# Rates of 'Thy 1-Non-Diagnostic' Thyroid FNA using the UK Royal College of Pathologists Thy Terminology. A systematic review of the literature comparing patients undergoing rapid on-site assessment (ROSE) and those that do not.

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RUNNING TITLE: '*Thy1 Thyroid FNA using the UK Royal College of Pathologists Terminology*'

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**Abstract**

**Introduction.** The UK Royal College of Pathologists (RCPath) Thy terminology is an internationally recognised system for reporting thyroid fine-needle aspiration. The terminology has been used throughout the United Kingdom and Ireland, in some parts of Italy and Switzerland, and elsewhere in the world. There is no systematic review of the literature which specifically addresses the use of the *non-diagnostic for cytological* diagnosis-*Thy1/Thy 1c* category in the UK RCPath terminology.

**Methods.** A comprehensive literature search of online databases was conducted in October 2019 specifically examining overall reported rates of Thy1 and Thy1c in aspirates classified according to the UK *Thy* terminology.

**Results.** 25 articles were identified showing a Thy1 rate of 13.4% (2540/18920). The studies were then stratified according to whether or not the patients underwent rapid on-site assessment (ROSE). 6.0% (353/5841; range 3.0-10.9%) of ROSE aspirates were Thy1 whereas 18.5% (2072/11204; range 7.9-43.3%) of non-ROSE patients were Thy1; ($p<0.05$). Three studies from 2016 reported Thy1c rates of 5.4%, 6.5% and 10.6% respectively, implying Thy1 rates excluding Thy1c aspirates of 20.9%, 8.7% and 12.7% respectively.

**Conclusion.** This systematic review of the literature shows relatively high rates of aspirates *non-diagnostic for cytological diagnosis-Thy1* in the peer-reviewed published literature using the UK terminology. Utilisation of ROSE appears to produce lower rates of Thy1 aspirates and ROSE should be considered if rates of *non-diagnostic for cytological diagnosis-Thy1/Thy 1c* are high.

**Keywords:** Thyroid – Cytology- Inadequate- Rapid On Site Evaluation – Thy Terminology- UK

## Introduction

The UK *Thy* terminology for reporting thyroid FNAC cytology is a standardised reporting terminology for thyroid fine-needle aspiration cytology (FNAC). The terminology evolved from pre-existing international[1] and UK terminology systems for reporting thyroid FNAC[2, 3] following the publication of the 2002 British Thyroid Association (BTA)/Royal College of Physicians of London *Guidelines for the Management of Thyroid Cancer in Adults*[4], the second edition in 2007[5] and the third edition in 2014[6]. In 2007 Bethesda National Cancer Institute Thyroid Fine Needle Aspiration (FNAC) State of the Science Conference took place[7] and in 2009 The UK Royal College of Pathologists (RCPath) published the first edition of the RCPath *Thy* terminology[8] which was revised in 2016[9]. The latest 2016 RCPath Thy terminology guidance has five major categories, namely the Thy1, *Non-diagnostic for cytological diagnosis*; Thy1c, *Non-diagnostic for cytological diagnosis – cystic lesion*; Thy2, *Non-neoplastic*; Thy2c, *Non-neoplastic – cystic lesion*; Thy3a, *Neoplasm possible – atypia / non-diagnostic*; Thy3f, *Neoplasm possible, suggestive of a follicular neoplasm*; Thy4, *Suspicious of malignancy* and Thy5, *Malignant*[9]. The *non-diagnostic for cytological diagnosis* category Thy1/Thy1c is the default diagnosis if a given sample is not of adequate epithelial cellularity or if the clinical setting suggests that the aspirate is not representative of the lesion. The purpose of this literature systematic review was to examine the peer-reviewed published literature to date utilising the UK RCPath Thy terminology to assess the published rates of Thy1 aspiration in the peer-reviewed literature, to identify specific patterns or trends and to ascertain the underlying reasons for Thy 1 aspirates.

