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REVIEW

Effectiveness and Limitations of Core Needle Biopsy in the Diagnosis of Thyroid Nodules: Review of Current Literature

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Fine needle aspiration (FNA) is currently accepted as an easy, safe, and reliable tool for the diagnosis of thyroid nodules. Nonetheless, a proportion of FNA samples are categorized into non-diagnostic or indeterminate cytology, which frustrates both the clinician and patient. To overcome this limitation of FNA, core needle biopsy (CNB) of the thyroid has been proposed as an additional diagnostic method for more accurate and decisive diagnosis for thyroid nodules of concern. In this review, we focus on the effectiveness and limitations of CNB, and what factors should be considered when CNB is utilized in the diagnosis of thyroid nodules.

Key Words: Thyroid; Neoplasm; Core needle biopsy; Ultrasonography

At present, thyroid nodules are a common problem. With advances in diagnostic technology and the widespread usage of high-resolution ultrasonography (US), approximately 19%–67% of otherwise healthy, asymptomatic individuals will eventually be found to have thyroid nodules.[1] Out of the vast amount of thyroid nodules detected, only 7%–16% of them will be eventually diagnosed as malignant.[1] Therefore, an accurate and efficient diagnostic tool is critical for triaging patients with nodular disease of the thyroid. Fine needle aspiration (FNA), especially under US guidance, is considered the gold standard for differential diagnosis of thyroid nodules, due to its simplicity, safety, cost-effectiveness, and diagnostic accuracy. Most authoritative guidelines recommend FNA for thyroid nodules detected on US as the next step in diagnosis.[1,2] FNA has been reported to have diagnostic sensitivity of 83%–98% and specificity of 70%–92% by various studies.[1-3]

One major drawback of FNA is non-diagnostic and indeterminate cytology results (including atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS], follicular neoplasm or suspicious for a follicular neoplasm [FN/SFN], and suspicious for malignancy), which comprises approximately 10%–33.6% and 15%–42% of all FNA samples,[4-7] respectively. According to the Bethesda System for Reporting Thyroid Cytopathology,[3] repeat ultrasonography-guided fine needle aspiration (US-FNA) is recommended for nodules with non-diagnostic or indeterminate cytology results, as repeat aspiration provides conclusive results in most of these nodules. However, about 9.9%–50% of nodules with initial non-diagnostic cytology,[8-10] and 38.5%–43% of nodules with indeterminate nodules[11,12] will once again be diagnosed with inconclusive results, which induces frustration and anxiety in the patient and leads to confusion in patient management and additional diagnostic medical costs.

Core needle biopsy (CNB) of the thyroid gland has been proposed as an additional diagnostic method to US-FNA, mainly to overcome the limitations of inconclusive cytologic diagnosis. CNB provides a large amount of tissue which enables histologic diagnosis, and additional immunohistochemical staining, if needed. Several studies have shown the usefulness of CNB in providing definitive diagnosis for thyroid nodules.[12-15] Neverthe-

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less, there currently remains a lack of evidence and no definite guideline on how CNB should be used in the diagnosis of thyroid nodules. The American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association (AACE/AME/ETA) guideline is the only authoritative guideline that mentions using CNB, and only in selective cases with inadequate cytology,[2] but the actual usage of CNB in clinical practice varies among institutions and radiologists. In this paper, we will review previous studies evaluating the diagnostic performance of CNB in order to discuss the effectiveness and limitations of CNB in the diagnosis of thyroid nodules.

