Original Article

Using multimodal ultrasound technology to improve the success rate of liver tumor puncture for lesions with poor visibility on conventional ultrasound imaging

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Background: The ability of conventional ultrasound (US)-guided liver biopsy to visualize certain liver lesions, particularly those affected by conditions like hepatitis or cirrhosis, which can obscure lesion boundaries and lead to inaccurate biopsy targeting, is limited. This study aimed to evaluate the potential of multimodal US techniques to improve the visibility of liver lesions that are indistinct under conventional US, and to enhance the success rate of percutaneous biopsies.

Methods: In total, 144 patients with liver masses and lesions that were not clearly visible on conventional US from October 2018 to January 2024 were enrolled in this retrospective analysis. The lesions of these patients exhibited poor visibility on conventional US, but the tumor location was visible on abdominal computerized tomography (CT) or magnetic resonance (MR) imaging scans. After excluding patients who did not undergo biopsy or patients with lesions that were remained not clearly visible on multimodal US examinations. Ultimately, a total of 95 patients were enrolled in this study. We analyzed the clinical and imaging data for all these patients. CT/MR-US fusion imaging was performed in 55 patients, contrast-enhanced ultrasound (CEUS) was performed in 95 patients, and high-frequency US was performed in 21 patients. The visibility of the lesions using these three techniques was evaluated, and the consistency between the biopsy pathology and the final diagnosis was analyzed.

Results: In the study, the detection rates of lesions using CT/MR-US fusion imaging, CEUS, and high-frequency US were 49.1%, 96.8%, and 76.2%, respectively. After confirming the target location of the lesions, all patients underwent percutaneous US-guided biopsy. The accuracy rate of the biopsies was 91.6%, and the positive concordance rate was 91.1%. Among the 13 patients with negative pathology findings after biopsy, 8 had false-negative results (based on follow-up laboratory tests and imaging results consistent with malignant tumor characteristics), resulting in a false-negative rate of 8.9%.

Conclusions: Multimodal US significantly improved the success of biopsies for liver lesions not clearly visible on conventional US, aiding in precise treatment planning.

Keywords: Liver tumor; fusion imaging; contrast-enhanced ultrasound (CEUS); high-frequency ultrasound; biopsy

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Introduction

With the advancement of multimodal ultrasound (US) techniques, the detection rate and diagnostic accuracy of liver nodules have significantly improved (1). Under current clinical guidelines, advanced imaging techniques, particularly multimodal US technology, play a crucial role in the diagnosis of liver nodules. Guidelines recommend that a comprehensive assessment and preliminary clinical diagnosis be made based on at least two definitive imaging modalities from the trio of contrast-enhanced computerized tomography (CT), contrast-enhanced magnetic resonance (MR) imaging, and contrast-enhanced ultrasound (CEUS) (2,3). Typically, when the lesion diameter is ≥2 cm, the accuracy of imaging diagnostics exceeds 90% (4). If definitive imaging is incongruous or fails to provide a clear diagnosis, a pathological examination (i.e., a fine-needle aspiration biopsy) may be performed to establish a definitive diagnosis as clinically necessary. Thus, histopathological and pathological examinations remain essential for the definitive diagnosis of liver nodules (5-8). Percutaneous liver biopsy guided by US is a primary method for obtaining pathological specimens, and its effectiveness and safety in clinical practice have been established (7,8).

Liver nodules can be influenced by liver conditions such as hepatitis, cirrhosis, and fatty liver, as well as factors such as lesion location, lung interference, and lesion size, which can make it challenging to visualize certain lesions or achieve satisfactory imaging results during conventional US examinations. To address this issue, technologies such as CT/MR-US fusion imaging, CEUS, and high-frequency US techniques have been applied (1). Fusion-imaging technology combines US with CT/MR images, increasing the accuracy of localization and guidance (9). CEUS uses the backscattering and non-linear effects of microbubble contrast agents to enable real-time imaging of lesions and their perfusion information (10). High-frequency US, which uses a higher-resolution linear array transducer, significantly improves image quality and facilitates the visualization and observation of lesions within the detectable range (11).

Previous studies have primarily focused on assessing the biopsy success rate using US contrast or fusion imaging alone (7,9,12,13), and relatively little research has been conducted on the biopsy success rate using a combination of multiple US techniques. Thus, this study aimed to consolidate the data of patients with non-visualized liver lesions on conventional US and, following the application of multimodal US, revisualize these lesions and conduct percutaneous liver biopsies. Specifically, the study explored the application of fusion imaging, CEUS, and high-frequency US in enhancing the visibility of liver masses and accurately locating them for percutaneous tissue biopsy. The study compared the biopsy results with the final diagnosis, and assessed whether multimodal imaging techniques improved the success rate of percutaneous liver biopsy for lesions that were not clearly visible under conventional US. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1392/rc).

