ORIGINAL PAPER

The histopathologic checkpoints for thyroid core needle biopsy compared with resection sections

Tugce Kiran, Beril Guler

Department of Pathology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

Introduction: The nuclear features that are thought to be classic indicators of thyroid nodules are not fully observed in core needle biopsies (CNB). The aim of this study was to evaluate the histopathological differences between CNB samples and resection sections.

Material and methods: The haematoxylin and eosin-stained CNB and resection sections of thyroid nodules were retrospectively re-evaluated in terms of nuclear and architectural parameters. The evaluations were conducted by 2 pathologists. Statistical analysis was applied in 80 selected cases diagnosed as benign ($n = 37$) and papillary carcinoma/suspicious for papillary carcinoma ($n = 43$).

Results: The nuclear findings in the CNB were more subtle than in the resection sections. The nuclei were smaller (measurements of the nuclear areas, major axes, and minor axes in CNB and resection sections were 52.62 μm^2, 9.89 μm, 6.75 μm, 129.18 μm^2, 14.53 μm, and 10.79 μm, respectively). Hypochromia was detected in 46.5% of the papillary carcinoma cases. Grooves and pseudoinclusions were the other nuclear features that could be detected. However, nuclear contour irregularity was the most reliable finding that could predict papillary carcinoma diagnosis in the CNB sections (v: 0.82, $p < 0.001$).

Conclusions: We believe that the histopathological differences we found have an important place in diagnostics and should be emphasized, and new diagnostic algorithms should be developed.

Key words: benign, malignant, core needle biopsy, thyroid, histopathological evaluation.

Introduction

Fine needle aspiration (FNA) aimed at sampling thyroid nodules for surgical triage is accepted as the gold standard [1]. Core needle biopsy (CNB) was first used as an alternative to FNA in the 1990s and has become more popular in recent years [2–9]. This method is the first option for nodules that are calcified, sonographically encapsulated, or show uncommon radiological malignancy features. It is the second option for nodules with a nondiagnostic previous FNA, with lesions that have received a diagnosis of atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS), and those with diagnostic variations [10, 11]. According to the literature, CNB is used as the first-line diagnostic tool in some centres [4–9, 12]. Most articles report decreased rates of nondiagnostic/unsatisfactory and AUS/FLUS diagnoses with CNB, leading to similar decreases in repeated biopsy, diagnostic surgery, and unnecessary follow-up rates [9, 7]. One of the advantages of the CNB method is the reportedly higher diagnostic guidance value for follicular neoplasm/suspicious for follicular neoplasm (FN/SFN) cases. It is also reported to have diagnostic superiority in the differential diagnosis of non-thyroid tissues, le-

sions, and especially parathyroid [13–15]. However, complication rates and features have been found to be no different than for FNA [15]. Because studies on CNB have a relatively short history, there is no globally accepted and routinely used pathological diagnostic classification similar to the Bethesda System [16]. However, an article by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group published in 2015 specified CNB diagnostic categories similar to the Bethesda System, and these have been referred to in many subsequent articles [17].

In this report, we also discuss the histopathological pitfalls when using CNB for routine haematoxylin and eosin (HE) evaluations compared with resection material. Although the diagnostic benefits of CNB are reported in many articles, data on the histopathological evaluation of structural and nuclear dimensions are quite limited. Core needle biopsy is used as the first preferred sampling method at the general surgery unit of our centre, independent of the nodule features. In our radiology unit, FNA is the primary method, and CNB can be preferred as a secondary method, although rarely. The aim of this study was to evaluate the strengths and weaknesses of CNB by sharing our observations on the histopathological differences based on difficulties in diagnosis.

Material and methods

Approximately 3000 thyroid core needle biopsy cases have been diagnosed at our department since 2014. For this study, 137 of 1337 CNBs that underwent resection were re-evaluated retrospectively for a one-year period. We evaluated selected cases regarding the histopathological features on routine HE sections. To obtain valid data, the groups were divided into 2 categories, and statistical analysis was applied to 80 selected cases diagnosed as benign ($n = 37$) and papillary carcinoma / suspicious for papillary carcinoma ($n = 43$).

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software (version 20; IBM, SPSS Inc., NY, USA). Differences in the frequencies of nuclear features for diagnosis of papillary carcinoma between malignant and benign cases on CNB sections were tested using χ^2 statistics. The estimated odds ratios (OR) with 95% confidence interval (CI) were determined for potential risk. All tests were accepted as statistically significant if the two-tailed p-value was less than 0.05.

All the cases going through the five-hour histological processing stages underwent the same procedures by the same technician following a 10% buffered formaldehyde fixation to ensure standardization. The sections were cut to a thickness of 2–3 microns on 2 slides with 3–5 sections on each slide, and routine HE staining was performed. The resection materials were similarly fixed in 10% buffered formaldehyde and overnight standard histological processing was applied. The first 100 cases were evaluated jointly by 2 pathologists using microscopes with training attachments so that a common language could be developed. Cases that presented diagnostic difficulties among the other shared cases were also evaluated jointly to reach a consensus.

The cases were classified into the CNB diagnostic categories specified by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group in the Jung *et al*. article [17]. There were 6 diagnostic groups using the structural and nuclear features as the basis within this context. The structural and nuclear features were then analysed according to the diagnostic groups.

Micro/macrofollicular, papillary, trabecular, insular, and solid patterns were mainly noted for structural evaluation. It was also possible to observe follicle diameters, distortion findings, alternate pattern features, the presence of fibrous capsules, colloid structures, and psammomatous calcification in the CNB samples where more material could be obtained.

