Viewpoint

Hepatocellular carcinoma surveillance: an open question

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Comment on: Moon AM, Weiss NS, Beste LA, *et al.* No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis. Gastroenterology 2018;155:1128-39.e6.

Submitted Feb 23, 2019. Accepted for publication Feb 26, 2019.
doi: 10.21037/hbsn.2019.02.10
View this article at: http://dx.doi.org/10.21037/hbsn.2019.02.10

We were very interested to read the study recently published in Gastroenterology by Moon *et al.* (1). Performed as a case-control study within the US Veterans Affairs health care system, the study aimed to assess the association between screening for hepatocellular carcinoma (HCC) and cancer related-mortality in patients with cirrhosis. The authors did not find any evidence that screening patients with cirrhosis by abdominal ultrasound (US) or alpha-fetoprotein (AFP) levels decreases HCC-related mortality.

Cirrhotic patients have an increased risk of developing of HCC. Surveillance for HCC is recommended in patients with cirrhosis and some categories of patients with chronic hepatitis B and C (2), and has been associated with improved early detection and survival (3). The European and American guidelines recommend HCC surveillance in this population using US with or without serum AFP every 6 months (2).

In the current study, the US screening program was not performed according to modalities and timing indicated by international guidelines. In fact, surveillance was not performed in the entire group of patients in the study, but in approximately only 80% of this population. Moreover, the surveillance was performed using either US or AFP, while practice guidelines recommend the use of US, with or without AFP. In particular, 238 HCC cases underwent a total of 492 US scans during the 4 years of detectable preclinical period (2.1 US scans/case in 4 years) which is much lower than biannual surveillance frequency. Finally, 40% of US scans were certainly performed because of the appearance of clinical manifestation and not for screening.

Another concern is the low proportion (16%) of patients who underwent potentially curative treatments (surgical resection 2.1%, percutaneous ablation 14.3%), although half the cases were diagnosed within Milan criteria (MC) (4), and therefore at a potentially curable stage. Moreover, not a single patient was treated with liver transplantation. In particular, among the patients within MC, only about 30% were treated with curative intent, while approximately 70% underwent palliative treatment. These results diverge from those reported by our retrospective study (5), conducted on a large Italian HCC population (5,192 patients) over a period of 15 years, in which approximately 70% of the patients with HCC within MC received a potentially curative treatment. A screening program is able to reduce cancer-related mortality only if successful treatments are available. Therefore, the discrepancy between the number of potentially curable HCCs and potentially curative treatments delivered in this study makes it difficult to establish the number of HCC-related mortalities ascribable to surveillance failure rather than to the inappropriateness of the administered treatment.

A key factor for effectiveness of HCC surveillance is the quality of US, that is strongly both patient- and operator-dependent. In fact, US detection of small HCCs may be challenged by several patient features, such as liver echo-texture, abdominal fat, meteorism, massive ascites and poor compliance with the breath hold command. Moreover, US effectiveness is superior in tertiary centers, where greater expertise is available (6). In order to optimize the efficiency of US as a surveillance test, the use of a combined sequential measure of static and dynamic AFP has been proposed, aimed at selecting those patients who deserve high quality US performed in a tertiary center (7). This index, obtained with the combination of AFP >10 ng/mL

or an increase of at least 1 ng/mL occurring during the 6 month-period before HCC detection, increased the sensitivity of AFP to 80% with a negative predictive value of 86.2% (7). Unfortunately, in the study by Moon *et al.*, 238 HCC cases underwent a total of 795 AFP measurements during the 4 years of detectable preclinical period (3.3 AFP measurements/case in 4 years), which is much lower than the frequency needed to adopted the above cited strategy.

In the current study, the population consists entirely of males, which is a potential selection bias. Males do, in fact, experience surveillance failure more frequently and are therefore diagnosed at a more advanced stage (8), which could partially justify the poor results of this study in terms of survival.

Finally, the authors assert that "screening could result in harm"; however, the cited risks are related to biopsy performed once US has detected a suspicious lesion. In this case, biopsy is part of the subsequent diagnostic process and not of the surveillance program. Moreover, histological assessment is not mandatory for the diagnosis of HCC in cirrhotic patients. In fact, the "typical" features at multiphasic imaging techniques, such as computed tomography and magnetic resonance imaging, have proven to be very robust with specificities close to 100% even in detecting HCC lesions as small as 1–2 cm in size (2).

Despite the results of this study, we believe that surveillance for HCC, performed according to international guidelines, is probably effective, although this has not been fully determined in randomized controlled trials (RCTs) in cirrhotic patients. However, we are unlikely to see new results on this topic from RCTs, because almost all patients, if adequately informed of surveillance risks and benefits, and probably most clinicians, would refuse to take part in such studies. Moreover, controls would frequently undergo abdominal US for reasons other than surveillance, invalidating the comparison with cases. The accepted conviction that HCC surveillance reduces the disease-specific mortality and the recommendations made by international guidelines are mainly based on the available proof-of-concept evidence that US screening can detect small asymptomatic tumors that are susceptible to radical treatment. Finally, cohort studies comparing the outcome of HCC patients diagnosed during or outside surveillance confirm the assumed surveillance benefit (6).

Cite this article as: Biselli M, Garuti F, Neri A. Hepatocellular carcinoma surveillance: an open question. HepatoBiliary Surg Nutr 2019;8(4):431-432. doi: 10.21037/hbsn.2019.02.10

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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