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Original Article

Ultrasonic features of thyroid nodules related to the false negativity in ultrasound-guided fine-needle aspiration for suspicious malignant thyroid nodules

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Abstract: Objective: The study was to investigate the ultrasonic features of thyroid nodules related to the false negativity in ultrasound-guided fine-needle aspiration (UGFNA) for suspicious malignant thyroid nodules. Methods: The cytopathological findings, post-operative pathological findings and findings from follow up were retrospectively analyzed in a total of 115 thyroid nodules, and the sensitivity, specificity, positive and negative predictive values (PPV and NPV), accuracy rate, and AUC of UGFNA were determined. The nodules were divided into three groups: false-negative group, true-negative group and true-positive group. In each group, the ultrasonic features (nodule maximum diameter, multiple or solitary nodule, margin, shape, echotexture, calcification, blood flow pattern, taller-than-wide on transverse view, and hypoechoic halo), sex, and age were analyzed to identify risk factors for false negativity in UGFNA. Results: The sensitivity, specificity, PPV, NPV, accuracy rate, and AUC of UGFNA were 74.5% (41/55), 95% (57/60), 93.2% (41/44), 80.3% (57/71), 85.2% (98/115) and 0.848, respectively. The maximum diameter, taller-than-wide shape, margin, and calcifications of the nodules were related to the false negativity among which the maximum diameter and calcifications of the nodules were independent predictors of false negativity ($P \leq 0.05$), but there were no significant differences in sex, age, multiple or solitary nodule, echotexture and blood flow pattern ($P > 0.05$). Conclusion: UGFNA is an effective diagnostic tool for thyroid nodules in ultrasound and helpful for clinical determination of appropriate treatment. The ultrasound characteristics of UGFNA benign nodule should be cautiously evaluated to minimize the false-negative diagnosis.

Keywords: Ultrasound-guided fine-needle aspiration, thyroid nodules, ultrasound characteristics

Introduction

Thyroid nodules have an increasing incidence and have become the most common endocrine disease. Ultrasound examination reveals 67% [1] of individuals have thyroid nodules. Thus, the identification of thyroid nodules is very common in clinical practice before surgery, and the clinical decision on the treatment of thyroid nodules is of great importance. Generally, patients with asymptomatic benign thyroid nodules usually need routine follow up, but surgical intervention is for patients with malignant thyroid nodules. Under certain conditions, the benign nodules also require ablation, such as percutaneous laser ablation [2]. The American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi (Italian Association of Endocrinologists), and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules in 2010 provide clinical recommendations for the diagnosis and management of thyroid nodules [3]. They recommend ultrasound-guided fine-needle aspiration (UGFNA) as the most accurate and cost-effective assessment of preoperative thyroid nodules, which helps to reduce the unnecessary thyroid nodule surgery and improves the management of thyroid nodules. However, there are still limitations for UGFNA because it has false-negative rate. The false-negative rate is defined as the percentage of patients with benign cytology who are later diagnosed with malignant lesions after thyroidectomy. It is a great concern because it reflects the miss-diagnosis of malignant lesions, which may delay the effective treatment, leading to a poor outcome. Some studies have