EFFECTIVENESS

CNB in thyroid nodules with initial non-diagnostic cytology

Although FNA has been established as an accurate diagnostic method for thyroid nodules by many authorized guidelines,[1-3] the diagnostic accuracy of FNA has been known to vary according to (1) the experience of the operator, (2) intrinsic characteristics of the targeted nodule, and (3) cytology interpretation.[16] These factors in particular, have significant influence on non-diagnostic cytology. As non-diagnostic aspirates are common causes of false-negative FNA results, the current guidelines recommend repeat FNA under US guidance,[1-3] yet approximately 20.4%–38.4% will once again be diagnosed as non-diagnostic.[2,10] Surgery is recommended for solid nodules with repeated non-diagnostic results for diagnostic purposes,[1-3] which seems rather extreme when considering the relatively low malignancy rates (6.6%–39.5%) of nodules with non-diagnostic cytology.[4,8,17] Hence, CNB has been used as an adjunctive diagnostic tool in nodules with initial non-diagnostic cytology; recent studies have reported diagnostic or conclusive results in 86%–98.9% of non-diagnostic nodules, and significantly lower non-diagnostic rates in CNB compared to repeat US-FNA (Table 1).[12,13,15,17,18] In reports that provide the diagnostic performances of CNB, high specificity and positive predictive values of 100% were commonly observed in CNB, suggesting that CNB enables malignancy-specific results, even in nodules with prior non-diagnostic results. Higher diagnostic rates obtained with CNB are only natural since CNB can obtain larger tissue samples that provide histopathologic information of the targeted nodule and the surrounding thyroid parenchyma. However, presently, only the AACE/AME/ETA guideline considers using US-CNB in "selected cases with inadequate FNA results."[2] Otherwise, no specific recommendation or indications have been established on using CNB as a follow-up diagnostic tool in nodules with non-diagnostic cytology. In addition, based on the low malignancy rates from repeat US-FNA (0.5%) or surgical resection (1.8%) in thyroid nodules with initial non-diagnostic cytology, a more conservative approach such as clinical or US follow-up has been proposed as a more appropriate alternative to additional invasive procedures such as follow-up FNA.[19] Thus, the role of CNB in contributing meaningful information in non-diagnostic nodules is still unclear.

CNB in nodules with indeterminate cytology

Indeterminate cytology, including AUS/FLUS, FN/SFN, and suspicious for malignancy categories of the Bethesda System for Reporting Thyroid Cytopathology,[3] is a diagnostic challenge since it harbors a higher risk of malignancy (5%–75%) but not sufficiently high to directly consider surgery. There have been continual efforts to improve the accurate detection of malignancy among these lesions, including US features and molecular analysis such as *BRAF* mutations.[7,20] CNB has been utilized in the diagnosis of thyroid nodules with indeterminate cytology;[12,14,21-24] in most studies, CNB is used to direct indeterminate nodules to either surgery or conservative management. Park *et al*.[21] showed a high detection rate of benign nodules in CNB (77.8%), compared to repeat FNA (35.2%) and surgery (38.7%), with high diagnostic accuracy. In addition, inconclusive rates of CNB (17.6%) have been reported to be significantly lower than repeat FNA (37.3%) in another study which included AUS nodules.[24]

Table 1. Results of the diagnostic performances of rFNA and CNB in thyroid nodules diagnosed as non-diagnostic on prior cytology

Reference	Total	rFNA	CNB	rFNA-ND (%)	CNB-ND (%)	Diagnostic performance of CNB				
						Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Samir *et al*.[18] (2012)	90	90 (100)	90 (100)	53	23	-	-	-	-	-
Na *et al*.[12] (2012)	64	64 (100)	64 (100)	28.1	1.6	71.4	100	100	88.6	91.1
Yeon *et al*.[15] (2013)	155	-	155	-	1.3	94.6	100	100	97.5	98.3
Lee *et al*.[17] (2014)	514	389 (75.7)	125 (24.3)	33.2	2.4	70	100	100	97.3	-
Choi *et al*.[13] (2014)	360	180 (50.0)	180 (50.0)	40.0	1.1	95.7	100	100	97.6	98.4

Values are presented as number (%) unless otherwise indicated.
rFNA, repeat fine needle aspiration; CNB, core needle biopsy; ND, non-diagnostic; PPV, positive predictive value; NPV, negative predictive value.

This information facilitates accurate patient management and reduces unnecessary surgery.

