



The Royal College of Pathologists

Pathology: the science behind the cure

## Standards and datasets for reporting cancers

### Dataset for thyroid cancer histopathology reports

April 2010

**Coordinators:** Professor Timothy J Stephenson, Sheffield Teaching Hospitals NHS Foundation Trust  
Dr Sarah J Johnson, Royal Victoria Infirmary, Newcastle upon Tyne

<b>Unique document number</b>	G098
<b>Document name</b>	Dataset for thyroid cancer histopathology reports
<b>Version number</b>	2
<b>Produced by</b>	Professor Timothy J Stephenson, Sheffield Teaching Hospitals NHS Foundation Trust Dr Sarah J Johnson, Royal Victoria Infirmary, Newcastle upon Tyne
<b>Date active</b>	April 2010
<b>Date for review</b>	April 2012
<b>Comments</b>	In accordance with the College's pre-publications policy, this document was on The Royal College of Pathologists' website for consultation from 22 February to 22 March 2010. 40 items of feedback were received and the authors considered them and amended the document if deemed appropriate. Please email <a href="mailto:publications@rcpath.org">publications@rcpath.org</a> if you wish to see the responses and comments.  Dr Peter Cowling Director of Communications

The Royal College of Pathologists  
2 Carlton House Terrace, London, SW1Y 5AF  
Tel: 020 7451 6700  
Fax: 020 7451 6701  
Web: [www.rcpath.org](http://www.rcpath.org)  
Registered charity in England and Wales, no. 261035  
© 2010, The Royal College of Pathologists



## Contents

Foreword .....	3
1. Introduction .....	3
2. Clinical information required on the specimen request form .....	4
3. Specimen handling, description and block selection.....	5
4. Microscopic report.....	6
5. Core data items.....	7
6. Non-core data items.....	10
7. Recommendation: TNM pathological staging (seventh edition, UICC).....	10
8. SNOMED coding.....	11
9. Audit criteria .....	11
10. References .....	12
Appendix A TNM staging (seventh edition, UICC).....	16
Appendix B SNOMED codes .....	18
Appendix C Dataset for thyroid cancer histopathology .....	19
Appendix D Thyroid carcinoma dataset monitoring sheet (AGREE standards) .....	21

## Foreword

The Cancer Datasets published by the Royal College of Pathologists are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate health care for specific clinical circumstances and are based on the best available evidence at the time the dataset was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

The dataset has been reviewed by the Cancer Services Working Group and was placed on the College website for consultation with the membership from 22 February to 22 March 2010. All comments received from the Working Group and membership have been addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of the Professional Standards Unit.

No major organisational changes have been identified that would hinder the implementation of the dataset.

Each year, the College will ask the authors of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be revised.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; there are none.

## 1. Introduction

### 1.1. Endocrine cancer datasets

The management of endocrine tumours is the responsibility of an appropriately experienced multidisciplinary team (MDT). Since these tumours bridge various anatomical divides, they are dealt with by a number of specialist teams. Because several mimics of thyroid carcinomas exist,<sup>1,2</sup> the pathologist reporting them should ideally have a special interest in endocrine pathology. Alternatively, he/she should have an interest in endocrine tumours in his/her area of systematic pathology or, if a general pathologist, should participate in a network with the opportunity for specialist pathology review since observer variation is well documented in thyroid tumours<sup>3,4</sup> and the range of prognostic features<sup>5</sup> can require experience in their recognition. The reporting pathologist should either be a core member of the Thyroid Cancer MDT or have access to a pathologist who is a core member, for review purposes.

Each group of tumours is dealt with in a separate section. Although the guidelines of The Royal College of Pathologists (RCPATH) are primarily aimed at collecting core data in the reporting of cancers, we suggest that the endocrine guidelines also provide a useful template for the reporting of benign endocrine tumours and for hyperplastic conditions. We have therefore included some of these options in the dataset proforma (see Appendix C, section on adjacent thyroid).

### 1.2. Thyroid cancer dataset

The proper handling and reporting of the thyroid tumour specimen is important as gross and histological features contribute to the staging of the tumour, and this has implications for prognosis and therapy. There are several systems for staging thyroid tumours. The Royal College of Physicians (RCP) and the British Thyroid Association's recent guidelines<sup>6</sup> recommended the use of the TNM system of staging, using both its pathological component and the suggested conversion to clinical staging. Our recommendation is to adopt the *seventh* edition,<sup>7</sup> as it reinstates a therapeutically important feature of the fifth edition which was deleted in the sixth edition. We have restricted our recommended data to the pathological component of TNM; the seventh edition<sup>7</sup> may be consulted for detail of how to map this to the recommended clinical stage if desired locally.

These proposals for the reporting of thyroid cancers should be implemented for the following reasons:

1. Pathological staging is important in deciding the correct clinical management of these tumours.
2. Outcome has been shown to be related to particular features (e.g. variants of papillary carcinoma; minimal or wide invasion in follicular carcinoma, and since publication of the previous thyroid cancer dataset, number of foci of capsular and/or vascular invasion in encapsulated follicular variant papillary carcinoma, number of foci of vascular invasion in both minimally invasive and widely invasive follicular carcinoma<sup>8,9</sup> and the proper definition of poorly differentiated thyroid cancer).<sup>10,11</sup> These features should therefore be included in histopathology reports to:
  - a) provide prognostic information to the surgeon/physician treating the patient;
  - b) provide accurate data for cancer registration and national datasets.

This document has been devised to include the data required for a careful assessment of a thyroid cancer specimen. Where possible, it is evidence based. It has been widely discussed and approved by the UK Endocrine Pathology Society ([www.ukeps.net](http://www.ukeps.net)), the British Thyroid Association ([www.british-thyroid-association.org](http://www.british-thyroid-association.org)), the British Association of Endocrine and Thyroid Surgeons ([www.baes.info](http://www.baes.info)) and the British Association of Head and Neck Oncologists ([www.bahno.org.uk](http://www.bahno.org.uk)). Panels of specialist and general histopathologists acting on behalf of the College have also reviewed it.

