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Performance Comparison in the "Follicular Neoplasm" Category Between the American, British, Italian, and Japanese Systems for Reporting Thyroid Cytopathology

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Abstract

It is now almost ten years that the United States of America, England, Italy and Japan have developed their own reporting system to classify thyroid lesions. Important confusion and uncertainties dominated the "follicular-patterned lesions", a category also known as the "gray zone". Every cytopathologist was using a personal terminology to describe and call lesions made up of a variable admixture of macro- and microfollicular structures. These personal views varied considerably between cytopathologists and generated a great deal of confusion among patients (the cytological report being almost incomprehensible to them), clinicians and even within the same cytopathology community. With the advent of national reporting systems, things changed in a better way and standardized reporting systems became the standard of practice in thyroid cytology. The outcome of the widespread use of standardized diagnostic categories was the reduction of descriptive diagnoses and the improved communication between cytopathologists, clinicians and patients. In this article we review the major reporting systems, analyze their similarities and differences in the "indeterminate" or "follicular-patterned" diagnostic categories, and when possible, try to assess their performance.

Keywords: Thyroid, fine-needle aspiration, reporting systems, indeterminate diagnostic category, diagnostic accuracy

Introduction

Thyroid fine-needle aspiration (FNA) is one of the most commonly performed medical procedures all around the world. It is safe and easy to perform, and when coupled with ultrasound, allows even non-palpable and deep-seated nodules to be precisely located and sampled (1, 2). As thyroid ultrasound alone has low specificity and sensitivity to detect thyroid malignancies, FNA has become a natural complement for the initial investigation of thyroid nodules. Consequently, a spectacular increase of thyroid FNA has been observed. Cytopathologists have thus been facing a wider spectrum of lesions requiring not only a precise morphological description but also a clear and concise diagnosis. Usually cytopathologists are aware of what is clearly benign and malignant, but they experience some limitations regarding the classification of lesions not belonging to these two extremities, the so-called "gray-zone" (3).

Another problematic issue is the meaning of the "Indeterminate" diagnostic category (DC). In some reporting systems, it encompasses all follicular lesions or follicular-patterned lesions for which a benign diagnosis cannot be warranted; in other words those lesions are composed of a variable amount of microfollicular structures, the percentage of which is increasing with the risk of malignancy. According to other reporting systems used worldwide, this DC also includes lesions with nuclear atypia such as those suspicious but insufficient for a diagnosis of papillary thyroid carcinoma (PTC), lesions that present nuclear atypia in a context of fixation/staining artifacts, or lesions that show morphological findings inconsistent with the clinical presentation.

If terminology defining follicular-patterned lesions is not clear, the same is true concerning the reporting of these lesions. In the past, a great majority of cytopathologists not even finished their reports with a final and clearly stated diagnosis, but used sibylline sentences reflecting their uncertainties. Some more audacious cytopathologists also signing out histopathological cases placed the follicular-patterned lesion in the benign category, knowing that a majority of these lesions turn out to be benign (or with a low degree of malignant potential) at histology. Other cytopathologists considered follicular-patterned lesions as malignant, leading to the impossibility to compare data from different institutions/hospitals. The unreliability of cytopathological reports and as a consequence the inability to identify malignancy in the follicular-patterned DC was responsible for the disuse of thyroid cytology. Fortunately, several cytological societies tried to set up a series of general recommendations. The first goal that had to be achieved was to keep thyroid cytology alive. New reporting systems were created and started to be used: the American, British, Italian and Japanese thyroid reporting systems. The standardization of the cytological report gained success immediately; it was not unusual to hear pathologists and clinicians refer to thyroid cytological results using acronyms related to DCs such as TIR3 for follicular lesion in the Italians reporting system (see below) instead of speaking of a lesion suspicious for a follicular neoplasm.

