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Original Article

Application of virtual touch tissue image quantification technique in the diagnosis of cervical lymph node metastasis in papillary thyroid carcinoma

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Abstract: Objective: This study aimed to investigate the application value of the virtual touch tissue image quantification (VTIQ) technique in the diagnosis of lymph node metastasis in patients with papillary thyroid carcinoma. Methods: Data of B ultrasound and VTIQ values of 105 cervical lymph nodes with a definite thyroid papillary carcinoma history were retrospectively analyzed. Lymph nodes were examined by conventional ultrasound primarily. Then, the shear wave velocity (SWV) values inside the lymph nodes were obtained under VTIQ mode. Effective measuring regions of SWV were needed at the first step of VTIQ mass mode, and repeated SWV measurements were performed under the VTIQ velocity mode in effective region to obtain the mean value, and receiver operating characteristic curve (ROC curve) for the sensitivity and specificity was applied to determine the optimal diagnostic threshold. Results: 31 benign and 74 malignant specimens were found in 105 cervical lymphoid tissues. Univariate analysis showed that there were significant differences in gravel calcification, mean SWV, aspect ratio > 2, and blood supply between benign and malignant nodes ($P < 0.05$), while there were no significant differences in location, size (diameter), age, and gender ($P > 0.05$). Multivariate analysis confirmed that gravel calcification and mean SWV were risk factors ($P < 0.05$). According to ROC curve, the detection limit of mean SWV was 2.695 m/s. Conclusions: VTIQ technique, by applying SWV, has an important application value in the diagnosis of lymph node metastasis in patients with papillary thyroid carcinoma.

Keywords: Virtual touch tissue image quantification, lymph nodes, ultrasound, papillary thyroid carcinoma

Introduction

Lymph nodes play an important role in human immunity, and many diseases will lead to its morphological and structural abnormalities [1]. With the development of ultrasound technology, the detection rate and diagnostic accuracy rate of cervical lymph nodes by ultrasound are getting higher and higher. Because of their non-invasion, low cost, high accuracy and repeatability, Gray-scale and color Doppler ultrasound become the preferred methods for clinical diagnosis of benign or malignant cervical lymph nodes and were widely used. For senior ultrasound physicians, a diagnosis of malignant lymph nodes could be made according to some special features of the nodules, such as low echo, small calcification, blurred boundaries, enriched internal blood flow signals, irregular shape and growth patterns of aspect ratio > 2. Because of the wide drainage range of cervical lymph nodes, different impacts of lymph nodes in disease immersion or different autoimmune responses, many benign lymph nodes generally show one or more malignant characteristics or overlapping of benign and malignant images on two-dimensional ultrasound images, easily leading to the diagnosis of the same disease with different images or the same images from different diseases by the conventional ultrasound, which bring certain difficulties to diagnosis [2]. Papillary thyroid carcinoma (papillary thyroid carcinoma, PTC) is one of the most common types of thyroid cancers, with a significant increased incidence especially in recent years. Although papillary thyroid carcinoma belongs to differentiated thyroid cancers with better prognosis than other types of thyroid cancers, more and more literatures report that PTC is prone to cervical lymph node metastasis, which is an important factor affecting the prognosis of PTC patients [3]. At present, whether prophylactic cervical lymph node dissection (CLND) is clinically needed for PTC during surgical procedures is still a highly controversial issue. Therefore, we intended to explore a noninvasive diagnostic method by retrospective analysis so as to analyze the risk factors of CLN metastasis in PTC patients, providing a basis for performing clinical preventive CLND. The virtual touch tissue imaging quantification (VTIQ) technique adopted the force of acoustic pulse radiation to generate lateral vibrations in the regions of interest (ROI) and to calculate the shear wave velocity (SWV) by intervals between adjacent peaks of shear waves and their wavelengths to detect the texture of the ROI tissues [4], providing assistance to the diagnosis and avoiding unnecessary traumatic diagnosis. By application of VTIQ, we compared the difference of the shear wave velocity between the benign and the malignant cervical lymph nodes in patients with papillary thyroid carcinoma and studied the application value of VTIQ in the detection of lymph node metastasis of papillary thyroid carcinoma.

