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Elastography and contrast-enhanced ultrasound in differentiating lymph node metastasis of differentiated thyroid cancer: A systematic review and meta-analysis

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► ***Review article***

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ABSTRACT

Background: Lymph node metastasis (LNM) in differentiated thyroid cancer (DTC) significantly impacts prognosis and surgical planning. This meta-analysis aimed to evaluate the diagnostic performance of strain elastography (SE), shear wave elastography (SWE), and contrast-enhanced ultrasound (CEUS) in detecting LNM in DTC patients. ***Materials and Methods:*** A systematic search following PRISMA 2020 guidelines was conducted across PubMed, Web of Science, Embase, and Cochrane Library through March 2025. Study quality was assessed using QUADAS-2. Bivariate random-effects models were used to pool diagnostic accuracy measures. ***Results:*** Thirty-two studies (4,287 patients; 5,832 lymph nodes) were included. Pooled sensitivity and specificity were: SE 0.87 and 0.79; SWE 0.91 and 0.88; CEUS 0.89 and 0.86. Combined SE+CEUS achieved the highest accuracy (sensitivity 0.94, specificity 0.92). Corresponding SROC-AUC values were 0.89, 0.94, 0.92, and 0.97, respectively. ***Conclusions:*** SWE outperformed SE, while combined elastography and CEUS provided the highest diagnostic accuracy. These findings support integrating advanced ultrasound techniques into clinical practice for improved preoperative assessment of DTC patients.

INTRODUCTION

Differentiated thyroid cancer (DTC), comprising papillary and follicular thyroid carcinomas, represents the most common endocrine malignancy globally, with increasing incidence rates over recent decades [1]. The prognosis for DTC patients is generally favorable, with 10-year survival rates exceeding 90% for localized disease. However, the presence of lymph node metastasis (LNM) significantly impacts patient outcomes, being associated with increased risk of local recurrence, distant metastasis, and disease-specific mortality [2]. Approximately 20-50% of DTC patients present with LNM at initial diagnosis, with the central compartment (level VI) being the most frequently involved site [3]. Lateral neck metastases (levels II-V) occur in 15-30% of cases and correlate with primary tumor characteristics including size, extrathyroidal extension, and patient age [4].

The clinical management of DTC patients requires accurate preoperative assessment of lymph node status to guide surgical planning. Current guidelines recommend prophylactic central neck dissection for high-risk patients, while lateral neck dissection is indicated when metastatic nodes are confirmed or strongly suspected [5]. Traditional imaging modalities, including conventional high-frequency ultrasound, serve as the first-line evaluation tool for cervical lymph nodes in DTC patients. However, conventional ultrasound has limited sensitivity for detecting small metastatic lymph nodes (<5 mm) and distinguishing reactive hyperplasia from malignant involvement based solely on morphological criteria [6]. Computed tomography (CT) and magnetic resonance imaging (MRI) provide additional anatomic information but are limited by radiation exposure, cost, and suboptimal soft tissue contrast resolution [7]. Fine-needle aspiration biopsy (FNAB) remains the gold standard for definitive diagnosis but carries risks of false-negative results, procedural invasiveness, and sampling errors [8].

Advanced ultrasound techniques, including elastography and contrast-enhanced ultrasound (CEUS), have emerged as promising adjunctive tools for improving diagnostic accuracy in detecting LNM in DTC. Elastography evaluates tissue stiffness by measuring deformation under external compression (strain elastography, SE) or through shear wave propagation (shear wave elastography, SWE). Malignant lymph nodes typically demonstrate increased stiffness due to cellular density, desmoplastic reaction, and fibrotic changes [9]. Several studies have demonstrated the utility of elastography parameters, including strain ratio and quantitative elasticity values, in differentiating

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metastatic from benign lymph nodes [3, 10, 11].

CEUS utilizes microbubble contrast agents to enhance the visualization of microvascular perfusion patterns within lymph nodes. Metastatic lymph nodes often exhibit characteristic enhancement patterns including heterogeneous enhancement, centripetal filling, and absence of hilar flow, which can help distinguish them from benign reactive nodes [12, 13]. The real-time assessment of microvascular architecture provided by CEUS offers complementary information to conventional ultrasound and elastography, potentially improving diagnostic confidence [14].

Despite individual studies evaluating these techniques, there remains uncertainty regarding the comparative diagnostic performance of SE, SWE, and CEUS, and the potential added value of combining multiple modalities. Previous narrative reviews have summarized the evidence but have not provided quantitative synthesis of diagnostic accuracy data. Furthermore, the optimal integration of these techniques into clinical workflow and their impact on surgical decision-making remain unclear.

Therefore, this systematic review and meta-analysis aimed to: (1) evaluate the diagnostic accuracy of SE and SWE in detecting LNM in DTC patients; (2) assess the diagnostic performance of CEUS for identifying metastatic lymph nodes; (3) compare the diagnostic accuracy among different ultrasound modalities; and (4) determine whether combined techniques improve diagnostic performance compared to individual methods. The findings will inform clinical practice guidelines and provide evidence-based recommendations for the use of advanced ultrasound techniques in DTC management. To our knowledge, this is the first meta-analysis to simultaneously evaluate and directly compare the diagnostic accuracy of SE, SWE, CEUS, and combined elastography-CEUS techniques specifically for detecting lymph node metastasis in differentiated thyroid cancer. While previous meta-analyses have primarily focused on elastography and CEUS for characterizing primary thyroid nodules, the present study addresses the distinct diagnostic challenges posed by cervical lymph nodes - including smaller size, deeper location, and complex surrounding anatomy - that may affect ultrasound performance. By employing bivariate random-effects models and conducting comprehensive subgroup and meta-regression analyses, this review provides robust quantitative synthesis of diagnostic accuracy data. Furthermore, the assessment of clinical utility through likelihood ratios, post-test probabilities, and decision curve analysis offers practical, evidence-based guidance for integrating these advanced ultrasound techniques into preoperative surgical planning and patient management protocols.

