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Is thyroid core needle biopsy a valid compliment to fine-needle aspiration?

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Fine-needle aspiration (FNA) has long been considered the first and an important diagnostic tool in the evaluation of thyroid nodules. The advantages of FNA include simplicity, safety, cost-effectiveness, high diagnostic accuracy, and low complication rate. Nevertheless, limitations associated with FNA include a substantial rate of inconclusive results and indeterminate interpretations. Therefore, core needle biopsy (CNB) of the thyroid gland has been proposed as a complementary or even alternate diagnostic method to evaluate thyroid nodules. Although controversial, a growing number of researchers have reported CNB to be an effective and safe sampling method for thyroid nodules, especially for cases with inadequate or indeterminate FNA yields. Skeptics highlight local pain and bleeding risk. Supporters highlight the potential likelihood of overcoming FNA limitations by obtaining a larger amount of tissue and using architecture and cellular details to guide possible ancillary testing. This review evaluates the indications, advantages, and disadvantages of CNB as compared with FNA of the thyroid gland.
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Introduction

Fine-needle aspiration (FNA) is considered to be the primary diagnostic tool used for evaluating thyroid nodules due to its simplicity, safety, cost-effectiveness, high diagnostic accuracy, and low complication rate.[1-4] Despite the advantages of FNA, documented limitations including the high rate of non-diagnostic (ND) or inadequate results and indeterminate cytology interpretations (eg, atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS] and suspicious for follicular neoplasm [SFN]), that make subsequent clinical management challenging.[1-10] Various published series report a ND range between 2% and 25%, and for indeterminate diagnoses a rate ranging between 2% and 30%.[1-5] Both editions of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) emphasize that re-aspirating ND nodules under ultrasound (US) guidance and with rapid onsite evaluation can help achieve a definitive diagnostic interpretation in up to 60% to 80% of cases.[1] For indeterminate cytology nodules, the second edition of TBSRTC suggests adding molecular testing to help improve surgical decision-making.[1] Nonetheless, publications document the variability and broad range of predictive values that result from molecular testing.[11-18]

Core needle biopsy (CNB) has shown high diagnostic sensitivity for general head and neck lesions. CNB has been suggested as a complementary or even alternate method to FNA, especially for those thyroid lesions with ND yields.[19-34] Differences between FNA and CNB of head and neck masses (including thyroid nodules) in adults investigated by Whitehorn et al in a review article showed that these biopsy modalities had similar diagnostic accuracy (93% FNA versus 96% CNB), sensitivity (89.3% FNA versus 93% CNB), specificity (96.5% FNA versus 99% CNB), positive predictive value (96.2% FNA versus 98% CNB), and negative predictive value (90.3% FNA versus 95% CNB).[27] In a study by Shin et al., focused specifically on thyroid gland, where the authors performed both FNA and CNB on 320 thyroid nodules that were followed up by surgery, they found that FNA was better than CNB.[35] Table 1 summarizes the findings of a systematic review and meta-analysis performed by Lan et al comparing the diagnostic accuracy for thyroid cancer utilizing US-guided FNA and CNB.[33] Based on their analysis involving 10,078 patients with 10,842 thyroid nodules, they concluded that FNA and CNB were equivalent as first-line diagnostic tools.[33]

Several groups, including the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinologists (ACE), Associazione Medici Endocrinologi (AME), and the Korean Society of Thyroid Radiology, have proposed using CNB for thyroid lesions after FNA reported as ND or indeterminate.[10,19,36] It must be emphasized that CNB is not a competitor to FNA in Society guidelines, but rather a complementary tool. In fact, CNB is suggested not only in the workup of repetitive ND and indeterminate lesions, but also for specific malignant thyroid tumors such as lymphoma (Fig. 1), anaplastic carcinoma (Fig. 2), medullary thyroid carcinoma, and metastases.[28-32] Of note, the American Thyroid Association (ATA) has not recommend the use of CNB for thyroid tumors.[7] CNB has several limitations including pain, bleeding, tumor cell displacement, and difficulty in approaching certain posterior thyroid gland lesions or those close to vital structures (ie, carotid artery or trachea).[33,34] Furthermore, safely obtaining an adequate CNB requires additional training, different service setting, and more robust access to additional medical personnel if complications arise.

