Original Article

Measurement of thyroglobulin level in lateral neck lymph node fine needle aspiration washout fluid in papillary thyroid cancer

Kwangsoon Kim^, Ja Seong Bae^, Jeong Soo Kim^

Department of Surgery, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea

Contributions: (I) Conception and design: K Kim, JS Kim; (II) Administrative support: JS Bae; (III) Provision of study materials or patients: K Kim, JS Kim; (IV) Collection and assembly of data: K Kim, JS Kim; (V) Data analysis and interpretation: K Kim, JS Bae; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Professor Jeong Soo Kim, MD, PhD. Department of Surgery, College of Medicine, Catholic University of Korea, 06591 Seoul, Republic of Korea. Email: btskim@catholic.ac.kr; Kwangsoon Kim, MD. Assistant professor, Department of Surgery, College of Medicine, Catholic University of Korea, 06591 Seoul, Republic of Korea. Email: noar99@naver.com.

Background: Thyroglobulin (Tg) level of fine needle aspiration (FNA) washout fluid (FNA-Tg) is useful to detect cervical lymph node (LN) metastasis in patients with papillary thyroid cancer (PTC). The objective of this study was to determine appropriate cutoff values of serum Tg (S-Tg) and FNA-Tg levels for diagnosis of lateral neck LN metastasis and investigate their diagnostic performance.

Methods: A total of 169 patients with PTC who underwent modified radical neck dissection (mRND) were retrospectively reviewed at Seoul St. Mary's Hospital (Seoul, Korea) from December 2011 to September 2019. Diagnostic performance of FNA-Tg, Tg ratio (FNA-Tg level/S-Tg level), and FNA-Tg combined with Tg ratio was evaluated by correlation with FNA cytology results.

Results: FNA-Tg level ≥20 ng/mL exhibited 86.6% sensitivity, 66.7% specificity, and 81.7% accuracy. Tg ratio ≥3 exhibited lower sensitivity but higher specificity (82.7% and 73.8%, respectively) than FNA-Tg level ≥20 ng/mL. FNA-Tg level ≥20 ng/mL combined with Tg ratio ≥3 had 81.9% sensitivity, 80.5% accuracy, and an integrated area under the curve (iAUC) of 0.790.

Conclusions: Measurement of FNA-Tg level increases preoperative diagnostic accuracy for the detection of metastatic LNs in patients with PTC. Diagnostic accuracy is higher using a 20 ng/mL FNA-Tg cutoff level. Tg ratio is also valuable and FNA-Tg combined with Tg ratio shows promise.

Keywords: Thyroglobulin washout; fine needle aspiration (FNA); lymph node metastasis; papillary thyroid cancer (PTC); modified radical neck dissection (mRND)

Submitted Jun 02, 2021. Accepted for publication Jul 30, 2021.
doi: 10.21037/gs-21-366
View this article at: https://dx.doi.org/10.21037/gs-21-366

Introduction

Papillary thyroid cancer (PTC) is the most common thyroid malignancy, accounting for 75–85% of all thyroid cancers. Its incidence has been significantly increasing worldwide over the last several decades (1-3). Although PTC has an excellent long-term prognosis due to its indolent features, up to 65% metastasize to the central compartment lymph nodes (LNs) (4-6), and metastases to the lateral neck LNs are observed in approximately 15% of patients at presentation and throughout long-term follow-up (7). Accurate diagnosis of LN metastasis, particularly those located in the lateral neck, is important to avoid unnecessary cervical neck dissection

^ ORCID: Kwangsoon Kim, 0000-0001-6403-6035; Ja Seong Bae, 0000-0002-6271-2105; Jeong Soo Kim, 0000-0002-9982-7838.

when managing PTC patients. Neck ultrasonography (US) and US-guided fine needle aspiration (FNA) cytology are the standard diagnostic modalities used (8-10); however, US-guided FNA cytology has variable sensitivity and specificity, depending on operator skill (11-13). In addition, adequate specimen acquisition is difficult in cases of highly vascular or cystic LN metastasis.

Recent studies have demonstrated that thyroglobulin (Tg) measurement from FNA washout fluid (FNA-Tg) is useful to detect cervical LN metastasis and has excellent diagnostic performance (14,15). According to the American Thyroid Association (ATA) management guidelines, FNA cytology and FNA-Tg measurement should be performed for suspicious LNs found on US (8). However, controversy regarding the optimal FNA-Tg cutoff value remains due to many factors, including the wide range of FNA-Tg levels, presence of serum Tg antibodies (TgAb), different FNA techniques, and variation between the different Tg measurement assay kits available (15,16). Grani *et al.* reported a 1.0 ng/mL FNA-Tg cutoff value but pointed out that better standardization of criteria for patient selection, Tg measurement methods, and cutoff values are needed (15).

Therefore, we aimed to determine appropriate cutoff values for serum Tg (S-Tg) and FNA-Tg to diagnose PTC lateral neck LN metastasis and investigate their diagnostic performance.

We present the following article in accordance with STROBE reporting checklist (available at https://dx.doi.org/10.21037/gs-21-366).

Methods

Patients

We retrospectively reviewed the medical records of 185 PTC patients who underwent modified radical neck dissection (mRND) at Seoul St. Mary's Hospital (Seoul, Korea) from December 2011 to September 2019. Five patients were excluded due to inadequate data and 11 due to loss of follow-up. Finally, 169 patients were included for analysis. Patients with LNs suspicious for malignancy on US but negative FNA cytology underwent LN biopsy for intraoperative frozen section examination; mRND was performed if the suspicious LNs contained malignancy. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of Seoul St. Mary's Hospital and the Catholic University of Korea (IRB No: KC20RISI0043), and the need for informed consent was waived due to the retrospective nature of this study.

US and FNA cytology

All patients underwent high-resolution neck US using 7–13 MHz high-frequency linear array transducers. Experienced radiologists evaluated all neck levels (I–VI) bilaterally and performed US-guided FNA on LNs suspicious or indeterminate for metastasis, which were characterized by round shape, loss of fatty hilum, microcalcifications, cystic changes, hyperechogenicity, and peripheral vascular flow on color Doppler images (17).

US-guided FNA was performed with the needle oriented either parallel or perpendicular to the US probe using a 23-gauge needle connected to a 2–10 mL pistol-grip syringe. Tissue samples were collected with 6 or 7 "to-and-fro" needle movements over 5–10 seconds and fixed in 95% ethanol for Papanicolaou staining and cytologic examination. The slides were examined by experienced cytopathologists and reported as either nondiagnostic, benign, suspicious for malignancy, or malignancy. Nondiagnostic and benign results were considered negative; suspicious for malignancy and malignancy results were considered positive.

Serum-Tg (S-Tg), TgAb and FNA-Tg analysis

After FNA, the needle and syringe were washed with 1 mL of normal saline; the washout solution was collected and submitted to the laboratory for measurement of FNA-Tg. Patients also underwent venipuncture to collect a blood sample for measurement of S-Tg and TgAb. Both S-Tg and FNA-Tg were measured using an immunoradiometric Tg assay (CIS Bio International, Saclay, France) with a functional sensitivity of 0.2 ng/mL. Serum TgAb concentration was measured using a radioimmunoassay (DIAsource, Rue du Bosquet, Belgium); serum TgAb level <60 IU/mL was considered negative (16). The Tg ratio was defined as FNA-Tg level/S-Tg level (18).

Preoperative US-guided needle localization

On the morning of surgery, neck US was performed for all patients undergoing surgery to evaluate the neck LN status and to search for the target LNs. Experienced radiologists performed the procedures. The radiologist marked the location of the target LNs on the skin with an oil-based pen to facilitate US-guided needle localization with 21-gauge

Table 1 Clinical characteristics of study patients

Characteristics	Value
Total patient number	169
Age (years)	42.9±13.6 (12–79)
≥45	70 (41.4)
<45	99 (58.6)
Male:female	1:2.3
Male	51 (30.2)
Female	118 (69.8)
Extent of operation	
TT with mRND	149 (88.2)
Only mRND	20 (11.8)
Tumor size (cm)	1.5±0.9 (0.3–5.0)
Serum Tg (ng/mL)	32.9±58.6 (0.02–357.7)
Serum TgAb (IU/mL)	137.2±560.2 (1.55–5,639.2)
Negative	132 (78.1)
Positive	37 (21.9)
FNA-Tg (ng/mL)	573.9±527.4 (0.00–2,853.8)
FNA result	
Negative for malignancy	42 (24.9)
Positive for malignancy	127 (75.1)

Data are expressed as patient's number (%), or mean ± SD (range). Negative TgAb: TgAb <60 IU/mL; positive TgAb: TgAb ≥60 IU/mL. Tumor size means the size of primary thyroid cancer. TT, total thyroidectomy; mRND, modified radical neck dissection; Tg, thyroglobulin; TgAb, thyroglobulin antibody; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; SD, standard deviation.

hookwire. The tip of the needle was targeted to pass through the center of the LNs in real time.

Postoperative management and follow-up

Patients were managed after surgery according to the ATA management guidelines (8). All patients were administered suppressive doses of L-thyroxine and received regular follow-up with physical examination, thyroid function testing, measurement of serum TgAb level, and US of the neck every 3–6 months and annually thereafter. Postoperative radioactive iodine (RAI) ablation (100–150 mCi) was performed 8–12 weeks after surgery; a diagnostic total body scan was performed 5–7 days after RAI ablation. If necessary, additional diagnostic imaging with computed tomography and/or positron emission tomography/computed tomography were performed.

Statistical analysis

Statistical analyses were performed using SPSS software version 24.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables are presented as means with standard deviation; categorical variables are reported as numbers with percentages. Groups were compared using the Student's *t*-test, chi-square test, or Wilcoxon rank sum test. Receiver operating characteristics (ROC) curve analysis was performed to determine the optimal cutoff value for S-Tg, FNA-Tg, and Tg ratio by calculating the integrated area under the curve (iAUC). Patients were stratified into two groups according to the optimal cutoff value (low or high) for each measured or calculated variable. Diagnostic performance of FNA-Tg, Tg ratio, and combined FNA-Tg and Tg ratio was assessed by calculating sensitivity, specificity, negative predictive value, positive predictive value, and accuracy. All tests were two-sided. $P<0.05$ was considered significant.

Results

Patient characteristics

Table 1 presents the clinical characteristics of the 169 study patients with PTC who underwent mRND. Mean age was 42.9±13.6 years (range, 12–79 years). Seventy patients (41.4%) were ≥45 years of age and 99 (58.6%) were <45 years of age. Fifty patients (30.2%) were male. A total of 149 (88.2%) were newly diagnosed with PTC and underwent total thyroidectomy (TT) with mRND for lateral neck LN metastases; 20 (11.8%) were patients with recurrent LN metastases diagnosed during follow-up after TT and underwent only mRND. Mean tumor size was 1.5±0.9 cm (range, 0.3–5.0 cm). Mean S-Tg and FNA-Tg levels were 32.9±58.6 and 573.9±527.4 ng/mL, respectively. Serum TgAb was positive (≥60 IU/mL) in 37 patients (21.9%). A total of 127 (75.1%) were positive for malignancy and 42 (24.9%) were negative for LN malignancy based on FNA cytology.

Comparison of clinical characteristics according to FNA cytology result and TgAb status

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Table 2 Comparison of clinical characteristics according to FNA cytology result

Characteristics	Negative (n=42)	Positive (n=127)	P value
Age (years)	43.1±15.1 (12–79)	42.9±13.2 (15–73)	0.946
Female	32 (76.2)	86 (67.7)	0.338
Tumor size (cm)	1.4±0.8 (0.3–3.7)	1.6±0.9 (0.4–5.0)	0.165
Serum Tg (ng/mL)	34.3±67.5 (0.32–357.7)	32.5±55.6 (0.02–283.1)	0.866
FNA-Tg (ng/mL)	214.9±399.5 (0.08–1,269.7)	692.6±511.6 (0.00–2,853.8)	<0.001
Serum TgAb			0.396
Negative	35 (83.3)	97 (76.4)	
Positive	7 (16.7)	30 (23.6)	

Data are expressed as patient's number (%), or mean ± SD (range). A statistically significant difference was defined as P<0.05. Negative TgAb: TgAb <60 IU/mL; positive TgAb: TgAb ≥60 IU/mL. Tumor size means the size of primary thyroid cancer. Tg, thyroglobulin; TgAb, thyroglobulin antibody; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; SD, standard deviation.

Table 3 Comparison of clinical characteristics according to serum TgAb status

Characteristics	Negative (n=132)	Positive (n=37)	P value
Age (years)	43.4±13.9 (12–79)	41.6±12.5 (15–73)	0.480
Female	86 (65.2)	32 (86.5)	0.014
Tumor size (cm)	1.5±0.9 (0.3–5.0)	1.6±0.8 (0.7–3.9)	0.535
Serum Tg (ng/mL)	39.3±64.4 (0.02–357.7)	10.4±15.7 (0.08–72.7)	0.008
FNA-Tg (ng/mL)	592.6±539.6 (0.00–2,853.8)	507.4±482.6 (0.00–1,592.8)	1.000
FNA cytology result			0.396
Negative for malignancy	35 (26.5)	7 (18.9)	
Positive for malignancy	97 (73.5)	30 (81.1)	

Data are expressed as patient's number (%), or mean ± SD (range). A statistically significant difference was defined as P<0.05. Negative TgAb: TgAb <60 IU/mL; positive TgAb: TgAb ≥60 IU/mL. Tumor size means the size of primary thyroid cancer. Tg, thyroglobulin; TgAb, thyroglobulin antibody; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; SD, standard deviation.

FNA cytology results are shown in *Table 2*. Mean age, gender, tumor size, S-Tg level, and serum TgAb status did not significantly differ between the negative and positive FNA cytology groups. However, mean FNA-Tg level was significantly higher in the positive group than the negative group (692.6±511.6 *vs.* 214.9±399.5 ng/mL, P<0.001).

Table 3 presents the comparison of clinical characteristics according to serum TgAb status. The proportion of female patients was significantly higher in the positive serum TgAb group than the negative group (86.5% *vs.* 65.2%, P=0.014). S-Tg level was significantly higher in the negative serum TgAb group (39.3±64.4 *vs.* 10.4±15.7 ng/mL, P=0.008). There were no significant differences between the groups in mean age, tumor size, FNA-Tg level, or FNA cytology results.

Comparison of clinical characteristics according to S-Tg and FNA-Tg levels

We evaluate the optimal cutoff value using the S-Tg and FNA-Tg levels from the ROC curve analysis. The patients were stratified into two groups according to S-Tg level: low S-Tg (<1 ng/mL, n=31, 18.3%) and high S-Tg (≥1 ng/mL, n=138, 81.7%). There were no significant differences between the groups except for serum TgAb status and FNA cytology results. The proportion of patients with positive FNA cytology results was significantly higher in the low S-Tg group (93.5% *vs.* 71.0%, P=0.010) (*Table 4*).

Table 5 shows the comparison of clinical characteristics according to FNA-Tg level with the patients stratified into

Table 4 Comparison of clinical characteristics in study patients stratified by serum Tg cutoff level of 1 ng/mL

Characteristics	Serum Tg <1 ng/mL (n=31)	Serum Tg ≥1 ng/mL (n=138)	P value
Age (years)	45.6±11.5 (27–73)	42.4±14.0 (12–79)	0.233
Female	22 (70.1)	96 (69.6)	0.878
Tumor size (cm)	1.5±0.6 (0.6–3.2)	1.5±0.9 (0.3–5.0)	0.714
FNA-Tg (ng/mL)	630.5±480.5 (0.15–1,708.2)	547.7±535.5 (0.00–2,853.8)	0.174
Serum TgAb			0.017
Negative	19 (61.3)	113 (81.9)	
Positive	12 (38.7)	25 (18.1)	
FNA cytology result			0.010
Negative for malignancy	2 (6.5)	40 (29.0)	
Positive for malignancy	29 (93.5)	98 (71.0)	

Data are expressed as patient's number (%), or mean ± SD (range). A statistically significant difference was defined as P<0.05. Negative TgAb: TgAb <60 IU/mL; positive TgAb: TgAb ≥60 IU/mL. Tumor size means the size of primary thyroid cancer. Tg, thyroglobulin; TgAb, thyroglobulin antibody; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; SD, standard deviation.

