Hepatocellular carcinoma recurrence in patients with curative resection or ablation: impact of HCV eradication does not depend on the use of interferon

S. Petta*, G. Cabibbo*, M. Barbara*, S. Attardo*, L. Bucci†, F. Farinati‡, E. G. Giannini§, F. Tovoli†, F. Ciccarese¶, G. L. Rapaccini**, M. Di Marco††, E. Caturelli‡‡, M. Zoli†, F. Borzio§§, R. Sacco¶¶, R. Virdone*, F. Marra***, M. Felder†††, F. Morisco‡‡‡, L. Benvegnù‡, A. Gasbarrini**, G. Svegliati-Baroni§§§, F. G. Foschi¶¶¶, A. Olivani****, A. Masotto††††, G. Nardone‡‡‡, A. Colecchia†, M. Persico‡‡‡‡, V. Boccaccio§§§§, A. Craxì*, S. Bruno§§§§, F. Trevisani†, C. Cammà* & for the Italian Liver Cancer (ITA.LI.CA) Group[1]

*Palermo, Italy.
†Bologna, Italy.
‡Padova, Italy.
§Genoa, Italy.
¶Zingonia, Italy.
**Rome, Italy.
††Seriate, Italy.
‡‡Viterbo, Italy.
§§Milan, Italy.
¶¶Pisa, Italy.
***Florence, Italy.
†††Bolzano, Italy.
‡‡‡Naples, Italy.
§§§Ancona, Italy.
¶¶¶Faenza, Italy.
****Parma, Italy.
††††Negrar, Italy.
‡‡‡‡Salerno, Italy.
§§§§Rozzano, Italy.

Correspondence to:
Prof. C. Cammà, Sezione di Gastroenterologia, Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Piazza delle Cliniche 2, Palermo 90127, Italy.
E-mail: calogero.camma@unipa.it

[1]Other members of the ITA.LI.CA group are listed in Appendix 1.

Authors' complete affiliations are listed in Appendix 2.

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SUMMARY

Background
In HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma (HCC), the time to HCC recurrence and the effects of sustained viral eradication (SVR) by interferon (IFN)-based or IFN-free regimens on HCC recurrence remain unclear.

Aim
To perform an indirect comparison of time to recurrence (TTR) in patients with successfully treated early HCC and active HCV infection with those of patients with SVR by IFN-based and by IFN-free regimens.

Methods
We evaluated 443 patients with HCV-related cirrhosis and Barcelona Clinic Liver Cancer Stage A/0 HCC who had a complete radiological response after curative resection or ablation. Active HCV infection was present in 328, selected from the Italian Liver Cancer group cohort; 58 patients had SVR achieved by IFN-free regimens after HCC cure, and 57 patients had SVR achieved by IFN-based regimens after HCC cure. Individual data of patients in the last two groups were extracted from available publications.

Results
TTR by Kaplan–Meier curve was significantly lower in patients with active HCV infection compared with those with SVR both by IFN-free ($P = 0.02$) and by IFN-based ($P < 0.001$) treatments. TTR was similar in patients with SVR by IFN-free or by IFN-based ($P = 0.49$) strategies.

Conclusion
In HCV-infected, successfully treated patients with early HCC, SVR obtained by IFN-based or IFN-free regimens significantly reduce tumour recurrence without differences related to the anti-viral strategy used.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related death in men globally, and the leading cause of mortality in patients with cirrhosis.[1, 2] Cirrhosis is the strongest risk factor for HCC, with hepatitis C virus (HCV) being a major risk factor in the Western world as well as in Japan.[3] Orthotopic liver transplantation (OLT) is the definitive treatment for removal of an HCC and cirrhotic liver, but it cannot be offered to all patients due to limitations, such as graft availability and rigorous selection criteria.[4–6]

When diagnosed in an early disease stage [(Barcelona Clinic Liver Cancer stage 0 or A (BCLC 0/A)], surgical resection and loco-regional ablation are potentially curative treatments, with 5-year survival rates of 60–80% and 40–70%, respectively.[4–6] Unfortunately, tumour recurrence contributes to long-term mortality after tentatively curative treatment of early HCC.[4–8] Although HCC tumour recurrence remains high overall (50% at 3 years and 70% at 5 years), the available evidence is highly heterogeneous and data are not available specifically for HCV-infected patients.