The following text outlines the approach to be taken in handling specimens. Aspects of best practice in handling thyroid specimens have been reviewed<sup>12</sup> and there are descriptions of the clinically-oriented pathology of the thyroid.<sup>13</sup> A synoptic reporting proforma has been provided as an *aide memoire* for the core data on these neoplasms. This may be supplemented by a more detailed written report.

It is beyond the scope of this document to discuss the details of fine needle aspiration (FNA) cytology of thyroid, but most lesions should have had FNA before surgery, so a differential diagnosis may be available. The cytopathologist should be a member of the MDT or have access to a pathologist who is. The descriptive cytology report will inform the clinical decisions on management. We recommend additional use of the numerical categories Thy1–5 as proposed in the guidelines of the RCP/British Thyroid Association,<sup>6</sup> recently updated by the RCPATH in consultation with the British Society for Clinical Cytology and other interested parties.<sup>14</sup>

Intraoperative frozen section is occasionally used to confirm the diagnosis of papillary carcinoma, medullary or anaplastic carcinoma, or to identify lymph node involvement. It should not be used to differentiate follicular carcinoma from adenoma. This is because follicular carcinoma is an architectural diagnosis, based on the finding of capsular or vascular invasion which can be very focal. Incision of an unfixed specimen can, additionally, disrupt the capsule rendering subsequent assessment of the fixed tissue difficult. Even with papillary carcinoma, which can be diagnosed on frozen sections, extra care needs to be taken as the characteristic nuclei with their clearing are an artefact of formalin fixation/paraffin processing and they may not be fully developed in frozen sections<sup>15,16</sup>

## **2. Clinical information required on the specimen request form**

This should include full patient details, clinical presentation, results of previous cytology and biopsies, and of imaging investigations. The patient's thyroid hormonal status should be given where relevant, together with details of any hormonal or drug therapy and any familial cancer or endocrine tumour syndromes. If the operation has resulted in multiple specimens or parts thereof, then these should be catalogued explicitly. Any specimens which may be

difficult to orientate should have orientation markers attached and these should be described on the specimen request form, with diagrams where words alone will not suffice.

### **3. Specimen handling, description and block selection**

#### **3.1. Gross examination**

The specimen will usually be described as total (or near-total) thyroidectomy; right or left hemithyroidectomy (+/- isthmus) or isthmusectomy. It should be noted whether the thyroid capsule appears intact on receipt (excluding the intrathyroidal margin on lobectomy specimens).

The specimen should be weighed, measured and described grossly, particularly if there are any unusual features. In thyroidectomy specimens, measurements of each lobe and isthmus (plus pyramidal lobe if present) should be noted where possible. The surface should be inked. The specimen should then be sliced (usually transversely) at intervals no thicker than a tissue block, and the cut surfaces of all the slices should be inspected.

The appearance and location(s) of the lesion(s) should be noted. The inclusion of a diagram or photograph in the records with annotation of block selection is best practice. It is important to record the greatest dimension of the lesion (or of the largest lesion, if multiple) as this defines the pT status. If this is < 20 mm, the macroscopic size should be confirmed or adjusted by the microscopic measurement of size. The presence of macroscopically-apparent direct extension beyond the thyroid, which is prognostic,<sup>17</sup> should be recorded, including which anatomical structures are invaded, to inform the pT3/4 staging. Clearances from the thyroid capsule and relevant resection margins should be measured and noted. The site of any possible parathyroid glands should be noted and they should be sampled if present.

The number and site of lymph nodes submitted or identified in the main specimen should be recorded, and all the nodes should be sampled. Sampling of formal neck dissections should follow protocols published with the guidelines for tumours of the head and neck (<http://www.rcpath.org/index.asp?PageID=1158>). Central/level VI lymph nodes are often submitted with known papillary carcinoma specimens.

#### **3.2. Block selection**

The number of blocks taken will vary according to the tumour type. Tumour type may be known or suspected from any preoperative cytology, enabling appropriate block taking when the specimen is initially dissected. Alternatively, the specimen may require extra blocks to be taken after the initial histological diagnosis has been made. The use of mega blocks may be considered to show resection margin relationships to large lesions and they may show the entire circumference of capsule of such lesions in one section.

##### **3.2.1. Papillary carcinoma (PTC)**

For papillary carcinoma, there are few published studies regarding sampling. Some recommend that the whole gland is processed.<sup>18</sup> However, a more practical approach is to block the whole tumour if the lesion is  $\leq$  20 mm in diameter; if larger, it should be sampled widely enough (as a compromise we suggest at least two blocks per cm diameter of tumour) to permit diagnosis and to assess whether the tumour is of uniform type. Blocks of the tumour edge and of the thyroid margin closest to the tumour should be taken to assess completeness of excision. Any surgical excision margin within the thyroid (e.g. isthmus margin in a lobectomy specimen) should be processed. Any apparent extrathyroidal extension should be sampled. Apparently normal tissue from the ipsilateral lobe and the contralateral lobe (where present) should be examined carefully for evidence of tumour. Any suspicious areas, such as nodules or pale scarred-looking areas, should be sampled. Even when no other lesions are identified by naked-eye examination, two blocks of normal-

looking tissue should be taken from each lobe. This is to assess whether the lesion is single or multifocal, as multifocal lesions have a poorer outcome,<sup>19</sup> and to look for other background conditions. The presence of multifocal disease is reflected in the staging; therefore, if one papillary microcarcinoma (equivalent to stage pT1a)<sup>7</sup> is found, the rest of the specimen should be examined carefully for multifocality.

