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ORIGINAL ARTICLE

Thyroid autoimmune antibodies in patients with papillary thyroid carcinoma: a double-edged sword?

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Abstract
Purpose The relationship between thyroid autoimmunity and thyroid cancer remains controversial. The objective of this study is to comprehensively analyze the association between thyroid autoimmune antibodies and disease statuses of papillary thyroid carcinoma (PTC).
Methods Patients were divided into different groups according to their final diagnoses after radioiodine therapy as well as their serum anti-thyroglobulin antibody (TgAb) and anti-thyroidperoxidase antibody (TPOAb) titers. Clinicopathologic characteristics were then compared between groups.
Results In all, 1126 PTC patients met the inclusion criteria. When compared with thyroid autoimmune antibody negative group, patients in positive group were young female predominant. After age and gender adjusted, patients in thyroid autoimmune antibody positive group had much more cervical metastatic node count and this effect was limited to the central compartment but not to the lateral compartment. Antibody positivity rate was much lower in patients with distant metastasis and multivariable logistic regression analysis showed positive status of antibody was a protective factor of distant metastasis of PTC with an OR value of 0.403 (95% CI 0.216–0.622, $p < 0.001$). Additionally, subgroup analysis demonstrated single TgAb positivity and combined positivity of TgAb and TPOAb were shown to be related to less distant metastatic disease.
Conclusions Positive thyroid auto-antibody status could be a risk factor of more metastatic cervical lymph nodes while a protective factor of distant metastatic disease in PTC patients. The association between thyroid autoimmunity and thyroid cancer can be patient and antibody specific. A systemic immunosupression status may exist in PTC patients with distant metastasis.

Keywords Thyroid autoimmunity · Papillary thyroid carcinoma · Metastasis · Radioiodine

Introduction

Chronic inflammation considered as a pre-cancer condition was first proposed by Virchow in 1863 and the relationship between inflammation and cancer has been verified by lots of clinical and epidemiological evidence [1–3]. In the development of papillary thyroid carcinoma (PTC), autoimmune thyroid disease/chronic thyroiditis is frequently found to be related [3]. Although this association has been suggested since the 1950s, the role of thyroid autoantibodies and/or chronic lymphocytic infiltration in the development and progression of thyroid cancer remains disputable [4–6].

Anti-thyroidperoxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb) are two kinds of important clinical markers for autoimmune thyroid diseases. Studies have been performed to investigate the cancer risk of TgAb and/or TPOAb in general population and their potential

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prognostic prediction value in PTC patients [7]. Studies have shown that presence of lymphocytic thyroiditis, history of autoimmune thyroid disease, or positive antibodies in patients with thyroid cancer is associated with a lower chance of recurrent/persistent diseases as well as mortality at follow-up [8–10]. While results from other studies indicated that thyroid cancer patients with positive serum TgAb after primary treatment had more aggressive disease and less favorable long-term outcomes than demographically similar patients without circulating TgAb [11–13]. This discordance could result from the selection bias of patients, the differences in detection methodology and the positive cutoff value of autoimmune antibodies.

PTC is considered as an indolent tumor because of its excellent prognosis with a 10-year-survival around 90%. However, approximately 10–15% of PTC patients will develop distant metastases and about 50% of them will die within 10 years of diagnosis [14–18]. Thus, the status of distant metastasis plays the most important role in the prognosis of PTC patients. However, owning to the limited number and low incidence of distant metastasis in PTC, few studies have investigated the effect of anti-thyroid antibodies in this condition with a relatively large cohort of patients [9]. In the current study, we systemically analyzed the association between the status of thyroid autoimmune antibodies (TgAb and TPOAb) and the clinicopathologic characteristics of PTC.

Materials and methods

Patients

The current study was performed at a single institution from December 2013 to December 2015. This study was approved by the ethics committee of our institution and written informed consent was achieved from each patient (for patient whose age was younger than 18 years, written informed consent was obtained from his/her statutory guardian additionally).