Currently, because of the burden of HCC recurrence and the lack of strategies with proven prevention efficacy, there is a serious unmet clinical need in the area of adjuvant therapy for patients treated for early HCC with persistent HCV infection.[9] In fact, the STORM randomised controlled trial of sorafenib as an adjuvant treatment after potentially curative therapy for HCC failed to show a significant treatment effect regarding HCC recurrence in either HCV-infected or uninfected patients.[10] Classical [11] and competing risk multistage [12] models have demonstrated clearly that sustained virological response (SVR) by interferon (IFN)-based therapies reduces the *de novo* occurrence of HCC in HCV-related cirrhosis with or without clinical portal hypertension. However, available data on the impact of SVR by IFN-based vs. newer IFN-free regimens on HCC recurrence are inconsistent. Specifically, when considering IFN-based regimens, five meta-analyses[13–17] of aggregate data of small randomised controlled trials in heterogeneous populations of patients with tentatively cured HCV-related early HCC showed conflicting results regarding the benefit of SVR on HCC recurrence. Moreover, some of these studies combined all IFN-treated patients with and without SVR, and the non-availability of individual data precluded the analysis of recurrence as a time-dependent variable. Otherwise, data for IFN-free regimens using direct antiviral agents (DAAs) indicate high rates of early HCC recurrence in small cohorts of HCV-related cured HCC patients, raising concerns about the as yet unproven benefit of adjuvant DAA-based therapy.[18, 19]

We aimed to estimate time to HCC recurrence in successfully treated early HCC patients with active HCV infection using the Italian Liver Cancer (ITA.LI.CA.) group cohort, and to compare the observed recurrence rate with that of patients with SVR achieved by IFN-based or IFN-free regimens, using pooled estimated individual data from the literature.

MATERIALS AND METHODS

Patients

Patients with successfully treated, HCV-related early HCC with active HCV infection. Currently, the ITA.LI.CA. database contains data from 6595 patients with HCC diagnosed consecutively from 1987 to 2015 at 24 Italian medical institutions. Since 2007, the ITA.LI.CA. database has included follow-up clinical and imaging data that were collected prospectively and updated every 2 years. After data collection and before statistical evaluation, the group coordinator (F.T.) examined the consistency of the datasets. If clarifications or additional information were needed, the data were resubmitted to the relevant centre. The presence of cirrhosis was determined according to histological findings or clinical evidence, and liver function was evaluated based on Child–Pugh[20] and MELD scores.[21] The presence of oesophageal varices was assessed by upper digestive endoscopy and was classified as absent, small, medium or large.[22]

The diagnosis of HCC was made by ultrasound-guided biopsy or by non-invasive criteria according to the guidelines published at the time of patient inclusion. Performance status (PS) was scored according to the Eastern Cooperative Oncology Group (ECOG) system.[23] HCC staging was assessed according to both the Milan criteria[24] and BCLC classification, and treatments were performed according to the BCLC schedule[4, 5] unless individual centre care providers chose different patient-tailored therapeutic options. Patients with early tumours (BCLC A) were considered for resection, OLT or local ablation. Transarterial chemoembolisation was performed in patients with intermediate-stage (BCLC B) tumours. Starting in July of 2008, compensated patients with advanced HCC (BCLC C) and patients with intermediate-stage HCC who were not eligible for or failed loco-ablative therapies were treated with sorafenib.

For this retrospective study of prospectively collected data, we included all early HCC patients with HCV-related compensated cirrhosis who achieved complete radiological response after tentatively curative treatment, either resection or ablation. The patient selection process is illustrated in Figure 1. Complete radiological response was determined by applying validated imaging criteria to multiphasic, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen approximately 1 month after either tumour resection or the last loco-regional treatment (thermal ablation). Blood cell counts, serum chemistry and serum α-fetoprotein (AFP) levels were measured by standard laboratory procedures. HCV markers were detected with commercial kits.

