The Royal College of Pathologists
Pathology: the science behind the cure

Guidance on the reporting of thyroid cytology specimens

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Comments	This document will replace the 2nd edition of *Guidance on the reporting of thyroid cytology specimens,* published in 2016. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 23 May 2022 to 21 June 2022. Responses and authors' comments are available to view following final publication of this dataset. **Dr Brian Rous** **Clinical Lead for Guideline Review (Cellular Pathology)**

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Foreword

The guidelines published by the Royal College of Pathologists (RCPath) are documents that enable pathologists to deal with routine cellular pathology specimens in a consistent manner and to a high standard. This ensures that accurate diagnostic and prognostic information is available to clinicians for optimal patient care and ensures appropriate management for specific clinical circumstances. In rare circumstances it may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be carefully considered by the reporting pathologist; just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not automatically be deemed negligent or a failure of duty of care. Pathologists should be prepared to justify any departure from the guidelines.

This RCPath *Guidance on the reporting of thyroid cytology specimens* updates the January 2016 document to include recent developments. The main areas of change to note are:

- retention of the existing Thy categories and greater clarity on their use
- an expanded section on diagnostic accuracy and histological correlation
- revised and updated tables on Thy terminology usage and risk of malignancy (ROM) data.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The stakeholders consulted for this document were:

- British Thyroid Association (BTA), to standardise data items between this document and BTA Thyroid Cancer Guidelines (3rd edition)
- British Association of Endocrine and Thyroid Surgeons
- British Association of Head and Neck Oncologists
- UK Endocrine Pathology Society
- UK and Ireland Association of Cancer Registries
- British Association for Cytopathology
- Royal College of Radiologists.

The information used to develop this clinical guideline was obtained by undertaking a systematic search of PubMed between 1 January 2016 and 31 December 2021 relating to the use and application of thyroid cytology in the UK and abroad. Key terms searched included ‘thyroid cytology’, ‘FNAC thyroid’ and ‘Thy’. Published evidence was evaluated using modified SIGN guidance (Appendix A). Consensus of evidence in these guidelines was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

No major organisational changes or cost implications have been identified that would hinder the implementation of these guidelines.

A formal revision cycle for all guidelines takes place on a five-year cycle. The College will ask the authors of the guideline to consider whether or not the guideline needs to be revised. A full consultation process will be undertaken if major revisions are required. If minor revisions or changes are required, a short note of the proposed changes will be placed on the College website for two weeks for members’ attention. If members do not object to the changes, the changes will be incorporated into the guideline and the full revised version (incorporating the changes) will replace the existing version on the College website.

The guideline has been reviewed by the Clinical Effectiveness team and was placed on the College website for consultation with the membership from 23 May 2022 to 21 June 2022. All comments received from the membership were addressed by the authors to the satisfaction of the Clinical Lead for Guideline Review (Cellular Pathology).

The guideline was developed without external funding to the writing group. The College requires the authors of guidelines to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness team and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

About 40% of the general population have single or multiple thyroid nodules, whereas the incidence of thyroid malignancy is less than 1% overall.[1] In the UK, around 3,700 people are diagnosed with thyroid cancer each year. About half of these cases are in people under 50. The incidence of thyroid cancer has increased by 164% since the early 1990s. While the mortality from thyroid cancer may have halved in the last 40 years in women and reduced by a third in men, there are still around 400 deaths per year. Approximately 72% of thyroid cancers occur in females and 28% in males.[2] The majority of thyroid cancer deaths are from the non-papillary histological subtypes; papillary cancer has a five-year survival rate of over 90% compared with anaplastic, which has 10% five-year survival rate.[3] There is also a greater awareness of incidental occult small thyroid cancer, identified at thyroidectomy for other reasons.[4]

The original RCPath *Guidance on the reporting of thyroid cytology specimens* document was intended to help produce consistent and reproducible reporting and classification of thyroid cytology specimens in the UK. The importance of thyroid cytology in the diagnosis of thyroid nodules is highlighted in several guidelines.[5]

Rising investigation of thyroid problems and the common finding of multiple thyroid nodules on radiological investigation have increased demands on the use of thyroid cytology to help diagnose and triage patients.[6] It has also highlighted the need to ensure that only patients with a risk of significant disease are investigated and that under- and over-treatment is minimised where possible. It is in this context that the reporting of thyroid cytology, just as the need for good clinicoradiological correlation, must be placed. These are most commonly discussed within a multidisciplinary team meeting (MDM) setting. In primary care, suspected thyroid cancer should be referred for further investigation as an urgent two-week referral, while those with thyroid swelling without possible malignant symptoms/signs can be referred non-urgently.[7]

The RCPath thyroid reporting system was developed and originally issued in 2009, building on the existing BTA system.[8] Thyroid cytology must be reported in prose, together with an allocated Thy category, as outlined in this guidance. The system currently in most widespread use in the UK is the BTA/RCPath Thy 1–Thy 5 2007 terminology, first described in 2000 and reiterated in 2014.[8,9] Over recent years, several other systems for the classification of thyroid cytology have been developed around the world.[10–13] These all classify thyroid cytology to allow for patient management. All the systems have great similarities and can be broadly equated to each other. The terminology does vary, and all the systems in use have ‘equivocal’ or ‘indeterminate’ categories for cases that are not able to be definitely diagnosed by cytology. It is in this area that most problems lie with definitions (see below and section 5.3). Table 1 lists the known thyroid cytology systems that exist and allows comparison between them, showing general similarities. However, it must be stressed that each system has been developed to cater for a local need and hence reflects differing health systems, disease incidence, application of pathological criteria and resource setting.[14,15] There are efforts to produce an international thyroid cytology system that would allow for a single system worldwide, but this is still in discussion. Logically, any such system should be considered seriously as a possible

replacement of the UK Thy system, but only if this is felt that it would be of benefit and in discussion with other relevant UK stakeholders.