## Material and Methods

### *The UK RCPath Terminology*

The 2016 UK RCPath terminology diagnostic criteria states that solid lesions which are adequate for diagnosis 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[9]. For *Thy1 non-diagnostic for cytological diagnosis* the RCPath guidance requires that the reason for an aspirate being *non-diagnostic for cytological diagnosis-Thy1* should be described in the cytology report, e.g. a sample that comprises entirely blood or so heavily bloodstained that epithelial cells or colloid cannot be visualized, samples that are acellular, or that have too low follicular epithelial cellularity to allow diagnosis not reaching the

cellular adequacy criterion, or aspirates which are technically unable to be evaluated, e.g. poorly spread, delayed air drying or fixation artefact, prominent crush artefact, or cells trapped in fibrin. There is a separate category for thyroid cysts, *Thy 1c*. These are cystic lesion fluid specimens which do not reach the follicular epithelial cell adequacy criterion and which contain mostly macrophages but without abundant colloid. The UK RCPath guidance suggests that cystic thyroid aspirates can be reported as '*the sample is in keeping with fluid from a cyst but there are no epithelial cells or colloid to confirm cyst type*'[9] and comments that there is a recognised risk of non-representative sampling especially in cystic papillary thyroid carcinomas. The RCPath guidance emphasises that it is important not to offer false reassurance on suboptimal epithelial cellularity, but equally recommends not to overstate the risk of malignancy in such cases, and suggesting careful assessment possibly with multidisciplinary discussion. The RCPath guidance aligns with The Bethesda System for Reporting Thyroid Cytology (TBSRTC) and other international reporting systems for reporting thyroid FNAC cytology, see table 1[7].

*Search strategy*

A comprehensive literature search was conducted using the online databases; Pubmed/MEDLINE, Scopus™ and ISI Web of Knowledge™. The search aimed to find original peer reviewed studies describing the rates of Thy1 aspirates among nodules cytologically classified according to the RCPath '*Thy*' system. A combination of the search subject terms ('thyroid' &, 'cytology' & 'Thy') was applied. A publication date starting limit of 2002 was applied as the first edition of the British Thyroid Association guidance was published in 2002[4]. The search was updated to October 16th, 2019 and no language restrictions were used. This approach identified a large number of studies; Pubmed/MEDLINE (91), Scopus™ (58) and ISI Web of Science (44)™. To expand the search, references in the retrieved articles were also screened to identify additional studies.

*Study selection*

The study inclusion criterion was peer-reviewed original articles reporting thyroid nodules undergoing FNAC and cytologically classified according to either the British Thyroid Association Guidance [4, 5] or the first[8] or second editions[9] of The RCPath Guidance on the Reporting of Thyroid Cytology. Dr Poller reviewed the titles and abstracts of the retrieved articles applying the study selection criteria and then

all authors independently reviewed the full-text of the remaining articles. Articles or audits available online but not published in peer-reviewed journals were excluded. Articles with overlapping patient or nodule data and case reports were not considered including patients undergoing rapid on-site assessment (ROSE) in one study where there was only one patient with a single Thy 1 aspirate in the group of patients undergoing ROSE [10].

*Data extraction*

For each included study, the following information was extracted independently in a piloted form: 1) study data (authors, year and journal of publication, country of origin, period of patient accrual); 2) number of cases in *Thy* 1 category; and 3) number of cystic cases in the Thy1c category if this was documented. Data was cross-checked, and any discrepancies were discussed and mutually resolved.

*Statistics.*

Cross tabulation chi-square was performed using *Statistica* 13.2, (formerly Dell Corporation, now Tibco Software Inc, 3303 Hillview Avenue, Palo Alto, Ca 94304, USA).

**Results**

In total 25 studies were identified. The publication dates ranged from 2009 to 2018 although patients were accrued from earlier time periods starting at the earliest in year 2000. In these 25 studies the total number of fine needle aspirates was 18,920 and the overall number of Thy1 aspirates reported was 2540 (13.4%); the range of Thy1 percentages in the individual studies was 3.0%-43.3%. In three studies (Gill et al. 2016[11], Glynn et al. 2016[12] and Parkinson et al. 2016[13]) it was possible to calculate number and/or percentage of Thy1c cystic aspirates. In the Gill et al. study[11] the percentage of Thy1c was 5.4%, in Glynn et al. 6.5% [12] and in Parkinson et al.10.6% [13]. These results are tabulated in table 2. It can be seen that exclusion of Thy1c cystic lesions does have an impact on Thy1 rates. If Thy1c cystic lesions are excluded according to the published literature the rate of Thy1 aspirates falls; in Gill et al. from 26.3% to 20.9 %[11], in Glynn et al. from 15.2% to 8.7%%[12] and in Parkinson et al. from 23.3% to 12.7%.[13]

