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ORIGINAL ARTICLE

Retrospective Study

Value of thyroglobulin combined with ultrasound-guided fine-needle aspiration cytology for diagnosis of lymph node metastasis of thyroid carcinoma

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Abstract

BACKGROUND

Surgery for thyroid carcinoma offers a good prognosis; however, cervical lymph node metastasis may occur in the early stage. An effective diagnostic method can accurately guide clinical surgical planning and the scope of lymph node dissection, ultimately improving patient prognosis.

AIM

To explore the diagnostic value of fine-needle aspiration of thyroglobulin (FNA-Tg) combined with ultrasound (US)-guided fine-needle aspiration cytology for cervical lymph node metastasis in thyroid carcinoma.

METHODS

We enrolled 209 pathologically confirmed thyroid carcinoma patients who visited our hospital between Jan 2017 and Dec 2020. Patients were tentatively diagnosed with cervical lymph node enlargement using preoperative US. They underwent US-guided fine-needle aspiration cytology and FNA-Tg. The value of single and combined application of the two methods for the diagnosis of cervical lymph node metastasis was calculated. The factors affecting FNA-Tg for diagnosis were analyzed using univariate and multivariate methods.

RESULTS

FNA-Tg values were significantly higher among patients with positive cervical lymph node metastasis. The sensitivity and specificity of US-guided fine-needle aspiration cytology, FNA-Tg, and US-guided fine-needle aspiration cytology + FNA-Tg were 85.48% and 90.59%, 83.06% and 87.06%, and 96.77% and 91.76%, respectively. The area under the receiver operating characteristic curve for US-guided fine-needle aspiration cytology, FNA-Tg, and the two combined, was 0.880, 0.851, and 0.943, respectively. A long diameter/short diameter ratio < 2, an

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insufficient number of acquired cells, a low serum thyroglobulin level, and an absence of typical metastatic US features increased the risk of cervical lymph node metastasis in thyroid carcinoma patients misdiagnosed using FNA-Tg.

CONCLUSION
The diagnostic value of FNA-Tg for detecting cervical lymph node metastasis is not high; however, combined with US-guided fine-needle aspiration cytology, it is significantly improved.

Key Words: Thyroid carcinoma; Ultrasonic guidance; Fine-needle aspiration cytology; Lymph node puncture; Thyroglobulin; Diagnosis

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Core Tip: Fine-needle aspiration of thyroglobulin (FNA-Tg) has relatively high diagnostic value in lymph node metastasis and recurrence of differentiated thyroid carcinoma. FNA-Tg combined with ultrasonic-guided fine-needle aspiration cytology has a certain meaning in the thyroid carcinoma with lymph node metastasis.

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INTRODUCTION

Common clinical diagnostic methods for cervical lymph node metastasis in thyroid carcinoma patients include ultrasound (US), computed tomography, magnetic resonance imaging, radionuclide scanning, and other imaging methods, as well as US-guided fine-needle aspiration cytology (FNAC). However, all of these methods have limitations[1,2]. US is the most commonly used imaging method; however, comorbid inflammatory lymphadenopathy can lead to misdiagnosis; accurate differentiation between benign and malignant nodules requires extensive experience[3]. FNAC can offer further cytological diagnostic support for lymph nodes with suspicious US results. However, incorrect sampling sites, insufficient sample sizes, small metastases, and cystic alteration of the lesion can lead to false-negative results[4]. Fine-needle aspiration of thyroglobulin (FNA-Tg) reportedly has a relatively high diagnostic value in lymph node metastasis and recurrence of differentiated thyroid carcinoma[5]. In this study, we primarily aimed to explore and describe the value of FNA-Tg combined with US-guided FNAC to diagnose cervical lymph node metastasis in patients with thyroid carcinoma and explore factors influencing the diagnosis.

MATERIALS AND METHODS

Data

A total of 209 pathologically diagnosed thyroid carcinoma patients who visited the Thyroid Surgery Department of Affiliated Hospital of Chengde Medical University between Jan 2017 and Dec 2020 were selected. The inclusion criteria were as follows: (1) Patients who met the diagnostic criteria of thyroid cancer according to the National Comprehensive Cancer Network Guidelines for thyroid cancer criteria[6]; (2) Patients with confirmed pathological diagnosis; (3) Patients aged 20 to 67 years; (4) Patients who presented with suspicious lymph node enlargement on preoperative cervical lymph node US and then underwent US-guided FNAC and FNA-Tg; and (5) Patients with complete data. The exclusion criteria were as follows: (1) Patients with a history of radiation and chemotherapy; and (2) Patients with lung infections and heart failure.

