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Review Article

Recurrence of hepatocellular carcinoma after direct acting antiviral treatment for hepatitis C virus infection: Literature review and risk analysis

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ABSTRACT

Although studies suggest decreased incident hepatocellular carcinoma (HCC) after treatment with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection, data are conflicting regarding risk and aggressiveness of recurrence in patients who have a history of treated HCC. This review analyses data available in literature in order to elucidate the impact of DAAs on the risk of HCC recurrence after successful treatment of the tumor. Overall 24 papers were identified. The available data cannot be considered definitive, but the initial alarmist data indicating an increased risk of recurrence have not been confirmed by most subsequent studies. The suggested aggressive pattern (rapid growth and vascular invasion) of tumor recurrence after DAAs still remains to be confirmed. Several limitations of the available studies were highlighted, and should drive future researches. The time-to-recurrence should be computed since the last HCC treatment and results stratified for cirrhosis and sustained viral response. Any comparison with historical series is of limited interest because of a number of biases affecting these studies and differences between enrolled patients. Prospective intention-to-treat analyses will be probably the best contribution to drive clinical practice, provided that a randomized trial can be difficult to design.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death worldwide [1]. In the last decades, a growing incidence of HCC was observed in most developed countries, being hepatitis C virus (HCV)-related hepatitis one of the main determinant of this phenomenon [2]. The introduction of second-generation directly-acting antivirals (DAAs) has dramatically changed the scenario of HCV infection. DAAs can achieve sustained virological response (SVR) rates in a percentage

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of cases as high as 95–98% [3]. Their extensive adoption is expected to lead to a progressive decrease in HCV-related HCC, even if an initial cumulative increase of HCC incidence could be observed because of the lower risk of liver decompensation and the higher survival expectancy of cirrhotic patients with SVR [4,5].

Two contemporary retrospective studies have advanced the hypothesis that successful treatment with the new DAAs may be associated with higher incidence and recurrence rates of HCC [6,7]. Moreover, an unusual increase of infiltrating tumors has been reported by these authors. Subsequently, controversial data have been published and several biomolecular hypotheses have been suggested [8]. These findings have been object of debate and could have major implications in the management of HCC patients. An urgent clarification is needed to drive clinical practice.

This review analyses the data available in the literature in order to clarify the impact of DAAs on the risk of HCC recurrence after successful treatment of the tumor.

2. Methods

2.1. Literature search

A systematic search of PubMed, Science Citation Index, and Embase databases was performed for articles published between January 2014 and January 2018 (cut-off date February 1, 2018) relevant to recurrence of HCC after DAAs. English language articles were selected using the keywords 'hepatocellular carcinoma'; 'HCC'; 'HCV'; 'DAA/directly-acting antivirals' and 'recurrence' to identify all reports that may pertain to the review issue. Manual cross-referencing was performed; and relevant references from selected papers were reviewed. Case reports were excluded.

3. Results

3.1. Literature selection

Overall, 24 papers (with 25 cohorts of patients) [6,7,9–30] reporting on HCC recurrence after DAAs treatment in patients with previously and successfully treated HCC (liver resection, ablation or trans-catheter arterial chemoembolization — TACE) were identified. Two papers only considered patients with HCC recurrence [25,27], two included also patients who underwent liver transplantation before starting DAAs [16,29], and one focused on radiological features of recurrences [28]. The paper by Petta et al. [12] compared the risk of HCC recurrence in untreated patients with the risk in patients receiving DAAs, but the paper was excluded from the present analysis because the data for the latter group (DAAs) were obtained from the study by Reig et al. [6]. In 2016 Minami et al. reported a time-to-event analysis on a small cohort of patients (n = 27) [14], but they presented an updated series (n = 163) [31] at the American Association for the Study of Liver Disease (AASLD) meeting in 2017. Both these data were analyzed. Calleja et al. [9] and Bielen et al. [16] had been contacted by the authors to obtain additional data about their series. Finally, a paper summarizing the abstracts presented at the AASLD Liver Meeting 2017 about HCC recurrence in DAAs-treated patients was also included in the present review [32].

3.2. Recurrence risk

The number of patients included in the studies ranges between 3 and 189. Most patients had limited disease burden at baseline, i.e. single HCC (67–94% of cases) [10,13–15,23,26,27,29] <5 cm in size (range of median size 1.8–4.7 cm) [10,13–16,23,26,27,29] and Barcelona-Clinic Liver Cancer (BCLC) stage 0/A (61–100% of cases) [6,7,10,11,16,20,23,24,26,29]. The majority of patients underwent hepatic resection or percutaneous ablation. Only four studies exclusively considered patients undergoing radical treatment [14,15,18,26], whereas 14 papers also included patients undergoing TACE or radiation treatments [6,7,10,11,13,16,17,19–21,23,24,29,31] and 4 papers did not detail the initial HCC treatment [9,15,22,30].

Follow-up management after HCC treatment was rather homogeneous among studies (when detailed), being performed every 3–6 months using Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or ultrasonography [6,9–13,16,18,23,26,27,29].

