The Egyptian Journal of Hospital Medicine (January 2024) Vol. 94, Page 500-505

Hepatocellular Carcinoma Recurrence Post Direct-Acting Antiviral and Its Relation to Time of Treating Chronic HCV Infection

Ali F. Soliman*[1], Mohamed F. Elgazzar[2], Mahmoud Elsakhawy[3], Hassan Zaghla[2], Eman Rewisha[2], Imam Waked[2]

Department of [1]Internal Medicine, Ministry of Health, Dakahlia, Egypt

Departments of [2]Hepatology and Gastroenterology and

[3]Radiology, National Liver Institute, Menofia University, Shebin Elkom, Egypt

***Corresponding author:** Ali F. Soliman, **Mobile:** (+20) 01096204162, **E-mail:** alisoliman198411@gmail.com

ABSTRACT

Background: There is a documented relationship between Hepatocellular Carcinoma (HCC) recurrence and Direct-Acting Antiviral (DAAs).

Objective: This study's overarching goal was to determine whether there is a correlation between the length of time between HCV treatments and the frequency of recurrence of HCC following successful ablation of HCC.

Patients and Methods: This retrospective study included 400 cases with chronic HCV infection and HCC who had a complete response to treatment. The patients also had to have attended the clinic for HCC recurrence during this time. A total of 200 cases with recurrent HCC were randomly assigned to one of four categories and then exposed to DAA (case group). Fifty patients in each of Groups 1, 2, and 3 began treatment 3, 6, 9, and 12 months following their curative HCC therapy, while 200 patients with recurrent HCC who were not exposed to DAAs served as the control group.

Results: The case group's recurrence rate increased significantly throughout the first six months, then decreased during the second half of the study.

Conclusion: It appears that the recurrence of HCC in individuals exposed to DAAs is more rapid and aggressive than in those who are not exposed to DAAs. We advise waiting at least one year after an ablative treatment's complete response before beginning DAA treatment.

Keywords: Hepatocellular carcinoma, Direct-acting antivirals, Hepatitis C virus infection.

INTRODUCTION

About 20 to 30% of persons who get chronic hepatitis C, which is caused by an infection with the hepatitis C virus (HCV), end up with cirrhosis of the liver. Each year, an estimated 3.5% of people with advanced liver cirrhosis may develop liver cancer **[1].**

In terms of cancer incidence and cancer-related deaths, hepatocellular carcinoma (HCC) is the second most common cancer in the world. New treatment options have improved the 5-year survival rate for HCC, but it is still quite low (15% in the US and 5% in developing countries) **[2].**

Due to their superior tolerability and SVR rates (over 90%) for most HCV genotypes, DAAs have lately supplanted previous treatment regimens **[3].**

Retrospective evaluations of HCC recurrence in studies have shown contradictory findings. Two studies, one in Italy involving 59 patients and the other a multicentre trial in Spain involving 58 patients, found that patients given DAAs had an unusually high recurrence rate after curative treatment (28% and 29% respectively) **[4].** On the other hand, observational study data suggest that persons with chronic hepatitis C and a history of HCC therapy are more likely to experience a recurrence of the cancer when using DAA medication **[4, 5].**

We aimed at this research to determine whether there was a correlation between the length of time between HCV treatments and the frequency of HCC recurrence following successful ablation of HCC.

PATIENTS AND METHODS

In retrospective analysis at the Outpatient Clinic at National Liver institute (NLI) at Menoufia University, 400 hepatocellular carcinoma cases who were infected with HCV and responded fully to ablative treatment for HCC (resection, thermal ablation, or ethanol injection) in accordance with EASL and AASLD recommendations for HCC management were included in this study in the duration between August 2017 and August 2018.

Inclusion criteria:

Age 18 years or older. Patients who had HCV related HCC. Patients who exposed to DAAs and achieved SVR. Patients who have successfully undergone ablative therapy for HCC (assessed by triphasic CT abdomen or dynamic MRI) before undergoing DAA therapy, in line with EASL and AASLD protocols for the management of HCC, are eligible to receive this treatment. HCC criteria: single focal lesion and size $\leq$ 5 cm before ablative therapy. Prior to DAA treatment, all patients included had a Child Pugh score of A and a performance status of 0.

