Carcinoma of the Thyroid Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided

◯ Information provided (select all that apply)

- ☐ Previous history of thyroid tumour or related abnormality, *specify*
- ☐ Relevant biopsy/cytology results, *specify*
- ☐ Imaging findings, *specify*
- ☐ Previous surgery/therapy, *specify*
- ☐ Relevant familial history, *specify*
- ☐ Presence of clinical syndrome, *specify*
- ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

◯ Not specified

☐ Total thyroidectomy

☐ Near total thyroidectomy

☐ Hemithyroidectomy

☐ Lobectomy

☐ Isthmusectomy

☐ Partial excision,[a] *specify type if possible*

☐ Lymph node dissection

☐ Other, *specify*

[a] *Anything less than a lobectomy excluding isthmusectomy, including substernal excision.*

OPERATIVE FINDINGS (Note 3)

◯ Not specified

Intra-operative macroscopic evidence of extrathyroidal extension

◯ Information not provided

◯ Not identified

◯ Identified, *specify location and tissue invaded*

Intra-operative impression of completeness of excision

◯ Information not provided

◯ Not identified

◯ R0/R1

◯ R2, *specify location*

Other, *specify*

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SPECIMEN(S) SUBMITTED (select all that apply) (Note 4)

- ◯ Not specified
- ☐ Thyroid gland
  - ☐ Left ☐ Right ☐ Isthmus
- ☐ Parathyroid gland(s)
- ☐ Lymph node(s), *specify site(s) and laterality*
- ☐ Other, *specify site(s) and laterality*

TUMOUR FOCALITY (Note 5)

- ◯ Unifocal
- ◯ Multifocal, *specify number of tumours in specimen (if >5 state such but no need to specify the number)*
- ◯ Cannot be assessed, *specify*

TUMOUR SITE (select all that apply) (Note 6)
(For the most clinically relevant tumour)

- ◯ Cannot be assessed
- ☐ Lobe
  - ☐ Left ☐ Right
- ☐ Isthmus
- ☐ Pyramidal lobe
- ☐ Soft tissue or muscle, *specify site(s) and laterality*
- ☐ Other, *specify site(s) and laterality*

TUMOUR DIMENSIONS (Note 7)

Maximum tumour dimension (largest tumour)

mm

Additional dimensions (largest tumour)

mm x mm

- ◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 8)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 9)
(Value list based on the World Health Organization (WHO) Classification of Tumours of Endocrine Organs (2025))

- ☐ Papillary thyroid carcinoma
  - ☐ Classic (usual, conventional) subtype
  - ☐ Columnar cell subtype
  - ☐ Diffuse sclerosing subtype
  - ☐ Encapsulated subtype
  - ☐ Infiltrative follicular variant
  - ☐ Hobnail subtype
  - ☐ Oncocytic subtype
  - ☐ Solid subtype
  - ☐ Tall cell subtype
  - ☐ Warthin-like subtype
  - ☐ Spindle cell subtype
  - ☐ Papillary carcinoma with fibromatosis/fasciitis-like/ desmoid type stroma
  - ☐ Other subtype, *specify*
- ☐ Follicular thyroid carcinoma (FTC)
  - ☐ FTC, minimally invasive
  - ☐ FTC, encapsulated angioinvasive
  - ☐ FTC, widely invasive
- ☐ Invasive encapsulated follicular variant papillary thyroid carcinoma
  - ◯ Encapsulated follicular variant papillary carcinoma, minimally invasive
  - ◯ Encapsulated angioinvasive follicular variant papillary carcinoma
  - ◯ Widely invasive follicular variant papillary carcinoma
  - ◯ Other invasive encapsulated follicular variant papillary thyroid carcinoma, *specify*
- ☐ Oncocytic carcinomas
  - ☐ Oncocytic carcinoma, minimally invasive
  - ☐ Oncocytic carcinoma, encapsulated angioinvasive
  - ☐ Oncocytic carcinoma, widely invasive
- ☐ High grade follicular cell-derived differentiated thyroid carcinoma
  - ◯ High grade follicular thyroid carcinoma, *specify subtype*
  - ◯ High grade invasive encapsulated follicular variant papillary thyroid carcinoma, *specify subtype*
  - ◯ High grade papillary thyroid carcinoma, *specify subtype*
  - ◯ High grade oncocytic carcinoma of the thyroid, *specify subtype*
  - ◯ High grade differentiated thyroid carcinoma, NOS
- ☐ Poorly differentiated thyroid carcinoma
  - ◯ Poorly differentiated thyroid carcinoma, NOS
  - ◯ Poorly differentiated oncocytic thyroid carcinoma
  - ◯ Other poorly differentiated thyroid carcinoma, *specify*

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HISTOLOGICAL TUMOUR TYPE (Note 9) **continued**

- ☐ Anaplastic thyroid carcinoma
  - ☐ Anaplastic thyroid carcinoma, NOS
  - ☐ Anaplastic thyroid carcinoma, squamous cell carcinoma subtype
- ☐ Medullary thyroid carcinoma
  - ◯ Low grade
  - ◯ High grade
- ☐ Mixed medullary and follicular-cell derived thyroid carcinoma
  - ☐ Mixed medullary-follicular carcinoma
  - ☐ Mixed medullary-papillary carcinoma
  - ☐ Mixed medullary and oncocytic carcinoma
  - ☐ Other mixed medullary and follicular-cell derived thyroid carcinoma, *specify*
- ☐ Salivary gland type carcinoma
  - ☐ Mucoepidermoid carcinoma
  - ☐ Secretory carcinoma
- ☐ Thymic neoplasms within the thyroid
  - ☐ Spindle epithelial tumour with thymus-like differentiation
  - ☐ Intrathyroid thymic carcinoma
- ☐ Thyroid tumours of uncertain cytogenesis
  - ☐ Sclerosing mucoepidermoid carcinoma with eosinophilia
  - ☐ Cribriform-morular thyroid carcinoma
- ☐ Embryonal thyroid neoplasm, thyroblastoma
- ☐ Other malignant thyroid tumours, *specify*

MITOTIC COUNT (Note 10)

- ◯ 0-2 mitoses/2 mm²
- ◯ 3-4 mitoses/2 mm²
- ◯ ≥5 mitoses/2 mm²

Exact mitotic count _____ /2 mm²

TUMOUR NECROSIS (Note 11)

- ◯ Not identified
- ◯ Present

TUMOUR ENCAPSULATION/CIRCUMSCRIPTION (Note 12)

- ◯ Encapsulated
- ◯ Infiltrative
- ◯ Other, *specify*

CAPSULAR INVASION (Note 13)

- ◯ Not applicable
- ◯ Not identified
- ◯ Present

LYMPHATIC INVASION (Note 14)

- ◯ Not identified
- ◯ Present

VASCULAR INVASION (Note 14)

- ◯ Not identified
- ◯ Present
  - **Type of vessel involved** (select all that apply)
    - ☐ Capillary
    - ☐ Vein
  - **Extent of vascular invasion**
    - ◯ Focal ◯ Extensive
      - Number of foci _____
  - **Extrathyroidal blood vessel invasion**
    - ◯ Not identified
    - ◯ Present

