## Original Article
# Combination of conventional ultrasound and tissue quantification using acoustic radiation force impulse technology for differential diagnosis of small thyroid nodules

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Abstract: Acoustic radiation force impulse (ARFI)-imaging is a novel ultrasound-based elastography method enabling quantitative measurement of tissue stiffness. This study aimed to evaluate diagnostic value of conventional ultrasound and tissue quantification by using acoustic radiation force impulse (ARFI) technology for differentiation of small thyroid solid lesions. Ninety thyroid masses were examined by using the conventional ultrasound and Virtual touch tissue quantification (VTQ) of ARFI. The shear wave velocity (SWV) (m/s) was also examined. Combined traditional ultrasound diagnosis criteria (CTUDC) of thyroid nodules were also evaluated. Receiver-operating characteristic curve (ROC) analysis was performed to assess the diagnostic performance. The final diagnosis was obtained from clinical histology findings. In conventional ultrasound patterns, A/T ≥ 1 had the highest area under curve, which could achieve to 0.6547. The mean value of SWV of thyroid microcarcinoma differed significantly from those of benign nodules (3.92±2.01 m/s vs. 2.52±1.09 m/s, P < 0.01). For differentiating between benign and malignant nodules, the sensitivity, specificity were 80.56% and 74.07%, respectively, which were based on the standard SWV (2.57 m/s). Meanwhile, the sensitivity and specificity could achieve 77.78% and 77.22%, respectively, which were based on CTUDC. The Area under ROC curve (AUC) of VTQ and CTUDC were 0.825 and 0.8226 respectively. Among the ninety thyroid masses, only five benign lesions were misdiagnosis as malignant ones if combination application of VTQ and CTUDC. In conclusion, the VTQ of ARFI technology can be applied in diagnosis of small thyroid nodules, which may be complement B-mode ultrasound and plays an important role in clinical applications.

Keywords: Thyroid nodule, papillary microcarcinoma, ultrasound, virtual touch tissue quantification

## Introduction

Clinically, the thyroid microcarcinoma always is defined by the size criteria as less than 1 centimeter for the largest diameter [1]. Since almost all the tumors are of papillary histotype, the preferred definition is now Micro-Papillary Thyroid Carcinoma (mPTC) [2, 3]. Nowadays that is the most commonly occurring differentiated thyroid cancer in many countries in patients older than 45 years, incidentally found during neck ultrasound [4]. The average autoptic prevalence of mPTC is around 10%, with wide range (2.0-35.6%) [5].

Generally, thyroid carcinomas are growing slowly and run an indolent course. Although majority of the thyroid carcinomas illustrated with the benign form, a small percentage of carcinomas lead to the regional and distant metastases and even death [6, 7]. Ultrasonography is the most frequently used tool for the clinical identification, assessment, and the follow-up processes of the thyroid nodules, primarily because it provides real-time scanning, easy performance, and cost-effectiveness without radiation [8]. In clinical, most of the small thyroid nodules are asymptomatic, therefore, the improved or enlarged knowledge of US features that different mPTC from benign ones is urgently needed.

The acoustic radiation force impulse (ARFI)-imaging is a novel kind of ultrasound-based elastography method, which could enable the

quantitative measurement of the tissue stiffness. Therefore, the quantitative application of ARFI technology is named the Virtual Touch tissue quantification (VTQ) technology.

Previous studies have also demonstrated that the VTQ technology can effectively differentiate some of the malignant thyroid lesions from the benign ones [9, 10]. However, in clinical, the diagnostic performance of VTQ in small thyroid masses has not been evaluated. This study aims to evaluate role of VTQ in the differentiation for the mPTC and the benign small nodules. Therefore, we conducted a prospective study for investigating whether combined application conventional ultrasound and VTQ could improve the differentiation of small thyroid lesions.

