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ORIGINAL RESEARCH

Diagnostic Significance of Ultrasound-Guided Fine-Needle Aspiration Biopsy and on-Site Assessment by Pathologists for Thyroid Micronodules

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Objective: Ultrasound-guided fine-needle aspiration biopsy (US-FNAB) is a safe and effective method for screening malignant thyroid nodules. The purpose of this study was to compare the diagnostic effectiveness of US-FNAB for nodules of different sizes.

Methods: A total of 1085 patients with thyroid nodules who underwent US-FNAB between January 2021 and July 2023 were included in the study. The patients were divided into three groups based on the maximum diameter of the nodules: there were 324 patients with thyroid nodules ≤5 mm in Group A, 537 patients with thyroid nodules between 6 mm and 10 mm in Group B, and 224 patients with thyroid nodules >10 mm in Group C. The US-FNAB satisfactory specimen rate, biopsy time and cytopathological results for the three groups were collected and compared with the postoperative pathological results.

Results: The US-FNAB satisfactory specimen rates for Groups A, B and C were 84.57% (274/324), 90.13% (484/537) and 94.64% (212/224), respectively. The average biopsy times for Groups A, B, and C were 100.84 ± 41.58 s, 91.20 ± 32.53 s, and 79.01 ± 29.62 s, respectively. In Groups A, B, and C, 103, 192 and 73 patients, respectively, underwent surgery, and the malignancy rates were 88.35%, 85.42% and 72.6%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of US-FNAB in Group A were 78.26%, 81.82%, 97.30%, 31.03%; respectively; those in Group B were 73.78%,85.71%,96.80%, and 35.82%, respectively; and those in Group C were 75.47%, 85.00%, 93.02% and 56.67%, respectively.

Conclusion: The US-FNAB satisfactory specimen rate for thyroid nodules ≤5 mm was relatively low, but the size of nodules had no effect on the diagnostic sensitivity of US-FNAB; additionally, nodules ≤5 mm had a higher probability of malignancy. Therefore, it is necessary to perform US-FNAB for thyroid nodules with a diameter ≤5 mm with malignant signs.

Keywords: thyroid nodules, ultrasound-guided fine-needle aspiration biopsy, microcarcinomas

Introduction

The thyroid is one of the largest endocrine glands in the human body and is composed of two connected glandular lobes. Thyroid nodules are common, and most lesions are benign, with thyroid hormone secretion remaining normal.[1] In Chinese adults, the prevalence of thyroid nodules with a diameter of more than 5mm found by ultrasonography reached 20.43%, of which 8–16% were malignants.[2] The most common pathological type of thyroid cancer is papillary thyroid carcinoma (PTC), and papillary thyroid microcarcinoma (PTMC) refers to PTC less than 10mm in diameter. With the popularization of physical examinations and advancements in ultrasound diagnosis, the detection rate of thyroid micronodules has significantly increased.[3] Although most thyroid cancers have a low degree of malignancy, they still

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pose a threat to patients' lives, health, and quality of life. Early diagnosis and intervention of thyroid cancer can effectively reduce the mortality of patients and improve the quality of life of patients.

Thyroid nodules can be morphologically diagnosed on ultrasound, but it is difficult to directly determine whether some nodules are benign or malignant. The need for surgical treatment and the selection of surgical methods are dependent on whether lesions are benign or malignant. Ultrasound-guided fine-needle aspiration biopsy (US-FNAB) of the thyroid is the preferred clinical method for the preoperative pathological diagnosis of thyroid nodules. Studies have shown that for organ transplant donors with thyroid nodules, US-FNAB can effectively diagnose the benign or malignant nature of thyroid nodules, thereby reducing unnecessary surgeries and complications, and minimizing the impact on transplant organs.[4,5] The Bethesda reporting system of thyroid cytopathology (TBSRTC) is the classification standard for US-FNAB diagnosis. Bethesda I–VI nodules have different values. The risk of malignancy for Bethesda class II nodules and III nodules is 0–3% and 10–30%, respectively.[6,7] Ultrasound-guided fine-needle aspiration biopsy (US-FNAB) can identify the nature of thyroid nodules before treatment. US-FNAB provides the basis for personalized and accurate treatment. However, for thyroid micronodules, the indications for US-FNAB are different in different guidelines[8]. Especially for nodules with a diameter less than 5mm, where there is limited research on the application of US-FNAB. This study retrospectively analyzed clinical data on the application of US-FNAB for thyroid nodules of different sizes, aiming to investigate the diagnostic significance of US-FNAB in thyroid microcarcinomas.

