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□ ORIGINAL ARTICLE □

Predictive Factors of Malignancy in Thyroid Nodules Diagnosed as Follicular Neoplasm or Hürthle Cell Neoplasm on FNA

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Purpose: The rate of malignancy in the follicular neoplasm (FN) or Hürthle cell neoplasm (HCN) of the thyroid gland is estimated as approximately 20～30%. Fine-needle aspiration biopsy (FNAB) and frozen section examination are restricted in differentiating between benign and malignant. The aims of this study are to compare the differences of clinicopathologic features and to determine the risk factors for malignancy in patients with FN or HCN. **Methods:** A retrospective study was conducted of patients with FN or HCN who were diagnosed by FNAB, and underwent surgery at our institution between Jan. 2005 to Jun. 2010. We analyzed the risk factors for malignancy and the differences of clinicopathologic features in patients with FN or HCN. **Results:** A total of 290 patients were enrolledin this study; 160 (55.2%) patients underwent thyroidectomy, 97 (60.6%) patients had FN, and 63 (39.4%) had HCN. Forty one (25.6%) patients were diagnosed as malignancy of these, 22 (22.7%) patients were FN and 19 (30.2%) were HCN (P=0.29). Two (2.1%) patients with FN and 10 (15.9%) with HCN (P=0.002) comcomitant papillary thyroid carcinoma were indentified by FNAB. Classification of nodules according to ultrasonographic findings in both neoplasms ($P<0.05$) and galectin-3 in FN ($P<0.05$) were predictive factors for malignancy. In addition, galectin-3 was a predictive factor for malignancy in indeterminate nodules on ultrasonography (USG) (P=0.028). **Conclusion:** Classification of nodules according to ultrasonographic findings and galectin-3 expression is helpful in predicting carcinoma of patients with FN or HCN.

Key Words: Follicular neoplasm, Hürthle cell neoplasm, Ultrasonography, Galectin-3

INTRODUCTION

The risks of malignancy in the follicular neoplasm (FN) or Hürthle cell neoplasm (HCN) of the thyroid gland is estimated approximately 20～30%.(*1*) Fine-needle aspiration biopsy (FNAB) is accepted as a standard diagnostic method of thyroid nodule and the frozen section examination are used during operation. However these procedures have their limits in differentiating benign and malignancy, since both lesions appear similar in cytologic specimens.(*2-5*) Therefore, in the absence of extrathyroidal tumor spread or lymph node metastases, the diagnosis of malignancy in both neoplasms are dependent solely on capsular and/or vascular invasion on permanent histology, that the majority of these patients undergo surgical exploration.(*3-6*)

FN is characterized by a predominance of follicular epithelial cells forming microfollicles with a paucity of colloid and encompasses benign follicular hyperplasia, follicular adenoma, follicular carcinoma, and the follicular variant of PTC.(*1,7*)

HCN denotes a set of tumors composed of 75% or greater Hürthle (oncocytic) cells derived from follicular epithelium, which is characterized cytologically as a large cell with abdundant eosinophilic, granular cytoplasm and a large hyperchromatic nucleus with a prominent nucleolus.(*1,3,8*) A variety of thyroid neoplasms are characterized as having oncocytic cytology. These include benign (Hürthle cell adenoma, granular cell tumor) and malignant

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(Hürthle cell carcinoma) neoplasms, variants of papillary thyroid carcinoma (PTC) (tall cell variant, oncocytic variant, and Warthin-like variant), and the oncocytic variant of medullary carcinoma.(*8*)

In the World Health Organization (WHO) classification, HCN are classified into variant categories of follicular adenoma, follicular carcinoma, papillary carcinoma, etc. However, some authors classify HCN into a separate and distinct category due to a higher prevalence of aggressive histology and biologic features such as a greater inclination toward regional lymph node or distant metastases and the differences in the genetic alterations such as aneuploidy.(*3,9,10*) Therefore, there are some controversies on the pathologic classification of HCN, its method of diagnosis, staging, and prognosis.

