



ORIGINAL ARTICLE

## Repeated fine-needle aspiration cytology for the diagnosis and follow-up of thyroid nodules<sup>☆</sup>



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### KEYWORDS

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### Abstract

**Introduction:** The recently-proposed Bethesda reporting system has offered clinical recommendations for each category of reported thyroid cytology, including repeated fine-needle aspiration (FNA) for non-diagnostic and atypia/follicular lesions of undetermined significance, but there are no sound indications for repeated examination after an initial benign exam.

**Objective:** To investigate the clinical validity of repeated FNA in the management of patients with thyroid nodules.

**Method:** The present study evaluated 412 consecutive patients who had repeated aspiration biopsies of thyroid nodules after an initial non-diagnostic, atypia/follicular lesion of undetermined significance, or benign cytology.

**Results:** The majority of patients were female (93.5%) ranging from 13 to 83 years. Non-diagnostic cytology was the most common indication for a repeated examination in 237 patients (57.5%), followed by benign (36.8%), and A/FLUS (5.6%) cytology. A repeated examination altered the initial diagnosis in 70.5% and 78.3% of the non-diagnostic and A/FLUS patients, respectively, whereas only 28.9% of patients with a benign cytology presented with a different diagnosis on a sequential FNA.

**Conclusions:** Repeat FNA is a valuable procedure in cases with initial non-diagnostic or A/FLUS cytology, but its routine use for patients with an initial benign examination appears to not increase the expected likelihood of a malignant finding.

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**PALAVRAS-CHAVE**

Glândula tireoide;  
Neoplasias da  
glândula tireoide;  
Biópsia por agulha  
fina;  
Neoplasias de cabeça  
e pescoço

**Repetição da punção por agulha fina para o diagnóstico e seguimento de nódulos de tireoide****Resumo**

**Introdução:** A classificação de Bethesda para relatórios citológicos de tireoide oferece recomendações clínicas para cada categoria diagnóstica, incluindo a repetição do exame de punção para exames citológicos não diagnósticos (ND) e atipia/lesão folicular de significado indeterminado (A/FLUS). Todavia, a repetição da punção para pacientes com exame citológico inicial benigno ainda é discutida.

**Objetivo:** Investigar a validade da punção repetida para o manejo de pacientes com nódulos tireoidianos.

**Método:** Estudo longitudinal histórico avaliando 412 pacientes consecutivos com biópsias aspirativas repetidas de nódulos da tireoide após exame inicial ND, A/FLUS, ou benigno.

**Resultados:** A citologia não diagnóstica foi a indicação mais comum para um exame repetido em 237 pacientes (57,5%), seguida por citologia inicial benigna (36,8%) e A/FLUS (5,6%). Um exame repetido alterou o diagnóstico inicial de 70,5% e 78,3% dos pacientes com citologia inicial não diagnóstica e A/FLUS, respectivamente, enquanto apenas 28,9% dos pacientes com uma citologia inicial benigna apresentaram um diagnóstico diferente em uma punção sequencial.

**Conclusões:** Repetir a punção aspirativa é um procedimento válido para pacientes com citologia inicial não diagnóstica ou atipia/lesão folicular de significado indeterminado, mas seu uso rotineiro em pacientes com exame inicial benigno parece não aumentar a probabilidade de malignidade para este grupo.

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**Introduction**

Thyroid nodules are common. Current data suggest that nodules are present in 5% to 10% of women and 1% to 2% of adult men.<sup>1-3</sup> Furthermore, nodules have been incidentally diagnosed *via* ultrasound scans in up to 67% of elderly females.<sup>4,5</sup> It is believed that 5% to 15% of these nodules are malignant.<sup>6</sup> Clinical and diagnostic findings are warranted to differentiate patients at risk for malignancy who require further workup. This enhanced diagnosis likely contributes to the increase in surgically treated thyroid cancers over the last decades, which affect 3.5–8.5/100,000 of women and 2.3/100,000 of men.<sup>7,8</sup> Fine-needle aspiration (FNA) biopsy has proved to be a valuable tool for the evaluation of these nodules, with a diagnostic accuracy of approximately 97% and pivotal clinical implications.<sup>9,10</sup> In general, FNA biopsy is recommended for solid hypoechoic nodules greater than 1 cm in largest dimension, mixed solid/cystic nodules greater than 2 cm, and microcentimeter nodules with suspect ultrasound features, such as microcalcifications and irregular borders. In addition, FNA is warranted for patients at high risk for thyroid cancer, including those with a familial history for this cancer or multiple endocrine neoplasia, and exposure to ionizing radiation in early life. The recently described Bethesda system for reporting thyroid cytopathology outlines six categories with correlating clinical recommendations for each category. A repeated FNA, within three to six months, is suggested for initial non-diagnostic examinations and also for patients with atypia/follicular lesions of undetermined significance (A/FLUS).<sup>11-13</sup> A sequential exam is not routinely recommended for patients with initial benign cytology, as most are judiciously followed-up with sequential clinical examination

