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**Systematic Review with Meta-Analysis: Recurrence of Hepatocellular Carcinoma
Following Direct Acting Antiviral Therapy**

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Neema Saraiya was involved in acquisition of data, interpretation of data, and critical revision of manuscript for important intellectual content.

Adam Yopp was involved in interpretation of data and critical revision of manuscript for important intellectual content.

Nicole Rich was involved in interpretation of data and critical revision of manuscript for important intellectual content.

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Neehar Parikh was involved in interpretation of data and critical revision of manuscript for important intellectual content.

Amit G. Singal was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript for important intellectual content, and study supervision. He is the guarantor of the article.

All authors approved the final version of the manuscript.

Abbreviations: AFP – alpha fetoprotein; BCLC - Barcelona Clinic Liver Cancer; CT - computed tomography; DAA – Direct acting antiviral; HCC - hepatocellular carcinoma; HCV – hepatitis C virus; MRI – magnetic resonance imaging; RESICT – response evaluation criteria in solid tumors; TACE - transarterial chemoembolization

ABSTRACT

Background: Although studies suggest decreased incident hepatocellular carcinoma (HCC) after direct-acting antivirals (DAA), data are conflicting regarding HCC recurrence and aggressiveness in patients who have a history of HCC with complete response.

Aim: Characterize HCC recurrence patterns after DAA therapy.

Methods: Two reviewers searched MEDLINE and SCOPUS from January 2015 to December 2017 and identified studies evaluating HCC recurrence patterns following DAA therapy. A pooled estimate was calculated using the DerSimonian and Laird method for a random effects model. The study was conducted in accordance with PRISMA guidelines.

Results: Among 24 studies (n=1820 patients), the proportion of patients with HCC recurrence following DAA therapy ranged from 0% to 59% (pooled estimate 24.4%; 95%CI 18.4 – 30.4%). Among 11 full text manuscripts, pooled HCC recurrence was 21.9% (95%CI 16.2% – 28.3%). Factors associated with recurrence included history of prior HCC recurrence and a shorter interval between HCC complete response and DAA initiation. Nine studies comparing DAA-treated and interferon-treated or untreated patients found similar recurrence among DAA-treated patients. Most (77.8%) patients with HCC recurrence were detected at an early tumor stage, of whom 64.7% received curative treatment. Study limitations included heterogeneous cohorts, potential misclassification of HCC absence prior to DAA, ascertainment bias for recurrence, and short durations of follow-up.

Conclusion: Current data suggest acceptable HCC recurrence rates after DAA therapy, particularly if DAA therapy is delayed at least 6 months after HCC complete response. However, data characterizing HCC recurrence after DAA therapy are of limited quality, highlighting the need for high-quality prospective studies.

Keywords: liver cancer, hepatitis C, recurrence, direct acting antiviral therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, with chronic hepatitis C (HCV) being the most common underlying etiology in the United States and Europe.¹ Liver transplantation, surgical resection, and local ablative therapy are potentially curative and associated with excellent long-term survival but are limited by tumor recurrence exceeding 50% at 5 years.²

Prior attempts at adjuvant pharmacologic therapy for HCC have failed to improve survival or reduce recurrence, with the exception of anti-viral therapy.³ Interferon-based therapy was associated with a significant reduction in HCC incidence in patients with HCV-related cirrhosis as well as HCC recurrence after curative therapy.⁴ The mechanism for reduction in HCC recurrence is unclear – whether related to sustained viral response (SVR) or direct interferon-related immune-mediated antitumor effect.⁵ This debate has become more relevant with the introduction of direct acting antiviral (DAA) therapy, which has replaced interferon-based therapy for HCV.⁶ Although studies have demonstrated improvements in fibrosis and

portal hypertension as well as decreased risk of incident HCC in patients with HCV-related cirrhosis, some observational studies suggest an *increased* risk and aggressiveness of HCC recurrence after DAA therapy.⁷⁻¹⁰

This issue remains a topic of debate, leading to uncertainty if or when to treat HCV-infected patients with a history of HCC.^{11, 12} These data have created fear among patients receiving DAA therapy and prompted some providers to withhold HCV treatment from patients with a history of HCC. The European Medicine Agency's Pharmacovigilance Risk Assessment Committee has required high quality data evaluating this association. Given the lack of randomized data evaluating this association, we are forced to rely on cohort studies and indirect comparisons across studies. The aim of this systematic review is to characterize HCC recurrence patterns following DAA-based therapy.

