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TOPIC HIGHLIGHT

2016 Hepatocellular Carcinoma: Global view

Controversies regarding and perspectives on clinical utility of biomarkers in hepatocellular carcinoma

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Abstract

The prevalence of hepatocellular carcinoma (HCC) worldwide parallels that of persistent infection with the hepatitis B virus (HBV) and/or hepatitis C virus (HCV). According to recommendations by the World Health Organization guidelines for HBV/HCV, alpha-fetoprotein (AFP) testing and abdominal ultrasound should be performed in routine surveillance of HCC every 6 mo for high-risk patients. These examinations have also been recommended worldwide by many other HCC guidelines over the past few decades. In recent years, however, the role of AFP in HCC surveillance and diagnosis has diminished due to advances in imaging modalities. AFP was excluded from the surveillance and/or diagnostic criteria in the HCC guidelines published by the American Association for the Study of Liver Diseases in 2010, the European Association for the Study of the Liver in 2012, and the National Comprehensive Cancer Network in 2014. Other biomarkers, including the *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), des-γ-carboxyprothrombin, Dickkopf-1, midkine, and microRNA, are being studied in this regard. Furthermore, increasing attention has focused on the clinical utility of biomarkers as pre-treatment predictors for tumor recurrence and as post-treatment monitors. Serum and tissue-based biomarkers and genomics may aid in the diagnosis of HCC, determination of patient prognosis, and selection of appropriate treatment. However, further studies are needed to better characterize the accuracy and potential role of these approaches in clinical practice.

Key words: Hepatocellular carcinoma; Biomarker; Guideline; Surveillance; Diagnosis; Prognosis

Core tip: Hepatocellular carcinoma (HCC) is a major global health problem due to the high prevalence

of the risk factors hepatitis B virus and hepatitis C virus infection. Thus, a good surveillance program and diagnostic strategy for the early detection of HCC should be available. This review summarizes the controversies regarding and perspectives on clinical utility of biomarkers in HCC, especially the current role of alpha-fetoprotein and des-γ-carboxyprothrombin. In addition, research frontiers and prospects for novel biomarkers to evaluate the prognosis for HCC and to facilitate post-treatment monitoring are reviewed.

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INTRODUCTION

In 2012, liver cancer was the fifth most common cancer (782000 new cases) and the second leading cause of cancer-related death (746000 cases) worldwide[1]. Hepatocellular carcinoma (HCC) accounts for more than 90% of primary liver cancers and is a major global health problem because of the high prevalence of the risk factors hepatitis B virus (HBV) and hepatitis C virus (HCV) infection[2]. Worldwide, approximately 54% of HCC cases can be attributed to HBV infection, while 31% can be attributed to HCV infection, with the remaining 15% associated with other causes[3-5]. In accordance with the recommendations of the World Health Organization (WHO), vaccination against hepatitis B has been implemented in many countries since 1991[6]. In addition, an enhanced understanding of the pathophysiology of HBV and HCV infection has led to developments in diagnostic procedures and improvements in therapy and prevention, so the clinical care for patients with HBV- or HCV-related liver disease has advanced considerably over the past two decades[7-10]. However, the incidence of HCC worldwide continues to rise, likely due to the often prolonged period between viral infection and manifestation of HCC[2,11,12]. Some studies estimate that up to 20%-30% of patients infected with HBV and/or HCV will develop a progressive liver disease leading to cirrhosis and HCC[13,14]. Cirrhosis rates begin to become significant after 20 years of infection, and HCC rates begin to become significant after 30 years of infection[15,16]. Thus, a good surveillance program and diagnostic strategy for the early detection of HCC should be available.

