Shear Wave Elastography: A New Ultrasound Imaging Mode for the Differential Diagnosis of Benign and Malignant Thyroid Nodules

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Context: Elastography uses ultrasound (US) to assess elasticity. Shear wave elastography (SWE) is a new technique that estimates tissue stiffness in real time and is quantitative and user independent.

Objectives: The aim of the study was to assess the efficiency of SWE in predicting malignancy and to compare SWE with US.

Design: Ninety-three patients and 39 control subjects were included in the study. Predictive value of SWE was assessed by correlation between elasticity, US parameters, and histology. Elasticity index (EI) was first analyzed alone. Scores have been constructed with echographic parameters, *i.e.* vascularity, hypoechogenicity, and microcalcifications (Score 1 = US Score), and with the same parameters plus EI (Score 2 = US+SWE Score). For statistical analysis, univariate and multivariate analysis and receiver operating characteristic curves were used.

Results: A total of 146 nodules from 93 patients were analyzed. Twenty-nine nodules (19.9%) were malignant. Mean (±SD) EI was 150 ± 95 kPa (range, 30–356) in malignant nodules *vs.* 36 ± 30 (range, 0–200) kPa in benign nodules ($P < 0.001$, Student's *t* test). For a positive predictive value of at least 80%, characteristics of tissue elasticity (cutoff, 65 kPa) were: sensitivity = 85.2%, and specificity = 93.9%. Characteristics of the US Score were: sensitivity = 51.9% [95% confidence interval (CI), 33.1; 70.7], and specificity = 97% (95% CI, 93.6; 1). Characteristics of the US+SWE Score were: sensitivity = 81.5% (95% CI, 66.9; 96.1), and specificity = 97.0% (95% CI, 93.6; 1).

Conclusion: Promising results have been obtained with SWE. This technique may be applied to multinodular goiters. Larger prospective studies are needed to confirm these results and to define the respective places of SWE, US, and FNA. **(*J Clin Endocrinol Metab* 95: 5281–5288, 2010)**

Palpable thyroid nodules are very common, with an estimated prevalence that ranges between 5.3% in women and 0.8% in men in the Whickham survey (1). Additionally, up to 68% of the general population has thyroid nodules, even when the thyroid gland is normal to palpation (2). The prevalence of such infracentimetric nodules discovered by ultrasonography increases with age (2, 3). The majority of thyroid nodules are benign (colloid nodule, follicular adenoma, cyst, and thyroiditis), but 5 to 15% are malignant (papillary, follicular, medullary, or anaplastic carcinoma) (2).

After clinical examination, thyroid ultrasound (US) is used as a first-line procedure to help differentiate benign and malignant nodules. Several US features have been associated with malignancy: microcalcifications, hypoechogenicity, intranodular vascularity, irregular margins, and

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Abbreviations: AUC, Area under curve; CI, confidence interval; EI, elasticity index; FNA, fine-needle aspiration; FTUMP, follicular tumor of uncertain malignant potential; kPa, kilo-Pascal; ROC, receiver operating characteristic; SWE, shear wave elastography; US, ultrasound.

absent halo sign (4). All of these features alone are poorly predictive of malignancy. In combination, their specificity increases, but sensitivity decreases (5). After clinical examination and thyroid US, fine-needle aspiration (FNA) biopsy has a central role in differentiating benign from malignant thyroid lesions. In expert centers, FNA provides useful results in 65–75% of examined nodules (6). Approximately 60–70% of aspirates prove to be cytologically benign, 5% are positive for papillary carcinoma, and 5–15% remain inconclusive. The remaining 15–25% of aspirates are indeterminate or suspicious (7). The latter two results offer a challenging dilemma for the clinician. Indeed, FNA is limited by sampling difficulties with inadequate collected specimens and by overlap in morphological signs between benignity and malignancy. When FNA results are indeterminate or suspicious, most clinicians recommend surgical excision. Then, the sensitivity of FNA will increase, whereas its specificity will decrease (8). The poor quality of FNA specimens may be the source of diagnostic errors with false-negative and false-positive results that reached 25 and 9.9%, respectively, in a recent multiinstitutional survey (9).

