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Comparison of Consecutive Results from Fine Needle Aspiration and Core Needle Biopsy in Thyroid Nodules

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Abstract There are papers suggesting the complementary role of core needle biopsy (CNB) in the diagnosis of thyroid nodules. By comparing the result of CNB and fine needle aspiration (FNA) cytology performed in consecutive cases of thyroid nodules, the role of CNB was evaluated. Retrospective reviews of 2131 FNA and 275 CNB which were performed as first-line biopsy for 2406 thyroid nodules in 2187 patients were performed. The ultrasound (US) feature of thyroid nodule was classified following the risk of malignancy suggested by American Thyroid Association (ATA) guideline. Rate of unsatisfactory and cellular atypia could be decreased significantly by first-line CNB in all US group, and the nodules with highly suspicious feature showed significant decrease in inconclusive result by first-line CNB. However, increased rates of architectural and follicular neoplasm (FN) were identified in CNB group especially in intermediate and low suspicious nodules, and the first-line CNB could not decrease the inconclusive result in these US groups. The diagnostic rate of neoplasm diagnosed by surgery following the result of architectural atypia or FN was not different between FNA and CNB even with significantly higher rate in CNB group. Furthermore, the sensitivity for follicular neoplasm (21.2 vs. 61.9%) was significantly higher in CNB group. The CNB can be considered in nodules with highly suspicious feature with advantage of significantly lower inconclusive diagnostic rate than FNA group. However, significantly increased diagnosis of architectural atypia or FN in other nodules by CNB is recognized and should be evaluated in future to understand the meaning.

Keywords Thyroid nodule · Fine needle aspiration · Core needle biopsy · Papillary thyroid carcinoma · Follicular neoplasm

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Introduction

The fine needle aspiration (FNA) cytology is still the gold standard for the diagnosis of thyroid nodules in the guidelines. However, the considerable rate of unsatisfactory or atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) result makes it difficult in counseling the patients and requires repeated biopsy procedure in such cases [1]. Recently, many papers reporting the advantage of core needle biopsy (CNB) over FNA for thyroid nodule were published and the role of CNB is reilluminated [2]. By comparing the consecutive result of FNA and CNB performed in thyroid nodule as primary modality of biopsy, we tried to define the advantage and disadvantage of CNB over FNA.

Materials and Methods

Patients

This study is a retrospective study including consecutive patients who underwent US-guided FNA or CNB ordered

in department of Head Neck Surgery outpatient clinics from October 2004 to July 2014. The study protocol was approved by the institutional review board of our institution (IRB No. B-1505-298-114). Inclusion criteria were all FNA or CNB performed as first-line modality for thyroid nodule during this period. The non-thyroidal diseases like lymphoma, tuberculosis, or parathyroid adenoma were excluded.

US-Guided FNA and CNB Procedures

FNA or CNB was guided by IU22 xMATRIX US system (Phillips Healthcare) and was performed by experienced radiologists. For the FNA, a 24-gauze needle with 10-cm^3 syringe was used basically; however, considering the vascularity and calcification, a 26-gauze needle was also selected. Two or three times of FNA were done for a nodule and the pass number is different according to the practitioner; however, passes were stopped when the blood is seen in the needle hub. Direct smear and cell block were used together generally. CNB was performed by automatic biopsy system Acecut (TSK laboratory, Tochigi-Ken, Japan). CNB was performed one time in most cases, but if needed, up to four times of CNB were performed for a nodule. The CNB specimen was prepared as formalin-fixed paraffin-embedded block. The patients were educated to compress the biopsy site for 15 min in FNA and 30 min in CNB, respectively.

Data Collection

The results of FNA were classified according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [3]. The Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group has published a pathology reporting system for thyroid CNB. In this system, the term "indeterminate" is used instead of AUS/FLUS [4]. However, as the basic system is similar to TBSRTC, the indeterminate results on CNB were described as AUS/FLUS in the current study to make comparison easier. In the current series, AUS/FLUS were subcategorized as cellular and architectural atypia. FNA results showing microfollicles or a predominance of Hürthle cells and CNB results indicating follicular proliferative lesions but not conclusive for follicular neoplasm (FN) were classified as architectural atypia.

The US findings were reviewed by the medical record and some items which are not described in the records were reevaluated by reviewing the US image by one senior author (Ahn SH). The US pattern and risk of malignancy suggested by American Thyroid Association (ATA) guideline were applied [5]. Shortly, high suspicion is defined as solid hypoechoic nodule with one or more of the following: irregular margin, microcalcification, taller than wide or disrupted rim calcification. Intermediate suspicion is hypoechoic solid nodule without findings of high suspicion. Low suspicion is isoechoic or hyperechoic solid nodule or partially cystic nodule with eccentric solid portion. Very low suspicion is spongiform or cystic nodule. Benign is purely cystic nodules.

