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High-frequency contrast-enhanced ultrasound in discriminating benign and malignant superficial lymph nodes: a diagnostic comparison

Shuyuan Liang[1†], Peng Han[1†], Xiang Fei[1], Lianhua Zhu[1], Liuqing Peng[1], Fang Xie[1] and Yukun Luo[1*]

Abstract

Background Lymph nodes are critical immune system components, filtering harmful substances and acting as indicators in various disease states, including cancer. Accurate differentiation between benign and malignant superficial lymph nodes is essential for diagnosis and treatment planning. However, conventional diagnostic methods often lack the required precision. High-frequency contrast-enhanced ultrasound (H-CEUS) offers improved temporal resolution and visualization of microvascular structures, potentially providing better diagnostic accuracy than standard contrast-enhanced ultrasound (CEUS).

Methods This study included 77 patients with suspected abnormalities in superficial lymph nodes. Each patient underwent H-CEUS and CEUS examinations, with diagnoses confirmed through biopsy or surgical resection. The diagnostic performance of H-CEUS and CEUS was evaluated using sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Chi-square tests and ROC curve analysis were employed to compare the efficacy of H-CEUS and CEUS in differentiating benign from malignant lymph nodes.

Results H-CEUS demonstrated superior diagnostic performance over CEUS, with higher sensitivity (95.92% vs. 83.67%), specificity (92.86% vs. 57.14%), and accuracy (94.80% vs. 74.03%). H-CEUS enhanced microvascular morphology visualization, facilitating more accurate differentiation between benign and metastatic lymph nodes. The area under the ROC curve for H-CEUS (0.944) was significantly greater than that for CEUS (0.704), indicating improved diagnostic capability.

Conclusion H-CEUS offers enhanced accuracy in diagnosing the nature of superficial lymph nodes, potentially improving clinical decision-making for patients with suspected lymph node malignancies. These findings support the integration of H-CEUS into routine clinical practice to achieve better diagnostic outcomes.

Keywords High-frequency contrast-enhanced ultrasound, Contrast-enhanced ultrasound, Superficial lymph nodes, Diagnostic efficacy, Microvascular visualization, Benign and malignant differentiation

†Shuyuan Liang and Peng Han regarded as co-first authors.

*Correspondence:
Yukun Luo
lyk301@163.com

[1]Department of Ultrasound Diagnosis, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, P. R. China

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Background

Lymph nodes are essential components of the immune system, distributed throughout the body, primarily responsible for filtering viruses, bacteria, and other harmful substances from lymph fluid [1, 2]. In various disease states, lymph nodes may exhibit enlargement or abnormalities, such as sclerosis, fixation, irregular texture changes, increased quantity, or causing pain, including benign inflammatory reactions, metastatic cancers, and lymphatic system disorders. Accurate early diagnosis is crucial for distinguishing between benign and malignant superficial lymph nodes (neck, armpits, and groin) to tailor appropriate treatment strategies and assess prognosis [3, 4]. However, conventional methods of examining superficial lymph nodes, such as palpation and routine ultrasound (US), have limitations in sensitivity and specificity. Consequently, there is an urgent need for more advanced and precise diagnostic technologies to meet the clinical demand for effectively distinguishing the nature of superficial lymph nodes.

Diagnostic imaging techniques are crucial in the clinical staging and diagnostic examinations of malignant tumors. Among these, the US is widely utilized and practical in this field. Specifically, in diagnosing tumor metastasis, US imaging of local or regional lymph node enlargement due to tumor metastasis is particularly essential for clear characterization. Contrast-enhanced ultrasound (CEUS) is used for imaging superficial lymph nodes, demonstrating high sensitivity and specificity in diagnosing malignant tumor involvement in superficial lymph nodes. However, studies have indicated that variations in diagnostic criteria, contrast agents, and imaging modalities can lead to certain heterogeneity in research outcomes. Consequently, a standardized CEUS technique in clinical practice to differentiate between benign and malignant superficial lymph nodes is necessary and imperative for future applications [5].

In recent years, CEUS technology has offered a new potential for distinguishing the nature of lymph nodes. CEUS, known for its non-invasive, radiation-free, and cost-effective characteristics, has been widely used to differentiate between benign and malignant lymph nodes. However, CEUS has certain limitations in temporal resolution and the display of microvascular morphology [6, 7]. To address this issue, high-frequency contrast-enhanced ultrasound (H-CEUS) technology has emerged. By increasing the frame rate of contrast images, H-CEUS can achieve higher temporal resolution, enabling clearer visualization of the enhancement pattern in the arterial phase of lymph nodes and microvascular morphology [8, 9].

Currently, CEUS is widely used for determining the nature of superficial lymph nodes, particularly in the qualitative assessment of tumor metastasis in enlarged lymph nodes. This includes common tumors in the head and neck, breast, lung, stomach, colon, ovarian cancer, and even melanoma for characterizing metastatic lymph nodes and distinguishing them from non-metastatic nodes for tumor staging. Additionally, it is applied in some malignant tumors, such as lymphoma, for assessing treatment response during chemotherapy [10–14]. Recent research on randomized controlled trials (RCTs) investigating the application of CEUS for the benign and malignant diagnosis of superficial lymph nodes has been extensive, further confirming its higher sensitivity, specificity, and accuracy compared to CEUS in the differentiation of benign and malignant superficial lymph nodes. These RCTs have consistently validated the diagnostic sensitivity, specificity, and accuracy of CEUS in superficial lymph nodes across various tumors as being between 77.8 and 98%, 80.0–99%, and 80–99%, respectively [15–19]. In contrast, the CEUS demonstrates a sensitivity and specificity of only 76% and 80% in diagnosing malignant lymph nodes in the neck, significantly lower than the results achieved with CEUS [12]. Utilizing a multimodal US diagnosis, lymph node hardness, perfusion patterns, and nodal characteristics can be examined, making it a robust tool and method for distinguishing between benign and malignant lymph nodes [20].

