

The Role of Fine-needle Aspiration Performed with Liquid-based Cytology in the Surgical Management of Thyroid Lesions

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Abstract. *Background: The aim of this retrospective study was to assess the accuracy and usefulness of cytological classification of fine-needle aspirates in determining the appropriate surgical treatment for thyroid lesions studied with conventional smears (CS) and liquid-based cytology (LBC) in a split-sample method. Patients and Methods: A total of 353 patients were studied with both CS and LBC. The cytological diagnoses were classified according to the British Thyroid Association into 5 groups: Thy1, inadequate; Thy2, non-neoplastic or benign group including goiter, thyrocytic hyperplasia without nuclear atypia and thyroiditis; Thy3 or indeterminate/follicular proliferation, including follicular neoplasm not otherwise specified and oxyphilic follicular neoplasm; Thy4, suspicious for malignancy, including follicular lesion with nuclear pleomorphism; Thy5, diagnostic for malignancy including papillary carcinoma and medullary carcinoma. The efficacy of thyroid fine-needle aspiration processed by CS with LBC in a split-sample method was evaluated. Results: Overall 164 patients were included in the Thy2, 97 in the Thy3, 49 in the Thy4, and 43 in the malignant Thy5 group. The percentage of unnecessary thyroidectomies decreased from 58.5 to 42% in our series. Conclusion: Our subclassification, according to the British Thyroid Association classification, attempts to reduce the number of Thy3 who undergo surgery. The comparison between the traditional management of thyroid lesions and our morphological categories with the use of CS and LBC together allows the number of unnecessary thyroidectomies to be reduced.*

The prevalence of palpable thyroid nodules in the worldwide population ranges from 4 to 7% (1, 2). Approximately 95% of these lesions are benign and thyroid cancer is responsible for only 0.4% of all cancer deaths (3, 4). The main cytological goal is to distinguish malignant lesions, which require appropriate surgical procedures, from benign nodules which, on the contrary, may be often treated conservatively. Fine-needle aspiration cytology (FNAC) has proven useful in the preoperative evaluation of patients with nodular thyroid disease and it represents the most widely used diagnostic test in selecting patients for surgery (5-10).

In the majority of centers performing FNAC, conventional smears (CS) with air-drying and alcohol fixation is the standard method used in processing FNAC samples. Liquid-based cytology (LBC) is an alternative processing method in which the aspirated material is preserved in a methanol-based fixative and then placed on LBC slides. The LBC method is gaining popularity worldwide as the method of choice for both gynecological and other non-gynecological smears, with a sensitivity and diagnostic accuracy as high as that of CS. A potential major advantage of LBC is the ability to perform immunocytochemical (ICC) studies, which may be required in some cases to reach a definitive diagnosis (11-14).

The aim of this study was to assess the accuracy and clinical usefulness of the cytological preoperative classification based on the morphological features of both CS and LBC smears because, in our opinion, analysis of frozen sections seems not to as accurate as cytology (15).

Patients and Methods

A retrospective review of the medical records of all patients undergone thyroid surgery between January 2000 and December 2006 in the Department of Surgery of the Catholic University in Rome was performed. Only patients who had a previous FNAC processed using both CS and LBC method were included in this study.

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Table I. Results of fine-needle aspiration cytology and the corresponding surgical findings in our series.

Group	Histology											
	Total	Goiter/ TH	Follicular adenoma carcinoma	PC	PC follicular variant	Microcarcinoma	Anaplastic	MTC	TT	TT+ND	Lob	Lob+ND
Benign group	164	131	29	0	1	3	0	0	0	144	0	20
Indeterminate group	97	50	19	9	3	16				38	34	25
Susp FLWNP	49	15	4	2	12	16				11	25	8
Malignant group	43	0	0	0	23	10	8	0	2	2	41	5
Total	353	196	52	11	39	45	8		2	195	100	53

TH: Thyroiditis, PC: papillary carcinoma, FLWNP: follicular lesion with nuclear pleomorphism, MTC medullary thyroid carcinoma, TT: total thyroidectomy, ND: nodal dissection, Lob: lobectomy.

