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Original Article

Usage and Diagnostic Yield of Fine-Needle Aspiration Cytology and Core Needle Biopsy in Thyroid Nodules: A Systematic Review and Meta-Analysis of Literature Published by Korean Authors

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Objectives. The usefulness of core needle biopsy (CNB) for the diagnosis of thyroid nodules remains controversial, and preferences vary across hospitals. The purpose of this study was to assess the actual use of CNB in Korea and to analyze the advantages and disadvantages of CNB through a systematic review and meta-analysis of papers published by Korean authors.

Methods. A meta-analysis of full-text publications published in English presenting data from Korea retrieved from the Embase literature database was performed.

Results. CNB led to a significantly lower proportion of non-diagnostic results than fine-needle aspiration (FNA). However, the frequency of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) did not decrease as a result of performing CNB in nodules with initial AUS/FLUS results, while it increased in consecutive cases. A subcategory analysis of AUS/FLUS showed that the increased frequency of AUS/FLUS findings on CNB was due to more frequent diagnoses of architectural atypia and follicular neoplasm, which resulted in a higher frequency of inconclusive findings in consecutive cases compared to FNA. Hospitals favoring CNB had a higher proportion of AUS/FLUS diagnoses. Although the complication rate did not differ significantly between CNB and FNA, serious complications of CNB did occur.

Conclusion. A reduced frequency of non-diagnostic results may be a definite advantage of CNB over FNA. However, the increased frequency of diagnoses of architectural atypia and follicular neoplasm should be considered when selecting CNB as a diagnostic tool.

Keywords. *Thyroid Nodule; Core Needle Biopsy; Aspiration Biopsies, Fine Needle; Thyroid Carcinoma*

INTRODUCTION

Core needle biopsy (CNB) has been used for thyroid nodules in Korea since the mid-to-late 2000s, and a paper published in 2011 was the first to assess the role of CNB in thyroid nodules [1]. Thereafter, various hospitals in Korea—especially Asan Medical Center—have published studies suggesting that CNB is advantageous over fine-needle aspiration (FNA) cytology. However, at academic meetings, we have encountered discordant opinions across hospitals regarding the role of CNB, with some practitioners feeling that CNB offers enough advantages to be considered as the first-line modality for biopsy and others believing that CNB confers no advantage over FNA. Previous meta-analyses of CNB evaluated its diagnostic accuracy based on its sensitivity or specificity for the diagnosis of malignancy or focused on specific conditions, such as nodules with non-diagnostic or atypia

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of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) results on previous FNA [2-11]. Therefore, there are limitations in the degree to which we understand the difference between CNB and FNA in real clinical settings based on those meta-analyses.

This systematic review and meta-analysis included all articles on CNB and/or FNA in thyroid nodules published by Korean authors to analyze the frequency of various Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) categories. The purpose of this study was, through a comprehensive review of consecutive data from Korea, to determine the circumstances in which hospitals favor CNB or FNA and to compare differences in results between CNB and FNA, with the goal of clarifying expectations related to the choice of a biopsy modality in Korea.

MATERIALS AND METHODS

Literature search

The Embase database was searched on September 18, 2019, using the terms "'thyroid'/exp OR thyroid" AND ("fine needle aspiration" OR "core needle biopsy") AND "Korea."

Inclusion criteria

The inclusion criteria were: (1) full-text original articles in English published by Korean authors, (2) presenting data from a specific hospital, (3) frequency of diagnoses reported using consecutive cases, and (4) results on thyroid nodules, especially differentiated thyroid carcinoma. Conference articles, reviews or meta-analyses, and articles reporting multi-center data were excluded. FNA findings were analyzed based on the TBSRTC, while CNB data were analyzed based on the proposal of the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group [12]. However, the reporting system proposed by the Korean Study Group uses the same system as TBSRTC, and the only difference is that AUS/FLUS in TBSRTC is expressed as an indeterminate lesion in the Korean Study Group proposal. In this paper, indeterminate results on CNB are collectively referred to as AUS/FLUS.

HIGHLIGHTS

- Core needle biopsy (CNB) can significantly decrease the frequency of non-diagnostic findings.
- CNB results in an increased frequency of findings of architectural atypia and follicular neoplasm.
- The preference for CNB is related to the frequency of atypia of undetermined significance/follicular lesion of undetermined significance results.
- The complication rate did not differ between fine-needle aspiration and CNB, but serious complications are possible in CNB.

Data analysis

A proportional meta-analysis was performed to compare the frequencies of diagnoses, and multiple comparisons were performed between six subgroups. The Bonferroni correction was applied to determine the *P*-values of inter-group differences. The proportional meta-analysis was performed using a comprehensive meta-analysis (Biostat, Englewood, NJ, USA). Forest plots were constructed using Excel (Microsoft Corp., Redmond, WA, USA).

RESULTS

Articles published by Korean authors on FNA or CNB in thyroid diseases

After removing duplicates, 965 records were retrieved from Embase. Screening of titles excluded 721 irrelevant records, leaving

Table 1. Number of papers on FNA or CNB in thyroid diseases published by authors from Korea

Index	Institute	FNA	CNB
1	Ajou University	2	0
2	Asan Medical Center	18	29
3	Busan Paik Hospital	17	0
4	Catholic University	10	3
5	Chung-Ang University	1	1
6	Chungbuk National University	1	0
7	Chungnam National University	4	0
8	Dong-A University	1	0
9	Ewha Womans University	1	0
10	Gacheon University	1	1
11	Yonsei University Gangnam Severance Hospital	7	0
12	Gangneung Asan Hospital	2	2
13	Gyeongsang National University	2	0
14	Hallym University	1	0
15	Human Medical Imaging	5	3
16	Inha University	2	0
17	Inje University	1	0
18	Kangbuk Samsung Hospital	1	0
19	Konkuk University	7	0
20	Korea University	7	0
21	Kyungpook National University	2	1
22	Myongji Hospital	1	0
23	National Cancer Center	2	0
24	Pusan National University	3	0
25	Samsung Medical Center	20	4
26	Seoul National University Boramae Hospital	2	0
27	Seoul National University Bundang Hospital	6	4
28	Seoul National University Hospital	8	2
29	Yonsei University Severance Hospital	65	4
30	Soonchunhyang University	1	0
31	Ulsan University Hospital	1	0
32	Yeouido St. Mary's Hospital	1	0
Total		204	54

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

244 records for abstract or full-text review. Before further exclusion from the qualitative synthesis, the frequency of publications on FNA and CNB was analyzed by hospital (Table 1). In total, 204 articles on FNA and 54 on CNB were published by authors from 32 hospitals. Papers on CNB were published by authors from only 11 of those 32 hospitals (34.4%), suggesting that specific hospitals favored CNB. After excluding 188 additional records, the meta-analysis finally included 56 records. The reasons for exclusion and the number of records included in the meta-analysis are described in Fig. 1.

Comparison of CNB and repeated FNA in thyroid nodules with non-diagnostic or AUS/FLUS results on initial FNA

Eleven studies reported biopsy results after initial non-diagnostic or AUS/FLUS results [1,13-22]. Of those papers, the study period of Yeon et al. [20] overlapped with that of another paper [13] published using data from the same hospital and was excluded.

