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Does Hepatocellular Carcinoma Surveillance Increase Survival in At Risk Populations? – Patient Selection, Biomarkers, and Barriers

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INTRODUCTION

Hepatocellular carcinoma (HCC) is globally the sixth most common cancer and fourth leading cause of cancer related death.[1] In the United States, the incidence and mortality of HCC continues to increase annually.[2] Prognosis for HCC is highly correlated with tumor stage. Early diagnosis is associated with a 5 year mortality of more than 70%, compared with < 20% when diagnosed at advanced stages.[3,4] Although multiple professional societies recommend screening for HCC among high-risk populations, the majority of patients with HCC are diagnosed at late stages, perhaps reflecting the prevailing low surveillance rates.[5,6] The purpose of this article is to provide an updated review of emerging evidence and controversies in HCC surveillance, with a focus on the impact of surveillance on mortality, at risk populations, emerging biomarkers, and strategies to increase surveillance.

DOES SURVEILLANCE IMPROVE HCC MORTALITY?

Significant controversy surrounding HCC surveillance exists due to the paucity of level I evidence showing survival benefit. The only two randomized control trials (RCT) that have assessed survival benefit were both performed in Chinese patients predominantly infected with hepatitis B. Zhang et al who randomized patients to ultrasound and AFP every 6 months or no surveillance found that surveillance improved detection of early stage HCC (61% vs. 0%), increased rates of curative therapy with resection (67% vs. 8%), and reduced mortality by 37%.[7] The second RCT randomized male patients to surveillance with AFP every 6 months, finding earlier diagnosis of early stage HCC (30% vs. 6%), but no survival benefit.[8]

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Other studies investigating HCC surveillance and mortality have been observational cohort studies, with the majority retrospective. A recent case control study of Veterans showed no impact of surveillance on HCC related mortality.[9] The main limitation of this study is that only half of the study sample received surveillance ultrasounds that were not at the recommended 6-month intervals. Furthermore, cases were defined as patients who died from HCC, which may reflect a different population compared with patients who are eligible for potentially curative therapies.

A meta-analysis of 47 observational studies found that surveillance improved detection of early-stage HCC (odds ratio [OR] 2.08), increased curative treatment rates (OR 2.24), and improved survival (OR 1.90).[10] The authors cited several limitations to the data: variation in survival benefit based on study location due to heterogeneous study populations and differences in rates and types of treatment offered across centers, different modalities and frequency of surveillance implemented, inadequate duration of follow up, and lack of adjustment for lead-time bias and liver function.

RCTs provide the finest evaluation of surveillance impact but are ethically challenging as most patients prefer surveillance.[11] Though high-quality data are lacking, there are currently no proposed alternatives to surveillance. With vast improvements in HCC treatment over recent years, including emerging options such as Y-90 and more systemic therapies, surveillance is likely to be beneficial. Once a patient is diagnosed with HCC, improved survival can be attained at hospitals offering the full complement of HCC treatments coupled with early subspecialist referral and multidisciplinary tumor board review.[12,13] Thus, screening of appropriate patients should continue in order to improve tumor stage at diagnosis, thus increasing the likelihood of offering potentially curative treatments once HCC is diagnosed.

WHO SHOULD UNDERGO SURVEILLANCE?

Most guidelines agree that patients with cirrhosis should be screened as they have the highest risk for developing HCC (Table 1).[14,15,16,17] European and American guidelines recommend excluding patients with Child-Pugh C cirrhosis who are not eligible for transplant as they have low anticipated survival and thus would unlikely receive a mortality benefit from surveillance. Subgroups of patients with hepatitis B should also undergo surveillance.[14,15,17]

It is unclear whether patients with advanced fibrosis would benefit from surveillance. European guidelines recommend consideration of non-cirrhotic F3 patients based on individual risk assessment as it can be difficult to define the transition from advanced fibrosis to cirrhosis.[15] Other non-cirrhotic populations receiving increased attention are patients with hepatitis C (HCV) and non-alcoholic fatty liver disease (NAFLD). Furthermore, multiple risk indices comprised of demographic and clinical factors have been proposed to identify patients at highest risk for HCC, although these require further validation before incorporation into routine clinical use.[18,19,20,21,22]