CS FNACs were performed with 23 to 27 G needle under sonographic or manual guidance. For the conventional smear, the material was immediately fixed in 95% ethyl alcohol and stained with Papanicolaou stain. For the LBC application, the aspirated material was diluted in Cytolit hemolytic and preservative solution (Hologic Cytyc, Co.) after rinsing the needle in the solution. The cells were spun at 1500 rpm then the sediment was transferred to PreservCyt (Hologic-Cytyc, Co) solution to be processed with a T2000 automated processor (Hologic Cytyc, Co.) according to the manufacturer's recommendations.

The resulting slide was fixed in 95% ethanol and stained with Papanicolaou stain. Unused cells were stored in PreservCyt solution for further additional investigation or for use on an immediate second LBC slide if necessary. The patients were informed that the cellular material was processed exclusively by the LBC with the Thin Prep 2000 method.

Data from 353 patients were collected. The cytological diagnoses were classified according to the British Thyroid Associations "Guidelines for Management of Thyroid Cancer" into five cytological groups of classification for nodular lesions (16): THY1, inadequate; Thy2, benign, including colloid nodule (CN), thyrocytic hyperplasia without nuclear atypia (THWNA) and thyroiditis (TH); Thy3 or follicular proliferation (FP) with follicular neoplasm not otherwise specified (FN) and oxyphilic follicular neoplasm (OFN); Thy4, suspicious including follicular lesion with nuclear pleomorphism (FLWNP); Thy5, malignant including papillary carcinoma (PC) and medullary carcinoma (MTC). Based on our morphological features, the category of THWNA was included in the benign category (Thy2) together with CN and TH. In our study the Thy1 group was excluded from descriptive statistics and discussion (17, 18).

Surgery was performed in cases of malignant or suspicious neoplasms diagnosed on the basis of the preoperative FNAC or to remove a nodular goiter for cosmetic or functional reasons. Regarding the surgical management, the operative strategy included a total thyroidectomy (TT) and in all patients with multinodular goiters and in all patients with cytological diagnosis of malignancy. Central neck dissection and lateral neck dissection were performed only in patients proven positive for lymph node metastasis or in those with poor prognostic factors. Lobectomy plus isthmusectomy, diagnostic lobectomy (19) was advised as the first step in patients with a single lesion showing either a clinical picture and/or a cytological diagnosis of Thy3 and Thy4 lesion. If the final histology yielded a diagnosis of malignant neoplasm, subsequent completion was carried out.

Results

Among of total of 353 patients, 267 were female and 86 male, with a median age of 45.8 (range 13 to 82) years. All the cases were analyzed with both methods and the diagnoses made by the concordance of CS and LBC. One hundred and sixty-four (46.5%) patients were included in the benign group (Thy2), 97 (27.4%) in the FP group (Thy3), 49 (13.9%) in the suspicious subsets (Thy4) and 43 (12.2%) patients in the malignant group (Thy5). Cases with a Thy 1 diagnosis, which numbered 4 and after a second LBC were included in the group of Thy2. A total of 295 thyroidectomies and 58 lobectomies were performed. All Thy5 43 patients underwent TT, with central nodal dissection plus unilateral modified radical neck dissection in 13 and bilateral in 3 (Table I).

One hundred and forty-four patients with Thy2 cytological diagnosis, 108 patients in the Thy3 and all patients in the Thy4 group underwent a TT for symptomatic diffuse and bilateral nodularity of the thyroid gland.

Fifty-eight patients (20 were in the Thy2 group, 25 were in the Thy3 group and 13 in the Thy4) with a single lesion of the gland underwent ipsilateral lobectomy plus isthmusectomy (diagnostic lobectomy) as an initial procedure.