CNB and repeated FNA in nodules with non-diagnostic initial FNA findings

Three papers [13,16,17] compared CNB and repeated FNA of nodules with non-diagnostic initial FNA results, while one paper [21] reported only the results of repeated FNA. The study details are summarized in Table 2. The proportional meta-analysis of the diagnoses for each criterion showed a significantly lower pooled proportion of non-diagnostic results for CNB than for FNA (1.6% vs. 34.4%, $P<0.001$) (Fig. 2A). The proportions of other diagnostic categories did not differ significantly between CNB and repeated FNA (Supplementary Fig. 1). Although the proportions

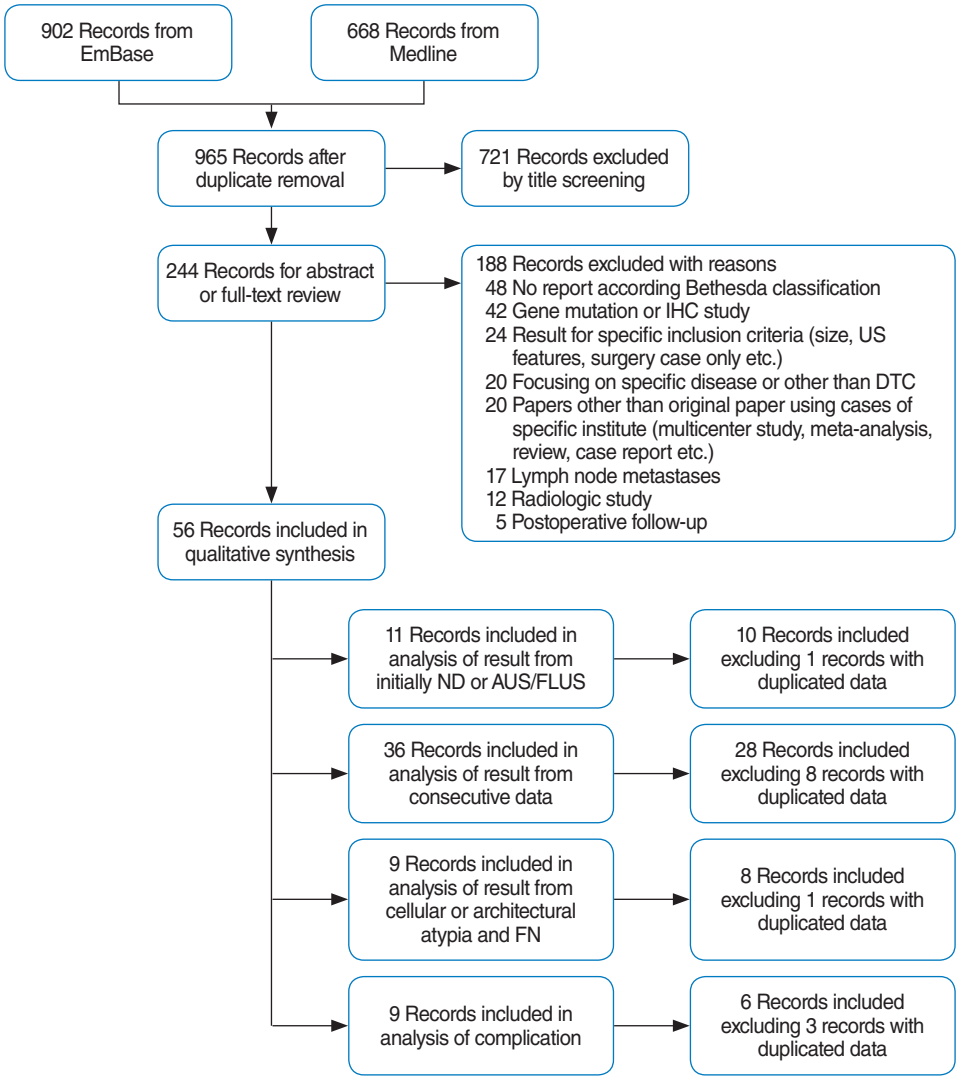


Fig. 1. Flow diagram illustrating the literature search protocol. IHC, immunohistochemistry; US, ultrasound; DTC, differentiated thyroid carcinoma; ND, non-diagnostic; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN, follicular neoplasm.

of follicular neoplasm/suspicious for follicular neoplasm diagnoses (FN/SFN; pooled proportion: 5.8% in CNB and 1.1% in FNA, *P*-value before the Bonferroni correction=0.021) and malignancy (pooled proportion: 16.6% in CNB and 5.0% in FNA, *P*-value before the Bonferroni correction=0.022) were higher in CNB than those in FNA, the differences were not statistically significant after the Bonferroni correction.

CNB and repeated FNA in nodules with AUS/FLUS findings on initial FNA

Seven papers [1,14,15,17-19,22] reported CNB or FNA results in nodules initially diagnosed as AUS/FLUS (Table 3). Among these seven papers, two reported only the results of FNA [15,19]. Others compared CNB and repeated FNA results and assessed the usefulness of CNB. However, Yoon et al. [22] concluded that despite the lower rates of inconclusive results from CNB than from repeated FNA, CNB did not decrease the rate of diagnostic surgery, reflecting a weakness of CNB.

The proportional meta-analysis showed significantly lower proportions of non-diagnostic findings on CNB than on FNA (pooled proportions: 3.0% vs. 11.8%, *P*=0.002) (Fig. 2B). The proportion of AUS/FLUS findings on CNB was lower than that observed for repeated FNA (pooled proportions: 24.1% vs. 35.2%) (Fig. 2C) but the difference was not statistically significant (*P*=0.379) due to the wide variability in CNB. Meanwhile, the proportion of FN/SFN diagnoses was significantly higher for CNB than for repeated FNA (8.0% vs. 1.7%, *P*=0.017) (Fig. 2D). The proportions of other diagnostic categories did not significantly differ between CNB and repeated FNA (Supplementary Fig. 2).

Proportions of diagnoses made using CNB or FNA in consecutive patients

Among the 56 studies included in the qualitative analysis, 36 included data on the proportions of diagnoses following the TB-SRTC or equivalent criteria [23-57]. Eight papers [24,36,39,40, 42,44,51,55] were excluded because their study periods overlapped with those of other papers reporting data from the same hospital; thus, the analysis included 28 papers. Five papers reported diagnostic findings for both CNB and FNA [30,33,43,54, 56], while four papers [23,26,27,31] reported CNB results only.

