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# Guidance on the reporting of thyroid cytology specimens

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## Contents

## 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. It may rarely 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 be deemed negligent or a failure of duty of care.

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

The stakeholders consulted for this document were:

- British Thyroid Association (www.british-thyroid-association.org), to standardise data items between this document and BTA/ *Thyroid Cancer Guidelines (3rd edition)*
- British Association of Endocrine and Thyroid Surgeons (www.baets.org.uk)
- British Association of Head and Neck Oncologists (www.bahno.org.uk)
- UK Endocrine Pathology Society (www.ukeps.com)
- UK Association of Cancer Registries (UKACR)
- National Cancer Intelligence Network (NCIN) Thyroid Clinical Reference Group.
- British Association for Cytopathology (www.britishcytology.org.uk).

The information used to develop this guideline was derived from a review of existing national and international guidance were it exists, relevant literature and good practice identified by the authors. It has been graded using modified SIGN guidance. The bulk of the evidence is level B to D or meets the 'Good practice point' (GPP) criteria (see Appendix A).

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

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 short notice of change 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 Department and Publishing Department and was on the College website for consultation with the membership from 27 October to 24 November 2015. All comments received from the membership were addressed by the author to the satisfaction of the Director of Publishing and Engagement.

This 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 Department 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 2–4%.[1] In the UK in 2011, around 2700 people were diagnosed with thyroid cancer, with around 1960 diagnosed in women and 770 in men. About half of these cases are in people under 50. Whilst 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 374 deaths per year from thyroid cancer.[2] The majority of thyroid cancer deaths are from the non-papillary histological subtypes, with papillary cancer having a one year survival rate of 99.5% as opposed to anaplastic which has 15%.[3] There is also a greater awareness of 'incidental' occult small thyroid cancer, identified at thyroidectomy for other reasons.[4]

The original RCPath thyroid cytology 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[6] have increased the demand on the use of thyroid cytology to help diagnose and triage patients. 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 if at all possible. It is in this context that the reporting of cytology must be seen, and that the need for good clinico-radiological correlation is undertaken, most commonly within a multidisciplinary team (MDT) setting. In primary care, suspected thyroid cancer should be referred for further investigation as an immediate referral, whilst those with thyroid swelling without possible malignant symptoms/signs can be referred non-urgently.[7]

The RCPath thyroid reporting system was developed by building on the existing British Thyroid Association (BTA) system,[8] and was originally issued in 2009. 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 directly equated to each other. The terminology does vary, and all the systems in use have an 'equivocal' category for cases that are not definitely diagnosable cytologically, and it is in this area that most problems lie with definitions (see below and section 5.3). Table 1 lists and allows comparison with the known thyroid cytology systems that exist, and shows the 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]

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 problems with any proposed system, we advise that retention of the RCPath approach is currently the best course of action. The working group has undertaken a literature review of available quality papers and, whilst 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, and any future revision of this guidance must build on this.

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 cytological diagnosis
- 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, and should show good intra- and inter-observer reproducibility between the various categories, while recognising the inherent difficulties in the 'equivocal' categories.[16] The use of the RCPath system has helped achieve all these aims.

This guidance 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] The workup of any patient requires full and appropriate clinical and ultrasound evaluation of the thyroid before the decision to perform thyroid cytology is undertaken. Additional information (including, depending on individual circumstances, biochemical and immunological [including thyroid autoantibodies] evaluation) may also be helpful. 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]

Thyroid cytology can provide a definite diagnosis of malignancy, with 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, or can be discharged or who may require surveillance. Since the incidence of thyroid malignancy is relatively low and only 1 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 9) 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 guidance will make a few specific points about thyroid cytology FNA[27–29] but will not reiterate the standard guidance on the taking of 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 the 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 experienced, trained staff to assess sample adequacy at the time of sample taking (rapid on-site evaluation, ROSE) can help reduce sample inadequacy.[34–37]

In most units, the sample taker will be a surgeon, endocrinologist, oncologist or radiologist, rather than a cytopathologist, but this will vary from unit to unit depending on resources and local preference and practice. To develop and maintain the necessary level of staff expertise in an institution, the number of staff who perform aspiration biopsies and the interpreting cytopathologists should be kept small. Each staff member who performs aspiration cytology must be subject to audit of their results. Staff members whose attempts at FNA repeatedly result in unsatisfactory specimens (suggested by the experience of the working group to be greater than 15%, see Tables 2–4) may be identified and education undertaken if appropriate. For this purpose, samples which are non-diagnostic (Thy1) should be separated from those samples which are non-diagnostic but from a cyst (Thy1c) for audit purposes, as the latter category should not be operator dependent. See section 5 for full definitions. There should be open discussion on this data, which is probably best done within a multidisciplinary setting. Ultrasound-guided FNA tends to have a higher adequacy rate than palpation-guided FNA.[38–40]

