Real-Time Elastosonography: Useful Tool for Refining the Presurgical Diagnosis in Thyroid Nodules with Indeterminate or Nondiagnostic Cytology

T. Rago, M. Scutari, F. Santini, V. Loiacono, P. Piaggi, G. Di Coscio, F. Basolo, P. Berti, A. Pinchera, and P. Vitti

Department of Endocrinology (T.R., M.S., F.S., V.L., A.P., P.V.), Department of Electric Systems and Automation (P.P.), Department of Oncology, Section of Cytopathology, Pathology 1 (G.D.C.) and 3 (F.B.), and Department of Surgery (P.B.), University of Pisa, 56124 Pisa, Italy

Background: Indeterminate and nondiagnostic patterns represent the main limitation of fine-needle aspiration (FNA) cytology of thyroid nodules, clinical and echographic features being poorly predictive of malignancy. The newly developed real-time ultrasound elastography (USE) has been previously applied to differentiate malignant from benign lesions. The aim of this study was to get further insights into the role of USE in the presurgical diagnosis of nodules with indeterminate or nondiagnostic cytology.

Patients: The study included 176 patients who had one (n = 138) or multiple (n = 38) nodules with indeterminate or nondiagnostic cytology on FNA, for whom histology was available after thyroidectomy. A total of 195 nodules (142 indeterminate, 53 nondiagnostic) were submitted to USE, and elasticity was scored as 1 (high), 2 (intermediate), or 3 (low).

Results: In indeterminate lesions, the score 1, describing high elasticity, was strongly predictive of benignity, being found in 102 of 111 benign nodules and in only one of 31 carcinomas ($P < 0.0001$). By combining the scores 2 and 3, USE had a sensitivity of 96.8% and a specificity of 91.8%. In nodules with nondiagnostic cytology, score 1 was found in 39 of 45 benign nodules and in only one of eight carcinomas ($P < 0.0001$). By combining the scores 2 and 3, USE had a sensitivity of 87.5% and a specificity of 86.7%.

Conclusions: USE may represent an important tool for the diagnosis of thyroid cancer in nodules with indeterminate or nondiagnostic cytology and may prove useful in selecting patients who are candidates for surgery. (***J Clin Endocrinol Metab* 95: 5274–5280, 2010**)

Nodular thyroid disease is a common finding in the general population, in particular in iodine-deficient areas. Thyroid nodules are palpable in 5% of subjects (1, 2) but are detectable by thyroid ultrasound (US) in up to 50% of the general population (3–5).

Only a minority of thyroid nodules are likely to cause significant health problems. Cytological examination of material obtained by fine-needle aspiration (FNA), due to its high sensitivity and specificity, is the best single test for differentiating malignant from benign thyroid lesions (6). The major limitation of FNA cytology is that 10 to 15% of specimens are nondiagnostic (7), and 10 to 20% are indeterminate (8–10). Thus, in about 30% of samples, FNA results are not conclusive (2, 3, 10–13). A nondiagnostic cytology may be found in cystic or hemorrhagic lesions that do not provide a sufficient number of cells for diagnosis. Furthermore, a substantial proportion of solid nodules also fail to provide sufficient material for cytological analysis (6, 7), a variable rate of malignancy being reported in solid nodules with persistently nondiagnostic

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-0901 Received April 20, 2010. Accepted August 3, 2010.
First Published Online September 1, 2010

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Abbreviations: FNA, Fine-needle aspiration; US, ultrasound; USE, US elastography.