The published literature was then reviewed to assess whether rapid on-site evaluation (ROSE) appeared to have any impact on Thy 1 aspiration rates. This literature review relied on the authors' methodology as published in the relevant articles. Of the 25 studies[10-34], 22 indicated whether or not ROSE was undertaken. If ROSE was not specifically mentioned in the methods section or elsewhere in the article it was assumed that ROSE was not undertaken. In three studies; Agarwal et al.[14], Lobo et al.[15] and Mehannah et al.[16] although ROSE was undertaken for some patients it was impossible to be certain of the exact numbers of patients undergoing ROSE and those that did not and so these three articles were excluded from further analysis. Data from Sharma et al.[24] is detailed in both Tables 3 and 4 as some patients underwent ROSE and some did not. Thyroid FNA patients undergoing ROSE assessment were excluded in one further article, Breeze et al.[10] as there was only one Thy 1 case in the ROSE patient subgroup.

Table 3 shows the results for the 6 studies with patients undergoing ROSE FNA's. In 6 published studies where ROSE was undertaken and reported using Thy terminology ROSE was undertaken by cytopathologists in three; Mihai et al.[17] Kelly et al.[33] and Khalil et al.[34]. In Sharma et al.[26] and Brophy et al.[27] ROSE was undertaken by biomedical scientists/cytotechnologists, and in Deandrea et al. the ROSE practitioners were not stated[19]. There were 353 of 5841 (6.0%) Thy1 aspirates in patients undergoing ROSE compared with 2072 (18.5%) Thy1 aspirates out of a total of 11204 FNAs for

patients that did not (Table 4). The rate of Thy1 aspirations for patients undergoing ROSE was much lower than for those which did not and this was statistically significant, $\chi 2= 380.25$, (df=1) $p<0.05$.

**Discussion**

This systematic review of the published literature shows wide variation in rates of Thy1 aspirates for thyroid FNAs reported using The British Thyroid Association and The UK Royal College of Pathologists Thy terminology. It also shows that the use of the '*Thy 1c'* category for cystic lesions as suggested in 2016 in the second edition of The Royal College of Pathologists Guidance on the Reporting of Thyroid Cytology Specimens does appear to have positively impacted on reported Thy1 rates if Thy1c aspirates are excluded.[11-13] The published literature shows an effect on Thy1 rates with utilisation of ROSE. Centres that utilise ROSE appear to have lower rates for Thy1 aspirates than those that do not.

The process involved in ROSE, an assessment which is undertaken by a biomedical scientist/cytotechnologist or by a qualified cytopathologist is that immediate feedback is given to the aspirator, not only on the quality of the sample, the cellularity and the need for re-aspiration, but also information may be given to the clinician and patient with a provisional diagnosis if a cytopathologist undertakes ROSE. A cytopathologist undertaking ROSE in combination with the sonographer or radiologist will have far more clinical information available than a cytopathologist situated remotely within a laboratory reporting aspirates received in the laboratory with only clinical information available from either the cytopathology clinical request form, and/or from reference to the archived images of the ultrasound of lesion(s) and the electronic patient record. It is therefore not surprising that ROSE whether undertaken by biomedical scientists or by cytopathologists tends to produce lower rates of Thy1 aspirates for thyroid FNA patients than for patients that do not undergo ROSE.

In this systematic review it was impossible to compare the use of ultrasound versus freehand FNA aspiration as most articles do not separately report the number of patients undergoing ultrasound FNA as compared to freehand FNA. However from 2010 onwards the majority if not all of patients would almost certainly have had fine-needle aspirates taken under ultrasound guidance as this appears to be the standard practice for most thyroid FNA's received in laboratories in the United Kingdom and in the other developed countries.