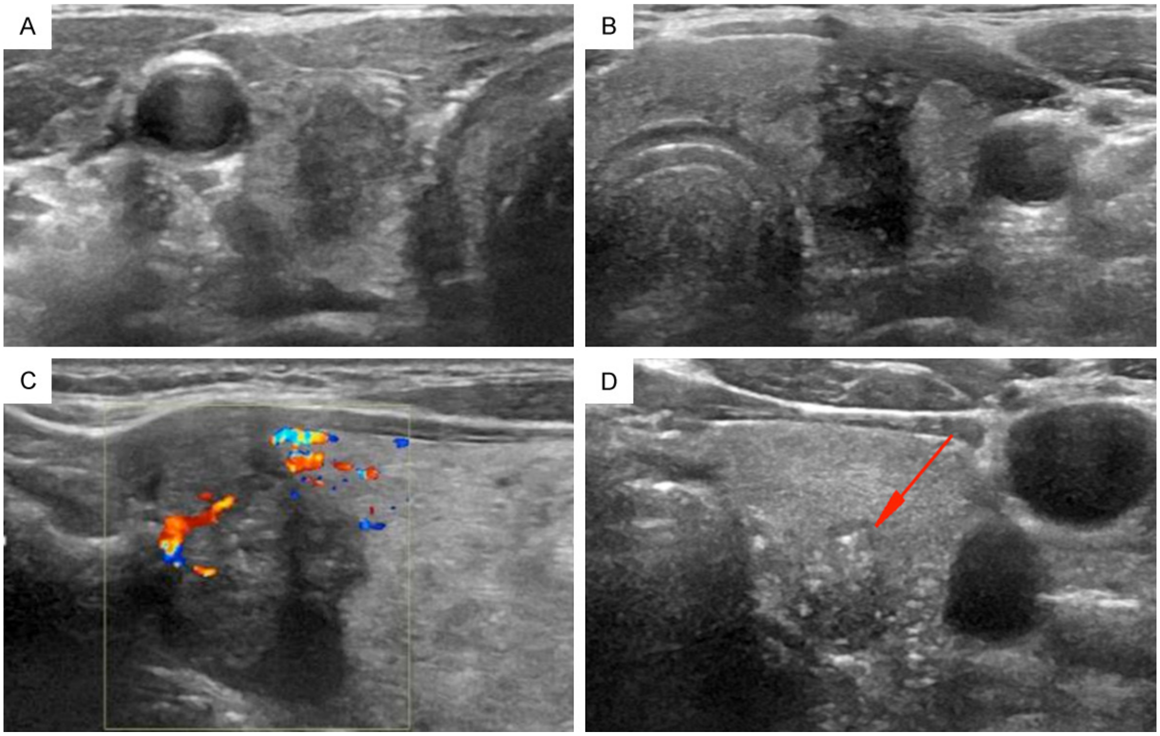

Figure 1. Ultrasound features of suspicious malignant thyroid nodules: A. Solid hypoechoic nodule with irregular margin and taller-than-wide shape. B. Solid hypoechoic nodule with extrathyroidal extension and taller-than-wide shape. C. Thyroid nodule with irregular margin and intranodular vascularization. D. Solid hypoechoic nodule with microcalcification (arrow).

attempted to explore the potential causes of false negativity, and reveal that the operator's experience, method of guidance, accurate localization of the lesion and the needle, number of aspirations, sampling technique, needle gauge, capability for immediate onsite cytological analysis, and other factors are related to the false negative rate [2, 4, 5]. However, to our knowledge, limited studies have been conducted to analyze the ultrasonic features of thyroid nodules with false-negativity. This study was undertaken to investigate the feasibility of ultrasonic features of thyroid nodules in the prediction of false-negativity of UGFNA. In this study, the findings from cytological examination after UGFNA were compared with postoperative histopathological findings and those from clinical follow up, and factors related to the false negativity were explored, which may help to improve the diagnostic accuracy of UGFNA.

Materials and methods

Subjects

Thyroid nodules were diagnosed in accordance with the 2010 AACE/AME/ETA guidelines for ultrasound-suspected malignancy. A total of 255 patients with thyroid nodules who received UGFNA between September 2015 and December 2016 in the First Affiliated Hospital of GuangXi Medical University and the First Affiliated Hospital of GuiZhou Medical University were retrospectively reviewed. The inclusion criteria were as follows: 1), cytology-positive nodules were confirmed by pathology; 2), cytology-negative nodules were followed up for more than 1 year or pathologically confirmed; 3), for a patient with multiple nodules, one of the nodules with the highest risk for malignancy was examined. Exclusion criteria were as follows: 1), cytology-positive nodules weren't confirmed by pathology; 2), cytology-negative nodules were followed up for less than 1 year. A total of 115 patients with 115 nodules were eventually included for analysis. There were 87 females (75.7%) and 28 males (24.3%), and the female to male ratio was 3:1. The mean age was 41.3±16.1 years (range: 13-87 years). The maximum diameter of these thyroid nodules ranged from 0.6 cm to 5.4 cm (mean: 2.1±1.1 cm). There were no contraindications to UGFNA in these patients, and informed consent was

Table 1. Distribution of UGFNA results in 115 patients

UGFNA results	Number of patients	Percentage
Positive malignant cells	27	23.5%
Suspicious malignant cells	14	12.2%
Follicular lesion/neoplasm	3	2.6%
Benign cells	63	54.8%
Undiagnosable	8	6.9%
Total	115	100%