Nuclear evaluation included the size-shape, membrane irregularity, and chromatin structure according to the triple scoring system [18]. Nuclear enlargement, elongation, and overlapping were the main criteria in the size-shape category. Contour irregularities, grooves, and the presence of pseudoinclusions were evaluated in the membrane irregularity category. Hypochromia, chromatin margination, and the presence of glassy nucleus were evaluated in the chromatin structure category.

Results

According to the statistical analysis of 80 cases, contour irregularity was the most reliable nuclear feature for distinguishing benign and malignant cases with OR: 110, 95% CI: 22.9–526.7, $p < 0.001$, and Cramer's values were lower as we observed (Table I).

The histological features were as follows according to our observations:

Core needle biopsies category I: nondiagnostic or unsatisfactory

Biopsy samples consisting mostly of stromal elements without thyroid follicles were classified in this group. Hence their histological differences were not examined.

Core needle biopsies category II: benign lesions

a. Benign follicular nodule: Similar to the resection sections, most CNB cases showed round follicular structures of various diameters with a moderate to large size within a mostly loose fibrous stroma. There

Table I. Distribution of nuclear and architectural features and statistical values according to 2 categories (benign and papillary carcinoma/suspicious for papillary carcinoma)

Diagnostic groups of CNB	Benign (n = 37)			Papillary carcinoma/ suspicious for papillary carcinoma (n = 43)			Statistical values		
Presence of nuclear and architectural features	Yes (n)	Yes (%)	No (n)	Yes (n)	Yes (%)	No (n)	p-value	Cramer's value	95% CI
Papillary pattern	1	2.7	36	21	48.8	22	*	*	*
Microfollicular pattern	0	–	37	6	13.9	37	*	*	*
Fibrous capsule like structure	0	–	37	3	6.9	40	*	*	*
Follicular pattern	37	100	0	35	81.3	8	*	*	*
Other patterns	0	–	37	3	6.9	40	*	*	*
Oncocytic changes	4	10.8	33	7	16.2	36	*	*	*
Nuclear enlargement	3	8.1	34	20	46.5	23	< 0.001	0.42	2.6–37
Hypochromia	0	–	37	20	46.5	23	*	*	*
Nuclear contour irregularity	4	10.8	33	40	93	3	< 0.001	0.82	22.9–526.7
Nucleolar margination	0	–	37	1	2.3	42	*	*	*
Nuclear groove	1	2.7	36	29	67.4	14	< 0.001	0.66	9.2–601
Hyperchromia	1	2.7	36	7	16.2	36	*	*	*
Nuclear pseudoinclusion	0	–	37	19	44.1	24	*	*	*
Nuclear overlapping	0	–	37	23	53.4	20	*	*	*
Nuclear clearing	0	–	37	0	–	43	*	*	*

CNB – core needle biopsies
** These characteristics were not included in the statistical analysis.*

was abundant colloid in most cases. Hyperfunction findings characterized by abortive papillary structures that also conformed to the clinical history and resection sections were seen in some CNB sections. Scalloping colloid was not seen in the CNB sections. An elongated columnar cytoplasm was also one of the hyperfunction features that could be observed in the CNB (Figure 1A). Degenerative changes that could also have developed secondarily to the previous FNA were seen in some of the CNB samples. Dystrophic calcification and old bleeding areas were present as well as wide hyalinization areas in some samples. The nuclear features received a score of less than 2 in the CNB and resection sections in all cases in this group.

b. Lymphocytic thyroiditis: In these cases where the stromal fibrosis is denser, the biopsy fragments were macroscopically larger and less fragile compared to other samples with a benign diagnosis. Secondary lymphoid follicle organization areas that resulted in germinal centre formation were seen in some cases. The lymphoplasmacytic infiltration was diffuse or in aggregate form in other cases (Figure 1B). Core needle biopsy samples enable evaluation of the structural pattern, especially in cases where Hurthle cell metaplasia and endocrine atypia were more prominent, as in Hashimoto's thyroiditis. Non-necrotizing granuloma foci with follicular structures or naked colloid in the centre were seen in a few cases (Figure 1C).

c. Non-thyroidal lesions: Parathyroid tissue proven with immunohistochemical parathormone staining was observed in one of the cases. The non-colloidal tissue with a trabecular or microfollicle-like pattern consisted of pure chief cells containing a hyperchromic nucleus with a small and monotonous appearance (Figure 1D).

Core needle biopsies category III: indeterminate lesions

a. Indeterminate follicular lesions with nuclear atypia: We observed thyroid tissue with colloid containing large-diameter follicles, similar to benign follicular nodules, in the cases classified in this group. However, mild nuclear enlargement or contour irregularity was seen in some of the epithelial cells composing these follicles. Hyperchromia was dominant instead of hypochromia in most of these epithelial cells (Figure 1E). The nuclear score was less than 2 in all cases. The final diagnosis on the resections was equally divided between benign and malignant for these cases.

b. Indeterminate follicular lesions with structural atypia: Thyroid tissue consisting completely of Hurthle cells or those that showed a pure microfollicular pattern was seen in the cases classified in this group (Figure 1F). In addition, fibrous capsules or adjacent normal thyroid tissue that could be evaluated as FN/FNS were not

