

ORIGINAL ARTICLE

Repetition of thyroid fine-needle aspiration cytology after an initial nondiagnostic result: Is there an optimal timing?



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KEYWORDS

Cytological interference;
Fine needle-aspiration cytology;
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Abstract

Introduction: It is suggested to wait at least 3 months to repeat a fine needle aspiration cytology (FNAC) to avoid possible inflammatory cytological changes induced by a previous procedure. This study evaluated the influence of the interval between 2 FNACs in a cohort with a previous non-diagnostic (ND) FNAC. We analysed the occurrence of ND or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) results in the second FNAC, based on the intervals between procedures.

Patients and methods: Retrospective study (2017–2020) including thyroid nodules with a ND result, subjected to another FNAC. Demographic, clinical and echographic data, interval between FNACs and their results were collected. We considered the intervals: \leq / $>$ 3 months and \leq / $>$ 6 months. Second FNAC results were classified as ND, AUS/FLUS or diagnostic (including the other Bethesda categories).

Results: Included 190 nodules (190 patients – 82.1% women, mean age 60 ± 13.7 years) with a first ND FNAC. The second FNAC results were: ND in 63 cases, AUS/FLUS in 9 and diagnostic in 118 cases. There were no statistical differences in FNAC results performed \leq 3 months (13 ND, 2 AUS/FLUS, 19 diagnostic) vs $>$ 3 months (50 ND, 7 AUS/FLUS, 99 diagnostic; $p=0.71$). Similarly, there were no statistical differences considering a longer time interval: \leq 6 months (32 ND, 3 AUS/FLUS, 59 diagnostic) vs $>$ 6 months (31 ND, 6 AUS/FLUS, 59 diagnostic; $p=0.61$).

Conclusions: Time interval between FNACs was not relevant to the final cytological result. Early FNAC repetition did not increase the cases of ND or AUS/FLUS.

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PALABRAS CLAVE

Citología por aspiración con aguja fina;
Interferencia citológica;
Intervalo de tiempo

Repetición de la citología por aspiración con aguja fina de tiroides después de un resultado inicial no diagnóstico: ¿existe un momento óptimo?**Resumen**

Introducción: Se propone esperar al menos tres meses para repetir una citología por aspiración con aguja fina (PAAF) para evitar cambios citológicos inducidos por un procedimiento previo. Este estudio evaluó la influencia del intervalo de tiempo entre dos PAAF. En una cohorte con una PAAF no diagnóstica (ND) analizamos la ocurrencia de resultados ND o de atipia de significado indeterminado/lesión folicular de significado indeterminado (AUS/FLUS) en una segunda PAAF, con diferentes intervalos entre procedimientos.

Material y métodos: Estudio retrospectivo (2017-2020) que incluye nódulos con primer resultado ND, remitidos a otra PAAF. Se consideraron dos intervalos entre PAAF: \leq />3 meses y \leq />6 meses. Los segundos resultados de PAAF se clasificaron: ND, AUS/FLUS o diagnóstico (incluidas otras categorías de Bethesda).

Resultados: Se incluyeron 190 pacientes (82,1% mujeres, edad media $60 \pm 13,7$ años) con una primera PAAF ND. Los segundos resultados de la PAAF fueron: ND en 63 casos, AUS/FLUS en nueve y diagnóstico en 118 casos. No hubo diferencias estadísticas en los resultados de PAAF realizados \leq 3 meses (13 ND, 2 AUS/FLUS, 19 diagnósticos) vs. >3 meses (50 ND, 7 AUS/FLUS, 99 diagnósticos) - $p=0,71$. Con un intervalo más amplio, no hubo diferencias estadísticas en los resultados de la segunda PAAF: \leq 6 meses (32 ND, 3 AUS/FLUS, 59 diagnósticos) vs. > 6 meses (31 ND, 6 AUS/FLUS, 59 diagnósticos) - $p=0,61$.

Conclusiones: El intervalo de tiempo entre PAAF no fue relevante para el resultado final. La repetición temprana de PAAF no aumentó los casos de ND o AUS/FLUS.

