

Current Practice of Hepatocellular Carcinoma Surveillance

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ABSTRAK

Karsinoma sel hati (KSH) adalah penyebab kematian akibat kanker yang kedua tertinggi di dunia. Hal ini disebabkan oleh heterogenitas biologis tumor dan terbatasnya pilihan pengobatan kuratif. Faktor prognostik yang paling signifikan adalah deteksi kanker pada stadium awal. Oleh karena itu, strategi surveilans sangat penting. Pasien yang berisiko tinggi terkena kanker hati harus menjalani pemeriksaan ultrasonografi (USG) dan pemeriksaan penanda tumor setiap enam bulan sekali untuk mendeteksi KSH pada stadium awal. Akan tetapi, dalam praktik sehari-hari, USG memiliki beberapa keterbatasan. Di samping itu, kepatuhan terhadap surveilans KSH juga tidak optimal karena berbagai alasan, baik dari sisi penyedia layanan kesehatan, pasien, maupun sistem pelayanan kesehatan. Pada artikel ini, kami akan membahas mengenai metode surveilans KSH terkini dan hambatan yang didapatkan dalam praktik sehari-hari.

Kata kunci: karsinoma sel hati, surveilans, ultrasonografi, penanda tumor, deteksi dini.

ABSTRACT

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide. This is due to the heterogeneity of the tumor biology and lack of curative treatment options. The most significant prognostic factor is detection at early stage and thus, surveillance strategies are of high importance. High-risk patients should undergo ultrasound and tumor marker tests at six-month interval in order to detect HCC at the earlier stage. However, in real-life practice, ultrasound has several limitations and the adherence to HCC surveillance is suboptimal due to various provider, patient, and health-care system factors. In this paper, we will address current methods of HCC surveillance and obstacles found in real-life practice.

Keywords: hepatocellular carcinoma, surveillance, ultrasound, tumor markers, early detection.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second most common cause of cancer-related death in the world.¹ The overall ratio of mortality due to liver cancer to incidence was 0.95 and most liver cancer (83%) was diagnosed in less well developed nations.¹ The dismal prognosis of this cancer was due to its aggressive nature and poor survival. Despite major progress in treatment, the

prognosis of HCC globally remains poor, because a greater number of patients with HCC may be asymptomatic until they are in the late-stage of the disease, which prevent them from receiving potentially curative treatment. When patients receive potentially curative therapy in the form of liver transplantation, surgical resection, or tumor ablation, a considerable improvement in survival is achieved (five years survival rate, 40%-70%).²⁻⁴ Therefore, regular surveillance in

high-risk population is the key for early diagnosis and improvement of HCC patient survival. This paper will review the approach to surveillance for HCC in high-risk patients and follow-up testing for lesions found during surveillance.

EPIDEMIOLOGY OF HCC

Hepatocellular carcinoma is the most common primary cancer of the liver and the second most common cause of cancer-related death. The incidence of HCC is estimated to be 554 000 cases per year in men, causing nearly a similar number of deaths globally per year. The regions of highest HCC incidence rates are Eastern and South-Eastern Asia, with estimated age-standardized rates >20 per 100,000 population.¹ Although currently low in the United States, the incidence of HCC has tripled since the early 1980s with the largest increase occurred among Hispanics followed by blacks and non-Hispanic whites.⁵ The age distribution of HCC varies by region, gender, and etiology.⁶ The rate of HCC in men is greater than that of women, with the male to female ratio ranging between 2:1 and 4:1, with the difference being much greater in high-risk areas.

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the main etiology of HCC cases, with chronic hepatitis B (CHB) infection being the major cause in all Asia-Pacific countries, except for Japan. In Japan, chronic hepatitis C (CHC) infection is the most common etiology of HCC, representing up to 70% of cases.⁷ However, there is also a substantial population of HCC patients (5-20%) who are negative for both markers of hepatitis B virus and hepatitis C virus infection [non-B, non-C (NBNC) hepatitis] in Japan and the incidence of NBNC-HCC has recently tended to increase.⁸ In Western countries and Africa, HCV is also a major cause of HCC, in addition to alcoholic liver disease, and possibly nonalcoholic fatty liver disease (NAFLD).⁹

The prognosis of liver cancer is unfavorable in most patients with HCC, even in developed countries. Patients with advanced HCC who are only eligible for palliative treatment have a median survival of less than one year,^{10,11} while those who are diagnosed in early-stage

can achieve 5-year survival rates of 70% with potentially curative treatment, such as transplant or resection.¹² Therefore, HCC surveillance has been recommended to detect HCC at an early stage, when curative treatment can be administered.

