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Should Core Needle Biopsy be Used in the Evaluation of Thyroid Nodules?

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Abstract Fine needle aspiration (FNA) is the first choice in thyroid nodules suspected of harboring malignancy on sonography in routine practice. However, sampling with core needle biopsy (CNB) is also being used, especially in cases with repeated nondiagnostic/indeterminate diagnoses. The aim of this study was the retrospective evaluation of CNB samples. A total of 604 thyroid CNB samples registered in the Department of Pathology at Bezmialem Foundation University Medical Faculty within the 1-year period between June 2014 and June 2015 were re-evaluated by correlation with previous FNA and later resection results. CNB was divided into diagnostic groups of insufficient, malignant, suspicious for malignancy, no evidence of malignancy/benign, atypia of uncertain significance (AUS)/follicular lesions of uncertain significance (FLUS), and follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN). Among the 604 cases, 15 cases (2.48 %) were classified as malignant and 9 cases (1.49 %) as suspicious for malignancy. No evidence of malignancy was seen in 512 cases (84.76 %). There were 26 (4.3 %) cases in the AUS/FLUS-FN/SFN group, and the sample was inadequate in 42 cases (6.95 %). Resection was performed for 17 of the cases classified as malignant or suspicious for malignancy, and all were found to be malignant. There were also 10 resected cases with a diagnosis of no evidence of malignancy, and all were found to be benign. We think that sampling with CNB may be useful especially in repeating inadequate biopsies or cases diagnosed with AUS/FLUS that have hesitations regarding clinical management. Larger series including comparisons with FNA and resection results are required.

Keywords Thyroid · Core needle biopsy · Nodules · Fine needle aspiration · Clinical management

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Introduction

Thyroid nodules are lesions that can be differentiated radiologically as they show differences with the surrounding thyroid parenchyma. They have been reported to be present in 19–68 % of the population with screening accompanied by high resolution ultrasound (US) [1]. They can appear as single or multiple solid, cystic, or complex structures with functional or nonfunctional features. The differentiation of malignant and benign is important in the clinical and surgical management of the nodules. Sampling is performed in some nodules in accordance with the recommendations of various published guidelines, starting with the American Thyroid Association (ATA) [1]. The number of operations has decreased, and the malignancy rate in the resected materials has increased.

Fine needle aspiration (FNA) has been used in the sampling of nodules as a customary, safe, inexpensive, and easy method for years. However, the experience of the performing surgeon/radiologist and the cytologist can sometimes cause technical restrictions. The atypia of uncertain significance/follicular lesions of uncertain significance (AUS/FLUS) category included in the Bethesda System of diagnosis classification can also lead to hesitations in clinical patient management. The rate of inadequate or indeterminate cases after FNA can go up to 30–40 % because of these reasons [2–5]. Repeated inadequate results are also encountered in FNAs previously diagnosed as inadequate [3–8].

Core needle biopsy (CNB) is recommended and used as an alternative method in certain centers, especially in selected cases. Although the method has been used since the 1950s, it has been avoided due to a concern with complications [9]. However, the complications are minimal and similar to FNA at present and usually do not require surgical intervention with the availability of high resolution ultrasound guidance and special needles (18–22 gauge). It has also been reported that when the diagnostic performance and sensitivity increase, inadequate results decrease and there is a significant increase in the diagnosis rate in calcified or cystic nodules especially when repeating FNAs diagnosed as inadequate with the help of the clear evaluation of structural characteristics aided by the larger tissue samples [6–15]. The ability to perform immunohistochemical (IHC) studies on paraffin blocks and evaluate mutation analysis when required can also be listed as significant advantages of the method [16–18].

We aimed to compare our results with CNB used as first choice in sampling of thyroid nodules at the General Surgery Department of our hospital with the previous results with FNA and later resection results of current cases and to analyze the diagnostic benefit in our study.

