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Evaluation of Bethesda IV-V thyroid nodules: clinical experience

Bethesda IV-V tiroid nodüllerinin değerlendirilmesi: klinik deneyim

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ABSTRACT

Introduction: The malignancy rate in cases operated for thyroid nodule is approximately 5-10%, and although this rate shows significant differences according to Bethesda categories, there is a high risk of malignancy in categories IV and V compared to other categories. In our study, we examined the clinicopathological factors affecting the success of cytological diagnosis in nodules diagnosed with Bethesda IV-V.

Material and Method: A total of 780 patients who were diagnosed with thyroid nodules and underwent surgery at our center between 2011 and 2021 were included in the study. The preoperative cytological diagnoses of the patients were categorized using the Bethesda classification system. The demographic data of the patients, Bethesda classification of the nodules, and postoperative histopathological examination results were evaluated in subgroups, and their significance was determined.

Results: The age group with the highest number of cases was 45-59 years, and the female/male ratio of the whole cohort was 3:1. The rate of palpable nodules was 41.8% for the malignant diagnosis group and 58.2% for the benign diagnosis group. In both malignant and benign groups, <20 mm nodules were found at statistically significantly higher rates compared to nodule groups of other diameters ($p<0.001$ for both). While 50% of those diagnosed with DC-IV have a diameter greater than 20 mm; It was observed that 43.5% of those diagnosed with DC-V were more intense in the 10-20 mm diameter range. When the FNAB cytological diagnoses of the cases are compared with the postoperative histopathological diagnoses, it is seen that 32.5% of the cases diagnosed with DC-IV and 78.3% of those diagnosed with DC-V were diagnosed as malignant. While 69.2% of the cases with a cytological diagnosis of DC-IV were PTC and 30.8% were OTC; 100% of the cases with DC-V diagnosis are PTC histopathologically.

Conclusion: Our study showed that the diagnostic success of FNAB was decreased in microcarcinoma and large-sized nodules, with 10-20-mm nodules being the most suitable size for the success of cytological diagnosis. The risk of malignancy was higher in the nodules smaller than 20 mm compared to those larger than 20 mm. OTC should be primarily considered in >20-mm nodules with a DC-V diagnosis and PTC in smaller nodules. While benign pathologies are considered in DC-IV diagnoses; If the diameter of DC-V cytologically diagnosed nodules is larger than 20 mm, OTC should be considered primarily, and if less than 20 mm, PTC should be considered.

Keywords: Thyroid neoplasms, thyroid nodule, fine-needle biopsy

ÖZ

Amaç: Tiroidde nodül nedeniyle opere edilen olgularda malignite oranı yaklaşık %5-10 olup, bu oran Bethesda kategorilerine göre önemli farklılıklar göstermekle birlikte diğer kategorilere göre kategori IV ve V'te yüksek malignite riski mevcuttur. Biz çalışmamızda Bethesda IV-V tanısı alan nodüllerde sitolojik tanı başarısını etkileyen klinikopatolojik etkenleri inceledik.

Gereç ve Yöntem: Çalışmaya merkezimizde 2016-2021 yılları arasında tiroid nodülü tanısı alan ve opere edilen 780 hasta dahil edildi. Hastaların preoperatif sitolojik tanıları Bethesda Sistemi kullanılarak sınıflandırıldı. Hastaların demografik verileri, nodüllerin Bethesda sınıflandırması ve postoperatif histopatolojik inceleme sonuçları alt gruplar halinde değerlendirilerek anlamlı sonuçlar raporlandı.

Bulgular: Olguların en yoğun olarak bulunduğu yaş grubu 45-59 olup, K/E oranın 3:1 olduğu görülmektedir. Malign tanı grubundaki nodüllerin %41,8'inin; benign tanı grubundakilerin %58,2'sinin palpabl olduğu görülmektedir. 20 mm<büyük nodüllerde hem malign hem benign grupta diğer çaptaki nodül gruplarına göre istatistiksel olarak anlamlı şekilde ($p<0,001$; $p<0,001$) daha yüksek oranda bulunmaktadır. DC-IV tanı alanların %50'i 20 mm<'den büyük çaplı iken; DC-V tanısı alanların %43,5'inin 10-20 mm çap aralığında daha yoğun olduğu görüldü. Olguların İİAB sitolojik tanıları ile postoperatif histopatolojik tanıları kıyaslandığında DC-IV tanısı konulan olguların %32,5'i ve DC-V tanı konulanların %78,3'ü malign tanı aldığı görülmektedir. DC-IV sitolojik tanılı olguların %69,2si PTK ve %30,8'i DTK iken; DC-V tanılı olguların %100 PTK histopatolojik tanılıdır.

