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Predictive Factors of Malignancy in Cytology of Indeterminate Follicular and Hürthle Cell Neoplasms of the Thyroid Gland

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The objective of the current study was to determine the risk of malignancy in patients with thyroid nodules with cytology of indeterminate follicular and indeterminate Hürthle cell neoplasm (HN). The cytologic diagnosis of follicular neoplasm (FN) or HN remains a diagnostic challenge. Often, surgery is recommended for such lesions. A retrospective analysis was performed on 80 patients who underwent thyroid surgery following a diagnosis of indeterminate FN and indeterminate HN in thyroid fine-needle aspiration biopsy. Sex; age; family history of thyroid cancer and radiation exposure; coexisting thyroid conditions, such as solitary nodule; multinodularity; cytologic diagnosis; sonographic features; type of surgical treatment; and histopathologic results were recorded. Of the 80 patients, 52 (65%) had FN on fine-needle aspiration biopsy cytology and 28 (35%) had HN. A total of 23 patients (28.7%) had primary thyroid cancers on surgical pathology, and 57 (71.3%) had benign diagnoses. Univariate analysis showed no differences between the benign and malignant groups by sex, nodule size, family history of thyroid cancer, history of radiation exposure, presence of solitary nodule or multinodularity in the nodular features. In multivariate binary logistic regression analysis, the factors that were statistically significant predictors of malignancy were microcalcification [odds ratio (OR), 10.9; 95% confidence interval (CI), 2.18–54.7; $P = 0.004$], being older than 45 years (OR, 4.2; 95% CI, 1.25–14.63; $P = 0.02$]. The independent predictors of malignancy in FN and HN are micorcalcification and being older than 45 years, the use of which may predict the risk of thyroid cancer.

Key words: Follicular neoplasm – Hürthle cell neoplasm – Malignancy

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Fine-needle aspiration biopsy (FNAB) is regarded worldwide as the first approach for the evaluation of thyroid nodules. It is a simple, safe, and cost-effective method, achieving a correct definition of the nature of thyroid nodules.[1] The FNAB diagnosis of an adequately sampled thyroid nodule generally can be grouped into benign, malignant, and indeterminate categories.[2] On fine-needle aspiration biopsy (FNAB), Hürthle cell neoplasm (HN) or follicular neoplasm (FN) is categorized as indeterminate for malignancy, with a 15% to 45% malignancy risk.[3–6] Because of indeterminate or suspicious findings on FNAB, surgery is needed to delineate whether or not the lesions are malignant.[5,7,8] Molecular markers, such as BRAF, RAS, RET/PTC, Pax8-PPARc, galectin-3, and cytokeratin, may ameliorate preoperative diagnostic accuracy, but these have not been widely used in routine practice.[9,10] Little is known about whether the indeterminate FN and HN cytology provides information regarding the risk or type of malignancy.[11–13]

The objective of the current study was to determine the risk of malignancy in patients with thyroid nodules with a cytology of indeterminate FN or indeterminate HN.

Patients and Methods

Study design

After approval by the Institutional Review Boards, data on 80 patients who underwent thyroidectomy (lobectomy or total thyroidectomy) from January 2006 to December 2014 at our clinic and who had a cytologic diagnosis of FN or HN indeterminate (Bethesda IV) according to the 2007 Bethesda classification, were retrospectively collected. We reviewed each patient's medical records, including hospital, outpatient clinic, and operating room reports. Patients with previous thyroidectomy for thyroid cancer, who were younger than 16 years, who had thyroid nodule < 1 cm, and who had presence of cytology suspicious for thyroid carcinoma were excluded. Sex; age; family history of thyroid cancer; history of radiation exposure; coexisting thyroid conditions, such as solitary nodule; multinodularity; cytologic diagnosis and sonographic features; type of surgical treatment; and histopathologic results were recorded.

FNABs were performed on all thyroid nodules $\geq$ 1 cm. All FNABs were done using ultrasound and were performed by an experienced radiologist using a 25-gauge needle attached to a 10-mL syringe. We performed FNAB of thyroid nodules under ultrasound guidance in 98% of patients. A minimum of 2 passes was made in 2 different areas of the nodule. Samples were stained with hematoxylin-eosin and Giemsa and were evaluated by 2 experienced cytopathologists in the pathology department of our hospital. Patients whose cytology results were reported as HN or FN and who underwent a total or a partial thyroidectomy were selected for the study. Nodule size was defined as the largest diameter of the index nodule in centimeters measured by ultrasound. Nodule components were described as solitary or multinodular. Calcification of the nodule was defined as microcalcification or no microcalcification.

