Differential diagnosis of primary thyroid lymphoma and papillary thyroid carcinoma by ultrasound combined with computed tomography

Dong Xu (xudong@zjcc.org.cn)
Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital)
Chanjuan Peng
Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital)
Dan Yi
Zhejiang Chinese Medical University
Ying Zhou
Hebei Provincial Hospital of Traditional Chinese Medicine
Jincao Yao
Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital)
Bo Chen
Shaoxing People's Hospital
Chen Yang
Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital)

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Abstract

Background: Primary thyroid lymphoma (PTL) and papillary thyroid carcinoma (PTC) are both thyroid malignancies, but their therapeutic methods and prognosis are different. This study aims to explore their sonographic and computed tomography （CT）features , and to improve the early diagnosis rate.

Methods: The clinical and imaging data of 50 patients with PTL and 100 patients with PTC confirmed by pathology were retrospectively analysed.

Results: There was no significant difference between PTL and PTC patients in gender ratio, echo texture, cystic change and aspect ratio (P>0.05), while the difference was significant in age, maximum diameter of nodule, asymmetric enlargement and Hashimoto's thyroiditis (P<0.001). PTL had a higher proportion than PTL in markedly hypoechoic, internal linear echogenic strands, posterior echo enhancement, rich vascularity, lack of calcification and homogeneous enhancement, with statistically significant difference (P<0.05), while PTC was proportionally higher than PTL in irregular border, circumscribed margin, capsular invasion and significant enhancement, also with statistically significant difference (P<0.001). Besides, PTL and PTC were significantly different in the non-contrast CT value mean, venous phase CT value mean, enhanced intensity and homogeneity of nodules (P<0.05). Multivariate logistic regression analysis showed that age, posterior echo enhancement, lack of calcification and homogeneous enhancement were independent risk factors (OR=1.226, 95%CI:1.056~1.423, P=0.007; OR=51.152, 95%CI: 2.934~891.738, P=0.007; OR=0.013, 95%CI: 0.000~0.400, P=0.013; OR=0.020, 95%CI: 0.001~0.507, P=0.018).

Conclusions: Certain sonographic and CT features as the presence of posterior echo enhancement and lack of calcification, homogeneous enhancement were valuable for distinguishing PTL from PTC.

Introduction

Primary thyroid lymphoma (PTL) is a malignant tumor originating from thyroid lymph tissue. The incidence rate is low, accounting for 5% of all thyroid malignancies and less than 3% of extranodal lymphoma[1, 2]. Thyroid lymphoma, which mostly occurs at 60–70 years old and the incidence rate of which is higher in the female than in the male. PTL is usually characterized as B-cell-derived Non-Hodgkin lymphoma, the most common type being diffuse large B cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue lymphoma (MALT). This disease is closely associated with Hashimoto thyroiditis (HT) and develops[3–5] in the setting of chronic thyroiditis. Positive serum thyroid peroxidase antibody(TPO Ab)or thyroglobulin antibody (TG Ab）can be considered as Hashimoto's thyroiditis. Some scholars, such as Xia [6], have classified PTL sonography appearances into two types: diffuse and non-diffuse. Until now, the preoperative diagnosis rate of PTL by ultrasound is low, and the result is easily misinterpreted as thyroid cancer or HT.

Papillary thyroid carcinoma (PTC), the most common pathological type of thyroid malignancies, accounts for 80% of the total thyroid cancer, the incidence rate of which has been increasing in the late

decades. With slow progression and low degree of malignancy, PTC is more common among young and middle-aged women. Previous studies showed that[7] the incidence of PTC capsular invasion was high, which affected the tumor and risk stages of thyroid cancer and then increased the risk of recurrence and death. Early diagnosis is thus particularly important.

