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Diagnostic accuracy and importance of Fine Needle Aspiration Cytology in the prediction of malignancy in thyroid nodules

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ABSTRACT

Objective: Since thyroid nodules have low malignant potential and thyroid cancers progress slowly, early diagnosis is important for a longer life expectancy. Fine needle aspiration (FNA) is a cost-effective method with an easy application, low complication rate and high diagnostic value. The aim of this study is to assess the diagnosis accuracy and prevalence of thyroid cancer by comparing the findings of FNA procedures performed in our center with definitive histopathology results of patients undergoing surgery after FNA and then comparing these results to the literature.

Materials and Methods: Cytology reports of 1040 patients who underwent thyroid FNA between January 2021 and October 2022 were retrospectively evaluated. Definitive histopathology results of 146 patients who underwent total or subtotal thyroidectomy were compared with preoperative FNA cytology results. Thyroid cytological results were classified according to the 2017 Bethesda system diagnostic categories.

Results: Cases with definitive histopathology results indicating malignancy accounted for 33.3% of non-diagnostic cases, 14.5% of benign, 18.5% of atypia or follicular lesion of undetermined significance (AUS)/FLUS, 33.3% of follicular neoplasm or suspected follicular neoplasm, 75.0% of suspected malignancy and 100% of malignant preoperative FNAC results. For malignant cases, FNA had a sensitivity of 47.5%, specificity of 98.1%, false-positive rate of 20.8%, false-negative rate of 17.2%, positive predictive value of 79.1%, negative predictive value of 82.8% and accuracy rate of 72.8%.

Conclusion: In this study, the prevalence of thyroid cancer exceeded the cancer rates predicted by the 2017 Bethesda classification. Thyroid cancer may be predicted by the follow-up of patients with solitary or multiple nodules without a surgical indication, and a repeat FNA when necessary.

Keywords: thyroid nodules, FNA, thyroid cancer

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INTRODUCTION

Thyroid nodules are given clinical attention when the patient notices or incidentally detected during a routine physical examination or a radiological examination such as carotid ultrasound (US), neck or thoracic computed tomography, magnetic resonance imaging and positron emission tomography scans. However, as non-palpable and palpable nodules of comparable sizes have similar risks of malignancy (1–4), patient history and physical examination, the serum thyroid stimulating hormone (TSH) level, thyroid and neck US and the presence of lymphadenopathy should be evaluated.

Nodules are selected for fine needle aspiration (FNA) based on the size of the nodule and the indication of malignancy by US findings. Suspicious US characteristics are good predictors of malignancy (4,5). Thyroid nodules are categorised according to the likelihood of malignancy in order to select the nodules to be examined by FNA. The American College of Radiology has proposed a system (Thyroid Imaging, Reporting and Data System [TIRADS]) for the selection of a nodule for FNA (6).

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According to this system, FNA should be performed on solid and hypoechoic nodules with a maximum diameter ≥1.5 cm and if one of the following sonographic characteristics is present on solid and hypoechoic nodules 1‑1.5 cm: irregular margins (≥1.5 cm), micro calcifications (≥1 cm), taller-than-wide on the transverse section (≥1 cm), macro calcifications (≥1.5 cm), peripheral (rim) calcifications (≥1.5 cm) and any combination of these (≥1 cm).

The results obtained from FNA are classified into six major categories, which inform the decision regarding the procedures in the next stage. The diagnostic categories of FNA results (Bethesda classification) (7) and cytological diagnoses are separately inspected and reported in detail. The risk of malignancy for nodules is defined as follows in the 2017 Bethesda system diagnostic: Class I: 5-10%, Class II: 0-3%, Class III: 6-18%, Class IV: 10-40%, Class V: 50-75%, and Class VI: 97-99% (7).

The goal of this study is to determine the diagnostic accuracy and prevalence of thyroid cancer by performing FNA at our center, comparing it to the definitive histopathology results in patients who underwent total or subtotal thyroidectomy after FNA, and then comparing these results with the existing literature.