EXTRATHYROIDAL EXTENSION (select all that apply) (Note 15)

- ◯ Cannot be assessed
- ◯ Not identified
- ☐ Invasion into perithyroid fibroadipose tissue
- ☐ Invasion into skeletal muscle
- ☐ Invasion into subcutaneous soft tissue, larynx, trachea, oesophagus or recurrent laryngeal nerve
- ☐ Invasion into prevertebral fascia or encasing the carotid artery or mediastinal vessel

MARGIN STATUS (Note 16)

- ◯ Not involved
  - Distance of tumour to closest margin _____ mm
- ◯ Involved, *specify (anterior or posterior)*
- ◯ Cannot be assessed, *specify*

LYMPH NODE STATUS (Note 17)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found

Number of lymph nodes examined _____

- ◯ Not involved
- ◯ Involved
  - Number of involved lymph nodes _____
  - ◯ Number cannot be determined
  - Location of involved lymph nodes, *specify*

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LYMPH NODE STATUS (Note 17) **continued**

Greatest dimension of largest lymph node with metastasis ____ mm

Greatest dimension of largest metastatic focus in lymph node ____ mm

Extranodal extension[b]

- ◯ Indeterminate
- ◯ Not identified
- ◯ Present

[b] *Extranodal extension is synonymous with extracapsular extension/spread.*

OTHER PATHOLOGY (select all that apply) (Note 18)

- ◯ None identified
- ☐ Follicular nodular disease
- ☐ Diffuse hyperplasia
- ☐ Chronic lymphocytic thyroiditis
- ☐ Follicular adenoma
- ☐ Oncocytic adenoma
- ☐ Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
- ☐ C-cell hyperplasia
  - ◯ Unilateral ◯ Bilateral
- ☐ Other, *specify*

PARATHYROID GLAND STATUS (Note 19)

- ◯ Not identified
- ◯ Present
  - Number of parathyroid gland(s) found ____
  - ◯ Normal
  - ◯ Involved by carcinoma
  - ◯ Hypercellular/enlarged

ANCILLARY STUDIES (Note 20)

- ◯ Not performed
- ◯ Performed
  - **Anaplastic thyroid carcinoma BRAF p.V600E status** (select all that apply)
    - ☐ BRAF p.V600E positive
    - ☐ BRAF p.V600E negative
    - ☐ Molecular studies
    - ☐ Immunohistochemistry
  - **Medullary thyroid carcinoma**
    - Ki-67 proliferation index ____ %
  - **Other, *record test(s), methodology and result(s)***

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 21)

- ◯ Not applicable
- ◯ Not identified
- ◯ Present, *specify site(s)*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[c] (Note 22)

TNM Descriptors (only if applicable) (select all that apply)

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - post-therapy

Primary tumour (pT)[d]

- ◯ TX[e] Primary tumour cannot be assessed
- ◯ T1 Tumour 2 cm or less in greatest dimension, limited to the thyroid
  - ◯ T1a Tumour 1 cm or less in greatest dimension, limited to the thyroid
  - ◯ T1b Tumour more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
- ◯ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
- ◯ T3 Tumour more than 4 cm in greatest dimension, limited to the thyroid or with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)
  - ◯ T3a Tumour more than 4 cm in greatest dimension, limited to the thyroid
  - ◯ T3b Tumour of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)
- ◯ T4[f] Includes gross extrathyroidal extension into major neck structures
  - ◯ T4a Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
  - ◯ T4b Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery

Regional lymph nodes (pN)

- ◯ NX[e] Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis
  - ◯ N1a Metastasis in level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum
  - ◯ N1b Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, III, IV or V) or retropharyngeal

[c] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12th July 2024).*

[d] *Including papillary, follicular, poorly differentiated, Hürthle cell and anaplastic carcinomas.*

[e] *TX and NX should be used only if absolutely necessary.*

[f] *T4 has been added for clarity from AJCC TNM 8th edition.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a Core element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope

The dataset has been developed for the pathology reporting of thyroid resection specimens for carcinoma. Core needle biopsies and metastasis to the thyroid gland are not included. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), tumours of uncertain malignant potential (UMP), thyroid carcinomas arising from struma ovarii, thyroid carcinomas arising in thyroglossal duct cysts, sarcomas and lymphomas are not covered in the dataset.

This dataset is designed for the reporting of a total thyroidectomy or a single laterality specimen i.e., left or right. If both are submitted separately or if surgeries are done at different time points (e.g., completion thyroidectomy after initial lobectomy), then separate datasets should be completed. If multiple carcinomas are found in the same specimen, the dataset should be completed for the most clinically relevant tumour which is the one with the highest T stage and/or the one that has the most aggressive histologic features. For example, in the case of a papillary thyroid carcinoma with gross extension into muscle associated with a papillary carcinoma without adverse histologic features, the dataset should be filled for the tumour with

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gross extra-thyroid extension. The less aggressive tumour should be reported with a description limited to basic histopathologic features (such as size and location) under the tumour focality element. If tumours of different lineage coincide in the same specimen, then a dataset should be completed for each of these tumours. For example, if a lobectomy contains separate medullary and papillary carcinoma, a dataset should be completed for each of these carcinomas.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours of Endocrine Organs, 5th edition, 2025.[2]

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Note 1 – Clinical information (Core and Non-core)

Any clinical information relevant to the thyroid disease should be recorded.

If a pre-operative fine needle aspiration (FNA) or core biopsy has been performed, this should be recorded and the results of that biopsy briefly stated. If imaging has been performed, this should be recorded and the results briefly stated.

Previous thyroid surgery or medical treatments like anti-thyroid drug or radioactive iodine should be noted. Previous exposure of the neck to radiotherapy (e.g., for treatment of Hodgkin lymphoma) should be noted. The indication for performing the surgery should be recorded as many thyroid cancers are found incidentally in thyroid specimens removed for a purpose other than cancer.

Family history of thyroid cancers or features of other endocrine tumours or syndromes should be recorded. It is worth noting that gastrointestinal manifestations of an endocrine syndrome may present before identification of an endocrine tumour.

Clinical or biochemical evidence of hyperthyroidism or hypothyroidism should be noted.

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Note 2 – Operative procedure (Core)

The thyroid gland ordinarily is composed of a right and a left lobe lying adjacent and lateral to the upper trachea and oesophagus. An isthmus connects both lobes, and in 20-30% of cases a pyramidal lobe is present extending cephalad anterior to the thyroid cartilage. Surgical management of thyroid tumours consists of either a lobectomy (removal of a lobe), a hemithyroidectomy (resection of lobe and isthmus), subtotal/near-total thyroidectomy or total thyroidectomy. Cases with lobectomy followed by completion thyroidectomy in the same operative procedure should be classified as total thyroidectomies. Other procedures include completion thyroidectomy, isthmusectomy, central compartment or lateral neck node dissection. In some instances, the type of procedure cannot be categorised and should be documented as ‘not specified’.