Table 5 Comparison of clinical characteristics in study patients stratified by FNA-Tg cutoff level of 20 ng/mL

Characteristics	FNA-Tg <20 ng/mL (n=45)	FNA-Tg ≥20 ng/mL (n=124)	P value
Age (years)	41.3±15.2 (12–79)	43.6±13.0 (15–73)	0.348
Female	35 (77.8)	83 (66.9)	0.191
Tumor size (cm)	1.4±0.8 (0.3–3.7)	1.6±0.9 (0.4–5.0)	0.349
Serum Tg (ng/mL)	29.7±62.3 (0.08–357.7)	34.2±57.4 (0.02–283.1)	0.658
Serum TgAb			0.675
Negative	34 (75.6)	98 (79.0)	
Positive	11 (24.4)	26 (21.0)	
FNA cytology result			<0.001
Negative for malignancy	28 (62.2)	14 (11.3)	
Positive for malignancy	17 (37.8)	110 (88.7)	

Data are expressed as patient's number (%), or mean ± SD (range). A statistically significant difference was defined as P<0.05. Negative TgAb: TgAb <60 IU/mL; positive TgAb: TgAb ≥60 IU/mL. Tumor size means the size of primary thyroid cancer. Tg, thyroglobulin; TgAb, thyroglobulin antibody; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; SD, standard deviation.

two groups: low FNA-Tg (<20 ng/mL, n=45, 26.6%) and high FNA-Tg (≥20 ng/mL, n=124, 73.4%). In contrast to the S-Tg analysis, the proportion of patients with positive FNA cytology results was significantly higher in the high FNA-Tg group (88.7% *vs.* 37.8%, P<0.001).

Comparison of clinical characteristics according to Tg ratio

The comparison of clinical characteristics according to Tg ratio is summarized in *Table 6*. We evaluate the optimal cutoff value using the Tg ratio from the ROC curve analysis. Patients were stratified into two groups: low Tg ratio (<3, n=53, 31.4%) and high Tg ratio (≥3, n=116, 68.6%). There were no significant differences in mean age, gender, tumor size, or serum TgAb status between the groups. The proportion of patients with positive FNA cytology results was significantly higher in the high Tg ratio group (90.5% *vs.* 41.5%, P<0.001).

Table 6 Comparison of clinical characteristics according to Tg ratio

Characteristics	Tg ratio <3 (n=53)	Tg ratio ≥3 (n=116)	P value
Age (years)	41.6±15.8 (12–79)	43.6±12.5 (15–73)	0.393
Female	41 (77.4)	77 (66.4)	0.206
Tumor size (cm)	1.6±1.0 (0.3–5.0)	1.5±0.9 (0.4–5.0)	0.868
Serum TgAb			0.874
Negative	41 (77.4)	91 (78.4)	
Positive	12 (22.6)	25 (21.6)	
FNA cytologic result			<0.001
Negative for malignancy	31 (58.5)	11 (9.5)	
Positive for malignancy	22 (41.5)	105 (90.5)	

Data are expressed as patient's number (%), or mean ± SD (range). A statistically significant difference was defined as P<0.05. Negative TgAb: TgAb <60 IU/mL; positive TgAb: TgAb ≥60 IU/mL. Tumor size means the size of primary thyroid cancer. Tg ratio, FNA washout Tg level/serum Tg level; Tg, thyroglobulin; TgAb, thyroglobulin antibody; FNA, fine needle aspiration; SD, standard deviation.

Table 7 Diagnostic performance of different modalities used in the correlation with FNA cytology results

Test	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	iAUC
FNA-Tg ≥20 ng/mL	86.6	66.7	62.2	88.7	81.7	0.766
Tg ratio ≥3	82.7	73.8	58.5	90.5	80.5	0.782
S-Tg <1 ng/mL and FNA-Tg ≥20 ng/mL	21.3	97.6	29.1	96.4	40.2	0.594
S-Tg <1 ng/mL and Tg ratio ≥3	22.0	97.6	29.3	96.6	40.8	0.598
FNA-Tg ≥20 g/mL and Tg ratio ≥3	81.9	76.2	58.2	91.2	80.5	0.790

Tg, thyroglobulin; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; NPV, negative predictive value; PPV, positive predictive value; iAUC, integrated area under the curve.

Diagnostic performance of FNA-Tg, Tg ratio, and FNA-Tg combined with Tg ratio

The diagnostic performance in the prediction of FNA cytology results with FNA-Tg, Tg ratio, and FNA-Tg combined with Tg ratio is shown in *Table 7*. FNA-Tg ≥20 ng/mL exhibited 86.6% sensitivity and 81.7% accuracy. Compared to FNA-Tg, Tg ratio ≥3 had lower sensitivity (82.7% *vs.* 86.6%), higher specificity (73.8% *vs.* 66.7%), and higher iAUC (0.782 *vs.* 0.766). FNA-Tg combined with Tg ratio exhibited 81.9% sensitivity, 80.5% accuracy, and an iAUC of 0.790.

Discussion

Preoperative assessment of cervical LN metastasis in patients with PTC determines the extent of surgery required for treatment. Neck US and US-guided FNA cytology are widely used methods for diagnosing primary thyroid lesions and LN metastasis (8-10). FNA cytology is highly accurate but produces false negative or nondiagnostic results in up to 20% of cystic, small, or highly vascular LNs (19-21).

Pacini *et al.* introduced Tg measurement from FNA washout fluid in 1992 for early detection of LN metastasis. Elevated FNA-Tg level indicated suspicion for metastasis, whereas an undetectable level indicated nondiagnostic or benign results (22). FNA-Tg measurement is an easily implemented method to increase diagnostic accuracy in suspicious LNs. Although several studies have demonstrated its usefulness, controversies remain regarding the optimal cutoff value, using different cutoff values based on thyroid or TgAb status, and others. Using 24 studies from 1975 to 2013, Grani *et al.* reported that FNA-Tg measurement had high accuracy in the early detection of cervical LN metastasis for differentiated thyroid carcinoma (DTC), but a better standardization of criteria for patient selection, and optimal cutoff values (15). Furthermore, Jeon *et al.* confirmed that FNA-Tg measurement was highly reliable in the diagnosis of cervical LN metastasis in patients with PTC, but high serum TgAb levels could interfere with FNA-Tg measurement (23). Various FNA-Tg cutoff values have been reported. That is because FNA-Tg levels are represented as a wide range in metastatic and non-metastatic LNs and the different techniques of FNA-Tg measurements were used with different functional sensitivities (12,20,24-26). Snozek *et al.* suggested that FNA-Tg cutoff value of 1 ng/mL compared favorably with the cytopathology for the detection of PTC in cervical LNs (25). Kim *et al.* recommended that FNA-Tg cutoff value was 10 ng/mL to differentiate metastatic LNs (24). Although FNA-Tg measurement is usually helpful for detecting LN metastasis, the optimal cutoff value of FNA-Tg is still been controversial.

The PTC patients in this study with malignant LN findings detected on preoperative FNA cytology underwent mRND upfront. Those with suspicious LNs on US but negative preoperative FNA cytology underwent intraoperative LN biopsy for frozen section histopathologic examination; mRND was performed if malignancy was detected. We attempted to improve the accuracy of preoperative diagnosis using FNA-Tg and S-Tg levels. FNA-Tg level ≥20 ng/mL had the best sensitivity (86.6%) with 81.7% accuracy and correlated with FNA cytology results. Conversely, FNA-Tg level of ≥20 ng/mL indicated that negative preoperative FNA cytology could be a false negative result. Therefore, intraoperative frozen section biopsy of suspicious LNs with FNA-Tg level of ≥20 ng/mL might still be necessary. Tg ratio of ≥3 showed slightly lower sensitivity but higher specificity and predictive accuracy than FNA-Tg level ≥20 ng/mL. An FNA-Tg level of ≥20 ng/mL with Tg ratio of >3 suggests a considerable possibility of malignancy. The combination of FNA-Tg and Tg ratio showed the highest iAUC (0.790) and had the best predictive accuracy. In case of FNA-Tg level of ≥20 ng/mL with Tg ratio of ≥3 but negative preoperative FNA cytology, we have to consider the possibility of false negative of preoperative FNA cytology.

A previous study reported that S-Tg level does not predict the diagnosis of metastatic LNs in patients with PTC (16). Interestingly, our data showed that the proportion of patients with positive FNA cytology was significantly higher in patients with S-Tg level <1 ng/mL than those with S-Tg level ≥1 ng/mL (93.5% *vs.* 71.0%, P=0.010). This result was probably due to thyroiditis and TgAb; the proportion of patients with positive serum TgAb was significantly higher in patients with S-Tg level <1 ng/mL (38.7% *vs.* 18.1%, P=0.017). Korea is an iodine-sufficient region, and iodine sufficiency is associated with thyroiditis (27). Therefore, patients with S-Tg level of <1 ng/mL could be diagnosed as higher positive FNA cytology than patients with S-Tg level of ≥1 ng/mL.

Preoperative neck US is commonly used to identify suspicious LNs (28-30). Suspicious findings for metastatic LNs include size enlargement, loss of fatty hilum, oval shape, hyperechogenicity, cystic composition, microcalcification, and peripheral vascularity. Hwang *et al.* reported that preoperative neck US had high sensitivity and specificity for predicting cervical LN metastasis in the lateral neck (28). We analyzed the results of a combination of various modalities with US features. The correlation of FNA cytology results with different modalities with US features is shown in Table S1. We expected better diagnostic performance when using US features with FNA-Tg and Tg ratio together. However, we found that diagnostic performance using US features together with FNA-Tg level and Tg ratio was rather low (sensitivity, 60.6%; accuracy, 66.9%).

This study has several limitations. It was retrospective in nature with a relatively small sample size and conducted in a single center. Thus, selection bias may have been introduced and our results may not be applicable to the general PTC patient population. In addition, FNA cytology and FNA-Tg measurement were only performed in LNs suspicious for malignancy. Diagnostic accuracy would have been more clearly identified if all LNs were examined. Finally, we did not consider other factors that affect S-Tg and FNA-Tg levels, such as thyroiditis and TgAb. The prevalence of Hashimoto's thyroiditis is high in Korea, which may have influenced the study results. A prospective or matched study that reflects the effect of Hashimoto's thyroiditis and TgAb would help to clarify their impact. Nonetheless, the most important strength of this study was that every patient was followed using a standardized protocol in a single institution, including S-Tg, FNA-Tg measurement and FNA cytology examination.

Conclusions

On the basis of the result from our study, FNA-Tg measurement increases preoperative diagnostic accuracy in detecting metastatic LNs in patients with PTC. Diagnostic accuracy is higher using a 20 ng/mL FNA-Tg cutoff level.

Tg ratio is also valuable. FNA-Tg level combined with Tg ratio shows promise to improve preoperative diagnostic accuracy in the detection of metastatic LNs.

Acknowledgments

Funding: This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2015R1D1A1A01058798).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-366

Data Sharing Statement: Available at https://dx.doi.org/10.21037/gs-21-366

Peer Review File: Available at https://dx.doi.org/10.21037/gs-21-366

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/gs-21-366). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of the Institutional Review Board at Seoul St. Mary's Hospital and the Catholic University of Korea (IRB No: KC20RISI0043), and individual consent for this retrospective analysis was waived.

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Cite this article as: Kim K, Bae JS, Kim JS. Measurement of thyroglobulin level in lateral neck lymph node fine needle aspiration washout fluid in papillary thyroid cancer. Gland Surg 2021;10(9):2686-2694. doi: 10.21037/gs-21-366

Supplementary

Table S1 Diagnostic performance of different modalities with US features used in the correlation with FNA cytologic result

Test	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	iAUC
0. US feature ≥2	68.5	54.8	36.5	82.1	65.1	0.671
1. FNA-Tg ≥20 ng/mL	86.6	66.7	62.2	88.7	81.7	0.766
2. Tg ratio ≥3	82.7	73.8	58.5	90.5	80.5	0.782
3. FNA-Tg ≥20 ng/mL and Tg ratio ≥ 3	81.9	76.2	58.2	91.2	80.5	0.790
0 + 1	63.8	81.0	42.5	91.0	68.0	0.724
0 + 2	60.6	83.3	41.2	91.7	66.3	0.720
0 + 3	60.6	85.7	41.9	92.8	66.9	0.790

US features: size enlargement, loss of fatty hilum, oval shape, hyperechogenicity, cystic composition, microcalcification, peripheral vascularity. Tg, thyroglobulin; FNA, fine needle aspiration; FNA-Tg, Tg level of FNA washout fluid; NPV, negative predictive value; PPV, positive predictive value; iAUC, integrated area under the curve; US, ultrasonography.

https://dx.doi.org/10.21037/gs-21-366