Doi:10.47572/muskutd.1039741

The Predictive Factors of Malignancy in Follicular Lesion of Undeterminated Significance

Önemi Belirsiz Foliküler Lezyonda Malignitenin Prediktif Faktörleri

Samet SAHIN[1], Hikmet PEHLEVAN OZEL[2], Yunus Nadi YUKSEK[2], Tanju TÜTÜNCÜ[2]

[1]Muğla Sıtkı Koçman University, School of Medicine, Department of General Surgery, Muğla
[2]Ankara City Hospital, Department of General Surgery, Ankara

Öz

Önemi belirsiz folliküler lezyon (ÖBFL) Bethesda Sınıflamasına göre önemi belirsiz atipi ile aynı üçüncü grupta tanımlanmıştır, ancak bu alt gruplar yapılan çalışmalara göre farklı malignite oranlarına ve tümör özelliklerine sahiptir. Bu çalışmada sitolojik olarak Bethesda Kategori III/ÖBFL tiroid nodüllü hastaların preoperatif klinikopatolojik özelliklerinin değerlendirilmesi amaçlandı. 44 hasta ince iğne aspirasyon sitolojisi (İİAS) sonuçlarına göre benign (pB) ve malign (pM) olarak iki gruba ayrıldı ve iki grubun ameliyat öncesi klinik, ultrasonografik bulguları ve İİAS sonuçları karşılaştırıldı. Tek değişkenli analizlere göre İİAS'ye göre hiopekojenite, mikrokalsifikasyon varlığı ve düzensiz çekirdek varlığı malignitede anlamlı olarak daha yüksek bulundu (tümü için $p<0.05$). Ayrıca mikrokalsifikasyonlar ($p=0.048$) ve hipoekojenite ($p=0.014$) lojistik regresyon analizine göre malignite için bağımsız risk faktörleri olarak bulundu. ÖBFL'li hastalarda ultrasonografide hipoekojenite ve mikrokalsifikasyon varlığında, tekrarlayan İİAS yerine malignite insidansının arttığı ve cerrahinin ön planda düşünülmesi gerektiği unutulmamalıdır.

Anahtar Kelimeler: Malignite, Önemi Belirsiz Foliküler Lezyon, Prediktif Faktörler

Abstract

Follicular lesion of undetermined significance (FLUS) is defined in the same Group III with the atypia of undetermined significance according to Bethesda Classification but these subgroups have different malignancy rates and tumor characteristics according to the studies. In this study, the aim was to evaluate the preoperative clinicopathologic features of the patients with cytological Bethesda Category III/FLUS thyroid nodules. The 44 patients were divided into two groups based on fine needle aspiration cytology (FNAC) results as benign (pB) and malignant (pM) and compared the preoperative clinical, ultrasonographic findings and FNAC results of two groups. According to the univariate analyses the presence of hiopechogenicity and presence of microcalcification are found to be significantly higher in malignancy ($p<0.05$ for all). Also, the presence of microcalcifications ($p=0.048$), and hypoechogenicity ($p=0.014$) were found to be independent risk factors for malignancy according to logistic regression analysis. In patients with FLUS, it should be remembered that the incidence of malignancy increases and treatment should be considered in the forefront of surgery instead of recurrent FNAC in the presence of hypoechogenicity and microcalcification in ultrasonography, and in patients with nuclear membrane irregularity according to FNAC.

Keywords: Malignancy, Follicular Lesion of Undetermined Significance, Predictive Factors

Introduction

Thyroid nodules are common in general population. By the introduction of ultrasound examination of the thyroid, nodules can be detected up to 50% of middle-aged patients. The overall risk of malignancy in all patients with a thyroid nodule is in between 5% to 7% (1). The fine needle aspiration cytology (FNAC) holds an important place for tracking thyroid nodules and to determine malignance. It is the gold standard method for the detection of malignancy in thyroid nodules or the detection of cancer suspicion.

