ORIGINAL RESEARCH

Lateral neck multilevel fine-needle aspiration cytology and thyroglobulin estimation in papillary thyroid carcinoma

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Abstract

Objective: To assess the accuracy of preoperative ultrasound-guided multilevel fine-needle aspiration (FNA) cytology and thyroglobulin (Tg) estimation in mapping metastatic levels in the lateral neck, in patients with papillary thyroid carcinoma (PTC).

Methods: Patients with PTC clinically metastasizing to the lateral neck who were initially treated at the Peking University Cancer Hospital from June 2018 to September 2020 were included. FNA was performed preoperatively in each suspicious neck level; cytological examination (FNA-C) and Tg measurement of the needle-washout fluid (FNA-Tg) were combined to determine metastasis. FNA-Tg cutoff value was calculated, and the accuracy of FNA at different levels were evaluated.

Results: In total, 111 patients underwent 124 lymph node dissections. The best cutoff value of FNA-Tg for the diagnosis of metastatic level was 1.0 ng/mL. Multilevel FNA showed sensitivity, specificity, positive predictive value, and negative predictive value in predicting single-level metastasis of 100%, 61.0%, 43.9%, and 100%, respectively. In 64 (51.6%) cases, the involved levels diagnosed by FNA were consistent with that diagnosed by postoperative pathology.

Conclusion: FNA-Tg improves the diagnostic performance of FNA-C in lateral neck lymph node metastases. However, limited accuracy was obtained for preoperative multilevel FNA in predicting the extent of metastasis in the lateral compartment.

KEYWORDS
fine-needle aspiration, lateral neck dissection, lymphatic metastasis, papillary thyroid carcinoma, thyroglobulin

1 | INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignant neoplasm.[1] It is associated with a very high rate of cervical lymph node metastasis (LNM). The incidence rate of regional neck disease is between 30% and 80%.[2,3] LNM is a risk factor for locoregional recurrence and has an impact on overall survival in older patients.

Ultrasound (US) is currently the most useful method for detecting nonpalpable metastatic cervical nodes in the lateral neck.[4] However, the criteria for malignancy is not specific enough, and the precision depends on the skill and experience of the operator. Fine-needle aspiration (FNA) has been widely used to confirm suspect LNM on US. Measuring thyroglobulin (Tg) in the needle-washout fluid (FNA-Tg) was initially suggested by Pacini et al to improve the sensitivity of FNA cytological analysis (FNA-C).[5] Several authors have reported this

method to have high sensitivity and specificity in diagnosing LNM.[6] However, there remains controversy on some issues, with a scarcity of studies validating the alleged benefit of FNA-Tg over FNA-C alone, and the variation of the cutoff levels for Tg measurement, which range from 0.9 to 39 ng/mL.[6] In addition, the reliability of a negative result judgment is inadequate if it is solely based on short-term follow-up without recurrence, rather than on postoperative pathological studies, due to the indolent growth pattern of PTC.[7]

The current guidelines of the American Thyroid Association recommend therapeutic lateral neck compartmental lymph node (LN) dissection for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.[8] However, the extent of dissection is controversial, since the accuracy of FNA in predicting the distribution of metastatic levels is not well defined. Detection of metastatic lymph nodes is generally based on the results of retrospective case series evaluating the pattern and frequency of LNM in postoperative histopathology,[9-11] which cannot be obtained prior to surgery. Whether US with FNA can accurately predict the distribution of metastatic LNs at different neck levels is still unknown.

This study attempted to evaluate the accuracy of cytological examination and Tg measurement in the needle-washout fluid in predicting the pattern of lateral neck metastasis, which may potentially help in the decision-making regarding the extent of the surgery.

2 | MATERIALS AND METHODS

2.1 | Patients

This prospective study was conducted at a tertiary hospital in Beijing, China. Ethics committee approval was obtained from the Institutional Review Board of the Peking University Cancer Hospital (No. 2018KT101). Consecutive patients treated for PTC by a single surgeon between June 2018 and September 2020 were included. A total of 456 patients with PTC underwent FNA of suspicious LNs in the lateral neck during this period. Out of these, 291 patients eventually underwent surgery at our institute; 82 were excluded due to a previous history of neck surgery or thermal ablation in the neck, and 98 with negative FNA-C and FNA-Tg results refused lateral LN dissection. A total of 111 patients were finally included.

All patients provided informed consent and underwent preoperative US-guided FNA. Total thyroidectomy and bilateral central neck dissection were performed, along with ipsilateral or bilateral lateral selective neck dissection of levels II (A + B), III, IV, and VB, followed by radioactive iodine.