Materials and methods

Subjects

82 patients with cervical lymph node disease who were definitely diagnosed with thyroid papillary carcinoma in Jiaxin First Hospital during Jan 2016 to Dec 2016 were enrolled, including 21 males and 61 females [aged between 11 and 67 years old (45.87±11.82 years old)]. Among 105 lymph nodes, the longitudinal diameter was 0.3~4.5 cm (1.19±0.74 cm), and the transverse diameter was 0.3~3.1 cm (0.88±0.56 cm). All patients had no treatment history of cervical lymph node. Those in whom the distance from the medial wall of the carotid artery was < 0.5 cm at transaction or the lymph node was uplifted above the skin or at the surgical incision scar were excluded (change to the inclusion criteria). Routine ultrasound and VTIQ were performed, and coarse needle re-biopsy or surgical resection was needed to obtain pathological results.

Instrument and methods

Siemens Acuson S3000 color Doppler ultrasound diagnostic instrument was applied, with a 9 L-4 probe, the transmission frequency 4.0~9.0 MHZ and a VTIQ imaging software. After the patient lied down or took a lateral position while the neck was exposed, operation was performed by a surgeon who had deep understanding and mastery of the VTIQ technique, and the clearest image section was selected. First, the two-dimensional ultrasound of lymph node was performed to record the location (I-VI) of the lymph node, longitudinal diameter * transverse diameter, longitudinal diameter/transverse diameter, internal echo, blood flow distribution, whether there was gravel calcification or not etc. According to Wu *et al*. [5], blood circulation inside the lymph nodes was divided into 5 types: Type I (portal type), with the radial blood flow signals generated by the aorta of the portal vessels; Type II (central type), with blood flow signals irregularly distributed in the central part of the lymph node; Type III (peripheral type), with blood flow signals surrounded by the lymph node, without branches to the lymph node; Type IV (mixed type), with blood flows with any two of the above 3 types; Type V (less blood flow type), without blood flow signal, or only few sporadic blood flows. Among them, the first and fifth type were defined as non-malignant lymph node detection criteria, and the rest were defined as malignant lymph node detection criteria. VTIQ was followed, noticing that no pressure should be placed on the probe, and large blood vessels in the neck should be avoided as far as possible. Finally, the pathological results by surgical resection or coarse needle biopsy were obtained.

There were four types of VTIQ modes which were displacement, mass, time and speed mode in turn, mainly focusing on VTIQ mass and speed analysis, and the images were viewed and saved in turn. The size of the measuring frame was adjusted while covering the frame in ROI of lymph nodes as far as possible, and large vessels, hydropic degeneration and non-functioning regions of the specimen were excluded. VTIQ mass test displayed multi-site distribution masses of shear wave of the specimen image, and low to high-parameter region were shown by red → yellow → green, and regions with green and unobvious difference

