



Research article

Meta-analysis of ultrasound for cervical lymph nodes in papillary thyroid cancer: Diagnosis of central and lateral compartment nodal metastases

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ABSTRACT

Purpose: To evaluate the performance of preoperative ultrasound in the diagnosis of cervical lymph nodes metastases (CLNM) of papillary thyroid cancer (PTC) and its value in assisting cervical lymph node dissection (CLND).

Methods: PubMed, EMBASE and Cochrane Library databases were searched to identify relevant studies up to Sep. 2017. Overall sensitivity, specificity, and diagnostic odds ratio (DOR) were used to assess the diagnostic efficacy of ultrasound in detecting central and lateral CLNM of PTC.

Results: Nineteen studies comprising 4014 patients were included in the meta-analysis. The pooled sensitivity, specificity, DOR and area under curve (AUC) of ultrasound in detecting central CLNM were 0.33 (95% confidence interval (95% CI): 0.31–0.35), 0.93 (95% CI: 0.92–0.94), 5.63 (95% CI: 3.50–9.04), and 0.69, respectively; and lateral CLNM were 0.70 (95% CI: 0.68–0.72), 0.84 (95% CI: 0.82–0.85), 18.7 (95% CI: 10.3–33.9) and 0.88, respectively. We found that the rate of central CLNM of PTC was 48.0%, and 36.2% of the dissected lymph nodes were metastatic, meanwhile, the rate of lateral CLNM of PTC was 59.2%, and 46.6% of the dissected lymph nodes were metastatic in the meta-analysis.

Conclusions: Preoperative ultrasound demonstrates poor sensitivity in the diagnosis of central CLNM, and good diagnostic efficacy for lateral CLNM of PTC. Prophylactic central CLND is recommended to PTC patients due to the high incidence of central CLNM and low diagnostic efficacy of ultrasound.

1. Introduction

The incidence of thyroid cancer has been increasing in the last decades across the world [1,2], and the increase is nearly exclusively due to papillary thyroid cancer (PTC) [3]. Although most PTC patients have better prognosis compared with those of other cancers, it is worthy of note that cervical lymph node metastases (CLNM) are commonly found in PTC patients [4]. Importantly, those with CLNM are associated with compromised survival in PTC patients, advocating for rigorous preoperative screening for nodal metastasis [5].

Ultrasound has been the first imaging technique in the assessment of CLNM of PTC preoperatively. Many studies have evaluated the effectiveness of preoperative ultrasound in diagnosis of CLNM [6]. These studies, however, reported results with large discrepancy. We therefore

integrated the published data to summarize the diagnostic efficacy of preoperative ultrasound in identifying CLNM of PTC stratified by central and lateral neck levels.

CLNM are divided into two groups the central neck compartment (N1a, level VI or VII) and the lateral compartment (N1b, level I–V). It is well accepted that therapeutic central cervical lymph node dissection (CLND) should be performed for clinically involved central nodes of PTC. However, it's controversial that prophylactic central CLND is performed on PTC patients with cN0 (clinically uninvolved central CLNM) according to ATA guidelines [7]. Therefore, accurate detection of CLNM of PTC is a prerequisite for intervention and prognostic evaluation, which can optimize surgical strategy, and benefit patients receiving radioiodine remnant ablation, and reduce the recurrence and mortality. In the present study, we comprehensively evaluated the

Abbreviations: AUC, area under curve; CT, computed tomography; CLNM, cervical lymph node metastases; CLND, cervical lymph node dissection; DOR, diagnostic odds ratio; FP, false positive; FN, false negative; FDG-PET/CT, fluorodeoxyglucose (18F) positron emission tomography/CT; MRI, magnetic resonance imaging; OR, odds ratio; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; SROC, summary receiver operator characteristic curves; TP, true positive; TN, true negative; 95% CI, 95% confidence interval

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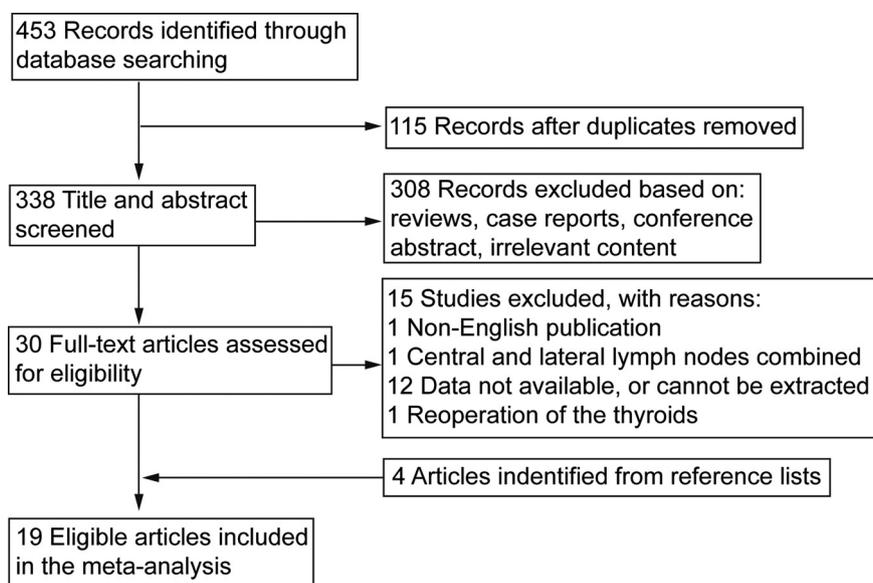


Fig. 1. Flowchart of the meta-analysis.

diagnostic accuracy of preoperative ultrasound in the assessment of central and lateral CLNM of PTC by pooled analysis.

