Original investigation

An Ultrasound-based Prediction Model for Occult Contralateral Papillary Thyroid Carcinoma in Adolescents and Young Adults

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Rationale and Objectives: To investigate the occult contralateral papillary thyroid carcinoma (PTC)-associated ultrasound (US) and clinical characteristics and establish a US-based model for the prediction of occult contralateral carcinoma in adolescents and young adults (AYAs) who were diagnosed with unilateral thyroid carcinoma preoperatively.

Materials and Methods: From January 2015 to December 2020, patients who were diagnosed with unilateral thyroid carcinoma by preoperative US examination and underwent total thyroidectomy or thyroid lobectomy with more than 60 months of US follow-up at our hospital were retrospectively collected. Univariate and multivariate analyses were applied to identify the independent risk factors associated with occult contralateral PTC in AYAs, on which a prediction model was developed. The performance of the model was evaluated with accuracy, sensitivity, specificity, and the area under the receiver operating characteristic curve.

Results: Occult contralateral PTC was found in 91 of 365 (24.9%) PTC patients with a median age at diagnosis of 26 years (interquartile range, 24−29 years). The multivariate analysis indicated that the presence of contralateral benign nodule, intra-tumoral calcification, and intraglandular dissemination were significantly associated with occult contralateral PTC in AYAs. The prediction model, which incorporated all independent predictors, yielded an area under the receiver operating characteristic curve of .661 (95% CI: .602−.719). The accuracy, sensitivity and specificity were 67.9%, 54.9%, and 72.3%, respectively.

Conclusion: The US-based prediction model proposed here exhibited a favorable performance for predicting occult contralateral PTC, which might be used to determine the appropriate extent of surgery for AYAs who had a preoperative diagnosis of unilateral thyroid carcinoma.

Key Words: papillary thyroid carcinoma; adolescents and young adults; ultrasound; occult; contralateral.

Abbreviations: PTC papillary thyroid carcinoma, **US** ultrasound, **AYAs** adolescents and young adults, **TT** total thyroidectomy, **TL** thyroid lobectomy, **AUC** area under the receiver operating characteristic curve, **LNM** lymph node metastasis, **ATA** American Thyroid Association, **FNA** fine-needle aspiration, **AJCC** American Joint Committee on Cancer, **ETE** extrathyroidal extension, **TI-RADS** Thyroid Imaging Report and Data System, **CLNM** central lymph node metastasis, **LLNM** lateral lymph node metastasis, **ROC** Receiver operating characteristic

INTRODUCTION

In recent years, the incidence of thyroid carcinoma in patients under 30 years has been increasing rapidly (1,2), accounting for nearly 10% of all malignancies in this age group (3). Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer (4). In adolescents and young adults (AYAs), PTC tends to exhibit some invasive biological behaviors, including higher rates of lymph node metastasis (LNM) extrathyroidal locoregional and distant occurrence (5−7), which place a higher demand on clinical management.

Total thyroidectomy (TT) is the optimal extent of surgery for patients with bilateral thyroid carcinoma (8), while for patients with a preoperative diagnosis of unilateral malignancy, the adequate extent of surgery is a matter of debate. Considering the high rate of complications, such as hematoma, recurrent laryngeal nerve injury and hypoparathyroidism (9), TT might not be an appropriate surgical approach for all patients with unilateral carcinoma. According to the latest American Thyroid Association (ATA) guidelines, thyroid lobectomy (TL) alone is sufficient for small, unifocal, intrathyroidal carcinomas without radiation therapy, familial thyroid carcinoma, or LNM (10). Nevertheless, PTC often

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presents as multiple foci (11,12), and the prevalence of occult contralateral carcinoma ranges from 13% to 56% (13).

Occult carcinoma is defined as a pathologically confirmed tumor that could not be recognized preoperatively. For patients who have undergone TL, occult contralateral PTC may lead to tumor recurrence, LNM and even reoperation, which will bring more surgical risks than the primary surgery. Considering the aggressive behavior of PTC in AYAs, the adequate extent of resection is of more significance (14). Thus, accurate identification of occult contralateral PTC in AYAs is valuable for treatment selection.