All patients had pathologically proven PTC and underwent near/total thyroidectomy. Before ^{131}I therapy, all patients were asked to withdraw thyroid hormone medication for 3–4 weeks and begin a low iodine diet for 2 weeks. An empirical treatment dose of ^{131}I was administered (30–100 mCi for residual thyroid ablation, 100–150 mCi for lymph node metastases and 150–200 mCi for distant metastases) under serum TSH level ≥ 30 mIU/L.

Groups and comparisons

Patients were recruited according to their different disease statuses, namely ablation group (without evidence of disease), lymph node metastasis group, and distant metastasis group.

Ablation group-without evidence of disease (A)

Inclusion criteria: (1) central compartment cervical node dissection was performed; (2) stimulating Tg (sTg, serum Tg level measured under TSH level ≥ 30 mIU/L) level ≤ 10 ng/mL; (3) no metastasis suspected diseases found in ^{131}I scintigraphy, neck ultrasound, chest CT scan, or other relative imaging modalities.

Exclusion criteria: (1) patient with existing metastatic disease at the time of radioiodine therapy; (2) other malignancy history.

Cervical lymph node metastasis (cLM) group

Inclusion criteria: (1) ^{131}I scintigraphy showed lymph node metastases (uptake foci were found beyond thyroid bed in the neck and it was congruent with a lymph node in anatomical imaging like CT) [19]; (2) metastasis suspected diseases found in neck ultrasound; (3) no other metastasis suspected diseases found in scintigraphy, chest CT scan or other relative imaging modalities; (4) serum sTg > 10 ng/mL and/or TgAb > 100 IU/mL; (5) or lymph node metastasis confirmed by pathology.

Exclusion criteria: (1) patient without any metastasis disease; (2) patients with confirmed distant metastasis; (3) other malignancy history.

Distant metastasis (DM) group

Inclusion criteria: (1) ^{131}I scintigraphy showed distant metastases (iodine uptake foci were localized to bones, lungs, or other soft tissue organs in accordance with characteristic anatomical imaging findings such as lytic bone lesions or small lung nodules); (2) metastatic lesions found in CT or other imaging modalities like magnetic resonance and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) even without iodine uptake in ^{131}I scintigraphy [15, 17]; (3) serum sTg > 10 ng/mL and/or TgAb > 100 IU/mL; (4) or distant metastasis confirmed by pathology.

Exclusion criteria: (1) patient without any distant metastatic disease; (2) other malignancy history. Recruited patients were then categorized according to their serum statuses of thyroid autoimmune antibodies: thyroid auto-antibody positive group (TgAb level ≥ 100.0 IU/mL [19, 20] or TPOAb level ≥ 35.0 IU/mL) and thyroid auto-antibody negative group (TgAb level < 100.0 IU/mL and TPOAb level < 35.0 IU/mL). Patients in thyroid auto-antibody positive group were subsequently divided into three sub-groups: single-TgAb positive group (TgAb

level ≥ 100.0 IU/mL and TPOAb level < 35.0 IU/mL), single-TPOAb positive group (TPOAb level ≥ 35.0 IU/mL and TgAb level < 100.0 IU/mL), co-positive group (TgAb level ≥ 100.0 IU/mL and TPOAb level ≥ 35.0 IU/mL).

Laboratory methods

Blood sample (4–5 mL) was collected from each patient 1 day before radioiodine therapy. After centrifuged, Tg, TgAb, and TPOAb titers were measured by electrochemiluminescence immunoassay kits (Roche Diagnostics GmbH) on the Cobas analyzer (Roche Cobas e601, Roche Diagnostics GmbH) within 12 h after sample collection. The measurement range of TgAb was 10–4000 IU/mL with a normal range of 0–115.0 IU/mL in our institution. And the measurement range of TPOAb was 5–600 IU/mL with a normal range of 0–35.0 IU/mL. The analytical sensitivity of Tg was 0.1 ng/mL with reference range 1.4–78 ng/mL

Radioiodine therapy evaluation in distant metastasis group

Patients in distant metastasis group were further divided into radioiodine-refractory PTC and non-radioiodine-refractory PTC. Criteria for radioiodine–refractory PTC were as following [21, 22]: (1) metastatic lesions do not take up radioiodine even after successful remnant thyroid ablation; (2) metastatic lesions lose the ability to take up radioiodine after previous evidence of uptake together with structure and/or serum based disease progression; (3) radioiodine uptake retained in some lesions but not in others together with structure and/or serum-based disease progression; (4) disease progresses despite substantial uptake of radioiodine.