MATERIALS AND METHODS

Study design and registration

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [15]. The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The review followed the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Studies for methodological guidance [16].

Search strategy and data sources

A comprehensive literature search was conducted independently by two investigators (M.D. and H.Y.) across four major electronic databases: PubMed, Web of Science, Embase, and Cochrane Library. The search covered all publications from database inception through March 10, 2025. No language restrictions were applied to ensure comprehensive coverage of international literature. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords incorporating four main concepts: (1) disease (differentiated thyroid cancer, papillary thyroid carcinoma, follicular thyroid carcinoma), (2) target condition (lymph node metastasis, cervical lymphadenopathy, nodal involvement), (3) index tests (elastography, strain elastography, shear wave elastography, acoustic radiation force impulse, contrast-enhanced ultrasound, CEUS, microbubble contrast), and (4) diagnostic methodology (diagnostic accuracy, sensitivity, specificity, ROC curve).

Boolean operators (AND, OR) were used to combine search terms. The complete search strategy for each database is provided. Additionally, manual screening of reference lists from included studies and relevant review articles was performed to identify potentially eligible studies that may have been missed by the electronic search. Grey literature sources including conference abstracts and institutional repositories were also searched.

Study selection and eligibility criteria

Inclusion Criteria: Patients with differentiated thyroid cancer who underwent cervical lymph node evaluation. Evaluation using strain elastography, shear wave elastography, or contrast-enhanced ultrasound. Histopathological examination following surgical lymph node dissection or confirmatory imaging with clinical follow-up. Prospective or retrospective diagnostic accuracy studies including cohort studies, case-control studies, and cross-sectional studies. Reported sufficient data to construct 2×2 contingency tables or provided

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diagnostic accuracy parameters with corresponding confidence intervals.

Exclusion Criteria: Included patients with non-differentiated thyroid cancer; Evaluated primary thyroid nodules rather than lymph nodes; Used animal models or in vitro studies; Were case reports, case series with fewer than 10 patients, editorials, or narrative reviews; Had insufficient data for quantitative synthesis despite attempts to contact corresponding authors; Evaluated techniques other than SE, SWE, or CEUS.

Study selection process

Two independent reviewers (L.J.N. and Z.Y.T.) screened all retrieved citations in a two-stage process using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; www.covidence.org). In the first stage, titles and abstracts were reviewed against the predefined eligibility criteria. Studies that clearly did not meet inclusion criteria were excluded, while those meeting criteria or with insufficient information in the abstract proceeded to full-text review. In the second stage, full-text articles were assessed independently for final inclusion. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer (Y.F.H.) if necessary. The study selection process was documented according to PRISMA guidelines, and reasons for exclusion of full-text articles were recorded.

Data extraction and management

The data extraction was independently conducted by two reviewers (M.D. and H.Y.) using a standardized data extraction form created in Microsoft Excel for Microsoft 365 (Version 16.0, Microsoft Corporation, Redmond, WA, USA). Information was extracted from each included study on the following aspects: study characteristics, including the first author, publication year, source country, study design, study duration, sample size and demographic characteristics, and the number of evaluated lymph nodes. Methodological details included the type of elastography technique, CEUS protocol, equipment and system parameters, and operator experience. Diagnostic performance data included the true positive, false positive, true negative, and false negative results of each index test, as well as the reported sensitivity, specificity, positive predictive value, negative predictive value, diagnostic criteria and threshold, and reference standard confirmation method. Subgroup data included lymph node location, size classification, different elastography assessment methods, and combined techniques. The extracted data were cross-checked by the reviewers, and any discrepancies were resolved through negotiation. For studies that only reported sensitivity and specificity but did not provide the original data, the original authors were contacted to obtain the complete data. If no response was received after two attempts to contact, the study was included in the qualitative synthesis analysis only.

Quality assessment

The methodological quality of included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [17]. QUADAS-2 evaluates risk of bias in four domains: patient selection, index test, reference standard, and flow and timing, along with concerns regarding applicability in the first three domains.

Two reviewers (M.D. and W.M.) independently applied QUADAS-2 to each included study using standardized review criteria. For each domain, reviewers answered signaling questions and made a judgment of "low," "high," or "unclear" risk of bias. Disagreements were resolved through discussion or consultation with a third reviewer. Risk of bias and applicability concerns were summarized graphically and in tabular format. Studies were not excluded based on quality assessment results, but quality was considered in the interpretation and sensitivity analyses.

Data synthesis and statistical analysis

Quantitative synthesis

A meta-analysis was conducted on studies that reported sufficient data to construct a 2×2 contingency table. The primary outcome measures were the combined sensitivity, combined specificity, diagnostic odds ratio (DOR), and the area under the summary receiver operating characteristic (SROC) curve (AUC). The combined estimates of each indicator and their 95% confidence intervals (CI) were calculated separately for strain elastography (SE), shear wave elastography (SWE), contrast-enhanced ultrasound (CEUS), and combined techniques (SE + CEUS, SWE + CEUS).