Materials and Methods

General Information

We collected the data of 1085 patients who underwent US-FNAB in our hospital between January 2021 and July 2023. The patients were divided into three groups based on the maximum diameter of the nodules. Group A included 324 patients with thyroid nodules ≤5 mm, Group B included 537 patients with thyroid nodules between 6 mm and 10 mm, and Group C included 224 patients with thyroid nodules >10 mm. This study was approved by the Ethics Committee of the Second Hospital of Jiaxing (JXEY-2021JX155), which accorded with the ethical standards formulated in the Helsinki Declaration. All subjects signed informed consent forms.

The inclusion criteria were as follows: (1) thyroid nodules with malignant imaging features suggested by conventional ultrasound: solid nodules, hypoechoic, microcalcifications, unclear edge, vertical growth, or aspect ratio greater than 1; (2) during follow-up, nodules that grew fast (increase of more than 50% in volume within 1 year) or the presence of new malignant ultrasound features; (3) for patients with multiple suspicious nodules, the nodules with the most malignant possibility were selected for aspiration and included into the group. The exclusion criteria were as follows: (1) pure cystic nodules and (2) abnormal coagulation function.

Instruments and Methods

The Mindray Resona7 (probe frequency 6.0 ~ 10.0 MHz) was used. First, the size, edge, boundary, shape, internal echo, and calcification of nodules were observed using conventional ultrasound; then, blood flow and distribution in and around the lesions were observed using colour Doppler.

US-FNAB: Venous blood was obtained from each patient within 1 week before surgery to perform routine blood tests and check coagulation function. Signed informed consent for aspiration biopsy was provided by each patient and his or her family before the procedure. Each patient was placed in the supine position during the procedure, and the neck skin was routinely disinfected with iodine, covered with a sterile drape and anaesthetized with 1% local infiltration of lidocaine hydrochloride. A 0.7×32 mm aspiration needle was used for puncture. The movement of the needle tip was observed in real time with ultrasound. Each nodule was aspirated 1 to 3 times.

The obtained tissue samples were transferred to glass slides. The quality of the specimen was evaluated visually. For satisfactory specimens, the slides were fixed in 95% ethanol for 1 h, followed by HE staining for analysis. For the specimens that could not be evaluated via the naked eye, rapid on-site evaluation (ROSE) cytology was performed, and rapid interpretation was performed under a microscope. The remnants in the syringe were washed into a liquid-based cell preservation solution and analysed after Pap staining. The cytology diagnostic results were divided into 6 categories

based on the Bethesda criteria:[9] I: undiagnosed or unsatisfactory diagnosis; II: benign; III: atypia of undetermined significance or follicular lesions of uncertain significance (AUS/FLUS); IV: follicular tumour or suspicious follicular tumour (FN); V: suspected malignancy (SUSP); and VI: malignant. Bethesda I specimens were defined as unsatisfactory, and Bethesda II~VI specimens were defined as satisfactory. The standard for sufficient specimens was the existence of at least six follicle cell masses, with each follicle cell mass containing at least 10 thyroid follicle cells. All cytology results were compared with the postoperative conventional pathological diagnosis, and the sensitivity, specificity, positive predictive value, and negative predictive value of US-FNAB were calculated.

Statistical Analysis

GraphPad Prism 5 software was used for the statistical analysis. Measurement data were analysed using ANOVA. Count data were compared using the χ^2 test. Differences between the three groups of samples was compared, and $P<0.05$ was considered statistically significant.

Results

Clinical and Aspiration Information of Nodules of Different Sizes

The 1085 patients with thyroid nodules were divided into three groups based on the maximum diameter of the nodules: Group A included 324 patients with thyroid nodules ≤5 mm, Group B included 537 patients with thyroid nodules between 6 mm and 10 mm, and Group C included 224 patients with thyroid nodules >10 mm (Table 1). The mean ages of the patients in Groups A, B, and C were 48.82 ± 13.66 years, 48.96 ± 13.75 years, and 51.17 ± 14.51 years, respectively, and there was no significant difference in age or sex among the three groups. The numbers of samples in Group A with 1 aspiration, 2 aspirations and 3 aspirations were 21, 281 and 22, respectively. The average number of aspirations was 2.00 ±0.36. The numbers of samples in Group B with 1 aspiration, 2 aspirations and 3 aspirations were 38, 469 and 30, respectively. The average number of aspiration was 1.98 ± 0.35. The numbers of samples in Group C with 1 aspiration, 2 aspirations, and 3 aspirations were 31, 179 and 12, respectively. In addition, the average biopsy times for Groups A, B, and C were 100.84 ± 41.58 s and 91.20 ±32.53 s and 79.01 ±29.62 s, respectively. Comprehensive analyses of the number of aspirations and biopsy time for the three groups indicated that the larger the nodule was, the fewer the number of aspirations, and the shorter the biopsy time.