Table 2. Summary of false negative results of UGFNA

Case	Age	Sex	UGFNA diagnosis	Histology
1	35	Female	Inadequate specimen	PC
2	22	Female	Nodular goiter	FALMT
3	66	Female	Nodular goiter	PTMC
4	51	Female	Nodular goiter	PTMC
5	39	Female	Nodular goiter	FVPC
6	39	Female	No tumor cells detected	PTMC
7	32	Female	Inadequate specimen	PC
8	35	Female	No tumor cells detected	PC
9	59	Female	No tumor cells detected	FVPC
10	54	Female	No tumor cells detected	PTMC
11	50	Female	No tumor cells detected	PTMC
12	56	Female	Nodular goiter	PC
13	32	Female	Nodular goiter	PTMC
14	33	Female	Hashimoto thyroiditis	PTMC

Notes: PTMC, papillary thyroid microcarcinoma; FVPC, follicular variant of papillary carcinoma; PC, papillary carcinoma (classical); FALMT, Thyroid follicular adenoma with local malignant transformation.

signed before the ultrasound examination. This study was approved by the Ethics Committees of two hospitals.

Ultrasonic signs of suspicious malignancy

A variety of ultrasonic characteristics of a thyroid nodule have been associated with a higher likelihood of malignancy, and no single ultrasonic feature or a combination of these features is adequately sensitive or specific to all malignant nodules. However, some features or a combination of these features are predictive for malignant thyroid nodules. These features include microcalcifications, hypoechoic signs; increased nodular vascularity, well-defined irregular margin; taller-than-wide shape on transverse view. The malignant thyroid nodule was suspected if one or more of above features was present (**Figure 1**).

Instrument for UGFNA

The color ultrasound scanner with an ACUSON-18L6HD UHF probe (SIEMENS S2000) was used for the UGFNA with 5-ml disposable plastic syringe and 23 G syringe needles.

Procedures for UGFNA

Before the examination, the patient was informed of the procedures of UGFNA and the related precautions. The bilateral thyroid and the isthmus were scanned, and the location, size, shape, internal structure and blood supply of the thyroid nodules were evaluated for the determination of the best puncture point and path. Patients lied in a supine position with a pillow under her/his shoulders, and the best puncture point and path were determined again. After routine disinfection, local anesthesia was done with 2% lidocaine. The thyroid nodule was punctured under the guidance of ultrasound with avoidance of blood vessels, nerves and trachea, as well as cystic necrosis. The tumor was punctured at different directions and the needle was withdrawn quickly when the light red debris were found at the needle cap. Then, the tissues were smeared evenly on the slide. The wound was pressurized for 10 min to prevent hematoma.

Diagnostic criteria of cytology

According to the 2010 AACE/AME/ETA guidelines for the clinical practice for the diagnosis and management of thyroid nodules, the cytological findings were categorized into 5 types [3]: positive malignant cells, suspicious malignant cells, benign (non-neoplastic) cells, follicular lesion/neoplasm, and undiagnosable cells. The positive for malignant cells, suspicious malignant cells and follicular lesion/neoplasm were regarded cytologically positive, and benign cells and undiagnosable cells cytologically negative.

Statistical analysis

The results of UGFNA were compared with those of pathological examination and those in follow-ups. ROC curve of the UGFNA for diagnosis evalution was analyzed with MedCalc® Version 1.4.2.0. The ultrasound characteristics were compared by using univariate analysis among three groups. Statistical analysis was performed with SPSS version 17.0. Quantitative

Table 3. Distribution of post-operative histopathological results (n=72)

Histopathological results	Number of patients	Percentage
Papillary carcinoma	50	69.4%
Thyroid lymphoma	4	5.5%
Thyroid follicular adenoma local malignant transformation	1	1.4%
Thyroid adenoma	2	2.8%
Subacute granulomatous thyroiditis	3	4.2%
Hashimoto thyroiditis	3	4.2%
Thyroid adenomatous hyperplastic nodules	1	1.4%
Nodular goiter	7	9.7%
Toxic nodular goiter	1	1.4%
Total	72	100%

