

The Role of Fine-needle Aspiration Biopsy in the Management of Patients with Thyroid Nodules

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Abstract. Fine-needle aspiration biopsy (FNAB) of the thyroid gland is the most cost-effective examination in the evaluation of thyroid nodules. The aim of this study was to present our experience from all patients who underwent thyroid FNA in the University Hospital of Ioannina, Greece, in the period 1993-2003, and its value in the diagnostic management of patients with thyroid nodules. FNA was performed in 900 patients of whom 753 were females and 147 males. The cases were classified according to diagnosis into five groups: benign/negative 628, primary carcinoma 28, metastatic carcinoma 5, suspicious/indeterminate 60 and non-diagnostic 179. Cytological findings were compared with histopathological findings and the statistical analysis in our data yielded the following results: sensitivity 92.1%, specificity 93.2%. These results are in accordance with the already published data in the international literature. In cases of differential diagnosis between adenomatoid hyperplasia and follicular neoplasia, four cases were diagnosed as hot nodules. In the benign group, three cases were diagnosed as nodular hyperplasia with cystic degeneration on FNA, but, after surgical treatment, histologically were diagnosed as papillary carcinomas. In the group of suspicious/indeterminate, two cases were diagnosed as suspicious for follicular neoplasia on FNA and, after surgical treatment, were diagnosed histopathologically as medullary carcinomas. In conclusion, we suggest that routine measurement of serum calcitonin is useful and mandatory in the detection of medullary carcinoma among patients with nodular thyroid diseases. Taking into consideration the clinical data can minimize false-positive and false-negative rates. We conclude that FNA is an effective screening test in the evaluation of the necessity for surgical treatment in patients with thyroid nodules.

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Key Words: Fine-needle aspiration, thyroid nodules.

In mountainous regions of Northern Greece, despite iodine deficiency, which has been reduced during the past 30 years, many new cases of non-toxic goiter still exist (1). Palpable thyroid nodules and thyroid enlargement are frequent in routine clinical practice, therefore a systematic clinical and diagnostic approach is needed (2).

Statistical data showed that thyroid tumors are more frequent in women than in men and affect all age groups, although in children the incidence is extremely low. Carcinoma of the thyroid is an uncommon type of cancer but, nonetheless, is the most common malignancy of the endocrine system and accounts for approximately 1% of total cancer cases in developed countries (3, 4). Differentiated tumors are highly treatable and usually curable. On this basis, it is very important to identify nodules, which are likely to be neoplastic. Fine-needle aspiration biopsy (FNAB) is well established and the best test in the primary diagnosis of benign and malignant disorders, with an accuracy approaching 95% (4-7). The main goal of thyroid FNA is to distinguish nodules that require surgical treatment from those which need a follow-up, consequently decreasing the number of thyroidectomies (8). Conventional tests in the diagnostic management of thyroid disease, including clinical history, serum hormonal levels, radionuclide scans and ultrasonography, are insufficient to identify and distinguish between benign and malignant thyroid nodules (9-11). The diagnostic problem in thyroid cytology is the inability to differentiate between benign and malignant follicular growth, and also multinodular goiter from follicular carcinoma (13-15).

The aim of this study was to estimate the diagnostic value of FNA in the preoperative diagnostic management of patients with solitary or multiple thyroid nodules.

Patients and Methods

A total of 900 patients, between 1993 and 2003, were referred to our outpatient department, Section of Endocrinology of the University of Ioannina, Greece. The FNABs were analyzed at the Cytopathology Laboratory of the University Hospital of Ioannina.

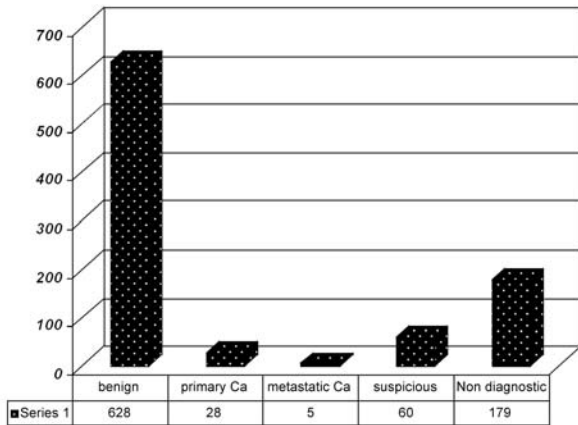


Figure 1. Frequency of the five diagnostic groups.