Methods

Patients

In total, 144 patients with non-visualized liver masses on conventional US from Nanjing Drum Tower Hospital from October 2018 to January 2024 were enrolled in this retrospective study. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) be aged 18 years or above; (II) have liver masses confirmed by MR or CT imaging; (III) have poorly visualized liver lesions on conventional US examinations; (IV) the CT/MR findings of diffuse liver masses with unclear borders necessitate the use of multimodal US techniques for better delineation of the lesions; (V) have liver lesions visualized by CT/MR-US fusion imaging, CEUS, or high-frequency US; and (VI) meet the guidelines for liver tumor biopsy, and have no contraindications for the procedure.

A target lesion display clarity score (12) was used to classify poor visibility, such that a target lesion was classified as having poor visibility if it was not visible on conventional US, or exhibited an echogenicity similar to that of the surrounding liver tissue, and less than 50% of the lesion's edge was clear.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) continued to have non-

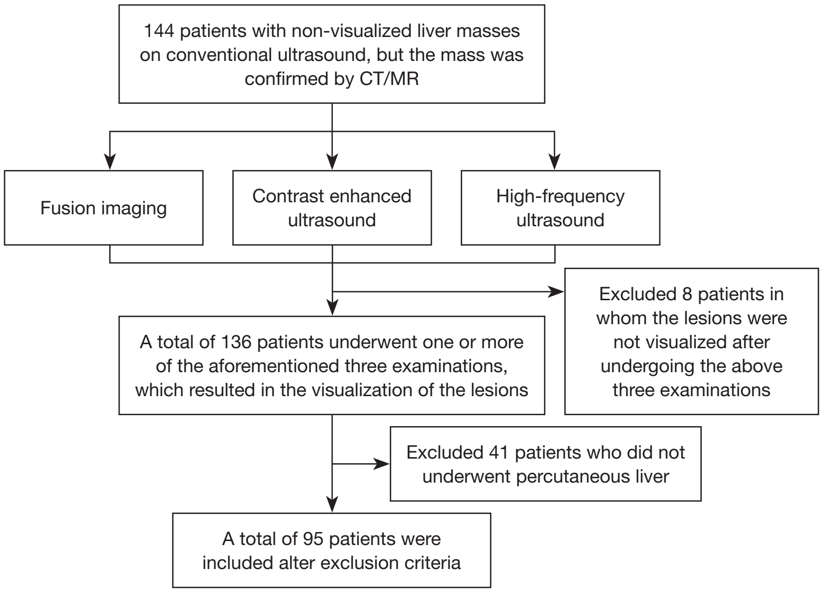

Figure 1 Patient inclusion flowchart for study. CT, computerized tomography; MR, magnetic resonance.

visualized lesions after CT/MR-US fusion imaging, CEUS, or high-frequency US; (II) after half a year of follow-up, had a high suspicion of benign lesions for which the risk of biopsy was deemed unnecessary; (III) had special liver lesions with characteristic appearances, such as hepatic hemangiomas, for which biopsy carries an unacceptable risk of complications; (IV) had been transferred to other hospitals; (V) had refused biopsy after being informed of the risks and benefits of the procedure; and/or (VI) had contraindications, such as coagulopathy, or other conditions that increased the risk of biopsy.

After excluding 8 patients with inadequately visualized or lesions that were not clearly visible on multimodal US, and 41 patients who did not undergo percutaneous liver tumor biopsy, a total of 95 patients who met the inclusion criteria were selected for inclusion in the analysis based on their clinical and radiological data (*Figure 1*).

A Kappa consistency analysis was also performed to evaluate inter-rater reliability. Two US physicians, one with over 20 years of experience, and the other with 3 years of experience, independently reviewed the conventional US images of the 95 patients to classify the visibility of the liver lesions. All patients underwent a complete blood count, liver function test, coagulation test, infectious disease test, digestive tract test, and electrocardiogram (ECG) before surgery. The patients were informed of the risks and potential complications of liver biopsy and signed informed consent forms. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of the Nanjing Drum Tower Hospital, Drum Tower Clinical Medical College, Nanjing Medical University (No. 2022-140-01).

Multimodal US assessment

Conventional US and fusion-imaging methods

The conventional examination was performed using a GE LOGIQTM E9 machine (GE Healthcare, USA) with a 1–5 MHz convex probe. The liver condition of each patient was first assessed, the presence of hepatitis or liver cirrhosis evaluated, and the adequacy of the lesion visualization determined. If the lesion was poorly visualized, the patient's CT/MR images were reviewed, and a preliminary assessment of the lesion location was performed before performing fusion imaging. The specific steps were as follows: (I) digital Imaging and Communications in Medicine-formatted CT or MR images were imported into the US machine; (II) the patient was positioned in a supine position. Single-plane registration was performed, followed by the selection of anatomical landmarks like the portal vein and hepatic vein bifurcation for point-to-point registration. After which, the CT/MR images were displayed side-by-side with the US images. Fine registration was then performed based on smaller vascular branches; and (III) the synchronized US images were then observed to detect the presence of the lesion based on the location of the lesions on the CT or MR images. The locations (left lobe, right lobe, or liver lobe junction), sizes, and numbers (single, multiple, or diffuse) of the recurrent lesions were recorded.

