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Nuclear features of papillary thyroid carcinoma: Comparison of Core needle biopsy and thyroidectomy specimens

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ABSTRACT

Background: Core needle biopsy (CNB) has been used as an alternative or a complementary method for diagnosis of thyroid nodules. However, morphological analysis of the nuclear features of papillary thyroid carcinoma (PTC) cells obtained via CNB remains unclear. Hence, we examined the differences between the PTC nuclear features in CNB and thyroidectomy specimens.

Methods: Ten PTC patients, who underwent both CNB and thyroidectomy, were selected. Microscopic photographs of three representative areas of the PTC and adjacent parenchyma were taken. Ten cells per photograph were chosen, and 1200 cells were evaluated (300 PTC and 300 follicular cells in the CNB and thyroidectomy specimens, respectively). The area, circumference, major axis, and minor axis were measured using an image analyzer. Detailed nuclear features (size and shape, membrane irregularity, chromatin characteristics) were scored using a 3-point scale.

Results: The mean nuclear area, circumference, major axis, and minor axis of PTC cells in the CNB specimen were 1.76, 1.34, 1.34, and 1.29 times larger than those of the follicular cells ($p < 0.001$); similar results were seen in the thyroidectomy specimens (2.04, 1.41, 1.37, and 1.37: $p < 0.001$). Comparative analysis revealed that these parameters were significantly smaller in the CNB specimens than those in the thyroidectomy specimens ($p < 0.001$). Nuclear grades were also lower in the former owing to poor chromatin characteristics (clearing and margination) ($p < 0.01$).

Conclusion: Considering that the PTC nuclei in CNB specimens are smaller with fewer irregularities and less clear than those in thyroidectomy specimens, we need to emphasize caution when using CNB specimens for diagnosis.

1. Introduction

Fine needle aspiration cytology (FNAC) has been accepted as the gold standard for the evaluation of thyroid nodules. However, recently, the usefulness of core needle biopsy (CNB), as an additional or alternative method, has been emphasized, for the differential diagnosis of thyroid nodules presenting an initial non-diagnostic cytology or indeterminate cytology [1,2]. Non-diagnostic FNAC results occur in 10–33.6% of thyroid nodules cases because of the nodule characteristics (i.e. calcification, cystic change), the skill of the aspirator and the cytopathologist's adherence to the diagnostic criteria. The malignancy rate of nodules with non-diagnostic results is relatively low that recommended successive diagnostic approach is to repeat the FNAC. However, repeated non-diagnostic results occur in 20.4–38.4% of such cases. The rate of occurrence of non-diagnostic results through CNB is as low as 1.1–2.4% [3-6]. Therefore, CNB can be considered as an effective alternative method for diagnosis in cases where an initial non-diagnostic result has been made.

Indeterminate cytology results include atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, and suspicious for malignancy, and having a malignancy rate of 5–75%; these occur 15–42% of all FNAC [7]. These indeterminate results make it difficult to conclude if a specimen is malignant or benign. Therefore, additional diagnostic techniques are applied, such as molecular analysis of BRAF mutation, immunohistochemical staining using cellblocks, and discrimination of the sonographic findings suggesting malignancies. CNB is another useful method for the diagnosis of thyroid nodules in cases of an indeterminate cytology result. In CNB, the detection rate of benign nodules is higher (77.8%) than in repeated FNAC (35.2%), thereby reducing the need for unnecessary surgery to confirm the benign nature of thyroid nodules [8]. In addition, the rate of repeated inconclusive results is significantly lower in CNB (17.6%) than in FNAC (37.3%) [9,10]. For the evaluation of follicular neoplasm (FN), CNB has an

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advantage in terms of the specimen, including the targeted nodule, fibrous capsule, and adjacent thyroid parenchyma. The presence of the fibrous capsule is the most important point in differentiating FN from nodular hyperplasia. Additionally, immunohistochemical staining can be applied to the CNB tissue [11,12].

CNB is of significant value for the diagnosis of thyroid diseases, such as metastasis, lymphoma, and anaplastic carcinoma, which do not necessarily require a surgery for treatment [13-15]. These are rare disease entities pertaining to the thyroid and require an appropriate amount of tissue for the exact diagnosis, to study a specific subtype or primary organ. CNB has a higher sensitivity over FNAC in these entities [14,15], and provides sufficient tissue for the performance of an ancillary test such as immunohistochemistry.

In keeping with these advantages, CNB is also considered a first-line diagnostic tool for thyroid nodules with suspicious features [16-18]. CNB is associated with low rates of non-diagnostic and inconclusive results, high diagnostic accuracy, and low rates of unnecessary diagnostic surgery.

The limitations of CNB have been described in terms of the associated complications and the technique. The complications associated with thyroid CNB procedures are massive hematoma, pseudoaneurysm, voice change (leading to disability), carotid injury, tracheal puncture, dysphagia, edema, vertebral puncture, vasovagal reaction, bleeding from the incision site, pain, infection, hemoptysis, nerve injury, and tinnitus [19-24]. Although their occurrence is rare (< 1%), critical events are included. It is required that experienced operators perform thyroid CNB.