Some centres which undertake thyroid FNA are able to produce acceptable results without the use of ROSE. This is well documented in the literature. Witt and Schmidt in a review and meta-analysis of 8

studies of thyroid FNA showed an average thyroid FNA adequacy rate without ROSE of 83% compared to 92% with ROSE, although the impact of ROSE depended heavily on the initial inadequacy rate[35]. It cannot be argued therefore that ROSE is *essential* to providing a high quality fine needle aspiration service with low rates for Thy1. The three centres from the UK that reported rates for Thy 1c aspirates do not undertake ROSE including one large-volume centre, Newcastle[11-13]. Centres that do not utilise ROSE will require good training in neck ultrasound to ensure nodule selection is clinically appropriate and to avoid unnecessary sampling, excellent cytopathology support with close communication between the imager/aspirator and the cytopathologist, and high volumes of neck FNA to provide familiarity with diagnostically challenging nodules to ensure familiarity with and to obtain good quality cytology samples from difficult cases. Given however the high published Thy1 rates for thyroid FNA, and also unpublished data from a recent UK Endocrine Pathology Society 8 centre national audit showing similar high rates for Thy 1 aspirates, achieving acceptable Thy1 rates appears to be challenging and difficult without wide adoption of ROSE. Some centres overseas report rates of TBSRTC category 1/non-diagnostic thyroid FNA (equivalent to the UK Thy1) below 5%. These centres with very low non-diagnostic rates for thyroid FNA undertake cytopathologist ROSE with immediate reporting in the clinic or ultrasound room[36] or cytopathologists may take their own ultrasound guided FNA's[37, 38]. This is also the experience of some centres in the UK, with Guy's and St Thomas's Hospital in London showing rates of inadequate head and neck/thyroid FNA of 6.5% with use of ROSE[39].

Meta-analyses of TBSRTC in Western patients showed a pooled non-diagnostic FNA rate of 12.9%[40] and for Asian patients 12.2%[41] although neither meta-analysis stratified patients according to ROSE utilization. A meta-analysis of the risk of malignancy (ROM) for patients with preoperative FNAC classified according to the UK Thy terminology showed comparable results to meta-analyses of other internationally recognised reporting terminologies for pooled risk of malignancy for surgically excised nodules. The results for pooled ROM were Thy 1 12%, Thy 2 5%, Thy 3 22%, Thy 3a 25%, Thy 3f 31%, Thy 4 79%, and Thy 5 98%[42]. Hence the performance of the UK Thy terminology appears similar to TBSRTC and other terminologies, although the range of reported Thy 1 rates in the published literature is higher than would be expected.

In undertaking this sort of systematic review it is difficult to make definitive recommendations as the case mix and clinical settings vary. In another widely used thyroid cytology reporting system, the TBSRTC, the non-diagnostic rate shows wide variability among centres (1.8%-23.6%), with an overall value of 12.9%[40]. In the authors' opinion there could be a minimum acceptable rate for Thy1 aspiration excluding Thy 1c cystic lesions of no more than 10% to 15%. This could be achievable in a UK setting if the UK National Health Service implemented the recent recommendations of The Royal College of Pathologists Tissue Pathways for Diagnostic Cytopathology[43] which recommend rapid on-site assessment for fine-needle aspiration. Implementation of ROSE for ultrasound guided thyroid FNA could be cost-effective; cost neutral according to the costings of an economic modelling exercise undertaken previously[44]. Part of the issue in the UK setting is that there is no nationally inter-professionally agreed maximum acceptable rate for Thy1 aspirates and that case-mix; the mix of cystic and solid lesions undergoing aspiration may vary as may local resources, training, expertise and facilities. The Royal College of Radiologists in an audit template published on the Royal College of Radiologists website makes a recommendation of a minimum adequacy criterion of 70% for thyroid FNA[45]. In the authors' opinion this is undemanding and could be revised upwards to at least 85%, corresponding to an overall Thy1 rate excluding Thy 1c aspirates of 15% or lower. The practicalities of implementation of rapid on-site assessment for thyroid FNA in conjunction with thyroid and head and neck ultrasound clinics needs further discussion and evaluation within the UK setting but the published evidence from this systematic review of the literature suggests that implementation of rapid on site assessment (ROSE) for thyroid FNAs would be beneficial in centres where Thy1 rates are high.