High-frequency US examination

A 9-MHz linear transducer was used for the high-frequency US examination. The patient adopted a supine or left lateral position. The conventional US examination was initially carried out using a convex array transducer. If the lesion was not visualized by conventional US but was closer to the hepatic capsule (≤1.5 cm) in CT/MRI, a high-frequency US examination was performed. The depth and focus were adjusted sequentially to visualize the lesion area with optimal clarity.

CEUS examination

For the CEUS examination, the patient adopted a supine or left lateral position. The optimal view was selected, and the CEUS mode was activated using a convex array transducer. US contrast agents, sulfur hexafluoride microbubbles (Sonovue) or perfluorobutane microspheres (Sonazoid), were administered at doses of 1.2 or 0.6 mL, respectively. The contrast agents were injected via peripheral venous bolus, followed by a 5-mL saline flush. The lesion was then observed in real-time dynamic mode for 2 minutes, and the images were stored. Following this, the entire liver was scanned again using the convex array transducer to check for any other lesions and to store the images. The arterial phase (10–20 seconds after contrast injection), portal venous phase (30–45 seconds after contrast injection), and delayed phase (120 seconds after contrast injection) were observed. In Sonazoid, the liver Kupffer phase was observed 10 minutes after injection. The enhancement degree was classified as high enhancement, iso-enhancement, low enhancement, or no enhancement, based on the comparison with the echogenicity of the liver parenchyma. The location, size, number of recurrent lesions, degree of enhancement, and enhancement patterns (homogeneous enhancement, inhomogeneous enhancement, peripheral rim enhancement, synchronous enhancement) were recorded.

High-frequency CEUS examination

This examination was performed on superficial and small lesions (with a diameter ≤1 cm) that were inadequately visualized or not detected at all using low-frequency probes. The lesions were also selected based on CT/MR scans indicating proximity to the liver capsule (a distance ≤1.5 cm), and contrast-enhanced CT or contrast-enhanced MR suggesting a potential malignancy. After completing the conventional CEUS examination, and performing local burst, a linear array transducer was used to activate the CEUS mode for reperfusion observation. The lesions were observed in real time for 3–5 minutes, and the dynamic images were stored.

Percutaneous liver biopsy

After excluding patients with contraindications for liver biopsy, the lesion location was determined using multimodal US to determine the puncture point and pathway, while avoiding blood vessels and vital organs. The freehand puncture method was used to complete the operation. Standard disinfection and draping were carried out, and after local anesthesia, a 17G cannula needle was punctured into the tumor under US guidance. Next, a 18G biopsy needle was inserted into the tumor through trocar, and 3–5 samples were obtained by cutting. The tissue was fixed in formalin. After biopsy, color Doppler US was used to determine if there was any bleeding. Each patient was instructed to fast for 4 hours, and placed on bed rest with electrocardiograph monitoring for 8 hours.

Statistical analysis

All statistical analyses were carried out using the SPSS version 27.0 software package (IBM, Armonk, NY, USA). A Kappa consistency test was used to evaluate the inter-rater reliability of the two US physicians with varying experience levels in classifying liver lesion visibility on conventional US. The Kappa statistic ranges from 0 to 1, where a value of 1 indicates perfect agreement between the two evaluators, a value of 0.75 or higher indicates a strong level of agreement, a value of 0.4–0.75 indicates a moderate level of agreement, and a value of less than 0.4 indicates poor agreement.

The demographic data were analyzed using descriptive statistics. The quantitative data are presented as the mean (standard deviation), or the median (interquartile range), and the categorical data are presented as the absolute (number) and relative (percentage) frequencies. The correct puncture rate was calculated as the number of true-positive samples divided by the total number of puncture cases.

Table 1 Demographic characteristics of patients

Characteristic	Value (N=95)
Sex, n (%)	
Male	67 (70.5)
Female	28 (29.5)
Age (years), median [IQR]	58 [50–65]
Previous disease history, n (%)	24 (25.3)
Hepatitis B	38 (40.0)
Hepatocirrhosis	5 (5.3)
Extrahepatic tumor	30 (73.7)
Past-operation history, n (%)	
Hepatectomy	7 (7.4)
Intrahepatic ablation therapy	2 (2.1)
Extrahepatic surgery	7 (7.4)
Laboratory indicators, n (%)	
HBsAg	32 (33.6)
AFP	36 (37.8)
CA199	48 (50.5)
CEA	11 (11.5)
Number of lesions, n (%)	
Nodular lesions	29 (30.5)
Massive lesions	12 (12.6)
Diffuse lesions	23 (24.2)
Small hepatocellular carcinoma lesions	31 (32.6)
Lesion localization, n (%)	
Left lobe	13 (13.6)
Right lobe	73 (76.8)
Junction of left and right lobes	9 (9.4)
Largest diameter of lesion (cm), mean (range)	2.7 (0.7–10.0)
Application of ultrasonic techniques, n (%)	
Fusion imaging	55 (57.9)
Contrast-enhanced ultrasound	95 (100.0)
High-frequency ultrasound	21 (22.1)