While the theoretical advantages of H-CEUS are evident, there is still a limited number of direct comparative studies between H-CEUS and CEUS in the benign and malignant differentiation diagnosis of superficial lymph nodes. Some studies suggest that H-CEUS may excel over CEUS in certain aspects, but these conclusions are mainly based on studies of different patient populations or lymph node types, making it challenging to draw universal conclusions. Furthermore, variations in equipment and methodologies often lead to discrepancies among results from different studies. Therefore, targeted studies directly comparing H-CEUS and CEUS under the same conditions are essential.

This study assesses the efficacy differences between H-CEUS and CEUS in the benign and malignant differentiation diagnosis of superficial lymph nodes by directly comparing their perfusion characteristic display, diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. We selected 77 samples diagnosed with suspected abnormalities in superficial lymph nodes using the conventional US for in-depth investigation, and pathological results were obtained through needle biopsy or surgical excision. The objective of this study is not only to comprehend the relative merits of the two technologies but also to provide new theoretical evidence and practical tools for the accurate diagnosis of superficial lymph nodes through this comparative research. Ultimately, this study seeks to offer clinicians more effective diagnostic methods and patients more precise personalized treatment plans.

Methods

Ethical declaration

This study has adhered strictly to international ethical guidelines and relevant regulations and has obtained approval from our institutional ethics committee (No. S2022-479-01). All patients involved in this study were fully informed about the research objectives, methods, potential risks and benefits, and other possible treatment options before participating and have voluntarily signed informed consent forms. An experienced medical team carried out all diagnostic and therapeutic procedures in this study to ensure the safety and comfort of each patient. The research team will take responsibility and provide appropriate medical intervention for any adverse reactions resulting from the study. Rigorous measures have been implemented to protect patient privacy in this study, with all personal information undergoing de-identification.

Research subjects

From July 2019 to December 2020, we selected 77 patients diagnosed with suspected abnormalities in superficial lymph nodes in the US. These patients underwent needle biopsy or surgical excision of the lymph nodes, and the pathological results for each lymph node are known.

Inclusion criteria are as follows: ① Lymph nodes exhibiting one or more abnormal US features (such as unclear hilum structure, cortical thickening (> 3 mm), heterogeneous echogenicity, irregular shape, indistinct corticomedullary differentiation, or presence of abnormal blood flow signals), requiring surgery or biopsy to obtain pathological results; ② Lymph nodes not previously treated with radiofrequency ablation or other therapies; ③ Complete patient information. Exclusion criteria are as follows: ① Patients with known allergies to US contrast agents [4, 14, 20].

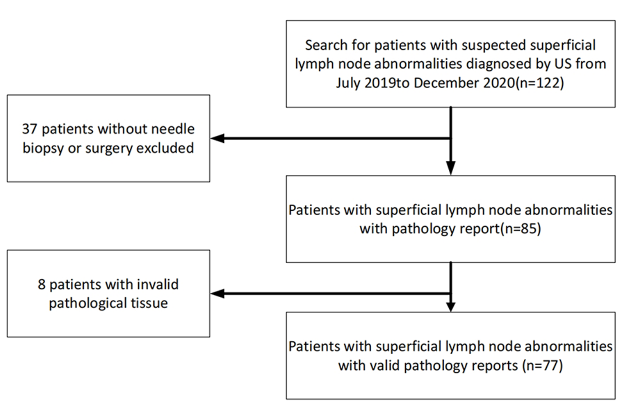

Fig. 1 Illustrates the patient selection process in this study. Note: US represents conventional US

For patients receiving US contrast agents for the first time, we assessed their risk of allergies by detailed inquiries about medical history and any history of allergies to other contrast agents or medications. Before examination, all patients were informed about potential allergic reactions and corresponding preventive measures.

In cases where patients presented multiple suspicious lymph nodes, we selected the largest and most easily observable superficial lymph nodes as the targets for routine and CEUS examinations. In total, 77 lymph nodes were included in the study. The flowchart depicting patient enrollment is illustrated in Fig. 1. Based on the pathological results, we categorized the lymph nodes into benign and malignant groups, with the malignant group further divided into metastasis and lymphoma subgroups.

Ultrasound examination

All patients underwent conventional US, CEUS, and H-CEUS examinations. All CEUS and H-CEUS procedures were performed by the same operator with over 10 years of experience in vascular ultrasound to ensure consistency and image quality. The image acquisition included continuous high-frame-rate recording of lymph node perfusion and real-time analysis of different lymph node characteristics. All images (US, CEUS, H-CEUS) were interpreted by two radiologists with over 10 years of experience in superficial vascular ultrasound. They independently assessed enhancement patterns, intensity, and vascular structural changes while remaining blinded to the patients' clinical data, final diagnosis, and other imaging results.

The ultrasound system used in this study was the Mindray Resona 7 (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China), equipped with an L11-3U probe operating at 3–11 MHz frequency. CEUS and H-CEUS utilized a low mechanical index (MI 0.06–0.08). The frame rate for CEUS images was 10 frames per second, while H-CEUS had a frame rate ranging from 48 to 110 frames per second. According to Giangregorio et al. (2023) [21], H-CEUS significantly enhanced microvascular visualization by improving temporal resolution and optimizing beam control.

H-CEUS employed the Zone Sonography Technology Plus (ZST+) platform, which transmits wide beams to cover a larger imaging area and integrates multiple echo data to ensure high signal-to-noise ratio and image clarity at high frame rates. ZST + also allows for a reduced field of view (FOV), enhancing lymph node perfusion feature visibility while maintaining the integrity of the target region, which is particularly beneficial for capturing micro-lesions with rapid perfusion. This technology increases the number of image lines per scan by transmitting weakly focused wide beams, thereby improving frame rate and optimizing the reception field's sound field synthesis, which enhances lateral resolution and penetration. Additionally, FOV can be narrowed to reduce the transmission path, improving frame rate while maintaining clear visualization of the target area.