Therefore, there is a need for another way to evaluate thyroid nodules. Over the last few years, a new diagnostic tool has emerged that uses US to assess tissue elasticity and stiffness to differentiate malignant from benign lesions. Stiffness is usually correlated with malignancy because benign lesions are supposed to be softer (10). Different techniques of elastography have been applied to thyroid nodules, based on real-time elastography and off-line processing of strain images (11–13), external compression (14–16), or carotid artery vibrations (17). However, the widespread applicability of these techniques is limited because they cannot be used in the evaluation of multinodular goiters, which represent about 40% of nodular thyroid glands (18). There is no consensus about the risk of cancer per patient, regardless of whether one or multiple nodules are present. Indeed, the prevalence of carcinoma was found to be lower in patients with a solitary nodule than in patients with multinodular thyroid (19, 20), but the prevalence was equal in another study (21). More recently, a technique has been developed that uses tracking of shear wave propagation through tissue to obtain the elastic modulus (22). This new shear wave elastography (SWE) is operator-independent, reproducible, and quantitative. It gives a local assessment of tissue elasticity at each point of interest of an organ. It has been used with success in the evaluation of breast lesions (23).

In an exploratory study, we have assessed the efficiency of SWE in predicting malignancy in solitary or multiple thyroid nodules, and we have compared SWE with conventional US features associated with malignancy.

Patients and Methods

Patients

The study was approved by the French National Committee for the Protection of Patients Participation in Biomedical Research Programs (Comité de Protection des Personnes CCP Sud 1; authorization no. 2006-A00657-44). Each patient and control gave written informed consent before enrollment. The study was conducted during a 10-month period.

Ninety-three patients with thyroid nodules who were referred to the Medical and Surgical Endocrinology Department of Timone University Hospital were included in the study. Sixty-one patients presented with a solitary nodule; 45 were female, age (mean ± SD) 54 ± 14 (range, 18–78) yr; and 16 were male, age 51.5 ± 12.9 (range, 28–76) yr. Subclinical hypothyroidism was found on two patients, and subclinical hyperthyroidism in one. All others were euthyroid. Thirty-two patients were referred for multiple thyroid nodules (multinodular goiters); 24 were female, age 56.4 ± 12.8 (range, 33–76) yr; and eight were male, age 58 ± 8.1 (range, 47–71) yr. Subclinical hyperthyroidism was found in four patients, and subclinical hypothyroidism in one. Seventy-nine patients underwent surgery: 47 of 61 patients with solitary nodules, and all 32 patients with multinodular thyroid glands. Fourteen of 61 patients in the solitary nodule group with a diagnosis of benign lesion after FNA examination were not operated.

Thirty-nine control patients with normal thyroid function and morphology were explored with US and SWE.

Conventional US and SWE

The system is equipped with all diagnostic US machines and transducers for conventional (B-mode, Harmonic imaging, Spatial Compounding imaging, and Amplitude Doppler) and SWE modes. Conventional US and SWE have been operated with the prototype of the Aixplorer, a new-generation US machine developed by SuperSonic Imagine (Les Jardins de la Duranne, Aix en Provence, France). The SWE was described in detail by Bercoff *et al.* (22). It consists of the generation of a remote radiation force by focused ultrasonic beams, the so-called "pushing beams," a patented technology called "Sonic Touch." Several pushing beams at increasing depths are transmitted to generate a quasi-plane shear wave frame that propagates throughout the whole imaging area. After generation of this shear wave, an ultrafast echographic imaging sequence, the Ulmtraast Imaging System, is performed to acquire successive raw radiofrequency dots at a very high frame rate (up to 20,000 frames per second). Based on Young's modulus formula, the assessment of tissue elasticity can be derived from shear wave propagation speed. A color-coded image is displayed, which shows softer tissue in blue and stiffer tissue in red. Quantitative information is delivered; elasticity index (EI) is expressed in kilo-Pascal (kPa). The clinical evaluation of this technique for breast lesion imaging is under investigation (23). Both steps of SWE are achieved using a linear US probe without requiring any intervention (as pressure) by the operator.