Cytology results for US-FNAB Nodules of Different Sizes

We calculated the proportions of Bethesda types I~VI among the three groups of samples (Table 2). Bethesda I specimens were defined as unsatisfactory, and Bethesda II~VI specimens were defined as satisfactory. The percentage of satisfactory specimens for Groups A, B, and C were 84.57% (274/324), 90.13% (484/537) and 94.64% (212/224), respectively, and the difference was statistically significant (P=0.0006), suggesting that larger

Table 1 Clinical and Aspiration Information for Nodules of Different Sizes

	≤5 mm (n=324)	**6 mm~10 mm (n=537)**	**>10 mm (n=224)**	**P**
Sex (male/female)	77/274	144/393	68/156	0.0669
Age (years)	48.82±13.66	48.96±13.75	51.17±14.51	0.0924
Number of aspirations				0.0129
1	6.48% (21)	7.08% (38)	14.29% (31)	
2	86.73% (281)	87.24% (469)	80.36% (179)	
3	6.79% (22)	5.59% (30)	5.36% (12)	
Average	2.00±0.36	1.98±0.35	1.91±0.44	
Biopsy time (s)				<0.0001
1 aspiration	53.95	46.58	42.88	
2 aspirations	100.98	91.57	82.21	
3 aspirations	143.86	141.90	127.42	
Average	100.84±41.58	91.20±32.53	79.01±29.62	

Table 2 Comparison of Bethesda Classifications for Nodules of Different Sizes

	≤5 mm (n=324)	6 mm~10 mm (n=537)	>10 mm (n=224)	P
Bethesda classification				<0.0001
I	15.43% (50)	9.87% (53)	5.36% (12)	
II	37.35% (121)	40.60% (218)	48.66% (109)	
III	14.51% (47)	11.92% (64)	11.61% (26)	
IV	0.31% (1)	1.68% (9)	6.25% (14)	
V	8.95% (29)	5.77% (31)	7.59% (17)	
VI	23.46% (76)	30.17% (162)	20.54% (46)	
Satisfactory specimen rate	84.57% (274)	90.13% (484)	94.64% (212)	0.0006

nodules are associated with satisfactory specimens. The proportions of Bethesda III specimens in Groups A, B, and C were 14.51% (47/324), 11.92% (64/537), and 11.61% (26/224), respectively. Compared with nodules >5 mm, for nodules ≤5 mm, there was a higher proportion of Bethesda III specimens, that is, there was a higher proportion of AUS/FLUS, suggesting that an accurate cytologic diagnosis is more difficult for nodules ≤5 mm. In addition, the proportions of Bethesda V and VI specimens in Groups A, B, and C were 32.41% (105/324), 35.94% (193/537), and 28.13% (63/224), respectively. The proportions of Bethesda V and VI specimens in Group C were the lowest, indicating that the potential for malignancy was lower for nodules with a diameter >10 mm.

Routine Histological and Pathological results for Nodules of Different Sizes After Surgery

In the ≤5 mm, 6 mm~10 mm, and >10 mm groups, 103, 192 and 73 patients underwent surgery, respectively. Using the postoperative histopathological results as the gold standard for diagnosis, the malignancy rates in the ≤5 mm, 6 mm~10 mm, and >10 mm groups were 88.35% (91/103), 85.42% (164/192), and 72.6% (53/73), respectively; the malignancy rate was highest in the ≤5 mm group, and the difference was significant (P=0.0092)(Table 3). The US-FNAB diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were 78.26%, 81.82%, 97.30%, and 31.03% for Group A; 73.78%, 85.71%, 96.80%, and 35.82% for Group B; and 75.47%, 85.00%, 93.02%, and 56.67%for Group C. The sensitivity and specificity of the three groups were all high. These results indicated that US-

Table 3 Histopathological Results for Nodules of Different Sizes and Analysis of the Diagnostic Performance of US-FNAB

	≤5 mm (n=103)		6 mm~10 mm (n=192)		>10 mm (n=73)	
	Bethesda II to IV	Bethesda V/VI	Bethesda II to IV	Bethesda V/VI	Bethesda II to IV	Bethesda V/VI
Benign histopathology	9	2	24	4	17	3
Malignant histopathological	19	72	43	121	13	40
Sensitivity	78.26%		73.78%		75.47%	
Specificity	81.82%		85.71%		85.00%	
Positive predictive value	97.30%		96.80%		93.02%	
Negative predictive value	31.03%		35.82%		56.67%	

FNAB was highly accurate in the identification of benign and malignant thyroid nodules, especially nodules with a diameter ≤5 mm.

