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Recent advances and issues in imaging modalities for hepatocellular carcinoma surveillance

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide. Early detection via surveillance plays a crucial role in enabling curative treatment and improving survival rates. Since the initial randomized controlled trial, biannual ultrasound (US) has been established as the standard surveillance method because of its accessibility, safety, and low cost. However, US has some limitations, including operator dependency, suboptimal sensitivity for early-stage HCC, and challenges such as a limited sonic window that may result in inadequate examination. Alternative imaging modalities, including contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), have demonstrated higher sensitivity for detecting very early-stage HCC. Recent advancements, such as low-dose CT with deep learning-based reconstruction, have enhanced the safety and feasibility of CT-based surveillance by reducing radiation exposure and amount of contrast media. MRI, particularly with gadoxetic acid or abbreviated protocols, offers superior tissue contrast and sensitivity, although its accessibility and cost remain challenges. Tailored surveillance strategies based on individual risk profiles and integration of advanced imaging technologies have the potential to enhance the detection performance and cost-effectiveness. This review highlights the recent developments in imaging technologies for HCC surveillance, focusing on their respective strengths and limitations. **(J Liver Cancer 2025;25:31-40)**

Keywords: Carcinoma, hepatocellular; Diagnostic imaging; Surveillance

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy globally and the third leading cause of cancer-related mortality.[1] Most individuals with HCC have risk factors such as liver cirrhosis and chronic hepatitis B infection. These well-recognized risk factors make HCC an appropriate target for surveillance programs. The goal of HCC surveillance is to identify the disease at a very early or early-stage when curative treatments, including surgical resection, liver transplantation, or local ablation, are feasible, ultimately improving the overall survival rates. In line with this, the current international guidelines for HCC management recommend surveillance for at-risk groups to improve survival outcomes.[2-5]

In 2004, a randomized controlled trial by Zhang et al.[6] first demonstrated that biannual ultrasound (US) combined with serum alpha-fetoprotein (AFP) measurement significantly improved the overall survival of patients with chronic hepatitis B compared with a control group. Consequently, biannual US was established as the standard imaging method for HCC surveillance. Although the effectiveness of this approach has been confirmed through randomized controlled trials and retrospective cohort studies,[6-9] US has some inherent limitations. These include its subjective nature, operator dependency, and low sensitivity in detecting very early or early-stage HCC, which is the primary target of surveillance. A meta-analysis estimated that

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the sensitivity of biannual US for detecting early-stage HCC was 63%, which is suboptimal.[10] Recent prospective studies have suggested even lower sensitivity for detecting very early-stage HCC, defined as a single HCC lesion equal to or less than 2 cm, with detection rates around 30% in high-risk patients with an annual HCC incidence exceeding 5%.[11,12]

To overcome the limitations of US, international guidelines recommend alternative imaging modalities, such as contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), particularly for patients with inadequate US results.[2-5] These modalities offer higher sensitivity for detecting early and very early-stage HCC compared to US but have their own challenges. CT is associated with concerns regarding radiation exposure and potential adverse reactions to iodinated contrast media. MRI, although highly sensitive, is limited by its high cost, restricted availability, and lengthy scan time. Technological advancements have gradually alleviated some of these challenges and efforts are underway to further enhance the utility of US and other imaging methods. This review focuses on recent developments in imaging technologies and strategies for HCC surveillance, emphasizing the strengths and limitations of various approaches.