Hepatitis C

HCV is the most common cause of HCC in developed nations and accounts for 34% of HCC cases in the United States.[23] Development of HCC in HCV in the absence of cirrhosis is uncommon. The annual incidence of HCC is 0.5% among patients with advanced fibrosis, sharply rising to 4% once cirrhosis develops.[24,25,26] Thus, most guidelines do not recommend surveillance in this population prior to the development of cirrhosis. A large VA study showed that achieving sustained virologic response (SVR) after direct-acting antiviral (DAA) therapy reduces HCC risk in patients with HCV cirrhosis by 72%.[27] There appears to be no difference in HCC risk after DAA therapy versus interferon-only therapies.[25] Nevertheless, patients with cirrhosis even after SVR remain at elevated risk for HCC and should continue to undergo surveillance.[28] Since fibrosis assessments such as Fibroscan, AST to Platelet Ratio Index, and Fibrosis-4 have not been validated in the post-SVR setting, non-invasive fibrosis staging should be completed prior to treatment.[28]

NAFLD

With the growing pandemics of obesity and diabetes, NAFLD is expected to become the most common etiology of liver disease related morbidity, mortality, and indication for liver transplantation in the near future.[29] In the United States, it is estimated that almost one in four individuals have NAFLD, of which 21% have non-alcoholic steatohepatitis (NASH).[30] Though NAFLD-related cirrhosis has a lower estimated annual incidence of HCC compared with HCV cirrhosis (2.6% vs. 4%), the prevalence of NAFLD far exceeds that of HCV. [31,32]

There is increasing concern that patients with NASH may develop HCC in the absence of cirrhosis. Small retrospective studies suggest that up to half of HCC cases associated with NASH had no antecedent diagnosed cirrhosis. [33,34,35] In a VA cohort of 1500 patients, 42% of patients with NAFLD-related HCC did not have cirrhosis, significantly higher compared with patients with alcohol or HCV-related HCC (28% and 14%, respectively; $p<0.05$).[36] Although existing data do not currently justify surveillance for HCC in NAFLD without cirrhosis due to the low incidence rate, this is an important area that needs more robust data and may have major implications on surveillance strategies.

HOW SHOULD SURVEILLANCE BE PERFORMED?

Current surveillance recommendations

Most guidelines recommend ultrasound +/− alpha-fetoprotein (AFP) with a surveillance interval of 6 months (Table 1).[14,15,16,17] MRI-based surveillance demonstrates superior sensitivity for early HCC detection but is limited by poor cost-effectiveness.[37] AFP has insufficient sensitivity and specificity to be used alone for surveillance, although data suggest improved performance for non-viral cirrhosis or HCV after virologic cure.[38,39] Recently, additional biomarkers have emerged in the diagnosis and prognostication of HCC. Although these serum-based biomarkers have been proposed for utilization in surveillance, only AFP has undergone phase III or IV validation in cohort studies.

Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3)

AFP-L3 is one of the three glycoforms of AFP. AFP is more sensitive than AFP-L3 (60% vs. 56%), but has lower specificity (90% vs. >95%) as AFP can be elevated in other liver disease such as acute and chronic viral hepatitis.[40,41,42,43] HCC that express AFP-L3 is thought to be more aggressive with the potential for rapid growth and early metastasis, and higher pre-treatment levels have been associated with tumor recurrence and poor prognosis.[44,45] Further research is needed to determine how AFP-L3 detection contributes to HCC surveillance.

Des-γ-carboxy prothrombin (DCP)

Des-γ-carboxy prothrombin (DCP) is an abnormal prothrombin with reduced γ carboxylase activity produced by tumor cells.[46] A meta-analysis estimates the sensitivity and specificity of DCP to be 71% and 84% respectively.[47] DCP appears to be correlated with tumor size, with superior performance to AFP in large tumors but not in small tumors.[48] DCP is also associated with advanced HCC.[49] Currently, DCP is rarely used alone but usually in conjunction with AFP for diagnosis of HCC and is recommended only by Japanese guidelines as a surveillance tool.[16]

GALAD Score

The GALAD score is biomarker based model that predicts the probability of having HCC comprised of gender, age, AFP-L3, AFP, and DCP.[50,51] A single center study showed that GALAD was superior to ultrasound for HCC diagnosis with a sensitivity of 91% and specificity of 85%; the combination of GALAD and ultrasound further improved performance to sensitivity 95% and specificity 91%.[52] Emerging data shows that GALAD improves detection of early stage HCC compared with AFP, AFP-L3, and DCP alone, including in NASH patients, a group in which ultrasound appears to have decreased sensitivity. [53,54,55] Even if GALAD test characteristics are comparable with ultrasound in ongoing clinical trials, a biomarker-based model may be a more practical approach to surveillance given the minority of patients who complete ultrasound based surveillance.