Discussion

US-FNAB is a safe, convenient and relatively accurate method for the preoperative diagnosis of thyroid nodules and can help ensure that patients with benign thyroid nodules do not undergo unnecessary surgeries. Many factors affect the cytology results of thyroid FNAB, for example, the quality of the cytology sample and the experience of the pathologist.[10,11] The amount of blood cells and the number of cells in a smear are important factors in determining smear quality. Some studies have shown that for nodules <10 mm, the frequency of unsatisfactory biopsy specimens increases with the decrease in nodule size. This may be due to the erroneous collection of surrounding thyroid tissue rather than components of small nodules[12]. Rapid on site evaluation (ROSE) cytology can be used to rapidly evaluate the quality and preliminary diagnosis of aspiration and biopsy specimens, among others. Some studies have shown that the quality of cytology specimens obtained from ROSE cytology is higher than that of specimens obtained from off-site rapid evaluation and that the number of aspirations and biopsy times for thyroid FNAB can be reduced.[13–15] In this study, all biopsies were analysed as on-site smears by a pathologist who evaluated them with the naked eye; some specimens underwent ROSE cytology. Although the size of nodules affected the quality of biopsy specimens, in general, the quality of biopsy samples in the three groups was high. Therefore, for thyroid micronodules, FNAB can be performed in combination with ROSE cytology based on the actual situation, helping to improve specimen quality.

According to the 2018 Chinese "Expert Consensus and Operating Guidelines for Ultrasound-Guided Fine Needle Aspiration Biopsy of Thyroid Nodules", the indications for US-FNAB for thyroid nodules are (1) thyroid nodules with a diameter >1 cm, with US-FNAB conducted for those with malignant signs on ultrasound; and (2) no routine needle biopsy for thyroid nodules ≤1 cm in diameter except US-FNAB considered if ultrasound indicates malignant signs, lymph node metastasis, or family thyroid cancer[16]. The 2009 ATA "Guidelines for the Treatment of Thyroid Nodules and Differentiated Thyroid Carcinoma" state that in general, only nodules larger than 1 cm in diameter need to be evaluated by FNAB; however, for high-risk patients with thyroid nodules, FNAB is recommended as long as the nodule is larger than 5 mm[17]. The samples included in this study were all thyroid nodules with malignant signs on ultrasound. Among the 368 patients who underwent surgery, the overall malignancy rate was 83.7%, with the highest rate in the ≤5 mm group (88.35%). Both total thyroidectomy (TT) and subtotal thyroidectomy (STT) patients have a low risk of early post-operative complications.[18] In this study, most patients underwent unilateral total thyroidectomy with tumor. However, because not all patients who received US-FNAB eventually underwent surgery, the criteria for surgery for the three groups of patients were not completely the same; all factors were comprehensively considered by the patient and the doctor. Previous studies have shown that smaller nodules, compared with large nodules, may have a higher malignancy rate. Therefore, when malignant signs are present on ultrasound, FNAB of thyroid nodules is a reasonable option.

US-FNAB has high sensitivity and specificity in the assessment of benign and malignant thyroid nodules, but it is still unknown whether the size of thyroid nodules has an effect on the cytological diagnosis results of US-FNAB.[19,20] In this study, the size of nodules had little effect on the cytological diagnosis results of US-FNAB, and the US-FNAB diagnosis for the three groups had high sensitivity and specificity. However, because Bethesda III was considered benign cytology and the proportion of such samples was high, the sensitivity and specificity of US-FNAB were affected to some extent. Recently, innovative research, including whole slide imaging and digital pathology, has been effectively improving cytopathology diagnosis.[21–23] In addition, multiple guidelines suggest that molecular testing of Bethesda III and IV samples could effectively improve the sensitivity of the preoperative diagnosis of thyroid nodules.[24,25] Therefore, reducing the proportion of Bethesda III specimens and developing molecular testing are effective ways to improve the diagnostic value of US-FNAB.

In summary, US-FNAB can be used in the clinical diagnosis of thyroid nodules of different sizes, and US-FNAB should also be considered for nodules with a diameter <5 mm with malignant signs. Additionally, to reduce the proportion of unsatisfactory specimens, the implementation of ROSE cytology can be considered.

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Disclosure

There are no conflicts of interest to declare.

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