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## Hepatocellular Screening Guidelines and Bellevue's High Risk Population

*Ramoncito David*

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death in the world.<sup>1</sup> The prevalence of this fatal disease greatly varies among different nations, due to the fact that almost 80% of cases are secondary to hepatitis B or C.<sup>2</sup>

The implementation of an effective vaccine against the hepatitis B virus (HBV) has reduced the prevalence of HBV carriers in North America to 0.1-2%; however, hepatitis B remains a global public health problem due its high prevalence in Asia and Africa, where 10-20% of the general population are carriers.<sup>3</sup>

Hepatitis C in the United States is more prevalent in urban areas with higher populations of immigrants and intravenous drug users. Bellevue's patient population is at high risk for hepatocellular carcinoma because of our many Asian, African, and IV-drug-using patients and our relatively high rates of hepatitis B and C.

According to the American Association for the Study of Liver Diseases (AASLD), patients at high risk for developing HCC should be entered into a surveillance program that screens them at regular intervals to check for new lesions in the liver. By examining current guidelines and looking at how they are applied at Bellevue, we can shed some light on the question of whether we are screening too many patients or too few.

The updated AASLD guidelines published in 2010 state that high-risk groups should be screened with ultrasonography every 6 months.<sup>4</sup> Ultrasound as a screening test for HCC has a sensitivity that ranges from 65% to 80% and a specificity greater than 90%. The main disadvantage of this test is that it is operator-dependent; hence the wide range in sensitivity.<sup>5</sup> In addition, lesions in the liver are more difficult to detect sonographically in obese and cirrhotic patients, further decreasing the sensitivity. However, due to its cost-effectiveness, safety, and efficacy, ultrasonography is the preferred HCC screening and surveillance modality.

Alpha-fetoprotein (AFP) is a serum marker that can be elevated in patients with primary liver cancer. The optimal threshold for elevated AFP levels in HCC screening tests was found to be 20 ng/mL, but even then a screening test employing this cut-off would have a sensitivity of only 60% and a positive predictive value of only 41.5% when the prevalence of HCC is assumed to be 5%, as seen in most liver clinics.<sup>6</sup> Some institutions use a combination of ultrasonography and AFP levels for screening, which results in increased sensitivity at the cost of a higher false positive rate.<sup>7</sup> However, screening with AFP alone is not recommended, since it was shown in the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis (HALT-C) Trial to be ineffective.<sup>8</sup> Interestingly, studies imply that AFP is even less sensitive for the diagnosis of HCC in African-Americans with cirrhosis due to hepatitis C.<sup>9</sup>

Some have suggested triple-phase CT scanning or MRI as alternative imaging options, but their use has not been studied in non-biased populations where there has not already been suspicion for HCC.<sup>10</sup> Moreover, given that the suggested interval time for screening is 6 months, CT scanning would expose the patient to high levels of radiation. Serial MRIs and triple-phase CTs would also accrue significant costs. However, given the availability of resources at some institutions and the lack of contrast-enhanced ultrasonography in the United States<sup>11</sup>, CT scanning may be the best option for screening since it has been shown to have high sensitivity for finding lesions and is not as user-dependent as ultrasonography. At Bellevue, surveillance for HCC in at-risk patients is done by CT scan or MRI every 6 months, which is typically the length of time it takes for tumor size to double.

Limiting screening to high-risk patients makes sense because of the potential harm involved: false positives can lead to further unnecessary testing and IV contrast can harm patients with renal insufficiency. The many risk factors for developing HCC include race, male gender, hepatitis B carrier state, chronic hepatitis C infection, hereditary hemochromatosis, cirrhosis, non-alcoholic fatty liver disease, diabetes, alpha-1-antitrypsin deficiency, exposure to environmental toxins (aflatoxin, contaminated drinking water), smoking, and alcohol abuse.<sup>12-15</sup> For non-cirrhotic hepatitis B patients, the AASLD guidelines suggest screening all Asian males over the age of 40, Asian females over the age of 50, patients with a positive family history of HCC, and Africans over the age of 20, regardless of carrier status or viral load. They also recommend screening all patients with cirrhosis of any etiology.<sup>16</sup>

