REVIEW

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Hepatocellular Carcinoma Occurrence and Recurrence after Antiviral Treatment in HCV-Related Cirrhosis. Are Outcomes Different after Direct Antiviral Agents? A Review

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ABSTRACT

Hepatitis C virus (HCV) infection is one of the major causes of hepatocellular carcinoma (HCC) worldwide. In the last decades, several studies have showed a lower rate of HCC occurrence or recurrence in patients with HCV-related cirrhosis after interferon-based antiviral therapies compared to untreated controls, even without reaching viral clearance. Unfortunately, interferon regimens could only yield viral clearance in approximately half of the patients. The recent development of new all-oral regimens with direct-acting antivirals (DAAs) has radically improved the cure rate to above 90%. In respect to these findings, many would have thought that interferon-free regimens would decrease the development and recurrence of HCC. Literature data have unexpectedly reported high rates of both the occurrence and recurrence of HCC after therapy with DAAs. However, it is probably too early to express some concerns. More recent data showed that both occurrence and recurrence of HCC are decreased by the DAAs. Interferon-free therapy is definitely not without limits. Together with the initial thoughts of an increased risk of HCC, these may lead to an unwanted restricted access to interferon-free regimens in specific subpopulations. This issue should be settled as soon as possible because millions of hepatitis C patients are and will be using DAAs in the present and future. Our purpose is to review the existing literature and to offer a more precise and rational interpretation of the existing data.

Key words: Hepatocellular carcinoma – HCV related liver cirrhosis – recurrence – direct antiviral drugs.

Abreviations: AFP: alpha-fetoprotein; DAA: direct antiviral agent; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HR: hazard ratio; IFN: interferon; LDV: Ledispavir; SMV: Simeprevir; SOF: Sofosbuvir; SVR: sustained virologic response.

INTRODUCTION

Hepatitis C virus (HCV) infects approximately 180 million people and is not only one of the leading causes of mortality worldwide, but also one of the major causes of hepatocellular carcinoma (HCC) [1]. This is the major type of liver cancer and the second leading cause of cancer mortality worldwide [2]. Tremendous efforts have been made in the last decades in order to decrease HCV incidence, but also HCV related complications, including HCC.

Until recently, interferon (IFN) based regimens have been the cornerstone of anti-HCV therapy, yielding HCV cures or sustained virologic response (SVR) in approximately 50% of patients [3]. Interestingly, the achievement of SVR in the IFN era has greatly reduced the incidence of HCC [4]. Unfortunately, the efficacy and safety of this treatment are suboptimal mainly due to the treatment failures, patients' intolerance or ineligibility.

In the last couple of years, the innovation of direct antiviral agents (DAAs) has removed some of these obstacles. There is now clear evidence of the benefits of DAAs therapy with high cure rates (>90%) of HCV for most patients` groups, as well as high acceptability by patients and providers [5]. Indeed, DAAs therapy is still in its infancy and intermediate and long-term outcomes are missing. However, some early data have appeared and the results seem to be more than promising. It has been suggested that the administration of DAAs may decrease liver stiffness after short-term observations [6]. Moreover, HCV eradication in the era of IFN-free has also been shown to reduce the hepatic venous pressure gradient in cirrhotic patients with portal hypertension. In respect to these findings, the HCV treatment has the potential to significantly change HCV-related

cirrhosis and its complications in the next decades. Few would have dreamed of such a highly potent weapon 20 years ago.

As more and more data becomes available, some authors observed that DAAs therapy might favor HCC occurrence or recurrence. Although these initial assumptions were not confirmed in subsequent studies, they raise some serious concerns. Another issue regards the affordability in resource-constraining areas, as an unexpected huge budget impact has resulted in wealthier countries [7]. This can affect the approval of DAAs for HCV infected patients with HCC, but also preclude therapy of patients with other cancers or HCV-associated malignancies (e.g., non-Hodgkin lymphomas) in resource-constraining areas. It took more than one decade for researchers, clinicians and other caregivers to prove the long-term outcomes of IFN-based therapies. Before such long-term survival benefits in the era of IFN-free become available, the hot issue nowadays in hepatology is related to the impact of DAAs therapy on HCC occurrence among chronic hepatitis C (CHC) patients or on recurrence after curative HCC treatment. This issue should be settled as soon as possible because millions of hepatitis C patients are and will be using DAAs. Our purpose is to review the existing literature and to offer a more precise and rational interpretation of the existing data. As far as we know, such a review has not been published before.