Table 2. Comparison of repeated FNA and CNB in thyroid nodules with non-diagnostic results on initial FNA

Study	Institute	Study period	Included case	Main outcome
Choi et al. (2014) [13]	Asan Medical Center	2008.10–2011.12	360 Consecutive nodules; 180 FNA and 180 CNB	Non-diagnostic results: 1.1% CNB vs. 40% FNA (*P*<0.001) Inconclusive results: 7.2% CNB vs. 72% FNA (*P*<0.001)
Lee et al. (2014) [16]	Catholic University	2008.10–2012.8	389 FNA, 125 CNB, retrospective	Non-diagnostic results: 2.4% CNB vs. 33.2% FNA (*P*<0.001)
Na et al. (2012) [17]	Human Medical Imaging	2009.2–2010.1	64 Nodules with simultaneous FNA and CNB, prospective	Non-diagnostic results: 1.6% CNB vs. 28.1% FNA (*P*<0.001) Inconclusive results: 12.5% CNB vs. 45.3% FNA (*P*<0.001)
Yoon et al. (2018) [21]	Severance Hospital	2010.1–2013.1	175 Repeated FNA for 322 nodules (≥1 cm)	Interval for repeated biopsy in nodules with initially non-diagnostic results: 6 months will be safe

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

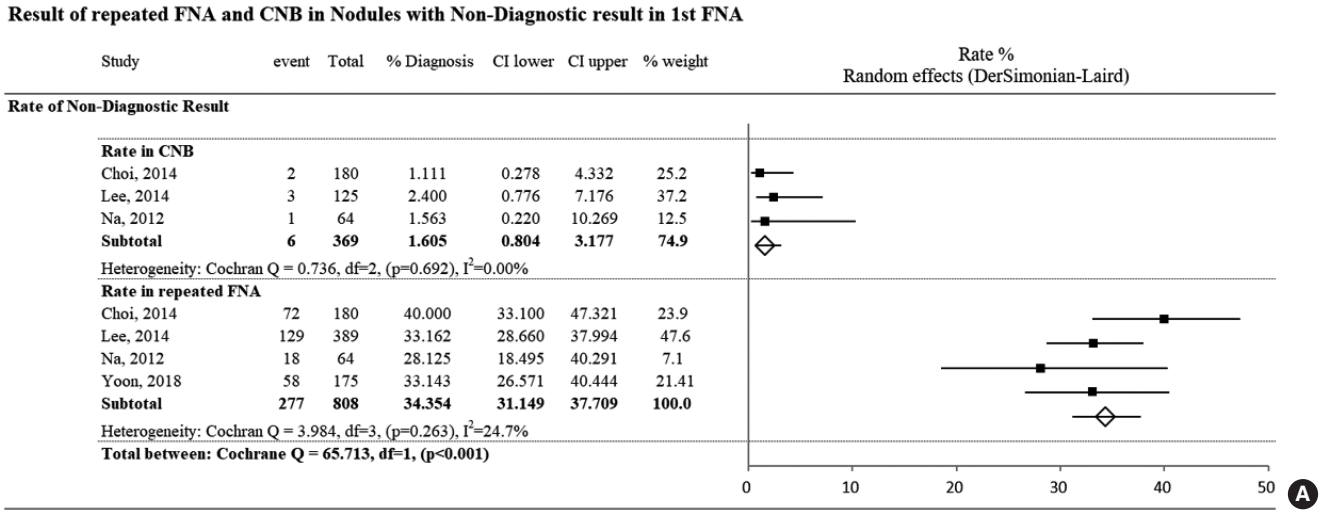


Fig. 2. Forest plot of the proportional analysis of diagnostic categories between core needle biopsy (CNB) and fine-needle aspiration (FNA) performed in nodules initially classified as non-diagnostic or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). (A) Proportion of non-diagnostic results in nodules with non-diagnostic results from initial FNA. (*Continued to the next page*)

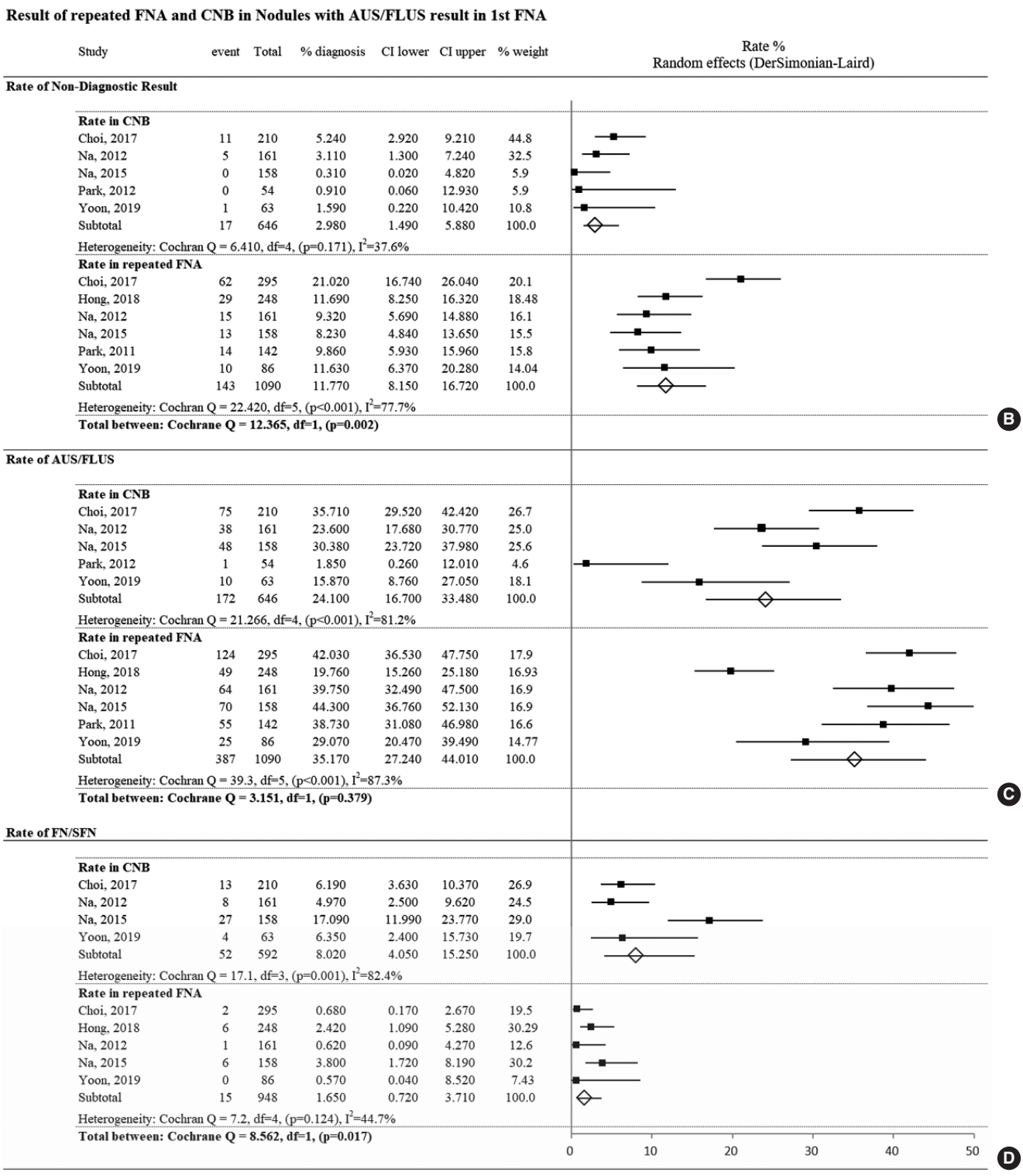


Fig. 2. (Continued) Proportion of diagnoses in nodules with AUS/FLUS results from initial FNA: non-diagnostic result (B), AUS/FLUS (C), and follicular neoplasm/suspicious of follicular neoplasm (FN/SFN; D). CI, confidence interval.

The other papers reported FNA data. Table 4 presents a detailed summary of each paper.