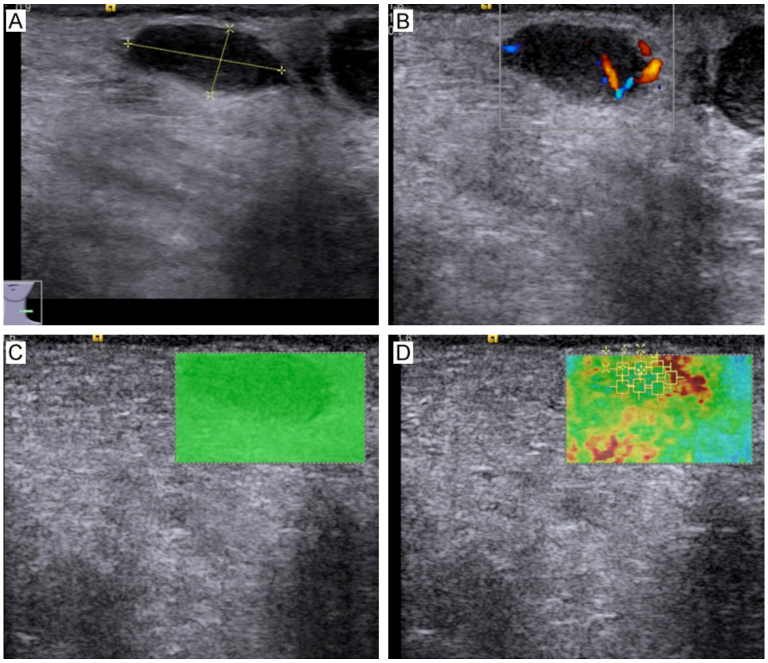

Figure 1. VTIQ graph of malignant lymph nodes. A. Lymph node gray-scale ultrasound showed solid and hypo-echo lymph nodes; B. Color ultrasonography, type IV according to Wu Classification; C. VTIQ mass graph of the lymph node, with the lymph node area showed a uniform green color, indicating a better mass of elastic imaging; D. VTIQ velocity graph (color) of the lymph node, with the lymph node mainly being yellow color and uneven distribution of red regions (representing hard texture); with the peripheral tissues being pale green or light blue (representing soft texture). ROI was placed inside the lymph nodes for SWV measurements (7 values were measured at the same time: 3.74 m/s, 3.62 m/s, 3.53 m/s, 3.35 m/s, 4.36 m/s, 3.32 m/s and 5 m/s, respectively).

indicated a better mass, a poor mass on the contrary. The SWV of ROI could be measured by observing VTIQ images of the lymph nodes in good quality region and suggesting the patients to avoid swallow and to hold their breath. In the velocity test of VTIQ, the two-dimensional space layout of the specimen and the multi-site imaging of the shear wave were presented in a single image. The SWV in the image was arranged from low to high, and the blue, green, yellow and red were changed.

The minimum range of ROI was 1.0 mm × 1.0 mm, and the ROI was placed in regions with different velocities of the lesions. Each lymph node was measured more than 5 times (**Figure 1**), and 5 similar measurement data were saved and the average data was listed. After confirming the ultrasonic application specification, if the hardness of the specimen was abnormal and exceeded the normal range of SWV 0~10 m/s for the machine, "HIGH" or "NA" was displayed; at this time, the general ultrasonogram could be applied for judgment; if the ROI was mainly solid, VTIQ images showed harder specimen, and thus "HIGH" was recorded as "10.0 m/s"; if the ROI was mainly liquid, VTIQ images displayed softer specimen, thus "NA" was recorded as "0.0 m/s", and the values were still saved according to the above method. In this study, the lymph nodes showing > 75% region with cyst or calcification were excluded. The SWV of VTIQ mass images and ROI which were unmatched after repeated tests were excluded from the analysis of the results. All data was stored in computer and compared with the pathological results, and then analyzed by another experienced non-clinical physician.

Statistical analysis

SPSS 19.0 software was used for statistical analysis. The measurement data were expressed as $\overline{X} \pm s$ and analyzed by *t* test; the enumeration data were analyzed by χ^2 test. ROC curve was drawn to determine the diagnostic threshold of the mean SWV. For the factors influencing benign and malignant judgment of the lymph nodes, univariate analysis was used, and the factors of statistical significance were then included in the Logistic study model for multivariate analysis. $P < 0.05$ was statistically significant.

Results

Characteristics of participants

Among 105 cervical lymphoid tissues, 31 were benign and 74 were metastatic lymphoid tissues of PTC. Univariate analysis of benign and malignant risk factors of 105 specimens in 82 patients showed statistically different effects of gravel calcification, mean SWV, aspect ratio > 2, blood supply of lymph nodes (CDFI) on benign and malignant characteristics of the specimens ($P < 0.05$), but there was no significant difference in location, size (diameter), age and gender ($P > 0.05$) (**Table 1**).

Table 1. Univariate analysis of benign and malignant characteristics of the lymph nodes

Lymph nodes	Malignant	Benign	Metastasis rate (%)	Statistical value	*P*
Gender				3.50[a]	0.061
Male	18	3	85.7%		
Female	39	22	63.9%		
Age (yrs)	47.00±12.11	43.28±10.90		1.32[b]	0.191
Size (cm)	0.83±0.52	1.00±0.64		-1.40[b]	0.165
Location				1.99[a]	0.573
II	8	6	57.1%		
III	32	11	74.4%		
IV	23	8	74.2%		
VI	11	6	64.7%		
Mean SWV (m/s)	3.21±0.43	2.52±0.38		7.76[b]	0.001
Aspect ratio				11.02[a]	0.000
> 2	2	7	22.2%		
< 2	72	24	75%		
Calcification (Gravel)				9.19[a]	0.002
No	48	29	62.3%		
Yes	26	2	92.9%		
CDFI				3.89[a]	0.048
I+V	15	12	55.6%		
II+III+IV	59	19	75.6%		

Notes: [a]compared by use of χ^2 test; [b]compared by use of *t* test.