METHODS

Literature search and Study Selection

We searched MEDLINE and SCOPUS databases from January 1, 2015 through December 1, 2017 using search terms: (liver ca\$ or hepatocellular ca\$ or hcc or hepatoma) and (hepatitis C or HCV) and (interferon-free or direct-acting antiviral or DAA). We also manually searched abstracts from the 2016 and 2017 American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and International Liver Cancer Association annual conferences. Additional studies that may have been missed by the electronic search were identified through manual searching of reference lists from applicable studies and consultation with experts in the field. If the applicability of an article could not be determined by title or abstract alone, the full text was reviewed. Articles and abstracts were independently evaluated for possible inclusion by two authors (N.S. and A.S.) and any uncertainties were resolved through discussion with another reviewer (N.P.). The study was conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.¹³

Studies were included for analysis if they evaluated HCC recurrence after DAA therapy in a cohort of patients with chronic HCV infection and a history of HCC with complete response. We included studies with complete response from surgical, local ablative, or locoregional therapies; however, we excluded cohorts focusing exclusively on post-transplant HCC recurrence and studies that included interferon-based regimens in combination with DAAs. Complete response in studies was typically defined using modified Response Evaluation Criteria in Solid Tumors (mRECIST), i.e. disappearance of arterial enhancement in all HCC

lesions. Studies may have been retrospective or prospective but were required to report the proportion of patients with recurrence after DAA therapy. Additional exclusion criteria included 1) non-English language, 2) non-human data, and 3) lack of original data. If publications reported data using the same cohort of patients, the study with more complete data was included.

Data extraction

Two authors (N.S. and A.S.) independently reviewed and extracted required information from eligible studies using standardized forms. A third investigator (N.P.) was available to resolve any discrepancies between the sets of extracted data. The data extraction form included the following study design items: geographical location and date of study, study design (prospective vs. retrospective), characteristics and size of study cohort, inclusion and exclusion criteria, HCC treatment regimen, median time from HCC treatment to DAA treatment, and duration of follow-up. In addition, the extraction form recorded the following primary data: proportion of patients with HCC recurrence and patterns of recurrence (i.e. tumor burden and HCC-directed treatment). Two authors (N.S. and A.S.) independently assessed study quality using a modified checklist based upon a modified version of the Newcastle-Ottawa quality assessment scale, with discrepancies resolved by consensus.¹⁴ Studies with less than one year of follow-up or loss to follow-up exceeding 5% were regarded as high risk of bias.

Statistical analysis

The aim of this study was to characterize HCC recurrence patterns after DAA therapy. For each individual study, the proportion of patients with HCC recurrence with 95% confidence intervals was calculated. Estimates of effect were pooled using a binomial-normal model and the DerSimonian and Laird method for a random effects model. Heterogeneity was initially evaluated graphically by examination of forest plots and statistically by the inconsistency index (I^2), with values $>50\%$ consistent with the possibility of substantial heterogeneity.¹⁵ Subgroup analyses were planned for HCC detection for predefined subsets of studies based on (i) prospective vs. retrospective study design, (ii) study location, (iii) duration of follow-up (iv) timing of DAA initiation, and (v) availability of full text manuscripts. We assessed for presence of heterogeneity between subgroups, with statistical significance defined as $p < 0.05$. We also performed a subgroup analysis among studies reporting early HCC recurrence after DAA initiation. We performed univariate and multivariate meta-regression analyses to evaluate the potential association between study-level covariates (study location, study design, sample size,

proportion of patients with early HCC, timing of DAA initiation, and length of follow-up) and HCC recurrence. A secondary analysis among studies reporting relative recurrence rates between DAA-treated and untreated patients, in which we determined a pooled estimate for the relative risk of recurrence using a random effects model. Publication bias was initially evaluated graphically by funnel plot analysis. Analyses were performed using STATA 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Literature search

Upon review of the 827 titles identified by the search strategy, 63 abstracts were further examined. Twenty-three publications underwent full-text review to determine their eligibility for the meta-analysis and four were excluded. The remaining 16 studies were selected after meeting all applicable inclusion criteria. Overall, 20 studies were excluded because they presented data on HCC occurrence but not recurrence, 11 had insufficient data for abstraction, 5 had overlapping cohorts, 4 exclusively characterized post-transplant HCC recurrence, and 7 studies were excluded for lack of original data (**Supplemental Figure**). Finally, review of American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and International Liver Cancer Association conference abstracts identified 7 additional studies and recursive literature searches identified 1 full-length manuscript and 2 letters to the editor that met inclusion criteria, producing a total of 26 studies.¹⁶⁻³⁹ The study by the ANRS collaborative study group included two distinct cohorts,²⁴ yielding a total of 27 cohorts. Two included studies reported relative HCC recurrence rates compared to interferon-treated or untreated patients but did not report absolute HCC recurrence rates,^{41,42} yielding 24 studies with 25 cohorts characterizing the primary outcome of absolute HCC recurrence rates after DAA initiation.