PTL and PTC differ in the therapeutic method, although they are both thyroid malignancies. The treatment for PTL is mainly chemotherapy and radiotherapy, with not so expected benefit of surgical resection[2, 8], while surgery is the preferred treatment for PTC[9, 10]. High frequency ultrasonography is the first choice of thyroid disease examination[11, 12], and studies [5, 13] have shown that CT is a supplementary diagnostic technique for thyroid diseases, due to its advantages in determining the location and range of tumors as well as its superiority to ultrasound in evaluating the infiltration range. Currently, few reports have been published on the difference of PTL and PTC in sonographic and CT features. Therefore, focusing on the comparative analysis of the sonographic and CT features of nodules between non-diffuse PTL and PTC, this study aims to provide reference for early clinical diagnosis and treatment and then avoid unnecessary radical thyroidectomy.

Material And Methods

Patient selection

From a retrospective review of the pathological database of our hospital from June 2008 to September 2021, 84 patients with PTL and 163 randomly selected patients with PTC with a maximum diameter larger than 2cm were included in our present study. Our inclusion criteria are as follows: (1) PTL or PTC that was confirmed by puncture or surgical pathology; (2) non-diffuse PTL in terms of the sonographic classification, and with the maximum diameter of PTC nodules larger than 2cm; (3) thyroid enhancement CT examination performed within two weeks before operation; (4) with detailed and complete clinical, imaging and graphic data, and no previous systemic lymphoma involving the thyroid. Patients were excluded if they had a history of systemic lymphoma and thyroid surgery, or if they had no complete clinical and imaging data. Finally, 50 patients with PTL and 100 patients with PTC were enrolled in this study (see Fig. 1). All their data were approved and reviewed by our hospital ethics committee (No: IRB-2020-287) in accordance with relevant guidelines and obtained through the clinical electronic medical record system. Patient records were anonymized and deidentified before analysis. Informed consent was obtained from all subjects or their legal guardian(s). The pathological results were observed and diagnosed by a physician with more than 5 years of pathological experience, and then reviewed by an expert with more than 10 years of pathological experience. All the pathological diagnoses were classified according to the 2018 WHO new classification standard.

Thyroid ultrasonography

Siemens S3000, Philips IU22 and GE LogiqE9 ultrasonic diagnostic instruments were used, and the probe frequency was 5-12mhz.

In the process, firstly, telling the patient to take the supine position and fully expose the neck, two experienced ultrasound physicians independently analyzed and pre-documented the images using double-blind method. Successively, they examined the size, border, margin, internal texture, internal echo, cystic change, calcification, aspect ratio, posterior echo, vascularity and capsular invasion of thyroid nodules, and documented the transverse and longitudinal images of thyroid nodules. Once divergence happened on ultrasonic signs, they initiated discussion and analysis and then made decision. According to the echo of lesions, the data were classified into three categories[6]: ① markedly hypoechoic: lower than the echo from anterior cervical banded muscle; ② hypoechoic: between the echo from anterior cervical banded muscle and that from normal thyroid parenchyma; ③ equal or high echo: similar to or higher than the echo from normal thyroid parenchyma. Aspect ratio refers to the anterior posterior diameter of the nodule versus the left and right diameter of the nodule[14]. Asymmetric thyroid enlargement is when the left lobe of the thyroid is larger than the right lobe or the right lobe is larger than the left lobe. Capsular invasion refers to invasion of the thyroid capsule, indicating external expansion of the thyroid. According to the classification of Adler Grades of Blood Flow[15], the images included: ① Grade-0, no blood flow signal; ② Grade-I, a small amount of blood flow and 1 or 2 dot-like or short rod blood flow signals; ③ Grade-II, moderate blood flow, 3 or 4 dot-like or 1 longer blood vessel in the lesion, and with a length and diameter approaching or exceeding the radius of the lesion; 4Grade-III, rich blood flow, ≥ 5 visible dot-like or 2 long blood vessels. Moreover, this study classified grades 0-I as absence/not vascularity and grades II-III as rich vascularity.

