ORIGINAL ARTICLE

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How can we Evaluate the Incidental Malignancy of a Thyroid Nodule Regarding Age?

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Abstract

Objective: Since the ultrasonography (US) examination and fine-needle aspiration (FNA) biopsy have been used in the clinicopathological evaluation of thyroid pathology, a progressive increase in the prevalence of incidental micropapillary carcinomas (IMC) has been reported. Here, we investigated the predictive factors of suspicious malignancy of thyroid nodules increasing with age.

Methods: A retrospective review of data of 173 patients who underwent FNA biopsy and subsequent thyroidectomy in the Clinic of General Surgery University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between December 2016-December 2019 years.

Results: The mean age of the patients was 46.7±22.6 (18-80). Most of the patients underwent total thyroidectomy (90.8%) based on the indication of FNA (47.4%) and toxic goiters (26.6%). The 76 patients were euthyroid (43.9%). The US showed that the hypoechogenicity and loss of the halo were the most common findings (60.1% and 57.8%, respectively). The number of patients more than 45 years who showed an irregular margin in the thyroid nodule was higher than younger patients (p=0.016). Although malignancy was mostly observed in young patients (100% vs. 87.5%, p=0.0022), IMC was seen more in older patients (33, 38.8% vs. 45, 51.1%, p=0.104). The loss of Halo and type of surgery had a significant effect on the presence of incidental carcinoma (odds ratio: 0.307 and 14.428, p=0.014 and 0.0026, respectively).

Conclusion: The old age, type of surgery, radiological findings including the loss of Halo might have a potential impact on the presence of IMC in the preoperative assessment of nodules regarding the management of surgical procedure.

Keywords: Thyroid nodule, thyroidectomy, aging

INTRODUCTION

Thyroid cancers are the most common cancers among youth and adults (1). The increasing age of thyroid cancer diagnosis starting at age 40 has been correlated with higher mortality due to cancer (2). The survival rates of young patients with thyroid malignancy are higher than older patients, but there is a tendency to treat these young patients with more aggressive therapies such as thyroidectomy. The primary treatment modality for thyroid cancers is lobectomy or thyroidectomy to remove all or part of the thyroid, respectively. The younger patients may live many decades after treatment and may have more risks for long-term health effects due to a more aggressive treatment (3).

There are a limited number of studies showing that age affects the thyroid cancer risk (4-6), and epidemiological analyses reported a positive association between thyroid nodule formation and advancing patient age (7,8). However, the details and mode of this association with other risk factors (linear mode or a threshold effect) are poorly understood.

There is a significant increase in the number of new cases of thyroid cancers (9). Specifically, several microcarcinomas, which are small thyroid cancers, are diagnosed following a surgery performed for benign thyroid pathology. The microcarcinomas which are incidentally diagnosed are called incidental thyroid cancers, and if the size of these tumors is smaller than or equal

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to 1 cm, they are called incidental micropapillary carcinomas (IMC) (10). There some studies that approved that smaller thyroid cancers have a better prognosis than larger ones (11), however, it should be considered that insignificant thyroid tumors, particularly those less than 1 cm in diameter, might have an unfavorable prognosis (12). Compared to the ratio of thyroid nodules, the frequency of IMCs is relatively uncommon (13). Since the ultrasonography (US) examination and fine-needle aspiration (FNA) biopsy have been introduced and commonly used in the clinicopathological evaluation of thyroid pathology, a progressive increase in the prevalence of IMC has been reported (14). Therefore, it appears crucial and beneficial for clinicians to establish a detailed correlation between the clinical and histopathological features of patients with IMC to predict the risk factors for the IMC. Primarily, we aim to understand the impact of aging and secondly, any correlation with the demographic and clinical features regarding the presence of incidental IMC in our population following thyroidectomy which is related to benign or malignant FNA biopsy.

METHODS

The study was conducted in the Clinic of General Surgery University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital and retrospectively analysed regarding the data which is collected between December 2016-December 2019. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (no: 2020.02.1.01.019; date: 07/02/2020). All procedures performed in this study involving human participants were under the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Patient consent could not be received from the patients due to the retrospective design of the study.