The age of the patients ranged from 12 to 85 years (mean=45.61). Out of the 900 patients, 147 (16.3%) (mean value =46.82) were males and 753 (83.7%) (mean value= 45.37) were females. The frequency of the five groups is shown in Figure 1.

Initially, each patient underwent physical examination, thyroid scan or ultrasonography, measurements of serum free triiodothyronine (T3), free thyroxin (T4), thyrotropin (TSH) levels and antithyroid autoantibodies.

FNA was performed in all patients who had palpable or visible thyroid nodule by ultrasonography. All FNAB, were performed by an endocrinologist (TA) using a 23-gauge, attached to a plastic syringe. A cytopathologist, who was in attendance during the aspiration in the outpatient department, immediately handled the aspirated material. After release of the vacuum, the needle was drawn, the obtained material expelled on glass slides and smears were made. Cystic lesions were completely aspirated and FNA was repeated on any residual mass. The smears were fixed immediately in 95% ethanol and stained using the method of Papanicolaou. Also the aspirates were routinely air-dried and stained with May-Grünwald-Giemsa (MGG) stain. The average number of FNA passes was 3 (range, 1-6). The cytopathologists followed the guidelines of the Papanicolaou Society of Cytopathology for adequacy in the interpretation of the slides (8). The FNAB was considered adequate if there were at least 5 or 6 groups of well-visualized follicular cells, each group consisting of 10 to 15 cells. A detailed description of the cellular component was done in all cases. Histological typing was additionally performed whenever possible, in the malignant cases. Evaluation of the smears was performed according to common cytological parameters: colloid, follicular cells, lymphocytes, macrophages and the overall architectural pattern. Five groups were identified: the first group non- diagnostic; the second, defined as benign, included cases such as colloid goiter, adenomatous goiter and lymphocytic thyroiditis; the third group, defined as "suspicious", included cases in which the smears showed atypical cells consistent with follicular neoplasia in which it was impossible to make a differential diagnosis between carcinoma and adenoma; the fourth group included the cases with diagnosis of primary thyroid carcinoma; and the fifth included the cases of metastatic carcinoma.

Results

Among the 900 cases, 179 (19.9%) were non-diagnostic, which means that the obtained material was inadequate following the already mentioned criteria (8) or from non-appropriate technical management of the obtained material. Among these 179 patients, only 127 had a complete follow-up that could be retrieved from the archives of the Endocrinological Department. Sixty-eight out of the 127 patients had a new thyroid aspiration. The diagnosis of those cases was: 43 cases were benign, 2 were suspicious (histologically verified, 1 malignant lesion and 1 hyperplastic goiter) and 4 had malignant cytological findings (histologically verified). Nineteen cases remained non-diagnostic. Of the remaining 59 patients out of 127 who were followed for more than two years, 27 had disease stability and 32 had disease resolution, 9 of the 179 patients with an initially non-diagnostic FNA had a surgical thyroid operation and 5 of them resulted as malignant tumor (Table I).

Out of the 628 cases with cytologically benign smears, 26 patients underwent a surgical treatment. This clinical management was adopted based on the clinical symptoms of these patients. The report of the Pathology Department for these patients was: 23 patients out of the 26 were benign and 3 were papillary carcinomas which were considered as false-negative FNA, and in one of these cases the opposite lobe was aspirated.

Out of the 60 suspicious cases, the results were: 3 follicular carcinomas, 44 follicular adenomas, 2 Hürthle cell adenomas, 3 fetal adenomas, 4 hyperplastic goiters, 2 Hashimoto thyroiditis and 2 medullary carcinomas.