Intraoperative frozen-section analysis was not routinely used in that it is not reliable and does not affect intraoperative decision-making.[14] If intraoperative frozen-section analysis returned suspicious for thyroid cancer or presence of a contralateral thyroid nodule, a total thyroidectomy was performed.

Cytology specimens are designated as FN when the cellular aspirate consists predominantly of follicular architecture, with a small subset of cells demonstrating any of the enlarged nuclei with powdery chromatin, nuclear membrane irregularities, nuclear grooves, intranuclear cytoplasmic invaginations, and small, peripherally located nucleoli. HN interpretation was made when FNAB cytology aspirates were composed of >75% Hürthle cells consisting of microfollicles formed by cells with abundant eosinophilic cytoplasm lacking lymphocytes having and a paucity of colloid cells.

Statistical analysis

Statistical significance between subgroups was determined using χ^2 test and Student *t*-test. Statistical analysis was performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois) after reviewing clinical interactions between variables. Variables with P values < 0.1 on univariate analysis were included in a multivariate analysis. Bivariate analyses using logistic regressions were performed to evaluate the risk factors for the presence of malignancy. A P value less than 0.05 was considered significant.

Results

We studied 80 patients who underwent thyroid lobectomy or total thyroidectomy after an FNAB with a diagnosis of FN or HN (Bethesda IV) according to the Bethesda classification criteria.

Table 1 Final pathology of study patients

	FN	HN	Total
Malignancy			
Papillary thyroid carcinoma	14	7	21
Hashimoto thyroiditis[a]	1	2	3
Follicular thyroid carcinoma	1	0	1
Hürthle cell thyroid carcinoma	0	1	1
Benign			
Follicular adenoma	4	6	10
Hürthle cell adenoma	1	3	4
Multinodular goiter	29	1	30
Hashimoto thyroiditis	2	8	10
Total	52	28	80

[a]Accompanied papillary carcinoma.

There were 65 total thyroidectomies and 15 lobectomies performed at the initial operation. Five patients underwent subsequent completion thyroidectomy because of malignancy identified on pathologic examination. The final pathology of study patients is explained in Table 1. Of the 80 patients, 52 (65%) had FN on FNAB cytology and 28 (35%) had HN. There were 23 patients (28.7%) with primary thyroid cancers on surgical pathology, and 57 patients (71.3%) had benign diagnoses. In the benign group, nodular goiter was found in 30 patients, follicular adenoma in 10, Hürthle cell adenoma in 4, and Hashimoto thyroiditis in 10. In the malignancy group, 20 patients had papillary carcinomas (18 classic type and 2 follicular variant), 2 had follicular carcinomas, and 1 had Hürthle cell carcinoma. Hashimoto thyroiditis was detected simultaneously in 3 patients with papillary thyroid cancer.

A comparison of age, sex, family history of thyroid cancer, history of radiation exposure, tumor size, sonographic criteria, and results of final histology from patients with benign or malignant lesion are detailed in Table 2. Univariate analysis showed no differences between the benign and malignant groups by sex, nodule size, family history of thyroid cancer, history of radiation exposure, or the presence of solitary or multinodular in the nodular features.

The median age of patients with malignant diagnosis on final histopathology (53.6 ± 2.5 years) was older than in those with benign diseases (45.7 ± 1.6 years; $P = 0.012$). Age also was categorized into 2 groups (>45 years and <45 years). Patients older than 45 years were statistically significantly more likely to have a malignant lesion than those younger than 45 years (74% versus 52.6%; $P = 0.027$). The benign nodules (median size, 2.6 ± 0.1 cm) were similar to the malignant nodules (median size, 2.4 ± 0.2 cm; $P = 0.68$). Nodule size was categorized into two groups (1–4 cm and ≥4 cm). The rates of malignancy in the nodules 1 to 4 cm and >4 cm were 27% and 35.3%, respectively ($P = 0.5$).

