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Original Article

Suspicious thyroid nodules 4 cm require a diagnostic lobectomy regardless of their benign fine needle aspiration results

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ABSTRACT

Background/objective: The diagnostic accuracy of fine needle aspiration biopsy (FNAB) seems limited in large thyroid nodules with Bethesda Cat. 2 result. We aimed to determine the incidence of carcinoma with benign cytology and the reason for the high false-positive rate in thyroid nodules ≥4 cm.
Methods: The records of 103 patients with thyroid nodules ≥4 cm with preoperative cytological diagnosis of Bethesda Cat. 2 who underwent thyroidectomy were consecutively reviewed. Characteristics between patients with malignant vs. benign pathology were compared.
Results: Forty patients (38.8%) had malignancy. Malignancy was subclassified into follicular variant of papillary thyroid carcinoma (43%), minimally invasive follicular thyroid carcinoma (20.0%), and minimally invasive Hurthle cell thyroid carcinoma (10.9%). Patients with malignant cytology had significantly more suspicious ultrasound findings than those with benign cytology ($p = 0.001$).
Conclusions: Preoperative FNAB showed high false-negative rates in patients with thyroid nodules ≥4 cm with benign cytology. These nodules have a high malignancy rate with suspicious ultrasound findings.

1. Introduction

Thyroid nodules are common, and their prevalence increases with age.[1] These nodules generally have a malignancy rate of less than 5%.[2] The prevalence of thyroid carcinoma is high in large thyroid nodules.[3] Recently, the incidence of thyroid cancer has been increasing in nodules larger than 4 cm in size.[4]

Fine needle aspiration biopsy (FNAB) is widely used in the diagnosis of thyroid nodules, and this procedure can help determine which patients should undergo thyroid surgery to diagnose and treat malignancy.[5,6] However, FNAB has its limitations, particularly in large thyroid nodules.[6,7] The false-negative rate of FNAB seems to be higher in larger nodules than in smaller nodules, and larger malignant nodules demonstrate a higher risk of metastasis and a poorer prognosis.[8,9] Thus, a delay in treatment may have a major impact. In previous studies, the presence of thyroid nodules larger than 4 cm with cytologic atypia, follicular lesions, or suspicious findings is considered an independent indication for thyroidectomy, regardless of FNAB results.[6,7,10] Nodules classified as benign in the Bethesda System for Reporting Thyroid Cytopathology have malignancy rates of 0%–3%, for which clinical follow-up is recommended.[11] However, among thyroid nodules larger than or equal to 4 cm, preoperative benign cytology has a high false-negative rate for carcinoma.[6,7,10] Whether patients with thyroid nodules ≥4 cm and benign cytology carry a higher risk of malignancy, and whether their management should be different than those with small nodules is unclear.[12] Therefore, the aims of this study were to determine the diagnosis of carcinoma with preoperative benign cytology that underwent surgery and to define the reason for the high false-positive rate in thyroid nodules larger than

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or equal to 4 cm in size.

2. Methods

We reviewed the consecutive patients referred to the Gangnam Severance Hospital from January 2010 to August 2014. We retrospectively collected data for all nodules that showed benign cytologic results on FNAB. A total of 901 patients were diagnosed with benign cytology that was confirmed by ultrasound (US)-guided FNAB. Among these patients, 123 had nodules larger than or equal to 4 cm in size. Of the patients with a thyroid nodule larger than or equal to 4 cm, 103 underwent thyroidectomy at the Department of Endocrine Surgery. According to the final pathology report, 63 patients had benign pathology and 40 were diagnosed as cancer (Fig. 1).

All patients underwent thyroid US and measurement of serum thyroid-stimulating hormone. Thyroid US and US-guided FNAB were performed by a radiologic specialist at our hospital. FNAB cytology slides were evaluated by our hospital cytopathologist. Both the FNAB results and the final pathology report were included in the study. Results were classified based on criteria and terminology analogous to those of the Bethesda System for Reporting Thyroid Cytopathology.[9] Patients with a benign nodule larger than or equal to 4 cm underwent thyroid lobectomy and isthmusectomy. Completion thyroidectomy was performed when indicated based on the presence of malignancy within the resected specimen.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data are presented as count and percentage, mean and standard deviation, or median and range. Data in the two groups were compared using Student's *t*-test, the chi-squared test, and Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant.

