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Ultrasonography Classification of the American Thyroid Association for Predicting Malignancy in Thyroid Nodules >1cm with Indeterminate Cytology: A Prospective Study

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ABSTRACT

The objective of this prospective study was to evaluate the ultrasonography classification of the American Thyroid Association (ATA) for predicting malignancy in thyroid nodules >1 cm with indication for fine-needle aspiration (FNA) whose cytology was indeterminate. Additionally, the combination of the ATA classification with Doppler analysis was evaluated. All patients with thyroid nodules >1 cm were eligible. Each nodule was assigned to one of the ATA categories. Exclusively or predominantly intranodular vascularity was considered suspicious. One hundred and thirty-seven patients with 143 nodules underwent FNA and those with indeterminate cytology (Bethesda category III or IV) were selected. All patients were referred for surgery. Among the 143 nodules evaluated, 92 were benign, 33 were malignant, 13 were noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), and 5 were tumors of uncertain malignant potential (TUMP). The rate of malignancy, including NIFTP and TUMP in this definition, was 80 %, 42.8 %, 13 %, 10 %, and 23 % for nodules with a high suspicion, intermediate suspicion, low suspicion, very low suspicion, and undefined ultrasonographic pattern, respectively. Considering NIFPT and TUMP as benign, these rates were 72 %, 22.4 %, 4.3 %, 0 %, and 15.4 %, respectively. The addition of Doppler analysis did not significantly improve the prediction of malignancy obtained with the ATA classification alone. The results of this prospective study show the usefulness of the ATA ultrasonographic classification for predicting malignancy specifically in thyroid nodules >1 cm with indeterminate cytology. The ATA category of the nodule should influence the decision for follow-up, molecular tests, or surgery.

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Introduction

Thyroid nodules are common in clinical practice. Among nodules with an indication for fine-needle aspiration (FNA), about 20 % exhibit indeterminate cytology (Bethesda categories III and IV) [1]. In general, approximately 10 to 40 % of these nodules are malignant [1, 2]. This frequency rules out exclusive follow-up for any patient with indeterminate cytology. On the other hand, the recommendation of surgery in all cases would result in unnecessary thyroidectomies in most of them. Therefore, information that could improve the prediction of malignancy in these nodules is important and should preferably be obtained in a simple, widely accessible and inexpensive way.

For the decision of observation or surgery in the case of nodules >1 cm with indeterminate cytology (categories III and IV), the American Thyroid Association (ATA) recommends the use of molecular tests, but only after considering clinical and ultrasonography (US) data (recommendations 15 and 16) [3]. Indeed, when the last two suggest a high probability of cancer the negative predic-

tive value of currently available molecular tests is still insufficient to rule out surgery [4]. The probability of malignancy provided by clinical and US data can also change the positive predictive value of molecular tests and consequently influence the extent of surgery. In addition, since molecular tests are still not widely available and are expensive, their use is not always possible. In this situation, the management will depend on the clinical data, US findings, and patient preference [recommendation 15], or surgery is recommended (recommendation 16) [3]. Therefore, US findings are important (i) when molecular tests are not possible and, even if available, (ii) for the definition of cases in which a negative test can actually rule out surgery, and (iii) can also change the prediction of malignancy when a test of low specificity is positive.

Although there is consensus regarding the role of US, different ultrasonographic classifications have been proposed for predicting malignancy in thyroid nodules. Due to its simplicity and easy categorization of nodules and because it considers features that must be described in US is well known and has been proposed by a Society of worldwide recognition, the ATA classification [3] has a tendency of being used more widely and easily at least in America. In addition, the new ultrasonography classification of European Thyroid Association (ETA) is very similar to that of ATA [5]. Thus, studies evaluating malignancy specifically in nodules with indeterminate cytology using the ATA classification are relevant for clinical practice. However, these studies were retrospective [6–8], did not adopt a uniform criterion for FNA indication and/or the criterion was not the same recommended by current guidelines [6–10], only patients with a decision for surgery were included (selection bias) [6, 7, 10], or histology was not obtained for all nodules [8, 9]. In addition, some cases considered "cancer" would nowadays be diagnosed as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) [11], which would probably change the originally reported malignancy rate [2]. Finally, the vascularization pattern of the nodule is not included in the ATA [3] and ETA [5] ultrasonographic classification, but some studies suggest the value of this parameter in nodules with indeterminate cytology [12].