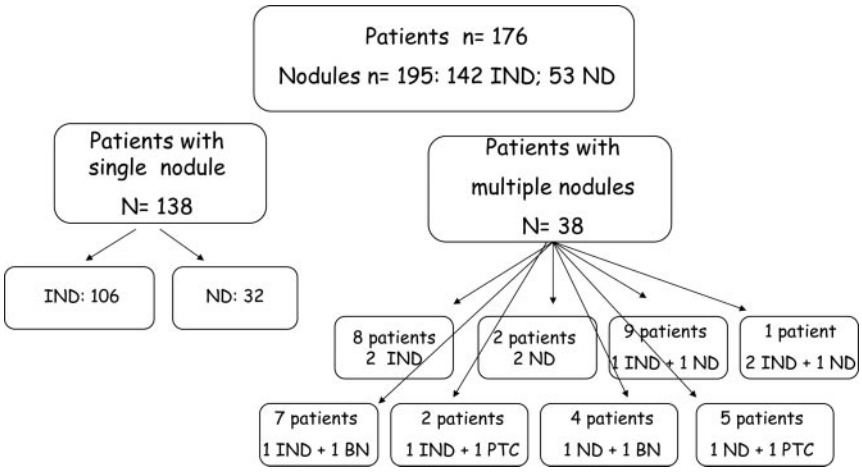

FIG. 1. Patients and nodules included in the study. IND, Indeterminate cytology; ND, nondiagnostic cytology; BN, benign cytology; PTC, papillary thyroid carcinoma on cytology.

FNA (13, 14). In addition, in 10 to 20% of all FNA specimens, although the collected material is adequate, cytology is classified as indeterminate, *i.e.* unable to discriminate between benign follicular adenoma and thyroid carcinoma, either follicular thyroid cancer or the follicular variant of a papillary thyroid carcinoma (14–16).

BRAF mutations or RET/PTC rearrangements have been found in 30–70% of papillary thyroid carcinomas (17). These genetic alterations can be detected in FNA material from nodules with indeterminate or inadequate cytology. Yet, not all papillary thyroid carcinomas have identifiable molecular aberrations, thus limiting the sensitivity of the molecular procedure (17–20). Furthermore, the search for gene alterations is time consuming and can be performed only by specialized laboratories (2).

Clinical data are of little help in the prediction of malignancy in indeterminate lesions (8). Although we have shown in a previous report that malignancy was more frequently observed in males than in females, in nodules larger than 3 cm and in single nodules rather than in multinodular glands, none of these differences reached statistical significance. Similarly, the echographic pattern was poorly predictive of malignancy. Apart from spot microcalcifications, no other ultrasonographic features were significantly associated with thyroid cancer (8, 21–23).

Recently, the newly developed US elastography (USE) has been applied to study the hardness/elasticity of nodules and to differentiate malignant from benign lesions (24). As for thyroid cancer, in 92 patients with a single thyroid nodule in whom histology was available, we found a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 98% (25, 26). These results were confirmed by other authors in smaller cytological series (27–30). In our early series, only a minority of nodules were indeterminate or nondiagnostic on FNA cytology. The aim of this study was to get further insights into the role of real-time USE in the presurgical risk stratification of indeterminate or nondiagnostic FNA cytology.

Patients and Methods

Patients

The study included 176 patients (mean age, 44 ± 13 yr; range, 8–74 yr; 130 females and 46 males). Selection criteria were as follows: 1) one or multiple nodules with indeterminate or nondiagnostic cytology that were suitable for USE, *i.e.* devoid of coarse calcifications or dominant cystic content; 2) indication for thyroidectomy. In the case of patients with indeterminate cytology, thyroid surgery was always advised, unless specific contraindications would occur. As for patients with nondiagnostic cytology, thyroid surgery was indicated for clinical suspicion of malignancy, the size of the nodule, or the occurrence of a coexisting nodule with cytology suspicious for malignancy.

A total of 138 patients had a single nodule, 106 of them with indeterminate cytology and 32 with nondiagnostic cytology. Thirty-eight patients had multiple nodules as detailed in Fig. 1. Overall, a total of 142 nodules with indeterminate cytology and 53 nodules with nondiagnostic cytology were submitted to USE.

