Update on follicular variant of papillary thyroid carcinoma with an emphasis on new terminology: noninvasive follicular thyroid neoplasm with papillary-like nuclear features

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Abstract

The most common papillary thyroid carcinoma (PTC) variant is the follicular variant, representing ~30% of all PTCs. The tumour is most common in middle aged (4th – 5th decades) women, who usually present with a single dominant nodule (about 3 cm). By definition, follicular architecture must be the dominant finding, while demonstrating the nuclear features of PTC. Papillary structures are <1% of volume, while necrosis, increased mitoses (>3/10 high power fields) and psammoma bodies are absent. The tumour category is divided into "encapsulated/well demarcated" and "invasive" types. The nuclear features include enlarged, elongated and overlapping nuclei; membrane irregularities (irregular contours, grooves and pseudoinclusions); chromatin clearing, margination and glassy nuclei. When the tumour is encapsulated/well demarcated ***without*** invasion, demonstrating the other inclusion and exclusion criteria, the new name of "Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features" (NIFTP) is used, a tumour that requires no additional treatment.

Keywords carcinoma; neoplasm invasiveness; papillary follicular/pathology; thyroid neoplasms/pathology; thyroid neoplasms/therapy

Introduction

The follicular variant of papillary thyroid carcinoma (FVPTC) is the most common variant of papillary thyroid carcinoma (PTC), accounting for about 30% of all PTCs.[1–5] Women are affected more frequently than men with a 3.6:1 female: male ratio. The overall mean age at presentation is in the 5th decade of life (mean 44 years), younger than microscopic PTC (mean 53 years) and tall cell variant (mean 56 years), but older than the diffuse sclerosing variant (mean 23 years).[5–7] Although there are slight variations based on presence or absence of invasion, the overall patient outcome is usually excellent for these tumours, with about 3% showing disease at last follow-up for the invasive group, but approaching zero for the noninvasive tumours, supporting the tumour as a biologically indolent rather than biologically aggressive group.[1]

There are two main types: *encapsulated* and *invasive* follicular variants, while the *diffuse*[8,9] and *macrofollicular* variants[9] are very rare, and thus not further discussed. "*Encapsulated papillary carcinoma*" is applied to *classical* PTC when there is a thick, well formed capsule, but with a dominant **papillary** rather than **follicular** architecture.[10,11] The discussion will be separated into the *invasive follicular variant* and the *encapsulated follicular variant*, with and without invasion.

Invasive follicular variant of papillary thyroid carcinoma

While the follicular architecture and the nuclear features of PTC (see below) are identical, this tumour shows an infiltrative growth, with infiltration into the adjacent parenchyma. There may be a thin capsule around the tumour, but for the most part this is a sclerotic, widely infiltrative tumour. This tumour type shows a metastatic potential and risk of recurrence that is higher than the noninvasive tumours, and similar to classical PTC.[4,12–14] In general, there is a higher frequency of extrathyroidal extension, frequent positive margins and frequent lymph node metastases, more frequently showing *BRAF* mutations rather than *RAS* mutations.[15–18]

Encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

The *encapsulated* type includes non-encapsulated or partially encapsulated (circumscribed) tumours, which are morphologically equivalent, showing a biologic behaviour that is different from the *invasive* FVPTC, even though all follicular variant tumours as a whole have a better outcome than classical PTC.[4,19] Both EFVPTC and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) have an excellent long term prognosis when managed conservatively.[3–5,12,14,15,19–32]

The tumours in this category have morphologically equivalent inclusions and exclusion criteria, with the separation between EFVPTC and NIFTP based on the presence of invasion. "*The Endocrine Pathology Society Conference for Re-examination of the Encapsulated Follicular Variant of Papillary Thyroid Cancer*" was convened March 20–21, 2015 in Boston, MA, and based on extensive evaluation of noninvasive cases, outcome data and the development of a set of inclusion criteria, this international group of thyroid gland specialists, has issued the term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[33] An algorithm may be employed to evaluate these tumours (Figure 1), helping to keep the diagnostic categories distinctive. This tumour (formerly encapsulated follicular variant of papillary thyroid carcinoma without invasion) is an exceedingly indolent tumour, with a very low risk of progression and showing a strong association with *RAS* mutations.[15–17,25,34]

Inclusion criteria

While a minimum size criterion is not stated, the inclusion criteria were established for ≥1.0 cm tumours. However, if the reason for

