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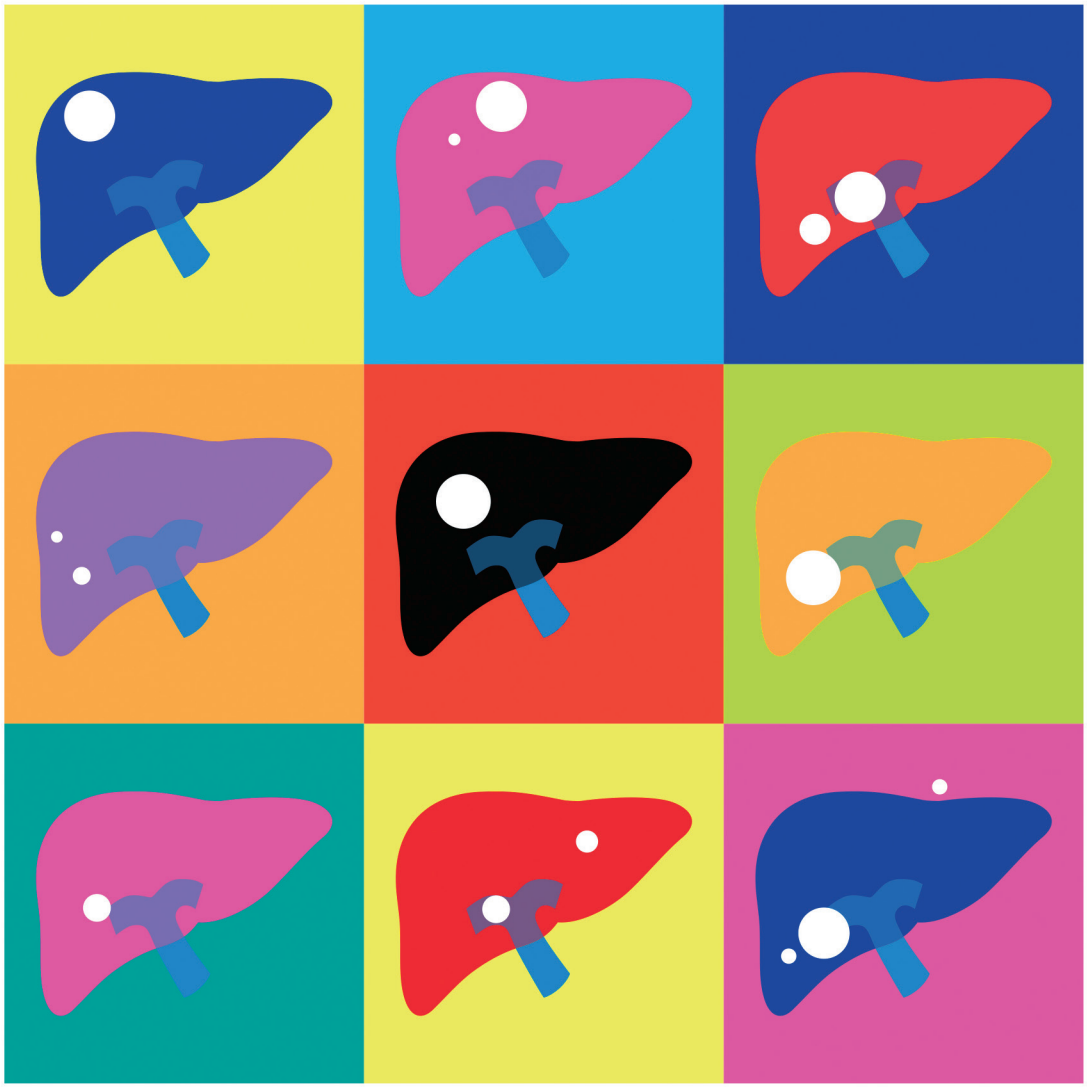

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Editorial

Surveillance for hepatocellular carcinoma: It is time to move forward

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Keywords: Hepatocellular carcinoma; Cancer screening; Surveillance; Survival

