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The evolving role of contrast-enhanced ultrasound in hepatocellular carcinoma: from diagnosis to therapeutic monitoring

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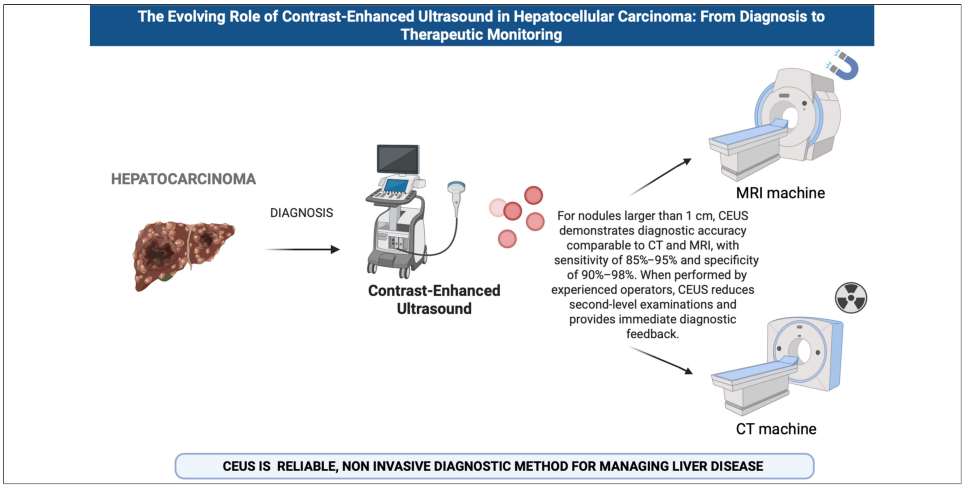

Abstract

Hepatocellular carcinoma (HCC) remains a significant global health issue, linked to chronic liver diseases such as viral hepatitis, cirrhosis, and metabolic dysfunction-related steatohepatitis. Early, accurate diagnosis is vital for treatment, but many cases are diagnosed at advanced stage. Contrast-enhanced ultrasound (CEUS) is a valuable, radiation-free tool for real-time liver lesion assessment with high accuracy. This review examines the growing role of ultrasound and CEUS in diagnosing, monitoring, and post-treatment care of HCC. CEUS has sensitivity and specificity similar to computed tomography and magnetic resonance imaging, especially for nodules ≥ 1 cm, and helps clarify uncertain Liver Imaging Reporting and Data System findings. Dynamic CEUS improves diagnosis by allowing microvascular perfusion measurement. Artificial intelligence (AI) and machine learning integration promises automated lesion classification and better consistency. CEUS is especially useful in outpatient and resource-limited settings, enabling quick decision-making and reducing delays. Meta-analyses and studies support CEUS for initial detection and post-treatment follow-up. As advanced ultrasound becomes more accessible, CEUS can be more widely used in hepatology. Future steps

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include standard protocols, clinician training, and AI integration. Overall, CEUS complements other imaging methods and aids precision medicine in liver cancer management.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and one of the leading causes of cancer-related mortality worldwide. According to the Global Cancer Statistics (GLOBOCAN) 2020 report, HCC ranks sixth in incidence among all malignant tumors and third in cancer-related deaths, with over 900,000 new cases and more than 800,000 deaths estimated each year[1]. The geographic distribution of the disease is heterogeneous, with significantly higher prevalence in East Asian countries and sub-Saharan Africa, where chronic hepatitis B virus infection is highly endemic. In Western countries, the leading cause is chronic hepatitis C virus infection, followed by metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH), excessive alcohol consumption, and other causes of chronic liver disease leading to cirrhosis. Liver cirrhosis is considered the most critical risk factor for HCC development, present in approximately 80%-90% of patients at diagnosis. However, recent studies have shown a progressive increase in the incidence of HCC even in non-cirrhotic livers, particularly in patients with advanced MASH or significant fibrosis, especially those with metabolic syndrome, type 2 diabetes mellitus, and obesity, as shown in Figure 1[2]. Early diagnosis of HCC is crucial for improving prognosis and expanding curative treatment options. When detected at an early stage, HCC can be successfully treated with surgical resection, liver transplantation, or locoregional ablation (radiofrequency or microwave), achieving 5-year survival rates above 70%. However, most patients are diagnosed at an advanced stage, when therapeutic options are limited and survival is significantly reduced[3,4]. For this reason, the international guidelines recommend regular surveillance programs for patients at risk, particularly those with cirrhosis or advanced fibrosis. In this setting, noninvasive liver imaging, particularly conventional ultrasound and contrast-enhanced ultrasound (CEUS), plays a central role in screening, diagnosing, and monitoring suspicious liver nodules[3-5]. CEUS, through the use of intravascular, non-nephrotoxic microbubbles, enables real-time evaluation of hepatic vascular perfusion, allowing for high diagnostic accuracy in lesion characterization and in identifying the typical vascular pattern of HCC. Recent studies have demonstrated that CEUS is comparable to computed tomography (CT) and magnetic resonance imaging (MRI) in terms of sensitivity and specificity, especially for nodules < 2 cm[6-8]. This narrative review aims to comprehensively examine the role of conventional ultrasound and CEUS in the diagnosis and surveillance of HCC, highlighting their strengths, limitations, and integration into clinical practice.

