Key Concepts

- Alpha fetoprotein is a surrogate marker for hepatocellular carcinoma (HCC) but is insensitive and very nonspecific; the medical literature is confusing due to different populations and sampling bias which both lead to over-estimation of the specificity of the test.
- Low levels of AFP are common in patients with chronic liver disease, particularly hepatitis C, and correlate with ALT, fibrosis stage, age and presence of steatosis.
- Additional markers such as AFP-L3%, des-carboxyprothrombin (DCP), and PIVKAI may improve the specificity of AFP, but their usefulness remains unproven.
- Inclusion of AFP in HCC surveillance protocols is controversial, but elevations >100-200 are quite specific for HCC and so AFP determinations may sometimes be helpful.
- A progressive rise in the AFP level in the absence of a lesion on ultrasound is suggestive of HCC and should prompt more frequent imaging or additional imaging modalities.

Patients with liver disease and advanced fibrosis are at increased risk for hepatocellular carcinoma (HCC). Regular surveillance has been shown to be effective in identifying patients with HCC at an earlier stage while they may still be good candidates for effective treatment options such as tumor ablation and/or liver transplantation [1-3]. Inclusion of alpha fetoprotein (AFP) in the testing done for HCC surveillance is controversial since it is neither sensitive nor specific [4]. While AFP is elevated in about 60% of patients with HCC, these levels are usually less than 100 ng/mL [5]. However, levels are also elevated in 10% to 33% of patients with chronic liver disease without HCC [5-7]. Host and disease factors such as ALT, AST, fibrosis stage, degree of steatosis, age and gender may also influence AFP levels and these should temper our reliance on the test [8-10]. The strong relationship to serum aminotransferase levels has led one group to suggest that the “normal” AFP cutoff float with ALT and/or AST level [8]. However, the association with higher stage of fibrosis is probably not relevant to this discussion since HCC surveillance is usually confined to those with advanced fibrosis. Use of a higher cutoff for AFP or other markers such as AFP-L3%, DCP and others may increase the accuracy of diagnosis of HCC when used in combination, but the added benefit is low [11,12]. To complicate interpretation of these reports even further, the estimated benefit of AFP (positive predictive value) in diagnosing HCC may be over-estimated because of selection of study group sizes that differ so dramatically from the true point prevalence of HCC in persons with cirrhosis (1-3% per year). Indeed, the most recent update of the AASLD Practice Guideline on Management of Hepatocellular Carcinoma weighed in on this issue and recommended that surveillance include imaging alone [13]. However, even imaging alone strategies suffer from insensitivity [5,14], especially for small tumors, leading...
many physicians to continue to test for AFP despite its limitations. Other arguments in favor of maintaining AFP in the surveillance algorithm include its low cost (sometimes not so low considering its lack of accuracy) and its perceived usefulness in following trends over time. In fact, a very high AFP level or a steady increase is AFP over time has been shown to be highly predictive of HCC and, in known HCC, in a greater chance of recurrence after ablation or transplantation [5, 15, 16]. Persistent elevation over time rather than fluctuating levels is also more suggestive of HCC [6].

References