Hepatic resection for two giant hepatocellular carcinoma after oral direct-acting antiviral therapy: Is there a relationship?

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ABSTRACT

Introduction: Direct-acting antiviral drugs have been recently introduced for management of chronic hepatitis C virus (HCV) patients. Those medications have achieved a dramatic improvement of sustained virologic response (SVR) reaching almost 90%. However, reports regarding the increased risk of occurrence or recurrence of hepatocellular carcinoma (HCC) in chronic HCV patients who achieved SVR after direct-acting antiviral drugs are controversial.

Methods: We report two cases of giant HCCs complicating chronic HCV infection after direct-acting antiviral drugs-based therapies and were managed by major hepatic resection.

Results: Two male patients with chronic HCV infection received several regimens oral direct acting antiviral drugs with a SVR for 3 and 6 months, respectively. They complained of progressive right hypochondrial pain and abdominal enlargement. Two large HCCs were diagnosed (16.2 cm * 17.6 cm * 16.9 cm, and 18 cm * 13 cm * 16.5 cm in dimensions) with markedly elevated serum alpha feto-protein (36,000 and 7,000 ng/ml, respectively). Due to the presence of adequate residual liver volume, the decision was to proceed for surgical resection. Central hepatectomy and extended right hemi-hepatectomy were performed, respectively. Patients had smooth postoperative course and were discharged after 10 and 9 days, respectively.

Conclusion: The relationship between direct-acting antiviral drugs and HCC is controversial. Those cases add support to the accumulating literature suggesting the relationship of HCC development in chronic HCV patients receiving direct-acting antiviral drugs. Further prospective studies with adequate long term follow up are needed to prove or disprove this relationship.

Key Words: Hepatocellular carcinoma, Direct-acting antiviral drugs, Hepatitis C virus, Case series

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Generally, 90% of HCC is associated with cirrhosis. Compared to other causes of cirrhosis, cases with chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections have shown a higher risk of developing HCC.[1]

Interferon-based regimens have been the mainstay of HCV management.[2] Recently, direct-acting antiviral drugs have been introduced. Those novel medications have achieved a dramatic improvement of sustained virologic response (SVR) rate reaching almost 90%.[3-6] However, it has been suggested the increased risk of occurrence or recurrence of HCC in chronic HCV patients who achieved SVR after direct-acting antiviral drugs.

Previous reports which investigated the long-term effects of
direct-acting antiviral drugs questioned the impact of those drugs on the occurrence or recurrence of HCC in patients with HCV related cirrhosis.\cite{3,7–9} Such finding was not seen in other cases treated with interferon-based regimens, and this endorsed specialists to propose that those drugs may play a significant role in the development of HCC.\cite{3,8,9} On the other hand, other studies have reported the opposite effect of direct-acting antiviral drugs on HCC occurrence or recurrence.\cite{10,11}

The relationship between direct-acting antiviral agents and HCC occurrence or recurrence and the underlying possible mechanisms remain controversial and there is no enough evidence to prove or disprove this relationship.

In this report, we describe two cases of giant HCCs complicating chronic HCV infection after direct-acting antiviral drugs-based therapies and were managed by major hepatic resection. This work has been reported in line with the PROCESS criteria.\cite{12}

2. CASE REPORT PRESENTATION

2.1 Case number 1

A 65 years male patient had a history of chronic HCV infection. Liver function tests were within normal range (Child-Pugh score class A), and triphasic computed tomography (CT) showed cirrhotic liver with no other abnormalities. The patient was planned to receive antiviral therapy.

The patient received oral direct acting antiviral therapy in the form of: Ombitasvir (12.5 mg), paritaprevir (75 mg), and ritonavir (50 mg) plus Ribavirin in August 2015 for 3 months, but relapse occurred after 6 months. Then he received Sofosbuvir (400 mg) plus Daclatasvir (60 mg) plus Ribavirin in October 2016 for 6 months, but also relapse occurred again. Finally, he received Sofosbuvir (400 mg) plus Simeprevir (150 mg) plus Ribavirin in April 2017 for 6 months. HCV polymerase chain reaction (PCR) after completion of the therapy was negative.

The patient was referred to our center complaining of progressive right hypochondrial pain and abdominal enlargement. Abdominal ultrasonography revealed cirrhotic liver with huge well defined central lesion 14 cm * 19 cm, mostly HCC, mild perihepatic ascites, with no other abnormalities.

