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Original Article

Nodule size is a key factor for differentiating benign and malignant thyroid nodules using virtual touch tissue quantification and conventional sonography

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Abstract: Thyroid nodules with different size may have different ultrasound features. We compared the differences of ultrasound features of small and large thyroid nodules and figured out the best features for small and large nodules for the differential diagnosis. 348 thyroid nodules included in this study were divided into four groups as small malignant nodules, small benign nodules, large malignant nodules and large benign nodules. The conventional sonographic features and quantitative elasticity features (VTQ, Virtual Touch Tissue Quantification and VTR, ratio of VTQ value of the nodule to that of the surrounding thyroid tissue) were observed and compared among the four groups. When compared with large malignant nodules, small malignant nodules were less frequently solitary, with macrocalcification, more frequently "taller than wide" and had lower VTQ and VTR. The most sensitive features for large nodules were with higher VTR and a solitary occurrence and those for small nodules were with higher VTQ, a taller than wide shape and marked hypoechogenicity. In conclusion, malignant thyroid nodules with different size had different conventional sonographic features and elastic features, which should be taken consideration during the differential diagnosis.

Keywords: Virtual touch tissue quantification, ultrasound, tumor size, thyroid carcinoma

Introduction

Thyroid nodules are a common clinical problem. High resolution ultrasound (US) showed the detection rate of thyroid nodules as 19-67% in random population [1]. Five to fifteen percent of thyroid nodules are malignant [2]. The incidence of thyroid nodules is rising rapidly. In the United States, thyroid nodules are increased with an estimated annual incidence rate of 0.1% per year; And the yearly incidence of thyroid cancer has increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002 [3, 4]. High-resolution US is the first choice and the most sensitive imaging method for the detection of thyroid nodules and for the differential diagnosis of benign and malignant thyroid nodules [5].

Thyroid nodules size is a key factor that affects both clinical diagnosis and management [6]. For example, for thyroid nodules larger than 10 mm, fine-needle aspiration biopsy (FNAB) is recommended to diagnose differentially between malignant thyroid nodules and benign ones. However, only nodules with suspicious ultrasound findings are recommended for FNAB when nodules are less than 10 mm [7].

Many studies have focused on the useful ultrasound features for the differential diagnosis of benign and malignant thyroid nodules. The suspicious malignant features included a solitary occurrence, a taller than wide shape, an ill-defined boundary, marked hypoechogenicity, the presence of microcalcification and/or macrocalcification and being stiff on ultrasound elastography [8-15]. And a few published studies showed the differences of ultrasound features between small and large thyroid nodules [16-19]. The study of Moon et al showed that the sensitivity of microcalcification for small nodules was lower than that for large ones [9]. The study by Szczepanek-Parulska E showed that the stiffness of thyroid nodules was correlated positively with nodule size [19].

But to our knowledge, there are no published papers explored the differences of ultrasound features between small and large thyroid nodules specifically and comprehensively. Therefore, the purpose of this study was to compare the differences of ultrasound features (including VTQ) between thyroid nodules with different size and to evaluate the best ultrasound features for small and large nodules for the differential diagnosis.

Materials and methods

Patients

Between December 2012 and February 2014, 385 thyroid nodules were imaged using both conventional ultrasound and VTQ imaging in our hospital. Of these, 19 cystic lesions of completely liquid nature were excluded in this study, as a cystic lesion was proven to be benign and needed no further differential diagnosis [6]. Another 18 nodules were excluded because the patients did not undergo thyroid surgery. Finally, 348 thyroid nodules in 258 patients (50 male and 208 female, mean age ± standard deviation, 51.8±12.1 years) were included in this study. Some of the nodules, especially small benign nodules, were resected simultaneously with a large or malignant nodule and were included in this study. This study was approved by the Ethics Committee of our hospital and written informed consent was obtained from every patient before the sonographic examination.

Conventional ultrasound

An ultrasound physician with 13 years' experience in sonography performed all the conventional sonographic examinations using an Acuson S2000 diagnostic ultrasound system (Siemens Medical Solutions) equipped with a linear array transducer (9L4, frequency range: 4.0 to 9.0 MHz). Patients were asked to be in a supine position with a fully exposed neck during the examination.

A thyroid was scanned carefully and thoroughly. When a target nodule was chosen, the size of the nodule was measured. A nodule with a maximal diameter smaller than 10 mm on a transverse plane was defined as small. Otherwise, it was defined as large. The recorded conventional ultrasound features included number (solitary or multiple), shape (oval to round or taller than wide), boundary (well or poorly defined), echogenicity (marked hypoechogenicity or other) and calcification (microcalcification, macrocalcification or no calcification) of each nodule. The definition of the ultrasound features was introduced detailedly in our previous study [20].