Materials and Methods

A total of 604 US-guided CNB samples evaluated in 1 year between June 2014 and 2015 were reinvestigated retrospectively. Previous single or multiple FNAs of 214 cases and later resection materials of 33 cases were reviewed and included in the study for comparison. Nodules for which CNB was used were radiologically grouped according to the "Thyroid image reporting and data system (TIRADS)" classification by our surgery clinic [19]. Samples were taken with using real-time US guidance (linear probe (12–5 MHz) with a Philips ultrasound system (Type-IU22® device, Philips HC, Best, The Netherlands) with spring-loaded 20 gauge and 9-cm full-core Bard® Monopty® biopsy needle (Bard Biopsy, Tempe, AZ, USA) in at least two cores and were fixed with 10 % buffered formalin. We obtained 2-μm serial sections to reveal fine architectural and nuclear details such as enlargement, chromatin clearing, molding, etc. which can be unachievable in thick sections in our daily experience. We stained them with hematoxylin eosin (HE) after routine automated processing at our unit. IHC HBME1 (Mesothelioma Ab-1, Mouse, ready-to-use, ThermoScientific, USA) was used in some cases to help in the diagnosis.

There is no globally accepted diagnostic standardization system for CNB such as the Bethesda system [2] for FNAs, so we determined the diagnosis classes ourselves for CNB evaluation. These were as follows:

1. Inadequate: Follicle-free, nonthyroid stromal tissues, etc.

   – Cystic nodules and minimum 0,5-cm length CNB materials were evaluated as adequate clinically. However, in pathologic evaluation, the follicle-free samples (muscular or fibrous stromal tissues) were included in inadequate category. For this reason, clinical and pathologic adequacy ratios were not correlated.

2. No evidence of malignancy/benign: Follicles with colloid and no structural and cytological atypia, lymphocytic thyroiditis, and inflammatory processes.
3. Suspicious for malignancy: Samples with structural and cytological atypia but not meeting all specific criteria for malignancy.
4. Malignant: Samples with structural and cytological atypia as well as malignant characteristics supported by IHC (Papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, medullary thyroid carcinoma, etc.).
5. Atypia of uncertain significance/follicular lesions of uncertain significance, follicular neoplasm (FN)/Suspicious for follicular neoplasm (SFN): Cases with characteristics that may be considered to belong to the AUS/FLUS group were described according to the morphologic characteristics while being reported. However, as the objective in using CNB was decreasing the number of cases in the AUS/FLUS group, cases with solid or trabecular structures without colloid, cases with nuclear enlargement or irregularity, staining suspicious with IHC or showing focal HBME1 positivity, were included in the "Suspicious for malignancy" category. Cases where an obvious structural abnormality was not observed, with some microfollicle structures or that did not show papillary nuclear features but contained nuclear enlargement and irregularity, and with no staining with HBME1 were included in the "no evidence of malignancy/benign" category.

   While biopsy samples consisting of pure microfollicle structures or Hürthle cells were interpreted as SFN, samples containing normal follicle structures or capsule like fibrotic/hyalinizing tissue at the periphery in addition to these characteristics were considered FN.

Results

Of the 604 cases in total, 15 (2.48 %) were grouped as malignant, 9 (1.49 %) as suspicious for malignancy, 512 (84.77 %) as no evidence of malignancy/benign, 26 (4.3 %) as AUS/FLUS-FN/SFN, and 42 (6.96 %) as inadequate.

Resection was performed in the 11 cases whose CNB was diagnosed as malignancy, and the 6 cases who were diagnosed as suspicious for malignancy. All (100 %) were diagnosed with malignancy afterwards. Of these malignancies, 15 were papillary thyroid carcinoma (PTC) (Fig. 1), 1 poorly differentiated thyroid carcinoma (Fig. 2), and 1 lymphoma. Previous FNA results were present for 9 of the 15 cases who were diagnosed with PTC on resection, and 1 was malignant, 1 benign, 1 AUS/FLUS, 5 inadequate in one sampling, and 1 inadequate in more than one sampling.