Few studies have investigated the efficacy of US-CNB in the diagnosis of FN of the thyroid gland.[23,25,26] CNB has been known to have advantages over FNA cytology in the diagnosis of FN in that the CNB specimen provides tissue samples which (1) visualizes the microscopic monotonous follicular proliferation and presence of fibrous capsules, and (2) enables additional immunohistochemical staining for differential diagnosis. Nasrollah *et al*.[26] introduced a new biopsy technique that uses targeting to include the nodular tissue, surrounding fibrous capsule, and extranodular parenchyma; based on this method, a recent study demonstrated the utility of CNB in preoperative diagnosis of FN with a significantly lower false-positive rate, unnecessary surgery rate, and higher malignancy rates compared to FNA.[25] However, in contrast, Hakala *et al*.[6] showed that while the sensitivity of CNB may be superior in the diagnosis of papillary thyroid carcinoma or other non-follicular thyroid lesions, CNB does not confer as much benefit as in the diagnosis of follicular tumors. Additionally, a meta-analysis by Novoa *et al*.[27] showed that FN was the reason for a high number of false-positive results from CNB in the thyroid when compared to other head and neck neoplasms, since CNB cannot differentiate between follicular adenoma and follicular carcinoma. Tissue sampling including obtaining an adequate amount of fibrous capsule and surrounding normal parenchyma, which is required for the diagnosis of FN[26] is not easy, even under US-guidance, and confounds the diagnosis between benign hyperplastic nodule and FN. In addition, for the diagnosis of follicular carcinoma, evaluation of the entire nodular capsule is required to detect the presence of capsular/vascular invasion, limiting the role of CNB as well as FNA as supported by the results of a prior study,[23] which showed that although the diagnosis of neoplasm was significantly higher in CNB, the overall malignancy rates did not show significant differences between CNB and FNA (46% to 48%, respectively). Presently, even with its ability to provide larger tissue volume for additional immunohistochemical staining, CNB, like FNA, has limited value in the differential diagnosis among subtypes of FN, serving only as a 'screening test,' rather than diagnostic for FN. Thus, CNB is not recommended for use in the differential diagnosis of FN since it does not provide additional diagnostic information, which is specified in the AACE/AME/ETA guidelines.[2]

CNB as a first-line diagnosis for thyroid nodules

At most institutions, CNB is used as a second-line diagnostic method, either as an adjunct or alternative to repeat FNA.[5,12-14,17,18,26,28] However, recently several studies have applied CNB in first-line diagnosis of thyroid nodules showing suspicious US features,[29,30] concluding that CNB has high conclusive rates and reduces false-negative or inconclusive results of FNA in solid nodules that carry high levels of suspicion for malignancy. Both studies were from single institutions with a limited number of patients. More evidence from a large study population is warranted before considering the application of CNB as a first-line

Table 2. Inconclusive rates of CNB in published literature

Reference	Reason for CNB	CNB-ND	CNB-AUS/FLUS	CNB-FN/SFN	Total inconclusive
Khoo *et al*.[31] (2008)	Referred for CNB by clinicians	-	-	-	37/320 (10.9)
Park *et al*.[21] (2011)	Prior indeterminate cytology	1/54 (1.8)	-	-	1/54 (1.8)
Sung *et al*.[14] (2012)	Previous non-diagnostic or indeterminate FNA result, suspected malignancy with benign cytology results, repeated scanty or bloody aspirates, thyroid malignancy other than differentiated cancer suspected	8/555 (1.4)	63/555 (11.4)	11/555 (2.0)	82/555 (14.8)
Na *et al*.[12] (2012)	Prior ND cytology	1/64 (1.6)	7/64 (10.9)	6/64 (9.4)	14/64 (21.9)
Na *et al*.[12] (2012)	Prior AUS/FLUS cytology	5/161 (3.1)	38/161 (23.6)	8/161 (5.0)	51/161 (31.7)
Ha *et al*.[5] (2013)	Suspicious US features, benign cytology	0/85 (0.0)	1/85 (1.2)	7/85 (8.2)	8/85 (9.4)
Yeon *et al*.[15] (2013)	Prior ND cytology	2/155 (1.3)	18/155 (11.6)	3/155 (1.9)	23/155 (14.8)
Lee *et al*.[17] (2014)	Prior ND cytology	3/125 (2.4)	5/125 (4.0)	11/125 (8.8)	19/125 (15.2)
Choi *et al*.[22] (2014)	Prior AUS cytology	1/84 (1.2)	13/84 (15.5)	5/84 (6.0)	19/84 (22.6)
Choi *et al*.[22] (2014)	Prior FLUS cytology	0/107 (0.0)	23/107 (21.5)	11/107 (10.3)	34/107 (31.8)
Choi *et al*.[13] (2014)	Prior ND cytology	2/180 (1.1)	11/180 (6.1)	3/180 (1.7)	16/180 (8.9)
Ha *et al*.[32] (2014)	Calcified nodules on US	2/272 (0.7)	25/272 (9.2)	12/272 (4.4)	39/272 (14.3)
Zhang *et al*.[30] (2014)	First-line diagnosis of thyroid nodules	4/369 (1.1)	7/369 (1.9)	11/369 (3.0)	22/369 (6.0)

Values are presented as number (%).
CNB, core needle biopsy; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; ND, non-diagnostic; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; FNA, fine needle aspiration; US, ultrasonography.