### 3.2.2. Follicular neoplasms

Follicular lesions that are not grossly invasive should be widely sampled at the interface between the tumour capsule and normal gland,<sup>15</sup> to detect capsular and/or vascular invasion. Some suggest that the total interface is examined histologically in all cases.<sup>20</sup> A more practical approach is to process small lesions ( $\leq 30$  mm in diameter) in their entirety and to take at least 10 blocks from larger lesions.<sup>21,22</sup> Where there are multiple nodules, the largest should be processed as described. Any others showing obvious encapsulation should also be sampled, as should those with unusual features, such as solid areas or a pale colour. Follicular lesions that are grossly invasive should be sampled widely enough to allow identification of any poorly differentiated carcinoma,<sup>10</sup> documentation of foci of vascular invasion,<sup>8,9</sup> measurement of distance to resection margins, and recognition of spread beyond the thyroid capsule with documentation of the tissues found to be invaded.

### 3.2.3. Medullary carcinoma

In cases of intrathyroidal medullary carcinoma, the specimen should be blocked adequately to confirm the diagnosis, recognise the relationship to the thyroid capsule and detect any extrathyroidal extension with definition of which tissues are invaded.<sup>18</sup> The non-involved gland may be examined for evidence of C-cell hyperplasia in an attempt to identify familial cases. C cells are usually found in the central parts of the middle and upper thirds of the lobes so these areas must be sampled. See section 5.3 regarding genetic testing for familial mutations which should be discussed at the MDTM and is tending to replace detailed histology for identification of C cell hyperplasia.

## 4. Microscopic report

There are a number of features that should be documented in all tumours, and specific features relating to the individual tumour types. Differentiated tumours may contain a minority component of more poorly differentiated tumour. Reports should specifically state whether or not any foci of poorly differentiated carcinoma have been found, as they may confer a worse prognosis.<sup>10,23</sup> Such poorly differentiated components may be recognised by tumour necrosis and elevated mitotic count,<sup>11</sup> as well as by growth pattern. Only when *poorly differentiated* carcinoma constitutes the *majority* ( $> 50\%$ ) of the tumour should the overall classification change. However, where there is *any* focus of *anaplastic change*, the tumour should be classified overall as undifferentiated/anaplastic (further, all anaplastic carcinomas are defined as stage pT4).<sup>7</sup>

### 4.1. Core data items for all malignant thyroid tumours

- Type of malignancy.
- Whether a carcinoma is a single lesion or multifocal.
- Maximum dimension of carcinoma (largest if multifocal).
- Closest distance to surgical resection margin.
- Extension into extrathyroidal tissues, which should be identified, and whether the extension is macroscopic or microscopic.
- Number of foci of any lymphatic/vascular invasion.
- Site and number of lymph nodes sampled and number of those involved.
- SNOMED codes, in a version approved by the local cancer registry.
-

## 4.2. Non-core data items

- Detailed tumour subtypes, beyond the core data, may be recorded.
- Incidental microscopic conditions in the background thyroid should be recorded:
  1. to account for macroscopically described lesions that have prompted block taking;
  2. when they may have affected the clinical impression of tumour extent (e.g. benign, background nodules); and
  3. when they may have clinical implications for the aftercare of the patient (e.g. thyroiditis).

## 5. Core data items

### 5.1. Papillary carcinoma

There are a number of variants which have to be defined as they are prognostically important.

#### Papillary microcarcinoma

A single classical papillary microcarcinoma ( $\leq 10$  mm in diameter) discovered incidentally in the examination of a hemithyroidectomy/thyroidectomy performed for another disease is not thought to have a significant risk of recurrence or metastasis. These should be defined separately.<sup>2,6,24</sup> When such a microcarcinoma is identified, any residual thyroid tissue should be examined carefully for multifocal disease. The report must state clearly whether there is unifocal or multifocal carcinoma as the recommended treatment differs.<sup>5,25–28</sup>

#### Clinical papillary carcinoma

These tumours present clinically as thyroid masses or with lymph node metastases. A number of variants of papillary carcinoma have been defined including the follicular variant, the encapsulated variant and the solid variant, all of which are thought to have a similar prognosis to the typical papillary carcinoma. It is important to differentiate the tall cell and columnar variants, as there is some evidence that these may show more aggressive behaviour.<sup>29,30</sup> The outcome of the diffuse sclerosing variant is a matter of debate.<sup>31,32</sup> As with follicular tumours, an oncocytic variant is also recognised but this should only be diagnosed when the characteristic nuclear features of papillary carcinoma are present. Papillary architecture in a follicular oncocytic tumour should not be misinterpreted.<sup>33,34</sup>

#### Follicular variant of papillary carcinoma (FVPTC)

Evidence is emerging that FVPTC should be divided into two entities: a non-encapsulated invasive type which has a metastatic potential like classical papillary carcinoma, and encapsulated type which has behaviour that is partially similar to follicular carcinoma.<sup>11,35</sup> In particular, encapsulated FVPTC has very low metastatic potential if no capsular or vascular invasion is found, leading some authors to recommend use of the term (which we have not adopted): “well differentiated tumors of uncertain malignant potential (WDT-UMP)”.<sup>36</sup> This metastatic potential increases significantly if four or more foci of capsular or vascular invasion are found in total, and even more if ten or more invasive foci are identified.<sup>11</sup> Some thyroid nodules have small, non-contiguous foci individually qualifying as FVPTC within them, posing a dilemma as to whether to regard these as multifocal microcarcinomas or as unifocal and equivalent to the maximum diameter of the whole nodule. The latter approach is recommended on the basis of molecular biological evidence that the entire extent of these lesions tends to have features of FVPTC.<sup>37</sup> The FVPTC may also show oncocytic change. As with the usual PTC, these are differentiated from oncocytic follicular tumours on the basis of nuclear features.