THE IMPACT OF IFN-BASED REGIMENS ON HCC OCCURRENCE

The IFN-based regimens were approved for the treatment of CHC a few decades ago, and there is enough data on long-term outcomes after therapy. Several studies have shown a potential benefit of IFN therapy in HCC prevention. An earlier multicenter study [8] conducted in Japan enrolled 2,890 CHC patients of whom 2,400 were treated with IFN and 490 left untreated. Hepatocellular carcinoma developed in 89 IFN-treated patients and in 59 untreated patients. Among untreated patients, the annual incidence of HCC increased with the degree of liver fibrosis, from 0.5% among patients with stage F0 or F1 fibrosis to 7.9% among patients with stage F4 fibrosis. The cumulative incidence in treated and untreated patients differed significantly for patients with stage F2 fibrosis ($p = 0.0128$) and for those with stage F3 fibrosis ($p = 0.0011$).

A more recent prospective study by Bruno et al., with a median follow-up of 9.6 years, evaluated only patients with HCV-related cirrhosis [9]. In the intention-to-treat analysis they included 1,368 patients with cirrhosis of whom 572 were untreated and 769 treated with IFN-based regimens (615 without SVR and 181 with SVR). Although the study did not focus on HCC occurrence but on HCV-related complications, they confirmed that SVR is associated with lower, but not negligible, risk of HCC occurrence. The study mainly focused on treated vs. non-treated patients with CHC.

Having as a primary outcome the HCC incidence in patients with SVR compared to those without SVR, a study from Asia included 33,005 patients treated with IFN/Peg-IFN with or without ribavirin. In 22,197 of them (10,738 with SVR and 11,290 without) a SVR could be documented. An annual HCC incidence rate of 3.27 per 1,000 persons-years (0.327%) was observed in the SVR group compared to 1.32 per 100 persons-years in the non SVR group; the unadjusted HR was 0.49 (95% CI, 0.46-0.53) for SVR versus non-SVR. The highest HCC risk was associated with the presence of cirrhosis, diabetes, older age, and genotype 3 [10].

Yoshida et al. [11] conducted an interesting study based on several assumptions using hypothetical extrapolation. The lifetime risk for HCC was calculated based on HCC incidence rates, stratified by sex, age, fibrosis stage, and outcome of IFN therapy. Besides a lower incidence of HCC in SVR patients compared to non-SVR and untreated patients, the study concluded that the gain in HCC free survival was greater when a patient was younger and fibrosis was more advanced. Patients with fibrosis stage F3 or F4 and younger than 50 years would gain more than 10 years with SVR [11].

There is solid ground for supporting the role of IFN therapy in HCC prevention. Irrespective of the type of IFN regimen, whether we talk about western or non-western countries, the benefits are real. Together with SVR, age and fibrosis are constantly associated with the risk of HCC occurrence.

THE IMPACT OF IFN-FREE REGIMENS ON HCC OCCURRENCE

Compared to IFN-based therapies, there is less evidence about the impact of DAAs therapy on HCC occurrence. In contrast to earlier reports in the IFN era, some observational studies reported a high incidence of HCC after viral clearance in the IFN-free era. Among the first published, the study conducted by Conti et al. [12] reported a high incidence of 3.2% after 24 weeks of follow-up. The first thoughts are to consider the above mentioned results as high; however, this was a retrospective monocentric study without a control group. The same authors (unpublished data) found a cumulative HCC occurrence rate of 3.2% at 1 year in an untreated historic population. Based only on this study, we can conclude that HCC occurrence remained probably higher than most expected, but there is definitely no increased risk. In another study, Cardoso et al. [13] reported a higher occurrence, of 7.4%. There was no significant difference in the baseline variables that could be associated with an increased risk of HCC [13]. A Letter to the Editor evidenced an incidence in the HCC rate of 6.6% [14].

In contrast to these initial findings, more adequately conducted studies on a higher scale found different results. Based on a longer follow-up and a larger cohort, Lawitz et al. [15] reported a risk of HCC at week 96 of 0.3% (16/5,433) in patients with CHC achieving SVR and 0.9% (5/536) in patients without SVR after the first DAA regimen. Notably, this study included also patients without cirrhosis, which might explain the low risk of HCC [15]. Based on these findings it would be inappropriate to even consider a higher occurrence of HCC in the era of IFN-free. Similar to these findings, a study from Spain, which included only patients with CHC and advanced fibrosis (F3/F4) reported an HCC incidence of 2.4% [16]. Prospective studies comparing treated vs. untreated patients seem to be unethical. However, in a prospective study from England, the investigators showed a reduction in liver cancer rates from 4% in 261 untreated patients over 6 months to 1.9% over 9 months after achieving viral clearance in 317 successfully treated patients [17]. A study from Scotland demonstrated

that the risk of HCC following SVR relates to the baseline risk factors and not to the use of DAAs [18].

