ULTRASONOGRAPHY

Combined fine-needle aspiration with core needle biopsy for assessing thyroid nodules: a more valuable diagnostic method?

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Purpose: This study aimed to evaluate the diagnostic value of combined fine-needle aspiration (FNA) with core needle biopsy (CNB) in thyroid nodules.

Methods: FNA and CNB were performed simultaneously on 703 nodules. We compared the proportions of inconclusive results and the diagnostic performance for malignancy among FNA, CNB, and combined FNA/CNB for different nodule sizes.

Results: Combined FNA/CNB showed lower proportions of inconclusive results than CNB for all nodules (2.8% vs. 5.7%, P<0.001), nodules ≤1.0 cm (4.9% vs. 7.3%, P=0.063), nodules >1.0 cm (2.0% vs. 5.0 %, P<0.001), nodules ≤1.5 cm (3.8% vs. 7.9 %, P<0.001), and nodules >1.5 cm (2.1% vs. 3.9 %, P=0.016). The sensitivity of combined FNA/CNB in predicting malignancy was significantly higher than that of CNB (89.0% vs. 80.0%, P<0.001) and FNA (89.0% vs. 58.1%, P<0.001) for all nodules. Within American College of Radiology Thyroid and Imaging Reporting and Data System grades 4–5, in the subgroup of nodules ≤1.5 cm, combined FNA/CNB showed the best sensitivity in predicting malignancy (91.4%), significantly higher than that of CNB (81.0%, P<0.001) and FNA (57.8%, P<0.001). However, in the subgroup of nodules >1.5 cm, the difference between combined FNA/CNB and CNB was not significant (84.2% vs. 78.9%, P=0.500).

Conclusion: Regardless of nodule size, combined FNA/CNB tended to yield lower proportions of inconclusive results than CNB or FNA alone and exhibited higher performance in diagnosing malignancy. The combined FNA/CNB technique may be a more valuable diagnostic method for nodules ≤1.5 cm and nodules with a risk of malignancy than CNB and FNA alone.

Keywords: Thyroid nodule; Biopsy; Fine-needle aspiration; Core needle biopsy; Ultrasonography

Key points: Combined fine-needle aspiration (FNA)/core needle biopsy (CNB) achieved a lower proportion of inconclusive results and more effective diagnostic performance than FNA and CNB alone. CNB alone may suffice without the addition of FNA in thyroid nodules >1.5 cm and American College of Radiology Thyroid and Imaging Reporting and Data System (ACR TI-RADS) 4–5 or in ACR TI-RADS 1–3 nodules. For nodules ≤1.5 cm with a risk of malignancy (ACR TI-RADS 4–5), the combined FNA/CNB technique may be a more valuable diagnostic method.

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Introduction

With the popularization of ultrasound imaging technology in thyroid nodule screening and the application of thermal ablation technology in treating benign thyroid nodules [1,2], a more effective and accurate biopsy method, either for the assessment of the malignancy risk in thyroid nodules or for the requirement of pathological diagnosis before thermal ablation, has consistently been the focus of clinical research on thyroid nodules.

Fine-needle aspiration (FNA) is the most commonly used tool for diagnosing thyroid nodules because of its convenience, safety, and effectiveness [3–5]. However, FNA also has some limitations, such as its relatively high proportion of inaccurate or inconclusive results [6–8] and its inadequacy for the preoperative management of follicular thyroid carcinoma, lymphoma, medullary carcinoma, and other malignant tumours [9–13]. In those cases, repeat FNAs or even surgery is essential. Unfortunately, repeat FNAs also have a high rate of inconclusive results, and some operations are performed unnecessarily [14–16]. In recent years, several studies have shown that core needle biopsy (CNB) has the potential to be an effective alternative first-line diagnostic tool for thyroid nodules by an experienced operator [9,17–20]. Compared to FNA, CNB significantly reduces the proportion of inconclusive results and has better diagnostic efficacy, and CNB is not associated with any obvious complications [21–23]. However, there will still be inconclusive results in varying degrees or insufficient efficacy in diagnosing malignancies when using CNB [24–26].

Previous studies have focused on comparisons between FNA and CNB, but there are differences in methods and techniques between the two tools. Whether the differences between these tools can become complementary conditions is worth exploring. Consequently, this retrospective study was conducted to determine whether the combination of FNA and CNB is more effective than either modality alone.

Materials and Methods

Compliance with Ethical Standards

The Institutional Review Board of the Second Affiliated Hospital of Shantou University Medical College approved this retrospective study (IRB: 2022-010), and the requirement for informed consent to obtain the clinical data was waived.

Study Population

From February 2018 to September 2021, all candidates for thyroid biopsy at the authors' centre were routinely recommended for combined diagnosis. In this study, the patient inclusion criteria were as follows: (1) biopsy due to a risk of malignancy according to the American College of Radiology Thyroid and Imaging Reporting and Data System (ACR TI-RADS); and (2) the need for preoperative pathology results prior to microwave ablation treatment. Patients who did not have a final clinical diagnosis were excluded from the study if they (1) were lost to follow-up or (2) had no postoperative pathology.

Based on previous research, we established the following diagnostic criteria for thyroid nodules [27–29]. A final diagnosis of malignancy was based on the results of the histopathologic examinations from surgical resections or on the FNA and/or CNB findings after immunohistochemistry. A benign nodule was ultimately diagnosed if one of the following conditions was met: the diagnosis was made at surgery; both the FNA and CNB yielded benign results; or the initial biopsy or repeat biopsy had at one benign result on either CNB or FNA, without any indeterminate or malignant results. The biopsy results were not considered benign if they showed a benign result and either an indeterminate (category III, IV, V) or malignant (category VI) result. In addition, a histopathologic examination of surgically resected tissue was required if one of the following conditions occurred: a combination of category III or IV with category I, II, III, or IV; or a combination of category I with category I, III, or IV.

Ultrasound-Guided FNA and CNB Procedures

The FNA and CNB procedures were performed by two interventional ultrasound physicians with more than 10 years of clinical experience. The ultrasound examinations and guidance were performed using 1 of 2 ultrasound systems: LOGIQ E9 (GE Healthcare, Chicago, IL, USA) with a linear high-frequency probe (ML6-15) and RS80A (Samsung Healthcare, Seoul, Korea) with a linear high-frequency probe (L3-12A). The ultrasound examinations were performed to observe the nodules and surrounding structures and to determine the puncture path before biopsy. All nodules were punctured in a cross-section or near cross-section with a freehand technique. After informed consent was obtained from the patient, FNA was first performed with a 23-gauge needle (Gallini SRL, Modena, Italy). FNA was performed using a thin-prep cytology test, and at least one sample was obtained from each nodule. After FNA, CNB was performed after confirming that there was no obvious bleeding. For CNB, a disposable 18-gauge, single- or double-action spring-activated needle (1.5-cm excursion; Bard Peripheral Vascular, Inc., Tempe, AZ, USA) was used to routinely remove 1 or 2 tissue specimens. Finally, the specimens were fixed with formalin for pathological examination. The patients were allowed to put pressure on the puncture site for 30 minutes and were required to stay in the observation room for 2 hours after the operation, and they could

leave after they had confirmed that they had no discomfort.

Cytological and Histological Analysis

The FNA cytological specimens and CNB histological specimens were retrospectively evaluated by two pathologists using a double-blind method. The FNA cytological diagnoses were classified into six categories according to the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) [30]. The CNB diagnostic criteria for thyroid nodules have not been standardized. Based on the histopathological results of FNA, the histological diagnoses of CNB were divided into the same six categories as the BSRTC [27,31]. The immunohistochemical results were not considered in the classification of the CNB histopathological results.

According to the recommendations of previous studies [28,29], in our study, the combined diagnostic criteria of FNA and CNB were defined as the same six categories as the BSRTC (Table 1). The combined diagnosis was categorized as a nondiagnostic result when both FNA and CNB produced a nondiagnostic result. When either FNA or CNB showed a benign lesion and the other test's results were not classified as category IV, V, or VI, the combined diagnosis was classified as benign. When the FNA or CNB result was category III and the other result did not belong to category II, IV, V, or VI, the combined diagnosis was defined as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). A combined diagnosis of follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN) was also determined when the FNA or CNB result was category IV and the other result did not belong to either category V or VI. When the FNA or CNB result was category V and the other did not belong to category VI, the combined diagnosis was suspicious for malignancy. When the FNA or CNB result showed a category VI tumour, the combined diagnosis was also defined as malignancy.

Table 1. Combined diagnostic criteria of the FNA/CNB results

Combined FNA/CNB	FNA	CNB
Nondiagnostic	I	I
Benign	II	I/II/III
	I/II/III	II
AUS/FLUS	III	I/III
	I/III	III
FN/SFN	IV	I/II/III/IV
	I/II/III/IV	IV
Suspicious for malignancy	V	I/II/III/IV/V
	I/II/III/IV/V	V
Malignancy	VI	I/II/III/IV/V/VI
	I/II/III/IV/V/VI	VI

FNA, fine-needle aspiration; CNB, core needle biopsy; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for a follicular neoplasm.

Data Analysis and Statistics

In our study, the nodules diagnosed as pathological category I (nondiagnostic) and category III (AUS/FLUS) were defined as inconclusive results. In addition, the malignancy criterion was defined as a diagnostic result indicative of malignancy (BSRTC category V/VI) [29,32]. The McNemar test was used to compare the various pathological diagnostic results, inconclusive results, and diagnostic sensitivity for malignancy among FNA, CNB, and combined FNA/CNB. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Demographic Data

A total of 703 nodules from 703 patients were included in this retrospective study (581 women and 122 men; mean age, 45±14 years; range, 11 to 82 years). The average size (maximum diameter) of the 703 thyroid nodules analyzed was 13.8±10.2 mm. Of the 703 nodules, 290 were classified as low-risk for malignancy (ACR TI-RADS 1–3), while the remaining 413 were classified as high-risk for malignancy (ACR TI-RADS 4–5). Overall, 155 nodules were diagnosed as malignant based on the histopathologic readings from surgical resection (n=56, 36.1%) or were diagnosed as malignant by FNA and/or CNB (n=99, 63.9%). In total, 548 nodules were finally diagnosed as benign nodules; they were determined by surgical diagnosis (n=75, 13.7%), both benign results on FNA and CNB (n=373, 68.1%), and one benign diagnosis on CNB combined with one nondiagnostic finding on FNA that had been stable size at least 12 months of follow-up (n=100, 18.2%).

The Final Diagnosis of Each Combined FNA/CNB Result and the Corresponding Malignancy Rates of the Nodules

Table 2 lists the FNA and CNB results for each nodule. Out of the 703 nodules, 239 nodules (34%) showed inconsistent results between FNA and CNB. Among these nodules, the group of 81 nodules (11.5%) with a category V or VI result had a malignancy rate of 100%; the group of 19 nodules (2.7%) with one of the results in category IV had a malignancy rate from 0%–100%. The group of 11 nodules (11.5%) with a category I FNA result and a category CNB III result had a malignancy rate of 72.7%; the group of 138 nodules (19.6%) with a category II result and a category I/II/III result had a malignancy rate of 0%. The remaining 464 nodules (66%) obtained consistent results between FNA and CNB, and the

malignancy rates of category I, category II, category III, category IV, category V, and category VI nodules were 0%, 0%, 66.7%, 20%, 100%, and 100%, respectively.

Table 2. The final diagnosis of each combined FNA/CNB result and the corresponding malignancy rates in the nodules

Diagnostic result		Final diagnosis (n=703)		Malignancy rate (%)
FNA	CNB	Benign (n=548)	Malignancy (n=155)	
Nondiagnostic	Nondiagnostic	3	0	0
Nondiagnostic	Benign	109	0	0
Nondiagnostic	AUS/FLUS	3	8	72.7
Nondiagnostic	FN/SFN	2	0	0
Nondiagnostic	Suspicious malignancy	0	12	100
Nondiagnostic	Malignant	0	11	100
Benign	Nondiagnostic	9	0	0
Benign	Benign	383	0	0
Benign	AUS/FLUS	5	0	0
Benign	FN/SFN	8	2	20
Benign	Suspicious malignancy	0	5	100
Benign	Malignant	0	2	100
AUS/FLUS	Benign	15	0	0
AUS/FLUS	AUS/FLUS	2	4	66.7
AUS/FLUS	FN/SFN	0	1	100
AUS/FLUS	Suspicious malignancy	0	10	100
AUS/FLUS	Malignant	0	8	100
FN/SFN	Benign	5	1	16.7
FN/SFN	FN/SFN	4	1	20
Suspicious malignancy	Benign	0	1	100
Suspicious malignancy	AUS/FLUS	0	1	100
Suspicious malignancy	Suspicious malignancy	0	12	100
Suspicious malignancy	Malignant	0	4	100
Malignant	Nondiagnostic	0	1	100
Malignant	Benign	0	6	100
Malignant	AUS/FLUS	0	4	100
Malignant	FN/SFN	0	1	100
Malignant	Suspicious malignancy	0	5	100
Malignant	Malignant	0	55	100

FNA, fine-needle aspiration; CNB, core needle biopsy; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for a follicular neoplasm.

Comparison of the Diagnostic Categories among FNA, CNB, and Combined FNA/CNB

The diagnostic results of FNA, CNB, and combined FNA/CNB are summarized in Table 3. Combined FNA/CNB showed significantly lower proportions of nondiagnostic and AUS/FLUS results than FNA or CNB (P=0.002) and a significantly higher proportion of malignancy results than FNA or CNB (P<0.001). Combined FNA/CNB showed significantly higher proportions of benign, FN/SFN, and suspicious for malignancy results than FNA (benign and suspicious for malignancy, P<0.001; AUS/FLUS, P=0.001, respectively). However, there were no significant differences in the benign, FN/SFN, and suspicious proportions between CNB and combined FNA/CNB (benign, P>0.999; AUS/FLUS, P=0.125; and suspicious for malignancy, P=0.453, respectively).

Comparison of Inconclusive Results among the FNA, CNB, and Combined FNA/CNB Diagnoses

Table 4 shows the inconclusive diagnostic results of FNA, CNB, and combined FNA/CNB. Inconclusive results for FNA, CNB, and combined FNA/CNB accounted for 26.7%, 5.7%, and 2.8% of the nodules, respectively. Combined FNA/CNB showed significantly lower proportions of inconclusive results than CNB in all nodules (P<0.001), nodules with size >1.0 cm (P<0.001), nodules with size ≤1.5 cm (P<0.001), and nodules with size >1.5 cm (P=0.016). However, there were no significant differences between CNB and combined FNA/CNB in the proportion of inconclusive nodules with size ≤1.0 cm (P=0.063). Additionally, CNB and combined FNA/CNB showed significantly lower proportions of inconclusive results than FNA (P<0.001), regardless of the nodule size.

Comparison of the Diagnostic Performance for Malignancy among FNA, CNB, and Combined FNA/CNB

The sensitivity of combined FNA/CNB in predicting malignancy was significantly higher than that of FNA and CNB alone for all nodules (P<0.001), nodules with ACR TI-RADS 4–5 (P<0.001), nodules with size ≤1.0 cm with ACR TI-RADS 4–5 (combined FNA/CNB vs. FNA, P<0.001; combined FNA/CNB vs. CNB, P=0.031), nodules with size >1.0 cm and ACR TI-RADS 4–5 (combined FNA/CNB vs. FNA, P<0.001; combined FNA/CNB vs. CNB, P=0.008), and nodules with size ≤1.5 cm with ACR TI-RADS 4–5 (P<0.001). The sensitivity of combined FNA/CNB in predicting malignancy was also significantly higher than that of FNA alone for nodules with size >1.5 cm and ACR TI-RADS 4–5 (P=0.004). However, there was no significant difference in sensitivity between combined FNA/CNB and CNB alone in predicting malignancy for nodules with size >1.5 cm and ACR TI-RADS 4–5 (P=0.050).

The sensitivity of CNB alone in predicting malignancy was

Table 3. Comparison of the diagnostic categories among FNA, CNB, and combined FNA/CNB

Diagnosis (category)	No. (%)			P-value		
	FNA	CNB	FNA/CNB	FNA vs. CNB	FNA vs. FNA/CNB	CNB vs. FNA/CNB
Nondiagnostic	148 (21.0)	13 (1.8)	3 (0.4)	<0.001	<0.001	0.002
Benign	414 (58.9)	520 (74.0)	521 (74.1)	<0.001	<0.001	>0.999
AUS/FLUS	40 (5.7)	27 (3.8)	17 (2.4)	0.105	0.001	0.002
FN/SFN	11 (1.6)	19 (2.7)	24 (3.4)	0.115	<0.001	0.125
Suspicious malignancy	18 (2.6)	44 (6.3)	41 (5.9)	<0.001	<0.001	0.453
Malignant	72 (10.2)	80 (11.4)	97 (13.8)	0.280	<0.001	<0.001

FNA, fine-needle aspiration; CNB, core needle biopsy; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for a follicular neoplasm.

Table 4. Comparison of the inconclusive results among the FNA, CNB, and combined FNA/CNB diagnoses

Diagnosis (inconclusive results)	No. (%)			P-value		
	FNA	CNB	FNA/CNB	FNA vs. CNB	FNA vs. FNA/CNB	CNB vs. FNA/CNB
All nodule sizes (n=703)	188 (26.7)	40 (5.7)	20 (2.8)	<0.001	<0.001	<0.001
Nodule size ≤1.0 cm (n=205)	73 (35.6)	15 (7.3)	10 (4.9)	<0.001	<0.001	0.063
Nodule size >1.0 cm (n=498)	115 (23.1)	25 (5.0)	10 (2.0)	<0.001	<0.001	<0.001
Nodule size ≤1.5 cm (n=316)	101 (32.0)	25 (7.9)	12 (3.8)	<0.001	<0.001	<0.001
Nodule size >1.5 cm (n=387)	87 (22.5)	15 (3.9)	8 (2.1)	<0.001	<0.001	0.016

FNA, fine-needle aspiration; CNB, core needle biopsy.

Table 5. Comparison of the diagnostic sensitivity for malignancy among FNA, CNB, and combined FNA/CNB

Diagnostic sensitivity for malignancy	FNA	CNB	FNA/CNB	P-value		
				FNA vs. CNB	FNA vs. FNA/CNB	CNB vs. FNA/CNB
All nodules (n=703)	58.1 (90/155)	80.0 (124/155)	89.0 (138/155)	<0.001	<0.001	<0.001
Nodules with ACR TI-RADS 1–3 (n=290)	0 (0/1)	0 (0/1)	0 (0/1)	NA	NA	NA
Nodules with ACR TI-RADS 4–5 (n=413)	58.4 (90/154)	80.5 (124/154)	89.6 (138/154)	<0.001	<0.001	<0.001
Nodules with size ≤1.0 cm and ACR TI-RADS 4–5 (n=188)	54.7 (47/86)	83.7 (72/86)	90.7 (78/86)	<0.001	<0.001	0.031
Nodules with size >1.0 cm and ACR TI-RADS 4–5 (n=225)	63.2 (43/68)	76.4 (52/68)	88.2 (60/68)	<0.001	<0.001	0.008
Nodules with size ≤1.5 cm and ACR TI-RADS 4–5 (n=267)	57.8 (67/116)	81.0 (94/116)	91.4 (106/116)	<0.001	<0.001	<0.001
Nodules with size >1.5 cm and ACR TI-RADS 4–5 (n=146)	60.5 (23/38)	78.9 (30/38)	84.2 (32/38)	0.065	0.004	0.500

Values are percentages, with numerator and denominator in parentheses.
FNA, fine-needle aspiration; CNB, core needle biopsy; NA, not applicable.

significantly higher than that of FNA alone for all nodules; nodules with all sizes; nodules with sizes of ≤1.0 cm, >1.0 cm, or ≤1.5 cm; and ACR TI-RADS 4–5 nodules (all, P<0.001). However, there was no significant difference in sensitivity between CNB alone and FNA alone in predicting malignancy for nodules with size >1.5 cm and ACR TI-RADS 4–5 (P=0.065). A comparison of the diagnostic sensitivity for malignancy among FNA, CNB, and combined FNA/CNB is shown in Table 5.

The specificity of FNA alone, CNB alone, and combined FNA/CNB in predicting malignancy for all nodules (regardless of size) was 100%: all nodules, 100% (548/548); nodules with ACR TI-RADS 1–3, 100% (289/289); nodules with ACR TI-RADS 4–5, 100% (259/259); nodules with size ≤1.0 cm and ACR TI-RADS 4–5, 100% (102/102), nodules with size >1.0 cm and ACR TI-RADS 4–5, 100% (157/157); nodules with size ≤1.5 cm and ACR TI-RADS 4–5, 100% (151/151); nodules with size >1.5 cm and ACR TI-RADS 4–5, 100%

(108/108).

Complications

In total, 39 patients (5.5%) had minor complications; 35 patients had intrathyroidal haemorrhage or oedema after puncture, but these complications disappeared after applying compression for half an hour. During the puncture, four patients had vagal reflexes due to hypertension, and they recovered quickly after oxygen and rest. Other than these, no major complications (0.0%), such as serious bleeding, tracheal injury, nerve damage, needle implantation, or infection occurred in this study.

Discussion

Our retrospective study demonstrated that the combined FNA/CNB diagnosis provided a lower proportion of inconclusive results than either FNA or CNB alone, and the diagnostic efficiency for malignant nodules also significantly improved. Especially in the assessment of nodules with size ≤1.5 cm and ACR TI-RADS 4–5, the application of combined FNA/CNB yielded a better diagnostic performance for malignancy than that of FNA or CNB alone.

In our study, FNA had a higher proportion of inconclusive results, and this result was similar to many previous studies [33–35]. Even though a more experienced operator may yield a better specimen, the internal composition of the nodule and the sample size may still be obstacles [27,36]. There are several possible reasons why FNA had higher inconclusive results. First, FNA results are closely related to the internal composition of thyroid nodules. Calcification, cystic degeneration, and an abundant vascular supply can affect the quality of the puncture specimens. Second, the quality of the samples obtained from operators with different clinical experiences can also vary greatly. An operator who is more skilled in their puncture technique is more likely to obtain a more representative and accurate tissue sample. Third, the samples that are obtained from FNA are relatively small, so it is impossible to complete immunohistochemical tests with these types of samples. These limitations of FNA sample quality and quantity also directly affected the diagnostic efficacy of FNA for malignant nodules. In this study, the sensitivity of FNA in predicting malignancy was only 58.1%, which was disappointing.

In recent years, it has been suggested that CNB may be used as an alternative first-line diagnostic tool for thyroid nodules, especially for more experienced operators [18,24,29]. Our study showed that compared with FNA, with CNB, the proportion of inconclusive results was reduced by 21%, and the sensitivity and accuracy in predicting malignancy increased by 21.9% and 4.8%, respectively, indicating satisfactory results. For some nodules with obvious calcification or an abundant blood supply, it is difficult to obtain a sufficient number of valid specimens using FNA. When a nodule is covered with calcified tissue, it is difficult for the fine needle to penetrate the nodule to access the tissue for sampling, and when the nodule has an abundant blood supply, a large number of blood cells are aspirated, resulting in an insufficient amount of follicular cells. In those cases, using a core needle can penetrate the target nodule to obtain a larger tissue sample, which not only provides more information about the internal structure and capsule of the nodules, but also provides additional immunohistochemical staining data for the differential diagnosis [37–39].

With reference to previous studies [18,28,29], and combined with the final malignant probability of the combined diagnosis, criteria for the combined diagnosis were formulated. The results showed that the combined diagnosis yielded a lower proportion of inconclusive results and a higher malignancy diagnosis efficiency than either FNA or CNB alone, suggesting that FNA and CNB can complement each other in terms of technology and methodology. This finding may be the result of the different methods and quantities of samples for FNA and CNB. First, the sampling methods were different. FNA was used to aspirate the target lesions directly, while CNB obtained specimens by reserving a certain forward stroke distance. Second, the specimens that were obtained via FNA versus CNB were different sizes. CNB can obtain a larger amount of tissue and more tissue samples than FNA, which could provide more information about the histological characteristics of the nodule, including the nodular capsule and the related cell nuclear features. Therefore, utilizing both methods to make a diagnosis combines the advantages of FNA and CNB, which contributes to the performance of the joint technique. In terms of inconclusive results, although the combined diagnosis was better than CNB alone, the reduced proportion of inconclusive results cannot be proportional to the procedural burden caused by the combined diagnosis, regardless of the nodule size. In this regard, it is suggested that CNB alone may be enough without the addition of FNA for the diagnosis of thyroid nodules, consistent with a recent study [29]. However, in terms of diagnostic performance for malignancy in thyroid nodules, the combined diagnosis shows more obvious advantages than CNB alone.

In this study, it was observed that the diagnostic specificity for malignancy reached 100%, regardless of nodule size or the diagnostic method used, which may be related to the diagnostic criteria. When the malignancy criteria are defined as diagnostic results indicative of BSRTC categories V and VI, the pathologist should identify typical malignant pathological changes before making a diagnosis. This may be the reason for the lack of false positives in the present research results, and similar findings can be

observed in previous studies [27,28]. Therefore, in cases of the same specificity, the diagnostic sensitivity for malignancy is particularly important. In this study, a total of 155 malignant nodules were diagnosed, of which 154 were ACR TI-RADS 4–5. Therefore, it is obviously unnecessary to advocate all nodules be subjected to the combined procedure to provide an efficiency diagnosis of malignancy. In the subclassification of nodule size, the combined diagnosis of nodules with size less than 1.5 cm and ACR TI-RADS 4–5 showed the best performance. The results showed that the sensitivity of the combined diagnosis reached 91.4%, an increase of 10.7% over CNB alone. In this study, 48 patients received a positive malignant diagnosis by using CNB, but the patients were misdiagnosed on FNA. Fourteen patients were confirmed to have malignant nodules by FNA, but those patients were misdiagnosed on CNB. Therefore, we reviewed the ultrasound images of the misdiagnosed nodules to search for possible causes. For the majority of the nodules at risk for malignancy, using CNB can obtain a larger sample size and more nodule information, resulting in more accurate results. However, for some small nodules, it is possible to obtain inaccurate sample information when using CNB due to the partial volume effect of ultrasound. There may be risk factors, such as haemorrhage, especially for small nodules located on the side of the thyroid envelope, near the inferior thyroid artery, or near the common carotid artery. During CNB, in order to keep a safe distance when using the needle tip, it is possible that the puncture needle may hit the target, but the needle slot does not take a valid sample, leading to a misdiagnosis. In contrast, during FNA, the operator can always control the needle tip inside the nodule to obtain the sample cells. In addition, nodules with malignancy risk are mostly lacking in blood supply, and a substantial amount of sample cells can be easily obtained via FNA. In such cases, FNA is superior to CNB. Therefore, a combined diagnosis can make the two technologies complement each other and can enhance the diagnostic efficiency. Unlike the largest malignant nodules, which had already been screened and treated, many malignant nodules based on exclusion findings are generally small. It is very important to improve the diagnostic sensitivity for malignant nodules, minimizing missed diagnoses to the greatest extent and thus avoiding further metastasis and deterioration of malignant nodules. In addition, CNB has been proven to be safe as an alternative first-line tool for thyroid diagnosis by an experienced operator, the incidences of which major complications have been reported to be as low as 0% to 0.09% [18,29,40]. In other words, it seems safe for experienced operators to add FNA to CNB, which has been verified in our research. Consequently, we believe that the combination of FNA and CNB may be a more valuable method to assess relatively small thyroid nodules at risk of malignancy.

Several limitations of this study should be addressed. First, this was a single-centre retrospective study. Some patients were excluded if they did not have a combined diagnosis or did not receive a final diagnosis, which might have led to case-selection bias. Moreover, not all of the final diagnoses of the patients were determined based on the postoperative pathology, which might have caused a small amount of error. Furthermore, the diagnostic criteria for the combined FNA/CNB diagnosis have not been standardized, especially for the combinations of categories II and III, and further research is needed to confirm the reliability of this standard. Finally, the development of major complications was prevented by the high level of experience of both operators in this study. However, the low degree of serious complications may not be applicable to other operators with different levels of experience in routine practice.

In summary, combined FNA/CNB can achieve a lower proportion of inconclusive results and a more effective diagnostic performance than FNA and CNB alone. For an experienced operator, to obtain the best procedural benefits, CNB alone may be enough without the addition of FNA in thyroid nodules with a size >1.5 cm and ACR TI-RADS 4–5 or nodules with ACR TI-RADS 1–3. However, for nodules with a size ≤1.5 cm and at risk of malignancy (ACR TI-RADS 4–5), to screen thyroid malignancies to the greatest extent and provide an accurate diagnostic basis for further clinical treatment, the combined FNA/CNB technique may be a more valuable and recommended diagnostic method.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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