Table 1 Comparison of diagnostic accuracy between FNA and CNB for thyroid cancer in 10,078 patients with thyroid nodules.

Parameter assessed	Fine-needle aspiration	Core needle biopsy
Sensitivity, %	0.72 [95% CI: 0.69-0.74]	0.99 [95% CI: 0.98-0.99]
Specificity, %	0.83 [95% CI: 0.81-0.85]	0.99 [95% CI: 0.98-0.99]
Positive likelihood ratio	41.71 (2.15-808.27)	51.56 (3.20-841.47)
Negative likelihood ratio	0.31 (0.22-0.42)	0.22 (0.15-0.32)
Overall ROC (AUC)	0.9025	0.7926

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating curve.
Table adapted from Lan et al.[33]

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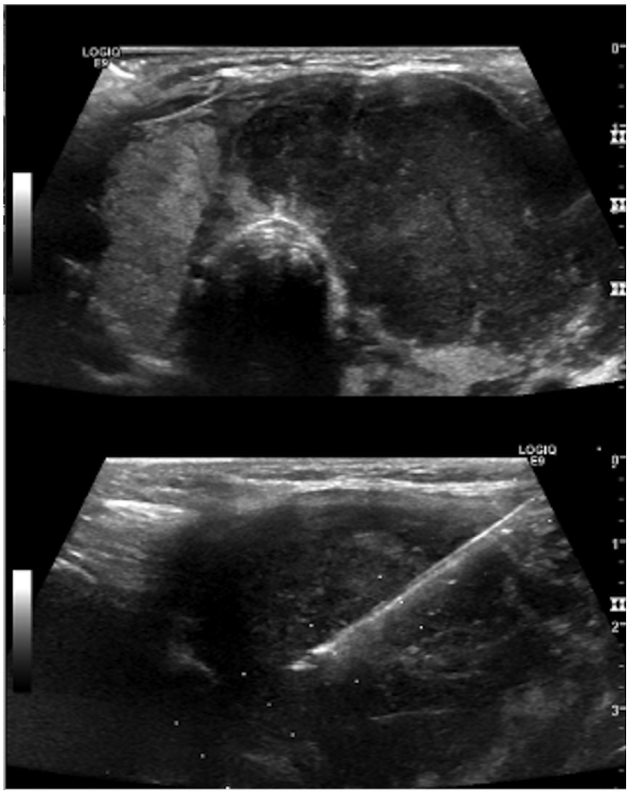

Figure 1 Ultrasound-guided core needle biopsy of a thyroid lymphoma using a 20-gauge needle (top). Left thyroid gland lobe at isthmus level showing the echogenic core needle tip within a hypoechoic solid mass (courtesy Dr. Scott Beasley).

This review evaluates the indications, advantages, and disadvantages of CNB as compared with FNA of the thyroid gland.

CNB for non-diagnostic cases

ND results are one of the major limitations of thyroid gland FNA.[1] Although the risk of malignancy for ND lesions is difficult to calculate as most ND nodules are not managed by surgery, the malignant rate among surgically excised nodules initially diagnosed as ND is between 9% and 32%.[1-4] A subset of ND nodules is surgically removed because of repetitive ND yields and/or concerning clinical-radiologic features. TBSRTC suggests a repeat FNA after a ND result may result in a more definitive diagnostic interpretation in up to 60% to 80% of cases, especially if such nodules have a minor cystic component.[1] After 2 or more ND specimens, patients are typically subjected to close clinical and sonographic follow-up or perhaps even surgery. Alternatively, in this clinical setting using CNB is suggested.[19-29]