Based on all this data we can conclude that there is no evidence of increased HCC occurrence in the IFN-free era. Moreover, compared to untreated patients, it seems to be a protective effect. We were all overwhelmed and enthusiastic by the development of innovative treatment in HCV with very high rates of SVR, and we probably expected the same results in terms of a markedly decreased HCC incidence. Unfortunately, the risk of HCC did not vanish and until further evidence, it probably will not decrease either, basically because of the presence of advanced fibrosis and advanced age.

THE IMPACT OF IFN COMPARED TO IFN-FREE BASED REGIMENS ON HCC OCCURRENCE

A wise judgment is required when comparing therapeutic strategies from different decades. A study from Japan reported that the incidence of HCC after SVR was 3.01% in patients who achieved SVR with IFN-based therapy, and 6.23% in patients who achieved SVR with IFN-free therapy [19]. In the same study, the patients who achieved SVR with IFN-free therapy were older and had higher pretreatment serum AFP, higher FIB-4 index, and lower platelet count than patients who achieved SVR with IFN-based therapy ($p < 0.0001$ for all). In a matched cohort analysis, the cumulative HCC rate was not different in patients treated with IFN and ribavirin and those treated with DAAs (log-rank test, $p=0.26$). Moreover, the multivariate Cox regression showed that the risk of developing HCC did not differ by the treatment group (Hazard Ratio [HR] = 0.67, $p = 0.56$), after adjustment for age, sex and baseline cirrhosis status [20]. Even when AFP values were significantly higher and the number of patients with advanced fibrosis (Fibroscan® >12.5 kPa or FibroTest® >0.75) was significantly increased in the Ledipasvir/Sofosbuvir (LDV/SOF) group compared with the PegIFN/RBV/Simeprevir group, a multicenter RCT found that the HCC incidence improved after only a 12-week LDV/SOF regimen to a similar degree as achieved with PegIFN/RBV/SMV [21]. In the IFN era there was strong evidence that patients with SVR had a decreased incidence of HCC. A group from Italy found similar results with DAAs therapy [22]. The studies that reported the incidence of HCC after DAAs therapies are highlighted in Table I.

As already mentioned, comparing DAAs therapy with IFN-based regimens is inappropriate. Patients treated with DAAs are older, with more advanced fibrosis and more likely to have decompensated cirrhosis. All the above studies used historical cohorts when comparing the two types of treatment. Patients from historical cohorts were treated mainly in the last decades. We had different imaging tools back then. The advances in ultrasound, CT or MRI in the last decades might also explain the initial reports of an increased risk of HCC with DAAs therapy. Based on these studies, there is clearly no evidence

Table I. Hepatocellular carcinoma (HCC) occurrence rate: summary of the published studies.

Author, year, reference	Country	Fibrosis stage (F4 %)	Total number, male sex (%)	Age median, (range) years	Follow-up Median years	HCC Incidence (%)	Comments	Risk factors	Study design
Conti 2016 [12]	Italy	F4 100%	207 (60.2)	63 (29-85)	0.5	3.1	No control group Single center study	Child-Pugh Class B, liver fibrosis low platelet	Retrospective
Cardoso 2016 [13]	Portugal	F4 100%	54 (70)	59 (41-81)	1	7.4	No control group, letter to the Editor	none	Retrospective
Kozbial 2016 [14]	Austria	F4 100%	16 (68.75)	62(48-72)	NA	6.6	No control groupl letter to the editor	NA	Retrospective
Lawitz 2016 [15]	United States	F4 20%	5433 (62.7)	54 (9.9)	1.7	0.3	No control group Only 20% were with cirrhosis	NA	Prospective
Nunez 2016 [16]	Spain	F3 13.8% F4 86.2%	339 (63)	58 (30-82)	1.35	2.4	No control group	NA	Retrospective
Cheung 2016 [17]	United Kingdom	F4 100% (Child B/C)	406	54 (28-79)	1.5	5.4	HCC incidence in non-SVR and untreated patients were 11.2 and 4.2%	NA	Prospective
Toyoda 2016 [19]	Japan	F4 37.7%	413 NA	NA		6.23	In patients treated with IFN: HCC incidence 3.01	Age, AFP value, FIB-4 index, low platelet count	Retrospective
Ji D. 2017 [20]	China	F4 48%	165 NA	NA	1.4	NA	Similar HCC occurrence rate in patients treated with DAAs and IFN		Prospective
Calvaruso 2017 [22]	Italy	F4 74.9%	3447 (58)	64.3	0.85	1.48	Incidence of HCC in non-SVR 4%	NA	Prospective

NA: not available

for an increased risk of HCC. Surely, the risk of HCC persists and performing screening is mandatory, despite curing HCV infection, especially in patients with advanced fibrosis (F3/F4).

