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Article

# Exploration of the clinical significance of rapid intraoperative measurement of lymph node thyroglobulin concentration in determining lymph node metastasis of papillary thyroid carcinoma

**Shiyi Zhao[1], Yue Xiang[1], Wei Yan[2], Dejie Chen[2,*]**

[1] College of Medicine, Wuhan University of Science and Technology, Wuhan 430081, China
[2] Department of Thyroid and Breast Surgery, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang 441021, China
*** Corresponding author:** Dejie Chen, fy7037@hbuas.edu.cn

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**Abstract: Objective:** This study aims to evaluate the diagnostic accuracy of thyroid globulin (Tg) detection in elution fluid for intraoperative judgment of lymph node metastasis, and to explore the potential role of biomolecular mechanical behavior in influencing the detection results. By rapidly quantifying Tg levels, the optimal cutoff value was determined, and its potential value in clinical applications was further assessed. **Methods:** This is a prospective study that included 65 patients with papillary thyroid carcinoma who underwent surgery at Xiangyang Central Hospital's thyroid surgery department from November 2022 to May 2023. A total of 150 cervical lymph node samples were collected. Tg levels were detected intraoperatively using colloidal gold immunochromatographic assay (FNA-TG-GICA), and results were compared with routine paraffin pathology findings. Particular attention was given to the reactivity of Tg molecules in the elution fluid. The optimal cutoff value for Tg test to judge the benign or malignant nature of lymph nodes was determined by plotting the ROC curve and calculating the AUC, to evaluate the diagnostic performance of the intraoperative Tg detection in identifying lymph node metastasis. **Results:** A total of 150 lymph node samples were included in this study, of which paraffin pathology verification showed 50 metastatic and 100 non-metastatic lymph nodes. The optimal cutoff value for Tg test was 77 ng/mL, with sensitivity of 94.00%, specificity of 96%, and accuracy of 95%. The AUC from the ROC curve analysis was 0.97, indicating high diagnostic accuracy. Further analysis revealed that most of the positive samples were metastatic lymph nodes, and all negative samples were non-metastatic, suggesting that the Tg test performs excellently in determining lymph node metastasis. **Conclusion:** Elution fluid Tg test demonstrates high accuracy in intraoperatively determining lymph node metastasis. With an optimal cutoff value of 77 ng/mL, it shows excellent sensitivity and specificity. This detection method serves as a rapid and reliable diagnostic tool, providing effective decision support for clinical practice.

**Keywords:** thyroid cancer; cervical lymph node metastasis; elution fluid; thyroglobulin; colloidal gold immunochromatography; biomolecular mechanics; cell response

In recent years, the incidence of thyroid cancer has been increasing annually worldwide, ranking third among malignant tumors in women. Papillary thyroid carcinoma (PTC) accounts for approximately 90% of all thyroid cancers [1,2]. Although PTC typically grows slowly, is minimally invasive, and has a favorable prognosis, 5%–60% of PTC patients still experience cervical lymph node metastasis, significantly increasing recurrence and mortality rates [3]. Accurate assessment of lymph node metastasis is crucial for intraoperative decision-making and patient prognosis. Currently, ultrasound and fine-needle aspiration cytology (FNAC) are

widely used for preoperative lymph node evaluation. However, their high false-negative rates and the inconclusiveness of some samples limit their clinical efficacy [4–6].

Thyroglobulin (Tg), as a thyroid tissue-specific protein, is considered a promising marker for intraoperative evaluation of lymph node metastasis, as its presence in lymph node washout fluid suggests potential metastatic thyroid tissue [7,8]. Traditional frozen section analysis is a common method for intraoperative assessment of lymph node metastasis, but it is complex and time-consuming. While paraffin pathology remains the gold standard for diagnosing lymph node metastasis, it is limited to postoperative confirmation and cannot provide real-time information [9–12]. Therefore, there is an urgent need for a faster intraoperative auxiliary diagnostic method.

This study utilizes colloidal gold immunochromatographic assay (FNA-TG-GICA) to detect intraoperative Tg levels, comparing the results with postoperative paraffin pathology to evaluate its accuracy in determining lymph node metastasis in PTC patients. Through prospective analysis, we plotted ROC curves and determined the optimal cutoff value, aiming to provide rapid and reliable evidence for real-time intraoperative diagnosis and to support clinical decision-making.

