

Diagnostic value of cytology, thyroglobulin, and combination of them in fine-needle aspiration of metastatic lymph nodes in patients with differentiated thyroid cancer

A systematic review and network meta-analysis

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Abstract

Background: To investigate the diagnostic performance of cytology (fine-needle aspiration cytology [FNAC]), thyroglobulin (fine-needle aspiration thyroglobulin [FNA-Tg]), and combination of them in the washout of fine-needle aspiration for those patients who have suspicious metastatic lymph nodes of differentiated thyroid cancer.

Methods: Databases, including PubMed, Embase, Web of Science and Cochrane Library were searched up to June 2019. The quality assessment of diagnostic accuracy scale-2 was used to conduct quality assessments, and publication bias was evaluated using the Deeks funnel plot. STATA version 14.0 was used to perform the meta-analysis.

Results: A total of 2257 patients with 2786 samples of suspicious metastatic lymph nodes of differentiated thyroid cancer were included in the meta-analysis. The results showed that the diagnostic value for detecting lymph node metastasis of differentiated thyroid cancer was as follows: combination of FNAC and FNA-Tg > FNA-Tg > FNAC. All differences of superiority among them are statistically significant. The sensitivity of the combination was 0.968 (95% confidence interval [CI]: 0.942–0.983), the specificity was 0.932 (95% CI: 0.856–0.969), the diagnostic score was 6.036 (95% CI: 4.892–7.181), the diagnostic odds ratio was 418.424 (95% CI: 133.167–1314.729), and the score of summary receiver operating characteristic was 0.99 (95% CI: 0.97–0.99).

Conclusions: The combination of FNAC and FNA-Tg is an excellent procedure in diagnosis of lymph nodes metastasis of patients with differentiated thyroid cancer, which should be highly recommended.

Abbreviations: CI = confidence interval, DOR = diagnostic odds ratio, DTC = differentiated thyroid cancer, FN = false-negative, FNAC = fine-needle aspiration cytology, FNA-Tg = fine-needle aspiration thyroglobulin, FP = false-positive, LN = lymph node, LR = likelihood ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, QUADAS = quality assessment of diagnostic accuracy scale, RDOR = relative diagnostic odds ratio, SROC = summary receiver operating characteristic, TgAb = antithyroglobulin, TN = true-negative, TP = true-positive, US = ultrasonography.

Keywords: diagnostic value, differentiated thyroid cancer, fine needle aspiration, lymph nodes metastasis

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1. Introduction

Differentiated thyroid cancer (DTC) is the most common endocrine cancer, with ninth place for incidence and mortality rate from 0.4% to 0.5% in both men and women, worldwide.^[1] Among them, the papillary cancer accounts for about 70%.^[2] The widely accepted risk factor for thyroid cancer is ionizing radiation, especially when exposure is in childhood. Meanwhile, other factors (obesity, smoking, hormonal exposures, and environmental pollution) might also play a specific role in the occurrence and development of cancer.^[3]

Patients with DTC generally have a good prognosis, especially those with low-risk disease. The recurrence rate is only 2.8% in patients who received curative surgery in the initial therapy.^[4] Nevertheless, the metastatic rate of cervical lymph nodes (LNs) is up to 15% in DTC patients.^[5] Therefore, long-term follow-up for patients with DTC, especially those with high-risk, is strongly recommended. In clinic, LNs metastasis was always detected by ultrasonography (US).^[6] However, this technique distinguishing benign from metastatic LN is highly depended on the experience of the doctor, which was considered to be

inaccurate.^[7] Therefore, US-guided fine-needle aspiration cytology (FNAC) is recommended for histological diagnosis of the LN metastasis for patients with DTC both before and after thyroid surgery.^[8] In some instances, the tissue material is inadequate for degeneration and cystic changes. As a result, the sensitivity of FNAC is not satisfactory enough, which varies from 75% to 80%.^[9]

Measurement of thyroglobulin in the washout of fine-needle aspiration (fine-needle aspiration thyroglobulin [FNA-Tg]) has been proved to be an additional tool for diagnosis of LN metastasis of DTC, especially for those inadequate material of FNAC.^[10] Several studies have demonstrated that FNA-Tg increases the sensitivity of FNA-C in identifying LN metastasis of DTC.^[11,12] However, a combination of FNAC and FNA-Tg can statistically improve the diagnostic accuracy of LN metastasis of thyroid cancer is still lacking in evidence. Whether this combination could be used routinely is unknown.

In this study, we aimed to determine the value of FNAC, FNA-Tg, and combination of FNAC and FNA-Tg for diagnosis of LN metastasis of DTC.

2. Methods

2.1. Literature search strategy

A systematic literature search was performed using PubMed, Embase, Web of Science, and Cochrane Library (until June 30, 2019). In each database, the following terms were combined as keywords: (thyroglobulin) and (“fine needle” or “fine-needle” or “fine needle aspiration” or “fine-needle aspiration”) and (thyroid) and (cancer or tumor or carcinoma). All articles sections, including abstracts, studies, and references were reviewed carefully. Articles in the reference list were screened to identify any potentially relevant studies.

This study was conducted in accordance with guidelines of the 1975 Declaration of Helsinki. The study and protocol were designed with approval from our institutional review board.

2.2. Inclusion criteria

The inclusion criteria were as follows:

- (1) patients with DTC;
- (2) LNs were detected by FNA biopsy before or after thyroidectomy;
- (3) cytology of FNA material and thyroglobulin level of FNA washout were measured simultaneously;
- (4) gold standard was the final pathology.

2.3. Exclusion criteria

The exclusion criteria were as follows:

- (1) articles that reported case reports, reviews, letters, and comments;
- (2) studies that did not provide precise number of benign or metastatic LN samples according to the classification standard of FNAC, FNA-Tg, or combination of FNAC and FNA-Tg; and
- (3) non-English publications.

If 2 studies were reported by the same institution, the one with the smaller sample size was excluded.

2.4. Data extraction and quality assessment

All studies were carefully reviewed. Data were extracted from each study by 2 independent researchers, including study ID (first author's name and publication year), country, the absolute number of patients and LN samples, gauge of fine needle, measurement of FNA washout, thyroid cancer type, cutoffs of FNA-Tg, absolute number of true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) test results and concomitant sensitivity, specificity and diagnostic accuracy. The absolute numbers of TP, FP, FN, and TN test results were retrieved from the articles. If the data were not available, e-mails were sent to the corresponding author to ask for complete data for meta-analysis. Any inconsistencies between reviewers were resolved by a third investigator through discussion.

The quality assessment of diagnostic accuracy scale-2 (QUADAS-2) was used to assess the quality of included diagnostic studies.^[13] The QUADAS-2 evaluates studies based on patient selection, index test, reference standard, and flow/timing. The results were categorized into low/high/unclear about each domain.

2.5. Outcomes of interests

First, combined sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated among FNAC, FNA-Tg, and combination of FNAC and FNA-Tg. Meanwhile, diagnostic score and diagnostic odds ratio (DOR) and summary receiver operating characteristic (SROC) were examined. Finally, 3 diagnostic tests were compared to identify the optimal method.

2.6. Statistical analyses

We used STATA software version 14.0 (StataCorp, College Station, TX) to perform the meta-analysis. Heterogeneity among studies was tested using Cochran *Q* and Higgins' *I*² statistics.^[14] For each article, we constructed data of TP, FP, FN, and TN into a 2 × 2 contingency table. The sensitivity, specificity, PLR, NLR, diagnostic score, and DOR were pooled and combined with their 95% confidence interval (CI) using the bivariate mixed-effects regression model. According to Moses–Littenberg method, SROC curves with pooled sensitivity and specificity were estimated.^[15] 0.5 was added to each cell in the table to avoid the calculation problem by having 0 values. The score of SROC was defined as excellent (≥0.97), very good (0.93–0.96), good (0.75–0.92), and reasonable (<0.75), respectively.^[16]

PLR above 5 and NLR 0.2 below were considered to provide strong diagnostic value.^[17] The post-test probability, calculated with likelihood ratio (LR), based on Bayes theorem, was used to evaluate clinical utility of diagnostic test.^[18] Pretest probability = prevalence of target condition. Post-test probability = LR × pretest probability / ([1 - pretest probability] × [1 - LR]).^[19] Diagnostic value between each 2 tests was compared using relative diagnostic odds ratio (RDOR) based on multivariate meta-regression.^[20,21] Publication bias of included studies was estimated using the Deeks funnel plot. A result was defined statistically significant with *P* < .05.

3. Results

3.1. Search strategy

After searching, 534 articles were identified in PubMed, 1234 in Embase, 449 in Web of Science, and 6 in Cochrane Library.

Besides, 10 articles were identified from the reference list of those researches. After duplicates were removed, 80 articles were screened. Forty-six articles were excluded for reasons of being non-English publications, case reports, or reviews. After reading the full-text articles, those that could not provide a precise data of outcomes of interest, used grouping standards that were different from those under consideration and contained irrelevant subjects were excluded. Finally, 19 articles were included in this meta-analysis (Fig. 1).

3.2. Cohort characteristics and quality of the studies

Nineteen studies were finally included in our analysis.^[22-40] Sample sizes varied from 30 to 376. With respect to the study region, 7 studies were performed in Korea, 4 in China, 2 in Turkey, 2 in USA, 1 in Brazil, 1 in Spain, 1 in Italy, and 1 in

France. The publication date ranged from 2009 to 2018 (Table 1). All studies provided precise data about FNA-Tg results. All studies except one provided precise data about FNAC results. Nine studies provided precise data about FNAC combined with FNA-Tg results. The golden standard is surgical histological examination result. All of these results were classified as TP, FP, FN, and TN, after compared with the gold standard (Table 2).

Quality assessment was conducted on all articles included in meta-analysis using QUADAS-2. Overall, these studies met most of the quality criteria.

3.3. Diagnostic performance of FNAC and FNA-Tg

The pooled sensitivity and specificity of FNAC were 0.813 (95% CI: 0.742-0.868) and 0.964 (95% CI: 0.852-0.992). The PLR

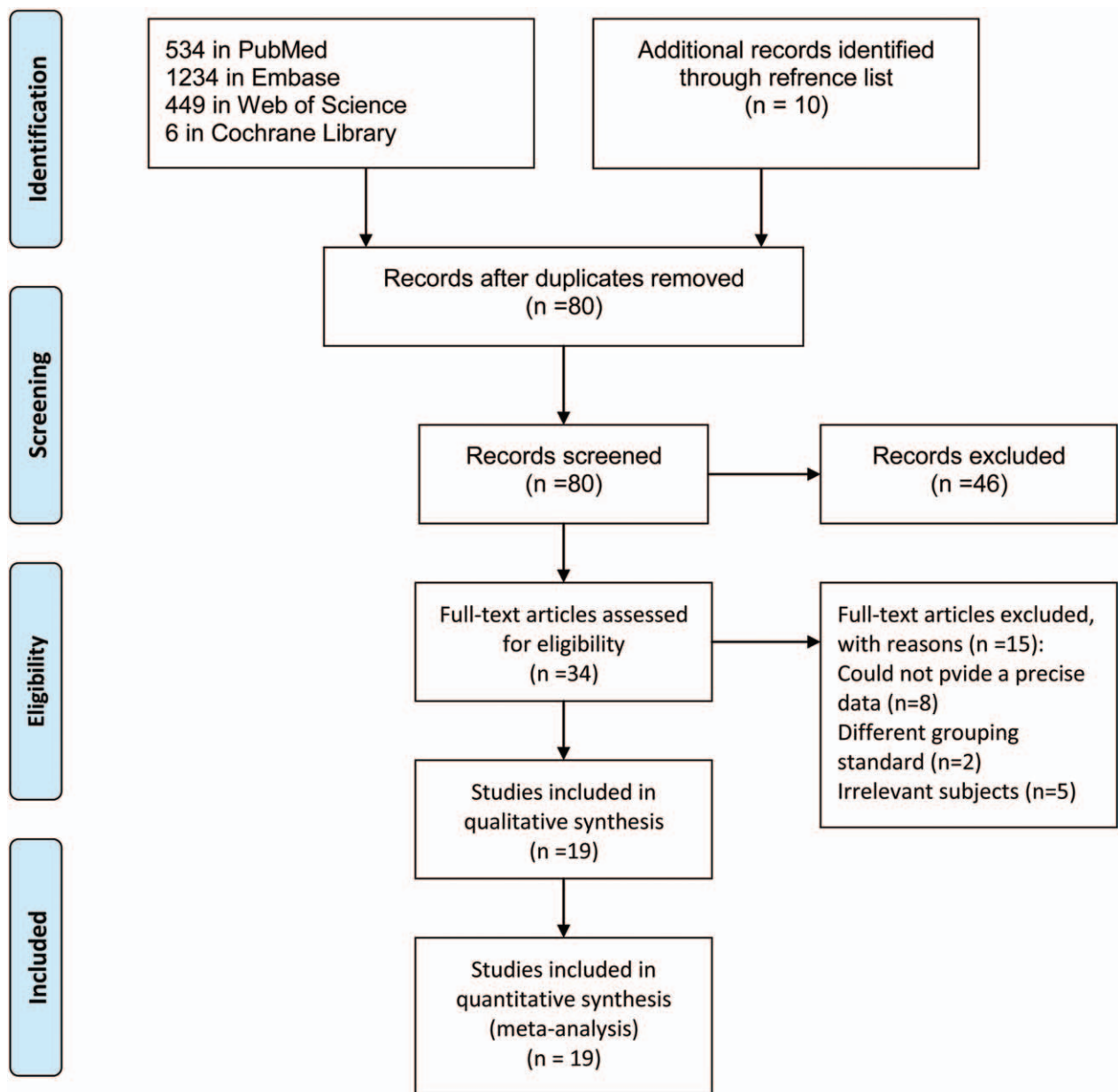


Figure 1. Flow diagram for study selection.

Table 1
Studies included in meta-analysis.

| Author | Year | Country | Study design | Patients | Female | Samples | Needle (gauge) | FNA-Tg measurement | Cancer type | Cutoffs (ng/mL) | AUC (95% CI) |
|--------------|------|---------|---------------|----------|---------|---------|----------------|--------------------|----------------|-----------------|---|
| Duval | 2017 | Brazil | Prospective | 38 | 28 | 119 | 21 | ECLIA | Differentiated | 4.41 | 0.984 (0.958, 1.0) |
| Li | 2016 | China | Retrospective | 124 | 101 | 163 | 21 | IRMA | Papillary | 1 | N/A |
| Degertekin | 2016 | Turkey | Retrospective | 95 | 40 | 165 | 22 | Unclear | Papillary | 1 | 0.969 (0.923, 1.0) |
| Shi | 2015 | China | Retrospective | 148 | Unclear | 148 | Unclear | Unclear | Papillary | 1/10 | N/A |
| Jo | 2015 | Korea | Retrospective | 273 | 221 | 370 | 23 | IRMA | Differentiated | 1 | N/A |
| Zhang | 2014 | China | Prospective | 58 | 42 | 68 | 21–25 | ECLIA | Differentiated | 1 | N/A |
| Casado | 2013 | Spain | Retrospective | 10 | Unclear | 16 | 21–25 | ECLIA | Differentiated | 2 | N/A |
| Baldini | 2013 | Italy | Prospective | 28 | 21 | 35 | 25 | IRMA | Differentiated | 1 | N/A |
| Suh | 2013 | Korea | Retrospective | 43 | Unclear | 47 | 23 | IRMA | Papillary | 1/10 | N/A |
| Kim | 2012 | Korea | Prospective | 68 | 52 | 91 | 21–23 | IRMA | Papillary | 1 | N/A |
| Sohn | 2012 | Korea | Retrospective | 92 | Unclear | 95 | 23 | IRMA | Papillary | 1/10 | 0.67 (0.5783, 0.7595)/0.73 (0.6435, 0.8197) |
| Bournaud | 2010 | France | Retrospective | 114 | Unclear | 122 | 27 | IRMA | Differentiated | 0.93 | N/A |
| Jeon | 2009 | Korea | Retrospective | 47 | Unclear | 76 | 21–23 | unclear | Papillary | 36 | N/A |
| Kim | 2009 | Korea | Prospective | 168 | Unclear | 168 | 23 | IRMA | Differentiated | 1/10 | 0.955 (0.926, 0.984) |
| Khadra | 2018 | USA | Retrospective | 138 | 106 | 138 | 25 | ICMA | Papillary | 1 | N/A |
| Eun | 2017 | Korea | Retrospective | 302 | 226 | 376 | 23 | unclear | Papillary | 1 | N/A |
| Zhao | 2017 | China | Prospective | 189 | Unclear | 196 | 22 | ECLIA | Papillary | 1 | 0.999 (0.997, 1.000) |
| Tang | 2016 | USA | Prospective | 97 | 75 | 168 | 22–25 | CIA | Differentiated | 1 | N/A |
| Salmaslıoğlu | 2010 | Turkey | Prospective | 225 | 165 | 225 | 22 | IRMA | Papillary | 1 | N/A |

AUC = area under curve, CI = confidence interval, CIA = chemiluminescent immunoassay, ECLIA = chemiluminescence assay, FNA = fine needle aspiration, ICMA = immunochemiluminometric assay, IRMA = immunoluminometric assay, Tg = thyroglobulin.

and NLR were 22.812 (95% CI: 5.271–98.711) and 0.194 (95% CI: 0.141–0.267). The diagnostic score, DOR and score of SROC were 4.768 (95% CI: 3.330–6.206), 117.695 (95% CI: 27.937–495.832), and 0.91 (95% CI: 0.88–0.93).

Meanwhile, the pooled sensitivity and specificity of FNA-Tg were 0.945 (95% CI: 0.905–0.969) and 0.888 (95% CI: 0.761–0.952). The PLR and NLR were 8.411 (95% CI: 3.790–18.663) and 0.062 (95% CI: 0.037–0.105). The diagnostic score, DOR and score of SROC were 4.908 (95% CI: 4.031–5.785), 135.331 (95% CI: 56.293–325.341), and 0.97 (95% CI: 0.95–0.98).

All of these results were shown in Table 3.

3.4. Diagnostic performance and evaluating clinical application of combination of FNAC and FNA-Tg

The pooled results were showed as follows: sensitivity was 0.968 (95% CI: 0.942–0.983) and specificity was 0.932 (95% CI: 0.856–0.969) (Fig. 2A and B). Diagnostic score and DOR were 6.036 (95% CI: 4.892–7.181) and 418.424 (95% CI: 133.167–1314.729). The score of SROC was 0.99 (95% CI: 0.97–0.99) (Fig. 3).

PLR and NLR of FNAC combined with FNA-Tg were 14.172 (95% CI: 6.497–30.912) and 0.034 (95% CI: 0.018–0.064), indicating that this test is good for detecting metastasis of thyroid cancer. Subsequently, we performed the Fagan nomogram to confirm the clinical application of this test. We found that if a pretest probability is 20%, the post-test probability of a positive result is 78%. Meanwhile, an NLR of 0.03 reduces the post-test probability to 1% for a negative test result (Fig. 4).

3.5. Network meta-analysis of FNAC, FNA-Tg, and combination of FNAC and FNA-Tg

The results suggested that the diagnostic value for detecting LN metastasis of thyroid cancer was as follows: FNAC combined

with FNA-Tg > FNA-Tg > FNAC. The differences of diagnostic value among them are statistically significant (Table 4).

3.6. Publication bias

There are no publication biases in pooled results of FNAC ($P > |t| = .253$), FNA-Tg ($P > |t| = .731$), and combination of FNAC and FNA-Tg ($P > |t| = .589$), according to Deeks funnel plot (Table 3).

4. Discussion

We demonstrated that combination of FNAC and FNA-Tg was superior to FNA-Tg or FNAC alone in diagnostic value of LNs metastases of DTC. Besides, FNA-Tg is better than FNAC. Moreover, differences of diagnostic value among these 3 methods are statistically significant. Overall, combination of FNAC and FNA-Tg is an excellent diagnostic method (SROC score = 0.99) for LNs metastases of DTC.

Accurate discrimination between benign and metastatic LNs is necessary in the diagnostic management of DTC. US and CT are the primary and noninvasive procedures for both pre- and postoperative assessment of thyroid malignancy. However, the diagnostic accuracy of US was far from satisfactory and CT was not widely accepted because of its high cost.

Cytological examination of FNA samples was reported to be an accurate method, with high sensitivity and specificity, for detection of metastatic LNs in general head and neck malignancies.^[41] The diagnosis of cervical LNs metastases of DTC is often complex because inflammatory lymphadenopathies and non-thyroidal cancer metastases are frequent in this region.^[42] Therefore, there are many FP and FN results. The accuracy of FNAC highly depends on the experience of cytopathologist.^[43] In the present study, we found that the sensitivity of FNAC is just 0.813 and the SROC score is 0.91, which is far from optimal.

Table 2

Pooled sensitivity, specificity, and accuracy of FNA-Tg, FNAC, and FNAC combined with FNA-Tg.

| Author | Year | Cutoffs of FNA-Tg | FNA-Tg | | | | | | | | | | FNAC | | | | | | | | | | FNAC+FNA-Tg | | | | | | | | | |
|--------------|------|-------------------|--------|----|----|-----|-------------|-------------|----------|-----|----|----|------|-------------|-------------|----------|-----|----|----|----|-------------|-------------|-------------|------|----|----|----|-------------|-------------|----------|------|--|
| | | | TP | FP | FN | TN | Sensitivity | Specificity | Accuracy | TP | FP | FN | TN | Sensitivity | Specificity | Accuracy | TP | FP | FN | TN | Sensitivity | Specificity | Accuracy | TP | FP | FN | TN | Sensitivity | Specificity | Accuracy | | |
| Duval | 2017 | 4.41 | 87 | 7 | 21 | 48 | 80.5 | 87 | 82.8 | 53 | 12 | 9 | 33 | 85.5 | 73.3 | 80.4 | 103 | 2 | 3 | 53 | 97.1 | 96.3 | 80.4 | 103 | 2 | 3 | 53 | 97.1 | 96.3 | 80.4 | | |
| Li | 2016 | 1 | 87 | 7 | 21 | 48 | 80.5 | 87 | 82.8 | 74 | 12 | 34 | 43 | 69.2 | 78.2 | 71.8 | 103 | 2 | 3 | 53 | 97.1 | 96.3 | 71.8 | 103 | 2 | 3 | 53 | 97.1 | 96.3 | 71.8 | | |
| Degertekin | 2016 | 1 | 34 | 0 | 3 | 14 | 91.9 | 100 | 94.1 | 64 | 0 | 30 | 54 | 68.1 | 100 | 79.7 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 79.7 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 79.7 | | |
| Shi | 2015 | 1 | 31 | 0 | 6 | 14 | 83.8 | 100 | 88.2 | 64 | 0 | 30 | 54 | 68.1 | 100 | 79.7 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 79.7 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 79.7 | | |
| Shi | 2015 | 1 | 86 | 6 | 8 | 48 | 91.5 | 88.9 | 90.5 | 64 | 0 | 30 | 54 | 68.1 | 100 | 79.7 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 79.7 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 79.7 | | |
| Shi | 2015 | 10 | 93 | 17 | 1 | 37 | 98.9 | 68.5 | 87.8 | 92 | 2 | 17 | 259 | 84.4 | 99.2 | 94.9 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 94.9 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 94.9 | | |
| Jo | 2015 | unclear | 44 | 1 | 2 | 21 | 95.7 | 95.5 | 95.6 | 92 | 2 | 17 | 259 | 84.4 | 99.2 | 94.9 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 94.9 | 90 | 2 | 4 | 52 | 95.7 | 96.3 | 94.9 | | |
| Zhang | 2014 | 1 | 44 | 1 | 2 | 21 | 95.7 | 95.5 | 95.6 | 35 | 3 | 11 | 19 | 76.1 | 86.4 | 79.4 | 45 | 1 | 1 | 21 | 97.8 | 95.5 | 79.4 | 45 | 1 | 1 | 21 | 97.8 | 95.5 | 79.4 | | |
| Casado | 2013 | 2 | 9 | 0 | 1 | 6 | 90 | 100 | 94.8 | 7 | 1 | 0 | 4 | 100 | 80 | 91.7 | 45 | 1 | 1 | 21 | 97.8 | 95.5 | 91.7 | 45 | 1 | 1 | 21 | 97.8 | 95.5 | 91.7 | | |
| Baldini | 2013 | 1 | 24 | 2 | 1 | 5 | 92.3 | 83.3 | 90.6 | 27 | 5 | 0 | 0 | 100 | 0 | 84.4 | 34 | 4 | 0 | 9 | 100 | 69.2 | 84.6 | 84.4 | 34 | 4 | 0 | 9 | 100 | 69.2 | 84.6 | |
| Suh | 2013 | 1 | 34 | 4 | 0 | 9 | 100 | 69.2 | 91.5 | 29 | 0 | 5 | 13 | 85.3 | 100 | 89.4 | 34 | 4 | 0 | 9 | 100 | 69.2 | 84.6 | 89.4 | 34 | 4 | 0 | 9 | 100 | 69.2 | 84.6 | |
| Suh | 2013 | 1 | 34 | 4 | 0 | 9 | 100 | 69.2 | 91.5 | 29 | 0 | 5 | 13 | 85.3 | 100 | 89.4 | 34 | 4 | 0 | 9 | 100 | 69.2 | 84.6 | 89.4 | 34 | 4 | 0 | 9 | 100 | 69.2 | 84.6 | |
| Kim | 2012 | 1 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | 34 | 5 | 15 | 37 | 69.4 | 88.1 | 78.0 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | 78.0 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | |
| Kim | 2012 | 1 | 46 | 4 | 3 | 38 | 93.9 | 90.5 | 92.3 | 17 | 0 | 25 | 53 | 40.5 | 100 | 73.7 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | 73.7 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | |
| Sohn | 2012 | 1 | 34 | 25 | 8 | 28 | 80.9 | 52.8 | 65.3 | 17 | 0 | 25 | 53 | 40.5 | 100 | 73.7 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | 73.7 | 34 | 2 | 0 | 11 | 100 | 84.6 | 95.7 | |
| Sohn | 2012 | 10 | 25 | 7 | 17 | 46 | 59.5 | 86.8 | 74.7 | 37 | 12 | 15 | 34 | 71.2 | 73.9 | 72.4 | 37 | 12 | 15 | 34 | 71.2 | 73.9 | 72.4 | 37 | 12 | 15 | 34 | 71.2 | 73.9 | 72.4 | | |
| Bournaud | 2010 | 0.93 | 48 | 1 | 4 | 45 | 92.3 | 97.8 | 94.9 | 37 | 12 | 15 | 34 | 71.2 | 73.9 | 72.4 | 37 | 12 | 15 | 34 | 71.2 | 73.9 | 72.4 | 37 | 12 | 15 | 34 | 71.2 | 73.9 | 72.4 | | |
| Jeon | 2009 | 36 | 53 | 2 | 3 | 18 | 94.6 | 90 | 93.4 | 45 | 0 | 11 | 20 | 80.4 | 100 | 85.5 | 54 | 2 | 2 | 18 | 90.0 | 94.7 | 85.5 | 54 | 2 | 2 | 18 | 90.0 | 94.7 | 85.5 | | |
| Kim | 2009 | 1 | 114 | 13 | 5 | 36 | 95.8 | 73.5 | 89.3 | 92 | 1 | 27 | 48 | 77.3 | 97.9 | 83.3 | 115 | 15 | 4 | 35 | 96.6 | 71.4 | 83.3 | 115 | 15 | 4 | 35 | 96.6 | 71.4 | 83.3 | | |
| Kim | 2009 | 1 | 108 | 5 | 11 | 44 | 90.8 | 89.8 | 90.5 | 92 | 1 | 27 | 48 | 77.3 | 97.9 | 83.3 | 115 | 15 | 4 | 35 | 96.6 | 71.4 | 83.3 | 115 | 15 | 4 | 35 | 96.6 | 71.4 | 83.3 | | |
| Khadra | 2018 | 1 | 68 | 2 | 3 | 19 | 95.8 | 90.5 | 94.6 | 56 | 0 | 14 | 21 | 80.0 | 100 | 84.6 | 112 | 6 | 7 | 43 | 94.1 | 87.8 | 84.6 | 112 | 6 | 7 | 43 | 94.1 | 87.8 | 84.6 | | |
| Khadra | 2018 | 1 | 68 | 2 | 3 | 19 | 95.8 | 90.5 | 94.6 | 56 | 0 | 14 | 21 | 80.0 | 100 | 84.6 | 112 | 6 | 7 | 43 | 94.1 | 87.8 | 84.6 | 112 | 6 | 7 | 43 | 94.1 | 87.8 | 84.6 | | |
| Eun | 2017 | 1 | 106 | 0 | 5 | 85 | 95.5 | 100.0 | 97.4 | 92 | 3 | 34 | 46 | 73.0 | 93.9 | 78.9 | 108 | 5 | 18 | 44 | 85.7 | 89.8 | 78.9 | 108 | 5 | 18 | 44 | 85.7 | 89.8 | 78.9 | | |
| Zhao | 2017 | 10 | 106 | 0 | 5 | 85 | 95.5 | 100.0 | 97.4 | 99 | 0 | 12 | 85 | 89.2 | 100 | 93.9 | 110 | 0 | 1 | 85 | 99.1 | 100 | 93.9 | 110 | 0 | 1 | 85 | 99.1 | 100 | 93.9 | | |
| Tang | 2016 | 1 | 20 | 5 | 1 | 117 | 95.2 | 95.9 | 95.8 | 12 | 0 | 1 | 121 | 92.3 | 100 | 99.3 | 110 | 0 | 1 | 85 | 99.1 | 100 | 99.3 | 110 | 0 | 1 | 85 | 99.1 | 100 | 99.3 | | |
| Tang | 2016 | 1 | 20 | 5 | 1 | 117 | 95.2 | 95.9 | 95.8 | 12 | 0 | 1 | 121 | 92.3 | 100 | 99.3 | 110 | 0 | 1 | 85 | 99.1 | 100 | 99.3 | 110 | 0 | 1 | 85 | 99.1 | 100 | 99.3 | | |
| Salmashroglu | 2010 | 1 | 200 | 55 | 0 | 0 | 100.0 | 0 | 78.4 | 190 | 33 | 10 | 22 | 95.0 | 40.0 | 83.1 | 190 | 33 | 10 | 22 | 95.0 | 40.0 | 83.1 | 190 | 33 | 10 | 22 | 95.0 | 40.0 | 83.1 | | |

FNAC = fine needle aspiration cytology, FNA-Tg = fine needle aspiration thyroglobulin, FN = false-negative, TP = true-positive, FP = false-positive, TN = true-negative, TP = true-positive.

Table 3
Summary of the results of combined sensitivity, specificity, positive, and negative likelihood ratio for FNAC, FNA-Tg, and FNAC + FNA-Tg.

| Test | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | Diagnostic score (95% CI) | DOR (95% CI) | SROC (95% CI) | P> t |
|-------------|----------------------|----------------------|------------------------|----------------------|---------------------------|-----------------------------|-------------------|------|
| FNAC | 0.813 (0.742, 0.868) | 0.964 (0.852, 0.992) | 22.812 (5.271, 98.711) | 0.194 (0.141, 0.267) | 4.768 (3.330,6.206) | 117.695 (27.937, 495.832) | 0.91 (0.88, 0.93) | .253 |
| FNA-Tg | 0.945 (0.905, 0.969) | 0.888 (0.761, 0.952) | 8.411 (3.790, 18.663) | 0.062 (0.037, 0.105) | 4.908 (4.031, 5.785) | 135.331 (56.293, 325.341) | 0.97 (0.95, 0.98) | .731 |
| FNAC+FNA-Tg | 0.968 (0.942, 0.983) | 0.932 (0.856, 0.969) | 14.172 (6.497, 30.912) | 0.034 (0.018, 0.064) | 6.036 (4.892, 7.181) | 418.424 (133.167, 1314.729) | 0.99 (0.97, 0.99) | .589 |

AUROC = area under the receiving-operation curve, DOR = diagnostic odds ratio, FNA = fine needle aspiration, FNAC = fine needle aspiration cytology, NLR = negative likelihood ratio, PLR = positive likelihood ratio, Tg = thyroglobulin.

FNA-Tg measurement in the washout was originally proposed by Pacini et al in 1992.^[44] This study suggested that high dose of FNA-Tg was always associated with LNs metastasis of thyroid cancer after initial therapy, including thyroidectomy and radioactive iodine ablation, whereas undetectable FNA-Tg frequently indicated benign disease, such

as inflammatory or lymphadenopathy. In last decade, several studies proved that the sensitivity and specificity of FNA-Tg for diagnosis of LN metastasis of DTC are superior to FNAC.^[11,42,43] In the present study, we found that the diagnostic value of FNA-Tg is superior to FNAC with statistical difference.

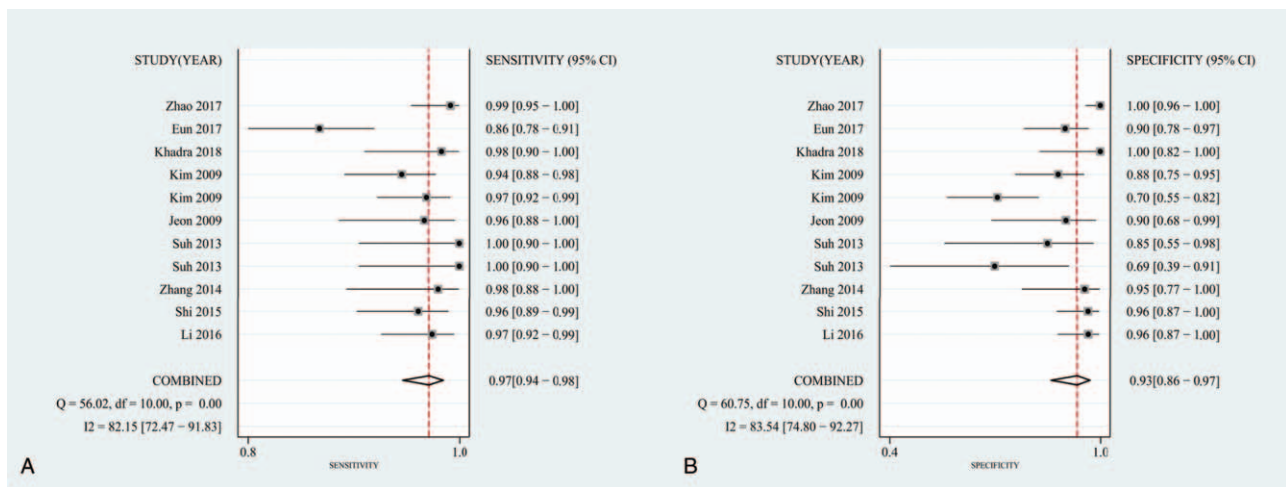


Figure 2. The diagnostic accuracy index of the combination of FNA and FNA-Tg. (A) Sensitivity, (B) Specificity. FNA = fine-needle aspiration, FNA-Tg = fine-needle aspiration thyroglobulin.

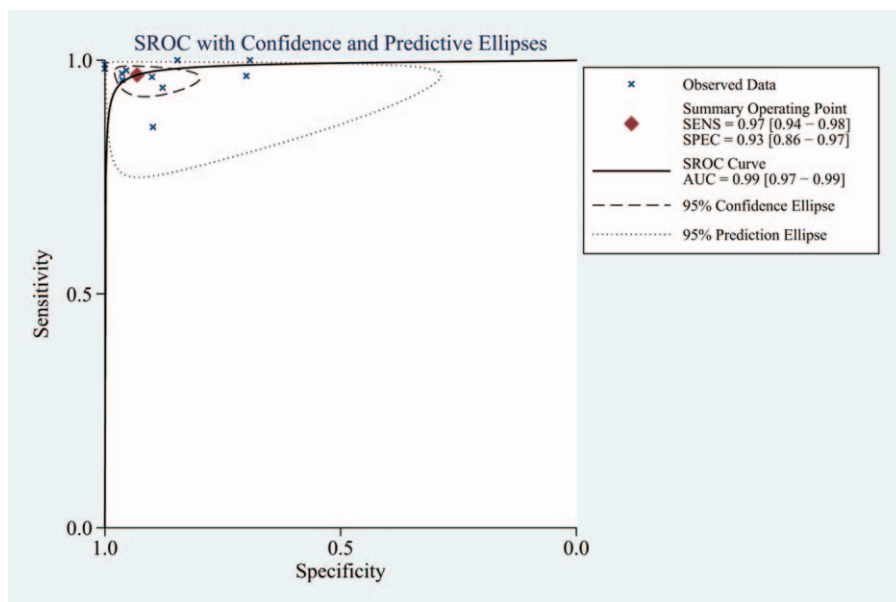


Figure 3. SROC curve of the combination of FNA and FNA-Tg. FNA = fine-needle aspiration, FNA-Tg = fine-needle aspiration thyroglobulin, SROC = summary receiver operating characteristic.

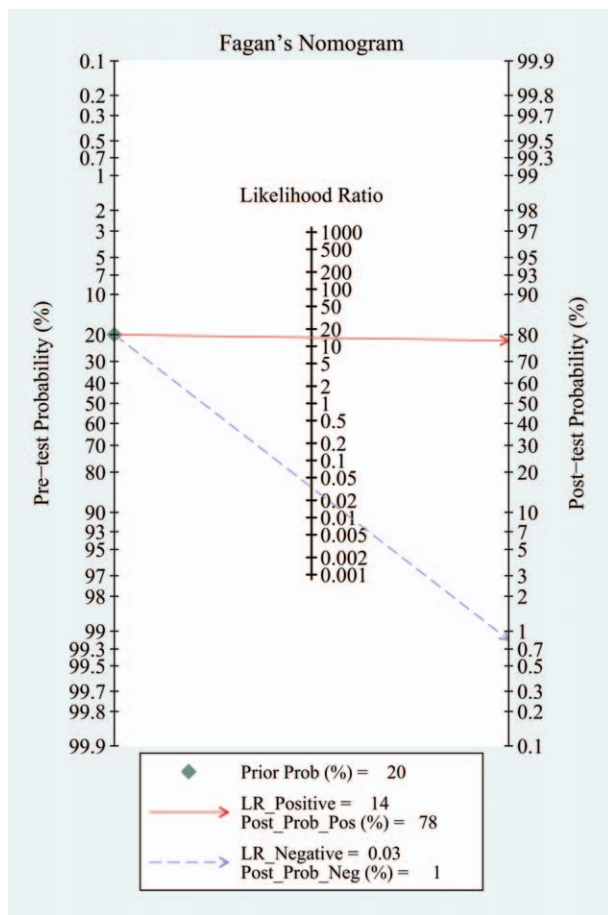


Figure 4. Fagan nomogram for the combination of FNAC and FNA-Tg. FNA = fine-needle aspiration, FNAC = fine-needle aspiration cytology, FNA-Tg = fine-needle aspiration thyroglobulin.

However, there are still some problems with this method. First, normal thyroid tissue synthesizes and secretes Tg, and its concentration in blood is closely associated with on the size of thyroid, hormones, and antithyroglobulin (TgAb). Tg and TgAb are antagonistic to each other. Baskin et al first suggested that TgAb in the peripheral blood would not affect the measurement of FNA-Tg in the washout, possibly because intracellular Tg is not exposed to circulating TgAb.^[45] After 2 years, Boi et al also identified that the diagnostic performance of FNA-Tg seemed to be not affected by TgAb.^[46] It is possibly because concentration of FNA-Tg in LN metastasis is much higher than TgAb in the washout fluid. The effect of TgAb on FNA-Tg is almost negligible. In addition, the dilution of washout fluid (1:50 or higher) results in the scarcity of TgAb. Nevertheless, a lower sensitivity and NPV of FNA-Tg in diagnosis of LN metastasis of

DTC was found by Jeon et al in 2013,^[47] which means the serum TgAb levels could lower the diagnostic performance of FNA-Tg. The same result was identified by Jo et al in 2015.^[28] Therefore, the interference of TgAb to FNA-Tg is still controversial. Second, due to the differences in sample treatment and thyroglobulin assays, the cutoff value of FNA-Tg remains controversial. There are various ways to identify the FNA-Tg threshold values, including mean + 2 standard deviation of FNA-Tg concentration in patients without LNs metastases, highest Tg concentration in patients with reactive LNs, FNA-Tg more than serum Tg level, fixed Tg values, and so on. Pak et al published a meta-analysis suggested that the best pre and postoperative cutoff value of FNA-Tg for diagnosis of LN metastasis of DTC were 0.9 ng/mL and 32.04 ng/mL, respectively.^[43] Another study suggested that the optimal cutoff value of FNA-Tg was 2.24 ng/mL and 1.09 ng/mL for patients before and after thyroidectomy, respectively.^[48] However, in the process of collecting information for the present study, we found that most studies defined the cutoff value of FNA-Tg as 1 ng/mL or 10 ng/mL. The main purpose of the present study is not to identify the optimal cutoff value of FNA-Tg, so the subgroup analysis has not been performed. The diagnostic value of FNA-Tg in LN metastasis of DTC should not be ignored, despite the controversy of optimal cutoff value. In addition, the subject of best cutoff value of FNA-Tg should be studied in more clinical trials.

Due to limit of financial condition and the deficiency of equipment, not all of the hospitals are able to test both the FNAC and FNA-Tg at the same time. Most of them only use the FNAC as the primary diagnostic method for suspicious DTC patients. However, according to the guidelines of European, Korean, and American Thyroid Association, the combination of FNAC and FNA-Tg is recommended for the patients with suspicious DTC.^[49-51] Its diagnostic accuracy is statistically superior.

Our study found that a combination of FNAC and FNA-Tg had statistically better diagnostic performance than FNAC or FNA-Tg alone. The score of SROC is 0.99, which means this is an excellent diagnostic method of LN metastasis of DTC. Meanwhile, the Fagan nomogram showed that the clinical application of combination of FNAC and FNA-Tg was obvious. The results showed that if the test is negative, the probability of LN metastasis of DTC would decrease only to 1%, but if the test is positive, the probability of LN metastasis of DTC would increase to 78%. Li et al also identified the same conclusion in their study published in 2016.^[33] For those obvious metastatic LNs, the level of FNA-Tg is frequently extremely high. However, for those FNA tissues, the FNA-Tg level of which is near the cutoff value, the FNAC could be used as additional diagnostic method to identify the histological result. Meanwhile, for those inadequate tissues of FNAC, the FNA-Tg is also an ideal additional diagnostic procedure.

There some limitations of our study. Some studies did not have precise data, as we sent an email to the author asking for them,

Table 4
Summary of network analysis results among studies.

| Test | RDOR | P | 95% CI |
|-----------------------------|-------|-------|------------|
| FNA-Tg versus FNAC | 3.54 | .0309 | 1.13–11.07 |
| FNAC + FNA-Tg versus FNAC | 16.01 | .0001 | 4.61–55.60 |
| FNAC + FNA-Tg versus FNA-Tg | 3.22 | .0325 | 0.89–10.88 |

CI = confidence interval, FNA = fine needle aspiration thyroglobulin, FNAC = fine needle aspiration cytology, RDOR = relative diagnostic odds ratio, Tg = thyroglobulin.

but the email had no response. Some results of our study had apparent heterogeneity. The sources of heterogeneity did not be found after regression and heterogeneity analysis.

In conclusion, combination of FNA and FNA-Tg is an excellent diagnostic procedure for LN metastasis of DTC. Compared to FNAC and FNA-Tg alone, the combination could statistically improve the diagnostic performance. This procedure should be recommended for patients with suspicious LN metastasis of DTC before or after initial therapy.

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Writing – review and editing: Yixin Xu.

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