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Note 3 – Operative findings (Core)

It is expected that the surgeon provides information regarding the presence or absence of gross extrathyroidal extension (ETE) at the time of the surgical procedure, in particular involvement of strap muscles, as well as to the completeness of excision. Gross ETE is a crucial element in the TNM8 Staging Systems.[3,4] The pathologist should indicate if the intra-operative data on gross ETE or margin completeness is not available at the time of pathology reporting.

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Note 4 – Specimen(s) submitted (Core)

The nature of the specimen and laterality (in lobectomy specimens and node dissection) must be reported.

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Note 5 – Tumour focality (Core and Non-core)

Multifocality is common in patients with papillary carcinoma and should be reported. It is defined as more than one focus of carcinoma in most publications.[5] This definition does not distinguish separate clonally unrelated primaries from intra-glandular spread. Some pathologists may prefer not to label tumours as multifocal if they believe the foci represent intraglandular spread.[6] Some authors define multifocality as the presence of two or more tumour foci separated by a distance of 5 millimetres (mm).[7] The consensus of the DAC is that the definition of multifocality should be left to the discretion of the pathologist.

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Note 6 – Tumour site (Core)

The thyroid may give rise to multiple foci of carcinoma in the same gland, designated as per the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) TNM8 with the descriptor '(m)'.[3,4] The designation of the tumour site - is applicable to the dominant excised carcinoma. The dominant tumour is defined as the most clinically relevant tumour because of its aggressiveness and/or its higher T stage. As such, it is often but not necessarily, the largest tumour. In cases of multiple lesions, the tumour characteristics of a second focus may be relevant and contribute to patient management, particularly if they are of a different histologic type (i.e., tumour 1 is papillary carcinoma and tumour 2 is medullary carcinoma). A second dataset should be generated for these instances. For additional tumour foci that do not alter management, only basic histopathological features (such as size and location) may be reported at the pathologist's discretion.

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Note 7 – Tumour dimensions (Core and Non-core)

The dimension is that of the microscopically proven dominant tumour, based upon a reconciliation of the imaging, macroscopic and microscopic findings. The dominant tumour is defined as the most clinically relevant tumour because of its aggressiveness and/or its higher T stage. As such, it is often, but not necessarily, the largest tumour. Tumour size has an impact on prognosis and is a component of TNM staging.[3,4,8] For example, papillary carcinomas measuring 10 mm or less are associated with an excellent prognosis, while tumours measuring over 40 mm are associated with a worse prognosis.[8] If the exact tumour size cannot be measured, the report should mention the reason such as specimen fragmentation or a grossly positive margin.

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Note 8 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise, in which case a subsequent reviewer would not have seen the gross specimen and would need to know the anatomic sites from which samples were taken for staging purposes. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 9 – Histological tumour type (Core)

All tumours of the thyroid should be given a type based on the most recent edition of the WHO Classification of Tumours of Endocrine Organs, 5th edition, 2025 (see Table 1).[2]

Papillary carcinoma and related lesions

Papillary carcinoma is the most common carcinoma type and consists of numerous named subtypes, though only a few of these currently have sufficient evidence to be considered clinically and biologically relevant. In the most recent WHO Classification, papillary thyroid carcinoma (PTC) is considered as mainly a BRAF p.V600E-like thyroid carcinoma and thus two entities that do not align with this molecular profile have been excluded, namely invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC) as RAS-like entity and cribriform morular thyroid carcinoma whose hallmark is dysfunction of APC and the beta-catenin pathway.[2] Below is the summary of the relevant entities. For further details refer to the latest WHO Blue Book.[2]

Classic papillary thyroid carcinoma (PTC) tall cell, hobnail and columnar subtypes

Classic (usual, conventional) papillary carcinoma is the most common and 'default' subtype of papillary carcinoma. Tall cell subtype of papillary carcinoma is a more aggressive subtype that has a higher prevalence of BRAF p.V600E mutations and is more frequently refractory to radioactive Iodine therapy.[9-11] Hobnail PTC is

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another aggressive subtype characterised by cells having nuclei that bulge from the apical surface.[2] High grade features (elevated mitotic count and tumour necrosis) are usually present and therefore many hobnail PTC qualify as high grade differentiated thyroid carcinoma (HGDTC).[12] The rare columnar cell PTC is a subtype characterised by columnar cells with pseudostratified nuclei. The prognosis of this entity depends on its encapsulation and infiltrative status.[13] Encapsulated tumours are usually minimally invasive and indolent while the infiltrative ones often display gross extra-thyroid extension, a large size and have high grade features (numerous mitoses, tumour necrosis).[13,14] Most can now be classified as HGDTC.[15] The term papillary microcarcinoma is not a histological subtype (used to define tumours measuring ≤10 mm) and should not be used anymore without a formal subtyping according to the most recent WHO Classification.[2] It is now required that these small tumours are subtyped as any other PTC (e.g., PTC classic subtype). The tumour formerly known as cribriform-morular variant of papillary thyroid carcinoma is no longer considered a form of papillary thyroid carcinoma in view of recent immunohistochemical evidence suggesting that these tumours may not be of follicular cell origin.[2,16] Therefore, these neoplasms are now labeled as cribriform morular thyroid carcinomas and they are under the category of thyroid carcinomas of uncertain cytogenesis.[16] Cribriform morular thyroid carcinoma should be distinguished from other thyroid neoplasms since they harbor *APC* or *CTNNB1* mutations and show an association with familial adenomatous polyposis coli (FAP), in some cases representing the first manifestations of the disease.[17]

Follicular variant and related lesions

Follicular variant of papillary carcinoma is important to document because it has been substratified based on outcome, mode of spread and molecular profile into completely encapsulated and infiltrative forms. Infiltrative follicular variant has a behaviour similar to classic papillary carcinoma, particularly in terms of propensity for nodal metastasis and are now classified as a subtype of PTC. Encapsulated follicular variant of PTC are RAS driven neoplasms that are extremely indolent when non-invasive (9,10). When invasive they tend to bypass lymph nodes and spread haematogenously in contrast to BRAF p.V600E-like PTC. They are, therefore, classified under a different section than PTC in the current WHO Classification as invasive encapsulated follicular variant of PTC.[2] The historical term variant is kept for IEFVPTC and infiltrative follicular variant while all other PTC variants are categorised as subtypes rather than variants. In the most recent WHO Classification,[2] IEFVPTC similarly to follicular and oncocytic carcinoma are subdivided into minimally invasive (capsular invasion (CI) only), encapsulated angioinvasive (any focus of vascular invasion) and widely invasive. For more details see paragraph on follicular and oncocytic carcinomas.

Many non-invasive encapsulated/well circumscribed follicular variants of papillary thyroid carcinoma can now be reclassified under the new designation NIFTP. This shift in nomenclature arose as an effort to encourage conservative management of these lesions given their extremely low risk of structural recurrence.[18] As NIFTP is not overtly malignant, it is technically not required to report these under this cancer protocol. However, it is encouraged to include them in the overall pathology report, though only limited parameters are relevant, namely size, laterality, and margin status.