## 1. Ethics

This study was approved by the Medical Ethics Committee of Xiangyang Central Hospital. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. The clinical trial procedures did not influence any final test results.

All individual participants included in this study provided written informed consent voluntarily.

## 2. Materials and methods

### 2.1. Study participants

The study enrolled 65 patients who underwent thyroid surgery for PTC at Xiangyang Central Hospital between November 2022 and May 2023. Inclusion criteria for this study were as follows:(1) No restrictions on participant age or gender; complete sample information (including patient medical record number/admission number/outpatient number, gender, age, sample type, and clinical diagnostic background information); (2) Patients diagnosed with PTC preoperatively. (3) Patients scheduled for prophylactic central lymph node dissection and/or therapeutic lateral cervical lymph node dissection; (4) All three criteria must be met, and tissue washout fluid samples and sample collection procedures must conform to predefined collection requirements. Exclusion criteria were as follows:(1) Samples exceeding the storage temperature or time requirements of the test reagents; (2) Patients who previously participated in this clinical trial (a patient may only be included in the study once); (3) Samples unsuitable for testing, such as those with evident microbial contamination; (4) Samples with incomplete patient information (including age, gender, sample collection time, clinical diagnosis, ward, or consulting department).

## 2.2. Experimental principle

The thyroglobulin (Tg) detection kit, independently developed in China, utilizes colloidal gold immunochromatographic assay (CGICA) technology for rapid intraoperative detection of Tg levels in human serum, plasma, whole blood, and tissue washout fluid. Gold-labeled mouse anti-human Tg monoclonal antibodies serve as the indicator markers. The detection zone (*T*) and control zone (*C*) on the nitrocellulose membrane are coated with paired mouse anti-human Tg monoclonal antibodies and sheep anti-mouse IgG polyclonal antibodies, respectively. During testing, the sample undergoes chromatographic migration through capillary action. Tg in the sample binds with the gold-labeled anti-Tg monoclonal antibody in the *T* zone to form a gold-labeled anti-Tg-Tg-anti-Tg complex, producing a wine-red band. The accompanying quantitative immunochromatographic reader measures the absorbance of the wine-red band in the *T* zone to determine the Tg concentration (ng/mL) in the sample. Based on pre-experimental results, the following thresholds were established: TG < 77 ng/mL: Indicates low risk of thyroid dysfunction and/or nodule metastasis.TG > 77 ng/mL: Indicates high risk of thyroid dysfunction and/or nodule metastasis. If both a strong wine-red reaction line appears at the detection line (*T*) and control line (*C*) and TG > 77 ng/mL, it suggests high risk of thyroid dysfunction and/or nodule metastasis. If a faint wine-red reaction line or no line appears at the detection line (*T*) and 0 ng/mL < TG < 77 ng/mL, it suggests low risk of thyroid dysfunction and/or nodule metastasis. If no wine-red reaction line appears at the control line (*C*), the test is invalid or the test strip has failed.