US

Following a successful randomized controlled trial by Zhang et al.,[6] B-mode US was established as the standard imaging modality for HCC surveillance. Furthermore, US remains the only imaging technique that has demonstrated survival benefits for HCC surveillance in at-risk populations. Repeated examinations are mandatory in surveillance programs. In this regard, current guidelines recommend B-mode US at 6-month intervals.[2-5] In the context of repeated examinations in a surveillance program, US has several distinct advantages over other imaging modalities, such as CT or MRI. These advantages include no radiation exposure, no need for contrast injection, low cost, and ease of assessment. Given these merits, US might be an ideal imaging modality for HCC surveillance without any examination-related risks. However, US has several limitations. For instance, subjectivity is one of the most important drawbacks of liver US examination, as the performance of US in detecting HCC heavily depends on the operator's experience and expertise. Another important challenge is the limited sonic window, which can compromise the detection performance of US, especially for small-sized HCC. Shadow of the rib, adjacent bowel such as the colon, and basal lung may interfere with liver visualization, and it is well known that certain parts of the liver, such as the dome, tip of the left lateral segment, and segment VI are difficult to visualize in US examination. Moreover, US has limited sensitivity in detecting very early or early-stage HCC, which is the primary target of surveillance programs. Singal et al.[10] conducted a meta-analysis of 13 studies involving 1,514 patients and reported that biannual US with AFP measurement had a sensitivity of 63% for detecting early-stage HCC. Another meta-analysis conducted by Tzartzeva et al.,[13] which included 32 studies comprising 13,367 patients with cirrhosis reported that the sensitivity of US in detecting early-stage HCC was 47%. Additionally, two recent prospective studies have claimed that the sensitivity of US was strikingly low (approximately 30%) for detecting very early-stage HCC in high-risk patients with an estimated annual HCC development risk exceeding 5%.[11,12] Given that the primary goal of HCC surveillance is to detect very early or early-stage HCC that is amenable to curative treatment to significantly improve the overall survival, the low sensitivity of US is clearly suboptimal for this purpose. To overcome these critical limitations of US, current international guidelines for HCC management recommend alternative surveillance strategies using CT or MRI to enhance the detection of very early or early-stage HCC, particularly in patients with inadequate US examination.[2-5] However, the current management guidelines do not provide clear criteria for an inadequate US examination. Consequently, the assessment of the US quality remains subjective and varies significantly among physicians.

To standardize the terminology, technique, interpretation, and reporting of HCC surveillance using US, and to enhance communication among different healthcare professionals, the American College of Radiology introduced the US Liver Imaging Reporting and Data System (LI-RADS) in 2017.[14-16] This system was updated in 2024.[17] The US LI-RADS provides the US visualization score as a tool for the assessment of US examination quality: VIS-A, no or minimal limitations, which means that there are no limitations or limitations if any are unlikely to meaningfully affect the sensitivity; VIS-B, moderate limitations, which may obscure small (<10 mm) observations; VIS-C, severe limitations, which may significantly lower the sensitivity of liver observations.[17] Following the introduction of the US LI-RADS algorithm, several retrospective and prospective cohort studies have been conducted to validate its effectiveness. These studies reported that the rate of VIS-C, which is considered a suboptimal examination, ranged from 1.6% to 35.2%.[18-20] Additionally,

VIS-C US examinations were significantly associated with higher false-negative rates of HCC detection, indicating reduced sensitivity.[18,19] Furthermore, Park et al.[21] recently reported that patients with suboptimal US visualization (VIS-B or VIS-C) had a significantly higher risk of developing HCC during follow-up than those with optimal visualization (VIS-A). Several intrinsic and extrinsic factors associated with the liver have been identified as risk factors for having VIS-C examination, which is associated with impaired hepatic visualization. These factors include parenchymal heterogeneity and presence of advanced cirrhosis and severe steatosis among the intrinsic factors, and excessive shadowing from the ribs, lungs, or bowel gas, large patient body habitus, and poor patient cooperation with inability to comply with breath-holding instructions as the extrinsic factors.[17,19,21] Given the high false-negative rate of HCC detection and increased risk of HCC development in patients with VIS-C examination, the recently updated US LI-RADS guidelines recommend repeating the US within 3 months for individuals with VIS-C examination.[17] This recommendation is supported by the findings of previous studies indicating that approximately half of the patients with limited visualization in baseline US studies achieved improved visualization upon repeat imaging.[17,22,23] However, if the repeated US examination still results in VIS-C, an alternative surveillance strategy using CT or MRI should be considered.[17] Moreover, patients with liver cirrhosis due to metabolic dysfunction-associated steatohepatitis or alcohol-related cirrhosis, Child-Pugh B or C disease, or a body mass index of 35 or higher are at a higher risk of persistent VIS-C in future US examinations. For these patients, proceeding directly to alternative surveillance strategies using CT or MRI may be more appropriate than re-attempting US imaging.[17] However, there are currently no supporting data to validate these updated recommendations for patients with VIS-C US examination, highlighting the need for further prospective studies with large patient cohorts. Another important issue related to the US visualization score in the US LI-RADS is its reproducibility among different physicians. The reported kappa values for the US visualization score ranged from 0.37 to 0.72, indicating moderate to good inter-observer agreement.[18,21,24,25]