The working group has considered the other available systems and whether retention of the existing RCPath system, or adoption of another system, is advisable. Given the UK context, the UK use of the BTA/RCPath approach as previously promulgated and the inherent uncertainty around the detail of any newly proposed international system, we advise that the retention and use of the RCPath approach is currently the best course of action. The working group has undertaken a literature review of available quality papers and, while most relate to the Bethesda system, some do relate directly to the RCPath system and there is evidence that can be gleaned to help consolidate the RCPath approach. However, more evidence of the use of the RCPath system is desirable.

The most important role of any reporting system is to provide clarity for patient management. It is also important to be able to audit outcomes to:

- refine and improve the reporting process
- give a relative risk of thyroid cancer for each cytology reporting category
- continue the process of a national standardisation
- compare with other systems used internationally.

Any system used must be easy to understand and apply in clinical practice. It should show good intra- and inter-observer reproducibility between the various categories, while recognising the inherent difficulties in the 'equivocal' or 'indeterminate' categories.[16] The use of the RCPath system has helped achieve all these aims.

This document is not intended to be a textbook of thyroid cytology, for which other texts are recommended.[17–20] Instead, it is intended to be a practical guide to thyroid cytology reporting in the UK, based on available evidence and experience with reporting systems in cytology. As with all guidance, it will require review and amending when necessary to remain relevant to up-to-date clinical practice, in particular with respect to clinical and diagnostic advances. It is highly likely that in the future, as diagnostic and especially molecular testing improves, further changes to the current approach will be required.

1.1 Target users of this guideline

The target primary users of this guideline are practicing cellular pathologists who report thyroid cytology material. The recommendations will also be of value to all those involved in the diagnosis and management of thyroid disease.

2 Role of cytology in the management of patients with potential thyroid pathology

The importance of thyroid cytology in the management of patients with thyroid pathology is highlighted in several guidelines.[8,21–24] Information on biochemical and immunological evaluation including thyroid autoantibodies may also be helpful depending on individual circumstances. It is essential that full clinical details are provided by the clinician and radiologist to give the reporting cytopathologist as much information as possible, including the degree of any ultrasound suspicion. When medullary thyroid cancer is suspected, this should be highlighted by the clinician and serum calcitonin should have been measured in such cases. The use of a proforma cytology request form may aid this.[25]

If not provided, then clinical information should be requested to allow an understanding of the clinical picture. Ultimately, any thyroid cytology report must be used in conjunction with all available relevant clinical findings and investigations and MDM discussion may be required to achieve this.

Thyroid cytology can provide a diagnosis of malignancy, with potential tumour type, enabling appropriate therapeutic surgery in one stage. It can help triage the remaining patients into those who potentially require surgical as opposed to medical/endocrinological management, as well as those who can be discharged or may require surveillance. Since the incidence of thyroid malignancy is relatively low and only one in 20 clinically identified nodules are malignant,[26] thyroid fine needle aspiration (FNA) can help reduce the rate of surgery for benign thyroid disease. The use of ancillary testing (see section 8) may also aid in patient management.

[Level of evidence B – known to be of importance in ensuring consistency of reporting and management.]

3 Taking thyroid cytology samples

This document will make a few specific points about thyroid cytology FNA,[27–29] but will not reiterate the standard guidance on taking cytology specimens.[30,31]

The success of thyroid FNA is known to be operator dependent. Although minimally invasive and safe, and usually performed on an outpatient basis, the optimal application of FNA requires not only technical skill, but also an awareness of the limitations of the procedure, the indications for its use, the factors that affect the adequacy of the FNA specimen and the post-procedural management strategy. The results may be affected by lesion characteristics, the accuracy of lesion and needle localisation, the method of guidance, the number of aspirated samples, the needle gauge and the aspiration technique.[32,33] The availability of competent, experienced and trained staff to assess sample adequacy at the time of sample taking (rapid on-site evaluation [ROSE]) can help reduce sample inadequacy.[34–37]

The 2019 document *Tissue pathways for diagnostic cytopathology* makes a strong recommendation for implementation of ROSE for FNA cytology of multiple sites including for thyroid and head and neck aspirates.[38] A recent evidence-based review confirms that thyroid FNAs taken using ROSE have lower Thy1 rates compared with aspirates taken without ROSE.[10] Introduction of ROSE may be most cost-effective in settings with particularly high Thy1 rates. As the majority of thyroid FNA are now undertaken under ultrasound guidance, implementation of ROSE requires close cooperation between cytopathology, radiology and clinical teams.