VTQ elastography

After conventional sonographic examination, VTQ was used to acquire the quantitative elastic information of the nodules and the surrounding thyroid tissues. The patients were instructed to hold their breath. The probe was positioned onto the skin gently with no pressure. The measurement methods of VTQ values for both the nodules and the surrounding thyroid tissue were introduced detailedly in our previous study [20, 21]. The ratio of VTQ value of the nodule to that of the surrounding thyroid tissue was calculated and recorded as VTR.

Statistical analysis

SPSS version 13.0 software (IBM Corporation, Chicago IL) was used for statistical analysis. $P<0.05$ was considered statistically significant difference. Comparisons of frequency distributions were performed by a χ^2 test. The data VTQ and VTR were presented as mean ± standard deviation and compared using student t tests. The cut off points of VTQ and VTR were calculated by a receiver operating characteristic (ROC) curve and compared using z test. The diagnostic value of selected criteria was assessed in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

Results

Grouping

According to histopathological examination after thyroid surgery, among the 348 thyroid nodules, 239 were benign and 109 were malignant. There were 186 nodular goiters, 48 adenomas, 5 thyroiditis, 102 papillary carcinomas, 4 follicular carcinomas and 3 medullary carcinomas.

Nodule sizes ranged from 4.5×3.5 mm to 52.1×62.4 mm. According to the maximal diameters of the nodules measured by conventional ultrasound, 108 nodules were small and 240 nodules were large.

Table 1. The conventional ultrasound features of the thyroid nodules

Features of Lesions	Small malignant nodules (n=41)	Large malignant nodules (n=68)	Small benign nodules (n=67)	Large benign nodules (n=172)
Solitary	11 (26.8)@	42 (61.8)*	10 (14.9)	60 (34.9)
Taller than wide	25 (61.0)#,@	8 (11.8)*	3 (4.5)	1 (0.6)
Poorly defined	21 (51.2)#	32 (47.1)*	12 (17.9)	22 (12.8)
Marked hypoechogenic	25 (61.0)#	30 (44.1)*	12 (17.9)	16 (9.3)
With microcalcification	15 (36.6)#	34 (50.0)*	11 (16.4)	33 (19.2)
With macrocalcification	9 (22.0)@	32 (47.1)*	12 (17.9)	24 (14.0)

#*P*<0.05 compared with small benign nodules; **P*<0.05 compared with large benign nodules; @*P*<0.05 compared with large malignant nodules.

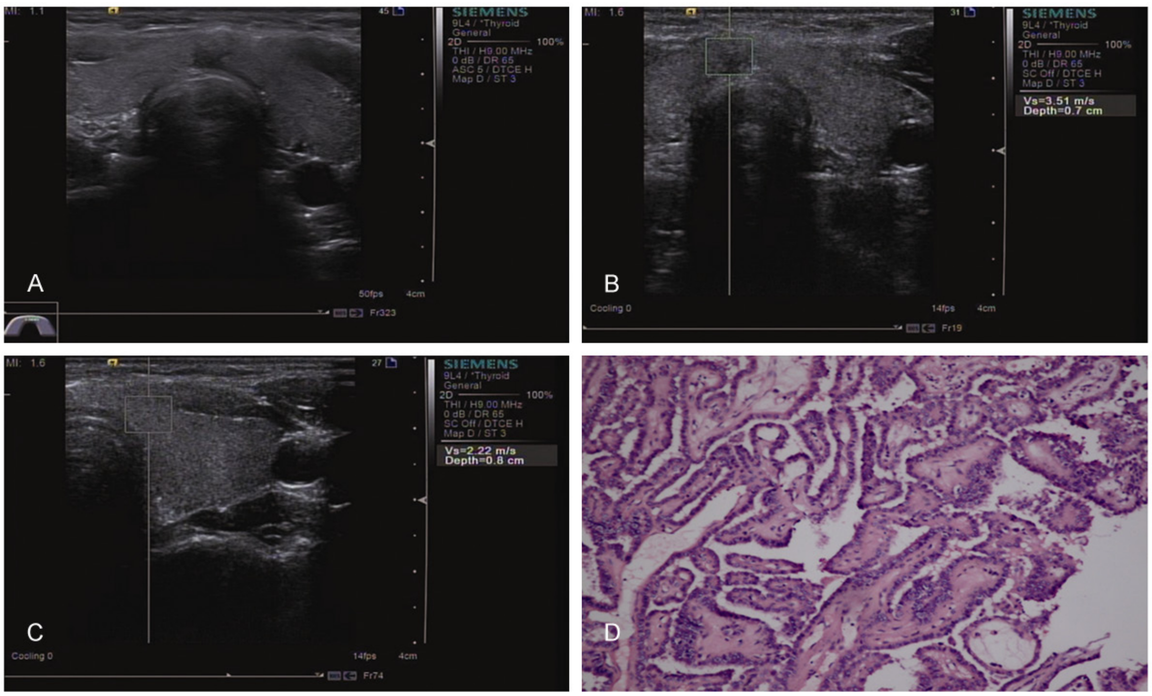

Figure 1. Micropapillary carcinoma in a 48-year-old female patient with a 5.5×5.3 mm nodule in the isthmus of thyroid gland. A. B-mode sonography showed a markedly hypoechoic, taller-than-wide, and poorly defined nodule with no calcification inside. B. VTQ value of the nodule was 3.51 m/s, which was higher than the cut-off point of 2.90 m/s. C. VTQ value of the surrounding thyroid tissue was 2.22 m/s. So VTR was 1.58, which was higher than the cut-off point of 1.41. D. Histopathologic examination confirmed the nodule as a micropapillary carcinoma. VTQ, virtual touch tissue quantification; VTR, the ratio of VTQ.

The nodules were divided into four groups as small malignant nodules (41 cases), small benign nodules (67 cases), large malignant nodules (68 cases) and large benign nodules (172 cases).

Conventional sonographic features

The conventional sonographic features of thyroid nodules were shown in **Table 1**; **Figures 1A**, **2A** and **3A**.

The features of number, shape, boundary, echogenicity and calcification were significantly different between large malignant nodules and large benign nodules. When compared with large benign nodules, large malignant nodules were more frequently solitary (61.8% vs. 34.9%, *P*=0.001), "taller than wide" (11.8% vs. 0.6%, *P*=0.000), poorly defined (47.1% vs. 12.8%, *P*=0.000), marked hypoechogenic (44.1% vs. 9.3%, *P*=0.000) and with microcalcification (50.0% vs. 19.2%, *P*=0.000) or macrocalfication (47.1% vs. 14.0%, *P*=0.000).

When compared with small benign nodules, small malignant nodules were more frequently

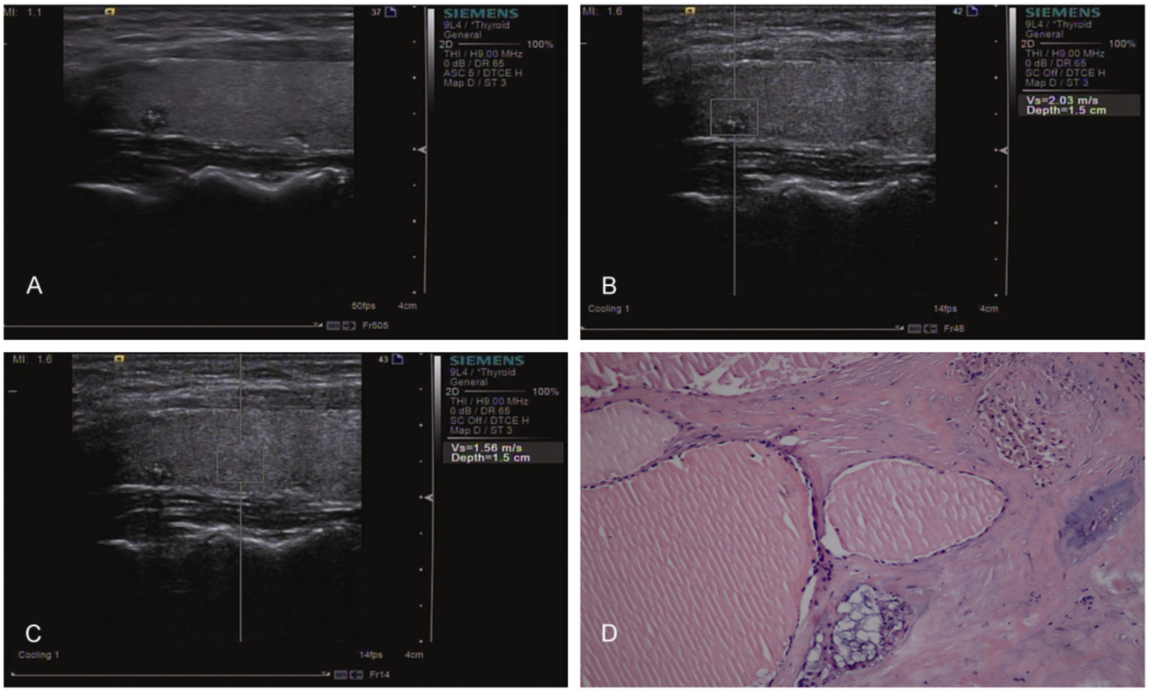

Figure 2. Nodular goiter in the same patient of **Figure 1** with a 3.2×4.3 mm nodule in right thyroid lobe. A. B-mode sonography showed a hypoechoic, oval, and well-defined nodule with microcalcification inside. B. VTQ value of the nodule was 2.03 m/s, which was lower than the cut-off point of 2.90 m/s. C. VTQ value of the surrounding thyroid tissue was 1.56 m/s. So VTR was 1.30, which was lower than the cut-off point of 1.41. D. Histopathologic examination confirmed the nodule as a nodular goiter. VTQ, virtual touch tissue quantification; VTR, the ratio of VTQ.

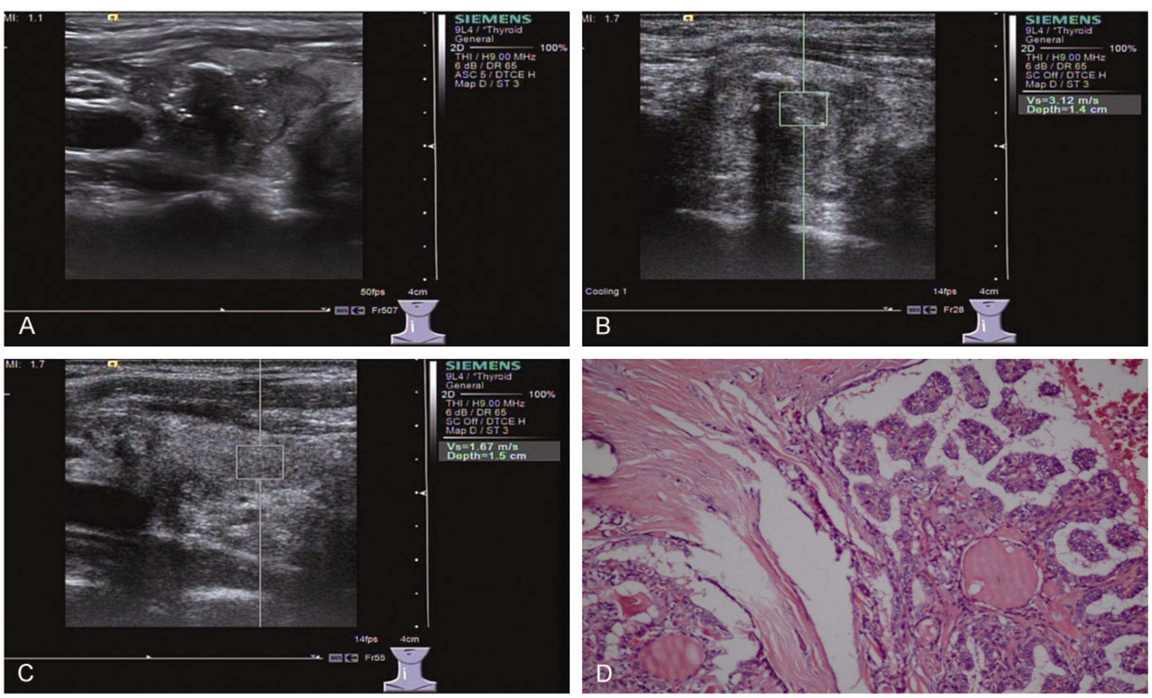

Figure 3. Papillary carcinoma in a 55-year-old female patient with a 15.5×24.5 mm nodule in the right thyroid lobe. A. B-mode sonography showed a hypoechoic, poorly defined and oval nodule with microcalcification and macrocalcification inside. B. VTQ value of the nodule was 3.12 m/s, which was higher than the cut-off point of 2.85 m/s. C. VTQ value of the surrounding thyroid tissue was 1.67 m/s. So VTR was 1.87, which was higher than the cut-off point of 1.42. D. Histopathologic examination confirmed the nodule as a papillary carcinoma. VTQ, virtual touch tissue quantification; VTR, the ratio of VTQ.

Table 2. Diagnostic efficiency of features useful in differentiation between benign and malignant nodules

Features of lesions	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Small nodules (n=108)					
Taller than wide	61.0	95.5	89.3	80	82.4
Poorly defined	51.2	82.1	63.6	73.3	70.4
Marked hypoechogenic	61.0	82.1	67.6	77.5	74.1
With microcalcification	36.6	83.6	57.7	68.3	65.7
Large nodules (n=240)					
Solitary	61.8	65.1	41.2	81.2	64.2
Taller than wide	11.8	99.4	88.9	74.0	74.6
Poorly defined	47.1	87.2	59.3	80.6	75.8
Marked hypoechogenic	44.1	90.7	65.2	80.4	77.5
With microcalcification	50.0	80.8	50.7	80.3	72.8
With macrocalcification	47.1	86.0	57.1	80.4	75.0

Table 3. Quantitative elastic features of the thyroid nodules

	Small malignant nodules (n=41)	Large malignant nodules (n=68)	Small benign nodules (n=67)	Large benign nodules (n=172)
VTQ of the nodule (m/s)	3.25±0.70#,@	3.86±1.70*	2.00±0.45	1.99±0.94
VTQ of the surrounding thyroid tissue (m/s)	2.00±0.31	1.88±0.36	1.86±0.42	1.89±0.36
VTR	1.67±0.49#,@	2.08±0.82*	1.11±0.28	1.07±0.53

#*P*=0.000 compared with small benign nodules; **P*=0.000 compared with large benign nodules; @*P*<0.01 compared with large malignant nodules. VTQ, virtual touch tissue quantification; VTR, the ratio of VTQ.

