CLINICAL STUDY

Benign fine-needle aspiration cytology of thyroid nodule: to repeat or not to repeat?

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Abstract

Context: Fine-needle aspiration cytology (FNAC) is the gold standard for evaluating thyroid nodules. It has a sensitivity rate of about 95%, i.e. false negative results represent up to 5% of cases. The value of repeated FNAC during follow-up is still controversial.

Objective: To evaluate the usefulness of repeating the FNAC for initially benign nodules.

Design and methods: All 5017 patients who underwent FNAC of the thyroid nodule in years 1991–2008 were retrospectively evaluated.

Results: Repeated FNAC was performed in 574 nodules with initially benign results. The number of repetitions varied from one to six. Repeatedly benign results were found in 498 cases, and malignant/suspicious results with initially benign cytology were found in 76 nodules (13.2%). Carcinoma was present in 13 out of the 58 surgically treated malignant/suspicious results of initially benign cytology.

Conclusions: A change from a benign FNAC result to a malignant/suspicious one was present in more than 13% of the patients with initially benign cytology; malignancy has been recognised on the basis of repeated FNAC in 2.3% patients. In the majority of cases, the repetition corrected wrong cytological interpretation of results other than colloidal goitre, especially Hashimoto's thyroiditis and regressive changes. We believe that repeating FNAC in patients with benign cytology in about a 1-year horizon can reduce the rate of undiagnosed tumours.

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Introduction

Thyroid nodules represent a common problem in endocrinology, with an estimated prevalence of 4–7% in the adult population for palpable nodules. The prevalence is higher in women (5%) than in men (1%) (1). The prevalence of nodules found during autopsies, operations or ultrasound examinations is considerably higher and increases with age (2–4). The majority of nodules are benign. Cancer can be present in 3–10% of nodules, depending on age, gender, radiation exposure history, family history, and other factors (5). Over the last few years, many advances have been achieved in diagnosing thyroid nodules. In addition, various clinical and radiological features have been studied to increase detection rate of differentiated thyroid carcinoma. Unfortunately, these features lack specificity and sensitivity (6–9), and none have been so far recommended for a routine use (10). Fine-needle aspiration cytology (FNAC) is a well-established method for evaluating thyroid nodules. The indications for FNAC are well established and described in several different guidelines (11–13). Patients with benign results of FNAC should be followed up due to the

known 5% false negative rate of thyroid FNAC (14). Some discrepancies can be found in the current guidelines of three different endocrine societies (The American Association of Clinical Endocrinologists (AACE), The American Thyroid Association (ATA) and The European Thyroid Association) as well as among clinicians. One area where there is no consensus among authors is the need to repeat aspiration cytology in a patient with benign FNAC result. The aim of this study was to determine the usefulness of repeated FNAC in a large series of patients followed up for more than 10 years.

Patients and methods

Results of FNAC of thyroid nodules performed in 5017 patients during a period from 1991 to 2008 at the Charles University, Faculty of Medicine and Teaching Hospital in Hradec Králové, were retrospectively analysed. The Ethic Committee of the Charles University, Faculty of Medicine and Teaching Hospital in Hradec Králové, has approved the study. A total of 6009 cytological diagnoses were reviewed. All FNACs

Figure 1 Results of 574 initially benign nodules after repeated FNAC are shown.

were performed under US guidance. Results of the FNAC were classified as unsatisfactory (non-diagnostic), benign and malignant/suspicious from malignancy (indeterminate). Unsatisfactory aspirates were excluded from further analysis. The results were evaluated as unsatisfactory if there were less than ten groups of cell, each containing at least ten elements. Benign aspirates included nodular goitres with or without regressive changes, and/or focal lymphocytic thyroiditis as well as Hashimoto's and de Quervain's subacute thyroiditis. The 'malignant/suspicious' category included follicular neoplasm, papillary carcinoma, anaplastic carcinoma, medullar carcinoma, lymphoma and metastatic carcinoma. These were diagnosed either as unequivocally malignant or with varying degrees of probability, and included uncertain findings that could not rule out malignancy. The pathological examination was performed after surgery (hemithyroidectomy or total thyroidectomy). The results were classified as benign (colloid nodular goitre, follicular adenoma, Hashimoto's thyroiditis) or malignant (follicular carcinoma, papillary carcinoma, anaplastic carcinoma, medullar carcinoma, lymphoma or metastatic carcinoma; 15, 16).