The contrast agent used in this study was SonoVue (Bracco, Italy), a physiological saline suspension containing stabilized sulfur hexafluoride microbubbles. Following the contrast agent injection, 5.0 mL of saline was simultaneously injected as a flush to ensure no residual contrast agent remained in the intravenous catheter. The contrast agent was administered via the antecubital vein at a 2.0 mg/2.5 mL. The CEUS examination lasted at least 2 min, during which video recordings of the ultrasound were made. A minimum of 20 min was allowed between the two contrast agent injections. The same operator performed all CEUS scans using the same examination protocol to eliminate inter-operator differences.

Patients were positioned supine with the examination site fully exposed. Target lymph nodes were first selected for conventional US, followed by CEUS and H-CEUS. The largest visible lymph nodes or those showing lymphatic hilum structures were prioritized for imaging. Lymph nodes with focal echo abnormalities, such as cystic degeneration or calcification, were preferentially assessed using these images.

For US examination, the long-to-short diameter ratio (L/R) (≥ 2, < 2) of the lymph nodes was measured, and the internal echotexture (homogeneous, heterogeneous), shape (regular, irregular), presence of lymphatic hilum structures, and Doppler flow signals were assessed.

For CEUS and H-CEUS, the enhancement pattern (centripetal, centrifugal, chaotic) was observed, enhancement homogeneity (homogeneous, heterogeneous) was evaluated, and the presence of lymphatic vessels and adjacent vascular structures was assessed.

Table 1 Clinical characteristics of 77 patients and US characteristics of lymph nodes

Characteristic	Benign lymph node (*n* = 28)	Malignant lymph node (*n* = 49)	F/χ^2	*P*
Mean age (years)*	49.04 ± 13.20	51.35 ± 12.18	0.840	0.362
Sex			4.241	0.039*
Male	22	27		
Female	6	22		
Max lesion size (cm)*	1.50 ± 0.54	2.23 ± 1.76	8.639	0.004**
L/R ratio			20.316	0.000**
≥ 2	18	7		
< 2	10	42		
Ultrasonic echo			5.722	0.017*
Homogeneous	23	27		
Inhomogeneous	5	22		
Shape			6.082	0.014*
Regular	25	31		
Irregular	3	18		
CDFI			1.649	0.199
Yes	25	38		
No	3	11		

Note L/R ratio: Long-to-short diameter ratio; CDFI: Color Doppler Flow Imaging; Data are means ± standard deviations. *$P < 0.05$; **$P < 0.01$

Observation parameters

The lymph node perfusion characteristics, including enhancement uniformity, enhancement pattern, and lymphatic and adjacent vascular structure features, were compared and analyzed in 77 samples using H-CEUS and CEUS. Based on the results of H-CEUS and CEUS, diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated. Additionally, ROC curves and the area under the curve (AUC) were computed based on the diagnostic outcomes of H-CEUS and CEUS.

Statistical analysis

The statistical analysis of this study will begin with descriptive statistics to calculate the mean, median, standard deviation, and range of all quantitative data, along with the frequency and percentage of qualitative data. Regarding the US image analysis, two physicians will conduct an inter-reader reliability analysis using Fleiss' kappa statistics for each feature assessment. Comparative analysis will employ chi-square tests, independent sample t-tests, or Mann-Whitney U tests to examine differences between H-CEUS and CEUS in various groups. Performance analysis will involve determining diagnostic sensitivity, specificity, PPV and NPV, and accuracy. Additionally, the diagnostic efficacy of both methods will be evaluated by calculating the area under the ROC curve. If necessary, multivariate logistic regression analysis will be utilized to assess the impact of various factors on diagnostic efficiency. All statistical tests will be conducted at a significance level of 0.05, where a P-value less than 0.05 will be deemed statistically significant. The statistical analysis of all data will be performed using SPSS 24.0 software (IBM Corporation, Armonk, New York, USA).

Results

Patient demographics and US characteristics of lymph nodes

As shown in Table 1, the study included 77 patients, with 28 males and 49 females aged 21 to 76 years. The mean age of the benign lymph node group was 49.04 ± 13.20 years, and that of the malignant lymph node group was 51.35 ± 12.18 years, with no significant age difference between the two groups ($p = 0.362$). The lymph nodes were distributed across different regions, with 42 located in the neck, 17 in the supraclavicular fossa, 9 in the axilla, 6 in the submandibular area, and 3 in the preauricular area. The maximum diameter of the lymph nodes ranged from 0.5 to 9.6 cm, with a mean maximum diameter of 1.97 ± 1.48 cm. The lymphoma group had significantly larger maximum diameters than the benign and metastatic groups ($F = 10.608$; $P = 0.000$).

Interobserver agreement was assessed using weighted Kappa statistics, which revealed high consistency between the two radiologists in evaluating lymph node characteristics (weighted $\kappa = 0.81$, 95% CI: 0.77–0.86). This high level of agreement ensured the reliability of the assessments, providing robust data support for subsequent CEUS and H-CEUS feature analyses.

Pathological examination results of 77 patients

As shown in Table 2, out of the 77 superficial lymph nodes examined, 28 were benign, 39 were metastatic, and 10 were lymphoma cases. Among the benign lymph nodes, there were 24 cases of reactive hyperplasia and 1 necrotizing lymphadenitis. The metastatic lymph nodes included 11 cases of papillary thyroid carcinoma and 7 cases of lung adenocarcinoma. Of the 10 lymphoma cases, 3 were Hodgkin's, and 7 were non-Hodgkin's.