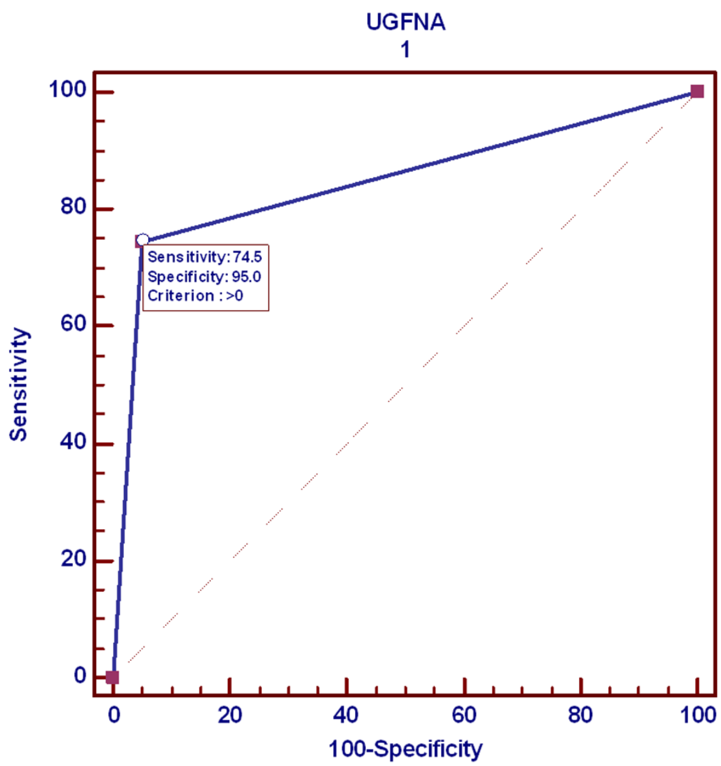

Figure 2. ROC curve of UGFNA for diagnosis evaluation. Notes: AUC=0.848, SE=0.037, 95% CI (0.769, 0.908), P<0.0001.

Table 4. Diagnostic performance of UGFNA

UGFNA results	Final results		Total
	Malignant	Benign	
Positive	41	3	44
Negative	14	57	71
Total	55	60	115

data are presented as means ± standard deviation (SD). Rates were compared with Chi-square test. Data with heterogeneity of variance were compared with rank sum test. The means between two groups and among three groups were compared with independent *t* test and one-way analysis of variance, respectively. A two-sided P<0.05 was considered statistically significant. Ultrasound chracteristics with statistical significance in univariate analysis were analysed with multivariate logistic regression to identify independent variables of the false negativity.

Results

The cytological findings in UGFNA

A total of 115 patients received UGFNA in this study. Of them, Positive malignant cells were found in 27 patients, suspicious malignant cells in 14, follicular lesions in 3, benign cells in 63, and undiagnosable cases in 8 (**Table 1**). Of patients with benign cells, nodular goiter was found in 24 patients, toxic nodular goiter in 4, subacute thyroiditis in 6, subacute granulomatous thyroiditis in 3, Hashimoto's thyroiditis in 8, no tumor cells detected in 15, adenoma in 1, hyperthyroidism with adenomatoid hyperplasia nodules in 1, and nodular goiter with adenomatous hyperplastic nodules in 1. Of patients with positive cytological results, thyroid lymphoma was found in 4 patients, and thyroid papillary carcinoma was noted in 37.

Post-operative pathological results and clinical results in follow up

Of 44 patients with positive cytological results, post-operative pathological examination showed malignant cells in 41 patients and benign

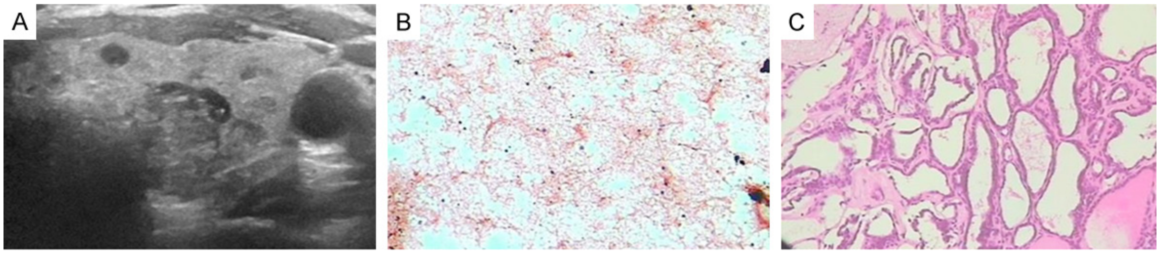

Figure 3. A 51-year-old woman with solid thyroid nodule in the right lobe. The nodule had the maximum diameter of 12 mm. A. Ultrasound examination showed hypoechogenicity, well-defined irregular margin, taller-than-wide shape and microcalcification in the nodule. B. The cytological examination after UGFNAC shows nodular goiter (hematoxylin and eosin [H&E] staining, magnification ×100). C. Pathological examination after thyroidectomy shows thyroid papillary microcarcinoma (0.2 cm) (H&E, magnification ×200).