ULTRASOUND: FROM PHYSICAL PRINCIPLES TO CLINICAL APPLICATION

Brightness mode (B-mode) ultrasonography is the fundamental modality for morphological evaluation of the liver. It operates through high-frequency ultrasound waves (> 2 MHz), which are reflected to varying degrees depending on the acoustic impedance of the tissues. The resulting echoes are processed in real time to generate two-dimensional grayscale images that delineate hepatic parenchymal structures[9-11]. The examination is typically performed using a convex probe (3.5-5 MHz) placed on the patient's upper abdomen in a supine or lateral decubitus position. Proper patient preparation, including fasting for at least 6 h, is essential to minimize interference from intestinal gas[11]. Color Doppler is an ultrasound technique that displays blood flow using color coding, allowing assessment of flow direction and velocity within hepatic vessels. It is essential for evaluating vascular patency and hemodynamic changes, although it provides limited information for lesion characterization. CEUS uses intravenously injected microbubbles to visualize blood flow within liver lesions in real time, helping to characterize nodules based on their vascular behavior. Its main limitation is the restricted field of view and reduced performance in difficult acoustic conditions. Despite its high sensitivity for real-time microvascular characterization of focal liver lesions, CEUS remains subject to important technical and anatomical limitations. Lesions located deep within the liver parenchyma