Thyroid enhanced CT examination

64 row spiral CT machine was used for scanning, the models of which included Siemens SOMATOM Definition Flash, Siemens sensation 16 and GE MEDICAL SYSTEMS Bright Speed. The CT scan parameters adopted in this study were as follows: 120kv; 200-250mA; matrix size, 512 × 512; pitch, 1.0; layer thickness, 3mm or 3.8mm. Single phase scanning was performed 45- 55s after contrast-scanning intravenous injection of non-ionic contrast agent iohexol through elbow vein. The value means of thyroid nodules in plain scanning stage and venous stage were measured by two senior radiologists. During the process, a clear section of the lesion was selected to avoid calcification and artefact, the circular region of interest (ROI) of more than 30mm² in diameter was placed in five regions of lesions with homogeneous density, and the mean CT value was read[1]. According to Liu et al.[16], CT enhancement was classified into: mild enhancement, <20HU; moderate enhancement, 20-50HU; significant enhancement, >50HU. In this study, the enhancement <50HU was classified as mild to moderate, and that >50HU as significant.

Statistical analysis

Statistical analyses were performed with SPSS version 25.0 software (IBM Corporation, Armonk, NY, USA). Normal and approximate normal distribution of data was determined by independent sample t-test, while non-normal distribution of data was determined by Wilcoxon rank sum test. Chi-square or Fisher exact test was adopted to compare the categorical data. Receiver Operating Characteristic (ROC) curve

was used to calculate the optimal cut-off value, set when the Youden index reached the maximum. The CT value means of the two groups of nodules in plain scan stage and venous stage were converted into binary data, determined by χ^2 test. The statistically significant factors in univariate analysis were included in the binary logistic regression analysis model and the level of statistical significance was defined as $P < 0.05$.

Results

In the clinical data, significant differences were found between patients with PTL and PTC in age [(63.06±10.14) years old vs. (41.63±15.06) years old], maximum diameter of nodule [(44.70±15.50) mm vs. (31.86±9.40) mm], asymmetric enlargement (74.0% vs. 57.0%) and Hashimoto's thyroiditis (78.0% vs. 23.0%), $P<0.05$. The difference in gender ratio (male/female: 19/31 vs. 24/76) is not statistically significant ($P=0.074$), as shown in Table 1.

In terms of sonographic characteristics, PTL was higher than PTC in the markedly hypoechoic (54.0% vs. 4.3%), internal linear echogenic strands (92.0% vs. 34.0%)(Fig.2), posterior echo enhancement (84.0% vs. 20.0%)(Fig.2), rich vascularity (72.0% vs. 54.0%) and lack of calcification (84.0% vs. 22.0%), with a statistically significant difference ($P<0.05$), while PTC was higher than PTL in irregular border (78.0% vs. 48.0%), circumscribed margin (78.0% vs. 50.0%) and capsular invasion (83.0% vs. 48.0%)(Fig.3), with a statistically significant difference ($P<0.05$), as shown in Table 2. Moreover, there was no significant difference between PTL and PTC in echo texture, cystic change and aspect ratio (P 0.05), also as shown in Table 2.

In terms of CT features, PTL and PTC were different in the non-contrast and venous phase CT value means, with a statistical significance ($P< 0.05$) and presented in Table 3. To be exact, in these two phases the lesion density of PTL was lower than that of PTC, namely, PTC was lower than PTL in the proportion of mild to moderate enhanced intensity (80.6% vs. 27.0%)(Fig.3), and higher than PTC in the proportion of homogeneous enhancement (45.5% vs. 7.0%)(Fig.2), with a statistical significance ($P< 0.001$), also as shown in Table 3.

Moreover, after the seven variables covering age, internal linear echogenic strands, posterior echo enhancement, lack of calcification, venous phase CT value mean, enhanced intensity and homogeneous enhancement were included for multivariate logistic regression analysis, this study discovered the independent predictive risk factors: age, posterior echo enhancement, lack of calcification and homogeneous enhancement, as shown in Table 4.

Discussion

Between these two thyroid malignancies, PTC is the most common type, characterized by low malignancy, high incidence rate, good prognosis and above 90% 10-year survival rate. Although PTL is rare, the treatment is mainly chemotherapy and radiotherapy, and the effect of surgery is limited [17, 18].