Triphasic Abdominal and pelvic magnetic resonance imaging (MRI) showed large capsulated liver mass at right sub-diaphragmatic and gall bladder fossa region showing heterogenous enhanced solid components and displaying mixed signal on both T1 and T2 images denoting cystic and bloody parts (see Figure 1). It is seen elevating the right diaphragmatic copula and anterior abdominal wall muscles, displacing the gastric pylorus, and abutting and stretching the hepatic artery. Multiple related anterior abdominal wall venous collaterals and mild perihepatic ascites. No other abnormalities were detected.

Triphasic abdominal CT showed huge soft tissue mass in right sub-phrenic region arising from segments IV and VIII. It shows heterogenous arterial enhancement with delayed washout. It measures 16.2 cm * 17.6 cm * 16.9 cm in dimensions.

Figure 1. Preoperative magnetic resonance imaging showing large central hepatic mass sparing the left lateral and right posterior sections
CT venography revealed patent compressed right hepatic vein with attenuated non-visualized middle and left hepatic veins. Patent markedly compressed inferior vena cava. CT portography revealed patent, markedly compressed portal vein. The left portal branch was markedly attenuated, while the right anterior branch was completely non-separable from the mass. Multiple anterior wall recanalized collaterals were noted (see Figure 2).

![Figure 2](image)

**Figure 2.** (A, B) Preoperative computed tomography venography showing failure of visualization of middle and left hepatic veins while the right hepatic vein is spared. (C, D) Preoperative computed tomography portography showing infiltration of left portal vein branch while right portal vein is spared.

CT volumetry showed that total liver volume excluding the mass was 1,123 cc, estimated residual liver volume was 976 cc, and residual liver percentage was 86%. Metastatic work up was performed (including non-contrast CT chest and bone scan) and was free from extrahepatic metastases.

Preoperative blood picture, and liver functions were within normal range (Child-Pugh class A). Preoperative serum alpha feto-protein was 36,000 ng/ml. The decision was to proceed for surgical resection.

Exploration revealed cirrhotic liver with large hepatic mass occupying segments IV, V and VIII. It is extending downwards on the gastric pylorus and transverse colon with multiple dilated collaterals on top (see Figure 3). Central hepectectomy (central bissectionectomy) was performed. The operation time was 6 hours, blood loss was 1,500 cc, and blood transfusion was 2 packed RBCs units.

The patient was transferred to intensive care unit for 48 hours for monitoring. The patient had smooth postoperative course and was discharged from hospital after 10 days.

![Figure 3](image)

**Figure 3.** Operative photo showing large central hepatic mass with multiple dilated collaterals on top (white arrows)

Grossly, the mass was capsulated 25 * 20 * 17 cm in size with multiple foci of hemorrhage and necrosis. Pathological examination showed grade III HCC, trabecular and acinar
forms with intact capsule and lympho-vascular emboli. The liver background showed macronodular cirrhosis.

2.2 Case number 2
A 56 years male patient had a history of chronic HCV infection. Liver function tests were within normal range (Child-Pugh score class A), and triphasic abdominal CT showed cirrhotic liver with small right hemi-liver lobe nodule (suspicious of cirrhotic nodule). The patient was planned to receive antiviral therapy.

The patient received oral direct acting antiviral therapy in the form of Sofosbuvir (400 mg) plus Ribavirin in February 2016 for 6 months, but relapse occurred after 3 months. Then he received Sofosbuvir (400 mg) plus Daclatasvir (60 mg) plus Ribavirin in December 2016 for 6 months, but also relapse occurred again after 6 months.

The patient was referred to our center complaining of progressive right hypochondrial pain and abdominal enlargement. Abdominal ultrasonography showed enlarged cirrhotic liver with large mass occupying most of the right hemi-liver, mostly HCC. No other abnormalities were detected.

Triphasic CT showed enlarged cirrhotic liver with large capsulated exophytic neoplastic mass occupying all segments of the right hemi-liver with peripheral intra-lesional arterio-venous shunts. It measures 18 cm * 13 cm * 16.5 cm in dimensions (see Figure 4).

Figure 4. Preoperative computed tomography showing the large right hemi-liver mass encroaching on segment IV

CT angiography showed that the mass is located between portal branches with no vascular thrombosis or infiltration. No other vascular abnormalities were detected (see Figure 5).

CT volumetry showed that total liver volume excluding the mass was 1,750 cc, estimated residual liver volume was 970 cc, and residual liver percentage was 55.4%. Metastatic work up was performed (including non-contrast CT chest and bone scan) and was free from extrahepatic metastases.