Exclusion criteria:

HCC patients secondary to other causes than hepatitis C or combined HCV and HBV infection. Incomplete response to HCC ablative treatment. Patients who did not achieve SVR to DAAs therapy (non SVR).

Received: 01/10/2023
Accepted: 01/12/2023

Groups:

Two groups were formed from the patients that were enrolled:

1- Case group:

Using HCV treatment time as a criterion, 200 patients with HCC recurrence who were exposed to DAAs were split into four groups.

Fifty patients in each group, which are classified according to DAA treatment intervals of 3, 6, 9, and 12 months following curative HCC treatment.

- Group 1: DAAs initiation after 3 months (exposed to DAAs outside NLI).
- Group 2: DAAs initiation after 6 months.
- Group 3: DAAs initiation after 9 months.
- Group 4: DAAs initiation after 12 months.

2-Control group: 200 patients of HCC recurrence with chronic HCV not exposed to DAAs**.**

Methods:

All data of the patients were collected from files from HCC unit in NLI.

I) Complete history taking, complete clinical examination and demographic data.

II) Laboratory Investigations:

- Complete blood count, INR and PT. - Biochemical tests: AST, ALT, Total bilirubin, Albumin, Alpha fetoprotein (AFP), blood urea and serum creatinine.
- Viral markers: Anti-HCV, HBs Ag and HBc antibodies. - Polymerase chain reaction (PCR) for HCV.

III) Radiological investigations:

Abdominal ultrasonography and triphasic C.T scan or dynamic MRI 1.5 Tesla were performed before HCC treatment, one month after ablation, before DAA and every 3 months after HCC ablation for all patients included.

IV)Pathological investigation:

The EASL and AASLD guidelines for HCC management were followed, including the use of true cut needles for liver biopsies and, where necessary, a pathological investigation.

Ethical approval: National Liver Institute Medical Ethics Committee of the Menofia University gave its approval to this study. All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

We used SPSS version 21, an application developed, for Windows, to analyse the data. First, we used a one-sample Kolmogorov-Smirnov test to make sure the data was normal. For the purpose of investigating correlations between category variables, the Chi-square test was utilised. When this was the case, we used the Monte Carlo and Fischer exact tests.

The Mc Nemar test was used to compare paired groups. A Student t-test was employed for parametric data, whereas the Mann Whitney test was employed for non-parametric data. We were able to compare the two datasets because of this. We employed the paired t-test for parametric data, the Wilcoxon signed rank test for non-parametric data, and both tests for matched groups. For comparing means, we used the analysis of variance, and for comparing medians, we used the Kruskal-Wallis test. A significant p-value was considered when it is equal or less than 0.05.

RESULTS

In terms of age, sex, profession, smoking, diabetes mellitus (DM), and family history, when comparing the case and control groups, no statistically significant difference was found (Table 1).

Table (1): Demographics and risk factors between control and case groups

Socio-demographic data	Control group (n=200)	Cases group (n=200)	P value
Age/y Mean±SD	59.15±7.24	57.89±6.95	0.077
Sex Male Female	177(88.5%) 23(11.5%)	172(86%) 28(14%)	0.454
Smoking	88(44%)	98(49%)	0.316
DM	61(30.5%)	54(27%)	0.439

Regarding type of treatment received for HCC before DAAs, the percentage of patients received RFA and E. I was significantly higher in cases group (P values = <0.001 and 0.001 respectively), while surgical resection was significantly higher among control (P value <0.001) (Table 2).