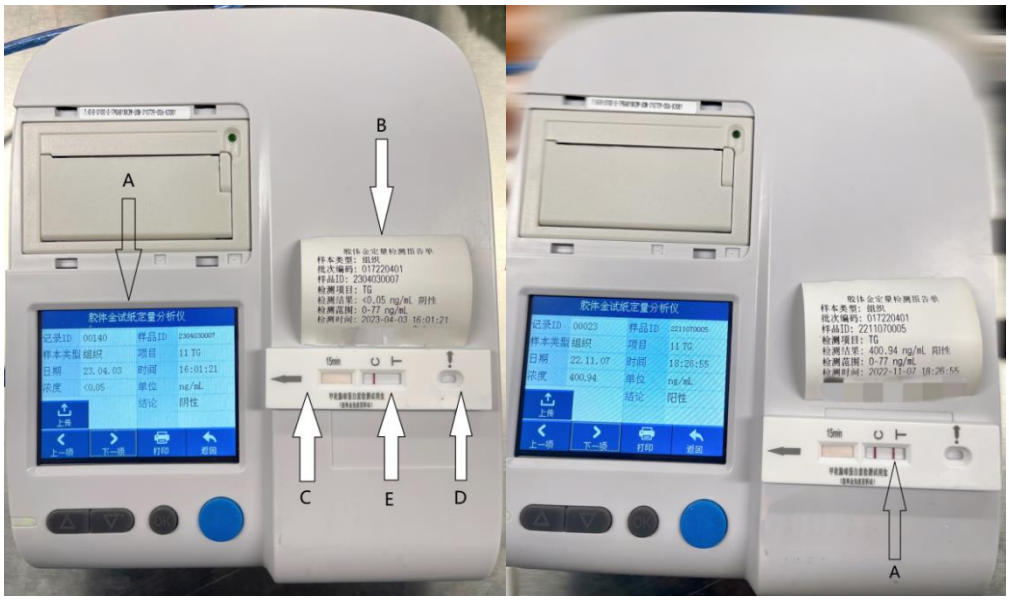
## 2.3. Experimental procedure

The surgeon identifies lymph nodes intraoperatively by visual inspection and palpation, targeting nodes that meet the following three criteria: long diameter > 2 mm, abnormal morphology, and firm texture. The identified lymph node is isolated and separated into segments. It is placed in one corner of a kidney dish, and surgical scissors are used to clean off any attached tissue while maintaining the integrity of the lymph node capsule. The isolated lymph nodes are sequentially placed in a 50 mL centrifuge tube containing 75% ethanol solution and washed for 10 s. They are then gently removed using surgical forceps and placed in another 50 mL centrifuge tube containing 0.9% saline solution for a further 10-s wash. After washing, the lymph node is carefully removed and placed on a 100-mesh cell sieve. Using surgical forceps, the lymph node is fixed in place while a 22G, 7 cm-long fine-needle aspiration needle is inserted into the lymph node capsule (ensuring the needle does not puncture through the lymph node). The needle core is removed, and the needle is gently moved back and forth in different directions within the capsule 10 times before withdrawal. A 5 mL syringe filled with 1 mL of 0.9% saline is used to inject saline into the centrifuge tube. The syringe is then used to repeatedly aspirate and flush the needle wall with saline three times, ensuring that the tissue fluid is fully collected into a 2 mL centrifuge tube. This completes the preparation of the tissue washout fluid.

The lymph node specimen and the tissue washout fluid are sent for pathological examination and analysis. The lymph node is carefully removed using surgical forceps, placed in individual specimen bags, and the corresponding sample information is

completed on the specimen bag labels. A complete pathology request form is also filled out, and both the sample and form are immediately sent to the pathology department.

Simultaneously, 80 μL of the prepared tissue washout fluid is pipetted into the sample inlet of a pre-labeled thyroglobulin test kit. The kit is incubated undisturbed for 15 min. After incubation, following the requirements of the test manual, the kit is inserted into the test strip slot of the colloidal gold quantitative analyzer in the direction of the arrow marks. The "Rapid Test" option is selected (ensuring the analyzer is pre-set for thyroglobulin detection). Once the reading is completed, the analyzer prints the test report, and the process is documented with photographs and relevant records (see **Figure 1a,b**).




**(a)** **(b)**

**Figure 1.** Tg Detection Equipment and Test Results. **(a)** This device is the Tg detection equipment. A displays the patient ID, test time, Tg concentration in the tissue washout fluid, and the test result for the current detection. B shows the printed output of A. C represents the Tg test strip. D is the sample inlet for tissue washout fluid. E indicates a negative result (only the C zone on the test strip shows a band); **(b)** another Tg detection result for lymph node tissue washout fluid from a different patient, with a distinct patient ID, test time, Tg concentration in the tissue washout fluid, and test result. A indicates a positive result for this test (both the C zone and T zone on the test strip show visible bands).

### 2.4. Observational indicators

The observational indicators in this study include patient age, gender, Tg, TgAb, ultrasound report, FNAC, FNA-Tg, lymph node diameter, and pathological results.

## 3. Statistical methods

Data were analyzed using SPSS 28.0 statistical software. Quantitative data were tested for normality and, if normally distributed, expressed as mean ± standard deviation ($x^{-}\pm s$\bar{x} \pm $sx^{-}\pm s$). Categorical data were expressed as frequency (rate), and comparisons between groups were conducted using the chi-square test.

The receiver operating characteristic (ROC) curve for FNA-Tg detection was plotted, and the area under the curve (AUC) was evaluated using the *Z*-test. The optimal cutoff value for determining lymph node metastasis via FNA-Tg was determined by calculating the Youden index.