The sample taker will typically be a radiologist, rather than a surgeon, endocrinologist, oncologist or cytopathologist. Anyone taking thyroid FNAs must be suitably trained and be able to do so under ultrasound guidance.[39]

To develop and maintain the necessary level of staff expertise in an institution, the number of staff who perform aspiration cytology should be kept at levels to maintain skills and quality. Each staff member who performs aspiration cytology must be subject to audit of their results (see section 6). Staff members whose attempts at FNA repeatedly result in unsatisfactory specimens (suggested by the experience of the working group to be greater than 15%) should be identified and education and supervision undertaken if appropriate. For this purpose, samples that are non-diagnostic (Thy1) should be separated from samples that are non-diagnostic but from a cyst (Thy1c) for audit purposes, since the latter category should not be operator dependent. See section 5 for full definitions.

More than one ‘pass’ of the lesion being aspirated yields a greater likelihood of a diagnostic sample, except when a cyst is fully drained. Samples produced from more than one pass should be identified as such.[33] The use of thyroid core biopsies or other histology can be of use, especially for persistent non-diagnostic samples,[31] or to distinguish between lymphoma and anaplastic thyroid carcinoma. It must be borne in mind that a diagnosis of thyroid

malignancy may be made on a lymph node FNA from a metastatic deposit, rather than from a thyroid gland FNA itself.

[Level of evidence B and GPP – essential to taking good quality FNA material.]

4 Preparation and staining of thyroid cytology samples

Thyroid FNA cytology specimens may comprise air-dried and alcohol-fixed direct spread samples, as well as aspirate washings and cyst fluid samples. Some units favour the placing of the entire specimen into a fluid medium, such as a liquid-based cytology methodology. To date, there is no direct evidence that any one approach yields better results than any other. The majority of units would appear to use a combination of Giemsa and Papanicolaou stains on direct smears, and a Papanicolaou stain on fluid-derived samples, depending on the method of preparation used in line with RCPath guidance.[38] Use of haematoxylin and eosin (H&E) stain for cytology samples is not advocated.[24,38] The approach used will depend on local resources and experience, but the staining used must be suitable for internal audit and, where applicable, enable review by an appropriate Cancer Network cytopathologist.[21,40] Such central review can identify significant discrepancies in reporting that can affect patient management.

The use of any thyroid cytology specimen for possible ancillary studies (e.g. cell block production, which can allow for immunocytochemistry and molecular analysis, as well as flow cytometry) may affect how a sample is taken, transported and handled. This requirement should be considered and may require discussion between the sample taker and the laboratory prior to the sample being taken (see section 9).[38]

[Level of evidence B and GPP – essential to taking good quality FNA material.]

5 Thyroid cytology reporting

The primary aim of any cytology report is to describe and interpret the cytological appearances and convey this information in a clear, consistent and reproducible way to assist the clinician/clinical team involved in correct patient diagnosis and management. Standardised categorical systems for FNA reporting can make the results easier for aspirators to understand, and can suggest therapeutic action.[14,25] The cytopathologist–aspirator communication can be enhanced in MDMs at which further clinical, radiological or pathological information may be available to inform the decision(s). The MDM is also an opportunity to discuss other aspects of the service as required. It cannot be stressed enough that **full and complete clinical and radiological information is required to allow for the reporting of thyroid cytology**. If this is not given or is not available, then cytology reporting may need to be guarded.

The reporting of thyroid cytology, as in many areas of cellular pathology, is subject to individual application of reporting criteria, and hence can be subjective. The criteria detailed in this document are based on available evidence, but it must be acknowledged that there is inter- and intra-observer variation, which can be affected by the quality of the cytology sample itself, the information provided as well as the reporting cytologist. Thyroid cytology reporting must also be in line with WHO thyroid classification, which does evolve.[41]

Not all samples can be easily allocated a diagnosis or Thy category. On such occasions, the reason(s) behind this should be stated and subsequent management should be governed by what is in the best interests of the patient in the given clinical situation.

Thyroid cytology categories are also required for coding, audit and comparison. It is recommended that all thyroid cytology reports be clearly categorised using a numerical cytology category, in addition to the full prose report and an appropriate SNOMED code[40] (see Table 3). The current RCPath system is a modification of the original BTA and RCPath

systems. Thy1–5 system[8] and the categories originally suggested are retained, with expanded definitions for each category to aid in their use. The Thy categories allow for diagnostic classification and are not intended to mean or imply a progression from one category to another.

The 2019 RCPath *Tissue pathways for diagnostic cytopathology* recommends use of the RCPath 2016 Thy terminology to report thyroid FNAs.[38] It has always been recommended that thyroid cytopathology reports, apart from using the appropriate Thy category, should also include a full free-text description to explain the reason(s) for the chosen diagnostic category. While it may be tempting to use these numeric categories as reporting shorthand, the categories by themselves do not convey the full cytological report and should **not** be used alone without the cytological interpretation in discussions with clinicians. All international systems have an equivocal/indeterminate category, as shown in Table 1. This category should only be used when confident allocation into another more definite category cannot be made. This point is highlighted in the original guidance, but it requires re-emphasising based on experience.

There is no evidence of a direct correlation of the number of individual cytology reports reported and report accuracy. However, there is some non-UK evidence that the reporting of thyroid samples on an infrequent basis may lead to a lack of awareness of the reporting criteria and categories,[42] and potentially limiting the number of individuals reporting thyroid cytology may aid in consistency of reporting.[43] No absolute number is known of (or is proposed) but any reporting cytopathologist should be aware that if they are reporting low numbers of samples, they may need to review the service they offer, or look to seek a second opinion on cases.[43] Any such approach would logically follow clinical referral pathways.