Of the cases whose CNB was diagnosed as no evidence of malignancy/benign, 10 were resected due to reasons such as nodule diameter, endocrine/hormonal instability, cosmetic reasons, and patient preference. All of the nodules sampled (100 %) had benign characteristics. An incidental papillary microcarcinoma focus was found in the other lobe only in one of the cases.

Three of the cases whose CNB diagnosis was AUS/FLUS were resected and 2 were reported as PTC and 1 as adenomatous nodule. Of the 3 cases in the FN group that underwent resection, 2 were diagnosed with Hürthle cell adenoma and 1 with follicular adenoma (100 %). Incidental papillary microcarcinoma was found in a focus other than the nodule described in one of the cases diagnosed with Hürthle cell adenoma.

There were 87 cases with one inadequate procedure and 22 cases with multiple [2–5] inadequate procedures in the FNA group. When the CNB results of these cases were evaluated, 5 cases that were diagnosed as inadequate in one procedure were also inadequate with CNB. The result of the remaining 74 cases was no evidence of malignancy/benign, including 16 lymphocytic thyroiditis cases. There were 3 AUS/FLUS, 3 suspicious for malignancy, and 2 malignant diagnoses. Of the cases with inadequate FNA samples after multiple procedures, 20 were benign, 1 was AUS/FLUS, and 1 was malignant with CNB.

CNB of the 16 cases that were diagnosed with AUS/FLUS with FNA previously showed no evidence of malignancy/benign in 14 and suspicious for malignancy in 1 and was inadequate in 1 case. No resection has been performed in these cases yet.

The findings are summarized in the Table 1.

No major complication requiring surgical treatment was seen in any of the cases. Subcutaneous hematoma developed in 2 patients and intranodular hemorrhage in 1 patient and did not require a surgical/medical procedure due to their self-limiting nature. Dysphagia developed in 1 patient for 7–10 days as a result of paravertebral muscle bleeding and recovered spontaneously later.