The study endpoint was time to recurrence (TTR), defined as the time from HCC treatment with curative intent to the first disease recurrence documented by radiological assessment. For this purpose, after tentatively curative treatment for HCC with a documented complete radiological response, all patients were followed in specific out-patient clinics. The follow-up protocol included clinical assessment by physical examination, ultrasound scans, and biochemistry every 3 months, as well as multiphasic CT or MRI every 6 months. HCC recurrence was diagnosed on the basis of combined abnormal findings on ultrasonography and on one additional dynamic imaging technique confirming hypervascularisation in the arterial phase with washout in the portal venous or late venous phase. All participating ITA.LI.CA centres had high-quality and updated radiological facilities. Recurrences were treated whenever possible according to treatment plans devised at each centre.

Patients with successfully treated, HCV-related early HCC with SVR following IFN-based therapy. We conducted a systematic review and meta-analysis of studies evaluating the efficacy of IFN to prevent HCC recurrence after tentatively curative treatment in HCV-related cirrhosis. We included only studies reporting HCC recurrence curves in patients with SVR, to obtain a pooled actuarial HCC recurrence curve in patients with successfully treated, HCV-related early HCC with SVR following IFN-based therapy. After a review of the literature, three studies[25–27] fulfilled the inclusion criteria.

Patients with successfully treated, HCV-related early HCC with SVR following DAA-based therapy. Data were obtained from a study by Reig and colleagues.[18] Specifically, we extracted the individual data from Figure 2 of the article, calculated the Kaplan–Meier probability estimates of HCC recurrence, and plotted a Kaplan–Meier curve.[28] We used the time of HCC treatment as the origin of the Kaplan–Meier curve,.

Statistical analyses

Experienced medical personnel collected data. Continuous variables were expressed as a median and range, whereas categorical data were reported as counts and percentages. Individual patient data on TTR were reported graphically in each of the involved studies and were extracted by means of specifically designed digitizing software.[29] The Kaplan–Meier method was used to estimate TTR probabilities. Statistical significance of differences in TTR was assessed by means of the log-rank test.

Potential predictors of TTR were evaluated in the HCV-infected cohort by fitting a Cox regression model. All baseline variables in Table 1 were evaluated by univariate analyses. Variables with $P \leq 0.10$ in the univariate analyses were included in the final multivariate

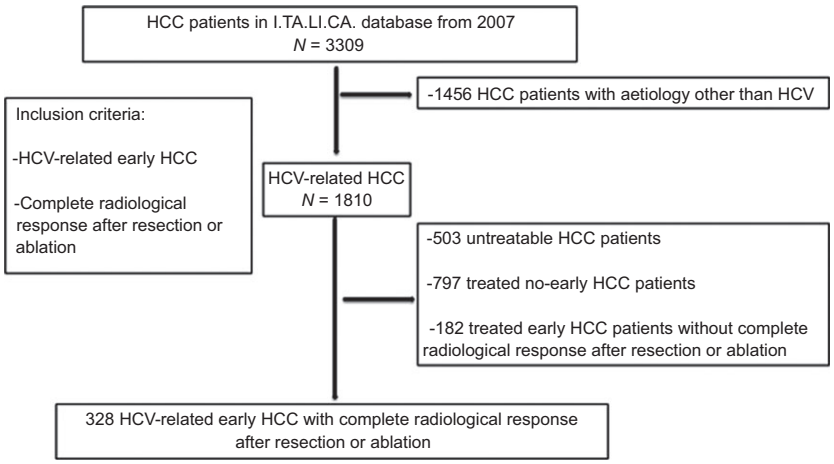

Figure 1 | Flow diagram of patient selection. ITA.LI.CA., Italian Liver Cancer; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