In addition to B-mode US, contrast-enhanced US (CEUS) can be used for HCC surveillance. The use of perfluorobutane gas-containing microbubbles (Sonazoid; GE Healthcare, Oslo, Norway) has introduced new opportunities in this field.[26] These microbubbles enable imaging during the post-vascular or Kupffer phase for over 60 minutes, in addition to vascular phase imaging. This extended duration provides sufficient time for comprehensive evaluation of the entire liver. Kudo et al.[27] were the first to report that Kupffer phase CEUS with perfluorobutane is effective for early HCC detection, as demonstrated in their prospective multicenter randomized controlled trial, in which HCC detected on Kupffer phase CEUS was significantly smaller (13.0 mm) than on B-mode US (16.7 mm, P=0.011). In contrast to the promising results of the initial study, a subsequent prospective study by Park et al.[28] showed that adding perfluorobutane-enhanced US to B-mode US did not significantly improve the detection rate of early-stage HCC (difference, 0.4%; P=0.16). However, it significantly reduced the false referral rate (difference, -3.2%; P<0.001).[28] The imaging quality of CEUS with perfluorobutane largely depends on the quality of the B-mode image. Consequently, the inherent limitations of B-mode US, such as impaired liver visualization in patients with VIS-C, cannot be entirely overcome, even with CEUS. Additionally, the use of perfluorobutane for HCC surveillance involves additional steps, including intravenous catheter insertion, increased acquisition time, and higher costs compared to B-mode US. Considering the contradictory findings of previous studies and these challenges, further large-scale studies are necessary to establish the clinical utility of CEUS with perfluorobutane as a reliable HCC surveillance tool.

CONTRAST ENHANCED MULTIPHASIC LIVER CT

CT offers several advantages over other imaging modalities such as US and MRI, including rapid scan times and high spatial and temporal resolution. Due to these strengths, contrast-enhanced multiphasic liver CT is a well-established imaging modality for the noninvasive diagnosis of HCC in at-risk patients. However, its use in the context of HCC surveillance remains underexplored, with only a limited number of studies reporting its application. Pocha et al.[29] conducted a randomized study involving 163 patients with compensated cirrhosis and reported that biannual US was marginally more sensitive and less costly for detecting early-stage HCC compared to annual CT. However, the clinical applicability of their study was limited due to several factors, including unclear criteria for positivity using each imaging modality, small sample size, and small number of HCC cases.

Repeated examinations at regular intervals are mandatory for implementation of surveillance programs. However, contrast-enhanced multiphasic CT has several critical drawbacks in this context. The most significant concern is radiation exposure. A single contrast-enhanced multiphasic liver CT scan delivers an

estimated radiation dose of 10-15 mSv, which is 2-5 times higher than the annual background radiation from the environment. Although the exact risk associated with repeated radiation exposure from CT scans is not yet fully known, it is widely accepted that radiation exposure should be kept as low as reasonably achievable. This precaution is based on evidence from a study of atomic bomb survivors, which suggested that the risk of developing radiation-induced malignancies is proportional to the exposed radiation dose.[30] In addition to radiation exposure, contrast-related risks are a significant concern in contrast-enhanced multiphasic liver CT. Because non-contrast CT images do not provide adequate tissue contrast for detecting HCC, the use of iodinated contrast media is essential for identifying and characterizing HCC in at-risk patients. The overall prevalence of hypersensitivity reactions to iodinated contrast media has been reported as 0.73%, with severe reactions occurring in 0.01% of cases.[31] Although the risk of adverse reactions is relatively low, it becomes more significant in the context of repeated CT examinations required for HCC surveillance. In addition to hypersensitivity reactions, contrast-induced nephrotoxicity is another critical concern. A recent study reported that approximately 1.7% of patients developed chronic kidney disease 2 years after a cancer diagnosis, potentially due to the repeated use of iodinated contrast media. The number of CT scans using iodinated contrast media injections has been identified as a significant factor contributing to long-term renal function impairment.[32] Given these risks, it is imperative to minimize both the radiation dose and amount of iodinated contrast media whenever possible to ensure patient safety during repeated CT-based surveillance for HCC.