Preoperative blood picture, and liver functions were within normal range (Child-Pugh class A) apart from serum bilirubin (1.9 mg/dl). Preoperative serum alpha feto-protein was 7,000 ng/ml. Also, the decision was to proceed for surgical resection.

Exploration revealed cirrhotic liver with large hepatic mass occupying the whole right hemi-liver. Extended right hemi-hepatectomy was performed including a part of segment IV. The operation time was 4 hours, blood loss was 2,000 ml, and blood transfusion was 3 packed RBCs units.

The patient was transferred to intensive care unit for 24 hours.
for monitoring. The patient had smooth postoperative course and was discharged from hospital after 9 days.

Grossly, the mass was capsulated 25 cm * 17 cm * 14 cm in size. The cut section showed pale greyish-yellow nodular lesion with intact capsule. Pathological examination showed grade III HCC, trabecular and acinar forms with intact capsule and lympho-vascular emboli. The liver background showed active macronodular cirrhosis.

**Figure 5.** (A, B) Preoperative computed tomographic portography showing tumor invasion of the right portal vein while left portal vein is spared. (C) Preoperative computed tomographic venography showing failure of visualization of the right hepatic vein while left and middle hepatic veins are spared. (D) Preoperative computed tomographic arteriography showing infiltration of the right hepatic artery

### 3. DISCUSSION

HCV infection is a global health problem that affects millions of people worldwide. HCV-infected individuals have a 2.4 times higher risk of all-cause mortality compared to the non-infected population, and 26.5 times the risk of liver-related mortality. HCV-induced progressive liver cirrhosis is a well-established high-risk factor for the development of HCC.

Egypt is considered one of the highest zones of HCV infection prevalence worldwide. Nowadays, chronic HCV infection, with predominance of genotype 4, is the principal cause of liver cirrhosis and HCC among Egyptians.

For long time, interferon-based regimens have been the mainstay of HCV management with a SVR in almost 50% of the patients. Previous studies found that the risk for HCC occurrence was markedly lower in patients who achieved SVR in comparison with those who did not achieve a SVR. However, due to the limited efficacy of interferon-based regimens beside its side effects including, neuro-psychiatric and myelosuppressive complications, limited its wide use.

In the recent years, direct-acting antiviral drugs have been introduced as a new hope for HCV patients. Initial reports regarding those novel medications have achieved a dramatic improvement of SVR rate reaching more than 90% of the HCV treated patients. So, it was assumed that, HCC occurrence and recurrence will continue to decrease with higher SVR rates with direct-acting antiviral drugs.

On the contrast, recent reports regarding this issue reported unexpectedly high rates of denovo HCC and HCC recurrence after achievement of SVR with those agents. Reig et al. firstly reported high recurrence rates of HCC at a median of 5.7 months after complete treatment with subse-
quent direct-acting antiviral drugs. They also reported that most of these recurrences were multifocal, and almost 20% of the cases had locally infiltrative or extrahepatic lesions. Cabibbo et al.[22] in a meta-analysis of 11 studies comparing interferon-based regimens and direct-acting antiviral drugs reported accelerated HCC recurrence at 6 months in patients receiving direct-acting antiviral drugs.

Other reports regarding this issue could not find clear relationship. Spârchez et al.[23] in a review article regarding this issue concluded that the current available literature is unclear and the risk of HCC needs to be better clarified with prospective randomized controlled trials. Kanwal et al.[24] found that the overall annual incidence of HCC was markedly higher in patients who did not achieve SVR with direct-acting antiviral drugs compared to those who did. They concluded that achieving SVR, reduces but does not eliminate the risk of de novo HCC, particularly in patients with cirrhosis. The results of those reports are quite conflicting and did not reach a solid evidence regarding the safety of those agents, and the appropriate candidates for those agents.

Previous reports explaining possible mechanisms for HCC development in association with direct-acting antiviral drugs focused on loss of immune control owing to clearance of HCV-specific T cells from the liver. The rapid decline of HCV viral load from the circulation induced by direct-acting antiviral drugs was associated with restored HCV specific CD8+ T cell function, memory T cell re-differentiation and lymphocyte deactivation, and normalized NK cell function.[25–28] However, the underlying mechanisms still unclarified.

Concerns have also been raised that HCCs that developed in relation to direct-acting antiviral drugs were more aggressive. They have higher frequency of multifocality and advanced stage.[29] In this report, we noticed abnormal large tumor sizes and high levels of preoperative serum AFP. These are strong indicators of the more aggressive behavior of those tumors than usually found in our practice.

