Comparison of two different standards of care in detecting malignant thyroid nodules using thyroid fine-needle aspiration

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Abstract. The aim of the present study was to verify the optimal method to obtain enough fine-needle aspiration (FNA) materials for detecting thyroid malignancy. A prospective study was performed by comparing two different regional standards of care. In one group a traditional FNA method mainly used in Asian countries, including China, was performed in which a single pass of a 22-G needle was applied with or without aspiration. In the other group, the method mainly used in Western countries was performed in which three passes of a 25-G needle with non-aspiration were undertaken for thyroid nodules. The study included 718 thyroid nodules from 695 patients. These nodules were allocated for three different methods of performing thyroid FNA. There were 332 thyroid nodules subjected to the traditional Asian FNA method using a 22-G needle with aspiration for 142 nodules and non-aspiration for 190 nodules. FNA using the Western method was performed with three passes of non-aspiration using 25 G for 386 nodules. All the FNAs were performed with the guidance of ultrasound. The components of the nodules were documented. All the samples were reported using the Bethesda System for Reporting Thyroid Cytopathology. Among the 22 G group, the non-diagnostic rate in the aspiration group was as high as 76.76%, which was significantly higher than 44.21% in the non-aspiration group ($P<0.01$). For the non-aspiration group, the non-diagnostic rate in the 25 G group was 34.97%, which was significantly lower than 44.21% in the 22 G group. In general, the non-diagnostic rate for the 25-G needle was 34.97%, which was significantly lower than 58.13% in all the 22 G groups. For the solid and mixed nodules, the non-diagnostic rate was lower in the 25-G needle group compared to the 22 G groups with statistical significance. The non-aspiration method using a 25-G needle with multiple passes can result in a higher diagnostic rate for thyroid FNA.

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Introduction

A thyroid nodule is a common clinical scenario (1,2). The prevalence of thyroid nodules is ~18-40% in Chinese adults (3-5); however, only 5-10 percent of all thyroid nodules are malignant. Although with the development of the ultrasound technique, several ultrasonographic characteristics have been associated with thyroid malignancy (6-10), individual ultrasound features are not accurate predictors of thyroid cancer (11). Thyroid fine-needle aspiration (FNA) has been recommended by various organizations for the more precise preoperative diagnosis of thyroid nodules (12-15). Our previous study demonstrated that a routine preoperative thyroid FNA for thyroid nodule is expected to be more cost-efficient in the care of thyroid nodules (16). However, regional variation exists between countries. Controversies remain as for which method should be applied. There is also an area of inconsistency concerning the choice of needles and techniques (17,18) in different countries with different standards of care.

Previous studies have used various types of needles, from 21 to 27 G, with and without aspiration (17,19,20). In the United States, a 25-G needle is a standard of care for thyroid FNA (21-24), while in Asian countries the 21-23 G needles are more frequently used, including in China (25-28). However, there has been no consensus as for which needle should be applied for the optimum diagnostic yield and there has been no direct comparison for the two major standards of care in

thyroid FNA (25 G in the United States verses 22 G in China). Further study is therefore required to reach a final consensus.

In order to determine the optimal technique to obtain the most adequate materials for the diagnosis of thyroid FNA, a prospective study was performed that compared the most frequently used 22-G needle in China, with or without aspiration, with the more commonly used 25-G needles in the United States with three passes of non-aspiration.

Patients and methods

Patients. The study was reviewed and approved for analysis by the Institutional Review Board of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China). All the patients signed the written form of consent prior to the procedure of thyroid FNA. There were 718 thyroid nodules from 695 patients recruited in the study between October 2013 and March 2014 at the Department of Endocrinology in The First Affiliated Hospital of Nanjing Medical University.