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, especially for persistent non-diagnostic samples, can be of use.[32]

Some centres may prefer to use alternative sampling techniques, such as samples taken with stylet needles,[42] core biopsies then spread for cytological evaluation or samples prepared with a ‘roll’ technique.[43,44] These are specialised techniques, which should not be used without sufficient local expertise. If such alternative techniques are used, this must be stated on the request form.

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

## 3.1. FNA training

In the UK there is currently no formal training of pathologists in FNA technique. Links to educational material on how to take an FNA are available on several websites, e.g. www.papsociety.org, www.liebertpub.com/videoendocrinology and www.pathlab.org.

# 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. There is no direct evidence to date 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. Previous guidance does not advocate the use of the H+E stain for cytology samples.[24,45] 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.[21,46] Such review can identify significant discrepancies in reporting that can affect patient management.[48,49]

Participation within a technical cytology EQA scheme is recommended, such as the one run by UK NEQAS CPT.[50]

The possible use of any thyroid cytology specimen for ancillary studies (e.g. immunocytochemistry, flow cytometry) may affect how a sample is taken, transported and handled. This requirement should be borne in mind and may require discussion between the sample taker and the laboratory prior to the sample being taken (see section 9).

*[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 the clinician involved. The report then assists the clinical team in making decisions about any further clinical action. Standardised categorical systems for FNA reporting can make the results easier for aspirators to understand, and suggest therapeutic action.[14,25] The cytopathologist–aspirator communication can be enhanced in multidisciplinary meetings (MDMs) at which further clinical and/or 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.

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, as well as the full prose report and the appropriate SNOMED code[46] (see Table 5). The RCPath system is a modification of the British Thyroid Association (BTA)/-RCP 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 (i.e. Thy2–Thy3a–Thy3f–Thy4–Thy5). Whilst 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 system have an equivocal/uncertain category (i.e. Thy 3a in this system), as shown in Table 1, and should only be used when confident allocation into another category cannot be made.

There is no evidence of a direct correlation of reporting volume and accuracy, but there is 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,[51] and potentially limiting the number reporting thyroid cytology may aid in consistency of reporting.[52] No absolute number is known of (or proposed) but any reporting cytologist must be aware that under these circumstance they may need to review the service they offer, or look to seek a second opinion on cases.[52] Any such approach would logically follow clinical referral pathways.

The Thy numerical categories are listed and explained below.

## 5.1 Non-diagnostic for cytological diagnosis – Thy 1/Thy 1c

The cellularity criterion (advocated by the BTA/RCP and all other known 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 10 well-visualised epithelial cells." However, this is a purely cytological criterion and does not take into consideration the clinical setting. A more pragmatic criterion taking into account the clinical context and findings is advocated, but can **only** be applied if sufficient clinical information is provided to the reporting cytologist.[54]

The reason for a non-diagnostic sample should be clearly stated in the cytology report. This category will include samples which are non-diagnostic.

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

- consist entirely of blood or are so heavily bloodstained that the epithelial cells 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) Those that are most likely related to the lesion:

- Cyst lesion fluid specimens which do not reach the follicular epithelial cell adequacy criterion stated above and which 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 epithelial cells or 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 which are non-diagnostic for the 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 risk of malignancy in such case must not be overstated (Tables 2, 3 and 4). Careful assessment is needed, possibly with MDM discussion if required.

## 5.2 Non-neoplastic – Thy 2/Thy 2c

Samples in this category should have sufficient epithelial cellularity to allow diagnosis and are 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, often with 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 Samples with almost exclusively/exclusively Hurthle cell samples would be classed within the Thy3f category (see below)*[55]
- other non-neoplastic conditions including normal thyroid tissue

- cyst lesion specimens which consist predominantly of colloid and macrophages, even if too few follicular epithelial cells are present to meet the adequacy criterion outlined above, 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').

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

### 5.3 Neoplasm possible – Thy3

Due to the limitations of FNA cytology, the nature of these lesions cannot be determined solely by FNA cytology and MDM discussion is recommended to decide further management.[56,57] The written text report should identify the nature of the cytological concern and any differential diagnosis made clear. The Thy3a and Thy3f categories are totally separate groups, and are not meant to imply any direct relationship or progression between themselves or any other Thy category but are used to reflect a real cytological diagnostic problem area (see Table 3).

