except one (n = 39) who was excluded because he was never cured and underwent liver transplantation outside of the Milan criteria (Figure 1A) and the restricted cohort (n = 23) because the clinical analysis evidenced that 16 patients did not actually receive "curative" HCC treatment. That is why we excluded these sixteen patients from the whole cohort of the 39 (41.0%). To summarize, 9 received chemoembolization, one radioembolization, and 6 other patients had at the blinded morphological analysis either parietal HCC spreading (in one) or an incomplete response after curative treatment of first HCC (in 5 patients)(Figure 1A).

Analysis of radiological patterns was based on CT/MRI LI-RADS and mRECIST guidelines (25, 27). The 2017 version of the Liver Imaging Reporting And Data System (LI-RADS), which is approved by the American College of Radiology, was used to standardize the interpretation of multiphase CT and MR imaging examinations in all patients (25). Lesions were stratified according to size (<10mm, 10 - 19mm, and >20mm in diameter), the presence of arterial

phase enhancement, and the following three additional features: washout, enhancing capsule and threshold growth.

The lesion was considered as a definitely HCC if:

- it was > 20 mm in diameter with hyperenhancement during the arterial phase and at least one additional feature; or
- it was between 10 and 19 mm in diameter with hyperenhancement during the arterial phase and two additional features OR one single additional feature and a significant increase in size (at least 50% in less than 6 months).

The lesion was considered as a probable HCC if:

- it was > 20 mm in diameter with hyperenhancement during the arterial phase despite the absence of any additional features;
- it was > 20 mm in diameter with no hyperenhancement during the arterial phase but one or two additional features;
- it was between 10 and 19 mm in diameter with hyperenhancement during the arterial phase, one additional feature and no significant change in size in 6 months;
- it was < 10 mm in diameter with hyperenhancement during the arterial phase and one or two additional features; or
- it was < 20 mm in diameter with no hyperenhancement during the arterial phase but at least two additional features.

The mRECIST classification was used to define the patient as a complete responder, partial responder, with stable disease or progressive disease (26-27).

### **Statistical analyses**

DAA+ and DAA- patients were compared using the Fisher's exact test for qualitative variables and the Mann-Whitney test for quantitative variables. Recurrence-free survival after initial HCC treatment was calculated as the time from curative treatment to the date of first abnormal CT scan or MR imaging result (diagnosis of recurrence). Overall, transplantation, and progression free survival was calculated as the time from the diagnosis of recurrence to the date of death or transplantation or one of the previous or mRECIST progression,

respectively, or the last follow-up visit, or May 1, 2018, whichever occurred first. Time-to-event variables were compared using the log-rank test. All statistical tests were two-tailed with an alpha risk 5%.

## Results

First analysis: the whole cohort (n=39)

The 39 patients (the whole cohort) who received a first treatment for HCC included 28 men and 11 women, median age 62 (57-71) years old, 36 (92.3%) with cirrhosis. Initial HCC were mostly Barcelona Clinic Liver Cancer stage 0 or A (94.8%). At the time of HCC recurrence, 11 HCC were Barcelona Clinic Liver Cancer (BCLC) stage 0, 20 BCLC stage A, 4 BCLC stage B and 4 BCLC stage C, respectively. Thirty-three of the 39 patients were interferon-experienced. The seventeen patients who received DAA therapy (4 in combination with PEG-IFN) before HCC recurrence (DAA+), which occurred 9 (IQR (5-13)) months after treatment, were compared to the 22 patients who did not receive prior DAA therapy (DAA-), including 6 who initiated DAA after recurrence (Figure 1B). The choice of administering DAA therapy or not was based on the physician's decision. Sofosbuvir plus ribavirin were given in 2 patients, sofosbuvir plus pegylated interferon and ribavirin in 4 patients, sofosbuvir plus simeprevir in 2 patients, sofosbuvir plus daclatasvir and ribavirin in 2 patients and sofosbuvir plus daclatasvir in 7 patients, respectively. The median (IQR) follow-up after the diagnosis of HCC recurrence was 17.8 months (13.5-23.2) in DAA+ and 25.8 months in DAA- (11.2-46.3) patients, respectively ( $p = 0.14$ ).