Sonuç: Çalışmamız mikrokarsinom ve büyük çaplı nodüllerde İİAB tanı başarısının düştüğünü, sitolojik başarı açısından en uygun nodül boyutunun 10-20 mm nodüller olduğunu göstermektedir. Malignite riski 20 mm'den küçük nodüllerde 20 mm'den büyük nodüllere göre daha yüksektir. DC-IV tanılarda bening patolojiler ön planda düşünülürken; DC-V sitolojik tanılı nodüllerin çapı 20 mm'den büyük ise ön planda DTK, 20mm'den küçük ise PTK düşünülmelidir.

Anahtar Kelimeler: Tiroid neoplazmaları, tiroid nodülü, ince iğne biyopsisi

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INTRODUCTION

Most of the adult population has one or more thyroid nodules (TN). It has been shown that with the widespread use of ultrasonography (USG), the rate of nodule detection has increased, reaching 50-70% (1). Although the possibility of cancer development in the presence of a nodule is the most important concern, it is known that only 5% of nodules have malignant properties (2,3). Thyroid cancers (TCs) are the most common endocrine tumors, with an incidence ranging from 1.2 to 2.6 in men and 2.0 to 4.4 in women per 100,000 population (4,5). Studies have shown that there is a relationship between TN and Graves' disease, parathyroid diseases, and chronic lymphocytic thyroiditis (6-8). The Bethesda classification system is used in the cytological evaluation of cases based on the results of the fine-needle aspiration biopsy (FNAB) of the thyroid (9). Malignancy rates have been reported as 1-4% for diagnostic category (DC) I, 0-3% for DC-II, 5-15% for DC-III, 15-30% for DC-IV, 60-75% for DC-V, and 97-99% for DC-VI (10,11).

The relationship between thyroid nodules and malignancy has been discussed for a long time. In our study, we aimed to retrospectively evaluate patients who were diagnosed with Bethesda DC-IV and DC-V nodules and underwent surgical treatment at our hospital over the last 10 years in terms of their demographic and histopathological features.

MATERIAL AND METHOD

The study was carried out with the permission of Gülhane Training and Research Hospital Clinical Research Ethics Committee (Date: 15.12.2021, Decision No: 2021/89). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Cases for which the surgical treatment decision was taken by the Endocrine Council of our hospital over the last 10 years were included in the study, and their data were obtained from the electronic patient files. This retrospective study included a total of 780 patients with complete epidemiological data and surgical and pathological reports. Cases with missing data were excluded from the study.

Data Collected/Recorded

The six-tier Bethesda classification system was used in all FNABs to report thyroid cytopathology (12). Cytological diagnoses were made as follows: DC-I: non-diagnostic or inadequate; DC-II: benign; DC-III: atypia or follicular lesion of uncertain significance (AUS/FLUS); DC-IV: follicular neoplasm or suspected follicular neoplasm; DC-V: suspicious for malignancy, and DC-VI: malignant.

Statistical Analysis

The statistical analyses of the study were performed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). When making comparisons between the groups, the chi-Square or Fisher's exact chi-square test was used for discrete data, and Student's t-test or the Mann Whitney-U test for continuous data. Statistical significance was defined as a p value of less than 0.05.

RESULTS

In our study, the age group with the highest number of cases was 45-59 years, and the female/male ratio of the whole cohort was 3:1. Two cases of medullary thyroid carcinoma (MTC) and one case of Hurthle cell carcinoma (HCC) were evaluated under the heading of other thyroid carcinomas (OTC) together with follicular thyroid carcinoma (FTC) due to the insufficient number of these diagnoses for statistical analysis (**Table 1**).

Table 1. Descriptive features of the cases included in the study

Variable	Number	Percentage
Gender		
Female	592	75.90
Male	188	24.10
Age, years		
<19	8	1.03
20-45	272	34.87
45-59	388	49.74
≥60	112	14.36
Diagnostic Group		
Malignant	378	48.46
PTC	354	45.38
OTC	24	3.08
Benign	402	51.54
NG/NH	258	33.08
MNG	18	2.31
GD	40	5.13
BTN	86	11.02
Total	780	100.00

PTC: Papillary Thyroid Carcinoma; Other Thyroid Carcinomas (OTC): Follicular Carcinoma, Hurthle Cell Carcinoma, Medullary Thyroid Carcinoma; NG/NH: Nodular Goiter/Nodular Hyperplasia; MNG: Multinodular Goiter; Benign Thyroid Neoplasms (BTN): Hurthle Cell Adenoma, Follicular Adenoma

