What Is the Ideal Core Number for Ultrasonography-Guided Thyroid Biopsy of Cytologically Inconclusive Nodules?

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ABSTRACT

BACKGROUND AND PURPOSE: Core needle biopsy of the thyroid under ultrasonographic guidance provides a larger tissue sample and may facilitate a more precise histologic diagnosis, reducing the need for repetitive fine-needle aspiration or a diagnostic operation. However, there is no consensus regarding the ideal number of specimens to be obtained for ultrasonography-guided core needle biopsy. The aim of this study was to decide the ideal core number for ultrasonography-guided core needle biopsy of cytologically inconclusive nodules.

MATERIALS AND METHODS: Sixty consecutive biopsies were performed in 60 thyroid nodules with Bethesda Category I or III cytology. Three biopsy cores were obtained for each thyroid nodule. The first biopsy specimens were taken from the nodule, while the second and third specimens obtained included the nodular tissue, nodular capsule, and surrounding parenchyma. Diagnostic ability was evaluated according to the following: protocol A, first specimen; protocol B, first and second specimens; and protocol C, all specimens. The McNemar test was used for statistical analysis.

RESULTS: Of the 60 nodules, diagnostic ability was achieved in 41 nodules (68%) with protocol A, in 56 nodules (93%) with protocol B, and in 58 nodules (97%) with protocol C. The diagnostic ability of protocols B and C was significantly higher than that of protocol A (all P values $< .001$). However, the diagnostic ability of protocol B was not significantly different from that of protocol C.

CONCLUSIONS: Ultrasonography-guided core needle biopsy for cytologically inconclusive thyroid nodules should obtain at least 2 core specimens with intranodular and capsule targets.

ABBREVIATIONS: AUS/FLUS = atypia of undetermined significance/follicular lesion of undetermined significance; CNB = core needle biopsy; FNA = fine-needle aspiration; US = ultrasonography

Ultrasonography (US)-guided fine-needle aspiration (FNA) is considered the criterion standard for the evaluation of thyroid nodules due to its simplicity, safety, cost-effectiveness, and diagnostic accuracy. However, a major limitation of FNA is the nondiagnostic and indeterminate cytology results that comprise approximately 10%–33.6% and 15%–42% of all FNA samples,^{1–4} respectively. The Bethesda System for Reporting Thyroid Cytopathology recommended repeat FNA for any nodule with initially nondiagnostic or indeterminate cytology results.⁵ However, repeat FNA does not seem to be a satisfactory solution because

approximately 17%–47% of nodules with initially nondiagnostic cytology^{6–9} and 38.5%–43% of nodules with initially indeterminate cytology^{10,11} will be rediagnosed with inconclusive results.

Core needle biopsy (CNB) of the thyroid gland under US guidance provides a larger tissue sample and may facilitate a more precise histologic diagnosis, reducing the need for repetitive FNA or a diagnostic operation.^{11–18} In addition, US-guided CNB for thyroid nodules by using a modern spring-activated biopsy needle has been reported to be a safe and well-tolerated procedure.^{19–23} However, to the best of our knowledge, there is no consensus regarding the ideal number of core specimens to be obtained for US-guided thyroid CNB.

The purpose of this study was to compare the diagnostic ability based on biopsy core numbers and to decide the ideal core number for US-guided thyroid biopsy of cytologically inconclusive nodules.

MATERIALS AND METHODS

The institutional review board of Samsung Medical Center, Sungkyunkwan University School of Medicine, approved this retrospective study and waived the informed consent requirement.

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FIG 1. Ultrasonographic images of a 43-year-old woman presenting with a 2.2-cm hypoechoic oval mass in the right lobe of the thyroid gland (A). The initial US-guided fine-needle aspiration reading was inconclusive. US-guided core needle biopsy was performed by using a disposable 18-ga, double-action spring-activated needle. The first biopsy specimen with an intranodular target was retrieved from the nodule (B); then, second and third biopsies were sampled to include the marginal portion of the thyroid mass with nodular tissue and surrounding parenchyma (C, margin target). An open-sample notch (arrows) can be well-visualized by US. The outer cutting cannula overlies the shaft of the biopsy needle, ready to fire (curved arrows). Diagnostic ability was not achieved with the first specimen; however, it was with the second and the third specimens. The core needle biopsy result was suggestive of follicular neoplasm. After the operation, the mass was confirmed as a minimally invasive follicular carcinoma.