The study protocol was approved by the institutional review board of Yonsei University College of Medicine, which waived requirements for patient approval and informed consent because of the retrospective nature of this study (#2018-0404-001).

3. Results

The 103 study participants comprised 17 men and 86 women (ratio, 1:5.1), with a mean age of 48.0 ± 1.4 years. The overall primary tumor malignancy rate was 38.8% (40 cases). The mean primary tumor size was 4.68 ± 0.08 cm on US and 3.66 ± 0.22 cm on final pathology. The number of FNAB procedures was 1 in 61 cases (59.2%), 2 in 26 cases (25.2%), 3 in 11 cases (10.7%), and 4 in 5 cases (4.9%). The 103 operations performed were approximately equally divided into less than total thyroidectomy (n = 52, 50.5%) and total thyroidectomy (n = 51, 49.5%) (Table 1).

Table 1
Demographic and pathologic features of 103 patients with thyroid nodules larger than or equal to 4 cm in size with benign cytology.

Variables	Outcomes
Patients, n	103
Male:female ratio, n (%)	17:86 (16.5:83.5)
Age (years), mean ± SD (range)	48.0 ± 1.37 (12–78)
Primary tumor characteristics	
Benign:cancer, n (%)	63:40 (61.2:38.8)
Size (cm), mean ± SD (range)	
Ultrasonography	4.68 ± 0.08 (4.0–8.4)
Pathologic	3.66 ± 0.22 (0.02–12.5)
Number of FNAB, n (%)	
1 time	61 (59.2)
2 times	26 (25.2)
3 times	11 (10.7)
4 times	5 (4.9)
Operation characteristics, n (%)	
Type, total:less than total	51:52 (49.5:50.5)
CCND, performed:not performed	54:49 (52.4:47.6)
LND, performed:not performed	3:100 (2.9:97.1)

SD, standard deviation; FNAB, fine needle aspiration biopsy; CCND, central compartment node dissection; LND, lateral compartment node dissection.

Among the 103 cases, 63 (61.2%) had a final diagnosis of benign lesion. Of the 63 benign lesions, adenomatous hyperplasia was present in 54 patients (85.7%) and follicular adenoma was found in 9 patients (14.3%). Of the 40 patients who had histologically confirmed thyroid cancer, 27 had papillary carcinoma (65.5%); 8, conventional papillary thyroid cancer (PTC) (29.6%); 17, follicular variant of PTC (63.0%); and 2, solid and oncocytic variant of PTC (7.4%). Other histologic types diagnosed as malignancy were minimally invasive follicular carcinoma (n = 8, 20.0%) and minimally invasive Hurthle cell carcinoma (n = 5, 10.9%) (Table 2).

A comparison of sex, age, tumor size on US, number of FNAB procedures, thyroiditis, multiplicity, and suspicious US findings in patients with benign or malignant lesions is presented in Table 3. Sex, mean age, mean tumor size on US, thyroiditis, and multiplicity did not differ between the two groups.

The number of FNAB procedures was higher in patients with malignant pathology with FNAB repeated more than 2 times (52.5%,

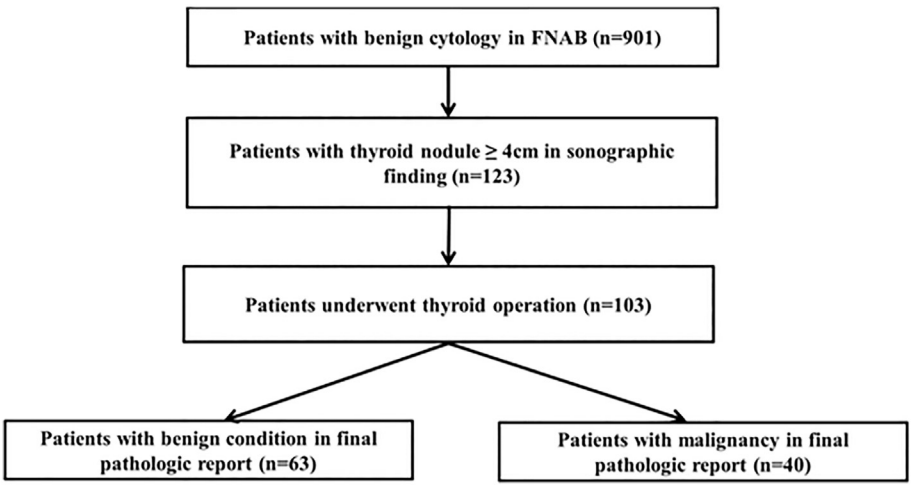

Fig. 1. Flowchart of patients with thyroid nodules larger than or equal to 4 cm in size with benign cytology.