FVPTC is subject to observer variability in its diagnosis,<sup>3,4</sup> which relies upon identification of the defining nuclear features for papillary carcinoma: optically clear, enlarged, oval nuclei which have frequent nuclear grooves, some intranuclear cytoplasmic inclusions and may

overlap each other.<sup>3,4</sup> The threshold for referring lesions thought to be FVPTC to an expert thyroid pathologist should be low. In the hands of such pathologists, and in laboratories regularly performing immunohistochemistry on such tumours, the expression of recognised markers of papillary carcinoma, including its variants, can be useful in the identification of FVPC. The markers found to be useful include cytokeratin 19, high molecular weight cytokeratins and HBME1.<sup>38,39</sup>

The adverse histological subtypes of the rare tall cell and the even rarer columnar cell PTC variants, defined by their cell height to width ratio and their detailed nuclear features, should be specifically mentioned if present in other than occasional small foci.<sup>20</sup> To prevent over-diagnosis of the variant, we suggest a stringent approach to diagnosis of the tall cell variant, whereby a height to width ratio of 3x is required in the majority (> 50%) of the tumour. At present, grading of such tumour has not been included in the reporting proforma, although there is emerging evidence that grade, especially presence of the poorly differentiated grade (however defined), is important in prognosis.<sup>11,40,41</sup>

## 5.2. Follicular neoplasms

A follicular neoplasm is defined as carcinoma on the basis of capsular and/or vascular invasion. Capsular invasion is characterised by complete penetration of the capsule, often with capsular blunt-ended breaks. Care should be taken in assessing this, as the invading tongue of tumour may stimulate the formation of a neocapsule.<sup>1,4</sup> Entrapment of groups of cells or follicles in the capsule is not defined as invasion. Distinction between this entrapment and true invasion may need levels to be cut and/or the taking of further blocks. Pseudoinvasive changes may be seen following FNA.<sup>42,43</sup> These are usually accompanied by inflammation, haemosiderin deposition and/or new fibrosis.<sup>43</sup>

Vascular invasion is defined as invasion of large calibre vessels within or beyond the tumour capsule. The tumour cells should normally project into the vessel lumen, attach to the luminal aspect of the vessel wall and be covered by endothelium.<sup>21</sup>

Minimally invasive tumours show only focal microscopic vascular and/or capsular invasion. It is important to indicate whether there is only capsular invasion or whether the tumour is angioinvasive, and to define the frequency of vascular invasion. Tumours showing only capsular invasion have a minimal risk of metastasis. However, those with vascular invasion have a higher risk, and this increases with the frequency of vascular involvement, being demonstrably worse if four or more foci of vascular invasion are documented.<sup>9,11</sup>

The tumour is defined as widely invasive when it shows obvious gross invasion or extensive microscopic infiltration of thyroid parenchyma, capsular or extratumoural vessels, or extrathyroidal tissues. In most cases, these are not difficult to recognise. However, where the diagnosis is made on the basis of histology, there are no absolute published criteria for defining the threshold. Some would put otherwise minimally invasive tumours with high incidences (e.g. 10 or more) of demonstrable vascular invasion into this category, although we recommend leaving these in the minimally invasive category and communicating the adverse prognosis through recording in the dataset the number of foci of vascular invasion found. Widely invasive tumours have a worse prognosis than the minimally invasive lesions<sup>11</sup> and the prognosis worsens still further in proportion to the number of foci of vascular invasion found.<sup>9</sup>

For diagnostic purposes, oncocytic (Hürthle cell) follicular tumours are regarded as a variant of follicular tumours and the criteria for the assessment of malignancy are the same. This category should be restricted to tumours comprising at least 75% oncocytic cells.<sup>18,33,34</sup> More focal oncocytic change can be found in ordinary follicular lesions. The distinction from oncocytic follicular variant of papillary carcinoma is made on the nuclear features, as outlined above. Other variants of follicular carcinoma including clear cell and signet ring cell tumours are described, but there is no evidence that their behaviour is significantly different.<sup>18</sup>

For thyroid carcinoma, including the follicular category, there is emerging evidence there may be higher grade variants of tumour that confer a worse prognosis. In particular, the finding of a trabecular or solid growth pattern and/or a mitotic count of 1–4 per 10 hpf is thought to be associated with an adverse prognosis,<sup>7</sup> although we have not extended the dataset specifically to include this in the current revision.

### 5.3. Medullary carcinoma

In best practice, the diagnosis should be confirmed by calcitonin immunoreactivity. In the written histology report, it is usual to describe the cellular pattern, but this has no prognostic significance,<sup>45</sup> so is omitted from the dataset. The presence of amyloid, confirmed by appropriate histochemical stains, is thought to confer a better prognosis, but does not influence treatment, so again this is omitted from the dataset. Tumour desmoplasia is thought to be an adverse prognostic indicator,<sup>46</sup> but has been omitted from the dataset until there is further confirmation. In less well-differentiated tumours, where calcitonin immunoreactivity is lost, positivity for carcinoembryonic antigen (CEA) may serve as a surrogate marker.<sup>47</sup> Loss of calcitonin immunoreactivity is now considered not to be of adverse prognostic significance.<sup>44</sup>

In the syndromes of multiple endocrine neoplasia (MEN) Type 2 and familial medullary thyroid carcinoma (FMTC), medullary carcinoma is often multifocal and preceded/accompanied by C-cell hyperplasia.<sup>48</sup> However, the histological evaluation of C-cell hyperplasia can be difficult, as the normal range is not properly defined.<sup>49</sup> In addition, extension of the tumour within the gland may produce nodules in the near vicinity. Finally, the presence of C-cell hyperplasia may not necessarily correlate with familial disease as there are data to suggest that mild degrees can be found around other tumours and in a variety of other pathological conditions.<sup>45</sup> We suggest, therefore, that this diagnosis is only made when nodules of C cells, confirmed by calcitonin immunoreactivity, are found in blocks that do not contain the main tumour. Diagnosing C-cell hyperplasia histologically is optional as clinical guidelines recommend that all newly diagnosed patients with medullary carcinoma have genetic testing for RET mutations to detect familial syndromes.<sup>50</sup>