It must be noted that not all tumours previously designated as non-invasive follicular variant of papillary thyroid carcinoma would qualify as NIFTP.[18] Several exclusionary criteria have been put forth in the initial publication of this entity and updated in the current WHO Classification[2] in order to ensure that the NIFTP category remains indolent[18] and are as follows: solid/trabecular or insular growth ≥30%, ≥1% true papillary growth , presence of psammoma bodies, tumour necrosis, ≥3 mitosis/2 mm^2, BRAF p.V600E mutation by immunohistochemistry or genotyping, morphology of another PTC subtype (such as tall cell). A key requirement for a NIFTP diagnosis is that the entire lesional border has been submitted for histologic evaluation. When a tumour fulfils these inclusion and exclusion criteria, NIFTP designation is appropriate. Of note, subcentimeter NIFTP and NIFTP with oncocytic features have been shown to have an outcome similar to NIFTP and now are accepted NIFTP subtypes in the current WHO Classification.[2,19,20] Encapsulated non-invasive follicular patterned tumours that contain NIFTP exclusion criteria should be termed Encapsulated non-invasive papillary carcinoma with a note highlighting the reason why they are not labelled as NIFTP

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(e.g., the diagnosis of conventional encapsulated PTC with predominant follicular growth pattern should be applied to those encapsulated non-invasive tumours that have psammoma bodies, ≥1% true papillae or are BRAF p.V600E positive by immunohistochemistry).

If an encapsulated follicular patterned tumour has questionable capsular/vascular invasion, the term of uncertain malignant potential (UMP) is used as a qualifier. These tumours are not required to be reported using this thyroid cancer protocol since their malignant potential has not been demonstrated yet. When the nuclear features of PTC are absent, these lesions are labelled as follicular tumour of uncertain malignant potential (FT-UMP), while if PTC nuclei are questionable or present, these neoplasms should be classified as well differentiated tumour of uncertain malignant potential (WDT-UMP).

Diffuse sclerosing subtype

Diffuse sclerosing subtype is a locoregionally aggressive tumour with a high rate of nodal metastasis and locoregional recurrence, though overall survival is good possibly because of the young age of the patients. Nonetheless, this subtype appears to necessitate more aggressive initial surgical management including more extensive node dissection.[21]

Other subtypes that may have distinctive histologic characteristics but are rare and with prognostic features not well defined and not validated include:

- Clear cell
- Oncocytic or oxyphilic
- Solid/trabecular
- Spindle cell
- Papillary thyroid carcinoma with fibromatosis/fasciitis-like stroma.

Follicular and oncocytic carcinomas

Follicular carcinoma is a well-differentiated thyroid carcinoma type defined by invasiveness in the absence of diagnostic nuclear features of papillary thyroid carcinoma. The diagnosis of follicular carcinoma and its distinction from follicular adenoma primarily depends on the identification of invasion of the tumour capsule and/or vascular spaces.

The most recent WHO Classification subdivides these carcinomas into minimally invasive (CI only), encapsulated angioinvasive (any focus of vascular invasion) and widely invasive.[2] The latter is defined as grossly apparent extensive invasion of the thyroid and/or extra-thyroid tissue with often prominent vascular invasion.[2] These widely invasive carcinomas are often characterised by loss of encapsulation and multiple invasive fronts radiating from the epicentre of the tumour. Oncocytic carcinoma previously known as Hürthle cell carcinoma is defined as a tumour composed of 75% of oncocytes lacking the nuclear features of papillary carcinoma and demonstrating capsular and/or vascular invasion.[2] The definitions of minimally invasive, angioinvasive and widely invasive oncocytic carcinoma mirror those of follicular carcinoma.

Although pathologists can diagnose benign from malignant thyroid tumours with very high accuracy, there are extremely rare cases with distant metastasis in a setting of non-invasive follicular and oncocytic carcinoma even after complete sampling of the tumour capsule.[22] There are also exceptional instances of regional nodal metastases without primary thyroid carcinoma found.[23] However, submission of the entire thyroid specimen and exhaustive multiple levels can help to identify a primary cancer.

While the majority of thyroid cancers of follicular cells are well differentiated and low grade, some are high grade, non-anaplastic or anaplastic (undifferentiated) carcinomas. These tumour types represent progression to an aggressive phenotype and are often seen with co-existent or antecedent well-

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differentiated carcinoma. While detailed histomorphologic review is beyond the scope of this protocol, salient features of both tumour types are listed below.

High grade follicular cell-derived non-anaplastic thyroid carcinoma

High grade non-anaplastic thyroid carcinoma of follicular cells have a prognosis in between the well differentiated indolent papillary thyroid carcinoma and the often fatal anaplastic carcinoma. These tumours are invasive with high grade features as defined by mitotic count and tumour necrosis and lack anaplastic histology.[2] They are subtyped as either poorly differentiated or HGDTCs if they retain the cytoarchitectural features of well-differentiated carcinomas of follicular cell derivation. According to the most recent WHO Classification, poorly differentiated thyroid carcinomas (PDTC) are tumours that display a solid, trabecular, and/or insular growth pattern, and show 1 or more of the following: 3 or more mitoses per 2 mm^2, tumour necrosis, and nuclear convolution (without other nuclear features seen in papillary carcinoma).[2,24] HGDTCs display the histologic features of well differentiated tumours, such as papillae and PTC nuclei, but must have a high mitotic count (5 mitoses/2 mm^2) or tumour necrosis. HGDTCs need be subclassified according to their dominant histotype. Most are high grade papillary thyroid carcinoma, usually of aggressive subtypes such as tall cell, hobnail, or columnar cell, but they can also be classic or follicular variant papillary thyroid carcinomas.[12,25-28] High grade follicular carcinomas are much less frequent and often widely invasive.[27,28] Oncocytic thyroid carcinomas often have a solid or trabecular growth, and therefore - when mitotically active or containing tumour necrosis - they usually fulfill the criteria for PDTC.[29,30] When there is no solid/trabecular/insular architecture, oncocytic thyroid carcinomas may fulfill criteria for HGDTC. Of note, encapsulated high grade follicular cell derived non-anaplastic thyroid carcinomas appear to have a more favourable prognosis than unencapsulated tumours, particularly if they show no vascular invasion with adequate sampling.[16,25,31,32] Very rarely, encapsulated non-invasive tumours of follicular cells with high grade features (high mitotic count/tumour necrosis) are encountered.[31] They usually have an indolent behaviour, although two cases were shown to develop distant metastasis.[16,33] There is currently no consensus on how to label these lesions given the paucity of outcome data. Further studies are needed to refine their nomenclature.

