Original Article
Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Predictive Factors Increasing the Risk of Malignancy in Thyroid Follicular Neoplasia

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Abstract

Aim: 22-42% of patients with thyroid nodules are diagnosed as Bethesda category IV “Follicular Neoplasia (FN)”. Although hemithyroidectomy (HT) is the recommended treatment for follicular neoplasia, some characteristics of the patient or the disease make total thyroidectomy (TT) the treatment of choice. The aim of this study is to evaluate our clinical results in patients with FN who underwent surgery and determine predictive risk factors in patients with malignant pathology results.

Methods: 364 patients were included in the study. Fine needle aspiration biopsy (FNAB) with a FN result was defined as a “target nodule”. Demographic, radiological and clinical characteristics of the two groups were determined. Two different types of surgical procedures were applied to the patients: HT or TT.

Results: The number of patients was 199 (54.7%) in Group 1 and 165 (45.3%) in Group 2. Malignancy was incidentally detected in 138 patients (37.9%) outside the target nodule. The risk of malignancy was higher in those under 45 compared to those aged 45 and older. Malignancy was observed in 123 (42.7%) of female patients and 42 (55.3%) of male patients. Additionally, the risk of malignancy increased in patients with nodules measuring 2 cm or larger.

Conclusions: In FN cases, the risk of malignancy increases in males, in nodules 2 cm and above, and in younger age groups. According to our data, the risk of malignancy in FN is 45.3%. Additionally, the rate of incidental thyroid cancer is 37.9%. We attribute the higher rates of these findings compared to literature to the increased frequency of thyroid cancer in our region.

***Keywords**: Follicular Neoplasia; nodule size; thyroid nodules*

1. Introduction

Thyroid diseases are common in our country, as they are worldwide. Ultrasound (US) detects nodules in 10-67% of the adult population, and in autopsy series, nodules are found in more than 50% of thyroid glands. The detection of malignancy in 9.2% to 14.8% of these nodules during cytological diagnosis emphasizes the importance of distinguishing between malignant and benign nodules [1]. However, since cytological examination may not always yield sufficient results, uncertainties can arise in the management of thyroid nodules. Thyroid nodules must be defined radiologically, clinically and most importantly cytologically for treatment planning. The average sensitivity of fine needle aspiration biopsy (FNAB) for detecting thyroid cancers has been found to be 83%, specificity 92%, and diagnostic accuracy 95% [2,3]. Bethesda System for Reporting Thyroid Cytopathology was introduced by the National Cancer Institute in 2009 in order to standardize the results of cytological sampling obtained through FNAB [4]. This reporting system, most recently updated in 2023 [5], still defines “Follicular Neoplasm (FN)” in category IV as a gray area (**Figure-1**). Problems encountered during the diagnostic process of patients in this category continue to pose significant challenges in treatment planning. Between 22-42% of patients undergoing FNAB receive a Bethesda category IV “Follicular Neoplasm” diagnosis [6]. The malignancy rate for Bethesda category IV ranges from 10-40% [4]. This category is among the most controversial groups within the system because it is not possible to differentiate between benign and malignant diseases cytologically in FN diagnosis. Cytological examination with FNAB is significantly successful in distinguishing between papillary thyroid carcinoma (PTC) and benign diseases. However, it is difficult to differentiate between

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follicular thyroid carcinoma (FTC) (**Figure-3**), follicular variant papillary thyroid carcinoma (fvPTC) (**Figure-4**), benign follicular adenoma (**Figure-2**), and diseases such as hyperplastic nodular goiter in cases of follicular lesions classified as FN [7-9].

Currently, while the recommended treatment method for patients diagnosed with FN is hemithyroidectomy (HT), the characteristics of the patient and the disease affect treatment management, and total thyroidectomy (TT) may be applied in selected cases. Reasons for performing TT include multinodular goiter, discrepancies between FNAB results and radiological and clinical findings, a family history that increases the risk of thyroid cancer, exposure to radiation in the head and neck area, the patient's preference to avoid a second surgical procedure in cases requiring completion thyroidectomy, and particularly in our country, the common occurrence of hypothyroidism (due to thyroiditis) in women, leading to them receiving levothyroxine treatment. There are ongoing discussions in the literature regarding the treatment methods applied in most series. The aim of this study is to evaluate the clinical outcomes in patients diagnosed with FN as a result of FNAB and undergoing surgery, as well as to investigate the impact of predictive factors we determine on the choice of surgical type concerning malignancy.

Figure 1

Follicular Neoplasia: Microfollicles composed of thyrocytes exhibiting nuclear atypia on a colloid-poor background *(MGG X100).*

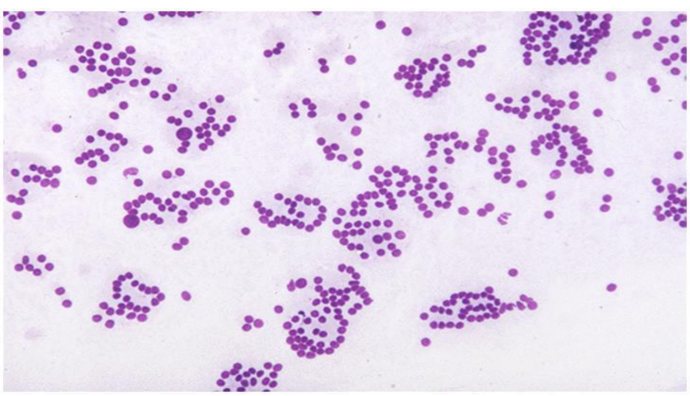


Figure 2

Follicular Adenoma: A lesion characterized by small follicles that are generally poor in colloid, surrounded by a thick fibrous capsule, exhibiting signs of pressure against the surrounding thyroid tissue *(HE X40).*

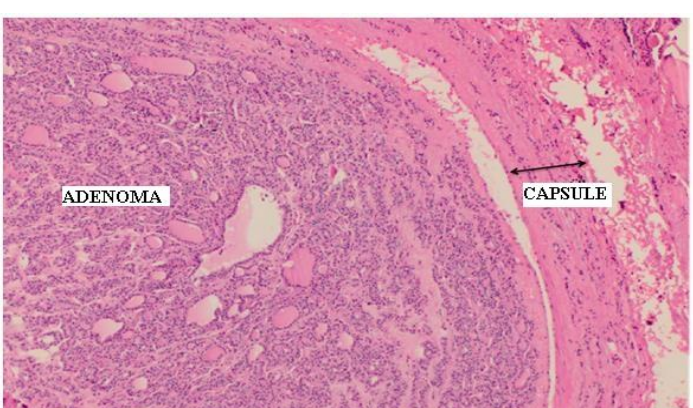


Figure 3

Follicular Carcinoma: A minimally invasive carcinoma characterized by microfollicular structures that exhibit complete capsule invasion and are poor in colloid *(HE X100).*

