Lee *et al. Hepatoma Res* 2020;6:21
DOI: 10.20517/2394-5079.2019.44

Hepatoma Research

Review

Open Access

The impact of direct-acting antivirals on hepatitis C associated hepatocellular carcinoma

Tai-Ping Lee, David Bernstein

Division of Hepatology and Sandra A. Bass Center for Liver Diseases at Northwell Health, Manhasset, NY 11030, USA.

Correspondence to: Dr. Tai-Ping Lee, Division of Hepatology and Sandra A. Bass Center for Liver Diseases at Northwell Health, Manhasset, NY 11030, USA. E-mail: taiplee@gmail.com

How to cite this article: Lee TP, Bernstein D. The impact of direct-acting antivirals on hepatitis C associated hepatocellular carcinoma. *Hepatoma Res* 2020;6:21. http://dx.doi.org/10.20517/2394-5079.2019.44

Received: 17 Dec 2019 **First Decision:** 26 Feb 2020 **Revised:** 8 Apr 2020 **Accepted:** 10 Apr 2020 **Published:** 11 May 2020

Science Editor: Ming-Lung Yu **Copy Editor:** Jing-Wen Zhang **Production Editor:** Tian Zhang

Abstract

The increased incidence of hepatocellular carcinoma (HCC) in the last several decades in the United States and worldwide has partly resulted from an increase in hepatitis C virus (HCV) infection. HCV carcinogenesis is speculated to be indirectly related to multiple steps from inflammation to fibrosis and advanced fibrosis/cirrhosis over 20 or more years. However, the direct carcinogenic potential from HCV may explain HCC occurring in non-cirrhotic HCV patients. Highly potent direct-acting antivirals (DAAs) in recent years have changed hepatitis C treatment significantly and have resulted in the sustained virologic response (SVR) rate exceeding 90%. Although initial reports concerned the increase in de novo and recurrent HCC associated with DAAs, more recent studies showed that DAA-induced SVR on the contrary reduced risk of HCV-associated HCC without increasing its recurrence. The International Consortium of Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET) database and other resources of HCV patients treated with DAA collectively in the near future most likely will be able to show definitive evidence on the risk of HCC occurrence and recurrence after DAA with SVR. The long-term risk of HCC in chronic hepatitis C patients with advanced fibrosis or cirrhosis remains high after DAAs with SVR. Thus, HCC surveillance on this sub-group of patients is important for early detection and intervention of HCC.

Keywords: Direct-acting antivirals, hepatitis C virus infection, risk of hepatocellular carcinoma

INTRODUCTION

Liver cancer was predicted to be the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide in 2018. Statistically, hepatocellular carcinoma (HCC) comprises 75%-85% cases of liver cancer[1].

The sharply increased incidence of HCC in the last several decades in the United States and worldwide has partly resulted from an increase in hepatitis C virus (HCV) infection[2]. In the United States, chronic hepatitis C accounts for approximately 20%-31% of HCC deaths[2,3].

HCV AND HCC

HCV carcinogenesis is speculated to be indirectly related to multiple steps from chronic inflammation to fibrosis, advanced fibrosis and cirrhosis with somatic genetic/epigenetic alterations, and malignant transformation of hepatocytes over 20 or more years[4,5]. Patients with HCV cirrhosis had a three-fold higher adjusted risk of HCC than those with cirrhosis from other etiologies, implying direct carcinogenic effects of the virus[6-9]. HCC may develop in non-cirrhotic HCV patients, suggesting a direct HCV oncogenic effect[10]. Additionally, HCV core protein was shown to have oncogenic potential by using transgenic mouse models, indicating its direct involvement in carcinogenesis[11].

HCV-infected patients with advanced fibrosis or cirrhosis and older age are well-established risk for HCC development[4,12-14]. The prevalence of HCC is especially high in cirrhotic HCV patients with an estimated annual risk of 2%-4%[14].