MATERIAL and METHODs

Cytology reports of 1040 patients who presented to the Endocrinology Clinic of our institution and underwent thyroid FNA between January 2021 and October 2022 were retrospectively evaluated. FNA was performed under imaging guidance with ultrasonography using 23- to 27-gauge (usually 25-gauge) needles without local anesthesia. Definitive histopathological diagnoses of 146 patients who underwent total or subtotal thyroidectomy were compared with the preoperative FNA cytology results. Serum TSH levels of all patients were recorded in units of IU/ml before FNA. In 3 cases, whose first thyroid fine needle aspiration cytology result was evaluated as benign, repeat aspiration was performed due to the increase in diameter of the nodule as a result of ultrasonographic follow-up. Cytological classification was performed according to the 2017 Bethesda system diagnostic categories for reporting thyroid cytopathology: class I, non-diagnostic (unsatisfactory); class II, benign; class III, atypia of undetermined significance (AUS) or FLUS; class IV, follicular neoplasm (or suspicious for follicular neoplasm); class V, suspicious for malignancy and class VI, malignant.

Definitive histopathological results obtained after surgery included one of the following diagnoses: benign lesions, papillary micro carcinoma, papillary carcinoma, follicular thyroid carcinoma, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) or medullary thyroid carcinoma.

Patients younger than 18 years of age were excluded in this study.

Written consent form was obtained from all participants.

Statistical analysis: Data analysis was performed by using SPSS-26 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). To determine normal distribution, the variables were evaluated using visual (histograms, probability plot) and analytical methods (Kolmogorov–Smirnov test). The continuous variables were expressed as mean and standard deviation. The differences between qualitative/categorical variables, such as gender distribution between groups were compared with the chi-square test since the values observed in the cells provided assumptions. Cohen's kappa coefficient was used to assess the extent to which the FNA results agree with the definitive pathology results of thyroidectomy surgery.

A two-tailed test was performed with p-value <0.05, denoting statistical significance.

RESULTs

From 1040 patients in whom FNA was performed on solitary or multiple thyroid nodules, a total of 146 patients (29 men; mean age, 42.7 ± 11.0 years) who subsequently underwent total or subtotal thyroidectomy were included in this study. Of them, 65.8% (n = 96) were euthyroid. The rates of hyperthyroid and hypothyroid patients according to TSH levels are summarised in Table 1. According to US results, 80.1% of the patients were multi-nodular and most commonly bilateral (76.7%). In all included patients, the maximum diameter of the nodule in those with solitary nodules and that of the dominant nodule in those with multiple nodules was ≥ 10 mm. Total thyroidectomy was the most frequently used surgical method (86.3%, n = 126) (**Table 1**).

Table 1. Demographic and clinical characteristics of the patients.

	Results (n = 146)
Age, years	42.7 ± 11.0
Gender, M/F, n (%)	29/117 (19.9/80.1)
TSH, IU/ml, n (%)	
<0,1	19 (13.0)
0,1–0,56	27 (18.5)
0,57–5,6	96 (65.8)
≥5,7	4 (2.7)
Number of nodules, n (%)	
Solitary nodule	29 (19.9)
Multi-nodular	117 (80.1)
Nodule location	
Right	19 (13.0)
Left	13 (8.9)
Bilaterally	112 (76.7)
Isthmus	1 (0.7)
Isthmus+right	1 (0.7)
Maximum diameter of dominant nodule, n (%)	
≥1 cm	146 (100)
Type of operation, n (%)	
Total thyroidectomy	126 (86.3)
lobectomy+isthmectomy	20 (13.7)

FNA was performed on the dominant nodule in all patients. Majority of the patients (56.8%) were benign, while none (6.2%) were malignant. Subsequently, 10 patients underwent a repeat FNA. Of the three non-diagnostic results obtained in the first FNA, one remained non-diagnostic, while one was shifted to AUS/FLUS and the other to malignant cytology. Patients with benign biopsy results remained benign after FNA. Of the six aspirations reported as AUS/FLUS, three remained as AUS/FLUS, while two changed to benign and one to suspected malignancy (**Table 2**).

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Table 2. Aspiration cytology and definitive pathology results.