HCC RECURRENCE IN TWO DIFFERENT ERAS: IFN BASED VERSUS IFN-FREE REGIMENS

Among the curative treatments, liver transplantation has limitations (graft availability, selection criteria, cost) and resection or local tumor ablations techniques are burdened by a 50% recurrence rate at 3 years [23, 24]. The potential benefits of IFN in preventing HCC recurrence after curative treatments have been suggested. A RCT evaluated 30 patients (15 patients treated with IFN-α and 15 patients in the control arm) with HCV-related HCC after curative resection. The recurrence rate was significantly lower in the IFN-α group than in the control group [25]. Another RCT included a total of 74 patients with HCV-related HCC treated by tumor ablation, 49 treated with IFN and 25 without treatment. The survival rate was higher in patients treated with IFN both at 5 years (68% vs. 48%) and 7 years (53% vs. 23%) [26].

All these RCTs were performed in Asia; however, similar findings have been reported also in Western countries. Mazzaferro et al. [27], on the subgroup analysis of single HCCs < 3 cm found out that the risk of HCC recurrence was significantly lower in the IFN-treated group with respect to the control group at both intention-to-treat and per-protocol analysis. Moreover, a more recent meta-analysis that included 7 RCT studies showed that IFN treatment significantly reduced the risk of tumor recurrence with a pooled risk ratio of 0.86 (95% CI 0.76 to 0.97) [28]. Irrespective of the IFN regimen used, of the geographical region and of the type of curative HCC treatment, albeit relatively small, prevention of HCC by IFN has been reported to be significant.

Contrary to IFN regimens, the new antiviral drugs permitted the achievement of SVR rates in over 90% of treated patients, irrespective of the liver fibrosis stage and moreover, were well tolerated [5]. Not surprisingly, such results have raised the hope of a drastic decline in HCC recurrence in those patients who experienced liver cancer in the past, and went through effective surgical or ablative treatment of the neoplastic lesions. The first two studies that evaluated the impact of DAAs therapy on the HCC recurrence after curative treatments showed the opposite results. The first one, conducted in Spain, by Reig et al., reported a high recurrence rate of 27.6% after a median follow-up of only 5.7 months [29]. There was no recurrence in those treated with TACE and when compared to a contemporary ablation. cohort for small HCC (unpublished data) the actuarial probability of recurrence was 2.45% at 4 months and 27.6% at 12 months. The other study showed similar results with a recurrence rate of 28.8% [12]. The first study has been seriously criticized by other researchers [30-32]. For instance, one article criticized the too heterogeneous treatment types, including both palliative and curative therapies for HCC [30]. Moreover, the investigators did not clearly specify whether all patients experienced complete remission of their cancer before being deemed disease-free prior to starting surveillance scans [30]. Other authors criticized the interval between HCC treatment and the initiation of DAAs, as being too long (median 11.2 months) [31]. An interesting study that evaluated the risk of HCC recurrence after liver transplantation showed a trend towards a higher risk of HCC recurrence compared to the risk of untreated patients [33].

Another recent study compared the outcomes of patients with HCV related cirrhosis and treated HCC (resection or ablation) after DAAs, IFN or no antiviral treatment (the last two from historical cohorts). The HCC recurrence free survival at 12 months was significantly higher in both DAAs and IFN group compared to the untreated [34].

A study from the ITA.LI.CA group performed an indirect comparison (from different studies) of tumor recurrence in patients with successfully treated early HCC and active HCV infection, which subsequently underwent either a successful (with SVR) IFN-based, IFN-free regimen or no antiviral treatment. The results showed that the SVR obtained by IFN-based or IFN-free regimens reduces tumor recurrence significantly without differences related to the antiviral strategy used [35].

