EDITORIAL

Surveillance for Hepatocellular Carcinoma: A Standard of Care, Not a Clinical Option

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Despite considerable progress in treatment, the overall prognosis of hepatocellular carcinoma (HCC) globally remains grim, because a majority of patients with HCC are identified with an advanced disease that almost invariably prevents the application of potentially curative treatments.[1] Although this accounts for global incidence and mortality rates of HCC to virtually overlap, the only hope for a cure rests on early diagnosis through surveillance with abdominal ultrasound (US) of patients at risk, an endpoint that is achieved in a minority of patients, most clustering in the developed world.[2] This is no surprise, because surveillance involves more than simply a screening test, being framed in a program where tests, recall policies, and quality control procedures are standardized, with significant economic consequences. Although the latter depend on multiple epidemiological and clinical factors, intervals of screening per se add to the never-ending dispute of effectiveness and cost–utility ratio of screening for HCC.[3] Indeed, although the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) share common recommendations for semiannual surveillance with abdominal US in all patients who are at risk for HCC,[2,4,5] the Japanese Association of the Liver recommends intensified screening every 3 or 4 months in men with viral cirrhosis or chronic viral hepatitis of increasing age, or in those who have a history of alcohol abuse, because these patients are considered at very high risk for HCC.[6] However, the strategy of intensified screening contrasts with the paradigm that the intervals of screening are not dictated by the level of HCC risk, which may range from 1% to more than 3% per year, but only by the growth rate of the tumor, which takes 6 months to double its volume, on average.[2]

Although it is crystal clear that intensified screening seeks to identify liver cancer at the smallest tumor size possible in order to optimize treatment, the effectiveness of this policy is largely questioned. This is also the message of the study by Trinchet et al. in this issue of HEPATOLOGY, where patients with cirrhosis were randomly allocated to standard (6-month) versus intensified (3-month) intervals of screening for HCC.[7] Following patient stratification by site and etiology (most arising from hepatitis C and alcohol), 43 centers in France and Belgium started surveillance with US, with or without serum alpha-fetoprotein determination. Ultimately, the study ended with the randomization of 1278 patients into the two interval arms of US screening only, because the protocol for alpha-fetoprotein was violated in a majority of the patients. This notwithstanding, the good quality of the study was granted by the high rate (88%) of compliance to the EASL guidelines–based protocol, during a median period of 47 months. Interestingly, the two study groups showed similar rates of cumulative 5-year incidence of HCC nodules (10.0% versus 12.3%), cumulative incidence of HCC $\leq$ 30 mm and $\leq$ 20 mm in diameter, access to curative treatments (62% versus 58%), and liver-related mortality (85% versus 86%). However, the fact that the 5-year cumulative incidence of focal lesions was higher in the 3-month arm (41% versus 28%) clearly heralds a greater economic burden to reach a final diagnosis, which might negatively affect morbidity and the cost–utility ratio of intensified screening.

Indeed, although the benefits are intuitive, the economic consequences of HCC surveillance strategies are generally poorly appreciated, due to the lack of randomized trials that have evaluated moderators of treatment outcome, such as compliance, heterogeneity of liver disease, and treatment effectiveness, which, in addition to tumor incidence, affect the cost–utility ratio of surveillance. The never-ending argument of cost–utility ratio of surveillance has, in fact, been analyzed by Markov modeling only, and moreover, in the

Abbreviations:: AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; US, ultrasound.

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frame of epidemiological and interventional assumptions which do not necessarily reflect real-life practice. This further underscores the chasm between efficacy and effectiveness of screening for HCC, which may also be inflated by the *a priori* decision to measure cost–utility ratios at less than US$ 50,000 for quality-adjusted life-year saved, an assumption that may conflict with policies of equitability while being influenced by the trends of economy, worldwide.[8] Among the many approaches to improve cost-effectiveness of HCC screening, strengthening prediction at the individual level through pretreatment patient stratification, on the basis of clinical or histological scores, provides uncertain benefits.[9,10] The same holds true for the exclusion of patients with severe comorbidities who do not fit criteria for curative therapies, because it might improve cost-effectiveness ratio of screening, albeit at the cost of introducing substantial ethical implications. Along the same lines, it is also debated whether screening should be restricted from aged individuals who would not have significant survival benefit if diagnosed with an HCC.

All these grey areas notwithstanding, the AASLD considers screening worthwhile in selected populations, such as in patients with hepatitis C who have $\geq$1.5% incidence of HCC, patients with hepatitis B who have $>$0.2% incidence, and in general, patients with cirrhosis,[2] thus reinforcing the expert opinion that surveillance for HCC is a standard of care, not a clinical option. This is clearly perceived by the majority of informed patients, who believe surveillance to be the only practical approach to improve prognosis of HCC, as reported by Poustchi et al. in this issue of HEPATOLOGY.[11] The authors used a survey in patients with cirrhosis carried out in three academic centers in Sydney, Australia, who were asked to enter a randomized, controlled trial of surveillance for HCC. Despite appreciating the relevance of a randomized, controlled study to determine the applicability, efficacy, and cost-effectiveness of HCC screening, the vast majority of informed responders (98%) preferred surveillance. As correctly stated by the authors, this survey clearly demonstrates that a randomized, controlled study of HCC surveillance is currently unfeasible in informed patients who have a disease such as cirrhosis, which is known to predispose to liver cancer; the reluctance of patients to participate in randomized, controlled trials derives from the fear of the arbitrary nature of the randomization process coupled with the patient desire to have an active role in medical decision-making. Apparently, cost-effectiveness of screening was less an issue among patients than it was among physicians, yet most of the physicians (74%) reported routine screening of all patients with cirrhosis. This contrasts with a population-based study in the United States where 6.6% of 3903 Medicare patients with HCC were shown to receive regular surveillance prior to diagnosis only,[12] a finding which replicates the low rate of screening uptake (12%) among hepatitis C–infected veterans with cirrhosis.[13] Interestingly, the fact that gastroenterologists, hepatologists, or physicians with an academic affiliation were more likely to perform surveillance than were pratictioners who are involved in community-based practices, suggests that barriers to screening, such as limited or outdated knowledge, lack of financial incentives, and limited access to appropriate testing and treatment, together work against screening effectiveness.

Thus, although the benefits of surveillance for HCC are appreciated by most physicians and patients, surveillance for HCC is still not a consolidated practice as it should be, even in resource-rich countries. To bridge the gap in screening for HCC, educational programs advocating screening in high-risk populations should be implemented to target both patients and stakeholders in the field, while waiting for a breakthrough in the strategy of screening to occur, which may lead to a switch of screening programs from hospitals to the community, with the aim to improve population's access.

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