Differences in the proportions of diagnoses on consecutive FNA between hospitals favoring or not favoring CNB

Twenty-four papers reporting the proportions of diagnoses made

Table 3. Comparison of repeated FNA and CNB in thyroid nodules with AUS/FLUS results on initial FNA

Study	Institute	Study period	Included case	Main outcome
Choi et al. (2017) [14]	Asan Medical Center	2008–2013.7	505 Consecutive nodules with 295 FNA and 210 CNB, retrospective	Rate of inconclusive results (non-diagnostic or AUS/FLUS): 40.9% in CNB vs. 63% in FNA (P<0.001)
Hong et al. (2018) [15]	Ewha Womans University	2011.1– 2014.12	Among 687 nodules with AUS/FLUS, repeated FNA in 248	Malignancy risk according to ultrasound findings and clinical features
Na et al. (2012) [17]	Human Medical Imaging	2009.2–2010.1	161 AUS/FLUS; simultaneous repeated FNA and CNB, prospective	AUS/FLUS results: 23.6% in CNB vs. 39.8% in FNA (P<0.001) Inconclusive results: 26.7% in CNB vs. 49.1% in FNA (P<0.001)
Na et al. (2015) [18]	Human Medical Imaging	2010.2– 2013.7	158 Consecutive AUS/FLUS nodules (≥1 cm) with simultaneous FNA and CNB	Comparison of subcategory of AUS/FLUS; nuclear atypia vs. follicular lesions with other atypia; CNB is more helpful for surgical decision-making than FNA
Park et al. (2011) [1]	Seoul National University Bundang Hospital	2005.2–2009.7	142 FNA and 54 CNB, retrospective	Non-diagnostic (unsatisfactory or indeterminate) rate was 1.8% in CNB and 48.6% in FNA
Park et al. (2015) [19]	Severance Hospital	2010.1– 2013.1	236 Repeated FNA	Malignancy rate in nodules with two consecutive results of AUS/FLUS
Yoon et al. (2019) [22]	Severance Hospital	2013.5– 2015.7	149 Nodules with 86 FNA and 63 CNB	Inconclusive results: 33.7% in FNA vs 11.1% in CNB (P=0.003). Diagnostic surgery rate was the same in both groups – CNB did not decrease the frequency of diagnostic lobectomy.

FNA, fine-needle aspiration; CNB, core needle biopsy; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance.

using FNA published from 14 hospitals were included. Seven of these hospitals also published data about CNB and reported its advantages over FNA; these hospitals were categorized as favoring CNB. One hospital focused on the weaknesses or disadvantages of CNB in four papers [22,43,58,59]; despite publishing papers on CNB, we categorized this hospital as not favoring CNB. Head and neck surgeons working at five other hospitals without a paper on CNB were contacted to obtain information on their use of CNB, and they confirmed that they rarely used CNB in clinical settings. Therefore, data from 14 papers [30,32-35,41,46,48-50,52,54,56,57] published by authors from eight hospitals favoring CNB were compared to data from 10 papers [25, 28,29,37,38,43,45,47,53,60] published by authors from six hospitals that did not favor CNB to identify differences in the proportions of diagnoses according to the TBSRTC. Fig. 3A shows the differences in the pooled estimates obtained by applying the TBSRTC criteria between hospitals that did or did not favor CNB. The most significant between-group difference was the higher frequency of AUS/FLUS findings at hospitals favoring CNB than at hospitals not favoring CNB (12.3% vs. 5.1%, P<0.001). In addition, benign diagnoses were more frequent at hospitals not favoring CNB than at those favoring CNB (60.5% vs. 51.3%, P=0.028). The proportions of other diagnoses did not significantly differ between these two groups of hospitals. Forest plots for each diagnosis are shown in Supplementary Fig. 3.

Differences in the proportions of diagnoses between consecutive FNA and CNB

Consecutive data on FNA (24 papers) and CNB (nine papers) were compared in a proportional meta-analysis. The frequency of the proportions of each TBSRTC category differed significantly between FNA and CNB (Fig. 3B). Non-diagnostic, benign, and suspicious for malignancy findings were significantly more common on FNA than on CNB. However, CNB had significantly higher proportions of AUS/FLUS, FN/SFN, and malignancy diagnoses than FNA. The forest plots for the proportional analysis are presented in Supplementary Fig. 4.

Proportional differences in AUS/FLUS diagnoses between FNA and CNB

AUS/FLUS includes various conditions for which cellular atypia/architectural atypia is a representative subcategory. To understand the reasons for the higher frequency of AUS/FLUS diagnoses on CNB, we analyzed proportional differences in subcategories of diagnoses and compared the malignancy risks of cellular/architectural atypia and FN/SFN diagnosed by FNA or CNB. Eight publications included data on the AUS/FLUS subcategory or the role of CNB in FN/SFN [18,24,30,34,61-65]. Park et al. [63] was excluded from the present meta-analysis due to overlap of the study period with other papers analyzing data from the same hospital; thus, the analysis included eight papers (Table 5).

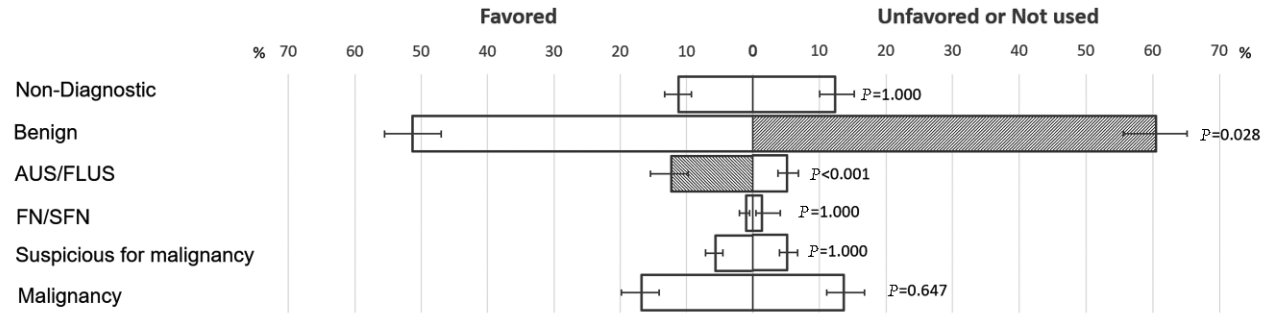
Cellular atypia versus architectural atypia

This analysis included seven papers. Ahn et al. [24] included both FNA and CNB results, Chung et al. [30] reported CNB results, and the others included FNA data [18,34,61,62,64]. Architectural atypia comprised approximately 71.9% of AUS/FLUS cases diagnosed by CNB; in contrast, cellular atypia comprised a pooled rate of 70.1% of AUS/FLUS cases diagnosed by FNA (Fig. 4A).

