Issues in Screening and Surveillance for Hepatocellular Carcinoma

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Individuals with chronic viral hepatitis and other forms of liver disease are at risk for developing hepatocellular carcinoma (HCC). When HCC presents with clinical symptoms, the tumor is typically very far advanced and the patient has few therapeutic options. Thus, screening and surveillance for HCC would appear to very appropriate. However, there is no definitive evidence that surveillance improves patient outcomes and current techniques lack sensitivity and specificity. Nonetheless, serial measurement of α-fetoprotein (AFP) levels in serum and hepatic ultrasound have become routine practice, despite a lack of evidence of their overall benefit. Clearly, better methods are needed for early diagnosis of HCC. Improved technology will ultimately have to be tested for improved patient outcome before becoming widely recommended.

A lthough there is clearly a need for early diagnosis of hepatocellular carcinoma (HCC), there is considerable controversy about the role of screening and surveillance in its management. It appears that some form of screening and surveillance for HCC is widely practiced in patients with chronic liver disease, but the optimal methods for surveillance and the ultimate impact of surveillance on patient survival remain uncertain. In assessing the value of surveillance in medical practice, the principles outlined by Prorok often are cited as a measuring stick. The application of these principles to surveillance for HCC is described later.

The Disease Must Be Common With Substantial Morbidity and Mortality

HCC is one of the most common solid malignancies worldwide and accounts for about 1 million deaths each year. Numerically, most of these cases occur in the Far East and are related to chronic infection with the hepatitis B virus (HBV) although, proportionally, chronic hepatitis C is more important in developed Western countries. It is estimated that about 17,000 new cases of primary liver cancer occur each year in the United States, most of this being HCC. Furthermore, El-Serag et al. have pointed out that the incidence of HCC has increased substantially in this country over the past 20–30 years. Generally, the incidence and mortality rates for HCC are approximately the same because this tumor has a very high mortality. Although effective treatments are available, these are applicable in only a relatively small proportion of cases so the impact of HCC is high.

The Target Population Must Be Readily Identifiable

HCC usually occurs against a background of chronic liver disease. Worldwide, chronic HBV and hepatitis C virus infection appear to be the most common underlying risk factors. Cirrhosis very often is found in association with HCC and may be caused by chronic viral hepatitis, alcohol consumption, non–alcohol-induced cirrhosis, and certain inherited metabolic diseases. Because accurate serologic tests are available to detect viral hepatitis, and the presence of cirrhosis often is known in advance, patients at risk for HCC are readily identifiable.

Surveillance Tests Must Have Low Morbidity but High Sensitivity and Specificity

The surveillance tests commonly used for detection of HCC are ultrasound examination of the liver and measurement of α-fetoprotein (AFP) levels in serum. Certainly, both of these tests can be thought of as having low morbidity but their sensitivity and specificity are fairly high. Sherman et al. assessed the predictive value of these tests in a randomized controlled trial of surveillance among Canadian patients with chronic HBV infection and found the sensitivity and specificity of AFP measurement to be 64% and 91%, respectively, using a

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There Must Be Standardized Recall Procedures

The requirement for standardized recall procedures refers to having a standardized plan for subsequent evaluation of patients found to have an abnormal surveillance test. Although various recall algorithms have been described in the context of liver disease, none has been tested rigorously in a prospective fashion. Furthermore, recall procedures differ for abnormal AFP values and for abnormal ultrasound findings. Thus, increases in serum AFP level need to be interpreted against a background of liver disease. Exacerbations of HBV infection are well known to sometimes result in marked increases of AFP level, which may last for many months. Pregnancy also may cause temporary increases in AFP levels. Thus, patients found to have increased serum AFP values typically have levels remeasured and require a more detailed clinical evaluation to determine causes for increases other than HCC. On the other hand, a new mass or hypodense lesion in the liver detected by ultrasound surveillance is very suggestive of HCC and requires complete evaluation. Typically, this involves further imaging by computerized tomography or magnetic resonance imaging and the presence of a hypervascular mass in the liver detected with 1 of these 2 procedures is considered by some to be diagnostic of HCC. The issue of whether all suspicious masses should be subjected to liver biopsy to prove the presence of HCC is controversial because of concerns about the possible spread of cancer along the needle track.

The Surveillance Tests Must Be Acceptable to the Target Population

In general, patients with chronic viral hepatitis or other liver diseases are aware of the possible long-term consequences of their condition, including HCC, making them amenable to reasonable strategies for surveillance. Given that ultrasound examination and a blood test for AFP are relatively easily performed, with few risks, most patients would consider surveillance with these techniques to be acceptable. Another aspect to this issue is the availability of surveillance. Because chronic viral hepatitis (particularly HBV infection) is prevalent in less-developed regions of the world, surveillance tests that are very expensive or that rely on complicated technology may not be readily available. Although ultrasound examination is not particularly technically complex, sensitive equipment is required and training for the examiner is needed. In inaccessible parts of Alaska, surveillance for HCC has relied solely on measurement of AFP levels, performed on blood specimens mailed at ambient temperature.

