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. In 2021 worldwide, the majority of thyroid FNA cytology aspirates are reported using TBS, or a Japanese adaptation of TBS although the UK RCPath and Italian terminology systems are also used. There is some variation between Western and Asian countries in the reported pooled risks of malignancy (ROM) in the various categories.

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, although with differences; eg some but not all publications from the UK show comparatively higher rates for non-diagnostic FNA (Thy1) and UK RCPath also classifies cysts in a slightly different way to the Bethesda system. The results obtained using the three major terminology systems, TBS, UK RCPath, and Italian, are all now validated by meta-analyses of ROM and all three terminologies show relatively moderate to good interobserver agreement in the different cytological categories, 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 and vascular invasion in suspected thyroid cancer, two of the major diagnostic criteria for malignancy. In 2017...
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 cytology27,28 with inevitable reductions in the risk of malignancy in the various TBS,2 UK RCPath,29 or Italian14 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%20-35 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.

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

| Terminology system | Bethesda | Italian |
|--------------------|----------|---------|
| Thy1               | I. Non-diagnostic or unsatisfactory | TIR 1 Non-diagnostic |
| Thy1c              | Non-diagnostic for cystic lesion | TIR 1c Non-diagnostic cystic |
| Thy2               | II. Benign | TIR 2 Non-malignant |
| Thy2c              | Non-neoplastic—cystic lesion | |
| Thy3a              | III. Atypia of undetermined significance or follicular lesion of undetermined significance | TIR 3A Low risk indeterminate lesion (LRIL) |
| Thy3f              | IV. Follicular neoplasm or suspicious for a follicular neoplasm | TIR 3B High risk indeterminate lesion (HRIL) |
| Thy4               | V. Suspicious for malignancy | TIR 4 Suspicious of malignancy |
| Thy5               | 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 |
|--------------------|-----------------------------|---------------------------|--------------------------|-------------------------|
| Bethesda4 (Western) | 21.5                        | 27.3                      | 75.1                     | 99.2                    |
| Bethesda4 (Eastern)| 45.0                        | 32.8                      | 88.1                     | 98.6                    |
| UK RCPath7         | 25                          | 31                        | 79                       | 98                      |
| Italian TIR14,15   | 17                          | 47                        | 85                       | 99                      |

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.4 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 RCPath4 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.3 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 interdisciplinary 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 an increased use of non-operative policies, ie surveillance for smaller thyroid nodules reported as cy

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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