베데스다 분류 IV 세포검사의 갑상선 결절:
초음파로 악성과 양성 감별진단이 가능한가?

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Thyroid nodules with Bethesda System IV Cytology: Can Ultrasonography Differentiate Malignancy from Benign?

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Purpose: The purpose of this study is to identify clinical and imaging parameters that can be used in differentiation of benign versus malignancy of preoperative FNA diagnosis of Bethesda system IV nodules.

Materials and Methods: We analyzed clinical, ultrasonographic, and CT findings of 28 thyroid nodules with Bethesda system IV cytology on FNA, which were proven as follicular or Hürthle cell neoplasms on surgical pathology.

Results: No statistically significant differences according to age, sex, and ultrasonographic parameters, including echogenicity, margin, calcification, shape, cystic component, and degree of vascularity and enhancement on CT were observed between benign and malignant follicular neoplasms. Only the lesion size was significantly different ($p<0.05$).

Conclusion: The size of follicular neoplasm is predictive of malignancy. If a thyroid nodule with the Bethesda IV cytology is larger than 24.5 mm, there will be a greater probability of malignancy.

Key words : Thyroid; Follicular neoplasm; Bethesda system

Introduction

Follicular neoplasms of the thyroid gland include benign follicular adenoma and follicular carcinoma. Hürthle cell adenoma and Hürthle cell carcinoma are considered oncocytic variants of follicular adenoma and follicular carcinoma, respectively [1].

Currently, a follicular carcinoma cannot be distinguished from a follicular adenoma based on cytological, sonographic, or clinical features alone [2, 3]. The distinction between benign and malignant follicular neoplasm can only be made by evaluating the presence of capsular or vascular invasion on the histological examination. Although Hürthle cell nodules are found less frequently with respect to the follicular pattern, histology is also needed for the final diagnosis [1]. The estimated rate of malignancy for follicular neoplasm is variable, ranging from 10–30% [1, 4].

According to the Bethesda system for reporting thyroid cytopathology, "follicular neoplasm" or "suspicious for a follicular neoplasm" is categorized as Bethesda IV. This result was regarded as a screening test and a definitive diagnostic procedure such as lobectomy is needed [5]. Patients with invasive follicular carcinoma on final pathology are treated

with an additional total thyroidectomy with or without remnant ablative therapy [3]. Hence, preoperative discrimination between benign versus malignancy is needed. However, several prior attempts to define parameters useful for identification of patients at higher risk of malignancy were far from satisfactory [1].

The purpose of this study was to identify clinical and imaging parameters that can be used in characterization of patients with an increased risk of having a thyroid follicular carcinoma who have preoperative FNA diagnosis of Bethesda system IV nodules.

Materials and Methods

Study population

From March 2010 to August 2012, 10,252 thyroid nodules underwent ultrasound-guided fine needle aspiration (US-guided FNA) at our institution. Of these, 79 (0.8%) were classified as Bethesda system IV on cytology. Among the nodules with Bethesda system IV, 32 were excluded for a lack of surgical treatment and 19 lesions with other than follicular or Hürthle cell neoplasms on surgical pathology were also excluded. A total of 28 thyroid nodules in 28 patients were included in this study. Clinical, ultrasound (US), computed tomography (CT), and pathologic records of these patients were reviewed.

Thyroid Ultrasound and Image Analysis

US was performed using 7- to 15-MHz (HDI 5000; Philips Medical Systems, Bothell, WA, USA) and 5- to 12-MHz linear array transducers (iU22; Philips Medical Systems). Real-time US examinations were performed by one of six radiologists with 5–15 years of experience in thyroid imaging. US features of thyroid nodules were analyzed prospectively by the radiologists performing the US examination according to echogenicity, margin, calcification, shape, cystic

