using these two variables with AST/ALT ratio has a sensitivity of 46% and specificity of 98% for cirrhosis (100). Albumin is commonly measured in patients suspected of progressing to cirrhosis. While it is not as sensitive as other markers, it is used as a marker of severity as part of the Child-Pugh classification of cirrhosis. AFP is more likely to be elevated as degree of hepatic fibrosis increases (296), especially in cirrhosis; AFP greater than 17.8 ng/mL has a sensitivity of 35%, specificity of 98.6%, and positive predictive value of 97.7% for cirrhosis. (297)

Recommendations

Biopsy is the only definitive marker of progression from chronic hepatitis to cirrhosis (IIB).

Laboratory markers of fibrosis should not be used except in research studies (IIIB, E).

Markers of hepatic function that may indicate progression to cirrhosis (AST/ALT ratio, albumin, prothrombin time, platelet count) should be measured every 3-6 months in patients with chronic hepatitis (IIIB).

HEPATOCELLULAR CARCINOMA

Primary liver cancer (hepatocellular carcinoma, HCC) is a serious late complication of chronic hepatic injury, particularly in cirrhosis due to HBV, HCV, and hemochromatosis. Infrequently, HCC is seen in patients with chronic HCV and in asymptomatic HBV carriers without cirrhosis. It is the fifth most common malignancy world-wide, and is particularly common in Eastern Asia and Africa. (298) The incidence of HCC has increased by 70% in the United States over the past 20 years, particularly among younger patients (299), and is increasing in other parts of the world as well. (298) The risk of developing HCC in cirrhosis due to chronic HBV or HCV infection is 1.5% per year. (300, 301) In a study of 448 cases of HCC, 75% occurred in patients with cirrhosis; however, in only 30% was cirrhosis recognized clinically before hepatocellular carcinoma was diagnosed. (302). These data suggest that screening programs, if instituted, must include patients with chronic hepatic injury as well as patients with diagnosed cirrhosis. In one study, however, hepatocellular carcinoma developed only in 325 patients with severe chronic hepatitis or cirrhosis, and not in any of 800 patients with mild or moderate chronic hepatitis. (303) Since patients with normal ALT generally have mild inflammation on biopsy (185, 217, 218), it is reasonable to exclude from screening those persons without cirrhosis and with normal ALT or less than severe hepatitis on biopsy. Other risk factors include male gender and age > 55 years.

The prognosis of patients with HCC detected by development of symptoms is grim, with few patients surviving over 6 months. Detection of small tumors offers the potential for curative resection, and forms the rationale for considering screening. Current practice suggests measurement of α-fetoprotein (AFP) and ultrasound of the liver every 6 months. (304) Unfortunately, AFP interpretation is complicated by intermittent elevations of AFP

in 12-13% of patients with chronic HBV or HCV (305), often (but not always) associated with transient increases in ALT. (306) A Consensus Development workshop recommended screening chronic HBsAg carriers at least once, and preferably twice, yearly with AFP only, while patients with other risk factors (known cirrhosis, family history) should have both AFP and ultrasound. (307) In chronic hepatic injury, high risk of HCC is present in patients with hemochromatosis or with cirrhosis due to HBV, HCV, and alcohol abuse. Other causes of chronic hepatic injury and cirrhosis have lower risk of HCC. (308)

In Western countries, the predictive value of AFP is low, often in the range of 10-30%, with sensitivity of AFP between 40-80%. (309, 310) In 147 patients with cirrhosis, none of the 30 patients with HCC had AFP > 105 ng/mL at the time of diagnosis and 60% had AFP < 20 ng/mL; however the frequency of HCC in patients with AFP < 50 ng/mL was 17%, compared with 42% in those with higher AFP. (310) In another study of 260 patients with cirrhosis, HCC developed in 26% of patients with initial AFP < 20 ng/mL, but 46% in those with higher levels. Moreover, those with even transient increases above 100 ng/mL had a significantly higher risk of HCC than those whose AFP was consistently < 20 ng/mL. (311) A decision analysis on published papers of screening for HCC in Western patients with compensated cirrhosis concluded that, for patients with a likelihood of survival of 85% at 5 years, screening would likely add 3-9 months to average life expectancy at a cost of $26,000 - $55,000 per year of life gained, figures that compare favorably to those of colon cancer and breast cancer screening. (312) In patients with lower likelihood of survival, screening provided minimal or no gain in life expectancy and does not appear indicated. A systematic analysis of all published studies concluded that there is inadequate data to determine the benefit of screening for HCC among patients with chronic liver disease. (313) If screening is used, frequency of testing of every 6 months appears to be optimal based on observed doubling times of HCC, reported to average around 3-5 months (314).

Des-γ-carboxy prothrombin has also been suggested as a screening test. Levels are elevated occasionally in chronic liver disease, but there is less overlap with values seen in HCC than for AFP. (315, 316) Occasional high levels are encountered in metastatic carcinoma to the liver, but they are usually minimally increased. While des-γ-carboxy prothrombin appears less sensitive (50-70%) than AFP, it is more specific. There is poor correlation between AFP and des-γ-carboxy prothrombin, and some tumors are only detected by des-γ-carboxy prothrombin. (315, 316) Vitamin K deficiency can also cause significant elevation; repeating testing after administration of vitamin K improves specificity. (315, 316) Recently, a more sensitive immunoassay has shown promise in detection of small HCC, with positivity in 27% of cases compared to 3% with older assays. (317) Assays for des-γ-carboxy prothrombin are not widely available, in contrast to AFP assays. Other laboratory tests, including AFP variants (318) and lectin affinity chromatography of alkaline phosphatase (319) have been evaluated in too few patients to make definitive recommendations. A recent study identified high levels of abnormal forms of GGT in 78 of 91 patients with HCC, but in only 2.5% of 116 patients with other liver diseases. (320)

Recommendations

Screening for hepatocellular carcinoma is of questionable benefit in Western populations (IIB, E).

Screening should be confined to high risk patients (those with severe chronic hepatitis or cirrhosis due to alcohol, HBV, HCV, or hemochromatosis) who are candidates for treatment of hepatocellular carcinoma, if detected (IIIB, E).

If screening is used, measurement of α-fetoprotein and ultrasound at intervals no more frequently than every 6 months is recommended (IIB).

There is currently little data to support the use of other tests (IIIB).