The number of lesions: the number of all lesions on CT/MR was used as the criterion. Lesion localization refers to the localization of lesions that were poorly visualized under conventional ultrasound but become visible after multimodal ultrasound imaging. Largest diameter of lesion refers to the maximum diameter of the observed mass in multimodal ultrasound that was not detected in conventional ultrasound examination. IQR, interquartile range; HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; CT, computerized tomography; MR, magnetic resonance.

The final diagnosis of each patient was determined based on a comprehensive assessment of their clinical history, laboratory tests, imaging, pathology results, and follow-up. Cases were classified as true-positive if the pathological diagnosis matched the final diagnosis, and were otherwise classified as negative.

Results

General results

A total of 95 patients were enrolled in this study, of whom 67 were male and 28 were female. The average age of the patients was 57.6 years (range: 33–83 years). Among the patients, 5 had concomitant liver cirrhosis, 38 had a history of hepatitis B, 1 had an autoimmune liver disease, 1 had a history of schistosomiasis, and 29 had a history of extrahepatic malignancies. Additionally, 7 patients had a history of liver tumor resection, 2 had undergone ablation therapy, and 7 had a history of other non-liver surgical treatments. The laboratory tests showed that 32 patients were positive for hepatitis B surface antigen, 36 had elevated alpha-fetoprotein levels, 48 had elevated carbohydrate antigen 199 levels, and 11 had elevated carcinoembryonic antigen levels. For further details on the demographic and clinical data of the patients, see *Table 1*.

Among the patients, 29 had nodular lesions, 23 had diffuse lesions, 12 had massive lesions, and 31 had small hepatocellular carcinoma (HCC) lesions. The average maximum diameter of the lesions was 2.7 cm (range: 0.7–10.0 cm). In this study, the statistical definition of lesion size referred to the maximum diameter of the first observed mass in multimodal US that was not detected in conventional US. The lesion sizes of the 23 patients with diffuse HCC were not included in the statistics. For patients with multiple lesions, the maximum diameter of the largest mass was selected for inclusion in the analysis.

Among the 32 patients who underwent MR-US fusion imaging examination, lesions recurred in 16 patients, of whom 2 underwent liver biopsies guided by MR-CEUS fusion imaging. Additionally, among the 23 patients who underwent CT-US fusion imaging examination, lesions recurred in 11 patients, of whom 1 underwent liver biopsy guided by CT-CEUS fusion imaging. The CEUS examination was conducted for all 95 patients, of whom 68 received Sonovue, 21 received Sonazoid, and 6 received a combination of Sonovue and Sonazoid. Further, high-frequency US was performed in 21 patients, including

Table 2 The consistency of poor visibility classification of liver lesions on conventional ultrasound by doctors with varying levels of experience

Senior physician	Junior physician		Total	Kappa	*U*	P
	Completely invisible	Unclearly displayed or blurred boundaries				
Completely invisible	79	2	81	0.784	7.650	<0.01
Unclearly displayed or blurred boundaries	3	11	14			
Total	82	13	95			

Table 3 Lesion visualization rate after multimodal ultrasound application

Visualization results	CT/MR-US fusion imaging	CEUS	High-frequency ultrasound
Visualization	27	92	16
Non-visualization	28	3	5
Visualization rate	49.1	96.8	76.2

CT/MR-US, computerized tomography or magnetic resonance-ultrasound fusion imaging; CEUS, contrast-enhanced ultrasound.

Table 4 Multimodality ultrasound-guided percutaneous liver biopsy (N=95)

Utilization results	Fusion imaging-gray scale ultrasound guided	Fusion imaging-high-frequency ultrasound guided	CEUS guided	Fusion imaging-CEUS guided	CEUS-high-frequency ultrasound guided
Number	23	1	56	3	12
Ratio (%)	24.2	1.1	58.9	3.2	12.6

CEUS, contrast-enhanced ultrasound.

2 cases of CEUS-high-frequency US-guided biopsies. No serious complications or deaths occurred in any of the patients after biopsy.

The reliability of conventional US poor visibility classification for liver lesions by two US doctors

In our study, two US specialists, one with over 20 years of experience, and the other with 3 years of experience, independently reviewed the conventional US images of the 95 patients. The Kappa value obtained from the analysis was 0.784, with a *U* statistic of 7.650 and a P value of less than 0.01 (*Table 2*).