2. Methods

2.1. Search strategy

Studies were identified in databases including PubMed, EMBASE, and Cochrane Library. We used the following strategies to retrieve studies: “ultrasonography or sonography or ultrasound or echotomography” and “thyroid neoplasm or thyroid carcinoma or thyroid cancer or thyroid tumor or thyroid tumour” and “papillary” and “lymph node or lymphatic node” and “sensitivity or specificity or diagnosis” in titles or abstract (up to Sep. 2017). In addition, references of the identified articles and review articles were searched manually for relevant studies. The meta-analysis was performed according to PRISMA statement [8].

2.2. Inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) the objective of the study was to evaluate the diagnostic efficacy of ultrasound in assessing CLNM of PTC; (2) the diagnostic gold standard was the pathological diagnosis of the resected lymph nodes; (3) the number of true positive (TP), false positive (FP), false negative (FN), and true negative (TN) determined by ultrasound could be obtained from the text; (4) studies were reported in English.

Studies with any of the following items were excluded: (1) the patients recruited in the study included other pathological types or underwent reoperation; (2) the sample data were incomplete, and TP, FP, FN, and TN could not be obtained; (3) data were analyzed with a combined analysis of central and lateral lymph nodes; (4) studies belonged to case reports, reviews, editorial, letters, meta-analyses, and meeting reports that did not provide sufficient data for evaluation.

2.3. Data extraction

The eligible articles were reviewed and the following original data were extracted: the first author, year of publication, area, study types, patient characteristics, CLND compartment, diagnostic criteria of ultrasound for CLNM, and diagnostic statistics such as TP, FP, FN, TN from each article.

2.4. Quality evaluation

Assessment of methodological quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [9]. The QUADAS-2 tool is composed of 7 items, including 4 risk of bias and 3 applicability assessments, with each item evaluated as “low risk”, “high risk”, or “unclear risk”. The assessment was performed by two reviewers (H.Q.Z and H.H.L), and disagreement was resolved by discussion.

2.5. Statistical analysis

Meta-DiSc 1.4 was used to examine the combined effect and heterogeneity. The presence of heterogeneity was evaluated with Cochran’s Q test and its extent was assessed with the I^2 statistics. The Spearman correlation coefficient of sensitivity and 1-specificity was calculated to estimate the threshold effect. If heterogeneity existed among studies, a random-effect model was used to calculate the sensitivity, specificity, diagnostic odds ratio (DOR), and area under the receiver operating characteristic curve (AUC) by integrating the TP, FP, FN, TN data. A value of 0.5 was added to all cells of studies that contained a count of zero to avoid potential problems in odds calculation. Subgroup analysis and meta-regression analysis were performed to explore the sources of heterogeneity. Next, the stability of the results was assessed by sensitivity analysis. Potential publication bias was analyzed using Deeks’ Funnel Plot Asymmetry Test provided by STATA 14.0 (STATA Corporation, College Station, TX, USA).

3. Results

3.1. Literature search and characteristics of the included studies

The literature screening process was shown in Fig. 1. We identified 453 records through searching the databases. Based on the inclusion and exclusion criteria, 19 articles including 4014 PTC patients were eventually included in the meta-analysis. Among the 19 studies, 15 studies focused on central CLNM [10–24], and 16 studies showed results of lateral CLNM of PTC [10–17,21–28]. The characteristics of the included studies were shown in Table 1.

Table 1
Characteristics of the studies in this meta-analysis.

Study (year)	Area	Study type	Patient enrollment	Sample (n) (Male/Female)	Age (Mean or median) (range)
Al-Hilli [26]	USA	R	NA	461 (176/285)	44
Choi [16]	Korea	R	Consecutive	299 (44/255)	45 (20-74)
Lee [27]	Japan	R	NA	70(24/46)	55(10-82)
Hwang [17]	USA	R	Consecutive	68	NA
Khokhar [18]	Island	R	Consecutive	227 (56/171)	51
Kim [10]	Korea	R	Consecutive	165 (25/140)	48 (16-78)
Na [22]	Korea	R	NA	176 (44/132)	43 (23-74)
Roh [11]	Korea	P	NA	133(29/104)	48 (21-75)
Shim [19]	Korea	R	Consecutive	143 (51/92)	49 (15-83)
Ahn [12]	Korea	R	Consecutive	37(7/30)	47(20-68)
Ito [25]	Japan	R	NA	560(48/512)	48 (13-82)
Ito [20]	Japan	R	NA	600(38/562)	52
Jeong [13]	Korea	R	Consecutive	26(7/19)	44 (17-73)
Lee [14]	Korea	R	Consecutive	184(150/34)	49 (22-75)
Sugitani [21]	Japan	P	Consecutive	361(68/293)	52 (16-81)
Yoon [28]	Korea	R	Consecutive	113(16/97)	46 (15-83)
Lee [15]	Korea	R	NA	252(45/207)	49 (15-82)
Morita [23]	Japan	P	NA	74 (12/72)	66 (16-84)
Choi [24]	Korea	R	NA	65 (9/56)	49 (23-77)

R, retrospective; P, prospective; NA, not available.