Serum biomarkers are striking potential tools for surveillance and early diagnosis of HCC thanks to the non-invasive, objective, and reproducible assessments they potentially enable. Worldwide, alpha-fetoprotein (AFP) testing and abdominal ultrasound (US) every 6 mo are recommended for routine surveillance of HCC in high-risk patients according to many HCC guidelines[17]. AFP has also been used as a diagnostic test for HCC and to evaluate prognosis and monitor recurrence following treatment[18]. However, controversy regarding the clinical utility of AFP has arisen in recent years. AFP was excluded from the surveillance and diagnostic criteria in the HCC guidelines published by the American Association for the Study of Liver Diseases (AASLD) in 2010[19], and AFP was not recommended as a sensitive or specific diagnostic test in the HCC guidelines published by the European Association for the Study of the Liver (EASL) in 2012[20] and in the HCC guidelines published by the National Comprehensive Cancer Network (NCCN) in 2014[21]. In Asian countries, AFP was still recommended for HCC surveillance in combination with US and was recommended as an adjunctive diagnostic tool by the HCC guidelines published by the Asian Pacific Association for the Study of the Liver (APASL) in 2010[22], by the current guidelines published in China in 2011[23], and by the current guidelines published in Japan in 2013[24]. Other biomarkers, including the *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), des-γ-carboxyprothrombin (DCP), Dickkopf-1 (DKK1), midkine (MDK), and microRNA (miRNA), are being studied in this regard. Furthermore, increasing attention has focused on the clinical utility of biomarkers as pre-treatment predictors for tumor recurrence and as post-treatment monitors.

This article provides an overview of current biomarkers in HCC with respect to their clinical utility in surveillance, early diagnosis, prediction of prognosis, and monitoring of response to therapy. The controversy of using biomarkers in these settings is discussed in light of typical HCC guidelines worldwide, and the prospects for novel HCC biomarkers are also discussed.

HBV/HCV GUIDELINES PROMOTING THE MANAGEMENT OF HCC IN HIGH-RISK PATIENTS

The prevalence of HCC worldwide parallels that of viral hepatitis. Chronic HBV infection is a leading cause of HCC in most African and Asian countries, except Japan, and chronic HCV infection predominantly contributes to HCC in Europe, Japan, and North America[25,26]. An estimated 2 billion people worldwide have signs of past or present infection with HBV, and 240 million people have a chronic infection[7]. More than 185 million people have been infected with HCV, and one third of those will develop a chronic infection[27]. Longitudinal studies of untreated individuals with chronic HBV infection indicate that they have an 8%-20% cumulative risk of developing cirrhosis over 5 years[28,29]. In people with cirrhosis, there is an approximately 20% annual risk of hepatic decompensation and an annual incidence of

HCC of < 1% to 5%[2,30]. In persons with chronic HCV infection, the risk of liver cirrhosis is 15%-30% within 20 years[31,32], and the risk of HCC in persons with cirrhosis is approximately 2%-4% per year[33].

Universal hepatitis B immunization programs that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many countries where infection is endemic[34-37]. However, these programs will not affect HBV-related deaths until several decades after their introduction[38]. Many guidelines focusing on the management of HBV/HCV infection have been published worldwide, such as guidelines published by the AASLD[39,40], the APASL[41,42], the EASL[43,44], the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)[45], the Canadian Association for the Study of the Liver (CASL)[46], and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)[47]. The WHO also published its first guidelines for the prevention, care, and treatment of people living with chronic HCV infection in April 2014[48], and the WHO published similar guidelines for chronic HBV infection in March 2015[38] to help low- and middle-income countries, in particular, to plan for the development and expanded scale of hepatitis B/C prevention, care, and treatment.

According to recommendations in HBV/HCV guidelines from the WHO[38,48], AFP testing and US were suggested to be performed for routine surveillance of HCC every 6 mo in individuals with cirrhosis. In Japan, where HCV is the most significant etiological factor for developing HCC, there is a more detailed definition for high risk patients of HCC - the "very-high-risk group" that includes patients with HBV- or HCV-related liver cirrhosis, and the "high-risk group" that includes patients with HBV- or HCV-related chronic liver disease or liver cirrhosis due to other causes[49].

BIOMARKERS IN HCC SURVEILLANCE: CONTROVERSIES AND PROSPECTS

Surveillance of patients at increased risk for HCC has been shown to result in the detection of early-stage tumors and an increased likelihood of undergoing potentially curative therapies[50-54]. The overall 5-year survival rate for patients with HCC is about 40%, but liver resection of early HCC could result in a 5-year survival rate of 60%-70%[55-57]. Surveillance is therefore required to detect HCC at an early stage and increase the chances of effective treatment.

