ULTRA SONO GRAPHY

Current status of image-based surveillance in hepatocellular carcinoma

Dong Hwan Kim[1], Joon-Il Choi[1,2]

[1]Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; [2]Cancer Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Korea

REVIEW ARTICLE

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Although the overall prognosis of patients with hepatocellular carcinoma (HCC) remains poor, curative treatment may improve the survival of patients diagnosed at an early stage through surveillance. Accordingly, ultrasonography (US)-based HCC surveillance programs proposed in international society guidelines are now being implemented and regularly updated based on the latest evidence to improve their efficacy. Recently, other imaging modalities such as magnetic resonance imaging have shown potential as alternative surveillance tools based on individualized risk stratification. In this review article, we describe the current status of US-based surveillance for HCC and summarize the supporting evidence. We also discuss alternative surveillance imaging modalities that are currently being studied to validate their diagnostic performance and cost-effectiveness.

Keywords: Liver; Hepatocellular carcinoma; Surveillance; Ultrasonography; Magnetic resonance imaging

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Correspondence to:
Joon-Il Choi, MD, PhD, Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea

Tel. +82-2-2258-1431
Fax. +82-2-599-6771
E-mail: dumkycji@gmail.com

Introduction

Primary liver cancer is the sixth most common cancer worldwide and the fourth most common cause of cancer death, with hepatocellular carcinoma (HCC) making up 75%–85% of all primary liver cancers [1,2]. The incidence of HCC has been rapidly rising in Western countries over the last 2 decades and is expected to continue to rise in the next decade [3,4]. However, the prognosis of patients with HCC is extremely poor, with a 5-year survival rate below 20% [5], except for the subset of patients who are diagnosed with early-stage HCC and are eligible for curative treatments such as surgical resection, local ablation, and liver transplantation [6]. Unlike other cancers, treatment of any but the earliest stages of HCC is usually ineffective [7]. Early detection of HCC amenable to curative treatments is therefore invaluable because it could lead to favorable survival and ultimately reduce disease-related mortality. In this regard, HCC surveillance programs are now being implemented and regularly updated based on the latest evidence to improve their efficacy. Understanding the essentials of HCC surveillance is crucial for the improvement of patient outcomes. In this article, we summarize the current status of image-based surveillance for HCC, present the supporting evidence, and discuss alternative imaging modalities that can be used as surveillance tools.

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Rationales for Surveillance

The objective of HCC surveillance is to reduce HCC-related mortality. A large-scale randomized controlled trial validated the efficacy of surveillance for HCC (ultrasonography [US] and measurement of α-fetoprotein [AFP] levels every 6 months) in 18,816 at-risk patients with hepatitis B virus (HBV) infection, irrespective of the presence of cirrhosis [8]. The results showed a 37% reduction in HCC-related mortality for those who underwent surveillance despite suboptimal adherence to the surveillance program (58.2%). Several lower-evidence cohort studies and meta-analyses have reinforced the benefits of surveillance in patients with cirrhosis in that surveillance detected more cases of early-stage HCC, provided a higher rate of curative treatments, and led to better survival than in the no-surveillance group [9–15]. In addition, several studies have controlled for lead-time bias, which is an inevitable methodological bias of cohort studies [16,17]. A meta-analysis by Singal et al. [15] reported that HCC surveillance was still associated with a significant improvement in survival after adjusting for lead-time bias (3-year survival rates of 39.7% for surveillance vs. 29.1% for non-surveillance, P<0.001). No randomized trials have been conducted in populations with other etiologies, including chronic hepatitis C virus (HCV) or steatohepatitis; thus, controversy remains regarding whether surveillance truly leads to a reduction in mortality in these populations, especially in Western countries where HBV infection is not common.

Several studies have investigated the benefits of HCC surveillance regarding cost-effectiveness and found that surveillance with US alone or in association with AFP, was generally a cost-effective strategy [18–25]. The cost-effectiveness of surveillance is largely dependent on the annual risk of HCC since the cost for a detected tumor is inversely proportional to the tumor incidence. Several studies have demonstrated that HCC surveillance should be offered for patients with cirrhosis of varying etiologies when the risk of HCC is 1.5% per year or greater [18,22,26]. However, in population-based surveillance with an HCC incidence lower than 1.5%, the low cost-effectiveness of surveillance is counter-balanced by the high numbers of the target population with preserved liver function who are more likely to receive curative treatments. Therefore, surveillance is deemed cost-effective if the expected HCC risk exceeds 0.2% per year in patients with HBV [27]. Given those findings, patients with liver cirrhosis of all etiologies or chronic HBV infection are the main target population for surveillance as an at-risk group for HCC, with the exception of Child-Pugh Class C patients in the context of the limited availability of liver transplantation.

Current Consensus on HCC Surveillance

Several international guidelines endorsed by major scientific societies have been published to establish a common standardized approach for the management of HCC [26,28–32]. There are slight differences in these guidelines in terms of target populations, surveillance tests, and surveillance intervals (Table 1) [33].

