Histological tumour type (Core)

All tumours of the thyroid should be given a type based on the most recent edition of the World Health Organization (WHO) Classification of Tumours of Endocrine Organs.[1]

Papillary carcinoma

Papillary carcinoma is the most common carcinoma type and consists of numerous named variants, though only a few of these currently have sufficient evidence to be considered clinically and biologically relevant. Thus efforts should be made to flag or document the following variants when present:

- Classic (usual, conventional)
- Follicular
    - Encapsulated/well demarcated follicular with invasion
    - Infiltrative follicular
    - Macrofollicular
- Tall cell variant
- Cribriform-morular variant
- Diffuse sclerosing variant
- Encapsulated variant
- Papillary microcarcinoma

Classical papillary thyroid carcinoma (PTC), tall cell and microcarcinoma variants

Classic (usual, conventional) papillary carcinoma is the most common and "default" variant of papillary carcinoma. Tall cell variant of papillary carcinoma is a more aggressive variant that has a higher prevalence of *BRAF* mutations and is more frequently refractory to radioactive Iodine therapy.[2-4] Papillary microcarcinomas are defined by their size (≤1 cm) and are extremely indolent and often incidental.[1] In this dataset, it is recommended but not required that they are subtyped according to their cytoarchitectural features (e.g., papillary microcarcinoma, classical)

Follicular variant and related lesions

Follicular variant of papillary carcinoma is important to document because it has recently been substratified based on outcome into completely encapsulated/well demarcated and infiltrative follicular variants which completely or partially lack a capsule. Infiltrative follicular variants have a behaviour similar to classic papillary carcinoma, particularly in terms of propensity for nodal metastasis, while the behaviour of encapsulated/well circumscribed follicular variant is more indolent, especially if non-invasive.[5,6]

There is a macrofollicular or diffuse follicular variant with diffuse involvement of the thyroid without formation of grossly discernible nodules.

Many, but not all, non-invasive encapsulated/well circumscribed follicular variants of papillary thyroid carcinoma can now be reclassified under the new designation non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). This shift in nomenclature arose as an effort to encourage conservative management of these lesions given their extremely low risk of structural recurrence.[7] It is noteworthy that the impact of this change worldwide varies according to countries. For example, many cases designated as NIFTP today were labelled in parts of Asia including Australia, as follicular adenomas and thus this new designation will have little effect on the practice of these pathologists. NIFTP remains an actionable surgical disease, albeit with a more conservative approach. 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.[7] Several exclusionary criteria have been put forth in the initial publication of this entity in order to ensure that the NIFTP category remains indolent[7] and are as follows: solid/trabecular or insular growth ≥30%, ≥1% true papillary growth (for more explanation see below), presence of psammoma bodies, tumour necrosis, ≥3 mitosis/10 high power fields (HPFs) at 400x magnification, tall cell, columnar, or cribriform morular morphology. 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.[8,9]

Multifocal NIFTP has not been well validated yet. In view of the small number of articles on these NIFTP scenarios, some pathologists do not label these unusual forms of this entity as NIFTP. In these situations, our opinion is that the designation, NIFTP, is not absolutely contraindicated. NIFTP is still an evolving diagnosis, and certain problematic areas have already been noted such as the quantification of true papillae. Because the initial criterion of <1%[7] papillae was noted to be subjective and difficult to apply, there was a suggestion that even 1 well-formed papilla as defined above should be considered exclusionary.[10] Studies are underway to resolve this issue. When an encapsulated non-invasive follicular patterned lesion with PTC nuclei does not fulfil the NIFTP inclusion criteria, they can be labelled as encapsulated variant. This variant is defined in the most recent WHO as an architecturally and cytologically typical PTC that is totally encapsulated but in the opinion of this expert panel it can be used to label encapsulated non-invasive follicular patterned lesions with PTC nuclei that do not meet the NIFTP criteria.[1]

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 (FTUMP) while if PTC nuclei are questionable or present the designation well differentiated tumour of uncertain malignant potential (WTUMP) is used.[1]

Diffuse sclerosing variant and cribriform-morular variants

The cribriform morular variant is a biologically distinct variant characterized by *APC* or beta-catenin mutations and shows an association with familial adenomatous polyposis coli, in some cases preceding recognition of colon polyps or other extracolonic manifestations.[11] Diffuse sclerosing variant is a locoregionally aggressive variant 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 variant appears to necessitate more aggressive initial surgical management including more extensive node dissection.[12]

Other variants that may have prognostic and therapeutic value but are rare and not well validated include:

- Clear cell
- Hobnail
- Oncocytic or oxyphilic
- Solid/trabecular

- Spindle cell
- Papillary thyroid carcinoma with fibromatosis/fasciitis-like stroma

Follicular and Hürthle (oncocytic) cell 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 subdivide these carcinomas into minimally invasive (capsular invasion (CI) only)), encapsulated angioinvasive (any focus of vascular invasion) and widely invasive. The latter is defined as grossly apparent extensive invasion of the thyroid and/or extra-thyroid tissue with often prominent vascular invasion.[1] These widely invasive carcinomas are often characterized by loss of encapsulation and multiple invasive fronts radiating from the epicenter of the tumour. Hürthle cell carcinoma is defined as a tumour composed of 75% of oncocytes lacking the nuclear features of papillary carcinoma demonstrating capsular and/or vascular invasion.[1] In the most recent WHO classification of endocrine tumours, Hürthle cell carcinoma is no longer considered a variant of follicular carcinoma because of different (overall more aggressive) behaviour, different molecular profile and less radioactive iodine avidity.[1] The definition of minimally invasive, angioinvasive and widely invasive Hürthle cell carcinoma mirrors 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 Hürthle cell carcinoma even after complete sampling of the tumour capsule.[13] There are also very rare instances of regional nodal metastases without primary thyroid carcinoma found.[14]

While the majority of thyroid cancers are well differentiated, a subset are poorly differentiated (historically known as insular, or trabecular, carcinoma) or undifferentiated (anaplastic). These tumour types represent progression to a more aggressive phenotype and are often seen with co-existent or antecedent well-differentiated carcinoma. While detailed histomorphologic review is beyond the scope of this protocol, salient features of both tumour types are listed below.

Poorly differentiated thyroid carcinomas (PDTC)

Poorly differentiated thyroid carcinomas (PDTC) have a prognosis in between the well differentiated indolent papillary thyroid carcinoma and the often fatal anaplastic carcinoma. According to the most recent WHO classification, poorly differentiated carcinomas 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 10 HPF, tumour necrosis, and nuclear convolution (without other nuclear features seen in papillary carcinoma).[1,15] As defined, PDTC is not the only tumour type that has prognostic features intermediate between well- differentiated and undifferentiated (anaplastic) carcinoma.[1] Other tumour types, including tall cell papillary carcinoma, can have guarded prognosis. Grading (based on high mitotic count and necrosis as used at Memorial Sloan-Kettering Cancer Center) identifies aggressive thyroid tumours of intermediate prognosis, regardless of their cytoarchitectural features.[1,16] Of note, encapsulated poorly differentiated thyroid carcinomas appear to have a more favourable prognosis than unencapsulated tumours, particularly if they show no capsular or vascular invasion with adequate sampling.[16,17]

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.[18] Undifferentiated carcinoma is almost invariably rapidly lethal. A better differentiated component such as PTC or Hürthle cell carcinoma may be found and its presence should be mentioned.

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