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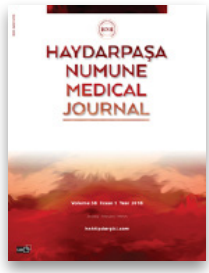

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ORIGINAL ARTICLE

The Prediction of Bethesda Category of Thyroid Nodule with Specific Sonographic Findings

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Abstract

Introduction: Ultrasound (US) is frequently performed for imaging of thyroid. So, the number of incidentally detected thyroid nodule and fine needle aspiration biopsy (FNAB) is increasing gradually. We aimed to depict specific sonographic characteristics of thyroid nodule in each cytological Bethesda category for planning patient management and reducing the number of unnecessary FNAB or short-term follow-up.

Methods: A total of 1488 patients [1260 women (85%) and 228 men (15%) with a mean age of 49 years] who had undergone US guided FNAB were included in the study. US and FNAB findings were reviewed retrospectively. US features (size, contour, echogenicity, multiplicity, solid/cystic nature, the existence of halo, calcifications, lymphadenopathy and thyroiditis) were recorded. The correlation of sonographic and cytological findings was investigated in each Bethesda category.

Results: A total of 1488 patients were enrolled in our study. Among Bethesda category 2 nodules, iso-/hyper-echogenicity, well-defined contour, solid plus cystic component, thin halo and multiplicity were more prevalent ($p<0.05$). Thick halo (7/75, 9.5%) and lymphadenopathy (4/75, 5.5%) were only observed in Bethesda category 6 nodules. Ill-defined/irregular contour was mostly seen in Bethesda category 5 (5/7, 71%) and category 6 (34/75, 45%) nodules ($p<0.05$). There was no statistically significant difference in microcalcification and thyroiditis between Bethesda categories ($p>0.05$).

Discussion and Conclusion: The prediction of Bethesda category of nodule with sonographic findings is possible in some Bethesda categories. The number of unnecessary FNABs and follow-up can be reduced.

Keywords: Bethesda; fine needle aspiration; thyroid nodules; ultrasound.

Thyroid nodules are extremely common endocrine disorders. Ultrasonography (US) is the first choice of imaging modality for thyroid and has an important role in the management of patients. US characteristics of thyroid nodule help clinicians decide whether the biopsy is needed or not. US-guided fine needle aspiration biopsy (FNAB) is the most effective method for the selection of surgery candidates[1,2].

The Bethesda system for reporting thyroid cytopathology provides us a standardization in reporting of thyroid fine-needle aspiration cytology[2,3]. According to 2017 revision of the Bethesda system for reporting thyroid cytopathology, thyroid nodules have been categorized into six categories: category 1- non-diagnostic or insufficient specimen; category 2- benign; category 3 - atypia of unde-

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termined significance or follicular lesion of undetermined significance; category 4 - follicular neoplasm or suspicious for a follicular neoplasm; category 5 - suspicious for malignancy; and category 6 – malignant[3, 4].

To the best of our knowledge, US findings of thyroid nodule in each Bethesda category have not been extensively investigated. Therefore, we aimed to depict specific sonographic characteristics of thyroid nodules in each cytological Bethesda category for planning further patient management.

Materials and Methods

Patients

The Institutional Review Board approved this retrospective study, and informed consent was waived. The consecutive 1501 patients who had undergone US guided FNAB of thyroid nodule at single institution were reviewed from the hospital information system between January 2015 and January 2016. Patients without US (n=13) were excluded. A total of 1488 patients [1260 women (85%) and 228 men (15%) with a mean age of 49 years (range: 12–88 years)] were included in this study.

Image Analysis

All US examinations were performed with high frequency (7.5 MHz) linear probe on Toshiba Aplio 300 US system (Toshiba Medical Systems, Tokyo, Japan). Cytological results were reviewed along with US findings of thyroid nodule before FNAB. Sonographic features such as the largest diameter, the contour (well-defined/ill-defined/irregular border), echogenicity (hypo-, iso-, hyper-echogenicity), the presence of calcifications (macro-/micro-calcifications), the existence of halo (thin/thick halo), multiplicity (single/multiple), solid/cystic nature of nodule, the presence of lymphadenopathy and the existence of thyroiditis findings were recorded by two radiologists (F.K. with 17 years' experience and M.D. with 3 years' experience in thyroid imaging) in consensus. The Bethesda classification system was used for reporting thyroid cytology. The correlation of sonographic findings and cytological results was investigated in each Bethesda category. The follow-up or surgical results of patients with Bethesda category 3 nodules were also recorded. Additionally, sonographic characteristics were also compared between benign and malignant group. Patients with Bethesda category 2 nodules and patients with Bethesda category 3 nodules without progression with at least 24 months of follow-up were included into group 1 (considered likely to be benign nodules). Patients with Bethesda category 4, 5 and 6 nodules and patients with Bethesda category 3 nodules with postoperative malignant histopathological results were classified into group 2 (nodules with malignancy risk)[5,6].