Patients

The selection criteria of the patients were based on the FNA biopsy and subsequent thyroidectomy, including all the data of demographics and clinical features. Patients with incomplete data were excluded from the study. Also, we excluded the patients without surgery during follow-up.

The data of patients, including the demographic features were sex, age, radiation exposure history, family history of thyroid diseases, type of surgery, the diameter of the nodule (mm). As clinical indications, FNA results, nodule size, compression/cosmetic, grave disease, toxic goiter, coexisting hyperparathyroidism was recorded. The outcomes of thyroid function tests, including free T3, free T4, and thyroid-stimulating hormone (TSH) and the corresponding diagnosis of hypothyroidism, euthyroidism, or hyperthyroidism were recorded. Normal ranges for serum-free T3, free T4, and TSH were 1.71-3.71 pg/mL, 0.70-1.48 ng/dL, and 0.35-4.94 IU/mL, respectively. Lymphadenectomy was performed from the central, regional, or central + regional. FNA cytology (FNAC) findings were determined following the Bethesda category, as well and an overall histopathological diagnosis (benign or malign) was recorded according to the pathology reports. All data were analyzed regarding the occurrence of incidental micropapillary carcinoma. IMC was determined as a well-differentiated single or multiple tumor smaller than 1 cm, diagnosed incidentally intra or extra-nodular region, inside or outside the same lobe with a benign or malign lesion. IMC was also confirmed by immunohistochemical positive staining for thyroglobulin, showing a follicular differentiation.

IMC with a size under 1 cm, which can coexist with benign or malignant nodules encountered in the same thyroid nodule, was examined by biopsy and correlated with the demographic and clinical features of all patients.

Ultrasound Imaging

Ultrasound imaging of the thyroid was performed by the Esaote Color Doppler US (MAG Technology Co, Ltd. Model: 796FDII Yung-ho City, Taipei, Taiwan) using a superficial probe (model no: LA523 13-4, 5.5-12.5 MHz) when the patient was in a supine position and the neck was hyperextended. The existence of a solitary nodule and the diameter of the nodule were recorded. Radiological findings recorded for each nodule involved echogenicity (hypoechoic or hyper- and isoechoic), margin (irregular or well-bordered), microcalcifications (absent or present), the peripheral halo (absent or present), increased vascularity (absent or present) and cervical lymph nodes (15).

Fine Needle Aspiration Cytology

All cytological and pathological examinations of thyroid samples were performed by an experienced cytopathologist. FNA biopsy was performed by the guidance of General Electric Logiq pro 200 US (Model number 2270968; GE Healthcare Korea, Seongnam SI, Gyean GGI-DO, Korea) using a 5.5-7.5 MHz probe, 27-gauge needle and a 20 mL volume syringe. All nodules showing one or more suspicious US indications, determined by the decision of the physician, were examined by FNAC. The aspiration samples were fixed by air drying and stained by May-Grunwald-Giemsa for cytological evaluation.

The Bethesda System for Reporting Thyroid Cytopathology System was used to analyze FNAC samples described as non-diagnostic or

unsatisfactory (I), benign (II), atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS) (III), follicular neoplasm/suspicious for follicular neoplasm (including oncocytic lesions) (IV), suspicious for malignancy (V), malignant (VI) (16).

Statistical Analysis

Power calculations were performed based on the use of two sample t-tests. Using two-sided tests with a significance level of 0.05, there was at least 80% power to detect large effect sizes of 0.8 or more between age groups. With the planned sample size, there was at least 80% power to detect large differences exceeding 30% in the percentage of age groups. Given the cross-sectional nature of these estimates, they provided conservative estimates of power, and small effect sizes were detectable when evaluating these outcomes in a longitudinal model. Power calculations were performed using G-Power version 3.1.