2.2 | Procedures

All patients underwent a preoperative neck US examination by experienced US specialists; suspicious LNs were mapped and reported. Indications for FNA included the following: (a) suspicious features of LNM: hyperechogenicity, cystic changes, unbalanced inner echo,

calcification, and a roughly round shape (long/transverse diameter ratio <1.5[12,13]; and (b) transverse diameter >0.8 cm without suspicious features. The most suspicious or biggest LN meeting the criteria at each level was selected for FNA. If there were no LNs meeting the criteria, FNA was not performed.

US-guided FNA was performed by the same group of experienced, high-volume thyroid surgeons in charge of the operations using a high-resolution US (Mindray M9, China) equipped with high-frequency (5-18 MHz) linear array transducers. A 23-gauge needle was used, attached to a 2-mL disposable syringe. Some of the aspirated material was directly smeared onto glass slides, and immediately immersed in 95% alcohol for staining. The remaining material in the syringe was injected into the preserving fluid for liquid-based cytology. The same needle and syringe set was rinsed within 1 mL of normal saline for the measurement of washout Tg levels.

LN compartments of the lateral neck were defined according to the classification standard proposed by the American Head and Neck Society and the Committee for Head and Neck Surgery.[14,15] The patients with positive FNA-C or elevated FNA-Tg (>1 ng/mL) results underwent lateral neck dissection on the positive side. The extent of dissection included levels II (IIA and IIB), III, IV, and VB. During neck dissection, the spinal accessory nerve, sternocleidomastoid muscle, and internal jugular vein were spared. We used the inferior border of the hyoid bone to define the boundary between levels II and III, and the inferior border of the cricoid cartilage to define the boundary between levels III and IV, respectively, and the posterior margin of the sternocleidomastoid muscle to define the boundary between levels IV and VB. The boundaries between different levels were marked with sutures during the operation; the neck dissection specimen was divided into levels and sublevels (IIA, IIB, III, IV, and VB) according to the suture marks and packed in separate containers, and then submitted to the histopathologist for paraffin embedding analysis.

2.3 | Statistical analysis

Descriptive statistics are reported as mean (±SD) or median (quartile) for continuous variables and frequencies (percentage) for categorical variables. The evaluation of FNA washout Tg in the diagnosis of metastatic LNs using receiver operating characteristic (ROC) analysis obtained the best cutoff value. If a metastatic LN could be seen in the specimen of a level by permanent pathology, the final result was taken as positive; otherwise, it was considered negative. Data were analyzed using SPSS version 22 software (SPSS, Chicago, Illinois). Results were calculated with 95% confidence intervals. $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Clinical and pathological characteristics

A total of 111 patients with PTC were included and 124 LN dissections were performed. Bilateral dissection was performed in

13 (11.7%) patients. The patients consisted of 37 men and 74 women (ratio: 1:2). The mean patient age was 39.5 ± 11.4 years. The mean size of the primary thyroid cancer was 2.0 ± 1.3 cm (range: 0.2-6.5 cm). Extrathyroidal extension was found in 30 (27.0%) patients, and extranodal extension in 59 (53.2%) patients. The serum Tg antibodies (TgAb) were elevated in 29 (26.1%) patients (the normal range in our institution is 0-115 IU/mL). Two patients had false-positive FNA results with no lateral neck metastasis during histopathological analysis.

Every suspicious level was aspirated in the outpatient department for 59 patients. In the remaining 52 patients, one level was aspirated in the outpatient department, and other suspicious levels were aspirated in the operating room under general anesthesia. We found suspicious lymph nodes in 301 neck levels, all of which were aspirated (one LN in each level). Each patient underwent aspiration of one to four lymph nodes, with an average of 2.4 ± 0.8. All the FNA specimens were examined cytologically except eight specimens, which were excluded from washout Tg testing because the levels had already been confirmed positive through FNA-C prior to the evaluation at our institute. Since levels IIA and IIB could not be distinguished under US, they were all recorded as level II preoperatively.

The number of harvested and pathological metastatic LNs at levels II (IIA and IIB), III, IV, and VB are listed in Table 1. Only one patient underwent level VA dissection due to positive FNA result; two of the six harvested lymph nodes were involved.

