Original Article

Accuracy of Elastography Alone and in Combination with Siriraj TIRADS in Predicting Thyroid Nodule Malignancy

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Objective: To evaluate the accuracy of elastography alone and a combination of elastography and Siriraj thyroid imaging reporting and data system (TIRADS) in predicting malignant risk of thyroid nodule.

Materials and Methods: Between June 2011 and May 2013, 114 thyroid nodules in 112 patients that underwent ultrasound (US), guided nodule's biopsy with US elastography, and had available pathologic results were included. Tissue stiffness on US elastography was retrospectively scored using the Ueno and Ito score, and grey scale ultrasonography was scored using the Siriraj TIRADS. Sensitivity and specificity were calculated for both US elastography alone and combination of US elastography and TIRADS.

Results: On the US elastography, 12 cases had a score of 1 and were all benign lesions, 53 cases had a score of 2 in which there was one malignant and 52 benign lesions, 40 cases had a score of 3 in which there was 4 malignant lesions and 36 benign lesions, eight cases had a score of 4 in which there was seven malignant lesions and one benign lesion. There was no lesion with a score of 5. Sensitivity and specificity of the US elastography were 58.3% and 99%, respectively. Sensitivity and specificity of combination of the US elastography and the Siriraj TIRADS were 58.3% and 100%, respectively.

Conclusion: The US elastography is a potential additional tool in diagnosis of malignant thyroid nodule with high specificity and high accuracy, especially when combined with the Siriraj TIRADS score that is used in cancer screening.

Keywords: Elastography, Siriraj TIRADS, Thyroid nodule malignancy

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Thyroid nodules have a high prevalence. About 40% of the adult population have thyroid nodules on ultrasonographic examination(1), and 7% of them are malignant(2). Several ultrasound (US) characteristics such as solid nodules, hypoechoic nodules, containing micro calcification, and central hypervascularization(3) have been used to identify nodules at risk for being malignant and the nodule chosen for fine needle aspiration (FNA) biopsy. The malignant thyroid nodules were confirmed or treated with thyroidectomy.

The US elastography is a recently developed technique that uses US to provide tissue stiffness by measuring the degree of distortion under the application of external force, based on the principle that the soft parts of tissue are more distorted compared to solid parts. In clinical evaluation, a firm or hard, solitary thyroid nodule that clearly differs from the rest of the gland suggests an increased risk of malignant involvement(4) because pathological processes change the structure and ultimately the elastic properties of the tissue(5). However, physical examination is very subjective and variable, so the US elastography has been applied to evaluate tissue stiffness.

Rago et al applied the Ueno and Ito elasticity score to classified elasticity color scale from one to five, and the study showed that the US elastography has a great potential as an adjunctive tool for diagnosis of thyroid cancer(6).

Furthermore, Horvath et al has developed thyroid imaging reporting and data system (TIRADS) to group thyroid lesions in different categories with a

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percentage of malignancy similar as the breast imaging reporting and data system (BIRADS) concept(7). However, because Horvath et al's reporting system has some overlapping findings and many details, it causes confusion when used in real practice. Therefore, in Thailand, Songsaeng et al(8) has been developing the Siriraj reporting system, which is simpler than Horvath et al's reporting system. Using the score, which has a high sensitivity of cancer prediction and moderate specificity, is sufficient to predict benign lesions.

The aim of the present study was to evaluate the accuracy of the US elastography alone and the combination of the US elastography and the Siriraj TIRADS in predicting malignant risk of thyroid nodule.

Materials and Methods

The present report was a 2-year retrospective study of the medical records between June 2011 and May 2013. The study included 112 patients with 114 thyroid nodules submitted for ultrasonography-guided FNA biopsy and a US elastography with a satisfactory specimen for pathological evaluation. Patients with mainly cystic nodule were excluded because of the US elastography cannot give information due to the main determinant nodule stiffness being fluid content(6).