Features of CEUS and H-CEUS lymph nodes

As indicated in Table 3, H-CEUS demonstrated centripetal enhancement in 85.71% (24/28) of benign lymph nodes (Fig. 2), which was significantly higher compared to 53.57% (15/28) seen with CEUS. H-CEUS also visualized hilar vessels in 78.57% (22/28) cases, a feature observed in only 50.00% (14/28) with CEUS.

Metastatic lymph nodes primarily exhibited centrifugal and heterogeneous enhancement (Fig. 3). H-CEUS showed centrifugal enhancement in 87.18% (34/39) of cases, a statistically significant increase compared to the 56.41% (22/39) observed with CEUS.

Furthermore, lymphoma nodes predominantly displayed uniform enhancement (Fig. 4), with no significant difference between H-CEUS and CEUS presenting uniform enhancement patterns.

Table 2 Surgical and pathological examinations of lymph nodes

Type	Pathologic Result	No. of Cases	Percentage(%)
Benign lymph node ($n = 28$)	Reactive lymph node	24	85.71%
	Necrotizing lymphadenitis	1	3.57%
	Granulomatous lymphadenitis	2	7.14%
	Tuberculous lymphadenitis	1	3.57%
Metastatic lymph node ($n = 39$)	Papillary thyroid carcinoma	11	28.21%
	Adenocarcinoma of lung	7	17.95%
	Invasive breast cancer	6	15.38%
	Squamous carcinoma	5	12.82%
	Poorly differentiated carcinoma	3	7.69%
	Small cell carcinoma	3	7.69%
	Medullary carcinoma	1	2.56%
	Pancreatic cancer	1	2.56%
	Neuroendocrine carcinoma	1	2.56%
Lymphomas ($n = 10$)	Hodgkin lymphoma	3	30.00%
	Non-hodgkin lymphoma	7	70.00%

Diagnostic value of H-CEUS and CEUS

As illustrated in Table 4, the comparison of diagnostic efficacy between H-CEUS and CEUS reveals that H-CEUS outperformed CEUS in various aspects. The sensitivity, specificity, PPV, NPV, and accuracy of H-CEUS were 95.92%, 92.86%, 97.92%, 92.86%, and 94.80%, respectively. In contrast, the corresponding values for CEUS were 83.67%, 57.14%, 77.36%, 66.67%, and 74.03%, demonstrating H-CEUS's superiority over CEUS. This outcome was further supported by the ROC curve analysis (Fig. 5), with the area under the curve (AUC) for H-CEUS at 0.944, compared to 0.704 for CEUS, which was statistically significant.

Discussion

Clinical evidence has confirmed the advantages and characteristics of H-CEUS in diagnosing and differentiating superficial lymph nodes. Compared to CEUS, H-CEUS exhibits good sensitivity, specificity, and accuracy in distinguishing between benign and malignant superficial lymph nodes. While CEUS allows for more blood flow information, enhancing diagnostic capabilities for lymph node lesions to a certain extent, it still has limitations. The frame rate of CEUS is related to imaging speed [22]. With a frame rate of 10 frames/s, observing the perfusion patterns within small-volume lymph node nodules with rapid arterial phase enhancement is challenging, affecting diagnostic accuracy [23]. On the other hand, H-CEUS improves temporal resolution by increasing the frame rate, thus capturing more arterial phase perfusion information and enhancing the accuracy of diagnosing benign and malignant superficial lymph nodes. Research suggests that leveraging the rapid arterial phase enhancement feature of H-CEUS for distinguishing between benign and malignant focal liver lesions offers a significant advantage, with sensitivity, specificity, accuracy, PPV, and NPV reaching 92.86%, 95.0%, 96.3%, 90.48%, and 93.75%, respectively. In comparison, with conventional CEUS, these values are 75.0%, 70.0%, 77.78%, 66.67%, and 72.91%, and the differences between the two approaches are statistically significant ($p < 0.01$) [24].

CEUS can identify vascular changes in tumor tissues with diameters smaller than 40 μm, offering low cost, safety, and good repeatability. With the capability to provide real-time evaluation of post-perfusion microvascular blood flow dynamics, CEUS aids in offering more pertinent information about lymph nodes, thus assisting in

Table 3 CEUS and H-CEUS characteristics of lymph nodes

Features	Benign ($n=28$)		$χ^2$	P	Metastatic ($n=39$)		$χ^2$	P	Lymphomas ($n=10$)		$χ^2$	P
	CEUS	**H-CEUS**			**CEUS**	**H-CEUS**			**CEUS**	**H-CEUS**		
Homogeneity			0.113	0.737			0.075	0.784			0.000	1.000
Homogeneous	22	23			9	8			9	9		
Inhomogeneous	6	5			30	31			1	1		
Enhanced mode			7.089	0.034*			10.571	0.005**			0.541	1.000
Centripetal	4	2			22	34			1	1		
Centrifugal	15	24			2	2			4	3		
Radial	9	2			15	3			5	6		
Hilar vessels			4.978	0.026*			0.000	1.000			0.392	1.000
Yes	14	22			2	2			1	2		
No	14	6			37	37			9	8		