Alpha fetoprotein has been identified as a strong predictor of patient’s survival and tumor recurrence after hepatic resection for HCC.[30] This relationship arises from the association between high serum AFP levels and tumor size, number and the presence of microvascular invasion.[31] Also, HCCs associated with high serum AFP level had a higher cell proliferative activity and more aggressive behavior.[32]

We previously identified AFP as a strong predictor for HCC recurrence after hepatic resection for HCC,[33] and in this report we noticed abnormal high levels of preoperative serum AFP levels than usually found in our practice.[15,34,35]

4. Conclusion

In conclusion, this case series adds support to the accumulating literature suggesting the relationship of HCC development in chronic HCV patients receiving direct-acting antiviral drugs. Further prospective studies with adequate long term follow up are needed to prove or disprove such relationship.

Conflicts of Interest Disclosure

The authors declare that there is no competing interest.

References

[1] Hoshida Y, Fuchs BC, Bardeesy N, et al. Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma. J Hepatol. 2014; 61(1 Suppl): 79-90.
[2] Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015; 385(9973): 1124-1135. https://doi.org/10.1016/S0140-6736(14)62401-6
[3] Baumert TF, Jüling F, Ono A, et al. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. BMC Medicine. 2017; 15(1): 52-61. PMid:28288626. https://doi.org/10.1186/s12916-017-0815-7
[4] Chung RT, Baumert TF. Curing chronic hepatitis C – the arc of a medical triumph. N Engl J Med. 2014; 370(17): 1576-1578. PMid:24720678. https://doi.org/10.1056/NEJMp1400986
[5] Yang JD, Aqel BA, Pungpapong S, et al. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. J Hepatol. 2016; 65(4): 859-869. PMid:27392425. https://doi.org/10.1016/j.jhep.2015.06.002
[6] Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol. 2016; 64(6): 1224-1231. PMid:26829205. https://doi.org/10.1016/j.jhep.2016.01.029
[7] Reig M, Marino Z, Perell C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016; 65(4): 719-726. PMid:27084592. https://doi.org/10.1016/j.jhep.2016.04.008
[8] Grandhe S, Fenrette CT. Occurrence and Recurrence of Hepatocellular Carcinoma After Successful Direct-Acting Antiviral Therapy for Patients with Chronic Hepatitis C Virus Infection. Gastroenterology & Hepatology. 2017; 13(7): 421-425.
[9] Okay E, Sari A, Odabaşoğlu H, et al. Hepatocellular carcinoma presenting as a huge intra-abdominal mass: A case report. Turk J Gastroenterol. 2014; 25: 330-332. PMid:25141325. https://doi.org/10.5152/tjg.2014.3255
[10] Afferenti A, Ju M, Catt J, et al. Successful hepatitis C treatment in advanced cirrhosis with DAA reduces HCC incidence. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract 944.
[11] Nagaoki Y, Akita H, Kobayashi T, et al. Hepatocellular carcinoma development in hepatitis C virus patients who achieved sustained viral response by interferon therapy and direct anti-viral agents ther-
apy. Presented at the American Association for the Study of Liver Diseases meeting; November 11-15, 2016; Boston, Massachusetts. Abstract S80.

[12] Agha RA, Fowler AJ, Ramrohan S, et al. The PROCESS Statement: Preferred Reporting of Case Series in Surgery. International Journal of Surgery. 2016; 36(Pt A): 319-323.

[13] Daw MA, El-Bouzedi AA, Ahmed MO, et al. Geographic integration of hepatitis C virus: a global threat. World Journal of Virology. 2016; 5(4): 170. PMid:27878104. https://doi.org/10.15501/wjv.v5.i4.170

[14] El-Zanaty F, Way A. Egypt Demographic and Health Survey 2008. Egyptian Ministry of Health - Cairo.

[15] Miller FD, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. Proc Natl Acad Sci USA. 2010; 107(33): 14757-14762. PMid:20696911. https://doi.org/10.1073/pnas.1008977107

[16] Abdel-Wahab M, El-Ghawalby N, Mostafa M, et al. Epidemiology of hepatocellular carcinoma in lower Egypt, Mansoura Gastroenterology Center. Hepatogastroenterology. 2007; 54(73): 157-62.