Target Population

The prevalence of cirrhosis among patients with HCC has been estimated to be 85%–95%, and the HCC incidence rate among patients with cirrhosis has been shown to be 2%–4% per year [3,34,35]. Accordingly, patients with cirrhosis of any cause are defined as the target population in all guidelines, except for the Asian Pacific Association for the Study of the Liver (APASL) guideline [32], in which the targets are limited to cirrhosis with HBV or HCV. In the Japanese Society of Hepatology (JSH) guideline [31], patients with cirrhosis and HBV or HCV are further stratified into an extremely high-risk population for HCC. Patients with HBV who do not have cirrhosis are recommended for surveillance in most guidelines, except for the APASL guideline, because of their high risk for HCC [32]. Numerous other factors are associated with HCC risk, such as non-cirrhotic fatty liver disease, older age, male sex, and diabetes mellitus. However, since these risk factors do not elevate the risk of HCC sufficiently to justify routine surveillance and the cost-effectiveness is thought to be low, surveillance is not formally recommended in patients with these risk factors.

Surveillance Tests

Currently, US is the standard surveillance modality and is acknowledged as the most appropriate imaging modality for HCC surveillance according to all international guidelines [26,28–32]. The widespread use of US could be attributed to its absence of risks, non-invasiveness, accessibility, cost-effectiveness, and capacity to detect the onset of other complications of cirrhosis early (Table 2). However, the sensitivity of US in surveillance settings is suboptimal despite its high specificity (around 90%) [36,37]. According to a meta-analysis by Singal et al. [14], the pooled sensitivity of US for detecting HCC at any stage was 94%, but it was only 63% for detecting early-stage HCC. In agreement with those results, another recent meta-analysis of 32 studies by Tzartzeva et al. [38] reported that the pooled sensitivity of US was 84% for HCC at any stage, but 47% for early HCC. Of note, there was a wide range in sensitivity for early HCC detection (from 21% to 91%), as well as considerable heterogeneity between studies (I^2=87%–94%) [14,38]. These results might imply a substantial inconsistency in the application of US surveillance; thus, there is a need to standardize the terminology,

Table 1. Summary of recommendations for surveillance by international guidelines

Continent	Society (year of publication)	Target population	Surveillance test	Surveillance interval
North America	AASLD[a] (2018) [26]	Cirrhosis of any etiology Chronic HBV carriers if Asian men >40 y, Asian women >50 y, African or African American, or family history of HCC	US, with or without AFP	6 mo
North America	LI-RADS[a] (2017) [28]	Cirrhosis of any etiology Chronic HBV carriers	US, with or without AFP	6 mo
Europe	EASL[a] (2018) [29]	Cirrhosis of any etiology Chronic HBV carriers at intermediate or high risk of HCC[b] F3 patients	US	6 mo
Asia	KLCA-NCC (2018) [30]	Cirrhosis of any etiology Chronic HBV or HCV	US and AFP	6 mo
Asia	JSH (2017) [31]	Cirrhosis with HBV or HCV (defined as extremely high-risk) Cirrhosis with other etiology or chronic HBV or HCV (defined as high-risk)	Extremely high-risk: US, tumor marker[c], and dynamic CT or dynamic/EOB MRI High-risk: US and tumor marker[c]	Extremely high-risk: US and tumor marker[c] every 3–4 mo, dynamic CT or dynamic/EOB MRI every 6–12 mo High-risk: 6 mo
Asia	APASL (2017) [32]	Cirrhosis with HBV or HCV	US and AFP	6 mo

AASLD, American Association for the Study of Liver Diseases; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; US, ultrasonography; AFP, α-fetoprotein; LI-RADS, Liver Imaging Reporting and Data System; EASL, European Association for the Study of the Liver; F3, fibrosis stage 3 according to the METAVIR system; KLCA-NCC, Korean Liver Cancer Association and the National Cancer Center; HCV, hepatitis C virus; JSH, Japanese Society of Hepatology; CT, computed tomography; EOB, ethoxybenzyl (gadoxetic acid); MRI, magnetic resonance imaging; APASL, Asian Pacific Association for the Study of the Liver; PIVKA-II, vitamin K absence or antagonist-II; AFP-L3, AFP lectin fracture.
[a]Exclude patients with Child-Pugh C, not awaiting liver transplantation. [b]According to the PAGE-B score, based on decade of age (0, 16–29; 2, 30–39; 4, 40–49; 6, 50–59; 8, 60–69; 10, ≥70), sex (male, 6; female, 0) and platelet count (0, ≥200,000/μL; 1, 100,000–199,999/μL; 2, <100,000/μL): a total sum of ≤9 is considered at low risk of HCC (almost 0% risk of HCC at 5 years) a score of 10–17 at intermediate risk (3% incidence of HCC at 5 years) and ≥18 is at high risk (17% risk of HCC at 5 years). [c]AFP, PIVKA-II, and AFP-L3 measurements.

