

**PROPOSITION FOR A UNIFYING REPORTING SYSTEM FOR  
THYROID CYTOPATHOLOGY IN SWITZERLAND**

*Proposition submitted to the Swiss Society of Cytopathology and open to discussion*


M. Bongiovanni - S. Crippa  
Institute of Pathology – Locarno


**If you are interested to participate to this discussion, please send me an e-mail.**

**We could meet once and share our experiences.**

**[massimo.bongiovanni@ti.ch](mailto:massimo.bongiovanni@ti.ch)**

*PD Dr. med. Massimo BONGIOVANNI  
FMH Pathology and Cytopathology  
Institute of Pathology  
Via in Selva 24  
CH – 6600 LOCARNO  
Switzerland*

 +41 91 81 60 888

 +41 91 81 60 899

 [massimo.bongiovanni@ti.ch](mailto:massimo.bongiovanni@ti.ch)

 [www.ti.ch/ICP](http://www.ti.ch/ICP)

## FOREWORD

Clinical management of patients with nodular thyroid pathology requires a multidisciplinary specialist approach determined primarily by the interaction between endocrinologist, nuclear doctor, radiologist, pathologist and surgeon. This implies a special effort towards successfully integrating diagnosis and preoperative planning with medical, surgical and post-surgical treatments. For this reason, it is necessary to adopt a "common language" that may facilitate personalized and standardized treatments within specific guidelines.

Over the past decade, several classification schemes for thyroid gland Fine-Needle Cytology (FNC), have been proposed by different professional organizations; most of these schemes consist of 4 to 6 diagnostic categories. In particular, in the recent years have been proposed:

- "guidelines for the management of thyroid cancer in adults" by the British Thyroid Association e Royal College of Physicians in 2002;
- "Consensus citologico" by the Italian Society of Pathology and Cytopathology - Italian Section of the International Academy of Pathology (SIAPEC-IAP) in 2007;
- "the Bethesda System" by the National Cancer Institute in 2009.

Most of these schemes are not always comparable with each other and this has led to confusion and differences in perceptions of diagnostic terminology in cytopathology reporting of thyroid FNC between cytopathologists and other clinicians.

This confusion is even more significant if it is considered that many pathology institutes do not adopt classes for the cytological diagnosis of thyroid lesions.

All classification systems provide a category for non-diagnostic FNC, a category for benign lesions and a category for malignant lesions. But there are also notable differences.

The main difficulty is represented by "borderline" lesions characterized either by "atypia" and/or by a "microfollicular pattern". For example the British and the Italian reporting systems provide a single category for all borderline lesions, named follicular lesion and follicular proliferation, respectively. In addition, the British and the Italian systems comprise a numeral coding for each category; instead the NCI system introduces two categories for borderline lesions:

“atypia/follicular lesion of undetermined significance” and “follicular neoplasm or suspicious for a follicular neoplasm”.

The recent publication of the Bethesda Thyroid Reporting System {Cibas, 2009 #114; Cibas, 2009 #115} prompts us to ask what’s going on in Switzerland. It took us less than few minutes to realize that everyone use his own classification system (not the new Bethesda Thyroid Reporting System, nor the British Thyroid Association System). Even in our country there is a need for uniformity in reporting thyroid FNC results for understanding the clinical utility of thyroid FNC. Sometime cytopathological reports differ from centre to center, even in the same city, and are so vague that their meaning is not clear even among cytopathologist and sometimes they are considered meaningless by our clinical colleagues. Consequently, slides are required for second opinion from outside center, before patients are directed to surgery and this means loose of time, money and delay in treatment. Moreover, apparently contradictory results do to the different terminology used, destabilize clinicians and patients itself, improving loss of confidence in cytopathologist’s jobs.

Terminology should be reliable, reproducible, valid, uniform and simple {Oertel, 2009 #113}.

For these reasons, thanks to the significantly experience gained in recent years, we developed a proposition for unifying operative management and a unifying reporting system for thyroid cytopathology in Switzerland.