Although Min et al. described briefly the artifacts of CNB, such as nuclear shrinkage, that could lead to a false-negative diagnosis [11], the limitations of thyroid CNB in pathologic aspects have been overlooked. Hitherto, no study has focused on the artifacts of thyroid CNB. We investigated the differences in the detailed nuclear features of PTC cells (in terms of morphologic parameters) in the same tumor that was obtained by CNB and thyroidectomy, respectively.

2. Materials and methods

2.1. Patient selection

Sixty nine thyroid CNB cases were performed at the Gachon University Gil Medical Center in 2015 and fifteen cases were diagnosed as suspicious for papillary carcinoma or papillary carcinoma according to the diagnostic categorization of the Pathology Reporting of Thyroid Core Needle Biopsy, proposed by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group [25]. Among them ten patients, who underwent thyroidectomy with final diagnosis of PTC, conventional type and available for retrospective review of the slides, were selected and reviewed. Two cores obtained by 18-gauge needle were submitted for each CNB specimen. This study was approved by the Institutional Review Board of Gachon University Gill Medical Center (Incheon, Korea) (IRB No. GCIRB2016-333). Clinical information on the 10 patients is summarized in Table 1.

2.2. Image and analysis

Using a DP70 digital camera (Olympus, Tokyo, Japan) and BX51 microscope (Olympus), 12 pictures of high power magnification (× 1000), observed with oil immersion, were taken for each patient; three of the PTC and 3 of the non-neoplastic thyroid parenchyma in the CNB specimen, and 3 of the PTC and 3 of the non-neoplastic thyroid parenchyma in the thyroidectomy specimen. The non-neoplastic thyroid parenchyma was selected at areas > 1 cm away from the PTC in the surgical specimen. Ten cells per photograph were chosen and 1200 cells were evaluated (300 PTC and 300 follicular cells in the CNB and thyroidectomy specimens, respectively). Cells detached from the stroma were excluded. The area, circumference, major axis, and minor axis of the nucleus were measured using the image analyzer software package i-Solution ver. 10.1 (IMT i-Solution, Vancouver, BC, Canada). The major axis is the longest diameter and the minor axis is the dimension perpendicular to the major axis.

Table 1
Clinical information.

No	Sex	Age	Core needle biopsy diagnosis	Size (cm)	Location
1	F	70	Papillary carcinoma	1.2	Right mid pole
2	M	52	Papillary carcinoma	1.8	Left upper pole
3	F	67	Papillary carcinoma	1.2	Left lower pole
4	F	55	Papillary carcinoma	0.9	Left lower pole
5	F	59	Papillary carcinoma	0.8	Left mid pole
6	F	50	Papillary carcinoma	1.1	Left mid pole
7	F	67	Papillary carcinoma	0.6	Right upper pole
8	F	52	Papillary carcinoma	0.3	Right mid pole
9	F	47	Suspicious for papillary carcinoma	0.5	Left mid pole
10	M	57	Suspicious for papillary carcinoma	2.2	Right upper pole

For the evaluation of detailed nuclear features, we used a 3-point scale, as previously described such as size and shape, membrane irregularity and chromatin characteristics [26]. In the size and shape category, the presence of nuclear enlargement, elongation, and overlapping was evaluated as 0 or 1. In the membrane irregularity category, the presence of an irregular contour, a groove and pseudo-inclusion was evaluated as 0 or 1. In the chromatin characteristic category, the presence of chromatin clearing, margination of chromatin to the nuclear membrane and glassy nuclei was evaluated as 0 or 1. The sum of the scores in these 3 categories (from 0 to 3) is the final nuclear score of the case. Two pathologists independently reviewed the 120 representative microscopic photographs.

2.3. Statistical analysis

SPSS for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Student's *t*-test was used to compare the results of area, circumference, major axis, and minor axis for differences in the PTC cells and non-neoplastic follicular epithelial cells between the CNB and thyroidectomy specimens. The Student's *t*-test was used to compare the nuclear scores according to the 3-point scale. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of the PTC cells and non-neoplastic follicular epithelial cells in the CNB specimen

Details on the measurement of morphologic parameters are shown in Tables 2 and 3. The mean nuclear area of the PTC cells in the CNB specimen was 19.56 ± 5.75 μm^2, which was 1.76 times larger than that of the non-neoplastic follicular epithelial cells in the same specimen ($t = 23.43$, $p < 0.001$). The mean nuclear circumference of the PTC cells in the CNB specimen was 18.31 ± 2.51 μm, which was 1.34 times longer than that of the non-neoplastic follicular epithelial cells in the same specimen ($t = 27.57$, $p < 0.001$). The mean nuclear major axis of the PTC cells in the CNB specimen was 5.44 ± 1.07 μm, which was 1.34 times longer than that of the non-neoplastic follicular epithelial cells in the same specimen ($t = 17.58$, $p < 0.001$). The mean nuclear minor axis of the PTC cells in the CNB specimen was 5.15 ± 1.01 μm, which was 1.29 times longer than that of the non-neoplastic follicular epithelial cells in the same specimen ($t = 15.26$, $p < 0.001$)