### 5.4. Poorly differentiated carcinoma

This group includes follicular cell-derived tumours with necrosis and/or with mitotic counts of 5 or more per 10 hpf.<sup>11</sup> Their growth patterns may be insular (the cells arranged in well-defined nests resembling pancreatic endocrine tumours),<sup>10</sup> trabecular or solid.<sup>51</sup> Before the tumour is placed in this category, the 'majority (> 50%)'<sup>7</sup> or 'predominant'<sup>11</sup> component should have this appearance. We have, however, included mention of minority components of poorly differentiated carcinoma in the dataset as there is a report that even the presence of a minor component of poorly differentiated carcinoma significantly worsens the prognosis.<sup>52</sup> It is also important to note that if the nuclei have the characteristic features of papillary carcinoma and the tumour has a solid growth pattern, then it should not be diagnosed as poorly differentiated carcinoma but as the solid variant of papillary cancer, which has a rather better prognosis than poorly differentiated carcinoma.<sup>51</sup>

It is important to recognise poorly differentiated carcinomas as they have a worse prognosis than differentiated carcinoma, although in the few instances where the poorly differentiated carcinoma only shows minimal invasion or is encapsulated, the prognosis is worsened to the same degree.<sup>11</sup> Poorly differentiated carcinoma usually expresses thyroglobulin, may or may not respond to radio-iodine treatment and is generally thought to represent part of the spectrum between differentiated and anaplastic tumours.<sup>53</sup> Where there is concern that a poorly differentiated appearing tumour may be C-cell derived (i.e. medullary carcinoma), the immunohistochemistry should include CEA and calcitonin antibodies as the term poorly differentiated carcinoma is reserved for follicular cell-derived tumours. Medullary carcinoma is classified as such irrespective of the growth pattern.

## 5.5. Undifferentiated/anaplastic carcinoma

Where a follicular or papillary carcinoma shows even a minor undifferentiated (anaplastic) component, the diagnosis is that of undifferentiated/anaplastic carcinoma.<sup>7</sup>

Most undifferentiated tumours will not have a surgical resection, but will be diagnosed by FNA or occasionally by open biopsy. Where a resection is performed, multiple blocks should be taken and immunostaining for thyroglobulin, TTF1 and calcitonin may be performed to attempt to identify a differentiated component. These stains are almost always negative in the anaplastic areas. Immunocytochemistry for cytokeratins (testing for a wide range is recommended) may confirm the epithelial nature.<sup>34,39</sup> Often, however, the diagnosis is one of exclusion, and the most important differential diagnosis to exclude is lymphoma,<sup>54,55</sup> as this has a radically different prognosis and treatment.

## 5.6 Mixed/combo combination tumours

When one or multiple foci recognisable as papillary carcinoma are present within what would otherwise be an encapsulated follicular adenoma, it is accepted convention to stage the tumour as a *unifocal* follicular variant papillary carcinoma equivalent to the *full size* of the encapsulated lesion.<sup>37</sup>

Other rare tumours include mixed follicular/medullary and mixed papillary/medullary carcinomas.<sup>56</sup> These may show immunohistochemical features of both components.

## 6. Non-core data items

### Tumour grade

We do not advocate use of tumour grading systems beyond the grades and types in the core data since only the latter have consistently proven to be of clinical significance.

### Histological subtypes beyond the core data

These may be included to facilitate teaching and research, and to demonstrate to any reviewing pathologist that they have been recognised, but their clinical significance has been proven to be low, compared with the core data.

### Parathyroids

Where possible parathyroid glands should be identified macroscopically, and processed to confirm their nature and the presence or absence of any pathology. The presence of any parathyroid tissue or glands should be stated in the report, to provide correlation with any clinical concerns over calcium status.

### Adjacent thyroid

It is recommended that pathological evidence of autoimmune thyroid disease (AITD) is recorded in the dataset. This may help elucidate the relationship between AITD and the pathogenesis of thyroid tumours and is good practice in correlating with clinical status. Incidental neoplasia may be found, such as incidental papillary microcarcinoma, prompting a search for multifocal disease or rendering an already-diagnosed papillary carcinoma multifocal.

## 7. TNM pathological staging (seventh edition, UICC)

The recommendation to use the *seventh* edition<sup>7</sup> (see Appendix A) is based on the fact that the pT1a cut-off is  $\leq 10$  mm, allowing the identification of papillary microcarcinomas as a separate group. This is important as they generally have a benign biological behaviour and may be treated by lobectomy and thyroid stimulating hormone suppression rather than total

thyroidectomy and radioactive iodine therapy.<sup>2,6</sup> In the *sixth* edition, these were grouped together with tumours up to 2 cm. The latter have a different prognosis and treatment, which led many groups at that time to recommend continued use of the fifth edition.

Resection (R) stage is deemed R0 when there is no microscopic evidence of true resection margin (RM) involvement. (No definition exists of a tumour distance from the RM that indicates RM involvement.) Microscopic RM involvement defines the stage as R1 while macroscopic RM involvement defines it as R2. For R2, the surgeon will typically infer that resection has been incomplete.

## **8. SNOMED coding**

See Appendix B.

## **9. Audit criteria**

The following standards are suggested as some of criteria that might be used in periodic reviews of the thyroid pathology service.