Thyroid function tests

Serum TSH, free T_3, free T_4, and thyroid autoantibodies were measured by chemiluminescent ELECSYS immunoassay.

sHistological examination

FNA smears were made using two samples collected from nodules in 14 patients. Conventional cytology, thyroid peroxidase, and dipeptidyl aminopeptidase-4 tests were routinely performed in three slides as previously reported (24). Tissue specimens were obtained after surgery from 79 patients. After fixation, embedding, and staining, tissue sections were examined by two pathologists. Histological typing was based on the World Health Organization criteria.

Statistical analysis

Descriptive statistics were applied to all variables collected. The univariate relation between US characteristics and malignancy was examined by the Fisher exact test for categorized variables. Most clinically and statistically relevant US variables associated with malignancy were incorporated to develop a scoring system. For all analyses, a two-tailed P value of less than 0.05 indicated statistical significance. Bootstrap resampling procedures were performed to generate these scoring systems and estimate the confidence intervals (CIs). From the bootstrap samples, we computed a score (Score 1 = US Score). For SWE, the optimal cutoff of EI for diagnosis of malignancy was chosen for a positive predictive value of at least 80%. Another score (Score 2 = US+SWE Score) has been constructed with US and SWE variables. The cutoff levels of both scores were determined for a positive predictive value of at least 80%. Receiver operating characteristic (ROC) curves were performed to estimate the capacity of both scores and SWE alone to predict malignancy using the area under curve (AUC), sensitivity, and specificity, with their 95% CIs. For the score's analysis, only patients with complete data sets for the parameters were included. All tests were two-sided, and a P value <0.05 was considered statistically significant. For analyzing the areas under those correlated ROC curves, a pair-wise comparison of ROC curves for Score 1 (US Score) and Score 2 (US+SWE Score) was performed with a nonparametric approach by using the theory on generalized U-statistics to generate an estimated covariance matrix (25). Analyses were performed with SPSS software (version 15.0; SPSS Inc., Chicago, IL), SPAD version 5.5 and MedCalc 10.4.5.0.

Results

Histology

In 61 patients with solitary nodules, a final diagnosis of malignancy was reported in 15 cases: nine papillary thyroid carcinomas, three follicular carcinomas, one differentiated follicular tumor of uncertain malignant potential (FTUMP), one medullary carcinoma, and one anaplastic carcinoma. In 46 cases, the histology of nodules was benign.

Histology was benign in 24 of 32 patients with multiple thyroid nodules. Fourteen malignant nodules were identified in eight patients: 11 papillary carcinomas, two follicular carcinomas, and one FTUMP. Multifocal malignant nodules were identified in five of eight patients. Sixty-nine benign nodules were recovered in the other 24 patients.

Conventional US patterns

The US features most predictive of malignancy were hypoechogenicity (sensitivity, 70.4%; specificity, 81.8%), absent halo sign (sensitivity, 92.6%; specificity, 41.4%), microcalcifications (sensitivity, 66.7%; specificity, 84.8%), and intranodular vascularity (sensitivity, 51.9%; and specificity, 93.9%). The presence of dense macrocalcifications larger than 2 mm was not predictive of malignancy, with a sensitivity of 22% and a specificity of 79.6%. This type of calcification was detected in 25 nodules by conventional US. Six of the 25 nodules were malignant (Table 1).

TABLE 1. Conventional US patterns and EI in 126 patients (out of 93 patients) with complete data set for all those parameters

	Benign (n = 99)	Cancer (n = 27)	Sensitivity	Specificity
Intranodular vascularity			51.9 (33.1; 70.7)	93.9 (89.2; 98.6)
Present	6	14		
Absent	93	13		
Microcalcifications			66.7 (48.9; 84.5)	84.8 (77.7; 91.9)
Present	15	18		
Absent	84	9		
Macrocalcifications			22.2 (6.5; 37.9)	79.6 (71.7; 87.5)
Present	20	6		
Absent	78	21		
Halo sign			92.6 (82.7; 100)	41.4 (31.7; 51.1)
Absent	58	25		
Present	41	2		
Hypoechogenicity			70.4 (62.4; 78.3)	81.8 (75.1; 88.6)
Present	18	19		
Absent	91	8		
EI			85.2 (71.8; 98.6)	93.9 (89.2; 98.6)
≥65 kPa	6	23		
<65 kPa	93	4		

Data are expressed as number of subjects or percentage (95% CI).