All patients gave their informed consent to participate to the study. All patients were euthyroid as assessed by normal values of serum TSH (normal values, 0.4–3.4 μU/ml; measured by a sensitive immunoradiometric assay, Delphia; Pharmacia, Turku, Finland); serum free T_4 (FT4) and free T_3 (FT3) measured by RIA (FT4, Liso-Phase; normal values, 7–17 pg/ml; FT3, Liso-Phase kit; normal values, 2.7–5.7 pg/ml; Technogenetics, s.r.l., Milan, Italy); and with undetectable serum calcitonin measured by an immunoradiometric assay (normal values, <10 ng/ml; CIS BIO International, Gif Sur Yvette, France).

FNA cytology and histology

FNA biopsy was carried out in patients with solitary nodules or multinodular goiter following the indications provided by current guidelines (2, 3, 11). FNA was performed under US guidance by a skilled endocrinologist using a 23-gauge needle attached to a 10-ml syringe. The material was air-dried, stained with Papanicolaou and Giemsa, and interpreted by an experienced cytologist. The adequacy of aspirates was defined according to the guidelines of the Papanicolaou Society (31). After thyroid surgery, formalin-fixed, paraffin-embedded tissue was stained by hematoxylin and eosin. The histological diagnosis was made according to the World Health Organization guidelines (32). The pathologist was blinded *vs.* the USE findings.

Thyroid US and USE

All patients were examined by conventional US and USE using a real-time instrument (Logos EUB 8500 machine with a linear transducer 8–13 MHz; Hitachi, Tokyo, Japan). An evaluation of the following US parameters was carried out: echogenicity (hyper-, iso-, or hypoechogenicity with respect to normal thyroid parenchyma), presence or absence of the halo sign, pres-