- Completeness of histopathology reports expressed as average proportion of the core data items recorded, or as proportion of the reports that successfully include 100% of the items – the standard is that all contain 100% of the items;
- Size distribution of tumour maximum diameters as a graph – the standard is that the distribution should be smooth and continuous with no obvious rounding of measurements, e.g. to nearest 0 or 5 figure;
- Number of lymph nodes found in specific specimen types;
- Inter- and intra-observer studies in classification of tumours.

## 10. References

1. Al-Sam S, Lakhani SR, Davies JD. *A Practical Atlas of Pseudomalignancy*. London: Hodder Arnold, 1998.
2. Lloyd RV, Douglas BR, Young WF. *Endocrine Diseases: AFIP Atlas of Nontumor Pathology*. Washington: American Registry of Pathology and Armed Forces Institute of Pathology, 2002.
3. Hirokawa M, Carney JA, Goellner JR, DeLellis RA, Heffess CS, Katoh R, *et al*. Observer variation of encapsulated follicular lesions of the thyroid gland. *Am J Surg Pathol* 2002;26:1508–1514.
4. Elsheikh TM, Asa SL, Chan JK, DeLellis RA, Heffess CS, LiVolsi VA, *et al*. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. *Am J Clin Pathol* 2008; 130: 736–744.
5. Stephenson TJ. Prognostic and predictive factors in endocrine neoplasia. *Histopathology* 2006;48:629–643.
6. *Guidelines for the Management of Thyroid Cancer* (2nd edition). Royal College of Physicians and British Thyroid Association, 2007.  
[http://www.british-thyroid-association.org/news/Docs/Thyroid\\_cancer\\_guidelines\\_2007.pdf](http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf)
7. Sobin LH, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours* (7<sup>th</sup> edition). Oxford: Wiley-Blackwell, 2009.
8. Ghossein RA, Hiltzik DH, Carlson DL, Patel S, Shaha A, Shah JP, *et al*. Prognostic factors of recurrence in encapsulated Hurthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer* 2006;106:1669–1676.
9. Collini P, Sampietro G, Pilotti S. Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hürthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. *Histopathology* 2004;44:35–39.
10. Decaussin M, Bernard MH, Adeleine P, Treilleux I, Peix JL, Pugeat M *et al*. Thyroid carcinomas with distant metastases: a review of 111 cases with emphasis on the prognostic significance of an insular component. *Am J Surg Pathol* 2002;26:1007–1015.
11. Ghossein RA. Problems and controversies in the histopathology of thyroid carcinomas of follicular cell origin. *Arch Pathol Lab Med* 2009;133:683–691.
12. Anderson CE, McLaren KM. Best practice in thyroid pathology. *J Clin Pathol* 2003;56:401–405.
13. Arora A, Tolley N, Tuttle RM. *Practical Manual of Thyroid and Parathyroid Disease*. Oxford: Wiley-Blackwell, 2009.
14. Royal College of Pathologists. *Guidance on the reporting of thyroid cytology specimens*. London, The Royal College of Pathologists, 2009.  
<http://www.rcpath.org/resources/pdf/g089guidanceonthereportingofthyroidcytologyfinal.pdf>
15. Thompson LDR. *Endocrine Pathology*. Philadelphia: Elsevier, 2006.
16. Osamura RY, Hunt JL. Current practices in performing frozen sections for thyroid and parathyroid pathology. *Virchows Arch* 2008;453:433-440.

17. Arora N, Turbendian HK, Scognamiglio T, Wagner PL, Goldsmith SJ, Zarnegar R *et al.* Extrathyroidal extension is not all equal: Implications of macroscopic versus microscopic extent in papillary thyroid carcinoma. *Surgery* 2008;144:942-948.
18. Rosai J, Carcangiu ML, DeLellis RA. *Atlas of Tumor Pathology: Tumors of the Thyroid Gland (3rd series)*. Washington: Armed Forces Institute of Pathology, 1992.
19. Loh KC, Greenspan FS, Gee L, Miller TR, Yeo PP. Pathological tumor-node metastasis (pTNM) staging for papillary and follicular thyroid carcinomas: a retrospective analysis of 700 patients. *J Clin Endocrinol Metab* 1997;82:3553–3562.
20. LiVolsi VA, Asa SL. *Endocrine Pathology*. Edinburgh: Churchill Livingstone, 2002.
21. Lester SC. *Manual of Surgical Pathology (2<sup>nd</sup> edition)*. Philadelphia: Churchill Livingstone, 2006.
22. Westra WH, Hruban RH, Phelps TH, Isacson C. *Surgical Pathology Dissection: An Illustrated Guide (2<sup>nd</sup> edition)*. London: Springer Verlag, 2003.
23. Sasaki A, Daa T, Kashima K, Yokoyama S, Nakayama I, Noguchi S. Insular component as a risk factor of thyroid carcinoma. *Pathol Int* 1996;46:939–946.
24. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. *World J Surg* 2008;32:747–753.
25. Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B *et al.* Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 1998;83:553–559.
26. Hay ID, Grant CS, van Heerden JA, Goellner JR, Ebersold JR, Bergstralh EJ. Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. *Surgery* 1992;112:1139–1147.
27. Lin JD, Kuo SF, Chao TC, Hsueh C. Incidental and nonincidental papillary thyroid microcarcinoma. *Ann Surg Oncol* 2008;15:2287–2292.
28. Chow SM, Law SC, Chan JK, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid – prognostic significance of lymph node metastasis and multifocality. *Cancer* 2003;98:31–40.
29. Prendiville S, Burman KD, Ringel MD, Shmookler BM, Deeb ZE, Wolfe K, *et al.* Tall cell variant: an aggressive form of papillary thyroid carcinoma. *Otolaryngol Head Neck Surg* 2000;122:352–357.
30. Ghossein R, LiVolsi VA. Papillary thyroid carcinoma tall cell variant. *Thyroid* 2008;18:1179–1181.
31. Albareda M, Puig-Domingo M, Wengrowicz S, Soldevila J, Matias-Guiu X, Caballero A, *et al.* Clinical forms of presentation and evolution of diffuse sclerosing variant of papillary carcinoma and insular variant of follicular carcinoma of the thyroid. *Thyroid* 1998;8:385–391.
32. Soares J, Limbert E, Sobrinho-Simões M. Diffuse sclerosing variant of papillary thyroid carcinoma. A clinicopathologic study of 10 cases. *Pathol Res Pract* 1989;185:200–206.
33. Asa SL. My approach to oncocytic tumours of the thyroid. *J Clin Pathol* 2004;57:225-232.