Statistical Analysis

For the statistical analyses, the MedCalc Statistical Software 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) package program was used. Parameters with normal distribution were investigated using Shapiro- Wilk test. Student t test was used for comparisons, Pearson's chi-square test, Kruskal-Wallis test or Mann-Whitney U test were used where appropriate, and $p<0.05$ was used to determine statistical significance.

Results

A total of 1488 patients who had undergone US-guided FNAB were enrolled in our study. All thyroid nodules had been categorized according to the Bethesda system for reporting thyroid cytopathology. The mean largest diameter of thyroid nodule was 20.1 mm (range 3–109 mm). A total of 17% FNAB results were non-diagnostic. Of 22 patients with Bethesda category 3 nodules, eight patients had undergone surgery. Among the histopathological results of these eight patients, six patients had malignancy with papillary thyroid cancer and two had benignity with adenomatous hyperplasia. In remaining 14 patients, no progression was observed with a mean follow-up period of 33 months (range 24–42 months). According to the follow-up and surgical results in Bethesda category 3 nodules, there were 16 (16/22, 73%) benign and six (6/22, 27%) malignant nodules. The malignancy rate in Bethesda category 3 nodules was estimated as 27%. There were 1133 patients in group 1 (considered likely to be benign nodules) and 103 patients in group 2 (nodules with malignancy risk).

Thyroid nodules with thin halo (268/1117, 24%), iso-echogenicity (372/1117, 33%) and hyper-echogenicity (135/1117, 12%) were more common in Bethesda category 2 nodules compared to Bethesda category 6 nodules ($p<0.05$). The ratio of hypo-echogenicity in Bethesda category 6 nodules (67/75, 89%) was significantly higher than that of Bethesda category 2 (610/1117, 54%) nodules ($p<0.05$). Among Bethesda category 2 nodules, the ratios of iso-/hyper-echogenicity, well-defined contour, solid plus cystic component, thin halo and multiplicity were significantly higher than those of Bethesda 3, 4, 5 and 6 categories ($p<0.05$) (Fig. 1a, b). Thyroid nodules with thick halo (7/75, 9.5%) and lymphadenopathy (4/75, 5.5%) were only

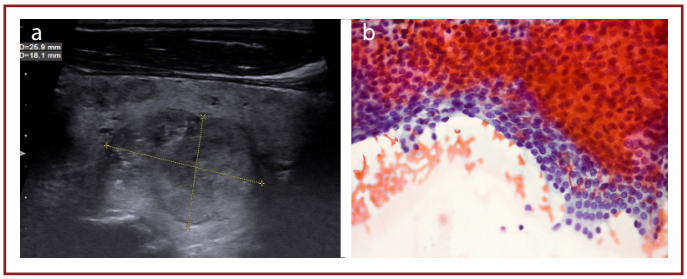

Figure 1. Sonographic image of Bethesda category 2 nodule with iso-echogenicity, sub-centimetric cystic areas, punctate calcifications and thin halo **(a)**. Cytological appearance of Bethesda category 2 nodule (Papanicolaou stain, × 40) **(b)**.

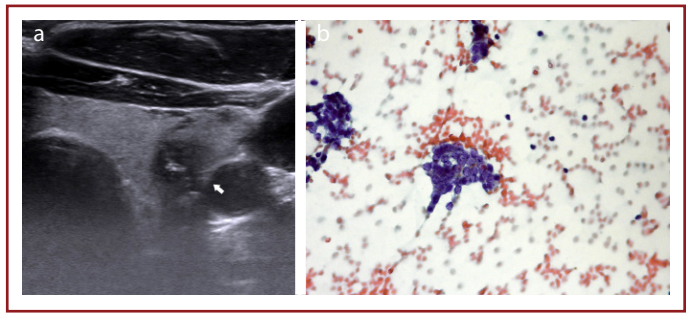

Figure 2. Sonographic image of Bethesda category 5 nodule with hypo-echogenicity, microcalcifications and ill-defined contours **(a)**. Cytological appearance of Bethesda category 5 nodule (Papanicolaou stain, × 10) **(b)**.

observed in Bethesda 6 nodules. Ill-defined/irregular contour was mostly seen in Bethesda category 5 (5/7, 71%) and category 6 (34/75, 45%) nodules (all p<0.05) (Fig. 2a, b). The solid composition of nodules was more frequent in Bethesda category 6 compared to Bethesda category 2 nodules (p<0.05). There was no statistically significant difference in the existence of micro-calcification and thyroiditis between Bethesda categories (p>0.05). Single nodule was more prevalent in Bethesda category 6 (24%) nodules than Bethesda category 2 (10%) nodules (p<0.05). The distribution of US findings of thyroid nodule in each Bethesda category are shown in Table 1.