## Materials and methods

### Patients

A total of 57 women patients and 29 men patients were enrolled in the department for surgical treatment from January 2012 to August 2013 in this study. All of the patients were recruited on the basis that they had been suspected to have solid thyroid masses based on conventional sonographic examinations.

On sonographic image, the patients who detected with a single or multiple thyroid nodules, which size between 5 mm to 10 mm were included. All patients underwent surgery with subsequent histological examination of the resected thyroid tissue. The present study was approved by the ethical committee of our institute. Also, all of the patients have been gave their consents and approved the present study.

### Conventional ultrasound

Conventional thyroid ultrasound and ARFI were performed by using the ACUSON S2000 ultrasound system (Siemens, CA, USA), which was fitted with a 9 Mhz linear transducer. Firstly, the conventional ultrasound was obtained for each nodule. The presence or absence of hypoechogenicity, blurred margins, microcalcification (presence of hyperechoic spots less than 2 mm, without acoustic shadowing), A/T ≥ 1 (taller than wide) of the thyroid nodules was examined. The pattern of the blood flow evaluated by color-Doppler imaging was classified as followings: The "no vascularity" was defined as no color-Doppler flow in the periphery or within the nodule. The "peripheral vascularity" was defined as flow in the peripheral position and absent or slight flow in the central part of the nodule. The "marked intranodular vascularity" was defined as more flow in the central part of the nodule than at the periphery.

### Virtual touch tissue quantification VTQ

In the VTQ examination, the patients were asked to hold their breath (an acoustic push pulse and detection pulses are used to calculate SWV), which increases with tissue stiffness. As general steps to perform VTQ, on B-mode US images, a target region was identified with an ROI with a fixed dimension of 6 mm × 5 mm. An acoustic push pulse was transmitted, and shear waves were generated in the target region. The shear waves were detected by sonographic detection pulses and the numeric values of the SWV (measured in m/s) was calculated and displayed on the monitor. The nodules were measured 5 times and the average value was calculated as SWV of nodules. The movement range of the ROI was small in the nodule when the size of the nodule was similar to the ROI. The repeatability of 5 times sampling was very high, and the measurements were in good agreement. The limits for measurement of the VTQ values (shear wave velocity) for this machine were 0 to 9 m/s. Values outside these limits were displayed as "X.XX m/s", the result was recorded as 9 m/s when the nodule was solid [11].

### Histopathological diagnosis

Hematoxylin and eosin staining assay were used for staining formalin-fixed, paraffin-embedded tumor tissue as well as normal parenchyma obtained from the contralateral thyroid lobe of each case. The histological diagnosis was performed by inviting two independent pathologists. When the discordant results were obtained, the agreement was found by conjoint re-examination of each case.

### Statistical analysis

Statistical data analysis was conducted using The SAS for Windows version 9.2 software package (SAS Inc, Cary, IL, USA). Data were expressed in terms of mean ± SD. Receiver-operating characteristic curve (ROC) analysis was performed to assess the diagnostic value of conventional ultrasound imaging and VTQ technique, and to determine the diagnostic

**Table 1.** Predictive value of conventional ultrasound features and VTQ in 90 thyroid lesions

| Criteria | Benign (n=54) | Malignant (n=36) | P-value | Sens (%) | Spec (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Hypoechogenicity | | | 0.00386 | 77.78 | 55.56 | 53.84 | 78.95 |
| Yes | 24 | 28 | | | | | |
| No | 30 | 8 | | | | | |
| Microcalcifications | | | 0.01152 | 38.89 | 85.18 | 63.64 | 67.64 |
| Yes | 8 | 14 | | | | | |
| No | 46 | 22 | | | | | |
| A/T ≥ 1 | | | 0.00369 | 61.11 | 70.37 | 57.89 | 73.07 |
| Yes | 16 | 22 | | | | | |
| No | 38 | 14 | | | | | |
| Blurred margins | | | 0.0321 | 58.33 | 64.81 | 52.50 | 70.00 |
| Yes | 19 | 21 | | | | | |
| No | 35 | 15 | | | | | |
| Intranodular vas. | | | 0.600 | 55.56 | 38.89 | 37.73 | 56.75 |
| Yes | 33 | 20 | | | | | |
| No | 21 | 16 | | | | | |
| SWV ≥ 2.572 m/s | | | 0.000 | 80.56 | 74.07 | 67.44 | 85.11 |
| | 14 | 29 | | | | | |
| | 40 | 7 | | | | | |