and imaging. Despite this practice, some data suggest that repeated FNA should also be considered for patients with an initial benign cytology in order to decrease the risk of false negatives and confirm the benign features of these nodules.<sup>14-20</sup> Therefore, the present study sought to evaluate the indications and validity of repeated FNA in the management of patients with thyroid nodules.

**Materials and methods**

This was a retrospective cohort study of 568 consecutive patients who had repeated aspiration biopsies of thyroid nodules evaluated in a single center between January of 1998 and December of 2010. Due to differences in thyroid cytology reporting over the study period, all cytological results were updated according to the 2010 Bethesda system for reporting thyroid cytology. All patients had an initial examination classified as non-diagnostic, benign, or A/FLUS, and at least one more repeated FNA within a maximum interval of 36 months between aspirations, in addition to no significant clinical or radiological changes in the previously evaluated dominant or single nodule. Patients with a repeated FNA within a time frame greater than the previously mentioned, and those with a cytology report of follicular neoplasm, suspected for malignancy or confirmed as malignant, were excluded. Descriptive and comparative statistical analyses were performed using SPSS 13.0 for Windows® and sought to assess the possibility of repeated aspiration to alter the initial diagnosis, with a particular interest in the rate of suspect/malignant findings on subsequent FNA stratified by initial cytological diagnosis. The results were expressed as frequencies and percentages,

**Table 1** Cytology results for initial *versus* repeated fine-needle aspiration (FNA).

FNA 2	FNA 1		
	Non-diagnostic benign A/FLUS		
ND	70 29.5%	19 12.5%	5 21.7%
B	106 44.7%	108 71.1%	10 43.5%
A/FLUS	25 10.5%	13 8.6%	5 21.7%
FN	24 10.1%	7 4.6%	2 8.7%
S/M	12 5.1%	5 3.3%	1 4.3%
= FNA 1	70 29.5%	108 71.1%	5 21.7%
≠ FNA 1	167 70.5%	44 28.9%	18 78.3%
Total	237	152	23

FNA 1, initial; FNA 2, repeated; ND, non diagnostic; B, benign; A/FLUS, atypia or follicular lesion of undetermined significance; FN, follicular neoplasia; S/M, suspicious/malignant cytology; =, similar FNA1; ≠, different FNA1.

and Fisher's exact test was used to compare the ratings of observed results between categories. This study was approved by the ethics committee of the institution (CEP 100046).

## Results

The final analysis included 412 patients ranging from 13 to 83 years of age (mean 49.3 years). The majority of patients were female (93.5%). The mean interval between initial and sequential examinations was 10.8 months for the entire cohort. However, this interval varied from 6.3 months for non-diagnostic cytology to 18.1 months and 13.8 months for benign and A/FLUS cytology, respectively. A non-diagnostic cytology was the most common indication for a repeated FNA in 237 patients (57.5%), followed by benign (36.8%), and A/FLUS (5.6%) at initial FNA (Table 1). A repeated examination altered the initial diagnosis in 70.5% and 78.3% of the non-diagnostic and A/FLUS patients, respectively, whereas only 28.9% of patients with a benign cytology presented with a different diagnosis on a sequential FNA. This difference between groups was significant, as patients with initial benign cytology had a much higher chance of a similar result on a sequential examination (Table 2). No significant difference was observed in the occurrence of a repeated FNA showing a suspect/malignant cytology for a non-diagnostic (5.1%), benign (3.3%), or A/FLUS (4.3%) initial exam (Table 3).