3.2. Quality assessment

The QUADAS-2 tool was applied to evaluate the quality of each study (Supplementary Fig. S1 and S2). The risk of patient selection bias was unclear in 8 studies because they did not specially indicate whether patient enrollment was consecutive or not. All studies did not describe whether the reference standard results interpreted with or without knowledge of the index test results, which represents the most critical issue about the methodological quality of the included studies. A high risk of flow and timing bias was observed in one study because the interval between the index test and reference standard was as long as 6 months, which might lead to disease progression [12]. Besides, 14 studies failed to indicate the interval between the index test and reference standard. All studies had low concerns regarding applicability.

3.3. Diagnostic efficacy of ultrasound in the diagnosis of central CLNM of PTC

Fifteen studies including 2810 patients assessed the diagnostic efficacy of preoperative ultrasound for central CLNM of PTC. As shown in Fig. 2, with use of a random-effects model, the sensitivity and specificity of each study regarding ultrasound in the diagnosis of central CLNM were combined, and the pooled sensitivity was 0.33 (95% confidence interval (CI): 0.31–0.35; $I^2 = 93.0\%$), the pooled specificity was 0.93 (95% CI: 0.92–0.94; $I^2 = 88.0\%$), the pooled diagnostic odds ratio (DOR) was 5.63 (95% CI: 3.50–9.04; $I^2 = 76.4\%$), the AUC was 0.69 (standard error 0.09), and Q^* was 0.65 (standard error 0.07).

3.4. Diagnostic efficacy of ultrasound in the diagnosis of lateral CLNM of PTC

Sixteen studies including 3044 patients evaluated the diagnostic efficacy of ultrasound for lateral CLNM of PTC. The pooled sensitivity was 0.70 (95% CI: 0.68–0.72; $I^2 = 96.7\%$), the pooled specificity was 0.84 (95% CI: 0.82–0.85; $I^2 = 95.2\%$), the pooled DOR was 18.66 (95% CI: 10.27–33.91; $I^2 = 83.8\%$), the AUC was 0.88 (standard error 0.03), and Q^* was 0.81 (standard error 0.03) (Fig. 3).

3.5. Heterogeneity exploration of the threshold effect

A large heterogeneity existed in the pooled analysis. Threshold effect was one of the primary sources of heterogeneity in diagnostic

accuracy test. The Spearman correlation coefficient obtained for the assessment of the threshold effect was 0.253 ($P = 0.345$) and 0.582 ($P = 0.014$) for central and lateral pooled analyses, respectively, which indicated the existence of threshold effect among studies for lateral CLNM of PTC. If heterogeneity was present due to threshold effect, a summary receiver operator characteristic curves (SROC) curve and the AUC were better than pooling sensitivities and specificities [29].

We therefore examined the diagnostic criteria of ultrasound in the diagnosis of CLNM of PTC. The ultrasound criteria for CLNM were inconsistent across studies (Supplementary Table S1). Microcalcification, hyperechogenicity, cystic change, and rounded shape were commonly considered as malignant characteristics of CLNM among the included studies [10,11,14–16,20,22,28]. Some studies determined CLNM using the size criteria (> 1 cm) [11,13,16–18,20,23] as opposed to others [12,14,15]. In addition, several studies identified CLNM as the absence of echogenic hilum [11,13,17,18,22,24], which was contrary to others [10,14]; and the rest did not refer to it [12,16,21,23,25,27]. Additionally, abnormal vascular pattern was considered suspicious characteristics for CLNM only in some studies [10,13,16,18,24,26,28]. These differences in CLNM criteria of ultrasound of the included studies might contribute to the generation of threshold effect associated with the heterogeneity in the meta-analysis.

3.6. Sub-group analysis

To further investigate the source of heterogeneity, we conducted subgroup analysis (Table 2). For detecting central CLNM, the heterogeneity of pooled specificity decreased from 88.0% to 0, and the AUC increased from 0.69 to 0.92, indicating that appropriated interval between index test and reference standard might be a source of heterogeneity. It was noted that both the pooled sensitivity and specificity of ultrasound were higher in prospective studies than those in retrospective ones in the determination of central and lateral CLNM, suggesting that the study type might be a source of heterogeneity as well. The subgroup analysis showed that the sensitivity and AUC of ultrasound were higher in the diagnosis lateral CLNM than the central neck compartment, as opposed to the specificity. The stability of these results was very good (Table 2).

