Unscheduled Screening Tests Cannot Be Termed as Surveillance

TO THE EDITOR:

We read with great interest the recent article by Atiq et al.[1] By assessing benefits and harms from hepatocellular carcinoma (HCC) surveillance, they found that over one-fourth of patients with cirrhosis experienced physical harm due to false-positive or indeterminate surveillance tests, which were more often related to ultrasound than alpha-fetoprotein. They pointed out that high false-positive or indeterminate results of ultrasound may induce unnecessary computed tomography or magnetic resonance imaging scans, which would cause some degree of physical harm, such as radiation exposure. We have the following concerns.

It cannot be neglected that a major limitation of this study was its retrospective nature. All 680 patients with cirrhosis stratified either to the surveillance or nonsurveillance groups were determined by researchers only after review of medical records. As the authors describe, "ultrasounds with indications including 'surveillance,' 'screening,' 'rule out HCC,' and 'cirrhosis' were classified as surveillance exams." However, the authors did not explain whether these patients underwent their regular or scheduled screening tests at every 6-month interval according to the recommendations from the American Association for the Study of Liver Diseases and the National Comprehensive Cancer Network.[2] As a matter of fact, if a rigorous standard is not set for screening interval (for example, undergoing a screening test once a year or more), these tests should not be termed as surveillance. This may explain why the detection rate of early HCC, even in those patients under "surveillance" was far from satisfactory in this study. In a word, the bias caused by stratification error may in all probability lead to an incorrect conclusion, and the reliability of this conclusion warrants careful interpretation and further validation.

In summary, clarification regarding the aforementioned omission would greatly solidify the conclusions made by Atiq et al. in their study.

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DOI 10.1002/hep.29287
Potential conflict of interest: Nothing to report.

REPLY:

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

In our recent article,[1] we reported that surveillance was associated with benefits including early tumor detection in nearly two thirds of patients who developed hepatocellular carcinoma (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. Wang et al. contested our definitions for screening benefits as well as screening harms, contending that 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, given that 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.[2] Early tumor detection and receipt of curative treatment are often used as surrogates[2]; however, these are recognized as being imperfect given the additional possibility of overdiagnosis. Wang et al. 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, given that 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.[3] Wang et al. argue that 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.[4] 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 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. Whereas suboptimal specificity has been previously described for alpha fetoprotein,[5] our study is one of the first to suggest that 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.[6]

Xu et al. 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, given that previous studies in the United States have demonstrated that less than 20% of patients undergo HCC surveillance and less than 5% undergo semiannual surveillance.[7,8] 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, multicenter 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.[9]

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.29286

This work was conducted with support from the AHRQ Center for Patient-Centered Outcomes Research (R24 HS022418). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or AHRQ.

Potential conflict of interest: Dr. Singal consults for, advises for, and is on the speakers' bureau for Bayer. He is on the speakers' bureau for and received grants from Gilead. He advises for Wako. Dr. Yopp is on the speakers' bureau for Bayer. He received grants from Merck and Peregrine.

Optimal Timing for Hepatitis C Antiviral Therapy in the Peritransplant Period?

TO THE EDITOR:

In their recent study, Chhatwal et al. performed a Markov-based microsimulation comparing pretransplant versus posttransplant treatment with direct-acting antiviral (DAA) agents in hepatitis C virus (HCV)–infected patients with decompensated cirrhosis who are awaiting liver transplantation (LT).[1] The study concluded that the optimal Model for End-Stage Liver Disease (MELD) score threshold for pretransplant treatment ranges between 23 and 27, depending on median wait time to LT within a United Network for Organ Sharing (UNOS) region. We think these recommendations should be reevaluated. Our concerns are as follows.

1. The UNOS regional MELD score thresholds for pretransplant DAA therapy should be further subdivided into ABO blood groups. For instance, the MELD score thresholds of 23 and 27 in UNOS regions 3 and 9, respectively, also approximate the mean MELD score at LT within these regions for blood type AB.[2] This threshold may result in "MELD purgatory" among patients with this rare blood type. Less profound variations in other ABO blood groups may exist as well and should be adjusted for in this model.
2. In 2016, UNOS region 5 experienced the highest regional mean MELD score of 32 at LT, which is not reflected in wait time to LT.[2] Without adjusting for regional variation in mean MELD score at LT and the mortality associated with it, this model may underestimate the threshold for pretransplant treatment in UNOS regions with organ shortage and high mean MELD at LT.
3. Because this was not a cost-effectiveness analysis, HCV-positive donor grafts should not have been excluded from this analysis given the excellent response rates with DAA agents in the posttransplant setting. In addition, the national percentage of usable HCV-positive donor grafts is reported to be under 5%, considerably lower than the 8% estimate used in this analysis.[3]
4. The following clinical outcomes were not assessed and should also be considered in the timing of DAA therapy: delisting due to clinical improvement or deterioration, reduction in posttransplant fibrosing cholestatic recurrent HCV infection, and reduction in retransplantation rates.