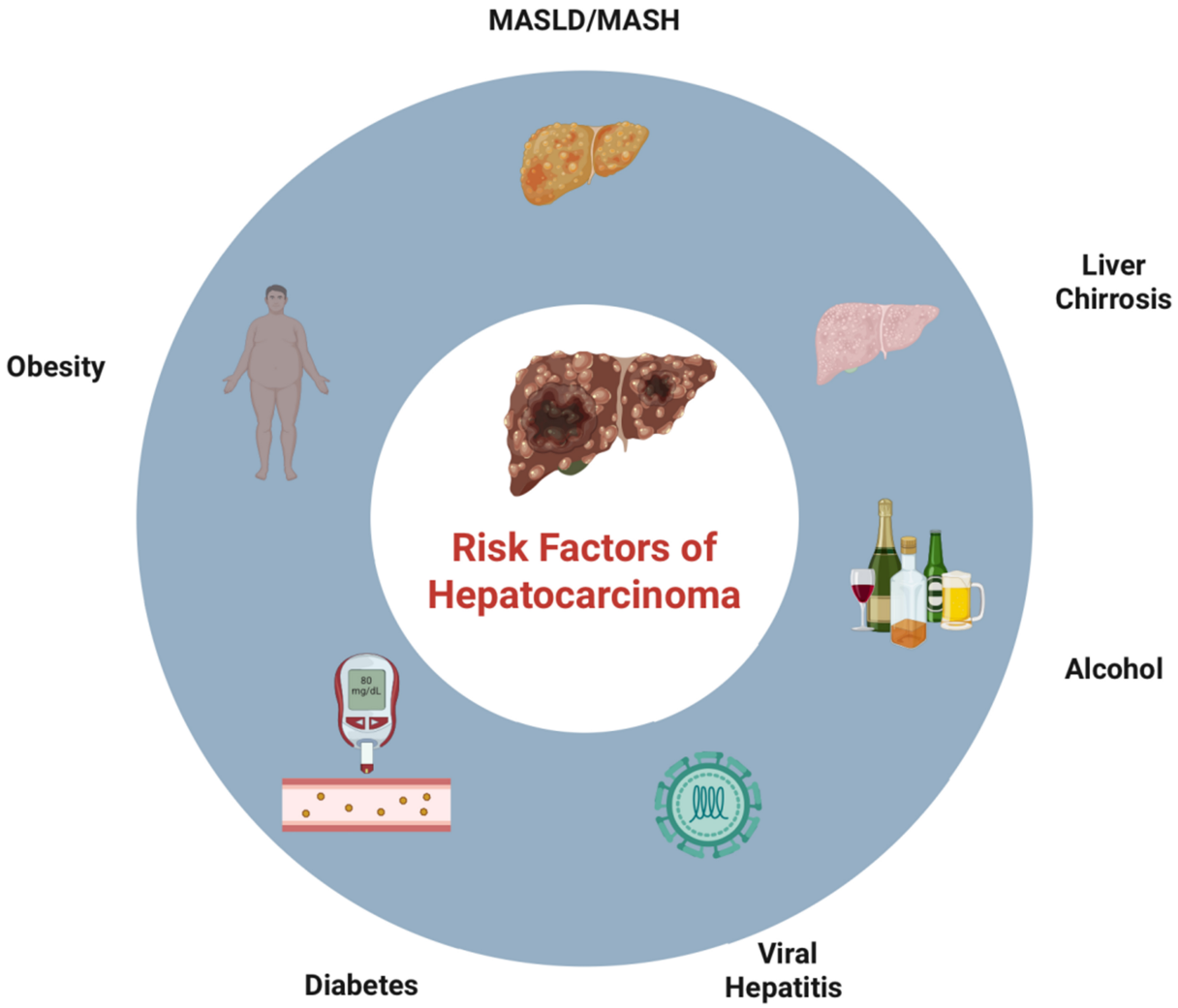

Figure 1. Visual description of HCC-associated risk factors. Created in BioRender. https://BioRender.com/onozqd8. MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; HCC: hepatocellular carcinoma.

may be incompletely visualized due to acoustic attenuation, particularly in obese patients, resulting in suboptimal contrast signal and reduced diagnostic confidence. Similarly, multifocal disease may be underestimated, as CEUS is inherently limited to the insonated field of view and does not provide whole-liver coverage comparable to CT or MRI. In addition, bowel gas and rib shadowing can obscure portions of the liver, precluding adequate assessment of lesion enhancement patterns. Consequently, while CEUS is highly effective for targeted lesion characterization, cross-sectional imaging with CT or MRI remains essential for comprehensive liver evaluation, staging, and detection of multifocal or extrahepatic disease. For example, a patient with cirrhosis underwent CEUS for evaluation of a suspected focal liver lesion detected on surveillance ultrasound. The lesion was located deep in the right hepatic lobe and was partially obscured by bowel gas, resulting in suboptimal visualization of arterial enhancement and inconclusive washout assessment. Moreover, CEUS evaluation was limited to the targeted lesion and did not allow reliable exclusion of additional small nodules elsewhere in the liver. Subsequent contrast-enhanced MRI demonstrated multifocal HCC with portal vein involvement, leading to disease upstaging and a change in clinical management[12]. To enhance the diagnostic sensitivity of abdominal ultrasound, color and power Doppler techniques are employed. These assess the frequency shift of ultrasound waves caused by the movement of red blood cells, allowing visualization of the direction, velocity, and quality of blood flow within intrahepatic and extrahepatic vessels[13]. This technique is crucial for evaluating portal vein patency

and identifying abnormalities such as flow reversal or decreased flow velocity, which are common in portal vein thrombosis or portal hypertension. Assessment of the hepatic artery may reveal compensatory hyperflow, stenosis, or turbulent signals, findings typically associated with post-transplant complications or infiltrative liver diseases[14]. Doppler ultrasound also evaluates hepatic veins, where absent or reversed flow may indicate advanced cirrhosis, hepatopulmonary syndrome, or Budd-Chiari syndrome[15]. Color and power Doppler can detect intrahepatic arterio-venous shunts and atypical vascular patterns in focal liver lesions, features that are important in differentiating benign from malignant nodules. In HCC, Doppler may reveal centripetal or peripheral flow, chaotic vascularization, and pulsatile signals[16]. Nonetheless, these techniques share the limitations of B-mode ultrasonography, with reduced sensitivity in detecting small lesions and in MASLD[17]. In the gastroenterology field, hepatic ultrasound is the first-line imaging tool for assessing the liver and biliary tract. It plays a pivotal role in the follow-up of chronic liver disease, particularly for HCC screening, and in the evaluation of focal liver lesions (such as cysts, hemangiomas, and dysplastic nodules) in patients without known liver disease. Furthermore, it is instrumental in monitoring complications such as ascites, portal vein thrombosis, and portal hypertension[18]. Its wide availability in both inpatient and outpatient settings makes it an indispensable diagnostic tool. The development of portable ultrasound devices and the integration of advanced technologies, such as CEUS, elastography, and fusion imaging, have further strengthened its clinical utility[19].

