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A dilemma at gray scale thyroid ultrasound: microcalcification or not? Differentiation with Acoustic Radiation Force Impulse Imaging – Virtual Touch Imaging

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Abstract

Aims: To evaluate the capacity of virtual touch imaging (VTI) of the acoustic radiation force impulse (ARFI) technique in the differential diagnosis of micro-echogenicities in thyroid nodules. **Material and methods:** The study comprised 28 patients. Gray scale and ARFI displacement maps were used during ultrasound examination. In the same session, fine needle aspiration biopsy (FNAB) samples were obtained from the dominant nodule having micro-echogenicities. Two radiologists blinded to the FNAB results and clinical data of the patients evaluated these images and rated ARFI echogenicities according to the degree of shining points on the displacement maps and classified them as isohypoechogenic, isohyperechogenic, and obvious hyperechogenic. To differentiate between benignancy and malignancy, "a new sign" was defined as follows: in the ARFI maps obtained by VTI, iso-echogenic or hyper-echogenic appearance of micro-echogenic foci was evaluated as benignancy and hypo-echogenic appearance of micro-echogenic foci was evaluated as malignancy. **Results:** The FNAB results indicated 14 cases and benign nodules in the other 14 cases. Interobserver agreement between the two radiologists was highly significant for the classification of the micro-echogenic foci (Kappa=0.659, $p<0.001$). When we reclassified the hyperechoic and isohyperechoic foci as "benign" and isohypoechoic foci as "malignant", the interobserver agreement between the two radiologists increased (Kappa=0.772, $p<0.001$). The evaluation of the first and second radiologists were highly concordant with the gold standard pathology results (Kappa=0.786, $p<0.001$ and Kappa=0.714, $p<0.001$, respectively). **Conclusions:** ARFI method with specific VTI features could be a very useful tool in the differentiation of malignant microcalcifications in thyroid nodules.

Keywords: microcalcification, ultrasonography, elastography, thyroid nodule, Acoustic Radiation Force Impulse Imaging

Introduction

Nodular thyroid disease is very common in the adult population with a prevalence of 40% [1]. Although most of them are benign, a considerable amount of thyroid nodules (5%-10%) are malignant [1,2]. Today, conventional ultrasound (US) is considered to be the best modality for the diagnosis and evaluation of thyroid nodules. Although being accurate at diagnosis, conventional US is not a satisfying and adequately reliable tool in the differentiation of benign and malignant nodules [3,4]. Malignancy criteria for the thyroid nodules by conventional US includes: microcalcifications, irregular margins, hypoechogenicity, a taller-than-wide shape, and predominantly centric intranodular vascularity [5,6]. However, specificity, sensitivity, negative, and positive predictive values of conventional US vary considerably between the studies [7,8].

A new US elastography technique, namely the acoustic radiation force impulse (ARFI) technique, has been recently introduced. ARFI technique is a non-invasive

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method that provides information about localized mechanical properties of the tissues using short-duration, high-intensity, and acoustic pulses to generate localized displacements in the target tissues [9]. Recently, several studies have shown the feasibility of the ARFI technique for the differentiation of thyroid nodules [10,11]. The presence of microcalcifications in thyroid nodules is considered a dominant criterion for malignancy [12].

Colloid debris or colloidal crystals usually do not form typical reverberation artifact known as the comet-tail artifact; this may lead to a diagnostic confusion. Additionally, this confusion may lead to over- or under-diagnosis [13]. The present study aimed at evaluating the capacity of virtual touch imaging (VTI) of the ARFI technique in the differential diagnosis of micro-echogenicities found in thyroid nodules.

Materials and methods

Approval for this study was obtained from the Local Ethics Committee of Istanbul University Cerrahpasa Medical Faculty. Twenty-eight patients with thyroid nodules containing micro-echogenicities were included (26 females and 2 males, mean age: 37 years) in this prospective study. All nodules were hypo-echogenic compared with the strap muscles. Nodules that were interpreted to have benign colloid crystals (with typical reverberation sign) were excluded. Nodules with micro-echogenities that were observed to have microcalcifications were included in the present study. Histopathological examination of the thyroid nodule specimens obtained by fine needle aspiration biopsy (FNAB) was performed in the same center. Nodules with Bethesda group 1 and 3 according to the histopathological findings of the specimens were excluded from the study. The nodules of 14 patients (13 females and 1 male; mean age: 35 years) were malignant and these patients were diagnosed as thyroid cancer. The nodules of the remaining 14 patients (13 females and 1 male; mean age: 38 years) were benign nodules (hyperplastic colloid nodules). The FNAB results of all benign nodules were reported as Bethesda group 2. None of the included malignant nodules were reported as Bethesda group 4. None of the cases with benign FNAB results were operated. Thirteen nodules with malignant FNAB results were operated: 11 were reported as classic papillary thyroid carcinoma, one was reported as follicular variant papillary carcinoma, and the histopathological results could not be obtained in one patient and this case was accepted as malignant (Bethesda group 5).

