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Original Article

Comparative analysis between ultrasound elastography and pathological examination on papillary thyroid carcinoma

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Abstract: The incidence of papillary thyroid carcinoma (PTC) is increasing recently. Although normally having lower malignancy and favorable prognosis, local recurrence of PTC is still correlated with malignant transformation. No clear preventive or managing strategy has been postulated against PTC so far, making the early diagnosis as critical important for improving life quality and extending life span. Current diagnostic approach for PTC mainly consists of color ultrasound combined with pathological examination after biopsy. This retrospective study collected both ultrasound and pathological examination results from patients with thyroid nodules in our hospital, in an attempt to investigate the diagnostic value of color Doppler ultrasound and elastography score. Diagnostic rates of elastography score for PTC and other thyroid cancers were 93.88% and 83.33%, respectively. The elastography score for benign nodules was significantly lower than that of malignant nodules, accompanied with remarkably higher ROI A value. The combined between gray scale/color Doppler ultrasound graph with elastography score shows a higher sensitivity (98.28%) and specificity (98.55%) with coincidence being 99.04%, suggesting a high diagnostic rate and accuracy for PTC. Area under curve (AUC) was 0.843, 0.864 and 0.904 for Ultrasound, Elastography score and Ultrasound+Elastography, respectively. Pathological examination after biopsy, however, is still required for results that cannot be deduced from ultrasound images. Color Doppler ultrasound can clearly reveal the granular calcification inside lesions, along with other features such as burrs on edge or hemodynamic indexes. In combined with elastography score, it can provide evidences for differential diagnosis of thyroid tumor, with significant clinical values.

Keywords: Papillary thyroid carcinoma, ultrasound diagnosis, pathological results

Introduction

Papillary thyroid carcinoma (PTC) is the most common differentiated thyroid cancer. Belonging to the thyroid minimal cancer, the maximal diameter of primary lesion of PTC is less than 1.0 cm. It is one of cancers with significantly elevated incidences recently [1]. PTC is commonly occurred in females between 20 and 40 years old. With chronic disease progress, no significant symptom can be observed under most circumstances. However, the internal bleeding of tumor cyst may suddenly enlarge the thyroid, which has nodular tumor lesions with clear boundary and can be moved with chewing movement [2]. Although having lower malignancy and favorable prognosis, the local recurrence may also be related with tumor recurrence. No clear preventive or managing strategy, however, has been proposed so far. Therefore the early diagnosis is of critical importance for improving patient life quality and extending life span. Color Doppler ultrasound examination is the most common method for early diagnosis of PTC.

Thyroid nodules are prominent symptoms of various thyroid diseases [3]. Multiple factors exist in the formation of thyroid nodular lesion, such as nodular goiter, malignant tumors, adenoma or inflammation. Therefore, the identification between normal thyroid nodule and thyroid cancer is of critical importance during diagnosis. Ultrasound elastography is one advanced ultrasound imaging technique recently as it can provide evidences based on the real-time

Table 1. Elastography score and pathology results of PTC

Nodular type		Pathology	Elastography score	Diagnostic rate
Malignant	PTC	98	92	93.88%
	Other cancers	18	15	83.33%
Benign		207	208	-
Total		323	323	-

Table 2. Elastography score and ROI A values of benign or malignant nodules

Nodular type	N	Elastography score	ROI A value
Benign nodules	207	1.95±0.672	0.0025±0.00123
Malignant nodules	116	4.08±0.364*	0.0009±0.00067*

Note: *, P<0.05 compared to benign nodules.

dynamic change of tissue deformation rate or differential tissue rigidity, thus providing evidences for differential diagnosis of thyroid nodules. Currently, most hospitals made diagnosis of benign/malignant thyroid nodules based on color Doppler ultrasound and elastography techniques. With the help of high-performance probe and equipment configuration, the diagnostic rate of PTC has made a leap [4].