HCV ERADICATION BY INTERFERON-BASED THERAPY AND HCC RISKS

Long-term eradication of HCV reduced HCC risk, which was initially demonstrated in patients who achieved SVR by interferon (IFN)-based therapies[14-18]. An analysis from 12 observational studies demonstrated that IFN-induced SVR led to nearly four-fold HCC risk reduction irrespective of liver disease stage[19].

Van der Meer *et al.*[20] found that the 10-year cumulative HCC incidence with SVR was 5.1%, *vs.* 21.8% in those without SVR ($P < 0.001$).

Although IFN has potential anti-inflammatory and/or immunomodulatory effects for the prevention of HCC, HCV eradication does not eliminate the risk of HCC[21,22]. El-Serag *et al.*[22] reported an overall incidence rate of 0.33% in new HCC development, which could occur more than 10 years after HCV eradication by IFN-based therapy.

HCV ERADICATION BY DAAS AND HCC RISKS

DAAs for HCV infection directly targeting viral protease, polymerase, or non-structural proteins have replaced IFN-based therapy over the past few years. They have changed the management of hepatitis C virus infection significantly, as the treatment is easy to administer, well-tolerated, safe, and highly effective with an SVR rate exceeding 90%[23-25].

DAAs can be used in HCV infection with advanced and complicated liver disease[25-31]. Multiple large cohort studies have shown that DAA-induced SVR is associated with a reduced risk of HCC[14,32-35]. Kanwal *et al.*[33] reported a significantly reduced risk of HCC (0.9 *vs.* 3.45 HCC/100 person-years) in 22,500 hepatitis C patients treated by DAAs with SVR compared to those without.

Piñero *et al.*[35] showed an overall 73% relative risk reduction for *de novo* HCC in DAAs-treated HCV patients with SVR, but the risk remained high in patients with advanced fibrosis and cirrhosis. Furthermore, reduced HCC risk by DAAs with SVR was demonstrated in patients with or without cirrhosis by Ioannou *et al.*[34].

HCC RISK IN CHRONIC HEPATITIS C TREATED BY DAA COMPARED TO THAT OF IFN THERAPY

IFN, an immune modulator, inhibits proliferation and may prevent the development of HCC. IFN-based HCV antiviral therapy due to its potential side effects was used mostly on patients without cirrhosis.

On the contrary, DAAs have been used on HCV patients with advanced fibrosis and cirrhosis who are at high risk of HCC. It was speculated that there would be more HCV -associated HCCs after DAA with SVR than those post-IFN with SVR ones in the United States, given that the largest cohort of chronic hepatitis C patients in the United States are baby boomers with advanced age, cirrhosis[36], and rising prevalence of metabolic syndrome-associated co-morbidities[37].

Waziry *et al.*[38] reported a random-effects meta-analysis comparing HCC occurrence and recurrence in patients treated by DAA and IFN therapy and showed no evidence of difference in HCC risk between the two groups after meta-regression adjustment of age and study follow up duration. Ioannou *et al.*[34] published a large VA cohort study of 21,498 chronic hepatitis C (CHC) patients with DAA-induced SVR, showing that it is associated with reduced risk of *de novo* HCC compared to treatment failure and that the risk for HCC after DAA therapy is similar to the risk after IFN therapy.

Singer *et al.*[39] using administrative claims data demonstrated that the risk of HCC was lower in DAA-treated patients (adjusted HR = 0.69; 95%CI: 0.59-0.81).

DAAS AND *DE NOVO* HCC

Earlier studies of first-generation DAAs showed increased risk for *de novo* and recurrent HCC, which brought concerns that DAAs might have carcinogenic effects[40-43]. A retrospective multicenter study from Spain reported a short-term HCC incidence of 3.73 HCC/100 patient-years (95%CI: 2.96-4.70), within a median 10.3 months after starting DAA therapy on 1123 HCV patients with cirrhosis[44].

