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.

There are two main types: encapsulated and invasive follicular variants, while the diffuse8,9 and macrofollicular variants9 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.1,12-14 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.1,19 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).19 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.15-17,25,44

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
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.

![Image](https://via.placeholder.com/150)

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

<table>
<thead>
<tr>
<th>Encapsulated or Well-demarcated</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Capsular and/or Lymphovascular invasion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;30% solid/insular/trabecular and/or &gt;1% true papillary pattern and/or Psammoma bodies identified and/or Tall cell or columnar cell variants</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Predominantly follicular pattern</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tumor necrosis and/or &gt;3 mitoses/10 HPFs</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nuclear features of papillary thyroid carcinoma (score 2 or 3)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>NIFTP</td>
<td>No</td>
<td>Yes</td>
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![Image](https://via.placeholder.com/150)

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

![Image](https://via.placeholder.com/150)

Figure 3 Well circumscribed tumour showing a thin irregular capsule around a follicular pattern tumour.
Nuclear features of papillary thyroid carcinoma: the characteristic nuclear features of PTC must be seen, although they are often focal and patchy in distribution. No minimum percentage of the tumour showing the nuclear features of PTC is quantified, but in general, identification of the nuclear features of PTC should be seen in at least three high power fields within a 3 mm linear area of tumour diameter. Interestingly, molecular studies have identified mutations in areas of the tumour that do not yet show morphological features of PTC, helping to support the notion that the whole nodule is one neoplasm. A nuclear features scoring system shows excellent reproducibility and is easily implemented (Table 1). The nuclear features are divided into three categories, with one point scored if the features are identified. When the score is 2 or 3, the nuclear features of PTC are confirmed. These features are as follows:

1) **Nuclear size and shape**: nuclear enlargement, nuclear elongation, and nuclear overlapping and crowding (Figure 5). Loss of nuclear polarity, with nuclei at the lumen, middle or basal zone of the cells is also a helpful finding.

2) **Nuclear membrane irregularities**: irregular nuclear contours, nuclear grooves and folds, "rat-bites" or demi-lune formations, and the presence of intranuclear cytoplasmic inclusions (Figure 6).

3) **Nuclear chromatin characteristics**: nuclear chromatin clearing, often with condensation or margination along the nuclear membranes resulting in accentuated nuclear margins, glassy nuclei, or fine, even, delicate, powdery nuclear chromatin (Figure 7). Small nucleoli are often preferentially noted along the membranes (Figure 8).

### Table 1

<table>
<thead>
<tr>
<th>Nuclear features</th>
<th>Score = 0</th>
<th>Score = 1</th>
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<tbody>
<tr>
<td><strong>1. Size and shape</strong></td>
<td>Enlargement, elongation, crowding, overlapping</td>
<td>Absent or only slightly expressed</td>
</tr>
<tr>
<td><strong>2. Membrane irregularities</strong></td>
<td>Irregular contours, grooves, folds, intranuclear cytoplasmic inclusions</td>
<td>Absent or only slightly expressed</td>
</tr>
<tr>
<td><strong>3. Chromatin characteristics</strong>:</td>
<td>Chromatin clearing, margination to the nuclear membranes, glassy nuclei, fine-even delicate chromatin</td>
<td></td>
</tr>
</tbody>
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Total score: 0 or 1: Not diagnostic.
Total score: 2 or 3: Diagnostic of PTC nuclei.

Figure 4 Well circumscribed or well demarcated, but unencapsulated tumour, distinctively separate from the surrounding parenchyma.

Figure 5 The nuclear features of papillary thyroid carcinoma identified in follicular patterned tumours. There is nuclear crowding, overlapping and enlarged nuclei.

Figure 6 There are nuclear contour irregularities, grooves and folds, with nuclear elongation.
Exclusion criteria

To apply the diagnosis of NIFTP, both inclusion and exclusion criteria must be met. Strict adherence to the exclusion criteria is required if the diagnosis is to be meaningful in clinical management and outcome. The following criteria, when identified, would exclude the use of NIFTP.