"taller than wide" (61.0% vs. 4.5%, *P*=0.000), poorly defined (51.2% vs. 17.9%, *P*=0.000), marked hypoechogenic (61.0% vs. 17.9%, *P*=0.000) and with microcalcification (36.6% vs. 16.4%, *P*=0.022). However, the frequency of being solitary (26.8% vs. 14.9%, *P*=0.141) and with macrocalcification (22.0% vs. 17.9%, *P*=0.624) had no significant differences between small malignant nodules and small benign nodules.

When compared with large malignant nodules, small malignant nodules were less frequently solitary (26.8% vs. 61.8%, *P*=0.001), with macrocalcification (22.0% vs. 47.1%, *P*=0.014) and more frequently "taller than wide" (61.0% vs. 11.8%, *P*=0.000). The frequency of being poorly-defined (51.2% vs. 47.1%, *P*=0.697), marked hypoechogenic (61.0% vs. 44.1%, *P*=0.114) and with microcalcification (36.6% vs. 50.0%, *P*=0.233) had no significant differences between small malignant nodules and large malignant nodules. There were not significant differences between the sonographic features of small and large benign nodules.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of useful features in differentiation between benign and malignant nodules were shown in **Table 2**. The most sensitive conventional ultrasound features for large nodules were a solitary occurrence and the presence of microcalcification (61.8% and 50%) and those for small nodules were a taller than wide shape and marked hypoechogenicity (both 61.0%). The most specific features for large nodules were a taller than wide shape and marked hypoechogenicity (99.4% and 90.7%) and those for small nodules were a taller than wide shape and the presence of microcalcification (95.5% and 83.6%).

Quantitative elastic results

The quantitative elastic features were shown in **Table 3**; **Figures 1B**, **1C**, **2B**, **2C**, **3B** and **3C**. VTQs and VTRs of small malignant nodules were significantly higher than those of small benign nodules. And VTQs and VTRs of large malignant nodules were significantly higher than those of large benign nodules.

Table 4. AUCs and the cut-off points of VTQ and VTR and their diagnostic efficiency

	VTQ		VTR	
	Small nodules	Large nodules	Small nodules	Large nodules
AUC (Confidence interval)	0.935 (0.871-0.974)*	0.932 (0.892-0.960)	0.846 (0.763-0.908)	0.923 (0.882-0.954)
Cut-off point (Youden index)	2.90 (0.707)	2.85 (0.718)	1.41 (0.539)	1.42 (0.725)
Sensitivity (%)	70.7	76.5	65.9	82.4
Specificity (%)	100	95.4	88.1	90.1
Positive predictive value (%)	100	86.7	77.1	76.7
Negative predictive value (%)	84.8	91.1	80.8	92.8
Accuracy (%)	88.9	90.0	76.9	87.9

VTQ, virtual touch tissue quantification; VTR, the ratio of VTQ; AUC, area under receiver operating characteristic curve. *$P<0.05$ compared with VTR of small nodules.

