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Fine Needle Aspiration Biopsy Results in The Light of Thyroid Tissue Pathology

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Abstract

Introduction: Thyroid cancer is the most common endocrine gland malignancy and thyroid fine needle aspiration biopsy (TFNAB) is used for its detection. The aim of this study was to analyze the cytological detected malignancy, the factors affecting it and the compatibility of surgical tissue pathology.

Materials and Methods: Patients who underwent TFNAB in the Endocrinology Outpatient Clinic were retrospectively analyzed in terms of age, gender, TSH (Thyroid stimulating hormone) value, nodule size, localization, initial and rebiopsy results (Bethesta 2023), and malignancy as tissue pathology (papillary thyroid cancer, follicular thyroid cancer) and multinodularity in those who underwent thyroidectomy after TFNAB.

Results: The study was conducted with data from 631 patients. A positive correlation was found between age and nodule size (r:0.08, p=0.040). TSH was found significantly higher in patients with B IV, V, VI (suspicion of neoplasia, suspicion of malignancy, malignancy) and AUS (BIII) cytology than in those with benign cytology (p=0.012). With the contribution of rebiopsy, the total cytological malignancy (Bethesta V, VI) (n:46) rate was 7.29%. Of the 84 thyroidectomized patients with tissue pathology, 50 (59.5%) were malignant and 34 (40.5%) were benign. In patients with malignant tissue pathology, 39 (78%) had multinodular goiter (MNG) and 11 (22%) had single nodules (p=0.031). TFNAB specificity was 60%, Negative Predictive Value (NPV) was 75%, False Positive Rate (FPR) was 40%.

Conclusion: TSH level was found significantly higher in cases with B III and IV, V, VI cytology results compared to benign cytology, and multinodularity was found to be significantly higher in cases with thyroid cancer compared to those with solitary ones in postoperative tissue pathology. As a result of surgery the specificity and NPV for TFNAB were found to be low and FPR was high compared to the literature.

Key words: Thyroid nodule; thyroid fine needle aspiration biopsy; malignant.

Introduction

Thyroid cancer accounts for approximately 2% of all cancers diagnosed worldwide and 95% of all endocrine cancers. Recent reports describe a continuing increase in the incidence of thyroid cancer worldwide (1). The clinical significance of thyroid nodules is that 5%–15% are malignant (2). Numerous studies have shown a prevalence of 2%–6% by palpation, 9%–35% by ultrasound, and 8%–65% in autopsy data. Ultrasonography (USG) is the most accurate and cost-effective method for evaluating thyroid nodules (3). Determining the malignant potential of a thyroid nodule is crucial in the follow-up and treatment of the disease, and thyroid fine needle aspiration biopsy (TFNAB) is the most accurate technique to determine this (2). TFNAB is considered the most important diagnostic tool for thyroid lesions because it is a relatively safe, simple, and cost-effective method.

Sensitivity and specificity in TFNAB were found to be approximately 83% and 92%, respectively. However, the false negative rate has been reported between 1% and 21%. A false negative result may cause delay in thyroid cancer treatment. Therefore, repeat biopsy is often required during follow-up (4,5). This study aimed to analyse cytologically detected malignancy, factors affecting it, and compatibility with surgical tissue pathology.

Material and Method

Permission was obtained from the Van Yuzuncu Yil University, Faculty of Medicine, Medical Center Ethics Committee for our retrospective planned research. Hospital records of 631 patients aged between 18 and 80 who underwent TFNAB due to thyroid nodules at the Endocrinology Clinic of Van Yuzuncu Yil University, Faculty of Medicine between June 2017 and June 2018 were retrospectively reviewed. Age, gender, TSH value, nodule size (cm), localization (right lobe, left lobe, isthmus), first and repeat TFNAB pathology results, surgical pathological diagnosis of patients who underwent surgery and their multinodularity parameters were analyzed. Primary TFNAB pathology results and repeat TFNAB pathology results were classified according to the Bethesta

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Table 1: Risk of malignancy and treatment recommendation according to the 2023 Bethesta classification 3rd edition