Results

Altogether 574 initially benign nodules were followed by repeated FNAC two or more times in 55 (9.6%) men and 519 (90.4%) women, aged from 15 to 92 years (mean 50.2, median 50). The clinical diagnosis of the

subjects with initially benign FNAC result was euthyroid nodular goitre in 418 patients (72.8%), 84 (14.6%) patients with nodules in Hashimoto's thyroiditis, 42 (7.3%) with toxic nodular goitre, 27 (4.7%) with cysts and three patients with subacute thyroiditis and nodules. Clinically, there were 501 euthyroid patients (87.3%), 31 (5.4%) with hypofunction and 42 (7.3%) with hyperfunction. The indication was single nodule in 176 cases and dominant nodule in multinodular goitre in 398 patients. In cases with toxic multinodular goitre, the FNAC was repeated only if the nodule proved to be cold on scintigraphy. FNAC was repeated once in 400 cases, twice in 107, thrice in 49, four times in 10, five times in seven patients and six times in one patient. The aspiration was repeated in the patients with benign first FNAC followed up at our department, provided the patient agreed. However, the indication was by the investigating physician so selection bias is probable (cases with suspicious US characteristics, uncertain FNAC result and growing nodules were aspirated more frequently). Thyroxine suppression therapy of euthyroid nodules is not routinely used at our institution.

There were 574 initially benign nodules sized from 8 to 90 mm (median 14 mm). Altogether 498 nodules had repeatedly benign cytological results. The histology was available in 153 of them (30%) and all nodules proved to be benign. Microcarcinoma located distant from the aspirated lesion was found in ten patients.

The cytological result changed to 'malignant/suspicious' in 76 nodules with initially benign cytology during the follow-up period. Fifty-eight (76%) of these patients underwent surgery; malignancy was confirmed in 13 cases – four papillary carcinomas, three follicular variants of papillary carcinoma, four follicular carcinomas, one medullar carcinoma and one poorly differentiated carcinoma (Fig. 1).

The mean follow-up period was 7 years, with detailed data shown in Table 1.

Discussion

Many authors use four categories of cytological results (benign, indeterminate, malignant and unsatisfactory). We used only three categories, as mentioned above: i) unsatisfactory; ii) benign; and iii) malignant/suspicious from malignancy. This is due to the fact that both 'malignant' as well as 'suspicious/indeterminate' results have the same clinical impact – thyroid surgery is

Table 1 Mean time of follow-up in repeated fine-needle aspiration cytology (FNAC) and number of positive changes.

No. of performed FNAC	2	3	4	5	6	7	Total
No. of nodules	400	107	49	10	7	1	574
Percentage of all 5017 FNAC	7.97%	2.13%	0.98%	0.20%	0.14%	0.02%	11%
No. of results changed from benign to suspicious	48	17	8	3	3	0	79
Mean time from first FNAC (years)	3.0	5.3	6.4	7.4	8.8	11.2	7.02

Table 2 Summary of studies of changes in initially benign cytology.