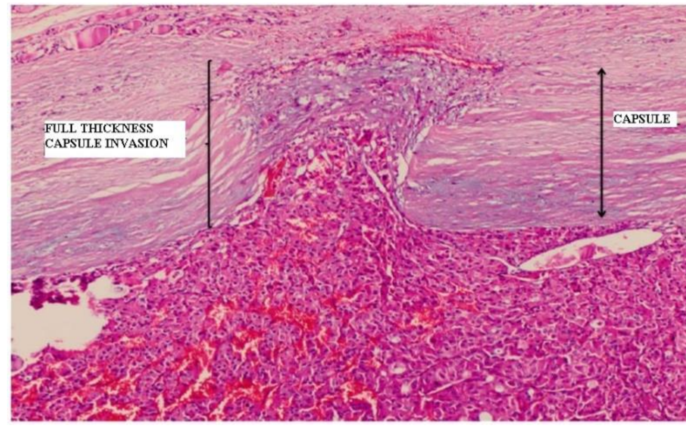
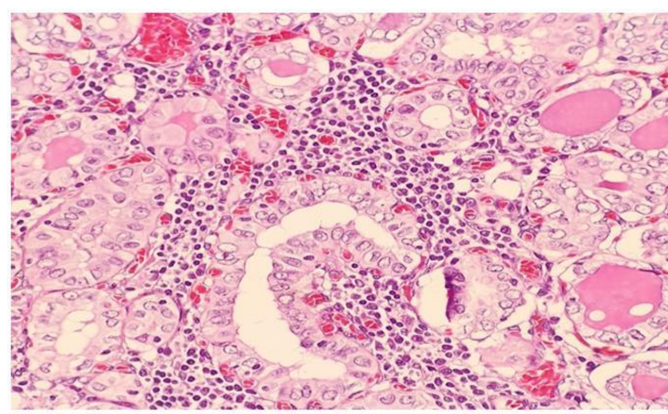


Figure 4

Follicular Variant Papillary Carcinoma: Follicular structures composed of thyroid cells exhibiting features of papillary carcinoma, characterized by nuclear enlargement, clearing, irregular nuclear membranes, peripheral placement of small single nucleoli, grooves, and intranuclear pseudoinclusions. The lesion is encapsulated and presents an infiltrative pattern, with no true papillary architecture observed *(HE X400).*



2. Materials and Methods

The data for our study were retrospectively obtained from the files of 364 patients who underwent surgery due to a diagnosis of follicular neoplasia (FN) at Başkent University School of Medicine Adana Dr. Turgut Noyan Application and Research Center between January 2016 and July 2021. Our study received approval from the Ethics Committee of Başkent University School of Medicine with the number KA 22/125. Patients who presented during the specified period and were found to have thyroid nodules through physical examination, laboratory, and radiological investigations, and for whom fine-needle aspiration biopsy (FNAB) was indicated, were included in the study. During this process, data were collected from patients with FN detected by FNAB who subsequently underwent surgical intervention. Data collected included age, gender, medical history (family history, radiation exposure to the head and neck, etc.), medications, comorbidities, previous thyroid surgeries, known thyroid diseases, presenting complaints, physical examination findings, ultrasound characteristics (echogenicity, calcification, vascularity, internal nodule structure, nodule borders, vertical and horizontal size ratios, halo, nodule size), pathology results (type of cancer in the target nodule), incidental cancer rates and types and rates of complementary thyroidectomy. Predictive risk factors for malignancy in follicular neoplasia were determined through a literature review. Nodules with FN diagnosed via FNAB were defined as the "target nodule." Patients were divided into two groups based on whether the target nodule was malignant or benign. Those with benign target nodules were classified as Group 1, while those with malignant target nodules were classified as Group 2. A comparative analysis was conducted between the two groups regarding demographic, radiological and clinical parameters. Additionally, both Group 1 and Group 2 were further subdivided into three subgroups based on nodule size. Nodules measuring 2 cm or less were classified as A (1A, 2A), those between 2-4 cm as B (1B, 2B), and those 4 cm or larger as C (1C, 2C). The malignancy risk based on nodule size was compared both between the two groups and within their respective subgroups. The types and subtypes of thyroid cancers in patients with malignant target nodules and incidental malignancies (nodules outside the target) were identified. Patients underwent either hemithyroidectomy (HT) or total thyroidectomy (TT). Those who underwent HT and were classified as high-risk for malignancy based on pathology results underwent complementary thyroidectomy.

2.1 Statistical Method

Statistical analyses were performed using SPSS version 25.0. The normal distribution of variables was assessed using the Shapiro-Wilk test. Descriptive analyses presented mean ± standard deviation and median (min-max) values. The Mann-Whitney U test was used for evaluating non-normally distributed variables between the two groups. Categorical variables were expressed in terms of frequency and percentage. The relationships between categorical variables were examined using the Chi-Square Test. Differences between groups were determined using Dunn's Bonferroni Test. Univariate logistic regression analysis was conducted to identify factors influencing the risk of malignancy. Independent variables with p-values of 0.25 or below were included in the model. A p-value of less than 0.05 was considered statistically significant.

3. Results

A total of 364 patients were included in the study. Group 1 consisted of 199 patients (54.7%), while Group 2 included 165 patients (45.3%). Of the patients, 288 (79.12%) were female and 76 (20.88%) were male. The average age was 46.77 ± 13.43 years, ranging from 14 to 81 years. There were 160 patients (43.96%) under 45 years old and 204 patients (56.04%) aged 45 and older. In Group 1, 62.30% of the patients were 45 years and older, while in Group 2, 37.70% were in the same age group. Univariate logistic regression analysis to determine factors influencing the risk of malignancy showed that age (under 45 and 45 and older) significantly affects the risk of malignancy. The risk of malignancy was higher for those under 45 years compared to those 45 and older ($p > 0.001$). Variables with a significance level of $p \leq 0.25$ would be included in the multivariate logistic regression model; however, only one independent variable, age, met this criterion. Among female patients, 123 (42.7%) were diagnosed with malignancy, while 42 male patients (55.3%) were diagnosed as well.