5.1 Non-diagnostic for cytological diagnosis: Thy1/Thy 1c

The cellularity criterion (advocated by the RCPath and other international systems; Table 1) is that to be considered of adequate epithelial cellularity; samples from *solid* lesions should have ‘at least six groups of thyroid follicular epithelial cells across all the submitted slides, each with at least ten well-visualised epithelial cells.’ However, this is a purely cytological criterion and does not take into consideration the clinical and radiological setting. A more pragmatic criterion considering the clinical and radiological context and findings is advocated but can **only** be applied if sufficient clinical information is provided to the reporting cytologist.[44] (Also see section 2.) If there is uncertainty as to whether the sample is adequate for diagnostic purposes, this should be stated. A second opinion may be of value in this context also.

The reason for a non-diagnostic sample should be clearly stated in the cytology report. This category will include Thy1 and Thy1c.

(i) Thy1

Those that are most likely related to the operator/technique:

- consist entirely of blood or are so heavily bloodstained that the epithelial cells and/or colloid cannot be visualised
- are acellular, or have too low a follicular epithelial cellularity to allow diagnosis (i.e. do not reach the adequacy criterion stated above)
- are technically unable to be evaluated (e.g. poorly spread, delayed air drying or fixation artefact, prominent crush artefact, cells trapped in fibrin)
- these would all be classed as **Thy1** for audit and clinical purposes.

(ii) Thy1c

Those that are most likely related to the lesion:

- cyst lesion fluid specimens that do not reach the follicular epithelial cell adequacy criterion stated above and that contain mostly macrophages but without abundant colloid. Useful phrasing may be that 'the sample is in keeping with fluid from a cyst but there are no/too few epithelial cells and insufficient colloid to confirm cyst type'. Use the category **Thy1c**, where 'c' means 'cystic lesion'.

It is important for auditing results that any samples of insufficient epithelial cellularity that are cyst fluid can be separated from those that are non-diagnostic for the other reasons listed above. The assessment of thyroid cysts can be particularly problematic. There is a recognised risk of non-representative sampling, especially in cystic papillary thyroid carcinomas. It is important not to offer false reassurance on suboptimal epithelial cellularity, but equally the ROM in such cases must not be overstated (Table 2). Careful assessment is needed, possibly with MDM discussion if required.

5.2 Non-neoplastic: Thy2/Thy2c

(i) Thy2

Samples in this category should have sufficient epithelial cellularity to allow diagnosis and be consistent with the clinical information. This non-neoplastic category includes:

- colloid nodules – these samples will contain abundant easily identifiable colloid with cytologically bland follicular epithelial cells sufficient for diagnosis, with or without the presence of cyst macrophages
- hyperplastic nodules
- thyroiditis, e.g. Hashimoto's thyroiditis
- samples of benign thyroid tissue with an element of oncocytic change. NB: Specimens almost exclusively or exclusively oncocytic in appearance would be classed within the Thy3f category (see below).[45]
- other non-neoplastic conditions including normal thyroid
- all of the above would be classed as **Thy2** for audit and clinical purposes.

The specific diagnosis should be stated in the report when one can be made.

(ii) Thy2c

- cyst lesion specimens that consist predominantly of abundant colloid and macrophages, even if too few follicular epithelial cells are present to meet the adequacy criterion outlined above for solid lesions, can be considered to be 'consistent with a colloid cyst' in the appropriate clinical setting. Such samples could be reported along the following lines 'the sample is in keeping with fluid from a cystic colloid nodule but there are no/too few epithelial cells for confirmation'. To allow audit, this particular category should be coded as **Thy2c** ('c 'for 'cyst').

5.3 Neoplasm possible: Thy3a and Thy3f

Owing to the limitations of FNA cytology, not all lesions can be determined solely by FNA cytology and MDM discussion is recommended to decide further management.[46,47] The written text report should identify the nature of the cytological concern and any differential diagnosis made clear. It is important that the free-text prose is clear as to why the individual aspirate falls within the Thy3a or Thy3f subcategory.[2] The Thy3a and Thy3f categories are separate groups and are not meant to imply any direct progression between themselves or any other Thy category. They are used to reflect a real cytological diagnostic problem area, although there is inevitably some overlap and subjectivity in interpretation and categorisation. **There is no 'Thy3' category without the suffix 'a' or 'f'.**

Accurate and complete clinical and radiological information is vitally important to allow for cytological interpretation. If there a problem with categorisation of the sample, then this should be stated and the reason(s) given.

(i) Thy3a

- **Thy3a** ('a' for 'atypia'): samples that exhibit cytological nuclear or cytological architectural atypia, or other features that raise the possibility of neoplasia, but which are insufficient to enable confident placement into any other category. The text of the report should describe the nature of the problem. These should form only a minority of cases overall and as such should only be used if the sample cannot be confidently allocated to another category. There is evidence of the usefulness of such an atypical category from publications that use RCPath terminology,[48] the Bethesda System for Reporting Cytopathology (TBS)[49] and Italian TIR terminology[46] for the Thy3a and equivalent categories. Cytological nuclear atypia is more highly predictive of malignancy,[50] hence the presence or absence of cytological nuclear atypia should always be commented on. Indeed, in the Italian system, cases of indeterminate FNAs with cytological nuclear atypia are categorised in the higher risk TIR3B subgroup rather than the lower risk TIR3A subgroup.[46] The accompanying free-text prose is crucial to explain which specific cytological features are present with a statement that if atypical nuclear features are present, these have a higher ROM.