3.7. Meta-regression analysis and sensitivity analysis

Meta-regression was further performed to investigate the potential

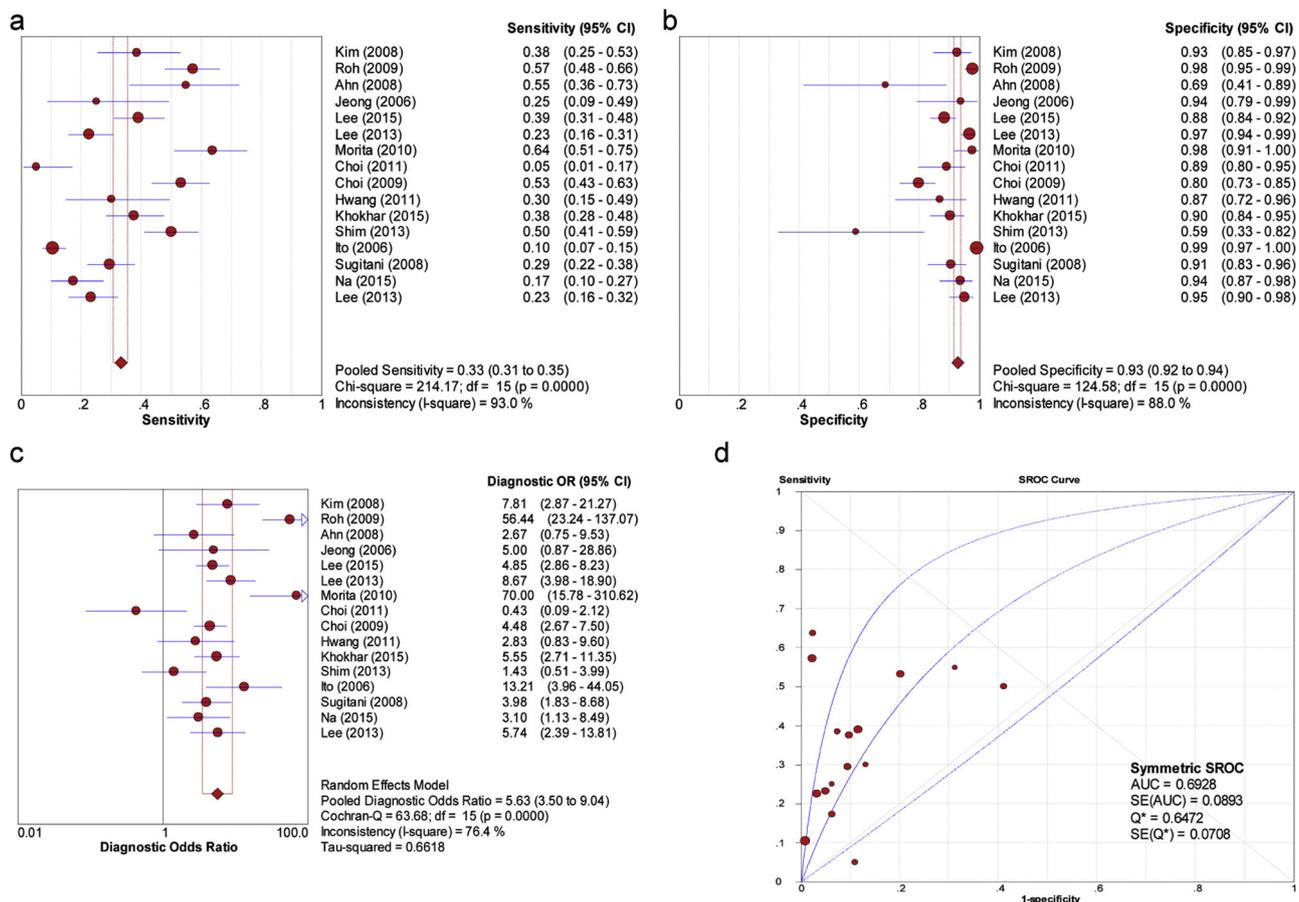


Fig. 2. Plot of individual studies and pooled sensitivity (a), specificity (b), DOR (c), and the SROC curve (d) of ultrasound in detecting central CLNM of PTC. The size of the circles indicates the weight of each study. DOR, diagnostic odds ratio; SROC, summary receiver operator characteristic curves; 95% CI, 95% confidence intervals; CLNM, cervical lymph node metastases; PTC, papillary thyroid cancer.

sources of heterogeneity (Supplementary Table S2). We found that the study design could affect the heterogeneity of the pooled effect ($P = 0.017$ and 0.006 for central and lateral CLNM, respectively). As shown in Table 2, if studies from different study design were selected for meta-analysis, the heterogeneity remained high. Meta-regression analysis did not solve the problem of heterogeneity. We further found that the criteria of lymph node diameter and vascular flow could affect the heterogeneity of the pooled effect for lateral CLNM ($P = 0.031$ and 0.052 , respectively), which might account for the existence of threshold effect linked with heterogeneity (Supplementary Table S2).

We sequentially excluded the following studies, which significantly deviated from the pooled effect size in the diagnosis of central CLNM: the studies of Ito et al, Roh et al, Ahn et al, Choi et al, Na et al, Shim et al, Choi et al, and Morita et al. Sensitivity analysis was performed on the remaining 7 studies. The results showed that the heterogeneity with respect to sensitivity was decreased from 93.0% to 55.5%, and the heterogeneity of specificity from 88.0% to 61.7% (Table 2). However, the heterogeneity of sensitivity and specificity of ultrasound for lateral CLNM was still high after excluding the studies deviated from the pooled effect size (data not shown).

3.8. Assessment of publication bias

As shown in the Deeks' funnel plot (Fig. 4), there was no significant publication bias of the included studies concerning preoperative ultrasound in the diagnosis of central and lateral CLNM of PTC.

3.9. The rate of central and lateral CLNM of PTC in the pooled analysis

We further evaluated the CLNM status by pooling the 19 studies. The rate of central and lateral CLNM of PTC was 48.0% and 59.2% respectively by patient-based analysis. In addition, the central and lateral CLNM rates of PTC were 36.2% and 46.6% respectively by node-based analysis (Table 3).