cells in 3 patients (follicular epithelium of the papillary atypical hyperplasia in 1 and denomas in 2 patients). Of 71 patients with cytological negative results, 28 patients underwent surgery during the follow-up period, of whom malignant nodules were found in 14 patients (false-negative results were noted in these patients [**Table 2**]) and benign nodules in 14 (subacute granulomatous thyroiditis in 3, Hashimoto's thyroiditis in 3, toxic goiter in 1, and nodular goiter in 7 patients); remaining 43 patients received follow-up by ultrasound examination for more than 1 year and no significant change was observed (thyroid nodules were regarded as being benign). Thus, a total of 55 patients were diagnosed with malignant thyroid nodules, of whom postoperative pathology confirmed thyroid papillary carcinoma in 50, thyroid lymphoma in 4 and thyroid follicular adenoma with local malignant transformation in 1 patient (**Table 3**).

Diagnostic performance of UGFNA

Pathological results and clinical results confirmed by follow up were regarded as the standard. Our results showed the diagnostic accuracy rate of UGFNA was 85.2% (98/115), the sensitivity, specificity, PPV, and NPV of UGFNA were 74.5% (41/55), 95% (57/60), 93.2% (41/44), and 80.3% (57/71), AUC was 0.848, SE and 95%CI were 0.0371, (0.769, 0.908), P< 0.0001 (**Figure 2**), respectively. These suggest that UGFNA have a high consistency with the final results (**Table 4**).

False-negative cases in UGFNA

False-negative results were found in 14 patients (12.2%) by UGFNAC: papillary microcarcinomas (n=7; 50%); follicular variant of papillary carcinoma (n=2; 14.3%); papillary carcinoma (classical) (n=4; 28.6%); thyroid follicular adenoma with local malignant transformation (n= 1; 7.1%). The age, sex, UGFNA results and histological results are summarized in **Table 2**). **Figure 3** shows a case of false-negative results in UGFNAC.

Factors related to the false negativity in UGFNA

UGFNAC results were compared with post-operative pathological examination, and then patients were classified as false negative, true negative and true positive groups. There are 14 patients in false negative group (preoperative benign results and post-operative malignant results), 14 in true negative group (preoperative and post-operative benign results) and 41 in true positive group (preoperative and post-operative malignant results). The ultrasound characteristics were compared by using univariate analysis among three groups. The maximum diameter, taller-than-wide shape, margin, and calcifications of the nodules were related to the false negativity, but there were no significant differences in sex, age, multiple or solitary nodule, echotexture and blood flow pattern (**Table 5**). The ultrasound chracteristics with statistical significance in univariate analysis were analysed with multivariate logistic regression to identify independent predictors (**Table 6**), which were the maximum diameter and calcifications with a mode of Y=0.0452-0.964X1+ 0.459X2 (maximum diameter was X1, and calcifications was X2).

Discussion

Aspiration biopsy of thyroid and neck mass was first proposed in 1930 by Martin and Ellis [7],

Table 5. Factors related to the false negativity of UGFNA

Factors	FNG (%)	TNG (%)	TPG (%)	χ^2/F	*P* value
Sex					
Male	1 (7%)	4 (29%)	15 (37%)	5.272	0.072
Female	13 (93%)	10 (71%)	26 (63%)		
Age					
Mean ± SD (years)	43±12.8	40.5±13.1	41.0±18.1	0.109*	0.897
Maximum diameter					
Mean ± SD (cm)	1.4±0.8	2.3±1.3	2.6±2.5	10.106*	0.006
Nodule number					
Multiple	7 (50%)	7 (50%)	28 (68%)	2.337	0.311
Solitary	7 (50%)	7 (50%)	13 (32%)		
Nodule margin					
Well-defined	11 (79%)	5 (36%)	31 (76%)	8.036	0.018
Ill-defined	3 (21%)	9 (64%)	10 (24%)		
Shape					
Regular	2 (14%)	3 (27%)	2 (5%)	3.285	0.193
Irregular	12 (86%)	11 (73%)	39 (95%)		
Echogenic pattern					
Hypoechoic	11 (79%)	7 (5%)	26 (63%)	11.439	0.076
Isoechoic	0 (0%)	0 (5%)	5 (12%)		
Inhomogeneous	2 (14%)	6 (43%)	10 (25%)		
Hyperechoic	1 (7%)	1 (7%)	0 (0%)		
Calcifications					
No	3 (21%)	11 (79%)	11 (27%)	18.315	0.019
Microcalcifications	4 (29%)	1 (7%)	20 (49%)		
Macrocalcifications	2 (14%)	1 (7%)	3 (7%)		
Coarse calcifications	4 (29%)	1 (7%)	5 (12%)		
Rim calcifications	1 (7%)	0 (0%)	2 (5%)		
Blood flow pattern					
None	11 (78.6%)	7 (50%)	25 (61%)	11.096	0.085
Peripheral only	0 (0%)	2 (14.3%)	0 (0%)		
Central	1 (7.1%)	0 (0%)	4 (9.7%)		
Chaotic	2 (14.3%)	5 (35.7%)	12 (29.3%)		
Taller-than-wide shape					
No	9 (64.3%)	14 (100%)	27 (65.9%)	6.687	0.035
Yes	5 (35.7%)	0 (%)	14 (34.1%)		
Hypoechoic halo					
No	12 (85.7%)	14 (100%)	34 (82.9%)	4.474	0.107
Yes	2 (14.3%)	0 (%)	7 (17.1%)		

