

## CLINICAL INQUIRIES

# What is the best surveillance for hepatocellular carcinoma in chronic carriers of hepatitis B?

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### EVIDENCE-BASED ANSWER

Screening patients with chronic hepatitis B infection (HBsAg+) for hepatocellular carcinoma by alpha-fetoprotein (AFP) or by AFP plus ultrasound (AFP/US) detects hepatocellular carcinoma tumors at earlier stages and increases resection rates

(strength of recommendation [SOR]: **B**, based on a systematic review of fair-quality randomized controlled trials). It is unclear whether screening with AFP or AFP/US improves disease-specific or all-cause mortality (SOR: **B**).

### CLINICAL COMMENTARY

#### Offer screening to all with chronic hepatitis B infection, but stratify risk for HCC first

Because no mortality benefit to screening for hepatocellular carcinoma has been shown, we should give added consideration to how we counsel our patients before offering screening, particularly since positive screening results can lead to further invasive studies. An important consideration for me is whether a patient has, or is at risk, for cirrhosis, because the incidence of hepatocellular carcinoma is higher if cirrhosis is present. Screening for coinfection with hepatitis C

or a history of alcohol abuse becomes especially critical in this situation. Biochemical evidence of chronic active liver inflammation, whatever the cause, should also be an important factor in deciding whether to screen. While I still offer screening to all patients with chronic hepatitis B infection, it helps to have stratified a patient's underlying risk for hepatocellular carcinoma first and counseling him or her accordingly.

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### ■ Evidence summary

Many serum markers and screening methods have been proposed to detect hepatocellular carcinoma at a treatable stage, but only 2—AFP and US—are in clinical use.<sup>1</sup>

A Cochrane systematic review on screening for hepatocellular carcinoma in the HBsAg+ population was published in 2003 and updated May 2004.<sup>2</sup> Our literature search did not find any subsequent relevant trials. The Cochrane review included 2 randomized control trials. The larger trial was performed in Shanghai, China

and included 18,816 HBsAg+ patients aged 35 to 55 years.<sup>3</sup> Subjects were recruited from their place of employment and randomized to either AFP/US every 6 months (n=9373) or to no screening (n=9443).

Fifty-one hepatocellular carcinomas were diagnosed in the control group and 86 in screened group. Screened subjects had a significantly higher percentage of tumors that were less than 5 cm at the time of diagnosis and a higher number of patients who underwent resection. While

## CLINICAL INQUIRIES

the 5-year survival for those with hepatocellular carcinoma in the screened group was higher, the disease-specific mortality rate was not statistically different between the 2 groups.

Additional data became available in 2002. The original study authors claimed the new data showed a statistically significant disease-specific mortality rate ratio of 0.63, favoring the screened group.<sup>4</sup> However, the Cochrane group performed their own analysis on the same data and determined that no statistically significant difference in the disease-specific mortality rates existed between the 2 groups.<sup>2</sup> Therefore, it is not clear whether these new data definitively demonstrate that screening provides any benefit.

The other randomized control trial took place in Toronto, and included 1069 patients, 71% of whom were of Asian ancestry. Subjects had AFP testing every 6 months, and half were randomly assigned to have US performed every 6 months.<sup>5</sup> Eight of the 11 incident tumors would have been diagnosed based on AFP levels alone, and 3 would have been missed with US alone. The authors conclude that for AFP, sensitivity=64.3% and specificity=91.4%; for US, sensitivity=78.8% and specificity=93.8%. However, their study was too small to determine if AFP/US is superior to AFP for hepatocellular carcinoma screening in a HBsAg+ population. They estimate that detecting such a difference would take a sample size of 10,000 or more.

Both studies have important flaws. Neither study applied a reference standard test (such as a computed tomography scan or magnetic resonance imaging) to both study arms. Carcinomas may have been undetected by either AFP or US. Without knowing the real prevalence of hepatocellular carcinoma, the true sensitivity and specificity for AFP, US, and AFP/US in these studies cannot be determined. Both studies included prevalent tumors (tumors diagnosed during the very first screening cycle) in their analysis. Approximately 20% of detected carcinomas in both stud-

ies were present at the start of the studies and did not represent newly incident tumors detected by regular screening.<sup>3,5</sup>

Both of these trials would be improved if they started with cohorts known to be disease-free at baseline. Additionally, the Shanghai study randomized patients in clusters. The only English-language report of this study did not describe whether adjustments for this were made in analysis;<sup>5</sup> failing to do so could overestimate the benefit of screening.

### Recommendations from others

The American Association for the Study of Liver Disease recommends that carriers of the hepatitis B virus who are at high risk for developing hepatocellular carcinoma—men aged >45 years, those with cirrhosis or a family history of hepatocellular carcinoma—should be screened periodically with AFP/US. Also consider periodic screening for low-risk HBsAg+ patients who are from an area where hepatocellular carcinoma is endemic (SOR: C, based on expert opinion or descriptive epidemiology).<sup>6</sup>

### REFERENCES

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### FAST TRACK

**As no mortality benefit to screening for hepatocellular carcinoma has been shown, stratify each patient's risk first**

CONTINUED ON PAGE 159