Bethesda Classification was developed by National Cancer Institute to ensure standardization in the assessment of thyroid nodule cytology in 2007. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) published in 2009 provided estimates of the risk of malignancy (ROM) in each category (2). Before Bethesda classification, there was no agreement on the number of diagnostic categories and predictive value of indeterminate diagnoses (3). According to this classification, the atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS) are defined in the same Group III, and these nodules carry a malignancy risk of 5% to 15% (2). Some studies have revealed that malignancy rates in nodules with AUS/FLUS cytology are higher than previously shown (4, 5). The Bethesda 2007 Thyroid Cytology Classification defines follicular lesion of undetermined significance as a heterogeneous category of cases that are not clearly benign or sufficiently atypical for a diagnosis of follicular neoplasm or malignancy suspicion (6). According to some studies, some clinicopathological factors have an increased risk of malignancy in this group such as male gender, nodule size and etc. (7). However, in the literature, the number of studies on the factors that increase cancer formation in the FLUS group is limited.

The aim of this study is to evaluate the preoperative clinicopathologic features of patients with cytological Bethesda Category III/FLUS thyroid nodules, and to determine the clinical,

	ORCID No
Samet SAHIN	0000-0003-0748-3458
Hikmet PEHLEVAN OZEL	0000-0002-9146-3742
Yunus Nadi YUKSEK	0000-0003-0442-8410
Tanju TÜTÜNCÜ	0000-0001-9058-465X

Başvuru Tarihi / Received: 22.12.2021
Kabul Tarihi / Accepted : 12.08.2022

Adres / Correspondence : Samet SAHIN
Muğla Sıtkı Koçman University, School of Medicine, Department of General Surgery, Muğla
e-posta / e-mail : sametsahin@mu.edu.tr

biochemical and ultrasonographic predictors of malignancy in these patients who undergo operation.

Material and Method

Between January 2013 and March 2019, the patients whose fine needle aspiration cytology (FNAC) results reported as 'follicular lesion of undetermined significance (FLUS)' and underwent surgery at Ankara Numune Training and Research Hospital at Department of General Surgery were included in the study. Patients whose data cannot be accessed from the hospital information management system were excluded. The information of 44 patients who met the criteria of the study was reached. We divided the patients into two groups based on FNAC results as benign (pB) and malignant (pM) and compared the preoperative clinical, ultrasonographic findings and FNAC results of two groups. The groups were compared in terms of age, gender, preoperative TSH results, preoperative ultrasonography findings (hypoechogenicity, irregular margin, solid or cystic component, microcalcification) and FNAC results (nuclear clarification, nuclear grooving, nuclear inclusion, irregular nuclear membrane).

Statistical analyses were conducted by using SPSS Statistics version 22 (SPSS, Inc., IBM Company, Armonk, NY, USA). Kolmogorov Smirnov test was used to evaluate the normality of continuous variables. Normally distributed variables expressed as mean values (± standard deviation) and compared with Student's t test. Non-parametric variables expressed as median (interquartile range) and compared with Mann-Whitney U test. Nominal variables were compared using Pearson's chi-squared test or Fisher's exact test. A binary multivariable logistic regression analysis was conducted after univariate analysis were assessed to find out variables associated with malignancy. Variables with $p<0.25$ in univariate analysis were selected for further evaluation of association between those parameters and malignancy with the multivariate logistic regression analysis and enter method was used in multivariable logistic regression analysis (8). p-value <0.05 was considered to indicate a statistically significant difference.

Results

The mean age of 44 patients is 45.23 (±10.64), 40 of the patients are female (90.9%) and 4 of them are male (9.1%). Of the 44 patients, 32 (72.7%) have pathology benign while 12 patients (27.3%) have malignancy. 9 of 12 patients have Papillary thyroid carcinoma (PTC), 2 have papillary microcarcinoma (PMC), and 1 patient has follicular thyroid carcinoma (FTC). The presence of hypoechogenicity and presence of microcalcification according to USare found to be significantly higher in malignancy ($p<0.05$ for all) (Table 1).

A binary multivariable logistic regression was performed to ascertain the effects of microcalcification, hypoechogenicity, number of nodules and presence of irregular spiculated margin on the likelihood that participants have a malignant disease. The logistic regression model was statistically significant, $\chi2(4) = 15.82$, $p<0.001$. The Nagelkerke R2 indicated 43.8 % of the variance in a malignant disease was accounted for by the predictors overall. When the goodness of fit of the models was examined with the Hosmer-Lemeshow test (chi-square=6.354, df=8 and p=0.608), it was found that the models were adequate for estimating a malignant disease. According to logistic regression analysis, the presence of microcalcifications were 13.24 and the presence of hypoechogenicity 9.74 times more likely to have malignancy than the absence of them ($p<0.05$ for all) (Table 2).

Discussion

In this study, it is revealed that the rate of malignancy is 27.3% in 44 patients whose FNAC results are evaluated as FLUS which is similar to recent studies. According to the American Thyroid Association (ATA) guidelines, the rate of malignancy described as 5-15% while in recent studies the rate of malignancy differs from 22.6% to 48% (4, 5). Based on the results of our study, the rate of malignancy seems to be open to change by means of the increased frequency of FNAC. In order to reveal the current malignancy rates, it is obvious that more meta-analyzes and studies involving more patients are necessary.

According to the study, there is no significant difference in gender and age between the groups. When the ultrasonographic findings are compared, it is found that the presence of microcalcification and the presence of hypoechogenicity are shown statically significant in the malignant group. Unlike the study proposed in this paper, Yoon et al. show that suspicious ultrasonography findings were not predictive for malignancy in FLUS patients (9) Hence, according to the FNAC results, there is no significant differences between malign and benign group.

The ATA guideline has described the US features highly suspicious for malignancy as follows: solid or partially cystic nodule with one or more of these features such as irregular margins, microcalcifications, taler shape, and evidence of extrathyroidal extension (10). Topaloglu et al. reported that malignancy is associated with microcalcification and higher AP/T ratio in ultrasonography, with thyroid nodules evaluated as Bethesda Category III in cytology (11). In this study, the association between microcalcifications and hypoechogenicity with malignancy in FLUS patients

is found. Also, in logistic regression analysis, these parameters are found to be independent from risk factors for malignancy. Also, in this paper, there is no association between TSH and malignancy similar to Marques et al. (12).

The management options for this category that are recommended by current guidelines follows; follow-up, repeat FNAC, thyroidectomy or perform core needle biopsy (10). However, there is no clear management algorithm for the FLUS group in the literature. According to BSRTC, recurrent FNACs are recommended in the AUS / FLUS group, regardless of subgroups (2). However, this approach should be reviewed if FNAC results are taken into consideration as well as other ultrasonographic parameters.

Although there is a long-time interval of 6 years in this study and the frequency of thyroid operations was approximately 500 per year in the studied clinic, the number of patients operated with FLUS is limited to only 40s which indicates the difficulty of evaluating the FLUS group as a separate group. So, it is obvious that there is a necessity of multi-center studies and studies involving a higher number of patients to show the malignancy rate and clinical, ultrasonographic findings associated with malignancy in FLUS patients.

To sum up, in patients with FLUS defined in the Group III according to BSRTC, it should be remembered that the incidence of malignancy increases and treatment should be considered in the forefront of surgery instead of recurrent FNAC in the presence of hypoechogenicity and microcalcification in ultrasonography.

Table 1. The comparison of clinic, ultrasonographic and FNAC findings between two groups.

	pB	pM	p-value
Age (±SD)	45.16 (11.38)	45.42 (8.83)	0.943[a]
Gender			
Female (%)	29 (90.6)	11 (91.7)	1.000[c]
Male (%)	3 (9.4)	1 (8.3)	
TSH (mg/dl) (±SD)	2.00 (1.28)	1.68 (1.19)	0.451[a]
Number of nodules (US) (Median (IQR 25-75))	2 (2-3)	3 (2.25-7.50)	0.106[b]
Size of nodule mm (US) (Median (IQR 25-75))	17(13-29.25)	20.5(15.5-31.75)	0.397[b]
Hypoechogenecity (US) (%)			
(+)	8 (25)	9 (75)	**0.005[c]**
(-)	24 (75)	3 (25)	
Cyctic/solid state (US) (%)			
Cyctic	7 (21.9)	2 (16.7)	
Solid	15 (46.9)	7 (58.3)	0.794[c]
Mixt	10 (31.3)	3 (25)	
Microcalcification (US) (%)			
(+)	2(6.3)	5 (41.7)	**0.011[c]**
(-)	30(93.7)	7 (58.3)	
Spiculated Margin (US) (%)			
Regular	20 (62.5)	5 (41.7)	0.214[d]
Irregular	12 (37.5)	7 (58.3)	
Nuclear Clearing (FNAC) (%)			
(+)	2 (6.3)	1 (8.3)	1.000[c]
(-)	30 (93.7)	11(91.7)	
Nuclear Grooving (FNAC) (%)			
(+)	4 (12.5)	2 (16.7)	0.658[c]
(-)	28 (87.5)	10 (83.3)	
Nuclear Inclusion (FNAC) (%)			
(+)	15 (46.9)	6 (50)	0.853[d]
(-)	17 (53.1)	6 (50)	
Nuclear Membrane (FNAC) (%)			
Regular	24 (75)	7 (58.3)	0.281[d]
Irregular	8 (25)	5 (41.7)	

[a]Student's t test, [b]Mann-Whitney U Test, [c]Fisher's Exact Test, [d]Pearson Chi Square Test. (US: Ultrasonography, FNAC: Fine needle aspiration cytology, pB: Group with benign pathology, pM: Group with malignancy).

Table 2. Multivariate logistic regression analysis of factors associated with malignancy

	B (S.E.)	Wald	Odds ratio (95% CI)	p-value
Microcalcification	2.58 (1.31)	3.9	13.24 (1.02-172.03)	0.048
Hypoechogenecity	2.28 (0.93)	6.02	9.74 (1.58-60.1)	0.014
Number of nodules	-0.02 (0.18)	0.02	0.98 (0.69-1.39)	0.902
Spiculated Margin	0.52 (0.85)	0.38	1.68 (0.32-8.8)	0.539

B: Estimate, S.E.: Standart error, CI: confidence intervals, US: Ultrasonography. In binary multivariable logistic regression analysis, enter method was used and absence of microcalcification, absence of hypoechogenecity, absence of speculated margin, absence of nuclear membrane irregularity was set as the reference categories. ($\chi 2(4) = 15.82$, NagelkerkeR2: 43.8%).

Ethics Committee Approval: Ethics committee approval was obtained from Muğla Sıtkı Koçman University Human Research Ethics Committee (24.11.2021/24/XIII) for the study.

References

1. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.
2. Cibas ES and Ali SZ. The Bethesda system for reporting thyroid cytopathology. Thyroid. 2009;19(11):1159-65.
3. Wang HH. Reporting thyroid fine-needle aspiration: literature review and a proposal. Diagn Cytopathol. 2006;34(1):67-76.
4. Ho AS, Sarti EE, Jain KS, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). Thyroid, 2014;24(5):832-9.
5. VanderLaan PA, Marqusee E, Krane JF. Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: should repeated FNA be the preferred initial approach?. Am J Clin Pathol. 2011;135(5):770-5.
6. Horne MJ, Chhieng DC, Theoharis C, et al. Thyroid follicular lesion of undetermined significance: Evaluation of the risk of malignancy using the two-tier sub-classification. Diagn. Cytopathol. 2012;40(5):410-5.
7. Cakir B, Bilginer M, Ozdemir D, et al. Hemithyroidectomy Seems to be a Reasonable Initial Surgical Approach in Patients with Cytological Bethesda Category III Thyroid Nodules: An Institutional Experience. Turk J Endocrinol Metab. 2018;22(2):57-63.
8. Hosmer Jr DW, Lemeshow S, Sturdivant RX. Applied logistic regression. John Wiley & Sons, 2013.
9. Yoon JH, Kwon HJ, Kim EK, et al. Subcategorization of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS): a study applying Thyroid Imaging Reporting and Data System (TIRADS). Clin Endocrinol. 2016;85(2):275-82.
10. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133.
11. Topaloglu O, Baser H, Cuhaci FN, et al. Malignancy is associated with microcalcification and higher AP/T ratio in ultrasonography, but not with Hashimoto's thyroiditis in histopathology in patients with thyroid nodules evaluated as Bethesda Category III (AUS/FLUS) in cytology. Endocrine. 2016;54(1):156-68.
12. Marques RR, Rafael AA, Santos FS, et al. Can we predict malignancy in AUS/FLUS by measuring TSH? In: Endocrine Abstracts. Bioscientifica, 2016.