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Diagnostic Value of Serum TSH, Ultrasound, and Enhanced CT in Papillary Thyroid Carcinoma with Lymph Node Metastasis

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Abstract: *Objective:* To explore the diagnostic value of serum TSH, ultrasound, and enhanced CT in papillary thyroid carcinoma with lymph node metastasis. *Methods:* 168 patients who underwent thyroidectomy in Shaanxi Provincial People's Hospital from January 2020 to December 2021 were selected as the research subjects. Based on the pathological nature (benign or malignant), they were divided into two groups, with 86 patients in the control group and 82 patients in the study group. Based on whether the pathology was accompanied with lymph node metastasis, the PTC group was divided into a lymph node metastasis group and a non-lymph node metastasis group, with 51 and 31 patients in the respective groups. Retrospective analysis was conducted to observe and analyze the pathological results of the thyroid nodules' thyroid ultrasound results, neck enhanced CT results, and thyroid function test serology results. *Results:* Compared with the PTC group, there were significant differences in TR classification, ultrasonic lymph nodes, and enhanced CT lymph nodes, but no significant differences in the course of disease, nodule distribution, and the number of nodules between the benign nodule group and PTC group; in the comparison of lymph node metastasis using ultrasound and enhanced CT, the number of patients with ultrasound lymph nodes without abnormal metastasis in the non-metastasis group was 28, while that of the metastasis group was 21; the number of patients with abnormal metastasis in the non-metastasis group was 3, while that of the metastasis group was 30. The number of patients with a single node without metastasis and metastasis was 14 and 8, respectively, whereas the number of patients with multiple nodes without metastasis and metastasis was 17 and 43, respectively. There were statistically significant differences in the number of ultrasound lymph nodes and nodules, but no statistically significant differences in TR classification, enhanced CT lymph nodes, nodules distribution, and disease course. *Conclusion:* Serum TSH can be used to identify the nature (benign and malignant) of thyroid nodules, and enhanced CT is better than ultrasound when evaluating complex lesions. It can be used as a supplement to ultrasound based on clinical context.

Keywords: Serum TSH; Ultrasound; CT; Thyroid papillary carcinoma; Lymph node

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1. Introduction

Papillary thyroid carcinoma is a differentiated thyroid carcinoma with high incidence rate, and 30% to 80% of patients will have cervical lymph node involvement. Lymph node metastasis is an important risk factor for the recurrence of thyroid cancer. The presence of cervical lymph node metastasis is an important basis for determining the clinical stage and treatment options [1]. Cervical lymph node tuberculosis is a common extrapulmonary tuberculosis, mainly manifested by cervical lymph node enlargement. In late stages, it may develop into a fistula, which requires a substantial amount of time to heal [2]. Before surgery, ultrasound

can precisely locate lymph nodes and provide a qualitative diagnosis. It is possible to detect lymph node metastases in 33% to 39% of cases with negative clinical palpation. The outline and enhancement pattern of lymph nodes can be appreciated in contrast-enhanced ultrasound, thus providing reference in clinical practice. With the continuous development of CT, there is a close relationship between the morphological features of primary thyroid cancer and lymph node metastasis, especially the texture features, such as microvessel density, new lymphatic vessel density, and elastic fiber distribution, which are all closely related to the degree of CT enhancement in primary thyroid cancer and can be used as an evaluation index of tumor malignancy as well as metastatic potential [3]. Serum thyroid markers are commonly detected by clinical immunological methods, among which calcitonin is useful in detecting medullary thyroid cancer [4], while other commonly used traditional serological tumor markers, such as carcinoembryonic antigen, have little reference significance for thyroid cancer. Studies have shown that the levels of thyroid stimulating hormone (TSH) [5], thyroglobulin [6], and thyroid autoantibody are all related to the occurrence of thyroid cancer [7].

2. Data and methods

2.1. General information

Hundred-and-sixty-eight patients who underwent thyroidectomy in Shaanxi Provincial People's Hospital from January 2020 to December 2021 were selected as the research subjects. According to the pathological nature (benign or malignant), they were divided into two groups, namely, with 86 cases in the control group and 82 cases in the study group. The average age of the patients was 49.63 ± 2.96 years. According to whether the pathology was accompanied by lymph node metastasis, the PTC group was divided into a lymph node metastasis group and a non-lymph node metastasis group, with 51 and 31 patients, respectively. Retrospective analysis was carried out, indicating no statistical difference in the general data of the patients. Moreover, the clinical data of all the patients were complete, and all patients underwent thyroidectomy.