3.2 | Cutoff level of FNA-Tg to identify lymphatic metastases

Of the 293 LNs subjected to washout Tg testing, 222 were confirmed as malignant by cytology or by permanent pathology. All of these LNs were resected; the median levels of Tg washout in malignant and non-malignant LNs were 734.5 (4.42-10 870) ng/mL and 0.07 (0.04-0.16) ng/mL, respectively (FNA-Tg values >50 000 ng/mL were taken as 50 000 ng/mL and values <0.04 ng/mL as 0.04 ng/mL, which are the upper and lower limits considered for FNA-Tg values in the institute's laboratory); the difference between the two groups had statistical significance ($P < .001$). Figure 1 shows the ROC area under the curve for

TABLE 1 Number of harvested and pathologic lymph nodes of the lateral neck among all patients

Neck level	Harvested lymph node (mean ± SD)	Pathologic lymph node (mean ± SD)
IIA	6.4 ± 3.7	0.6 ± 0.9
IIB	4.0 ± 2.3	0.1 ± 0.3
III	8.5 ± 4.5	2.3 ± 1.9
IV	9.8 ± 5.7	2.1 ± 2.0
VB	3.8 ± 3.2	0.1 ± 0.4
Total	31.8 ± 10.7	5.2 ± 3.5

Abbreviation: SD, standard deviation.

the detection of LN involvement in the examined samples. The area under the curve was 0.897, which was statistically significant ($P < .001$). According to ROC analysis, the best cutoff value of Tg for the diagnosis of metastatic level was 1.0 ng/mL.

3.2.1 | Diagnostic value of FNA in identifying metastatic neck levels

We consider the "metastasis of a level" as a standard (instead of the LN). Using FNA-C alone, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in detecting metastatic levels were 69.4%, 100%, 100%, and 51.1%, respectively. The accuracy of FNA-C was 76.8%. Based on the threshold of the washout Tg level, using FNA-Tg alone, the sensitivity, specificity, PPV, NPV, and accuracy were 83.8%, 90.1%, 96.4% and 64.0%, respectively. The accuracy of FNA-Tg was 85.3%. When FNA-C was combined with FNA-Tg (either positive was counted as positive), the sensitivity, specificity, PPV, NPV, and accuracy were 85.6%, 90.1%, 96.4%, 66.7%, and 86.7%. The diagnostic accuracy of FNA-C plus Tg was significantly higher than that of FNA-C alone (Table 2).

Among the 139 cases with negative FNA-C results, 43 were positive in FNA-Tg testing; of these, 83.7% (36/43) were diagnosed as malignant in histopathology. The remaining 96 were FNA-Tg negative, and 32 (33.3%) of them were malignant. Basing on this cutoff level, the FNA-Tg results correctly concluded more than half (53%, 36/68) of malignant cases with false-negative FNA-C results.
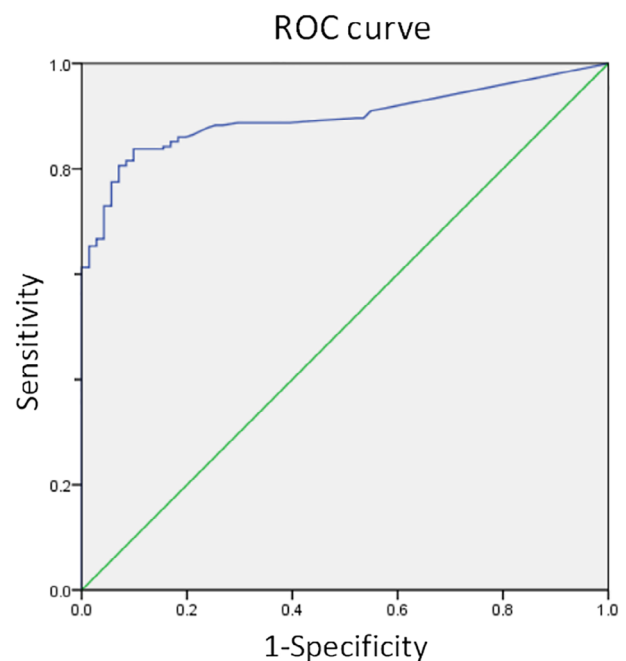

FIGURE 1 Area under the receiver operating characteristic curve for the detection of lymph node metastasis using fine-needle aspiration-thyroglobulin (FNA-Tg)

Specific to each level, the sensitivity of US-guided FNA in identifying metastatic levels was high for levels IV (84.0%), followed by level III (77.5%), and was low for levels II (57.4%) and VB (42.9%). The specificity of FNA for diagnosing metastatic levels was high for all the levels (91.7%-100%). The PPV was lowest for

level II and the NPV was lowest for level III. The accuracy at levels II, III, IV, and VB were 78.2%, 80.6%, 85.5%, and 96.8%, respectively (Table 3).