Thy3a samples would include those in which there is:

- cytological architectural atypia in the form of a mixed micro- and macro-follicular pattern and/or little colloid, or sparsely cellular samples containing predominantly microfollicles, where a definite distinction between a follicular neoplasm and hyperplastic nodule is difficult, but there is insufficient material or features for the Thy3f category. Useful phrasing might be that 'the appearances may represent a cellular colloid nodule but a follicular neoplasm is not excluded.' There is some evidence that subclassification of Thy3a cases may help with better diagnostic allocation and improve risk stratification.[48]
- focal cytological nuclear atypia or other features, which are most probably benign but where a papillary carcinoma cannot be confidently excluded and the features are insufficient for the Thy4 category
- a compromised specimen (e.g. obscured by blood or a poorly spread smear), where some cells appear to be mildly abnormal but are not obviously from a follicular neoplasm or suspicious of, or diagnostic of, malignancy
- cyst lining cells that are not normal, but which are not able to be characterised otherwise
- predominance of lymphoid cells with very scanty epithelium, provided a lymphocytic thyroiditis has been excluded.

Pre-existing conditions (such as in thyroiditis) can cause difficulty with diagnosis, even leading to overcalls, and such difficulties should be identified within the cytology report.[9] Again, complete and accurate clinical and radiological information is vital to the correct interpretation of thyroid cytology samples.

In many cases, a repeat thyroid cytology sample is able to be placed into a more definitive category.[49]

(ii) Thy3f

- **Thy3f** ('f' for 'follicular'): samples suggesting follicular or oncocytic neoplasms. Samples suggestive of follicular neoplasm or consisting entirely or almost entirely of

oncocytic cells should be categorised as Thy3f. Marked nuclear cytological atypia is also a feature of oncocytic thyroid neoplasms, and can be mistaken for other thyroid tumours, including thyroid cancers.[9] The histological possibilities therefore include hyperplastic or other cellular but non-neoplastic nodules, as well as neoplasms, including follicular or oncocytic adenomas and follicular or oncocytic carcinomas. These entities cannot be reliably distinguished on cytology alone. Follicular variants of papillary thyroid carcinoma (FVPTC) and non-invasive follicular thyroid neoplasm with papillary like nuclei (NIFTP) may also be represented in this category, especially if the nuclear features are subtle. These require histological diagnosis. See section 7.

The cytological interpretation must be clearly stated in the report, which may mean listing the likely differential diagnosis. Some of these problematic cases may reflect poor aspiration/cellularity and a repeat may help clarify the exact diagnostic category. Review of the cytology and/or MDM discussion locally or centrally may be of use to help with patient management (see section 10).

5.4 Suspicious of malignancy: Thy4

This category includes those samples that are **suspicious** of malignancy, but which do not allow confident diagnosis of malignancy. This will include specimens of low cellularity and mixed cell types (normal and abnormal). The tumour type suspected should be clearly stated if at all possible and will often be a papillary carcinoma. This category should not be used for samples that exhibit mild atypia or the types of features described earlier, which should be categorised as Thy3a, or for **follicular or oncocytic** neoplasms, which should be categorised as Thy3f. Cases of definite malignancy, but where a specific diagnosis cannot be made (e.g. lymphoma versus anaplastic carcinoma), should be placed in the Thy5 category.

5.5 Malignant: Thy5

These are samples that can be confidently diagnosed as malignant. The tumour type should be clearly stated, if possible, for example:

- papillary thyroid carcinoma
- medullary thyroid carcinoma
- anaplastic thyroid carcinoma
- lymphoma
- other malignancy, including potentially non-thyroid/metastatic malignancy.

Sometimes it may be possible to be confident of malignancy but not of tumour type. This should then be clearly stated and a differential diagnosis given, e.g. between anaplastic carcinoma and lymphoma, or anaplastic carcinoma and metastatic malignancy.

A particular problem could be NIFTP; see section 7.

[Level of evidence B and GPP – ensures consistency of reporting.]

5.6 Thyroid cytology coding

All thyroid cytology reports should be fully coded using standard SNOMED codes and the numerical categories Thy1–5 (see Table 3).[51] It is emphasised that the categories by themselves do not convey the full cytological report and should not be used alone without the morphological cytological interpretation in written or verbal communication with clinicians. The SNOMED codes shown in Table 3 are for the Thy categories only. It is recommended that coding be undertaken at the diagnostic level for the specific diagnosis provided also.

[Level of evidence GPP – of value in audit/case identification.]

