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REVIEW

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Thyroid FNA terminology: The case for a single unified international system for thyroid FNA reporting

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Abstract

The use of reporting terminologies for thyroid FNA cytology enables standardisation and international alignment of the reporting of thyroid cytology results, which is essential. There are currently three major internationally recognised systems: Bethesda (TBS), UK RCPath (Thy), and Italian (TIR). A fourth terminology system used in Japan has identical categories to TBS but with different nomenclature. The aim of this review is to discuss the strengths and weaknesses of the TBS, UK RCPath, and TIR systems, and to make the case for international terminology harmonisation and standardisation.

KEYWORDS

FNA, international, standardisation, terminology, thyroid

1 | INTRODUCTION

There have been long-standing efforts to standardise thyroid FNA reporting terminology. In 2008 The Bethesda System for Reporting Thyroid Cytopathology (TBS) was launched.[1] In 2021 worldwide, the majority of thyroid FNA cytology aspirates are reported using TBS,[2,3] or a Japanese adaptation of TBS although the UK RCPath[4] and Italian[5] terminology systems are also used (see Tables 1 and 2). With TBS there is some variation between Western and Asian countries in the reported pooled risks of malignancy (ROM) in the various categories.[6]

2 | DIAGNOSTIC PERFORMANCE OF THE VARIOUS TERMINOLOGIES

The UK RCPath terminology shows similar diagnostic performance to TBS as measured by ROM in the various categories,[7] although with differences; eg some but not all publications from the UK show comparatively higher rates for non-diagnostic FNA (Thy1)[8] and UK RCPath also classifies cysts in a slightly different way to the Bethesda system.[4] The results obtained using the three major terminology systems, TBS,[2] UK RCPath,[4] and Italian,[5] are all now validated by meta-analyses of ROM[7,9-15] and all three terminologies show relatively moderate to good interobserver agreement in the different cytological categories,[16-21] although there is still a need for international thyroid FNA terminology standardisation.

3 | PROBLEMS IN ACHIEVING INTERNATIONAL STANDARDISATION

Historically, efforts to achieve standardisation in international thyroid cytology terminology have been held back by the fact that the final histopathological diagnosis in a significant number of cases in thyroid disease can be subjective and is subject to significant interobserver variation. There are well known problems of interobserver variation in the assessment of capsular[22,23] and vascular invasion[24] in suspected thyroid cancer, two of the major diagnostic criteria for malignancy. In 2017

TABLE 1 Comparison of the UK RCPath with the Bethesda and Italian terminology systems

UK RCPath	Bethesda	Italian
Thy1 Non-diagnostic for cytological diagnosis Thy1c Non-diagnostic for cytological diagnosis—cystic lesion	I. Non-diagnostic or unsatisfactory	TIR 1 Non-diagnostic TIR 1c Non-diagnostic cystic
Thy2 Non-neoplastic Thy2c Non-neoplastic—cystic lesion	II. Benign	TIR 2 Non-malignant
Thy3a Neoplasm possible—atypia/non-diagnostic	III. Atypia of undetermined significance or follicular lesion of undetermined significance	TIR 3A Low risk indeterminate lesion (LRIL)
Thy3f Neoplasm possible, suggesting follicular neoplasm	IV. Follicular neoplasm or suspicious for a follicular neoplasm	TIR 3B High risk indeterminate lesion (HRIL)
Thy4 Suspicious of malignancy	V. Suspicious for malignancy	TIR 4 Suspicious of malignancy
Thy5 Malignant	VI. Malignant	TIR 5 Malignant

TABLE 2 Risk of Malignancy (ROM) of the UK RCPath, Bethesda, and Italian terminology systems

Terminology system	Pooled ROM III/Thy3a/TIR3A	Pooled ROM IV/Thy3f/TIR3B	Pooled ROM V/Thy4/TIR4	Pooled ROM VI/Thy5/TIR5
Bethesda[6] (Western)	21.5	27.3	75.1	99.2
Bethesda[6] (Eastern)	45.0	32.8	88.1	98.6
UK RCPath[7]	25	31	79	98
Italian TIR[14,15]	17	47	85	99

the *WHO Classification of Tumours of the Endocrine Organs* introduced revised terminology for encapsulated follicular thyroid neoplasms.[25] Prior to 2016, in some centres with higher diagnostic rates for papillary thyroid cancer over 20% of newly diagnosed thyroid cancers were diagnosed as encapsulated follicular variant of papillary thyroid carcinoma. In most cases after 2017 these tumours would now be re-designated NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features), a very low risk of malignancy lesion and not a cancer.[26] This in turn has consequences for the diagnosis of thyroid cancer on FNA cytology[27,28] with inevitable reductions in the risk of malignancy in the various TBS,[2] UK RCPath,[29] or Italian[14] terminology cytological categories, although the size of the reduction in the risk of malignancy depends on the cytological category and the overall prevalence of NIFTP. Published rates of NIFTP range from 0%-2% to over 20%[30-35] depending on the institutional diagnostic threshold for NIFTP, which in turn rests principally on the criteria for papillary carcinoma-type nuclei used in histopathological assessment in the relevant centre.