Statistical analysis

Continuous variables were reported as mean ± SD or median/range and comparisons of continuous variables between two groups were performed using the Student's *t*-test (assuming equal variances) or Welch-test (assuming unequal variances). Categorical variables were reported as absolute numbers and percentages. The chi-square statistic or Fisher exact test were used to compare categorical variables. Predictive modeling was performed using multivariable logistic modeling techniques to correct for possible clinically relevant factors. A *P*-value of <0.05 was considered statistically significant. All analyzes were performed by using the Statistical Package for the Social Sciences, version 20.0 (SPSS, Chicago, IL, USA).

Results

In all, 1126 PTC patients (733 in ablation group, 180 in lymph node metastasis group, and 213 in distant metastasis

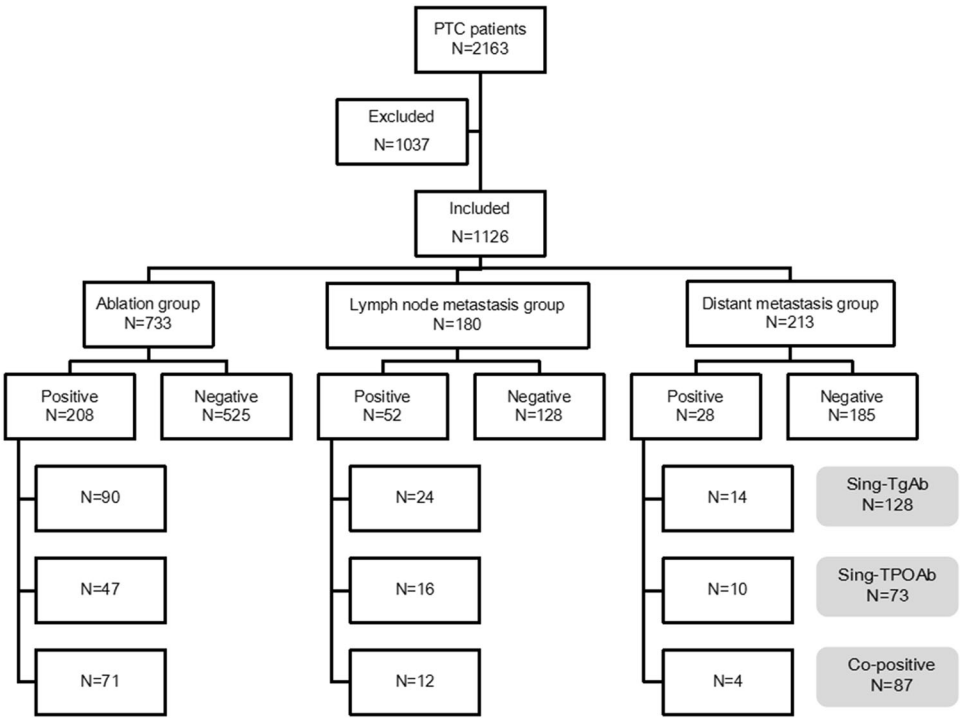

Fig. 1 Outline of patient grouping

Table 1 Basic clinical characteristics comparison in different groups

	Total/1126			Ablation group/733			Lymph node metastasis group/180			Distant metastasis group/213		
	P/288	N/838	P-value	P/208	N/525	P-value	P/52	N/128	P-value	P/28	N/185	P-value
Age/years			0.010			0.001			0.715			0.280
<45 /range	183/16–44	459/11–44		138/16–44	278/14–44		32/20–44	75/13–44		13/16–44	106/11–44	
≥45 /range	105/45–74	379/45–82		70/45–71	247/45–73		20/45–60	53/45–82		15/45–74	79/45–82	
Gender			0.000			0.000			0.002			0.691
Male	52/18.1	312/37.7		30/14.4	184/35.0		10/19.2	56/43.8		12/42.9	72/38.9	
Female	236/81.9	526/63.5		178/85.6	341/65.0		42/80.2	72/56.2		16/57.1	113/61.1	
T stage			0.489			0.769			0.231			0.394
T1	197/68.4	550/66.4		158/76.0	379/72.2		30/57.7	88/68.8		9/32.1	83/44.9	
T2	38/13.2	140/16.9		22/10.6	65/12.3		7/13.5	13/10.2		9/32.1	62/33.5	
T3	30/10.4	76/9.2		18/8.6	54/10.3		9/17.3	10/7.8		3/10.7	12/6.5	
T4	23/8	72/8.7		10/4.8	27/5.2		6/11.5	17/13.3		7/25.0	28/15.1	
Maximum diameter	1.8 ± 1.1	1.9 ± 1.0	0.896	1.4 ± 0.89	1.3 ± 0.9	0.674	1.7 ± 1.4	2.0 ± 0.9	0.143	2.6 ± 1.7	2.4 ± 1.2	0.327
N stage			0.995			0.921			0.228			0.679
N0	20/6.9	57/6.9		20/9.6	49/9.3		0/0.0	6/4.7		0/0.0	2/1.1	
N1	264/91.7	769/92.9		184/88.5	468/89.1		52/100.0	121/94.5		28/100.0	180/97.3	
Nx	4/1.4	12/1.4		4/1.9	8/1.5		0/0.0	1/0.8		0/0.0	3/1.6	
Tumor foci			0.391			0.861			0.324			0.214
Unifocal	127/44.1	394/47.6		93/44.7	231/44		23/44.2	67/52.3		11/39.3	96/51.9	
Multifocal	161/55.9	444/53.6		115/55.3	294/56.0		29/55.7	61/47.7		17/60.7	89/48.1	
Location			0.509			0.965			0.262			0.654
Unilateral	136/47.2	428/51.7		98/47.1	252/48		25/48.1	77/60.2		13/46.4	99/53.5	
Bilateral	131/45.5	357/43.1		94/45.2	235/44.8		23/44.2	46/35.9		14/50.0	76/41.1	
