

Is Doppler ultrasound of additional value to gray-scale ultrasound in differentiating malignant and benign thyroid nodules?

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SUMMARY

The objective of this study was to evaluate whether Doppler ultrasound (DUS) is of additional value to gray-scale ultrasound (GSUS) in predicting the benign or malignant nature of thyroid nodules. A total of 1,502 solid thyroid nodules ≥ 10 mm were evaluated. Suspicious vascularity (predominantly or exclusively central blood flow) was observed in only 5% of the nodules. This finding showed 96% specificity, but only 15% sensitivity. GSUS alone showed sensitivity and specificity of 88.7% and 68.2%, respectively, which did not improve with the addition of DUS (sensitivity of 89.4% and specificity of 66.4%). In non-suspicious nodules on GSUS, the type of vascularity on DUS did not modify the risk of malignancy, which was low. In suspicious nodules on GSUS, suspicious vascularity on DUS increased the risk of malignancy, but non-suspicious vascularity did not reduce this risk. DUS provided no additional value to GSUS in predicting the benign or malignant nature of thyroid nodules. *Arch Endocrinol Metab.* 2015;59(1):79-83

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INTRODUCTION

The current indications for fine-needle aspiration (FNA) of thyroid nodules < 10 mm are highly selective (1-7). FNA is also not necessary in the case of autonomous or cystic nodules ≥ 10 mm. In the remaining cases, ultrasonographic characteristics of the nodule (composition, echogenicity, shape, margins, halo, calcifications) are important for the indication of FNA and for estimating the risk of malignancy. Nodule vascularity has also been proposed to be of diagnostic value, but many authors question this proposal (3,4,8-11).

In addition to the controversy regarding the use of Doppler US for the differentiation of benign and malignant nodules, there is no consensus which type of vascularity would be considered suspicious of malignancy. Some organization such as the American Thyroid Association (2), American Association of Clinical Endocrinologists and European Thyroid Association (12), European Society for Medical Oncology (5), and National Comprehensive Cancer Network (7) consider “increased intranodal vascularity” as suspicious, without requiring that vascularity is predomi-

nantly or exclusively intranodal. Others such as the Society of Radiologists in Ultrasound (1), French Society of Endocrinology (13), and Brazilian Society of Endocrinology (6) propose only “predominantly or exclusively central” blood flow to be defined as suspicious.

Finally, even when vascularity is taken into consideration, other ultrasonographic characteristics of the nodule continue to be important, i.e., Doppler US does not replace gray-scale ultrasound (GSUS). It is therefore important to know whether (i) an apparently benign nodule on GSUS becomes suspicious when Doppler US reveals suspicious vascularity and the probability of the nodule being benign increases when Doppler US is also not suspicious; (ii) a suspicious nodule on GSUS is no longer suspicious when Doppler US is not suspicious and its risk of malignancy increases when Doppler US is also suspicious.

The objective of the present study was to determine whether Doppler US is of additional diagnostic value to GSUS in predicting the nature of solid thyroid nodules ≥ 10 mm.

SUBJECTS AND METHODS

Design

Prospective study.

Patients

Consecutive patients who had at least one thyroid nodule ≥ 10 mm were selected. The following nodules ≥ 10 mm were excluded: cystic, complex (mixed) or hot nodules on ^{131}I scintigraphy (performed on patients with low TSH). Thus, nontoxic solid or predominantly solid nodules ≥ 10 mm were included. The study was approved by the local Research Ethics Committee.

Doppler US

Ultrasound was performed with a linear multifrequency 12-MHz transducer for morphological analysis (gray-scale) and for power Doppler evaluation. Ultrasound was performed by three experienced radiologists. Suspicious ultrasonographic findings were microcalcifications, hypoechogenicity, microlobulation or irregular margins, and a taller-than-wide shape (being greater in the anteroposterior dimension than in the transverse dimension) (1). The type of blood flow of all thyroid nodules was evaluated before US-guided FNA. Using the first classification, three types of vascularity were identified (14): type 0, no vascularity – defined as no flow at the periphery or inside the nodule; type 1, peripheral vascularity – defined as flow only at the periphery of the nodule, and type 2, intranodular vascularity – defined as flow inside the nodule regardless of flow at the periphery. Using the second classification, four types of vascularity were identified (adapted from 15,16): type 0, no vascularity; type 1, peripheral vascularity; type 2, peripheral and intranodular vascularity; type 3, exclusively or predominantly intranodular vascularity.

FNA

FNA was performed with a 22-gauge needle and a 5- or 10-mL syringe and was guided by US. The smears were analyzed by pathologists experienced in thyroid pathology. The cytological diagnosis was classified as benign, indeterminate (follicular lesion of undetermined significance, atypia of undetermined significance, suspicious of or follicular neoplasm), suspicious of malignancy or malignant, or inadequate. All patients were referred for surgery, except for those with benign cytology. Only the

cytological or histological diagnosis of the thyroid nodule included in the study was considered for analysis.

Statistical analysis

Fisher's exact test or the χ^2 test was used to detect differences in the proportion of cases. A p-value of less than 0.05 was considered to be significant.

RESULTS

There were 1,106 eligible patients (902 women; age range: 9-83 years, median of 48 years) with 1,502 solid nodules ≥ 10 mm and all of them underwent FNA. Cytology was benign in 1,135 nodules (75.5%). A cytology result classified as malignant or suspicious of malignancy, indeterminate, or inadequate was observed in 87 (5.6%), 190 (12.6%), and 90 (6%) nodules, respectively. Since 10 patients with 12 nodules refused or had contraindications to thyroidectomy, histology was available for 355 of 367 nodules with non-benign cytology. One hundred sixty of these 355 nodules were malignant. The 10 patients with indeterminate ($n = 3$) or inadequate ($n = 7$) cytology and without available histology were at low clinical risk of malignancy (2-7,12,13,17), and the nodules showed no growth after 24 months of follow-up.

Considering the first classification, suspicious vascularity (type 2) was observed in 64.6% of the nodules. This findings showed 70% sensitivity, but only 36% specificity. The frequencies of nodules without apparent flow, with exclusively peripheral flow, or with intranodal flow did not differ between benign and malignant lesions (Table 1). In addition, the risk of malignancy did not differ according to the type of vascularity (Table 1).

Table 1. Distribution of the type of vascularity (first classification) on Doppler US in benign and malignant nodules and probability of malignancy according to vascularity

Type of vascularity	Benign nodules	Malignant nodules	Probability of malignancy
Type 0	82 (6.1%)	8 (5%)	8/90 (8.9%)
Type 1	401 (29.9%)	40 (25%)	40/441 (9%)
Type 2	859 (64%)	112 (70%)	112/971 (11.5%)
	1,342	160	160/1502 (10.6%)

Using the second classification, suspicious vascularity (type 3) was seen in only 5% of the nodules. This finding showed 96% specificity, but only 15% sensitivity. The initial probability of malignancy did not decrease in the absence of predominantly or exclusively intrano-

dal vascularity, but increased significantly [from 10.6% to 31.6% ($p < 0.001$)] in the presence of this vascularity (Table 2).

Table 2. Distribution of the type of vascularity (second classification) on Doppler US in benign and malignant nodules and probability of malignancy according to vascularity

Type of vascularity	Benign nodules	Malignant nodules	Probability of malignancy
Type 0	82 (6.1%)	8 (5%)	8/90 (8.9%)
Type 1	401 (29.9%)	40 (25%)	40/441 (9%)
Type 2	807 (60.1%)	88 (55%)	88/895 (9.8%)
Type 3	52 (3.9%)	24 (15%)	24/76 (31.6%)
	1,342	160	160/1,502 (10.6%)

Next, it was determined whether Doppler US using the second classification would be useful in addition to GSUS. The sensitivity and specificity of GSUS alone were 88.7% and 68.2%, respectively. Considering vascularity type 3 as “suspicious” and types 0-2 as “non-suspicious”, the addition of Doppler US did not change the sensitivity (89.4%) or specificity (66.4%) of GSUS. In the case of non-suspicious nodules on GSUS, Doppler US did not change the risk of malignancy, which was low irrespective of the type of vascularity (Table 3). In the case of suspicious nodules on GSUS, vascularity type 3 found in only 9% of these nodules increased the risk of malignancy [from 25% to 45% ($p < 0.002$)], but the other types of vascularity (types 0-2) did not reduce the probability of malignancy (Table 3).

Table 3. Probability of malignancy in suspicious and non-suspicious nodules on gray-scale ultrasound (GSUS) combined with type of vascularity on Doppler US (second classification)

Type of vascularity	Non-suspicious nodules on GSUS	Suspicious nodules on GSUS
Type 0	0/44	8/46 (17.4%)
Type 1	6/299 (2%)	34/142 (24%)
Type 2	11/566 (1.94%)	77/329 (23.4%)
Type 3	1/25 (4%)	23/51 (45%)
	18/934 (1.9%)	142/568 (25%)

DISCUSSION

Some characteristics of the study deserve to be highlighted. The design was prospective and a large number of nodules ($n = 1,502$) were analyzed. The nature of the nodules was defined by cytology or histology in > 99% of lesions. The nodules were selected according to current practice, in which FNA is recommended excep-

tionally for nodules < 1 cm (1-7). The two classifications most frequently used to define the type of nodule vascularity were evaluated (1,2,5-7,12,13,17). Instead of analyzing only the performance of Doppler US for the differentiation of benign and malignant nodules, its additional contribution to GSUS was also evaluated, since the latter is always obtained and its value has been well established. In addition, the rate of malignancy (approximately 10%) is in accordance with that observed in subjects with nodular thyroid disease (1,3-5,12,13), minimizing the probability that the predictive values obtained are under- or overestimated.

In the present study, the absence of blood flow was uncommon (only 5% of the nodules), probably because of the characteristics of the nodules studied (≥ 10 mm and solid). The expertise of the examiners may have also contributed to this finding. Grouping nodules with central flow, regardless of peripheral flow (first classification), the risk of malignancy was not higher in this group when compared to nodules without detectable flow or with exclusively peripheral flow. The risk of malignancy was only higher when predominantly or exclusively central flow was considered (second classification), although this flow was seen in only 15% of malignant nodules. Anyway, the second classification evaluated in this study provided better results. The Society of Radiologists in Ultrasound (1), French Society of Endocrinology (13) and Brazilian Society of Endocrinology (6) adopt a similar classification; however, we emphasize that the first classification is still used in the recommendations of the American Thyroid Association (2), American Association of Clinical Endocrinologists and European Thyroid Association (12), European Society for Medical Oncology (5), and National Comprehensive Cancer Network (7).

Even considering the second classification, we found no additional value of Doppler US to GSUS. In terms of clinical practice, two findings should be highlighted. First, only 2.7% of non-suspicious nodules on GSUS exhibited suspicious vascularity on Doppler US and the risk of malignancy of these nodules continued to be low. Second, among suspicious nodules on GSUS, although suspicious vascularity on Doppler US had increased the risk of malignancy, this risk remained high even in the absence of suspicious vascularity. Therefore, Doppler US did not change the indication for FNA based only on GSUS. In fact, many studies showing the usefulness of Doppler US analyzed its separate performance, but did not evaluate its additional value to GSUS (18).

Some factors can affect the performance of Doppler US. Power Doppler imaging is more sensitive in detecting the slow flow of small vessels and is more specific than color Doppler (19-21). It is important to use minimal probe pressure when evaluating superficial lesions to avoid obliteration of low-velocity blood flow. In addition, interobserver variability in describing blood flow in the nodule is possible. Power Doppler imaging was used in the present study and all radiologists were well aware of the effect of compression on Doppler US images. It should be noted that no blood flow was detected in only 5% of the nodules. Although previous studies have shown good interobserver agreement in the localization of nodule vascularity (22,23), we randomly selected 15 patients with 20 nodules to be evaluated by all three examiners and agreement in the type of vascularity was obtained for these nodules in all assessments (unpublished data). Moreover, the sensitivity and specificity of Doppler US calculated for each examiner were identical (unpublished data). In fact, the prospective design of the study, pre-establishing the types of vascularity, contributed to these uniform results.

Suspicious blood flow might be less frequent in nodules < 10 mm (11,24,25); as a consequence, there would be no reason to imagine that the contribution of Doppler US found in the present study (in nodules \geq 10 mm) is greater for infracentimetric nodules. In addition, the indications for FNA are highly selective in the latter case (1-7) and the evaluation of nodules > 10 mm is of greater practical applicability. We evaluated only solid or predominantly solid nodules. Since mixed nodules show a lower risk of malignancy (1,4,12,13,17), it is unlikely that Doppler US is more useful in the case of these nodules.

In our study, 92.5% (148 of 160) of malignancies were papillary thyroid carcinoma (PTC). Our study thus predominantly reflects the vascularity of PTC. However, we emphasize that the PTC accounts for up to 95% of differentiated thyroid carcinomas. In recent large series, even in nodules with “follicular neoplasm” or “follicular lesion of undetermined significance” cytology, 85% of malignant nodules were PTC (26,27). The classical and limited differential diagnosis between adenoma and follicular carcinoma is no longer appropriate for current cases of indeterminate cytology. In fact, the criteria for differentiating benign and malignant thyroid nodules and for recommending FNA are thus weighted for detecting

PTC (1-7,12,13,17). There is report that central flow is significantly associated with malignancy in follicular neoplasm, but did not evaluate its additional value to GSUS (18).

The vascularity, resistance index or pulsatility index was not quantified; only the pattern of vascularity was evaluated. No recommendations for the use of these parameters or objective cut-off values exist for predicting the malignancy of thyroid nodule (1-7,12,13,17).

In the present study, Doppler US provided no additional value to GSUS in defining the nature of thyroid nodules.

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