Study Characteristics

Characteristics of the 24 studies (i.e. 25 cohorts) reporting the absolute proportion of patients with HCC recurrence after DAA therapy are described in **Table 1**. The majority of cohorts were retrospective (n=19) and only available as abstracts or letters to the editor (n=14). Thirteen cohorts were conducted in Europe, ten in Asia, and two in the United States. Studies included a total of 1820 DAA-treated patients, although most cohorts (n=19) included less than 100 patients, resulting in imprecise estimates for HCC recurrence with wide confidence intervals. Most patients had achieved HCC complete response after resection or ablation;

however, 25-50% of patients in some studies had received non-curative therapies including transarterial chemoembolization (TACE). Duration of follow-up to assess recurrence ranged from 3 to 36 months, although some studies defined recurrence from date of HCC treatment and others evaluated recurrence from date of DAA initiation. Although most studies only included single-arm cohorts, 7 of the studies included a comparator arm of interferon-treated and/or untreated patients. Two additional studies did not report the absolute proportion of patients with HCC recurrence but compared relative recurrence between DAA-treated patients and interferon-treated or untreated patients, yielding a total of 9 comparative studies (**Table 2**).

HCC Recurrence following DAA Therapy

The pooled point estimate for HCC recurrence following DAA therapy was 25.1% (95%CI 19.4 – 31.2%); however, there was significant statistical heterogeneity ($I^2 = 86\%$) (**Figure 1**). The proportion of patients with HCC recurrence varied widely between studies, ranging from 0% to 59% within 2 years (**Table 1**). In subgroup analyses, pooled estimates for HCC recurrence were similar between prospective and retrospective cohort studies (23.9% vs. 25.6%, $p=0.76$), studies with duration of follow-up shorter or longer than 12 months (21.9% vs. 27.6%, $p=0.29$), and studies in which HCC recurrence was assessed starting at DAA initiation vs. other times (24.6% vs. 26.0%, $p=0.84$). However, HCC recurrence was higher in studies conducted in the United States compared to Europe and Asia (43.3% vs. 22.1% vs. 28.9%, $p<0.001$). There continued to be significant heterogeneity, with I^2 values remaining greater than 70%, in all subgroup analyses. Among the 11 studies with data regarding “early” recurrence, the proportion with recurrence within 6 months ranged from 5% - 29%, with a pooled proportion of 10.3% (95%CI 6.3 – 14.4%; $I^2 = 49\%$).

Among the 11 studies available as a full text manuscript, the pooled HCC recurrence rate was 21.9% (95%CI 16.2% - 28.3%), although there continued to be statistical heterogeneity with $I^2 >75\%$. In subgroup analyses, pooled estimates for HCC recurrence were similar between prospective and retrospective cohort studies (18.6% vs. 22.9%), studies with duration of follow-up shorter or longer than 12 months (22.6% vs. 22.0%), studies in which HCC recurrence was assessed starting at DAA initiation vs. other times (22.7% vs. 21.1%), and studies conducted in Europe and Asia (20.1% vs. 25.7%). There was no association between HCC recurrence and study location, study design, sample size, the proportion of patients with early HCC, median time from HCC treatment to DAA initiation, or median length of follow-up in meta-regression analyses.

The most commonly reported factor associated with increased recurrence within included studies was the interval between HCC complete response and DAA initiation. Reig and colleagues found higher recurrence (41% vs. 23%) in patients treated within 4 months of HCC complete response,²¹ whereas Ogawa reported this association using a cut-off of 1 year (HR 0.31, 95%CI 0.10 – 0.77),²⁰ and Minimi et al using a cut-off of 2 years (HR 0.34).⁴⁰ Similarly, Kolly et al found patients with a longer timeframe between HCC treatment and DAA therapy had significantly lower hazards of recurrence (HR 0.91, 95%CI 0.85 – 0.96).³¹ A history of prior HCC recurrence was also associated with increased risk of HCC recurrence following DAA therapy (HR 2.2-2.3), as reported by Minami, Cabibbo, and Ikeda.^{17, 18, 40} Although many studies reported no difference in HCC recurrence by classic risk factors including degree of liver dysfunction, tumor burden, or alpha fetoprotein (AFP) levels, each was found to be associated with higher recurrence in one study. Conti described higher recurrence in those with increased liver stiffness (OR 1.19, 95%CI 1.01 – 1.39),²³ Ogawa and Cabibbo found higher recurrence in those with a history of multifocal HCC (HR 2.34, 95%CI 1.05 – 5.39)²⁰ and larger HCC lesions (HR 2.73, 95%CI 1.23 – 6.06)¹⁷ respectively, Minami reported higher recurrence in those with AFP-L3 > 15% (HR 3.08) or DCP > 40 mAU/mL (HR 2.0),⁴⁰ and Ogawa found higher recurrence in patients who underwent non-curative procedures such as TACE (HR 2.31, 95%CI 1.04 – 5.15).²⁰