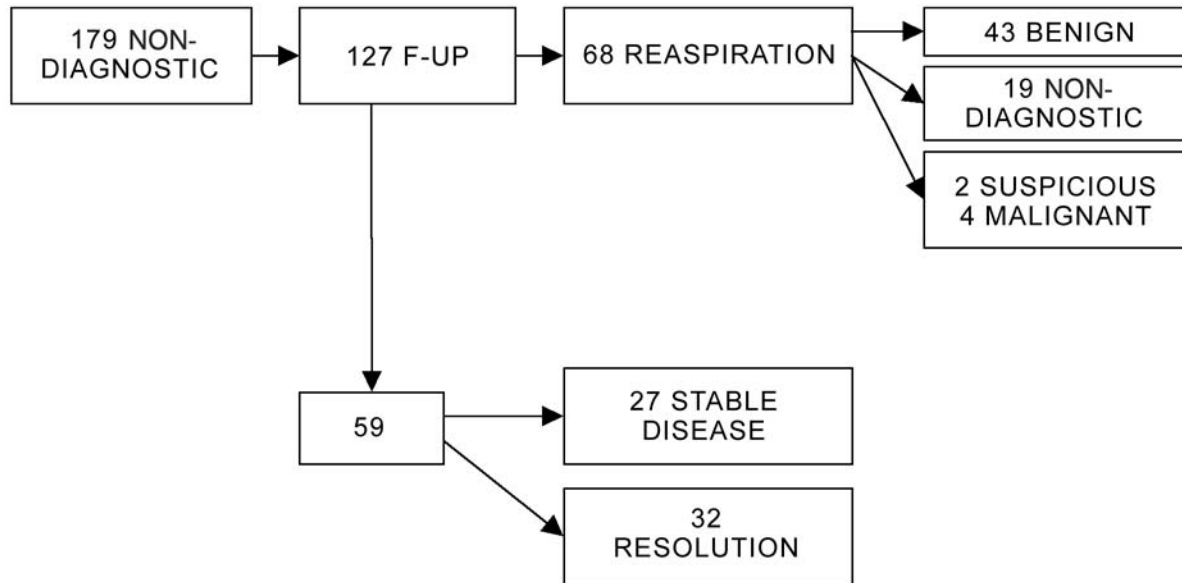
The 33 cases cytologically classified as positive were divided into primary thyroid carcinomas and metastatic as follows: 21 papillary carcinomas, 1 follicular carcinoma, 1 Hürthle cell tumor, 1 anaplastic carcinoma, 1 lymphoma and 5 metastatic carcinomas. The cases of metastatic carcinomas were not treated surgically. In these positive cases, the cytological examination permitted the diagnosis of these malignant lesions and the classification of their histotype, which was confirmed by the pathologists' reports. Three out of these 33 cases, classified as positive in FNA, after surgical treatment and compared with the reports of the pathologists, were diagnosed as Hashimoto thyroiditis and 1 as atypical follicular adenoma. These cases were considered as false-positive.

Taking into account these results, we established the sensitivity of FNA as a diagnostic method as 92.1% and specificity 93.2%, according to the proposed calculating formula.

Discussion

In 1930, Martin and Ellis, at the Memorial Sloan-Kettering Cancer Centre in New York, USA, were the first to report

Table I. Clinical management of the non-diagnostic group.



their experience with FNA biopsy. However, in the USA, serious criticism and several problems arose which has practically precluded the method. Nevertheless in Europe, especially in Sweden, FNA has been used routinely for several decades in the clinical management of palpable masses (15). There is a continuous need, in routine clinical practice, for methods that can provide reliable results in a short time and at low cost: FNA biopsy seems to fulfill this objective. The cytological examination of FNA specimens is the best test for the management of patients with thyroid nodules. It is extremely useful to select and categorize patients and gives the clinicians important information in order to proceed in surgical treatment or to follow a conservative management. The application of FNA in clinical practice is a guide test. It has reduced the number of thyroid surgical operations for benign nodules and also has increased the number of diagnosed cancer cases preoperatively. Consideration of those cases of FNA biopsies which are not diagnostic or suspicious remains. For statistical analysis reasons, the positive cases and suspicious ones were included in the 'positive' group and all other diagnostic categories in the negative group. Sensitivity (true-positives/[true-positives+false-negatives]) measures the proportion of positive cases detected by the method in a population, while specificity (true-negatives/[true-negatives+false-positives]) measures the proportion of negative cases detected by the test in a population.