Other biomarker-based models

Multiple other new biomarkers are currently under development and investigation. An algorithm consisting of AFP, fucosylated kininogen, age, gender, serum alkaline phosphatase, and alanine transaminase improved detection of early stage HCC (AUC 0.98).[56] A small phase II study of a methylated DNA markers panel demonstrated an AUC of 0.96.[57] Another model combining AFP and vitamin K absence/antagonist-II, age, and gender had an AUC of 0.95.[58] As biomarkers require several phases of validation, these are not ready for routine use but may be applied in the clinical setting in the future if demonstrated to be easily measured, cost effective, and accurate.[59,60]

ARE PATIENTS UNDERGOING SURVEILLANCE?

Barriers to Surveillance

Globally, only 37% of HCC is diagnosed through surveillance, with < 20% of patients undergoing surveillance per recommended guidelines in the United States.[61,62] Barriers include patient, clinician, and health system factors (Figure 1). Although most patients with cirrhosis receive liver care through their primary care providers, fewer than half are routinely screened for HCC.[63] Though specialist care increases surveillance rates, it is not widely feasible given lack of access to subspecialty care in some areas.[64,65] Obstacles to surveillance reported by primary care providers include suboptimal knowledge about HCC guidelines, limited time in clinic, and competing clinical priorities.[66,67]

Barriers from the patient perspective include lack of knowledge about risk for HCC, difficulty with scheduling, costs of surveillance, difficulty of travel to imaging centers, and lower adherence to increased ultrasound lead time (difference between when an ultrasound was ordered and requested exam date).[68,69] Surveillance is substantially lower among patients who are non-white and of low socioeconomic status, which unfortunately extends to HCC mortality as well.[70,71] If surveillance is ordered by a provider, patient adherence appears to be high, suggesting that strategies focused on reducing clinician and health care system barriers may be most impactful. [72]

Strategies to Improve Surveillance

HCC surveillance is a complex process that requires providers to accurately identify high-risk patients and order appropriate surveillance testing. The health system must then schedule tests, and patients must adhere to recommendations. Thus, approaches should be taken to address each step of the process (Figure 1). Educating primary care providers about HCC guidelines and sending routine clinical reminders may improve surveillance rates.[73] Health care systems should aim to automate HCC surveillance and bolster patient support services. In a RCT, patients who were mailed outreach invitations combined with patient navigation services had significantly increased HCC surveillance rates compared with usual care.[74] Chronic disease management programs with nursing based protocols, patient education and automatic reminders are also effective.[75] Furthermore, utilization of telehealth may help expand access to specialist care and minimize surveillance appointment lead time. [76] Finally, lessons from other cancer screening programs may be applied to HCC surveillance, such as patient-directed prompts, systematic mass surveillance programs, and programs designed to reduce racial and socioeconomic barriers.[77]

CONCLUSIONS

Though there is some controversy related to the benefit of HCC surveillance, existing evidence suggest that there is likely mortality benefit in diagnosing early-stage disease, especially with advances in treatment options. Emerging data suggest that patients with HCV cirrhosis or advanced fibrosis who achieve SVR should continue to receive surveillance. Further data are needed to determine the value of surveillance in patients with NAFLD in the absence of cirrhosis or with advanced fibrosis of other etiologies. Newer

biomarkers such as AFP-L3, DCP, and the GALAD score are increasingly utilized in the diagnosis and prognostication of HCC, with future research aimed at investigating their application in surveillance. Strategies should be employed on the patient, clinician, and health care system level, drawing from research in this population and other cancer populations in order to improve surveillance rates and ultimately to reduce morbidity and mortality from HCC.