Ultrasound (US) is the first-line imaging modality for PTC (15,16), nevertheless, it can detect only lesions larger than 2mm. Moreover, US is operator-dependent and limited by the experience of the physician. Fine-needle aspiration (FNA) is the most accurate method to confirm PTC preoperatively (17), but it can be performed only on US-visible nodules, and, as an invasive procedure, it carries the risks of bleeding and infection (18). Therefore, identifying the risk factors for occult contralateral PTC, and developing a convenient prediction model might be helpful.

Although several studies have explored the predictive factors related to occult contralateral PTC (19,20), the primary population included was middle-aged and elderly, and the occult contralateral PTC-associated characteristics in AYAs are still unknown. In addition, only patients who received TT were included in the previous studies (21) and the characteristic of patients with occult contralateral PTC who initially underwent TL have not been previously reported. This study aimed to investigate the occult contralateral PTC-associated US and clinical characteristics, and to develop a US-based prediction model for AYAs with a preoperative diagnosis of unilateral thyroid tumor.

METHODS

Patients Selection

This study was approved by the Institutional Review Board at our center and the requirement for informed consent was waived for its retrospective nature. From January 2015 to December 2020, 3546 consecutive patients with the age at diagnosis younger than 30 years of age were recruited for the study. All patients underwent preoperative US examination and thyroid surgery, and had a pathological diagnosis of PTC at our institution. The inclusion criteria were as follows: (i) patients with high suspicion of unilateral thyroid carcinoma by preoperative imaging; (ii) patients who underwent TT or received TL initially with an adequate US follow-up period of more than 60 months. The exclusion criteria were as follows: (i) suspicious lesions detected during follow-up without pathological confirmation; (ii) history of neck surgery or radiation therapy; (iii) incomplete pathology or US data. The presence of occult contralateral PTC was confirmed by postoperative pathological examination in patients who received TT initially. In patients who received TL as the initial approach of surgery, occult contralateral PTC was considered present if suspicious lesions were detected in the residual thyroid lobe during follow-up and eventually confirmed by pathology. Otherwise, no occult contralateral PTC was considered. The endpoint of follow-up was February 2022. Finally, a total of 365 patients were enrolled in this study, 215 of whom underwent TT, and 150 of whom underwent TL. The flowchart of patient selection was shown in Figure 1.

Clinicopathological Data Collection

Surgical procedures of patients were performed according to the 8th American Joint Committee on Cancer (AJCC) staging systems and ATA guidelines (10,22). Baseline clinical data, including age at diagnosis, gender, initial symptoms and family history of thyroid cancer, were obtained from medical records. Hashimoto's thyroiditis was diagnosed according to the titers of thyroglobulin and thyroid peroxidase antibodies (23). Experienced pathologists at our institution reviewed the slides and validated the results on the pathological reports, including the pathological maximum diameter, presence of intraglandular dissemination and extrathyroidal extension (ETE), as well as the lymph nodes status.

US Examination and Image Evaluation

All patients routinely underwent preoperative thyroid and neck US examinations by radiologists with more than 5 years of experience. Images of suspicious thyroid lesions and cervical lymph nodes were stored in the digital workstation for a secondary assessment. The evaluation of US images was performed independently by two radiologists with 5+ years of experience in thyroid US, when it came to a dispute, the final diagnosis was made by another radiologist with more than 10 years of expertise.

The assessment of US images included multifocality (yes or no), contralateral benign nodules (yes or no), maximum diameter on US, the background of the thyroid (normal or abnormal), Thyroid Imaging Report and Data System (TI-RADS) grade of the suspected lesion (24), US-reported lymph node status (normal, central lymph node metastasis (CLNM), lateral lymph node metastasis (LLNM) or CLNM +LLNM), orientation (parallel or vertical), margin (circumscribed, poorly defined, irregular or extrathyroidal extension, or discrete mass), echogenicity (hyperechoic, isoechoic, hypoechoic, markedly hypoechoic), intra-tumoral calcification (yes or no), and types of intra-tumoral calcifications (microcalcification, macrocalcification, and mixed-calcification). When multiple foci were present ipsilaterally, we only assessed the lesion with the highest TI-RADS grade. When more than one lesion with the same highest TI-RADS grade, the US features of the largest lesion were assessed.