Note CEUS: Contrast-Enhanced Ultrasound; H-CEUS: High-Frame-Rate Contrast-Enhanced Ultrasound; *$P<0.05$; **$P<0.01$

clinical diagnosis [25, 26]. A comparative study evaluating the roles of CEUS and PET/CT in lymphoma diagnosis and prognosis assessment showed a certain correlation between the two, with quantitative CEUS proving more beneficial for lymphoma diagnosis [27]. Leveraging excellent temporal and spatial resolution post-vascular perfusion capture, H-CEUS can differentiate and diagnose small lesions in the liver following cirrhosis, highlighting its clinical diagnostic superiority [21]. Vascular lesions, structures, and stent positioning assessments are frequently required in interventional procedures. However, current methods such as Doppler measurements, duplex US, or phase-contrast magnetic resonance imaging are all prone to flow velocity influences or face challenges in adhering to standard protocols. H-CEUS, combined with Particle Image Velocimetry (PIV) and Echo PIV, overcomes the abovementioned shortcomings. The integration of high-frame-rate echo PIV of H-CEUS enables quantification of high-velocity (≥ 1 m/s) blood flow in the heart and aorta, facilitating the diagnosis of vascular lesions [28, 29]. H-CEUS primarily conducts imaging detection and diagnosis of tissue and vascular lesions through echoes and blood flow. In addition to its application in distinguishing benign and malignant superficial lymph nodes, it is widely used for diagnosing focal liver lesions, differentiating cholesterol polyps and gallbladder adenomas, and detecting liver metastasis of gastrointestinal stromal tumors [24, 30, 31]. The differential diagnosis of superficial lymph nodes holds significant clinical importance, especially in early tumor detection and staging [32]. H-CEUS and CEUS have been employed in numerous studies in lymph node diagnosis [14]. However, their efficacy in lymph node diagnosis has not been thoroughly compared. This study aims to fill this gap by comparing the performance of H-CEUS and CEUS in distinguishing benign and malignant lymph nodes. Unlike prior research, this study not only broadens the application scope of H-CEUS but also offers a direct comparison between the two imaging techniques for the first time.

On the other hand, high-frame-rate CEUS enhances temporal resolution by increasing the frame rate, allowing for improved capture of arterial-phase perfusion dynamics and enhancing the accuracy of superficial lymph node malignancy assessment. However, this technique relies on reducing the FOV to maintain high frame rates, which may lead to information loss when imaging larger lymph nodes. This limitation is particularly evident with linear-array probes, where the restricted imaging range may hinder comprehensive visualization of the lymph node and its surrounding structures, affecting the assessment of peripheral vascularization and overall perfusion.

To mitigate the diagnostic limitations associated with FOV reduction, this study adopted a targeted approach

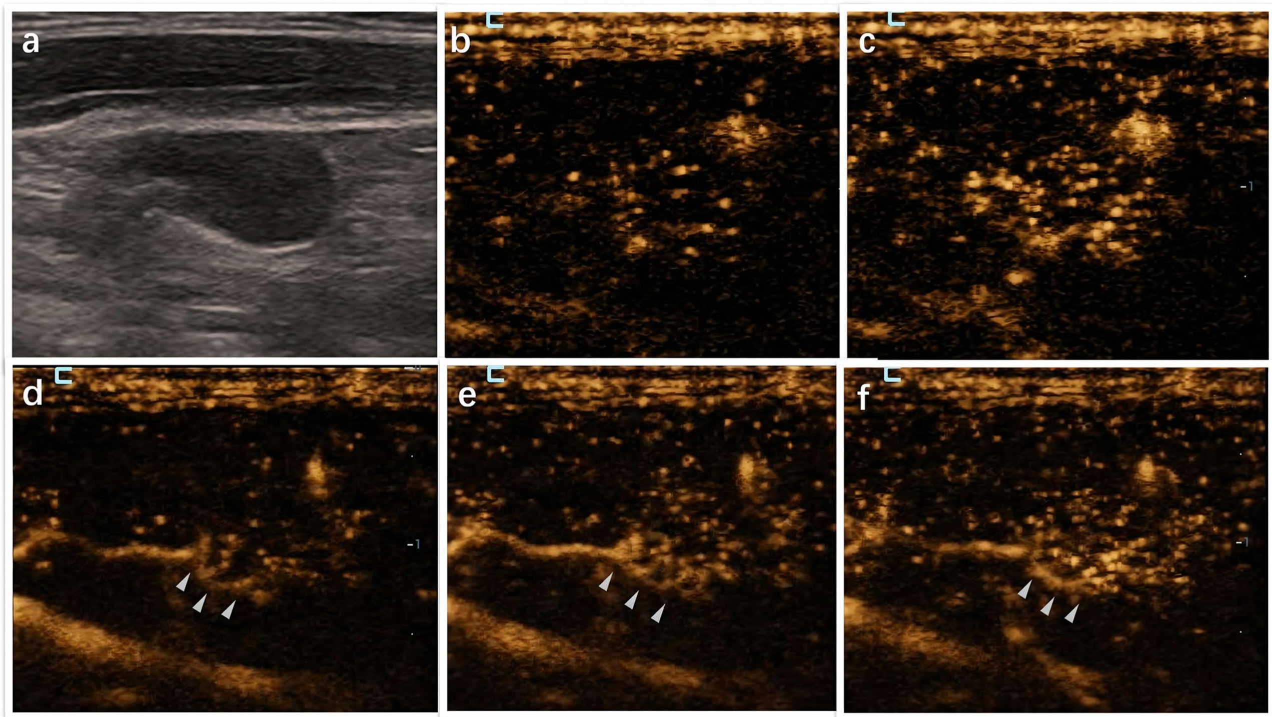

Fig. 2 Displays US images of benign lymph nodes. Note: (**a**) shows the US image of a benign lymph node, while (**b**, **c**) reveal the CEUS images of lymph nodes displaying an irregular enhancement pattern, and (**d**, **e**, **f**) present benign lymph nodes' H-CEUS images exhibiting a centripetal enhancement pattern. The triangles indicate subclavian vessels in benign lymph nodes

