Original Article

Correlation between sonographic features and pathological findings of cervical lymph node metastasis of differentiated thyroid carcinoma

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Background: The aim of this study is to evaluate the relationship between the sonographic features and pathological findings of cervical lymph node metastasis of differentiated thyroid carcinoma (DTC).

Methods: A total of 49 patients who had thyroid surgery and lateral or central cervical lymph node dissection from October to December 2019 in our hospital were selected. All the lymph nodes included in the dissection were examined by intraoperative ultrasound and were divided into 5 groups according to the sonographic characteristics (A: overall hyperechoic group; B: hypoechoic with punctate hyperechoic group; C: mass hyperechoic group; D: cystic degeneration group; E: hypoechoic group without punctate hyperecho). All samples were sent to the Pathology Department according to the area of origin and classified and numbered for comparative analysis of the microscopic pathology and the sonogram.

Results: A total of 120 suspicious metastatic lymph nodes were finally screened out by intraoperative ultrasound. The sonographic signs of these suspicious metastatic lymph nodes in the lateral and central regions of the neck were significantly different from the normal lymph nodes. Besides, the indicators including sensitivity, specificity, accuracy, positive predictive value and negative predictive value of intraoperative ultrasound for detecting lateral and central lymph nodes were 89.04% *vs.* 82.98%, 93.83% *vs.* 80.00%, 90.97% *vs.* 81.10%, 92.86% *vs.* 70.91%, and 90.48% *vs.* 88.89%, respectively. The pathological features of metastatic lymph nodes were shown as follows: group A, diffuse distribution of follicular structure; group C, focal distribution of follicular structure; group B and E, atypical follicular epithelial cells with or without papillary structure. Necrosis and liquefaction were observed in group D.

Conclusions: The relationship between sonographic features and follicular structure of metastatic lymph nodes are firmly related. A correct understanding of these features is practical to improve the diagnostic rate of conventional ultrasonography and reduce the incidences of misdiagnosis.

Keywords: Thyroid carcinoma; lymph node metastasis; intraoperative ultrasound

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Introduction

The incidence of lateral cervical lymph node metastasis in patients with thyroid cancer can reach 37.3%. Studies have shown that patients with lymph node metastasis are more likely to have a relapse and experience metastasis, which can adversely affect their long-term survival rate (1-3). The sonographic features of metastatic lymph nodes in differentiated thyroid carcinoma are more specific than those of other organ tumors, and mainly include hyperechoic changes, microcalcification, and cystic changes (4,5). Ultrasonography is the first choice for the evaluation of cervical lymph node metastasis of thyroid cancer. However, the sensitivity and specificity of ultrasonography in the diagnosis of lateral and central cervical lymph node metastasis are 84–94% and 80–98%, and 40–51% and 71–78%, respectively. This is important because the presence or absence of lymph node metastasis seriously affects the choice of treatment plan (especially the surgical method) (6-8). The purpose of this study was to investigate the relationship between the sonographic features and the pathological findings of cervical metastatic lymph nodes in differentiated thyroid carcinoma, so as to better understand and fully evaluate the cervical lymph node metastasis of thyroid cancer. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-21-253).

Methods

General data

A total of 49 patients, 15 males and 34 females, with a mean age of 48±9.2 years (range, 19–81 years) who had suspicious metastatic lymph nodes from thyroid cancer according to intraoperative ultrasonography and who had been prepared for subtotal thyroidectomy or total thyroidectomy and lateral and central cervical lymph node dissection from October 2019 to December 2019 in our hospital were selected. All patients underwent comprehensive ultrasound examination before operation to evaluate the thyroid lesions, and central and lateral cervical lymph nodes. Apart from a few small suspicious lymph nodes that were marked by preoperative body surface examination, all the other lymph nodes dissected were evaluated, marked, and grouped by intraoperative ultrasound *in vitro*. Two professional sonographers with the operational experiences more than 5-year made the diagnosis from the ultrasonic images. If their opinions diverged, the ultrasonic images would be submitted to the superior doctors for a further diagnostic decision. Results of routine pathological examination were considered as the gold standard for making the diagnosis. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of The First Affiliated Hospital of Soochow University (NO. 114) and informed consent was taken from all the patients.

Instruments and methods

An Esaote MyLab Alpha portable ultrasonic diagnostic instrument (model Sl3116) with a frequency of 10–22 MHz was applied to check the lymph nodes.