See Article on Page 851

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-induced mortality.[1,2] Tumor stage is an important factor of determining prognosis; however, less than 20% of patients with HCC are diagnosed at very early or early stages.[3-6] Nevertheless, a small portion of patients is diagnosed early on, and persistent efforts have been made to improve outcomes. Many academic societies recommend HCC surveillance for at-risk populations,[3,7-9] and the Korean government has launched a nationwide liver cancer screening program in 2003. A 16-year cohort report from one institution shows that the diagnosis rate of very early or early stages of HCC is increasing significantly.[10]

Cancer screening/surveillance mainly aims to reduce disease mortality. Stage migration (i.e., the detection of cancer at its early stages) is a surrogate endpoint that cannot replace mortality.[11] Although whether screening should be performed is a critical issue for both individuals and public health, only two randomized controlled trials have been conducted for HCC surveillance in Chinese patients with chronic hepatitis B.[12,13] One of those trials compared surveillance using serum alpha-fetoprotein with no surveillance[13] and did not demonstrate any survival benefit, yet the surveillance strategy using serum alpha-fetoprotein is far less developed than the strategy currently used.[13] The other randomized controlled trial adopted serum alpha-fetoprotein and ultrasound as surveillance tests; however, they used a cluster sampling method.[12] Methodological flaws may have necessitated further evaluation with a well-designed randomized controlled trial for HCC surveillance.[14] Nevertheless, research on methods rather than the necessity of surveillance tests is needed as early detection and treatment owing to surveillance tests are conventionally known to affect the prognosis of HCC.

In this issue of *Clinical and Molecular Hepatology*, Sohn et al.[15] investigated the impact of the National Liver Cancer Screening Program (NLCSP) on the receipt of curative treatment for HCC and the all-cause or liver-related mortality. The surveillance group showed a significantly lower mortality rate (12 vs. 22 deaths per 1,000 person-years; adjusted hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.55–0.56) and a higher proportion of receiving curative treatment for HCC

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than the non-surveillance group (adjusted HR, 5.64; 95% CI, 5.48–5.81). This study demonstrated the benefit of HCC surveillance in patients aged ≥40 years with chronic hepatitis B, hepatitis C, or cirrhosis.

Despite its results, a major concern of this study is its lack of capturing HCC surveillance performed by private health care providers. Some patients in the non-surveillance group may have undergone HCC surveillance, not by the NLCSP, but by private health care providers. Despite the ambiguity of the control group, the nationwide HCC surveillance program increased the probability of receiving curative treatment for HCC and decreased the overall and liver-related mortality rates.[15] Another limitation is the indirectness of the study. Ideally, surveillance for HCC should improve the detection of early-stage HCC (stage migration), yet the present study compared the rate of receiving curative treatment for HCC instead of detecting early-stage HCC. Receiving local ablation, surgical resection, or transplantation does not necessarily indicate that HCC was detected early on. However, stage migration is just one of the surrogate endpoints,[11] the most important endpoint is mortality.

Observational studies without randomization are prone to bias and uncontrolled confounding. Allocating patients into the surveillance group or determining the effect of surveillance is sometimes complicated. Previously, a matched case-control study on patients with cirrhosis found no association between HCC surveillance and reduction of HCC-related mortality.[16] This study has been criticized in that cases comprised patients who received abdominal ultrasound or serum alpha-fetoprotein tests 4 years before diagnosis. However, the present study by Sohn et al.[15] considered HCC surveillance as a time-varying variable to control immortal time bias and limited the effect of HCC surveillance until 6 months after surveillance, since surveillance for HCC is recommended every 6 months. Moreover, the analyses were adjusted rigorously to control for potential confounders, including antiviral therapy, type of liver disease, comorbidities, and socioeconomic status, in addition to baseline demographics.

