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Evaluation of clinical, biohumoral, and morphological findings of the thyroid gland as possible predictors of risk for cancer in patients with atoxic nodular and multinodular goiter

Evaluacija kliničkih, biohumoralnih i morfoloških nalaza tiroidne žlezde kao mogućih prediktora rizika od karcinoma kod bolesnika sa atoksičnom nodoznom i multinodoznom strumom

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Abstract

Background/Aim. Thyroid nodules are usually asymptomatic and may occur in 68% of the general population. In most cases, they are discovered incidentally. As malignancy is proven in 10–15% of cases, a rational diagnostic approach is necessary. The aim of this retrospective study was to examine and grade different characteristics of patients with nodular and multinodular atoxic goiter in order to identify the potential predictors for the assessment of thyroid cancer risk. **Methods**. The study included 275 patients with nodular and multinodular atoxic goiter hospitalized at the Clinic for Endocrinology of the Military Medical Academy, Belgrade, Serbia, from January 1, 2017, to October 1, 2022, for preoperative preparation. The most relevant clinical, biohumoral, and pathomorphological characteristics were analyzed. **Results.** Patients with multiple thyroid nodules were older (57.21 ± 13.16 vs. 49.36 ± 15.83 years, $p < 0.001$) and had higher body mass index (29.12 kg/m^2 vs. 26.50 kg/m^2, $p = 0.004$) compared to patients with one nodule. On the other hand, patients with one thyroid nodule had a higher level of the thyroid-stimulating hormone than patients with multiple nodules (1.73 mIU/L vs. 1.21 mIU/L, $p < 0.0001$). Comparison of patients with and without proven thyroid cancer has shown a highly significant association between the higher categories of Bethesda classification and the presence of cancer (Bethesda IV–VI vs. Bethesda II–III, 52.2% vs. 22.3%, respectively, $p = 0.002$). **Conclusion**. Considering all the observed parameters, the cytological finding of fine needle aspiration biopsy emerged as the only one with predictive relevance for assessing thyroid cancer risk.

Key words:
biopsy, fine needle; goiter; neoplasm staging; thyroid neoplasms; thyroid nodule.

Apstrakt

Uvod/Cilj. Nodusi tiroidne žlezde (TŽ) su najčešće asimptomatski i mogu se naći u 68% opšte populacije. U većini slučajeva otkrivaju se slučajno. S obzirom na to da u 10–15% slučajeva bude dokazan malignitet, neophodan je racionalan dijagnostički pristup. Cilj ove retrospektivne studije bio je da se ispitaju i rangiraju različite karakteristike bolesnika sa nodoznom i polinodoznom atoksičnom strumom radi identifikacije faktora od prediktivnog značaja za procenu rizika od postojanja karcinoma TŽ. **Metode**. U studiju je bilo uključeno 275 bolesnika sa nodoznom i polinodoznom atoksičnom strumom, koji su bili hospitalizovani u Klinici za endokrinologiju Vojnomedicinske akademije, Beograd, Srbija, u periodu od 01. januara 2017. godine do 01. oktobra 2022. godine, radi pripreme za hirurško lečenje. Analizirane su najznačajnije kliničke, biohumoralne i patomorfološke karakteristike. **Rezultati.** Bolesnici sa više nodusa u TŽ bili su stariji (57,21 ± 13,16 godina vs. 49,36 ± 15,83 godina, $p < 0,001$) i imali su viši indeks telesne mase (29,12 kg/m^2 vs. 26,50 kg/m^2, $p = 0,004$) u poređenju sa bolesnicima sa jednim nodusom. Nasuprot tome, bolesnici sa jednim nodusom u TŽ imali su viši nivo tireostimulišućeg hormona u odnosu

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na bolesnike sa dva i više nodusa (1,73 mIU/L vs. 1,21 mIU/L, $p < 0,0001$). Rezultati poređenja bolesnika sa i bez dokazanog karcinoma TŽ pokazali su da postoji značajna povezanost između viših kategorija Bethesda klasifikacije i pojave karcinoma (Bethesda IV–VI 52,2% vs. Bethesda II–III 22,3%, $p = 0,002$). **Zaključak.** Od svih posmatranih parametara citološki nalaz aspiracione biopsije tankom iglom izdvojio se kao jedini sa prediktivnim značajem za postojanje karcinoma TŽ.

