Diagnostic value of multiple diagnostic methods for lymph node metastases of papillary thyroid carcinoma: A systematic review and meta-analysis

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Objective: This study compared the diagnostic value of various diagnostic methods for lymph node metastasis (LNM) of papillary thyroid carcinoma (PTC) through network meta-analysis.

Methods: In this experiment, databases such as CNKI, Wanfang, PubMed, and Web of Science were retrieved according to the Cochrane database, Prisma, and NMAP command manual. A meta-analysis was performed using STATA 15.0, and the value of the surface under the cumulative ranking curve (SUCRA) was used to determine the most effective diagnostic method. Quality assessments were performed using the Cochrane Collaboration’s risk of bias tool, and publication bias was assessed using Deeks’ funnel plot.

Results: A total of 38 articles with a total of 6285 patients were included. A total of 12 diagnostic methods were used to study patients with LNM of PTC. The results showed that 12 studies were direct comparisons and 8 studies were indirect comparisons. According to the comprehensive analysis of the area of SUCRA, US+CT (86.8) had the highest sensitivity, FNAC had the highest specificity (92.4) and true positive predictive value (89.4), and FNAC+FNA-Tg had higher negative predictive value (99.4) and accuracy (86.8). In the non-invasive method, US+CT had the highest sensitivity, and the sensitivity (SEN) was [OR=0.59, 95% confidence interval (CI): (0.30, 0.89)]. Among the invasive methods, the combined application of FNAC+FNA-Tg had higher negative predictive value (99.4) and accuracy (86.8). In the non-invasive method, US+CT had the highest sensitivity, and the sensitivity (SEN) was [OR=0.62, 95% CI: (0.26, 0.98)], the specificity (SPE) was [OR=1.12, 95% CI: (0.59, 1.64)], the positive predictive value was [OR=0.98, 95% CI: (0.59, 1.37)], the negative predictive value was [OR=0.64, 95% CI: (0.38, 0.90)], and the accuracy was [OR=0.71, 95% CI: (0.31, 1.12)].
Conclusion: In the non-invasive method, the combined application of US+CT had good diagnostic performance, and in the invasive method, the combined application of FNAC+FNA-Tg had high diagnostic performance, and the above two methods were recommended.

KEYWORDS
lymph nodes metastasis, diagnostic value, network meta-analysis, multiple diagnostic methods, papillary thyroid carcinoma

1 Introduction

Thyroid cancer (TC) is one of the most common endocrine tumors worldwide, with an incidence rate of 3.1% and a mortality rate of 0.4% (1). The increase in papillary thyroid carcinoma (PTC) is the main reason for the increased incidence of adenocarcinoma (2). Although PTC has a good prognosis, the probability of distant cervical lymph node metastasis (LNM) in PTC patients reaches 90% (3), so the status of LN is also an important basis for judging recurrence and LN dissection (4). At the same time, for patients with LNM of PTC, the operation caused by persistent LNs recurrence will increase the risk of postoperative complications such as dyspnea, asphyxia, hypoparathyroidism, etc. (5, 6). Therefore, preoperative diagnosis is an important means for PTC patients to avoid persistent LNs recurrence and reduce complications.

At present, the commonly used methods for diagnosing the metastasis of LNM of PTC include CT, magnetic resonance imaging (MRI), IWBS, US, strain elastography (SE-US), Contrast-Enhanced Ultrasonography (CEUS), FNAC and other detection methods. But each of these methods has its advantages and disadvantages; In a single diagnostic method, ultrasound (US) is the main basis for clinical diagnosis of PTC (7), and the accuracy of the ultrasound results in the neck is high (8). However, the identification of LNM of PTC often needs to be judged by doctors’ experience, which is often regarded as an inaccurate method (9). For patients with lymph node infiltration or distant metastasis of DTC after surgical resection, ultrasound-guided fine-needle aspiration cytology (FNAC) can be performed, and the sensitivity can reach 70–80% (10), while the sensitivity of computed tomography (CT) can reach 94.5% (11). In recent years, combined diagnostic methods such as US + CT (12) and US+ Contrast-Enhanced Ultrasonography (CEUS) (13) have also been commonly used to diagnose the LNM of PTC. Among these studies, the preoperative diagnostic performance of different diagnostic methods for LNM of PTC has been evaluated and analyzed or only one or two diagnostic methods have been compared, but a thorough evaluation has not been performed. Since different diagnostic methods have different diagnostic efficacy, and the diagnostic efficacy of the same diagnostic method is different in different studies, we conducted a meta-analysis to evaluate the diagnostic performance of different diagnostic methods for LNM of PTC so as to obtain the optimal diagnostic protocol.

In this study, we summarized the available evidence, investigated and compared a variety of different diagnostic techniques through network meta-analysis and the use of two or more published direct comparative studies, and concluded the optimal diagnostic protocol for LNM of PTC through comprehensive analysis. The results of this study will provide more evidence-based data for the development of guidelines and will guide patients with LNM of PTC to use appropriate diagnostic methods for preoperative or postoperative evaluation.

2 Methods

2.1 Retrieval strategy

We used keywords such as “Thyroid Neoplasms”, “lymph node”, “Neoplasm Staging”, “Lymphatic Metastasis”, and “Elasticity Imaging Techniques” in PubMed, Embase, Web of Science, CNKI, and Wanfang databases for retrieval. In order to obtain more sufficient data, we also screened the references of the retrieved articles (Table 1).

2.1.1 Inclusion and exclusion criteria

Inclusion criteria: ① Research subjects: PTC patients diagnosed with LNM. ② Study type: A randomized controlled...
TABLE 1 Search strategy.

| No. | Retrieval type                                                                 |
|-----|-------------------------------------------------------------------------------|
| #1  | lymph node [Mesh]                                                              |
| #2  | Neoplasm Staging [Mesh]                                                        |
| #3  | Staging, Neoplasm [Title/Abstract]                                             |
| #4  | Tumor Staging [Title/Abstract]                                                 |
| #5  | TNM Staging System [Title/Abstract]                                            |
| #6  | TNM Classifications [Title/Abstract]                                           |
| #7  | preoperative staging [Title/Abstract]                                          |
| #8  | Lymphatic Metastasis [Mesh]                                                    |
| #9  | Lymphatic Metastases [Title/Abstract]                                          |
| #10 | Lymph Node Metastasis [Title/Abstract]                                         |
| #11 | Lymph Node Metastasis [Title/Abstract]                                         |
| #12 | Metastasis, Lymph Node [Title/Abstract]                                        |
| #13 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 |
| #14 | Thyroid Neoplasms [Mesh]                                                       |
| #15 | Neoplasm, Thyroid [Title/Abstract]                                             |
| #16 | thyroid carcinoma [Title/Abstract]                                             |
| #17 | thyroid cancer [Title/Abstract]                                                |
| #18 | thyroid neoplasm [Title/Abstract]                                             |
| #19 | Cancer of the Thyroid [Title/Abstract]                                         |
| #20 | Thyroid Cancers [Title/Abstract]                                               |
| #21 | #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20                                    |
| #22 | ultrasound contrast [Title/Abstract]                                           |
| #23 | Elasticity Imaging Techniques [Mesh]                                           |
| #24 | Elastography [Title/Abstract]                                                  |
| #25 | Elastograms [Title/Abstract]                                                   |
| #26 | B-mode [Title/Abstract]                                                        |
| #27 | Ultrasonography [Mesh]                                                         |
| #28 | Diagnostic Ultrasound [Title/Abstract]                                         |
| #29 | Ultrasound Imaging [Title/Abstract]                                            |
| #30 | Ultrasonic Imaging [Title/Abstract]                                           |
| #31 | Ultrasonic Diagnosis [Title/Abstract]                                         |
| #32 | Ultrasonic Diagnosis [Title/Abstract]                                         |
| #33 | Ultrasound-Guided Fine-Needle aspiration [Title/Abstract]                      |
| #34 | Magnetic Resonance Imaging [Mesh]                                              |
| #35 | MRI Scan [Title/Abstract]                                                      |
| #36 | Positron Emission Tomography Computed Tomography [Mesh]                        |
| #37 | PET-CT Scan [Title/Abstract]                                                   |
| #38 | 18F-FDG PET/CT [Title/Abstract]                                                |
| #39 | 131I [Title/Abstract]                                                          |
| #40 | IWB [Title/Abstract]                                                           |
| #41 | 131I scintigraphy [Title/Abstract]                                             |
| #42 | #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41                                        |
| #43 | #13 AND #21 AND #42                                                            |

The study was conducted and two or more functional or non-invasive diagnostic methods should be included. Gold standard: postoperative histopathology reports. Outcome indicators: It can reflect the sensitivity (SEN), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), and accuracy of various diagnostic methods for LNM in patients with PTC.

Exclusion criteria: ① There were less than 2 diagnostic methods in the study; ② There were no clear inclusion and exclusion criteria in the study; ③ Reviews and lecture-type literature. ④ Literature for which the full text cannot be obtained.

2.2 Literature screening

Two researchers (Qiao-Li Li, Si-Rui Wang) read the titles and abstracts of the retrieved literature respectively. According to the inclusion and exclusion criteria established in this study, the literatures that did not meet the inclusion criteria were excluded, and the literatures that might meet the inclusion criteria and other related literatures were obtained and the relevant literatures were further intensively read. Articles with disagreements that were difficult to determine whether to be included were determined through discussion or consultation with a third party (Jun Li).

2.3 Quality evaluation of literature

For the RCT study, according to the method provided by the Cochrane Handbook, the research group adopted the risk of bias assessment tool of the Cochrane Collaboration (14) (RevMan v.5.3.5, Cochrane Collaboration, Oxford, UK), evaluated the methodological quality of the included studies from 6 aspects, and made the judgment of “yes” (low bias), “no” (high bias) and “unclear” (lack of relevant information or uncertainty of bias).

2.4 Data extraction

The data extracted in this study mainly included: (1) Characteristics of studies in the literature (author, publication time, country, study type, gold standard, etc.) (2) Subject characteristics (sample size, gender of patients, mean age or age range) (3) Effect indicators.

2.5 Statistical analysis

We grouped them according to different diagnostic methods and performed a network meta-analysis using the extracted diagnostic tools for the diagnostic performance of lymph node metastases.

We used Stata software (version-15.1) to perform the aggregation and analysis of NMA using Markov Chain Monte Carlo Subset Simulation in a Bayesian-based framework.
according to the instruction manual for Prisma NMA (15). We used the nodal method to quantify and demonstrate the agreement between direct and indirect comparisons. Through the calculation of the instructions in the Stata software and whether the P value was greater than 0.05, it was judged whether the consistency check was passed.

Network diagrams of different exercise interventions were presented and described using Stata software. In the resulting network diagram, each node represented a different diagnostic approach, and the lines connecting the nodes represented direct head-to-head comparisons between interventions. The size of each node and the width of the connecting lines were proportional to the number of studies.

The diagnostic performance of each diagnostic method was analyzed by the area under SUCRA, and the certainty that one method was superior to the other was measured. Although SUCRA could effectively express the percentage of diagnostic performance of each diagnostic method, there was a possibility that there was no actual clinical significance between the diagnostic methods. In order to detect whether there was publication bias in some studies, funnel plots were generated for each diagnostic efficacy, and symmetry criterion were used to check.

3 Results

3.1 Selection and characteristics of literature

A total of 4490 articles were extracted through literature search of the database and reference extraction, of which we excluded 1247 duplicate articles. Of the remaining 3243 articles, there were 2829 articles, 59 pathology reports, 699 review articles, 10 letters, and 72 meta-analyses and systematic reviews. 2061 articles not related to this study were excluded by review of the title and abstract. Among the remaining 414 articles, 376 articles failed to obtain the full text or failed to meet the inclusion criteria, and finally 38 articles were included, with a total of 6285 people. (Figure 1). The articles we included all fulfilled the requirement that the study population was patients with LNM of PTC and that their diagnoses were shown preoperatively or postoperatively by two or more diagnostic methods, such as US, CT, and MRI, and the data for direct comparison in the results were evaluated (Table 2).