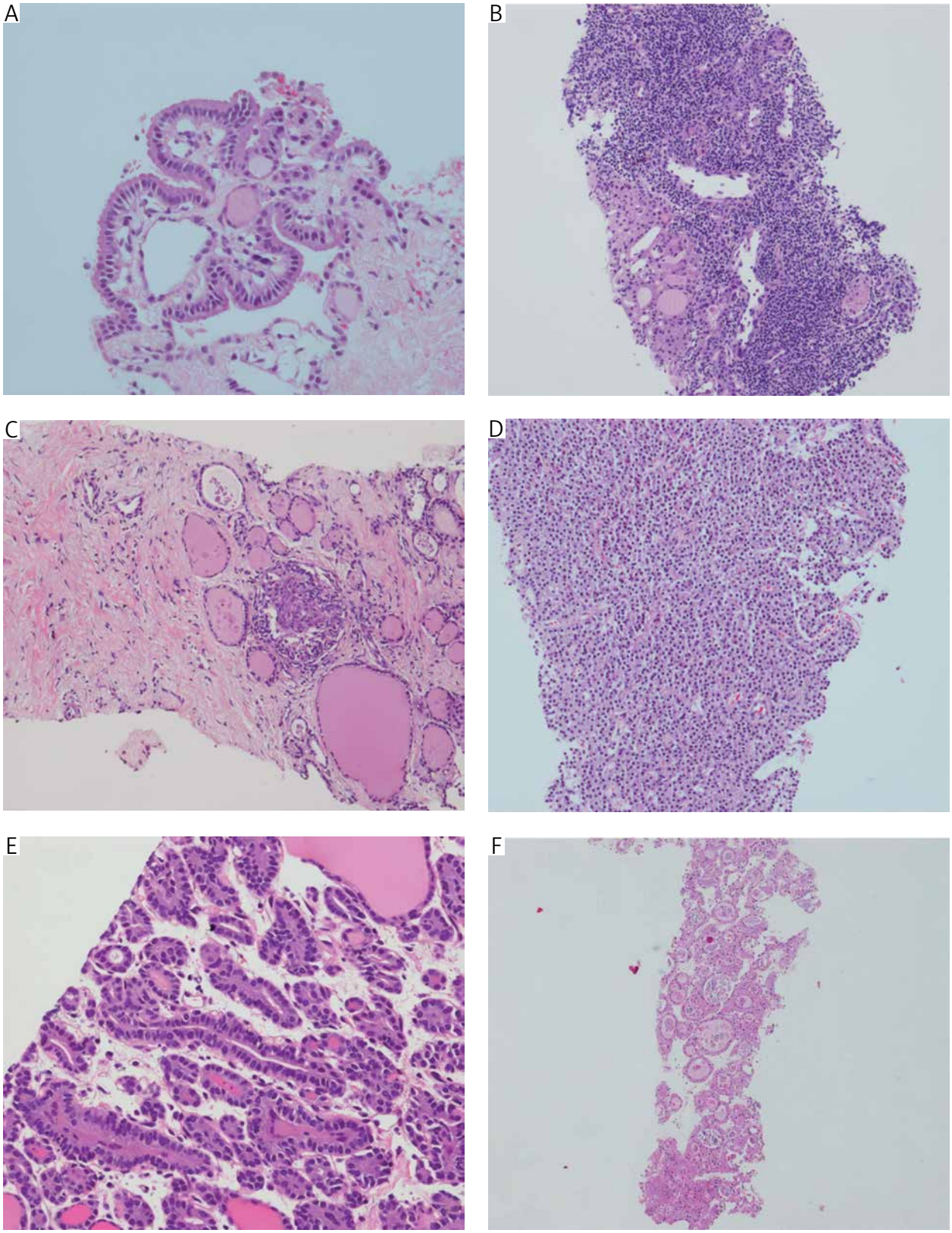

Fig. 1. A) Papillary hyperplastic nodule, hyperfunction findings with elongated columnar cytoplasm, haematoxylin and eosin (HE) 200×; **B**) Lymphocytic thyroiditis, HE 100×; **C**) Granuloma formation HE 100×; **D**) Parathyroid tissue, HE 100×; **E**) Follicle epithelial cells with hyperchromatic nuclei with irregular contour, HE 200×; **F**) Hurthle cell proliferation showing microfollicular and follicular patterns without capsule or normal thyroid tissue, HE 40×

observed. Lymphoplasmacytic inflammatory infiltration was not seen, even in scattered areas. There was no difference between the resection and CNB sections of this group other than the nuclear size.

Core needle biopsies category IV: follicular neoplasm/suspicious for follicular neoplasm

In contrast to CNB category IIIb, microfollicular organization/Hurthle cell proliferation areas that were encapsulated or alternate to normal thyroid tissue in adjacent regions were seen in this category (Fig. 2A, B). The resection material received diagnoses of follicular adenoma, minimal invasive follicular carcinoma, Hurthle cell papillary carcinoma, and follicular hyperplasia. Histopathological comparison with the resection material showed that the nuclei were smaller in the CNB sections as they were in category IIIb. Correct interventional sampling is important in differentiating this group from category IIIb. The radiological evaluation of the encapsulated solid nodules is therefore important.

Core needle biopsies category V–VI: suspicious for malignancy/malignant

As in all the other groups, the fact that the structural pattern could be evaluated with a large amount of material in this diagnostic category again provided an advantage with the CNB samples. The classic, follicular, and all other variants and their patterns were identical in the CNB and resection sections (Figure 2C). Follicular structures that had been altered to demonstrate an infiltrative appearance were also noted in some cases. A classic spindle cell pattern was noted in one, while oncocytic morphology was dominant in the other 2 cases diagnosed with medullary carcinoma, i.e. other than papillary carcinoma (Fig. 2D, E). Psammomatous calcification, one of the indicators used in addition to the pattern in the diagnosis of papillary carcinoma, could be discerned as clearly in the CNB samples as in the resection material (Figure 2F).

