



The Royal College of Pathologists

Pathology: the science behind the cure

NIFTP addendum to the RCPATH

Dataset for thyroid cancer histopathology reports

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Comments	<p>This document is an explanatory statement on NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) and is an addendum to the current (February 2014) <i>Dataset for thyroid cancer histopathology reports</i>. It has been issued to provide interim guidance for pathologists to understand the NIFTP terminology and explain how and when to apply it.</p> <p>Dr Lorna Williamson Director of Publishing and Engagement</p>

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NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features) – an explanatory statement

Background

On 14 April 2016 an article was published proposing the new term of '*NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)*' for a carefully defined subset of non-invasive encapsulated follicular variant papillary thyroid carcinoma (FVPTC).¹ This proposal followed an international multidisciplinary consensus study (the UK representative was Dr David N Poller, Portsmouth). The term has been welcomed internationally, because it avoids the label of 'cancer' for a very low-risk tumour.² NIFTP tumours are follicular-derived tumours with a very low risk of malignancy that may harbour RAS gene mutations, PAX8/PPARG translocations and THADA fusions. BRAF V600E mutations are not identified in NIFTP tumours if the strict diagnostic criteria for NIFTP are applied.

Criteria for diagnosis

Non-invasive encapsulated FVPTCs (eFVPTCs) are discussed in the existing RCPATH *Dataset for Thyroid Cancer Histopathology Reports* in section 5.3.2 on page 11.³

For a diagnosis of NIFTP, the criteria are strict. The entire capsule of the lesion must be embedded and examined histologically, and the following criteria should be met (see Figure 1 and references 1, 4 and 5).⁴⁻⁵ In diagnosing NIFTP tumours attention should be given to uniform and careful tissue fixation and tissue processing of the specimen as it is well known that suboptimal tissue fixation may give rise to artefactual nuclear clearing and features that may in some cases mimic a NIFTP type tumour. The diagnosis of NIFTP tumours should not be attempted on frozen sections as the nuclear features of NIFTP and the capsule of the lesion and invasion of the surrounding thyroid cannot be adequately assessed on frozen section.

Inclusion criteria – major features:

- encapsulation or clear demarcation
- follicular growth pattern with less than 1% papillae
- if solid, trabecular or insular patterns seen these in total should be **less** than 30% of the total tumour volume
- no psammoma bodies
- nuclear features of papillary thyroid carcinoma (enlargement, crowding/overlapping, elongation, irregular contours, grooves, pseudo-inclusions, chromatin clearing)
- nuclear score should be 2 or 3 (see Figure 2).

Inclusion criteria – minor features:

- dark colloid
- irregularly shaped follicles
- 'sprinkling sign'
- follicles cleft from stroma
- multinucleated giant cells within follicles.

Major diagnostic features

A = nuclear pseudoinclusions

B = nuclear grooves

Minor diagnostic features

C = dark colloid

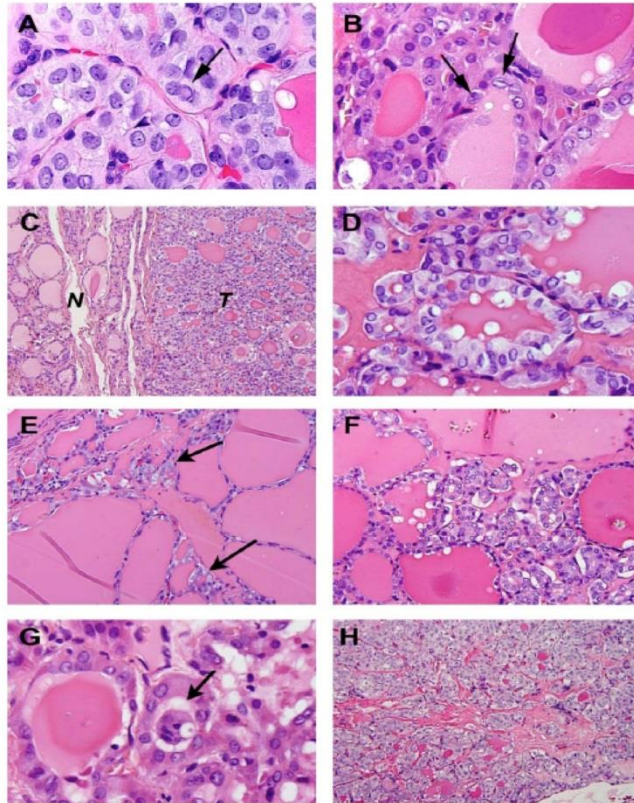
D = irregularly shaped follicles with haphazard placement of follicular cell nuclei along the basement membrane of the follicle

E = sprinkling of the follicles lined by cells showing characteristic nuclear features of PTC (arrows) in a background of follicles with benign appearing cells

F = follicles clefting from stroma

G = multinucleated giant cells

H = intratumoural fibrosis



Adapted from Nikiforov Y et al JAMA Oncology 2016 doi:10.1001/jamaoncol.2016.0385 with permission

Figure 1: Major and minor diagnostic features of NIFTP

Exclusion criteria:

- any capsular or vascular invasion; **but if the whole capsule has not been examined thoroughly then the default diagnosis is still non-invasive encapsulated FVPTC (eFVPTC) and it is NOT a NIFTP**
- true papillary structures in more than 1% of tumour volume
- psammoma bodies
- infiltrative border
- tumour necrosis (not associated with FNA)
- increased mitoses (defined as at least 3 per 10 hpf)
- cell/morphological characteristics of any other papillary thyroid carcinoma variant (e.g. tall cell, columnar cell, cribriform morular, diffuse sclerosing, etc.)
- oncocytic lesion.