Isthmus	21/7.3	53/6.4		16/7.7	38/7.2		4/7.7	5/3.9		1/3.6	10/5.4	

P thyroid auto-antibody positive group, *N* thyroid auto-antibody negative group

T/N stage was evaluated before radioiodine therapy according to the results of surgery and pathology

group) met the inclusion criteria and were enrolled in the current study. Positive thyroid autoimmune antibody status was found in 288 (25.58%) patients with single-TgAb positivity in 128 (11.37%), single-TPOAb positivity in 73 (6.48%), and co-positivity in 87 (7.73%) patients (Fig. 1).

Positive thyroid auto-antibody status was young female predominant in PTC patients

Clinical characteristics including age, gender, T/N stage, and tumor foci/location were compared between groups (Table 1). In the whole cohort population, when compared to thyroid autoimmune antibody negative group, patients in thyroid autoimmune antibody positive group were younger (40.1 ± 12.1 vs. 43.1 ± 13.1 years, $P = 0.001$; 62.54% younger than 45 years vs. 54.77% younger than 45 years, $P = 0.010$) and female predominant (female/male 236/52 vs. female/male 526/312, $P < 0.001$). While, there was no significant difference in other characteristics like T/N stage and tumor foci/location between thyroid autoimmune antibody positive and negative group.

In addition, these clinical characteristics were further compared in ablation, lymph node metastasis, and distant metastasis groups between thyroid autoimmune antibody positive and negative patients, respectively (Table 1). The results showed that there was no significant difference in characteristics including T/N stage and tumor foci/location between thyroid autoimmune antibody positive and negative patients of each group as well. The effect of significant difference in age was retained in ablation group (39.7 ± 11.6 years vs. 43.7 ± 12.0 years, $P < 0.001$; 66.35% younger than 45 years vs. 52.95% younger than 45 years, $P = 0.001$), while no significant difference was achieved in lymph node metastasis (40.4 ± 12.6 years vs. 41.5 ± 14.5 years, $P = 0.610$; 61.54% younger than 45 years vs. 58.59% younger than 45 years, $P = 0.715$) and distant metastasis group (42.3 ± 15.0 years vs. 42.4 ± 15.1 years, $P = 0.958$; 46.43% younger than 45 years vs. 57.30% younger than 45 years, $P = 0.280$). The effect of significant difference in gender was retained in ablation group (female/male 178/30 vs. female/male 341/184, $P < 0.001$) and lymph node metastasis group (female/male 42/10 vs. female/male 72/56, $P = 0.002$), while no significant difference was achieved in distant metastasis group (female/male 16/12 vs. female/male 113/72, $P = 0.691$) between thyroid autoimmune antibody positive and negative patients.

