Adding to the Evidence Base: Effectiveness of Hepatocellular Carcinoma Surveillance in Clinical Practice

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Hepatocellular carcinoma (HCC) is the fifth most common solid cancer diagnosed globally and is the second leading cause of cancer mortality among adult males worldwide.[1] In the United States, HCC is the fastest growing cause of cancer deaths.[2] HCC incidence increased 3-fold between 1975 and 2009 and has had a recent plateauing of the trend.[3] Despite advances in treatment, most HCC patients present with advanced stage and have low survival (median ~8 months, 5-year survival < 15%).[4] The primary contributor to the low overall survival for HCC is that the majority of patients are diagnosed at an advanced stage for which viable treatment modalities are unavailable. Potentially curative therapies for HCC exist and include surgical resection and liver transplantation. Surgical resection is the primary therapeutic option for patients without advanced cirrhosis and with well-preserved liver function and relatively preserved portal pressure. Among candidates who receive resection, 5-year survival can exceed 50%. Liver transplantation is the treatment of choice for HCC patients with decompensated cirrhosis, with 5-year recurrence-free survival close to 70%. Thus, all the major clinical practice guidelines and most of the professional societies recommend HCC surveillance with abdominal ultrasonography with and without alpha fetoprotein performed every 6 months in the high-risk population.

However, the impact of screening on treatment outcomes and survival for HCC remains contentious. The National Cancer Institute Liver Cancer Screening (Physician Data Query) recently concluded "Based on fair evidence, screening of persons at elevated risk does not result in a decrease in mortality from hepatocellular carcinoma."[5] These authors and others point out that the only published randomized controlled trial, which enrolled 18,816 patients from Shanghai who had hepatitis B, was impaired by several methodological flaws that limit generalizability of its findings to other populations.[6] They also suggest that the majority of the patients included in the trial were hepatitis B surface antigen carriers and did not have a background of cirrhosis, which lowers the sensitivity of abdominal ultrasonography in the nodular cirrhotic liver. Furthermore the potential significant impact of lead-time bias (an improvement in survival as a result of a diagnosis made earlier in the disease course) and length-time bias (earlier detection of slower growing tumor with favorable tumor biology) has been invoked to question the effectiveness of screening for HCC.

The ideal solution to this problem is a controlled trial with patients randomized to surveillance and no surveillance. However, such a trial is unrealistic because

Abbreviations: HCC, hepatocellular carcinoma.

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of the need for a prohibitively large sample size. Furthermore, it may indeed be unethical given the wide dissemination of the current practice guidelines that recommend surveillance. The vast majority of patients are not willing to participate in trials that have a no-screening arm, as discovered by a group of investigators from Australia that failed to enroll patients to the no-surveillance group and had to end their study.[7] Thus, at present we are left with observational case control and cohort studies to determine the impact of HCC screening on patient outcomes; however, these studies are prone to lead- and length-time bias. In a recent meta-analysis of 22 studies,[8] only five included evaluation of lead-time bias. In three of these studies, the survival advantage initially identified in the screening group disappeared when statistical techniques to adjust for lead time were introduced, assuming the doubling time of 90, 120, or more days. This led the authors of this systematic review to conclude that the strength of evidence in support of HCC screening was very low.

In the September issue of *Hepatology Communications*, Tong et al.[9] describe the outcomes of a single center cohort of 357 well-characterized patients with HCC in the setting of chronic viral hepatitis. This study adds to the few available studies that appropriately account for lead-time bias when assessing the survival advantage associated with HCC screening. Tong et al. estimated the lead time by calculating the doubling time (129 days) of tumors from 166 patients in the surveillance group who had serial imaging with contrast-enhanced computed tomography or magnetic resonance imaging. A lead time of 3.4 months was adjusted for by adding this time to the survival time of the no-surveillance group (however, most studies subtract lead time from the screening group). They report a median survival advantage of 26 months for the 175 patients diagnosed by surveillance compared with 158 patients diagnosed without surveillance after controlling for lead-time bias. The overall and the disease-free survival at 1, 3, and 5 years were significantly higher among the surveillance group than in the no-surveillance group; the survival advantage remained significant in the subset of patients with baseline cirrhosis.

The current report highlights the fact that patients who undergo screening have a higher likelihood of being diagnosed at an earlier stage of the disease and are much more likely to receive potentially curative therapy. Specifically, 83% of patients in the screening group were identified within the Milan criteria compared to 29% in the no-surveillance group. Correspondingly, liver transplantation was performed in 22% of patients in the surveillance group, and only 6% of patients were identified without surveillance. Nearly 50% of patients in the no-surveillance group received supportive care only.

The current work remains hampered by limitations inherent in retrospective cohort analyses. For example, there was an imbalance in the patient characteristics between the surveillance and no-surveillance groups; more patients in the no-surveillance group had chronic hepatitis B, while chronic hepatitis C was more common in the surveillance group. A recent study by An et al.[10] has shown that tumor doubling time varies significantly between hepatitis B virus- and hepatitis C virus-related tumors (77 days versus 137 days) and can account for the survival advantage in the surveillance group. The broad time frame (3 decades) of cohort accrual also adds a potential variable, which is difficult to account for, although the authors were able to show that surveillance was beneficial regardless of the era of diagnosis and treatment. In addition, the evaluation of potential harms related to screening was not documented. Despite these limitations, the study provides strong convergent validity to a few other recent reports that found remarkably similar results.[11-13] Patients who underwent surveillance had earlier stage HCC, were more likely to receive curative treatments, and lived longer than those who had HCC diagnosed incidentally or because of symptoms; these beneficial effects persisted after accounting for lead-time bias in these studies. Short of a large clinical trial, these consistent results across multiple studies (and multiple settings) provide the best (albeit not the highest) level evidence to support HCC screening.[14]

This study also highlights the inherent difficulty in ensuring patient compliance with the currently recommended interval of surveillance. In a structured community-based clinic, one third (56/173) of patients in the screening group received screening at time intervals beyond (13-36 months) the current guideline-recommended interval. These data call for systematic implementation of robust patient recall procedures to maximize the effectiveness of HCC screening.[15-17]

Overall effectiveness of HCC surveillance depends on successful implementation of the cancer care continuum. These include identification of the target patient population and linking them to regular liver care, development of simpler and better biomarkers for HCC identification, ensuring patient compliance with HCC screening, enhancing provider knowledge about existing treatment options, and improving care coordination across multiple disciplines to ensure timely

treatment of screen-detected HCC.[18,19] Each of these steps will need a concerted effort. There is sufficient evidence to support that HCC surveillance (when applied to the right patient and in the right context) works. We believe it is time to move beyond this debate. We need to focus on implementing, testing, and improving the disparate steps in the HCC care continuum with an eye toward improving patient outcomes.

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