The 2014 Italian Reporting System for Thyroid Cytology: Comparison with the National Reporting Systems and Future Directions

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Abstract

The main purpose of the management of patients with thyroid nodules is the distinction of those who are candidate to surgery in respect to those who can simply be clinically followed. This decision primarily relies on the morphologic classification of cytologic samples obtained by fine-needle aspiration, complemented by clinical and imaging findings and, in selected cases, by molecular analysis. Various 4- to 6-tiered reporting schemes for thyroid cytology have been proposed and their validity has been demonstrated in several studies. The most controversial points concern the definition of the “indeterminate” cytology and the consequent nonnegligible rate of unnecessary diagnostic surgery. An update of the 2007 Italian Consensus Statement for the reporting and classification of thyroid nodule cytology was planned during the period of 2011-2014 and it has been devised by a Committee composed of five pathologists and five endocrinologists, representing the National Societies of Pathology and Endocrinology. The 2014 Italian Reporting System for Thyroid Cytology, on the previous 5-tiered reporting scheme, includes a sub-classification of the “non diagnostic” diagnoses introducing the category TIR 1C for cystic lesions and the separation of the “indeterminate” category (TIR 3) into two subclasses (TIR 3A and TIR 3B) with expected different risks of malignancy and different managements. A definition of the cytologic criteria of inclusion in the different categories and a prospective multicenter trial are also planned to validate the effectiveness of the system.

Keywords: Thyroid neoplasms, aspiration cytology, classification, diagnosis

Introduction

Nodular lesions of the thyroid represent a very common problem for the clinician as well as a diagnostic challenge for the pathologist. Up to 5% of the general population has a palpable thyroid nodule although only approximately 5% of these clinically apparent thyroid nodules actually harbor malignancy (1, 2). The real challenge, faced by the general practitioners, endocrinologists, surgeons, and pathologists, is to reach an accurate preoperative diagnosis of malignancy and to ensure that patient receives a timely and appropriate treatment. Fine-needle aspiration (FNA) is the only test that can provide a definitive preoperative diagnosis of malignancy. The sensitivity and specificity of FNA are reported to be 68–98% and 56–100%, respectively (3).

Fine-needle aspiration biopsy (FNAB) is also regarded as the most accurate method for selection of the patients with thyroid nodules for surgery or for the ‘wait and see’ management, and it is a very cost-effective diagnostic test. The aim of the present paper is to present the new Italian six-tiered reporting system for thyroid cytology (4), which originally was intended as an update of the previous system SIAPEC-IAP devised in 2007 (5). The Committee who accomplished this task, sponsored by the SIAPEC-IAP (Italian Society for Anatomic Pathology and Cytology, joint with the Italian Division of the International Academy of Pathology) in agreement with the Italian Society of Endocrinology (SIE), Association of Medical Endocrinologists (AME), and Italian Association of Thyroid (AIT), was composed by ten specialists in thyroid diseases, five pathologists and five endocrinologists. The previous SIAPEC-IAP reporting system (Table 1) was a five-tiered classification which included the following categories: TIR 1 - non diagnostic; TIR 2 - negative for neoplasia; TIR 3 - indeterminate/follicular proliferation; TIR 4 - suspicious for malignant neoplasm; and TIR 5 - positive for malignancy. The latest Italian Reporting System (Table 2) introduces the additional subgroup of TIR 1C (cystic) in the non-diagnostic group and the subdivision of the indeterminate category (TIR 3) into TIR 3A (low-risk indeterminate lesion) and TIR 3B (high-risk indeterminate lesion). The almost contemporary American Bethesda Reporting System for Thyroid Cytology (TBSRTC) (6) identified six categories, of them the nondiagnostic, benign and malignant diagnostic groups are similar to, whereas the indeterminate lesions are different from the Italian and British classifications; the indeterminate lesions in TBSRTC are classified into three categories: 1) atypia of undetermined significance and follicular lesions of undetermined significance (AUS/FLUS); 2) follicular neoplasm or suspicious for follicular neoplasm (FN/SFN); and 3) suspicious for malignancy (SM) (7).