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Introduction

Thyroid nodules are common in the adult population and fine needle aspiration cytology (FNAC) is the gold standard for their evaluation, playing an important role in their management.^{1,2}

FNAC is a highly sensitive screening method for thyroid nodules. In about 35–45% of thyroid FNAC results are inconclusive not only because of non-diagnostic (ND) specimens (low/no cellularity or poor preservation) – Bethesda I,³ but also due to indeterminate/atypical features – Bethesda III.^{4,5} In these cases, it is recommended to repeat FNAC.¹ The ideal timing for repetition has not yet been established, it being suggested that is adequate to wait at least 3 months after the first FNAC.^{1,6,7} Earlier repeat FNAC is thought to increase the chance of a reparative atypia of follicular cells with the potential for false positive results.¹ The potential diagnostic pitfalls that can occur may result from reactive histologic changes following puncture (large nuclei, nuclear grooving or nuclear clearing along the needle tracts).⁸ As these alterations in pathology have been reported to have an occurrence that peaks within 20–40 days after the FNAC, it is suggested to wait a period of 3–6 months, when it is necessary to repeat a FNAC.^{8,9}

The aim of our study was to determine if time interval between FNACs influences their results. We therefore reviewed the data of patients with an initial ND FNAC and repeated FNAC, analysing 2 different time intervals between FNACs and their results.

Patients and methods**Patient cohort**

We conducted a retrospective analysis of medical records of adult patients with a first ND FNAC and repeated FNAC between 2017 and 2020 at our Hospital.

Variables

An ND FNAC result was considered according to the Bethesda guidelines.⁵

We analysed patients' demographic data (age, gender), clinical information (previous cervical radiotherapy and family history of thyroid carcinoma), nodule ultrasound (US) data (size, echogenicity, composition and presence of microcalcifications), the time interval between the first and the second FNACs and the second FNAC results. Variables were collected at the time of the first FNAC from the medical records.

The second FNAC results were analysed according to the interval between FNACs. A smaller (\leq />3 months) and a wider (\leq />6 months) interval between FNACs were considered.

The second FNAC results were classified in three categories: ND, atypia of unknown significance/follicular lesion of unknown significance (AUS/FLUS) or diagnostic (including the other Bethesda categories).⁵

Procedures

FNACs were all US-guided and were all performed by experienced radiologists or endocrinologists.

Nodules were classified as solid, cystic or mixed. If mixed with a cystic portion < 50%, the nodules were named as mixed predominantly solid, and if mixed with a cystic portion > 50%, they were classified as mixed predominantly cystic.¹

The size of a thyroid nodule was determined according to the maximum dimension on US.

Nodules' echogenicity was classified as hyper-, iso- or hypoechogenic in comparison with the echogenicity of the thyroid parenchyma. Markedly hypoechogenic refers to an appearance of the nodule darker than the surrounding strap muscles. Calcifications were categorised as micro or macrocalcifications.¹

As there was inconsistent reporting of vascularity between reports, it was not considered.

The decision to perform a FNAC was taken according to the EU-TIRADS classification.¹⁰

Each nodule was aspirated 2–3 times, using a 23-gauge needle attached to a 10mL syringe. Three to four alcohol-fixed smears were prepared from the aspirate for Papanicolaou staining, and the remainder was prepared for ThinPrep® by rinsing the needle hub in cytolyte. All the FNAC cytological reports were done by experienced pathologists and the samples were reviewed before being analysed. Final pathology was classified according to the Bethesda System.⁵

Statistical analysis

Statistics were performed using SPSS 22. The significance level was set at $p < 0.05$.

For univariate analysis, an independent *t*-test was used for continuous variables and a Chi-squared or Fisher's exact test for categorical data. Multivariate logistic regression was performed for analysis of time impact (as a continuous variable) in the second FNAC result.

Ethical issues

Informed consent was obtained from the patients. The study was approved by the local Ethics Committee.

