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Results of the Bethesda System in Patients Undergoing Thyroidectomy-A Single-Center Experience

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Abstract

Objective: To compare preoperative fine needle aspiration biopsy (FNAB) and postoperative histopathological findings in patients undergoing thyroidectomy and to validate the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Methods: Data from 366 patients who underwent thyroidectomy between 2014-2016 were analyzed retrospectively and the variables related to thyroid cancer were investigated.

Results: Of 366 patients, 44 (12%) were male and 322 (88%) were female. Regarding FNAB results according to TBSRTC, 23 (6.3%) patients had category I, 79 (21.6%) had category II, 128 (35%) had category III, 113 (30.9%) had category IV, nine (3.8%) patients had category V and 14 (2.5%) had category VI cytology. Histopathological examination revealed thyroid cancer in 65 (17.7%) patients. The Bethesda System was found to have a sensitivity of 73.9% and a specificity of 96%. There was no association between thyroid cancer and other variables except male gender.

Conclusion: Although TBSRTC has an acceptable sensitivity and specificity, the risk of malignancy in category III and IV patients may vary. Therefore, multidisciplinary approach should be considered during treatment planning and surgical treatment option should be kept in mind.

Keywords: Fine needle aspiration biopsy, Bethesda System, thyroid nodule, thyroid cancer, thyroidectomy

INTRODUCTION

The incidence of thyroid nodules increased to 50%-70% with the use of high-resolution ultrasonography (US) (1). The incidence of cancer in thyroid nodules varies between 2% and 15% (2). Fine needle aspiration biopsy (FNAB) has an important role in the evaluation of thyroid nodules and the detection of cancer risk. Early diagnosis of clinically insignificant thyroid cancers is possible with FNAB, and patients are protected from unnecessary surgery and associated complications (3). With the widespread use of FNAB, conflicting reports between pathologists have started to emerge in the evaluation of cytology. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed in 2007 to eliminate terminological confusion. According to TBSRTC, FNAB results are divided into six categories: non-diagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance, follicular nodule/suspicious follicular nodule, suspicious for malignancy and malignant (Table 1) (4).

Central and Eastern Black Sea region are endemic regions for thyroid nodules. The aim of this retrospective analysis was to validate TBSRTC by comparing FNAB and histopathological (HP) results of 366 patients who underwent total thyroidectomy in Samsun Training and Research Hospital General Surgery Clinic between 2014-2016.

METHODS

The demographic characteristics of the patients, FNAB results according to TBSRTC, characteristics of single nodule or multinodular goiter, nodule diameters and HP results were recorded. All biopsies were taken under the guidance of an

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US by a radiologist with a 22 gauge needle and 10 cc injector in outpatient clinic settings. TBS was used for cytological classification. Repeat FNAB was planned for patients who had a non-diagnostic FNAB cytology. Follow-up or surgical treatment was suggested to patients with a second non-diagnostic FNAB cytology. Patients with nodule growth or suspicious US findings (solid hypoechoic nodules or cystic, microcalcified nodule with extra-thyroidal extension and irregular margins) during the follow-up period and patients who accepted surgery instead of follow-up were included in the study. Thyroidectomy was performed due to various indications other than cancer (cosmetic causes, trachea compression, hyperthyroidism) in patients with benign cytology. The HP findings of the patients were compared with the preoperative cytology results. Incidence of malignancy, suspected malignancy with benign cytology in TBSRTC, sensitivity and specificity of malignant cytology category, and the positive predictive and negative predictive values (PPD and NPD) were calculated in groups divided according to TBSRTC. In addition, the presence of a significant relationship between cancer incidence and age, gender, single nodule/multinodularity and nodule diameter parameters was investigated.