Table 2. Multivariate analysis of benign and malignant characteristics of cervical lymph nodes

Items	B	SE	*P*	OR	95% CI	
					Lower	Upper
Calcification (gravel)	2.24	0.93	0.012	10.42	1.66	66.67
Mean SWV	3.96	0.70	0.001	52.63	13.3	200.00

Note: B: Partial regression coefficient; SE: Standard error; OR: OR value

Influencing factors

The factors affecting the benignancy or malignancy of cervical lymphoid tissues such as gravel calcification, mean SWV, aspect ratio > 2, blood supply (CDFI) were analyzed by multivariate analysis and the results showed that the effect of gravel calcification, mean SWV on the malignant degree of the specimens had statistical difference ($P < 0.05$) (**Table 2**).

ROC

According to ROC curve, the cutoff value of SWV was 2.695 m/s. Sensitivity was 89.20%, specificity was 77.40%, Youden index was 0.666, and AUC was 0.879 (**Figure 2**). Multivariate analysis confirmed that gravel calcification and SWV were the risk factors for cervical lymph nodes ($P < 0.05$). Univariate analysis showed that there were significant differences of gravel calcification, mean SWV, aspect ratio > 2, and blood supply between benign and malignant nodes ($P < 0.05$), while there were no significant differences of location, size (diameter), age, and gender ($P > 0.05$). As shown in **Tables 3** and **4**, there was no significant difference ($P > 0.05$) between mean SWV > 2.695 and aspect ratio > 2 or blood supply of the specimen (CDFI: II+III+IV) in differencting malignant nodes from benign ones.

Discussion

The use of ultrasound identifying thyroid papillary carcinoma with or without lymph node metastasis depends primarily on the size of the specimen, aspect ratio, proportion of medulla, blood flow, morphology, etc [6], but in two-dimensional ultrasound images, there are often many malignant lymph nodes showing one or more benign characteristics or overlapping with benign and malignant imaging, which makes the diagnosis more difficult [7]. In this study, the effects of gravel calcification, mean SWV, aspect ratio > 2, blood supply of lymph nodes (CDFI) on the benign and malignant characteristics of the specimens were statistically different ($P < 0.05$), while there were no statistically significant differences ($P > 0.05$) in terms of size, location, age and gender. Multivariate analysis confirmed that gravel calcification and SWV were the risk factors for cervical lymph nodes ($P < 0.05$), whereas aspect ratio and CDFI were not ($P > 0.05$). The actually reason was that

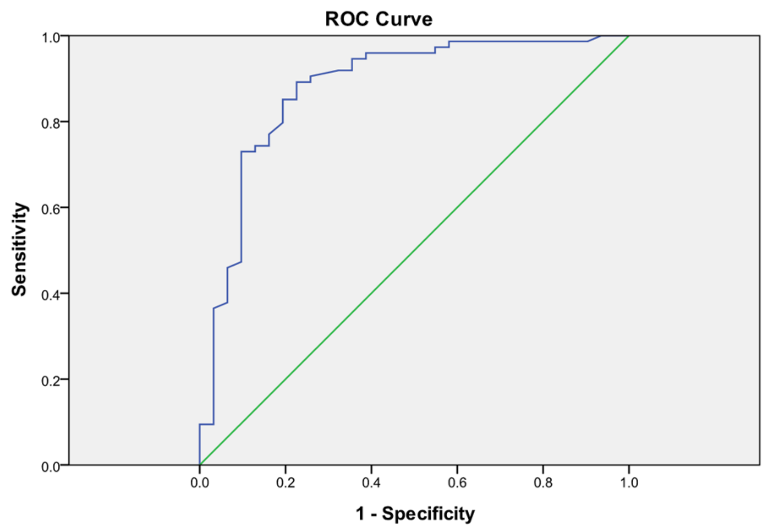

Figure 2. ROC curve of SWV. The cutoff value was 2.695 m/s. Sensitivity was 89.20%, specificity was 77.40%, Youden index was 0.666, and AUC was 0.879.

