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ORIGINAL ARTICLE

Features of lymph node metastasis of papillary thyroid carcinoma in ultrasonography and CT and the significance of their combination in the diagnosis and prognosis of lymph node metastasis

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Summary

Purpose: *To investigate the characteristics of lymph node (LN) metastasis of papillary thyroid carcinoma (PTC) with ultrasonography (US) and spiral computed tomography (CT) and the significance of their combination in the diagnosis and prognosis of LN metastasis.*

Methods: *A total of 93 PTC patients admitted to and treated in the oncology department of our hospital were randomly enrolled in this study. LN imaging signs were explored by US, CT and their combination. Through the comparison with pathological findings, the diagnostic efficiency of three methods in LN metastasis in patients with PTC was analyzed. Postoperatively, all patients were followed up for 1-3 years to analyze the relationship between LN metastasis and the prognosis of PTC.*

Results: *Among 93 PTC patients, 69 (74.19%) had LN metastasis, and 24 (25.81%) had not. US examination revealed that metastatic LN were hypoechoic and obviously calcified, and had aspect ratio >1 and strong blood flow signals. Among them, there were significant differences in calcification and blood flow between LN metastasis group and non-metastasis group ($p<0.05$). CT images indicated that metastatic LN were swollen, had low-density and were calcified with abundant blood flow signals. In addition, the edge, calcification and CT reinforced examination showed obvious differences between the LN metastasis group and the non-metastasis group ($p<0.05$). The sensitivity, specificity and accuracy of US alone in the diagnosis of LN metastasis were clearly better than those of CT alone ($p<0.05$), while their combination was better than both US and CT alone in the sensitivity, specificity and accuracy in the diagnosis of LN metastasis ($p<0.05$). Follow-up data suggested that the 3-year recurrence or metastasis rates of patients in the metastasis and non-metastasis groups were 4.54 and 11.27%, respectively, showing a statistically significant difference ($p<0.05$).*

Conclusions: *US combined with CT can make up for the deficiencies of each examination alone, and improve the sensitivity and specificity of PTC LN metastasis detection. It is worthy of clinical promotion.*

Key words: *CT, metastasis, lymph node, papillary thyroid carcinoma, ultrasonography*

Introduction

Thyroid cancer is a malignant tumor originated from follicular epithelial cells or thyroid parafollicular cells [1]. In recent years, thyroid cancer has an increasing incidence rate year by year, and can be found in populations of all ages, which is more common in children or young (<40 years

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old) women [2,3]. In general, thyroid cancer has relatively slow development and comparatively long course in comparison with tumors in other organs [4]. Pathologically, thyroid cancer is mainly divided into medullary carcinoma, papillary thyroid carcinoma (PTC), follicular adenocarcinoma and undifferentiated carcinoma. Among them, PTC accounts for 60-80% of thyroid cancer cases. Although PTC grows slowly, it can often metastasize to neck lymph nodes (LN) via lymph vessels [5]. It is worth noting that some primary lesions of PTC are very small, and metastases are often firstly found clinically [6]. Active surgical treatment should be performed for PTC patients with LN metastasis. For patients who are diagnosed with PTC by intraoperative pathological examination, and whose tumor invades extra thyroidal tissues or multifocal patients, the whole thyroid tissue should be removed, and central LN dissection should be performed routinely. For patients with suspected LN metastasis in the lateral region of the neck through preoperative imaging, functional neck LN dissection should also be performed at the same time [7]. Therefore, accurate diagnosis of neck LN metastasis from PTC before operation is very important for the choice of clinical treatment regimens and the prognosis of patients. In recent research and treatment guidelines, CT examination is included in the essential preoperative examinations for accurate diagnosis of neck LN metastasis from PTC [8]. However, many subsequent studies have found that CT examination does not reach the expectations in terms of the diagnosis of LN metastasis in the lateral region of the neck [9].

This study aimed to evaluate the diagnostic efficiency of CT and US examinations and the combination of the two in PTC LN metastasis and the effectiveness evaluation in the patient prognosis.

Methods

Clinical data

A total of 93 patients with PTC admitted to and treated in the oncology department of our hospital from March 2011 to March 2014 were randomly selected. All patients had accessible metastatic LN before operation, and PTC patients with metastatic LN underwent total thyroidectomy or selective neck dissection. Patients without metastasis were diagnosed by biopsy, all tumors were examined by one pathologist, and tumor size and the presence of LN metastasis were recorded completely. Patients with extrathyroidal extension or distant metastasis were excluded. Each patient had a corresponding archived paraffin-embedded tissue. All patients signed informed consent, and this study was approved by the clinical ethics committee of the Second Affiliated Hospital and Yuying Children's Hospital.