CLINICAL APPLICATIONS OF CEUS

CEUS utilizes intravascular microbubbles composed of gas, such as sulfur hexafluoride in Sonovue or perfluorobutane in Sonazoid, encapsulated within lipid or protein shells. These microbubbles, with a diameter between 1 and 4 micrometers, are too large to extravasate into the interstitial space and therefore remain confined within the bloodstream. When insonated, they oscillate and emit nonlinear harmonic signals, which can be detected in real time, enabling high sensitivity in the assessment of microvascular perfusion[20]. Sonovue acts solely as a blood-pool agent, allowing for the visualization of the conventional arterial, portal, and late vascular phases. In contrast, Sonazoid also enables imaging during the Kupffer phase, which occurs between 10 and 30 min after injection. This phase reflects the activity of liver-resident macrophages (Kupffer cells) and proves especially useful for identifying lesions that lack such cells, including HCC and metastases[21]. Comparative studies have shown that both contrast agents offer similar sensitivity, approximately 80%, and extremely high specificity, reaching 100%, in the diagnosis of HCC. While the Kupffer phase provides additional diagnostic information, it does not appear to increase sensitivity significantly[22]. The CEUS examination consists of multiple phases. The arterial phase, which occurs within the first 10-30 s after contrast administration, is characterized by rapid tumor enhancement, known as arterial phase hyperenhancement (APHE). This typically appears as a strong, early hyperintensity of the lesion relative to the surrounding liver parenchyma, a hallmark feature of HCC[23,24]. During the portal venous phase (30-120 s), the hepatic parenchyma enhances more intensely, while malignant lesions often become iso- or hypoenhancing, displaying earlier washout compared to healthy liver tissue[22]. This is followed by the late phase (beyond 120 s), during which washout becomes more pronounced. A delayed and mild washout is characteristic of HCC and is observed in over 95% of cases that initially exhibit APHE[25]. With Sonazoid, it is also possible to perform imaging during the Kupffer phase, typically 10-15 min after contrast injection. During this phase, normal liver tissue retains the microbubbles due to the presence of Kupffer cells and appears uniformly echogenic. In contrast, lesions lacking Kupffer cells remain hypoenhancing, creating a so-called "Kupffer defect"[24]. Together, these phases reflect both the tumor's vascular architecture and the functional integrity of the hepatic macrophage system. APHE combined with delayed washout remains a key diagnostic criterion for HCC[25]. To facilitate standardized interpretation, the CEUS Liver Imaging Reporting and Data System (LI-RADS), developed by the American College of Radiology, provides a classification framework for hepatic lesions in at-risk patients, ranging from LR-1 (definitely benign) to LR-5 (definitely HCC). This system is based on enhancement and washout patterns

Table 1. Typical imaging findings of common hepatic nodules across B-mode ultrasound, CEUS, and CT/MRI

Lesion	B-mode ultrasound (typical)	CEUS (typical enhancement pattern)	CT/MRI (typical dynamic pattern)	Key clue(s) for differentiation
HCC	Variable echogenicity; may be hypo/iso/hyperechoic; may show mosaic/heterogeneity	Non-rim APHE followed by late, mild washout; with Sonazoid: Kupffer-phase defect	Arterial hyperenhancement + washout (portal/delayed) ± enhancing capsule; ancillary features may support diagnosis	Washout late and mild is typical for HCC in at-risk patients (CEUS LI-RADS concept)
Hemangioma	Often well-defined, hyperechoic (may be heterogeneous if large)	Peripheral, discontinuous nodular enhancement in arterial phase with progressive centripetal fill-in; usually no washout (persistent enhancement)	Peripheral nodular discontinuous enhancement with progressive fill-in on delayed phases	"Peripheral nodular + fill-in" is the classic hallmark
FNH	Often iso/hypoechoic; may show central scar (not always visible)	Rapid, intense arterial hyperenhancement often with centrifugal spoke-wheel pattern; iso/hyperenhancement in portal and late phases (no washout)	Strong arterial enhancement; typically iso in portal/delayed; central scar may enhance late (MRI)	No washout + spoke-wheel arterial pattern strongly suggests FNH
HCA	Variable; may be heterogeneous; may show intralesional fat/hemorrhage signs	Usually arterial hyperenhancement, often heterogeneous; portal/late phase isoenhancement is common; washout may occur in a minority (pitfall)	Arterial hyperenhancement; variable portal/delayed behavior; MRI may show fat/hemorrhage depending on subtype	Clinical context (young women, hormones) + variable imaging; can overlap with HCC → consider MRI/subtyping when needed
iCCA	Often hypoechoic/heterogeneous; may be ill-defined	Frequently rim APHE with early and/or marked washout (LR-M pattern)	Peripheral/rim arterial enhancement with progressive delayed enhancement; capsular retraction may be present	Rim APHE + early/marked washout favors non-HCC malignancy
Metastases	Often multiple; target/bull's-eye appearance may be seen	Commonly rim APHE and early, marked washout	Variable; often peripheral enhancement; diffusion restriction on MRI	Variable; often peripheral enhancement; diffusion

