Impact of a shortened surveillance interval on hepatocellular carcinoma survival

Do Young Kim¹

Kwang-Hyub Han^{*1}

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The surveillance of hepatocellular carcinoma (HCC), which has been a standard of care in the management of patients with chronic liver diseases, greatly contributed to the early detection of liver cancers amenable to curative treatment. Nonetheless, the current strategy for HCC surveillance does not seem to be ideal and the problems may mostly arise from the incompleteness of surveillance tools. As revealed by a study using the cohort of the HALT-C trial, the most common reason for identifying HCC at a late stage was an absence of detection despite adherence to surveillance, which clearly implies that better surveillance tools are required [1]. Ultrasonography (US) is a noninvasive, safe and easy-to-apply method in HCC surveillance, showing a sensitivity of 65–80% [2]. However, the performance characteristics of US becomes poor in obese patients or nodular cirrhotic livers. The role of adding serum α -fetoprotein (AFP) measurement complementary to US is still in debate between eastern and western countries. Unfortunately, a marked progress has not yet been made in terms of development or discovery of novel noninvasive imaging (or a serum biomarker) that could outperform US or AFP.

Looking at the recommendation by American Association for the Study of Liver Diseases, the proposed interval of 6–12 months for HCC surveillance is based on the tumor doubling time [3,4]. Although initial studies of small sample size reported that there was no difference in the rate of early HCC detection or survival between 6 and 12 months [5,6], in an Italian study, the median survival of patients with a 6-month interval was significantly longer than those with a 12-month interval, after correction of lead-time bias [7]. Furthermore, in a 15-year prospective Korean study, the corrected 5-year survival of patients, whose surveillance interval was less than 6 months, was significantly higher compared with those with an interval of more than 6 months [8]. Accordingly, the superiority of a 6-month interval compared with a 12-month interval was confirmed both in hepatitis C and B virus-related chronic liver diseases. Based on such recent data, a 6-month interval should be preferred over 12 months in clinical practice.

A basic concept regarding HCC surveillance is that determination of interval should be made according to the tumor growth rate, not by the degree of tumor

“...the current evidence suggests that shortening of ultrasonographic surveillance to 3–4 months does not impact on survival of hepatocellular carcinoma patients.”

¹Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

^{*}Author for correspondence: Tel.: +82 2 2228 1949; Fax: +82 2 393 6884; gihankhys@yuhs.ac

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development risk [3]. However, as stated above, the failure to detect lesions appropriately is the most frequently encountered situation in patients diagnosed with HCC beyond early stage, despite surveillance. Hence, the issue of shortening the HCC surveillance interval may come from the attempt to make up for the limitation of US itself or operational imperfection. To address this issue, a multicenter European study has been conducted, where 1278 cirrhotic patients were randomized to US every 6 or 3 months [9]. HCC was diagnosed in 123 patients (9.6%), and there was no difference in HCC incidence between the two groups. The prevalence of HCC <3 cm, which was the main end point of that study, was also not different, although the incidence of small lesions (≤ 10 mm) was higher in the 3-month group compared with the 6-month group. Finally, the cumulative 5-year survival was found to be similar between the randomized groups. The result of this trial could make clinicians believe that shortening surveillance interval from 6 to 3 months is useless in terms of small HCC detection or survival increase, at least in western countries.

A recently published Taiwanese study also tried to investigate whether a shortened surveillance interval could improve patient survival [10]. A total of 744 patients with chronic hepatitis C or B virus infection were prospectively enrolled and randomized to US every 4 or 12 months. Although there was no difference in cumulative 3-year HCC incidence between the two groups, the 4-month group had significantly more patients with tumor ≤ 2 cm compared with the 12-month group. However, contrary to the results from aforementioned Korean or Italian studies, the 4-year overall survival was not different between two groups. The reason why patients in the 4-month group did not achieve a better survival than those in the 12-month group could be explained by nonadherence of early stage patients to curative treatment, such as resection or ablation, owing to various reasons including old age or comorbidities. The survival of the 4-month group tended to be higher compared

with the 12-month group in early follow-up period; however, the survival curves in the two groups merged in later periods. Obviously, the effectiveness of surveillance strategy has led to the decrease of mortality due to HCC. Thus, the current evidence suggests that shortening of US surveillance to 3–4 months does not impact on survival of HCC patients.

Should we therefore be satisfied with a surveillance interval of 6 months using US? Is there no room for increasing surveillance outcome by modifying surveillance strategy? Interestingly, the two prospective European and Taiwanese studies adopted only US for HCC surveillance. However, although western liver society does not accept the role of serum AFP measurement in HCC surveillance owing to its low sensitivity and specificity, it is a routine practice to combine US and AFP in many eastern and even some western countries. We recognize that 6 months is the most appropriate interval if HCC surveillance is performed with only US, based on the accumulated evidence.

The remaining issue is whether or not shortening the surveillance interval could be beneficial when both US and AFP are utilized. It is helpful for us to remind that most HCCs are detected at an early stage in Japan, where a shortened surveillance interval and combination of US and several tumor markers such as serum AFP and PIVKA-II are already the standard of care. Although the cost-effectiveness of surveillance is one of the most important factors to consider, the improvement of sensitivity to diagnose HCC at an early stage is also an important issue.

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