This study analyzed both gray-scale and colored Doppler ultrasound images along with elastography results from those patients who underwent surgeries in our hospital due to thyroid nodules from January 2013 to January 2016, in an attempt to investigate the diagnostic rate and value of colored Doppler ultrasound in diagnosis of PTC, in conjunction with pathological examination from tissue biopsy during the surgery.

Materials and methods

Research objects

In this study, we collected a total of 323 patients consisting of 147 males and 176 females who received thyroid nodules by out-patient surgery from January 2013 to January 2016 in Qujing First People's Hospital of Yunnan. Patient age were distributed from 17 to 72 years, with concentration of age at 40~50 years old and median age being 43.85±2.64 years old.

The study protocol was approved by the Research Ethics Committee of Qujing First People's Hospital of Yunnan, and all patients gave their informed consent before study commencement.

Equipment

In this study, we used HI Vision 900 colored ultrasound equipment (HITACHI, Japan) with probe frequency between 6.0 MHz and 13.0 MHz.

Ultrasound examination

Patients were kept at supine position, with the elevation of neck and backward of head, in order to expose the neck skin and to avoid the swallowing action during examination. The ultrasound examination consists of two sessions. Firstly, the normal scan was performed to visualize those thyroid nodules, for which detailed examination including number, size, morphology, boundary, length/width ratio, surrounding halo, internal echo, calcification or expansion of neck lymph nodes were examined and recorded. Elastography was then performed on thyroid nodules using 9 MHz probe and ultrasound elastography software. Based on the color distribution and respective ratios, the five-grade scale (by Kamoi et al) was used to evaluate the elastography images by blind observers [5]. The score was made by more than two specialists in ultrasound. In a 5-poitn scale, zero point represented evenly distributed green in both lesion and peripheral tissues, suggesting the cystic nature of lesion. 1 score: evenly distribution of green in both lesion and adjacent tissues. 2 points: green or blue-green in lesion area; 3 points: mosaic blue-green in lesion areas, with prominent blue color; 4 points: mostly blue color in lesion area; 5 points, the whole lesion was covered by blue entirely. Blinded scoring was then performed by specialist in ultrasound imaging. Those patients with elastography score lower than 2, were believed as having benign tumors. Those with higher elastography score than 3 points, however, were treated as having malignant tumors.

After obtaining 2D images and elastography images, analysis software was used to trim the region of interest within the lesion. Normal thyroid tissues were also collected with similar shape, size and darkness. A further assay for the elastography changing rate was measured targeting the green area with even distribution for calculating ROI A value. Moreover, the form ratio was also calculated based on the color distribution in lesion area [6].

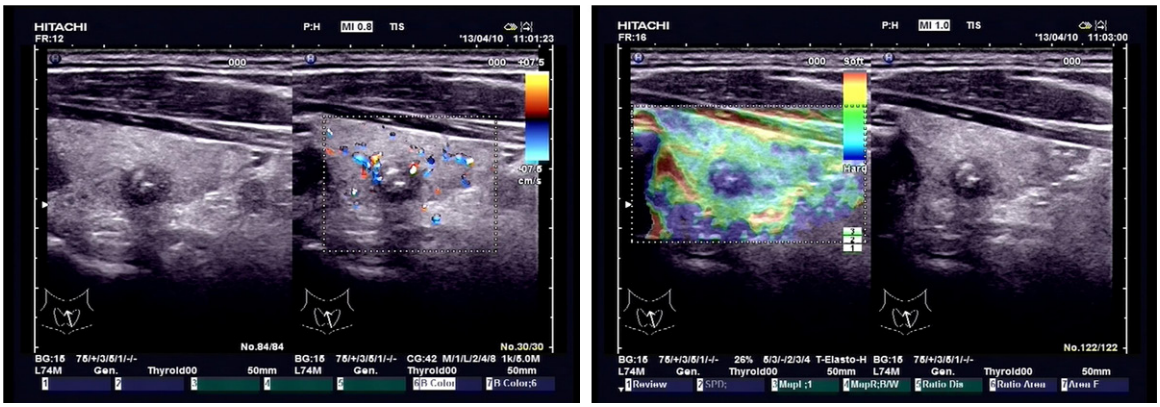

Figure 1. PTC with metastasis in central lymph node but not in anterior neck lymph node.