Nine studies compared HCC recurrence in DAA-treated (n=947) patients to interferon-treated (n=210) and/or untreated (n=641) patients (**Table 2**).^{22, 24, 30, 32, 34, 37, 41, 42} Five studies reported no significant difference in HCC recurrence between DAA-treated and untreated patients in multivariable analyses, while two studies found significantly lower HCC recurrence among DAA-treated patients. Among the five studies reporting relative risk of recurrence with 95% confidence intervals, DAA-treated patients had a lower pooled recurrence risk than untreated patients (OR 0.55, 95%CI 0.25 – 0.85). All three studies comparing DAA-treated and interferon-treated patients reported no difference in HCC recurrence between the two groups; however, only unadjusted analyses were reported.

HCC Recurrence Patterns

Patterns of HCC recurrence including tumor burden and HCC-directed treatment after DAA therapy are detailed in **Table 3**. The majority of patients (77.8%, 95%CI 72.9-82.1) with HCC recurrence across studies were detected at an early stage, and two-thirds of those found at an early stage (64.7%, 95%CI 57.9-71.2) received curative treatment with liver transplant, resection or ablation. Only three studies described response to HCC therapy.^{18, 21, 37} Reig and

colleagues reported that 32% of patients had tumor progression within 6 months of recurrence,²¹ whereas Singal et al reported 17% had progressive disease after HCC-directed therapy³⁷ and Ikeda et al observed rapid tumor progression in only 5% of patients.¹⁸

Quality Assessment

Quality assessment of included studies is provided in **Table 4**. Most studies had appropriate representativeness of the cohort and exposure ascertainment. There was heterogeneity in cohorts with several studies including patients with non-early stage HCC, high AFP levels, multiple prior HCC recurrences, or treatment with locoregional therapies who are all at higher risk of HCC recurrence than their counterparts. There was also heterogeneity in the length of time between HCC complete response and DAA initiation, which is associated with risk of HCC recurrence. Whereas some studies required patients to have HCC complete response for at least 3-6 months, other studies included patients who were treated immediately after HCC-directed treatment. Most studies ascertained HCC recurrence through medical records but only 7 excluded patients with any suspicious nodules prior to DAA initiation and only 5 included prospective surveillance protocols. There were an additional 11 studies that explicitly stated they required documented absence of HCC (but not suspicious nodules) on imaging prior to DAA initiation, and 8 retrospective studies reported a recommended surveillance protocol after HCC complete response but were regarded as medium risk of bias given potential for underuse of surveillance in clinical practice. Seven studies did not explicitly state they excluded HCC prior to DAA initiation and 12 studies did not describe their surveillance protocol after HCC complete response so were regarded as having a high risk of bias. Most studies had short follow-up periods less than one year as well as high (>10%) or unknown loss to follow-up. Although comparative studies performed multivariable or propensity-score matched analyses, there were remaining issues with confounders including degree of liver dysfunction and immortal time bias.

DISCUSSION

There is ongoing uncertainty about the potential risks and benefits of DAA therapy in patients with a history of HCC. In this comprehensive systematic review, we found a pooled estimate of 24.4% for HCC recurrence after DAA therapy, although this point estimate must be interpreted in the context of its wide confidence intervals, clinical heterogeneity within and between studies, and methodological limitations of current data. While there are few comparative studies with interferon-treated or untreated patients, these data suggest DAA-treated patients have similar if not lower recurrence than interferon-treated or untreated

patients. 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 characterized treatment response or post-recurrence prognosis. Current studies have notable limitations including risk for misclassification of HCC complete response prior to DAA initiation and ascertainment bias, precluding definitive conclusions about the risk of HCC recurrence and highlighting the need for higher quality data.