Anaplastic (undifferentiated) carcinoma

Undifferentiated carcinoma represents the most extreme form of tumour progression and consists of a high grade malignancy with spindled, pleomorphic, squamoid, or even rhabdoid morphology.[34] Undifferentiated carcinoma is almost invariably rapidly lethal. A better differentiated component such as PTC, FTC, or oncocytic carcinoma may be found and its presence should be mentioned. Of note, thyroid tumours with the histopathologic features of squamous cell carcinoma (previously known as squamous cell carcinoma of thyroid) are now recognised as a subtype of anaplastic thyroid carcinoma in the 5th edition of the WHO Classification.[2] Every anaplastic thyroid carcinoma should be reflexively tested for the BRAF p.V600E mutation using genotyping or the antibody directed at the mutated protein (VE1).[35-37] The latter was found to be highly reliable as well as very sensitive and specific for this mutation. This testing should be urgently performed since BRAF p.V600E mutated anaplastic carcinoma patients are candidate for BRAF and MEK inhibitors.[37,38] This therapeutic modality has been shown to be clinically active and, in some instances, produces impressive responses and hence has been approved by the FDA[39] In anaplastic carcinoma associated with a better differentiated component, it is encouraged to report the proportion of the anaplastic carcinoma. This is an optional (non-core) item.

Medullary thyroid carcinoma

This C cell derived carcinoma can now be graded under low and high grade using the International Medullary Thyroid Carcinoma Grading System (IMTCGS).[40]

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Table 1 : World Health Organization Classification of tumours of the thyroid.[2]

Descriptor	ICD-O codes[a]
Follicular thyroid carcinoma	8330/3
Medullary thyroid carcinoma	8345/3
Invasive encapsulated papillary thyroid carcinoma	8343/3
Papillary thyroid carcinoma	8260/3
Infiltrative follicular variant of papillary thyroid carcinoma	8340/3
Columnar cell papillary thyroid carcinoma	8344/3
Oncocytic papillary thyroid carcinoma	8342/3
Oncocytic carcinoma of the thyroid	8290/3
Insular carcinoma	8337/3
Anaplastic thyroid carcinoma	8020/3
Mixed medullary-follicular carcinoma	8346/3
Mixed medullary-papillary carcinoma	8347/3
Mucoepidermoid carcinoma	8430/3
Secretory carcinoma	8502/3
Hyalinizing trabecular tumour	8336/1
Cribriform carcinoma, not otherwise specified (NOS)	8201/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).[41] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site.

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Note 10 – Mitotic count (Core and Non-core)

The mitotic status should be reported in every thyroid carcinoma since it is an essential defining criterion for HGDTC and PDTC. It is also an essential parameter of the IMTCGS.[40] This is a two tiered grading system based on mitotic count, tumour necrosis (refer to **Note – 11 TUMOUR NECROSIS**) and Ki-67 proliferation index (refer to **Note – 20 ANCILLARY STUDIES**). A medullary carcinoma is considered high grade if it has any of the following three features: 1) 5 or more mitosis per 2 mm^2; 2) tumour necrosis; and 3) Ki-67 proliferation index ≥5%.[24,25] This IMTCGS has been shown to be an independent prognostic factor of outcome in a large international cohort of patients.[40] The vast majority of thyroid carcinomas (whether follicular or C cell derived) have very low mitotic activity and a mitotic count is required only in those cases with elevated mitotic activity (≥3 mitoses/2 mm^2). Mitotic count should be performed in the area of highest mitotic activity in 2 mm^2 which is approximately equivalent to 10 consecutive HPFs on most microscopes.[31,42] The Ki-67 proliferation index has been shown to correlate with outcome.[43,44] It has not been utilised in the commonly used definitions of HGDTC and PDTC and thus is not a required element for these entities. It is, however, a required element for the grading of medullary thyroid carcinoma. Ki-67 proliferation index should be performed manually or via image analysis; if the latter, specifying methodology, software, or technique is suggested.[45]

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Note 11 – Tumour necrosis (Core)

Tumour necrosis should be reported in every thyroid carcinoma since it is an essential defining criterion for HGDTC and PDTC as well as an essential parameter for grading medullary thyroid carcinoma.[2,24,25,40] Tumour necrosis is characterised by fragmented, devitalized cells, intermixed with karyorrhectic debris and apoptotic bodies, sometimes with comedo-like appearance. It should be differentiated from infarct-like necrosis related to previous FNA or ischemic changes within the tumour. Reactive changes seen in the infarct-like necrosis such as hyalinization or fibrosis, haemorrhage, hemosiderin laden macrophages, cholesterol clefts or calcification, should be separated from *bona fide* tumour necrosis.

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Note 12 – Tumour encapsulation/circumscription (Core)

The presence of a fibrous capsule or a well demarcated tumour border (i.e., well circumscribed tumour edge directly adjacent to benign thyroid parenchyma with no intervening capsule) is a crucial element in thyroid carcinomas. In follicular and oncocytic tumours, the invasion of the capsule and its vessels define malignancy.[2] Even in high grade tumours such as PDTC and HGDTC, the presence of a capsule was shown to convey a better outcome.[16,25] When a tumour infiltrates the surrounding non-neoplastic parenchyma and is not completely encapsulated/well demarcated, it should be labelled as infiltrative. Infiltrative papillary carcinomas are usually different from their encapsulated counterparts in regard to metastatic spread (propensity for nodal rather than distant metastasis) and genetic mutations (BRAF p.V600E rather than RAS mutations).[46,47]

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Note 13 – Capsular invasion (Core)

There is no consensus as to the definition of CI. While there is universal agreement that complete transgression of the capsule constitutes CI,[48] some authorities do not require complete transgression of the capsule.[49] Figure 1 depicts the various histologic appearances associated with the presence or absence of CI. According to Chan (2007),[48] a given neoplasm should not be diagnosed as carcinoma if complete capsular penetration cannot be proven after extensive sampling except in the following circumstance. This situation occurs when a satellite tumour nodule, morphologically similar to the main tumour, is lying just outside the tumour capsule (Figure 1e). This appearance results from failure to identify the point of capsular penetration. In equivocal cases of CI, the entire capsule, irrespective of tumour size, should be processed in attempt to clarify whether CI is present. Deeper sections of representative paraffin block(s) should be performed in the areas of concern in order to exclude CI.[48] Despite enhanced histologic examination, there are cases where the presence of CI is questionable. In this instance the term uncertain CI should be used. There is no need to report on the number of foci of CI since it has not been shown to have clinical value. CI is a core element for encapsulated tumours only while it is not applicable to non-encapsulated neoplasms.

