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Evaluation of Risk Factors for Malignancy Obtained by Means of Fine Needle Aspiration Biopsies in Thyroid Nodules and Surgical Outcomes of Patients with Bethesda Category III (AUS/FLUS)

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Rezumat

Evaluarea riscului de malignitate al nodulilor tiroidieni prin biopsie cu aspirație cu ac fin și rezultatele chirurgicale ale pacienților din categoria Bethesda III (AUS/FLUS)

Context: Nodulii încadrați în categoria „atipii cu semnificație nedeterminată" reprezintă un grup heterogen de formațiuni tumorale cu risc de malignitate nedeterminat. Scopul acestui studiu este examinarea citologică detaliată a acestor formațiuni pentru a determina criteriile citomorfologice care pot diferenția cazurile benigne de cele maligne, corelarea acestor criterii cu aspectul ecografic şi compararea cu rezultatul histopatologic final la pacienții tratați chirurgical.

Metode: Preparatele încadrate în categoria Bethesda 3 au fost reevaluate; prezența sau absența unuia dintre cei 11 parametri (hipocromazie, nucleu oval, coloid, pseudoincluziuni intranucleare, nuclei identați, nuclei fragmentați, nuclei voluminoşi izolați, nuclei cu contur neregulat, dimensiune nucleară, tipar microfolicular, nucleoli distincți) şi corelarea parametrilor semnificativi din punct de vedere statistic cu rezultatele chirurgicale şi cu descrierea ecografică.

Rezultate: Rezultatele a 206 proceduri de aspirație cu ac fin (FNA) au fost clasificate ca Bethesda 3. Un total de 53 de pacienți au fost operați; în 28 (52,8%) dintre aceste cazuri rezultatul histopatologic a fost benign, iar 25 (47,1%) de cazuri, a fost malign. 32 (15,5%) de pacienți au acceptat intervenția chirurgicală directă; în 53 de

cazuri s-a practicat aspirația cu ac fin, repetată la intervale de 3-6 luni, iar cei cu diagnostic de malignitate şi interpretare Bethesda 3 repetată au fost operați. Cei 121 de pacienți (69,5%) la care nu s-a practicat biopsie au fost chemați pentru controale ecografice la intervale de 3-6 luni. Dintre cei 11 parametri citomorfologici evaluați, 7 s-au dovedit a fi semnificativi statistic (p<0,05) pentru malignitate. Când cel puțin 3 dintre aceşti parametri au fost pozitivi, rata de malignitate a fost de 92%. Malignitatea a fost prezentă la 19 (61,3%) dintre pacienții cu noduli cu risc ridicat (TIRADS ≥ 4), comparativ cu doar 6 (35,8%) dintre pacienții cu risc scăzut (TIRADS ≤ 3); a existat o corelație semnificativă între prezența malignității şi scorul TIRADS (p=0,015). Preparatele care prezentau atipii nucleare au fost strâns corelate cu grupul cu risc ridicat din punct de vedere ecografic.
În concluzie, parametrii care indică atipia nucleară, prezența a mai mult de 3 factori citomorfologici, scorul TIRADS ≥4 au fost asociați semnificativ cu malignitatea; Atipia nucleară a fost strâns asociată cu scorul TIRADS ridicat. Nu a fost găsită o corelație semnificativă între prezența „tiparului microfolicular" şi malignitate.

Cuvinte cheie: atipie de semnificație nedeterminată, biopsie cu ac fin, atipie nucleară, atipie microfoliculară, TIRADS

Abstract

Background: The nodules diagnosed as the "atypia of undetermined significance" category are a heterogenous group with an indeterminate risk of malignancy. This study aimed to perform a detailed cytological examination of the preparations to determine the cytomorphological criteria that may be useful to distinguish benign cases from malignant ones, correlate them with ultrasonographic findings, and compare them with the final pathological result in surgically treated patients.
Methods: The preparations of patients classified as Bethesda 3 were re-evaluated; presence or absence of one of 11 parameters (hypochromasia, oval nucleus, colloid, intra-nuclear pseudoinclusions, nuclear grooving, nuclear moldering, isolated nuclear enlargement, nuclear irregularity, nuclear size, microfollicular pattern, distinct nucleoli) and correlating with surgical outcomes by adding ultrasonographic findings to statistically significant parameters.
Results: Two hundred and six fine needle aspirations (FNA) procedures were classified as Bethesda 3. A total of 53 patients underwent surgery; 28 (52.8%) of them were benign, and 25 (47.1%) were malignant. Thirty-two (15.5%) accepted direct surgery; 53 patients underwent repeat FNA at 3-6 month intervals and those with malignancy and repeated Bethesda 3 interpretation were operated. One hundred twenty-one (69.5%) patients who did not undergo biopsy were invited for ultrasonographic controls at 3-6 month intervals. Among the 11 cytomorphologic parameters evaluated, 7 were found to be statistically significant (p<0.05) with malignancy. When at least 3 of these parameters were positive, the malignancy rate was 92%. Malignancy was present in 19 (61.3%) of the patients with high risk nodules (TIRADS ≥ 4), compared to only 6 (35.8%) of the low-risk (TIRADS ≤ 3); there was a significant correlation between the presence of malignancy and TIRADS score (p=0.015). The preparations that displayed nucleus atypia were closely associated with the ultrasonographically high-risk group.
Conclusion: The parameters indicating nuclear atypia, presence of more than 3 cytomorphological factors, TIRADS score ≥ 4 were significantly associated with malignancy; nuclear atypia were closely associated with the ultrasonographically high TIRADS. No significant correlation was found between the presence of "microfollicular pattern" and malignancy.

Key words: atypia of undetermined significance, fine needle biopsy, nuclear atypia, microfollicular atypia, TIRADS

Introduction

The smears obtained by Fine Needle Aspiration (FNA) are reported according to the Bethesda system; among the six categories, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) has emerged as the most controversial category; this heterogenous group does not fulfill the criteria of thyroid carcinoma. Initially associated risk of malignancy was reported to be about 5 to 15% (1), but different results have been notified in the current literature (1-5). The 2015 American Thyroid Association Management Guidelines recommend a repeat FNA or molecular tests to assess the malignancy risk and to decide the case management (5,6). However, repeated FNA and molecular tests or ultrasonography have shown limited efficacy (7,8). This study aimed to determine the cytomorphological criteria that would approximate the diagnosis of malignancy by detailed cytological examination of patients included in the non-deterministic and highly heterogeneous Bethesda 3 category and correlate them with ultrasonographic findings.

Methods

This study was designed in a retrospective nature and approved by the Ethics Committee of Gaziosmanpasa Research and Training Hospital (no: 19/30.01.2019). ACR TI-RADS (Reporting and Data System) classification was used for ultrasonographic evaluation of thyroid nodules. Patients with a TIRADS score of ≤ 3 were considered as low risk, and those with a score of ≥ 4 were considered as high risk. The records of all patients with radiologically suspect nodules who underwent FNA were classified by the Bethesda reporting system between January 2014 to December 2018 at Gaziosmanpasa Training and Research Hospital were reviewed; the report as AUS/FLUS (Bethesda 3) provided the material for this study. If the first FNA was classified as Bethesda 3, a repeat of the FNA was recommended. If the second FNA for nodules with AUS/FLUS revealed follicular neoplasm, suspicious for malignancy or malignancy, the surgery was recommended. The patient's FNA, classified under Bethesda 3 (benign, nondiagnostic), was managed concerning ultrasonographic features. Patients who accepted surgery underwent total thyroidectomy or lobectomy plus isthmectomy. The objective of this retrospective study was to study the cytological signs observed on slides categorized as Bethesda 3 in correlation with surgical follow-up and pre-operative radiological features.

FNA was performed under ultrasound guidance using a 26-28 gauge needle with 2-4 aspirates. The rapid on-site evaluation was performed to check the adequacy of smears; alcohol-fixed smears were prepared and stained with Hematoxylin-eosin and Papanicolaou stains. The smears were reported according to the criteria of Bethesda System for Reporting Thyroid Cytopathology. To overcome possible differences in interpretation in histopathological evaluation, Bethesda 3 preparations were reinterpreted by two experienced pathologists, and the 11 cyto-morphological parameters were analyzed: presence or absence of hypochromasia, of oval nucleus, of colloid, of intranuclear pseudoinclusions, of nuclear grooving, of nuclear moldering, of isolated nuclear enlargement, of nuclear irregularity, of microfollicular pattern, of distinct nucleoli, and the nuclear size.

Statistical Analysis

The data analysis was performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp) software version 22.0. The Mann-Whitney U Test was used to establish the relationships of the parameters. The Chi-square test was applied to categorical data for analysis. Utilizing ROC analysis, the cut-off value was determined. Results were evaluated using a 95% confidence interval, and $p<0.05$ was deemed statistically significant (A p-value less than 0.05 was considered significant).

Results

From January 2014 to December 2018, the FNA procedures of 206 patients were classified as Bethesda 3; 53 patients underwent surgery. The age of these patients ranged from 18 to 76 years; the mean age was 46.2 (±12.3).The gender distribution showed a female preponderance, with 46 (86.8%) females and 7 (13.2%) males.

Among all patients who underwent surgery, 28 (52.8%) were benign, and 25 (47.1%) were malignant. Among all patients who underwent surgery, 23 (92%) had papillary thyroid cancer, and 2 (8%) had medullary thyroid cancer.

Of 206 patients categorized as Bethesda 3, 32 (15.5%) accepted direct surgery; of 174 patients, 53 (30.4%) underwent repeat IAB at 3-6 month intervals depending on the condition (*Fig. 1*) and those with malignancy were directly operated, second biopsy was interpreted as Bethesda 3 and repeat surgery was recommended; 21 (12.6%) of the patients with repeat IAB were operated and 12 (6.8%) of them were reported as malignancies (*Fig. 1*); 121 (69.5%) patients without biopsy were invited for ultrasonographic controls at

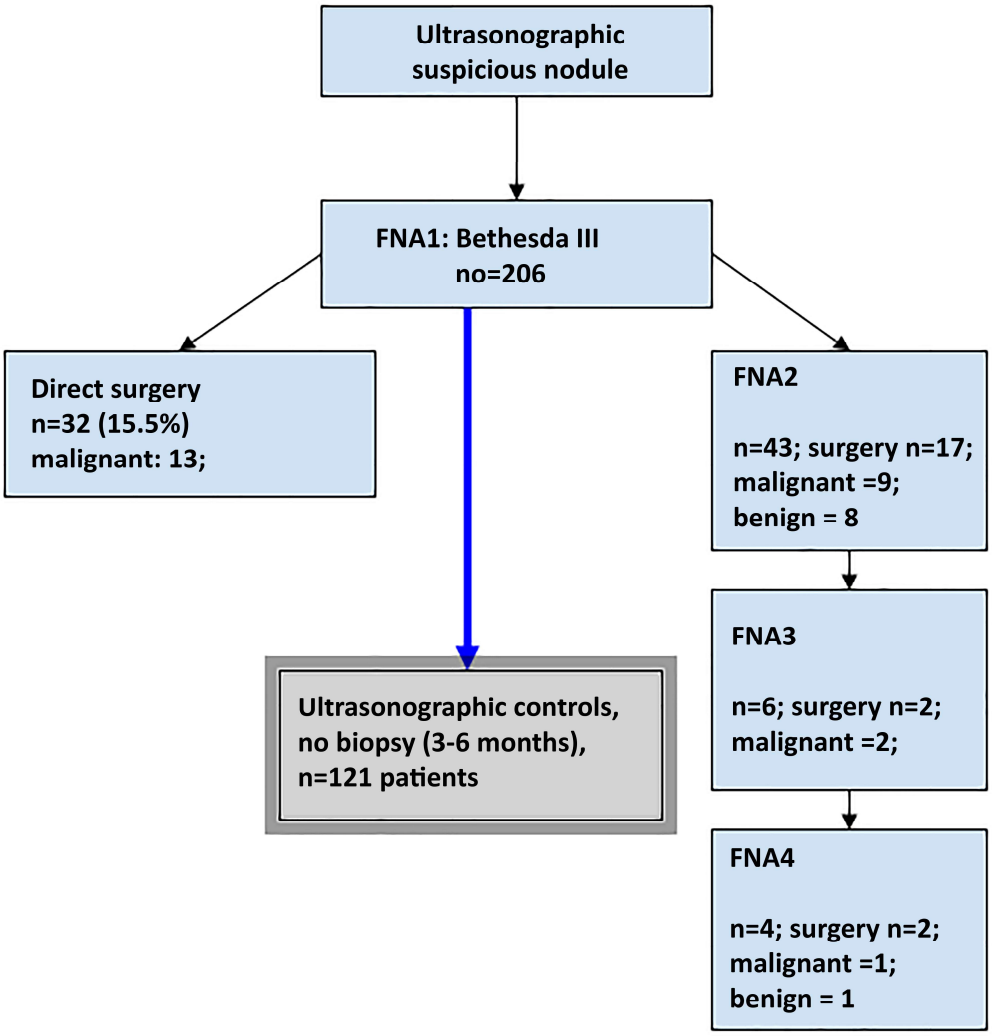


Figure 1. "Flow chart" showing patients categorized as Bethesda 3

Table 1. Associations of statistically significant cytomorphologic parameters with malignancy.

PARAMETER (n=28 cases)	benign (n= 25cases)	malignant	p-value	specificity	sensitivity
Presence or absence of hypochromasia (pale nucleus)					
Non-existent	24 (85.7%)	8 (32%)	0.001	24/28(85%)	17/25(68%)
Existent	4 (14.2%)	17 (68%)			
Colloid existence/absence					
Non-existent	9 (32.1%)	2 (8%)	0.001	9/28(32%)	
Partially existent	19 (67.8%)	9 (36%)			
Excessively existent	0	14 (56%)			
Presence or absence of nuclear grooving					
Non-existent	22 (78.5%)	3 (12%)	0.001	22/28(78%)	22/25(88%)
Existent	6 (21.4%)	22 (88%)			
Presence or absence of nuclear irregularity					
Non-existent	22 (78.5%)	6 (24%)	0.001	22/28(78%)	19/25(76%)
Existent	6 (21.4%)	19 (76%)			
Presence or absence Intra-nuclear pseudoinclusion					
Non-existent	27 (96.4%)	7 (28%)	0.001	27/28(96%)	18/25(72%)
Existent	1 (3.5%)	18 (72%)			
Presence or absence of isolated large nucleus					
Non-existent	25 (89.2%)	10 (40%)	0.001	25/28(89%)	15/25(60%)
Existent	3 (10.7%)	15 (60%)			
Nuclear size					
< 1 erythrocyte	7 (25%)	0	0.023		
1-2 erythrocyte	15 (53.5%)	11 (44%)			
> 2 erythrocyte T	6 (21.4%)	14 (56%)			

3-6 months intervals. Seven of the 11 cytomorphological parameters evaluated in this study were statistically significant ($p<0.05$) with malignancy (presence of hypochromasia, presence or absence of colloid, nucleus cleavage, nuclear irregularity, pseudoinclusion within nucleus, presence of isolated large nucleus, and nuclear size).

The ratios of sensitivity and specificity are shown in *Table 1*.

A score was determined by assigning a value of 1 to each of the 7 parameters statistically associated with malignancy. ROC analysis demonstrated a sensitivity of 0.92 and a specificity of 0.929 at a value of 2.5 in this scoring; according to the analysis, when at least three parameters were positive, there was a 92% probability that the case was malignant; values 0-1-2 in the scoring were deemed malignant with a 92% probability (*Fig. 2*).

In the cases which hypochromasia, nuclear grooving, nuclear irregularity, intranuclear pseudoinclusion, isolated large nucleus and nuclear size growing were observed, there were complex, branching, randomly oriented papillae with fibrovascular cores or sometimes follicular architecture in the Hematoxylin-Eosin sections of the tissue. The neoplastic cells showed change of nuclear size and shape,

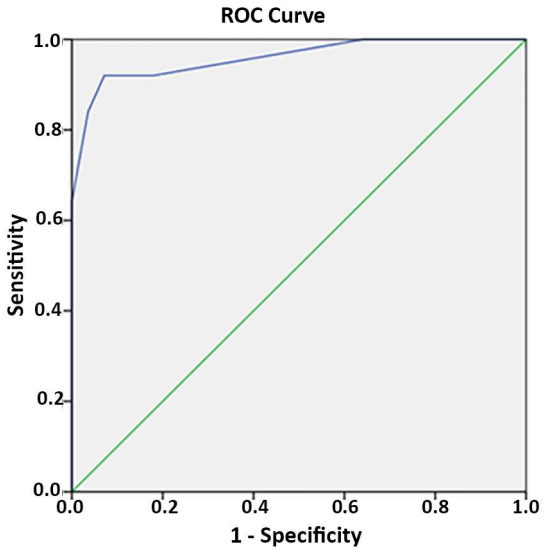


Figure 2. ROC analysis after scoring of statistically significant cytomorphologic factors.

nuclear enlargement, elongation and overlapping, clear chromatin, chromatin margination, ground glass nuclei, nuclear membrane irregularity. These cases were diagnosed as papillary carcinoma. In the cases in which microfollicular pattern and poor colloid were observed, trabecular or solid pattern of follicles were observed in the Hematoxylin - Eosin sections of the tissue. In some of these cases, there were capsular invasion, vascular invasion or adjacent thyroid parenchyma invasion, these cases were diagnosed as follicular carcinoma.

Ultrasonographic ACR-TIRADS classification was applied to review thyroid nodules (*Fig. 3*) retrospectively; 22 patients (41.5%) were considered ultrasonographically low risk (TIRADS score ≤ 3), and 31 patients (58.5%) were considered higher risk (TIRADS score ≥ 4). While only 6 (35.8%) of the low-risk patients had malignancy, 19 (61.3%) of the high-risk patients had malignancy; there was a significant correlation between the presence of malignancy and TIRADS score (p=0.015).

Among the seven parameters associated with malignancy, those whose preparations displayed only nucleus atypia (nucleus cleavage, p=0.01, oval nucleus, p=0.024), and isolated large nucleus, p=0.04, was closely associated with the ultrasonographically high-risk group.

Discussion

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) consists of six categories, standardized the interpretation of thyroid cytopathology, then facilitated the management of thyroid nodules. Among these six categories, the Bethesda Category 3 (AUS/FLUS) nodules remain ambiguous, and there is a heterogenous category with an unclear risk of malignancy; the initial risk of malignancy for an AUS/FLUS nodules suggested by the BSRTC are between 5% to 15% (1,5,9) another authors reported a wide range malignancy risk: 16% (11), and 46% (5).

Re-biopsy after a Bethesda 3 result in the initial FNA biopsy is still debatable: the BSRTC recommends repeating the FNA in this situation, whereas the ATA's position is less clear. Allen S. Ho et al. (3) reported that

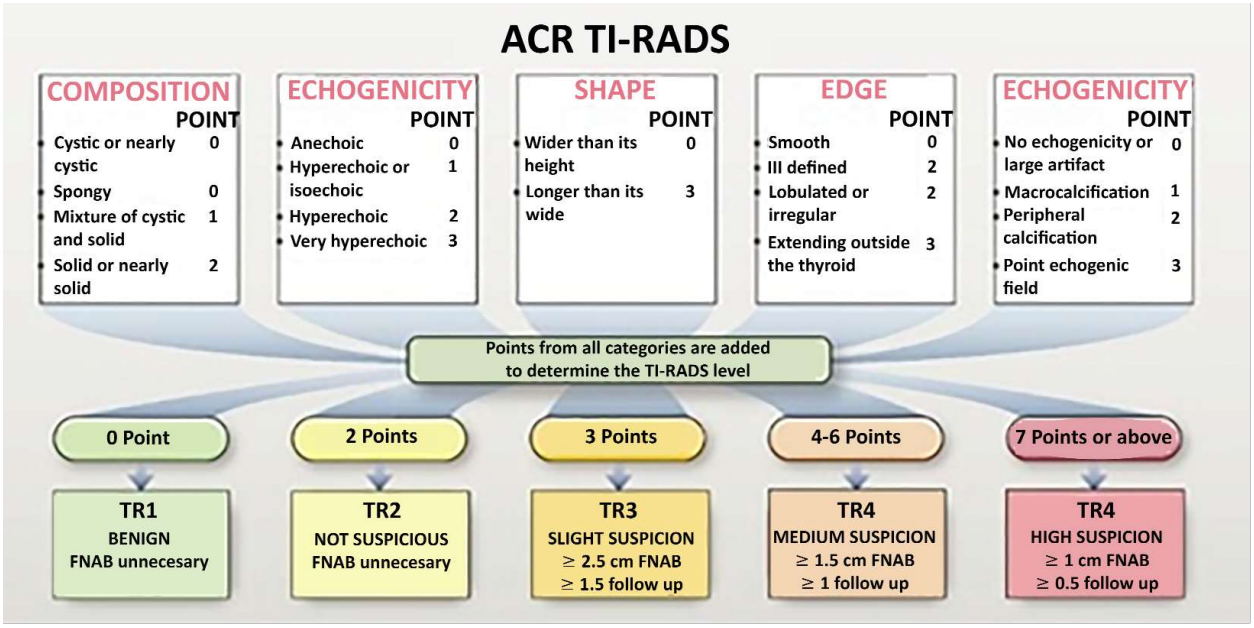


Figure 3. ACR-TIRADS ultrasonographic classification (Franklin N. Tessler, William D. Middleton, Edward G. Grant, Jenny K. Hoang, Lincoln L. Berland, Sharlene A. Teefey. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee.2017 American College of Radiology 1546-1440/17 http://dx.doi.org/10.1016/j.jacr.2017.01.046)

56.3% of repeat FNA biopsies were not evaluated as Bethesda 3, indicating that the procedure is beneficial. Vanderlaan et al. (11) reported malignancy in 9.4% of the operated patients, but the repeat FNA of these patients yielded favorable results. In our study, only 32 (15.5%) of 206 patients classified as Bethesda 3 in the first FNA accepted direct surgery, 43 (24.7%) of the remaining 174 patients accepted FNA a second time, 6 (3.4%) accepted FNA a third time, and 4 (2.2%) patients accepted FNA a fourth time. Twelve (22.6%) of the 21 patients who consented to repeat FNA and underwent surgery were found to have malignancy, which is comparable to the result reported by Renshaw et al. (12) (28.6%).

Seven of the 11 cytomorphological parameters evaluated retrospectively in our study were associated with malignancy ($p<0.05$); when at least three parameters are positive in ROC analysis, the case is 92% likely to be malignant; conversely, those with 0-1-2 are expected to be benign. Aydoğdu et al. (13) determined nuclear cleavage and nuclear overlap findings as independent variables in multivariate logistic regression analysis; if either of these parameters was detected, they deemed the possibility of malignancy sufficient to warrant a more thorough examination. In addition, they demonstrated that the total scoring of each cytomorphological parameter that achieved statistical significance among the examined cytomorphological parameters was statistically significant compared to those without positive findings; they reported that a malignancy diagnosis could be made with a specificity rate of 97% if the score was 4. In their research, nuclear pseudoinclusion, cleavage, nuclear overlap, and nuclear angularity were the most prominent morphologic characteristics for identifying malignancy.

In a univariate analysis of Bethesda 3 preparations showing nuclear atypia (enlarged nuclei, nuclear grooving, and irregular nuclei), Ki Hong et al. (14) reported a high risk of malignancy - 16% malignancy if the number of identified nuclear atypia was < 2 and 45.4% malignancy if ≥ 2; the multivariate analysis that included these parameters and the presence of ultrasonographic "spiculated margin", showed nuclear grooving and irregular nuclei as independent factors for malignancy. Although numerous studies have reported that "irregular nuclei" is not strongly associated with malignancy, their presence was reported as a significant prognostic factor in favor of malignancy in the present study. Although "nuclear grooving" was reported as an important finding in this study, it is a non-specific finding for thyroid cancer in the literature, as it is found in Hashimoto's thyroiditis, follicular adenoma, and Hurthle cell neoplasm (14). However, some studies (15,16) have reported that nuclear grooving is useful in diagnosing papillary thyroid cancer, particularly follicular variants (17). In our study, nuclear grooving demonstrated a specificity of 78% and a sensitivity of 88%.

In our study, nuclear inclusions were observed in only 3.5% of the normal preparations, whereas 72% of the patients with malignancy (specificity: 96%, sensitivity: 72%). This finding is consistent with most of the literature (18), but Ki Hong et al. (14) reported that this parameter is not very well correlated with malignancy.

The Bethesda 3 category is a heterogeneous group and the idea that approaching malignancy may benefit from subgrouping has recently gained attention (19,20). According to Chandra et al. (21), patients with nuclear atypia (nuclear grooving, nuclear inclusions) had a higher likelihood of having cancer than those with architectural disturbances (24.1% vs. 19.2%), especially when it came to papillary type cancer. With a sensitivity of 88% for the presence of clefting, 76% for angularity, 72% for pseudo inclusion, and 78%, 78%, and 72% specificity for malignancy, patients with nuclear atypia (clefting, angularity, and pseudo inclusion) were statistically significantly associated with malignancy (PTC) in our study, statistics showed no correlation between a microfollicular pattern and cancer.

According to reports, smears classified as Bethesda 3with the presence of focal nuclear atypia have a risk of malignancy that is 2-3 times higher than that of smears without

(AUS cases with cytological atypia had a risk of malignancy of 28–97%, but those with architectural disturbances had only a 5-27% risk of malignancy) (22,23). Tiffany Rui Xuan Gan et al. (24) demonstrated in their study that in preparations classified as Bethesda 3, 36.8% of cases with nuclear atypia and only 14.7% of cases with architectural atypia were associated with malignancy; as a result, they considered Bethesda 3 patients with nuclear atypia to be a risky subgroup. The same group noted that although this difference could not be statistically supported, patients with only "structural defects" were more likely than those with nuclear atypia to have malignancies in FNA repeats (70.6% vs. 48.7%). They recommend direct hemithyroidectomy in patients with nuclear atypia, but repeating FNA in Bethesda 3 patients with "structural abnormality" would clarify the diagnosis in 67.6% of these patients. Alternatively, Hyeon J et al. (19) suggest BRAF mutation analysis for risk stratification of similar patients.

Before FNA procedure and during follow-up, ultrasonographic findings of Bethesda 3 patients become more significant (24,25,26); numerous studies have demonstrated that sonographic findings of "indeterminate nodules" help assess the risk of malignancy (27,28); irregular nodule borders, the presence of microcalcifications, a taller than wide shape, and hypoechogenicity findings indicate malignancy. According to Ki Hong et al. (14), cytological evidence of nuclear grooving and irregular nuclei and the ultrasonographic finding of "spiculated margins" were all significantly correlated with malignancy. In ultrasonographic assessments of cases classified as Bethesda 3, Kuru et al. (25) evaluated solid nodules, microcalcification within the nodule, nodule diameter 2 cm, and young patients (< 65 years) as independent risk factors for malignancy; they stated that the risk of malignancy increased by 53% if more than two of these ultrasonographic criteria were positive. Malignancy was not present if there were no ultrasonographic findings suspicious of malignancy.

Ultrasonographic findings that may be considered suspicious: microcalcification, irregular margins, taller-than-wide configuration, and hypoechogenicity; these findings are found in 18-50% of nodules with AUS/FLUS cytology and are associated with a malignancy rate of 79.3%, whereas the malignancy rate of AUS/FLUS cases with ambiguous ultrasonographic findings was found to be low (24.7%) (29). Many suspicious sonographic findings fit the TI-RADS classification 4-5 (30). In our study, ultrasonographic findings of 53 operated patients were reviewed according to TI-RADS classification, and 22 (41.5%) patients were evaluated as low risk (TIRADS $\leq$ 3), and 31 (58.5%) patients were evaluated as high risk (TI-RADS $\geq$ 4); only 6 (11. 3%) of the low-risk patients were found to have cancer at surgery, 19(35.8%) of the sonographic high-risk patients were found to have cancer; statistically, there was a significant correlation between TIRADS score and the presence of malignancy (p=0.015). Among the 7 parameters associated with malignancy, those whose preparations showed only nucleus atypia (nucleus cleavage, p=0.01, oval nucleus, p=0.024), isolated large nucleus, p=0.04) were closely related and associated with the ultrasonographically high-risk group.

Because this was a retrospective study performed at a single academic institution, it has several limitations. First, the study had a small sample size; second, the FNA's were performed by different persons with different level of experience, and this fact could have resulted in artefactual changes during smear preparations. Also, the molecular mutations test was nor applied as additional diagnostic tools, especially for nuclear atypia subgroup.

In conclusion, the parameters indicating nuclear atypia (hypochromasia, presence of colloid, nucleus irregularity, intra-nuclear pseudoinclusion, isolated large nucleus, nucleus size) were significantly associated with malignancy. When at least 3 of these factors were positive, the malignancy rate was 92%. Following the literature, no significant correlation was found between the presence of "microfollicular pattern" indicating structural defect and malignancy in our study. When the

TIRADS score was ≥ 4, 61.3% of the patients were found to be malignant, and patients with nuclear atypia (nuclear clefting, oval nucleus, isolated large nucleus) were closely associated with the ultrasonographically high TIRADS group.

Conflict of Interest

The authors declare no conflict of interests.

Author's Contributions

Concept and design: DG,EK. Data collection and manuscript preparation: DG,EK,MÖ, PÇ,BK.

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