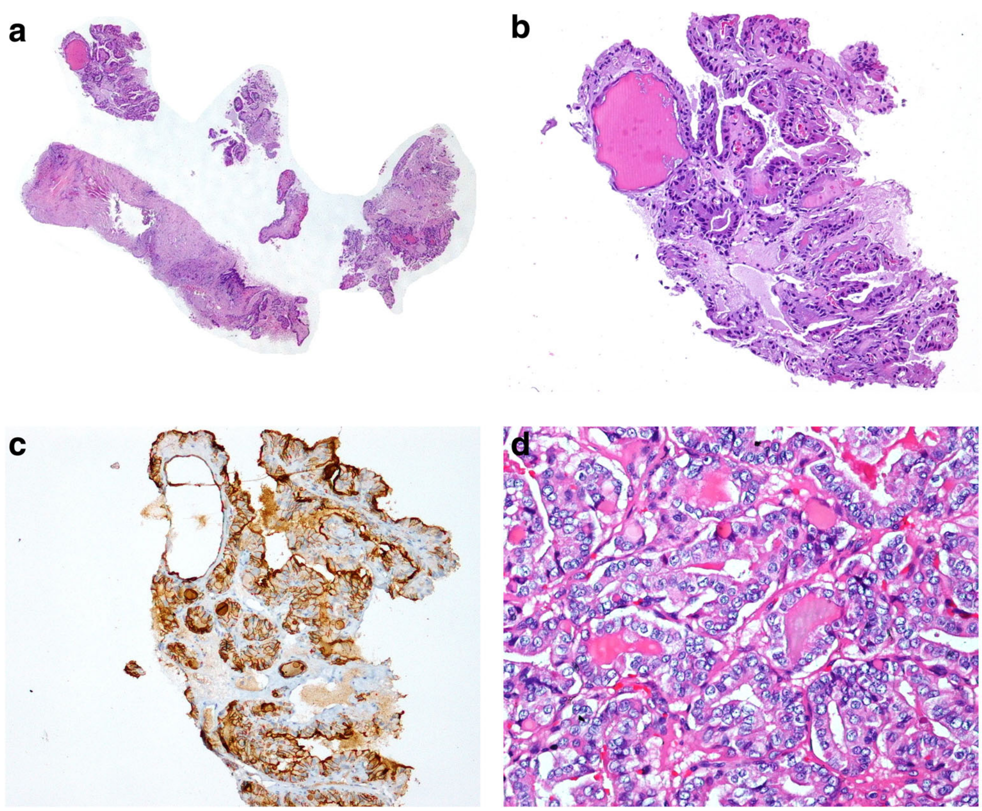

Fig. 1 **a-b** Core needle biopsies of papillary thyroid carcinoma. Biopsy samples show structural, and cytological, atypia features of papillary thyroid carcinoma (hematoxylin and eosin ×2, ×10), **c** diffuse and strong membranous immunohistochemical staining for HBME1 (×10), **d** the nuclear enlargement and chromatin clearing are more prominent in resection section (hematoxylin and eosin ×2)

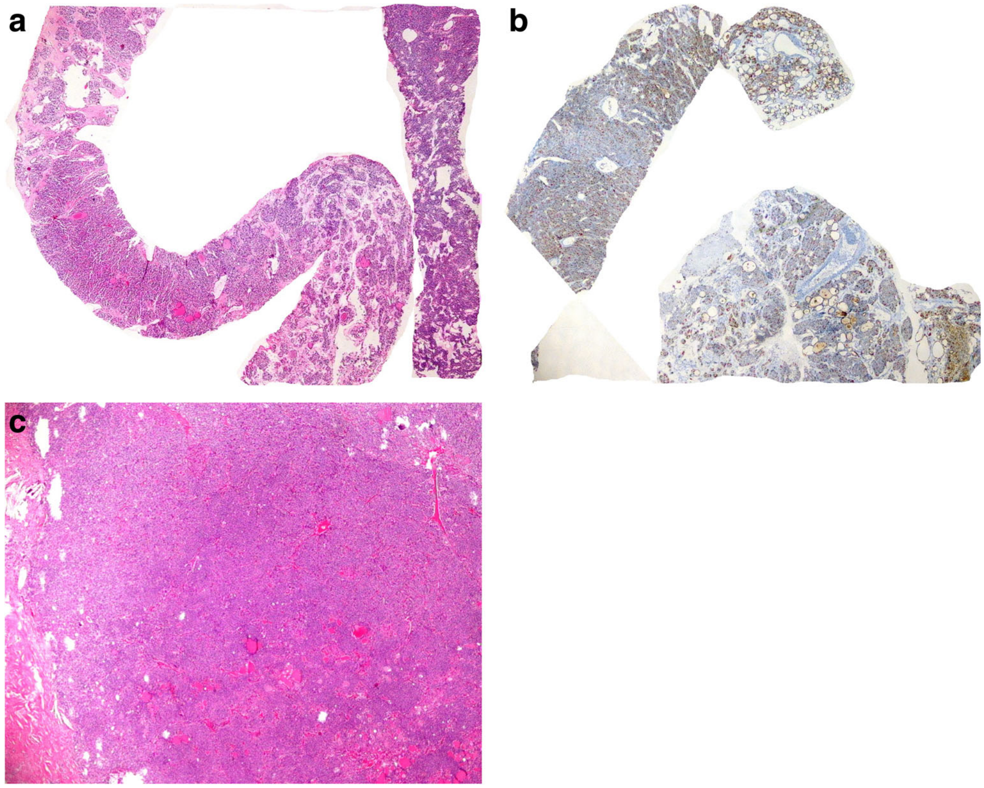

Fig. 2 **a** Core needle biopsies of poorly differentiated thyroid carcinoma, solid, trabecular, and follicular growth patterns (hematoxylin and eosin ×2), **b** Patchy strong/moderate expression of HBME1, membranous staining (×2), **c** resection section (hematoxylin and eosin ×2HE)