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diagnostic tool.

Khoo *et al.*[31] showed that no significant differences existed in the non-diagnostic rates between US-FNA alone and US-FNA combined to CNB, but there was a trend towards increased complications in US-FNA combined to CNB. This study concluded that the addition of CNB to US-FNA does not decrease non-diagnostic results, and may only increase morbidity from the procedure. A recent meta-analysis by Li *et al*.[33] showed similar results: the area under the receiving operator characteristics curves did not show significant differences between FNA (Az, 0.905) and CNB (Az, 0.745) in the preoperative diagnosis of thyroid nodules and Az values even lower in CNB. However, in some cases, especially in the diagnosis of lymphoma or anaplastic carcinoma, CNB has been reported to be helpful in specific diagnosis.[28] Hence, the clinical and imaging features of the patient must also be considered when deciding which patients will benefit from CNB when applied in the diagnosis of thyroid lesions.

LIMITATIONS AND FURTHER CONSIDERATIONS NEEDED FOR CORE NEEDLE BIOPSY

Complications from CNB

Commonly known complications that can occur after CNB are post-biopsy hematomas, bleeding from the incision site, pain, infections, transient hemoptysis, and nerve injuries.[27,34,35] Reported complication rates are low, ranging from 0.5%–1.0%,[27] with similar patient tolerability and discomfort between FNA and CNB.[36] However, CNB is not always technically feasible, especially in nodules located posteriorly or in close approximation to important structures such as the carotid artery or trachea. Therefore, complications are bound to occur with CNB, even under US-guidance. Bergeron and Beaudoin[34] reported an iatrogenic arteriovenous fistula formation after CNB causing tinnitus. From this case report, we can see that although complication rates are low, CNB can lead to severe and critical complications. While US-FNA may be more feasible for relatively less experienced operators, CNB must be performed with experienced radiologists with dedicated training who are familiar with the radiologic features of important anatomic structures within the cervical region to minimize major complications.

Inconclusive results on CNB

Based on the tissue samples obtained from CNB, higher conclusive rates are reported in the majority of the studies mentioned above. Even so, inconclusive results are unavoidable in thyroid CNB with reported rates ranging from 6.4%–26.7%,[12,13,15,17,22,28] reaching 31.8% when including FN in the inconclusive category (Table 2). As larger tissue samples are provided for histologic diagnosis, higher conclusive results are naturally expected. Yet, similar to FNA, a considerable proportion of thyroid nodules are once again diagnosed as inconclusive on CNB; in fact, a recent study from our institution suggested that 72.7% may be FN.[37] This is important and must always be considered when choosing CNB as the next step for thyroid nodules with prior inconclusive results.

Lack of standardization in CNB pathologic classification

Management guidelines are established based on the clinical outcomes of non-diagnostic, AUS/FLUS, or FN/SFN cytology,[1-3] but currently, there are no reporting systems that can be used as a reference for CNB specimens as in the Bethesda System for Reporting Thyroid Cytopathology nor further management guidelines according to the diagnostic results from CNB. For appropriate application of CNB in the diagnosis of thyroid nodules, a systematic diagnostic approach and definitive management guidelines need to be established first to minimize confusion on the indications for CNB and further management as needed.

CONCLUSION

CNB may have a complementary role to FNA especially in nodules with inconclusive cytologic diagnosis by providing definitive diagnosis that helps to triage patients who need surgery and minimize unnecessary invasive procedures. CNB withholds a considerable proportion of inconclusive results which must be acknowledged. In addition, it must be performed by an experienced radiologist to minimize severe complications from procedures. There should be careful selection of patients who may benefit from CNB. Ultimately, we must keep in mind that CNB is still a complementary diagnostic tool to FNA and not an alternative.

Conflicts of Interest

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

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