Notes: FNG, false negative group; TNG, true negative group; TPG, True positive group. *, F value.

and has been accepted and applied in clinical practice since 1980s. With the development of color Doppler ultrasound technology, ultrasound can clearly display the location, size, and surrounding tissues of the thyroid, which is helpful for the real time guidance of thyroid puncture. Thus, puncture under the guidance of ultrasound has a high safety. To date, UGFNA of the thyroid nodule has been an accurate, effective and economic method in the diagnosis of thyroid nodules, which may reduce the need for additional imaging and unnecessary surgery [8, 9].

Thyroid nodules are very common in general population, a majority of thyroid nodules is benign, and malignant thyroid nodules account for only 5%-15% [10]. In the present study, 61.7% (71/115) of patients were diagnosed with benign nodules and 38.3% (44/115) with malignant ones by cytological examinations. There is evidence showing that great improving the detection rate of malignant and also reduce the unnecessary puncture through the risk assessment. Hence risk stratification is essential before biopsying them [11]. In order to avoid over-treatment, identification of benign nodules from malignant nodules is of great importance. UGFNA is a great tool for the differential diagnosis on thyroid nodules, reducing the unnecessary surgery, in the present study, the malignant results were found in 47.8% (55/115) of patients, of whom thyroid papillary carcinoma was noted in 50 patients (90.9%; 50/55). This indicates that papillary carcinoma is the most common malignant thyroid nodule and UGFNA has a high PPV for papillary thyroid carcinoma. Pathology in the diagnosis of thyroid cancer mainly depends on the structural changes in the nucleus. cytological smear can more clearly display the structure of the nucleus than the histopathology did

Table 6. Multivariate logistic regression results for false negativity in UGFNA

	β	SE	Wald x^2	P	OR	95% CI
Maximum diameter	-0.964	0.474	4.146	0.04	0.381	0.151, 0.965
Nodule margin	-1.062	1.059	1.006	0.32	0.346	0.043, 2.755
Calcifications	0.459	0.235	3.821	0.05	1.582	0.999, 2.506
Taller-than-wide shape	0.206	0.718	0.082	0.77	1.229	0.301, 5.023

Notes: maximum diameter as X1; calcifications as X2. Mode: Y=0.0452-0.964X1+0.459X2.

[12], which can be employed for the early diagnosis. Thus, UGFNA cytology is the gold standard in the preoperative diagnosis of thyroid nodules. UGFNA is usually performed on ultrasonographically suspicious nodules for further treatment stratification or the thyroid with nodular change before surgery [13].

The sensitivity of UGFNA ranges between 65% and 98% and its specificity is about 73-100% [14-17]. Muratli et al [18] reported that the sensitivity and specificity of UGFNA were 87.1% and 64.6%, respectively, and the PPV, NPV and accuracy rate were 76.1%, 79.5%, and 77.3%, respectively. In this study, the sensitivity and specificity of UGFNA were 74.5%, and 95%, respectively, and the PPV, NPV and accuracy rate were 93.2%, 80.3%, and 85.2%, respectively, which were consistent with previously reported. However, UGFNA still has limitations in the diagnosis of the thyroid. As shown in previous studies, the false-negative rate of UGFNA was reported to be between 1% and 7.3% and false-positive rate was about 1%-15.5% [14, 15, 18, 19]. In the present study, results showed the false-positive rate was 2.6% and the false-negative rate was 12.2%, suggesting a lower false-positive rate of UGFNA as compared to previously reported. Samulski et al [20] reported that the false negative rate of FNA was 14.3%, which was consistent with our findings. **Table 2** showed the final pathological results of false-negative nodules in cytology. PTMC was found in 50% (7/14) of patients with false-negative results, PC in 28.6% (4/14), FVPC in 14.3% (2/14) and FALMT in 7.1% (1/14). The false-negativity in these 14 cases might be ascribed to the unskilled technique, small size of the nodular lesion, focal localization of the lesion, insufficient tissues sampled due to concern of focal bleeding, local lesion necrosis secondary to by degeneration. This reflects UGFNA has limited performance in the accurate diagnosis of PTMC. Therefore, to improve the puncture technique is one of important way to increase the diagnostic accuracy of UGFNA, and elevating the diagnostic cytopathology is also critical [4].