In the ultrasonographic examination of 780 patients, a total of 958 thyroid nodules were visualized. Although 684 dominant nodules were detected in the histopathological examinations, the physical examination of the patients showed that 41.8% of the nodules in the malignant diagnosis group and 58.2% of the benign diagnosis group were palpable. When evaluated according to the diameters of the dominant nodules, nodules larger than 20 mm were found in both the malignant and benign groups at statistically significantly higher rates compared to smaller nodules ($p<0.001$). In the nodule group smaller than 20 mm, benign diagnoses were found at a higher rate than malignant diagnoses (59.8% vs 34.8%, respectively), although this was not statistically significant ($p=0.173$) (**Table 2**).

Table 2. Evaluation of dominant nodule size and histopathological diagnostic features

	Malignant		Benign		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Number of patients	378	48.5	402	51.5	780	100.0
Number of dominant nodules	316	46.2	368	53.8	684	100.0
Number of palpable nodules	210	41.8	292	58.2	502	100.0
Number of nodules detected by USG	440	45.9	518	54.1	958	100.0
Dominant nodule features	**Malignant**		**Benign**		**Total**	
	Number	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Number						
Single nodule	106	33.5	90	24.5	196	28.6
Multiple nodules	210	66.5	278	75.5	488	71.4
Size						
<5 mm	16	5.1	8	2.2	24	3.5
5-10 mm	80	25.3	58	15.8	138	20.2
10-20 mm	110	34.8	82	22.3	192	28.1
≥20 mm	110	34.8	220	59.8	330	48.2
Total nodules	316	46.2	368	53.8	684	100.0

USG: Ultrasonography

Considering the distribution of Bethesda categories according to the dominant nodule size on the ultrasonographic examination, 55% of those diagnosed with DCI-II-III and 50% of those diagnosed with DC-IV had a diameter greater than 20 mm; 43.5% of those diagnosed with DC-V and 48.1% of those diagnosed with DC-VI were in the 10-20 mm diameter range. While 23% of those diagnosed with DCI-II-III were in the 10-20 mm diameter range; 45% of those diagnosed with DC-IV are nodules with a diameter of 10-20 mm. The diagnosis of DC-II was found to be statistically significantly higher in the nodules larger than 20 mm compared to the smaller nodules ($p<0.001$). The cytological diagnosis of DC-IV was higher in the 10-20 mm and >20 mm groups compared to the nodules smaller than 10 mm ($p<0.05$). In addition, the diagnosis of DC-IV was made at a significantly higher rate in the 10-20 mm and >20 mm groups compared to DC-V ($p<0.05$). When DC-I was excluded from evaluation, the most common cytological diagnosis was DC-VI at a rate of 28.89%, and the nodules with this diagnosis were mostly in the range of 10-20 mm in diameter ($p<0.001$). DC-VI was observed at a significantly higher rate among the nodules smaller than 10 mm and in the range of 10-20 mm compared to those larger than 20 mm ($p<0.001$) (**Table 3**).

Table 5 compares the cytological diagnoses of FNAB and postoperative histopathological diagnoses of the cases. While 32.5% of the cases diagnosed with DC-IV were diagnosed with malignant histopathology; It is seen that 78.3% of the cases with DC-VI diagnosis are malignant. While 69.2% of the cases with a cytological diagnosis of DC-IV were PTC and 30.8% were OTC; 100% of the cases with DC-V diagnosis are PTC histopathologically. In the cytological examination of the biopsies taken, it was seen that postoperative malignant histopathological diagnosis were made in 17.14% of the operated cases that were evaluated as benign. When evaluated in terms of the success of cytological diagnosis, it was found that FNAB was more successful in the NG cases than in the MNGs ($p<0.05$). The malignancy rates were similar between the DC-III and DC-IV groups (34.48% and 32.5%, respectively). The rate of benign pathologies was higher among the DC-IV cases ($p<0.05$). In the OTC diagnosis group, which also included follicular carcinomas, there was a higher rate of DC-I and DC-IV nodules. However, when the DC-IV cases were evaluated within themselves, it was seen that the histopathological diagnosis of PTC was significantly higher than that of OTC ($p<0.001$). The malignancy rate was higher in the DC-V and DC-VI cases (78.26% and 71.15%). In the histopathological examination of the DC-V cytological diagnoses, 78.26% were PTCs, and the relationship between PTC and other diagnoses in the DC-V group was statistically significant ($p<0.05$). In addition, the diagnosis of PTC was observed at a higher rate in the DC-V cases than in OTCs ($p<0.001$).