Reducing the radiation dose and amount of iodinated contrast media in contrast-enhanced liver CT inevitably degrades the image quality owing to photon deficiency from a lower radiation dose and decreased contrast from the reduced amount of iodinated contrast media. To address these challenges, recent advancements in CT technology have aimed to maintain image quality while minimizing these risks. In this context, Yoon et al.[33] reported that dual-energy CT with low monoenergetic images and iterative reconstruction techniques can achieve a 30% reduction in both the radiation dose and amount of iodinated contrast media compared to standard-dose CT without compromising the capability to detect HCC lesions in at-risk patients. Based on these promising results, a prospective intra-individual comparison study was initiated to evaluate the performance of biannual low-dose liver CT versus biannual US for HCC surveillance in high-risk patients with an estimated annual incidence of HCC development exceeding 5%.[12] In this study, low-dose liver CT demonstrated a significantly higher sensitivity for HCC detection compared to US (83.3% vs. 29.2%, P<0.001), highlighting the clinical potential of low-dose liver CT as an alternative surveillance tool to US.

Deep-learning-based reconstruction has recently been introduced in liver CT imaging, offering substantial advancements in image quality. By effectively reducing the image noise, this technology improves the CT image quality while enabling significant reductions in the radiation dose. Several studies have demonstrated that deep learning-based reconstruction can lower the radiation dose by 30-67% without compromising image quality or the ability to detect focal liver lesions compared with standard-dose liver CT.[34-38] Additionally, the combination of deep learning-based reconstruction with contrast-boosting algorithms has enabled simultaneous reduction of both the radiation dose and iodinated contrast media by 30% while maintaining detection rates for focal liver lesions equivalent to those of standard-dose liver CT.[39,40] Despite these promising developments, the clinical effectiveness of deep-learning-based CT protocols for HCC surveillance has not been fully established and remains under investigation. To support the routine clinical implementation of low-dose CT protocols utilizing deep learning algorithms for HCC surveillance, further studies involving larger patient cohorts are necessary to generate robust clinical evidence.

MRI

MRI, known for its excellent tissue contrast, has shown outstanding performance in the noninvasive imaging diagnosis of HCC. Furthermore, MRI with liver-specific contrast agents has demonstrated the highest sensitivity in detecting small HCCs, as reported in a meta-analysis.[41] Another significant advantage of MRI over contrast-enhanced liver CT is the absence of radiation exposure, which makes it a safer option for repeated examinations. Therefore, MRI has been explored as a potential modality for HCC surveillance. The MRI protocol for HCC surveillance can be categorized according to the use and type of gadolinium-based contrast agents.

Full sequence MRI with gadoxetic acid

A straightforward approach to HCC surveillance using MRI is the application of a full-sequence MRI protocol with gadoxetic acid. This protocol aligns with the standard diagnostic protocol for HCC. Gadoxetic acid provides a hepatobiliary phase (HBP)

with excellent tissue contrast, enabling gadoxetic acid-enhanced liver MRI to achieve the highest sensitivity for detecting HCC, particularly small lesions, compared with other imaging modalities.[41] This advantage makes gadoxetic acid-enhanced liver MRI a potentially superior imaging modality for HCC surveillance, especially because the primary goal of surveillance is to detect very early- or early-stage HCC. The superiority of gadoxetic acid-enhanced MRI for surveillance is supported by the results of a prospective intra-individual comparison study conducted by Kim et al.,[11] which demonstrated a significantly higher sensitivity for detecting very early-stage HCC than US (84.8% vs. 27.3%, P<0.001) in high-risk patients with an annual HCC development risk exceeding 5%. Despite these advantages and promising results of the initial study, full-sequence MRI using gadoxetic acid has several limitations. Imaging acquisition requires more than 30 minutes, and this long scan time, coupled with high costs, restricts its widespread clinical application. Technical challenges also arise during the arterial phase, as transient severe motion is more common with gadoxetic acid than with extracellular contrast agents, potentially degrading the image quality.[42] Additionally, liver function can affect the diagnostic performance. Impaired liver function can result in heterogeneous and diminished hepatic parenchymal enhancement, reducing lesion conspicuity in HBP. This limitation may decrease the sensitivity of HCC detection and increase the likelihood of pseudolesion.