Discussion

FNA is a classic, cost-effective, minimally invasive, and easily applied standard first choice approach in the clinical follow-up and surgical approach for thyroid nodules. However, unsatisfactory/nondiagnostic result rates vary (2–40 %) from center to center [1, 2, 5, 8, 20, 21]. These results are directly related to the technical capability of the persons who perform the procedure and evaluate the material. Besides, the rate of AUS/FLUS, a heterogeneous diagnosis group that

Table 1 The comparison of CNB diagnoses with previous FNA and later resection diagnoses

CNB diagnosis groups	*n* (%)	Resection	FNA
Malignant	15 (2.48 %)	17 Malignant (100 %)	1 Malignant
Suspicious for malignancy	9 (1.49 %)		1 Benign
			1 AUS/FLUS
			5 Inadequate in one sample
			1 Inadequate in multiple samples
Benign	512 (84.77 %)	10 Benign (100 %)	2 Suspicious for malignancy
			14 AUS/FLUS
			73 Benign
			74 Inadequate in one sample
			20 Inadequate in multiple samples
AUS/FLUS	26 (4.3 %)	2 Malignant	2 AUS/FLUS
FN/FSN		1 Benign	4 Benign
		3 Follicular neoplasm	3 Inadequate in one sample
			1 Inadequate in multiple samples
Inadequate	42 (6.96 %)	–	1 AUS/FLUS
			6 Benign
			5 Inadequate in one sample
Total	604	33	214

may lead to indecision in patient management, varies (3–32.2 %) among the observers [2, 5, 8, 21].

Although CNB was used in the diagnosis of thyroid nodules in ancient years, it remained in the background due to limited technical facilities and the complications [9]. However, the complications decreased with the use of high resolution US and the development of appropriate biopsy needles, leading to similar complication rates and types with FNA. Thus, CNB implementation is gradually increasing in various centers, partly as the first choice and partly as a solution for the repeated inadequate samples with FNA, and it is sometimes also used concurrently with FNA [3, 6–8, 11, 12, 22–28].

CNB has high diagnostic sensitivity for both malignant and benign lesions [6]. The malignancy detection rate of CNB was up to 98 % in a study where the consistency of CNB results with resection results determined. Similar sensitivity rates are also reported for benign cases [6]. Choi et al. [8] found a malignancy detection rate of 87.2 % with CNB in cases with inadequate diagnoses following multiple FNA samples. CNBs (97 %) were found to show significantly higher diagnostic accuracy rates when compared with FNAs (78 %) in the study of Trimboli et al. [12]. We found 100 % consistency with resection material (17 malignant, 10 benign cases) in the differentiation of malignant and benign cases with CNB. However, a high resection rate is required to enable more realistic interpretation of the positive predictive value of CNB.

An important point of note is that the nuclear enlargement and chromatin clearing specific to papillary carcinoma are not as prominent in the CNB biopsy material of cases resected with a diagnosis of malignant or suspicion of malignancy as in resection material. This handicap has also been reported by Jung et al. [10] where it was also mentioned that nuclear artifacts that can mimic papillary carcinoma could be found in benign follicle cells. One reason why follicle cells are observed to be smaller and darker in biopsy samples may be because the small tissues become over fixated after going through the same process as the large ones. Therefore, we think that different fixation solutions or processes with a shorter duration can be tried for CNBs.