The objective of this prospective study was to evaluate the ultrasonographic classification of ATA [3] for predicting malignancy in thyroid nodules > 1 cm with indication for FNA according to current recommendations [3], whose cytology was indeterminate (Bethesda category III or IV). Additionally, we evaluated whether Doppler analysis improves the performance of the ATA classification. Histology was obtained for all nodules and the histological diagnosis of NIFTP [11] was also included.

Patients and Methods

This was a prospective study. The selection criteria of the patients, indications for FNA, and surgery were pre-established and rigorously followed. The study was approved by the Research Ethics Committee of our Institution (Santa Casa de Belo Horizonte) and informed consent was obtained from all subjects.

All euthyroid patients with thyroid nodules > 1 cm consecutively seen by the authors from 2014 to 2017 were initially eligible (n = 881). In view of the need for individual management, subjects with a history of familial thyroid carcinoma, subjects exposed to radiation in childhood or adolescence, subjects with a known diagnosis of thyroid carcinoma (previously submitted to partial thyroidectomy), and oncologic patients with nodules detected incidentally by FDG-PET were not included (n = 36). FNA guided by US was performed in the case of nodules with some suspicious finding (see below), solid hypoechoic nodules, solid iso- or hyperechoic nodules ≥ 15 mm, and complex or spongiform nodules ≥ 20 mm [13, 14]. Thus, 708 patients underwent FNA and 140 with indeterminate cytology (Bethesda categories III or IV) were selected. Cases initially exhibiting category III cytology were only included when a second FNA (interval of 3 months) confirmed indeterminate result [13–15]. All patients were referred for surgery. Three patients without condition for surgery were excluded. Finally, 137 patients with 143 nodules > 1 cm with indeterminate cytology were included.

Ultrasound was performed with a linear multifrequency transducer for morphological analysis (gray scale) and for power Doppler evaluation. The nodule was classified as hyper-, iso-, or hypoechoic to the surrounding thyroid parenchyma or as markedly hypoechoic when compared to the adjacent strap muscle. Margins were classified as smooth, infiltrative/spiculated/microlobulated (i. e., irregular), or ill-defined. Calcifications, if present, were classified as microcalcifications or macrocalcifications (including eggshell calcifications). In the simultaneous presence of macro- and microcalcifications, microcalcifications were defined. Shape was classified as taller than wide (greater in its anteroposterior dimension than in its transverse dimension) or wider than tall. Each nodule was assigned to one of the ATA categories before FNA [14]: "high suspicion", "intermediate suspicion", "low suspicion", and "very low suspicion". The "undefined" category corresponded to iso- or hyperechoic nodules with some suspicious finding, that is, irregular margins, microcalcifications, a taller than wide shape, and rim calcifications with a small extrusive soft tissue component [16]. The type of blood flow of all thyroid nodules was evaluated before FNA: type 0, no vascularity; type 1, peripheral vascularity; type 2, peripheral and intranodular vascularity; type 3, exclusively or predominantly intranodular vascularity, which is considered suspicious of malignancy [12, 17–19]. US/Doppler was performed by radiologist experienced in thyroid imaging (A.L.S.) and the original images were revised separately by the other author experienced in thyroid imaging (P.W.R.) and the category of each nodule was defined and then compared. Disagreement between the two authors (category of the nodules) occurred in only two nodules. These nodules were reanalyzed by the authors and their category was defined eventually.

The cytology smears and histology slides were analyzed by pathologist experienced in thyroid pathology (M.B.N.) who was unaware of the results of the imaging method (US). On histology, the nodules were defined as benign, malignant, tumor of uncertain malignant potential (TUMP), or NIFTP. The last two were diagnosed according to the criteria defined by Williams [20] and Nikiforov et al. [11], respectively.

Fisher's exact test and the Mann–Whitney U-test were used for statistical analysis. A p-value less than 0.05 was considered significant.

Results

One hundred and twelve of the 137 patients included were women, ranging in age from 18 to 71 years. Among the 143 nodules ana-

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lyzed, 92 were benign, 33 were malignant [15 invasive or infiltrative encapsulated follicular variants of papillary thyroid carcinoma (FVPTC), 13 classical PTC, and 5 follicular carcinomas], 13 were NIFTP [11], and 5 were TUMP [20]. According to the ATA ultrasonographic classification [3, 14], 25 nodules were classified as high suspicion, 49 as intermediate suspicion, 46 as low suspicion, 10 as very low suspicion, and 13 as undefined.