Providers and patients must weigh the potential for increased early HCC recurrence against demonstrated long-term benefits of DAA therapy. Patients treated for HCC are at risk for both early and late recurrence, with early recurrence typically related to intrinsic tumor factors, while late recurrence is associated with cirrhosis-related factors such as active viremia and degree of liver dysfunction.^{43 44} It has been hypothesized that rapid decrease in HCV viral load with DAAs results in decreased immune surveillance of microscopic HCC tumor clones and hence an increased risk of early HCC recurrence.^{21 45} Conversely, as seen with interferon-based therapies, successful treatment with DAAs can result in fibrosis regression and improvements in portal hypertension and liver dysfunction, shown to be the major driver of death in patients with HCC complete response and untreated HCV infection.⁴⁶ Further, DAA therapy may reduce risk of late HCC recurrence, by decreasing HCV viremia and improving liver function.^{10, 47} Unfortunately, current studies are limited by short durations of follow-up, precluding adequate characterization of early vs. late recurrence, highlighting a need for studies with longer durations of follow-up.

Identifying predictors for increased early recurrence may identify subgroups in whom DAA therapy should be avoided. Few predictors for early recurrence were consistently reported except history of prior HCC recurrence and the interval between HCC complete response and DAA initiation, with shorter intervals being associated with higher risk of recurrence. Delaying DAA therapy may allow for longer duration of immune surveillance of existing microscopic HCC clones. Delaying DAA treatment can also create a longer time to verify HCC complete response, thereby minimizing the chance of misclassification bias. The sensitivity of one-time CT or MRI for small HCC lesions is low, with sensitivities of only 40-50% for subcentimeter lesions and 60-70% for 1-2 cm lesions.⁴⁸ Given the lack of urgency for HCV therapy after HCC complete response, it appears prudent to wait at least 6 months after HCC complete response to initiate DAA therapy, which would typically allow for 2-3 interim multi-phase CT or MRI scans to confirm durable HCC response.

Notably, most studies to date are single-arm, retrospective cohort studies with clinical heterogeneity in tumor burden, HCC treatments leading to complete response, and follow-up

periods. When interpreting the proportion of patients with HCC recurrence in these single arm studies, it is important to consider the natural history of HCC after complete response, in which many patients will have HCC recurrence independent of DAA therapy. HCC recurrence after complete response can vary substantially depending on which HCC-directed treatment received. While surgical resection and local ablative therapies are considered curative, recurrence rates approach 25-35% within the first year and 50-60% within 2 years.^{44, 49, 50} Further, up to 25-50% of patients in some studies received TACE, which is typically not curative and associated with a high risk of recurrence.⁵¹ Further, patients with high-risk tumor characteristics (e.g. multifocal HCC or elevated AFP) have higher recurrence rates than their counterparts; however specific data regarding these risk factors and subgroup analyses were not reported in many studies

In addition to concerns about clinical heterogeneity within study populations, we noted potential for misclassification and ascertainment biases. Several studies did not exclude patients with suspicious nodules prior to DAA treatment or included patients with HCC complete response for short periods of time. Therefore, it is likely some patients already had recurrent HCC at the time of DAA initiation, which would lead to an overestimation of post-DAA HCC recurrence. On the other hand, most studies did not include a standardized surveillance protocol to assess for HCC recurrence. Prior studies have demonstrated underuse of HCC surveillance in patients with cirrhosis and the same issue may plague post-treatment patients, leading to an underestimation of post-DAA recurrence.^{52, 53} These limitations highlight the need for high-quality prospective studies with strict inclusion criteria and a standardized surveillance protocol. Although comparative studies suggest recurrence rates among DAA-treated patients may be similar to interferon-treated and untreated patients, these analyses are limited by potential for confounders such as degree liver dysfunction. These studies can also be limited by immortal time bias, as patients with early recurrence would typically not receive DAA treatment and therefore would be over-represented in the untreated group. Given the high prevalence of limitations in study design, we propose minimum criteria for future studies in this area (**Table 5**).

A prior systematic review comparing HCC occurrence and recurrence following interferon-and DAA-based therapy only included 10 studies characterizing recurrence after DAA therapy,⁵⁴ whereas we identified 26 studies – including several recent prospective studies. Waziry and colleagues also included cohorts evaluating post-transplant recurrence, but we excluded these studies given post-transplant recurrence could be driven by a different mechanism. Finally, our study also characterized patterns of HCC recurrence and highlighted

limitations of available data, which informed our recommendations for minimum reporting criteria.

Although our study provides a comprehensive summary of current literature, limitations of available data hindered our ability to make strong conclusions about the potential association between DAA therapy and HCC recurrence. In fact, only three studies did not have high risk of bias for at least one category of the Newcastle-Ottawa quality assessment scale. There was also significant heterogeneity between studies, including different patient selection criteria, timing of DAA therapy, and durations of follow-up. Second, an individual-level meta-analysis would be more powerful, but we did not have patient-level data to perform subgroup analyses by degree of tumor burden, type of HCC treatment, or time between HCC complete response and DAA initiation. Given most data were obtained from small single-center cohorts, included studies may suffer from reporting bias. Factors associated with recurrence were based on descriptive review of included studies, with differential reporting and meta-analysis of these factors was not possible. In addition, we excluded non-English studies due to practical considerations, which may further bias the results.