CEUS: Contrast-enhanced ultrasound; APHE: arterial phase hyperenhancement; CT: computed tomography; MRI: magnetic resonance imaging; FNH: focal nodular hyperplasia; HCA: hepatocellular adenoma; iCCA: intrahepatic cholangiocarcinoma; HCC: hepatocellular carcinoma; LI-RADS: Liver Imaging Reporting and Data System; B-mode: brightness mode.

observed during CEUS[26]. For LR-5 lesions, diagnostic specificity can reach 95%-100%, with interobserver agreement exceeding 90% in experienced centers. Currently, the integration of the Kupffer phase into LI-RADS is under investigation, as the official criteria apply exclusively to blood-pool agents, such as Sonovue[22,27-32]. Table 1 shows the typical imaging findings of common hepatic nodules. CEUS plays a valuable role in the management of HCC during both radiofrequency ablation (RFA) and surgical resection. In the periprocedural setting, CEUS improves lesion conspicuity and targeting, particularly for small or iso-echoic HCC nodules that are poorly visible on B-mode ultrasound, thereby facilitating accurate needle placement during RFA. Immediately after ablation, CEUS allows real-time assessment of treatment efficacy by demonstrating the absence of intralesional enhancement and enabling prompt detection of residual viable tumor, which may be retreated during the same session. In surgical resection, intraoperative CEUS enhances detection of additional small lesions and refines margin assessment, contributing to more accurate surgical planning. However, CEUS does not replace CT or MRI for preoperative staging or postoperative surveillance, which remain essential for comprehensive evaluation of disease extent and recurrence[33].

COMPARATIVE EVALUATION OF CEUS *VS.* CT AND MRI

Advantages of CEUS include an excellent safety profile (absence of ionizing radiation, nephrotoxicity, or systemic reactions to the contrast agent), the capability for real-time imaging, cost-effectiveness, and portability, features particularly beneficial in patients with fragile health or those hospitalized. Furthermore, CEUS is repeatable and can be utilized to guide or monitor locoregional treatments[27,34-36]. Among its limitations are a narrow field of view, operator dependence, suboptimal performance in obese patients or

Table 2. Summary of recent meta-analyses on CEUS

Reference	Sample size	Number of studies	Aim	Sensitivity	Specificity
Zhang *et al*. (2023)[52]	1,434	9	Evaluation of CEUS for early diagnosis of HCC	0.92	0.93
Wang *et al*. (2023)[54]	831	5	Diagnostic performance of CEUS LI-RADS algorithms for HCC	0.79 for LI-RADS 5 0.86 for LI-RADS 4/5	0.81 for LI-RADS 5 0.70 for LI-RADS 4/5
Zhang *et al*. (2017)[56]	More than 4,827 patients (the numbers of patients were not mentioned in two studies	53	Evaluation of CEUS for diagnosis of HCC	0.85	0.91

CEUS: Contrast-enhanced ultrasound; HCC: hepatocellular carcinoma; LI-RADS: Liver Imaging Reporting and Data System.

those with deep or gas-masked lesions, and challenges in assessing multifocal disease. Efforts are ongoing to standardize the technique, particularly with the introduction of novel agents, such as Sonazoid, which enables imaging during the macrophage phase[36-39]. For nodules larger than 1 cm, CEUS has demonstrated diagnostic accuracy comparable to CT and MRI, with sensitivity ranging from 85%-95% and specificity between 90%-98%. In some instances, CEUS can clarify indeterminate MRI findings (LI-RADS 3/4), particularly when Kupffer phase imaging is employed[28,40-45]. Because CEUS contrast agents remain strictly intravascular, this modality provides superior visualization of the vascular architecture of focal liver lesions compared to CT and MRI, proving especially useful for characterizing indeterminate nodules[46-48]. When performed by experienced operators, CEUS can reduce the need for second-level examinations, thereby lowering costs and providing immediate diagnostic feedback[49,50]. It is particularly advantageous for patients with anxiety or claustrophobia towards tomographic imaging techniques[51-52]. Recent literature supports the role of CEUS in hepatology practice. In this regard, a recent meta-analysis of nine studies and 1,434 patients reported sensitivity of 92% and specificity of 93%, with an area under the curve(AUC) of 0.95 and a diagnostic odds ratio (DOR) > 150, underscoring the impact of technological advancements and operator experience on diagnostic performance[53]. Direct comparative studies have shown that, for hepatic lesions ≥ 1 cm, CEUS sensitivity for detecting APHE is comparable to or superior to that of MRI. Specificity is also high, ranging from 90% to 98%, consistent with values reported for CT and MRI[54,55]. Limitations of CEUS include a lower diagnostic yield for deep, multifocal, or anatomically challenging-to-visualize lesions, particularly in contexts where tomographic imaging provides a broader overview and is less operator-dependent. Nevertheless, CEUS remains a valid, noninvasive, and real-time imaging option for characterizing hepatic lesions[56]. Recently, the use of CEUS in follow-up after locoregional treatments [e.g., transarterial chemoembolization (TACE) or percutaneous ablation] was analyzed, demonstrating 85% sensitivity and 94% specificity, confirming its efficacy in early detection of tumor recurrence or persistence[57]. A summary of recent meta-analyses on CEUS is shown in Table 2.