However, all US-guided biopsies were conducted after obtaining consent of the patients.

Patient Selection

From a retrospective review of the pathologic data base of our institution between June 2013 and December 2013, 102 patients with 105 cytologically inconclusive nodules underwent US-guided thyroid biopsy. We excluded 9 nodules because <3 core biopsy specimens had been obtained (mean, 1.9 cores). Of these 9 nodules, 5 were located near the common carotid artery. The remaining 4 nodules were relatively small (mean, 0.9 cm; range, 0.8–1.2 cm) and deeply located in the thyroid gland. We also excluded 36 nodules of 34 patients because they were not followed up after benign results on US-guided CNB. Finally, 60 thyroid nodules of 59 patients were included in this study. The Bethesda Categories on the initial FNA were I (nondiagnostic) in 45% (27/60) or III (atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS]) in 55%, 33/60). We retrospectively reviewed the medical records for information including age, sex, pathologic findings, ultrasonographic findings, and follow-up and surgical results.

Ultrasonography and Ultrasonography-Guided Core Needle Biopsy Procedures

High-resolution US by using a 7- to 12-MHz linear transducer (iU22; Philips Healthcare, Bothell, Washington) was applied for the guidance of CNB. US-guided CNB procedures were performed by 2 experienced radiologists specializing in thyroid imaging with 11 and 7 years of experience, respectively, and by 1 senior resident under the supervision of 1 expert in 1 case.

US-guided CNB was performed by using a disposable 18-ga, double-action spring-activated needle (1.1-cm excursion with a 7-mm sample notch) (TSK Ace-cut; Create Medic, Yokohama, Japan) after administration of local anesthesia with 1% lidocaine. Using a freehand technique, we obtained 3 biopsy specimens for each thyroid nodule. The first biopsy specimens were retrieved from the nodule (intranodular target). The second and third biopsy specimens targeted the capsular portion (margin target) of the thyroid nodule to include a suspicious nodule, a capsule if present, and surrounding normal parenchyma (Fig 1). Previ-

ously, Han et al²⁴ recommended the modified CNB technique, including both nodular tissue and the capsule of the nodule and/or extranodular thyroid tissue. We routinely performed US-guided CNB for cytologically inconclusive nodules by using this protocol with 3 cores from June 2013. For identification of the different biopsy sites involved, each biopsy specimen was placed in a separate bottle of formalin and labeled. All specimens were then sent to the pathology department for diagnosis.

Histologic Analysis

One pathologist with 15 years of experience in thyroid cytopathology, who was unaware of the official pathology report, reviewed the slides of all patients. Each specimen was mounted on a separate slide.

The diagnostic criteria of CNB have not yet been standardized for thyroid nodules. For this study, CNB histology diagnoses were modified into the same 6 categories as in the Bethesda System according to the histopathology results of CNB.²⁵

The “intranodular target” was defined as a biopsy that targeted the nodular tissue of the tumor. The “margin target” was defined as a biopsy specimen that sampled nodular tissue, the nodular capsule (if present), and surrounding normal parenchyma. The “diagnostic ability” was established when the specimens included targeted tissue areas and were enough for conclusive results of CNB at the same time. The diagnostic ability, based on the specimen numbers, was assessed according to the following: protocol A, first specimen; protocol B, first and second specimens; and protocol C, first, second, and third specimens.

Statistical Analysis

Statistical analysis was performed with the SPSS, Version 22 (IBM, Armonk, New York) computer software program. The McNemar test was used to compare differences in the diagnostic abilities among the core biopsy protocols. A statistically significant difference was defined as $P < .05$.