Results of lesion display by multimodal US

In this study, 95 patients encountered difficulties in visualizing lesions during conventional US examinations. Among these, 55 patients underwent fusion imaging examinations, and for 27 of them, their lesions were successfully visualized, yielding a CT/MR-US visualization rate of 49.1%. Further, CEUS was performed in all 95 patients, and lesions were visualized for 92 patients, resulting in a CEUS visualization rate of 96.8%. Additionally, of the 21 patients for whom lesion visualization difficulties arose during conventional US examinations, 16 patients had their lesions visualized by high-frequency US, resulting in a high-frequency US visualization rate of 76.2% (*Table 3*).

Methods of percutaneous liver biopsy and pathological results

In this study, following the identification of the target using multimode US, appropriate biopsy methods were selected. A total of 24 patients underwent gray-scale US-guided biopsy. Among these patients, after the lesion location was clearly identified by CT/MR-US fusion imaging, conventional gray-scale US guidance was used for 23 patients, and high-frequency gray-scale US guidance was used for 1 patient. Additionally, 71 patients underwent CEUS-guided biopsy.

Of these, CEUS guidance alone was used in 56 patients, a combination of fusion imaging and CEUS guidance was used in 3 patients, and high-frequency imaging and CEUS guidance were used in 12 patients (*Table 4*).

After conducting needle biopsies, the pathological results of the 95 patients were analyzed. The findings revealed that 82 patients had positive pathological results (82/95, 86.3%). The biopsy pathology included 39 cases of HCC, 16 cases of intrahepatic cholangiocarcinoma (ICC), 22 cases of metastatic adenocarcinoma, 3 cases of hepatic adenoma, 1 case of vascular sarcoma, and 1 case of mixed HCC-ICC. Further, no malignant tumor cells were found in the pathological results of 13 patients. By combining imaging studies and laboratory tests, 8 cases were identified as false negatives. Of the 5 true negative cases, 2 were attributed to post-chemotherapy changes, while 3 cases were diagnosed as inflammatory lesions with no observed progression during follow-up. The overall accuracy rate of the biopsies in this study was 91.6% (87/95), with a positive predictive value of 91.1% (82/90) and a false-negative rate of 8.9% (8/90). In addition, nine patients with recurrent liver cancer after liver biopsy underwent US radio-frequency ablation. No severe complications such as death or bleeding occurred.

Discussion

Percutaneous liver biopsy involves the insertion of a needle through the skin and into the liver to obtain a tissue sample for diagnostic purposes, staging, or treatment planning for various liver conditions, and remains an important diagnostic procedure for liver masses (14). With advancements in imaging technologies, such as US, CT, and MR imaging, percutaneous liver biopsy can now be more precisely targeted toward specific lesions, enhancing biopsy accuracy and reducing the overall risk of complications (15).

Conventional gray-scale US is the preferred method for percutaneous liver biopsy due to its convenience, real-time visualization, and low costs. Its diagnostic accuracy is above 90% (16). However, the presence of acoustic artifacts can significantly impede the visualization of liver tissues. For instance, acoustic shadowing (17), a common artifact resulting from the absorption or reflection of US waves by certain structures like bones or gas, can obscure underlying tissues. This is particularly problematic in cases of subcutaneous emphysema or when there is air within the gastrointestinal tract. Additionally, conditions like fatty liver disease, hepatitis, and cirrhosis can profoundly affect the echotexture of the liver, making it challenging to discern lesions amid the altered tissue architecture (13). The increased echogenicity in fatty liver, and the heterogeneous texture in hepatitis and cirrhosis can lead to a masking effect, where lesions are less conspicuous against the bright liver background or are obscured by fibrotic tissue. To address these limitations, the optimization of US settings, the employment of higher-frequency transducers for better resolution, and the use of techniques such as CEUS can be beneficial. These approaches help to reduce artifacts and improve the delineation of liver lesions, thereby facilitating more accurate diagnosis and guided interventions.

Percutaneous echo-guided biopsy for hepatic tumor diagnosis also has certain performance limitations. Factors such as tumor type, size, and location significantly influence its effectiveness. The diagnosis of diffuse liver tumors is often restricted by multiple factors. These tumors tend to exhibit a fusion pattern between lesions with indistinct borders, which can make it challenging to differentiate between liver cirrhosis and severe liver damage in conventional US examinations. *Figure 2* shows a representative case of diffuse HCC. Larger tumors may contain internal necrosis that is difficult to visualize using conventional US before liquefaction occurs, which can lead to false-negative biopsy results. Necrotic tissue often appears homogeneous and hypoechoic, which can make it challenging to distinguish from the surrounding tissue. This is especially true when the necrosis is not associated with significant fluid or blood flow, which is typically visualized more clearly on US.