Table 4. Summary of included papers for the analysis of results from consecutive cases

Study	Institute	Study period	Included patient	Main outcome	Favored CNB?
Choe et al. (2018) [26]	Asan Medical Center	2012.1–2012.12	538 CNB	Evaluation of diagnostic performance and safety of CNB	Favored
Chung et al. (2017) [31]	Asan Medical Center	2008.10–2011.11	1,313 CNB	Malignancy risk of suspicious nodules with benign CNB results, results for 166 included nodules	
Chung et al. (2019) [30]	Asan Medical Center	2015.1–2015.12	2,267 CNB 2,014 FNA	Risk of malignancy according to cellular atypia, architectural atypia, follicular neoplasm	
Suh et al. (2017) [54]	Asan Medical Center	2013.1–2013.12	2,114 CNB 2,708 FNA	Efficacy and safety of CNB for initially detected thyroid nodule compared with FNA	
Moon et al. (2015) [48]	Asan Medical Center	2011.7–2011.8	534 FNA	Value of gross visual assessment of specimen adequacy for liquid-based FNA	
Nam-Goong et al. (2004) [49]	Asan Medical Center	2000.1–2001.12	317 FNA	Rate of malignancy in incidentally detected thyroid nodules	
Ahn et al. (2018) [23]	Chung-Ang University	2014.9–2015.11	89 CNB	Comparison of efficacy of CNB using 18-G and 20-G needles	Favored
Hong et al. (2018) [33]	Gangneung Asan Hospital	2010.2–2014.12	782 CNB 782 FNA	Evaluation of diagnostic efficacy in consecutive cases with simultaneous CNB and FNA	
Hong et al. (2017) [32]	Human Medical Imaging	2010.1–2011.5	1,651 FNA	Risk of malignancy according to FNA and US features in thyroid nodule (≥1 cm)	Favored
Sung et al. (2012) [56]	Human Medical Imaging	2008.8–2009.12	555 CNB 555 FNA	Evaluation of diagnostic accuracy in consecutive patients with simultaneous FNA and CNB	
Hyeon et al. (2014) [34]	Samsung Medical Center	2011.4–2012.4	6,402 FNA	Malignant risk between cellular and architectural atypia with BRAF mutation results	Favored
Lee et al. (2017) [46]	Samsung Medical Center	2013.7–2013.12	1,925 FNA	Validation of the Bethesda system	
Park et al. (2016) [50]	Samsung Medical Center	2010.8–2010.10	622 FNA	Diagnostic performance of US for each Bethesda classification	
Choe et al. (2018) [27]	Seoul National University Bundang Hospital	2013.1–2014.12	1,998 CNB	Malignancy rate and utility of reporting system for CNB suggested by the Korean Study Group	Favored
Kim et al. (2018) [41]	Seoul National University Bundang Hospital	2012.1–2014.12	5,549 FNA	Cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and its impact on risk of malignancy	
Yoo et al. (2018) [57]	Seoul National Hospital	2016.1–2016.4	200 FNA	Usage of on-site gross visual assessment of FNA for liquid-based cytology	Favored
Jung et al. (2008) [35]	Catholic University	2006.3–2006.6	193 FNA	Comparison of liquid-based method and conventional smears in FNA	Favored
Seok et al. (2018) [52]	Gacheon University	2014.12–2016.2	1,487 FNA	Diagnostic performance of FNA in terms of reducing the number of pathologists responsible for thyroid cytology	Favored
Lee et al. (2018) [60]	Busan Paik Hospital	2017.1–2017.5	112 FNA	Factors influencing sample adequacy in liquid-based cytology	Not favored
Kim et al. (2012) [38]	Busan Paik Hospital	2007.7–2009.6	1,456 FNA	Assess adequacy and efficacy of the one-sampling technique in thyroid FNA	
Song et al. (2012) [53]	Inha University	2004.6–2009.9	6,508 FNA	Evaluation of the effectiveness of the Bethesda system	Not favored
Kim et al. (2008) [37]	Konkuk University	2005.8–2006.7	500 FNA	Rate of malignancy in incidentally found thyroid nodules	Not favored
Chang et al. (2013) [25]	Korea University Guro Hospital	2007.6–2009.11	4,290 FNA	Comparison of liquid-based cytology and the conventional method	Not favored
Choi et al. (2011) [28]	Severance Hospital	2008.4–2008.12	4,077 FNA	Ultrasound features and clinical factors associated with inadequate specimens in thyroid FNA	Not favored
Lee et al. (2011) [45]	Severance Hospital	2002.9–2003.7	1,048 FNA	Comparison of FNA results with ultrasound features	
Kim et al. (2015) [43]	Severance Hospital	2013.1–2014.11	84 CNB 6,194 FNA	Evaluation of the frequency of conclusive results in FNA and CNB	
Moon et al. (2014) [47]	Severance Hospital	2010.1–2013.1	13,251 FNA	Malignancy risk of nodules diagnosed as benign by FNA according to ultrasound features	
Chong et al. (2016) [29]	Yeoido St. Mary Hospital	2013.5–2013.11	506 FNA	Comparison of Easyprep and Surepath in thyroid FNA	Not favored

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



	Total N = 25,051				Total N = 37,918			
	event	% event	Lower limit	Upper limit	event	% event	Lower limit	Upper limit
Non-Diagnostic	2,687	11.18	9.30	13.38	6,018	12.43	10.03	15.30
Benign	12,063	51.27	47.00	55.52	21,712	60.46	55.56	65.16
AUS/FLUS	3,309	12.33	9.74	15.49	2,360	5.10	3.76	6.88
FN/SFN	307	1.04	0.52	2.07	458	1.43	0.48	4.21
Suspicious for malignancy	1,780	5.70	4.52	7.17	1,851	5.19	3.98	6.75
Malignancy	4,791	16.85	14.20	19.89	5,543	13.72	11.14	16.80

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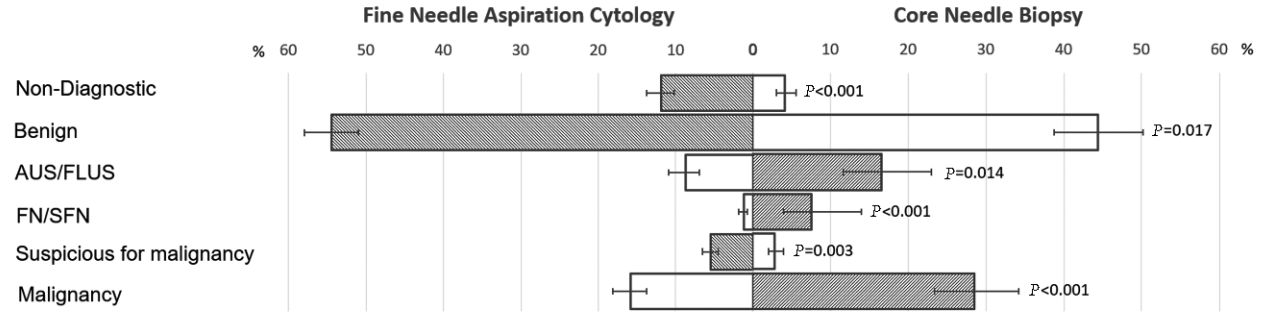


	Total N = 62,881				Total N = 9,740			
	event	% event	Lower limit	Upper limit	event	% event	Lower limit	Upper limit
Non-Diagnostic	8,705	11.90	10.25	13.76	468	4.13	3.07	5.54
Benign	33,775	54.49	50.95	57.98	4,156	44.38	38.74	50.16
AUS/FLUS	5,669	8.75	6.95	10.96	1,628	16.58	11.68	22.98
FN/SFN	765	1.16	0.72	1.88	786	7.55	3.94	14.01
Suspicious for malignancy	3,631	5.47	4.54	6.57	266	2.82	2.02	3.94
Malignancy	10,334	15.84	13.80	18.11	2,514	28.52	23.42	34.24