In this study, 19.9% of the FNA biopsies were reported as non-diagnostic. These biopsies should not be considered as being benign, because practical experience has shown

that most of the cases are associated with a high probability of thyroid malignancy. In the international literature, 10% to 20% of thyroid FNA biopsies are non-diagnostic (16, 17). Our experience showed that a repeat aspiration of an initially inadequate FNA report in clinically suspected lesions yields greater diagnostic sensitivity, from 78.9% to 92.1%. Padel *et al.* described the sensitivity of cytology for detection of malignancy ranging from 64% for the first FNAC to 91% for patients who had more aspirates in breast lesions (18).

We agree with Gharib *et al.* (5) and Merchant *et al.* (19) in their recommendation to repeat aspiration, followed by a selective surgical treatment, in cases with non-diagnostic cytological findings. Also, we have recommended a repetition of FNA in cases of benign thyroid nodules, when the clinical appearance of the patient changes in the follow-up (20). In this study, we performed a second reaspiration in 68 patients, resulting in 4 malignancies, 2 suspicious, 48 benign and 19 non-diagnostic cases.

In the second group, called benign, 3 false-negative cases were found when cytological findings were compared with histological diagnosis. Two cases of macrofollicular type of papillary carcinoma were erroneously diagnosed as nodular hyperplasia with cystic degeneration. Similar findings have been documented by Albores-Saavedra *et al.* (21) in a study of the macrofollicular variant of papillary thyroid carcinoma. Such a false-negative diagnosis is based on the grossly gelatinous appearance and on the histologically large follicles with abundant colloid. However, the follicles are outlined by cuboidal rather than flat epithelial cells with the

nuclear features of papillary carcinoma (crowding, clearing nuclear irregularities, creases and inclusions). A thyroid cyst that refills immediately after FNA or a cyst with gross blood is suspicious for cystic papillary carcinoma (21). Our experience showed, in agreement with other published reports, that we should be very careful every time we treat patients with multinodular goiter (22, 23). A classic multinodular gland is rarely suspicious for carcinoma (24). The last false-negative case was a female patient with microinvasive papillary carcinoma; FNA was performed on the controlateral lobe, where a solitary nodule was present.

In this study, 5 of the 60 patients with the diagnosis of a suspicious lesion on FNA showed a malignant nodule. In the literature, a suspicious diagnosis is associated with a malignant nodule in 20-40% of cases (22-27). Conservative medical management is recommended in patients with thyroid nodules when better diagnostic tools are lacking. A surgical treatment should be appropriate following certain criteria such as: if the patient is less than 20 or greater than 60 years old, if the nodule is growing rapidly and has reached a large size (>4cm) and in males. In females with small nodules, with or without hormone suppression, a repeated biopsy would be a prudent choice.

Out of the suspicious cases, two were "hot nodules". For this reason the measurement of the serum thyroid-stimulating hormone level is necessary to identify patients with unsuspected thyrotoxicosis (28). The treatment for follicular neoplasm is lobectomy followed by total thyroidectomy for histologically proven carcinomas larger than 1.0 cm (29, 30). In this group, in 2 cases that were diagnosed as medullary carcinomas, the measurement of serum calcitonin was a useful tool for the early detection of this malignancy among patients with nodular thyroid diseases (31). False-positive diagnoses represent about 0.8-13.4% in different series (32, 33). Almost all these cases result from mistaking hyperplastic nodules and Hürthle cell lesions as papillary or follicular carcinoma. In our experience, the cytological patterns of Hashimoto's lymphocytic thyroiditis may cause substantial interpretive difficulties. The atypical oncocytes (Hurthle cells) may show significant nuclear abnormalities and may be mistaken for cancer cells (34).

Our data confirmed the diagnostic accuracy of FNA and our goal to minimize the false-negative diagnoses. In conclusion, we believe that FNA is the best diagnostic test in the evaluation of thyroid nodules and is very helpful in guiding the clinician in the appropriate management of each case.

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Received September 24, 2004

Revised February 7, 2005

Accepted February 21, 2005