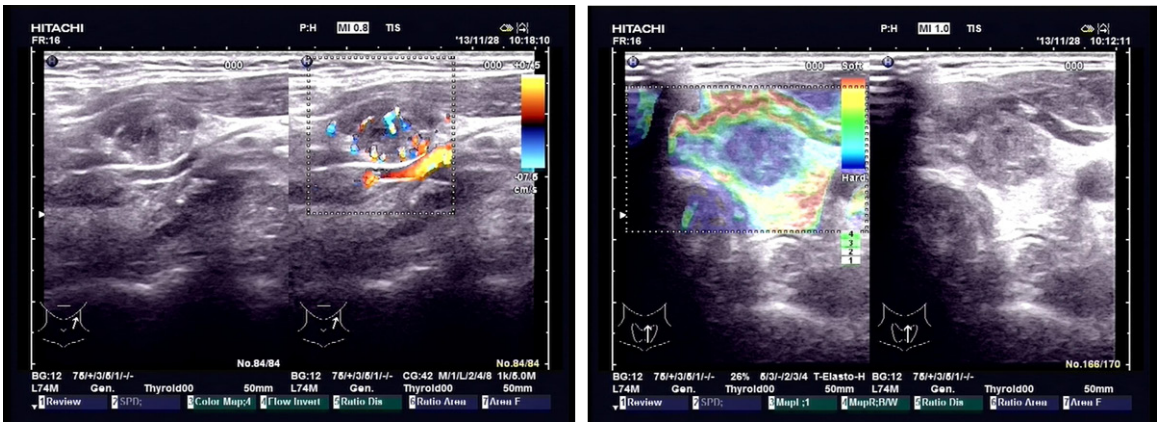

Figure 2. PTC with metastasis in anterior neck lymph node.

Statistical method

SPSS19.0 software was used to analyze all collected data, in which measurement data were presented as mean ± standard deviation (SD). Student t-test was used for comparison between two groups. Categorical data were presented as percentage and analyzed by chi-square test. A statistical significance was defined when $P<0.05$.

Results

Ultrasound and pathology examination results of PTC

In all 323 patients, there were 207 cases of benign nodules and 116 patients with malignant nodules, including 98 PTC cases (28 males and 70 females, occupying 71.43%) and 18 cases with other types of thyroid cancer (see **Table 1** for a summary). All patients received normal ultrasound and elastography examination before the surgery, and have undergone pathological examination after surgery. No significant difference was observed between the two diagnostic approaches ($P>0.05$). As shown in **Table 1**, elastography score had higher accuracy but with certain misdiagnosis rate. Therefore the biopsy of suspected thyroid lesion when ultrasound is inconclusive is necessary.

Elastography score of benign/malignant nodules and ROI A values

The elastography score of benign nodule was significantly lowered than that of malignant nodules ($P<0.05$), accompanied with remarkably higher ROI A values ($P<0.05$, **Table 2**).

Ultrasound features of PTC

Total of 108 malignant nodules were identified within 116 malignant nodules by ultrasound examination and 200 benign nodules were

Table 3. Analysis of ultrasound examination and elastography score on the PTC diagnosis

	Sensitivity (%)	Specificity (%)	Youden index	Coincidence (%)	Kappa value	Positive prediction (%)	Negative Prediction (%)
Ultrasound examination	87.93	93.72	81.65	95.98	81.81	93.27	88.70
Elastography score	92.24	94.69	86.93	96.59	86.60	95.61	90.68
Combined approach	98.28	98.55	96.83	99.04	96.64	99.03	97.44

Table 4. Univariate and multivariate logistic regression (LR) analyses for prediction of papillary thyroid carcinoma