Other tissues that are challenging to visualize with conventional US include non-vascular cysts, infarctions, lacerations, and hematomas (18). The application of multimodal US techniques can enhance the visualization of challenging cases by providing additional functional and morphological information, thereby improving the diagnostic accuracy and procedural success rates. Moreover, tumors located at the top of the liver, smaller tumors, and those adjacent to vital organs are difficult to clearly visualize with conventional US, which can complicate accurate biopsy targeting and affect biopsy accuracy. As a result, new techniques are required to enhance US examination visualization capabilities and improve biopsy success rates for such tumors.

With the continuous advancement of imaging technology, imaging techniques such as US, CT, and MRI can display real-time images simultaneously from different angles using transducers. CT/MR-US fusion imaging technology improves the visualization of lesions

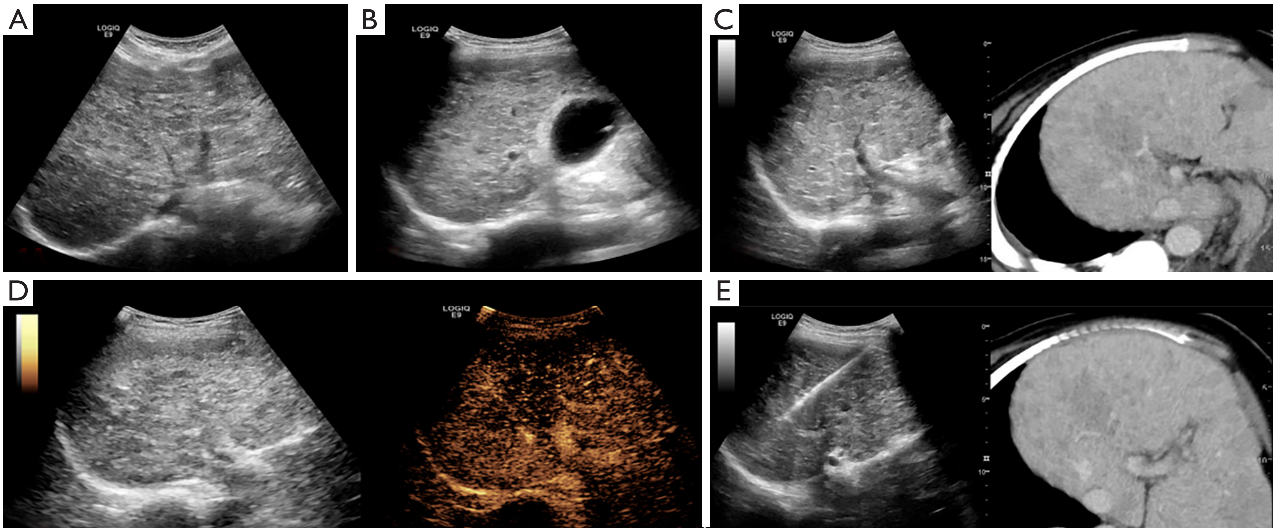

Figure 2 Scans of a 41-year-old female patient with a history of chronic hepatitis B for over a decade. (A,B) Gray-scale ultrasound examination revealed disrupted liver structure, indistinct lesion boundaries, and heterogeneous internal echoes. Color Doppler imaging demonstrated intravascular thrombus formation in the portal vein. (C) Despite CT-US fusion imaging, the lesion boundaries remained unclear. (D) Following the administration of 1.2 mL of Sonovue, arterial phase imaging showed diffuse and uneven enhancement, with non-enhancing necrotic areas visible within it. (E) Percutaneous liver biopsy guided by gray-scale ultrasound under CT-US fusion imaging guidance, avoiding the necrotic area identified after contrast agent injection. Histopathological examination of the biopsy specimen confirmed the diagnosis of diffuse HCC, and was consistent with the final diagnosis. CT, computerized tomography; US, ultrasound; HCC, hepatocellular carcinoma.

that cannot be seen with conventional US, revealing the three-dimensional relationship between the hepatic vascular system and the lesions (19). There have been multiple literature reports on the clinical research of MR/CT-US fusion imaging technology, which is currently primarily focused on improving the success rate of ablation. However, there are relatively few reports on the application of fusion imaging for liver biopsies of lesions that cannot be visualized with conventional US (20-22).

In the present study, 95 patients with unclear lesions on routine US were examined, and the accuracy rate of biopsy reached 91.6%. The lesion visualization rate after CT/MR-US fusion imaging was 49.1% (27/55), and after lesion visualization, the percutaneous liver biopsy success rate under the guidance of fusion imaging and gray-scale US reached 85.2% (23/27). This enabled tumors that were not visualized on conventional US to be clearly identified, targeted, and successfully biopsied under the guidance of fusion imaging.