34. Montone KT, Baloch ZW, LiVolsi VA. The thyroid Hürthle (oncocytic) cell and its associated pathologic conditions: a surgical pathology and cytopathology review. *Arch Pathol Lab Med* 2008;132:1241–1250.
35. Rivera M, Tuttle RM, Patel S, Shaha A, Shah JP, Ghossein RA. Encapsulated papillary thyroid carcinoma: a clinico-pathologic study of 106 cases with emphasis on its morphologic subtypes (histologic growth pattern). *Thyroid* 2009;19:119–127.
36. Rosai J. The encapsulated follicular variant papillary thyroid carcinoma: back to the drawing board. *Endocr Pathol* 2010; 21; 7-11.
37. Baloch ZW, LiVolsi VA. Our approach to follicular-patterned lesions of the thyroid. *J Clin Pathol* 2007;60:244–250.
38. Prasad ML, Pellegata NS, Huang Y, Nagaraja HN, de la Chapelle A, Kloos RT. Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the differential diagnosis of thyroid tumors. *Mod Pathol* 2005;18:48–57.
39. Lam KY, Lui MC, Lo CY. Cytokeratin expression profiles in thyroid carcinomas. *Eur J Surg Oncol* 2001;27:631–635.
40. Akslen LA, LiVolsi VA. Poorly differentiated thyroid carcinoma – it is important. *Am J Surg Pathol* 2000;24:310–313.
41. Akslen LA, LiVolsi VA. Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. *Cancer* 2000;88:1902–1908.
42. Baloch ZW, LiVolsi VA. Post fine-needle aspiration histologic alterations of thyroid revisited. *Am J Clin Pathol* 1999;112:311–316.
43. LiVolsi VA, Merino MJ. Worrisome histologic alterations following fine-needle aspiration of the thyroid (WHAFFT). *Pathol Annu* 1994;29:99–120.
44. Polyzos SA, Patsiaoura K, Zachou K. Histological alterations following thyroid fine needle biopsy: a systematic review. *Diagn Cytopathol* 2009;37:455–465.
45. Franc B, Rosenberg-Bourgin M, Caillou B, Dutrieux-Berger N, Floquet J, Houcke-Lecomte M *et al.* Medullary thyroid carcinoma: search for histological predictors of survival (109 proband cases analysis). *Hum Pathol.* 1998;29:1078–1084.
46. Koperek O, Scheuba C, Cherenko M, Neuhold N, De Micco C, Schmid KW, *et al.* Desmoplasia in medullary thyroid carcinoma: a reliable indicator of metastatic potential. *Histopathology* 2008;52:623-630.
47. Kakudo K, Takami H, Katayama S, Matsuura N, Kamoshida S, Miyauchi A, *et al.* Carcinoembryonic antigen and nonspecific cross-reacting antigen in medullary carcinoma of the thyroid. *Acta Pathol Jpn* 1990;40:261–266.
48. LiVolsi VA. C cell hyperplasia/neoplasia. *J Clin Endocrinol Metab* 1997;82:39–41.
49. Mete O, Asa SL. Composite medullary and papillary thyroid carcinoma in a patient with MSN 2B. Case report and review of C-cell lesions of the thyroid. *Pathol Case Rev* 2009; 14: 208-213.
50. Bugalho MJ, Domingues R, Sobrinho L. Molecular diagnosis of multiple endocrine neoplasia Type 2. *Expert Rev Mol Diagn* 2003;3:769–779.

51. Volante M, Collini P, Nikiforov YE, Sakamoto A, Kakudo K, Katoh R, *et al.* Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. *Am J Surg Pathol* 2007;31:1256–1264.
52. Nishida T, Katayama S, Tsujimoto M, Nakamura J, Matsuda H. Clinicopathological significance of poorly differentiated thyroid carcinoma. *Am J Surg Pathol* 1999;23:205–211.
53. Lam KY, Lo CY, Chan KW, Wan KY. Insular and anaplastic carcinoma of the thyroid: a 45-year comparative study at a single institution and a review of the significance of p53 and p21. *Ann Surg* 2000;231:329–338.
54. Royal College of Pathologists and BCSH. *Best Practice in Lymphoma Diagnosis and Reporting*, 2008.  
[http://www.bcsghguidelines.com/pdf/best\\_practice\\_lymphoma\\_diagnosis.pdf](http://www.bcsghguidelines.com/pdf/best_practice_lymphoma_diagnosis.pdf)
55. Royal College of Pathologists. *Tissue Pathways for Lymph Node, Spleen and Bone Marrow Trephine Biopsy Specimen*, 2008.  
<http://www.rcpath.org/resources/pdf/g062tplymphspleenbonefinalmay08.pdf>
56. Monden T, Mori M. Many faces of mixed medullary-follicular and papillary carcinoma of the thyroid. *Intern Med* 1998;37:909–910.