In summary, there are conflicting data about the potential for increased HCC recurrence after DAA therapy; however most studies have methodological limitations. Ongoing multi-center retrospective and prospective studies should provide some insight into this controversial issue; we highlighted some suggested minimum reporting requirements to avoid the pitfalls of current studies. While awaiting these data, it is likely prudent to wait at least 6 months after HCC complete response before initiating DAA therapy.

FIGURE LEGENDS

Figure 1. Proportion of patients with recurrence of hepatocellular carcinoma following direct-acting antiviral therapy

Supplemental Figure. Map of literature search and study selection

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Table 1. Characteristics of studies reporting HCC recurrence rates after DAA therapy

Author Year	Study location	Study Design	Number DAA-HCC patients (% early)	AFP level prior to HCC treatment	Type of HCC treatment	Time from HCC treat to DAA	Follow-up Start	Follow-up Period	Recurrence (95% CI)
Bielen 2017 ^{16*}	Belgium	Retrospective	41 (83%)	46 ± 70	Transplant 51% Resection 24% Ablation 22% TACE 3%	12 months	End of DAA treatment	32 months	14.6 (5.6 – 29.2)
Cabibbo 2017 ^{17*}	Italy	Prospective	143 (100%)	18 ± 26	Resection 36% Ablation 46% TACE 18%	11 months	Start of DAA treatment	8.7 months	20.3 14.0 - 27.8
Ikeda 2017 ^{18*}	Japan	Retrospective	177 (NR)	17 (2 – 4730)	Resection 31% Ablation 46% TACE 20% Radiation 3%	10.7 months	Start of DAA treatment	20.7 months	34.6 27.9 - 41.7
Nagata 2017 ^{19*}	Japan	Retrospective	83 (100%)	NR	Resection or ablation	NR	HCC treatment	27.6 months	27.1 18.2 – 36.9
Ogawa 2017 ^{20*}	Japan	Prospective	152	7	Resection 40%	14.4 months	Start of DAA	17 months	17.5

			(95%)	(5 – 16)	Ablation 32% TACE 15% Multimodal 12% Radiation 1%		treatment		(11.9-23.9)
Reig 2017 ^{21*}	Spain	Retrospective	77 (97%)	10 (1 - 369)	Resection 36% Ablation 53% TACE 10%	11.2 months	Start of DAA treatment	8.2 months	27.3 (17.7 - 38.6)
Virlogeux 2017 ^{22*}	France	Retrospective	23 (91%)	13 (2 - 170)	Resection 26% Ablation 61% Other 13%	7.1 months	Start of DAA treatment	35.7 months	47.8 (26.8 - 69.4)
Conti 2016 ^{23*}	Italy	Retrospective	59 (98%)	NR	Resection 32% Ablation 41% TACE 8% Multimodal 17%	12.4 months	End of DAA treatment	5.5 months	28.8 (17.8 - 42.1)
ANRS 2016 ^{24*}	France	Retrospective	189 (NR)	NR	NR	NR	Start of DAA treatment	20.2 months	12.7 (8.3 - 18.3)
ANRS 2016 ^{24*}	France	Retrospective	13 (NR)	NR	NR	>3 months	Start of DAA treatment	21.3 months	7.6 (0.2 - 36.0)

Rinaldi 2016 ^{25*}	Italy	Retrospective	15 (100%)	NR	Resection 14% Ablation 86%	11.3 months	Start of DAA treatment	2.8 months	6.7 (0.2 - 32.0)
Zavaglia 2017 ²⁶	Italy	Retrospective	31 (84%)	10 (2 - 278)	Resection 42% Ablation 19% TACE 13% Multimodal 26%	19.3 months	Start of DAA treatment	8 months	3.2 (0 - 16.7)
Zeng 2016 ²⁷	China	Retrospective	10 (100%)	NR	Ablation 100%	NR	End of DAA Treatment	15 months	0 (0 - 25.9)
Torres 2016 ²⁸	USA	Prospective	8 (NR)	51 (6 - 7258)	Resection 50% Ablation 38% Proton therapy 12%	7.5 months	Start of DAA treatment	12 months	0 (0 - 31.2)
Gheoghe 2017 ²⁹	Romania	Retrospective	20 (NR)	NR	NR	NR	DAA treatment	6 months	20.0 (5.7 - 43.7)
Granata 2017 ³⁰	Italy	Prospective	65 (83%)	NR	NR	9 months	Start of DAA treatment	18 months	27.7 (17.3 - 40.2)
Kolly 2017 ³¹	Germany, Belgium, Switzerland	Retrospective	56 (NR)	NR	Ablation, resection or TACE	NR	HCC treatment	21 months	1-year 19% 2-year 44%