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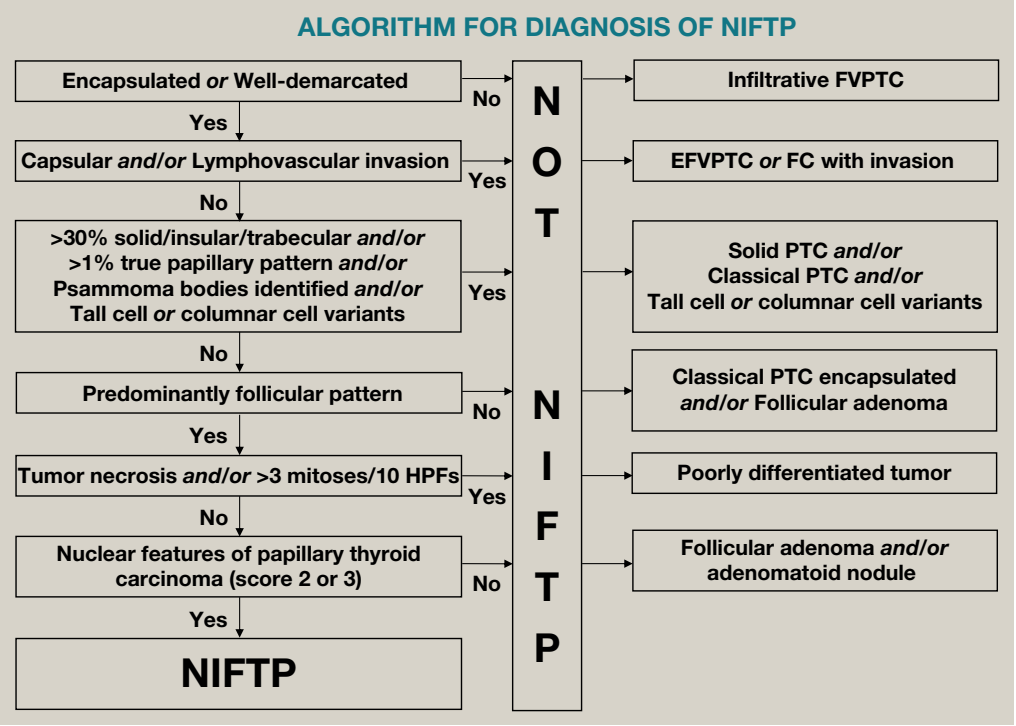

Figure 1 Algorithm for the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclei (NIFTP).

the surgery is a single tumour mass that is <1.0 cm, then "microscopic" or "incidental" is not appropriate nomenclature, and perhaps NIFTP can be applied in this unique setting for a small tumour (i.e., not incidental). In general, NIFTP are larger (mean 2.7 cm) than classical PTC.[4,5,14,24,30,32]

Encapsulated/Partially encapsulated: the tumours are very well delimited or circumscribed, with the majority encapsulated (Figures 2 and 3), surrounded by a well formed fibrous connective tissue capsule, although occasional tumours are partially encapsulated (Figure 4). Smooth muscle-walled vessels in the fibrosis help to confirm the presence of a true capsule.

Follicular growth: the tumour should demonstrate a dominant follicular pattern (Figures 2–5). The follicles are often monotonously similar, but variable sized follicles may be seen. True papillae, if identified, must be <1% of the overall tumour volume. If papillary structures are easily identified, the tumour should not be classified as a follicular variant tumour. Colloid is easily identified, is often hypereosinophilic or dark (in comparison to surrounding parenchyma), with scalloping or peripheral clearing noted. Intratumoral, acellular, eosinophilic fibrosis is frequently present. Isolated crystalloids and/or giant cells may be seen in the colloid, but these features are not diagnostic or exclusive.

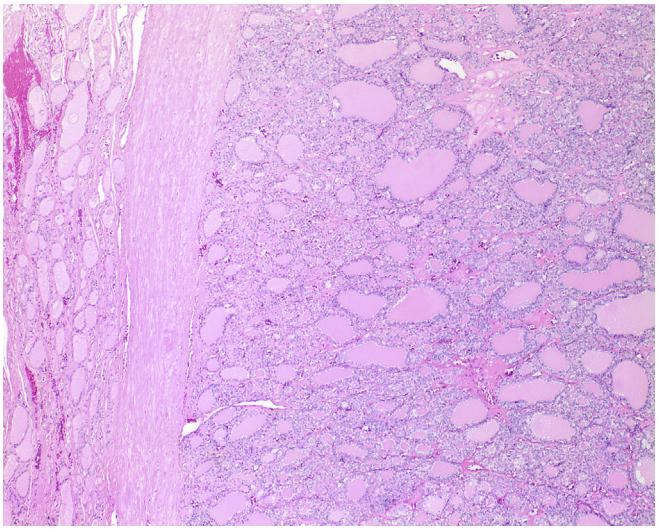

Figure 2 A thick fibrous connective tissue capsule surrounds a follicular pattern tumour.

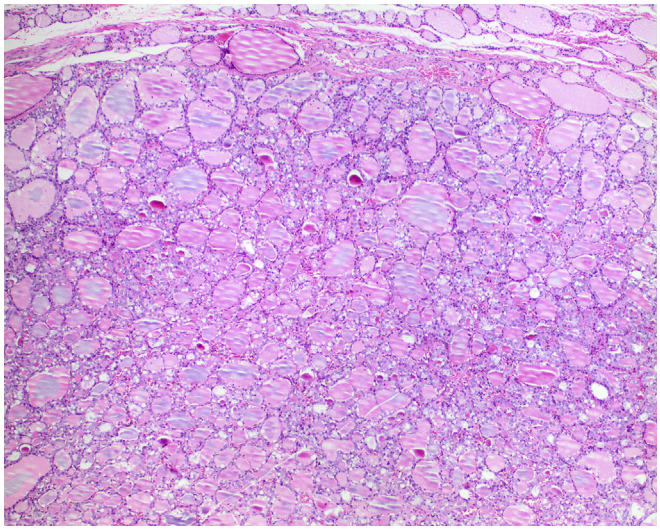

Figure 3 Well circumscribed tumour showing a thin irregular capsule around a follicular pattern tumour.