## Appendix A Pathological TNM staging (UICC edition 7)<sup>7</sup>

- pTX Primary tumour cannot be assessed
- pT0 No evidence of primary tumour
- pT1a ≤ 10 mm, limited to thyroid
- pT1b ≤ 20 mm but > 10 mm, limited to thyroid
- pT2 > 20 mm, ≤ 40 mm, limited to thyroid
- pT3 > 40 mm, limited to thyroid or any tumour with minimal extrathyroidal extension, e.g. extension to sternothyroid muscles or perithyroid soft tissues
- pT4a Tumour invades beyond thyroid capsule and invades any of: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
- pT4b Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery

*All anaplastic carcinomas are considered pT4 tumours*

- pT4a Anaplastic carcinoma limited to thyroid
- pT4b Anaplastic carcinoma extends beyond thyroid capsule

Multifocal tumours (≥ 2 foci) of all histological types should be designated (m), the largest focus determining the classification, e.g. pT2(m)

- pNX Cannot assess regional lymph nodes
- pN0 No regional nodes involved
- pN1a Metastasis in level VI (pretracheal, paratracheal and prelaryngeal/Delphian) lymph nodes
- pN1b Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, III, IV or V) or retropharyngeal or superior mediastinal lymph nodes

M1 Distant metastases proven histologically (MX is not used in TNM v7 which considers that proof of M0 cannot be arrived at by surgical pathology alone)

- RX Cannot assess presence of residual primary tumour
- R0 No residual primary tumour
- R1 Microscopic residual primary tumour
- R2 Macroscopic residual primary tumour

## Clinical staging

This is mentioned for ease of reference as it may be mentioned in MDT discussion and in relation to clinical trials, but we recommend that pathology reports include only the pathological TNM staging. The translation of the pathological data into staging differs with the tumour type.<sup>6</sup>

In papillary and follicular carcinoma, there is evidence that prognosis is poorer in older patients and therefore different criteria are applied to patients under 45 years from those to patients aged 45 years and older. In medullary carcinoma, no age stratification applies.

All undifferentiated/anaplastic tumours are regarded as categories within stage IV.

### Papillary or follicular under 45 years

Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1

### Papillary or follicular 45 years or over

Stage I	T1a, T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3	N1b	M0
	T4a	N0, N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

### Medullary carcinoma

Stage I	T1a, T1b	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3	N1b	M0
	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

### Anaplastic/undifferentiated carcinoma

All are considered stage IV

Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

## Appendix B SNOMED codes

The codes for the more common types are:

Thyroid	TB6000 or T96000, depending on SNOMED edition used
Papillary carcinoma*	M80503
Follicular carcinoma*	M83303
Poorly differentiated carcinoma	M80213
Anaplastic carcinoma	M80203
Medullary carcinoma	M85103
C-cell hyperplasia	T96050 + M72000

\*When Hürthle (oncocytic) differentiation present, add M82903



Surname..... Forenames..... Date of birth.....  
Hospital no.....

---

**For all tumour types**

Confined to thyroid

Unifocal  Multifocal

Size ..... mm

Minimal extension beyond thyroid capsule into sternothyroid or perithyroidal soft tissues only, pT3

Microscopic extension beyond thyroid capsule into subcutaneous soft tissues, larynx, trachea, oesophagus or recurrent laryngeal nerve, pT4a

Microscopic extension beyond thyroid capsule into prevertebral fascia, mediastinal vessels or encasement of carotid artery, pT4b

Any macroscopic extension beyond thyroid capsule, pT4b

Lymphatic/vascular invasion Yes  Number of foci found ..... Uncertain  No

Total number of lymph nodes ..... Number of lymph nodes positive .....

Site of lymph nodes involved .....

Unilateral Level VI  Any other group  Unable to assess

Excision margins Free of tumour  Minimum distance .....mm  
Tumour present on microscopy  Tumour present macroscopically

---

**Adjacent thyroid**

Normal  Mild thyroiditis  Severe thyroiditis  Nodular goitre   
C-cell hyperplasia (medullary carcinoma only) Yes  No  Uncertain   
Other (define).....

**Comments**.....

---

**Parathyroids** identified Number ..... Site(s) ..... Pathology .....

---

**Stage** pT ..... pN ..... M1?  R .....

**Signature** ..... **Date**..... **SNOMED code TB6 M**.....

## Appendix D Thyroid carcinoma dataset monitoring sheet

The Cancer Datasets of the Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines ([www.agreecollaboration.org](http://www.agreecollaboration.org)). The sections of this dataset that indicate compliance with each of the AGREE standards are indicated in the table.

AGREE Standard	Section of dataset
<b>SCOPE AND PURPOSE</b>	
1. The overall objective(s) of the guideline is (are) specifically described	1
2. The clinical question(s) covered by the guidelines is (are) specifically described	1
3. The patients to whom the guideline is meant to apply are specifically described	1
<b>STAKEHOLDER INVOLVEMENT</b>	
4. The guideline development group includes individuals from all the relevant professional groups	1
5. The patients' views and preferences have been sought	N/A
6. The target users of the guideline are clearly defined	1
7. The guideline has been piloted among target users	Feedback follows use of a previous edition
<b>RIGOR OF DEVELOPMENT</b>	
8. Systematic methods were used to search for evidence	1
9. The criteria for selecting the evidence are clearly described	1
10. The methods used 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	3-5, 10
13. The guideline has been externally reviewed by experts prior to its publication	1
14. A procedure for updating the guideline is provided	Foreword
<b>CLARITY OF PRESENTATION</b>	
15. The recommendations are specific and unambiguous	3-5
16. The different options for management of the condition are clearly presented	3-5
17. Key recommendations are easily identifiable	3-5
18. The guideline is supported with tools for application	Appendix C
<b>APPLICABILITY</b>	
19. The potential organisational barriers in applying the recommendations have been discussed	1,3
20. The potential cost implications of applying the recommendations have been considered	N/A
21. The guideline presents key review criteria for monitoring and/or audit purposes	3-7
<b>EDITORIAL INDEPENDENCE</b>	
22. The guideline is editorially independent from the funding body	1
23. Conflicts of interest of guideline development members have been recorded	1