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Diagnostic accuracy of fine needle aspiration of the thyroid: a comparative study of the technique with and without ultrasonography

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Summary. *Background and aim of the work:* Fine needle aspiration biopsy (FNAB) of thyroid is an indispensable procedure in the evaluation of patients with thyroid nodules. The aim of this study was to evaluate the benefit of ultrasonography (USG)-guided FNAB compared to the conventional method. *Methods:* In this comparative cross-sectional study FNAB samples were collected in 1984 (G1) and 2011 (G2). In G1 (113 patients) FNAB was performed by palpation, and in G2 (1,049 patients) it was USG-guided. Statistical analysis included sensitivity, specificity, positive/negative predictive value, and likelihood ratio. Associations were considered statistically significant when *p-value*≤0.05. *Results:* The percentage of unsatisfactory material was 24% in G1 and 7.8% in G2. The sensitivity/specificity in G1 were 40% / 71%, and in G2, 83% / 94.7%. In G2, it was possible to select 77.7% of malignant nodules for surgery, while in G1 only 10%. In G2, the frequency of malignancies was similar between nodules smaller and larger than 1 cm (Fisher's exact test *p-value*=0.33). *Conclusions:* Our data confirm that FNAB is a valid technique for screening malignant thyroid nodules, especially when guided by USG. Since subcentimetric nodules harbor malignancy as much as larger nodules, we recommend performing FNAB in all thyroid nodules, regardless of size.

Key words: thyroid gland nodules, nodular goiter, thyroid needle aspiration, differentiated thyroid cancer, cytopathology

«Accuratezza diagnostica dell'utilizzo dell'ago aspirato sottile per la tiroide: studio comparativo della tecnica con e senza ecografia»

Riassunto. *Contesto e scopo dello studio:* L'agoaspirato della tiroide (FNAB) è una procedura indispensabile per la valutazione di pazienti con noduli alla tiroide. Questo studio intende valutare i benefici derivanti dall'agoaspirato con ultrasonografia guidata (USG) paragonato al metodo tradizionale. *Metodi:* In questo studio comparativo trasversale, i campioni ottenuti con FNAB sono stati raccolti nel 1984 (G1) e nel 2011 (G2). Nel G1 (113 pazienti) FNAB è stato eseguito attraverso la palpazione, nel G2 (1.049 pazienti) è stato eseguito un USG. Le analisi statistiche comprendevano sensibilità, specificità, valore predittivo positivo/negativo e rapporto di verosimiglianza. Le associazioni sono state considerate statisticamente significative in presenza di p-value≤0.05. *Risultati:* La percentuale di materiale non soddisfacente è stata del 24% nel G1 e del 7,8% nel G2. La sensibilità/specificità nel G1 sono state del 40% / 71% e nel G2 del 83% / 94,7%. Nel G2 è stato

possibile selezionare 77,7% di noduli maligni per chirurgia, mentre nel G1 solo il 10%. Nel G2, la frequenza di neoplasie maligne era simile tra i noduli più piccoli e più larghi di 1 cm (Test di Fisher p-value=0,33). *Conclusioni:* I nostri dati confermano che FNAB è una tecnica valida per lo screening dei noduli maligni della tiroide, specialmente quando guidata con USG. Dal momento che i noduli più piccoli di 1 cm potrebbero essere maligni così come quelli più larghi, raccomandiamo di eseguire FNAB per tutti i noduli tiroidei, indipendentemente dalle dimensioni.

Parole chiave: noduli tiroidei, noduli del gozzo, agoaspirato della tiroide, cancro differenziato della tiroide, citopatologia

Introduction

Despite the high prevalence of thyroid nodules (1), the low frequency of malignancy in them makes it impractical to perform surgical removal in all cases, considering the morbidity/mortality of the procedure. Before the use of fine needle aspiration biopsy (FNAB) of the thyroid, selection of patients with thyroid nodules for surgery was only based on clinical criteria. These days, ultrasonographic aspects and nodule consistency, or the presence of atypical cervical lymphadenopathy, are factors still considered in the indication for surgery in subjects with indeterminate cytological diagnosis.

The introduction of ultrasonography (USG) in the study of thyroid nodules confirmed the high prevalence of these lesions in the general population (1, 2) and has become an auxiliary element of great value in guiding FNAB, providing access to minor lesions with less risk of puncturing large vessels. Furthermore, in cases of multinodular goiters, by USG it is possible to select nodules with ultrasonographic predictors of malignancy, which must have priority in cytological evaluation, improving the sensitivity and specificity of the technique.