US examination

Instrument: a Siemens Sacuson Antares color Doppler US diagnostic device and a 7-12 MHz linear-array broadband probe. The patient rested in supine and lateral position to fully expose the anterior region of neck. Then, all-round scan (transverse, longitudinal and beveling scan) was performed on thyroid bilobar, isthmus and bilateral neck LN using two-dimensional gray-scale US to carefully observe the location, size, number, edge, internal echo level and calcification of the thyroid mass. Blood flow in each nodule was detected via color Doppler flow imaging and graded by Alder's semi-quantitative method. Bilateral neck was carefully checked to observe and record swollen LN. Diagnostic criteria for LN metastasis in US: local or diffuse high-level echo, small or coarse calcification, cystic degeneration and subround shape (short and long diameter <1.5 cm).

Spiral CT examination

A Siemens Somatom Definition AS 128-slice spiral CT scanner (Siemens, Germany) was used to perform plain and enhanced scans on the neck. The patient was placed in supine position and was asked to have calm breathing before examination so as to eliminate nervousness. Scan parameters: tube voltage was 120 KV, tube current bulb tube speed was 0.4 s/r, collimation was 63×0.605 mm, and pitch was 1.1. Plain scan was carried out firstly, followed by enhanced scan in two phases (arterial phase and venous phase).

Enhanced scan: Contrast agent iopamido (370 mg/mL) 1.0 mL/kg was injected from the right antecubital vein at a flow rate of 2.5-3.0 mL/s (the total volume was about 60-80 mL, and then normal saline was injected for tube washing at the same flow rate. The delayed time of scan was 30 s in arterial phase and 60 s in venous phase).

Statistics

The experimental results were analyzed using statistical software GraphPad Prism software (Version 5.01, GraphPad Software, San Diego, Chile). Continuous data meeting the normality were expressed as mean ± standard deviation and analyzed using variance test, while paired *t*-test was used for pairwise comparisons. Statistical significance was set at $p<0.05$. Sensitivity = number of true-positive / (number of true-positive + number of false-negative results) *100%. Specificity = number of true-negative / (number of true-negative + number of false-positive results) *100%. Positive predictive value = true positive / (true positive + false positive). Negative predictive value = true negative / (true negative + false negative).

Results

Histomorphological examination of PTC LN via hematoxylin-eosin (HE)

All 93 patients were diagnosed with PTC by biopsy or pathological examination after surgical

resection, among which 69 patients (74.19%) had LN metastasis and 24 (25.81%) had not. Papillary epithelial masses, a large number of lymphocytes, psammoma bodies and nuclear abnormal cells were often found through HE staining, which were typical microscopic manifestations of PTC (Figure 1).

Signs of PTC metastatic LN in US

The size and shape of PTC metastatic LN were not specific, namely, they could appear similar to normal LN, and also showed increased volume or round shape. High-level echo was a sign of PTC metastatic LN in US images, while single or multiple anechoic zones could be found in enlarged metastatic LN, indicating that there was liquefactive necrosis in LN. Calcification was manifested by strong spot echo, which was mostly located in LN surroundings. In addition, metastatic LN showed abundant blood flow signals, which mainly were mixed blood flow signals and differed significantly from normal LN blood supply (Figure 2).