Overall, these data confirm CEUS as a reliable, safe, and highly performant technique, effective for both initial diagnosis and post-treatment surveillance, with performance comparable, and in some aspects superior, to CT and MRI[54]. CEUS is particularly advantageous for patients contraindicated for contrast-enhanced CT or MRI, such as those with chronic or advanced renal disease or known allergies to iodine or gadolinium. It is important to emphasize that CEUS contrast agents are not nephrotoxic and do not carry a risk of nephrogenic systemic fibrosis. According to the 2020 guidelines of the World Federation for Ultrasound in Medicine and Biology, CEUS is recommended as a first-line modality in patients with renal insufficiency and focal liver lesions, regardless of cirrhosis status. In cirrhotic patients, CEUS can be used for initial diagnosis, whereas CT/MRI are indicated for comprehensive staging when feasible[58]. Indeed, CEUS contrast agents contain neither iodine nor gadolinium; they consist of inert gas microbubbles stabilized by phospholipid or protein shells, exhibiting an excellent safety profile with severe adverse

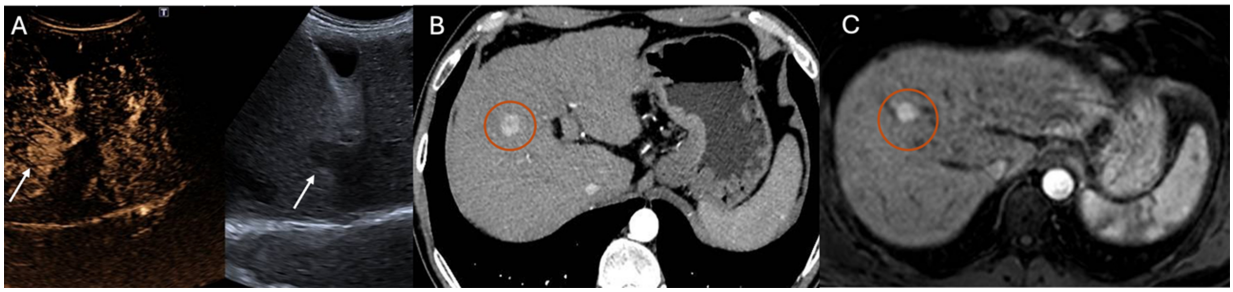

Figure 2. Detection of HCC using CEUS after contrast agent administration (SonoVue®) (A), arterial-phase CT (B), and arterial-phase MRI (C). Arrows in (A) indicate the HCC lesion, while circles in (B and C) highlight the tumor area identified on cross-sectional imaging. HCC: Hepatocellular carcinoma; CEUS: contrast-enhanced ultrasound; CT: computed tomography; MRI: magnetic resonance imaging.

Table 3. Comparative summary of advantages, limitations, and preferred use of CEUS, CT, and MRI in the diagnostic pathway

Modality	Key advantages	Key limitations	Preferred clinical use
CEUS	No ionizing radiation; excellent safety profile; non-nephrotoxic contrast agent; real-time assessment; portable and cost-effective; repeatable; useful to guide/monitor locoregional treatments	Limited field of view; operator dependence; reduced performance in obesity or deep/gas-masked lesions; limited assessment of multifocal disease and extrahepatic spread (whole-liver staging not feasible)	First-line problem-solving for targeted characterization of a known lesion (especially in patients unsuitable for iodinated/gadolinium contrast); outpatient/point-of-care characterization; early post-treatment assessment of residual/recurrent disease
CT (multiphase)	Whole-liver coverage; fast acquisition; widely available; less operator-dependent; suitable for global assessment and staging	Ionizing radiation; iodinated contrast-related risks (allergy/ nephrotoxicity); less suitable for repeated follow-up in some patients	Comprehensive staging (whole liver, vascular invasion, extrahepatic disease) and second-line when CEUS is inconclusive or technically limited
MRI (dynamic contrast-enhanced)	No ionizing radiation; high soft-tissue contrast; multiparametric evaluation; strong overall performance for characterization and staging	Longer acquisition time; limited availability/cost; contraindications in some patients; patient intolerance/claustrophobia; gadolinium-related concerns in severe renal impairment	Second-line characterization of indeterminate lesions and staging when feasible; preferred when a broader, multiparametric assessment is required

