

Diagnostic performance of contrast-enhanced ultrasound vs. conventional ultrasound for lymph node metastasis in patients with thyroid cancer: A meta-analysis

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Abstract. The ability of conventional ultrasound (US) and contrast-enhanced (CE)US to diagnose lymph node metastasis in patients with thyroid cancer has been explored, but there is a lack of a pooled analysis. In the present study, a meta-analysis was performed to explore the diagnostic performance of conventional US and CEUS for lymph node metastasis in patients with thyroid cancer. The PubMed, Web of Science, Embase and Cochrane Library databases were searched to identify studies related to the diagnosis of lymph node metastasis using CEUS and conventional US in patients with thyroid cancer published until February 2024. This meta-analysis incorporated 9 studies, involving a total of 1,226 patients with thyroid cancer. The quality assessment of diagnostic accuracy studies-2 tool suggested that the quality of the included studies was good. A summary receiver operating characteristic analysis was performed to assess the diagnostic performance of conventional US and CEUS. The pooled sensitivity [95% confidence interval (CI)], specificity (95% CI) and the area under curve (AUC) of conventional US for diagnosing lymph node metastasis were 0.77 (0.73-0.80), 0.72 (0.68-0.76) and 0.7925, respectively, in patients with thyroid cancer, while the parameters of CEUS were 0.85 (0.82-0.88), 0.86 (0.82-0.89) and 0.9216, respectively. Overall, the pooled sensitivity, specificity and AUC of CEUS for diagnosing lymph node metastasis were higher than those of conventional US in patients with thyroid cancer (all $P < 0.001$). Deeks' asymmetry test suggested that no publication bias existed in this meta-analysis. In conclusion, CEUS shows a better ability to

diagnose lymph node metastasis than the conventional US in patients with thyroid cancer.

Introduction

Thyroid cancer is the most common endocrine cancer, accounting for 3.0% of all cancer cases and contributing to 0.4% of cancer-related deaths in 2020, worldwide (1,2). Lymph node metastasis occurs in ~30-61% of patients with thyroid cancer, which affects treatment strategies and patients' prognosis (3-5). The American Thyroid Association guidelines recommend conventional ultrasound (US) for the evaluation of lymph node metastasis in patients with thyroid cancer (6). However, current research indicated that the sensitivity and specificity of conventional US for diagnosing lymph node metastasis ranged from 33 to 70% and 84 to 93%, respectively, in patients with thyroid cancer, which suggested a considerable risk of diagnostic errors (7-9). Therefore, investigating a potential method to improve the diagnosis of lymph node metastasis may be important in enhancing the management of patients with thyroid cancer.

Contrast-enhanced (CE)US is a novel imaging technique that utilizes microbubble-based US contrast media (such as Sonovue and Sonazoid) to provide detailed information about the vascularity and perfusion patterns of lymph nodes (10-12). Of note, several studies compared the diagnostic performance of CEUS and conventional US for lymph node metastasis in patients with thyroid cancer (13-21). For instance, one study reported that the sensitivity and specificity of CEUS for diagnosing lymph node metastasis were 0.97 and 0.90, and they were 0.81 and 0.80 for conventional US in patients with thyroid cancer (21). Another study reported that the sensitivity and specificity of CEUS were 0.89 and 0.88 for diagnosing lymph node metastasis, which were 0.75 and 0.84 for the conventional US in patients with thyroid cancer (16). However, there is a lack of meta-analyses to synthesize the data of the previous studies and compare the diagnostic performance of CEUS and conventional US for lymph node metastasis in patients with thyroid cancer. On the other hand, a previous meta-analysis reported that CEUS had a good ability to diagnose lymph node metastasis in patients with papillary thyroid cancer, with a pooled

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sensitivity and specificity of 0.80 and 0.90, respectively (22). However, this previous meta-analysis only included studies that reported the diagnostic performance of CEUS for lymph node metastasis in patients with papillary thyroid cancer (22). Considering that conventional US is the recommended imaging method to evaluate lymph node metastasis, and there is still room for improvement in its diagnostic performance, it is meaningful to compare the diagnostic performance between conventional US and CEUS. This comparative analysis may provide evidence regarding the superior imaging method for diagnosing lymph node metastasis, thereby improving the management of patients with thyroid cancer.

Therefore, the current meta-analysis aimed to explore the sensitivity, specificity and area under curve (AUC) of CEUS and conventional US for diagnosing lymph node metastasis in patients with thyroid cancer.