Frequency, percentage values are described for the categorical variables. Mean, standard deviation, median, minimum and maximum values are described for the continuous variables. Normal distribution testing of continuous variables was performed using the Kolmogorov-Smirnov test. Categorical variables were compared with chi-square analysis. When appropriate, the categorical variables were analyzed by Fisher's Exact and Fisher-Freeman-Halton test. For the variables that did not execute the normal distribution assumption, Mann-Whitney U test was used for a comparison of two independent groups. Binary logistic regression was performed to determine the effect of variables on incidental carcinoma. A receiver operating characteristic (ROC) curve was constructed to assess the sensitivity and specificity of the loss of Halo to diagnose the IMC. The ideal cut off value was determined using the Youden index and accordingly, the sensitivity and specificity of the loss of Halo were calculated. The change in the related areas under the curve (AUC) was tested using the DeLong test (17). Pearson correlation coefficient analysis (Pearson's r measures the linear correlation between the IMC and the clinicopathological findings of thyroid nodules.

Statistical analyses were performed using NCSS 11 (Number Cruncher Statistical System, 2017 Statistical Software) and MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium). A p value <0.05 was set as significant.

RESULTS

The demographic and clinical features of all patients are presented in Table 1. The total number of patients was 173, 74% of these patients were female and 26% were male. The mean age of all patients was 46.7±22.6 (18-80 years). Only one patient younger than 45 (0.6%) had radiation therapy on the neck, and three patients (1.7%) had a family history of thyroid carcinoma (Table 1).

Most of the patients underwent total thyroidectomy (90.8%) based on the indication of FNA (47.4%) and the presence of toxic goiter (26.6%). The rarest surgical indications were coexisting hyperparathyroidism and the nodule size (2.9% and 5.2%, respectively). The mean diameter of nodules was found 22.6±14.9 mm. No significant difference was found in the surgical indications and diameter of nodules between the patients ≤45 and >45 years old (Table 1).

The 76 patients were euthyroid (43.9%). Hyperthyroidism is the rarest status of thyroid function among patients (15.1%). There was no significant difference in the distribution of any thyroid function between the patients ≤45 and >45 years old (Table 1).

Radiological examination showed that the hypoechogenicity and loss of Halo were the most common findings among patients without any significant difference between age groups (60.1% and 57.8%, respectively). The number of patients older than 45 years (30.7%) who showed an irregular margin in the thyroid nodule was significantly higher than younger patients (p=0.016). Comparing FNAC findings, the suspicious nodules for cancer and AUS/FLUS were the most predominant cytopathological diagnoses among the patients (28.9% and 23.1%, respectively) but no significant difference was found between the age groups (Table 1).

The detailed pathological analysis of the thyroid specimens indicated that the most common histopathological diagnosis was the papillary carcinoma and Hashimoto's thyroiditis among the patients (39.3% and 26.6%, respectively). However, there was no significant difference between the age groups in terms of the pathology of the thyroid nodules. Other pathological diseases are given in Table 1. Depending on the overall pathological diagnoses, 85 patients under 45 years (100% of the younger age group) had a diagnosis of thyroid malignancy, while 77 patients older than 45 (87.5% of older age group) had malignancy, (p=0.0022). Lastly, 45.1% of patients were diagnosed with an IMC, without any difference among age groups (Table 1). Even though, malignancy was mostly seen in the young population (>45 years old), (85, 100% vs. 77, 87.5%, p=0.0022), the IMC was seen more likely in older population (>45 years old), (33, 38.8% vs. 45, 51.1%, p=0.104), (Table 1).

Logistic regression univariate analysis of patients based on the presence of IMC (Table 2) indicated that the loss of Halo defined