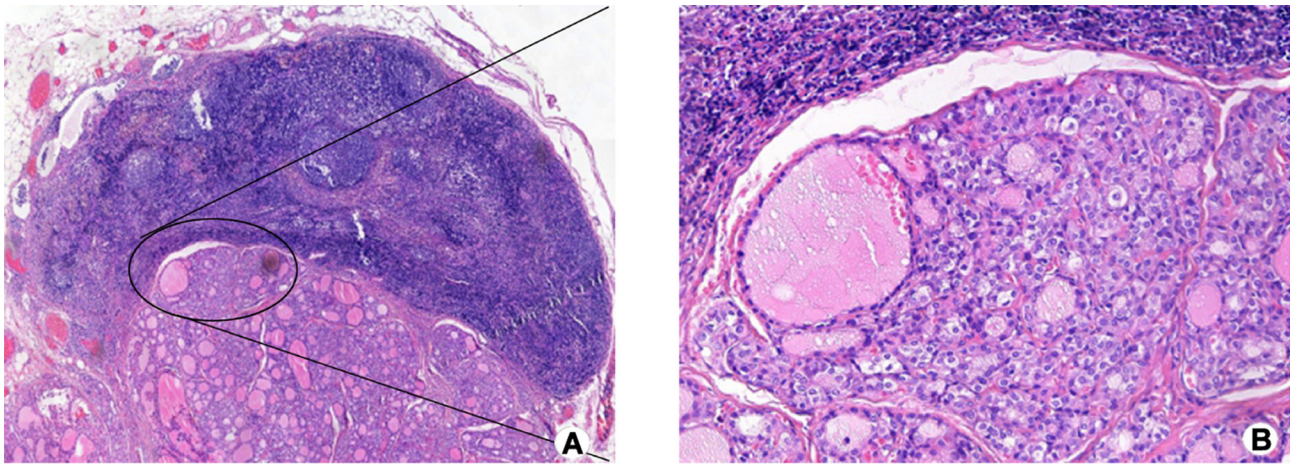

Figure 1. Pathomorphological examination of PTC LN via HE staining. **(A)** ×200, and **(B)** ×400. HE staining showed papillary epithelial masses, a large number of lymphocytes, psammoma bodies and nuclear abnormal cells in PTC.

Table 1. Relationships between LN metastasis in 93 PTC patients and features of nodule in US images

US findings	*n*	*Situation of LN metastasis*		x^2	*p value*
	93	*Metastasis (n=69)*	*Non-metastasis (n=24)*		
Location				1.42	>0.05
Left lobe	50	37	13		
Right lobe	43	32	11		
Diameter (mm)				0.98	>0.05
≤5	57	44	13		
>5	36	25	11		
Echo				1.15	>0.05
Low-level echo	38	29	9		
High-level echo	26	21	5		
Mixed echo	29	19	10		
Nodule edge				0.75	>0.05
Clear	39	28	11		
Blurry	54	41	13		
Calcification				9.84	<0.05
Yes	50	46	4		
No	43	23	20		
Blood flow				7.52	<0.05
I-II	30	13	17		
III-IV	63	56	7		