Materials and methods

Search strategy. The PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofscience.com>), Embase (<https://www.embase.com>) and Cochrane Library (<https://www.cochranelibrary.com>) databases were systematically searched to identify studies related to the diagnosis of lymph node metastasis using CEUS vs. conventional US in patients with thyroid cancer. The key words used for the search were as follows: ‘Contrast-enhanced ultrasound’, ‘CEUS’, ‘contrast-enhanced’, ‘ultrasound’, ‘ultrasonography’, ‘US’, ‘thyroid cancer’, ‘thyroid carcinoma’, ‘lymphatic metastasis’ and ‘lymph node metastasis’. Entries added from inception to February 2024 were included. JHG and YL conducted the search. In case of any disagreements, the remaining authors (LPZ, XGW, YLW and TXZ) were consulted. The lists of references of the articles were also searched to find any missed studies. For studies with incomplete data, it was attempted to contact the study investigators to retrieve those data, but no response was received. This meta-analysis was conducted in accordance with the PRISMA statement (23). It was attempted to register the meta-analysis on PROSPERO (<https://www.crd.york.ac.uk/PROSPERO/>) but restrictions were encountered, as the ‘diagnostic test accuracy review’ category was unavailable for selection.

Eligibility criteria. The inclusion criteria for study selection were as follows: i) Patients were diagnosed with thyroid cancer based on pathological findings from either surgical or needle biopsy procedures; ii) patients underwent CEUS and conventional US (B-Mode and Doppler) simultaneously for the detection of lymph node metastasis; iii) studies with complete 2x2 contingency tables or with sufficient data to reconstruct 2x2 contingency tables to assess the diagnostic efficacy using CEUS and conventional US; and iv) studies were published in English. On the other hand, the exclusion criteria were: i) Studies without pathological examination as the reference standard; ii) studies reported on the use of CEUS or conventional US alone in detecting lymph node metastasis; iii) case reports, animal experiments, reviews or meta-analyses.

Data extraction and risk of bias. Characteristics including the first author's name, year of publication, study design, sample size, age at diagnosis, gender, contrast agent for CEUS and

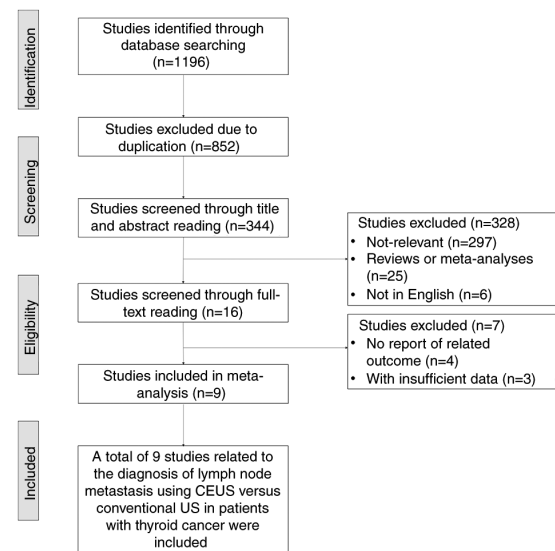


Figure 1. Flow chart of study selection. CEUS, contrast-enhanced ultrasound.

details of the ultrasound machine were retrieved from the included studies. Besides, 2x2 contingency tables containing values of true-positive, false-positive, false-negative and true-negative for the diagnostic efficacy of CEUS and conventional US were also collected. If the studies did not have direct data on 2x2 contingency tables, they could be calculated using sensitivity, specificity, positive predictive value or negative predictive value. To evaluate the quality of the included studies, the quality assessment of diagnostic accuracy studies (QUADAS)-2 tool was used (24).

Statistical analysis. MetaDiSc (ver.1.4) (25) and STATA statistical software (ver.14.0; StataCorp LP) were used for data synthesis, and determination of the pooled sensitivity with 95% confidence interval (CI), pooled specificity with 95% CI, summary receiver operating characteristic (SROC) curve and diagnostic odds ratio (DOR) were conducted. The Chi-square test and I^2 test were conducted to evaluate the heterogeneity; $P < 0.05$ indicated heterogeneity for the Chi-square test and $I^2 \geq 50\%$ for the I^2 test. The random-effects model was used for data synthesis. Deeks' funnel plot analysis was conducted to assess publication bias, in which the Deeks' asymmetry test was used. The robustness assessment was conducted by omitting individual studies one by one. The Z-test was used to compare the diagnostic performance between US and CEUS. $P < 0.05$ was considered to indicate statistical significance.

Results

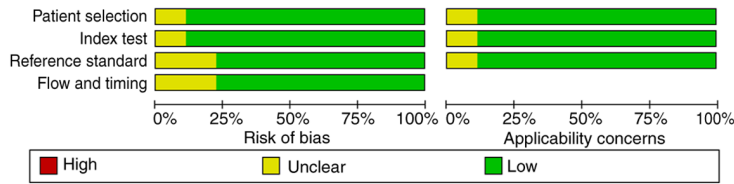
Study selection. A total of 1,196 studies were identified through database searching. Subsequently, 852 duplicated studies were excluded and the remaining 344 studies were screened based on title and abstract reading. Subsequently, 328 studies were excluded because they were irrelevant ($n=297$), reviews or meta-analyses ($n=25$) or not written in English ($n=6$). A total of 16 studies were further screened based on full-text reading and 7 studies were excluded. Finally, a total of 9 studies were included in this meta-analysis (13-21) (Fig. 1).