This category includes:

- **Thy3a:** samples that exhibit cytological/nuclear or 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 Thy3 cases and as such should only be used if the sample cannot be confidently allocated to another category. This group is classed as **Thy3a** ('a' for 'atypia'). There is evidence that *nuclear* atypia is more often followed by malignant histology than *architectural* atypia.[58] Such situations would include:
  a) samples in which there is *architectural* 'atypia', in the form of a mixed micro- and macrofollicular pattern (approximately equal proportions of each), and/or little colloid, where a definite distinction between a follicular neoplasm and hyperplastic nodule is difficult. Useful phrasing might be that 'the appearances may represent a cellular colloid nodule but a follicular neoplasm is not excluded'
  b) sparsely cellular samples containing predominantly microfollicles
  c) focal *nuclear* atypia or other *cytological* changes, which are most probably benign but where a papillary carcinoma cannot be confidently excluded
  d) 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 indicative of, malignancy
  e) atypical 'cyst lining cells'
  f) predominance of lymphoid cells with very scanty epithelium, provided a lymphocytic thyroiditis has been excluded.

  In many cases, a repeat thyroid cytology sample is able to be placed into a more definitive category.[64]

- **Thy3f:** samples suggesting follicular neoplasms. These are likely to form the majority of the Thy3 category. The histological possibilities therefore include hyperplastic or other cellular but non-neoplastic nodules, as well as neoplasms, including follicular adenomas and follicular carcinomas. Follicular variants of papillary thyroid carcinoma without clear nuclear features of papillary thyroid cancer may fall into this category. These cannot be reliably distinguished on cytology alone. This group is to be classed as **Thy3f** ('f' for

'follicular'). Samples consisting almost exclusively/exclusively of oncocytic cells (greater than 75% of the total cell content) would be placed in this category.[56]

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 MDT discussion locally or centrally may be of use to help in 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 features as described earlier, which should be categorised as Thy3a, or for follicular 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, e.g.:

- 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.

The target is for greater than 99% positive predictive value of all Thy5 cytology reports for malignancy on histology.

*[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 5).[47] 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.

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

## 6 Thyroid cytology audit

It is essential, as with all cytology, that reporting categories and outcomes are audited.[16] The proportion of cases reported as each category will vary with the local case mix and aspirating protocols, so the most valid audit of accuracy is proven clinical outcomes, which will predominantly be those cases where histology is available. Any cases which have histology

performed should have the histology reported in line with RCPath guidance[46,47] 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 (Tables 2–4).[10,59]

Any correlation between cytology and histology **must** be with the *targeted* lesion, as pickup of malignant lesions can skew the correlation when identified incidentally (see Table 3).[4]

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.[50] 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 as compared to the text report, rate of insufficient samples per individual aspirator, 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 MDT members and shared with other relevant interested parties as necessary (e.g. commissioners, Cancer Peer Review). Monitoring thyroid cytology reporting using tools such a CUSUM graph can help identify trends with time.[60]

Content and timeliness of histopathology reports should be audited against the recommendations in these guidelines.

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

The following are recommended by the RCPath as key performance indicators (KPIs) – see *Key Performance Indicators – Proposals for implementation* (July 2013) on www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html

- Diagnostic cytopathology (and histopathology) cases that are reported, confirmed and authorised within seven and ten calendar days of the procedure.

  *Standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days*.

- Monitoring delayed cellular pathology reports requires there to be a documented system in place to identify, manage and report cases remaining unreported longer than is anticipated. Exception reporting must be undertaken of all cases (including decalcified cases) remaining unreported after 20 calendar days).

  *Standard: 100% compliance*.

A template for thyroid cytology audit can be found on The Royal College of Pathologists website (www.rcpath.org/profession/quality-improvement/conducting-a-clinical-audit/clinical-audit-templates.html)

## 7 Diagnostic accuracy

Published data regarding thyroid cancer detection for thyroid FNA[48,61] indicate a sensitivity for malignancy of typically between 65% and 98%, specificity of 76–100%, with a false-negative rate of 0–5%, a false-positive rate of 0–5.7%, and an overall accuracy of 69–97%.[62,63] One of the problems with comparison of international data is how results are categorised and analysed. It is hoped that a greater international consensus on how this is done will aid such comparisons (Table 1). That said, results such as those quoted should be achievable and sustainable with suitable training and audit (Tables 2–4). However, the quoted outcome figures will depend on length of follow up and ultimately correlation with any surgical specimens (if taken).[64] Some data currently exists on the overall percentage of report categories and outcome on the RCPath system itself (Table 3). However, Bongiovanni *et al*

(2012) in their meta-analysis of the TBS system literature indicated indicative FNA category and outcomes rates, as shown in Table 4.[61]

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

## 8 External quality assurance

A technical EQA scheme is now available, operated by UK NEQAS CPT.[50] No known routine UK interpretative thyroid cytology scheme exists, although one may develop in the future. All laboratories should ideally be compliant with UKAS or a similar scheme, and hence achieve relevant ISO standards.