The 5-year survival rate of stage-IE thyroid lymphoma is as high as 75–89%, while the annual survival rate of stage-IIE thyroid lymphoma is reduced to 25–40% [2, 19]. The prognosis of thyroid lymphoma depends on the stage, so early diagnosis is crucial. PTL has the features of older onset age, markedly hypoechoic, internal linear echogenic strands, posterior echo enhancement, lack of calcification, rich vascularity, low CT density and homogeneous mild to moderate enhancement, while PTC retains the features of hypoechoic, irregular border, calcification, easy capsular invasion and heterogeneous significant enhancement. Ultrasound combined with CT is conducive to the diagnosis of early PTL and papillary carcinoma.

This study retrospectively reviewed the clinical and imaging features of 50 PTL patients and 100 PTC patients, and found that there was no significant difference in gender ratio between patients with PTL and PTC, both occurring commonly in the female. Comparatively, PTL (aged 63.06 ± 10.14 years) was greater than PTC (aged 41.63 ± 15.06 years) in the age of onset (63.06 ± 10.14 years old) with a statistical significance ($P < 0.001$), which is similar to the prior reports by Acar et al. [3] and Ota et al.[20], and was also higher than PTC in the incidence with asymmetric enlargement and Hashimoto's thyroiditis. Studies have shown that most PTL originate in the setting of HT, with which the patients carry a 40–80 folds higher risk of thyroid lymphoma than the healthy population, and HT is the recognized risk factor for PTL[5, 21]. Of the PTL group (78.0%, 39/50) in this study, their pathology confirmed the evidence of HT, which is consistent with previous results reporting 30–90% PTL patients with HT[22].However, according to the study of Mukasa[23], the incidence rate of PTC was higher than that of PTL in the patients with HT and Graves, which is inconsistent with the present result and suggested to be the influence of sample size and selection bias. Based on the significant correlation between HT and thyroid malignancy, some scholars[23, 24] proposed that the former was a precancerous lesion, which might be controversial and is expected to conduct in-depth investigation into monitoring the HT development so as to early detect, diagnose and treat PTL and PTC.

In the current study, the nodule size of PTL and PTC group was correspondingly 44.70 (± 15.50) mm and 31.86 (± 9.40) mm, and PTL lesions were obviously larger, with an average size of about 45mm, which is similar to the reports of GU et al. [25].Besides, this study also found that the most common echo type of PTL and PTC lesions was the markedly hypoechoic and the hypoechoic respectively, and that the proportion of markedly hypoechoic was significantly higher in PTL than in PTC (78% vs. 4.3%). Xia et al. [6] argued that the markedly hypoechoic type in PTL as one of its typical features, might be attributed to the high consistency of its tumor cell morphology and size. The present study demonstrated that the proportion of internal linear echogenic strands was higher in PTL than in PTC, while previous studies [26] showed that this echo's hypoechoic structure might result from the degree of fibrous tissue proliferation. Additionally, in our study most nodules' posterior echo enhancement was significantly higher in PTL than in PTC (84%, 42/50). Logistic regression analysis indicated that this enhancement was an independent predictor of PTL, which is consistent with the result of Ota et al.[20], who concluded that posterior echo enhancement was a sonographic characteristic reliably distinguishing PTL from other diseases, and might be related to the large number of lymphocyte infiltration in PTL. Their subjects' pathology revealed that lymphoma cells grew densely and homogeneously with same shape and size, which produced very

small acoustic impedance difference and attenuation and finally posterior echo enhancement. Generally, posterior echo enhancement is prone to occurring in cystic nodules or benign solid tumors but rarely in the type of malignant tumors. However, once markedly hypoechoic nodule is found in the thyroid, the posterior echo will be significantly enhanced, a highly visible symptom of PTL.

With respect to calcification, the rate of PTL group in this study was only 16% (8/50), significantly lower than that of PTC group (78.0%, 78/100). Logistic regression analysis showed that lack of calcification was an independent predictor of PTL, which is consistent with the result of the research by Gu et al. [25]that lack of calcification was a characteristic manifestation of PTL. In contrast, no subject with calcification in PTL was found in their study, but 8 in the present research, which might be influenced by the small sample size of their study and their situation of most PTL complicated with HT.