Table 2 Comparison of clinical characteristics based on malignant and benign pathology

	Benign	Malignant	*P* value
No. of patients	57	23	
Age, y, mean ± SD	45.7 ± 1.6	53.6 ± 2.5	0.012[a]
>45 y (n = 23), n (%)	6 (26)	17 (74)	0.027[a]
<45 y (n = 57), n (%)	27 (47.4)	30 (52.6)	
Sex, n (%)			
Male (n = 21)	14 (66.7)	7 (33.3)	0.592
Female (n = 59)	43 (72.9)	16 (27.1)	
Family history of thyroid cancer, n	3	2	0.577
History of radiation exposure, n	6	3	0.75
Hashimoto thyroiditis, n (%)	10/57 (17.5)	3/23 (13)	0.61
Nodule features			
Size, cm, mean ± SD	2.6 ± 0.1	2.4 ± 0.2	0.68
1–4 cm (n = 63), n (%)	46 (73)	17 (27)	
>4 cm (n = 17), n (%)	11 (64.7)	6 (35.3)	0.5
Microcalcification, n (%)	3/57 (5)	7/23 (30.4)	0.003[a]
Solitary (n = 18), n (%)	10 (55.6)	8 (44.4)	0.094
Multinodular (n = 62), n (%)	47 (75.9)	15 (24.1)	
Diagnosis on FNAB, n (%)			
HN (n = 28)	20 (71.5)	8 (28.5)	0.97
Follicular lesion (n = 52)	37 (71.2)	15 (28.8)	

[a]Statistically significant.

In multivariate binary logistic regression analysis, the factors that were statistically significant predictors of malignancy were microcalcification [odds ratio (OR), 10.9; 95% confidence interval (CI), 2.18–54.7; $P = 0.004$], age > 45 years (OR, 4.2; 95% CI, 1.24–14.28; $P = 0.02$). However, the presence of solitary nodule could independently predict the existence of malignant diagnosis (Table 3).

Hashimoto thyroiditis was found to be at a similar rate between the malignant and benign lesions (13% versus 17.5%; $P = 0.61$). Patients with microcalcification on nodule had a higher malignancy rate than those with without microcalcification (30.4% and 5%; $P = 0.003$). There was no difference in the malignan-

Table 3 Variables to predict the existence of thyroid cancer in binary logistic regression analysis

	OR (95% CI)	*P* value
Age > 45 y	4.2 (1.25–14.63)	0.02[a]
Microcalcification	10.9 (2.18–54.7)	0.004[a]
Solitary nodule	1.8 (0.540–6.48)	0.323

[a]Statistically significant.

Table 4 Comparison of clinical characteristics based on FNAB

	FN	HN	*P* value
No. of patients	52	28	
Age, y, mean ± SD	46.1 ± 1.7	51.4 ± 2.4	0.087
>45 y (n = 44), n (%)	27 (61.4)	17 (38.6)	0.449
<45 y (n = 36), n (%)	25 (69.5)	11 (30.5)	
Sex, n (%)			
Male (n = 21)	15 (61.5)	6 (28.5)	0.467
Female (n = 59)	37 (62.8)	22 (37.2)	
Family history of thyroid cancer, n	4	1	0.448
History of radiation exposure, n	5	4	0.534
Hashimoto thyroiditis (n = 13), n (%)	3 (5.7)	10 (35.7)	0.001[a]
Nodule features			
Size, cm, mean ± SD	2.61 ± 0.17	2.49 ± 0.23	0.681
>4 cm (n = 17), n (%)	11 (64.7)	6 (35.3)	0.977
1–4 cm (n = 63), n (%)	41 (65)	22 (35)	
Microcalcification (n = 10), n (%)	8 (15.3)	2 (7.1)	0.26
Solitary (n = 18), n (%)	12 (66.7)	6 (33.3)	0.865
Multinodular (n = 62), n (%)	40 (38.6)	22 (35.4)	
Diagnosis of final pathology, n (%)			
Benign (n = 57)	37 (65)	20 (35)	
Malignant (n = 23)	15 (28.8)	8 (28.5)	0.97

[a]Statistically significant.

cy rate between follicular lesion and Hürthle cell lesion (28.8 versus 28.5; $P = 0.97$).

Characteristics of patients with thyroid FNAB cytology HN or FN are summarized in Table 4. Univariate analysis showed no differences between the groups by sex, age, family history of thyroid cancer, history of radiation exposure, and presence of solitary nodule or multinodularity in the nodular features. Hashimoto thyroiditis was found to occur at a higher rate in HN [3 (5.7%) versus 10 (35.7%); $P = 0.001$], which was the only significant difference.