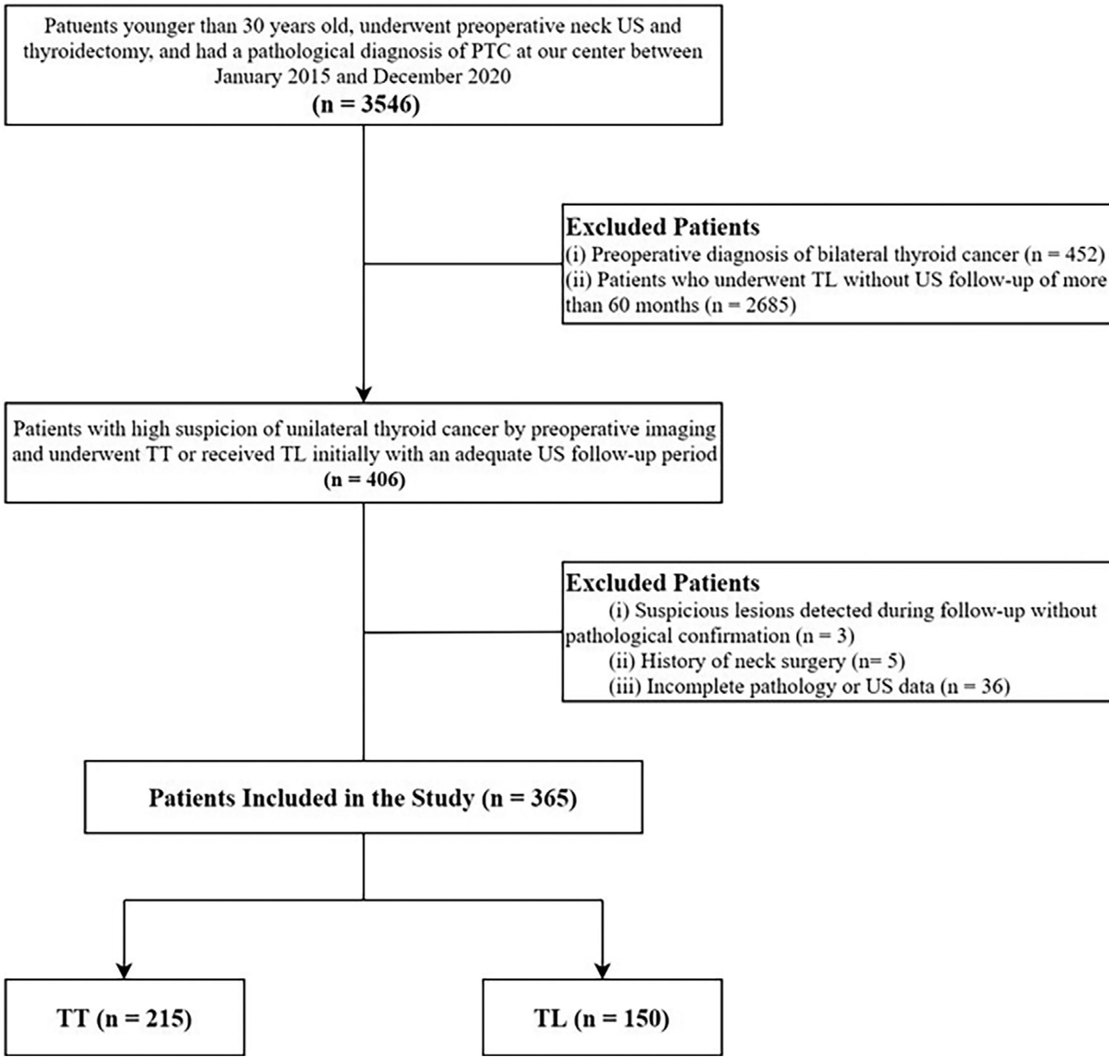

Figure 1. Flowchart of patient selection. PTC, papillary thyroid carcinoma; TT, total thyroidectomy; TL, thyroid lobectomy; US, ultrasound. (Color version of figure is available online.)