In the present study, results showed small nodular size, taller-than-wide shape, well-defined margin, microcalcification and coarse calcification were related to the false-negativity of UGFNA (**Table 5**), among which the maximum diameter and calcifications were identified as independent predictors of the false-negativity of UGFNA by multivariate logistic regression analysis (**Table 6**). The size of thyroid nodules was compared among three groups, and results indicated that the smaller size of thyroid nodules tended to increase the likelihood of false-negativity, which was also supported by previous studies. Sakorafas et al [21] reported that it was difficult for the biopsy of small nodules which increased the sampling error. Microcalcifications are also common in malignant nodules. Coarse calcifications are thought to represent dystrophic calcifications in fibrous or necrotic nodules [22] and often seen in the nodules of multinodular goiter. Some investigators consider it a feature of benignity [23]. However, coarse calcifications are significantly associated with the false negativity of UGFNA in our study, which was also consistent with previously reported [24, 25]. Microcalcification or coarse calcification should thus be considered an indication for FN. Rare serious adverse reactions including trauma occur during UGFNA, and only a small number of patients have local pain, bleeding or infection after UGFNA [27]. In our study, adverse reactions were not observed, implying that UGFNA has a good safety. However, clinicians should also take cautions in the UGFNA to avoid the injury to the blood vessels, nerves and trachea; the puncture site should be pressurized for 10 min after patients must press; the pressurization time should be prolonged if the nodule is rich in blood flow.

In summary, UGFNA has a better accuracy in the diagnosis for thyroid nodules. Patients with negative results in UGFNA should be followed up, and also should focus on thyroid ultrasound risk stratification results and other clinical examination, if necessary, review or re-UGFNA [28], or even surgery are required to reduce the rate of missed diagnosis [29]. Our results suggest that the benign nodules in UGFNA should be viewed with caution as false-negative results, a close follow up or repeat UGFNA may be considered if UGFNA shows a benign thyroid nodule with small nodule size and microcalcification or coarse calcification.

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Disclosure of conflict of interest

None.

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References

[1] Russ G, Leboulleux S, Leenhardt L and Hegedus L. Thyroid incidentalomas: epidemiology, risk stratification with ultrasound and workup. Eur Thyroid J 2014; 3: 154-163.

[2] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM and Wartofsky L. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.

[3] Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedus L and Vitti P. American association of clinical endocrinologists, associazione medici endocrinologi, and European thyroid association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2010; 16 Suppl 1: 1-43.

[4] Kim MJ, Kim EK, Park SI, Kim BM, Kwak JY, Kim SJ, Youk JH and Park SH. US-guided fine-needle aspiration of thyroid nodules: indications, techniques, results. Radiographics 2008; 28: 1869-1886; discussion 1887.

[5] Howlett DC, Harper B, Quante M, Berresford A, Morley M, Grant J, Ramesar K and Barnes S. Diagnostic adequacy and accuracy of fine needle aspiration cytology in neck lump assessment: results from a regional cancer network over a one year period. J Laryngol Otol 2007; 121: 571-579.

[6] Mamoon N, Jamy R and Khan AH. Evaluation of fine needle aspiration cytology as a screening tool in thyroid lesions. J Pak Med Assoc 2013; 63: 1120-1123.

[7] Martin HE and Ellis EB. Biopsy by needle puncture and aspiration. Ann Surg 1930; 92: 169-181.

[8] Wu HH, Jones JN and Osman J. Fine-needle aspiration cytology of the thyroid: ten years experience in a community teaching hospital. Diagn Cytopathol 2006; 34: 93-96.

[9] Yang J, Schnadig V, Logrono R and Wasserman PG. Fine-needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. Cancer 2007; 111: 306-315.