	Results (n = 146)
Fine needle cytology result of the dominant nodule, n (%)	
Non-diagnostic or unsatisfactory	12 (8.2)
Benign	83 (56.8)
AUS/FLUS	27 (18.5)
Follicular neoplasm or suspicious for a follicular neoplasm	3 (2.1)
Suspicious for malignancy	12 (8.2)
Malignant	9 (6.2)
Repeat aspiration cytology results, n (for 10 patients)	
Non-diagnostic or unsatisfactory	1
Benign	3
AUS/FLUS	4
Follicular neoplasm or suspicious for a follicular neoplasm	1
Malignant	1
Definite pathological result, n (%)	
Benign lesions	106 (72.6)
Papillary micro carcinoma	15 (10.3)
Papillary carcinoma	20 (13.7)
Follicular thyroid carcinoma	1 (0.7)
NIFTP	2 (1.4)
Medullary thyroid carcinoma	2 (1.4)

Abbreviations: AUS/FLUS, Atypia of undetermined significance or follicular lesion of undetermined significance; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features.

Table 3. Demonstrating the diagnostic value obtained by comparing the fine needle aspiration results with the definitive pathology results.

	N = 146
FNR	17.2%
FPR	20.8%
Sensitivity	47.5%
Specificity	98.1%
PPV	79.1%
NPV	82.8%
Accuracy	72.8%
κ	0.11
p-Value	<0.001

Abbreviations: FNR, false-negative rate; FPR, false-positive rate; PPV, positive predictive value; NPV, negative predictive value; κ, Cohen's kappa coefficient.

For malignant cases, thyroid FNA cytology had a sensitivity of 47.5%, specificity of 98.1%, false-positive rate of 20.8%, false-negative rate of 17.2%, positive predictive value of 79.1%, negative predictive value of 82.8% and accuracy rate of 72.8% (**Table 3**).

Definitive pathology results obtained via surgery were compared with the results with a significant difference. Of the cases with definitive histopathology results indicating malignancy, 4/12 (33.3%) were non-diagnostic, 12/83 (14.5%) were benign, 5/27 (18.5%) were AUS/FLUS, 1/3 (33.3%) were follicular neoplasm or suspected follicular neoplasm, 9/12 (75.0%) were suspected malignancy and 9/9 (100%) were malignant ($p < 0.001$) (**Figure 1**). According to post-hoc analysis, cases with malignant cytology or suspected malignancy were similar in terms of results and cases with follicular neoplasm, but different from the others. Those with follicular neoplasm were not significantly different from any of the groups (due to low number of cases).

The incidence of cancer in patients with solitary nodules and those with multi-nodular goiter was 41.4% (n = 12/29) and 23.9% (n = 28/117), respectively, with no significant difference ($p = 0.059$). After grouping the patients based on TSH levels, malignancy rates were compared: 3/4 (75%) of patients with TSH >5.6 IU/mL, 32/96 (33.3%) of patients with TSH = 0.56–5.6 IU/mL, 3/27 (11.1%) of patients with TSH = 0.1–0.56 IU/mL and 2/19 (10.5%) of patients with TSH <0.1 IU/mL; the first two groups had significantly higher rates than the others ($p = 0.006$) (**Figure 2**).