The initial HCC treatment in the 39 patients with HCC recurrence was thermoablation in 18, surgery in 5 and combination therapy (transarterial chemoembolization (TACE) + thermoablation) in 6, chemoembolization in 9 and radioembolization in one patient, respectively. All the patients in the DAA- group had detectable HCV RNA on RT-PCR at the time of HCC recurrence. Eleven of the 17 DAA+ patients achieved a sustained virological response (SVR) more than 12 weeks before HCC recurrence, 1 achieved a SVR less than 12 weeks before recurrence, HCC recurrence occurred during DAA therapy in 4 who achieved a SVR, and one patient did not respond.

The baseline characteristics of both groups were similar (Table 1), except the MELD score which was lower in the DAA+ than in the DAA- group ( $8 \pm 2$  vs  $10 \pm 4$ ,  $p=0.0286$ ) at inclusion in the cohort (Table 1). There was no difference in the rate of radiological ascites in the DAA+ and DAA- groups (18.0 vs 23.0%,  $p=0.99$ ), portal hypertension (47.0 vs 59.0%,  $p=0.53$ ) or splenomegaly (41.0 vs 64.0%,  $p=0.21$ ).

The median time from initial tumor treatment to DAA treatment (defined by the time from the date of initial tumor treatment and the first dose of DAA treatment) was 11 (6-17) months (Figure 2A). The median time from DAA treatment (first dose) to HCC recurrence (defined by the time from the first dose of DAA treatment and the diagnosis of HCC recurrence) was 9 (5-13) months (Figure 2A). The median time to HCC recurrence (defined by the time from the date of initial tumor treatment and the diagnosis of HCC recurrence) was not different between the DAA+ and DAA- groups (20 vs 18 months,  $p=0.73$ )(Figure 2B).

There was no difference between the DAA+ and DAA- groups for the rate of unifocal (vs multifocal) recurrence (53 vs 36%,  $p=0.35$ ), nodular (vs infiltrative) forms (94 versus 95%,  $p=0.99$ ), mean diameter of the largest nodule (15.0 vs 20.5 mm,  $p=0.42$ ), or the rate of portal invasion (5.9 vs 13.6%,  $p=0.62$ ), respectively.

There was no difference between the DAA+ and DAA- groups for the occurrence of new hepatic nodules after diagnosis and/or treatment of HCC recurrence ( $p=0.19$ ), new non hepatic lesions after diagnosis and/or treatment of HCC recurrence ( $p=0.63$ ) or for the mRECIST time to progression ( $p=0.25$ )(Figure 2C).

Four patients had extra-hepatic HCC at the time of recurrence.

Seven and 10 patients died, 1 and 7 liver transplantations were performed in the DAA+ and DAA- groups, respectively(Figure 1 B) with no difference in overall survival and/or transplantation-free survival (median 17.8 vs 23.9 months, respectively,  $p=0.71$ )(Figure 2D).

Second analysis: the restricted cohort (n = 23)

Our first analysis evidenced that some patients did not actually receive “curative” treatment: chemoembolization in 9 patients, radioembolization in one, while 6 other patients had at the blinded morphological analysis either parietal HCC spreading (in one) and an incomplete response after curative treatment of first HCC (in 5 patients) (Figure 1A). That is why we

excluded these sixteen patients from the whole group of the 39 (41.0%). This “restricted cohort” (n=23) was not different from the whole cohort and included 17 men and 6 women, median age 60 (57-71) years old, 22 (96%) with cirrhosis. The ten patients who received DAA therapy before the recurrence of HCC (DAA+), which occurred 12 (IQR 9-14) months after treatment, were compared to the 13 patients who did not receive DAA therapy (DAA-) including 3 who initiated DAA after HCC recurrence (Figure 1B). The median (IQR) follow-up was 19 (8-23) and 31 (21-51) months in the DAA+ and DAA- groups, respectively ( $p = 0.03$ ). In the restricted cohort, the median MELD score was not statistically different between DAA+ and DAA- ( $p = 0.12$ )(Table 2).