Several systemic literature reviews regarding the utility of CNB after previous ND FNA results have been performed. Suh et al conducted a meta-analysis to determine the utility of CNB for evaluating thyroid nodules with a previous ND FNA result.[22] In their review of 1028 thyroid nodules evaluated, they found that CNB had a significantly lower ND rate (6.4%) compared with repeat FNA (36.5%) ($P < 0.0001$); that CNB had significantly higher sensitivity (89.8%) than repeat FNA (60.6%) ($P = 0.022$); but that specificity was similar (CNB 99.2% versus repeat FNA 99.0%; $P = 0.576$). Pyo et al investigated 26 studies, finding that CNB more frequently achieved conclusive results than repeat FNA for thyroid lesions initially reported on aspirates to be ND or AUS/FLUS.[23] Wolinski et al summarized 4 publications showing that CNB had a distinct diagnostic advantage over repeated FNA for ND lesions.[24] Some authors have ascribed these variances to the different needle diameters for FNA and CNB.[27-35] Needle diameters for CNB range from 18- to 22-gauge, whereas for FNA needle diameters range from 25- to 27-gauge. Of note, when Yeon et al performed CNB with an 18-gauge needle after an ND FNA they achieved diagnostic results in 98% of cases.[26] Hong et al confirmed in a series of 212 consecutive patients that primary CNB was effective in reducing the rate of inconclusive results to 10.9% and a nondiagnostic rate of 0.8%.[32] The same authors also found no significant difference in the rate of inconclusive results between CNB and combined CNB/FNA cases (10.9% versus 9.7%, respectively). Son et al, in an analysis of 1216 consecutive cases of thyroid nodules subject to CNB, found that first-line CNB resulted in a higher rate of conclusive results than second-line CNB for cases with a prior ND finding.[34] These reports suggest that first-line CNB, as well as CNB for thyroid nodules with a prior ND result, may reduce the need for additional repeat FNAs, offer more definite diagnoses, and thereby minimize inappropriate surgery. Indeed, CNB may be especially helpful when sampling thyroid nodules with extensive fibrosis, calcifications, and a predominant cystic component that may increase the risk for ND results by FNA.

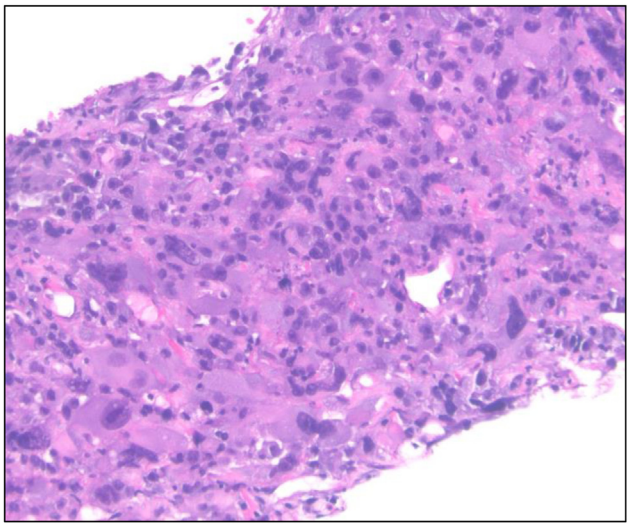

Figure 2 Thyroid CNB of an anaplastic thyroid carcinoma (Hematoxylin and eosin stain, magnification ×10).

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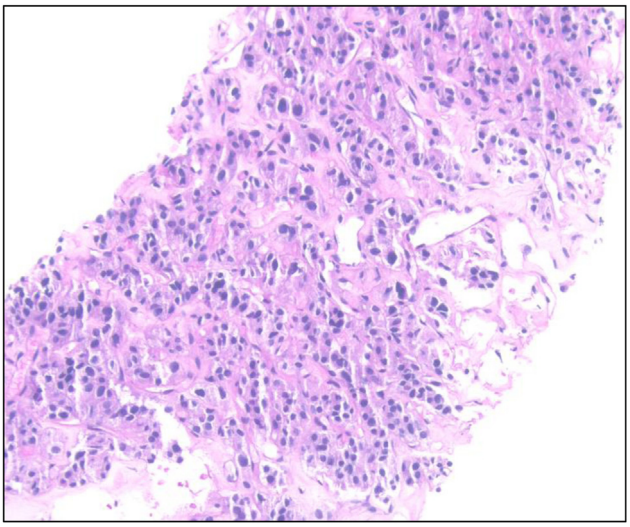

Figure 3 Thyroid CNB of an oncocytic proliferation without a capsule (Hematoxylin and eosin stain, magnification ×10). Molecular testing performed on FNA (ThyroSeq, Pittsburgh, PA) revealed that this neoplasm was *NRAS* positive.

