

## research article

# Thyroid cancer detection rate and associated risk factors in patients with thyroid nodules classified as Bethesda category III

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**Background.** Ultrasound guided fine-needle aspiration (FNA) is a standard procedure for thyroid nodules management and selecting patients for surgical treatment. Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), as stated by The Bethesda System for Reporting Thyroid Cytopathology, is a diagnostic category with an implied malignancy risk of 5–15%. The aim of our study was to review cytology and histopathology reports, as well as clinical and ultrasound data, for thyroid nodules reported as AUS/FLUS, in order to evaluate the malignancy rate and to assess factors associated with malignant outcome.

**Patients and methods.** A total of 112 AUS/FLUS thyroid nodules in 105 patients were evaluated, of which 85 (75.9%) were referred to surgery, 21 (18.8%) were followed-up by repeat FNA and 6 nodules (5.3%) were clinically observed. Each was categorized in two final diagnostic groups - benign or malignant, which were further compared to clinical data of patients and ultrasonographic features of the nodules.

**Results.** Final diagnosis of malignancy was reached in 35 cases (31.2%) and 77 (68.8%) had benign lesions. The most frequent type of cancer was papillary thyroid carcinoma (PTC) - 58.1% PTC and 25.8% had follicular variant of PTC. Patients' younger age, smaller nodule size, hypoechoic nodule and presence of calcifications were shown to be statistically significant risk factors for malignancy.

**Conclusions.** The rate of malignancy for the AUS/FLUS diagnostic category in our study was higher than estimated by the Bethesda System. Clinical and ultrasound factors should be considered when decision for patient treatment is being made.

Key words: thyroid nodule; cytology; fine-needle aspiration; ultrasonography; thyroid carcinoma

## Introduction

Thyroid nodules are very common finding in the general population. Their detection increases with the use of high frequency ultrasound (US) with a varying prevalence of up to 68%<sup>1</sup>, higher in females compared to males and increasing with age.<sup>2</sup> A proper management of thyroid nodules is needed because, even though most cases are of benign eti-

ology, they still carry a malignancy risk, roughly around 5–15% of all detected nodules.<sup>3–5</sup> According to the American Cancer Society, among both men and women, the largest annual increase of cancer incidence rates in the USA from 2006 to 2010 was for thyroid cancer.<sup>6</sup> US guided fine-needle aspiration (FNA) has become the initial test for evaluation of thyroid nodules, a standard tool for detecting thyroid cancer and it provides a better selection

of patients for surgical treatment. In order to have a uniform terminology for reporting the results of FNA and a better communication and understanding among cytopathologists and clinicians, in 2007 The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed. The implementation of TBSRTC has improved the quality of FNA reporting and has reduced the overall rate of unnecessary thyroid surgeries.<sup>7</sup> However, Bethesda category III (atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [FLUS]) carries controversy as a result of inconsistent usage among pathologists and institutions, its heterogeneity and difficulty to determine the true risk of malignancy for an AUS/FLUS nodule because not all cases in this diagnostic category are referred to surgical treatment.<sup>8</sup> The aim of this study was to evaluate the malignancy risk of thyroid nodules reported as Bethesda category III (AUS/FLUS) on initial FNA and to assess the clinical and US factors associated with malignancy outcome.

## Patients and methods

We retrospectively reviewed 4738 cases of thyroid US guided FNAs that were performed at the outpatient's thyroid unit of the Institute of Pathophysiology and Nuclear Medicine, Faculty of Medicine, Ss Cyril and Methodius University, Skopje, from January 2012 to December 2016. In this period, 281 out of the 4738 (5.93%) thyroid nodules were diagnosed as Bethesda Category III. Among them 175 cases were excluded: 167 because of no available data for follow-up and eight because of multinodular goiter (no data about the specific nodule that was category III on FNA, and therefore no significant relation with the histology outcome). The remaining 112 nodules in 105 patients were included in this study. Clinical outcome for the aspirated thyroid nodule was categorized in two final diagnostic groups – benign and malignant. Benign final diagnostic group included: nodules with confirmed benign diagnosis on histopathology report after surgical treatment, nodules diagnosed as Bethesda category II on repeat FNA (rFNA) and nodules which were clinically monitored for at least 6 months with no increase on US (same in size or decreased). Malignant final diagnostic outcome was defined as confirmed malignancy on histopathology report after immediate surgery or Bethesda category V or VI on rFNA (and later confirmed on histopathology). Decision for surgical treatment

was mostly based on clinical features (such as age, nodule size), US characteristics of the nodule in question and patient preference.

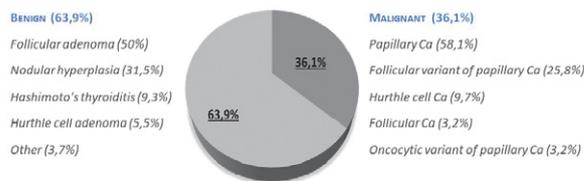
Clinical features, US findings and pathology records were reviewed for each case. The final diagnostic groups were compared for age, gender, nodule size, US features (nodule composition, echogenicity, vascularization and calcifications) and results from a thyroid <sup>99m</sup>Tc-pertechnetate scan. According to the scan, the thyroid nodules were classified into one of three groups: hypofunctioning (cold nodule with reduced radioisotope uptake), isofunctioning nodule (with radioisotope uptake comparable to the surrounding non-nodular tissue) and hyperfunctioning (hot nodule with increased <sup>99m</sup>Tc-pertechnetate tracer uptake).

Ultrasonography for detecting thyroid nodules was performed with a high-resolution broadband linear array transducer (LN 12-3, Philips HD6 machine). Cameco syringe pistol with 20ml syringe and 21G needle were used for the US guided FNA of the nodules. Each US examination and subsequent FNA was performed by the same nuclear medicine specialist. The cytology smears were prepared when needle contents were expelled onto a glass slide and smeared using a second slide. Two types of slides were done for each lesion: one fixed in 95% ethanol and Papanicolaou stained, and other air dried and May Grunwald-Giemsa stained. Cytology findings were reported by a cytopathologist with more than 10 years experience in the field at the Institute of pathology, Faculty of Medicine, Ss Cyril and Methodius University, Skopje.

Statistical analysis was performed using IBM SPSS Statistics v20 software. Categorical variables for US features and malignancy rates were compared using  $\chi^2$  tests and Fisher's exact tests when appropriate. Continuous variables were compared using t-test. Logistic regression analysis was performed to assess the odds ratios for the risk of malignancy according to clinical and US features and multivariate logistic regression with a backward stepwise selection method was performed to select independent predictors of malignancy. In all cases p-value < 0.05 was considered statistically significant.

## Results

A total of 112 Bethesda category III nodules from 105 patients were included in this study. The clinical data and US features of all nodules are shown in Table 1. Among the 112 nodules, 35 (31.2%) had



**FIGURE 1.** Histologic outcomes of Bethesda Category III nodules from patients who underwent direct surgical treatment. Malignancies were found in 36.1% of AUS/FLUS nodules who were managed with surgery without a repeat cytology. Papillary Thyroid Carcinoma and its Follicular variant were the most common types of cancer, accounting for a total of 83.9% of all malignancies. Among the benign lesions, Follicular adenomas presented in 50% of these cases, and Nodular hyperplasia was second in line with a frequency of 31.5%.

final diagnosis of malignancy and 77 (68.8%) had benign lesions. Of the total number, 85 nodules (75.9%) from 81 patient received direct surgical treatment, 21 (18.8%) were followed-up by rFNA and 6 (5.3%) were clinically observed. The malignancy rate for patients who received immediate surgical treatment was 36.1%. Papillary thyroid carcinoma (PTC) accounted for most of the malignant outcomes (58.1% PTC and 25.8% follicular variant of PTC) and among the benign histopathology outcomes, 50% of the cases were follicular adenoma (Figure 1). Of the 21 nodules undergoing rFNA, 16 (76.2%) were categorized as benign lesions (Bethesda II, none of whom underwent surgical treatment), 1 (4.8%) was suspicious for follicular neoplasm (Bethesda IV, later confirmed as Follicular Adenoma on histopathology report), and in 4 (19.0%) the second FNA was suspicious for malignancy (Bethesda V, later histopathologically confirmed malignancy in all 4 cases, all of whom were PTC). The remaining 6 nodules were monitored within an average of 7.6 months, in which time they showed no changes or regression in the US evaluation.

A comparison of clinical data and the final diagnostic outcome – benign or malignant group, is summarized in Table 2. Patients with malignant outcome were significantly younger than those with benign outcome ( $p < 0.01$ , OR 0.953) and malignant nodules were significantly smaller in size than the benign nodules ( $p < 0.05$ , OR 0.952). The mean age and nodule size for patients referred to surgery was  $51.96 \pm 12.33$  years and  $24 \pm 9.33$ mm, and  $56 \pm 13.72$  years and  $21.6 \pm 9.69$ mm for patients managed with rFNA or observation, although these differences were not statistically significant. Thyroid scan was performed in total of 60 cases (53.6%) and univariate analysis showed no signifi-

**TABLE 1.** Clinical data of patients and US features of Bethesda category III nodules

Variables		
<b>Patients, n</b>	105	
<b>Age (y), range</b>	$52,9 \pm 12,7^*$	(24–77)
<b>Gender</b>		
Male	18	17.10%
Female	87	82.90%
<b>Thyroid nodules, n (total)</b>	<b>112</b>	
<b>Benign</b>	<b>77</b>	<b>68.8%</b>
<b>Malignant</b>	<b>35</b>	<b>31.2%</b>
<b>Nodule size (mm), range</b>	$23,4 \pm 9,4^*$	(8–60)
<b>US features</b>		
<b>Composition</b>		
Solid	83	74.1%
Mixed	25	22.3%
Cystic	4	3.6%
<b>Echogenicity</b>		
Anechoic	3	2.7%
Hypoechoic	56	50.0%
Isoechoic	47	42.0%
Hyperechoic	6	5.4%
<b>Calcifications</b>		
No calcifications	88	78.6%
Microcalcifications	17	15.2%
Macrocalcifications	7	6.3%
<b>Vascularisation</b>		
No vascularisation	20	1.9%
Low	18	16.1%
Peripheral	16	14.3%
Central	58	51.8%
<b>Thyroid scan</b>		
No scan	52	46.4%
Hypofunctioning (Cold)	19	17.0%
Isofunctioning	34	30.3%
Hyperfunctioning (Hot)	7	6.3%

\* Mean  $\pm$  standard deviation

cant difference between the benign and malignant groups by thyroid scan characteristics (Table 2).

As shown in Table 3, when US features of benign and malignant Bethesda III nodules were compared, most of the malignant nodules had solid composition on US (82.9%); however, this difference was not statistically significant. On the other

TABLE 2. Comparison of clinical data of benign and malignant thyroid nodules in 105 patients with Bethesda III cytology report

Variables	Final outcome		p-value
	Benign (n = 71)	Malignant (n = 34)	
<b>Age (y),</b> <b>range</b>	54.9 ± 11.7* (25–77)	48 ± 14.2* (24–71)	< 0.01 (0.005) OR 0.953 (95% CI 0.922–0.986)
<b>Gender</b>			ns (0,506)
Male	14 (19.7%)	4 (11.7%)	
Female	57 (80.3%)	30 (88.3%)	
<b>Nodule size (mm),</b> <b>range</b>	24.6 ± 9.1* (10–60)	20.7 ± 9.8* (8–47)	< 0.05 (0.048) OR 0.952 (95% CI 0.907-1.00)
<b>Thyroid scan</b>	<b>number of nodules:</b>		ns (0.117)
Hypofunctioning (Cold)	10 (23.8%)	9 (50.0%)	
Isofunctioning	25 (59.5%)	9 (50.0%)	
Hyperfunctioning (Hot)	7 (16.7%)	0 (0.0%)	

\* mean ± standard deviation; n = number of patients; OR = odds ratio; ns = non significant

TABLE 3. Comparison of US features of benign and malignant thyroid nodules with Bethesda III cytology report

Variables	Final outcome		p-value
	Benign n = 77 (68.8%)	Malignant n = 35 (31.2%)	
<b>Composition</b>			ns (0.372)
Solid	54 (70.1%)	29 (82.9%)	
Mixed	20 (26.0%)	5 (14.3%)	
Cystic	3 (3.9%)	1 (2.9%)	
<b>Echogenicity</b>			
Anechoic	3 (3.9%)	0 (0.0%)	ns (0.999)
Hypoechoic	31 (40.3%)	25 (71.4%)	< 0.01 (0.003) OR 3.710 (95% CI 1.565–8.795)
Isoechoic	38 (49.4%)	9 (25.7%)	< 0.05 (0.021) OR 0.355 (95% CI 0.147–0.856)
Hyperechoic	5 (6.5%)	1 (2.9%)	ns (0.216)
<b>Calcifications</b>			
No calcifications	68 (88.3%)	20 (57.1%)	< 0.01 (0.000) OR 0.176 (95% CI 0.067–0.463)
Microcalcifications	8 (10.4%)	9 (25.7%)	< 0.05 (0.042) OR 2.986 (95% CI 1.041-8.564)
Macrocalcifications	1 (1.3%)	6 (17.1%)	< 0.05 (0.012) OR 15.724 (95% CI 1.814–136.318)
<b>Vascularisation</b>			
No vascularisation	10 (13.0%)	10 (28.6%)	ns (0.051)
Peripheral	15 (19.5%)	1 (2.9%)	< 0.05 (0.046) OR 0.122 (95% CI 0.015–0.961)
Central	41 (53.2%)	17 (48.6%)	ns (0.646)
Low	11 (14.3%)	7 (20%)	ns (0.447)

n = number of nodules; ns = non significant; OR = odds ratio

hand, hypoechogenicity ( $p < 0.01$ ), presence of microcalcifications ( $p < 0.05$ ) and macrocalcifications ( $p < 0.05$ ) were significant risk factors of malignancy on univariate analysis, with odds ratios of 3.710, 2.986 and 15.724, respectively. Isoechogenicity ( $p < 0.05$ ), absence of calcifications ( $p < 0.01$ ) and peripheral vascularization ( $p < 0.05$ ) of the nodules were US features significantly associated with benign outcome.

On multivariate logistic regression model, age ( $p < 0.0001$ , OR 0.964, 95% CI 0.950–0.979), hypoechogenicity ( $p = 0.005$ , OR 3.914, 95% CI 1.516–10.106), microcalcifications ( $p < 0.05$ , OR 3.601, 95% CI 1.102–11.772) and macrocalcifications ( $p = 0.01$ , OR 21.001, 95% CI 2.058–214.296) remained as significant independent predictors of malignancy.

## Discussion

The Bethesda System for Reporting Thyroid Cytopathology proposes limited usage of diagnostic category III (AUS/FLUS) of approximately 7% or less of all thyroid FNAs.<sup>8</sup> In our study, in a period of 4 years, only 5.93% of all thyroid FNAs were reported as AUS/FLUS which is within the recommended 7%. On the other hand, according to TBSRTC, the risk of malignancy for this diagnostic category is estimated to be only 5–15%,<sup>8</sup> but in our retrospective study the malignancy rate was considerably higher; final diagnosis of malignancy had 31.2% of all cases included and 36.1% of the cases who underwent immediate surgical resection. PTC and its follicular variant accounted for 83.9% of all malignant tumors. Recent studies have also reported malignancy rates well above the predicted 5–15%. Gweon *et al.* reported a relatively high overall risk of malignancy for initial Bethesda III thyroid nodules of 55.5% and even higher for nodules with direct surgery (78.3%).<sup>9</sup> Ho *et al.* presented a range of the true prevalence of malignancy, lying between a lower-bound estimate of 26.6% which included all AUS/FLUS nodules (assuming all observed nodules were benign, decision subject to verification bias) and an upper-bound estimate of 37.8% risk of malignancy which was calculated based only on the AUS/FLUS nodules selected to undergo surgery after initial or repeated Bethesda III cytology.<sup>10</sup> In other studies, the risk of malignancy was found to be 35.3–59.5%<sup>11–13</sup>, again higher compared to the proposed one in the Bethesda System. On the other hand, in their cohort study, Nagarkatti *et al.* reported an overall malignancy rate of 15.7%, even though almost 75% of the in-

cluded 203 patients had surgery and they also found that PTC was the most common, with total of 70% of all cases.<sup>14</sup> In another study with a total of 96 malignant diagnoses even 90% of them were papillary carcinomas.<sup>15</sup>

In most of the cases, different clinical and especially ultrasonographic features impact the decision for AUS/FLUS nodule management, considering that some of those features have association with higher malignancy risk. Several studies have shown various results about the influence of age as a risk factor of thyroid malignancy. Ryu *et al.* reported that older age ( $\geq 40$  years) is associated with an increased risk of malignancy<sup>11</sup>, whereas others found that age is not a significant predictor of malignancy in AUS/FLUS nodules.<sup>9,13</sup> Conversely, Godazandeh *et al.* reported that in younger patients the prevalence of thyroid carcinoma is higher<sup>16</sup>, and in another study surgery without rFNA is recommended for younger patients.<sup>14</sup> Latter findings are in concordance with our results that younger age is a significant independent factor for malignancy in this Bethesda diagnostic category. Nevertheless, this could be because of a selection bias based on younger patients being referred to surgery more often in our study, though this finding was not statistically significant. Nodule size is reported to have no predictive value of malignancy and it should not be used as a reliable factor for clinical decision making<sup>16,17</sup>, although Kamran *et al.* suggest a threshold of approximately 2 cm in nodule diameter with strong evidence that size  $> 2$  cm is associated with an increased risk of well-differentiated thyroid cancer.<sup>18</sup> We found that nodules in malignant group are significantly smaller than those in the benign group, but on the multivariate analysis this factor was not confirmed to be an independent predictor for malignancy. We found that nodules in malignant group are significantly smaller than those in the benign group, but on the multivariate analysis this factor was not confirmed to be an independent predictor for malignancy.

According to the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, hyperfunctioning nodules do not require FNA, since they rarely harbor malignancy.<sup>19</sup> Although it is generally accepted that the risk of cancer in a hyperfunctioning thyroid nodule is low, in 14 case series which Mirfakhraee *et al.* recently reviewed, the risk was estimated to be 3%.<sup>20</sup> In our study, the total number of evaluated nodules which underwent thyroid scintigraphy

was not sufficient to estimate the malignancy risk in AUS/FLUS hyperfunctioning thyroid nodules; nevertheless, there was no malignant hyperfunctioning nodule in our group.

Marked hypoechogenicity, microcalcifications, irregular margins, taller than wide shape, and central vascularization are considered US features most likely related to malignancy.<sup>21,22</sup> In a meta-analysis including nine studies and a total of 1851 nodules with indeterminate cytology aspirates, only the presence of microcalcifications was significantly associated with malignancy and central vascularization presented with the best specificity (96%).<sup>3</sup> This finding is consistent with our results regarding microcalcifications as predictor of malignancy, with OR of 3.601 on multivariate analysis. We found that macrocalcifications are as well associated with malignancy in Bethesda III nodules ( $p = 0.012$ ). Both (micro- and macrocalcifications) are considered as suspicious US features by the Korean Society of Thyroid Radiology.<sup>23</sup> Similarly, Jeong *et al.* reported that presence of micro and macrocalcifications had significantly higher odds compared with no calcifications (OR: 5.17 and 12.22, respectively). However, they did not find statistically significant odds for marked hypoechogenicity ( $p = 0.17$ ).<sup>12</sup> In a previous study, with 395 analyzed Bethesda III nodules, when the US features of repeat Bethesda III nodules were evaluated, there was again no significant association between marked hypoechogenicity of the nodule and malignant outcome.<sup>13</sup> The reason for this discrepancy from our results, considering the relatively high statistical significance for hypoechoic nodules that we found ( $p = 0.003$ ), might be in the absence of further subclassification into mild, moderate and marked level of hypoechogenicity in our study. We did not find any significance between central vascularization of the nodules and malignant outcome, a result in concordance with a meta-analysis performed on 5 studies including 540 nodules, which indicated that there was no significant difference in internal vascularity (95% CI: -72.067, 2.824) between malignant and benign thyroid nodules.<sup>24</sup> We did not evaluate margins and taller than wide shape, since these parameters were not always available in the US reports included in this study.

Because this was an observational retrospective study it had several limitations. First, 62.3% of all AUS/FLUS nodules (175/281) were excluded from the analysis because of lack of follow-up data. Second, the decision for clinical management in some extent was influenced from patient preference so that potential clinical or US risk factors

were not considered. And finally, observed nodules without histopathological confirmation could have been subject of a verification bias, since they can also carry a malignant potential. Given that most of the published studies are also retrospective, this could contribute to the vast variations in the malignancy rates detected for AUS/FLUS nodules. Therefore, more prospective studies using Bethesda System are required in order to provide further insight and define more accurate risk stratification and patient management recommendations. Recent studies have also emphasized the importance of molecular testing, particularly BRAF<sup>V600E</sup> mutation detection and its role as an adjunct to clinical and US features for better decision making.<sup>25,26</sup> In a study which included 52 nodules with indeterminate cytology, molecular testing had positive predictive value of 100% for these lesions.<sup>27</sup> In another recently published meta-analysis with a total of 88 studies included, the mutation rate of BRAF<sup>V600E</sup> was 13.77% in AUS/FLUS category with a low sensitivity (40.1%) but significantly high specificity of 99.5% while evaluating the diagnostic value of BRAF<sup>V600E</sup> testing.<sup>28</sup> Therefore, molecular analysis can additionally help clinicians in guiding patient management, if routinely available.

## Conclusions

In conclusion, the risk of malignancy in AUS/FLUS nodules in our study was higher than estimated by TBSRTC. Recommendation for further management should not be based solely on pathology reports from FNA or rFNA. All clinical and US risk factors (such as patient age, hypoechogenic nodules and presence of calcifications) should be taken into consideration in reaching final decision for patient treatment.

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