Ključne reči:
biopsija tankom iglom; gušavost; neoplazme, određivanje stadijuma; tireoidna žlezda, neoplazme; tireoidni nodusi.

Introduction

Thyroid nodules are usually asymptomatic and may occur in 68% of the general population [1]. In most cases, they are discovered incidentally during diagnostic procedures that are not primarily targeted at the thyroid gland. Since malignancy is proven in 10–15% of cases [2], a rational diagnostic approach is needed. The evaluation of patients with thyroid nodules comprises case history, clinical examination, biohumoral testing, ultrasound (US) examination, and fine needle aspiration biopsy (FNAB). The clinical examination includes the assessment of the number and size of nodules, their consistency, mobility during swallowing, pain on palpation, and the presence of enlarged lymph nodes on the neck. Biohumoral testing includes the measurement of thyroid-stimulating hormone (TSH). TSH values below the lower reference threshold represent an indication for thyroid scintigraphy with Iodine-123, -131 (I-123, I-131) or Technetium -99m, as pertechnetate, in order to assess the functionality of the nodule ("hot nodule", functional adenoma). Considering the low incidence of medullary carcinoma and, at the same time, not ignoring its malignant potential and often falsely elevated calcitonin values, there is still a debate regarding routine calcitonin measurement in patients with newly discovered thyroid nodule [3]. The simplest, most accessible, and most informative radiological method for the visualization of a thyroid nodule is the US examination. US characteristics that indicate the benign nature of the nodule comprise a cystic appearance, iso- or hyperechoicity, clear boundaries, and a "halo" surrounding a nodule. On the other hand, the US findings of a hypoechoic nodule with vague boundaries, microcalcifications, dominant solid component, increased vascularization, pathologically altered neck lymph nodes, as well as the elastographic "solid" nodules are signs of suspected malignancy [4]. These characteristics imply the necessity of FNAB of the suspected nodule. In order to standardize the US findings and adequately assess the cancer risk, the Thyroid Imaging, Reporting and Data System (TI-RADS) was adopted. TI-RADS takes into account the composition, shape, edges, echogenicity, and presence of echogenic focuses [5]. The cytological findings are classified according to the last, third version of Bethesda classification published in 2023 [6]. In patients whose cytological findings indicate a benign lesion, clinical and US monitoring is indicated. The latest version of the Bethesda classification emphasizes the relevance of molecular testing in cases where cytological findings correspond to categories III-VI [7]. In order to preoperatively assess the risk of cancer and avoid unnecessary surgical treatment in patients with cytological findings of the Bethesda III category, it is necessary to consider molecular testing [8, 9]. Bethesda IV-VI categories are indicated for surgical treatment in order to make a definite pathohistological verification. In patients with Bethesda V and VI categories, molecular testing may help decide the extent of surgery [10]. Considerable compressive symptoms are also an indication for surgical treatment, regardless of the cytological findings [11]. The aim of this retrospective study was to examine and grade the clinical and biohumoral characteristics and morphological features of the thyroid gland in patients with nodular and multinodular atoxic goiter in order to identify the possible predictors for the assessment of thyroid cancer risk.

Methods

This retrospective study included 275 patients with nodular and multinodular atoxic goiter hospitalized at the Clinic for Endocrinology of the Military Medical Academy (MMA), Belgrade, Serbia, from January 1, 2017, to October 1, 2022, for preoperative preparation. The ethical principles for medical research involving human subjects stipulated in the Declaration of Helsinki (1964) and subsequent amendments of the declaration were applied. Indication for surgical treatment was established on the cytological findings, ultrasonographic features of the nodule extremely suspicious for malignant lesion, or on the presence of pronounced compressive symptoms.

