ORIGINAL RESEARCH

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The Performance Analysis of the Thyroid Nodule Size to Predict the Coexistence of Micropapillary Carcinoma

Mikropapiller Karsinom Birlikteliğini Tahmin Etmekte; Tiroid Nodül Boyutu Performans Analizi

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Abstract

Objective: Incidental micropapillary carcinoma (IMC) is the most common variant of thyroid malignancies. There are unmet needs regarding the efficacy of nodule size in the prediction of the coexistence of IMC. We aimed to measure the effect of nodule size on the prediction of the coexistence of IMC.

Method: The data of 194 patients who underwent biopsy for fine-needle aspiration cytology and subsequent thyroidectomy in a research and training hospital between January 2017 and February 2020 were analyzed retrospectively. The patients were divided into three groups according to the sizes of thyroid nodules as 0-10 mm, 11-20 mm, and >20 mm. Logistic regression analysis was performed.

Results: The patients with nodule size between 0 mm and 10 mm mostly showed hypothyroidism (51.0% vs. 28.8% vs. 41.8%) while patients with size between 11 mm and 20 mm mostly had euthyroidism (44.2% vs. 45.1% vs. 41.8%, p=0.0175). Both malignancy (51.9% vs. 49.0% vs. 42.9%, p=0.544) and IMC (65.4% vs. 51.0% vs. 56.0%, p=0.32) were observed more likely in patients with moderate size (11-20 mm). We found the following variables to be predictors for the coexistence of IMC: absence of halo [odds ratio (OR): 4.50, 95% confidence interval (CI): 1.61-14.71, p=0.007], and interestingly decrease in vascularity [OR: 0.33, 95% CI: 0.12-0.87, p=0.030], and total thyroidectomy, [OR: 4.55, 95% CI: 2.30- 9.56, p<0.001].

Conclusion: With increased nodule size (>2 cm), we reported more IMC inside the thyroid gland. However, the nodule size has the low performance to be a predictor for the coexistence of IMC in the thyroid gland.

Keywords: Malignancy, nodule size, thyroidectomy

Öz

Amaç: İnsidental mikropapiller karsinom (İMK), tiroid malignitelerinin en yaygın mikropapiller varyantıdır ve son on yılda insidansı artmaktadır. Tiroid bezinde İMK varlığını tahmin etmede nodül boyutunun etkinliğine ilişkin veriler yeterli değildir. Bu retrospektif çalışmada nodül boyutunun, İMK'lerin tiroid bezinde diğer lezyonlarla bir arada bulunmasının öngörülmesine etkisini araştırdık.

Yöntem: Ocak 2017-Şubat 2020 tarihleri arasında ince iğne aspirasyon sitolojisi ve ardından tiroidektomi için biyopsi yapılan 194 hastanın verileri retrospektif olarak incelendi. Hastalar tiroid nodüllerinin boyutlarına göre 0-10 mm, 11-20 mm ve >20 mm olarak üç gruba ayrıldı.

Bulgular: Nodül boyutu 0-10 mm arasında olan hastalarda en çok hipotiroidizm (%51,0, %28,8 ve %41,8) görülürken, boyutu 11-20 mm arasındaki hastalarda en çok ötiroidizm görüldü (%44,2, %45,1 ve %41,8, p=0,0175). Hem malignitenin (%51,9, %49,0 ve %42,9, p=0,544) hem de İMK'nin (%65,4, %51,0 ve %56,0, p=0,32), orta büyüklükte (11-20 mm) nodül boyutu olan hastalarda görülme olasılığı yüksekti. Aşağıdaki değişkenlerin İMK'nin görülmesini daha fazla etkilediğini bulduk: halo yokluğu [olasılık oranı (OO): 4,50, %95 güven aralığı (GA): 1,61-14,71, p=0,007], vasküleritede azalma [OO: 0,33, %95 GA: 0,12-0,87, p=0,030] ve total tiroidektomi [OO: 4,55, %95 GA: 2,30-9,56, p<0,001].

Sonuç: Nodül boyutunda artışla (>2 cm) birlikte tiroid bezi içinde daha fazla İMK'ye rastlanmıştır. Bununla birlikte, nodül boyutunun tiroid bezinde İMK bulunma riski için prediktif bir faktör olma potansiyeli düşüktür.

