EDITORIAL

Precision HCC Surveillance: It Is All in the Number (Needed)

Amit G. Singal[1,2] · Neehar D. Parikh[1,2] · Yujin Hoshida[1,2]

Although precision medicine is typically discussed in the context of therapeutic decisions, there has been increasing interest in applying this concept to cancer screening. Precision screening moves away from a "one-size-fits-all" approach, tailoring screening intensity to individual risk profiles. While studies have examined precision screening for breast, colorectal, and lung cancer screening programs, fewer data evaluate this concept for hepatocellular carcinoma (HCC) surveillance in patients with cirrhosis. Current guidelines from the American Association from the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) both continue to recommend surveillance for all patients with cirrhosis due to any etiology, despite the known wide variation in HCC risk between patients [1].

In this issue of *Digestive Diseases and Sciences* [2], Dr. Curran and colleagues characterized the risk/benefit ratio of HCC surveillance across a gradient of risk, as assessed by multiple HCC risk-stratification scoring systems based on routine clinical data, including aMAP, Toronto HCC risk index, ADRESS, and the HCC risk score, in 482 patients with cirrhosis. Patients were followed for a median of 5.3 years, over which time they completed a mean of 6.6 ultrasound exams, with 22 developing HCC. Seventeen patients with HCC were detected by surveillance, of whom 13 (76.5%) were detected at an early stage. Conversely, 88 patients had false-positive surveillance results that triggered cross-sectional imaging. Overall, the number needed to benefit (NNB) and number needed to harm (NNH) were 241 and 36, respectively, though this risk/benefit ratio varied widely across risk groups. Across HCC risk scores, the NNB was substantially higher in patients at low risk of HCC compared

with higher risk patients, whereas the NNH was relatively stable across risk groups.

These data help advance the concept of precision HCC surveillance, highlighting a need for larger studies in this area. Nevertheless, a few notable limitations must be considered when interpreting study results. First, HCC incidence in this study was only 0.2% at 1 year and 1.2% at 3 years – substantially lower than that reported in other cohorts of patients with cirrhosis, which typically report annual HCC incidence of 1–2% per year. This discrepancy not only resulted in a limited number of HCC cases diagnosed (and broad confidence intervals for NNB) but also underestimated HCC surveillance benefits vis-à-vis other cohorts with higher HCC incidence. Second, surveillance adherence was only ~68%, leading to over one third of HCC being detected outside of surveillance or beyond an early stage. Improved adherence would have also increased surveillance benefits. Admittedly, adherence in this study was higher than that reported in a recent meta-analysis by Wolf and colleagues [3]; furthermore, since increased adherence may have also increased surveillance harms, it is unclear if this would have altered the risk/benefit ratio. Third, accurate risk stratification models are necessary for precision screening, but c-statistics of the risk stratification scores in this study ranged from only 0.64–0.72. It is unclear if the clinical data alone used by these scoring systems will be sufficient; incorporating novel genetic and biomarker risk stratification tools may help improve risk assessments in the future [4]. Risk assessment in this study was also only performed at baseline; more accurate risk stratification may require longitudinal reassessments at regular intervals given changes in patient status and HCC risk over time.

The authors notably quantify NNB and NNH, although the magnitude of benefit and harms substantially differ. Benefits of early HCC detection translate into curative treatment eligibility and improved survival, whereas most harms of HCC surveillance consisted solely of the risks inherent in cross-sectional imaging. The magnitude of harms also varies between patients, with some patients undergoing a single CT or MRI (mild harm), some undergoing repeated

✉ Amit G. Singal
amit.singal@utsouthwestern.edu

1 Division of Digestive and Liver Diseases, UT Southwestern Medical Center, 5959 Harry Hines Blvd, POB 1, Suite 420, Dallas, TX 75390-8887, USA

2 Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI 48320, USA

cross-sectional imaging (moderate harm), and others undergo biopsy (severe harm). Just as benefits can increase across risk strata, it is possible the severity of harms may be increased in high-risk patients, with providers more apt to order repeated cross-sectional imaging and/or biopsies given increased concern for possible HCC. Therefore, a multiplier accounting for severity of harms and magnitude of benefits would help better understand the risk/benefit ratio across these risk scores when discussing results with patients.