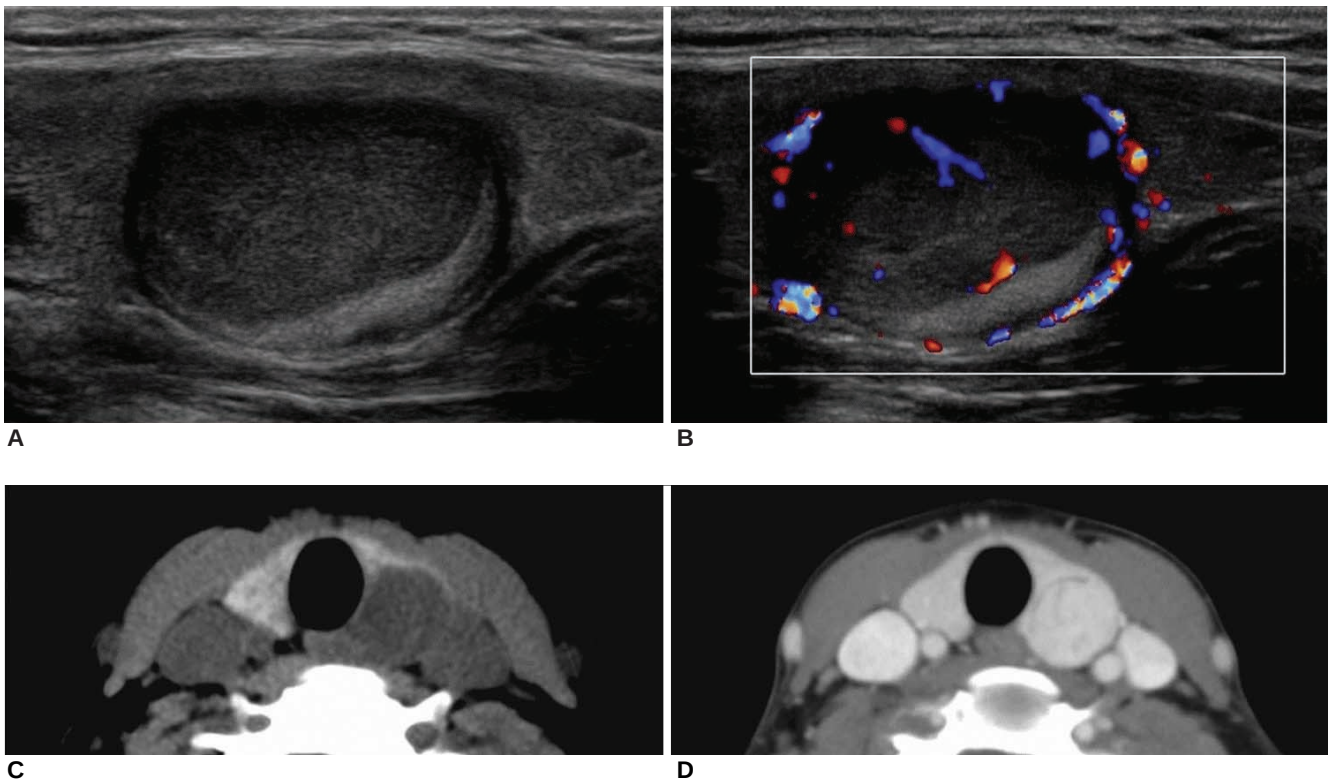

Fig. 1. Follicular adenoma in a 31-year-old woman.
A. Longitudinal sonogram of the left lobe of the thyroid shows a circumscribed hypoechoic nodule with a hypoechoic rim. **B.** Color Doppler sonogram shows central and peripheral vascularity. **C, D.** Axial pre-contrast and contrast enhanced CT image shows strong enhancement of the tumor.

component, and vascularity of the nodules [4], and the data were entered into a database using a computerized spreadsheet (Excel; Microsoft. Redmond, WA, USA).

Echogenicity was divided into hyperechoic, isoechoic, hypoechoic, and marked hypoechoic. For mixed solid and cystic nodules, echogenicity of the solid components was used in the classification. Margins were classified as circumscribed, microlobulated, and irregular. Shape was designated as either parallel or nonparallel. Calcifications were divided into microcalcifications, macrocalcifications, eggshell calcifications, and no calcifications. Hypoechoic rim and cystic change were divided into presence and absence. Vascularity was categorized as peripheral, central, or both peripheral and central calcifications (Figs. 1, 2).