Results

The data refer to 190 thyroid nodules from 190 patients, of which 156 (82.1%) were women, with a mean age of 60 ± 13.7 years. Nodules were subjected to a second FNAC following a previous ND result. The second FNAC results were ND in 63 cases, benign in 116 cases, AUS/FLUS in 9 cases, follicular neoplasm/suspicious follicular neoplasm in 1 case and malignant in another case. There was a reclassification of the first FNAC result in 118 (62%) patients, by the repetition of the procedure.

The mean Interval between FNACs was 7 ± 3.2 months (range 1–21).

Comparative analysis of demographic, clinical and echographic data among patients grouped based on the time

interval between the first and second FNAC did not reveal differences (Table 1).

There were no differences in the results of the second cytologies in the sub-analyses carried out based on the length of the time interval (Tables 2–4).

In the ≤ 3 months group, the mean time between FNACs was 2.9 ± 0.3 months (median 3 months); whereas in the >3 months group it was 7.8 ± 2.9 months (median 7 months).

In the ≤ 3 months group, the diagnostic FNACs (55.9%) were all benign. In the >3 months group, diagnostic FNACs were benign in 97 cases, malignant in 1 and follicular neoplasm/suspicious follicular neoplasm in another case.

In the ≤ 6 months group, the mean time between FNACs was 4.3 ± 1.2 months (median 4 months); whereas in the >6 months group, the mean period between the two FNACs was 9.5 ± 2.4 months (median 9 months).

The diagnostic FNACs, in the ≤ 6 months group, were benign in 58 cases and malignant in the remaining case. In the >6 months group, there were also 58 benign cases and one follicular neoplasm/suspicious follicular neoplasm result.

A regression analysis did not demonstrate that time interval between FNACs, considered as a continuous variable, had an impact on cytological results ($p = 0.22$).

Regarding the patients with a second ND or an AUS/FLUS FNAC, 9 (12.5%) underwent surgery. None had a malignant histology result.

Discussion

Current guidelines recommend repeating FNAC in the event of an ND or AUS/FLUS result.¹ The waiting period between FNACs is not well established, it being stated that waiting 3–6 months might avoid potential false positive results relating to FNAC-induced cytological changes.

In a cohort of 190 patients, we evaluated two potential FNAC waiting intervals (a smaller and a larger) and their cytological results in order to determine if the waiting period might influence the cytological results.

Particular to this study is the evaluation of two different time intervals between FNACs in a cohort of patients who underwent two FNACs, with a second one performed after a first ND result. Additionally, as the subgroups of patients in each time interval were homogeneous in terms of demographic, clinical or echographic data, we consider that any possible factor that could also influence the second FNAC results was eliminated.

In contrast with the idea that it is necessary to wait between procedures to avoid post-FNAC reparative cellular atypia,¹¹ we did not observe an increase of AUS/FLUS cases among FNACs performed with an interval of less than 3 months. This is in line with data from other studies.^{12–14} Moreover, there were no more cases of ND results if the time between FNACs was increased. Furthermore, on dividing the FNACs results between three 3 time intervals (≤ 3 / >3 to ≤ 6 / >6 months), we also verified that our results were consistent and that there were no differences between groups in terms of the cytological outcomes.

Some authors have evaluated the time interval $</\geq 3$ months, in a cohort of patients with a first AUS/FLUS FNAC, and did not find any increase of malignant results in the sec-

Table 1 Demographic, clinical and echographic data.

	≤3 months (n = 34)	>3 months (n = 156)	p-Value
Female – n (%)	30 (88.2%)	126 (80.8%)	0.303
Age – mean ± DP (years)	59.4 ± 14.1	60.1 ± 13.7	0.799
Radiation exposure – n (%)	–	6 (3.8%)	0.245
Thyroid cancer in family – n (%)	–	6 (3.8%)	0.245
Nodule size – Q ₂ [Q ₁ ; Q ₃] (mm)	24.5 [19.5; 35]	25 [18.3; 32]	0.889
Echogenicity – n (%)			
Hyperechogenic	2 (5.9%)	10 (6.4%)	0.894
Hypoechoogenic	17 (50%)	85 (54.5%)	
Isoechoogenic	14 (41.2%)	54 (34.6%)	
Markedly hypoechoogenic	1 (2.9%)	7 (4.5%)	
Composition – n (%)			
Cyst	1 (2.9%)	3 (1.9%)	0.297
Mixed	17 (50%)	57 (36.5%)	
Solid	16 (47.1%)	96 (61.5%)	
Microcalcifications – n (%)	6 (17.6%)	28 (17.9%)	0.967
	≤6 months (n = 94)	>6 months (n = 96)	p-Value
Female – n (%)	79 (84%)	77 (80.2%)	0.491
Age – mean ± DP (years)	60.1 ± 13.6	59.9 ± 13.9	0.925
Radiation exposure – n (%)	4 (4.3%)	2 (2.1%)	0.392
Thyroid cancer in family – n (%)	1 (1.1%)	5 (5.2%)	0.102
Nodule size – Q ₂ [Q ₁ ; Q ₃] (mm)	25 [19.5; 35]	23 [18.3; 31.8]	0.111
Echogenicity – n (%)			
Hyperechogenic	6 (6.4%)	6 (6.3%)	0.533
Hypoechoogenic	53 (56.4%)	49 (51%)	
Isoechoogenic	33 (35.1%)	35 (36.5%)	
Markedly hypoechoogenic	2 (2.1%)	6 (6.3%)	
Composition – n (%)			
Cyst	2 (2.1%)	2 (2.1%)	0.984
Mixed	36 (38.3%)	38 (39.6%)	
Solid	56 (59.6%)	56 (58.3%)	
Microcalcifications – n (%)	15 (16%)	19 (19.8%)	0.491

Table 2 Fine needle aspiration cytology results by time-to-repetition ≤3 months versus >3 months.

	≤3 months (n = 34)	>3 months (n = 156)	p-Value
ND – n (%)	13 (38.2%)	50 (25.5%)	0.71
AUS/FLUS – n (%)	2 (5.9%)	7 (4.5%)	
Diagnostic FNAC – n (%)	19 (55.9%)	99 (63.5%)	

Table 3 Fine needle aspiration cytology results by time-to-repetition ≤6 months versus >6 months.

	≤6 months (n = 94)	>6 months (n = 96)	p-Value
ND – n (%)	32 (34%)	31 (32.3%)	0.61
AUS/FLUS – n (%)	3 (3.2%)	6 (6.3%)	
Diagnostic FNAC – n (%)	59 (62.8%)	59 (61.4%)	

Table 4 Fine needle aspiration cytology results with three time-to-repetition intervals.

	≤3 months (n = 34)	>3 ≤ 6 months (n = 60)	>6 months (n = 96)	p-Value
ND – n (%)	13 (38.2%)	19 (31.7%)	31 (32.3%)	0.53
AUS/FLUS – n (%)	2 (5.9%)	1 (1.7%)	6 (6.3%)	
Diagnostic FNAC – n (%)	19 (55.9%)	40 (66.7%)	59 (61.4%)	

and FNAC.¹⁵ In our study, in the cases that were operated on after the second FNAC (with ND or AUS/FLUS results), there were no malignant histological results.

By repeating a FNAC, regardless of the time interval between procedures, it was possible to achieve a diagnostic result in the second FNAC in the majority of the cases. This data is similar to the results of Orija et al. who reported a diagnosis rate of up to 60% with sequential FNACs.¹⁶ However, there are other authors that reported a lower reclassification rate of 34.6% with FNAC repetition.¹⁷

In conclusion, we consider that the time interval between FNACs was not relevant to the final cytological result. Therefore, a strict waiting period between FNACs may not be necessary to avoid misinterpretation of FNACs results. Early FNAC repetition did not increase the cases of ND or AUS/FLUS.

Conflict of interest

None. This research has not received specific aid from public sector agencies, commercial sectors or non-profit entities.

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