Variables	Univariate LR, OR (95% CI)	*P*	Multivariate LR, OR (95% CI)	*P*
Age	1.14 (0.87-1.63)	0.329	1.02 (0.81-1.52)	0.715
Ultrasound examination	1.67 (0.76-2.27)	0.024	1.42 (1.03-1.85)	0.048
Elastography score	2.45 (0.98-2.96)	0.012	2.81 (1.23-3.47)	0.036
ROI A value	1.97 (0.83-2.63)	0.021	0.86 (0.63-1.43)	0.513

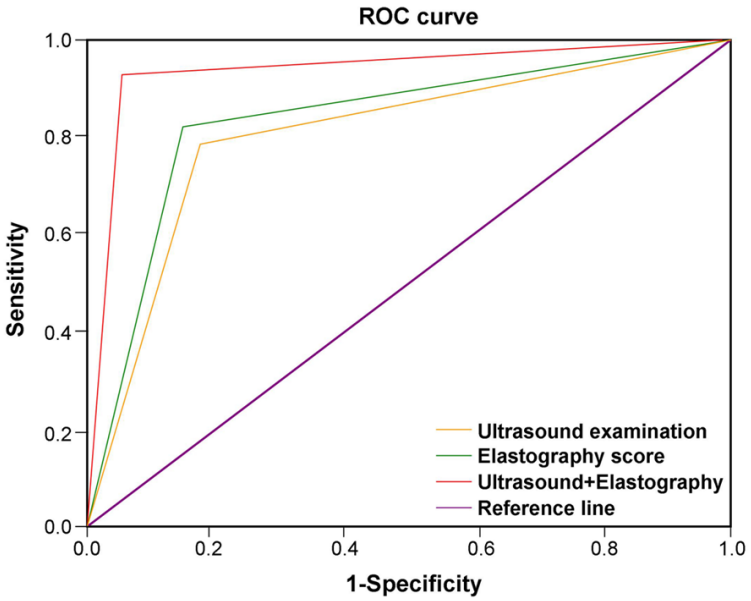

Figure 3. ROC curves for Ultrasound examination, Elastography score and Ultrasound+Elastography score in diagnosis of papillary thyroid carcinoma. ROC, receiver operating characteristic.

detected within 207 benign nodules. No significant difference was found between these two diagnostic results (P>0.05). Representative ultrasound examination results were shown in **Figure 1**, which consists of left panel, which was original 2-D images from routine ultrasound examination, along with 3-D imaging for blood flow direction and range, and ultrasound elastography images on the right panel. In ultrasound images of PTC patients, the edge of lesion was blurred or clear, with irregular morphology (saw-like or crab feet-like shape). Heterogeneous low-echo can be observed inside the tumor, with point or grouped strong echo. In color Doppler ultrasound image, newly formed vessels or artery/venous fistula were revealed. As shown by left panels of **Figures 1** and **2**, cyst-like solid echo frequently represented papillary carcinoma accompanied with lymph node metastasis, along with sand-like strong echo signals in internal solid area, as well as colored blood flow signal on the lymph node edge (**Figures 1** and **2**).

Analysis of ultrasound examination and elastography score on the PTC diagnosis

Effect of single ultrasound examination or elastrography score and combined approach on the PTC diagnosis were shown in **Table 3**. A higher sensitivity, specificity and coincidence (>95%) were observed for combined approach than single approach, suggesting a higher value of combined approach in the PTC diagnosis.

Receiver operating characteristics analysis for predictive capacity

Based on the results of receiver operating characteristics (ROC) analysis, the area under the curve (AUC) was 0.843 [95% confidence inter-

val (CI), 0.812-0.943], 0.864 [95% CI, 0.792-0.853] and 0.904 [95% CI, 0.872-1.012] for Ultrasound examination, Elastography score and Ultrasound+Elastography score, respectively (**Table 4**). Meanwhile, the statistical differences in the AUC were also evaluated between the Ultrasound examination, Elastography score and Ultrasound+Elastography, and the reference (**Figure 3**, AUC=0.5, all of the *P* values less then 0.001). Furthermore, there were significant difference for the AUC in Ultrasound examination compared to Ultrasound+Elastography, and Elastography score compared to Ultrasound+Elastography (**Figure 3**, both of P<0.05), while there was not difference between the Ultrasound examination and Elastography score (**Figure 3**, P>0.05).