**Table 2** Probability of different repeated fine-needle aspiration cytology report between groups.

FNA 1	<i>p</i> <sup>a</sup>
ND × B	<0.001
ND × A/FLUS	0.630
B × A/FLUS	<0.001

ND, Non diagnostic; A/FLUS, atypia or follicular lesion of undetermined significance; B, benign.

<sup>a</sup> Fisher's exact test; *p* < 0.008.

**Table 3** Comparison of the risk of malignancy for a repeat fine-needle aspiration between groups.

Malignancy rates compared	<i>p</i> <sup>a</sup>
ND × B	0.457
ND × A/FLUS	1.000
B × A/FLUS	0.576

ND, non diagnostic; A/FLUS, atypia or follicular lesion of undetermined significance; B, benign.

<sup>a</sup> Fisher's exact test; *p* < 0.008.

Surgical treatment outcome data was obtained from 26.6% (63/237) of patients with an initial non-diagnostic FNA, and for 21.7% (5/23) of patients with an A/FLUS cytology, whereas only 14.5% (22/152) of patients with an initial benign diagnosis had surgery. Histologic data are summarized in Table 4.

## Discussion

Clinical and incidental findings of thyroid nodules have become common, mainly due to increased awareness of this condition and readily-available high resolution ultrasound diagnostic techniques. Most of these nodules are benign, with limited surgical indications. Obviously, it would be ideal to operate only those patients with malignant tumors and those whose clinical symptoms required surgical management. The use of FNA for thyroid cytology dates back to the early 1950s, with the goal of identifying nodules with an increased risk for malignancy. FNA has gradually evolved as a key diagnostic tool and is responsible for an increase of surgically treated thyroid cancers; at present, 50% of thyroidectomies are due to malignant tumors, whereas this rate was less than 14%.<sup>21</sup> FNA cytology reports based on the recently proposed Bethesda system are associated with sensitivity, specificity, and diagnostic accuracy rates of 97%, 50.7%, and 68.8%, respectively.<sup>22</sup> Despite these figures, thyroid cytology may be affected by non-diagnostic specimens in approximately 10% of cases,<sup>23</sup> and is particularly challenging A/FLUS cases.

Non-diagnostic FNA was the most common indication for a repeated examination in this series, with 70.5% resulting in a different diagnosis from the first cytology. It is interesting to note that 44.7% of the initial non-diagnostic FNA were re-classified as a Bethesda 2 (benign cytology), allowing for non-surgical management and clinical follow-up when appropriate, whereas only 5.1% presented with a second exam that was suspect/malignant. Furlan et al.<sup>24</sup> also observed that 100% of their patients with initial

**Table 4** Histological outcome according to initial fine-needle aspiration cytology.

P1	Outcome	
	Benign	Malignant
Non-diagnostic	Nodular hyperplasia – 40 Hashimoto's thyroiditis – 6 Hurthle cell adenoma – 4 Follicular adenoma – 2 (82.5%)	Papillary carcinoma – 9 Hurthle cell carcinoma – 2 (17.5%)
Benign	Nodular hyperplasia – 14 Hashimoto's thyroiditis – 3 (77.3%)	Papillary carcinoma – 5 (22.7%)
A/FLUS	Follicular adenoma – 1 Nodular hyperplasia – 2 (60%)	Papillary carcinoma – 2 (40%)

P1, initial fine-needle aspiration cytology; A/FLUS, atypia or follicular lesion of undetermined significance.

non-diagnostic cytology were re-classified into a different Bethesda category in a sequential FNA. A decrease in the percentage of non-diagnostic results was also observed by Orija et al.,<sup>25</sup> who found that sequential FNA provided a diagnosis in up to 60% of these cases. Therefore, the Bethesda recommendation for a repeat exam after three to six months after the first FNA is supported. Coorough et al.<sup>26</sup> also observed that a repeat FNA yielding another non-diagnostic finding had twice the chance of presenting with carcinoma at final histology, compared to a 5% risk of malignancy in patients who had a diagnostic cytology prior to surgical intervention. The present study included 63 patients with an initial non-diagnostic cytology who underwent surgical resection, and observed that 17.5% of them had a malignant tumor at final pathology. These results are similar to those of Jo et al.,<sup>27</sup> who evaluated a group of 57 non-diagnostic thyroid aspirates followed by surgical resection and observed a 20% risk of malignancy after a non-diagnostic FNA, which would favor the need for a repeated FNA for this group of patients. The Bethesda reporting system states that a repeat FNA might also be considered for A/FLUS lesions, but the benefit of this approach is yet to be fully captured.

In the present study, it was observed that 5.6% of the repeated FNA were due to a A/FLUS cytology, which is consistent with an expected 7% rate of A/FLUS,<sup>13</sup> and 43.5% of these patients were classified as a Bethesda 2 (benign cytology) in a sequential FNA, whereas only 21.7% persisted as A/FLUS. These figures are similar to those reported by Chen et al.<sup>28</sup> who examined 26 patients with A/FLUS nodules and had a repeated FNA that was benign in 42.3% of cases, whereas 23.07% persisted as A/FLUS. Although their incidence of suspicious for malignancy was 15.38%, which is three times higher than the 4.3% rate observed in the present study, these differences are reasonable as the true incidence of malignancy for A/FLUS is still unknown, and a 5% to 15% malignant rate is an acceptable range of variability. The use of repeat FNA for A/FLUS lesions has also proved to be a cost-effective strategy when compared to a standard diagnostic lobectomy.<sup>29</sup> Despite these findings, roughly 60% of patients who have an initial A/FLUS cytology are still referred for surgery without a sequential FNA,<sup>24</sup> and this approach is expected to change with increased

compliance with the Bethesda reporting system recommendations. In the present study, it was observed that 40% of surgically treated patients with an initial A/FLUS cytology had a malignant tumor diagnosed at histology. These figures correlate with those of Vander Laann et al.,<sup>30</sup> who found a malignant diagnosis in 41% to 43% of patients after a single or consecutive A/FUS FNA, respectively. However, any further consideration regarding the relative risk of malignancy of patients with A/FLUS cytology and its correlation to histological findings was beyond the objective of this study and would be limited by the small number of patients included.

There is also an ongoing debate whether patients with benign cytology may also benefit from routine repeat FNA to reduce the risk of false negative results. Some authors have shown that approximately 90% to 98% of patients with an initial benign diagnosis will not change after multiple FNAs, and concluded that routine repeated examinations should not be considered for all patients.<sup>17,31–33</sup> It has been found that the rates of change for suspicious/malignant lesions for repeated FNA after an initial benign cytology range from 0.5% to 5%. Orlandi et al.<sup>34</sup> evaluated patients with benign nodular disease and suggested that at least three sequential FNAs would be required for the diagnosis to change to malignant in 2.25% of cases, considering that 97.7% of the examinations maintained the same benign cytological pattern after two to six repeated FNAs. These findings were similar to those of Illouz et al.,<sup>35</sup> in which 86% of patients who presented with suspicious/malignant changes after a repeated FNA for benign cytology required at least three sequential exams for that change to be observed. These observations have led some authors to favor repeat FNA for all patients with benign nodular goiters.<sup>36–38</sup> In the present study, it was observed that 3.3% of the initially-benign FNAs were reported as suspicious/malignant cytology after a single sequential exam and these were the only patients to present a positive histologic finding for malignancy at surgical histology. Furthermore, the projected likelihood of malignancy for patients with an initial benign FNA, considering the observed risk of malignancy after surgery for each cytological report on sequential exam, would increase for 8.5%. These figures are not significantly higher than the expected 5% to 15% rate of malignancy for any solid nodule.

It is interesting to note that at least 91.5% of patients with an initial benign cytologic report would avoid unnecessary diagnostic surgery as a sequential FNA alone would not significantly increase the likelihood of a malignancy report. This is also supported by the findings of Rosario et al.<sup>39</sup> suggesting that suspicious ultrasonographic characteristics (such as microcalcification, hypoechogenicity, irregular margins, and predominantly central flow) could be used as a criterion to select those patients with an initial benign cytology that would benefit from a repeat exam, since 17% of patients with these findings would present with a malignant change in a sequential FNA compared to 0.5% to 5% malignant changes whether a routine repeat FNA was offered to all patients with a benign cytology.

## Conclusion

Repeat FNA is a valuable procedure in cases with initial non-diagnostic or A/FLUS cytology, providing information that might have implications regarding clinical follow-up *versus* surgical intervention.

Its routine use for the follow-up of all patients with an initial benign examination seems not to increase the expected likelihood of a malignant lesion and should likely be used for selected cases.

## Conflicts of interest

The authors declare no conflicts of interest.

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