

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Current Status of Alpha-Fetoprotein Testing

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G&H Is alpha-fetoprotein testing useful for diagnosing and/or monitoring hepatocellular carcinoma?

MS Alpha-fetoprotein (AFP) testing is useful in the diagnosis of hepatocellular carcinoma (HCC) only if the serum concentration of AFP is markedly elevated. However, most patients with HCC who are diagnosed through screening processes do not have high AFP levels; often, their AFP levels are not elevated at all. Patients with later-stage disease are more likely to have markedly elevated AFP levels, but they also show other signs of disease; either they are symptomatic, or they show radiologic findings. With more advanced HCC, AFP testing is occasionally helpful to confirm a radiologic diagnosis, but generally radiologic imaging alone is sufficient. Therefore, I do not think that AFP testing has much of a role in the diagnosis of HCC.

A similar argument applies regarding the use of AFP testing to monitor patients with HCC. It is true that if you treat an AFP-producing cancer, the AFP level declines, and if the cancer recurs, the AFP level tends to rise again. However, patients with HCC are monitored on a regular basis by ultrasound or computed tomography scan, and these technologies are fairly sensitive for detecting recurrence. If clinicians were to detect an elevated AFP level, they would perform a radiologic study and would find the tumor. However, clinicians should be performing radiologic studies anyway to monitor patients with HCC, so it is not clear to me that AFP testing adds any value. I do not routinely use AFP testing for either diagnosis or monitoring.

G&H Are there any special cases in which you would use AFP testing?

MS I perform AFP testing approximately 3–4 times per year when I have patients in whom there is some uncertainty about the diagnosis and I am unable to do a biopsy. Generally, if a clinician cannot make a radiologic diagnosis, then a biopsy is necessary. In the occasional case in which a biopsy cannot be performed, however, then AFP testing can be helpful.

G&H Aside from HCC, what other conditions can cause an elevation in AFP level?

MS Testicular cancer causes elevations in AFP level, but that is not generally a source of diagnostic confusion. More importantly, a significant number of patients with cirrhosis will have an elevated AFP level, and the clinical significance of this finding is unclear. A study that examined a fairly large number of patients over a period of 13–14 years found that approximately 90% of AFP elevations were not associated with cancer. Instead, most cases involved a transiently elevated AFP level; if patients were followed over this period, approximately 13–14% would have an elevated AFP level at some point. In patients with cirrhosis, an elevated AFP level is a marker for increased risk of HCC; therefore, a clinician is more likely to find a tumor in a patient who has an elevated AFP level than in someone who does not. However, this use of AFP level does not qualify it as a screening test.

G&H Can imaging help to clarify the diagnosis in patients who have an elevated AFP level?

MS Radiology is often used to examine patients who have an elevated AFP level. While there will be cases in which radiology is not particularly helpful because the tumor is diffuse and infiltrating, these cases are quite rare. If radiology is inconclusive and the AFP level is elevated,

a clinician cannot assume that the AFP elevation is due to cancer; it is still necessary to do a biopsy to make the diagnosis. The reason a biopsy is necessary is because occasionally cholangiocarcinoma can cause HCC, and because the elevated AFP level might be due not to HCC but to the underlying cirrhosis.

G&H Given the limited diagnostic value of AFP testing, is an elevated AFP level really a cause for concern?

MS First, one should not make the assumption that clinicians are performing regular AFP testing. Routine AFP testing is certainly not recommended; the guidelines for HCC screening specifically exclude the use of AFP testing because it is insufficiently sensitive and insufficiently specific for use as a screening test. Nonetheless, many clinicians do not accept this recommendation and continue to perform AFP testing despite the evidence against its use. So the question is: If a patient has an elevated AFP level but the clinician does not find evidence of cancer, is there a cause for concern? The answer is no. If the AFP level is dramatically elevated and the clinician suspects that he or she is missing the cancer, then further testing is indicated, but a mildly elevated AFP level is not a particular cause for concern. While an elevated AFP level does indicate a slightly higher risk for the development of cancer, it does not change the protocol for screening these patients.

G&H What other laboratory tests could be used in place of AFP testing?

MS There are several tests that are being developed, particularly for use as screening tests for HCC; however, none of them have been adequately tested. The des-gamma-carboxy prothrombin (DCP) test is more sensitive than AFP

testing, but it is still insufficiently sensitive to regularly detect early-stage disease. The biggest problem with both DCP and the *Lens Culinaris* agglutinin-reactive fraction of AFP is that both, like AFP, are markers of advanced disease. While these newer tests are more sensitive, they are still not useful as screening tests.

The main difficulty when screening for HCC is that the clinician is trying to find a tumor that is only approximately 2.0–2.5 cm in diameter, and a tumor of that size is unlikely to release enough of any biochemical marker to be readily detectable. While there will be occasional patients in whom HCC is detected by serologic screening tests, these cases are quite rare. For example, my colleagues and I ran a screening study for 15 years. Our very first case, in 1989, was diagnosed by a rise in AFP level; since then, we have not diagnosed a single case because of an elevated AFP level when the ultrasound was negative. The ultrasound was positive every time the AFP test was positive, and the ultrasound was positive in many cases when the AFP test was negative. In short, ultrasound is a better screening test than AFP testing.

Suggested Reading

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