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Abbreviations

AFP	alpha-fetoprotein
DCP	Des-γ-carboxy prothrombin
HCV	Hepatitis C virus
HCC	hepatocellular carcinoma
AFP-L3	Lens culinaris agglutinin-reactive fraction of AFP
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
OR	odds ratio
RCT	randomized control trial

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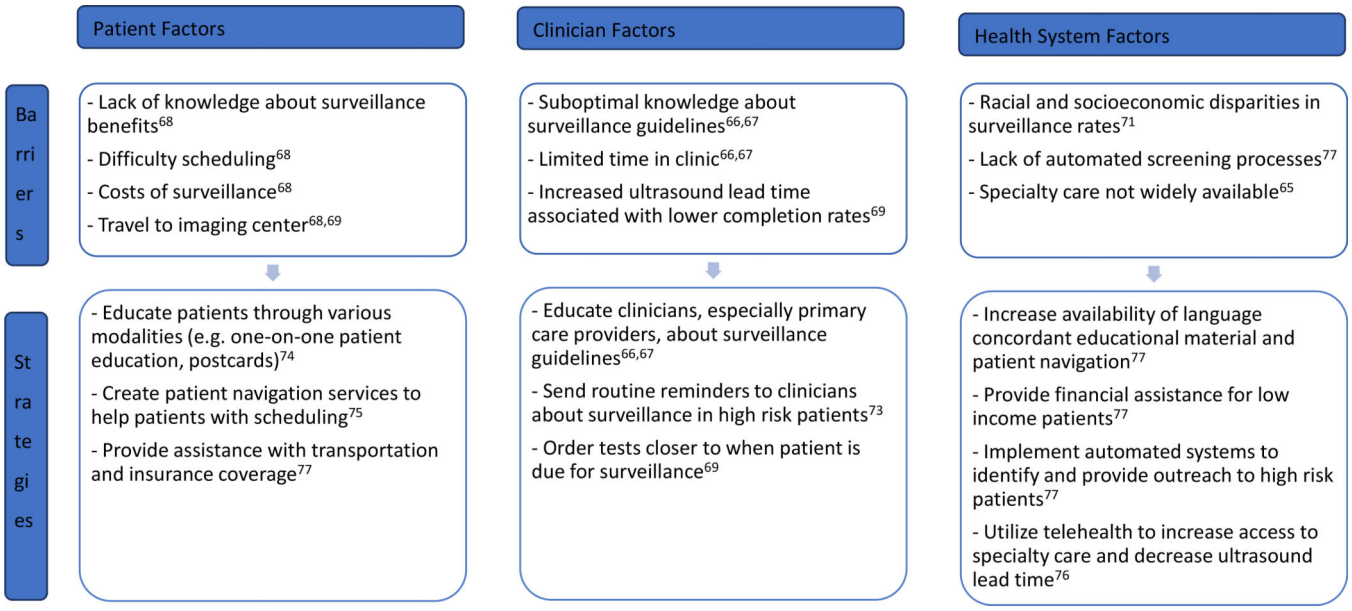

Figure 1.
Barriers to hepatocellular cancer surveillance and potential strategies for improvement

Table 1.

Comparison of major society guidelines for hepatocellular carcinoma surveillance

Society	American Association for the Study of Liver Diseases	European Association for the Study of the Liver	Japan Society of Hepatology	Asian Pacific Association for the Study of the Liver
Population	Child-Pugh A or B cirrhosis Child-Pugh C cirrhosis awaiting transplant Hepatitis B: Asian males > 40 years Asian females > 50 years Family history of HCC African and/or North American blacks	Child-Pugh A or B cirrhosis Child-Pugh C cirrhosis awaiting transplant Hepatitis B at intermediate or high risk of HCC according to PAGE-B score Non-cirrhotic F3 patients, regardless of etiology, may be considered based on individual risk assessment	High risk: Cirrhosis Chronic hepatitis B Chronic Hepatitis C Extremely high risk: Cirrhosis due to hepatitis B Cirrhosis due to hepatitis C	Cirrhosis Hepatitis B: Asian males > 40 years Asian females > 50 years Family history of HCC Africans > 20 years old
Modality	Ultrasound +/− AFP	Ultrasound	Ultrasound + AFP, DCP, AFP-L3	Ultrasound + AFP
Surveillance interval	Every 6 months	Every 6 months	Every 6 months for high risk patients Every 3–4 months for extremely high risk patients	Every 6 months