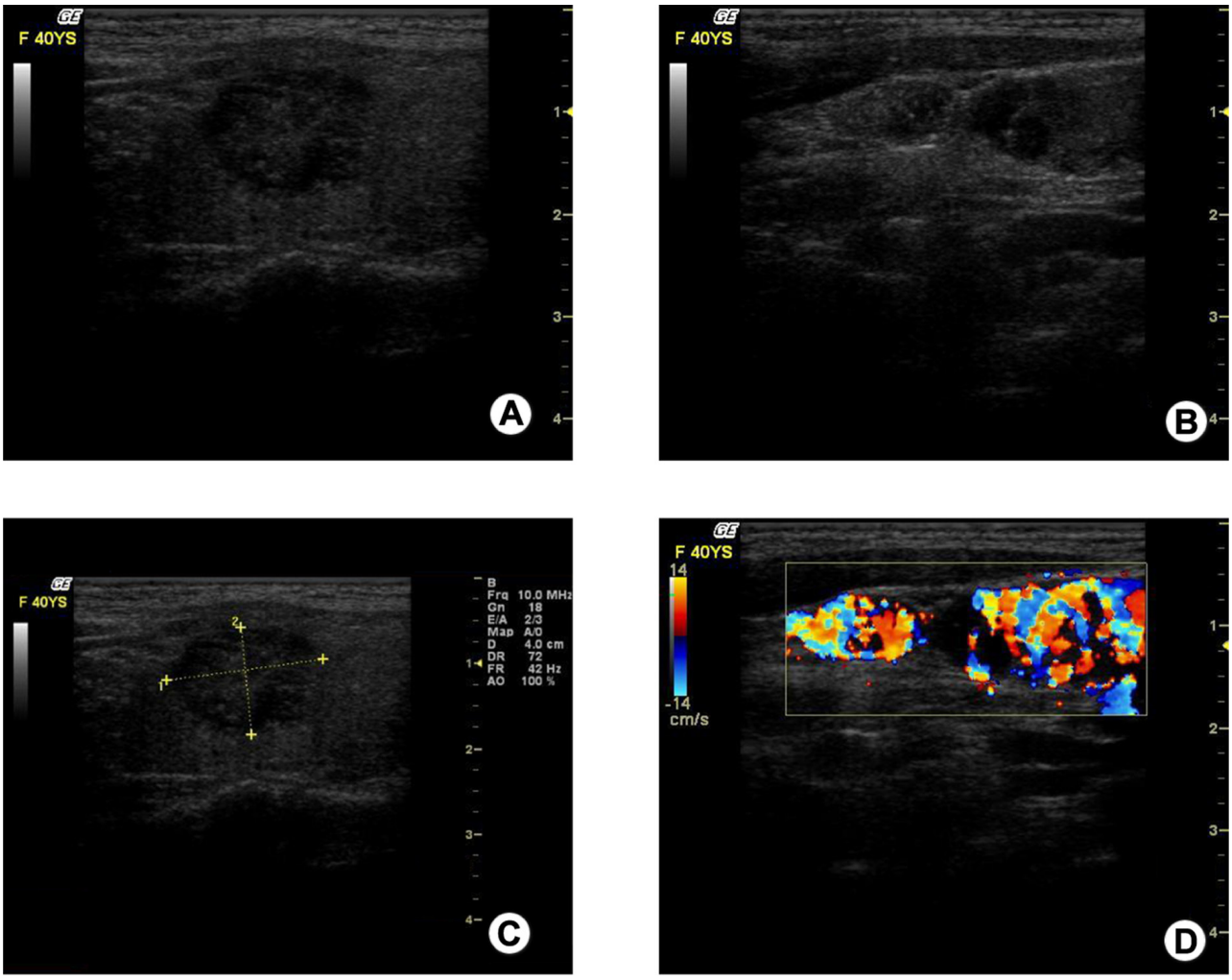

Figure 2. Signs of PTC metastatic LN in US. A female patient aged 40 years presented with sore throat and pathologically diagnosed with PTC. US findings are the followings: **(A)** shows the right thyroid occupying lesion with typical malignant features such as low-level echo, spiculated edge and obvious calcification. **(B)** shows the right neck LN with features of microcalcification, cortical high-level echo and cystic degeneration. **(C)** shows thyroid size with an aspect ratio greater than 1 and **(D)** shows strong blood flow signals within the metastatic LN.

Relationships between LN metastasis and features of nodules in US images

A total of 69 PTC patients with LN metastasis and 24 PTC patients without metastasis pathologically diagnosed were grouped. US imaging revealed no statistical differences in nodule size, diameter, echo and edge between PTC LN metastasis group and non-metastasis group ($p>0.05$). However, there were significant differences in PTC LN nodule calcification and blood flow shown in US images between two groups ($p<0.05$) (Table 1).

Signs of PTC metastatic LN in CT

The appearance of tumor in CT was solitary and lobulated nodules or masses, with irregular shapes. Varying degrees of low-density areas were found in lesions. A small number of patients mainly had cystic tumor, with uneven cyst wall. The edge was blurry, mixed with the surrounding fat gap and organ demarcation. The majority of patients had calcification, such as sand-like calcification, small nodular calcification and mixed calcification. After enhancement, partial tumor edge was "peninsula" nodular enhancement, and partial edge had the sign of visible "enhanced residual circle". In addition, enhanced cyst wall and papillary tubercle were found in cystic lesions after enhancement, and lesions were smaller and appeared as homogeneous low-density in plain scan, with relatively uniform enhancement before and after enhancement (Figure 3).

Features of thyroid LN metastasis and non-metastasis in CT

According to the results of spiral CT and enhanced CT examinations, the pathological features

of 93 cases of PTC nodules with LN metastasis and without metastasis were analyzed. The results (Table 2) showed that nodular envelope invasion, nodule diameter, morphology and necrosis showed no significant differences between PTC LN metastasis group and non-metastasis group (p>0.05), but evident differences existed in edge, calcification and CT enhancement examination between two groups (p<0.05).

Appraisal value of US, CT and combined examination in LN metastases in the central and lateral regions of the neck

The sensitivity, specificity and accuracy of US alone in the detection of PTC LN metastasis were 77.53, 75.0 and 84.06%, respectively. Those of CT alone in the detection of PTC LN metastasis were 67.0, 60.0 and 75.36%, respectively. Those of