[10] Yoon JH, Lee HS, Kim EK, Moon HJ and Kwak JY. Malignancy risk stratification of thyroid nodules: comparison between the thyroid imaging reporting and data system and the 2014 American thyroid association management guidelines. Radiology 2016; 278: 917-924.

[11] Franco Uliaque C, Pardo Berdun FJ, Laborda Herrero R and Lorenz CP. Usefulness of ultrasonography is the evaluation of thyroid nodules. Radiologia 2016; 58: 380-388.

[12] Crippa S, Mazzucchelli L, Cibas ES and Ali SZ. The Bethesda system for reporting thyroid fine-needle aspiration specimens. Am J Clin Pathol 2010; 134: 343-344; author reply 345.

[13] Feldkamp J, Fuhrer D, Luster M, Musholt TJ, Spitzweg C and Schott M. Fine needle aspiration in the investigation of thyroid nodules. Dtsch Arztebl Int 2016; 113: 353-359.

[14] Bagga PK and Mahajan NC. Fine needle aspiration cytology of thyroid swellings: how useful and accurate is it? Indian J Cancer 2010; 47: 437-442.

[15] Haberal AN, Toru S, Ozen O, Arat Z and Bilezikci B. Diagnostic pitfalls in the evaluation of fine needle aspiration cytology of the thyroid: correlation with histopathology in 260 cases. Cytopathology 2009; 20: 103-108.

[16] Amrikachi M, Ramzy I, Rubenfeld S and Wheeler TM. Accuracy of fine-needle aspiration of thyroid. Arch Pathol Lab Med 2001; 125: 484-488.

[17] Gharib H and Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med 1993; 118: 282-289.

[18] Muratli A, Erdogan N, Sevim S, Unal I and Akyuz S. Diagnostic efficacy and importance of fine-needle aspiration cytology of thyroid nodules. J Cytol 2014; 31: 73-78.
[19] Layfield LJ, Reichman A, Bottles K and Giuliano A. Clinical determinants for the management of thyroid nodules by fine-needle aspiration cytology. Arch Otolaryngol Head Neck Surg 1992; 118: 717-721.
[20] Samulski TD, Shutty C, LiVolsi VA, Montone K and Baloch Z. The reliability of thyroid nodule ultrasound features and size to predict malignancy in fine needle aspiration specimens: Practical utility for the evaluating pathologist. Diagn Cytopathol 2015; 43: 471-477.
[21] Sakorafas GH. Thyroid nodules; interpretation and importance of fine-needle aspiration (FNA) for the clinician-practical considerations. Surg Oncol 2010; 19: e130-139.
[22] Anil G, Hegde A and Chong FH. Thyroid nodules: risk stratification for malignancy with ultrasound and guided biopsy. Cancer Imaging 2011; 11: 209-223.
[23] Park CS, Kim SH, Jung SL, Kang BJ, Kim JY, Choi JJ, Sung MS, Yim HW and Jeong SH. Observer variability in the sonographic evaluation of thyroid nodules. J Clin Ultrasound 2010; 38: 287-293.
[24] Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, Cronan JJ, Doubilet PM, Evans DB, Goellner JR, Hay ID, Hertzberg BS, Intenzo CM, Jeffrey RB, Langer JE, Larsen PR, Mandel SJ, Middleton WD, Reading CC, Sherman SI and Tessler FN. Management of thyroid nodules detected at US: society of Radiologists in ultrasound consensus conference statement. Radiology 2005; 237: 794-800.
[25] Kim BK, Choi YS, Kwon HJ, Lee JS, Heo JJ, Han YJ, Park YH and Kim JH. Relationship between patterns of calcification in thyroid nodules and histopathologic findings. Endocr J 2013; 60: 155-160.
[26] Yoon SJ, Yoon DY, Chang SK, Seo YL, Yun EJ, Choi CS, Bae SH. "Taller-than-wide sign" of thyroid malignancy: comparison between ultrasound and CT. AJR Am J Roentgenol 2010; 194: w420-424.
[27] Polyzos SA and Anastasilakis AD. Systematic review of cases reporting blood extravasation-related complications after thyroid fine-needle biopsy. J Otolaryngol Head Neck Surg 2010; 39: 532-541.
[28] Maia FF, Matos PS, Pavin EJ, Vassallo J and Zantut-Wittmann DE. Value of repeat ultrasound-guided fine-needle aspiration in thyroid nodule with a first benign cytologic result: impact of ultrasound to predict malignancy. Endocrine 2011; 40: 290-296.
[29] Cibas ES and Ali SZ. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2009; 132: 658-665.