In the present study, we investigated the differences in diagnostic value between thyroid FNAB guided by palpation and by USG in relation to material sufficiency and accuracy in selecting malignant nodules for surgery.

Materials and methods

We compared two groups of patients with nodular goiters who underwent FNAB. In both groups the sample collection was performed by the same physician. In the first group (G1), the 113 palpation-guided FNAB were performed in 90 consecutive patients from the Outpatient Clinic for Thyroid Gland Diseases, at the School Hospital Complex under Prof. Edgard Santos, Federal University of Bahia (C-HUPES/UFBa), in 1984. The second group (G2) included 1,049 FNAB samples performed at the Department of Ultrasonography and Pathology of the São Rafael Hospital, Monte Tabor Foundation (HSR), in 2011. The study was previously approved by the HSR Ethics Committee in Research and all the patients gave their informed consent to participate in this study.

Samples were considered suitable for diagnosis when, in at least two slides, there were six or more groups of well-preserved follicular cells, each group consisting of at least ten cells (3) or a smaller number of cells with atypia (4, 5). In those patients whose first FNAB presented insufficient material to determine cytological diagnosis, a second FNAB was performed. When the second FNAB was satisfactory for diagnosis, the latter was considered as definitive.

The cytological study was performed by a single observer in G1, and cytological diagnoses were graded as follows: unsatisfactory material, negative for malignancy, suspicious for malignancy and positive for malignancy. Fifty subjects from G1 were referred for thyroidectomy.

The cytological evaluation in G2 was performed by several members of the service staff, who randomly analyzed a certain number of tests in their work routine. During collection of the G2 data the Bethesda classification had already been proposed (6, 7) and pathologists were free to use it or not, a fact that was considered in the analysis of data. Thirty-nine patients were identified as candidates for surgery, out of 96 sub-

jects diagnosed with Bethesda III-VI (or other equivalent diagnoses). The 10 patients with nodules larger than 3 cm all underwent surgery.

In both groups, the type of surgery the patients underwent was total thyroidectomy.

FNAB technique

In G1, the nodules were fixed with one hand and the executor aspirated the material with the other, making two or three punctures in palpable nodules. The slides did not identify the lobe affected, only the patient's name, and it was not possible to distinguish if the palpable lesion corresponded to only one or several confluent nodules.

In G2, the nodules were partly fixed by the ultrasonographer with the transducer unit of the USG device, while the other observer punctured inside the lesion away from the fluid-filled areas (cysts) or caliber vessels. In the presence of true cysts, we proceeded to aspiration of the fluid, which was sent for analysis by cell-block technique after centrifugation. In complex nodular lesions, we attempted to aspire solid parts. Nodules larger than 3cm in the largest diameter were evaluated on their upper, middle and lower third part, with the same radial movements, and, when they were heterogeneous (suggesting they were confluent nodules) we aimed to puncture areas with different patterns of echogenicity. When there was more than one nodule in the same lobe, we started by puncturing the largest nodules or those with ultrasonographic features suggestive of malignancy (8-11). The collected material was placed on microscope slides, identified with the patient's name and the nodule location (RL for right lobe, LL for left lobe, and I for isthmus).

On average, six blades were made per aspirated nodule in both G1 and G2, which were immediately fixed in a solution of ethanol 96%, and then stained with Papanicolau staining. Congo red staining was used in those cases suspected of medullary carcinoma.

Statistical analysis

Data were stored and analyzed using the *Statistical Package for the Social Sciences* version 20.0 (SPSS®, *IBM*). To evaluate the association of malignancy with categorical variables (size of the nodules in uninodular goiters; ≤1cm and >1cm) we used Pearson's test, and the association was considered statistically significant when $p\text{-}value \leq 0.05$.

Data analysis in G1 took into consideration the material aspirated as a whole, while in G2 each thyroid lobe was considered. The 49 patients who underwent surgery in G2 enabled us to make 93 comparisons between cytological and histopathological diagnosis (considering the lobes studied). When we sought to evaluate whether the nodule size affects the possibility of malignancy we considered the single nodules separately, which were classified as ≤1cm and >1cm in their largest diameter.

In order to make the diagnosis classifications applied in both groups compatible, unsatisfactory material was considered as Bethesda I, negative for malignancy as Bethesda II, suspicious for malignancy as Bethesda III-V, and positive for malignancy as Bethesda VI.