Colloid features are one of the ancillary findings that can be evaluated in CNB sections. However, nuclear findings in CNB material can create a disadvantage, especially for the unaccustomed observer, when compared with structural features. Nuclear enlargement, one of the main accepted criteria in the histopathological diagnosis of papillary carcinoma, was not the same as that seen in the resection materials in any of the CNB sections. We also measured the nuclear major axis, minor axis, and nuclear area on the CNB and resection sections of one randomly selected case. The measurements of the nuclear major axis, minor axis, and nuclear area were 9.89 μm, 6.75 μm, 52.65 μm^2, 14.53 μm, 10.79 μm, and 129.18 μm^2 in the CNB and resection sections, respectively (Fig. 3A, F). Also, nuclear clearing and nucleolar margination could not be seen in the CNB sections. Chromatin was also found to have a powdery appearance in the sections of some cases with a malignant diagnosis that also included thyroid tissue as an internal control. Despite the hypochromia, which is a common finding in FNA samples, the nuclei were more hyperchromatic in the CNB than the resection sections. Nuclear contour irregularity could be found more commonly in CNB cases when compared with the other criteria in the triple scoring system. A nuclear groove was also one of the papillary carcinoma features that could be seen in the CNB sections. Intranuclear pseudoinclusions could be seen in the CNB cases at rates similar to those of the resection sections. The nuclei were seen to be smaller in medullary carcinoma cases, just like papillary carcinoma, and the classic "salt-and-pepper" chromatin feature could not be observed.

Based on these observations, we used the following algorithm for the histopathological evaluation of the CNB samples (Figure 4).

Discussion

The use of CNB as the diagnostic method of first choice is still controversial. However, its use as an alternative diagnostic method or in addition to FNA in selected nodules is gradually becoming more popular [3, 6, 8, 13, 14, 17, 19, 20]. It is claimed that the use of CNB decreases the inadequacy rates and is preferred for cases diagnosed as AUS/FLUS with FNA because of suboptimal technique. Although many articles report the high diagnostic sensitivity of CNB, there is little and limited discussion on the relevant histopathological features. However, the histopathological features of the samples in our research are different from the nuclear features observed in both resection sections and FNA samples.

The Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group [17] have reported that follicular cells are smaller and have denser chromatin in CNB sections compared to resection sections. It is also reported that intranuclear pseudoinclusions, accepted as quite specific to papillary carcinoma, can be artificially observed in CNB materials [17]. Seok *et al*. [21] compared the nuclear features of thyroid papillary carcinomas in CNB and thyroidectomy material based on the nuclear field and peripheral major/minor axis dimensions. They found that CNB sections mostly had smaller nuclei, less prominent nuclear membrane irregularity, and less hypochromia. We found the nuclear size to be smaller compared with the resection materials in all the diagnostic groups in our study, similar to the findings in the literature. The nuclear hypochromia, which was seen in almost all of the papillary carcinoma cases, was observed as hyperchromia or mild/suspected hypochromia in the CNB samples. It is possible that nucleolar