Table 2. Characteristics of ultrasonography and potential alternative imaging modalities for HCC surveillance

Modality	Advantage	Disadvantage
Ultrasonography (US)	Cheap Accessibility Cost-effectiveness High level of evidence for surveillance No contrast agent-related complications	Lower sensitivity, particularly in patients with advanced cirrhosis or obesity Operator dependency
Contrast-enhanced US	Real-time observation No contrast agent-induced nephrotoxicity or hypersensitivity Reduced false referral rate, compared with B-mode US	Same as above Expensive Lack of evidence for HCC surveillance, especially for cost-effectiveness
Low-dose liver CT	Radiological hallmarks of HCC[a] Relatively stable in patients with advanced cirrhosis or obesity	Lack of evidence for HCC surveillance Radiation hazard Contrast agent-induced complications Expensive
Contrast-enhanced abbreviated MRI using gadoxetic acid[b]	Highly sensitive (80.6%–91.6%) No radiation hazard Relatively stable in patients with advanced cirrhosis or obesity	(Very) expensive Requires costly facilities Lengthy room occupancy time Contrast retention in human tissues
Contrast-enhanced abbreviated MRI using extracellular agent[c]	Radiological hallmarks of HCC[a] No radiation hazard Relatively stable in patients with advanced cirrhosis or obesity	(Very) expensive Requires costly facilities Contrast retention in human tissues
Non-contrast MRI[d]	No radiation hazard No contrast agent-related complication Shorter examination time Relatively stable in patients with advanced cirrhosis or obesity	Expensive Requires costly facilities Slightly poorer performance than contrast-enhanced MRI

HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; T2WI, T2-weighted imaging.
[a]Arterial enhancement and portal venous/delayed washout. [b]Consisting of hepatobiliary phase with DWI or T2WI. [c]Consisting of dynamic contrast enhancement alone with or without T2WI. [d]Consisting of DWI and T2WI, with or without T1 in- and out-of-phase imaging.

interpretation, and reporting of US results in surveillance settings. Motivated by this need, American College of Radiology developed the US Liver Imaging Reporting and Data System (LI-RADS) algorithm in 2017 [28]. The US LI-RADS recommends assigning two scores: a US category from 1 to 3, which determines the need for follow-up, and a visualization score from A to C, which is used to communicate the expected level of sensitivity of the examination (Fig. 1). The US category is assessed according to the US imaging findings. When not definitely benign lesions measuring at least 10 mm in diameter or a new thrombus in a vein is noted, the lesions are assessed as US-3 (positive). Not definitely benign lesions smaller than 10 mm in diameter are assessed as US-2 (subthreshold). An absence of lesions or definitely benign observations are assessed as US-1 (negative). Each US examination is assigned a visualization score using the following classifications: score A, no or minimal limitations; score B, moderate limitations; and score C, severe limitations (Tables 3, 4). The US LI-RADS also suggests technical recommendations for optimal US scanning along with some tips to

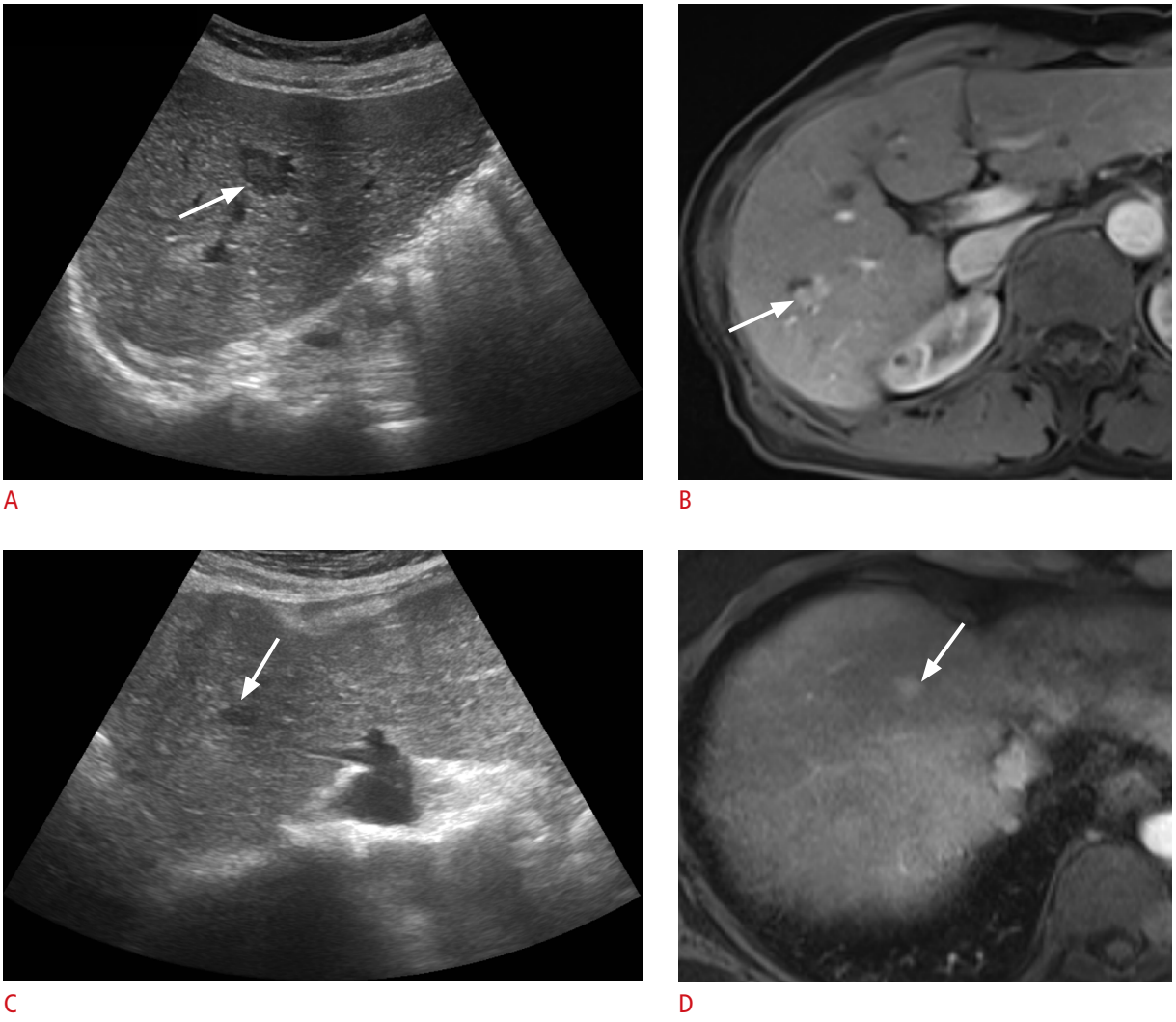
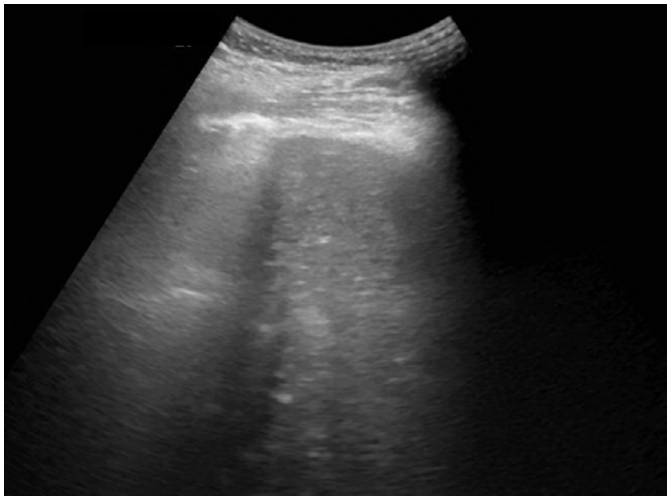