The US equipment was the Philips iU22 (Philips Healthcare, Andover, MA) that provided the advanced breast mode protocol with a 5 to 12 MHz linear probe. The US elastographic measurement was performed during the US examination, by using the same probe. Then, a box was highlighted by the specialized radiologist in an area that included the nodule to be evaluated. Consequently, the US elastogram was displayed over the B-mode grey scale images with color scale ranging from red, for softest or highly compressible tissue, to blue for hardest or non-compressible tissues. The US elastographic images were matched with the elasticity color scale. Accordingly, thyroid tissue-to-nodule strain ratio or elasticity index was also measured to provide quantitative values for nodule hardness compared to the normal tissue.

The FNA biopsy was performed by the same radiologist, under the US guidance using a 25-gauge needle attached to a 10-cc syringe. Upon aspiration a negative pressure was maintained until blood appeared in the hub of the syringe. Few drops of blood were placed on four glass slides. Three glass slides were placed in 95% alcohol and one glass slide was sent in an air-dry technique. Then, routine histological study was performed. Seventy-nine nodules with inadequate cytologic results, including only cyst fluid in 42 nodules, obscuring blood in 18 nodules, no follicular cell in 13 nodules, and air-drying artifact in 6 nodules, were excluded from the study. The histological result of the FNA biopsy was classified as benign, atypia of undetermined significance or malignant. According to the standard pathological criteria, 14 nodules were reported as atypia of undetermined significance, therefore, were excluded. The 62 aspirated thyroid nodules without US elastography performed and another 20 mainly cystic (>50%) nodules were also excluded. Finally, the remaining 114 nodules were included in the present study.

A third-year radiology resident and a 12-year experienced radiologist, blinded to the histopathological result reviewed the conventional images and scored each nodule on the basis of the Siriraj TIRADS, which classification was as categorized below:

TIRADS 0: normal thyroid gland without thyroid nodule.

TIRADS 1: cyst, colloidal cyst with comet tail. Meaning highly suggestive of benign nodule.

TIRADS 2: spongioform pattern: heterogenous echo, macrocalcification and benign calcification, cystic nodule with intramural solid component. Meaning probably benign. Advised management to follow up US in the next six months.

TIRADS 3: well-defined mass with micro-calcification. Meaning undeterminated. Advised management to go on FNA biopsy and short-term follow up US if non-diagnostic cytologic result.

TIRADS 4: ill-defined mass with or without microcalcification. Meaning probably malignant. Advised management to FNA biopsy and do an immediate re-aspiration if non-diagnostic FNA result.

TIRADS 5: spiculated mass, outgrowth lesion. Meaning highly suggestive of malignancy. Advised management to consider surgery regardless of FNA biopsy result.

TIRADS 6: proven malignancy. Advised management to go on further appropriate action.

The US elastography images were reviewed and scored by another third-year radiology resident and the 12-year experienced radiologist blinded to the histopathological result using the Ueno and Ito elasticity score(6) as described below (Figure 1):

Score 1: elasticity in the whole nodule

Score 2: elasticity in a large part of the nodule

Score 3: elasticity only at the peripheral part of the nodule

Score 4: no elasticity in the nodule

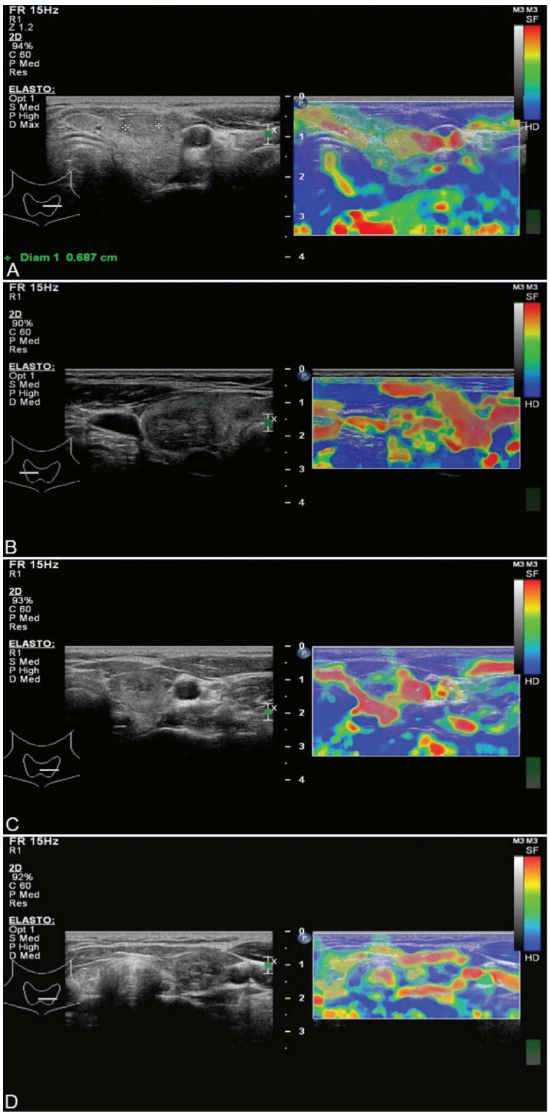

Figure 1. (A) Benign follicular nodule (Ueno and Ito elasticity score 1), (B) Benign follicular nodule (US elasticity score 2), (C) Nodular goiter (US elasticity score 3), and (D) Papillary thyroid carcinoma (US elasticity score 4).

Score 5: no elasticity in the nodule and in the posterior shadowing.

The elasticity index was calculated by choosing the region of interest (ROI) and obtained the ratio of elasticity of nodule to adjacent normal tissue (thyroid tissue-to-nodule strain ratio) (Figure 2).

Statistical analysis

The SPSS Statistics 18.0 was used for the statistical analysis. Interobserver agreement on scoring of the US elastography between the third-year resident and the 12-year experienced radiologist was analyzed by using kappa statistics. Sensitivity, specificity, and accuracy were calculated for the US elastography score and divided as score 1, 2, and 3 as benign and score 4 and 5 as malignant[6]. The Siriraj TIRADS was divided as score 1, 2, 3 as benign and score 4 and 5 as malignant, then sensitivity, specificity, and accuracy of combination of the US elastography and the Siriraj TIRADS were also calculated. A p-value of less than 0.05 was considered to indicate a significant difference. ROC curve analysis of elasticity index was used to estimate cut-off value to predict cancer.

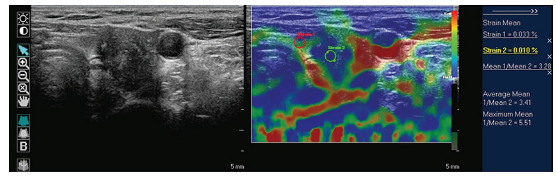

Figure 2. The elasticity index calculation by choosing the region of interest and obtaining the ratio of elasticity of nodule to adjacent normal tissue.

Results

One hundred fourteen nodules from 112 patients were included in the present study. Of the 114 nodules, 102 (89.5%) were benign at histology with nodular goiter, benign follicular nodule, benign cystic lesion, follicular adenoma, and four thyroiditis. Of 114 nodules, 12 (10.5%) had the final diagnosis of malignancy with six papillary thyroid carcinoma, four papillary microcarcinoma, one suspected of follicular neoplasm of oncocytic type, and one follicular carcinoma.

The kappa statistic of inter-observer agreement for the US elastography score was 1.0. The number and percentage of benign and malignant nodules in each US elastrography and Siriraj TIRADS categories are shown in Table 1 and 2.

Sensitivity and specificity of the US elastography were 58.3% and 99% as shown in Table 3, and positive predictive value of 87.5% and negative predictive value of 95.3%. One and two of three papillary microcarcinoma had a score of 2 and 3, respectively (Figure 3).

Three papillary microcarcinoma had the Siriraj TIRADS category of 4. One of six papillary thyroid carcinoma had score of 3 and the suspected follicular neoplasm, oncocytic type, which histological diagnosis from total thyroidectomy showed nodular

Table 1. US elastography

Elastography	Benign (n=102) n (%)	Malignant (n=12) n (%)	Total (n=114) n (%)
1	13 (100)	0 (0.0)	13
2	52 (98.1)	1 (1.9)	53
3	36 (90.0)	4 (10.0)	40
4	1 (14.3)	7 (87.5)	8
5	0 (0.0)	0 (0.0)	0

US=ultrasound

Table 2. Siriraj TIRADS

TIRADS	Benign (n=102) n (%)	Malignant (n=12) n (%)	Total (n=114) n (%)
1	0 (0)	0 (0)	0
2	25 (100)	0 (0)	25
3	30 (100)	0 (0)	30
4	44 (83)	9 (17)	53
5	3 (50)	3 (50)	6

TIRADS=thyroid imaging reporting and data system

Table 3. Sensitivity and specificity of US elastography

US elastography	Final pathological diagnosis, n (%)		Total
	Benign	Malignant	
Score 1, 2, 3	101 (99.0)	5 (41.7)	106
Score 4, 5	1 (1.0)	7 (58.3)	8
Total	102	12	114

US=ultrasound

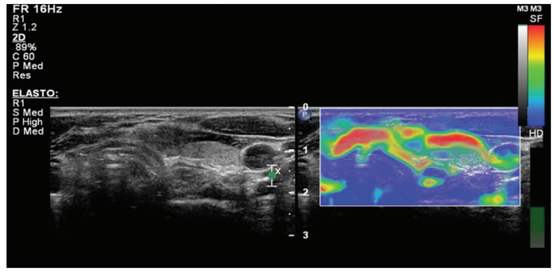

Figure 3. Papillary microcarcinoma at left side of isthmus had US elasticity score 3.

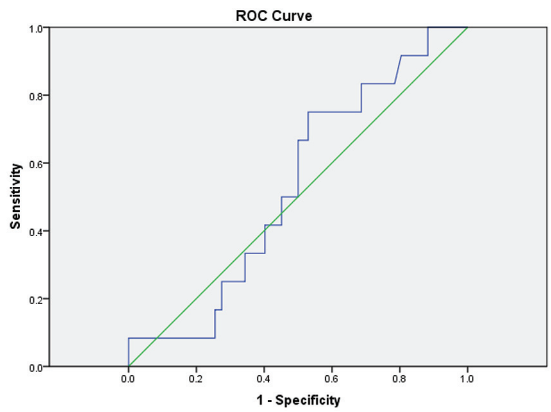

Figure 4. The ROC curve for distinguishing malignant from benign thyroid nodules using elasticitiy index.

goiter with oncocytic cell metaplasia had score of 3.

US elastography measurement was independent from nodule size and their position within thyroid lobe. High specificity and fair sensitivity were still observed with p-value of 0.094 for size and 0.954 for location, as shown in Table 4 and 5. However, there was increased sensitivity of the US elastography in larger (greater than 2 cm) nodules.

Fifty-nine thyroid nodules with malignant categories of the Siriraj TIRADS had 52 nodules, assessed as benign, and seven nodules assessed as malignant on the US elastography, as shown in Table 6.

The seven nodules with malignant categories on the Siriraj TIRADS and the US elastography had a final histological diagnosis of malignancy. In the present study, malignant categories of the Siriraj TIRADS (score 4 to 5) in combination with malignant scores of the US elastography (score 4 to 5) had specificity of 100%, sensitivity of 58.3%, negative predictive value of 93.5%, and positive predictive value of 100% for malignant thyroid nodules, compared with 53.9% specificity and 100% sensitivity as shown in Table 7.

The elasticity index of all malignant nodules in the present study was higher than 0.57. Using an elasticity index cut-off value of 0.57 led to sensitivity of 100% and specificity of 11.8% in detecting malignant thyroid nodules. An elasticity index cut-off value of 3.215 led to sensitivity of 25% and specificity of 72.5%. The ROC curve to distinguish malignant from benign thyroid nodules using elasticity index is shown in Figure 4. The area under the ROC curve for diagnostic malignant nodules was 0.532.

Discussion

The US elastography is a technique developed to evaluate degree of distortion of tissue under application of external force that represents tissue stiffness. It has recently been used for the investigation of many

Table 4. Sensitivity and specificity of US elastography according to size of thyroid nodules

Size	Score	Benign	Malignant	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
0.1 to 1 cm	1 to 3	16	2	50.0 (6.8 to 93.2)	94.1 (71.3 to 99.9)
	4 to 5	1	2		
1.1 to 2 cm	1 to 3	33	2	60.0 (14.7 to 94.7)	100.0 (89.4 to 100.0)
	4 to 5	0	3		
>2 cm	1 to 3	52	1	66.7 (9.4 to 99.2)	100.0 (93.2 to 100.0)
	4 to 5	0	2		

US=ultrasound; CI=confidence interval

Table 5. Sensitivity and specificity of US elastography according to position of nodules in thyroid lobe

Position in thyroid lobe	Score	Benign	Malignant	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Upper	1 to 3	83	4	50.0 (15.7 to 84.3)	98.8 (93.5 to 99.9)
	4 to 5	1	4		
Lower	1 to 3	18	1	75.0 (19.4 to 99.4)	100.0 (81.5 to 100.0)
	4 to 5	0	3		

US=ultrasound; CI=confidence interval

Table 6. Siriraj TIRADS and US elastography

Categories	Total number of nodules	Benign elastography (score 1 to 3)	Malignant elastography (score 4 to 5)
Benign Siriraj TIRADS	55	54	1
Malignant Siriraj TIRADS	59	52	7

US=ultrasound; TIRADS=thyroid imaging reporting and data system

Table 7. Increased diagnostic accuracy of the Siriraj TIRADS in detection of malignant thyroid nodule, by combining the results of Siriraj TIRADS with US elastography

Categories	Sensitivity	Specificity	PPV	NPV	Accuracy
Siriraj TIRADS	100%	53.9%	20.3%	100%	58.8%
US elastography	58.3%	99%	87.5%	95.3%	94.7%
Siriraj TIRADS with US elastography	58.3%	100%	100%	95.3%	95.6%

TIRADS=thyroid imaging reporting and data system; PPV=positive predictive value; NPV=negative predictive value

disease conditions in many organs. This provided additional diagnostic information from routine anatomical image. Similar to clinical evaluation(4), a firm or hard consistency solitary thyroid nodule noted by tissue stiffness on the US elastography that differs from the rest of the gland, is suggestive of an increased risk of malignant involvement.

In a previous study(6) of Ueno and Ito consisting of 92 thyroid nodules in which 31 of them were malignant nodules of papillary thyroid carcinoma, invasive follicular carcinoma, and medullary carcinoma, using the US elastography scoring system for predicting malignancy, they found high elasticity scores (4 to 5) related to greater nodular consistency representing malignancy (sensitivity 97% and specificity of 100%). The authors' study was in correlation to the previous study(6) in term of high specificity (99% versus 100%) but not high sensitivity (58.3% versus 97%). Fair sensitivity found in the present study was attributed to three of five (60%) pathological proved malignant thyroid nodules, which were scored in range of benign US elastography score but came out to be

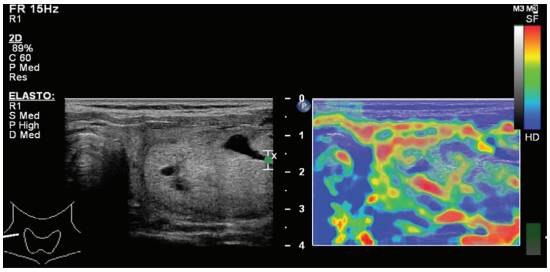

Figure 5. Papillary thyroid carcinoma with US elasticity score 3 There is large area of red, yellow and green (soft elasticity) with some area of blue (hard elasticity) cause heterogenous elasticity in the large nodule.

a microcarcinoma. Similarly, Moon et al reported the same finding as the present study[9]. Ninety-seven of 126 (76.9%) nodules of papillary microcarcinoma were classified into soft Rago score with a score 1 to 3, using a similar scoring system as Ueno and Ito. However, by using the scoring systems of either Rago or Ueno and Ito, the scores for evaluating all kinds of malignant thyroid nodule with the US elastography seemed still imperfect.

The predictivity of the US elastography is found independently from the nodule size and position within the thyroid lobe in the present study as well as reported by previous studies[6,10]. Nevertheless, we observed inconsistent minimal increases in sensitivity and specificity on centimeter nodules compared to sub-centimeter nodules. False result in elastography study related to non-uniform pressure given through a large, sized larger than 3-cm, malignant nodule with a pathologic finding of papillary thyroid carcinoma has been reported on the Egyptian study[11]. The finding was in agreement with one of our false negative large thyroid nodules (Figure 5). Previous mention of the US elastography limitations included predominant cystic lesions where the external pressure is not transmitted, the shell calcification caused no compressibility[12], and the nodule close to the carotid artery created elastographic images from the arterial pulsation[13].

The elasticity score index is a semi-quantitative analysis providing a quantitative value for the hardness of the nodule compared to the normal tissue. Selection of the reference tissue might affect the results, Zhi et al[12] study of elastography on solid breast nodule recommended the breast tissue at the same depth as the lesions to be used as the reference. Recent study[9] reported that using an elasticity index cut-off value of 3.5 led to a sensitivity of 88% and a specificity of 86.4% (AUC of 0.87) in differentiating benign and malignant thyroid nodules. That study used longitudinal thyroid view to provide enough reference tissue at the same depth with the target nodule as reference. Another study[13] using ROI at the center of the thyroid nodule as the lesion and the surrounding thyroid tissue in the same depth for reference reported that a strain ratio of 2.9 or greater had a sensitivity of 87% and a specificity of 92%. In contrast to previously reported studies, the authors failed to find a cut-off value with good sensitivity and specificity related to the area under the ROC curve. The reason is probably related to inappropriate selection of a reference tissue and placement of reference tissue plane. Heterogeneous elasticity of thyroid parenchymal tissue from patient factor such as age or underlying disease was speculated to be the cause of the difficulty to locate a proper ROI in reference to thyroid tissue. However, as of now, and as far as we know, there was no such study regarding elastography and normal developing and aging thyroid tissue and disease that affected thyroid parenchymal tissue such as Grave's disease, goiter, or Hashimoto's thyroiditis yet.

The conventional ultrasonography is an important method in thyroid nodule screening for malignancy and in guiding FNA biopsy. Many studies suggested some suspicious ultrasonographic features that raises suspicion of malignancy and established basic criteria to select nodules for FNA biopsy to minimize cost and maximize benefit[2-6]. Our prior study developed a practical and convenient TIRADS for the management of thyroid nodule, so-called the Siriraj TIRADS[8]. That Siriraj TIRADS score was applied in the present study. The thyroid nodules with the Siriraj TIRADS score of 1, 2, 3 have a low probability of malignancy with high sensitivity. However, using only the Siriraj TIRADS to evaluate the thyroid nodules, 64.8% of specificity was achieved and may falsely lead to over further investigate, for example FNA. However, the FNA is acceptable as it comes with low risk of complication, which is about 1%[14]. It is still invasive, not fully safe, and has risk of complication such as neck pain or discomfort, hematoma, infection, and transient neck swelling[15].

With even minimal risk of FNA, the present study was conducted with an aim for improvement of diagnostic specificity and accuracy in detecting malignant thyroid nodule, and if possible, to replace FNA. Seemingly, the US elastography alone was close and the US elastography combined with conventional US (with the Siriraj TIRADS) result in high specificity, which was even closer to fulfill that

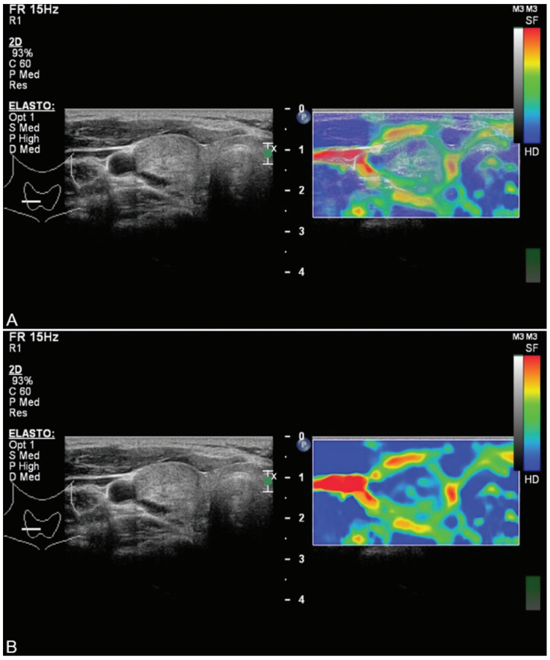

Figure 6. US elastographic images. (A) Fusion of conventional US images and colored showed large area of green color (soft elastography) in right thyroid nodule. (B) colored US elastography showed central area of blue color (hard elastography) which was not obviously seen in fused image.

purpose(16). As was already stated on the AACE/AME/ETA guidelines 2010 for diagnosis and management of thyroid nodules(4) and from the present study, the authors believe that the US elastography with combined conventional US study are more beneficial for assessment of thyroid nodule rather than MRI and CT. While doing the present study, the potential benefit of the US elastography as a guiding tool for choosing a specific area within the thyroid nodule representing malignancy was also suspected. The topic needs further larger population study for verification.

The limitation of the present study was small population of malignant thyroid nodules to represent the prevalence of malignant nodules in the study patients sent for FNA biopsy. Second, the analyzed images in the US elasticity evaluation were the fusion of B-mode grey scale images and the colored US elastographic images. That may cause some distortion of color in elastographic images and affected the process of choosing the tissue plane and placing the ROI of reference tissue as shown in Figure 6. However, the technical error happened in only the early phase of the study. Being familiar with the software is necessary and is recommended. For the last limitation, the present study lack of thyroid nodule that has US elastography scoring of 5. However, it did not affect the statistical evaluation of the results. Nodule with either grade 4 or 5 was classified within the same group of malignant potency. Further study with large number of malignant thyroid nodules are encouraged to find the relationship between subtype of malignant thyroid nodule and pattern of elastography that may eventually able to avoid unnecessary FNA.

Conclusion

The US elastography proved to be a potential tool in diagnosis of malignant thyroid nodule with high specificity and high accuracy. Higher accuracy can be achieved when it is combined with conventional US study (with the Siriraj TIRADS score). Routine use in clinical practice is recommended. With their good quality, replacement of FNA may be possible in the future.

What is already known on this topic?

The US elastography is a tool in diagnosis of malignant thyroid nodule.

What this study adds?

When combined with the Siriraj TIRADS score, which is used in cancer screening, the US elastography is a potential tool in diagnosis of malignant thyroid nodule.

Conflicts of interest

The authors declare no conflict of interest.

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