	Nondiagnostic (Bethesta I)	Benign (BethestaII)	Atypia of undetermined significance (Bethesta III)	Suspicion of follicular neoplasia (BethestaIV)	Suspicious for malignancy (Bethesta V)	Malign (Bethesta VI)
Malignity risk rate (%)	5-20	2-7	13-30	23-34	67-83	97-100
Management	TFNAB Repetition	Clinical and ultrasound follow-up	TFNAB repetition, molecular testing, diagnostic lobectomy or follow-up	Molecular testing, diagnostic lobectomy	Molecular testing, lobectomy or total thyroidectomy	Lobectomy or total thyroidectomy

Table 2: Age, nodule size and TSH levels

		n	Mean ± St. Dev.	Minimum	Maximum	p
Age	Female	559	45.20±12.949	18	78	0.063
	Male	72	48.19±11.618	24	74	
	Total	631	45.55±12.831	18	78	
TSH (mU/l)	Female	559	1.384±1.515	0.0	2.0	0.054
	Male	72	1.030±0.966	0.0	6.3	
	Total	631	1.344±1.467	0.0	24.0	
Nodule size	Female	559	2.089±1.021	0.6	8.0	0.83
	Male	72	2.115±0.926	1.0	4.5	
	Total	631	2.092±1.010	0.6	8.0	

2023 system. Pathological diagnoses of patients who underwent surgery were divided into two groups as benign and malignant (6). (Table 1) TSH measurements are made by 3rd generation immunoradiometric (IRMA) method or immunochemiluminescence (ICMA) methods. Analytical and functional sensitivities of these methods are less than 0.01 mU/mL. mU/mL is used as the unit. TSH was studied in Van Yuzuncu Yil University, Medical Center Biochemistry Laboratory with ABOTT brand Architect Ci16200 autoanalyzer. Biopsies were performed with 0.7x32 mm black tip (22G) syringes. TFNAB was performed under USG guidance in Van Yuzuncu Yil Faculty of Medicine Endocrinology outpatient clinic and the biopsies were studied in Van Yuzuncu Yil University Faculty of Medicine Pathology Laboratory.

Ethical approval: This study was approved by the Ethical Committee of Van Yuzuncu Yil Univeristy with decision number 2019/11-10 on 5 July 2019.

Statistical analysis: Descriptive statistics for continuous variables among the features emphasized are expressed as Mean, Standard Deviation, Minimum and Maximum values, while for categorical variables they are expressed as number and percentage. In comparisons to be made according to categorical variables in terms of continuous variables; One-Way Analysis of Variance or Kruskal-Wallis analysis were used. Following the variance analysis, Duncan multiple comparison test was used to determine different groups. Pearson correlation coefficients were calculated to determine the relationship between continuous variables. Chi-square test was used to determine the relationship between categorical variables. In the calculations, the statistical significance level was taken as $p<0.05$ and SPSS (ver:20) statistical package program was used for the calculations.

Results

The study was conducted with data from 631 patients, 559 (88.6%) female and 72 (11.4%) male, aged 18-78, who underwent TFNAB. The mean age of the patients was 45.5±12.8, and when we grouped them as 18-50 and over 50, the frequency

of TFNAB was 63.4% between 18-50 years of age and 36.6% over 50 years of age. The mean nodule size was 2.1±1 cm and the mean TSH level was 1.34±1.46 mU/l. (Table 2) A significant positive correlation was found between age and nodule size (p: 0.040, r: +0.082).

Table 3: Comparison of biopsy pathology results according to gender

		Bx result							
		Nondiagnostic (Bethesta I)	Benign (BethestaII)	Atypia of undetermined significance (Bethesta III)	Suspicion of follicular neoplasia (Bethesta IV)	Suspicion of Hurthle cell neoplasia (Bethesta IV)	Suspicious for malignancy (Bethesta V)	Malign (BethestaVI)	Total
Female	Number	190	242	86	2	1	28	10	559
Male	Number	17	34	17	0	0	2	2	72
General	Number	207	276	103	2	1	30	12	631
	General%	32.8	43.7	16.3	0.3	0.2	4.8	1.9	100
				Chi-square: 6.346	p = 0.386				

