

**PREOPERATIVE THYROID FINE NEEDLE ASPIRATION BIOPSY FINDINGS IN PATIENTS UNDERGOING TOTAL THYROIDECTOMY FOR NODULAR GOITER**

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**Abstract**

**Objective:** Our purpose was to retrospectively investigate the postoperative histopathological results of the 53 patients who underwent total thyroidectomy operation at our hospital and compare them to their preoperative ultrasound-guided fine-needle aspiration biopsy (TFNAB) results.

**Methods:** Surgical records of the patients were reviewed together with preoperative thyroid fine-needle aspiration cytology (TFNAC) results.

**Results:** The mean age ( $\pm$ SD) of 53 patients (12 males, 41 females) was  $50\pm 12.3$  years (min: 19, max: 77). Mean age was  $56.3\pm 12.8$  years (min: 34, max: 77) for males and  $48.1\pm 11.6$  years (min: 19, max: 69) for females ( $p=0.14$ ).

Preoperative TFNAC results of 53 patients were: 11, Bethesda-1; 9, Bethesda-2; 14, Bethesda-3; 13, Bethesda-4 and 6 were Bethesda-5, respectively. Postoperative pathology results of 53 patients were of 23, nodular goiter; of 24, thyroid papillar carcinoma; of 3, chronic lymphocytic thyroiditis; 2, follicular adenoma; 1, amiloidosis, respectively. The patients who were diagnosed as papillary thyroid carcinoma were determined malign; the others were determined as benign. So the ratio of malignancy of the patients who were operated was 45%.

The rate of malignancy was 30% for patients with TFNAC results indicating Bethesda-1 and Bethesda-2 which did not strongly suggest malignancy but who underwent total thyroidectomy on the basis of other clinical manifestations; for patients operated due to a higher probability of malignancy as suggested by TFNAC results indicating Bethesda-3 and above categories, the malignancy rate was 55%.

**Conclusion:** TFNAC results should be taken into account in addition to clinical and ultrasonographic features when considering surgery for such patients.

**Keywords:** Thyroid nodule, Thyroid cancer, Thyroid fine-needle aspiration biopsy.

## Introduction

Thyroid nodules can be detected by palpation in about %5 of the patients [1, 2], and higher detection rates, up to 60% and 70%, may be achieved with the use of ultrasound [3, 4]. At autopsy, 50% of the population is found to have a thyroid nodule [5]. While most of the thyroid nodules are generally benign, approximately 5-9% are malignant on histopathological examination [1-5]. A thyroid ultrasound scan is recommended in the evaluation of any suspected thyroid nodule detected during physical examination or by an imaging method [6, 7]. A thyroid ultrasound helps in assessment of the size and echogenicity of the thyroid tissue and provides information on several aspects of the thyroid nodule including its shape, size, echogenicity, margin regularity, blood flow as well as its elastosonographic features and the presence of any macro- or microcalcifications within the nodule; based on the US findings, it can be determined whether the nodule is benign or malignant [8-10]. Additionally, ultrasonography of the head and neck allows an assessment of the neck lymph nodes for metastases from thyroid cancers [11]. Thyroid cancer is the most common endocrine cancer but it occurs at a very low rate, accounting for only %1 of all malignancies [3, 12]. The annual incidence of thyroid cancer was reported at 3.5 per 100 000 in females and 1.3 per 100,000 in males in England and Wales [13]. Once a suspected thyroid nodule is detected by thyroid ultrasound, the first thing to do is cytological examination of the nodule in question by ultrasound-guided fine needle aspiration biopsy (UG-FNAB) [14]. Only in this way can a need for thyroid surgery or its type and scope be established for a patient. TFNAB is the primary diagnostic method for preoperative stratification of the malignant cases and for preventing

unnecessary surgical operations. According to some reports, annual rate of preoperatively diagnosed thyroid carcinoma increased from 24% to 56% owing to TFNAB [15]. Moreover, it was reported that TFNAB resulted in a decrease in the use of surgical procedures for all thyroid disorders from 61% to 14%, while increasing the percentage of diagnosed thyroid carcinoma cases from 8.3% to 37.3% [16].