Using the subset of Asian HBV carriers as a study group, we can look more closely at the impact that screening has on mortality. A 2004 trial based in Shanghai, randomized 18,816 Chinese patients between the ages of 35 to 59 with chronic hepatitis B to an active surveillance group followed with an AFP level and ultrasound every 6 months or to an observation group to be followed for up to 20 years. After 5 years they found that mortality due to HCC was significantly lower in the surveillance group compared to the observation group (83 per 100,000 vs. 132 per 100,000, mortality rate ratio 0.63, 95% CI 0.41-0.98).<sup>17</sup> The 37% decrease in mortality was attributed to detection of the lesions at an earlier stage in the surveillance group. The number needed to treat (NNT) for this sample was 2,041. Since the treatment offered in the study was resection, it is important to note that in the setting of chronic hepatitis B, HCC may arise prior to the development of cirrhosis, thus improving the prognosis for non-cirrhotic patients undergoing resection.

Given the demonstrated benefit of early detection of HCC through screening, it is important to examine whether we healthcare providers are using screening to its full potential. Cost-effectiveness is one way to assess this, and it is generally accepted that surveillance is cost-effective in cirrhotics who have an expected annual incidence of HCC greater than 1.5% per year. Since the incidence of HCC in cirrhotic liver disease of any etiology typically ranges from 3% to 8% per year, it is clear that screening for these high-risk groups is cost-effective and potentially life-saving, given the high mortality rate associated with HCC.<sup>18,19</sup>

In terms of the actual costs of screening tests, one study performed a cost-utility analysis comparing the incremental costs of four of the most commonly used screening modalities vs. no screening: AFP level alone, abdominal ultrasound and AFP, abdominal triple-phase CT and AFP, and abdominal MRI and AFP. Utilizing Medicare reimbursement data as a standard of cost, they found that screening with ultrasonography and AFP level had an incremental cost-utility ratio of \$26,689 per quality-adjusted life year, while abdominal CT and AFP was associated with an incremental cost-utility ratio of \$25,232 per quality-adjusted life year. AFP alone is not a viable option due to lack of efficacy, and MRI with AFP had a significantly higher cost-utility ratio of \$118,000 per quality-adjusted life year.<sup>20</sup> According to this data, abdominal CT with AFP level appears to be the most cost-effective screening modality. More inclusive criteria for screening with CT and AFP would inevitably result in a marginal increase in financial burden, with the incremental costs being dependent on the number of new patients meeting the revised criteria.

Before considering a change in the criteria for screening, it is important to evaluate how well the current guidelines work when implemented at a hospital with a high volume of at-risk patients. Here at Bellevue we see many patients with chronic hepatitis B, most of whom are immigrants from China who likely acquired the viral infection by vertical transmission during birth. These patients have had a longer course of infection compared to patients who acquired HBV at a later age. They can develop HCC earlier in their lives, prior to reaching the age at which screening is recommended according to the AASLD guidelines. When there is no family history and no clinical finding of cirrhosis prompting us to screen these patients, they are often not diagnosed unless the lesion is found incidentally or the disease

reaches an advanced stage and becomes symptomatic. Ironically, these young patients with non-cirrhotic livers are also the ones who would benefit most from early detection and subsequent resection. Unfortunately, they are not usually screened since they do not meet the criteria under the current guidelines. Thus it would be helpful to establish more sensitive criteria for identifying patients who are at higher risk for developing early onset hepatocellular carcinoma. One study has shown that in young HBV patients, smoking and cirrhosis were significant risk factors for developing HCC.<sup>21</sup> In order for clinicians to implement the tool of screening in a more cost-effective and efficacious manner, further studies need to be done to elucidate important risk factors such as those that can be incorporated into a targeted algorithm for screening that includes those patients at highest risk for developing HCC at a young age.

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