This proposal is part of a comprehensive international comparison, active mainly in Europe, and aims to harmonize the theoretical and practical aspects emerged in many scientific works in recent years. Our aim was not to create a new classification system, but provide a reasonable summary of more significant international experiences pointing out the critical elements.

## INTRODUCTION

Under the term FNC or FNA, it means a cytological drawing by fine needle, which can be made with or without aspiration, with a needle from 22G to 27G. The caliber of the needle should be contained in the medical report. In the presence of solid nodules and vascularization it is suggested the drawing without aspiration. The drawing is carried out preferably by using ultrasound examination, especially in cases of multinodular and cysts with solid components. It is recommended, where possible, the presence of cytopathologist for the evaluation of the aspirate. Direct smear on slides of aspirated material is the basic method recommended.

Thin layer techniques (Liquid Based Cytology, LBC), which currently have not shown any real advantage over traditional methods, should be performed only in centers with proven experience or by cytopathologists with a specific training. The cell block is considered an extra and is useful when needing further investigation.

The main purpose of the FNC is to select patients with nodular thyroid disease according to that require medical or surgical therapy. His accuracy in the diagnosis of non-functioning thyroid nodule is 95%.

The ideal quality parameters suggest a percentage of false negative < 2%, and false positive < 3%. The cytology report should be descriptive and, where possible, write a diagnostic conclusion, preferably accompanied by a code number indicating a category of homogeneous lesions for risk of malignancy and treatment option. The latter represents a rough indication because the cytological diagnosis should be evaluated in the context of clinical and instrumental exams. Application forms should contain the essential clinical information, the site and mode of drawing.

We favor a classification system that links together all the borderline lesions; the cytopathological evaluation of borderline lesions should always be accompanied by a microscopic description and possibly by a short management advice. It is critical to recognize that experience and technical procedures in performing thyroid FNC are equally important as evaluating the resulting cytologic smears, and that high quality in the former aspects reduces the number of borderline lesions. Decisions on patient's management must be taken in a clinical context rather than barely reflect a cytologic "diagnostic" category.

## **CONTENT**

We propose to use a five categories reporting system, because the diagnostic category of atypical cells (FLUS) according to the Bethesda system, should be used less than possible and is not reproducible.

The 5 categories that are in discussion are:

**NON DIAGNOSTIC-UNSATISFACTORY**

**BENIGN**

**FOLLICULAR LESION**

**SUSPICIOUS FOR MALIGNANCY**

**MALIGNANCY**

## **NON DIAGNOSTIC-UNSATISFACTORY**

The reports "not diagnostic" should not exceed 20% of FNC. Others state that 5% of unsatisfactory should be allowed and 10% should be the maximum {Oertel, 2007 #6}. The key for the success for thyroid FNC consist of an adequate or representative cell sample and the expertise in thyroid cytology {Bukhari, 2008 #21; Kapur, 2007 #86}{Nguyen, 1991 #16}. The not diagnostic reports may be inadequate and/or not representative. This percentage varies primarily in relation to technical factors. A sample inadequate is so defined because of badly smeared and/or poorly fixed and/or badly stained, while a not representative sample is so defined because does not have a sufficient number of cells belonging to the lesion to make the diagnosis. The assessment of inadequate and/or unrepresentative should be mentioned in the report with reference to the reason. An adequate sample is defined when it is well smeared (monolayered), fixed and stained (usually Papanicolaou staining). A representative sample is defined as such when it contain enough epithelial cells. The criteria for determining representativity of thyroid FNC are not well settled and it varies from institution to institution {Dey, 2007 #17} {Hamburger, 1988 #18} {Kini, 2008 #19}. As the most important thyroid cytopathologists suggest, a minimum of 5 to 6 groups of follicular cells, each group containing at least 10 cells, are required to be present on the same smear to permits the diagnosis {Goellner, 1987 #13} or on at least two slides that were prepared from separate FNA samples {Hamburger, 1994 #14; Hamburger, 1989 #15}. More permissive criteria were also described, demanding 10 clusters of follicular cells with 20 cells inside each cluster {Nguyen, 1991 #16}. According to Kini, if you have stricter adequacy criteria, then you will minimize the risk of false-negative diagnoses {Kini, 2008 #19}. Some unrepresentative cases, evaluated in the appropriate clinical setting, can be attributed to the benign category:

- a) smears consisting of abundant homogeneous colloid with rare thyrocytes;
- b) smears consisting exclusively of lymphocytes in Hashimoto thyroiditis clinically diagnosed (after excluding a lymphoma);
- c) smears consisting of red blood cells, necrotic material and macrophages from hemorrhagic pseudocysts; if after emptying the cystic component, residual solid part would still be present, this must be immediately reaspired. Ultrasound is crucial to guide the FNC in the solid component. If not solid part are present FNC can be considered consistent with cystic content.

In summary, a diagnostic smear should contain well-visualized, well-stained cellular material and must provide assessment of architectural patterns of tissue fragments. Moreover it must provide details of nuclear morphology, demonstrates cytoplasmic characteristics, as well as demonstrate the presence of peculiar characteristic (colloid, psammoma bodies, and amyloid). The cytological diagnosis is made only on representative and adequate samples.

*Operative tip:* FNC repetition in the opinion of the clinician.

## **BENIGN / NEGATIVE FOR MALIGNANT CELLS**

Benign category encompassed a great variety of lesion that space from inflammatory lesions to hyperplastic and colloid lesions. It accounts almost 70% of cases {, 2003 #47}{Gharib, 1993 #11}. In presence of adequate material, inflammatory lesions, such as lymphocytic thyroiditis (Hashimoto/s), granulomatous thyroiditis and sub-acute thyroiditis (De Quervain), are quite characteristic, do to the presence of an admixture of inflammatory cells (lymphocytes, plasma cells, macrophages, epithelioid cells arranged in granulomas) and follicular cells or oncocytes. Also hyperplastic and colloidal lesions are easily identified, due to the presence of large sheet of follicular cells, sometimes in tridimensional cluster containing colloid, and variable amount of colloid in the background of the smear. More passes are needed in case of colloidal nodules to pick up some benign appearing follicular cells. These cells have round, uniform nuclei with well distributed chromatin and dark color {Oertel, 2000 #33}{Clark, 2005 #22}. With proper cytopreparation, the majority of the hyperplastic goiters can be differentiated from follicular adenomas {Kini, 2008 #19}. False-negative results (benign FNC diagnosis and malignant tumor on histology) are possible. This is usually due to suboptimal smear, sampling error, interpretative mistakes {Gharib, 1993 #11}{Castro, 2003 #58} .

*Operative tip.* Follow-up and/or FNC repetition in the opinion of the clinician or at the suggestion of cytopathologists, to reduce the possibility of false negative.

### **Summary of cytomorphologic criteria for this category:**

- At least 5-6 sheets of 10-20 cells of follicular cells

#### *Normal features*

- Normal thyroid follicles (normal size range is 50–500mm in diameter).

#### *Hyperplastic features*

- Abundant colloid, thick and thin, relative to follicular cells
- Macrofollicular architectural pattern (“honeycomb” sheets)
- A heterogeneous population of follicular cells, involutinal and hyperplastic type; some oxiphilic cells
- Follicular cells with round nuclei with coarse and granular chromatin
- Variable number of histiocytes
- In Graves’ disease bloodstained smears with little colloid and hyperplastic epithelial cells with an abundant pale vacuolated cytoplasm

*Acute thyroiditis and chronic/lymphocytic (Hashimoto's) thyroiditis*

- Neutrophil granulocytes
- Cell debris and necrotic cells

*Subacute thyroiditis*

- Large multinucleate giant cells with numerous nuclei and phagocytosed colloid
- Degenerating follicular cells with paravacuolar granules
- Mixed cell reaction: epithelioid cells, histiocytes, and lymphocytes in a dirty background with thin colloid