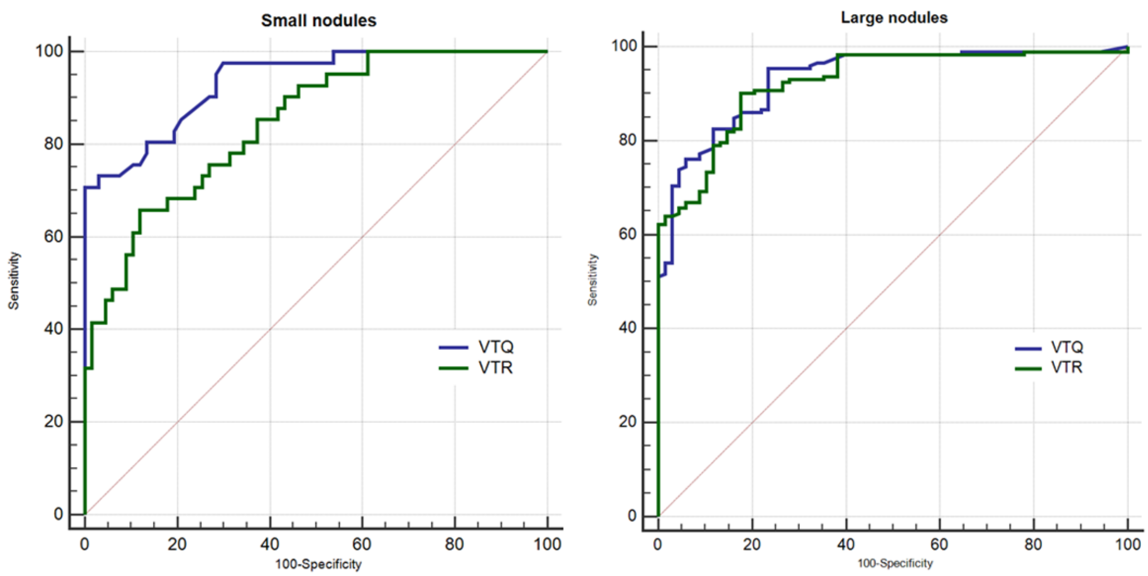

Figure 4. Receiver operating characteristic (ROC) curve of VTQ and VTR. The AUCs of VTQ and VTR of small nodules had significant difference (*P*=0.001), while the AUCs of VTQ and VTR of large nodules had no significant difference (*P*=0.496). VTQ, virtual touch tissue quantification; VTR, the ratio of VTQ; AUC, area under receiver operating characteristic curve.

VTQs of small malignant nodules were significantly lower than those of large malignant nodules (3.25±0.70 vs. 3.86±1.70, *P*=0.003), so were VTRs (1.67±0.49 vs. 2.08±0.82, *P*=0.000). VTQs and VTRs between small benign nodules and large benign nodules had no significant differences (*P*>0.05).

The areas under ROC curve and the cut-off points were shown in **Table 4**; **Figure 4**. The cut-off points of VTQ for small nodules and large nodules were 2.90 m/s and 2.85 m/s accordingly. The cut-off points of VTR for small nodules and large nodules were 1.41 and 1.42 accordingly. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of VTQ and VTR were shown in **Table 4**.

The AUCs of VTQ and VTR of small nodules had significant difference (z=3.223, *P*=0.001), which meant that VTQ was more accurate than VTR for the differentiation between small malignant nodules and small benign nodules. The AUCs of VTQ and VTR of large nodules had no significant difference (z=0.680, *P*=0.496).

Discussion

Many studies have confirmed the value of conventional ultrasound and ultrasound elastography for differentiating malignant and benign thyroid nodules [8-11]. In this study, we focused on the sonographic features of thyroid nodules with different size and we found that thyroid nodules with different size had different features both in conventional ultrasound and ultrasound elastography.

The features of number, shape, boundary, echogenicity and calcification for a thyroid nodule in ultrasound are important for the differential diagnosis of malignancy or benignity. In our study, we found that for the large thyroid nodules, malignant nodules were more frequently solitary, marked hypoechogenic, taller than wide, poor defined or with microcalcification or macrocalcification compared with large benign nodules. However, for the small nodules, a solitary occurrence and the presence of macrocalcification had no significant difference between malignant and benign nodules. These results were partly different with our previous study which showed that the presence of microcalcification had no significant difference between small malignant and benign nodules (34.4% vs. 17.9%, *P*=0.246) [20]. The difference may be caused by the enlarged sample size (from 71 small thyroid nodules to 108). And it also indicated that microcalcification was not very sensitive for the differential diagnosis of a small nodule, which supported the points of Moon et al that the sensitivity of microcalcification for small nodules was lower than that for large ones [9].

When compared with large malignant nodules, small malignant nodules were more frequent taller than wide and less frequently solitary or with macrocalicification. Our results was similar with the study of Popowicz which showed that a taller than wide shape was more sensitive for small nodules (smaller than 15 mm) than large ones [18]. This was the first time to point a solitary occurrence was less sensitive for small nodules than large ones and this result still needs to be confirmed further. In our study, the most sensitive features for large nodules were a solitary occurrence and the presence of microcalcification (61.8% and 50%) and those for small nodules were a taller than wide shape and marked hypoechogenicity (both 61.0%). The most specific features for large nodules were a taller than wide shape and marked hypoechogenicity (99.4% and 90.7%) and those for small nodules were a taller than wide shape and the presence of microcalcification (95.5% and 83.6%). Therefore, when a thyroid nodule is differentially diagnosed using conventional ultrasound, the nodular size should be taken into consideration as the diagnostic accuracy of ultrasound criteria is dependent on tumor size.