Statistical Analysis

SPSS 23.0 (IBM Corparation, Armonk, New York, United States) program was used for statistical analysis. While mean, standard error and minimum-maximum values were used for quantitative variables, categorical variables were expressed as n (%). Independent samples-t test was used for comparing the quantitative data of the two groups and chi-square test was used to compare the categorical data. $P<0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 50.47 (18-79) years. Forty-four (12%) patients were male (88%) and 322 were female. The median nodule diameter was calculated as 21.44 mm (4-65). A single nodule was detected in US in 152 (41.5%) patients, while the remaining 214 (58.5%) patients had multinodular goiter (Table 2). According to TBSRTC, 23 (6.3%) patients had category I, 79 (21.6%) had category II, 128 (35%) had category III, 113 (%30.9) had category IV, nine (3.8%) patients had category V and 14 (2.5%) had category VI cytology (Figure 1). HP examination revealed thyroid cancer in 65 (17.7%) patients. Papillary microcarcinoma was detected in 30 of 65 patients (8.2%) and papillary carcinoma in 34 patients (9.3%). Medullary thyroid cancer was seen in one (0.3%) patient. Of the remaining 301 patients, 290 (79.2%) had benign nodules, six (1.6%) had follicular adenoma and five (1.4%) had Hurthle cell adenoma. Table 3 shows the HP results of the patients divided into six categories according to TBSRTC after thyroidectomy. Thyroid cancer was found in six of 79 patients with benign cytology. Considering category II, V and VI, TBSRTC was found to have a sensitivity of 73.9% and a specificity of 96%. In addition, PPD was calculated as 73.9%, NPD was 92.4% and accuracy was 88.2%. The incidence of cancer was found to be higher in men compared to women (31.8% vs. 18.8%, $p=0.009$).

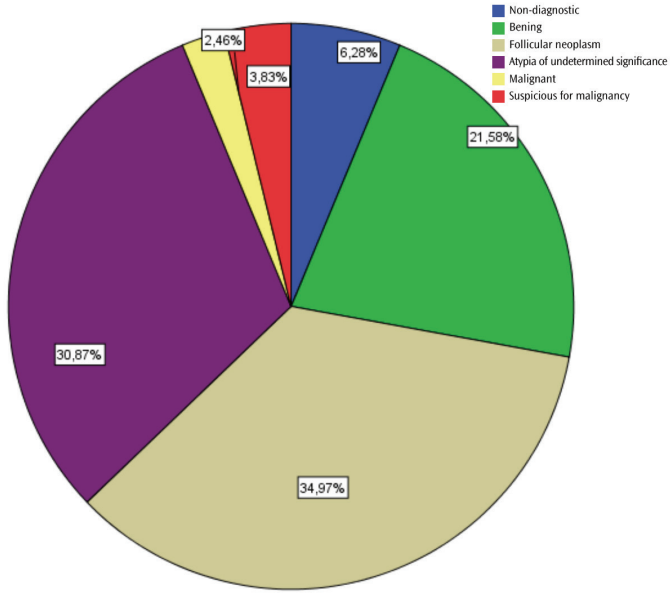

Figure 1. Distribution of FNAB results according to Bethesda criteria
FNAB: Fine needle aspiration biopsy

Table 1. The Bethesda System

Diagnostic category	Risk of malignancy (%)	Treatment recommendation
Non-diagnostic or unsatisfactory	1-4	Repeat fine needle aspiration biopsy
Benign	0-3	Follow-up
Atypia of undetermined significance/follicular lesion of undetermined significance	~5-15	Repeat fine needle aspiration biopsy
Follicular neoplasm	15-30	Lobectomy
Suspicious for malignancy	60-75	Lobectomy/near-total thyroidectomy
Malignant	97-99	Near-total thyroidectomy

There was no statistically significant difference between benign and malign HP groups in terms of nodule diameter, single nodule or multinodular goitre on US findings and age (p=0.097, p=0.267, p=0.863, respectively) (Table 4). According to FNAB results, when the patients in category III and IV were evaluated separately, male gender was found to be a risk factor for thyroid cancer in the category III group (p=0.015); no relationship was found between thyroid cancer and age, gender, nodule diameter and nodular/multinodular goiter in the category IV (Table 5).