The final histology resulted in a diagnosis of malignant neoplasm in 105 patients (30%): out of these 92 were PC (among them 45 follicular variants and 8 microcarcinomas), 11 follicular carcinomas, and 2 MTCs were detected. No patients with a false-positive FNAC were found: all 41 cases with FNAC diagnostic of PC were histologically confirmed as well as the 2 with MTC. Out of 164 patients with a benign cytological diagnosis (Thy2), 4 (2%) showed a malignant lesion at histology. Fifty-eight patients out of 146 (39.7%) with a diagnosis of Thy3 and Thy4 presented a malignant lesion at the final histology: 11 were follicular carcinomas and 47 PCs (in which 32 follicular variants were present). Fourteen out of 58 patients undergoing diagnostic lobectomy (8/13 Thy4, 61%; 4/15 OFN Thy3,

Table II. *Descriptive statistics of all 353 cases modified according to the proposed morphological classification of follicular proliferation (FP) thyrocytic hyperplasia without nuclear atypia is included in the benign category other FPs are included in the malignant category.*

Specificity	64.5%
Sensitivity	96.1%
Diagnostic accuracy	73.9%

26.6%; 2/10 FN Thy3, 20%) had a malignant neoplasm confirmed at histology. Thus they required a staged completion of the thyroidectomy within 7 to 15 days from the initial surgery.

Descriptive statistics. In Table II, the descriptive statistical analysis of the cytohistological correlations are reported; THWNA is included in the benign category causing a high increase in the specificity along with the diagnostic accuracy of the FNAC (73.9%). It must be pointed out that in our data the categories of FN and OFN (Thy3), which are considered malignant, include some histologically confirmed benign lesions. On the basis of our descriptive statistics, the indeterminate category of FN and OFN should not be excluded from our classification. In this instance, the clinical management of those cases classified as FN and OFN should refer to the clinical setting instead of to the cytological picture alone.

Statistical analysis was performed by using a commercially available statistics software package (SPSS 10.0 for Windows®; SPSS Inc., Chicago, IL, USA).

Discussion

Thyroid nodules are a common finding and most of them, even neoplastic ones, follow a favourable course (1). Because many surgically removed thyroid nodules are demonstrated to have a benign nature at histology, it is important to reduce the number of unnecessary surgical procedures, and, to achieve this goal, an accurate preoperative diagnosis should be done (18, 20-23).

FNAC is the best diagnostic test available today, with an accuracy and sensitivity exceeding 95% in many series (10, 24-26). One of the most important drawbacks of this technique is the large proportion of inadequate smears obtained (because of mechanical or air-drying artifacts, or fibrin clots) which impairs the efficacy of the cytological diagnosis. One possibility to minimize this inconvenience is to submit part of the all aspirated material in a liquid fixative and this is the philosophy of liquid-based cytology (LBC).

In our laboratory experience, the introduction of LBC in thyroid FNAC since 2000, in association with CS, showed

all the problems previously reported in literature, due, in particular, to the lower self-confidence of cytopathologists with the different morphological features of LBC. The use first of CS and then of LBC, with the possible application of ICC in difficult cases, has radically modified the management of thyroid nodules by reducing the number of patients requiring surgery of a rate ranging from 23 to as much as 50% in different series (1, 27).

Accordingly, the incidence of carcinoma had increased from 15% to 30% in patients who had a preoperative cytodiagnosis requiring a surgical treatment (4, 6).

Despite the improvements of diagnostic tools, including FNAC, the rate of patients with benign nodules undergoing surgery is still two to four times higher than for those with malignant ones (28-30). In fact, while the accuracy of the FNAC diagnosis for most thyroid neoplasms (*e.g.* PC, MTC and anaplastic carcinoma) approaches 100%, it declines for follicular-patterned lesions, where the rate of indeterminate diagnosis is high, especially because of difficulties in discriminating benign from malignant histotypes (21, 23, 31-34). This category of lesion is a diagnostic problem because the morphological criteria for a diagnosis of malignancy, *i.e.* capsular or vascular invasion, cannot be reliably assessed on a cytological smear.

In most series (5, 28), 5% to 8% of aspirates are diagnostic of malignancy (in our experience, this was 12%), 10% to 20% are considered suspicious for but not conclusive of a malignancy (in our Centre, Thy4 was less than 10%), 2% to 5% fail to provide an adequate specimen, and the remaining are benign, usually CN or TH.