**Invasion:** any invasion would move the tumour to an invasive EFVPTC rather than NIFTP. This includes capsular penetration (excluding post fine needle aspiration site), infiltration into adjacent parenchyma, extrathyroidal extension (in adipose tissue or skeletal muscle), perineural invasion, and/or lymphovascular invasion (Figure 9). Tumour within an endothelial lined space within the capsule or in vessels outside of the tumour, often accompanied by thrombus or showing wall attachment (i.e., not free floating tumour) would qualify as vascular invasion. In order to adequately exclude invasion, sampling of the tumour-to-capsole-to-parenchyma junction must be sufficient. Complete embedding of the interface of the tumour to capsule or parenchyma is advocated, realizing certain practical limitations may occasionally need to be taken into consideration. Practically, three sections (not blocks) per cm of tumour diameter would yield an initial meaningful tumour periphery evaluation.

**Pattern of growth:** by definition, the tumour should show a nearly exclusive follicular architecture. Occasionally, other patterns may be seen, such as a solid, trabecular or insular architecture. However, these other patterns of growth cannot exceed 30% of the overall tumour volume (Figure 10). Further, the presence of any other recognized variant (such as tall cell, hobnail, cribriform-morular, or columnar cell variants), would exclude the use of NIFTP (Figure 11).
**Papillary structures:** true papillary structures with fibrovascular cores must be <1% of the overall tumour volume. If there are easily identified papillae (Figure 12), EFVPTC or NIFTP cannot be applied.

**Psammoma bodies:** psammoma bodies represent dead papillae which have been surrounded by laminated layers of calcium. Thus, any psammoma bodies would preclude a diagnosis of EFVPTC or NIFTP. Importantly, in thyroid specimens with more than one tumour, psammoma bodies within lymphatics may represent intraglandular spread from a different, topographically separate tumour, requiring further investigation.

**Tumour necrosis:** areas of true tumour necrosis (comedonecrosis or confluent geographic necrosis) not associated with a fine needle aspiration site, exclude the diagnosis of EFVPTC and NIFTP.13,36

**Increased mitoses:** if there are >3 mitoses per 10 high power fields (using a 400× magnification), the tumour cannot be diagnosed as EFVPTC or NIFTP (Figure 13). Again, increased mitoses immediately adjacent to a fine needle aspiration site may be seen. Generally, tumours that show increased mitoses, tumour necrosis along with a more solid/insular or microfollicular pattern are classified as poorly differentiated thyroid carcinoma.37

**Cytoplasmic quality:** cells with oncocytic (oxyphilic, Hürthle, Ashkenazy) cytoplasm are not included in the definition of EFVPTC or NIFTP.

Thus, based on these inclusion and exclusion criteria, a diagnosis of either an EFVPTC or NIFTP can be rendered. Any invasion would exclude the diagnosis of NIFTP, but the encapsulated tumour would result in a diagnosis of EFVPTC with invasion. If there is a solid, insular or trabecular pattern of >30% of the tumour volume, then a solid variant of PTC would be diagnosed. When papillae or psammoma bodies are present, a classical PTC would be the most likely diagnosis. Obviously, if the nuclear features of PTC are not present, then the tumour may be a follicular adenoma or carcinoma, or potentially an adenomatoid nodule, depending on the presence or absence of a capsule and whether invasion was seen.

**Fine needle aspiration**

A discussion about fine needle aspiration is beyond the scope of this histologic review, but suffice it to say, the preoperative evaluation of follicular variant tumours is difficult, with a high false negative (29%) and a low true predictive value (range of 9 –58%).32,20,38–41 Most tumours are classified in follicular neoplasm or atypia of undetermined significance/follicular lesion of undetermined significance, Bethesda categories III or IV.
(71%), although many are also classified as suspicious for malignancy or malignant (categories V or VI; 29%). If molecular techniques are applied, the tumours often reveal a RAS mutation, although other mutations are infrequently identified. NIFTP is a diagnosis of surgical pathology material only, and the overlapping nuclear features with invasive EFVPTC makes a preoperative FNA diagnosis unreliable. NIFTP should be listed as a differential diagnosis on indeterminate categories.