On preoperative multilevel FNA evaluation, 66 solitary-level metastases and 58 multiple-level metastases were noted. In those with solitary-level metastasis, FNA proved metastatic lymph nodes were mostly located at level IV (n = 34, 51.5%), followed by level III (n = 30, 45.5%), and level II (n = 2, 3.0%); no single level V metastasis was found. Pathology confirmed solitary-level disease in 29/66 (43.9%) cases, and two cases with no metastasis in the lateral neck (false positive). All the clinically positive multilevel LNs were confirmed as multiple-level metastases in histopathology. The sensitivity, specificity, PPV, and NPV of FNA-C plus FNA-Tg in predicting single-level metastasis were 100%, 61.0%, 43.9%, and 100%, respectively.

According to permanent pathology, the distribution of metastatic levels in 64 (51.6%) cases was consistent with the preoperative FNA findings (Figure 2). Occult metastatic levels were detected in 54 (43.5%) cases, those that had pathologically positive levels beyond diagnosis during preoperative evaluation. False-positive levels were

TABLE 2 Diagnostic value of preoperative FNA-C or FNA-C with Tg for 293 lateral cervical levels in comparison with histopathology. The sensitivity, specificity, and accuracy of FNA-C vs FNA-C plus Tg were compared using McNemar's test

Histopathology(n)	FNA-C		FNA-C + Tg		
	+	−	+	−	P
+ (222)	154	68	190	32	
− (71)	0	71	7	64	
Sensitivity	69.4%		85.6%		<.001
Specificity	100%		90.1%		.016
Accuracy	76.8%		86.7%		<.001

Abbreviations: FNA-C, fine-needle aspiration cytology; Tg, thyroglobulin.

TABLE 3 The performance of preoperative evaluation fine-needle aspiration cytology with thyroglobulin measurement in the diagnosis of lymph node metastases at different levels

Level	Preoperative diagnosis (n)	Histopathology		SE (%)	SP (%)	PPV (%)	NPV (%)	Accuracy (%)
		+	−					
II	+ (35)	31	4	57.4	94.3	88.6	74.2	78.2
	− (89)	23	66					
III	+ (80)	79	1	77.5	95.5	98.8	47.7	80.6
	− (44)	23	21					
IV	+ (86)	84	2	84.0	91.7	97.7	57.9	85.5
	− (38)	16	22					
Vb	+ (3)	3	0	42.9	100	100	96.7	96.8
	− (121)	4	117					

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity.
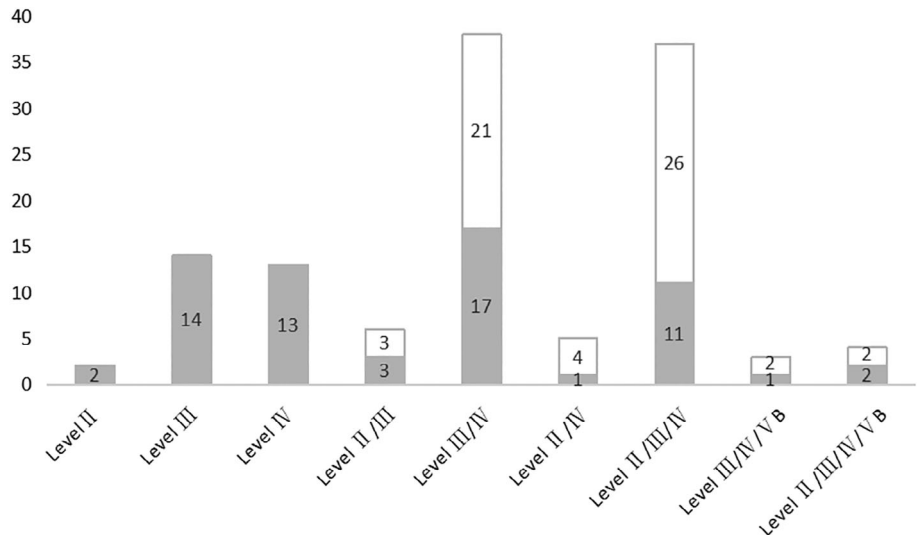

FIGURE 2 The distribution of metastatic levels in permanent pathology, and the proportion of cases consistent with preoperative fine-needle aspiration (FNA) diagnosis. Gray segment: Consistent with preoperative FNA diagnosis. White segment: Inconsistent with preoperative FNA diagnosis

found in seven (5.6%) cases, those that had less pathologically positive levels compared to those observed during preoperative evaluation.