There Must Be an Acceptable and Effective Therapy

This final principle has been a stumbling block to the introduction of widespread surveillance for HCC. Now, however, several potentially curative forms of therapy are available for early HCC, including resection, liver transplantation, and chemical or radiofrequency ablation. All of these treatments are able to eliminate tumors less than 5 cm in diameter, provided they are in an accessible location within the liver and that liver function itself is adequate. It is only liver transplantation, though, that can eliminate small tumors successfully, even in the face of hepatic decompensation. Furthermore, liver transplantation is the only modality of therapy that eliminates the risk for development of new HCCs. Unfortunately, only a minority of patients diagnosed with HCC have tumors amenable to one of these forms of potentially curative therapy, even within surveillance programs. But this fact makes it even more urgent to develop more effective forms of surveillance for HCC.

There are several other issues related specifically to the surveillance for HCC which are not discussed by Prorok.

Surveillance Intervals

The optimal interval for HCC surveillance is not known. Ideally, this should depend on knowledge of the growth rate of HCC and related premalignant lesions. Very little such information is available, although a study based on ultrasound examination and reported in the 1980s suggests that HCC is a relatively slow growing tumor. The median doubling time was estimated to be 117 days (range, 29–398 days) and doubling time was less than 150 days in most cases. The use of a surveillance interval of 6 months allows most tumors to experience at least one doubling between surveillance intervals and would appear to allow ample opportunity to detect most tumors before they become more than 5 cm in diameter. Clearly, additional prospective studies are needed to validate this surveillance interval.
Are There Individuals Who Should Not Be Screened?

Surveillance is not recommended for the general population given the low overall rate of HCC (approximately 5 per 100,000 per year; 0.0005%). A commonly accepted rate that requires surveillance is greater than .2% per year. Clearly, this threshold is exceeded in patients with established cirrhosis in whom the risk is estimated to be 1%–4% per year. Among individuals with chronic HBV infection, those with high risk for HCC have been recommended for screening (mean age >45 y, persons with cirrhosis, those with a family history of HCC), whereas inactive carriers of HBV generally are thought to be at low risk and are not usually screened. Because the risk for developing HCC is very low in patients with chronic hepatitis C who do not have cirrhosis, surveillance is not thought to be necessary in noncirrhotic patients with chronic hepatitis C. It is also debatable whether patients at risk for HCC, but with other life-threatening illnesses or who could not be expected to tolerate potentially curative therapy, should be subjected to surveillance.

Do Surveillance Programs Work?

Perhaps the major issue preventing widespread introduction of programs to screen for HCC is the lack of evidence that surveillance is associated with prolonged survival of patients with chronic viral hepatitis or other forms of chronic liver disease. Most of the available evidence comes from retrospective studies and does not take into account lead-time bias as a potential confounding variable. Certainly, routine surveillance appears to result in a greater rate of detection of smaller and lesser-stage tumors compared with those detected because of clinical symptoms. Furthermore, these smaller tumors appear to be more amenable to potentially curative therapies such as resection and transplantation because of their smaller size, but there is still no conclusive evidence that this process ultimately alters the outcome of the patient. A prospective controlled trial of surveillance has been reported among patients with chronic HBV infection. Screened subjects had a liver ultrasound performed and serum AFP levels measured every 6 months whereas controls had no screening. The screened group generally had HCC detected at an earlier stage and also had improved 1-year and 2-year survival rates.

Cost Effectiveness

Attempts have been made to estimate the financial costs associated with surveillance and the costs incurred by nonsurveillance. Even here the results are controversial. Thus, Mima et al.16 found that in Japan, the cost per tumor detected using ultrasound and AFP level testing every 6 months was approximately $25,000, whereas researchers in Switzerland estimated the cost of surveillance per year of life saved to be between $26,000 and $55,000.17 These estimates are within the range considered acceptable. However, Bolondi et al.18 in Italy estimated the cost per year of life saved to be $112,996, an amount exceeding the $50,000 typically considered acceptable.

Medical Malpractice Liability

There is little information available about whether nonsurveillance for HCC in patients at risk represents a potential malpractice liability. However, a recent survey of practicing hepatologists suggested that many of them practice some form of regular surveillance for HCC despite their belief that surveillance is not cost effective and does not prolong survival.19 Sixty-four percent of respondents in this survey indicated that nonsurveillance poses a malpractice liability.

Summary and Conclusions

It appears, therefore, that HCC is a suitable disease for surveillance programs because it is relatively common, at least in patients with liver disease, and has very high mortality rates. However, the current surveillance tests have less than optimal sensitivity and specificity. Surveillance should be performed at intervals of 6–12 months based on tumor growth estimates. As presently practiced, the cost effectiveness of surveillance for HCC is barely acceptable. Clearly, there is a pressing need for newer tests with greater accuracy in diagnosis of early HCC. When this occurs, surveillance is likely to have a sound scientific basis and become universally practiced.

References


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