Editorial

Hepatocellular Carcinoma Surveillance and Treatment: A Way to Reduce Cancer-related Mortality in Cirrhotic Patients

Xiangjun Qian[1], Xiaotong Yan[2], Xiangwei Zhai[2], Ni Li[3], Chunfeng Qu[4]* and Fengmin Lu[1]*

[1]*Department of Microbiology & Infectious Disease Center, School of Basic Medical Sciences, Peking University Health Science Center, Beijing, China;* [2]*Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, China;* [3]*Office for Cancer Screening, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China;* [4]*State Key Lab of Molecular Oncology & Immunology Department, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Citation of this article: Qian X, Yan X, Zhai X, Li N, Qu C, Lu F. Hepatocellular carcinoma surveillance and treatment: A way to reduce cancer-related mortality in cirrhotic patients. J Clin Transl Hepatol 2019;7(1):1–2. doi: 10.14218/JCTH.2019.00002.

In the issue of *Gastroenterology* published October 2018, the article by Moon *et al.*[1] demonstrated that screening patients with cirrhosis for hepatocellular carcinoma (HCC) by ultrasound scan (USS), measurement of serum α-fetoprotein (AFP), each alone or in combination, was not associated with the decreased HCC-related mortality. In this matched case control study, all the study patients were registered in detail in the U.S. Department of Veterans Affairs. The study included 238 cases who died of HCC with cirrhosis, and the same number of matched controls with cirrhosis who had been enrolled in U.S. Department of Veterans Affairs care for the 4 years before the index date and alive at the time of their matched case's death. The study retrospectively collected each case's USS and AFP screening data for 4 years before the date of HCC diagnosis or the equivalent index date in controls. Authors found that there was no significant difference of frequency of routine screening between the cases and controls. Therefore, the authors interpreted these results as indicating that the routine screening would not reduce cancer-related mortality.

Actually, routine surveillance with USS with or without AFP every 6 months in at-risk patients is generally recommended by all professional societies worldwide and has become the standard of health care.[2] As shown in a recent systematic review on surveillance cited by the American Association for the Study of Liver Diseases (commonly known as the AASLD) Guidelines for the treatment of HCC,[3] patients with cirrhosis who underwent HCC surveillance had an increase in the detection of early-stage HCC and more curative treatments (61.8% vs. 38.2%) compared to patients with no previous surveillance, and more importantly those patients with cirrhosis who underwent HCC surveillance had a higher 3-year survival rate (50.8% vs. 27.9%).

Santi and colleagues' report[4] also demonstrated that more surveillance benefits could be achieved by semiannual surveillance in patients with cirrhosis compared to the annual program. Unfortunately, in the study by Moon *et al.*[1] the overall ultrasound examinations were 492 and 503 in cases and controls respectively over the 4-year study period, which meant that both in cases and controls on average the ultrasound exam was conducted every second year and was much less than the semiannual surveillance frequency with ultrasound recommended by guidelines.[2] Noticeably, only 56.7% patients received USS or AFP tests within 1 year before the index date in their study. All these questions might reduce the efficacy of surveillance and therefore preclude the reach of real conclusions when evaluating the effectiveness of recommended screening program.

The aim of screening is to reduce disease-related mortality and is usually achieved through a diagnosis of the disease at the early stage that in turn enhances the applicability and improves cost-effectiveness of therapies.[5] Several factors would influence the usefulness and applicability of screening, such as the incidence of the surveyed disease in the target population, the availability of efficient diagnostic test(s) at bearable costs and acceptability for the target population, and the availability of treatments and their effectiveness.[5] In Japan, HCC tends to be diagnosed at a relatively early stage, which is attributed to the established daily practice for screening HCC among high-risk patients, and the survival rates have also shown an obvious improvement.[6]

Thus, improvement in survival seen with surveillance appears to be due to higher early-stage detection and higher curative treatment rates.[3] Obviously, receipt of a timely and proper treatment is clearly associated with the effectiveness of screening to improve patient survival. As recommended by the AASLD Guidelines,[3] patients with early-stage HCC and Child-Pugh A cirrhosis should preferentially undergo resection and radiofrequency ablation rather than transarterial chemoembolization and systematic chemotherapy (sorafenib), and the latter were only recommended for patients with cirrhosis and

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, α-fetoprotein; HCC, hepatocellular carcinoma; USS, ultrasound scan.