Table (2): Type of TTT for HCC before DAAs between control and different study

Type of TTT for HCC before DAAs	Control (n=200)	Group (1) (n=50)	Group (2) (n=50)	Group (3) (n=50)	Group (4) (n=50)	Test of significance			
						P1	P2	P3	P4
RFA	42(21%)	36(72%)	28(56%)	26(52%)	39(78%)	<0.001*	<0.001*	<0.001*	<0.001*
E. I	15(7.5%)	10(20%)	13(26%)	15(30%)	4(8%)	0.008*	<0.001*	<0.001*	0.905
MWA	12(6%)	4(8%)	7(14%)	8(16%)	4(8%)	0.605	0.056	0.019*	0.605
surgical resection	131 (65.5%)	0(0%)	2(4%)	1(2%)	1 (2%)	<0.001*	<0.001*	<0.001*	<0.001*
Resection +RFA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	-	-	-	1.0
Resection + ethanol injection	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	-	-	-	1.0

Recurrence rate was higher among case group within first 6 months (72%) after DAAs while control group was 13.5% and higher among control group within second 6 months after HCC ablation (86.5%), while case group was 28% with statistically significant difference (p- value <0.001*) (Table 3).

Table (3): Recurrence between control and study groups.

Recurrence	Control (n=200)	Cases group (n=200)	P value
After 6m	27(13.5%)	144(72%)	<0.001*
After 12m	173(86.5%)	56(28%)	

Regarding recurrence rate among studied groups, it was noted that recurrence rate was significantly higher among cases after 6 months (70%), while it was higher among control group after 12 months (86.5%) (P value <0.001) (Table 4).

Table (4): Recurrence between control and different study subgroups.

Recurrence	Control (n=200)	Group (1) (n=50)	Group (2) (n=50)	Group (3) (n=50)	Group (4) (n=50)	Test of significance			
						P1	P2	P3	P4
After 6m	27(13.5%)	32(64%)	29(58%)	35(70%)	48(96%)	<0.001*	<0.001*	<0.001*	<0.001*
After 12m	173(86.5%)	18(36%)	21(42%)	15(30%)	2(4%)				

Portal vein thrombosis (PVT) was significantly higher in case subgroup 1 (12/50) than control group (12/200) with P=0.001. Lymph nodes (LNs) and distant metastasis were significantly higher in subgroup 1 (15/50) than in control group (6/200) with P=≤0.001 (Table 5).

Table (5): Portal vein thrombosis and metastasis in recurrent HCC among control group and case subgroups.

	Control group (n=200)	Group (1) (n=50)	Group (2) (n=50)	Group (3) (n=50)	Group (4) (n=50)	Test of significance			
						P1	P2	P3	P4
PVT	12 (6%)	12 (24%)	6 (12%)	4 (8%)	2 (4%)	0.001	0.14	0.61	0.58
LNs and distant metastasis	6 (3.0%)	15 (30%)	8 (16%)	3 (6%)	2 (4%)	≤.001	0.003	0.31	0.72

DISCUSSION

A major contributor to liver cirrhosis and hepatocellular cancer, chronic hepatitis C virus infection affected 58 million individuals globally in 2023 [6]. Treatment with diazepam has been both effective and well-tolerated since 2014 [7]. Recurrence rates of HCC may be higher among patients who successfully use the new DAAs, according to two recent retrospective studies [6-8].

The current study aimed to assess the frequency of early HCC recurrence in cirrhotic individuals who had undergone DAA treatment, as well as the relationship between the length of time between HCC ablation and the start of viral C treatment. The case and control groups did not differ significantly from one another with respect to age or sex., and there were also no differences between the case subgroups. Also, we did not report significant difference regarding smoking or diabetes between control, case groups and case subgroups.

The case groups had a significantly higher HCC recurrence rate in the first six months after DAAs compared to the control group (DAAs untreated) in the same time period (p=0.001). Additionally, when comparing case subgroup 1 to the control group, which had almost the same amount of time for follow-up, the rate was found to be significantly higher in case subgroup 1 in the same time period (p=<0.001). This indicated that compared to individuals who did not get DAAs, those who do are more likely to experience an early HCC recurrence following ablative therapy. In hand with our study, **Conti *et al.*** [8] reported that during a 6-month follow-up period following the end of DAAs therapy, 17 out of 59 patients (28.8%) who had previously had resection, ablation, or TACE experienced a recurrence of HCC. In addition, **El Kassas *et al.*** [9] showed that 35.7% of patients treated with DAAs experienced an early recurrence following HCC ablation, compared to 25.4% of patients treated with non-DAAs. According to **Reig *et al.*** [4], DAA treatment was linked to an increased risk of HCC recurrence at an earlier stage. In contrary to the current study, the first study evaluated recurrence after DAAs and included comparative non DAAs group where there was no increased risk of HCC recurrence linked with DAA medication compared to no treatment, according to a French collaborative cohort trial of 267 patients with HCV and previously treated HCC (adjusted HR 1.09, 95% CI 0.55-2.16) [10]. In research conducted by **Minami *et al.*** [11] where they randomly assigned 942 patients to one of three groups—DAAs, INF, or control—no increased risk of early recurrence was seen in the IFN group, despite prior reports that IFN improved recurrence-free survival.