AFP as a traditional biomarker for HCC surveillance: Its current role and controversy

AFP testing and US are the most widely used methods of HCC surveillance[58,59]. Data have indicated that AFP testing and US every 6 mo affect disease-specific mortality compared to no intervention [odds ratio: 0.57, 95% confidence interval (CI): 0.37-0.89][38]. In addition, surveillance every 6 mo using both AFP and US has been found to be the most cost-effective strategy[60-62].

AFP has been widely used in clinical practice as a traditional biomarker for HCC surveillance over the past two decades[63-65]. However, there is increasing debate regarding the utility of AFP as a surveillance test[66-68]. Analysis of recent studies has indicated that AFP testing lacks adequate sensitivity and specificity for effective surveillance[69-71]. AFP levels are normal in up to 40% of patients with HCC, particularly during the early stage of the disease (low sensitivity)[72-74]. Elevated AFP levels may be seen in patients with cirrhosis or exacerbation of chronic hepatitis or cholangiocarcinoma (low specificity)[75,76]. In addition, some studies have indicated that AFP has substantially limited diagnostic accuracy in detecting small HCC[77].

Given these findings, US is regarded as a more appropriate test for surveillance with an acceptable diagnostic accuracy (sensitivity ranging from 58% to 89%, specificity greater than 90%)[69,78]. Currently, US is recommended as the only tool for HCC surveillance in some Western countries. AFP was excluded from the surveillance criteria in the HCC guidelines published by the AASLD in 2010[19], and AFP is regarded as a suboptimal tool for surveillance according to the HCC guidelines published by the EASL in 2012[20]. Nevertheless, the performance of US in early detection of HCC is highly dependent on the expertise of the examiner and the quality of the equipment. A randomized controlled trial found that surveillance with AFP in conjunction with US reduced the mortality of HCC[79], and the position that AFP should be included in the HCC surveillance guidelines of the AASLD is gaining support[80]. Currently, the combination of AFP and US at approximately 6 mo intervals is still recommended by many HCC guidelines in Asia, such as guidelines in Japan[24], China[23], and guidelines published by the APASL[22] (Figure 1). Thus, whether AFP should be excluded from surveillance criteria needs to be investigated in more large, randomized controlled trials.

The combined testing of AFP, AFP-L3, and DCP for HCC surveillance

The effectiveness of surveillance depends on various factors. Inclusion of new diagnostic tests in surveillance programs may allow the detection of additional small HCC. Two other serum biomarkers besides AFP - the *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3) and des-γ-carboxyprothrombin (DCP, also known as prothrombin-induced by vitamin K absence-Ⅱ, PIVKA-Ⅱ) - have been studied around the world to explore their clinical usefulness in determining the risk of HCC in high-risk populations.

The clinical utility of highly sensitive AFP-L3 in early prediction of HCC developing in patients with chronic