The frequency of malignancy in each category of the ATA classification [3, 14] is shown in ▶ **Table 1**. The frequency of malignancy in nodules classified as undefined according to the ATA ultrasonographic classification [16] because they were iso- or hyperechoic but exhibited some suspicious US finding (see Methods) was lower than that of highly suspicious nodules and similar to that of nodules with intermediate suspicion (▶ **Table 1**).

Indeed, excluding NIFTP [11] and TUMP [20] from the cancer cases, the frequency of malignancy in thyroid nodules > 1 cm with indeterminate cytology decreased from 35.6 % to 23 %. This reduction was more evident in nodules with the intermediate suspicion US pattern [3, 14] (from 42.8 % to 22.4 %).

The addition of Doppler analysis of vascularization did not significantly improve the prediction of malignancy in these nodules > 1 cm with intermediate cytology when compared to the ATA classification alone (▶ **Table 2**).

▶ **Table 1** Frequency of malignancy in thyroid nodules > 1 cm with intermediate cytology according to the ultrasonography classification of the American Thyroid Association [3, 14].

Ultrasonographic category	Malignancy on histology
High suspicion (n = 25)	18 (72 %)[a]
	20 (80 %)[b]
Intermediate suspicion (n = 49)	11 (22.4 %)[a]
	21 (42.8 %)[b]
Low suspicion (n = 46)	2 (4.3 %)[a]
	6 (13 %)[b]
Very low suspicion (n = 10)	0[a]
	1 (10 %)[c]
Undefined (n = 13)	2 (15.4 %)[a]
	3 (23 %)[b]

TUMP: Tumor of uncertain malignant potential; NIFTP: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features; [a] Considering NIFTP and TUMP as benign; [b] Considering NIFTP and TUMP as malignant.

Discussion

As mentioned earlier, previous studies have limitations (retrospective design, lack of a criterion for FNA indication, selection bias of the patients, lack of information about cases of NIFTP) [6–10]. We highlight some characteristics of the present study. This study was prospective and the indication for FNA and management were pre-defined and rigorously followed. Only nodules with an indication for FNA according to current guidelines [3, 13, 14] were included, which approximates the study to clinical practice. All patients with category III cytology underwent FNA repetition since this is the recommended management when molecular tests are not available [2, 3, 13–15]. Certainly, one of the problems of previous studies is that only patients undergoing surgery were included [6, 7, 10]. Since US could have influenced the decision of surgery, this selection bias may have contaminated the rate of malignancy found in the ultrasonographic categories. In the present study, histology was obtained in all cases and we analyzed the rate of malignancy with and without exclusion of NIFTP and TUMP [2, 11, 20]. Finally, in addition to evaluating the ATA ultrasonographic classification, the possible value of its combination with Doppler was analyzed.

▶ **Table 2** Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the ultrasonography classification of the American Thyroid Association (ATA) [3, 14] alone and combined with Doppler analysis of thyroid nodules > 1 cm with indeterminate cytology.

	Malignancy (without NIFTP or TUMP)		Malignancy, NIFTP or TUMP	
	ATA classification	ATA classification with Doppler	ATA classification	ATA classification with Doppler
Sensitivity	18/33 (54.5 %)[a]	22/33 (66.6 %)[a]	20/51 (39.2 %)[a]	26/51 (51 %)[a]
	29/33 (87.8 %)[b]	30/33 (90.9 %)[b]	41/51 (80.4 %)[b]	43/51 (84.3 %)[b]
Specificity	103/110 (93.6 %)[a]	90/110 (81.8 %)[a]	87/92 (94.5 %)[a]	78/92 (84.8 %)[a]
	65/110 (59 %)[b]	59/110 (53.6 %)[b]	59/92 (64.1 %)[b]	53/92 (57.6 %)[b]
NPV	103/118 (87.3 %)[a]	90/101 (89.1 %)[a]	87/118 (73.7 %)[a]	78/103 (75.7 %)[a]
	65/69 (94.2 %)[b]	59/62 (95.1 %)[b]	59/69 (85.5 %)[b]	53/61 (86.9 %)[b]
PPV	18/25 (72 %)[a]	22/42 (52.4 %)[a]	20/25 (80 %)[a]	26/40 (65 %)[a]
	29/74 (39.2 %)[b]	30/81 (37 %)[b]	41/74 (55.4 %)[b]	43/82 (52.4 %)[b]

TUMP: Tumor of uncertain malignant potential; NIFTP: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features; [a] Considering only highly suspicious nodules as positive US; [b] Considering only highly suspicious nodules and nodules with intermediate suspicion as positive US.

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The rate of malignancy found in the present series for nodules > 1 cm with indeterminate cytology was higher than that expected originally by the Bethesda System [15], but similar to that reported in more recent series [1, 2]. Furthermore, previously, most nodules > 1 cm were submitted to FNA, while greater rigor currently exists in the indication for FNA, a fact that may contribute to the higher rate of malignancy when the current indications for FNA are followed [3, 13, 14], as done in the present study. The exclusion of nodules classified as NIFTP or TUMP on histology reduced the malignancy rate from 35.6 % to 23 %, in agreement with previous studies [2]. One interesting observation is that NIFTP and TUMP mainly had an impact on the rate of malignancy in the case of nodules with the "intermediate suspicion" US pattern.

Based on the results of the present study, we believe that the ATA ultrasonographic classification [3, 14] can be used for decision-making in nodules > 1 cm with indeterminate cytology. In the case of "highly suspicious" nodules, the risk of malignancy was > 70 %. Considering this pre-test probability, even if currently available molecular tests are negative, the risk of malignancy would still be ≥ 20 % [4] and surgery could not be ruled out. In the case of these nodules, molecular tests would be useful to define the extent of surgery if lobectomy would be an option. No case of malignancy was observed among the few "very low suspicion" nodules, which were submitted to FNA because of their size ≥ 2 cm [3, 13, 14]. This finding supports the recommendation that patients could be spared from FNA [3, 5, 13, 14]. If FNA were performed because of the size of the nodule, unless a reason for surgery other than malignancy exists, follow-up would only be an acceptable management, even if cytology is indeterminate. Among "low suspicion" nodules, 4.3 % were carcinomas, 8.7 % were NIFTP, and 87 % were benign. Prompt indication of surgery in these cases resulted in unnecessary thyroidectomies in > 85 % of patients. Although NIFTP is considered a surgical lesion [11], because of its very low metastasizing potential [11, 21], in our opinion monitoring is an option that should be discussed with the patient when molecular tests are not available and the nodules are not large. If molecular tests were performed, except for the presence of specific mutations such as $BRAF^{V600E}$, a positive result would have a low positive predictive value [4], mainly indicating diagnostic surgery. Probably, the nodules for which molecular tests would be more useful are those with the "intermediate suspicion" US pattern. In these nodules, a negative result or "suggestive of a benign nature" has a sufficient negative predictive value for the decision of follow-up, while surgery (diagnostic if the test is less specific or oncologic if the test is highly specific) is necessary in the case of a positive result. Finally, previous studies suggest the risk of malignancy in undefined nodules according to the ATA ultrasonographic classification to be similar to that of "intermediate suspicion" nodules [16, 22]. The present results obtained for the few undefined nodules according to the ATA classification with indeterminate cytology agree with this observation. Thus, the same management could be extrapolated to these nodules.

We recognize limitations of our study. First, the sample consisted of only 143 nodules because of the prospective design, careful indication for FNA as currently recommended, and the sole inclusion of nodules with indeterminate cytology (including the need for FNA repetition in cases with initial Bethesda III cytology). Nevertheless, differences were observed between groups. In addition, this is the study evaluating the ATA classification with the highest number of nodules with indeterminate cytology [6–10]. However, the small number of nodules in each category did not permit to separately evaluate the value of Doppler analysis of nodule vascularization for each category. Second, considering the reasons addressed in the introduction of this article, we used the ATA ultrasonographic classification [3, 14], very similar to ETA [5], but the risk of malignancy might be different if other ultrasonographic classifications are employed. Finally, another limitation was that we did not perform molecular tests.

In conclusion, the results of this prospective study show the usefulness of the ATA ultrasonographic classification in predicting malignancy specifically in sporadic thyroid nodules > 1 cm with indeterminate cytology. The ATA category of the nodule should be considered in the decision for exclusive follow-up and indication for molecular tests and surgery. Apparently, Doppler analysis of vascularization did not significantly improve the prediction of malignancy obtained with the ATA classification alone.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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