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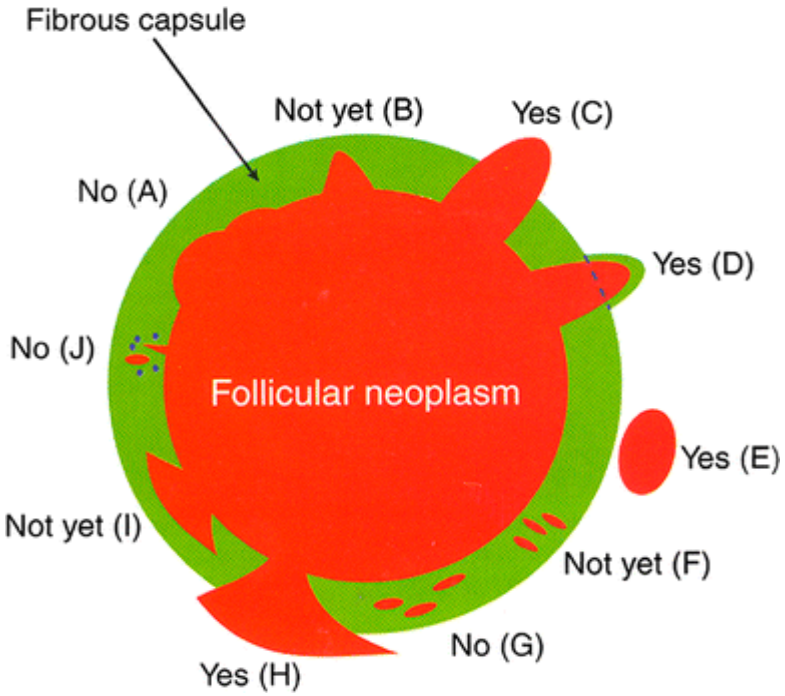

Figure 1: Capsular invasion. Capsular invasion (CI): Schematic drawing for the interpretation of the presence or absence of CI. The diagram depicts a follicular neoplasm (orange) surrounded by a fibrous capsule (green). **a** bosselation on the inner aspect of the capsule does not represent CI; **b** sharp tumour bud invades into but not through the capsule suggesting CI requiring deeper sections to exclude or confirm the presence of CI; **c** tumour totally transgresses the capsule invading beyond the outer contour of the capsule qualifying as CI; **d** tumour clothed by thin (probably new) fibrous capsule but already extending beyond an imaginary (dotted) line drawn through the outer contour of the capsule qualifying as CI; **e** satellite tumour nodule with similar features (architecture, cytomorphology) to the main tumour lying outside the capsule qualifying as CI; **f** Follicles aligned perpendicular to the capsule suggesting invasion requiring deeper sections to exclude or confirm the presence of CI; **g** Follicles aligned parallel to the capsule do not represent CI; **h** Mushroom-shaped tumour with total transgression of the capsule qualifies as CI; **i** mushroom-shaped tumour within but not through the capsule suggests invasion requiring deeper sections to exclude or confirm the presence of CI; **j** neoplastic follicles in the fibrous capsule with a degenerated appearance accompanied by lymphocytes and siderophages does not represent CI but rather capsular rupture related to prior FNA. Reproduced with permission from Chan J (2007). *Tumours of the thyroid and parathyroid glands*. Diagnostic Histopathology of Tumours. Fletcher CDM. Churchill Livingstone Elsevier, Philadelphia.[48]

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Note 14 – Lymphatic invasion (Core) and **Vascular invasion** (Core and Non-core)

As per the 5th edition of the WHO Classification,[2] in all endocrine and neuroendocrine neoplasms lymphatic invasion should be distinguished from angioinvasion (blood vessel invasion (BVI)). For the purpose of harmonisation between the reporting guides of various organs, the term vascular invasion refers to BVI and the type of vessel involved by BVI (capillary or vein) should be mentioned. All follicular carcinomas and the vast majority of oncocytic carcinomas spread hematogenously to distant sites bypassing lymph nodes, while most papillary carcinomas (with the notable exception of invasive encapsulated follicular variant papillary carcinoma) preferentially spread to lymph nodes. It is therefore assumed and has been confirmed by

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immunohistochemistry that the vessels invaded by tumour in IEFVPTC, follicular and oncocytic carcinoma are blood vessels while those in infitrative papillary carcinoma are usually but not always lymphatic spaces.[50,51] Invasion of the latter is however difficult to detect on hematoxylin and eosin (H&E) except in the rare diffuse sclerosing variant.[2,50] Furthermore, distinguishing between lymphatic and blood vessel invasion can be challenging. For example, red blood cells can be seen in thyroid lymphatics involved by PTC and intermediate sized lymphatics with a smooth muscle wall can be involved by PTC.[50] Based on the type of carcinomas and the histologic appearance of the vessel (e.g., large extra-thyroid vessel), the pathologist can in most instances indicate the type of vessel involved by tumour. There are however instances where this is not possible especially in small vessels in infiltrative PTC. In that situation, immunostaining for CD31, ERG and D2-40 can resolve the issue.

Since BVI is a crucial diagnostic and prognostic feature, the criteria for its identification should be well delineated.The majority of authors agree that BVI should involve capsular or extra-capsular vessels in encapsulated tumours (Figure 2). In infiltrative tumours partially encapsulated or totally lacking a capsule, BVI can be present within the tumour nodule. These images (Figure 2) depict intracapsular BVI with tumour thrombus attached to the vessel wall, covered by endothelium or associated with fibrin. Tumour thrombus covered by endothelial cells qualifies as BVI (Figure 2b). However, endothelialization is not a requirement if the tumour is attached to the vessel wall (Figure 2c) or admixed with a fibrin thrombus (Figure 2d). If the tumour is encapsulated, intra-tumoural or subcapsular vessels do not qualify for BVI and should not be interpreted as such (Figure 2a). One study has raised the caveat that tumour cells within vascular lumina unassociated with thrombus, and tumour cells underlying intact endothelium could represent 'pseudoinvasion' given the fenestrated, endothelial network of endocrine organs.[52] When this more stringent criterion of BVI is applied, the incidence of BVI in differentiated thyroid carcinoma decreased drastically from 7-62%[53-57] to 3%,[52] while the risk of distant metastasis in association with the mere existence of BVI becomes 35% highlighting the importance of fibrin associated tumour thrombi. While some experts have challenged the validity of some criteria to define BVI (scenarios B and C on Figure 2), the common consensus is to apply the criteria used in Figure 2 to define BVI.

In regard to the extent of BVI, several papers have shown that the presence of 4-5 foci of BVI in encapsulated follicular/oncocytic carcinoma confers a much worse outcome than lower number of BVI foci.[58-60] Other authors have found that the presence of two or more foci of vascular invasion as a negative predictor of disease free survival.[61] This difference may be due to the methods used to count foci of vascular invasion. The most recent American Thyroid Association (ATA) guidelines classify a patient in a high risk category, if having 4 foci or more of BVI, while focal BVI (<4 foci) in an intrathyroidal follicular carcinoma will put the patient in low risk group.[62] More importantly, the National Comprehensive Cancer Network (NCCN) 2025 guidelines have defined minimal vascular invasion as a few foci (1-4) of vascular invasion, and does not mandate radioactive iodine (RAI) administration in an intrathyroidal, well defined, follicular or oncocytic carcinoma, with minimal vascular invasion.[63] Consequently, it is important to report the extent of BVI in encapsulated thyroid carcinoma by counting the foci of BVI. It is noteworthy that most papers that validated the importance of BVI cutoffs have counted individual vessel sections invaded by tumour separately, as different foci. In regard to PTC, the presence of BVI was shown to impart poorer outcome.[56] Furthermore any focus of BVI in PTC will put the patient in an intermediate risk category according to the most recent ATA guidelines.[62] It is therefore mandatory to report on the status of BVI in PTC (i.e., core item). There is no evidence that the number of BVI foci impact prognosis in non-encapsulated PTC. Counting the BVI foci in non-encapsulated PTC is therefore not a core item. It is however a core item in those PTC which are completely encapsulated. In a small proportion of surgically operable, but locally aggressive differentiated thyroid carcinomas, tumour is identified within perithyroidal large veins or the internal jugular vein as large plugs of tumour thrombus. These patients often have synchronous distant metastases or are at higher risk to develop these subsequently. Whilst the presence of extrathyroidal BVI is not considered a separate core item in addition to BVI, there may be benefit in noting this finding if present.