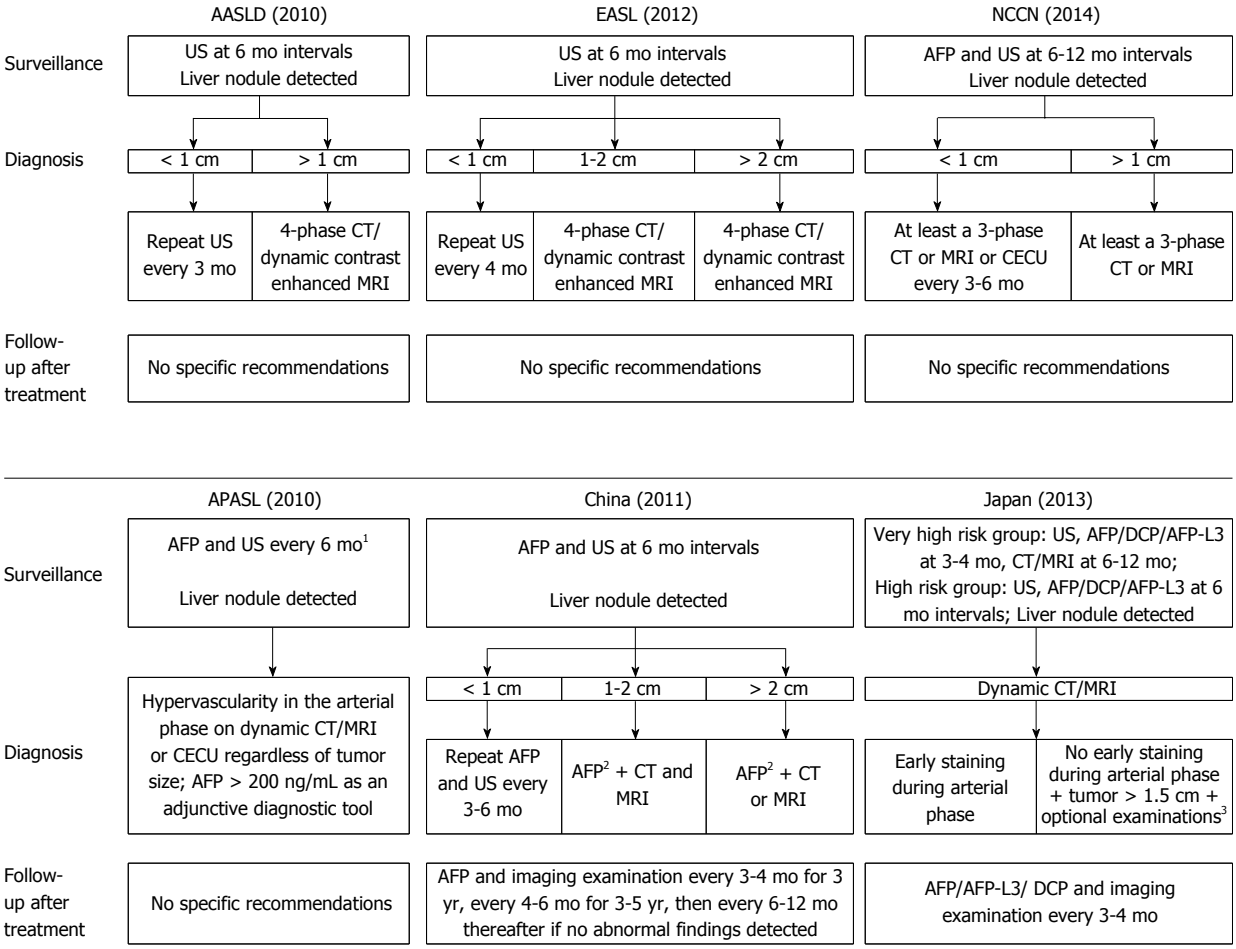

Figure 1 The clinical utility of biomarkers according to typical hepatocellular carcinoma guidelines worldwide. A: Typical hepatocellular carcinoma (HCC) guidelines in Western countries; B: Typical HCC guidelines in Asian countries. [1]Alpha-fetoprotein (AFP) alone is not recommended for diagnosis of HCC; the measurement of both AFP and des-γ-carboxyprothrombin (DCP) provides a higher level of sensitivity without decreasing specificity; [2]AFP ⩾ 400 ng/mL over 1 mo or AFP ⩾ 200 ng/mL over 2 mo; [3]Optional examinations include computed tomography (CT)-angiography, liver-specific contrast-enhanced magnetic resonance imaging (MRI), contrast ultrasound (US), or liver tumor biopsy.

HBV or HCV infection was recently evaluated in a large Japanese study, and results indicated that elevated AFP-L3 was an early predictor of HCC development even if AFP levels were low and suspicious US findings were absent. Elevated AFP-L3 was noted in 34.3% of patients 1 year prior to diagnosis of HCC[81]. Numerous studies have found that the combined testing of DCP and AFP has a sensitivity of 47.5%-94.0% and a specificity of 53.3%-98.5% in early detection of HCC, and these figures are higher than those for either marker alone[82-84]. In some countries such as Japan, combined measurement of DCP and AFP-L3 reportedly increased the detectability of small HCC[85,86].