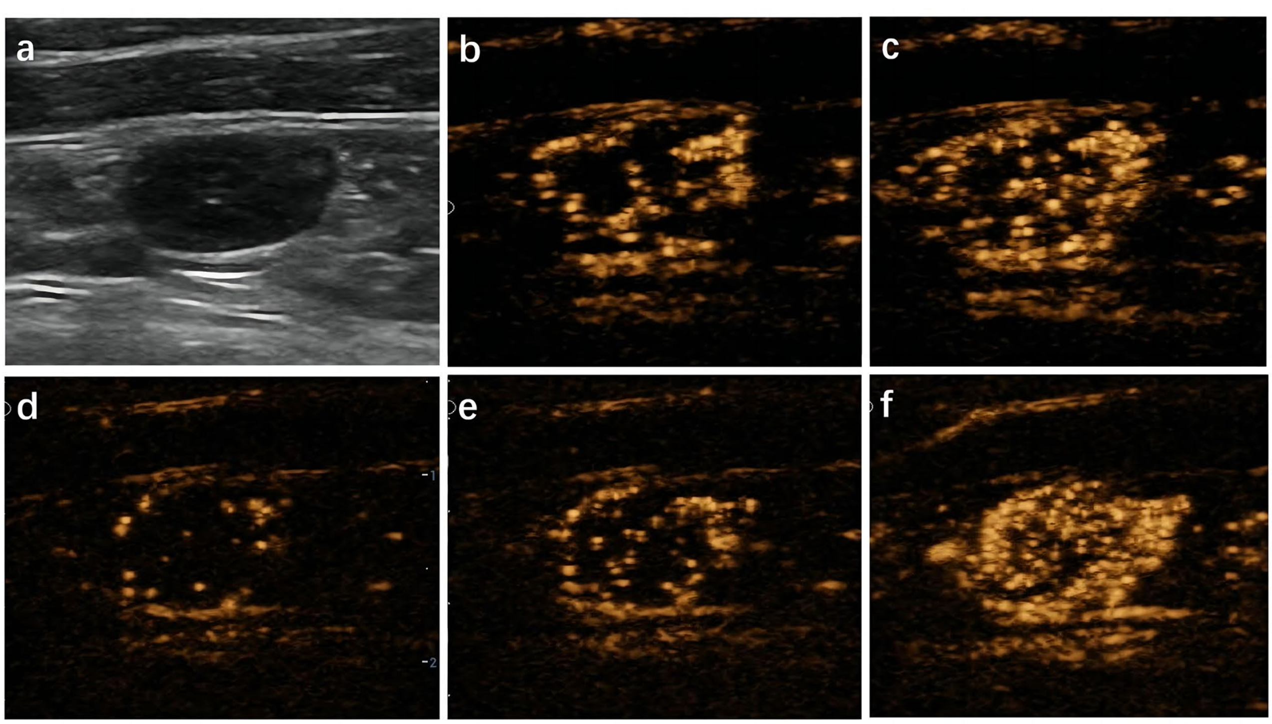

Fig. 3 Showcases US images of metastatic lymph nodes. Note: (**a**) depicts the US image of a metastatic lymph node, whereas (**b**, **c**) show the CEUS images displaying an irregular enhancement pattern, and (**d**, **e**, **f**) exhibit the H-CEUS images of metastatic lymph nodes depicting an outward spreading enhancement pattern

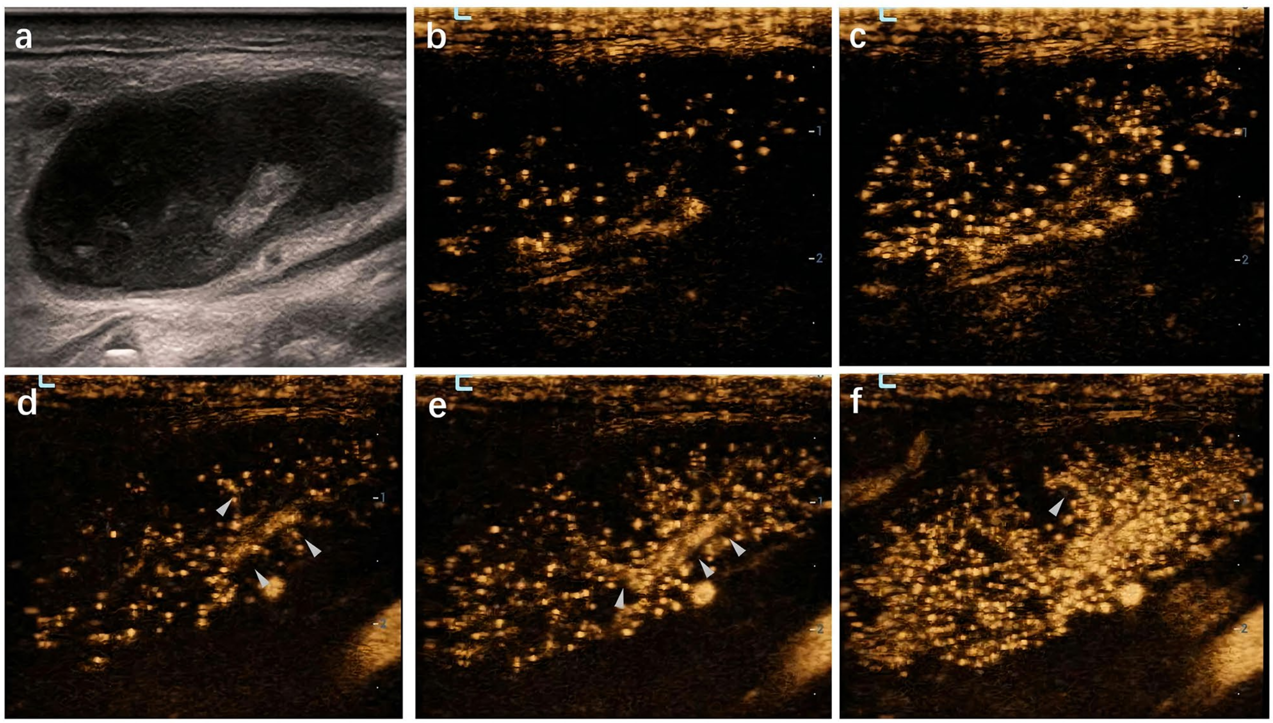

Fig. 4 Demonstrates US images of lymphoma. Note: (**a**) illustrates the US image of lymphoma, (**b**, **c**) exhibits the CEUS images with an irregular enhancement pattern, and (**d**, **e**, **f**) presents the H-CEUS images of lymphoma. The triangles point to the dendritic capillaries