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**Table 1 Internationally used terminology systems for Thyroid FNAC Cytology**

| RCPath | Bethesda | Italian | Australian | Japanese |
|---|---|---|---|---|
| **Thy1**<br>Non-diagnostic for cytological diagnosis<br><br>**Thy1c**<br>Non-diagnostic for cytological diagnosis – cystic lesion | **I**.<br>Non-diagnostic or unsatisfactory | **TIR 1**<br>Non-diagnostic<br><br>**TIR 1c**<br>Non-diagnostic cystic | 1<br>Non-diagnostic | 1<br>Inadequate |
| **Thy2**<br>Non-neoplastic<br><br>**Thy2c**<br>Non-neoplastic – cystic lesion | **II**.<br>Benign | **TIR 2**<br>Non-malignant | 2<br>Benign | 2<br>Normal or benign |
| **Thy3a**<br>Neoplasm possible – atypia / non-diagnostic | **III**.<br>Atypia of undetermined significance or follicular lesion of undetermined significance | **TIR 3A**<br>Low risk indeterminate lesion (LRIL) | 3<br>Indeterminate or follicular lesion of undetermined significance | 3 Indeterminate<br>B others |
| **Thy3f**<br>Neoplasm possible, suggesting follicular neoplasm | **IV**.<br>Follicular neoplasm or suspicious for a follicular neoplasm | **TIR 3B**<br>High risk indeterminate lesion (HRIL) | 4<br>Suggestive of a follicular neoplasm | 3 Indeterminate<br>A follicular neoplasms<br>A-1 favor benign<br>A-2 borderline<br>A-3 favor malignant |
| **Thy4**<br>Suspicious of malignancy | **V**.<br>Suspicious for malignancy | **TIR 4**<br>Suspicious of malignancy | 5<br>Suspicious of malignancy | 4<br>Malignancy suspected |
| **Thy5**<br>Malignant | **VI**.<br>Malignant | **TIR 5**<br>Malignant | 6<br>Malignant | 5<br>Malignancy |

**Table 2**

| Authors | Patients Accrued | Publication Year | | Total Number of FNA | Total Thy1 | % Thy 1 | % Thy 1c if stated |
|---|---|---|---|---|---|---|---|
| Mihai et al. [17] | Jan 2000-Dec 2007 | 2009 | UK | 2809 | 166 | 5.9 | |
| Tysome et al. [18] | Nov 2005-Dec 2007 | 2009 | UK | 520 | 57 | 11.0 | |
| Agarwal et al. [14] | 2006 | 2009 | UK | 230 | 18 | 7.8 | |
| Deandrea et al. [19] | 2000-2008 | 2010 | Italy | 927 | 51 | 5.5 | |
| Lobo et al. [15] | Jan 2008-Aug 2010 | 2011 | UK | 873 | 33 | 3.8 | |
| Raggiunti et al. [20] | Oct 2009-May 2010 | 2011 | Italy | 617 | 50 | 8.1 | |
| Maqbali et al. [21] | Mar 2005-Sept 2010 | 2012 | UK | 1657 | 264 | 15.9 | |
| Burgess et al. [22] | Jan 2011-June 2011 | 2013 | UK | 184 | 37 | 20.0 | |
| Mehanna et al. [16] | Nov 2008-May 2012 | 2013 | Ireland | 765 | 63 | 8.2 | |
| Breeze et al. [10] | 2012 | 2014 | UK | 76 | 20 | 26.3 | |
| Poller et al. [23] | May 2013-Jan 2014 | 2014 | UK | 207 | 50 | 24.1 | |
| Doddi et al. [24] | Jul 2006-Jul 2011 | 2015 | UK | 621 | 269 | 43.3 | |
| Sharma et al. [25] | Aug 2012-Feb 2013 | 2015 | UK | 292 | 74 | 25.3 | |
| Sharma et al. [26] | Jan 2010-Dec 2014 | 2015 | India | 945 | 75 | 7.9 | |
| Brophy et al. [27] | Jan 2011-Dec 2013 | 2015 | Ireland | 1032 | 80 | 7.7 | |
| Sakai et al. [28] | Sept 2011-Dec 2013 | 2016 | UK | 66 | 14 | 21.2 | |
| Gill et al. [11] | Not stated | 2016 | UK | 355 | 93 | 26.3 | 5.4 |
| Glynn et al. [12] | Jul 2008-Jul 2011 | 2016 | UK | 413 | 63 | 15.2 | 6.5 |
| Parkinson et al. [13] | Jan 2008-Dec 2014 | 2017 | UK | 2329 | 544 | 23.3 | 10.6 |
| Musa et al. [29] | Jan 2010-Dec 2016 | 2017 | Saudi Arabia | 269 | 111 | 41.3 | |
| Giusti et al. [30] | Jan 2011-Dec 2014 | 2017 | Italy | 1932 | 193 | 10.0 | |
| Kavanagh et al. [31] | Jul 2006-Mar 2013 | 2017 | Ireland | 724 | 156 | 21.5 | |
| Kelly et al. [33] | 2008-2012 | 2017 | Ireland | 293 | 25 | 8.5 | |
| Liu et al. [32] | Aug 2014-May 2015 | 2017 | UK | 96 | 13 | 13.0 | |
| Khalil et al. [34] | Not stated | 2018 | UAE | 688 | 21 | 3.0 | |
| **TOTAL** | | | | **18920** | **2540** | **13.4** | |