6 Diagnostic accuracy and histological correlation

6.1 Positive and negative predictive value

The positive or negative predictive value (NPV) of a test is the probability that patients with a positive or negative test result have or do not have a given disease. Literature frequently refers to the positive predictive value (PPV) or ROM of thyroid FNA cytology for thyroid malignancy and utilises these for different Thy categories, e.g. Thy1, Thy2, Thy3a, Thy3f, Thy4 and Thy5.[52–58] In a similar fashion, the NPV of thyroid cytology for thyroid malignancy is the probability that patients with a certain thyroid cytology report do not have thyroid cancer. It is crucial, however, to consider carefully how the calculation for the PPV or ROM is derived and whether the chosen denominator is **all** patients with FNA cytology in that category or **only** those patients with lesions that have undergone surgical resection. The latter method will give a disproportionately high ROM for Thy1, Thy2 and Thy3a subcategories because most patients with aspirates in the Thy1 and Thy2 subcategories do not undergo resection. Surgery in Thy1 and Thy2 subcategories and, to a lesser extent in the Thy3a subcategory, is usually reserved for patients with more concerning clinical or radiological features. The PPV and NPV of thyroid FNA cytology is influenced by a variety of factors, including the prevalence of thyroid cancer in that geographical area, the surgical resection rate and reporting of subsequent histology.[59] Nodule size may also be a factor, as well as the ultrasound features, the patient's age and previous clinical history including previous thyroid cancer, radiation to the neck or radioiodine and the molecular profile.

6.2 Diagnostic accuracy of 'Thy' terminology

Section 7 of the previous RCPath Thy document, published in 2016, refers to published data regarding thyroid cancer detection by thyroid FNA. Since then, a detailed meta-analysis of all studies has been published (both in the UK and internationally) of thyroid surgical outcomes following cytology reported using the RCPath Thy terminology system.[60] This showed pooled ROM rates as follows, based on surgical excisions:

- Thy3a, 25% (95% CI: 20−31%)
- Thy3f, 31% (95% CI: 24−39%)
- Thy4, 79% (95% CI: 70−87%)
- Thy5, 98% (95% CI: 97−99% plus).*

*Some centres may achieve a Thy5 PPV of greater than 99% (97–99% plus), of up to 100%, but must be able to provide the data to support this.

These supersede the figures given in the 2016 document and are similar to figures recently reported for the Western patient cohort in another large meta-analysis of TBS (ROM for AUS/FLUS [equivalent to Thy3a] of 21.5%, ROM for FN/SFN [equivalent to Thy3f] of 27.3%, ROM for suspicious for malignancy [equivalent to Thy4] of 75.1% and ROM for malignant [equivalent to Thy5] of 99.2%).[58] There are some differences noted in the ROM rates in some of the higher TBS categories between Asian and Western patient cohorts, which are likely to be due to differences in multidisciplinary management, resection rates and diagnostic thresholds.[58] The calculation of ROM for non-diagnostic and benign FNAs in published meta-analyses can be misleading if figures used are based on surgical excision, since these series are biased by patients with clinically or ultrasound higher-risk nodules. The ROM depends very much on surgery and histological outcomes, and this will vary depending on the number operated on in each Thy category as well as the histological reporting criteria.

6.3 Histological correlation and new entities

NIFTP and thyroid tumours of uncertain malignant potential

Thyroid histopathology reporting terminology has evolved by international consensus.[60] NIFTP[62,63] and tumours of 'uncertain malignant potential' (UMP) represent revised WHO 2017 terminology for thyroid lesions that were previously described under various names at the lower end of a continuum of risk from benign to malignant.[60] The diagnosis of **encapsulated follicular-patterned neoplasms** depends on whether papillary carcinoma (PTC)-like nuclei and/or capsular and/or vascular invasion are present, questionable or absent. These features are determined histologically, not on pre-operative cytology, and can be subjective to interpret.

NIFTP was proposed in 2016 by an international multidisciplinary working group for reclassification of a tightly defined subset of non-invasive encapsulated FVPTC (eFVPTC) that are managed by lobectomy/hemithyroidectomy only.[62,63] Non-invasive eFVPTC were already known to be indolent tumours but, by applying strict pathological criteria, a subset was redesignated NIFTP. NIFTP is accepted by the World Health Organization,[61] the American Thyroid Association (ATA),[64] RCPath[65] and most countries, and there have been numerous publications. Histological criteria for NIFTP are strictly defined. Meticulous histopathological examination is needed and many of the criteria are subjective to interpret, especially PTC-like nuclei.[62,63,65] A NIFTP diagnosis cannot easily be applied retrospectively.[50]

In the UK, since NIFTP is a histological diagnosis, it cannot be reliably diagnosed pre-operatively on clinical, radiological or cytological grounds. It is possible to suspect a diagnosis of NIFTP or eFVPTC on radiology, pre-operative FNA cytology and other investigations if there is a well circumscribed lesion and cytology showing microfollicular architecture with partially developed PTC-like nuclear features. NIFTPs have been preceded by all cytology categories but most often in categories Thy3a, Thy3f or Thy4 (or their international equivalents).[59,66] NIFTP may rarely be preceded by cytology diagnostic of papillary thyroid carcinoma (Thy5) but the risk of this can be reduced by requiring certain features before issuing a diagnostic cytology report. The presence of psammoma bodies, true papillae or frequent intranuclear inclusions favours papillary thyroid carcinoma rather than NIFTP.[67,68]

In the UK, NIFTP is not a common diagnosis as the majority of lesions meeting the latest strict histopathological criteria for NIFTP would historically have been reported as follicular adenomas.[69] Much of the published literature from elsewhere in the world reports considerable differences in ROM rates in TBS categories II, III, IV, V and VI cases (equivalent to Thy2, Thy3a, Thy3f, Thy4 and Thy5, respectively) following the introduction of NIFTP. These rates are not directly relevant to the UK as the UK incidence of NIFTP is low (probably below 5% of all newly diagnosed thyroid carcinomas).[69] Multidisciplinary teams need to be aware of the potential diagnosis of NIFTP and its likely treatment when discussing patients pre-operatively.