Table 4 Diagnostic efficacy of CEUS and H-CEUS for lymph nodes

Imaging technique	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
H-CEUS	95.92% (92.14-97.72%)	92.86% (89.27-95.98%)	97.92% (94.64-99.28%)	92.86% (89.27-95.98%)	94.80% (92.34-96.58%)
CEUS	83.67% (77.56-88.94%)	57.14% (47.09-67.07%)	77.36% (69.87-83.56%)	66.67% (57.74-74.62%)	74.03% (66.28-80.23%)

Note: CEUS: Contrast-Enhanced Ultrasound; H-CEUS: High-Frame-Rate Contrast-Enhanced Ultrasound; PPV: Positive Predictive Value; NPV: Negative Predictive Value. Data in parentheses represent 95% confidence intervals

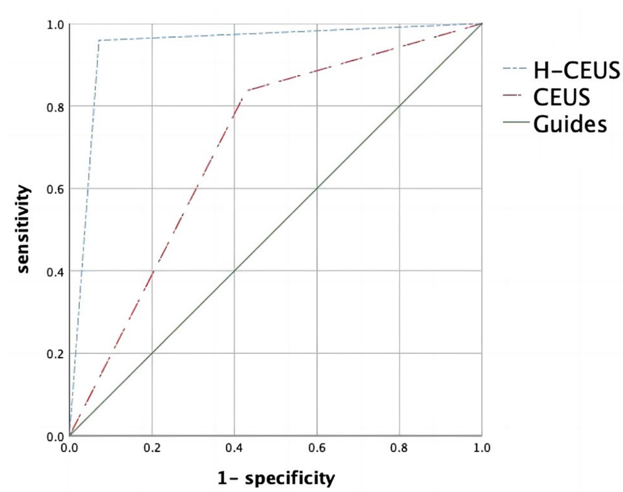

Fig. 5 Displays the ROC curve evaluating the efficacy of H-CEUS and CEUS in discriminating between benign and malignant superficial lymph nodes. Note: The diagnostic accuracy of H-CEUS exceeds that of CEUS, determined by measuring the area under the ROC curve

by focusing on the region of interest and using segmented scanning for larger lymph nodes to ensure complete coverage of critical areas. Additionally, low-frame-rate CEUS images were incorporated for supplementary analysis, providing a more comprehensive evaluation. Previous studies have recommended multi-angle probe movement and multiplanar imaging to enhance FOV coverage [23]. Nonetheless, the trade-off between FOV reduction and improved temporal resolution remains a key challenge in high-frame-rate CEUS applications. Future advancements should focus on optimizing image processing algorithms and developing higher-performance probes to expand the FOV while maintaining high frame rates, thereby achieving more comprehensive and precise diagnostics.

In previous studies comparing H-CEUS with conventional CEUS in the diagnosis of lymphatic vessels and sentinel lymph nodes, H-CEUS overcomes several limitations such as tissue artifacts, microbubble rupture leading to reduced image contrast, limited spatiotemporal

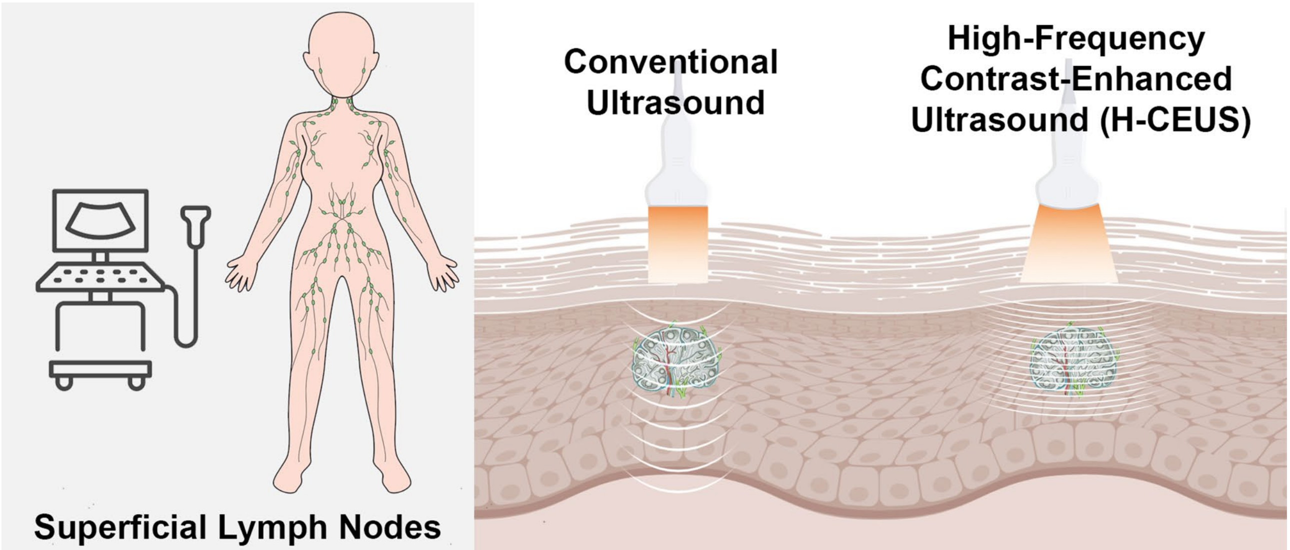

Fig. 6 Illustrates US imaging utilizing the strong scattering properties of liquid microbubble contrast agents. Note: By injecting contrast agents containing microbubbles into the bloodstream, US Doppler signals are enhanced, improving the clarity and resolution of US images. Malignant superficial lymph nodes, rich in vasculature, exhibit enhanced scattering of microbubbles within the blood vessels. H-CEUS improves the temporal resolution of images by increasing the frame rate and facilitating the differentiation between benign and malignant lymph nodes. (**a**) Using a standard probe, the US distinguishes benign superficial lymph nodes with light gray shadows. (**b**) H-CEUS with a high-frequency probe identifies dark gray malignant lymph nodes, enhancing the diagnosis of characteristics of superficial lymph nodes