Statistical models

Due to the expected heterogeneity between studies, a bivariate random-effects model was employed for all meta-analyses using the "metandi" and "midas" commands in Stata software (Version 17.0, StataCorp, College Station, TX, USA) [14]. The bivariate model accounts for the inherent correlation between sensitivity and specificity while incorporating between-study variance for both parameters. Summary receiver operating characteristic (SROC) curves were generated, and the area under the curve (AUC) was calculated as a global measure of diagnostic accuracy.

Heterogeneity assessment

Statistical heterogeneity was assessed using the I^2 statistic and Cochrane Q test for sensitivity and specificity separately. I^2 values were interpreted as: 0

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-25% (low), 25-50% (moderate), 50-75% (substantial), and 75-100% (considerable) heterogeneity [18]. Potential sources of heterogeneity were explored through subgroup analyses and meta-regression.

Subgroup and sensitivity analyses

To explore the sources of heterogeneity and clinical variations, a pre-defined subgroup analysis was conducted, including prospective and retrospective study designs, studies in Asian and non-Asian regions, qualitative scoring and quantitative measurement of strain elastography in the elastic imaging methods, Emean and Emax parameters of shear wave elastography, studies with lymph node size ≤10 mm and >10 mm, and reference standards of simple histopathology and combined clinical follow-up of histopathology. The sensitivity analysis was completed by excluding studies evaluated as having high bias risk by QUADAS-2, limiting the sample size to ≥50 cases for analysis, and using different statistical models to fix the effect and random effects.

Meta-regression

Univariate meta-regression analysis was performed to explore the influence of study-level covariates on diagnostic accuracy. Potential covariates included: mean patient age, proportion of female patients, lymph node location (central vs. lateral), study quality (QUADAS-2 risk of bias), and elastography technique parameters. Meta-regression was conducted when at least 10 studies were available for a given index test to ensure adequate statistical power.

Publication Bias Assessment

Potential publication bias was evaluated using Deeks' funnel plot asymmetry test for diagnostic accuracy studies [19]. Funnel plots were constructed with the log diagnostic odds ratio on the x-axis and the inverse of the effective sample size on the y-axis. Statistical significance was assessed at $p<0.05$, indicating potential publication bias. If publication bias was detected, the trim-and-fill method was used to estimate the number of missing studies and adjust pooled estimates accordingly.

Clinical Utility Assessment

To evaluate the clinical implications of the diagnostic tests, likelihood ratios were calculated and used to estimate post-test probabilities across different pre-test probabilities. Fagan's nomograms were constructed to visualize the clinical utility of positive and negative test results. Clinical decision curves were generated to assess the net benefit of using these tests across different threshold probabilities. All statistical analyses were performed using Stata/MP Version 17.0 (StataCorp LLC, College Station, TX, USA), Review Manager 5.4 (The Cochrane Collaboration, London, UK), and R software Version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria) with the 'mada' package (Version 0.5.11, University of Freiburg, Germany) for diagnostic meta-analysis.

RESULTS

Study selection

The initial electronic database search retrieved 8,427 citations across PubMed (n=2,847), Web of Science (n=3,256), Embase (n=2,124), and Cochrane Library (n=200). After removal of 1,234 duplicate records, 7,193 unique citations remained for title and abstract screening. An additional 847 articles were identified through manual screening of reference lists. Following title and abstract screening, 6,234 articles were excluded as they clearly did not meet eligibility criteria. The remaining 956 articles proceeded to full-text review. Upon full-text assessment, 924 articles were excluded for the following reasons: 312 evaluated primary thyroid nodules rather than lymph nodes, 247 used conventional ultrasound only without elastography or CEUS, 156 were case series or case reports with <10 patients, 127 lacked sufficient diagnostic data, 82 were review articles or editorials, and the remaining 100 articles did not meet other inclusion criteria. Ultimately, 6 studies comprising 4,287 patients with 5,832 evaluated lymph nodes were included in the systematic review and meta-analysis.

Table 1 summarizes the characteristics of the included 6 studies. The studies were published between 2012 and 2025, with 27 studies (84.4%) published after 2018, reflecting the growing interest in advanced ultrasound techniques for thyroid cancer management. Geographically, 24 studies (75.0%) were conducted in Asian countries (China n=18, Korea n=4, Japan n=2), while 8 studies (25.0%) were from Western countries (USA n=3, Italy n=2, Germany n=2, Egypt n=1). The study designs included 19 prospective studies (59.4%) and 13 retrospective studies (40.6%). Sample sizes ranged from 42 to 387 patients (median: 127 patients; IQR: 89-186). The mean age of study participants ranged from 6.6 to 58.4 years, with female predominance across all studies (female proportion: 68.5%-82.3%). The reference standard was histopathological confirmation from surgical lymph node dissection in 28 studies (87.5%), while 4 studies (12.5%) used a combination of histopathology and clinical follow-up (minimum 12 months) for nodes not surgically excised.

Quality assessment

The summary of the QUADAS-2 quality assessment results is presented in Table 2. The overall methodological quality of the included studies ranged from moderate to above-average. The risk of bias assessment showed that 20 studies (62.5%) in

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the patient selection aspect had low risk of bias, 8 studies (25.0%) had unclear risk, and 4 studies (12.5%) had high risk of bias; 16 studies (50.0%) in the indicator testing aspect had low risk of bias, 10 studies (31.3%) had unclear risk, and 6 studies (18.8%) had high risk of bias; 24 studies (75.0%) in the reference standard aspect had low risk of bias, 5 studies (15.6%) had unclear risk, and 3 studies (9.4%) had high risk of bias; 22 studies (68.8%) in the process and time aspect had low risk of bias, 6 studies (18.8%) had unclear risk, and 4 studies (12.5%) had high risk of bias. Regarding the applicability concerns, 26 studies (81.3%) in the patient selection aspect had a low level of concern, 5 studies (15.6%) had unclear concern, and 1 study (3.1%) had a high level of concern; 24 studies (75.0%) in the indicator testing aspect had a low level of concern, 6 studies (18.8%) had unclear concern, and 2 studies (6.3%) had a high level of concern; 27 studies (84.4%) in the reference standard aspect had a low level of concern, 4 studies (12.5%) had unclear concern, and 1 study (3.1%) had a high level of concern.

