Diagnostic Value of Real-Time Shear Wave Elastography in Diagnosing Thyroid Cancer

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Thyroid nodules are a common pathology found in 50 to 60% of otherwise healthy people. Diagnostic imaging techniques are help discriminating between benign and malignant nodules, while fine needle aspiration is still a gold standard. Shear wave elastography, a recent imaging technique, holds the promise to become reliable diagnostic tools and is currently used in combination with ultrasound. We here report data obtained in a series of 52 thyroid nodules analysed by means of elastography, as well as conventional and Doppler ultrasound. We found no differences in age, nodule and thyroid volume, length, width, thickness and maximum diameter between benign and malignant lesions. Several sonographic patterns are considered to be predictive of malignancy, out of which we only found the intranodular blood flow to be statistically significant. By the means of shear wave elastography we have first assessed tissue elasticities, which are shown in a range of colours, depending on tissue elasticity/stiffness. Then, we have measured and recorded four parameters automatically displayed by the system, namely SWE-mean, SWE-max, SWE-SD and SWE-ratio. Data analysis showed all these quantitative parameters had good sensitivity, specificity, positive predictive value, negative predictive value and area under the curve, as calculated by the ROC curve. As with these parameters, the cut-off points were lower than in literature, still able to indicate reliable diagnoses, which were confirmed by histopathological exam. Our conclusion is that shear wave elastography has great potential for reliably and accurately diagnosing thyroid malignancies.

Keywords: shear wave elastography, thyroid nodule, thyroid cancer

Thyroid nodules are a common pathology found in 50 to 60% of otherwise healthy people [1]. Diagnostic imaging techniques allow for the detection of thyroid nodules as small as 0.2 cm and this seems to be an important reason for the increased incidence of this condition [2]. Although less than 5% of the thyroid nodules are cancerous, discriminating between benign and malignant types is the issue at stake, considering the need to accurately and timely diagnose thyroid cancer, as well as to avoid unnecessary treatment of benign disease, such as thyroidectomy, which has a 1-6% risk of procedure-related complications and may require lifelong thyroid replacement therapy [3].

Almost 300,000 new cases of thyroid cancer were estimated in 2012 around the world, out of which more than 75% were found in women, while the age standardized rate for world population was 6.1/100,000 women as compared to 1.9/100,000 men [4]. The five-year prevalence in 2012 was 3.7% in both sexes (5.4% in women and 1.8% in men), as computed by the International Agency for Research on Cancer [5] based on estimates for 2018 [6]. Thyroid cancer deaths account for 0.5% of all cancer deaths in both sexes, with 0.8% in women and 0.3% in men [4]. The worldwide increased incidence of thyroid cancer is largely attributable to the improved methods of detection, particularly during the last two decades as a result of the widespread use of thyroid and neck ultrasounds [7]. However, data on mortality trends are divergent, with some reporting stable rates [8] or even a steady decline [2], and others showing slightly increased mortality rates are recorded mainly in men [9].

Diagnostic procedures include thyroid ultrasound (US), fine-needle aspiration cytology, molecular testing for gene mutations, and laboratory evaluation of thyroid hormones and serum calcitonin [10]. Other imaging techniques, such as MRI, CT, PET/CT or scintigraphy are recommended for diagnosis or preoperative staging of disease in certain situations, while US elastography has more recently emerged as a promising technique [11] able to provide additional information to conventional ultrasound findings.1 Hard or firm nodules are associated with a higher risk of malignancy [1 ,12]. thus assessment of tissue stiffness by the means of elastography is very useful in discriminating between benign and malignant lesions [13]. Strain and shear wave elastography are currently used in clinical practice to assess stiffness/elasticity of tissues, using an externally applied force (strain elastography) or transverse-oriented shear waves [14].

The most recent guidelines [15] devoted to the use of elastography in thyroid diseases conclude shear wave elastography (SWE) has good sensitivity and specificity, with high inter-observer agreement, and may be useful in assessing malignancy of thyroid nodules. Here we report the use of real-time shear wave elastography in a series of 32 patients with thyroid nodules to assess the diagnostic performance of this technique in predicting malignancy.