Yasui 2017 ³²	Japan	Retrospective	46 (NR)	NR	NR	NR	End of DAA treatment	6 months	14.3 (5.4 – 28.5)
Minami 2017 ³³	Japan	Retrospective	163 (91%)	NR	Resection 14 Ablation 147 Radiotherapy 1 TACE 1	8 months	Start of DAA treatment	14.5 months	47.9 (40.0 - 55.8)
Ohki 2017 ³⁴	Japan	Retrospective	20 (100%)	13 (7 – 25)	Ablation 100%	7.6 months	HCC treatment	24 months	35.0 (15.4 - 59.2)
Sangiovanni 2017 ³⁵	Italy	Prospective	101 (98%)	NR	Resection 28% Ablation 48% TACE 10% Multi-modality 14%	12 months	Start of DAA treatment	11.1 months	32.7 (23.7 - 42.7)
Singal 2017 ³⁷	USA	Retrospective	207 (87%)	16 (7 – 52)	Resection 19% Ablation 27% TACE 37% Multi-modality 16%	7.2 months	HCC treatment	22.7 months	45.9 (39.0 - 52.9)
Urabe 2017 ³⁶	Japan	Prospective	63 (NR)	NR	NR	24.3 months	Start of DAA treatment	10.9 months	38.5 (26.2 - 51.2)

Tokoro2016 ³⁸	Japan	Retrospective	22 (NR)	NR	NR	NR	Start of DAA treatment	16.2 months	59.1 (36.4 - 79.3)
Tsuda 2016 ³⁹	Japan	Retrospective	36 (NR)	NR	NR	NR	Start of DAA treatment	11.4 months	25.0 (12.1 - 42.2)

DAA – direct acting antiviral; HCC – hepatocellular carcinoma; NR – not reported; TACE – transarterial chemoembolization

* available as full length manuscript

Table 2: Characteristics of studies with direct comparisons of HCC recurrence rates

Author Year	Study location	Study Arms	Number of patients	Comparison of Recurrence
Virlogeux 2017 ²²	France	DAA-treated and untreated	23 / 45	1.7 vs. 4.2/100 person-months in DAA-treated and untreated patients (adjusted HR 0.24, 95%CI 0.10 – 0.55)
ANRS 2016 ²⁴	France	DAA-treated and untreated	189 / 78	0.73 vs. 0.66/100 person-months in DAA-treated and untreated patients (adjusted HR 1.04, 95%CI 0.53 – 2.07)
ANRS 2016 ²⁴	France	DAA-treated and untreated	13 / 66	1.1 vs. 1.7/100 person-months in DAA-treated and untreated patients (adjusted HR 0.40, 95%CI 0.05 – 3.03)
Granata 2017 ³⁰	Italy	DAA-treated and untreated	65 / 186	Time to recurrence: 23.2 vs. 23.0 months

				in DAA-treated and untreated patients
Yasui 2017 ³²	Japan	DAA-treated and IFN-treated	46 / 26	Proportion: 14% vs. 22% in DAA-treated and IFN-treated (p=0.50)
Joko 2017 ⁴¹	Japan	DAA-treated and IFN-treated	368 / 148	No difference in early recurrence between DAA-treated and IFN-treated patients
Ohki 2017 ³⁴	Japan	DAA-treated, IFN-treated, and untreated	20 / 20 / 20	35% vs. 55% vs. 55% in DAA-treated, IFN- treated, and untreated patients (p=0.38)
Singal 2017 ³⁷	USA	DAA-treated and untreated	207 / 127	Proportion: 46% vs. 50% in DAA-treated and untreated patients (adjusted OR 0.80, 95%CI 0.48-1.35)
Tanaka 2017 ⁴²	Japan	DAA-treated, IFN-treated, and untreated	16 / 16 / 119	Lower recurrence in DAA-treated than untreated group (adjusted HR 0.56, 95%CI 0.26-0.97)