Table 2. Distribution of patients according to age, gender, nodule diameter and ultrasonography results

Age: mean (min-max, SD)	50.47 (18-79, 13.073)
Gender	
Male (%)	44 (12%)
Female (%)	322 (88%)
Nodule diameter (mm): Mean (min-max, SD)	21.44 (4-65, 10.864)
Ultrasonography	
One nodule (%)	152 (41.5%)
Multinodular (%)	214 (58.5%)

DISCUSSION

In the last half century, as in all over the world, the incidence of thyroid cancer increases and mortality due to thyroid cancer decreases. The most important reason for the increase in the incidence of thyroid cancer is the development of diagnostic methods (5). Nowadays, the FNAB is widely used as the first-line diagnostic method in the management of thyroid

Table 3. Histopathological results of the patients categorized by the Bethesda System

	Histopathological results							
Bethesda category	**B**	**FA**	**HCA**	**PMC**	**PC**	**MTC**	**Total**	**Risk of malignancy (%)**
I	16	3	2	0	2	0	23	8
II	72	0	1	3	2	1	79	7.6
III	99	1	2	13	13	0	128	20.3
IV	97	2	0	9	5	0	113	12.3
V	3	0	0	2	4	0	9	66.6
VI	3	0	0	3	8	0	14	78.5

B: Benign, FA: Follicular adenoma, HCA: Hürthle cell adenoma, PMC: Papillary microcarcinoma, PC: Papillary carcinoma, MTC: Medullary thyroid carcinoma

Table 4. Comparison of patients divided according to histopathological results

	Benign	**Malign**	**p**
Age (mean, SD)	50.52 (13.025)	50.22 (13.389)	0.916
Gender			
Male: n (%)	30 (68.2)	14 (31.8)	**0.009**
Female: n (%)	271 (83.7)	51 (16.3)	
Nodule diameter: mm (mean, SD)	21.88 (10.858)	19.42 (10.743)	0.680
NG/MNG (%)	121/180 (33/49)	31/34 (8.4/9.2)	0.266

NG: Nodular goiter, MNG: Multinodular goiter, SD: Standard deviation

Table 5. Comparison of AUS and FN subgroups

	AUS			**FN**		
	Benign	**Malign**	**p**	**Benign**	**Malign**	**p**
Age (mean, SD)	49.24 (12.596)	53.69 (15.278)	0.082	49.79 (13.485)	46.79 (10.349)	0.230
Gender						
Male: n (%)	7 (54.9)	6 (46.1)	0.015	7 (70)	3 (30)	0.77
Female: n (%)	95 (82.7)	20 (17.3)		92 (89.4)	11 (10.6)	
Nodule diameter: mm (mean, SD)	21.21 (11.764)	20.77 (11.368)	0.442	20.30 (9.261)	17.29 (6.787)	0.129
NG/MNG (%)	43/59 (33.5/46)	12/14 (9.3/10.9)	0.713	39/60 (34.5/53)	8/6 (7/5.3)	0.207

AUS: Atypia of undetermined significance, FN: Follicular neoplasm, NG: Nodular goiter, MNG: Multinodular goiter, SD: Standard deviation

nodules according to US findings. The incidence of cancer after thyroidectomy has increased from 10-20% to 50%. Thanks to the FNAB, unnecessary surgeries and associated complications and cost decreased significantly (6). The widespread use of FNAB has brought along the need for standardization in the reporting of cytology results, for this purpose, TBSRTC was developed in 2007 and the cytology results were divided into six categories.

In order to accept the FNAB material sufficient for diagnosis, the material should consist of minimum 5-6 separate groups consisting of at least 10 follicular epithelial cells (4). In studies conducted, 89-95% of FNAB samples from thyroid nodules were reported to be sufficient for diagnosis. While 55-74% of the cytology examinations are reported as category I, category IV and V vary between 2-5% (7-10). Similar data were obtained in our study. In our series, 93.7% of the samples were sufficient for diagnosis and the rate of category IV-V was 6.2%. However, unlike other studies, category II rate was 21.5% in our study. The reason for this difference is the exclusion of category II patients who were not indicated for surgical treatment and inclusion of patients who underwent thyroidectomy only. The prevalence of cancer in category II cytology varies between 1-3.2% in large case series and meta-analyzes (11-16). In our study, preoperative cytology of 79 patients was reported as category II and six patients (6.32%) had thyroid cancer. In this group, cancer was detected in only one of 32 patients with single nodule and in five of 47 patients with multiple nodules. The cytological examination of the patients with multinodular goiter is taken from the dominant nodule and cancer is observed in non-dominant nodules in these patients. It is natural that the incompatibility with the literature is due to this reason. Regarding 32 patients with single nodules, the incidence of cancer is 3.1%, which is parallel to the literature.

The incidence of cancer in category 5 and category 6 cytology varies between 60-75% and 97-99%, respectively, in the original article in which TBSRTC was defined and in subsequent meta-analysis with a considerable number of cases (4, 8, 17). In our study, these rates were determined as 66.6% and 78.5%, respectively. In our cases, the incidence of cancer, especially in category VI cytology, is low compared to the literature. There may be two reasons for this difference: the experience of the pathologist in TBSRTC and the low number of cases. However, considering the accuracy of 88.6% when the categories II, V and VI are considered together, we believe that TBSRTC can be used safely in these categories. In the light of the information obtained from the guidelines, the general approach in category II cases is follow-up and surgical treatment in the presence of indications for surgery other than cancer. In contrast, the approach is surgical treatment in category V and VI. The main problem in clinical practice is category III and IV cases.

The definition “atypia of undetermined significance/follicular lesion of undetermined significance” is used for cytology specimens consisting of cells with unexpected structural and nuclear atypia in benign changes and with no risk other than that (18). This cytological description constitutes 1-27% of FNAB results (19). The cancer risk in Bethesda category III is reported to be between 5% and 15%, although many studies have reported that cancer rates vary between 17-39% (4, 20-27). In our study, the incidence of thyroid cancer was 20.3% in patients with category III cytology. In the American Thyroid Association guideline, considering the suspected clinical and sonographic characteristics, category III patients are advised to undergo repeat biopsy or molecular study instead of follow-up or diagnostic surgery (28).

In some studies, it has been suggested that core biopsy is more useful and tolerable than FNAB (29, 30). However, the American Association of Clinical Endocrinologists, the Italian Association of Clinical Endocrinologists and European Thyroid Association joint guideline concludes that core biopsy does not provide additional benefit but increases morbidity. Again in this guide, it is emphasized that malignancy criteria (head and neck radiation history, family history, <14->70 years, male gender, fixed nodule, fast growing nodule, etc.) have low predictive value and that there is yet not enough data to suggest that US elastography can be used routinely. In addition, it was emphasized that surgery should be considered primarily in these cases, considering that molecular tests are expensive and can be performed in only private centers (31). It has also been shown that some of the patients that underwent repeat FNAB and interpreted as benign had malignancy after resection (32). In these patients, it would be most appropriate to plan the treatment by a multidisciplinary council with a surgeon, medical endocrinologist, radiologist and cytopathologist with considering the opinion of the patients. Another category “follicular nodule/suspicious follicular nodule” constitute approximately 10-25% of all FNABs. In various studies, malignancy rates in category IV cases have been reported between 18-28% (9, 33-35). In our study, the rate of malignancy was lower than expected (12.3%).

In general, there are some differences between TBSRTC and our results. Among the reasons for these differences, the experience of the cytopathologist, FNAB method and the endemic nature of our region can be considered. When risk factor analysis

was performed, only male gender was found to be significant and other parameters were statistically insignificant. For the validation of TBSRTC, cohort studies with larger cases are needed in our region.

CONCLUSION

Thyroid FNAB has an important role in the management of thyroid nodules. Although TBSRTC is guiding, it may be incompatible with published studies. This difference is directly related to the experience of the pathologist, the method of FNAB and even the resources of the healthcare center. In conclusion, the clinician should act with other departments in the management of a thyroid nodule and should be in a patient-oriented multidisciplinary approach.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., Ö.B., K.Y., Concept: S.O., Ö.B., Design: S.O., K.Y., Data Collection or Processing: S.O., Ö.B., K.Y., Analysis or Interpretation: S.O., K.Y., Literature Search: S.O., Ö.B., K.Y., Writing: S.O., Ö.B.

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