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) is used for cytological evaluation of the thyroid tissue obtained by TFNAB [17]. The system divides FNA reports in six diagnostic categories: Bethesda-1: Non-diagnostic or insufficient, Bethesda-2: Benign, Bethesda-3: atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS), Bethesda-4: follicular neoplasm or suspicion for a follicular neoplasm (FN/SFN), Bethesda-5: suspicious for malignancy and Bethesda-6: Malignant. Estimated malignancy rates based on TFNAB results are 1-4% for Bethesda-1, 0-3% for Bethesda-2, %5-15 for Bethesda-3, 15-30% for Bethesda-4, 60-75% for Bethesda 5 and 97-99% for Bethesda-6. The rates of insufficient TFNAB as reported in the literature ranges between 10% and 28.2% [17].

In Tekirdag Government Hospital, the endocrinology outpatient clinic has been serving patients since 2013 where patients diagnosed with thyroid nodules are followed and decisions for thyroid surgery considered as per current guidelines for management of thyroid disorders. In the present study, we aimed to retrospectively review the results of TFNAB procedures performed within a period of 1 year for patients seen in the endocrinology outpatient clinic as well as preoperative TFNAC results for those patients who underwent total thyroidectomy at our hospital.

## Materials and Methods

**Subjects:** A total of 484 UE-TFNAC reports were reviewed retrospectively for 388 patients who were followed between September 2013 and September 2014 at the Tekirdag Government Hospital Endocrinology Outpatient Clinic. Among those with UG-TFNAB records, surgical reports were available for 53 patients who were operated at the Department of General Surgery of Tekirdag Government Hospital. These records were reviewed together with preoperative TFNAC results. The study protocol was prepared in accordance with the Helsinki Declaration and the written informed consent was obtained from all volunteers to use their personal data.

### Method:

When preoperative laboratory tests were retrospectively reviewed for 53 operated patients, thyroid function tests were found to be consistent with either euthyroidism or subclinical hyperthyroidism or subclinical hypothyroidism (data not shown). Thus, patients were not compared with respect to their thyroid function tests.

**UG-TFNAB procedure:** Before UG-TFNAB, informed and signed consent were obtained from all patients. After thyroid physical examination, the patient was kept in the supine position with hyperextension of the neck with a rolled pillow. The nodule is localized with a 10 MHz transducer prior to biopsy. The overlying skin is cleansed with iodine. Local anesthetic, lidocaine spray (Vemcaine® 10% pump spray) was routinely administered to the neck region of the skin. Sampling was carried out using a fine needle (caliber 22 Gauge), manual aspiration with a 5- 10 ml syringe. Once the needle was introduced into the solid part of the nodule, negative syringe pressure was applied. No serious complications were seen during the procedure. After aspiration, smear was placed on slides and air-dried.

Two to three slides from each patient were stained with Wright-Giemsa stain to confirm the presence of follicular cells. The slides were subsequently stained with May-Grünwald-Giemsa stain.

Additionally, pathological examination was performed for thyroid tissues obtained during total thyroidectomy and results were compared with preoperative TFNAC reports.

**Statistical analysis:** All statistical analysis were done by Statistical Package for Social Sciences (SPSS for Windows, version 15; Chicago; IL). The results are presented as mean, standard deviation (SD), minimum and maximum levels. Sensitivity, specificity, positive and negative predictive values for Bethesda category regarding to Bethesda-4, Bethesda-5 and Bethesda 4+5 reports were done.