Fig. 1. Representative examples of the Ultrasound Liver Imaging Reporting and Data System (US LI-RADS).
A, B. The patient is a 64-year-old man with hepatitis B viral cirrhosis and surgically confirmed hepatocellular carcinoma (HCC). Surveillance US (A) shows a 1.4-cm hypoechoic nodule (arrow) in hepatic segment VI. The nodule was classified as US LI-RADS category 3 with a visualization score of A. This nodule shows hyperenhancement (arrow) on the arterial-phase image (B) of gadoxetic acid–enhanced magnetic resonance imaging (MRI) and a washout appearance on the portal venous-phase (not shown). C, D. The patient is a 68-year-old woman with cryptogenic liver cirrhosis. Surveillance US (C) shows a 0.9-cm hypoechoic nodule (arrow) in hepatic segment VIII. The nodule was classified as US LI-RADS category 2 with a visualization score of A. After 3 months, follow-up gadoxetic acid–enhanced MRI shows a 1.2-cm nodule with arterial-phase hyperenhancement (arrow, D) in hepatic segment VIII and hepatobiliary-phase hypointensity (not shown). This nodule was categorized as computed tomography (CT)/MRI LI-RADS category 4 and was subsequently treated with radiofrequency ablation.



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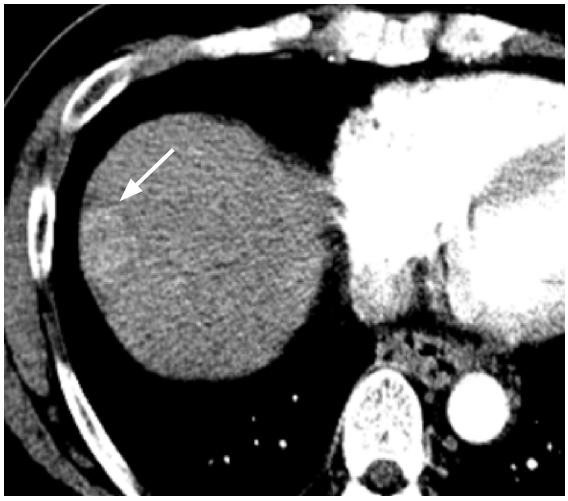

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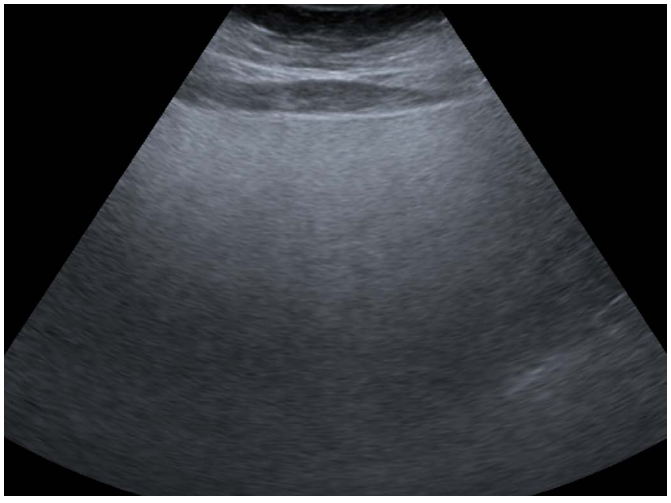