Randomized controlled studies provide the highest level of evidence; however, they require time and several thousand patients.[14] Moreover, the recall strategy should be optimized, and follow-up cross-sectional imaging should be performed on time.[17] Most patients diagnosed with early-stage HCC through surveillance should be curable and receive the standard of care throughout the follow-up period. Such studies are also seemingly unfeasible since more than 99% of informed patients declined participating in a randomized controlled trial for HCC surveillance.[18] This Australian study has been criticized for not providing sufficient information on the potential harm of HCC surveillance. However, a recent multicenter prospective study from the United States also supported the patients' preference for surveillance benefits over surveillance-related harms or inconvenience.[19]

It is time to move forward from debating about whether randomized controlled trials on the necessity of HCC surveillance should be performed. In most clinical practice guidelines, at-risk populations commonly include patients with cirrhosis and hepatitis B virus infection.[3,7-9,20] There has been a debate on HCC surveillance for patients with chronic hepatitis C and nonalcoholic fatty liver disease without cirrhosis.[21] Despite some concerns, the present study enrolled patients aged ≥40 years with chronic hepatitis B, hepatitis C, or cirrhosis since they are the target population of the NLCSP in Korea and demonstrated the overall survival benefit of patients receiving the NLCSP compared with patients in the non-surveillance group.[15] The survival benefit was observed across etiology subgroups in the present study. However, further studies are warranted to confirm the benefit of HCC surveillance in patients with chronic hepatitis C without cirrhosis.

It is recognized that a small portion of patients will develop HCC even in traditional at-risk populations. Risk stratification can help refine the surveillance strategy.[20,22,23] Patients with very low risk may be exempted from repeated (and life-long) surveillance, while patients with very high risk may need more intensive surveillance. The benefit of HCC surveillance in patients with nonalcoholic fatty liver disease or advanced fibrosis (F3) after hepatitis C virus (HCV) viral eradication is unclear. The annual incidence of HCC has been reported to be 0.5% in patients with F3 fibrosis after HCV virologic cure and 2.1% in patients with cirrhosis.[24] The annual incidence has been reported to be 3.78% and 0.03% in patients with

Abbreviations:

CI, confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MRI, magnetic resonance imaging; NLCSP, National Liver Cancer Screening Program

cirrhotic and non-cirrhotic nonalcoholic liver disease, respectively.[25] The incidence of HCC in non-cirrhotic patients with virologically cured hepatitis C or nonalcoholic fatty liver disease was lower than thresholds. Even in patients with chronic hepatitis B, some had minimal risk of developing HCC (annual incidence of <0.1%).[26,27] In contrast, high-risk patients are recommended to undergo HCC surveillance at shorter intervals or with more sensitive tools, such as computed tomography (CT) or magnetic resonance imaging (MRI).[9] Given that ultrasound has advantages in that it does not require contrast agents or radiation hazards, its low sensitivity leads to the development of a more effective imaging tool. Moreover, ultrasound has the limited ability to visualize the liver in patients with obesity[28] or a very nodular liver. Although contrast-enhanced low-dose CT may be an option for HCC surveillance,[29] the risks of radiation hazards and contrast agents still exist. Non-enhanced MRI would be a viable option since there is no risk of exposure to radiation or contrast. A recent meta-analysis demonstrated much higher sensitivity (86.8%) and specificity (90.3%) in abbreviated non-contrast MRI.[30] A long scan time and high cost limit the widespread use of MRI; however, semiannual contrast-enhanced MRI can be cost-effective for patients with sufficient risk of developing HCC (annual incidence of 3%).[31] Abbreviated MRI requires less time and cost than conventional contrast-enhanced MRI; therefore, abbreviated MRI may serve as a surveillance tool in the future. However, the optimal sequence and definition of patients with "sufficient" high risk remain to be assessed.

Accumulating studies indicate that HCC surveillance is of value and provides a survival benefit.[32] Clearly, more evidence is needed. However, it is obvious that our focus should not be on whether HCC surveillance is necessary, but on whom should be exempted from it and whom should undergo intensive strategies.

Authors' contribution

Study conceptualization: BHK and JWP; Drafting of the manuscript: BHK; Critical revision of the manuscript: BHK, YC, and JWP

Conflicts of Interest

The authors have no conflicts to disclose.

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