In terms of CT features, nodules of PTL and PTC mostly showed a low density during the non-contrast phase, the average CT value of PTL was lower than that of PTC, and the density was more homogeneous. However, after enhanced scanning, PTL tended to have a mild to moderate homogeneous enhancement, while PTC mostly showed a heterogeneous significant enhancement, with a statistically significant difference. The results show that the CT features of PTL in this study are consistency with those offered in previous literature[11], while these features of PTC are somewhat different from those obtained in the previous findings, such as by Kim et al.[27], who argued that the CT of PTC mostly performed with homogeneous low density, and showed a significant homogeneous enhancement after enhanced scanning, which might be related to the larger PTC nodules we chose.

Several limitations are identified in this study: (1) as a retrospective study, relatively long in the sampling period and subjective in the evaluation of sonographic and CT features; (2) small sample size and sample selection bias. Besides, the study also indicates that further improvements include collection of larger samples in the later stage, combination of new technologies in sonographic elasticity, radiography, iconography, etc.

Conclusion

This study investigated the clinical values of sonographic and CT features in differentiating PTL and PTC. Both have certain characteristics in sonographic and CT manifestations. The combination of the two contributes to improving the early diagnosis rate of the two diseases and providing reference for clinical diagnosis and treatment. Preoperative early diagnosis is crucial for formulating a best-laid treatment plan and improving prognosis so as to avoid unnecessary radical thyroidectomy.

Declarations

Authors' contributions

Guarantor of integrity of the entire study: D Xu. Study concepts and design: C Peng, D Yi.

Literature research: C Peng, J Yao. Clinical studies: D Yi, Y zhou, B Chen.

Experimental studies / data analysis: C Peng, D Yi. Statistical analysis: D Yi, C Peng.

Manuscript preparation: All authors. Manuscript editing: C Yang, D Xu.

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Availability of data and materials

Our data can not be made publicly available for ethical reasons. Data are from the present study whose authors may be contacted at xudong@zjcc.org.cn or Department of Ultrasound, Zhejiang Cancer Hospital, Hangzhou, China.

Ethics approval and consent to participate

This study obtained approval from the Independent Ethics Committee of the Zhejiang Cancer Hospital (**No: IRB-2020-287**) to identify patients diagnosed with primary thyroid lymphoma in our center. Patient records were anonymized and deidentified before analysis. Informed consent was obtained from all subjects or their legal guardian(s).

Consent for publication

Not applicable.

Competing interests

All authors declared no conflicts of interest.

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Tables

Table 1

Comparison of clinical features between patients with PTL and PTC

Clinical features	PTC	PTL	Statistics	*P* value
	n=100	n=50		
Sex			χ^2 =3.195	0.074
Male	24 24.0%	19 38%		
Female	76 76.0%	31 62%		
Age years mean±SD	41.63±15.06	63.06±10.14	t'=-10.307	0.001
asymmetric enlargement			χ^2 =4.118	0.042
Yes	57(57.0%)	37(74.0%)		
No	43(43.0%)	13(26.0%)		
Hashimoto's thyroiditis			χ^2 =41.583	0.001
Yes	23(23.0%)	39(78.0%)		
No	77(77.0%)	11(22.0%)		