Preoperative ultrasonography

Patients were placed in the supine position with their neck fully exposed. Routine ultrasound examination was performed on the thyroid and cervical lymph nodes. The frequency, depth, focus, gain, and dynamic range of the sound velocity probe were adjusted as appropriate. The images of thyroid and cervical lymph nodes were recorded and stored. If necessary, the suspicious lymph nodes in the lateral cervical region were localized on the body surface before operation.

Intraoperative ultrasonography

The dissected tissues containing lymph nodes were placed between the ultrasound pads, and the space between the ultrasound pad and the lymph nodes was filled with the appropriate amount of normal saline. The SL3116 linear array probe was used to scan, explore, and record all ultrasound-detectable lymph nodes and their sonographic features. According to the sonographic characteristics, the dissected lymph nodes were divided into the 5 following groups: group A = overall hyperechoic; B = hypoechoic with suspicious signs, such as punctate hyperecho and disappearance of the lymph node hilum or L/S <2; C = hyperechoic mass in the cortex; D = cystic degeneration; E = hypoechoic, with lymph node hilum being visible and no suspicious malignant signs. All samples were sent to the Pathology Department according to the originating region (central region, lateral cervical region II, lateral cervical region III/IV), given a sonographic classification after numbering, and then packed. Finally, the pathological pictures (HE, ×20/×40/×100) and the sonographic images were compared and analyzed.

Table 1 Comparison of intraoperative ultrasonic features between the lateral and central cervical lymph nodes

Ultrasonic features	Region II/III/IV			Region VI			Total			
	Positive (n=70)	Negative (n=84)	P	Positive (n=55)	Negative (n=72)	P	Positive (n=125)	Negative (n=156)	F	P
Group A	31 (44.29)	0	0.000	15 (27.27)	2 (2.78)	0.000	45 (31.03)	2 (1.28)	57.586	0.000
Group B	17 (24.29)	2 (2.38)	0.000	18 (32.73)	6 (8.33)	0.001	35 (28.00)	8 (5.13)	28.009	0.000
Group C	14 (20.00)	5 (5.95)	0.008	6 (10.91)	0	0.006	20 (16.00)	5 (3.20)	14.016	0.000
Group D	3 (4.29)	1 (1.19)	0.330	0	0	–	3 (2.40)	1 (0.64)	–	0.326
Group E	5 (7.14)	76 (90.48)	0.000	16 (29.09)	64 (88.89)	0.000	21 (16.80)	140 (89.75)	150.907	0.000

Group A: hyperechoic on the whole; group B: hypoechoic with suspicious signs (such as punctate hyperechoic, disappearance of the lymph node hilum or L/S <2); group C: nodular hyperechoic in the cortex; group D: cystic change; group E: hypoechoic as a whole without suspicious malignant signs. The difference was statistically significant when P<0.05.

Table 2 Diagnostic efficiency of intraoperative ultrasound for lateral and central lymph nodes (%)

Group	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
LCR	89.04 (65/73)	93.83 (76/81)	90.97 (141/154)	92.86 (65/70)	90.48 (76/84)
CCR	82.98 (39/47)	80.00 (64/80)	81.10 (103/127)	70.91 (39/55)	88.89 (64/72)

LCR, lateral cervical region; CCR, central cervical region; PPV, positive predictive value; NPV, negative predictive value.

Statistical analysis

SPSS v. 22.0 software (IBM Corp.) was used for statistical analysis. The measurement data are expressed as mean ± standard deviation ($\bar{x}\pm s$). Chi square test and Fisher exact test were used for counting data. The difference was considered to be statistically significant at P value <0.05.

Results

A total of 281 lymph nodes were detected by intraoperative ultrasound, and 120 suspicious metastatic lymph nodes were screened out *in vitro*. The suspicious metastatic lymph nodes in the lateral and central regions of the neck showed significantly different sonographic signs from those of the normal lymph nodes in group A (27.27–44.29% *vs.* 0–2.78%; P=0.000, P=0.000, respectively), group B (24.29–32.73% *vs.* 2.38–8.33%; P=0.000, P=0.001, respectively), and group C (10.91–20.00% *vs.* 0–5.95%, P=0.008, P=0.006, respectively). There was no significant difference in the sonographic signs between normal lymph nodes and the lymph nodes in group D (4.29% *vs.* 1.19%; P=0.330). There was a significant difference between differentiating the normal lymph nodes from metastatic lymph nodes in the lateral cervical region versus the central region (7.14–29.09% *vs.* 88.89–90.48%; P=0.000, P=0.000, respectively) in group E. However, the misdiagnosis rate of group E was higher in the central cervical region than in lateral cervical region (29.09% *vs.* 7.14%, P=0.009; *Table 1*).