4. Discussion

In this study, we investigated the diagnostic efficacy of preoperative ultrasound in the assessment of CLNM of PTC by pooling 19 individual studies with 4041 patients. Although ultrasound is the first imaging technique in the detection of CLNM of PTC, we found that the pooled sensitivity, specificity and AUC of ultrasound were 0.33, 0.93, and 0.69, respectively, suggesting that ultrasound has high false negative rate, and poor diagnostic accuracy in assessing central CLNM of PTC. Meanwhile, the pooled sensitivity, specificity and AUC of ultrasound for lateral CLNM were 0.70, 0.84 and 0.88, respectively, indicating its good diagnostic efficacy.

Previous studies reported that the rate of central CLNM of PTC patients staged as cN0 was 15.9%–53% [30–32]. In the present study, the pooled rate of central CLNM of PTC was 48.0%, suggesting the high incidence of central CLNM of PTC. At the same time, ultrasound showed poor performance in identifying central CLNM. Other imaging techniques such as computed tomography (CT), fluorodeoxyglucose (18F) positron emission tomography/CT (FDG-PET/CT), and magnetic resonance imaging (MRI) were not superior to ultrasound in the assessment of central CLNM of PTC [13,23,33–35]. The poorer diagnostic

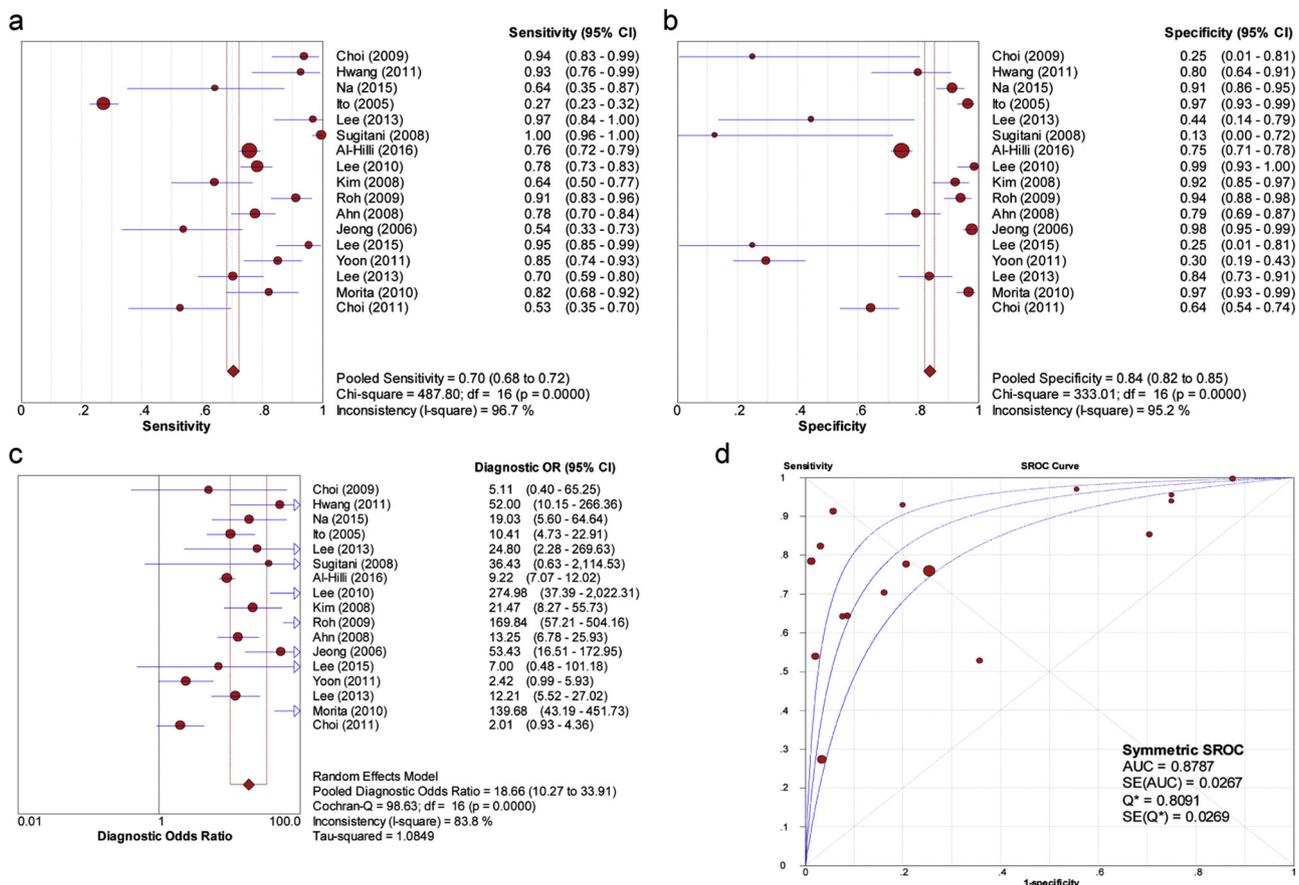


Fig. 3. Plot of individual studies and pooled sensitivity (a), specificity (b), DOR (c), and the SROC curve (d) of ultrasound in detecting lateral CLNM of PTC. The size of the circles indicates the weight of each study. DOR, diagnostic odds ratio; SROC, summary receiver operator characteristic curves; 95% CI, 95% confidence intervals; CLNM, cervical lymph node metastases; PTC, papillary thyroid cancer.

accuracy of ultrasound for central CLNM might stem from the anatomical complexity of the thoracic inlet and the low accuracy of the imaging characteristics for nodal malignancy. Considering the high rate of central CLNM and the poor diagnostic efficacy of ultrasound, prophylactic central CLND should be recommended to all PTCs.