In group 2 (nodules with malignancy risk), hypo-echogenicity, ill-defined/irregular contour, solid composition, being single and the existence of micro-calcifications were more prevalent than those of group 1 (considered likely to be benign nodules) (p<0.05). Additionally, nodules with thin halo was significantly higher in group 1 (p<0.05). There was no statistically significant difference in the association with thyroiditis between group 1 and 2 (p>0.05). The statistical relationship between group 1 and 2 are summarized in Table 2.

Table 1. The distribution of US characteristics of thyroid nodules according to cytopathological results as a gold standard

US Characteristics	Cytological Bethesda Categories											
	1 (n=252)		2 (n=1117)		3 (n= 22)		4 (n=15)		5 (n=7)		6 (n=75)	
	n	%	n	%	n	%	n	%	n	%	n	%
Hypo-echogenicity	175	69.5	610	54	13	59	8	53.5	6	86	67	89
Iso-echogenicity	57	22.5	372	33	9	41	6	40	1	14	4	5.5
Hyper-echogenicity	20	8	135	12	-	-	1	6.5	-	-	4	5.5
Well-defined contour	223	88.5	993	89	17	77	14	93.5	4	57	41	54.5
Ill-defined/irregular contour	29	11.5	124	11	5	23	1	6.5	3	43	34	45.5
Solid	147	58	615	55	17	77	9	60	5	71.5	62	82.5
Mixed (solid+cystic)	105	41.5	502	45	5	23	6	40	2	28.5	13	17.5
Single	35	14	114	10	4	18	1	6.5	1	14	18	24
Multiple	217	86	1003	90	18	81	14	93.5	6	86	57	76
Calcifications (+)	37	14.5	265	24	8	36	3	20	2	28.5	18	24
Micro-calcifications	17	7	159	14	5	23	2	13.5	2	28.5	15	20
Macro-calcifications	18	7	97	9	2	9	1	6.5	-	-	3	4
[a]Micro + macrocalc.	2	0.7	9	1	1	4.5	-	-	-	-	-	-
Thin halo (+)	50	20	268	24	4	18	4	26.5	-	-	-	-
Thick halo (+)	-	-	-	-	-	-	-	-	-	-	7	9.5
[b]Ass. w thyroiditis	15	6	173	15.5	1	4.5	1	6.5	-	-	16	21.5
Lymphadenopathy	-	-	-	-	-	-	-	-	-	-	4	5.5

[a]Micro + macrocalc.: Thyroid nodules with micro- and macro-calcifications, [b]Ass. w thyroiditis: Associated with thyroiditis.

Table 2. The relationship between US characteristics of group 1 (considered likely to be benign nodules) and group 2 (nodules with malignancy risk) according to cytopathological results

	Group 1 (n=1133)	Group 2 (n=103)	p*
US characteristics			
Hypo-echogenicity	617	87	<0.00001
Iso-echogenicity	381	11	
Hyper-echogenicity	135	5	
Well-defined contour	1009	60	<0.00001
Ill-defined/irregular contour	124	43	
Solid	626	82	<0.00001
Mixed (solid+cystic)	507	21	
Single	114	24	<0.00001
Multiple	1019	79	
Calcifications (+)	267	29	
Microcalcifications	159	24	0.011
Macrocalcifications	99	4	0.087
[a]Micro + macrocalc	9	1	
Thin halo (+)	272	4	<0.00001
Thick halo (+)	0	7	
Associated w thyroiditis	173	18	0.553
Lymphadenopathy (+)	0	4	

[a]Micro + macrocalc: Nodules with micro- and macro-calcifications;
* Pearson's chi-square test, p<0.05 was used to determine statistical significance.

Discussion

There are several guidelines to identify low and high suspicious nodules for malignancy by British Thyroid Association, American Thyroid Association (ATA), American Association of Clinical Endocrinologists (AACE/ACE/AME) and Thyroid Imaging Reporting and Data System (TI-RADS) classifications[7-13]. Some sonographic findings such as solid content, hypo-echogenicity, micro-lobulations, irregular margins, micro-calcifications and taller shape are defined as suspicious features of malignancy[7-13]. The sonographic findings in our study were not categorized according to guidelines. Because, there are some differences between these guidelines[7-13]. Moreover, some additional US features such as the existence of surrounding halo, multiplicity, associated lymphadenopathy and thyroiditis findings which are not included in TI-RADS classification were also evaluated to delineate specific US findings for each Bethesda category in our study.