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

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

## 9 Ancillary testing

Ancillary immunohistochemical techniques can be helpful for diagnosis of specific thyroid lesions. Examples are:

- medullary thyroid carcinoma, typically calcitonin +ve, CEA+ve, chromogranin +ve, synaptophysin +ve, TTF1 +ve, thyroglobulin –ve
- assisting in confirming the diagnosis in problematic cases/to help better classify the type of tumour thyroid primary well differentiated papillary carcinoma – typically thyroglobulin +ve, TTF1 +ve, HBME1 +ve, PAX 8 +ve, CK19 +ve and CD56 –ve.[67]
- lymphomas or other rarer primary thyroid lesions or metastatic tumours to the thyroid gland area, e.g. head and neck squamous cell carcinoma, other metastatic carcinomas or melanoma.

Immunohistochemistry can be performed on cytology or cell block material if available.

The use of molecular markers to aid in diagnosis and patient stratification for possible further treatment has grown significantly since the original guidance was written. Many laboratories may not be able to perform these further 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.[65–68]

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

## 10 Clinical action

The recommendations for clinical action as advocated by the BTA[7] are endorsed in general but it is considered preferable *not* to include these general clinical recommendations in cytology reports as not all relevant clinical and/or radiological information may be available to the cytopathologist at the time of reporting. Any decisions about patient management must 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, [62,64] and ones even classed as Thy1/1c or Thy2/2c categories, can benefit from MDT discussion, especially if there is any concern. Depending on local arrangements these may be reviewed/discussed locally or as part of a network MDT approach.

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## 12 Tables

### Table 1: Equivalence of terminology of thyroid cytology classifications

| RCPath | Bethesda[10] | Italian[11] | Australian[12] | Japanese[13] |
|---|---|---|---|---|
| **Thy 1**<br>**Non-diagnostic for cytological diagnosis**<br><br>**Thy 1c**<br>**Non-diagnostic for cytological diagnosis – cystic lesion** | **I. Non-diagnostic or unsatisfactory**<br>Virtually acellular specimen<br>Other (obscuring blood, clotting artefact, etc.)<br><br>Cyst fluid only | **TIR 1**<br>**Non-diagnostic**<br><br>**TIR 1c**<br>**Non-diagnostic cystic** | **1**<br>**Non-diagnostic** | **1**<br>**Inadequate** |
| **Thy 2**<br>**Non-neoplastic**<br><br>**Thy 2c**<br>**Non-neoplastic, cystic lesion** | **II. Benign**<br>Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)<br>Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context<br>Consistent with granulomatous (subacute) thyroiditis<br>Other | **TIR 2**<br>**Non-malignant** | **2**<br>**Benign** | **2**<br>**Normal or benign** |
| **Thy 3a**<br>**Neoplasm possible – atypia/non-diagnostic** | **III. Atypia of undetermined significance or follicular lesion of undetermined significance** | **TIR 3A**<br>**Low risk Indeterminate lesion (LRIL)** | **3**<br>**Indeterminate OR**<br>**Follicular lesion of undetermined significance** | **3**<br>**Indeterminate B Others** |
| **Thy 3f**<br>**Neoplasm possible, suggesting follicular neoplasm** | **IV. Follicular neoplasm or suspicious for a follicular neoplasm**<br>Specify if Hürthle cell (oncocytic) type | **TIR 3B**<br>**High risk Indeterminate lesion (HRIL)** | **4**<br>**Suggestive of a follicular neoplasm** | **3**<br>**Indeterminate A Follicular neoplasms**<br>**A-1 Favour benign**<br>**A-2 Borderline**<br>**A-3 favour malignant** |
| **Thy 4**<br>**Suspicious of malignancy** | **V. Suspicious for malignancy**<br>Suspicious for papillary carcinoma<br>Suspicious for medullary carcinoma<br>Suspicious for metastatic carcinoma<br>Suspicious for lymphoma<br>Other | **TIR 4**<br>**Suspicious of malignancy** | **5**<br>**Suspicious of malignancy** | **4**<br>**Malignancy suspected** |