**Table 3 Patients Undergoing Rapid On Site Evaluation (ROSE)**

| Authors | Publication Year | | Total FNA | Total Thy1 | Thy1 % | ROSE Practitioner(s) |
|---|---|---|---|---|---|---|
| Mihai et al.[17] | 2009 | UK | 2809 | 166 | 5.9 | Pathologist |
| Deandrea et al.[19] | 2009 | Italy | 927 | 51 | 5.5 | Not stated |
| Sharma et al.[25] | 2010 | UK | 92 | 10 | 10.9 | Biomedical Scientist |
| Brophy et al.[27] | 2015 | Ireland | 1032 | 80 | 7.7 | Biomedical Scientist |
| Kelly et al.[33] | 2015 | Ireland | 293 | 25 | 8.5 | Pathologist |
| Khalil et al.[34] | 2017 | UAE | 688 | 21 | 3.0 | Pathologist |
| **Total** | | | **5841** | **353** | **6.0** | |

**Table 4 Patients Not Undergoing Rapid on Site Evaluation (ROSE)**

| Authors | Publication Year | | Total Number of FNA | Total Thy1 | % Thy 1 | % Thy1c if stated |
|---|---|---|---|---|---|---|
| Tysome et al. [18] | 2009 | UK | 520 | 57 | 11.0 | |
| Raggiunti et al.[20] | 2011 | Italy | 617 | 50 | 8.1 | |
| Maqbali et al. [21] | 2012 | UK | 1657 | 264 | 15.9 | |
| Burgess et al. [22] | 2013 | UK | 184 | 37 | 20.0 | |
| Breeze et al. [10] | 2014 | UK | 69 | 19 | 27.5 | |
| Poller et al. [23] | 2014 | UK | 207 | 50 | 24.1 | |
| Doddi et al. [24] | 2015 | UK | 621 | 269 | 43.3 | |
| Sharma et al. [25] | 2015 | UK | 200 | 64 | 32.0 | |
| Sharma et al. [26] | 2015 | India | 945 | 75 | 7.9 | |
| Sakai et al. [28] | 2015 | UK | 66 | 14 | 21.2 | |
| Gill et al. [11] | 2015 | UK | 355 | 93 | 26.2 | 5.4 |
| Glynn et al. [12] | 2016 | UK | 413 | 63 | 15.2 | 6.5 |
| Parkinson et al. [13] | 2016 | UK | 2329 | 544 | 23.3 | 10.6 |
| Musa et al. [29] | 2017 | Saudi Arabia | 269 | 111 | 41.3 | |
| Giusti et al. [30] | 2017 | Italy | 1932 | 193 | 10.0 | |
| Kavanagh et al. [31] | 2017 | Ireland | 724 | 156 | 21.5 | |
| Liu et al. [32] | 2017 | UK | 96 | 13 | 13.0 | |
| **TOTALS** | | | **11204** | **2072** | **18.5** | |