CEUS is a specialized form of US imaging that involves the intravenous injection of microbubble contrast agents. Due to its high safety profile and real-time visualization of vascular perfusion within lesions, CEUS has been widely used in the evaluation of focal liver lesions, and has been added to the American College of Radiology Liver Imaging Reporting and Data System (CEUS LI-RADS) (23,24). CEUS greatly enhances the diagnostic accuracy of US in detecting and characterizing focal liver lesions (10). There have been numerous literature reports on clinical studies involving CEUS technology, most of which have primarily focused on characterizing differences among different tumor types (25-27). However, there have been relatively fewer reports on the application of fusion imaging to visualize lesions that cannot be detected with conventional US and guide liver biopsies.

In the present study, 96.8% (92/95) of the lesions were detected after CEUS, and 60.8% (56/92) of the lesions were detected after percutaneous liver biopsy guided only by CEUS. Notably, for larger tumors or diffuse tumors in liver segments, US-guided biopsy under CEUS was particularly important. In these patients, the two-dimensional US examination often showed scattered echoes, unclear tumor boundaries, and the merging of diffuse tumors. After CEUS, the boundaries of the lesions and the presence of necrotic areas within the tumors could be clearly determined.

By avoiding the necrotic areas during biopsy under US guidance, satisfactory results were obtained. In our study, of the 23 patients with diffuse liver cancer, 17 (73.9%) obtained positive pathological results under US guidance. Among the 8 patients with larger tumors (a maximum lesion diameter ≥5 cm), 5 (62.5%) obtained positive pathological results under US guidance.

While CEUS significantly improves the detection and characterization of focal liver lesions, we recognize that small HCCs may not exhibit the typical malignant features on contrast imaging, often appearing similar to benign lesions (28). This poses a significant challenge in differential diagnosis. Our study, adhering to the clinical diagnostic guidelines for liver tumors (2,3), excluded small liver nodules that were still considered benign after long-term follow-up. However, the atypical presentation of small HCC on CEUS underscores the necessity of integrating multimodal US techniques and developing artificial intelligence technologies to enhance the diagnostic accuracy of such lesions. This integrated approach is pivotal in the accurate characterization of liver lesions, particularly when conventional imaging modalities fall short.

High-frequency US is a technique that uses a high-frequency linear US probe (5–12 MHz) to image superficial suspicious lesions in the liver. During the imaging process, continuous adjustments of depth and focus are necessary to ensure the clear imaging of the suspicious lesions (29). Research (30) has shown that the additional use of a high-frequency transducer in conventional abdominal examinations can detect new liver lesions in a significant number of patients. Importantly, the use of such high-frequency transducers does not significantly extend the overall examination time. Clinical research on high-frequency US is currently limited, and has primarily focused on enhancing the detection rate of superficial lesions using high-frequency US contrast imaging.

In the present study, after undergoing high-frequency US examinations, 16 patients had a lesion visualization rate of 76.2% (16/21). Following lesion visualization, additional US techniques were employed for all 16 of these patients. Among whom, 9 (56.2%) underwent CEUS examination, and 7 (43.8%) underwent a combination of fusion imaging and CEUS. In high-frequency US, the higher the frequency, the faster the attenuation, making it less sensitive to blood flow detection. Therefore, in clinical practice, it is common to combine high-frequency US with CEUS to obtain clearer internal blood perfusion information for superficial liver lesions. *Figure 3* shows the images of a patient with metastatic adenocarcinoma on the surface of the liver capsule.

The advancement of multimodal US technology for liver tumor imaging would benefit from the standardization of US examination procedures to ensure consistent image acquisition and interpretation. Future improvements may include the development of more effective contrast agents and user-friendly analytical software to facilitate the widespread adoption of these techniques. Additionally, research should aim to optimize the US examination process, particularly for challenging cases with poor visibility on conventional imaging. Addressing these aspects will be crucial in enhancing the clinical utility of multimodal US in the management of liver tumors.

This study had a number of limitations. First, based on the exclusion criteria of this study, patients who did not show lesions even after undergoing multimodal US and did not undergo percutaneous liver biopsy were excluded. This might have led to a higher lesion detection rate after conducting the three US examinations of the included patients. Second, while the present study demonstrated good inter-rater reliability in classifying the visibility of liver lesions between two physicians, it is important to acknowledge that in clinical practice, the visibility of liver lesions is often influenced by the model of the US equipment and the technique of the sonographer. Consequently, subsequent investigations should focus on advancing the management strategies for patients with liver tumors through a collaborative diagnostic model that incorporates the expertise of multiple US specialists to enhance both the accuracy and dependability of the evaluations. Third, while our study showed the potential of multimodal US techniques in enhancing the visibility of liver lesions with poor conventional US visibility, a comparative analysis of the effectiveness between different diagnostic methods, as well as their correlation with biopsy results and overall diagnosis, was beyond the scope of this study. The limitations of this study are primarily due to the low incidence of such lesions, incomplete examination data sets, and the non-independence of patient samples. Our primary goal was to assess the potential of these techniques in improving biopsy success rates for poorly visualized liver lesions. We acknowledge the importance of further research in this area, and are actively working toward enhancing the diagnostic workflow for these patients.