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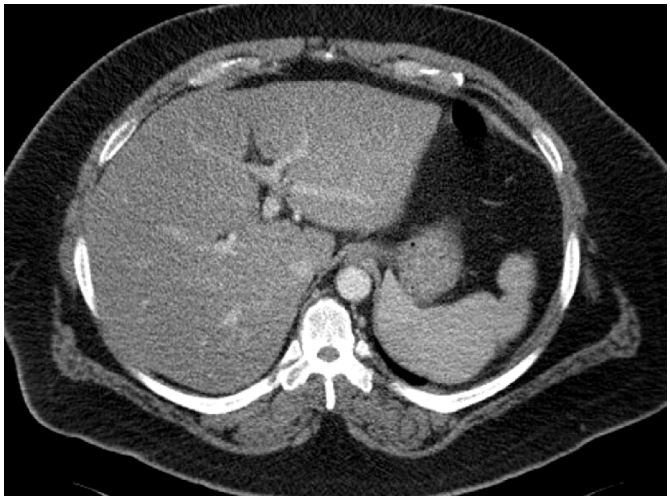

H

Fig. 1. E, F. The patient is a 52-year-old man with chronic hepatitis B and hepatocellular carcinoma. Surveillance US (E) shows no observation, but some portions of the right hemiliver was not visualized due to posterior shadowing from the lung. Therefore, the patient was assigned a US LI-RADS category 1 with a visualization score of B. On liver dynamic CT, there was a 2.5-cm nodule with arterial-phase hyperenhancement (arrow, F) in the right hepatic dome, followed by a washout appearance on delayed phase (not shown). This nodule was diagnosed as HCC based on the typical imaging findings. G, H. The patient is a 46-year-old man with alcoholic liver cirrhosis and severe fatty liver disease. Surveillance US (G) shows no observations (US LI-RADS category 1), but the visualization score was assigned as C because the posterior two-thirds of the liver could not be visualized by US due to severe fatty liver disease. However, there was no observation suggesting HCC on liver dynamic CT (H).

improve liver visualization [39]. These standardized protocols can help improve the quality of surveillance US and the communication between radiologists and referring clinicians. Son et al. [40] reported that the US-3 category demonstrated high specificity, but low sensitivity, for diagnosing HCC and that the visualization score C had a higher false-negative rate than scores A or B. Kang et al. [41] reported a high diagnostic yield of US-guided biopsies with visualization scores of A (91.1%) or B (74.5%), but not for those with a score of C (42.9%). In Korea, the US experts of Korean Society of Ultrasound in Medicine are working on standardizing the US scanning protocol for HCC surveillance and educating physicians under the Korean National Cancer Screening Program [42–44].

Serological tumor markers including AFP, prothrombin induced by vitamin K absence II (PIVKA-II), or the ratio of glycosylated AFP (L3 fraction) to total AFP have been evaluated for surveillance of HCC. AFP is the most widely used of these biomarkers. In a systematic review of five studies of HCV patients, the sensitivity of an AFP level higher than 20 ng/mL ranged from 41% to 65% and the specificity

Table 3. Categories of US LI-RADS observations

US category	Concept	Definition
US-1 negative	No US evidence of HCC	No observation or only definitely benign observations
US-2 subthreshold	Observations detected that may warrant short-term US surveillance	Observations <10 mm in diameter, not definitely benign
US-3 positive	Observations detected that may warrant multiphase contrast-enhanced imaging	Observations ≥10 mm in diameter, not definitely benign or new thrombus in vein

Adapted from Ultrasound LI-RADS v2017. American College of Radiology, 2018. Available from: https://www.acr.org/Clinical-Resources/Reportingand-Data-Systems/LI-RADS/Ultrasound-LI-RADS-v2017, with permission of the American College of Radiology [28].
US, ultrasonography; LI-RADS, Liver Imaging Reporting and Data System; HCC, hepatocellular carcinoma.

Table 4. Visualization scores of US LI-RADS

US visualization score	Concept	Examples
A: No or minimal limitation	Limitations if any are unlikely to meaningfully affect sensitivity	Liver homogeneous or minimally heterogeneous Minimal beam attenuation or shadowing Liver visualized in near entirety
B: Moderate limitation	Limitations may obscure small masses	Liver moderately heterogeneous Moderate beam attenuation or shadowing Some portions of liver or diaphragm not visualized
C: Severe limitation	Limitations significantly lower sensitivity for focal liver lesions	Liver severely heterogeneous Severe beam attenuation or shadowing Majority (>50%) of liver not visualized Majority (>50%) of diaphragm not visualized