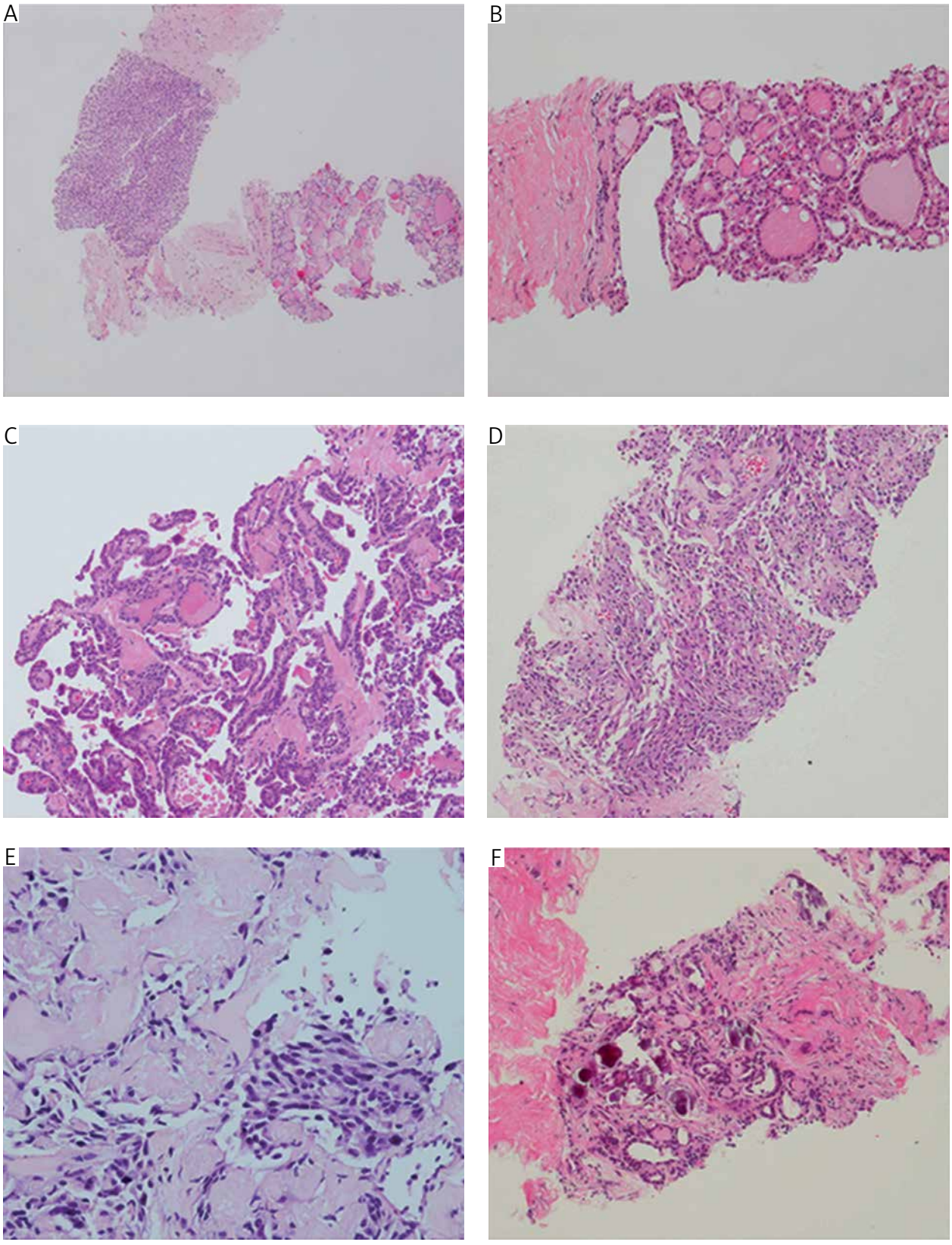

Fig. 2. A) Suspicious for follicular neoplasm, haematoxylin and eosin (HE) 40×; **B**) Suspicious for Hurthle cell follicular neoplasm, HE 100×; **C**) Papillary thyroid carcinoma with papillary pattern, HE 100×; **D**) Medullary carcinoma with spindle cell pattern, HE 100×; **E**) Amyloid deposits, HE 200×; **F**) Widespread psammomatous calcification, HE 100×

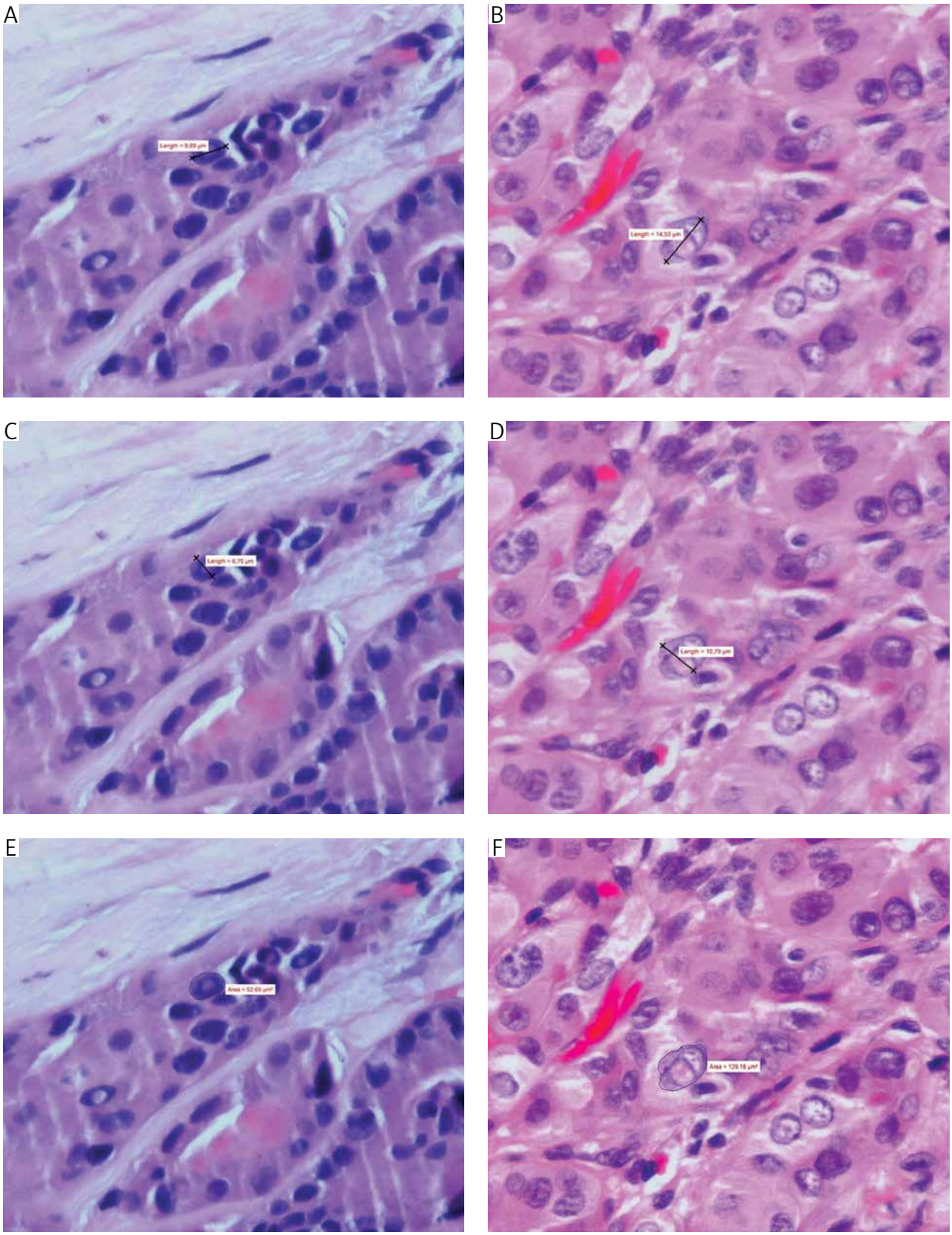

Fig. 3. A) Haematoxylin and eosin (HE) 600× nuclear major axis of CNB; B) HE 600× nuclear major axis of resection; C) HE 600× nuclear minor axis of CNB; D) HE 600× nuclear minor axis of resection; E) HE 600× nuclear area of CNB; F) HE 600× nuclear area of resection