Thyroid CT Image Analysis

Of the 28 patients, 21 underwent neck CT. CT scans were performed using a 64-slice multidetector CT (MDCT) scanner (Somatom Sensation 64; Siemens Medical Solutions, Erlangen, Germany). Scanning was performed in a craniocaudal direction at end-inspiratory suspension with patients in the supine position. After acquisition of the scout image for localization of the target lesions, we obtained pre and post-contrast CT images. After injection of contrast material, post-contrast images were obtained at 60 seconds. All CT data were transferred to our picture archiving and communication system (PACS) (Centricity 1.0; GE Medical Systems, Mt Prospect, IL,

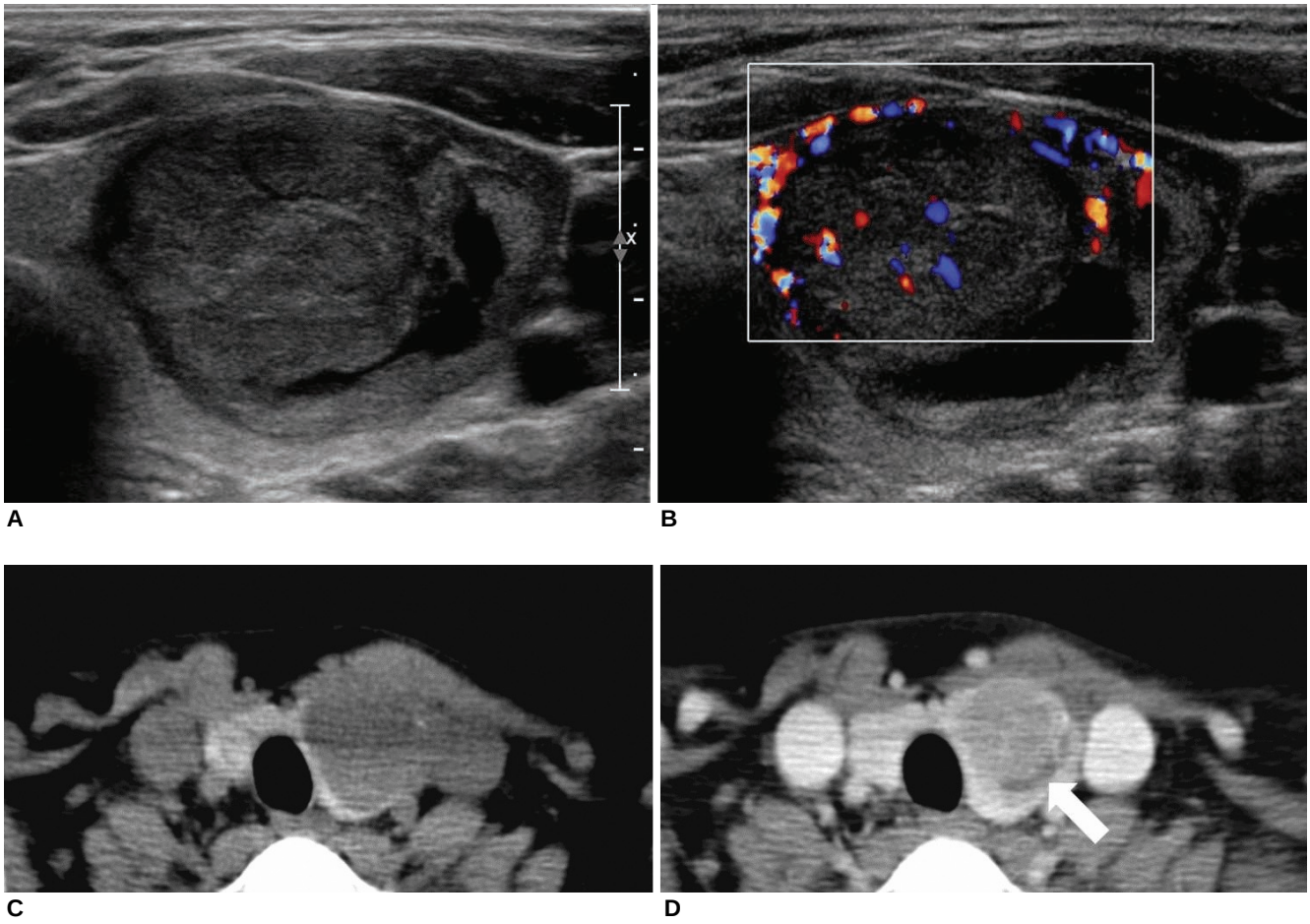

Fig. 2. Follicular carcinoma in a 33-year-old woman.
A. Transverse sonogram of the left lobe of the thyroid shows a complex cystic lesion with a circumscribed margin and a hypoechoic rim. **B.** Color Doppler sonogram shows internal and peripheral vascularity in the solid parts of the tumor. **C, D.** Axial pre-contrast and contrast enhanced CT image shows the tumor with moderate enhancement. Cystic portion is also visible (arrow).

USA), which displayed all images on monitors (1536 × 2048 image matrices, 60-foot-lambert luminescence). Images were evaluated in one image interpretation section by consensus of two radiologists (E.J.S. and M.R.Y.) who had 20 and four years of experience in thyroid imaging interpretation. They classified enhancement degree of thyroid nodule on CT images corresponding to aspirated lesion on US, as none, moderate, or strong, blind to FNA and surgical pathologic results (Figs. 1, 2).

US-FNA and Cytological Analysis

US-FNA was performed by the same radiologist performing the real-time US examinations. US-FNA was performed using a 23-gauge needle attached to a 2-mL disposable syringe without using an aspirator. Papanicolaou staining was performed on two alcohol-fixed smears, while the remainder was prepared for ThinPrep by rinsing the needle in Cyolyte (Hologic, Marlborough, MA, USA). On-site evaluation was not performed routinely.

All cases were reported by one cytopathologist using a six-tiered diagnostic system with the Bethesda System for Reporting Thyroid Cytopathology [5]. Cytological diagnoses were made as follows: 1) nondiagnostic or unsatisfactory (Bethesda system I), 2) benign (Bethesda system II), 3) AUS/FLUS (Bethesda system III), 4) follicular neoplasm or suspicious for a follicular neoplasm (Bethesda system IV), 5) suspicious for malignancy (Bethesda system V), and 6) malignant (Bethesda system VI). Cellular specimens with abundant follicular cells arranged in a microfollicular pattern with little or no colloid or cellular specimens with a predominant population of Hürthle cells were reported as follicular neoplasms.

Data and Statistical Analysis

Histologic results from the surgical pathology were used as a standard reference. A benign outcome was defined as a benign surgical tissue diagnosis of follicular adenoma, Hürthle cell adenoma. Outcomes were classified as malignant when a histologic diagnosis of follicular carcinoma, Hürthle cell carcinoma was made based on surgical resection of the aspirated nodule. Outcome classification was based solely on the diagnosis made on the targeted nodule. Benign and malignant groups were compared on the basis of the following: clinical characteristics (age, sex); US characteristics (lesion size, composition, echogenicity, margin, hypoechoic rim, shape, calcification, and vascularity); CT characteristics (degree of enhancement). Categorical variables for US features were compared statistically for the malignancy rate using the Student's T-test, χ^2 or Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed for evaluation of cutoff values of size for prediction of the malignancy potential.

Statistical analyses were performed using SPSS software (version 19.0, IBM, Somers, NY, USA). Difference was considered statistically significant at $p < 0.05$.

Result

Patient Statistics

Of the 28 patients included in our study, 20 patients (71.4%) were female and eight patients (28.6%) were male. The mean age of the patients was 42.3 years (range: 21–71 years). The mean size of thyroid nodules on US was 27.5 mm (range: 8–59 mm). Clinical features of the patients are summarized in Table 1. No statistically significant differences according to age, sex were observed between the benign and malignant groups.