The shortest time between last curative HCC treatment and DAAs initiation was of 0.5 months [14]. However, the mean/median time was highly variable, ranging from 2 to 21.5 months [6,7,9–11,13,15,16,19,21–23,25–27,29]. Three studies reported the median time between HCC diagnosis and DAAs treatment: 46.8 [31], 22.8 [15] and 9.6 [30] months, respectively. Five studies reported the median time between the last negative radiological assessment and DAAs therapy: 1.7 months in three studies, maximum 3 months in one and 14.4 months in one [6,11,15,19,26].

The mean/median follow-up after DAAs ranged between 3 and 21.6 months [6,7,11,14,15,17–22,26,29,31]. The proportion of HCC patients treated with DAAs that had a recurrence (i.e., number of events/number of patients at risk) was highly variable, ranging from 0% to 47.9% [6,7,9–11,13–17,19,21–24,29–31]. These values are not rates because they do not derive from time-to-event analyses.

The data of the analyzed studies are summarized in Table 1 and in Supplementary Table 1.

3.3. Time-to-event analyses

Sixteen papers from 15 study groups (Minami et al. published two series), including 17 cohorts of patients, performed a time-to-event analysis of HCC recurrence [6,9–11,13–15,17,18,20,21,23,24,26,29,31]. In two papers, this was not explicitly reported in the manuscript, but the data were extrapolated from the figures [24] or the tables [17]. Regarding the paper by Reig et al. [6], the time-to-event analysis performed by Cammà et al. was considered [33]. Finally, since Torres et al. collected less than 10 patients and did not report recurrences, their paper was not considered in the review of time-to-event data [21]. The results of time-to-event analyses are summarized in Table 2.

Two papers (including 3 patient cohorts) [15,23] reported the rate of HCC recurrence per 100 person-months ranging from 0.73 and 1.73. El Kassas et al. reported an adjusted rate (for time since HCC complete radiological response, sex, age, Child–Pugh score, and history of gastroesophageal varices) of HCC recurrence per 100 person-months of 3.82 after DAAs exposure [26].

Twelve study groups performed a Kaplan–Meyer analysis [6,9–11,13–15,17,18,20,23,24,31], and one paper performed a Poisson regression [26]. The time to recurrence was calculated in different ways: from the last HCC treatment in 8 papers [6,9,14,17,18,20,23,29], from the initiation of DAAs therapy in 9 papers [9–11,13,15,17,20,26,31] and from the end of DAAs therapy in one study [24]. In the last two groups, the mean/median time between the last HCC treatment and DAAs start ranged from 8 to 21 months.

Considering the HCC recurrence rate from the initiation of DAAs treatment, the following figures were reported: 9.6–23.0% at 6 months, 23.1–45.7% at 12 months, and 38.9–54.5% at 24 months. Of note, 4 studies reported the number of patients who developed HCC recurrence during the DAAs treatment [6,11,16,17].

Considering the time since the last HCC treatment, the recurrence rate was 0–7% at 6 months, 8.7–30% at one year and 27.9–42% at two years. We plotted the available curves of recurrence since the last HCC treatment in a single graph (Fig. 1). A recent meta-analysis by Cabibbo et al. [34] theoretically provided the benchmark for HCC

Table 1
Characteristics of the analyzed studies.