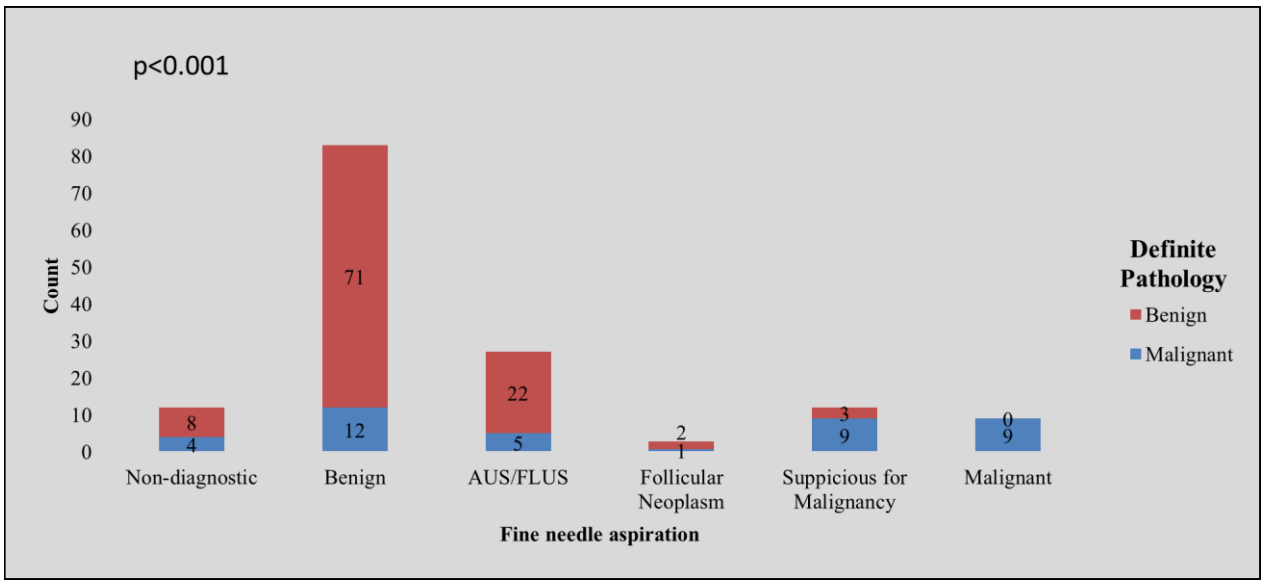

Figure 1. Comparison of definitive pathology results according to the results of aspiration cytology.

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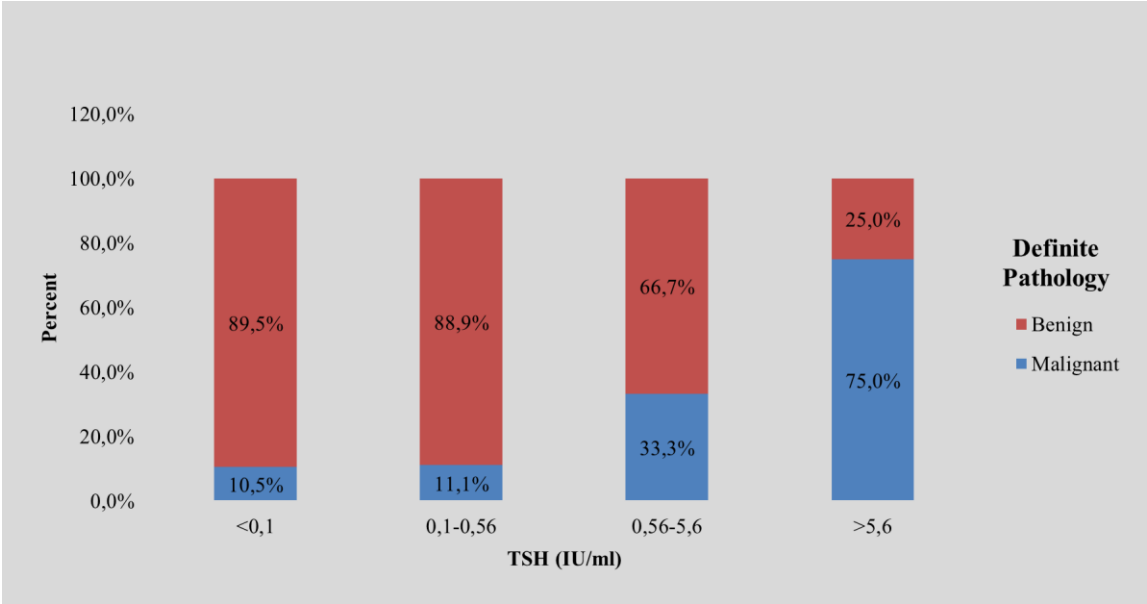

Figure 2. Comparison of definitive pathology results according to serum TSH levels.

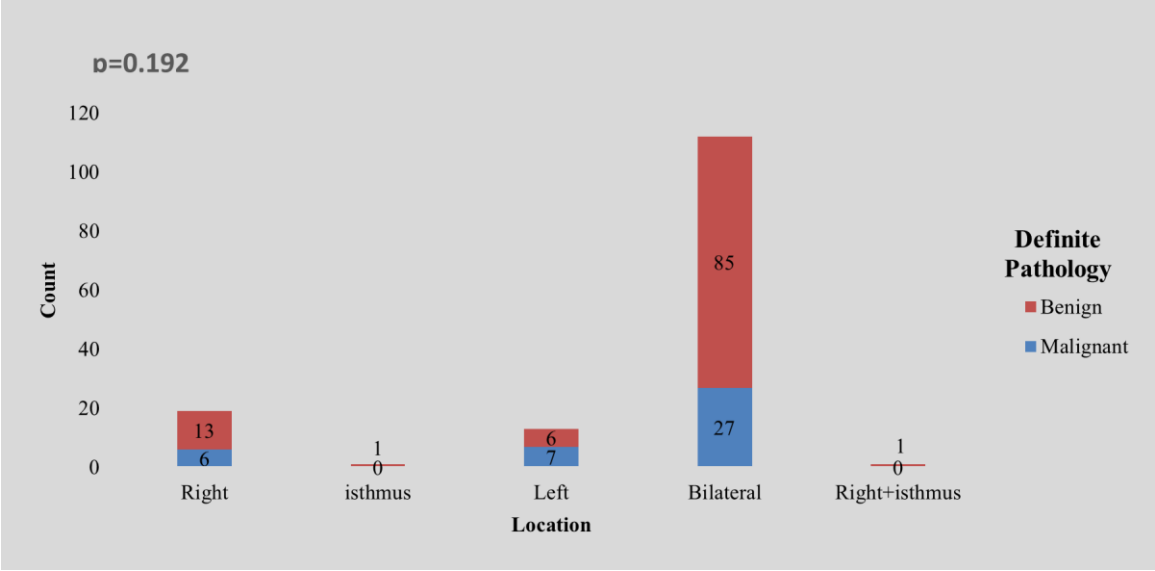

Figure 3. Pathological results according to nodule location.

Table 4. Comparison of results of the present study and previous studies

Study	Year	Number of patients	Sensitivity	Specificity	Accuracy	Negative predictive value	Positive predictive value
Cusick et al. (18)	1990	283	76	58	69	64	72
Afroze et al. (19)	2002	170	61.9	99.31	94.58	94.74	92.86
Ko et al. (20)	2003	207	78.4	98.2	84.4	66.3	99
Al-Hureibi et al. (21)	2003	196	38	89.9	72	73.2	66.7
Kessler et al. (22)	2005	170	79	98.5	87	76.6	98.7
Mahar et al. (23)	2006	125	98	70	91	93	91
Haberal et al. (24)	2009	260	92.6	91.6	91.9	96.5	83.5
Muratli et al (12)	2013	126	87.1	64.8	77.3	79.5	76.1
Present study	2022	146	47.5	98.1	72.8	82.8	79.1

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DISCUSSION

The prevalence of thyroid cancer in this study was higher than predicted by the 2017 Bethesda classification. When cases were classified based on serum TSH levels, the prevalence of malignancy was higher in those with a TSH level > 5.6 IU/mL, and this finding was consistent with the literature.

Thyroid nodules constitute a common global clinical problem. Epidemiological studies have shown that palpable thyroid nodules are detected in approximately 5% and 1% of women and men, respectively, living in iodine-sufficient areas of the world (8). Meanwhile, thyroid nodules were detected in 19–68% of randomly selected individuals who were examined by high-resolution US, with higher rates in women and the elderly (9,10).

Since thyroid nodules have low malignant potential and thyroid cancers progress slowly, early diagnosis is important for a longer life expectancy.

FNA can be easily performed and is cost-effective with a low complication rate and high diagnostic value. Currently, FNA is the preferred diagnostic method in the initial stage of assessing thyroid nodules (11).

According to the 2017 Bethesda system diagnostic, the risk of malignancy for nodules is defined as follows: 5–10% for class I, 0–3% for class II, 6–18% for class III, 10–40% for class IV, 50–75% for class V and 97–99% for class VI (7).

In this study, definitive histopathology results indicating malignancy were found in 33.3% of non-diagnostic cases, 14.5% of benign cases, 18.5% of AUS/FLUS cases, 33.3% of follicular neoplasm or suspected follicular neoplasm cases, 75.0% of suspected malignancy cases and 100% of malignant cases with preoperative FNA results; the higher malignancy rates were obtained in almost all categories compared to the rates predicted by the Bethesda classification.

This may be attributed to the fact that FNA was evaluated by different pathologists, or the actual malignancy rates are higher than those predicted by the 2017 Bethesda classification. Since most of the patients in this study had multiple nodules and not all nodules could be examined with FNA, it seems reasonable to consider broader surgical indications, given that not all nodules in patients with multiple nodules were examined via FNA.

The sensitivity, specificity, positive predictive value, and negative predictive value of thyroid FNA in malignant cases vary from 38% to 98%, 64.6% to 99.31%, 66.7% to 92.86%, and 64% to 96.5%, respectively (**Table 4**) (12). In the present study, these values were determined as 47.5%, 98.1%, 79.1% and 82.8%, respectively, which were moderately consistent with the literature. Thus, the lower sensitivity may be attributed to the fact that thyroid FNA cytologies were not evaluated by the same pathologist or that nodules other than those assessed by aspiration were malignant, as not all nodules were evaluated with aspiration in patients with multiple nodules.

Follicular epithelial-derived thyroid cancers are divided into three categories: papillary cancer (85%), follicular cancer (12%) and anaplastic cancer (3%). Papillary and follicular cancers are distinct cancer types and are typically treated in a similar manner, despite their several biological differences. Most anaplastic (undifferentiated) cancers arise from differentiated cancers.

Other malignancies of the thyroid include medullary thyroid cancer (MTC) (may be familial as a component of the multiple endocrine neoplasia type 2 [MEN2] syndrome or may be found as isolated familial MTC) and primary thyroid lymphoma. Breast cancer, colon cancer, renal cancer and malignant melanoma metastasise to the thyroid.

In a study that evaluated the histopathological data of 117 patients who underwent thyroid surgery, the prevalence of thyroid cancer increased by year and varies between 12.5% and 37.0% (13)

In the present study, when evaluated for a follicular epithelium origin, the subclasses of thyroid cancer were determined as papillary micro carcinoma (39.4%), papillary carcinoma (52.6%), follicular thyroid carcinoma (2.6%) and NIFTP (5.2%); there were no cases of anaplastic cancer. MTC accounted for 5.0% of all cases of thyroid cancer. The prevalence of thyroid cancer was 27.3% based on definitive histopathology, which is consistent with data from the literature. Hence, the absence of anaplastic (undifferentiated) thyroid cancer, thyroid lymphoma and metastasis to thyroid cancer were associated with the low number of cases.

The serum TSH level is an independent risk factor for predicting malignancy in patients with thyroid nodules. In a study conducted with 1500 patients, the prevalence rates of malignancy in patients with serum TSH concentrations <0.4 mU/L, 0.4–0.9 mU/L, 1–1.7 mU/L, 1.8–5.5 mU/L and >5.5 mU/L were 2.8%, 3.7%, 8.3%, 12.3% and 29.7%, respectively (14).

Other studies have shown that high serum TSH levels in cancer diagnosis aressociated with a more advanced cancer stage (15,16). In the present study, the prevalence of malignancy was 75% in TSH >5.6 IU/mL, 33.3% in TSH = 0.56–5.6 IU/mL, 11.1% in TSH = 0.1–0.56 IU/mL and 10.5% in TSH <0.1 IU/mL, demonstrating consistency with the literature with a higher overall cancer prevalence. Our findings suggest that the higher prevalence rates are attributable to papillary micro carcinoma.

Patients with multiple thyroid nodules and those with solitary nodules have an equal risk of malignancy (5,17). The American Thyroid Association Management Guidelines recommend that each nodule >1 cm is evaluated with regard to FNA criteria due to an independent risk for malignancy (8). In the present study, the comparison between patients with solitary and multiple nodules did not show a significant difference, which is also consistent with the literature.

CONCLUSION

In this study, the prevalence of thyroid cancer was higher than the rates predicted using the 2017 Bethesda classification. Thyroid cancer may be prevented by follow-up of patients with solitary or multiple nodules without surgical indication and a repeat FNAC when necessary. Multi-centre, prospective studies should include more cases and also consider scintigraphic data for patients with hyperthyroidism.

Limitations: The limitations of this study were its single-centre and retrospective nature, the evaluation of FNACs by different pathologists, the low number of cases and the evaluation of definitive histopathology by different pathologists. More cases included in multi-center prospective trials, evaluation of thyroid fine needle aspiration cytology by the same cytopathologist, and analysis of materials in patients undergoing surgery by the same pathologist may reduce the mistake rate.

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Author Contributions: HA, RD: designed and directed the study. Data collection, analysis and interpretation of results **HA:** wrote the final draft of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study. This study was approved by the Research Ethics Committee of Batman Training and Research Hospital, Batman, Turkey (Decision: 326/28.11.2022). All methods applied were carried out in accordance with the relevant rules and regulations.

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