Though conventional ultrasound features of thyroid nodules had excellent specificity, the sensitivity was not satisfied. Elastography is a useful method for the differential diagnosis of thyroid nodules. The studies of Zhang FJ et al and Zhang YF et al have proved that VTQ, the quantitative elastography, could differentiate malignant thyroid nodules from benign ones with both high sensitivity and high specificity [22, 23]. In this study, we confirmed the significant differences between the VTQ values of malignant and benign nodules for both large and small nodules. Also, our results showed that the VTQ values of small malignant nodules were significantly lower than those of large malignant nodules. It suggests that large malignant nodules were stiffer than small malignant nodules. Although there has been no previous studies using VTQ to evaluate the stiffness difference of small and large malignant nodules, our result was similar with the studies about breast carcinomas which found that the average mean stiffness for malignancies less than 15 mm was significantly lower than that of cancers larger than 15 mm and large invasive sizes had statistically significant positive association with high mean stiffness value [24, 25]. But our results may be affected by the limitation of the fixed ROI size of 5×6 mm as some nodules in this study were smaller than that. Some surrounding thyroid tissue could be included in the nodular ROI, which may change the results of the stiffness of the nodule itself. So our results need to be testified by new elastic technologies with smaller ROI and by comparing the pathological features between small and large malignant nodules.

In spite of the significant differences between the VTQ values of small and large malignant nodules, our results showed that the cut-off points of the VTQ value for large nodules and small nodules were same (2.87); And the sensitivity and specificity of the VTQ value for large nodules and small nodules were similar (for large nodules, 76.5% and 95.3%; For small nodules, 75.6% and 97.0%). So, for both large nodules and small nodules, the same diagnostic indices could be used and we can expect similar diagnostic efficiency.

In this study, the relative stiffness of thyroid nodules was reflected using VTR. We found that the diagnostic efficiency of the VTQ values was better than that of VTR for small nodules while similar with that of VTR for large nodules. One probable reason for it may be the influence of the surrounding thyroid tissue as thyroid with diffuse disease was not excluded in this study. And some diffuse thyroid disease such as Basedow-Graves' disease and chronic autoimmune thyroiditis may have higher thyroid stiffness than healthy thyroid [26, 27]. As the VTQ values of small malignant nodules were lower than those of large malignant nodules, VTRs of small nodules were more affected than those of large nodules. As the diagnostic efficiency of the VTQ values for both small nodules and large nodules was not lower than that of VTR, we recommended using the VTQ value to differentiate thyroid nodules, especially for small nodules.

Our study had some limitations. First, the fixed size of ROI may affect the VTQ values of some small thyroid nodules as some surrounding thyroid tissue could be included in the nodular ROI. Second, instead of a big sample size, there were only a few types of thyroid nodules included in this study. Third, the pathological examination in this study was only for the final diagnosis of malignancy or benignity without the examination of stiffness.

In conclusion, VTQ with conventional ultrasound could differentiate malignant and benign thyroid nodules accurately. Malignant thyroid nodules with different size had different conventional ultrasound features and elastic features, which should be taken into consideration during the differential diagnosis.

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Disclosure of conflict of interest

None.

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References

[1] Tan GH and Gharib H. Thyroid incidentalomas: Management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997; 126: 226-231.

[2] Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med 2004; 351: 1764-1771.

[3] Brito JP, Yarur AJ, Prokop LJ, McIver B, Murad MH and Montori VM. Prevalence of thyroid cancer in multinodular goiter versus single nodule: A systematic review and meta-analysis. Thyroid 2013; 23: 449-455.

[4] Davies L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006; 295: 2164-2167.

[5] Solbiati L, Osti V, Cova L and Tonolini M. Ultrasound of thyroid, parathyroid glands and neck lymph nodes. Eur Radiol 2001; 11: 2411-2424.

[6] Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, Cronan JJ, Doubilet PM, Evans DB, Goellner JR, Hay ID, Hertzberg BS, Intenzo CM, Jeffrey RB, Langer JE, Larsen PR, Mandel SJ, Middleton WD, Reading CC, Sherman SI, Tessler FN. Management of thyroid nodules detected at US: society of radiologists in ultrasound consensus conference statement. Ultrasound Q 2006; 22: 231-8.

[7] Kim DW, Lee EJ, Kim SH, Kim TH, Lee SH, Kim DH and Rho MH. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules: comparison in efficacy according to nodule size. Thyroid 2009; 19: 27-31.

[8] Peccin S, deCastro JA, Furlanetto TW, Furtado AP, Brasil BA and Czepielewski MA. Ultraono graphy: is it useful in the diagnosis of cancer in thyroid nodules? J Endocrinol Invest 2002; 25: 39-43.

[9] Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, Kim J, Kim HS, Byun JS, Lee DH; Thyroid Study Group, Korean Society of Neuro- and Head and Neck Radiology. Benign and malignant thyroid nodules: US differentiation-multicenter retrospective study. Radiology 2008; 247: 762-770.

[10] Brito JP, Gionfriddo MR, AlNofal A, Boehmer KR, Leppin AL, Reading C, Callstrom M, Elraiyah TA, Prokop LJ, Stan MN, Murad MH, Morris JC and Montori VM. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab 2014; 99: 1253-1263.