Therapeutic central CLND is well accepted for patients with clinically involved CLNM (cN1) disease. However, the significance for routine prophylactic level VI neck dissection for clinically node-negative (cN0) PTC remains unclear according to the recommendations of ATA guidelines (2015) [7,36]. The controversies mainly focused on the limited outcome improvement, temporary morbidity such as hypocalcemia and recurrent laryngeal nerve dysfunction, and the microscopic nodal upstaging [7,37]. Kim et al found that macroscopic CLNM significantly affected disease recurrence, whereas microscopic CLNM had only marginal effects on recurrence compared with non-metastatic patients with PTC [31]. However, this might result from the short-term follow-up, inexpert surgical skills, or other confounders.

Recently, a meta-analysis showed that patients who underwent total thyroidectomy and prophylactic central CLNM had a significantly reduced risk of locoregional recurrence (risk ratio = 0.66, $P = 0.008$) [38]. Lundgren et al found that patients with CLNM experienced a higher mortality in differentiated thyroid cancer, and incomplete surgical excision was associated higher mortality, particularly in patients with stage I disease [39]. The presence of CLNM was associated with compromised overall survival in PTC patients younger than 45 years undergoing surgery for stage I, and a change point of six or fewer metastatic lymph nodes might present prognostic significance, advocating for rigorous evaluation for nodal metastases [5]. More recently, the CLNM number (> 5) was found to be a significant risk factor for persistence/recurrence for N1a patients [40]. Together, the

canonical and comprehensive central CLND are recommended, which may benefit PTC patients in the long run.

It is indicated that disease persistence/recurrence and distant metastases are significantly more frequent in PTC patients with lateral CLNM (cN1b) compared with patients of central CLNM (cN1a) and cN0 diseases [40]. Therapeutic lateral CLND is recommended for PTC patients with clinically apparent CLNM detected by palpation or imaging according to ATA guidelines [7]. We found that the lateral CLNM rate was 59.2% in the integrated analysis by patient-based analysis. Previous studies found that the CT and FDG-PET/CT did not provide additional benefit over ultrasound in the diagnosis of lateral CLNM of PTC [23,24,28,33], which was also not routinely recommended by ATA [7]. Therefore, ultrasound should be routinely performed on the lateral neck of patients with thyroid nodules, which can provide good diagnostic information in assessing CLNM status. Furthermore, ultrasound-guided fine-needle aspiration (FNA) cytology, molecular mutation testing (*BRAF*, *RAS*, *RET/PTC*, and *PAX8/PPAR γ*) and FNA thyroglobulin assay (FNA-Tg) toward suspicious lymph nodes can facilitate the determination of metastatic nodal diseases [41–43].

We found that the diagnostic criteria of ultrasound in the detection of CLNM of PTC were not consistent across studies. Microcalcification (16/19 studies), hyperechogenicity (14/19 studies), cystic change (15/19 studies), and rounded shape (17/19 studies) were commonly considered as malignant characteristics of CLNM by ultrasound among the included studies. However, Lee et al used the size criteria only to assess CLNM [27]. In addition, the absence of an echogenic hilum was considered as metastatic feature in 6 studies [11,13,17,18,22,24], which was contrary to others [10,14]. However, one study found that any suspicious ultrasound features (cystic change, calcification, hyperechogenicity, and round shape) except for loss of fatty hilum showed

Table 2
Subgroup analysis and sensitivity analysis of the diagnostic performance of ultrasound for central and lateral CLNM.