The consistency between FNA-Tg detection results and paraffin pathology results was evaluated using Kappa consistency testing. A significance level of $\alpha = 0.05$\alpha = 0.05, $\alpha = 0.05$ was set for all statistical tests.

## 4. Results

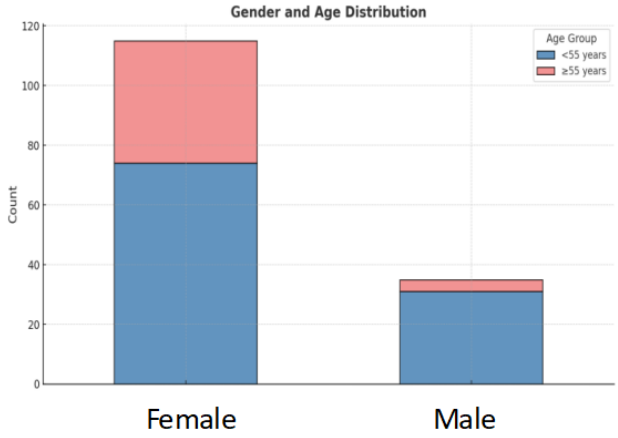



**Figure 2.** Distribution of patient gender and age characteristics.

**Figure 2** illustrates the distribution of gender and age among the study participants. According to the figure, the proportion of female patients in the total sample is significantly higher than that of male patients. Among the female group, a larger proportion of patients are under 55 years old. Additionally, although the total number of male patients is lower, the proportion of those under 55 years old is also relatively high.

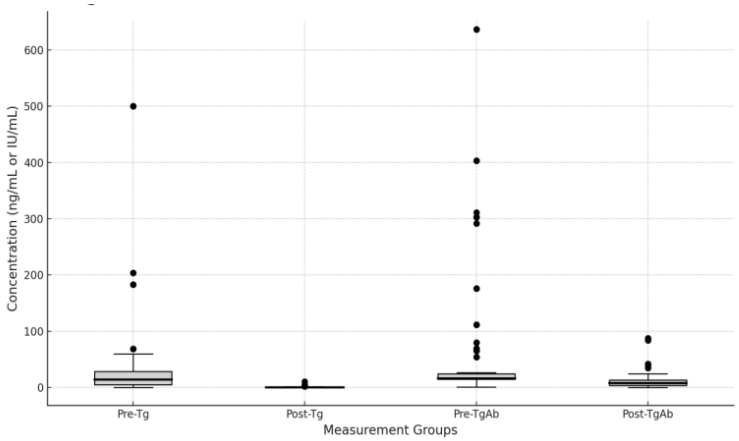



**Figure 3.** Changes in serum Tg and TgAb levels preoperatively and one month postoperatively.

**Figure 3** presents the statistical results of serum Tg and TgAb levels before and after surgery. Serum Tg levels: The preoperative mean value was 34.96 ng/mL, with a

median of 13.80 ng/mL, a minimum value of 0.04 ng/mL, and a maximum value of 500.00 ng/mL, showing a wide range of fluctuation. Postoperatively, the mean serum Tg level decreased to 0.74 ng/mL, with a median of 0.47 ng/mL, and the maximum value dropped to 10.60 ng/mL, indicating a significantly narrower range of fluctuation. Serum TgAb levels: The preoperative mean value was 60.32 IU/mL, with a median of 16.40 IU/mL and a maximum value of 637.00 IU/mL, displaying a broad range of variation. Postoperatively, the mean TgAb level decreased to 12.08 IU/mL, with a median of 7.92 IU/mL, and the maximum value reduced to 87.69 IU/mL. Although the range of fluctuation was reduced compared to preoperative levels, considerable individual variation persisted.

**Table 1.** Pathological results of lymph node metastasis via paraffin pathology.

| Tg value > 77 ng/mL | Paraffin Pathology Results | | Total |
|---|---|---|---|
| | G+ | G− | |
| Positive | 47 | 4 | 51 |
| Negative | 3 | 96 | 99 |
| Total | 50 | 100 | 150 |

G+ indicates lymph node metastasis confirmed by paraffin pathology. G− indicates no lymph node metastasis confirmed by paraffin pathology. $T > 77$ ng/mL indicates a positive result from the Tg test strip, while $T \leq 77$ ng/mL indicates a negative result (the cutoff value of 77 ng/mL was selected based on its diagnostic performance, aligning with the experimental cutoff value of 59.65 ng/mL and clinical practice).