The classification of indeterminate category (Thy3, FP 27.4 % in our series) adopted in our Institution (17, 18) attempts to reduce the number of FP candidates submitted to surgery and at the same time to avoid any increase of false negative cases. Category Thy4 can be considered at high risk for malignancy and should be addressed by surgery whereas the truly indeterminate category is FN (Thy3), which yields a low though not irrelevant risk of malignant occurrence (20% in our series). The category of OFN deserves individual discussion because the cytological features of Hurthle cells do not allow a reliable discrimination between malignant and benign lesions, so that surgical removal is almost always indicated, the only exception being a oxyphilic hyperplastic nodule in lymphocytic thyroiditis.

The comparison between the traditional management of thyroid lesions and our proposal based on our morphological categories (Figure 1) allows a reduction of unnecessary thyroidectomies from 58% to 42%, with a poorly significant increase of the false-negative rate (from 1.9% to 2.4%).

In conclusion, the cytodiagnostic categories requiring surgical treatment are represented by the group of the malignancies (mostly PC which, in our series, did not show any false-positive diagnosis) and by the FP categories

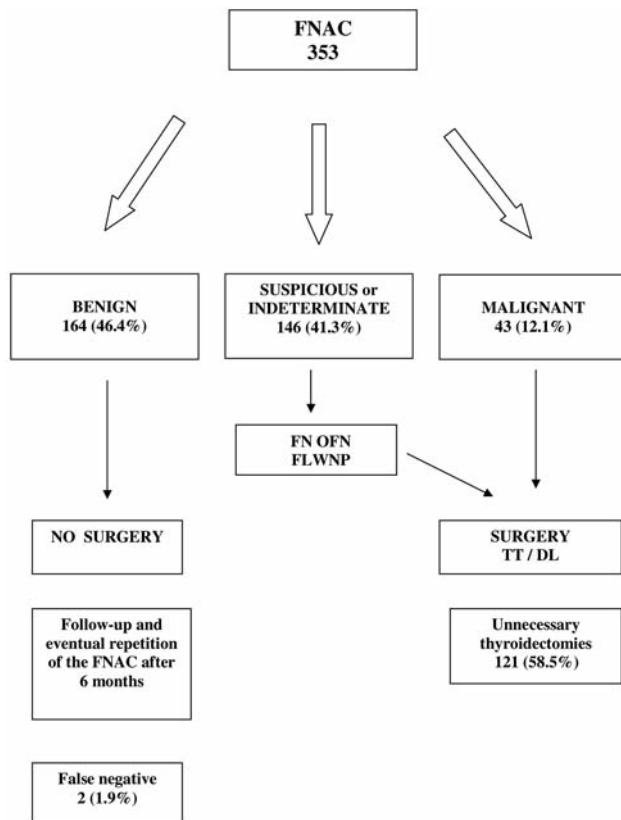


Figure 1. Proposal for surgical management of thyroid nodules based on fine-needle aspiration cytology (FNAC) results in our series. THWNA: Thyrocytic hyperplasia without nuclear atypia, FN: follicular neoplas, OFN: oxyphilic follicular neoplasm, TT: total thyroidectomy, FLWNP: follicular lesion with nuclear pleomorphism, DL: diagnostic Lobectomy.

(including Thy3 and Thy4). THWNA is included in the benign group (Thy2) with CN and TH and should only be followed-up.

Based on the above cytological classification and on the results of our series, the recommended surgical procedure may be the following (Figure 1): all patients with FNAC positive for PC, MTC and anaplastic carcinoma are candidates for TT. Central neck dissection is indicated in patients with clinically positive lymph nodes or in patients with poor prognostic factors.

A modified neck dissection is indicated when a preoperative FNAC or an intraoperative frozen-section examination (FS) carried out on an enlarged cervical node detects metastatic disease. Patients with a cytological diagnosis of FN, FLWNP and OFN undergo TT if the lesion is enclosed in a nodular goiter, diagnostic lobectomy if the nodule is single.

The routine use of FS on thyroid lesions has been discontinued in our Institution and it has been replaced by the

cytological classification based on FNAC and LBC (35-37). Nevertheless, FS retains its importance in the recognition of the parathyroid glands and in the detection of nodal metastases.

A possible development of this classification could be the use of ICC and molecular techniques applied to FP which may further distinguish those lesions which are candidate for surgery, and the use of FS examination only on lesions classified as suspicious on cytology (33).

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