中文題目：C 型肝炎併肝癌使用口服抗病毒藥後腫瘤快速復發-個案報告及文獻回顧

英文題目：Rapid recurrence of hepatocellular carcinoma in a patient undergoing direct-acting antiviral agents therapy for chronic hepatitis C-a case report and literature review

作　　者：陳建安[1]，謝秉欣[1]，孫定平[2]，劉綺霞[3]，許銘仁[1]，林勤益[1]，郭行道[1]，郭樂明[1]，孫啟書[1]，馮意哲[1]，林政頤[1]，林育民[1]

服務單位：[1]奇美醫院內科部胃腸肝膽科; [2]奇美醫院外科部一般外科暨移植外科 [3]奇美醫院影像醫學部放射診斷部

Chronic hepatitis C infection is the leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide.[1] HCC may occur at an average 3.5% annual rate when liver cirrhosis is established.[2] Current HCV cure rate with IFN-free regimens has increased SVR rates over 90% within a very short time.[2.3.] However, there are limited data of the association between DAA and HCC recurrence.

We have found a 56 y/o woman with history of treatment naïve chronic hepatitis C (Genotype 1b) without cirrhosis. She was diagnosed as HCC, BCLC stage A, with hepatic tumors in S6 (4.0cm) and S5 (0.8cm) on CT (2016/11/01) and MRI (2016/11/09). She received Da Vinci hepatectomy on 2016/11/10. Pathology reported tumor involves visceral peritoneum (pT4) but tumor margin was free. Non-tumor part fibrotic stage was F3 (Ishak score). Two months later, sonogram suggested no tumor recurrence then she received Ledipasvir/Sofosbuvir for eight weeks since 2017/02/12. Pre-treatment HCV RNA: 1,617,623 IU/mL. However, a palpable mass over the RLQ was noticed on 2017/03/15. HCV RNA was undetectable. CT found a 13cm tumor in pelvic cavity on 2017/03/20 (Fig.1). She received resection on 2017/3/23 which pathology was consistent with recurrence of the previous HCC.

HCV-induced inflammation is a strong promoter of tumor development and resolution of HCV infection may reduce incidence of HCC with successful IFN therapy.[2] Surprisingly, Reig *et al.* found 27.6% of HCC recurrence occurred in 58 HCV-related cirrhotic patients who had a previous HCC compared with 3.2% of cirrhotic patients without history of HCC after a following time of 5.7 months after starting DAA.[1.3] Conti *et al.* analyzed the occurrence of HCC in 344 HCV-related cirrhotic patients without active HCC, who were treated with DAA. After 24 weeks following, HCC was detected in 26 patients (7.6%): 17 of 59 patients (28.81%) in previous HCC group and 9 of 285 patients (3.16%) in group without previous HCC.[1.2] Reig claimed tumor dormancy results from immune surveillance controlling tumor outgrowth, hostile tumor microenvironment, or tumor cells being quiescent.[4]

IFN-free DAA therapy can rapidly achieve viral suppression but reduce inflammation may cause immune surveillance downregulation.[1,2,3] Otherwise, miR-122 level decreased on IFN-free DAA therapy which plays a central role in suppressing viral replication and controlling hepatocarcinogenesis.[1] Extrahepatic cancer development would become apparent If immune cancer surveillance is distorted. Chronic inflammation such as long-lasting HCV infection increases the risk of extrahepatic cancer and transformed cells may stay subclinical or even remain indolent for a long period.[4]

These observed studies may have bias, such as small sample size, elder, cohort with more advanced liver disease, and short observation time. A French cohorts did not observe an increased risk of HCC recurrence after DAA treatment.[5] Moreover, from a meta-analysis of 41 studies (13,875 patients) of initial or recurring HCC following DAA treatment, no evidence for different HCC occurrence or recurrence following a cure from DAA or interferon-based regimens is found.[6]

We observed a patient who started DAA therapy three months after receiving curative surgery for her ruptured HCC. Rapid peritoneal recurrence of her HCC was found within only four weeks after initiating DAA therapy. A recent study found that median volume doubling times (TVDT) of patient with HCV related HCC was 137.2 (range: 22.4-851.2) days.[7] The calculated tumor volume was $784.4cm^3$ (13.1*10.7*10.7*0.523). We expected the CT with 5 mm thick slices may miss tumor with 4mm in diameter in the initial examination. That is, CT may miss tumor with the volume of $0.335cm^3$ (0.4*0.4*0.4*0.523). The calculated TVDT was about 14.55 days between the two CT examination (140 days). The explanations of the rapid recurrence of HCC may be more aggressive tumor behavior or DAA accelerated the tumor cell growth.

Though recent debate seems more favor no increased recurrence of HCC after curative treatment[5,6]; however, the effects of DAA on the imaging-undetectable HCC foci after curative therapy is yet to be clarified. In conclusion, we suggest longer observation after curative HCC therapy to see if there is any early recurrence of HCC before initiating DAA therapy.

Reference:

1. Liu C-H, Kao J-H. **Hepatocellular carcinoma recurrence after interferon-free direct acting antiviral treatment for chronic hepatitis C virus infection: fact or fiction?** Transl Cancer Res. 2016 Aug;5(S2):S192–5.

2. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. **Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals.** J Hepatol. 2016 Oct;65(4):727–33.
3. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. **Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy.** J Hepatol. 2016 Oct;65(4):719–26.
4. Reig M, Boix L, Mariño Z, Torres F, Forns X, Bruix J. **Liver Cancer Emergence Associated with Antiviral Treatment: An Immune Surveillance Failure?** Semin Liver Dis. 2017;37(2):109–18.
5. Pol S. **Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts.** J Hepatol. 2016;65(4):734–40.
6. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, et al. **No evidence for higher risk of hepatocellular carcinoma occurrence or recurrence following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression.** J Hepatol 2017;66:S12.
7. An C, Choi YA, Choi D, Paik YH, Ahn SH, Kim M-J, et al. **Growth rate of early-stage hepatocellular carcinoma in patients with chronic liver disease.** Clin Mol Hepatol 2015;21:279–86.