Table 1

Demographic data of the patients

		Benign (n=199) (Group 1)		Malignant (n=165) (Group 2)		p
		n	%	n	%	
Complaint	Neck swelling	22	(11.06)	28	(16.97)	0.248
	Incidental	23	(11.56)	24	(14.55)	
	Goiter follow-up	43	(21.61)	40	(24.24)	
	Hypothyroidism	5	(2.51)	4	(2.42)	
	Hyperthyroidism	7	(3.52)	2	(1.21)	
	Compression sign	10	(5.03)	10	(6.06)	
	Extrathyroidal endocrine disease	29	(14.57)	16	(9.70)	
	Nodule detected on PET/BT scan	3	(1.51)	5	(3.03)	
	Signs of thyroiditis	1	(.50)	3	(1.82)	
	Pain in neck	9	(4.52)	2	(1.21)	
Concomitant thyroid disease	Hyperthyroidism	37	(18.59)	23	(13.94)	0.623
	Hypothyroidism	12	(6.03)	12	(7.27)	
	Thyroid nodule	57	(28.64)	47	(28.48)	
	Thyroid cancer operation	1	(0.50)	0	(0.00)	
	Thyroidectomy (Benign pathology)	6	(3.02)	2	(1.21)	
Family history of thyroid cancer	Yes	8	(4.02)	9	(5.45)	0.518
	No	191	(95.98)	156	(94.55)	
Levothyroxin use	Yes	19	(9,55)	14	(8,48)	0.725
	No	180	(90,45)	151	(91,52)	
Sex	Female	165	(82,91)	123	(74,55)	0.051
	Male	34	(17,09)	42	(25,45)	

Although the malignancy rate was higher in male patients, there was no statistically significant difference between genders regarding malignancy rates (p = 0.051). The average age of patients in Group 2 was 44.26 ± 14.02 years, while the average age in Group 1 was 48.81 ± 12.59 years. There was a statistically significant difference in the ages of patients between both groups, with Group 1 having a higher average age (p = 0.001).

Reasons for hospital admission included palpable neck swelling in 50 patients (13.74%), incidental detection of thyroid nodules in 47 patients (12.91%), known follow-up of multinodular goiter in 83 patients (22.80%), follow-up due to hypothyroidism in 9 patients (2.47%), follow-up due to hyperthyroidism in 9 patients (2.47%), compressive symptoms in 20 patients (5.49%), diagnosis at another center in 64 patients (17.58%), follow-up due to non-thyroidal endocrine disorders in 45 patients (12.36%) and thyroid nodules detected on PET/CT in 8 patients (2.20%). One patient (0.27%) was under follow-up due to recurrence after thyroidectomy (malignancy). Thirteen patients (3.57%) were under follow-up due to benign thyroidectomy, 4 patients (1.10%) presented with thyroiditis symptoms, and 11 patients (3.02%) presented with complaints of pain in the neck and throat.

Both Group 1 (21.61%) and Group 2 (24.24%) had the most common reason for admission as the detection of FN from biopsies performed on patients under follow-up for multinodular goiter. When comparing presenting complaints between the two groups, no statistically significant difference was found (p > 0.05). In terms of medical history, 60 patients (16.48%) had hyperthyroidism (37 in Group 1 and 23 in Group 2), and 33 patients (9%) had hypothyroidism (19 in Group 1 and 14 in Group 2). There was no statistically significant difference regarding functional disorders between the groups (p > 0.05). A family history of thyroid cancer was present in 17 patients (4.67%) (8 in Group 1 and 9 in Group 2), and one patient had previously been operated on for papillary thyroid cancer. No statistically significant difference was observed between the groups regarding family history (p > 0.05) (**Table-1**).

Preoperative ultrasound (USG) examination evaluated features for malignancy in nodules: microcalcifications were present in 31.32%, solid components in 99.45%, irregular borders in 6.89%, absence of halo in 66.21%, hypoechogenicity in 75.6%, anteroposterior to transverse diameter ratio greater than 1 in 40.3%, and vascularity in 51.3% of patients. When comparing all USG parameters between Groups 1 and 2, no statistically significant differences were found (**Table-2**).

63.32% of patients in Group 1 and 55.76% in Group 2 were found to have bilateral thyroid nodules in the USG examination. In terms of cystic characteristics of nodules, significant differences were observed among benign groups and malignant groups with nodule sizes smaller than 20 mm, between 20 mm and 40 mm, and larger than 40 mm (p = 0.032). Among those with malignant nodules larger than 40 mm, 50% had cystic features, while 19.32% in the 20-40 mm group and 31.31% in the benign group had cystic features.
Cases in Group 2 were subdivided according to nodule size in order to evaluate the relationship between malignancy risk and size. Those with nodules measuring 2 cm or less were classified as 2A, those between 2-4 cm as 2B, and those 4 cm or larger as 2C. There were 89 patients in Group 2A, 66 in Group 2B, and 10 in Group 2C.

The average nodule size across all groups was 20.71 ± 10.08 mm. The average nodule size in Group 1 was 20.86 ± 9.31 mm, while in Group 2 it was 20.53 ± 10.97 mm.

When comparing nodule sizes between groups, no statistically significant difference was observed (p > 0.05). The average nodule size in Group 2A was found to be 12.66 ± 3.54 mm. The nodule size in Group 1 was larger than that in Group 2A, and the results were statistically significant (p < 0.001) (**Table-3**). There was no statistically significant difference in average age between Groups 1 and 2A. The average nodule size in Group 2B was 27.53 ± 5.87 mm, which was significantly larger compared to Group 1 (p < 0.001). The average age of patients in Group 2B was 43.49 ± 14.77 years, and they were significantly younger than those in Group 1 (p = 0.040) (**Table-3**). The average nodule size in Group 2C was found to be 47.90 ± 8.02 mm, which was also statistically significantly larger than that in Group 1 (p < 0.001) (**Table-3**).

