ORIGINAL RESEARCH

Factors Associated with Malignancy in Patients with Maximal Thyroid Nodules ≥2 Cm

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Purpose: The relationship between large thyroid nodules and the risk of malignancy is controversial. This study aimed to examine the relationship between thyroid nodule size and the risk of malignancy of maximal thyroid nodules ≥2 cm and the risk of accompanied by occult thyroid carcinoma.

Methods: This was a retrospective study of patients who underwent near-total or total thyroidectomy for thyroid nodules from January 2016 to January 2019 at the First Affiliated Hospital,Zhejiang University School of Medicine. Clinical, biochemical, and pathological characteristics were examined for association with malignancy using univariable, multivariable, and receiver operating characteristic curve analyses.

Results: Finally, 367 patients (277 females (75.5%) and 90 males (24.5%)) with a mean age of 49.0±13.5 years were included. Multivariable logistic regression analysis showed that age (OR=0.959, 95% CI: 0.939–0.979, $P<0.001$), Hashimoto's thyroiditis (OR=2.437, 95% CI: 1.162–5.112, $P=0.018$), the diameter of maximal nodule (small) (OR=0.706, 95% CI: 0.541–0.919, $P=0.010$), and punctate echogenic foci (OR=2.837, 95% CI: 1.598–5.286, $P<0.001$) were independently associated with malignancy. Of 223 patients who had non-suspicious malignant nodules (TI-RADS <4), 12.7% (n=29) patients showed malignancy at postoperative pathology. Only age was associated with occult PTC in the univariable analyses (OR=0.962, 95% CI: 0.934–0.991, $P=0.011$). When TPOAb was used as a continuous variable for statistical analysis, it showed a significant difference in the ROC curve, and the results showed TPOAb >31.4 mIU/L was more associated with occult PTC ($P=0.006$). A predictive model including four independent risk factors of malignancy showed an optimal discriminatory accuracy (area under the curve, AUC) of 0.783 (95% CI=0.732–0.833).

Conclusion: Relatively young age (<54.5 years), Hashimoto's thyroiditis, the diameter of the maximal nodule, and punctate echogenic foci were independently associated with thyroid malignancy in patients with maximal thyroid nodules ≥2 cm. Young age (<54.5 years) and TPOAb >31.4 mIU/L were associated with occult PTC.

Keywords: thyroid nodule, thyroid carcinoma, nodule size, age

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Introduction

A thyroid nodule is a common clinical and radiological finding (lifetime incidence of up to 50–65% in healthy individuals).[1,2] Most nodules are benign (about 90%), but a significant proportion (10%) is malignant.[1,3] With the improvements in imaging modalities, more thyroid nodules are discovered, and thyroid carcinoma incidence had increased substantially worldwide in recent years.[4–7] The growing use of ultrasound (US) and fine-needle aspiration (FNA) contributes significantly to the rise of this incidence due to their high diagnostic specificity.[8–11]

Nevertheless, there are still some limitations in diagnosing malignancy in large thyroid nodules. It has been reported that the sensitivity of FNA decreases when it is used to assess the malignancy of large nodules (>3 cm).[12] Another study also reported that the relatively high false-negative risk of large nodules (≥3 cm) with benign cytology was found in FNA.[13] In addition, large thyroid nodules are often accompanied by microscopic occult cancer, which can only be detected by postoperative pathology.[14,15] Indeed, FNA samples only a small part of the nodule, and malignant foci can easily be missed, especially in large nodules. Therefore, it is critical to examine large nodules' features and clarify the association between the features of large nodules and the risk of malignancy.