CEUS: Contrast-enhanced ultrasound; CT: computed tomography; MRI: magnetic resonance imaging.

reactions occurring in less than 0.01% of cases. In this way, recent studies conducted in high-risk populations have confirmed that CEUS can be performed safely without the need for premedication or precautionary measures[59]. In patients with renal insufficiency, Sonazoid (perflubutane-based) has demonstrated an excellent safety profile, with no requirement for renal function screening. Furthermore, no increase in adverse events even in renally impaired patients, without the need for hydration or preventive interventions[60]. The ease of use in outpatient and non-radiological settings makes CEUS a practical and versatile imaging modality [Figure 2][59]. It is important to mention that in patients with HCC, Real-time Virtual Sonography (RVS) with CT or MRI fusion imaging can improve detection and targeting of lesions that are poorly visible on conventional ultrasound or CEUS alone, particularly when lesions are small, deeply located, or obscured by bowel gas. By synchronizing real-time ultrasound with previously acquired cross-sectional images, RVS facilitates accurate localization and characterization of known HCC nodules and supports CEUS assessment and image-guided interventions. Nevertheless, RVS remains dependent on an adequate acoustic window and does not allow whole-liver evaluation or reliable detection of additional lesions, vascular invasion, or extrahepatic spread; therefore, CT or MRI remains essential for comprehensive HCC staging and treatment planning[60]. Table 3 shows a comparative summary of advantages, limitations, and preferred use of CEUS, CT, and MRI in the diagnostic pathway [Table 3].

CLINICAL CONSIDERATIONS AND FUTURE PERSPECTIVES

The use of CEUS significantly impacts clinical practice, particularly when prompt therapeutic decisions are required. It enables the real-time characterization of liver lesions, providing immediate access to treatment options, streamlining the diagnostic process, and reducing reliance on more invasive or expensive tests. In multidisciplinary teams, CEUS is a helpful tool for guiding management, assisting in deciding between surgery, ablation, or active surveillance[36]. The growing availability of advanced ultrasound machines in hepatology clinics enables the direct incorporation of CEUS into outpatient visits. This approach enables quick, point-of-care diagnoses, enhances patient adherence to follow-up, and reduces referrals to radiology or hospitals for further tests[61-63]. Additionally, CEUS in remote or resource-limited centers broadens diagnostic access across larger areas. Successful implementation in outpatient settings requires proper training for medical staff and logistical planning for contrast agent supplies. Despite these challenges, the clinical and organizational advantages, such as increased efficiency and patient-centered care, make CEUS a crucial part of liver disease diagnosis[64-67]. Recent advances include the integration of artificial intelligence (AI) into CEUS, offering new diagnostic and treatment insights. With the increasing use of immune checkpoint inhibitors in the treatment of HCC, there is growing interest in imaging biomarkers capable of capturing early and dynamic treatment responses. CEUS, through real-time evaluation of tumor microvascular perfusion, may provide complementary information to conventional size-based criteria by detecting early changes in intratumoral enhancement that reflect immune-mediated vascular remodeling or necrosis. This may be particularly relevant in the context of immunotherapy, where atypical response patterns such as pseudoprogression or delayed responses can limit the accuracy of CT- or MRI-based assessments alone. Although current evidence remains limited and CEUS is not yet incorporated into standardized response criteria for immunotherapy, preliminary data suggest that CEUS-derived perfusion parameters could contribute to early response monitoring and treatment adaptation. Further prospective studies are needed to validate the role of CEUS as an adjunct imaging tool for immunotherapy response assessment in HCC[68]. AI holds promise for automating the analysis of enhancement patterns, aiding in the classification of liver nodules, and predicting treatment outcomes. These technologies help reduce variability between observers and standardize interpretations across operators. Machine learning models trained on large CEUS datasets can identify features of malignant lesions, boosting sensitivity and accuracy beyond traditional visual assessment[69,70]. Furthermore, dynamic CEUS (D-CEUS), combined with advanced software, enables the objective measurement of microvascular blood flow, providing clinicians with more precise data for personalized cancer monitoring[68]. Based on current research, an integrated diagnostic approach can be suggested for managing liver nodules in cirrhotic patients. When a suspicious lesion ≥ 1 cm is found, initial assessment should include B-mode ultrasound combined with CEUS. If CEUS shows a typical pattern, APHE followed by washout, HCC can be diagnosed, and the lesion classified as LI-RADS 5[36]. In cases with atypical vascular features, further evaluation with MRI or CT is recommended. For indeterminate nodules (LI-RADS 3 or 4), D-CEUS offers detailed perfusion analysis[33]. If uncertainty persists, a biopsy may be necessary to obtain a definitive diagnosis. Post-treatment, early CEUS and follow-up D-CEUS at one month are advised to evaluate treatment response and detect residual or recurrent disease. These protocols, supported by multicenter studies and expert hepatology groups, have proven to improve diagnostic accuracy and resource management[50]. Future perspectives and validated clinical applications of CEUS are summarized in Table 4.

