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Hepatocellular carcinoma tumour markers: Current role and expectations

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A B S T R A C T

Tumour markers could be helpful along the continuum of care for patients with hepatocellular carcinoma; however, there is insufficient data for routine use of most current biomarkers in clinical practice. Therefore, the backbone of early detection, diagnosis and treatment response for hepatocellular carcinoma remains imaging-based. Alpha fetoprotein is the best studied of all biomarkers and may be of benefit for early detection when used in combination with ultrasound. Several other biomarkers, including AFP-L3, DCP, osteopontin, and GP73, are also being evaluated for early detection of hepatocellular carcinoma in phase III biomarker studies. Serum and tissue-based biomarkers and genomics may aid in HCC diagnosis, prognosis, and treatment selection; however, further studies are needed to better characterize their accuracy and potential role in clinical practice.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and leading cause of death among patients with cirrhosis. The continuum of care for patients with HCC extends from early detection efforts to diagnosis to treatment to survivorship and predicting potential recurrence. Although accurate tumour markers could be helpful along this entire continuum, the lack of ideal biomarkers has posed a challenge to HCC management. The ideal tumour marker would be readily available, cost-effective, minimally invasive, reproducible, and highly accurate. Unfortunately, most current tumour markers are limited by insufficient accuracy for routine use in clinical practice.

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Recently, advances in technology and an increased understanding of HCC biology have led to the discovery of novel biomarkers. In this review, we provide a summary of several biomarkers for HCC early detection, diagnosis, and prognosis that are in various stages of evaluation.

Early detection of hepatocellular carcinoma

Surveillance for HCC is recommended in all patients with cirrhosis and has been associated with improved early detection and survival [1]. More accurate assessment of HCC risk among patients with cirrhosis may allow targeted application of HCC surveillance programs. Accurate HCC prediction could identify high-risk patients to whom early detection efforts can be targeted and a group of low-risk patients in whom surveillance efforts should be avoided. Tumour markers have been incorporated in predictive models; however, most have been limited by suboptimal accuracy or lack of external validation and are not routinely used in clinical practice [2–4].

Although both radiologic tools and serologic markers exist for HCC early detection (Table 1), surveillance is currently primarily imaging-based. Guidelines from the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend surveillance using ultrasound alone, citing insufficient accuracy of current biomarkers [5,6]. However, most HCC continue to be diagnosed beyond an early stage due to underuse of HCC surveillance and insufficient sensitivity of current surveillance tools [7–12]. These data highlight the urgent need for more accurate biomarkers to improve early HCC detection.

Alpha fetoprotein

Alpha fetoprotein (AFP) is the best-studied serologic test for HCC surveillance and the only biomarker that has undergone all five phases of biomarker development [13,14](Table 2). A systematic review evaluating AFP in cirrhotic patients, using a cut-off level of 20 ng/mL, showed sensitivities and specificities of 41–65% and 80–94% respectively HCC at any stage [15]. Although 20 ng/mL is the most commonly used cut-off in clinical practice, this value was derived from a study in which only one-third of patients had early HCC [16]. Given the correlation between AFP levels and tumour burden, a lower cut-off can permit higher sensitivity for early stage detection. A multicenter phase 2 biomarker study among 836 patients (419 with HCC and 417 with cirrhosis) found AFP, using a lower cut-off of 10.9 ng/mL, had a sensitivity as high as 66% for early stage HCC [17]. Recent studies also suggest the accuracy of AFP may be improved by adjusting for degree of hepatic inflammation and/or aetiology of liver disease. Whereas AFP tends to correlate with ALT levels in patients with chronic viral hepatitis in the absence of HCC, AFP often increases disproportionately to ALT levels in those with HCC [18]. Similarly, AFP has higher specificity and overall accuracy among HCV-negative patients than HCV-positive patients (c-statistic 0.89 vs. 0.83, $p = 0.007$) [19]. A lower cut-off of 11 ng/mL in patients with non-viral liver

Table 1
Biomarkers for early detection of hepatocellular carcinoma.

Biomarker	Phase of biomarker development
AFP	5
AFP-L3	2
DCP	2
Osteopontin	2
GP73	2
Glypican 3	2
SCCA	2
microRNAs (e.g. miR-21)	2
Canavaninosuccinate	2
Glycochenodeoxycholic acid	2
Urine glycocholic acid	2