The median time from initial tumor treatment to DAA treatment (defined by the time from the date of initial tumor treatment and the first dose of DAA treatment) was 11 (6-17) months. The median time to HCC recurrence (time from the date of initial tumor treatment to the diagnosis of HCC recurrence) did not differ between the DAA+ and DAA- groups (22 vs 17 months,  $p = 0.10$ )(Figure 3A).

There was no difference in the rate of unifocal recurrence (50 vs 31%,  $p = 0.42$ ), nodular (vs infiltrative) forms (100 vs 100%), the mean diameter of the largest nodule (13.5 vs 16 mm,  $p = 0.13$ ) or the rate of portal invasion (0.0 vs 7.7%,  $p = 0.99$ ) between DAA+ and DAA- patients, respectively.

There was no difference between DAA+ and DAA- groups for the occurrence of new hepatic nodules ( $p = 0.45$ ) or the mRECIST time to progression ( $p = 0.92$ )(Figure 3B).

Three patients died in each group of this restricted cohort; 1 and 6 liver transplantations were performed in the DAA+ and DAA- patients, respectively, (Figure 1B) with no difference in overall survival and/or transplantation-free survival ( $p = 0.59$ )(Figure 3C).

## **Discussion**

This retrospective blinded analysis of HCC recurrence kinetics in a well-defined study population first argues against the “curative” efficacy of the first treatment of HCC in one third of patients despite they were treated in French expert centers and second does not support any negative impact of DAA therapy on the recurrence, severity or progression of

HCC. To the best of our knowledge, this is the first blinded analysis of tumor growth comparing DAA treated and untreated patients in addition to other studies evidencing the absence of deleterious impact of DAAs on tumor growth (11-12, 18-23). Progression-free survival is an important end-point in advanced disease settings. As suggested by Dodd et al “blinded independent central review (BICR) of progression in randomized clinical trials has been advocated to control bias that might result from errors in progression assessments” even if they may introduce bias (29).

There was indeed no difference in median time to HCC recurrence or tumor aggressiveness (the rate of unifocal recurrence, nodular (vs infiltrative) forms, mean diameter of the largest nodule, rate of portal invasion, overall survival and/or transplantation-free survival) or the occurrence of new hepatic nodules and mRECIST time to progression between DAA+ and DAA- patients in our study.

Moreover, there was no difference in tumor characteristics at recurrence, in particular the number and diameter of nodules, the rate of focal or infiltrative forms or vascular invasion, between the two groups, suggesting that DAA treatment does not increase tumor growth. In addition, there was no statistical difference in the number of new hepatic nodules or mRECIST progression time between the 2 groups, suggesting that DAAs do not increase tumor aggressiveness.

These results are in contrast to the retrospective studies which resulted in the FDA/EMA warning (1, 3, 5-6) which are similar to results from Hassany et al, who showed in 62 HCV-related cirrhotic patients after successful treatment of first HCC, receiving DAAs therapy a high rate of HCC recurrence (42%), especially within the first 6 months of treatment initiation (4). Our results support other retrospective and prospective analyses that did not find any risk of HCC recurrence in HCV-infected patients (11-12, 18-23). Although DAA treatment did not modify the risk of HCC recurrence (18), it did decrease the risk of de novo HCC compared to untreated patients after weighting for heterogeneities in treated and untreated patients (15). We hypothesize that the discrepant results on the risk of HCC in prior studies are mainly related to methodological pitfalls (15), as initially suggested (2). Cabibbo et al, in a large prospective cohort, including 143 consecutive patients with complete response after curative treatment of HCC and treated with DAAs, found a comparable risk of HCC recurrence but not higher to that reported in literature in DAA