Discussion

Recently, the incidence of thyroid cancer is rapid increasing at all age groups, especially in young or middle aged women. In cancer subtyping, papillary carcinoma consists of more than 80% of total cases, leaving few follicular carcinoma and myeloid carcinoma [7, 8]. Due to the complicated pathological types of thyroid cancer, and its frequent occurrence with other thyroid diseases, special biological features and complicated representation in ultrasound images all lead to the difficulty in early diagnosis of PTC.

The rapid increasing incidence of thyroid tumor in recent years [7, 9] may be related with the alternation of disease itself, as well as the application of novel ultrasound technique. Comprehensive consideration strengthened the recognition of thyroid cancer for clinicians, thus improving the diagnostic rate of thyroid cancer [10].

Compared to 2D images, 3D results can be used to judge the direction of blood vessels, the relationship between lesion and adjacent tissues, and the objective evaluation of blood perfusion in the area of interest, besides all features of 2D results. Normal thyroid soma showed evenly distributed echoes with moderate strength, accompanied with echoless vessels, which had clear boundary against adjacent structures. Inside the gland there was no significant blood flow signal, leaving only pointes or thread-like signals. By the composing of 98 PTC patients' medical records, we found PTC had the following features: thyroid cancer cell had large volume, with over-laying growth, less mesenchymal compared to normal cells, which showed infiltrative growth. Therefore, PTC showed low-echo signal, with length/width ratio larger than 1, along with irregular shape, blurred boundary, no capsid, and unsmooth edge with burr-like structure. Meanwhile, other scholars also postulated that the cyst alternation of neck lymph node may be one important indicator for metastasis of PTC [11]. By the analysis of 16 cases of thyroid minimal cancer, we found the unsmooth edge of tumor edge with burrs was the difference between thyroid minimal cancer and other benign nodules, no matter if the boundary is clear or not in ultrasound image. Other scholars proposed similar views, as those lesions with atypical shape or unclear boundary had higher invasiveness compared to those nodules with clear and sharp boundary [12]. It should be noted that in certain patients, one can only observe focally limited or diffused micro-calcification without significant lesion. When the diameter of micro-calcification is less than 2 mm, and is presented as diffused or grouped signals, without shadows or tails, the possibility of thyroid cancer should be considered [13]. Other scholars believed that micro-calcification had high specificity in diagnosing the property of thyroid tumor [14]. In a comparative perspective, benign nodules had higher contents of calcification, causing it higher hardness, especially when the peripheral nodules showed calcification [15-17].

Besides the identification of disease based on normal images of thyroid, this study also introduced ultrasound elastography imaging and related score system. The elastography imaging score was initially developed for treating breast disease, and was later employed for diagnosing thyroid disease [18]. Due to its ease in use, it has been widely accepted by most scholars [19, 20]. Although with certain advantages, ultrasound elastography imaging technique still had certain limitation, mainly attributed to subjective influence from operators, including variation of pressure and vibration frequency [21]. Moreover, tumors at depth received lower pressure than shallow tumor, thus affecting the deduction of results. In summary, elastography imaging should be combined with gray-scale ultrasound, colored

Doppler ultrasound or other imaging technique for disease diagnosis [22].

In summary, various thyroid diseases had unique hemodynamic features besides variation of ultrasound images. Colored Doppler ultrasound can accurately reveal sand-like calcification inside lesions, burrs on the edge and blood flow distribution, thus providing evidences for diagnosis and differentiation of thyroid tumors, with significant clinical values, making it the primary examination for diagnosing thyroid tumor [23]. However, for those lesions hard to be deduced by ultrasound, directed biopsy followed by pathology examination should be pursued to minimize the occurrence of mis-diagnosis.

Disclosure of conflict of interest

None.

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