*Chronic/lymphocytic (Hashimoto's) thyroiditis*

- Oxiphilic and "squamous" transformation of epithelial cells in background of lymphocytes
- Several polymorphous lymphoid cells as in reactive lymphadenitis with scant hyperplastic or normal epithelial cells
- Scantly or no colloid

### **FOLLICULAR NEOPLASM (SUSPICIOUS FOR A FOLLICULAR NEOPLASM).**

This is the most challenging diagnostic category of thyroid FNC. It is usually recognized as the category of the “follicular neoplasm or lesion”. It is constituted from all follicular lesions: adenomatoid hyperplasia, adenoma and follicular carcinoma, all of oncocytic lesions and some cases of follicular variant of papillary carcinoma.

It is well known that for follicular lesions FNC is a “depistage” test {Baloch, 2002 #42}{El Hag, 2003 #43}{El Hag, 2003 #43}. This category constitutes about 20% to 30% of cytological examinations. In these cases, cytology is unable to provide a diagnostic conclusion that is possible only with histological examination. Especially benign follicular thyroid adenomas and malignant follicular thyroid carcinomas (FTC) have similar morphology and the criteria for the distinction of these two entities is based on capsular or vascular invasion that are only detectable in histology and that requires total examination of the capsule. {Kini, 2008 #19}{Miller, 2004 #12}{Caraway, 1993 #44; Carpi, 2000 #45; Cersosimo, 1993 #46}{Carpi, 2008 #9}.

The subsequent medical act that follows such diagnosis is surgery (at least hemithyroidectomy). Different proportion of malignancy have been reported in the literature concerning this category {Carpi, 1996 #48; Carpi, 2000 #45}{Miller, 2004 #12}{Carpi, 1996 #49; Carpi, 2002 #50}{Gharib, 1984 #51; Goldstein, 2002 #52; Hall, 1989 #53}{Tuttle, 1998 #51; Yang, 2007 #50}{Baloch, 2008 #30}, but it is usually lower than 50% {Carpi, 2008 #9}{De May, 1995 #55}. In our series about the 80% of cases are benign lesions and 20% are malignant at histological examination. FTC is the malignancy more frequently diagnosed on histology after a cytological diagnosis that down in this category.

Some cases may be included in this category because of relevant cytological changes, which are too weak to be included in the suspicious category, but that can not be considered definitely benign. The inclusion of these cases in the category "low risk" must be justified by an adequate description in the report.

Most clinicians accept the fact that the cytologic diagnosis is probabilistic and could be benign on follow up {Baloch, 2002 #42}{Greaves, 2000 #95; Hamberger, 1982 #96; La Rosa, 1991 #97}. No other preoperative findings alone, such as clinical info {Raber, 2000 #56; Rago, 2007 #57}{Baloch, 2002 #42}, US findings {Raber, 2000 #56; Rago, 2007 #57; Rago, 2007 #58}, and laboratory results {Rago, 2007 #58}{Papotti, 2005 #59; Vasko, 2004 #60} can be useful to better define what cases should go directly to surgery.

In our experience the interaction with the clinicians is very important; the clinical-laboratory field and ultrasound's knowledge may be useful to limit the rate of follicular lesion reports.

Moreover, it assumes importance the integration of ultrasound and 99m Tc-MIBI scintigraphy that provides information about metabolic-proliferative activity of the lesion.

For a MIBI-active nodule in cytological follicular lesion category, the surgical excision is strongly indicated (Giovannella L,2010; Theissen P, 2009; Dietlein M, 1998)

Some immunohistochemical markers (Gal-3, HBME-1, CK-19) may enhance the diagnostic accuracy, and although they have not yet reached an attested predictive value, may be used in strict diagnostic protocols aimed to an alternative definition between positive cases among the markers (to start to a surgical confirmation) and negative cases, deserving of follow-up.

In this category we should place all hypercellular smears that contain a population of follicular cells arranged predominantly in microfollicular and/or syncytial structures with scant or no colloid {De May, 1995 #55}. Microfollicles are small follicular groups of approximately 6 to 12 follicular cells in a ringlike or wreathlike arrangement, sometimes with a small droplet of central dense colloid. These structures should involve greater than 50-75% of the cellular groups. The mere presence of microfollicles is not equal to neoplasia or carcinoma, as follicular adenomas are usually microfollicular in architecture. There is prominent nuclear overlapping and crowding of the follicular cells with noticeable uniform appearance. Significant nuclear atypia may or may not be present, but presence of nuclear atypia is not a criterion to place a lesion in this category.

In our routine practice, we consider the percentage of microfollicles to be  $\geq 50\%$  of the lesion for place a lesion in this category.

Furthermore, in this category we should place a cellular smear with a uniform and pure population of oncocytic cells (Hurthle cells) dyscohesive or in microfollicles; oncocytic cells have well-defined cell borders, large polygonal abundant densely granular cytoplasm, enlarged round nuclei, distinct central nucleoli or macronucleoli. Nuclei are often eccentrically placed, giving a plasmacytoid appearance, and binucleation is common. Colloid, a characteristic feature associated with hyperplastic nodules, is very scant or absent; background chronic inflammation, a feature associated with Hurthle cells in Hashimoto's thyroiditis, is also not present.

*Operative tip.* Surgical excision of the lesion and histological examination. The intraoperative histological examination is not recommended because not useful in these cases. The operative decision must always take account of the clinical and instrumental context.

**Summary of cytomorphologic criteria for this category:**

- Cellular, often bloody smears with scanty or no colloid
- Microfollicles with small droplet of central dense colloid ( $\geq 50\%$ )
- Syncytial cell aggregates with nuclear crowding and overlapping; trabecular or rosette-like structures
- In oncocytic proliferations pure population of Hurthle cells, mainly isolated or in microfollicles, without lymphocytes and plasma cells

## **SUSPICIOUS FOR MALIGNANCY**

This category includes samples characterized by cytological features suggesting or strongly in favor of malignancy, but where not all diagnostic criteria for malignancy are fulfilled. Usually this category constitutes about 5% of cytological examinations.

You can see only few cells from malignant tumor, therefore numerically insufficient to establish a diagnosis, or cells which cytological atypia but not sufficient to do a diagnosis of malignancy. Most cases are PTCs at definite histology, and less frequently medullary thyroid carcinomas (MTC), lymphomas or metastatic diseases. Some authors reported cancer follow up rates up to 75%, when rendering such diagnoses {Wu, 2003 #98}{Logani, 2001 #99}.

*Operative tip.* Possible repetition of the FNC in the opinion of the clinician or at the suggestion of cytopathologists. Surgery with intra-operative histology examination.

### **Summary of cytomorphologic criteria for this category:**

- Incomplete nuclear features of PTC
- Incomplete cytologic features of MTC, lymphoma, carcinoma not otherwise specified or other extrathyroid malignant neoplasia

## **MALIGNANT CELLS / POSITIVE FOR MALIGNANT CELLS**

This category accounts 5-15% of the cytologic diagnosis and comprises PTC, MTC, lymphomas, metastases as well as less differentiated types (PDTC and ATC). In general, the sample contains cells that have indubitable characteristics that permit classification in this category and further specify the type of malignant neoplasm dealing with. The medical report must contain an adequate description of cytology. The definitive diagnosis in cases of differentiated carcinoma is histological.

*Operative Tip.* Surgery for differentiated carcinomas. The surgical option should always take into account clinical context and cytopathological report. It must be recommended the continuation of the diagnostic and therapeutic iter in cases of anaplastic carcinoma, lymphoma or metastatic tumor.