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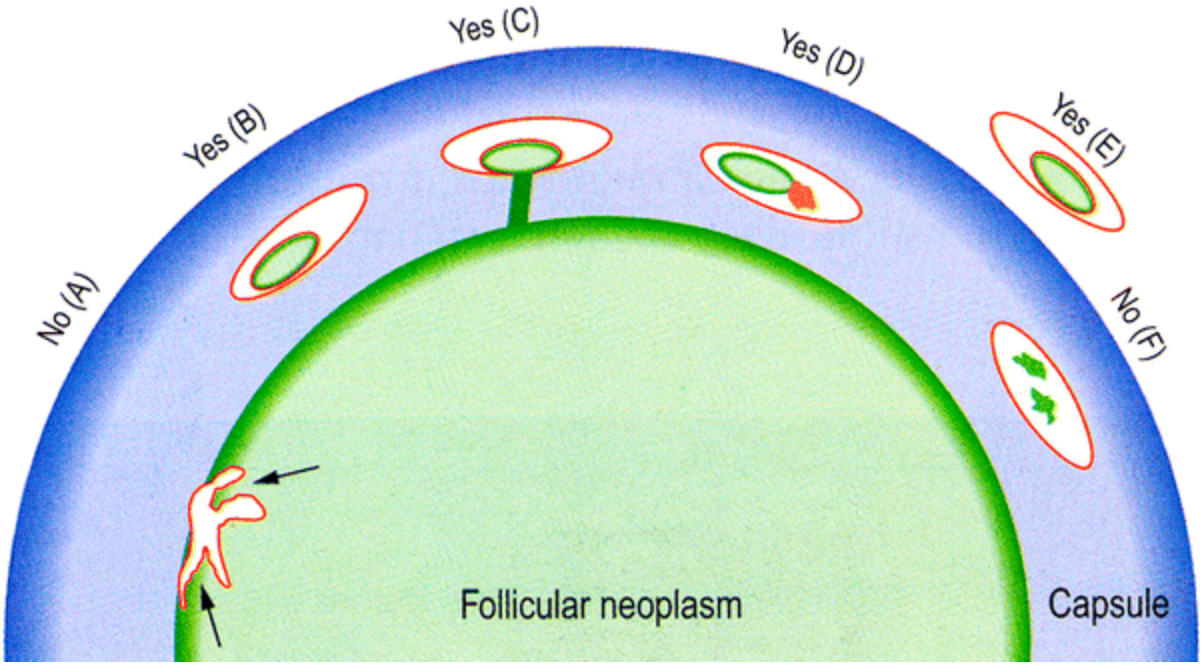

Figure 2: Blood vessel invasion (BVI). Schematic drawing for the interpretation of the presence or absence of BVI. The diagram depicts a follicular neoplasm (green) surrounded by a fibrous capsule (blue). **a** Bulging of tumour into vessels within the tumour proper does not constitute BVI. **b** Tumour thrombus covered by endothelial cells in intracapsular vessel qualifies as BVI. **c** Tumour thrombus in intracapsular vessel considered as BVI since it is attached to the vessel wall. **d** Although not endothelialized, this tumour thrombus qualifies for BVI because it is accompanied by a fibrin thrombus. **e** Endothelialized tumour thrombus in vessel outside the tumour capsule represents BVI. **f** Artefactual dislodgement of tumour manifesting as irregular tumour fragments into vascular lumen unaccompanied by endothelial covering or fibrin thrombus. Modified from the original version in Chan J (2007). *Tumours of the thyroid and parathyroid glands*. Diagnostic Histopathology of Tumours. Fletcher CDM. Churchill Livingstone Elsevier, Philadelphia.[48] Reproduced with permission.

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Note 15 – Extrathyroidal extension (Core)

Extrathyroidal extension (ETE), defined as tumour extension beyond the thyroid capsule into the adjacent soft tissue, is a common pathologic finding detected in 23.5% of all papillary thyroid carcinomas.[64] ETE has long been considered as an adverse prognostic factor with an increased risk of recurrence and mortality.[64-67] It can be further subdivided into two categories: 1) minimal (or microscopic) ETE, which is invasion into the immediate perithyroidal soft tissue, detected solely at microscopic level and not appreciated clinically or grossly at the time of surgery; and 2) extensive (or gross) ETE that is defined as gross direct extension of the carcinoma into strap muscles (e.g., sternohyoid, sternothyroid, thyrohyoid, and omohyoid muscles), subcutaneous tissue, adjacent viscera (e.g., larynx, trachea, and oesophagus), or recurrent laryngeal nerve, and is typically established clinically by imaging or during the operation. These two categories of ETE bear different prognostic values: the risk of recurrence associated with minor ETE is approximately 3 to 9%,[68-74] compared with 23 to 40% risk of recurrence in patients with gross ETE.[28,68,69,71-73,75] Furthermore, several studies have shown that microscopic ETE is not an independent predictor for persistent disease, recurrence free survival and disease specific survival.[28,70,71,74,76,77] The NCCN 2025 guidelines recommend completion thyroidectomy and post-operative RAI for lesions with gross ETE, while the administration of 30 millicurie (mCi) of iodine 131 is considered optional for patients with a primary tumour of <4 cm (40 mm), clinical M0

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and minor ETE.[63] Histologically, the thyroid gland is devoid of a well-defined capsule in many areas along its periphery, and the follicles are often intermingled with adipose tissue or even skeletal muscle.[78] Therefore, the very definition of microscopic ETE is problematic and subjective, and a universally accepted pathologic criterion for ETE is lacking. The fact that microscopic ETE is associated with poor interobserver agreement[78] and does not affect recurrence and survival raise concerns of whether microscopic ETE alone is sufficient to upstage a patient. Because of all the above, in the AJCC and UICC 8th editions, microscopic ETE has been removed entirely from the staging system of differentiated thyroid carcinoma.[3,4] Gross ETE invading strap muscles only, by a tumour of any size, will be staged as pT3b, while gross ETE with invasion into subcutaneous soft tissue, larynx, trachea, oesophagus, or recurrent laryngeal nerve will be staged as pT4a. In view of the above, the pathologists' role is 1) to document status of ETE in the pathology report (indicating whether microscopic or gross); and 2) correlate the histologic findings with the surgeon's intra-operative assessment of extrathyroidal extension.

