WHEN TO REPEAT THYROID FINE NEEDLE ASPIRATION CYTOLOGY?

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SUMMARY – The aim of of the study was to investigate the possible changes of primary fine needle aspiration (FNA) diagnoses after subsequent check ups. We investigated 948 thyroid nodules and the main indications for repeat FNAs were inadequate/indeterminate FNA findings and growing nodules at ultrasound check up. FNA findings were subdivided into inadequate, benign, low-risk lesion (includes cellular follicular lesion, suspicious of follicular/Hürthle cell neoplasm, atypical Hürthle cell hyperplasia), follicular/Hürthle cell neoplasm, high-risk lesion (includes lesions suspicious of malignancy), and malignant. Of the total of 948 nodules, repeat FNA diagnoses remained within the same category in 709 (75%) nodules. Out of 38 primary inadequate FNAs, 7 (18%) remained inadequate, 24 (63%) were benign, and 3 (8%) were categorized as high-risk/malignant. Out of 659 primary benign FNAs, 587 (89%) remained benign, and 11 (2%) were categorized as high-risk/malignant. Out of 169 primary low-risk lesion FNAs, 66 (39%) remained low-risk, 65 (38%) were benign, and 10 (6%) were categorized as high-risk/malignant. Out of 43 primary high-risk lesion FNAs, 20 (46%) remained high-risk, 2 (5%) were benign, 3 (7%) were categorized as a low-risk lesion, and 13 (30%) were categorized as malignant. Out of 35 FNAs that were primary follicular/Hürthle cell neoplasm, 27 (77%) remained follicular/Hürthle cell neoplasm, 1 (3%) was categorized as benign, 4 (11%) were categorized as a low-risk lesion, and 3 (8%) as high-risk/malignant. In conclusion, repeat thyroid FNA is useful in most cases of primary inadequate/indeterminate FNA findings, as well as in the evaluation of growing nodules.

Key words: *Fine-needle aspiration cytology; Thyroid disease; Thyroid cancer*

Introduction

Thyroid nodules are the most common thyroid disease usually detected on neck palpation or ultrasonography[1]. The incidence of clinically palpable thyroid nodules is approximately 4%-7%[2,3]. When thyroid nodules are detected by ultrasonography, the incidence increases to 30%-50%[4,5]. Even though thyroid cancer is present in approximately 0.0004% of the general population[6], with detected thyroid nodules this incidence is approximately 5%[3,7].

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Fine-needle aspiration (FNA) is considered to be the most effective test available for distinguishing between benign and malignant thyroid nodules, with accuracy approaching 95%[8]. It has a high diagnostic efficiency, which largely depends on the aspirator's and the cytologist's expertise[9-11]. It is an accurate and cost-effective method that allows prompt decisions regarding management of the patient and has a low false-negative rate, ranging between 0.7% and 11%, with an average of approximately 5%[9,12,13].

In most cases of cytologic diagnosis of thyroid cancer, surgery is considered to be the optimal decision and it is the preferred option in cases with indeterminate cytology[8]. It has been reported that repeat FNA in patients with benign diagnoses would contribute to

the identification of previously overlooked malignant lesions and thus reduce the false-negative rate[14]. The general opinion is that when the initial FNA yields an unsatisfactory specimen, repeat FNA should be performed several weeks later. However, when the initial FNA is judged to be satisfactory, general opinion is that repeat FNA is not worthwhile or is of limited usefulness[15-19].

Considering the lack of consensus on the role of repeat FNA, our aim was to investigate the possible changes of primary FNA diagnoses after subsequent check ups.

Material and Methods

During a nine-year period, we investigated the possible changes of primary FNA diagnoses of 948 nodules in 721 patients, 643 (89.2%) women and 78 (10.8%) men, at University Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center. Patient age ranged from 6 to 88 years, median 55 years.

During the same period, the total number of patients seen at the thyroid cytology service was 9473 and the overall inadequate, benign, low risk, follicular/Hürthle cell neoplasm, high risk and malignant rates were 2.3%, 82.9%, 7.6%, 3.4%, 1.2% and 2.5%, respectively.

All patients underwent ultrasound guided FNA performed by a cytopathologist using a 23-gauge needle attached to a 10-mL syringe. Aspirates were smeared for conventional cytology (MGG staining) and interpreted by the cytopathologist experienced in thyroid cytology. The smeared aspirates were considered adequate for cytologic diagnosis when the smear contained at least six fragments containing a minimum of 10 well-preserved follicular cells.