Cytopathologic Results

Of the 47 thyroid nodules classified as Bethesda system IV on FNA that underwent thyroidectomy, six lesions were diagnosed as follicular adenoma, and 13 lesions were diagnosed as follicular carcinoma on final pathology. Five lesions were Hürthle cell adenomas, and four lesions were Hürthle cell carcinomas. The remainder of the lesions consisted of four adenomatous hyperplasias and 15 papillary carcinomas (Table 2), which were excluded in the study population.

Malignancy rate of Bethesda system IV nodules with definitive surgery was 68.1%.

US features

Insignificant differences in echogenicity, margin, shape, calcification, cystic component, and vascularity were observed between follicular adenomas and carcinomas ($p > 0.05$). Only lesion size was significantly different between the follicular adenoma and carcinoma groups ($p < 0.05$). When diagnostic criteria for size of follicular carcinoma of more than 24.5 mm were applied, sensitivity, specificity were 81.8%, 70.6%, respectively.

CT features

Twenty patients underwent neck CT. Nine lesions with adenoma on surgical pathology consisted of five (55.6%) strongly enhanced lesions and four (44.4%) moderately enhanced lesions; 11 lesions with

Table 2. Surgical Histology on Thyroidectomy of Thyroid Nodules Classified as Bethesda System IV on Fine Needle Aspiration Biopsy

Histology	Number (%)
Follicular adenoma	6 (12.8%)
Follicular carcinoma	13 (27.7%)
Hürthle cell adenoma	5 (10.6%)
Hürthle cell carcinoma	4 (8.5%)
Adenomatous hyperplasia	4 (8.5%)
Papillary carcinoma	15 (31.9%)
Total	47 (100%)

Table 1. Clinical Parameter, Ultrasonographic and CT Findings of Follicular and Hürthle Cell Adenomas and Carcinomas

		Adenoma (n=11)	Carcinoma (n=17)	P-value
Age*		38.2 ± 7.4	44.9 ± 15.7	0.141
Sex	Male	2 (18.2%)	6 (35.3%)	0.419
	Female	9 (81.8%)	11 (64.7%)	
Size (mm)*		21.2 ± 9.9	31.6 ± 14.3	0.046
Echogenicity	Isoechoic	3 (27.3%)	5 (29.4%)	0.875
	Hypoechoic	7 (63.6%)	9 (52.9%)	
	Markedly hypoechoic	1 (9.1%)	3 (17.6%)	
Margin	Circumscribed	11 (100%)	16 (94.1%)	1.000
	Microlobulated	0 (0%)	1 (5.9%)	
	Irregular	0 (0%)	0 (0%)	
Hypoechoic rim	Presence	4 (36.4%)	10 (58.8%)	0.246
	Absence	7 (63.6%)	7 (41.2%)	
Shape	Parallel	10 (90.9%)	14 (82.4%)	1.000
	Non-parallel	1 (9.1%)	3 (17.6%)	
Cystic change	None	7 (63.6%)	6 (35.3%)	0.142
	Presence	4 (36.4%)	11 (64.7%)	
Calcification	Microcalcification	0 (0%)	0 (0%)	0.361
	Macrocalcification	0 (0%)	1 (5.9%)	
	Eggshell	0 (0%)	3 (17.6%)	
	None	11 (100%)	13 (76.5%)	
Vascularity	Peripheral	3 (27.3%)	4 (23.5%)	0.718
	Central	0 (0%)	2 (11.8%)	
	Both	7 (63.6%)	8 (47.1%)	
	None	1 (9.1%)	3 (17.6%)	
Enhancement on CT	Strong	5 (55.6%)	6 (54.5%)	1.000
	Moderate	4 (44.4%)	5 (55.6%)	

Note.— CT; computed tomography.
*Results are given as the mean ± SD. Chi-square test, Fisher's exact test, and unpaired Student's t test were used for comparison of the clinical, ultrasonographic, and CT characteristics of patients with follicular carcinoma and adenoma.

carcinoma on surgical pathology, six (54.5%) strongly enhanced lesions, and five (45.5%) moderately enhanced lesions. No significant difference in these degrees of enhancement were observed between follicular adenoma and carcinoma ($p > 0.05$) (Table 1).

Discussion

The cytological, clinical, and imaging distinction of benign from malignant follicular neoplasm remains problematic. Due to the lack of specific genetic alterations, molecular analysis of different oncogenes is also not helpful in the case of follicular carcinoma [1, 6].

This study reports results obtained from 79 patients with thyroid nodules who underwent thyroidectomy after a cytological diagnosis of Bethesda IV. Ultrasonographic findings, including echogenicity,

Table 3. Clinical Parameter, Echographic Patterns, and CT Features of 41 Patients with Follicular, Hürthle Cell Neoplasm and Papillary Neoplasm on Surgical Pathology

		Follicular and Hürthle cell neoplasm (n=28)		Papillary neoplasm (n=15)	
		(n)	(%)	(n)	(%)
Age*		42.3 ± 13.3	47.3 ± 10.8		
Sex	Male	8	28.6	2	13.3
	Female	20	71.4	13	86.7
Size (mm)*		27.5 ± 13.6	17.3 ± 11.1		
Echogenicity	Hyperechoic	0	0	1	6.7
	Isoechoic	8	28.6	6	40
	Hypoechoic	16	57.1	7	46.7
	Markedly hypoechoic	4	14.3	1	6.7
Internal echogenicity	Inhomogeneous	17	60.7	6	40
	homogenous	11	39.3	9	60
Margin	Circumscribed	27	96.4	7	46.7
	Microlobulated	1	3.6	1	6.7
	Irregular	0	0	7	46.7
Hypoechoic rim	Presence	14	50	4	26.7
	Absence	14	50	11	73.3
Shape	Parallel	24	85.7	9	60
	Non-parallel	4	14.3	6	40
Cystic change	None	13	46.4	13	86.7
	Presence	15	53.6	2	13.3
Calcification	Microcalcification	0	0	1	6.7
	Macrocalcification	1	3.6	2	13.3
	Eggshell calcification	3	10.7	1	6.7
	None	24	85.7	11	73.3
Vascularity	Peripheral	7	25	9	60
	Central	2	7.1	0	0
	Both	15	53.6	3	20
	None	4	14.3	3	20
Underlying echotexture	Homogenous	28	100	11	73.3
	Heterogeneous	0	0	4	26.7
Enhancement on CT	Strong	11	39.3	5	55.6
	Moderate	9	32.1	4	44.4

Note.— CT; computed tomography.
*Results are given as the mean ± SD unless otherwise specified.

margin, calcification, shape, cystic component, and vascularity, and clinical features, including age, sex, did not differ significantly between follicular adenoma and carcinoma.

The reported ultrasonographic findings of follicular neoplasms are a solid mass with inhomogeneous internal echogenicity and a surrounding hypoechoic rim. They infrequently showed an irregular margin and intranodular calcifications [4]. In this study, 46.4% (13 lesions) of follicular neoplasms were completely solid, 60.7% (17 lesions) showed inhomogeneous internal echogenicity, and 50% (14 lesions) showed a hypoechoic rim. Calcification was found in 14.3% (four lesions) and none of the follicular neoplasms had an irregular margin (Table 1).

Male gender, old age, large size, and previous history of head and neck irradiation have been reported by several authors as statistically significant parameters distinguishing patients at risk [7], but not by others [1, 3, 8, 9].

Ultrasonographic features distinguishing benign and malignancy are also controversial. Miyakawa et al. suggested that an irregular margin without a hypoechoic halo was more frequent in follicular carcinomas than in follicular adenomas. They also suggested that intranodular cystic degeneration was rarely observed in follicular carcinomas [10]. Jeh et al conducted a retrospective review of the ultrasonographic findings of 23 patients with follicular carcinomas; a hypoechoic rim was observed in 86.6%, few follicular neoplasms had calcifications (only four among the 23 cases), however, none of the cases had microcalcifications. A solid mass without cystic change was observed in 82.6% of follicular carcinomas [4]. Fukunari et al. reported that no significant US patterns, such as internal echography, calcification, or findings of invasion are useful for a differential diagnosis that includes follicular adenoma and carcinoma, except for the low degree of cystic degeneration [2]. Rago et al. claimed that, apart from the presence of spot microcalcifications, all other previously described ultrasound patterns suggestive of thyroid carcinoma did not show a significant association with malignancy [1].

Vascularity on color Doppler sonography was also studied. Intranodular blood flow in a follicular neoplasm was a characteristic finding of follicular carcinoma in prior studies [2, 3, 11]. However, Frates et al claimed that color Doppler imaging cannot play a role in the differential diagnosis of thyroid cancer [12]. Doppler sonography performed in our series revealed intranodular vascularity in seven adenomas (63.6%) and in 10 carcinomas (58.9%).

As a variant of follicular neoplasms, Hürthle cell neoplasms are considered to have US features similar to those of follicular neoplasms [13]. Because of their relative rarity, several efforts at clarification of the differential point between the Hürthle cell adenoma and carcinoma have been made presumably but not yet with consensus [13–15]. In our study, although not shown here, no statistically significant difference in the sonographic, CT parameters were observed between follicular and Hürthle cell neoplasm.

In this study, 15 papillary carcinomas were also found on operative pathology of Bethesda IV thyroid nodules. Eleven of them were papillary microcarcinomas and the remaining four of them were papillary carcinomas. Known sonographic features of papillary carcinoma include completely solid or prominently solid nodule, hypoechogenicity, compared with the strap muscles, an irregular margin, microcalcification in the nodule, a taller than wide orientation, and increased intranodular vascularity [4].

In this study, 86.7% were solid nodules, however, hypoechogenicity accounted for only 53.4%, and lesions with an irregular margin were 33.3%; and 26.7% presented a taller than wide shape. Microcalcification was found in only 6.7% and macrocalcification and eggshell calcification accounted for 20%; and intranodular vascularity was observed in 20% of lesions (Table 3). Combination of more than two malignant features accounted for 40.0%; and only two lesions (13.3%) showed no malignant sonographic features. This is in agreement with a previously reported series of papillary carcinoma.

In conclusion, after an initial FNA result categorized

as Bethesda system IV diagnosis, neither US nor clinical parameter has yielded satisfactory differential guidelines for thyroid adenoma and carcinoma, except size of the follicular neoplasm. If a thyroid nodule is larger than 24.5 mm, there will be a greater probability of malignancy with sensitivity, specificity of 81.8%, 70.6%.

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요 약

목적: 본 연구의 목적은 수술 전 세침흡인세포검사로 베데스다 분류 IV로 진단된 갑상선 결절 중에서 수술 병리 결과상 소포암종 또는 Hürthle세포암종을 예측할 수 있는 특징적인 임상적, 영상적 소견이 있는지 알아보는데 있다.

대상 및 방법: 본 저자는 세침흡인세포검사로 베데스다 분류IV로 진단된 갑상선 결절 중 수술 병리 검사상 소포종양 또는 Hürthle세포종양으로 진단된 28개 결절의 임상적, 초음파, 전산화 단층촬영상 소견을 분석했다.

결과: 양성과 악성 소포종양간에 나이, 성별, 초음파상 에코음영, 경계, 석회화, 모양, 액화 여부, 혈관분포와 CT상 조영 증강 정도는 유의한 차이가 없었다. 단지 병변의 크기만 통계적으로 유의한 차이를 보였다.

결론: 소포종양의 크기는 악성 여부를 예측하는 데 도움이 된다. Bethesda IV의 갑상선 결절이 24.5 mm보다 크면, 악성의 가능성이 높다.

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