In this study, we tried to find the risk factors of malignancy in the patients with FN or HCN diagnosed by FNAB and to compare the differences of the clinicopathologic features between the two neoplasms.

METHODS

A retrospective study was done the patients with FN or HCN, who were diagnosed by FNAB, and underwent operation at our institution between Jan. 2005 to Jun. 2010. During this period, 290 patients with thyroid nodule(s) were diagnosed with FN or HCN by FNAB and 160 patients out of 290, (55.2%) 97 patients were FN and 63 patients were HCN underwent operation at our institution. The patients were evaluated for their clinicopathology classification as we outlined in out tables and the the USG findings, levels of thyroglobulin, TPO antibody, and galectin-3 were measured to determine whether these clinical factors can differentiate and predict carcinoma. Only the status of the dominant nodule (malignant versus benign) was used for the analysis of factors correlating with the presence of malignancy. The institutional review board approved this study and waived the requirement for informed consent.

Nodules were classified into benign, indeterminate, and suspicious for malignancy according to ultrasonographic findings. When at least one nodule was indentified the following characteristics were described marked hypoechogenicity, microcalcification spiculated or lobulated margins, increased intra-nodular vascularity, or taller than width pattern, and decided it as "suspicious for malignancy." A benign lesion was defined as a nodule with following; complete cystic, predominantly cystic nodule with comet tail artifact, or a spongiform appearance. As for indeterminate nodules, it was decided when neither of previously mentioned criterias were not fit. A FNAB diagnosis of FN was defined as an adequate specimen consisting of abundant follicular epithelial cells in sheets, in microfollicles or a trabecular pattern, with minimal or no colloid. The nodules accounted for greater than 75% Hürthle cells-follicular cells with eosinophilic cytoplasm, enlarged, round nuclei with prominent nucleoli, with little or no colloid on the smear were classified as a HCN. A diagnosis of follicular or Hürthle cell carcinoma was made by histopathologic illustration of capsular and/or vascular invasion on permanently fixed tissue specimens.

An univariate analyses of the differences of the clinicopathologic features and the risk factors of malignancy in patients with both neoplasms by the Chi-square and Fisher`s exact test in nominal variables (e.g., gender, galectin-3), Student t-test in parametric variables (e.g., age, tumor size) was used. Any significant variables identified from univariate then would be subjected to multivariate logistic regression model. Statistical analyses were performed using SPSS version 15.0 for Windows. (SPSS Inc., Chicago, IL, USA) A P value of <0.05 was considered statistically significant.

RESULTS

Among 160 patients, 97 (60.6%) patients were FN and 63 (39.4%) were HCN, diagnosed by FNAB, underwent thyroidectomy. There were 37 males (23.1%) and 123 females (76.9%) with a mean age of 48.6±12.4 years (range, 20～82 years) at the time of FNAB forthyroid nodule. The mean tumor size measured by USG was 24.2±15.6 mm (range, 3～78) and mean pathologic tumor size was 21.2±15.2 mm (range, 3～73). According to the ultrasonographic findings, 45 patients were subdivided into suspicious for malignancy, 4 patients, benign and 111 patients were classified into indeterminate nodule. Intraoperative frozen section was preformed in 129 (80.6%) patients. On the Frozen section, 13 (10.1%) patients were diagnosed as malignancy, 40 (31.0%) patients as benign and 76 (58.9%) patients were deferred. Total thyroidectomy was performed in 58 patients, including 26 completethyroidectomy and 1 modified radical neck dissection (MRND). 19 patients underwent initialtotal thyroidectomy because of multinodular goiter involving contralateral lobe. Subtotal thyroidectomy and lobectomy with isthmusectomy was performed in 5 and 96 patients, respectively. 1 patient only underwent tumor enucleation. Incidental papillary thyroid carcinoma was found in 19 patients (11.9%) (Table 1).