resolution resulting in decreased information capture, and delayed lymphatic flow affecting the efficacy of Doppler-based examinations [33, 34]. Research suggests that utilizing H-CEUS for ultrasonography, a high frame rate combined with Singular Value Decomposition (SVD) filtering significantly reduces tissue artifacts, while slower flow velocities enhance image contrast and signal persistence, making it more sensitive to US amplitude and MI. Corrections applied to the probe significantly improve vascular image contrast before SVD filtering. Additionally, the study confirms the importance of optimizing US amplitude by demonstrating that H-CEUS visualizes blood flow in rabbit lymph nodes when the velocity is below 3 mm/s [35–38]. These findings highlight the advantages and characteristics of H-CEUS in vivo and in vitro, particularly in lymph node detection [33]. In contrast, our study focuses more on the practical application and comparative diagnostic efficacy in clinical settings, emphasizing the utility and reliability of this technology. The results of our practice demonstrate that H-CEUS is superior to conventional CEUS.

The principle of CEUS involves injecting contrast agents into the peripheral veins to enhance the contrast between different tissues, thus improving the detection rate of lesions (Fig. 6). CEUS relies on scattering microbubbles within blood vessels to image pathological tissues. H-CEUS enhances temporal resolution by increasing the frame acquisition rate, allowing for better visualization of arterial-phase perfusion information, thereby improving diagnostic sensitivity, specificity, and accuracy [33, 39].

In this study, H-CEUS and CEUS showed similar performance in terms of enhancement homogeneity, with no significant differences between the two. This result aligns with existing studies, indicating comparability between H-CEUS and CEUS in lymph node perfusion characteristics. However, this result raises new questions regarding situations where H-CEUS may outperform CEUS. Further research may need to consider more complex lymph node features and clinical contexts. The study revealed significant differences in enhancement patterns between benign and metastatic lymph nodes. Compared to CEUS, H-CEUS provides a clearer visualization of the microvascular morphology of lymph nodes. This finding corroborates certain existing studies and underscores the potential value of H-CEUS in lymph node differential diagnosis [40]. These results may guide future quantitative analysis of lymph nodes and the development of new diagnostic algorithms.

This study through H-CEUS may help assess lymph node blood perfusion more accurately by clearly displaying the microvascular morphology of lymph nodes, thus enhancing diagnostic precision. In comparison to existing research, this finding highlights the specific advantages of H-CEUS in lymph node differential diagnosis and may encourage the incorporation of H-CEUS into broader clinical practice [41–43].

This study directly compared H-CEUS and CEUS, revealing that H-CEUS demonstrates higher sensitivity, specificity, and accuracy in differentiating the nature of superficial lymph nodes. Its advantages lie in the superior temporal resolution and more apparent enhancement patterns, providing more valuable diagnostic information. While CEUS also exhibits high diagnostic efficacy, H-CEUS outperforms in certain aspects, such as enhancement homogeneity and visibility of portal vessels. These findings indicate that H-CEUS holds greater clinical utility in distinguishing benign and malignant lymph nodes.

Compared to existing literature, the primary innovation of this study is the first direct comparison of the efficacy of H-CEUS and CEUS in lymph node diagnostics. The study also highlights significant differences in enhancement patterns between benign and malignant lymph nodes, offering a fresh perspective for differential diagnosis of lymph nodes. These discoveries not only enhance current scientific understanding but also have the potential for a direct impact on clinical practice.

While this study has made significant progress, there are still technical challenges in applying H-CEUS and CEUS, such as optimizing image resolution and quality. Future research should explore overcoming these challenges to enhance the efficacy of lymph node differential diagnosis. It may require developing new imaging techniques and diagnostic algorithms compared to existing solutions.

Some limitations of this study include a relatively small sample size and a focus on lymph nodes in the neck. Additionally, differences between equipment and operators may influence the results. Future research should consider larger sample sizes and multicenter study designs to validate this study's findings.

Overall, this study provides new theoretical foundations for diagnosing the nature of superficial lymph nodes by directly comparing H-CEUS and CEUS's efficacy in the differential diagnosis of the lymph nodes. Compared to existing research, this study confirms certain viewpoints and introduces new observations and insights. Future work may focus on further optimizing techniques, expanding the scope of application, and incorporating H-CEUS more extensively into clinical practice.

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Author contributions
Shuyuan Liang and Peng Han contributed equally to this work. Shuyuan Liang and Peng Han designed the study, analyzed the data, and drafted the manuscript. Xiang Fei and Lianhua Zhu were involved in data collection and interpretation. Liuqing Peng and Fang Xie contributed to the statistical analysis and manuscript revision. Yukun Luo supervised the study, provided critical revisions, and finalized the manuscript. All authors approved the final version of the manuscript.

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Data availability
The data generated or analyzed for this study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
This study does not involve animal ethics. The clinical ethics approval was obtained from the Chinese PLA General Hospital ethics committee (Approval No. S2022-479-01). All patients involved in this study have voluntarily signed informed consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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