Comparison of Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value

The FNA or CNB performed on the nodules which were operated on and the final pathology is confirmed are collected separately and compared the diagnostic accuracy of each biopsy procedure based on the surgical pathology.

Analysis

The significance of proportional variable was measured using the chi-square test and Fisher exact test. SPSS version 20.0 for Windows was used (IBM, Armonk, NY).

Results

CNB Was Preferred as First-Line Modality in Nodules with Suspicious Features

From October 2004 to July 2014, 2406 nodules from 2187 patients were evaluated with US-guided FNA or CNB. The age was ranged from 4.5 to 95.3 years with an average of 50.7 years. There were 490 male and 1697 female patients. Right thyroid nodule was 1222 cases and left is 1124 and 60 were on isthmus. The average nodule size was 1.73 cm in the largest dimension and ranged from 0.23 to 9.92 cm. The indication of biopsy was generally more than 0.5 cm in size but in nodules with highly suspicious features, biopsy was performed in nodules less than 0.5 cm if patients want.

The first-line biopsy modality of our institute was FNA until 2008. From 2009, CNB is started to be used as first-line modality. It occupies 8.9% in 2009 and 2010. From 2011, CNB is performed as first-line biopsy in 28.9% of patients. Additionally, the diagnostic criteria have changed by TBSRTC in 2009. Comparing the before and after TBSRTC, unsatisfactory and AUS/FLUS result is increased by adopting TBSRTC because detailed diagnostic criteria are offered about adequacy of specimen and criteria for AUS/FLUS by this system.

FNA was performed primarily in 2131 nodules (88.6%) and CNB in 275 nodules (11.4%). Table 1 shows the demographic finding between groups. The age, sex ratio, and size were not different between groups. However, the distribution of US findings was significantly different

Table 1 Demographic finding of nodules with the first FNA vs. first CNB group

	1st FNA group ($N = 2131$)	1st CNB group ($N = 275$)	p value
Age	50.9 ± 0.5	50.3 ± 1.4	0.392
Male:female	455:1676	72:203	0.068
Nodule size (cm)			
Maximal diameter (average, (range))	1.71 (0.23~9.92)	1.82 (0.27~7.00)	0.155
Minimal diameter (average, (range))	1.01 (0.14~4.93)	1.07 (0.23~3.56)	0.142
USG finding: solidity			
Solid	1395 (65.5%)	236 (85.8%)	<0.001
Cyst ≤50%	205 (9.6%)	14 (5.1%)	
Spongiform	239 (11.2%)	22 (8.0%)	
Cyst >50%	130 (6.1%)	3 (1.1%)	
Cystic	162 (7.6%)	0	
Echogenicity			
Hypoechoic	840 (39.4%)	159 (57.8%)	<0.001
Isoechoic	916 (43.0%)	93 (33.8%)	
Hyperechoic	195 (9.2%)	23 (8.4%)	
Cystic	180 (8.4%)	0	
Calcification			
Microcalcification	324 (15.2%)	61 (22.2%)	0.004
Macrocalcification	168 (7.9%)	27 (9.8%)	
No calcification	1639 (76.9%)	187 (68.0%)	
ATA risk stratification			
High suspicion	366 (17.2%)	73 (26.5%)	<0.001
Intermediate suspicion	480 (22.5%)	85 (30.9%)	
Low suspicion	1115 (52.3%)	117 (42.5%)	
Very low suspicion, benign	170 (8.0%)	0	

between groups and CNB was preferred as first-line biopsy for the nodules having higher chance of malignancy.

Unsatisfactory Results Were Significantly Decreased by First-Line CNB

Because the US features between FNA and CNB group showed significant difference, the result of each modality was analyzed according to the risk stratification based on US features suggested by ATA. In FNA group, there was 11.9 to 20.6% of the unsatisfactory result. However, this rate was decreased to 2.4 to 2.6% by selecting CNB as first-line modality and this statistically significant reduction of unsatisfactory result was observed in all US groups (Table 2).

CNB Could Decrease the AUS/FLUS and Inconclusive Results Only in Highly Suspicious Group

In highly suspicious group, the FNA resulted in 21.9% of AUS/FLUS result. In contrary, selecting the CNB as first-line modality could decrease the AUS/FLUS result to 9.6% and showed significant difference. The total inconclusive results including unsatisfactory, AUS/FLUS, and follicular neoplasm (FN) were 36.9% in FNA group and 17.8% in CNB group ($p = 0.002$). Additionally, by avoiding the AUS/FLUS result effectively, the rate diagnosis of malignancy in the first biopsy was 39.9 and 67.1% respectively and showed significant difference (Table 2).

Diagnosis of Architectural Atypia or FN Increased Significantly in Intermediate or Low Suspicious Nodules by First-Line CNB

However, the rate of AUS/FLUS was similar in intermediate suspicious group (19.2 vs. 18.8%) and even higher in CNB group in low suspicious group (11.7 vs. 27.4%). Rate of FN was increased by doing CNB as first-line modality in all US groups (Table 2). With the subcategorical analysis of AUS/FLUS, cellular atypia was found to be the main component of AUS/FLUS in FNA group (80.1%). Contrary to FNA, architectural atypia occupied 80% of AUS/FLUS diagnosed by CNB. The diagnosis rate of architectural atypia was especially high in intermediate and low suspicious groups. There was a consistent finding of decrease in cellular atypia

Table 2 Comparison between FNA and CNB by ultrasound feature: risk stratification suggested by ATA

	High suspicion (N = 439)		Intermediate suspicion (N = 565)		Low suspicion (N = 1232)		Very low suspicion or benign (N = 170)	
	FNA (N = 366)	CNB (N = 73)	FNA (N = 480)	CNB (N = 85)	FNA (N = 1115)	CNB (N = 117)	FNA (N = 170)	CNB (N = 0)
Unsatisfactory	54 (14.8)	2 (2.7)	99 (20.6)	2 (2.4)	133 (11.9)	3 (2.6)	37 (21.8)	0
Benign	85 (23.2)	11 (15.1)	210 (43.8)	35 (41.2)	823 (73.8)	60 (51.3)	128 (75.3)	0
AUS/FLUS	80 (21.9)	7 (9.6)	92 (19.2)	16 (18.8%)	130 (11.7)	32 (27.4)	5 (2.9)	0
FN	1 (0.3)	4 (5.5)	11 (2.3)	19 (22.4)	11 (1.0)	20 (17.1)	0	0
Susp. Malig	42 (11.5)	4 (5.5)	19 (4.0)	1 (1.2)	11 (1.0)	0 (0)	0	0
Malignant	104 (28.4)	45 (61.6)	49 (10.2)	12 (14.1)	7 (0.6)	2 (1.7)	0	0
Repeated biopsy	136 (37.2%)	6 (8.2%)	162 (33.8%)	6 (7.1%)	273 (24.5%)	13 (11.1%)		
	$p < 0.001$		$p < 0.001$		$p = 0.001$			
Inconclusive	36.9 vs. 17.8% ($p = 0.002$)		42.1 vs. 43.5% ($p = 0.813$)		24.6 vs. 47.0% ($p < 0.001$)		–	
Malignancy	39.9 vs. 67.1% ($p < 0.001$)		14.2 vs. 15.3% ($p = 0.740$)		1.6 vs. 1.7% ($p = 1.000$)			

AUS/FLUS atypia of undetermined significance/follicular lesion of undetermined significance, *FN* follicular neoplasm, *Susp. Malig* suspicious for malignancy, *Inconclusive* unsatisfactory+AUS/FLUS+FN, *Malignancy* Susp. Malig + malignant

and increase in architectural atypia by CNB in all US groups (Table 3).

The Rate of Malignancy or Neoplasm in Cellular or Architectural Atypia and FN Showed No Difference Between FNA and CNB Group

Table 4 summarizes the final result according to the first biopsy result to see the accuracy of biopsy result. For this analysis, we excluded the nodules which cannot be followed up. However, the patients who are diagnosed as benign nodule in FNA or CNB and followed up without surgery are included. The malignancy is defined as nodules with confirmative diagnosis of follicular carcinoma (FC) or papillary thyroid carcinoma (PTC). The neoplasm includes the malignant nodule and follicular adenoma (FA) together. The rate of neoplasm or malignancy of cellular or architectural atypia and FN did not show difference between FNA and CNB groups.

CNB Showed Significantly Higher NPV in Diagnosis of PTC

Among 2406 nodules, we performed surgery for 629 nodules (26.1%). There were 143 benign nodules, 88 FA, 20 FC, and 377 PTC (including 50 FVPTC). For these 629 nodules, 490 FNA and 139 CNB were performed as first-line biopsy. The CNB showed higher negative predictive value (NPV) in diagnosing PTC (56.6 vs. 75.5%, $p = 0.001$) and sensitivity in diagnosing FN (21.2 vs. 61.9%, $p < 0.001$). In contrast, the specificity for diagnosing FC or FN was significantly higher in FNA group (98.3 vs. 84.5%, $p < 0.001$) (Table 5).

Discussion

The purpose of this article was the evaluation about the efficacy of FNA and CNB according to the US finding to find out the appropriate indication for first-line CNB. As this study is a retrospective study, the selection of CNB for the first-line biopsy is made by radiologist according to the risk of non-diagnostic result. Therefore, subgroup analysis according to the US finding is essential for comparison of efficacy between FNA and CNB objectively. The risk stratification system of US finding suggested by ATA can be an appropriate grouping method for this purpose. The very low suspicion or benign nodule was not an indication of CNB in our study because these nodules do not have solid portion to do CNB. In other

Table 3 Subcategorical analysis of AUS/FLUS according to FNA vs. CNB

ATA risk	FNA (N = 307/2131, 14.4%)		CNB (55/275, 20.0%)	
	Subcategory			
	Cellular atypia	Architectural atypia	Cellular atypia	Architectural atypia
High	72/366 (19.7%)	8/366 (2.2%)	4/73 (5.5%)	3/73 (4.1%)
Intermediate	73/480 (15.2%)	19/480 (4.0%)	3/85 (3.5%)	13/85 (15.3%)
Low	97/1115 (8.7%)	33/1115 (3.0%)	4/117 (3.4%)	28/117 (23.9%)
Total	246/307 (80.1%)	61/307 (19.9%)	11/55 (20.0%)	44/55 (80.0%)

Table 4 Rate of neoplasm after diagnosis of cellular, architectural atypia, and follicular neoplasm according to the FNA vs. CNB

	Cellular atypia		Architectural atypia		Follicular neoplasm	
	FNA (202)[a]	CNB (7)[a]	FNA (49)[a]	CNB (37)[a]	FNA (21)[b]	CNB (41)[b]
Benign	99 (49.0)	3 (42.9)	33 (67.3)	19 (51.4)	4 (19.0)	5 (12.2)
FA	20 (9.9)	–	7 (14.3)	12 (32.4)	10 (47.6)	22 (53.7)
FC	1 (0.5)	–	4 (8.2)	2 (5.4)	4 (19.0)	4 (9.8)
FVPTC	14 (6.9)	1 (14.3)	4 (8.2)	4 (10.8)	3 (14.3)	8 (19.5)
PTC	68 (33.7)	3 (42.9)	1 (2.0)	–	–	2 (4.9)
Malignancy	83 (41.1)	4 (57.1)	9 (18.4)	6 (16.2)	7 (33.3)	14 (34.1)
Neoplasm	103 (51.0)	4 (57.1)	16 (32.7)	18 (48.6%)	17 (80.9)	36 (87.8)

Number of patients is excluding the patients with follow-up loss. There was no statistically significant difference in rate of malignancy or neoplasm

FA follicular adenoma, *FC* follicular carcinoma, *FVPTC* follicular variant papillary thyroid carcinoma, *PTC* papillary thyroid carcinoma

[a] Number of patients who did further evaluation including second biopsy or surgery

[b] Number of patients who did surgery

Table 5 Sensitivity, specificity, PPV, and NPV of FNA and CNB performed in pathologically confirmed nodule ($N = 629$)

Pathology	FNA ($N = 490$)		CNB ($N = 139$)	
PTC				
	PTC	Others	PTC	Others
PTC	174	135	45	23
Others	5	176	0	71
	Sensitivity	56.3%	66.2%	$p = 0.174$
	Specificity	97.2%	100%	$p = 0.087$
	PPV	97.2%	100%	$p = 0.086$
	NPV	*56.6%*	*75.5%*	$p = 0.001$
Follicular carcinoma				
	FN	Others	FN	Others
FC	4	10	4	2
Others	17	458	37	96
	Sensitivity	28.6%	66.7%	$p = 0.161$
	Specificity	*96.4%*	72.2%	$p < 0.001$
	PPV	19.0%	9.8%	$p = 0.426$
	NPV	97.9%	98.0%	$p = 1.000$
Follicular neoplasm (carcinoma and adenoma)				
	FN	Others	FN	Others
FN	14	52	26	16
Others	7	417	15	82
	Sensitivity	21.2%	*61.9%*	$p < 0.001$
	Specificity	*98.3%*	84.5%	$p < 0.001$
	PPV	66.7%	63.4%	$p = 1.000$
	NPV	88.9%	83.7%	$p = 0.170$

Significantly higher value is presented as italic

PPV positive predictive value, *NPV* negative predictive value, *FNA* fine needle aspiration cytology, *CNB* core needle biopsy, *PTC* papillary thyroid carcinoma, *FN* follicular neoplasm (includes follicular or Hürthle cell adenoma and cancer)

nodules, CNB showed significantly lower rate of unsatisfactory. AUS/FLUS rate was significantly lower in high suspicion group but became higher in low suspicion group. The rate of inconclusive result is significantly decreased by first-line CNB in highly suspicious nodules. However, the inconclusive result showed no difference in intermediate suspicious nodules and significantly increased in low suspicious nodules by CNB. This increase of inconclusive result was due to increased diagnostic rate of architectural atypia and FN.

Cellular and architectural atypia are not defined separately in Bethesda system and just suggested the criteria for AUS/FLUS. However, the clinical difference between cellular and architectural atypia is reported in many previous papers [6–8]. Comparing the biopsy result from FNA and CNB, consistent finding was decreased rate of unsatisfactory and cellular atypia result irrespective of US findings. However, the increased diagnosis of architectural atypia and FN in CNB is newly recognized during this analysis. This increase in the rate of architectural atypia in CNB made the AUS/FLUS rate higher than FNA in low suspicious nodules. As the architectural atypia result in CNB is regarded as suggesting FN, diagnostic surgery was recommended to most of the patients rather than repeated biopsy. That will be the reason that the rate of second biopsy is significantly higher in FNA group in all US groups. Another concern was about the risk that CNB may send more patients to the surgery with lower rate of neoplasm or malignancy due to false-positive result for architectural atypia or FN. Therefore, we tried to compare the rate of malignancy and neoplasm (including FA and malignancy) for each biopsy result whether there is difference between FNA and CNB group. Basically, the rate of neoplasm and malignancy showed no difference

between FNA and CNB including architectural atypia and FN. It suggests that CNB does not increase false positive for FN, but the FNA may miss many follicular neoplasms.

For the diagnosing FN, the CNB showed significantly higher sensitivity. However, sensitivity for the diagnosis of FC failed to show significant difference due to the small number of FC in our series. Although the specificity for diagnosis of FN was higher in FNA than CNB, it looks like due to the very low incidence of follicular neoplasm in FNA group. About the sensitivity and specificity of FNA and CNB, there is confusing data across the papers. Recent meta-analysis used five papers which compared the FNA and CNB performed simultaneously in one nodule [9]. Interestingly, the papers analyzed data from 1997 to 2001 reported lower sensitivity and higher specificity in CNB [10, 11] and papers with recent data from 2008 to 2011 reported higher sensitivity and lower specificity in CNB group as our result [12, 13]. Therefore, considering very low sensitivity of FNA for FN, the increased rate of architectural atypia and FN in CNB may have advantage in terms of screening neoplasm from benign nodule. But increased rate of architectural atypia and FN makes it difficult in counseling the patients about the needs of diagnostic surgery. The limitation of this article is that the data is from a single institute. The variability of sensitivity and specificity of FNA according to the institution is a well-known fact and perhaps we need more data from a multi-center study. Also, the standardized pathologic report form of CNB needs to be developed and we need a definition about architectural atypia in CNB in the future. Another is that as this is a retrospective analysis, the demographic finding of each group cannot be homogenized.

In summary, first-line CNB in nodules with highly suspicious features have advantage of significantly decreased rate of the inconclusive result. And this result is in concordance with literature which reported the usefulness of CNB in solid nodules with high risk of malignancy or in the nodules with calcification [14, 15]. The meaning and usefulness of increased rate of architectural atypia and FN by CNB in intermediate and low suspicious group needs further evaluation with multi-institutional study in the future.

Conclusions

CNB has advantage over FNA by decrease of unsatisfactory result in most nodules and in the nodules with high suspicious features, the rate of AUS/FLUS can be decreased significantly and will be effective in saving the repeated biopsy. Therefore, in terms of decreasing inconclusive results, the first-line CNB can be considered in nodules with suspicious features of malignancy. But for the diagnosis of follicular neoplasm, the significantly increased rate of diagnosis by CNB should be considered in selecting tools of biopsy and the meaning of increased architectural atypia or FN in CNB should be investigated further in future study.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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