Likely behaviour

These tumours, when diagnosed carefully as above, have a very low risk of adverse outcome, with a low recurrence rate that is likely to be less than 1% in the first 15 years.¹ There is now good evidence to suggest that treatment of NIFTP tumours may be de-escalated to lobectomy alone without the necessity for completion thyroidectomy or radioiodine treatment, subject to local case-based multidisciplinary discussion and also future confirmation of this principle by UK and other international professional bodies such as The

Criteria for scoring the nuclear features of suspected NIFTP lesions

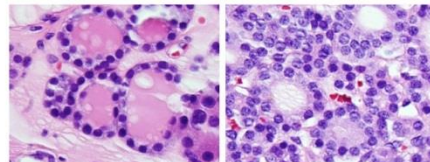
Nuclear score: sum of three nuclear features (each 0 or 1)
 Total score will vary between 0 and 3
 A score of 2 or 3 is required for a diagnosis of NIFTP

Nuclear features:

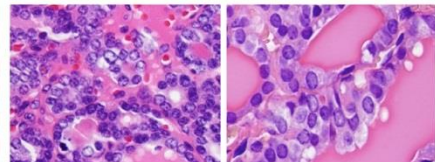
1. Size and shape

- Enlargement
- Elongation
- Overlapping

Absent/insufficiently expressed (0)

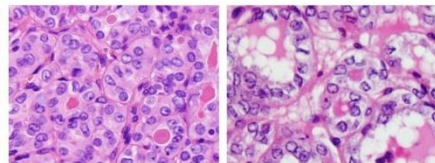
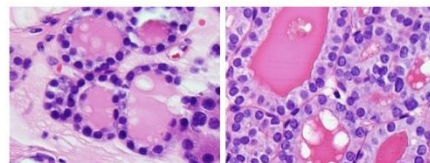


Present/sufficient (1)



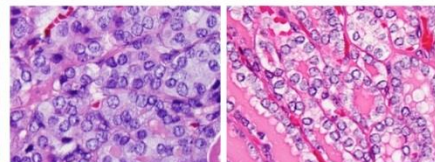
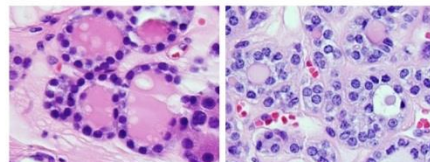
2. Membrane irregularities

- Irregular contours
- Grooves
- Pseudoinclusions



3. Chromatin characteristics

- Chromatin clearing
- Margination of chromatin to membrane
- Glassy nuclei



Slight changes not sufficient to call 'Yes'!

Adapted from Nikiforov Y et al JAMA Oncology 2016 doi: 10.1001/jamaoncol.2016.0385 with permission

Figure 2: Criteria for scoring the nuclear features of suspected NIFTP lesions

The future

The new term has been accepted for inclusion in the revised WHO 'Blue Book' for thyroid tumours, due 2017, and will then have an International Classification of Disease (ICD) code. This addendum has been issued to provide interim guidance for pathologists to understand the NIFTP terminology and explain how and when to apply it.

Reporting

While the term embeds into international thyroid diagnostic parlance, and pending publication of the new WHO 'Blue Book', we recommend that 'NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)' is used in conjunction with the current terminology for maximum clarity. Importantly, 'NIFTP' should only be used when all the criteria listed above are met. For example, the diagnosis could be given with wording such as 'Non-invasive encapsulated follicular variant of papillary thyroid carcinoma, also now referred to as NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclei)' or even as 'NIFTP, formerly known as non-invasive encapsulated follicular variant of papillary thyroid carcinoma'.

UKEPS position statement

The above is also the advice of the UK Endocrine Pathology Society, as given in their May 2016 position statement (www.ukeps.com/NIFTP_Position_Statement.html).

Implications for cytology

Most NIFTP lesions are likely to have yielded pre-operative cytology in the Thy3a, Thy3f or Thy4 categories. There is a possibility that NIFTP could yield diagnostic Thy5 cytology, indicating papillary thyroid carcinoma, producing a mismatch with a benign neoplasm histology diagnosis. This has challenging implications for multidisciplinary teams (MDTs) and also the calculations of cytology-histology accuracy and resulting risks of malignancy.⁶⁻⁸ Pending advice from the RCPATH's Cytology Terminology Group and The British Association for Cytopathology, and further evidence of accuracy of radiological prediction, we advise vigilance when reporting thyroid cytology and discussing cases in MDT meetings, especially for those lesions with a well-circumscribed outline on ultrasound when the alternative possibility of NIFTP should be flagged.

Additional NIFTP resource

www.NIFTP.org

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