**Molecular findings**

The diagnosis of FVPTC and NIFTP is a haematoxylin and eosin based interpretation. However, it is well documented that these tumours tend to cluster with other follicular patterned tumours rather than classical papillary carcinoma. The Total Cancer Genome Atlas for papillary thyroid carcinoma showed the vast majority of classical PTC clustered with BRAF V600E type tumours, without overlapping with the RAS (H, N or KRAS) or PAX8/PPARγ cluster of tumours. By contrast, RAS (H, N or KRAS) or PAX8/PPARγ is seen in follicular patterned thyroid tumours. Thus, follicular patterned tumours can have similar molecular findings, even though nuclear features may be different. Thus, the FVPTC is really two tumours: 1) the noninvasive, partially or completely encapsulated FVPTC showing a genotypic and behavioural profile that is similar to follicular adenoma/carcinoma, and 2) invasive (infiltrative) FVPTC showing a genotypic and behaviour profile similar to classical PTC, including BRAF mutation status. Therefore, if a tumour is encapsulated/partially encapsulated and noninvasive, meeting the strict criteria established above, it would be classified as NIFTP, probably showing a RAS mutation, and associated with an exceedingly indolent clinical behaviour.

**Immunohistochemistry**

While follicular variant tumours are classified based on standard and well prepared haematoxylin and eosin stained slides, immunohistochemistry may sometimes be of value. When all three markers (HBME-1, galectin-3, and CK19) are positive in a follicular-pattern tumour, a diagnosis of EFVPTC or NIFTP may be confirmed. However, it is important to emphasis there is significant variability in expression in individual cases, limiting widespread application.

**Clinical treatment and patient outcome**

Based on the concept of the American Thyroid Association (ATA) “Risk Continuum” or “Risk Stratification”, NIFTP would fit in at the lowest point on the continuum, matching the recommendations of lobectomy or surgery only without 131I radiotherapy, with patients experiencing an excellent long term clinical outcome. Prophylactic central neck lymph node dissection is not required for NIFTP. Staging is not performed, as NIFTP is not considered a malignant neoplasm. Presently, clinical follow-up strategies are being evaluated, but the same intensive follow-up for a papillary thyroid carcinoma is unwarranted. When lymphovascular invasion is present (whether the tumour is encapsulated or not), completion thyroidectomy with follow-up radioablative iodine is advocated, along with long term clinical follow-up. Although not specifically studied, pediatric patients may be included in this new category with the same treatment recommendations.

**Conclusion**

The FVPTC has several types, primarily separated based on invasion. When the strict inclusion and exclusion criteria are employed, the term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) should be used to avoid overtreatment of an exceedingly indolent tumour. In tumours with invasion, the currently recommended surgery and radioablative iodine treatments can be employed as appropriate.

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**Practice points**

- Follicular variant of papillary thyroid carcinoma has two main categories: invasive and encapsulated/well demarcated without invasion (the latter now reclassified NIFTP)
- The noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has the following criteria:
  - Inclusion criteria: encapsulated/well demarcated, a follicular architecture with <1% papillae, and the nuclear features of papillary carcinoma (score of 2 or 3)
  - Exclusion criteria: any invasion, psammoma bodies, tumour necrosis, >3 mitoses/10 high power fields, >30% solid/trabecular/insular growth, characteristics of other papillary thyroid carcinoma variants (such as tall cell or columnar cell)
- Follicular variant tumours usually have RAS rather than BRAF mutations
- Noninvasive tumours require no additional therapy