The subdivision of specimens regarding cytologic diagnoses was as follows: unsatisfactory/inadequate specimen means that definitive diagnosis is not possible and a repeat FNA is recommended (none or few cells in the smear; the finding of only peripheral blood cells from lesions with different clinical characteristics (e.g., solid thyroid nodule) or cystic fluid with macrophages from pseudocystic lesions).

Benign lesions include nodular goiter, adenomatoid nodule, and thyroiditis.

Low-risk lesions include cellular follicular lesion, suspicious of follicular/Hürthle cell neoplasm, atypical Hürthle cell hyperplasia, and follicular/Hürthle cell neoplasm.

High-risk lesions include lesions suspicious of malignancy, i.e. suspicious of papillary carcinoma, and malignant lesions.

The cytomorphological criteria for each of the above mentioned FNA diagnostic category of follicular lesions were strictly followed. For cytomorphological characterization of adenomatoid nodules, at least one of the following findings was considered to be obligatory: numerous sheets of follicular cells with a scant colloid or enlarged follicular cells or numerous microfollicles. Differential diagnosis includes adenomatoid nodule of nodular goiter and follicular adenoma. Cellular follicular lesions were characterized by the following findings: few acinar structures with a predominance of normal appearing sheets of follicular cells or slightly atypical nuclei. Differential diagnosis includes adenomatoid nodule of nodular goiter, follicular adenoma and a low possibility of well-differentiated carcinoma. A cellular follicular lesion is best described as "probably neoplastic". The cytomorphological criterion for "suspicious for follicular neoplasm" was the finding of numerous acinar structures predominating over normal appearing sheets of follicular cells. On differential diagnosis, adenomatoid nodule of nodular goiter, follicular adenoma and well-differentiated carcinoma were included. The cytomorphological criteria for follicular neoplasm were one or both of the following findings: acinar structures without the presence of normal appearing sheets of follicular cells or acinar structures with moderately atypical nuclei. The diagnosis was based on the inclusion of follicular adenoma, well-differentiated carcinoma and adenomatoid nodule of nodular goiter, even though the latter is of low possibility.

The main indications for repeat FNA were inadequate/indeterminate FNA findings, and for initially benign FNAs growing nodules (an increase of the nodule diameter higher than 20%) or appearance of certain ultrasonographic features (e.g., microcalcification or intranodular hypervascularity) favoring malignancy on ultrasound check up. All patients were clinically examined, with an additional ultrasound check and an obligatory serum TSH test performed prior to

Table 1. Patients with initially inadequate fine needle aspiration (FNA) and repeat FNA

Repeat FNA	No. of cases	% (95% CI[a])
Inadequate	7	18 (9-34)
Benign	24	63 (47-77)
Low-risk	4	11 (4-25)
Follicular/Hürthle cell neoplasm	0	0 (0-11)
High-risk/malignant	3	8 (2-21)
Total	38	

[a]Confidence interval by modified Wald method

Table 3. Patients with initially low-risk fine needle aspiration (FNA) and repeat FNA

Repeat FNA	No. of cases	% (95% CI[a])
Inadequate	11	7 (4-11)
Benign	65	38 (31-46)
Low-risk	66	39 (32-47)
Follicular/Hürthle cell neoplasm	17	10 (6-16)
High-risk/malignant	10	6 (3-11)
Total	169	

[a]Confidence interval by modified Wald method

the FNA procedure. Some of the patients were also tested for thyroid autoantibodies prior to the aspiration. Most of the patients were euthyroid and some of them were hypothyroid.

Two FNAs were performed in 550 (76.4%), 3 FNAs in 123 (17.0%), 4 FNAs in 38 (5.3%), 5 FNAs in 7 (0.9%) and 6 FNAs in 2 (0.3%) patients. The time elapsed between two consecutive FNAs varied from 1 to 109 (median 14) months.

Confidence intervals were computed by the modified Wald method[20].

Results

Of the total of 948 nodules, repeat FNA diagnoses remained within the same category in 709 (75%) nodules. Adequate material was obtained in 82% of initially inadequate repeat FNAs. Three (8%) repeat FNAs were categorized as a high-risk/malignant lesion (Table 1). Of 659 initially benign FNAs, 587 (89%) remained benign, and 11 (2%) FNAs were categorized as a high-risk/malignant lesion (Table 2). Of 169 initially low-risk FNAs, 66 (39%) remained low-risk, 65 (38%) FNAs were changed to benign, and 10 (6%) were changed to a high-risk/malignant lesion (Table 3). Of 35 FNAs that were initially follicular/Hürthle cell neoplasm, 27 (77%) remained follicular/Hürthle cell neoplasm. One (3%) FNA was categorized as benign and 3 (9%) FNAs were categorized as a high-risk/malignant lesion (Table 4). Out of 43 initially high-risk lesions, two (5%) were changed to benign and 13 (30%) to obviously malignant lesion (Table 5).

There were four cases of initially obviously malignant lesions (all papillary carcinomas) and repeat FNA was performed on patient request. Repeat FNA confirmed the initial diagnosis.

Table 2. Patients with initially benign fine needle aspiration (FNA) and repeat FNA

Repeat FNA	No. of cases	% (95% CI[a])
Inadequate	10	1 (1-3)
Benign	587	89 (86-91)
Low-risk	34	5 (4-7)
Follicular/Hürthle cell neoplasm	17	3 (2-4)
High-risk/malignant	11	2 (1-3)
Total	659	

[a]Confidence interval by modified Wald method

Table 4. Patients with initially follicular/Hürthle cell neoplasm fine needle aspiration (FNA) and repeat FNA

Repeat FNA	No. of cases	% (95% CI[a])
Inadequate	0	0 (0-12)
Benign	1	1 (0-16)
Low-risk	4	11 (4-26)
Follicular/Hürthle cell neoplasm	27	77 (61-88)
High-risk/malignant	3	8 (2-23)
Total	35	

[a]Confidence interval by modified Wald method

Table 5. Patients with initially high-risk fine needle aspiration (FNA) and repeat FNA

Repeat FNA	No. of cases	% (95% CI[a])
Inadequate	3	7 (2-19)
Benign	2	5 (0-16)
Low-risk	3	7 (2-19)
Follicular/Hürthle cell neoplasm	2	5 (0-16)
High-risk	20	46 (32-61)
Malignant	13	30 (18-45)
Total	43	

[a]Confidence interval by modified Wald method

Discussion

We investigated the possible changes of primary FNA diagnoses after subsequent check ups to find out when a repeat FNA is most useful. Opinions found in the literature on the usefulness of repeat FNA during long-term follow-up are controversial[12,14,15,21]. Repeat FNA is recommended by various authors in the follow-up of benign thyroid nodules to confirm the initial cytologic diagnosis because the presence of suspicious clinical changes would make the cytologic benign diagnosis less reliable. Erdogan *et al.*[22] and Liel *et al.*[19] have reported changes from benign to malignant in nodules with suspicious clinical changes and conclude that repeat FNA in patients with initially benign cytologic diagnoses should be performed in these cases. Lucas *et al.*[15] conclude that repeat FNA is of limited usefulness in cytologically benign nodules without any clinical changes. On the contrary, Orlandi *et al.*[23] concluded that the appearance of clinical changes did not necessarily result in the development of carcinoma and aspiration performed at different time of evolution at different sites of the nodule would contribute to obtaining a more representative specimen.

In our study, repeat FNA was performed in 948 nodules and 709 (75%) nodules remained within the same diagnostic category.

Studies of non-diagnostic FNA report the incidence of malignancy to be 5%-10% among non-diagnostic thyroid nodules[24,25]. Alexander *et al.*[26] confirm this finding and report a 13% rate of non-diagnostic ultrasound-guided FNAs of thyroid nodules over a 6-year period. They suggest that persistent evaluation of initially non-diagnostic thyroid nodules is mandatory and should be pursued promptly. In their study, when evaluating initially non-diagnostic FNA, repeat FNA was diagnostic in 63% of cases, and 5% of initially non-diagnostic specimens were malignant on repeat FNA. In our series, repeat FNA was diagnostic in 82% of cases, whereas 8% of initially non-diagnostic FNAs were high risk/malignant lesions on repeat FNA.

In a retrospective review of 235 patients with an initially benign diagnosis, Chehade *et al.*[27] concluded that repeat FNA reduced the rate of false-negative diagnosis from 5.2% to <1.3%.

Hamburger[14] reports that FNA confirmed the same diagnosis in 91% of cases, and concludes that the reliability of repeat FNA would be preferable to surgical intervention. Dwarakanathan *et al.*[21] report that repeat FNA cytology confirmed benign cytologic diagnosis in 93% of cases, while in the remaining 7% the diagnosis changed to suspicious for malignancy or malignant, confirming carcinoma in four patients undergoing surgery. According to Furlan *et al.*[28] and Flanagan *et al.*[29], repeat FNA improves diagnostic accuracy. In their series, the confirmation of the initially benign diagnosis ranged between 91% and 100%[14, 15], whereas the initially benign FNAs were confirmed in 89% of all cases included in our study. Repeat FNA changed to high risk/malignant lesion in 2% of cases.

Oertel *et al*[30] report on 117 patients with initially inconclusive FNAs that underwent a repeat procedure. In 73 (62.4%) cases, the FNA diagnosis was benign, 37 (31.6%) remained inconclusive and 4 (3.4%) changed to suspicious/malignant. In our series, 39% of initially low-risk lesion FNAs remained within the same category on repeat FNA, 38% changed to benign, 10% changed to follicular/Hürthle cell neoplasm, and 6% changed to high-risk/malignant lesion.

The cytomorphological criteria for follicular neoplasm are generally well-defined. In our series, the great majority (77%) of initially follicular/Hürthle cell neoplasm FNAs remained in the same diagnostic category on repeat FNA. Only one (3%) lesion was changed to benign, and three (9%) were changed to a high-risk/malignant lesion. In the absence of an outcome measure as reliable as histologic verification, all judgments on the true nature of aspirated nodules should be cautiously taken as prone to non-differential misclassification.

Patients with a high-risk of malignancy FNA, although without clearly malignant features, usually immediately underwent surgical treatment. However, some patients within this group at a risk of surgery could benefit from repeat FNA prior to operation. In our series, most (76%) patients with initially high-risk of malignancy FNA had high-risk of malignancy FNA or obviously malignant repeat FNA. Only two (5%) initially high-risk lesion FNAs changed to benign.

Our results allow us to make the following conclusions:

- repeat thyroid FNA is recommended in all cases of initially inadequate FNAs;
- repeat thyroid FNA is recommended in benign FNAs only if clinically suspicious signs develop;
- repeat thyroid FNA is recommended as the next procedure in initially low-risk of malignancy FNAs;
- repeat thyroid FNA is not recommended in follicular/Hürthle cell neoplasm FNAs; and
- repeat thyroid FNA could be useful in some patients at risk of surgery with initially high-risk of malignancy FNAs.

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Sažetak

KADA TREBA PONOVITI CITOLOŠKU PUNKCIJU ŠTITNE ŽLIJEZDE?

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Cilj ove studije bio je istražiti moguće promjene primarne dijagnoze citološke punkcije nakon kasnijih kontrola. Istražili smo 948 čvorova štitne žlijezde, a osnovne indikacije za ponovljenu punkciju bili su neadekvatni/neodređeni citološki nalazi, kao i porast čvorova na ultrazvučnoj kontroli. Citološke dijagnoze podijeljene su u neadekvatne, benigne, lezije niskog rizika (celularne folikularne lezije, sumnjive na folikularnu neoplazmu/neoplazmu Hürthleovih stanica i atipičnu hiperplaziju Hürthleovih stanica), folikularne neoplazme/neoplazme Hürthleovih stanica, lezije visokog rizika (lezije sumnjive na malignitet) i maligne lezije. Od 948 čvorova citološka dijagnoza nakon ponovljene punkcije ostala je unutar iste kategorije u 709 (75%) čvorova. Od 38 primarno neadekvatnih citoloških punkcija 7 (18%) je bilo neadekvatno nakon ponovljene punkcije, 24 (63%) benigno, a 3 (8%) su kategorizirane kao visok rizik/maligno. Od 659 primarno benignih citoloških punkcija 587 (89%) je ostalo benigno, a 11 (2%) je kategorizirano kao visok rizik/maligno. Od 169 lezija niskog rizika 66 (39%) je ostalo u istoj kategoriji, 65 (38%) je bilo benigno, a 10 (6%) visokog rizika/maligno. Od 43 lezije visokog rizika malignosti 20 (46%) je ostalo u istoj kategoriji, 2 (5%) su bile benigne, 3 (7%) su bile lezije niskog rizika malignosti, a 13 (30%) maligno. Od 35 folikularnih neoplazma/neoplazma Hürthleovih stanica 27 (77%) je ostalo u istoj kategoriji, 1 (3%) je bila benigna, 4 (11%) su bile lezije niskog rizika malignosti, a 3 (8%) visokog rizika/maligne. Ponovljena citološka punkcija korisna je u većini slučajeva primarno neadekvatnih ili neodređenih citoloških dijagnoza, kao i kod evaluacije čvorova štitne žlijezde koji rastu.

Ključne riječi: *Citološka punkcija; Bolesti štitne žlijezde; Karcinom štitne žlijezde*