4 | STRENGTHS AND WEAKNESSES OF THE VARIOUS TERMINOLOGY SYSTEMS

It would be useful to highlight some of the strengths and weaknesses of the various terminology systems. Worldwide, TBS is the single most utilised terminology for thyroid FNA reporting and most peer-reviewed publications use TBS. As also highlighted above, there are quite wide variations in the reported outcomes of TBS when comparing published results of Western practice with Asian practice.[6] TBS also emphasises specific management for each diagnostic category.[2] The UK RCPath system takes a less prescriptive attitude, stating that the patient management decisions should be made by multidisciplinary teams and that all patients with higher-risk, eg Thy 4 and Thy 5 FNA (equivalent to TBS category V/Italian TIR 4, and TBS category VI/Italian TIR 5), should be discussed within the multidisciplinary setting, whereas the need for multidisciplinary discussion of lower risk fine needle aspirates is at the discretion multidisciplinary teams.[4] All three terminologies, TBS,[2] UK RCPath[4] and Italian,[5] have indeterminate categories; in TBS these are categories III and IV,[2] in UK RCPath they are Thy 3a and 3F,[4] and in the Italian system they are TIR 3A and TIR 3B.[5] Meta-analyses of the three systems show that the one system which demonstrates the most progressive incremental risk of malignancy in the indeterminate categories is the Italian system,[14,15] as cases without cytological atypia are placed in a lower risk indeterminate category, TIR 3A (pooled ROM 17%), while cases with cytological atypia are placed in a higher risk category of the Italian system, TIR 3B (pooled ROM 47%). The TIR 3A and TIR 3B categories are designed to separate indeterminate nodules according to differing risks of malignancy into lower risk and higher

risk lesions (Table 1).[5] By contrast, TBS and UK RCPath in Western patient cohorts have pooled ROMs of 21.5% and 25% for Cat III/Thy3a, and pooled ROMs of 27.3% and 31% for Cat IV/Thy 3f. Most of the basic aspects of all three terminology systems are similar, although the Italian system provides the greatest incremental increase in ROM in the indeterminate categories.

5 | THE FUTURE

TBS terminology[2] will be revised with anticipated publication of the third edition in 2023-2024. At the current time it is not known whether the UK RCPath[4] and TIR[5] terminologies will be aligned and consolidated into a single universal thyroid cytology reporting terminology. However, this may not matter if the respective working groups formulating these terminologies are able to cooperate in ensuring that the various diagnostic subcategories align with the other international systems. This will be particularly important in the context of clinical trials, evaluations of peer-reviewed literature, or commercial studies. Examples include development or introduction of new molecular methods, validation of artificial intelligence routines for thyroid nodule assessment using ultrasound and histopathology, eg for assessment of ultrasound characteristics,[36] or morphometry of papillary carcinoma-type nuclei to ascertain whether a particular lesion is benign or malignant.[37] It will therefore be essential that molecular pathology methods, histopathology terminologies, and cytopathology terminologies are very much aligned so that the clinical results obtained in one part of the world can be extrapolated with ease and utilised in other parts of the world. In the authors' opinion the recently highlighted issue of the variation in cytopathology results obtained between Eastern and Western cytological practice[6] can be attributed to multidisciplinary treatment differences and diagnostic threshold differences, at least some of which are based on differing care pathways for the management of nodules. In Japan and some other parts of Asia there is increased use of non-operative policies, ie surveillance for smaller thyroid nodules reported as cytologically malignant.[38] The inherent subjectivity of many of the diagnostic cytology subcategory thresholds, as shown by interobserver reproducibility studies which indicate only moderate levels of interobserver concordance and comparatively poor interobserver concordance for some indeterminate categories, eg Thy3a, is also another likely explanation.[16]

6 | CONCLUSION

In conclusion, while thyroid reporting cytology terminology should by definition align with histopathology terminology, like any other computer algorithm or expert system it is only as good as its validation benchmarks. Where there are known international geographic and inter-institutional differences in diagnostic thresholds for thyroid lesions and cancer, particularly for histopathologically subjective diagnoses such as NIFTP (published rates ranging from 0%-2% to over 20%[30-35]), these issues create a problem for comparative studies of thyroid FNA cytology in different countries. Molecular pathology holds promise in terms of refining diagnostic thresholds in borderline diagnostic cases. It is now widely accepted that the presence of specific gene mutations in histopathology or cytopathology specimens from the thyroid, eg *BRAF V600E* mutations in a primary thyroid lesion, are almost always associated with thyroid carcinoma, similarly less common gene mutations such as *TP 53* and *TERT* promoter mutations, and some other less common translocations are almost invariably associated with thyroid carcinoma.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

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REFERENCES

1. Baloch ZW, LiVolsi VA, Asa SL, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. *Diagn Cytopathol*. 2008;36:425-437.
2. Ali SZ, Cibas ES. *The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria, and Explanatory Notes*, 2nd edn. Basel, Switzerland: Springer; 2017.
3. Poller DN, Baloch ZW, Fadda G, et al. Thyroid FNA: new classifications and new interpretations. *Cancer Cytopathol*. 2016;124:457-466.
4. Cross P, Chandra A, Giles T, et al. *Guidance on the Reporting of Thyroid Cytology Specimens*, 2nd edn. London, UK: Royal College of Pathologists; 2016.
5. Nardi F, Basolo F, Crescenzi A, et al. Italian consensus for the classification and reporting of thyroid cytology. *J Endocrinol Invest*. 2014;37:593-599.
6. Vuong HG, Ngo HTT, Bychkov A, et al. Differences in surgical resection rate and risk of malignancy in thyroid cytopathology practice between Western and Asian countries: a systematic review and meta-analysis. *Cancer Cytopathol*. 2020;128(4):238-249.
7. Poller DN, Bongiovanni M, Trimboli P. Risk of malignancy in the various categories of the UK Royal College of Pathologists Thy Terminology for Thyroid FNA cytology: a systematic review and meta-analysis. *Cancer Cytopathol*. 2020;128(1):36-42.
8. Poller DN, Doyle V, Trimboli P, Bongiovanni M. Rates of Thy 1-non-diagnostic thyroid fine needle aspiration using the UK Royal College of Pathologists Thy Terminology. A systematic review of the literature comparing patients who undergo rapid on-site evaluation and those who do not. *Cytopathology*. 2020;31(6):502-508.
9. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. *Acta Cytol*. 2012;56:333-339.
10. Sughayer MA, Abdullah N. The Bethesda System for reporting thyroid cytopathology: a meta-analysis. *Acta Cytol*. 2017;61:172.
11. Krauss EA, Mahon M, Fede JM, Zhang L. Application of the Bethesda Classification for Thyroid Fine-Needle Aspiration: institutional experience and meta-analysis. *Arch Pathol Lab Med*. 2016;140:1121-1131.

12. Straccia P, Rossi ED, Bizzarro T, et al. A meta-analytic review of the Bethesda System for Reporting Thyroid Cytopathology: has the rate of malignancy in indeterminate lesions been underestimated? *Cancer Cytopathol*. 2015;123:713-722.
13. Sheffield BS, Masoudi H, Walker B, Wiseman SM. Preoperative diagnosis of thyroid nodules using the Bethesda System for Reporting Thyroid Cytopathology: a comprehensive review and meta-analysis. *Expert Rev Endocrinol Metab*. 2014;9:97-110.
14. Trimboli P, Crescenzi A, Castellana M, Giorgino F, Giovanella L, Bongiovanni M. Italian consensus for the classification and reporting of thyroid cytology: the risk of malignancy between indeterminate lesions at low or high risk. A systematic review and meta-analysis. *Endocrine*. 2019;63:430-438.
15. Trimboli P, Fulciniti F, Paone G, et al. Risk of Malignancy (ROM) of thyroid FNA diagnosed as suspicious for malignancy or malignant: an institutional experience with systematic review and meta-analysis of literature. *Endocr Pathol*. 2020;31:52-56.
16. Kocjan G, Chandra A, Cross PA, et al. The interobserver reproducibility of thyroid fine-needle aspiration using the UK Royal College of Pathologists' classification system. *Am J Clin Pathol*. 2011;135:852-859.
17. Ezzat NE, Abusinna ES, Hafez NH, Alieldin NH. Inter-observer reproducibility of the Royal College system for reporting thyroid cytology: experience of the Egyptian National Cancer Institute. *J Egypt Natl Canc Inst*. 2018;30:85-91.
18. Awasthi P, Goel G, Khurana U, Joshi D, Majumdar K, Kapoor N. Reproducibility of "The Bethesda System for Reporting Thyroid Cytopathology:" A retrospective analysis of 107 patients. *J Cytol*. 2018;35:33-36.
19. Bhasin TS, Mannan R, Manjari M, et al. Reproducibility of 'The Bethesda System for reporting Thyroid Cytopathology': a multicenter study with review of the literature. *J Clin Diagn Res*. 2013;7:1051-1054.
20. Ahmed S, Ahmad M, Khan MA, et al. The interobserver reproducibility of thyroid cytopathology using Bethesda Reporting System: analysis of 200 cases. *J Pak Med Assoc*. 2013;63:1252-1255.
21. Crescenzi A, Trimboli P, Basolo F, et al. Exploring the Inter-observer agreement among the members of the Italian Consensus for the classification and reporting of thyroid cytology. *Endocr Pathol*. 2020;31:301-306.
22. Zhu Y, Li Y, Jung CK, et al. Histopathologic assessment of capsular invasion in follicular thyroid neoplasms-an observer variation study. *Endocr Pathol*. 2020;31:132-140.
23. Franc B, de la Salmonière P, Lange F, et al. Interobserver and intraobserver reproducibility in the histopathology of follicular thyroid carcinoma. *Hum Pathol*. 2003;34:1092-1100.
24. Mete O, Asa SL. Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. *Mod Pathol*. 2011;24:1545-1552.
25. Lloyd RV, Osamura RY, Kloppel G, Rosai J. *WHO Classification of Tumours of Endocrine Organs*, Vol. 10, 4th edn. Lyon, France: IARC WHO; 2017.
26. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol*. 2016;2:1023-1029.
27. Bongiovanni M, Giovanella L, Romanelli F, Trimboli P. Cytological diagnoses associated with noninvasive follicular thyroid neoplasms with papillary-like nuclear features according to the bethesda system for reporting thyroid cytopathology: a systematic review and meta-analysis. *Thyroid*. 2019;29:222-228.
28. Rossi ED, Faquin WC, Baloch Z, et al. Noninvasive follicular thyroid neoplasm with Papillary-Like Nuclear Features (NIFTP): update and diagnostic considerations-a review. *Endocr Pathol*. 2019;30:155-162.
29. Johnson SJ, Stephenson TJ, Poller DN. *NIFTP Addendum to the RCPath Dataset for Thyroid Cancer Histopathology Reports*. London, UK: Royal College of Pathologists; 2016.
30. Mainthia R, Wachtel H, Chen Y, et al. Evaluating the projected surgical impact of reclassifying noninvasive encapsulated follicular variant of papillary thyroid cancer as noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Surgery*. 2018;163:60-65.
31. Wong KS, Strickland KC, Angell TE, et al. The flip side of NIFTP: an increase in rates of unfavorable histologic parameters in the remainder of papillary thyroid carcinomas. *Endocr Pathol*. 2017;28:171-176.
32. Rosario PW, Mourão GF, Nunes MB, Nunes MS, Calsolari MR. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Endocr Relat Cancer*. 2016;23:893-897.
33. Parente DN, Kluijfhout WP, Bongers PJ, et al. Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: is NIFTP truly benign? *World J Surg*. 2018;42:321-326.
34. Bychkov A, Jung CK, Liu Z, Kakudo K. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice: perspectives for surgical pathology and cytopathology. *Endocr Pathol*. 2018;29:276-288.
35. Poller DN, Johnson SJ, Stephenson TJ. Diagnosis of NIFTP in the UK. *J Basic Clin Med*. 2017;6:63-64.
36. Thomas J, Haertling T. AIBx, Artificial intelligence model to risk stratify thyroid nodules. *Thyroid*. 2020;30:878-884.
37. Girolami I, Marletta S, Pantanowitz L, et al. Impact of image analysis and artificial intelligence in thyroid pathology, with particular reference to cytological aspects. *Cytopathology*. 2020;31:432-444.
38. Ito Y, Miyauchi A. Active surveillance of low-risk papillary thyroid microcarcinomas in Japan and other countries: a review. *Expert Rev Endocrinol Metab*. 2020;15:5-12.

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