B

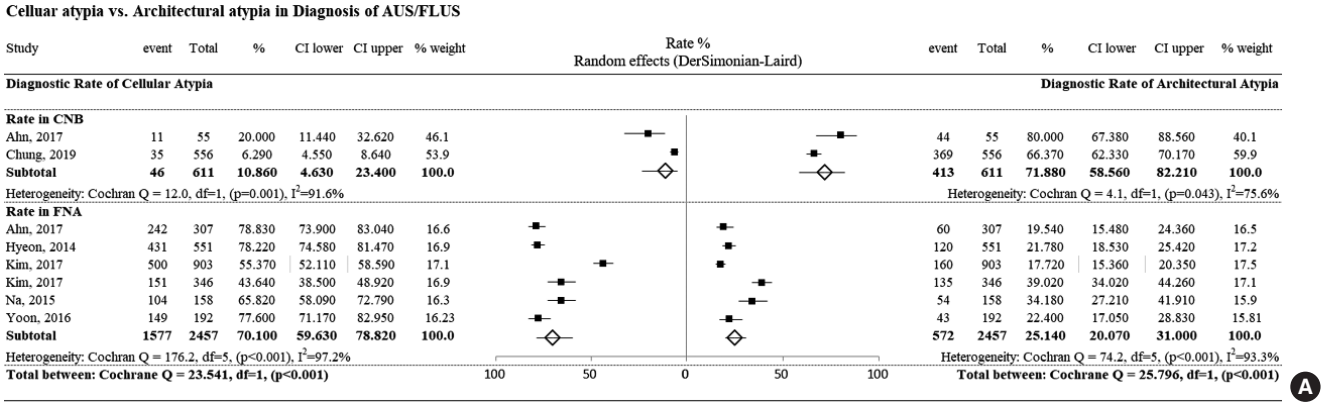
Fig. 3. Comparison of pooled estimates of the proportions of diagnoses for each Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) category from consecutive data. The hatched bar indicates a statistically significant increase in diagnostic frequency. (A) Comparison of fine-needle aspiration (FNA) results between hospitals favoring core needle biopsy (CNB) or FNA. (B) Comparison of CNB and FNA results. AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm.

Malignancy risk of cellular or architectural atypia and FN/SFN diagnosed by CNB or FNA

The malignancy rate of cellular or architectural atypia was analyzed based on six papers [24,30,34,61,62,64]. The pooled risk of malignancy in nodules with both cellular and architectural atypia did not differ significantly depending on whether they were diagnosed using CNB or FNA. The pooled malignancy risk of cellular atypia in CNB and FNA was 27.0% and 32.8%, respectively (Fig. 4B) and 12.7% and 9.6% for architectural atypia, respectively (Fig. 4C). Three papers reported the pooled risk of malignancy of FN/SFN [24,30,65], also without significant differences (34.2% for CNB and 28.5% for FNA) (Fig. 4D).

Complications of CNB and FNA

Nine papers [23,26,36,54,55,58,66-68] reported complications after CNB or FNA. Three papers [26,55,67] included cases overlapping with other papers from the same institution; thus, the final analysis included six papers. While the proportional meta-analysis showed that the pooled complication rate of CNB (1.5%) was higher than that of FNA (0.7%), the difference was not statistically significant (P=0.351) (Supplementary Fig. 5). Table 6 lists the complications observed after FNA and CNB. Hematoma was the only reported complication of FNA. However, in patients who underwent CNB, although very rare, more serious complications were reported, including pseudoaneurysm



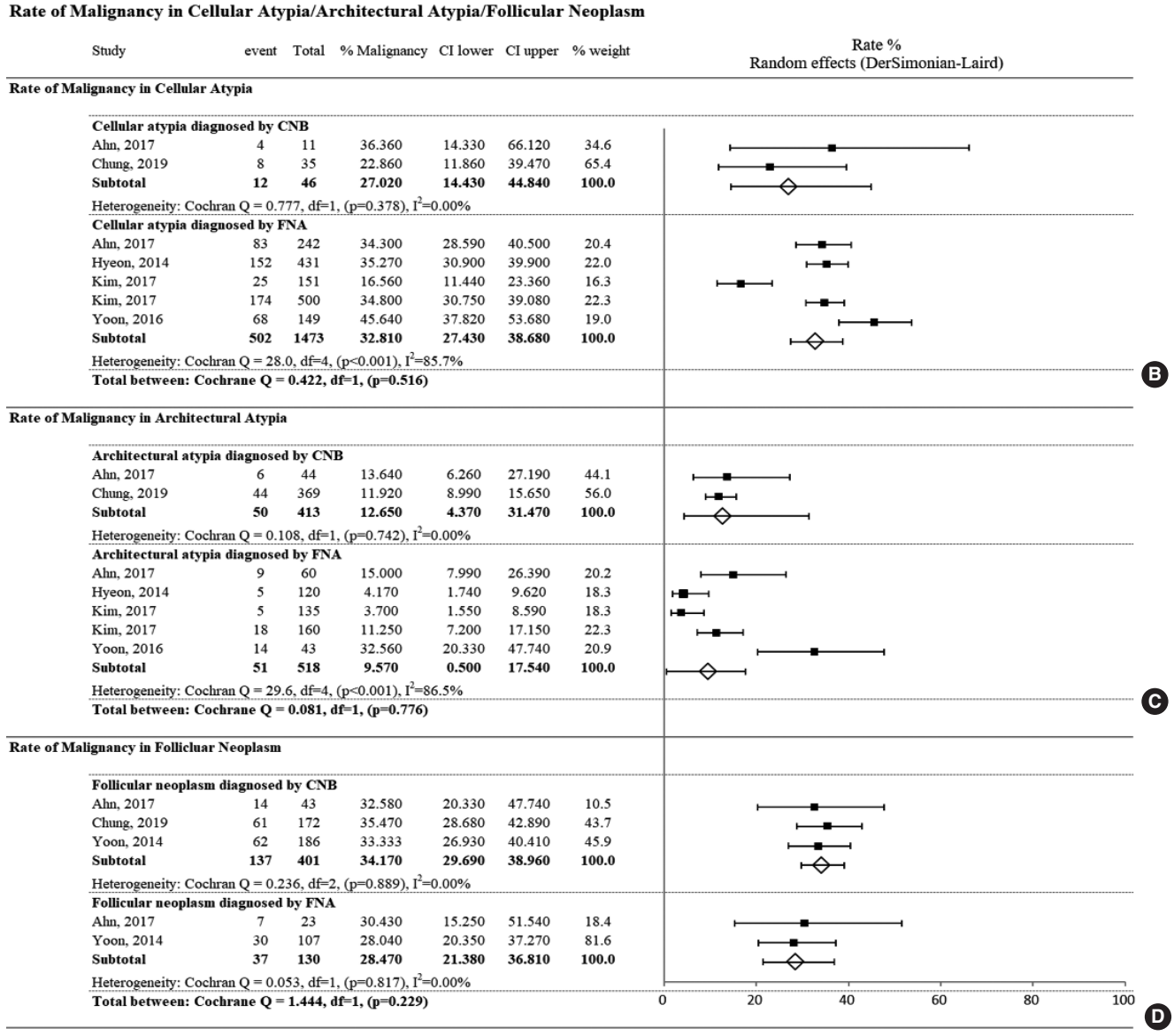


Fig. 4. Forest plot of the proportional analysis. (A) Diagnostic frequency of cellular and architectural atypia in atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) diagnosed by core needle biopsy (CNB) and fine-needle aspiration (FNA) cytology. (B) Comparison of risk of malignancy diagnosed by CNB and FNA: cellular atypia (B), architectural atypia (C), and follicular neoplasm (D). CI, confidence interval.