Positive thyroid auto-antibody status was associated with more metastatic cervical lymph node

The association between the status of thyroid autoimmune antibody and cervical lymph node involvement of PTC at thyroidectomy was evaluated in ablation group. Theoretically, patients in ablation group were all without evidence of disease and all metastatic lymph nodes were resected. Two hundred and four patients with positive thyroid autoimmune antibody (four patients with Nx were excluded) and 204 age-/gender-matched patients with negative thyroid autoimmune antibody were analyzed. Total number of excised node (central compartment node count and lateral compartment node count) and total number of metastatic node (central compartment node positive count and lateral compartment node positive count) were compared between thyroid autoimmune antibody positive group and age-/gender-matched thyroid autoimmune antibody negative group. The results demonstrated that patients with positive thyroid autoimmune antibody had much more central compartment metastatic node count (4.2 ± 3.8 vs. 2.9 ± 2.6, $P = 0.005$) and total number of excised central compartment node count (9.0 ± 5.6 vs. 5.8 ± 3.4, $P < 0.001$). However, lateral compartment metastatic node count and total number of excised lateral compartment node count were not significantly different between the two groups (Table 2).

Table 2 Thyroid autoimmune antibody and cervical lymph node metastasis

	N/204	P/204	*P*-value
Age/years			
Mean ± SD	40.6 ± 11.3	40.0 ± 11.6	0.991
Gender			1.000
Male	28	28	
Female	176	176	
T stage			0.605
T1	147	154	
T2	30	22	
T3	15	18	
T4	12	10	
Tumor foci			0.842
Unifocal	89	91	
Multifocal	115	113	
Location			0.861
Unilateral	90	95	
Bilateral	96	93	
Isthmus	18	16	
Node with metastasis count			
Central node positive count	2.9 ± 2.6	4.2 ± 3.8	0.005
Lateral node positive count[a]	3.8 ± 3.3	5.0 ± 5.1	0.059
Total node count			
Central node count	5.8 ± 3.4	9.0 ± 5.6	<0.001
Lateral node count[a]	15.8 ± 12.3	19.1 ± 15.2	0.098
Metastatic-to-excised lymph node ratio			
Central node positive count	0.54 ± 0.34	0.49 ± 0.33	0.688
Lateral node positive count[a]	0.32 ± 0.26	0.31 ± 0.27	0.882

P thyroid auto-antibody positive group, *N* thyroid auto-antibody negative group

[a] Lateral compartment cervical node dissections were performed in 101 and 78 patients in thyroid auto-antibody positive group (*P*) and thyroid auto-antibody negative group (*N*), respectively

Thyroid auto-antibody positivity rate was much lower in distant metastasis group

Thyroid autoimmune antibody positivity rate was compared in ablation, lymph node metastasis and distant metastasis groups. The positivity rate was much lower in distant metastasis group when compared to ablation and lymph node metastasis groups (13.15 vs. 28.38 vs. 28.89%, $P < 0.001$). Age and gender adjusted multivariable logistic regression analysis showed thyroid autoimmune antibody positivity was a protective factor of distant metastasis of PTC with an OR value of 0.403 (95% CI 0.216–0.622, $P < 0.001$).