2.2. Methods

(1) Contrast enhanced ultrasound

Toshiba Aplio 400, a color doppler ultrasound, with probe frequency of 7.5~13.0 MHz was used. SonoVue, produced by the Italian Bracco Group, was used as the contrast agent, and 5 ml of normal saline was added to form a suspension. The patients assumed a horizontal or lateral position and exposed their necks fully. The largest lymph node was selected as the subject of observation. Routine ultrasound was used to observe its zoning, the ratio of long to short diameter, lymph hilus, internal necrosis, calcification, blood flow distribution (lymph hilus type, peripheral type, mixed type, and no blood flow type), and resistance index. Then, contrast-enhanced ultrasound was performed. The patients were instructed to breathe quietly and avoid swallowing as much as possible; 2 ml of contrast agent was rapidly injected through the vein located at the elbow, and 5 ml of normal saline was then used to flush the tube. At the same time, the start timing key and dynamic storage key were pressed, and the perfusion process of the contrast agent in the enlarged lymph nodes was recorded. According to the echo changes of lymph nodes before and after contrast-enhanced ultrasound, the lymph node enhancement modes were divided into homogeneous enhancement, heterogeneous enhancement, and non-enhancement. Non-uniform enhanced lymph nodes were divided into non-ring (no ring enhancement after enhancement), thin ring (enhanced ring thickness ≤ 2.0 mm), and thick ring (enhanced ring thickness > 2.0 mm) according to the thickness of circular enhancement [8-10], which refers to the circular hyperecho around the lymph nodes, where the degree of echo enhancement is greater than that in the inner and peripheral parenchyma of the lymph nodes; the reinforced ring was measured at the thickest point.

(2) Serum TSH

Each patient's venous blood was drawn from the anterior elbow on an empty stomach in the morning, and serum TSH level was detected by double-antibody sandwich method. All procedures were carried out in strict accordance with the instructions given on the kit.

(3) CT quantitative parameter determination

All patients underwent PTC resection and received CLNM (central lymph node metastasis) pathological examination. Routine plain CT scan and dual-phase, dual-energy enhanced CT scan of the neck were done before surgery. The dual-source CT machine and data processing workstation were used for plain neck CT and dual-phase arteriovenous scan. The scanning parameters were set as follows: the voltage was 100 kV, the pitch was 0.8, the layer thickness was 1.0 mm, and the layer spacing was 0.7 mm. The patients assumed the supine position with their shoulders relaxed. Their lower jaws were raised as much as possible, and the patients were requested to refrain from swallowing during the examination. The scanning range was from the skull base to the aortic arch, and the moving direction of the probe scanning was from the foot to the head. The conventional scanning mode was set for plain scanning, and the dual energy mode was used for enhanced scanning. Iohexol and ioversol (300 mg I/ml) were used as contrast agents; the dose was 1.5 to 2.0 ml/kg, and the total amount was 95 to 100 ml. During scanning, the trigger threshold was set to 100 HU, and arterial phase scanning and venous phase scanning were performed successively.

2.3. Observation indicators

The pathological results of the thyroid nodules, thyroid ultrasound results, neck enhanced CT results, and thyroid function test serology results were observed and analyzed.

2.4. Statistical analysis

SPSS 25.0 was used to analyze the data. The counting and measuring data were expressed in n/% and $\bar{x} \pm s$, respectively, and χ^2 test was carried out. T-test showed that the difference was statistically significant ($p < 0.05$).

3. Results

3.1. Comparison of disease course, ultrasound results, and enhanced CT results between benign nodule group and PTC group

There were significant differences in TR classification, ultrasound lymph nodes, and enhanced CT lymph nodes, but no significant differences in the course of disease, nodule distribution, and number of nodules between the benign nodule group and the PTC group, as shown in **Table 1**.

Table 1. Comparison of disease course, ultrasound results, and enhanced CT results between benign nodule group and PTC group

Group		Benign nodule (n = 86)	PTC group (n = 82)	$\bar{x}$	*p*
Course of disease	< half a year	26	24	0.5709	0.9031
	< 1 year	32	29		
	< 5 years	6	7		
	< 10 years	10	12		
	≥ 10 years	12	10		

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Group		Benign nodule (n = 86)	PTC group (n = 82)	$\bar{x}$	*p*
Nodule distribution	Unilateral	45	46	0.2406	0.6238
	Bilateral	41	36		
Number of nodules	Single	39	40	0.1984	0.6560
	Multiple	47	42		
Ultrasound TR classification	TR3	42	4	46.1672	< 0.05
	TR4	26	62		
	TR5	18	16		
Ultrasound lymph nodes	No abnormality	76	21	67.7625	< 0.05
	Abnormal	10	61		
Enhanced CT lymph nodes	No abnormality	50	24	14.1969	< 0.05
	Abnormal	36	58		

3.2. Comparison of lymph node metastasis with ultrasound and enhanced CT

In the comparison of lymph node metastasis with ultrasound and enhanced CT results, the number of patients with ultrasound lymph nodes without abnormality in the non-metastasis group was 28, while that of the metastasis group was 21; the number of patients with abnormal ultrasound lymph nodes in the non-metastasis group was 3, while that of the metastasis group was 30. The number of patients with single node without metastasis and metastasis was 14 and 8, respectively, whereas the number of patients with multiple nodes without metastasis and metastasis was 17 and 43, respectively. There were statistically significant differences in the number of ultrasound lymph nodes and nodules, but no statistically significant differences in TR classification, enhanced CT lymph nodes, nodules distribution, and course of disease as shown in **Table 2**.