Adapted from Ultrasound LI-RADS v2017. American College of Radiology, 2018. Available from: https://www.acr.org/Clinical-Resources/Reportingand-Data-Systems/LI-RADS/Ultrasound-LI-RADS-v2017, with permission of the American College of Radiology [28].
US, ultrasonography; LI-RADS, Liver Imaging Reporting and Data System.

ranged from 80% to 94% for HCC at any stage [45]. However, it remains controversial whether this marker has any additional role or impact on survival in comparison to US alone. The above mentioned meta-analysis in 2014 [15] reported odds ratios with statistical significance between no surveillance and US alone, and between no surveillance and US plus AFP for detecting early-stage HCC (2.04 [95% confidence interval (CI), 1.55 to 2.68] vs. 2.16 [95% CI, 1.80 to 2.60]); however, there was no statistically significant difference between the two surveillance methods. Moreover, the meta-analysis reported odds ratios showing significant differences between no surveillance and US alone, and between no surveillance and US with AFP for receipt of curative treatment (2.23 [95% CI, 1.83 to 2.71] vs. 2.19 [95% CI, 1.89 to 2.53]); however, similarly, no significant differences were reported between the two surveillance methods. According to a systematic review included in the 2018 American Association for the Study of Liver Diseases guideline [26], there was no statistically significant difference between the two strategies for improving survival despite the trends toward a higher risk ratio for US with AFP (1.86 [95% CI, 1.76 to 1.97]) than for US alone (1.75 [95% CI, 1.56 to 1.98]). Furthermore, insufficient research has been conducted on PIVKA-II and AFP-L3, which are only recommended for surveillance in the JSH guideline [31].

Surveillance Intervals

All guidelines recommend surveillance at 6-month intervals except for the Japanese guideline [31], which recommends follow-up every 3–4 months for extremely high-risk patients (Table 1). The rationales for the 6-month interval are largely based on tumor doubling time, survival benefit, and cost-effectiveness. The mean tumor doubling time of small HCCs (<5 cm) was estimated to be around 4 to 7 months [46,47]. With regard to the clinical outcomes, an Italian prospective study comparing 6-month versus 12-month interval surveillance showed that 6-month interval surveillance led to a significantly higher detection rate of early-stage HCC (43.0% vs. 21.2%), treatment applicability (81.8% vs. 69.6%), and patient survival even after correction for the lead time (40.3 months vs. 30.0 months) [12]. Meanwhile, a randomized trial by Trinchet et al. [13] revealed that 3-month interval surveillance did not significantly increase the likelihood of detecting early-stage HCCs (79.2% vs. 70.0%), or improve the amenability to curative treatment (62.3% vs. 58.3%) or 5-year survival (84.9% vs. 85.8%), compared to surveillance at 6-month intervals. Lastly, cost-effectiveness studies have demonstrated that biannual US-based surveillance improves quality-adjusted life expectancy at acceptable costs [18,19,23].

Alternative Surveillance Imaging Modalities

Ideally, the performance of alternative surveillance tests should be verified in a prospective surveillance setting that reflects real-world conditions. As a substitute, some authors have attempted to simulate a surveillance setting by retrospectively enrolling consecutive patients with HCC risk factors who have not been previously diagnosed or treated with HCC. However, in diagnostic settings, the prevalence of HCC could be exaggerated and various selection biases tend to occur, hindering the application of these results to the surveillance setting.

Limitations of US

The sensitivity of US for detecting HCC is particularly impaired in some situations, leading to surveillance failure and poor survival outcome. First, the inherent distortion of the appearance of liver parenchyma by underlying pathologic changes of advanced or macronodular cirrhosis can obscure HCC on US [48,49]. Furthermore, US may generate false-positive findings for HCC in the background of macronodular cirrhosis, resulting in unnecessary recall procedures, which causes additional cost and potential harm to patients [50]. It is especially worth noting that patients with HBV infection were found to be more likely to exhibit parenchymal macronodularity than patients with HCV infection [49,51]. Second, the presence of an inadequate echogenic window is significantly associated with surveillance failure [49]. An inadequate echogenic window is frequently present in obese patients [49,52], but can also be associated with various extrinsic factors (e.g., rib cage or bowel obscuring) or patient factors (e.g., inability to cooperate) (Fig. 1). Third, several tumor-related factors, such as subcapsular location (Fig. 2), small size, and infiltrative tumor type, can significantly impair the sensitivity of US [48,50,53]. According to recently published multicenter studies from the United States, the US LI-RADS visualization score was C in 3.0%–4.2% of patients undergoing HCC surveillance [54,55]. Considering these drawbacks of US, several guidelines proposed alternative imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) for patients with an inadequate US surveillance results [26,29,30]. Table 2 summarizes these alternative modalities under investigation.