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Note 16 – Margin status (Core and Non-core)

The margin status of a surgical resection for thyroid carcinoma is a core element and can be divided into three categories: a R0 resection (microscopically negative margin), a R1 resection (grossly complete resection with microscopically positive margin), and a R2 resection (grossly positive margin or incomplete resection).[3] The macroscopic status of the margins should be communicated to the pathologist by the operating surgeon. Histologically, a positive margin is defined by the presence of tumour cells at the inked tissue border and/or the outer aspect of the thyroid gland.[79-82] Several studies have shown that a microscopically positive margin is not an independent predictor for recurrence and disease free survival, especially after adjusting for tumour stage and ETE.[80-82] Taken these into consideration, the current ATA guideline has only included incomplete R2 resection as a feature of high risk lesions.[62] Lang et al (2016) have shown that a microscopically positive posterior margin is an independent predictor for recurrence free survival with a 23-fold risk of recurrence, while a positive anterior margin did not pose a significant risk for recurrence.[80] However, studies are scant on the prognostic effect of the positive margin location, hence, this is non-core. Nevertheless, we encourage pathologists to ink the anterior and posterior margins differently when processing thyroid specimens and document the status of anterior and posterior margins separately in the pathology report. There is no data to date on the prognostic value of close margins as an independent or co-variable. Therefore, reporting distance of tumour to margin is non-core.

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Note 17 – Lymph node status (Core)

Increasing evidence has shown that various characteristics of nodal metastases, e.g., number, size, and extranodal extension (ENE), may provide additional prognostic information. Thus, detailed features of nodal disease ought to be included in the pathology report, and be considered in risk stratification and staging systems.[76,83-90] A meta-analysis by Randolph et al (2012) has shown that small volume subclinical microscopic pathologic N1 disease, i.e., five or fewer subcentimeter metastatic lymph nodes, conveys little prognostic impact on recurrence free survival and disease specific survival in PTC, compared with clinically evident macroscopic nodal disease involving more than 5 lymph nodes, especially those with ENE.[83] The greatest dimension of the largest metastatic deposit in a lymph node should be measured. It is accepted it can be difficult to distinguish multiple small metastases in one large deposit. Many authors recommend measuring the greatest dimension end to end in a single slide including discontinuous deposits.[91] Taking this data into

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consideration, the NCCN 2025 guidelines no longer recommend completion thyroidectomy and post-operative RAI in small volume pN1a disease, i.e., <5 involved nodes with metastasis <2 mm in largest dimension.[63] Histologic features of the nodal metastasis that have been incorporated in the ATA initial risk stratifications included number of involved lymph nodes (>5 is considered as intermediate risk) and size of the metastatic lymph nodes (≥3 centimetres (cm) as high risk). The presence of psammoma bodies alone in a node is subject to controversy. While some practicing pathologists do not consider these as metastasis, the DAC are in agreement with the College of American Pathologists in considering these lymph nodes as positive for metastatic carcinoma.[42]

Extranodal extension (ENE) is not an uncommon finding, being reported in up to 12% of PTC overall and 33% of nodal metastatic PTC.[76,87] Similar to ETE, a well-defined, consensus, histologic diagnostic criterion for ENE is currently lacking.[42,92] A study by Du et al (2016) has shown that involvement of perinodal adipose tissue appears to be the most consistent diagnostic criteria of ENE, being considered by eleven participating endocrine pathologists as ENE.[92] However, the overall agreement in diagnosing ENE is only fair among expert pathologists.[92] Nevertheless, studies have repeatedly demonstrated the association between ENE and persistent and/or recurrence disease.[76,83-89] Hence, it is important to document ENE in the pathology report of a differentiated thyroid carcinoma.

A seven compartment nomenclature is used to define anatomic lymph nodes compartments. Central neck refers to level VI (peri-thyroidal, paralaryngeal, paratracheal, and prelaryngeal (Delphian)) and VII (upper mediastinal). Lateral neck refers to level I (submental/submandibular), II (upper jugular), III (mid jugular), IV (lower jugular) and V (posterior triangle).[93]

At the current time, no additional special techniques should be used other than routine histology for the assessment of nodal metastases (i.e., sentinel lymph node-type protocols are not advocated). However, confirmation by immunohistochemical staining, including thyroglobulin for papillary carcinoma and calcitonin and neuroendocrine markers (e.g., chromogranins, synaptophysin) for medullary carcinoma, may be required.

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Note 18 – Other pathology (Core and Non-core)

The presence of chronic lymphocytic thyroiditis, follicular adenoma, Oncocytic adenoma, NIFTP and follicular nodular disease (previously known as nodular hyperplasia) for example can help explain the clinical/imaging/cytologic findings.

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Note 19 – Parathyroid gland status (Core)

The number and status of the parathyroid glands in the specimen should be mentioned for surgical quality assurance purposes.

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Note 20 – Ancillary studies (Core and Non-core)

Ancillary studies may be used to determine lineage, disease classification or subclassification; as prognostic biomarkers; or to indicate the likelihood of patient response to specific therapies. In that regard, BRAF p.V600E testing by immunostaining or genotyping is core in anaplastic thyroid carcinoma since BRAF p.V600E mutated tumours may respond to MAPK inhibitors.[39] Immunostain for BRAF p.V600E mutation is an easy to perform, robust and rapid assay to select patients for BRAF inhibitor therapy. It can be done in lieu of genotyping.[36,37]

In established cases of medullary thyroid carcinoma, Ki-67 proliferation index is obligatory for grading using the IMTCGS.[40] Thus, BRAF p.V600E and Ki-67 testing are core elements in the setting of anaplastic and medullary thyroid carcinoma, respectively.

In cases in which the diagnosis is suspected to be medullary carcinoma, immunostaining for calcitonin, chromogranin, synaptophysin, carcinoembryonic antigen (CEA) and thyroglobulin may be performed to confirm the diagnosis. Calcitonin, monoclonal CEA, chromogranin and synaptophysin are also helpful to identify C-cell hyperplasia.

Thyroglobulin, thyroid transcription factor-1 (TTF-1) and PAX8 may indicate that a tumour is of follicular cell origin. TTF-1 is more sensitive than thyroglobulin however, TTF-1 can be positive in other cancers such as lung adenocarcinoma and small cell carcinoma of any primary site. Anaplastic thyroid carcinoma is negative for thyroglobulin, positive focally for TTF-1 in a small percentage of cases, but labels for PAX-8 in a substantial number of cases.[94]

Excluding BRAF p.V600E immunostain that indicates malignancy, it is not possible to differentiate benign and malignant thyroid tumours by using other immunohistochemical markersWhile other markers such as cytokeratin 19 and HBME-1 have been proposed as discriminating between benign and malignant thyroid lesions, there are too many exceptions in routine clinical practice and use of these markers is not considered helpful in making this distinction.

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Note 21 – Histologically confirmed distant metastases (Core)

The presence of histologically confirmed distant metastasis is a key component of staging.[2,3]

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Note 22 – Pathological staging (Core)

TNM staging should be assessed according to the agreed criteria of the UICC and AJCC 8th editions.[3,4]

TNM staging applies to all tumour types, including anaplastic carcinoma, which hitherto had automatically been staged as stage 4 irrespective of all other details.

The UICC/AJCC TNM 8th edition staging applies to carcinomas and includes papillary, follicular, poorly differentiated, Hürthle cell (oncocytic), anaplastic, and medullary carcinoma.[3,4]

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

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,[3,4] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[95]

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