Table 1. Demographic and clinical features of the patients in comparison of the age					
Variable		**Total n=173**	**Age ≤45 n=85**	**Age >45 n=88**	**p°**
Sex n (%)	Female Male	128 (74) 45 (26)	65 (76.5) 20 (23.5)	63 (71.6) 25 (28.4)	0.465
Age (year)	Mean ± SD Min-max	46.7±22.6 18-80	35.8±7.3 18-45	57.1±8.4 46-80	-
Radiation history	n (%)	1 (0.6)	1 (1.2)	0 (0)	0.308*
Family history	n (%)	3 (1.7)	1 (1.2)	2 (2.3)	0.580*
Surgical indication n (%)	FNA Nodule size Compression/cosmetic Graves' disease Toxic goiter Coexisting hyperparathyroidism	82 (47.4) 9 (5.2) 17 (9.8) 14 (8.1) 46 (26.6) 5 (2.9)	40 (47.1) 6 (7.1) 10 (11.8) 6 (7.1) 21 (24.7) 2 (2.4)	42 (47.7) 3 (3.4) 7 (8.0) 8 (9.1) 25 (28.4) 3 (3.4)	0.797**
Status of thyroid function n (%)	Hypothyroidism Euthyroidism Hyperthyroidism	71 (41.0) 76 (43.9) 26 (15.1)	35 (41.2) 35 (41.2) 15 (17.6)	36 (40.9) 41 (46.6) 11 (12.5)	0.591
Type of surgery n (%)	Lobectomy Total thyroidectomy	16 (9.2) 157 (90.8)	10 (11.8) 75 (88.2)	6 (6.8) 82 (93.2)	0.262
The diameter of the nodule (mm)	Mean ± SD Min-max	22.6±14.9 3.0-70.0	23.7±14.9 3-65	21.6±14.8 4-70	0.267***
Radiological findings n (%)	Hypo echogenicity	104 (60.1)	47 (55.3)	57 (64.7)	0.203
	Irregular margin	40 (2.3)	13 (15.3)	27 (30.7)	**0.016**
	Microcalcifications	46 (26.6)	18 (21.2)	28 (31.8)	0.113
	Loss of Halo	100 (57.8)	50 (58.8)	50 (56.8)	0.924
	Increased vascularity	23 (13.3)	13 (15.3)	10 (11.4)	0.447
	Cervical lymph nodes	62 (35.8)	34 (40)	28 (31.8)	0.262
FNAC findings n (%)	Non-diagnostic/unsatisfactory Benign AUS/FLUS Follicular neoplasm Cancer suspicious Cancer	16 (9.2) 31 (17.9) 40 (23.1) 12 (6.9) 50 (28.9) 24 (13.9)	8 (9.4) 15 (17.6) 22 (25.9) 4 (47.1) 22 (25.9) 14 (16.5)	8 (9.1) 16 (18.2) 18 (20.5) 8 (9.1) 28 (31.8) 10 (11.4)	0.684
Lymphadenectomy	Central Regional Central + regional	13 (7.5) 14 (8.1) 4 (2.3)	8 (9.4) 8 (9.4) 3 (3.5)	5 (5.7) 6 (6.8) 1 (1.1)	0.468
Pathology	Adenomatous nodule	17 (9.8)	5 (5.9)	12 (13.6)	0.465
	Colloidal nodule	20 (11.6)	9 (10.6)	11 (12.5)	
	Hemorrhagic cyst	3 (1.7)	1 (1.2)	2 (2.3)	
	Graves' disease	6 (3.5)	3 (3.5)	3 (3.4)	
	Hashimoto's thyroiditis	46 (26.6)	28 (32.9)	18 (20.5)	
	Follicular adenoma	2 (1.2)	1 (1.2)	1 (1.1)	
	Hurthle cell adenoma	1 (0.6)	0 (0)	1 (1.1)	
	Follicular carcinoma	0 (0)	0 (0)	0 (0)	
	Papillary carcinoma	68 (39.3)	32 (37.6)	36 (40.9)	
	Hurthle cell carcinoma	3 (1.7)	1 (1.2)	2 (2.3)	
	Poor differentiated carcinoma	2 (1.2)	2 (2.4)	0 (0)	
	Medullary carcinoma	5 (2.9)	3 (3.5)	2 (2.3)	
Overall pathology	Benign Malign	11 (6.4) 162 (93.6)	0 (0) 85 (100)	11 (12.5) 77 (87.5)	**0.0022**
Incidental micropapillary carcinoma	n (%)	78 (45.1)	33 (38.8)	45 (51.1)	0.104

Normally distributed data were recorded as mean ± standard deviation, SD: Standard deviation, FNAC: Fine-needle aspiration cytology, AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance. °Chi-square analysis, *Fisher's Exact test, **Fisher-Freeman-Halton test, ***Mann-Whitney U test (p value <0.05 as significant)

by the US had a significant effect on the presence of incidental carcinoma [odds ratio (OR): 0.307; 95% confidence interval (CI): 0.125-0.751; p=0.014]. As we expected, the type of surgery, such as total thyroidectomyhad a considerable effect on seeIMC (OR: 14.428; 95% CI: 1.861-112.01; p=0.0026), (Table 2).

Logistic regression multivariate analysis of patients based on the presence of IMC (Table 3) also indicated that the loss of Halo significantly increased the risk of the presence of IMC by 4.036 times (95% CI: 1.499-10.864; p=0.006). Moreover, total thyroidectomy was helpful to find IMC18.13 times more than lobectomy (95% CI: 2.121-148.59; p=0.007) (Table 3).

The correlation between the ratio of IMC and the clinical and pathological findings of thyroid nodules (Table 4) revealed that there was a higher correlation between the total thyroidectomy and the presence of IMC (r=0.249; 95% CI: 0.104-0.384; p=0.0009). Additionally, the loss of Halo was also significantly

Table 2. Univariate analysis of patients based on the presence of incidental micropapillary carcinoma

Variable		Odds ratio*	95% CI	p
Sex		0.966	0.488-1.912	0.920
Age		1.010	0.988-1.034	0.374
Radiation history		0.401	0.016-9.997	0.364
Family history		0.604	0.054-6.791	0.680
Surgical indication	FNA Nodule size Compression/cosmetic Graves' disease Toxic goiter Coexisting hyperparathyroidism	0.827 1.028 2.933 1.103 0.969 0.196	0.454-1.507 0.266-3.967 0.916-9.395 0.366-3.328 0.492-1.909 0.022-1.799	0.640 0.968 0.104 0.861 0.928 0.256
Status of thyroid function	Hypothyroidism Euthyroidism Hyperthyroidism	1.562 0.849 0.661	0.843-2.896 0.464-1.551 0.286-1.527	0.206 0.704 0.447
Type of surgery	Total Thyroidectomy	14.438	1.861-112.01	**0.0026****
Diameter of nodule		0.988	0.967-1.008	0.236
Radiological findings	Hypo echogenicity Irregular margin Microcalcifications Loss of Halo Increased vascularity Cervical lymph nodes	1.011 1.293 0.915 0.307 0.720 0.899	0.548-1.864 0.637-2.626 0.464-1.806 0.125-0.751 0.299-1.736 0.482-1.679	0.973 0.595 0.934 **0.014** 0.611 0.862
FNAC findings n (%)	Non-diagnostic/insufficient Benign AUS/FLUS Follicular neoplasm Cancer suspicious Cancer	0.610 0.835 1.146 0.809 0.950 1.772	0.216-1.720 0.391-1.853 0.561-2.340 0.250-2.616 0.491-1.837 0.715-4.393	0.498 0.835 0.846 0.957 0.878 0.305
Lymphadenectomy	Central Regional Central + regional	3.165 1.876 1.407	0.931-10.766 0.618-5.691 0.193-10.273	0.065 0.267 0.737
Pathology	Adenomatous nodule Colloidal nodule Hemorrhagic cyst Graves' disease Hashimoto's thyroiditis Follicular adenoma Hurthle cell adenoma Papillary carcinoma Hurthle cell carcinoma Poor differentiated carcinoma Medullary carcinoma	1.571 1.265 1.656 0.815 0.764 4.198 0.271 0.570 0.404 9.541 0.819	0.553-4.462 0.489-3.27 0.147-18.62 0.160-4.159 0.388-1.502 0.198-88.81 0.011-6.73 0.218-1.493 0.036-4.546 0.519-175.4 0.05-13.321	0.550 0.805 0.680 0.806 0.543 0.566 0.921 0.357 0.863 0.110 0.888
Overall pathology	Benign or malign	1.472	0.415-5.225	0.774

FNAC: Fine-needle aspiration cytology, CI: Confidence interval, AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance, Logistic regression*, p value <0.05 as significant**

correlated with the presence of IMC (r=0.204; 95% CI: 0.057-0.343; p=0.0071).

The result of ROC analysis for the loss of Halo to predicting the IMC is given in Figure 1. The AUC from the set tested was found as 0.64 (95% CI: 0.57-0.71), the sensitivity and specificity were 0.69 (95% CI: 0.48-0.85) and 0.59 (95% CI: 0.50-0.70), respectively.

