



## Recent Advances in Core Needle Biopsy for Thyroid Nodules

Chan Kwon Jung<sup>1</sup>, Jung Hwan Baek<sup>2</sup>

<sup>1</sup>Department of Hospital Pathology, College of Medicine, The Catholic University of Korea; <sup>2</sup>Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Core needle biopsy (CNB) was introduced as an alternative diagnostic tool to fine-needle aspiration (FNA), and is increasingly being used in the preoperative assessment of thyroid nodules. CNB provides a definitive diagnosis in most cases, but it sometimes may be inconclusive. CNB has the advantage of enabling a histologic examination in relation to the surrounding thyroid tissue, immunohistochemistry, and molecular testing that can provide a more accurate assessment than FNA in selected cases. Nevertheless, CNB should be performed only by experienced experts in thyroid interventions to prevent complications because CNB needles are larger in caliber than FNA needles. As recent evidence has accumulated, and with improvements in the technique and devices for thyroid CNB, the Korean Society of Thyroid Radiology released its 2016 thyroid CNB guidelines and the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group published a consensus statement on the pathology reporting system for thyroid CNB in 2015. This review presents the current consensus and recommendations regarding thyroid CNB, focusing on indications, complications, and pathologic classification and reporting.

**Keywords:** Thyroid nodule; Biopsy, needle; Guideline; Classification; Radiology; Pathology

### INTRODUCTION

Fine-needle aspiration (FNA) cytology is the gold-standard diagnostic method for the preoperative diagnosis of thyroid nodules [1,2]. Although thyroid aspiration cytology using a large needle was initially introduced in the 1920s, FNA using a 23- to 27-gauge needle has been a mainstream diagnostic modality in the triage of thyroid nodules since the 1980s in most countries because of its diagnostic accuracy and safety [3-7]. Core needle biopsy (CNB) of the thyroid was first introduced as an alternative to FNA in the 1990s [4] and is now widely used for the preoperative examination of thyroid nodules in Korea, with excel-

lent results, because of advances in core needle devices (thinner needles and automatic devices), biopsy technology (new sampling technique) and ultrasound machine (high resolution) [8]. In this review, we present an overview of the indications, complications, and pathologic classification of thyroid CNB.

### CURRENT GUIDELINES AND RECOMMENDATIONS

As evidence has accumulated regarding thyroid CNB, the Korean Society of Thyroid Radiology (KSThR) released its 2016 thyroid CNB guidelines [9]. These guidelines include recom-

**Received:** 23 November 2017, **Revised:** 30 November 2017,

**Accepted:** 4 December 2017

**Corresponding author:** Jung Hwan Baek

Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 86 Asanbyeongwon-gil, Songpa-gu, Seoul 05505, Korea

**Tel:** +82-2-3010-4348, **Fax:** +82-2-476-0090, **E-mail:** radbaek@naver.com

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**Table 1.** Consensus Statement and Recommendations on Thyroid CNB from the Korean Society of Thyroid Radiology [9]

Item	Consensus statement and recommendations
Indication of CNB	
R1	CNB could be alternative to FNA in evaluation of thyroid nodules in selected cases
Device and procedure of CNB	
R2	Modern CNB devices, particularly 18–21-gauge, spring-activated, core needles, are recommended for procedure
R3	Patients with bleeding tendency, such as those taking anti-coagulation medications or with disorders affecting coagulation cascade, should be thoroughly evaluated and any problems corrected before CNB
R4A	CNB should be performed by experienced operators under US guidance
R4B	Manual compression of biopsy site should be performed immediately after procedure for 20 to 30 minutes
Utility of CNB as a second-line alternative tool when previous FNA has indeterminate result	
R5	CNB can be used as alternative to FNA for thyroid nodules with non-diagnostic cytology in previous FNA
R6	CNB may be used as alternative to FNA for thyroid nodules with atypia (follicular lesion) of undetermined significance in previous FNA
R7A	CNB has advantages to differentiate encapsulated follicular neoplasm from non-neoplastic nodule
R7B	CNB cannot differentiate follicular thyroid carcinoma from follicular adenoma
R8	CNB may be used as alternative to FNA for calcified thyroid nodules
Utility of CNB as first-line diagnostic tool	
R9	CNB may achieve low rates of non-diagnostic and inconclusive results for initially detected thyroid nodules. However, utility of CNB as first-line diagnostic tool for these nodules is uncertain based on current evidence
Utility of CNB for cases of difficult diagnosis	
R10A	CNB can be used as alternative to FNA in patients with clinical and radiological features of uncommon malignancies (anaplastic carcinoma, lymphoma, or medullary carcinoma)
R10B	CNB can be used as alternative to FNA for thyroid nodules with US-cytology discordance in previous FNA
Complications of CNB	
R11	CNB is safe, well-tolerated, and associated with low incidence of complications when performed by experienced operators

CNB, core needle biopsy; FNA, fine-needle aspiration; US, ultrasound.

reporting system for thyroid CNB was published by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group in 2015 [10]. The six categorical diagnoses used in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) were retained in the reporting system for thyroid CNB in order to ensure effective communication between pathologists and clinicians, with less likelihood of misinterpreting the pathologic results [1,10].

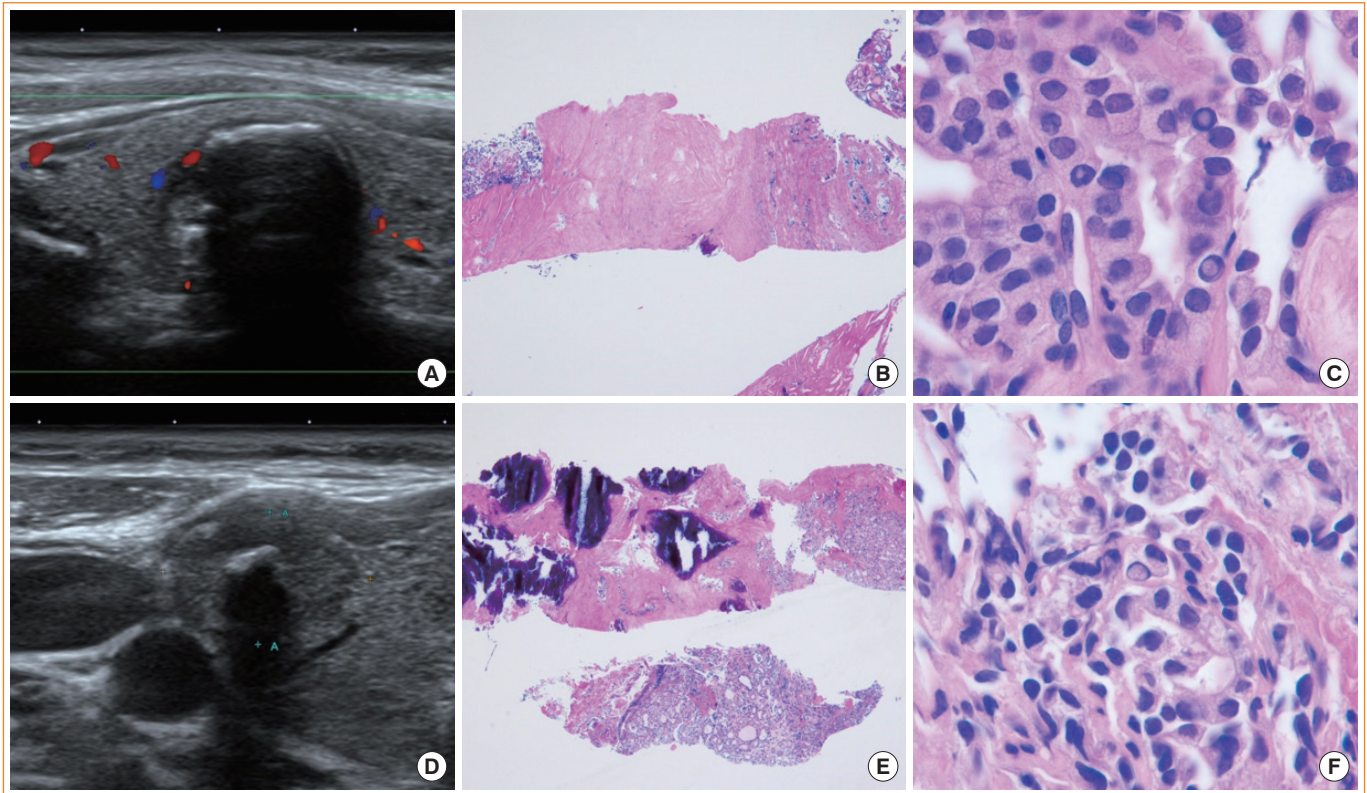
The current thyroid guidelines of the American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi, British Thyroid Association, and KSThR permit the limited use of CNB for thyroid nodules, whereas the American Thyroid Association does not recommend CNB [2,9,11].

## INDICATIONS

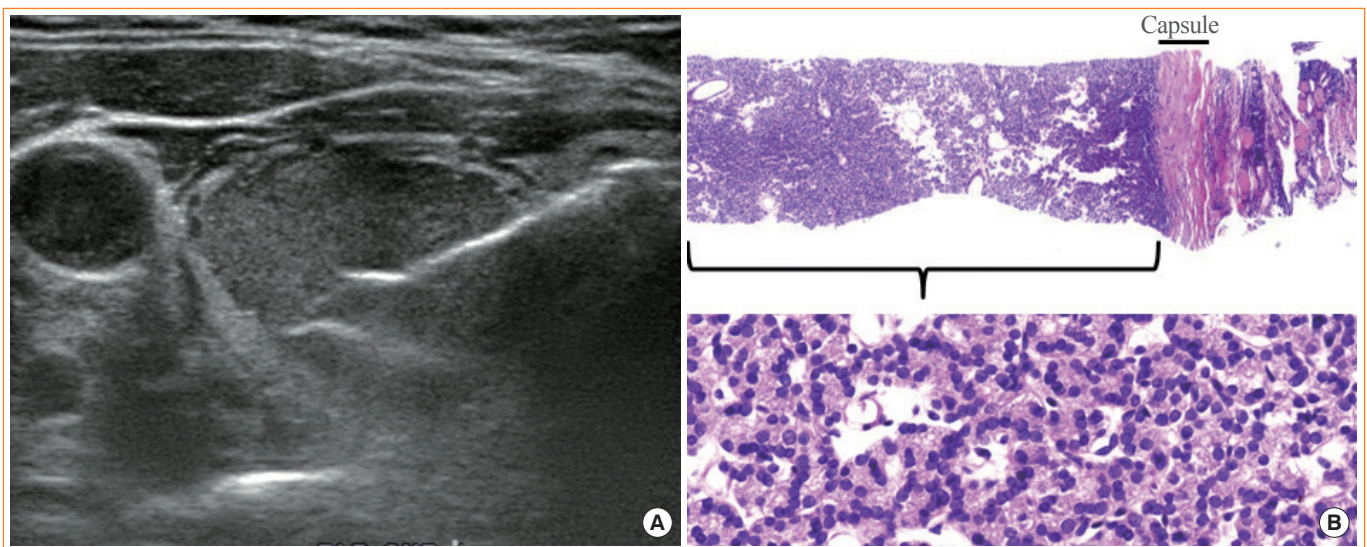
The most widely accepted indications for CNB in the literature include previous FNA results of non-diagnostic [12–15] and atypia of undetermined significance [15–17]. The tissue obtained by CNB provides more abundant material than FNA cytology, especially in cases with marked sclerosis and calcification. A recent meta-analysis of published data showed that the non-diagnostic and inconclusive rates of CNB were 5.5% (95% confidence interval [CI], 2.2% to 8.7%) and 8.0% (95% CI, 4.4% to 11.5%), respectively, whereas the non-diagnostic and inconclusive rates of FNA were 22.6% (95% CI, 12.2% to 33.0%) and 40.2% (95% CI, 25.1% to 55.3%), respectively [18]. In another meta-analysis of thyroid nodules with initially non-diagnostic FNA results, the non-diagnostic rate (6.4%; 95% CI, 3.3% to 16.1%) of follow-up CNB was significantly lower than that of repeated FNA (36.5%; 95% CI, 29.9% to 43.1%) [13]. In large cohort CNB studies, the false-negative rates of CNB ranged from 1% to 3% [19–21].

Although CNB may not be the method of choice for all thyroid nodules, previous studies have demonstrated the advantages of histologic diagnoses made using CNB specimens over the cytological diagnosis using FNA for several specific diseases. Malignant lymphoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, and parathyroid lesions can be confirmatively diagnosed with CNB based on the histologic morphology in conjunction with immunohistochemistry [22–24]. While calcified nodules and degenerating nodules are often diagnosed as unsatisfactory with FNA because of the aspiration of acellular or paucicellular material, scant cellular nodules can be diagnosed as specific disease entities with CNB (Fig. 1) [25–27].

recommendations regarding indications and complications, and are summarized in Table 1. A consensus statement on the pathology



**Fig. 1.** Examples of core needle biopsy (CNB) in thyroid nodules with initial non-diagnostic fine-needle aspiration cytology. (A) On the ultrasound findings of case 1, there is a well-defined hypoechoic solid nodule with rim calcification. (B) CNB of the nodule shows scanty cellular and sclerotic nodules (H&E stain,  $\times 40$ ). (C) A high-power view shows the typical histologic features of papillary carcinoma (H&E stain,  $\times 1,000$ ). (D) An ultrasound image from case 2 shows a 1.5-cm, ill-defined hypoechoic solid nodule with macrocalcifications. (E) CNB shows marked calcification sclerosis, and focally follicular proliferative lesions (H&E stain,  $\times 40$ ). (F) A high-power view of the follicular lesion shows the histologic findings of papillary carcinoma (H&E stain,  $\times 1,000$ ).



**Fig. 2.** Current core needle biopsy technique. (A) The specimen notch shown in ultrasound should include the tumor tissue, tumor capsule, and adjacent normal parenchyma. (B) Histologic examination of the specimen shows the tumor tissue with a microfollicular growth pattern, tumor capsule, and surrounding thyroid tissue (H&E stain,  $\times 40$ , upper;  $\times 400$ , lower). This case should be diagnosed as a follicular neoplasm.

Follicular-patterned lesions include nodular hyperplasia, follicular adenoma, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), the follicular variant of papillary thyroid carcinoma (PTC), and follicular thyroid carcinoma. While FNA and CNB cannot differentiate follicular adenoma from follicular carcinoma and NIFTP from the invasive encapsulated follicular variant of PTC because vascular or capsular invasion cannot be assessed without surgery, it is possible to divide these follicular-patterned lesions into almost certainly benign non-neoplastic lesions and follicular neoplasms with a risk of malignancy. NIFTP and the follicular variant of PTC are diagnosed based on nuclear features in conjunction with architectural atypia showing a follicular growth pattern. For the diagnosis of follicular neoplasm with CNB, it is recommended that the tissue sampling of CNB should include tumor tissue, the tumor capsule, and adjacent normal parenchyma (Fig. 2).

A few studies have suggested that CNB is valuable as a first-line tool for diagnosing initially detected thyroid nodules [21,28]. Suh et al. [21] reported that CNB had a non-diagnostic rate of 1.3% and an inconclusive result rate of 5.9%, a high diagnostic accuracy of 97.6%, and a complication rate of 0.2%.

## SAFETY AND COMPLICATIONS

The current thyroid guidelines suggest that CNB is a safe, tolerable procedure [15,29]. The complication rate is also acceptable (0% to 4.1%), with a low rate of major complications (0% to 1.9%). Recently a large-population single-center study showed no procedure-related deaths, and low rates of major (0.06%) and minor (0.79%) complications [30]. To minimize complications, CNB should be performed by well-trained doctors under real-time ultrasound monitoring. Moreover, knowledge of the neck anatomy, anatomical variations, and potential complications is also required for the safe performance of CNB [31].

## PATHOLOGY REPORTING SYSTEM

The pathology reporting system of CNB is based on the six TB-SRTC categories [10] and is summarized in Table 2. There is only one difference in terminology between the CNB reporting system and TBSRTC. The diagnostic category III for CNB is referred to as an “indeterminate lesion,” which corresponds to “atypia of undetermined significance” or “follicular lesion of undetermined significance” in TBSRTC. Subclassification based on the cytologic and/or architectural atypia in category III and IV was encouraged to enhance communication with clini-

**Table 2.** Diagnostic Categories of Thyroid Core Needle Biopsy from the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group [10]

Item	Diagnostic category
I	Nondiagnostic or unsatisfactory Normal thyroid tissue only Extrathyroid tissue only (e.g., skeletal muscle, mature adipose tissue) A virtually acellular specimen Acellular/paucicellular fibrotic nodule Blood clot only Other
II	Benign lesion Benign follicular nodule or consistent with a benign follicular nodule Hashimoto's thyroiditis Granulomatous (subacute) thyroiditis Nonthyroidal lesion (e.g., parathyroid lesions, benign neurogenic tumors, benign lymph node) Other
III	Indeterminate lesion
IIIA	Indeterminate follicular lesion with nuclear atypia Follicular proliferative lesions with focal nuclear atypia Follicular proliferative lesions with equivocal or questionable nuclear atypia Atypical follicular cells embedded in a fibrotic stroma
IIIB	Indeterminate follicular lesion with architectural atypia Microfollicular proliferative lesion lacking a fibrous capsule or the adjacent nonlesional tissue in the specimen Solid or trabecular follicular lesion lacking a fibrous capsule or the adjacent nonlesional tissue in the specimen Macrofollicular proliferative lesion with a fibrous capsule Hürthle cell proliferative lesion lacking a fibrous capsule or the adjacent nonlesional tissue in the specimen
IIIC	Other indeterminate lesions
IV	Follicular neoplasm or suspicious for a follicular neoplasm
IVA	Follicular neoplasm with nuclear atypia
IVB	Follicular neoplasm with architectural atypia Microfollicular proliferative lesion with a fibrous capsule Mixed microfollicular and normofollicular proliferative lesion with a fibrous capsule Solid/trabecular follicular proliferative lesion with a fibrous capsule
IVC	Follicular neoplasm, Hürthle cell type Hürthle cell proliferative lesion with a fibrous capsule
V	Suspicious for malignancy Suspicious for papillary carcinoma, medullary carcinoma, poorly differentiated carcinoma, metastatic carcinoma, lymphoma, etc.
VI	Malignant Papillary thyroid carcinoma, poorly differentiated carcinoma, undifferentiated (anaplastic carcinoma), medullary thyroid carcinoma, lymphoma, metastatic carcinoma, etc.

cians and pathologists. Each diagnostic category in the TB-SRTC has an implied risk of malignancy and clearly recommended clinical management steps regarding the triage of the patient for clinical follow-up, repeated FNA, or surgery. However, only limited data have been reported regarding the risk of malignancy in each diagnostic category of CNB.

## CONCLUSIONS

Thyroid CNB has been used as an alternative second option to FNA in patients with a previous non-diagnostic or indeterminate diagnosis, and is now suggested as a first-line tool for the diagnosis of thyroid nodule in selected cases. Recent studies have provided evidence for the efficacy and safety of thyroid CNB. Although the current thyroid CNB guidelines and pathologic reporting system are now widely available and affordable, further validation studies should be continued.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## ACKNOWLEDGMENTS

This study was partially supported by a grant (HI16C2013) of the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea.

## ORCID

Chan Kwon Jung <https://orcid.org/0000-0001-6843-3708>

Jung Hwan Baek <https://orcid.org/0000-0003-0480-4754>

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