DC-I was seen at a lower rate in the OTC cases than in the PTC cases (41.7% vs 56.5%), and there was no cytological diagnosis of DC-V and DC-VI among the OTC cases. Since benign-malignant distinction can be made by evaluating capsule/vascular invasion in BTN and OTC cases, the cytological diagnosis was postoperatively confirmed in 55% of the patients ($p<0.001$). In addition, the histopathological confirmation of the cytological diagnoses of NG and PTC was found to be similar (71.15% and 72.22, respectively; $p<0.001$).

When the relationship between the accuracy of cytological diagnosis and nodule diameter was evaluated,

it was determined that a DC-II diagnosis provided more accurate results in the 5-10 mm and >20 mm nodules compared to smaller nodules (p<0.05 and p<0.001, respectively). In the PTC cases with a DC-VI cytological diagnosis, the success of the diagnosis decreased if the nodule was smaller than 5 mm (p=0.122), but the success rate was significantly higher in all the larger nodules groups (p<0.05). When the nodule sizes of all the cases and the correlation of cytological and histopathological diagnoses were evaluated, it was seen that the nodule group with the most successful diagnosis rate was 10-20 mm, and the success rate decreased in the 5-mm and >20-mm nodules.

Table 3. Evaluation of FNAB diagnoses according to the nodule diameter on ultrasonography

Fine needle aspiration biopsy diagnoses	<10 mm		10-20 mm		≥20 mm		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
DC-I	102	26.8	92	24.2	186	49.0	380	100
DC-II	2	2.8	14	19.4	56	77.8	72	100
DC-III	8	13.8	12	20.7	38	65.5	58	100
DC-IV	4	5.0	36	45.0	40	50.0	80	100
DC-V	14	30.4	20	43.5	12	26.1	46	100
DC-VI	36	34.6	50	48.1	18	17.3	104	100
Total Nodules	166	22.4	224	30.3	350	47.3	740	100.0

*Percentage of rows are taken. DC Diagnostic Categories; DC-I: Non-diagnostic, DC-II: Benign, DC-III: Atypia of uncertain significance or follicular lesion of uncertain significance (AUS-FLUS), DC-IV: Follicular neoplasm (FN) or suspected FN, DC-V: Suspected malignancy, DC-VI: Malignant

Table 4. Evaluation of histopathological diagnoses according to the nodule diameter on ultrasonography

Histopathological diagnoses	<10 mm		10-20 mm		≥20 mm		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
NG	48	28.9	54	24.1	156	44.6	258	34.86
MNG	0	0.0	2	0.9	16	4.6	18	2.43
BTN	6	3.6	34	15.2	46	13.1	86	11.62
OTC	2	1.2	4	1.8	18	5.1	24	3.24
PTC	110	66.3	130	58.0	114	32.6	354	47.84
Total	166	22.4	224	30.3	350	47.3	740	100.0
BTN	**<10 mm**		**10-20 mm**		**≥20 mm**		**Total**	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
FA	4	66.7	22	64.7	42	91.3	68	79.1
HCA	2	33.3	12	35.3	4	8.7	18	20.9
Total	6	6.9	34	39.5	46	53.5	86	100.0

*Forty cases diagnosed with Graves' disease were not included in the table. PTC: Papillary Thyroid Carcinoma, OTC: Other Thyroid Carcinomas, MNG: Multinodular Goiter, BTN: Benign Thyroid Neoplasms, FA: Follicular Adenoma, HHA: Hurthle Cell Adenoma

Table 5. Evaluation of FNAB cytological diagnoses and histopathological diagnoses

FNAB	Malignant		Benign		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
DC-I	210	55.6	172	47.5	382	51.6
DC-II	12	3.2	58	16.0	70	9.5
DC-III	20	5.3	38	10.5	58	7.8
DC-IV	26	6.9	54	14.9	80	10.8
DC-V	36	9.5	10	2.8	46	6.2
DC-VI	74	19.6	30	8.3	104	14.0
Total	378	51.1	362	48.9	740	100.0
FNAB	**PTC**		**OTC**		**Total**	
	Number	Percent	Number	Percent	Number	Percent
DC-I	200	56.5	10	41.7	210	55.6
DC-II	8	2.3	4	16.7	12	3.2
DC-III	18	5.1	2	8.3	20	5.3
DC-IV	18	5.1	8	33.3	26	6.9
DC-V	36	10.2	0	0.0	36	9.5
DC-VI	74	20.9	0	0.0	74	19.6
Total	354	93.7	24	6.3	378	100.0

FNAB: Fine-Needle Aspiration Biopsy, PTC: Papillary Thyroid Carcinoma, OTC: Other Thyroid Carcinomas, DC Diagnostic Categories; DC-I: Non-diagnostic, DC-II: Benign, DC-III: Atypia of uncertain significance or follicular lesion of uncertain significance (AUS-FLUS), DC-IV: Follicular neoplasm (FN) or suspected FN, DC-V: Suspected malignancy, DC-VI: Malignant

DISCUSSION

The p revalence o f t hyroid n odules i ncreases w ith a ge, with most being detected after the age of 40 years, and only 5% of these nodules are reported to be malignant (13,14). Although female gender was dominant in our study, there was no difference between the benign and malignant diagnosis groups in terms of mean age. Consistent with the literature, the age group with the highest incidence of cases was 40-59 years, and the male patients were older.

Although more than 90% of TNs are small and non-palpable lesions, they can present with microcarcinomas (15,16). In our study, the cases with a benign diagnosis had a significantly higher rate of palpable nodules than those with a malignant diagnosis. We consider this to be due to the high rate of microcarcinomas in cases with a histopathological diagnosis of PTC. In a study conducted by Kamran et al. (17), it was shown that large nodules had increased malignancy rates, but the relationship between size and malignancy was not linear. In the same study, the threshold value for an increased malignancy risk was accepted as approximately 20 mm, and the malignancy rate did not increase in larger nodules. In our results, the rate of increased malignancy in nodules smaller than 20 mm was 58.2%; the malignancy rate is reduced by 33.3% in nodules larger than 20 mm, which is similar to the literature.

In a review including 13 studies, it was reported that the mean risk of malignancy for the cytological diagnosis of follicular neoplasm was in the range of 10-45% for Hurthle cell type (DC-IV) and the average value was 22% (18-20). In our results, the cytological diagnosis of DC-IV was significantly higher in the 10-20-mm and >20-mm nodule groups. Unlike the PTC cases, most of the OTC cases were found to have nodules larger than 20 mm (75% vs. 32.2%). In light of these data, OTC should be considered primarily if the suspicious nodule diameter is larger than 20 mm, and PTC otherwise.

In our study, the diameter of the nodules in which FNAB was most successful was in the 10-20 mm range, which is compatible with the literature. In addition, the rate of a DC-IV cytological diagnosis was significantly higher in the nodules of 10-20 mm and those larger than 20 mm compared to DC-V. This was considered to be due to the radiologically late manifestation of follicular and Hurthle cell neoplasms. The nodules with a cytological diagnosis of DC-V and DC-VI were found to be mostly in the 10-20-mm diameter range.

In previous studies, it is stated that cytology has its own limitations, and it may not be able to distinguish between follicular hyperplastic and adenomatoid nodules, follicular adenoma, and some follicular variants of PTC; however, for most PTCs and poorly differentiated or undifferentiated carcinomas, the cytology report usually provides diagnostic utility (21). Pagni et al. (22) found that while the sensitivity of FNAB was 67.7% in microcarcinomas, it was 85.7% in carcinomas larger than 10 mm in diameter, and the sensitivity of FNAB was lower (31.8%) in large PTCs (>20 mm) due to tumor heterogeneity, confirming that USG-FNAB sensitivity is strongly correlated with tumor size. Our results are also consistent with the data reported in the literature in that the highest cytological success was obtained from the nodule group of 10-20 mm in diameter. In our study, the histopathological diagnosis of OTC was lower in the cases without a successful cytological diagnosis (DC-I) than in the PTC cases (41.7% versus 56.5%). We consider that most of the cases were caused by microcarcinomas, which are difficult to diagnose cytologically.

CONCLUSION

Our study showed that nodule size directly affected histopathological diagnosis and cytological success. Diagnostic success decreased in microcarcinomas and larger-diameter nodules, and the 10-20-mm nodules constituted the group with the highest cytological diagnostic accuracy. The risk of malignancy was higher in the nodules smaller than 20 mm than in those larger than 20 mm. The rate of benign pathological diagnosis is higher in DC-IV cases compared to DC-V. Therefore, especially in nodules with a cytological diagnosis of DC-V, a diameter greater than 20 mm should be considered in favor of OTC, and smaller nodules should indicate the presence of PTC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gülhane Training and Research Hospital Clinical Research Ethics Committee (Date: 15.12.2021, Decision No: 2021/89).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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