HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Current Status of Hepatocellular Carcinoma Surveillance

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G&H What evidence is currently available showing the benefits of hepatocellular carcinoma surveillance?

NP The benefits of hepatocellular carcinoma (HCC) surveillance have been evaluated in several cohort studies in patients with cirrhosis. In the *Journal of Hepatology*, a large meta-analysis of such studies recently found that HCC surveillance has been associated with early-stage HCC detection, curative therapy receipt, and improved survival. Looking at studies controlled for lead time bias and length time bias, which are common sources of bias in cohort studies, the benefits of HCC surveillance were consistent.

HCC surveillance benefits have also been evaluated in patients with chronic hepatitis B virus (HBV). A large randomized controlled trial from China showed reduced HCC-related mortality rates in patients with chronic HBV randomized to ultrasound vs those not receiving ultrasound. However, this study had several methodologic flaws that make the results difficult to apply to contemporary populations. In addition, it is unclear whether these results are applicable to countries with smaller HBV populations and a larger proportion of patients with cirrhosis, such as the United States.

G&H What factors influence the effectiveness of current HCC surveillance programs?

NP When discussing the effectiveness of HCC surveillance, several issues should be considered. One critical issue is adherence to ultrasound-based screening, which is currently very poor. Meta-analyses of observational studies have shown that less than a quarter of at-risk patients undergo screening for HCC. In addition, ultrasound can be variable in terms of its performance. Ultrasound is dependent upon a number of patient-related factors, including obesity, presence of ascites, and underlying etiology of liver disease. Ultrasound is also dependent upon factors related to providers, such as their experience with performing the technique, how well they can visualize the liver, and the ability of the reader to accurately identify an abnormal lesion.

G&H What are the potential harms of HCC surveillance?

NP Whenever thinking about any type of surveillance or screening program for cancer, it is important to consider the potential harms that may occur physically, psychologically, and financially. Although some data are currently available regarding harms in HCC surveillance, this is still an emerging topic for which more data are required.

Physical harms are aspects of the surveillance tests that can cause harm to the patient. For example, if a nodule is found that is not a cancer and the patient undergoes a biopsy, there may be some physical harms. Harms can even be categorized as unnecessary imaging, for example, if a patient has a false-positive ultrasound result and undergoes a diagnostic magnetic resonance imaging (MRI) or computed tomography (CT) scan, which can lead to harms that are financial and physical (eg, radiation exposure during CT scan).

There are also psychological costs of going through a diagnostic workup and having uncertainty about a test result. If a patient has a positive test result, waiting for the results of follow-up imaging can also have psychological harms, as can a diagnosis of cancer.

There are also financial harms associated with HCC surveillance, including the cost of the test, copayments

(which are direct costs to the health care system), costs of downstream testing, and indirect costs to the patient (which include missed time at work, transportation costs, and parking costs).

G&H Which patient populations are at risk for HCC, and have they been changing?

NP In general, the at-risk population in the United States consists of patients with cirrhosis of any etiology, and the current recommendation is that all patients with cirrhosis should be screened for HCC. There is a growing population of noncirrhotic patients with fatty liver disease who are presenting with HCC, but that is not a screened population at this time.

There have been changes in the epidemiology of cirrhosis over the past decade, with cirrhosis now being caused more often by metabolic liver diseases such as fatty liver disease and alcohol-related liver disease and less often by viral hepatitis–related diseases. Notably, several studies have shown that ultrasound-based HCC surveillance is less effective in patients with metabolic liver diseases.

With the recent advances in hepatitis C virus (HCV) treatments now making near-universal cure possible, there has been some questioning as to whether patients who achieve HCV cure still require HCC surveillance. It is sometimes thought that surveillance for HCC is no longer needed once HCV has been cured. However, based on the current US guidelines, patients with cirrhosis who are cured of their HCV should continue surveillance for HCC. On the other hand, if cured patients do not have cirrhosis, they do not need to undergo HCC surveillance according to current guidelines.

G&H What are the current best practices, along with their supporting evidence, for HCC surveillance?

NP There is general consensus among many of the major international guidelines (eg, from the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Asian Pacific Association for the Study of the Liver) that the data available thus far support the use of HCC surveillance in at-risk patients. However, there is some nuance regarding exactly which populations would benefit from surveillance. In the United States, the current best practice is to use abdominal ultrasound plus serum alpha-fetoprotein (AFP) every 6 months to screen patients at risk for HCC (ie, those with cirrhosis). This recommendation is supported by the aforementioned meta-analysis of cohort studies that showed that ultrasound-based surveillance was associated with early detection, curative treatment receipt, and overall survival compared with patients who did not receive surveillance. That is the best evidence we currently have, although there are caveats because of the lack of randomized data in patients with cirrhosis.

It is important to note that this surveillance should continue every 6 months indefinitely. Some people mistakenly think they can undergo surveillance once a year or intermittently, but intermittent surveillance is associated with reduced detection of early HCC.

The use of AFP as part of surveillance has been shown to improve early-stage sensitivity of ultrasound from approximately 45% to 63%. Several other biomarkers, such as Lens culinaris agglutinin-reactive AFP (AFP-L3) and des-γ-carboxy prothrombin (DCP), are currently undergoing evaluation or validation but are not yet recommended for routine clinical practice. Methylated DNA markers are under investigation as well and appear to be promising; early validation data suggest that these markers may eventually supplant ultrasound-based surveillance.

G&H Should MRI or CT be used instead of ultrasound in any scenarios for HCC surveillance?

NP MRI or CT as routine surveillance practice has not been supported by cost-effectiveness analyses at this point because of cost and access issues that have been seen with cross-sectional imaging. With CT in particular, radiation exposure every 6 months can potentially incur significant harms.

However, there are scenarios of poor visualization with ultrasound where doctors may consider interspersing MRI or CT in the surveillance protocol, although those algorithms have not been clearly worked out. There are interesting emerging data looking at abbreviated MRI in these populations, as this technique involves shorter sequences of MRI. Essentially, instead of a 45-minute scan, a 15-minute scan is used, which could improve access issues. However, thus far abbreviated MRI does not have a separate billing code from regular MRI, limiting cost savings and clinical utilization.

In addition, we lack guidance on whether there should be a body mass index (BMI) cutoff for ultrasound-based surveillance. At this point, we do not have a strict BMI cutoff. More important is liver visualization. Liver Imaging Reporting and Data System (LI-RADS) scores range from A (good visualization) to C (poor visualization). In the most recent guidelines, if a patient has a LI-RADS visualization score of C, it is recommended that providers consider cross-sectional imaging for surveillance. However, the intensity of that imaging (how often patients should undergo it and whether it should be

interspersed with ultrasound) is somewhat unclear based on the current guidance. Obesity and metabolic liver diseases are risk factors for poor visualization on ultrasound, which can lead to a higher risk of undetected HCC.

G&H Could you discuss the cost-effectiveness research conducted thus far involving HCC surveillance?

NP Several cost-effectiveness analyses have compared different strategies of HCC surveillance. As previously mentioned, MRI-based surveillance and CT-based surveillance are not cost-effective as general strategies. My colleagues and I recently compared ultrasound vs ultrasound plus AFP and found that the latter strategy was more cost-effective for HCC surveillance, supporting its inclusion in the most recent US guidance.

There have been several cost-effectiveness analyses looking at different patient populations as well, in particular patients with cured HCV with cirrhosis to determine whether HCC surveillance remains cost-effective. There does appear to be some stopping rules for surveillance as patients become older, but these have not been well validated.

G&H Has any research looked at different HCC surveillance intervals?

NP A randomized trial by Trinchet and colleagues compared surveillance intervals of every 3 months vs every 6 months. No difference was found between these intervals in terms of early-stage detection, which is why 6-month intervals are used. There has not been research on longer intervals, such as every 12 months. Some analyses have examined tumor doubling time; based on modeling of how tumors grow, a 6-month interval appears to make sense for early detection.

G&H What are the priorities of research?

NP The biggest priorities are validation of alternative surveillance methods and improving test sensitivity and specificity. There is a lot of excitement about abbreviated MRI, which will be evaluated in a large clinical trial through the US Veterans Administration. Patients will be randomized to abbreviated MRI vs ultrasound, the gold standard for screening, to provide prospective data on this comparison. Another abbreviated MRI study will be launching soon in France.

Biomarker-based screening validation is an area where much effort will be put forth over the next several years, both in the earlier stages of novel biomarkers as well as larger validation studies of biomarkers that have already been studied. For example, the GALAD panel (which stands for gender, age, AFP-L3, AFP, and DCP) has been demonstrated to be sensitive and specific in phase 3 biomarker validation studies. A large phase 4 biomarker validation study is planned in the United States to compare the use of ultrasound plus AFP vs the GALAD score.

Methylated DNA panels are also being studied, and recent data on DNA fragmentomics (involving fragments of genetic material from HCC) have shown excellent performance in early validation studies, with larger validation trials being awaited. A lot of research is currently underway, and we are hopeful to have novel ways of detecting HCC in the near future.

There is also hope that with blood-based biomarkers becoming increasingly validated, there will be a rise in adherence to surveillance and therefore more effective surveillance strategies. There is room for improvement in adherence to HCC surveillance; as noted, a large recent meta-analysis found that adherence is less than 25% in patients with cirrhosis. Another priority for improving HCC early detection is developing better ways of identifying cirrhosis in the primary care setting. Many patients are diagnosed with cirrhosis and HCC at the same time; if they were known to have cirrhosis, their HCC might have been found at an earlier stage because they would have been undergoing surveillance for HCC.

Disclosures

Dr Parikh serves as a consultant for Exact Sciences and Freenome, has served on the advisory board of Wako/Fujifilm, and has received research funding from Target PharmaSolutions, Exact Sciences, and Glycotest.

Suggested Reading

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