Statistical Analysis

All statistical analyses were performed by using the SPSS v 26.0 software (IBM, Armonk, NY, USA) and R software (version 4.1.1, www.Rproject.org). Patients were categorized into two groups based on the presence of occult contralateral PTC. Continuous variables were presented as the median (interquartile range) and compared by Mann−Whitney U test. Categorical variables were compared to chi-square test or Fisher's exact test. Binary univariate and multivariate logistic regression analyses were used to determine the independent risk factors that were correlated with occult contralateral PTC. Odds ratios with 95% confidence intervals were recorded to quantify the correlations between covariates and outcomes. The prediction model was established based on the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was plotted to evaluate the performance of the model. The optimal threshold of the model was set according to the maximum Youden index, and the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity and specificity of the model were calculated. Statistical significance was set at a p-value $< .05$.

RESULTS

Patients and Tumor Characteristics

A total of 365 patients were included in this study, occult contralateral PTC was present in 91 patients, 74 (81.3%) of whom underwent TT, and 17 (18.7%) who underwent TL initially were found to have contralateral PTC during follow-up (Fig. 2). Of the 274 patients with unilateral PTC, 141 (51.5%) underwent TT, and 133 (48.5%) underwent TL initially showed no suspicious lesions in the residual lobe during follow-up (Fig. 3). The median follow-up period of patients who underwent TL was 67 months (interquartile range, 62−72 months). The baseline characteristics of patients were summarized in Table 1.

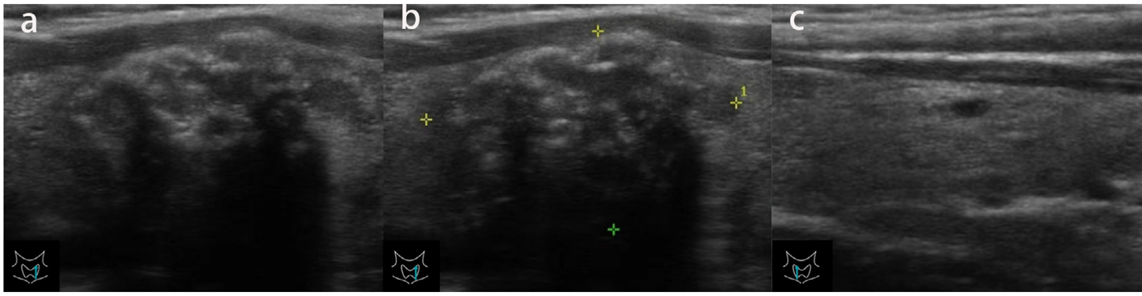

Figure 2. A 29-year-old female with a 28-mm papillary thyroid carcinoma in the left lobe and a 4-mm occult papillary thyroid carcinoma in the right lobe confirmed by surgical pathology. (A), (B) Grayscale images of calcification within the nodule in the left lobe. (C) A benign-looking nodule is shown in the right lobe. (Color version of figure is available online.)

US and Clinicopathological Characteristics Associated With Occult Contralateral PTC

In the univariate analysis, US features such as contralateral benign nodule ($p < .001$) and intra-tumoral calcification ($p = .006$) were significantly associated with the presence of occult contralateral PTC. However, multifocality, tumor size, US background of thyroid, TI-RADS grade, US-reported lymph nodes status and other sonographic features of the thyroid lesion were not significantly correlated with occult contralateral PTC (all $p > .05$). Details were shown in Table 2.

Among all clinicopathological variables, intraglandular dissemination was identified to be a significant predictor for occult contralateral PTC ($p = .033$). No significant differences were found between negative and positive occult contralateral PTC in terms of other clinicopathological characteristics, including the age at diagnosis, gender, initial symptoms, family history, Hashimoto's Thyroiditis, BRAF mutation, tumor size, extrathyroidal extension, and pathological lymph node status (all $p > .05$, Table 3).

Subsequently, contralateral benign nodule ($p < .001$), intratumoral calcification ($p = .016$) and intraglandular dissemination ($p = .042$) were identified to be independent risk factors for occult contralateral PTC in AYAs by multivariate logistic regression analysis (Table 4). Then a predictive model was thereby established, which yielded an AUC of .661 (95% CI: .601−.719) for predicting occult contralateral PTC (Fig. 4) with the cutoff value of -.959. The accuracy, sensitivity, and specificity of the prediction model were 67.9%, 54.9%, and 72.3%, respectively.