Table 5. Comparison of subcategories of AUS/FLUS and the malignancy rate in AUS/FLUS and FN

Study	Institute	Study period	Included case	Main outcome
Ahn et al. (2017) [24]	Seoul National University Bundang Hospital	2004.10–2014.7	2,131 Consecutive FNA and 275 CNB; 307 AUS/FLUS in FNA and 55 AUS/FLUS in CNB, 21 FN in FNA, 41 FN in CNB	Consecutive comparison of results between FNA and CNB; frequency of cellular and architectural atypia and its malignancy risk, malignancy risk of FN
Chung et al. (2019) [30]	Asan Medical Center	2015.1–2015.12	556 AUS/FLUS obtained from CNB; classified as architectural, cytologic, both, oncocytic, 172 SFN included	Architectural atypia in 66.4%, cytologic atypia in 6.3%, risk of malignancy was 22.9%–88.9% in cytologic atypia, 11.9%–40.0% in architectural atypia. The malignancy rate of SFN was evaluated.
Hyeon et al. (2014) [34]	Samsung Medical Center	2011.4–2012.4	551 AUS/FLUS from 6,402 FNAs; 431 AUS, 120 FLUS	Malignancy risk and frequency of BRAF mutation in each subcategory
Kim et al. (2017) [61]	Seoul National University Bundang Hospital	2010.1–2014.8	903 AUS/FLUS from FNA; 500 cellular atypia, 160 architectural atypia	Malignancy risk; 48.2% in cellular atypia, 14.2% in architectural atypia
Kim et al. (2017) [62]	Asan Medical Center	2012.1–2012.12	94 AUS/FLUS from FNA; subcategorized as nuclear, architectural, oncocytic, or both	Higher malignancy rate in nuclear atypia (65.8%)
Na et al. (2015) [18]	Human Medical Imaging	2010.2–2013.6	158 AUS/FLUS from FNA, nuclear atypia vs. follicular lesions with other atypia	CNB showed higher proportions of benign and FN diagnoses, especially in follicular lesions with other atypia
Yoon et al. (2016) [64]	Severance Hospital	2011.7–2013.1	192 AUS/FLUS from FNA, 149 AUS vs. 43 FLUS	Malignancy rate according to the TIRADS
Yoon et al. (2014) [65]	Asan Medical Center	2008.10–2013.12	107 FN patient from 231 FNA, 107 FN from 186 CNB performed surgery	Among patients with surgery, non-neoplasm was 30.8% in FNA, 4.7% in CNB, higher rate of malignancy in CNB group (57.9% vs. 28%)

AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN, follicular neoplasm; FNA, fine-needle aspiration; CNB, core needle biopsy; SFN, suspicious for follicular neoplasm; TIRADS, thyroid Imaging Reporting and Data System.

Table 6. Complications following CNB or FNA

Study	Institute	Study period	Included case	Main outcome
Ahn et al. (2018) [23]	Chung-Ang University Hospital	2014.9–2015.11	20G CNB; 81 cases 18G CNB; 86 cases	20G CNB: 2 hematomas 18G CNB: 2 hematomas, 1 pseudoaneurysm
Chae et al. (2017) [58]	Severance Hospital	2012.1–2012.12	5,121 FNA vs. 183 CNB	43 Hematomas in FNA, 9 hematomas in CNB
Ha et al. (2017) [66]	Asan Medical Center	2008.1–2013.3	6,687 CNB	53 Complications: 2 massive hematomas, 1 pseudoaneurysm, 1 prolonged voice change 42 small to moderate hematomas, 2 carotid injuries, 3 cases of transient voice change, 1 tracheal puncture, 1 dysphagia, 12 cases of edema, 3 cases of vertebral puncture, 1 vasovagal reaction
Kim et al. (2019) [68]	Seoul National University Bundang Hospital	2015.7–2015.12	87 FNA vs. 80 CNB	3 Hematomas in FNA, 2 hematomas in CNB
Jung et al. (2018) [36]	Busan Paik Hospital	2017.1–2017.4	21G FNA; 38 cases 23G FNA: 50 cases	1 Hematoma in 21G FNA
Suh et al. (2017) [54]	Asan Medical Center	2013.1–2013.12	2,708 FNA vs. 2,114 CNB	2 Hematomas in FNA, 7 hematomas in CNB

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

due to carotid or tracheal injuries.

DISCUSSION

The 2015 guideline of the American Thyroid Association briefly noted papers on the usefulness of CNB for the description of non-diagnostic or AUS/FLUS results [69]. Many papers have reported the results of CNB in thyroid nodules; a PubMed search with the term 'core needle biopsy[ti] thyroid' resulted in 117 records, of which 68 (58.1%) were from Korea. However, even with the high interest in CNB in Korea, perceptions of CNB vary among hospitals. Some hospitals apply CNB as an important testing method, while others think it is unnecessary. This systemic review evaluated how hospitals in Korea viewed CNB for thyroid nodules. As shown in Table 1, authors from many hospitals have

published studies on FNA, while researchers from only one-third of hospitals (34.4%) have published studies on CNB, illustrating the differences in perceptions of CNB in Korea.

Advantages of CNB in nodules initially classified as non-diagnostic or AUS/FLUS on FNA

The use of CNB as a secondary test in nodules initially classified as non-diagnostic or AUS/FLUS by FNA is a relatively commonly accepted indication. In addition, meta-analyses have shown that CNB of nodules with initial non-diagnostic or inconclusive results by FNA yields significantly fewer non-diagnostic or inconclusive findings than obtained using FNA [6,7,9]. In the present meta-analysis, CNB showed significantly fewer non-diagnostic findings than repeated FNA in nodules with non-diagnostic findings on initial FNA (1.6% vs. 34.4%, $P<0.001$), with homogeneous results across papers. A comparison of CNB and repeated FNA in nodules initially diagnosed as AUS/FLUS using FNA showed complex results. In this scenario, significantly fewer non-diagnostic results were observed for CNB than for FNA, and the results of CNB were homogeneous. However, the proportion of AUS/FLUS diagnoses did not significantly differ between CNB and repeated FNA, although the pooled estimate of AUS/FLUS diagnoses was lower in CNB than in repeated FNA (24.1% vs. 35.2%). The forest plot showed extensive heterogeneity between studies, which explains the lack of statistical significance. Simultaneously, the proportion of FN/SFN diagnoses was significantly higher on CNB. While previous meta-analyses assessed CNB and FNA after initial AUS/FLUS findings [6,8,9], they focused on the proportions of inconclusive findings, including non-diagnostic findings and AUS/FLUS combined, and showed a decreased frequency of inconclusive findings for CNB. Therefore, whether we should really expect a lower likelihood of repeated diagnosis of AUS/FLUS by selecting CNB rather than FNA is unclear, and the higher frequency of FN/SFN diagnoses obtained by CNB may result in an increased diagnostic surgery rates, as described by Yoon et al. [22]. Therefore, while CNB resulted in significantly fewer non-diagnostic results in nodules with initially non-diagnostic or AUS/FLUS results, its effects on decreasing the frequency of AUS/FLUS findings are unclear.