Discussion

In this study, we have evaluated the risk of malignancy for patients with thyroid nodules with cytology of indeterminate FN and indeterminate HN. Our results show that the malignancy risk is significantly higher in patients older than 45 years and those with the presence of nodular microcalcification. Several studies report that the rate of malignancy in indeterminate HN or FN to be 17.6% to 41%, which is consistent with our study.[3,15–18] Many investigators have attempted to identify malignancy risk factors in order to avoid unnecessary thyroidectomy.[3,5,12,13,15–18] The major limitation of thyroid FNAB is its incapability to distinguish malignancy from benign in FN and HN.[7,19] Eventually, thyroidectomy is needed in that only histologic evaluation can discriminate between these neoplasms.[20,21] Petric *et al*[16] and Mihai *et al*[22] found that the risk of carcinoma was higher in men than in women (43% versus 23%, and 38% versus 26%, respectively). However, we found no significant difference in the incidence of malignant thyroid tumor between male and female patients. The malignancy rate in men in our study was 33.3%, whereas in women it was 27.1%. Similarly, other studies reported that sex was not associated with malignancy.[15,23,24]

Whether nodule size exhibits a risk factor for malignancy in indeterminate neoplasms is still a debate. Many authors reported that the size of FN or HN increases the risk of malignancy.[13,25–29] In our patients, the malignancy rate did not differ in patients with a tumor diameter of 1 to 4 cm or >4 cm. Similar to our study, Suh *et al*[15] and Petric *et al*[16] found that tumor diameter has a poor accuracy for predicting malignancy in follicular or Hürthle cell thyroid neoplasms. Also, Ibrahim *et al*[30] recently analyzed prediction for the risk of malignancy in follicular neoplasms according to nodule size: <3 cm, ≥3 cm, <4 cm, and ≥4 cm. They suggested that increased thyroid nodule size does not increase the malignancy rate.

Several studies stated that patients with carcinoma were older than those with a benign disease.[28,29,31] Similarly, we reported that patients older than 45 years were statistically significantly more likely to have a malignant lesion than those with younger than 45 years, which is also an independent risk factor for malignancy by 4.2 times by regression analysis. However, our results have not been supported by other recent papers, in which the authors have reported similar risks of malignancy for age without any statistical difference.[15–17,23,32]

The relationship between Hashimoto thyroiditis and thyroid cancer is still a matter of debate.[33,34] Rago *et al*[17] and Pu *et al*,[18] who analyzed FN and HN together, found that malignancy is not associated with Hashimoto thyroiditis, in parallel with our study. Unlike our study, Zhang *et al*[35] suggested that Hashimoto thyroiditis is associated with a significantly higher risk of papillary carcinoma, and the incidence of papillary carcinoma is much higher in male HT patients.

Another possible sign of malignancy in thyroid nodules is the presence of microcalcification within the nodules.[17,36] However, other studies reported

that none of the ultrasonographic features were found to be associated with malignancy in HN or FN.[23,37,38] In the present study, the presence of microcalcification was found at a higher rate in the malignancy group. The presence of microcalcification within the nodules increased the risk of malignancy by 10.9 times by regression analysis in the present study. A number of studies have shown a correlation between the presence of a solitary nodule and malignancy.[39–41] However, Tutuncu *et al*[38] recently reported that the presence of a solitary nodule in the nodules was found not to be significantly correlated with malignancy in FN and HN, in parallel with our study.

We also noted the risk of malignancy to be 28.5% in the HN group and 28.8% in the FN group, suggesting that an FNAB diagnosis of HN does not predict more malignancy than FN. We attribute this to the similarity of the patient's demographic data regarding FN and HN, which enabled us to compare groups more accurately. Similarly, Pu *et al*[18] and Sorrenti *et al*[3] showed the prevalence of malignancy was similar in FN and HN. Conversely, Giorgadze *et al*[2] showed there was much higher risk of malignancy for the diagnosis of HN than for FN.

The limitations of the present study are that it was retrospective and we selected patients who had undergone an operation. Another limitation of our study was the lack of immunohistochemical markers, which may be hopeful for diagnosis of thyroid nodules in cytologically indeterminate lesions. Regarding the risk factors for malignancy, we compared our results with the literature. Although our results are consistent with those from different studies, other studies' results are not. We speculate this is due to several reasons, such as different study population and different patient inclusion or exclusion criteria.

In conclusion, this study shows that there is no difference between FN and HN regarding the rate of malignancy. The independent predictors of malignancy in FN and HN are: microcalcification and being older than 45 years, the use of which may predict risk of thyroid cancer requiring a thyroidectomy in patients with thyroid nodules of indeterminate cytology, and may prevent unnecessary thyroidectomy or reduce completion thyroidectomy.

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