The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of intraoperative ultrasound in the diagnosis of lateral and central lymph nodes were 89.04% *vs.* 82.98%, 93.83% *vs.* 80.00%, 90.97% *vs.* 81.10%, 92.86% *vs.* 70.91%, and 90.48% *vs.* 88.89%, respectively (*Table 2*).

The pathological microscopic features of metastatic lymph nodes in each group were the following. In the lymph nodes in group A, there were diffuse thyroid follicular structures, which were composed of atypical thyroid follicular epithelial cells; in group C, there were thyroid follicles distributed in clusters in the lymph nodes; and in group B and E there were atypical thyroid follicular epithelial cells distributed in clusters or diffused in the metastatic lymph nodes, with or without papillary structures. There were significant differences in the ultrasonic features between the lymph nodes in group A, C, B, and E, and the normal lymph nodes (95.74% *vs.* 0.00% *vs.*4.30%, P=0.000; 80% *vs.* 0.00% *vs.* 20%, P=0.000; 0.00% *vs.* 81.40% *vs.* 18.60%, P=0.000; 0.00% *vs.* 13.04% *vs.* 86.96%, P=0.000; respectively). Necrosis and liquefaction

Table 3 Comparison of the ultrasonic features and pathological characteristics of the lymph nodes in the different groups

Pathological characteristics	Ultrasonic features				
	Group A (n=47)	Group B (n=43)	Group C (n=25)	Group D (n=4)	Group E (n=161)
Diffused or clustered follicular structures, n (%)	45 (95.74)	0	20 (80.00)	0	0
Diffused or clustered atypical follicular epithelial cells with or without papillary structure, n (%)	0	35 (81.40)	0	0	21 (13.04)
Others, n (%)	2 (4.30)	8 (18.60)	5 (20.00)	4 (100.00)	140 (86.96)
P	0.000	0.000	0.000	0.094	0.000

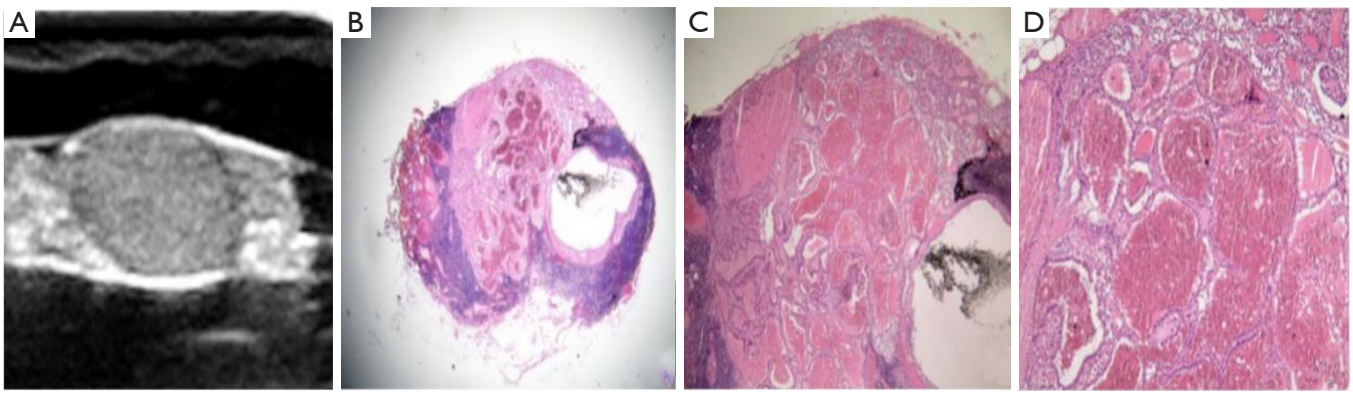

Figure 1 Pathological microscopic features of metastatic lymph nodes in group A. (A) Intraoperative ultrasonography showing several lymph nodes in the lateral and central regions of the neck, with the echo of lymph node hilum having disappeared, and overall hyperechoic changes. Microscopically, diffused follicular structures were seen in the lymph nodes, and some of the follicular cavities had hemorrhage. Hematoxylin and eosin (HE) staining ×10 (B), ×40 (C), and ×100 (D).

were observed in the lymph nodes in group D, and there was significant difference in the ultrasonic features between the lymph nodes in group D and the normal lymph nodes (0.00% *vs.* 0.00% *vs.* 100%, P=0.094; *Table 3*; *Figures 1-4*).