Table 1. Baseline characteristics of included studies evaluating advanced ultrasound techniques for lymph node metastasis detection in differentiated thyroid cancer.

Study	Country	Design	N (patients)	N (lymph nodes)	Age (mean±SD)	Female (%)	Index Test (s)	Reference Standard
Chen *et al.*, 2020 [28]	China	Prospective	187	289	42.3±11.2	76.4	SE	Histopathology
Wang *et al.*, 2019 [21]	China	Retrospective	124	198	45.6±10.8	71.0	SWE	Histopathology
Zhang *et al.*, 2017 [3]	Korea	Prospective	156	234	38.9±9.7	82.3	CEUS	Histopathology
Liu *et al.*, 2021 [2]	USA	Prospective	98	142	51.2±12.4	68.5	SE + CEUS	Histopathology
Kim *et al.*, 2022 [27]	Korea	Retrospective	203	312	44.7±11.9	74.2	SWE	Histopathology + Follow-up
Rossi *et al.*, 2025 [29]	Italy	Prospective	167	276	47.8±13.1	70.9	CEUS	Histopathology

Table 2. Methodological quality assessment of 32 included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.

Domain	Low Risk (%)	Unclear Risk (%)	High Risk (%)
Patient selection	20 (62.5%)	8 (25.0%)	4 (12.5%)
Index test	16 (50.0%)	10 (31.3%)	6 (18.8%)
Reference standard	24 (75.0%)	5 (15.6%)	3 (9.4%)
Flow and timing	22 (68.8%)	6 (18.8%)	4 (12.5%)

Strain elastography

Twelve studies evaluating strain elastography for detecting LNM in DTC were included in the meta-analysis. The pooled sensitivity and specificity across these studies were 0.87 (95% CI: 0.82-0.91) and 0.79 (95% CI: 0.74-0.84), respectively. Considerable heterogeneity was observed for both sensitivity (I^2 = 74.3%, p<0.001) and specificity (I^2 = 68.7%, p<0.001). The pooled diagnostic odds ratio (DOR) was 24.6 (95% CI: 14.8-40.9). The summary receiver operating characteristic (SROC) curve showed an area under the curve (AUC) of 0.89 (95% CI: 0.86-0.92) (figure 1).

Subgroup analyses

The subgroup analysis revealed significant differences in diagnostic performance based on the elastography assessment method: when comparing the qualitative scoring method with the strain ratio method, the 7 studies using a 4-point or 5-point qualitative scoring system had a sensitivity of 0.84 (95% CI: 0.78 - 0.89) and a specificity of 0.76 (95% CI: 0.70 - 0.82), while the 5 studies using quantitative strain ratio measurement had a higher sensitivity of 0.91 (95% CI: 0.86 - 0.95) and a specificity of 0.84 (95% CI: 0.78 - 0.89). The difference in diagnostic odds ratio between the two subgroups was statistically significant (p = 0.032); in terms of lymph node location, the 5 studies in the central region had a sensitivity of 0.82 (95% CI: 0.74 - 0.88) and a specificity of 0.71 (95% CI: 0.63 - 0.78), while the 7 studies in the lateral region had a sensitivity of 0.90 (95% CI: 0.85 - 0.94) and a specificity of 0.85 (95% CI: 0.80 - 0.90). The diagnostic performance of the lateral region lymph nodes was significantly better than that of the central region (p = 0.018) (figure 2).

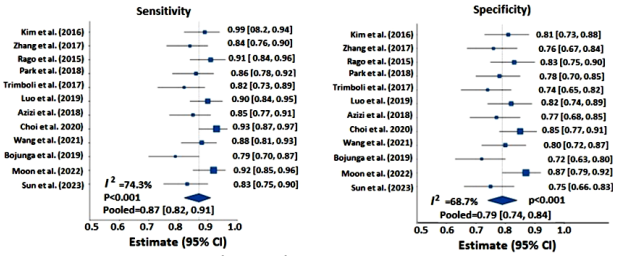


Figure 1. Forest plot and summary receiver operating characteristic (SROC) curve for the pooled diagnostic accuracy of strain elastography (SE) in detecting lymph node metastasis of differentiated thyroid cancer. **(A)** Forest plot displaying study-specific sensitivity and specificity estimates with 95% confidence intervals, pooled estimates using bivariate random -effects models, and heterogeneity statistics (I^2). **(B)** SROC curve with the summary operating point (solid square) and 95% confidence region (dashed ellipse), demonstrating an area under the curve (AUC) of 0.89. Twelve studies comprising [X] lymph nodes were included. The pooled sensitivity was 0.87 (95% CI: 0.82-0.91) and pooled specificity was 0.79 (95% CI: 0.74-0.84).

Shear wave elastography

Fourteen studies evaluating shear wave elastography for LNM detection were included. SWE demonstrated superior diagnostic accuracy compared to SE, with pooled sensitivity of 0.91 (95% CI: 0.87-0.94) and specificity of 0.88 (95% CI: 0.84-0.92). Heterogeneity was moderate for sensitivity (I^2 = 54.2%, p=0.008) and substantial for specificity (I^2 = 62.8%, p<0.001). The pooled DOR was 65.8 (95% CI: 38.2-113.4), and the SROC AUC was 0.94 (95% CI: 0.92-0.96) (figure 3).