Author	Design	#	Cirrhosis N (%)	SVR N (%)	FU Protocol (months)	Interval last assessment of complete response — DAAs (median, months)	Interval last HCC treatment — DAAs (median, months)	Interval DAAs — recurrence (median, months)	Previous HCC treatment		Proportion of recurrences[e] N (%)
									Type	Single/multiple N (%)	
Reig et al. [6]	Retrospective	58	55 (94.8)	39/40 (97.5)[a]	6	1.7	11.2	3.5	Resection, ablation, TACE	NA	16 (27.6)
Calleja et al. [9]	Retrospective	70	55 (78.5)	66 (94.3)	6–9	NA	20[d]	6.7	NA	NA	21 (30)
Ikeda et al. [10]	Retrospective	177	NA	155 (89.6)	3–4	NA	10.7	20.7	Resection, ablation, TACE, PRT	89 (50.3)/88 (49.7)	61 (34.5)
Cabibbo et al. [11]	Prospective	143	143 (100)	138 (96)	3–6	1.7	NA	NA	Resection, ablation, TACE	101 (70.6)/42 (29.4)	29 (20.3)
Ogawa et al. [13]	Prospective	152	90 (59.2)	152 (100)	3–6	NA	14.4	NA	Resection, ablation, TACE, PRT	NA	26 (17.1)
Minami et al. [31]	Retrospective	163	NA	150 (92)	NA	NA	NA	NA	Resection, ablation, RT, TACE	65 (39.8)/98 (60.1)	78 (47.9)
Conti et al. [7]	Retrospective	59	59 (100)	53 (89.8)	NA	NA	12	NA	Resection, ablation, PEI, TACE	NA	17 (28.8)
Pol et al. ANRS — CO22 Hepater [15]	Prospective	189	152 (80)	148/161 (91.9)[a]	NA	14.4	NA	NA	NA	NA	24 (12.7)
Pol et al. ANRS — CO12 CirVir [15]	Prospective	13	13 (100)	8/8 (100)[a]	NA	NA	at least 3	37.1	Resection, ablation	13 (100)	1 (7.7)
Bielen et al. [16]	Retrospective	19	13 (81.2) 3 pts no data	15 (78.9)	6	NA	10[d] if resection 14[d] if ablation	21	Resection, ablation, TACE	NA	6 (31.6)
Shimizu et al. [17]	Retrospective	23	15 (65.2)	23 (100)	NA	NA	14	7.5	Resection, ablation, TACE, SBRT	NA	10 (43)
Nagata et al. [18]	Retrospective	83	NA	77 (92.7)	3–12	NA	NA	NA	Resection, ablation	83 (100)	22 (29)
Zavaglia et al. [19]	NA	31	31 (100)	26 (83.9)	NA	1.7	19.3	8	Resection, ablation, TACE	NA	1 (3.2)
Kolly et al. [20]	Prospective	47	40 (85.1)	NA	NA	NA	21.5[d]	9.6[d]	Resection, ablation, TACE	47 (100)	20 (42.6)
Torres et al. [21]	Prospective	8	7 (87.5)	6 (75)	NA	NA	7.5	–	Resection, ablation, Proton therapy	NA	0
Rinaldi et al. [22]	Prospective	15	15 (100)	NA	NA	NA	11.3[d]	3	NA	NA	1 (6.7)
Virlogeux et al. [23]	Retrospective	23	23 (100)	22 (95.6)	3–6	NA	7.2	13	Resection, ablation, TACE, RT	23 (100)	11 (47.8)
Cheung et al. [30]	Prospective	29	29 (100)	18 (62.1)	NA	NA	NA	NA	NA	NA	2 (6.9)
Ida et al. [24]	Retrospective	26	NA	26 (100)	NA	NA	4.2 if recurrence 21.2 if no rec.	NA	Resection, ablation, TACE	11 (42.3)/15 (57.7)	12 (46.2)
El kassas et al. [26]	Prospective	53	53 (100)	41 (77.4)	3–6	3	8	16	Resection, ablation	NA	20 (37.7)
Adhoute et al. [29]	Retrospective	22[b]	22 (100)	19 (86.4)	3–6	NA	12	NA	Resection, ablation, TACE, LT (n = 3)	NA	9 (40.9) 8/19 (42.1)[c]

PRT: particle radiation therapy, TACE: trans-arterial chemoembolization; PEI: percutaneous ethanol injection; LT: liver transplant.

[a] Considering patients that had already reached the 12-week follow-up period.

[b] Three patients had liver transplantation.

[c] Excluding the patients undergoing liver transplantation.

[d] Mean value.

[e] Number of event (recurrence)/number of patients at risk.

Table 2
Results of time-to-event analyses.

Author	N recurrences/100 p-months	Recurrence rates from last HCC treatment				Recurrence rates from DAAs start				Recurrence details
		6 months	12 months	18 months	24 months	6 months	12 months	18 months	24 months	
Reig et al. [6]	NA	7%	12.9%			NA				13 pts (81.3%) new intrahepatic lesion: 5 pts single HCC, 4 pts ≤3 HCC ≤3 cm, 1 pt multifocal HCC, 3 pts infiltrative pattern and/or extra-hepatic lesions 3 pts (18.7%): intrahepatic growth
Calleja et al.[9]	NA		30%			12.9%	30%			5/21 pts (23.8%) aggressive, untreatable recurrences
Ikeda et al. [10]	NA	NA				9.6%	30.1%		38.9%	13 pts (76.5%) single HCC 4 (23.5%) 2–3 HCC 0% >3 HCC or with macroscopic vascular invasion
Cabibbo et al. [11]	NA	NA				12%	26.6%	29.1%		62% BCLC A; 21% BCLC B; 7% BCLC C; 10% BCLC D
Ogawa et al. [13]	NA	NA				1-yr in non-cirrhotic: 6.5% 1-yr cirrhotic: 23.1%				28 pts intrahepatic growth, 24 pts nodular pattern, 5 pts infiltrative pattern, 1 pt macrovascular invasion NA
Minami et al. [14,31]	NA		21.1%		29.8%		38%		54.5%	1/78 pt (1.3%) extrahepatic recurrence
Pol et al. ANRS — CO22 Hepater [15]	0.73	NA				1-yr: ≈10%[b]				NA
Pol et al. ANRS — CO12 CirVir [15]	1.11	NA				NA				NA
Shimizu et al. [17]	NA	0%	8.7%	23.1%	27.9%	17.4%	45.7%	52.4%	52.4%	NA
Nagata et al. [18]	NA	5-yr: 45.1% 3-yr SVR: 22.9%; 3-yr no-SVR: 40%				NA				NA
Kolly et al. [20]	NA	4%	19%		42%	23%	42%			NA
Virlogeux et al. [23]	1.7	≈6%[b]	≈13%[b]	≈26%[b]	≈31%[b]	NA				NA
Ida et al. [24]	NA	NA				≈20[b,c]	≈35%[b,c]			5 pts (42%) BCLC 0; 6 pts (50%) BCLC A; 1 pt (8%) BCLC C (vascular invasion)
El kassas et al. [26]	4.06[a]	NA				NA				95% of pts new site of recurrence 30% of pts >3 HCC
Adhoute et al. [29]	NA	Time to progression: 12 months				NA				BCLC A: 44%; B 22%; C 33%

NA: not available.
[a] Adjusted for covariates.
[b] Data derived from the article's figure.
[c] The authors reported recurrence-free survival computed since the end of DAAs treatment.