Discussion

Differentiated thyroid carcinoma mainly includes papillary thyroid carcinoma and follicular carcinoma, with good prognosis. The 10-year survival rate of papillary thyroid carcinoma can reach more than 90% and the prognosis of follicular carcinoma is slightly worse than that of papillary carcinoma (9-11). However, studies have shown that the recurrence rate of thyroid cancer with lymph node metastasis is higher and may have a certain impact on the long-term survival rate. Therefore, the full evaluation of cervical lymph node metastasis in patients with thyroid cancer before operation is of great significance for the selection of surgical methods and prognosis (12-17).

Conventional ultrasonography is the preferred imaging examination method for thyroid-related diseases (12) and has high diagnostic efficiency for metastatic lymph nodes in the lateral cervical region, but the detection rate for lymph node metastasis in the central neck is not high. This study showed that the sensitivity, specificity, and accuracy of intraoperative ultrasound in the diagnosis of metastatic lymph nodes in the lateral and central regions were 89.04% *vs.* 82.98%, 93.83% *vs.* 80.00%, and 90.97% *vs.* 81.10%, respectively, which were higher than those reported previously, especially in the central region (6,7,18,19). We analyzed the possible reasons for this discrepancy: (I) the metastatic lymph nodes in central neck are easily missed in routine ultrasound examination on the body surface due to their deep location and small volume, while the detection rate of the metastatic lymph nodes in central neck are greatly improved by intraoperative ultrasound; (II) the influence of intratracheal air increases the difficulty of surface ultrasound detection. Compared with the metastatic