3.2 Quality assessment and publication bias

The 38 articles we included (11–13, 15–45, 47, 49) included 36 retrospective studies and 2 prospective studies. We performed a network meta-analysis using STATA 15.0 (14), and 38 articles were assessed for quality, risk of bias and applicability issues using QUADAS-2 (50). The overall quality of the articles was satisfactory, but there may be potential bias in personnel selection. Among the 38 articles, 8 articles had unclear risk of bias, and 2 articles had high risk. In terms of index testing, because some doctors did not strictly implement blinding in the processing of results, there were 12 literatures with unclear risk of bias. In terms of reference standard bias, there were 6 articles with unclear risk of bias, because it was not indicated whether there was an appropriate time interval between the trial to be
| First Author          | Year | Country | Design | NO. of patients | Gender (M/F) | Histology | LN level | Diagnostic method | NO. of patients | Gender (M/F) | Histology |
|-----------------------|------|---------|--------|----------------|--------------|-----------|----------|------------------|----------------|--------------|----------|
| Artır Salmaslıoğlu   | 2010 | Turkey  | RCT    | 225            | 60/165       | 225PTC    | ALL      |                   |                |              |          |
| Ari Chong             | 2017 | Korea   | RCT    | 85             | 71/14        | 85PTC     | C, L     |                   |                |              |          |
| Byung Hyun Byun       | 2012 | Korea   | RCT    | 200            | 41/255       | 200PTC    | ALL, C   |                   |                |              |          |
| C. De Crea            | 2014 | Italy   | RCT    | 38             | 16/22        | 38PTC     | C        |                   |                |              |          |
| Cezur Samanci         | 2019 | Turkey  | RCT    | 32             | 13/19        | 26PTC, 6FTC| ALL      |                   |                |              |          |
| D.W.Lee               | 2013 | Korea   | RCT    | 252            | 45/207       | 252PTC    | C, L     |                   |                |              |          |
| David Lesnik          | 2013 | USA     | RCT    | 162            | NA           | 162PTC    | C, L     |                   |                |              |          |
| Enke Baldini          | 2013 | Italy   | RCT    | 28             | 7/21         | 21PTC, 2MTC,2ATC | ALL      |                   |                |              |          |
| Eunhee Kim            | 2008 | Korea   | RCT    | 165            | 25/140       | 165PTC    | ALL      |                   |                |              |          |
| Eun NL                | 2017 | Korea   | RCT    | 302            | 76/226       | 302PTC    | ALL      |                   |                |              |          |
| Fazrana Alam          | 2008 | Japan   | RCT    | 37             | 12/25        | 37PTC     | ALL      |                   |                |              |          |
| Han Sin Jeong         | 2006 | Korea   | RCT    | 26             | 7/19         | 26PTC     | ALL      |                   |                |              |          |
| Harry S. Hwang        | 2009 | USA     | RCT    | 42             | NA           | 42PTC     | ALL      |                   |                |              |          |
| Jasna Mihailovic      | 2010 | Serbia  | RCT    | 40             | 15/25        | 39PTC, 1FTC| ALL      |                   |                |              |          |
| Jeon SJ               | 2009 | Korea   | RCT    | 47             | NA           | 47PTC     | ALL      |                   |                |              |          |
| Ji Soo Choi           | 2009 | Korea   | RCT    | 299            | 44/255       | 186PTMC, 113PTC | ALL      |                   |                |              |          |
| Ji-Hoon Jung          | 2015 | Korea   | RCT    | 193            | 25/168       | 151PTMC, 42PTC | ALL      |                   |                |              |          |
| Jia Zhan              | 2019 | China   | RCT    | 56             | 16/40        | 56PTC     | C        |                   |                |              |          |
| Johann-Martin Hempel  | 2016 | Germany | RCT    | 46             | 27/19        | 16PTMC    | ALL      |                   |                |              |          |
| Jun Ho Lee            | 2015 | Korea   | RCT    | 78             | 26/52        | 78PTC     | ALL      |                   |                |              |          |
| Kim MJ                | 2012 | Korea   | PRO    | 68             | 16/52        | 68PTC     | ALL      |                   |                |              |          |
| Khadra                | 2018 | USA     | RCT    | 138            | 31/106       | 138PTC    | ALL      |                   |                |              |          |
| Lei Chen              | 2019 | Korea   | RCT    | 46             | 6/40         | 46PTC     | ALL      |                   |                |              |          |
| Li J                  | 2016 | China   | RCT    | 124            | 23/101       | 124PTC    | ALL      |                   |                |              |          |
| Shi HJ                | 2015 | China   | RCT    | 148            | NA           | 148PTC    | ALL      |                   |                |              |          |
| So Yeon Yang          | 2019 | Korea   | RCT    | 453            | 108/345      | 453PTC    | ALL      |                   |                |              |          |
| Sohn YM               | 2012 | Korea   | RCT    | 92             | NA           | 92PTC     | ALL      |                   |                |              |          |
| Suh YJ                | 2013 | Korea   | RCT    | 43             | NA           | 43PTC     | ALL      |                   |                |              |          |
| Tong Tong Liu         | 2018 | China   | RCT    | 75             | 20/55        | 75PTC     | C        |                   |                |              |          |
| Yanfang Wang          | 2021 | China   | RCT    | 120            | 37/83        | 120PTC, 165PTMC | C        |                   |                |              |          |
| Ying Liu              | 2021 | China   | RCT    | 600            | 211/389      | 600PTC    | C        |                   |                |              |          |
| Ying Wei              | 2020 | China   | RCT    | 24             | 14/10        | 24PTC     | ALL      |                   |                |              |          |
| Yoon Jung Choi        | 2010 | Korea   | RCT    | 589            | 121/468      | 589PTC    | C, L     |                   |                |              |          |
| Young Lan Seo         | 2012 | Korea   | RCT    | 20             | 4/16         | 19PTC 1PTMC | ALL      |                   |                |              |          |

(Continued)
evaluated and the gold standard. Two articles had unclear risk of bias with respect to follow-up time. In terms of applicability, all literatures showed no high risk of bias in patient selection, index test, and reference standard. (Figure 2) The authors’ assessment of each domain for included study. This study used funnel plots to detect possible publication bias, and the results showed that the distribution of funnel plots was roughly symmetric, suggesting that there was no publication bias or other bias in the study (Figure 3).

3.3 Pairwise meta-analysis

Through the results of SEN, SPE, PPV, NPV, and Accuracy of various diagnostic methods, a network meta-analysis graph can be made (Figure 4), in which the gridlines in the analysis diagram represented a direct comparison between the two groups of diagnostic methods, the thickness of the gridlines represented the number of articles included, and the size of the solid dots at both ends of the gridlines represented the sample size. Of the 38 studies compared, 12 were direct comparisons and 8 were indirect comparisons. We performed a direct pairwise comparison of SEN, SPE, PPV, NPV, and Accuracy for each method of diagnosing LNM of PTC. Meta-analyses of the results can be used to make direct comparisons. There were 3 studies comparing MRI with PET/CT, 2 studies comparing CT with FNA-Tg, 16 studies comparing US with CT, 6 studies comparing FNAC with FNA-Tg, 3 studies comparing US+CEUS with US, 5 studies comparing CT with PET/CT, 7 studies comparing US with CEUS, 2 studies comparing CT with FNAC, 2 studies comparing US with FNAC, 9 studies comparing US+CT with US, 6 studies comparing US with PET/CT, 3 studies comparing US+CEUS with CEUS, 9 studies comparing US+CT with CT, 2 studies comparing MRI with PET/CT, 3 studies comparing MRI with CEUS, and 3 studies comparing FNAC with FNA-Tg+FNAC. As shown in the figure.

3.4 Network meta-analysis

The OR values and 95% confidence intervals (CI) of SEN, SPE, PPV, NPV, and Accuracy measured by different diagnostic methods for LNM of PTC were statistically analyzed, and the statistical differences were judged by calculation.

3.4.1 SEN

According to the area under the cumulative ranking curve (SUCRA), the SEN of different diagnostic methods for lymph node metastasis can be obtained. The descending order was as follows: US+CT(86.8)>FNAC+FNA-Tg(86.6)>FNA-Tg(86.6)>CT(70.2)>US(51.8)>CEUS(44.5)>SE-US(42.2)>MRI(33.4)>IWBC(31.7)>PET/CT(31.7)>US+CEUS(1.0). Among them, US+CT (OR=0.59, 95%CrI:(0.30,0.89)) and FNAC+FNA-Tg[OR=0.62,95%CI:(0.26,0.98)] ranked first and second, respectively, and had significant advantages compared with other diagnostic methods. There was significant heterogeneity between MRI and US, PET/CT in terms of sensitivity (P<0.05). The probability ranking of diagnosis methods to SEN was ranked first by US+CT in the SUCRA (SUCRA:86.8% as shown in Figure 5). A comparison between the two different diagnosis methods was shown in (Figure 6).

3.4.2 SPE

According to the area under the cumulative ranking curve (SUCRA), the SPE of different diagnostic methods for lymph node metastasis can be obtained. The descending order was as follows: FNAC(92.4)>FNAC+FNA-Tg(85.8)>FNA-Tg(80.5)>CEUS(75.4)>SE-US(64.4)>US(48.5)>CT(42.9)>PET/CT(34.5)>IWBC(32.6)>US+CT(27.1)>MRI(15.5)>US+CEUS(0.4). The analysis of the results showed that compared with US+CEUS, FNAC [OR=1.16,95%CI:(0.65,1.66)] and FNAC+FNA-Tg [OR=1.12,95%CI:(0.59,1.64)] had significant advantages. In terms of specificity (P<0.05), there was significant heterogeneity in the comparison between FNAC and US, FNA-Tg and US, and FNAC and CT. The probability ranking of diagnosis methods to

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**TABLE 2** Continued

| First Author | Year | Country | Design | NO. of patients | Gender (M/F) | Histology | LN level | Diagnostic method | NO. of patients | Gender (M/F) | Histology |
|--------------|------|---------|--------|----------------|-------------|-----------|----------|------------------|----------------|-------------|-----------|
| Yurong Hong  | 2017 | China   | RCT    | 573            | 148/425     | 162       | PTC      | ALL              | 200            | 10          | PTC       |
| Zeming Liu   | 2014 | China   | RCT    | 70             | NA          | 70        | DTC      | C, L             | 100            | 10          | DTC       |
| Zhao H       | 2017 | China   | PRO    | 189            | NA          | 189       | PTC      | ALL              | 100            | 10          | PTC       |

Lymph node level (LN level), All: All cervical LN; C: Central LN; L: Lateral LN.

PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; FTC, Follicular thyroid carcinoma; MTC, Medullary thyroid cancer; SE-US, strain elastography; US, Ultrasound; FNAC, fine-needle aspiration cytology; FNA-Tg, fine-needle aspiration thyroglobulin; IWBS, 131I whole-body; 18F-FDG PET/CT, F-18 fluoro-deoxyglucose positron emission tomography/computed tomography; CT, Computed tomography; CEUS, Contrast-Enhanced Ultrasonography; MRI, Magnetic Resonance Imaging.
FIGURE 2
Bias risk of the included studies (QUADAS 2 criteria).
SPE was ranked first by FNAC in the SUCRA (SUCRA: 92.4% as shown in Figure 7). A comparison between the two different diagnosis methods was shown in Figure 8.

### 3.4.3 PPV

According to the area under the cumulative ranking curve (SUCRA), the PPV of different diagnostic methods for lymph node metastasis can be obtained. The descending order was as follows: FNAC(89.4) > FNAC+FNA-Tg(81.6) > CEUS(77.6) > FNA-Tg(73.9) > SE-US(58.7) > US(51.3) > PET/CT(48.7) > CT (44.5) > US+CT(43.9) > IWBC(18.6) > MRI(11.3) > US+CEUS(0.3). The analysis of the results showed that compared with US + CEUS, FNAC [OR = 1.01, 95%CI: (0.63, 1.38)] and FNAC+FNA-Tg [OR = 0.98, 95%CI: (0.59, 1.37)] had significant advantages. There was no significant difference in specificity (P<0.05). The probability ranking of diagnosis methods to PPV was ranked first by FNAC in the SUCRA (SUCRA: 89.4% as shown in Figures 9). A comparison between the two different diagnosis methods was shown in Figure 10.

### 3.4.4 NPV

According to the area under the cumulative ranking curve (SUCRA), the NPV of different diagnostic methods for lymph node metastasis can be obtained. The descending order was as follows: FNAC+FNA-Tg(81.6) > FNAC(77.6) > CEUS(69.3) > FNA-Tg(67.8) > US+CEUS(51.3) > SE-US(48.7) > PET/CT(44.5) > CT (43.9) > US+CT(43.9) > IWBC(18.6) > MRI(11.3) > US(51.3). The analysis of the results showed that compared with US + CEUS, FNAC [OR = 1.00, 95%CI: (0.63, 1.38)] and FNAC+FNA-Tg [OR = 0.98, 95%CI: (0.59, 1.37)] had significant advantages. There was no significant difference in specificity (P<0.05). The probability ranking of diagnosis methods to NPV was ranked first by FNAC in the SUCRA (SUCRA: 89.4% as shown in Figures 9). A comparison between the two different diagnosis methods was shown in Figure 10.
node metastasis can be obtained. The descending order was as follows: FNAC+FNA-Tg(99.4)>FNA-Tg(89.0)>US+CT(72.2)>CEUS(65.6)>CT(58.5)>US(52.0)>FNAC(49.9)>IWBC(31.4)>SE-US(28.8)>PET/CT(27.1)>MRI(25.6). The analysis of the results showed that compared with US+CEUS, FNAC+FNA-Tg (OR=0.64, 95%CI: (0.38, 0.90) and FNA-Tg [OR=0.57, 95%CI: (0.31, 0.82)] had significant advantages. In terms of specificity (P<0.05), there was significant heterogeneity between MRI and US, PET/CT. The probability ranking of diagnosis methods to NPV was ranked first by FNAC+FNA-Tg in the SUCRA (SUCRA: 99.4% as shown in Figures 11). A comparison between the two different interventions was shown in Figure 12.

3.4.5 Accuracy

According to the area under the cumulative ranking curve (SUCRA), the Accuracy of different diagnostic methods for lymph node metastasis can be obtained. The descending order was as follows: FNAC+FNA-Tg(99.4)>CT(81.6)>FNA-Tg(76.0)>SE-US(61.6)>FNAC(59.8)>CEUS(57.8)>US+CT(52.4)>IWBC.

![Graphs by Treatment](image)

![Rank](image)

**Figure 5**

A = CEUS, B = CT, C = FNA-Tg, D = FNAC, E = FNAC+FNA-Tg, F = IWBC, G = MRI, H = PET/CT, I = SE-US, J = US, K = US+CEUS, L = US+CT.

**Figure 6**

League table on SEN.
(39.0) > US(37.2) > MRI(28.6) > PET/CT(18.7) > US+CEUS(0.5).

The analysis of the results showed that compared with US + CEUS, FNAC+FNA-Tg[OR=0.71, 95%CI:(0.31,1.12)] and FNA-Tg[OR=0.67, 95%CI:(0.35,0.99)] had significant advantages. In terms of specificity (P<0.05), there was significant heterogeneity between CT and US+CT, PET/CT and US, and PET/CT and US+CT. The probability ranking of diagnosis methods to ACC was ranked first by FNAC+FNA-Tg in the SUCRA (SUCRA: 99.4% as shown in Figure 13). A comparison between the two different diagnosis methods was shown in Figure 14.

4 Discussion

This meta-analysis aimed to evaluate the diagnostic performance of multiple diagnostic methods for predicting LNM of PTC. A total of 38 studies with 6285 patients were
summarized and analyzed. Among the 12 diagnostic methods, we found that the combined diagnosis of CT+US and FNAC+FNA-Tg was the most effective diagnostic method for the recurrence and metastasis of LNM of PTC. A total of 6 articles were included in the comparison of US and CT, and the diagnostic performance of CT and US for LNM of PTC, such as sensitivity and specificity, were statistically analyzed. By analyzing the data we found that for the sensitivity of US and CT, the values of SUCRA were 51.8 and 70.2, respectively, while the value for the combined diagnosis of US+CT was 86.8. David (49) et al. found that the accuracy of US may be affected due to the difficulty in distinguishing between the metastatic lymph nodes immediately adjacent to the thyroid and the thyroid itself. In addition, some normal anatomical structures cause distinct acoustic shadows that effectively obscure the area behind them, including air-filled structures such as the larynx and trachea, as well as the clavicle and jawbone, areas deep in the sternum. This greatly limits the assessment of the mediastinal and retropharyngeal regions by ultrasound, regardless of the operator’s interest and expertise. However, all of these areas

FIGURE 9
A = CEUS, B = CT, C = FNA-Tg, D = FNAC, E = FNAC+FNA-Tg, F = IWBC, G = MRI, H = PET/CT, I = SE-US, J = US, K = US+CEUS, L = US+CT.

Graphs by Treatment

Rank

FIGURE 10
League table on PPV.
are commonly seen on CT, and CT scans in the central neck are twice as sensitive as US. Zhao H et al. (51) found that CT had higher sensitivity in the central region and throughout the lateral regions. However, ultrasound had a higher specificity in the central and whole lateral regions. CT can better reduce the missed diagnosis rate, while US can better avoid misdiagnosis. Therefore, this suggested that clinicians should consider the combination of CT and US when diagnosing LNM of PTC. This was consistent with our results that the combined diagnosis method of CT+US could more accurately diagnose LNM for better clinical decision-making.

This time, a variety of diagnostic methods for lymph node metastasis of thyroid cancer were compared. As far as we know, although some authors have published meta-analyses of two or more diagnostic methods for lymph node metastasis of thyroid cancer, our network meta-analysis was the first to comprehensively analyze the currently known diagnostic methods. As far as the retrieved literature is concerned, there are obviously more studies...
on US and CT than those on other diagnostic methods, indicating that these two diagnostic techniques are easier for statistical analysis through direct comparison, and at the same time indicating that US and CT are more widely accepted by everyone, while there are few studies that directly compare CEUS with FNA-Tg. It is recommended to carry out more original research on the comparative analysis of the diagnostic performance of these two diagnostic methods. At the same time, there are many studies comparing CT, US, and PET/CT in their diagnostic performance for lymph node metastasis of thyroid cancer, which also shows that these three studies have obvious comparative value (52). Through analysis, we found that such invasive diagnostic methods such as the combined application of FNAC, FNA-Tg and FNAC+ FNA-Tg had better diagnostic performance. Although non-invasive diagnostic methods were more popular, except for the combined application of US+CT (19, 33), the diagnostic performance of other diagnostic methods was not ideal.

PTC is generally considered to be a tumor with a low probability of metastasis and recurrence. In some patients,
PTC also occurs with lymph node metastasis and local recurrence (53). Studies have shown that tumor size, extrathyroidal extension and vascular invasion are independent risk factors for lymph node metastasis (54). However, extrathyroid extension and vascular infiltration are not helpful to surgeons undergoing surgery, and imaging features such as tumor size and shape can effectively improve the ability of preoperative diagnosis of PTC lymph node metastasis (55).

At present, most hospitals mostly use this non-invasive method of US and CT for preoperative or postoperative evaluation and examination of patients with LNM of PTC. However, US also has its own limitations. US is far from satisfactory in sensitivity and accuracy for lymph node metastasis. It cannot observe deeper tissues or lymph node metastasis, and the accuracy of the result often depends on the experience of the diagnostician, etc. CT is generally considered to be a diagnostic method that plays a key role in the diagnosis of lymph node metastasis of thyroid cancer, especially in the evaluation of deeper tissues (56). CT is slightly inferior to US in evaluating the diagnostic value of central and lateral cervical lymph nodes. Therefore, the combination of CT and US has been evaluated in 11 studies. In our study, regarding the sensitivity to thyroid nodules and lymph node metastasis, we found that the sensitivity of US+CT in the diagnosis of thyroid nodules and lymph node infiltration was superior to the sensitivity of FNAC and FNA-Tg alone.

FNAC was highly specific in the analysis, and Suh YJ et al. (36, 37, 39) found that the threshold values of FNA-Tg established in different experiments were different. If the threshold value of FNA-Tg was specified as 1ng/mL, and levels greater than 1ng/mL were accepted as the surgical indication, then NPV was 0%. Non-metastatic lymph nodes ranged in value from 2-32 ng/mL. The SPE, PPV, NPV and Accuracy of FNA-Tg were significantly lower than those of FNAC. When the critical value of FNA-Tg was 28.5ng/mL, the SPE, PPV, NPV and Accuracy were significantly higher than those of FNAC. Therefore, further experiments are required to determine the optimal critical value of FNA-Tg. Based on our analysis, the diagnostic performance of the combination of FNAC+FNA-Tg was significantly superior to that of FNAC and FNA-Tg alone. In the combination application of FNAC and FNA-Tg, the values of PPV, NPV and Accuracy in SUCRA were 81.6, 99.4 and 86.8 respectively, which had obvious advantages in the diagnosis of LNM of PTC and also proved that the combination application of FNAC and FNA-Tg was one of the necessary diagnostic methods for accurate diagnosis of benign and malignant lymph node metastasis.

Although the combined diagnosis has higher diagnostic performance than the single diagnosis method, the price of the same part of the examination will be correspondingly increased, and the economic burden of different examination methods for patients is different. In China, some routine examinations such as CT,MRI,US,PET/CT are within the range of 100–800 RMB (57), which will not cause great economic pressure for most families. Moreover, the combination diagnosis of CT and US can also obtain relatively accurate results. However, the prices of FNAC and FNA-Tg are about 2000RMB, which is much more expensive compared with conventional examinations. Moreover, most of the patients undergoing such examinations are patients with LNM of PTC, who need to go to the hospital for regular reexamination in addition to the expenses required for daily treatment, so that they need to bear a heavier economic burden. Therefore, during the examination, we should not blindly pursue more accurate diagnosis performance of the disease, but we should be more concerned about their demands and the economic pressure they can bear from the perspective of patients. In the United States, the average cost of these routine imaging examinations in upper-level academic hospitals ranges from $686.13 to $1,390.12. The reason for the higher price in the United States may be that most residents have purchased health insurance, and they can only go to the designated hospitals with medical insurance for examinations, resulting in that they cannot go to the hospitals with lower costs for relevant examinations. At the same time, the price of related examinations is less transparent. Hospitals with lower prices may be stimulated by higher-priced hospitals, leading to price increases. All these have correspondingly increased the economic burden of consumers.

4.1 Limitation

At present, there are many diagnostic methods for lymph node metastasis of papillary thyroid carcinoma, but there are still differences in these diagnostic values, and further analysis and standardization are needed. (1) Compared with previous meta-analyses, we have included more diagnostic methods, but few articles have included some diagnostic methods, and their reliability required more experiments to verify. (2) It was found in the study that the results of direct comparison between interventions were less, and most of them were the results of indirect comparison. This would also affect the final quality evaluation results, which meant that further more direct comparison between different diagnostic methods was needed in the study. (3) Some results showed obvious heterogeneity in our study, but no source of heterogeneity was found after heterogeneity analysis. In view of the above shortcomings, it is recommended that the readers reasonably refer to and select the diagnostic methods in this study based on the clinical practice and actual results.

5 Results

In conclusion, we believe that the combined application of CT+US and FNAC+FNA-Tg is the optimal solution for the
diagnosis of lymph node metastasis in papillary thyroid carcinoma, but further prospective studies on its cost-effectiveness and clinical diagnostic performance are still needed.

Author contributions

Study concept and design: S-RW, Q-LL. Acquisition of data: Q-LL, MC, TS, S-RW, FT. Analysis and interpretation of data: C-IC, S-RW, FT. Drafting of the manuscript: S-RW, FT. Critical revision of the manuscript for important intellectual content: JL. Approval of the final manuscript: JL, L-NS, TS, C-IC, S-RW, FT. Study supervision: JL.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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