Ultrasound examinations of the cases were performed with a 9 MHz linear transducer by a single radiologist (DY) using the ACUSON S2000 HELX Evolution (Siemens, Erlangen, Germany) device. Gray scale imaging was performed using the abundant ultrasound gel ensuring full contact with the skin. In the present study, there were no dense microcalcifications and macrocalcifications that might interrupt ARFI examination. Different from the shear wave elastography (SWE), the size of the region of interest (ROI) could be changed during ARFI examination. After routine gray scale imaging, VTI window was activated. After selecting the largest ROI covering the nodule, a pulse wave was transmitted at the ARFI mode. Meanwhile, on the US monitor, while there were gray scale image and the ROI on the left side, the VTI image was generated on the right side in the dual window. The gray scale and VTI displacement maps of the nodule were compared by targeting the simultaneous small ROIs and micro-echogenic foci. We selected the ROI as a section having a more prominent micro-echogenic foci and used the largest possible ROI in that region to cover a large part of the nodule. During the examination, the gray scale images showing micro-echogenic foci were recorded. Immediately after the sections of these micro-echogenicities were shown, the images were recorded with ARFI method and gray scale displacement maps were obtained. All nodules were located 1-4 cm in depth and there was no obvious artifact that might interrupt the ARFI examination. Nodules and micro-echogenicities within the lesions were marked with small ROI and projections of these micro-echogenicities were found on the ARFI map. Digital images of the US examinations were recorded and stored. These images were evaluated by two different radiologists blinded to the FNAB results and clinical data. The radiologists rated ARFI echogenicities according to the degree of shining points on the displacement maps and divided them into three separate classes: isohypoechogenic, isohyperechogenic, and obvious hyperechogenic.

In the present study, to differentiate between benignancy and malignancy, “a new sign” was defined as follows: in the nodules containing echogenic foci on the gray scale window, iso-echogenic or hyper-echogenic appearance of these micro-echogenic foci in the ARFI maps obtained by VTI were interpreted as benign and hypo-echogenic appearance of these micro-echogenic foci in the ARFI maps obtained by VTI were interpreted as malignant.

In the same session, FNAB samples were obtained directly by targeting the dominant nodule with micro-echogenicities. The samples were spread as a thin layer to a slide and dried in air and transferred to the cytopathology laboratory. The materials were stained with May-Grünwald-Giemsa (MGG) stain in the pathology laboratory. Pathological examination was performed under a light microscope.

In Figures 1 and 2, we exemplified our work in two nodules (a benign and a malignant nodule).

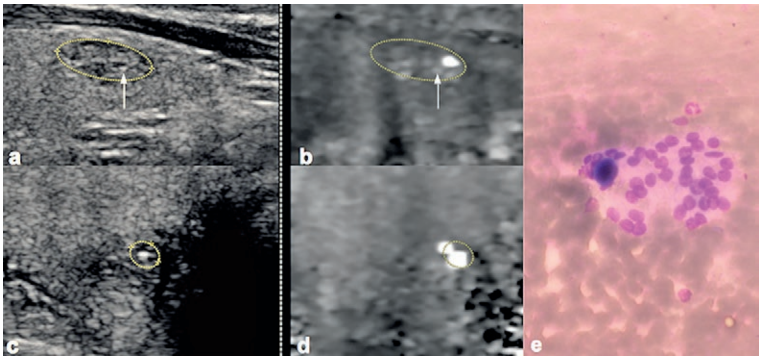

Fig 1. A 54-year-old female patient. Fine needle aspiration biopsy (FNAB) was performed on the nodule containing microcalcifications in the lower pole of the left thyroid lobe; a) on the gray scale image, micro-echogenic foci are seen through the entire nodule (ellipsoid area), b) visualization of the shining foci with virtual touch imaging (VTI), c) one of the marked dominant echogenic foci on the gray scale image shows (d) augmented homogeneous shining on the VTI image (smaller encircled areas), e) cytopathological image: cellular aspirate of hyperplastic nodule contains colloidal monolayer sheet of cells and colloid and blue material. The cells have narrow and pale cytoplasm, small nuclei with regular contours, and light chromatin (May-Grünwald-Giemsa (MGG) stain, ×400 magnification).

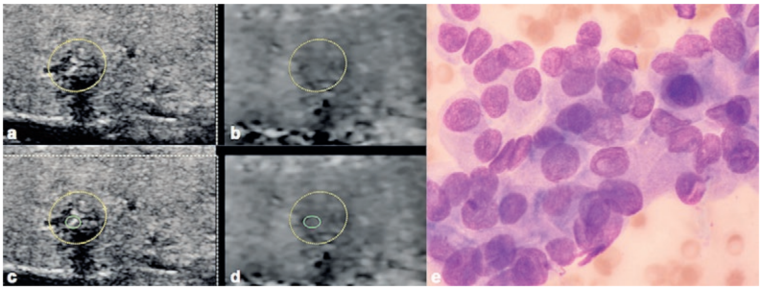

Fig 2. A 38-year-old female patient. Fine needle aspiration biopsy (FNAB) was performed on the nodule containing microcalcifications in the lower pole of the right thyroid lobe; a) many micro-echogenic foci are seen within the nodule (encircled areas) on the gray scale image, b) on the virtual touch imaging (VTI), these hyperechoic foci do not appear as on the gray scale image, c) the dominant one of the micro-echogenic foci on the gray scale image appears as isoechogenic on the VTI image (d) as encircled small areas, e) cytopathological image: hypercellular aspirate has a monolayer sheet of colloidal cells, with papillary architecture. No colloid material. In addition to having dense squamoid cytoplasm, cells with enlarged, overlapping eccentric nuclei with irregular contours plus intranuclear inclusions and dark, fine granular chromatin represent papillary thyroid carcinoma (May-Grünwald-Giemsa (MGG) stain, ×1,000 magnification).

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (version 15.0; SPSS Inc., Chicago, IL, USA) for Windows. Statistical significance level was set at $p<0.05$ with a confidence interval of 95%. Concordance between the data obtained by two different radiologists was evaluated using the Kappa analysis. Additionally, based on the gold standard, discrimination powers of the radiologists were also evaluated. The sensitivity, specificity and accuracy values for two radiologists in discriminating the malignant and benign lesions were also calculated.

Results

Among the nodules of 28 patients, the first radiologist identified 12 ARFI echogenicities as hyperechoic, 5 ARFI echogenicities as isohyperechoic, and 11 ARFI echogenicities as isohypoechoic. The second radiologist identified 13 ARFI echogenicities as hyperechoic, 5 ARFI echogenicities as isohyperechoic, and 10 ARFI echogenicities as isohypoechoic. Interobserver agreement between the two radiologists was highly significant for the classification of the micro-echogenic foci with a Kappa value of 0.659 ($p<0.001$; Table I). When we reclassified the hyperechoic and isohyperechoic foci as "benign" and isohypoechoic foci as "malignant", the interobserver agreement between the two radiologists increased; the Kappa value was 0.772 ($p<0.001$; Table II).

The evaluation of the first radiologist was highly concordant with the cytopathology results (Kappa value=0.786, $p<0.001$; Table III). When we accepted the evaluation of the first radiologist as a diagnostic test, the sensitivity, specificity, and accuracy values for the first

Table I. Interobserver agreement between the two radiologists for classifying the micro-echogenic foci

		Second radiologist			p	Kappa Value
		Hyperechoic n (%)	Isohyperechoic n (%)	Isohypoechoic n (%)		
First radiologist	Hyperechoic, n (%)	11 (91.7)	1 (8.3)	0 (0.0)	<0.001	0.659
	Isohyperechoic, n (%)	2 (40.0)	2 (40.0)	1 (20.0)		
	Isohypoechoic, n (%)	0 (0.0)	2 (18.2)	9 (81.8)		

Table II. Interobserver agreement between the two radiologists for identifying benign (hyperechoic and isohyperechoic) and malignant (isohypoechoic) nodules

		Second radiologist		p	Kappa Value
		Benign n (%)	Malignant n (%)		
First radiologist	Benign, n (%)	16 (94.1)	1 (5.9)	<0.001	0.772
	Malignant, n (%)	2 (18.2)	9 (81.8)		

Table III. Concordance of the evaluation of the first reader with the gold standard pathology results

		First Radiologist		p	Kappa Value
		Benign, n (%)	Malignant, n (%)		
Pathology result	Benign, n (%)	14 (100.0)	0 (0.0)	<0.001	0.786
	Malignant, n (%)	3 (21.4)	11 (78.6)		

Table IV. Concordance of the evaluation of the second radiologist with the gold standard pathology results

		First Radiologist		p	Kappa Value
		Benign, n (%)	Malignant, n (%)		
Pathology result	Benign, n (%)	14 (100.0)	0 (0.0)	<0.001	0.714
	Malignant, n (%)	4 (28.6)	10 (71.4)		

radiologist in discriminating the malignant and benign lesions were 0.79, 1.00, and 0.89, respectively. The evaluation of the second radiologist was also highly concordant with the gold standard cytopathology results (Kappa value=0.714, $p<0.001$; Table IV) and in this case, the sensitivity, specificity, accuracy values for the second radiologist in discriminating the malignant and benign lesions were 0.71, 1.00, and 0.86, respectively.

Discussions

Virtual Touch Imaging is available in some US systems (the ACUSON S2000™ and ACUSON S3000™ ultrasound systems) implementing ARFI technology for the evaluation of tissue stiffness. VTI provides a qualitative gray scale map (elastogram) of relative stiffness for a user-defined ROI. With the use of VTI, the stiff tissue can be differentiated from the soft tissue even it appears isoechoic with conventional US imaging [10]. This technology has been used for routine thyroid ultrasound examination in our institution since 2012. The new sign, which was defined in the present study for the nodules containing micro-echogenicities, particularly necessitates the use of VTI mode and have a different method and goal from the other elastography techniques in the real time or shear wave mode, which have been used in the literature [10,14].

To date, in both strain and SWE techniques, physicians always compared the stiffness values of the nodule and parenchyma to differentiate malignant lesions from benign lesions [15-17]. In these studies, by US elastography combined with gray scale ultrasonography, the researchers have tried to differentiate benign and malignant thyroid nodules with a relatively significant degree of sensitivity ranging from 75% to 96%. Different from these studies, in the present study, we aimed to evaluate the ability of the ARFI technique to differentiate microcalcifications and calcified colloid debris via the estimation of micro-displacements induced by ARFI at gray scale maps.

To the best of our knowledge, there is no any other study emphasizing this distinction in the literature. We noticed that malignant micro-calcific foci show less displacement than the surrounding tissues on the ARFI map, since malignant micro-calcific foci are possibly heavier than colloids. In fact, we started the present study when we evaluated the first ARFI and cytopathology results of the patients referred to our center who had thyroid nodules with micro-echogenic foci. As is known, the presence of microcalcifications within a thyroid nodule is a well-recognized major risk factor for papillary carcinoma. If these echogenicities are small-sized, have no posterior acoustic shadowing and no typical reverberation artifact, differential diagnosis of these echogenicities from calcified benign colloidal echogenicities is not usually possible with conventional US [14]. Even though it has not been reported previously, it was considered that SWE could be useful in the differentiation of malignant microcalcifications [18].

We introduced our initial results of the new sign that differentiates the two groups of micro-echogenicity in thyroid nodules to avoid performing unnecessary FNAB. The present study has some limitations. Firstly, the number of patients was relatively insufficient for a new sign. However, selecting and classifying the thyroidal nodules containing micro-echogenic foci without reverberation, which are suspicious for malignant microcalcification, and ensuring the standardization number of cases requires a long time; it took a 3-year period for the number of patients included in the present study. Since we only aimed to differentiate the microcalcifications, other characteristics of nodules including gray scale properties at ARFI displacement maps and SWE features were not used in the present study in order not to go beyond the purpose of the present study.

In **conclusion,** according to the initial findings found in the present study, VTI compression displacement gray scale maps might be useful in the differential diagnosis of micro-echogenic foci in the thyroid nodules. By only looking at the echogenicity degrees on the ARFI displacement map, it would be possible to differentiate malignant and benign micro-echogenic foci in thyroid nodules with an accuracy rate of 86%. We suggest that the characteristic shining pattern at ARFI displacement maps may be one of the major criteria that could prove valuable information in the differentiation of malignant microcalcifications of thyroid nodules.

Conflict of interest: none**.**

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