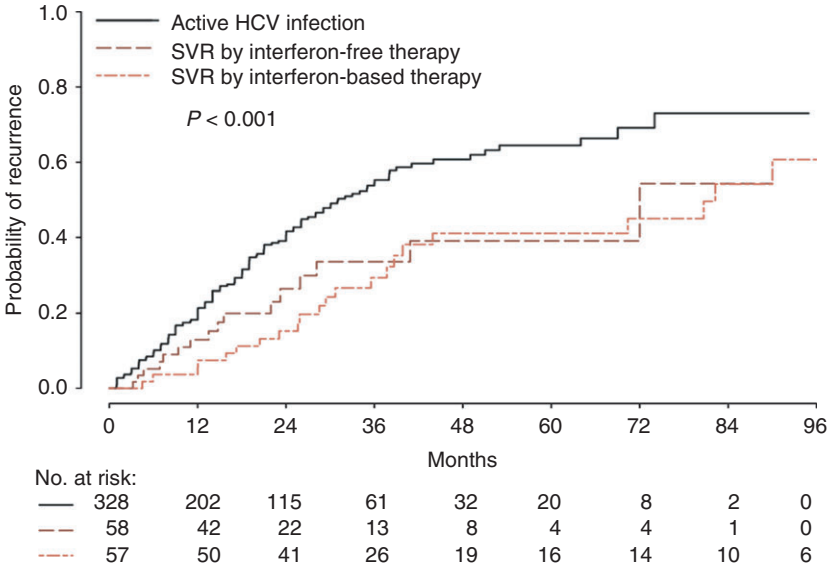

Figure 2 | Time to HCC recurrence in 443 patients with curative resection or ablation of HCC in HCV-related cirrhosis according to HCV infection status: 323 patients with active HCV infection (group 1), 58 patients with SVR by IFN-free regimens (group 2), and 57 patients with SVR by IFN-based regimens (group 3). Overall Log-rank $P < 0.001$. Log-rank group 1 vs. group 2 $P = 0.02$. Log-rank group 1 vs. group 3 $P < 0.001$. Log-rank group 2 vs. group 3 $P = 0.49$.

Table 1 | Baseline characteristics of 443 patients with complete response after HCC treatment, stratified according to HCV infection status

	Groups		
	Active HCV infection ($N = 328$)	SVR by IFN-free therapies ($N = 58$)	SVR by IFN-based therapies* ($N = 57$)
Age, median [range] (years)	72.1 [40–85]	66.3 [45–83]	62.0 [43–80]
Male sex, *n* (%)	217 (66)	40 (69)	41 (72)
Resection, *n* (%)	88 (27)	20 (34)	25 (44)
BCLC, *n* (%)			
0	99 (30)	16 (28)	
A	229 (70)	42 (72)	57 (100)†
Child–Pugh, *n* (%)			
A	307 (94)	50 (91)	46 (90)
B	21 (6)	3 (5)	5 (10)
C	0	2 (4)	0
Performance status			
0	328 (100)	58 (100)	57 (100)
Albumin, median [range] (g/dL)	3.7 [2.3–5.1]	4.0 [2.0–5.0]	Not reported
Bilirubin, median [range] (mg/dL)	0.9 [0.3–2.9]	1.0 [0.3–6.0]	Not reported
Creatinine, median [range] (mg/dL)	0.8 [0.4–7.7]	0.8 [0.4–2.4]	Not reported
Platelets, median [range] ($\times 10^9$/L)	121 [24–332]	101 [33–229]	Not reported
PT, median [range] %	81.0 [37–117]	77.5 [12.6–100]	Not reported
AFP, median [range] (ng/mL)	22.94 [1–950]	11.45 [1–369]	24 [1–13 846]

* Patient characteristics for the SVR by Interferon group were deduced from those related to the entire IFN arm.

† Number of BCLC 0 patients not available.

model. To prevent variable co-linearity effects, MELD, BCLC and Child–Pugh scores were not included in the same multivariate model.

For all analyses, $P < 0.05$ were considered statistically significant. All p values were two-tailed, and all confidence intervals (CIs) were 95%. The R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria) was used to perform analyses and plot results.