Study characteristics	Study (n)	Patient (n)	Pooled sensitivity	I ² for sensitivity	Pooled specificity	I ² for specificity	AUC
Central CLNM							
Overall [10,11,12,13,14,15,16,17,18,19,20,21,22,23,24]	15	2810	0.33 (0.31-0.35)	93.0%	0.93 (0.92-0.94)	88.0%	0.69
Consecutive patient [10,12,13,14,16,17,18,19]	8	1149	0.43 (0.39-0.47)	57.4%	0.86 (0.83-0.88)	71.5%	0.64
Inconsecutive patients [11,15,20,21,22,23,24]	7	1661	0.26 (0.24-0.29)	95.3%	0.96 (0.95-0.97)	75.6%	0.92
Retrospective studies [10,12,13,14,15,16,17,18,19,20,22,24]	12	2242	0.30 (0.27-0.32)	92.1%	0.92 (0.90-0.93)	88.6%	0.68
Prospective studies [11,21,23]	3	568	0.47 (0.41-0.52)	93.3%	0.96 (0.94-0.98)	75.9%	–
Node-based analysis [10,11,12,13,14,15,23,24]	8	936	0.40 (0.36-0.44)	91.1 %	0.94 (0.92-0.95)	81.4%	0.83
Patient-based analysis [15,16,17,18,19,20,21,22]	8	2126	0.29 (0.26-0.32)	94.0%	0.92 (0.90-0.93)	91.6%	0.66
Appropriate interval [10,13,14,22,24]	5	616	0.29 (0.24-0.34)	86.5%	0.90 (0.88-0.93)	0	0.92
Inappropriate interval [11,12,15,16,17,18,19,20,21,23]	10	2194	0.34 (0.32-0.37)	94.5%	0.93 (0.92-0.95)	91.4%	0.66
Publication year after 2010 [14,15,17,18,19,22,24]	7	1115	0.31 (0.28-0.34)	88.0%	0.92 (0.90-0.93)	78.9%	0.66
Before 2010 [10,11,12,13,16,20,21,23]	8	1695	0.35 (0.32-0.38)	95.4%	0.94 (0.92-0.95)	92.2%	0.73
Sample size > 100 patients [10,11,14,15,16,18,19,20,21,22]	10	2540	0.32 (0.29-0.34)	93.2%	0.93 (0.92-0.94)	90.0%	0.65
Sample size < 100 [12,13,17,23,24]	5	270	0.40 (0.33-0.48)	91.6%	0.91 (0.87-0.94)	70.5%	0.82
Sensitivity analysis [10,13,14,15,17,18,21]	7	1535	0.31 (0.27-0.34)	55.5%	0.92 (0.91-0.94)	61.7%	0.65
Lateral CLNM							
Overall [10,11,12,13,14,15,16,17,21,22,23,24,25,26,27,28]	16	3044	0.70 (0.68-0.72)	96.7%	0.84 (0.82-0.85)	95.2%	0.88
Consecutive patient [10,12,13,14,16,17,21,28]	8	1253	0.85 (0.82-0.88)	91.3%	0.83 (0.79-0.86)	95.9%	0.87
Inconsecutive patients [11,15,22,23,24,25,26,27]	8	1791	0.65 (0.62-0.67)	97.5%	0.84 (0.82-0.86)	95.1%	0.89
Retrospective studies [10,12,13,14,15,16,17,22,24,25,26,27,28]	13	2476	0.67 (0.65-0.69)	96.5%	0.82 (0.80-0.84)	95.4%	0.84
Prospective studies [11,21,23]	3	568	0.94 (0.90-0.96)	90.2%	0.94 (0.91-0.97)	89.6%	0.97
Node-based analysis [10,11,12,13,14,15,23,24,26,27,28]	11	1580	0.77 (0.75-0.79)	80.0%	0.82 (0.80-0.84)	96.2%	0.86
Patient-based analysis [15,16,17,21,22,25]	6	1716	0.55 (0.51-0.59)	98.6%	0.90 (0.87-0.93)	90.1%	0.88
Continuation							
Study characteristics	Study (n)	Patient (n)	Pooled sensitivity	I ² for sensitivity	Pooled specificity	I ² for specificity	AUC
Appropriate interval [10,13,14,22,24,27]	6	686	0.74 (0.70-0.78)	84.6%	0.90 (0.88-0.92)	94.4%	0.83
Inappropriate interval [11,12,15,16,17,21,23,25,26,28]	10	2358	0.69 (0.67-0.71)	97.8%	0.81 (0.78-0.83)	95.2%	0.89
Publication year after 2010 [14,15,17,22,24,26,28]	7	1319	0.77 (0.74-0.80)	83.7%	0.74 (0.71-0.77)	93.8%	0.82
Before 2010 [10,11,12,13,16,21,23,25,27]	9	1725	0.65 (0.62-0.68)	98.0%	0.94 (0.93-0.96)	88.1%	0.92
Sample size > 100 [10,11,14,15,16,21,22,25,26,28]	10	2704	0.68 (0.66-0.71)	97.8%	0.81 (0.79-0.83)	95.1%	0.86
Sample size < 100 [12,13,17,23,24,27]	6	340	0.76 (0.72-0.80)	78.0%	0.90 (0.87-0.92)	95.1%	0.88

CLNM, cervical lymph node metastases; AUC, area under curve.

better diagnostic performance than the additional introduction of loss of fatty hilum in the identification of CLNM [44]. Furthermore, only 7 of 19 studies adopted abnormal vascular pattern as the metastatic status of CLNM [10,13,16,18,24,26,28]. Peripheral or diffusely increased vascularization was considered as the suspicious feature for CLNM according to European thyroid association (ETA) [45]. We further explored the effect of ultrasound criteria such as lymph node diameter (> 1 cm or not), long axis to short axis ratio, and vascular flow on the threshold effect, and found that lymph node diameter and vascular flow of ultrasound could lead to heterogeneity for lateral CLNM of PTC. We can expect that the accuracy of ultrasound in the diagnosis of CLNM

increased with the enlargement of lymph node size [26]. However, almost 50% of PTC patients were demonstrated to be central CLNM pathologically even these lymph nodes were cN0 ones clinically and by imaging [32], which indicates the necessity of prophylactic central CLND. One must note that any single sonographic feature is inadequately sensitive for detection of metastatic lymph nodes of differentiated thyroid cancer [28]. The combination of the suspicious characteristics and introduction of other detection methods for CLNM may be an alternative approach [46].