Abbreviated MRI with contrast agent

Although full-sequence MRI with gadoxetic acid has a significantly higher sensitivity for HCC detection than US, its long scan time poses a major barrier to its widespread clinical use. To address this limitation, abbreviated MRI (AMRI) protocols, which include only the most essential sequences for HCC detection, have been developed and investigated. While both gadoxetic acid and extracellular contrast agents can be used in AMRI protocols, most current studies are using gadoxetic acid because of the superior tissue contrast provided by the HBP, which is particularly effective for identifying small lesions.

AMRI with gadoxetic acid typically includes HBP imaging, diffusion-weighted imaging (DWI) for lesion detection, and T2-weighted sequences to maintain specificity by excluding lesions, such as cysts or hemangiomas, which exhibit bright signals on T2-weighted images. Several retrospective studies evaluating this approach have reported promising results, with sensitivity rates of 80-90% and specificity rates of 91-98% for detecting HCC.[43-45] Meta-analyses have also indicated sensitivity and specificity rates of 84-94% and 91-94%, respectively, suggesting the potential utility of AMRI with gadoxetic acid as a surveillance tool for HCC.[46,47] However, these results should be interpreted with caution because of the study design limitations. Most of the studies were retrospective, raising concerns regarding selection bias. Additionally, the incidence of HCC in these studies ranged from 16.4% to 18.2%, which is unrealistically high compared to that in real-world clinical settings, limiting the generalizability of the findings. Further prospective studies are necessary to accurately evaluate the effectiveness of AMRI with gadoxetic acid in HCC surveillance. Ongoing studies are addressing this issue (NCT06312826 and NCT04288323). Another important consideration for AMRI with gadoxetic acid is the need for recall examinations when positive findings are detected. Because this protocol does not include dynamic sequences, such as arterial and portal venous phases, which are required for the non-invasive imaging diagnosis of HCC, a confirmatory diagnosis cannot be made with AMRI alone. To address this issue, protocols using extracellular agents that include only dynamic sequences may help to characterize lesions identified on AMRI with gadoxetic acid, potentially reducing the need for additional imaging studies.[26]

Although the majority of AMRI protocols using contrast agents utilize gadoxetic acid due to the high tissue contrast provided by the HBP, dynamic contrast-enhanced AMRI (DCE-AMRI) has also been evaluated as a potential tool for HCC surveillance. To optimize the scan time, DCE-AMRI typically includes only dynamic contrast-enhanced sequences, consisting of pre-contrast fat-suppressed T1-weighted imaging, arterial phase, portal venous phase, and delayed phase, which are essential sequences for the non-invasive imaging diagnosis of HCC.[48] A potential advantage of DCE-AMRI over AMRI with gadoxetic acid is its ability to facilitate noninvasive imaging diagnosis of HCC, potentially reducing the need for recall examinations. In a retrospective study on a population with an HCC prevalence of 32.6%, Khatri et al.[49] reported that the sensitivity and specificity of DCE-AMRI for detecting HCC were 92.1% and 88.6%, respectively, suggesting its potential as a surveillance tool for HCC. Several prospective studies (NCT03731923 and NCT05828446) are currently underway to further evaluate the detection performance of DCE-AMRI in HCC surveillance.

Risks associated with the use of gadolinium-based MRI contrast agents

Although gadolinium-based MRI contrast agents are generally

Table 1. Summary of prospective studies comparing alternative tests to US for HCC surveillance

Imaging modality	Study	Study period	Study design	Target population	Primary outcome	Number of patients	Number of patients developed HCC	Sensitivity (%)
Low dose dynamic CT	Yoon et al.[12] (2020)	2014-2016	Intra-individual comparison	High risk patients*	Sensitivity	137	24	83.8
Full MRI with gadoxetic acid	Kim et al.[11] (2017)	2011-2014	Intra-individual comparison	High risk patients*	Sensitivity	407	37	84.8
Non-contrast MRI	Kim et al.[56] (2024)	2015-2017	Intra-individual comparison	High risk patients*	Sensitivity	208	31	71.0†
Perfluorobutane-enhanced US	Park et al.[28] (2019)	2014-2016	Intra-individual comparison	HBV or HCV related cirrhosis	Sensitivity	524	6	100
Perfluorobutane-enhanced US	Kudo et al.[27] (2019)	NA	Randomized controlled trial	HBV or HCV related cirrhosis‡	Maximum size of detected HCC	309	52	100

HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available.
*High risk patients have an estimated annual risk of developing HCC greater than 5%; †Sensitivity of annual non-contrast MRI; ‡HBV- or HCV-related liver cirrhosis with age >20 years, portal hypertension or platelet count <130,000/mL.

considered safer than iodinated contrast media used in CT, they are not without risks. Similar to iodinated CT contrast media, gadolinium-based agents can cause hypersensitivity reactions with an incidence rate of approximately 0.4%.[50] A distinct concern specific to gadolinium-based agents is the potential for gadolinium accumulation in the body, particularly in the basal ganglia. This phenomenon has been observed with almost all types of gadolinium-based contrast agents, including gadoxetic acid.[51] Although the clinical significance of this accumulation, particularly its relationship with neurological symptoms, remains unclear, it may be an important consideration in clinical practice, especially for patients requiring repeated contrast-enhanced MRI scans.

Non-contrast MRI

Considering the risks and costs associated with gadolinium-based MRI contrast agents, non-contrast MRI, which includes DWI and T2-weighted imaging, has emerged as a promising alternative for HCC surveillance.[52,53] Among these sequences, DWI is highly effective for detecting HCC, while T2-weighted imaging helps in excluding benign lesions, such as hemangiomas and cysts, which typically exhibit bright signal intensity.[26] In a retrospective analysis of a prospectively constructed cohort of high-risk patients with an annual HCC development risk exceeding 5%, Park et al.[54] demonstrated that non-contrast MRI had a significantly higher sensitivity for detecting very early-stage HCC than US (79.1% vs. 27.9%, P<0.001). Meta-analyses have also indicated that the sensitivity and specificity of non-contrast MRI for HCC detection is 83-87% and 87-91%, respectively.[46,47,55] Recently, Kim et al.[56] reported the results of a prospective intra-individual comparison of biannual US and annual non-contrast MRI for HCC surveillance in a similar high-risk population with an annual HCC development risk exceeding 5%. In their study, the sensitivity of annual non-contrast MRI for detecting HCC was slightly higher than that of biannual US (71.0% vs. 45.2%, P=0.077), and the diagnostic yield was significantly greater (4.26% vs. 1.43%, P<0.001) with comparable false referral rates (2.91% vs. 3.06%, P=0.885). Additionally, simulations involving alternating US and non-contrast MRI at 6-month intervals showed a significant improvement in sensitivity for HCC detection compared with biannual US alone (83.9% vs. 45.2%, P=0.006). These findings suggest that non-contrast MRI could serve as an effective alternative surveillance strategy, particularly for high-risk patients, either as a standalone modality or in combination with US. Several prospective studies (NCT05657249,

Table 2. Summary of alternative imaging modalities for HCC surveillance

Imaging modality	Key sequence to detect HCC	Merits	Consideration
Contrast enhanced multiphasic liver CT	Arterial phase imaging	Short scan time with high spatial resolution Enabling confirmative diagnosis	Radiation exposure Contrast related risk
Full sequence MRI with gadoxetic acid	Hepatobiliary phase imaging	Provides highest sensitivity to detect HCC Enabling confirmative diagnosis No radiation exposure	Long scan times Highest cost Contrast related risk
AMRI with gadoxetic acid	Hepatobiliary phase imaging	Shorter scan time than full MRI No radiation exposure	Necessity of recall exam Contrast related risk
DCE-AMRI	Arterial phase imaging	Shorter scan time than full MRI Enabling confirmative diagnosis No radiation exposure	Contrast related risk
Non-contrast MRI	Diffusion weighted imaging	Shorter scan time than full or other AMRI No radiation exposure No contrast related risk	Necessity of recall exam
Perfluorobutane-enhanced US	Kupffer phase imaging	No radiation exposure Enabling confirmative diagnosis Reduce the false referral of B-mode US	Inherent limitations of B-mode US including poor sonic window

HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; AMRI, abbreviated MRI; DCE-AMRI, dynamic contrast-enhanced abbreviated MRI; US, ultrasound.

NCT04455932, NCT05429190, and NCT05716620) are currently underway to clarify the clinical role of non-contrast MRI in HCC surveillance.