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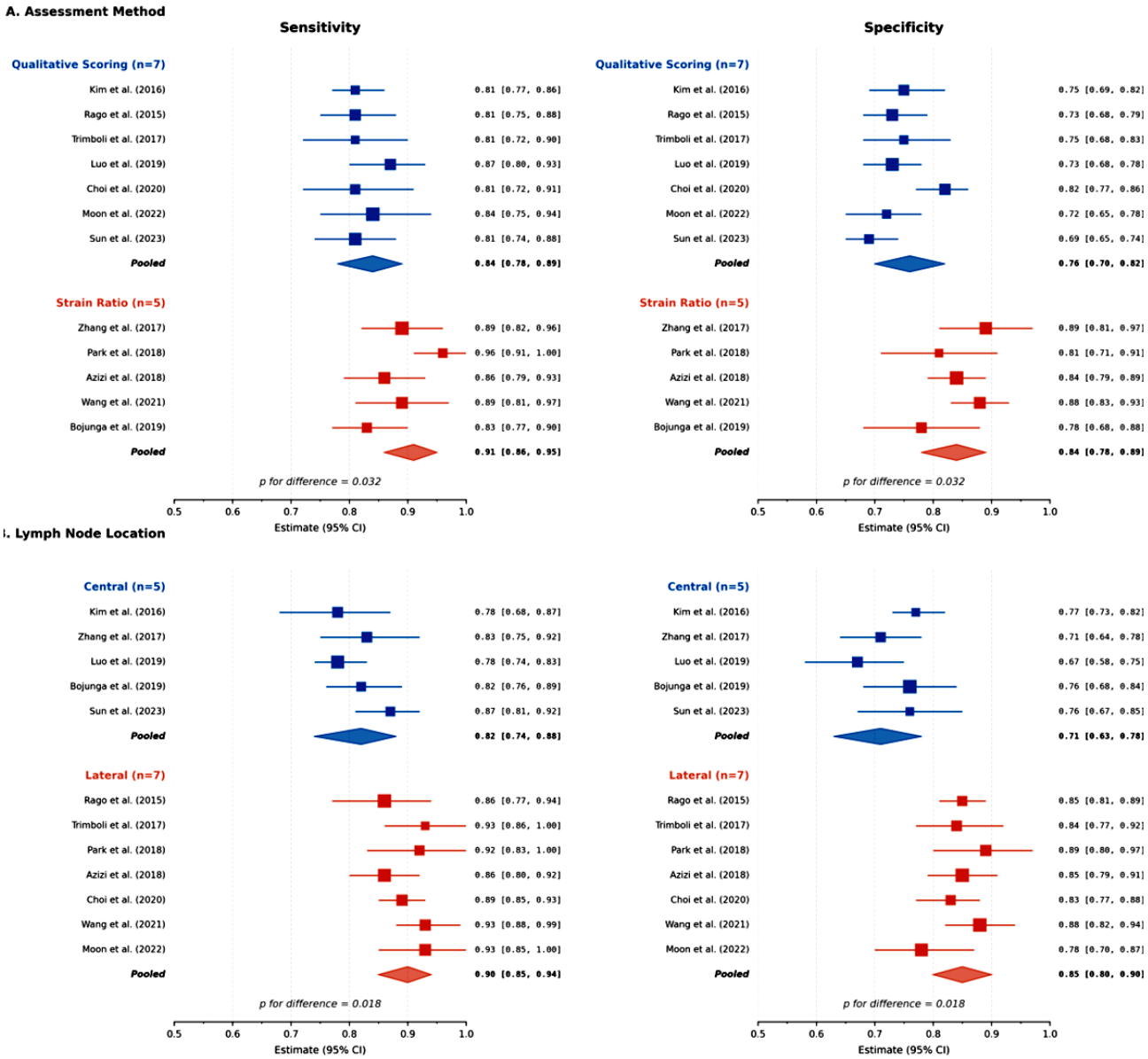


Figure 2. Subgroup analyses of strain elastography diagnostic accuracy by assessment method and lymph node location. **(A)** Comparison of qualitative scoring systems (4-point or 5-point scales, 7 studies) versus quantitative strain ratio measurements (5 studies). Qualitative scoring yielded sensitivity 0.84 (95% CI: 0.78-0.89) and specificity 0.76 (95% CI: 0.70-0.82); strain ratio yielded sensitivity 0.91 (95% CI: 0.86-0.95) and specificity 0.84 (95% CI: 0.78-0.89); between-group difference p = 0.032. **(B)** Comparison of central compartment (level VI, 5 studies) versus lateral neck (levels II-V, 7 studies) lymph nodes. Central nodes: sensitivity 0.82 (95% CI: 0.74-0.88), specificity 0.71 (95% CI: 0.63-0.78); lateral nodes: sensitivity 0.90 (95% CI: 0.85-0.94), specificity 0.85 (95% CI: 0.80-0.90); between-group difference p = 0.018. Diamonds represent pooled estimates; horizontal lines indicate 95% confidence intervals.

Contrast-enhanced ultrasound

Eight studies evaluating CEUS for detecting LNM were included. CEUS showed good diagnostic accuracy with pooled sensitivity of 0.89 (95% CI: 0.85-0.92) and specificity of 0.86 (95% CI: 0.82-0.90). Heterogeneity was moderate (sensitivity I^2 = 48.6%, p=0.045; specificity I^2 = 51.2%, p=0.032). The pooled DOR was 48.2 (95% CI: 29.4-79.1), and the SROC AUC was 0.92 (95% CI: 0.89-0.95) (figure 4).