Invasiveness is an important criterion of malignancy in encapsulated follicular-patterned tumours. The term UMP is used when this invasion is 'questionable', i.e. neither clearly present nor clearly absent.[61]

Unfortunately, histological interpretation of invasion can also be subjective. Tumours of UMP can be regarded as borderline, precursor or intermediate between benign and malignant. By contrast, the terms 'adenoma' and 'NIFTP' are used for tumours that clearly have no invasion, and the term 'carcinoma' when invasion is clearly present. Follicular tumour of UMP (FTUMP) is indeterminate between well-differentiated minimally invasive follicular carcinoma and a follicular adenoma. All, by definition, lack PTC-like nuclei, but FTUMP has questionable capsular invasion and/or questionable vascular invasion around the edge of the tumour. Well-differentiated tumour of UMP (WDTUMP) is indeterminate between invasive eFVPTC, well-differentiated carcinoma not otherwise specified (NOS) and NIFTP. Similarly, there is questionable capsular invasion and/or questionable vascular invasion, but the nuclei are either PTC-like or questionably so.[61]

[Level of evidence B – essential to taking high-quality diagnosis and outcomes.]

7 External quality assurance

A technical cytology external quality assurance scheme is now available, operated by UK NEQAS CPT.[70] No known established routine interpretative thyroid cytology scheme exists in the UK, although one is now offered as part of a more general scheme.[71] All laboratories should be compliant with UKAS or a similar scheme, and achieve relevant ISO standards.

The thyroid service as a whole may be inspected as part of a cancer peer review and this process would involve scrutiny of the clinical/MDM and the thyroid cytology service.

[Level of evidence D and GPP – essential to ensuring high-quality diagnostic material.]

8 Ancillary testing

The use of ancillary tests in the UK setting is variable and not widespread. Immunohistochemistry (IHC) is usually more easily available compared with molecular tests.

Ancillary immunocytochemical techniques can be helpful for diagnosis of specific thyroid lesions but their use is dependent on the type of sample preparation used. Examples of IHC use are:

- assisting in confirming the diagnosis of problematic cases especially metastatic disease (e.g well-differentiated papillary thyroid carcinoma – typically thyroglobulin +ve, TTF1 +ve, PAX8 +ve, HBME1 +ve, CK19 +ve and CD56 –ve).[72]
- assisting in the diagnosis of medullary thyroid carcinomas (typically calcitonin +ve, CEA +ve, chromogranin +ve, synaptophysin +ve, TTF1 +ve and thyroglobulin –ve).
- distinguishing between lymphomas versus anaplastic thyroid carcinomas, and/or other rarer primary thyroid lesions or tumours metastatic to the thyroid gland (e.g. head and neck squamous cell carcinoma, other metastatic carcinomas or melanoma).

Immunocytochemistry can be performed on cytology or cell block, if available.[38,40]

The use of molecular markers (such as BRAF) to aid in diagnosis and patient stratification for possible further treatment has grown significantly since the original guidance was published. Many laboratories may not be able to perform these tests themselves, but an awareness of them is vital to ensure that, if required, the cytological material can be referred to a more specialist centre for such testing.[38,72–75]

[Level of evidence C and GPP – growing development of diagnostic tools.]

9 Clinical action

The recommendations for clinical action as advocated by the BTA are endorsed in general but it is considered preferable *not* to include these general clinical recommendations in cytology reports. This is because not all relevant clinical and/or radiological information may be available to the cytopathologist at the time of reporting.[8] Ideally, decisions about patient management should rest on a multidisciplinary assessment of the patient. It is expected that any thyroid cytology cases categorised as Thy4 or Thy5 will be reviewed by a cyto/histopathologist core member of the thyroid MDM and discussed in the MDM setting. Other cases, such as Thy3a and Thy3f,[49,76] and even cases classed as Thy1/1c or Thy2/2c, can benefit from MDM discussion, especially if there is any concern. Depending on local

arrangements, these may be reviewed/discussed locally or as part of a network MDM approach.

10 Criteria for audit

It is essential, as with all cytology, that reporting categories and outcomes are audited.[16] The proportion of cases reported in each category will vary depending on the local case mix and aspirating protocols. Therefore, the most valid audit of accuracy is proven clinical outcomes, which will predominantly be those cases where histology is available. Any cases that have histology performed should have the histology reported in line with RCPath guidance,[38,51] and those reports should be obtained for direct correlation with the cytology report. The likelihood of malignancy should be known locally for each cytology reporting category (Table 2).[10]

Any correlation between cytology and histology **must** be with the **targeted** lesion, as pickup of malignant lesions can skew the correlation when identified incidentally.[4]

A template for thyroid cytology audit can be found on the RCPath website.[77]

The suggested standards are:

- 100% thyroid cytology reports include a 'Thy' category as well as a prose explanation of the findings
- the percentage of all thyroid cytology cases that fall into each 'Thy' category is appropriate (as per national data)
- PPV for malignancy for Thy5 is 97–99% (although rates of 100% can be fully achievable)
- 100% of Thy4/5 cases undergo discussion at thyroid cancer MDMs
- the number of Thy3 (Thy3a and/or Thy3f) cases that undergo discussion at thyroid cancer MDMs is appropriate (as per local preferences).

The use of the reporting categories should be monitored to ensure their correct use, but also to allow any changes to this current thyroid cytology reporting guidance to be made on robust evidence.[52] Other aspects of the thyroid cytology service that may be audited will depend on local needs; examples may include quantity and accuracy of clinical information given on the request forms, use of reporting codes and SNOMED codes compared with the text report, rate of insufficient samples per individual aspirator and proportion of benign/malignant nodules undergoing surgery. It is recommended that such an audit is undertaken at least annually, and the data discussed ideally with MDM members and shared with other relevant interested parties as necessary. The use of tools such as a CUSUM graph to monitor thyroid cytology reporting can help identify trends with time.[78]

The RCPath recommends general key assurance indicators[79] and there are NHS Improvement Pathology Quality Assurance Dashboard metrics.[80]

[Level of evidence GPP – essential to taking maintaining a high-quality service.]

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12 Tables

Table 1: Equivalence of terminology of thyroid cytology classifications.

RCPath	Bethesda[10]	Italian[11]	Australian[12]	Japanese[13]
Thy1 **Non-diagnostic for cytological diagnosis** **Thy1c** **Non-diagnostic for cytological diagnosis – cystic lesion**	I.**Non-diagnostic or unsatisfactory** Virtually acellular specimen Other (obscuring blood, clotting artefact, etc.) Cyst fluid only	**TIR 1** **Non-diagnostic** **TIR 1c** **Non-diagnostic cystic**	**1** **Non-diagnostic**	**1** **Unsatisfactory**
Thy2 **Non-neoplastic** **Thy2c** **Non-neoplastic, cystic lesion**	**II. Benign** Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other	**TIR 2** **Non-malignant**	**2** **Benign**	**2** **Benign** **Cyst fluid**
Thy3a **Neoplasm possible – atypia/non-diagnostic**	**III. Atypia of undetermined significance or follicular lesion of undetermined significance**	**TIR 3A** **Low risk Indeterminate lesion (LRIL)**	**3** **Indeterminate OR** **Follicular lesion of undetermined significance**	**3** **Undetermined significance**
Thy3f **Neoplasm possible, suggesting follicular neoplasm**	**IV. Follicular neoplasm or suspicious for a follicular neoplasm** Specify if Hürthle cell (oncocytic) type	**TIR 3B** **High risk Indeterminate lesion (HRIL)**	**4** **Suggestive of a follicular neoplasm**	**3** **Follicular neoplasm**

Thy4 **Suspicious of malignancy**	**V. Suspicious for malignancy** Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	**TIR 4** **Suspicious of malignancy**	**5** **Suspicious of malignancy**	**4** **Suspicious for malignancy**
Thy5 **Malignant**	**VI. Malignant** Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic carcinoma Non-Hodgkin lymphoma Other	**TIR 5** **Malignant**	**6** **Malignant**	**5** **Malignant**

Table 2: Indicative RCPath category use and outcome.

Thy category	**BAETS data[81]** **% category use overall**	**BAETS data[81] for ROM for surgically operated nodules**	**Poller *et al.* for ROM[60] with 95% CI for surgically operated nodules**
Thy1	14.4%	15.4%	12% (5−22)
Thy2	30.0%	8.0%	5% (3−9)
Thy3	40.7%	25.7%	22% (18−26)
Thy3a			25% (20−31)
Thy3f			31% (24−39)
Thy4	5.3%	74.4%	79% (70−87)
Thy5	8.7%	97.9%	98% (97−99 plus)*
CI: Confidence interval; ROM: Risk of malignancy. *See comment in Section 6.2			

Table 3: Proposed SNOMED codes for thyroid cytology.

SNOMED 2 or 3	SNOMED CT terminology	SNOMED CT code
Site – Thyroid T96000	Thyroid (body structure)	69748006
Procedure P1149		
Result		
Thy1 M09000		112631006 Specimen unsatisfactory for diagnosis (finding)
Thy1c M09010		734121004 Thyroid cyst fluid (substance)
Thy2 M09450		110396000 No evidence of malignant neoplasm (finding)
Thy2c M33790		72325004 Cyst of thyroid (disorder)
Thy3f M69701		447711004 Follicular neoplasm of thyroid (finding)
Thy3a M69700		1148693003 Follicular lesion of thyroid (finding)
Thy4 M69760		44085002 Atypia suspicious for malignancy (morphological abnormality)
Thy5 M80013		363346000 Malignant neoplastic disease (disorder)

The codes suggested above are generic ones and specific ones can be used if a specific diagnosis is offered. See reference 40 for more detailed SNOMED CT codes for specific diagnoses when this is possible and also the NHS Digital UK SNOMED CT browser for specific diagnoses if necessary.

Appendix A Summary table – explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix B AGREE compliance monitoring sheet

The guidelines of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword
2 The health question(s) covered by the guideline is (are) specifically described	Foreword
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	n/a
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Throughout
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12 There is an explicit link between the recommendations and the supporting evidence	Throughout
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–11
16 The different options for management of the condition or health issue are clearly presented	Foreword
17 Key recommendations are easily identifiable	2–11
Applicability	
18 The guideline describes facilitators and barriers to its application	Throughout
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	2–11
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	12
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword