

Diagnostic Value of Contrast-enhanced Ultrasound Combined with Fine Needle Aspiration Biopsy in Suspected Malignant Partially Cystic Thyroid Nodules

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Abstract

Objective: To investigate whether contrast-enhanced ultrasound (CEUS)- guided fine needle aspiration biopsy (FNAB) of suspected malignant partially cystic thyroid nodules can reduce the inadequate sampling rate and improve the diagnostic yield of suspected malignant partially cystic thyroid nodules. **Methods:** The fine needle aspiration biopsy data of suspected malignant partially cystic thyroid nodules identified for the first time and untreated in the First Affiliated Hospital of Jinan University from January 2018 to October 2020 was retrospectively analysed. A total of 176 nodules in 154 patients were included in this study, among which 101 nodules received CEUS-guided FNAB (the CEUS-FNAB group) and 75 nodules received color Doppler ultrasound-guided FNAB (FNAB group). **Results:** There was no statistical significance in the age, sex, nodule size, and categories of Thyroid Imaging, Reporting and Data System (TI-RADS) between the two groups. The inadequate sampling rate of the CEUS-FNAB group was significantly lower than that of the FNAB group (4.0% vs 30.7%, $P = 0.000$). The detection rate of the CEUS-FNAB group for malignancy was higher than that of the FNAB group (5.3% vs 14.9%, $P = 0.044$). The proportion of adequate cells obtained in the CEUS-FNAB group was significantly higher than that in the FNAB group (69.1% vs 44.2%, $P = 0.000$). **Conclusion:** Contrast-enhanced ultrasound-guided fine needle aspiration biopsy reduced the inadequate sampling rate of partially cystic thyroid nodules, increased the proportion of adequate cells obtained by puncture, and improved the diagnostic yield of suspected malignant partially cystic nodules. An accurate biopsy of suspected malignant partially cystic thyroid nodules can be achieved with contrast-enhanced ultrasound.

Keywords

Thyroid; Partially cystic thyroid nodules; Contrast-enhanced ultrasound; Fine needle aspiration biopsy.

1. Introduction

Partially cystic thyroid nodules (PCTNs) refer to thyroid nodules that have both solid and cystic portions. Most PCTNs are the result of degenerative change of benign thyroid nodules, and only a few PCTNs actually have epithelial tissue [1]. With the development of people's health awareness, thyroid ultrasound is increasingly used in the diagnosis of thyroid diseases, and the detection rate of thyroid diseases is also increasing year by year. The detection rate of thyroid nodules in the population is between 20% and 76%, of which malignant tumors account for between 7% and 15% [2-4]. Papillary carcinoma is the most common pathological type of malignant thyroid cancer, representing about 80% [5-6] of all thyroid cancer cases. Cystic change occurs in about 10% to 28% of papillary thyroid cancer [7], which means a considerable part of malignant thyroid tumors are partially cystic, and previous studies have shown that about 4.6% to 14.3% of PCTNs are malignant [8-10]. In a recent study, Shi et al. retrospectively

analyzed 338 cases of surgically confirmed partially cystic thyroid nodules, 50 of which were malignant, with a malignancy rate of about 14.8% [11]. The benign and malignant manifestations of PCTNs, such as the presence of calcific foci, the blood flow inside the nodules, and the ratio of cystic portion to the solid portion, overlap with each other. These manifestations are not very characteristic, which makes it difficult to accurately diagnose PCTNs and likely to result in misdiagnosis.

Fine needle aspiration biopsy (FNAB) is the most accurate and cost-effective examination for assessing thyroid nodules. It helps to reduce unnecessary thyroidectomy and determine the appropriate surgical plan [13-16]. However, the literature reported that the inadequate sampling rate of FNAB for thyroid nodules can reach 10%-25.5% [16-17], and the percentage of invalid specimens of partially cystic nodules with the ratio of the solid portion less than or equal to 50% can be as high as 80% [17], which requires a second needle biopsy or diagnostic surgical resection [16-17]. The main reason for inadequate sampling is the lack of diagnostically significant amount of cells.

Contrast-enhanced ultrasound is a technique using a contrast agent to enhance the backscatter echo and reflect the microvascular blood perfusion of normal and pathological tissues, which can significantly improve the sensitivity and specificity of diagnosis. The angiographic features of thyroid cancer are the unclear borders of nodules and irregular shapes during enhancement. The enhanced patterns are mostly uneven and low enhancement with a lack of blood supply. However, there are few literature reports on the contrast-enhanced ultrasound pattern of PCTNs. Zhang Bo [18] et al. analyzed the contrast-enhanced features of 41 PCTNs, and the results showed that 87.1% (27/31) of benign PCTNs presented an annular enhancement pattern, and 80.0% (8/10) of malignant PCTNs presented an uneven enhancement. While the sample size is small, it is certainly enlightening. This study aims to find out whether the active area of suspected malignant PCTNs can be identified by contrast-enhanced ultrasound in clinical practice to guide the FNAB to avoid the degenerative or necrosis areas without contrast agent perfusion in the nodules, reduce the impact of invalid cells on the specimens, accurately perform FNAB, and increase the diagnostic yield of FNAB for malignant PCTNs.

2. Subjects and Methods

2.1. Research Subjects

176 nodules in 154 patients who underwent FNAB of the thyroid in the First Affiliated Hospital of Jinan University from January 2018 to October 2020 were retrospectively analysed. All patients signed an informed consent document form before undergoing FNAB. Inclusion criteria: (1) Partially cystic space-occupying lesions of the thyroid detected by conventional ultrasound; (2) the nodules were scored and classified based on the Thyroid Imaging, Reporting and Data System (TI-RADS) of the American College of Radiology (ACR) [19], and patients with nodules in TI-RADS 4 and above were included; (3) nodules in TI-RADS 4 with a maximum diameter of more than 15mm, and nodules in TI-RADS 5 with a diameter greater than 10mm. Exclusion criteria: patients with (1) severe coagulation abnormalities; (2) long-term use of anticoagulants; (3) frequent coughing and swallowing, were unable to cooperate during the puncture procedure. The interval between the first ultrasound examination and the fine needle aspiration biopsy did not exceed 14 days. Patients were divided into two groups based on different fine needle aspiration biopsy methods. Patients who underwent two-dimensional ultrasound-guided fine needle biopsy were defined as the FNAB group, and patients who underwent contrast-enhanced ultrasound-guided fine needle aspiration biopsy were defined as the CEUS-FNAB group.

2.2. Instrument and Methods

2.2.1 Conventional Ultrasound Examination

Philips IU ELITE ultrasound system (Philips Medical Systems corporation) with an L12-5 transducer was used. Each patient underwent conventional ultrasound to assess the nodules' location, quantity, size, shape, echo, aspect ratio, margin, calcification, blood supply and the relationship with surrounding tissues. The nodules were then classified based on TI-RADS.

2.2.2 Contrast-enhanced Ultrasound

Philips IU ELITE ultrasound system (Philips Medical Systems corporation) with an L9-3 transducer was used for contrast-enhanced ultrasound examination and contrast-enhanced ultrasound-guided FNAB. The bolus injection was given by quickly injecting 2.0-2.4 mL SonoVue (Bracco) through the cubital vein, and then the tube was flushed with 5 mL of normal saline. The system's built-in low mechanical index imaging conditions were selected. Two images were displayed on the screen to allow real-time observation of the contrast enhancement modes in both the lesion area and surrounding normal thyroid tissue. The dynamic video starting from the beginning to the first 2 minutes was saved for offline analysis. The target area of the puncture would be the intranodular contrast enhancement area should the perfusion defect area be identified in the arterial phase.

2.2.3 Fine needle aspiration biopsy

Philips IU ELITE ultrasound system (Philips Medical Systems corporation) with an L12-5 transducer was used. Color Doppler was applied firstly to evaluate whether there were large blood vessels on the puncture route to prevent the needle from entering the blood vessels. The drape was routinely sterilized. The FNAB group underwent ultrasound-guided fine needle aspiration biopsy by putting the 23G biopsy needle into suspicious nodules. Sample collection was performed for 3 to 4 times on each nodule, with 6 to 7 needle aspirations each time (within 5 to 10 s), and the samples of the nodules were taken from multiple angles under ultrasound guidance. In the CEUS-FNAB group, multiple sample collections from different angles on the target area were performed using the same method as the FNAB group after the target area has been confirmed under the guidance of contrast-enhanced ultrasound. Both groups used the non-negative pressure method to collect samples. All obtained cellular fluid was made into ThinPre Cytology slides. After two centrifugation, two slides were automatically produced using an automated cytology slide stainer (Tripath Imaging, BD, USA). The results were interpreted by cytopathologists after HE staining. All conventional ultrasound, contrast-enhanced ultrasound, and FNAB were completed by 2 sonographers with more than 10 years of applicable experience.

2.2.4 Interpretation of Cytopathological Results

According to the 2017 Bethesda System for Reporting Thyroid Cytopathology [20], the thyroid FNAB report was divided into 6 categories: I, nondiagnostic; II, benign; III, atypia of undetermined significance (AUS); IV, follicular neoplasm; V, suspicious for malignancy; VI, malignant. Satisfactory FNAB specimens must contain at least 6 groups of thyroid follicular epithelial cells suitable for observation, and each group comprises at least 10 cells. Those in Bethesda category I were defined as unsatisfactory sample collection, and in Bethesda category II or higher were satisfactory sample collection. Based on the experience of cytopathology specialist, the satisfactory specimens were divided into two groups according to the amount of cells they contained: the group with medium amount of cells and the group with adequate amount of cells.

2.2.5 Diagnostic Methods

Using cytopathological results as the diagnostic criteria, Bethesda II is benign, Bethesda VI is malignant, and Bethesda V is suspicious for malignancy.

2.3. Statistical Methods

The SPSS 22.0 statistical software was used. The measurement data was expressed by mean $\pm$ standard deviation, and the independent t-test was used to compare the two sample means. The count data was expressed by percentage (%) and was compared by Chi-Square test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient Characteristics

Among the 154 patients enrolled, 34 were males, aged between 20 and 75 years, with an average age of 48.2 years; 120 were females, aged between 16 and 75 years, with an average age of 48.4 years. 176 nodules were in TI-RADS 4 and above. The maximum diameter of the nodules was 10-43mm, and the average diameter was 17.5mm. 75 nodules in 64 patients were included in the FNAB group, and 101 nodules in 90 patients were included in the CEUS-FNAB group. There was no statistical significance in the age, sex, nodule size, and the TI-RADS classification between the two groups. Refer to Table 1.

Table 1. Clinical Characteristics of 154 Patients with Thyroid Nodules

Characteristic	FNAB group (n=64/75)	CEUS-FANB group (n=90/101)	P
Age (year)	47.3 $\pm$ 13.2	46.9 $\pm$ 14.9	0.833
Sex (female/male)	50/14	70 /20	0.959
Nodule size (mm)	17.1 $\pm$ 5.6	17.9 $\pm$ 6.7	0.424
TI-RADS 4	50	66	
TI-RADS 5	25	35	0.085

FNAB: Fine needle aspiration biopsy; CEUS: Contrast-enhanced ultrasound; TI-RADS: Thyroid Imaging, Reporting and Data System;

3.2. FNAB Sampling Success Rate and the Amount of Sampling Cells

Table 2. Cells Obtained for Diagnosable Thyroid Nodules in FNAB(n, %)

		Number of patients with medium amount of cells obtained in FNAB (n)	Number of patients with adequate amount of cells obtained in FNAB (n)
ALL	FNAB	29 (55.8%)	23 (44.2%)
	CEUS-FNAB	30 (30.9%)	67 (69.1%)
	χ^2	1.552	21.916
	P	0.213	0.000
TI-RADS4	FNAB	23 (63.9%)	13 (36.1%)
	CEUS-FNAB	24 (37.5%)	40 (62.5%)
	χ^2	1.096	13.73
	P	0.295	0.000
TI-RADS5	FNAB	9 (56.3%)	7 (43.7%)
	CEUS-FNAB	9 (25.7%)	26 (74.3%)
	χ^2	0.735	12.623
	P	0.391	0.000

CEUS: Contrast-enhanced ultrasound; FNAB: Fine needle aspiration biopsy; TI-RADS: Thyroid Imaging, Reporting and Data System;

The inadequate sampling rate in the CEUS-FNAB group was 4.0% (4/101), which was significantly lower than that in the FNAB group (30.7%, $P=0.000$) (Table 3). Among the smears of satisfactory specimens, the proportion of adequate amount of cells (69.1%) in the CEUS-FNAB group was significantly higher than that in the FNAB group (44.2%, $P = 0.000$). The amount of cells obtained from the nodule specimens between the two groups was also statistically significant (Table 2).

Table 3. Bethesda Categories for the FNAB and CEUS-FNAB Groups(n, %)

Bethesda category		I Non- diagnostic	II Benign	III AUS/FLUS	IV FN / SFN	V Suspicious for malignancy	VI malignancy
ALL	FNAB	23 (30.7%)	26 (34.7%)	11 (14.7%)	4 (5.3%)	7 (9.3%)	4 (5.3%)
	CEUS- FNAB	4 (4.0%)	57 (56.4%)	12 (11.9%)	4 (4.0%)	9 (8.9%)	15 (14.9%)
	χ^2	23.636	8.185	0.294	0.004	0.009	4.049
	P	0.000	0.004	0.588	0.947	0.923	0.044
TI- RADS4	FNAB	14 (28.0%)	19 (38.0%)	9 (18.0%)	3 (6.0%)	3 (4.0%)	2 (4.0%)
	CEUS- FNAB	2 (3.0%)	40 (60.6%)	8 (12.1%)	3 (4.5%)	6 (9.1%)	7 (10.6%)
	χ^2	14.917	5.817	0.786	0.000	0.071	0.934
	P	0.000	0.016	0.375	1.000	0.790	0.334
TI- RADS5	FNAB	9 (36.0%)	7 (28.0%)	2 (8.0%)	1 (4.0%)	4 (16.0%)	2 (8.0%)
	CEUS- FNAB	0 (0.0%)	17 (48.6%)	4 (11.4%)	1 (2.9%)	4 (11.4%)	9 (25.7%)
	χ^2	12.134	2.571	0.000	0.000	0.016	1.988
	P	0.000	0.109	1.000	1.000	0.898	0.159

CEUS: Contrast enhanced ultrasound; FNAB: Fine needle aspiration biopsy; AUS: Atypia of undetermined significance; FLUS: Follicular Lesion of Undetermined Significance; FN: Follicular Neoplasm; SFN: Suspicious for a follicular neoplasm. TI-RADS: Thyroid Imaging, Reporting and Data System;

3.3. Nodule Diagnostic Yield

The malignancy rate of the CEUS-FNAB group was about 14.9% (15/101), which was higher than that of the FNAB group (5.3%, $P=0.044$) and was statistically significant (Table 3). There was no statistical significance in the malignancy rate of suspicious nodules between the CEUS-FNAB group and the FNAB group (8.9% vs 9.3%, $P = 0.923$) (Table 3). The nodules in the two groups were regrouped based on TI-RADS categories. The malignancy rate of TI-RADS4 nodules in the CEUS-FNAB group was slightly higher than that in the FNAB group, but there was no statistical significance (10.6% vs 4%, $P = 0.334$) (Table 3). The malignancy rate of TI-RADS5 nodules in the CEUS-FNAB group was slightly higher than that in the FNAB group, but there was no statistical significance (25.7% vs 8%, $P = 0.159$) (Table 3).

4. Discussion

PCTNs are common findings in ultrasound examination of the thyroid, but it is more difficult to accurately diagnose PCTNs in clinical practice. In this study, we compared the sampling success

rate of suspected malignant PCTNs between the contrast-enhanced ultrasound-guided FNAB and FNAB examinations and the diagnostic yield of malignant tumors to explore whether FNAB of suspected malignant PCTNs can be guided by contrast-enhanced ultrasound to improve the satisfaction rate of the puncture specimens and the diagnostic yield of PCTNs.

In this study, we performed contrast-enhanced ultrasound-guided FNAB examination on 101 nodules in 90 patients and FNAB examination on 75 nodules in 64 patients. It was found that the sampling success rate of the CEUS-FNAB group was significantly higher than that in the FNAB group (96% vs 69.1%, $P=0.000$) and the amount of cells obtained in the CEUS-FNAB group was significantly more than that in the FNAB group (69.1% vs 44.2%, $P=0.000$). The between-group dispersion was statistically significant. The diagnostic yield of malignant nodules in the CEUS-FNAB group was higher than that in the FNAB group (14.9% vs 5.3%, $P=0.044$), and the between-group dispersion was statistically significant.

FNAB is currently the safest and most accurate method for diagnosing thyroid nodules, and can effectively avoid unnecessary thyroid surgery [15-17, 21-22]. Studies have shown that medical workers have avoided 25% of unnecessary thyroidectomy through FNAB [23], and FNAB can effectively increase the rate of surgical resection of thyroid malignancies to 50% [24]. However, the accuracy of FNAB diagnosis is based on obtaining a satisfactory and adequate amount of cell specimens. Therefore, it is necessary to obtain as many cell specimens as possible in FNAB. A retrospective analysis of literature showed that, the sampling success rate of FNAB sampling in China over the past decade was between 77.66% and 99.6%, and the accuracy rate was between 61.8% and 98.8% [25]. Patients whose FNAB result is unable to achieve a definite diagnosis usually need to undergo another fine needle aspiration biopsy [26]. Repeated biopsy will cause patient anxiety and result in a certain degree of waste of medical resources. Therefore, it is particularly important to obtain adequate amount of cells in the first FNAB, which is very meaningful to subsequent diagnosis and treatment. Although causes of inadequate sampling include tumor size, location, degeneration and necrosis, improper sampling site, or inexperienced operator [17, 25, 27-28], the presence of necrotic cystic area in the nodule is considered the most important factor of inadequate sampling [29-30]. The cystic and necrotic portions in the nodules are usually associated with the presence of remote hemorrhage, cystic degeneration, or necrosis due to insufficient blood supply in the nodules. This cannot be easily identified by two-dimensional ultrasound, especially when the liquefaction is not complete. While Color Doppler can identify blood flow signals in nodules, it is not sensitive to the identification of necrotic liquefaction. PCTNs have less solid portions, which makes it more difficult to obtain adequate effective cells in FNAB. Therefore, accurately identifying the active area in PCTNs and effectively avoiding the necrotic liquefaction area are the key to the success sampling in fine needle aspiration biopsy.

Contrast-enhanced ultrasound realizes real-time display of tissue microvascular perfusion under low mechanical index, which can significantly enhance the grayscale and Doppler signals from the blood pool, and sensitively reflect the blood supply features and microcirculation condition of the lesion. Ultrasound contrast agents are not radiative or toxic to liver and kidney, neither will they affect thyroid function [31]. There are not many reports on the CEUS of PCTNs. The study by Yang Xiaoyong et al. [32] pointed out that the characteristics of PCTNs contrast-enhanced ultrasound are that in benign PCTNs, the solid portion is characterized by even enhancement, surrounded by more annular high enhancements; partially cystic thyroid cancer is dominated by uneven enhancement, and annular enhancement is rarely seen. There are few reports of thyroid puncture guided by contrast-enhanced ultrasound. A few studies have shown that contrast-enhanced ultrasound-guided liver puncture biopsy can achieve a more accurate diagnosis and reduce the number of punctures [33-34]. This means that it is theoretically feasible to use contrast-enhanced ultrasound to identify the active area and guide the doctor

to collect as many cells as possible in the fine needle aspiration biopsy of suspected malignant PCTNs and achieve a more accurate diagnosis.

This study shows that contrast-enhanced ultrasound-guided FNAB can make more PCTNs diagnosable and improve the diagnostic yield of malignant tumors. This is consistent with Garca-pascual's report [35] that the incidence of malignant tumors among PCTNs that could not be diagnosed by FNAB cytology was 11.1% (4/36) and that the malignancy rate of PCTNs with suspicious ultrasound features in the NCCN guidelines was 15.6%. In clinical practice, most patients underwent FNAB examination because conventional ultrasound results could not provide a clear diagnosis. In terms of diagnosis, contrast-enhanced ultrasound can make up for the shortcomings of conventional ultrasound diagnosis and provide more information for diagnosis. On the other hand, it also helps increase the amount of cells obtained in FNAB, thereby improving the diagnostic efficiency of FNAB.

The shortcoming of this article is that the number of cases is small and may be affected by some sort of selection bias. We chose PCTNs with certain suspicious signs in conventional ultrasound examinations. These patients underwent FNAB because of suspicious ultrasound features. However, Wenbo Li et al. [8] pointed out in their research that a cystic nodule with a size of about 40mm which was diagnosed as most likely benign was diagnosed as malignant in FNAB and proved to be a papillary carcinoma in the surgery. This may lead to certain bias in the estimation of the incidence of cancer in PCTNs. Furthermore, we did not make specific grouping comparisons based on the size of nodules, so large-scale prospective clinical studies are still needed to test the application value of contrast-enhanced ultrasound-guided fine needle aspiration biopsy of PCTNs.

In summary, the contrast-enhanced ultrasound-guided fine needle aspiration biopsy of suspected malignant PCTNs can improve the satisfaction rate of cytopathological materials and reduce the occurrence of inadequate sampling. FNAB under the guidance of contrast-enhanced ultrasound helps increase the diagnostic yield of suspected benign and malignant PCTNs, reduce unnecessary surgical resections, and provide more evidence to support the subsequent diagnosis and treatment for patients.

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