Malignancy Rates in Bethesda Category AUS/FLUS: Single Center Experience

Bethesda Kategori ÖBA/ÖBFL için Malignite Oranları: Tek Merkez Deneyimi

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ÖZET

Amaç: Tiroid nodüllerinin prevelansı yüksek olmasına rağmen, bu nodüller için malignite oranları düşüktür. Bu nedenle, cerrahi yaklaşım gerektiren malign nodülleri, benign nodüllerden ayırmak çok önemlidir. Ultrasonografi, ultrasonografi eşliğinde ince iğne aspirasyonu ve ayrıca Tiroid Sitopatolojisi için Bethesda Raporlama Sistemi tiroid nodüllerinin değerlendirilmesinde fayda sağlamaktadır. Ancak, bu sistem 'Önemi Belirsiz Atipi/ Önemi Belirsiz Foliküler Lezyon (ÖBA/ÖBFL)' olarak adlandırılan problemli bir kategori içermektedir. Bu kategori için son zamanlarda bildirilen malignite yüzdeleri %5 ile %96,7 arasında değişmektedir. Bu çalışmada merkezimizde incelenen ilk ince iğne aspirasyon tanısı ÖBA/ÖBFL olan tiroid nodüllerindeki malignite oranlarının sunulması amaçlanmaktadır.

Yöntem: Yedi yıl süresince, Trakya Üniversitesi Tıp Fakültesi Patoloji Anabilimdalı'nda (Edirne, Türkiye) incelenen hastaların tanıları (ince iğne aspirasyon ve tiroidektomi) geriye dönük olarak değerlendirildi.

Bulgular: İnce iğne aspirasyon sitolojisinde ÖBA/ÖBFL tanısı alan 153 hastadan 68'inde (%44,4) histopatolojik tanı papiller tiroid karsinomu, 1'inde (%7) foliküler karsinom ve 1'inde (%7) de medüller karsinom idi.

Tartışma ve Sonuç: Tiroid Sitopatolojisi için Bethesda Raporlama Sistemi bazı tanı kategorilerinde standardizasyon sağlamışsa da, ÖBA/ÖBFL kategorisi hala subjektif sitolojik kriterleri barındırmakta ve farklı çalışmalarda oldukça değişken histolojik malignite oranları bildirilmektedir. Bu nedenle, immünositokimya ve özellikle moleküler testler gibi yardımcı yöntemlerin kullanılması tiroid nodüllerinin preoperatif tanısında faydalı olabilir.

Anahtar Kelimeler: Tiroid Karsinomu, Sitoloji, Önemi Belirsiz Atipi/ Önemi Belirsiz Foliküler Lezyon

ABSTRACT

Introduction: Although the prevelance of thyroid nodules is high, the rate of malignancy in these nodules is low. Thus, the distinction between the malignant nodules requiring surgical approach and the benign ones is very important. Ultrasound, ultrasound guided fine needle aspiration and also The Bethesda Reporting System for Thyroid Cytopathology are useful tools for interpretation of thyroid nodules. However, this system includes a problematic category titled as 'Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance (AUS/FLUS)'. The reported percentages of malignancy in these nodules range between 5-96,7%, recently. We aimed to present the rate of malignancy in thyroid nodules with initial fine needle aspiration diagnosis as AUS/FLUS.

Methods: The final diagnosis (fine needle aspiration and thyroidectomy) of patients who presented at the Department of Pathology of the Trakya University Medical Faculty (Edirne, Turkey) were reviewed for seven years.

Results: Histological diagnosis was papillary thyroid carcinoma in 68 (44,4%), follicular carcinoma in 1 (0.7%) and medullary carcinoma in 1 (0.7%) of the 153 patients with prior fine needle aspiration diagnosis as AUS/FLUS.

Discussion and Conclusion: Although, The Bethesda Reporting System for Thyroid Cytopathology have provided standardisation in some of categories, the category of AUS/FLUS remains to be including subjective cytological criteria and subsequent malignancy rates are highly variable in different reports. So, ancillary tools

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such as immunocytochemistry and particularly molecular tests may be appropriate in preoperative diagnosis of thyroid nodules.
Keywords: Thyroid Carcinoma, Cytology, Atypia of Undetermined Significance/Follicular Lession of Undetermined Significance

Introduction:

Although the prevalence of thyroid nodules is high, the rate of malignancy in these nodules is low. Thus, the distinction between the malignant nodules requiring surgical approach and the benign ones is very important. Ultrasound (US), ultrasound guided fine needle aspiration (USGFNA) and also The Bethesda Reporting System for Thyroid Cytopathology (BRSTC) are useful tools for interpretation of thyroid nodules. The system includes six categories; nondiagnostic as category 1, benign as category 2, atypia of undetermined significance and follicular lesion of undetermined significance (AUS/FLUS) as category 3, suspicious for follicular neoplasia and follicular neoplasia (FNS/FN) as category 4, suspicious for malignancy (SFM) as category 5 and finally, malignant as category 6 (1). The system informs the rates of malignancy and also requires the type of management for each category (2). However, this system includes a problematic category titled as 'Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance (AUS/FLUS)' (2). BRSTC declares the rate of malignancy for category AUS/FLUS as 5-15% (1,2), but the reported percentages of malignancy in these nodules range between 6% (3) and 96,7 (4), recently.

The present study aims to present the experience of single center which is located in the northwest part of Turkey aboutthe rates of malignancy in thyroid nodules with prior FNA diagnosis as AUS/FLUS.

Methods:

The final diagnoses of FNA materials of patients who presented at Department of Pathology of Trakya University Medical Faculty (Edirne, Turkey) were reviewed for seven years (March 2007- March 2014). The patients with preoperative initial FNA diagnosis as Bethesda Category 3, namely AUS /FLUS and subsequent thyroid surgery (lobectomy/thyroidectomy) were included in the study group. Cytological examination of FNA materials were performed by liquid based preparings and conventional smears. The diagnosis of FNA materials were grouped according to BRSTC (Table 1) (1,2). Histopathological examination was performed by obtaining at least 4 samples, mean 8 samples per lobe. If there was any gross pathological mass or lesion, these areas were demonstrated totally for microscopic evaluation. The lesions containing suspicious (but not diagnostic) nuclear features for papillary carcinoma in conventional Hematoxylin-eosin (H&E) stained slides, otherwise immunohistochemistry was performed by using antibodies such as HBME-1, Galectin-3 and cytokeratin 19. Encapsulated nodules were interpreted carefully for capsular or vascular invasion.

Prior FNA diagnosis and postoperative histopathological diagnosis of the patients were documented. The results were presented as numbers and percentages.

Results:

Out of 6290 patients who had been performed USGFNA, 410 (6,5%) patients had been diagnosed as Bethesda Category 3, namely AUS /FLUS. In this group, 153 patients had undergone thyroid surgery. 124 (81%) of the patients were female, 29 (19%) of the group included male patients.

Malignant tumors were present in 70 (45,8%) of the patients. Histological diagnosis was papillary thyroid carcinoma (PTC) in 67 (43.7%) of the patients. One of the patients had been diagnosed as well differentiated tumor with unknown malignant potential. The histopathological reevaluation converted this diagnosis into follicular variant of papillary carcinoma. The final percentage of PTC was

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Table 1: The Bethesda System forreporting thyroid cytopathology: recommended diagnostic categories, implied risk of malignancy, and recommended clinical management (1, 2).

Diagnostic category	***Risk of malignancy (%)***	***Management*** [a]
(I) Nondiagnostic or unsatisfactory (ND/UNS) *Cyst fluid only* *Virtually acellular specimen* *Other (obscuring blood, clotting artifact, etc.)*		Repeat FNA with ultrasoundguidance
(II) Benign *Consistent with a benign follicular nodule (includes ,colloid nodule etc.)* *Consistent with lymphocytic (Hashimoto) thyroiditis in theproperclinical context* *Consistentwithgranulomatous (subacute) thyroiditis* *Other*	0-3	Clinicalfollow-up
(III) Atypia of undetermined significance or follicularlesion of undetermined significance (AUS/FLUS)	5–15[b]	Repeat FNA
(IV) Follicular neoplasm or suspicious for follicular neoplasm (FN/SFN) *-specifyifHurthle cell (oncocytic) type*	15–30	Surgical lobectomy
(V) Suspicious for malignancy (SFM) *Suspicious for papillary carcinoma* *Suspicious for medullary carcinoma* *Suspicious for metastatic carcinoma* *Suspicious for lymphoma* *Other*	60–75	Near-total thyroidectomy or surgical lobectomy [c]
(VI)Malignant *Papillarythyroidcarcinoma* *Poorlydifferentiatedcarcinoma* *Medullarythyroidcarcinoma* *Undifferentiated (anaplastic) carcinoma* *Squamouscellcarcinoma* *Carcinomawithmixedfeatures (specify)* *Metastaticcarcinoma* *Non-Hodgkinlymphoma* *Other*	97–99	Near-total thyroidectomy [c]

[a]Actual management may depend on other factors (e.g.,clinical and sonographic) besides the FNA interpretation.
[b]Estimate extrapolated from histopathologic data from patients with “repeated atypicals” .
[c]In the case of “suspicious for metastatic tumor” or a “malignant” interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

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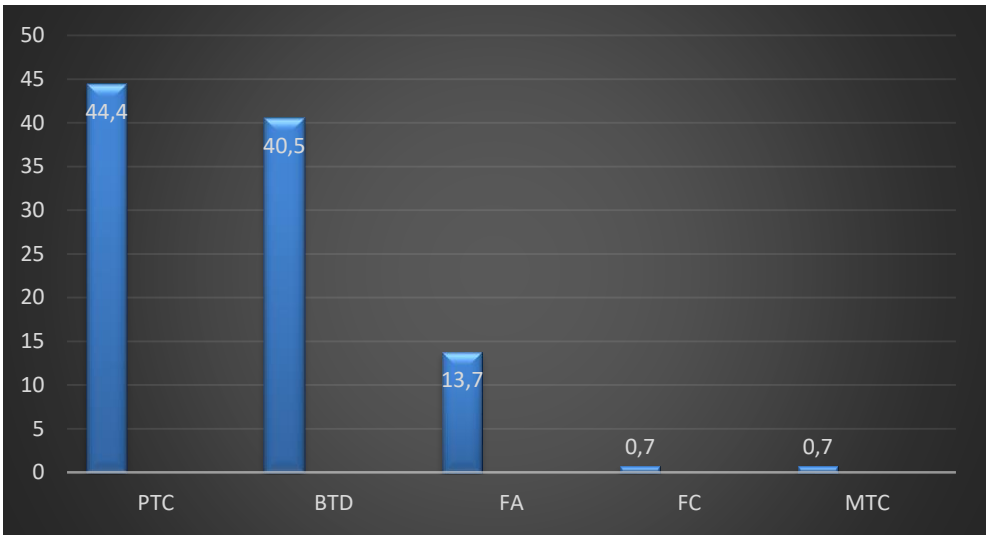

Figure 1: Histopathological diagnosis of the patients with prior cytological diagnosis as AUS/FLUS
PTC: Papillarythyroidcarcinoma, BTD: Benignthyroiddisease, FA: Follicular adenoma, FC: Follicularcarcinoma, MTC: Medullarythyroidcarcinoma

44,4% (68/153) (Fig 1). Histological variant was conventional PTC in 21 (30,9%) of the cases diagnosed as PTC and follicular variant PTC in 46 (67,6 %) of the patients in PTC group. One of the patients (1,4%) had clear cell variant PTC (Fig 2). The tumor size was ≤ 10mm in 40 (58,8%) of the patients. Histopathological diagnosis was follicular carcinoma in 1 (0.7%) of the patients and medullary carcinoma in 1 (0.7%) of the patients with prior FNA diagnosis as AUS/FLUS.

The only benign tumor of the follicular epithelial cells, namely follicular adenoma was present in 21 (13,7%) of the cases. Benign nonneoplastic thyroid diseases including lymphocytic thyroiditis and follicular nodular disease were present in 11(7,2%) and 51(33,3%) of the patients, respectively.

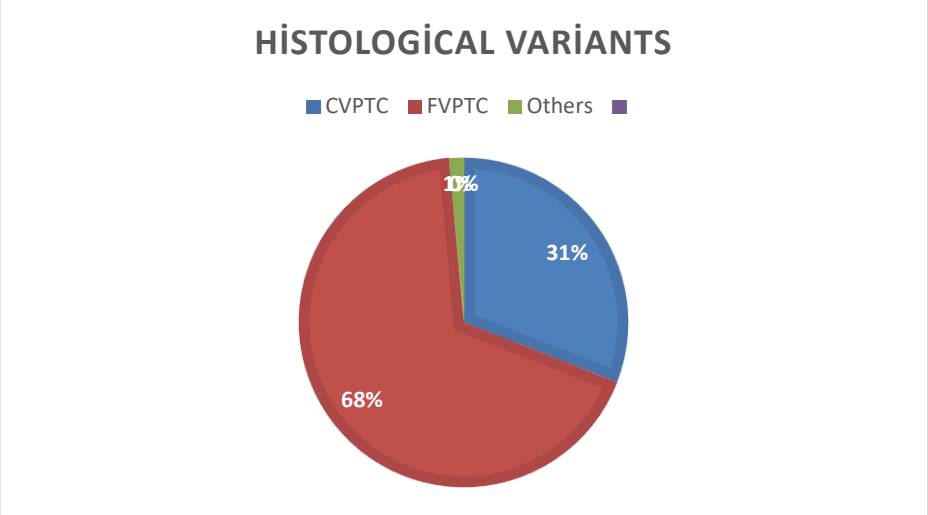

Figure 2: Histological variants in papillary thyroid carcinoma.
CVPTC: Conventional variant papillary carcinoma
FVPTC: Follicular variant papillary carcinoma

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Discussion:

Bethesda Reporting System for Thyroid Cytopathology predicts the risk of malignancy as 5-15% in Category 3; AUS/FLUS (1,2). However, the published reports after the widespread use of BRSTC informed highly variable risk of malignancy ranging between 6 %-96,7% in this group (3-8). The malignancy rate in AUS/FLUS category of our center was 45,8% and is placed centrally in previosly reported wide risk spectrum (3-8).

The percentage of AUS/FLUS for FNA materials is reported as 7% in BRSTC. The rate of this category in our center was close to the recommended rates by BRSTC. Although, BRSTC have standardized the cytopathological diagnosis in FNA of thyroid gland, there are surviving problems in Categories 3, 4 and 5 due to the subjective cytological evaluation and interobserver variability (1,2,9,10). But the main problem emerges in category 3; AUS/FLUS, since the management of other two categories somehow contains surgery. BRSTC suggests repeat FNA for the initial diagnosis of Category 3 in the absence of any other risk such as suspicious or malignant radiological images (1,2). Probable cause of these percentages of category 3 may be the numerical expression of endocrine atypia. As the thyroid gland is an endocrine organ, follicular epithelial cells also have endocrine atypia in their nature. Besides, some of the benign thyroid diseases or some of the therapies for benign diseases may result worrisome endocrine atypia. So, clinical information should be considered in the interpretation of FNA of thyroid nodules in addition to the cytological evaluation.

In our study, higher rates of malignancy in histopathology may be explained by triage of the patients for surgery as it was reported by some authors previously (11). In our center, nearly all of the thyroid nodules diagnosed as AUS/FLUS are discussed in multidisciplinary conferences and if there is no unsettling radiological feature in US imaging of the nodule, the management goes on by repeating FNA as it is recommended by BRSTC (2). So, indication for surgery is defined by eliminating false-positive results in cytology by following USFNA in the background of clinical and radiological data. The most common malignancy was PTC with the percentage of 44,4% and most of the tumors were microcarcinomas and follicular variant in the study group. It is well documented that FVPTC does not express the conventional nuclear features of PTC and may localize the cytological diagnosis in subcategories. This may be one of the causes resulting the higher malignancy rates in histology as reported in several reports (12, 13).

The widespread use of liquid-based preparations have generated ancillary tools in the cytological interpretation via availability of cell blocks. These tools contain immuno-cytochemistry and molecular analysis. Immunocytochemical studies including HBME-1 and Galectin 3 may have value in specimens diagnosed as AUS/FLUS, especially in the means of conventional variant of PTC. Molecular analyses can be descriptive and exclusive in differentiating malignancy and benign diseases. Molecular alterations of several genes such as point mutations of *BRAF, K/NRAS, TERT, TSHR* genes and fusions in *THADA, PPRG* and *NTRK3* genes may reveal the malignant potential of the nodule (rule-in tests) (14). On the other side, gene expression classifier tests may exclude the malignant potential (rule-out tests) (15).

Conclusion:

Although, The Bethesda Reporting System for Thyroid Cytopathology have provided standardization in some of categories, the category of AUS/FLUS remains to be including subjective cytological criteria and subsequent malignancy rates are highly variable in different reports. So, ancillary tools such as immunocytochemistry and particularly molecular tests may be appropriate in preoperative diagnosis of thyroid nodules.

Conflict of Interest: None

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