Anahtar kelimeler: Malignite, nodül boyutu, tiroidektomi

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Introduction

Thyroid nodules are typically benign lesions with a prevalence of 2-6% with palpation, 19-35% with routine ultrasound imaging (USG), and 8-65% in biopsy (1). The incidental malignant tumors of the thyroid gland can be detected by postoperative examination because of benign lesions. Additionally, incidental thyroid carcinoma is the most common pathological type with an incidence ranging from 3% to 20.3% (2,3). Incidental micropapillary carcinoma (IMC) is the most common micropapillary variant (3), with an increasing incidence in the past decades, due to developments and much use of diagnostic procedures, which enable the detection of smaller tumors, particularly IMC in the nodules of a diameter smaller than 10 mm according to the World Health Organization classification system (4). It is controversial whether or not the size of the thyroid nodule is correlated with the presence of IMC and other clinicopathological features of patients (5,6). Despite the fact that the prognostic advantage of IMCs has been an issue of debate in recent studies (6-8), there is a lack of information about the predictive value of the size of thyroid nodules in the risk and early diagnosis of IMC among thyroid cancers (9-11). Although most IMCs were discovered incidentally on Fine Needle Aspiration Cytology (FNAC) during the pathological examination of benign lesions, there are unmet needs regarding the efficacy of nodule size in the prediction of the presence of IMCs in the thyroid gland. We investigated the effect of the nodule size on the prediction of the association of IMCs in the thyroid gland with ultrasonographical non-visualized adjacent malignancies. Our retrospective study is a good clinical tool to consider the nodule size as a predictive factor for the presence of IMC in the thyroid gland. It is important to consider the thyroid nodule size during outpatient follow-up to suspect the further association of IMC in the thyroid gland.

Materials and Methods

A retrospective review of the data of 194 patients who underwent FNA biopsy and subsequent thyroidectomy in the General Surgery Department of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between January 2017 and February 2020 was performed. This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (no: 2020.02.1.03.021, date: 07/02/2020). All procedures were consistent with the principles of the Helsinki Declaration. The 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 data of demographics and clinical features. The patients with incomplete data were excluded from the study. The data of patients including the demographic features were about sex, age, radiation history, family history of thyroid diseases, type of surgery, and the diameter of the nodule (mm). As clinical indications, FNA, nodule size, compression/cosmetics, Grave's disease, toxic goiter, and coexisting hyperparathyroidism were recorded. The diagnoses with thyroid function tests, including hypothyroidism, euthyroidism, or hyperthyroidism, were recorded. Lymphadenectomy was performed as central, regional, or central with regional levels. FNA cytology (FNAC) findings were determined by the Bethesda category, and an overall histopathological diagnosis (benign or malignant) was recorded according to the pathology reports. All data were analyzed by comparing the outcomes with the nodule size and IMC. The sizes of thyroid nodules were determined according to the recent ATA guidelines and the patients were divided accordingly into three groups as 0-10 mm, 11-20 mm, and >20 mm (12). IMC was determined as a well-differentiated single tumor or multiple tumors smaller than 1 cm, diagnosed incidentally in intra- or extranodular region, inside or outside the same lobe with a benign or malignant lesion. IMC was also confirmed by immunohistochemically positive staining for thyroglobulin, showing a follicular differentiation. We included IMC in intranodular region and inside the same lobe with a benign or malignant lesion.

USG

Ultrasound (US) imaging of the thyroid was performed by the Esaote Color Doppler US (MAG Technology Co, Ltd. Model: 796FDII Yung-ho City, Taipei, Taiwan). Radiological findings recorded for each nodule included the 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 (13).

FNAC

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).

The aspiration samples were evaluated by May-Grunwald-Giemsa for cytological examination. The Bethesda System for Reporting Thyroid Cytopathology system was used to analyze FNAC samples described in the literature (14).

Statistical Analysis

The categorical variables were reported as percentages and also continuous variables as mean with standard deviation for descriptive statistics. The chi-square test for categorical variables and t-test for continuous variables were performed by univariate analysis comparing patients with the coexistence of IMC. The dataset was diverged arbitrarily into two cohorts: 75% of patients were used in a training set, and the remaining 25% were used as a test set. A clinically applicable prediction model for the coexistence of IMC was created by a selection-based analysis ($p<0.05$ in univariate analyses of the unadjusted covariates based on the per-operative assessment). The determination of predictive variables for the coexistence of IMC to control potential confounders was utilized by multivariable logistic regression. The test set identified the sensitivity, specificity and receiver-operating characteristic curve (receiver operating characteristic curve) of each model. The bootstrapping to generate a 95% confidence interval of the sensitivity and specificity was performed. Significance was the level of $p<0.05$. R software version 3.4.2. was used for analysis.

Results

Outcomes Regarding Nodule Size

A comparison of patient characteristics based on the increase in nodule size was evaluated (Table 1). The total number of patients was 194, 75.3% of these patients were female, and 24.7% were male. The mean age of all patients was 46.6±13.1 years (18-89 years). Only one patient having a nodule size larger than 20 mm (0.52%) had radiation therapy on the neck, and three patients (1.55%) had a family history of thyroid carcinoma. The mean diameter of nodules was found as 22.2±14.8 mm. Euthyroidism was diagnosed in 84 patients (43.3%). Hyperthyroidism was the rarest status of thyroid function among all patients (15.5%). The patients with nodule size between 0 mm and 10 mm mostly showed hypothyroidism (51.0% vs. 28.8% vs. 41.8%, p=0.0175) while patients with size between 11 mm and 20 mm mostly had euthyroidism (44.2% vs. 45.1% vs. 41.8%, p=0.0175). The ratio of overall benign pathology (53.1%) was higher than that of malignancies (46.9%) among all patients. Lastly, 57.2% of all patients were diagnosed as IMC, without any difference among the groups. Both a malignancy (49.0% vs. 51.9% vs. 42.9%, p=0.544) and IMC (51.0% vs. 65.4% vs. 56.0%, p=0.32) were observed more likely in the patients with a moderate nodule size (11-20 mm). Especially, malignancy was observed in the nodules less than 2 cm (Table 1, 2).

Outcomes Regarding IMC

We reported, based on univariate regression (Table 3), that thyroid function status (euthyroidism, hyperthyroidism), absence of halo, and total thyroidectomy in the intraoperative features emerged to be associated with the coexistence of IMC. Increase in nodule size did not seem to predict eventual coexistence of IMC [odds ratio (OR): 1.066, 95% confidence interval (CI): 0.757-1.501, p=0.712], (Table 2).

In our latest multivariable prediction model, there were 6 variables, which were identified according to either they were statistically significant on the univariate analysis or they had been formerly mentioned in the literature as potential predictors for the coexistence of IMC: thyroid function status (euthyroidism, hyperthyroidism), radiological absence of halo radiological vascularity, and surgery (total thyroidectomy), overall malignant pathology and pathological differentiation (nodular goiter, etc.). Briefly, we reported some of the findings to be a predictor for the coexistence of IMC: absence of halo (OR: 4.50 95% CI: 1.61-14.71, p=0.007), and interestingly decrease in vascularity (OR: 0.33, 95% CI: 0.12-0.87, p=0.030), and total thyroidectomy, (OR: 4.55, 95% CI: 2.30-9.56, p<0.001), (Figure 1).

The area under curve of the test set was 0.72 (95% CI: 0.61-0.78), sensitivity and specificity were 0.56 (95% CI: 0.38-0.72) and 0.79 (95% CI: 0.64-0.92), respectively (Figure 2). Our model was pretty good at detecting the true negatives of IMC, but average at detecting true positives of IMC.

Discussion

Thyroid nodules are clinically indicated for thyroid dysfunction and compressive symptoms; however, they are mostly critical in the diagnosis of thyroid malignancies. The ratio of malignancy in thyroid nodules diagnosed by biopsy has been reported between 4.0% and 6.5% and generally unconventional of the nodule size (15,16). However, IMCs which are incidentally diagnosed at the time of thyroidectomy are much more common than the overall malignancies (up to 36%) (17). Consistent with our findings, malignancy was observed

Table 1. Demographic and clinical features of the patients in comparison to the nodule size

Variables		Total n=194	Nodule size			p
			0-10 mm n=51	11-20 mm n=52	>20 mm n=91	
Sex, n (%)	Female	146 (75.3)	44 (86.3)	39 (75)	63 (69.2)	0.078
	Male	48 (24.7)	7 (13.7)	13 (25)	28 (30.8)	
Age (year)	Mean ± SD	46.6±13.1	48.6±13.6	47.2±12.3	45.1±13.1	0.276
	Min-max	(18-89)	(22-74)	(21-78)	(18-80)	
Radiation history	n (%)	1 (0.52)	0 (0)	0 (0)	1 (1.1)	0.566
Family history	n (%)	3 (1.55)	0 (0)	0 (0)	3 (3.3)	0.178
Status of thyroid function n (%)	Hypothyroidism	78 (40.2)	26 (51.0)	15 (28.8)	38 (41.8)	**0.0175**
	Euthyroidism	84 (43.3)	23 (45.1)	23 (44.2)	38 (41.8)	
	Hyperthyroidism	30 (15.5)	2 (3.9)	14 (26.9)	14 (15.4)	
Type of surgery n (%)	Lobectomy	19 (9.8)	8 (15.7)	4 (7.7)	7 (7.7)	0.257
	Total thyroidectomy	175 (90.2)	43 (84.3)	48 (92.3)	84 (92.3)	
Diameter of nodule (mm)	Mean ± SD	22.2±14.8	7.05±2.1	15.0±2.3	34.9±11.8	**<0.0001**
	Min-max	(3-70)	(3-10)	(11-20)	(21-70)	
Radiological findings n (%)	Hypo echogenicity	119 (61.3)	38 (74.5)	33 (63.5)	49 (53.8)	-
	Irregular margin	47 (24.2)	19 (37.3)	7 (13.5)	21 (23.1)	-
	Microcalcifications	51 (26.3)	19 (37.3)	10 (19.2)	22 (24.2)	0.214
	Loss of halo	29 (14.9)	8 (15.7)	6 (11.5)	15 (16.5)	-
	Increased vascularity	26 (13.4)	4 (7.8)	5 (9.6)	17 (18.7)	-
	Cervical lymph nodes	73 (37.6)	24 (47.1)	23 (44.2)	26 (28.6)	-
Pathology (%)	Toxic nodular goiter	43 (22.1)	6 (11.8)	10 (19.2)	27 (29.7)	0.058
	MNG	60 (30.9)	20 (39.2)	15 (28.8)	25 (27.5)	-
	Papillary carcinoma	81 (41.7)	25 (49.0)	24 (46.2)	32 (35.2)	-
	Hurthle cell carcinoma	10 (5.3)	0 (0.0)	3 (5.8)	7 (7.7)	-
FNAC findings n (%)	Non-diagnostic/insufficient	20 (10.3)	8 (15.7)	1 (1.9)	11 (12.1)	0.065
	Benign	34 (17.5)	10 (19.6)	7 (13.5)	17 (18.7)	
	AUS/FLUS	41 (21.1)	9 (17.6)	9 (17.3)	23 (25.3)	
	Follicular neoplasm	12 (6.2)	0 (0)	6 (11.5)	6 (6.6)	
	Cancer suspicious	58 (29.9)	15 (29.4)	22 (42.3)	21 (23.1)	
	Cancer	28 (14.4)	9 (17.6)	7 (13.5)	12 (13.2)	
Overall pathology n (%)	Benign	103 (53.1)	26 (51.0)	25 (48.1)	52 (57.1)	0.544
	Malignant	91 (46.9)	25 (49.0)	27 (51.9)	39 (42.9)	
IMC	n (%)	111 (57.2)	26 (51.0)	34 (65.4)	51 (56.0)	0.320

SD: Standard deviation, FNAC: Fine needle aspiration cytology, AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance, IMC: Incidental micropapillary carcinoma, MNG: Multinodular goiter

at the rate of 36% in patients with IMC (p=0.0008). Although the prognostics of IMC are controversial, early diagnosis and treatment of IMC are still crucial since the small size alone does not lower the risk of incidental thyroid malignancies (3,6,18,19). Consistent with our study, overall malignancy was reported more likely in the nodules less than 2 cm (49% vs. 51.9% vs. 42.9%, p=0.544). Additionally, the diameter of nodule size has no impact to induce the coexistence of IMC (51% vs. 65.4% vs. 56%, p=0.32). Since this risk of malignancy is high, such nodules including IMCs require urgent examination and diagnosis. Therefore, we investigated the effect of the nodule size on the prediction of the association of IMCs in patients' pathological specimen with ultrasonographical non-visualized adjacent malignancies. We found that an increase in nodule size did not seem to predict the eventual coexistence of IMC (OR: 1.066, 95% CI: 0.757-1.501, p=0.712).

In current literature, it was shown that high TSH level prior to surgery was shown with a higher risk of differentiated

Table 2. Demographic and clinical features of the patients in comparison to the presence of IMC

Variables		Total n=194	IMC		p
			Absent n=83	Present n=111	
Sex, n (%)	Female	146 (75.3)	60 (72.3)	86 (77.5)	0.509
	Male	48 (24.7)	23 (27.7)	25 (22.5)	
Age (year)	Mean ± SD	46.6±13.1	45.6±13.2	47.4±13.0	0.343
	Min-max	(18-89)	(18-78)	(18-80)	
Status of thyroid function n (%)	Hypothyroidism	78 (40.2)	41 (49.4)	38 (34.2)	0.078
	Euthyroidism	84 (43.3)	33 (39.8)	51 (45.9)	
	Hyperthyroidism	30 (15.5)	9 (10.8)	21 (18.9)	
Type of surgery n (%)	Lobectomy	19 (9.8)	15 (18.1)	4 (3.6)	**0.0019**
	Total thyroidectomy	175 (90.2)	68 (81.9)	107 (96.4)	
Diameter of nodule (mm)	Mean ± SD	22.2±14.8	22.7±16.0	21.8±13.8	0.988
	Min-max		(3-70)	(4-65)	
Radiological findings n (%)	Hypo echogenicity	119 (61.3)	52 (62.7)	68 (61.3)	-
	Irregular margin	47 (24.2)	20 (24.1)	27 (24.3)	-
	Microcalcifications	51 (26.3)	25 (30.1)	26 (23.4)	0.356
	Loss of halo	29 (14.9)	7 (8.4)	22 (19.8)	-
	Increased vascularity	26 (13.4)	13 (15.7)	13 (11.7)	-
	Cervical lymph nodes	73 (37.6)	32 (38.6)	41 (36.9)	-
FNAC findings n (%)	Non-diagnostic/insufficient	20 (10.3)	7 (8.4)	13 (11.7)	0.598
	Benign	34 (17.5)	13 (15.7)	21 (18.9)	
	AUS/FLUS	41 (21.1)	17 (20.5)	24 (21.6)	
	Follicular neoplasm	12 (6.2)	3 (3.6)	9 (8.1)	
	Cancer suspicious	58 (29.9)	28 (33.7)	30 (27.0)	
	Cancer	28 (14.4)	14 (16.9)	14 (12.6)	
Overall pathology n (%)	Benign	103 (53.1)	32 (38.6)	71 (64.0)	**0.0008**
	Malign	91 (46.9)	51 (61.4)	40 (36.0)	

SD: Standard deviation, FNAC: Fine needle aspiration cytology, AUS/FLUS: Atypia of undetermined significance or follicular lesion of undetermined significance, IMC: Incidental micropapillary carcinoma

thyroid carcinoma while hyperfunctioning was not considered as a protective factor. Also, incidental thyroid carcinoma is found to be more in euthyroid patients. (4,20). We reported that the patients diagnosed with IMC more likely showed euthyroidism, suggesting that the preoperative status of thyroid function might induce the coexistence of IMC in the thyroid gland.

It might be considered that TSH concentration is promptly related to the size of the malignant nodule, regardless of the other kind of nodule. Furthermore, TSH concentrations were found to be increased with differentiated thyroid carcinoma inside the dominant nodule in these patients compared to those with a benign dominant nodule (4,20). Consistently, we found that the nodule size between 0 mm and 10 mm was mostly indicative of hypothyroidism while the size between 11 mm and 20 mm was mostly indicative of euthyroidism. The nodule size larger than 20 mm showed similar rates of hypothyroidism and euthyroidism among patients. The rates of hyperthyroidism among patients with middle and large size nodules were significantly larger than those among patients with a smaller size, suggesting that TSH concentrations might be correlated with the coexistence of IMC regarding the increase in nodule size.

In some studies, it has been reported that nodule size has a low potential impact on the presence of malignancy regardless of the diameter such as a nodule smaller than 1 cm or larger in the presence of doubtful ultrasonographic findings (21). Small nodules are suggested to be biopsied only if there is more than one suspicious ultrasonographic feature, extracapsular growth, abnormal cervical lymph nodes, or high-risk history. Likewise, a diameter of 1 cm can be utilized for solid nodules that have only one doubtful ultrasonographic finding, such as microcalcifications or hypo echogenicity (22), which is consistent with our findings

including irregular margins in the nodule size less than 1 cm. In addition, we especially reported a correlation with the coexistence of IMC between the decreased vascularity (OR: 0.33, 95% CI: 0.12-0.87, p=0.030) and loss of halo (OR: 4.50, 95% CI: 1.61-14.71, p=0.007) in thyroid tissue.

Table 3. Unadjusted covariates of patients based on the coexistance of incidental micropapillary carcinoma

	OR	95% CI	p
Age	1.010	0.988-1.033	0.340
Thyroid function	1.616	1.063-2.456	0.024*
Surgery	5.900	1.879-18.525	0.002*
Hypo echogenicity	0.942	0.524-1.694	0.844
Irregular margin	1.012	0.521-1.967	0.970
Increased vascularity	0.714	0.312-1.634	0.042*
Microcalcifications	1.355	0.583-3.144	0.479
Loss of halo	2.683	1.086-6.627	0.032*
Cervical lymph nodes	0.933	0.519-1.678	0.818
FNAC findings	0.631	0.090-0.885	0.0277
Pathology	1.866	0.997-3.494	0.051
Overall pathology	0.353	0.196-0.636	0.0005*
Nodule size	1.066	0.757-1.501	0.712

OR: Odds ratio, FNAC: Fine needle aspiration cytology, CI: Confidence interval, *p-value <0.05

There are various controversies about the nodule size, as a variable for predicting malignancy, and the management of treatment. Currently, Al-Hakami et al. (23) reported that the majority of malignancy risk was found in nodules less than 2 cm in contrast to nodules larger than 2 cm. The baseline cancer risk of 64.8% was observed in the thyroid nodules diameter of 1.0-1.9 cm. The general ratio of malignancy in nodules larger than 2 cm were 17.6%, 10.6%, and 7% (nodules 4.0 cm) (20). In the present study, we divided the nodule sizes into three groups as 0-1.0 cm, 1.1-2.0 cm, and the size larger than 2 cm. The patients with medium-sized nodules (1.1-2.0 cm) showed more malignancy in overall pathology while the patients with smaller and larger sizes showed more likely benign pathology.

In the present study, the incidence of IMC was higher among the patients with nodule size between 1.1 cm and 2.0 cm but no significance was shown between the groups regarding the coexistence of IMC. Al-Hakami et al. (23) demonstrated that the nodular size of 1.0-1.9 cm was

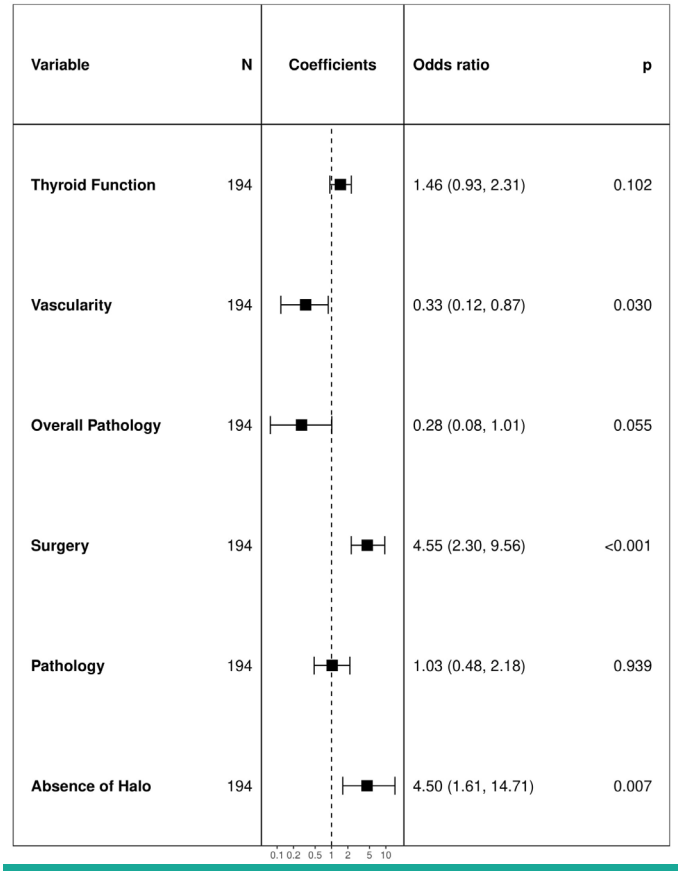

Figure 1. Adjusted covariates for the coexistance of incidental micropapillary carcinoma

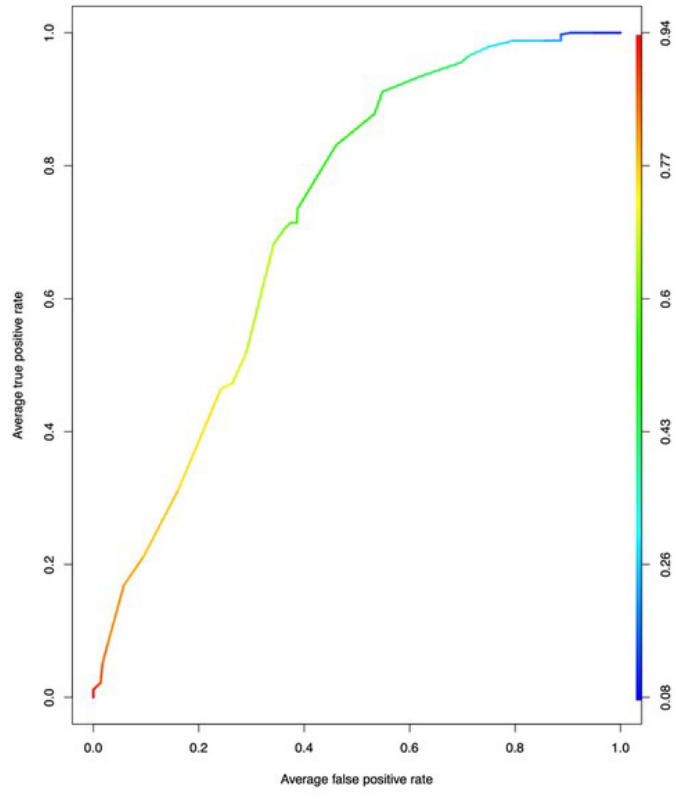

Figure 2. Prediction model of incidental micropapillary carcinoma

primarily contained in the papillary carcinoma, likewise Kamran et al. (24) observed that increasing nodule size had a contrary correlation with a papillary carcinoma, which is similar to our findings (49% vs. 46.2% vs. 35.2%, p=0.124). Contrary to our findings, El-Gammal et al. (25) have shown that larger nodule sizes over 2 cm have more papillary carcinomas. Therefore, we observed that the size of the nodule had a low potential to be a predictive factor for the coexistence of IMC in the thyroid gland (p=0.712).

Study Limitations

The limitations in our study were that small sample size was analyzed from the data of a single center and thyroid surgery group was 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, observation, and recall biases. Also, no stepwise or any other machine learning models were further used to measure the performance of our prediction model.

Conclusion

Despite these limitations, this study is a clinically valuable diagnostic tool showing that the nodule size might be a good predictor for the coexistence of IMC in the thyroid gland regarding the absence of halo and vascularity. Another strength of the study was the outcome that the patients diagnosed with IMC more likely had euthyroidism or hyperthyroidism and were observed mostly in total thyroidectomy specimens. However, there are still debates about the pathological assessment of IMC in the thyroid gland. Therefore, defining a cut-off nodule size for the potential coexistence of IMC in a thyroid gland requires studies with large sample size and further clinical trials.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital approved the study protocol (decree number: 2020.02.1.03.021, date of approval: 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.

Informed Consent: Patient consent form was not required due to the nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A.H., Y.A., A.A., G.E., Design: N.A.H., Y.A., A.A., G.E., Data Collection or Processing: Y.Ü., T.V.A., M.T., S.M., A.A., Analysis or Interpretation: N.A.H., C.E., G.E., Y.Ü., A.A., Drafting Manuscript: N.A.H., Y.A., M.V., T.V.A., Critical Revision of Manuscript: Y.A., C.E., S.M., M.V., Final Approval and Accountability: N.A.H., S.M., G.E., M.T., Y.A., Technical or Material Support: Y.Ü., G.E., T.V.A., C.E., M.T., Supervision: N.A.H., Y.A., M.V.

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