The British Thyroid Association together with the Royal College of Pathologists immediately followed the TBSRTC in subclassifying the follicular neoplasms (FN) into the two subgroups of Thy3a (atypia), corresponding to the Bethesda AUS/FLUS, and Thy3f (follicular neoplasm), corresponding to the FN/SFN of the NCI Conference, with a good diagnostic agreement among cytopathologists (8-10). It should be noted that in the British system, all cases categorized either as indeterminate or suspicious should be referred to the multidisciplinary team in order to establish a correct management.

Though the most recent updates, the Italian and British reporting systems have joined the Bethesda philosophy in devising...
Table 1: First Italian reporting system for thyroid cytology (ref. 5)

<table>
<thead>
<tr>
<th>Code</th>
<th>Diagnostic Category</th>
<th>Histological Correspondence</th>
<th>Suggested Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR 1</td>
<td>Non diagnostic</td>
<td>Non defined</td>
<td>Repeat US-guided FNA after at least 1 month</td>
</tr>
<tr>
<td>TIR 2</td>
<td>Non malignant/benign</td>
<td>Goiter, granulomatous and lymphocytic thyroiditis</td>
<td>Follow-up</td>
</tr>
<tr>
<td>TIR 3</td>
<td>Indeterminate/inconclusive (Follicular Proliferation)</td>
<td>Follicular adenoma, follicular carcinoma, follicular variant of papillary carcinoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>TIR 4</td>
<td>Suspicious of malignancy</td>
<td>Mostly follicular variant of papillary carcinoma</td>
<td>Surgery (consider frozen section)</td>
</tr>
<tr>
<td>TIR 5</td>
<td>Malignant</td>
<td>Papillary, medullary and anaplastic carcinoma, lymphoma, metastasis</td>
<td>Surgery (only for papillary and medullary carcinoma)</td>
</tr>
</tbody>
</table>

Table 2: New Italian reporting system for thyroid cytology (ref. 4)

<table>
<thead>
<tr>
<th>Code</th>
<th>Diagnostic Category</th>
<th>Risk of malignancy (%)</th>
<th>Suggested actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIR 1</td>
<td>Non diagnostic</td>
<td>Non defined</td>
<td>Repeat US-guided FNA after at least 1 month</td>
</tr>
<tr>
<td>TIR 1C</td>
<td>Non-diagnostic-cystic</td>
<td>Low (variable on the basis of clinical findings)</td>
<td>Evaluate in the clinical setting and/or repeat FNA</td>
</tr>
<tr>
<td>TIR 2</td>
<td>Non malignant/benign</td>
<td>&lt;3</td>
<td>Follow-up</td>
</tr>
<tr>
<td>TIR 3A</td>
<td>Low-risk indeterminate lesion (LRIL)</td>
<td>&lt;10*</td>
<td>Repeat FNA/clinical follow-up</td>
</tr>
<tr>
<td>TIR 3B</td>
<td>High-risk indeterminate lesion (HRIL)</td>
<td>15-30*</td>
<td>Surgery</td>
</tr>
<tr>
<td>TIR 4</td>
<td>Suspicious of malignancy</td>
<td>60-80</td>
<td>Surgery (consider frozen section)</td>
</tr>
<tr>
<td>TIR 5</td>
<td>Malignant</td>
<td>&gt;95</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

*The expected rate of malignancy for the TIR 3 subcategories is mainly based on clinical experience and only partially supported by the evidence of the published data.

a 6-tiered scheme, and another important institution, the Japan Thyroid Association, has recently published in English its national guidelines (Table 3). The latter includes a suggestion for reporting the cytology of thyroid nodules from a minimum of six to a maximum of eight categories, depending on whether or not the cytologist chooses to subdivide the follicular neoplasm/indeterminate group (11, 12).

Cyto-histological comparison in indeterminate diagnoses

The main purpose of a reporting system for thyroid cytology is to distinguish the nodular lesions that should be addressed to surgery from those that can be clinically followed-up. The majority of the thyroid nodules (60-80% in different studies) show a cytological picture, which can be easily classified either as benign (nodular goiter or thyroiditis) or malignant (usually papillary carcinoma (PTC)). A smaller though variable portion of these nodules yields nondiagnostic (5-15%), and a variable amount of these lesions falls into the indeterminate category (10-25%) (13, 14). The latter represents a continuous range of morphologic pictures identified by a poor amount of colloid and an increased cellularity. These findings, at the histological level, identify three types of tumors: 1) follicular adenoma (FA), a benign tumor with a predominant microfollicular architecture and usually encased by a continuous fibrous capsule; 2) follicular carcinoma (FTC), the malignant counterpart of the FA sharing with the former the follicular structure but showing features of aggression to the fibrous capsule and the adjacent vessels; and 3) PTC, especially its follicular variant (FVPTC) that shows a histological pattern similar to the fibrous but is composed by follicular cells with clearing and prominent pleomorphism of the nuclei (15-17).

The possibility that a lesion exhibiting an indeterminate picture corresponds to an adenoma instead of an FTC or a FVPTC (which belongs to the group of well-differentiated thyroid carcinomas, WDTC) is of critical importance because the risk of malignant yield represents the ultimate goal of the FNA technique and affects the evaluation of its efficacy. The histological diagnosis of WDTC can be difficult in some instances and some cytological criteria (such as clear nuclei) are also poorly reproducible between experts and pathologists in such a manner that the true malignant nature of the encapsulated form of FVPTC has been discussed (16, 17). The majority of WDTC pursue an indolent clinical course, especially the FVPTC and the PTC under 1 cm of size (microPTC, mPTC), so that, according to Ito et al. (18), their evolution can be
followed by periodical sonographic examinations until they become as clinically relevant as to be addressed to surgery. Although some clinicians do not agree with this strategy, the low aggressiveness of WDTC does not seem to justify the high amount of surgical procedures and is sometimes carried out for diagnostic purposes. In fact, the diagnostic lobectomy suggested for indeterminate diagnoses is necessary to sample and appropriately examine the capsule of a thyroid tumor in order to make a differential diagnosis between FA and FTC. Nonetheless, there is a progression in the atypical features of the follicular cells which can be used as predictor of risk of likelihood of malignancy in WDTC. There are two types of atypia of the follicular cells: i) architectural atypia that is the presence of follicular cells aggregated in microfollicles; and ii) nuclear atypia, which includes clearing, elongation and irregularity of the nuclei (7). The latter seems more strongly related to the risk of malignancy of a follicular-patterned lesion than the former (19-22). Based on this feature, the first published reporting systems from U.K. and Italy identified only one category of true indeterminate diagnoses (Thy 3 for BTA and TIR 3 for the Italian SIAPEC system), which represented the most debated group causing the vast majority of unnecessary surgical procedures. However, the last updates of those systems have subdivided the indeterminate category into two subgroups, which are identified, similarly to the TBSRTC, by the different weight of the architectural in respect to the nuclear atypia and by the different risk of malignant occurrence.

The new Italian reporting system

In 2011, an Italian Committee composed by five pathologists and five endocrinologists selected by the national societies of pathology and endocrinology (see above) was established with the aim to update the previous reporting system. However, in light of the previous published experiences of other national reporting system Committees (British and American), the group made a project with the purpose to revise the morphologic criteria for inclusion in each category, to update the clinical actions by including novel diagnostic techniques and to validate the new system. The project of the 2014 reporting system is different from the previous one and emphasizes some points of diffornity in comparison to the Anglo-Saxon systems. The first point is the different weight of the criteria of atypicality. Though the architectural atypia (see above) remains the basis for distinguishing low-risk and high-risk lesions (TIR 3A from TIR 3B), a significant degree of nuclear atypia warrants the inclusion of a lesion in one of the high-risk categories (TIR 3B or TIR 4) which are being addressed to surgery. For this reason, the Italian Committee expects that the low-risk category (TIR 3A) might result in 5-10% rate of malignant occurrence at histology compared to the 5-15% of expected range for the homologous categories of the British and American systems. The new Italian reporting system has also included in the suggested actions for the non-diagnostic category (TIR 1) the possibility to use, in cases of repeated non-diagnostic results, the core-needle biopsy (CNB) technique. CNB allows the sampling of the lesion with a 20 to 22 spring-activated needle useful to obtain a thin biopsy which can be processed as histological specimen. This technique has been extensively studied by some Korean and Italian groups and it can also be used to get materials for performing immunohistochemical procedures such as galectin-3, HBME-1 and cytokeratin 19 in indeterminate lesions (23, 24). Immunocytochemical staining may be also applied to the materials processed by liquid-based cytology (LBC), which is specifically mentioned in the reporting system though it is recommended to be used only in institutions with specific experience (25, 26).

As a follow-up of the Italian project, the five pathologist members of the committee have planned a study for the revision of the morphologic criteria of the reporting categories based on both

Table 3: Synopsis of the most important national reporting systems

<table>
<thead>
<tr>
<th>UK RCPATH</th>
<th>ITALY</th>
<th>USA BETHESDA</th>
<th>JAPAN THYROID ASSOCIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic category</td>
<td>Diagnostic category</td>
<td>Terminology</td>
<td>Terminology</td>
</tr>
<tr>
<td>Thy1/Thy1c Non-diagnostic for cytological diagnosis</td>
<td>TIR 1: Non-diagnostic</td>
<td>I. Non-diagnostic</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>Unsatisfactory, consistent with cyst</td>
<td>TIR 1C: Cystic</td>
<td></td>
<td>A. Follicular Neoplasm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• A1 favor benign</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• A2 border-line</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• A3 favor malignant</td>
</tr>
<tr>
<td>Thy2/Thy2c Non-neoplastic</td>
<td>TIR 2: Non-malignant/benign</td>
<td>II. Benign</td>
<td>Normal or benign</td>
</tr>
<tr>
<td>Thy 3a Neoplasm possible – atypia present</td>
<td>TIR 3A: Low-risk indeterminate lesion (LRIL)</td>
<td>III. Atypia of undetermined significance (AUS) or follicular lesion u.s. (FLUS)</td>
<td>Indeterminate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B. Others (atypia in non-follicular neoplasm)</td>
</tr>
<tr>
<td>Thy3f Neoplasm possible - follicular neoplasm suspected</td>
<td>TIR 3B: High-risk indeterminate lesion (HRIL)</td>
<td>IV. Follicular neoplasm or suspicious for a follicular neoplasm</td>
<td></td>
</tr>
<tr>
<td>Thy 4 Suspicious of malignancy</td>
<td>TIR 4: Suspicious of malignancy</td>
<td>V. Suspicious of malignancy</td>
<td>Malignancy suspected</td>
</tr>
<tr>
<td>Thy 5 Diagnostic of malignancy</td>
<td>TIR 5: Malignant</td>
<td>VI. Malignant</td>
<td>Malignancy</td>
</tr>
</tbody>
</table>
the individual evaluation and collegial discussion of 120 selected cytological cases. Finally, the committee has proposed a multicentric national study to validate the system.

**Hurthle cell lesions**

Unlike follicular cells, which show atypical features directly related to the progression to a malignant neoplasm, Hurthle (or oxyphilic or oncocytic) cells (HC) exhibit nuclear pleomorphism and cytoplasmic coarseness which may be more prominent in completely benign nodules (e.g. chronic thyroiditis). For this reason, Hurthle cell lesions (HCL) are considered as an individual category for which there is no possibility to identify a direct correlation between cellular atypia and malignant nature. Since the reports on the histological outcome of Hurthle cell neoplasm (HCN) are numerous though controversial (ranging from 9 to 75%) and the course of Hurthle cell carcinomas can be sometimes aggressive (with bone and lung metastases and poor sensitivity to radioiodine) lesions composed almost exclusively by HC are regarded as to be included in the high-risk categories (27, 28).

However, a few reports involving large and well studied cohorts demonstrate that HCN have a risk of malignant occurrence lower than estimated so they represent a flaw in the assessment of the real risk of malignancy of the indeterminate categories, especially the non-surgical ones (TIR 3A, Thy 3a and AUS/FLUS) (29-31).

Hurthle cells may be identified as a predominant component (more than 75% of the cells) in many cases of nodular goiter and chronic thyroiditis, the latter can be suspected at sonographic examination and often identified by the circulating antibodies of anti-thyroglobulin and anti-thyroidperoxidase. Based on the relatively low risk of malignant occurrence (less than 15%) and the possibility to identify a chronic thyroiditis in the clinical work-up, HCN might be included in the low-risk indeterminate group in order to repeat the sampling of the lesion and to avoid the surgical removal of a likely benign nodule.

**Special techniques on LBC-processed material**

Literature data show that several papers have been set out on the use of ancillary techniques (including immunocytochemistry and molecular analysis) in thyroid fine-needle aspiration cytology (FNAC), even in LBC-processed material. The application of a combined immunocytochemistry panel, especially made up of HBME-1, Galectin-3 and Cytokeratin 19, (32, 33) may be able to discriminate between low and high risk of malignancy in IL with at least 92% diagnostic accuracy in concordant positive cases. However, the expression of a panel of antibodies cannot provide more than a suggestion of malignancy whilst the higher specificity of molecular detections, classified as "rule-out" or "rule-in" tests, become a strong indicator of cancer enabling physicians to tailor the correct management and follow-up for each individual patient (34-36).

In this perspective, new diagnostic markers of malignancy have been identified also on FNAC based on the assumption that BRAF, RET/PTC or RAS mutations are found in more than 70% of PTC, which is the most frequent thyroid malignancy. These BRAF mutations, involved in the activation of MAPK-Kinase pathway, are associated with parameters predictive of a more aggressive tumor behavior such as extra-thyroidal extension, advanced tumor stage at presentation and lymph node or distant metastases (37-39).

Another promising field is represented by the microRNAs (miRNAs) inasmuch as MAPKinase or other DNA pathways did not provide complete and exhaustive achievements. These miRNAs, defined as negative regulators of gene expression with a role in regulating cells proliferation, differentiation and survival, seem to be mostly up-regulated in classical PTCs, while the new promising miR-375 resulted up-regulated in PTC, FVPC and also in medullary thyroid carcinoma (40).

**Future developments**

The presence of several national reporting systems seems, at first glance, to add some confusion in the management of thyroid nodules. However, the need for classifying thyroid cytology arises from the requests of clinicians who treat these patients in a way similar to the Bethesda system for reporting cervical cytology. The reporting schemes that are currently published, including the one by the Japanese Thyroid Association, reflect the difficulties in identifying well-defined categories within a continuous progression of the atypical features of follicular cells, which may prompt substantially different treatments, especially clinical follow-up vs. surgery. The differences between the systems are also based on the social conventions such as the choice of malignant risk for surgical procedure, which is different in the Western reporting systems in respect to the Japanese classification. Probably "in medio stat virtus". Based on the indolent clinical course of WDTC, even if the size of tumor is greater than 1 cm, the threshold for sampling a thyroid nodule should be kept at the size of 1 cm and this guideline probably would decrease the amount of suspicious tumors by at least 20%. The second recommendation might be to increase the malignant risk for surgery from 15% to at least 25-30%, with a further reduction of unnecessary surgical procedures of at least 30%. These two procedures would obviously increase the number of malignant tumors kept untreated from the operative viewpoint but, nonetheless, they could be followed-up with clinical and sonographic evaluation, preventing an infrequent but possible aggressive evolution. Molecular techniques might be extremely useful in indentifying those cases that may behave more aggressively and may benefit from a preferential surgical removal. Based on these recommendations, a global reporting system might include only 5 categories: nondiagnostic, benign (malignant risk < 3%), indeterminate (malignant risk, 5-30%), suspicious (malignant risk, 30-90%), and malignant (malignant risk > 90%) with the threshold between conservative and surgical treatment at 30% of malignant risk. In this reporting scheme HCL should be included in the indeterminate rather than in the suspicious category because the risk of malignant outcome at histology is lower than expected.

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