DISCUSSION

In this study, we investigated the incidence of occult contralateral PTC in patients under 30 years of age, and established a prediction model by incorporating US and clinical characteristics for an individualized prediction of occult contralateral PTC in AYAs. This prediction model may serve as an easy-to-use tool for determining the extent of surgery and optimizing the clinical decision-making.

Our results showed that the presence of contralateral benign nodule, intra-tumoral calcification and intraglandular dissemination were independent predictors of occult contralateral PTC. The positive association between contralateral benign nodule and the presence of occult contralateral PTC has been well documented in several studies (19,21,25). Our study indicated that the presence of contralateral benign nodule was related to an increased likelihood of malignancy in the contralateral lobe. The obscuration of tumor foci by benign nodules, or lesions without apparent malignant sonographic features (26), might contribute to this finding. Notably, the presence of intra-tumoral calcification was also a significant predictor for occult contralateral PTC. Although calcification, particularly microcalcification, has been found to be associated with the aggressiveness of PTC in many studies (27,28), the correlation between calcification and occult contralateral PTC in this study was the first to be reported. Calcifications usually develop from the proliferation of blood vessels and dense fibrous tissue and the deposition of calcium salts (29). Li et al. retrospectively analyzed the relationship

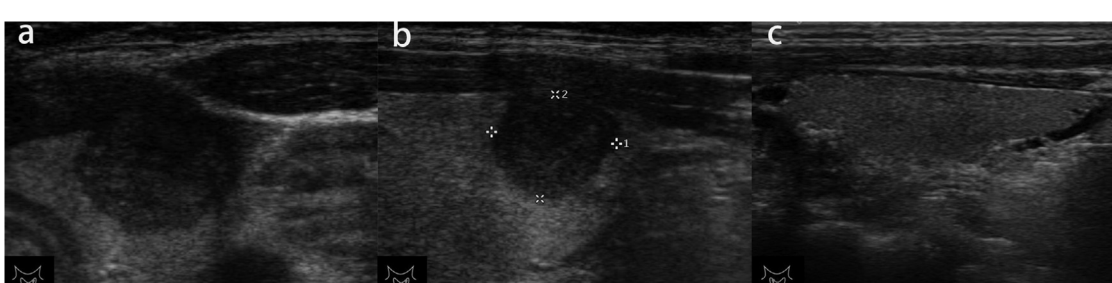

Figure 3. A 23-year-old female with a 11-mm papillary thyroid carcinoma in the left lobe was confirmed to have no occult carcinoma in the right lobe after total thyroidectomy. (A), (B) Grayscale images of no calcification within the nodule in the left lobe. (C) No benign-looking nodules were found in the right thyroid. (Color version of figure is available online.)

TABLE 1. Baseline Characteristics of 365 PTC Patients

Characteristics	No. *(%)*
Age at diagnosis (years)	
Median	26.0
(Interquartile range)	24.0−29.0
Gender (%)	
Female	251(68.8)
Male	114(31.2)
Multifocality on US (%)	
Yes	311(85.2)
No	54(14.8)
Maximum diameter on US (mm)	
Median	12.0
(Interquartile range)	7.0−20.0
TI-RADS (%)	
4A	36(9.9)
4B	80(21.9)
4C	139(38.1)
5	95(26.0)
6	15(4.1)
US-reported lymph nodes status (%)	
Normal	181(49.6)
CLNM	32(8.8)
LLNM	30(8.2)
CLNM+LLNM	122(33.4)
Pathological maximum diameter (mm)	
Median	14.0
(Interquartile range)	9.0−24.0
Intraglandular dissemination (%)	
Yes	16(4.4)
No	349(95.6)
Extrathyroidal extension (%)	
Yes	51(13.9)
No	314(86.1)
Pathological lymph nodes status (%)	
No metastasis	97(26.6)
CLNM	111(30.4)
LLNM	9(2.5)
CLNM+LLNM	148(40.5)

Data are the number of patients and percentage if not specified. CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; TI-RADS, Thyroid Imaging Report and Data System; US, ultrasound. Significant differences are highlighted in boldface.