'is the adjusted t-test value

Table 2

Comparison of sonographic characteristics of PTL and PTC

Characteristic	PTC	PTL	Statistics	*P* value
	n=100	n=50		
Nodule size (mm, x±s)	31.86±9.40	44.70±15.50	t'=-5.384	<0.001
Echo texture			χ^2 =0.000*	1.000
Homogeneous	1(1.0%)	0(0.0%)		
Heterogeneous	99(99.0%)	50(100%)		
Echogenicity			χ^2 =56.504	<0.001[a]
Markedly hypoechoic	6(4.3%)	27(54.0%)		
Hypoechoic	129(91.5%)	23(46.0%)		
Equal or high echo	6(4.3%)	0(0.0%)		
Internal linear echogenic strands			χ^2 =45.054	<0.001
Yes	34(34.0%)	46(92.0%)		
No	66(66.0%)	4(8.0%)		
Aspect ratio≥1			χ^2 =0.917*	0.338
Yes	10(10.0%)	2(4.0%)		
No	90(90.0%)	48(96.0%)		
Margin			χ^2 =13.787	<0.001
Regular	22(22.0%)	26(52.0%)		
Irregular	78(78.0%)	24(48.0%)		
Posterior echo enhancement			χ^2 =56.305	<0.001
Yes	20(20.0%)	42(84.0%)		
No	80(80.0%)	8(16.0%)		
Cystic change			χ^2 =3.043*	0.081
Yes	12(12.0%)	1(2.0%)		
No	88(88.0%)	49(98.0%)		
Calcification			χ^2 =52.380	<0.001

Mirco/coarse	78（78.0%）	8（16.0%）		
None	22（22.0%）	42（84.0%）		
Vascularity			χ^2 =4.500	0.034
Absence/not rich vascularity	46（46.0%）	14（28.0%）		
Rich vascularity	54（54.0%）	36（72.0%）		
Capsular invasion			χ^2 =18.803	（0.001
Yes	83(83.0%)	24(48.0%)		
No	17(17.0%)	26(52.0%)		

Note: a is the Fisher exact test（’ is the adjusted t-test（* is the adjusted χ2 value

Table 3

Comparison of CT features of PTL and PTC

CT features	PTC	PTL	Statistics	*P* value
	n=100	n=50		
non-contrast CT value (HU)mean	47.30±10.57	45.07±7.19	t'=1.514	0.134
Venous phase CT value(HU)mean	111.94±21.44	78.37±19.94	t=7.638	0.001
non-contrast CT value				
≤50.17	61(61.0%)	25(80.6%)	χ^2 =4.050	0.044
50.17	39(39.0%)	6(19.4%)		
Venous phase CT value				
≤102.67	29(29.0%)	27(90.0%)	χ^2 =35.019	0.001
102.67	71(71.0%)	3(10.0%)		
Enhanced intensity			χ^2 =28.449	0.001
Mild to moderate	27(27.0%)	25(80.6%)		
significant	73(73.0%)	6(19.4%)		
Homogeneity			χ^2 =26.578	0.001
Homogeneous	7(7.0%)	15(45.5%)		
Heterogeneous	93(93.0%)	18(54.5%)		

' is the adjusted t-test value

Table 4

Multivariate Logistic regression analysis of PTL and PTC

	OR	95%CI		*P* value
		Low	Upper	
Age	1.226	1.056	1.423	**0.007**
Internal linear echogenic strands	1.102	0.097	12.485	0.938
Posterior echo enhancement	51.152	2.934	891.738	**0.007**
Lack of calcification	0.013	0.000	0.400	**0.013**
Venous phase CT value	0.084	0.003	2.145	0.134
Enhanced intensity	0.651	0.032	13.109	0.779
homogeneous enhancement	0.020	0.001	0.507	**0.018**