RESULTS

Patient and Tumor Characteristics

The patient population comprised 47 women (79.7%) and 12 men (20.3%) with a mean age of 48.5 ± 10.8 years (range, 21–73

years). The mean tumor size was 2.2 cm (range, 0.9–6.0 cm). Of the 60 nodules, 36 were in the right lobe; 22, in the left lobe; and 2, in the isthmus. In all patients, CNB procedures were tolerable and were completed without immediate critical complications. Perinodular hemorrhage occurred in 1 patient. In this patient, we applied manual compression for 20 minutes around the hemorrhage site. There was no evidence of major complications resulting in hospitalization.

Diagnostic Ability of Core Needle Biopsy

After CNB, 34 nodules (56.7%) were diagnosed as follicular neoplasm or suspicious for follicular neoplasm; 8 (13.3%), as benign; 7 (11.7%), as suspicious for malignancy; 7 (11.7%), as malignant; and 4 (6.7%), as AUS/FLUS (Table 1). According to the CNB results, 80% (48/60) of all cases were recommended for surgery. In addition, 4 cases with AUS/FLUS histology and 1 case with benign histology were surgically removed for pathologic confirmation or for cosmetic reasons.

Of the 53 nodules removed surgically, 28 cases (52.8%) were confirmed as benign and 25 cases (47.2%) were malignant. Among the 25 malignant nodules, there were 14 follicular variants of papillary thyroid carcinoma (56.0%), 6 follicular carcinomas (24.0%), and 5 papillary thyroid carcinomas (20.0%). For 7 patients with benign core biopsy results who did not undergo an operation, follow-up imaging showed no change in the size of any of the specimens.

Pathologic evaluation according to specimen cores is summarized in Table 2. In the first specimen group, targeted nodular

tissue was successfully retrieved in 59 of 60 cases (98.3%). In the second and third specimen groups, specimens including the nodular tissue, capsular portion, and surrounding parenchyma were retrieved in 46 (76.7%) and 41 cases (68.3%), respectively. The diagnostic ability, defined as a conclusive result of CNB, was 68.3% (41/60) with protocol A (first specimen), 93.3% (56/60) with protocol B (first and second specimens), and 96.7% (58/60) with protocol C (first, second, and third specimens). The diagnostic ability of protocols B and C was significantly higher than that of protocol A ($P < .001$ and $P < .001$, respectively). However, there was no significant difference in diagnostic ability between protocols B and C ($P = .500$). Therefore, protocol B was the most optimal method.

With protocol A, 19 of the 60 first specimens failed to achieve diagnostic ability. Among these 19 cases, 15 demonstrated diagnostic ability with the subsequent second biopsy specimens in protocol B. These were diagnosed as follicular neoplasm ($n = 8$), suspicious for follicular neoplasm ($n = 5$), and nodular hyperplasia ($n = 2$) by CNB and were confirmed as follicular adenoma ($n = 9$), follicular carcinoma ($n = 4$) (Fig 1), and nodular hyperplasia ($n = 2$), respectively, following the operation. Of the 19 failed cases in protocol A, diagnostic ability was achieved for 2 cases with protocol C, while the remaining 2 cases remained inconclusive even with protocol C and subsequently underwent an operation. Two nodules diagnosed as follicular neoplasms with protocol C were confirmed by an operation as follicular adenomas. Two persistent inconclusive nodules were revealed as nodular hyperplasia.

For the 25 malignancies of the 60 nodules, diagnostic ability was achieved in 21 cases (84%) by using protocol A and in 25 cases (100%) with protocol B (Table 3). Among these 25 malignancies, all 19 papillary thyroid carcinomas, including 14 follicular variants and 5 classic types, could be diagnosed by using protocol A. However, of the 29 follicular neoplasms, including 23 follicular adenomas and 6 follicular carcinomas, only 14 (48.3%) were diagnosed with protocol A. The diagnostic ability for follicular neoplasm was 93.1% (27/29) with protocol B and 100% (29/29) with protocol C. For cases of nodular hyperplasia, diagnostic ability was established in 66.7% (8/12) of cases with protocol A and in 83.3% (10/12) with both protocols B and C.

DISCUSSION

US-guided CNB has been suggested as a complementary diagnostic technique for thyroid nodules.^{2,11,18,20,22} Although CNB may not always be technically feasible and requires a significant amount of experience in image-guided thyroid intervention, recent studies have revealed that US-guided CNB of the thyroid

Table 1: CNB results and surgical diagnoses in 60 cytologically inconclusive thyroid nodules^a

Diagnostic Category	CNB Result (n = 60)	Surgical Diagnosis (n = 53)	
		Benign (n = 28)	Malignant (n = 25)
Benign	8 ^b	NH (n = 1)	
AUS/FLUS	4	NH (n = 1) FA (n = 3)	
FN or SFN	34	FA (n = 20) NH (n = 3)	FC (n = 5) FVPTC (n = 5) PTC in NH (n = 1) FVPTC (n = 6) FC (n = 1) PTC (n = 4) FVPTC (n = 3)
Suspicious for malignancy	7		
Malignancy	7		

Note:—FA indicates follicular adenoma; FC, follicular carcinoma; NH, nodular hyperplasia; FVPTC, follicular variant of papillary thyroid carcinoma; PTC, papillary thyroid carcinoma.

^a Data are number of nodules.

^b The remaining 7 nodules showed no change on follow-up US.

Table 2: Pathologic evaluation according to biopsy core specimens^a

Pathologic Evaluation	First Specimen (Intranodular Target) (n = 60)	Second Specimen (Margin Target) (n = 60)	Third Specimen (Margin Target) (n = 60)
Nodular tissues	23 (38.3)	7 (11.7)	8 (13.3)
Capsule	0	0	1 (1.7)
Surrounding parenchyma	0	5 (8.3)	4 (6.7)
Nodular tissue and capsule	8 (13.3)	1 (1.7)	4 (6.7)
Capsule and surrounding parenchyma	1 (1.7)	1 (1.7)	2 (3.3)
Nodular tissue, capsule, and surrounding parenchyma	28 (46.7)	46 (76.7)	41 (68.3)

^a Data are number of nodules. The numbers in the parentheses are percentages.

Table 3: Diagnostic ability according to the 3 different protocols^a

Protocol	Diagnostic Ability	P Value
A (intranodular target)	41/60 (68.3)	<.001 ^b
B (intranodular + margin target)	56/60 (93.3)	.500 ^c
C (intranodular + margin + margin target)	58/60 (96.7)	<.001 ^d

^a Data are numbers of nodules. The numbers in the parentheses are percentages.

^b Significantly different from protocol B ($P < .05$).

^c Not significantly different from protocol C ($P > .05$).

^d Significantly different from protocol A ($P < .05$).

gland is safe^{22,26} and can help patients avoid repetitive FNA or a diagnostic operation.^{11–18} However, to the best of our knowledge, there is no study regarding the diagnostic ability based on the specimen numbers or the ideal number of core specimens to be obtained in the thyroid field. Among the recent studies that have highlighted the value of CNB for diagnosing thyroid nodules,^{11,15–19,27,28} only 5 provided information on the number of core specimens.^{16–18,27,28} In these, most patients had undergone biopsy comprising 1–2 cores, with additional cores taken according to the preference of the individual radiologist.

In the present study, 3 biopsy specimens were sampled for each thyroid nodule. Several previous studies have evaluated the effects of the number of core specimens on diagnostic accuracy and upgrade rates for image-guided CNB, particularly in the breast and prostate.^{29–36} It is important that biopsy specimens be representative of the tumor and reach a reasonable level of agreement on histologic grading between core biopsy and surgical excision specimens. However, while an excessive number of biopsy specimens cannot eliminate the potential for upgrading to a carcinoma diagnosis, it can increase the rate of complications, such as bleeding, pain, and infection. Therefore, the determination of an optimal number of biopsy specimens is required to obtain the highest yield; this will potentially depend on the pathology of individual organs.

We obtained the second and third specimens according to the modified technique by Han et al.²⁴ In addition, almost all the US-guided CNBs were performed by 2 experienced thyroid radiologists, and all biopsy specimens were reviewed by an expert pathologist. These are essential prerequisites for the successful diagnostic results. Recently, several studies have concluded that CNB demonstrates high rates of conclusive and accurate diagnoses in patients previously categorized as nondiagnostic or AUS/FLUS by FNA,^{11,19,24,37} consistent with the findings of the present study.

In the present study, the diagnostic ability was 93.3% (56/60) with protocol B (first and second specimens) and 96.7% (58/60) with protocol C (first, second, and third specimens). In addition, the diagnostic ability of protocols B and C was significantly higher than that of protocol A ($P < .001$ and $P < .001$, respectively). We found that the intranodular target could easily obtain the target tissues compared with the margin target because the margin target should include the capsule of the nodule, nodular tissue, and surrounding parenchyma. However, the intranodular target was limited in its evaluation of the presence of the capsule of the nodule, a major differential factor between nodular hyperplasia and follicular neoplasm (which manifests as completely encapsulated).²⁴ Protocol A failed to achieve diagnostic ability for 19 first specimens. Among these 19 failed cases, diagnostic ability was

achieved in 15 and 2 cases with protocols B and C, respectively. Following the operation, these were confirmed as follicular adenoma ($n = 11$), follicular carcinoma ($n = 4$), and nodular hyperplasia ($n = 2$). In contrast, of the 25 malignancies, 19 papillary thyroid carcinomas were diagnosed with the intranodular target specimens (the first specimens). Therefore, a well-retrieved intranodular target specimen is potentially sufficient for the diagnosis of papillary thyroid carcinoma; the capsule of the nodule is therefore not critical for the diagnosis of papillary thyroid carcinoma. In our protocols, the diagnostic ability was not obtained in 2 cases. These patients were managed with a diagnostic operation and were confirmed as having nodular hyperplasia after the operation.

In the current study, CNB results revealed that 80% of cytologically inconclusive thyroid nodules were indicated for a subsequent operation. After the operation, the malignancy rates were 41.7% (25/60) in all nodules, 32.4% (11/34) in the follicular neoplasm or suspicious for follicular neoplasm group, 100% (7/7) in the suspicious for malignancy group, and 100% (7/7) in the malignancy group. In the CNB-proved follicular neoplasm or suspicious for follicular neoplasm group, 3 nodules were confirmed by an operation as nodular hyperplasia. In the diagnosis of malignancy, there were no false-positive cases of CNB. However, in several previous studies of US-guided thyroid biopsy,^{15,16,18,27,28} variable false-positive and malignancy rates have been reported (0%–18.2% and 14.3%–57.9%, respectively).

The limitations of our study include its retrospective design and potential selection bias. However, we sympathize with the idea of the modified CNB technique,²⁴ and validated this technique.²⁴ In addition, our subjects performed well under routine CNB protocols because the guidelines for CNB procedures are well-established.^{2,11,15,17–19,27,37–41} Another potential limitation is that the diagnostic categories in the histologic diagnosis of CNB have not yet been standardized. However, in this study, CNB results were categorized according to the 6 categories of the Bethesda System. Furthermore, the adequacy of CNB may be highly dependent on the skill and experience of the examiner. However, US-guided CNB of the thyroid gland can be performed safely with appropriate training and qualifications because the use of thyroid-dedicated biopsy needles has been generalized since an automated biopsy gun with an 18-ga needle was introduced.

CONCLUSIONS

US-guided CNB for cytologically inconclusive thyroid nodules should obtain at least 2 core specimens. In cases of papillary thyroid carcinoma, optimum results can be expected when a single biopsy retrieves well-targeted nodular tissue (intranodular target). However, obtaining a second core-containing nodular tissue, the capsule of the thyroid nodule, and surrounding parenchyma (margin target) is essential for the diagnosis of follicular neoplasm or nodular hyperplasia.

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