CONCLUSIONS

HCC is a major challenge in hepatology, with rising incidence and associations with chronic liver conditions. Ultrasound imaging, particularly B-mode ultrasound, is crucial for diagnosis, surveillance, and monitoring, although it is limited in detecting small or deep lesions[70]. CEUS is increasingly used as a second-line tool due to real-time vascular assessment, no ionizing radiation, and safety in renal impairment. Studies show

Table 4. Validated clinical applications and future perspectives in the clinical application of CEUS

Category	Item	Descriptions	Expected impact	References
Already validated/currently applied	Integration of CEUS in outpatient hepatology clinics	Routine use of CEUS during outpatient diagnostic practice for real-time characterization of liver lesions	Rapid diagnosis, improved follow-up adherence, reduced need for radiological referrals	[36,61,63]
Already validated/currently applied	Integrated diagnostic algorithms	Structured approach using B-mode ultrasound, CEUS, D-CEUS, MRI/CT, and biopsy	Improved accuracy in HCC diagnosis and treatment stratification	[33,36,50]
Already validated/currently applied	Post-treatment CEUS surveillance	Early CEUS and 1-month D-CEUS to assess therapy response	Early detection of residual or recurrent disease	[50]
Future perspective	Use of CEUS in remote and resource-limited settings	Deployment of CEUS where access to CT/MRI is limited	Expanded diagnostic access and equity in care delivery	[61-63]
Future perspective	Staff training and logistical support	Training clinicians and ensuring contrast agent availability in outpatient settings	Essential for safe, effective CEUS implementation in decentralized settings	[64-67]
Future perspective	AI integration	Application of AI algorithms to better evaluate CEUS patterns	Standardization, reduced interobserver variability, improved diagnostic accuracy	[68,69]
Future perspective	Machine learning for predictive modeling	Development of machine learning models based on large CEUS datasets	Enhanced lesion classification and outcome prediction	[68,69]
Future perspective	D-CEUS with perfusion quantification	Use of software-assisted D-CEUS to measure microvascular flow	Personalized monitoring of tumor response and recurrence	[68]

CEUS: Contrast-enhanced ultrasound; D-CEUS: dynamic contrast-enhanced ultrasound; AI: artificial intelligence; MRI: magnetic resonance imaging; CT: computed tomography; HCC: hepatocellular carcinoma; B-mode: brightness mode.

that the sensitivity and specificity of CEUS are comparable or superior to CT and MRI, making it reliable for diagnosing and characterizing HCC and other liver lesions. Integrating CEUS speeds up patient stratification and decision-making, improving management. It is also valuable for early post-treatment monitoring of therapies such as ablation and TACE, detecting residual tumor or progression. D-CEUS provides quantitative microvascular perfusion data, adding functional insights[71]. AI technologies promise further advancements by enabling automated interpretation and reducing variability. These tools position CEUS as a vital part of liver oncology and precision medicine. This review emphasizes CEUS as both a complement to cross-sectional imaging and a standalone tool, especially for indeterminate nodules, improving LI-RADS classification and guiding therapy, potentially reducing invasive procedures. Broader CEUS use in hepatology, with training and standardized protocols, can enhance early HCC diagnosis and healthcare outcomes, especially in resource-limited centers.

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Authors' contributions

Conceptualized and designed the review: Abenavoli L, Laganà D
Wrote, reviewed, and edited the manuscript: Gambardella ML, Passante E, La Torre G
Provided figures and tables: Passante E, Battaglia C
Reviewed and approved the final manuscript as submitted: Manti F, Console D
Read and approved the final manuscript: Abenavoli L, Luzza F, Laganà D

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