In addition, it remains unclear whether nodule size is associated with the risk of malignancy. Some studies found that when the patients were divided into different size groups, smaller nodules had a higher malignancy rate than larger nodules, which means nodule size is inversely related to malignancy risk, regardless of other factors.[16,17] In contrast, Raparia et al[18] reported that in nodules >2 cm, the malignancy rate is significantly higher than that in nodules <2 cm. To add to the controversy, other studies also concluded that for nodules >3 cm, there is no relationship between malignancy rate and nodule size.[19,20]

Besides nodule size, other factors also have been reported to be related to thyroid carcinoma. A recent study showed that obesity was significantly related to the risk of papillary thyroid carcinoma (PTC).[21] Hashimoto's thyroiditis (HT), the typical cause of hypothyroidism, can destroy thyroid cells and then result in an autoimmune condition,[22] and a growing body of evidence indicates that HT is associated with the risk of developing PTC.[23–25] The levels of thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) can be used as the predictor for thyroid autoimmunity and many studies have shown that TgAb, TPOAb, and thyroid-stimulating hormone (TSH) are associated with an increased risk of malignancy.[26–29]

Therefore, this study aimed to examine the relationship between thyroid nodule size and the risk of malignancy of maximal thyroid nodules ≥2 cm and the risk of accompanied by occult thyroid carcinoma, as well as the implication of factors like obesity, HT, TPOAb, TgAb, and TSH. Given that 80–85% of thyroid carcinomas are PTCs,[30] this study focuses on patients diagnosed with PTC or benign nodules at postoperative pathological examination.

Methods
Study Design and Patients
This retrospective study included patients who underwent near-total or total thyroidectomy for thyroid nodules from January 2016 to January 2019 at the Department of Thyroid Surgery,The First Affiliated Hospital,Zhejiang University School of Medicine. This study was approved by the Ethics Review Committee of the First Affiliated Hospital,Zhejiang University School of Medicine and conducted in accordance with the Helsinki Declaration. The need for written informed consent was waived by the committee as all data were used retrospectively. All clinical data were anonymized for the analysis.

The inclusion criteria were 1) the maximal diameter of the largest thyroid nodule was ≥2 cm at the preoperative US, and 2) the postoperative pathological examination showed PTC or benign nodule. Patients diagnosed with non-PTC thyroid cancer, with a history of other major diseases, or hypoimmunity were excluded.

Clinicopathological Characteristics
The medical records and pathology reports of each patient were reviewed. The following clinicopathological characteristics were extracted from the charts: sex, age, family history, smoking, obesity (body mass index (BMI) ≥28 kg/m^2), HT, TPOAb, TgAb, preoperative TSH, thyroglobulin (Tg), diameter, location, Thyroid Imaging, Reporting, and Data System (TI-RADS) classification (≥4/<4),[31] and FNA. If FNA was performed, whether the nodule or the largest nodule was malignant was included in this analysis. In addition to the above variables, cancer focus in intraoperative frozen, postoperative complications (hoarseness, coughing, and numbness in the hands and feet), or type of surgery (unilateral/bilateral) were also considered.

US Imaging Analysis
The US examinations were performed using a Siemens Acuson X300 color ultrasonic diagnostic instrument. The examinations were conducted and recorded by senior experience sonographers according to ACR TI-RADS.[31] The following US parameters of the maximal nodules were recorded: (1) nodule size, (2) composition (cystic, mixed cystic and solid, solid), (3) echogenicity, (4) shape, (5) margin, and (6) echogenic foci (large comet-tail artifacts, punctate echogenic foci, peripheral or punctate echogenic foci). Occult thyroid cancer referred to cancer that was not found preoperatively but was incidentally found

during or after thyroidectomy.[14] So, patients with TI-RADS<4 (except those with cancer detected by FNA) were classified as those with no cancer before surgery.

Thyroid Hormones and Autoantibodies

Preoperative thyroid biochemical parameters were measured using an automated chemiluminescent immunoassay system (Advia Centaur; Siemens, Munich, Germany). Normal reference ranges were ≤55 ng/mL for Tg, 0.35–4.94 mIU/L for TSH, 0.0–100.0 IU/mL for TPOAb, and 0.0–60.0 U/mL for TgAb.

Statistical Analysis

All statistical analyses were performed using SPSS 25.0 for Windows (IBM Corp, Armonk, NY, USA). Descriptive statistics are presented as medians (ranges) for continuous variables and numbers and percentages for categorical variables. The chi-square test and Fisher's exact test were used for categorical variables. The Mann–Whitney *U*-test was used for continuous variables. Univariable and multivariable logistic regression analyses (backward) were performed to evaluate the association between malignancy and clinicopathological characteristics. Receiver operating characteristic (ROC) curve analyses were performed to examine the predictive power of different combinations of clinical, laboratory, and pathological characteristics. The cut-off age value of 54.5 was obtained through the ROC curve. The areas under the curves (AUCs) were derived from the ROC curves. A *P*-value of < 0.05 was considered statistically significant.