The rate of HCC recurrence among case subgroups within the first 6 months after DAAs treatment showed a rising increase in the recurrence rate within the different case subgroups from group 1 to group 4 (3 months, 6 months, 9 months and 12 months after HCC ablation) (64%, 58%, 70% and 96% respectively). This indicated that there was an elevated risk of early HCC recurrence when DAAs were administered within one year following the completion of ablation for HCC. Groups 3 and 4, which were treated eight and twelve months after ablation respectively had a greater rate of HCC recurrence in the second half of the study compared to patients treated with DAAs in the first half of the study. Similar to these findings, Based on a North American multicenter cohort study included 111 HCV patients, **Singal *et al.*** [12] discovered that the likelihood of early recurrence may differ according to the timing of DAA treatment initiation. The patients' ages ranged from 53 to 20.8 months. Recurrence of HCC occurred in 44.0% of individuals whose HCC CR occurred within the last three months. The percentage was 50.0% for individuals whose HCC CR occurred four to six months ago. This brings us to our last point: 36.9% of patients whose DAAs had been in place for over than six months.

According to the findings of a multivariable Cox analysis conducted by **Ogawa *et al.*** [13] on 152 patients with HCC related to HCV, the risk of HCC recurrence was significantly increased by the interval of one year between the last treatment for HCC and exposure to DAAs (HR: 3.20; 95% CI: 1.29-9.65; P=0.0011).

Patients who used DAAs within the first year after HCC treatment had a higher risk of HCC recurrence, according to **Ahn *et al.*** [14]. One possible explanation for this finding is that DAAs have a profound effect on reducing viral replication right from the start of treatment. They also decrease the expression of genes that promote interferon alpha and type II and III interferons, which could impact the likelihood of hepatocellular carcinoma (HCC) development or recurrence after therapy. Additionally, DAAs increase angiotensin-2 and vascular endothelial growth factor, two factors that contribute significantly to hepatic tumour growth [15]. For many reasons, including inadequate ablation or the possibility of extra lesional micro metastases, a greater early HCC recurrence rate (first 6 months) was linked to the early commencement of DAAs (case subgroups 1 and 2) [16]. Radiological evidence suggested that DAA-induced immune reconstitution by sudden viral clearance initiates a transient immunosuppressive phase that promotes tumour development [17-19]. Against our study, **Cabibbo *et al.*** [20], found no statistically significant effect of timing of DAAs initiation on HCC recurrence. Recurrence of HCC was not found to be significantly affected by the date of DAA beginning, according to **Adhoute *et al.*** [21].

While, the control group did not differ significantly from the experimental group with respect to platelet or white blood cell counts one month or one year following ablation (p= 0.009). There was a significant difference with respect to haemoglobin level. Case group haemoglobin and platelet levels were

significantly higher one year following DAAs (P=<0.001). The haemoglobin level as well as platelet count were found to be significantly higher in case subgroups one year after receiving DAAs from group 1 to 4 in a descending order (p- value <0.001) with no significant differences between case subgroups as regards WBC count. This is consistent with data collected by **Bachofner *et al.*** [22] after HCV cure by DAAs**.** In contrary to the current study, **Fouad *et al.*** [23]**,** reported that hemoglobin levels and white blood cell count were lower significantly among DAAs group after receiving DAAs than among untreated group**.**