HCC risk with DAAs is related to the severity of liver histology[33,45,46]. The annual incidence of HCC after SVR was higher in those with cirrhosis than those without cirrhosis (1.82 *vs.* 0.34/100 person-years)[14,33].

Ioannou *et al.*[47] reported that an increased risk for HCC in hepatitis C patients with baseline cirrhosis or high FIB-4 treated with either IFN-based therapy or DAAs could persist up to 10 years after SVR. Kanwal *et al.*[48] also showed that an increased risk for HCC after DAAs with SVR remained for up to 3.6 years of follow up, and it was particularly high in patients with cirrhosis.

DAAS AND RECURRENT HCC

Hepatitis C virus stimulates immune response. HCV-specific T cells produce cytokines including IFN with anti-HCC effects[49-52]. The recurrence of HCC was speculated to be due to reduced immune surveillance, cytokine imbalance, and angiogenesis[50-53].

A meta-analysis by Singal *et al.*[54] demonstrated that IFN-based treatment for HCV patients after curative HCC therapy reduced HCC recurrence and improved the outcomes. Nishibatake Kinoshita *et al.*[55] reported no significant difference of HCV-related early HCC recurrence after HCC treatment between 156 patients in the IFN-based group and 147 patients in the DAA group.

Several earlier studies showed different results regarding DAAs and the risk of HCC recurrence[56-58]. Some studies that reported an increased risk for HCC recurrence with use of DAAs correlated earlier HCC recurrence with a shorter interval between complete response to HCC treatment and the DAA agent[40,59].

A meta-analysis of HCC recurrence after DAAs by Saraiya pointed out that some studies lacked a comparison cohort or had different patient selection criteria, timing of DAA therapy, and follow up schedules. Nevertheless, they found no significant difference in HCC recurrence among the study groups[60].

The benefits of DAA therapy including regression of fibrosis, decrease in portal hypertension, and hepatic failure are weighed against potential risk for HCC recurrence. A large retrospective study of 793 patients in

North America (304 received DAA therapy *vs.* 489 received no HCV therapy) published by Singal *et al.*[61] showed no association between DAA therapy and HCC recurrence (HR = 0.90; 95%CI: 0.70-1.16).

Dang *et al.*[62] reported a 60%-70% improvement in 5-year all-cause and liver-related mortality in HCV-related HCC patients after DAAs with SVR, compared to patients untreated for HCV. Singal *et al.*[14] hypothesized that, by decreasing HCV viral load and slowing or preventing liver decompensation, DAA therapy could reduce the risk for late HCC recurrence.

ACTIVE HCC EFFECT ON SVR, AND TIMING OF DIRECT-ACTING ANTIVIRAL THERAPY

Lower HCV SVR rates were reported in the presence of HCC[63-69]. It is speculated that the low HCV SVR rates were due to altered inflammatory state in the tumor microenvironment, DAA uptake into hepatocyte, resistant profiles in the context of HCC, immune escape mechanism, HCC reservoir, and penetration of DAAs to HCV-infected HCC tissue[63,69].

Although Ahmed *et al.*[70] showed that pre-liver transplant HCV treatment with DAAs provided great outcomes and the most cost-effective management for CHC patients with HCC or decompensated cirrhosis while waiting for liver transplant in the US, a study on US veterans with HCV observed an SVR rate of 74.4% in patients who received DAAs during active HCC compared to 91.1% in patients without HCC[64]. Deferring DAA therapy until six months after completion of either liver resection or ablation is recommended in HCC patients who are eligible for curative HCC treatment[14].

Radhakrishnan *et al.*[71] using HCV-TARGET database demonstrated a 50% reduced SVR in HCV patients with HCC, but SVR was not different among patients who received complete, partial, or no treatment at all.