Factors related to differences in CNB preferences between hospitals

Favoring CNB means using CNB as often as necessary, but not as a primary test. In contrast, not favoring CNB means that there is little use of CNB in clinical settings, which was confirmed by clinicians at each hospital. The reason for including only Korean papers was to confirm each hospital's preference for CNB by personal contact with head and neck surgeons working at the hospital. A proportional analysis was performed to investigate differences in diagnoses made using the TBSRTC classification across hospitals. Although there was considerable heterogeneity between studies, significantly higher proportions of AUS/FLUS diagnoses were observed in papers published by authors from hospitals favoring CNB than in papers published by authors from other hospitals (12.3% vs. 5.1%). Therefore, we carefully suggest that differences in the patterns of pathological diagnoses may influence the preference for CNB and that the increased rate of inconclusive results from frequent AUS/FLUS findings may contribute to favoring CNB. A meta-analysis by Suh et al. in 2016 [8] compared the sensitivity of FNA between studies originating within and outside of Asia, and reported significantly higher sensitivity outside of Asia than within Asia (85% vs. 64%). Considering that nine out of the 10 Asian papers cited in their paper were by Korean authors, this finding can be interpreted that the sensitivity of FNA performed in Korea is inferior to that of FNA performed in the West. The reason for this difference in sensitivity might be due to differences in the mindset of patients undergoing surgery. In Korea, patients often do not understand why surgery was performed if they hear that the nodule was not cancer after surgery. Therefore, diagnoses may be more conservative than suggested by TBSRTC. The risk of malignancy suggested by TBSRTC in AUS/FLUS, suspicious for malignancy, and malignant nodules is 5%–15%, 60%–75%, and 97%–99%, respectively [70]. However, the corresponding risks of malignancy are much higher in Korea; for instance, the risk of malignancy of AUS/FLUS and suspicious for malignancy nodules is approximately 30% and more than 90%, respectively, according to our unpublished data. Therefore, many nodules that could be diagnosed as suspicious for malignancy according to TBSRTC may be diagnosed as AUS/FLUS in Korea, which may lower the sensitivity of FNA. Moreover, the frequency of non-diagnostic results on CNB was higher in papers outside of Asia. This finding may also explain the relative lack of interest in CNB in Western countries.

Comparison of CNB and FNA based on results from consecutive cases: expectations from first-line CNB

The results of consecutive cases in which CNB and FNA were performed were compared to estimate how the proportional frequency of diagnoses would be affected by using CNB as the first-line modality. The proportions of diagnoses for all categories differed significantly between CNB and FNA even after Bonferroni correction of the *P*-value. An important point is that the patient population is not the same for CNB and FNA. FNA may be frequently performed in cystic nodules to remove fluid, while CNB may be preferred in solid nodules. This difference should be considered when interpreting these results. Therefore, benign and malignant diagnoses are more frequent for FNA and CNB, respectively. Apart from these two diagnostic results, the frequencies of inconclusive findings also differed. CNB showed significantly fewer non-diagnostic findings, an observation consistent with those for CNB performed in secondary biopsy procedures. Moreover, suspicion for malignancy was less frequently reported for CNB. However, AUS/FLUS and FN/SFN were diagnosed sig-

nificantly more frequently on CNB than on FNA. Therefore, the rates of inconclusive findings (non-diagnostic and AUS/FLUS) were nearly the same between CNB and FNA (20.7% for both). However, a diagnosis of FN/SFN also results in diagnostic surgery and is sometimes considered to be an inconclusive finding. Therefore, if FN/SFN is included, the proportion of inconclusive results was higher for CNB than for FNA (28.3% vs. 21.8%). Based on these results, it may be difficult to recommend the generalized use of CNB in thyroid nodules if the purpose is to decrease the frequency of inconclusive findings. Another meta-analysis comparing the efficacy of CNB and FNA for diagnosing malignancy also showed no significant difference between the two modalities [2,4].

Increased frequency of AUS/FLUS on CNB due to increased diagnoses of architectural atypia

There is continuing interest regarding differences in the risk of malignancy between subcategories of AUS/FLUS. Authors at our institution also published a meta-analysis showing different risks of malignancy between cellular and architectural atypia [71]. Many researchers have suggested that cellular and architectural atypia should be classified separately in TBSRTC [72], and the CNB diagnostic criteria proposed by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group are divided into IIIA (indeterminate follicular lesion with nuclear atypia) and IIIB (indeterminate follicular lesion with architectural atypia) accordingly. Although only two papers reported AUS/FLUS subcategories in CNB results, a proportional analysis could be performed for comparison with FNA. In this analysis, 72% of the nodules classified as AUS/FLUS by CNB had architectural atypia, while 70% of the nodules classified as AUS/FLUS by FNA had cellular atypia; in other words, the two tests had opposite patterns of findings. Therefore, the higher frequency of AUS/FLUS diagnoses using CNB is in line with the higher frequency of FN/SFN findings, and using CNB appears to increase the likelihood of diagnosis of FN.

Similar risk of malignancy in cellular/architectural atypia and FN/SFN between CNB and FNA

If CNB results in the overdiagnosis of architectural atypia or FN/SFN, the malignancy rate would be expected to be lower for CNB than for FNA. However, the proportional meta-analysis showed no significant difference between CNB and FNA; thus, the increased diagnosis of architectural atypia or FN/SFN is not due to overdiagnosis. The potential to miss cases of FN/SFN by using FNA requires further study.

Complications of CNB and FNA

Although the proportional analysis showed no significant difference in the complication rate between CNB and FNA, the complication rate of CNB was higher than that of FNA (1.5% vs. 0.7%) and serious problems including injury to the carotid artery were reported. Therefore, to avoid complications, caution is required when performing CNB.

The results of this meta-analysis indicate that CNB has the following advantages and disadvantages. First, CNB can avoid non-diagnostic results in many cases, both in secondary biopsies after initial non-diagnostic or AUS/FLUS results and in first-line biopsies. Second, CNB results in significantly increased frequencies of architectural atypia and FN/SFN diagnoses, especially as a first-line modality, and therefore could increase the need for diagnostic surgery. However, as Yoon et al. [65] suggested, if FNA misses FN/SFN, that could be another advantage of CNB, a possibility that requires additional study. Third, the different AUS/FLUS diagnosis patterns between FNA and CNB may explain why the proportion of AUS/FLUS was not lower on CNB than on repeated FNA in nodules initially diagnosed as AUS/FLUS on FNA. Secondary CNB in nodules diagnosed as cellular atypia by FNA may be effective because CNB may decrease the frequency of cellular atypia or suspicion for malignancy findings. However, in other cases, the increased diagnosis of architectural atypia and FN/SFN may increase the frequency of inconclusive findings. In conclusion, CNB has a definite advantage in decreasing the frequency of non-diagnostic results; however, CNB as a first-line biopsy technique should be selected carefully to decrease the risk of inconclusive results. Furthermore, hospitals with low rates of non-diagnostic or AUS/FLUS findings may have a minimal need for CNB.

CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.21053/ceo.2020.00199.

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