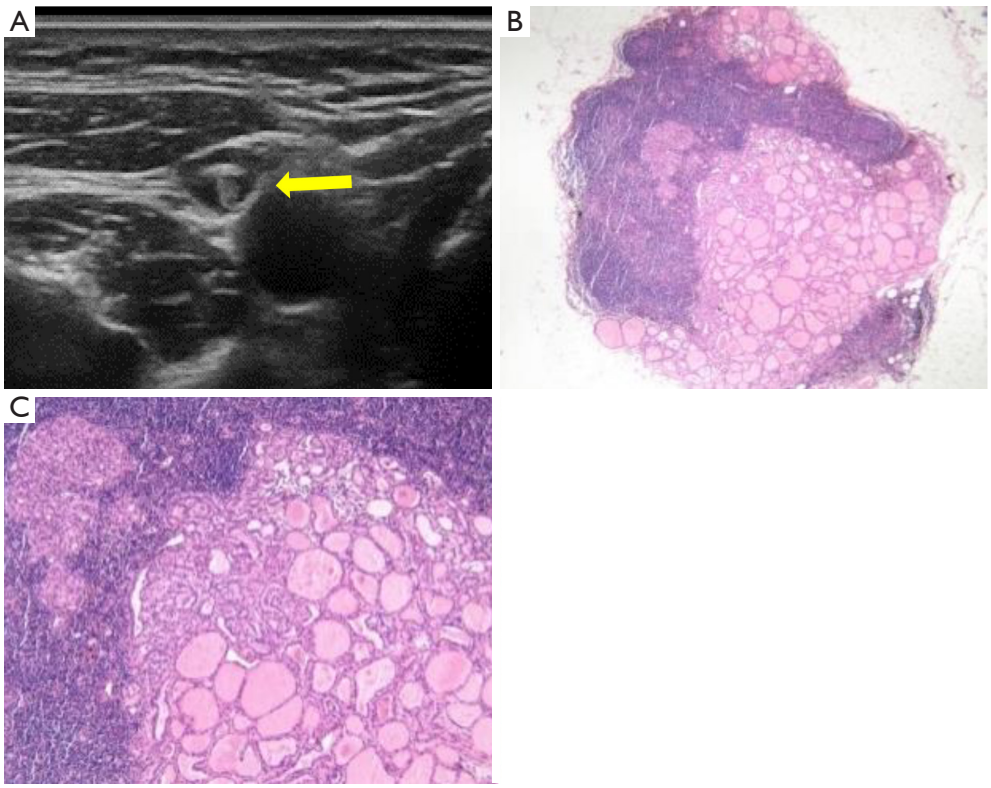

Figure 2 Pathological microscopic features of metastatic lymph nodes in group B. (A) Body surface ultrasonography showing lymph nodes and the echo of lymph node hilum in the lateral cervical region III and nodular hyperechoic changes (as shown by the yellow arrow). Microscopically, thyroid follicular structures which were composed of atypical thyroid follicular epithelial cells were observed in clusters. Hematoxylin and eosin (HE) staining ×10 (B) and ×40 (C).

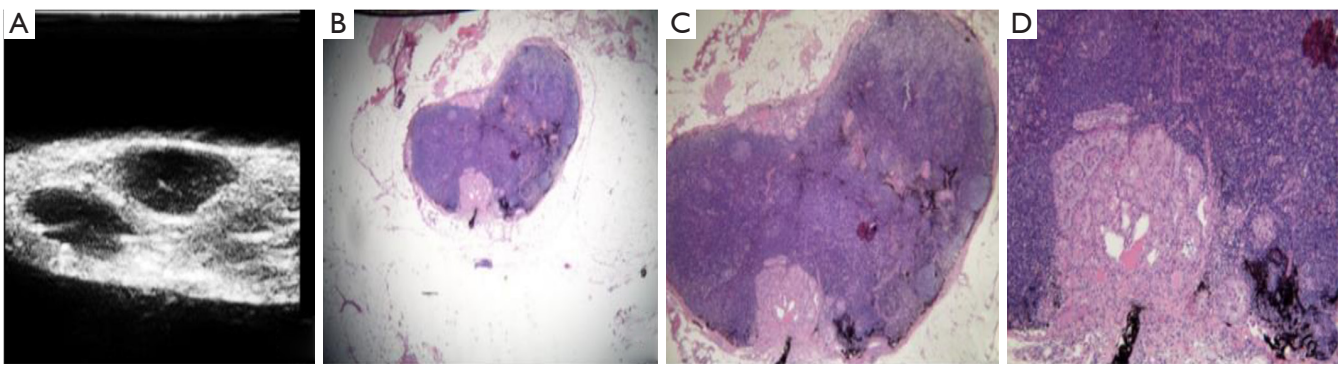

Figure 3 Pathological microscopic features of metastatic lymph nodes in group E. (A) Intraoperative ultrasonography: showing several lymph nodes in the lateral and central regions of the neck, with the echo of lymph node hilum having disappeared. Microscopically, it was mainly composed of atypical follicular epithelial cells, with a papillary structure and a few scattered follicular structures. Hematoxylin and eosin (HE) staining ×10 (B), ×40 (C) and, ×100 (D).