Sensitivity, specificity, positive and negative predictive values of FNAB were calculated for both groups. Sensitivity was calculated by dividing the number of FNAB-positive nodules by the number of malignant nodules (histopathology). Specificity was calculated by dividing the number of FNAB-negative nodules by the number of benign nodules (histopathology). Indeterminate diagnosis cases were not considered for this calculation.

The likelihood ratio was used for diagnostic tests with more than two possible results, such as cytopathology.

Results

Group 1

Clinical data of patients who did not undergo surgical treatment were not recovered. The first FNAB performed in each patient frequently exhibited unsatisfactory material for diagnosis, but as more tests were performed, the smears showed greater cellularity, especially in cases of malignancy and lymphocytic thyroiditis. The 50 patients who underwent surgery had normal thyroid function and clinical parameters; only the consistency of the nodule helped in predict-

ing malignancy. Forty (80%) patients had thyroid consistency described as elastic. Out of the five cases of cancer, three (60%) had a hard and stony gland consistency.

One case had a smear with unsatisfactory material for diagnosis, there being few follicular cells, and some cells with voluminous hyperchromatic nuclei and scanty cytoplasm. It was the only case in which cytological analysis alone indicated surgical treatment. It was a papillary thyroid carcinoma.

Group 2

Of the 1,049 patients, 903 (86.1%) were female, and the mean age was 49.97±14.7 years (ranging from 7-88 years). Table 1 shows the demographic, cytological and histopathological characteristics in both groups. 7.8% of FNAB in G2 patients exhibited insufficient material, but only 2.1% of punctures produced unsatisfactory material for diagnosis in patients who underwent surgery. Two cases recorded in this group refer to patients with multinodular goiters in whom there was cytological diagnosis of Bethesda IV and V in one of the lobes, and the material was insufficient for diagnosis in the contralateral lobe. Patients who underwent surgery given the enlargement of the gland (10 cases) did not present any unsatisfactory material.

Table 2 refers to the distribution of the 1,521 nodules according to their location in the gland; we note that 57.3% of the patients examined suffered from uninodular goiters. Of the 96 patients with diagnosis or suspicion of malignancy, 75 (78.1%) had uninodular goiters. In patients from this group who underwent surgery, 63.3% had uninodular goiters. However, of those patients who underwent surgery due to an increase in thyroid volume, 90% had multinodular goiters. In this group the consistency of nodules was not evaluated.

Table 1. Demographic, cytological and histopathological characteristics from both groups evaluated by FNAB and surgery.

	Group 1	Group 2	Proportions Test
Gender			
Male	3	8	
Female	47	41	
Age (years)	39.3±12.0	45.6±16.1	
Cytopathological diagnosis			
Unsatisfactory material (Bethesda I)	12 (24%)	2 (2.1%)	0.0001
Negative for malignancy (Bethesda II)	33 (66%)	37 (39%)	0.018
Suspicion for malignancy (Bethesda III-V)	3 (6%)	44 (47%)	0.000000
Positive for malignancy (Bethesda VI)	2 (4%)	10 (10.7%)	0.37
Histopathological diagnosis			
Adenomatous goiter	28 (56%)	43 (46.2%)	
Follicular adenoma	13 (26%)	2 (2.1%)	
Thyroiditis + follicular adenoma	1 (2)		
Adenomatous goiter + follicular adenoma	1 (2)		
Hashimoto's thyroiditis	2 (4)	3 (3.2%)	
Benign Hürthe's tumor		3 (3.2%)	
Papillary carcinoma	4 (8%)	40 (43%)	
Follicular carcinoma	1 (2%)	0 (0)	
Medullary carcinoma	0 (0)	2 (2.1%)	
Total	50 (100) nodules	93 (100) nodules	

Table 2. Distribution of nodules in G2, according to their location in the thyroid gland.

Type of goiter	Lobes	Number of subjects	Number of nodules
Uninodular	Right lobe	325	325
	Left lobe	265	265
	Isthmus	12	12
Multinodular	Right and left lobes	390	780
	Right lobe and isthmus	18	36
	Left lobe and isthmus	14	28
	Right lobe, left lobe and isthmus	25	75
	Total	1,049	1,521

Table 3. Percentage of malignancy in thyroid nodules from G2 in the preoperative evaluation by FNAB using the Bethesda classification.