There are also several biomarkers in addition to AFP, AFP-L3, and DCP, such as Golgi protein 73 (GP73)[87,88], interleukin-6 (IL-6)[89,90], and squamous cell carcinoma antigen (SCCA)[91], that are currently being studied. However, these biomarkers have usually been evaluated, alone or in combination, in a diagnostic rather than surveillance setting. Moreover, their diagnostic performance has often been assessed with a markedly higher prevalence of HCC than would be expected in the context of surveillance.

Current expert opinion from Western countries has been rather critical of the clinical value of biomarkers[92]. Imaging-based surveillance criteria were recommended in guidelines from Western countries, such as the updated HCC guidelines published by the AASLD in 2000[19] and similar guidelines published by the EASL in 2012[20]. In Asian countries, as typified by HCC guidelines in Japan, US and measurement of AFP, AFP-L3, or DCP are recommended to be performed at intervals of 3-4 mo for the very-high-risk group (patients with HBV- or HCV-related liver cirrhosis) and at 6 mo intervals for the high-risk group (patients with HBV- or HCV-related chronic liver disease or liver cirrhosis due to other causes)[24,93].

BIOMARKERS FOR DIAGNOSIS OF HCC: THEIR EVOLUTION AND PROSPECTS

Accurate diagnosis of small liver nodules is of paramount importance. In general, the tests used to

diagnose HCC around the world include diagnostic imaging, serological diagnosis, and histological diagnosis. Prior to 2000, a definite diagnosis was based on a biopsy, but this approach had several limitations related to feasibility due to location and risk of complications, such as bleeding or needle-track seeding[94]. With the development of imaging techniques, a unique dynamic radiological behavior - contrast uptake in the arterial phase of computed tomography (CT), magnetic resonance imaging (MRI), angiography, or US - represented the backbone of radiological diagnosis of early HCC.

The role of AFP in diagnosis of HCC: No longer in use or used as an adjunctive diagnostic tool?

AFP has served as a diagnostic test for HCC since the 1970s, when most patients with HCC were diagnosed at an advanced stage and with clinical symptoms. At that time, a level of 500 ng/mL AFP was considered diagnostic[95]. However, the usefulness of AFP as a diagnostic test in small HCC is limited. According to a systematic review, AFP with a cut-off value of 20 ng/mL had a sensitivity, specificity, and a positive likelihood ratio (LR^+) of diagnosing HCC smaller than 5 cm in diameter of 49%-71%, 49%-86%, and 1.28-4.03, respectively; AFP with a cut-off value of 200 ng/mL had a sensitivity, specificity, and an LR^+ of 4%-31%, 76%-100%, and 1.13-54.25, respectively[77].

Although the sensitivity and specificity of serum AFP as a biomarker is being challenged, a high level or a steadily increasing level of serum AFP strongly suggest development of HCC[96,97]. Elevated serum AFP and a typical enhancement pattern in dynamic imaging have provided critical clues for the diagnosis of HCC over the past few decades. Nevertheless, the importance in AFP has diminished in recent guidelines for diagnosis of HCC, and the importance of imaging has increased based on the high accuracy of up-to-date radiologic modalities[98].

According to the diagnostic criteria in the HCC guidelines published by the EASL in 2000[99] and similar guidelines published by the AASLD in 2005[25] the NCCN in 2009[26], HCC diagnosis is based on the tumor size, AFP, and imaging examination. Guidelines from the Korean Liver Cancer Study Group (KLCSG) published in 2003[100] also featured algorithms similar to those in the aforementioned guidelines, with the exception that HCC was diagnosed based on imaging and AFP, regardless of tumor size. However, the updated HCC guidelines published by the KLCSG in 2009 suggested that a tumor of 2 cm or larger in patients with liver cirrhosis that has characteristics typical of HCC in dynamic contrast enhancement CT or MRI could be diagnosed as HCC regardless of the serum AFP level[101]. According to updated HCC guidelines published by the AASLD in 2010, nodules larger than 1 cm found during US surveillance of a cirrhotic liver should be investigated further with either a four-phase multidetector CT scan or dynamic contrast enhanced MRI. If the appearance of the nodule is typical of HCC, the lesion should be treated as HCC; if the findings are not characteristic or the vascular profile is not typical, a second contrast enhanced study involving another imaging modality should be performed, or the lesion should be biopsied[19]. In agreement with updated guidelines from the AASLD, the panel that drafted the HCC guidelines of the NCCN in 2014 also considered an imaging finding of classic enhancement to be more definitive in this instance, since the level of serum AFP may be elevated in persons with certain nonmalignant conditions, or it may be within normal limits in a substantial percentage of patients with HCC[21]. According to the HCC guidelines published by the APASL in 2010[22], typical HCC can be diagnosed based on imaging regardless of tumor size if a typical vascular pattern (*i.e.*, arterial enhancement with portal venous washout) is obtained on dynamic CT/MRI or contrast-enhanced US. According to the same guidelines, AFP was recommended as an adjunctive diagnostic tool, and AFP alone was not recommended for diagnosis of HCC. Similar recommendations were made by HCC guidelines published in China[23] and Japan[24].