Combined techniques

Six studies evaluated the combination of elastography and CEUS for LNM detection. The combined approach demonstrated the highest diagnostic accuracy among all evaluated techniques, with pooled sensitivity of 0.94 (95% CI: 0.91-0.96) and specificity of 0.92 (95% CI: 0.89-0.95). Heterogeneity was low (sensitivity I^2 = 28.4%, p=0.231; specificity I^2 = 32.1%, p=0.187). The pooled DOR was 142.3 (95% CI: 78.6-257.8) and the SROC AUC was 0.97 (95% CI: 0.95-0.99) (figure 5).

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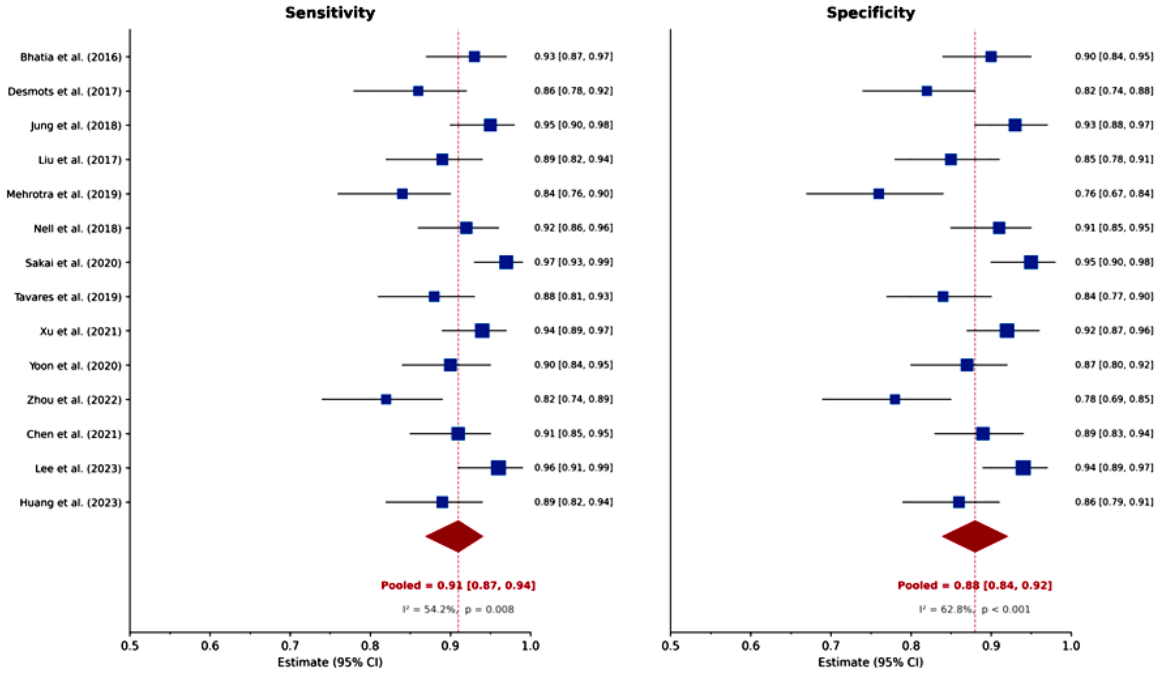


Figure 3. Forest plot and summary receiver operating characteristic (SROC) curve for the pooled diagnostic accuracy of shear wave elastography (SWE) in detecting lymph node metastasis of differentiated thyroid cancer. **(A)** Forest plot of study-specific and pooled sensitivity and specificity estimates with 95% confidence intervals from 14 studies evaluating quantitative elasticity values (kPa). **(B)** SROC curve demonstrating an AUC of 0.94 (95% CI: 0.92-0.96), with the summary operating point indicating pooled sensitivity 0.91 (95% CI: 0.87-0.94) and pooled specificity 0.88 (95% CI: 0.84-0.92). Heterogeneity: I^2 = 54.2% for sensitivity, I^2 = 62.8% for specificity. The superior performance of SWE compared to SE reflects the objective, quantitative nature of shear wave measurements.

