Reporting Thyroid Cytology

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The Italian SIAPEC-AIT 2014 classification, the 2017 Bethesda System for Reporting Thyroid Cytology (TBSRTC), the 2016 UK Royal College of Pathologists (RCPath) thyroid reporting system, and the 2019 Japanese reporting system for thyroid aspiration cytology (JRSTAC2019) represent the most widely used reporting systems among clinicians and pathologists for the purpose of cytologically diagnosing, estimating the potential risk of malignancy (ROM), and defining the most appropriate treatment for a patient with a thyroid nodule. Although all the systems use overlapping diagnostic categories and morphologic criteria, they differ on the basis of the criteria for inclusion in the cytologic categories, which may, in turn, affect the ROM of a given category and the clinical management of the patient, particularly with regard to the “indeterminate” categories.

Keywords: thyroid reporting systems ; indeterminate category ; thyroid cytology

1. Introduction

The diagnosis of thyroid nodules represents an important problem for clinicians and pathologists, especially regarding the diagnostic framing and the choice of the most appropriate treatment. More than 50% of the general population may have a thyroid nodule, detected by instrumental diagnostic methods such as ultrasonography, but only 5% of them present malignant characteristics and behavior [1][2][3].

In addition to clinical and ultrasonographic examination, the study of thyroid nodules is performed by fine needle aspiration (FNA) or needle aspiration, a rapid, effective, safe, and cost-effective procedure. This technique allows, through fine needle aspiration under ultrasound guidance, to prepare cytological preparations and study the morphology of the cells of the lesion [4]. However, between 15% and 25% of lesions are cytologically indeterminate, i.e., they present a morphological picture that does not allow them to be identified with certainty as benign or malignant [3].

In order to distinguish nodules to be sent for surgical treatment from those to be observed over time with clinical and ultrasonographic examinations, classifications (or reporting systems) based on cytological criteria have been drawn up.

Among the reporting systems, the Italian SIAPeC-AIT classification, in its latest version updated in 2014/(CI14) and *The Bethesda System for Reporting Thyroid Cytopathology*, proposed in 2007 and updated in 2017 (TBSRTC) are among the most widely used in the world [5][6] together with the *Guidance On The Reporting Of Thyroid Cytology Specimens* from The UK Royal College Of Pathologists [7] and *The Japanese reporting system for thyroid aspiration cytology* [8].

2. Italian 2014 and Bethesda 2017 Classifications: Common Issues

Both reporting systems identify six categories, respectively, non-diagnostic, non-neoplastic/benign, indeterminate (two categories for each system), suspected of malignancy, and diagnostic for malignancy (**Table 1**). For each of these categories, a risk of malignancy (ROM) is also defined, i.e., the estimated risk that a lesion may be malignant on histologic examination, which represents the main difference between the two systems (see below).

Table 1. Comparison between 2014 Italian SIAPEC-AIT classification, 2017 Bethesda and 2016 UK RCPath reporting system for thyroid cytology.

2014 Italian SIAPEC-AIT Reporting System	2017 Bethesda Reporting System for Thyroid Cytology	2016 UK Royal College of Pathologists System
TIR 1 Non-diagnostic **TIR 1C Non-diagnostic—cystic**	**I. Non-diagnostic**	**Thy1: Non-diagnostic** **Thy1c: Non-diagnostic—cystic**
TIR 2 Benign	**II. Benign**	**Thy2: Non neoplastic** **Thy2c: Non neoplastic—cystic**

2014 Italian SIAPEC-AIT Reporting System	2017 Bethesda Reporting System for Thyroid Cytology	2016 UK Royal College of Pathologists System
TIR 3A Low-risk indeterminate lesion	III. Atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS)	Thy3a: Neoplastic possible, atypia/non diagnostic
TIR 3B High-risk indeterminate lesion (oncocytic lesions included)	IV. Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) (oncocytic lesion FNHCT/SFNHCT included)	Thy3f: Neoplastic possible, suggesting follicular neoplasm
TIR 4 Suspicious of malignancy	V. Suspicious of malignancy	Thy4: Suspicious of malignancy
TIR 5 Malignant	VI. Malignant	Thy5: Malignant

The SIAPEC-AIT and the Bethesda system use overlapping morphological criteria such as the degree of cellular atypia and architectural atypia to determine the correct inclusion of thyroid nodules in the various categories, especially for nodules with indeterminate features.

Architectural atypia is defined by the amount of microfollicles in the cytologic preparation while cytologic atypia consists in the identification of irregularities of the follicular cell nuclei (elongation, clarification, nuclear grooves).

The probability that a nodule presenting cytologic atypia may be malignant appears to be higher in the literature than that of a nodule presenting only architectural atypia: in some works, cytologic atypia indicates 50% of the ROM compared with 24% of architectural atypia [9], while in others this difference is even higher (33.3% versus 7.7%) [10].

In both systems the risk of malignancy for benign nodules is very low (less than 3% in both systems) [6][11] and for those suspected to be malignant (79–89%) [11][12] and malignant (more than 97%) [11][12], the risk is significantly high, and this finding is of fundamental importance to determine the therapeutic strategy (i.e., follow-up in the former and surgery in the latter). For indeterminate lesions, the estimated ROM is variable between the two systems, but an estimated risk of malignancy greater than 15% for indeterminate categories that are candidates for clinical and ultrasonographic follow-up (TIR 3A in CI14 and AUS/FLUS in TBSRTC) may create management problems for the clinician and the patient. In the Italian classification, the low-risk category (TIR 3A) has an expected ROM between 12 and 22% [13], whereas the high-risk category (TIR 3B) has an expected ROM between 40 and 55% [13]. In contrast to the 2008 TBSRTC, in which the ROMs were similar to those of the 2014 Italian classification, those of the 2017 edition are higher. In fact, AUS/FLUS results in a ROM estimated between 10 and 30% and the FN/SFN category is in a range between 25 and 40% [11], creating doubts regarding the choice of patient management between conservative therapy (expected for AUS/FLUS lesions) and surgical therapy (expected for FN/SFN lesions).

The recognition in the recent edition of the *WHO classification of Endocrine Tumors* (2017) of a new nosological entity, NIFTP (non-invasive follicular tumor with papillary-like nuclear features—see below) should result in a reduction of ROMs, especially in the indeterminate categories of both classification systems [3].

3. Indeterminate Diagnoses in the Italian Classification 2014

The 2014 Italian classification analyzes the morphologic characteristics of thyroid nodule cells to place them in the most appropriate diagnostic category. It was recently observed that the ROM for indeterminate lesions was slightly higher than estimated, reporting a value of 17% for the TIR3A category and 47% for the TIR3B category [13]. However, similar to the ROM observed in other reporting systems, this parameter for the low-risk indeterminate categories (TIR3A and AUS/FLUS) is affected by the fact that the majority of nodules with this diagnosis are not referred for surgery [14].

3.1. Indeterminate Low-Risk Lesions (TIR 3A)

CI14 defines TIR 3A as a lesion of increased cellularity with numerous microfollicular structures in a colloid-poor context, or rare clusters of microfollicular structure cells that may also present with oncocytic metaplasia [6].

In the assessment of ROM, the TIR3A includes lesions presenting mainly architectural atypia while excluding those presenting cytological atypia above the mild grade; therefore, the estimated risk of malignancy in low-risk indeterminate lesions is lower than in the Bethesda classification [3][6]. The introduction of NIFTP reduces the ROM of this category in a non-significant way (from 15.9% to 14% according to Straccia et al. [14]).

Treatment for TIR3A type lesions is conservative with follow-up and repeat aspiration 6 months after the first one. Surgical option (lobectomy) should be considered if clinical or ultrasound parameters worsen [6].

3.2. Indeterminate High-Risk Lesions (TIR 3B)

TIR 3B corresponds to a high cellularity lesion with microfollicular/trabecular structure, containing little colloid and with presence of moderate to severe cytological atypia. Also included in this category are Hürthle cell or oncocytic cell lesions, thyrocyte-derived cells that exhibit abundant finely granulated cytoplasm, reflecting an excess of mitochondria, often associated with a core polymorphism and prominent nucleoli [6].

The TIR 3B category, with surgical option as the treatment of first choice [6], includes all lesions presenting moderate to severe cytologic atypia, with progressive stratification of malignancy risk [13], and oncocytic lesions. However, a recent study observed a significant difference in ROM in this category between follicular cell and Hürthle cell lesions, showing a ROM of 59% for the former group and 9% for the latter, respectively [14]. The latter finding suggests that Hürthle cell lesions, of which a considerable proportion are non-neoplastic forms, should be included in the indeterminate low-risk category (TIR 3A) to reduce the amount of inappropriate surgery.

4. Indeterminate Diagnoses in the 2017 Bethesda Classification

The recent 2017 version of the Bethesda Classification (TBSRTC), following analysis of recent literature and meta-analysis, presents a reassessment of the risk of malignancy of AUS/FLUS and FN/SFN lesions increased to 10–30% (compared with 5–15% in the previous version) and 25–40%, respectively, compared with 15–30% in 2008 [3][15].

4.1. AUS/FLUS

Bethesda defines an AUS/FLUS as a nodular lesion that exhibits a degree of atypia, primarily nuclear and/or architectural that does not allow the lesion to be associated with a suspected neoplastic lesion or suspected of malignancy [16].

The extremely heterogeneous picture of AUS/FLUS lesions and the remodelling of a higher ROM than the previous Bethesda edition has led some authors to propose a sub-classification of nodules based on morphological atypia, with a higher ROM for nodules presenting nuclear atypia than those with only architectural atypia, the presence of oncocytic features presenting a lower ROM, and atypia not otherwise specified [9]. In this way, it is possible to distinguish nodules that will be treated with a conservative approach, with a repeat FNA within 3–6 months [17], from those that will be sent for surgery.

Recently, the use of molecular tests for mutations, in particular BRAF V600E, N-RAS and TERT, such as Afirma-GEC and ThyroSeq assay is being implemented in clinical practice in order to distinguish among the various AUS nodules those that will go to surgery [18], but routine use is limited by a suboptimal cost–benefit ratio [19] and variability in test performance [18].

4.2. FN/SFN Follicular Neoplasms; FNHCT/SFNHCT Oncocytic Neoplasms

FN/SFN refers to a thyroid aspirate comprising follicular cells, many of which exhibit architectural alteration characterized by cell crowding or microfollicular formation, and mild cytologic atypia such as nuclei enlargement, nuclear membrane alteration, and mild chromatin shedding [16]; presenting histologic counterpart including a wide range of clinical entities such as follicular adenoma, Hürtle cell lesion, NIFTP, and others.

In Bethesda, a particular category is represented by Hürthle cell (oncocytic) neoplasms (and suspected neoplasms) Some laboratories prefer the use of the term SFNHCT because many needle aspirates diagnosed as oncocytic neoplasms result on histologic examination as hyperplastic lesions with a predominant oncocytic component (15–26%) [20].

Both FN/SFN and FNHCT/SFNHCT lesions are treated surgically with lobectomy [17].

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