In addition, subgroup analysis showed that the prospective studies had higher pooled sensitivity and specificity relative to those of

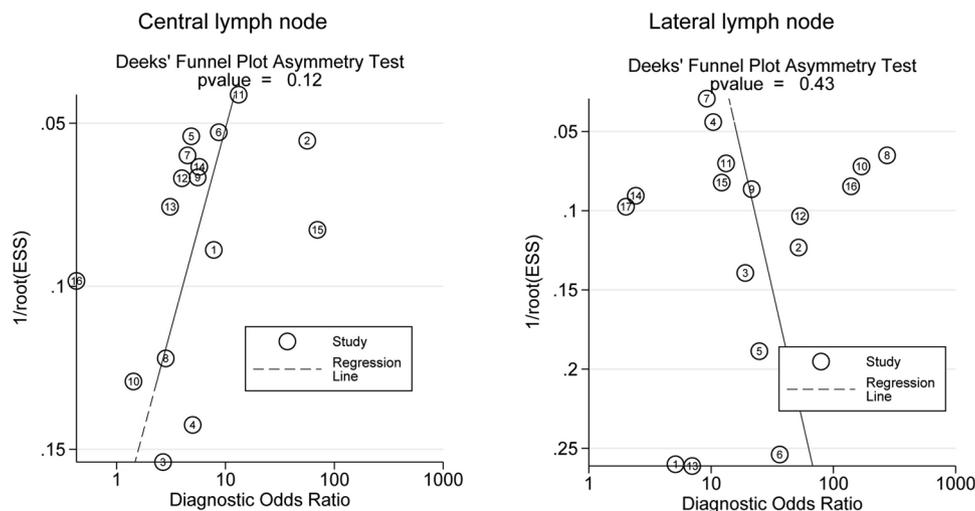


Fig. 4. Deeks' funnel plot to evaluate publication bias.

Table 3
The CLNM status of PTC by patient- or node-based analysis.

Study (year)	Analysis method	CLND	Metastasis (n) ^a	Total (n) ^b
Al-Hilli [26]	Node-based	Lateral	580	1170
Choi [16]	patient-based	Central; lateral	111; 49	299; 53
Lee [27]	Node-based	Lateral	254	331
Hwang [17]	patient-based	Central; lateral	30; 28	68;68
Khokhar [18]	patient-based	Central	104	227
Kim [10]	Node-based	Central; lateral	52; 53	133;144
Na [22]	patient-based	Central; lateral	81; 14	176;176
Roh [11]	Node-based	Central; lateral	119; 80	379;201
Shim [19]	patient-based	Central	126	143
Ahn [12]	Node-based	Central; lateral	31; 134	47; 216
Ito [25]	patient-based	Lateral	359	560
Ito [20]	patient-based	Central	258	600
Jeong [13]	Node-based	Central; lateral	20; 26	52;260
Lee [14]	Node-based	Central; lateral	136; 44	368;48
Sugitani [21]	patient-based	Central; lateral	136; 127	231;130
Yoon [28]	Node-based	Lateral	61	122
Lee [15]	Node-based	Central; lateral	133; 74	410; 148
	patient-based	Central; lateral	112; 32	252; 41
Morita [23]	Node-based	Central; lateral	66; 45	148; 201
Choi [24]	Node-based	Central; lateral	40; 36	113; 134

^{a,b} indicates the number of lymph nodes or patients with CLNM by node- or patient-based analysis in the central or lateral neck compartments, respectively. CLNM, cervical lymph node metastases; CLND, cervical lymph node dissection; PTC, papillary thyroid cancer. Node-based analysis: Central CLNM rate = 597/1650 = 36.2%; Lateral CLNM rate = 1387/2975 = 46.6%. Patient-based analysis: Central CLNM rate = 958/1996 = 48.0%; Lateral CLNM rate = 609/1028 = 59.2%.

retrospective studies, which was further validated by meta-regression analysis. In the methodological quality assessment, the included studies suffered from potential risks of bias in “reference standard” for the absence of interpretation between reference standard results and the index test results. Besides, the interval between the index test and reference standard was poorly described. Additionally, the risk of patient selection bias might be higher than expected for many studies failed to describe the patient enrollment pattern. Last but not least, the accuracy of ultrasound diagnosis is operator dependent, indicating that the operators’ experience may also be a source of heterogeneity. Although we comprehensively investigated the heterogeneity by threshold effect analysis, subgroup analysis, meta-regression analysis and sensitivity analysis, the heterogeneity still existed. Therefore, the results in the present study should be interpreted with caution. The solution of these problems with strict clinical and methodological design might improve the diagnostic efficacy of preoperative ultrasound in the assessment of CLNM of PTC.

5. Conclusion

In the present study, we integrated the published studies to investigate diagnostic efficacy of preoperative ultrasound in assessing CLNM and its value in CLND of PTC. Ultrasound shows poor performance in the detection of central CLNM of PTC. In addition, almost 50% of PTC patients suffer from central CLNM. Prophylactic central CLND should be performed on patients with PTC due to the high incidence of central CLNM and the poor performance of preoperative imaging. Meanwhile, the application of ultrasound and/or combined with FNA cytology/molecular testing/Tg assay can facilitate the determination of lateral CLNM of PTC preoperatively.

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Ethical approval

All the data involved in this study were extracted from published articles.

Declaration of interest

None.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejrad.2019.01.006>.

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