The strongest evidence against a high risk of HCC recurrence comes from the ANRS collaborative study group on HCC [36]. This study included three different cohorts and further details of each cohort is highlighted in Table II. Moreover, three other letters to the editor and one poster presentation from AASLD 2017 meeting found no evidence of the increased risk of HCC recurrence [30, 31, 37, 38].

An interesting finding came from the Reig group [39]. After updating their cohort outcomes with more patients who were followed-up, the results not only confirmed their initial findings but also exposed a more aggressive pattern of recurrence and faster tumor evolution.

Based on these studies, we can draw a few early conclusions. All the initial studies reported a rather unexpectedly persistent high incidence of HCC after curative treatments and not a higher incidence. There is no evidence to support a high recurrence of HCC, but there is some evidence to state that DAAs therapy may reduce the risk of HCC recurrence compared with untreated patients. Whether there is any difference in HCC recurrence in the IFN era compared to IFN-free era, there is no clear evidence. Nowadays, a prospective comparison of outcomes on HCC prophylaxis of DAAs towards IFN-based therapy is no more conceivable, due to obvious ethical reasons. Although not increased, an early recurrence cannot be excluded. Whether DAAs therapy just shortens the time until recurrence in patients who otherwise would have developed recurrence anyway in their long course disease, is not known.

Regarding the more aggressive pattern of recurrence and faster tumor evolution reported in theory, this is a plausible finding. It is possible that small HCCs that are not visible by imaging techniques, after treatment with DAAs will act differently.

After DAAs therapy there is a change in the microenvironment, the cancer cells have learned to adapt to the new conditions, probably acquiring new mutations and in the end changing both the genotype and the phenotype. As many cancer cells change their phenotype after chemotherapy, could the same thing not be true for DAAs therapy?

Table II. Hepatocellular carcinoma (HCC) recurrence rate: summary of the published studies.

Author (year), reference	Country	Total number, male sex (%)	Age median, years	Follow-up Median years	HCC Recurrence (%)	Treatment For previous HC	Comments	Disease free time to initiating DAAs	Study design
Reig 2016 [29]	Spain	58 (69)	66.3	0.5	27.6	Resection, Ablation, TACE	43.8% of the recurrent HCC happened < 4 months between HCC treatment and last assessment of complete response	Median 11.2 months	Retrospective Multicentre
Conti 2016 [12]	Italy	59 (67.8)	72	0.5	28.8	Resection, Ablation, TACE	35.5% and 73% of the recurrent HCC happened within 1 and 2 years after primitive HCC treatment	Median 446 days	Retrospective Single center
Vukotic 2016 [34]	Italy	16 (72)	70	NA	NA	Resection, Ablation	HCC recurrence-free survival at 12 months was significantly higher in both DAAs and PegIFN groups compared to untreated (p = 0.009)	Median 9 months	Retrospective
Young 2016 [33]	United States	18 (NA)	NA	NA	27.8	LT	In untreated patients the HCC recurrence: 9.5% (p = 0.06)	NA	Retrospective
Petta 2017 [35]	Italy	58 (69)	66.3	1.5	26.3	Resection, Ablation	Time to recurrence was significantly lower in DAAs treated compared to untreated (p=0.02)	Median 11.2 months	Retrospective
ANRS Study group 2016 [36]	France	189 (78)	62	2.2	0.73/100 vs. 0.66/100 Person/ month	Resection, Ablation, LT	HCC recurrence did not differ from that of untreated controls (p=0.8)	Median 20.2 months	Prospective
ANRS Study group 2016 [36]	France	13 (85)	61	1.8	1.11/100 vs. 1.73/ 100 person/ month	Resection, Ablation	HCC recurrence did not differ from that of untreated controls (p = 0.38)	90 treated Person-Month	Prospective
ANRS Study group 2016 [36]	France	314 (82)	61	5.8	2.1	LT	No group control	NA	Prospective
Zeng 2016 [37]	China	10 (NA)	NA	1.5	0	Ablation	No group control	NA	Retrospective
Virlogeux 2017 [38]	France	227 (76)	62	NA	39	NA	In untreated patients HCC recurrence was 73% (p = 0.008)	Median 7.2 months	Retrospective

LT: liver transplant; NA: not available.