Contrast-Enhanced Ultrasonography

With the aid of microbubble contrast agents, the use of contrast-enhanced ultrasonography (CEUS) has been increasing and several studies have validated its usefulness for early detection and diagnosis of HCC [56–58]. To standardize the interpretation, reporting, and techniques for CEUS in at-risk patients for HCC, the CEUS LI-RADS was developed in 2016 and was revised in 2017

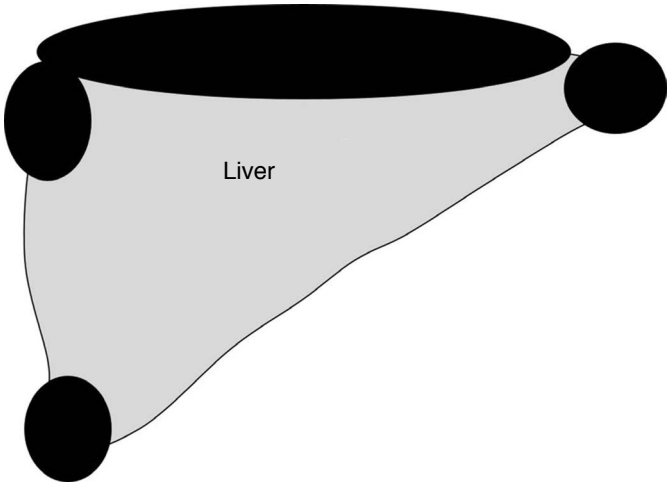

Fig. 2. Subcapsular areas where hepatocellular carcinoma can be missed easily by ultrasonography (US). Some subcapsular areas (shown in black) may not be visualized on US, especially in obese patients.

Table 5. Diagnostic table of CEUS LI-RADS

	No APHE		APHE (not rim[a], not peripheral discontinuous globular[b])	
	<20[c]	≥20	<10	≥10
No washout of any type	CEUS LR-3	CEUS LR-3	CEUS LR-3	CEUS LR-4
Late and mild washout	CEUS LR-3	CEUS LR-4	CEUS LR-4	CEUS LR-5

Adapted from CEUS LI-RADS v2017 CORE. American College of Radiology, 2017. Available from: https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/CEUS-LI-RADS-2017-Core.pdf?la=en, with permission of the American College of Radiology [59].

CEUS, contrast-enhanced ultrasonography; LI-RADS, Liver Imaging Reporting and Data System; APHE, arterial phase hyperenhancement.

[a]Rim APHE indicates CEUS LR-M. [b]Peripheral discontinuous globular indicates hemangioma (CEUS LR-1). [c]Nodule size (mm).

[59]. The CEUS LI-RADS categorizes each hepatic observation according to its likelihood of benignity and HCC (i.e., LR-1 to LR-5) according to CEUS features (Table 5) [59]. However, despite its advantages, including no radiation hazard and no contrast-induced nephrotoxicity, CEUS is still mainly used for diagnostic purposes in clinical practice and is not recommended for surveillance in all international guidelines [26,28–32]. A multicenter prospective trial in 2019 reported promising results for CEUS as an alternative tool for HCC surveillance, and the addition of perfluorobutane-enhanced US (Kupffer phase with or without vascular-phase US) to conventional B-mode US significantly reduced the false referral rate despite no significant increase in the detection rate of early HCC [60]. Further trials are needed on the efficacy of CEUS in patients

with fatty liver disease, which is becoming increasingly common, especially in Western countries [61], and on its cost-effectiveness as a surveillance test for HCC.

Computed Tomography

The role of CT for HCC surveillance is uncertain since the performance characteristics of CT have been primarily evaluated in diagnostic and staging studies. In a randomized trial in 2013 comparing biannual US to annual triple-phase-contrast CT, biannual US was marginally more cost-effective and more sensitive than CT (sensitivity, 71.4%; specificity, 97.5% vs. sensitivity, 66.7%; specificity, 94.4%, respectively) [62]. In addition, potential harms associated with ionizing radiation and contrast-related toxicity always accompany the use of CT. Recently, a prospective randomized trial has been conducted on populations at risk for HCC to compare standard-dose liver CT and "double low-dose liver CT," in which both the doses of both radiation and contrast medium were reduced by 30% using low monoenergetic images [63]. Double low-dose liver CT provided better focal liver lesion conspicuity than standard-dose CT, suggesting that some of the aforementioned shortcomings of CT could be overcome. Further trials are warranted to determine whether low-dose liver CT provides acceptable sensitivity and specificity for detecting early HCC and is cost-effective.

Magnetic Resonance Imaging

Despite the high diagnostic performance of MRI compared to US or dynamic CT in detecting HCC [64–66], MRI is not routinely recommended for HCC surveillance given the lack of evidence on its accuracy and cost-effectiveness. Notably, the main drawbacks of MRI are its limited accessibility due to a lengthy examination time and the need for costly facilities. However, Kim et al. [50] recently published a prospective surveillance study of 407 patients with cirrhosis and reported that gadoxetic acid–enhanced MRI yielded a very high sensitivity of 84.8%, compared to the strikingly low sensitivity of 27.3% of US for detecting very early HCC. This low sensitivity may be due to the small size of the detected HCCs (mean size, 1.6 cm) with the majority (66.7%) being at very early stages (Barcelona Clinic Liver Cancer stage of 0, single nodule <2 cm). In addition, the study population was composed of those at high risk for HCC with an annual risk of >5%. Therefore, these patients may have been more likely to have advanced liver cirrhosis with distorted liver parenchyma, which may limit the detection of HCC on US. That study was a single-arm study, meaning that patients underwent both US and MRI. In this situation, if a small tumor is detected on MRI first, US might lose its chance to detect HCC in the next surveillance round. In the light of cost-effectiveness, MRI surveillance might be justified in patients at higher risk for HCC development, and several published cost-effectiveness models have shown that surveillance with gadoxetic acid–enhanced MRI outperformed biannual US in high- and intermediate-risk patients [67,68]. However, the long imaging acquisition time of full-protocol gadoxetic acid–enhanced MRI can hamper its widespread use in surveillance settings. Therefore, an abbreviated MRI protocol, including the hepatobiliary phase using gadoxetic acid with diffusion-weighted imaging (DWI) or T2-weighted imaging (T2WI), has been adopted and has shown high sensitivity (80.6%–91.6%) and specificity (90.7%–96.1%) in several retrospective studies [69–72]. Another abbreviated MRI protocol using an extracellular contrast agent, consisting of a dynamic study alone with or without T2WI, has proven its potential as a surveillance tool in a few studies [73,74]. Nevertheless, contrast-enhanced abbreviated MRI protocols still have insurmountable flaws caused by the gadolinium-based contrast agent itself, such as long-term retention in human tissues [75].

Non-contrast MRI consisting of DWI and T2WI could be a candidate for an alternative surveillance modality for HCC. A prospective surveillance study published in 2020 [76] found that the sensitivity of non-contrast MRI for diagnosing HCC was 77.1%–79.1%, with a specificity of 97.9%. This result is somewhat different from those of previous studies that analyzed the accuracy of non-contrast MRI (sensitivity, 82.9%–91.7%; specificity, 76.4%–90.7%), but those studies were retrospective in nature or were performed in a diagnostic setting [77–79]. Moreover, a recent comparative study simulating HCC surveillance reported similar sensitivity and specificity between non-contrast MRI and abbreviated MRI using gadoxetic acid [80]. Given those findings in the literature, non-contrast MRI might be anticipated to be more cost-effective than contrast-enhanced abbreviated MRI, as a corollary of the lack of a requirement for contrast agents and shorter examination time. The length of the examination time is another important factor regarding the efficacy of surveillance utilization, and that of non-contrast MRI has been reported to be about 6 to 10 minutes [76–78]. Two prospective trials are currently underway to compare the effectiveness of biannual US and biannual or annual non-contrast MRI in patients with cirrhosis [81,82].

Cost-Effectiveness of Alternative Imaging Modalities

MRI or CT can improve the detection of early HCCs, but may not be cost-effective if performed in all at-risk patients. Moreover, these alternative modalities may be most justified for the subset of patients who are prone to US surveillance failure or who have a sufficiently high risk of developing HCC. Goossens et al. [67] reported that a risk-stratified surveillance strategy (i.e., abbreviated MRI for high- and intermediate-risk patients with cirrhosis and US

for lower risk patients) was more cost-effective than a non-stratified strategy (biannual US for all patients). Another recently published cost-effectiveness model revealed that biannual surveillance using gadoxetic acid–enhanced MRI was more cost-effective than US in patients with compensated cirrhosis [68]. In this study, MRI surveillance was more cost-effective than US surveillance when the HCC incidence rate was 3% per year with a cost-effectiveness threshold of $20,000/quality-adjusted life year [68]. These might imply that MRI surveillance could be an acceptably cost-effective option as the HCC incidence rate increases. On the other hand, since the cost of surveillance tests varies from country to country, the cost-effectiveness may also differ for each country. For example, in South Korea, the national medical insurance fee is $70–120 for surveillance liver US, $200–230 for dynamic CT, $300–330 for non-contrast liver MRI, and $450–500 for full-sequence MRI. Therefore, the cost for biannual US is similar to that of annual dynamic CT.

Conclusion

Surveillance of patients at risk for HCC has led to the identification of early-stage HCCs, receipt of curative treatment, and improvements in patients' survival. Biannual US is currently the HCC surveillance strategy of choice generally accepted by international societies. However, regarding the low sensitivity of US for early-stage HCC, complementary strategies with alternative surveillance modalities could be options for high-risk patients. MRI with an abbreviated protocol or CT might be effective means of HCC surveillance tailored to patients at higher risk of developing HCC. In light of the limited data evaluating these alternative modalities for surveillance purposes, future studies are needed on the cost-effectiveness, potential harms, and accessibility to surveillance resources associated with these approaches. The performance of US surveillance itself should also be enhanced by optimizing and standardizing the scanning protocol and quality control of physicians and sonologists who perform US examinations. Adoption of the US LI-RADS can be helpful for this purpose.

ORCID: Dong Hwan Kim: https://orcid.org/0000-0002-2932-2367; Joon-Il Choi: https://orcid.org/0000-0003-0018-8712

Author Contributions

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Conflict of Interest

Joon-Il Choi (Activities related to the present article): No relevant relationships; (Activities not related to the present article): The author previously received grants from Bayer Healthcare, Guerbet Korea, Bracco Korea, GE Healthcare, and Starmed, and the author previously received honoraria from Bayer Healthcare, Samsung Medison, Samsung Eletronics, Guerbet Korea, Bracco Korea; (Other relationships): Nothing to declare. Dong Hwan Kim: Nothing to declare.

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