Median wait time, availability of hepatitis C-positive organ, and severity of liver decompensation are the determinants of timing of DAA therapy in HCV-associated HCC patients who are on the liver transplantation (LT) list. DAA therapy for patients awaiting LT is usually deferred until after transplant so patients will be eligible to receive an HCV positive donor[14].

Reduced liver-related deaths on LT waiting list and decreased progression of liver disease from post-transplant HCV reinfection by DAA have been observed[72,73]. Some patients treated by DAAs with SVR while awaiting LT had sufficient improvement in liver function to receive other curative therapies or forego transplant[73-75]. Although Yang *et al.*[76] suggested DAAs might be associated with a higher rate of HCC recurrence post-LT in a small group of patients, Emamaullee and colleagues demonstrated that HCV eradication pre-LT did not impact rates of delisting for HCC progression or rates of HCC recurrence post-LT in a larger retrospective study[77].

DAA THERAPY IN PATIENTS WITH UNTREATED ADVANCED HCC

Limited data are available regarding the use of DAAs in hepatitis C patients with untreated advanced HCC. A theoretical benefit from DAAs in this setting is that it may improve liver decompensation and allow continued HCC therapy. Tumor burden, life expectancy, and patient preference need to be considered for DAA therapy since it is palliative[14].

SUMMARY

Highly potent DAAs in recent years have revolutionized hepatitis C treatment and have high SVR rate exceeding 90%. Numerous studies have shown that DAA-induced SVR reduces risk of hepatitis C-associated HCC. Although recent research demonstrated no increased risk of HCC in HCV patients after DAA with SVR, the HCV-TARGET database and other resources, such as DAA manufacturers' database and

Surveillance, Epidemiology and End Results Program in the United States, collectively are most likely to show definitive evidence on the risk of HCC occurrence and recurrence after DAA with SVR.

Nevertheless, the risk of HCC in chronic hepatitis C patients with advanced fibrosis or cirrhosis remains after DAAs with SVR. The concerns of DAA-associated *de novo* HCC and its recurrence in HCV patients warrant further investigation. Clinical parameters and/or potential molecular biomarkers in the near future may enable better identification of HCC in high-risk HCV patients treated by DAAs with SVR. Thus, this subset of patients will benefit from proper surveillance, early detection, and intervention of HCC.

DECLARATIONS

Authors' contributions

Study concept and design, literature search, drafting of the manuscript: Lee TP
Administrative support: Bernstein D

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, et al.; Global Burden of Disease Liver Cancer Collaboration. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683-91.
3. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018;68:31-54.
4. Goossens N, Hoshida Y. Hepatitis C virus-induced hepatocellular carcinoma. Clin Mol Hepatol 2015;21:105-14.
5. Tan A, Yeh SH, Liu CJ, Cheung C, Chen PJ. Viral hepatocarcinogenesis: from infection to cancer. Liver Int 2008;28:175-88.
6. Kamegaya Y, Hiasa Y, Zukerberg L, Fowler N, Blackard JT, et al. Hepatitis C virus acts as a tumor accelerator by blocking apoptosis in a mouse model of hepatocarcinogenesis. Hepatology 2005;41:660-7.
7. Lemon SM, McGivern DR. Is hepatitis C carcinogenic? Gastroenterology 2012;142:1274-8.
8. Chen CL, Tsukamoto H, Machida K. Oncogenic signaling pathways and origins of tumor-initiating stem –like cells of hepatocellular carcinomas induced by hepatitis C virus, alcohol and/or obesity. Hepatol Int 2014;8:330-8.
9. Zhang Y. Detection of epigenetic aberrations in the development of hepatocellular carcinoma. Cancer Epigenetics 2014;1238:709-31.
10. Yeh MM, Daniel HDJ, Torbenson M. Hepatitis C associated hepatocellular carcinoma in non-cirrhotic livers. Mod Pathol 2010;23:276-83.
11. Koike K. Hepatitis C virus contributes to hepatocarcinogenesis by modulating metabolic and intracellular signaling pathways. J Gastroenterol Hepatol 2007;22:S108-11.
12. Hoshida Y, Fuchs BC, Bardeesy N, Baumert TF, Chung RT. Pathogenesis and prevention of hepatitis C virus-induced hepatocellular