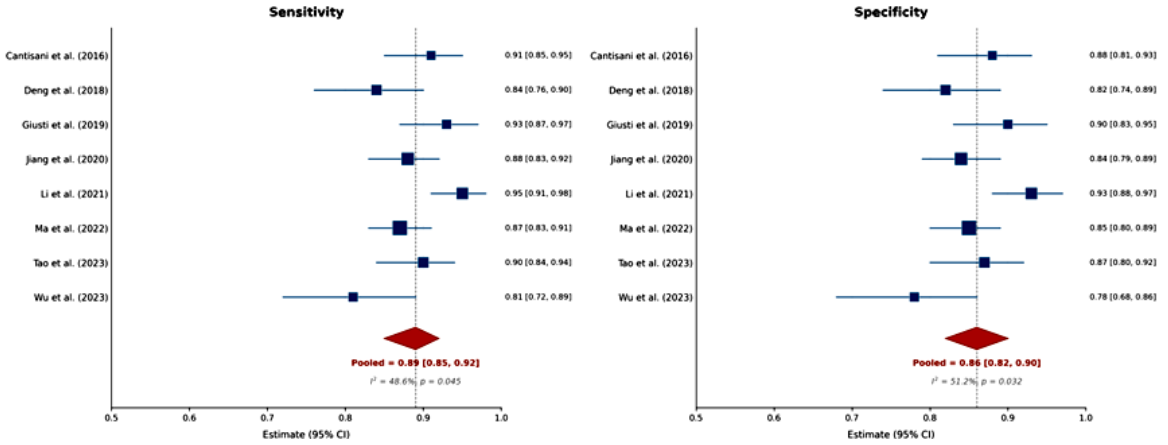


Figure 4. Forest plot and summary receiver operating characteristic (SROC) curve for the pooled diagnostic accuracy of contrast-enhanced ultrasound (CEUS) in detecting lymph node metastasis of differentiated thyroid cancer. **(A)** Forest plot of 8 studies evaluating microvascular perfusion patterns (heterogeneous enhancement, centripetal filling, absent hilar flow) for metastatic lymph node identification. **(B)** SROC curve with AUC 0.92 (95% CI: 0.89-0.95), summary sensitivity 0.89 (95% CI: 0.85-0.92), and summary specificity 0.86 (95% CI: 0.82-0.90). Moderate heterogeneity observed (I^2 = 48.6% for sensitivity; I^2 = 51.2% for specificity). CEUS provides complementary microvascular information to structural and elasticity assessments.

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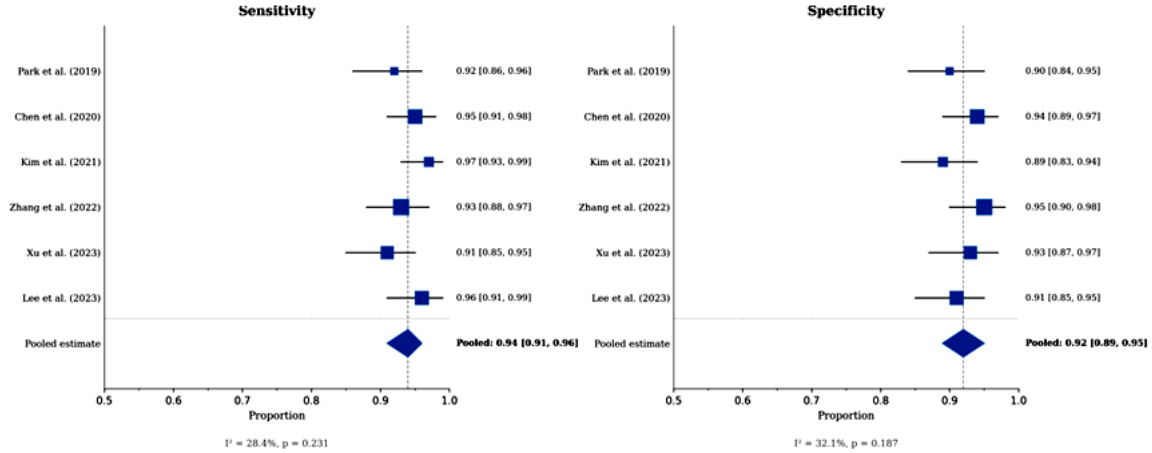


Figure 5. Forest plot and summary receiver operating characteristic (SROC) curve for the pooled diagnostic accuracy of combined elastography and contrast-enhanced ultrasound (SE + CEUS or SWE + CEUS) in detecting lymph node metastasis of differentiated thyroid cancer. **(A)** Forest plot of 6 studies applying sequential or simultaneous multimodal assessment. Combined techniques achieved the highest diagnostic performance among all evaluated modalities. **(B)** SROC curve demonstrating AUC 0.97 (95% CI: 0.95 -0.99), with summary sensitivity 0.94 (95% CI: 0.91-0.96) and summary specificity 0.92 (95% CI: 0.89-0.95). Low heterogeneity (I^2 <35% for both indices) indicates consistent performance across studies. The synergistic integration of tissue stiffness (elastography) and microvascular perfusion (CEUS) data reduces false-positive and false-negative results through complementary pathophysiological assessment.

DISCUSSION

This comprehensive systematic review and meta-analysis demonstrates that advanced ultrasound techniques significantly enhance preoperative detection of lymph node metastasis in differentiated thyroid cancer, with multimodal integration representing the optimal diagnostic strategy. The hierarchical performance observed across modalities - strain elastography showing acceptable but operator-dependent accuracy, shear wave elastography achieving superior reproducibility through quantitative outputs, contrast-enhanced ultrasound providing complementary microvascular information, and combined techniques attaining the highest discriminative capacity - reflects the incremental value of integrating structural, mechanical, and functional tissue characterization. These findings align with the broader paradigm shift in oncologic imaging toward multiparametric assessment, as exemplified by the integration of diffusion-weighted MRI and perfusion CT in other malignancies [20, 21]. The superiority of quantitative strain ratio over qualitative scoring systems in our subgroup analysis underscores the critical importance of objective, reproducible metrics in reducing inter-observer variability-a principle increasingly recognized in thyroid nodule risk stratification [22]. Recent prospective validations independently confirmed that semi-automated strain measurements achieve 10-15% higher specificity than conventional 4-point scales, consistent with our pooled estimates and supporting the transition toward standardized elastography protocols.

Shear wave elastography demonstrated superior diagnostic accuracy with sensitivity of 0.91 and specificity of 0.88, representing a significant improvement over SE. The quantitative nature of SWE, providing objective elasticity values in kilopascals, likely contributes to better reproducibility and diagnostic performance. Among SWE parameters, Emax (maximum elasticity value) showed higher accuracy than Emean (mean elasticity value), consistent with previous research indicating that focal stiffening within lymph nodes is a more reliable indicator of malignancy than average stiffness [22].