After applying the inclusion and exclusion criteria, 150 lymph node samples were analyzed, among which 50 were confirmed as metastatic lymph nodes (G+), and 100 were non-metastatic lymph nodes (G−) (see **Table 1**). To evaluate the consistency between intraoperative rapid detection of lymph node thyroglobulin (Tg) concentration and pathological results in determining lymph node metastasis, a cutoff value of 77 ng/mL was used for Tg detection.

Results showed that among the 51 samples with Tg detection values > 77 ng/mL, 47 were confirmed as metastatic lymph nodes (G+), and 4 were non-metastatic lymph nodes (G−), indicating successful identification of most metastatic lymph nodes (see **Table 1**). Among the 99 samples with Tg detection values ≤ 77 ng/mL, 3 were metastatic lymph nodes (G+), and 96 were non-metastatic lymph nodes (G−), with the majority correctly identified as non-metastatic.

**Table 2.** Comparison of sensitivity, specificity, and other performance indicators across four detection methods.

| Methods | Sensitivity | Specificity | Accuracy | Positive Predictive Value | Negative Predictive Value |
|---|---|---|---|---|---|
| Preoperative Ultrasound | 0.84 | 0.92 | 0.89 | 0.84 | 0.92 |
| Preoperative FNAC | 0.9 | 0.95 | 0.93 | 0.9 | 0.95 |
| Intraoperative Frozen Section Analysis | 0.93 | 0.92 | 0.92 | 0.91 | 0.93 |
| Intraoperative FNA-Tg | 0.94 | 0.96 | 0.95 | 0.92 | 0.96 |

As this study did not collect results from intraoperative frozen section (IFS)

examinations, a direct comparison between IFS and the other detection methods used in this study was not possible. Therefore, IFS data from previous studies were referenced and compared with the results of preoperative ultrasound (US), fine-needle aspiration cytology (FNAC), and intraoperative FNA-Tg, with paraffin pathology serving as the diagnostic gold standard (see **Table 2**). According to the literature, the sensitivity of IFS is approximately 93% (95% CI: 0.85–0.98), specificity is about 92% (95% CI: 0.84–0.97), and accuracy is 92% (95% CI: 0.87–0.96) [9,13–15].

In the diagnostic performance analysis, FNA-Tg demonstrated the best sensitivity, specificity, and accuracy, outperforming IFS, FNAC, and US. Specifically, FNA-Tg showed the strongest ability to detect positive cases, while US exhibited relatively low sensitivity, making it more suitable for auxiliary screening. Both FNA-Tg and FNAC performed well in excluding negative cases, particularly in terms of specificity and negative predictive value. Overall, FNA-Tg outperformed other methods across multiple metrics, highlighting its high accuracy and reliability for intraoperative rapid diagnosis.

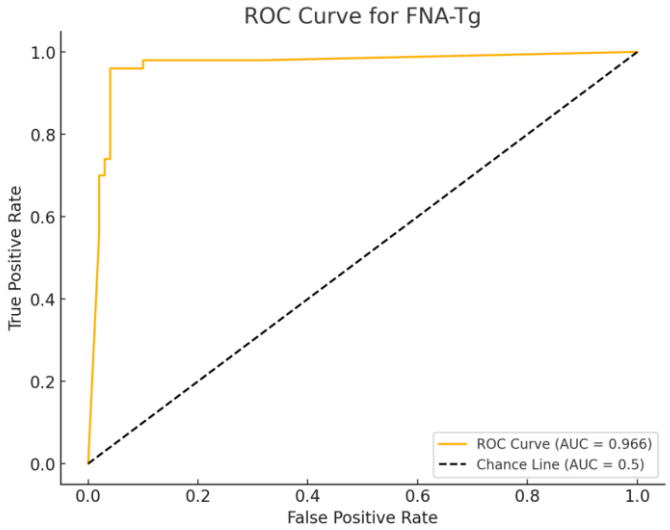



**Figure 4.** ROC Curve for FNA-Tg.

According to quantitative ROC analysis, FNA-Tg showed excellent performance in predicting lymph node metastasis in papillary thyroid carcinoma. The area under the ROC curve (AUC) was 0.966, demonstrating the high diagnostic efficiency of FNA-Tg in clinical practice. This result was obtained by calculating the sensitivity and specificity corresponding to different FNA-Tg cutoff values (see **Figure 4**). The standard error of the AUC was 0.087, with a 95% confidence interval ranging from 0.796 to 1.137, indicating strong statistical reliability. Further analysis revealed a Z statistic of 5.357 and a PPP-value of less than 0.001, significantly higher than 0.5, further confirming the diagnostic efficacy of FNA-Tg.