To further investigate whether the association was antibody specific or not, subgroup analysis was performed. Clinical characteristics in different subgroups were demonstrated in Supplementary Tables 1–3. Multivariable logistic regression analysis showed single-TgAb positivity and co-positivity of TgAb and TPOAb, but not single-TPOAb positivity were protective factors of distant metastasis of PTC with their OR values of 0.473 (95% CI 0.261–0.858, $P = 0.014$), 0.157 (95% CI 0.056–0.438, $P < 0.001$) and 0.609 (95% CI 0.300–1.234, $P = 0.169$), respectively.

Metastatic disease was relatively infrequent in thyroid autoimmune antibody positive patients

Of the 288 patients with positive thyroid autoimmune antibody status and 838 patients with negative thyroid autoimmune antibody status, their final diagnosis results were different. When compared to thyroid autoimmune antibody negative group, metastatic disease was much less frequent in thyroid autoimmune antibody positive group (9.72 vs. 22.08%, $P < 0.001$). Antibody specific analysis showed that metastatic disease was much infrequent in single-TgAb positive and co-positive group when compared to antibody negative group (10.94 vs. 22.08%, $P = 0.004$ and 4.60 vs. 22.08%, $P < 0.001$). Although metastatic

disease was also infrequent in single-TPOAb positive group, no statistically significant difference was achieved (13.70 vs. 22.08%, $P = 0.094$).

Radioiodine treatment evaluation in distant metastasis group

Two hundred and thirteen patients were included in distant metastasis group with 28 patients divided into thyroid autoimmune antibody positive group and 185 patients divided into thyroid autoimmune antibody negative group. All patients in distant metastasis group received at least two courses of radioiodine therapy at the time of treatment evaluation. Finally, 78 of 213 patients had radioiodine–refractory diseases with ten patients in thyroid autoimmune antibody positive group and 68 patients in thyroid autoimmune antibody negative group, respectively. However, the incidence of radioiodine–refractory disease in those two groups showed no significant difference (35.7 vs. 36.8%, $P = 0.915$).

Discussion

The current study demonstrated that PTC patients with positive thyroid autoimmune antibody had more metastatic cervical lymph nodes and this effect was limited to the central compartment but not to the lateral compartment. The association between thyroid autoimmune antibody and lymph node metastasis still remains controversial and the existing data are conflicting. Vasileiadis et al. [23] reported that the rate of lymph node metastasis in PTC patients with positive TgAb was statistically significantly increased compared with the rate of PTC patients with negative TgAb (20.3 vs. 10%). Recently, Donangelo et al. [10] found that a larger number of cervical lymph nodes were excised in the TgAb positive group than in the TgAb negative group (14.5 ± 12.1 vs. 10.4 ± 11.0, $P < 0.0001$) but the number of metastatic cervical lymph nodes was similar (3.8 ± 6.0 vs. 3.2 ± 4.6, $P = 0.9203$). Selection bias of patients, the difference of detection methodology and the positive cutoff value of TgAb could contribute to the different results. Based on the result of the current study, the extent of central compartment node dissection should be carefully determined in PTC patients with positive status of thyroid autoantibody.

This study also evaluated the association between the status of thyroid autoimmune antibody and distant metastatic disease in PTC with a relative large cohort of patients ($N = 213$). Our results showed that patients with positive autoimmune antibody had half as much distant metastatic disease as negative antibody patients (9.72 vs. 22.08%), which indicating thyroid autoimmune antibody could be a protective factor that prevents the development of distant metastasis in PTC patients. In addition, single TgAb positivity as well as combined TgAb and TPOAb positivity, but not single TPOAb positivity, were shown to be related to less distant metastatic disease. However, as the distant metastasis rate in co-positive group was the lowest, we believed that TPOAb positivity could also contribute to this effect as a secondly factor. The phenomenon of antibody specificity has been indentified in previous studies [2, 24]. Kim et al. [24] reported that TgAb, but not TPOAb, was an independent risk factor for thyroid cancer. Azizi et al. [2] prospectively examined 2100 patients with 2753 thyroid nodes and they found that TgAb was a significant predictor of thyroid cancer in multivariate analysis with an OR value of 2.24 (95% confidence interval (CI) 1.57–3.19). However, thyroid cancer was not associated with serum concentrations of TPOAb. Wu et al. [11] found that the coexistence of TgAb and TPOAb demonstrated a greater risk for PTC than isolated positive TgAb or TPOAb. The mechanism of this phenomenon is not known. The rationale of the protective effect of thyroid autoimmune antibody is based on that the autoimmune response to thyroid specific antigens enhances the destruction of cancer cells expressing thyroid-specific antigen in PTC [25]. Specific antigen expressed in the differentiated cancer cell may be the most essential factor that contributes to the phenomenon of antibody specificity. Further intensive studies into this phenomenon of antibody specificity may lead to a better understanding of tumorigenesis and metastasis development of PTC.

Above were the two main findings of our study that positive thyroid auto-antibody status was associated with the presence of more cervical metastatic lymph nodes at thyroidectomy, but at the same time, it was associated with the absence of distant metastatic disease. These points seem to be paradoxical. However, it may be hypothesized that when the differentiated thyroid cancer cell expressing thyroid-specific antigen invades into the lymphatic vessel, the presence of thyroid autoimmune antibody makes it easier to locate to the lymph node. On the contrary, when the cancer cell invades into the blood vessel, the presence of autoimmune antibody makes it more difficult to locate to other soft tissue organs. Basic researches are needed to illuminate the underline mechanisms that why thyroid autoimmunity shows different effects on cervical lymph node and distant metastasis of PTC.

The outcome of radioiodine therapy in patients with distant metastatic disease was also evaluated in the current study. Our results demonstrated that the status of thyroid autoimmune antibody was not associated with outcome of radioiodine treatment in PTC patients with distant metastatic disease. The phenomenon that local radiotherapy is associated with regression of distant metastatic disease from

the irradiated site is known as "abscopal effect" [26]. This phenomenon indicates that the host immunology could be an efficient anti-tumor factor, which makes immunotherapy a new way in malignance-treatment modality. Based on this knowledge, we hypothesized that treatment with radioiodine as a systemic internal radiotherapy in patients with positive thyroid autoimmune antibody could achieve a better outcome. Although with negative result, this point should be further investigated with a larger cohort of patients.

Limitations have to be mentioned in the current study. Firstly, history of thyroiditis/lymphocytic infiltration was not reported. Thyroid autoimmunity can be explained differently. Previous studies have demonstrated it variously either as lymphocytic infiltration in or around thyroid cancer [8, 27], as classical Hashimoto's thyroiditis with Hurthle cells and germinal centers [28], or as positive serum thyroid antibody alone [9, 29]. In our current study, thyroid autoimmunity was simply defined as positive TgAb or TPOAb and all measurements were performed in one institution with the same method, which could effectively reduce the selection bias. Secondly, selection bias may potentially influence the result [30, 31]. The patients entered into this study were those PTC patients that underwent total thyroidectomy and were selected to receive radioiodine treatment, while others were not included. Also, patients with autoimmune thyroid disease could be diagnosed with thyroid cancer earlier than those without autoimmune thyroid disease. Later diagnosis may show greater chance of distant metastases. Thirdly, metastatic lesions were not all proved by histology. Although histopathology is the gold standard for diagnosis, radioiodine scintigraphy and other imaging modalities together with serum sTg level can provide high sensitivity and specificity for detection of lesions derived from differentiated thyroid carcinoma. Finally, although a relative large cohort of patients were included in the current study, the number of patients with positive thyroid autoimmune antibody in distant metastasis group ($N = 28$) was still not enough to make a statistically significant result during the radioiodine therapy assessment.

In conclusion, our study demonstrated that positive thyroid autoimmune antibody status was young female predominant in PTC patients. After age and gender adjusted, thyroid autoimmune antibody status could be a risk factor of more cervical metastatic lymph nodes while a protective factor of distant metastasis in PTC patients. The association between thyroid autoimmunity and thyroid cancer is patient and antibody specific. The finding that thyroid auto-antibody positivity rate was much lower in distant metastasis group could also indicate a systemic immunosupression status in PTC patients with distant metastasis, which may reveal new strategies for the treatment of this disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study was approved by the ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital.

Informed consent Written informed consent was achieved from each patient (for patient whose age was younger than 18 years, written informed consent was obtained from his/her statutory guardian additionally).

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