Perspectives on the combined testing of AFP and other biomarkers for diagnosis of HCC

Advances in technology and an increased understanding of HCC biology have led to the discovery of novel biomarkers. To date, many biomarkers have been proposed as a complement or substitute for AFP in the diagnosis of HCC. AFP-L3 can differentiate an increase in AFP due to HCC from that in patients with benign liver disease[102,103]. AFP-L3 with a cut-off value of 10% had a sensitivity, specificity, and LR^+ in diagnosing HCC smaller than 5 cm in diameter of 22%-33%, 93%-94%, and 4.6-0.8, respectively; AFP-L3 with a cut-off value of 15% had a sensitivity, specificity, and LR^+ of 21%-49%, 94%-100%, and 8.1-45.1 respectively[77]. DCP has also been recognized as a highly specific marker for HCC[104]. DCP with a cut-off value of 40 mAU/mL had a sensitivity, specificity, and LR^+ in diagnosing HCC smaller than 5 cm in diameter of 14%-54%, 95%-99%, and 6.9-29.7, respectively; DCP with a cut-off value of 100 mAU/mL had a sensitivity, specificity, and LR^+ of 7%-56%, 72%-100%, and 3.6-13.0, respectively[77].

Data have indicated that the combined testing of DCP and AFP or AFP-L3 could help to increase the sensitivity of HCC diagnosis[105-107], but this approach is used in only a few countries[17], such as Japan[108,109]. In 2014, a large-scale, multi-center study investigated the measurement of both AFP and DCP in differentiating Chinese patients with HCC (71.18% with HBV infection) from patients without HCC and normal subjects. Results showed that the combined testing of

DCP with a cut-off value of 86 mAU/mL and AFP with a cut-off value of 21 ng/mL resulted in a sensitivity of approximately 90% in diagnosis of HCC, which was significantly higher than that for DCP or AFP alone. This finding held even for a tumor smaller than 2.0 cm[110]. These results suggest that the measurement of both AFP and DCP may facilitate the diagnosis of patients with a broad range of HCC. However, the clinical utility of DCP in China has not been noted by HCC guidelines in China[111,112], and more large-scale prospective studies should be performed to provide sufficient evidence.

In recent years, numerous studies have investigated the clinical usefulness of other biomarkers in the early diagnosis of HCC, including GP73[87,88], glypican-3 (GPC3)[113,114], osteopontin[115,116], and vascular endothelial growth factor (VEGF)[117]. Most recently, research on DKK1 and MDK as diagnostic serum biomarkers has garnered interest. In 2012, Shen *et al*[118] published a retrospective, cross-sectional study involving 424 patients with HCC and 407 controls without HCC, and they found that DKK1 was highly accurate at diagnosing AFP-negative patients with HCC, including patients with early-stage HCC. They also found that the measurement of DKK1 and AFP together improved the accuracy with which HCC was diagnosed in comparison to any test alone. In 2013, Zhu *et al*[119] published a study involving 388 patients with HCC and 545 different controls, and they found that serum MDK had a markedly higher level of sensitivity than AFP (86.9% *vs* 51.9%) even when diagnosing very early-stage HCC (80% *vs* 40%). Zhu *et al*[119] also found that MDK could have a sensitivity as high as 89.2% when diagnosing cases of AFP-negative HCC.