Results
Characteristics of Patients

Finally, 367 patients with maximal thyroid nodules size ≥2 cm and diagnosed with PTC or benign nodules were included in this study. Of the 367 patients, there are 277 females (75.5%) and 90 males (24.5%), the mean age is 49.0±13.5 years (range 14–76), and 112 (30.5%) cases were determined to be PTC, and 255 (69.5%) were benign nodules (Table 1). Compared with patients with benign nodules, those with malignant nodules were younger (*P*<0.001), had higher frequencies of HT (*P*=0.016), TPOAb positivity (*P*=0.034), TgAb positivity (*P*=0.015), ACR TI-RADS ≥4 (*P*<0.001), solid nodule (*P*<0.001), punctate echogenic foci (*P*<0.001), suspicious malignant nodules at preoperative US (*P*<0.001), malignancy at FNA (*P*<0.001), malignancy at preoperative

pathological examination (*P*<0.001), positive intraoperative frozen sections (*P*<0.001), bilateral surgery (*P*=0.001), postoperative complications (*P*<0.001), had a lower frequency of hyperthyroidism (*P*=0.050), and had smaller nodules (*P*<0.001) (Table 1). The patients with a maximal malignant nodule had a higher risk of thyroid gland invasion (*P*=0.002), central lymph node metastasis (*P*<0.001), and cervical lymph node metastasis (*P*=0.010) (Table 2).

Risk Factors for Thyroid Carcinoma

Univariable and multivariable logistic regression analyses showed that age (OR=0.959, 95% CI: 0.939–0.979, *P*<0.001), HT (OR=2.437, 95% CI: 1.162–5.112, *P*=0.018), the diameter of maximal nodule (small) (OR=0.706, 95% CI: 0.541–0.919, *P*=0.010), and punctate echogenic foci (OR=2.837, 95% CI: 1.598–5.286, *P*<0.001) were independently associated with malignancy (Table 3).

Risk Factors for Thyroid Carcinoma in Cases with Nodules (ACR TI-RADS<4)

Of 223 patients who had non-suspicious malignant nodules (ACR TI-RADS <4), 12.7% (n=29) patients showed malignancy at postoperative pathology, which was significantly lower than in the whole group of patients. Among them (n=29), the largest modules were found to be malignant in six (20.7%) cases (Table 4). Compared with the patients with benign nodules, those with malignant nodules were younger (*P*<0.001) and had higher frequencies of malignant FNA (*P*=0.001), malignant largest nodule preoperatively (*P*<0.001), and cancer focus on intraoperative cancer sections (*P*<0.001) (Table 4). There were no associations with multifocality, invasion, and lymph node metastases (Table 5). Only age was associated with occult PTC in the univariable analyses (OR=0.962, 95% CI: 0.934–0.991, *P*=0.011; Table 6). But TPOAb, TGAb, TG, and TSH were used as continuous variables for statistical analysis; only TPOAb showed a significant difference in the ROC curve, and it showed that TPOAb >31.4 mIU/L was associated with occult PTC (*P*=0.006).

ROC Analysis of the Independent Factors for Malignancy

The ROC curve analysis showed that the AUC of age in predicting malignancy was 0.638 (95% CI: 0.577–0.699), with a sensitivity of 57.7% and a specificity of 69.9% at

Table 1 Demographics and Clinical Characteristics of the Patients with Benign Lesions or PTC

Characteristics	Patients with Benign Nodules (n=255)	Patients with PTC (n=112)	P
Age, year, mean (range)	51.02 (14–76)	44.36 (15–75)	<0.001

Sex, n (%)
  Male
  Female
	
	64 (25.1)
	191 (74.9)
		