Table 2. Comparison of lymph node metastasis with ultrasound and enhanced CT

Group		Non-lymph node metastasis (n = 31)	Lymph node metastasis (n=51)	$\bar{x}$	*p*
Ultrasound TR classification	TR3	10	19	0.2399	0.8870
	TR4	11	16		
	TR5	10	16		
Ultrasound lymph nodes	No abnormality	28	21	19.3648	< 0.05
	Abnormal	3	30		
Enhanced CT lymph nodes	No abnormality	22	38	0.1232	0.7256
	Abnormal	9	13		
Nodule distribution	Unilateral	12	24	0.5457	0.4601
	Bilateral	19	27		
Course of disease	< half a year	8	16	1.0866	0.7803
	< 1 year	5	11		
	< 5 years	6	9		
	< 10 years	7	8		
	≥ 10 years	5	7		
Number of nodules	Single	14	8	8.5326	< 0.05
	Multiple	17	43		

4. Discussion

Accurately determining the presence of cervical lymph node metastases in PTC prior to surgery is crucial for determining the extent of neck lymph node dissection. At present, conventional ultrasound is widely used in the evaluation of cervical lymph node status before surgery and has proven to have high sensitivity. However, the qualitative diagnosis of lymph nodes with both benign and malignant characteristics is often challenging. Contrast-enhanced ultrasound (CEUS), as a microvascular imaging technique, can display the distribution of smaller blood vessels in the lymph nodes. Despite the fact that there are several studies on the use of CEUS in studying lymph nodes, there are more qualitative analyses than quantitative analyses, and the majority of earlier literatures have selected whole lymph nodes as the region of interest (ROI). The difference with previous studies is that the central and peripheral regions of lymph nodes were selected as ROI in this study to refine the analysis of the characteristics of lymph node outcomes and their quantitative parameters were analyzed to reduce the impact of subjective factors and individual differences.

Routine tests related to thyroid function include TSH, FT3, FT4, TG, anti-TG, anti-TPO, TSH receptor antibody, and calcitonin. TSH and FT3 are commonly used to evaluate thyroid function. Anti-TPO and anti-TG are commonly used to diagnose and differentiate Hashimoto's thyroiditis and Graves' disease. Calcitonin is an important marker of medullary thyroid carcinoma. Some studies have shown that the serum TSH level of patients with malignant thyroid nodules is higher than that of patients with benign diseases. In more aggressive tumors, TSH increases in proportion [11]. This study revealed that preoperative serum TSH concentration could independently predict thyroid nodule malignancy. The reason may be that the combination of TSH and receptors on thyroid cells can activate many growth promoting pathways in normal and malignant thyroid cells. Therefore, high-dose levothyroxine can be used to inhibit TSH after thyroidectomy to prevent recurrence. However, some studies have shown that the effect of inhibiting TSH on differentiated thyroid cancer is poor [12], in which its mechanism requires further investigation. The differentiation methods of thyroid nodules recommended by the current guidelines include four components: clinical history and examination, serum TSH, ultrasound examination, and fine needle aspiration examination if necessary. If the serum TSH level is low, thyroid scanning should be performed to distinguish between solitary hot nodules in multiple thyroid nodules, thyrotoxic goiter with multiple nodules, or less common, thyroiditis or Graves' disease. Despite being easy to operate and has few contraindications, ultrasound is highly operator-dependent. Therefore, thyroid ultrasonography should be performed on palpable nodules by professionals with rich experience in this field. Despite the fact that the current high-resolution ultrasound can detect very small lesions, it still can clearly display superficial organs and tissues. However, the guidelines suggest that routine thyroid cancer screening is not recommended except for high-risk groups, because the detection of early thyroid cancer has not been shown to improve the survival rate. Based on the clinical and ultrasound risk factors for thyroid cancer, fine needle aspiration should only be performed for nodules ≥ 1.0 cm [13-15].

In conclusion, serum TSH can be used to identify the benign and malignant nature of thyroid nodules, and enhanced CT is better than ultrasound in evaluating complex lesions. It can be used as a supplement to ultrasound based on clinical context.

Disclosure statement

The authors declare no conflict of interest.

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