Figures

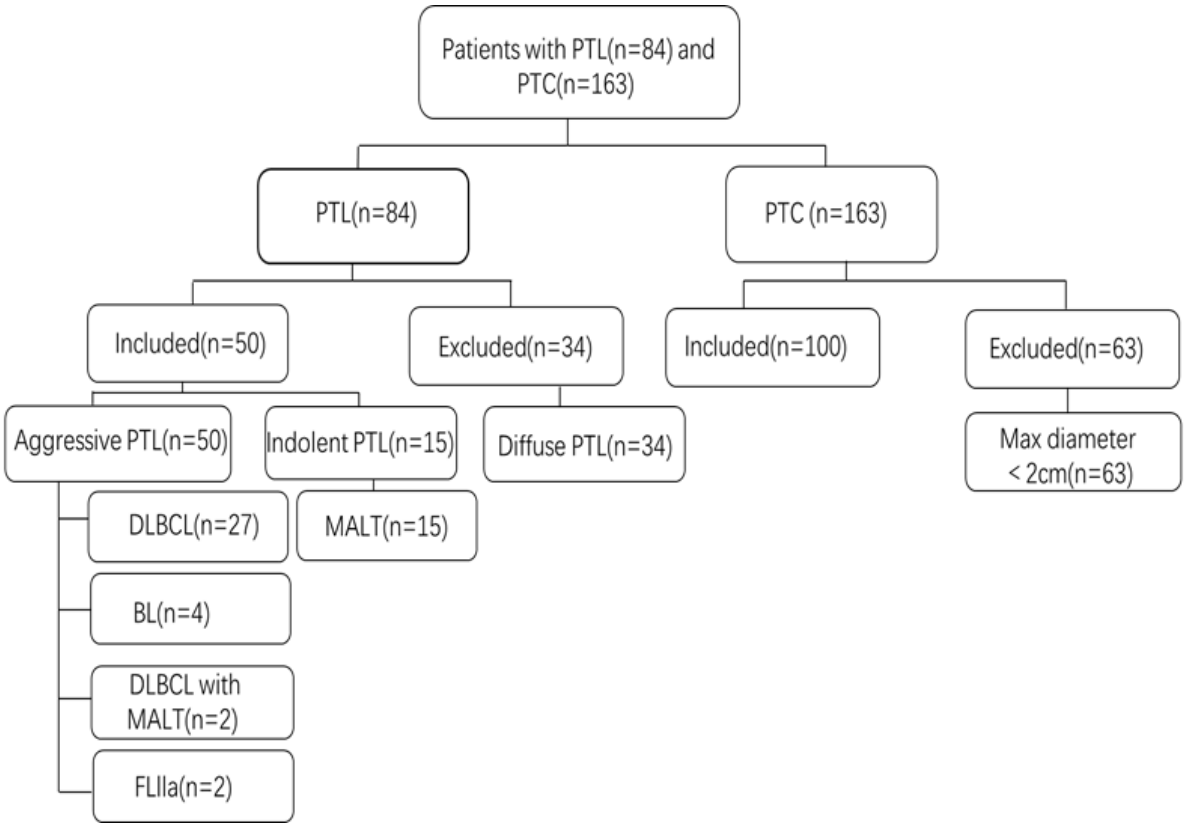

Figure 1

Flow chart of study participants.

Figure 2

A 70-year-old female patient with neck tumor for more than 4 months. (A) Transverse image of ultrasonography, showing a heterogeneous hypoechoic nodule with circumscribed margin on the right lobe of thyroid. The arrows show the internal linear echogenic strands; (B) Longitudinal image of ultrasonography. The arrow shows a significant posterior echo enhancement; (C) Blood flow spectrum, showing rich blood flow signals; (D) Non-contrast CT. The arrow shows the CT of the right lobe of thyroid; (E) Venous phase CT, showing homogeneous mild enhancement in the right lobe nodule and the density of it is lower than that of the thyroid parenchyma; (F) Pathological results, showing B-cell lymphoma in the MALT marginal area of thyroid (*400).

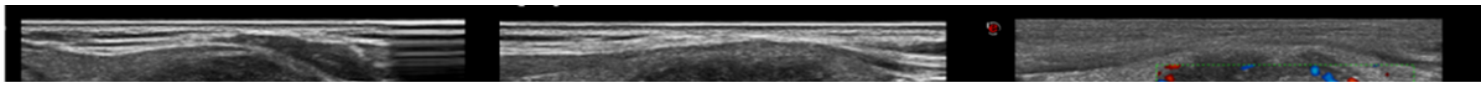

Figure 3

A 50-year-old female patient with neck tumor for 3 months. (A) Transverse image of ultrasonography, showing heterogeneous hypoechoic nodules on the left lobe of thyroid with irregular border ; (B) Longitudinal image of ultrasonography. The arrows show the internal small calcification; (C) Blood flow spectrum, showing rich blood flow signals; (D) Non-contrast CT, showing low-density nodules on the left lobe of thyroid; (E) Venous phase CT, showing heterogeneous significant enhancement of nodules in the left lobe of thyroid; (F) Pathological results, showing papillary thyroid carcinoma (* 400).