Quantitative analysis also revealed a Youden index of 0.92, with sensitivity and specificity both reaching 96%. Numerical calculations of the diagnostic performance at various FNA-Tg cutoff values identified 59.65 ng/mL as the optimal diagnostic threshold. At this cutoff value, FNA-Tg achieved the best balance in diagnosing lymph node metastasis, effectively identifying positive cases while accurately excluding negative ones. This result was derived by evaluating the sensitivity and specificity

across different cutoff values.

Despite the ROC curve analysis identifying 59.65 ng/mL as the optimal diagnostic cutoff, this study decided to retain 77 ng/mL as the cutoff for FNA-Tg. The 77 ng/mL threshold has been validated as an effective clinical standard in multiple studies [9], and in this study, FNA-Tg achieved a sensitivity of 94% and specificity of 96% at this cutoff. Although the sensitivity at 77 ng/mL is slightly lower than the 96% achieved at 59.65 ng/mL, the sensitivity and specificity at 77 ng/mL remain excellent. Furthermore, this value aligns with findings from previous studies, ensuring high diagnostic accuracy.

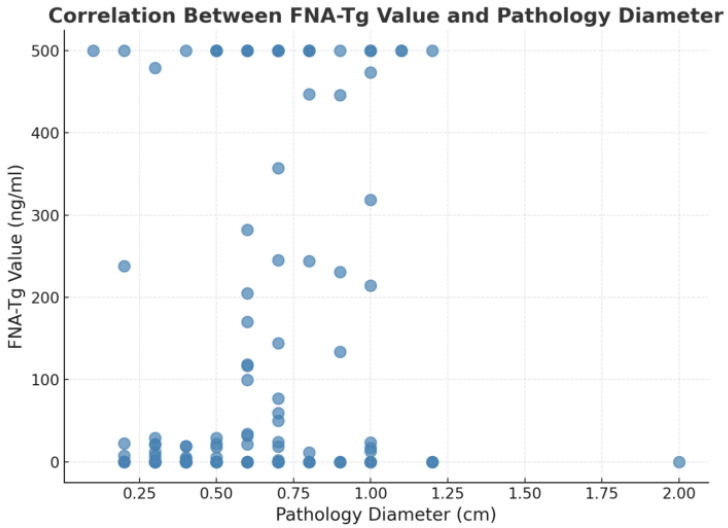



**Figure 5.** Correlation between lymph node diameter and FNA-Tg values.

The scatter plot reveals a distinct pattern in the relationship between intraoperative FNA-Tg values and lymph node pathological diameter (see **Figure 5**). For lymph nodes with smaller diameters (< 1.0 cm), FNA-Tg values vary widely, with some samples reaching close to 500 ng/mL. As the pathological diameter increases, particularly for lymph nodes > 1.0 cm, FNA-Tg values do not show a clear upward trend and remain relatively stable.

This finding suggests that FNA-Tg values are more closely associated with the metastatic nature of the lymph nodes rather than their pathological diameter.

## 5. Discussion

This study evaluated the diagnostic value of the colloidal gold immunochromatographic assay (FNA-TG-GICA) for rapid intraoperative detection of Tg levels to assess lymph node metastasis status in PTC patients. Results demonstrated that at an optimal cutoff value of 77 ng/mL, the sensitivity and specificity of Tg detection were 94% and 96%, respectively, with an AUC of 0.97 on the ROC curve, indicating extremely high diagnostic accuracy.

These findings highlight the significant clinical application potential of the FNA-Tg GICA method as a rapid intraoperative auxiliary tool. It can provide immediate support for surgical decision-making, helping to optimize the extent of surgery and improve patient outcomes.

Fine-needle aspiration cytology (FNAC) is one of the standard methods for evaluating suspicious lymph node enlargement. It is widely used due to its minimal invasiveness, simplicity, and relatively high accuracy. However, FNAC has a high false-negative rate of approximately 8%, and its diagnostic outcome is closely tied to the operator's expertise. It is also easily affected by smear quality, and contamination with blood or colloid [5,6]. In contrast, fine-needle aspiration washout fluid thyroglobulin (FNA-Tg) directly measures Tg concentration in washout fluid, avoiding interference from cellular morphology. Numerous studies have confirmed its high sensitivity in diagnosing cervical lymph node metastases associated with PTC [16–18]. In this study, the FNA-Tg GICA method demonstrated diagnostic performance similar to that of frozen section analysis, providing a rapid and reliable basis for intraoperative assessment of lymph node metastasis.

This study also specifically addressed the potential interference of serum Tg (sTg) with FNA-Tg detection. Previous research has suggested that tissue compression or blood contamination during the lymph node aspiration process may cause sTg "leakage," thereby affecting FNA-Tg accuracy [19,20]. Therefore, strict standardized operating procedures were implemented in this study to minimize the impact of sTg and ensure the reliability of the test results. Although some studies have suggested that sTg might lead to false-positive FNA-Tg results [21–23], research by Sun et al. [24] found no significant correlation between sTg and FNA-Tg levels [18], supporting the reliability of FNA-Tg detection.

Compared to traditional frozen section analysis, FNA-Tg GICA detection is faster and more convenient, providing immediate information on metastasis during surgery. For low-risk patients, FNA-Tg can help surgeons reduce unnecessary dissection, thereby lowering the risk of complications. For high-risk patients, it enables more extensive dissection to ensure the removal of potential metastatic areas, allowing some patients to undergo postoperative I131 therapy [9,10]. In primary hospitals where frozen biopsy is unavailable, FNA-Tg GICA detection is simple to operate and easy to implement. It effectively reduces the risk of misjudging metastasis intraoperatively and decreases the likelihood of requiring a second surgery [9].

This study has achieved certain results but still has some limitations. Firstly, the sample size was limited and obtained from a single institution, which may affect the generalizability of the findings. Future studies should collaborate with multiple medical institutions to expand the sample size and conduct multicenter research. Additionally, the scope of the study should be extended from the central lymph nodes to lateral cervical lymph nodes and other cervical or even distant metastatic lymph nodes to more comprehensively evaluate the clinical value of FNA-Tg testing. Furthermore, to improve the reliability and stability of the testing methods, reproducibility and stability experiments are recommended to determine appropriate storage and usage conditions for reagents. It is also necessary to investigate the impact of common interfering substances on test results and enhance anti-interference capability through process optimization or correction methods. Future studies could also delve deeper into the mechanisms of Tg in PTC lymph node metastasis, analyzing its regulatory expression and its relationship with relevant signaling pathways, while exploring whether the combined detection of Tg with other molecular markers could enhance diagnostic accuracy. By refining study designs, optimizing technical

approaches, and setting clear timelines, future research is expected to further improve the clinical applicability and scalability of the testing methods.

In conclusion, this study confirmed the diagnostic value of the FNA-Tg GICA method in assessing lymph node metastasis intraoperatively in PTC patients. With 77 ng/mL as the optimal cutoff value, this detection method demonstrated high sensitivity and specificity, indicating that it can serve as a rapid and effective auxiliary diagnostic tool, providing reliable support for clinical decision-making. Future multicenter studies will further validate its applicability and explore its potential use in different populations.

**Author contributions:** Conceptualization, SZ and YX; methodology, SZ and WY; software, SZ; validation, SZ, YX and WY; formal analysis, YX; investigation, SZ; resources, WY; data curation, WY; writing—original draft preparation, SZ; writing—review and editing, SZ; visualization, YX; supervision, DC; project administration, DC; funding acquisition, DC. All authors have read and agreed to the published version of the manuscript.

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**Ethical approval:** This study followed the Declaration of Helsinki and was approved by the Ethics Committee of Xiangyang Central Hospital (Approval No. 2022-031). All participants were informed of the study's purpose, procedures, and potential risks before voluntarily signing the informed consent. Participants' privacy and data protection were strictly adhered to, ensuring confidentiality. All procedures complied with relevant ethical standards to ensure participants' rights and safety.

**Conflict of interest:** The authors declare no conflict of interest.

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