Experimental part

Materials and methods

Patients

This is a prospective study conducted from January 2012 to December 2016 in the Endocrinology Department, affiliated with the University of Medicine and Pharmacy

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Victor Babes Timisoara (UMFVBT) and County Clinical Emergency Hospital Pius Brinzeu Timisoara (SCJUT). We included 32 patients (28 women and 4 men), mean age 54.5 years (min. 29 years, max. 76 years), who refused fine-needle aspiration biopsy, out of 42 cases in which the diagnosis of multinodular goiter was confirmed. Patients excluded from this study had mainly cystic lesions, the benign or malignant nature of which is poorly discriminated by elastography [13, 16]. We have recorded the following patient data: gender, age, body mass index (BMI), size of thyroid lobes, number, volume and type of nodules, and histological diagnosis of the excised nodule.

Patients included in this study had solitary thyroid nodules or multinodular goiter with nodule volumes ranging from 0.02 to 20.2 mL (SD ±5.4) and thyroid volumes between 5.15 and 48.28 mL(SD ±11.47). A total number of 52 nodules were analysed by means of elastography, as well as conventional and Doppler ultrasound. All patients then underwent either lobectomy or total thyroidectomy in the 2nd Surgery Clinic of SCJUT and the final blinded histo-pathologic diagnosis performed on the excised thyroid tissue served as reference standard. Informed consent was given by all patients prior to inclusion in this study.

Equipment

We have performed the 2D-SWE by means of an Aixplorer™ ultrasound system (SuperSonic Imagine, Aix-en-Provence, France), using a SC5-1 linear transducer. As first described by Bercoff et al., [17] the supersonic shear wave imaging uses an acoustic radiation force generated by focused ultrasonic pushing beams that are successively focused at different depths, thus creating a shear source moving at supersonic speed and obtaining quasiplane shear waves that distribute throughout the area under investigation. By measuring the speed of shear wave propagation, tissue elasticity can be determined and is expressed both qualitatively (as a colour) and quantitatively [18]. Hence, on the elastographic image soft tissue appears in blue and hard tissue in red, while the quantitative estimation of elasticity is expressed in kilo-Pascal (kPa) [19]. This technique allows for the scanning of the entire imaging area in a single acquisition, with a frame rate ranging between 5,000 and 30,000 images per second depending on tissue properties [20].

Conventional and Doppler Ultrasound, and Shear Wave Elastography

In order to achieve improved characterization and quantification of tissue stiffness, we have concurrently used ultrasound and shear waves. Thus, all patients were examined during a single procedure by conventional ultrasound (B-mode), Doppler ultrasound and shear wave elastography using the same equipment. We have first evaluated the sonographic features of each nodule by conventional US, namely number of nodules and volume, length, width and thickness, as well as maximum diameter of each nodule, aspect of margins (well-defined or irregular), echogenicity (hyper-, hypo- or isoechoic) as compared with normal surrounding tissue, intranodular homogeneity, presence or absence of halo sign and microcalcifications/eggshell macrocalcifications, as well as presence of transonic areas inside nodules. Presence or absence of blood flow was then assessed by colour-flow Doppler and defined as absent blood flow, perinodular; (slight) intranodular blood flow; and (marked) perinodular and intranodular.

Finally, we performed real-time SWE and assessed the findings using the five-point scale originally proposed by Ueno and Itoh [21] for breast cancer diagnosis. The elastographic image and the B-mode image have been concurrently shown, with two separate screens displaying the elastographic image and the sonographic image, respectively. The following quantitative parameters were recorded, which are automatically displayed by the elastography system used: the mean elasticity index of the nodule (SWE-mean), the maximum elasticity index of the nodule (SWE-max), the standard deviation in the elasticity index (SWE-SD) and the ratio between elasticities of the mass and of the normal surrounding thyroid tissue (SWE-ratio), all expressed in kilo-Pascals (kPa).

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) programme (version 17.0 for Windows, SPSS Inc., Chicago, Illinois, USA) and the EpiInfo (version 7) programme. We split our sample of 52 nodules in two groups, malignant (26.9%, 14 nodules) and benign (73.1%, 38 nodules). All data were compared using a chi square test, with a p-value <0.05 considered to be statistically significant. Histological diagnosis served as reference standard.

Results and discussions

Histology

All patients underwent surgical treatment in the 2nd Surgery Clinic of SCJUT, consisting in either lobectomy or total thyroidectomy. After surgery, histopathologic diagnosis was performed according to the World Health Organization guidelines [22] by a pathologist who was blinded regarding the elastography findings.

A histological diagnosis of malignancy was made in 14 nodules (26.9%). All were papillary carcinomas: 4 were classical variant, 6 - follicular variant, 1 mixed (classical-follicular) and 3 microcarcinomas. Only 2 (22.22%) of the 9 patients with malignancies were men, both with solitary nodules (accounting for 14.29% of the total number of nodules). The remaining 38 nodules (73.1%) were benign: 18 cystic colloid nodules, 6 oxyphilic adenomas, 10 hyperplasic nodules, 2 follicular adenomas, and one with autoimmune thyroiditis with no other changes.

Conventional and Doppler US

As mentioned above, we have assessed the sonographic features of each nodule. Data regarding age, nodule and thyroid volume, length, width, thickness and maximum diameter for benign and malignant lesions were recorded. The mean age of patients in the two groups of patients was similar (55.7±12.88 years in the group of patients with benign nodules and 51.4 ±13.86 years in the study group), with no statistically significant difference between groups (p-value = 0.42). Similarly, patients with both benign and malignant masses had comparable nodule volumes (mean values 3.4±5.86 mL for malignant nodules and 3.01±5.32 mL for benign ones), which turned out to have no statistical significance (p-value = 0.73). Likewise, the mean values of length (malignant 14.85 mm, benign 16.41 mm), width (anteroposterior diameter: malignant 13.82 mm, benign 13.01 mm), thickness (malignant 17.28 mm, benign 14.68 mm), and maximum diameter (malignant 18.5 mm, benign 18.31 mm) revealed no statistically significant differences between malignant and benign nodules.

We have also studied the US features considered to be predictive of malignancy (table 1) and only found statistically significant differences in respect of intranodular blood flow (p-value = 0.010).

US feature			Benign (n=38) no. (%)	Malignant (n=14) no. (%)	P value
Margins	Well-defined		22 (57.9%)	6 (42.9%)	0.344
	Irregular		16 (42.1)	8 (57.1%)	
Echogenicity	Hyperechoic		1 (2.6%)	-	0.306
	Hypoechoic		31 (81.6)	13 (92.9%)	
	Isoechoic		6 (15.8%)	1 (7.1%)	
Homogeneity	Homogeneous		9 (23.7%)	3 (21.4)	0.867
	Inhomogeneous		29 (76.3)	11 (78.6%)	
Halo sign	Present		11 (28.9%)	4 (28.6%)	0.979
	Absent		27 (71.7%)	10 (71.4%)	
Microcalcifications	Present		4 (10.5%)	3 (21.4%)	0.473
	Absent		34 (89.5%)	11 (78.6%)	
Transonic areas	Present		21 (55.3%)	9 (64.3%)	0.568
	Absent		17 (44.7%)	5 (35.7%)	
Blood flow	Present	Intranodular	10 (26.3%)	10 (71.4%)	0.010
		Perinodular	13 (34.2%)	4 (28.6%)	
		Peri-and intranodular	2 (5.3%)	-	
	Absent		13 (34.2%)	-	

Table 1
ULTRASOUND FEATURES OF NODULES

Shear wave elastography

Different tissue elasticities were shown in a range of colours, with blue for maximum tissue elasticity, green for average elasticity and dark red for stiff areas, which were assigned scores from 1 to 5 according to Ueno scale: [23] score 1 indicates normal elasticity in the hypoechoic lesion, score 2 implies some areas of stiffness, score 3 is suggestive for stiffness in the centre of the lesion and elasticity in the peripheral areas, score 4 indicates stiffness in the whole lesion, but not the surrounding area, and score 5 means both the lesion and the surrounding area are stiff.

In our study, an elasticity score (ES) 4 was highly predictive of malignancy, as confirmed by histopathologic examination. However, only 21.4% of these nodules had ES 4. Conversely, no benign nodule with an ES 4 was found, with most of them (84.2%) having ES 1 and 2. Figure 1 shows SWE and US images of two nodules in our study with ES 1 and 4, respectively.

As mentioned above, we have recorded four quantitative parameters (SWE-mean, SWE-max, SWE-SD and SWE-ratio), the values of which were rather dispersed among the two groups. Nevertheless, the mean, as well as the median values proved to be higher in the malignant nodules group (table 2), indicating that these nodules generally display higher quantitative elasticity indices, which is consistent with findings in literature. All the SWE parameters recorded in the present study have reached statistical significance ($p<0.05$) in discriminating between malignant and benign lesions.

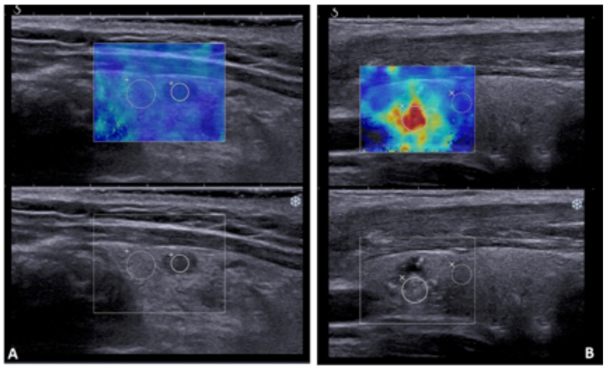

Fig. 1. SWE and US images of a benign (A) and a malignant nodule (B). A – A 64-year old woman with cystic colloid nodule, ES 1 on SWE. US shows a homogeneous hypoechoic nodule, with regular margins, no microcalcifications and absence of halo sign. **B** – A 39-year-old woman with mixed papillary carcinoma, ES 4 on SWE. US shows a nonhomogeneous hypoechoic nodule, with spiculated irregular margins and microcalcifications.

Parameter		Mean value	Median value	P-value
SWE-mean	Benign	21.79 kPa	20.35 kPa	0.003
	Malignant	38.91 kPa	26.65 kPa	
SWE-max.	Benign	45.27 kPa	39.70 kPa	0.032
	Malignant	73.63 kPa	54.00 kPa	
SWE-SD	Benign	7.24 kPa	5.58 kPa	0.040
	Malignant	12.81 kPa	9.40 kPa	
SWE-ratio	Benign	1.15 kPa	1.01 kPa	0.010
	Malignant	2.044 kPa	1.55 kPa	

Table 2
MEAN AND MEDIAN VALUES OF SWE PARAMETERS

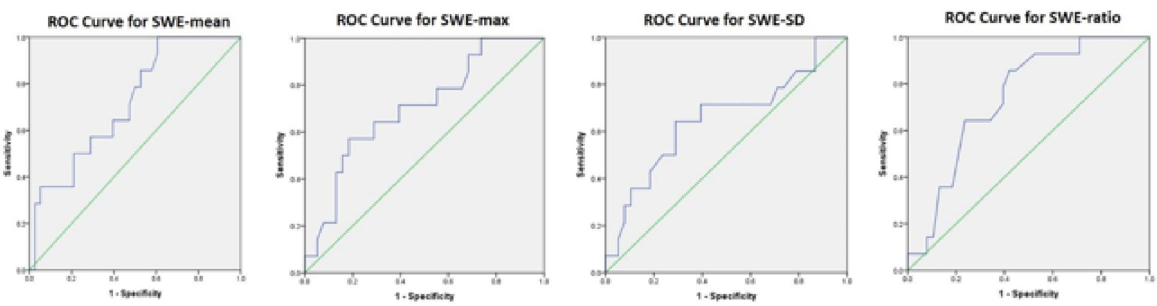

Fig. 2. ROC curves for the four SWE parameters

Parameter	Cut-off value	Sensitivity	Specificity	PPV	NPV	AUC
SWE-mean	20.08 kPa	71.4%	52.5%	35.7%	83.3%	71.8%
SWE-max.	53.95 kPa	64.3%	60.5%	37.5%	82.1%	70.1%
SWE-SD	8.72 kPa	64.3%	60.5%	37.5%	82.1%	65.2%
SWE-ratio	1.19 kPa	71.4%	60.5%	42.3%	88.5%	74.0%

Table 3
DIAGNOSTIC PERFORMANCE OF SWE PARAMETERS

The diagnostic performance of the four SWE parameters was also assessed by the Receiver Operating Characteristics (ROC) curve. We then used ROC curves to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The cut-off point was decided by the ROC curve, at highest sensitivity and specificity levels. The highest area under the ROC curve (AUC) was seen for SWE-ratio. All the above-mentioned data are shown in figure 2 and table 3.

Sensitivities and specificities of the SWE parameters were good, while the positive predictive values were rather low, which was expected since the prevalence of disease was low in the whole group. However, negative predictive values were high enough to confidently rule out malignancy in a high proportion of nodules included in this study. AUC also exhibited good levels, given that the perfect test has a value of 1, and showing a good accuracy of the four SWE-parameters in differentiating benign from malignant thyroid masses.

Shear wave elastography is a useful diagnostic tool providing valuable information based on the measurement of tissue elasticity. Although it has recently emerged, with the first commercial equipment only available since 2003, [24] it holds great promise to become the gold standard in the diagnosis of thyroid nodules. A meta-analysis [25] of 15 studies comprising a total of 1,867 thyroid nodules in 1,525 patients calculated pooled sensitivity and specificity for detection of malignant thyroid nodules to be 84.3% and 88.4%, respectively, with an AUC of 93%. The PPV in the studies included in the meta-analysis ranged between 27.7 and 44.7%, while NPV range was 98.1 to 99.1%. Another meta-analysis [26] aimed at assessing the ability of SWE to discriminate between benign and malignant thyroid nodules included five studies comprising 469 patients in total, with 698 thyroid nodules, out of which 130 were malignant. The pooled sensitivity, specificity, PPV and NPV were 0.84, 0.90, 7.39, and 0.20, respectively, showing good diagnostic accuracy, while the summary AUC was 0.92. The cut-off values range in these studies was 34.5 to 90.34 kPa.

In our study, we have calculated sensitivities, specificities, PPVs, NPVs, AUCs and cut-off values for each of the four parameters, SWE-mean, SWE-max, SWE-SD and SWE-ratio, with results comparable to those reported in the literature. SWE-mean and SWE-ratio yielded the highest sensitivity (71.4%), although with less specificity (52.5% and 60.5, respectively). The maximum specificity was 60.5%, for three of the parameters (SWE-max, SWE-SD and SWE-ratio). The positive predictive value ranged between 35.7 and 42.3%, consistent with data in the literature. Similarly, we have obtained high negative predictive values for all four SWE parameters, which has the potential to reduce unnecessary invasive diagnostic procedures in patients with benign masses. The AUC was good for all parameters, although lower than in other studies.

The cut-off values reported in the literature range from 34.5 kPa to 90.34 kPa. Bhatia et al. [27] have assessed the reliability of SWE in 176 neck lesions, out of which 40 thyroid nodules, and got a cut-off value of 34.5 kPa for the mean elasticity index, while Szczepanek-Parulska et al. [18] obtained the best odds ratio at a cut-off value of 50 kPa, with very high sensitivity, but less specificity. Sebag et al. [19] and Veyrieres et al. [28] found very similar cut-off values for discriminating between benign and malignant masses, 65 kPa and 66 kPa, respectively. The highest cut-off was reported by Wang et al. [29] to be as high as 90.34 kPa.

We established in our study a cut-off for the mean elasticity index of 20.08 kPa, with good sensitivity and lower specificity, and a higher cut-off point for SWE-max, namely 53.95 kPa, with fair specificity and sensitivity. The cut-off values in this study were lower than those reported in literature, but we here reported separate data for each of the parameters.

According to data available in the literature, several US features (irregular margins, hypoechogenicity, inhomogeneity, absence of halo sign, presence of microcalcifications, transonic areas and blood flow) were found to predict malignancy in thyroid nodules when considered together [1,13,15,30,31]. In our study, however, we found only the intranodular blood flow to be statistically significant, for the many of the benign nodules also displayed the other features mentioned above.

There is a consensus in the literature regarding the reliability of diagnostic information yielded when a combination of ultrasound and shear wave elastography is used, and our study found this to be true to some extent, provided only one US feature was statistically significant.

Conclusions

Despite the levels of the four SWE parameters obtained in our study were generally lower than that reported in the literature, we believe this research adds to the evidence that shear wave elastography has great potential for reliably and accurately diagnosing thyroid malignancies.

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