Received: 7 January 2019; Revised: 27 February 2019; Accepted: 1 March 2019

***Correspondence to:** Fengmin Lu, Department of Microbiology & Infectious Disease Center, School of Basic Medical Sciences, Peking University Health Science Center, 38 Xueyuan Rd, Haidian District, Beijing 100191, China. Tel: +86-10-82805136, Fax: +86-10-82805136, E-mail: lu.fengmin@hsc.pku.edu.cn; Chunfeng Qu, State Key Laboratory of Molecular Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Pan-jia-yuan South Lane, Chaoyang District, Beijing 100021, China. Tel: +86-10-87783103, Fax: +86-10-67713917, E-mail: quchf@cicams.ac.cn

middle to advanced HCC who are not candidates for resection or transplantation. Unfortunately, in the study of Moon *et al.*,[1] though a relatively high proportion (51.3%, 122 cases) of HCC was diagnosed within Milan criteria, there were no detailed information to explain the proportion of therapies that patients received. Among the analyzed 238 cases, only 5 cases (2.1%) received partial hepatectomy and 30 cases (12.7%) received radiofrequency ablation, which is obviously not according to Milan criteria and AASLD guidance.

We cannot directly jump to the conclusion of Moon and colleagues' study[1] since we cannot rule out the potential impact of the application of high rates of conservative treatment on an increase of mortality of these 238 cases. Meanwhile, it also raised concern that conservative modality or therapy selective bias would reduce the creditability of the conclusion of the study, and we believe this debatable point merits further attention. Since all the cases were derived from the Corporate Data Warehouse, it is unknown whether the proportion of the analyzed 238 cases could represent all cirrhosis-related HCC patients in the system regarding the cirrhosis-related HCC staging and treatment received. As the proportion of alive cirrhosis-related HCC was not included in the analysis, the representative of the selected 238 fetal HCC cases should have been considered when the results were interpreted.

The HCC incidence rate among patients with cirrhosis has been shown to be 2-4% per year.[3] Improvement in survival rate could be achieved through implementation of early detection and curative treatment of HCC, so it is necessary to carry out the routine surveillance for HCC in cirrhotic patients. Just as Dr. GS Cooper wrote in the editorial,[2] it is premature to abandon the current process of HCC surveillance, though these results have confirmed the inadequacies of current HCC surveillance strategies. Clinical practices have realized the low compliance to the repeated screening, unnecessary follow-up procedures, and anxiety in the patients with cirrhosis. Also as suggested by Dr. GS Cooper in the editorial,[2] alternative options for HCC surveillance are required. In addition to monitoring regular protein biomarkers, detection of the genetic alterations in circulating tumor DNA in peripheral blood of the at-risk individuals showed promise for finding curable HCC.[7–9] With the discovery of new monitoring indicators, a better modality of HCC surveillance to further improve survival is needed.

Acknowledgment

This work was supported by the National S & T Major Project for Infectious Diseases (No.2017ZX10201201).

Conflict of interest

The authors have no conflict of interests related to this publication.

References

[1] Moon AM, Weiss NS, Beste LA, Su F, Ho SB, Jin GY, *et al*. No association between screening for hepatocellular carcinoma and reduced cancer-related mortality in patients with cirrhosis. Gastroenterology 2018;155:1128–1139. e6. doi: 10.1053/j.gastro.2018.06.079.
[2] Cooper GS. Should we abandon current hepatocellular carcinoma screening practices? Gastroenterology 2018;155:972–974. doi: 10.1053/j.gastro.2018.09.001.
[3] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, *et al*. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380. doi: 10.1002/hep.29086.
[4] Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, *et al*. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010; 53:291–297. doi: 10.1016/j.jhep.2010.03.010.
[5] EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182–236. doi: 10.1016/j.jhep.2018.03.019.
[6] Kudo M, Izumi N, Ichida T, Ku Y, Kokudo N, Sakamoto M, *et al*. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res 2016;46: 372–390. doi: 10.1111/hepr.12697.
[7] Xu RH, Wei W, Krawczyk M, Wang W, Luo H, Flagg K, *et al*. Circulating tumour DNA methylation markers for diagnosis and prognosis of hepatocellular carcinoma. Nat Mater 2017;16:1155–1161. doi: 10.1038/nmat4997.
[8] Cohen JD, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, *et al*. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science 2018;359:926–930. doi: 10.1126/science.aar3247.
[9] Qu C, Wang Y, Wang P, Chen K, Wang M, Zeng H, *et al*. Detection of early-stage hepatocellular carcinoma in asymptomatic HBsAg-seropositive individuals by liquid biopsy. Proc Natl Acad Sci U S A 2019. doi: 10.1073/pnas.1819799116.