DAA – direct acting antiviral; IFN - interferon

Table 3. Patterns of HCC recurrence after DAA therapy

Author Year	Number with HCC recurrence	Tumor burden at time of recurrence	HCC-directed Treatment
Bielen 2017 ¹⁶	6	33% BCLC A, 33% BCLC B, 17% BCLC C, 17% unknown	17% resection 33% TACE and 50% supportive care
Cabibbo 2017 ¹⁷	29	62% BCLC A, 21% BCLC B, 7% BCLC C, 10% BCLC D	38% resection or ablation 45% TACE and 7% systemic therapy
Reig 2017 ²¹	21	90% BCLC A, 10% BCLC B	38% transplant, resection or ablation

			19% TACE and 29% systemic therapy
Conti 2016 ²³	17	56% unifocal and 70% diameter <2 cm	Not reported
Rinaldi 2016 ²⁵	1	100% BCLC A	Patient treated with ablation
Granata 2017 ³⁰	18	76% monofocal, 12% multifocal, 12% advanced	Not reported
Yasui 2017 ³²	6	100% BCLC A	Not reported
Minami 2017 ³³	78	86% BCLC A, 13% BCLC B, 13% BCLC C	85% resection or ablation 14% TACE and 1% supportive care
Ohki 2017 ³⁴	7	100% BCLC A	86% ablation 14% TACE
Sangiovanni 2017 ³⁵	33	79% BCLC A, 6% BCLC B, 6% BCLC C, 9% unknown	52% transplant, resection or ablation 42% TACE and 6% systemic therapy
Singal 2017 ³⁷	95	74% within Milan Criteria	27% transplant, resection or ablation 54% TACE and 7% systemic therapy
Tokoro 2016 ³⁸	13	Diameter 1.2 cm (0.7 – 2.0)	Not reported
Tsuda 2016 ³⁹	9	56% unifocal, 22% 2-3 nodules, 22% >3 nodules	Not reported

BCLC – Barcelona Clinic Liver Cancer; HCC – hepatocellular carcinoma

Table 4. Quality assessment of studies by checklist

Author Year	Representative cohort	Ascertainment of exposure	Outcome not present at start	Assessment of outcome	Sufficient follow-up period	Adequacy of follow-up
Bielen 2017 ¹⁶	*	*	High	High	*	High
Cabibbo 2017 ¹⁷	*	*	*	*	High	Unknown

Ikeda 2017 ¹⁸	*	*	Medium	Medium	*	*
Ngata 2017 ¹⁹	*	*	High	Medium	*	Unknown
Ogawa 2017 ²⁰	*	*	*	*	*	Unknown
Reig 2017 ²¹	*	*	*	Medium	High	*
Virlogeux 2017 ²²	*	*	*	Medium	*	High
Conti 2016 ²³	*	*	Medium	Medium	High	*
ANRS 2016 ²⁴	*	*	Medium	High	*	Unknown
ANRS 2016 ²⁴	*	*	Medium	High	*	Unknown
Rinaldi 2016 ²⁵	*	*	*	Medium	High	Unknown
Zavaglia 2017 ²⁶	*	*	*	High	High	High
Zeng 2016 ²⁷	*	*	High	Medium	*	*
Torres 2016 ²⁸	*	*	Medium	*	High	Unknown
Gheoghe 2017 ²⁹	*	*	Medium	High	High	Unknown
Granata 2017 ³⁰	*	*	*	*	*	Unknown
Kolly 2017 ³¹	*	*	High	High	*	Unknown
Yasui 2017 ³²	High	*	High	High	High	Unknown
Minami 2017 ³³	*	*	Medium	High	*	High
Ohki 2017 ³⁴	*	*	High	High	*	Unknown

Sangiovanni 2017 ³⁵	*	*	Medium	*	High	High
Singal 2017 ³⁷	*	*	Medium	High	*	Unknown
Urabe 2017 ³⁶	*	*	Medium	High	High	Unknown
Tokoro 2016 ³⁸	*	*	High	Medium	*	Unknown
Tsuda 2016 ³⁹	*	*	Medium	High	High	Unknown

High = high risk of bias; Medium = intermediate risk of bias; * = low risk of bias

Table 5: Minimum reporting recommendations for future studies

1. Presence of cirrhosis and Child Pugh score at baseline
2. Baseline tumor burden and median AFP prior to HCC treatment
3. Number of prior HCC recurrences
4. Types of HCC treatment leading to complete response
5. Confirmation of HCC complete response immediately preceding DAA therapy
6. Time from HCC treatment to DAA initiation
7. Time from last HCC complete response assessment to HCC recurrence
8. HCC surveillance protocol and adherence
9. Tumor burden at time of recurrence, treatment of recurrence, and response to treatment
10. Predictors of HCC recurrence after DAA therapy