The combination of significant US features (hypoechogenicity, microcalcifications, and intranodular vascularity) increased the specificity of thyroid ultrasonography. These characteristics were used for the construction of Score 1 (US Score) (values between 0 and 100, high values predicting malignancy). Absent halo sign was not included in the final construction of US Score because it did not reach statistical significance with the other parameters. The US Score equation was: 42.18 (if intranodular vascularity = yes) + 6 (if hypoechogenicity = no) + 30.70 (if hypoechogenicity = yes) + 27.13 (if microcalcification = yes). For a positive predictive value of at least 80%, the cutoff level of the US Score for malignancy was defined as 63.6. From the ROC curves, the characteristics of this score to predict a nodule's malignancy were: sensitivity = 51.9% (95% CI = 33.1; 70.7), specificity = 97% (95% CI = 93.6; 100), positive predictive value = 82.4% (95% CI = 64.3; 100), and negative predictive value = 88.1% (95% CI = 82.0; 94.2). The AUC was 84.7 (95% CI = 74.5; 94.9) ($P < 0.001$) (Fig. 1A).

Shear wave elastography

EI was significantly higher in malignant nodules [150 ± 95 (30–356) kPa] than in benign nodules [36 ± 30 (0–200) kPa] and normal thyroid glands [15.9 ± 7.6 (5–35) kPa] ($P < 0.001$). The cutoff level of EI for malignancy was estimated as 65 kPa, for a positive predictive value of at least 80%. With this cutoff value, from the ROC curves, the characteristics of EI to predict malignancy were: sensitivity = 85.2% (95% CI, 71.8; 98.6), specificity = 93.9% (95% CI, 89.2; 98.6), positive predictive value = 80% (95% CI, 65.4; 94.6), negative predictive value = 95.9% (95%

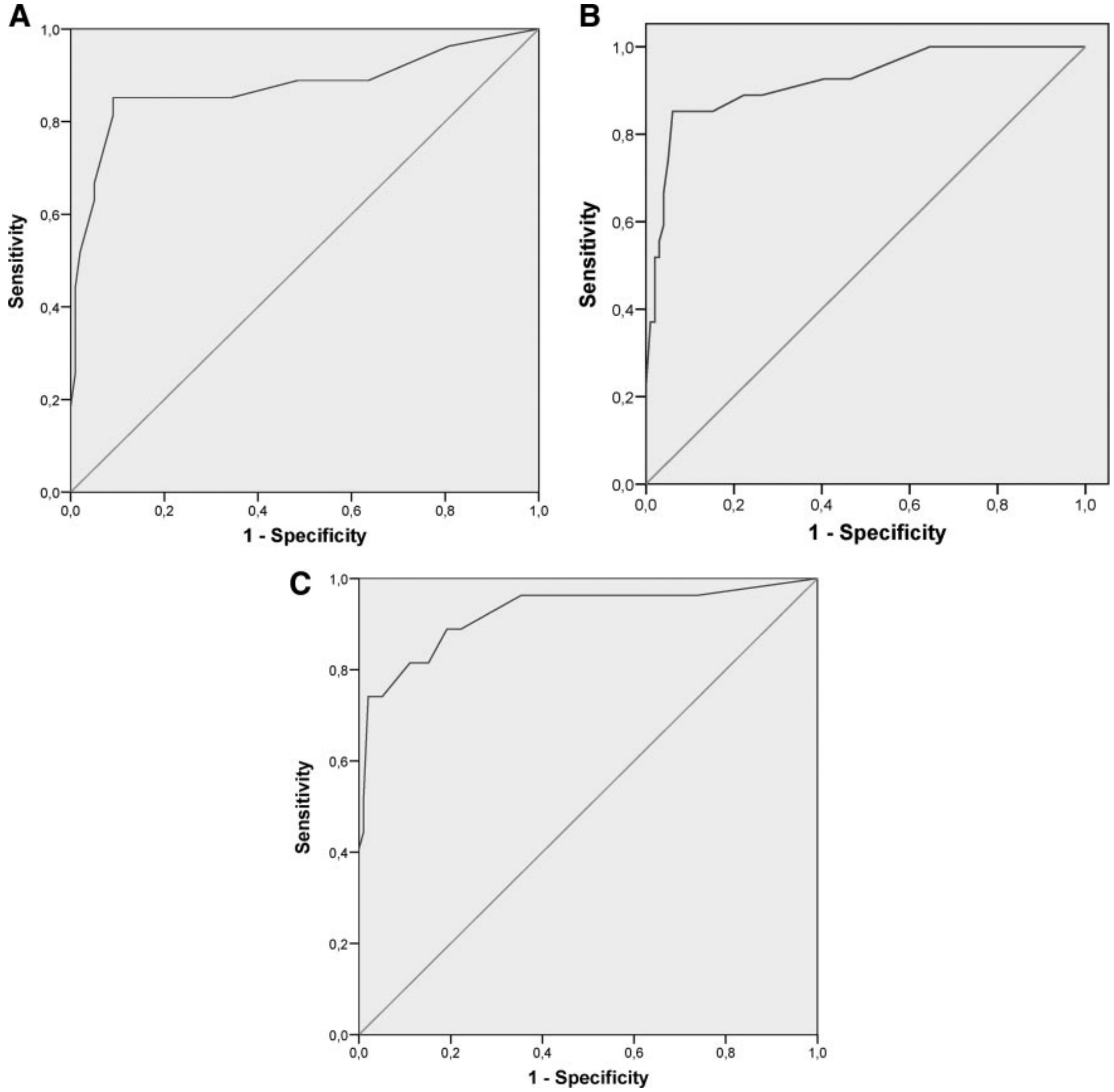

FIG. 1. ROC curves (area under the ROC curve) for changes in scores and nodule's malignancy. A, ROC curve for changes in Score 1 (US Score) (AUC = 84.7%). Area under the ROC curve for changes in Score 1 (US Score) and nodule's malignancy. B, ROC curve for the EI of at least 65 kPa (AUC = 93.6%). Area under the ROC curve for changes in index elasticity and nodule's malignancy. C, ROC curve for the Score 2 (US+SWE Score) (AUC = 93.4%). Area under the ROC curve for changes in Score 2 (US+SWE Score) and nodule's malignancy.

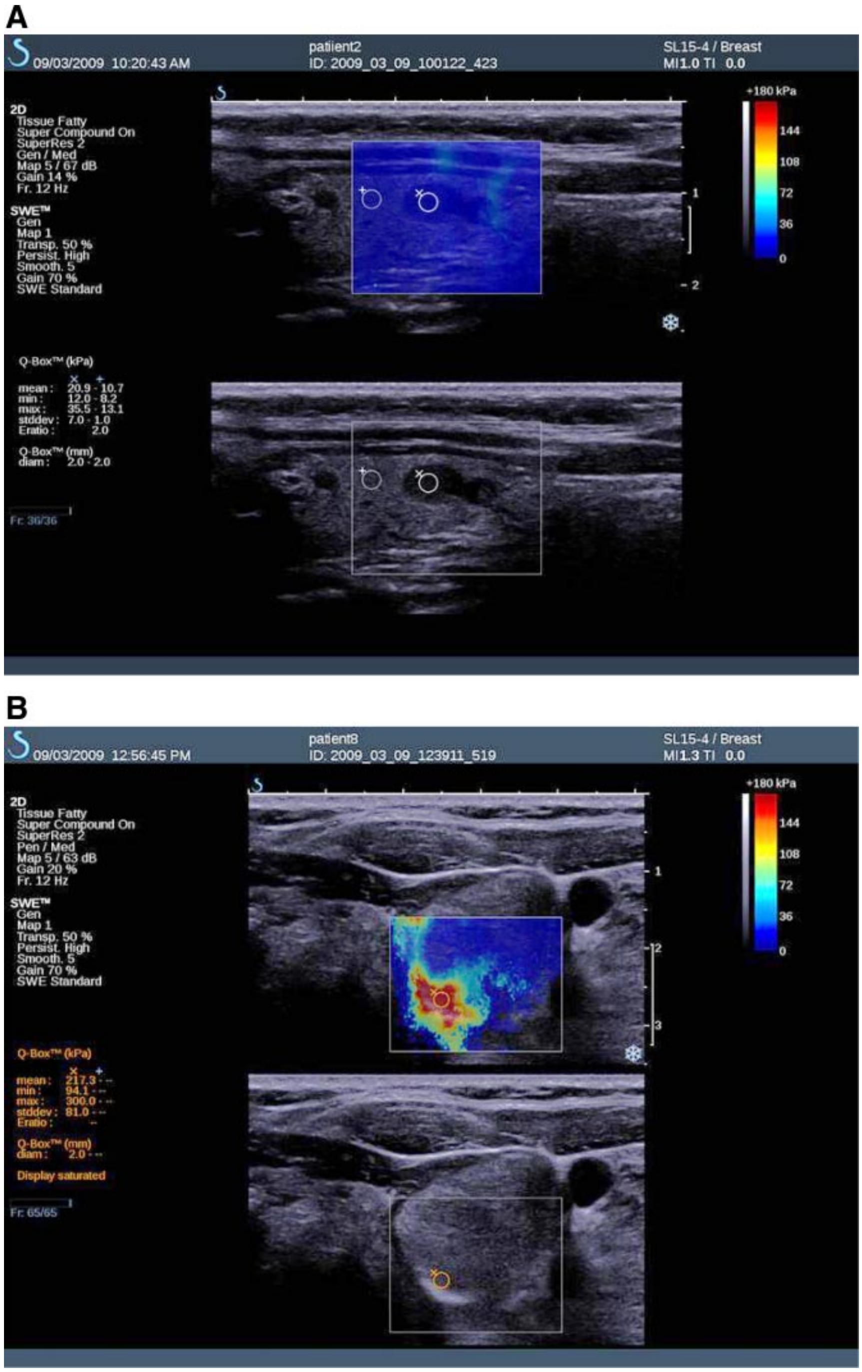

FIG. 2. Thyroid nodule images obtained on US elastography of a benign thyroid nodule (A) and a papillary carcinoma (B).

CI, 92.0; 99.8), and AUC = 93.6 (95% CI, 86.9; 100) (Fig. 1B). Figure 2 shows the B-mode and SWE images (sagittal views) of a benign nodule (Fig. 2A) and papillary carcinoma (Fig. 2B). In four of 25 malignant nodules (three papillary carcinoma, and one FTUMP), EI was lower than 65 kPa. EI was higher than the cutoff value in all follicular carcinoma and in the single cases of medullary and anaplastic carcinomas (Table 2).

The Score 2 = US+SWE score was constructed with US features and EI with the following equation: 39.95 (if intranodular vascularity = yes) + 32.73 (if EI > 65 kPa) + 14.90 (if hypoechogenicity = yes) + 13.42 (if microcalcifications = yes). The cutoff level of US+SWE score for malignancy (for a positive predictive value ≥ 80%) was defined as 42.5. From the ROC curves, the characteristics of this score to predict malignancy were: sensitivity = 81.5% (95% CI, 66.9; 96.1), specificity = 97.0% (95% CI, 93.6; 100), positive predictive value = 88% (95% CI, 75.3; 100), negative predictive value = 95.0% (95% CI, 90.7; 99.3), and AUC = 93.4 (95% CI, 86.4; 100) (Fig. 1C). The US characteristics and US+SWE scores of malignant nodules with an EI lower than 65 kPa suggest that two of four nodules are indeed malignant (Table 3). In 25 nodules, macrocalcifications were detected by US. Six of 25 nodules were malignant, and EI was higher than 65 kPa in five of six. Nineteen of 25 nodules were benign, and EI was higher than 65 kPa in five of 19.

The difference between area under Score 1 and Score 2 ROC curves was statistically significant ($P = 0.001$) using a nonparametric approach.

Discussion

In our experience, SWE was a powerful tool for the diagnosis of malignancy in thyroid nodules. EI was significantly higher in malignant than benign nodules. Using a cutoff level of 65 kPa, the sensitivity and specificity of the technique were 85.2 and 93.9%, respectively. These data are in agreement with previous reports based on other methods of elastography. Indeed, in three studies using real-time elastography with off-line processing of strain images, the sensitivity ranged between 82 and 88%, and the specificity between 81.8 and 96% (11–13). With a commercial US apparatus using a freehand compression applied on the neck region and a real-time measurement on a numerical scale, the sensitivity and specificity were estimated between 94 and 100% and between 81 and 100%, respectively (14–16).

SWE is operator-independent and more reproducible than static elastography. It offers other advantages. First,

TABLE 2. EI of malignant thyroid nodules according to their histological subtypes

Characteristics	n	EI, mean ± SD (kPa)	Range
Solitary nodules (n = 61)			
Papillary carcinoma	9	148 ± 98	40–356
Follicular carcinoma	3	117 ± 72	70–200
Medullary carcinoma	1	263	
Anaplasic carcinoma	1	200	
FTUMP	1	30	
Multiples nodules (n = 83)			
Papillary carcinoma	11	162 ± 109	30–323
Follicular carcinoma	2	250	
FTUMP	1	180	

it is quantitative. Second, it provides local elasticity estimation of nodules that is unaltered by the presence of a hard area in the vicinity. This is of major interest in cases of multinodular thyroid. This group of patients may represent up to 40% of all patients referred for thyroid nodules (18). As indicated previously, the risk of cancer per patient in this group has been appreciated either lower (19, 20) or equal (21) to that in solitary nodules. Most cases of multinodular goiters are not suitable for static elastography because the nodule to be examined with this technique must be clearly distinguishable from other nodules in the thyroid gland (7, 26).

The accuracy of EI measurement may also be altered if nodules are close to the carotid artery because arterial pulsation may create elastographic images and therefore alter the adequate acquisition and accurate interpretation of the data. In nodules with a diameter greater than 3 cm, adequate compression of the whole nodule may not be obtained. Similarly, elastography using external compression was considered unreliable in nodules with calcified shells or rims because the US beam does not cross these macrocalcifications, and no tissue strain is obtained by the probe pressure (14, 26). In these cases, SWE may offer some advantages over this technique. In our study, 19 of 25 thyroid nodules with macrocalcifications were benign, and SWE measurement was valid in 14 cases. Although SWE may be used in the presence of macrocalcifications, one must be cautious in the interpretation of SWE. In previous literature, coarse or rim macrocalcifications have been documented as having no diagnostic value for cancer (27, 28), although they have been shown to double the risk of malignancy in one recent study (21). The association of nodule macrocalcifications with an EI higher than 65 kPa may indicate surgery, although the false-positive rate for benign nodules may reach 26% as shown in our study.

Other US elastography techniques are time consuming and not routinely useful. The US elastography using generation of tissue movement by carotid artery is still limited to the research area because it needs a long time after processing for calculation of the thyroid nodule stiffness (17). The first technique of real-time elastography and off-line processing of strain images is also time-consuming because analysis after data acquisition takes over 30 min (11–13). Thyroid nodule SWE updates elasticity information in real time, and this information is directly interpreted by the radiologist in a straightforward manner, as in the traditional workflow of standard US.

The subtype of thyroid nodules may be the source of variations in EI. Indeed, in the evaluation of breast lesions, a good relationship was found between elasticity score and histology (23, 28). Papillary carcinoma is the most frequent subtype of malignant thyroid nodules. Increased cellularity and cellular compaction, the main characteristics of papillary carcinoma, are the histological basis for hypoechogenicity and stiffness. As indicated above, EI was significantly higher in papillary carcinoma than in benign nodules. However, follicular and other histological variants of papillary carcinoma are possible. In our study, EI in malignant nodules ranges from 30 to 356 kPa, with four of 20 malignant nodules with EI less than 65 kPa, not significantly different from those of benign thyroid nodules. The combination of several conventional US features highly suggestive of papillary carcinoma has been found in two of four cases. In the two other cases, a 9.2-mm papillary carcinoma and a FTUMP, none of these conventional US features have been found (Table 3). In contrast, follicular carcinomas are composed of small microfollicles with variable amounts of colloid. Therefore, their echogenicity and EI may depend on their cellular content. Conventional US is not predictive in follicular lesions (29), although irregular halo and iso- or hyperechogenicity have been described in follicular thyroid cancer (30). In our study, EI ranges from 70 to 250 kPa with a possible

TABLE 3. Echographic characteristics in patients with malignant nodules and EI < 65 kPa

Patient ID	Histology	Hypoechogenicity	Microcalcification	Central vascularity	No halo sign	EI (kPa)
A1	Papillary (foll. variant)	0	0	0	+	50
A6	Papillary (foll. variant)	+	+	+	0	30
B36	Papillary	+	+	+	+	40
B27	FTUMP	+	0	0	0	30

Foll. variant, Follicular variant of papillary carcinoma; 0, absent; +, present.

correlation with stroma content that will need further study. Similar data have been obtained by Rago *et al.* (14). However, elastography was not efficient for diagnosis of follicular carcinoma in two other studies (13, 15). More studies in correlation with various histological criteria will be helpful in understanding this discrepancy. Two cases of FTUMP are present in our series. In one case, EI was 30 kPa, and in the other case EI was 180 kPa.

The place of SWE in the evaluation of thyroid nodules for potential malignancy needs to be established. Actually, this evaluation is based upon clinical examination, conventional US characteristics, and FNA above all. Despite its benefits, FNA is limited by sampling and cytological diagnostic difficulties. US-guided FNA (31), more detailed classification of inconclusive aspirates (18), as well as multidisciplinary and institutional efforts for the evaluation of thyroid nodules (18) have significantly improved the diagnosis of thyroid cancer. In our study, a cutoff value of 65 kPa alone provided a positive predictive value of 92.3%, suggesting that SWE might be considered as a first-line imaging technique for thyroid nodules because it provides a sensitivity of 85.2% and a specificity of 93.9%. On the basis of EI determination with a cutoff value of 65 kPa, four cases of malignant nodules, including one FTUMP, would have been missed. The 13.8% rate of false-negative tests is not acceptable. Further evaluation of these nodules by an expert radiologist reduces false-negative results to two cases previously detailed. On the other hand, EI was higher than 65 kPa in 6.1% of benign nodules. This rate could be considered acceptable because FNA and possibly thyroid surgery are indicated for this condition. Indeed, the sensitivity of the combination of several conventional US characteristics is much lower (51.9%). Therefore, almost 50% of the malignant nodules would have been missed. The specificity is high (97%), when thyroid US is performed by experienced radiologists. The construction of the US+SWE score with the combination of EI and US characteristics associated with cancer gives a sensitivity of 81.5% and a specificity of 97%. On the basis of this score, about 18% of the malignant nodules would have been missed.

The lower sensitivity of US characteristics, alone or in association with EI, leads us to support SWE as the first-line procedure in the evaluation of thyroid nodules. When EI is at least 65 kPa, further exploration is needed by FNA or thyroid surgery. For nodules with an EI of less than 65 kPa, careful evaluation of US signs associated with cancer may add useful information for the management of patients. Indeed, in our study, US signs suggestive of carcinoma were found in two of four cases with EI of less than 65 kPa. The successive use of SWE and US characterization was effective, except in a 9.2-mm papillary carcinoma and one FTUMP. Further studies are needed to test whether thyroid SWE has the potential to reduce the number of FNA biopsies by detecting benign thyroid nodules using an EI cutoff value.

In conclusion, promising results have been obtained with SWE in the evaluation of thyroid nodules. This newly developed technique may be applied to multinodular goiters. It seemed easy to apply. Larger prospective studies are needed to confirm our results, define the respective place of SWE *vs.* US and FNA, and test the diagnostic accuracy of our algorithm.

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