Table 2

Malignancy risk of the nodule with follicular neoplasia cytology according to ultrasound findings

		Benign (n=199) (Group 1)		Malignant (n=165) (Group 2)		p
		n	%	n	%	
Echogenity	Hypoechoic	149	(75.25)	126	(76.36)	0.425
	Hyperechoic	4	(2.02)	1	(0.61)	
	Isoechoic	36	(18.18)	26	(15.76)	
	Heterogenous	9	(4.55)	12	(7.27)	
Microcalcification	Yes	60	(30.15)	54	(32.73)	0.598
	No	139	(69.85)	111	(67.27)	
Solid component	Yes	197	(99.49)	163	(99.39)	0.999
	No	1	(0.51)	1	(0.61)	
Cystic	Yes	62	(31.31)	47	(28.68)	0.584
	No	136	(68.69)	117	(71.34)	
Mixed	Yes	59	(29.80)	48	(29.27)	0.912
	No	139	(70.20)	116	(70.73)	
Border	Regular	181	(91.41)	157	(95.15)	0.161
	Irregular	17	(8.59)	8	(4.85)	
Vascularity	Decreased	96	(48.48)	80	(48.48)	0.999
	Increased	102	(51.52)	85	(51.52)	
Halo	Yes	68	(34.17)	55	(33.33)	0.866
	No	131	(65.83)	110	(66.67)	

Table 3

Comparison of nodule size and age in Group 1 and 2A, 2B, 3C

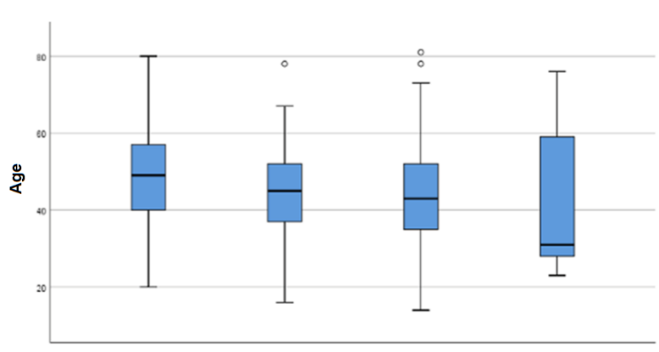
		Benign (Group 1)		Malignant <20 mm (Group 2A)		p
		Mean ± sd	Median (min-max)	Mean ± sd	Median (min-max)	
Group 1 vs 2A	Age	48.81±12.59	49(20-80)	45.16±12.70	45(16-78)	0.202
	Nodule size	20.68±9.18	20(5-55)	12.66±3.54	12(6-19)	<0.001
		Benign (Group 1)		20 mm≤ Malignant <40 mm (Group 2B)		
		Mean ± sd	Median (min-max)	Mean ± sd	Median (min-max)	
Group 1 vs 2B	Age	48.81±12.59	49(20-80)	43.49±17.77	43(14-81)	0.040
	Nodule size	20.68±9.18	20(5-55)	27.53±5.87	27(20-40)	<0.001
		Benign (Group 1)		Malignant ≥40 mm (Group 2C)		
		Mean ± sd	Median (min-max)	Mean ± sd	Median (min-max)	
Group 1 vs 2C	Age	48.81±12.59	49(20-80)	41.69±19.10	31(23-76)	0.191
	Nodule size	20.68±9.18	20(5-55)	47.90±8.02	45(42-70)	<0.001

Table 4

Incidental thyroid cancer exccept target thyroid nodule

	Benign (Group 1)		Malignant <20 mm (Group 2A)		Malignant 20-40 mm (Group 2B)		Malignant >40 mm (Group 2C)	
	n	%	n	%	n	%	n	%
Micropapillary carcinoma	60	88.24	36	90.00	21	75.00	2	100.00
PTC/Follicular variant	6	8.82	3	7.5	4	14.29	-	-
PTC/Classical variant	-	-	1	2.50	1	3.57	-	-
PTC/Tall cell variant	1	1.47	-	-	1	3.57	-	-
PTC/Oncocytic variant	-	-	-	-	1	3.57	-	-
Hurthlecell carcinoma	1	1.47	-	-	-	-	-	-

** PTC: Papillary thyroid cancer.*

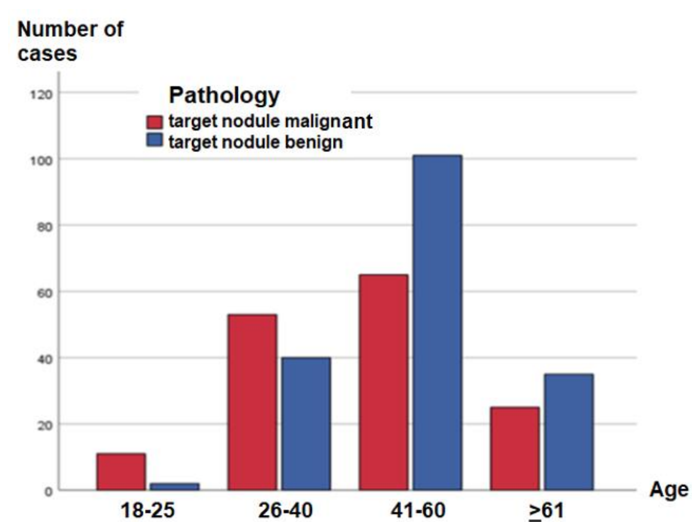


Graph 1

The relationship between nodule size and patient age and malignancy

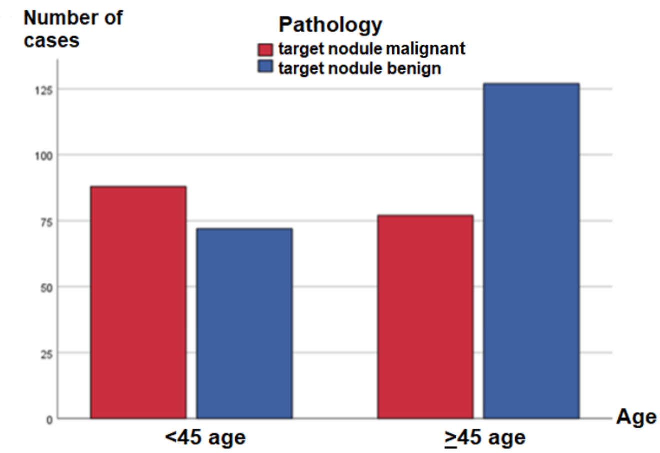
When benign (Group 1) and malignant cases in each of the three subgroups (Group 2A, 2B, 2C) were evaluated together according to age distribution, it was determined that the increase in nodule size and younger patient age increased the likelihood of malignancy ($p < 0.001$) (**Graph-1**).

