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**Optimal surveillance program for hepatocellular carcinoma - getting ready, but not yet**

Wong GL. Perfect HCC surveillance

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**Abstract**

Hepatocellular carcinoma (HCC) secondary to chronic viral hepatitis is a major health problem in Asian-Pacific regions due to the endemics of chronic hepatitis B and C virus infection. HCC surveillance has been recommended to patients who are at risk to develop HCC. Unfortunately, a significant proportion of patients still died in long run due to tumor recurrence. The key components of an optimal surveillance program include an accurate tumor biomarker and optimal surveillance interval. Serum alpha-fetoprotein (AFP), despite of being the most widely used biomarker for HCC surveillance, it was criticized as neither sensitive nor specific. Other HCC biomarkers, including lectin-reactive AFP (AFP-L3), des-gamma carboxyprothrombin, are still under investigations. Recent study showed cancer-associated genome-wide hypomethylation and copy number aberrations by plasma DNA bisulfite sequencing to be accurate with both sensitivity and specificity close to 90% in detecting HCC in a case-control study. Concerning the optimal surveillance interval, we believe one size does not fit all patients. Accurate risk prediction to assist prognostication with well-validated HCC risk scores would be useful to decide the need for HCC surveillance. These key components of an optimal HCC surveillance program should be further validated at a surveillance setting.

**Key words:** Antiviral therapy; Biomarkers; Hepatocellular carcinoma; Hepatocellular carcinoma risk scores; Liver stiffness measure; Surveillance program

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**Core tip:** The key components of an optimal surveillance program include an accurate tumor biomarker and optimal surveillance interval for hepatocellular carcinoma (HCC). Cancer-associated genome-wide hypomethylation and copy number aberrations by plasma DNA bisulfite sequencing are two promising genomic markers of HCC. Risk prediction by HCC risk scores may assist prognostication and to decide the optimal surveillance interval.

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**INTRODUCTION**

Hepatocellular carcinoma (HCC) secondary to chronic viral hepatitis is a major health problem in Asian-Pacific regions due to the endemics of chronic hepatitis B and C virus infection[1]. Antiviral therapy reduces the risk but does not eliminate HCC[2]. Therefore cancer surveillance remains indispensable to patients who remain at high risk despite antiviral therapy, namely those with cirrhosis[3].

**BENEFITS OF HCC SURVEILLANCE**

It has been recommended to offer HCC surveillance to patients who are at risk to develop HCC for almost a decade[4].The surveillance program recommended at that time was composed of the 6-monthly trans-abdominal ultrasonography and serum alpha-fetoprotein (AFP) testing. HCC surveillance improves prognosis of patients by identifying tumors of smaller sizes, fewer numbers of tumors, and longer overall survival[5]. Unfortunately, nearly 40% of patients still died in 5 years even they had received regular HCC surveillance[5]. This implies the current HCC surveillance is still far from perfect.

**THE PERFECT HCC BIOMARKER – DOES IT EXIST?**

The key components of the perfect surveillance program include an accurate tumor biomarker and optimal surveillance interval. Serum AFP is the most extensively applied biomarker for HCC surveillance[3]. However, its low sensitivity (20% to 65%) and specificity (50% to 94%) in discovering early HCC has resulted in the latest American guidelines abandoning AFP but using ultrasonography alone as the single surveillance tool[6]. Despite it has been recently demonstrated the high specificity of AFP in patients receiving antiviral therapy[7], it is well known that this commonly adopted tumor marker remains suboptimal.

There have been a handful of HCC biomarkers, *e.g.*, lectin-reactive AFP (AFP-L3), des-gamma carboxyprothrombin (DCP), under investigations[8].Despite some of the biomarkers appeared promising initially, subsequent studies could not always reproduce the similar results[9]. Hence the latest European guidelines still commented that accurate tumor biomarkers for early detection of HCC needed to be developed. Such biomarkers (*i.e.*, AFP, AFP-L3 and DCP) are indeed suboptimal for routine clinical practice[3].