Despite high inadequacy rates reported with FNAs, the CNB inadequacy rate was 5.8 % in the study of Paja et al. [6] which is the largest series. This rate was reported as 1.1–3.2 % in other publications [7, 8, 11, 12]. Our inadequacy rate was 6.96 % and similar to the literature. It was observed that muscle tissue, stromal fibrosis and hyalinizing tissue fragments in our cases diagnosed as inadequate had a gray-white color and more solid rigid appearance, while the biopsy samples belonging to the follicle structure containing thyroid parenchyma were macroscopically pinker and more fragile. Our number of insufficient biopsy samples is gradually decreasing by conveying this feedback to the surgeon. Another option following an inadequate sample with FNA is repeating the FNA procedure. However, the calcifications that may develop in the nodule in repeated FNAs constitute one of the most important factors for nondiagnostic samples and the diagnostic rate in repeated FNAs is 13 to 61.8 % in the literature [6–8, 21, 29, 30]. The diagnostic rate with CNB is quite high in such cases (98 %) [6–8, 11, 12]. Similarly, 95.37 % of the cases diagnosed as inadequate in previous single or multiple FNA procedures were diagnosed with CNB.

The AUS/FLUS category that can lead to clinical hesitation in patient follow-up and high interobserver variability is an important point in favor of CNB. While this diagnosis group makes up 10–33.6 % of FNA diagnoses [15], high malignancy rates of 5–75 % have been reported in surgical follow-up [2]. Although an adequate diagnosis is provided with repeated FNAs for most nodules, 38.5–43 % of the cases still result in an indeterminate diagnosis [11, 31]. The indeterminate diagnosis rate was found to be significantly lower with CNB in the studies by Na et al.(45.3 % versus 12.5 %) [11] and Choi et al.(72 % versus 7.2 %) [8] where repeated FNA and CNBs were compared in cases diagnosed as indeterminate. CNB provided more guidance for clinical follow-up in 15 of our 16 cases diagnosed with AUS/FLUS. Malignancy was not found in 14 of these cases, the AUS/FLUS diagnosis was changed to suspicious for malignancy in 1, and the remaining sample was reported as inadequate. We concluded that CNB could be diagnostically superior to cytology with these results.

The Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group, as reported by Jung et al. [10], recommended regarding CNB reporting that follicular proliferative lesions with a well-formed fibrous capsule or adjacent thyroid parenchyma could be diagnosed as FN/SFN. Min et al. [27] have investigated the role of CNBs in the preoperative diagnosis of follicular neoplasms and reported CNBs to decrease biopsy repeats but not to be superior to FNAs in this group. Yoon et al. [32] have similarly reported that CNBs decrease unnecessary surgery thanks to the higher malignancy detection rate and lower false-positive rate. Resection diagnoses of 3 cases were found to be consistent with biopsy diagnoses in our CNBs that facilitated evaluation of the structural pattern thanks to the large tissue samples. FN/SFN is still the most difficult diagnostic group in CNB samples. The reason is the difficulty of including the capsule or normal and neoplastic areas in the same core in all biopsy samples and the inability to take every biopsy sample of the same size. Another challenge for pathologists is that the FN/SFN diagnostic criteria used for CNB are not as standardized and clear as in cytology.

Patient tolerability and complication rates of CNB were also evaluated in various articles. Nasrallah et al. [14] reported in their study that no difference was present between CNB and FNA procedures in terms of comfort and tolerability. Complications encountered in CNBs are reported to have frequency similar to FNAs (0–3.6 %) and to be minor complications (transient hoarseness, hematoma, transient parenchymal edema, bleeding, bruising, swelling, rash, itching) [6–8, 11, 14, 28, 33, 34]. Minor complications not requiring medical or surgical intervention were found in 4 (0.66 %) of our cases with a rate and characteristics that were similar to the literature.

Conclusion

While FNA continues to be the first choice for the diagnostic biopsy of thyroid nodules at our radiology unit, the General Surgery department uses CNB as the first choice. CNB is an effective diagnostic method that can be tolerated with minimal complications by the patient. Additional procedures such as immunohistochemical or molecular evaluations can also be used, and it was found to have decreased the number of repeat procedures and number of unnecessary surgeries when there is a radiological suspicion of malignancy, especially in certain diagnosis groups in the Bethesda classification, when we compared previous FNA and later resection results of our cases. While it is optimum for evaluating structural changes, it may have limitations regarding nuclear changes in some cases. Evaluation of larger series and comparison with more resection results are required.

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