| RCPath (cont'd) | Bethesda[10] | Italian[11] | Australian[12] | Japanese[13] |
|---|---|---|---|---|
| **Thy 5**<br>**Malignant** | **VI. Malignant**<br>Papillary thyroid carcinoma<br>Poorly differentiated carcinoma<br>Medullary thyroid carcinoma<br>Undifferentiated (anaplastic) carcinoma<br>Squamous cell carcinoma<br>Carcinoma with mixed features (specify)<br>Metastatic carcinoma<br>Non-Hodgkin lymphoma<br>Other | **TIR 5**<br>**Malignant** | **6**<br>**Malignant** | **5**<br>**Malignancy** |

**Table 2: The Bethesda system (TBS) for reporting thyroid cytopathology (with RCPath Thy system equivalents) with implied risk of malignancy**

| Diagnostic category (TBS/RCPath) | TBS risk of malignancy (%)[61,69,70] |
|---|---|
| Unsatisfactory BTS I/Non-diagnostic for cytological diagnosis (Thy1/Thy1c) | 0–10 |
| Benign BTS II/Non-neoplastic (Thy2/Thy2c) | 0–3 |
| Atypia of undetermined significance or follicular lesion of undetermined significance BTS III/<br>Neoplasm possible – atypia/non-diagnostic (Thy 3a) | 5–15 |
| Follicular neoplasm or suspicious for a follicular neoplasm BTS IV/<br>Neoplasm possible – suggesting follicular neoplasm Thy 3f | 15–30 |
| Suspicious for malignancy BTS V/<br>Suspicious of malignancy Thy4 | 60–75 |
| Malignant BTS VI/Malignant Thy5 | 97–100 |

**Table 3: Indicative RCPath category use and outcome** [71–73]

| RCPath category | % use of catgeory | PPV for malignancy (%) (in cases with proven appropriate histology) |
|---|---|---|
| Thy 1/1c | 18–22 | 4 |
| Thy 2/2c | 42–51 | 1.4 |
| Thy 3a | 5–10 | 17 |
| Thy 3f | 14–16 | Up to 40 |
| Thy 4 | 2–4 | Up to 68 |
| Thy 5 | 5–10 | Up to 100 |

**Table 4: Indicative FNA rate by category and outcome (where known) based on TBS system** [61]

| TBS category | % use of category | % malignant of known outcome cases (histology/clinical) |
|---|---|---|
| I | 13 | 16.8 |
| II | 59 | 3.7 |
| III | 9.6 | 15.9 |
| IV | 10.1 | 26.1 |
| V | 2.6 | 75.2 |
| VI | 5.4 | 98.6 |

**Table 5: Proposed SNOMED codes for thyroid cytology**
**(but see also reference 46 for more detailed SNOMED codes)**

| | |
|---|---|
| Site – Thyroid | T96000 |
| Procedure | P1149 |
| **Result** | |
| Thy1 | M09000 |
| Thy1c | M09010 |
| Thy2 | M09450 |
| Thy2c | M33790 |
| Thy3f | M69701 |
| Thy3a | M69700 |
| Thy4 | M69760 |
| Thy5 | M80013 |

## 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 cancer type<br>or<br>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 cancer type<br>or<br>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 cancer type<br>or<br>Extrapolation evidence from studies described in B. |
| **Grade D** | Non-analytic studies such as case reports, case series or expert opinion<br>or<br>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, 1 |
| 3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described | Foreword, 1 |
| **Stakeholder involvement** | |
| 4 The guideline development group includes individuals from all the relevant professional groups | Foreword, 1 |
| 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, 1 |
| 8 The criteria for selecting the evidence are clearly described | Foreword |
| 9 The strengths and limitations of the body of evidence are clearly described | Foreword |
| 10 The methods for formulating the recommendations are clearly described | 1 |
| 11 The health benefits, side effects and risks have been considered in formulating the recommendations | 1 |
| 12 There is an explicit link between the recommendations and the supporting evidence | 2–10 |
| 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 | All sections |
| 16 The different options for management of the condition or health issue are clearly presented | 10 |
| 17 Key recommendations are easily identifiable | 2–10 |
| **Applicability** | |
| 18 The guideline describes facilitators and barriers to its application | Foreword |
| 19 The guideline provides advice and/or tools on how the recommendations can be put into practice | 1 |
| 20 The potential resource implications of applying the recommendations have been considered | Foreword |
| 21 The guideline presents monitoring and/or auditing criteria | 6 |
| **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 |