Table 3. Comparison of mean SWV > 2.695 versus CDFI (II+III+IV)

Lymph nodes	Malignant	Benign	χ^2	*P*
SWV_{mean} > 2.695	66	8	2.522	0.112
CDFI (II+III+IV)	59	15		

Table 4. Comparison of mean SWV > 2.695 with aspect ratio > 2

Lymph nodes	Malignant	Benign	χ^2	*P*
Aspect ratio > 2	72	2		0.097
SWV_{mean} > 2.695	66	8		

Note: two theoretical frequencies < 5, so Fisher exact test method was applied.

when the tumor invaded the lymphoid tissue and destructed the cortex of the specimen, resulting in heterogeneous cell proliferation and the emergence of fibrosis, and then the damage of lymph node vessels led to inadequate blood supply, calcium deposition and tissue necrosis. So it was said that gravel calcification may represent a greater malignancy. In addition, the cancer cells could increase the surrounded connective tissue. After a period of time, the malignant cells infiltrated the peripheral lymph nodes and increased the hardness of the specimen. Therefore, the higher the SWV was, the faster the velocity was and the higher the hardness was, which is more likely to reflect a higher possibility of malignancy [8]. The basic structure of the non-specific proliferative lymphatic tissues in benign specimens has not been changed or damaged, and only the lymphocyte responses was increased and the volume of lymphatic tissues rose, without adhesion to the peripheral tissues, and there is low velocity and softer hardness [9]. Other circumstances which may cause deviation of the measurement are some special circumstances, such as carotid pulsations and respiratory movements, which often result in a rapid velocity.

Ultrasonic elastography is a newly developed ultrasound technology, with a special diagnostic significance, also named as "electronic palpation" [10], which can access the hardness information of the specimens non-invasively and provide more diagnostic information for routine ultrasound imaging in the detection of benign and malignant tumors and diseases. It is mainly applied in the detection of female breast, muscle and thyroid at home and abroad. The elasticity of the tissue is associated with its own microstructure. By the palpation for qualitative judgment and lesions detection, the theory is that the hardness (or elasticity) changes of the specimens are closely related to the biopsy pathology. The development of elastic imaging technology promotes the improvement of the tissue hardness imaging, that is to say, the pathological specimens are more and more clearly characterized. Because the elastic coefficients of different specimens are different, the deformation degrees are different under the action of external force, which can be made into a color image or a specific value by capturing the echo information before and after deformation. In general, the specimens with smaller elasticity and larger change of post-oppression position will be red, while those with larger elasticity and smaller change of post-oppression position will be blue, and the tissues with middle elasticity will become green; so the hardness of the specimen can be determined by the image color. Ultrasound elastography makes the contents of imaging examination more abundant, removing some shortcomings of gray-scale ultrasound, displaying lesion and fixing the location for examination more flexibly.

VTIQ is a newly developed elasticity imaging technology which is called the third generation ARFI technology. Lymph nodes can be quantitatively and qualitatively analyzed by SWV which is calculated by time difference of peak interval of the shear wave (produced by the transverse vibration of the specimen by the force of the acoustic pulse radiation), and the wavelength; the higher SWV value suggests the harder specimen, quantitatively confirming the ROI elastic characteristics. The shear wave velocity is positively proportional to the texture and hardness of lymph node [4]. So the use of this detective technology can make elastic quantization for the benignancy or malignancy of cervical lymphatic tissues. VTIQ makes up for several shortcomings of previous generations of elasticity imagings, such as semi quantization, incompatibility for ≤ 5 mm lesions, the need of repeated extraction, difficult determination of some SWVs, failing to acquire the SWV at a specific site, presence of deviation due to large ROI, relative blindness of the establishment of ROI, etc. It is reported at home and abroad that VTIQ is mainly applied in the diagnosis of breast and thyroid disease [11-13], while less is used in the diagnosis of lymph nodes. In deeply monitoring group by VTIQ, the site is accurate without injury, and different texture regions in lymph nodes can be directly visualized; in addition, the VTIQ check regions are wider (0~10.0 m/s), in which SWV can be measured repeatedly within the same VTIQ rate image so as to detect the hardness characteristics of lymph nodes. Therefore, VTIQ can be used to compensate for the shortcomings of ARFI elasticity imaging in clinical detection. ARFI elastography become more objective and rational in the detection of lymph nodes. It's worth mentioning that there is no statistical difference in the mean SWV, aspect ratio > 2, and blood supply of the specimen, so VTIQ can not completely replace the conventional ultrasound for the diagnosis of the benign and malignant lymph nodes, which only provides an important parameter for diagnosis.

At present, although VTIQ still is affected by the carotid pulse and respiration and may cause a certain deviations, this study indicates that VTIQ technology can be used in the differentiation of benign or malignant cervical lymphoid tissue in papillary thyroid carcinoma patients in a certain extent, providing a reference for clinical treatment schedules.

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Disclosure of conflict of interest

None.

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