



# Standardisation of thyroid cytology terminology and practice: are modifications necessary? – a narrative review

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**Abstract:** Universally accepted guidelines for diagnosis and management of any disease are desirable. Standardization of thyroid cytology reporting is aimed at guiding and improving clinical decision-making and management. However, socio-economic, and local factors and differences in disease prevalence and patterns require modification to suit local settings. ‘One size fit all’ approach is not possible for any disease diagnosis or management. The same concept is applicable in diagnosis and management of thyroid nodules. An additional special issue is the well-known high inter and intra-observer variability in the histological and cytological diagnosis of thyroid neoplasms. Despite this, thyroid cytology has a very significant influence in the management of thyroid diseases. An approach based on common principals with appropriate modifications that suits countries or continents is desirable and sustainable. The principals of TBSRTC have served as a framework for similar tiered classifications for reporting thyroid cytopathology. This article discusses globally available professional guidelines based on a common framework with appropriate modifications, with the universal aim of risk stratification of thyroid nodules.

**Keywords:** Thyroid cytology; terminology; modifications

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## Introduction

Standardisation of thyroid cytology reporting is aimed at achieving improved quality of practice and clinical decisions for optimal management. A global standard for thyroid cytology is the ideal. The Bethesda system for reporting thyroid cytology (TBSRTC) infused great enthusiasm around the world to standardize a challenging area of cytopathology (1). Prior to this many other systems have been in operation mainly in an ‘ad hoc’ fashion within institutions and countries (2-5). Currently, in addition to the TBSRTC developed in the USA, there are several reporting systems and guidelines recommended and adopted by professional societies in countries such as UK, Japan, Italy and Australia (5-8). Some recommendations are not restricted to reporting terminology but have

either included a range of pre and post-analytical issues or aligned with parallel guidelines of related societies. These ‘modifications’ are linked to many variables and issues related to thyroid diseases itself and socio-economic and geographical variation.

Firstly, epidemiology of thyroid diseases differs in different geographical locations. Secondly, variable local health care delivery systems and socio-economic factors dictate judicious use of state funds and reimbursements or personal resources for investigations and management of thyroid nodules. Thirdly, there is a significant variation in interpretation and management of thyroid neoplasms across the globe. It can be argued that thyroid neoplasms are by far the best example of a neoplasm subject to a very high inter and intra observer variability (9,10). In addition to epidemiological and geographical differences pre-

analytical issues may vary according to socio economic and health economic influences. These fundamental issues have a great impact on thyroid cytology practice. Therefore, considering the variability in the epidemiology, health care delivery systems and, diagnostic and management strategies it is imperative that the modifications are necessary to suit one's requirements. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at <http://dx.doi.org/10.21037/gs-2019-catp-25>).

## Methods and discussion

### *Global trends of thyroid diseases and the influence by Asia*

According to the GLOBOCAN estimates, 48% of all new thyroid cancer cases are diagnosed in Asia with an incidence of 60% and prevalence of 57.4% (11). Among Asian countries Japan and Korea have made a great contribution to the international community with evidence-based experience of diagnosing and managing thyroid tumours (12-14). Thyroid malignancies represent approximately 5% of all thyroid nodules and malignancies presenting as a diffuse enlargement is extremely rare (15,16). Equally, about 60% of thyroid nodules show benign cytology in clinical practice (1-8). An allowance should be made to these figures depending on the geographical location and associated environment factors. If hotspots, such as locations and countries with increased exposure to radiation and iodine deficiency are excluded above figures may be generalized globally. It is noteworthy that benign and malignant cytological categories are comparable in incidence and do not appear to provoke significant controversy in terms of categorisation or diagnostic criteria in a global setting (1-8). When malignant and benign diagnoses are excluded approximately 35% of cytological diagnosis of all thyroid nodules fall into an 'inconclusive/uncertain group' (1-8). This uncertain group that includes non-neoplastic and benign neoplastic lesions as well as a proportion of differentiated malignant neoplasms is the central focus that needs guidance in terms of sampling, interpretation, terminology and management. The risk of malignancy (ROM) and risk of neoplasms (RON) within this group and prognosis of these neoplasms as well as the management appear variable (12,17-19). Although those thyroid lesions that are suspicious for malignancy could be included in the uncertain group they should be regarded with a different emphasis to the above (1-8).

Compared to the Western experience, Asian studies have shown low resection rates and high ROM in the cytologically uncertain group of thyroid nodules (13,20,21). This is believed to be due to the conservative management approach by Asian clinicians (21). However, national mortality rates are comparable in countries such as United States, Korea, Israel, Canada, France, Italy and Australia (22,23).

There is also an argument against over sampling leading to detection of indolent lesions referred to as incidentalomas (24). The overuse of radiology to detect such lesions followed by a diagnosis of malignancy, most commonly papillary thyroid carcinoma often results in surgery in spite of standard guidelines for radiological sampling of thyroid nodules (25).

It is obvious that the ROM of a cytological category of a thyroid nodule cannot be equated to risk of clinically significant disease (14,26). There is hardly any other human malignancy than thyroid that has proven to have distinctly variable outcomes (27). Among the 5% of malignant thyroid nodules, clinically aggressive thyroid malignancies are anaplastic and poorly differentiated carcinoma, some angioinvasive and widely invasive follicular carcinomas, a proportion of medullary carcinomas, aggressive lymphomas and rare metastases, in addition to a small proportion of aggressive papillary thyroid carcinomas. Of these, widely invasive and angioinvasive follicular carcinomas and poorly differentiated carcinomas are often categorised cytologically as suggestive/suspicious of follicular neoplasms or a related category based on the "classical repetitive microfollicular pattern" (1-8). Hemithyroidectomy is offered to these lesions in many countries. The Japanese approach includes sub-categorisation of 'follicular neoplasms' into low and high-risk lesions on cytomorphology with conservative management offered for low risk follicular patterned neoplasms (6). Apart from the above group, the other clinically significant malignancies are often categorized as suspicious or malignant followed by appropriate management. It is the general impression that over diagnosis and overtreatment of thyroid neoplasms is a larger issue than underdiagnoses (21,28-32). It is also interesting to note the geographic variability of prevalence of thyroid cancer over diagnosis and malpractice claims (33,34).

### *Recent WHO recommendations*

A notable change in the practice of thyroid neoplasms was the recent introduction of the tumour type referred

to as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) by World Health Organization (WHO) for those tumours previously termed encapsulated follicular variant of papillary thyroid 'carcinoma' (EFVPTC) (35). This remarkable change to the approach of diagnosis of follicular patterned thyroid neoplasms further supports the historic lack of robust histological diagnostic criteria for low grade, differentiated follicular patterned neoplasms (9,36-38). Over time many studies have highlighted the variability in histological diagnosis, cytological categorization and management for EFVPTC with significant geographical differences (37-42). Recognition of RAS and BRAF molecular pathways of thyroid tumorigenesis has cemented the need for new approaches in both histological and cytological diagnosis (43). In this regard it is interesting to note the assertion by some Japanese pathologists to recognize RAS and BRAF like nuclear features in cytology (44). Following this change by WHO, a substantial amount of evidence emerged with regards to the variable prevalence of NIFTP lesions globally. It appears that the prevalence is much less in Asia than in the West (45). An equally important realization is the variability of impact of this change on ROM and RON of thyroid cytology categories (39-42). These observations further confirm the necessity for modifications for pathological interpretation, recommendations and management in this group of thyroid nodules. A modified approach based on scientific principles and that accommodates these variabilities would not have a negative impact but allows flexibility for patient management in different settings.

Ironically there are groups that believe overzealous dependence on guidelines may even limit one's independent approach to diagnosis and management (46).

### ***Molecular testing in thyroid cytology***

Molecular testing with the hope of improving the prediction of ROM in the uncertain group has been recommended by TBSTCR (1,47). The economic and logistical issues of this approach need to be re-visited as evidence appears variable on its acceptance, value and cost effectiveness (48). Additionally, positive predictive value of molecular testing for inconclusive nodules has reduced with the recent WHO revision of encapsulated FVPTC as NIFTP (49,50). However, the value of BRAF mutation testing to confirm a diagnosis of papillary thyroid carcinoma by upgrading the suspicious category appears to

be universally accepted (51-53).

### ***FNA collection and preparation of material***

Both direct and ultrasound guided aspirations with and without rapid on-site evaluation (ROSE) is practiced globally depending on the available resources (54,55). Liquid base cytology (LBC) is used in some centers. LBC techniques may be useful if material is collected by inexperienced, in particular non-pathology staff with no exposure to cytology techniques. Important diagnostic cytological features are often lost in LBC preparations and cytology staff needs re-training, hence the technology is mandated in many countries (56,57).

Considering the variety of issues discussed above it is apparent that strict global standardisation is hard to achieve and modifications based on a common framework is more realistic. *Table 1* shows a general overview of well-known systems across the globe.

### **The Bethesda system for reporting thyroid cytology (TBSRTC, USA)**

The revised version that was published in 2017, focused on guidelines for management based on the evidence that was gathered following its inception in 2008 (1). As expected, there was emphasis on reclassification of non-invasive (encapsulated and/or circumscribed) follicular variant of papillary thyroid carcinoma by the WHO as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). In order to eliminate NIFTPs from the malignant category the revised version recommends that a suspected papillary thyroid carcinoma with an exclusive follicular architecture, especially one that lacks intranuclear cytoplasmic pseudoinclusions and psammoma bodies to be interpreted as suspicious of malignancy rather than malignant. It is also acknowledged that follicular neoplasms, FVPTCs and NIFTPs cannot be accurately distinguished by cytology alone due to their overlapping cytomorphological features as opposed to PTC signified by the classical cytoarchitecture. Classical papillary thyroid carcinoma is characterized by monolayered sheets and papillary structures while the variants show features. The fact that NIFTPs were categorised as encapsulated FVPTC (thereby as a malignancy) prior to WHO revision would explain at least in part the higher rate of ROMs reported in some studies. Current literature suggests that the rates of FVPTC and NIFTP appear significantly low in Asian practice compared to the West (37,41,42). Implied risks

**Table 1** A general comparison of global systems

Categories	USA [2008]	United Kingdom [2011]	Italy [2014]	Australia [2014]	Japan [2013]
1	Non-diagnostic/unsatisfactory	Thy1. Non diagnostic further subdivided: non-cystic; cystic	TIR1. Non-diagnostic: and cystic	Non-diagnostic	1. Inadequate (non-diagnostic)
2	Benign	Thy2. Non-neoplastic	TIR2. Non-malignant/ benign	Benign	2. Normal benign
3	Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)	Thy 3a. Neoplastic possible—atypia	TIR3a. Low risk indeterminate lesion	Indeterminate or follicular lesion of undetermined significance	3a. Indeterminate-Follicular
4	Follicular neoplasm suspicious for follicular neoplasm ((FN/SFN)	Thy 3f. Neoplastic possible- Suggesting a follicular neoplasm	TIR3b. High risk indeterminate lesion	Suggestive of follicular neoplasm	3b. Indeterminate-others
5	Suspicious of malignancy	Thy 4. Suspicious of malignancy	TIR4. Suspicious of malignant	Suspicious of malignancy	4. Malignancy suspected
6	Malignant	Thy 5. Malignant	TIR5. Malignant	Malignant	5. Malignancy

of malignancy have been revised in the second edition of TBSRTC as a response to the WHO revision. ROM was revised as 6–18% from 10–30%, 10–40% from 25–40% and 45–60% from 50–75% for categories 3, 4 and 5 respectively reflecting an overall reduction (58). The management recommendations in the TBSRTC system includes molecular testing as an adjunct to the cytopathological examination for the inconclusive group of nodules. However, positive predictive value of molecular testing has reduced with the introduction of NIFTP (49,50).

### The British thyroid Association–RCPATH system

This system that was introduced in 2002 was revised in 2009 (see *Table 1*). More recently the cytology terminology with additional comments was embedded in management recommendations by the British thyroid Association guidelines for management of thyroid cancer 2014 (5). Multidisciplinary approach is emphasised in the British system. Effectively, the system has six categories similar to the others. The differences include subdividing non-diagnostic categories to cystic and non-cystic lesions and the most challenging uncertain group placed under the umbrella term of “neoplasm possible”. Within this umbrella category those with atypia and others suggesting a follicular neoplasm are separated.

### The Japanese system

Even within Japan, there are a few related systems used for

cytology reporting and management of thyroid nodules. They include General Rules for the Description of Thyroid Cancer (GRDTC) published by the Japanese Society of Thyroid Surgery (JSTS) in 2005 and updated in 2016, and the national reporting system (the Japanese system) for thyroid FNA cytology published by the Japan thyroid Association in 2013 (6,21). The Japanese system was included in the clinical guidelines published by the Japan Thyroid Association (JTA) in 2013. The Japanese system was adapted from Toriya’s diagnostic system characterized by two or three sub classifications of the indeterminate (uncertain) group (2). Japanese system emphasised sub classification of the two categories within the uncertain group based on cytomorphology and on the molecular basis of RAS and BRAF driven pathways. Even within Japan there is variability in using the systems. Although GRDTC widely used, some high-volume thyroid surgery centers prefer the Japanese system (see *Table 1*) as many patients with a diagnosis of follicular neoplasm do not undergo diagnostic thyroidectomy.

### The Italian system

The Italian Society for Anatomical Pathology and Cytopathology–International Academy of Pathology in conjunction with clinical groups formulated a system in 2007 followed by a revision in 2014 (7). There are again six categories with the uncertain group divided into low risk indeterminate and high-risk indeterminate lesions (see

**Table 2** Risk of malignancy in ‘inconclusive categories’ in Australia (59-62)

Category	Risk of malignancy
3	9.3–13%
4	15.3–24.4%
5	79–84.7%

*Table 1*). The lower risk lesions are offered repeat FNA and or clinical follow-up and the high-risk lesions are offered surgery. One important difference to other systems is that nodules with repeated inadequate cytology samples are recommended to be sampled by core needle biopsy and LBC.

### The Australasian reporting guidelines

Historically, cytological categories have been used in Australia for thyroid cytology reporting (3,59). The Australasian reporting guidelines are based on the general framework of the 6 categories of the Bethesda system with a modified approach. Modifications were necessary to streamline standardisation within the country while maintaining well established and “time tested” systems that were operational previously, yet embracing positive aspects of the TBSRTC. First edition was completed and published in 2014 and a subsequent review was published in “Pathology” (8). The second edition was published in 2019 incorporating updated WHO terminology for EFVPTCs and updates on molecular basis of thyroid tumours (60). The opinions were based on local experiences and local data including follow-up studies in two states in Australia (59,61). The study done in Western Australia and published in 2010 used 6 categories and mirrored the TBSRTC system published in 2010 and the study done in New South Wales subsequently used the TBSRTC system, enabling easy comparison of the data (59,61). However it should be noted that the numbers in our studies are relatively small compared to those of Asian series due to the lower prevalence of thyroid neoplasms locally. In Australian guidelines the use of the term ‘atypia’ is discouraged in the general diagnostic category in the uncertain group with low ROM (equivalent to Bethesda category 3) to avoid confusion among clinicians that may result in over-treatment. The term ‘Indeterminate’ is recommended in the Australasian guidelines for the equivalent of TSBRTC category 3. Most cases in this category would have a benign follow up as shown in the above-mentioned studies in

Australia that showed a malignancy rate of only 13% and 9.3% (59,61) (*Table 2*). A detailed analysis of the West Australian cohort showed a minimum of 33% of PTCs in this category were “follicular variants of papillary thyroid carcinoma”, only 22% were classical PTCs and others were PTCs, unclassified (unpublished data). As such implied ROM in this category with the recent revision of EFVPTC as NIFTP may be even low.

The use of the term ‘suspicious of follicular neoplasms’ is not recommended for category 4 (those lesions that show a strong likelihood of a follicular neoplasm) as only 15–24% of nodules were malignant (59,60), hence the word suspicious could be misleading. The spectrum of entities ranges from benign to malignant and include cellular hyperplastic nodule, follicular adenoma, follicular carcinoma, Hürthle cell neoplasm and follicular variant of papillary thyroid carcinoma (FVPTC). Lesions that are highly suggestive of a neoplasm with minimal, subtle nuclear features are often included in this category. Australian experiences suggest a high ROM in the suspicious for malignancy category (category 5) 79% and 83% respectively in the 2 studies (61,62). We also recommend BRAF mutation testing to confirm papillary thyroid carcinoma in those in those nodules that are otherwise categorised as suspicious for PTC (62).

It is important to note the ROMs reported in both studies were closer to those projected in revised TBSRTC based on WHO 2017 revision of NIFTPs. This observation reflects high quality cytology practices as well as higher thresholds for diagnosis of FVPTC in Australia. Australasian practice recommends emphasis on the presence of monolayered sheets or papillary formations to represent papillary nature of papillary thyroid carcinoma with the expectation to avoid misdiagnosis of NIFTPs as malignant (60). The expert committee that formulated guidelines is of the opinion that in Australasia, the prevalence of NIFTP (former EFVPTC) is not as high as is reported in the United States.

### Conclusions

In conclusion, the implied ROM for a cytological diagnosis of a thyroid nodule essentially guides the clinical decision for definitive surgical management or other aggressive types of treatment. Therefore, the most important aim of performing thyroid fine-needle aspiration is for the accurate diagnosis of malignant neoplasms and appropriate risk stratification of uncertain nodules. However, it is apparent that there are

significant differences in both cytological and histological diagnosis of thyroid neoplasms worldwide due to medico-social and geographic variations. Therefore, a globally accepted strict standardised approach does not appear feasible. A common framework of risk categorisation based on cytological features of a thyroid nodule that would encompass local factors appears to be a satisfactory approach.

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