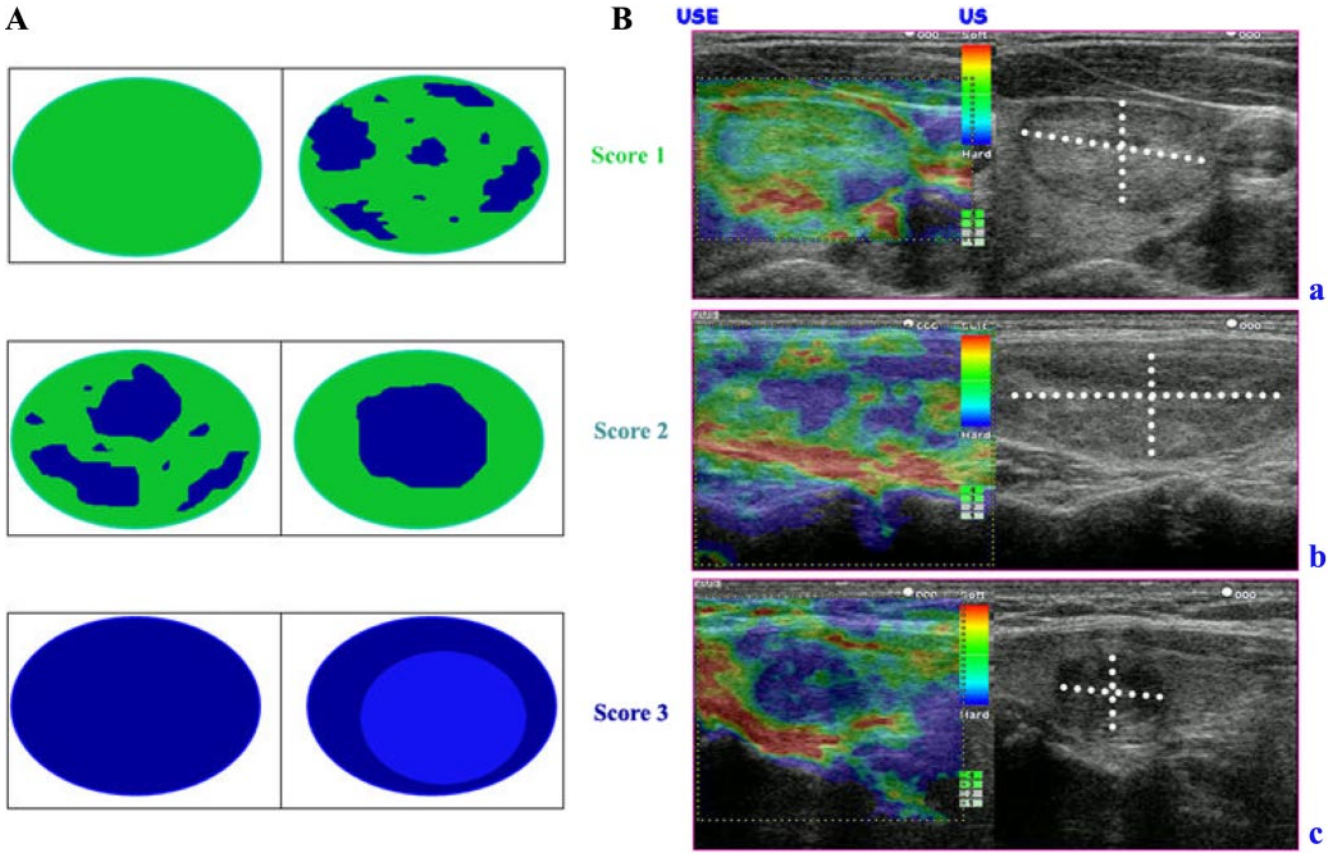

FIG. 2. Elasticity score. A, Score 1, Elasticity in the whole or in a large part of the nodule; score 2, elasticity only at the peripheral part of the nodule; score 3, no elasticity in the nodule and in the posterior shadowing. B, Ultrasound elastography (USE) and conventional US (US) of three thyroid nodules with an elasticity score 1 (a), score 2 (b); and score 3 (c).

ence of spot microcalcifications (hyperechoic spots less than 2 mm, without acoustic shadowing), and color flow Doppler pattern defined as type I absence of blood flow, type II perinodular and absent or slight intranodular blood flow, and type III marked intranodular and absent or slight perinodular blood flow (33).

USE measurement was performed during the US examination, using the same real-time instrument and the same probe as above. All examinations were performed by the same operator (T.R.). Static and moving images were recorded to be reviewed subsequently by two additional skilled US examiners. The agreement on the scoring of USE was 95%. In particular, scoring was coincident in 185 of 195 nodules. In 10 nodules with discrepant judgment, score 2 was applied. USE was performed unblinded as to the general criteria of selection, but the observer was unaware of the cytological results of specific nodules. The principle and methodology of USE have been previously described (24). In brief, the probe was placed on the neck, applying a light pressure, and a box was highlighted by the operator, which included the nodule and sufficient surrounding thyroid tissue to be evaluated. The principle of USE is to acquire two ultrasonographic images (before and after tissue compression by the probe), and to track tissue displacement by assessing the propagation of the US beam by a dedicated software. The US elastogram was displayed over the B-mode image in a color scale that ranged from red, for components with greatest elastic strain (*i.e.* softer components), to blue for those with no strain (*i.e.* harder components). To minimize the inter- and intraobserver variability, the freehand compression applied on the neck region was standardized by real-time measurement displayed on a numeric scale to maintain an intermediate level optimal for USE evaluation. This technique is easy to perform and requires no more than 3 to 5 min.

The USE image was matched with an elasticity color scale. To simplify thyroid nodular classification, the score developed by Ueno and Ito (34) for the breast was modified as follows: score 1 included scores 1 and 2 of the previous classification and defined nodules with high elasticity; score 2 was maintained as an intermediate score; score 3 included scores 4 and 5 of the previous classification and defined nodules with low elasticity (Fig. 2).

Statistical analysis

Parametric tests were used for statistical evaluation. Results obtained in different groups of patients were compared using the χ^2 test (and Fisher's exact test when appropriate), Student's *t* test for paired data, and logistic regression analysis. Predictivity was assessed using the Galen and Gambino test (35).

Results

Histology

Among 142 nodules with indeterminate results on FNA cytology, 31 (21.8%) had a final diagnosis of malignancy on histology: 26 were papillary thyroid carcinomas (17

TABLE 1. Predictive value of conventional US patterns in 142 thyroid lesions with indeterminate cytology that resulted benign nodules (n = 111) or carcinoma (n = 31) on histology

Histology	BN (n)	CA (n)	Sens (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)	*P* value (Fisher's test)
Absence of halo sign	23	7	22.6	79.3	23.3	78.6	66.9	0.81
Hypoechogenicity	60	17	54.8	45.9	22.1	78.5	47.9	1.00
Spot microcalcifications	40	10	32.3	64	20	77.2	57	0.83
Type III vascularization	0	1	NV	NV	NV	NV	NV	NV
US combination								
# 1	13	5	16.1	88.3	27.8	79	72.5	0.54
# 2	6	2	6.4	94.6	25	78.4	75.4	1.00
# 3	17	5	16.1	84.7	22.7	78.3	69.7	1.00

BN, Benign nodules; CA, carcinoma; Sens, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; NV, not valuable. US pattern combination: # 1, no halo sign + hypoechogenicity; # 2, no halo sign + spot microcalcifications; # 3, hypoechogenicity + spot microcalcifications.

follicular variant, seven classic variant, one tall cell variant, and one trabecular variant), and five were minimally invasive follicular carcinomas. The remaining 111 (78.2%) nodules were benign on histology: 90 were follicular adenomas, 11 were hyperplastic nodules, three were oxyphilic adenomas, and seven were follicular adenomas with foci (<5 mm) of papillary carcinoma.

Among 53 nodules with nondiagnostic cytology, eight (15%) were papillary thyroid carcinomas on histology (five follicular variant; three classic variant). The remaining 45 (85%) nodules were benign on histology: 25 were follicular adenomas, 17 were hyperplastic nodules, and three were follicular adenomas with foci of papillary carcinoma.

Conventional US

Single US patterns were not predictive of malignancy. As previously shown (8), the combination of echographic patterns could increase the specificity, but decreased the sensitivity of conventional US in nodules with both indeterminate and nondiagnostic cytology. The most predictive combination was the absence of halo sign with the presence of spot microcalcifications (Tables 1 and 2).

US elastography

In nodules with indeterminate cytology, score 1 was found in 103 cases, one carcinoma, and 102 benign lesions; score 2 was observed in 14 cases, six carcinomas, and eight benign nodules; score 3 was found in 25 cases, 24 carcinomas, and one benign nodule (Table 3).

In patients with nondiagnostic lesions on cytology, score 1 was found in 40 nodules, one carcinoma, and 39 benign lesions; score 2 was observed in four nodules, one carcinoma, and three benign nodules; score 3 was found in nine nodules, six carcinomas, and three benign lesions (Table 3).

Thus, in nodules with indeterminate cytology, the score 1, describing high elasticity, was strongly predictive of benignity, being found in 102 of 111 benign nodules on histology and in only one of 31 with a final diagnosis of carcinoma ($P < 0.0001$) (Fig. 3A). Thus, by combining the scores 2 and 3, USE had a sensitivity of 96.8%, a specificity of 91.8%, a positive predictive value of 76.9%, a negative predictive value of 99.0%, and an accuracy of 92.9% in the prediction of malignancy. In patients with nondiag-

TABLE 2. Predictive value of conventional US patterns in 53 thyroid nodules with nondiagnostic cytology that resulted in benign nodules (n = 45) or carcinoma (n = 8) on histology

Histology	BN (n)	CA (n)	Sens (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)	*P* value (Fisher's test)
Absence of halo sign	9	2	25	80	18.2	85.7	71.4	0.66
Hypoechogenicity	17	4	50	62.2	19	87.5	60.4	0.70
Spot microcalcifications	15	5	62.5	66.7	25	90.9	66	0.14
Type III vascularization	0	0	0	NV	NV	NV	NV	NV
US combination								
# 1	4	3	37.5	91.1	42.9	89.1	90.6	0.06
# 2	2	5	62.5	98.6	71.4	93.5	71.7	<0.01
# 3	9	2	25	80	18.2	85.7	84.9	0.66

BN, Benign nodules; CA, carcinoma; Sens, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; NV, not valuable. US pattern combination: # 1, no halo sign + hypoechogenicity; # 2, no halo sign + spot microcalcifications; # 3, hypoechogenicity + spot microcalcifications.

TABLE 3. Predictive value of USE in 142 thyroid lesions with indeterminate cytology and 53 thyroid nodules with nondiagnostic cytology that resulted in benign nodules or carcinoma on histology

Cytology	No. of BN	No. of CA	Total no.
Indeterminate	111	31	142
Score 1	102	1	103
Score 2	8	6	14
Score 3	1	24	25
Nondiagnostic	45	8	53
Score 1	39	1	40
Score 2	3	1	4
Score 3	3	6	9

BN, Benign nodules; CA, carcinoma.

nostic lesions on cytology, the score 1 was found in 39 of 45 cases with a final diagnosis of benign nodule, and in only one of eight with a final diagnosis of carcinoma ($P < 0.0001$) (Fig. 3B). Thus, by combining the scores 2 and 3, USE had a sensitivity of 87.5%, a specificity of 86.7%, a positive predictive value of 53.8%, a negative predictive value of 97.5%, and an accuracy of 86.8% in the prediction of malignancy.

Overall, in all nodules with either indeterminate or nondiagnostic cytology, by combining the scores 2 and 3, USE had a sensitivity of 94.9%, a specificity of 90.3%, a positive predictive value of 71.1%, a negative predictive value of 98.6%, and an accuracy 91.3% in the prediction of malignancy.

Discussion

The main limitation of FNA cytology of thyroid nodules is the substantial proportion of indeterminate lesions and nondiagnostic aspirates. Among patients with a cytological diagnosis of indeterminate lesion, 25% display a final diagnosis of malignancy on histology (8), the follicular variant of papillary carcinoma being the most frequent histotype. Unfortunately, no clinical features or molecular studies of different oncogenes are accurate enough to differentiate malignant from benign nodules. Thus, the recommended treatment of indeterminate lesions remains the surgical excision of the nodule (1–3). As for nondiagnostic cytology, the surgical treatment may be indicated based on clinical or US features suggestive of malignancy, or on compressive symptoms due to the nodular size (1–3).

In the present study, we found a prevalence of 22% thyroid cancers among nodules with indeterminate cytology, thus confirming our previous series (8, 9, 12). As for nondiagnostic cytology, the rate of cancer on histology (15%) may appear rather large, compared with previous reports (13, 14). Differences may depend on the criteria used to select nodules that have to be surgically removed. In the present study, many nodules were selected based on suspicious features of malignancy, thus overestimating the true prevalence of the disease within the entire category of nodules with nondiagnostic cytology.

USE is a newly developed diagnostic tool that evaluates the degree of distortion of US beam under the application of an external force and is based upon the principle that the softer parts of tissues deform easier than the harder parts under compression, thus allowing a semi-quantitative determination of tissue elasticity (24). Malignant thyroid nodules such as papillary thyroid carcinoma, the most common histotype, display a lower elasticity with respect to benign lesions as reported by us (25) and others (27–30). Preliminary data obtained in a limited number of patients suggested that USE might be useful in the differential diagnosis of nodules with indeterminate cytology (25).

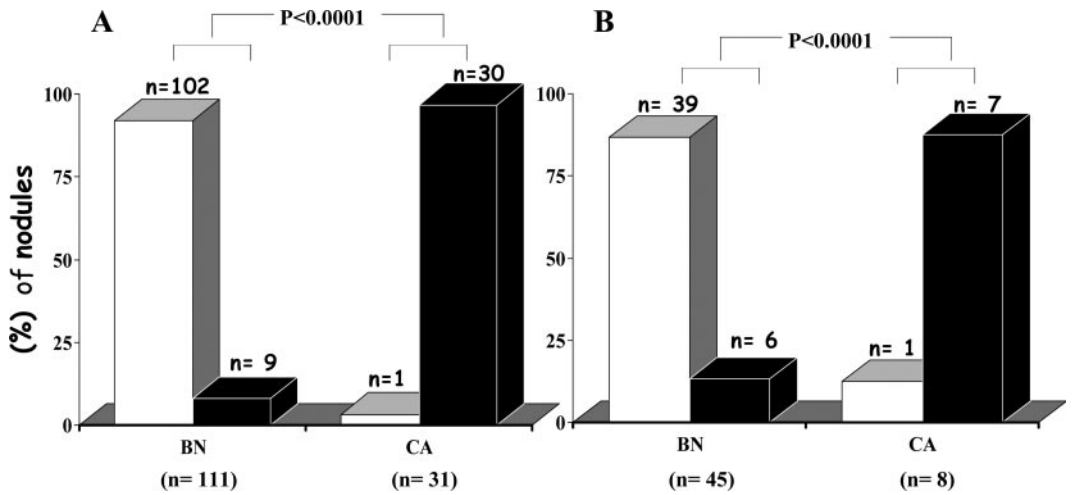

FIG. 3. Elasticity score in nodules with indeterminate cytology (A) and in nodules with nondiagnostic cytology (B) in relation to the final histology of benign lesion (BN) or carcinoma (CA). Score 1, □; score 2–3, ■.

This study was undertaken to specifically address the predictive value of USE in patients with indeterminate or nondiagnostic specimens on FNA. Results obtained in this large series of patients confirm that a greater nodular stiffness is associated with malignancy in both categories of nodules. On the other hand, conventional US maintains its pivotal importance in the selection of nodules in which US elastosonography is reliable, *i.e.* nodules devoid of coarse calcifications and prevalent solid composition (25). We adopted a simplified score system for the description of patterns observed at US elastography. Score 1 included nodules with high elasticity, score 2 was maintained in cases in which the pattern of color distribution was inhomogeneous and difficult to interpret, and score 3 included nodules with low elasticity. Using this score classification, the predictivity of US elastography was highly rewarding. Indeed, score 3 was associated with malignancy with high specificity, although the sensitivity was not optimal. Much more rewarding were the negative predictive values of the pattern of high elasticity score 1, to exclude malignancy in both indeterminate and nondiagnostic nodules. Indeed, score 1 was found in 102 of 111 indeterminate lesions with a benign diagnosis at histology and in only one of 31 with a final diagnosis of malignancy. Similar findings were observed in the group of nondiagnostic lesions, although sensitivity and specificity were lower. This implies that nodules with high elasticity, which represent the largest proportion of nodules with indeterminate or nondiagnostic cytology, have a minimal probability to bear malignancy. We have to draw attention to the fact that in this study USE was performed in patients known to be candidates for thyroid surgery, and in principle this could have influenced the score toward malignancy. Prospective studies based on a totally blinded evaluation will be necessary to provide conclusive evidence about the role of USE in the management of thyroid nodules.

If further confirmed, the implications of our findings in the clinical management of indeterminate or nondiagnostic lesions are likely to be relevant because USE might restrict the indications of surgical therapy to the subgroup of patients with higher risk of thyroid cancer. The low number of false-negative results at USE, together with the low progression rate of differentiated thyroid cancer, would allow most patients to be placed in follow-up without significant costs in terms of prognosis. USE could also be helpful to define the extent of thyroidectomy (total or lobectomy) for these lesions.

In conclusion, we propose USE as an important tool in the presurgical risk stratification of thyroid cancer in nodules with indeterminate or nondiagnostic cytology, high elasticity being highly associated with benign histology.

Acknowledgments

Address all correspondence and requests for reprints to: Teresa Rago, M.D., Department of Endocrinology, University of Pisa, Via Paradisa, 2, 56124 Pisa, Italy. E-mail: rago@endoc.med.unipi.it.

Disclosure Summary: The authors have nothing to declare.

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