Table 4: Descriptive statistics and comparison cytological results according to malignant (neoplasia suspicion, malignanat and suspicion), benign and atypia of undetermined significance pathology results

		n	Mean ± St. Dev.	Min.	Max.	p
Age	Benign	299	45.41 ±13.082	19	76	0.313
	AUS*	99	47.89 ±12.080	18	78	
	Bethesda IV,V,VI	49	42.59 ±12.441	19	68	
	Total	348	45.65 ±12.855	18	78	
Thyroid stimulating hormone (TSH)	Benign	299	1.196 ±1.0944	0.0	8.4	0.012
	AUS*	99	1.727 ±2.6196	0.0	24.0	
	Bethesda IV,V,VI	49	1.406 ±0.8397	0.0	3.3	
	Total	348	1.336 ±1.5593	0.0	24.0	
Nodule Size	Benign	299	2.069 ±0.9672	0.6	7.0	0.184
	AUS*	99	2.292 ±1.1916	0.8	8.0	
	Bethesda IV,V,VI	49	2.127 ±1.1802	1.0	8.0	
	Total	348	2.124 ±1.0465	0.6	8.0	

Anova ***** Atypia of undetermined significance

The first TFNAB cytology result was reported as 12 malignant (%1.9), 30 suspicious for malignancy (4.8%), 1 suspected Hurthle Cell Neoplasia (0.2%), 2 suspected Follicular Neoplasia (0.3), 103 Atypia of Undetermined Significance (AUS) (16.3%), 276 Benign (43.7%), 207 Nondiagnostic (32.8%). No relationship was found between gender and cytology result (p=0.380). 42 out of 631 (6.65%) patient cytology who received pathological diagnosis were in the Bethesta V, VI. 6.79 % (n: 38/559) of those were female and 8.9% (n: 4/72) were male. (Table 3) As a result of rebiopsy, 447 out of 631 patients (70.9%) received a pathological diagnosis, while 184 remained nondiagnostic (29.1%). Repeat biopsy was performed in 36 nondiagnostic and 26 AUS patients. Of the nondiagnostic patients, 23 were diagnosed, 1 malignant (B VI) and the others benign, while AUS was reported as 3 malignant (B VI) and 1 benign. Only rebiopsy could be performed in 17.39% of nondiagnostic cases and 63.8%were newly diagnosed. Accordingly, 43.5% of the rebiopsies (n: 62) were diagnosed. While a total of 71% of the patients were diagnosed, 3.8% were diagnosed as a result of rebiopsy. Of the 447 patients diagnosed, 390 were female and 57 were male. With the contribution of rebiopsy, the rate of Bethesta V and VI (suspicion of malignancy

and malignancy) rate increased to 7.29% (n: 46). Of the cytological diagnosed 45 (11.5%) out of 390 female patients were Bethesta IV, V, VI and 4 (7%) of the 57 male patients were at Bethesta V, VI. In total, 45 (91.8%) of the 49 patients diagnosed with Bethesta IV, V, VI were female and 4 (8.2%) were male. No statistically significant relationship was found between gender and malignancy (p=0.368). Of the 49 patients with B IV, V, VI nodules, 25 (51.0%) had nodules in the right lobe, 22 (44.9%) in the left lobe, and 2 (4.1%) in the isthmus. When the pathology results with and without B IV, V, VI were compared statistically with the nodule location, no significant difference was found between them (p=0.955). Of the 49 patients with B IV, V, VI, 45 (91.8%) received a diagnosis after a single biopsy, while 4 (8.2%) required more than one biopsy before receiving a final diagnosis. When those with multiple biopsies were compared with those with a single biopsy in terms of malignancy, no significant difference was found. For TSH, a statistically significant relationship was found between benign, group of B IV, V, VI and AUS (p=0.012), while no significant relationship was found with age and nodule size (Table 4).

Table 5: Comparison between Nodule Size Grouping and cytological neoplasia suspicion, malignancy and suspicion

			Nodule Size group			Total
			<2 cm	2-4cm	>4cm	
Maligniy	Not malignant	Number	206	173	19	398
		%	51.7	43.4	4	100
	Bethesda IV,V,VI	Number	26	21	2	49
		% in malignancies	*53.1	42.9	4.1	100
Total		Number	232	194	21	447
		General %	51.9	43.4	4.7	100

Chi-square:1.615 p=0.806

When malignancy was compared by grouping according to nodule size as <2 cm, 2 to 4 cm and >4 cm, no statistically significant difference was found (p=0.806). The highest malignancy rate was seen in nodules smaller than 2 cm (11.2% vs 10.8, 9.5%, respectively). (Table 5) In our center, the preoperative cytology results of 84 patients who underwent total thyroidectomy were 37 malignant (B V, VI), 26 AUS, suspicion of neoplasia (BIII, IV), 12 benign, and 9 nondiagnostic. Of the 9 patients whose TFNAB results were nondiagnostic, 3 were malignant (33%) in tissue pathology. Of the 26 patients whose TFNAB results were BIII, IV, 13 were malignant (50%). Of the 37 patients whose TFNAB results were malignant, 31 were malignant (83.7%) and 6 were benign (16.3%) in tissue pathology. Of the 12 patients whose TFNAB results were benign, 3 were diagnosed as malignant (25%) after surgery. After total thyroidectomy, 50 (59.5%) of the tissue pathology was reported as malignant and 34 (40.5%) as benign. Of the 50 patients diagnosed with malignant pathology, 39 (78%) were multinodular (MNG) and 11 (22%) were single nodules. Multinodularity was detected more in the group diagnosed surgically as malignant than in those diagnosed surgically as benign (p=0.031). (Table 6)

Table 6: Comparison of operated cases diagnosed as malignant and benign in terms of single nodule and multinodularity.

			Single nodule	Multi Nodular Goiter (MNG)	Total
Surgical outcome	Benign	Number	15	19	34
		Benign in %	%45	%55	
	Malign	Number	11	39	50
		Malign in %	%22	%78	
	Total	Number	26	58	84

Chi-Square:4.632 p=0.031

Table 7: Comparison of benign and malignant results with Thyroid FNAB and surgical pathology results.

	TFNAB Bethesta IV, V,VI	TFNAB benign	Total
Surgery malignant	31	3	34
Surgery benign	6	9	15
Total	37	12	49

The tissue pathologies and TFNAB results of the patients were divided into benign and malignant groups and compared. After excluding the suspicious cases (non-diagnostic and AUS) reported with TFNAB, the sensitivity in TFNAB was found to be 91.2%, specificity 60%, PPD 83.8%, NPV 75%, YNO 8%, YPO 40%. (Table 7)

Discussion

It is known that the frequency of thyroid nodules increases with age, and the sonographic frequency reaches 50% over the age of 50. In our country, the sonographic prevalence between the ages of 18-65 is 23.5%, while it has been determined that this frequency is 37.4% over the age of 65 (7). In the study conducted by Conradie et al., the median age of patients who underwent thyroid biopsy was reported as 50 (8). In our study, the mean age of patients with thyroid nodules who underwent TFNAB was 45.5±12.8, and it was detected more frequently between the ages of 18-50 with a rate of 63.4% compared to those over the age of 50.

In the literature, it is reported that thyroid nodules are 3-4 times more common in women than in men (9). However, in the study by Conradie et al., the number of women who underwent surgery based on cytology was 5 times more than men (8). Similarly, in our study, women who needed TFNAB were 7.7 times more than men. In the literature, the malignancy rate of patients who underwent thyroid aspiration biopsy varies between 5% and 15% (4,10,11). In our study, the rate of Bethesta V, VI as a result of TFNAB was determined as 7.29% when all pathology results were evaluated. This rate is consistent with the literature. The incidence of thyroid cancer in women is 3-4 times higher than in men (12,13). In our study, the number of women diagnosed with Bethesta IV, V, VI by TFNAB was 11.2 times higher than in men, but no significant relationship was found between gender and thyroid cancer.

Follicular thyroid cancer tends to occur in older people, with the mean age in most studies being greater than 50 years, or about 10 years older than for typical papillary thyroid cancer (14). In our study, no significant relationship was found between malignancy and age. Repeated biopsies are considered necessary to increase overall diagnostic accuracy (15). In the study by Li-Ying Huang et al., 61.6% of 276 thyroid cancer patients had a single aspiration biopsy before diagnosis, while 38.4% had more than one aspiration before cancer was diagnosed (4). In our study, 91.8% of 49 patients with TFNAB Bethesta IV, V, VI were diagnosed with one aspiration biopsy and 8.2% with more than one biopsy. The rebiopsy rate was found to be lower than in the literature. It has been reported in the literature that initial nondiagnostic (Bethesta I) TFNAB rates can be as high as 10%-20% and that when repeated aspiration is performed, up to 38% of the initial nondiagnostic nodules may remain undiagnosed (15). In our study, the nondiagnostic rate in the initial TFNAB was 32.8%, which is high compared to the literature. In the study of Conradie et al., this rate was 38%, similar to ours (8). With the rebiopsy performed in our cases, 11% of all nondiagnostic patients were diagnosed. This rate is lower than the literature. However, only rebiopsy could be performed in 17.39% of nondiagnostic cases and 63.8% were newly diagnosed. This may be related to distribution of nondiagnosed patients other centers and the experience of the person performing the procedure, the materials used, inappropriate target selection, and the fact that some lesions cannot be diagnosed with TFNAB (16). In one study, malignancy rates were reported as 11.4% and 11.9% in cases with nondiagnostic initial TFNAB cytology (17). In our cases, malignancy was detected in 3 of the 9 patients who underwent surgery and whose TFNAB results were nondiagnostic before the TFNAB (33%). Our malignancy rate is higher in nondiagnostic TFNABs compared to the surgical result. The low rebiopsy rate was also associated with a high rate of false negative results. Godazandeh et al. reported that there was no statistically significant relationship between nodule size and its nature (malignant/benign) (18). In our study, no statistically significant relationship was found between BIV, V, VI (suspicion of neoplasia, suspicion of malignancy and malignancy) and nodule size. However, the suspicion of neoplasia, malignancy and suspicion of malignancy rate was higher when the nodule size was <2 cm. The size of the nodule alone is not reliable in predicting malignancy, and other factors such as increased anteroposterior diameter, microcalcification, and irregular borders related to nodule character should be considered in medical decision-making (18). In general, it is reported that the probability of cancer is lower in patients with multinodular goiter (MNG) compared to those with single thyroid nodules, but recent studies have yielded contradictory results. Brito et al. reported in a meta-analysis that the probability of cancer is lower in patients with MNG compared to those with single thyroid nodules (19). Frates et al. described that the probability of cancer is independent of the number of nodules, and that the probability of cancer within a nodule decreases as the number of nodules increases (20). Rabal et al. showed that the malignancy rate is higher in single nodules compared to patients with MNG (21). Other studies report similar malignant disease incidence in patients with MNG and single nodules (22,23). In our study, in contradiction with the literature, MNG was significantly higher in patients with surgical malignancy (78%)

compared to those with solitary nodules (22%) (p=0.031). Accordingly, in our study, the rate of malignancy was found to be increased in patients with MNG. The relationship between serum TSH concentration and thyroid cancer is also a subject of study. TSH has been reported as an independent predictor of malignancy in thyroid nodules (24). While low TSH levels are a benign indicator in most cases, normal or high TSH levels are reported to indicate a possible malignant potential of the nodule (9). Even higher TSH levels have been associated with advanced thyroid cancer (25). Our study also showed a statistically significant positive relationship between TSH and suspicion of neoplasia, malignancy and suspicion of malignancy (p=0.012).

In different studies, the sensitivity of TFNAB is reported as 65-98%, specificity as 72-100%, positive predictive value (PPV) as 35-100%, negative predictive value (NPV) as 83-100%, false negative rate (FPR) as 0.4-21%, false positive rate (FPR) as 0-28% (4, 26-29). In our study, the sensitivity for TFNAB is 91.2% and specificity as 60%. Specificity is low compared to the literature. Again, PPV is 83.3%, NPV is 75% and NPV is also lower than the literature. When we compare in the same way, while FNR is similar at 8%, FPR is high at 40%. False negative thyroid results can delay thyroid cancer treatment and negatively affect the results (4). A high false positive rate can result in unnecessary surgery. The limited number of cases screened in this study can be criticized as a weakness. The results can be clarified more accurately with studies that include larger case series and longer follow-up.

Study limitations: The limited number of cases screened in this study can be criticized as a weakness. The results can be clarified more accurately with studies that include larger case series and longer follow-up.

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A statistically significant positive relationship was found between TSH and suspicion of neoplasia, suspicion of malignancy, malignancy (BIV, V, VI). The rate of reaching a result with rebiopsy is also low compared to the literature. Contrary to the literature, the postoperative malignancy rate was found to be higher in multinodular cases. In our study, specificity and NPV in TFNAB were low and FPR was high compared to the literature. Technique, experience-expertise at each stage, evaluation, improvement of communication between clinics regarding patient data and rebiopsy will improve all these rates.

Ethical approval: This study was approved by the Ethical Committee of Van Yuzuncu Yil Univeristy with decision number 2019/11-10 on 5 July 2019.

Conflict of interest: The authors declare no competing interests.

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