Ethics

Management of the ITA.LI.CA database conforms to all Italian laws on privacy, and this study met the ethical guidelines of the Helsinki Declaration. The Institutional Review Boards of the participating centres approved this study.

RESULTS

Baseline features of studied populations

The baseline features of patients with successfully treated HCC and cirrhosis with active HCV infection (hereafter group 1), with SVR achieved by IFN-free (hereafter group 2) and with SVR achieved by IFN-based (hereafter group 3) regimens are summarised in Table 1.

The indirect comparison revealed that the prevalence of male sex was similar among the three groups, ranging from 66% in group 1 to 72% in group 3. Median age decreased progressively from viraemic patients (72 years) to those achieving SVR by IFN-free treatment (66 years), and further to those achieving SVR by IFN-based (62 years) therapies. More than 90% of patients in all three groups had compensated Child A cirrhosis, with similar values of baseline liver function and kidney indexes, such as albumin, bilirubin and creatinine (data not available for group 3).

All patients had BCLC A HCC and therefore a performance status of 0. The proportion of patients who underwent HCC resection increased progressively from those with active HCV infection (27%), to those achieving a SVR following IFN-free regimens (34%), and further to those achieving SVR following IFN-based therapies (44%). Median serum α-FP levels were similar among groups.

Follow-up

The median length of follow-up after tentatively curative HCC treatment was similar in patients with active HCV infection (17 months, range 1–95 months) and those with SVR following IFN-free regimens (18 months, range 3–90 months), but was higher in those achieving SVR following IFN-based therapies (34 months, range 0–138 months).

Recurrences

During follow-up, HCC recurrence developed in 142/328 (43.3%) patients with active HCV infection, in 16/58 (27.6%) patients achieving SVR following IFN-free regimens, and in 22/57 (38.6%) patients achieving SVR following IFN-based therapies (Table 2). The 6-month recurrence rates were 9.5%, 5.2% and 3.7%, and the 2-year recurrence rates were 40.6%, 26.3% and 15.2% in patients with active HCV infection, with SVR achieved following IFN-free treatment, and with SVR achieved following IFN-based therapies, respectively. Consistent with these data, TTR by Kaplan–Meier curves was

Table 2 | Follow-up of 443 patients with complete response after HCC treatment, stratified according to HCV infection status

	Groups		
	Active HCV infection (*N* = 328)	SVR by IFN-free therapies (*N* = 58)	SVR by IFN-based Therapies* (*N* = 57)
Recurrence during follow-up, *n* (%)	142 (43.3)	16 (27.6)	22 (38.6)
Follow-up length, median (range)	17 (1–95)	18 (3–90)	34 (0–138)
Recurence rates			
6-month	9.5%	5.2%	3.7%
1-year	21.0%	12.9%	5.6%
2-year	40.6%	26.3%	15.2%
3-year	54.5%	33.5%	29.3%
4-year	60.7%	39.1%	41.1%
5-year	64.5%	39.1%	41.1%
Median time to recurrence, mo. (95% CI)	31 (26–38)	72.0 (40.8–N.A.)	82.3 (39.8–N.A.)

significantly shorter in patients with active HCV infection compared with those with SVR achieved following either IFN-free ($P = 0.02$) or IFN-based ($P < 0.001$) treatments. TTR was similar in patients with SVR achieved following IFN-free or IFN-based ($P = 0.49$) strategies (Figure 2). Consistent with these data, recurrence rates at 6 months, 1 year, 2 years and 3 years did not differ significantly between these two groups ($P = 0.66$, $P = 0.19$, $P = 0.34$ and $P = 0.95$ respectively).

Notably, among patients with active HCV infection, Kaplan–Meier TTR was similar between those who had previously undergone IFN-based treatment ($n = 101$) and those naïve to anti-viral therapy ($n = 127$) ($P = 0.57$) (Figure S1). Finally, owing to the availability of individual data in the viraemic patient group, we were able to determine by multivariate analysis that bilirubin (HR = 1.43; 95% CI = 1.02–2.00; $P = 0.03$), creatinine (HR = 1.42; 95% CI = 1.11–1.83; $P = 0.006$) and α-FP (HR = 1.001; 95% CI = 1.000–1.003; $P = 0.04$) were the only independent predictors of HCC recurrence examined (Table S1).