	No. of initially benign	No. of results changed to suspicious	Percentage (%)	Operated	Malignancy	Percentage (%)
Aguilar <i>et al.</i> (1998) (24)	184	1	0.5	90	3	1.6
Cáp <i>et al.</i> (2000) (29)	253	27	10.7	22	7	2.8
Dwarkanathan <i>et al.</i> (1993) (30)	196	13	6.6	10	4	2.0
Erdogan <i>et al.</i> (1998) (25)	216	3	1.4	3	3	1.4
Flanagan <i>et al.</i> (2006) (23) ^a	57	23	40.4	23	9	15.8
Hamburger (1987) (31) ^b	205	18	8.8	10	6	2.9
Chehade <i>et al.</i> (2001) (21)	235	12	5.1	9	2	0.9
Illouz <i>et al.</i> (2007) (22) ^b	282	35	12.4	31	7	2.5
Lucas <i>et al.</i> (1995) (24)	135	0	0.0		0	0.0
Menéndez Torre <i>et al.</i> (2007) (28)	358	18	5.0	12	7	2.0
Merchant <i>et al.</i> (2000) (36)	45	0	0.0	0	0	0.0
Mittendorf & McHenry (1999) (32)	45	4	8.9		1	2.2
Morosini <i>et al.</i> (1996) (37) ^b	471	8	1.7	14	0	0.0
Orlandi <i>et al.</i> (2005) (27) ^b	306	7	2.3			
Shin <i>et al.</i> (2006) (26)	187	44	23.5		6	3.2
Gabalec present results (2009)	574	76	13.2	58	13	2.3
Total	3749	289	7.7		68	1.8

^aOnly operated.^bAdapted data.

indicated in both cases (3, 11, 17). The main goal of thyroid FNAC is the early differentiation between non-malignant and malignant nodules (18). FNAC is a well-established method and its reliability depends on several factors, such as the skill of the physician or the experience of the cytopathologist. Use of ultrasonography in FNAC increases significantly the sensitivity, specificity and accuracy compared with conventional palpation-guided FNAC (9). Thyroid FNAC sensitivity, specificity, false positive and false negative rates differ significantly among various authors. Sensitivity varies between 56 and 100%, and specificity between 52 and 100%. A positive predictive value is estimated to be 34–100%, whereas a negative predictive value is 83–100% (9, 15). Suspicious or clearly malignant results are an indication for surgery and histopathological evaluation of the lesion, while inadequate results should be followed by repeated aspiration. In terms of the follow-up of benign cytological results, no consensus has been reached so far. These different opinions are reflected in different recommendations in the guidelines of three important societies of endocrinology. The AACEs and Associazione Medici Endocrinologi guidelines suggest simple follow-up of cytologically benign thyroid nodules. Repeated ultrasonography is not recommended. Repeating FNAC should be performed only for enlarging nodules, recurrent cysts or for nodules not shrinking after thyroxine therapy. The ATA guidelines suggest clinical follow-up for 6–18 months, without US guidance for easily palpable benign nodules. FNAC repetition or surgery is reserved for enlarging nodules only. These and other differences among guidelines are well reviewed by Gharib (19). Some authors recommend repeating FNAC always when the nodule is enlarging, has more than 4 cm in diameter,

shows no shrinkage of the nodule occurs after levothyroxine therapy and in cases of recurrent cysts.

Wiersinga has recommended repeating palpation and FNAC, 1 year after a benign FNAC result (20). During the last decade, several studies evaluated the risk of carcinoma in subsequent FNAC after initially benign cytology. The false negative rate can be reduced by repeating FNAC by 4.5–5.9% (21–23), from the initial 5.2–6.7 to 0.8–1.3 (21, 22). Subsequent results have cumulatively changed in about 7% of the cases, and carcinoma was found in about 2%. This relevant number of carcinomas can be detected by repeated FNAC according to many authors (21–32). Some authors tried to find out how many times FNAC should be repeated. Illouz (22) proposes a minimum of three adequate benign results as appropriate. However, some authors have reported low false negativity (33, 34), and declare no or only limited benefit from repeated FNAC (34–37). Data are summarised in Table 2.

In our series, we analysed the results of FNAC of thyroid nodules in 5017 patients, of which 574 with initially benign results underwent repeated FNAC. Thyroid carcinoma with initially benign cytology was found in 13 patients (2.3%) upon repeated FNAC. This result is in agreement with other series. The duration of the follow-up period still remains a question. Relevant data from longer studies are limited. Different authors propose time intervals ranging from 6 to 12 months (38) up to 3 years or more (22). In our series, the interval was variable depending on referral of patients for follow-up investigation. Malignancy can be detected even in an interval of 10 years in a relatively stable nodule.

A detailed look at histologically verified malignant tumours with FNAC result changed from benign to suspicious (Table 3) shows that initial cytological results were almost exclusively cases of Hashimoto's thyroiditis

Table 3 Detailed look at 13 histologically verified malignancies with initially benign cytology.

Patient No.	Initial cytological result (s)	Subsequent cytological result	Histology	Nodule size at first FNAC (mm)	Tumour size (mm)	Interval between FNACs (month)
1	HT	Susp carcinoma	Poorly differentiated carcinoma	60	90	13
2	Colloid goitre with regressive changes	Follicular neoplasia	FVPC	25	30	83
3	Benign	Follicular neoplasia	PC			31
4	HT	Follicular neoplasia	MC	25	30	24
5	Cyst and regressive changes	Follicular neoplasia	FC	33	25	57
6	Follicular adenoma	Follicular neoplasia	PC	9	15	39
7	Colloid goitre with regressive changes	Susp PC	FC	8	12	32
8	HT	Follicular neoplasia	FC	16	18	13
9	HT	Oncocytic tumour	FC	20	27	79
10	Microfollicular adenoma	Susp PC	PC		20	131
11	HT	Susp PC	FVPC	16	26	63
12	HT	Susp PC	PC	19	19	48
13	Colloid goitre with regressive changes	Follicular neoplasia	FVPC	14	31	66
Mean						52
Median						50

HT, Hashimoto's thyroiditis; PC, papillary carcinoma; FC, follicular carcinoma; MC, medullar carcinoma; FVPC, follicular variant of papilocarcinoma.

or with severe regressive changes. First FNAC specimens were for the purpose of our study and were all re-evaluated by a single experienced cytopathologist (A R). In the majority of cases, the false negative result was considered as misinterpretation of the cytological features, and the sample should have been classified as suspicious. In three cases, prominent regressive changes in the tumour were the cause of misinterpretation that precluded recognition of characteristic tumour features. These specimens should have been qualified as non-diagnostic. In one case, only the first FNAB was clearly benign colloidal goitre, and the nodule was probably missed by the initial fine-needle biopsy. When regressive changes are present, repetition of FNAC should be therefore always considered. Similar to other retrospective studies, we have also found several limitations in our survey. Various periods between subsequent FNACs are present depending on when patients were referred for second investigation. FNAC was not repeated systematically in all patients so that selection bias is probable. Cases with suspicious US characteristics, FNAC result other than unequivocal colloidal goitre, and growing nodules were aspirated more frequently. Not all of the patients were operated on, and carcinoma cannot be ruled out with certainty when the histopathological examination was not performed. Carcinoma was present in 22.41% of the operated nodules with suspicious results of repeated FNAC. Carcinoma was also present in 6.54% in initially benign FNAC results remaining benign on repetition. These results represent in all ten cases papillary microcarcinomas with no clinical significance, present distant of the investigated nodule. To the contrary, the malignancies discovered on the basis of suspicious

results of repeated FNAC were clinically important tumours larger than 10 mm misdiagnosed on the first evaluation. The size of the nodule did not change considerably in the majority of papillary carcinomas.

These results confirm the usefulness of repeated aspiration during follow-up in patients with initially benign FNAC result. In our series, it was able to identify malignancy missed at first FNAC in 2.3% of cases. Usually, it corrected misinterpretation of samples by cytopathologists, especially when the initial result was other than colloidal goitre. We believe that repeating FNAC in patients with benign cytology in about a 1-year horizon can reduce the rate of undiagnosed tumours.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the scientific work reported. F Gabalec, J Čáp, A Ryška, T Vašátko and V Ceeová have nothing to declare.

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