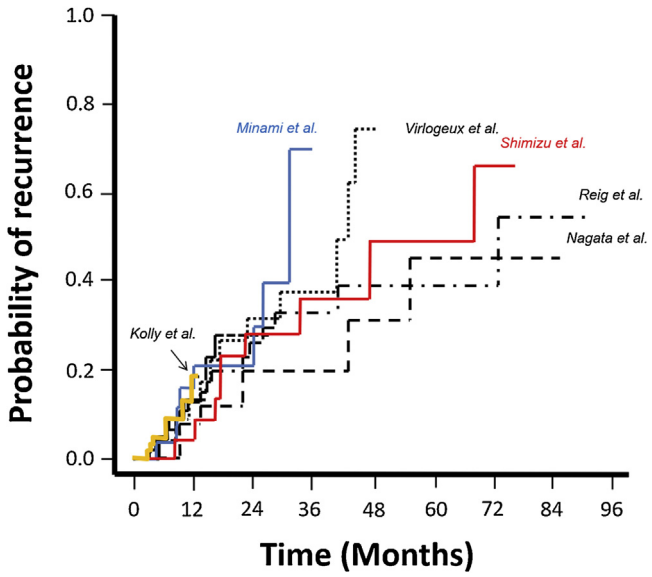

Fig. 1. The curves of HCC recurrence rates since the last HCC treatment of six different cohorts of patients treated with DAAs [6,14,17,18,20,23] have been plotted in a single graph. All the curves available in the literature have been included.

recurrence rate after curative treatments in patients with active HCV infection. However, any comparison between historical data of HCC recurrence in untreated HCV patients and the present data of HCC recurrence after DAAs-treated patients is impossible. First, the series after DAAs are affected by an "immortal time" bias [35], i.e. in the DAAs group only patients without recurrence at the time of this treatment were considered. Further, patients receiving DAAs have high heterogeneity in terms of interval HCC treatment-DAAs, and type and number of treatments of HCC before DAAs.

Nevertheless, some data about recurrence after DAAs deserve consideration. Interestingly, the one-year recurrence rate was significantly and inversely associated with the proportion of SVR achieved ($p = 0.008$, Fig. 2a): the one year after the HCC treatment. An association was also observed for cirrhosis: the higher the proportion of cirrhotic patients, the higher the one-year recurrence rate ($p = 0.285$, Fig. 2b).

3.4. Comparative analyses

Nine studies (10 cohorts of patients) compared the risk for HCC recurrence of DAAs treated patients with the risk in other populations [10–12,14,15,23,26,29]. Before considering the results of these studies, the same cautionary note reported for survival analyses is mandatory. All comparisons of DAAs patients with historical series have poor reliability because the DAAs group is affected by an "immortal time" bias [35] and include heterogeneous patients (wide range of interval HCC treatment-DAA, mixed radical and non-radical treatments for HCC, and combination of first and iterative recurrences). In six studies the DAAs-treated patients were compared with untreated patients [10,11,15,23,26,29]. Of these, only one paper [25] reported a higher recurrence rate in the DAAs group, while 3 papers (4 cohorts) reported similar figures [11,15,29] and 2 reported a low recurrence risk in DAAs patients [10,23]. Intriguingly, one paper reported a similar recurrence rate between patients receiving interferon (IFN)-based and IFN-free treatments [18]. Two studies compared the 3 arms (DAAs, IFN-based treatment and untreated patients): one showed similar recurrence rates [14]; the second observed a significant reduction of tumor recurrences in successfully treated patients, without differences between IFN-based or IFN-free regimens groups [12].

Considering the studies presented at the AASLD meeting in 2017, 14 abstracts analyzed the data of 5346 patients [32]. The risk for HCC recurrence in DAAs treated cases was unchanged in 8 studies (in comparison with untreated patients in 7 studies and with patients treated with IFN in one study) and was reduced in 3 (in comparison with untreated patients in 2 studies and with patients treated with IFN in one study).

In summary, only one paper reported an increased risk of HCC recurrence in patients treated with DAAs compared to untreated ones [26], and none reported an increased risk in patients treated with DAAs in comparison with those treated with IFN. The results of comparative studies are summarized in Fig. 3.