SWV: Shear wave velocity; Sens: Sensitivity; Spec: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; Vas: Vascularity.

sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Then, the cut-off values of SWV were optimized. Wilcoxon rank sum test was performed to determine whether the SWV were different between the two groups. In this case, final histopathologic diagnosis was used as the reference standard. *P* < 0.05 was considered statistically significant.

## Results

### Patient characteristics

Ninety-four patients were examined in this prospective study. Eight patients were excluded from the study because lack of the pathologic results, therefore, the final study was consisted of 86 patients (fifteen patients had two nodules, two patients had 1 malignant nodule in the left thyroid lobe and one malignant nodule in the right thyroid lobe, the nodules that exceeded 10 mm were not include in this study). The mean age of the examined patients was 45±10 years (range, 19 to 73 years), who had 90 thyroid lesions (mean size 7.2±1.5 mm, range, 5.4 to 9.6 mm). Histological examination indicated 36 malignant nodules (papillary thyroid microcarcinomas) and 54 benign nodules (37 nodular goiters, 14 follicular adenomas, 1 subacute thyroiditis, and 2 atypical adenoma).

### Conventional US

The results of B-mode ultrasound criteria were listed in **Table 1**. The Area under the ROC curve (AUC) of the presence or absence of hypoechogenicity, microcalcification, blurred margins, A/T ≥ 1, type III color-flow Doppler pattern was 0.6574 (95% CI: 0.5612-0.7536), 0.6204 (95% CI: 0.5265-0.7142), 0.6157 (95% CI: 0.5118-0.7197), 0.6574 (95% CI: 0.5559-0.7589) and 0.5278 (95% CI: 0.4225-0.633), respectively.

The pattern of type III color-flow Doppler pattern, taken alone, was not predictive of malignancy (P=0.60). The combination of echographic patterns increased the specificity but decreased the sensitivity of thyroid US (**Table 2**). The synchronous presence of A/T ≥ 1 and micro-calcification had the highest specificity (94.44%), but the lowest sensitivity (19.44%).

### Combined traditional ultrasound diagnosis criteria (CTUDC) of thyroid nodules

In order to investigate whether two or more conventional US characteristics (including the

**Table 2.** Predictive value of combination of conventional ultrasound features and CTUDC in 90 thyroid lesions

| | BN (n=54) | CA (n=36) | *P*-value | Sensitivity % | Specificity % | Accuracy % |
|---|---|---|---|---|---|---|
| Hypoechogenicity/microcalcifications | | | 0.0042 | 27.78 | 92.29 | 66.67 |
| Both present | 4 | 10 | | | | |
| One absent | 50 | 26 | | | | |
| Hypoechogenicity/A/T ≥ 1 | | | 0.0121 | 52.78 | 87.04 | 73.33 |
| Both present | 7 | 19 | | | | |
| One absent | 47 | 17 | | | | |
| Hypoechogenicity/blurred margins | | | 0.0072 | 38.89 | 83.33 | 65.56 |
| Both present | 9 | 14 | | | | |
| One absent | 45 | 22 | | | | |
| Microcalcifications/A/T ≥ 1 | | | 0.0039 | 19.44 | 94.44 | 64.44 |
| Both present | 3 | 7 | | | | |
| One absent | 51 | 29 | | | | |
| CTUDC | | | 0.0215 | 77.78 | 77.22 | 70.00 |
| Positive | 15 | 28 | | | | |
| Negative | 39 | 8 | | | | |

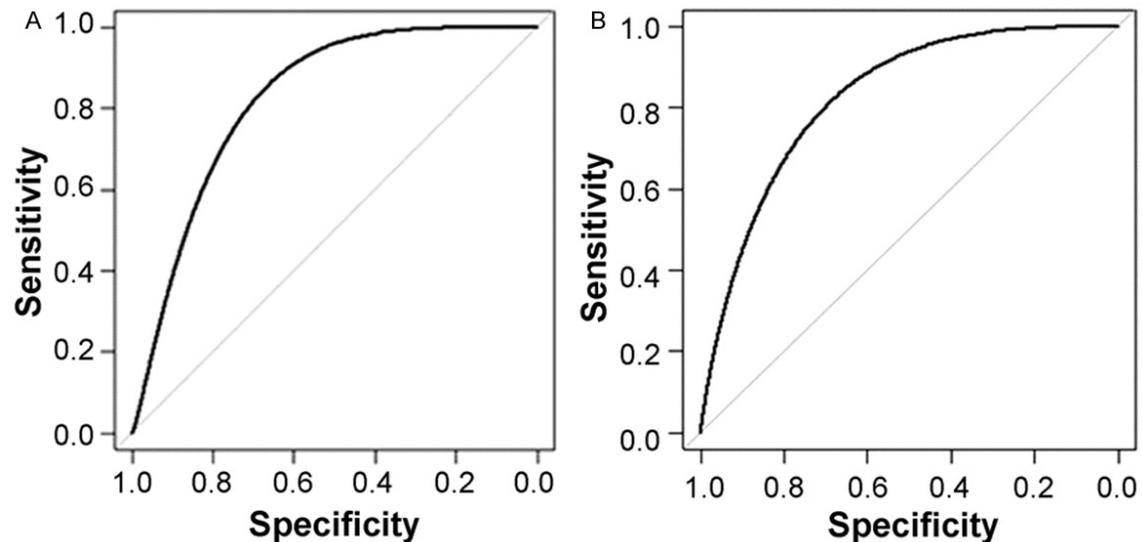CTUDC: Combined traditional ultrasound diagnosis criteria.



**Figure 1.** Receiver-operating characteristic curve (ROC) for distinguishing between micro-papillary thyroid carcinoma (n=36) and benign thyroid lesions (n=54): A. Combined traditional ultrasound diagnosis criteria AUC value =0.8226 (95% CI: 0.7187-0.8997); B. Virtual Touch tissue quantification AUC value =0.825 (95% CI: 0.7187-0.8997).

presence of hypoechogenicity, microcalcification, A/T ≥ 1 and blurred margins) exhibited simultaneously in the nodule that suggest malignancy, the nodule were CTUDC positive and assumed to be malignancy. The sensitivity and specificity of this method is relatively satisfactory (77.78% and 77.22%, respectively) (**Table 2**). The AUC of this method was 0.8226 (95% CI: 0.7187-0.8997) (**Figure 1A**).

*Virtual touch tissue quantification VTQ*

The mean SWV of benign lesions was 2.52±1.09 m/s (range 1.429-9.00) (**Figure 2A**), and the mean SWV of malignant lesions was 3.92±2.01 m/s (range 2.01-9.00) (**Figure 2B**). There were significant differences between the SWV of benign and the malignant lesions (P < 0.01) (**Figure 2C**). The cut-off level for SWV for malig-
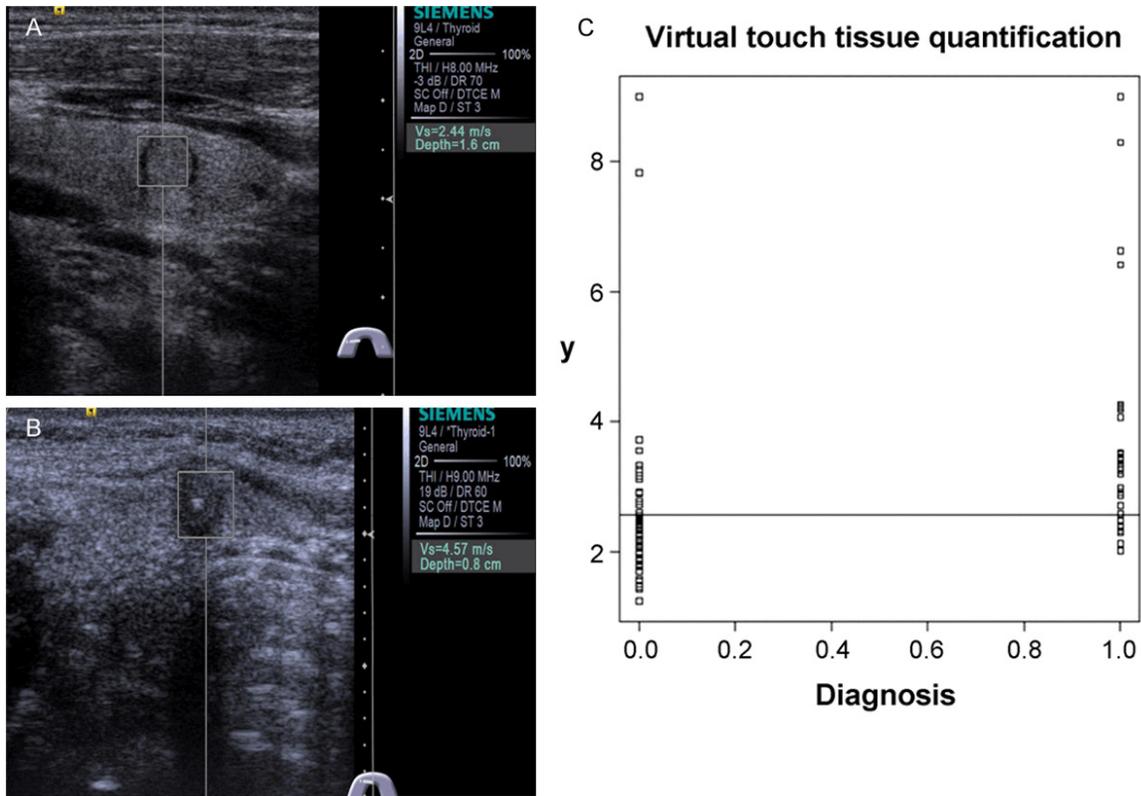
**Figure 2.** A. The Virtual Touch tissue quantification (VTQ) images of benign thyroid nodule in a 46-year-old woman. Shear wave velocity (SWV) was 2.44 m/s in the nodule. B. VTQ images of mPTC in a 37-year-old woman. SWV was 4.57 m/s in the nodule. C. Scatterplot shows distribution of the shear wave velocity. There are significant differences between the SWV of benign and malignant lesions ($P < 0.01$).

**Table 3.** Comprehensive analysis of the CTUDC and VTQ in 90 thyroid lesions

| Ultrasound classifications | Ultrasound presentations | Malignant | Benign | Total |
|---|---|---|---|---|
| Malignant | VTQ ≥ 2.57 m/s + CTUDC positive | 21 | 5 | 26 |
| Intermediate | VTQ < 2.57 m/s + CTUDC positive or VTQ ≥ 2.57 m/s + CTUDC negative | 15 | 19 | 34 |
| Benign | VTQ < 2.57 m/s + CTUDC negative | 0 | 30 | 30 |

nant lesions was estimated to be 2.57. By using the ROC curves, the SWV predicted malignancy with a sensitivity of 80.56%, specificity of 74.07% and gave an AUC of 0.825 (95% CI: 0.738-0.9001) (**Figure 1B**). In 90 thyroid lesions, The VTQ value of 4 lesions display as X.XX, one was benign, 3 was malignant.

*CTUDC + VTQ*

The results of comprehensive analysis for the CTUDC and VTQ were shown in **Table 3**. The malignant nodules were all classified as malignant and intermediate group; none of the malignant nodules were misdiagnosis as benign one. Only five benign lesions were misdiagnosis as malignant ones. Total of 37.78% (34/90) of nodules were classified into the intermediate group, meanwhile, in intermediate group, 44.11% (15/34i) was malignant, and 55.89% (19/34) was benign.

**Discussion**

The detection rate of smaller thyroid nodules has increased since the advent of high-resolution ultrasonography, although in small nodules it may be difficult to differentiate benign from malignant nodules. Ultrasound-guided fine-needle aspiration (US-FNA) is the most accurate method for diagnostic evaluation of thyroid nodules. According to the American thyroid association guidelines, US-FNA is recommend-

ed for nodules less than 10 mm, when the clinical information or US features are suspicious. The US features suggesting malignancy in large nodules may not be seen in all small nodules with high confidence due to the difficulty in assessing the internal architecture.

In the present study, the pattern of marked intra-nodular vascularity, taken alone, was not predictive of mPTC (AUC=0.5278). The diagnostic accuracy of color Doppler US remains controversial with respect to the differentiation of benign and malignant thyroid nodules [12, 13]. This may be caused of the technical parameters, such as settings of the wall filter, nodule depth, and pulse repetition frequency or unstandardized definition of vascularity patterns. Some studies also defined intra-nodular vascularity as blood flow within the nodule and neglected blood flow at the periphery [14, 15]. While other studies defined as more flow in the nodule than in the surrounding thyroid gland and more flow in the central part of the nodule than at the periphery [16]. Hong *et al.* [17] found that marked intranodular vascularity was more commonly observed in large thyroid nodules (especially for the nodules diameter > 10 mm) compared to the small thyroid nodules (for the nodules diameter range from 5 mm to 10 mm) in both malignant and benign nodules. Due to the unsatisfactory diagnostic performance of intranodular vascularity in this study and the controversial results of intranodular vascularity in previous studies in diagnosis of thyroid nodules, we did not adopt the intranodular vascularity in CTUDC in this study.

In this study, the B-mode ultrasound features has almost similar diagnostic performance in thyroid mPTC, and the AUC values were range from 0.6157 to 0.6574. The results also indicated that the hypoechogenicity and microcalcification has the highest sensitivity (77.78%) and specificity (85.18%), respectively. None of the B-mode ultrasound features are capable of detecting all canceous nodules, and almost 70% of histologically proved benign nodules may have one of the suspicious B-mode ultrasound features [18]. In present study, the combination of echographic patterns increased the specificity, but decreased the sensitivity of thyroid US, which is consistent with the previous report [19]. Rago *et al.* [19] assessed the combinations of two or three ultrasound features, and reported a wide range of sensitivities (3%

to 69%) and specificities (72% to 100%). According to our previous experience, we attempted to evaluate whether the CTUDR is a new criterion combined application of US features result in better diagnostic performance of mPTC. In this study, CTUDR has balanced and relatively satisfactory sensitivity and specificity (77.78% and 77.22%, respectively), the AUC of this method was 0.8226, significantly higher than single application of any conventional US indicator (the AUC range from 0.6157 to 0.6574). Furthermore, the CTUDR is entirely feasible in clinical work, does not require a complicated setup and only require an operator who can do the routine thyroid US and a one-time cost of the equipment.

Thyroid US elastography has been shown with the feasibility as a noninvasive screening tool, which can complement to traditional US to differentiate thyroid lesions [20, 21]. Other scientists [22, 23] evaluated the efficacy of US elastography in differential diagnosis of small thyroid nodules.

ARFI is a new technique of elastography that has been recently introduced into clinical practice and can overcome the limitations of previous elastography techniques that is capable of quantitatively measure the stiffness of nodules. In the present study, the SWV value of malignant small nodules were significantly higher compared to that of benign nodules. VTQ predicted malignancy with a sensitivity of 80.56%, and with a specificity of 74.07%, and gave an AUC of 0.825, higher than the AUC reported by Dighe et al. [23], which calculated a semi-quantitative index for each nodule. The best SWV cutoff value was 2.57 m/s in the present study, similar with 2.47 to 3.59 m/s reported in the previous study [24], these findings suggested that VTQ can effectively identify malignancy in thyroid nodules $\geq$ 10 mm in diameter. Using the SWV assessment method, VTQ had better diagnostic performance (AUC of 0.825) in small thyroid noudles as compared to any B-mode ultrasound feature (AUC=0.6157-0.6574).

However there are some limitations of the VTQ in clinical application, first, The SWV value of some nodules were displayed as X.XX m/s, the reason for a value of X.XX m/s include operator movements, patient respiration and tissue that was too hard and out of the range of the

machine. The target region with fixed dimension (6 mm × 5 mm) of VTQ limited it in diagnosis of the nodule that had a greatest diameter of 5 mm or less. Therefore, we believe that the diagnostic accuracy of small thyroid nodules can be improved by comprehensive analysis of the Structural information that can be revealed by conventional ultrasound and texture information than can be revealed by VTQ.

There is an overlap of elasticity between benign and malignant thyroid lesions in this study. Fourteen benign masses were recognized as malignant because their SWVs were above the 2.57 m/s threshold. On the other hand, seven malignant masses were misdiagnosed as benign because their SWVs were below the cutoff value. In the 21 misdiagnosis cases, six nodules were minimum lesions that the maximum diameter were range from 5 mm to 6 mm with the size small than the ROI of VTQ, therefore some normal surrounding tissue was included in the ROI and affected the result. Comprehensive analysis of the Structural information and texture information of the misdiagnosis cases were done to improve the diagnostic accuracy. In these fourteen benign masses recognized as malignant in VTQ, five nodules were also CTUDR positive, misdiagnosis as malignant lesions; nine nodules were assumed to be intermediate ultimately because they are CTUDR negative. All of the seven malignant masses misdiagnosed as benign had two or more conventional US characteristics that predictive of malignant thyroid lesion, were CTUDR positive, assumed to be intermediate ultimately.

After the Comprehensive analysis of CTUDR and VTQ of the small thyroid nodules, only five benign lesions were misdiagnosis as malignant ones, Histopathologic examination showed that two of the five benign lesions contained clustered micro-calcification. These might have altered the stiffness of the nodules. Apart from this, two atypical adenomas and one subacute thyroiditis have increased stiffness. Yang et al.'s report [25] indicate that subacute thyroiditis have greater hardness because of histological changes (disappearance of the follicular epithelium, replaced by a rim of histiocytes and giant cells, interstitial fibrosis, infiltration of lymphocytes, and plasma cells).

Our study had some limitations. Firstly, our study included a relatively small number of cases; the cutoff value of SWV needs to be confirmed in further studies with larger samples. Secondarily, only a few pathological types of thyroid lesions were studied. For example the malignant lesions included in our study were all mPTC. Further studies with various thyroid lesions are needed to confirm our results. Third, the size of ROI (0.5 cm × 0.6 cm) was fixed and could not be altered which affect the placement of ROI. In some cases, the surrounding tissue would inevitably be included in the ROI, which could affect the accuracy of VTQ.

In conclusion, the VTQ of ARFI technology can be applied in diagnosis of small thyroid nodules. The combination of conventional US and SWV measurements did significantly improve the diagnostic performance in diagnosis of mPTC. The current guidelines for managing small thyroid nodules could be improved by taking the elastography results into account in addition to US features and clinical information.

## Acknowledgements

## Disclosure of conflict of interest

None.

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