HCC SURVEILLANCE RECOMMENDATIONS

Target Population

The major risk factor for the development of HCC is liver cirrhosis, which is mainly caused by HBV, HCV, alcoholic liver disease, and NAFLD. Cirrhosis is present in about more than 80% of patients with HCC.¹³ The risk of HCC in cirrhotic patient is not uniform because different etiologies of cirrhosis are associated with different incidence of HCC. HCV infection is associated with the highest HCC incidence in cirrhotic patients, with a 5-year cumulative incidence as high as 30%.¹⁴ In HBV-associated cirrhosis, the 5-year cumulative HCC risk is 15% in high endemic areas and 10% in the West, while in alcoholic cirrhotics, the 5-year cumulative risk is 8%.¹⁴ However, there is limited data on HCC risk in NAFLD-associated cirrhosis. Additional risk factors for developing HCC include intake of aflatoxin-contaminated food, diabetes, obesity, certain hereditary conditions such as hemochromatosis, and various metabolic disorders.^{15,16} These additional risk factors may influence decision making for offering HCC surveillance.

Current Guidelines

Surveillance for hepatocellular carcinoma (HCC) have already been described in guidelines published by the American Association for the Study of Liver Diseases (AASLD),¹⁷ the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer (EASL-EORTC),¹⁸ and the Japan Society of Hepatology (JSH).¹⁹ The AASLD practice guideline on the management of hepatocellular carcinoma states that high-risk population is defined as those with cirrhosis and those with chronic HBV infection regardless of cirrhosis (**Table 1**). The EASL-EORTC guidelines also recommend surveillance in chronic hepatitis C patients and advanced liver

Table 1. High-risk groups for whom hepatocellular carcinoma (HCC) surveillance is recommended

Population at risk	HCC risk per year
Cirrhosis	
- Hepatitis B	3–8%
- Hepatitis C	3–5%
- Primary biliary cirrhosis	3–5%
- Non-alcoholic steatohepatitis	NA
- Genetic hemochromatosis	NA
- Alpha-1 antitrypsin deficiency	NA
- Autoimmune hepatitis	NA
Hepatitis B positive without cirrhosis (Hepatitis B surface antigen positive)	
- Asian male >40 years	0.4–0.6%
- Asian female >50 years	0.3–0.6%
- Africans >20 years	NA
- Family history of HCC	NA (incidence higher than without family history)

NA = not available

fibrosis.²⁰ This is supported by a study in the United States that found HCC occurrence in patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis (Metavir F3).²¹ However, the guidelines do not recommend Child-Pugh C cirrhotic patients to obtain regular surveillance, except when those patients are in the transplant-waiting list.²⁰

The JSH guideline classifies patients into high-risk group (patients with chronic hepatitis B/C or cirrhosis) and a super high-risk group (patients with hepatitis B/C cirrhosis). For super high-risk group, it is recommended that dynamic computed tomography (CT)/ magnetic resonance imaging (MRI) be performed every 6–12 months. The sensitivity of MRI to detect curable HCC lesion is significantly higher than that of ultrasonography.²² However, this modality is limited by the high-cost and resources needed. Cost-effectiveness of a cancer-screening program depends not only on the test's performance, but also the test's cost and the availability of treatment modalities that significantly prolong survival.^{23,24}

Surveillance Tests

Modalities that can be used for HCC surveillance tests comprise of imaging and

serological tests. Ultrasonography is the most widely used imaging test for surveillance. The sensitivity of US for detecting tumors before they present clinically, was 94%, but US was less effective for identifying early HCC, with a sensitivity of 63%.²⁵ When US was combined with alpha-feto protein (AFP), there was an insignificant increase of sensitivity to 69%.²⁵ A retrospective study from Japan found that ultrasound (US) surveillance at 6-month intervals performed by highly skilled operators was able to detect tumors of 1.6 ± 0.6 cm.²⁶ However, in real clinical practice, the sensitivity of ultrasound alone as a surveillance program was 44%, while in combination with AFP, the sensitivity improved significantly to 90%.²⁷ The characteristics of liver cirrhosis, which include fibrous septa and regenerative nodules, produce a course pattern on US, which may decrease the ability of US to detect small tumors. Furthermore, ultrasound is reported to be less accurate in visualizing the liver in patients with morbid obesity.^{28,29}