Cytological diagnosis	Malignancy/total number of nodules (% Malignancy)	Likelihood ratio
Bethesda I	0/1 (0%)	
Bethesda II	2/21 (9.5%)	0.7
Bethesda III	4/8 (50%)	0.85
Bethesda IV	9/14 (64.2%)	1,5
Bethesda V	11/12 (91.6%)	10
Bethesda VI	10/10 (100%)	>277

The Bethesda classification was used in 70.9% of the G2 patients who underwent surgery (Table 3). Using the proportions test we note that the amount of unsatisfactory material was much greater when FNAB was performed by palpation (Fig. 1). With USG-guided FNAB and using the Bethesda classification one observed an increase in the percentage of undetermined cases. Cytological diagnosis of malignancy were given by palpation-guided FNAB and USG-guided FNAB, without distinction. The sensitivity and specificity of FNAB in G2 were higher than in G1 (Table 4).

In G1, FNAB found 10% of malignancies; in G2 it allowed us to select 77.7% of malignant nodules, excluding those patients operated on due to the large size of the goiter. There was no difference in the size of the thyroid nodule (whether ≤1 or >1cm) regarding the benign or malignant nature of the lesion (Table 5).

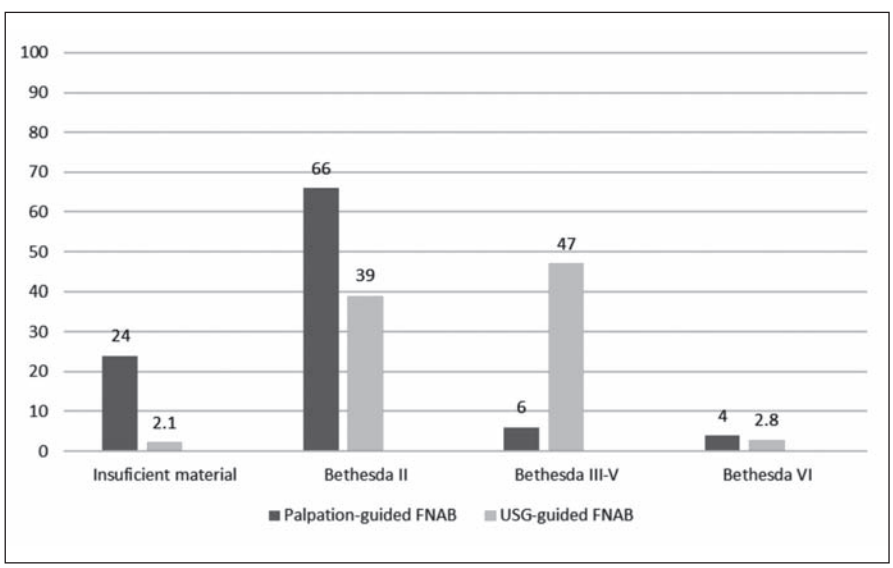

Figure 1. Proportions test among the cythological diagnosis levels.

Table 4. Sensibility, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FNAB in both groups.

	Sensibility	Specificity	PPV	NPV
Group 1	40%	71%	100%	97%
Group 2	83%	94.7%	100%	94.6%

Table 5. Frequency of malignancy in nodular goiters, according to their largest diameter (47 nodules).

	≤1 centimeter	>1 centimeter	p-value
Right lobe	7 (12%)	5 (12%)	
Left lobe	8 (9%)	10 (11%)	
Isthimus	1 (3%)	0 (0%)	
Total	16 (24%)	15 (23%)	0.33

Discussion

The increase in life expectancy in patients with well-differentiated thyroid tumors when properly treated (12, 13) encourages us to seek ways of enhancing the technique that best selects patients for surgery (14). Palpation-guided FNAB is currently still performed in other centers (15). The current study is similar to Coorough *et al.*, which performed palpation-guided FNAB until 2005 (16).

Our results confirm that FNAB is a valid technique for evaluating thyroid nodules, with a reasonable sensitivity and high specificity even without the use of USG (17). This fact was previously evidenced by several authors (16, 17). The superiority of the technique in the parameters assessed in G2 probably results from the use of USG for selecting areas to be punctured. However, other factors such as improved preparation of smears and greater familiarity by pathologists with the technique may have played a part.

The insufficiency of aspirated material was quite different in the two groups, and in G2 it was slightly lower than reported in the literature, where it ranges from 11-16% of cases (5, 18-21).