Table I. Characteristics of included studies.

Author, year	Study design	Sample size	Age at diagnosis, years	Gender (M/F)	Contrast agent for CEUS		Ultrasound machine	(Refs.)
					Type	Dosage		
Xiang, 2014	Retrospective	82	Median: 42.0; Range: 18.0-72.0	28/54	SonoVue	5.0 ml 0.9% saline and SonoVue were mixed by oscillation, then a contrast bolus of 1.2 ml was injected, followed by a 5.0-ml saline solution flush	MyLab X90 vision system (Esaote)	(13)
Hong, 2017	Prospective	573	Mean: 49.5; SD: 13.8	148/425	SonoVue	5.0 ml 0.9% saline and SonoVue were mixed by oscillation, then a contrast bolus of 1.2 ml was injected, followed by a 5.0-ml saline solution flush	MyLab Twice system (Esaote)	(14)
Zhan, 2019	Prospective	56	Mean: 52.6; SD: 13.5	16/40	SonoVue	5.0 ml 0.9% saline and SonoVue were mixed by oscillation, then a contrast bolus of 1.2 ml was injected, followed by a 5.0-ml saline solution flush	Acuson S2000 system (Siemens AG); Aplio 400 (Toshiba)	(15)
Chen, 2020	Retrospective	46	Mean: 47.1; SD: 13.9	6/40	SonoVue	5.0 ml 0.9% saline and SonoVue were mixed by oscillation, then a contrast bolus of 1.2 ml was injected, followed by a 5.0-ml saline solution flush	LOGIQ E9 US system (GE Healthcare)	(16)
Wang, 2021	Retrospective	120	Mean: 44.2; SD: 11.7	37/83	SonoVue	1.8-2.0 ml of the suspension was rapidly pushed into the patient's peripheral vein	iU22 system (Philips)	(17)
Wei, 2021	Prospective	24	Mean: 39.9; SD: 10.9	14/10	Sonazoid	0.1 ml of Sonazoid in 2 ml of saline was injected	LOGIQ E9 US system (GE Healthcare)	(18)
Zhang, 2022	Prospective	126	Median: 46.0; Range: 19.0-77.0	31/95	SonoVue	5.0 ml 0.9% saline and SonoVue was mixed by oscillation. A contrast bolus of 2.4 ml was injected, followed by a 5.0-ml saline solution flush	Not mentioned	(19)
Xiao, 2023	Prospective	135	Median: 36.0; IQR: 30.0-46.0	35/100	Sonazoid	An intravenous bolus injection of 0.015 ml/kg of Sonazoid, followed by 5 ml of saline	ACUSON Sequoia system (Siemens AG)	(20)
Zhang, 2023	Prospective	64	Mean: 45.0; SD: 12.0	12/52	Sonazoid	Mixing the dry powder with 2 ml of sterilized water	MyLab Twice system (Esaote)	(21)

Ultrasound machine was described with the system (manufacturers, country). CEUS, contrast-enhanced ultrasound; M, male; F, female; SD, standard deviation; IQR, interquartile range.

A



B

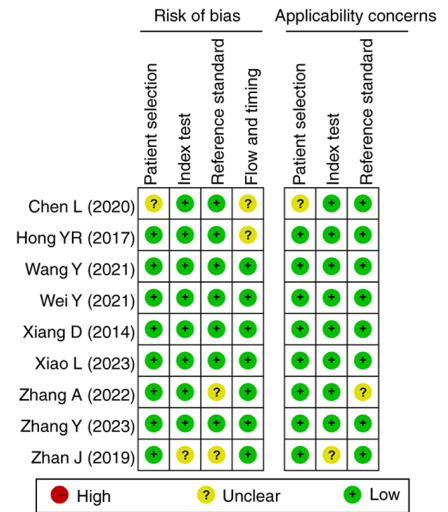


Figure 2. Risk of bias assessed using quality assessment of diagnostic accuracy studies-2 tools. (A) The proportion of studies with high, unclear and low risk of bias, as well as applicability concerns. (B) Detailed information on each study with high, unclear and low risk of bias, as well as applicability concerns.

Features of screened studies. The 9 studies included comprised 1,226 patients with thyroid cancer. There were 3 retrospective studies and 6 prospective studies (13-21). The contrast agent for CEUS was SonoVue in 6 studies and Sonazoid in 3 studies. The detailed features of the included studies are provided in Table I. All included studies were conducted in China. The region was Zhejiang province in 2 studies, Shanghai municipality in 1 study, Beijing municipality in 3 studies, Gansu province in 1 study, Fujian province in 1 study and Guangdong province in 1 study (Table SI).

Quality assessment. Analysis with QUADAS-2 tools suggested that most of the included studies had a low risk of bias and applicability concerns (Fig. 2A). Detailed information on each study with regard to high, unclear and low risk of bias or applicability concerns is shown in Fig. 2B.

Diagnostic performance of conventional US and CEUS for lymph node metastasis in patients with thyroid cancer. Regarding the sensitivity of conventional US for diagnosing lymph node metastasis in patients with thyroid cancer, heterogeneity existed among the 9 studies ($I^2=83.6\%$, $P<0.001$). Meta-analysis with the random-effects model suggested that the pooled sensitivity (95% CI) was 0.77 (0.73-0.80) (Fig. 3A). Regarding specificity, there was heterogeneity among the 9 studies ($I^2=79.8\%$, $P<0.001$). Meta-analysis with the random-effects model indicated that the pooled specificity (95% CI) was 0.72 (0.68-0.76) (Fig. 3B). SROC curve analysis suggested that the AUC was 0.7925 (Fig. 4).

Regarding the sensitivity of CEUS for diagnosing lymph node metastasis in patients with thyroid cancer, heterogeneity existed in all 9 studies ($I^2=73.9\%$, $P<0.001$). Meta-analysis with the random-effects model suggested that the pooled sensitivity (95% CI) was 0.85 (0.82-0.88) (Fig. 5A). In terms of specificity, there was heterogeneity in 9 studies ($I^2=89.2\%$, $P<0.001$). Meta-analysis with the random-effects model revealed that the pooled specificity was 0.86 (0.82-0.89) (Fig. 5B). The AUC of the SROC curve was 0.9216 (Fig. 6).

The pooled sensitivity, specificity and AUC of CEUS for diagnosing lymph node metastasis were higher than those of conventional US in patients with thyroid cancer (all $P<0.001$), which suggested that CEUS had a better diagnostic performance for lymph node metastasis (Table II).

Subgroup analysis based on study types. In the retrospective studies, the pooled sensitivity (95% CI), pooled specificity (95% CI) and AUC of the SROC curve of conventional US for diagnosing lymph node metastasis were 0.74 (0.66-0.81), 0.67 (0.56-0.76) and 0.8089. In the prospective studies, these values were 0.78 (0.74-0.81), 0.74 (0.69-0.78) and 0.8006. Regarding CEUS, the pooled sensitivity (95% CI), pooled specificity (95% CI) and AUC of the SROC curve of CEUS for diagnosing lymph node metastasis were 0.84 (0.77-0.89), 0.71 (0.61-0.80) and 0.9550, respectively, in the retrospective studies. These values were 0.85 (0.82-0.88), 0.90 (0.86-0.92) and 0.9403, respectively, in the prospective studies (Table SII).

In the retrospective studies, the pooled sensitivity ($P=0.041$) and AUC ($P=0.002$) of CEUS for diagnosing lymph node metastasis were significantly higher than those of conventional US. In the prospective studies, the pooled sensitivity ($P=0.003$), specificity ($P<0.001$) and AUC ($P<0.001$) of CEUS for diagnosing lymph node metastasis were higher than those of conventional US (Table SIII).

Analysis for DOR. The pooled DOR (95% CI) of conventional US and CEUS for diagnosing lymph node metastasis were 7.26 (4.38-12.03) and 34.90 (15.06-80.85) in patients with thyroid cancer. The DOR of CEUS was numerically higher than that of conventional US, but the difference lacked statistical significance ($P=0.102$) (Table SIII).

Publication bias. Deeks' funnel plot asymmetry test revealed that no publication bias existed in the conventional US for diagnosing lymph node metastasis in patients with thyroid cancer ($P=0.153$) (Fig. 7A). Additionally, no potential publication bias existed regarding CEUS for diagnosing lymph node metastasis in patients with thyroid cancer ($P=0.502$) (Fig. 7B).

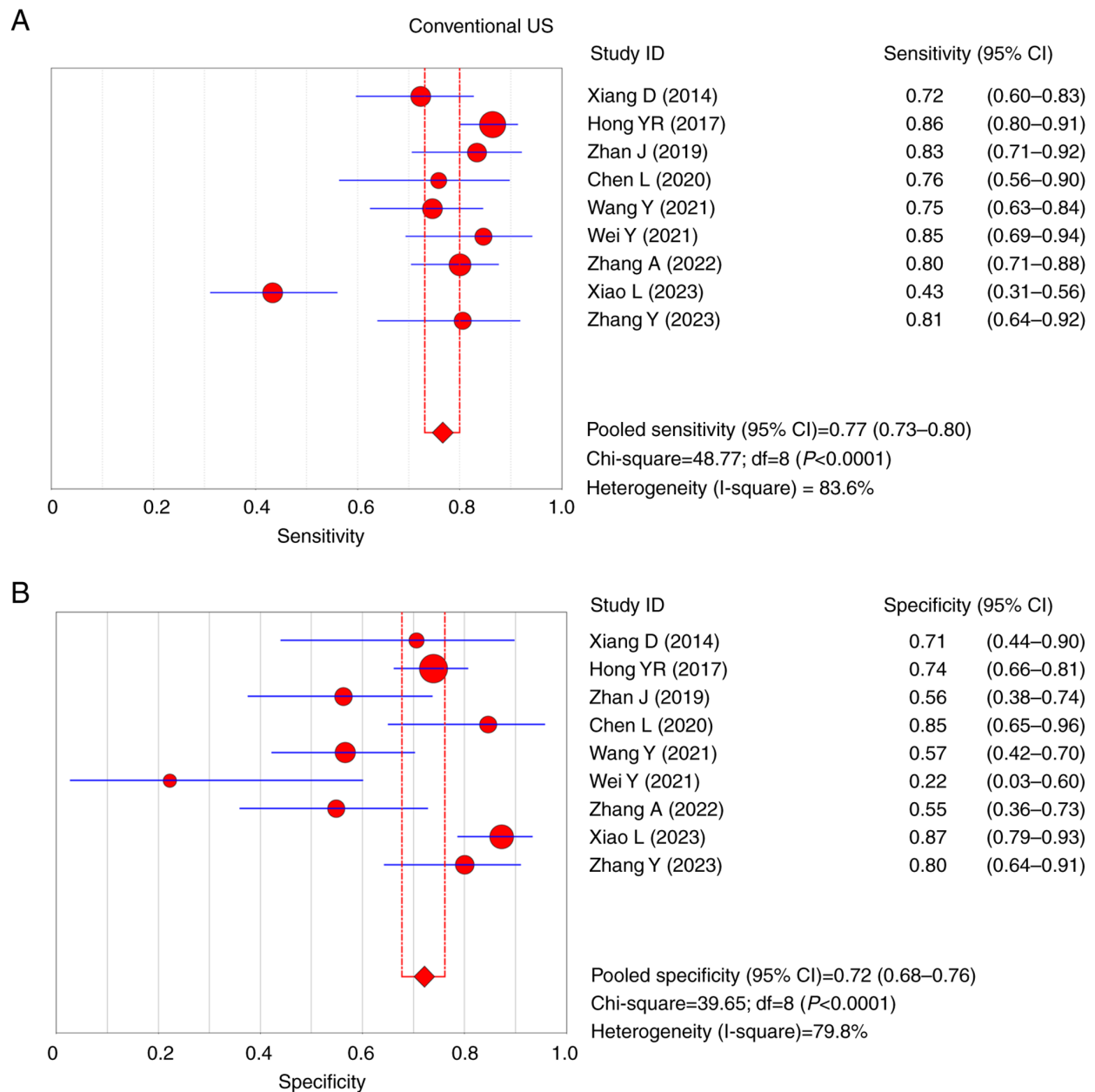


Figure 3. Forest plots for sensitivity and specificity of conventional US. (A) Sensitivity and (B) specificity of conventional US for diagnosing lymph node metastasis in patients with thyroid cancer. US, ultrasound; df, degrees of freedom.

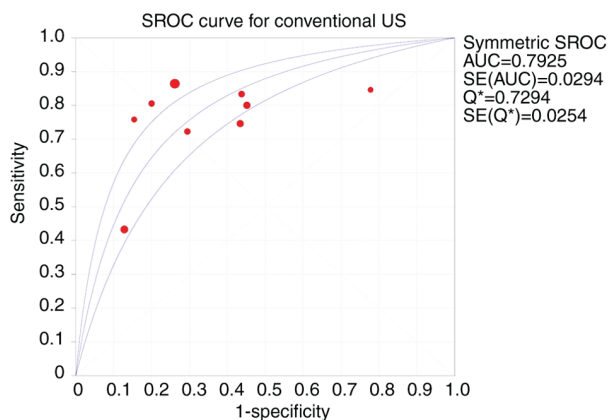


Figure 4. SROC curve of the diagnostic performance of conventional US. US, ultrasound; SROC, summary receiver operating characteristic; AUC, area under the SROC curve; SE, standard error.

Table II. Comparison of the two methods.

Items	P-value
Pooled sensitivity	<0.001
Pooled specificity	<0.001
AUC of SROC	<0.001

SROC, summary receiver operating characteristic; AUC, area under the SROC curve.

Robustness. Omitting any single study did not markedly influence the pooled sensitivity, specificity or AUC of the SROC curve of conventional US and CEUS for diagnosing lymph

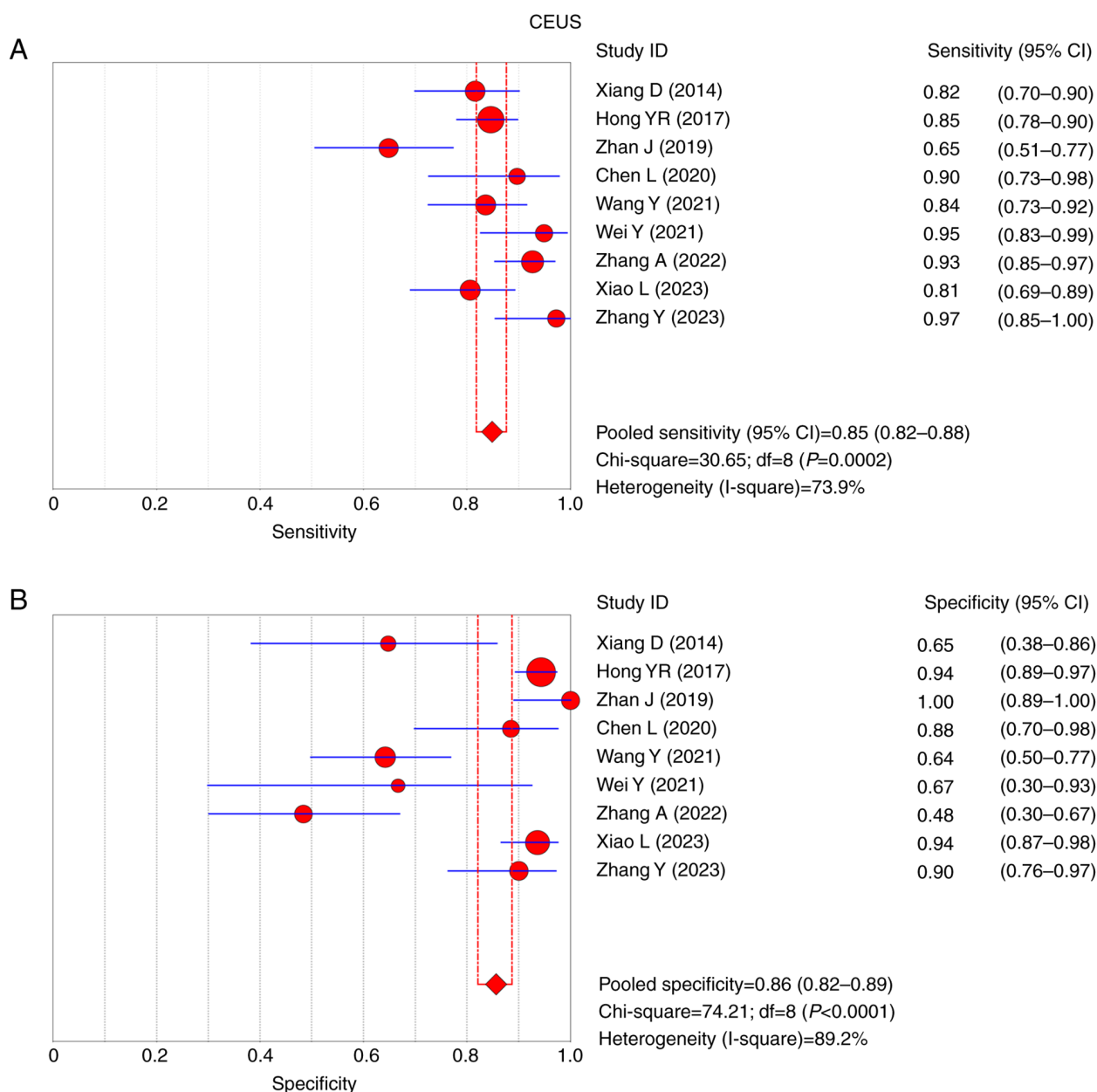


Figure 5. Forest plots for sensitivity and specificity of CEUS. (A) Sensitivity and (B) specificity of CEUS for diagnosing lymph node metastasis in patients with thyroid cancer. CEUS, contrast-enhanced ultrasound; df, degrees of freedom.

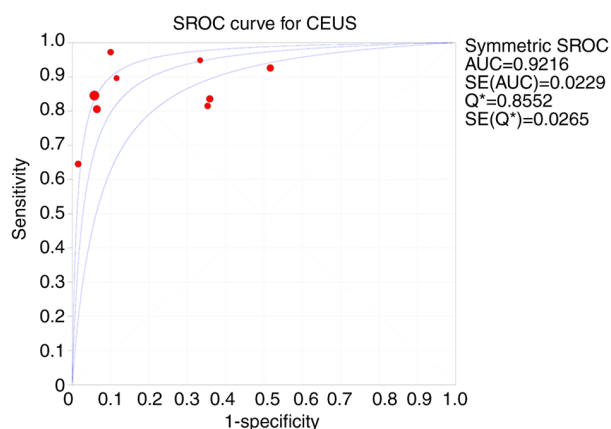


Figure 6. SROC curve of the diagnostic performance of CEUS. CEUS, contrast-enhanced ultrasound; SROC, summary receiver operating characteristic; AUC, area under the SROC curve; SE, standard error.

node metastasis, indicating the acceptable robustness of the present meta-analysis (Table SIV).

Discussion

Conventional US is the preferred method for diagnosing lymph node metastasis, and previous meta-analyses have explored its pooled sensitivity and specificity in patients with thyroid cancer (9,26–29). For instance, one previous meta-analysis indicated that the pooled sensitivity and specificity of conventional US for diagnosing lymph node metastasis of the overall neck region were 0.484 and 0.890, respectively, in patients with thyroid cancer (26). Another meta-analysis reported that the pooled sensitivity and specificity were 0.593 and 0.911 regarding the ability of conventional US to diagnose lymph node metastasis of the whole neck region in patients

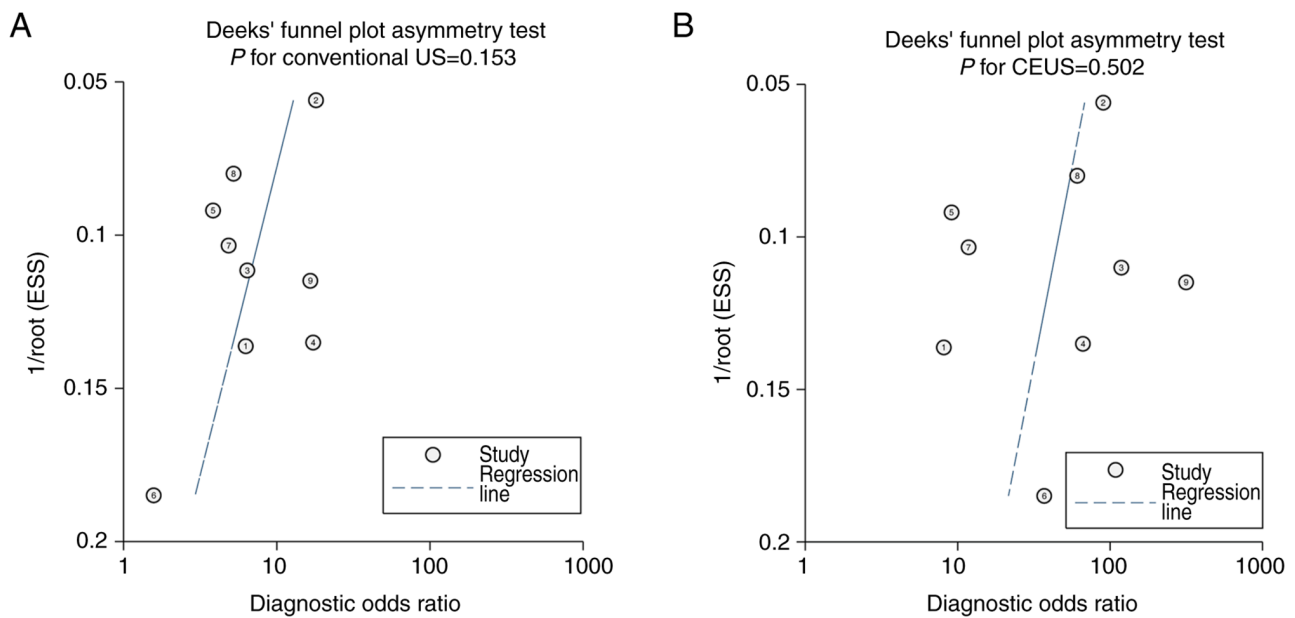


Figure 7. Publication bias assessed by Deeks' funnel plot asymmetry test. Deeks' funnel plot asymmetry test for (A) conventional US and (B) CEUS. CEUS, contrast-enhanced ultrasound. ESS, effective sample size.

with thyroid cancer (28). In the present meta-analysis, it was discovered that the pooled sensitivity and specificity of conventional US in discriminating lymph node metastasis in patients with thyroid cancer were 0.77 and 0.72, respectively. By comparison with previous meta-analyses (26,28), the sensitivity of conventional US for diagnosing lymph node metastasis was higher in our meta-analysis, but the specificity was lower. Different diagnostic strategies could lead to different sensitivity and specificity. Certain studies may apply strict strategies of the conventional US for diagnosing lymph node metastasis, which may have led to high specificity and low sensitivity. Other studies may apply less strict strategies, contributing to high sensitivity and low specificity. In the enrolled studies of this meta-analysis, the diagnostic strategies may be to balance the sensitivity and specificity of conventional US for diagnosing lymph node metastasis as much as possible. Therefore, sensitivity and specificity were relatively balanced in the present meta-analysis. On the other hand, the overall prognosis of patients with thyroid cancer was satisfactory (5-year survival rate of nearly 100%), suggesting the enhancement of the sensitivity of conventional US for diagnosing lymph node metastasis may not markedly improve their prognosis (5,30,31). However, improving the specificity could prevent overdiagnosis and overtreatment (32,33); therefore, other studies in the previous meta-analyses may put more emphasis on the specificity of conventional US for diagnosing lymph node metastasis (26,28). Furthermore, it was found that the AUC of SROC was 0.7925, which suggested that conventional US had an acceptable ability to diagnose lymph node metastasis in patients with thyroid cancer with an AUC of 0.7925.

CEUS is a novel technique used to discriminate metastatic lymph nodes with considerable diagnostic performance in certain cancers, including thyroid cancer (22,34,35). According to a previous meta-analysis, the pooled sensitivity, specificity and AUC of CEUS in diagnosing lymph node metastasis

were 0.80, 0.90 and 0.90 in patients with papillary thyroid cancer (22). In the present meta-analysis, the pooled sensitivity and specificity of CEUS in diagnosing lymph node metastasis were 0.85 and 0.86 in patients with thyroid cancer. In addition, SROC curve analysis suggested that the AUC of CEUS for diagnosing lymph node metastasis was 0.9216 in patients with thyroid cancer. The present findings were comparable to those of the previous meta-analysis (22). The findings of the current meta-analysis revealed that CEUS showed a good ability to diagnose lymph node metastasis in patients with thyroid cancer. A potential reason would be that CEUS utilizes the injection of a contrast agent to improve the visualization of blood flow and perfusion patterns in the lymphatic system, which enhanced the diagnostic performance for lymph node metastasis (12,36,37). Therefore, CEUS had a good ability to diagnose lymph node metastasis in patients with thyroid cancer.

According to the present findings, the pooled sensitivity, specificity and AUC of CEUS for diagnosing lymph node metastasis were higher than those of conventional US in patients with thyroid cancer, which indicated that the diagnostic performance of CEUS for lymph node metastasis was superior to that of conventional US. It should be clarified that this meta-analysis involved both retrospective and prospective studies. Therefore, heterogeneity and confounding factors would exist in these two types of studies, which may have further influenced the present findings. Taking this into account, subgroup analysis based on study type was conducted. It was found that in retrospective and prospective studies, the diagnostic performance of CEUS for lymph node metastasis was better than that of conventional US, which enhanced the reliability of the present findings. Therefore, CEUS could serve as a promising diagnostic method for lymph node metastasis in patients with thyroid cancer. In this meta-analysis, QUADAS-2 tools and Deeks' funnel plot asymmetry test were applied to assess the quality and publication

bias, respectively. These tests suggested that the quality of the present meta-analysis was good and no publication bias existed. Methodologically, forest plots of sensitivity and specificity, as well as Deeks' funnel plots that were used, were in line with previous meta-analyses (9,22,28,38,39). Therefore, the present findings may be reliable.

Histopathology by fine-needle aspiration biopsy is the gold standard for diagnosing lymph node metastasis in patients with thyroid cancer (40). However, this method is invasive, which may lead to infection, bleeding and pain (41). The present meta-analysis discovered that CEUS had a better diagnostic performance for lymph node metastasis than conventional US in patients with thyroid cancer. In addition, it was found that the pooled DOR of CEUS for diagnosing lymph node metastasis was 34.90, which was numerically higher than that of conventional US at 7.26. A higher DOR indicated a stronger ability of the diagnostic test to distinguish between those with the disease and those without (42). Therefore, it was speculated that CEUS may potentially reduce the need for biopsies regarding the diagnosis of lymph node metastasis. However, more shreds of evidence are required to validate this speculation.

In the present meta-analysis, forest plots of sensitivity and specificity were used rather than forest plots showing the hazard ratio (HR) or OR. The reason was as follows: The forest plots of sensitivity and specificity provided different information compared to forest plots showing HR or OR values. Forest plots of sensitivity and specificity focus on the diagnostic performance of a test, while HR or OR forest plots focus on the magnitude and direction of an association between an exposure and an outcome (43,44). In the present meta-analysis, since the diagnostic performance of US and CEUS was being evaluated, the sensitivity and specificity were the most appropriate metrics. The HR or OR would not be applicable, as no exposure or intervention was being assessed.

Several limitations should be mentioned for this meta-analysis: i) All studies were conducted in China, which restricted the generalizability of this meta-analysis; ii) the strategies of CEUS or US for diagnosing lymph node metastasis were inconsistent among the included studies, which could affect the results of this meta-analysis; iii) the contrast agents for CEUS were different, which may have influenced the results of this meta-analysis.

In summary, CEUS is superior to the conventional US for diagnosing lymph node metastasis in patients with thyroid cancer. In clinical practice, CEUS may serve as a potential method to diagnose lymph node metastasis in patients with thyroid cancer. Further studies should delve deeper into evaluating the diagnostic performance of CEUS for lymph node metastasis in specific lesions, such as central and lateral cervical areas, and comparing it to other imaging modalities, such as computed tomography or magnetic resonance imaging, to further validate its role in thyroid cancer management.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TZ and JG contributed to the conception and design of the study. YL and LZ were responsible for the acquisition, analysis and interpretation of the data. XW and YW contributed to methods, data interpretation, manuscript drafting and critical revisions of the intellectual content. TZ and JG confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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