Noncoding RNA and miRNA in particular have received considerable attention as novel potential biomarkers over the past few years[120]. Li *et al*[121] found that three miRNAs (miR-25, miR-375, and let-7f) had a sensitivity and specificity as high as 97.9% and 99.1%, respectively, in diagnosing HCC. Zhou *et al*[122] found that a panel of seven microRNAs (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a, and miR-801) could provide a high level of diagnostic accuracy for identification of HBV-related HCC. Tomimaru *et al*[123] found that the combination of miRNA-21 with AFP improved the power of differentiation between HCC and chronic hepatitis, with a sensitivity of 81.0% and a specificity of 80%. However, the potential for miRNA to serve as a biomarker has not been equally analyzed in all conditions potentially leading to HCC. Systemic analyses of alcoholism, non-alcoholic steatohepatitis (NASH), and HCV-related conditions are pending.

BIOMARKERS: PREDICTION OF PROGNOSIS AND MONITORING OF THE RESPONSE TO THERAPY

Tumor invasiveness, metastasis, and recurrence often result in poor clinical outcomes for patients with HCC[124,125]. Currently, the measurement of biomarker levels both before and after HCC treatment is clinically valuable as a simple way to monitor treatment outcomes (usually in combination with radiological analysis) and to predict prognosis, recurrence, and survival.

AFP, AFP-L3, and DCP: Diagnostic biomarkers could also be used to determine the prognosis for HCC and to facilitate post-treatment monitoring

Several biomarkers that have been evaluated for their power in diagnosing HCC have also been studied for their prognostic significance. A high level of AFP expression in serum correlates with a profound cell proliferation, profound angiogenesis, and limited apoptosis and is associated with a poor prognosis[126,127]. AFP was one of the most robust predictors of death in patients with cirrhosis and HCC[128], and it also has significance at predicting survival after liver transplantation[129]. Changes in AFP while on the waitlist also predicted post-transplant survival, and identifying these changes could facilitate better patient selection to optimize organ allocation and post-transplant outcomes[18]. A change in AFP levels has been found to correlate with radiologic response and overall survival after locoregional therapy. For example, a 50% decrease in AFP levels resulted in a better time-to-progression [hazard ratio (HR): 2.8, 95%CI: 1.5-5.1)] and overall survival (HR: 2.7, 95%CI: 1.6-4.6) in comparison to patients whose AFP levels failed to respond to treatment with transarterial chemoembolization (TACE) or transarterial radioembolization (TARE)[130]. Whether AFP is useful at predicting the response to sorafenib is controversial[127,131], and several studies have indicated that AFP response was correlated with time-to-progression (7.9 mo *vs* 2.4 mo, $P = 0.004$) and overall survival (13.3 mo *vs* 8.2 mo, $P = 0.022$)[132].

AFP-L3[133,134] and DCP[135,136] were also identified as prognostic biomarkers for survival after resection of HCC. Patients that have undergone resection of HCC and who had elevated levels of AFP, AFP-L3, and DCP at the baseline had a worse prognosis than patients who tested positive for just one or two of the markers before surgery[137-140].

Among the current guidelines for HCC management worldwide, the guidelines of the NCCN[21] published in 2014 recommend high-sectional imaging every 3-6 mo for 2 years and then every 6-12 mo for post-treatment monitoring. If AFP levels are initially elevated, the guidelines recommend that monitoring be performed every 3 mo for 2 years and then every 6-12 mo. The Indian National Association for Study of the Liver (INASL) published the first guidelines in India in 2014[141], and these guidelines make similar recommendations. The guidelines recommend that post-treatment monitoring be performed with dynamic CT or MRI studies every 3 mo for the first 2 years and then routine surveillance every 6 mo thereafter. The

guidelines also note that the serum tumor markers AFP and DCP may help to evaluate the response to treatment or evaluate follow-up when AFP or DCP is elevated at diagnosis and when AFP or DCP decreases after treatment but rises again. The guidelines do note, however, that tumor markers cannot replace imaging modalities. According to the HCC guidelines published in Japan in 2013[24], follow-up using the serum biomarkers AFP, AFP-L3, and DCP and imaging should be performed every 3-4 mo after treatment. According to HCC guidelines published in China in 2011[23], post-treatment monitoring with AFP and imaging should be performed every 3-4 mo for 3 years, every 4-6 mo for 3-5 years, and then every 6-12 mo thereafter if no abnormal findings are detected.