The dysregulated signaling pathways in HCC have been under intensive study for both diagnostic and therapeutic targets[10]. Nonetheless, HCC often involves heterogeneous pathogenesis such that multiple genes are involved (Table 1). This made using a single or a few genomic markers as HCC biomarker infeasible. Recently, cancer-associated genome-wide hypomethylation and copy number aberrations by plasma DNA bisulfite sequencing has been found to be accurate with both sensitivity and specificity close to 90% in detecting HCC in a case-control study[11]. The remaining issue of such genomic sequencing is that it is rather costly (approximately US$10000 per assay). Apart from further validation of these novel genomic biomarkers in a surveillance setting, further optimization of the assay to reduce the cost yet maintaining the accuracy would be essential to make it applicable and accessible to more patients.

**OPTIMAL SURVEILLANCE INTERVAL – DOES ONE SIZE FITS ALL?**

There would be much economic implication in many low-to-middle economic countries if all patients at risk of HCC received antiviral therapy together with HCC surveillance. Therefore an accurate risk prediction would be able to help prognostication, deciding on the need for antiviral therapy as well as HCC surveillance. Several well-established risk factors for HBV-related HCC include advanced age, male gender, high viral load, cirrhosis. These factors are the core components of three well-validated HCC risk scores: CU-HCC[12], GAG-HCC[13] and REACH-B scores[14]. These risk scores were confirmed to be accurate in forecasting HCC up to 10 years in patients with chronic hepatitis B (CHB) who were mostly treatment-naïve.

Their validity and applicability have been recently illustrated in a large cohort of patients receiving antiviral treatment entecavir[15]. A reducion in risk scores after antiviral therapy renders to a lower risk of HCC[15]. CU-HCC score was further optimized with liver stiffness measure (LSM) by transient elastography[16]. This new LSM-HCC score excludes future HCC with high negative predictive value (99.4%-100%) at 5 years[16]. All these observations support to apply these HCC risk scores in CHB patients. Levels of care and intensities of HCC surveillance accordingly to the risk profile of patients should be offered accordingly. Patients at intermediate or high risk of HCC should receive regular HCC surveillance, despite the use of antiviral treatment[5,17].

**CONCLUSION**

The key components of a perfect HCC surveillance program are getting ready. They should be further validated at a surveillance setting in order to understand how exactly they can benefit our patients. Data on the cost-effectiveness of such a perfect HCC surveillance program would be useful to our policy maker. The days of HCC becoming a mostly curable disease are getting closer and closer.

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**Table 1 Major cancer genes involved in the pathogenesis of hepatocellular carcinoma**

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| --- | --- | --- |
| **Gene** | **Type** | **Pathways** |
| *MYC* | Oncogene | Proliferation control |
| *EGF* | Oncogene | EGFR signaling (mitogenic signaling) |
| *TGFA* | Oncogene | EGFR signaling (mitogenic signaling) |
| *APC* | Tumor suppressor gene | Wnt-signaling |
| *PTEN* | Tumor suppressor gene | PI3K/Akt/mTOR signaling |
| *AKT* | Oncogene | PI3K/Akt/mTOR signaling |
| *HGF* | Oncogene | Growth factor |
| *MET* | Oncogene | Growth factor receptor |
| *PDGFR* | Oncogene | Growth factor receptor |
| *RAS* | Oncogene | Ras/MAPK signaling |
| *P53* | Tumor suppressor gene | Stress response, cell cycle inhibition |
| *E2F1* | Oncogene | Cell cycle |
| *CCND1* | Oncogene | Cell cycle |
| *Telomerase* | Oncogene | Cell senescence |

Modified from Zender *et al*[10]. EGFR: Epidermal growth factor receptor; MAPK: Mitogen-activated protein kinases; PI3K/AKT/mTOR: Phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin.