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Superior Diagnostic Yield of Core Needle Biopsy Over Fine Needle Aspiration in Diagnosing Follicular-Patterned Neoplasms: A Multicenter Study Focusing on Bethesda IV Results

Leehi Joo[1,2], Jung Hwan Baek[3], Jungbok Lee[4], Dong Eun Song[5], Sae Rom Chung[3], Young Jun Choi[3], Jeong Hyun Lee[3]

[1]Department of Radiology, Health Screening and Promotion Center, Asan Medical Center, Seoul, Republic of Korea
[2]Department of Radiology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[3]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea
[4]Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea
[5]Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

Objective: To compare the diagnostic outcomes of core needle biopsy (CNB) and fine-needle aspiration (FNA) using Bethesda IV as a test-positive criterion for diagnosing follicular-patterned neoplasms in a large multicenter cohort.

Materials and Methods: This retrospective study included 5463 thyroid nodules ≥1 cm from 4883 patients (4019 females, 864 males; mean age 53.8 years) that underwent FNA or CNB across 26 hospitals in Korea between June and September 2015. The final diagnosis in cases diagnosed as Bethesda IV (follicular neoplasm) in biopsies were confirmed by surgical pathology. The primary study outcome was the diagnostic yield, defined as the proportion of nodules with follicular-patterned neoplasms confirmed at surgery after receiving Bethesda IV results on biopsy (FNA or CNB), among all that underwent biopsy. Secondary outcomes included false referral rate (FRR) and positive predictive value (PPV). All nodules were analyzed before matching (823 and 4640 nodules for CNB and FNA, respectively) and after nodule matching in a 1:2 ratio (799 and 1571 nodules, respectively) according to age, sex, nodule size, and Korean Thyroid Imaging Reporting and Data System (K-TIRADS) category. Additionally, the diagnostic yields of various histological subtypes of follicular-patterned neoplasms and nodule subgroups were analyzed.

Results: CNB demonstrated a significantly higher diagnostic yield than FNA both before (9.0% vs. 0.5%; $P < 0.001$) and after matching (9.0% vs. 0.6%; $P < 0.001$). CNB consistently had higher diagnostic yields than FNA for most histological subtypes and all subgroups. FRR was not significantly different between the CNB and FNA groups after matching (0.4% vs. 0.1%; $P = 0.337$). The PPV was consistently greater than 90% for both methods, with no significant difference.

Conclusion: CNB had a higher diagnostic yield than FNA for follicular-patterned neoplasms, with no significant difference in FRR using Bethesda IV as the test-positive criterion.

Keywords: Diagnostic yield; Thyroid neoplasms; CNB; FNA; False referral rate

INTRODUCTION

In the diagnosis of thyroid nodules, fine-needle aspiration (FNA) is the standard method [1] but has notable limitations, including high rates of nondiagnostic (11.2%–12.9%) and atypia of undetermined significance/follicular

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Corresponding author: Jung Hwan Baek, MD, PhD, Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
• E-mail: radbaek@naver.com

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lesion of undetermined significance (AUS/FLUS) (6.2%–9.6%) results [2,3], often requiring repeat procedures or even surgery [4,5]. Core needle biopsy (CNB), although more invasive, offers better tissue sampling, reducing nondiagnostic (2.8%) and AUS/FLUS (1.2%) outcomes with a minor complication rate of 2.8%, as reported by Kim et al. [3]. It has proven effective as a first-line [6-12] and second-line [3,13-17] diagnostic tool for thyroid nodules.

Although relatively rare, follicular-patterned neoplasms present with unique diagnostic challenges. Ultrasound (US) cannot reliably differentiate between malignant and benign follicular-patterned neoplasms [18-21], and FNA is limited in distinguishing between non-neoplastic conditions, such as nodular hyperplasia and follicular-patterned neoplasms, as well as between benign and malignant forms of these neoplasms [22-24]. Diagnostic ambiguity can lead to unnecessary surgeries or delays in appropriate treatment.

However, CNB provides histological structural information [25], and when it includes a fibrous capsule, it can aid in resolving diagnostic ambiguity [3,14,26,27]. A study by Ahn et al. [28] suggests that employing a so-called "modified technique" improves diagnostic concordance and sensitivity for follicular-pattern thyroid lesions [26]. Nevertheless, studies directly comparing FNA and CNB in diagnosing follicular-patterned neoplasms are limited.

In a study by Yoon et al. [24], CNB was shown to have significantly lower false positive and unnecessary surgery rates than FNA in diagnosing follicular-patterned neoplasms. However, assessing their true diagnostic performance is inherently challenging because not all nodules undergo confirmatory surgeries. Moreover, to our knowledge, no study has comprehensively compared the frequencies of FNA and CNB in accurately diagnosing follicular-patterned neoplasms in real-world clinical practice. Therefore, we aimed to compare the diagnostic outcomes of these two biopsy methods for diagnosing follicular-patterned neoplasms using Bethesda IV at the biopsies as the test-positive criterion to assess their clinical utility and efficiency in a large dataset from a multicenter cohort.

MATERIALS AND METHODS

Study Population

In this retrospective study, patient data were collected from 26 hospitals in Korea as part of the Thyroid Imaging Network of Korea registry [29-31]. Ethical approval for this retrospective study was obtained from the Institutional Review Board of the authors' institution (IRB No. 2018-1186), and approval for collecting anonymized data was obtained from the Institutional Review Board of each participating institution. Due to the study's retrospective nature and the use of anonymized records, the requirement for informed consent was waived. Patients who underwent thyroid US between June and September 2015 were included in this study. The inclusion criterion was nodules of at least 1 cm in size and patients who had undergone either FNA or CNB. Patients were excluded if their thyroid nodules were <1 cm, imaging quality was poor, or biopsy results were inconclusive. Of the 22775 patients who underwent thyroid US across 26 institutions, 16877 patients were excluded for various reasons such as lack of an index test (FNA or CNB) (n = 4502), nodules smaller than 1 cm (n = 12130), and suboptimal image quality (n = 245). An additional 1015 patients with 1102 nodules were excluded because of

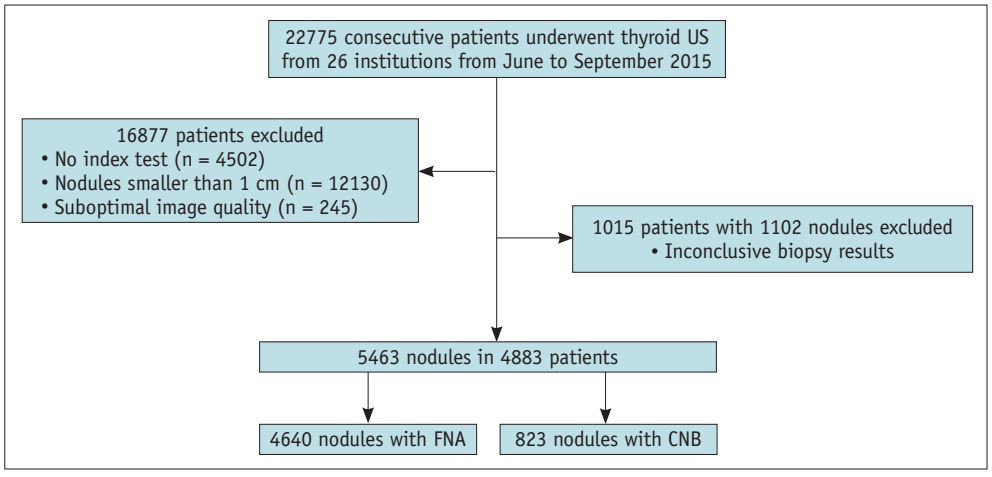

Fig. 1. Flowchart of the study population. US = ultrasound, FNA = fine-needle aspiration, CNB = core needle biopsy

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inconclusive biopsy results (Fig. 1). Ultimately, 5463 thyroid nodules, including 98 follicular-patterned neoplasms, from 4883 patients (4019 females and 864 males; mean age 53.8 years, age range 19–93 years) were analyzed.

US Examination and Image Analysis

All US examinations were performed using high-resolution US systems equipped with 5–14 MHz linear probes. Stored in Digital Imaging and Communications in Medicine (DICOM) format, the US images were reviewed by 17 experienced radiologists on an online platform (AIM AiCRO: https://study.aim-aicro.com). These radiologists, each with 8–22 years of experience in thyroid imaging, were responsible for retrospectively reviewing and interpreting the sonographic features of the thyroid nodules included in this study. To ensure a consistent interpretation of the US criteria, two initial meetings established a consensus on lexicon usage based on the 2016 Korean Thyroid Imaging Reporting and Data System (K-TIRADS) [32]. As part of a pre-study training session, the reviewers evaluated the US features of 15 biopsy-confirmed thyroid nodules that were not included in the study, focusing on their internal content, echogenicity, shape, orientation, margins, calcifications, and the presence of spongiform appearance or comet-tail artifacts. All radiologists blinded to the biopsy results and final diagnoses independently assessed these features. Although the US reviews were conducted as part of a broader database-building effort and not exclusively for this study, they adhered to the standardized K-TIRADS protocol, minimizing potential variability and ensuring consistency relevant to the study's objectives.

US-Guided Biopsy and Cytological and Histological Analysis

Patients with thyroid nodules underwent US-guided FNA or CNB in accordance with Korean guidelines across all 26 hospitals [32-34].

FNA findings were categorized into six groups following the Bethesda System for Reporting Thyroid Cytopathology: I (nondiagnostic, formerly nondiagnostic or unsatisfactory), II (benign), III (atypia of undetermined significance, formerly atypia of undetermined significance/follicular lesion of undetermined significance), IV (follicular neoplasm, formerly follicular neoplasm/suspicious for a follicular neoplasm), V (suspicious for malignancy), and VI (malignancy) [4]. Since the CNB diagnostic criteria for thyroid nodules were not fully standardized at the time of the study, as in FNA, CNB histological results were reclassified into six groups based on pathologists' reports from each institution, following the Bethesda System [14,24,35]. Although the biopsy results and surgical reports for this study cohort were based on the guidelines at the time, we aimed to use updated terminology throughout the study. For the initial use of terms in the manuscript, the current terminology and terminology used during the study period are provided in parallel. Biopsy results classified as Bethesda IV were considered positive.

Reference Standard

Nodules with an initial test-positive result (Bethesda IV) on biopsies were surgically removed, and histopathological confirmation was used as the reference standard. Nodules confirmed as follicular-patterned neoplasms after surgery were classified as true positives. Follicular-patterned neoplasm [36] refers to a thyroid tumor characterized predominantly by a (micro)follicular growth pattern. It includes various pathological entities, such as follicular adenoma/oncocytic adenoma, follicular carcinoma/oncocytic carcinoma, and follicular variant papillary thyroid carcinoma with poorly differentiated carcinoma. Conversely, nodules that tested positive on the initial biopsy but disease-negative upon surgical confirmation were considered false positives.

Study Outcomes

The primary outcome was the diagnostic yield of FNA or CNB for follicular-patterned neoplasms. The diagnostic yield was defined as the proportion of nodules with follicular-patterned neoplasms confirmed at surgery after receiving Bethesda IV results on biopsy (FNA or CNB), among all that underwent biopsy [37]. Secondary outcomes included the false referral rate (FRR) and positive predictive value (PPV). FRR was defined as the proportion of nodules with diagnoses other than follicular-patterned neoplasms confirmed at surgery after receiving Bethesda IV results on biopsy (FNA or CNB), among all that underwent biopsy [37]. PPV was defined as the proportion of nodules with follicular-patterned neoplasms confirmed by surgery among those classified as Bethesda IV on FNA or CNB.

Diagnostic yields were analyzed for various histological subtypes of follicular-patterned neoplasms, defined as the proportion of nodules confirmed as each histological subtype by surgery after receiving Bethesda IV results on biopsy (FNA or CNB), among all that underwent biopsy. The diagnostic yields and FRRs were also compared between FNA and CNB in subgroups of nodules according to age, sex, location, nodule

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size, and K-TIRADS category.

Statistical Analysis

In addition to the analysis of the entire dataset, matched samples were analyzed to mitigate potential selection bias due to differences in age, sex, size, and K-TIRADS categories between the FNA and CNB groups. The nodules were matched in a 1:2 ratio based on age (±5 years) and sex using the greedy algorithm. Standardized differences were evaluated to assess the covariate balance. The chi-square test or Fisher's exact test was used to compare the diagnostic yields and FRRs between the FNA and CNB groups in the total dataset before matching, while a generalized estimating equation was used for the matched dataset. An odds ratio (OR) with FNA as the base category and its 95% confidence interval (CI) was calculated as statistical parameters for comparing FNA and CNB in the subgroups. OR was calculated using exact logistic regression or conventional logistic regression, depending on the sample size, for the total unmatched dataset and (exact) conditional logistic regression for the matched dataset. Accordingly, the *P*-values reflected the matched/adjusted analysis for the matched dataset and the unmatched/unadjusted analysis for the entire dataset. All analyses were conducted using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Patient and Nodule Characteristics

The characteristics of the study sample are presented in Table 1. A total of 5463 nodules were included in the analysis, of which 4640 (84.9%) underwent FNA and 823 (15.1%) underwent CNB.

Diagnostic Yield of Biopsy in Diagnosing Follicular-Patterned Neoplasms

Among the 5463 included nodules, the test-positive rate was 1.9% (102 of 5463 nodules; 95% CI: 1.5%, 2.2%), the diagnostic yield was 1.8% (98 of 5463 nodules; 95% CI: 1.5%, 2.2%), the FRR was 0.07% (4 of 5463 nodules; 95%

Table 1. Patient and nodule characteristics

	Entire cohort (5463 nodules)			Matched cohort (2308 nodules)		
	FNA (n = 4640)	CNB (n = 823)	Standardized difference	FNA (n = 1571)	CNB (n = 799)	Standardized difference
Age, yr*	53.8 ± 12.7	53.3 ± 12.9	-0.040	53.4 ± 12.4	53.2 ± 12.87	-0.013
Age category, yr			0.087			0.087
<40	639 (13.8)	138 (16.8)		221 (14.1)	134 (16.8)	
≥40, <60	2461 (53.0)	408 (49.6)		840 (53.5)	397 (50.0)	
>60	1540 (33.2)	277 (33.7)		510 (32.5)	268 (33.5)	
Sex			-0.092			-0.014
Female	3859 (83.2)	655 (79.6)		1275 (81.2)	644 (80.6)	
Male	781 (16.8)	168 (20.4)		296 (18.8)	155 (19.4)	
Location			0.090			<0.001
Left	2045 (44.1)	393 (47.8)		755 (48.1)	383 (47.9)	
Right	2391 (51.5)	404 (49.1)		770 (49.0)	391 (48.9)	
Isthmus	204 (4.4)	26 (3.2)		46 (2.9)	25 (3.1)	
Size, cm*	20.1 ± 10.2	24.2 ± 12.9	0.357	22.6 ± 11.6	23.6 ± 12.2	0.087
Size category, cm			0.326			0.036
≥1, <2	2842 (61.3)	378 (45.9)		748 (47.6)	377 (47.2)	
≥2, <4	1535 (33.1)	349 (42.4)		669 (42.6)	340 (42.6)	
≥4	263 (5.7)	96 (11.7)		154 (9.8)	82 (10.3)	
K-TIRADS			0.127			<0.001
2	279 (6.0)	31 (3.8)		51 (3.3)	27 (3.4)	
3	2563 (55.2)	431 (52.4)		847 (53.9)	428 (53.6)	
4	1228 (26.5)	244 (29.7)		464 (29.5)	236 (29.5)	
5	570 (12.3)	117 (14.2)		209 (13.3)	108 (13.5)	

Unless otherwise stated, data are shown as number of nodules with percentages in parentheses.
*Data are mean ± standard deviation.
FNA = fine-needle aspiration, CNB = core needle biopsy, K-TIRADS = Korean Thyroid Imaging Reporting and Data System

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CI: 0.02%, 0.1%), and the PPV was 96.1% (95% CI: 90.3%, 98.9%). In the matched cohort of 2370 nodules, the overall diagnostic yield increased to 3.4% (81 of 2370 nodules; 95% CI: 2.7%, 4.2%), the FRR was 0.2% (4 of 2370 nodules; 95% CI: 0.0%, 0.3%), and the PPV was 95.3% (95% CI: 90.8%, 99.8%).

The diagnostic outcomes are summarized in Table 2. When comparing FNA and CNB, notable differences in the test-positive rate and diagnostic yield were observed in the total population and the matched cohort. In the total population, the test-positive rate for FNA was 0.5% (25 of 4640; 95% CI: 0.3%, 0.8%), significantly lower than 9.4% for CNB (77 of 823; 95% CI: 7.4%, 11.4%; $P < 0.001$). FNA had a diagnostic yield of 0.5% (24 of 4640; 95% CI: 0.3%, 0.8%), whereas CNB showed a significantly higher yield of 9.0% (74 of 823; 95% CI: 7.1%, 11.2%) ($P < 0.001$). Similarly, in the matched cohort, CNB demonstrated a significantly higher test-positive rate of 9.4% (75 of 799; 95% CI: 7.4%, 11.4%) compared to 0.6% for FNA (10 of 1571; 95% CI: 0.2%, 1.0%; $P < 0.001$). CNB achieved a significantly higher diagnostic yield of 9.0% (72 of 799; 95% CI: 7.0%, 11.0%) compared to 0.6% for FNA (9 of 1571; 95% CI: 0.2%, 1.0%; $P < 0.001$).

The specific histological subtypes involved in follicular-patterned neoplasms include follicular adenoma, which is

Table 2. Diagnostic yield, false referral rate, and positive predictive value of initial FNA and CNB in diagnosing follicular-patterned neoplasm

Outcomes	Entire cohort			Matched cohort		
	FNA (n = 4640)	CNB (n = 823)	*P*	FNA (n = 1571)	CNB (n = 799)	*P*
Test positive (Bethesda IV) rate	25 (0.5) [0.3, 0.8]	77 (9.4) [7.4, 11.4]	<0.001	10 (0.6) [0.2, 1.0]	75 (9.4) [7.4, 11.4]	<0.001
Diagnostic yield-overall	24 (0.5) [0.3, 0.8]	74 (9.0) [7.1, 11.2]	<0.001	9 (0.6) [0.2, 1.0]	72 (9.0) [7.0, 11.0]	<0.001
Diagnostic yield-subcategories						
Benign	10 (0.2) [0.1, 0.4]	34 (4.1) [2.9, 5.7]	<0.001	2 (0.1) [0.02, 0.5]	34 (4.3) [2.9, 5.7]	<0.001
Follicular adenoma	10 (0.2) [0.1, 0.4]	34 (4.1) [2.9, 5.7]	<0.001	2 (0.1) [0.02, 0.5]	34 (4.3) [2.9, 5.7]	<0.001
Malignant	14 (0.3) [0.1, 0.5]	38 (4.6) [3.2, 6.1]	<0.001	7 (0.5) [0.1, 0.8]	36 (4.5) [3.1, 5.9]	<0.001
Follicular thyroid Ca	7 (0.2) [0.06, 0.3]	20 (2.4) [1.5, 3.7]	<0.001	2 (0.1) [0.02, 0.5]	19 (2.4) [1.3, 3.4]	<0.001
MIFTC	5 (0.1) [0.03, 0.3]	17 (2.1) [1.2, 3.3]	<0.001	1 (0.1) [<0.01, 0.4]	17 (2.1) [1.1, 3.1]	<0.001
WIFTC	2 (0.04) [0.01, 0.2]	3 (0.4) [0.1, 1.1]	0.027	1 (0.1) [<0.01, 0.4]	2 (0.3) [0.03, 0.9]	0.264
Oncocytic Ca	3 (0.1) [0.01, 0.2]	0 (0.0)		2 (0.1) [0.02, 0.5]	0 (0.0)	
FVPTC	4 (0.1) [0.02, 0.2]	16 (1.9) [1.1, 3.1]	<0.001	3 (0.2) [0.04, 0.6]	16 (2.0) [0.1, 3.0]	<0.001
Poorly differentiated Ca	0 (0.0)	2 (0.2) [0.03, 0.9]		0 (0.0)	1 (0.1) [<0.01, 0.1]	
False referral rate	1 (0.02) [<.01, 0.1]	3 (0.4) [0.1, 1.1]	0.012	1 (0.1) [<0.01, 0.2]	3 (0.4) [<0.01, 0.1]	0.337
Positive predictive value	24 (96.0) [79.6, 99.9]	74 (96.1) [89.0, 99.2]	1.000	9 (90.0) [55.5, 99.8]	72 (96.0) [88.8, 99.2]	0.270

Data other than odds ratio are presented as the number of nodules, with percentages shown in parentheses and 95% confidence intervals in brackets. When rounding percentages to one decimal place as per the general guideline leads to a loss of accuracy, the values are instead reported to two decimal places to more accurately represent the data. Diagnostic yield = test-positive and disease-positive cases/total cohort size, False referral rate = test-positive and disease-negative cases/total cohort size, Positive predictive value = test-positive and disease-positive cases/test-positive cases.
FNA = fine-needle aspiration, CNB = core needle biopsy, Ca = carcinoma, MIFTC = minimally invasive follicular thyroid carcinoma, WIFTC = widely invasive follicular thyroid carcinoma, FVPTC = follicular variant of papillary thyroid carcinoma

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benign, and several malignant neoplasms, including follicular carcinoma, minimally invasive follicular thyroid carcinoma, widely invasive follicular thyroid carcinoma (WIFTC), oncocytic (formerly Hürthle cell) carcinoma, follicular variant of papillary thyroid carcinoma, and poorly differentiated carcinoma. CNB consistently showed significantly higher diagnostic yields across various subtypes than FNA (Table 2), both before and after matching, except for WIFTC.

False Referral Rate and Positive Predictive Value of Biopsy in Diagnosing Follicular-Patterned Neoplasms

The FRR and PPV values are listed in Table 2. The pathologies contributing to FRR include nodular hyperplasia and intrathyroidal parathyroid adenoma. Regarding the FRR, CNB showed a higher rate of 0.4% (3 of 823; 95% CI: 0.1%, 1.1%) compared to 0.02% for FNA (1 of 4640; 95% CI: <0.01%, 0.1%), with statistical significance (P = 0.012). However, after matching, although CNB still had a higher FRR of 0.4% (3 of 799; 95% CI: <0.01%, 0.1%) compared to 0.1% for FNA (1 of 1571; 95% CI: <0.01%, 0.2%), this difference was no longer statistically significant (P = 0.337).

The PPV for FNA (96.0%; 95% CI: 79.6%, 99.9%) and CNB (96.1%; 95% CI: 89.0%, 99.2%) in the total cohort and the matched cohort (FNA: 90.0%; 95% CI: 55.5%, 99.8%; CNB: 96.0%; 95% CI: 88.8%, 99.2%) showed no statistically significant differences before and after matching.

Subgroup Analysis

CNB consistently showed a significantly higher diagnostic yield than FNA across most subgroups, including age, sex, location, size, and K-TIRADS, with some exceptions in smaller subgroups, likely due to the limited sample sizes (Table 3). Interestingly, the interaction between sex and biopsy method was statistically significant before matching (P for interaction = 0.013) but not after matching (P for interaction = 0.447), suggesting that the apparent difference in diagnostic yield between sexes was mitigated when confounding factors were controlled. CNB showed ORs of 29.415 and 11.804 for K-TIRADS 3 and 24.693 and 10.954 for K-TIRADS 4 before and after matching, respectively (P < 0.001). Notably, the P-value for the interaction between biopsy methods within the subgroups was not statistically significant. This suggests that these factors did not significantly alter the difference in the diagnostic yield between CNB and FNA, indicating a generally consistent effect of CNB across these subgroups. Although the FRR analysis was limited by the small number of cases, FRR showed no significant differences between CNB and FNA across all subgroups where statistically valid results were available post-matching (Table 4).

DISCUSSION

Our study evaluated the diagnostic yield and other related outcomes of CNB and FNA using a large dataset from a multicenter cohort of 5463 nodules (4640 FNA, 823 CNB). CNB showed a significantly higher diagnostic yield than FNA, both before (9.0% vs. 0.5%; P < 0.001) and after matching (9.0% vs. 0.6%; P < 0.001). CNB had higher diagnostic yields than FNA for most histological subtypes of follicular-patterned neoplasms, irrespective of whether the lesions were benign or malignant. There were no statistically significant differences between the two biopsy methods in FRR or PPV (FRR: 0.4% vs. 0.1%; PPV: 96.0% vs. 90.0% after matching). Overall, CNB demonstrated advantages over FNA for the diagnosis of follicular-patterned neoplasms.

The higher diagnostic yield of CNB for follicular-patterned neoplasms aligns with the expectation that CNB should outperform FNA given its ability to collect larger tissue samples and assess architectural features, which FNA lacks. Despite this, the absence of a significant difference in the PPV between CNB and FNA suggests that CNB classifies Bethesda IV more accurately. Previous studies [3,38] support this, showing higher Bethesda IV rates in the CNB group (17.5% vs. 2.0% and 15.7% vs. 3.4%; both P < 0.001), likely due to CNB's improved histological evaluation. Conversely, these studies found a higher AUS/FLUS rate in the FNA group (6.2% vs. 1.2%, P < 0.001 and 40.9% vs. 29.4%, P = 0.009). This suggests that follicular-patterned neoplasms may be more frequently misclassified as AUS/FLUS by FNA. Such inaccuracies, as suggested in another study in which similar surgical and malignancy rates were reported regardless of the tumor size or diagnostic method, imply that follicular-patterned neoplasms may be underdiagnosed or inaccurately categorized in FNA samples with follicular architecture [3]. These errors can lead to further diagnostic procedures, such as repeat biopsy or surgery, delayed treatment, and increased healthcare costs. The similar FRR between CNB and FNA suggests that CNB improves the diagnostic yield without increasing unnecessary surgeries, where Bethesda IV is classified through biopsy, but no follicular-patterned neoplasms are found upon surgery.

To investigate whether certain characteristics favored CNB, we performed a subgroup analysis and applied matching to control for confounding variables, such as

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Table 3. Comparison of diagnostic yields between FNA and CNB in subgroups

Subgroups	Entire cohort					Matched cohort				
	FNA (n = 4640)	CNB (n = 823)	OR	*P*	*P* for interaction	FNA (n = 1571)	CNB (n = 799)	OR	*P*	*P* for interaction
Age category, yr					0.233					0.095
<40	4 (0.6)	20 (14.5)	24.424 [8.630, 69.123]	<0.001		2 (0.9)	20 (15.0)	21.225 [2.76, 163.221]	0.003	
≥40, <60	13 (0.5)	43 (10.5)	21.583 [11.602, 40.148]	<0.001		4 (0.5)	41 (10.3)	68.626 [9.413, 500.292]	<0.001	
>60	7 (0.5)	11 (4.0)	8.8 [3.482, 22.363]	<0.001		3 (0.6)	11 (4.1)	6.094 [1.668, 22.262]	0.006	
Sex					0.013					0.447
Female	15 (0.4)	61 (9.3)	25.659 [14.600, 45.093]	<0.001		6 (0.5)	59 (9.2)	22.434 [8.993, 55.962]	<0.001	
Male	9 (1.2)	13 (7.7)	7.060 [3.020, 16.503]	<0.001		3 (1.0)	13 (8.4)	11.363 [2.545, 50.723]	0.002	
Location					0.781					0.360
Left	7 (0.3)	28 (7.1)	21.187 [9.403, 47.735]	<0.001		1 (0.1)	28 (7.3)	55.018 [7.484, 404.483]	<0.001	
Right	17 (0.7)	44 (10.9)	16.749 [9.526, 29.449]	<0.001		8 (1.0)	42 (10.7)	12.808 [5.428, 30.228]	<0.001	
Isthmus	0 (0.0)	2 (7.7)	NA			0 (0.0)	2 (8.0)	NA		
Size category, cm					0.725					0.963
≥1, <2	7 (0.3)	19 (5.0)	20.506 [8.768, 47.961]	<0.001		2 (0.3)	19 (5.0)	18.526 [4.312, 79.599]	<0.001	
≥2, <4	14 (0.9)	39 (11.2)	13.349 [7.221, 24.678]	<0.001		6 (0.9)	38 (11.2)	14.536 [5.713, 36.981]	<0.001	
≥4	3 (1.1)	16 (16.7)	15.254 [4.672, 49.802]	<0.001		1 (0.7)	15 (18.3)	23.499 [4.266, 129.439]	<0.001	
K-TIRADS					0.302					0.799
2	1 (0.4)	3 (9.7)	22.801 [3.200, 162.472]	0.002		0 (0.0)	3 (11.1)	NA		
3	8 (0.3)	38 (8.8)	29.415 [13.886, 62.310]	<0.001		3 (0.4)	38 (8.9)	24.693 [7.618, 80.032]	<0.001	
4	12 (1.0)	26 (10.7)	11.804 [5.930, 23.496]	<0.001		6 (1.3)	25 (10.6)	10.954 [3.787, 31.686]	<0.001	
5	3 (0.5)	7 (6.0)	11.006 [3.037, 39.885]	<0.001		0 (0.0)	6 (5.6)	NA		

Data other than OR are presented as the number of relevant nodules, with diagnostic yield in percentage shown in parentheses. The 95% confidence intervals for OR values are in brackets. When rounding percentages to one decimal place as per the general guideline leads to a loss of accuracy, the values are instead reported to two decimal places to more accurately represent the data. Diagnostic yield = test-positive and disease-positive cases/total cohort size.
FNA = fine-needle aspiration, CNB = core needle biopsy, OR = odds ratio, NA = not applicable, K-TIRADS = Korean Thyroid Imaging Reporting and Data System

age, sex, size, and K-TIRADS. This enabled a more accurate comparison of diagnostic yields and FRR between FNA and CNB. Through this analysis, we confirmed that these factors did not significantly affect the differences in the diagnostic yield, demonstrating the consistent advantages of CNB across various subgroups.

While previous studies have focused on diagnostic performance, which measures a test's inherent accuracy, our study emphasizes diagnostic yield—a measure of how effectively a test identifies diseases in real-world clinical settings that bridges the gap between diagnostic performance and diagnosis-related patient outcomes

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Table 4. Comparison of false referral rates between FNA and CNB in subgroups

Subgroups	Entire cohort					Matched cohort				
	FNA (n = 4640)	CNB (n = 823)	OR	*P*	*P* for interaction	FNA (n = 1571)	CNB (n = 799)	OR	*P*	*P* for interaction
Age category, yr					0.722					0.731
<40	1 (0.2)	1 (0.7)	4.644 [0.477, 45.205]	0.186		1 (0.2)	1 (0.7)	2.0 [0.125, 31.975]	0.624	
≥40, <60	0 (0.0)	1 (0.3)	NA			0 (0.0)	1 (0.3)	NA		
>60	0 (0.0)	1 (0.0)	NA			0 (0.0)	1 (0.4)	NA		
Sex					0.625					0.691
Female	1 (0.03)	3 (0.5)	13.798 [2.033, 93.656]	0.007		1 (0.03)	2 (0.5)	6.0 [0.624, 57.681]	0.121	
Male	0 (0.0)	0 (0.0)	NA			0 (0.0)	0 (0.0)	NA		
Location					0.958					0.954
Left	0 (0.0)	1 (0.3)	NA			0 (0.0)	1 (0.3)	NA		
Right	1 (0.04)	2 (0.5)	9.899 [1.302, 75.233]	0.027		1 (0.04)	2 (0.5)	4.0 [0.363, 44.113]	0.258	
Isthmus	0 (0.0)	0 (0.0)	NA			0 (0.0)	0 (0.0)	NA		
Size category, cm					0.631					0.876
≥1, <2	1 (0.04)	3 (0.8)	17.656 [2.597, 120.042]	0.003		1 (0.04)	3 (0.8)	6.0 [0.624, 57.681]	0.121	
≥2, <4	0 (0.0)	0 (0.0)	NA			0 (0.0)	0 (0.0)	NA		
≥4	0 (0.0)	0 (0.0)	NA			0 (0.0)	0 (0.0)	NA		
K-TIRADS					0.970					0.967
2	0 (0.0)	0 (0.0)	NA			0 (0.0)	0 (0.0)	NA		
3	0 (0.0)	0 (0.0)	NA			1 (0.04)	2 (0.5)	4.0 [0.363, 44.113]	0.258	
4	1 (0.03)	2 (0.3)	9.38 [1.236, 71.181]	0.030		0 (0.0)	0 (0.0)	NA		
5	0 (0.0)	1 (0.9)	NA			0 (0.0)	1 (1.1)	NA		

Data other than OR are presented as the number of relevant nodules, with false referral rate in percentage shown in parentheses. The 95% confidence intervals for OR values are in brackets. When rounding percentages to one decimal place as per the general guideline leads to a loss of accuracy, the values are instead reported to two decimal places to more accurately represent the data. False referral rate = test-positive and disease-negative cases/total cohort size.
FNA = fine-needle aspiration, CNB = core needle biopsy, OR = odds ratio, NA = not applicable, K-TIRADS = Korean Thyroid Imaging Reporting and Data System

[37,39]. Using data from a large multicenter cohort, we demonstrated that CNB has a higher diagnostic yield than FNA in identifying follicular-patterned neoplasms, making it more clinically relevant. This suggests that CNB can reduce the need for unnecessary additional tests or surgeries, resulting in more streamlined and accurate diagnoses and more efficient resource use. In addition, despite the higher diagnostic yield of CNB, the FRR was similar between CNB and FNA, indicating no significant difference in unnecessary diagnostic surgeries between the two methods. Meanwhile, previous studies have reported no substantial differences in complication rates between CNB and FNA [25,40-43].

In clinical practice, biopsies are typically used to diagnose malignant nodules; however, they are also performed to confirm benignity before ablation therapy. Follicular-patterned neoplasms, though ultimately confirmed surgically, frequently present as low-suspicion nodules [19,21], making them potential candidates for thermal ablation. Because FNA often results in inconclusive findings, CNB could provide a more definitive and efficient diagnosis of follicular-patterned neoplasms. This approach may reduce the risk of the inadvertent ablation of nodules requiring surgical intervention, thereby improving treatment precision and patient safety.

This study had several limitations. First, it was a retrospective study. However, efforts have been made

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to minimize selection bias by conducting large-scale, multicenter studies. Second, the choice between FNA and CNB is inevitably influenced by potential confounding factors such as patient and nodule characteristics, institutional characteristics, and physician preference. However, we performed a matched analysis to mitigate this selection bias. Third, many patients were excluded due to the lack of an index test, inconclusive biopsy results, or suboptimal imaging quality, which may have introduced selection bias. However, the large multicenter design and robust matching to control for confounding variables strengthen the reliability and generalizability of our findings. Fourth, the limited number of FRR cases may restrict the statistical power, affecting the findings' generalizability. However, the low FRR in this large multicenter cohort of over 5400 nodules is, in itself, clinically meaningful for reducing unnecessary surgery. Future studies with larger sample sizes are required to validate these findings. Fifth, the variability in US indications and performers across institutions is an inherent limitation reflecting real-world clinical practice. However, a standardized retrospective review by 17 experienced radiologists using the contemporaneous K-TIRADS minimized inter-observer variability and ensured consistency in image classification. Sixth, US and pathological reviews were not specifically conducted for this study. Although the US reviews adhered to the standardized K-TIRADS protocol, minimizing variability, this study relied on existing pathology reports rather than a centralized pathology review. This approach reflects real-world clinical practice but limits alignment with the latest WHO classification, including molecular criteria. Future studies should incorporate pathological reviews and updated diagnostic standards to enhance the validity and reliability of the findings. Seventh, this study did not include data on complications or adverse effects of CNB and FNA. However, it is commonly accepted that the complication rates between the two groups do not differ significantly, as noted in one systematic review and meta-analysis that reported rates of 0.01% for CNB and 0.0% for FNA [40].

In conclusion, CNB demonstrated a significantly higher diagnostic yield than FNA in identifying follicular-patterned neoplasms, with no significant difference in FRR using Bethesda IV as a test-positive criterion. This highlights CNB's utility in clinical practice, considering the diagnostic challenges of follicular-patterned neoplasms and their impact on diagnosing and treating thyroid nodules.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to institutional and ethical restrictions related to patient data sharing, but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Leehi Joo. Data curation: Jung Hwan Baek, Sae Rom Chung, Young Jun Choi, Jeong Hyun Lee. Formal analysis: Jungbok Lee. Investigation: Leehi Joo, Jung Hwan Baek. Methodology: Leehi Joo. Project administration: Leehi Joo. Resources: Leehi Joo, Jung Hwan Baek, Sae Rom Chung, Young Jun Choi, Jeong Hyun Lee. Software: Jungbok Lee. Supervision: Leehi Joo, Jung Hwan Baek. Validation: Leehi Joo, Jung Hwan Baek, Jungbok Lee. Visualization: Leehi Joo. Writing—original draft: Leehi Joo. Writing—review & editing: Leehi Joo, Dong Eun Song, Jung Hwan Baek.

ORCID IDs

Leehi Joo
https://orcid.org/0000-0002-5527-0476
Jung Hwan Baek
https://orcid.org/0000-0003-0480-4754
Jungbok Lee
https://orcid.org/0000-0002-1420-9484
Dong Eun Song
https://orcid.org/0000-0002-9583-9794
Sae Rom Chung
https://orcid.org/0000-0003-4219-7166
Young Jun Choi
https://orcid.org/0000-0001-7098-5042
Jeong Hyun Lee
https://orcid.org/0000-0002-0021-4477

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[1]Department of Radiology, Cha University Gangnam Medical Center
[2]Department of Radiology, Chung-Ang University Hospital, Chung-Ang University College of Medicine
[3]Department of Radiology, Konkuk University Medical Center, Konkuk University Scool of Medicine
[4]Department of Radiology, Gyeongsang National University Hospital
[5]Department of Radiology, Korea University Anam Hospital
[6]Department of Radiology, Kosin University College of Medicine
[7]Department of Radiology, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea
[8]Department of Radiology, Dongguk University Ilsan Hospital
[9]Department of Radiology, GangNeung Asan Hospital, University of Ulsan College of Medicine
[10]Department of Radiology, Seoul Metropolitan Government Seoul National University Boramae Medical Center
[11]Department of Radiology, National Cancer Center
[12]Department of Radiology, Soonchunhyang University Seoul Hospital
[13]Department of Radiology, Nowon Eulji Medical Center, Eulji University
[14]Department of Radiology, Seoul National University Bundang Hospital
[15]Department of Radiology, Inje University Haeundae Paik Hospital
[16]Department of Radiology, Seoul St. Mary's Hospital College of Medicine, the Catholic University of Korea
[17]Department of Radiology, Hanyang University Guri Hospital, Hanyang University College of Medicine
[18]Department of Radiology, Ajou University School of Medicine
[19]Department of Radiology, Chonnam National University Hwasun Hospital
[20]Department of Radiology, University of Ulsan College of Medicine, Asan Medical Center
[21]Department of Radiology, Seoul National University Hospital
[22]Department of Radiology, Thyroid Center, Daerim St. Mary's Hospital
[23]Department of Radiology, Busan Paik Hospital, Inje University College of Medicine
[24]Department of Radiology, Eunpyeong St. Mary's Hospital

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