MOLECULAR MECHANISMS OF HCC OCCURRENCE OR RECURRENCE WITH DAAs THERAPY

Certainly, there is a difference in the kinetics of viral suppression between IFN-based and IFN-free regimens. Hepatitis C virus eradication occurs in the first days after therapy with DAAs and it takes longer for prior regimens. IFNs are known to exert an antiproliferative effect, have intrinsic effects on tumor by regulation of angiogenesis and moreover, can regulate the activity of almost all immune cell types, which instead induces a strong immune response against malignancy [40]. One of the first studies showed a rapid restoration of proliferative HCV-specific CD8+ T cells in the majority of the patients with SVR12 within 4 weeks of therapy, suggesting that IFN-free therapy mediated antigen removal may restore CD8+ T cell function [41]. Similar studies showed that the rapid decline of HCV viral load by DAAs was associated with restored HCV specific memory T cell dedifferentiation, lymphocyte deactivation and normalized natural killer cell function [42-44]. Mir-122, which plays a central role in orchestrating hepatocarcinogenesis was recently found to be decreased in serum samples after IFN-free therapy [45]. IFN-free therapy leads to the downregulation of type II and III IFNs, their receptors and IFN stimulated genes [46].

A very recent study has investigated the predictive role of the natural killer group 2 member D (NKG2D), an activating receptor for the MHC class I chain-related protein A/B (MICA/B) and other ligands [47]. NKG2D is a well known immunoreceptor with implications in activating the immune responses against both infected and transformed cells. The

results of the study showed that a higher pre-treatment NKG2D expression and a rapid decrease of NKG2D at the end of the treatment significantly correlate with early HCC emergence in the IFN-free DAA-treated patients [47].

Further insights into the molecular mechanisms might elucidate when is better to treat HCV infection with DAAs in patients who developed HCC: before or after the tumor curative treatment? One study found that SVR was significantly lower in patients with active HCC compared to those without HCC (79.1% [95%CI 74.4-83.1] vs. 93.1% [95%CI 92.6-93.5]) [48]. Similar results were confirmed by Prenner et al. [47, 49], who showed that the presence of active HCC had a negative impact on achieving SVR. Moreover, the failure to obtain a SVR after DAAs may predict the occurrence of HCC [47]. Based on these studies, due to a higher probability of achieving SVR, the patients with HCV related cirrhosis who developed HCC should be treated with DAAs after the tumor complete response has been achieved.

We do not have any biological explanation of these findings. It is possible that viral factors such as resistance-associated substitutions and quasispecies may differ in patients with HCC and contribute to treatment failure. More studies are required to clearly establish the molecular changes of DAAs therapy. Nonetheless, it would be crucial to identify the adequate laboratory or genetic biomarkers with a prognostic value that might help us to identify the patients at risk of HCC in the IFN-free era.

HCC SCREENING IN THE ERA OF IFN-FREE REGIMENS

Without doubt, screening for HCC should be performed despite the recent development of the innovative treatment for CHC. Particularly, elderly patients with advanced cirrhosis could benefit the most. There is no consensus on how to screen. There is no reliable data whether to use ultrasound alone or ultrasound and biomarkers (for instance AFP). Some may think to perform ultrasound every 3 months instead of 6-month intervals considering the low interval since DAAs treatment and HCC occurrence. There are no RCT studies investigating the cost-benefits of ultrasound every 3 months compared to 6 months' intervals. Others may think performing ultrasound earlier than at a 6-month interval is unsuitable, since there is a concern regarding a more aggressive and more advanced stage at the time of diagnosis. Maybe the best option, although not evidence based, is to perform ultrasound at 3-month intervals in the first year and at 6-months interval thereafter.

CONCLUSIONS

Although the initial reports were in favor of an increased risk of HCC occurrence or recurrence after DAAs, we now have strong evidence against this. Based on the above studies there is no increased risk of HCC occurrence or recurrence after DAAs treatment. Indeed, the era of IFN-free has just started and until intermediate and long-term data becomes available, many issues are not yet solved. We do not still know whether different regimens or different genotypes have an impact on HCC occurrence or recurrence. When is the optimal time to start DAAs therapy in patients with HCV related HCC: before or after tumor treatment? While in terms of HCC occurrence things seem to be clear, the risk of HCC recurrence needs to be better clarified. Randomized control trials are urgently required. Another interesting question is whether DAAs therapy in patients with previous HCC shortens the time to recurrence? Does IFN-free therapy change the phenotype of HCC into a more aggressive and faster development? Do we have enough weapons to deal with the recurrent HCC after DAAs therapy? We need patience, because we need more than one decade from now to understand the true benefits of IFN-free therapy. Time is a crucial variable that will hopefully answer all these questions in the future.

Conflicts of interest: No conflict to declare.

Authors' contribution: Z.S. and T.M. performed the literature review, the initial draft of the manuscript and the manuscript writing. Z.S. approved the final manuscript.

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