[17] Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013; 158: 329-37. PMid:23460056. https://doi.org/10.7326/0003-4819-158-5-201303050-00006

[18] El-Serag HB, Kanwal F, et al. Risk of hepatocellular carcinoma after sustained virological response in veterans with hepatitis C virus infection. Hepatology. 2016; 64: 130-137. PMid:26946190. https://doi.org/10.1002/hep.28535

[19] van der Meer AJ, Feld JJ, Almasio PL, et al. Risk of cirrhosis related complications in patients with advanced fibrosis following hepatitis C virus eradication. J Hepatol. 2017; 66: 485-493. PMid:27708714. https://doi.org/10.1016/j.jhep.2016.10.017

[20] Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016; 65: 727-733. PMid:27349488. https://doi.org/10.1016/j.jhep.2016.06.015

[21] Ravi S, Axley P, Jones D, et al. Unusually high rates of hepatocellular carcinoma after treatment with direct acting antiviral therapy for hepatitis C related cirrhosis. Gastroenterology. 2017; 152: 911-912. PMid:28161225. https://doi.org/10.1053/j.gastro.2016.12.021

[22] Cabibbo G, Petta S, Barbára M, et al. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver International. 2017; 37(8): 1157-66. PMid:28061016. https://doi.org/10.1111/liv.13387

[23] Sánchez Z, Mocan T. Hepatocellular Carcinoma Occurrence and Recurrence After Antiviral Treatment in HCV-Related Cirrhosis. Are Outcomes Different after Direct Antiviral Agents? A Review. Journal of Gastrointestinal & Liver Diseases. 2017; 1: 26.

[24] Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology. 2017; 153(4): 996-1005. PMid:28642197. https://doi.org/10.1053/j.gastro.2017.06.012

[25] Martin B, Hennecke N, Lohmann V, et al. Restoration of HCV-specific CD8+ T cell function by interferon-free therapy. J Hepatol. 2014; 61(3): 538-43. PMid:24005492. https://doi.org/10.1016/j.jhep.2014.05.043

[26] Burchill MA, Golden-Mason L, Wind-Rotolo M, et al. Memory re-education and reduced lymphocyte activation in chronic HCV infected patients receiving direct-acting antivirals. J Viral Hepat. 2015; 22(12): 983-91. PMid:26482547. https://doi.org/10.1111/jvhe.12466

[27] Serti E, Chepa-Lotreza X, Kim YJ, et al. Successful interferon-free therapy of chronic hepatitis C virus infection normalizes natural killer cell function. Gastroenterology. 2015; 149(1): 190-200. PMid:25754160. https://doi.org/10.1053/j.gastro.2015.03.004

[28] Perello MC, Fernandez-Carrillo C, Londono MC, et al. Reactivation of herpesvirus in patients with hepatitis C treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol. 2016; 14(11): 1662-6. PMid:27211502. https://doi.org/10.1016/j.cgh.2016.05.016

[29] Romano A, Capra F, Piovessan S, et al. Incidence and pattern of “de novo” hepatocellular carcinoma in HCV patients treated with oral DAAs. In Hepatology 2016 Oct 1 (Vol. 63, No. 1 SUPP, pp. 10A-10A). 111 RIVER ST; HOBOKEN 07030-5774, NJ USA: WILEY-BLACKWELL.

[30] Lai Q, Melandro F, Pinheiro RS, et al. Alpha-fetoprotein and novel tumor biomarkers as predictors of hepatocellular carcinoma recurrence after surgery: a brilliant star raises again. Int J Hepatol. 2012; 2012: 893103.

[31] Zhou YM, Yang JM, Li B, et al. Risk factors for early recurrence of small hepatocellular carcinoma after curative resection. Hepatobiliary Pancreat Dis Int. 2010; 9: 33-7.

[32] Peng SY, Chen WJ, Lai PL, et al. High alpha-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: significance of hepatitis virus infection, age, p53 and betacatenin mutations. Int J Cancer. 2004; 112: 44-50. PMid:15305374. https://doi.org/10.1002/ijc.20279

[33] Wahab MA, Shelta A, Hamed H, et al. Predictors of recurrence in hepatitis C virus related hepatocellular carcinoma after hepatic resection: a retrospective cohort study. Eurasian Journal of Medicine. 2014; 46(1): 36-41. PMid:25610292. https://doi.org/10.5152/eajm.2014.07

[34] Abdel-Wahab M, El-Husseiny TS, El Hanafi E, et al. Prognostic factors affecting survival and recurrence after hepatic resection for hepatocellular carcinoma in cirrhotic liver. Langenbeck’s Archives of Surgery. 2010; 395(6): 625-32. PMid:20358380. https://doi.org/10.1002/cgh.22079

[35] Abdel-Wahab M, Sultan A, El-Ghawalby N, et al. Hepatic resection in cirrhotic liver for treatment of hepatocellular carcinoma in Egyptian patients. Experience with 140 cases in a single center. Hepatogastroenterology. 2004; 51(56): 559-63.