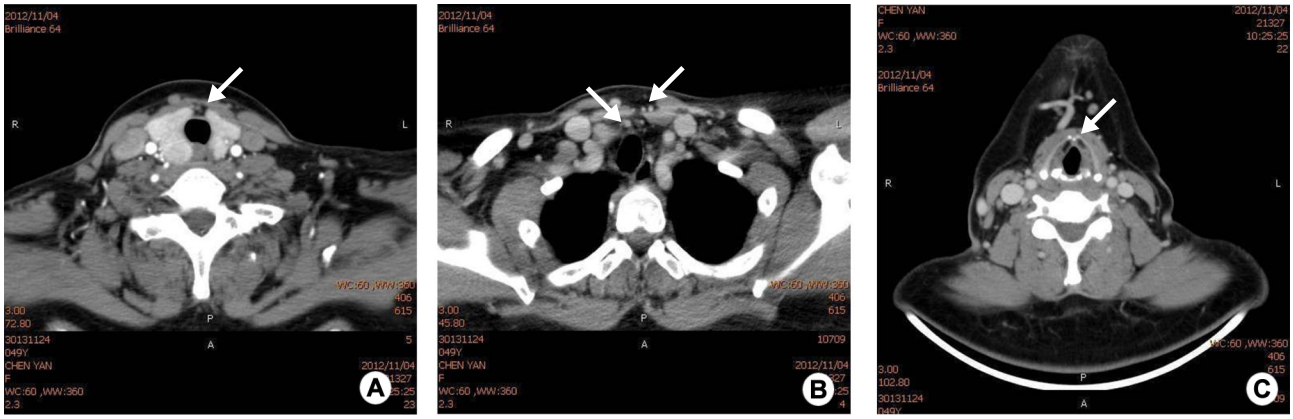

Figure 3. Signs of PTC metastatic LN in CT in a female PTC patient aged 43 years. **A:** White arrow shows the central area of the upper anterior thyroid with low-density masses with fuzzy boundaries. **B:** White arrows show lesions that are moderately enhanced, enlarged LN can be seen in the right side of neck, with necrosis in LN. **C:** White arrow shows the central region of the of the upper thyroid that has also a number of small nodules with punctate calcifications in the lesions. No affected signs are found in the cricoid cartilage, carotid sheath and sternocleidomastoid.

Table 2. Relationships between LN metastasis in 93 PTC patients and features of nodule in CT images

CT findings	*n*	*Situation of LN metastasis*		x^2	*p value*
	93	*Metastasis (n=69)*	*Non-metastasis (n=24)*		
Envelope invasion				0.82	>0.05
Yes	57	46	11		
No	36	23	13		
Diameter (mm)				1.31	>0.05
≤5	52	34	18		
>5	41	35	6		
Shape				1.65	>0.05
Regular	35	25	10		
Irregular	58	44	14		
Nodule edge				5.23	<0.05
Clear	39	16	23		
Blurry	54	50	4		
Calcification				4.15	<0.05
Yes	46	40	6		
No	47	29	18		
Necrosis				1.26	>0.05
Yes	45	33	12		
No	48	36	12		
Enhancement				8.36	<0.05
Yes	38	21	17		
No (moderate + obvious)	55	48	7		

Table 3. Appraisal value of US, CT and combined examination in LN metastases in the central and lateral regions of neck

Examination method	*Appraisal value (%)*				
	Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Accuracy*
US	69/89 (77.53)*#	24/32 (75.0)*#	69/77 (89.61)*#	24/44 (54.55)*#	58/69 (84.06)*#
CT	69/103 (67.0)*	24/40 (60.0)*	69/85 (81.18)*	24/58 (41.38)*	52/69 (75.36)*
Combined examination	69/82 (84.15)	24/28 (85.71)	69/73 (94.52)	24/37 (64.86)	62/69 (89.85)

Compared with the combined examination, *p<0.05; compared with CT, #p<0.05.

Table 4. Postoperative metastasis and recurrence rates of PTC patients with LN metastasis [n (%)]

LN metastasis	*n*	*1-year recurrence or metastasis*	*3-year recurrence or metastasis n (%)*
Negative	24	0	1 (4.54)
Positive	69	0	8 (11.27)
x^2			6.23
p value			0.011

the combined examination were 84.15, 85.71 and 89.85%, respectively. The results of US alone were significantly better than those of CT alone (p<0.05), and those of the combined examination were superior to those of US and CT alone (p<0.05) (Table 3).

Correlations of LN metastasis in PTC patients with postoperative metastasis and recurrence

All 93 PTC patients were followed up. As shown in Table 4, the 1-year recurrence or metastasis rates in 24 LN non-metastasis patients and 69 LN metastasis patients were 0, while the 3-year recurrence or metastasis rates were 4.54% and 11.27%, respectively, showing a significant statistical difference (p<0.05).