The serological test that most widely used in clinical practice is serum AFP. However, AFP has several limitations as a surveillance test. Firstly, AFP levels may be fluctuating in patients with cirrhosis, especially in those with exacerbation of underlying liver disease.³⁰ Secondly, only less than 20% of tumors present with abnormal serum AFP level at early stage.³¹ At the level of 10 ng/mL, the sensitivity and specificity of AFP was 77% and 78%, respectively.³²

Other serological tests for HCC surveillance are protein-induced by vitamin K absence or antagonist-II (PIVKA-II), also known as Des- γ -carboxy-prothrombin (DCP), and AFP lectin fraction (AFP-L3). These serological tests are usually used in combination and are routinely used in Japan.¹⁹ The available evidence regarding these serological tests in the surveillance setting is still inconclusive. In a French study, at a cut-off of 42 mAu/mL, PIVKA-II had a sensitivity and specificity of 77% and 82%, respectively, versus 61% and 50% for AFP at a cut-off of 5.5 ng/mL, for the diagnosis of early HCC.³³ An observational study from South Korea found that at a cut-off of 10 ng/mL, AFP was the best single biomarker in diagnosing HCC. However, the diagnostic value of AFP was improved by

combining it with PIVKA-II (>40 mAU/mL), but adding AFP-L3 (>10%) did not contribute to the capacity to distinguish between HCC and non-HCC.³⁴ Another study by Lim et al³⁵ found that PIVKA-II was superior to AFP or AFP-L3 in detecting overall HCC and combining PIVKA-II with the other two tests resulted in better accuracy than PIVKA-II alone.³⁵ In contrary, Durazo et al found that PIVKA-II had the highest sensitivity for HCC diagnosis and combining two or three markers of HCC did not give significant benefit. This discrepancy might be related to different etiologies and study population.³⁶ Durazo et al.³⁶ included similar number of hepatitis B and hepatitis C, and defined chronic viral hepatitis with or without cirrhosis as a control group, while Lim³⁵ only included cirrhotic patients with hepatitis B as the dominant etiology.

Interval of HCC surveillance

A 6-month interval is currently recommended by AASLD and EASL-EORTC guidelines, but the Japanese guidelines propose a 3-4-month interval in super-high-risk patients (hepatitis B-related liver cirrhosis and hepatitis C-related liver cirrhosis). Based on median HCC volume doubling time, which is reported to be 85 – 171 days,³⁷⁻³⁹ a 6-month interval is a reasonable choice. One randomized-controlled trial (RCT) comparing ultrasound performed at 3- or 6-month intervals showed no significant difference in HCC detection rate between the two groups.⁴⁰ However, when compared with 12-month interval, a 6-month interval gave better performance in terms of stage migration⁴¹ and survival.⁴² A meta-analysis also demonstrated a better sensitivity for ultrasound to detect early HCC in 6-month interval than in 12-month interval.²⁵

Recall Policy

A recall policy is of highly importance in dealing with an abnormal finding during routine ultrasound or serological tests. Abnormal ultrasound results are a newly detected focal lesion or a known hepatic lesion that enlarges and/or changes its echo pattern.⁴³ Increase of AFP, PIVKA-II, or AFP-L3 serum level should also raise a suspicion of HCC in the absence of focal lesion detected during ultrasound.⁴⁴ When a

surveillance test is abnormal, the next diagnostic tests are triple-phase or triphasic abdominal CT or MRI. Triple-phase technique acquires images at three different time points, or phases, following the administration of contrast agent, i.e. arterial phase, portal-venous phase, and delayed phase. The radiological hallmark of HCC is the presence of contrast uptake (enhancement) in the arterial phase and washout in the portal venous or delayed phase. Finding of a liver mass with this radiological hallmark in a cirrhotic patient is considered diagnostic for HCC (**Figure 1**). We propose an algorithm, which is adapted from the Japanese, EASL, and AASLD guidelines, and are currently used in Indonesia.⁴⁵