Have the new classification systems lead to a consensus and a standardized terminology concerning the "Indeterminate" DC? Are the diagnostic performances comparable among the different reporting systems? The aim of this study is to compare and assess

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Table 1. Comparison between the four thyroid fine-needle aspiration reporting systems

American, 2008 (abbreviation)	**English, 2011** (abbreviation)	**Italian, 2014** (abbreviation)	**Japanese, 2013** (abbreviation)
Non-diagnostic or unsatisfactory cyst fluid only (I)	Non-diagnostic for cytological diagnosis (Thy1) Unsatisfactory, consistent with cyst (Thy1c)	Non diagnostic (TIR1) Non diagnostic - cystic (TIR1C)	Inadequate (non-diagnostic) (1)
Benign (II)	Non-neoplastic (Thy2/Thy2c)	Non-malignant/benign (TIR2)	Normal or benign (2)
Atypia of undetermined significance or follicular lesion of undetermined significance. (AUS/FLUS) (III)	Neoplasm possible - atypia/non-diagnostic (Thy3a)	Low-risk indeterminate lesion (LRIL) (TIR3A)	Indeterminate (3) Follicular neoplasm (3A) Others (3B)
Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) (IV)	Neoplasm possible - suggesting follicular neoplasm (Thy3f)	High-risk indeterminate lesion (HRIL) (TIR3B)	
Suspicious of malignancy (V)	Suspicious of malignancy (Thy4)	Suspicious of malignancy (TIR4)	Malignancy suspected (4)
Malignant (VI)	Malignant (Thy5)	Malignant (TIR5)	Malignancy (5)

the performance of the American, British, Italian and Japanese systems for reporting thyroid cytopathology regarding the indeterminate follicular-patterned DC.

The American (Bethesda) reporting system

The American reporting system, known under the acronym TBSRTC (The Bethesda System for Reporting Thyroid Cytology), is probably the most diffusely used. It is born from the initiative of the National Cancer Institute in 2007 in Bethesda (MD, United States). The Conference was preceded by long and profitable web-based discussions guided by steering committees in charge of orientating the discussion to the proper segment. Andrea Abate organized the conference and Syed Z. Ali and Edmund S. Cibas were the editors driving the publication of the Bethesda Atlas (4). A web-based atlas of images is also available. This system, that has not been revised yet, is a 6-tiered system consisting of the following six DCs: 1) non-diagnostic/unsatisfactory (ND/U); 2) benign (B); 3) atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS); 4) follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN); 5) suspicious for malignancy (SM); and 6) malignant (M). The most important and innovative feature of this system, probably explaining its immediate success, is the association of the DCs with a malignancy risk and a proposed action. This scheme helps to standardize not only the reporting terminology, but also to clarify treatment options (Table 1).

The English (RCPath) reporting system

The English system was started in 2002 by the British Thyroid Association (BTA)-Royal College of Pathologists (RCPath). By 2007, the terminology comprising five DCs became rapidly widespread in UK. In 2009, the RCPath published a modified system under the name of "Guidance on the reporting cytology specimens" that was put on the RCPath for comment before its definitive release (5). It comprised the following DCs: non-diagnostic (also reported as Thy1), under which was created a new subcategory, namely the Thy1c ("c" for cystic lesion with macrophages and no colloid); non-neoplastic (Thy2), with a subcategorization (Thy2c) for cystic lesions containing macrophages and colloid and can be considered non-neoplastic in the appropriate clinical setting; neoplasm possible (Thy3), that encompasses the most common Thy3f ("f" for follicular lesion) and Thy3a ("a" for atypia) for cases containing architectural and/or nuclear atypia insufficient to be placed in a higher category or cases compromised by preparation/staining artifacts; suspicious of malignancy (Thy4); and malignant (Thy5). More recently, the BTA released the third edition of their guidelines for the management of thyroid cancer (6). In the preface to the section dedicated to FNA cytology, following the 2009 RCPAth "Guidance on the reporting cytology specimens", are enumerated some points of good practice (5). It is stated, for example, that the numerical category (Thy1-5) should also be written along with a descriptive paragraph containing the interpretative findings. It is also stated that the UK DCs map exactly TBSRTC DCs (Table 1).

The Italian (SIAPEC/IAP) reporting system

The Italian system was originally issued in 2007 by the Italian Society for Anatomic Pathology and Cytopathology (SIAPEC)-International Academy of Pathology (IAP) in association with the Italian Society of Endocrinology and the Endocrinologist Medical Association (7). This was a 5-tiered system consisting of the following DCs: 1) non-diagnostic, also reported as (TIR1), 2) negative for malignant cells (TIR2), 3) inconclusive/indeterminate (follicular proliferation) (TIR3), 4) suspicious for malignancy (TIR4), and 5) diagnostic of malignancy (TIR5). It has been recently revised by the SIAPEC in agreement with the Italian Society of Endocrinology, the Endocrinologist Medical Association and the Italian Association of Thyroid (see the article by Fadda G *et al*. in the present issue for more explication).

Briefly, the two most important additional features present in the revised version are 1) the association of a malignancy risk to each DC, in analogy with TBSRTC and 2) new subcategories in the TIR1 and TIR3 DCs. In particular, a new subcategory of TIR1, called TIR1 cystic (C), covers aspirates only containing cyst fluid, a material in itself non-diagnostic that can however be considered benign if US and clinical features point toward a benign lesion. The TIR3 DC was splitted into low and high risk of malignancy (Table 1).

The Japanese reporting system

The Japanese thyroid reporting system was issued in 2005, as published by the Japanese Society of Thyroid Surgery based on the recommendations of the Papanicolaou society (8). This was a 5-tiered system consisting of the following DCs: 1) inadequate (non-diagnostic), 2) normal or benign, 3) indeterminate, 4) malignancy suspected (not conclusive for malignancy), and 5) malignancy. In 2013, the Japan Thyroid Association proposed a new version of the reporting system, the more evident modifications being the subcategorization of the Indeterminate DC (9, 10). This DC has been divided into A: Follicular neoplasms; and B: Others. Cases with papillary carcinoma-type nuclei are excluded from category A. The "follicular neoplasms" are cases with architectural atypia in the sense of microfollicular structures and are further subdivided into A-1: favor benign; A-2: borderline; and A-3: favor malignant; depending on cellular atypia, loss of cellular cohesiveness, loss of cell polarity and architectural features (trabecular, tubular, microfollicular growth patterns). The use of these three subcategories remains optional in cytological reports. In the group "Indeterminate A" are also included cases of the PTC, follicular variant. The "Others" are lesions that are not follicular, but that harbor features of undetermined significance, in most cases represented by equivocal nuclear features of PTC.

Indeterminate and atypical category

For 5-tiered reporting systems, the "gray zone" is represented by the Thy3 DC (UK classification), the TIR3 DC (Italian classification), and the Indeterminate DC (Japanese classification). The American classification comprises formally another DC for "atypical cases": the AUS/FLUS that together with the FN/SFN and the Suspicious for Malignancy DC are often considered together into the "Indeterminate" category. If we want to compare similar DC, we have to split the Indeterminate DC into subgroups. According to different papers, it is clearly stated that the UK Thy3a DC is equivalent to the AUS/FLUS DC (11, 12). For the Italian classification, the TIR3A could also be considered equivalent to the AUS/FLUS DC, and the management of both DC is repeat FNA (13). For the Japanese classification, Indeterminate B DC is the one that matches best the AUS/FLUS concerning the atypical nuclei scenarios, as in the Japanese classification this category does not include cases with poor preservation/fixation/staining (9). Considering incidence and risk of malignancy in the American, UK, Italian and Japanese classifications, these are reported to be <7% and 5-15%, 4.6% and 9.5-43%, <10% and <10%, and 3.2% and 40-60%, respectively. The lower malignancy risk observed in the Italian classification is probably related to the atypical nuclear features being placed in the TIR3B category. In the AUS/FLUS DC of the Bethesda system, if we only consider the nuclear atypia scenario, then the malignancy risk is much higher than reported, varying from 38% to 56% (14-16).

Follicular neoplasm

When speaking of FN, we refer histologically to nodular hyperplasia, follicular adenoma and follicular carcinoma, i.e. lesions that require surgical excision for accurate diagnosis. Meticulous microscopic examination of the capsule surrounding follicular proliferations looking for vascular and/or capsular invasion is mandatory for a diagnosis of malignancy. The cytological alter ego of what is described above is the "follicular-patterned lesion". No definitive cytological diagnosis can be made and usually the material is composed of a variable admixture of mainly microfollicular structures. For these lesions, thyroid FNA is considered a screening test, orientating patients toward surgery. Several synonyms are used to indicate this category: follicular neoplasm/suspicious for a follicular neoplasm/neoplasm possible (suggesting follicular neoplasm). It is referred to FN in this article.

Correspondence in the different classification systems can be established as follows: FN/SFN in the American system, Thy3f in the UK system, TIR3B in the Italian system and Indeterminate A-3 in the Japanese system. Some classification schemes, as the Japanese one, tried to further stratify FN according to cellular atypia, loss of cell polarity, loss of cellular cohesiveness, and structural abnormality in order to further prevent unnecessary surgeries (9).

Is it possible to compare the diagnostic accuracy of the FN DC? In a paper published in 2012, no significant differences were demonstrated in the positive predictive value (PPV) for the FN DC between the American and the Italian reporting systems (26.5% *vs*. 32.1%, $P = 0.2531$) (17). Differences were noted in the rate of cases diagnosed as FN (4.6% *vs*. 23.8%, $P < 0.0001$) and in the percentage of patients that underwent surgery (56.4% *vs*. 78.8%, $P < 0.0001$), probably indicating that medico-legal issues affected more USA-based clinicians than European-based ones. Data from the Japanese classification are not really comparable to the other reporting systems, as patients with FN are further stratified into Favor benign, Borderline and Favor malignant subcategories. Most importantly, the reported malignancy risk for the American FN DC of 15-30% that per se requires surgical treatment in the United States is not considered in Japan so high to require surgical treatment, at least not-without any other adjunct evaluation. Despite these limitations, cases placed in the FN DC are 4.3% in a recent analysis (Sugino *et al*. in the present issue), being more similar to the above reported study in the Italian classification (4.6%) and far away for the data reported by a meta-analysis of 10.1% in the American classification (18). Medico-legal issues are probably less an obstacle to report thyroid cytology in Japan. However, data from the article by Sugino *et al*. from the Ito Hospital, Tokyo, Japan, presented a PPV value of 35.7% in the FN DC as a whole. If we look at the Indeterminate DC A-3 (Favor malignant), the PPV value is extremely high (50%) (9).

In a study about the UK classification, FN DC (Thy3f) represented 13.6% of total cases (12). No data are available so far concerning the frequency and the malignancy risk in the new TIR3B DC, but the authors of the revised Italian classification hope that its frequency will be lower than 10% and that its cancer risk will be comprised between 20% and 30% (13).

In consideration to the treatment of FN lesions, something similar to the Japanese proceeding is also present in the UK classification scheme, where a surgical action is not formally required for patients with a Thy3f lesion: these situations are better discussed in multidisciplinary meetings.

Different approaches

Probably the most striking difference between all these classification systems is the discussion (British, Italian and Japanese systems) or not (American system) of FN cases in multidisciplinary meetings before deciding if surgery is indicated and the threshold of malignancy risk adequate for surgery between Western countries and Japan, Japan being more conservative in this aspect.

Conclusions

In our opinion, we are far from using a common and worldwide diffuse reporting system concerning FN of the thyroid. Each reporting system uses different acronyms, terminology and to a certain extent definitions (FN/SFN, Thy3, TIR3, Indeterminate) and this fact does not facilitate standardization of reporting systems and communication between people. Moreover, European countries have a different approach for the management of FN in comparison to United States and Western countries have a more aggressive approach concerning FN in comparison to Japan.

Conflicts of Interest: None

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