Discussion

Most PTCs are irregular lumps, often invading the local surrounding normal tissues (LNs in the central and lateral regions of the neck), and most patients are presented with occasionally found neck masses in clinical practice [10]. It has been reported in the literature that 70% of PTC patients have local LN metastasis [11]. This is consistent with the results of this study. In this study, pathological examination indicated that among 93 patients with PTC, 69 had LN metastasis, and the metastasis rate reached 74.19%. Some authors have believed that LN metastasis is an important factor in predicting the recurrence and survival of patients with PTC [12]. Data from the Memorial Sloan Kettering Cancer Center in New York have indicated that the presence of neck LN metastasis has a significant effect on the relapse of patients. It is basically the same with the results of the study by Yue et al. [13]. The follow-up data in this study showed that the 3-year postoperative recurrence rate of PTC patients with LN metastasis was significantly higher than that of those without LN metastasis, indicating that there is a close relationship between LN metastasis and postoperative recurrence. In order to detect the disease as soon as possible and avoid the risks of disease recurrence and secondary surgery, improving the accurate diagnostic rate of LN metastasis is an important clinical research topic.

Color Doppler ultrasonography is a noninvasive examination method, with simple and quick clinical features results and is widely used in the examination and qualitative diagnosis of superficial LN [14]. High-level echo is a sign in US images and often found in the cortex of metastatic LN, which may be related to the deposition of globulin in the cortex [15]. Cystic lesions and necrosis are frequently found in swollen LN metastases, which show single or multiple anechoic zone in US [16]. Neck LN calcification can be observed in a variety of benign and malignant lesions, and PTC metastatic LNs have fine-grained, stippled, patchy and discontinuous egg shell calcification, among which fine-grained calcification is generally considered as a feature in the diagnosis of thyroid cancer [17]. Strong punctate echo is a sign in US. In our study, there were 46/69 (66.67%) patients with LN calcification in the metastasis group, and 4/22 (18.19%) patients with LN calcification in non-metastasis group, suggesting that LN calcification is a highly specific index used to determine LN metastasis. In

addition, LN metastasis has abundant blood flow signals, while normal LN mostly has mixed blood flow signal [18], and the two are significantly different. Therefore, US is considered as a preferred method to diagnose and examine LN metastasis.

CT examination has high spatial and density resolution, helping to observe LN and the surrounding tissue in detail, showing more complete and continuous images, and being able to accurately show the size, internal structure and location of LN. Metastatic LN is often swollen, with blurry edge and cystic degeneration or liquefactive necrosis in some LNs [19]. In this study, the edge, calcification, and CT enhancement detection showed significant differences between LN metastasis and LN non-metastasis group. There were 48/69 (69.57%) and 7/22 (31.81%) cases of LN enhancement in metastasis group and non-metastasis group, respectively. This fact suggests that enhancement also has a certain value in the determination of LN metastasis in the central area. For LN with cystic degeneration, a uniform enhancement was observed in the solid portion in CT images, while cystic degeneration or the necrosis part had no significant enhancement, but had a ring-enhancement in the periphery. In addition, PTC metastatic LN can be significantly enhanced for their abundant blood supply and iodine absorption characteristics of thyroid tissue. Meanwhile, normal LN have low enhancement in CT images. Thus, scanning at 25 s after the injection of 75 mL iodinated contrast agent is recommended by several authors [20].

Calcification, nodal edge, blood flow, and degree of CT enhancement are important factors in determining PTC LN metastasis through US or CT [21]. The results of our study showed that the sensitivity, specificity and accuracy of US alone in detecting PTC LN metastasis were 77.53, 75.0 and 84.06%, respectively. Those of CT alone in detecting PTC LN metastasis were 67.0, 60.0 and 75.36%, respectively. The results of US alone were better than those of CT alone. Studies have shown that CT has a poor resolution for suspicious LN less than 1 cm, which is an important reason leading to its low diagnostic efficiency.

Although US is the preferred examination method in clinical practice, it has some limitations, e.g. in the superficial region US is easy to neglect the LN in the central region covered by the thyroid gland. Compared with US, CT can objectively and comprehensively assess the entire neck. As a result, CT detection can make up for this loophole and improve the detection rate. Therefore, in this study, the sensitivity, specificity and accuracy of the combined examination were 84.15, 85.71 and 89.85%, respectively.

Conclusions

The results of the present study indicate that in the preoperative assessment of LN in patients with PTC, the combined examination of US and CT is superior to each method alone in the diagnosis of LN metastases in the central and bilateral regions of the neck and is worthy of clinical promotion.

Conflict of interests

The authors declare no conflict of interests.

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