The distinctive patients' epidemiological and clinical features comprised gender and age, body mass index, presence of compressive symptoms, smoking status, presence of comorbidities, family history of thyroid diseases, previously diagnosed primary hypothyroidism, and primary hyperparathyroidism. The analyzed biohumoral parameters included the concentration of thyroid stimulating hormone (TSH), thyroglobulin, calcitonin and thyroid-specific antibodies (Abs) – thyroid peroxidase (TPO) Abs and thyroglobulin (Tg) Abs. Most patients underwent FNAB, and the cytological findings were interpreted by cytologists specializing in the thyroid gland. The cytological findings were classified according to the Bethesda classification.

The pathohistological findings were interpreted by an experienced pathologist in the field of thyroid pathohistology and classified according to World Health Organization classification. The tumor stage was established according to TNM classification for malignancies, which

includes the size of the tumor (T), the extent to lymph nodes (N), and the presence of metastasis (M).

Data were presented as mean ± standard deviation or median with interquartile range, where appropriate. The between-the-group difference was calculated using the Chi-square test, Student's *t*-test for independent samples, and Mann-Whitney *U* test, where appropriate. All tests were performed as two-tailed, and a *p*-value of < 0.05 was considered statistically significant. Data analysis was performed in the statistical software package SPSS, version 25 (IBM Corporation, Armonk, NY, USA).

Results

The study included 275 patients with an average age of 54.2 ± 14.7 years, 196 (71.3%) women and 79 (28.7%) men. A total of 105 (38.2%) patients had one nodule, and 170 (62.8%) patients had two or multiple nodules, of which 48 (17.4%) had two nodules, and 122 (44.4%) had more than two nodules. FNAB was performed with 202 (73.5%) patients. Total thyroidectomy was done in 267 (97.1%) and lobectomy in 8 (2.9%) patients. The pathohistological findings indicated the benign nature of the nodules in 118 (42.9%) patients, whereas cancer was proven in the remaining 157 (57.1%) patients. Demographic and clinical characteristics and cytological and pathohistological findings of the thyroid gland of all patients are given in Tables 1 and 2.

The results obtained from comparing patients with one and two or more nodules are presented in Table 3. Gender, smoking status, Tg values, TPO Abs, Tg Abs, FNAB cytological findings, and pathohistological findings did not differ significantly between the two groups. On the other hand, patients with two or more nodules were significantly older than patients with one nodule (57.2 ± 13.1 years vs. 49.4 ± 15.8 years, $p < 0.001$) and had a significantly higher body mass index (29.1 kg/m^2 vs. 26.5 kg/m^2, $p = 0.004$). Multinodular goiter occurred significantly more often in patients older than 50 ($p < 0.001$). On the other hand, patients with one nodule had a significantly higher TSH level compared with the patients with multinodular goiter (1.73 mUI/L vs. 1.21 mUI/L, $p < 0.001$).

In an additional analysis, we compared patients with and without proven thyroid cancer (Table 4). Age, gender, smoking status, body mass index, TSH, TPO Abs, Tg Abs, Tg, number of nodules, and dimensions of the dominant nodule did not differ significantly between these two groups.

Table 1

Demographic and clinical characteristics of patients

Characteristics	Value
Age, years	54.2 ± 14.7
Female gender	196 (71.3)
Smoker	52 (32.9)
Former smoker	24 (15.2)
Non-smoker	82 (51.9)
No comorbidities	107 (39.1)
Diabetes	39 (14.2)
Cardiovascular diseases	96 (35.1)
Autoimmune diseases	9 (3.3)
Carcinoma	16 (5.8)
COPD	4 (1.5)
Pituitary adenoma	3 (1.1)
BMI, kg/m²	28.4 ± 5.3
Presence of compressive symptoms	86 (35.4)
Family history of thyroid nodes/carcinoma	54 (28.6)
1 node in thyroid gland	105 (38.2)
2 nodes in thyroid gland	48 (17.4)
> 2 nodes in thyroid gland	122 (44.4)
Dimension of dominant node, mm	28 (19–39)
Hypothyroidism	25 (9.1)
Primary hyperparathyroidism	13 (4.7)
TSH, mIU/L	1.42 (0.89–2.18)
TPO Abs, IU/mL	3.2 (0.8–38.28)
Tg Abs, IU/mL	0.3 (0.1–13.96)
Tg, ng/L	48 (17.35–160.9)
Calcitonin, pg/mL	2.0 (1.0–2.47)

COPD – chronic obstructive pulmonary disease; BMI – body mass index; TSH – thyroid stimulating hormone; TPO – thyroid peroxidase; Abs – antibodies; Tg – thyroglobulin.
Values are expressed as mean ± standard deviation or numbers (percentages), except for dimension of dominant node, TSH, TPO Abs, Tg Abs, Tg, and calcitonin, which are presented as median (interquartile range).
***Note:* reference ranges for TSH, Tg, calcitonin, TPO Abs, and Tg Abs are 0.34–5.60 mIU/L, 3.50–77.00 ng/L, 0.50–9.82 pg/mL, < 9.0 IU/mL, and 0.0–4.0 IU/mL, respectively.**

Table 2

Cytological and histopathological parameters

Parameters	Patients
FNAB not done	73 (26.5)
Bethesda classification	
I	13 (4.7)
II	27 (9.8)
III	46 (16.7)
IV	50 (18.2)
V	59 (21.5)
VI	7 (2.5)
Total thyroidectomy	267 (97.1)
Lobectomy	8 (2.9)
Pathohistological benign finding	118 (42.9)
Pathohistological malignant finding (carcinoma)	157 (57.1)
Type of carcinoma	
papillary	76 (48.4)
micropapillary	51 (32.5)
hurthle cell	10 (6.4)
follicular	8 (5.1)
medullary	7 (4.4)
poorly differentiated thyroid carcinoma	3 (1.9)
well-differentiated tumor with uncertain malignant potential	2 (1.3)
T staging	
T1a	64 (42.4)
T1b	28 (18.5)
T2	30 (19.9)
T3a	19 (11.9)
T3b	10 (6.6)
T4	1 (0.7)
N staging	
Nx	56 (37.1)
N0	74 (49)
N1a	13 (8.6)
N1b	8 (5.3)
Radioiodine therapy, yes	88 (56.8)

FNAB – fine needle aspiration biopsy; T – extent of the tumor according to Tumor Nodes Metastasis (TNM) classification; N – extent of spread to the lymph nodes according to TNM classification.
Results are expressed as numbers (percentages).

Table 3

Demographic and clinical characteristics of patients with different numbers of nodes in the thyroid gland

Characteristics	1 node (n = 105)	≥ 2 nodes (n = 170)	*p*-value
Age, years	49.4 ± 15.8	57.2 ± 13.1	< 0.001
Age ≥ 50 years	43	124	< 0.001
Age < 50 years	62	46	
Female	71	125	0.293
Male	34	45	
Smoker	28	48	0.732
Nonsmoker	28	54	
BMI, kg/m²	26.5 (22.9–30.0)	29.1 (25.4–32.9)	0.004
TPO Abs, IU/mL	4.60 (0.95–102.65)	3.00 (0.80–35.67)	0.280
Tg Abs, IU/mL	0.70 (0.10–22.35)	0.25 (0.10–10.00)	0.232
Tg, ng/L	42.12 (13.48–164.85)	52.00 (19.51–159.80)	0.214
TSH, mIU/L	1.73 (0.95–3.00)	1.21 (0.82–1.78)	< 0.001
Cytological finding			
Bethesda II–III	27	46	0.159
Bethesda IV–VI	55	61	
Carcinoma	62	95	0.645
No carcinoma	43	74	

For abbreviations, see Table 1.
Values are expressed as numbers or median (interquartile range), except for age which is presented as mean ± standard deviation.

Table 4

Demographic and clinical characteristics of patients with and without thyroid carcinoma

Characteristics	Thyroid carcinoma		*p*-value
	No (n = 118)	Yes (n = 15)	
Age, years (mean ± SD)	53.13 ± 14.86	55.67 ± 14.40	0.156
Age ≥ 50 years, n	78	89	0.114
Age < 50 years, n	40	68	
Female, n	91	105	0.063
Male, n	27	52	
Smoker, n	28	48	0.291
Nonsmoker, n	37	45	
BMI, kg/m² (Me, IQR)	28.44 (24.88–32.00)	28.00 (24.00–31.70)	0.693
TPO Abs, IU/mL (Me, IQR)	3.90 (1.10–34.38)	2.25 (0.80–40.67)	0.688
Tg Abs, IU/mL (Me, IQR)	0.20 (0.10–10.10)	0.55 (0.10–15.52)	0.344
Tg, ng/L (Me, IQR)	45.43 (15.32–130.25)	54.45 (19.30–216.25)	0.134
TSH, mIU/L (Me, IQR)	1.42 (0.81–2.23)	1.42 (0.91–2.14)	0.73
1 nodule in thyroid gland, n	43	62	
≥ 2 nodules in thyroid gland, n	75	95	0.606
Dimension of dominant node, cm (Me)	28.6	27.05	0.836
Dimension of dominant node, cm (n)			
≤ 1	4	8	
1–2	26	40	0.784
2–3	35	41	
> 3	48	67	
Cytological finding, n			
Bethesda II–III	38	35	
Bethesda IV–VI	34	82	0.002

SD – standard deviation; n – number; Me – median; IQR – interquartile range. For other abbreviations, see Table 1.

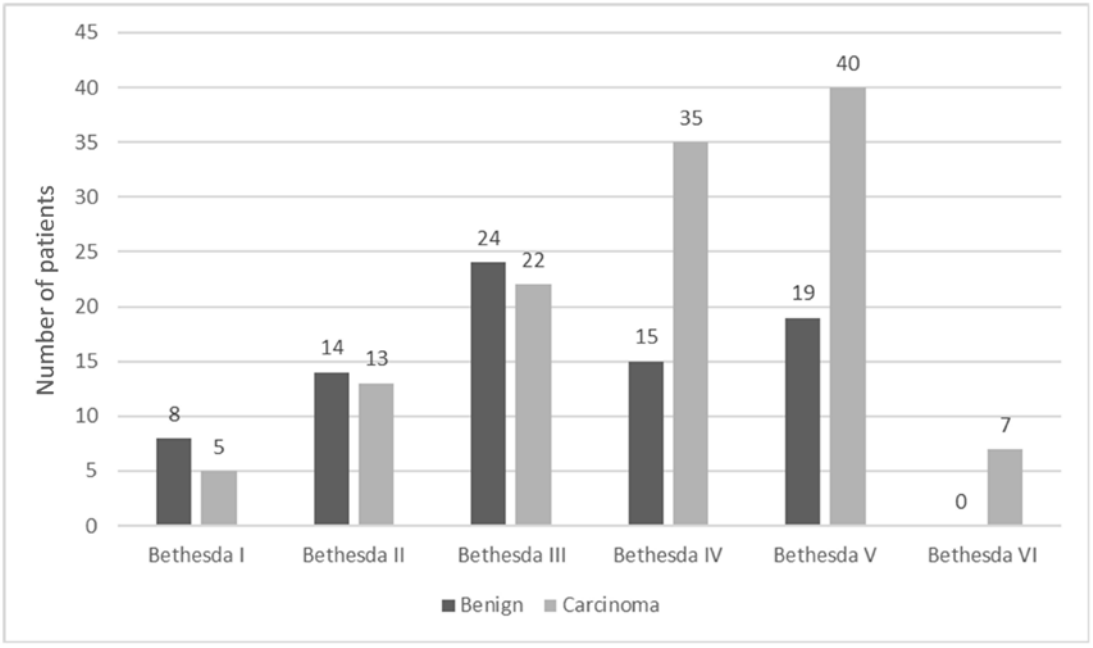

Fig. 1 – Distribution of benign and malignant findings in different categories of Bethesda classification.

The interpretation of FNAB cytological findings proved to be somewhat more complicated. However, there was a statistically significant association between the higher categories of the Bethesda classification and the cancer presence. Thyroid cancer was significantly more often diagnosed in patients with FNAB Bethesda category IV-VI compared to Bethesda II and III cytological findings (52.2% vs. 22.3%, $p = 0.002$). The distribution of diagnosed thyroid cancer for each Bethesda category is shown in Figure 1.

Discussion

Thyroid nodules are common and can be detected by palpation in 5% of women and 1% of men and/or in as many as 68% of the general population when thyroid imaging is applied [1, 12, 13]. The results of previously published studies show that nodules occur significantly more often in women [14, 15] and their incidence increases with age [16]. Previous studies showed that multinodular goiter is more

common than nodular goiter and that patients with thyroid nodules are usually euthyroid [15, 17]. These observations were in accordance with our results, where 25 of 275 patients were treated for hypothyroidism, and the remaining were euthyroid (9.1% vs. 90.9%).

Comparing the patients with nodular and multinodular goiter, we found that those with multinodular goiter were older and that multinodular goiter occurred significantly more often in patients older than 50 years, which was in accordance with the results of a study by Carlé et al. [18]. In the available literature, we did not find many studies that examined the above-mentioned parameters in relation to the number of thyroid nodes. A study by Elbalka et al. [17] showed that multinodular goiter was more common in women and that nodules in nodular goiter were larger than the dominant nodule within multinodular goiter.

Thyroid carcinomas are the most common endocrine cancers [19], and in the last 30 years, they have recorded a significant increase in incidence [16, 20, 21]. There is still an ongoing debate whether this is an actual incidence increase of thyroid cancer or a consequence of a more frequent use of US and cytological diagnostics [22, 23]. Surprisingly, a more precise diagnosis of thyroid cancers and their detection in early stages is not accompanied by a mortality rate reduction [20]. In order to avoid excessive and unnecessary diagnostics, there is ongoing work on the identification of predictive risk factors for the occurrence of thyroid cancers. However, the results of the earlier studies have not always been consistent.

It is generally considered that thyroid cancers occur more often in women [24] and at a particular age [25]. This was only partially confirmed by our study. Namely, cancer was more often diagnosed in women compared to men (66.88% vs. 33.12%, respectively). However, comparing patients with and without cancer did not prove a specific gender effect on cancer occurrence (p = 0. 063). When comparing the same groups by age, whether using the average age (p = 0.156) or the cut-off age of 50 (p = 0.114), the years of life showed no association with the increasing risk of developing thyroid cancer. Meta-analysis of prospective observational studies pointed to an increased risk of developing thyroid cancer with a higher body mass index [26], which was not observed in our results. A possible explanation might be the smaller sample size of our study population. Mack et al. [27] pointed to surprising results of a potentially protective effect of smoking against the development of thyroid cancers. A possible explanation for this finding was that smoking might decrease estrogen levels, which was considered responsible for increasing the risk of thyroid cancer and the incidence of cancer in women, especially in particular age groups [28]. In our study, body mass index (p = 0.693) as an indirect indicator of diet and smoking status (p = 0.291) were not shown to be important risk factors for developing thyroid cancer.

Although most of the patients with thyroid cancer were euthyroid, the results of some studies showed a rise in cancer risk with the increase in the TSH value within the reference limits [29]. Previous studies have not reached a uniform conclusion on the correlation between thyroid cancer occurrence and TPO Abs and Tg Abs [30, 31]. It is well-known that Tg values may be elevated in various thyroid diseases. Therefore, Tg is not a sufficiently sensitive and specific marker for thyroid cancer diagnosis [32]. Examining these biohumoral parameters in our study cohort, we found no association between TSH (p = 0.73), Tg (p = 0.134), TPO Abs (p = 0.688), and Tg Abs (p = 0.344) with the risk for thyroid cancer development.

Analyzing numerous US characteristics, Frates et al. [33] showed that the risk for thyroid cancer did not increase with the number and dimensions of the nodules, despite the generally accepted opinion that larger nodules are associated with a higher cancer risk [34]. A study by Kamran et al. [35] showed that the presence of nodules larger than 2 cm in diameter is associated with a higher risk of thyroid cancer. In our study, we compared the patients with and without thyroid cancer relative to the mean value of the dimensions of the dominant nodule (p = 0.836). We have also performed a subanalysis, classifying the nodules by size into four groups: < 1 cm, 1–2 cm, 2–3 cm, and > 3 cm. In both cases, it was shown that the nodule size did not affect the risk of cancer. Moreover, in our study, there was no difference in the frequency of cancer occurrence in patients with nodular vs. multinodular goiter (p = 0.645).

The FNAB is considered the most reliable diagnostic procedure with the best benefit-risk ratio for screening thyroid nodules for cancer [36, 37]. Of all the analyzed parameters in our study, the FNAB cytological finding was the only one showing a strong association with cancer occurrence. Namely, higher Bethesda classification categories were associated with a higher risk of developing cancer (p = 0.002), with a frequency of cancer in Bethesda categories V and VI of 67.8% and 100%, respectively, compared to 38.5%, 48.1%, 47.8%, and 70% in Bethesda categories I, II, III, and IV, respectively. Results for the Bethesda III category agreed with the results of previous studies where the frequency of 6–48% was an actual cancer ratio in this category [38, 39]. A more detailed subcategorization of the Bethesda III category could help estimate the risks of cancer occurrence better and avoid unnecessary surgical interventions [40]. In our study, cancer frequency in the Bethesda IV category was in concordance with the results of some previous studies [41, 42]. The high frequency of carcinoma in the Bethesda I category could be explained by not repeating the FNAB in previous studies, which would have otherwise delivered a better sample for a more precise classification of cytological findings.

The incidence of various types of thyroid cancer in our study was similar to the findings of previous major studies [5, 43]. In our study, papillary cancer was the most common type (48.4%), followed by micropapillary cancer present in 32.5% of patients. It was followed by oncocytic carcinoma, historically known as the Hurthle cell carcinoma (6.4%), follicular carcinoma (5.1%), medullary carcinoma (4,4%), poorly differentiated carcinoma (1.9%), and well-differentiated tumor of uncertain malignant potential (1.3%). Furthermore, cancer was diagnosed in the first stage in 60.9% of patients (T1a – 42.4%, T1b – 18.5), and less frequent in the

more advanced stages (T2 – 19.9%, T3a – 11.9%, T3b – 6.6%, T4a – 0.7%). Relying on these findings, it could be concluded that the indications for surgical treatment were well established, and the patient selection was properly made.

Several study limitations should be mentioned. First, patients from only one healthcare center were included, which can be potentially unrepresentative of the general population. Second, FNAB was performed only on the dominant nodule and/or ultrasonographically suspicious nodules, not on all existing nodules in patients with multinodular goiter. Finally, there are a few missing data on observed parameters.

Conclusion

Evaluation of thyroid nodules remains a diagnostic challenge in everyday clinical practice. Apart from clinical findings, biohumoral testing, and ultrasonographic characteristics, FNAB is necessary for nodules presenting with suspected malignant features on US examination. Our work demonstrated the importance of FNAB and Bethesda classification in the evaluation of thyroid nodules in patients with atoxic nodular and multinodular goiter, once again proving that the higher Bethesda categories imply a higher thyroid cancer risk.

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