Atypical focal hepatic mass should be evaluated further by conducting biopsy or MRI with liver-specific contrast. Liver specific MRI contrast agent is gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA, Primovist in Europe and Eovist in the USA), which has up to 50% hepatobiliary excretion in the normal liver. After intravenous injection, Gd-EOB-DTPA distributes into the vascular and extravascular spaces during the arterial, portal venous, and delayed phases, and increasingly into the hepatocytes and bile ducts during the hepatobiliary phase.⁴⁶ If Gd-EOB-DTPA-MRI shows a hypervascular mass during arterial phase without venous washout, a diagnosis of HCC can be made if the mass shows hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-MRI.⁴⁴ Biopsy is sometimes difficult to be done in small nodules which is not visualized during ultrasound examination. Contrast-enhanced ultrasound (CEUS) is also an alternative examination for atypical focal hepatic mass. Decreased uptake in the Kupffer phase on CEUS is indicative for HCC.⁴⁷

If diagnosis of HCC is not established, it is recommended to repeat Gd-EOB-DTPA MRI or triple-phase CT/MRI and tumor biomarkers three months later. When there is no evidence of tumor growth, the patient continues routine surveillance tests every six months. If growth is present, MRI with liver-specific contrast or biopsy or CEUS may be repeated or the tumor is treated as HCC.

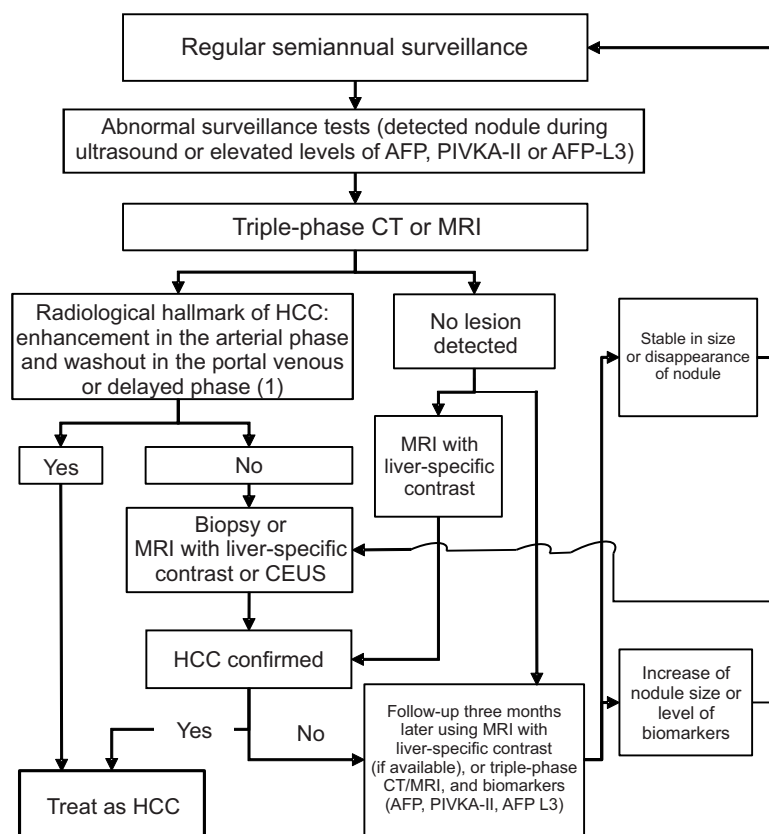


Figure 1. Recall policy algorithm for patients with abnormal results during HCC surveillance tests. AFP: alpha-feto protein, AFP-L3: AFP lectin fraction, CEUS: contrast-enhanced ultrasonography, Gd-EOB-DTPA: gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid, PIVKA-II: proteins induced by vitamin K absence-II.

EFFICACY OF HCC SURVEILLANCE

There are two randomized controlled trials that have been published on HCC surveillance. The first study was conducted in a population of nearly 19,000 Chinese patients with chronic HBV infection, regardless of the presence of cirrhosis.⁴⁸ In this study, the patients were randomized to US and AFP measurements every six months versus no surveillance. Although the adherence to screening was only 58% in the screened group, HCC mortality rate could be reduced to 37%. The second RCT was performed in 5,581 chronic HBV patients in China, with serum AFP repeated every six months.⁴⁹ Although screening with semiannual AFP resulted in earlier diagnosis of HCC, but the overall mortality rate did not differ significantly between the screened group and control group, because therapy for the patients found by screening was ineffective.