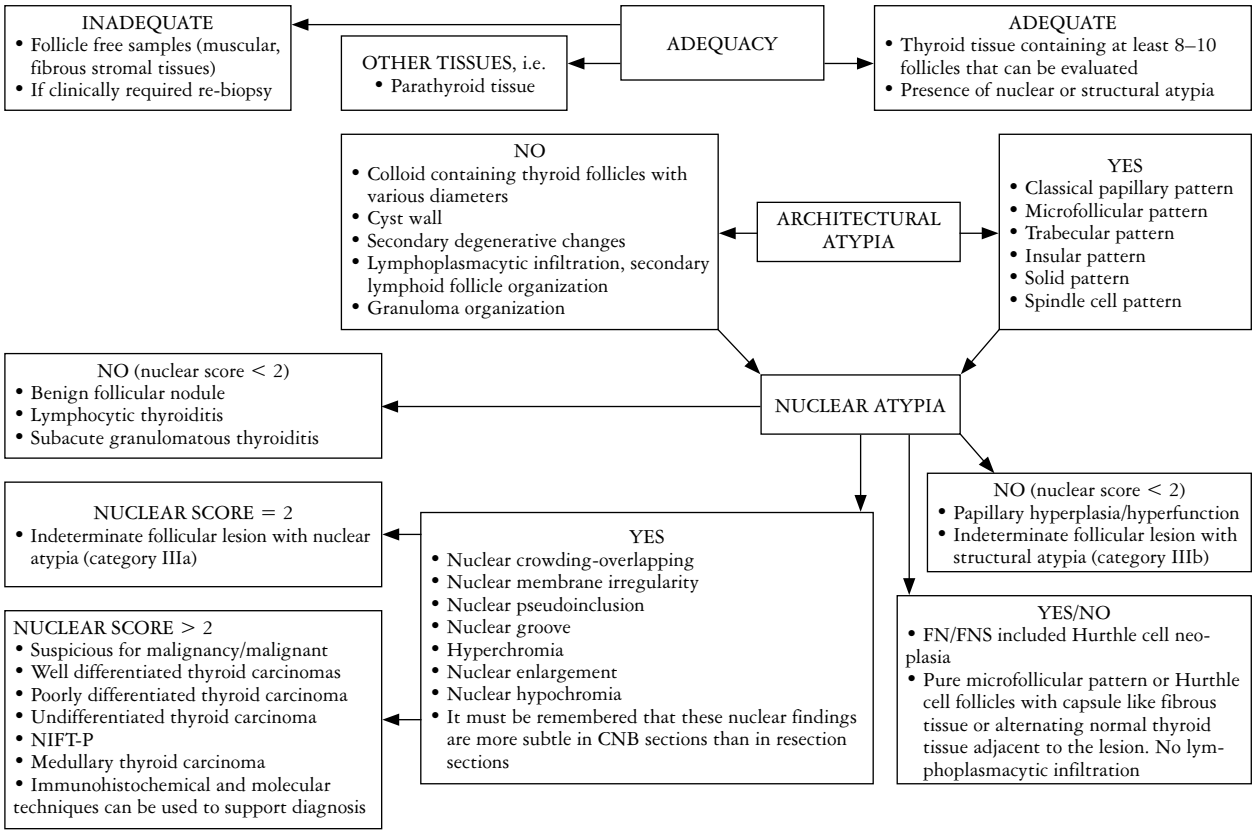

Fig. 4. An algorithm proposal for the evaluation of core needle biopsies samples

CNB – core needle biopsies

margination could not be observed because of hyperchromia. Nuclear folding, crowding, and overlapping were the more clearly recognizable nuclear features of the papillary carcinoma. Nuclear membrane irregularity, which we believe to be the most reliable feature for the diagnosis of papillary carcinoma, was most similar to the resection sections in the CNB sections. In some of the cases with a diagnosis of papillary carcinoma, nuclear pseudoinclusions were seen clearly and bore resemblance to the resection sections. However, they were not observed, even artificially, in any of the benign cases.

In the literature, comparative studies with alternative fixation solutions or periods have reported morphological differences, especially in small biopsies, due to the variations in the penetration and attachment rates. The effects of a long fixation period on the nuclear size and chromatin features have been defined as shrinkage and condensation [22–26]. Core needle biopsy samples and resection materials are similarly fixed with 10% buffered formaldehyde solution at our laboratory. A short process is used for CNB samples that have been exposed to similar fixation solutions and fixation periods, without taking the tissue size differences into account. Even if similar histological architectural features can be ensured, it has not been possible to prevent microscopic differences in nuclear size and chromatin features. One reason for these differences could be overfixation of the tissue. One could try shorter fixation periods or alternative fixatives to prevent such problems.