DISCUSSION

Several studies are comparing the possible effect of increasing age on the risk of thyroid malignancy, reporting some conflicting findings as we consider (18,19). A large-scale, prospective analysis examining this possible effect in the patients presenting with thyroid nodules confirmed an increased prevalence with increasing age and a reduced risk of malignancy in these nodules, which is opposite to what we found such as a high amount of IMC correlated with increasing age (20). Although thyroid nodules are more common and more likely benign among older patients, there are also studies suggesting that the aggressive nature of thyroid cancers is more likely to augment with increasing age (20). Contrary to our findings, the number of older patients (>45 years) who showed an irregular margin in the thyroid nodule was significantly higher than younger patients. Depending on the overall pathological diagnoses, all young patients and 87.5% of older patients had a diagnosis of thyroid malignancy, with a considerable difference between the age groups. Even though the malignancy was mostly seen in the young population, the IMC was seen more likely in the older population, suggesting that early relevant diagnosis of thyroid nodules provides a critical step for the optimal outcome.

Throughout the recent decades in Turkey, regarding the changes in the surgical approach for thyroid nodules with lower Bethesda class (Bethesda classes I, II, and III), the suggestions for the surgery have been re-considered. Therefore, follow-up of suspicious nodules and repeating FNAC is generally recommended for the clinical management of these thyroid nodules (21). A very recent

Table 3. Multivariate analysis of patients based on the presence of incidental micropapillary carcinoma

Variable	Odds ratio*	95% CI	p
Type of surgery	18.13	2.212-148.59	**0.007****
Loss of Halo	4.036	1.499-10.864	**0.006****

CI: Confidence interval, Binary Logistic regression*, p value <0.05 as significant**

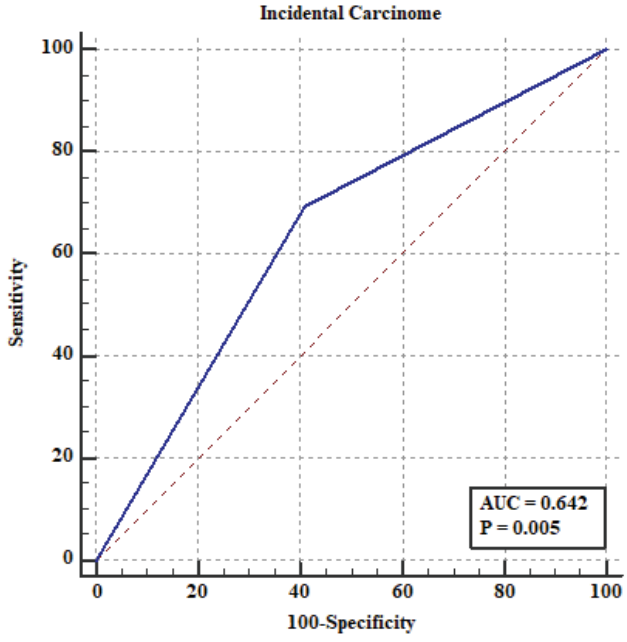

Figure 1. ROC analysis for the loss of Halo to predict the incidental micropapillary carcinoma
AUC: Area under the curve, ROC: Receiver operating characteristic

Table 4. Correlation between the incidental micropapillary carcinoma and the clinical and pathological findings of thyroid nodules

Variable		Pearson r*	95% CI	p
Status of thyroid function		0.112	-0.039-0.257	0.145
Type of surgery		0.249	0.104-0.384	**0.0009****
Diameter of nodule		-0.091	-0.237-0.060	0.236
Radiological findings n (%)	Hypo echogenicity	0.003	-0.147-0.152	0.973
	Irregular margin	0.054	-0.096-0.202	0.479
	Microcalcifications	-0.019	-0.168-0.130	0.800
	Loss of Halo	0.204	0.057-0.343	**0.0071****
	Increased vascularity	0.056	-0.094-0.203	0.466
	Cervical lymph nodes	0.025	-0.124-0.174	0.741
FNAC findings		-0.084	-0.231-0.066	0.270
Overall pathology		0.046	-0.104-0.194	0.551

FNAC: Fine needle aspiration cytology, CI: Confidence interval, *Pearson correlation coefficient (r), **p value <0.05 as significant

study from Turkey reported malignancy rates ranging from 10 to 30% for Bethesda class III and 25-40% for class IV, while we did not find any correlation or impact regarding the Bethesda and aging process in our study (22). An evaluation of thyroid nodules in the Turkish population reported that age, gender, and thyroid status were not associated with increased risk of malignancy but irregular margins and microcalcifications have an impact, which is consistent with our findings while the younger population had more malignancy. They concluded that US features, especially microcalcification, is a critical predictor of malignancy without age, gender, and thyroid status and we evaluated especially loss of Halo and irregular margins affected the IMC increasing with age (23). Uyar et al. (24) evaluated patients with suspicious solitary nodules undergoing bilateral total thyroidectomy for the presence of malignancy and concluded that irregular margins, microcalcification, increased vascularity, and detection of cervical lymphadenopathy were correlated with malignancy in solitary nodules. Consistently, the irregular margin among the radiological findings of thyroid nodules was observed commonly in older patients due to a possible increase in Bethesda classification based on the FNA biopsy results.

The diagnosis of incidental carcinoma in patients who have undergone thyroidectomy for a benign disease is quite common. A retrospective analysis of the findings of surgical intervention to establish the incidence of the carcinoma reported 50% that the only way to determine the exact benign feature of the thyroid disease is FNAC (25). Even we analysis retrospectively, we performed similar features as Atli et al. (26) which was prospectively defined the risk factors predicting thyroid malignancy to establish management criteria for thyroid incidentalomas. Their multivariate analyses revealed that the independent clinical predictors of malignancy were a fixed nodule, cervical lymphadenopathy, euthyroidism, and a patient age <23 years or more than 45 years that we measured among >45 years old. Moreover, they found a significant association between the independent nodule features with malignancy and microcalcifications, irregular margin, solid appearance on USG, consistent with some findings. As we measured, IMC was determined in 45.1% of the patients with benign or malignant nodules encountered in the same thyroid nodule or lobule following thyroidectomy. Logistic regression analysis indicated that the loss of Halo on USG significantly increased the risk of the presence of IMC by 4.036 times. Moreover, a total thyroidectomy was effective in the diagnosis of IMC for 18.13 times more than lobectomy. It was reported that the correlation between the ratio of IMC and the clinical and pathological findings of thyroid nodules was more likely with the total thyroidectomy and he loss of Halo. Supporting these results, ROC analysis for the loss of Halo presented relatively high sensitivity and specificity for predicting potential IMC presence. Depending on the radiological findings of a thyroid nodule, a simple follow-up including an FNAC might be proposed for managing suspicious malignancy regardless of the diameter measurements.

Study Limitations

However, the limitation in our study were that small sample sizes have been analyzed retrospectively from the data of a single center and thyroid surgery group from a restricted region, which may limit the generalization to other regions and groups. Secondly, our study was limited by its retrospective analysis, including measurement, observational, and recall biases. Also, no stepwise or any other machine learning models were further used to measure the performance of our prediction model. Even although we have some limitations, the current study has some clinical diagnostics, which could measure the predictors of the presence of IMC, which guide the surgical decision based on both the FNAC and radiological results regardless of the diameter measurements.

CONCLUSION

Due to the increased incidence of IMC in patients operated for benign thyroid disease, an accurate preoperative assessment with a careful selection of nodules for FNAC correlated with US patterns is becoming a necessity in the choice of surgical procedure. Especially with careful investigation of malignancy in the young population (>45 years old) and the presence of the IMC in the older population (>45 years old) have been warranted in larger sample size populations regarding our outcomes.

Consequently, the patient age, surgical approach, and radiological findings such as loss of Halo, may help consider the potential presence of IMC in overall pathological examinations that might warrant a careful surgical management of patients with thyroid nodules.

Ethics

Ethics Committee Approval: The study was conducted in the Clinic of General Surgery University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital and retrospectively analysed regarding the data which is collected between December 2016-December 2019. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (no: 2020.02.1.01.019; date: 07/02/2020).

Informed Consent: Patient consent could not be received from the patients due to the retrospective design of the study.

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Authorship Contributions

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