Other studies on HCC surveillance were population and non-population-based cohorts

and cost-effectiveness analysis, which mostly showed the advantage of surveillance to detect early-stage HCC.^{40,50-53} A meta-analysis of prospective cohort studies found that HCC surveillance using a combination of ultrasound and AFP was highly efficacious, with a sensitivity of 69% to detect HCCs at an early stage.²⁵ However, HCC surveillance does not give any benefit in advanced cirrhosis (Child-Pugh C patients) because their poor liver function adversely affects the overall mortality.⁵²

HCC SURVEILLANCE IN REAL-LIFE PRACTICE

Although HCC surveillance has been proven to be efficacious in finding early-stage HCC, its utilization rates in real-life practice are low. A recent systematic review showed that pooled surveillance rate was only 18%.⁵⁴ The surveillance rates were significantly higher among patients followed in subspecialty

gastroenterology clinics compared to those followed in primary care clinics (51% vs 17%, respectively). Another retrospective study also found that even among patients closely followed by expert hepatologists in academic centers, nearly 30% of patients had inconsistent HCC surveillance.⁵⁵ According to a web-based survey of primary care providers in USA, barriers to HCC surveillance included not being up-to-date with HCC guidelines, difficulties in communicating effectively with patients about HCC surveillance, and more important issues to manage in clinic.⁵⁶

The Quality in the Continuum of Cancer Care conceptual model categorizes surveillance process failures as an (a) absence of screening, (b) absence of follow-up for abnormal tests, or (c) absence of detection despite completing screening and follow-up.⁵⁷ Absence of surveillance, defined as lack of ultrasound performed for surveillance purposes within the 12-month period before HCC diagnosis, was found in 75% of patients.⁵⁸ Furthermore, failure of detection, defined as inability of ultrasound to detect suspicious lesion within the year prior to HCC diagnosis, was found in 11.4% of patients.⁵⁸

In a recent retrospective study by Wong et al,⁵⁹ ultrasound only detected 19% of single tumors less than 2 cm in diameter. There are several limitations of surveillance program using ultrasound. Coarse liver echotexture, obesity, thickened adipose tissue, increased waist circumference, uncooperative patient, a lot of bowel gas, and difficulty of position change due to limited patients' movement, are some patients' factors which can interfere an ultrasound exam. Furthermore, ultrasound exam is highly operator-dependent and the result is related to operator skill and experience. To solve this problem, Kim et al suggests a screening strategy using MRI with liver-specific contrast.²² In this prospective study, 407 patients received paired ultrasound and MRI screenings. As a result, HCC detection rate of MRI was significantly higher than that of ultrasound (86% versus 27.9%, respectively). However, MRI with liver-specific contrast is costly and not widely available. It is still a long way before MRI can be applied as HCC surveillance test in daily practice.

There are several components involved in implementing HCC surveillance in clinical practice: (1) providers ability to identify high-risk patients, (2) providers referral for surveillance, (3) patients knowledge and acceptance about the tests, (4) health care system schedule of the tests, and (5) adherence of patients to surveillance recommendation.²⁷ Furthermore, effective treatment for early-stage HCC patients should be available in order to make HCC surveillance program beneficial. An example of successful nationwide surveillance program is shown by Japan. Japan has succeeded in improving its HCC patients' 5-year survival rate from 5.1% in 1978–1980 to 42% in 2001–2005.⁶⁰ One of the key for the success is the government involvement in preventive measures against HCC and hepatitis. Screening of individuals at high risk for HCC is covered by the national health insurance and the social insurance system.⁶¹

CONCLUSION

HCC surveillance tests should be performed in patients with cirrhosis and in adult patients with chronic hepatitis B, regardless of cirrhosis. Combination of ultrasound and tumor marker for HCC surveillance is recommended in a six-month interval. Serum AFP is the most common tumor marker investigated for HCC surveillance and the efficacy of combination with other tumor markers (PIVKA-II and AFP-L3) for HCC surveillance needs further study. Implementation of HCC surveillance in real-world practice is a complex process and HCC surveillance is still underutilized. Value of HCC surveillance is also determined by the availability of effective treatment for early-stage HCC.

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