Although non-contrast MRI has shown promise as a surveillance tool for HCC, several important considerations must be addressed before its application in clinical practice. The performance of non-contrast MRI in detecting HCC relies heavily on DWI, which is susceptible to artifacts, making the acquisition of high-quality DWI images essential. Additionally, not all HCCs exhibit diffusion restriction, and small, well-differentiated early HCCs may lack this feature, potentially limiting the sensitivity of non-contrast MRI for HCC detection. In some cases, well-differentiated early HCCs may contain an intratumoral fat component, resulting in a signal drop on opposed-phase imaging compared with in-phase imaging on dual-echo T1-weighted sequences. Therefore, dual-echo T1-weighted imaging can serve as a complementary tool to DWI to enhance HCC detection.

CONSIDERATIONS IN CHOOSING IMAGING MODALITY FOR HCC SURVEILLANCE

While designing effective surveillance programs for HCC, it is crucial to consider not only the detection performance of various imaging modalities but also their accessibility and cost-effectiveness. The cost-effectiveness of a surveillance program is influenced by several factors, including the cost of diagnostic tests, diagnostic performance, incidence of HCC in the target population, and survival benefits achieved through early treatment.[57-59] As the diagnostic yield of surveillance tests can vary across patient groups with different levels of HCC risk, tailoring surveillance programs based on risk stratification is a reasonable approach. Previous studies have shown that risk-stratified HCC surveillance strategies using MRI for high- and intermediate-risk patients with cirrhosis are more cost-effective than the current non-stratified biannual US approach for all cirrhotic patients.[60,61] Further prospective studies are required to better define the appropriate target population for alternative surveillance modalities, including contrast-enhanced CT, full-sequence MRI with gadoxetic acid, and various AMRI protocols.

In terms of the detection performance, most prospective studies comparing alternative imaging modalities such as contrast-enhanced multiphasic liver CT or MRI with biannual US have demonstrated that these alternatives have a significantly higher sensitivity for HCC detection (Table 1). However, these findings warrant careful interpretation. Most studies have focused

on high-risk patients with an annual HCC development exceeding 5%, limiting the generalizability of the results to broader surveillance populations. Furthermore, most studies were designed as intra-individual comparisons of two surveillance modalities rather than as randomized controlled trials, which provide the highest level of evidence. Another important consideration is the primary outcome of these studies. Most studies have focused on the sensitivity of HCC detection rather than overall survival, which is the ultimate goal of surveillance. This introduces the possibility of lead-time bias, in which earlier detection may not necessarily translate into improved survival outcomes. Therefore, although alternative imaging modalities may offer superior sensitivity, their actual impact on overall survival remains uncertain and requires further investigation through well-designed randomized controlled trials. Furthermore, cost-effectiveness analyses comparing alternative surveillance methods with US-based surveillance are necessary to determine the most suitable approach for specific target populations.

CONCLUSIONS

Given the high burden of HCC and its well-defined risk factors, the proper implementation of surveillance programs is essential for improving overall survival. Following the success of the first randomized controlled trial, biannual US has been established as the standard imaging modality for HCC surveillance despite its inherent limitations. The US LI-RADS algorithm was introduced to address the subjectivity of US examinations, offering a standardized assessment tool for examination quality and follow-up recommendations. Contrast-enhanced multiphasic liver CT shows significantly higher sensitivity than US for detecting very early-stage HCC in high-risk patients. However, concerns regarding radiation exposure and use of iodinated contrast media remain. Recent advancements, such as deep-learning-based reconstruction, have helped to mitigate these risks by reducing radiation doses and amount of iodinated contrast media required for CT imaging while maintaining the image quality and detection performance. MRI shows excellent performance in detecting small HCC lesions, with both full-sequence MRI using gadoxetic acid and non-contrast MRI demonstrating significantly higher sensitivity for detecting very early-stage HCC in high-risk patients compared to US. Nevertheless, the high cost and limited accessibility of MRI remain significant barriers to its widespread use. Each imaging modality currently employed for HCC surveillance has distinct advantages and limitations (Table 2). The diagnostic yield and cost-effectiveness of a particular modality may vary depending on the patients' risk of developing HCC. Therefore, it is crucial to tailor surveillance programs based on individual risk profiles. Additionally, potential risks associated with each modality and the availability of medical resources should be considered while designing HCC surveillance programs to maximize their effectiveness and equity.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethics Statement

This review article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, IBR approval is not necessary.

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Data Availability

Not applicable.

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