[11] Azar N, Lance C, Nakamoto D, Michael C and Wasman J. Ultrasonographic thyroid findings suspicious for malignancy. Diagn Cytopathol 2013; 41: 1107-1114.

[12] Cakir B, Aydin C, Korukluoğlu B, Ozdemir D, Sisman IC, Tüzün D, Oguz A, Güler G, Güney G, Kuşdemir A, Sanisoglu SY and Ersoy R. Diagnostic value of elastosonographically determined strain index in the differential diagnosis of benign and malignant thyroid nodules. Endocrine 2011; 39: 89-98.

[13] Cassinotto C, Lapuyade B, Aït-Ali A, Vergniol J, Gaye D, Foucher J, Bailacq-Auder C, Chermak F, Le Bail B and de Lédinghen V. Liver fibrosis: noninvasive assessment with acoustic radiation force impulse elastography-comparison with fibroscan M and XL probes and fibro test in patients with chronic liver disease. Radiology 2013; 269: 283-292.

[14] Bojunga J, Dauth N, Berner C, Meyer G, Holzer K, Voelkl L, Herrmann E, Schroeter H, Zeuzem S and Friedrich-Rust M. Acoustic radiation force impulse imaging for differentiation of thyroid nodules. PLoS One 2012; 7: e42735.

[15] Zhan J, Diao XH, Chai QL and Chen Y. Comparative study of acoustic radiation force impulse imaging with real-time elastography in differential diagnosis of thyroid nodules. Ultrasound Med Biol 2013; 39: 2217-2225.

[16] Sharma A, Gabriel H, Nemcek AA, Nayar R, Du H and Nikolaidis P. Subcentimeter thyroid nodules: utility of sonographic characterization and ultrasound-guided needle biopsy. AJR Am J Roentgenol 2011; 197: W1123-1128.

[17] Kim DW, Lee YJ, Eom JW, Jung SJ, Ha TK and Kang T. Ultrasound-based diagnosis for solid thyroid nodules with the largest diameter <5 mm. Ultrasound Med Biol 2013; 39: 1190-1196.

[18] Popowicz B, Klencki M, Lewiński A and Słowińska-Klencka D. The usefulness of sonographic features in selection of thyroid nodules for biopsy in relation to the nodule's size. Eur J Endocrinol 2009; 161: 103-111.

[19] Szczepanek-Parulska E, Woliński K, Stangierski A, Gurgul E and Ruchała M. Biochemical and ultrasonographic parameters influencing thyroid nodules elasticity. Endocrine 2014; 47: 519-527.

[20] Zhang HP, Shi QS, Gu JY, Jiang L, Bai M, Liu L, Wu Y and Du L. Combined value of virtual touch tissue quantification and conventional sonographic features for differentiating benign and malignant thyroid nodules smaller than 10 mm. J Ultrasound Med 2014; 33: 257-264.

[21] Gu JY, Du LF, Bai M, Chen H, Jia X, Zhao J and Zhang X. Preliminary study on the diagnostic value of acoustic radiation force impulse technology for differentiating between benign and malignant thyroid nodules. J Ultrasound Med 2012; 3: 763-771.

[22] Zhang FJ and Han RL. The value of acoustic radiation force impulse (ARFI) in the differential diagnosis of thyroid nodules. Eur J Radio 2013; 82: e686-690.

[23] Zhang YF, Xu HX, He Y, Liu C, Guo LH, Liu LN and Xu JM. Virtual touch tissue quantification of acoustic radiation force impulse: a new ultrasound elastic imaging in the diagnosis of thyroid nodules. PLoS One 2012; 7: e49094.

[24] Evans A, Whelehan P, Thomson K, McLean D, Brauer K, Purdie C, Baker L, Jordan L, Rauchhaus P and Thompson A. Invasive breast cancer: Relationship between shear-wave elastographic findings and histologic prognostic factors. Radiology 2012; 263: 673-677.

[25] Vinnicombe SJ, Whelehan P, Thomson K, McLean D, Purdie CA, Jordan LB, Hubbard S and Evans AJ. What are the characteristics of breast cancers misclassified as benign by quantitative ultrasound shear wave elastography? Eur Radiol 2014; 24: 921-926.

[26] Sporea I, Sirli R, Bota S, Vlad M, Popescu A and Zosin I. ARFI elastography for the evaluation of diffuse thyroid gland pathology: preliminary results. World J Radiol 2012; 4: 174-178.

[27] Sporea I, Vlad M, Bota S, Sirli RL, Popescu A, Danila M, Sendroiu M and Zosin I. Thyroid stiffness assessment by acoustic radiation force impulse elastography (ARFI). Ultraschall Med 2011; 32: 281-285.