The final histopathologic diagnoses for the 160 patients diagnosed with FN or HCN on FNAB are shown in Table 2. 119 (74.4%) were diagnosed as benign in 75 (77.3%) patients of FN and 44 (69.8%) of HCN. 41 (25.6%) patients were diagnosed as

Table 1. Demographic characteristics of 160 patients with Follicular neoplasm (FN) or Hürthle cell neoplasm (HCN)

Characteristics	Subgroup	N (160)	%
FNAB results	FN	97	60.6
	HCN	63	39.4
Gender	M	37	23.1
	F	123	76.9
Age		48.6±12.4 (20～82)	
Tumor size on USG (mm)		24.2±15.6 (3～78)	
Pathologic tumor size (mm)		21.2±15.2 (3～73)	
Classification of according to USG finding	Benign	4	2.5
	Indeterminate	111	69.4
	Suspicious for malignany	45	28.1
Frozen section	Benign	40	31.0
	Deferred	76	58.9
	Malignancy	13	10.1
Permanent pathology	Benign	119	74.4
	Malignancy	41	25.6
Incidental PTC		19	11.9
Operation method	Enucleation	1	0.6
	Lobectomy	96	60
	Subtotal thyroidectomy	5	3.1
	Completion thyroidectomy	26	16.3
	Total thyroidectomy	31	19.4
	Total thyroidectomy with modified radical neck dissection	1	0.6

Table 2. Final histopathologic diagnoses in 160 patients who underwent operation under diagnosis of follicular neoplasm or Hürthle cell neoplasm on FNAB

Histopathologic diagnosis		Follicular neoplasm (N=97)		Hürthle cell neoplasm (N=63)	
		N	%	N	%
Follicular adenoma		39	40.2	7	11.1
Hürthle cell adenoma		1	1	21	33.3
Nodular hyperplasia		31	32	13	20.6
Hyalinizing trabecular adenoma				1	1.6
Hashomotos thyroiditis		1	1	1	1.6
Lymphocytic thyroiditis		2	2.1	1	1.6
Parathyroid hyperplasia		1	1		
Total benign nodule		75	77.3	44	69.8
Follicular carcinoma	MIC	8	8.2	4	6.3
	WIC	1	1		
	UMB	3	3.1	1	1.6
Hürthle cell carcinoma	MIC			3	4.8
	UMB			2	3.2
Medullary carcinoma		1	1		
Poorly differentiated carcinoma		1	1		
Papillary carcinoma	Classic	1	1	6	9.5
	Follicular variant	6	6.2	2	3.2
	Solid variant	1	1		
	Oncocytic variant			1	1.6
Total malignant nodule		22	22.7	19	30.2

MIC = minimally invasive carcinoma; WIC = widely invasive arcinoma; UMB = unknown malignant behavior.

Table 3. The comparisons of 160 patients who underwent operation after the diagnosis of follicular neoplasm or Hürthle cell neoplasm on FNA

Characteristics		Follicular neoplasm (N=97)	Hürthle cell neoplasm (N=63)	P value
Gender (%)	M	22 (22.7)	15 (23.8)	0.869
	F	75 (77.3)	48 (76.2)	
Age		47.7±12.3	50.1±12.6	0.24
Concomitant PTC (%)	Negative	95 (97.9)	53 (84.1)	0.002
	Positive	2 (2.1)	10 (15.9)	
Classification of according to USG finding	Idetermi nate	72	39	0.542
	Malignant	24	21	
Tumor size on USG (mm)		26.5±16.9	20.8±12.9	0.017
Pathologic tumor size (mm)		23.3±16.7	17.9±12.1	0.019
Preoperative thyroglobulin (Tg)		180.6±325.4	124.4±232.3	0.412
Anti Tg antibody		54.8±139.3	64.0±121.4	0.764
TPO antibody		41.9±126.3	82.4±213.9	0.314
Frozen section	Benign	21	19	0.939
	Defer	55	21	
	Malignancy	4	9	
Galectin-3	Negative	62	36	0.074
	Positive	14	17	
Incidental PTC	Negative	89	52	0.078
	Positive	8	11	
Permanent pathology	Benign	75	44	0.29
	Malignant	22	19	

malignant in which—22 (22.7%) patients were FN and 19 (30.2%) were HCN. The difference in rates of malignancy between FN and HCN was not significant statistically (P=0.29) (Table 3).

The comparisons of the both neoplasms are shown in Table 3. The mean tumor size measured with USG was 26.5±16.9 mm and 20.8±12.9 mm, and the mean pathologic tumor size was 23.3±16.7 mm and 17.9±12.1 mm, respectively. In patients with both neoplasms, FNs were statistically significant larger than the HCNs (P=0.017, P=0.019). 2 (2.1%) patients in FN and 10 (15.9%) in HCN (P=0.002) had concomitant PTC in FNAB. However, there were no differences between the two neoplasms in gender, age, finding in ultrasonographic findings, preoperative levels of thyroglobulin, TPO antibody, and the presence of galectin-3 (Table 3).

In the comparison of benign and malignant nodules in FN & HCN, the classifications according to ultrasonographic finding in both neoplasms (P＜0.05, RR 3.889; 95% CI, 1.205～12.555 vs RR 3.887; 95% CI, 1.164～9.853, respectively) and galectin-3 in FN (P＜0.05, RR 4.200; 95% CI, 1.106～15.955) were predictive factors for malignancy on univariate and multivariate analyses (Table 4).

In the comparison of indeterminate nodule on USG, there were no significant differences in the probability of malignancy in both neoplasms (P=0.307). The positivity of galectin-3 was only independent predictive factor for malignancy (P=0.024) (Table 5).

DISCUSSION

Thyroid nodules are commonly indentifiable with modern widespread use of high-resolution cervical USG. In fact, the prevalence of clinically inapparent thyroid nodules by USG is now estimated at 20～76% of the general population, with a prevalence similar by autopsy in approximately 50%.(*11*) FNAB is currently the best triage test for the preoperative evaluation of thyroid nodules.(*12,13*) However, FNAB cannot distinguish between benign and malignant in FN or HCN occupying 15～30% of FNAB specimens due to the similar cytologic appearance.(*1,2,14*) In addition, repeated FNAB or core needle biopsy (CNB) is not recommended since it creates confusion and does not provide additional useful information for the management.(*1,15*) Therefore, the majority of these patients undergo surgical exploration; thyroid lobectomy is the recommended initial surgical approach and total thyroidectomy is indicated in larger tumors (＞4 cm), marked atypia, a history of radiation exposure, and bilateral nodular disease. (*11,16*)

In our study, the incidence of malignancy in patients with FN

or HCN was 25.6% and that HCN is slightly higher than FN-22.7% in FN and 30.2% in HCN, however there are no statistically significant differences (P=0.290). This malignancy rate correlates with other studies.(*1,11,16,17*) Also, if incidental malignancies are included and the patients with concomitant PTC were excluded, the incidence of clinically significant carcinoma was 31.8% in patients with FN or HCNs and was no statistically significant differences between both neoplasms (P=0.125). The incidence of concomitant PTC diagnosed by FNA was statistically significantly higher in HCN (P=0.002, Table 3).

The limited value of FNA and frozen section examination as the diagnosis was deferred in 76 (58.9%) patients in our study, several clinical factors have been investigated for their potential value in predicting carcinoma and determining the extent of thyroid surgery. While certain clinical features such as male gender and nodule size (≥4 cm), older patient age, or cytologic features such as presence of atypia can improve the diagnostic accuracy for malignancy in patients with indeterminate cytology,(*18-21*) overall predictive values are still low and even has been reported conflicting results.(*17*)

Recently, many potential immunohistochemical and molecular markers such as galectin-3, cytokeratin-19 (CK19), HBME-1, thyroid transcription factor 1 (TTF-1), RET/PTC gene rearrangements, and B-raf mutations have been studied to improve diagnostic accuracy for indeterminate nodules.(*22-24*) Recently, a large prospective studies have confirmed the ability of genetic markers (B-raf, RAS, RET/PTC) and protein markers (galectin-3) to improve preoperative diagnostic accuracy for patients with indeterminate thyroid nodules.(*23,24*)

In our study, patients with an indeterminate FNAB results showed, there were no significant differences in age, gender, nodule size in patients with and without carcinoma. Carcinoma was more common in the patients with suspicious for malignancy in USG and positivity of galectin-3 was independent predictive factors as shown in multivariate logistic regression.

Many authors claimed that the diameter of the tumor can increase the risk of malignancy.(*16,18,19,25,26*) According to the ATA guideline, initial total thyroidectomy is recommended in patients with indeterminate nodules who have large tumors (>4 cm) due to an increased risk for malignancy. Taneri et al.(*26*) found in HCN that there was no malignancy among the tumors less than 1 cm diameter. Malignancy rate in their patients with tumor diameter between 1 to 4 cm and greater than 4 cm was 24% and 43%, respectively. However, several studies concluded that nodule size does not predict thyroid malignancy.(*17,27,28*) In our patients, tumor diameter was not predictive factor for carcinoma as shown by Table 4. Malignant tumors in patients with large (≥4

Table 4. The comparison of benign and malignant nodule in FN & HCN.

Characteristics		Follicular neoplasm (N=97)		P value		RR (95% CI)	Hürthle cell neoplasm (N=63)		P value		RR (95% CI)
		Benign (N=75)	Malignant (N=22)	Univariate	Multivariate		Benign (N=44)	Malignant (N=19)	Univariate	Multivariate	
Gender	M	16	6	0.571			9	6	0.353		
	F	59	16				35	13			
Age		47.6±12.7	48.2±11.0	0.82			49.86±13.1	50.5±11.5	0.849		
Classification of according to USG finding	Benign	1	0	0.002	0.023	3.889 (1.205~12.555)	3	0		0.025	3.387 (1.164~9.853)
	Indeterminate	61	11				30	9			
	Malignant	13	11				11	10			
Tumor size on USG (mm)		25.5±15.7	29.7±21.1	0.391			21.3±13.3	19.5±12.1	0.602		
Pathologic tumor size (mm)		22.1±14.8	27.4±21.9	0.263			18.8±13.3	15.9±8.9	0.391		
Preoperative thyroglobulin (Tg)		143.8±293.5	332.5±422.5	0.263			120.1±218.0	132.7±268.5	0.887		
Anti Tg antibody		63.1±153.4	18.7±11.4	0.368			31.7±28.9	128.5±196.9	0.156		
TPO antibody		46.5±139.1	20.3±9.9	0.6			85.1±260.0	77.8±109.5	0.934		
Galectin-3	Negative	52	10	0.011	0.035	4.200 (1.106~15.955)	27	9	0.52		
	Positive	7	7				11	6			
Incidental PTC	Negative	70	19	0.376			38	14	0.283		
	Positive	5	3				6	5			

Table 5. The comparisons of indeterminate nodules on USG

Characteristics		Benign (N=91)	Malignant (N=20)	P value	
				Univariate	Multivariate
FNAB results	FN	61	11	0.307	
	HCN	30	9		
Gender	M	22	6	0.587	
	F	69	14		
Age		47.5±12.8	46.7±12.0	0.794	
Tumor size on USG (mm)		25.0±15.3	27.7±20.4	0.515	
Pathologic tumorsize (mm)		21.6±14.6	23.7±17.7	0.59	
Galectin-3	Negative	62	9	0.028	0.024
	Positive	10	6		
Preoperative thyroglobulin (Tg)		126.2±267.8	366.9±431.4	0.12	
Anti Tg Antibody		53.9±141.9	27.2±16.0	0.539	
TPO antibody		64.0±203.0	65.9±107.5	0.977	

cm) indeterminate tumors were only 26.9%. Furthermore, in patients with HCN, malignant nodules were smaller (15.9±8.9 cm) than benign nodules (18.8±13.3 cm). Also, other clinical factors such as older age, male gender were not associated with a higher risk of carcinoma in patients with FN or HCN (Table 4). Therefore, clinical factors were not helpful in predicting carcinoma and selecting patients for more extensive thyroidectomy in patients with FN or HCN and initial total thyroidectomy might be inappropriate surgical procedure in patients with large tumor.

Currently, USG has become essential tool in the examination of the thyroid gland to detect tumor or noduledue to a non-invasive, rapid, and easily reproducible imaging study. Follow up study of thyroid nodule such as USG-guided FNA, preoperative and intraoperative staging, lymph node mapping, deciding surgical extent, and surveillance of patients with thyroid cancer is helpful. (*29*) When classified into benign, indeterminate, and malignant nodule according to the previous described criteria in our study, negative predictive values in benign nodules were 100% all in FN or HCN and positive predictive values in malignant nodules were 84.6% and 90.9% in FN or HCN, respectively (Table 4). Therefore, if it were classified into benign or malignant nodules on USG, strategy of observation or initial total thyroidectomy might be appropriate. However, many patients with FN or HCN in our series (69.4%) were classified into indeterminate nodule by USG (Table 1). Hence, it is essential to determine which thyroid nodules have a high malignant potential on the basis of their FNAB.

Recently, a number of studies of potential markers to discriminate benign from malignant thyroid tumors are investigated and several molecules have been identified by immunochemistry and reverse-trasnscriptase polymerase chain reaction (RT-PCR) as potential targets for immunocytodiagnosis of thyroid malignant disease.

Among these, expression of the β-galactosil-binding protein galectin-3 restricted to malignant transformed thyroid cells reported to be promising. Bartolazzi et al.(*30*) have reported that the sensitivity and specificity of galectin-3 immunostaining in discriminating benign from malignant thyroid nodules were more than 99% and 98% respectively, and the positive predictive value and diagnostic accuracy were 92% and 99%. However, in indeterminate FNs, they have reported that the overall sensitivity of the galectin-3 was 78% and specificity was 93%, and positive predictive value was 82% and negative predictive value was 91%.(*23*)

In our study, expression of galectin-3 was tested in 129 patients. The expression of the galectin-3 was independent factor for risk of malignancy in FN, the sensitivity and specificity in FN were 41.2% & 88.1% and positive predictive value & negative predictive value were 50.0% & 83.9% (Table 4). The expression of the galectin-3 was also independent risk factor for malignancy in indeterminate nodule on USG, the sensitivity and specificity in indeterminate on USG were 40.0% & 86.1%, respectively and positive predictive value & negative predictive value were 37.5% & 87.3, respectively (Table 5). Therefore, if it were only based on galectin-3 expression, unnecessary surgical procedures and potentially missing malignancies are possible. Hence, it should be used as complementary diagnostic method for deciding in the surgical method of indeterminate neoplasm.

CONCLUSION

In conclusions, if HCN is diagnosed by FNA, the more careful

preoperative work-up may be required since the malignant potential of HCN is slightly higher than FN and the incidence of concomitant PTC is statistically significantly higher in HCN. The classification, according to ultrasonographic findings and galectin-3 expression are helpful in predicting carcinoma and selecting surgical option in small portion of patients with FN or HCN. However, some more improvements are needed in predicting malignancy and selecting more extensive surgical procedure in many patients with FN or HCN.

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