### Results

Of 484 TFNAC results, 87 (18%) were reported as Bethesda-1, 325 (67%) as Bethesda-2, 26 (5.5%) as Bethesda-3, 20 (4%) as Bethesda-4 and 26 (5.5%) as Bethesda-5. Surgical records were reviewed together with preoperative TFNAB results for 53 patients who were operated at the Department of General Surgery of Tekirdag Government Hospital. The mean age ( $\pm$ SD) of 53 patients (12 males, 41 females) was  $50\pm 12.3$  years (min: 19, max: 77). Mean age was  $56.3\pm 12.8$  years (min: 34, max: 77) for males and  $48.1\pm 11.6$  years (min: 19, max: 69) for females with no significant age difference between sexes ( $p=0.14$ ). Preoperatively, 14 patients had nodules in the left thyroid lobe, 22 had nodules in the right lobe and 17 had bilateral thyroid and isthmus nodules. With respect to the longest diameter of the nodules, mean nodule diameter was  $26\pm 11.8$  mm (median 27; min: 10 max: 50). When preoperative TFNAB reports were reviewed on the basis of Bethesda classification, 11 were Bethesda-1

(insufficient), 9 were Bethesda-2 (benign), and 6 were Bethesda-5 (Table 1). 14 were Bethesda-3, 13 were Bethesda-4

**Table 1: Comparison of TFNAB and histological diagnoses among 53 subjects**

HISTOPATHOLOGICAL EXAMINATION						
TFNAB	BENIGN		MALIGNANT			TOTAL
			Tumor		Overall	
			≥ 1 cm	<1 cm		
Bethesda-1	8	3	0	3	11	
Bethesda-2	6	2	1	3	9	
Bethesda-3	9	1	4	5	14	
Bethesda-4	6	5	2	7	13	
Bethesda-5	0	4	2	6	6	
<b>TOTAL</b>	29	16	8	24	53	

For patients classified as Bethesda-3 and above, decision for surgical operation was taken due to suspicion for malignancy cytologically. Decision for surgery was considered due to having more than two insufficient TFNAB results for patients who were classified as Bethesda-1 and Bethesda-2 patients were operated due to the presence of multinodular goiter, enlarged nodules and/or an ultrasound examination of the thyroid gland demonstrating suspicious for malignancy findings.

When postoperative pathology results were reviewed, 23 were reported as nodular goiter, 24 as papillary thyroid carcinoma, 3 as chronic lymphocytic thyroiditis, 2 as follicular adenoma and 1 as amyloidosis. Those nodules diagnosed as papillary thyroid carcinoma were identified as malignant tumors and the remaining patients as benign tumors. The rate of malignancy among operated patients was 45%. Of 24 patients with malignant tumors, 6 were males and 18 were females and 6 males and 13 females had benign tumors. Mean ages ( $\pm$ SD) were  $51.1 \pm 14.3$  and  $49.3 \pm 10.3$  years for patients with malignant and benign tumors, respectively ( $p$  for difference=0.61).

When preoperative TFNAB results were examined for 24 patients diagnosed with papillary carcinoma, 3 were classified as Bethesda-1, 3 as Bethesda-2, 5 as Bethesda-3, 7 as Bethesda-4 and 6 as Bethesda-5. An examination for subtypes of papillary carcinoma revealed that 14 were reported as follicular variant of papillary carcinoma, 7 as classical variant of papillary carcinoma, 2 as oncocyctic variant of papillary carcinoma and 1 as diffuse sclerosing variant of papillary carcinoma. Of 24 thyroid papillary cancers, tumor diameter was less than 1 cm for 8 cases (papillary thyroid microcarcinoma) and more than 1 cm for 16 cases. Among 8 patients with papillary thyroid microcarcinoma, preoperative TFNAB results were reported as Bethesda-2 ( $n=1$ ), Bethesda-3 ( $n=4$ ), Bethesda-4 ( $n=2$ ) and Bethesda-5 ( $n=2$ ). Of 16 patients with a tumor diameter of more than 1 cm, preoperative TFNAB results were reported as Bethesda-1 ( $n=3$ ), Bethesda-2 ( $n=1$ ), Bethesda-3 ( $n=2$ ), Bethesda-4 ( $n=5$ ) and Bethesda-5 ( $n=4$ ) (Table 1).

Based on preoperative TFNAC results, it was found that papillary carcinoma was diagnosed in 3 of 11 patients classified as

Bethesda-1 (27%), 3 of 9 patients classified as Bethesda-2 (33%), 6 of 14 patients classified as Bethesda-3 (36%), 7 of 13 patients classified as Bethesda-4 (54%) and all 6 of 6 patients classified as Bethesda-5 (100%) (Table 1). Thyroid nodules were reported as malignant in 18 of 33 (55%) patients on the basis of TFNAC reports indicating Bethesda-3 or above tumors. Among operated patients, 6 of 20 patients (30%) with preoperative results indicating Bethesda-1 and 2 diagnoses were reported as having malignant tumors. Assuming that Bethesda 4 and above categories indicated a higher probability of malignancy, we divided patients into two groups. One group included patients classified as Bethesda 1-3 (benign) and the other included patients

classified as Bethesda-4 and above (malignant) and we observed that the frequency of papillary carcinoma was 11/34 (32%) in the former and 13/19 (68%) in the latter. When preoperative TFNAC reports and postoperative pathology reports were compared for Bethesda-4 patients with suspicious for malignancy findings, the sensitivity, specificity, positive predictive and negative predictive values for TFNAC were 29%, 79%, 54% and 58% respectively; the corresponding figures for Bethesda-5 were 25%, 100%, 100% and 62%, respectively. Assuming that Bethesda-4 and higher categories altogether indicated a suspicion for malignancy, the corresponding figures were 54%, 79%, 68% and 68% respectively (Table 2).

**Table 2: Comparison of preoperative Bethesda-4 and 5 FNAC results with postoperative pathology reports**

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
<b>Bethesda-4</b>	29%	79%	54%	58%
<b>Bethesda-5</b>	25%	100%	100%	62%
<b>Bethesda-4+5</b>	54%	79%	68%	68%

**Discussion**

TFNAB is considered the gold standard for preoperative assessment of thyroid nodules [18, 19]. For the assessment of thyroid nodules, TFNAB may provide more precise results and much higher sensitivity for the discrimination between malignant and benign thyroid nodules when used with thyroid ultrasound examination in addition to clinical and laboratory findings of patients.

The present study was a retrospective study; thus, we conducted an interpretation of data using hospital records from patients who underwent total thyroidectomy only. Detailed ultrasonographic characteristics of

these patients were not available in our hospital database. However, some fundamental data could be retrieved from patient history and surgical operation notes including the number of nodules and indications for surgery. Laboratory test results were unremarkable. Thus, we roughly divided patients into two groups on the basis of operative indication; one group consisted of those patients who underwent surgery based on their clinical and ultrasonographic features and the other included patients who were operated due to their TFNAC results. The rate of malignancy was 30% for patients with TFNAC results indicating Bethesda-1 and

Bethesda-2 which did not strongly suggest malignancy but who underwent total thyroidectomy on the basis of other clinical manifestations; for patients operated due to a higher probability of malignancy as suggested by TFNAC results indicating Bethesda-3 and above categories, the malignancy rate was 55%. This suggests that TFNAC results should be taken into account when considering surgery for such patients. Nevertheless, a malignancy rate of 30% as observed in 20 patients with TFNAC results indicating Bethesda-1 and Bethesda-2 diagnoses is quite high compared to that in general population. We think that such a high malignancy rate may be explained by the fact that a high risk of malignancy was considered as suggested by preoperative clinical and ultrasonographic features of the patients, although we do not have enough data to confirm this argument. This clearly indicates the need to document thyroidectomy indications in a more detailed way when total thyroidectomy is considered due to reasons other than TFNAC results suggesting malignancy. On the other hand, considering TFNAC results for all of our patients under follow-up, the frequency of Bethesda-1 (insufficiency) diagnoses in our cases was consistent with those reported in literature. Operative indications in our patients classified as Bethesda-1 included multinodular goiter, ambiguous ultrasonographic findings and insufficient results from repeated TFNAB procedures, all of which precluded exclusion of malignancy risk for these patients. Moreover, some patients had a combination of these findings.

A major limitation of the present study was the use of data from a small number of patients who underwent a surgical operation (thyroidectomy) within a period of 1 year. Fourteen patients with a TFNAC report indicating a Bethesda-3 nodule were

operated, 5 of who were diagnosed with thyroid papillary cancer. These 5 cases included 2 cases of follicular variant, 2 cases of classical variant and 1 case of oncocytic variant. In the current study, a high malignancy rate of 36% was found for Bethesda-3 patients with an estimated malignancy risk of 5% to 10% as indicated by a TFNAC report. However, Bethesda-3 category was indicated in TFNAC reports for 5.5% of all patients who underwent TFNAB. The malignancy rate that is proposed in literature for the heterogeneous group categorized as Bethesda-3 is below 7% [20]. The corresponding rate found in our facility is consistent with literature. Additionally, 36% malignancy rate in the 5.5% of the study sample represents the probability of thyroid papillary cancer in roughly 1.9% of all patients. Another interesting finding of our study was the high malignancy rates among operated patients with Bethesda-4 and Bethesda-5 TFNAC results (54% and 100%, respectively). This finding underscores the importance of TFNAB in determining preoperative malignancy risk. However, these percentages are considerably higher compared to those reported in literature for Bethesda-4 and Bethesda-5 (15-30% and 60-75%, respectively) [17]. Interpretation of Bethesda-4 findings is quite difficult because they suggest the presence of a follicular carcinoma and there is not any highly specific test available for follicular cancer [21-23]. In the present study, although preoperative TFNAC report indicated Bethesda-4 category, all malignant tumors were postoperatively found out to be papillary carcinoma rather than follicular carcinoma. Among 7 patients diagnosed with papillary cancer, 4 had follicular variants and 3 had classical variants. Similarly, difficulties involved in the preoperative diagnosis of follicular

carcinoma using Bethesda-4 category were mentioned in the literature [17, 22]. Possibly our patients with a diagnosis of Bethesda-4 could have been reported as Bethesda-5. Also, all Bethesda-5 cases were diagnosed with papillary carcinoma. At that point, when these findings are put in perspective we might say that evaluation of a limited number of thyroid follicular cells through TFNAB can preclude reaching a definitive diagnosis of malignancy. Maybe that is the reason we did not come across a TFNAC report indicating Bethesda-6 at our facility. In our hospital, surgery is considered for all patients who are classified as Bethesda-4, Bethesda-5 or Bethesda-6 by TFNAC results. Thus, a surgical decision made on the basis of a preoperative TFNAC result indicating Bethesda-5 did not have any unfavorable consequences for patients. However, subtotal thyroidectomy has been recommended in literature for patients classified as Bethesda-4 indicated by a TFNAC report when the nodule is unilateral [6, 24, and 25]. However, we chose to perform total thyroidectomy for patients classified as Bethesda-4 in consultation with endocrinology and general surgery departments since most of the tumors found in these patients were multinodular and we could not afford taking the risk of facing a papillary cancer due to technical difficulties involved in the discrimination between a malignant tumor and a benign one by TFNAC. Our decision proved to be true because the rate of papillary carcinoma in operated patients following a Bethesda-4 report was 54% (7/13 patients).

Similar to the assumption made for Bethesda-3, we might say that there is a probability of malignancy of 2.2% and 5.5% among patients classified as Bethesda-4 and Bethesda-5 in the entire population if we consider that Bethesda-4 and Bethesda-5 categories are reported in 4% and 5.5% of

all TFNAC reports and presume that malignancy rates which are comparable with ours are obtained postoperatively. However, this is only a deduction rather than a robust conclusion since it is based on a small number of patients undergoing total thyroidectomy.

As can be readily seen in **Table-2**, TFNAB showed a considerably high specificity and high positive predictive and negative predictive values particularly for patients diagnosed with Bethesda-5. Additionally, postoperative malignancy rate among patients with a preoperative TFNAC report indicating a Bethesda-4 or 5 diagnosis was much higher than the average rate reported in literature. This finding clearly shows that close coordination between endocrinology and general surgery departments while making a decision for total thyroidectomy resulted in successful postoperative outcomes.

In conclusion, the surgical success rate and prestige of a facility will definitely improve and workload will be reduced if surgical operations are performed for appropriate indications in that facility.

**Conflict of Interest:** None.

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Written informed consent was obtained from the patients for publication of their individual details in this manuscript. The consent form is held by the authors in the patients' clinical notes and is available for review by the Editor-in-Chief.

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