DISCUSSION

In the present study, we found 6-month and 2-year HCC recurrence rates of 9.5% and 40.6% in a large cohort of patients with HCV-related early HCC who achieved a complete radiological response after tentatively curative resection or ablation. Furthermore, we demonstrated that SVR by IFN-based or IFN-free regimens reduced the HCC recurrence rate significantly without differences related to the therapeutic strategy. We also identified baseline AFP, bilirubin and creatinine levels as independent predictors of HCC recurrence, indicating that factors related to tumour aggressiveness (i.e. AFP),[30] advanced liver disease (i.e. bilirubin) and liver disease prognosis (i.e. bilirubin and creatinine) increase tumour recurrence risk.

Hepatocellular carcinoma recurs frequently in patients infected with HCV, and adjuvant therapies with drugs like sorafenib that directly treat HCC lack efficacy.[10] These facts highlight the unmet clinical need for adjuvant therapy for patients treated for early HCC but with persistent HCV infection. In this clinical setting, viral eradication could act as an adjuvant strategy, leading to reduced HCC recurrence, similar to its impact for HCC *de novo* occurrence.[11, 12] However, data on the impact of IFN-based or IFN-free regimens on HCC recurrence are inconclusive and/or conflicting.[13–17]

To address this relevant concern, we assessed the effect of SVR on HCC recurrence by comparing TTR in patients with HCV viraemia with that observed in patients achieving SVR by IFN-based or IFN-free antiviral therapies. Data for patients with active HCV infection were those previously reported from the ITA.LI.CA cohort. Data for patients in SVR achieved by IFN-based therapies were obtained by pooling individual data of studies estimating the effect of IFN-based SVR on HCC recurrence in HCV patients. Data for patients in SVR by IFN-free therapies were obtained by individual data extracted from the study of Reig and colleagues.[18] Notably, when comparing the three curves, we clearly demonstrated that SVR, whether achieved via IFN-based or IFN-free regimens, significantly reduces HCC recurrence rate, with no difference between the two therapeutic strategies. We observed lower 1-year and 2-year recurrence rates, even if not statistically different, in patients treated with IFN compared with those who received IFN-free therapies. This trend could be related to the fact that the former group may be enriched with patients without early HCC recurrence because early HCC recurrence during IFN-based therapy led to therapy drop out and no SVR.

Consistent with all the above-quoted data, the present study suggests that the positive impact of anti-viral therapy on HCC recurrence is only the effect of virological eradication, regardless of the regimen. It is worth noting that the published experimental data also support the idea that IFN *per se* has anti-fibrotic, anti-proliferative, anti-angiogenic and anti-tumoural effects,[31, 32] suggesting its potential benefit on HCC recurrence also in the absence of SVR. Despite these interesting speculations, when evaluating patients with active HCV infection separately according to previous exposure to IFN, no differences in HCC recurrence rates were observed. Consistent with these data, while half of patients in the DAA group[17] had been treated with IFN, no additional benefit in terms of HCC recurrence reduction was observed in patients achieving SVR by DAA compared with those achieving SVR by IFN.

From a clinical point of view, our study (i) demonstrated that all HCV-infected patients with successfully treated early HCC should undergo virological eradication to reduce the probability of HCC recurrence; (ii) provided evidence about the clinical utility of IFN-free antiviral regimens in this clinical setting, where DAAs have been until now used without any proof of their effectiveness. Consistent with these data, IFN-free therapies should be preferred to IFN-based regimens due to their safety profile and high virological effectiveness, as well as the possibility to safely treat sicker patients; (iii) finally

provided a benchmark for the HCC recurrence rate in HCV-infected patients to be used as comparator for new adjuvant strategies.