		26 (23.2)
		86 (76.8)
			0.792

Family history, n (%)	7 (2.7)	3 (2.7)	>0.999
Other tumors, n (%)	6 (2.4)	1 (0.9)	0.680
Smoking, n (%)	29 (11.4)	9 (8.0)	0.457
Obesity, n (%)	28 (11.0)	12 (10.7)	>0.999
Hashimoto's thyroiditis, n (%)	24 (9.4)	21 (18.8)	0.016
TPOAb (positive), n (%)	25 (9.8)	20 (17.9)	0.034
TGAb (positive), n (%)	29 (11.4)	21 (18.8)	0.015

TSH (mIU/L), n (%)
  <0.35
  0.35–4.94
  >4.94
	
	27 (10.6)
	218 (85.5)
	10 (3.9)
		
		3 (2.7)
		103 (92.0)
		6 (5.3)
			0.050

Tg (ng/mL), n (%)
  >55
  ≤55
	
	139 (54.5)
	116 (45.5)
		
		58 (51.8)
		54 (48.2)
			0.635

Diameter of maximal nodules (US), cm, mean (range), n (%)	3.7 (2–9.2)	3.3 (2–7)	<0.001

Location of maximal nodules, n (%)
  Left
  Isthmus
  Right
	
	121 (47.5)
	7 (2.7)
	127 (49.8)
		
		61 (54.5)
		3 (2.7)
		48 (42.8)
			0.382

ACR TI-RADS level of maximal nodule, n (%) ≥4 <4	 41 (16.1) 214 (83.9)	 68 (60.7) 44 (39.3)	<0.001

Composition of maximal nodules, n (%)
  Cystic
  Mixed cystic and solid
  Solid
	
	17 (6.7)
	118 (46.3)
	120 (47.0)
		
		4 (3.6)
		24 (21.4)
		84 (75)
			<0.001

Multifocality, n (%)	193 (75.7)	90 (80.4)	0.348
Punctate echogenic foci, n (%)	54 (21.2)	51 (45.5)	<0.001
Suspicious malignant nodules (ACR TI-RADS ≥4) in preoperative ultrasonography (US), n (%)	54 (21.2)	82 (73.2)	<0.001

FNA, n (%)
  No
  Yes
 	
    Benign
    Malignant
	
	247 (96.9)
	
	8 (3.1)
	0 (0)
		
		77 (68.7)
		
		3 (2.7)
		32 (28.6)
			<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Patients with Benign Nodules (n=255)	Patients with PTC (n=112)	P
Maximal nodules pathology, n (%)			<0.001
Benign	255 (100)	52 (46.4)	
Malignant	0 (0)	60 (53.6)	
Cancer focus in intraoperative frozen, n (%)	1 (0.4)	101 (90.2)	<0.001
Type of surgery, n (%)			0.001
Unilateral	106 (41.6)	25 (22.3)	
Bilateral	148 (58.0)	87 (77.7)	
Isthmus	1 (0.4)	0 (0)	
Postoperative complication, n (%)	21 (8.2)	29 (25.9)	<0.001

Abbreviations: PTC, papillary thyroid carcinoma; TPOAb, thyroid peroxidase antibodies; TGAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone; US, ultrasonography; TI-RADS, Thyroid Imaging, Reporting, and Data System; FNA, fine-needle aspiration.

Table 2 Clinicopathological Characteristics of Patients with PTC According to the Maximal Nodule Pathology

Characteristics, n (%)	Benign Maximal Nodules (n=52)	Malignant Maximal Nodules (n=60)	P
Multifocal carcinoma	15 (28.8)	21 (35.0)	0.532
Extrathyroidal extension	0	10 (16.7)	0.002
Central lymph node metastasis	13 (25.0)	39 (65.0)	<0.001
Cervical lymph node metastasis	6 (11.5)	22 (36.7)	0.010

a cut-off value of 54.5 years. The AUC of maximal nodule diameter in predicting malignancy was 0.645 (95% CI: 0.585–0.706), with a sensitivity of 58.5% and a specificity of 70.6% at a cut-off value of 3.59 cm.

When age, HT, maximal nodule diameter, and punctate echogenic foci were combined, the optimal AUC had a favorable value of 0.783 (95% CI: 0.732–0.833) (Figure 1), with a sensitivity of 70.0% and a specificity of 73.5%. For patients with ACR TI-RADS <4 nodules, the ROC curve analysis showed that the AUC of age in predicting malignancy was 0.651 (95% CI: 0.549–0.752), with a sensitivity of 54.9% and a specificity of 75.2% at a cut-off value of 54.5 years (Figure 2). For patients with ACR TI-RADS <4 nodules, the ROC curve analysis showed that the AUC of TPOAb in predicting malignancy was 0.649 (95% CI: 0.581–0.713), with a sensitivity of 53.9% and a specificity of 75.9% at a cut-off value of 31.4 mIU/L (Figure 3). Multivariate variable logistic regression analysis showed that patient's age (<54.5 years) (OR=0.221, 95% CI: 0.115–0.428, P<0.001) and diameter of the maximum nodule (<3.59 cm) (OR=0.461, 95% CI:

Table 3 Univariable and Multivariable Analysis of Risk Factors for Thyroid Carcinoma

Characteristics	Univariable Analyses			Multivariable Analysis		
	OR	95% CI	P	OR	95% CI	P
Age (years)	0.964	0.947–0.980	<0.001	0.959	0.939–0.979	<0.001
Hashimoto's thyroiditis	2.212	1.173–4.169	0.014	2.437	1.162–5.111	0.018
TSH (<0.35 vs.0.35–4.94)	0.293	0.086–1.003	0.051			
(>4.94 vs 0.35–4.94)	2.152	0.609–7.603	0.234			
TPOAb (positive)	2.096	1.102–3.986	0.024			
TGAb (positive)	2.255	1.190–4.275	0.013			
Diameter of maximal nodules (cm) (US)	0.603	0.466–0.780	<0.001	0.706	0.541–0.919	0.010
Composition of maximal nodules (mixed cystic and solid vs cystic)	0.864	0.267–2.797	0.808			
(solid vs cystic)	3.000	0.975–9.235	0.055			
Punctate echogenic foci	3.202	1.980–5.176	<0.001	2.837	1.598–5.286	<0.001

Abbreviations: TPOAb, thyroid peroxidase antibodies; TGAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone; US, ultrasonography.

Table 4 Demographics and Clinical Characteristics of Patients with No Suspicious Malignant Nodules in Preoperative Ultrasonography (TI-RADS <4)

Characteristics	Patients with Benign Nodules (n=194)	Patients with PTC (n=29)	P
Age, years, mean (range)	50.45 (17–76)	43.83 (20–72)	0.009
Sex, n (%)			0.651
Male	50 (25.8)	6 (20.7)	
Female	144 (74.2)	23 (79.3)	
Family history, n (%)	5 (2.6)	1 (3.4)	0.571
Other tumors, n (%)	4 (2.1)	0 (0)	>0.999
Smoking, n (%)	24 (12.4)	1 (3.4)	0.214
Obesity, n (%)	21 (10.8)	2 (6.9)	0.746
Hashimoto's thyroiditis, n (%)	18 (9.3)	4 (13.8)	0.502
TPOAb (positive), n (%)	21 (10.8)	4 (13.8)	0.500
TGAb (positive), n (%)	23 (11.9)	3 (10.3)	0.737
TSH (mIU/L), n (%)			0.447
<0.35	17 (8.8)	1 (3.4)	
0.35–4.94	172 (88.6)	28 (96.6)	
>4.94	5 (2.6)	0 (0)	
Tg (ng/mL), n (%)			0.399
>55	110 (56.7)	13 (44.8)	
≤55	84 (43.3)	16 (55.2)	
Diameter of maximal nodules (US), cm, mean (range), n (%)	3.81 (2–9.2)	3.59 (2.4–5.5)	0.243
Location of maximal nodules, n (%)			0.672
Left	98 (50.5)	15 (51.7)	
Isthmus	7 (3.6)	2 (6.9)	
Right	89 (45.9)	12 (41.4)	
ACR TI-RADS level of maximal nodule, n (%)			0.002
≥4	0 (0)	0 (0)	
<4	194 (100)	29 (100)	
Composition of maximal nodules, n (%)	16 (8.2)	1 (3.4)	0.172
Cystic			
Mixed cystic and solid	99 (51.0)	11 (38.0)	
Solid	79 (40.8)	17 (58.6)	
Multifocality, n (%)	140 (72.2)	19 (65.5)	0.510
Punctate echogenic foci, n (%)	25 (12.9)	25 (86.2)	1.000
FNA, n (%)			0.001
No	192 (99.0)	26 (89.7)	
Yes			
Benign	2 (1.0)	1 (3.4)	
Malignant	0 (0)	2 (6.9)	
Maximal nodules pathology, n (%)			<0.001
Benign	194 (100)	6 (20.7)	
Malignant	0 (0)	23 (79.3)	
Cancer focus in intraoperative frozen, n (%)	1 (0.5)	23 (79.3)	<0.001

(*Continued*)

Table 4 (Continued).

Characteristics	Patients with Benign Nodules (n=194)	Patients with PTC (n=29)	P
Type of surgery, n (%) 　Unilateral 　Bilateral 　Isthmus	 84 (43.3) 109 (56.2) 1 (0.5)	 9 (31.0) 20 (69.0) 0 (0)	0.412
Postoperative complication, n (%)	16 (8.2)	3 (10.3)	0.720

Abbreviations: PTC, papillary thyroid carcinoma; TPOAb, thyroid peroxidase antibodies; TGAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone; US, ultrasonography; TI-RADS, Thyroid Imaging, Reporting, and Data System; FNA, fine-needle aspiration.

Table 5 Clinicopathological Characteristics of Patients with PTC (with No Suspicious Malignant Nodules in Preoperative Ultrasonography) According to Maximal Nodules Pathology

Characteristics, n (%)	Benign Largest Nodules (n=23)	Malignant Largest Nodules (n=6)	P
Multifocal carcinoma	2 (8.7)	1 (16.7)	>0.999
Extrathyroidal extension	0 (0)	1 (16.7)	0.208
Central lymph node metastasis	2 (8.7)	2 (33.3)	0.140
Cervical lymph node metastasis	2 (8.7)	0 (0)	>0.999

Table 6 Univariable of Risk Factors for Thyroid Carcinoma (TI-RADS<4)

Characteristic	OR	95% CI	P
Age (years)	0.962	0.934–0.991	0.011

Abbreviations: OR, odds ratio; CI, confidence interval.

0.259–0.819, P=0.008) were independently associated with risk factors for malignancy (Table S1).

Discussion

This study aimed to examine the relationship between thyroid nodule size and the risk of malignancy in patients with maximal thyroid nodules ≥2 cm and the risk of accompanied by occult thyroid carcinoma, as well as the implication of other factors. The results suggested that relatively young age (<54.5 years), Hashimoto's thyroiditis, the diameter of the maximal nodule, and punctate echogenic foci were independently associated with thyroid malignancy in all patients. A predictive model including four variables (age, HT, maximal nodule diameter, and punctate echogenic foci) showed an optimal discriminatory accuracy in predicting malignancy. Only age was

associated with PTC in patients with occult PTC (ACR TI-RADS <4).

The study revealed that patients of a relatively young age (<54.5 years) were more likely to have thyroid carcinoma, in line with previous studies.[32,33] Nevertheless, the association between age and thyroid carcinoma is controversial. One study suggested a weak association between age and malignancy in multinodular goiters (MNG).[34] Therefore, further study is needed for the association between age and thyroid malignancy.

In the univariable analyses of all patients, the small diameter of the maximal nodule was independently associated with malignancy, with a cut-off point of 3.59 cm, according to the ROC curve. These results indicated that for nodules ≥2 cm and <3.59 cm, smaller nodules had a higher risk of malignancy, which was supported by
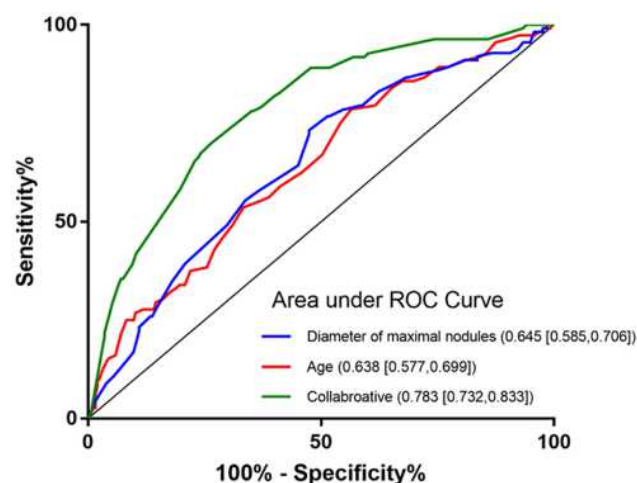

Figure 1 Receiver operating characteristic (ROC) curve analysis of the age and diameter of maximal nodules for predicting thyroid carcinoma in all included patients (n=367). The results showed that the cut-off value of age was 54.5. At this value, sensitivity was 57.7%, and specificity was 69.9%. The results showed that the cut-off value of the diameter of the largest nodules was 3.59 cm. At this value, sensitivity was 58.5%, and specificity was 70.6%. The sensitivity was 70.0%, and specificity was 73.5% for the collaborative prediction model.
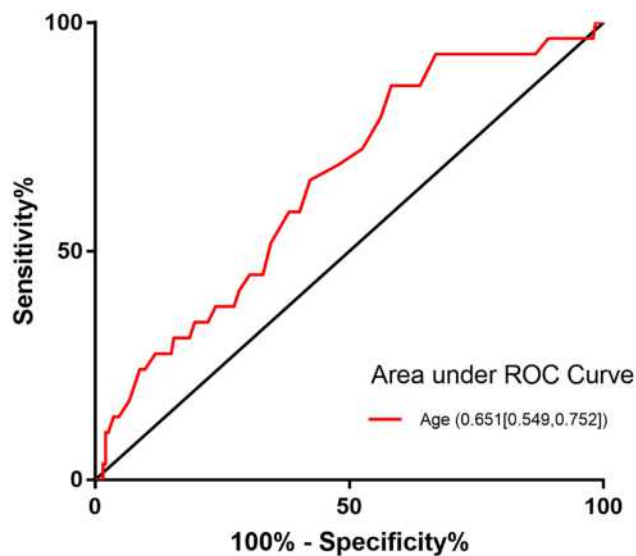
Figure 2 Receiver operating characteristic (ROC) curve analysis of the age for predicting thyroid carcinoma in patients with ACR TI-RADS <4 nodules (n=223). The results showed that the cut-off value of age was 54.5. At this value, sensitivity was 54.9%, and specificity was 75.2%.
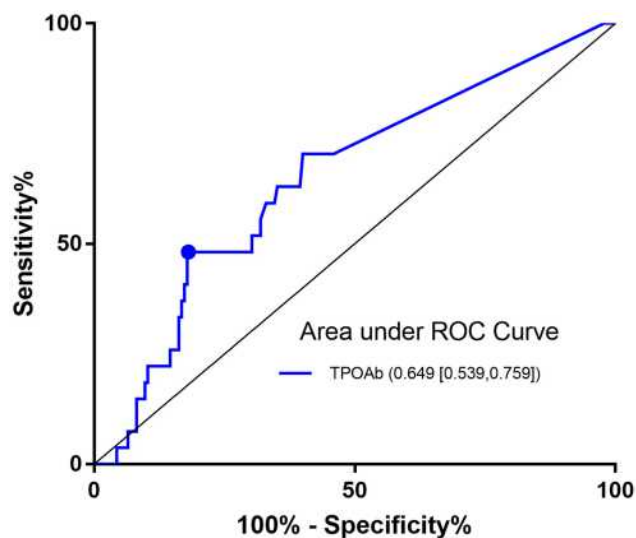

Figure 3 Receiver operating characteristic (ROC) curve analysis of TPOAb for predicting thyroid carcinoma in patients with TI-RADS <4 nodules (n=223). The results showed that the cut-off value of TPOAb was 31.4. At this value, sensitivity was 53.9%, and specificity was 75.9%. (*P*=0.006).

previous studies.[16,21] In addition, among the patients diagnosed with PTC, 53.6% (n=60) of the patients showed malignant nodules, which was higher than in patients diagnosed with benign nodules. Moreover, patients with the largest nodule being malignant also had higher likelihoods of thyroid gland invasion and lymph node metastasis. These results highlighted the

important role of the features of maximal nodules in evaluating the risk of PTC.

The ROC curve analysis showed that age (AUC=0.638) and the maximal nodule size could predict malignancy (AUC=0.645) and that the predictive model yields an even better predictive power (AUC=0.783). Such results are supported by a study by Liu et al[35] who showed that age, TgAb, hypoechogenicity, and punctate echogenic foci could be combined into a predictive model with an AUC of 0.808; this previous model was constructed with any sizes of thyroid nodules. In a small group of patients with nodules of different size, Girardi et al[36] showed that irregular shape, absence of halo, age, homogeneous US texture, punctate echogenic foci, and solid content could be combined into a model, but they did not determine its predictive power using ROC curves. A model that included TSH, male sex, punctate echogenic foci, and irregular margins had an AUC of 0.77.[37] Of note, those previous models included all thyroid nodules, irrespective of size, while the present study included only maximal nodules ≥2 cm. Nevertheless, the most optimal model remains to be determined.

Intriguingly, when we excluded suspicious malignant nodules (ACR TI-RADS ≥4), HT, largest nodule shape (solid), and punctate echogenic foci, the diameter of the largest nodule was not associated with PTC. ACR TI-RADS is a risk stratification system that can classify thyroid nodules according to their appearance at US.[31] Punctate echogenic foci, the shape, and the diameter of nodules contribute to the score of TI-RADS.[31] In this study, the whole case analysis showed the important influence of the maximal nodule size on the risk of malignancy, but no effect on cases of ACR TI-RADS <4, which showed that nodule size was a more significant factor for cases ACR TI-RADS ≥4. Thus, a TI-RADS assessment is necessary for the initial diagnosis, and when the cases are evaluated as TI-RADS ≥4, the maximal nodule size becomes a crucial factor for PTC. Nevertheless, occult PTC is a clinical issue and can easily be missed. A relatively young age (<54.5 years) in the presence of ACR TI-RADS <4 lesions might make the physicians suspicious of the possible presence of an occult PTC. Our results showed that the incidence of occult PTC was 12.7%. Interestingly, TPOAb, TGAb, TG, and TSH were used as continuous variables for statistical analysis, and only TPOAb showed a significant difference in the ROC curve; the results

showed that the incidence of occult PTC increased significantly (>20%) when TPOAB >31.4 mIU/L (AUC=0.649) (*P*=0.006). And the size of the nodule was not a predictor of occult PTC. It is also suggested that patients with enlarged cervical lymph nodes have a high rate of occult PTC.[38] Only 29 patients had occult PTC in this study, which is too small to perform a reliable analysis of associated factors and additional studies are still necessary.

This study had some limitations, as well. First, this was a single-center study, and only patients with PTC were included, so the generalizability of the findings is unknown. Second, the data that could be analyzed were limited to those available in the patient charts, as this was a retrospective study. Third, FNA was not performed in most patients because the nodules were large (3–7 cm) and led to a feeling of neck compression, extending even behind the sternum, requiring surgery even if benign. Therefore, most of the patients strongly refused FNA and requested first-intention definitive surgery.

In conclusion, relatively young age (<54.5 years), HT, a smaller diameter of the maximal nodule, and punctate echogenic foci were independently associated with PTC in patients with maximal thyroid nodules ≥2 cm. When only considering non-suspicious malignant nodules (ACR TI-RADS <4), relatively young age (<54.5 years) and TPOAb >31.4 mIU/L were associated with occult PTC. The predictive model of malignancy might aid clinicians in making better clinical decisions.

Data Sharing Statement
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
This study was approved by the Ethics Review Committee of the First Affiliated Hospital,Zhejiang University School of Medicine and conducted in accordance with the Helsinki Declaration. The need for written informed consent was waived by the committee as all data were used retrospectively. All clinical data were anonymized for the analysis.

Patient Consent for Publication
Not applicable.

Author Contributions
All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure
The authors declare that they have no conflicts of interest.

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