between intra-tumoral calcification and biological behavior of PTCs in 13,995 patients and found that intra-tumoral calcification was positively correlated with tumor multifocality and invasiveness of PTC (30). Occult contralateral PTC is a form of multifocality, and multifocality is also a manifestation of aggressiveness (31). Therefore, the positive correlation between intra-tumoral calcification and occult contralateral PTC is justified. Furthermore, our results showed that the morphology of calcification was not significantly related to occult contralateral tumors. Therefore, the presence of calcification, as a whole, was included as an independent factor in the prediction model. Consistent with our study, previous

TABLE 2. Univariate Analysis of US Characteristics Between Negative and Positive Occult Contralateral PTC Patients

Characteristics	Occult Contralateral PTC		*p*
	Negative	Positive	
No. of patients	274(75.1)	91(24.9)	
Multifocality (%)			.387
Yes	38(70.4)	16(29.6)	
No	236(75.9)	75(24.1)	
Contralateral benign nodule (%)			< **.001**
Yes	86(63.7)	49(36.3)	
No	188(81.7)	42(18.3)	
Maximum diameter on US (mm)			.331
Median	13.0	16.0	
(Interquartile range)	9.0-23.5	9.0-25.0	
US background of Thyroid (%)			.632
Normal	191(75.8)	61(24.2)	
Abnormal	83(73.5)	30(26.5)	
TI-RADS (%)			.382
4A	26(72.2)	10(27.8)	
4B	61(76.3)	19(23.7)	
4C	111(79.9)	28(20.1)	
5	65(68.4)	30(31.6)	
6	11(73.3)	4(26.7)	
US-reported lymph nodes status (%)			.308
Normal	142(78.5)	39(21.5)	
CLNM	23(71.9)	9(28.1)	
LLNM	19(63.3)	11(36.7)	
CLNM+LLNM	90(73.8)	32(26.2)	
Orientation (%)			.068
Parallel	221(73.2)	81(26.8)	
Vertical	53(84.1)	10(15.9)	
Margin (%)			.278
Circumscribed	22(88.0)	3(12.0)	
Poorly defined	97(74.0)	34(26.0)	
Irregular or extrathyroidal extension	151(73.7)	54(26.3)	
No discrete mass	4(100.0)	0(0)	
Echogenicity (%)			.565
Hyperechoic	1(100.0)	0(0)	
Isoechoic	45(80.4)	11(19.6)	
Hypoechoic	207(73.4)	75(26.6)	
Markedly hypoechoic	21(80.8)	5(19.2)	
Intra-tumoral calcification (%)			**.006**
Yes	223(72.4)	85(27.6)	
No	51(89.5)	6(10.5)	
Types of Intratumoral Calcifications (%)			0.599
Microcalcification	133(70.7)	55(29.3)	
Macrocalcification	11(68.7)	5(31.3)	
Mixed calcification	79(76.0)	25(24.0)	

Data are the number of patients and percentage if not specified. Significant differences are highlighted in boldface. CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; TI-RADS, Thyroid Imaging Report and Data System; US, ultrasound. Significant differences are highlighted in boldface.

TABLE 3. Univariate Analysis of Clinicopathological Characteristics Between Negative and Positive Occult Contralateral PTC Patients

Characteristics	Occult Contralateral PTC		*p*
	Negative	Positive	
No. of patients	274(75.1)	91(24.9)	
Age at diagnosis (years)			.938
Median	26.0	27.0	
(Interquartile range)	24.0-29.0	24.0-29.0	
Gender (%)			.350
Female	192(76.5)	59(23.5)	
Male	82(71.9)	32(28.1)	
Initial symptoms (%)			.766
PE or unintentional discovery	244(75.3)	80(24.7)	
Palpable mass, hoarse or pain	30(73.2)	11(26.8)	
Family history (%)			.766
No	241(73.9)	85(26.1)	
Yes	33(73.2)	6(26.8)	
Hashimoto's thyroiditis (%)			.346
Yes	114(72.6)	43(27.4)	
No	160(76.9)	48(23.1)	
BRAF mutation (%)			.449
No	8(72.7)	3(27.3)	
Yes	10(55.6)	8(44.4)	
Pathological maximum diameter (mm)			.688
Median	12.0	12.0	
(Interquartile range)	7.0-20.0	6.0-20.0	
Intraglandular dissemination (%)			**.033**
Yes	8(50.0)	8(50.0)	
No	266(76.2)	83(23.8)	
Extrathyroidal extension (%)			.135
Yes	34(66.7)	17(33.3)	
No	240(76.4)	74(23.6)	
Pathological lymph nodes status (%)			.936
No metastasis	74(76.3)	23(23.7)	
CLNM	83(74.8)	28(25.2)	
LLNM	6(66.7)	3(33.3)	
CLNM+LLNM	111(75.0)	37(25.0)	

Data are the number of patients and percentage if not specified. CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; PE, physical examination; PTC, papillary thyroid carcinoma. Significant differences are highlighted in boldface.

studies have reported that intraglandular dissemination was an indicator of progressive and multifocal PTC (32−34). Intraglandular dissemination is thought to be a form of metastasis for thyroid carcinoma, by which the disseminated lesions may spread bilaterally through the intralobular lymphatics network (35), which may contribute to the increased risk of occult contralateral PTC in patients with intraglandular disseminated tumors.

TABLE 4. Multivariate Analysis for Predictive Factors of Occult Contralateral PTC in Adolescent and Young Adults

Parameters	Multivariate Analysis		
	β	OR (95%CI)	*p* Value
Intercept	-2.538		
Contralateral benign nodule			
Yes	0.947	2.578 (1.576, 4.243)	**< .001**
No			
Intra-tumoral calcification			
Yes	1.106	3.021 (1.324, 5.263)	**.016**
No			
Intraglandular dissemination	1.081	2.948 (1.024, 8.504)	**.042**
Yes			
No			

CI, confidence interval; OR, odds ratio; PTC, papillary thyroid carcinoma. β is the regression coefficient. Significant differences are highlighted in boldface.

Inconsistent with our observations, some US and clinicopathological characteristics such as ipsilateral multifocality, tumor size and pathological and US-reported lymph node status have been frequently selected as risk factors for occult contralateral PTC in previous whole-population-based studies (13,19,36,37). However, in a sizeable children-targeted study, tumor size and lymph node status were also found irrelevant to the occult contralateral PTC (38). We speculate that different participant selection strategies may result in this inconsistency, which implies differences in the characteristics of AYAs patients with PTC compared to that of the entire population.

Previous studies on occult contralateral PTC included only patients who underwent TT (13,19,36). However, successful prediction of occult contralateral PTC brings more clinical significance to patients who underwent TL initially. In our study, the overall incidence of occult contralateral cancer was as high as 24.9%, and 17 (11.3%) of 150 patients who underwent TL initially presented with pathologically confirmed contralateral PTC nodules during follow-up. Due to the aggressive nature of PTC in young patients, in this study, we focused on the occult contralateral PTC in patients under 30 years old. Occult carcinoma in the residual thyroid gland may lead to tumor recurrence, LNM, and reoperation, of which the difficulty is much greater than the primary surgery. Reoperation might aggravate the clinical and patient burden, and have an adverse effect on the long-term life quality of patients. Therefore, for PTC patients with a high risk of occult contralateral carcinoma, adopting more aggressive treatment protocols, such as TT as the primary surgery and receiving more frequent follow-up is reasonable. In this context, we developed a convenient prediction model to predict occult contralateral PTC in AYAs, which made it possible for clinicians to select the individualized treatment for patients.