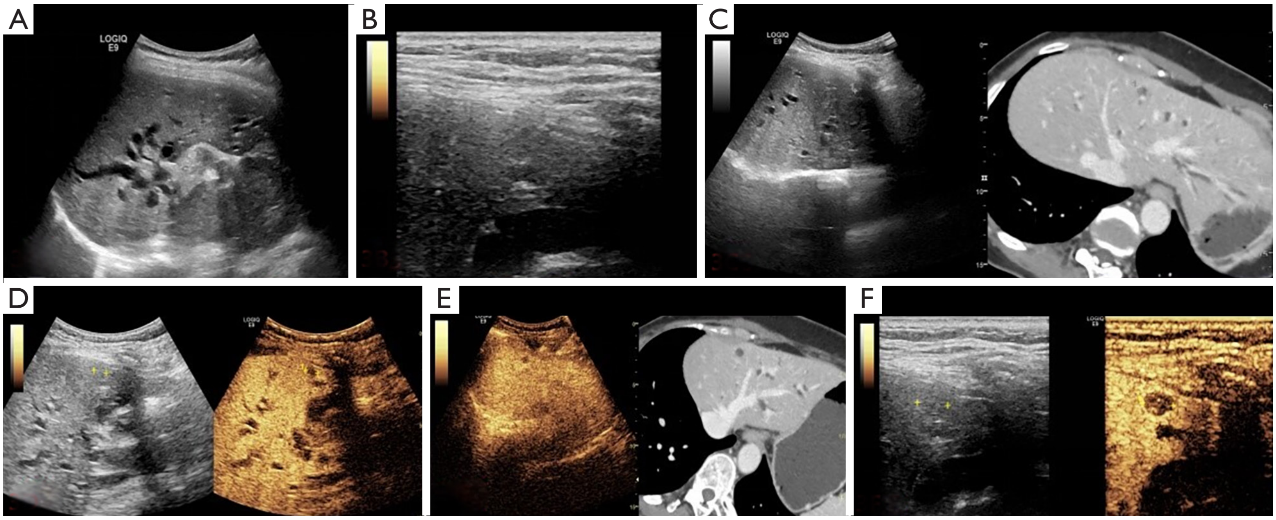

Figure 3 Scans of a 52-year-old female patient with elevated AFP and CA199 levels on laboratory examination. (A) Gray-scale ultrasound showed multiple hypoechoic masses in the abdominal, mild dilation of intrahepatic bile ducts, but no obvious liver lesions. (B) Despite using a high-frequency probe, no significant liver parenchymal masses were observed. (C) After MR-US fusion imaging, multiple anechoic areas were visible within the liver, but no apparent solid masses were seen. (D) Following the administration of 0.6 mL of Sonazoid contrast agent, a low-enhancement lesion measuring approximately 0.8 by 0.7 cm was observed in the arterial phase, and the lesion beneath the hepatic capsule of the right anterior lobe. (E) MR-CEUS fusion imaging confirmed that the location of the lesion corresponded to the position indicated on MR imaging. (F) During the hepatocyte phase, a high-frequency ultrasound examination was performed, and the lesion still displayed hypoechoic changes. Subsequently, a percutaneous liver biopsy was conducted under the guidance of CEUS-high-frequency ultrasound. The pathological result confirmed metastatic adenocarcinoma, which was consistent with the final diagnosis. AFP, alpha-fetoprotein; CA199, carbohydrate antigen 199; MR, magnetic resonance; US, ultrasound; CEUS, contrast-enhanced ultrasound.

Conclusions

This study showed that multimodal US technology significantly improved the visibility of liver lesions that were poorly visualized on conventional US, leading to a higher success rate in percutaneous biopsies. The detection rates of lesions using CT/MR-US fusion imaging, and high-frequency US examination were 49.1%, 96.8%, and 76.2%, respectively. The accuracy rate of the biopsies was 91.6%, while the positive concordance rate reached 91.1%. However, our research was limited by an inability to directly compare diagnostic methodologies, due to the specific nature of our patient samples and study design. Future investigations with larger, independent cohorts, and a framework conducive to comparative analyses should be conducted to compare the efficacy of various imaging-guided biopsy techniques. Nonetheless, our findings highlighted the significant potential of multimodal US in augmenting diagnostic precision. We advocate for continued research into the role of multimodal US in liver lesion diagnostics to expand on our preliminary findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-1392/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1392/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the

Institutional Ethics Committee of the Nanjing Drum Tower Hospital, Drum Tower Clinical Medical College, Nanjing Medical University (No. 2022-140-01). Informed consent was obtained from all the patients.

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