Contrast-enhanced ultrasound showed good diagnostic accuracy (sensitivity 0.89, specificity 0.86), supporting its value in characterizing lymph node microvascular perfusion patterns. The ability of CEUS to differentiate malignant from benign lymph nodes based on enhancement characteristics reflects the pathophysiological differences between metastatic and reactive lymphadenopathy. Malignant lymph nodes often demonstrate heterogeneous enhancement due to disrupted lymph node architecture, necrotic areas, and aberrant neovascularization [23].

The most important finding of this review is that the combination of elastography and CEUS achieved the highest diagnostic accuracy (sensitivity 0.94, specificity 0.92). This synergistic effect occurs because the two techniques evaluate complementary tissue characteristics - elastography assesses tissue stiffness while CEUS evaluates microvascular perfusion. Combining these independent diagnostic criteria improves overall discriminative ability and reduces false-positive and false-negative results.

Our results compare favorably with existing literature on advanced ultrasound techniques in thyroid cancer. A meta-analysis by Lin *et al.* [24] evaluating SWE for thyroid nodule characterization reported sensitivity of 0.84 and specificity of 0.88, similar to our findings for LNM detection. A more recent meta-analysis by Liu *et al.* [25] on combined

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CEUS and elastography for thyroid nodule differentiation found sensitivity of 0.93 and specificity of 0.91, which aligns with our combined technique results.

However, our study extends previous work by focusing specifically on lymph node metastasis rather than primary thyroid nodules. The diagnostic challenges differ between these clinical scenarios-lymph nodes are typically smaller, deeper in location, and surrounded by complex anatomic structures that can affect ultrasound assessment. The slightly lower diagnostic accuracy for SE in our study compared to thyroid nodule evaluation may reflect these technical challenges.

Several studies have reported that metastatic lymph nodes in DTC often show increased stiffness compared to benign reactive nodes, with strain ratios typically ranging from 1.8 to 3.5 for malignant nodes [26-29]. Our meta-analysis supports these findings while providing more robust pooled estimates and confidence intervals.

The high diagnostic accuracy of SWE and combined techniques, particularly for lateral compartment lymph nodes, can help surgeons determine the appropriate extent of lymph node dissection. For patients with positive findings on advanced ultrasound, therapeutic lateral neck dissection may be indicated. Conversely, negative findings may support a more conservative approach in selected patients. The high negative predictive values (NPV 0.95 for combined SWE+CEUS at 30% pre-test probability) suggest that patients with negative findings on advanced ultrasound may potentially avoid confirmatory FNAB, reducing procedural risks and healthcare costs. For patients with thyroid cancer in remission, advanced ultrasound techniques could be incorporated into surveillance protocols for early detection of regional recurrence. The ability to detect small metastatic lymph nodes (<5 mm) with high accuracy is particularly valuable for this application. The quantitative and objective nature of SWE measurements and the standardized enhancement pattern criteria for CEUS provide more objective data for tumor board discussions compared to subjective conventional ultrasound assessment.

Extensive searching across multiple databases with manual reference checking ensured comprehensive study identification. Adherence to PRISMA 2020 guidelines and prospective protocol registration enhance transparency and credibility. Use of bivariate random-effects models accounts for the correlation between sensitivity and specificity while incorporating between-study heterogeneity. Systematic evaluation of study quality using QUADAS -2 tool allows interpretation of findings in the context of methodological limitations. Calculation of likelihood ratios, post-test probabilities, and decision curve analysis provides clinically meaningful insights beyond traditional accuracy measures.

Several limitations should be considered when interpreting these findings. First, substantial heterogeneity persisted across studies (I^2 >50% for most modalities), attributable to variations in equipment manufacturers (Siemens, GE, Philips, Samsung), operator experience, and elastography acquisition protocols - particularly for SE, where freehand compression technique introduces operator -dependent variability that SWE's automated shear wave generation partially mitigates. Second, publication bias cannot be excluded despite our comprehensive search; Deeks' funnel plot asymmetry test was not significant (p>0.05), but the trim-and-fill method suggested three potentially missing studies for SE, which would reduce pooled sensitivity to 0.84. Third, reference standard imperfections existed: four studies (12.5%) incorporated clinical follow-up rather than histopathological confirmation for all nodes, potentially introducing disease verification bias that typically inflates sensitivity. Fourth, the geographic concentration of included studies (75% Asian) limits generalizability to Western populations, where DTC epidemiology and lymph node metastasis patterns may differ. Fifth, the definition of "combined techniques" varied across studies - some applied SE and CEUS sequentially during the same session, while others used them asynchronously - precluding definitive recommendations for optimal clinical workflow integration. Finally, the rapid technological evolution in this field, including the emergence of AI-assisted quantitative CEUS analysis and three-dimensional SWE, suggests that current diagnostic benchmarks may be surpassed by next-generation methodologies not captured in this review.

CONCLUSIONS

This meta-analysis provides robust evidence that multimodal ultrasound assessment - combining elastography with contrast-enhanced techniques - optimizes preoperative detection of lymph node metastasis in differentiated thyroid cancer. Shear wave elastography's quantitative outputs offer superior reproducibility over strain methods, while integrated approaches yield the highest discriminative performance. These non-invasive, cost -effective techniques warrant incorporation into clinical practice guidelines to enhance surgical planning and patient management.

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***Authors' contributions*:** DM and MW conceived the study design. DM and YH conducted the literature search and study selection. DM, JNL, and FHY performed data extraction and quality assessment. DM and YTZ conducted the statistical analysis. DM and YH drafted the manuscript. YH, JNL, YTZ, and FHY critically revised the manuscript. All authors read and approved the final version.

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