Further, the study only accounted for physical harms of surveillance, without accounting for potential psychological or financial harms, paralleling the current state of HCC literature. A recent systematic review of surveillance benefits and harms identified only 4 studies enumerating physical harms and no studies characterizing psychological or financial harms [5]. Psychological harms, which can occur at any time during the screening process, may include fear of abnormal surveillance results, anxiety after a positive result, and depression after a cancer diagnosis. Financial harms can relate to direct costs of testing as well as indirect costs, e.g., parking or transportation, and opportunity costs such as missed work. As above, future studies should not only enumerate psychological and financial harms but also examine possible variation in the frequency and severity by patient risk profiles.

Similarly, though the study used early tumor detection, the most direct effect of surveillance, as a measure of benefit, the best measure of surveillance benefit is improved survival, a measure that incorporates downstream processes including timely diagnostic evaluation and guideline-concordant treatment [6]. Larger studies in the future examining NNB should also include these downstream measures, including the proportion of patients undergoing curative treatment and net survival benefit.

The risk/benefit ratio of HCC surveillance is important when considering several current vigorous debates in the field, including in populations such as non-cirrhotic nonalcoholic fatty liver disease (NAFLD). It has become increasingly clear that up to one fourth of HCC in patients with NAFLD occur in the absence of cirrhosis. Nevertheless, cohort studies have demonstrated that patients with non-cirrhotic NAFLD have a very low annual incidence rate of HCC. As found in this study, one would anticipate a high NNB relative to NNH, suggesting that HCC surveillance in this population is of little value. As with cirrhosis, it is possible that risk stratification tools in the future may identify a high-risk subgroup of non-cirrhotic NAFLD for which the NNB/NNH may be more acceptable.

The framework of NNB/NNH can also inform discussions regarding the value of emerging surveillance modalities. Although the current study focuses on surveillance using ultrasound and AFP, the only strategy to be sufficiently validated for use in clinical practice, this combination misses over one third of early-stage HCC, highlighting a need for superior surveillance tests [7]. Case–control data for several alternative proposed blood and imaging-based strategies demonstrate higher test performance than ultrasound and AFP, although validation in phase III and phase IV biomarker cohort studies are needed to confirm clinical utility. Beyond assessments of sensitivity for early-stage HCC detection, it will be important to measure potential screening harms, including diagnostic evaluation for false positive or indeterminate results. If validated, the emergence of several possible surveillance strategies would facilitate consideration of more "complex" precision approaches, wherein low-risk patients may be spared surveillance and simply undergo observation until risk profiles change, intermediate-risk patients may undergo ultrasound- or biomarker-based surveillance, and high-risk patients undergo MRI-based surveillance. A prior decision analysis suggested that such an approach would be cost effective compared to current one-size-fits-all strategy of ultrasound-based surveillance, although this study preceded the current understanding of surveillance harms [8].

An ongoing multicenter study is prospectively collecting data on surveillance benefits and harms in a large cohort of patients with cirrhosis, which should help further inform patient–provider communications about HCC surveillance benefit/harm ratio. It will also be important to determine how both providers and patients would incorporate these data into shared decision making regarding HCC surveillance initiation. A prior survey of providers suggested that providers are accepting of risk-based surveillance in concept but are uncomfortable stopping surveillance in low-risk patients [9]. A multicenter survey also found that patients place greater importance on surveillance benefits than potential harms or surveillance logistics [10]. Therefore, these data may provide a better understanding of surveillance value but not move us closer to precision screening in practice.

Although precision HCC surveillance may not be "around the corner," there have been recent advances in both HCC risk stratification models and available surveillance modalities. As these foundational elements are validated and become readily available in clinical practice, the concept of precision HCC surveillance transitions from being fanciful to an aspirational goal that can be achieved in our lifetime.

Declarations

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