Structural features are as important as nuclear features in the histopathological evaluation of thyroid nodules. Core needle biopsy is not as successful as FNA in evaluating nuclear atypia. However, the results of these samples where a large amount of material can be obtained are similar to those of resection material in terms of pattern analysis. Papillary and follicular patterns are among the most common architectural features [27]. Other patterns we were able to detect in the CNB sections included trabecular, solid, and Warthin-like. The relatively straightforward evaluation of structural features has facilitated the diagnosis in medullary carcinoma cases. Rough colloid and amyloid deposits frequently create confusion in FNA material, depending on the quality of the stain [28–30]. The fact that stromal features can be evaluated together with the epithelial component in CNB sections facilitates the defining of these deposits. Similarly, colloid features can be discerned more easily than with FNA. Psammoma bodies are also detectable microscopic features in CNB sections. Another advantage of the method is the ability to support the diagnosis with immunohistochemical studies or molecular methods, because histopathological sections are available.

The Bethesda Category III (AUS/FLUS), which can create confusion in clinical management, is determined according to cytological or structural atypia [16]. The Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group [17] states that the indeterminate lesion category (IIIa–IIIb–IIIc) corresponds to this diagnosis in the Bethesda classification. Some recent publications report that sampling with CNB decreases diagnostic rates for AUS/FLUS compared to FNA [3, 14, 31, 32]. The reactive cellular changes observed in lymphocytic thyroiditis cases can lead to the inclusion of the case in the AUS/FLUS category by raising suspicion in FNA samples [33, 34]. It is possible to obtain larger biopsy samples in Hashimoto thyroiditis cases accompanied by stromal fibrosis because the thyroid gland has features that are similar to lymphoid tissue. The follicular and stromal features are evaluated together while primarily taking the structural pattern into account in these cases, and it is therefore possible to disregard the inflammation-related groove, mild nuclear paleness, and atypia findings in this way. It is possible to make a diagnosis of lymphocytic thyroiditis more confidently using CNB material, and there is therefore a decrease in our rate of AUS/FLUS diagnoses (8.3% vs. 3.3%).

Jung *et al*. [17] have classified the FN/SFN group as category IV and defined its limits with CNB. Although the evaluation of a microfollicular, solid, or trabecular patterns is an advantage of CNB, it is not always possible to differentiate whether adjacent fibrous/hyalinized tissue is a real capsule or an area of intranodular degenerative hyalinization. The evaluation can be especially misleading in cases that have previously undergone FNA or CNB. We therefore believe this diagnostic group has limitations also for CNB samples. Similarly, we think that making a diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features, which requires the whole nodule and capsule to be sampled and then evaluated with serial sections, is not possible with CNB due to the criteria.

The differential diagnosis of Hurthle cell type follicular neoplasia includes medullary carcinoma variants, parathyroid tissue, and histiocytes in FNA samples. Although they do not have the characteristic sharply delineated cytoplasmic density [35, 36], we believe CNB samples facilitate the diagnosis with this structural evaluation advantage in these cases.

Conclusions

Many recent studies have reported that CNB is superior to FNA in the diagnostic classification of thyroid nodules. In contrast, there are few data on histopathological evaluation. Using structural assessment for the categorization of thyroid lesions is reassuring in these samples. However, the nuclear features, another essential element of diagnosis, show important differences that could lead to diagnostic errors when compared with resection materials. We believe more studies sharing findings on the histopathological evaluation of CNB samples are needed because these special biopsies require more experience in all the pathology processes from fixation to microscopic evaluation.

Core needle biopsies is not yet a globally accepted routine diagnostic method in thyroid nodule classification and management. In this article, the histopathological differences among thyroid CNB materials are discussed.

This technique provides an advantage in terms of architectural properties and amyloid-like intercellular accumulation evaluation.

More abundant and high-quality samples can be obtained for immunohistochemical and molecular evaluation.

However, nuclear features that have not been histopathologically described in detail may cause diagnostic difficulties.

The authors declare no conflict of interest.

REFERENCES

1. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.
2. Baek JH. Current status of core needle biopsy of the thyroid. Ultrasonography 2017; 36: 83-85.
3. Guler B, Kiran T, Arici DS, Aysan E, Sonmez FCJE. Should core needle biopsy be used in the evaluation of thyroid nodules? Korean J Radiol 2016; 27: 352-358.
4. Aysan E, Kiran T, Idiz UO, et al. The diagnostic ability of core needle biopsy in nodular thyroid disease. Ann R Coll Surg Engl 2017; 99: 233-236.
5. Trimboli P, Nasrollah N, Guidobaldi L, et al. The use of core needle biopsy as first-line in diagnosis of thyroid nodules reduces false negative and inconclusive data reported by fine-needle aspiration. World J Surg Oncol 2014; 12: 61.
6. Kim HC, Kim YJ, Han HY, et al. First-line use of core needle biopsy for high-yield preliminary diagnosis of thyroid nodules. AJNR Am J Neuroradiol 2017; 38: 357-363.
7. Zhang M, Zhang Y, Fu S, Lv F, Tang J. Thyroid nodules with suspicious ultrasound findings: the role of ultrasound-guided core needle biopsy. Clin Imag 2014; 38: 434-438.
8. Hong MJ, Na DG, Kim SJ, Kim DS. Role of core needle biopsy as a first-line diagnostic tool for thyroid nodules: a retrospective cohort study. Ultrasonography 2018; 37: 244-253.
9. Suh CH, Baek JH, Lee JH, et al. The role of core-needle biopsy as a first-line diagnostic tool for initially detected thyroid nodules. Thyroid 2016; 26: 395-403.
10. Choi YJ, Baek JH, Suh CH, et al. Core-needle biopsy versus repeat fine-needle aspiration for thyroid nodules initially read as atypia/follicular lesion of undetermined significance. Head Neck 2017; 39: 361-369.

