HCC Surveillance: Striving for a Better Balance of Benefits and Harms

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We appreciate the letters from Dr. Wang[1] and Dr. Xu[2], which raise interesting points that are worthy of further discussion.

In our recent manuscript, "An Assessment of Benefits and Harms of Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis"[3], we reported surveillance was associated with benefits including early tumor detection in nearly two-thirds of patients who developed HCC; however, surveillance-related physical harms, defined as diagnostic evaluation for false positive or indeterminate screening results, were also observed in over one-fourth of patients. Dr. Wang and colleagues contested our definitions for screening benefits as well as screening harms, contending early tumor detection was too narrow a definition for benefits and receipt of diagnostic evaluation for false positive results was too liberal for defining screening harms.

The best measure of surveillance benefits would be improvement in overall survival, as this is the goal of cancer screening programs. However, improvement in overall survival can be difficult to demonstrate definitively in cohort studies given the possibility of confounding, lead-time, and length-time bias.[4] Early tumor detection and receipt of curative treatment are often used as surrogates;[4] however, these are recognized as being imperfect given the additional possibility of overdiagnosis. Wang and colleagues suggest expanding the definition of screening benefits to include any tumor detection, given potential improvement in survival with palliative therapies such as transarterial chemoembolization. However, doing so would only amplify biases of using surrogates of survival and would further overestimate surveillance benefits. In fact, some would argue that our definition of early stage using Milan Criteria is too liberal and that we should instead have used unifocal lesions less than 2 cm, as this is the stage at which microvascular invasion is least likely and curative therapies are most effective.

Surveillance harms can include physical, psychological, and financial harms, although we focused on the proportion of patients experiencing physical harms.[5] Wang and colleagues argue these tests should not be considered as harms given the necessity of diagnostic evaluation in those with positive screening results to achieve screening benefits. Our definition of screening physical harms is based on a well-accepted conceptual model and taxonomy used to characterize screening harms for other cancers, including colorectal and breast cancer.[6] The necessity for diagnostic evaluation among those with true positive screening results does not diminish the harms related to false positive or indeterminate results. In fact, evaluation of diagnostic test performance using receiver operator characteristic (ROC) curve analysis acknowledges the inherent trade-off between sensitivity and specificity and the importance of characterizing both aspects. Our study extends beyond simply measuring the number of false positive surveillance tests but also measures how often these results led to follow-up diagnostic evaluation. While suboptimal specificity has been previously described for alpha fetoprotein[7], our study is one of the first to suggest this may also be an issue for abdominal ultrasound. The specificity for ultrasound was lower than previously reported in efficacy trials for several reasons including its operator dependency, suboptimal image quality in patients with obesity or nonalcoholic steatohepatitis, and high proportions of diagnostic evaluation for patients with indeterminate ultrasound results.[8]

Dr. Xu and colleagues highlight our study's retrospective nature and the intermittent use of HCC surveillance. Although all patients in our study had at least one surveillance test, less than one-third underwent three or more surveillance exams and less than 5% underwent semiannual surveillance over the 3-year period. However, our study reflects surveillance utilization in everyday clinical practice, as prior studies in the US have demonstrated less than 20% of patients undergo HCC surveillance and less than 5% undergo semiannual surveillance.[9,10] Although increased surveillance exposure could magnify observed screening benefits, the

proportion of patients experiencing screening harms would also likely increase proportionally. In our study, screening harms increased from 11.9% among those with one surveillance exam to nearly one-third of patients with multiple surveillance exams. Therefore, we would not anticipate the risk-benefit ratio to substantially change in the setting of increased surveillance exposure; however, we are currently performing a prospective multi-center cohort study to confirm these results under different study settings.

Overall, our study should not be taken as an indictment on HCC surveillance. Instead, our data are meant to inform how we can better balance surveillance benefits and harms and thereby improve the overall value of HCC surveillance for our patients in clinical practice.[11]

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