CNB for indeterminate cases

Thyroid nodules with an indeterminate FNA interpretation according to TBSRTC include cases reported as AUS/FLUS (5%-15% risk of malignancy) or follicular neoplasm /SFN (15%-30%) risk of malignancy.[1] AUS/FLUS is a heterogeneous diagnostic category that includes benign and malignant thyroid lesions.[1,11-18] For resolving thyroid nodules interpreted as AUS/FLUS on FNA, the 2015 ATA guideline proposed using repeat FNA or molecular testing.[7] Repeat FNA may not be a satisfactory solution, however, as there is often a persistent AUS/FLUS diagnosis. Furthermore, molecular testing cannot definitively separate benign or malignant lesions.[11-18] As such, the role of CNB in evaluating indeterminate thyroid nodules must be considered. Although CNB has been reported to be more definitive than FNA for nodules with a previous diagnosis of AUS/FLUS,[36-42] other authors have found CNB to be comparable with FNA for indeterminate diagnoses.[32-43] Choi et al analyzed the role of CNB by comparing it with repeat FNA for thyroid nodules with initial AUS/FLUS cytology results in a series of 505 consecutive nodules.[40] They found that CNB had significantly lower inconclusive results than repeat FNA (40.9% for CNB versus 63% for FNA). Similarly, Na et al reported CNB to reduce the incidence of inconclusive results (26.7% for CNB versus 49.1% for FNA) for thyroid nodules with a previous AUS/FLUS diagnosis.[30]

CNB has been reported to reduce the high rate of preoperative indeterminate diagnoses for follicular neoplasms. CNB in patients with follicular thyroid carcinoma has been shown to correctly result in patients advancing to surgery than after FNA.[42] However, in a study by Paja et al including 4412 consecutive CNB (300 of which were repeat biopsies), the positive predictive value for a follicular lesion diagnosis was only 12.2%, but for a malignant diagnosis was 98.6%.[39] One major limitation of CNB to diagnose follicular lesions is that very limited (ie, focal) lesion-to-parenchyma interface is sampled (Fig. 3). CNB cannot reliably diagnose follicular neoplasms because capsular evaluation is very limited—a crucial factor in differentiating between a hyperplastic nodule and a follicular capsulated neoplasm.[22-37] Hahn et al evaluated the yield of taking US-guided CNB from 80 intermediate and low suspicion thyroid nodules targeting lesional-to-parenchymal tissue, margins, and surrounding normal parenchyma.[37] They found that 2 biopsies that included the margin and surrounding normal tissue was most effective for diagnosing a thyroid neoplasm and confirming malignancy.

One advantage of CNB over FNA is that it facilitates evaluation of architectural pattern, while providing sufficient tissue upon which to perform immunohistochemistry studies.[40-46] Nevertheless, Choi et al report that CNB was helpful for nodules with nuclear atypia, but not for nodules with architectural atypia.[44]

Thus, although CNB seems to provide greater diagnostic accuracy over repeat FNA for thyroid nodules previously interpreted as AUS/FLUS, this technique still results in inconclusive findings. Although more extensive sampling of thyroid nodules to include their capsule margin is beneficial, CNB cannot definitively separate between follicular neoplasms that warrant surgical removal from hyperplastic nodules that do not require surgical intervention.

Conclusions

FNA is widely accepted as the diagnostic tool of choice in the evaluation of thyroid nodules, accepting inherent limitations due to ND results and indeterminate lesions. CNB of the thyroid gland might represent a good complimentary diagnostic tool in patients with an initial inadequate or indeterminate FNA result. Advantages of CNB over FNA are the ability to sample larger amounts of tissue, assess histological architecture, and more easily perform immunohistochemistry when needed. CNB offers greater diagnostic accuracy over repeat FNAs for nodules with a prior AUS/FLUS interpretation. Nevertheless, CNB is more invasive, requiring specific training, and may have more significant complications. Further, even when multiple samples are taken from the periphery of the nodule, CNB may still not reliably differentiate which follicular lesions require surgical treatment. As such, each technique has a complimentary role in thyroid nodule evaluation, used to achieve the best outcome for the patient in the most efficient and effective manner possible.

Conflicts of interest disclosures

The authors have no conflicts of interest to declare.

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