Before the implementation of this study, the research plan was submitted to the Medical Ethics Committee of our hospital for approval and then implemented after the decision and document of the Medical Ethics Committee.

Instrument check and FNAC method

For FNAC, the patients were placed supine with a soft pillow under their neck to fully expose the puncture site. After routine disinfection of the puncture site, 1% lidocaine was applied under local anesthesia. A 22 G cell puncture needle (Yako, Japan) was selected, and the fine needle was inserted into the center of the lymph node under US guidance. The needle was rapidly retracted and inserted back and forth in different needle channels five times. Subsequently, the puncture needle was pulled out, the aspirated tissue was placed onto the slide, smeared, and fixed for pathological examination. Each lymph node was punctured at least three times. After HE staining, the smears were reviewed by two senior pathologists, and the cancer cells were either determined to be positive for lymph node metastases, or if no cancer cells were found, or if the number of cells was insufficient, the cells were determined to be negative.

FNA-Tg testing method

For FNA-Tg measurement, 0.5 mL of 0.9% normal saline was absorbed with a 1-mL syringe, the needle was rinsed, and 1 mL of eluent was prepared. The supernatant was extracted after centrifugation at 3000 r/min for 5 min. Subsequently, the Tg content was detected using the COBAS E601 electrochemical analyzer (Roche, Basel, Switzerland) and an immunochemiluminescence method.

The judgment standards[7] were as follows: FNA-Tg > 1.0 ng/mL was diagnosed as positive thyroid cancer lymph node metastasis, and FNA-Tg ≤ 1.0 ng/mL was diagnosed as negative thyroid cancer lymph node metastasis.

Statistical analyses

In this study, age and other measurement indexes were tested for normal distribution, and all were in line with approximate normal distribution or normal distribution, which was expressed by mean ± SD. A *t*-test was performed using SPSS software (IBM Corp., Armonk, NY, USA). The measured data were analyzed using an χ^2 test. For multivariate analysis, a logistic regression model was used to draw the ROC curve and obtain the area under the curve (AUC). The test level was $\alpha = 0.05$.

RESULTS

Ultrasonographic findings of cervical lymph node metastases in positive and negative patients

On US, patients with positive cervical lymph node metastasis showed significantly higher rates of cortical centripetal thickening, hypoechogenicity of the cortex and the medulla, long diameter/short diameter ratio < 2, partial liquefaction or fusion of lymph nodes, abundant internal blood supply, and hilar absence than patients with negative lymph node metastasis ($P < 0.05$) (Table 1).

Comparison of FNA-Tg values in positive and negative patients with cervical lymph node metastasis

FNA-Tg values were significantly higher in patients with positive cervical lymph node metastasis than those with negative lymph node metastasis ($P < 0.05$) (Table 2).

Value of FNAC alone and FNA-Tg alone and their combination for the diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma

Considering pathological results as the gold standard, a four-grid table was prepared (Table 3). The sensitivity and specificity of FNAC in the diagnosing cervical lymph node metastasis of thyroid carcinoma were 85.48% and 90.59%, respectively. The sensitivity and specificity of FNA-Tg for diagnosing cervical lymph node metastasis of thyroid carcinoma were 83.06% and 87.06%, respectively. The sensitivity and specificity of FNAC + FNA-Tg for diagnosing cervical lymph node metastasis of thyroid carcinoma were 96.77% and 91.76%, respectively (Table 4).

Figure 1 shows the results of US-guided FNA examination of cervical lymph nodes and postoperative pathological examination of lymph nodes in patients with papillary thyroid carcinoma with positive lymph node metastasis.