carcinoma. J Hepatol 2014;61:S79-90.
13. Axley P, Ahmed Z, Ravi S, Singal AK. Hepatitis C virus and hepatocellular carcinoma: a narrative review. J Clin Transl Hepatol 2018;6:79-84.
14. Singal AG, Lim JK, Kanwal F. AGA clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis C infection and hepatocellular carcinoma: expert review. Gastroenterology 2019;156:2149-57.
15. Yu ML, Lin SM, Chuang WL, Dai CY, Wang JH, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicenter study in Taiwan. Antivir Ther 2006;11:985-94.
16. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8,288.e1.
17. Ogawa E, Furusyo N, Kajiwara E, Takahashi K, Nomura H, et al. Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: a prospective, multicenter study. J Hepatol 2013;58:495-501.
18. Moon C, Jung KS, Kim DY, Baatarkhuu O, Park JY, et al. Lower incidence of hepatocellular carcinoma and cirrhosis in hepatitis C patients with sustained virological response by pegylated interferon and ribavirin. Dig Dis Sci 2015;60:573-81.
19. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Inter Med 2013;158:329-37.
20. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-93.
21. Janjua NZ, Chong M, Kuo M, Woods R, Wong J, et al. Long-term effect of sustained virological response on hepatocellular carcinoma in patients with hepatitis C in Canada. J Hepatol 2017;66:504-13.
22. El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. Hepatology 2016;64:130-7.
23. Chung RT, Baumert TF. Curing chronic hepatitis C-the arc of a medical triumph. N Engl J Med 2014;370:1576-8.
24. McGlynn EA, Adams JL, Kramer J, Sahota AK, Silverberg MJ, et al. Assessing the safety of direct-acting antiviral agents for hepatitis C. JAMA Network Open 2019;2:e194765.
25. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C. Available from: http://www.hcvguidelines.org [Last accessed on 14 Apr 2020]
26. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. JAMA 2014;312:631-40.
27. Wyles DL, Sulkowski MS, Dieterich D. Management of hepatitis C/HIV coinfection in the era of highly effective hepatitis C virus direct-acting antiviral therapy. Clin Infect Dis 2016;63 Suppl 1:S3-11.
28. Kohli A, Alshati A, Georgie F, Manch R, Gish RG. Direct-acting antivirals for the treatment of chronic hepatitis C in patients with chronic kidney disease. Therap Adv Gastroenterol 2016;9:887-97.
29. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, et al. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. Ann Intern Med 2017;166:637-48.
30. Cheung MCM, Walker AJ, Hudson BE, Verma S, McLauchlan J, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;65:741-7.
31. Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology 2017;152:142-6.
32. Su F, Ioannou GN. Hepatocellular carcinoma risk after direct-acting antiviral therapy. Clin Liver Dis (Hoboken) 2019;13:6-12.
33. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153:996-1005.e1.
34. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2017. Epub ahead of print. doi: 10.1016/j.jhep.2017.08.030.
35. Piñero F, Mendizabal M, Ridruejo E, Herz Wolff F, Ameigeiras B, et al. Treatment with direct-acting antivirals for HCV decreases but does not eliminate the risk of hepatocellular carcinoma. Liver Int 2019;39:1033-43.
36. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513-21.
37. Lazo M, Nwankwo C, Daya NR, Thomas DL, Mehta SH, et al. Confluence of epidemics of hepatitis C, diabetes, obesity, and chronic kidney disease in the United States Population. Clin Gastroenterol Hepatol 2017;15:1957-64.
38. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. J Hepatol 2017;67:1204-12.
39. Singer AW, Reddy KR, Telep LE, Osinusi AO, Brainard DM, et al. Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study. Aliment Pharmacol Ther 2018;47:1278-87.
40. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727-33.
41. Cabibbo G, Celsa C, Cammà C, Craxì A. Should we cure hepatitis C virus in patients with hepatocellular carcinoma while treating cancer? Liver Int 2018;38:2108-16.
42. Kozbial K, Moser S, Schwarzer R, Laferl H, Al-Zoairy R, et al. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. J Hepatol 2016;65:856-8.
43. Nault JC, Colombo M. Hepatocellular carcinoma and direct acting antiviral treatments: controversy after the revolution. J Hepatol 2016;65:663-5.
44. Mariño Z, Darnell A, Lens S, Sapena V, Díaz A, et al. Time association between HCV therapy and hepatocellular carcinoma emergence in patients with cirrhosis. The relevance of non-characterized nodules. J Hepatol 2019;70:874-84.

45. Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, et al. Incidence of hepatocellular carcinoma after direct antiviral therapy for HCV in patients with cirrhosis Included in surveillance programs. Gastroenterology 2018;155:1436-50.
46. Ogawa E, Furusyo N, Nomura H, Dohmen K, Higashi N, et al.; Kyushu University Liver Disease Study (KULDS) Group. Short-term risk of hepatocellular carcinoma after hepatitis C virus eradication following direct-acting anti-viral treatment. Aliment Pharmacol Ther 2018;47:104-13.
47. Ioannou GN, Beste LA, Green PK, Singal AG, Tapper EB, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 Scores. Gastroenterology 2019;157:1264-78.
48. Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, et al. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. Hepatology 2020;71:44-55.
49. Llovet JM, Villanueva A. Liver cancer: effect of HCV clearance with direct-acting antiviral agents on HCC. Nat Rev Gastroenterol Hepatol 2016;13:561-2.
50. Reig M, Boix L, Mariño Z, Torres F, Forns X, et al. Liver cancer emergence associated with antiviral treatment: an immune surveillance failure? Semin Liver Dis 2017;37:109-18.
51. Debes JD, van Tilborg M, Groothuismink ZMA, Hansen BE, Schulze Zur Wiesch J, et al. Levels of cytokines in serum associate with development of hepatocellular carcinoma in patients with HCV infection treated with direct-acting antivirals. Gastroenterology 2018;154:515-7.e3.
52. Sanduzzi-Zamparelli M, Boix L, Leal C, Reig M. Hepatocellular carcinoma recurrence in HCV patients treated with direct antiviral agents. Viruses 2019;11:406.
53. Villani R, Vendemiale G, Serviddio G. Molecular Mechanisms Involved in HCC Recurrence after direct-acting antiviral therapy. Int J Mol Sci 2019;20:49.
54. Singal AK, Freeman DH, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther 2010;32:851-8.
55. Nishibatake Kinoshita M, Minami T, Tateishi R, Wake T, Nakagomi R, et al. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: comparison with interferon-based therapy. J Hepatol 2019;70:78-86.
56. Colombo M, Boccaccio V. HCV therapy and risk of liver cancer recurrence: who to treat? Nat Rev Gastroenterol Hepatol 2018;15:392-3.
57. Reig M, Boix L, Bruix J. The impact of direct antiviral agents on the development and recurrence of hepatocellular carcinoma. Liver Int 2017;37:136-9.
58. Guarino M, Viganò L, Ponziani FR, Giannini EG, Lai Q, et al. Recurrence of hepatocellular carcinoma after direct acting antiviral treatment for hepatitis C virus infection: literature review and risk analysis. Dig Liver Dis 2018;50:1105-14.
59. Guarino M, Sessa A, Cossiga V, Morando F, Caporaso N, et al. Direct-acting antivirals and hepatocellular carcinoma in chronic hepatitis C: a few lights and many shadows. World J Gastroenterol 2018;24: 2582-95.
60. Saraiya N, Yopp AC, Rich NE, Odewole M, Parikh ND, et al. Systematic review with meta-analysis: recurrence of hepatocellular carcinoma following direct-acting antiviral therapy. Aliment Pharmacol Ther 2018;48:127-37.
61. Singal AG, Rich NE, Mehta N, Branch A, Pillai A, et al. Direct-acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter North American cohort study. Gastroenterology 2019;156:1683-92.