Sonographic findings help us to decide whether FNAB is required or not. However, the cytological diagnosis can sometimes be difficult. No cellular atypia is observed in some thyroid malignancies such as follicular neoplasm. To differentiate follicular adenoma/adenomatous nodule from follicular cancer, surgery is required to detect the invasion of capsule or blood vessels[4]. The degree of atypia can also influence the diagnosis of malignancy. In a study by Nandedkar et al.[2], the sensitivity, specificity, and diagnostic accuracy ratios of fine needle aspiration cytology based on Bethesda classification was 85.7%, 98.6%, and 97.7%, respectively. In another study, FNAB was found as a reliable procedure with false negative ratio of 2% in differential diagnosis of ≥3 cm benign and malignant nodules[14].

Several studies were conducted to evaluate the sonographic features of some Bethesda categories. Heller et al.[15] reviewed common sonographic features in Bethesda categories. The following imaging characteristics have a high risk of malignancy: irregular margins, calcifications, micro-lobulations, marked hypo-echogenicity, disorganized vascularization and it having a taller than wider shape[15]. Additionally, the relationships among Bethesda categories for specific US findings were also evaluated in our study. Park et al.[16] detected that 10.5% of 441 thyroid nodules with non-diagnostic FNAB results were malignant. These malignant nodules had the intermediate or highly suspicious sonographic findings such as solid content, hypo-echogenicity, micro-lobulated or irregular borders, micro-calcifications and taller-than-wide shape (all p<0.05) [16]. Similarly, the most of these sonographic findings were more prevalent in our group with the risk of malignancy. Kim et al.[17] hypothesized that thyroid nodules (n=1230) with benign cytological findings at initial FNAB also had a malignancy risk with a low rate of 2%. They found no association between false negative ratio of nodules and the sonographic features[17]. In another retrospective study, Park et al.[18] investigated the sonographic characteristics of Bethesda categories 3, 5 and 6 thyroid nodules which are surgically confirmed as papillary thyroid cancer. The tumor size and the frequency of central lymph node metastasis was lower in papillary thyroid cancers with pre-operative Bethesda category 3 and 5 than those of Bethesda category 6[18]. Cho et al.[19] found a relationship between lymph node metastasis of papillary thyroid cancer and high suspicious US pattern on the 2015 ATA guidelines, regardless of Bethesda category (p<0.05). In our study, all malignant nodules with lymph node metastasis also had high suspicious US findings and lymphadenopathy was only observed in Bethesda category 6 nodules.

The coexistence of thyroiditis and thyroid cancer has been still conflicting[1,20,21]. Some previous studies hypothesized that thyroiditis and thyroid cancer association was related to function of thyroid gland except hypothyroidism[20,21].

Nonetheless, de Alcântara-Jones et al.[1] showed that there was no statistical relationship between thyroiditis and papillary thyroid cancer. Our result was consistent with this study.

In previous studies, there were some discrepancies about the malignancy rates in Bethesda categories. Bethesda category 2 nodules are considered benign, but there was also a low risk of malignancy (0-3%) in Bethesda category 2 nodules[3,4]. Bethesda category 3, 4, and 5 nodules have 4-8%, 15-30%, and 60-75% risk of malignancy, respectively[3,4]. In another study, the malignancy rate was detected 16% in Bethesda category 3 (n=478) and 17% in Bethesda category 4 (n=137) nodules without incidental cancers[6]. Moreover, Ho et al.[22] found higher malignancy rates (26.6-37.8%) in Bethesda category 3 nodules. This agreed with our estimated malignancy rate (27%) in Bethesda category 3 nodules.

We investigated that whether the prediction of Bethesda category of thyroid nodule with some sonographic findings is possible or not. Iso-/hyper-echogenicity, well-defined contour, solid plus cystic component, thin halo and multiplicity can be considered likely to be specific sonographic findings of Bethesda category 2. Additionally, the existence of lymphadenopathy and thick halo are the sonographic findings of Bethesda category 6 nodules. Since there was no statistical difference among Bethesda category 3, 4, 5 and 6 nodules, hypo-echogenicity, solid nature, ill-defined/irregular contour, and the existence of micro-calcifications were more common in Bethesda category 5 and 6 nodules compared to Bethesda category 3 and 4 nodules. Furthermore, hypo-echogenicity, ill-defined/irregular contour, solid composition, being single and micro-calcifications are more specific for malignant nodules.

The results of our study are subject to some limitations. First, retrospectively collected data was analyzed. Second, Bethesda category 2 and Bethesda category 3 nodules without progression with at least 24 months of follow-up were considered likely to be benign. Third, the sonographic findings were not classified according to TIRADS or ATA guidelines.

Conclusion

In conclusion, the prediction of Bethesda category of nodule with sonographic findings is possible in some Bethesda categories. Specific US findings can decrease the number of unnecessary FNABs and short-term follow-up. Moreover, the discordance between US and cytological findings may easily be detected by the help of sonographic prediction of Bethesda category.

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Conflict of Interest: None declared.

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