### **Summary of cytomorphologic criteria for this category:**

- Cytologic features of PTC
- Cytologic features of MTC
- Cytologic features of poorly differentiated or anaplastic thyroid carcinoma
- Cytologic features of other extrathyroid malignant neoplasia

### **FNC: Critical points**

The FNC aspirate is the more accurate procedure to define the nature of a nodular lesion but, nevertheless, is not able to give definitive answers in all cases. Defining the nature of a lesion is not just respond to a generic question about the need for surgical excision, but also provides guidance on the extent of surgery. Accordingly, the FNC is a milestone in planning treatment and in that sense, the interdisciplinary communication significantly affect the operating management of thyroid nodule. A recent approach to the cytologic diagnosis based on diagnostic categories is an important tool through which the cytopathologists can communicate the result of the FNC.

It is obvious that where there are no diagnostic categories, the report can sometimes appear "unfinished" at the eyes of the specialist which follows the patient. The absence of a classification in categories or classes and, especially for dubious lesions, the absence of an operative tip in the diagnosis, could result in less standardized therapy. However, there is some common criticism observable in daily clinical practice, knowledge of which can greatly improve communication between specialists.

In "non-diagnostic" category are not included only inadequate cases for bad preparation but also those not representative due to scanty or absence of epithelial cells. The cases not representative may result from colloid-cystic lesions or hide a cystic tumor, which should be excluded by repeated sampling.

In "benign" category are included the negative for malignant cells cases, which by definition must be adequate and representative; if these two requirements are met and the indication of goodness integrates well with the clinical context, it is justified a conservative approach. However, there are special conditions in which surgical excision may be indicated despite a negative cytology such as, for example, a scintigraphic study that shows uptake of  $^{99m}\text{Tc}$ -pertechnetate or radioactive iodine at level of cervical lymph nodes or a high risk clinical and/or anamnestic context, compression, esthetical phenomenon.

In "follicular lesion" category are included all of the follicular lesions, represented by a broad spectrum of proliferations, from adenomatoid hyperplasia to neoplasia with microfollicular pattern. In these situations, surgical excision should be indicated, but in any case the operative decision should take account of the clinical-instrumental context. We understand that this type of

lesions, at histological examination, will be benign with high probability (approx. 80%); nevertheless the histological confirmation can not be avoided in most cases. There are also no definitive data on safety in the long-term observation of these lesions, some of which may progress and take aggressive biological characteristics.

In “suspicious for malignancy” category are included lesions with suspicious cytologic features but not enough to establish a diagnosis of malignancy. As mainly cases are suspected of papillary carcinoma is not contradictory the operative tip of the FNC repetition, rather than surgical excision for diagnostic purposes. Do not forget that the goal of preoperative diagnosis, in the good management of nodular thyroid disease, requires an appropriate surgical planning; the latter may differ significantly in front of cancer detection and its histologic type (papillary carcinoma, medullary carcinoma) and can also include lymphadenectomy of the central or/and side compartment. If also the repetition of FNC does not allow reaching a final report it is useful to request intraoperative diagnosis; this, at least in some cases, may favor a diagnosis of cancer by avoiding to patient, as sometimes unavoidable, a surgery in two steps.

#### Technical Drawing

Two operators are preferable; the collaboration with cytopathologist increases the probability to obtain adequate and representative material (Thyroid biopsy: what is the measure of success? R. Yu, A. Simsir, J Cangiarella, J Waisman – Comunication at 35<sup>th</sup> European congress of cytology , Lisbon 2009 september). Direct smear on slide of the aspirated material is the recommended basic method.

The thyroid FNC should always be ultrasound-guided to assess the location of the needle, to be sure to hit the target nodule, and especially in cystic-solid nodules, to be sure to sample the solid areas. The ultrasound probe can be provided with a real guide wire, with side entrance, which offers the advantage of providing greater accuracy at the target compared to the drawing without a guide, but does require a pre-entry angle (30° or 45°) and does not allow more needle excursions; it is certainly recommended for deep or small dimensions lesion, less than 1 cm.

Once the needle tip is within the nodule, “back and forth” movements (approximately 10 to 15 times over 5 to 10 seconds) of the needle are made with changing the direction of the needle associated with needle rotation on its axis; the material will be obtained by capillary.