This study has some limitations. The main limitation lies in the comparison of groups arising from different populations and the potentially variant severity of underlying liver disease. In addition, recurrence rates in the retrospective ITA.LI.CA. cohort could be affected by several confounding factors, such as alcohol intake, metabolic comorbidities and HCV genotype. However, we are confident about the strength of our results because we used individual data for each group, and because all patients had early HCC treated by resection or ablation. Overall, the strict patient selection criteria resulted in a generally homogeneous population. Finally, the generalisability of these results to different populations and settings is not known. As our study included only patients with successfully treated early HCC, we did not determine whether the impact of SVR on HCC recurrence is the same in patients with more advanced HCC at baseline.

In conclusion, our results demonstrated that in patients with successfully treated, HCV-related early HCC, SVR obtained by IFN-based or IFN-free regimens reduces tumour recurrence significantly without differences related to the anti-viral strategy used. These data support the current use of IFN-free regimens in this particular clinical setting and provide proof of their clinical effectiveness in terms of reducing HCC recurrence.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Time to HCC recurrence in 323 cirrhotic patients with curative resection or ablation of HCC and with active HCV according to previous exposure to IFN-based therapies. Log-rank $P = 0.57$.

Table S1. Independent predictors of time to recurrence in the HCV-infected cohort by fitting a Cox regression model.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: S Petta, G Cabibbo, M Barbara, S Attardo, L Bucci, F Farinati, E G Giannini, F Tovoli, F Ciccarese, G L Rapaccini, M Di Marco, E Caturelli, M Zoli, F Borzio, R Sacco, R Virdone, F Marra, M Felder, F Morisco, L Benvegnù, A Gasbarrini, G Svegliati-Baroni, F G Foschi, A Olivani, A Masotto, G Nardone, A Colecchia, M Persico, V Boccaccio, A Craxì, S Bruno, F Trevisani, C Cammà had full control of the study design, data analysis and interpretation, and preparation of article. All authors were involved in planning the analysis and drafting the article.

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APPENDIX 1
OTHER MEMBERS OF THE ITA.LI.CA GROUP

Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum – Università di Bologna: Maurizio Biselli, Paolo Caraceni, Alessandro Cucchetti, Marco Domenicali, Fabio Piscaglia, Annagiulia Gramenzi, Alessandro Granito, Donatella Magalotti, Carla Serra, Giulia Negrini, L. Napoli, Lucia Napoli, Veronica Salvatore, Francesca Benevento; *Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova*: Alessia Gazzola, Francesca Murer, Caterina Pozzan, Veronica Vanin; *Dipartimento di Medicina Interna, Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova*: Alessandro Moscatelli, Gaia Pellegatta, Antonino Picciotto, Vincenzo Savarino; *Unità Operativa di Chirurgia, Policlinico S. Marco, Zingonia*: Paolo Del Poggio, Stefano Olmi; *Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma*: Nicoletta de Matthaeis; *Unità Operativa di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia*: Claudia Balsamo, Elena Vavassori; *Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo*: Paola Roselli; *Unità Operativa di Medicina Protetta, Ospedale Belcolle, Viterbo*: Serena Dell'Isola, Anna Maria Ialungo, Elena Rastrelli; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Gastroenterologia, Università di Palermo:* Francesca Rini, Andrea Costantino; *Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna 2, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo*: Andrea Affronti, Marco Affronti, Marta Mascari; *Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano*: Andrea Mega; *Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma*: Maurizio Pompili, Emanuele Rinninella; *Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa*: Valeria Mismas; *Dipartimento di Medicina Interna; Ospedale per gli Infermi di Faenza, Faenza*: Anna Chiara Dall'Aglio, Valentina Feletti, Arianna Lanzi, Federica Mirici Cappa, Elga Neri, Giuseppe Francesco Stefanini, Stefano Tamberi; *Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma, Parma:* Elisabetta Biasini, Gabriele Missale; *Dipartimento di Medicina Clinica e Chirurgia, Unità di Gastroenterologia, Università di Napoli "Federico II", Napoli:* Maria Guarino; *Clinica di Gastroenterologia, Università Politecnica delle Marche, Ancona*: Alessio Ortolani; *Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar*: Maria Chiaramonte, Fabiana Marchetti, Matteo Valerio; *Medicina Interna ed Epatologia, Dipartimento di Medicina Sperimentale e Clinica – Università di Firenze, Firenze*: Sami Aburas, Andrea L. Inghilesi; *Dipartimento di Medicina Diagnostica e Prevenzione, Azienda ospedaliero-universitaria di Bologna, Unità Operativa di Radiologia*: Alberta Cappelli, Rita Golfieri, Cristina Mosconi, Matteo Renzulli; *Dipartimento di Medicina Clinica e Chirurgia, Unità di Epato-Gastroenterologia, Università di Napoli "Federico II", Napoli*: Piero Coccoli, Marco Sanduzzi Zamparelli.

APPENDIX 2
AUTHORS' COMPLETE AFFILIATIONS

Salvatore Petta, Giuseppe Cabibbo, Marco Barbara, Simona Attardo: Section of Gastroenterology, University of Palermo, Palermo, Italy; Laura Bucci: Unità di Semeiotica Medica, Alma Mater Studiorum – Università di Bologna, Bologna, Italy; Fabio Farinati: Unità di Gastroenterologia, Università di Padova, Padova, Italy; Edoardo G. Giannini: Unità di Gastroenterologia, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Università di Genova, Genova, Italy; Francesco Tovoli: Unità di Medicina Interna, Alma Mater Studiorum – Università di Bologna, Bologna, Italy; Francesca Ciccarese: Divisione di Chirurgia, Policlinico San Marco, Zingonia, Italy; Gian Lodovico Rapaccini: Unità di Medicina Interna e Gastroenterologia, Università Cattolica di Roma, Rome, Italy; Maria Di Marco: Divisione di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italy; Eugenio Caturelli: Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo, Italy; Marco Zoli: Unità di Medicina Interna, Alma Mater Studiorum – Università di Bologna, Bologna, Italy; Franco Borzio: Unità di Radiologia, Ospedale Fatebenefratelli, Milan, Italy; Rodolfo Sacco: Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Roberto Virdone: Divisione di Medicina Interna, Ospedale Villa Sofia – V. Cervello, Università di Palermo, Palermo, Italy; Fabio Marra: Medicina Interna ed Epatologia, Università di Firenze, Florence, Italy; Martina Felder: Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano, Italy; Filomena Morisco: Unità di Gastroenterologia, Università di Napoli "Federico II", Naples, Italy; Luisa Benvegnù: Dipartimento di Medicina Molecolare – Università di Padova, Padova, Italy; Antonio Gasbarrini: Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma, Rome, Italy; Gianluca Svegliati-Baroni: Dipartimento di Gastroenterologia, Politecnico-Università delle Marche, Ancona, Italy; Francesco Giuseppe Foschi: Dipartimento di Medicina Interna, Ospedale per gli Infermi di Faenza, Faenza, Italy; Andrea Olivani: Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; Alberto Masotto: Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar, Italy; Gerardo Nardone: Unità di Epato-Gastroenterologia, Università di Napoli "Federico II", Naples, Italy; Antonio Colecchia: Unità di Gastroenterologia, Alma Mater Studiorum – Università di Bologna, Bologna, Italy; Marcello Persico: Internal Medicine and Hepatology Unit, University of Salerno, Salerno, Italy; Vincenzo Boccaccio: Humanitas University and IRCCS Istituto Clinico Humanitas, Rozzano, Italy; Antonio Craxì: Section of Gastroenterology, University of Palermo, Palermo, Italy; Savino Bruno: Humanitas University and IRCCS Istituto Clinico Humanitas, Rozzano, Italy; Franco Trevisani: Unità di Semeiotica Medica, Alma Mater Studiorum – Università di Bologna, Bologna, Italy; Calogero Cammà: Section of Gastroenterology, University of Palermo, Palermo, Italy.