Arrangement. These nodules were allocated for thyroid FNA with two different regional standards of care in thyroid FNA. For the group using the traditional standard of care in China, one pass of a 22-G needle attached to a 10 ml syringe (0.7x32 mm; Shangdong Weigao Group Medical Polymer Co., Ltd., Shandong, China) with or without aspiration was used and no local anesthesia was applied prior to the procedure. The aspiration method was applied with mild suction during the FNA process, while during the non-aspiration method the needle was only moved back and forth several times within the nodule without the suction force applied. In the other group using the Western method, the same endocrinologists (X.L., Z.W., D.C. and H.C.) performed FNA using three passes of the 25-G needle attached to a 5 ml syringe (0.5x38 mm; Becton, Dickinson and Co.) with local anesthesia of 2% lidocaine prior to the FNA. All the FNAs were performed with the guidance of ultrasound. All the patients were recruited according to a reference sequence. Patients were not selected for a specific method.

In total there were 332 thyroid nodules subjected to FNA using the 22-G needle (traditional method) with aspiration for 142 nodules and non-aspiration for 190 nodules. FNA with three passes of non-aspiration was performed using the 25-G needle (Western method) for 386 nodules.

FNA procedure. The patient was placed in a supine position with a rolled towel behind the lower cervical spine to extend the neck. After the lesion was localized, the overlying skin was cleaned with 75% ethyl alcohol. A high-resolution (6-18 MHz; MyLab 60 system; Esaote, Genoa, Italy) linear-array transducer, with a sterile cover placed over its head, was used for the ultrasound examination and real-time guiding. The component of nodules was documented as solid, cystic and mixed. Ultrasound was performed by one radiologist with >10 years experience of performing thyroid ultrasound (L.W.).

A 22-G needle attached to a 10 ml syringe (traditional method) or a 25-G needle attached to a 5 ml syringe (Western method) was used for each preset time. The transducer was placed directly over the lesion. The patient was instructed not to swallow or speak during the insertion of the needle. A freehand biopsy technique was used, and the syringe attached to the needle was placed just above the transducer. The needle was introduced parallel or perpendicular to the transducer according to the location of the nodule and the preference of the performer, and the needle tip or sheath was carefully monitored during the procedure. When the needle reached the target, the biopsy was performed with or without aspiration according to the preset date using different methods. During the procedure, all the needle movements were continuously visualized in real-time.

Cytopathology preparation and interpretation. The collected material was expelled on glass slides, smeared and fixed in 95% ethyl alcohol immediately following FNA. Staining was performed using the Papanicolaou method. All the samples were reported using the Bethesda System as follows: Non-diagnostic (ND), benign (B), atypia of undetermined significance (AUS), suspicious for follicular neoplasm (FOL), suspicious for malignancy (SUS) and malignant (M) (29). Notably, the ND rate of each group was the primary concern of the study. All the slides were reviewed by attending cytopathologists (Y.W. and R.R) first, and subsequently confirmed by chief cytopathologists (Y.W. and Q.Y.). When any discrepancy occurred, the final decision was made following the discussion with the chief executive cytopathologist (Z.Z).

Statistical analysis. Quantitative data were shown as mean ± standard deviation, whereas numbers and percentage were provided for the qualitative data. Quantitative data were compared using independent samples t-test. Percentages were compared using the χ^2 test. All the tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed with SPSS software, version 13.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Comparison of the baseline characteristics for the different FNA technique groups. In total there were 718 nodules from 695 patients recruited in the study with a mean age of 49.80±13.37 years and 81.2% female patients. The average age, gender percentage and nodule component of each group were generally comparable (Table I).

Non-diagnostic rate comparison between the three groups. The ND rate was compared between groups with different needle sizes and methods. In the 22 G group, non-aspiration showed a decreased ND rate as compared to aspiration (44.21 vs. 76.76%, $P<0.001$; Table II). In the non-aspiration group, a lower ND rate was revealed in the 25-G needle group compared to the 22-G needle group (34.97 vs. 44.21%, $P=0.032$; Table II). Notably, the ND rate in the 25 G group was significantly lower than in the all 22 G group (34.97 vs. 58.13%, $P<0.001$; Table II).

Non-diagnostic rate comparison between the three groups according to different nodule content. The ND rate was compared between groups with different aspiration techniques according to nodule components. In the solid nodule group, the ND rate in the 25 G group was significantly lower than

Table I. Comparison of the baseline characteristics of the three groups with different FNA techniques.

Variables	22 G aspiration	22 G non-aspiration	25 G non-aspiration	Total	P-value[a]	P-value[b]
Number	142	190	386	718		
Age, years	49.50±13.63	50.45±13.46	49.59±13.23	49.80±13.37	0.526	0.462
Gender					0.405	0.592
Female	118 (83.1)	151 (79.5)	314 (81.3)	583 (81.2)		
Male	24 (16.9)	39 (20.5)	72 (18.7)	135 (18.8)		
Component					0.383	0.178
Solid	80 (56.3)	110 (57.9)	254 (65.8)	444 (61.8)		
Mixed	35 (24.6)	36 (18.9)	61 (15.8)	132 (18.4)		
Cystic	27 (19.0)	44 (23.2)	71 (18.4)	142 (19.8)		

[a]22 G aspiration verses 22 G non-aspiration; [b]22 G non-aspiration verses 25 non-aspiration.

Table II. Non-diagnostic rate comparison between 22 G aspiration, 22 G non-aspiration and 25 G non-aspiration.

Aspiration	ND, n (%)	Benign, n (%)	AUS, n (%)	FOL, n (%)	SUS, n (%)	M, n (%)	Total, n (%)
22 G aspiration	109 (76.76)	21 (14.79)	8 (5.63)	2 (1.41)	2 (1.41)	0	142
22 G non-aspiration	84 (44.21)[a]	59 (31.05)	26 (13.68)	8 (4.21)	13 (6.84)	0	190
All 22 G	193 (58.13)	80 (24.10)	34 (10.24)	10 (3.01)	15 (4.52)	0	332
25 G non-aspiration	135 (34.97)[b,c]	169 (43.78)	45 (11.66)	7 (1.81)	25 (6.48)	5 (1.30)	386

[a]22 G non-aspiration verses 22 G aspiration, P<0.001; [b]25 G non-aspiration verses 22 G non-aspiration, P=0.032; [c]25 G non-aspiration verses all 22 G, P<0.001.

Table III. Non-diagnostic rate comparison between 22 G aspiration, 22 G non-aspiration and 25 G non-aspiration according to different nodule component.

Aspiration	ND, n (%)	Benign, n (%)	AUS, n (%)	FOL, n (%)	SUS, n (%)	M, n (%)	Total, n (%)
Solid	164 (36.94)	163 (36.71)	61 (13.74)	14 (3.15)	37 (8.33)	5 (1.13)	444
22 G aspiration	59 (73.75)	12 (15.00)	6 (7.50)	1 (1.25)	2 (2.50)	0	80
22 G non-aspiration	37 (33.63)[a]	36 (32.73)	19 (17.27)	7 (6.36)	11 (10.00)	0	110
All 22 G	96 (50.52)	48 (25.26)	25 (13.16)	8 (4.21)	13 (6.84)	0	190
25 G non-aspiration	68 (26.77)[b,c]	115 (45.27)	36 (14.17)	6 (2.36)	24 (9.45)	5 (1.97)	254
Mixed	61 (46.21)	54 (40.91)	14 (10.61)	2 (1.52)	1 (0.76)	0	132
22 G aspiration	27 (77.14)	6 (17.14)	1 (2.86)	1 (2.86)	0	0	35
22 G non-aspiration	14 (38.89)[a]	15 (41.67)	6 (16.67)	0	1 (2.78)	0	36
All 22 G	41 (57.75)	21 (29.58)	7 (9.86)	1 (1.41)	1 (1.41)	0	71
25 G non-aspiration	20 (32.79)[b,c]	33 (54.10)	7 (11.48)	1 (1.64)	0	0	61
Cystic	103 (72.54)	32 (22.54)	4 (2.82)	1 (0.70)	2 (1.41)	0	142
22 G aspiration	23 (85.19)	3 (11.11)	1 (3.70)	0	0	0	27
22 G non-aspiration	33 (75.00)[a]	8 (18.18)	1 (2.27)	1 (2.27)	1 (2.27)	0	44
All 22 G	56 (78.87)	11 (15.49)	2 (2.82)	1 (1.41)	1 (1.41)	0	71
25 G non-aspiration	47 (66.20)[b,c]	21 (29.58)	2 (2.82)	0	1 (1.41)	0	71

In the solid group, [a]22 G non-aspiration verses 22 G aspiration, P<0.001; [b]25 G non-aspiration verses 22 G non-aspiration, P=0.184; [c]25 G non-aspiration verses all 22 G, P<0.001. In the mixed group, [a]22 G non-aspiration verses 22 G aspiration, P=0.001; [b]25 G non-aspiration verses 22 G non-aspiration, P=0.543; [c]25 G non-aspiration verses all 22 G, P=0.004. In the cystic group, [a]22 G non-aspiration verses 22 G aspiration, P=0.307; [b]25 G non-aspiration verses 22 G non-aspiration, P=0.319; [c]25 G non-aspiration verses all 22 G, P=0.091.

the all 22 G group (26.77 vs. 50.52%, P<0.001; Table III). There was a mild decrease in the 25 G non-aspiration group compared to the 22 G non-aspiration group without statistical significance (26.77 vs. 33.63%, P=0.184; Table III). In the 22 G group, non-aspiration showed a significantly lower ND rate as compared to the aspiration group (33.63 vs. 73.75%, P<0.001). A similar trend was revealed in the mixed nodule group. In the cystic nodule group, the ND rate was higher compared to the mixed or solid groups. However, no significant difference was shown between groups with different methods.

Discussion

FNA is the most cost-effective procedure for preoperative diagnosis for thyroid nodules. However, a well-accepted guideline for the optimal technique for thyroid FNA has not been established (17). There have been studies using various needle types (regular needle, needle with a stylet or spinal needle) (30-32) and different needle sizes (from 21 G to 27 G) (22,33,34) with or without aspiration (35-37) during the procedure. Although there is certain evidence supporting more finer needle and non-aspiration techniques towards more adequate cytology sampling, controversies remain. In China, 21-22-G needles are mainly used, whereas in the United States the 25-G needle with multiple passes is a standard of care for thyroid nodules. No study has ever compared the two major standards of care for patients with thyroid nodules.

The present study compared the most frequently used 22-G needle in China with the 25-G needle commonly used in the United States. In the 22 G group, one single pass of the non-aspiration technique showed a significantly lower non-diagnostic value compared to a single pass of the aspiration technique by 42.4% (Table II), further confirmed the previous results in the study by Romitelli *et al* (35) who used a 25-G needle in the aspiration and non-aspiration groups. In the non-aspiration group, three passes of the 25-G needle showed an even lower non-diagnostic rate compared to one pass of the 22-G needle, which decreased by 20.9% (Table II).

Numerous factors influence the diagnostic rate in thyroid FNA, among which the nodule component is an extremely important factor (24). A sub-analysis was performed by further categorizing the nodules into different groups by their appearance under ultrasounography (Table III). In general, the more cystic the percentage of each nodule, the higher the rate of non-diagnostic, with the lowest ND rate in the solid nodule using a 25-G needle at 26.77% and the highest in the cystic nodule using 22 G aspiration at 85.19%. A similar trend was found in each group with lowest rate of ND in the 25 G non-aspiration group and highest in the 22 G aspiration group.

One limitation of the present study is that the ND rate in solid nodules was 26.77% higher compared to the results from Brigham and Women's Hospital (BWH) and Boston Children's Hospital, which was ~13% (21,24,38). One of the important factors lies in the different sample preservation techniques. In BWH, liquid-based cytology using the ThinPrep technique was well-established, which was believed to potentially achieve the maximum sample preservation by obtaining as much of the residual samples from the needles rinsed with CytoLyt solution (21). In traditional smears, there would be a certain degree of sample residual left in the needle base following the smear, which would potentially influence the meeting of the adequacy criteria. The second reason would be the intraobservor deviation in interpreting the smears (39) and lack of experience in using the Bethesda System compared to the cytopathologists in BWH who have >15 years experience since 2009 (29).

In conclusion, the Western method using multiple passes with a 25-G needle is superior in comparison to the traditional method in China using the 22-G needle with or without aspiration in thyroid FNA for obtaining a sufficient sample for cytology interpretation. Multiple passes using the 25-G needle non-aspiration method is applicable for further and wider clinical practice in thyroid FNA, particularly in Asian countries, including China.

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