Given that patient age could be another predictor of the malignancy potential of nodules diagnosed with FN, cases were evaluated in four age groups. Among 16 patients ages between 18-25 years, 11 (68.75%) had malignancies, while 5 (31.25%) had benign diagnoses. Among 108 patients ages between 25-40 years, 55 (50.93%) had malignancies and 53 (49.07%) had benign diagnoses. Among 168 patients ages between 41-60 years, 70 (41.67%) had malignancies and 98 (58.33%) had benign diagnoses. Among 72 patients over 61 years old, 29 (40.28%) had malignancies and 43 (59.72%) had benign diagnoses. The malignancy rate was found to be higher in younger age groups (**Graph-2**). In the 25-40 age group, the number of malignant pathologies exceeded that of benign, but this trend reversed in the 41-60 age group, suggesting that predictions regarding malignancy and age will differ between these two groups. A repeated chi-square analysis suggested that 160 cases were under 45 years of age, while 204 were 45 years and older.



Graph 2

Distribution of pathology results by age groups



Graph 3

Distribution of pathology results according to age 45

Among those under 45, 88 (55%) were diagnosed with malignancy, and 72 (45%) were diagnosed with benign pathology. Among those over 45 yaers, 77 (27.7%) were diagnosed with malignancy and 127 (62.3%) were diagnosed with benign pathology. The likelihood of FN cytology nodules being malignant was found to be statistically significantly higher in cases under 45 years ($p < 0.001$). In the group under 45 years of age, 88 (55%) cases were diagnosed with malignant pathology, and 72 (45%) cases were diagnosed with benign pathology. In the group over 45 years of age, 77 (27.7%) cases were diagnosed with malignant pathology, and 127 (62.3%) cases were diagnosed with benign pathology. The likelihood of malignancy in FN cytology cases was found to be statistically significantly higher in the group under 45 years of age ($p<0.001$) (**Graph-3**).

Upon examining the pathological evaluations of patients, the most frequently seen histological subtype in Group 2A, where the target nodule was malignant, was micro-papillary thyroid cancer (n = 44, 49.44%). The most commonly seen subtype in Group 2B was follicular variant papillary thyroid cancer (n = 34, 51.52%), and similarly, in Group 2C, the most frequently seen subtype was also follicular variant papillary thyroid cancer (n = 7, 70%). Among all malignant cases (165 patients), the most frequently observed histological subtypes were micro-papillary thyroid cancer in 48 (29%) patients and follicular variant papillary thyroid cancer in 57 (34.5%) patients. Follicular thyroid cancer was observed in 8 (4.8%) patients.

Incidental thyroid malignancies were observed in 138 patients (37.9%) outside of the target nodule. Among these, 119 had micropapillary thyroid cancer, 13 had follicular variant papillary thyroid cancer, 2 had classic variant papillary thyroid cancer, 2 had tall cell variant papillary thyroid cancer, 1 had oncocytic variant papillary thyroid cancer, and 1 had Hurthle cell carcinoma. The rate of incidental thyroid cancer was observed to be 34.1% (68 out of 199 patients) in Group 1 and 42.4% (70 out of 165 patients) in Group 2. In both groups, the most frequently observed histological type was micro-papillary thyroid cancer (88.24% in Group 1 and 84.29% in Group 2) (**Table-4**). In Group 1, 130 patients and in Group 2, 118 patients underwent bilateral total thyroidectomy, while 69 patients in Group 1 and 47 patients in Group 2 underwent unilateral thyroidectomy. There was no statistically significant difference between the two groups regarding the surgical technique. In Group 2, 27 patients (16.36%) underwent complementary thyroidectomy due to incidental thyroid malignancy, compared to 3 patients (1.51%) in Group 1. This included 13 patients in Group 2A, 13 in Group 2B, and 1 in Group 2C.

4. Discussion

Thyroid nodules are morphological changes that can be distinguished from normal thyroid tissue through ultrasound (USG) examinations. They occupy space within the parenchyma and have different consistencies. Thyroid nodules are more commonly seen in endemic regions and are one of the most frequently encountered conditions in clinical practice. Approximately 5% of women and 1% of men worldwide have palpable nodules. Ultrasound examinations reveal thyroid nodules in 10-68% of the population [1, 10, 11, 12, 13].A thyroid nodule can be noticed by the patient themselves, but more frequently, it is detected during physical examinations or through radiological imaging methods (such as neck ultrasound, PET/CT, CT, MRI, etc.). Nowadays with the increasing use of imaging methods for diagnostic and screening purposes for various reasons, there has been a notable rise in the number of thyroid nodules and consequently, thyroid cancers [14,15]. Some authors argue that the increase in the number of nodules, especially cancer cases, cannot be solely explained by the rise in imaging techniques [16, 17]. This is because the relative increase in cancer cases is observed not only in small-sized nodules but also in larger ones. Approximately 5-14% of thyroid nodules are malignant [1, 18]. Therefore, the medical history, physical examination, imaging, and cytological evaluations of patients with thyroid nodules should be conducted thoroughly and carefully. Regardless of how the diagnosis is made, as the detection rate of thyroid nodules increases, so do the uncertainties regarding the clinical approach to these nodules. This situation emphasizes the importance of understanding the malignancy risk associated with nodules detected in the preoperative period.

For the evaluation of incidentally detected or clinically noticed thyroid nodules, total neck ultrasound is the primary imaging method. In these ultrasound examinations, patients in the risk group undergo Fine Needle Aspiration Biopsy (FNAB) for cytological evaluation of the nodule. FNAB is the gold standard method for diagnosing nodules with high accuracy through a simple procedure [19, 20]. However, although FNAB can aid in distinguishing malignant from benign nodules, uncertain results can create clinical dilemmas, and pathologists cannot provide a clear diagnosis for approximately 30% of thyroid nodules for various reasons [21].

To standardize pathological interpretations, the Bethesda Reporting System, updated by the National Cancer Institute in 2023 [5], is utilized. The category IV diagnosis of FN within this reporting system is still defined as a gray area in clinical studies. In this category, distinguishing between benign and malignant disease is not possible cytologically. Various studies have shown that approximately 27-52% of lesions diagnosed as FN by FNAB are often malignant upon histopathological examination. The most frequently observed malignancy is Papillary Thyroid Carcinoma (PTC), followed by Follicular Thyroid Carcinoma (FTC) [22, 23]. The majority of such nodules (48-73%) are benign, meaning many patients are subjected to unnecessary diagnostic surgeries. Thyroid surgeries can lead to serious complications such as thyroid hormone imbalance, hypoparathyroidism, recurrent laryngeal nerve injury, bleeding, and infection, in addition to increasing hospitalization costs[24].

