EDITORIAL

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

Grace Lai-Hung Wong

Grace Lai-Hung Wong, Department of Medicine and Therapeutics, 9/F Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong, China

Grace Lai-Hung Wong, Institute of Digestive Disease, the Chinese University of Hong Kong, Hong Kong, China

Grace Lai-Hung Wong, State Key Laboratory of Digestive Disease, the Chinese University of Hong Kong, Hong Kong, China

Author contributions: Wong GLH was responsible for the conception, writing, review and revision of the manuscript.

Conflict-of-interest statement: Grace Lai-Hung Wong has served as an advisory committee member for Otsuka and Gilead. She has also served as a speaker for Abbvie, Bristol-Myers Squibb, Echosens, Furui, Gilead and Otsuka.

Correspondence to: Grace Lai-Hung Wong, MD, Department of Medicine and Therapeutics, 9/F Prince of Wales Hospital, the Chinese University of Hong Kong, 30-32 Ngan Shing Street, Shatin, Hong Kong, China. wonglaihung@cuhk.edu.hk
Telephone: +852-26323538
Fax: +852-26373852

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

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.

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-mo 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 carbo-xyprothrombin (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 United States $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

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

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.

REFERENCES

1   **Chan HL**, Sung JJ. Hepatocellular carcinoma and hepatitis B virus. *Semin Liver Dis* 2006; **26**: 153-161 [PMID: 16673293 DOI: 10.1055/s-2006-939753]

2   **Wong GL**, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, Iu HW, Leung JM, Lai JW, Lo AO, Chan HY, Wong VW. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology* 2013; **58**: 1537-1547 [PMID: 23389810 DOI: 10.1002/hep.26301]

3   **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

4   **Bruix J**, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051]

5   **Wong GL**, Wong VW, Tan GM, Ip KI, Lai WK, Li YW, Mak MS, Lai PB, Sung JJ, Chan HL. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver Int* 2008; **28**: 79-87 [PMID: 17900247 DOI: 10.1111/j.1478-3231.2007.01576.x]

6   **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

7   **Wong GL**, Chan HL, Tse YK, Chan HY, Tse CH, Lo AO, Wong VW. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. *Hepatology* 2014; **59**: 986-995 [PMID: 24123097 DOI: 10.1002/hep.26739]

8   **Lok AS**, Sterling RK, Everhart JE, Wright EC, Hoefs JC, Di Bisceglie AM, Morgan TR, Kim HY, Lee WM, Bonkovsky HL, Dienstag JL. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. *Gastroenterology* 2010; **138**: 493-502 [PMID: 19852963 DOI: 10.1053/j.gastro.2009.10.031]

9   **Bertino G**, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellualar carcinoma serum markers. *Semin Oncol* 2012; **39**: 410-433 [PMID: 22846859 DOI: 10.1053/j.seminoncol.2012.05.001]

10 **Zender L**, Villanueva A, Tovar V, Sia D, Chiang DY, Llovet JM. Cancer gene discovery in hepatocellular carcinoma. *J Hepatol* 2010; **52**: 921-929 [PMID: 20385424 DOI: 10.1016/j.jhep.2009.12.034]

11 **Chan KC**, Jiang P, Chan CW, Sun K, Wong J, Hui EP, Chan SL, Chan WC, Hui DS, Ng SS, Chan HL, Wong CS, Ma BB, Chan AT, Lai PB, Sun H, Chiu RW, Lo YM. Noninvasive detection of cancer-associated genome-wide hypomethylation and copy number aberrations by plasma DNA bisulfite sequencing. *Proc Natl Acad Sci USA* 2013; **110**: 18761-18768 [PMID: 24191000 DOI: 10.1073/pnas.1313995110]

12 **Wong VW**, Chan SL, Mo F, Chan TC, Loong HH, Wong GL, Lui YY, Chan AT, Sung JJ, Yeo W, Chan HL, Mok TS. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J Clin Oncol* 2010; **28**: 1660-1665 [PMID: 20194845 DOI: 10.1200/JCO.2009.26.2675]

13 **Yuen MF**, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, But DY, Chan AO, Wong BC, Mizokami M, Lai CL. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009; **50**: 80-88 [PMID: 18977053 DOI: 10.1016/j.jhep.2008.07.023]

14 **Yang HI**, Yuen MF, Chan HL, Han KH, Chen PJ, Kim DY, Ahn SH, Chen CJ, Wong VW, Seto WK; REACH-B Working Group. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; **12**: 568-574 [PMID: 21497551]

15 **Wong GL**, Chan HL, Chan HY, Tse PC, Tse YK, Mak CW, Lee SK, Ip ZM, Lam AT, Iu HW, Leung JM, Wong VW. Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. *Gastroenterology* 2013; **144**: 933-944 [PMID: 23415803 DOI: 10.1053/j.gastro.2013.02.002]

16 **Wong GL**, Chan HL, Wong CK, Leung C, Chan CY, Ho PP, Chung VC, Chan ZC, Tse YK, Chim AM, Lau TK, Wong VW. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. *J Hepatol* 2014; **60**: 339-345 [PMID: 24128413 DOI: 10.1016/j.jhep.2013.09.029]

17 **Wong GL**, Wong VW. Risk prediction of hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy. *World J Gastroenterol* 2013; **19**: 6515-6522 [PMID: 24151375 DOI: 10.3748/wjg.v19.i39.6515]

Baishideng®