Regarding bilirubin and AST, they were improved among control group (one year after HCC ablation), while albumin and INR showed no significant improvement one year after HCC ablation. INR, albumin, bilirubin and AST were improved in case group one year after DAAs (p=<0.001). The hematological and biochemical parameters were improved in DAAs-treated groups due to the stoppage of the hazardous effect on the liver by virus eradication and improvement of the microenviroment inside the liver; regression of the inflammatory mediators, cytokines and fibrosis after HCV eradication. In our study, the included patients had early cirrhosis (child A and SVR) and because the vascular supply was still in its early stages, the septal fibrosis in early cirrhosis is easier to break down, which preserves the liver parenchyma and makes reversal of the disease more feasible [24]**.** AFP increased in both control and case groups as recurrence of HCC became more aggressive. Similarly, Patients with HCC who received DAAs had a considerably higher survival rate, lower bilirubin levels, and higher albumin levels compared to patients who did not receive DAAs, according to a multicenter retrospective analysis [25]**.**

Against our study, **Minami *et al.*** [11] reported significantly higher total bilirubin among DAAs group and comparable ALT levels**. Kuromatsu *et al.*** [26]**,** on the other hand to the current study, reported that AST level was higher significantly among treated group**.**

Regarding portal vein thrombosis (PVT), lymph nodes (LNs) metastasis and distant metastasis, they were significantly higher among case group than among control group. In concordance of the current study, **Fouad *et al.*** [23] reported that untreated group had larger number of lesions but smaller in size than DAAs with statistically significant difference between both groups**. Romano *et al.*** [27] showed that tumours behave aggressively following DAAs, with an increased frequency of nodules and extrahepatic metastases, indicating that tumour growth is faster than typical in these patients. Patients who underwent DAA treatment had more aggressive recurrence relative to the initial tumour features, according to **Reig *et al.*** [4]**.** When comparing the two groups, **Brozzetti *et al.*** [28] found that the number of recurring lesions was significantly higher in the DAAs group**.** In contrary to the current study, both groups were comparable regarding recurrent lesions site and number between DAAs group and control group in an earlier study by **Minami *et al.*** [11]**. Zanetto *et al.*** [29] found no significant differences in tumour progression (number, size, site and vascular invasion) according to RECIST in the HCV+ DAAs-treated group (35% versus 17% respectively) or in HCC dropout rates (13% versus 13%, respectively) or HCC recurrence after LT in the DAAs-untreated group (n = 46). (12.5% versus 8.3% respectively) [30]**.**

Regarding portal vein thrombosis with recurrent lesions, it had higher frequency among case group than among control group with significant difference. Similarly, **Fouad *et al.*** [23] reported that vascular invasion reflected by portal vein thrombosis was more frequent with DAAs confirming his results about the aggressiveness of the lesions with DAAs**.** Similarly, **Abdelaziz *et al.*** [30] reported higher vascular invasion in with recurrent lesions in DAAs group**. Reig *et al.*** [4] reported more invasive vascular invasion together with increased size and multiplicity of lesions after DAAs**.** In contrary to the current study, **Pinero *et al.*** [31]**,** did not report statistically significant difference between both groups regarding portal vein thrombosis with recurrent lesions**.** A number of hypotheses have been suggested to account for the severity of HCC recurrence; for example, some have linked HCC progression to preexisting risk factors such advanced fibrosis grade [32]**.** Another idea suggests that DAAs speed up viral clearance, which in turn disrupts immune surveillance. This disruption could lead to the restoration of innate immunity and an increase in the proliferation of cancer cells due to a decrease in IFN activation [29]**.** In addition, a reduction in the number of cytotoxic activities of natural killer cells in the liver is one of the immune system modifications found after HCV eradication, which favours a faster evolution of HCC foci [33]**.**

Regarding type of DAA regimen, it had no significant effect on HCC recurrence, which is similar to that reported by **Mashiba *et al.*** [34]**.** The groups that received and that did not receive DAAs for HCC did not differ substantially with respect to the following treatment methods: radiofrequency ablation, microwave ablation, ethanol injection, or surgical resection. Similarly, when it came to the treatment modality of HCC, **Conti *et al.*** [8] found no significant difference between the two groups**. Huang *et al.*** [35], reported comparable distribution of different treatment modalities between both groups**.**

CONCLUSION

It appeared that the recurrence of HCC in individuals exposed to DAAs was more rapid and aggressive than in those who are not exposed to DAAs. It is advised to wait at least one year after ablative treatment of HCC had produced a complete response before administering DAA.

Financial support and sponsorship: Nil
Conflict of Interest: Nil

REFERENCES

1. **Zhang W, Aryan M, Qian S *et al.* (2021):** A focused review on recent advances in the diagnosis and treatment of viral hepatitis. Gastroenterology Research, 14: 139-56.
2. **Wen N, Cai Y, Li F *et al.* (2022):** The clinical management of hepatocellular carcinoma worldwide: A concise review and comparison of current guidelines: 2022 update. Bio Science Trends, 16: 20-30.
3. **Webster D, Klenerman P, Dusheiko G (2015):** Hepatitis C. Lancet, 385: 1124-1135.
4. **Reig M, Mariño Z, Perelló C *et al.* (2016):** Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol., 65: 719-26.
5. **Nault J, Colombo M (2016):** Hepatocellular carcinoma and direct acting antiviral treatments: controversy after the revolution. Journal of Hepatology, 65: 663-665.
6. **WHO (2023):** Hepatitis C. http://www.who.int/news-room/fact-sheets/details/hepatitis-c
7. **Huang C, Yu M (2020):** Unmet needs of chronic hepatitis C in the era of direct-acting antiviral therapy. Clinical and Molecular Hepatology, 26: 251-57.
8. **Conti F, Buonfiglioli F, Scuteri A *et al.* (2016):** Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. Journal of Hepatology, 65: 727-733.
9. **El Kassas M, Funk A, Salaheldin M *et al.* (2018):** Increased recurrence rates of hepatocellular carcinoma after DAA therapy in a hepatitis Cinfected Egyptian cohort: a comparative analysis. J Viral Hepat., 25: 623-30.
10. **Anrs T (2016):** Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. Journal of Hepatology, 65: 734-740.
11. **Minami T, Tateishi R, Nakagomi R *et al.* (2016):** The impact of direct-acting antivirals on early tumor recurrence after radiofrequency ablation in hepatitis C-related hepatocellular carcinoma. Journal of Hepatology, 65: 1272-1273.
12. **Singal A, Rich N, Mehta N *et al.* (2019):** Direct-acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter North American cohort study. Gastroenterology, 156 (6): 1683–1692.
13. **Ogawa E, Furusyo N, Nomura H *et al.* (2018):** Short-term risk of hepatocellular carcinoma after hepatitis C virus eradication following direct-acting anti-viral treatment. Aliment Pharmacol Ther., 47 (1): 104–113.
14. **Ahn Y, Lee H, Kim D *et al.* (2021):** Independent risk factors for hepatocellular carcinoma recurrence after direct-acting antiviral therapy in patients with chronic hepatitis C. Gut Liver, 15: 410-9.
15. **Sung P, Shin E (2021):** Immunological Mechanisms for Hepatocellular Carcinoma Risk after Direct-Acting Antiviral Treatment of Hepatitis C Virus Infection. Journal of Clinical Medicine, 10: 221-26.
16. **Sherman M (2008):** Recurrence of hepatocellular carcinoma. The New England Journal of Medicine, 359 (19): 2045–2047.
17. **Chu P, Nakamoto N, Taniki N *et al.* (2017):** On-treatment decrease of NKG2D correlates to early emergence of clinically evident hepatocellular carcinoma after interferonfree therapy for chronic hepatitis C. PloS One, 12 (6): e0179096. doi: 10.1371/journal.pone.0179096.
18. **Sanduzzi-Zamparelli M, Boix L, Leal C *et al.* (2019):** Hepatocellular Carcinoma Recurrence in HCV Patients Treated with Direct Antiviral Agents. Viruses, 11: 406. doi: 10.3390/v11050406
19. **Villani R, Facciorusso A, Bellanti F *et al.* (2016):** DAAs Rapidly Reduce Inflammation but Increase Serum VEGF Level: A Rationale for Tumor Risk during Anti-HCV Treatment. PloS One, 11 (12): e0167934. doi: 10.1371/journal.pone.0167934
20. **Cabibbo G, Petta S, Calvaruso V *et al.* (2017):** Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct- acting antivirals? A prospective multicentre study. Alimentary Pharmacology & Therapeutics, 46: 688-695.
21. **Adhoute X, Penaranda G, Raoul J *et al.* (2018):** Hepatocellular carcinoma recurrence in hepatitis C virus-related cirrhosis treated with direct-acting antivirals: a case–control study. European Journal of Gastroenterology & Hepatology, 30: 368-375.
22. **Bachofner J, Valli P, Kroger A *et al.* (2017):** Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int., 37(3):369–376.
23. **Fouad M, El Kassas M, Ahmed E *et al.* (2021):** Tumor characteristics of hepatocellular carcinoma after direct-acting antiviral treatment for hepatitis C: Comparative analysis with antiviral therapy-naive patients. World Journal of Hepatology, 13: 1743-52.
24. **Shiha G, Soliman R, Mikhail N *et al.* (2020):** Changes in hepatic fibrosis stages after achieving SVR following direct-acting anti-viral treatment: a prospective study. Gastro Hep., 2 (1): 39–48.
25. **Ochi H, Hiraoka A, Hirooka M *et al.* (2021):** Direct-acting antivirals improve survival and recurrence rates after treatment of hepatocellular carcinoma within the Milan criteria. J Gastroenterol., 56: 90-100.
26. **Kuromatsu R, Ide T, Okamura S *et al.* (2022):** Hepatitis C Virus Elimination Using Direct Acting Antivirals after the Radical Cure of Hepatocellular Carcinoma Suppresses the Recurrence of the Cancer. Cancers, 14: 2295. doi: 10.3390/cancers14092295
27. **Romano A, Capra F, Piovesan S *et al.* (2016):** Incidence and pattern of" de novo" hepatocellular carcinoma in HCV patients treated with oral DAAs. Hepatology. Wiley-Blackwell, Pp: 31-71. https://link.springer.com/chapter/10.1007/3-540-28977-1_3
28. **Brozzetti S, Tancredi M, Bini S *et al.* (2021):** HCC in the Era of Direct-Acting Antiviral Agents (DAAs): Surgical and Other Curative or Palliative Strategies in the Elderly. Cancers, 13: 3025. doi: 10.3390/cancers13123025
29. **Zanetto A, Shalaby S, Vitale A *et al.* (2017):** Dropout rate from the liver transplant waiting list because of hepatocellular carcinoma progression in hepatitis C virus-infected patients treated with direct-acting antivirals. Liver Transpl., 23: 1103-1112.
30. **Abdelaziz A, Nabil M, Abdelmaksoud A *et al.* (2019):** Tumor behavior of hepatocellular carcinoma after hepatitis C treatment by direct-acting antivirals: comparative analysis with non-direct-acting antivirals-treated patients. European Journal of Gastroenterology & Hepatology, 31: 75-79.
31. **Piñero F, Boin I, Chagas A *et al.* (2020):** Direct- acting antivirals and hepatocellular carcinoma: no evidence of higher wait- list progression or posttransplant recurrence. Liver Transplantation, 26: 640-650.
32. **El Kassas M, Elbaz T, Salaheldin M *et al.* (2019):** Impact of treating chronichepatitis C infection with direct-acting antivirals on the risk of hepatocellular carcinoma: The debate continues - A mini-review. J Adv Res., 17: 43-48.
33. **Innes H, Barclay S, Hayes P *et al.* (2018):** The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: Role of the treatment regimen. J Hepatol., 68: 646-654.
34. **Mashiba T, Joko K, Kurosaki M *et al.* (2018):** Does interferon-free direct-acting antiviral therapy for hepatitis C after curative treatment for hepatocellular carcinoma lead to unexpected recurrences of HCC? PLoS One, 13: e0194704. doi: 10.1371/journal.pone.0194704
35. **Huang A, Mehta N, Dodge J *et al.* (2018):** Direct- acting antivirals do not increase the risk of hepatocellular carcinoma recurrence after local- regional therapy or liver transplant waitlist dropout. Hepatology, 68: 449-461.