untreated patients (21). Adhoute et al, compared in a retrospective case control study of 22 cirrhotic patients with complete response to HCC treatment who received DAAs therapy to 49 patients: they did not find any difference between the 2 groups in HCC recurrence rates, in time to progression at recurrence and HCC pattern (11). Nakano et al, in a prospective study of 459 patients, who had HCC cured with surgery or ablation therapy before the use of DAAs, found that only a high level of AFP and multiple occurrences of HCC before antiviral therapy were associated with a high risk of HCC recurrence (20). Preda et al, in a prospective analysis of 24 patients with HCV-associated cirrhosis who had HCC cured and received DAAs therapy found a significantly lower HCC recurrence rate/100 patient-years and an higher survival without recurrence in the DAA-HCC group versus control, respectively, for the resection+thermoablation group and also in the TACE group (19). This is the first study on a small number of patients showing that DAA therapy significantly reduced the recurrence rate of HCC and improved survival without recurrence. Finally, Guarino et al, in a meta-analysis of data available (24 papers) in order to elucidate the impact of DAAs on the risk of recurrence after successful treatment of HCC did not confirm an increasing risk of HCC recurrence associated with DAAs (23).

One Japanese study investigating the influence of HCV eradication by DAA therapy on the development of HCC strongly suggests that DAA do not enhance the development of HCC (30). This study prospectively evaluated changes in non-hypervascular hypointense nodules (NHHNs) by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) in 401 patients who did not have a history of HCC before the initiation of DAA therapy with periodic follow-up after therapy. The progression of NHHNs detected at baseline to typical HCC, as indicated by hypervascularization and the incidence of newly emergent NHHNs was analyzed. Patients who achieved a sustained virologic response (SVR) were compared with propensity score-matched patients with persistent HCV infection. This study showed that there was no difference in the incidence of hypervascularization of NHHNs to typical HCC in patients with NHHNs at baseline or in the new emergence of NHHNs between study patients and propensity score-matched patients with persistent HCV infection. The authors concluded that during a 2-year observation period after SVR, the eradication of HCV by IFN-free DAA therapy did not suppress or enhance HCC development. One Italian prospective study including 3,917 patients with F3-

F4 fibrosis treated by DAA between January 2015 and June 2016 (SVR12 in 97.2 % of F3, in 92.7 % of F4 Child-Pugh A and 80% of F4 Child-Pugh B/C) did not show any increased risk associated with DAAs with an incidence of HCC of 1.64 % patients/year (95% CI: 1.18-2.21), which is not different from a historical control group (14). In that study the overall incidence of HCC was 0.97%/year (95% CI 0.73-1.26) and the incidence in the entire cohort of patients with cirrhosis was 1.18% patients/year (95% CI 0.92–1.49). The incidence of HCC depended upon the severity of underlying liver disease. During the first year the incidence was 0.46% (95% CI: 0.12-1.17) in F3 fibrosis, 1.49 % (95% CI: 1.03-2.08) in Child-Pugh A cirrhosis and 3.61 % (95% CI: 1.86-6.31) in Child-Pugh B cirrhosis, respectively, and during the second year 0% in F3 fibrosis, 0.20% (95% CI 0.05–0.51) in Child Pugh A cirrhosis and 0.69% (95% CI 0.08–2.49) in Child-Pugh B cirrhosis, respectively. These differences were statistically significant ( $p = 0.00008$ ).

One important limitation in all of these studies is the diagnosis of a so-called “HCC cure”. Our blinded reading showed that the definition of a cure was over-estimated in 41% of patients. These 16 patients were wrongly considered to be cured in expert centers either because the blinded radiological analysis evidenced in fact an incomplete response (persistent hepatic or extra-hepatic tumor ( $n= 6$ )) or non curative treatment (TACE, for example) ( $n= 10$ ). Thus, these patients should not be considered to have recurrent HCC but rather progressive HCC before DAA therapy. This shows the difficulty of contrast-enhanced CT and/or MR imaging, especially after ablation in cirrhotic livers and the risk of misleading interpretations. Only 23 of the 39 patients in our study received truly curative HCC treatment. Interestingly, the short-term probability of mRECIST progression-free, overall and transplantation-free survival was not statistically different between the whole cohort and the restricted cohort (around 25% at 6 months and 70% at 1 year for both groups).

It is interesting to note that more severe lesions (> 2 or 3 nodules or infiltrative forms of HCC) occurred more rapidly after the initiation of DAAs, suggesting a causal relationship between tumor growth and DAA, but this was not supported by our results. DAA therapy did not decrease the risk of recurrence of HCC and did not improve survival. This is in contrast to previous studies on HBV. Indeed, NUCs-associated viral suppression was associated with a doubling of overall survival even in Chinese patients receiving palliative treatment for HCC or



support therapies (31). The short follow-up in patients receiving DAA therapy in our study (18 months) could explain the lack of benefit in treated versus untreated patients.

The main weakness of our study is the small sample size that predisposes to a beta error due to low power. Other significant limitation of our study is the lack of standardization of both HCV and HCC treatments; since follow up and monitoring methods were based on the physician decision, this could affect differences in the recurrence rate and tumor progression: our multicenter study was conducted in a real life setting explaining the lack of standardization but there was no difference between groups (DAA+ and DAA-) at baseline and we could not see how the lack of standardization could cancel a positive association between DAA and HCC. Finally, possibilities of curative or palliative therapeutic options for the treatment of recurrent HCC are highly important to improve mRECIST progression time and the probability of survival in patients. Because of the small number of patients in our study, it was impossible to correlate treatment of the recurrence and impact of DAA on the prognosis of HCC.

The timing between the treatment of HCC and of HCV must be better defined, as there is no evidence to date showing that associating HCV treatment with palliative therapy for HCC is beneficial.

## **Conclusion**

Our blinded analysis of HCC recurrence following “curative” treatment of initial tumor does not show that DAA therapy has any significant impact on the severity or progression of HCC recurrence and evidences that “HCC cure” may be debatable.

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**Figures captions:**

Figure 1: Panel A. Flow chart of the whole cohort (HCC recurrence after a so-called curative treatment); Panel B. Flow chart of the restricted cohort, namely patients with HCC recurrence who received actual curative treatment (surgery or radio-ablation) without evidence of any active tumor.

Figure 2: Panel A. Calculation of median time for DAA treatment regarding the time of “curative” treatment of first HCC and the time of HCC recurrence; Panel B. Median time to HCC recurrence (time from the date of curative treatment and the diagnosis of recurrence) in the whole cohort; Panel C. mRECIST time to progression-free survival in the restricted cohort. Panel C. Median overall and liver transplantation-free survival in the whole cohort.

Figure 3: Panel A. Median delay of HCC recurrence (time between the date of curative treatment and diagnosis of recurrence) in the restricted cohort; Panel B. Median overall and liver transplantation-free survival in the restricted cohort; Panel B. mRECIST time to progression-free survival in the restricted cohort. Panel C. Median overall and liver transplantation-free survival in the restricted cohort.

**Table 1:** Baseline characteristics of patients in groups who were given direct acting antivirals (DAA<sup>+</sup>) or not (DAA<sup>-</sup>) in the whole cohort.

	Whole cohort n= 39	DAA+ n= 17	DAA- n= 22	p
Median (IQR) age	62 (57-71)	65 (51-82)	61 (57-71)	0.63
Male/Female	28/11	12/5	16/6	0.99
IFN experienced n (%)	33 (84)	14 (82)	19 (86)	0.99
1 <sup>st</sup> generation PI* experienced n (%)	6 (15)	3 (18)	3 (14)	0.99
Cirrhosis n (%)	37 (95)	17 (100)	20 (91)	0.50
Genotypes n 1/2/3/4/unknown	25/3/7/3/1	13/2/2/0/0	12/1/5/3/1	0.34
Alcohol consumption n (%)	19 (49)	7 (41)	12 (55)	0.52
Median HCV duration (IQR) (y)	15 (9-21)	18 (13-22)	14 (7-20)	0.11
AFP (log) (ng/mL)	2.6 ± 1.2	2.6 ± 1.3	2.6 ± 1.3	0.99
MELD score	9 ± 3	8 ± 2	10 ± 4	0.0286
ascites n (%)	8 (20)	3 (18)	5 (23)	0.99
Porto systemic shunt and collateral veins	21 (54)	8 (47)	13(59)	0.53
Splenomegaly	21(54)	7 (41)	14 (64)	0.21

\*PI = protease inhibitor

**Table 2:** Baseline characteristics of patients in groups DAA+ and DDA- in the restricted cohort

	restricted cohort n= 23	DAA+ n= 10	DAA- n= 13	p
Median age	60 (57-71)	60 (57-65)	62 (59-75)	0.40
Male/Female	17/6	8/2	9/4	0.66
INF experienced n (%)		9 (90)	12 (92)	0.99
1 <sup>st</sup> generation PI* experienced n (%)	4	2	3	0.999
Cirrhosis n (%)	22	10 (100)	12 (92)	0.99
Genotypes n 1/2/3/4/unknown	12/3/7/1/0	6/2/2/0/0	6/1/5/1/0	0.70
Alcohol consumption n (%)	14	5	9	0.41
HCV duration (y)	15 (8-20)	16 (13-18)	15 (7-20)	0.82
AFP (log)	2.5 ± 1.3	2.5 ± 1.3	2.5 ± 1.3	0.90
MELD score	9 ± 3	8 ± 2	9 ± 3	0.12
ascites n (%)	5	2	3	0.99
Porto-systemic shunt and collateral veins	13	5	8	0.67
Splenomegaly	13	4	9	0.22

\*PI= protease inhibitor



Figure 1 A

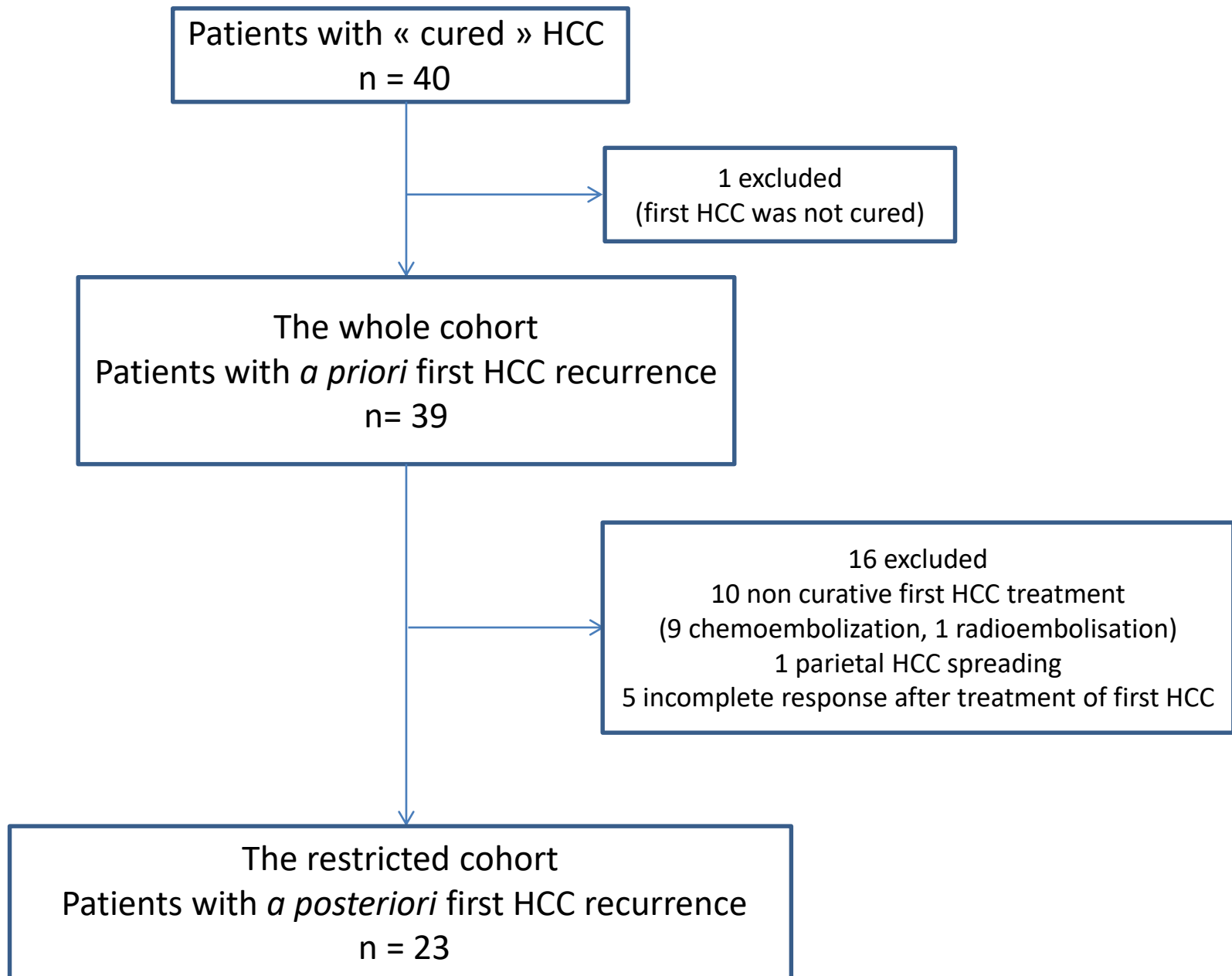


Figure 1 B

The whole cohort  
n = 39

The restricted cohort  
n = 23

DAA +  
n = 17

DAA -  
n = 22

DAA +  
n = 10

DAA -  
n = 13

Alive  
n = 9

Death  
n = 7

LT  
n = 1

Alive  
n = 5

Death  
n = 10

LT  
n = 7

Alive  
n = 6

Death  
n = 3

LT  
n = 1

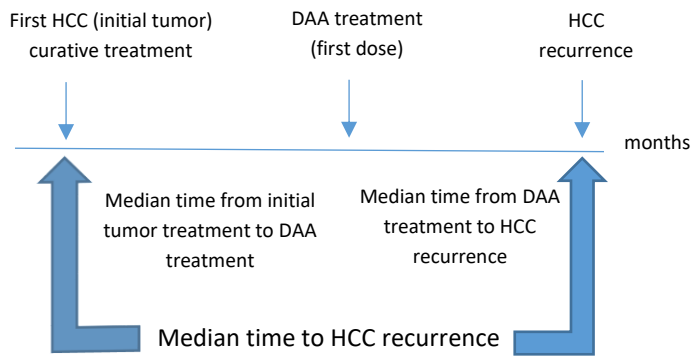
Alive  
n = 4

Death  
n = 3

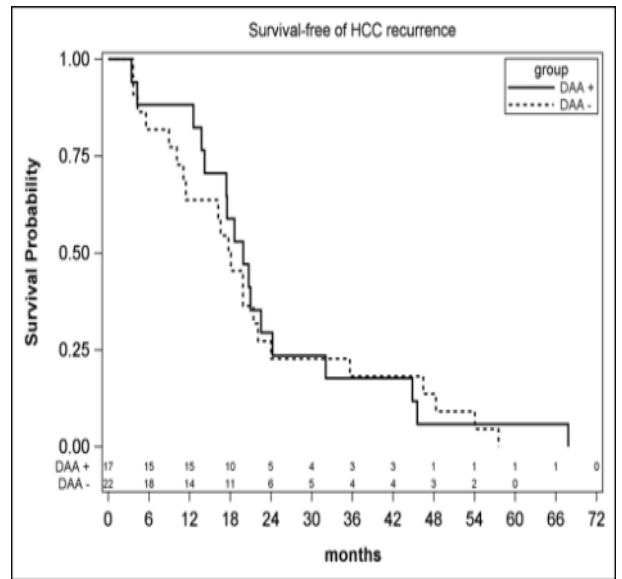
LT  
n = 6

Figure 2

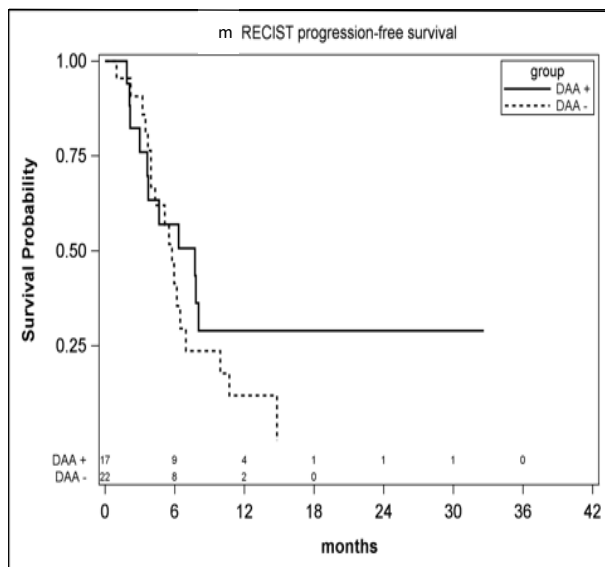
A



B



C



D

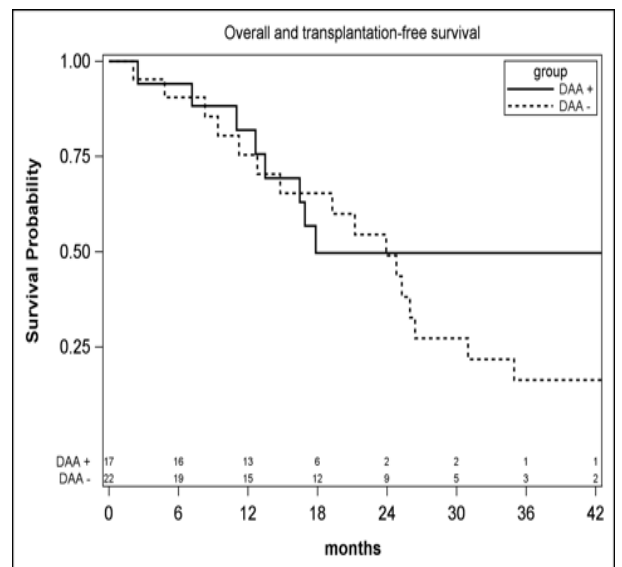
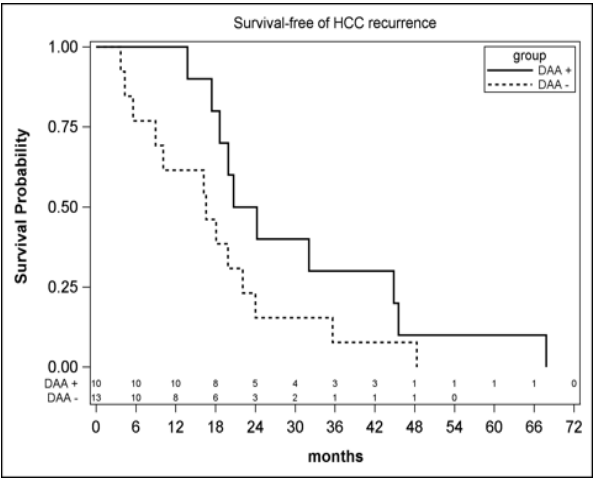
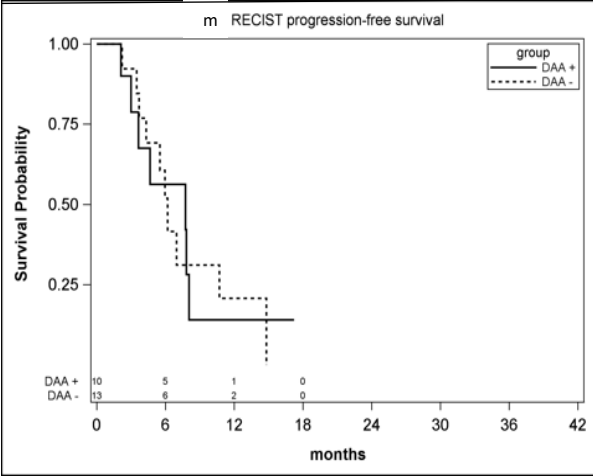


Figure 3

A



B



C