Table 2
Final histologic classification in pathology report.

Pathology	Number
Benign, n (%)	63
Adenomatous hyperplasia	54 (85.7)
Follicular adenoma	9 (14.3)
Malignancy, n (%)	40
Papillary thyroid carcinoma	27 (65.5)
Conventional	8 (29.6)
Follicular variant	17 (63.0)
Solid and oncocytic variant	2 (7.4)
Minimal invasive follicular carcinoma	8 (20.0)
Minimal invasive Hurthle cell carcinoma	5 (10.9)

21 of 40 patients) than in patients with benign pathology with FNAB repeated more than 2 times (33.3%, 21 of 63 patients). These findings showed a trend toward statistical significance ($p = 0.053$).

The number of patients with malignant pathology who presented with suspicious US findings (42.5%, 17 of 40 patients) was significantly more than the number of patients with benign pathology (14.3%, 9 of 63 patients) ($p < 0.001$) (Table 3).

4. Discussion

The prevalence of thyroid nodules increases throughout life, and the inclusion of nodules that are detected by US greatly increases this prevalence.[10,13] In cases of nodules diagnosed with benign cytology, no further immediate treatment is required. However, in the case of nodules larger than 4 cm or those causing compressive or structural symptoms, or based upon clinical concern, surgery may be considered.[14]

FNAB is commonly used as a preoperative test because of its very high accuracy.[15] However, several studies have reported a high malignancy rate in 3–4-cm nodules.[10,16,17] If a thyroid nodule with preoperative benign cytology and a size larger than or equal to 4 cm is diagnosed as malignant on the final pathology report, clinicians will experience difficulty in re-operation. According to the 2015 American Thyroid Association Management Guideline, in patients with thyroid cancer larger than 4 cm, the initial surgical procedure should include a near-total or total thyroidectomy.[14] Therefore, if a patient is diagnosed with malignancy in the final pathology report after surgery, total thyroidectomy with central neck node dissection may be needed. This situation can cause discomfort for both the patient and the surgeon.

Considering these factors, why is the false positive rate high in benign nodules larger than 4 cm in size? In the present study, we found that follicular carcinoma or follicular variant of PTC was found in 75% (30 of 40 patients) of cases of benign nodules larger than 4 cm in size (Table 2). FNAB is most useful if the cytologic diagnosis is classic PTC, but it has limitations in the diagnosis of follicular or oncocytic (Hurthle cell) neoplasm and follicular variant of PTC.[18,19] For the above reasons, benign nodules larger than 4 cm in size have a high false-negative rate. Another reason is that large thyroid nodules may have malignant cells in only part of the mass. Such findings were not revealed in the present study.

The estimated risk of malignancy of thyroid nodule with benign cytology (Bethesda Cat. 2) is known to be of 0–3%, whereas an actual risk of malignancy in nodules surgically excised is higher (2.5%, median range of 1–10).[12] Recent study showed that the malignancy rate of nodules with Bethesda Cat. 2 was 8.8%, with the most common final pathology of PTC (88.9%) and follicular carcinoma (6.3%).[20] Yoon et al recently reported the sensitivity of FNA and CNB in diagnosis of malignancy according to different size ranges, showing that the sensitivity was lowest in nodules bigger than 4 cm.[21] Another study showed that the performance of FNA for detecting cancer in nodules 3 cm or larger was relatively poor with a sensitivity of 50%, whereas the specificity (100%), PPV (100%), and NPV (93.4%) were excellent.[22]

Therefore, what is the best approach to reduce false-negative rates with preoperative FNAB diagnosis in thyroid nodules larger than 4 cm in size? In the present study, we compared groups with benign vs. malignant pathology based on final pathology reports. In the case of nodules diagnosed with benign cytology on the preoperative FNAB test, the rate of suspicious US findings was significantly higher in patients with malignancy on final pathology ($p < 0.001$; Table 3). Therefore, even if thyroid nodules larger than 4 cm in size have benign cytologic findings, surgical treatment may be considered if the nodule has suspicious US findings. Sutton et al showed that not US features but age is associated with falsely benign FNA biopsy in a nodule larger than 4 cm. [23] However, our study could not find any age difference.