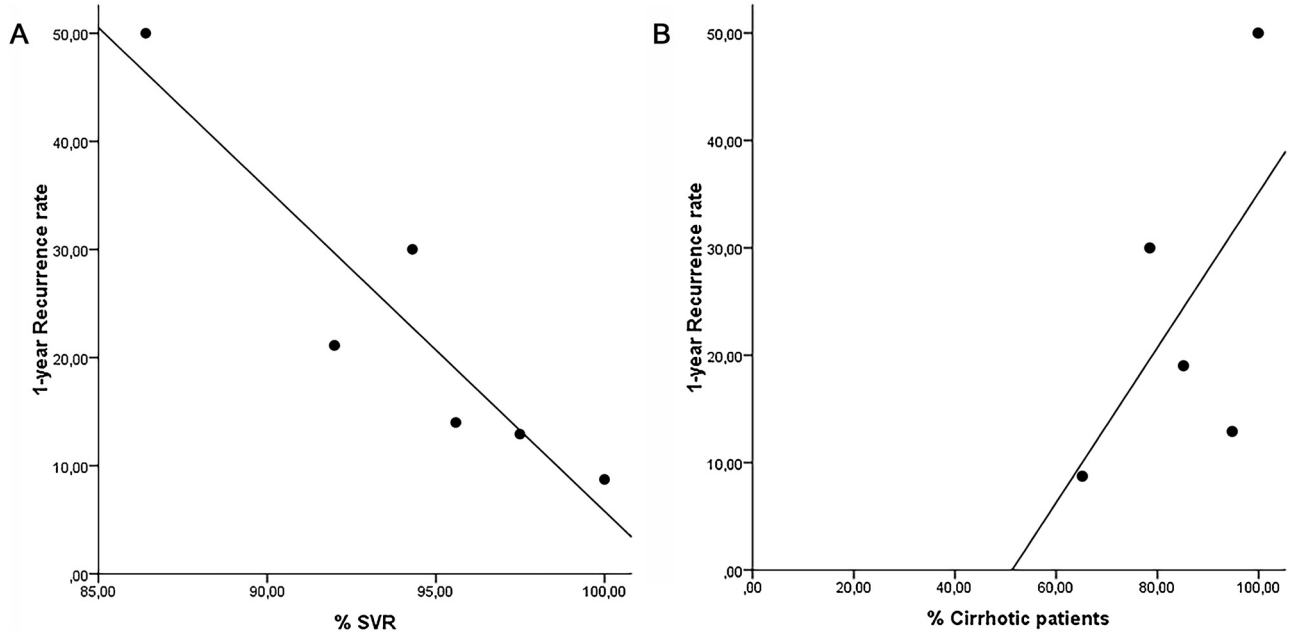

Fig. 2. The HCC recurrence rates one year after the DAAs administration reported in the literature have been considered. Their association with the proportion of SVR achieved after DAAs and the proportion of cirrhotic patients included in the cohorts have been analyzed. (a) An inverse association between the one-year recurrence rate and the proportion of SVR achieved after DAAs. (b) A direct association between the one-year recurrence rate and the proportion of cirrhotic patients included in the cohorts.

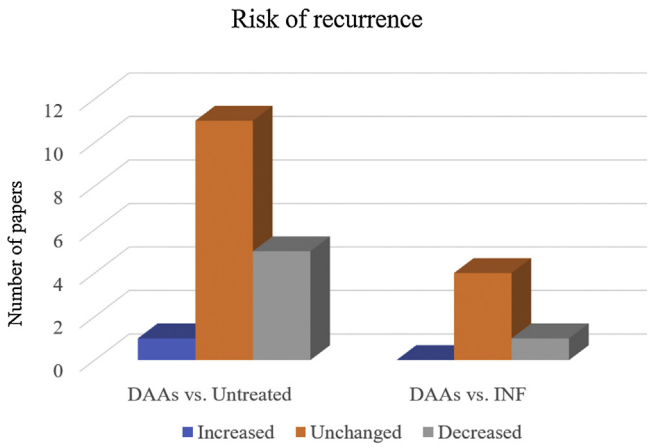

Fig. 3. The results of studies analysing the risk of HCC recurrence in patients treated with DAAs in comparison with the risk of HCC recurrence in untreated patients or in patients receiving INF are summarized. The number of papers showing an increased, unchanged or decreased recurrence risk in the DAAs group vs. the no-treatment group (left part of the figure) or vs. the INF group (right part) is shown.

3.5. Predictors of recurrence

Twelve studies analyzed the predictors of HCC recurrence in DAAs treated patients [6,7,10,11,13,17,18,20,23,26,29,31]. One additional paper analyzing predictors of recurrence was not considered because it included patients undergoing liver transplantation [16].

The SVR rate was one of the most commonly analyzed parameter. Its prevalence ranged between 62% and 100%. Nagata et al. [18] reported that the cumulative incidence of HCC recurrence in patients who achieved SVR was much lower than in those without SVR (at 3 years, 22.9% vs. 40.0%; p = 0.022), but this difference was not confirmed by other authors [10,11,26]. Nevertheless, as reported above, in the present review we observed a significant and inverse association between the SVR rate and one-year recurrence risk (Fig. 2a), supporting the data of Nagata et al. [18].

The time between the last HCC treatment and DAAs start has been identified as a predictor of recurrence by 5 authors, i.e. the shorter the time, the higher the risk of recurrence [6,13,20,29,31].

Ogawa et al. [13] reported a higher recurrence risk (Hazard Ratio — HR 2.31 95% CI 1.04–5.15, p = 0.041) when non-curative treatments (trans-arterial therapy/radiotherapy) were adopted; the highest risk was observed when the time between HCC treatment and DAAs initiation was <1 year. Although it may be questioned whether TACE can be considered potentially curative, other studies did not confirm its association with HCC recurrence in patients treated with DAAs [6,7,10,20,23].