4 | DISCUSSION

US is a cheap and noninvasive modality to evaluate cervical LNs; however, it has the limitation of operator dependence. FNA is the most accurate and cost-effective method for the detection of metastatic LNs in thyroid cancers,[8] and measuring Tg in the needle-washout fluid could further improve the diagnostic performance. Determining the level of cervical LN metastasis is essential for good surgical planning; therefore, we evaluated the usefulness of FNA-C + Tg in this study.

FNA-Tg has been widely used in the preoperative diagnosis of LNM. In a meta-analysis of diagnostic accuracy in patients with PTC with existing thyroid gland, the pooled sensitivity and specificity of FNA-Tg was 86.2% and 90.2%, respectively.[6] However, most of the previous studies involved aspiration of only one LN in the lateral neck, and the node was kept under observation, without surgical intervention, if the result was negative. The specificity of FNA is difficult to assess on follow-up because of the indolent nature of PTC.[16] In the present study, all the suspicious levels were evaluated by FNA. Further, if one LN was positive, all other aspirated LNs, including the clinically negative ones, were resected and analyzed. Since a substantial number of negative LNs were verified pathologically, a more accurate specificity and NPV could be achieved in this study.

Although many studies have been conducted on FNA-Tg, its diagnostic threshold is very difficult to determine.[17] Some authors have used the mean value +2 SD of negative nodes,[18,19] or the upper value of reference range of serum Tg,[20] or other such varying criteria.[21] However, the predominant opinion has been to consider the best cut-off derived by an ROC curve analysis.[22-24] As suggested by different authors, the cutoff values range from 0.2 to 50 ng/mL, but have not been unanimously established. Based on the present study, the Tg cutoff value for the detection of LN metastases was 1.0 ng/mL, which is consistent with the results of our previous study[25] and those of several others.[26-28]

The pattern of LNM in patients with PTC is generally sequential, and skip metastasis rarely occurs. Most of the patients (7/8) diagnosed as having level II/IV metastasis were eventually found to have occult level III metastasis. However, the incidence of occult metastasis at level II was relatively low in patients with preoperative metastasis at level III/IV or III/IV/V, probably because the level II LNs are located far away from the primary tumor compared to other levels. The understanding of these patterns may be helpful for planning surgery.

There were several possible reasons for false-positive cases in this study. The influence of other components in the solution, the so-called "matrix effect," may result in an elevated Tg level in the normal LNs.[29] Another reason could be the inaccurate separation of specimens into different levels. The lateral neck is a continuous entirety, and there are no natural anatomical boundaries between different levels. By identifying anatomical landmarks to ensure the accuracy of

LN assigning before and during operation, we may reduce the impact of systematic error.

There were 32 false-negative levels in our study. The false-negative results of FNA-C reported in previous studies were usually due to lack of follicular epithelial cells, for example, in cystic or calcified LNs. The false-negative FNA-Tg results might be because of undifferentiated thyroid carcinoma. However, an important cause for false negatives is the limitation of the US technique. Metastatic LNs not detected on preoperative imaging are not uncommon; however, it is seldom discussed in previous studies because prophylactic lateral neck dissection is generally opposed. Subclinical occult lateral neck LNM was reported in 20% to 69% of patients with PTC with stage N0 disease.[28] In patients with unilateral N1b PTC, contralateral lateral LN involvement could be found in about one-third of patients, despite the preoperative US being negative.[30] The incidence of occult lateral neck LNM was 47.8% in patients with N0/N1a stage PTC in a meta-analysis,[31] indicating that the conventional imaging methods cannot accurately detect the metastatic LNs. However, it is unclear whether these microscopic metastases would progress to clinically significant disease if they are not included in the dissection. A prospective controlled study with long-term follow-up is needed to answer this question.

5 | CONCLUSIONS

Our results demonstrated that FNA-Tg improves the diagnostic performance of FNA-C in detecting lateral neck LNM. However, limited accuracy was obtained for preoperative multilevel FNA in predicting the extent of metastasis in the lateral compartment. Clinicians should be careful when considering either "limited" or "superselective" compartment dissection based on preoperative evaluation of lateral neck LNs in patients with thyroid cancer.

CONFLICT OF INTEREST
The authors declare no potential conflict of interest.

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