There is no complete consensus on the recommended treatment for Bethesda Category IV thyroid nodules, but the most commonly applied method, also included in the ATA guidelines [25], is hemithyroidectomy (HT). Recently, molecular tests for risk assessment have emerged to avoid unnecessary surgical interventions. However, these molecular tests are quite expensive and difficult to access.

Given that a significant portion of these nodules is benign after surgery, it is believed that this group of patients faces unnecessary surgical morbidity risks. On the other hand, if the final pathology result is malignant, the possibility of complementary thyroidectomy arises. The risks of surgical complications associated with secondary interventions (such as recurrent laryngeal and superior laryngeal nerve injuries, hypoparathyroidism, etc.) increase with complementary thyroidectomy.

Additionally, varying rates of thyroid malignancy based on geographic regions, the presence of Hashimoto's disease accompanying Bethesda category IV FN in patients, the existence of concurrent multinodular disease, and social factors such as patients' refusal to consider a second surgery raise the option of total thyroidectomy (TT) in patients classified as high-risk radiologically and clinically, despite being in the gray area cytologically.

This controversial situation and uncertainty highlight the need for research into preoperative assessment criteria that could be used to determine the overall malignancy risk of these nodules or the risk rates specific to clinics (such as geographic differences and hospitals located in regions with high cancer prevalence) and emphasize the necessity for treating patients based on these results [22, 26, 27].

Numerous studies in the literature have investigated demographic, clinical, and radiological predictive factors for malignancy in FN. Common and differing results have been reported, and the factors predicting malignancy risk in patients have not been fully established. Age, male gender, large nodule size, ultrasound characteristics, and cytological features have been reported as primary risk factors for identifying patients at risk of malignancy. However, variables determining malignancy in follicular neoplasms remain a topic of debate [28].

Among the predictive factors, ultrasound characteristics have been studied, with solid structure of the nodule, microcalcifications, or hypoechoic patterns being associated with malignancy [2]. In our study, all ultrasound variables believed to increase the risk of malignancy in nodules during the preoperative period were evaluated, and no differences in ultrasound characteristics were found between malignant and benign groups. Since all patients in our study were evaluated by the same radiology team, we believe that misleading factors related to the radiologist are at their lowest level. Consequently, we observed that ultrasound findings were not effective in distinguishing between benign and malignant FN. For thyroid nodules classified as EU-TIRADS 5, a decision for fine needle aspiration biopsy (FNAB) is typically made [29]. We attribute the primary reason for features increasing malignancy risk, or in other words, the EU-TIRADS category, not actually increasing malignancy risk to the frequent demonstration of EU-TIRADS 5 category features in benign nodules as well. In another study, similar to ours, no difference in ultrasound characteristics was found between benign and malignant follicular thyroid lesions [30]. Similarly, Sillery et al. demonstrated that the ultrasound characteristics of follicular adenomas and follicular thyroid carcinomas (FTC) are similar [31]. There are controversial results regarding additional potential ultrasound features associated with follicular malignancy, such as the absence or presence of a halo, hypoechogenicity or isoechogenicity, unclear borders, and the absence of cystic changes [22, 27, 31-33].

It is a well-known fact that the presence of a solid component in thyroid nodules increases the risk of malignancy. In contrast, the presence of a cystic component significantly decreases this risk. In our study, we also demonstrated that as nodule size increases, the rate of malignancy rises. We noted that the cystic nature of the nodule serves as an indicator that reduces the likelihood of malignancy. Interestingly, while the probability of cancer in solid nodules increases with nodule size, this is not the case for cystic nodules, where the risk of malignancy does not rise despite an increase in size.

Malignancy rates in FN show variations between clinics. These differing rates are influenced not only by clinical data but also by the demographic and ethnic characteristics of the patients. Bongiovanni et al. reported a malignancy rate of 26.1% in FN cases [34]. In another study by Kim et al., the malignancy rate was noted as 35.1% [28]. They attributed this higher rate compared to literature reports to ethnic differences. They mentioned that most previous studies were conducted in the United States, while in their own country, Korea, the prevalence of thyroid cancer is high. Similarly, another study conducted in Korea by Yim et al. reported a malignancy rate of 48% [35]. In another study, the malignancy rate in Bethesda Category IV nodules was found to be 48.9%. Additionally, incidental malignancy was detected in 30.7% of patients, leading to a total malignancy rate of 79.6% [36]. In our study, the malignancy rate among patients diagnosed with FN who underwent surgery was found to be 45.3%. This rate is higher than that reported in many studies in the literature. Similar to the studies from Korea, we attribute this high rate to the elevated prevalence of thyroid cancer in the region where the study was conducted.

In our study, incidental malignancy was observed outside the target nodule in 138 of the 364 patients (37.9%). In Group 1, the rate of incidental thyroid cancer was 34.1% (68/199 patients), while in Group 2 it was 42.4% (70/165 patients). In both groups, the most frequently observed histological type was micro-papillary thyroid cancer. Another study highlighting the regional differences affecting the incidence of thyroid cancer reported that 721 patients underwent surgery for FN, with 402 (55.7%) having total thyroidectomy (TT) and 319 (44.3%) having hemithyroidectomy (HT), resulting in a malignancy rate of 24% (176/721 cases). The patients in this study were operated on in two different regions. The malignancy rate was recorded as 34.9% in Sardinia and 18.9% in Campania. Additionally, the risk of malignancy was higher in those who underwent TT (31%) compared to those who had HT (16%). However, considering that the malignancy rate remains low even after routine TT, there is commentary suggesting that surgical interventions may signify "overtreatment" in many cases. The study states that Sardinia is an endemic goiter region, with a very high incidence of autoimmune diseases (especially Hashimoto's thyroiditis), which likely contributes to the observed higher malignancy rates. For these reasons, it is emphasized that when making surgical decisions, not only clinical and radiological data but also ethnic and regional factors may play a role in malignancy risk. This situation explains the prevalence of TT selection in endemic regions, a regional risk factor [37]. Other studies also highlight that the structure of at-risk populations and the clinical-pathological characteristics of cancer may vary significantly based on ethnic origin and geographic location [38].

In our study, 27 patients (16.36%) in Group 2 and 3 patients (1.51%) in Group 1 (who were found to have incidental thyroid malignancy) underwent complementary thyroidectomy. Bilateral total thyroidectomy (TT) was performed on 130 patients in Group 1 and 118 patients in Group 2, while unilateral thyroidectomy was performed on 69 patients in Group 1 and 47 patients in Group 2. The high rate of TT in our study can be attributed to the presence of hyperthyroidism in 60 patients (16.48%) (37 in Group 1 and 23 in Group 2) and hypothyroidism/Hashimoto's disease in 24 patients (6.59%) (12 in Group 1 and 12 in Group 2). Additionally, 17 patients (4.67%) had a family history of thyroid cancer (8 in Group 1 and 9 in Group 2), and one patient had previously been operated on for papillary thyroid cancer. Furthermore, ultrasound examinations revealed that bilateral thyroid nodules were present in 63.32% of patients in Group 1 and 55.76% in Group 2. The endemic nature of thyroid diseases and cancer in our region also plays a significant role in our broader surgical practices.

In a study, the most frequently encountered malignant pathologies in FN cases were identified as PTC (53.4%) and FTC (40.49%). Moreover, nearly one-third of the malignancies (37.7%) were fvPTC. The authors suggested that the high rate of fvPTC cases may be due to the possibility of misdiagnosis or incorrect diagnosis of truly malignant cases as a result of fine-needle aspiration biopsy (FNAB) [28]. These malignant cases were diagnosed correctly post-surgery due to the absence of tumor capsule and vascular invasion findings. In our study, the most common histological subtypes observed in the malignant group were micropapillary thyroid carcinoma in 48 patients (29%) and fvPTC in 57 patients (34.5%). In eight patients (4.8%), FTC was observed. When examining the pathological evaluations of the patients' subgroups (2A, 2B, 2C), the most common histological subtype in Group 2A was micropapillary thyroid carcinoma, in Group 2B it was fvPTC, and similarly in Group 2C it was also fvPTC.

A study investigating factors that help predict malignancy after preoperative FN diagnosis analyzed 368 thyroidectomy samples. The authors found that 60% of nodules with cytological nuclear changes associated with PTC were malignant [39]. In another study involving 98 FN cases, the malignancy rates for atypical and non-atypical FN were reported as 44.4% and 6.8%, respectively, thus supporting the predictive value of the presence of atypical FN [8]. In our study, there was no data related to nuclear atypia in cytological examinations, and thus, an assessment could not be made regarding this predictive risk factor. Due to the retrospective nature of our study, there are parameters with data deficiencies, which constitutes the most significant limitation of our research.

Another clinical variable investigated for predicting malignancy in FN is gender. Many studies have shown that male gender is significantly associated with a diagnosis of malignancy [40, 41]. In a study based on multivariable analyses, Najafian et al. indicated that male gender, a family history of thyroid cancer, and a history of head and neck radiation exposure are associated with malignancy in follicular neoplasms of the thyroid [30]. In our study, malignancy was detected in 42.7% of female patients and 55.3% of male patients. According to these findings, the rate of malignancy in male patients was significantly higher, similar to the literature. However, there was no statistically significant difference (p=0.051). Additionally, there was no statistically significant difference in the distribution of 17 cases with a family history of thyroid cancer between groups 1 and 2, and our study found that a family history of thyroid cancer was not a determining factor for predicting malignancy in FN.

None of our cases had a history of radiation exposure to the head and neck region. Considering that patient age could be another determinant in predicting the malignancy potential of FN cytology, the cases were evaluated according to age ranges. The group with the highest rate of malignancy was the youngest age group, 18-25 years. In the two youngest age ranges, 18-25 and 26-40 years, the number of malignant pathologies exceeded that of benign ones; however, this trend reversed in the 41-60 age range. This suggests that any prediction of malignancy with age might lie between these two groups. Additionally, studies highlighting that being under 45 years old is a risk factor for malignancy were also considered[30, 41]. Based on these data, a repeated chi-square analysis indicated that 160 cases were under 45 years old, while 204 cases were 45 years or older. Among those under 45, 88 (55%) cases were malignant, and 72 (45%) were diagnosed with benign pathologies. Among those over 45, 77 (27.7%) cases were malignant, and 127 (62.3%) cases were benign. The likelihood of FN cytology nodules being malignant was statistically significantly higher in cases under 45 years (p<0.001).

The literature presents conflicting results regarding nodule size and the risk of malignancy. Tuttle et al. reported that tumor sizes greater than 4 cm are associated with an increased risk of malignancy [42]. Schlinkert et al. emphasized that the risk of malignancy in follicular neoplasms is higher in larger tumors [41]. Another study showed that a tumor size greater than 2.1 cm increases the risk of malignancy [43]. In Lee KH et al.'s study, tumor size (>2.5 cm) and ultrasound findings suggestive of malignancy were proposed as determining factors [44], whereas Lee SH et al. found that only high TG levels and the presence of calcifications on ultrasound were significant predictive factors [27]. Overall, there are discussions about the utility of clinical characteristics, including nodule size, in predicting malignancy. According to one view, while the risk of PTC decreases with larger nodules, the risk of FTC increases as nodule size increases [45]. Recent studies suggest that nodule size in thyroid FN predicts malignancy potential [46]. This is consistent with the American Thyroid Association guidelines, which recommend total thyroidectomy for follicular lesions larger than 4 cm due to the increased risk of malignancy [47]. In contrast, some studies argue that there is no significant difference in nodule size between benign and malignant groups [27]. There are also studies that claim there is no relationship between increasing nodule size and malignancy rates [48]. In our study, when examining the relationship between nodule size and malignancy, it was observed that nodules 2 cm and smaller are frequently benign, while malignancy rates are higher in nodules between 2-4 cm and in those 4 cm and larger. Our findings parallel those of many studies in the literature. Differences in results from studies exploring the relationship between nodule size and malignancy risk may arise from variations in study populations and assessment criteria. According to authors who argue that nodule size is not proportional to malignancy risk, malignant thyroid nodules, especially undifferentiated types, may have a higher likelihood of growing faster than benign lesions. Furthermore, they are more likely to have a suspicious or malignant FNAB, which leads to earlier surgical intervention. In contrast, benign nodules are often monitored longer before surgery, during which time they may also grow. As in our study, authors who support the notion that the increase in nodule size is proportional to the increase in malignancy risk argue that the false-negative rate for FNAB increases with nodules larger than 4 cm [45].

The relationship between Hashimoto's thyroiditis and thyroid cancer remains a topic of debate [49, 50]. Studies by Rago et al. and Pu et al., which examined FN and Hürthle cell neoplasms together, showed that malignancy was not associated with Hashimoto's thyroiditis[32, 51]. In contrast to these studies, Zhang et al. suggested a significant association between Hashimoto's thyroiditis and the risk of PTC, reporting a much higher incidence of PTC in male patients with Hashimoto's thyroiditis [52]. In our study, all 33 patients with Hashimoto's thyroiditis underwent total thyroidectomy. Nineteen patients were in Group 1, and 14 were in Group 2. The frequency of malignancy in these patients was observed to be 42%, which is consistent with the overall malignancy rate. It was noted that Hashimoto's thyroiditis did not increase the risk of malignancy in nodules with FN.

Recently, molecular biomarkers such as BRAF, RAS, RET-PTC, or PAX8-PPARγ mutations are being researched for the diagnosis of thyroid nodules. BRAF mutations are observed in up to 83% of PTCs [53-55], while NRAS mutations are commonly found in FN [56]. In one study, NRAS mutations were observed in 22.3% of patients, with a higher prevalence of NRAS mutations in the malignant group (%13.8 vs. %30.4, p=0.013). Additionally, in the same study, multivariable analysis revealed that NRAS mutation was an independent risk factor for a malignancy diagnosis [28]. Similarly, Bae et al. reported that the overall malignancy rate in NRAS mutation cases was significantly higher compared to those without the mutation[57]. Furthermore, many studies have demonstrated that immunohistochemical markers such as galectin-3, HBME1, and cytokeratin-19 improve the sensitivity and specificity in differentiating benign cases from malignant cases in nodules preoperatively. However, due to various reasons such as operator-dependent factors, differences in analytical methods, and the overlap between follicular adenomas and differentiated thyroid carcinomas, these markers have not gained widespread acceptance in clinical practice [58, 59]. In our study, we did not have data related to molecular and immunohistochemical markers, so we could not draw conclusions about the predictive effects of the existing markers.

In a study conducted by Najafian et al., it was found that despite some differences in the presentation characteristics of benign and malignant follicular thyroid nodules, independent preoperative variables for malignant follicular thyroid lesions included male gender, positive family history, history of thyroid cancer, and a history of head and neck radiation [30]. Conversely, being over 45 years of age, presenting with dysphagia or a sensation of pressure, having a nodule larger than 4 cm, accompanying hyperthyroidism, and the presence of multinodular goiter emerged as preoperative indicators for benign follicular thyroid lesions. The correct combination of all clinical indicators may assist in making preoperative decisions for patients with follicular lesions. In our study, patients with malignancy were often younger and male. It was observed that malignancy increased in lesions measuring 2 cm or larger. There was no statistically significant difference in the presenting complaints between Groups 1 and 2. Our study observed that changes in thyroid function tests did not differ between benign and malignant groups. However, literature indicates that hyperthyroidism is more common in benign follicular thyroid lesions [30]. Given that hyperfunctioning thyroid nodules have a higher likelihood of being hot nodules, it is not surprising to observe such a relationship [60].

Recently, a gene expression classifier (Afirma) has been found to be quite useful in distinguishing between benign and malignant nodules in follicular lesions. This gene expression classifier has been reported to have a sensitivity of 90% for both indeterminate lesions and FN. The specificity and negative predictive value for FN are 49% and 94%, respectively. However, as mentioned above, access to these tests is often limited due to cost constraints. This situation highlights the search for other predictive factors that could potentially replace these molecular tests, which is a central theme of our study.

According to literature data, the increase in FN diagnoses has led to more thyroid surgeries, revealing a relatively low malignancy rate (MR) associated with FN (10-40%) [4, 9, 44]. Furthermore, neither preoperative ultrasound features, molecular markers, nor intraoperative pathology consultations have sufficient sensitivity to predict malignancy [61]. On one hand, total thyroidectomy (TT) may increase the need for medication and the risk of surgical complications due to excessive surgical intervention; on the other hand, hemithyroidectomy (HT) might not require medication or may only require low doses, with a lower risk of surgical complications, although it may sometimes necessitate complementary thyroidectomy. These two extremes represent the surgical treatment options for managing FN. Despite numerous studies in the literature, management guidelines remain debated; endocrinologists or head and neck surgeons are divided into those who support routine TT and those who oppose it. Additionally, surgical treatment options for FN vary between institutions and even among surgeons within the same institution. Current evidence confirms that patients with FN should be better evaluated preoperatively to avoid unnecessary diagnostic surgery.

The differences in malignancy rates in the literature suggest that the biological behavior of the disease may vary by geographical region. Demographic, clinical and radiological predictive risk factors associated with patients yield different results across studies. Currently, the use of molecular tests recommended for FN is limited. Due to cost concerns and issues with institutional access, these tests have not yet been adopted into routine practice. Furthermore, discussions continue regarding frozen section pathology examinations performed during surgery and how treatment strategies should be determined accordingly. In light of all this data, many factors must be considered when selecting the type of surgery for patients with FN. It should be noted that TT might be overtreatment in cases of FN where the risk of malignancy is relatively low. Conversely, performing HT without considering possible risk factors could lead to additional surgical interventions, increasing costs and surgical complications. While a more conservative surgical approach is recommended for FN patients, there is a need for multicenter, multifactorial analyses based on prospective randomized studies aimed at reducing unnecessary diagnostic surgeries and increasing preoperative diagnostic accuracy.

5. Conclusion

According to the results of our study, the risk of malignancy in FN cases increases in males, nodules larger than 2 cm, and younger age groups. Our data indicate that the malignancy risk in FN is 45.3%. Additionally, the incidental thyroid cancer rate outside of the targeted FN nodule was found to be 37.9%. These rates are higher than those reported in the literature, likely due to the high prevalence of thyroid cancer in our region. Furthermore, the presence of concurrent Hashimoto's disease, the detection of multiple nodules on ultrasound examinations and a history of thyroid cancer in some patients have led to a more frequent preference for total thyroidectomy (TT) in our surgical choices. However, it has been observed that these variables do not increase the risk of malignancy in FN.

Statement of ethics

Ethical approval was obtained from the Başkent University School of Medicine with the number KA 22/125.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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