Table 1 Ultrasonographic findings of cervical lymph node metastases in positive and negative patients, *n* (%)

Pathological results	*n*	Cortical centripetal thickening		Hypoechogenicity of cortex and medulla		Long diameter/short diameter < 2		Partial liquefaction or fusion of the lymph nodes		Rich internal blood supply		Hilum deletion	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Positive cervical lymph node metastasis	124	69 (55.65)	55 (44.35)	55 (44.35)	69 (55.65)	67 (54.03)	57 (45.97)	39 (31.45)	85 (68.55)	63 (50.81)	61 (49.19)	32 (25.81)	92 (74.19)
Negative cervical lymph node metastasis	85	34 (40.00)	51 (60.00)	26 (30.59)	59 (69.41)	30 (35.29)	55 (64.71)	14 (16.47)	71 (83.53)	31(36.47)	54 (63.53)	11 (12.94)	74 (87.06)
χ^2 value		4.939		4.027		7.120		5.980		4.188		5.108	
P value		0.026		0.045		0.008		0.014		0.041		0.024	

ROC curve analysis of FNAC and FNA-Tg alone and in combination for diagnosis of cervical lymph node metastasis in thyroid carcinoma patients

An ROC curve was drawn adopting the pathological results as the gold standard. Results showed that the AUC value for FNAC diagnosis of thyroid carcinoma with cervical lymph node metastasis was 0.880. The AUC value for FNA-Tg diagnosis of thyroid carcinoma with cervical lymph node metastasis was 0.851. The AUC value for FNAC + FNA-Tg for diagnosing thyroid carcinoma with cervical lymph node metastasis was 0.943 (Figure 2).

Univariate analysis of the influence of FNA-Tg alone on the diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma

Patients were divided into groups based on FNA-Tg differential diagnosis. The univariate analysis showed that the differences between the two groups were statistically significant ($P < 0.05$), including the rate of long diameter, long diameter/short diameter lymph node ratio, the number of collected cells, serum thyroid stimulating hormone (TSH), serum Tg, and US characteristics (Table 5).

Multivariate analysis of the influence of FNA-Tg on the single diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma

The results of FNA-Tg differential diagnosis of cervical lymph node metastasis were adopted as dependent variables, and the statistically significant indexes, such as long diameter, long diameter/short diameter lymph node ratio, the number of collected cells, serum TSH, serum Tg, and characteristics of US signs, were adopted as independent variables to establish a logistic regression model. A long diameter/short diameter ratio < 2, insufficient number of acquired cells, low level of serum Tg, and absence of typical US signs of lymph node metastasis were found to increase the risk of cervical lymph node metastasis in patients with thyroid carcinoma misdiagnosed

Table 2 Comparison of fine-needle aspiration thyroglobulin values between positive and negative patients with cervical lymph node metastasis (mean ± SD)

Pathological results	*n*	FNA-Tg (ng/mL)	*t* value	*P* value
Positive cervical lymph node metastasis	124	1.56 ± 0.47	14.526	0.000
Negative cervical lymph node metastasis	85	0.77 ± 0.21		

FNA-Tg: Fine-needle aspiration thyroglobulin.

Table 3 The comparison of pathological diagnosis results between single and combined diagnosis of fine-needle aspiration and fine-needle aspiration thyroglobulin

FNA	Pathological results		Total	FNA-Tg	Pathological results		Total	FNA + FNA-Tg	Pathological results		Total
	Positive	Negative			Positive	Negative			Positive	Negative	
Positive	106	8	114	Positive	103	11	114	Positive	120	7	127
Negative	18	77	95	Negative	21	74	95	Negative	4	78	82
Total	124	85	209	Total	124	85	209	Total	124	85	209

FNA: Fine-needle aspiration; FNA-Tg: Fine-needle aspiration thyroglobulin.

Table 4 Value of fine-needle aspiration and fine-needle aspiration thyroglobulin alone and in combination in the diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma (%)

Diagnostic method	Sensitivity	Specificity	Rate of missed diagnosis	Misdiagnosis rate	Positive predictive value	Negative predictive value
FNA	85.48	90.59	14.52	9.41	92.98	81.05
FNA-Tg	83.06	87.06	16.94	12.94	90.35	77.89
FNA + FNA-Tg	96.77	91.76	3.23	8.24	94.49	95.12

FNA: Fine-needle aspiration; FNA-Tg: Fine-needle aspiration thyroglobulin.

using FNA-Tg ($P < 0.05$) (Table 6).

DISCUSSION

Our study showed that patients with positive cervical lymph node metastasis had significantly higher rates of cortical centripetal thickening, hypoechogenicity of the cortex and medulla, long diameter/short diameter ratio < 2, partial liquefaction or fusion of lymph nodes, abundant internal blood supply, and hilar absence than patients with negative lymph node metastasis ($P < 0.05$). These are the typical US characteristics of lymph node metastasis. The normal oval structure of the lymph nodes can be destroyed by the cancer cells; they have an irregular or round shape with a change in the vertical and horizontal diameter ratio. The internal structure can also be destroyed. In the case of lymph node metastasis, the lymphadenocortex involvement occurs first, leading to the loss of the cutaneous medulla structure. Moreover, the infiltration of cancer cells destroys the normal blood supply to the lymph nodes, and US usually reveals an uneven blood supply to the lymph nodes.

Tg is secreted by normal thyroid tissue and differentiated thyroid carcinoma and is a marker of tumor protein in peripheral blood[8,9]. Tg expression is negligible in normal lymph nodes; d, it can be expressed in differentiated thyroid carcinoma, and lymph node metastasis and its concentration in tissue puncture fluid are much higher than that in serum[10]. Detecting FNA-Tg levels in the eluent of needle biopsy samples can help reach the differential diagnosis of cervical lymph node metastasis in thyroid carcinoma. In this study, we adopted specific reference values for detecting positive

Table 5 Univariate analysis of influence of fine-needle aspiration thyroglobulin on the single diagnosis of cervical lymph node metastasis in patients with thyroid carcinoma

Index	Correct diagnosis (n = 177)	Error diagnosis (n = 32)	t/χ^2 value	P value
Age (yr)	49.3 ± 5.8	48.2±6.6	0.966	0.335
Gender, n (%)			0.140	0.708
Male	67 (37.85)	11 (34.38)		
Female	110 (62.15)	21 (65.63)		
Short diameter of lymph node (cm)	0.62 ± 0.11	0.60 ± 0.08	0.982	0.327
Long diameter of lymph node (cm)	1.38 ± 0.20	1.29 ± 0.23	2.288	0.023
Long diameter/short diameter, n (%)			6.965	0.008
< 2	88 (49.72)	24 (75.00)		
≥ 2	89 (50.28)	8 (25.00)		
Number of collected cells, n (%)			15.034	0.000
Insufficient	11 (6.21)	9 (28.13)		
Sufficient	166 (93.79)	23 (71.88)		
Serum TSH (ng/mL)	2.09 ± 0.39	2.31 ± 0.46	-2.854	0.005
Serum TgAb (IU/mL)	20.83 ± 5.17	22.15 ± 5.83	-1.303	0.194
Serum Tg (ng/mL)	18.94 ± 4.20	16.84 ± 4.00	2.621	0.009
Number of cervical lymph node metastases	3.41 ± 0.84	3.15 ± 0.76	1.634	0.104
Characteristics of ultrasonic signs, n (%)			4.885	0.027
Signs of metastasis	142 (80.23)	20 (62.50)		
No signs of metastasis	35 (19.77)	12 (37.50)		

TSH: Thyroid stimulating hormone; Tg: Thyroglobulin.

Table 6 Logistic model of the influencing factors in fine-needle aspiration thyroglobulin diagnosis of lymph node metastasis

Factors		SE	Walds	P value	OR	95%CI	
Long diameter of lymph node	0.611	0.412	2.199	0.138	1.842	0.822	4.131
Long diameter/short diameter	0.741	0.338	4.806	0.041	2.098	1.082	4.069
Number of collected cells	-0.612	0.296	4.275	0.047	0.542	0.304	0.969
Serum TSH	0.285	0.217	1.725	0.216	1.330	0.869	2.035
Serum Tg	-0.442	0.186	5.647	0.025	1.556	1.081	2.240
Characteristics of ultrasonic signs	0.804	0.358	5.044	0.037	2.234	1.108	4.507
Constant term	1.309	0.684	3.662	0.091	3.702	0.969	14.149

TSH: Thyroid stimulating hormone; Tg: Thyroglobulin; OR: Odds ratio.

lymph node metastasis using FNA-Tg. The FNA-Tg value was significantly higher in patients with positive lymph node metastasis than patients with negative lymph node metastasis (P < 0.05). This suggests that because the thyroid tissue has a secretory function in the lymph node tissue, it may appear as lymph node metastasis due to the biological characteristics of the cell. Currently, FNAC is considered the most direct method to diagnose lymph node properties, as it can directly obtain the cells of the lesion and its tissue. However, its smear can be affected by factors such as blood, glia, and cell count, leading to a low sensitivity[10-12]. When the lymph nodes are too small and the smear cells are insufficient, the sensitivity and specificity of FNAC diagnosis can be reduced, leading to an increase in false negatives, affecting the clinical

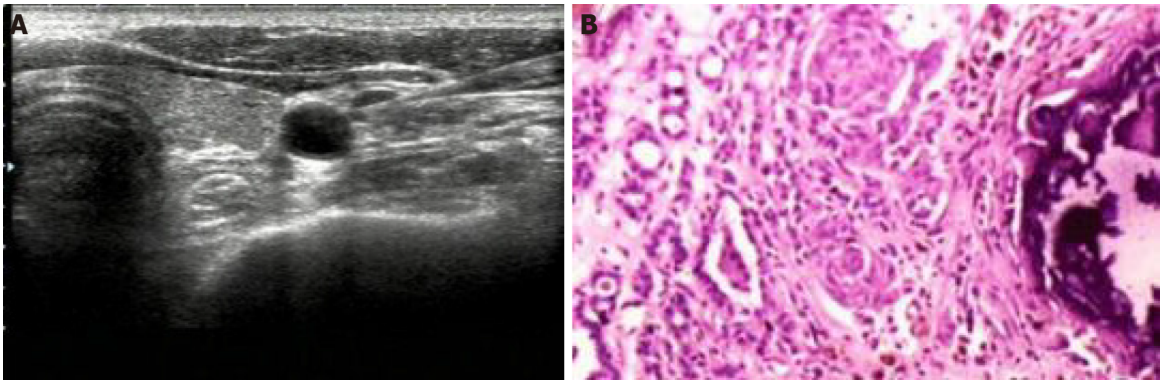

Figure 1 Ultrasound-guided fine-needle aspiration cytology examination and pathological results. A: Ultrasound-guided fine-needle aspiration cytology examination of cervical lymph nodes; B: Postoperative pathological results (Hematoxylin and eosin staining, ×100).

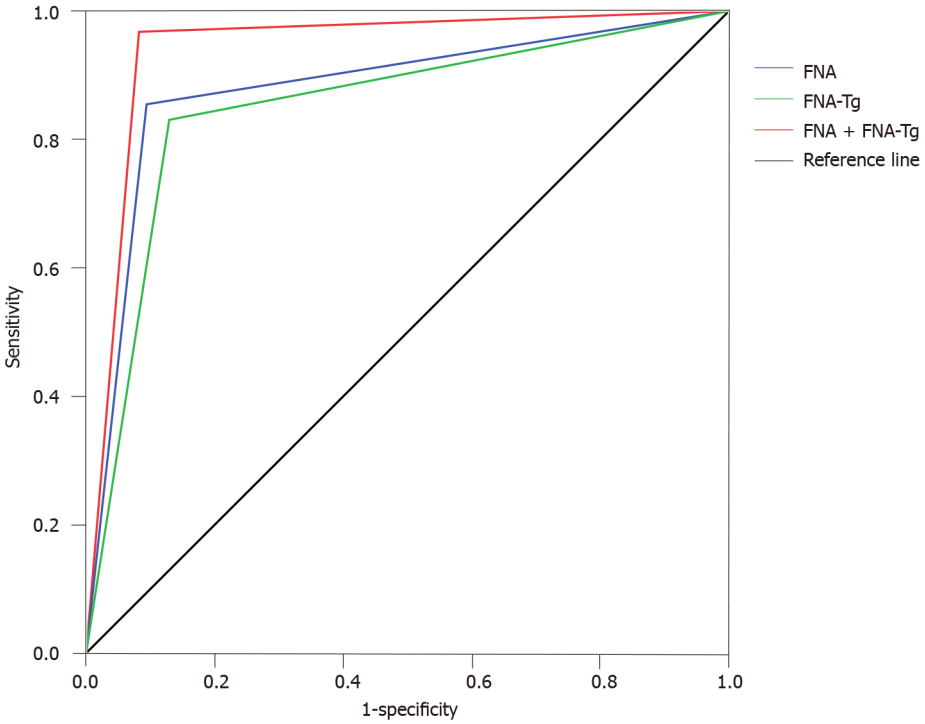

Figure 2 Receiver operator characteristic curve of cervical lymph node metastasis in thyroid carcinoma patients diagnosed by three methods. FNA: Fine-needle aspiration; FNA-Tg: Fine-needle aspiration thyroglobulin.

diagnostic efficiency, and reducing the predictive accuracy[13].

Affected by many factors, the positive threshold of FNA-Tg remains controversial [14,15]. Although previous studies have reported that the diagnostic sensitivity of FNA-Tg was better than that of FNAC[16], our results showed no significant difference in sensitivity between the two methods. The small sample size in this study might have affected the sensitivity and specificity of the results. We found that the sensitivity and specificity of FNAC + FNA-Tg were superior for the diagnosis of cervical lymph node metastasis, thereby providing higher diagnostic accuracy. This may be because metastatic lymph nodes in thyroid carcinoma may be accompanied by significant cystic changes, which could be easily missed by FNAC examination alone. Lymph node eluting fluid has high Tg expression, which is of great help to the diagnosis. Cervical lymphoid node enlargement has many causes, and cytological examination alone is often insufficient for making a precise diagnosis. However, if combined with eluent FNA-Tg examination, the accuracy of diagnosis is improved.

In this study, a univariate analysis of the influence of FNA-Tg findings on the diagnosis of cervical lymph node metastasis revealed a significant difference between the two groups ($P < 0.05$) in terms of the rate of long diameter, the long diameter/short diameter ratio of the lymph nodes, the number of collected cells, serum TSH

level, serum Tg level, and US characteristics. The multivariate analysis showed that a long diameter/short diameter ratio of < 2, an insufficient amount of acquired cells, low level of serum Tg, and absence of typical US signs increased the risk of cervical lymph node metastasis in patients with thyroid carcinoma misdiagnosed by FNA-Tg (P < 0.05).

Some studies[17] have reported that the loss of thyroid tissue and inhibition of serum TSH after thyroidectomy may decrease serum Tg levels, and the levels of serum Tg can independently influence the diagnosis of FNA-Tg. Inhibition of serum TSH can reduce the serum Tg level, and a false negative FNA-Tg diagnosis is possible. In contrast, when serum Tg is not reduced, a false positive FNA-Tg diagnosis is possible [18]. Therefore, it is suggested that FNA-Tg should be tested after TSH stimulation. The diagnostic performance of the FNA-Tg diagnostic threshold varies with thyroid status and serum Tg concentration, but there is no doubt that FNA-Tg detection as an auxiliary diagnostic method can bring about all of its unique advantages.

In this study, patients with suspicious cervical lymph node findings on US were studied. FNAC and FNA-Tg were performed to determine whether or not the diagnosis was thyroid lymph node metastatic carcinoma. Compared with previous studies[19,20], in our study, univariate and multivariate analyses of factors affecting FNA-Tg diagnosis were conducted for the first time, and the results were highly reliable. However, there were also some limitations to our study. The detection process and threshold setting lacked unified standards. Moreover, the factors affecting the test results were numerous and unclear. Thyroid inflammation, autoimmune diseases, and endocrine system diseases can all affect the serum Tg determination to some extent, especially in patients with false-positive and false-negative results. Therefore, underlying diseases should also be considered.

CONCLUSION

In conclusion, when diagnosing thyroid carcinoma patients with cervical lymph node metastasis, FNA-Tg can be affected by various factors, and its diagnostic value alone is not high; however, combined with FNAC, the sensitivity and specificity of diagnosis are significantly improved, providing a significant reference value to guide the treatment.

ARTICLE HIGHLIGHTS

Research background

Fine-needle aspiration cytology (FNAC) can offer further cytological diagnostic support for lymph nodes with suspicious ultrasound (US) results.

Research motivation

Fine-needle aspiration of thyroglobulin (FNA-Tg) reportedly has a relatively high diagnostic value in lymph node metastasis and recurrence of differentiated thyroid carcinoma.

Research objectives

We explore and describe the value of FNA-Tg combined with US-guided FNAC to diagnose cervical lymph node metastasis in patients with thyroid carcinoma.

Research methods

A total of 209 pathologically diagnosed thyroid carcinoma patients who visited the Thyroid Surgery Department of the Hospital were selected.

Research results

The sensitivity and specificity of US-guided FNAC, FNA-Tg, and US-guided FNAC + FNA-Tg were 85.48% and 90.59%, 83.06% and 87.06%, and 96.77% and 91.76%, respectively.

Research conclusions

Combined with US-guided FNAC, it is significantly improved.

Research perspectives

The detection process and threshold setting lacked unified standards.

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