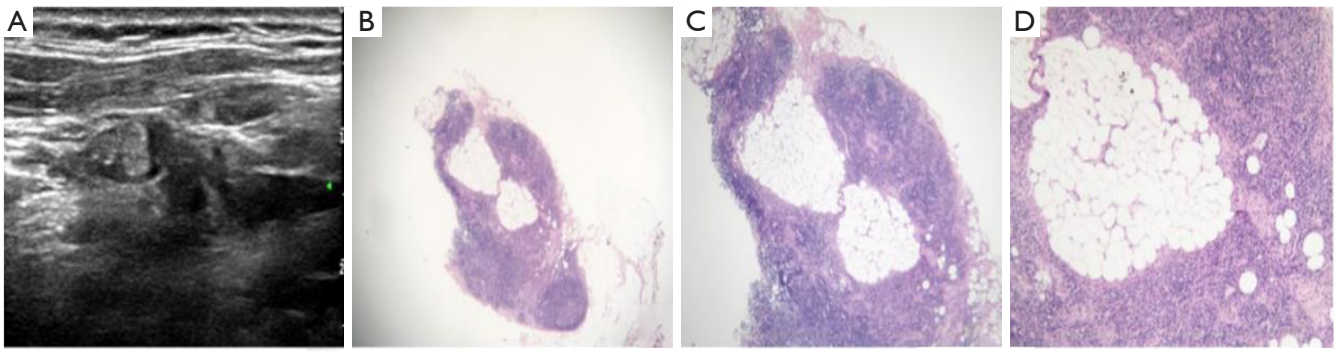

Figure 4 Pathological microscopic features of metastatic lymph nodes in group D. (A) Body surface ultrasonography showing multiple lymph nodes and the echo of the lymph node hilum in lateral cervical regions III and IV, with nodular hyperechoic changes in the cortex. Microscopically, clusters of adipocytes were found in the lymph node. Hematoxylin and eosin (HE) staining ×10 (B), ×40 (C), and ×100 (D).

lymph nodes from other systems, metastatic lymph nodes of thyroid cancer often have their own typical sonographic features: microcalcification, hyperechoic mass or whole hyperechoic changes, cystic changes, etc. (4,5,20). The results of this study showed that features A, B, and C, 3 conventional ultrasonographic features in the prediction of lateral and central lymph node metastasis, were statistically significant, but feature D showed no statistical significance in the prediction of lateral and central lymph node metastasis (P=0.330). The reason for this may be that the total number of lymph nodes with feature D is too small, which might have resulted in serious bias in the statistical analysis. In addition, the misdiagnosis rate of normal lymph nodes based on feature E was higher in the central region than in the lateral cervical region (29.09% *vs.* 7.14%, P=0.009), indicating that hypoechoic metastatic lymph nodes were more likely to be misdiagnosed, especially in the prediction of central lymph nodes. When Hashimoto's thyroiditis is complicated, central cervical lymph nodes with reactive hyperplasia can be easily misdiagnosed as metastatic lymph nodes when the shape is almost round (21).

The results showed that the unique ultrasonographic features of thyroid metastatic lymph nodes were closely related to their pathological structures: under microscopy, the overall hyperechoic metastatic lymph nodes showed diffuse follicular structure under microscope; while the nodular hyperechoic metastatic lymph nodes in the cortex showed clustered follicular structures. We further analyzed the reasons for this: the echo level of tissues or lesions on ultrasound images is related to the number of acoustic interfaces and the acoustic impedance difference of media on both sides of the interface (22).

In the follicular structure of metastatic lymph nodes, the epithelium of the follicle and the colloid in the follicular cavity form acoustic interfaces with a large acoustic impedance difference. When a large number of follicles are densely present, a large number of acoustic interfaces are formed, resulting in high echo changes. In group A, 2 cases were misdiagnosed because one of them was a hyperechoic parathyroid gland and the other was residual thyroid tissue. In group C, 5 lesions of the same patient were misdiagnosed as metastatic lymph nodes when they were actually fat cells in clusters under microscopy. Fat cells have a similar diameter to that of follicles and contain lipid droplets, which can also form acoustic interface. Therefore, when nodular hyperechogenicity appears in cervical lymph nodes of patients with thyroid cancer, it is necessary to be careful to identify whether there is focal steatosis in the lymph nodes. Heterotypic follicular epithelial cells clustered or diffusely distributed with or without papillary structures were observed under microscopy in group B and group E. The components were relatively simple, and there were no or very few acoustic interfaces with large acoustic impedance difference. Therefore, hypoechoic changes were observed. The echo level was similar to that of the lymph node cortex and was difficult to distinguish. Therefore, due to the lack of other typical signs, the lymph nodes in group E were easily misdiagnosed. If necessary, fine-needle aspiration cytology guided by ultrasound should be performed to avoid misdiagnosis.

The limitations of this study are that no quantitative analysis of the follicular structure of metastatic lymph nodes under microscopy was performed. Furthermore, there was the limited sample size, and we failed to study the cystic

changes of metastatic lymph nodes more deeply.

In summary, the unique sonographic features of metastatic lymph nodes in differentiated thyroid carcinoma are closely related to the content of follicular structure in lymph nodes. A correct understanding of these features is helpful to improving the diagnostic rate of conventional ultrasonography and to reducing the incidences of misdiagnosis and missed diagnoses.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/gs-21-253

Data Sharing Statement: Available at http://dx.doi.org/10.21037/gs-21-253

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-21-253). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of The First Affiliated Hospital of Soochow University, (NO. 114) and informed consent was taken from all the patients.

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