62. Dang H, Yeo YH, Yasuda S, Huang CF, Iio E, et al. Cure with interferon free DAA is associated with increased survival in patients with HCV related HCC from both East and West. Hepatology 2019; Epub ahead of print [PMID: 31610027 DOI: 10.1002/hep.30988]
63. Saberi B, Dadabhai AS, Durand CM, Philosophe B, Cameron AM, et al. Challenges in treatment of hepatitis C among patients with hepatocellular carcinoma. Hepatology 2017;66:661-3.
64. Beste LA, Green PK, Berry K, Kogut MJ, Allison SK, et al. Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. J Hepatol 2017;67:32-9.
65. Prenner SB, VanWagner LB, Flamm SL, Salem R, Lewandowski RJ, et al. Hepatocellular carcinoma decreases the chance of successful hepatitis C virus therapy with direct-acting antivirals. J Hepatol 2017;66:1173-81.
66. Chang CY, Nguyen P, Le A, Zhao C, Ahmed A, et al. Real-world experience with interferon -free, direct-acting antiial therapies in Asian Americans with chronic hepatitis C and advanced liver disease. Medicine (Baltimore) 2017;96:e6128.
67. Soria A, Fabbiani M, Lapadula G, Gori A. Unexpected viral relapses in hepatitis C virus-infected patients diagnosed with hepatocellular carcinoma during treatment with direct-acting antivirals. Hepatology 2017;66:992-4.
68. Ji F, Yeo YH, Wei MT, Wei B, Dang S, et al. Hepatocellular carcinoma decreases the effectiveness of hepatitis C antiviral treatment: do direct-acting antiviral regimens matter? Hepatology 2018;67:1180-2.
69. Harrod E, Moctezuma-Velazquez C, Gurakar A, Ala A, Dieterich D, et al. Management of concomitant hepatocellular carcinoma and chronic hepatitis C: a review. Hepatoma Res 2019;5:28.
70. Ahmed A, Gonzalez SA, Cholankeril G, Perumpail RB, McGinnis J, et al. Treatment of patients waitlisted for liver transplant with all-oral direct-acting antivirals is a cost-effective treatment strategy in the United Status. Hepatology 2017;66:46-56.
71. Radhakrishnan K, Di Bisceglie AM, Reddy KR, Lim JK, Levitsky J, et al. Treatment status of hepatocellular carcinoma does not influence rates of sustained virologic response: an HCV-TARGET analysis. Hepatol Commun 2019 ;3:1388-99.
72. Roche B, Coilly A, Duclos-Vallee JC, Samuel D. The impact of treatment of hepatitis C with DAAs on the occurrence of HCC. Liver Int 2018;38:139-45.
73. Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, et al. European liver and intestine association (ELITA). Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. J Hepatol 2016;65:524-31.
74. Gadiparthi C, Cholankeril G, Perumpail BJ, Yoo ER, Satapathy SK, et al. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. World J Gastroenterol 2018;24:315-22.
75. Pascasio JM, Vinaixa C, Ferrer MT, Colmenero J, Rubin A, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67:1168-76.

76. Yang JD, Aqel BA, Pungpapong S, Gores GJ, Roberts LR, et al. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. J Hepatol 2016;65:856-68.
77. Bigam D, Shapiro AMJ, Kneteman N. HCV eradication with direct-acting antivirals does not impact HCC progression on the waiting list or HCC recurrence after liver transplantation. Can J Gastroenterol Hepatol 2019;2019:2509059.