Interestingly, 4 authors [10,11,13,31] observed that patients who underwent more than one HCC treatment before DAAs initiation had a higher recurrence rate than those treated only once (in the study by Ikeda et al. 50% vs 19.1%). In agreement, Cabibbo et al. [11] reported a hazard ratio of 2.22 (95% CI 1.02–4.83, p = 0.043) for post-DAAs recurrence in patients with clinical history of prior HCC recurrence as compared to patients without prior HCC recurrence).

The following additional predictors of HCC recurrence were reported: tumor size 11, liver cirrhosis 13, liver stiffness 7, patient's age 7, 20, serum alpha-fetoprotein-L3 (AFP-L3) 31 and Des-gamma-Carboxy Prothrombin (DCP) [31], anti-HBc [17], and Wisteria floribunda agglutinin positive Mac-2 binding protein (WFA^+M2BP) [18].

3.6. Aggressiveness of recurrences

Some authors speculated about a major aggressiveness of the recurrent tumor in DAAs treated patients [6,10,11,26–28]. However, it should be noted that a definition of HCC aggressiveness does not exist in literature, or at least an agreement on its definition has not been reached as yet.

Although most recurring tumor were diagnosed in BCLC stage 0 or A [6,11,16,20,22–24,26,29], the authors identified as signs of HCC aggressiveness the following factors: fast tumor growth with a low response rate to ablation [27], percentage of infiltrative [6,11] or multifocal [26] tumor pattern, and radiological signs of microvascular invasion (mVI) [28]. Specifically, Renzulli et al. [28] compared the prevalence of radiological features predictive of mVI in HCC recurring after DAAs therapy and in tumors diagnosed before DAA treatment in the same patients. They showed that mVI was present in 70.7% of nodules recurred after DAAs treatment, a significantly higher proportion with respect to HCC detected before DAAs (33.3%, p = 0.0007). This difference was confirmed even in the case of small nodules with a diameter between 10 and 20 mm. El Kassas et al. [26] observed that 30% of patients with a recurrent HCC after DAAs exposure had more than three nodules vs. 18% in the DAAs non-exposed population with recurrence, but the limited sample size did not allow to clarify whether or not this difference was significant.

Considering the studies presented at the AASLD meeting in 2017, three reported an aggressive pattern of recurrence after DAAs treatment and three noticed a rapid HCC recurrence [32]. However, a case-control study did not confirm these data because the pattern of recurrence was similar in patients with and without exposure to DAAs [29].

Recently, Critelli et al. [36] studied, although in a non-DAAs related contest, molecular characteristics of the HCC aggressiveness, showing that growth speed and outcome of HCC are associated to specific molecular signatures of neo-angiogenesis, to prominent features of epithelial-mesenchymal transition with extremely poor cell differentiation, to clear-cut activation of transforming growth factor-beta 1 (TGF-β1) signaling and to the finding of programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) overexpression as sign of severe microenvironment immunosuppression [36]. Moreover, in a preliminary previous and prospective study [37], the same authors reported that 25% of new HCCs diagnosed under surveillance have a very rapid growth with a doubling volume time <2 months, regardless of initial BCLC classification. This fast-growing subgroup of patients can be biologically characterized very accurately by a 5-gene transcriptomic hepatic signature including angiopoietin-2 (ANGPT2), delta-like ligand 4 (DLL4), neuropilin (NRP)/tolloid (TLL)-like 2 (NETO2), endothelial cell-specific molecule-1 (ESM1), and nuclear receptor subfamily 4, group A, member 1 (NR4A1). This gene signature was associated with a worse prognosis (median survival of 11 vs 41 months).

On this basis, some hypotheses have been suggested to explain the potential aggressiveness in the DAAs contest. It has been assumed that a major role is played by a downregulation of the anti-tumor response by the immune system caused by the brutal DAAs-induced HCV clearance, which could boost the growth of invisible foci of malignant cells [6,27]. It is well known that recurrence after a complete response to ablative treatment may be due to dissemination of cells before the treatment and to the appearance of new oncogenic clones within the underlying cirrhotic liver from already committed cells with genetic damage [38]. In fact, the viral clearance causes rapid downregulation of IFN stimulating genes (ISGs) in the liver and blood. The observed immunological changes include a down-regulation of antigen-specific T cells, with a restoration of proliferative HCV-specific $CD8^+$ T cells after 12 weeks of DAA therapy in most SVR patients [39], and a decline of IFN-inducible protein-10 (IP-10), monocyte chemoattractant protein 1, macrophage inflammatory protein 1 beta and IL-18 levels [40–42]. In contrast to the recovery of virus-specific $CD8^+$ T cells and natural killer (NK) cells, DAAs therapy in HCV patients is not

followed by a restoration of the mucosal-associated invariant T (MAIT) cells [43]. Moreover, during DAAs therapy NK cells, which mediate target-cell apoptosis through surface expression of TNF-related apoptosis-inducing ligand (TRAIL), show a decrease in TRAIL expression [44,45].

According to this "immune escape hypothesis", it can be inferred that, once HCV infection is cleared, small tumors already present but not radiologically evident might accelerate their growth. Nonetheless, it is very difficult to prove whether this mechanism is a major cause of the supposed greater aggressiveness of HCC recurrence.

Finally, Carr and Guerra [46] developed an HCC aggressiveness index, based on tumor diameter, multifocality, portal vein invasion and alpha-fetoprotein levels, which was able to stratify patients in 3 groups with different survival. To date, no paper reporting a potential major aggressiveness of HCC recurrence after DAAs adopted either the Carr and coll. index or homogeneous and validated criteria to define the tumor aggressiveness. A prospective study aimed to evaluate the recurrence pattern and the outcome of patients with recurrent HCC exposed or not to DAAs treatment seems to be the only way to solve this debate and reach an agreement about the reliable definition of HCC aggressiveness.

3.7. Management of recurrences

Treatment of recurring HCCs included different approaches across studies. Ida et al. [24] used curative treatments (liver resection or radiofrequency ablation) in almost all cases of recurrence, while in the cohort from Cabibbo et al. [11] TACE was the most common treatment (45%). In the study by Abdelaziz et al. [27] chemoembolization was adopted in 51.1% of cases, whereas local ablation and resection were used in a minority of cases (8.9% and 4.4%, respectively). Disease control was achieved in about half of cases (51.1%), while in one third of patients (33.3%) only supportive treatment was possible. Similarly, in the studies by Reig et al. [6] and Calleja et al. [9] 18.7% (3/16) and 23.8% (5/21) of patients, respectively, were qualified for supportive care. Conversely a higher percentage of untreatable recurrence was reported by Bielen et al. [16] (50%).

3.8. Limitations of the available studies

Several limitations of the analyzed studies should be considered. First, only 8 studies (including 9 cohorts of patients) had a prospective design [11,13,15,20–22,26,30], 6 of them including a time-to-event analysis. In addition, few papers collected an adequate number of patients (>50 patients in 10 papers and >100 in 5) to provide reliable information.

Second, the interval between HCC treatment and DAAs therapy, which has a crucial importance in setting the risk of tumor recurrence, was extremely variable. In fact, the recurrence curve obtained by a meta-analysis of the untreated harms of studies about HCV-patients undergoing curative treatment for HCC showed a parabolic shape, with the maximal risk rate over the first years [34]. Consequently, considering the timing of DAAs initiation, at least 3 different temporal scenarios with a different "intrinsic" risk can be identified (Fig. 4):

- HCC recurrence in patients exposed to DAAs within the first 3 years after successfully treated HCC (high risk of recurrence with a rate of 22/100 py);
- HCC recurrence in patients exposed to DAAs between 3 and 5 years after successfully treated HCC (intermediate risk of recurrence with a rate of 8/100 py);

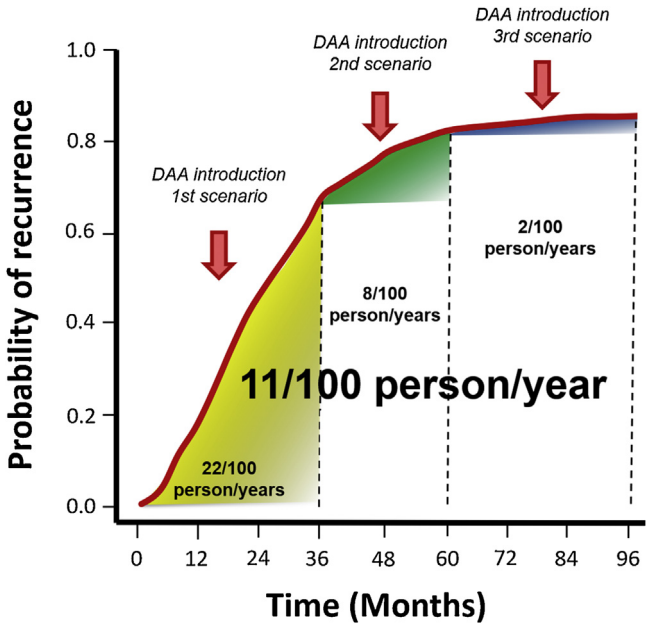

Fig. 4. The HCC cumulative recurrence rate after curative treatment for HCC in HCV-patients without DAAs treatment is extracted from a recent meta-analysis (red curve) [34]. It has a parabolic shape, with the maximal recurrence risk over the first years. Consequently, at least 3 different temporal scenarios with a different "intrinsic" risk of HCC recurrence can be identified according to the timing of DAAs introduction: (1) HCC recurrence risk in patients with the introduction of DAAs during the first 3 years is high (22/100 p/y, yellow area); (2) HCC recurrence risk in patients with the introduction of DAAs between 3 and 5 years is intermediate (8/100 p/y, green area); (3) HCC recurrence in patients with the introduction of DAAs after 5 years is low (2/100 p/y, blue area). The overall number of recurrence/100 person/year of untreated HCV infection have been derived from the meta-analysis by Cabibbo et al. [34].

- HCC recurrence in patients exposed to DAAs 5 years after successfully treated HCC (low risk of recurrence with a rate of 2/100 py).

Therefore, the time to HCC recurrence should be calculated considering the last HCC curative treatment as the starting point. The alarmist data about high recurrence rates in DAAs treated patients could be simply related to the fact that DAAs were initiated in most patients during the period of highest recurrence risk.

Third, 14 papers included both patients receiving potentially curative treatments (surgery and ablation) and palliative treatments (chemoembolization and radiation treatments) before DAAs therapy [6,7,10,11,13,16,17,19–21,23,24,29,31]. Four papers included patients with multiple HCC treatments [10,11,24,31], while 13 papers did not detail the number of HCC treatments received before DAAs [6,7,9,13,15–17,19,21,22,26,29,30], making it difficult to provide solid evidence on the effect of DAAs therapy on the individual risk.

Fourth, two main determinants of HCC recurrence should be always considered, i.e. liver cirrhosis and SVR. As we found in this review, both these parameters may impact recurrence risk. The variability of the reported recurrence rate may be therefore ascribed, at least in part, to the different proportion of cirrhotic patients included in the studies (range 59.2%–100%), which was detailed in 16 papers (with 17 cohorts of patients) [6,7,9,11,13,15–17,19–23,24,26,29,30], and of the SVR rate observed (range 62%–100%), which was reported in all but two papers [20,22]. Unfortunately, only few studies [10,11,13,18,20,26] stratified the recurrence rate according to the presence of cirrhosis and/or the achievement of SVR.

Finally, any comparative analysis between DAAs group and historical series suffers from at least one major limitation, i.e. the "immortal time" bias [35]. In fact, in the DAAs group only patients

without recurrence at the time of this treatment were considered. A prospective intention-to-treat analysis, starting from the time of HCC cure and with an early DAAs initiation is therefore mandatory to know the real risk of cancer recurrence in patient undergoing antiviral treatment.

4. Discussion

The potential risks and benefits of DAA therapy in patients with a history of HCC are still a matter of debate. Some authors suggested a reduction of the recurrence risk in comparison to patients with untreated HCV infection, although these conclusions must be interpreted in the context of the clinical heterogeneity within and between studies and methodological limitations of current data. However, all these indirect comparisons with historical data suffer from biases favoring (immortal bias) or disfavoring (analyses not considering the time elapsed between HCC cure and initiation of the therapy) DAAs treated patients with respect to those untreated or treated with IFN. Moreover, the patients may differ in term of the previous oncologic history and proportion of cirrhotic cases.

Patients with a history of HCC are at risk for recurrence that can be related to intrinsic tumor factors and underlined liver disease such as active viremia and degree of liver function [47]. It has been hypothesized that the HCV eradication induced by DAAs results in reduced immune surveillance dysregulating the anti-tumor response and boosting the growth of still undetected microscopic HCC tumor clones [6,27]. On the other hand successful antiviral treatment can result in fibrosis regression and improvements in portal hypertension and liver function, shown to be the major driver of death in patients with successfully treated HCC and active HCV infection [48]. In this context, DAAs may reduce risk of HCC recurrence by HCV eradication and liver function improvement [49].

The identification of factors evaluating the risk of HCC recurrence is mandatory to define patients subgroups in whom DAA therapy should be avoided. Several predictors for recurrence were reported in literature, like the history of prior HCC recurrence and the interval between HCC successful treatment and DAA initiation, with longer intervals being associated with lower risk of HCC recurrence because of a lower risk that residual tumor cells are still present at the DAA initiation. In this direction, some authors suggested to delay and defer DAA treatment till there is a well-established complete radiological response, reducing in this way the chance of misclassification bias [50,51].

An aggressive pattern (rapid growth and vascular invasion) of tumor recurrence after DAAs has been pointed out, but still remains to be confirmed. Most patients with HCC recurrence across studies were found at an early stage and underwent curative treatments, suggesting recurrence following DAA therapy is not aggressive; however, few data regarding treatment response or post-recurrence long-term prognosis are available. Considering the poor evidences against DAAs and the clear benefits in terms of liver function in case of SVR, the choice of treating these patients with antiviral drugs seems to be justified.

The limitations of the available studies should drive future researches and avoid the pitfalls of several already published studies. First, time-to-event analyses are mandatory. Based on the "immune escape" hypothesis, the impact of DAAs therapy on tumor recurrence justifies the relationship between the onset of recurrence and the time elapsed since the last curative treatment. Therefore, it is advisable to calculate the time to recurrence considering the last HCC curative treatment as starting point. Further, it sounds logical to consider an interval period between the radiological evidence of HCC eradication and the start of DAAs to exclude the presence of "prevalent" tumors, even if an agreement about the adequate duration of this time interval is lacking.

Second, the proportion of cirrhotic patients and the percentage of SVR should be considered to properly interpret the data. The crucial contribution of these two factors to the risk of recurrence, even after DAAs, strengthens the hypothesis that DAAs treatment is irrelevant (or even protective from recurrence, according to some studies) in the natural history of HCC.

Finally, any comparison with historical series is of limited interest because of a number of biases affecting these studies and differences between enrolled patients. Prospective intention-to-treat analyses will be probably the best contribution to drive clinical practice, provided that a randomized trial can be difficult to design.

5. Conclusions

The available data about the risk of HCC recurrence after DAAs treatment in HCV patients cannot be considered definitive, but the initial alarmist data indicating an increased risk of recurrence have not been confirmed by most subsequent studies. Nonetheless, since there are no clear evidences of a detrimental effect of DAAs on HCC recurrence, we believe that DAAs should not be denied to these patients, as well as, it is mandatory to maintain an active surveillance for HCC.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.08.001.

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