11. Trimboli P, Giovanella L. Reliability of core needle biopsy as a second-line procedure in thyroid nodules with an indeterminate fine-needle aspiration report: a systematic review and meta-analysis. Ultrasonography 2018; 37: 121-128.
12. Suh CH, Baek JH, Lee JH, et al. The role of core-needle biopsy in the diagnosis of thyroid malignancy in 4580 patients with 4746 thyroid nodules: a systematic review and meta-analysis. Endocrine 2016; 54: 315-328.
13. Min HS, Kim JH, Ryoo I, Jung SL, Jung CK. The role of core needle biopsy in the preoperative diagnosis of follicular neoplasm of the thyroid. APMIS 2014; 122: 993-1000.
14. Na DG, Min HS, Lee H, Won JK, Seo HB, Kim JH. Role of core needle biopsy in the management of atypia/follicular lesion of undetermined significance thyroid nodules: comparison with repeat fine-needle aspiration in subcategory nodules. Eur Thyroid J 2015; 4: 189-196.
15. Na DG, Baek JH, Jung SL, et al. Core needle biopsy of the thyroid: 2016 consensus statement and recommendations from Korean Society of Thyroid Radiology. Korean J Radiol 2017; 18: 217-237.
16. Cibas ES, Ali SZJT. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017; 27: 1341-1346.
17. Jung CK, Min HS, Park HJ, et al. Pathology reporting of thyroid core needle biopsy: a proposal of the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group. J Pathol Transl Med 2015; 49: 288-299.
18. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016; 2: 1023-1029.
19. Ha EJ, Baek JH, Na DG, et al. The role of core needle biopsy and its impact on surgical management in patients with medullary thyroid cancer: clinical experience at 3 medical institutions. Am J Neuroradiol 2015; 36: 1512-1517.
20. Jung CK, Baek JH. Recent advances in core needle biopsy for thyroid nodules. Endocrinol Metab (Seoul) 2017; 32: 407-412.
21. Seok JY, An J, Cho HY, Kim Y, Ha SY. Nuclear features of papillary thyroid carcinoma: comparison of core needle biopsy and thyroidectomy specimens. Ann Diagn Pathol 2018; 32: 35-40.
22. Buesa RJJA. Histology without formalin? Ann Diagn Pathol 2008; 12: 387-396.
23. Fox CH, Johnson FB, Whiting J, Roller PP. Formaldehyde fixation. J Histochem Cystochem1985; 33: 845-853.
24. Lassalle S, Hofman V, Ilie M, et al. Assessment of morphology, antigenicity, and nucleic acid integrity for diagnostic thyroid pathology using formalin substitute fixatives. Thyroid 2009; 19: 1239-1248.
25. Paavilainen L, Edvinsson Å, Asplund A, et al. The impact of tissue fixatives on morphology and antibody-based protein profiling in tissues and cells. J Histochem Cystochem 2010; 58: 237-246.
26. Park HS, Lee S, Haam S, Lee GDJH. Effect of formalin fixation and tumour size in small-sized non-small-cell lung cancer: a prospective, single-centre study. Histopathology 2017; 71: 437-445.
27. Lloyd RV, Buehler D, Khanafshar EJH. Papillary thyroid carcinoma variants. Pathology 2011; 5: 51-56.
28. Ojha SS, Naik LP, Kothari KS, Fernandes GC, Agnihotri MAJA. Amyloid goiter: cytomorphological features and differential diagnosis on fine needle aspiration cytology: a case report. Cytopathol Histopathol 2014; 36: 241-244.
29. Michael CW, Naylor BJA. Amyloid in cytologic specimens. Differential diagnosis and diagnostic pitfalls. Acta Cytol 1999; 43: 746-755.
30. Canberk Ş, Firat P, Schmitt F. Pitfalls in the cytological assessment of thyroid nodules. Turk Patoloji Derg 2015; 31: S18-S33.
31. Na DG, Kim JH, Sung JY, et al. Core-needle biopsy is more useful than repeat fine-needle aspiration in thyroid nodules read as nondiagnostic or atypia of undetermined significance by the Bethesda system for reporting thyroid cytopathology. Thyroid 2012; 22: 468-475.
32. Ahn SH, Park SY, Choi SI. Comparison of consecutive results from fine needle aspiration and core needle biopsy in thyroid nodules. Endocr Pathol 2017; 28: 332-338.
33. Garg S, Naik LP, Kothari KS, Fernandes GC, Agnihotri MA, Gokhale JC. Evaluation of thyroid nodules classified as Bethesda category III on FNAC. J Cytol 2017; 34: 5.
34. Kiernan CM, Broome J, Solórzano CC. The Bethesda system for reporting thyroid cytopathology: a single-center experience over 5 years. Ann Surg Oncol 2014; 21: 3522-3527.
35. Agarwal C, Raychaudhuri S, Batra A, Pujani M, Dhingra S. Medullary carcinoma of thyroid mimicking Hurthle cell neoplasm on cytology: a diagnostic dilemma. Diagn Cytopathol 2019; 47: 943-947.
36. Sriphrapradang C, Sornmayura P, Chanplakorn N, Trachoo O, Sae-Chew P, Aroonroch R. Fine-needle aspiration cytology of parathyroid carcinoma mimic Hürthle cell thyroid neoplasm. Case Rep Endocrinol 2014; 2014: 680876.

Address for correspondence:

Tugce Kiran, MD
Department of Pathology
Faculty of Medicine
Bezmialem Vakif University
Istanbul, Turkey
e-mail: tugceesenkiran5@gmail.com