The clinical parameters of patients with nodular goiters do not allow malignancy to be diagnosed (21). Nevertheless, in G1 the consistency of nodules while performing FNAB pointed to the malignant nature thereof. Most of the malignant nodules had a marked increase in consistency. Based on this characteristic, elastography may be an additional tool for identifying malignant thyroid nodules (22, 23).

Most of the patients evaluated by FNAB and those who underwent surgery with a suspicion of malignancy had uninodular goiters. However, patients with benign nodules operated on because of the increased volume of the gland nearly all had multinodular goiters. This suggests that the surgical indication in cases of large benign goiters may have been influenced by the multiplicity of nodules. There persists in the literature some doubt whether the presence of a single nodule increases the possibility of malignancy (21, 24, 25).

When assessing different levels of FNAB diagnosis by likelihood ratio, it is clear that a Bethesda II diagnosis excludes malignancy with great accuracy. For Bethesda III and IV there was a paradox (probably due to the small number of cases): while simple frequency revealed that over 50% of these nodules were malignant, the likelihood ratio tended to rule out malignancy. Previous data show that Bethesda III nodules are malignant in 5-20% of cases (4). Bethesda V and VI are practically equivalent regarding malignancy. This fact is consistent with several studies in which the false positive rate at these levels (especially level VI) is extremely low (19).

The Bethesda classification was not used by the majority of pathologists in G2. It separated the benign (Bethesda II) from malignant nodules (Bethesda VI), while among the indeterminate diagnoses (Bethesda III to V) the likelihood ratio is not well defined. This classification needs to be tested and adjusted regarding cytological parameters, since levels III to V, which correspond to the category suspected of malignancy, do not separate benign and malignant nodules with any higher precision than the previous classification (used in G1).

The high frequency of malignant nodules, as seen in our caseload, may be a result of improvements in FNAB technique. Nevertheless some authors believe that there is an actual increase in the incidence of malignant thyroid nodules (26).

Surprisingly, in the present study 20% of cancers were follicular carcinomas in G1, while in G2 there were no cases of this type of tumor. Considering that the number of patients studied in G2 is about eightfold greater than in G1, the absence of follicular carci-

noma in this group becomes even more significant. A similar survey by Coorough *et al.* also failed to reveal any case of follicular carcinoma or oxyphilic follicular cell tumor in a cohort of 3,981 patients (16). This "disappearance" of follicular carcinoma has attracted the attention of several authors from different parts of the world (26-28). It is believed that the status of iodine supplementation may be the determining factor for this. Medullary carcinoma of the thyroid did not appear in G1, possibly due to the small number of patients. In G2, it accounted for 4.8% of malignant tumors, similar to previous reports (29).

Between 10 and 34% of FNAB diagnoses result as unspecified (19, 28), and in our work 9.2% of the material collected was considered suspicious for malignancy. It is known that a major limitation of FNAB in the diagnosis of malignancies consists in its inability to distinguish follicular adenoma and carcinoma. Considering the "disappearance" of malignant follicular nodules, FNAB will have greater diagnostic power, since the technique is quite accurate for diagnosing papillary tumors. Like other authors (4), we cannot explain the cause of the increase in the percentage of indeterminate diagnoses in G2.

In fact, one limitation of our study is that there is a large gap between data collection in both groups, which has implications regarding changes in pathological classification of thyroid malignancies, as well as the fact that different pathologists analyzed the samples from both groups. However, submitting patients to palpation-guided FNAB these days for research purposes would be ethically reprehensible. Thus, considering the principle of non-maleficence, we chose to collect data for G1 retrospectively.

It can be argued that only a small part of our sample affords pathological confirmation of the diagnosis. Obviously, in G1 and G2 the decisive criteria for thyroidectomy were the clinical features and the cytological analysis, respectively. Considering the postoperative morbidity associated with thyroidectomy, such a course was assessed on an individual basis by the medical staff involved in patient care. Thus, the study protocol had no interference in therapeutic recommendations.

The Brazilian and American guidelines recommend investigation by FNAB in nodules larger than 1cm and in those with ultrasonographic features suggestive of malignancy, regardless of size (10, 11). In the present work, there was no difference in the frequency of malignancy among nodules smaller and larger than 1 cm. Hence, like previous authors (9, 30) we also believe that FNAB should be performed in nodules of any size, especially when solid, hypoechogenic, with microcalcifications and irregular margins.

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