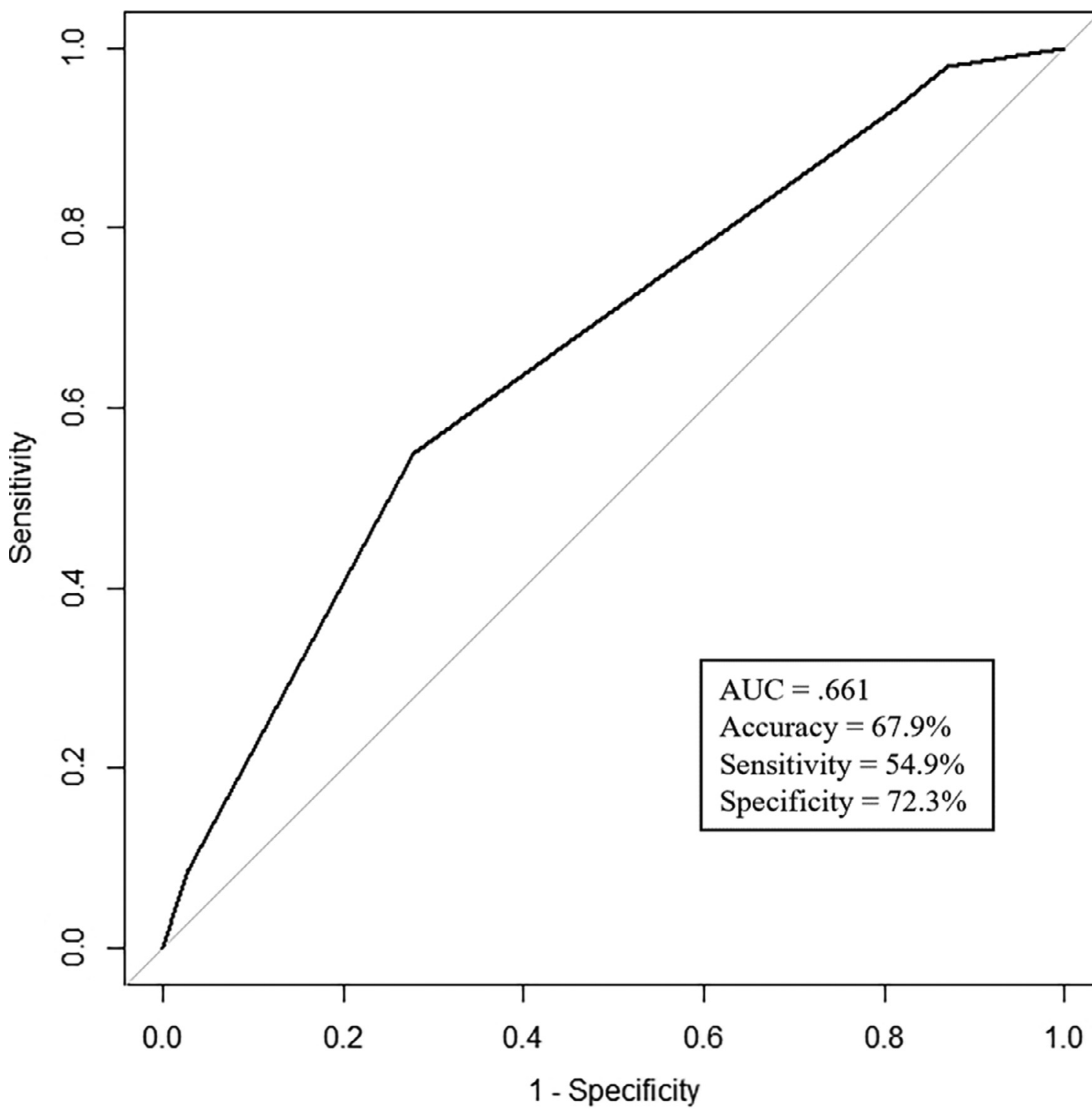

Figure 4. Receiver operating characteristic curves of the US-based model for predicting occult contralateral papillary thyroid carcinoma in adolescents and young adults. (Color version of figure is available online.)

With easily accessible US and clinicopathological characteristics, young patients with a high risk predicted by the prediction model can be selected to perform TT, and unnecessary TT may be avoided for those with a low risk of occult contralateral PTC.

The study had several limitations which we hope to address in subsequent studies. First, as a retrospective study conducted in a single medical center, the inherent selection bias was inevitable. Second, the findings of this study lacked external validation. Thus, a prospective multi-center study with larger sample size is required. Furthermore, since the US data was extracted only from two-dimensional US images, the diagnostic capability of the prediction model was not as satisfactory as expected. In future studies, latest technological parameters from shear wave elastography, contrast-enhanced US, radiomics, and deep learning will be incorporated to improve the performance of the prediction model.

CONCLUSION

Contralateral benign nodule, intra-tumoral calcification and intraglandular dissemination were identified as the independent predictors for occult contralateral PTC in AYAs, and the consequent prediction model may be important in guiding the clinical management.

AUTHOR CONTRIBUTION

YT designed the study. YW and DS collected and analyzed the data. YT and YW wrote the paper. CC provided

administrative support. All authors contributed to the article and approved the submitted version. We thank Changming Zhou for his kind help with the statistical analysis.

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