In cases in which malignant cells constitute a portion of a mass, repeat FNAB can be a viable alternative. However, when a thyroid nodule is benign on both initial and repeat FNAB, the likelihood that it is a truly benign nodule is nearly 100%.[24] In the present study, nevertheless, the number of FNAB procedures in patients with malignancy on final pathology was greater, but not statistically significant (52.5%, 21 of 40 patients, $p = 0.053$; Table 3). The American Thyroid Association guidelines do not recommend surveillance anymore if a nodule has undergone repeat US-guided FNA with a second benign cytology 12. However, our results showed that repeated FNAB in cases of benign cytology results may have limitations in providing an accurate diagnosis for benign thyroid nodules larger than 4 cm in size.

The combination of FNAB and core needle biopsy (CNB) has a higher adequacy rate and sensitivity in the diagnosis of thyroid nodules with indeterminate cytology.[25–27] CNB still has many limitations, but it can reduce the false-negative rate. In addition, molecular analysis has been shown to have a significant diagnostic value for thyroid nodules with indeterminate cytology. Molecular markers have been used preoperatively to evaluate genetic mutations and rearrangements (*BRAF V600E*, *NRAS*, *HRAS*, *KRAS*, *RET/PTC* and *PAX8/PPARγ*),[28] along with the use of gene expression

Table 3
Comparison between benign condition and malignancy in final pathology report.

Variables	Benign (n = 63)	Malignancy (n = 40)	p-value
Male:female ratio, n (%)	12:51 (19.0:81.0)	5:35 (12.5:87.5)	0.429
Age (years), mean ± SD	49.0 ± 13.5	46.4 ± 14.5	0.362
Size in US (cm), mean ± SD	4.75 ± 0.95	4.56 ± 0.54	0.248
Numbers of FNAB			0.053
One:more than two, n (%)	42:21 (66.7:33.3)	19:21 (47.5:52.5)	
Thyroiditis, n (%)	10 (15.9)	10 (25.0)	0.254
Multiplicity, n (%)	45 (71.4)	24 (60.0)	0.229
Suspicious US finding, n (%)	9 (14.3)	17 (42.5)	0.001

SD, standard deviation; US, ultrasound; FNAB, fine needle aspiration biopsy.

classifiers.[29] A recent study showed that pathologic results are not explained by available molecular testing results in tumors larger than 4 cm, whereas molecular testing is useful in tumors small than 4 cm.[30] Molecular studies have not yet been widely used owing to their low cost effectiveness, and further studies are warranted to be an alternative diagnostic tool for benign thyroid nodules larger than 4 cm in size. [31]

To prevent unnecessary second operations after thyroid lobectomy, intraoperative frozen sections can occasionally confirm malignancy.[32,33] However, the usefulness of intraoperative frozen sections is low in follicular variant of PTC and FTC.[34,35] As mentioned in this study, the use of intraoperative frozen sections was poor because thyroid nodules larger than 4 cm in size tended to have malignant histopathology of follicular neoplasms such as follicular carcinoma and follicular variant of PTC.

The above account does not provide a perfect alternative solution to reduce false-negative rates in thyroid nodules larger than or equal to 4 cm in size with benign cytology. Therefore, clinicians should consider the performance of diagnostic lobectomy or follow-up observation of suspicious US patterns.

In conclusion, preoperative FNAB had high false-negative rates in patients with thyroid nodules larger than or equal to 4 cm in size with benign cytology. These nodules demonstrate follicular growth patterns, such as those found in FTC, Hurthle cell carcinoma, and follicular variant of PTC. These neoplasm types are difficult to diagnose with preoperative FNAB. They have a high malignancy rate with suspicious US findings. Therefore, in case of such findings, diagnostic lobectomy rather than repeated FNAB should be considered.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2021.08.005.

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