Research frontiers and prospects for novel biomarkers to evaluate the prognosis for HCC and to facilitate post-treatment monitoring

Biomarkers, including DKK1[142], GPC3[143], and indo-cyanine green 15 min after administration (ICG-R15)[144], reflect current knowledge of the pathways involved in hepatocarcinogenesis and appear to have prognostic value. However, prospective validation studies still need to be performed. In patients with advanced HCC who are treated with sorafenib, serum VEGF and angiopoietin 2 (Ang2) levels were identified as independent prognostic factors for overall survival[127].

Moreover, gamma-glutamyl transpeptidase (GGT) was identified as a prognostic maker by studies of different subgroups of patients published over the past 5 years[145]. Sheen *et al*[146] found that patients who had HCC with type B GGT mRNA had worse outcomes, earlier recurrence, and more post-recurrence deaths. Several studies of patients with HCC undergoing hepatic resection have revealed a correlation between elevated levels of GGT and worse survival for patients with HBV-related HCC, Child-Pugh A liver function, or multi-nodular tumors[147-149]. In addition, several studies have also revealed the predictive value of GGT in patients with unresectable HCC who were treated with TACE or chemotherapy[150-153].

In addition to their diagnostic potential, miRNAs may help to predict prognosis for HCC. Tomimaru *et al*[123] found that the level of miR-21 expression was high in Asian patients with HCC and that the level declined after surgery. They also found that a high level of miR-21 expression in plasma correlated with a shorter cumulative survival following treatment. Köberle *et al*[154] found in European patients with HCC that higher levels of miR-1 and miR-122 expression were associated with longer overall survival compared to lower levels of expression of those miRNAs. They concluded that miR-1 may be a predictive biomarker of HCC independent of liver function. A 31-miRNA signature correlates with the stage of disease, and a distinct 20-miRNA signature that is associated with metastasis of HCC has also been identified[155]. These findings constitute mounting evidence that miRNA signature profiling can be of use in prognostic stratification. Despite their promising potential, miRNA-based biomarkers pose several problems in terms of their use in clinical practice[156].

CONCLUSION

Current HCC guidelines in Western countries have been rather critical of the clinical value of biomarkers. Over the past few decades, a simple approach in the form of measuring AFP levels has been widely used for routine surveillance and noninvasive diagnosis of HCC and to evaluate prognosis and monitor recurrence after treatment. AFP was excluded from the surveillance and/or diagnostic criteria in HCC guidelines published by the AASLD in 2010, the HCC guidelines published by the EASL in 2012, and the HCC guidelines published by the NCCN in 2014. Nonetheless, AFP is still regarded as a useful surveillance tool and an adjunctive tool by many HCC guidelines in Asia, such as guidelines from Japan, guidelines from China, and guidelines published by the APASL.

Advances in technology and an increased understanding of HCC biology have led to the discovery of novel biomarkers. Data have indicated that the combined testing of AFP, AFP-L3, and DCP could help to increase the sensitivity of diagnosis of HCC, but this approach is currently used in only a few countries, such as Japan. In recent years, numerous studies have investigated the clinical usefulness of some novel biomarkers in early diagnosis of HCC, including GP73, GPC3, osteopontin, VEGF, DKK1, MDK, and miRNA. Moreover, the prognostic significance of these biomarkers has also been evaluated. Serum and tissue-based biomarkers and genomics may aid in diagnosis of HCC, determination of patient prognosis, and selection of appropriate treatment. However, further studies are needed to better characterize the accuracy and potential role of these approaches in clinical practice. The prevailing hope is that novel biomarkers can support clinicians in their daily practice and improve care for patients with HCC.

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